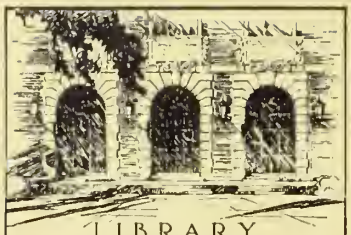


SEMINAR TOPICS

CHEMISTRY 435 II SEMESTER 1959-1960

ACID CATALYZED ALDOL CONDENSATIONS

Reported by M. L. Poutsma February 15, 1960

INTRODUCTION:

A common synthetic tool for the formation of carbon-carbon bonds is the base-catalyzed aldol condensation of aldehydes and ketones to produce β-hydroxy ketones or α,β-unsaturated ketones. This reaction has a less widely studied acid-catalyzed analogue which can be useful synthetically since the product formed generally depends on the catalyst. For example, the condensation of benzaldehyde and methyl ethyl ketone in base leads to condensation at the methyl group of the ketone, while acidic conditions give condensation at the methylene group (1). Recently several nitro-

$$C_6H_5CHO + CH_3COCH_2CH_3 \xrightarrow{\text{base}} C_6H_5CH{=}CHCOCH_2CH_3$$

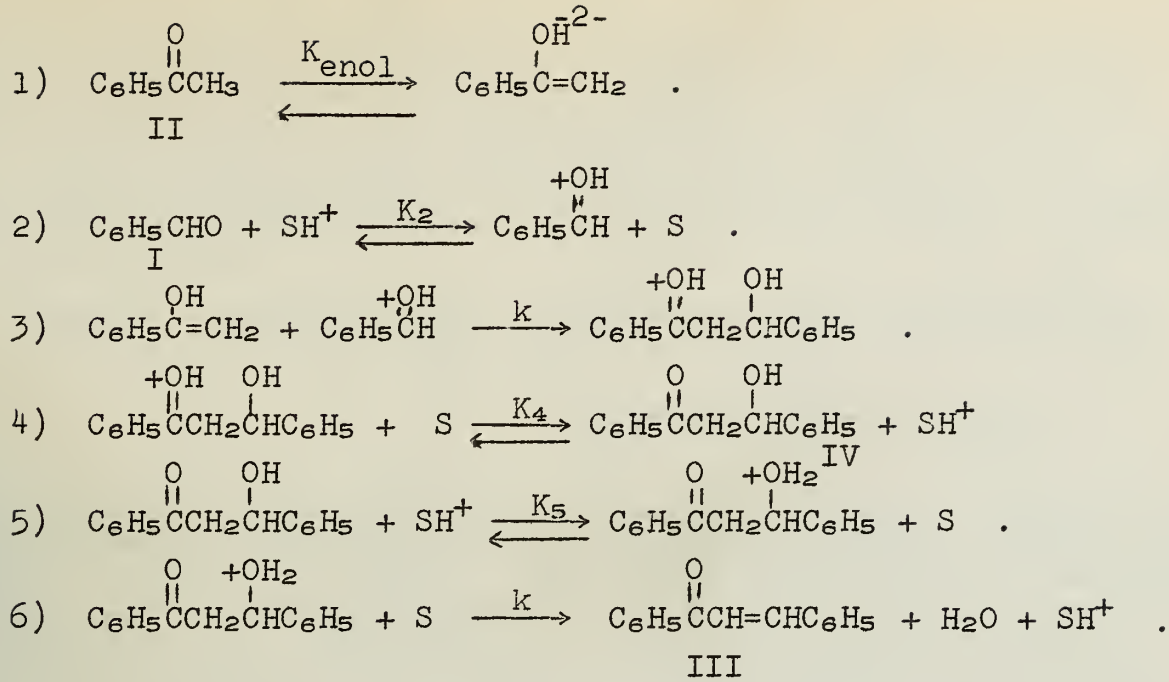
$$C_6H_5CHO + CH_3COCH_2CH_3 \xrightarrow{\text{acid}} C_6H_5CH{=}C(CH_3)COCH_3$$

hydroxy-acetophenones have been condensed with benzaldehyde in good yields by the use of $AlCl_3$ as catalyst (2). This seminar will consider the mechanism of the acid-catalyzed aldol condensation as studied primarily by Noyce and coworkers.

BENZALDEHYDE AND ACETOPHENONE:

Noyce and Pryor (3) studied the reaction of benzaldehyde (I) with acetophenone (II) in moist acetic acid catalyzed by sulfuric acid to yield trans-chalcone (III) in over 95% yield. The kinetic course of the reaction was followed spectrophotometrically by the appearance of III. It was found that the conversion of cis-chalcone to III was much faster than the condensation reaction and that the equilibrium position was practically 100% trans in the medium used (4). With acetophenone in large excess (3×10^{-2}M) the reaction was clearly first order in I (initial concentration was 9×10^{-4}M). With benzaldehyde in similar excess the reaction was also first order in II. In acetic acid containing 0.60M water and 0.699M sulfuric acid, the over-all second order rate constant (determined by dividing pseudo-first order constants by the concentration of flooded reagent) was 6.67×10^{-5} l.m.$^{-1}$sec.$^{-1}$ at 28.0°C. This second order rate constant was determined at varying sulfuric acid concentrations and found to be proportional to h_o, while (second order constant)/(H_2SO_4) increased threefold over a tenfold increase in the molar concentration of H_2SO_4. The over-all result was then: $d(III)/dt = (2.26 \times 10^{-7} \text{l.m.}^{-1}\text{sec.}^{-1})(I)(II)\ h_o$ using values of h_o measured in moist acetic acid by Gold and Hawes (5). h_o is Hammett's acidity function (6) defined by: $h_o = a_{H^+} f_B / f_{BH^+}$ where f_B and f_{BH^+} are the activity coefficients for any uncharged basic indicator, B, and its conjugate acid. If this ratio of activity coefficients is independent of the indicator chosen, h_o is a measure of hydrogen ion activity; this criterion seems well established in aqueous acids, but the extension to solutions in acetic acid is somewhat questionable. Nevertheless, a transition state consisting of one benzaldehyde molecule, one acetophenone molecule, and one proton seems very likely.

The following reaction scheme is suggested:



Steps 2), 4), and 5) should be rapid and reversible since they involve proton transfers to oxygen. The half-life of enolization of II in aqueous sulfuric acid of the same h_o as the reaction solution used for condensation is 0.23 hrs.; the half-life of a typical condensation is 60 hrs. Although the enolization would not be expected to follow h_o, the values seem to be different enough to warrant writing step 1) as an equilibrium. The bromination of II in the reaction medium is completed within 10 min., supporting a rapid enolization (7). We must choose between steps 3) and 6) as the rate limiting step; both of these give a transition state of the proper composition.

To gain further insight into the final elimination step, Noyce and coworkers (8) prepared the intermediate ketol (IV) by the method of Schopf (9). In dilute base IV was found to undergo two competitive first order reactions: dehydration to III and reversal to a mixture of I and II. The general occurence of dealdolization reactions suggested the possibility of reversal of the condensation under acidic conditions also. When IV was treated with the acetic acid-sulfuric acid reagent, the results shown in Figure 1 were obtained by measuring formation of III spectrophotometrically. Both under anhydrous and moist conditions there is a rapid formation of III followed by approach to the same limiting slope at

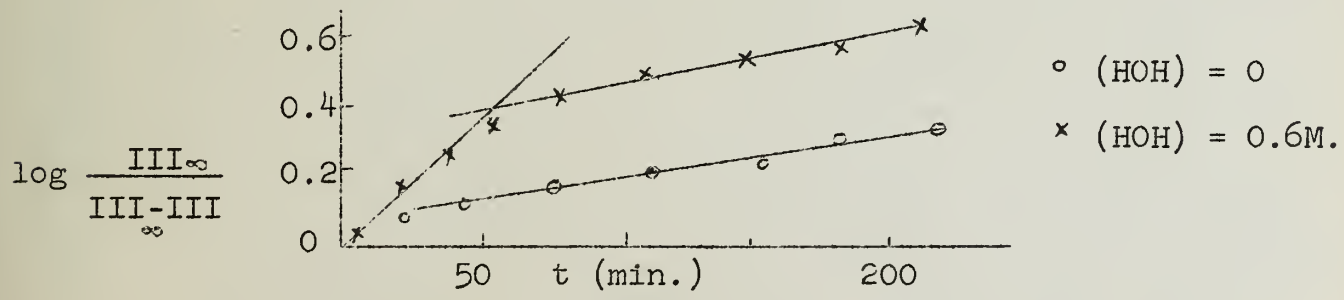
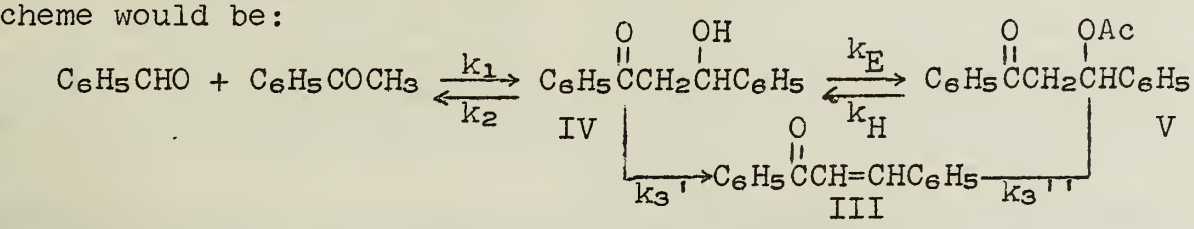


Figure 1.

about 4% of a half-life under anhydrous conditions and 40% of a half-life with 0.6M water present. Secondly, under anhydrous con-

ditions, there was practically no formation of I from IV (determined by difference between IV_o and III_∞), but with 0.6M water present 24% of IV went to starting materials. This behavior suggests the presence of more than one path for formation of III, only one of which operates past a certain point in the reaction. Since acid-catalyzed esterification of alcohols is well known, a possible scheme would be:



Under anhydrous conditions the ketol would be rapidly converted to its acetate and most of III would arise by elimination of the elements of acetic acid from V. The initial faster rate of formation of III would represent dehydration of IV before it can be completely converted to V. The failure to form much starting material would require $k_E \gg k_2$. The results in moist acetic acid produce the same limiting slope; hence the limiting rate must be the same: elimination from the acetate. The larger extent of reversal and the slower approach to a limiting slope would now be possible if k_E were smaller so that k_2 and k_3' could compete with it during the initial stages of the reaction. This explanation requires the rate of hydrolysis of the acetate, k_H, to be very slow. The enhancement of esterification under anhydrous conditions may be due to a trace of acetic anhydride left from the preparation of anhydrous acetic acid.

The limiting slope in Figure 1 gives a value of $k_3'' = 7.6 \times 10^{-5}$ sec.$^{-1}$ at 26° and $(H_2SO_4) = 0.699$M. For a twofold increase in sulfuric acid concentration, the linear dependence on h_o is satisfactory. From the initial slope of Figure 1 which represents formation of III from IV by direct dehydration before much V has had time to form, k_3' is estimated as 3.2×10^{-4} sec.$^{-1}$

Throughout this consideration of the competitive reactions of the ketol, IV, we have ignored the condensation reaction described by k_1. The highest initial concentration of IV used was 10^{-4}M; hence the concentrations of I and II formed by the dealdolization could never exceed 10^{-4}M. Based on the constants determined, $t_{1/2}$ for k_1 is 42,000 hrs. if I_o and II_o are each 10^{-4}M while $t_{1/2}$ for k_3'' is 2.5 hrs. The assumption to ignore the condensation step is obviously justified at these starting concentrations. However, since the condensation of I and II as thus far outlined consists of a slow bimolecular step (condensation) followed by a unimolecular step (elimination from IV or V) with a rate constant of almost equal magnitude (except for units), one would expect the rate of condensation to approach the rate of elimination at higher starting concentrations of I and II; then there would be no one slowest step and the kinetics should become more complex. At $(I)_o = 1.9 \times 10^{-2}$M and $(II)_o = 0.26$M in acetic acid with 0.6M water and 0.699M sulfuric acid, the formation of chalcone showed an initial induction period as expected followed by approach to a limiting slope. The induction period represents the approach to a steady state concentration of intermediate acetate. A second complication arises above about 0.3M acetophenone; here the pseudo-first order rate constants derived from the limiting slopes do not increase as fast as expected from $(II)_o$. This could be due to a decrease in the

activity coefficient for II so that the use of concentrations for activities is no longer valid at this high a concentration.

The rates of condensation of several p-substituted benzaldehydes with acetophenone were determined under similar conditions; the results are shown in Table I (10). These results were obtained at low initial concentrations of reactants so there is no induction period and the actual rate of condensation is the rate-controlling process. Two opposing effects of p-substituents would be operative in the general reaction scheme postulated. Electron donation should

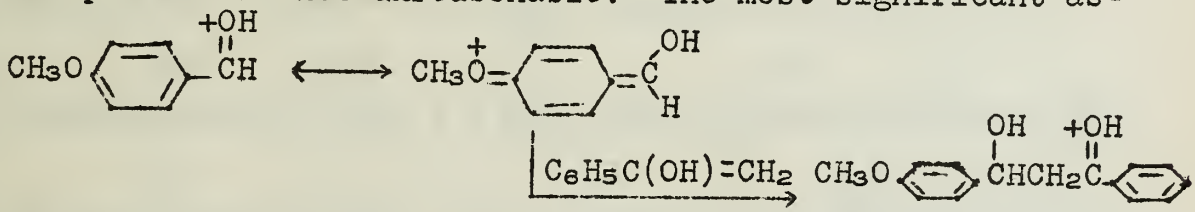
Table I

Rates of reaction of substituted benzaldehydes with acetophenone in acetic acid, 0.6M water and 0.699M sulfuric acid at 28.0° C.

p-X	$k \times 10^{-5}$ (l.m.$^{-1}$sec.$^{-1}$)	ΔH (kcal.)*	ΔS (e.u.)*
-H	6.70	11.6	-53
$-NO_2$	6.50	10.3	-57
-Cl	7.76	11.2	-54
$-OCH_3$	13.32	11.0	-55

*From measurements at 46.3°C.

cause a more basic aldehyde which would exist to a higher degree as its protonic salt. However, the extra resonance stabilization must be lost in forming the C-C bond since the aldehyde carbon becomes attached to four groups. Hence the small difference between p-methoxy and p-nitro is not unreasonable. The most significant as-



pect is that the plot of log k/k_o vs. σ has a tendency to be concave upward with anisaldehyde above the best straight line. Although the C-C bond formation is the slowest step, alterations in the relative rates of subsequent reversal and dehydration would affect the attempted σ-ρ correlation. This problem will be considered more extensively later in the seminar.

BENZALDEHYDES AND METHYL ETHYL KETONE:

The condensation of anisaldehyde (VI) and methyl ethyl ketone (VII) in acetic-sulfuric acids was found (11) to give 96 ± 1% of the product of methylene condensation (3-methyl-4-anisyl-3-buten-2-one) and less than 2% of the alternative product (1-anisyl-1-penten-3-one). With MEK in large excess the kinetic dependence of product formation on anisaldehyde is first order, but an induction period does occur above 0.3M MEK. Below 0.3M MEK a satisfactory bimolecular constant (k_o = 8.27 x 10^{-5} l.m.$^{-1}$sec.$^{-1}$ in acetic acid with 0.4M H_2SO_4 and 0.56M water at 25.14°C. where k_o = k'/(MEK) and k' is the limiting rate constant under pseudo-unimolecular conditions) is obtained, but, above 0.3M, k_o fell off. Hence the behavior is similar to that of the benzaldehyde and acetophenone case; the induction period again suggests the presence of an intermediate of some stability.

Noyce has solved the kinetic equations for the situation:

$$\text{A (VI and VII)} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{B (X)} \xrightarrow{k_3} \text{C (VIII)}$$

using rate constants determined below. When the reaction was quenched at the time calculated for maximum B, a 10% yield of the acetate (X) of the intermediate ketol (IX) was isolated. The purified acetate was subjected to the reaction conditions and the formation of both VI and VIII was followed spectrophotometrically. Starting with 2.38×10^{-2}M X in acetic acid with 0.4M H_2SO_4 and 0.56M water, the ratio of product produced to anisaldehyde produced was constant (1.44) throughout the reaction and values for the first order rate constants were determined as $k_2 = 7.92 \times 10^{-5}$ sec.$^{-1}$ for the formation of VI and $k_3 = 11.33 \times 10^{-5}$ sec.$^{-1}$ for the formation of VIII at 25.15°C.

A consistent mechanism would be:

1) $\underset{\text{VII}}{CH_3\overset{O}{\overset{\|}{C}}CH_2CH_3} \underset{}{\overset{K_{enol}}{\rightleftharpoons}} CH_3\overset{OH}{\overset{|}{C}}{=}CH{-}CH_3$

2) $\underset{\text{VI}}{CH_3OC_6H_4\overset{O}{\overset{\|}{C}}H} + SH^+ \overset{K_2}{\rightleftharpoons} CH_3OC_6H_4\overset{+OH}{\overset{\|}{C}}H + S$.

3) $CH_3OC_6H_4\overset{+OH}{\overset{\|}{C}}H + CH_3CH{=}\overset{OH}{\overset{|}{C}}CH_3 \underset{k_2'}{\overset{k_1'}{\rightleftharpoons}} CH_3OC_6H_4\overset{OH}{\overset{|}{C}}HCH(CH_3)\overset{+OH}{\overset{\|}{C}}CH_3$.

4) $CH_3OC_6H_4\overset{OH}{\overset{|}{C}}HCH(CH_3)\overset{+OH}{\overset{\|}{C}}CH_3 + S \overset{K_4}{\rightleftharpoons} \underset{\text{IX}}{CH_3OC_6H_4\overset{OH}{\overset{|}{C}}HCH(CH_3)\overset{O}{\overset{\|}{C}}CH_3} + SH^+$.

5) $CH_3OC_6H_4\overset{OH}{\overset{|}{C}}HCH(CH_3)\overset{O}{\overset{\|}{C}}CH_3 + HOAc \overset{K_{eq}}{\rightleftharpoons} \underset{\text{X}}{CH_3OC_6H_4\overset{OAc}{\overset{|}{C}}HCH(CH_3)\overset{O}{\overset{\|}{C}}CH_3} + H_2O$.

6) $CH_3OC_6H_4\overset{OAc}{\overset{|}{C}}HCH(CH_3)\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow{k_3} \underset{\text{VIII}}{CH_3OC_6H_4CH{=}C(CH_3)\overset{O}{\overset{\|}{C}}CH_3} + HOAc$.

The difference between this scheme and that suggested for the benzaldehyde-acetophenone case is the speed of step 5). The easy formation of starting materials from the acetate here requires a much more facile hydrolysis of the acetate than in the former case. To confirm the hypothesis of a ketol-acetate equilibrium, the ketol (4.24×10^{-3}M) was subjected to the same reaction conditions as the acetate had been and formation of VI and VIII again measured. The values of k_2 and k_3 obtained were 8.50×10^{-5} and 11.9×10^{-5} sec.$^{-1}$, respectively, in good agreement with those presented above. Thus IX and X are in rapid equilibrium with each other. Because of this equilibrium between ketol and acetate, which seems to lie well toward the acetate, the observed k_2 determined by starting essentially with this equilibrium mixture is then smaller than the actual rate constant for cleavage of the ketol itself.

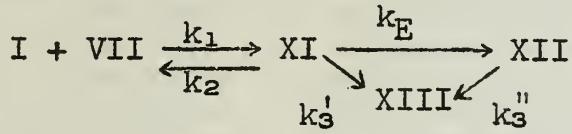
As further confirmation of this general reaction path, Noyce has solved for k_1^o, the true rate constant for condensation of VI and VII, from the measured values of k_2, k_3, and k' by using the integrated kinetic equations. The value calculated was $14.2 \pm 0.2 \times 10^{-5}$

$l.m.^{-1}sec.^{-1}$ compared to a value of 14.8 obtained experimentally from the initial disappearance of VI (before reversal becomes important) under the same reaction conditions.

The evidence so far does not justify the exclusion from the reaction scheme of some production of product from dehydration of the ketol. However, Noyce and Snyder (12) measured k_3 starting with the acetate in acetic acid containing 0.2--1.0 M H_2SO_4 and 0--0.56M H_2O; (log k_3+H_0) was a good constant even under anhydrous conditions. Pure acetate under anhydrous conditions can eliminate only by losing the elements of acetic acid. Since k_3 seems independent of the water concentration, the authors conclude that no significant amount of dehydration of the ketol occurs under moist conditions unless fortuitously the rate constants for dehydration and elimination from the acetate are equal.

The condensation step, k_1^o, measured from the disappearance of VI, follows h_o satisfactorily; this supports the condensation of protonated anisaldehyde and the enol of MEK. The bromination of MEK is instantaneous under the reaction conditions; hence the enolization of MEK, step 1), must be very rapid.

The extension (13) of the reaction to benzaldehyde (I) and MEK supports the general scheme postulated for anisaldehyde with some relative modification. The initial induction period at reasonably high concentrations persists; initial rates of disappearance of benzaldehyde are first order in I as expected. The intermediate ketol (4-phenyl-4-hydroxy-3-methyl-2-butanone) (XI) exhibited unexpected behavior in the reaction medium, however. There was an initial rather rapid formation of product (4-phenyl-3-methyl-3-buten-2-one) (XIII) along with a production of starting materials. However, after about 50% reaction, the concentration of I failed to increase further and the formation of product had fallen to a slower limiting rate first order in ketol. If the ketol and its acetate (XII) were in rapid equilibrium as with anisaldehyde, the production of I should parallel that of XIII throughout the whole of the reaction. Noyce has suggested that the rate of hydrolysis of the acetate ester must be very slow here. The point of cessation of production of I occurs when all the remaining ketol has been converted to its acetate; after this, elimination occurs only through the acetate. Estimates were obtained for all these



rate constants in acetic acid with 0.2M H_2SO_4 and 0.01M H_2O as follows:

a) k_2--reversal step from XI--from initial rate of formation of I from XI.
b) k_3''--elimination from the acetate--from limiting slope for production of XIII from XI after production of I ceases.
c) k_3'--dehydration of the ketol--from the initial rate of production of XIII from XI before k_3'' becomes important.
d) k_E--esterification of the ketol--the ratio of I/XIII formed from XI represents $k_2/(k_E+k_3')$. Then k_E is calculable based on k_2 and k_3'.

The results of such determinations carried out with low enough

concentrations of XI so that condensation can be ignored were:

$$k_2 = 11.9 \pm 0.5 \times 10^{-5} \text{ sec.}^{-1}$$
$$k_E = 23.1 \pm 1.0 \times 10^{-5} \text{ sec.}^{-1}$$
$$k_3' = 15.7 \pm 1.0 \times 10^{-5} \text{ sec.}^{-1}$$
$$k_3 = 3.5 \pm 0.1 \times 10^{-5} \text{ sec.}^{-1}$$

The variations from the parallel condensation of anisaldehyde and MEK are then the occurrence of a significant amount of dehydration of the ketol and the much smaller size of k_H, the rate of hydrolysis of the ketol acetate.

With p-nitrobenzaldehyde and MEK as substrates, an induction period again suggests an intermediate. Reactions of the ketol (4-p-nitrophenyl-4-hydroxy-3-methyl-2-butanone) showed no detectable reversal of the condensation step. Secondly, there was no evidence for acetylation of the ketol. Hence, the reaction has but one path: starting materials give the ketol which dehydrates to the product.

A summary of the results with substituted benzaldehydes and MEK is presented in Table II.

Table II

Rates of various processes in anhydrous acetic acid with 0.2 M H_2SO_4 at 25.00°C.

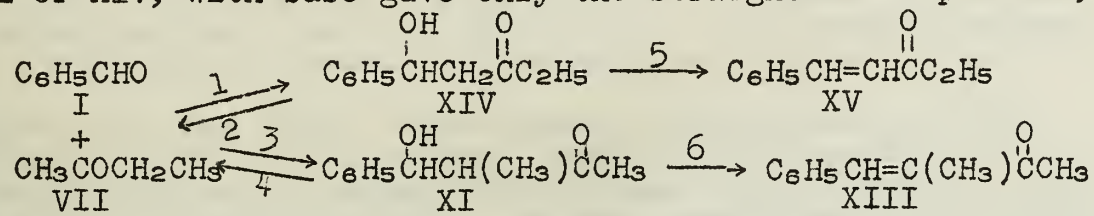
Constant (x 10^5)	p-OCH_3	H	p-NO_2
k_1^o (l.m.$^{-1}$sec.$^{-1}$)	13.2	9.53	4.31
k_2 (sec.$^{-1}$)	Large	11.9	Very small
k_E (sec.$^{-1}$)	Large	23.1	Very small
k_3' (sec.$^{-1}$)	.....	15.7	8.0
k_3 (sec.$^{-1}$)	7.8	3.49	.....

If a Hammett correlation is attempted for the initial condensation step, as determined from the initial rate of disappearance of aldehyde, a curve is obtained which is concave upward (the point for H is too low). With p-nitrobenzaldehyde, the rate constant thus measured is the true rate constant for condensation (k_1) since no reversal can occur; with anisaldehyde no correction is needed either since the ketol formed is very rapidly converted almost entirely into its acetate. With benzaldehyde, the rate of esterification is slower and the observed constant from the disappearance of I should be multiplied by a factor $(k_2 + k_3' + k_E)/(k_3' + k_E)$ to give the true rate constant for condensation. If these values of k_1^o shown in Table II are then plotted, an excellent Hammett plot is obtained with $\rho = -0.4$. This type of factor may cause the non-linear plot mentioned earlier for condensation of benzaldehyde and acetophenone, but more data are needed here.

The sensitivity of k_2 to electronic effects is seen to be that expected from the nature of the condensation postulated. The rate of esterification is also quite sensitive to electron donation although quantitative data are lacking. The effect may be more than that expected for the usual acid-catalyzed esterification reactions. For example, the acid-catalyzed hydrolysis of p-nitrobenzyl acetate in 60% acetone shows only a 10% decrease in

rate compared to benzyl acetate (14). A possibility (in light also of the dehydration evidence to be discussed below) is protonation of the hydroxyl group of the ketol, loss of water to give a benzylic carbonium ion, and recombination with solvent to give the protonated acetate.

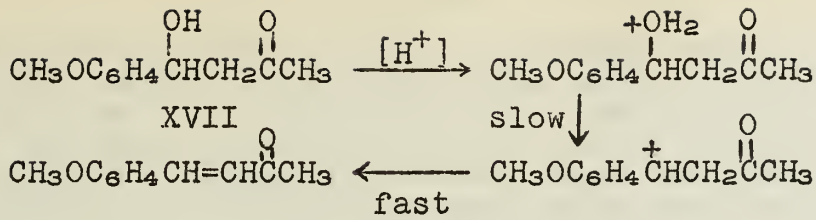
The problem of product selectivity in the reaction of benzaldehyde and MEK in acid and base was studied by Stiles, Wolf, and Hudson (15). The two possible ketols were prepared by independent means and subjected to acid and base. Treating either ketol, XI or XIV, with base gave only the straight chain product,



XV. Dilute acid converted XIV to XV and XI to XIII. Thus in acid the product specificity must reflect specificity in the condensation step with $k_3 \gg k_1$ since no XV is formed in acidic condensations of I and VII. In base, the dehydration, k_6, must be very slow and both equilibria (k_1/k_2 and k_3/k_4) must occur to allow formation of XV from XI. This pattern of specificity is consistent with the fact that bromination of MEK, which proceeds by a rate-limiting enolization, occurs at the methyl group in basic media and at the methylene group under acidic conditions (16).

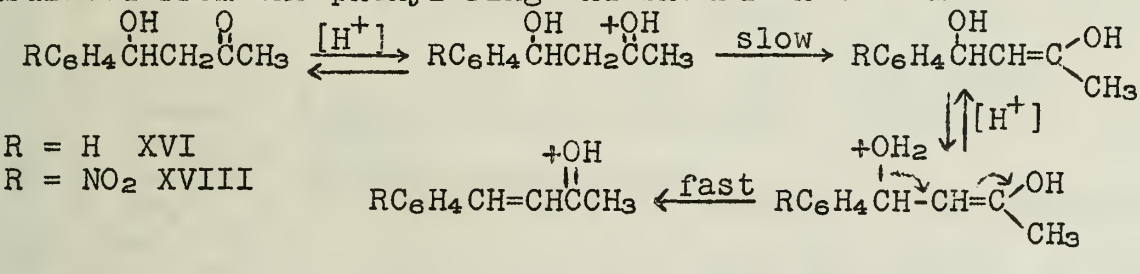
DEHYDRATION OF β-HYDROXY KETONES:

Noyce and Reed (17) prepared 4-phenyl-4-hydroxy-2-butanone (XVI), the intermediate in a base-catalyzed aldol condensation of benzaldehyde and acetone, and the p-methoxy (XVII) and p-nitro (XVIII) analogues and studied their dehydration to α,β-unsaturated ketones in aqueous sulfuric acid. The relative rates of p-methoxy: p-hydrogen: p-nitro in 1M sulfuric acid at 25°C. were 2.28: 1.05: 1.00. The rates for XVII gave a reasonable correlation with h_o, but the rates for XVI and XVIII fall somewhere intermediate between a linear dependence on h_o and on the concentration of catalyzing acid. Thus the rate for the p-methoxy compound increases much faster with increasing acidity, the relative rates at 3.5 M sulfuric acid being 8.5: 1.0: 1.0. The rate of dehydration of XVII was also insensitive to substituting perchloric acid for sulfuric acid at the same h_o value, but the rate for XVI decreased on making this change. The rate of acid-catalyzed dehydration of β-(p-methoxyphenyl)-β-hydroxy-propionic acid was found to be of approximately the same magnitude as the rates observed in the present case, but was some 10^7 times faster than the rate of its p-nitro analogue. This large rate enhancement due to electron donation in the propionic acid series supports a mechanism involving reversible protonation of the hydroxyl group, the loss of water in the slow step to give a benzylic carbonium ion stabilized by electron releasing groups, and rapid loss of the adjacent proton to form the product. This sequence would be expected to follow h_o since the transition state consists of one substrate molecule and a proton. Such a mechanism could be operative for XVII.



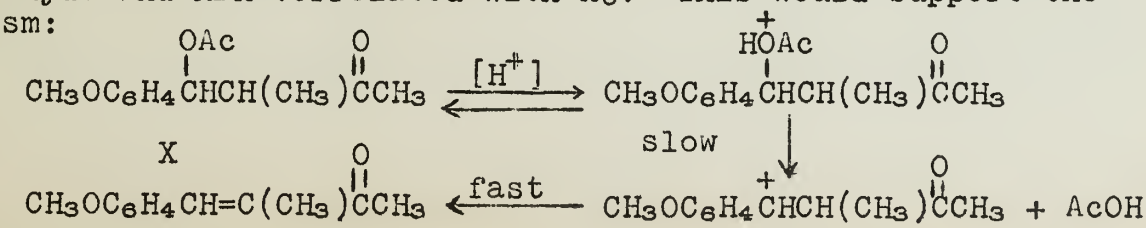
Lima (18) studied the first order dehydration of the series of alcohols: p-$RC_6H_4CH_2CHOHC_6H_4R'$-p by p-toluenesulfonic acid in dibutyl ether. With R' = H and R varied, $\rho = -0.55$; with R = H and R' varied, $\rho = -3.86$, following Brown's σ^+. Under these conditions 2-phenylethanol was not dehydrated. This general behavior supports the benzylic carbonium ion mechanism proposed above.

However, XVI and XVIII, which show no significant rate depression due to electron withdrawal, could not follow this carbonium ion mechanism. An alternative mechanism is suggested which involves a slow enolization step. In this mechanism the slow step is insulated from the phenyl ring and should show a small substi-



tuent effect. If log k for the dehydration of XVI is plotted against log k_{enol} at varying acidities (all aqueous sulfuric acid), a good linear correlation results; k_{enol} is the rate constant for the enolization of acetophenone determined by Hammett and Zucker (19) by rates of iodination. On this hypothesis, the dehydration of XVII proceeds partly through the enolization mechanism at a rate comparable to that for the unsubstituted case, and partly through the carbonium ion mechanism; this latter fraction increases markedly as the concentration of acid is increased due to its h_o dependence. If the rate constants for XVII at varying acidities are decreased by an appropriate amount to compensate for the enolization as estimated from XVI and XVIII, the resulting constants, which represent the extent of the ionization mechanism, also correlate satisfactorily with h_o. This conclusion rests on the assumption that enolization would not be expected to follow h_o, but rather the concentration of hydronium ion (19). Some question as to the usefulness of the acidity function concept arises from the recent report of Bell (20) that the enolization of acetone in HCl seems to be approaching a better dependence on h_o than on the concentration of hydronium ion at higher acidities.

Earlier it was noted that the rate, k_3'', of the loss of the elements of acetic acid from the ketol acetate (X) formed from anisaldehyde and MEK correlated with h_o. This would support the mechanism:



Note the similarity to the proposed solvolytic esterification of the ketol itself which would involve the same p-methoxy stabilized benzylic carbonium ion. Obviously such a mechanism alone could not account for the small substituent effect on k_3' and k_3'' shown in Table II. However, analogously to the cases mentioned above in aqueous sulfuric acid, the coexistence of the enolization mechanism could explain it. The rate of dehydration of the ketol formed from p-nitrobenzaldehyde and MEK significantly did not correlate well with h_o. These conclusions will require further quantitative data over a wider range of acidities for additional verification.

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NITRATION AT OXYGEN AND NITROGEN CENTERS

Reported by D. Wedegaertner February 22, 1960

Nitroamines were prepared as far back as 1893,[1] and the conversion of glycerol into nitroglycerine by nitric acid has long been a reaction of great commercial importance. In spite of this the mechanism of nitration of amines and alcohols has only recently been elucidated.[2,3] This seminar is concerned with the mechanism of N- and O-nitration when nitric acid is employed as the nitrating source.

The predominance of the nitronium ion mechanism in aromatic nitration has been well established, and the nitronium ion as a discrete chemical entity is well known, its existence having been verified by a number of methods.[4] Aromatic nitration through attack of nitronium ion was kinetically demonstrated at first in non-hydroxylic solvents, and in hydroxylic but non-aqueous solvents,[5,6] and later even in the solvent water.[7-9] Since aromatic nitration occurs by the attack of nitronium ion upon carbon, it would be not unreasonable to expect that nitration at oxygen and nitrogen might occur by a similar electrophilic attack of nitronium ion upon those atoms. Based upon kinetic studies of aromatic nitration, the nitronium ion mechanism of nitration has been formulated as follows:[2]

Step I $HNO_3 + HNO_3 \underset{}{\overset{K_1}{\rightleftharpoons}} H_2NO_3^+ + NO_3^-$ (fast)

Step II $H_2NO_3^+ \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} NO_2^+ + H_2O$ (slow)

Step III $NO_2^+ + XH \xrightarrow{k_3} XH\cdot NO_2^+$ (slow)

Step IV $XH\cdot NO_2^+ + NO_3^- \xrightarrow{k_4} XNO_2 + HNO_3$ (fast)

(-X = -Ar, -OR, -NRR')

The following rate expression is obtained from the above scheme using the steady state approximation:

$$-\frac{d[XH]}{dt} = \frac{k_3k_2K_1\ [HNO_3]^2[XH]}{[NO_3^-](k_{-2}[H_2O]+k_3[XH])}$$

Step I of the above scheme is a rapidly reversible hydrogen transfer reaction. The nitric acidium ion formed in equilibrium concentration in step I next undergoes a slow dehydration reaction to produce nitronium ion and water. The nitronium ion thus formed can then either react with the water to give back nitric acidium ion or it can react with XH which leads to the formation of nitration product. $XH\cdot NO_2^+$ may not be a reactive intermediate as indicated, but instead may represent a transition state. It can be easily seen from the rate equation that the nitration reaction will be either zero- or first-order in substrate, depending upon whether $k_3[XH] \gg k_{-2}[H_2O]$ or $k_{-2}[H_2O] \gg k_3[XH]$ respectively. A firm proof of the mechanism requires the observation of both limiting kinetic forms, and of the transition between them, which may be effected by changing the balance of competition between the two consumers of formed nitronium ion.

This seminar will deal in some detail with kinetic studies carried out on both N- and O-nitrations in nitromethane solution. The kinetics were followed by dilatometry. Dilatometry requires a

difference in volume between reactants and products. A dilatometer essentially consists of a bulb with a capillary tube at its top and a capillary tube or tap at the bottom of the bulb for filling. After the bulb is filled, the reaction is followed by observing the rising or falling of the meniscus in the capillary tube. In the case of nitration there is a volume contraction as the reaction proceeds. The distance, l, travelled by the meniscus of a dilatometer is accurately proportional to the amount by which the reaction under investigation has proceeded. The formula for the concentration of reactants at time, t, is $(l_\infty - l_t)\frac{D}{R}$, where D equals the fractional volume change for unit length travelled by the meniscus (constant for a given dilatometer), and R equals the fractional volume change per g-mol. of reaction (constant for a given reaction).[4] The volume contraction accompanying the N-nitrations was about 1/4 that previously observed in C-nitration, but the dilatometers which had been used in C-nitrations were sufficiently accurate for the N-nitrations. In the case of O-nitration, however, the volume contraction is 1/40 that of C-nitration, and a dilatometer with an accuracy of an order of magnitude greater is required. The fractional volume changes per unit scale length for various dilatometers used were as follows: D_1=0.00195, D_2=0.000190, D_3=0.0000564 (used in the O-nitrations). In practice, the temperature variation of the thermostat was about 0.0005°C. The scale readings of the dilatometer were made with a cathetometer which had an accuracy of $\pm$ .01mm.

O-Nitration

Using O^{18}-labeled nitric acid Klein and Menster proved that the esterification reaction between nitric acid and cellulose was indeed an O-nitration by showing that for each alcoholic group converted, the replacement was of -H by $-NO_2$, with two oxygen atoms from the nitrating medium, and not of -OH by $-NO_3$ with 3 oxygen atoms from the medium.[10]

The mechanism of oxygen exchange between nitric acid and water, that is the O-nitration of water, has been studied using O^{18} labeled water.[7-9] From the identity of the absolute rate of exchange in aqueous concentrated nitric acid with the absolute rate in the same medium of an aromatic nitration, so organized that the organic substrate captures almost all the nitronium ion, the kinetic order becoming zero, it was shown that the nitronium ion mechanism is responsible for the O-nitration of water.

Evidence for the nitronium ion mechanism in O-nitration was furnished by the demonstration that in aqueous perchloric acid the rate expression for the formation of isoamyl nitrate is first-order in nitric acid and first-order in isoamyl alcohol and that the log of the rate constant for the nitration of isoamyl alcohol by nitric acid varies with acidity according to an acidity function of the form C_0 but not H_0.[11-14] It was found that better agreement between the rate constant and the acidity function could be obtained using the ratio $[NO^+]/[HNO_2]$ rather than $[R^+]/[ROH]$, where ROH is a triphenylcarbinol type indicator, because NO^+ and HNO_2 are more nearly like NO_2^+ and HNO_3 respectively. The fact that the reaction follows C_0 is evidence for the nitrating species being the nitronium ion, and the lack of agreement with H_0 rules out the possibility of nitric acidium ion being the nitrating species even in aqueous perchloric acid solution (Fig. 1).

The nitration of methyl alcohol in initially dry nitromethane was studied kinetically by dilatometry.[3,15] With alcohol concentrations not above .09M and nitric acid concentrations not above 2.5M a typical volume-time curve for a zero-order nitration is obtained. After some initial irregularity the plot is a straight line of negative slope which turns sharply to one of zero slope when the reaction is complete. The zero-order rate constant can be calculated from the negative slope.

Fig. 1 Plot of log k, log $\frac{[NO^+]}{[HNO_2]}$ and H_o vs $HClO_4$ (%)

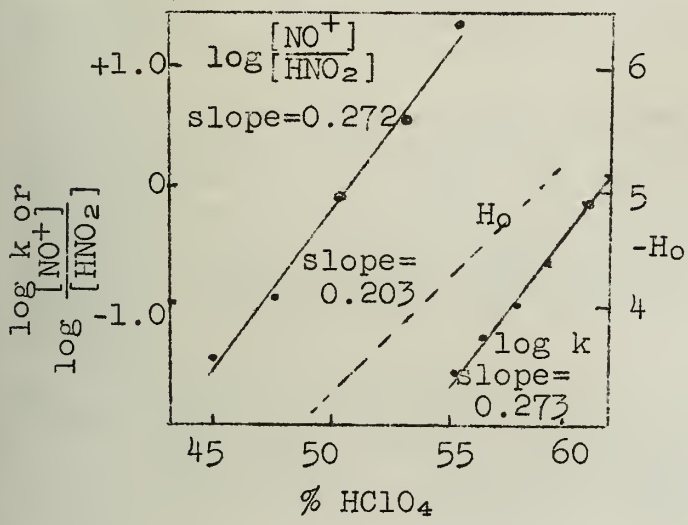


Fig. 2 Volume-time curve for nitration of methyl alcohol (0.2M) by nitric acid (4M) in nitromethane at 25°C.

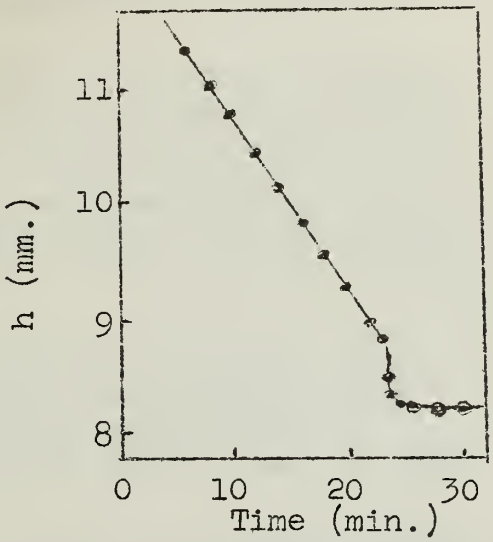


Table 1 Zero-order rate constants (k_o in moles $l.^{-1}$ $sec.^{-1}$) for the nitration of methyl alcohol by 2.5M nitric acid in nitromethane at 25°C.

$[MeOH]_o$	0.0233	0.0236	0.0244	0.0356	0.0400	0.0524	0.0580	0.0653	0.0830
$10^5 k_o$	1.65	1.61	1.69	1.74	1.69	1.62	1.72	1.66	1.74

(Average k_o = 1.68 X 10^{-5} mole $l.^{-1}$ $sec.^{-1}$)

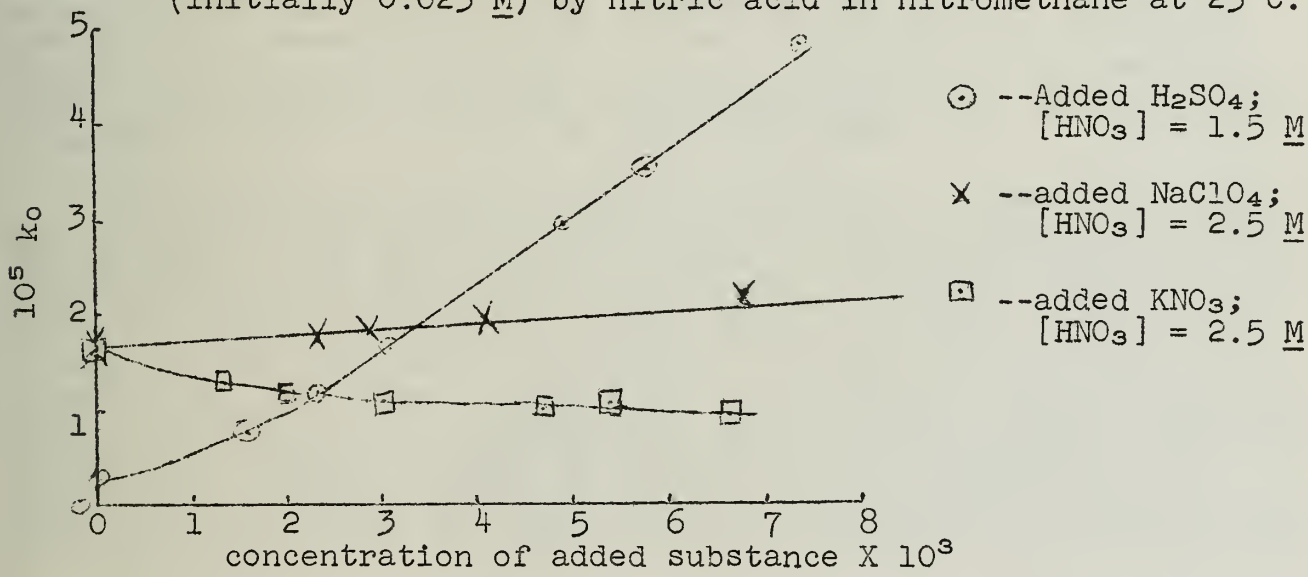
When higher initial concentrations of methyl alcohol (.1M or more) are used, the sloping portion of the volume-time curve is not absolutely straight, its initial gradient being appreciably greater than that over the latter part of the curve. The cause of this is not established. The authors feel that this may be due to some kinetic solvent effect of methyl alcohol. Since water is being formed as methyl alcohol is being used up, it would seem that if the acceleration were due to an accelerating effect of co-solvent, the water would produce a greater acceleration than methyl alcohol due to the fact that water has a higher dielectric constant (ions are formed from neutral species in the kinetically significant part of the mechanism). Thus if a co-solvent effect were under observation it would be expected that the rate should increase during the latter portion of the reaction instead of at the start. The greater reaction rate at higher alcohol concentration observed for the first part of reaction may possibly be due to the reaction of another nitrating species at the higher alcohol concentration.

The rate rises as a steep function of the nitric acid concentration in these zero-order nitrations. If the acid concentration is

increased above 3 M, producing somewhat fast runs, a new discontinuity then appears at the end of the downward sloping branch of the volume-time curve (Fig. 2). Instead of turning abruptly horizontal, it abruptly turns to a much more steeply downward-sloping direction, and after a short exponential course becomes horizontal. This is regarded as a thermal effect, arising from dissipation of the heat of reaction. This effect is not seen in the less sensitive types of dilatometers, nor in the sensitive ones unless the runs are fast. During the first few minutes of a run, the dilatometer contents will attain a steady temperature such that the heat generated by the reaction is lost to the thermostat at the same steady rate. When the nitration stops, the temperature of the dilatometer contents falls to that of the thermostat, and thus the resulting cooling-curve appears as the exponential contraction.

Other than the disturbances mentioned, all nitration runs of methyl alcohol with a constant excess of nitric acid in initially dry nitromethane followed the zero-order kinetic form with satisfactory precision. Since the contents of the dilatometer did not provide sufficient material for a satisfactory product isolation, a larger scale run was conducted in a flask under the same conditions of nitration from which methyl nitrate was isolated and identified.

Fig. 3 Effects of added sulfuric acid, sodium perchlorate and potassium nitrate on the zero-order rate constants (k_o in moles $l.^{-1}$ $sec.^{-1}$) of nitration of methyl alcohol (initially 0.025 M) by nitric acid in nitromethane at 25°C.



The purpose of studying the reaction kinetics with added sulfuric acid, sodium perchlorate, and potassium nitrate was to confirm the previously expressed nitronium ion mechanism with respect to step I. It can be seen that the addition of strong acid will increase the concentration of nitric acidium ion and hence the rate of formation of nitronium ion will increase, which will be manifested by an increase in the zero-order rate constant. As can be seen in Fig. 3, this is indeed the case. The added sulfuric acid even in quite low concentration wholly takes the place of that nitric acid molecule in step I which acts as the proton donor. The accelerating effect of added sulfuric acid is at first small, but soon increases linearly with added acid. The system will act as a buffer at very low concentrations of added sulfuric acid, so that for the addition of a given quantity of strong acid, there will be

less than an equivalent amount of nitric acidium ion produced. As the added acid concentration increases, the buffering capacity of the system will be lost, and further addition of sulfuric acid will produce an equivalent increase in the concentration of nitric acidium ion, and thus a linear increase in the rate of formation of nitronium ion, which is seen as an increase of the zero-order rate constant.

The addition of sodium perchlorate causes an increase in the zero-order rate constant. This is the normal salt effect to be expected, for according to the nitronium ion mechanism, ions are being produced form neutral species in the kinetically significant part of the mechanism (Steps I and II), and an increase in ionic strength would facilitate the formation of these ions.

Added potassium nitrate causes a decrease in the zero-order rate constant. The added nitrate ion deprotonates the nitric acidium ion formed in step I, (the equilibrium of step I is shifted to the left) thus the stationary concentration of nitric acidium ion is decreased. This in turn causes a decrease in the rate of formation of nitronium ion, which is measured by the zero-order nitration rate.

Varying amounts of water were added to the nitrating medium in order to promote reversal of the dehydration of nitric acidium ion, so that step II of the scheme would be included in the pre-equilibrium part of the mechanism. Thus by adding a sufficient amount of water so that the rate of the reverse reaction of step II would be much greater than step III, the nitronium ion would be held in a steady state concentration and the rate of production of methyl nitrate would become dependent upon the concentration of methyl alcohol. The kinetic form thus would shift from zero- to first-order in methyl alcohol (i.e. when $k_{-2}[H_2O] \gg k_3[XH]$).

In adding increasingly greater quantities of water up to about the initial substrate concentration (0.025 M), no detectable effect on the rate of the zero-order nitration is observed compared to the reaction carried out in initially dry nitromethane. When water is added in greater quantities (0.1 M), then zero-order kinetics are preserved, but the rate of reaction is actually accelerated by the added water. This can be understood as a general medium effect of water acting as a polar co-solvent. Since charged species are being formed from neutral species in the kinetically significant part of the scheme (steps I and II), added water would be expected to accelerate the zero-order reaction by increasing the ionizing power of the medium.

When the water content is raised above 0.2 M, the reaction rate begins to fall and the reaction order simultaneously begins to rise from zero towards one, at first in the later part of the course of the reaction, but eventually throughout. By the time that the added water concentration has reached 0.882 M, the reaction is exactly first-order in methyl alcohol. Further increasing the water concentration causes a steady decrease in the rate, but the first-order kinetic form is unchanged.

Table 2 Zero- and first-order rate constants (k_0 in moles $l.^{-1}$ $sec.^{-1}$ and k_1 in $sec.^{-1}$) of nitration of methyl alcohol (0.025 M) by nitric acid (2.5 M) in nitromethane containing initially added water.

$[H_2O]$	10^5k_o	Order	$[H_2O]$	10^5k_o	Order	$[H_2O]$	10^4k_1	Order
0.0	1.65	0	0.249	~1.9	~0	0.779	~11.9	~1
0.068	1.88	0	0.392	~1.7	mixed	0.882	8.53	1
0.122	2.25	0	0.511	~1.6	mixed	1.00	4.22	1
0.188	2.07	0				1.13	1.92	1

O-Nitration of Other Mono- and Poly-hydric Alcohols p-Nitrobenzyl alcohol is readily nitrated in initially dry nitromethane solution. The aromatic nitro group serves to deactivate the aromatic ring toward nitration and also to reduce the tendency toward oxidation of the side chain. Strict zero-order kinetics are observed only for the first 90% of the total reaction, after which the volume-time graph undergoes some rounding as it runs into the horizontal branch representing complete reaction. This is probably due to the electron-withdrawing effect of the aromatic nitro group deactivating somewhat the alcoholic oxygen atom, causing the alcohol to be less reactive toward nitronium ion. The volume contraction is about the same as that accompanying the nitration of methyl alcohol. p-Nitrobenzyl nitrate was isolated from the reaction medium. Neopentyl alcohol is much less reactive than the previously mentioned alcohols. In initially dry nitromethane the reaction shows a strong departure from zero-order kinetics, and has an absolute rate much below that of the zero-order nitrations.

Table 3 Zero-order rate constants (k_o in moles $l.^{-1}$ $sec.^{-1}$) for the nitration of mono- and poly-hydric alcohols by 2.5 M nitric acid in nitromethane at 25°C.

	$[MeOH]$	$[C_2H_4(OH)_2]$	$[HO(CH_2)_3OH]$	$[C_3H_5(OH)_3]$
10^5k_o------	1.69	0.83	0.84	0.88

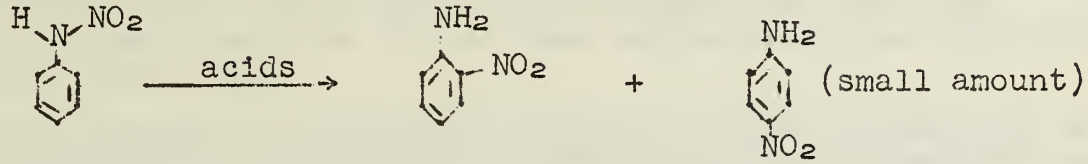
The nitrations of ethylene glycol and trimethylene glycol in initially dry nitromethane with nitric acid in constant excess follow zero-order kinetics leading to the formation of the corresponding dinitrates. The zero-order rate constants are one-half that applying to the nitration of methyl alcohol. For the glycols twice as much nitronium ion must be formed, compared to methanol, for complete nitration to occur. Thus the zero-order rate constants for the glycols would be expected to be one-half that for methyl alcohol.

The O-nitration of glycerol passes through two kinetically well separated phases, a zero-order succeeded by a first-order course. The reaction proceeds to about two thirds completion at a rate almost equal to the rate of nitration of the glycols after which the reaction is completed at a much diminished rate showing first-order kinetics. This is interpreted as being due to the uptake of two nitronium ions by the primary alcoholic groups of glycerol as fast as the nitronium ion is formed. The relatively unreactive secondary alcoholic group of propan-2-ol-1,3-dinitrate is then a less successful competitor with water for the nitronium ion formed. This compound reacts only slowly with the steady state concentration of nitronium ion, giving first-order reaction kinetics.

N-, C-Nitro Rearrangement

An interesting aspect about the N-nitration of certain aromatic amines is the fact that the N-nitro group can undergo rearrangement into the aromatic ring. Bamberger found that phenylnitroamine, phenylmethylnitroamine, and similar arylnitroamines undergo rearrangement upon treatment with aqueous strong acids or with hydrogen chloride in organic solvents to yield mainly o-nitroaniline or its

derivatives, sometimes accompanied by a small amount of the p-nitro-derivative also.[16-18]



Having found that the treatment of primary and secondary amines with the neutral nitrating agent, nitrogen pentoxide, often leads to N-nitration, it was suggested that the aromatic C-nitration of these amines by strongly acidic nitrating agents consists of an N-nitration followed by an acid catalyzed intramolecular rearrangement of the N-nitro to the C-nitro compound.[19,20] The intramolecularity of the rearrangement, however, was an assumption, at that time, not necessitated by the facts.

The hypothesis of indirect aromatic nitration was tested by measuring the proportions of o-, m- and p- isomers obtained by the nitration of aniline and by the action of acid upon phenylnitroamine.[21,22] When both reactions were carried out under the same reaction conditions, a completely different isomer distribution was obtained in each case, thus leaving no doubt that the C-nitration and the rearrangement are entirely different processes and proceed by different paths.

Table 4 Proportions of nitro compounds formed by nitration of aniline and by rearrangement of phenylnitroamine.

Process	o-%	m-%	p-%
Nitration------$PhNH_3NO_3$, 85% aq.H_2SO_4, 10°C	6	34	59
Rearrangement--$PhNH{\cdot}NO_2$, 85% aq.H_2SO_4, 10°C	93	0	7

Orton attempted to test the possibility that the isomerization of the nitroamine might be an intermolecular rearrangement.[23] In some cases nitroamines in acid solution could be observed to nitrate a foreign aromatic compound, thus proving that a nitrating agent was present in those conditions. With other nitroamines, however, the nitration of a foreign aromatic compound could not be observed.

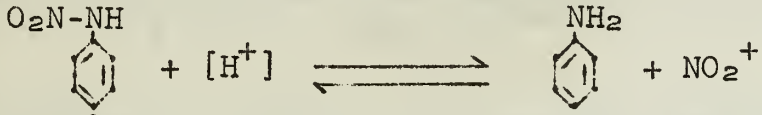
Hughes and Jones have further examined the rearrangement.[22] p-Nitrophenyl-N-methylnitroamine underwent rearrangement in the presence of acids ranging from formic acid to sulfuric acid, and in a number of solvents including water, ethyl alcohol, acetic acid and ethyl ether to give N-methyl- 2,4-dinitroaniline. It was found that under no condition could any denitration of the nitroamine be detected, either by the formation of p-nitro-N-methylaniline in the presence of an easily nitrated foreign substance (p-xylene or phenol), or by the actual nitration of the added substance. When the rearrangement of N-methyl-N,2,4-trinitroaniline into N-methyl- 2,4,6-trinitroaniline in either 80% aqueous sulfuric acid or in pure sulfuric acid was examined, it was found that the nitroamine readily underwent denitration. This was shown by the isolation of the denitration product N-methyl-2,4-dinitroaniline in the presence of easily nitratable substances (p-xylene, phenol, or dimethylaniline) and also by the isolation of nitration products of the added materials. However, it was found that nitric acid added in an equivalent amount was unable to nitrate the denitration product, N-methyl- 2,4-dinitroaniline to the rearranged product, N-methyl- 2,4,6-trinitroaniline under the conditions in which the rearrangement itself readily took place. Thus the rearrangement cannot be occuring by acidolysis of

the N-nitro group with a subsequent C-nitration by nitronium ion from the medium. For even though the nitration of foreign aromatic compounds can be observed, nitric acid is unable to C-nitrate N-methyl- 2,4-dinitroaniline in the same medium where the rearrangement readily takes place.

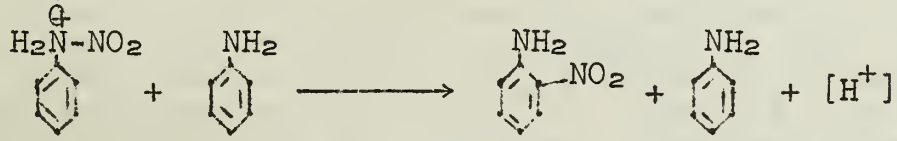
The rearrangement of phenylnitroamine has been carried out in 74% aqueous sulfuric acid containing N^{15} labeled nitric acid.[24] No label was found in the nitration products, o- and p-nitroaniline. Thus in this case, the C-nitro compounds derive their aromatic nitro group directly from the N-nitro group of phenylnitroamine, without any exchange with the nitric acid in solution.

A chain mechanism may be written for the rearrangement as follows

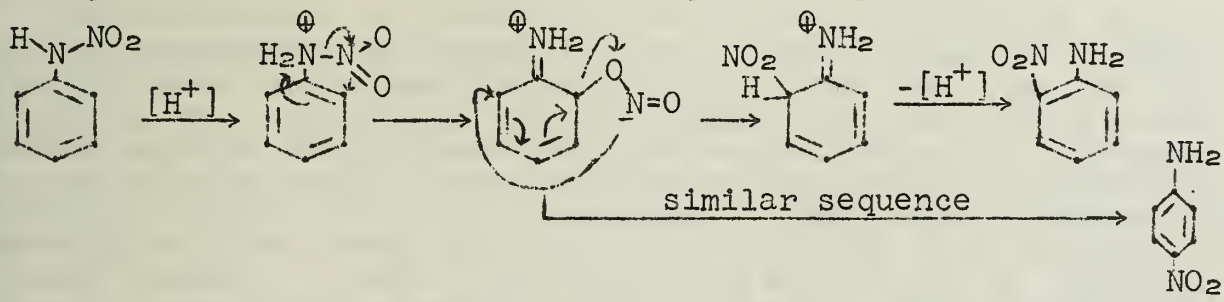
(Initiation)



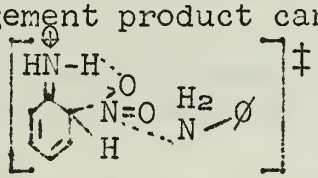
(Propagation)



Various intramolecular mechanisms can be written for the rearrangement,[25] of which the following is one possibility:



The chain mechanism has the advantage that the preferential ortho orientation of the rearrangement product can be explained by a hydrogen bonded transition state,



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However, ortho orientation in the intramolecular mechanism may be rationalized as being due to an interaction of the positively charged immonium nitrogen atom with the terminal oxygen atom of the group undergoing rearrangement.

The fact that p-nitrophenyl-N-methylnitroamine did not nitrate phenol is evidence against the chain mechanism, for hydrogen bonding would be expected to stabilize the transition state of this highly reactive aromatic compound also. The fact that no labeled nitrogen is incorporated into the aromatic nucleus when phenylnitroamine is rearranged in the presence of N^{15} labeled nitric acid also casts doubt upon the chain mechanism. It would seem likely that at least a small percentage of the free aniline formed in low steady state concentration would be either N- or C-nitrated by nitronium ion from the medium.

It is not possible at present, however, to decide which of the two mechanisms is correct. It can be seen that the rate expression

for the chain mechanism is second-order in nitroamine while the intramolecular rearrangement is first-order in nitroamine. If the rate law were determined experimentally, a decision could be made between these two mechanisms.

Whether N- or C-nitration of a given aromatic amine will occur depends upon the nature of the aromatic amine involved and the nitrating medium employed. In an acidic medium C-nitration will take precedence over N-nitration if the aromatic nucleus employed is reasonably reactive. N-nitration occurs preferentially with non-acidic nitrating agents such as N_2O_5 or in acidic media if the aromatic nucleus in highly unreactive. With strongly acidic conditions aromatic amines are nitrated, presumably through their conjugate acid, by nitric acid to give the m-nitro derivative. At lower acidities nitration through the free base ensues to yield predominantly the o- and p- nitro compounds.[26]

N-Nitration

The N-nitrations of guanidine and N-methyl-guanidine by nitric acid in 71-82% sulfuric acid solutions were shown to be first-order in amine and the first order in nitric acid, and also to closely follow the acidity function C_0 but not H_0.[27,28] This has been taken as evidence for the existence of the nitronium ion mechanism in these nitrations.

The N-nitration of N-methyl- 2,4,6-trinitroaniline by nitric acid in nitromethane was studied by the kinetic method.[2,15] This secondary amine was chosen for study due to the fact that the aromatic ring was incapable of being nitrated, nor could the N-nitro compound undergo rearrangement to the C-nitro compound. Moreover, this amine is so weakly basic that heavy protonation in nitration conditions seemed likely to be avoidable. Zero-order kinetics were observed, and the average value for the zero-order rate constant was $2.89 \cdot 10^{-5}$ moles $l.^{-1}$ $sec.^{-1}$ in 3 M nitric acid at 25° C. After a number of runs, the contents of the dilatometer were examined and a high yield of N-methyl-N,2,4,6-tetranitroaniline was isolated.

Table 5 Zero-order rate constants (k_0 in moles $l.^{-1}$ $sec.^{-1}$) for nitration of N-methyl- 2,4,6-trinitroaniline and of toluene (initially about 0.1 M) by nitric acid in nitromethane at 25°C.

$[HNO_3]$	2.0	2.5	3.0	3.5	4.0	4.5
$10^5 k_0$(amine)	0.675	1.41	2.89	6.04	9.64	14.9
$10^5 k_0$(toluene)	0.688	1.69	3.34	6.80*	12.7	----

*Value for ethylbenzene

The rate of nitration of N-methyl- 2,4,6-trinitroaniline increases steeply with increasing concentration of nitric acid. In 2 M-nitric acid the absolute nitration rates of the secondary amine and of toluene are nearly identical. At higher nitric acid concentrations the rate for nitration of the amine drops behind the rate for the benzenoid hydrocarbons. A reasonable explanation for this phenomenon is that the fractional amount of amine in the protonated form increases as the nitric acid concentration increases. Thus the basicity of the amine is enough to reduce the equilibrium concentration of nitric acidium ion at a given nitric acid concentration relative to that of the hydrocarbon solution. Since the rate of formation of nitronium ion, as measured by the zero-order rate constant, is proportional to the concentration of nitric acidium ion, this would explain the greater difference in rates as nitric acid

concentration is increased.

The addition of sulfuric acid, sodium perchlorate, sodium nitrate, and water to the nitromethane solution of nitric acid and N-methyl-2,4,6-trinitroaniline produced the same effects as were observed in the experiments on O-nitration. These results have in a like manner been interpreted as verification of the nitronium ion mechanism in N-nitration.

Measurements have also been made on the zero-order N-nitrations of N-ethyl, N-propyl, and N-n-butyltrinitroaniline by 3 M nitric acid in nitromethane at 25°C. The results obtained were similar to those described above. Measurements have also been made on the N-nitration under similar conditions of N-iso-propyl- 2,4,6-trinitroaniline. In this case a mixed kinetic order in amine is obtained. Also, the reaction rate, as approximated by a zero-order plot, is only about 0.6 as large as the nearly common rate applying to the other N-alkyl analogues. This decreased reactivity is probably due to the steric shielding of the electron pair on nitrogen due to the isopropyl group.

****

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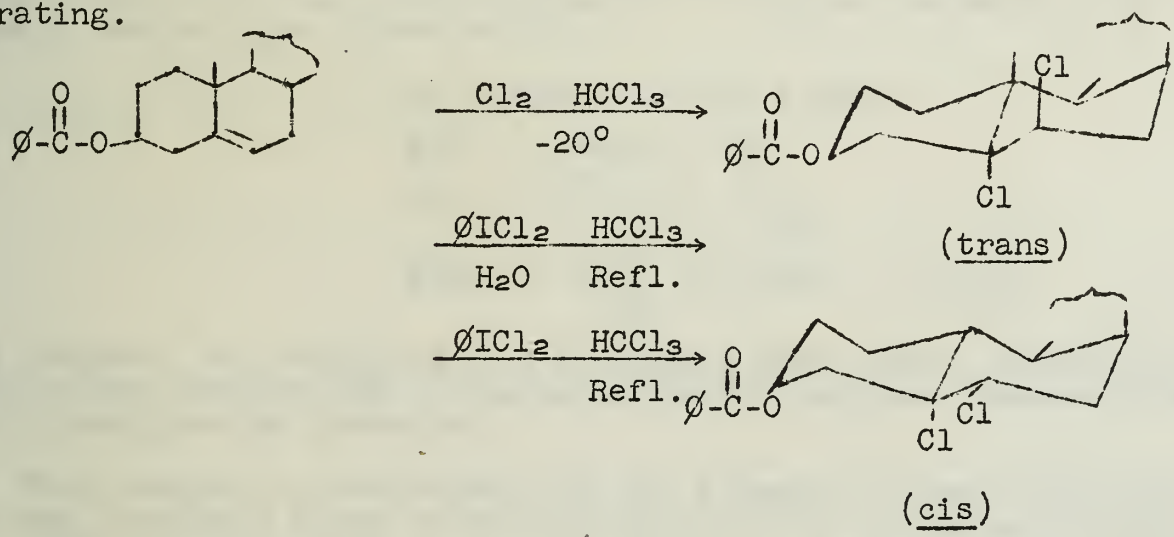
DISSOCIATION OF IODOBENZENE DICHLORIDES

Reported by J. J. Looker February 29, 1960

INTRODUCTION

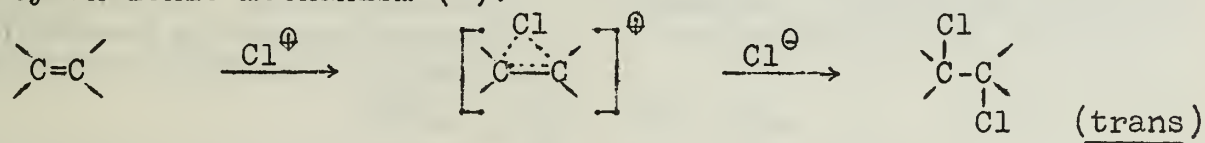
The reaction of iodobenzene dichloride with olefins has been shown to yield the same addition compound as the reaction of chlorine itself (1). Benzalacetophenone, stilbene, and cyclohexene react to give the same products with either reagent. This suggests that iodobenzene dichloride dissociates into molecular chlorine and iodobenzene, and that molecular chlorine is the chlorinating species in both cases.

The stereochemistry of the products from certain olefins indicates that the chlorinating species may not be the same. The reaction of cholesteryl benzoate with chlorine was found to give an isomer of the product formed when iodobenzene dichloride was used (2). It was shown by Barton and Miller that chlorine gave the trans product (5α, 6β), while the dichloride gave the cis product (5α, 6α) (3). If a trace of water was present in the latter reaction, the trans product was obtained. This might indicate that two mechanisms are operating.

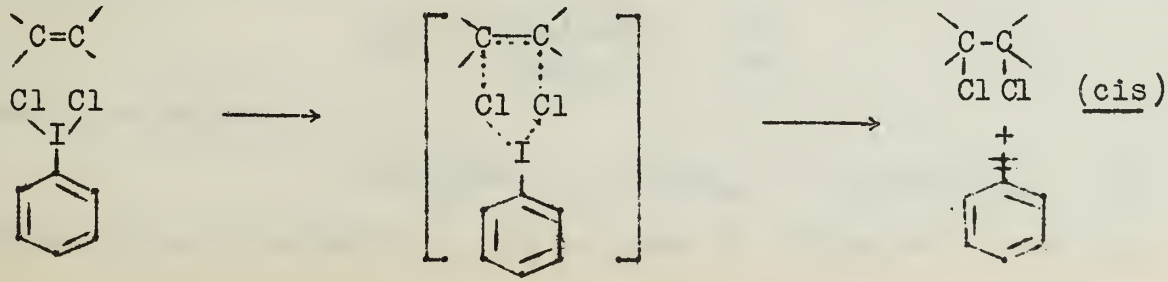


An alternative explanation is that the cis product is unstable when water is present in the reaction mixture and rearranges to the trans isomer. This possibility was not investigated.

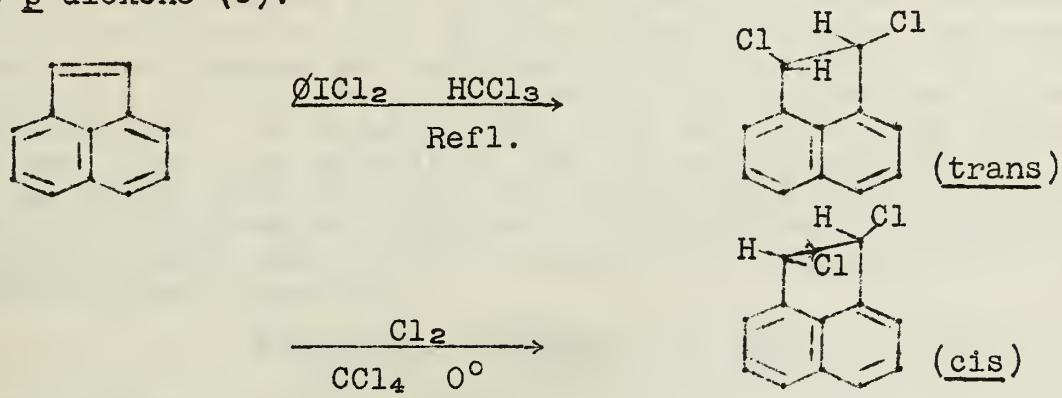
These observations were explained by assuming that chlorine added by an ionic mechanism (4).



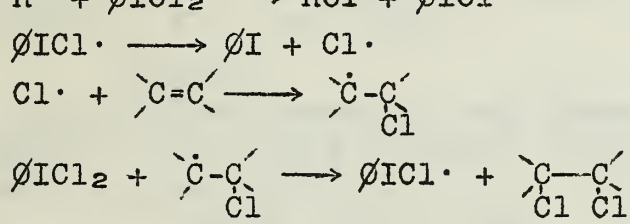
The cis product can be explained by a molecular mechanism.



It was found that addition of chlorine to acenaphthene gave the trans product when iodobenzene dichloride was the species providing chlorine, and that the cis product was obtained with free chlorine (5). The same result was found by Summerbell and Lunk when chlorine was added to p-dioxene (6).



Still another unexpected product was observed by Bloomfield in the case of rubber (7). The product with free chlorine was the substitution product, and that from iodobenzene dichloride in carbon tetrachloride was the addition product. A radical mechanism was proposed to explain the latter result.



This proposal was supported by the finding that quinol retarded the reaction and yielded 27% of the substitution product. However, there was no catalysis by peroxide.

This seminar is concerned with the attempts to test the above theories through a study of the dissociation of iodobenzene dichloride. This investigation involved studying the rates of dissociation and formation of various dichlorides in polar and non-polar solvents.

POLAR SOLVENTS

The strong absorption of the dichloride in the ultra-violet region (230-280 mμ) allows the rate of formation or dissociation of it to be followed spectrophotometrically. The expected rate law for dissociation according to equation 1

$$\text{ØICl}_2 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{ØI} + \text{Cl}_2 \qquad (1)$$

$$K_{eq} = \frac{(\text{ØI})(\text{Cl}_2)}{(\text{ØICl}_2)} = \frac{k_1}{k_2} \qquad (2)$$

is given by equation 3.

$$-\frac{d(\text{ØICl}_2)}{dt} = k_1\,(\text{ØICl}_2) - k_2(\text{ØI})(\text{Cl}_2) \qquad (3)$$

Integrated forms of equation 3 can be used to determine k_1 and k_2

graphically (8).

Investigation of the formation and dissociation of iodobenzene dichloride in acetic acid showed that the dichloride equilibrates with its components at a measurable rate (See table I)(9). Values of k_1 and K_{eq} are in fair agreement for equilibration from either direction. When a substance known to be very reactive toward chlorine like pentamethylbenzene or cyclohexene was included in the experiment, the rate of chlorination was found to be independent of hydrocarbon and iodobenzene concentrations. It depended only upon the dichloride concentration. Values of k_1 were calculated for dissociation of the dichloride in the presence of the reactive hydrocarbons mentioned above, assuming the rate law given by equation 4. This value of k_1 is in agreement with k_1 values calculated from Data for equilibration of the dichloride from either direction.

$$\frac{d(Ar\text{-}Cl)}{dt} = -\frac{d(\emptyset ICl_2)}{dt} = k_1(\emptyset ICl_2) \qquad (4)$$

The mechanism proposed for this reaction is the following:

$$\emptyset ICl_2 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \emptyset I + Cl_2 \qquad (5)$$

$$ArH + Cl_2 \xrightarrow{k_3} ArCl + HCl \qquad (6)$$

Here $k_3(ArH) \gg k_2(\emptyset I)$, and the dissociation of the dichloride is the rate determining step. The activation energies for dissociation and chlorination were found to be 20 kcal. per mole.

Table I

Rate Constants, Equilibrium Constants, and Thermodynamic Constants for Reactions in Acetic Acid.

	25°		45°			
	$10^3 k_1$ sec^{-1}	$10^3 K_{eq}$	$10^3 k_1$ sec^{-1}	$10^3 K_{eq}$	ΔH^o kcal/mole	Eq kcal/mole
Formation	0.16	2.0				
Dissociation	0.15	1.5	1.3	4.3	9.9	20.1
Chlorination	0.20		2.2			20.2

A Hammett plot was made for k_1 and k_2 in both acetic acid and nitromethane. Values of k_1 in acetic acid are insensitive to ring substituents (10). The formation reaction in acetic acid (k_2) has a negative value of rho, although the fit was not good enough to calculate the value. Similar data for dissociation and formation in nitromethane show the reverse (11). Here k_1 has rho greater than zero. The values of k_2 are independent of the ring substituent. The significance of the data obtained in nitromethane is obscured by the inconsistancy of the results from several runs. There are also only three points on the graph, due to the insolubility of the dichlorides in this solvent.

The thermodynamic constants for the dissociation of various dichlorides in acetic acid are summarized in table II (10). The large negative entropies of activation are particularly noteworthy. They can be explained by assuming that molecules of solvent are included in the activated complex. This suggests that a polar solvent might be helpful for the formation of the activated complex. The large de-

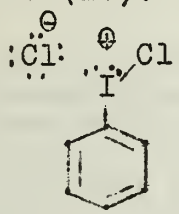
Table II

Thermodynamic Constants for Dissociation of Dichlorides in Acetic Aci

Dichloride	ΔH_d^o kcal $m.^{-1}$	ΔS_d^o eu	E_1 kcal $m.^{-1}$	$-\Delta S_1^{\ddagger}$ eu	$-\Delta S_2^{\ddagger}$ eu
Unsubstituted	9.9	20.4	20.2	10.4	30.8
p-COOH	9.8	24.4	18.3	16.8	41.2
p- 	9.0	17.7	18.6	14.8	32.5
m-Cl	7.6	16.9	19.4	13.1	30.1

crease in entropy was also observed for dissociation in nitromethane (11). Another possible explanation is that the I-Cl bond vibrations are being hindered in the activated complex.

From these observations and a knowledge of the structure of the dichloride, a transition state was proposed for this equilibration process. The geometry of the iodobenzene dichloride molecule is known from X-ray studies (12). The ICl_2 group is perpendicular to the plane of the benzene ring. It is also known that the dichloride is more polar than iodobenzene (dipole moment: 2.61D vs 1.3D)(13). Since polar solvents aid formation and dissociation, and since the entropies of activation for dissociation and formation in acetic acid are large negative values (see below), the transition state probably is more polar than either the dichloride or iodobenzene. The activated complex may be pictured as follows (10):



It is assumed that the complex is solvated, and that the chlorine atoms are close enough together to form a chlorine molecule when the complex collapses.

Rate constants and thermodynamic constants for the same reaction in acetic acid and nitromethane are summarized in table III (11).

Table III

Rate and Thermodynamic Constants for Equilibration in Nitromethane and Acetic Acid

	Dichloride	$10^5 k_1$ sec^{-1}	$10^2 k_2$ $m^{-1}l^{-1}sec^{-1}$	E_1^a kcal/mole	$\Delta S_1^{\ddagger}$ eu	E_2^a kcal/mole	$\Delta S_2^{\ddagger}$ eu
Acetic Acid	Unsubstituted	17	9	19.6	-12	12.6	-23
	m-Cl	15	1.0	19.4	-13	11.8	-30
Nitromethane	Unsubstituted	1.8	4.4	12.5	-40	2.7	-57
	m-Cl	7.6	2.1				

The rate of dissociation in the less polar acetic acid is slightly greater than the rate in the more polar nitromethane. It would be expected that the rate of dissociation would increase as the polarity of the solvent increased, if the activated complex were more polar than the reactants (14). The activation energy for dissociation in

nitromethane is 7-10 kcal. per mole less than that in acetic acid. The failure of this lowering of the activation energy due to the increased polarity of nitromethane to appear in the rate constant is due to the large negative entropy change associated with the solvation of the activated complex in nitromethane.

NON-POLAR SOLVENTS

In contrast to polar solvents, the formation and dissociation of the dichloride in dry, non-polar solvents like carbon tetrachloride does not take place (15). The activation energy for dissociation in non-polar solvents is probably large. A trace of a polar catalyst like iodine monochloride or water and hydrogen chloride is necessary for the reaction to take place. The reaction proceeds at a measurable rate when catalyst is present. The reaction is second order with respect to the catalyst when iodine monochloride is used. The activated complex must involve two molecules of the catalyst, or a dimer, which provides the necessary polar environment supplied by the solvent in the case of polar solvents.

These facts are in agreement with the previous findings that addition of chlorine by means of iodobenzene dichloride in chloroform or carbon tetrachloride does not involve dissociation into free chlorine unless a trace of water is present. The nature of the chlorine providing species in the case of non-polar solvents was not investigated.

It was found that iodine monochloride, water, and hydrogen chloride would catalyze the dissociation of iodobenzene dichloride in polar solvents as well as non-polar solvents(11). The effect of iodine monochloride was investigated in both acetic acid and nitromethane. The reaction was first order with respect to ICI in both solvents. It is a better catalyst in nitromethane than in acetic acid. Experimental difficulties prevented calculation of the energy of activation in nitromethane. The catalyzed reaction rate constant was 26.1 $mole^{-1}$ $l.sec.^{-1}$ in nitromethane and 0.95 $mole^{-1}$ $l.sec.^{-1}$ in acetic acid. The entropy of activation for the catalyzed reaction (-29eu) in acetic acid agrees with that for the uncatalyzed reaction (-23 ± 5e.u.) within limits of experimental error. The activation energy is lowered by 10 kcal. per mole in acetic acid for the catalyzed reaction. The energy of activation for the catalyzed reaction was 9.3 kcal per mole. It is known that acetic acid interacts with iodine monochloride, but that the polar, non-hydroxylic nitromethane does not (16). Thus the catalyst would be relatively free to act in nitromethane, but not in acetic acid.

Equilibrium constants for dissociation of the dichloride in the three solvents studied are 4, 20, and 200 x 10^{-4} for nitromethane, acetic acid, and carbon tetrachloride respectively. The degree of dissociation increases as the solvent becomes less polar. Thus the products are less polar than the dichloride. Positive values of rho were obtained for Hammett plots made with K_{eq} measured in acetic acid and nitromethane. Rho for acetic acid, although the plot was not good, was + 1.8, and rho for nitromethane was + 2.4 (11). The degree of dissociation thus increases as the substituent becomes more electron withdrawing.

ORTHO EFFECT

There are two observations which suggest that a group ortho to

the reaction site might sterically affect the reaction. The first is that some dichlorides with ortho substituents have not been obtainable by the usual procedure (17). The 2,5-dichloro-3,4,6-trimethyl- and 2,3,4,6-tetrachloroiodobenzene dichlorides are two examples. The dichloride of pentamethyliodobenzene can be prepared, but decomposes on standing (10). The second observation is that the transition state for formation and dissociation is probably highly solvated in polar solvents (11)(10). If effective solvation is necessary to lower the activation energy, then groups close to the reaction site might be effective solvation inhibitors, and thus cause a decrease in the rate constant.

The presence of an ortho effect should appear in the equilibrium constants for various hindered and unhindered compounds. Values which can be compared are listed in Table IV. It would be expected that large differences should exist between the constants for the two isomers if steric factors were operative (18). Measurement of K_{eq} for several isomers showed that no large differences exist (19). It can be concluded that the ICl_2 group does not have to be coplanar with the phenyl ring for maximum stability of the dichloride.

The values of the rate constants (k_1) for dissociation of the dichlorides are also similar for hindered and unhindered cases (19). (See table IV). These values are all between 1 and 4×10^{-4} sec.$^{-1}$ Thus, solvation is not hindered by neighboring groups although it is essential for dissociation. There are cases of ortho group participation which are considered below.

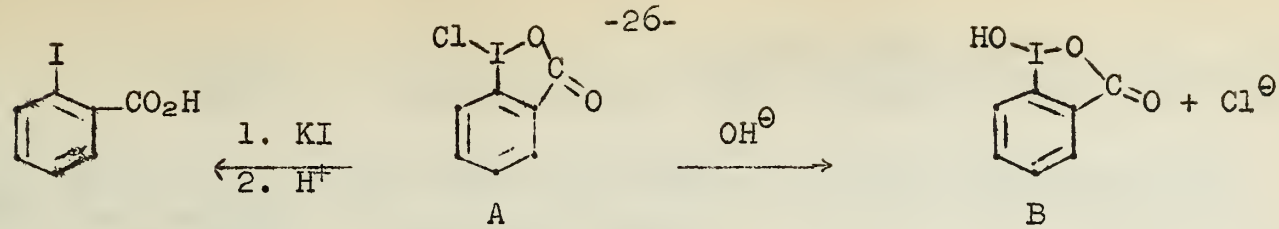
Table IV

EQUILIBRIUM AND DISSOCIATION CONSTANTS FOR ORTHO AND PARA SUBSTITUTED DICHLORIDES IN ACETIC ACID AT 25°

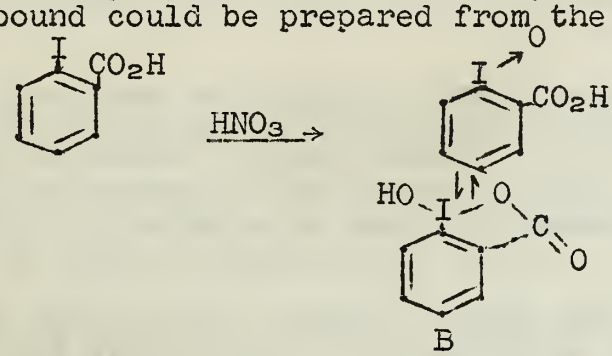
Hindered dichlorides	$10^3 K_{eq}$	$10^4 k_1$ sec^{-1}	Unhindered dichlorides	$10^3 K_{eq}$	$10^4 k_1$ sec^{-1}
O-Iodo Toluene	1.09	2.53	p-Iodo Toluene	0.75	2.65
2-Iodo-1,3-Dimethyl Benzene	0.7	1.15	2-Iodo-1,4-Dimethyl Benzene	0.79	1.72
1-Iodonaphthalene	2.83	3.86	2-Iodonaphtalene	2.29	2.24
O-Iodo biphenyl	1.11	1.61	p-Iodo-biphenyl	0.30	2.35
O-chloro-iodobenzene	23	1.9	m chloro-iodobenzene	13.2	1.48

THE ORTHO CARBOXYL GROUP

Attempts to prepare ortho-carboxyliodobenzene dichloride for this study yielded a solid which rapidly decomposed to hydrogen chloride and a yellow powder designated A (22). Dissociation took place in air or in polar solvents. Since this compound was soluble in dilute aqueous potassium iodide, and had the molecular formula $C_7H_4O_2ClI$, it was given the lactone structure below.

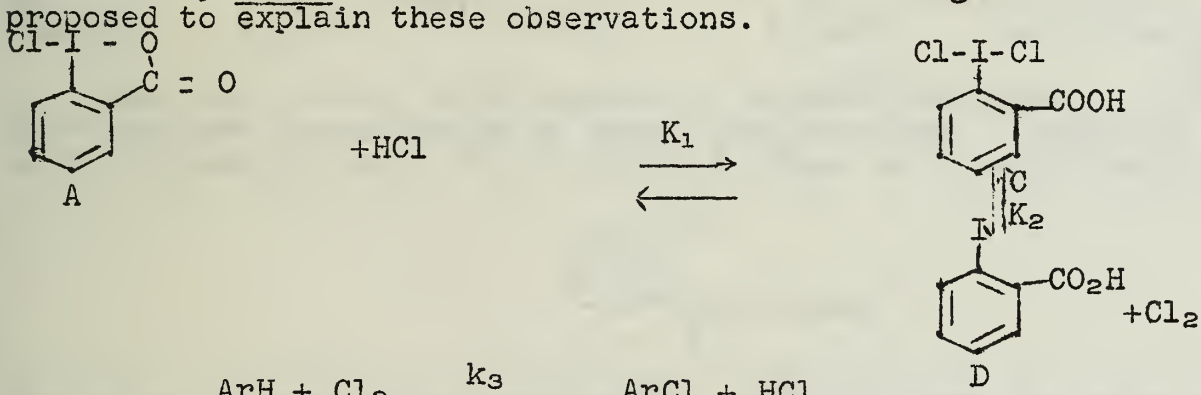


Acidification of the aqueous potassium iodide solution of A gave ortho-iodobenzoic acid. Acidification of a basic solution of A yielded a white solid which was assigned structure B. The decomposition of the dichloride of ortho iodobenzoic acid to compound A and the conversion to B had been investigated previously (20). The structure of B was proposed from its analysis and from the fact that the same compound could be prepared from the iodo acid with nitric acid (21).



This compound was not investigated further.

Compound A was found to be an effective chlorinating agent for aromatic hydrocarbons (22). The products are O-Iodobenzoic acid and the monohalo aromatic compound. A qualitative investigation of this reaction in acetic acid showed that it was first order in hydrocarbon, compound A, and in hydrogen chloride. The reaction was retarded by ortho-iodobenzoic acid. The following mechanism was proposed to explain these observations.



$$ArH + Cl_2 \xrightarrow{k_3} ArCl + HCl$$

The rate law for this mechanism is

$$\frac{d(ArCl)}{dt} = \frac{k_3 k_1 k_2 \ (A) \ (HCl) \ (ArH)}{(D)}$$

By use of k_1 and k_2 and the following relations, an expression can be derived which relates the chlorine concentration to initial concentrations of starting materials and k_1 and k_2.

$$(HCl)_i = (C) + (Cl_2) + (HCl)$$

$$(A)_i = (A) + (C) + (Cl_2) + (ArCl)$$

$$(D) = (D)_i + (Cl_2) + (ArCl)$$

The subscript i refers to initial concentrations. Substitution of this expression into the above rate law gives the following:

$$\frac{d(ArCl)}{dt} = \frac{k_3K_1K_2(A)(HCl)_i(ArH)}{[1+K_1\{(A)+(HCl)-(Cl_2)\}](D)+K_1K_2[(HCl)_i+(A)-(Cl_2)]}$$

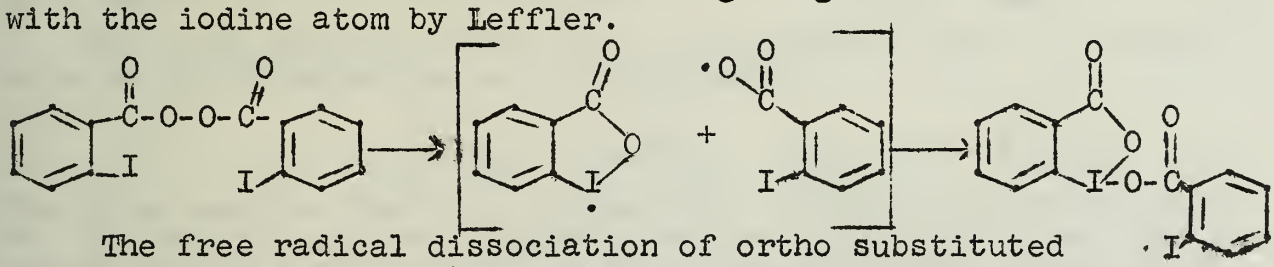
If $[Cl_2]$ and $[HCl]$ are neglected because of their smallness, the rate law becomes

$$\frac{d(ArCl)}{dt} = \frac{k'(A)(HCl)_i(ArH)}{(D)[1 + K_1(A)] + K_1K_2[(HCl)_i + (A)]}$$

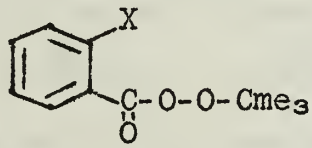
where $k' = k_3K_1K_2$. Assuming $(D)=(D)_i + (ArCl)$, all quantities necessary to calculate k' can be measured. Values of k' were found to be constant for various concentrations of starting materials. Thus, it can be concluded that the proposed mechanism explains these data.

The dissociation constant (k_1) for the dichloride of ortho iodobenzoic acid in acetic acid is too large to measure. The meta and para isomers have normal values (about 2×10^{-4} sec^{-1}). Since this same behavior is observed for the dichloride of the methyl ester of this acid, the large rate constant cannot be explained by any participation of the carboxyl proton (22).

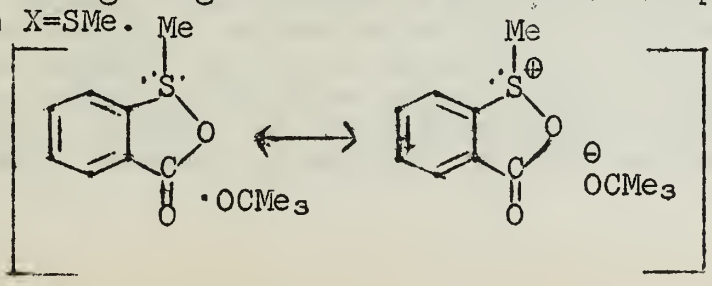
Participation by an ortho carboxyl group has been observed in other reactions. The free radical decomposition of bis-(O-iodobenzoyl)-peroxide was found to be on the order of 10^3 times faster than for benzoyl peroxides with other ortho substituents (23)(24). This effect was attributed to the large magnetic field associated with the iodine atom by Leffler.



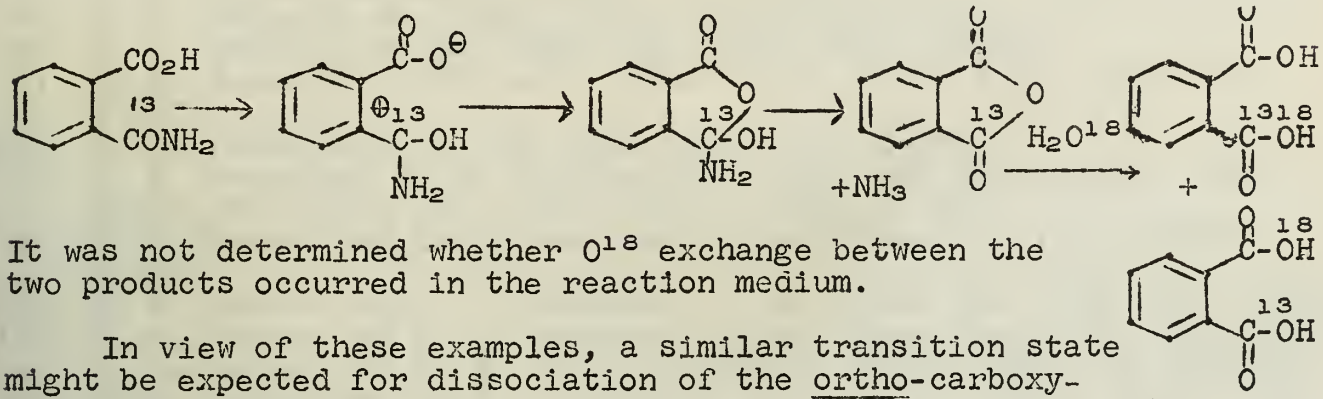
The free radical dissociation of ortho substituted peroxides was investigated by Martin and Bentrude. Compounds of the following type, where X=SMe, H, CMe_3, or I were studied (25).



The rate of dissociation when X=SMe was 2×10^4 times the rate when X=H. Since the rate for X=CMe_3 was equal to the rate for X=H, there was probably no steric factor. The iodine atom would be expected to be a better participating group than the sulfur atom if magnetic factors were important since iodine possesses a larger nuclear magnetic moment. The rate when X=I was only 20 times the rate when X=H. The following singlet transition state was proposed for this reaction when X=SMe.

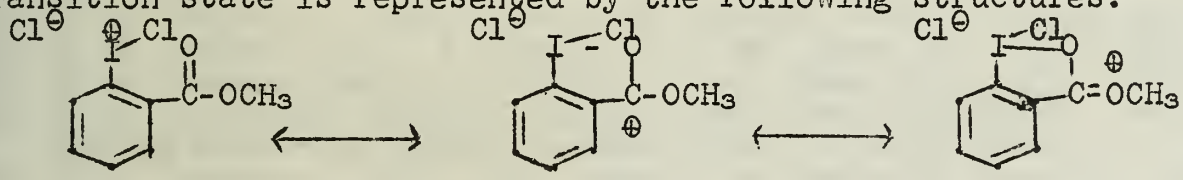


A thiro example is afforded by the hydrolysis of phthalamic acid (26). Hydrolysis of the amide takes place 10^5 times as fast as benzamide at the same pH. The reaction is dependent upon the concentration of undissociated phthalamic acid and independent of pH from pH 1 to 5. Hydrolysis of the acid labeled with C^{13} in the carboxamide group with H_2O^{18} showed O^{18} in both carboxyl groups of the product. The following mechanism was proposed to explain these results:



It was not determined whether O^{18} exchange between the two products occurred in the reaction medium.

In view of these examples, a similar transition state might be expected for dissociation of the ortho-carboxyiodobenzene dichloride and its methyl ester. The stabilized transition state is represented by the following structures.



The following groups in the ortho position were also found to cause rapid dissociation of the dichloride.

$$-NH-\overset{O}{\overset{\|}{C}}-CH_3 \qquad -NH-\overset{O}{\overset{\|}{C}}-\phi \qquad -CH_2-OH \qquad -\overset{O}{\overset{\|}{C}}-NH-\phi$$

The rates were too fast to be measured. Estimated rate constants for the ortho substituted dichlorides were 60 to 100 times the constants for the meta or para isomer. The activating effect of these groups can be explained in the same manner as for the carboxyl group. Three other ortho groups which were expected to show activating effects gave normal dissociation rates. These were the following:

$$-\overset{O}{\overset{\|}{C}}-Cl \qquad -O-\overset{O}{\overset{\|}{C}}-CH_3 \qquad -O-\overset{O}{\overset{\|}{C}}-\phi$$

There is no geometrical reason why these groups should not be able to stabilize the transition state in the same manner as the other groups.

Two possible partial explanations for this unexpected behavior were offered. First, the hydrogen bound to nitrogen might be involved in the stabilization of the activated complex. Perhaps hydrogen bonding to the chlorine atom helps to stabilize the transition state. Second, the strongly electron withdrawing group attached to the carbonyl carbon atom could effectively reduce the ability of the carbonyl group to participate in the charge delocalization. This effect would also appear with the ortho methyl ester, but it does not. Neither of the explanations is very convincing; there is probably another underlying factor responsible for the difference.

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MECHANISMS OF THE CHROMIC ACID OXIDATIONS OF SECONDARY ALCOHOLS AND ALDEHYDES

Reported by G. W. Burton March 3, 1960

Chromic acid is a very useful reagent for the oxidation of organic compounds. It can be used under a variety of conditions for oxidizing such substances as alcohols, aldehydes, hydrocarbons, olefins, and ethers. The present seminar will be concerned with the mechanisms of chromic acid oxidations of secondary alcohols and aldehydes.

Kinetics of the Oxidation of Secondary Alcohols

Westheimer and Novick investigated the kinetics of the oxidation in aqueous solution of isopropyl alcohol to acetone (1). The reaction was found to go essentially to completion. The observed rate law is:

$$-\frac{d(Cr(VI))}{dt} = k_4(CH_3CHOHCH_3)(HCrO_4^{\ominus})(H^{\oplus})^2$$

In very dilute acid, a term first order in acid becomes appreciable. When 2-deutero-2-propanol was oxidized, an isotope effect, k_H/k_D, of approximately six was observed (2). Manganous ions in large concentration reduced the rate by one half, and one mole of manganese dioxide was formed for every two moles of isopropyl alcohol oxidized (3,4).

Proposed Mechanisms

From the above data Westheimer (3) has defined several mechanisms which fulfill the conditions imposed by the kinetics. One such mechanism is:

$$HCrO_4^{\ominus} + CH_3CHOHCH_3 \longrightarrow Cr(IV) + CH_3COCH_3 \qquad (1)$$

$$Cr(IV) + CH_3CHOHCH_3 \longrightarrow Cr(II) + CH_3COCH_3 \qquad (2)$$

$$Cr(II) + Cr(VI) \longrightarrow Cr(III) + Cr(V) \qquad (3)$$

$$Cr(V) + CH_3CHOHCH_3 \longrightarrow Cr(III) + CH_3COCH_3 \qquad (4)$$

In the presence of manganous ion the following reactions occur:

$$Cr(IV) + Mn^{++} \longrightarrow Cr(III) + Mn^{+++} \qquad (5)$$

$$2Mn^{+++} + 2H_2O \longrightarrow MnO_2 + Mn^{++} + 4H^{\oplus} \qquad (6)$$

These equations fulfill the conditions that in the presence of manganous ions, one manganese dioxide molecule is oxidized for every two molecules of alcohol oxidized, and excess manganous ion depresses the rate by one half since it competes with the alcohol for the intermediate chromium species. There are also several other ways that the transitory species could react to obtain the proper kinetics and stoichiometry. However the first stage of the mechanism always involves equation 1, which includes the rate-determining step.

Mechanisms proposed for the first stage of the reaction are:

a. $H_3CrO_4^{\oplus} + CH_3CHOHCH_3 \longrightarrow H_4CrO_4 + CH_3\overset{\oplus HO}{\overset{\|}{C}}CH_3$

$$\text{b.}\quad HCrO_4^{\ominus} + 2H^{\oplus} + CH_3CHOHCH_3 \xrightleftharpoons{\text{fast}} (CH_3)_2CHOCrO_3H_2^{\oplus} + H_2O$$

$$(CH_3)_2CHOCrO_3H_2^{\oplus} + H_2O \xrightarrow{\text{slow}} CH_3COCH_3 + H_2CrO_3 + H_3O^{\oplus}$$

Mechanism a. involves a hydride ion transfer in the rate-determining step, while mechanism b. involves formation of a chromate ester in a prior fast equilibrium followed by removal of a proton by water (or some other base) in the rate-determining decomposition of the ester.

Further Kinetic Work

Because the chromate ester is such an integral part of mechanism b, Westheimer et al. (5,6) have investigated the chemistry of the chromic acid ester. An ester can be formed in toluene or benzene, but it cannot be isolated because of its instability. The actual ester formed was probably the chromate diester, since the purest solution of ester contained approximately two molecules of alcohol for each chromium atom. The analysis of the ester is quite difficult and complicated because it was usually formed in dilute solutions of the order of 0.0002-0.002 molar. The ester was also found to be decomposed by light. It is thought to be the neutral ester because it can be extracted from an aqueous solution by an organic solvent and the solution of ester in benzene cannot be extracted into aqueous bicarbonate or carbonate.

Qualitative experiments upon the ester in benzene, involving addition of a small amount of dry pyridine, quinoline, or dimethylaniline, show rapid decomposition of the ester with the formation of acetone.

A kinetic investigation of the decomposition of the diisopropyl chromate ester was also done (6). There are two possible paths of decomposition, hydrolysis and internal oxidation-reduction. In the absence of water, diisopropyl chromate in benzene underwent oxidation-reduction (to ketone, alcohol, and chromium (IV)) in a reaction which was approximately first order in pyridine and in ester. When a large excess of isopropyl alcohol was present, the rate was inversely proportional to the alcohol concentration. In wet benzene both hydrolysis and oxidation-reduction occur, with hydrolysis being the major portion of the reaction of the ester. Hydrolysis is also accelerated by pyridine and retarded by isopropyl alcohol; however hydrolysis is more strongly retarded than is oxidation-reduction by excess alcohol. Rates of hydrolysis are large and could not be accurately measured. The retardation of internal oxidation-reduction in dry benzene by excess isopropyl alcohol can be explained in terms of a complex involving pyridine hydrogen bonded to the alcohol. The equations

$$\text{Pyridine} + \underline{i}\text{-PrOH} \xrightleftharpoons{K} \text{complex} \qquad (7)$$

$$\text{Pyridine} + \text{ester} \xrightarrow{k} \text{products} \qquad (8)$$

wherein pyridine is abstracting a proton in the rate-determining step, lead to the rate law

$$\text{rate} = \frac{k(Py)_T(\text{ester})}{1 + K\,(\underline{i}\text{-PrOH})}$$

In this rate law $(Py)_T$ is the total pyridine added. Isopropyl alcohol must be in large excess for this rate law to be valid. Hence, if K(i-PrOH) is much larger than one, the inverse alcohol dependence will be observed.

The facts observed by Westheimer and his co-workers are consistent with the ester mechanism. Due to experimental difficulties, some of the quantitative data are probably rather crude. The existence of an ester species certainly doesn't disqualify the hydride transfer mechansim since the acid chromate ion might still react with the free alcohol.

The kinetics of the oxidation of isopropyl alcohol in 86.5% acetic acid have also been investigated (7). The rate was found to be first order in alcohol, acid chromate ion and hydrogen ion. A plot of log k against H_o yielded a straight line with a slope of -1. An interesting phenomenon observed was that the rate was 250 times as fast in acetic acid as in an aqueous solution of the same H_o. (The rate is 2500 times as fast as in a solution of the same hydrogen ion concentration.) This fact has been explained by Westheimer in terms of the esterification equilibrium. If the oxidation is visualized as occurring by the reactions:

$$HCrO_4^{\ominus} + H_3O^{\oplus} \rightleftharpoons H_2CrO_4 + H_2O \qquad (9)$$

$$H_2CrO_4 + CH_3CHOHCH_3 \rightleftharpoons (CH_3)_2CHOCrO_3H + H_2O \qquad (10)$$

$$(CH_3)_2CHOCrO_3H + H_2O \longrightarrow CH_3COCH_3 + HCrO_3^{\ominus} + H_3O^{\oplus} \qquad (11)$$

a change in solvent going to one of less water and also poorer solvating power would shift the equilibrium of equation (9) to the right. The equilibrium of equation (10) will also be shifted to the right by a medium of less water. Hence, the concentration of the ester would be greater in acetic acid solution than in water. The decomposition of the ester, equation (11), will be slower since there is probably a separation of charge in the transition state which would be better solvated in aqueous media than in acetic acid. Cohen and Westheimer feel that the effects involved in equations 9 and 10 will overbalance the effect of equation 11 leading to a larger concentration of ester and accordingly a faster rate. They also mention the possibility of species such as $CH_3CO_2CrO_3H$, which would be a better oxidizing agent, being present in acetic acid. It is interesting to note that this same rate increase in going to acetic acid has also been observed in the oxidation of hydrocarbons (8). Since hydrocarbons cannot go by an ester mechanism, the effect of the acetic acid medium on chromium (VI) should not be dismissed.

Substituent Effects

In the hydride ion transfer mechanism the hydrogen is being removed with its pair of electrons; thus, electron donating groups would be expected to increase the rate since a positive charge is being formed on the carbon involved. In the ester mechanism the hydrogen is being abstracted by base as a proton; hence electron withdrawing groups should assist in the reaction, with a corresponding rate increase. From these observations it might be concluded that a Hammett sigma-rho treatment of substituted secondary aryl alcohols would assist in determining which of the proposed mechanisms is correct. Such a kinetic study was undertaken by Kwart and Francis (9) on a series of substituted α-phenylethanols.

A Hammett plot of seven substituted alcohols using sigma constants yielded a straight line of slope -1.01 when the reaction was run in 30% acetic acid. If the reaction was run in a 60% benzene-40% pyridine mixture, rho was -0.37; while, if it was carried out in pure benzene, rho was -0.52. Since electron donating groups accelerated and electron withdrawing groups retarded the reaction, it might be concluded that the hydride ion transfer mechanism is the favored pathway for chromic acid oxidation.

In the ester mechanism, if rho for esterification were negative and greater than the positive rho expected for decomposition, the overall rho would be negative. Kwart and Francis carried out a series of experiments to find the order of magnitude and the sign of rho for esterification. They obtained equilibrium constants for the interchange of chromate diesters of substituted 2-phenyl-2-propanols according to the following equation,

$$(X\text{-}TO)_2CrO_2 + p\text{-}Cl\text{-}SOH \rightleftharpoons p\text{-}Cl\text{-}SOCrO_2OT\text{-}X + X\text{-}TOH \qquad (12)$$

where X-TOH is a substituted 2-phenyl-2-propanol and p-Cl-SOH is α-(p-chlorophenyl)-ethanol. The rate of decomposition of the ester on the right was taken as a measure of the position of equilibrium. The equilibrium constant for the reaction is defined in the standard way. If the kinetic data are analyzed for K_{eq} and log K_{eq} is plotted against sigma for the various substituents, a straight line with a slope of 0.94 is obtained. These studies were made using benzene as solvent. For application in esterification the sign must be reversed or $\rho_{esterifn} = -0.94$. Since

$$\rho_{decomp} = \rho_{obs} - \rho_{esterifn} \qquad (13)$$

and using the value of ρ_{obs} of -0.37, ρ_{decomp} is calculated to be 0.57 (-0.37-(-0.94)). The calculation where ρ_{obs} is -0.52 yields a value of 0.42 for ρ_{decomp}. The sign of ρ_{decomp} obtained by this method is in agreement with the electron demand requirements for the decomposition of the chromate ester. The values of the rhos used in these calculations are in the area where it becomes hard to use them as a diagnostic tool, since small values of rho are usually considered nonreliable. The data which were used in the calculation are rather crude; however, the results do seem to indicate that the dominating substituent effect may be found in the chromate ester equilibrium.

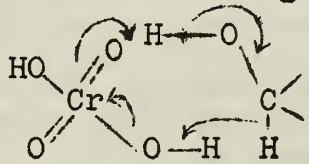
Structural and Conformational Effects on Oxidation Rates

Schreiber and Eschenmoser (10) have investigated some conformational effects in the oxidation of substituted cholestanols. The results of their work are reported in Table 1.

Table 1
Relative Rates of Oxidation of Epimeric Alcohols

Epimeric Pair	1	2	3	4	6	7
	Hydroxycholestane					
$k_{axial\ OH}$	1.3	15	3.0	17	18	3.7
$k_{equatorial\ OH}$						

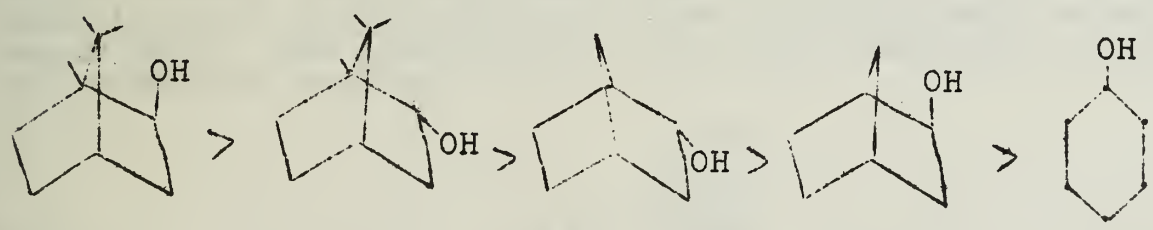
They described the results in terms of the ester mechanism. In the compounds where a 1,3 interaction between the methyl and the substituent can occur, the rate accelerating effect was ascribed to steric relief of strain in forming the ketone from the chromate ester. It has also been observed (11) that the data fit within the framework of the hydride ion transfer mechanism. In the transition state, the C-H bond is undergoing attack. Hence, the compound with the more accessible equatorial hydrogen (thus an axial hydroxyl) will be ozidized more easily. This is the case with all the cholestanols, that $k_{ax\ OH} > k_{eq\ OH}$. It was also thought in the case of the 1,3 methyl interaction, the O-H bond is caused to be oriented away from the methyl group and thus favoring a cyclic transition state of the type



Since esterification is known to be sensitive to steric hindrance, substituents could hinder an axial hydroxyl group to such an extent that esterification would become the slow step. (The rate of decomposition would also be increasing due to steric relief of strain.) If this occurs, the oxidation of the equatorial isomer would become faster than the oxidation of the axial isomer. This trend is not observed in the data given, but a methyl group may not be bulky enough. The relative rates of a system where the angular methyl group has been replaced by a t-butyl group would be interesting. Rocek and Krupicka feel that if the ester mechanism were operating the trend would be observed, since the decrease in the size of the equilibrium constant for esterification would not be overshadowed by the favorable factor of decrease in strain in going to the ketone.

Work has also been done on the evaluation of strain relief as a rate-determining factor (12). Some data for chromic acid oxidation of various secondary alcohols in 30% acetic acid at 30° are presented in Table II.

Table II
Relative Rates of Oxidation of Secondary Alcohols

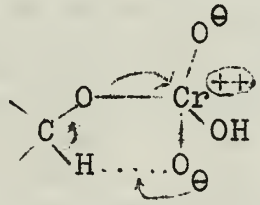


Isoborneol	Borneol	Endo-Norborneol	Norborneol	Cyclohexanol
49.1	25.0	9.67	3.85	1.0

When these data are discussed in terms of the ester mechanism, several interesting points can be obtained. The rate of oxidation of isoborneol is two times faster than the rate of oxidation of borneol. If the esterification equilibrium were the rate-controlling

factor, borneol would oxidize faster since it would be easier to esterify. If decomposition of the ester were more important, isoborneol would oxidize faster than borneol since the proton being removed would be more accessible to base and there would be a relief of strain due to steric crowding between the ester and the bridge gem-dimethyl group. Thus it may be concluded that decomposition of the ester is sterically more sensitive than the esterification equilibrium is. This effect also shows up in the norborneol, endo-norborneol case. The oxidation of endo-norborneol should be faster if the decomposition of the ester is the rate-controlling factor, since again approach of base for proton removal is easier and greater relief of crowding is obtained. Oxidation of norborneol would be faster than its epimer if the esterification equilibrium were the rate-controlling factor, since it would be easier to esterify. The fact that endo-norborneol is oxidized two and one half times faster than norborneol is evidence that decomposition of the ester is the rate-controlling factor. In the decomposition of the chromate ester there will be two steric effects operating, relief of strain of the ester group due to non-bonded interactions, and ease of approach of base for removal of the proton. Since it seems that the rate-controlling factor when steric considerations are made is the decomposition of the ester, a comparison of isoborneol with endo-norborneol may provide evidence as to whether relief of strain or approach of base is more important in the rate-controlling step for the series of compounds from which this data was obtained. If relief of strain is more important, then isoborneol will oxidize faster than endo-norborneol, since the chromate ester will be sterically more hindered. If ease of approach of base to the hydrogen is more important, then endo-norborneol will oxidize faster than isoborneol. Since isoborneol oxidizes faster than endo-norborneol, this leads to the conclusion that steric relief of crowding is more important than the ease of approach of base for removal of the proton. Since this work was done in 30% acetic acid, the external base removing the proton is probably water. As the size of the external base is increased, steric hindrance to approach of base for the removal of the proton may become more important than steric acceleration due to relief of crowding.

From the conclusions drawn in their work, (a) that the sterically important factor in controlling the overall rate of oxidation is the decomposition of the ester and (b) that steric relief of strain of the chromate ester is more important than approach of a base for proton removal, Kwart and Francis have proposed a cyclic transition state in which an electron rich oxygen of the chromate ester is acting as base. This modification of the ester mechanism pictures the transition state as,



Steric hindrance by neighboring groups of the oxygen would prevent rotation about the C-O bond and would increase the probability that the ester attain the cyclic transition state since the Cr-O-C angle would become smaller due to repulsion of hindering groups. The data on steric effects were obtained in 30% acetic acid. The rate

expression for this reaction calls for the transition state to be composed of alcohol, an acid chromate ion, and either one or two hydrogen ions. Stochiometrically the cyclic transition state corresponds to these species minus a molecule of water. However, no kinetics have been run in 30 per cent acetic acid to determine if the acid dependence of the rate law is H_0, C_0, or $H_3O^{\oplus}$. In 86.5% acetic acid the rate follows H_0, but this should not be extrapolated to 30% acetic acid.

Kwart and Francis (12) have investigated the stereoelectronic effect as an influence in the rate-determining step of the ester mechanism. Because of a lack of space, this subject will not be discussed in the seminar.

O-H Isotope Effect

The hydride ion transfer mechanism as proposed by Rocek and Krupicka involves a process concerted with the loss of the hydrogen from the hydroxyl group of the alcohol. Thus, this mechanism should show an O-H isotope effect. The oxidation of isopropyl alcohol has been carried out in D_2O and H_2O solutions (13). The observed isotope effect was interpreted in terms of the rate expression,

$$\text{velocity} = [k_3(H^{\oplus}) + k_4(H^{\oplus})^2]\ [HCrO_4^{\ominus}]\ [CH_3CHOHCH_3]$$

The results were as follows:

$$\frac{k_3^{D_2O}}{k_3^{H_2O}} = 2.4\ ,\quad \frac{k_4^{D_2O}}{k_4^{H_2O}} = 6.3$$

This is not the result to be expected for a normal isotope effect involving hydrogen bond breaking in the rate-determining step. The ionization of most acids is greater in H_2O than in D_2O by a factor of 2.5-3 (14). Hence the concentration of D_2CrO_4 in D_2O should be about two and one half times as large as the concentration of H_2CrO_4 in H_2O. Thus the rate in D_2O for a reaction proceeding through undissociated chromic acid (first order in hydrogen ion) would be 2.5 times as fast; while a second order reaction would be $(2.5)^2$ or 6.25 times as fast, if it is assumed that there is no O-H bond breaking in the transition state. It is perhaps fortuitous that these calculated results are in such close agreement with the experimental results. If a normal isotope effect were operating, such that the O-H bond was being broken in the transition state, k^{D_2O}/k^{H_2O} would not be as large as is observed and it is even possible that $k^{H_2O}/k^{D_2O} > 1$. Thus it seems probable that the rate-determining step does not involve breaking or stretching of the O-H bond, and it can be concluded that a cyclic transition state is improbable for the hydride ion transfer mechanism. Any mechanism where the proton on the oxygen is being removed at the same time as the hydride ion should also be ruled out. Thus, if the hydride ion mechanism is the pathway of chromic acid oxidation, then the hydrogen on the oxygen must be removed in a fast reaction after the rate-determining step.

Summary

As of yet there seems to be no clear cut evidence available which allows a definite decision to be made as to whether the hydride ion transfer mechanism or the ester mechanism is correct.

The formation of the diisopropyl chromate ester in benzene and its similarity in reaction to oxidation of alcohols adds weight to the arguments in favor of the ester mechanism. The lack of O-H isotope effect would be in favor of an ester mechanism, since the removal of the hydroxyl hydrogen would probably be a driving force in the reaction by hydride ion transfer. One area that may prove fruitful in distinguishing the two choices is steric considerations. Better quantitative data may allow a clear cut choice between the two mechanisms.

Mechanism of Aldehyde Oxidation

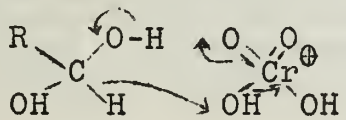
The kinetics of the oxidation of benzaldehyde have been measured (15,16). The rate law was first order in benzaldehyde, and first order in acid chromate ion. The acid dependence was found to be a more complicated function than simple first order dependence. An H_0 plot of data collected for 75-90% acetic acid gave a slope of one. A Hammett sigma-rho correlation yielded a rho of 1.02. Rate measurements showed that $\Delta H^{\ddagger} = 12.6$ kcal. and $\Delta S^{\ddagger} = -28$ entropy units. When α-deuterobenzaldehyde was oxidized, an isotope effect, kH/kD, of 4.3 was noted. As in the alcohol oxidation, manganous ion was found to decrease the rate. Because of experimental difficulties, it could not be determined whether chromium (IV) or chromium (V) is formed in the rate-determining step. Since the kinetic data of aldehyde oxidation are similar to the data obtained in the oxidation of isopropyl alcohol, it is not unreasonable to postulate the first stage of oxidation as a two electron transfer reaction. In line with this assumption, a mechanism similar to the previously described ester mechanism has been presented. This mechanism is formulated in terms of a chromic acid ester of hydrated benzaldehyde,

$$C_6H_5CHO + HCrO_4^{\ominus} + 2H^{\oplus} \underset{}{\overset{\text{fast}}{\rightleftharpoons}} C_6H_5\overset{H}{\underset{OH}{C}}OCrO_3H_2^{\oplus} \qquad (14)$$

$$C_6H_5\overset{H}{\underset{OH}{C}}OCrO_3H_2^{\oplus} + H_2O \xrightarrow{\text{slow}} C_6H_5COOH + H_3O^{\oplus} + H_2CrO_3 \qquad (15)$$

This mechanism satisfies the experimental data which have been obtained. No prediction of the sign of rho can be made since substituent effects in the prior equilibria could dominate any substituent effect for the rate-determining step. The mechanism has been written as if water were the base removing the proton in the slow step, but the reaction could also proceed by means of a cyclic transition state, since in a formal sense this extra water molecule does not occur in the elements of the transition state as defined by the rate law. The number of molecules of water in the transition state does not seem to have been rigorously determined.

A hydride ion transfer mechanism has also been proposed for the chromic acid oxidation of aldehydes (17). This mechanism, which also involves the hydrated form of the aldehyde, pictures the transition state as follows:



Electron donating groups would assist the removal of the hydride ion; hence for this step in the mechanism a negative rho would be required.

However, a larger positive rho might be found for the equilibrium of the hydration of the aldehydes. When rate studies were run with substituted hydrated acetaldehydes (the hydrogen of the methyl group being systematically replaced with chlorines), a plot of the logarithm of the relative rate vs σ^* yielded a straight line with ρ^* of -1.2. Thus, the fastest rate was observed with acetaldehyde hydrate and the slowest rate with trichloroacetaldehyde hydrate. This evidence is in agreement with the type of electron demand required in the hydride ion transfer mechanism. The effect observed in the case of the aromatic aldehydes was explained with a similar type of explanation as used by Kwart and Francis to explain the substituent effect observed in secondary alcohol oxidation. The effect of electron donating groups in the hydration of aldehydes is to decrease the electrophilicity of the carbonyl group. The equilibrium would thus be shifted in favor of the hydrate, if electron withdrawing groups are added, with a concurrent increase in the rate of the reaction. In the case of aromatic aldehydes, this concentration effect could very well overshadow the decrease in reactivity in the hydride ion transfer step, if this mechanism were operating. The evidence of Rocek and Krupicka can be interpreted in terms of the ester mechanism. In the esterification of hydrated aldehydes, electron withdrawing groups would shift the equilibrium in favor of the hydrate and thereby slow the reaction.

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The data which have been presented on the mechanisms of chromic acid oxidation of aldehydes do not permit a definite choice to be made as to whether the chromic acid ester mechanism or the hydride transfer mechanism is correct. Further work should be done to determine if a one or two electron transfer occurs in the first step of the reaction.

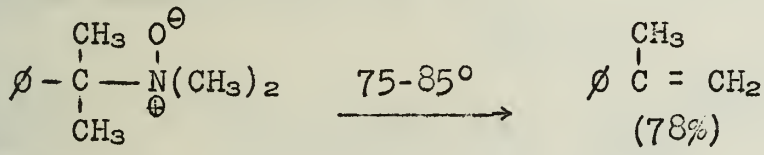
MECHANISM OF THE PYROLYSIS OF ALIPHATIC AND ALICYCLIC TERTIARY AMINE OXIDES

Reported by R. J. Sauer March 7, 1960

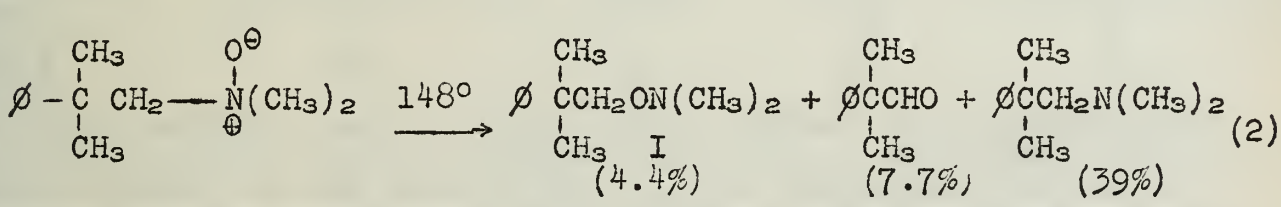
The pyrolytic decomposition of tertiary amine oxides to give olefins and dialkylhydroxylamines is another member of the class of reactions which proceed via a cis-elimination. Certain of the synthetic and mechanistic aspects of the pyrolysis have been reviewed elsewhere (1,2). Reactions of the type (3) will not be discussed

since few mechanistic conclusions can be drawn from them. This seminar will, therefore, be concerned with a discussion of the factors which appear to be operating in the pyrolysis of tertiary amine oxides in which the nitrogen is not a member of an heterocyclic ring.

Study of this reaction established that a β-hydrogen atom was required for elimination (4):



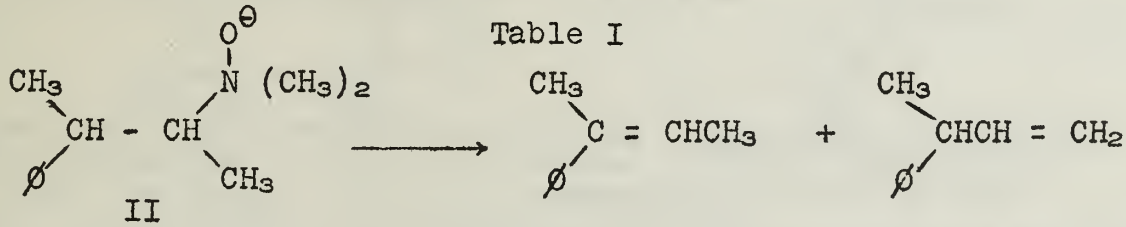
(1)



(2)

The fact that elimination occurs in the absence of α-hydrogens but not in the absence of β-hydrogens strongly suggests the involvement of a β-hydrogen atom in the elimination. Rearrangements to form compounds analogous to I have been observed in many instances where elimination is difficult or impossible (5). Loss of oxygen from the amine oxide has been observed to occur in many pyrolyses and is apparently independent of whether the primary reaction is elimination or rearrangement.

Verification of the predominantly cis-nature of the elimination has been accomplished by a study of the decomposition of racemic threo- and erythro-2-(N,N-dimethylamino)-3-phenylbutane oxide (II) (6). The results are summarized in Table I.

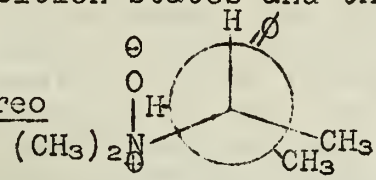
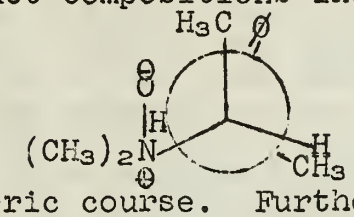


II

Table I

Isomer	%cis	%trans	%unconjugated
threo-II	94(93)	0.1(0.2)	7(7)
erythro-II	4(2)	89(90)	7(8)

It was observed qualitatively that the threo-isomer underwent elimination more readily than the erythro. Consideration of the transition states and the product compositions indicate that the

threo   erythro

elimination follows the cis steric course. Furthermore, the relative rates of elimination are in the order to be expected on the basis of the less serious eclipsing effects present in the threo-isomer relative to the corresponding effects in the erythro case. It might also be conjectured that other factors, such as thermodynamic stability of the olefin or stabilization of the transition state by the phenyl group, are operative here since the elimination favors the conjugated olefin in both cases by a factor of about 13.

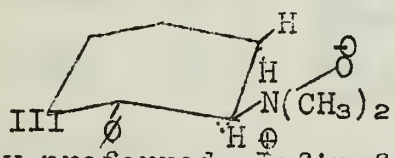
Cram has pointed out an interesting comparison between the preceeding amine oxide pyrolysis and pyrolysis of the analogous xanthate esters (Table II) (6,18).

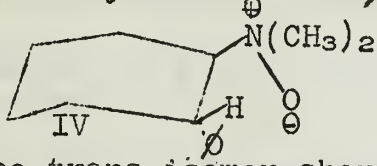
Table II

Isomer	Total olefin (%)	Olefin Composition %cis	%trans	%unconjugated
threo	76	36	11	40
erythro	91	5	51	33

These data indicate that the amine oxide elimination is considerably more stereospecific than the xanthate pyrolysis. Furthermore, the greater tendency of the amine oxides to give conjugated olefins is attributed to a greater degree of double bond character in the amine oxide transition state than in the xanthate transition state.

Evidence for the steric course of the reaction also comes from the pyrolysis of cis- and trans- 2-phenyl-N,N-dimethylcyclohexylamine oxide (7). The trans-isomer gave a 96% yield of olefin which was shown by vapor phase chromatography to consist of 85% of 1- and 15% of 3-phenylcyclohexene. The cis-isomer, on the other hand, gave a 72% yield of olefin which an ultraviolet spectrum indicated to be 98% pure 3-phenylcyclohexene. Assuming that the dimethylamine oxide group has steric requirements similar to t-butyl and that the requirements be in the order dimethylamine oxide > phenyl,


III


IV

the sterically preferred olefin from the trans-isomer should be 3-phenylcyclohexene. It may be, however, that an electronic, rather than the steric effect, is determinant since the predominant olefin formed is 1-phenylcyclohexene.
For the cis-isomer it is not possible to draw an analogous transition state which would lead to 1-phenylcyclohexene. Although these and subsequent transition states have been represented in the extreme "boat" form of cyclohexane, similar arguments should hold if they were represented in the pseudo-chair conformation of cyclohexene.

Interesting phenomena are observed in the pyrolysis of N,N-dimethylcycloalkylamine oxides (8). Cope has shown that rings containing through eight carbons undergo elimination to give exclusively cis-cycloalkenes, but that, when the rings are enlarged to nine or ten members, the products are exclusively the trans olefins. The rationale for this is to be found in the fact that in the normal conformation of the nine- and ten-membered rings, the C_β-H_β(trans) and C_α-$N^\ominus$ bonds are nearly co-planar. Thus, for cis-cyclooctan-3-yldimethylamine oxide, it is to be expected that the elimination should proceed via a cis-course to give the observed cis, cis-1,3-cyclooctadiene as the sole diolefinic product (9).

The pyrolysis of a number of trialkylamine oxides has been studied (10) and leads to some interesting conclusions regarding the factors determining the direction of elimination.

Table III

Olefins from Amine Oxides of the Type $R_1R_2CH_3\overset{\oplus}{N}-O^\ominus$

R_1	R_2	Yield(%)	Olefin composition (mole %)	R_2/R_1[a] (calc)	R_2/R_1 (obs.)
sec-butyl	methyl	91	67.3 1-butene, 11.7 cis-2-butene, 21, trans-2-butene	0.667[b]	0.49[b]
3-pentyl	methyl	86	29.2 cis-2-pentene, 70.8 trans-2-pentene	1.0[c]	0.41[c]
ethyl	n-propyl	82	62.5 ethene, 37.5 1-propene	0.667	0.60
ethyl	iso-propyl	90	27.5 ethene, 72.5 1-propene	2.0	2.64
ethyl	n-butyl	85	55.5 ethene, 44.5 1-butene	0.667	0.80
ethyl	i-butyl	85	67.6 ethene, 32.4 i-butene	0.33	0.48
ethyl	t-butyl	76	14.2 ethene, 85.8 i-butene	3.0	6.06
n-propyl	n-butyl	62	43.1 propene, 56.9 1-butene	1.0	1.32
n-propyl	i-butyl	73	58.8 propene, 41.2 i-butene	0.50	0.70
n-butyl	i-butyl	86	64.8 1-butene, 35.2 i-butene	0.50	0.54
n-propyl	i-amyl	80	44.1 1-butene, 55.9 3-methyl-1-butene	1.0	1.27
ethyl	β-phenyl-ethyl	85	1.2 ethene, 98.7 styrene	0.667	70.0
n-propyl	n-decyl	55	40.4 propene, 59.6 1-decene	1.0	1.47

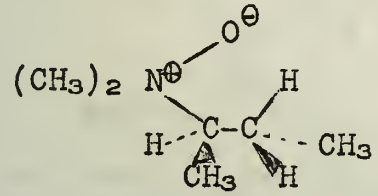
[a] Based on the number of β-hydrogen atoms in R_1 and R_2. [b] Ratio of 2-butene/1-butene. [c] Ratio of cis-2-pentene/trans-2-pentene.

It is evident from the relatively close agreement in most cases between the calculated and observed values of the R_2/R_1 ratios that the elimination is nearly statistical when R_1 and R_2 are alkyl

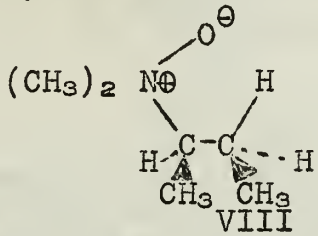
groups. In some instances where calculated and observed values differ, the preference is slightly in favor of elimination of the more highly substituted olefin. It is inferred from these data that 1) either the nature of the alkyl group exerts little or no effect on the elimination or 2) that the operative effects are additive from one compound to another.

It has also been argued that the relative acidities of the available hydrogen atoms, as a consequence of inductive effects, should determine the course of the elimination. However, if acidity were the directing factor, it would seem that the deviations of observed from calculated quantities should be much greater.

While inductive effects do not appear to be dominant, several of the cases listed in Table III indicate that eclipsing effects may be important in the transition state. In the decomposition of N,N-dimethyl-sec-butylamine oxide, the transition state (VII)

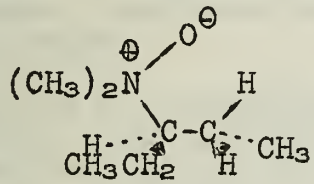


VII

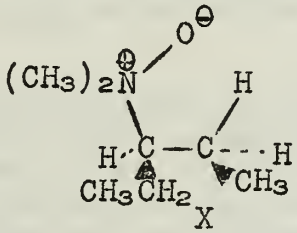


VIII

leading to trans-olefin is favored since the methyl-methyl eclipsing interactions of VIII, leading to cis-olefin, are absent. Similarly, for N,N-dimethyl-3-pentylamine oxide, the product ratio is determined almost solely by the steric factors operative in the transition states (IX and X).



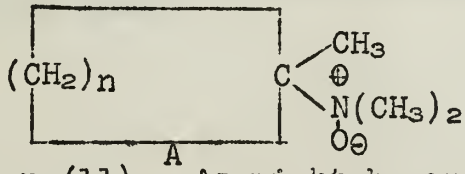
IX



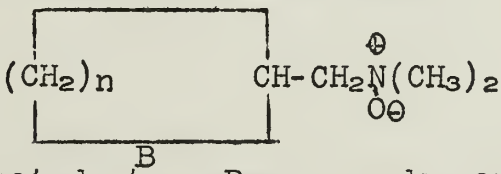
X

It is also of interest to consider the pyrolysis of methyl-ethyl-β-phenylethylamine oxide. Examination of the possible transition states indicates that there should be little or no hindrance to elimination from eclipsing interactions. Cope attributes the preference for styrene to the enhanced acidity of the benzylic hydrogen atoms and to stabilization of the incipient double bond by the phenyl group. This might imply that the double bond character in the transition state is greater with aralkyl than with simple alkyl substituents on the nitrogen atom.

Amine oxides of types A and B have been subjected to thermal



A



B

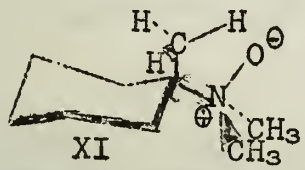
decomposition (11). As might be anticipated, type B compounds gave almost exclusively the exo-methylenic olefins. On the other hand, type A compounds gave mixtures of exo and endo olefins which can be seen to arise as a result of the steric requirements of the various ring systems.

Table IV

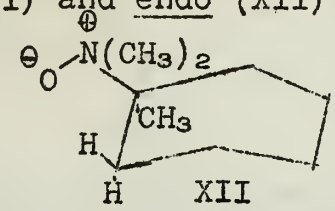
Olefins Obtained from Amine Oxides of Type A

n	Olefin yield(%)	Amine recovered(%)	Composition (%) exo	endo
4	77	2	2.5	97.5
5	84	3	97.2	2.8
6	84	2	15.2	84.8

The striking extent of exo elimination for the 1-methylcyclohexylamine (n=5) must be related to the relative energies of the transition states leading to exo (XI) and endo (XII) elimination.



XI

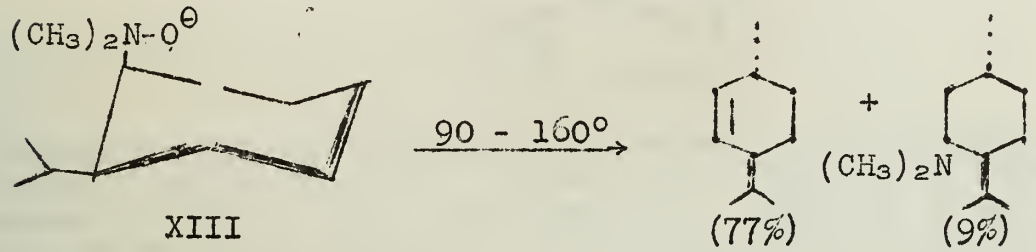


XII

It has been suggested that XI should be of lower energy than XII since it requires orientation of only the N - O bond, while endo elimination requires N - O orientation as well as conformational changes. From analogous arguments, the near-planarity of the cyclopentyl ring should afford a co-planar transition state leading to endo olefin more easily than one leading to exo-olefin. The cycloheptyl compound is not subjected to the stringent conformational restrictions of either of the previous compounds and, hence, undergoes both exo and endo elimination to an intermediate degree.

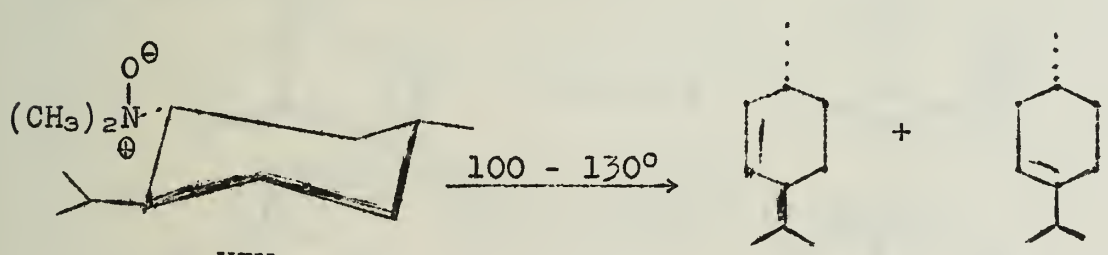
It has been suggested (12) that pyrolysis of the 1-methylcycloalkyl acetates (12,13) parallels, in a general sense, the pyrolysis of the corresponding amine oxides. However, the lower degree of specificity in acetate eliminations may reflect the differences between the 6- and 5-membered transition states and the resultant steric restrictions imposed upon them. Although complete eclipsing of groups is not necessary in the transition state for acetate eliminations, it would be expected to be nearly complete for the amine oxides and the latter would appear to offer a more nearly ideal situation for the development of double bond character in the transition state. DePuy has concluded on the basis of deuterium isotope effect studies on 1-methylcyclohexyl acetate (14) that, for the acetates, the transition state shows a large degree of concerted bond breaking and considerable double bond character. However, no similar work has been done in the amine oxide series and no conclusions of this type can be made at the present time.

Additional indications of operative steric effects are available from the thermal decompositions of N,N-dimethyl-(-)-menthyl- and -(+)-neomenthylamine oxides (15). It is to be expected that the neomenthylamine oxide (XIII), having only one cis-β-hydrogen atom, should give only 2-menthene on decomposition.



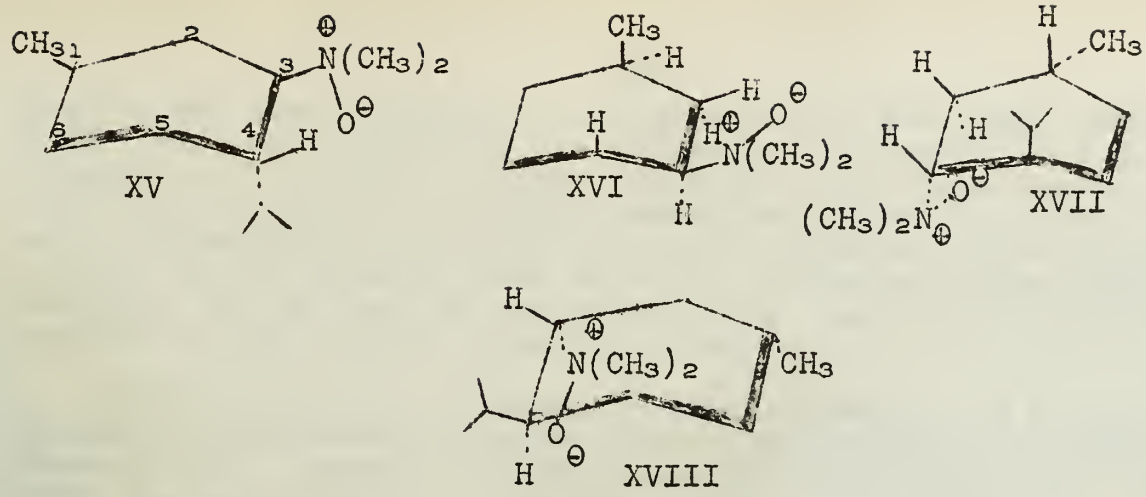
XIII

Analysis of the products by both acid-catalyzed racemization and vapor phase chromatography showed that the sole olefinic product was optically pure (+)-trans-2-menthene. The corresponding (-)-menthylamine oxide (XIV), however, has two available cis-β-hydrogen atoms and, on pyrolysis, could give both 2- and 3-menthene. The reaction gave an 85% yield of an olefinic mixture of which 65% was 2-menthene and 35% 3-menthene.



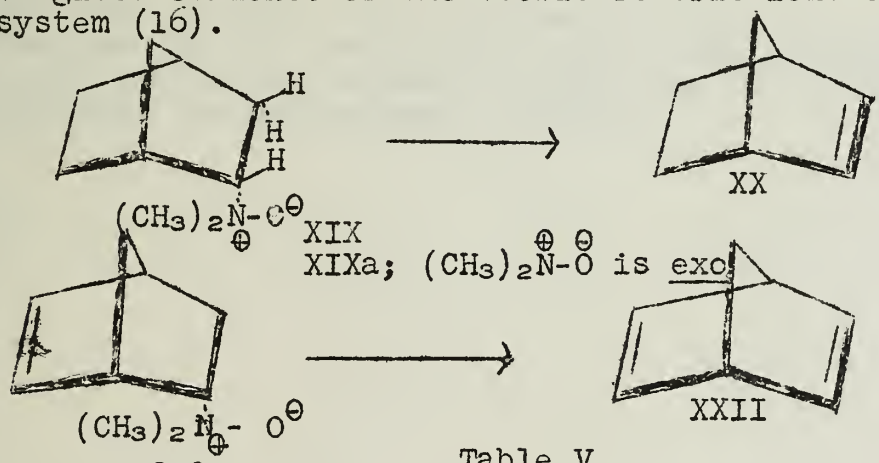
XIV

These latter products and their relative quantities may be rationalized by considering the possible transition states:



Structure XVII may probably be disregarded at the outset since it would necessitate both the isopropyl and dimethylamine oxide groups assuming "axial" conformations. Further, XV and XVIII would also be unfavorable to the extent that the C_3-H vs. C_4-isopropyl and the 1,3-diaxial $(CH_3)_2\overset{\oplus}{N}$-$\overset{\ominus}{O}$ vs. CH_3 interactions act to destabilize the transition states. The most favorable transition state, therefore, is XVI, which would lead to 2-menthene in agreement with the experimental results. For the production of 3-menthene, structure XV would appear most likely.

Thermal decomposition of amine oxides of the norbornyl series gives evidence of the steric restrictions of a rigid ring system (16).



XIX
XIXa; $(CH_3)_2\overset{\oplus}{N}$-$\overset{\ominus}{O}$ is exo

XXI
XXIa; $(CH_3)_2\overset{\oplus}{N}$-$\overset{\ominus}{O}$ is exo.

Table V

Compound	Olefin yield(%)	Amine recovered(%)	exo/endo
XIX	2.9	25	22.4
XIXa	65	4	
XXI	1.4	28	22.9
XXIa	32	13	

The easier elimination of the exo-isomers has been attributed to steric acceleration of C-N⊕ bond breaking due to the proximity of the saturated C_6 (in XIXa) and to anchimeric assistance by the double bond (in XXIa). The fact that the ratio of olefins formed from elimination in the exo-and endo-isomers is constant at about 22 (see Table V, "exo/endo") suggests that the steric requirements of both the norbornyl and norbornenyl compounds are

similar and that hindrance to elimination of the endo-isomers stems from interactions of the quaternary nitrogens with the 1,2-ethylene or 5,6-ethano bridges. Cope has also shown that pyrolysis of the corresponding quaternary ammonium hydroxides gives consistently higher yields of olefins XX and XXII than do the amine oxides. It is inferred that this fact reflects a more highly developed double bond in the amine oxide transition states which results in some degree of steric strain.

Another instance of amine oxide elimination, in a bicyclic system with somewhat different steric requirements, has been observed (17). endo-5-Dimethylamino-bicyclo[2.2.2.] oct-2-ene oxide yields bicyclo[2.2.2]octa-2,5-diene on pyrolysis:

$(CH_3)_2N\text{-}O^{\ominus}$ XXII (70%)

The higher yield of diene from the endo-amine oxide in this instance relative to the norbornene case is indicative of the less severe steric effects operating in the bicyloöctene system (13).

The work that has been discussed here appears to have characterized the statistical and steric factors operating in amine oxide pyrolyses; however, little can be concluded concerning electronic or thermodynamic effects.

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SOME ASPECTS OF ALKALOID BIOGENESIS

Reported by H. B. Renfroe March 10, 1960

Introduction

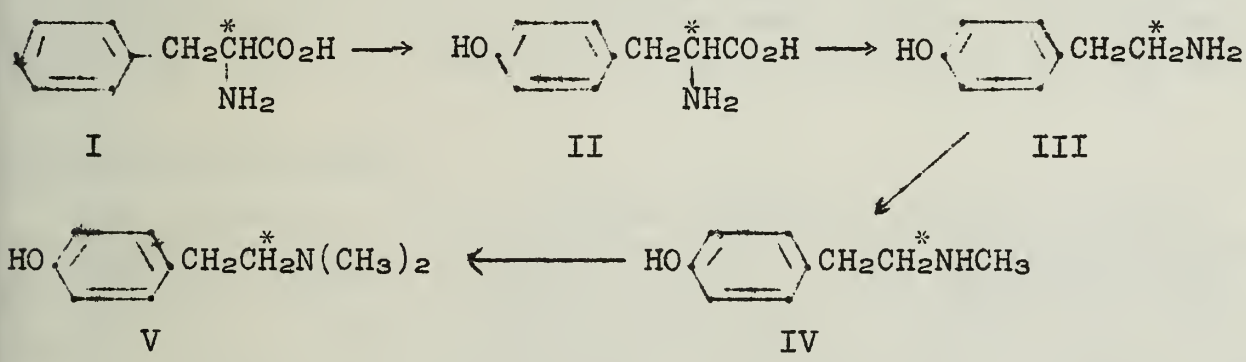
The mode of biogenesis of naturally occurring substances has aroused much interest in recent years. While theories of biogenesis for whole classes of natural products have been proposed (1,2), relatively little experimental verification has followed so far. Experimentation has finally been stimulated by the availability of isotopes of the light elements--^{15}N, ^{18}O, ^{2}H, ^{3}H, and most important -^{14}C. Biogenetic studies on alkaloids, in particular have been greatly improved because of this, and this seminar will present some conclusions gleaned from "stem-feeding" experiments using labeled suspected precursors. Since present concepts of alkaloid biogenesis have been based primarily on inspection of alkaloid skeleta, an additional purpose of this seminar will be to present recent advances to the present level of knowledge concerning alkaloid biogenetic theory.

ISOTOPE STUDIES

Hordenine

An alkaloid of simple structure which occurs in barley is hordenine (V), whose biogenetic pathway has been established (3-8) as shown in Scheme I. The administration of phenylalanine (I),

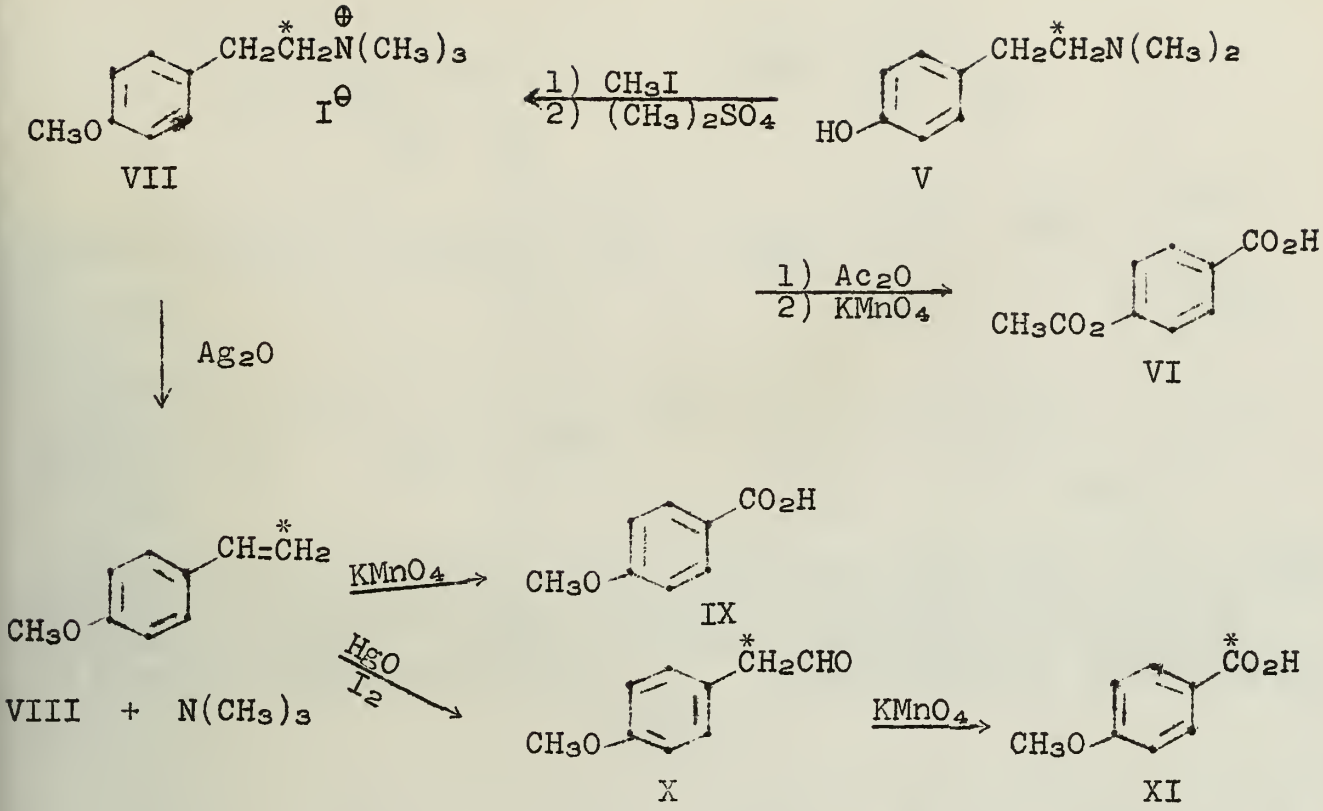
SCHEME I



tyrosine (II), tyramine (III), or N-methyltyramine (IV), labeled in the α-position with C^{14} to an aqueous nutrient solution in which the roots of barley plants were growing, produced radioactive hordenine with the label in the same position as in the precursors. From a consideration of the percent incorporation of ^{14}C into the alkaloid, it could be concluded that tyramine was closer to hordenine than tyrosine, which was closer than phenylalanine; this agrees with the above scheme. The methyl groups of hordenine arise by transmethylation from methionine and formate, also studied with ^{14}C.

Hordenine was degraded for location of the label as shown in Scheme II. Acetylation and oxidation of V yielded p-acetoxybenzoic acid (VI) which was inactive. Transformation of hordenine to p-vinylanisole *via* Hofmann produced a compound (VIII) with the same

SCHEME II

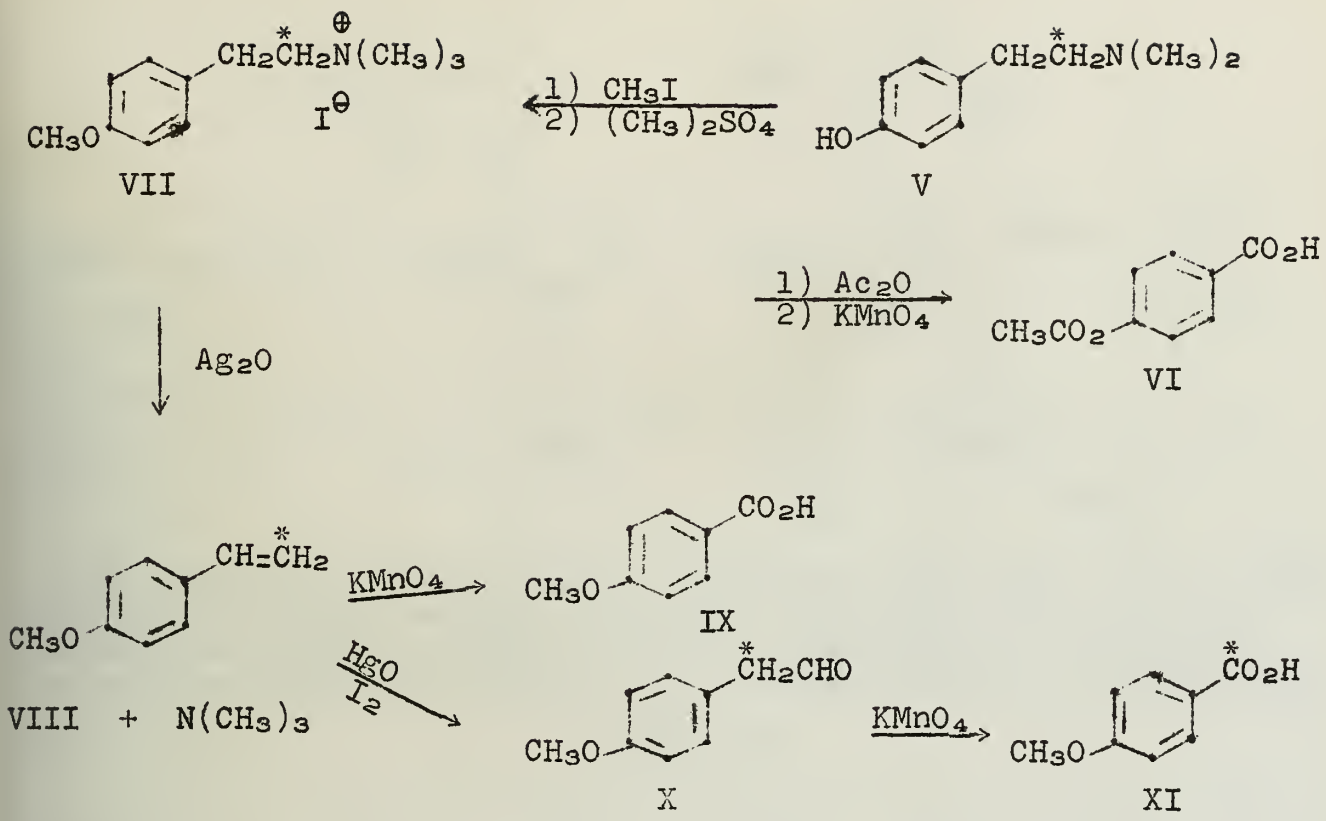


activity as hordenine; that is, there was no activity in the trimethylamine. Oxidation of VIII produced inactive anisic acid (IX) but treatment with mercuric oxide and iodine followed by oxidation gave rise to anisic acid (XI) with the same activity as hordenine, thus showing the lable was originally in the α position to the nitrogen atom.

Nicotine and Anabasine

The biogenesis of two pyridine alkaloids, nicotine (XXXIII) from Nicotiana tabacum and anabasine (XXXIV) from Nicotiana glauca, has been the subject of intensive study. It has been shown that the pyrrolidine ring of nicotine arises from ornithine (9,10)(XIV). Glutamic acid -2-^{14}C (XII) and proline (XVII), symmetrically labeled, also are incorporated into nicotine, presumably like ornithine (XIV) through intermediates XV and XVI (11), as in other biological systems. In Scheme III is shown a plausible pathway for the formation of the pyrrolidine ring of nicotine, as suggested by labeling experiments. Decarboxylation of XVI gives rise to XVIII wherein the label has become randomized by the symmetrical anion XVII. Degradation of the isolated alkaloid showed in all cases equal activity at C-2 and C-5 of the pyrrolidine ring (12). Another symmetrical intermediate by which the label could be randomized would be putrescine (XIX), arising from ornithine by decarboxylation. Analagously, the suspected precursor of the piperidine ring of anabasine was lysine (XXII), which did produce radioactivity in the piperidine ring (9). However, all the label was located at C-2 rather than equal distribution between C-2 and C-6. Cadaverine (XXVI), which can arise from lysine by decarboxylation, produced anabasine with the activity evenly distributed between C-2 and C-6, when administered to Nicotiana glauca plants (13). Lysine must therefore be converted into the

SCHEME II



activity as hordenine; that is, there was no activity in the trimethylamine. Oxidation of VIII produced inactive anisic acid (IX) but treatment with mercuric oxide and iodine followed by oxidation gave rise to anisic acid (XI) with the same activity as hordenine, thus showing the lable was originally in the α position to the nitrogen atom.

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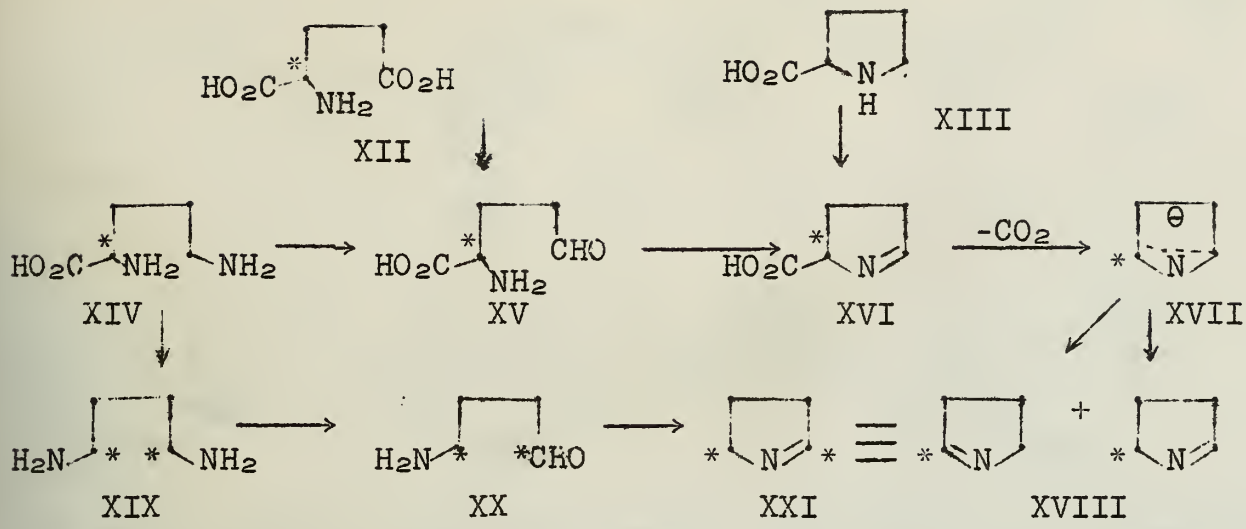
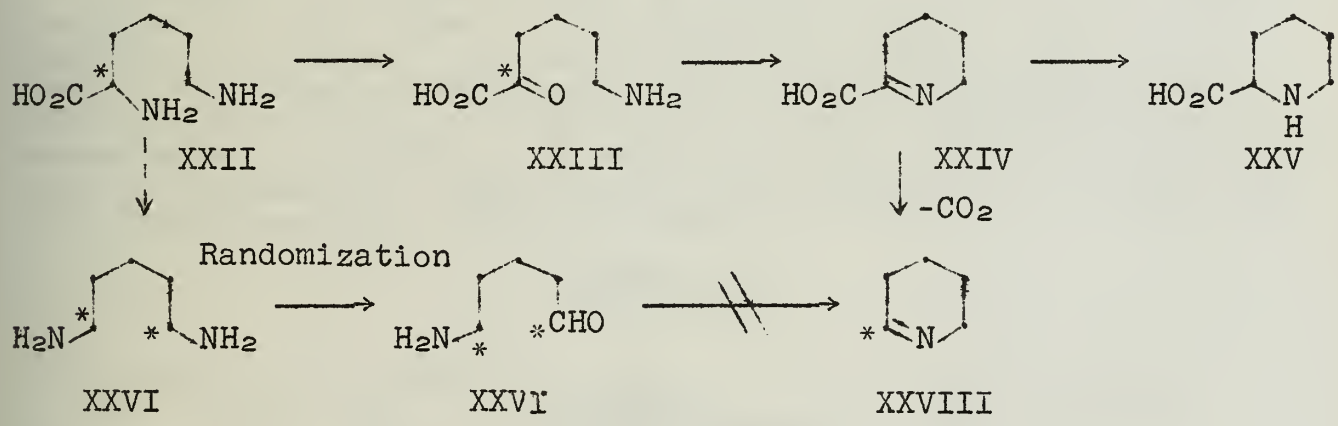
SCHEME III



piperidine ring of anabasine by a different route than that by which ornithine is converted into nicotine. In Scheme IV is shown a reasonable pathway. It has been shown that pipecolic acid (XXV) is produced <u>via</u> XXIII and XXIV (14). Decarboxylation of XXIV would

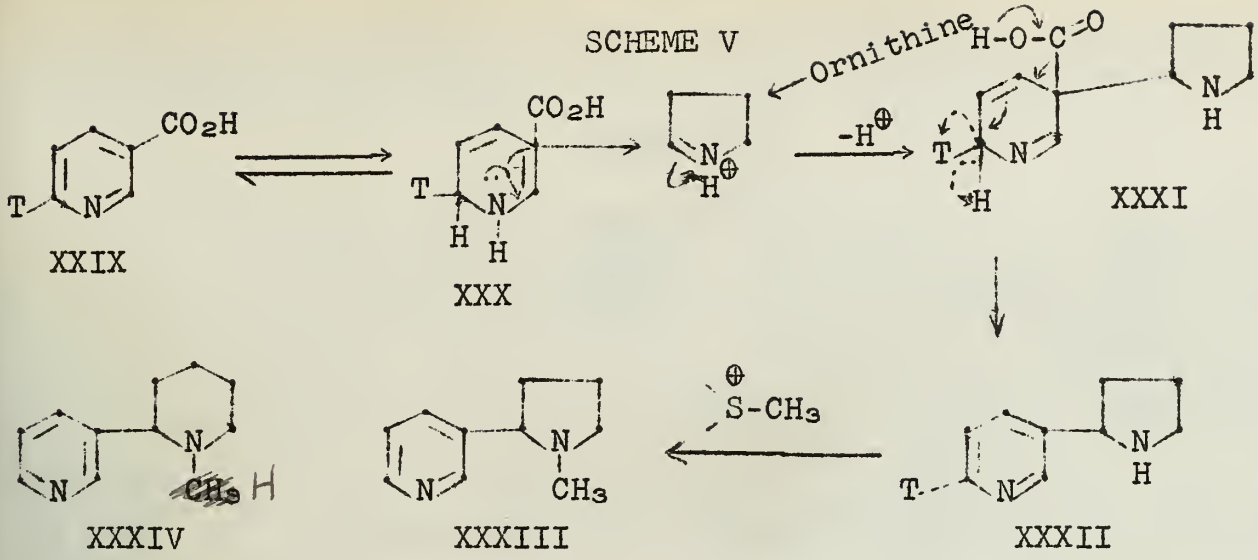
SCHEME IV



give rise to Δ'-piperideine (XXVIII) without randomization of the label. The conversion of lysine could not proceed through free cadaverine, since the label would be randomized in such a symmetrical compound, unless perhaps the cadaverine is bound to the enzyme during its chemical existence in the plant.

The pyridine ring of both anabasine and nicotine has been shown to arise from nicotinic acid (XXIX) (15) with loss of carbon dioxide. In addition, the feeding of four possible nicotinic acids ring-labeled with ^{3}H or ^{2}H showed approximately equal incorporation with acids labeled in the 2,4, and 5 positions, but the acid labeled in the 6 position produced incorporation lessened by a factor of 10. To test the possibility that a 6-pyridone intermediate was formed, 6-hydroxynicotinic acid-^{15}N and 1-methyl-6-oxynicotiniamide-2-^{3}H were administered to excised roots, and found not to be incorporated (17). A possible pathway for the condensation of pyridine and pyrrolidine or piperidine rings to form nicotine or anabasine is shown in Scheme V (18), in agreement with in vitro data (19,20).

SCHEME V

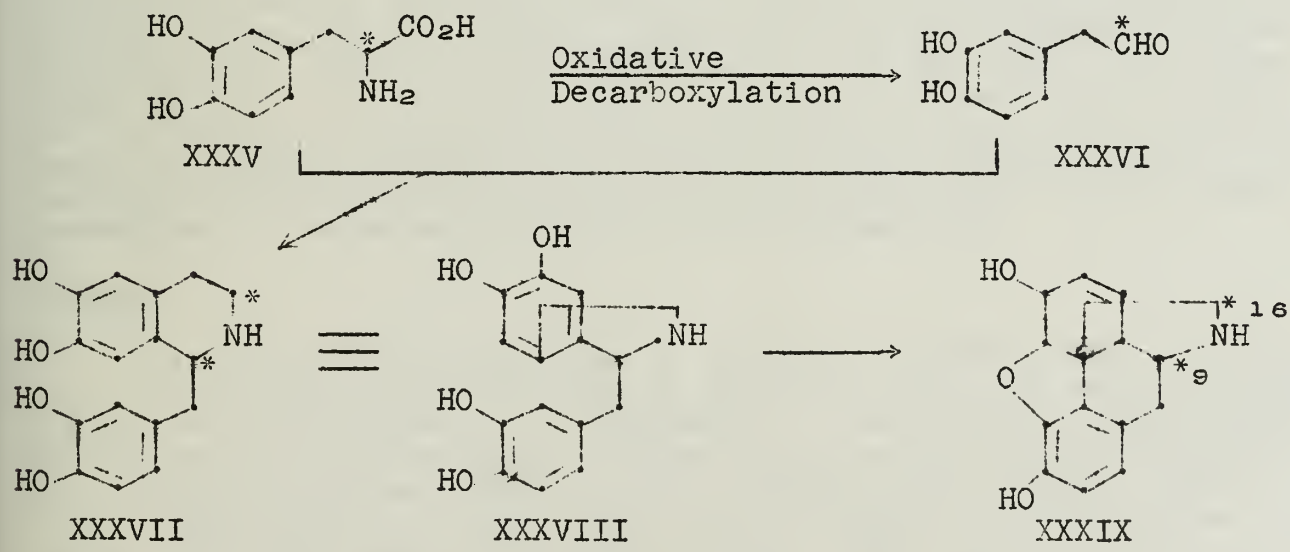


The methyl groups of the non-aromatic rings arise by trans-methylation with methionine (21) and choline (22). The degradation of nicotine and anabasine was accomplished by nitric acid oxidation, producing nicotinic acid. This compound was decarboxylated in boiling quinoline and the carbon dioxide evolved trapped as barium carbonate.

Morphine

Robinson has suggested that the morphine skeleton is formed in the plant by cyclization of norlaudanosine (XXXVII) (2), which is produced by a Mannich reaction in which decarboxylation occurs between 3,4-dihydroxyphenylalanine (XXXV) and 3,4-dihydroxyphenylacetaldehyde (XXXVI), which arises by oxidative decarboxylation of a second molecule of (XXXV). By rotation of the formula it can be seen that two cyclizations, and reduction and dehydration of ring A will give rise to morphine (XXXIX) (Scheme VI).

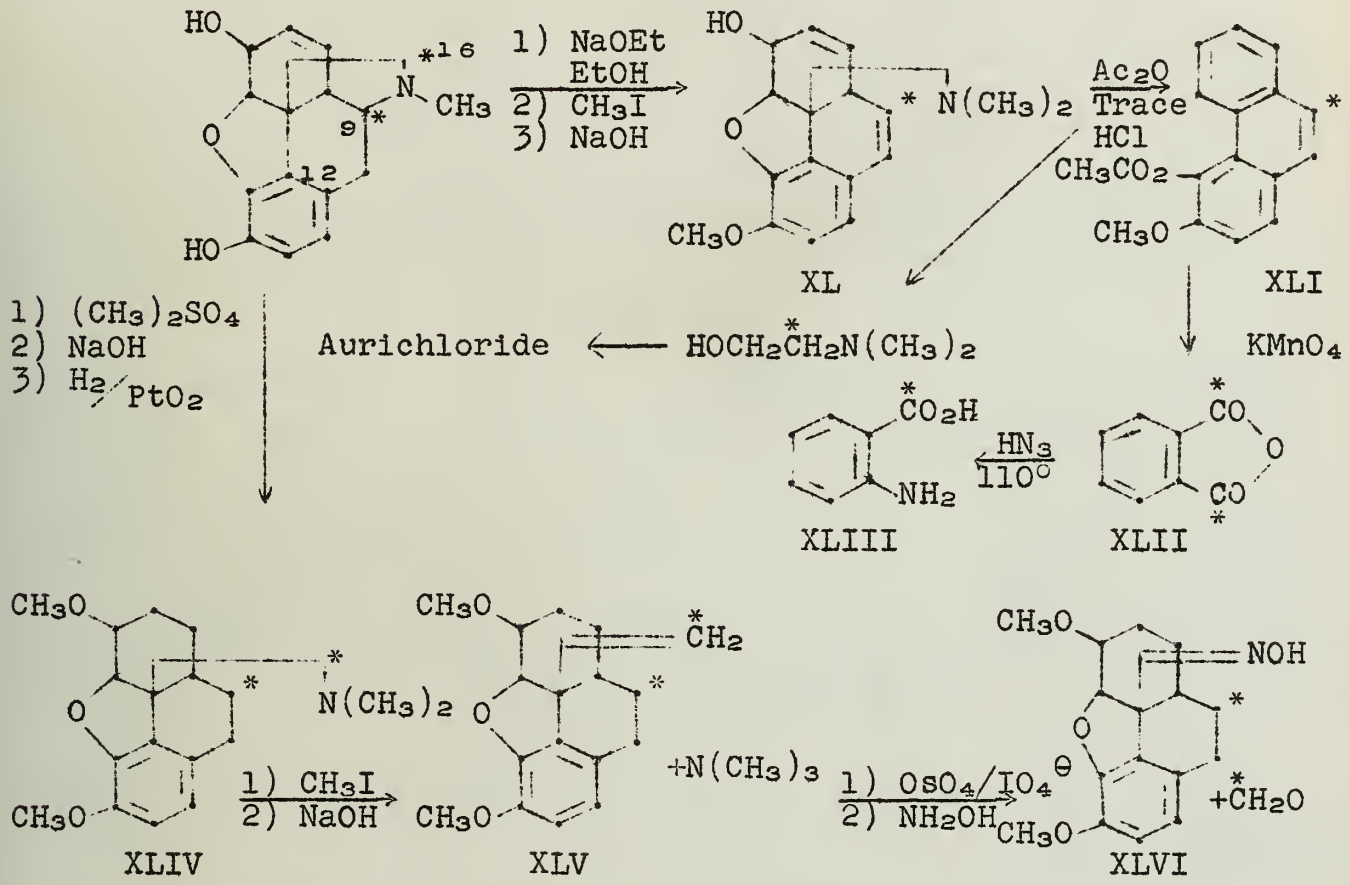
SCHEME VI



If this scheme is correct, then feeding 3,4-dihydroxyphenylalanine -2^{14}C to opium poppies should result in labeling of morphine at C-9 and C-16 (23). In the degradations of Scheme VII, one half of the

activity of the morphine isolated was present in XLI, the other half in the dimethylethanolamine. XLII had an activity equivalent to XLI,

SCHEME VII



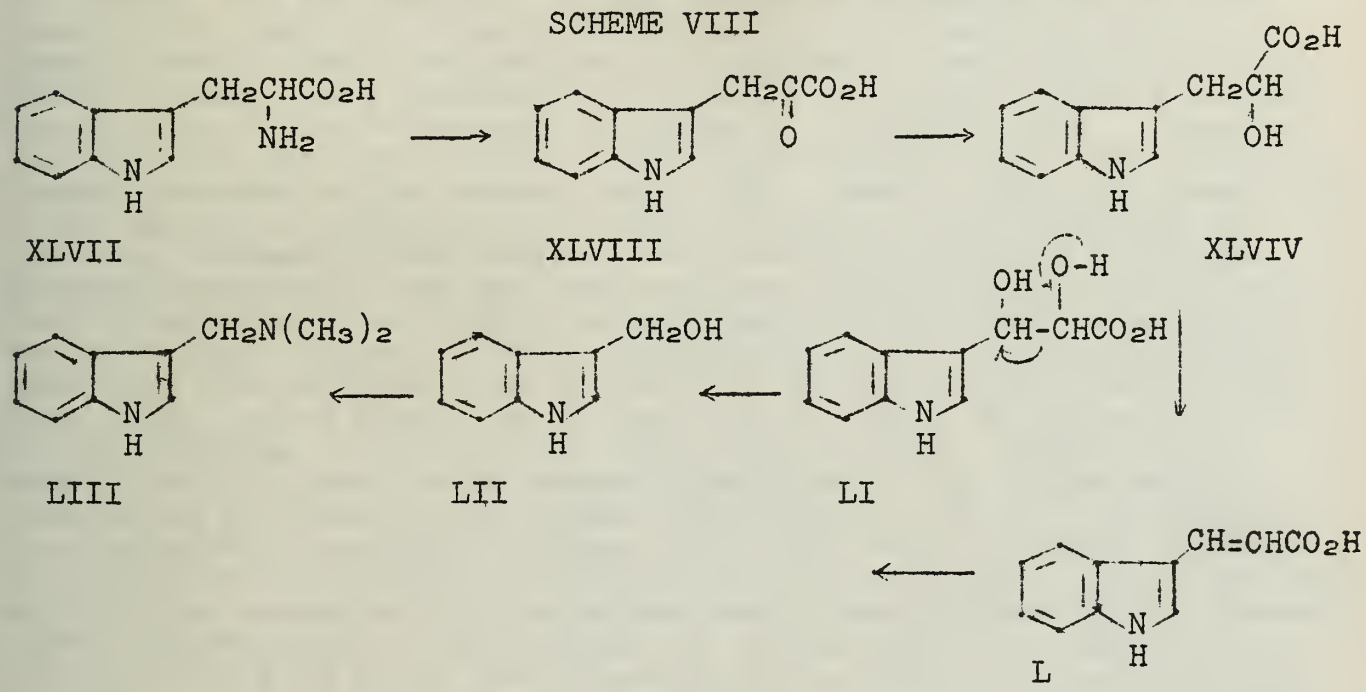
indicating that the carbon atoms lost in this step were inactive. The activity of XLIII was one-half that of XLII which indicates that all the activity of the anhydride was present in the carbonyls with none in the aromatic ring. The second series of degradations involving isolation of formaldehyde (C-16) as the dimedon derivative indicated that one-half of the total activity of morphine was present at C-16 (24). Three possibilities exist, for the other half from these results: a) half the activity at C-9, b) half the activity at C-12, or c) any ratio of activity between C-9 and C-12. Since no known biogenetic scheme could produce specific labeling at C-12, it was proposed that in XLI all the activity was located at C-9, and therefore the experimental data support Scheme VI.

Gramine

Due to the wide occurrence of tryptophan (XLVII) and its metabolites in nature, the biogenesis of gramine (LIII) appeared interesting since if tryptophan is a precursor, a complicated rearrangement of the side chain must occur. When the amino acid labeled in the β-position to the carboxyl was fed to germinating barley, radioactive gramine was produced (25), but it appeared possible that the amino acid could have been hydrolyzed to indole and serine, a reversal of its accepted biogenesis (26). The serine could then have given rise to a one-carbon fragment which could conceivably have been incorporated into gramine. The simultaneous feeding of tryptophans one labeled in the 2 position of the nucleus and a second in

the β-position of the side chain, in a known ratio of activities, produced gramine with the same ratio of activity between the two positions thus demonstrating that cleavage of the side chain at the 3 position had not occurred (27). Administration of 3-indolealdehyde and 3-indolylacetic acid failed to produce active gramine (28). From these results it was supposed that amination necessary for the formation of gramine occurred before the rupture of the side chain, that is on an indolyl compound still containing a three carbon side chain. Such a supposition is supported by the fact that β-(3-indolyl)-acrylic acid (L) and β-(3-indolyl) lactic acid (XLVIX) are known to occur in barley. In subsequent experiments 3-indolyl pyruvic acid-β-C^{14}, and 3-indolyl acrylic acid-β-C^{14} gave rise to radioactive gramine. The following pathway has been proposed in Scheme VIII. The rupture of LI would be an aldolase-type catalysed reaction similar

SCHEME VIII

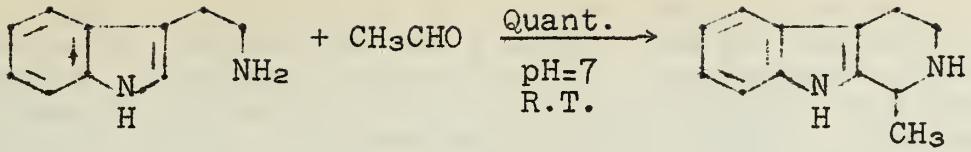


to the cleavage of fructose-1,6-diphosphate. The transformation of LII to LIII must not involve 3-indolealdehyde as an intermediate, but would be a displacement by ammonia or its equivalent on a derivative of the hydroxyl such as phosphate.

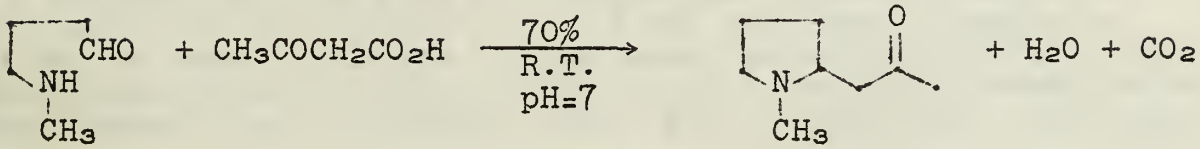
Labeling experiments have been most helpful in elucidation of biogenetic pathways, but in at least one instance ambiguity has arisen in the interpretation of data. Lysergic acid, which has been postulated to arise from tryptophan in all proposed schemes (29), has been isolated from tryptophan-feeding experiments with low incorporation of activity (30,31). Labeling experiments have also been employed with strachydine (31-37) and hyoscyamine (38,39).

BIOGENETIC THEORY

The determination of alkaloid structures has led to a vast body of biosynthetic theory whose main common thesis is the assumed intimate relationship between alkaloid biosynthesis and amino acid metabolism. There have been laboratory experiments patterned after these biogenetic proposals, and conducted under "physiological conditions"(40-43) with and without enzymes. The syntheses of hygrine (LV) and tetrahydroharmane (LIV) are examples. These <u>in vitro</u>



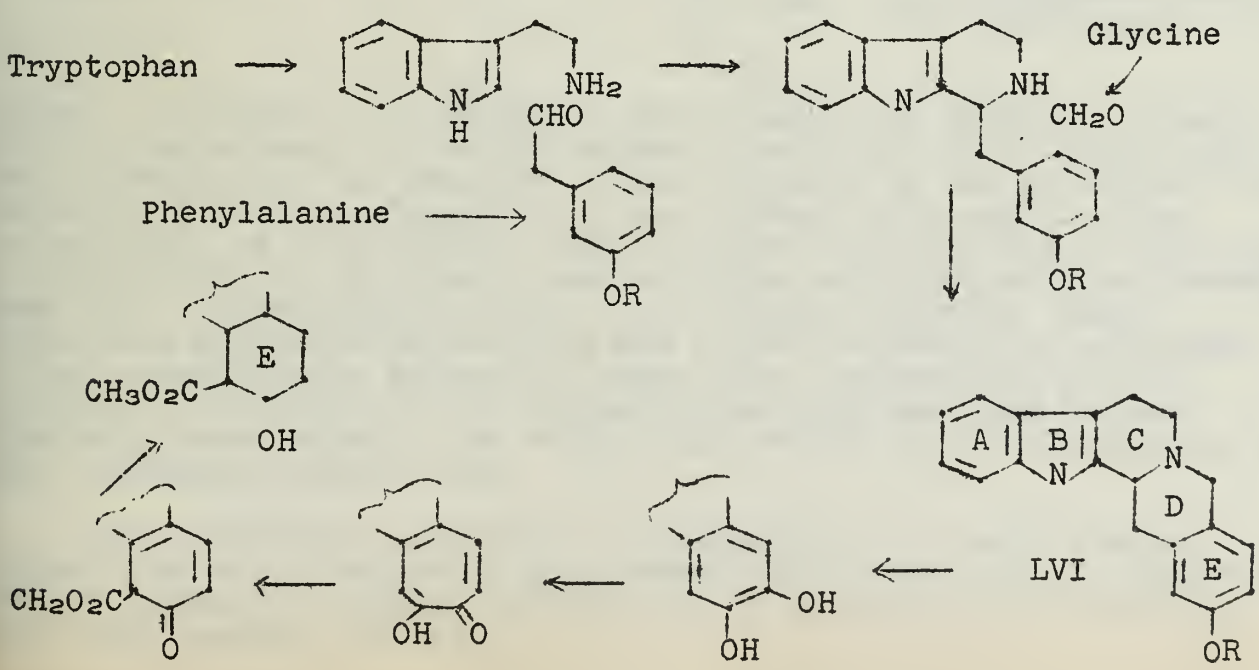
LIV



LV

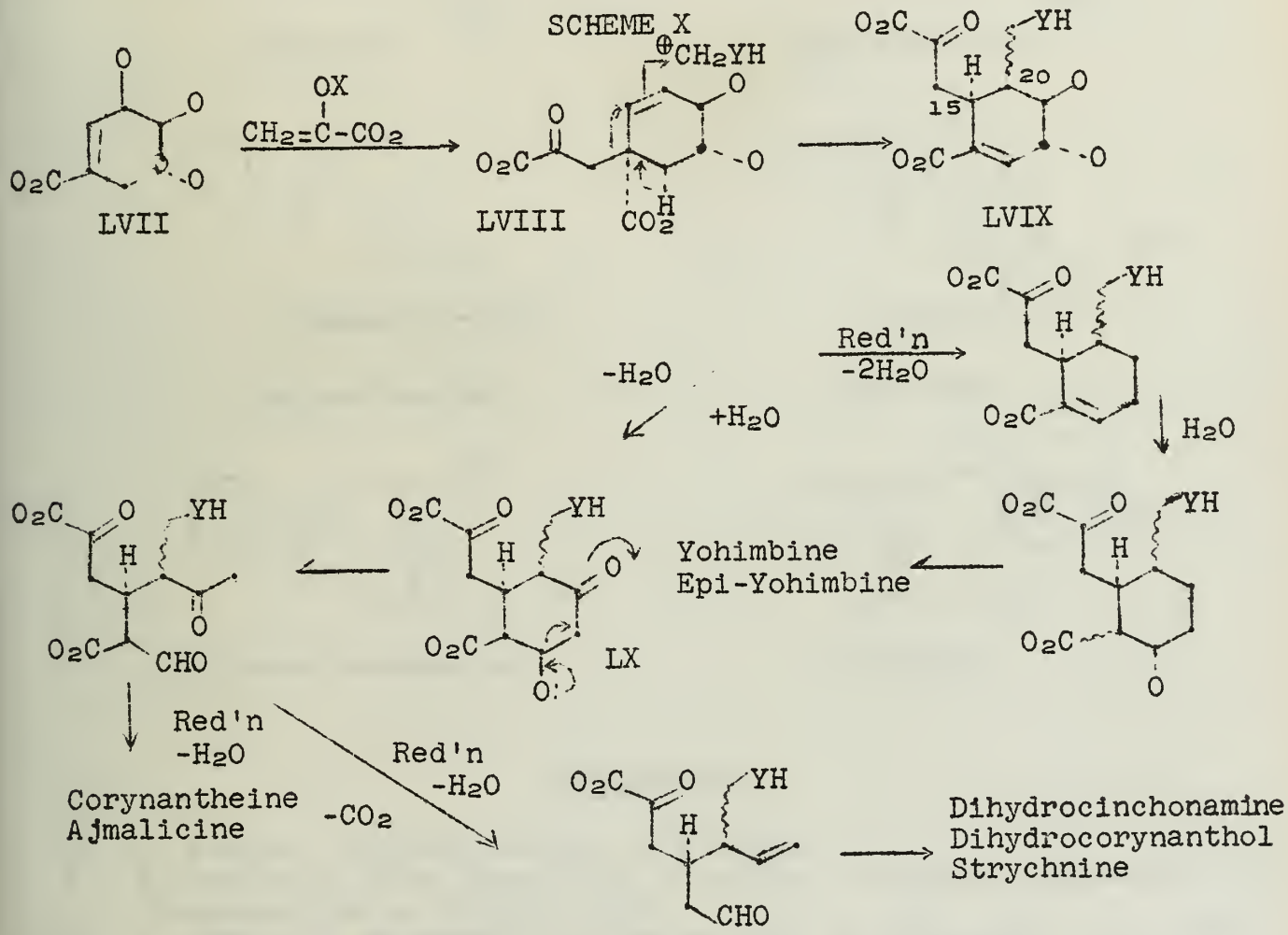
experiments may have nothing to do with the formation of the alkaloids in nature, but the facility of the transformations points out the possibility that the natural reactions may be closely related, although nearly always enzymatically catalyzed. For a long time the alkaloid-amino acid relationship formed a basis for theories attempting to explain the existence of alkaloids in plants (44). Recently the proposal has been made that the structures of many alkaloids depend somewhat on the acetate unit (45). Wenkert (46) has developed a new theory of biogenesis for indole alkaloids incorporating as limiting factors stereochemical considerations, the use of carbohydrate precursors, and the idea that the unique steps involved in the formation of the closely related pentacyclic indole alkaloids occur at later stages in their biogenesis. Stereochemical results show that the configuration of the C(15)-H bond in all alkaloids of this class, where known, is α. Despite the great profusion of stereoisomerism in this class, this unique center, which is non-equilibratible, must be of utmost importance in the biogenesis of indole and phytochemically related alkaloids. For over two decades the pentacyclic yohimbine nucleus (LVI) has been considered to arise in nature by interaction of the amino acids tryptophan, phenylalanine, and glycine according to the Barger-Hahn Scheme (Scheme IX). However, three interdependent difficulties are discernible: a) the state of oxidation of ring E, b) the formation of the absolute configuration at C-15, c) the origin of the carbomethoxy group of ring E (Robinson

SCHEME IX



extension). These deficiencies revolve exclusively around the phenylalanine portion of the skeleta and a substitute for the amino acid seemed required. Compounds satisfying this requirement which have also been shown to be the precursors of phenylalanine in bacteria (47) are shikimic (LVII) and prephenic acids (LVIII). The new theory suggests that the latter could furnish the carbon atoms of ring E and part of ring D of the yohimbe and related alkaloids. A broad scheme has been devised, only a few pertinent examples of which may be shown in Scheme X (the second substituent of all singly bonded oxygen atoms has been omitted so as to avoid differentiation between hydroxyl and O-attached alkyl, acyl, phosphoryl, and enzymic

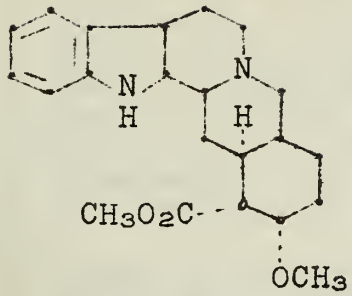
SCHEME X



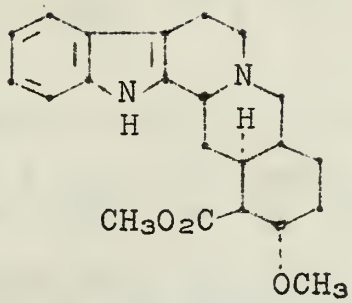
units). In Scheme X is depicted the formation of LVIII by nucleophilic displacement of the C-5 oxygen of shikimic acid (LVII), and then formation of the required stereochemistry at the potential C-15 position in LVIX by migration of the pyruvate side chain. The substituents at C-15 and C-20 can be either cis or trans in LVIX due to interaction of the double bond with the conjugate acid of formaldehyde (Y=O), formaldimine (Y=NH), or N formaltryptamine (Y=NR). Subsequent hydration-dehydration and oxidation reduction processes "in an unpredictable sequential order" and condensation of the pyruvate side chain into C-2 of an indole ring can lead to the alkaloids shown above. The retro-aldo opening of LX is analogous to the "Woodward fission" (48).

Once biogenetic principles are developed to a more advanced degree they can be employed as a useful structural tool by the natural product chemist. Several applications to structural elucidations have been reported (48-51).

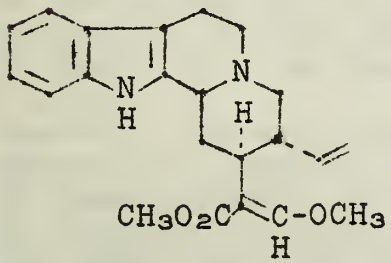
SCHEME XI



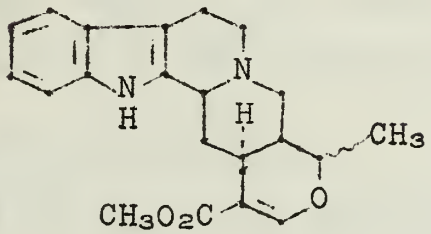
Yohimbine



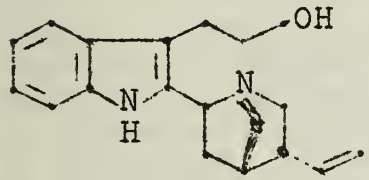
epi-Yohimbine



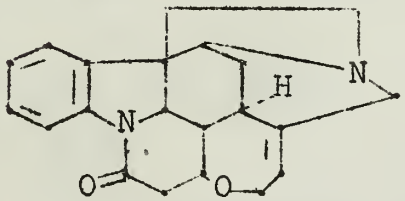
Corynanthenine



Ajmalicine



Dihydrocinchonamine



Strychnine

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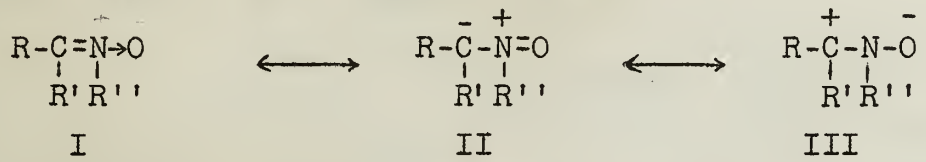
THE CHEMISTRY OF NITRONES

Reported by W. W. Gale March 14, 1960

Quite recently a considerable amount of interest has been placed on the chemistry of nitrones. A review article has been written on the synthesis and reactions of these compounds, but it is rather brief and out-of-date (1). A recent seminar at M. I. T. has, in addition, covered several aspects of the chemistry of the Δ -pyrroline-1-oxides, which represent a class of cyclic nitrones (2).

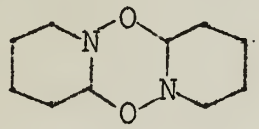
Nitrones have the general formula represented by structure I, and they were so-named because many of their reactions resemble those of carbonyl compounds. The two most important contributing canonical forms of I are II and III; the latter resembling the polar structure written in the case of the carbonyl compounds.



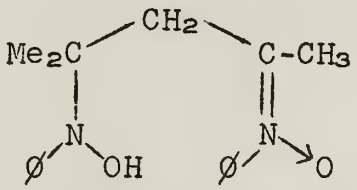
I II III

There are several methods available for the synthesis of nitrones. The interaction of aldehydes and ketones with N-substituted hydroxylamines produces nitrones, and this represents one of the most common methods used. The oxidation of N,N-disubstituted hydroxylamines with a wide variety of oxidizing agents, the most common of which are; mercuric oxide, cupric acetate, oxygen and tetrammine copper (II), and potassium hexacyanoferrate (III) also gives rise to nitrones (3). The synthesis of 5- and 6-membered cyclic nitrones can be carried out very conveniently by the reduction of γ- and δ- nitrocarbonyl compounds with zinc dust and aqueous ammonium chloride (4).

It is interesting to note that aliphatic nitrones in which R and R' are not aromatic nuclei have not been obtained as monomeric species (5). The 6-membered cyclic nitrones have also not been obtained as monomers. For example, Δ'-piperidine-1-oxide has been found to exist as the dimer (IV), and the product of the reaction between acetone and phenylhydroxylamine exists as an "aldol-type" dimer (V), which is usually the case with aliphatic nitrones (5,6). However, it is interesting to note that the 5-membered cyclic nitrones have been reported to be monomeric (4).



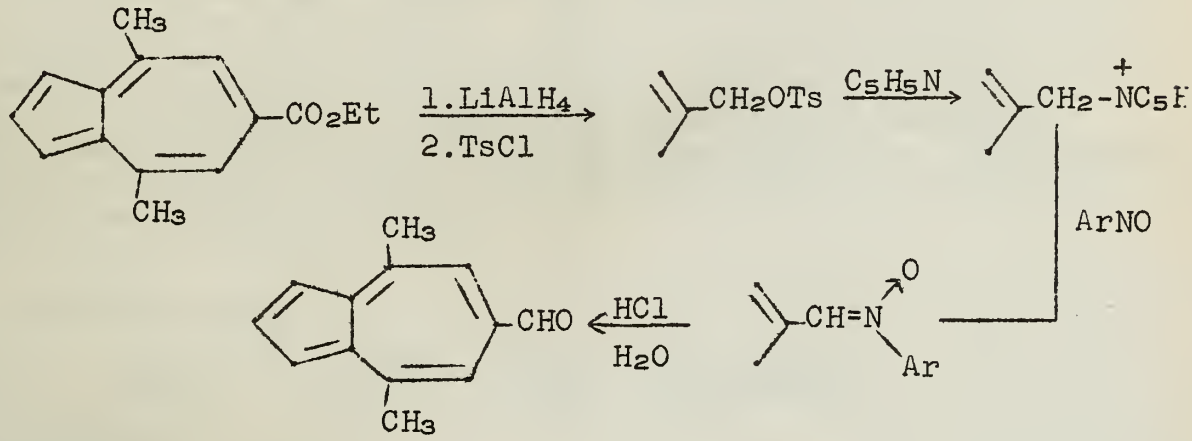
IV



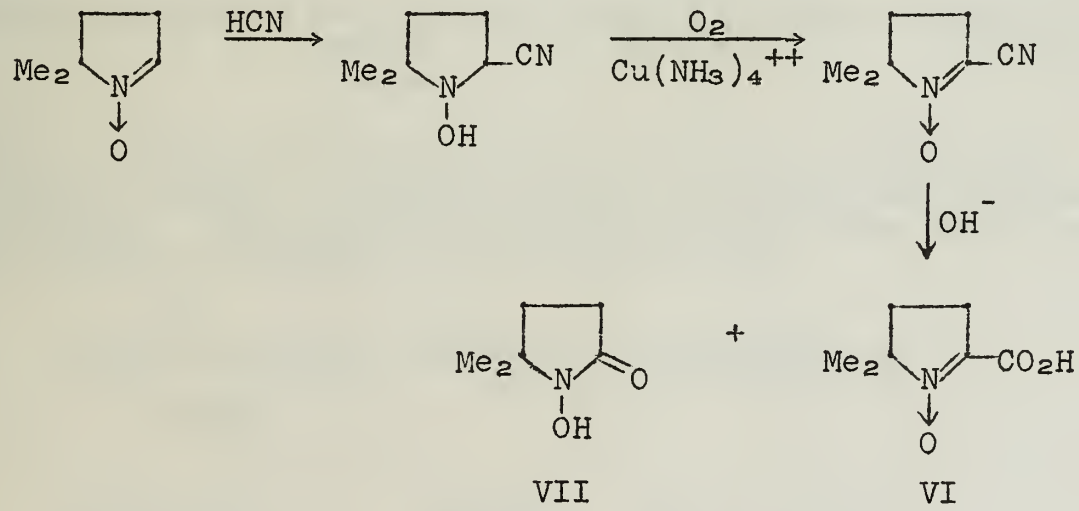
V

The nitrones have very characteristic absorption spectra in both the ultraviolet and infrared regions. Their ultraviolet absorption is in the range 229-235 mμ (ε ~9000), and they exhibit strong infrared absorption in the 1600-1620 cm^{-1} region. In the Δ'-pyrroline-1-oxides it has been observed that an alkyl substituent in the 2-position gives rise to a bathochromic shift in the infrared spectrum, and the absorption is found in the region of 1570-1590 cm^{-1} (5).

One of the characteristic reactions which nitrones undergo is their hydrolysis to the corresponding carbonyl compounds. However, this reaction is very difficult to bring about in the case of the cyclic nitrones (7). A rather interesting synthetic application of the hydrolysis of acyclic nitrones is given in the reaction sequence below in which the ethyl ester of 4,8-dimethylazulene-6-carboxylic acid is converted to the 6-aldehyde in good yield (8).



As stated previously many of the reactions of nitrones are analogous to those of carbonyl compounds. However, addition to the carbonyl function affords a 1,2-adduct whereas in the case of nitrones a 1,3-adduct is isolated. One example of the 1,3-additions which nitrones undergo is found in the synthesis of a 5,5-dimethylnitrone derivative of the amino acid, proline (VI) (5).

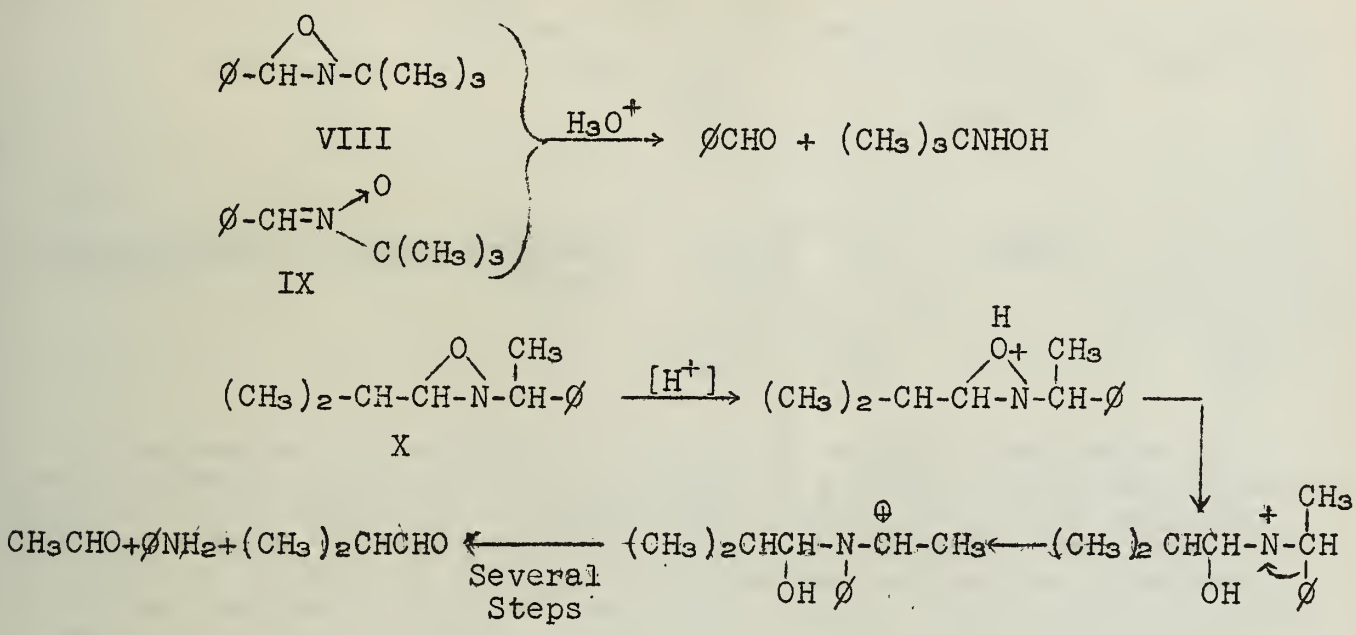


Compound VII probably arose through the displacement of cyanide by hydroxyl as in the case of acyl cyanides. The structure of the cyclic hydroxamic acid, VII, was confirmed by its synthesis from the reduction of methyl 4-methyl-4-nitropentanoate with zinc dust and aqueous ammonium chloride.

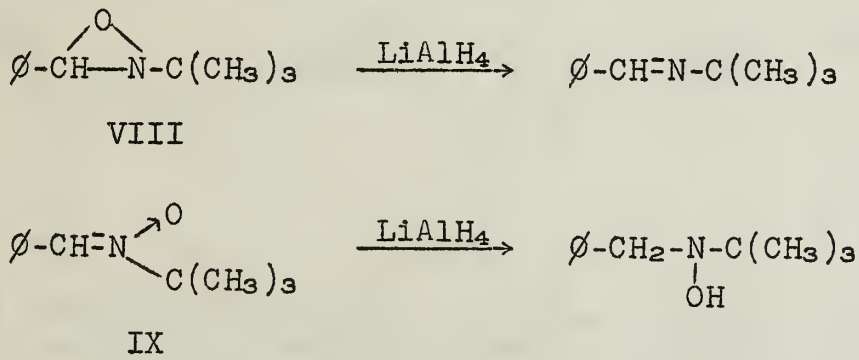
Recent work on the irradiation of nitrones has revealed that they are converted to oxazirans (9,10,11). The oxazirans are isomeric with their nitrone precursors and represent an unusual type of compound since they contain 3-membered rings in which each of the atoms

is different. Previous methods available for the synthesis of oxazirans include the oxidation of imines with organic peracids and hydrogen peroxide (12,13). It has also been observed that in many cases the original nitrone can be obtained from oxazirans by the application of heat (14).

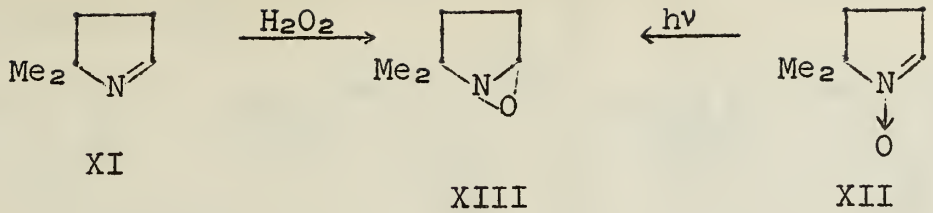
The oxazirans are extremely reactive compounds. Upon hydrolysis they usually afford the same products as their corresponding nitrones, but rearrangements are not uncommon. Thus, the acid hydrolysis of 2-t-butyl-3-phenyloxaziran (VIII) and benzal-t-butylnitrone (IX) both yield benzaldehyde and t-butylhydroxylamine. However, the acid hydrolysis of 2-α-phenethyl-3-isopropyloxaziran yields rearranged products presumably through the mechanism presented below. The corresponding nitrone, however, affords the expected products, isobutyraldehyde and α-phenethylhydroxylamine.



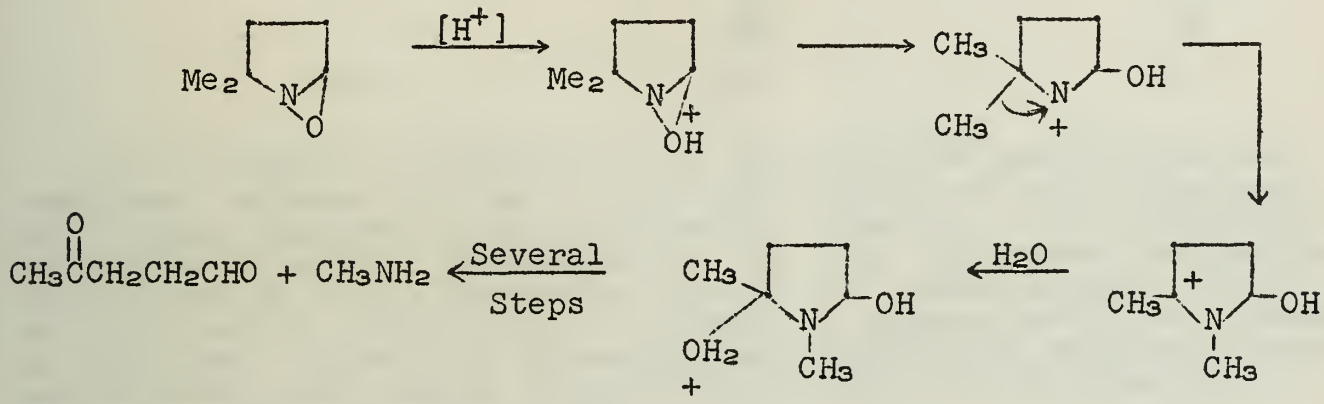
Another striking difference in the reactivity of oxazirans and their isomeric nitrones is noted in their reduction with lithium aluminum hydride. The oxaziran is reduced to the imine while the less reactive nitrone is reduced to the hydroxylamine.



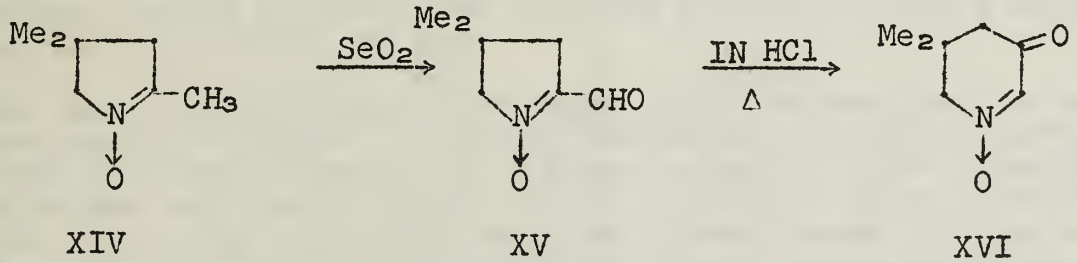
Bicyclic oxazirans have also been prepared by irradiation of cyclic nitrones or by oxidation of cyclic imines with hydrogen peroxide. Thus, 5,5-dimethyl-Δ'-pyrroline (XI) and 5,5-dimethyl-Δ'-pyrroline-1-oxide (XII) have been converted to the oxaziran, XIII (15).



Treatment of the oxaziran, XIII, with dilute acid causes its rearrangement to laevulaldehyde, isolable as its bis-2,4-dinitrophenylhydrazone, and methylamine. A possible reaction scheme analogous to the rearrangement of X is given below.

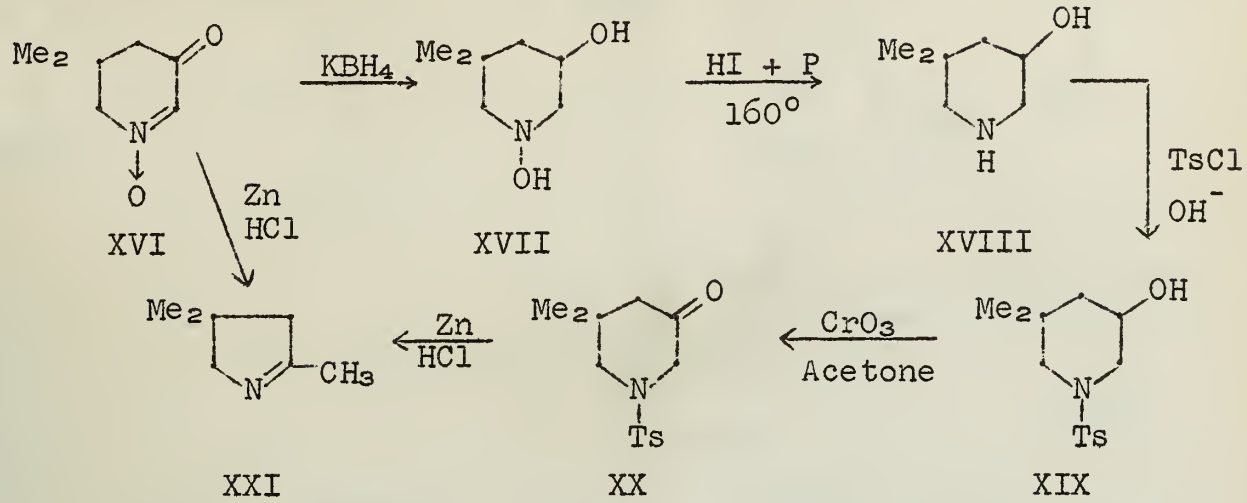


Another well-recognized reaction of carbonyl compounds is their oxidation with selenium dioxide to α-dicarbonyls. Upon treatment of 2,4,4-trimethyl-Δ'-pyrroline-1-oxide (XIV) with selenium dioxide a dark oil was isolated. The infrared spectrum of this oil as well as its ability to give carbonyl derivatives is consistent with the proposed structure (XV) (16). When XV was heated with one normal hydrochloric acid, a crystalline isomer was isolated and assigned structure XVI on the basis of spectral evidence. The infrared spectrum of XVI showed strong bands at 1653 and 1546 cm^{-1} which could be attributed to a carbonyl and a nitrone group in conjugation with one another.

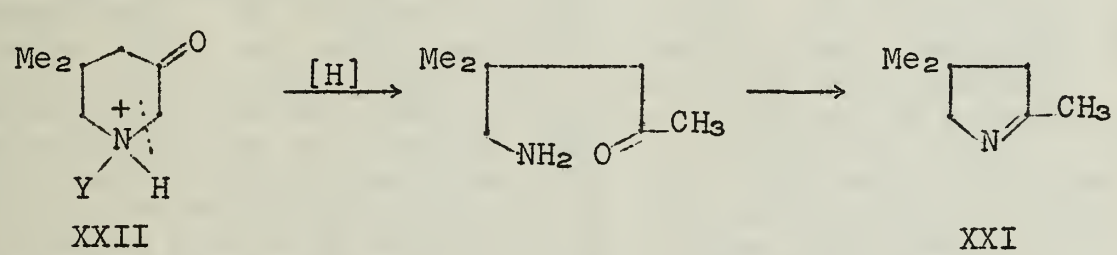


When a Clemmensen reduction of XVI was carried out, the product was found to be 2,4,4-trimethyl-Δ'-pyrroline (XXI). It is interesting to note that this would be the product expected from XV and not XVI. In order to investigate this reaction more fully, XVI was reduced with aqueous potassium borohydride to give the expected β-hydroxyhydroxylamine (XVII), which when treated with phosphorus and hydriodic acid at 160°C. gave rise to the known compound, 5-hydroxy-3,3-dimethylpiperidine (XVIII). The N-tosylate derivative was formed, and then it was oxidized to the keto derivative, XX.

Treatment of XX under Clemmensen conditions again gave the ring-contracted product, XXI.

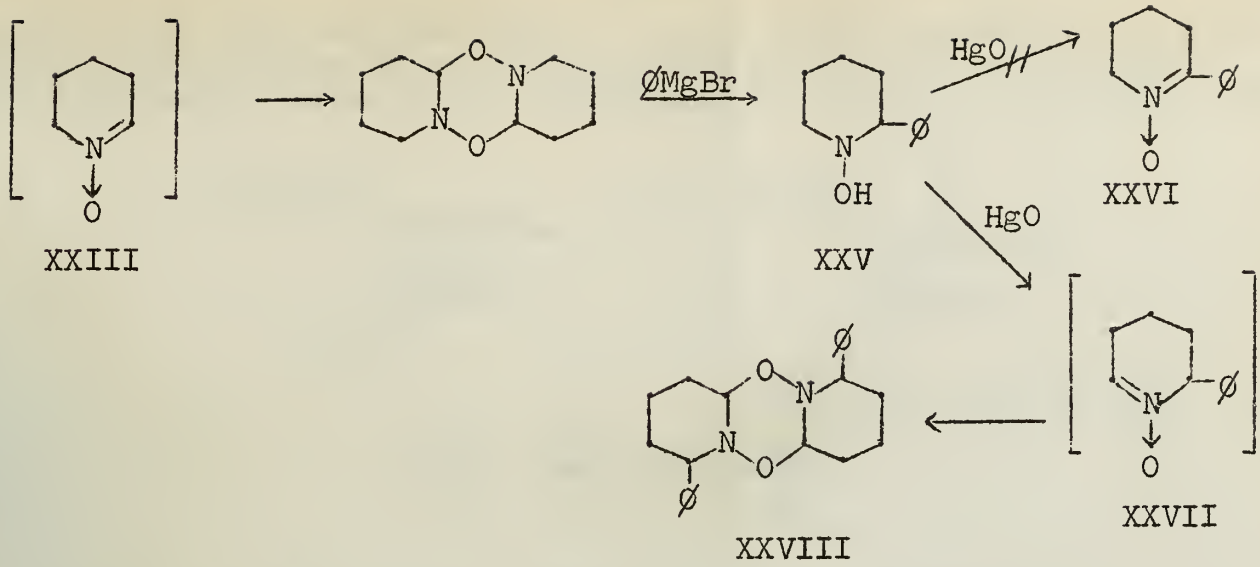


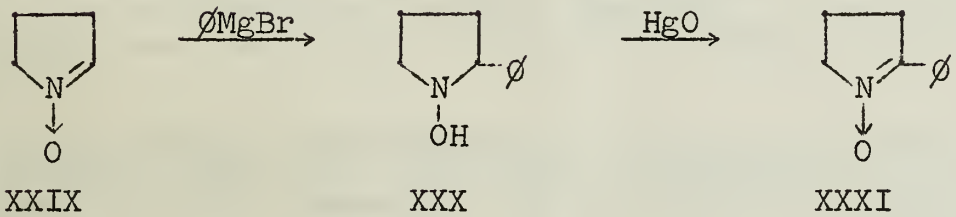
The formation of the base (XXI) from both XVI and XX provides additional evidence for the formulation of XVI, and both reductions are further examples of ring contraction observed in the Clemmensen reductions of cyclic, α-aminoketones (17,18). The common intermediate is believed to be the protonated form of the ketopiperidine (XXII), with Y= H or Ts, which would be expected to undergo reductive cleavage as indicated. After this cleavage has occurred, the resulting aminoketone could then undergo cyclization with the loss of water to yield the observed product, XXI.



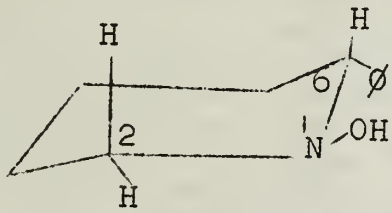
The fact that hydrogenolysis of the N-O bond in XVI occurs rapidly is further supported by the observation that two moles of hydrogen are absorbed rapidly while the third mole (causing reduction of the ketone to the alcohol) was absorbed much more slowly when XVI was catalytically reduced to XVII.

Some rather interesting differences exist between the 5- and the 6-membered cyclic nitrones. All the 5-membered ones which have been synthesized have been found to be monomeric, but all the 6-membered ring homologues have been found to exist as dimers under identical conditions (19). The following reaction scheme shows this as well as another noticeable difference between the two ring homologues.





The other difference can be seen in the dehydrogenation of the cyclic hydroxylamine (XXV) with mercuric oxide. The product that was isolated was not the expected nitrone, XXVI, but the dimer of the nitrone XXVII. In contrast to this behavior, the 5-membered cycli hydroxylamine (XXX) was dehydrogenated under the same conditions to give the expected nitrone (XXXI) (20). This difference could be explained on the basis of a steric argument. The cyclic hydroxylamine (XXV) probably has the conformation XXXII in the ground state in which both substituents occupy equatorial positions. The axial hydrogen atom at C-6 is more hindered than the equatorial one at C-2. After the elctrophilic attack by mercuric oxide at the 1-position and the loss of a hydrogen atom from the hydroxyl group have taken place, the equatorial hydrogen at C-2 is removed; and the products, mercurous oxide and the cyclic nitrone, XXVII, which dimerizes spontaneously, are formed.

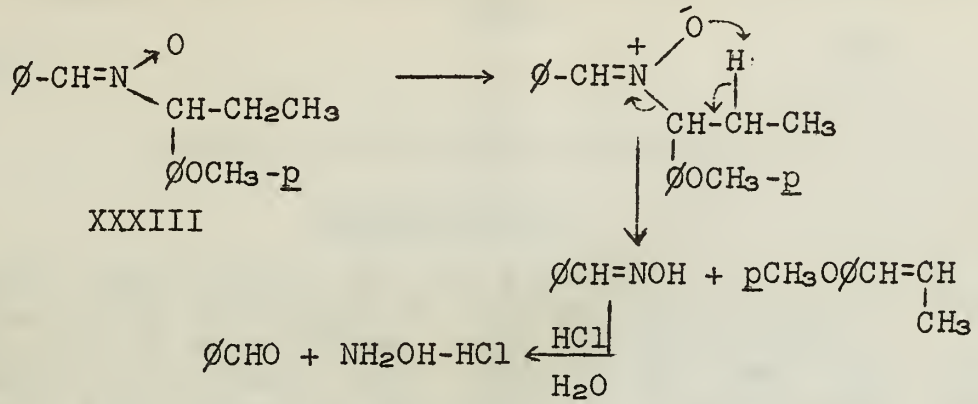


XXXII

In the case of the 5-membered cyclic hydroxylamine (XXX), however, the situation is quite different. The hydrogen atoms at C-2 and C-5 are both about equally accessible, but the hydrogen atom at C-2 is activated by the phenyl group and its removal gives rise to the observed nitrone in which there is present a conjugated system.

It has been reported that N-α-(p-methoxyphenyl)-propylbenzaldoxim (XXXIII) when heated with concentrated hydrochloric acid gave rise to anethole, hydroxylamine hydrochloride, and benzaldehyde (21). It was

thought that this reaction might be quite similar mechanistically to that proposed for the thermal decomposition of N,N-dimethyl-(α-phenethyl)-amine oxide into N,N-dimethylhydroxylamine and styrene (22).

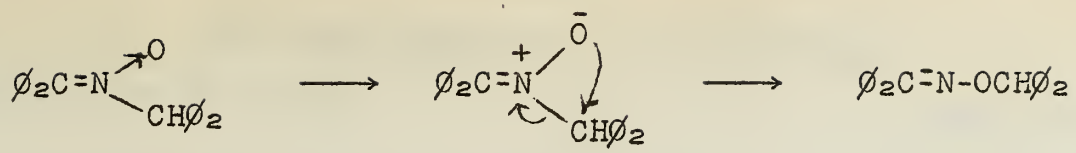


Since it had been found that amine oxides undergo thermal rearrangement to the corresponding O-alkyl compounds, it was decided to see if the nitrones would behave in a manner analogous to that cited above (23).

It was found that the rearrangement of the nitrone (XXXIV) to the O-alkyl compound (XXXV) was essentially quantitative at the end of one-half hour at 200°C. Moreover, it was possible to conduct this rearrangement in diethylcarbitol and to follow the kinetics of this reaction by determining the decrease in absorption of XXXIV at 310 mμ. in the ultraviolet spectrum.

It was found that the reaction followed first order kinetics. The activation energy was determined to be 40 kcal/mole, and the entropy of activation was found to be 13.6 e.u. The large positive entropy of activation can be explained in two ways. The first, and slightly more plausible, way is that the nitrone is more highly solvated than the less polar activated complex, in which the combined solvent molecules have been lost, at least in part, resulting in a less rigid structure for the transition state. A second explanation is that the benzhydryl group becomes detached as a carbonium ion in the transition state, which would give rise to an increase in the number of translational degrees of freedom in the transition state, and hence a positive entropy of activation. The latter explanation is not as likely as the first since the analogous rearrangement of benzylmethylaniline oxide to O-benzyl-N-methyl-N-phenylhydroxylamine can be carried out in the presence of aqueous sodium hydroxide without the formation of any benzylalcohol (24).

The fact that the rearrangement of XXXIV to XXXV follows first order kinetics and does not proceed <u>via</u> a carbonium ion mechanism provides evidence that the reaction is intramolecular. The transition state would then be essentially a 3-membered ring in which the benzhydryl group becomes bound to oxygen at virtually the same time that it becomes detached from nitrogen as shown below.



XXXIV XXXV

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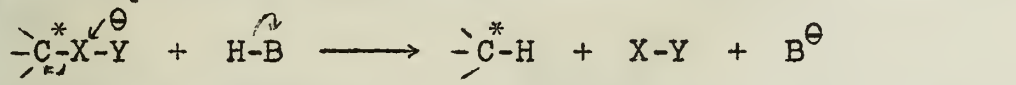
THE STEREOCHEMISTRY OF SE1 REACTIONS

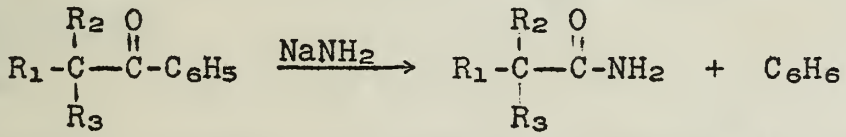
Reported by D. F. O'Brien March 21, 1960

Until recently the stereochemistry of non-organometallic electrophilic substitution has not been studied systematically. In nucleophilic substitution considerable work has shown that a carbonium ion mechanism may lead to retention, inversion, or racemization, depending in part on the solvent. It might also be expected that carbanions are subject to effect of the solvent. In this seminar the stereochemistry of carbanions will be discussed. The reactions studied may be formulated

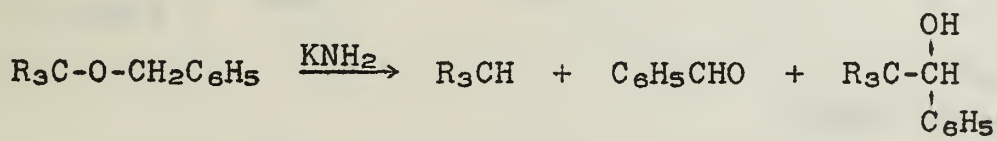


where XY is the leaving group, HB the electrophile and C the seat of substitution. In most cases X is a carbon and Y an oxygen atom. The compound cleaved is then either an alcohol or ketone. Cleavages of secondary or tertiary alcohols by bases to yield a hydrocarbon and aldehyde or ketone, respectively, have been known since 1890 (1). A recent use of the reaction is the cleavage of 1,2,2,2-tetraphenyl ethanol to give triphenyl methane and benzaldehyde (2). The base was sodium ethoxide, and the yields were 50 and 72% in the two solvents ethanol and benzene, respectively.

It has been known since the first of this century that non-enolizable ketones may be cleaved by sodium amide to yield a hydrocarbon and an amide (3). The reaction generally goes as shown, if R_1, R_2 and R_3 are small alkyl groups. However, the larger the number of carbons in the Rs the more benzamide will be produced.



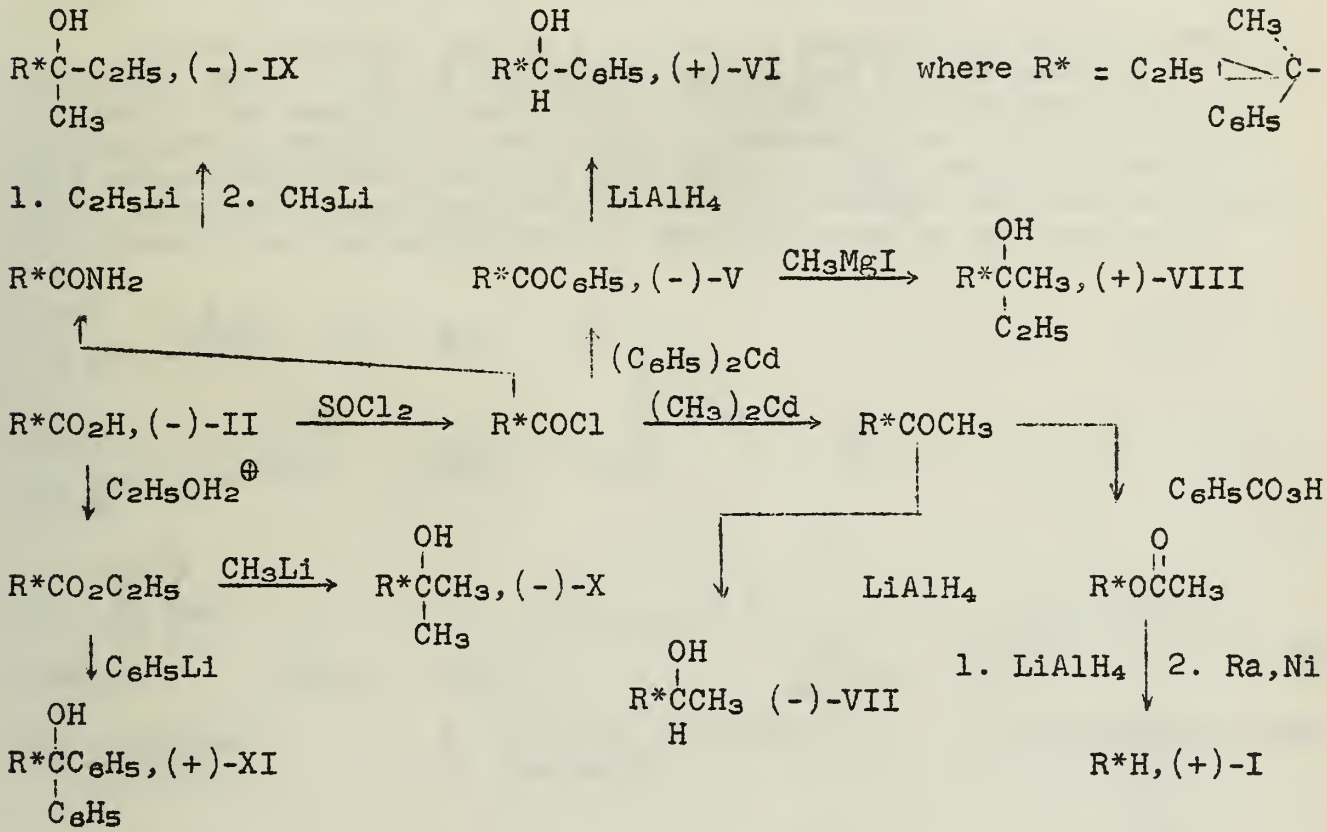
This reaction is synthetically useful in making amides, and has been reviewed (4,5). Ketones may also be cleaved by alcoholic bases. This reaction proceeds in the same manner as above. In the case of trityl ketones, triphenyl methane is obtained in 80 to 90% yield (7). In some cases X is an oxygen and Y a carbon atom, and the reaction is a base catalyzed cleavage of an ether. This type of cleavage of benzyl ethers has been known since 1905 (8), and has recently been studied (9,10). The products of such a cleavage are a hydrocarbon, benzaldehyde, and also an alcohol, which is a rearrangement product.



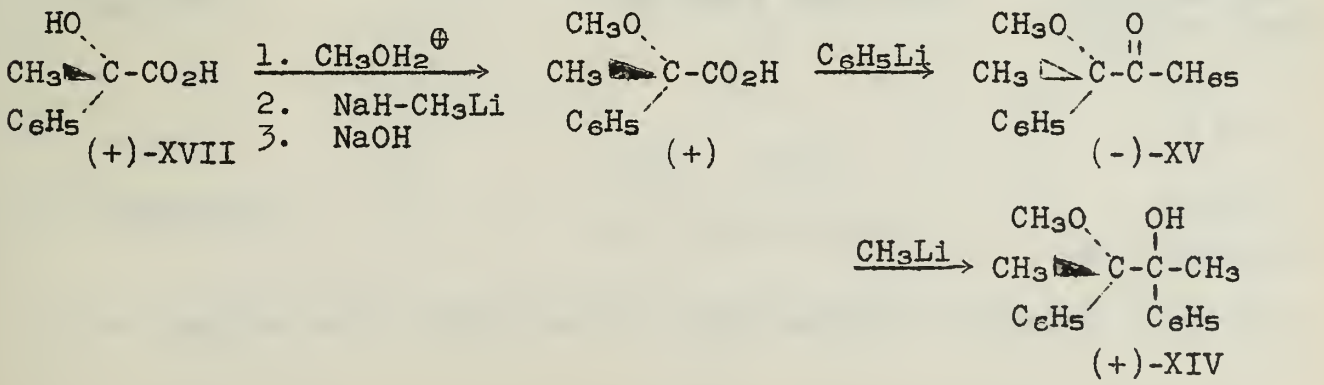
In any stereochemical study the knowledge of the relative configurations of reactants and products is a prerequisite. In the reactions to be discussed the seat of substitution has ethyl, phenyl and either methyl or methoxyl groups attached to it. Therefore, the cleavage product is either 2-phenylbutane or 1-methoxy-

1-phenylethane. The majority of the compounds used in the studies were prepared from optically active isomers of 2-methyl-2-phenylbutanoic acid (II), the absolute configuration of which has been assigned (11). The absolute configuration of 2-phenylbutane (I) has also been established (12,13). In Chart 1 the various stereospecific routes to the starting materials and a route relating the configurations of I to II are shown.

Chart 1 (14)

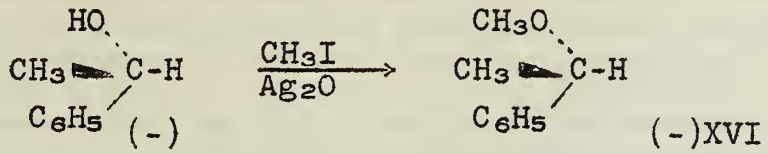


The tertiary alcohol (+)-2-phenyl-2-butanol (15) was converted to (-)-2-benzyloxy-2-phenylbutane (16). Both of these compounds have the same configuration as (+)-2-phenylbutane (12). The compounds, (+)-2,3-diphenyl-3-methoxy-2-butanol (XIV), a diastereomeric mixture configurationally homogeneous at the seat of substitution, and (-)-1,2-diphenyl-2-methoxy-1-propanone (XV), were prepared from optically pure atrolactic acid (XVII) as follows (17).



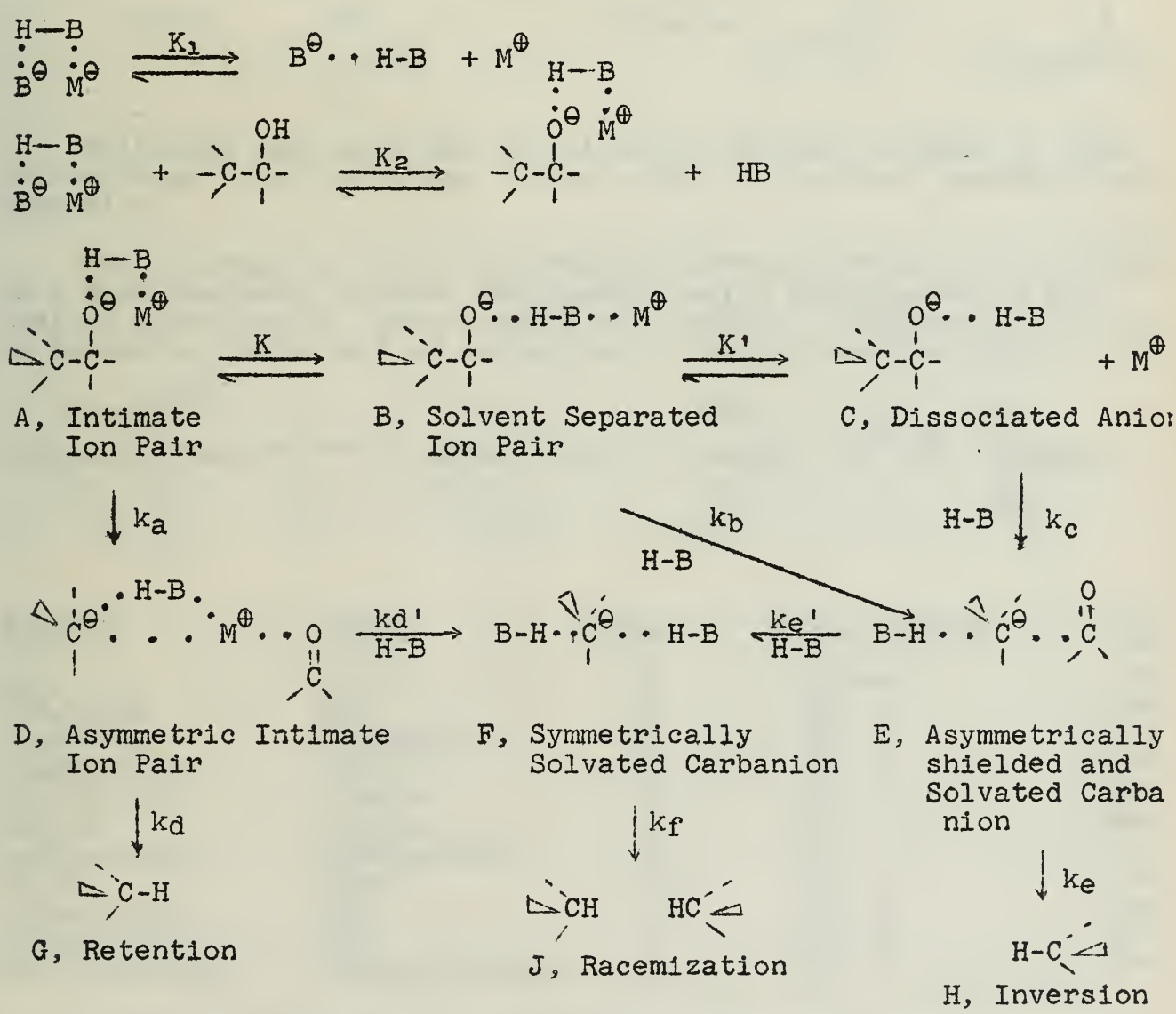
The absolute configuration of 1-methoxy-1-phenylethane (XVI), the product of the cleavages of XIV and XV, has been shown by Mislow (19)

Cram prepared optically pure (-)-XVI (20), from (-)-α-phenylethanol whose configuration was assigned as shown (21).



PROPOSED MECHANISM OF BASIC CLEAVAGE OF ALCOHOLS

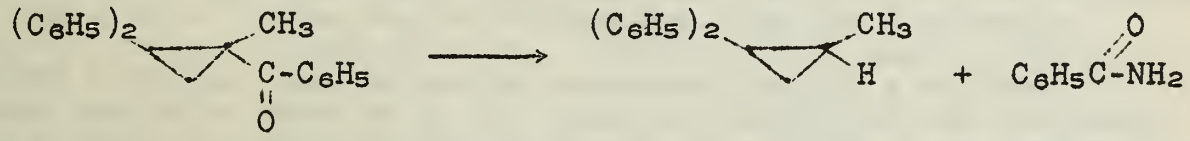
In the reaction medium a series of equilibria may be postulate as shown below. HB is the electrophile and $M^{\oplus}$ the metal ion. Because of the usually rapid rates at which acid-base and salt dissociation reactions occur, it is assumed that these equilibria are established more rapidly than the cleavage reaction occurs. This chart also includes the mechanistic scheme proposed by Cram (2 to account for the experimental results about to be discussed.



Three species which might undergo cleavage are included, A,B, and C.

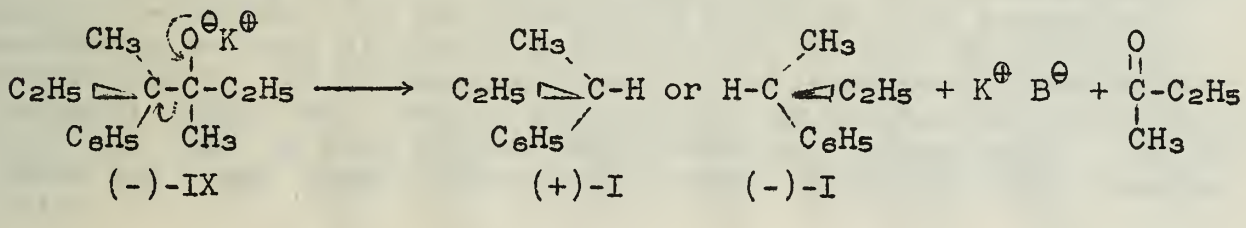
STEREOCHEMICAL STUDIES

The ketones and alcohols shown in Chart 1, Nos. V to XI, were all cleaved in N-methylaniline with potassium N-methylanilide to give 2-phenylbutane (I) of retained configuration (14). The tertiary alcohols were found to cleave at a low temperature, and under conditions where I was optically stable. The ketones cleaved at higher temperatures, and I was found to partially racemize at these temperatures with the base and electrophile used. Because the alcohols cleaved more easily, the various experiments to determine the effect of solvent, temperature, leaving group, etc. on the stereochemistry were run using alcohols. Previous to the work of Cram, the cleavage of (-)-1-benzoyl-1-methyl-2,2-diphenylcyclopropane α_D^{24} -32.5°, by heating with sodium amide in toluene was reported by Walborsky (23). The products were (+)-1-methyl-2,2-diphenyl cyclopropane and benzamide, however the relative configuration of these two compounds is not known at present.



Walborsky felt that the retention of optical activity in this Haller Bauer reaction, might indicate that a concerted mechanism was operative.

The cleavage of (-)-3,4-dimethyl-4-phenyl-3-hexanol (IX), which is a diastereomeric mixture configurationally homogeneous at the seat of substitution, was examined in a number of different solvents to determine the effect of solvent on the steric course (24).



Solvent	Base	% Yld. I	% opt. purity	ϵ^{oC}
C_6H_6	KOtBu	41	93 Ret	2^{20}
$(CH_3)_3COH$	KOH	76	89 "	6^{20}
$C_6H_5NHCH_3$	$C_6H_5NKCH_3$	41	89 "	11^{19}
$CH_3CHOHC_2H_5$	KOs-Bu	61	85 "	19^{20}
$CH_3(CH_2)_3OH$	KOn-Bu	54	72 "	18^{25}
C_2H_5OH	KOC_2H_5	91	60 "	27^{20}
$H_2NCH_2CH_2NH_2$	$KNHCH_2CH_2NH_2$	57	19 "	16^{18}
CH_3OH	$KOCH_3$	79	11 "	34^{18}
$O(CH_2CH_2OH)_2$	KOH	71	23 Inv.	35^{20}
$HOCH_2CH_2OH$	KOH	6	48 "	35^{20}
$HOCH_2CHOHCH_2OH$	$KOCH_2CHOHCH_2OH$	38	50 "	46^{20}

The product 2-phenylbutane (I) was determined to be optically stable under the conditions of the experiments, except in the case of ethylenediamine as solvent. In that case, I racemized 4%. Therefore, the % optical purity of the product in ethylenediamine is minimal. In this case part of the starting material was isolated before the reaction went to completion and was found to have retained

its optical activity, which indicates that racemization of I did not take place through a reversal of the first step to give racemic reactant. In the above cleavages of IX, the temperature was varied but not enough to greatly affect the steric course. Its effect will be examined later.

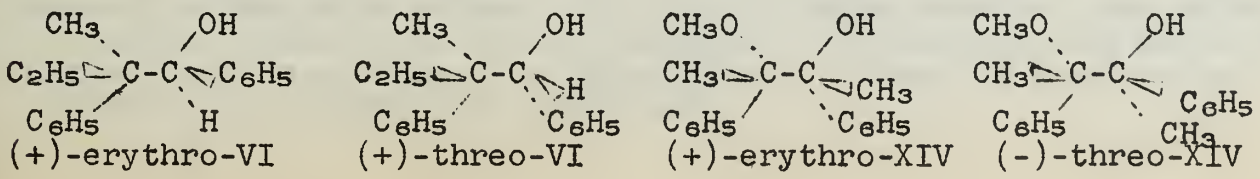
As noted from the results above, there is a definite solvent effect, to the extent of changing the predominate steric course from 93% retention to 51% inversion. Similarly the cleavages of (-)-2,3-dimethyl-3-phenyl-2-pentanol (X), (+)-2,3-diphenyl-3-methyl-2-pentanol (VIII), (+)-3-methyl-3-phenyl-2-pentanol (VII), and (+)-1,2-diphenyl-2-methyl-1-butanol (VI) in representative solvents, dioxane, t-butyl alcohol, methanol, ethylene glycol and diethylene glycol, indicated a dependence of steric course on solvent.

The results indicate the possibility of two mechanisms, one which occurs with retention and the other which occurs with inversion, or three mechanisms, the first two plus one that occurs with racemization. The steric course may be correlated with the dielectric constant of the particular solvent. The fact that such a correlation exists may indicate that inversion proceeds through a solvent separated ion pair, such as B, but does not establish its existence. This is a rough correlation due to temperature differences in the reactions, and the fact that the dielectric constant is temperature dependent.

The effect of temperature on the steric course was investigated in dioxane, methanol, and ethylene glycol. In dioxane (+)-2,3-diphenyl-3-methoxy-2-butanol (XIV) was cleaved with potassium t-butoxide as base at 100°, 125°, 150° and 180° with the results being 95, 84, 77, and 69% retention, respectively. (-)-3,4-Dimethyl-4-phenyl-3-hexanol (IX) was cleaved in methanol with potassium methoxide as base at 180° and 210° giving 25 and 9% inversion, respectively. In diethylene glycol (+)-2,3-diphenyl-3-methyl-2-pentanol (VIII) was cleaved with potassium diethylene glycoxide at 150° and 180° to give 60 and 54% inversion, respectively. In all cases the lower temperature gave the more stereospecific results (20).

Earlier it was pointed out that there are either two mechanisms operative, retention and inversion, or three mechanisms, the above two plus a separate one for racemization. To explain the temperature effect by the first possibility the k_{ret}/k_{inv} ratio would have to have a temperature coefficient that changes sign with the nature of the solvent, because in dioxane k_{ret}/k_{inv} decreases as the temperature increases, while in glycol k_{ret}/k_{inv} increases as the temperature increases. This does not seem as plausible as three paths, in which the racemization mechanism becomes more important at higher temperatures.

Both (+)-2,3-diphenyl-3-methoxy-2-butanol XIV and (+)-1,2-diphenyl-2-methyl-1-butane (VI) are diastereomeric mixtures. The (+)-erythro-VI, (+)-threo-VI, (+)-erythro-XIV, and (-)-threo-XIV were prepared and the cleavages of these diastereomers studied (25).



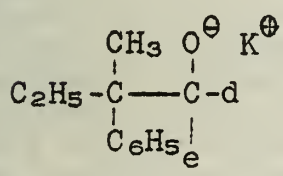
Both XIV and VI were cleaved in dioxane with potassium t-butoxide, and in glycol with the potassium salt of the glycol as base. Because VI is a secondary alcohol, and equilibration of diastereomers may occur, a control run was conducted at 200°. It indicated that cleavage occurs much faster than equilibration. The starting material was recovered unchanged from the reaction mixture. No evidence of homolytic cleavage was found.

The results tabulated demonstrate than within ±1% both diastereomers give the same balance of products.

Starting Material	Solvent	Temp.	% Yld	% Opt. Purity
(+)-erythro-VI	Dioxane	150	85	82 Ret.
(+)-threo-VI	"	150	83	81 "
(+)-erythro-VI	Ethylene Glycol	244	83	42 Inv.
(+)-threo-VI	"	244	78	41 "
(+)-erythro-XIV	Dioxane	100	56	95 Ret.
(-)-threo-XIV	"	100	74	93 "
(+)-erythro-XIV	Diethylene Glycol	170	6	48 Inv.
(-)-threo-XIV	"	170	24	49 "

Since the starting materials were diastereomeric, the transition states in which the carbon-carbon bond is broken are diastereomeric, and thus the ground and transition states are of different energies. If either the inverted and/or the retained product was produced in a concerted process (C-C bond broken and C-H bond made at the same time) it would be unusual to attain the same stereochemical results for each diastereomer. When two different reactants give the same ratio of products under a variety of conditions, it is probable that the reactions possess a common intermediate (29).

In either retention and inversion solvents, the stereochemical result depends only secondarily on the leaving group (25).



Solvent-electrophile	d	e	Steric Result
Dioxane-$(CH_3)_3COH$	CH_3	CH_3	95% R
	CH_3	C_2H_5	96% R
	CH_3	C_6H_5	96% R
	H	C_6H_5	82% R
Ethylene or diethylene glycol	CH_3	CH_3	52% I
	CH_3	C_2H_5	48% I
	CH_3	C_6H_5	55% I
	H	C_6H_5	42% I

In a concerted process, a greater change in stereospecificity would be expected as the leaving group was varied. Considering this evidence, it appears that discrete high energy intermediates intervene in all three reaction sequences, as depicted earlier in the overall mechanistic scheme. In view of these results, the retention of optical activity in the cleavage of (-)-1-benzoyl-1-methyl-2,2-diphenylcyclopropane may be interpreted in terms of a mechanism including an intermediate carbanion.

It was also noted that the steric course of electrophilic substitution is insensitive to the concentration of the electrophile over a range of 0.1 to 13 N in retention solvents. This conclusion was drawn from the observation that (-)-2,3-dimethyl-3-phenyl-2-pentanol (X) was cleaved in a 0.1 N solution of t-butyl alcohol in dioxane to yield 95% retention. When X was cleaved in pure t-butyl alcohol, 13 N, the steric course was 90% retention (24). However this does not clearly demonstrate a lack of concentration effect, as the solvent was changed. Furthermore the step from D to F involves a solvent molecule, and in retention solvents, in which some racemization occurs, an increase in electrophile concentration should decrease the stereospecificity. To examine this possibility the alcohol should be cleaved in a solvent like dioxane, with a low concentration of electrophile. Then the electrophile concentration may be varied greatly without changing the solvent.

In these experiments the concentration of $M^{\oplus}$ is probably constant because the basic catalyst is not consumed in the reaction, and the equilibrium governed by K_2 must lie far to the left since the solvent is much more concentrated than the starting alcohol. Therefore little of the metal is in the form of A at any one time. In the scheme described earlier, under the conditions that $[M^{\oplus}]$ is constant, the relative amounts of D and E produced are governed by equation 1 (26).

$$(1) \quad \frac{D}{E} = \frac{ka[M^{\oplus}]}{k_b[M^{\oplus}] + k_cKK'} \qquad (2) \quad \frac{D}{E} = \frac{ka}{kbK}$$

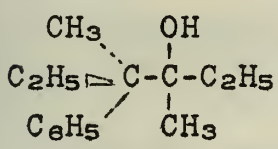
If $k_bK[M^{\oplus}] >> k_cKK'$, then equation 2 governs $\frac{D}{E}$. Since $[M^{\oplus}]$ appears in (1) but not in (2) an experiment to detect a common ion effect was conducted.

Three different alcohols, (+)-2,3-diphenyl-3-methyl-2-pentanol (VIII), (-)-3,4-dimethyl-4-phenyl-3-hexanol (IX), and (-)-2,3-dimethyl-3-phenyl-2-pentanol (X), were cleaved in various solvents, glycols and methanol, with potassium salts in different concentrations (25). In methanol the concentration of potassium methoxide was varied by a factor of 40 in the cleavage of VIII. The overall steric result varied between 46 and 40% inversion. Using the same conditions in the cleavage of IX, while varying the potassium methoxide concentration by a factor of 5 the steric result was invariant at 25% inversion. Results in other systems were comparable, and indicate the lack of a common ion effect on the stereochemistry of these reactions. Therefore only equation 2 is consistent with the conditions observed. This also indicates that the species C does not contribute greatly to the mechanistic scheme.

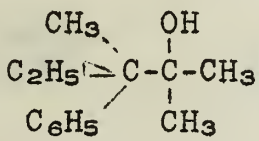
Both 2,3-diphenyl-3-methyl-2-pentanol (VIII) and 2-methyl-1,1,2-triphenyl-1-butanol (XI) were cleaved in t-butyl alcohol with potassium t-butoxide as base, and with a quaternary ammonium salt as base (22). System VIII with potassium salt gives 84% retention, and with the ammonium salt gives 1% inversion. System XI with potassium gives 90% retention, and with ammonium yields racemic product. These results indicate that the presence of metal ions is required for the operation of the retention mechanism. In diethylene glycol, XI was cleaved with potassium and ammonium salts, and gave 16 and 20% net inversion, respectively. Therefore the metal cation is not required for the inversion or racemization mechanism. Therefore D should include the metal ion while E doesnot, as is depicted in the mechanism shown.

The effect of changing the metal from potassium to lithium was examined. (+)-VIII was found to cleave in t-butyl alcohol with potassium t-butoxide at 102° to give a 64% yield of 2-phenylbutane of 84% retention. Under the same conditions using lithium t-butoxide, no reaction was observed (25). In glycols lithium salts generally gave lower yields than potassium salts, also. This effect of the metal cation on the rate of cleavage reactions has been observed before (27). It is probably due to the smaller radius of the lithium ion which makes the oxygen metal bond stronger and the cleavage of A slower than when the metal is potasssium. The values of ka and Kk_b would be expected to be smaller with the tighter bound lithium ion.

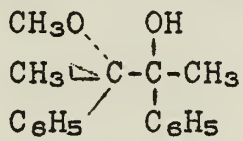
In retention solvents lithium salts usually give higher stereospecificity than potassium salts. (-)-3,4-Dimethyl-4-phenyl-3-hexanol (IX) in t-butyl alcohol gave 98% retention with lithium t-butoxide and 93% retention with the potassium salt. (-)-2,3-Dimethyl-3-phenyl-2-pentanol (X) in dioxane with 1% t-butyl alcohol gave 99% retention with lithium and 95% retention with potassium. (+)-2,3-Diphenyl-3-methoxy-2-butanol (XIV) in dioxane with 1% t-butyl alcohol gave 86% retention with lithium and 77% retention with potassium (25).



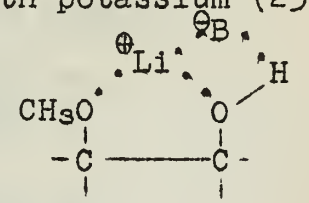
IX



X



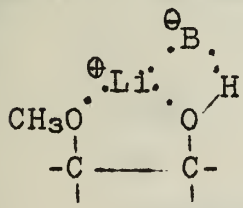
XIV



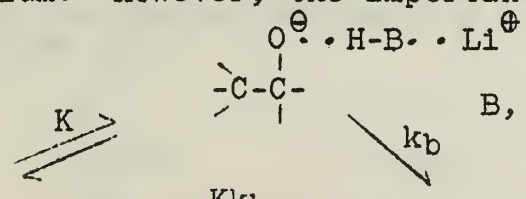
In the cases of X and IX very little difference is noted between lithium and potassium. In the case of XIV there is a significant difference, owing to the fact that it has two oxygens which may coordinate the metal ion. Lithium is smaller and would be more easily coordinated by the two oxygens than potassium and therefore be better orientated for retention than the potassium (28).

In extreme inversion solvents in some cases potassium salts give higher stereospecificity than lithium salts. IX in ethylene glycol gave 50% inversion with potassium and 48% inversion with lithium. X in glycol gave 52% inversion with potassium and 27% inversion with lithium. XIV in glycol gave 49% inversion with potassium and 38% inversion with lithium (25).

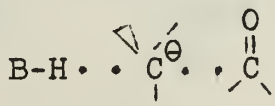
Again in IX there is not any significant difference, but in XIV and X there is. The results noted for XIV were explained by noting that the coordination of lithium by the two oxygens shifts the equilibrium K back towards A, therefore the result is less inversion, than with potassium. However, the important factor is the overall



A, Intimate Ion Pair



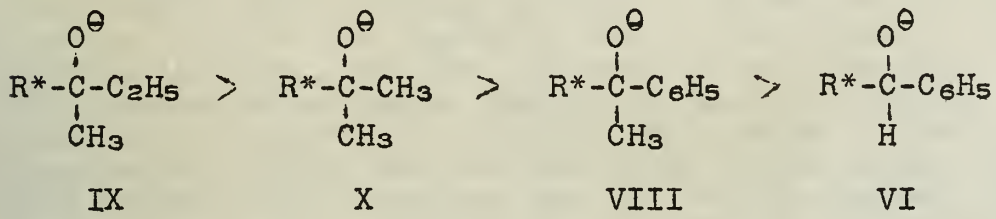
B, Solvent Separated Ion Pair



E, Asymmetrically shielded and solvated Ion Pair

transition state in going from A to E. In this case the tightly bound lithium would slow the step Kk_b, whether there is an intermediate between A and E or not. The same explanation is valid for the behavior of X.

In intermediate solvents, such as dimethyltetraethylene glycol and methanol, retention was found to decrease and inversion to increase as the basic character of the leaving group decreased. The results are tabulated below (22).



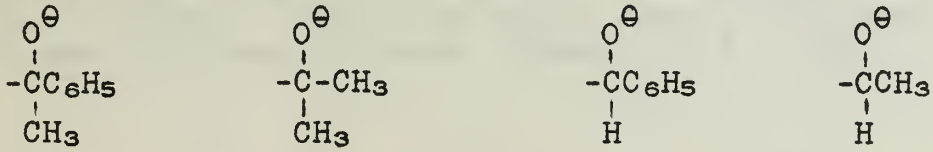
IX X VIII VI

Decreasing Basicity →

Solvent	Compound	Steric Result
$CH_3O(CH_2CH_2O)_4CH_3$, $CH_3(OCH_2CH_2)_4OK$	IX	60% Ret
	X	54% "
	VI	7% "
CH_3OH, CH_3OK	IX	25% Inv.
	VIII	42% "
CH_3OH, CH_3OLi	IX	40% Inv.
	VIII	56% "

In intermediate solvents both A and B cleave, presuming that they both exist. The less basic the compound the greater the possibility of having a solvent separated ion pair, B. The more B present, the more the steric course will tend towards inversion as observed. This is also true of the formation of E from A, without going through an intermediate B. The results tabulated above indicate that in intermediate solvents lithium salts cleave compounds with more inversion than potassium salts. In going from the intimate ion pair A, to E it would appear that the lithium salt would give less inversion, because Kk_b would be slower in the case of lithium than potassium. This should be the case whether B exists or not. However the opposite effect is observed, and the proposed mechanism does not easily account for the results observed in this case.

Again considering the mechanism of inversion, two effects were noted which complement the mechanistic scheme. First, in extreme inversion solvents, the larger the leaving group the more stereospecific the reaction (29).



Order of decreasing size →

55 52 48 29

Order of decreasing % inversion →

All cleavages were in diethylene glycol, with potassium diethylene glycoxide as base, at 210°. This would be expected if the inversion depends on the orientation of the solvent molecule from the back side, as in E. Second, if inversion does involve a backside solvation as in E, some dependence on electrophile concentration should be noted in extreme inversion solvents. However, there should not be a great deal of driving force provided by the solvation for two reasons. The negative charge in the carbanion is spread over the benzyl carbon and the benzene ring, and the benzyl carbon is hindered in the starting material. Therefore the distance from the proton donor at the backside and the electrons of the bond being broken is large, and the solvation is of a general type. This means the inversion mechanism depends on having a medium in which a high probability exists that random orientation of the unhindered hydroxyl groups will place the electrophilic in the proper position. At best, the highest net inversion was 60%, which suggests that a probability factor was more important than a specific configurational requirement.

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NEW DEVELOPMENTS IN CARBENE CHEMISTRY

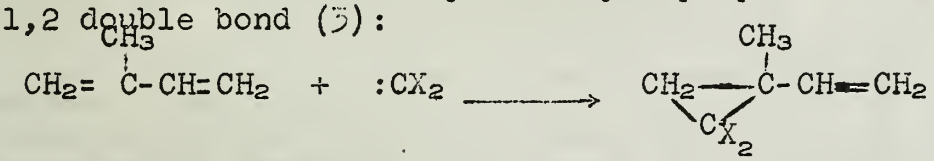
Reported by J. A. Haefner March 24, 1960

INTRODUCTION

The chemistry of carbenes (divalent carbon intermediates) has received a great deal of attention in the chemical literature and much of the work in this field has been critically surveyed (1,2). This seminar will deal with the recent developments in carbene chemistry which have not been previously reviewed.

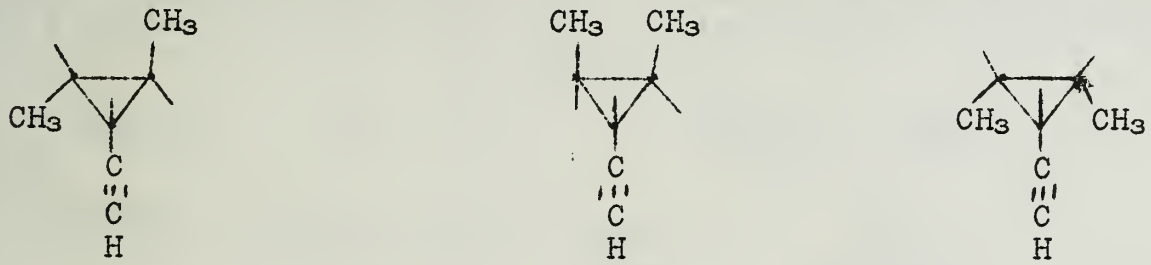
CARBENE ADDITION TO MULTIPLE BONDS

As with monoolefins the addition of dihalocarbenes to isoprene leads to cyclopropane derivatives. In this instance the conjugated diene yields almost exclusively that cyclopropane formed by addition at the 1,2 double bond (3):



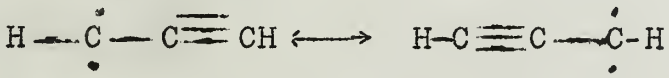
Dichloro- and dibromocarbenes gave as the only isolable products 1,1-dichloro-2-methyl-2-vinylcyclopropane (30%) and 1,1-dibromo-2-methyl-2-vinylcyclopropane (20%)(4). The latter compound was very unstable. Similar type compounds, 2,2-dihalocyclopropanone acetals which are prepared from dihalocarbenes and ketene acetals, undergo pyrolysis on distillation to give α-haloacrylic esters (5,6).

Evidence for new types of divalent carbon intermediates has been obtained by their formation of cyclopropanes in the presence of olefins. The photolysis of diazopropyne in the presence of cis-2-butene resulted in a mixture of three isomeric 2,3-dimethyl-1-acetylenylcyclopropanes (I,II,III) in ratios of 1:2.5:4.0.

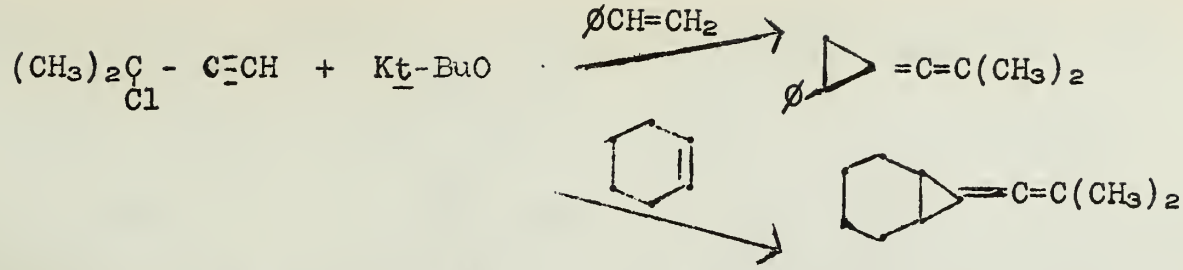


I II,III

In the presence of trans-2-butene the diazo compound decomposed to give the same three isomers in ratios of 63:2.3:1 (7). These products are explained by postulating an acetylenic carbene, propargylene, as an intermediate:



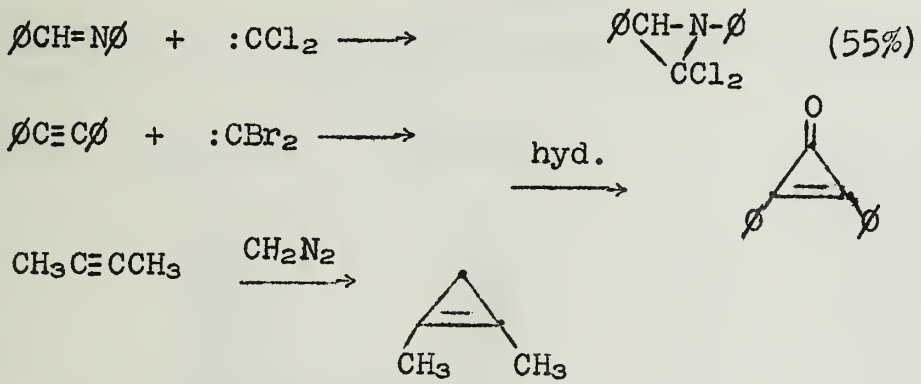
Since isomeric products were obtained it was proposed that addition of the intermediate to the double bond is non-stereospecific. This is said to classify the intermediate as a diradical, as opposed to a non-radical electrophilic species in which the two unshared electrons would have their spins paired (1). Treatment of 2-chloro-2-methyl-3-butyne with base in the presence of styrene or cyclohexene yields an alkenylidenecyclopropane (8):



These products were explained by assuming the formation of an alkenylidenecarbene ($R_2C{=}C{=}C{:}$) as an intermediate.

The reaction of methylene ($:CH_2$) with ketene at 20°K was recently investigated by irradiating diazomethane in a nitrogen support containing the ketene (9). Besides the expected products, ethylene and carbon monoxide, the infrared spectrum taken at 20°K showed two new bands at 1825 cm^{-1} and 1725 cm^{-1}. It was proposed that the 1825 cm^{-1} band was due to the formation of cyclopropanone in the reaction. Extrapolation from known carbonyl absorptions in cyclic ketones gives a predicted value of about 1815-1820 cm^{-1} for cyclopropanone. When the most volatile constituents of the reaction mixture were removed at low temperatures, material remained which at room temperature showed a broad absorption at 2950 cm^{-1} and a strong band at 1815 cm^{-1} in the infrared. The 1815 cm^{-1} band was assumed to be the same one observed at 1825 cm^{-1} at low temperature. Additional evidence for the three-membered ring ketone was provided by the fact that addition of diazomethane caused the 1825 cm^{-1} absorption to disappear and new bands to appear at 1775 cm^{-1} and 1760 cm^{-1}. This would indicate formation of cyclobutanone and possibly cyclopentanone. From this work it seems likely that cyclopropanone can be formed as a stable compound by addition of methylene to the double bond of ketene at very low temperatures.

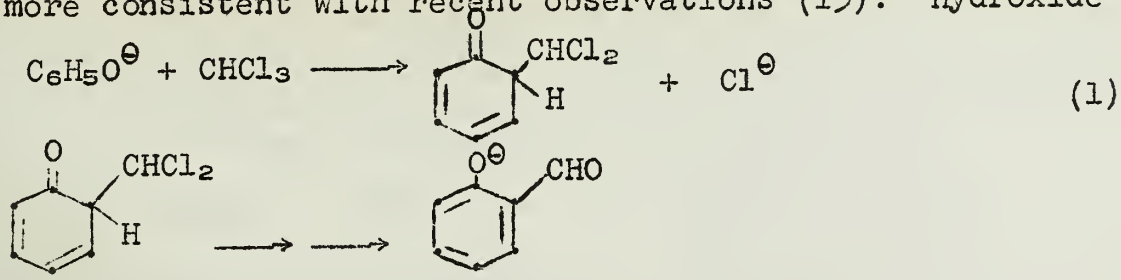
Most interest in carbene addition reactions has been concerned with the carbon-carbon double bond. However, it has been observed that a carbene will also add to the carbon-nitrogen double bond and the carbon-carbon triple bond (10,12,36):

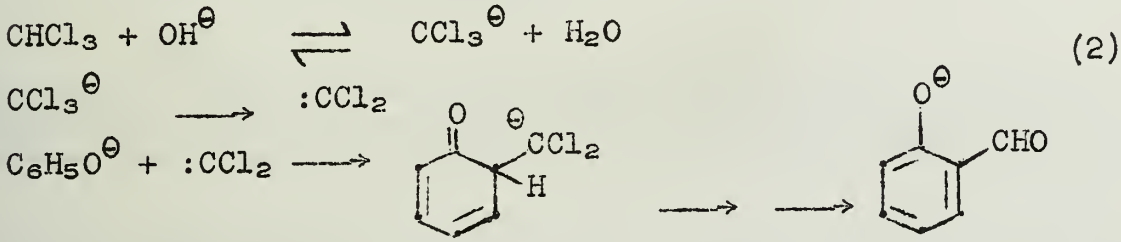


REACTION WITH OTHER NUCLEOPHILES

Since it has been shown that the reaction of haloforms with aqueous base proceeds through a dihalocarbene intermediate (1), it is not unreasonable to suspect that the Reimer-Tiemann reaction might also involve a carbene intermediate. Although this reaction of phenols with chloroform in aqueous alkali has been explained as an S_N2 attack of the o- or p-carbon atom of a phenoxide ion on chloroform followed by tautomerism of the quinoid type intermediate and rapid hydrolysis (eq.1), postulation of dichloromethylene

formation and its subsequent reaction with phenoxide ion (eq. 2) is more consistent with recent observations (13). Hydroxide ion





was found to have a powerful catalytic effect on the reaction. Under one set of conditions there was more than a 16-fold increase in the rate of chloroform disappearance when sodium hydroxide was added. In this latter case, product analysis showed that 45% of the chloroform that reacted entered into the Reimer-Tiemann reaction. The mechanism of equation 1 cannot explain this effect of hydroxide ion. Rate constants were calculated from the following second-order rate equation:

$$K = \frac{2.303}{t[a(3+f)-b]} \log \frac{b(a-x)}{a[b-(3+f)x]}$$

where $a=[CHCl_3]_o$; $b=[OH^{\ominus}]_o$, $x=\Delta[CHCl_3]_t$ and f= the fraction of the chloroform giving formate. The values obtained (Table I) were reasonably constant, thus supporting the mechanism of equation 2.

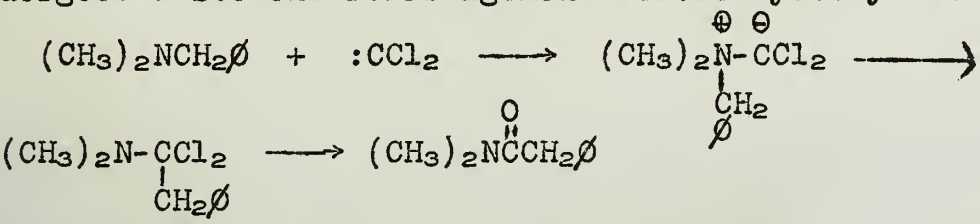
TABLE I

Kinetics of the reaction of chloroform with aqueous alkali and sodium phenoxide at 35.0°(13).

$[C_6H_5ONa]_o$	$[CHCl_3]_o$	$[NaOH]_o$	f	k x 10^4 (Liters/mole-sec.)
1.127	0.0127	0.133	0.32	2.93±0.19
1.101	.0241	.160	.45	2.91± .09
1.072	.0196	.066	.39	3.37± .07
0.742	.0267	.165	.60	3.18± .09
.582	.0187	.082	.53	3.50± .14
.583	.0253	.196	.50	3.28± .09
.202	.0250	.181	.70	2.95± .06
.000	.0293	.166	.27	2.87± .05
.000	~ .03	~ .04	.15	2.41± .03

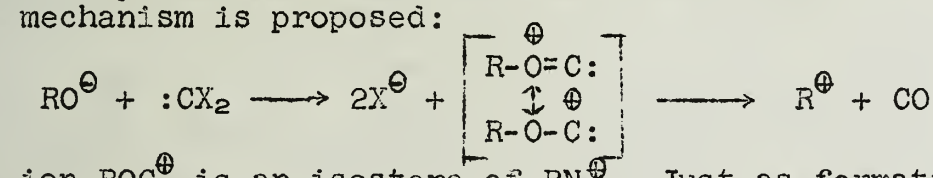
Another reaction under study which takes place in the presence of a haloform and base is the formylation of secondary amines. Preliminary communications (15,16) indicate that this reaction also involves a dihalocarbene intermediate. In reactions with piperidine, diphenylamine and several dialkyl amines, chloroform is believed to give dichlorocarbene initially (eq. 2). This then attacks the amine

producing a dichloromethylamine which under the reaction conditions is hydrolyzed to the corresponding formamide. In one instance dimethylbenzylamine, a tertiary amine, was converted to N,N-dimethyl-α-phenylacetamide. Here it was proposed that dichlorocarbene reacts with the amide to give a nitrogen "ylid" intermediate which undergoes a Stevens rearrangement before hydrolysis:



The reaction does not occur through hydrolysis of chloroform to formate and reaction of formate with the amine, since aqueous sodium formate does not react when mixed with a secondary amine.

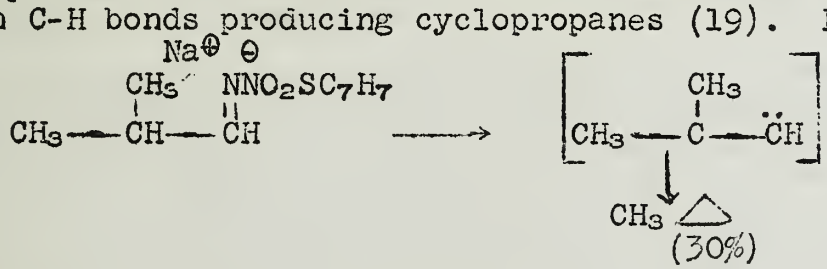
The reaction of alkoxides with haloform in alcohol solutions to give carbon monoxide and olefins has been recently investigated (17,18). The order of reactivity of alcohols (tertiary > secondary > primary) and the structure of the olefins obtained are consistent with the postulation of a carbonium ion intermediate. The following mechanism is proposed:



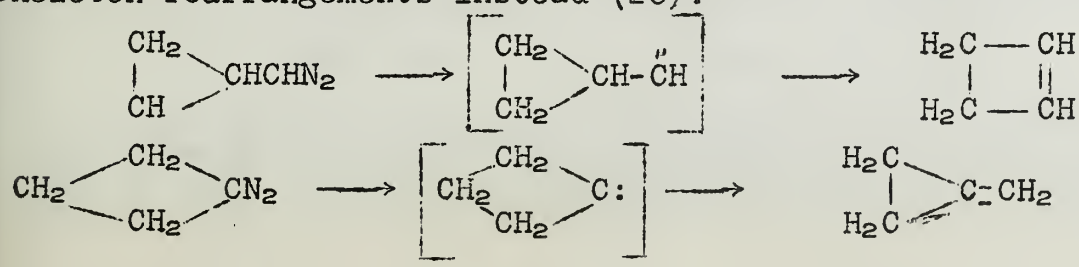
The ion $ROC^{\oplus}$ is an isostere of $RN_2^{\oplus}$. Just as formation of molecular nitrogen serves as the driving force for decomposition of $RN_2^{\oplus}$ to produce carbonium ions it is proposed that formation of carbon monoxide would serve as a driving force in the decomposition of $ROC^{\oplus}$.

INSERTION REACTIONS

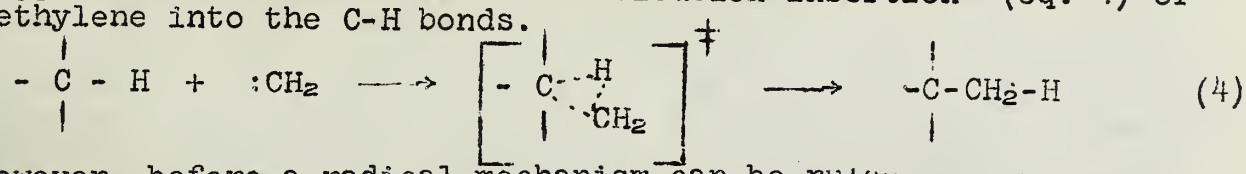
Carbene reactions which on the surface involve the insertion of the divalent carbon species between two covalently bonded atoms have been observed in several systems. When the salts of aliphatic tosylhydrazones were decomposed thermally or in an aprotic solvent, the proposed carbene intermediate underwent intramolecular insertion between C-H bonds producing cyclopropanes (19). For example:



Not all tosylhydrazones have been found to give intramolecular C-H insertion products. Systems where such an insertion would mean synthesizing the bicyclo[1·1·0]butane system gave carbon-skeleton rearrangements instead (20):

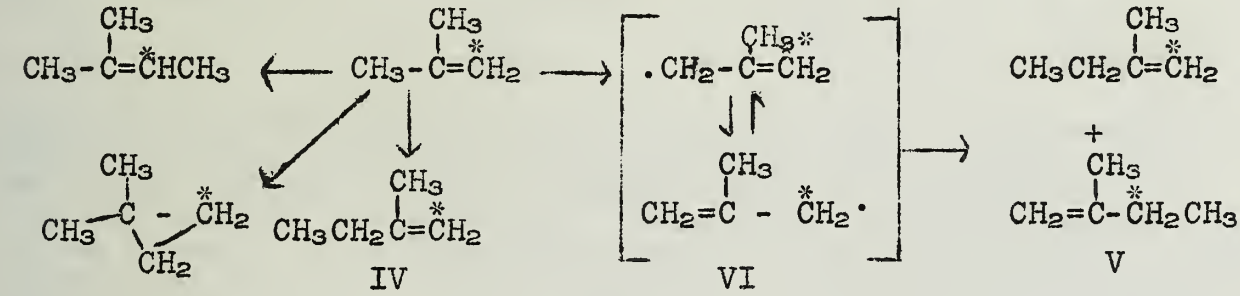


The reaction of methylene with cis- and trans-2-butene has been reported to produce cis- and trans-2-pentene, respectively (21,22). The observed retention of the double bond configurations was suggested as evidence for a "substitution insertion" (eq. 4) of methylene into the C-H bonds.

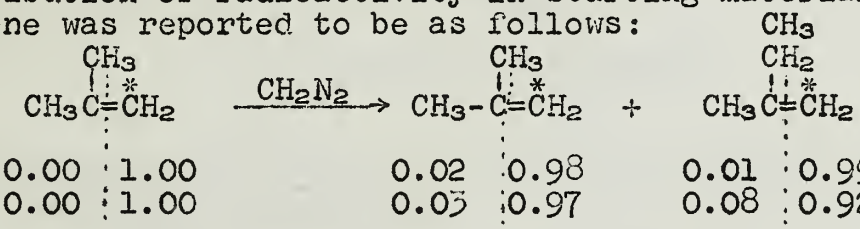


(4)

However, before a radical mechanism can be ruled out it must be demonstrated that intermediate crotyl radicals would not retain their configurations under the conditions of the reaction. The first clear evidence in support of a simple direct insertion mechanism (eq. 4) has come from an investigation of the insertion of methylene into the allylic C-H bond of 2-methylpropene-1-C^{14} (23). If the mechanism is concerted, the 2-methyl-1-butene would be expected to show radioactivity in the 1-position alone (IV). If a step-wise process with free intermediates were involved, activity would appear in both the 1- and 3-positions (V).



The reaction was run in both the liquid and gas phase. The products were separated by vapor phase chromatography and identified by comparing their infrared spectra with those of authentic samples. Distribution of radioactivity in starting material and 2-methyl-1-butene was reported to be as follows:



Liquid phase	0.00	1.00	0.02	0.98	0.01	0.99
Gas phase	0.00	1.00	0.03	0.97	0.08	0.92

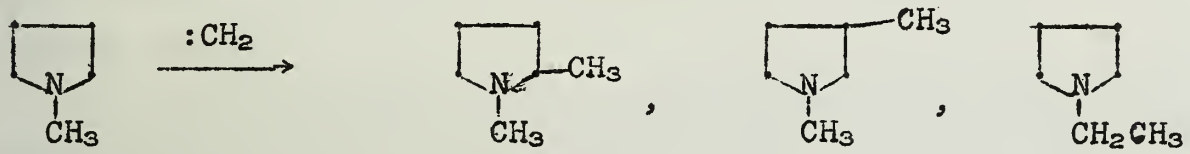
The distribution in 2-methyl-1-butene is far from the 0.50-0.50 value predicted by the free radical mechanism and thus it is clear that direct insertion (eq. 4) occurs, even in the gas phase. The results indicate that about 16% of the reaction proceeds through a radical intermediate (VI) in the gas phase. It is probable that even a larger percentage of 2-methyl-1-butene is converted to a free radical through the abstraction of a hydrogen atom by methylene (24)(eq. 5) since some of the intermediate radical (VI) will undoubtedly be lost by coupling and will not appear in the above results. The hydrogen abstraction reaction of methylene with hydrocarbons (eq. 5) has been studied (24). Evidence for equation

$$RH + :CH_2 \longrightarrow CH_3\cdot + R\cdot \qquad (5)$$

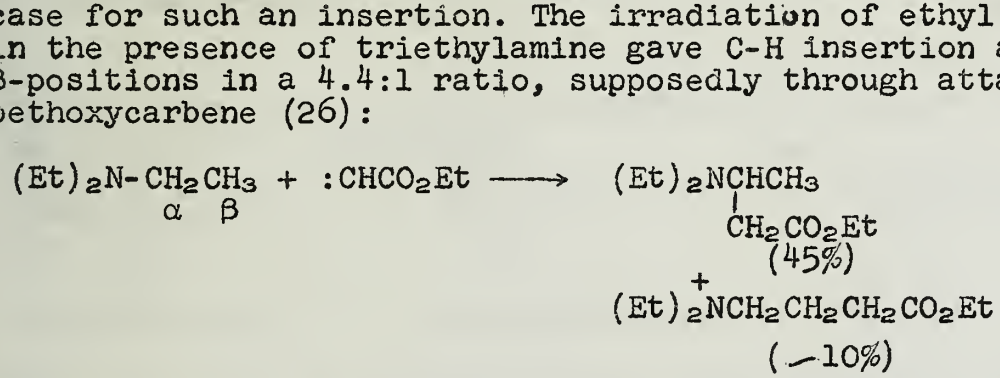
5 was found by decomposing diazomethane in hydrocarbons both in the absence and presence of molecular oxygen. Those products which could result from coupling and disproportionation of intermediate free radicals disappeared when oxygen was present.

The reaction of methylene with ethers has been studied with vapor phase chromatography (25). Ethyl n-propyl and ethyl i-propyl ethers were obtained from diethyl ether in the ratio of 55.5:44.5, near the statistical value 60:40 which would be expected if the direct insertion mechanism (eq. 4) were operating. The reaction of methylene with tetrahydrofuran yielded α- and β-methyltetrahydrofuran in an α:β ratio of 1.26. No tetrahydropyran could be detected in the reaction products. Therefore it appears that no insertion into the C-O bond occurred. Further support for preferential insertion into C-H bonds was found in the reaction of diethyl ether with methylene-C^{14}. The ethyl n-propyl ether obtained in this experiment was shown to have all of its radioactivity in the γ-position of the n-propyl group (11).

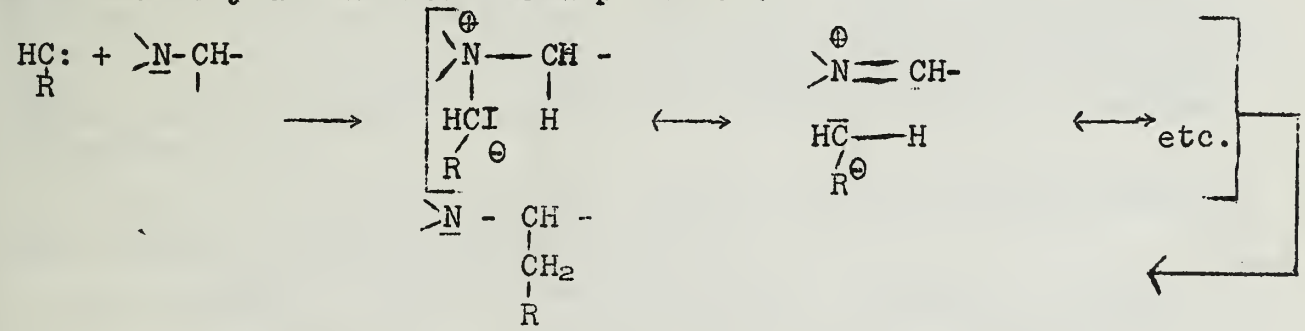
Methylene reacts with N-methylpyrolidine giving three products (26):



No N-methylpiperidine was found in the products. This compound might have been detected if insertion into the C-N bond were occurring. Since it did not appear, there is no proof in this case for such an insertion. The irradiation of ethyl diazoacetate in the presence of triethylamine gave C-H insertion at the α- and β-positions in a 4.4:1 ratio, supposedly through attack by carbethoxycarbene (26):

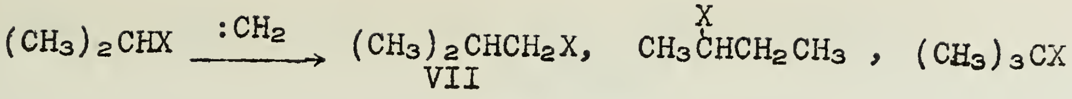


The following mechanism was proposed to explain the selectivity of carbethoxycarbene for the α-position:



This type of mechanism could also explain the deviation from statistical product ratio values observed in the reaction of methylene with ethers.

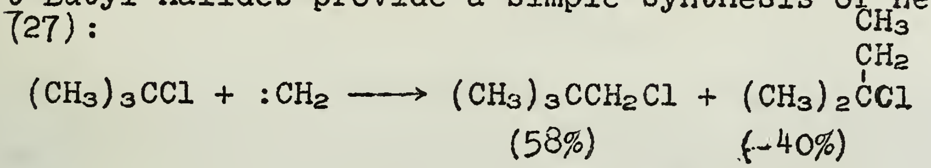
Investigation of the photolysis of diazomethane in solutions of alkyl halides has revealed that methylene will attack carbon-halogen bonds much more readily than C-H bonds. Isopropyl halides give primarily isobutyl halides (VII) (27):



$$(CH_3)_2CHX \xrightarrow{:CH_2} \underset{\text{VII}}{(CH_3)_2CHCH_2X}, \quad CH_3\overset{X}{C}HCH_2CH_3, \quad (CH_3)_3CX$$

X=Cl, Br

t-Butyl halides provide a simple synthesis of neopentyl halides (27):

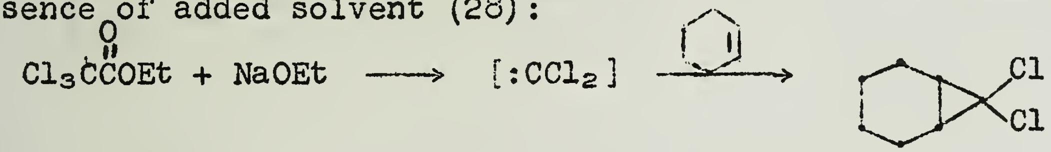


$$(CH_3)_3CCl + :CH_2 \longrightarrow \underset{(58\%)}{(CH_3)_3CCH_2Cl} + \underset{(\sim 40\%)}{(CH_3)_2\overset{\overset{CH_3}{CH_2}}{C}Cl}$$

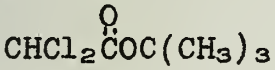
The H:X ratio in the t-butyl halides is 9:1 and thus the selectivity of methylene is very marked in this example. Superficially these reactions involve insertion of CH_2 into the C-X bond, but previously studied reactions of halogen compounds with diazomethane (14) indicate that a radical process may be involved rather than a simple insertion.

CARBENE SOURCES

High yields (72-88%) of cyclopropanes have been reported to result from the use of ethyl trichloroacetate as a dihalocarbene precursor in reactions with olefins, either in the presence or absence of added solvent (28):

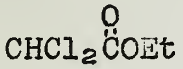


Similar compounds have been treated with potassium t-butylate in the presence of isobutylene.



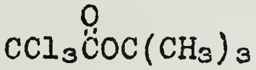
$$CHCl_2\overset{O}{C}OC(CH_3)_3$$

VIII



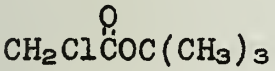
$$CHCl_2\overset{O}{C}OEt$$

IX

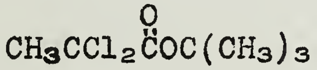


$$CCl_3\overset{O}{C}OC(CH_3)_3$$

X



$$CH_2Cl\overset{O}{C}OC(CH_3)_3$$

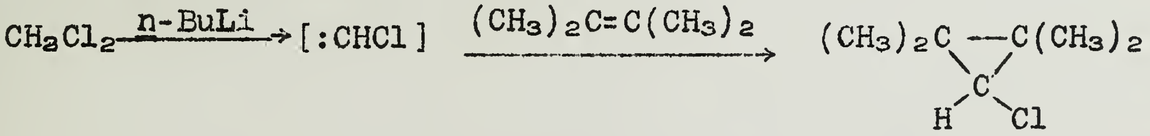


$$CH_3CCl_2\overset{O}{C}OC(CH_3)_3$$

$CHCl_2CN$

Only VIII, IX, and X show ability to give carbenes (29). Various mechanisms have been suggested for the formation of dichlorocarbene from the dichloroacetates (VIII, IX) (30). However, the correct mechanism cannot be established until more data are available. A recently discovered method of producing dichlorocarbenes which does not require basic reaction conditions consists in heating sodium trichloroacetate in an aprotic solvent such as 1,2-dimethoxyethane (31).

Methylene chloride has been reported to give chlorocarbene when treated with n-butyllithium (32):



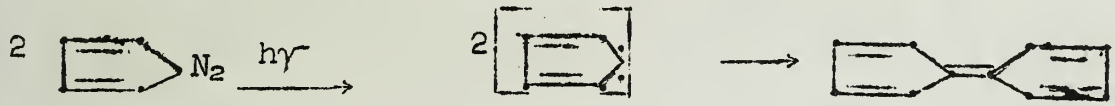
A carbene intermediate has been postulated to explain the ethylenic products obtained in the pyrolysis of two silicon compounds (33):

$$CHFCl{-}CF_2{-}SiCl_3 \longrightarrow [CHFCl{-}\ddot{C}F] + SiFCl_3$$
$$\downarrow$$
$$CHF{=}CFCl$$

$$CFCl_2{-}CF_2SiCl_3 \longrightarrow [CFCl_2{-}\ddot{C}F] + SiFCl_3$$
$$\downarrow$$
$$CFCl{=}CFCl$$

The proposed rearrangement of an intermediate carbene is supported by the formation of trifluoroethylene in an analogous rearrangement of trifluoromethylcarbene produced by the photochemical decomposition of its parent diazo compound (34).

An attempt was made recently to prepare stable divalent carbon species by irradiation of diazomethane, diphenyldiazomethane and diazocyclopentadiene at 20°K (9). The photolysis reactions were studied by ultraviolet-visible and infrared spectrophotometry but no divalent species could be identified. In the irradiation of diazocyclopentadiene in a perfluorocyclic ether matrix at 77°K the ultraviolet spectrum of the products proved to be identical with that of fulvalene which has been prepared by Doering (35). This compound could have been formed in the following way:



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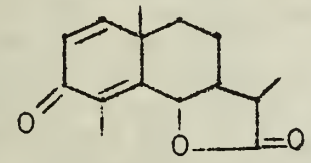
PSEUDOSANTONIN

Reported by J. W. Van Dyke March 28, 1960

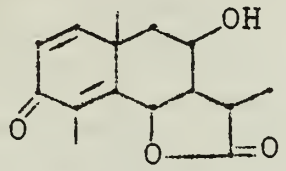
Introduction

The flower heads of Artemisia maritima from India have yielded four related sesquiterpenic compounds, santonin (I), β-santonin (I), artemisin (II), and a hydroxy-keto-lactone, ψ-santonin. ψ-Santonin was isolated by F. and H. Smith, Ltd. in 1935 (1).

The valuable anthelmintic properties of santonin have long been known, but these properties are not shown by ψ-santonin.



I



II

Structure of Pseudosantonin

ψ-Santonin, $C_{15}H_{20}O_4$, has been characterized as a hydroxy-keto lactone. It forms an oxime, a 2,4-dinitrophenylhydrazone, and a quinoline derivative, $C_{22}H_{23}O_3N$, by condensation with o-aminobenzaldehyde. These reactions indicate a grouping $-CO-CH_2-$(2).

ψ-Santonin reacts slowly with aqueous sodium hydroxide and is reprecipitated unchanged when the resulting solution is acidified. When an attempt is made to form a methyl ester (from sodium salt) a compound is obtained which gradually loses methyl alcohol and yields ψ-santonin. This evidence points to a relatively stable γ- or δ-lactone and together with the carbonyl group accounts for three of the four oxygen atoms present in the molecule. Infrared absorption at 1775 cm^{-1} (CCl_4) indicates a γ-lactone.

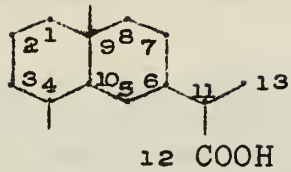
Clemo and Cocker (2) obtained a monoacetyl derivative of ψ-santonin with difficulty and in poor yield; the hydroxyl group then was erroneously assumed to be tertiary. Thus, the fourth oxygen atom is accounted for.

Catalytic reduction by hydrogen over palladized charcoal yields a dihydro-compound, $C_{15}H_{22}O_4$, which reacts immediately with $NaHCO_3$, and is reprecipitated unchanged on acidification. Dihydro-ψ-santonin thus possesses a carboxyl group, and must be formed by the hydrogenolysis of the lactone ring.

Hydrogenation of ψ-santonin over Adams' catalyst (PtO_2, H_2O) gives an acid, hexahydro-ψ-santonin, $C_{15}H_{26}O_4$. This acid has no carbonyl group and yields a monoacetyl compound which is also a lactone.

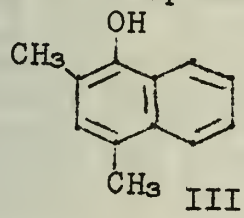
Dihydro-ψ-santonin is reduced with sodium amalgam to an acid, tetrahydro-ψ-santonin, $C_{15}H_{24}O_4$, which does not give the reactions of a carbonyl compound. It is readily converted to a monoacetate, which is also a lactone.

Nomenclature

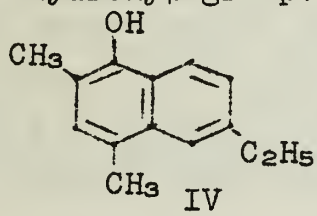


(Santanic acid)

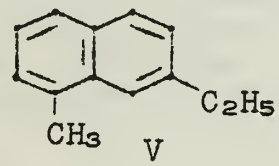
When ψ-santonin is treated with sulfuric acid (55%) or anhydrous formic acid at 50°, a dark solution is formed, from which a crystalline compound, $C_{15}H_{18}O_3$, is obtained. This compound is phenolic and has been given the name desmotropo-ψ-santonin. It fails to couple with diazotized p-nitroaniline, but is readily benzoylated and methylated in alkaline solution. It is not reduced with palladized charcoal and hydrogen. Aromatization of desmotropo-ψ-santonin is effected by fusion with KOH at 320°. A compound, $C_{12}H_{12}O$, corresponding to a dimethyl-naphthol is obtained (2). It was found to be identical with 2,4-dimethyl-1-naphthol (III). When desmotropo-ψ-santonin is dehydrogenated over Pd, 2,4-dimethyl-6-ethyl-1-naphthol (IV) is formed (3,4). It is clear that ψ-santonin has a carbonyl at a position corresponding to the hydroxyl group.



III



IV

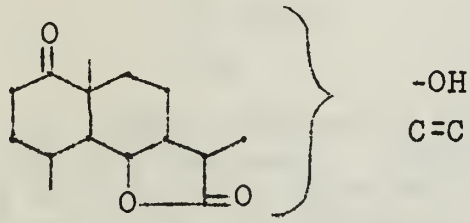


V

When dihydro-ψ-santonin is treated with amalgamated zinc and hydrochloric acid, a gum is obtained which on distillation with selenium yields an oil whose picrate is identical with that obtained from 1-methyl-7-ethyl naphthalene (V). This is also obtained from santonin and artemisin. In the production of 1-methyl-7-ethyl naphthalene, a methyl group is lost, which is characteristic of compounds containing angular methyl groups. The other carbon atom lost in this reaction, from analogy with santonin and from the application of the isoprene rule, is the carbon derived from the carbonyl group of the lactone ring, placing an α-propionyl group at position 6 in ψ-santonin. The position of fusion is likewise assumed from analogy with santonin. The fusion is later proved to be correct.

This evidence together with the production of 2,4-dimethyl-6-ethyl-1-naphthol shows that ψ-santonin contains a methyl group at position 4 and a methyl group at either position 9 or 10 (9 preferred). The latter methyl group migrates in some way to position 2, during treatment with acid.

Tentative structure

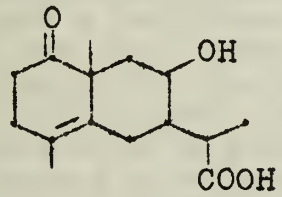


As mentioned before, Clemo and Cocker reported that ψ-santonin is acetylated with difficulty and in low yield (30%), indicating a tertiary hydroxyl group. Reinvestigation of the reactivity of the hydroxyl group by Dauben and Hance (5) showed that ψ-santonin reacts readily with acetic anhydride and sodium acetate under the conditions

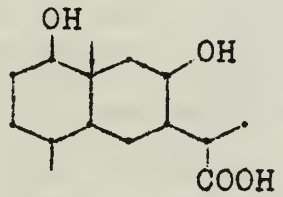
of Clemo and Cocker to yield a liquid acetate in 70% yield. All attempts to crystallize the acetate fail but saponification yields ψ-santonin.

Evidence showing the nature of the hydroxyl grouping is gained by oxidation of ψ-santonin with chromic acid in acetic acid. A product is isolated in 70% yield which possesses the proper analytical values for a diketone, $C_{15}H_{18}O_4$, but melts with a broad and variable range. The intensity of the carbonyl band both in the ultraviolet and infrared is double that of the starting material. This oxidation shows that the original hydroxyl grouping is secondary (5).

The location of the hydroxyl function has been determined by a study of the lactones in the ψ-santonin series. In the infrared γ-lactones absorb at about 1770 cm^{-1} and δ-lactones at about 1740 cm^{-1}. When dihydro-ψ-santonin (VI) is heated with acetic anhydride, the lactone of VI, 1-ketosanten-12,7-olide (VII) is obtained. Further reduction of VI first with sodium amalgam and then with platinum and hydrogen in acetic acid yields 1,7-dihydroxy-santanic acid (VIII). This saturated dihydroxy acid on treatment with acetic anhydride gives rise to the acetate lactone of VIII, 1-acetoxy-santan-12,7-olide (IX). In both cases lactonization occurs on the original hydroxyl group of ψ-santonin. Lactones VII and IX display lactonic carbonyl bands at 1769 and 1763 cm^{-1} ($CHCl_3$), respectively, thus indicating the presence of a γ-lactone in each case. Both free hydroxyl and lactonic hydroxyl groupings in ψ-santonin are in positions γ to the lactone carbonyl group (5).

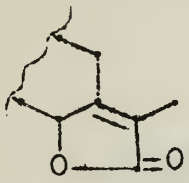


VI (in error)

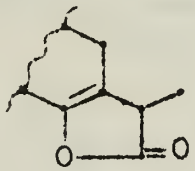


VIII

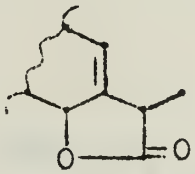
The presence of one olefinic double bond is shown by the formation of a monoepoxide when ψ-santonin is treated with perbenzoic acid. There is much evidence pertaining to the location of the double bond (6,7,8). Three wrong positions for the double bond had been postulated for ψ-santonin (X_a, X_b, X_c), before the correct position was finally determined.



X_a



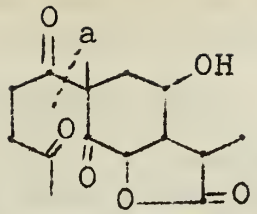
X_b



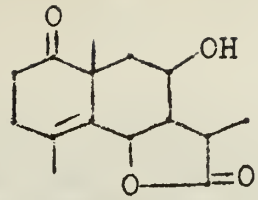
X_c

Cocker and coworkers (9) added evidence in support of the 4-10 position for the double bond in ψ-santonin. Ozonolysis of ψ-santonin and reduction of the ozonide with hydrogen over palladized charcoal yields a crystalline solid (XI), $C_{15}H_{20}O_6$. This results from the cleavage of the double bond, as shown by the absence of the IR absorption band of ψ-santonin due to the double bond (1658 cm^{-1}; $CHCl_3$). Hydrolysis of XI with cold aqueous barium hydroxide yields levulinic acid, indicating the presence of the Ac. $(CH_2)_2.CO$-group, derived from the decomposition (a) of the β-diketone system

shown in XI.



XI



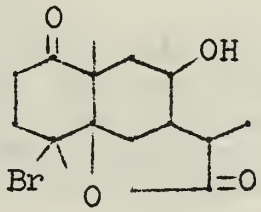
XII

With the assumptions mentioned before the above data permit only one structure (XII) to be assigned to ψ-santonin, with the hydroxyl group at C_7 and the double bond between C_4 and C_{10}. Systematic degradation later proved this structure to be correct.

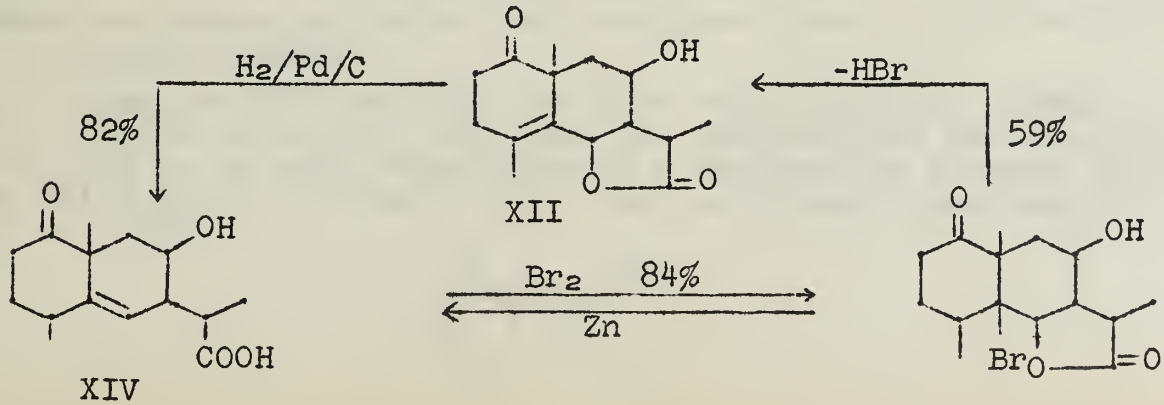
The acetate of ψ-santonin does not show absorption in the olefinic hydrogen region in the NMR, giving proof of a tetrasubstituted double bond (10).

Structure of Dihydro-ψ-santonin

It is well-known that treatment of an unsaturated acid with bromine in the presence of base often gives rise to a bromolactone if the relationship of these functional groups is proper. A crystalline bromolactone is obtained from dihydro-ψ-santonin. This bromolactone upon treatment with zinc and ethanol regenerates dihydro-ψ-santonin (10). If no bond migration occurs in going from ψ-santonin to dihydro-ψ-santonin, the bromolactone would be of the δ-type shown in XIII. Such a δ-lactone is known to absorb at about 1740 cm^{-1} in the IR. It was found that the bromolactone absorbs at 1775 cm^{-1}, a value expected of a γ-lactone. Dihydro-ψ-santonin is either a β,γ- or γ,δ-unsaturated acid. The bromolactone upon dehydrohalogenation gives rise to ψ-santonin and therefore one end of the double bond in dihydro-ψ-santonin must be at C_5. Since the double bond in ψ-santonin has been shown to be between C_4 and C_{10}, the more likely position for the double bond in the hydrogenolysis product is between C_5 and C_{10} as shown in XIV. The sequence of reactions can be summarized as shown below (10).



XIII



XII

XIV

XV

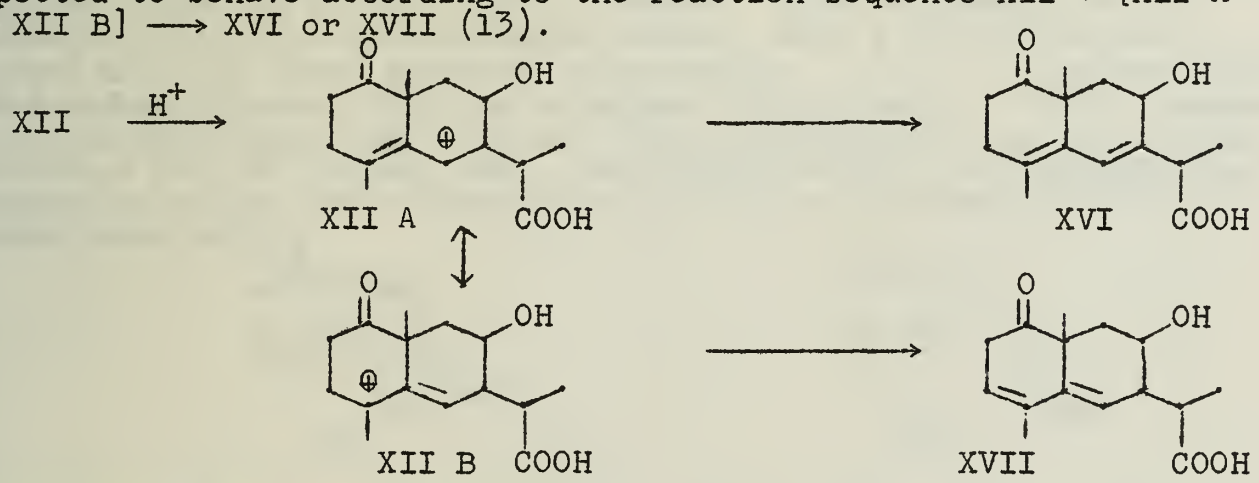
The NMR spectrum of the methyl ester of XIV showed absorption in the olefinic hydrogen region (10).

Structure of ψ-santonic acid

When ψ-santonin is treated with HCl, an acid, $C_{15}H_{20}O_4$, is obtained which has been given the name ψ-santonic acid. This acid yields a phenylhydrazone and a 2,4-dinitro-phenylhydrazone with difficulty (11) and a derivative with o-amino-benzaldehyde, indicating the presence of a keto-methylene group. ψ-Santonic acid possesses two ethylenic groups, as shown by the fact that it absorbs two atoms of oxygen when titrated with perbenzoic acid and a diepoxide, $C_{15}H_{20}O_6$, is produced. ψ-Santonic acid also absorbs two molecules of hydrogen in the presence of palladized charcoal, and tetrahydro-ψ-santonic acid results ($C_{15}H_{24}O_4$).

The carbon skeleton is the same as in ψ-santonin, since tetrahydro-ψ-santonic acid upon Clemmensen reduction followed by selenium dehydrogenation gives rise to 1-methyl-7-ethyl-naphthalene (12).

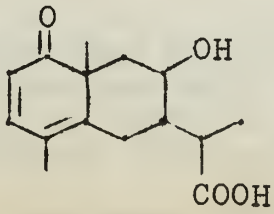
ψ-Santonic acid is formed by the conversion of the γ-lactone in ψ-santonin to an unsaturated acid. ψ-Santonin (XII) would be expected to behave according to the reaction sequence XII → [XII A ↔ XII B] ⟶ XVI or XVII (13).



Bands in the IR (oil mull) are found at 1707 cm^{-1} (unconjugated six-membered ring ketone) and at 1605 and 1570 cm^{-1} (conjugated diene system) (12). The UV spectrum of the acid shows an intense maximum at 234.5 mμ (ε 15,000) due to the conjugated diene. It is not due to a conjugated ketone since the 2,4-dinitrophenylhydrazone of the acid retains this band.

Dauben and Hance and Cocker and coworkers favor structure XVII for the following reasons:

1.) Structure XVII explains the slow base-catalyzed isomerization of ψ-santonic acid (11, 12). The new compound has an absorption maximum at 330 mμ, a value suggestive of a homoannular dienone (XVIII). Compound XVIII would be formed by the base-catalyzed isomerization of XVII but not XVI.

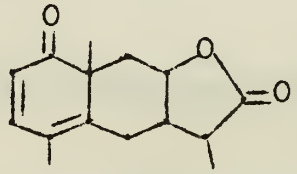


XVIII

If XVII is correct, an explanation is possible for the IR and UV spectra of the anhydro derivative of ψ-santonic acid, which is prepared by heating the acid at 200° for 10 minutes (13).

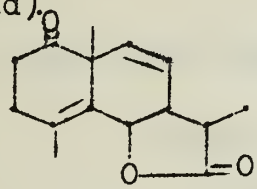
UV: 320 mμ (log ε 3.69)
IR: 1663, 1633, 1567 cm^{-1} (O=C-C=C-C=C); 1768 cm^{-1} (butanolide system)

Anhydro-ψ-santonic acid would have structure XIX (1-keto-$\Delta^{2,4(10)}$-santadien-12,7-olide).

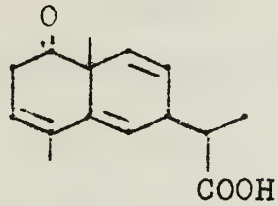


XIX

2.) Further evidence for the formation of a $\Delta^{3,5(10)}$-dienic system in the acid-catalyzed dehydration of the allylic lactone system is obtained by examination of a reaction of 1-keto-$\Delta^{4(10),7}$-santadien-12,5-olide (anhydro-ψ-santonin) (XX), a product formed from ψ-santonin tosylate. When XX is allowed to react with dilute HCl under similar conditions (12), a trienic acid displaying an absorption maximum at 240 mμ (ε 10, 150) is formed. Such an absorption is characteristic of a heteroannular diene. Only a $\Delta^{3,5(10)}$-dienic system will fit these spectral requirements. A $\Delta^{4(10),5}$-system would give a conjugated triene with the original Δ^{7}-bond and a $\Delta^{2,4(10)}$-system would give a homoannular dienone. Therefore XXI must be the correct structure for the trienic acid, and structure XVII is therefore the correct structure for ψ-santonic acid (1-keto-7-hydroxy-$\Delta^{3,5(10)}$-santadienic acid).



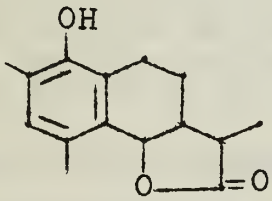
XX



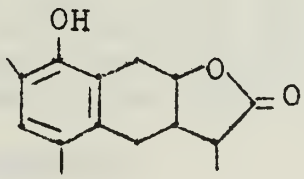
XXI

Structure of desmotropo-ψ-santonin

When ψ-santonin is treated with warm 55% H_2SO_4, two compounds (stereoisomers), $C_{15}H_{18}O_3$, are isolated which have been given the name desmotropo-ψ-santonin (14). One desmotropo-ψ-santonin is also obtained when ψ-santonic acid is heated (50°) with concentrated H_2SO_4. Structure XXII was first assigned to these desmotropo-compounds.



XXII

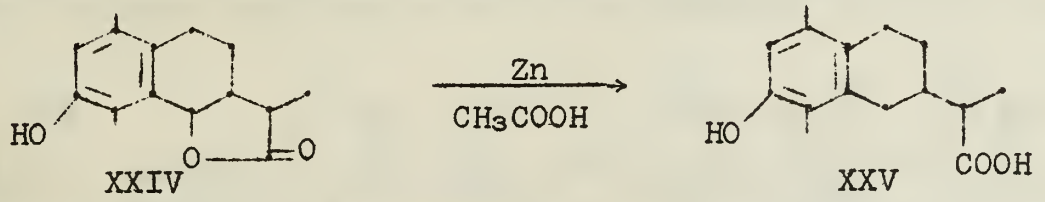


XXIII

Since the acid XVII, which does not have a hydroxyl at C_5, can be transformed into desmotropo-ψ-santonin, the position of lactonic fusion was reexamined. Since the lactones are of the saturated γ-type (1765 cm^{-1}, $CHCl_3$), structure XXIII would be possible.

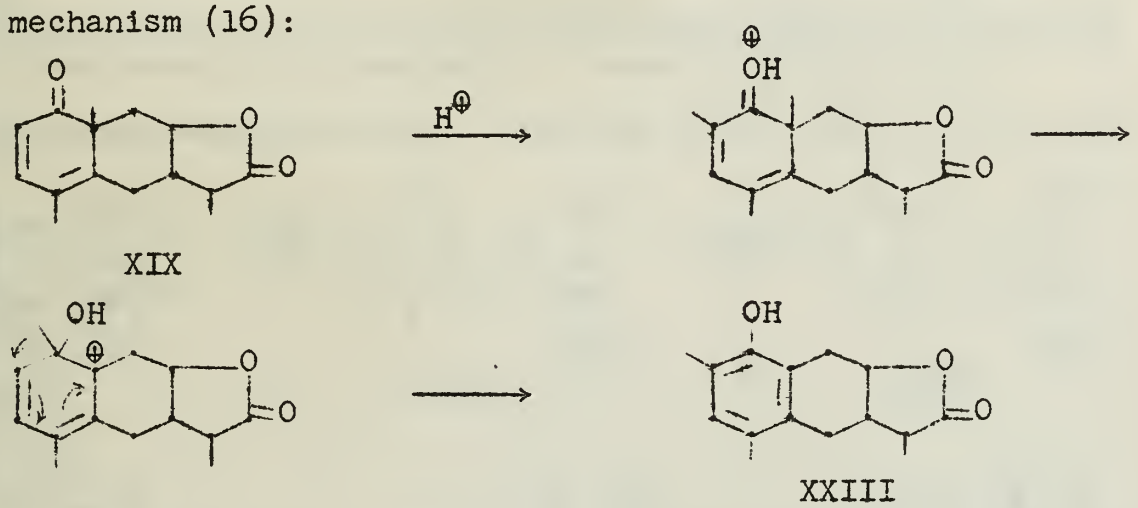
In the santonin series, the desmotropo-compounds XXIV, which are

benzylic esters, show a special reactivity in that upon treatment with zinc and acetic acid, they are reduced to desmotroposantonous acids XXV (15). Desmotropo-ψ-santonins are recovered unchanged from a similar treatment (12). The inactivity to these reagents



strongly suggests that XXIII represents the structure of the desmotropo-ψ-santonins.

Possible mechanism (16):



The four desmotropo-compounds so far isolated are as follows (16,17):

ψ-santonin; m.p. 184-6°; $[\alpha]_D^{20}$-169

H_2SO_4 ↓

+ β-desmotropo-ψ-santonin; m.p. 189°; $[\alpha]_D^{20}$ + 68

+ α-iso-desmotropo-ψ-santonin; m.p. 251-53; $[\alpha]_D^{20}$ + 68.5

+ β-desmotropo- $\xrightarrow{\Delta \text{ anhyd.} K_2CO_3}$ + α-desmotropo-; m.p.171-2°; $[\alpha]_D^{20}$+153

+ α-iso-desmotropo- $\xrightarrow{\Delta \text{ above m.p.}}$ + β-iso-desmotropo-;m.p.268-70°; $[\alpha]_D^{20}$ + 165

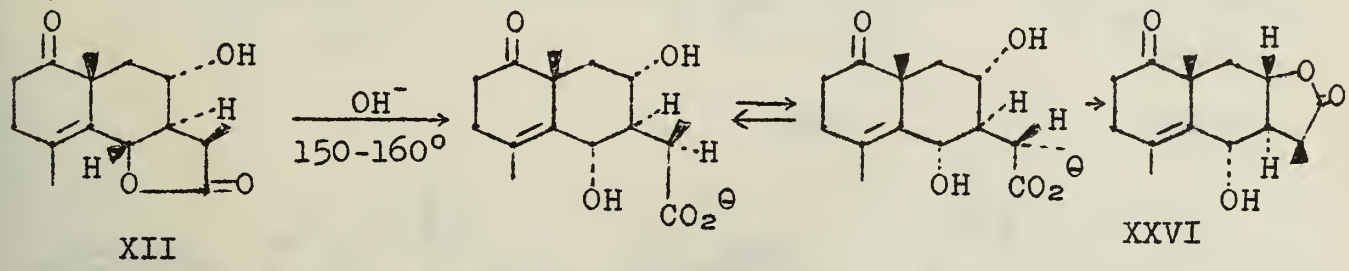
These last transformations are probably produced by the inversion of C_{11} through the enol, and it is unlikely that C_6 and C_7 are affected. The four dextro forms have been obtained, but so far attempts to invert C_6 and C_7 by acidic reagents have failed.

Stereochemistry of ψ-santonin and related compounds

The base-catalyzed elimination of a tosyl group is a trans elimination and favors the formation of a methine (18), but with ψ-santonin the elimination is away from the methine group. The hydroxyl group (C_7) and the tertiary hydrogen on C_6 are cis (5).

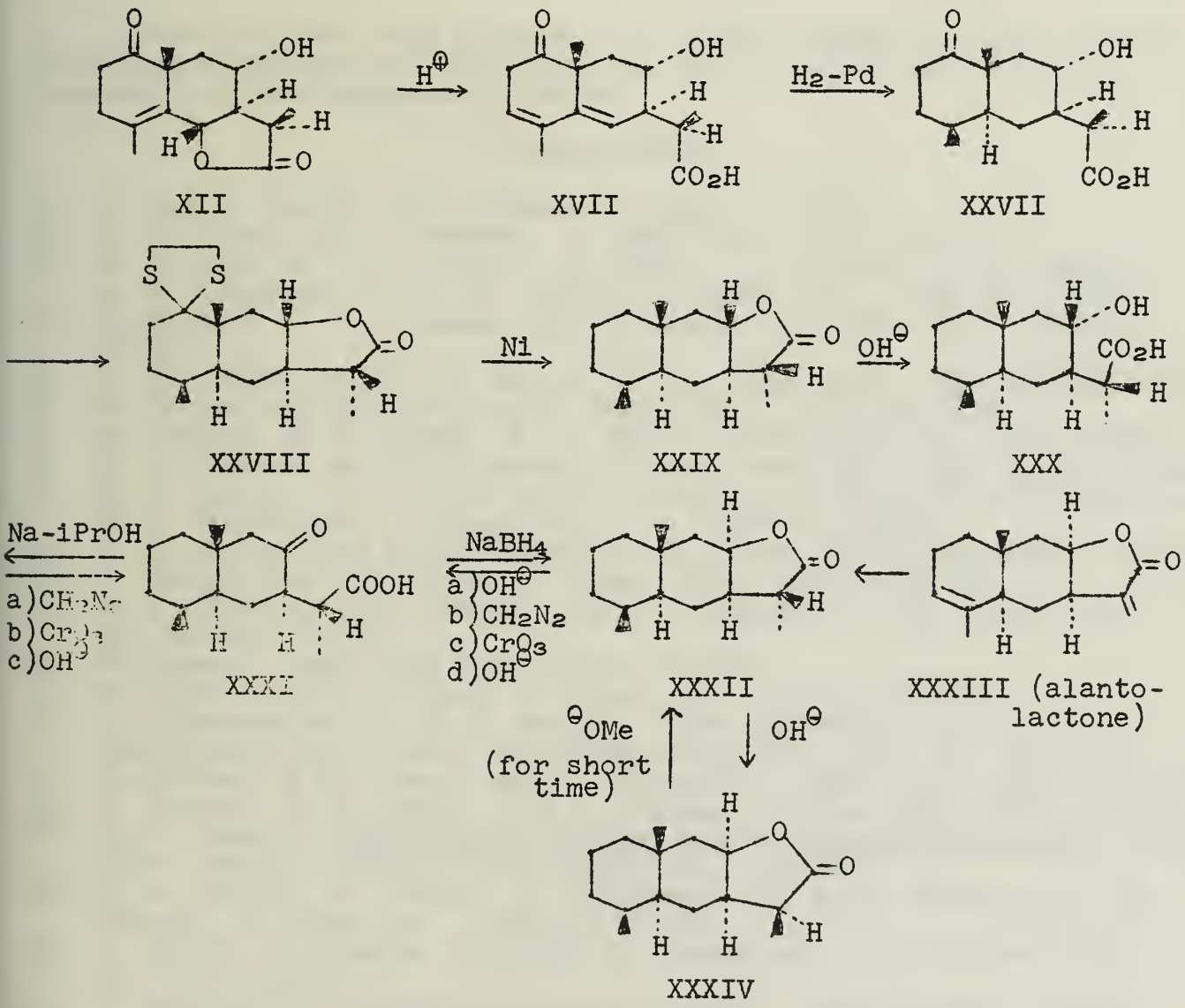
ψ-Santonin is stable to K_2CO_3 in boiling xylene, a reagent which causes epimerization of the 11-methyl group when in the unstable configuration (19).

When ψ-santonin is heated with KOH to 150-160° and then acidified, an isomeric, levorotatory compound, iso-ψ-santonin XXVI is obtained. Iso-ψ-santonin is stable to K_2CO_3 in boiling xylene. If in iso-ψ-santonin the original lactone ring of ψ-santonin were present the 11-methyl group would be in the unstable configuration (19).

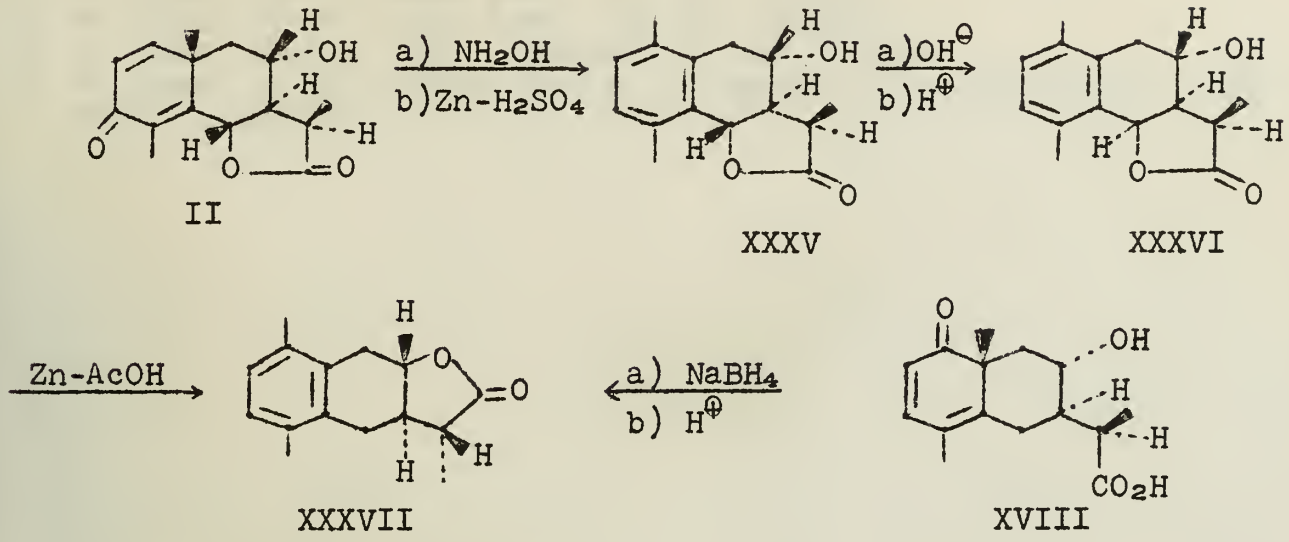


The stereochemistry of ψ-santonin has been shown at all centers except C_5 by degradation to compounds of known configuration.

SCHEME A (Tetrahydroalantolactone) (Postions 6,7,9) (20, 21, 22, 23)



SCHEME B (Artemisin) (Position 6,7,11) (23, 24, 25, 26, 27)



Chopra, Cocker, and coworkers (19) have summarized many of the reactions mentioned in this paper and there include the stereochemistry of the compounds involved.

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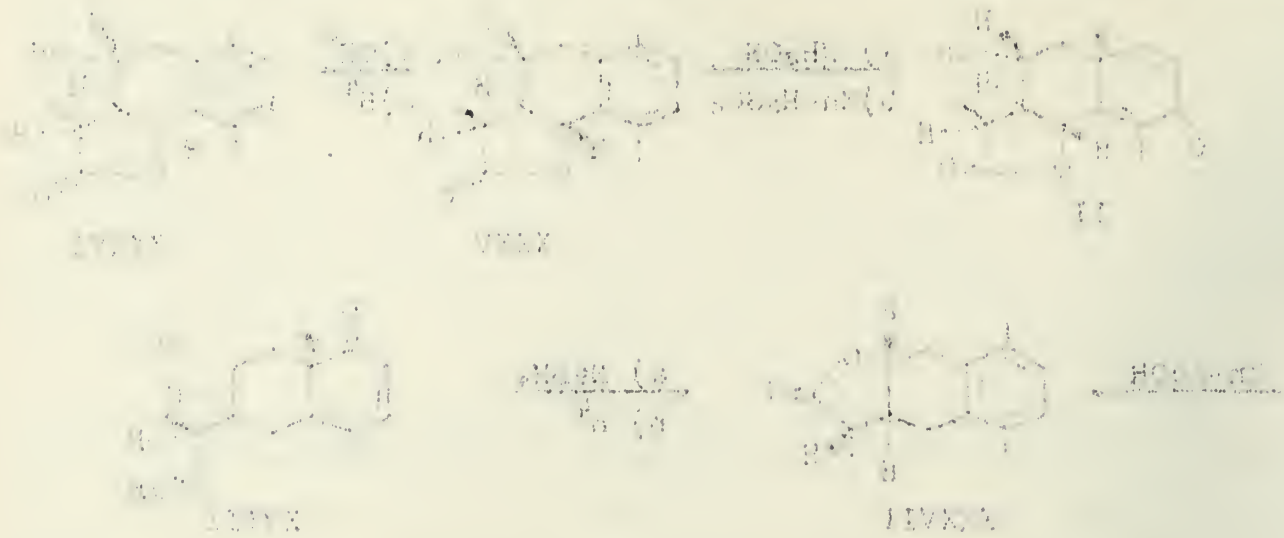

Chemical conversions (IV) and conversions (V) were accomplished using of the reactions described in this paper and above including the effects of the substituent functions.

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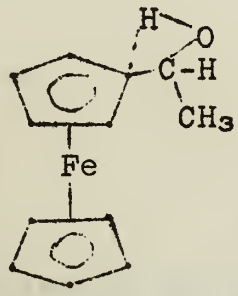
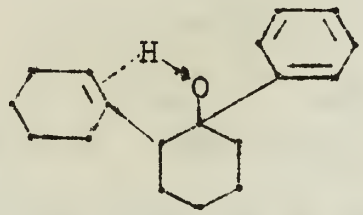
INTRAMOLECULAR INTERACTION BETWEEN HYDROXYL GROUPS AND π-ELECTRONS

Reported by D. B. Borders March 31, 1960

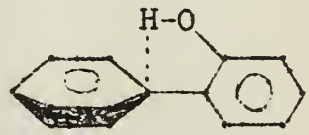
This seminar reviews intramolecular hydrogen bonding between hydroxyl groups and π-electrons as illustrated by α-hydroxyethylferrocene (I). Investigations of this subject, thus far, have in-



I



II



III

volved techniques of identifying the bonding involved and studies on electronic and steric influences on the OH...π bond.

In 1957 Trifan, Weinman, and Kuhn claimed the first observation of intramolecular hydrogen bonding to π-electrons (1). They found that α-hydroxyethylferrocene (I) showed two hydroxyl stretching frequencies in the infrared spectrum. The higher frequency band at 3617 cm.$^{-1}$ was due to free hydroxyl groups while the lower band 3574 cm.$^{-1}$ indicated associated hydroxyl groups. The low frequency band was concentration independent but temperature dependent which suggested intramolecular hydrogen bonding which they regarded as π-interaction. Similarly, β-phenylethanol exhibited the same corresponding absorptions at 3630 cm.$^{-1}$ and 3601 cm.$^{-1}$, respectively, but with reversed intensities, thus supporting the view of the greater π-electron lability in ferrocene compounds.

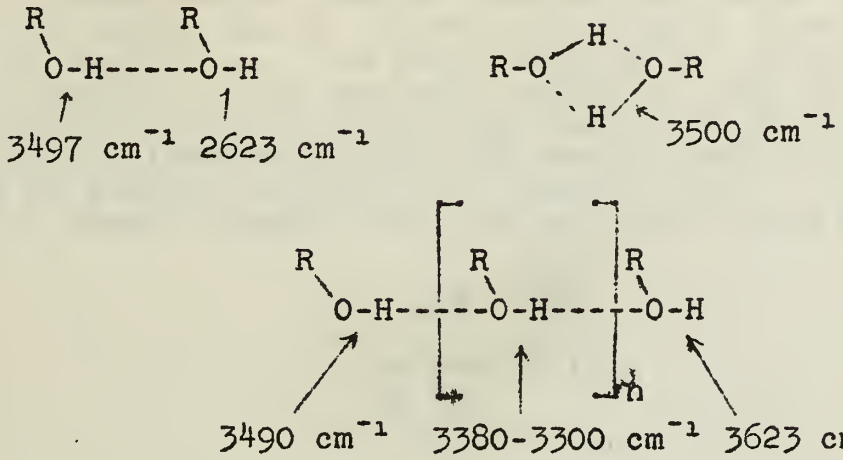
A few months before Trifan published these results, Anet and Bavin appeared with a paper concerning the intramolecular hydrogen bonding in compounds related to structure II. They proposed bonding by interaction to the ethylenic π-electrons (2). Perhaps, however, the true credit for the first observed case should go to Luttke and Mecke, who in 1950 re-evaluated Wulf's data on o-phenylphenol (III) and o-cyanophenol vibrational frequencies in the infrared region of the first overtone (3,4). They noted split hydroxyl absorptions and attributed the effect to intramolecular hydrogen bonding to the π-electrons.

Previous to this work similar spectral effects had been observed in the case of α,β-dimesityl-β-phenylvinyl alcohol and related compounds by Buswell, Rodebush and McWhitney. However, the nature of this effect was not understood (5). Related unexplainable spectral effects were also reported by Fox and Martin (6a). Prey and Berbalk found that intramolecular H-bonding occurred in o-phenolacetylenes (6b).

TYPES OF HYDROXYL HYDROGEN BONDING

The effect of temperature and concentration on the infrared spectra of various alcohols in the O-H stretching region has led to

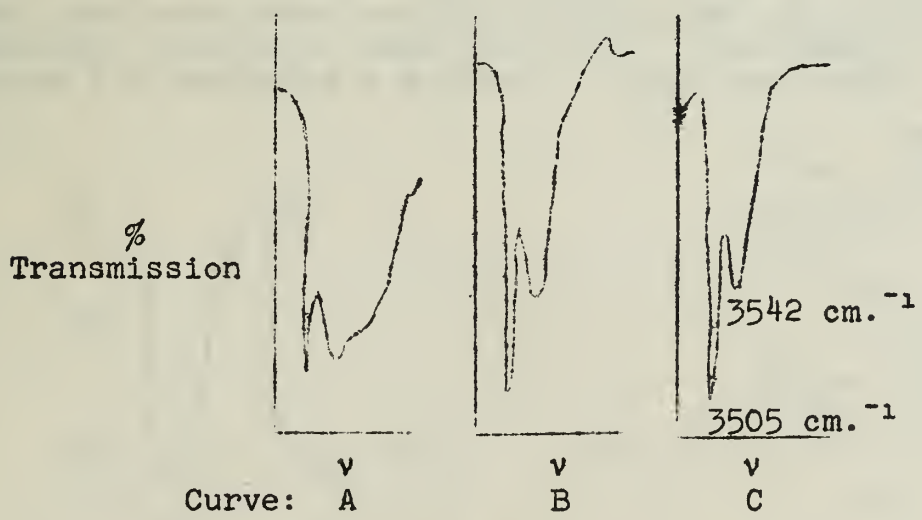
the following approximate band assignments in monomers, dimers, and polymers (7,8):



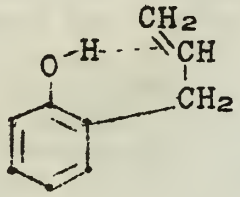
The intensities of the various bands can be used to determine the equilibrium concentration of each species. The intensity of the associated bands increases as the concentration of alcohol (in an inert solvent) increases. The free hydroxyl absorptions are most apparent at low concentrations or high temperatures since these conditions tend to minimize the number of hydrogen bonds.

Intramolecular hydrogen bonding differs from intermolecular hydrogen bonding in that the former is independent of concentration. The intramolecular hydrogen bonding can therefore be studied at concentrations too low for appreciable dimer or polymer formation (0.005 molar). The high degree of resolution required for such studies can be obtained by using lithium fluoride prisms which give optimum resolution in the 2000-4000 cm.$^{-1}$ region (9). In order to study spectra at low concentrations, near 0.005 molar, cells with path lengths of 1-2 cm. may be used.

The effect of concentration on the various infrared O-H stretching bands is illustrated by the spectra given below for 2-allylphenol (10). In this case the intramolecular hydrogen bonding results from π-interaction.



In curve A (0.7 molar) bands due to free hydroxyl groups and both the intra- and intermolecular hydrogen bonds can be observed. The broad band due to intermolecular hydrogen bonding decreases considerably in curve B (.07 molar) and is entirely lacking in curve C (.007 molar) The sharp band at 3605 cm.$^{-1}$ in each curve is due to free hydroxyl groups and is nearly at the same wave number as that of phenol. The intramolecular hydrogen bond absorbing sharply at 3542 cm.$^{-1}$ results from the O-H group interacting with the π-electrons of the ethylenic bond to give an average $\Delta\nu_{OH}$ shift of about 63 cm.$^{-1}$. This shift corresponds to those observed for intermolecular bonds between olefins



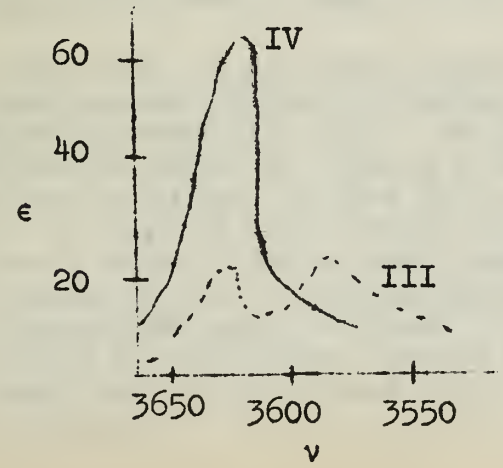
and phenols (11).

Badger has shown that the displacement of the associated bond from the free hydroxyl band ($\Delta\nu$) provides a measure of the force constant or bond energy of the OH H-bond and presumably of other related hydrogen bonds (12,13). This relationship varies in an almost linear fashion and provides a semi-quantitative measure of the hydrogen bond energy.

As in the case of 2-allylphenol above, weak intramolecular hydrogen bonds frequently take preference over stronger intermolecular bonds. Jaffe' has pointed out that this effect results from the higher negative entropy change required by intermolecular hydrogen bond formation (14).

STERIC EFFECTS

The steric requirements imposed on a molecule in order to have intramolecular hydrogen bonding to π-electrons provides a method of distinguishing between isomers in a number of cases. A good example of this application is the differentiation between cholesterol (III) and epicholesterol (IV)(15,16). Figure 2 shows the spectra of these compounds which readily distinguish the epicholesterol by the associated absorbency near 3590 cm.$^{-1}$. The method could also provide a means for analyzing a mixture of these compounds.



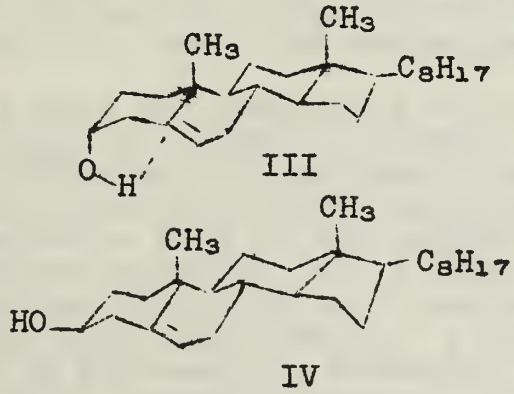
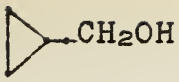


Fig. 2

$HC{\equiv}C(CH_2)_2CH_2OH$

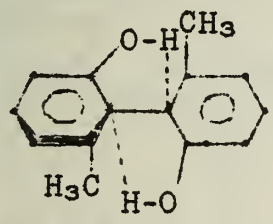
V



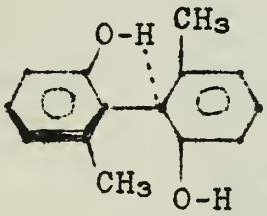
VI

A number of other isomers have been differentiated by this technique by Schleyer, Trifan, and Bacskai (16). They have also investigated the generality of this type of interaction by studying the infrared spectra of the compounds having different numbers of methylene groups between the hydroxyl group and the π-electrons (16). With the phenyl, vinyl, and acetylenic compounds intramolecular hydrogen bonding was observed when the number of methylene groups equaled one or two. Only in the case of the acetylenic compound V was there any interaction when the number of methylene groups equaled three. The intensity of bonded relative to the non bonded band decreased as the number of methylene groups separating the two functional groups increased, while at the same time the strength of the hydrogen bond increased (larger $\Delta\nu$). In the case of the cyclopropane derivatives, a possible interaction was noted only when one methylene group separated the ring and the hydroxyl group. This compound (VI) gave a peak at 3615 cm.$^{-1}$ with a shoulder at 3621 cm.$^{-1}$.

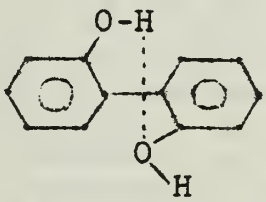
Intramolecular hydrogen bonding to π-electrons is observed in dihydroxybiphenyls when the hydroxyl groups are in the 2,2'-positions but not when they are at the 3,3' or 4,4'-positions (17). Dihydroxybiphenyls with substituents in the 6,6'-positions display OH...π absorption near 3550 cm.$^{-1}$ with a relatively small $\Delta\nu_{1/2}$ since there is little change in the OH....π bond distance due to oscillations about the common bond between rings (structure VII). In this case about 3-5% of the molecules display free hydroxyl absorptions



VII



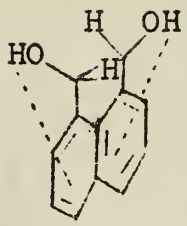
VIII



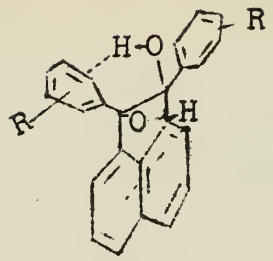
IX

(~3600 cm.$^{-1}$) resulting from structure VIII. If there is no hindrance from the 6,6'-positions, about 15% of the molecules take on conformation IX in which OH....O (~3490 cm.$^{-1}$) bonding occurs. In this case the distance in the OH....O bond is constantly changing due to oscillation around the bond between the rings; therefore, the associated hydroxyl band at 3490 cm.$^{-1}$ is broad and washed out.

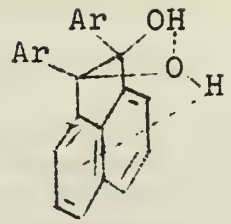
Moriconi <u>et al</u>. have studied steric and electronic effects on intramolecular hydrogen bonding in <u>cis</u>- and <u>trans</u>-1,2-diaryl-1,2-acenaphthalenediols (18). In the trans series they found that the unsubstituted diol (X) showed a strong hydroxyl absorption at 3600 cm.$^{-1}$ which was assigned to the OH...π-electron bond to the naphthalene ring. In diaryl substituted acenaphthalenediols (XI) a lower frequency more intense band appeared at 3549-3574 cm.$^{-1}$ and was attributed to OH....π bonding to the aryl substituents. A shoulder still appeared near 3600 cm.$^{-1}$ and it increased in intensity according to the order, phenyl > p-tolyl < m-xylyl < mesityl (Fig. 3). The position of this band also showed a slight shift to lower frequencies.



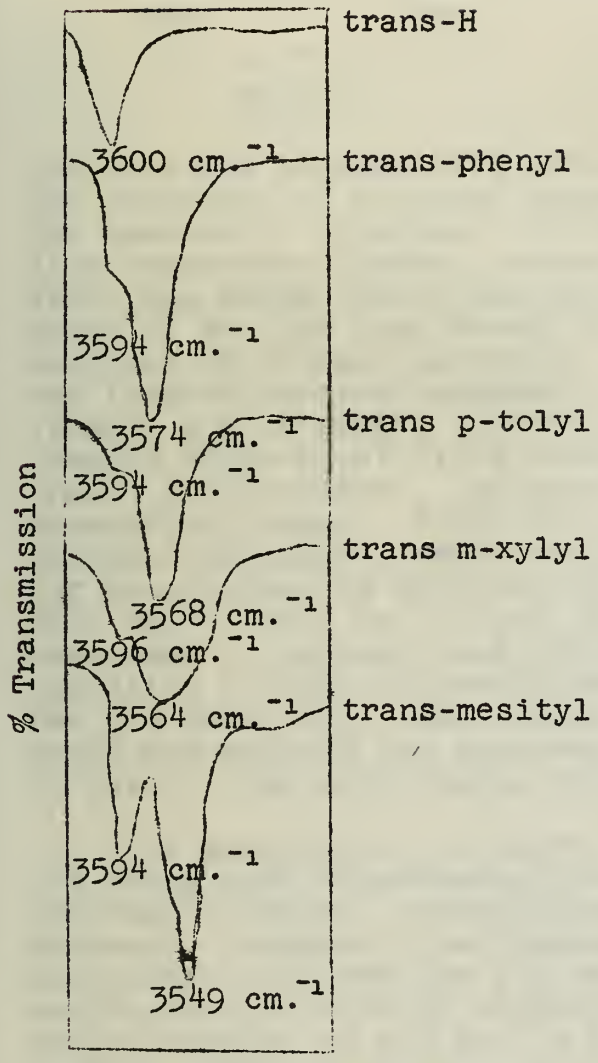
X



XI



XII



Concentration: ∿ .005 M. in CCl_4

Fig. 3

These changes in band intensities and positions can be interpreted as a combination of steric and electronic affects. Alkyl substituents on the benzene ring increase the electron density of the ring and thus increase the strength of the bond to the ring. This results in a shift of the corresponding OH....π spectral band to a lower wave length and increases its relative intensity as seen in going from phenyl to p-tolyl-substituted acenaphthalenediol. More methyl groups substituted on the benzene ring would increase this affect. However, their position of substition on the ring causes steric interactions which force the hydroxyl groups more into the field of the naphthalene nucleus, thus shifting the equilibrium to more π-bonding involving naphthalene. Consequently, the observed spectral effect is an increase in the intensity of the band near 3596 cm.$^{-1}$ in going to m-xylyl and mesityl derivatives. The greater intensity of the lower frequency band in the phenyl derivative again shows that the OH group displaced two carbon atoms from the ring is sterically more favorable for interaction. The cis-series of these compounds shows π-bonding to the naphthalene nucleus and also OH....O bonding as represented by figure XII. Increasing the steric effects from substituents with the cis-compounds increases OH....O bond strength by decreasing the OH....O bond distance. The hydrogen bond due to π-interaction is hardly influenced.

In a study on the effect of chain lengths on the OH....π bond, Oki and Iwamura (19,20) found that saturated alcohols have spectral features like those which had been attributed to OH....π bonding in unsaturated alcohols. Figure 4 shows the spectrum of allyl alcohol as an asymmetric band with a shoulder near 3630 cm.$^{-1}$ and a peak near 3605 cm.$^{-1}$ which were considered as abosrptions due to

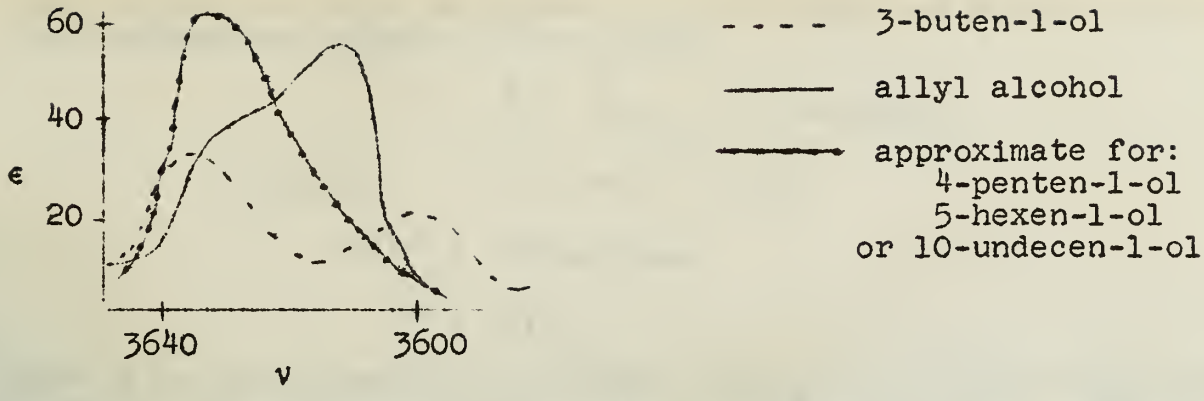


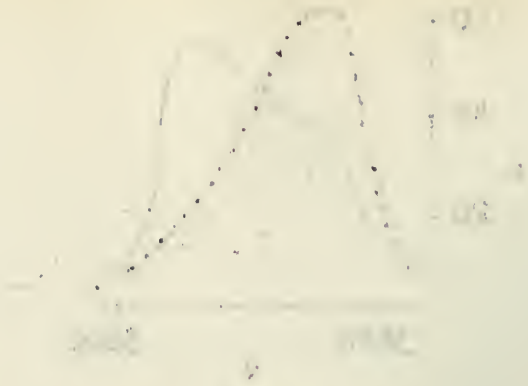
Fig. 4

the free and π-associated hydroxyl groups respectively. The peaks for 3-buten-1-ol are more separated, however, of inverse intensity. The spectra of 4-penten-1-ol, 5-hexen-1-ol, and 10-undecen-1-ol also give asymmetric hydroxyl absorptions. Association resulting from π-electrons seems highly improbable in these last three examples, because of the low bond energy from OH....π association and the large decrease in entropy necessary to form such a bond. In addition, Oki and Iwamura observed asymmetric hydroxyl absorption bands for ethanol and isopropyl alcohol by using a high resolution instrument (Perkin Elmer Model 112 G double pass high precision grating infrared spectrometer). Methanol, tert-butanol, and phenol showed symmetrical peaks. Previous to this work it had been known that primary, secondary, and tertiary alcohols display hydroxyl stretching absorptions at slightly different wave numbers (approximately 3637 $cm.^{-1}$, 3627 $cm.^{-1}$, and 3617 $cm.^{-1}$ respectively). Attempts had been made to explain this phenomenon in terms of mesomeric or inductive effects of substituents influencing the force constant in the O-H bond (22). This would explain the shift in frequency but would not explain the asymmetry of the bands, assuming the asymmetry to result from overlapping bands.

The possibility of dimers or other associated species is ruled out since such structures do not exist at the low concentrations used for these spectral observations (7,8). Since structures such as methanol, t-butanol, and phenol, in which rotational conformations around the C-O bond are all equivalent, have symmetrical bands, Oki and Iwamura attributed asymmetrical bands to rotational isomers. An energy barrier of 0.8 to 0.9 Kcal./mole for the C-O bond would be sufficient for the presence of isomers at room temperature. Previous investigations had shown the rotational energy barrier for the C-O bond in methanol to be 0.9-1.0 Kcal./mole (22).

Since the infrared bands attributed to OH....π bonding are frequently observed as shoulders on asymmetric free hydroxyl absorptions, bands due to rotational isomers about the C-O bond can introduce considerable error in the determination of the OH....π contribution. To correct for this effect, the wave numbers responsible for the various conformations were determined by comparing the free hydroxyl absorptions within two groups* of alcohols: 1. methanol ethanol, isopropyl alcohol, and t-butyl alcohol. 2. benzyl alcohol, benzhydrol, and triphenylcarbinol. This was accomplished by assuming the asymmetric curves were composed of two overlapping bands which followed the Lorentz expression (19,20). The integrated

*The alcohols listed are representative types from 12 alcohols in group 1 and 8 alcohols in group 2.



band intensities were determined by the method of Ramsay (21) using four parameters because of two bands:

$$A = \frac{\pi}{2} \cdot \Delta\nu_{1/2} \cdot \ln(I_o/I)_{max}$$

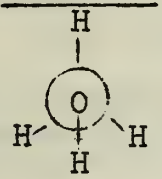
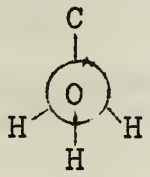
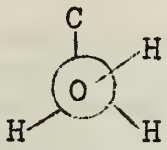
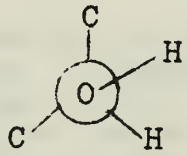
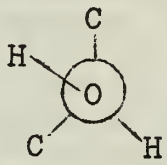
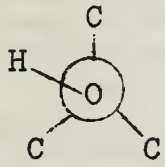
$$\ln(I_o/I)\nu = a/[(\nu-\nu_o)^2 + b^2]$$

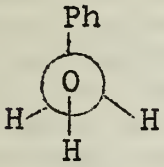
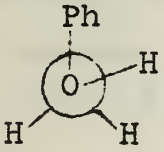
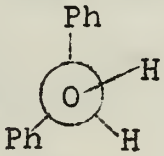
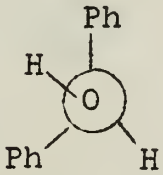
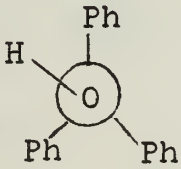
$$a/b^2 = \ln(I_o/I)_{max}$$

$$2b = \Delta\nu_{1/2}$$

where A is the integrated intensity, $\Delta\nu_{1/2}$ is the half band width, ν_o the amount expressed by the wave number at the band center, and a and b are parameters. The values obtained for the various rotational isomers are given in Table I.

TABLE I

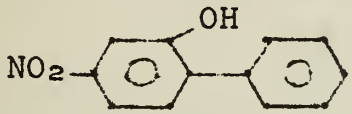
Type	Methanol	Ethanol	i-propyl alcohol	t-butyl alcohol	ν (cm.$^{-1}$)
I			---	---	3644-3636
II	---			---	3626-3629
III	---	---			3615-3618

Type	Benzyl alcohol	Benzhydrol	Triphenyl carbinol	ν (cm.$^{-1}$)
IV		---	---	3644-3636
V			---	3616-3619
VI	---			3608-3611

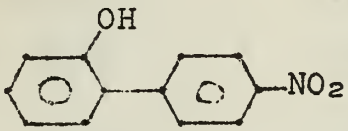
The difference in wave numbers between the corresponding conformations of the alkyl and aromatic alcohols results from hydrogen bonding to the electrons of the aromatic rings. In other words, the frequencies given for the aromatic compounds are those of rotational isomers with an added effect of lowering the frequency from OH....π interactions.

ELECTRONIC EFFECTS

The degree of electronic effect on the OH....π bond is illustrated by the change in hydrogen bond strength in the biphenyl structures XIII and XIV (22). The $\Delta\nu_{max}$ between the free and interacted forms of compounds XIII and XIV are 44.0 cm.$^{-1}$ and 21.4 cm.$^{-1}$ respectively,



XIII



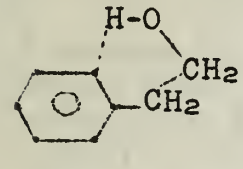
XIV

	XIII	XIV
Associated OH:	3553.8 cm.$^{-1}$	3579.6 cm.$^{-1}$
Free OH:	3597.8 cm.$^{-1}$	3601.0 cm.$^{-1}$

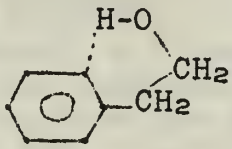
thus the hydrogen bond to the electrons in compound XIII is stronger. These compounds represent two extremes of electronic effects from 4- and 4'-positions.

There has been some consideration as to the site of hydrogen bonding to the unsaturated system. Goldman and Crisler have proposed hydrogen bonding through the 1-position in 2-phenylethanols (23). Their conclusion is based on the $\Delta\nu$ between free and associated hydroxyl stretching absorptions in the first overtone region. Phenylethanol has a $\Delta\nu$ between the free and associated absorptions of 52 cm.$^{-1}$ (free OH 7100 cm.$^{-1}$, associated 7048 cm.$^{-1}$) whereas p-methoxy-phenylethanol gives 79 cm.$^{-1}$ (free OH 7100 cm.$^{-1}$, associated 7021 cm.$^{-1}$). The Hammett σ_m and σ_p values for the CH_3O-group are respectively +0.12 and -0.27. The electron density resulting from the CH_3O-substituent is higher at the para-position and lower at the meta compared to the effect when hydrogen is the substituent. As a result, hydrogen bonding para- to the methoxy-group should show a $\Delta\nu_{OH}$ greater than that for the unsubstituted compound while bonding meta- to the methoxy group should give a $\Delta\nu_{OH}$ less than that for the unsubstituted compound. Since p-methoxy-phenylethanol gave a larger $\Delta\nu_{OH}$ than phenylethanol, the OH....π bond was considered as the type shown by structure XVII.

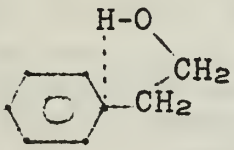
In contrast to this proposal, Oki and Iwamura have suggested hydrogen bonding to the ortho position (XV) or to a position



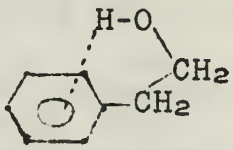
XV



XVI



XVII



XVIII

intermediate between positions one and two (XVI) (24). Structure XVI is supported by the fact that a given substituent either meta or para to the 2-position gives almost the same associated OH....π wave number. Different substituents in either the meta or para

positions give different wave numbers, however (Table II). This means that a change in electron density at 1 or 2-positions does not influence the OH....π bond but a change in the electron density of the entire ring does. Structure XVIII, which would also fulfill this requirement, is ruled out primarily on the basis of steric requirements. The π-complexing between the 1 and 2-positions of an

TABLE II

Substituent	Position	$\Delta\nu_{OH}$	A_I/A_f*
H_2N	m	37.5	1.50
	p	37.2	1.14
CH_3O	m	33.5	1.19
	p	33.5	1.03
CH_3	m	32.7	1.06
	p	33.2	0.93
H		29.6	0.86
Cl	m	24.2	0.645
	p	25.3	0.64
NO_2	m	20.0	0.207
	p	21.0	0.253

*A - interacted and free integrated absorption intensities

aromatic ring has been shown by x-ray diffraction for a complex between silver ions and benzene (25).

A comparison of the integrated absorption intensities of substituents in either the meta or para positions suggests structure XV, however. Substituents which increase the electron density of the ortho-positions also increase the intensity of the associated band. The ratio of the interacted OH bond intensity to the free OH bond intensity is given in Table II. A small error is introduced by the rotational isomer contribution which is included in the associated hydroxyl absorption.

A somewhat similar line of reasoning suggests that hydrogen bonding to the π-electrons in benzyl alcohols occurs at the 1-position (26).

If the log $\frac{A_i/A_f}{(A_i/A_f)_o}$ for benzyl alcohols is plotted against the σ values of Hammett, a linear relationship is obtained. The ratio A_i/A_f is the comparison of interacted and free integrated absorption intensities for a substituted benzyl alcohol while $(A_i/A_f)_o$ is the same relationship for the unsubstituted alcohol. Since a more linear plot of σ-values vs. log A_i/A_f is obtained when the 1-position rather than the 2-position is considered meta or para to the substituents on the benzyl alcohols, OH....π bonding to the 1-position is further supported (26).

A linear plot is also obtained in the case of 2-phenylethanols if the substituents are taken as meta or para to the 2-position

A plot with the substituents meta or para to the 1-position gives a larger scattering of points. These results are further evidence for H-bonding to the 2-position for 2-phenylethanols. However, a plot of the σ_m and σ_p values vs. $\Delta\nu_{OH}$ (with respect to either the 1 or 2-position) gives a scattering of points. This effect in contrast suggests the H-bond may be intermediate between the 1 and 2-positions.

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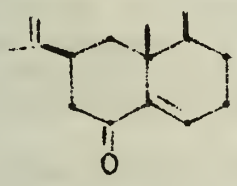
EREMOPHILONE

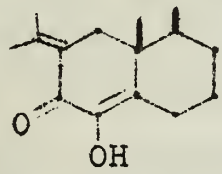
Reported by C. R. Johnson April 4, 1960

Sesquiterpenoid chemistry offers a wide range of oxygen function ring size, and mechanistic change tailored to fascinate the organic chemist. Many interesting challenges provided by eremophilone and congeners, the first bicyclic sesquiterpenoid ketones recorded, have survived three decades of investigation.

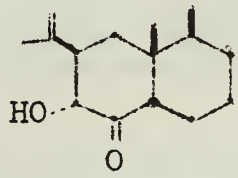
The late Sir John Simonsen and collaborators obtained three closely related crystalline ketones from the wood oil of the small Australian tree, Eremophilia michelli, known vernacularly as buddah wood or bastard sandalwood (1,2). The structures of eremophilone (I), hydroxyeremophilone (II), and hydroxydihydroeremophilone (III) are of particular interest since they present exceptions to the classical isoprene rule, i.e., their architecture cannot be dissected into three isopentane residues.



I

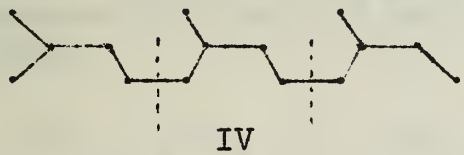


II

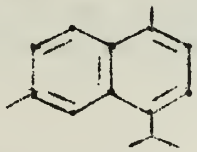


III

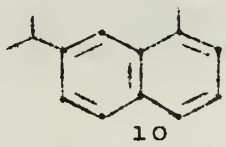
Today sesquiterpenes are considered as compounds whose carbon skeletons can be derived from a farnesane chain (IV) of three isoprene units, either per se, or as an intermediate in biosynthesis. Before 1921, there was no consanguine biogenetic theory for the terpene series. With the introduction of sulfur dehydrogenation by Ruzicka in the early twenties and the subsequent selenium refinement of Diels, large numbers of sesquiterpenes were shown to afford either cadalene (V) or eudalene (VI). The former retains all fifteen carbon atoms arranged in a cyclized farnesane chain (IV). It was then rational to conclude that an angular methyl group from position 10 was eliminated in dehydrogenation to eudalene (VI) (3).



IV



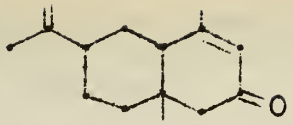
V



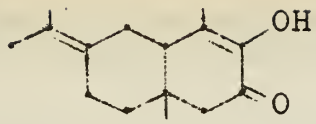
VI

STRUCTURAL STUDIES

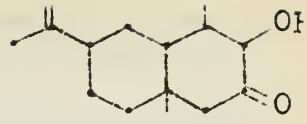
Reduction of eremophilone (I) with sodium and ethanol gave dihydroeremophilol, which afforded eudalene (VI) on dehydrogenation with selenium. Ozonolysis of dihydroeremophilol provided formaldehyde and a methyl ketone. A hydroxymethylene derivative was obtained from eremophilone by condensation using sodium and amyl formate, while catalytic hydrogenation furnished a tetrahydroketone. Alkaline hydrogen peroxide produced an epoxide, eremophilone oxide. The above observations are indicative of an isopropenyl group not in conjugation with a $-CH_2-CO-C{=}C<$ system. Superimposing these data on an isoprenoid framework based on eudalene, Simonsen, Bradfield, and Penfold proposed structure VII for eremophilone (1).



VII



VIII

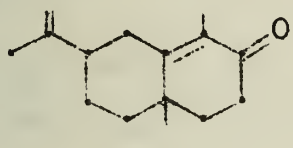


IX

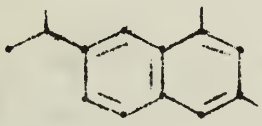
The enolic character of hydroxyeremophilone (II) was shown by a ferric chloride test. The benzoate of hydroxyeremophilone gave on ozonolysis, not formaldehyde, but acetone, indicating an isopropylidene side chain. In a reaction to be reviewed later, eremophilone oxide, on digestion with acetic acid and sodium acetate, gave hydroxyeremophilone, identical with the "natural" product. Based upon the earlier formulation for eremophilone (VII), hydroxyeremophilone was then represented by VIII.

The keto-alcohol, hydroxydihydroeremophilone, then assigned structure IX, gave on catalytic hydrogenation a dihydro derivative, from which tetrahydroeremophilone was prepared by reduction with sodium amalgan, thus demonstrating, by analogy from the camphor series the presence of an α-ketol grouping in hydroxydihydroeremophilone. Upon ozonolysis formaldehyde was produced (1).

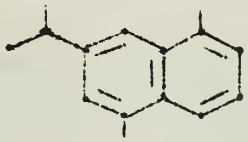
Four years later, in 1936, in connection with work on an Indian sesquiterpenoid ketone, α-cyperone (X), Simonsen and coworkers treated tetrahydroeremophilone with methyl Grignard reagent (4). Aromatization of the product with selenium did not give the expected 1,3-dimethyl-7-isopropylnaphthalene (XI), but, rather, 1,5-dimethyl-7-isopropylnaphthalene (XII), clearly showing that the carbonyl group in eremophilone and related ketones must be in position 5 and not 3 as had previously been assigned.



X

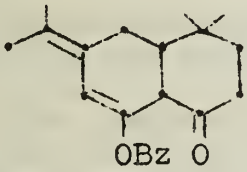


XI

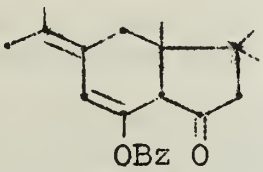


XII

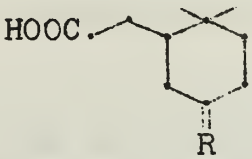
Earlier results were reviewed, but no tenable structure was evident. With care being taken to be obedient to the isoprene rule, structures XIII and XIV were considered for hydroxyeremophilone benzoate.



XIII



XIV

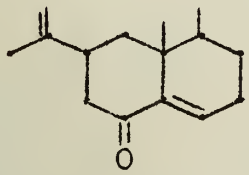


XVa R = O
XVb R = H_2

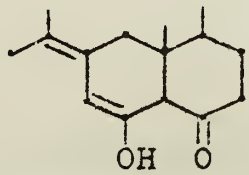
The degradation of hydroxyeremophilone (II) seemed to be a promising line of attack. On prolonged ozone oxidation of hydroxyeremophilone benzoate, a keto-acid, $C_{10}H_{16}O_3$, was obtained. Based upon the hypothetical structure XIII for the benzoate, the keto-acid would be XVa and its Clemmensen reduction product, XVb. The

phenacyl ester from the natural source was compared with the ester of synthetic 2,2-dimethylcyclohexylacetic acid (XVb) (5) and found not to be identical.

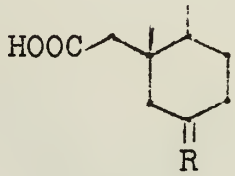
Shortly thereafter, Robinson, on consideration of the published data, suggested that eremophilone was represented by XVI and hydroxyeremophilone by XVII (6). The keto-acid obtained above would then be XVIIIa, yielding on reduction the acid XVIIIb.



XVI



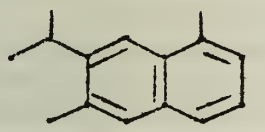
XVII



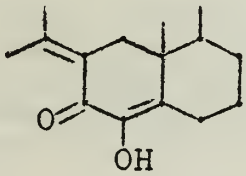
XVIIIa R = O
XVIIIb R = H_2

By subjecting the methyl ester of the cyclohexylacetic acid to the action of selenium, o-xylene was obtained in almost theorectical yield. Later, an enantiomorph of XVIIIb was synthesized (7) and shown to afford racemic acid XVIIIb on admixture with the natural acid.

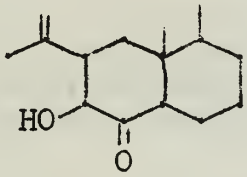
In opposition to the proposed structure XVII, many of the reactions and properties of hydroxyeremophilone were suggestive of vicinal oxygen functions, e.g., oxidation with lead tetraacetate, and since eremophilone oxide can be transformed to this hydroxyketone, one of these functional groups must be a position 5 (8). Catalytic hydrogenation of the methyl ether of hydroxyeremophilone, followed by the addition of methyl magnesium iodide and dehydrogenation of the product with selenium, furnished 1,6-dimethyl-7-isopropylnaphthalene (XIX). It follows, then, that hydroxyeremophilone must be XX.



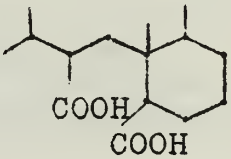
XIX



XX



XXI



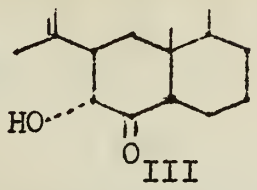
XXII

The glycol prepared from hydroxyeremophilone or dihydrohydroxyeremophilone yielded on oxidation with lead tetraacetate followed by permanganate a dibasic acid, considered to be XXII.

By re-interpretation of previous work, hydroxydihydroeremophilone was assigned structure XXI.

The observed ultraviolet spectra of eremophilone (XVI) (9), λ_{max} 243 mμ (ε 8,000) and 319 mμ (ε 800) and the diosphenol, hydroxyeremophilone (XX), λ_{max} 274 mμ (ε 1600) and 309 mμ (ε 9,000), are compatible with modern correlations. The last paper by the Simonsen group (in collaboration with Gillam) was particularly noteworthy in that it was one of the earliest examples of the effective use of ultraviolet spectroscopy in structural studies (8).

STEREOCHEMISTRY



III

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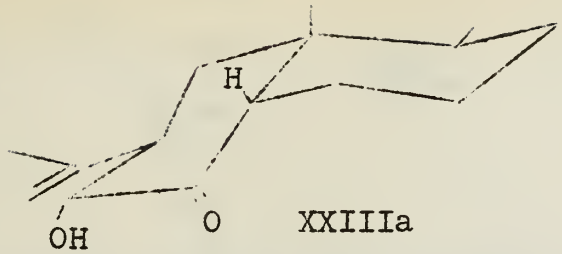
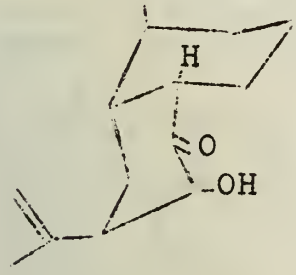
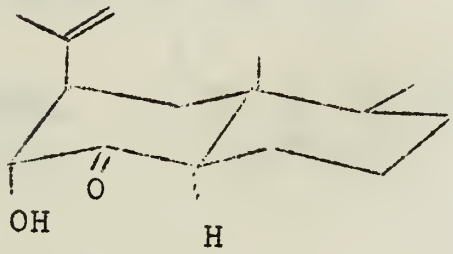


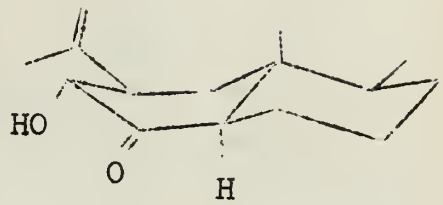
XXIIIa



XXIIIb



XXIVa



XXIVb

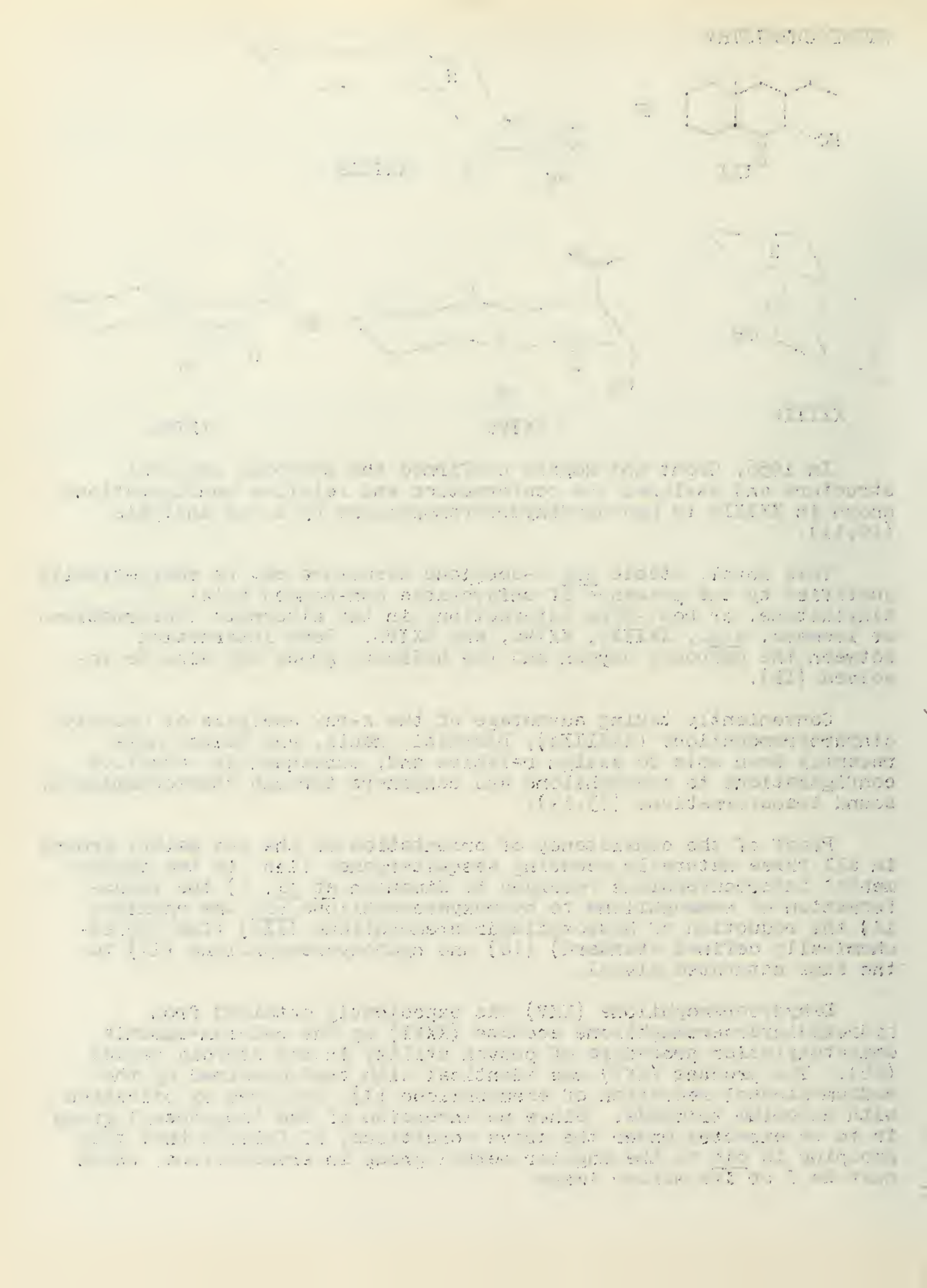
In 1956, Grant and Rogers confirmed the proposed skeletal structure and assigned the conformation and relative configurations shown in XXIIIa to hydroxydihydroeremophilone by x-ray analysis (10,11).

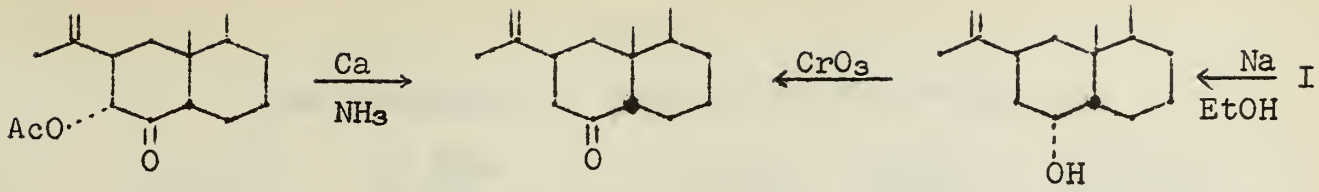
This novel, stable cis-α-decalone structure may be energetically justified by the presence of unfavorable non-bonded axial, 3-alkylketone, or boat-type interactions in the alternate conformations or isomers, e.g., XXIIIb, XXIVa, and XXIVb. Some interaction between the carbonyl oxygen and the hydroxyl group may also be involved (12).

Conveniently taking advantage of the x-ray analysis of hydroxydihydroeremophilone (XXXIIIa), Djerassi, Mauli, and Zalkow have recently been able to assign relative and, subsequently, absolute configurations to eremophilone and congeners through stereochemically sound transformations (13,14).

Proof of the consistency of orientation of the two methyl groups in all three naturally occuring sesquiterpenes lies in two experimental interconversions recorded by Simonsen et al: i) the transformation of eremophilone to hydroxyeremophilone via the epoxide; ii) the reduction of hydroxydihydroeremophilone (III) (the stereochemically defined standard) (10) and hydroxyeremophilone (II) to the same saturated glycol.

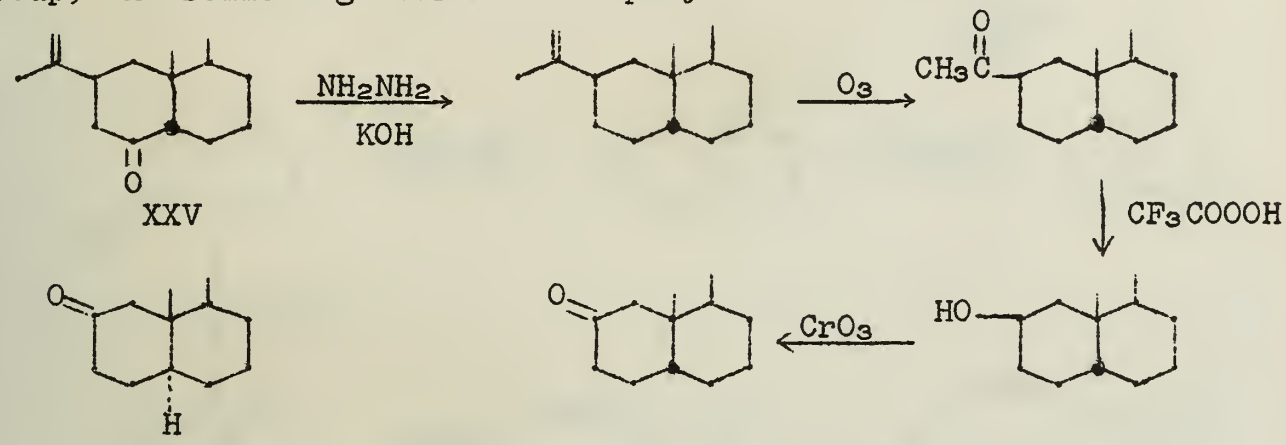
Dihydroeremophilone (XXV) was expediently obtained from hydroxydihydroeremophilone acetate (XXVI) by the calcium-ammonia deacetoxylation procedure of proven utility in the steroid series (15). The product (XXV) was identical with that obtained by the sodium-alcohol reduction of eremophilone (I), followed by oxidation with chromium trioxide. Since no inversion of the isopropenyl group is to be expected under the above conditions, if follows that this grouping is cis to the angular methyl group in eremophilone, which must be I or its mirror image.





XXVI XXV

To provide direct chemical evidence for the cis ring juncture, itself a direct consequence of the orientation of the isopropenyl group, the following course was employed:



XXV XXVIII XXVII

The ketone (XXVII) obtained from cis-dihydroeremophilone (XXV) was shown to differ from authentic trans-ketone (XXVIII) by infrared and rotatory dispersion comparisons (13). Some ambiguity resides in this sequence, since in at least one case (16), the Wolff-Kishner reduction has been shown to proceed by "kinetic-controlled" reduction of a thermodynamically unstable isomer.

Hydroxyeremophilone methyl ether (XXIX) was hydrogenated using palladium on charcoal to methoxytetrahydroeremophilone. Alkaline equilibration at the epimerizable center followed by demethoxylation with calcium-liquid ammonia provided trans-3-isopropyl-5,10-dimethyl-2-decalone (XXX). A stereochemically valid synthesis of the latter by the Wayne State workers has served to define the absolute configurations for the series.

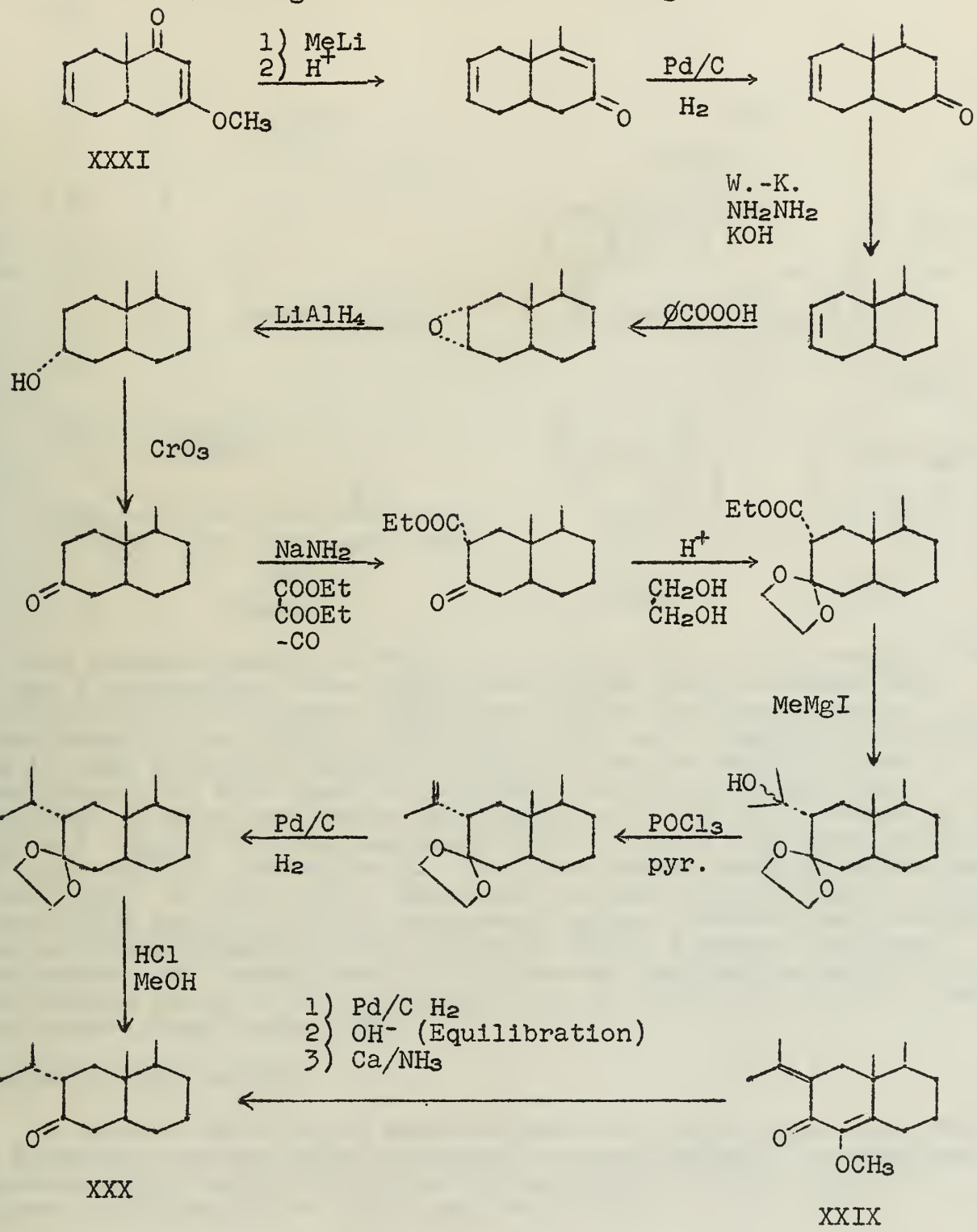
Ketone (XXXI) (of known absolute configuration (17), since its enantiomorph gives rise to rings C and D in the Woodward steroid synthesis) has been converted to trans-3-isopropyl-5,10-dimethyl-2-decalone (XXX) by the methods of scheme 1. The stereoformula I, II, and II for eremophilone, hydroxyeremophilone, and hydroxydihydroeremophilone, respectively, then are absolute representations.

Klyne, some years earlier, had assigned the absolute stereochemistry intrinsic in formula XXXII by the method of molecular roation differences. However, the steric "analogue", Δ^5-cholesten-4-one (XXXIII), available to him did not account for any rotational contribution by the isopropenyl group (18).

In 1956, Djerassi and associates, in an effort to resolve the inherent uncertainty, examined the rotatory dispersion (R.D.) curves of eremophilone and model compounds used by Klyne in the above assignment (19). Although made by incorrectly surmising the orien-

Scheme 1

The Assignment of Absolute Configuration



tation of the isopropenyl group, a brief survey of the design of the dispersion investigation might prove instructive.

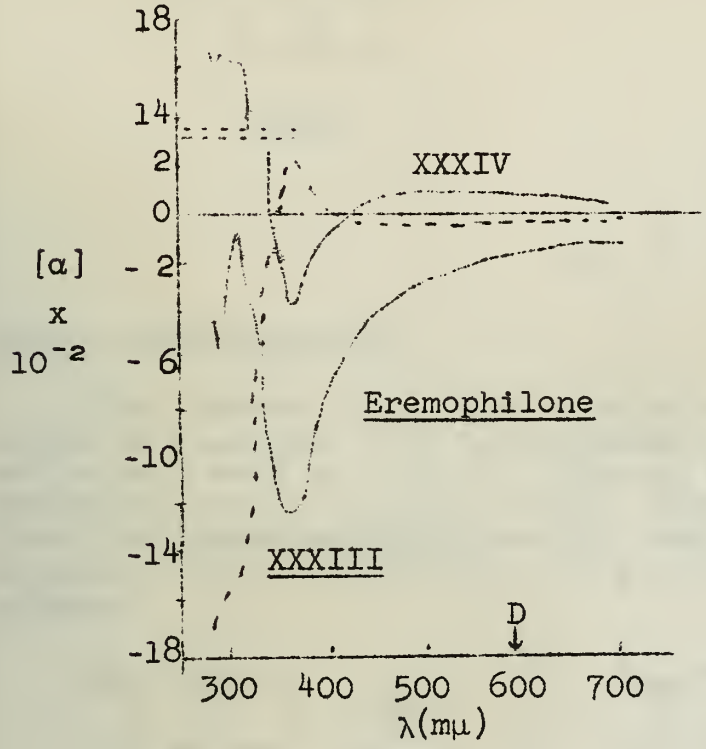
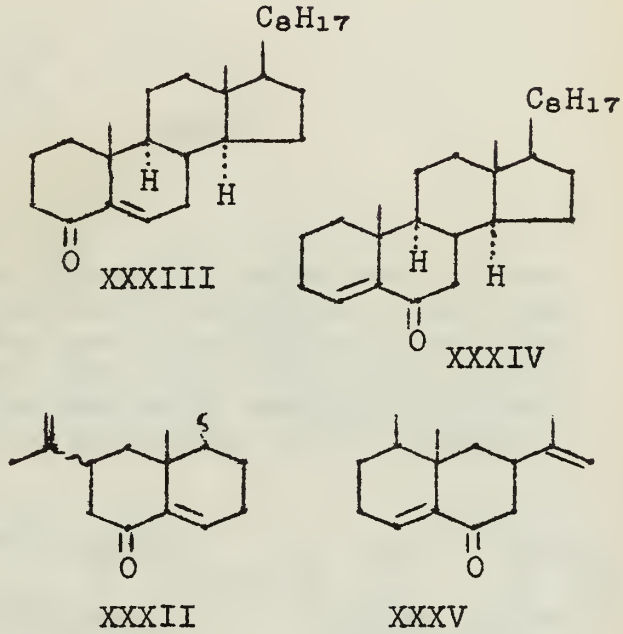


Figure 1



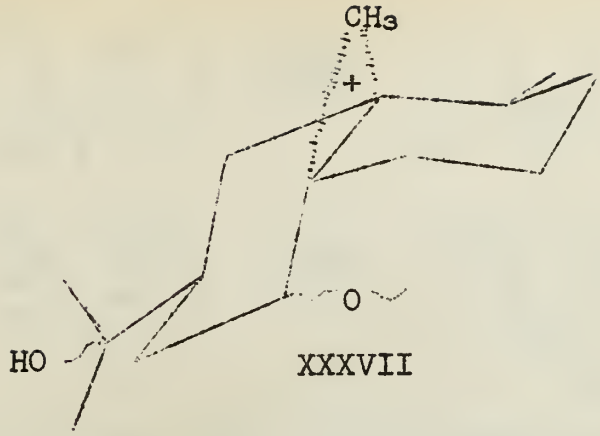
The general shapes of the R. D. curves (Fig. 1) of eremophilone (I) and Δ^4-cholesten-6-one (XXXIV) are quite similar except the entire curve of the former shows more negative values, whereas Δ^5-cholesten-4-one (XXXIII) (Klyne's model) and eremophilone compare only in that both show negative rotations at the sodium D line. These dispersion data lead to expression XXXV for eremophilone. The "validity" of this assignment was supported by the R. D. curve of the "cis" and "trans" tetrahydroeremophilone compared with coprostanone and cholestanone, respectively. The more stable product was assumed to be "trans" at that time. The establishment of the correct orientation (vide supra) for the isopropenyl group rendered the steroidal model compounds inappropriate. Unfortunately a recent published correlation, the octant rule in its present qualitative state, is of questionable value in the interpretation of the R. D. curves in this multi-substituted series (20).

BIOGENETIC IMPLICATIONS

In other eudalene-type sesquiterpenoids, where known and where the asymmetry has not been destroyed by unsaturation, the absolute stereochemistry exhibited is that of expression XXXVI, e.g., eudesmol, α-cyperone, α- and β-santonin (21).

The demonstration of the absolute configurations of the eremophilone family provides for the intriguing biogenetic implication of a common eudalenoid precursor, from which the Eremophilia ketones could arise by Wagner-Meerwein migration of the methyl group (XXXVII) (6, 14, 18, 22).

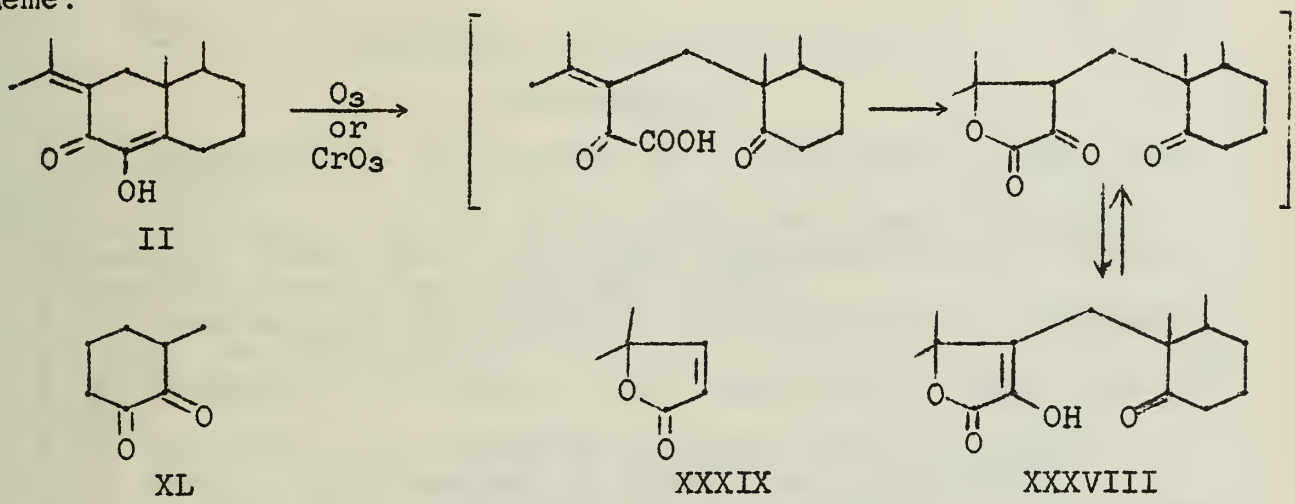
XXXVI



XXXVII

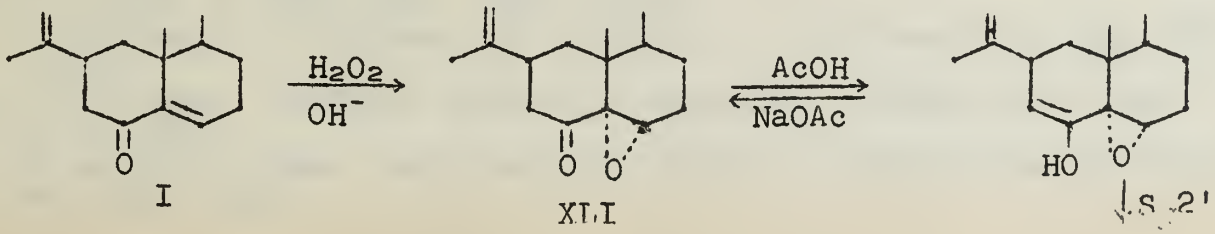
NOVEL TRANSFORMATIONS

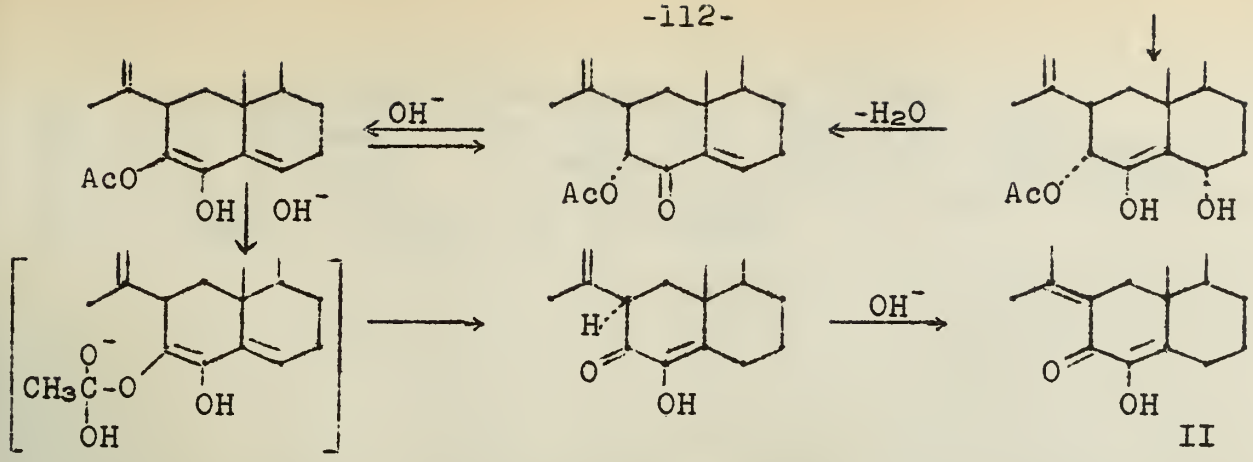
The Simonsen group had obtained a "phenolic" substance, formulated as $C_{12}H_{18}O_3$, from hydroxyeremophilone by prolonged ozonolysis or chromic acid oxidation. Geissman has now shown this to have the empirical formula $C_{12}H_{22}O_4$ (23). Based upon the established structure for hydroxyeremophilone (II) and ultraviolet analysis, he has proposed structure XXXVIII, being formed according to the annexed scheme.



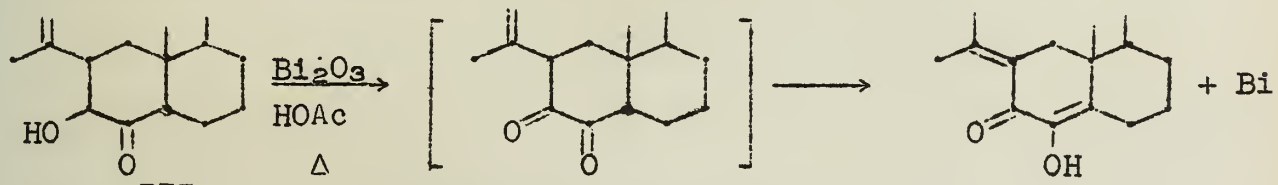
The C_{15} "phenol" (XXXVIII) exhibits λ_{max} at 238 mμ (ε log 3.88) and an isolated carbonyl absorption at 295 mμ. Ionization by 0.1 N alkali produces a bathochromic shift of 39 mμ. Close parallels are found in comparable dicarbonyl systems (e.g., XL) Typically, acetylation of an enolic hydroxyl group cancels its contribution to the U. V. spectrum, and, indeed, the spectrum of the acetate (of XXXVIII) shows an end-absorption plateau that is substantially that of model α,β-unsaturated-γ-lactones (e.g., XXXIX) (24).

With the structure and stereochemistry established, and very interesting conversion of eremophilone oxide (XLI) to hydroxyeremophilone (II) deserves further scrutiny. Several authors (8,21,25) have proposed mechanistic schemes for the reaction. A pausible modification is shown.





The facile and efficient bismuth oxide acyloin oxidation method of Rigby (26) has been used to convert hydroxydihydroeremophilone (III) to hydroxyeremophilone (II) in 91% yield (13).



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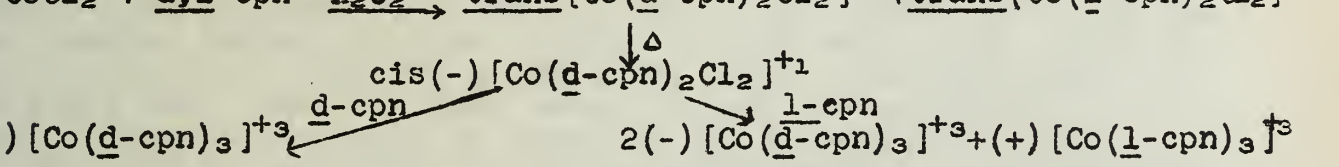
CONFORMATIONAL EFFECTS IN COMPLEX IONS

Reported by W. J. McMurray April 7, 1960

I. INTRODUCTION:

In his coordination theory, Werner predicted that hexacoordinated metals would possess an octahedral configuration and as a result were potentially optically active. The experimentation on the stereochemistry which followed in the next thirty years to test this hypothesis brought to light the existence of a high degree of stereospecificity in reactions of complex ions. The experiments of Jaeger and Blumendal provide a classic example (1). Many other examples are discussed in various reviews (2-5).

Jaeger and Blumendal isolated from the oxidation of cobaltous chloride in the presence of racemic trans-1,2-cyclopentanediamine (cpn) only trans $[Co(\underline{d}\text{-cpn})_2Cl_2]^+$ and trans $[Co(\underline{l}\text{-cpn})_2Cl_2]^+$ with no trace of the mixed product trans $[Co(\underline{d}\text{-cpn})(\underline{l}\text{-cpn})Cl_2]^{+1}$.*



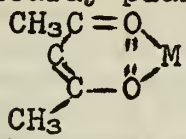
Further, it was observed that upon heating, trans-$[Co(\underline{d}\text{-cpn})_2Cl_2]^{+1}$ was rearranged to cis-$[Co(\underline{d}\text{-cpn})_2Cl_2]^{+1}$. The latter reacted smoothly with dextro-trans-1,2-cyclopentanediamine (d-cpn) to give (-)-$[Co(\underline{d}\text{-cpn})_3]^{+3}$ and (+)-$(Co(\underline{l}\text{-cpn})_3]^{+3}$. It should be noted that there are eight possible isomers-Dddd, Ddd1, Dd11, D111, Lddd, Ldd1, Ld11, and L111. Jaeger's explanation for these and similar results was based on the symmetry of the complexes. He pointed out that all the cations having three identical molecules will possess the rather high degree of symmetry D_3 (symmetry of d and l quartz) provided the substituents themselves have a single binary axis (6). This explanation did not account even qualitatively for the properties of the complexes and hence is unsatisfactory.

II. RING GEOMETRY

It would appear that the stereochemistry of an octahedral complex depends on two factors; the first is the orientation of the donor atoms about the metal ions, and the second is the spatial arrangement of the chelate rings formed by the coordination of the ligands to the metals (7). It is assumed that the orientation of the donor atoms of a chelating ligand is the same, within the limits of the geometrical requirements of the newly formed ring, as for a non-chelating ligand. For this reason, this factor will not be further considered. With ligands such as α-amino acids and acetylacetonates, the spatial factor becomes negligible because these chelate rings are nearly planar. The former adopts a lower degree of puckering than an ethylenediamine ring because of the 120° angle associated with the carboxyl group. The latter is

*The symbols d and l refer to the rotation of the optically active ligand; D and L specify the theoretical configuration of the whole complex which is not necessarily related to the sign of the rotation in a convenient wavelength of light. The symbols (-) and (+) refer to the direction the light is rotated by the complex.

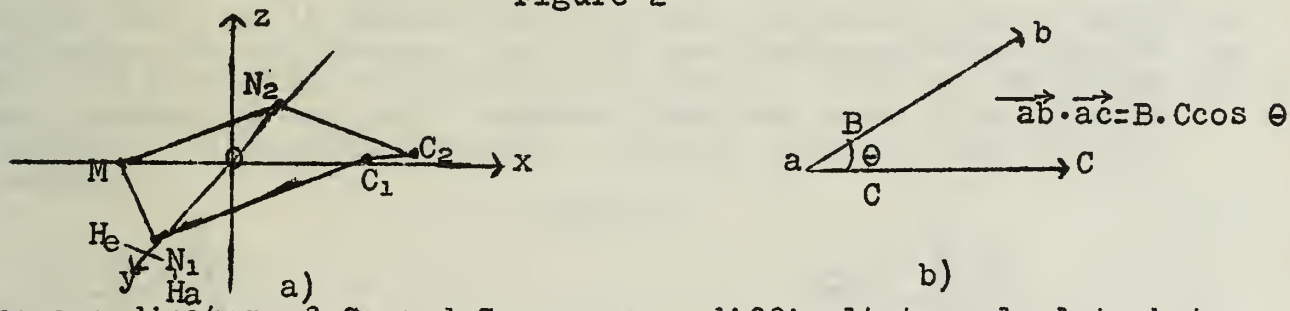
nearly planar because of the conjugated structures of the form



(7). However, with flexible, non-planar rings which can rotate internally about the carbon-carbon single bond, the spatial requirements become significant. Hence, it appears that the stereochemistry of complex metal ions depends mainly upon the geometry of the metal ring and therefore, the explanation of the stereochemistry of the complex ions becomes a problem in conformational analysis of flexible rings.

Of important interest now is the molecular geometry of the metal chelate ring. A method for accurately calculating the molecular geometry of the rings was developed by Corey and Sneen (8). The method involves the use of simple trigonometric relations and vector analysis to calculate the unknown coordinates of a ring. The molecule of interest is oriented on a three dimensional coordinate system in such a way as to simplify the calculations and the interpretations of the results. Considering one of the three rings for the case in question, the five membered ethylenediamine chelate ring was oriented on the coordinate system so that the xy plane passed through the metal and the two nitrogens (see Fig. 2a) The standard values for bond length and bond angle were employed (C-C 1.54Å, C-N 1.47Å, M-N 2.00Å, ∠NCC 109.5°, and ∠MNC 109.5°). The angle NMN, fixed by these other values, was calculated to be 86.2°. With the molecule in question the coordinates of M,N, and N_1 could be calculated by simple trigonometric relationships e.g., OM (the x coordinate of the metal atom)=2.00 COS 43.1°=1.46.

Figure 2



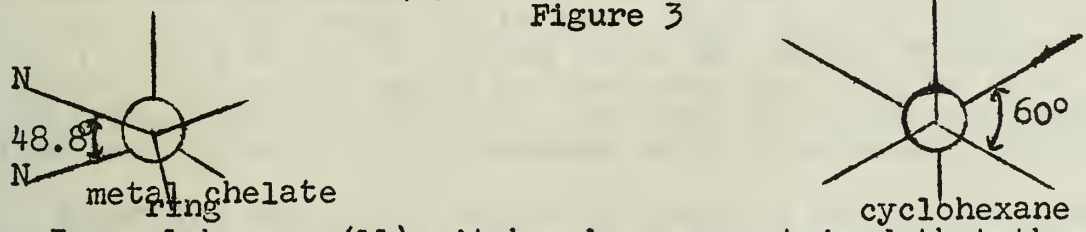
The coordinates of C_1 and C_2 are more difficult to calculate but can be obtained by use of vector analysis, simple trigonometric relations and the relationship that the dot product of two vectors with a common origin is equal to the product of the absolute value and the cosine of the angle which separates the two vectors (see Fig. 2b)(9). The following results were obtained (7).

Atom	Coordinates (X, Y, Z)	Ring Angle	X-Ray Values(10)
M	(-1.46, 0, 0)	86.2	87.+
N_1	(0, 1.37, 0)	109.5°	109.5
N_2	(0, -1.37, 0)	"	"
C_1	(1.28, 0.74, 0.30)	"	109.b
C_2	(1.28, -0.74, -0.30)	"	"
$H_a(N_1)$	(0.05, 1.85, -0.98)		
$H_e(N_1)$	(-0.22, 2.14, 0.76)		
θ		48.8	48

An examination of the calculated values for the Z coordinates indicate that the metal chelate ring is markedly puckered. The projection of the C-N bonds when observed looking down the C-C bond forms an angle θ of 48.8°. This is illustrated in the Newman

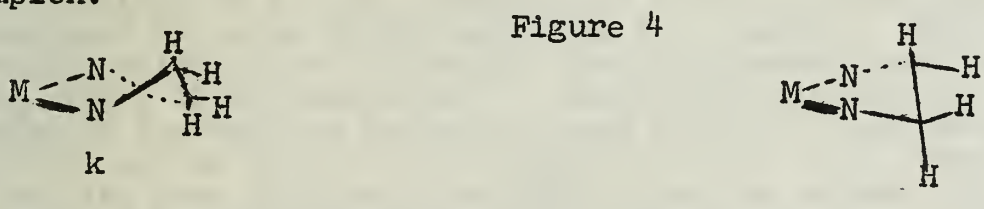
projection formulas in Fig. (3). It will be recalled that the Θ value for cyclohexane is 60°. Further comparisons with cyclohexane appear to be valid. As in cyclohexane, the hydrogens on the metal chelate ring are staggered relative to each other, a situation which is energetically favorable. Also it will be noted that the hydrogens are not equivalent i.e., they possess about 80% (relative to cyclohexane) axial and equatorial character. The hydrogens on the nitrogens also possess axial and equatorial character but to a lesser extent (7).

Figure 3



In cyclohexane (11), it has been ascertained that the axial orientation is of higher energy than the equatorial. For an octahedral complex, the energy difference ($\Delta F_a - \Delta F_e$) between axial and equatorial orientations is expected to be larger because of the large axial groups on the metal. By analogy to the interconversion of the chair forms of cyclohexane by internal rotation, it is apparent that the skew form of the metal chelate ring can be converted to a skew form which is the mirror image of the original form (Fig. 4). This internal rotation converts the axial substituents to equatorial and vice versa. The two forms of the metal chelate ring are arbitrarily designated as k and k'. Because this conversion k $\rightarrow$k' only involves rotation about the carbon-carbon single bond, it is considered that the energy difference (about 9.7 kcal/mole for cyclohexane (12)) for an ethylenediamine ring is too small to give rise to classical isomerism. With the knowledge of the geometry of the metal chelate, the next step is to examine the geometric relationship between the three chelate rings of the complex.

Figure 4



GEOMETRICAL RELATIONSHIP BETWEEN CHELATE RINGS

Complex ions containing chelate rings are spiro compounds i.e., an atom is both a member of a ring and a substituent on another ring. Having shown that chelate rings can exist in two forms, k and k', it is now important to determine the effect of these rings on each other. Considering a complex containing ethylenediamine chelate rings (k and k' forms are of equal energy), the difference in energy between the various possible conformational forms in solution arise from two sources, first, the non-bonded interactions between the rings and secondly, the differences in solvation. Because of the similiarity in charge distribution and solvent accessibility in the various forms, the differences in solvation energy are assumed to be negligible (7).

Examination of a square planar complex containing only two chelate rings can give us an idea of some of the possible non-bonded interactions. In a square planar complex, there are three possible forms, kk, k'k' and kk'(≡k'k). The first two are enantiomeric and of equivalent energy. An examination of the models

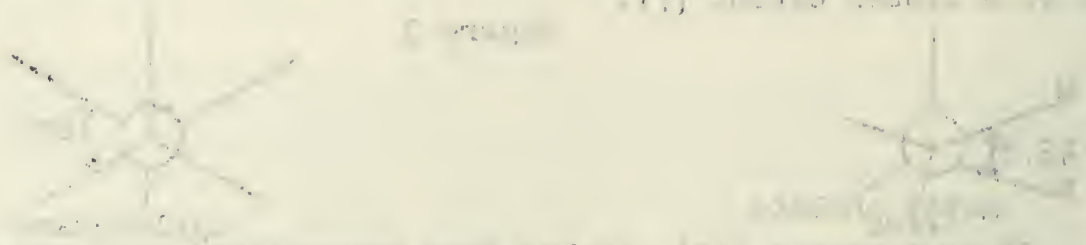
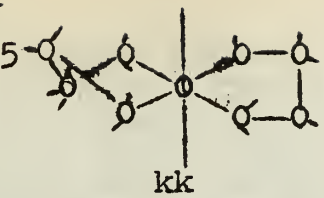


Figure 5

kk'



kk

illustrated in Fig. (5), indicate that in the kk' form, the hydrogens on the donor nitrogens on different rings are eclipsed while those in the kk (k'k') form are skewed. Calculations using the hydrogen-hydrogen potential function of Mason and Kreevoy (13) indicate that the energy difference ($E_{kk'}-E_{kk}$) is about 1 kcal/mole. (7) This is not a precise value but merely reflects an order of stability i.e., it would be predicted that the kk (k'k') form would prodominate in solution. However, if solvation energy differences exist, it is uncertain which form would predominate.

Regarding the trans complex containing two chelate rings to be similar to the square planar complex, the conclusions made on the ethylenediamine chelate rings should be applicable to rings formed by trans-1,2-cyclopentanediamine and allow explanation of the experimental results observed by Jaeger and Blumendal. First, it should be observed that d-cpn and l-cpn possess fixed, skew configurations and as a result each enantiomer can form chelate rings of only one configuration. Therefore, designating the dextro isomer arbitrarily as k, and the levo as k', the observed products of the oxidation of cobaltous chloride in racemic cpn can be rewritten as trans-$[Co(kk)Cl_2]^+$ and trans-$[Co(k'k')Cl_2]^+$. The product trans-$[Co(kk')Cl_2]^+$ was not isolated. As previously shown, square planar complexes of the configuration kk' are energetically unstable relative to the kk form by about 1 kcal/mole. Therefore, the failure to isolate the complex trans-$[Co(l\text{-cpn})(d\text{-cpn})Cl_2]^+$ can be attributed to its instability relative to trans-$[Co(d\text{-cpn})_2Cl_2]^+$ and trans-$[Co(l\text{-cpn})_2Cl_2)^+$.

Evaluation of the geometrical relationships for octahedral complexes are more complicated for two reasons. First, for a given configuration about the metal, four different forms are possible, kkk, kkk', kk'k', and k'k'k'. Secondly, calculations of the relative energies for various forms are more difficult and have only been carried out on the two forms kkk and k'k'k' (7). These calculations are more difficult for the following reason. First, a large number of hydrogen-hydrogen interactions must be evaluated between hydrogens on the same ring and on different rings. Secondly, the non-bonded interactions between the carbons of a ring and the hydrogens of the NH_2 group must be determined. The calculations indicate that one form, arbitrarily designated as kkk, is more stable than the other by approximately 1.8 kcal/mole (7). The main difference between the two forms arises from the carbon-hydrogen interactions. It should be pointed out that the carbon-hydrogen interactions were calculated using the hydrogen-hydrogen potential function. As a result, the calculations are more conservative than if a carbon-hydrogen potential function were used (7). Again the value 1.8 kcal/mole is to indicate only an order of stability such that assuming no differences in solvation energy, the kkk form will predominate in solution. The kkk' and kk'k' forms will possess energies which are intermediate between kkk and k'k'k' and the order of stability would be kkk > kkk' > kk'k' > k'k'k'. If the configuration about the metal is inverted i.e., D to L, the order of stability is reversed.

Because of the thermodynamic difference between these two forms, it is convenient to name the two extreme forms kkk and k'k'k'. If one regards the complex in a position so that it appears like a propellor on its side, it will be noted that in one form (kkk) the carbon-carbon bond is parallel to the trigonal axis through the metal; this form is called "lel". The k'k'k' form has its carbon-carbon bond oblique to the trigonal axis; this form is designated as the "ob" form (7).

It should now be possible to rationalize the stereospecific effects observed by Jaeger and Blumendal for tris chelated complexes. The experimental results illustrated on page 114 can be rewritten in terms of our k and k' convention as (-)-$[Co(kkk)]^{+3}$ for the product of the reaction of cis(-)$[Co(d\text{-cpn})_2Cl_2]^+$ with d-cpn. Because of its stability and the fact that the products are equilibrium controlled, this must be the stable "lel" form rather than the "ob" form. Therefore, it is not surprising that the product of the reaction of cis(-)$[Co(kk)Cl_2]^+$ with k' is a two to one mixture of the enantiomeric "lel" forms (-)$[M(kkk)]$ and (+)$[M(k'k'k')]^{+3}$.

That the products are equilibrium controlled has been substantiated by Dwyer (14). He has reported the isolation of both (+)111 and (-)111 complexes from tris-levo-propylenediamine cobalt (III) complexes. The measured equilbrium constant for the reaction (+)111 $\rightleftharpoons$ (-)111 catalyzed by charcoal was found to be 5.75 and hence ΔF^{o}=-1.02±0.05 kcal/mole which is in the range of the theoretical calculation. Also, mixed tris diamines have been isolated in the platinum series e.g., ±$[Pt(en)_2(l\text{-pn}]^{+4}$, ±$[Pt(l\text{-pn})_2en]^{+4}$ and ±$[Pt(d\text{-pn})_2(l\text{-pn})]^{+4}$ and these did not racemize in boiling aqueous solution (15). It should be mentioned that platinum complexes are very stable to racemization and disproportionation compared to cobalt complexes. It is probable that the thermodynamic instability of cobalt complexes relative to platinum precludes the isolation of these mixed complexes.

Examination of the formation constants for various ligands illustrated in Table I corroborates the conclusions made on the thermodynamic basis.

Table I (16)
Formation Constants of Cu(II) and Ni(II) with various Ligands

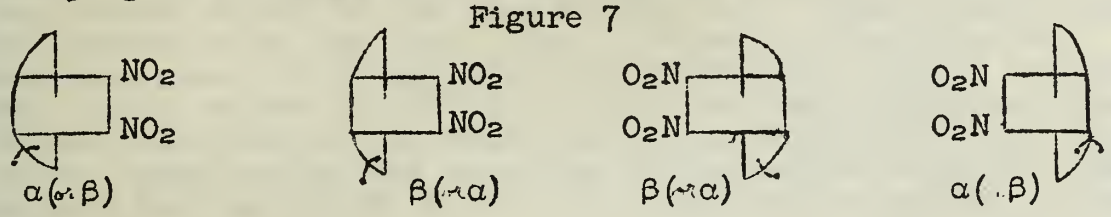
Ligand	Log $K_t(0^o)$ Cu(base)	Log $K_t(0^o)$ Ni(base)
ethylenediamine	21.29	20.05
propylenediamine	21.77	19.77
butylenediamine(active)	22.87	20.39
butylenediamine(meso)	21.55	16.74
isobutylenediamine	21.19	15.98
stilbenediamine(active)	21.23	19.61
stilbenediamine(meso)	17.50	8.69(only two ligands)
Trimethylenediamine	18.46	13.81

Briefly, Table I illustrates that the mesobutylenediamine (m-bn) is less stable than the active isomer. This is expected for m-bn must have one methyl group axial whereas the optically active ligand has both groups equatorial. Further, isobutylenediamine(i-bn) which possesses a destabilizing axial methyl has a formation constant of the same magnitude as m-bn. Meso-stilbenediamine(m-stien) reflects the increased steric effect of the phenyl

group both in the fact that it has a small formation constant and that it only forms a bis complex. Table I also reflects the instability of the six membered chelates (trimethylenediamine) relative to the five membered. This supports the conclusion that these ring systems are forced into a more highly folded conformation because of the metal nitrogen bond distance. These geometrical requirements cause a destabilization due to compression and eclipsing interactions resulting from the closer proximity of the axial substituents.

Positional or geometrical-optical isomerism is a phenomonon which can exist when unsymmetrical ligands e.g.,i-bn, are the chelating agents. Positional isomerism is illustrated in Fig. 7

Figure 7



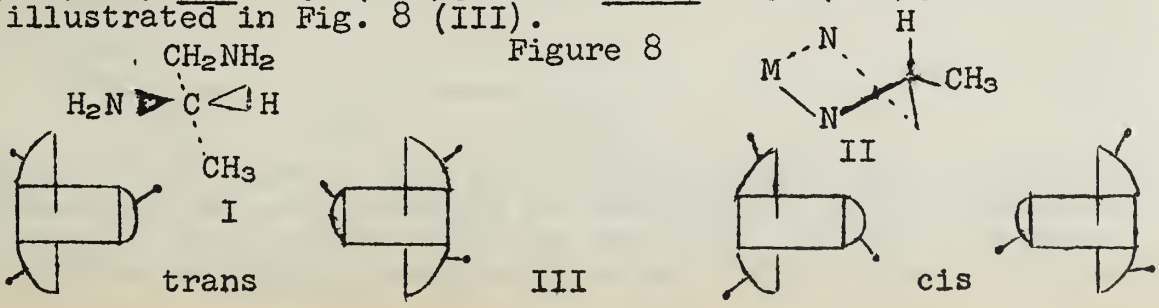
for the complex cis[Co(en)(i-bn)$(NO_2)_2]^+$ where 1 represents the methyl groups of ibn. The relative stabilities of these isomers can not be predicted from the conformational explanation. However, in the complex cis[Co(en)(ibn)$(NO_2)_2$], one of the few authenticated examples of positional isomerism, the resolved isomers Dα, Dβ,Lα, and Lβ showed no differences in the rate of racemization (17). Therefore, the possibility is that no stability differences exist and that the failure of these isomers to be isolated is due to their identical solubilities. This is supported by Dwyer's failure to isolate geometrical-optical isomers from his work on the mixed platinum complexes or with $\pm$(Co(d,l-pn)$_3]^{+3}$ (14).

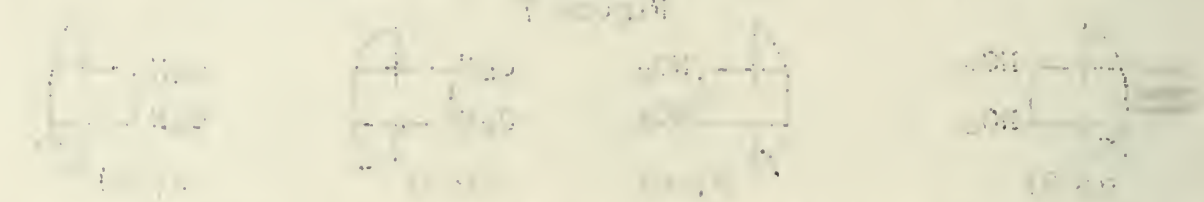
As a corollary to this conformational analysis, one can deduce the absolute configuration of a complex, or knowing this, determine the absolute configuration of the ligand. To determine the absolute configuration of the complex, one must know the relative configuration of the ligands about the metal and the absolute configuration of the ligands (7). This can be illustrated using the complex (+)-[Co(d-pn)$_3]^{+3}$.

The absolute configuration of dextro-propylenediamine(d-pn) is known (Fig. 8 (I)) having been related to L-alanine. The metal chelate ring must then have the absolute configuration represented in Fig. 8 (II).

Because propylenediamine is an unsymmetrical ligand, a tris chelate containing rings of the same absolute configuration can exist in four diastereomeric forms, cis-D-[Co(ddd)$]^{+3}$ trans D-[Co(ddd)$]^{+3}$, cis-L-[Co(ddd)$]^{+3}$ and trans-L-[Co(ddd)$]^{+3}$. These are illustrated in Fig. 8 (III).

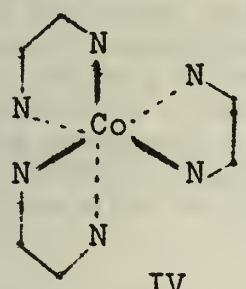
Figure 8



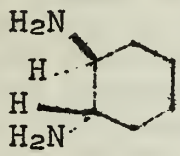


For a given orientation of the ligands about the metal, the configuration of the chelate which gives the stable "lel" form is known i.e., the orientation of the atoms of the ring to give the "le form is known. This information can be determined by a study of models. A ligand which has a fixed configuration can assume an orientation about the metal to give the "lel" form, or the orientation to give the "ob" form. Experimentally only two forms of tris-dextro-propylenediamine cobalt (III) have been isolated and these have been designated as (D)ddd and (L)ddd. These assignments were made on the basis of insufficient data so that the possibility still exists that these could be cis-trans isomers. Therefore, the designation (+)ddd and (-)ddd would be better. The equilibrium constant of 5.75 obtained from the reaction (-)ddd $\rightarrow$ (+)ddd indicate that the (+)ddd isomer is the more stable (14). The (+)ddd isomer is then assumed to be the "lel" form. Therefore, knowing the absolute configuration of dextro-propylenediamine, having assumed that the (+)ddd isomer is the "lel" form, and knowing the orientation of the bidentate groups about the metal which gives the "lel" form for a ligand having the absolute configuration of d-pn, then the absolute configuration of the (+) isomer can be specified (Fig. 9 (IV)).

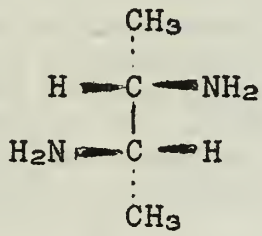
Fig. 9



IV



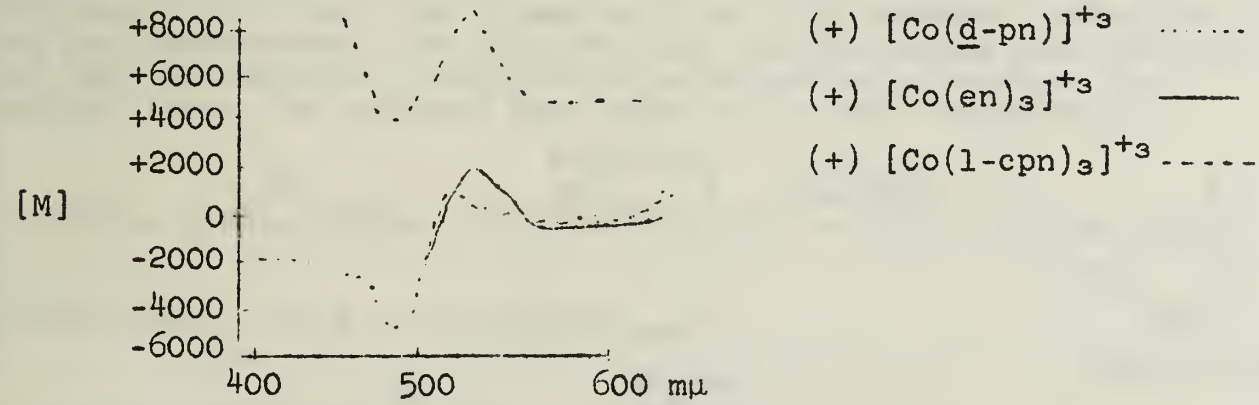
V



VI

The similarity of the optical rotatory dispersion curves for the complexes (+) $[Co(en)_3]Br_3 \cdot 2H_2O$, (+) $[Co(d\text{-pn})_3]Br_3 \cdot 2H_2O$ and (+) $[Co(l\text{-cpn})_3]Cl_3$, illustrated in Fig. 10, indicate that they all have the same absolute configuration (4). This was confirmed by x-ray analysis for tris-ethylenediamine cobalt (III) (7). These being

Fig. 10



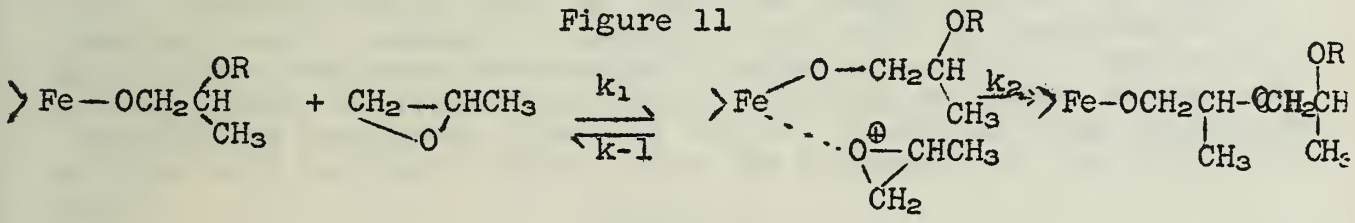
the stable "lel" forms, then the chelate ring Co(l-cpn) must have the same absolute configuration as the Co(d-pn) ring. Therefore, levo trans-1,2-cyclopentanediamine must have the same absolute configuration as dextro-propylenediamine. The absolute configuration

of l-cpn is illustrated in Fig. 9 (V). This assignment has not been confirmed by other methods.

A third possibility now arises: knowing the absolute configuration of the ligands, it might be possible to predict the direction light is rotated at the sodium D line (589 mμ) by a complex. For example, d-2,3-butylenediamine has been assigned the absolute configuration represented in Fig. 9 (VI). Noting that like d-pn, it possesses the L-configuration, one would predict that the rotation of the stable form of $[Co(d\text{-}2,3\text{-}bn)_3]^{+3}$ would be greater than the rotation of the complex formed from l-2,3-bn. Again no experimental confirmation of this prediction could be found.

An interesting theory, resulting from the explanation of stereospecific effects in complex ions, has been proposed to explain the stereospecific polymerization of dl-propylene oxide by ferric chloride. Price had shown that 30-40% of the polymer is a racemic mixture with an isotactic structure, i.e., each successive asymmetric center has the same configuration (18). Because this crystalline polymer was of higher molecular weight and precipitated from solution, Price proposed that the stereospecificity was a result of the insoluble, heterogeneous, asymmetric surface generated by the polymer. He had also shown that a product with the same molecular rotation was obtained from the polymerization of l-propylene oxide by ferric chloride or potassium hydroxide. This indicated that the ferric chloride polymerization occurred by a frontside attack with retention of configuration. Price proposed a mechanism for polymerization in which the reaction proceeds through internal displacement in the complex at a surface site to give optically active crystalline polymer (19).

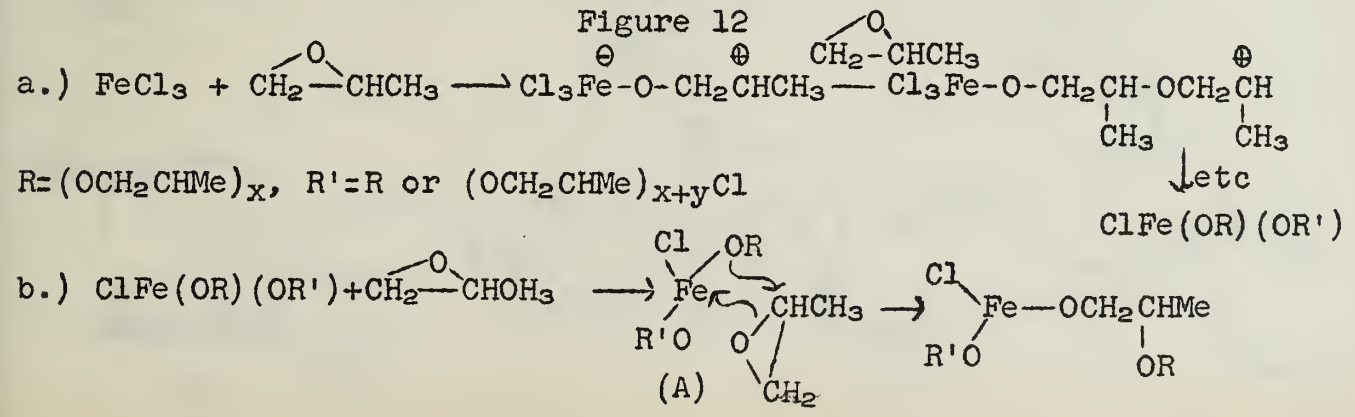
Figure 11



If the displacement occurs in solution an amorphous polymer results.

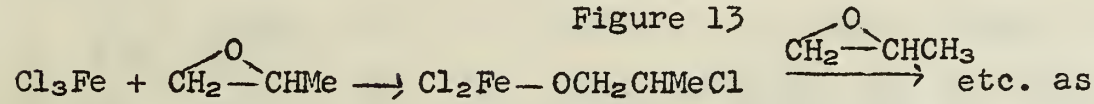
Gee proposed a pair of alternative mechanisms for the polymerization of propylene oxide (20). It is illustrated in Fig. 12. Robinson stated that the formation of a fully charged carbonium ion was unnecessary. He proposed that the mechanism was concerted and that the cationic charge dissipated before it reached its maximum value. He proposed that only the second mechanism was

Figure 12



necessary Fig. 13. This second mechanism proposess an intermediate (Fig. 9)(A)) which would not account for the stereospecificity

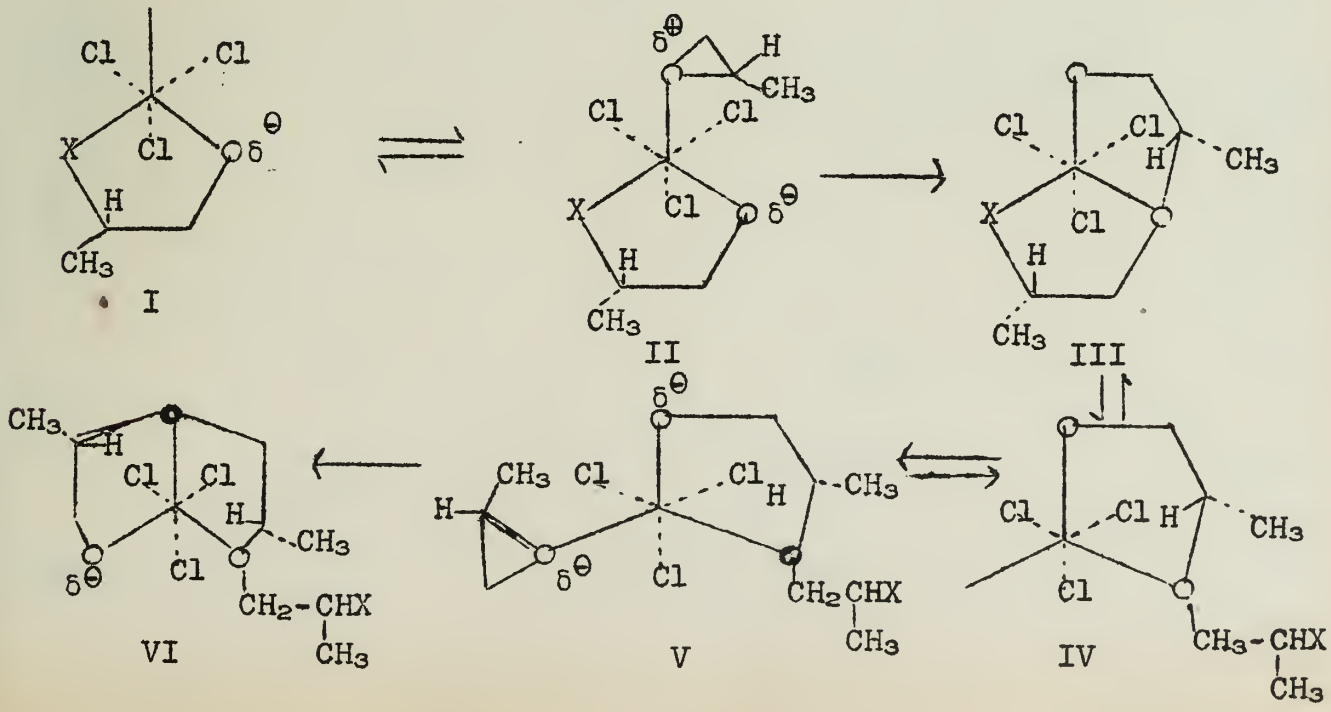
Figure 13

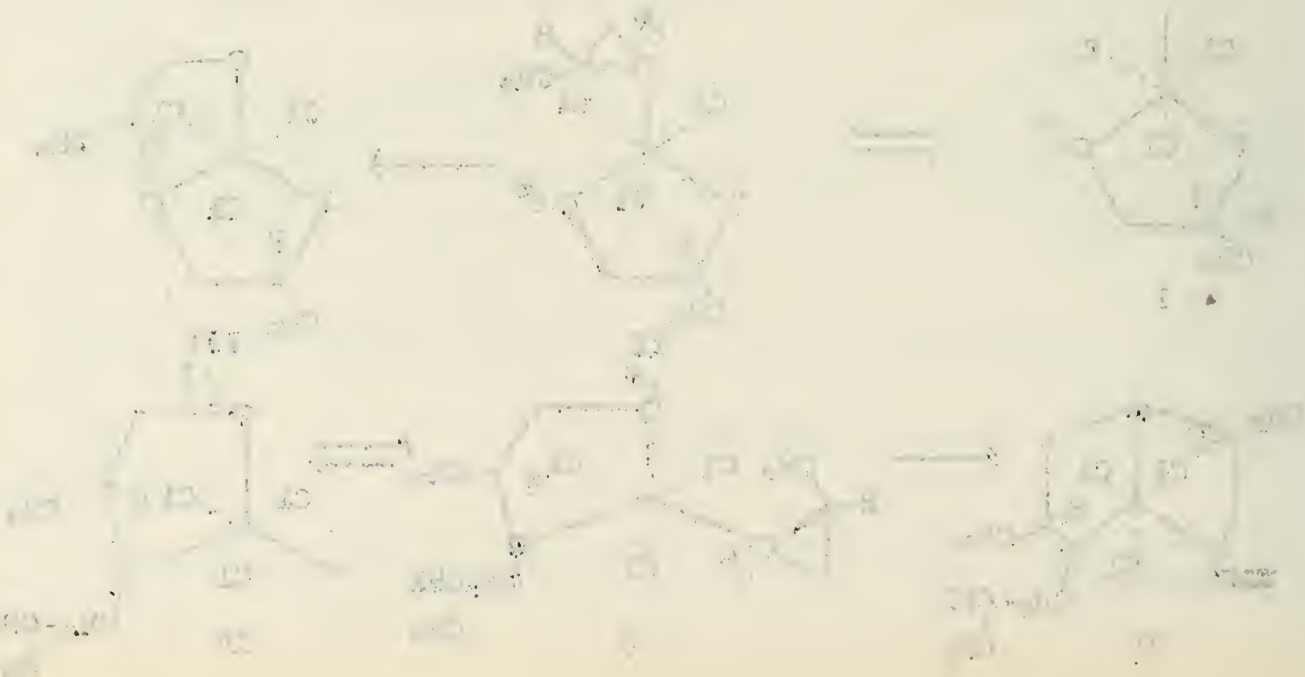


that is observed, i.e., it does not explain why one enantiomer should react preferentially.

Corey (21) has proposed a mechanism which is based on the conformational effects in complex ions and the tendency of iron to form octahedral complexes. It does not require surface effects to be present. The essentials of the mechanism are presented in Fig. (14). The initial step involves coordination of the iron with one enantiomer (say d) and a terminating group X to form the unstable tetragonal pyramid I. This in turn reacts reversibly with a second molecule of d-propylene oxide to form the octahedral complex II. The nucleophilic oxygen can attack the asymmetric center by front side attack with retention of configuration to form complex III. It is assumed that the transition state resembles the product and therefore, the conversion of II→III is facile when both propylene oxide molecules possess the same configuration. If this is not the case, it is assumed that II dissociated to I, then, to recomplex with an alike enantiomer. The complex III which contains the same enantiomer will then have both methyl groups equatorial, a conformation previously shown to be the most stable. Complex III then dissociates at one coordination position, to yield IV, an unstable tetragonal pyramid which then complexes with another molecule of propylene oxide (preferentially with an identical enantiomer as in II)to form the stable octahedral complex V and this is converted to VI which again possesses both methyl groups equatorial. Therefore, the net result is a polymerization catalyzed by three of the six coordination positions (three of the six vertices of an octahedron) of iron with constant control over the asymmetry of the adding units.

Figure 14





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THE STRUCTURE OF TRICHOTHECIN AND ITS HYDROLYSIS PRODUCTS

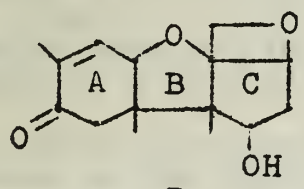
Reported by H. J. Havera April 11, 1960

Trichothecin is an antifungal substance produced by the fungus Trichothecium rosium.[1,2,3] It is the isocrotonic ester of the ketonic alcohol, trichothecolone. Structure I is proposed for trichothecolone on the basis of the properties of degradation products which are obtained by oxidation, alkaline fission, and dehydrogenation.[4]

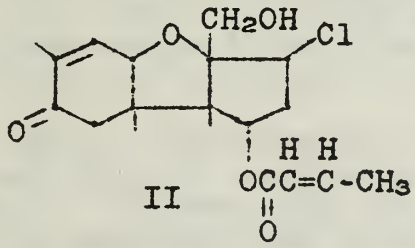
The most satisfactory yields of trichothecin have been obtained by growth of the fungus for a period of 28 days at 25°C. It was extracted from the culture filtrates with ether or chloroform and purified by chromatographic methods on activated alumina.[5]

Hydrolysis of trichothecin with a cold methanolic solution of potassium hydroxide gave the ketonic alcohol, trichothecolone and β-methoxybutyric acid, presumably formed by the addition of methanol to isocrotonic acid. Trichothecin was readily hydrogenated at atmospheric pressure with palladium on charcoal, and two moles of hydrogen were taken up to give tetrahydrotrichothecin.[6] This uptake was accounted for by saturation of one double bond in the isocrotonic ester group and a second double bond in the trichothecolone part of the molecule. Trichothecin contained a reactive carbonyl group, which was retained in tetrahydrotrichothecin. There are three C-methyl groups and no methoxyl groups. The infrared spectrum of trichothecin had bands at 1670 (α,β-unsaturated ketone), 1710 and 1177 (α,β-unsaturated ester), and 1650 cm.$^{-1}$ (ethylenic unsaturation).[4] Absence of a band in the region of 3400 cm.$^{-1}$ and indifference to acetic anhydride or benzoyl chloride indicated no hydroxyl groups. There was no benzenoid absorption. Thus, the functional groups of trichothecin were shown to be two ethylenic double bonds, a ketonic group, and an ester group.

Trichothecin reacted with concentrated hydrochloric acid to form a chlorohydrin (II), $C_{19}H_{25}O_5Cl$. The infrared spectrum of this compound showed a band associated with a hydroxyl group which was also confirmed by quantitative acetylation. The chlorohydrin was still ketonic. Hydrolysis of the chlorohydrin with methanolic potassium hydroxide at room temperature gave trichothecolone chlorohydrin (III), which was also formed by the action of 10N hydrochloric acid on trichothecolone. Thus, the hydrochloric acid had reacted with the trichothecolone part of the molecule.



I



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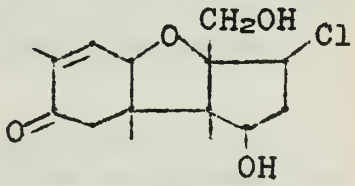

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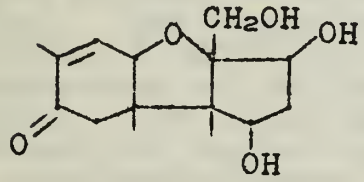

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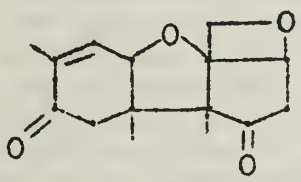

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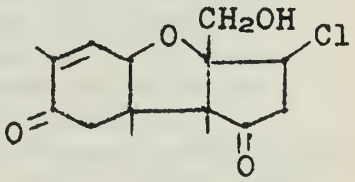
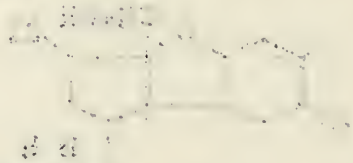
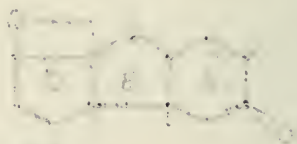
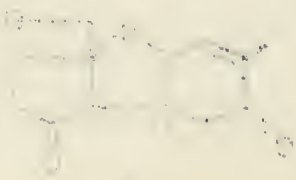


VI

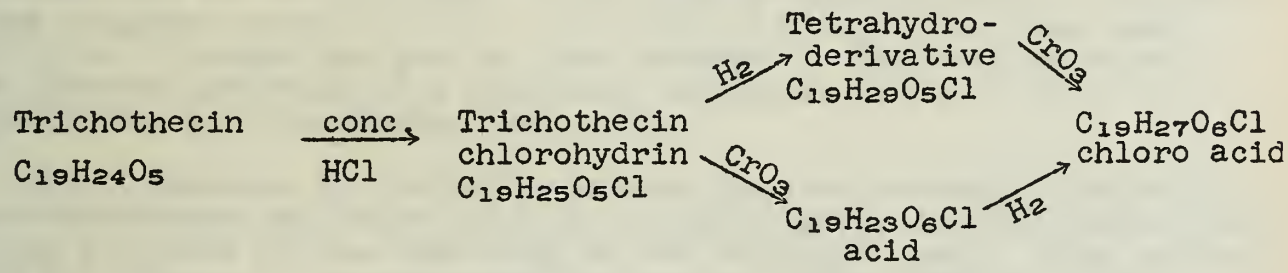






When trichothecin was boiled in 0.1N hydrochloric acid, addition of water took place, giving a glycol, $C_{19}H_{26}O_6$, hydrolyzed by cold alkali to trichothecolone glycol(IV), which was also obtained from trichothecolone. Quantitative acetylation indicated that there were three hydroxyl groups present in trichothecolone glycol, and it is assumed that two of these have been formed by opening of an oxygen ring. Trichothecolone glycol absorbed one mole of hydrogen at ordinary temperatures to form dihydrotrichothecolone glycol which was also prepared by the action of boiling 0.5N sulfuric acid on dihydrotrichothecolone. The glycols from trichothecin and trichothecolone were both ketonic.

Hydrogenation of trichothecin chlorohydrin at ordinary pressures gave tetrahydrotrichothecin chlorohydrin which on oxidation with chromic acid gave a chloro acid, $C_{19}H_{27}O_6Cl$, with no loss of carbon. The chloro acid no longer contained a hydroxyl group, but was still ketonic and formed an amide. Oxidation of trichothecin chlorohydrin with chromic acid gave an acid, $C_{19}H_{23}O_6Cl$, which on hydrogenation gave the crystalline chloro acid, $C_{19}H_{27}O_6Cl$.



The reaction with hydrochloric acid can be explained by assuming that trichothecin contained an oxide ring which was easily opened by strong acids with the formation of a hydroxymethyl group. Oxidation of the latter then resulted in the formation of a carboxylic acid with no loss of carbon. Cold alkaline hydrolysis of the saturated chloro acid $C_{19}H_{27}O_6Cl$ gave a hydroxy-chloro acid $C_{15}H_{21}O_5Cl$.

TRICHOTHECOLONE

The keto-alcohol trichothecolone $C_{15}H_{20}O_4$ has one active hydrogen (hydroxyl group). Its infrared spectrum has bands at 1650 (C=C), 1670 (C=C-C=O), and 3510 cm.$^{-1}$ (hydroxyl), but no benzenoid absorption. It forms a semicarbazone, a 2,4-dinitrophenylhydrazone, and an acetyl derivative. The infrared spectrum of acetyltrichothecolone contained no hydroxyl band, which indicated that normal esterification had occurred. Cold alkaline hydrolysis of trichothecin 2,4-dinitrophenylhydrazone yielded trichothecolone 2,4-dinitrophenylhydrazone, identical with that prepared from the alcohol.

Trichothecolone gave a negative haloform test, indicating the absence of the CH_3CO-group, and did not react with phthalic anhydride as expected of a primary alcohol. It absorbed one mole of hydrogen in the presence of palladium on charcoal, the product still being ketonic. The absorption of the carbonyl group in the infrared spectrum of dihydrotrichothecolone was 1695 cm.$^{-1}$ and that of trichothecolone was 1670 cm.$^{-1}$; the change indicating loss of α,β conjugation. The ultraviolet absorptions of trichothecin and trichothecolone suggest that trichothecolone is an α or β-monosubstituted α,β-unsaturated ketone by comparison with Woodward's values for α,β-unsaturated ketones (monosubstituted α or β-2250±50A°; disubstituted

αβ or ββ-2390 ± 50 A°; trisubstituted α,β,β-2540 ± 50 A°).[7] Hydrogenation caused disappearance of the bands.

	λ_{max} A°	ε	λ_{max} A°	ε
Trichothecin	2170	18,000	2150	19,000
Trichothecolone	2240	8,000	2260	8,000
	In hexane		In methanol	

OXIDATION PRODUCTS OF TRICHOTHECOLONE

Oxidation of trichothecolone with chromic acid gave trichothecodione (V). This compound gave a mono-semicarbazone, a mono-2,4-dinitrophenylhydrazone, and in small yield a bis-2,4-dinitrophenylhydrazone. Dihydrotrichothecolone gave on oxidation dihydrotrichothecodione which also formed a mono-2,4-dinitrophenylhydrazone. The infrared spectra of these diones did not contain the hydroxyl band (3510 cm.$^{-1}$) of trichothecolone. Bands at 1670 cm.$^{-1}$ for trichothecodione and at 1710 cm.$^{-1}$ for dihydrotrichothecodione, assigned to the original ketonic group, were present along with a new band at 1735 cm.$^{-1}$ which was due to a new carbonyl. This was in agreement with the presence of a secondary alcoholic group in trichothecolone and its dihydro derivative.[4]

The difference in frequency between the two carbonyl groups in trichothecodione indicated that the hydroxyl group in trichothecolone was not attached to the same ring as the carbonyl group. The carbonyl group at 1735 cm.$^{-1}$ is unconjugated and in a five membered ring.

The second carbonyl group in trichothecodione was unreactive to ketonic reagents. The ultraviolet absorption showed a maximum at 2250 A° (ε 8600) and its semicarbazone at 2680 A° (ε 21,700), characteristic of an α,β-unsaturated ketone. This suggested that the original carbonyl of trichothecolone was the more reactive one in trichothecodione. The characteristic reactions of α,β- and α,γ-diketones were absent. The dione did not give a ferric chloric test or a copper complex. Trichothecodione yielded a chlorohydrin (VI) with 10N hydrochloric acid, similar to that of trichothecin, so that the oxide bridge is still intact in the dione. The chlorohydrin was still ketonic.

DEHYDROGENATION OF TETRAHYDROTRICHOTHECODIOL

Trichothecolone was hydrogenated in the presence of Raney nickel, and tetrahydrotrichothecodiol, $C_{15}H_{26}O_4$, was obtained. This compound had no carbonyl absorption in the infrared spectrum but had three active hydrogen atoms, and analysis of its acetyl derivative indicated the presence of three acetyl groups. This suggested that hydrogenolysis had occurred.

Decomposition of tetrahydrotrichothecodiol was obtained at 140° with palladium on charcoal. The products consisted of three moles of water, p-xylene, p-xylenol, and two ketones, $C_7H_{10}O$ and $C_7H_{12}O$. Reduction of a mixture of these compounds gave a saturated ketone $C_5H_6Me_2O$ whose 2,4-dinitrophenylhydrazone and semicarbazone were identical with those of 2,3-dimethylcyclopentanone. 2,3-Dimethylcyclopent-2-enone gave a semicarbazone and 2,4-dinitrophenylhydrazone identical with those of the ketone $C_7H_{10}O$.[8]

Interpretation

The bulk of the oxygen in the starting material was accounted for by formation of 3 moles of water and of the cyclopentanones. The 15 carbon atoms of tetrahydrotrichothecodiol were accounted for by those present in p-xylene and dimethylcyclopentanone. The dehydrogenation products contained 4 C-methyl groups, whereas tetrahydrotrichothecodiol contained 3 C-methyl groups.[4]

These observations suggest that the precursors of p-xylene and of 2,3-dimethylcyclopentanone exist as independent rings in tetrahydrotrichothecodiol and that a 5-membered carbon ring substituted by a hydroxyl group in tetrahydrotrichothecodiol and a keto group in trichothecodione gives rise to the cyclopentanone. The position of the carbonyl band in the infrared spectrum of trichothecolone (1670) cm.$^{-1}$ indicates that it is in a 6-membered ring; isolation of p-xylenol from the dehydrogenation of tetrahydrotrichothecodiol supports the presence of a C_6 ring.

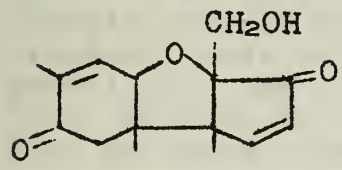
High pressure hydrogenation of trichothecolone glycol and dehydrogenation of the product also gave p-xylene, 2,3-dimethylcyclopentanone, and 2,3-dimethylcyclopent-2-enone. p-Xylene and the same cyclopentanone were also isolated by dehydrogenation of the hydrogenated neutral compound (VII) which is obtained by oxidation of trichothecolone glycol with chromic acid.[9,10,11] High pressure hydrogenation of an acid XX prepared by oxidation of the primary alcohol in neotrichothecodione (XVI) and hydrogenation of the ethylenic bonds, followed by usual dehydrogenation also gave p-xylenol and 2-methylcyclopentanone (scheme 3). Isolation of 2-methylcyclopentanone here supports the interpretation that the methylene group of the methyleneoxy-bridge in trichothecolone is in the β-position with respect to the hydroxyl group in 2,3-dimethylcyclopentanone. The carboxyl group of acid XX is assumed to have been lost by decarboxylation.[4]

ALKALINE FISSION OF TRICHOTHECODIONE

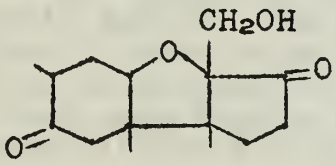
When trichothecodione was heated for 3 minutes with 10% sodium hydroxide, neotrichothecodione (XVI) was isolated. Boiling for 2 minutes with an excess of 10% sodium hydroxide gave p-xyloquinone and p-xyloquinol. These products were consistant with the assumption that trichothecolone contains a 6-membered ring having 2-methyl groups in the 1,4-position to each other and also 2 oxygen atoms in the 1,4-position to each other.

FURTHER C_{15} AND C_{14} OXIDATION PRODUCTS

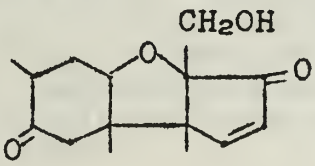
Oxidation of trichothecolone glycol (IV) with aqueous chromic acid at room temperature gave a neutral compound VII, (λ_m 2270 A°, ϵ 13,500) and γ 3440 (OH), 1710 and 1680 cm.$^{-1}$ (both C=O), which formed a mono-2,4-dinitrophenylhydrazone and a monoacetate.



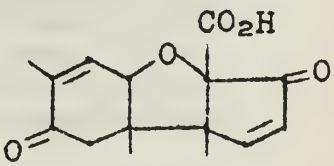
VII



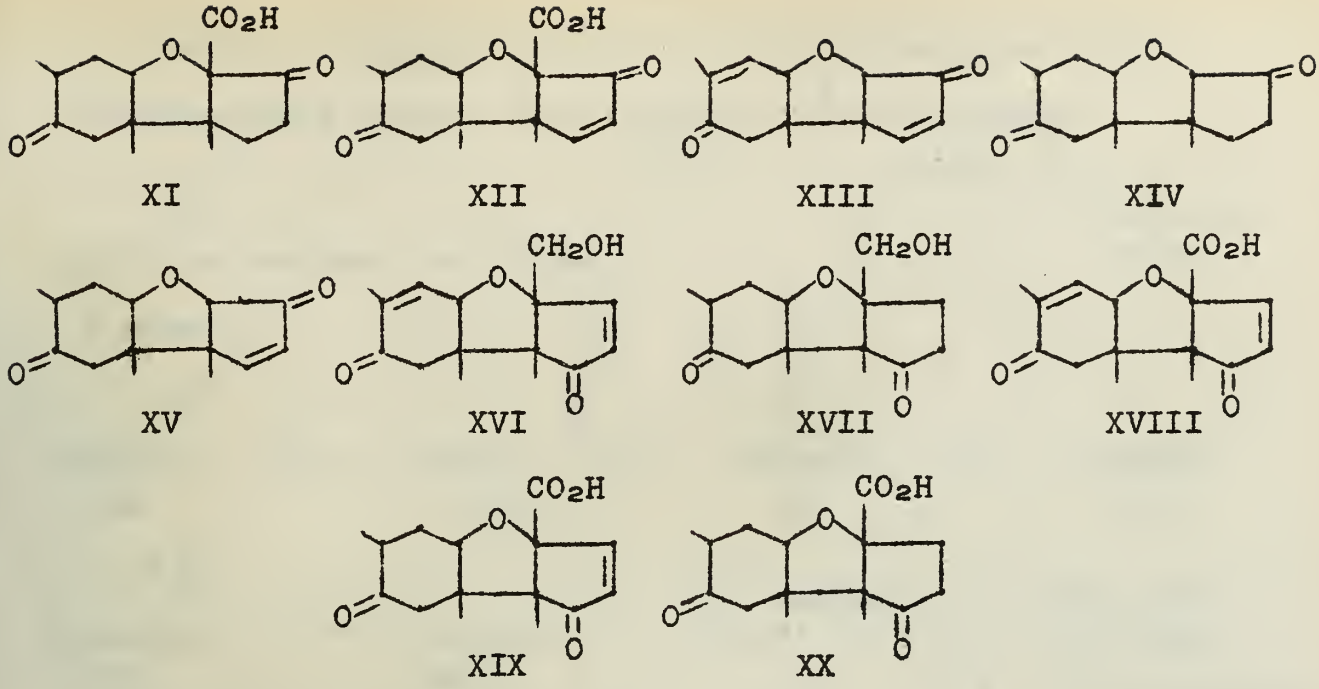
VIII



IX



X

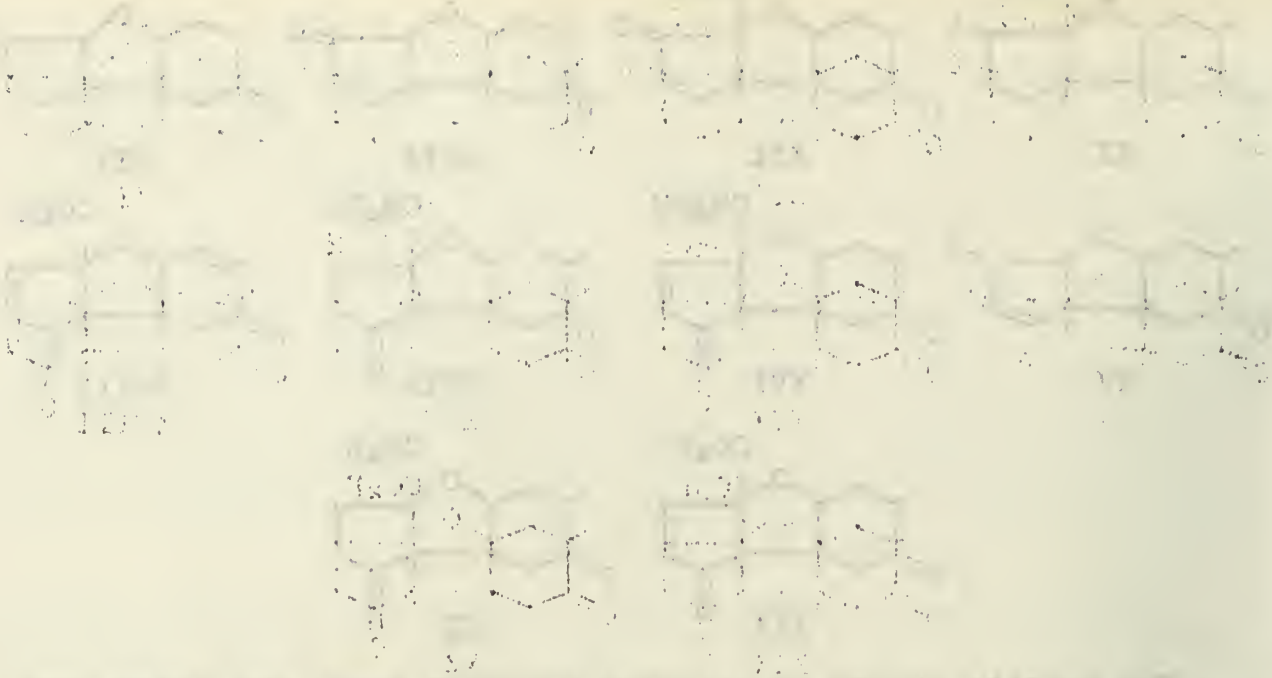


The acetate showed no infrared hydroxyl band, but there were bands for an ester group and bands at 1680 cm.$^{-1}$ and 1750 cm.$^{-1}$ Compound VII absorbed 2 moles of hydrogen giving compound VIII which formed a mono-2,4-dinitrophenylhydrazone. When dihydrotrichothecolone glycol was oxidized with aqueous chromic acid, an unsaturated diketone IX was obtained, having an ultraviolet absorption maximum at 2190 A° (ϵ 6250), forming a mono-2,4-dinitrophenylhydrazone, and giving on hydrogenation the ketone VIII.

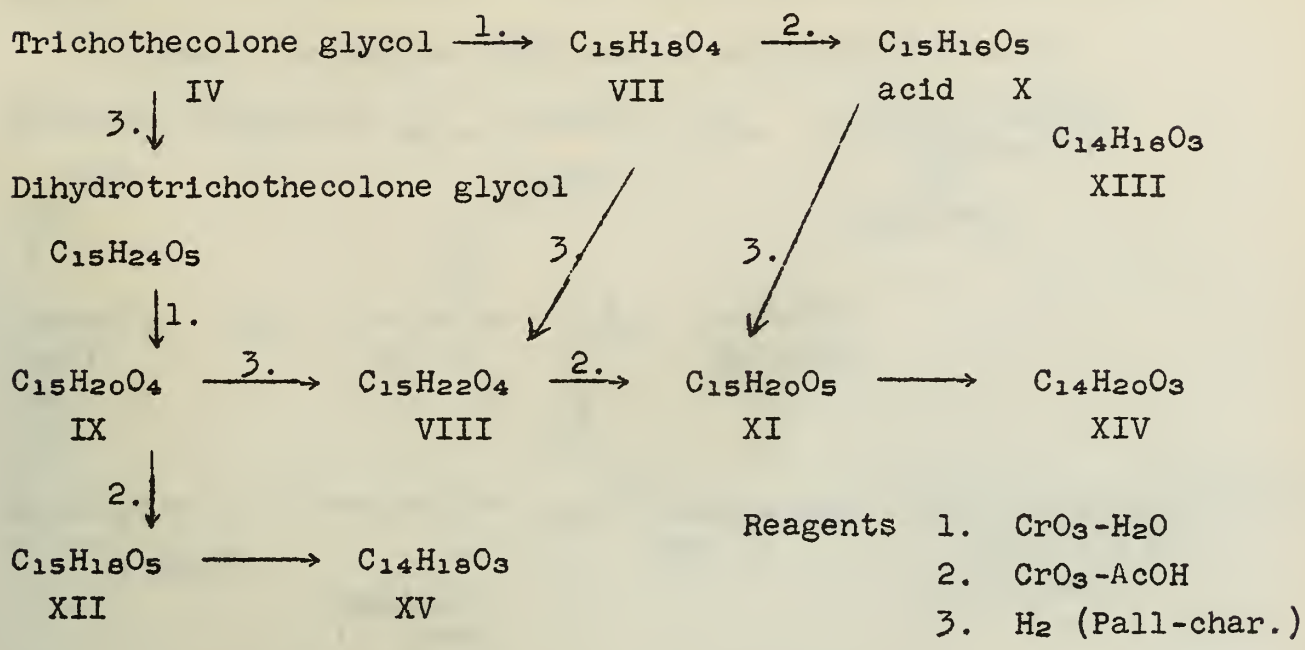
Formation of compound VII by aqueous chromic acid from trichothecolone glycol (IV) may be explained on the basis of oxidation to a keto group of the secondary hydroxyl group formed in ring C and loss of water from the resulting β-hydroxy ketone. Quantitative acetylation of compound VII showed only one hydroxyl group whereas trichothecolone glycol had three. The hydrogenation of compound VII to VIII and the increased intensity in the ultraviolet absorption spectrum of VII suggest that a new ethylenic link has been formed during oxidation.

Compounds VII, VIII, and IX were oxidized to acids by the action of chromic acid in acetic acid. Compound (VII), $C_{15}H_{18}O_4$, gave the acid (X), $C_{15}H_{16}O_5$. Its ultraviolet absorption showed a maximum at 2270 A° (ϵ 12,500). Oxidation of the compound (VIII), $C_{15}H_{22}O_4$, gave the acid $C_{15}H_{20}O_5$ (XI) and of the compound (IX), $C_{15}H_{20}O_4$, gave the acid $C_{15}H_{18}O_5$ (XII).

The acid-catalyzed opening of the oxygen bridge in trichothecin has been shown to give rise to a primary hydroxyl group which is present in structures IV, VII, VIII, and IX. The primary hydroxyl group is stable to cold aqueous chromic acid, but is attacked by chromic acid in acetic acid.[12] The acids which are formed by this treatment lost carbon dioxide on melting and gave ketones. The behavior of the acids on melting was suggestive of β-keto acids. Their failure to react with aqueous ferric chloride suggests that they may be α,α-disubstituted β-keto acids.[4]



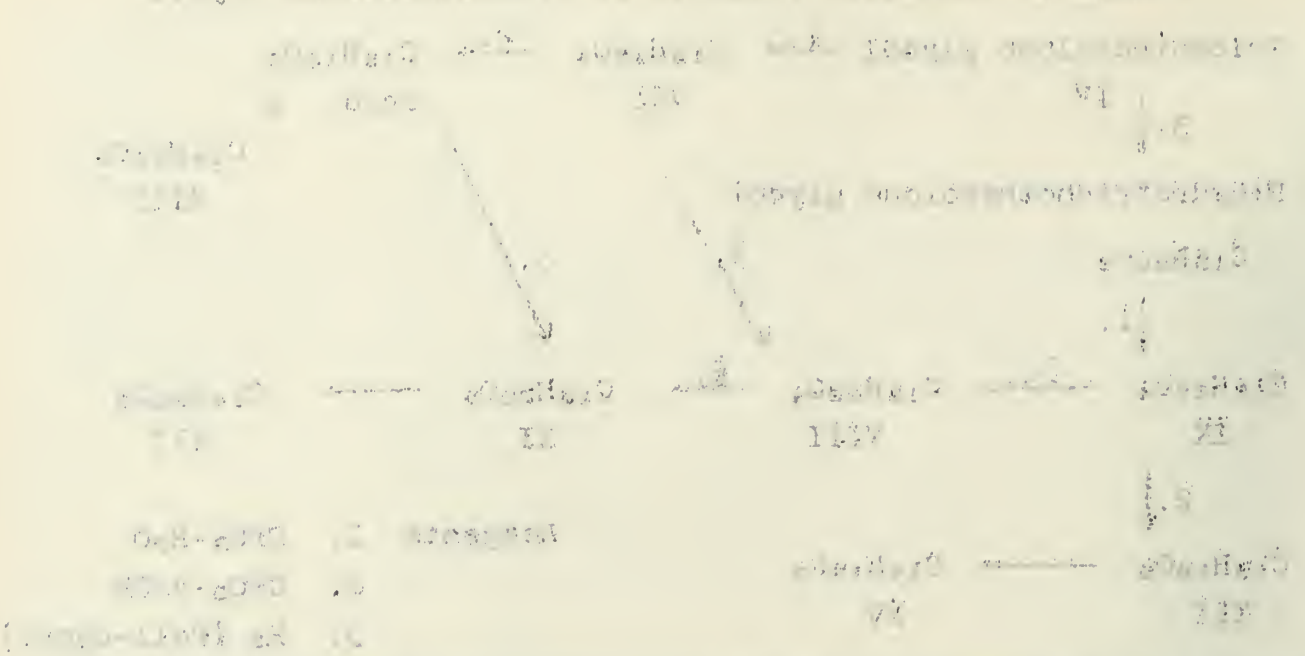
Scheme 1 Oxidation Products of Trichothecolone Glycol



ISOMERS OF TRICHOTHECODIONE AND DIHYDROTRICHOTHECODIONE

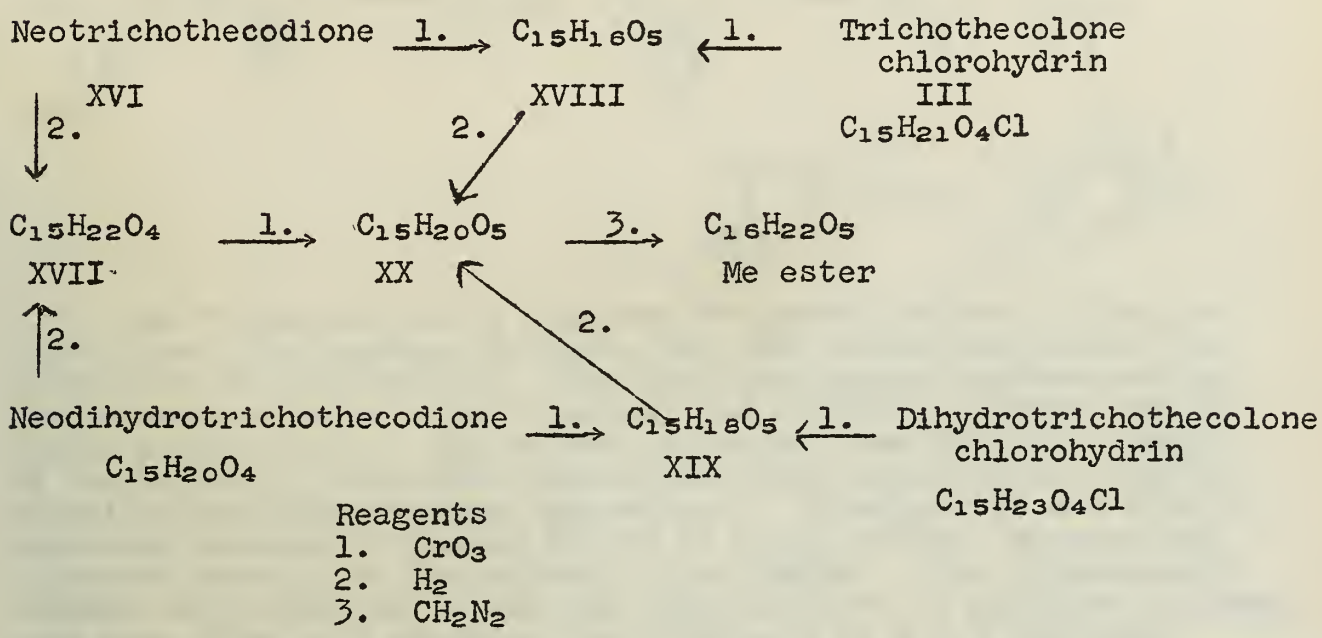
When trichothecodione (V) was warmed with ammonia, sodium carbonate solution or with one equivalent of sodium hydroxide, isomerization occurred giving neotrichothecodione (XVI). Similarly, dihydrotrichothecodione gave neodihydrotrichothecodione. Both neocompounds gave mono-2,4-dinitrophenylhydrazones. It was very probable that the isomerization involved the opening of a methyleneoxybridge and the elimination of an oxygen atom from the β-position to a carbonyl group. In support of this hypothesis it was found that neotrichothecodione contained a hydroxyl group. The infrared spectra of these compounds showed strong absorption due to a hydroxyl group and to ketonic bands at 1700 cm.$^{-1}$ and 1720 cm.$^{-1}$.

Neotrichothecodione was found to possess two ethylenic double bonds, and neodihydrotrichothecodione one double bond by quantitative hydrogenation, both giving the compound (XVII), $C_{15}H_{22}O_4$, confirming the presence of a new ethylenic bond. The intensity of the ultraviolet absorption of neotrichothecodione (λ_m 2200 A^o, ϵ 12,910) indicated that the new ethylenic bond in neotrichothecodione was conjugated with a keto group. Also in support of this hypothesis, neotrichothecodione contained a hydroxyl group, being oxidized by chromic acid to compound (XVIII), $C_{15}H_{18}O_5$ (scheme 2). These acids were hydrogenated to the same saturated acid (XX), $C_{15}H_{20}O_5$, proving that a new ethylenic double bond had been introduced during the isomerization of trichothecodione. Oxidation of the compound XVII with chromic acid gave the acid XX. The acids XVIII-XX were not decarboxylated on melting, and differed from those obtained from the trichothecolone series. The β-elimination of water involved when the methyleneoxy-bridge was opened during the alkaline isomerization of trichothecodione was similar to the β-elimination of hydrogen chloride from trichothecolone chlorohydrin when it was oxidized with chromic acid. The products of oxidation of the chlorohydrins were identical with those obtained from the corresponding derivatives in the neotrichothecodione series. Thus, oxidation of trichothecolone chlorohydrin (III) gave acid XVIII, and oxidation of dihydrotrichothecolone chlorohydrin, acid XIX. These acids were both hydrogenated to acid



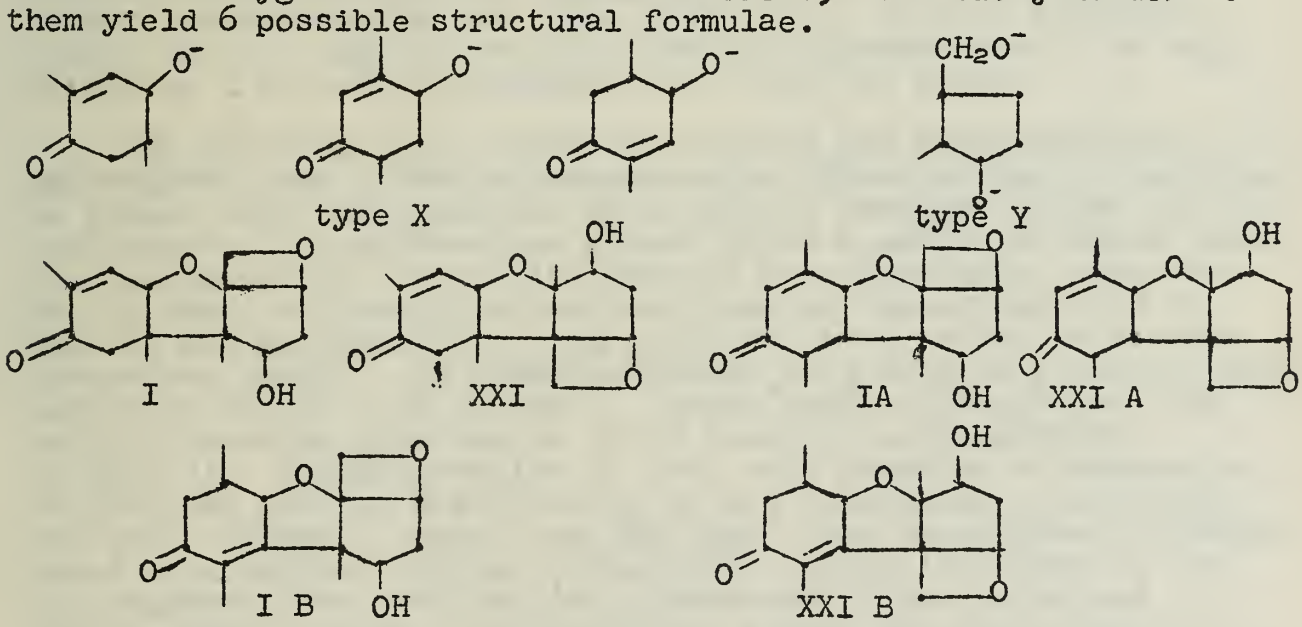
XX, identical with that obtained from the neotrichothecodione series.

Scheme 2 Oxidation Products of Neotrichothecodione



STRUCTURE OF TRICHOTHECOLONE

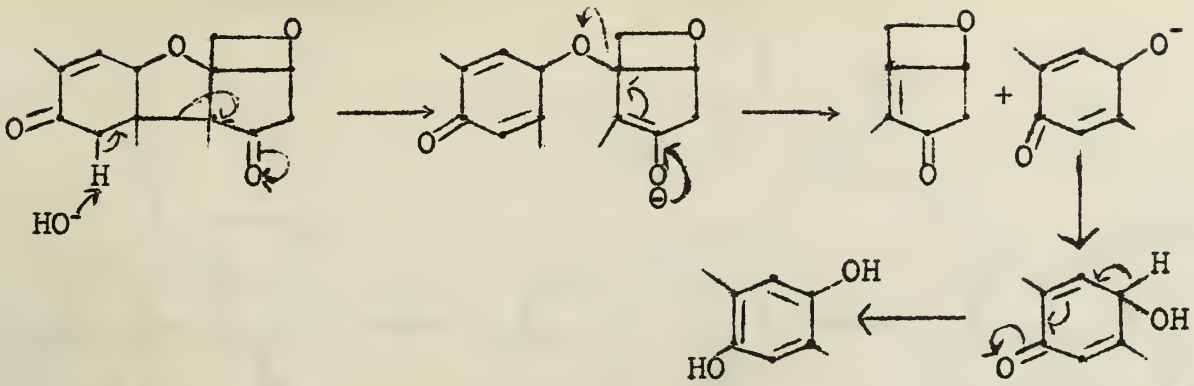
The degradation fragments can thus be arranged to conform to the skeletal types (X) and (Y). These types comprise all the carbon and oxygen atoms in trichothecolone; suitable junctions of them yield 6 possible structural formulae.



Substances IA, IB, XXIA, and XXIB would each be expected to yield a 15-carbon compound containing an aromatic 6-membered ring on mild dehydrogenation, yet this did not occur when trichothecolone derivatives were treated with hydriodic acid, and this evidence favors formulas I and XXI, each with a quaternary carbon atom in the 6-membered ring.

The easy breakdown of trichothecolone by alkali[13], involving rupture of a C-C bond, is due to the alkaline cleavage of a 1,5 diketone followed by β-elimination of the substituted alkoxy-group.

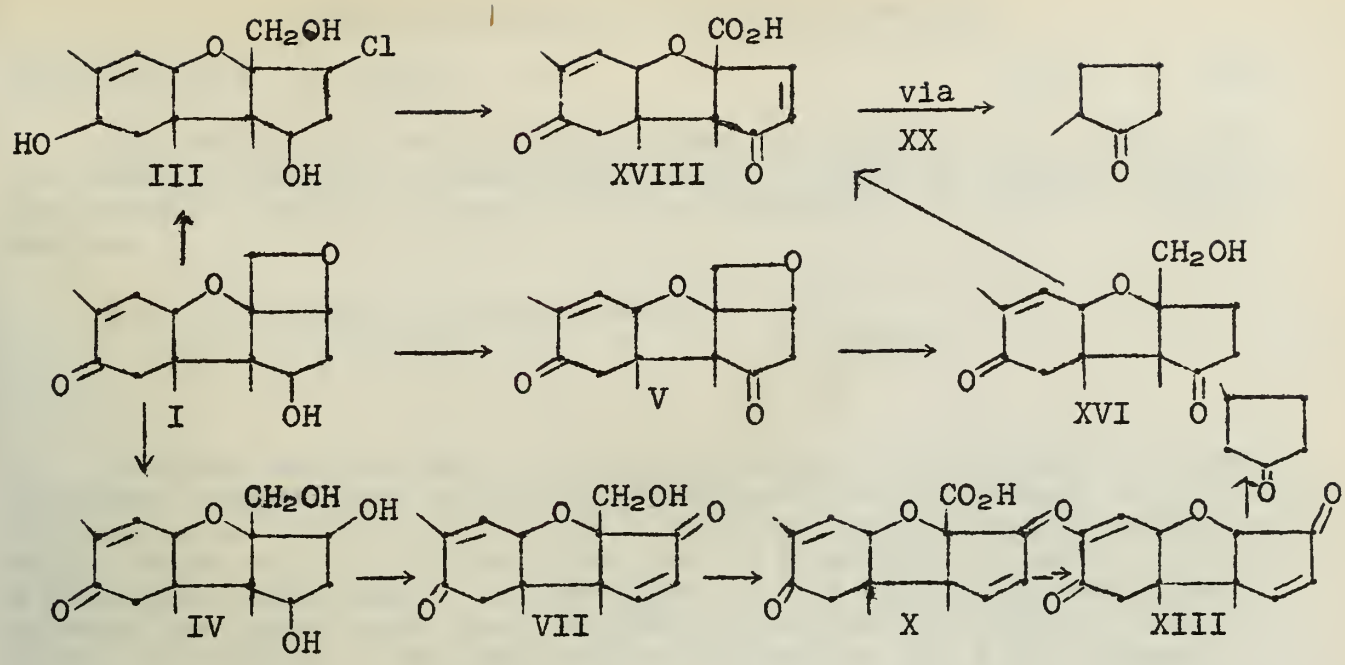
A likely mechanism is as follows:



The 4-membered oxide ring may be opened before, during, or after the 1,5 diketone cleavage, but this would not affect the formation of p-xyloquinol. The trichothecodione corresponding to IA would also be a 1,5 diketone and alkaline cleavage should yield p-xyloquinol. The trichothecodione from IB would contain a vinylogous 1,3-diketone system and would probably not undergo alkaline cleavage at room temperature. Structure IB can also be excluded because it should absorb at about 2480A° whereas the observed absorption in methanol is at 2260A°. The trichothecodiones corresponding to XXI and XXIA contain 1,6 diketone systems, and that from XXIB contains the vinylogue of a 1,4 diketone system.[14] Structures IA and XXIA would be expected to be converted, probably by air oxidation under alkaline conditions into a C_{15} phenol, but this reaction has never been observed with trichothecolone derivatives. Structures IB and XXIB have highly substituted ethylenic double bonds, which might be expected to undergo hydrogenation only with difficulty, whereas trichothecolone and its derivatives were readily hydrogenated.[4] So only structure I is left in agreement with all the facts.

The difference in properties between the trichothecolone chlorohydrin and of the trichothecolone glycol series is believed to depend upon the oxidation of different hydroxyl groups in the two series. Trichothecolone glycol gives a series of acids which are decarboxylated on melting whereas trichothecolone chlorohydrin gives a different series which are not decarboxylated on melting but are identical with acids obtained in the neotrichothecodione series. On dehydrogenation acid XX gave 2-methyl cyclopentanone by route of scheme 3. Under similar conditions, the acid XI would be expected to yield 3-methyl cyclopentanone (scheme 3). Dehydrogenation of this acid required a temperature of 350° and yielded a mixture of 2- and 3-methylcyclopentanone. Recently, Fishman, Jones, and Whiting[15] have accumulated evidence based on alkaline fission of diketonic derivatives into C_7 and C_8 fragments that confirms the structures of the acids and ketones derived from trichothecolone glycol and chlorohydrin on the basis of formula I. They also confirmed the view that different hydroxyl groups are involved in the oxidation of trichothecolone cylorohydrin and of trichothecolone glycol (scheme 3).

Scheme 3 Routes to Ketonic Dehydrogenation Products from Trichothecolone Chlorohydrin and Glycol



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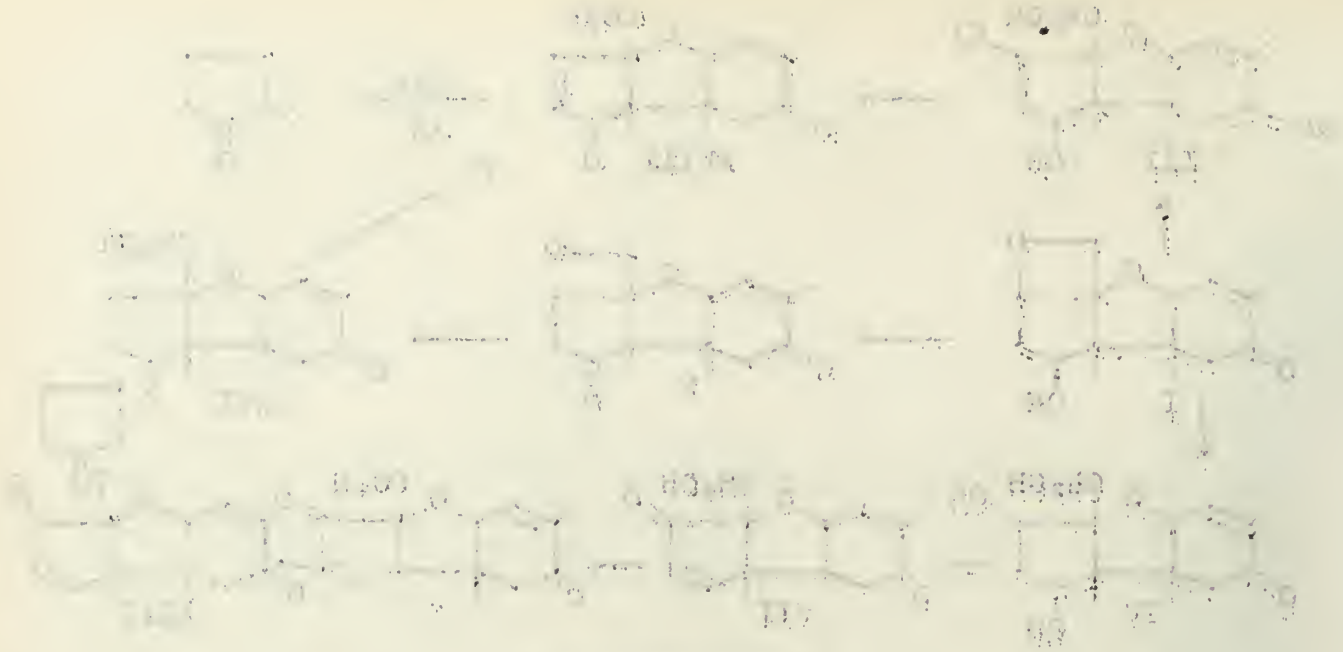


THE DECOMPOSITION OF N-CHLOROAMINES

Reported by A. E. Yethon April 18, 1960

Treatment of N-chlorodialkyamines in sulfuric acid under the influence of heat or ultra-violet light, followed by basification of the reaction mixture, results in the formation of cyclic tertiary amines.

$R'\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}NClR \longrightarrow$ 

Studies carried out on the cyclization of long chain aliphatic compounds showed that pyrrolidine derivatives are formed in preference to piperidine derivatives (1,2). Cyclization of N-chloromethyl-n-octyl amine results in the formation of 1-methyl-2-n-butyl pyrrolidine. N-Chloromethylamylamine is converted to 1,2-dimethylpyrrolidine. However two cases have been reported in which cyclization resulted in the formation of the piperidine nucleus as the sole product. N-chloro-N-methylcyclooctylamine gave N-methylgranatinine (II)(3). Similarly N-chloro-4-ethylpiperidine gave quinuclidine as the only tertiary amine product (4).

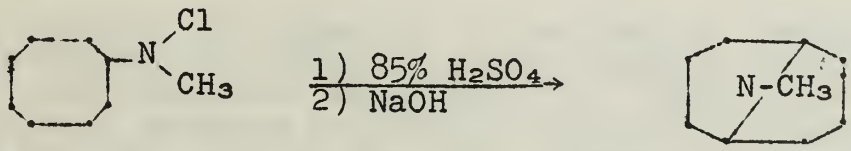
Chloroamines can be prepared by the action of hypochlorous acid, sodium hypochlorite or t-butyl hypochlorite on the amine in question (2,5). N-Chlorosuccinimide has also found use as a reagent for the preparation of chloroamines in the steroid series (6).

This seminar will deal mainly with the decomposition of N-chlorodialkyamines in sulfuric acid, with emphasis on the mechanism of this reaction. The use of N-chloroalkylamines in synthesis will also be discussed.

The use of the simplest chloroamines, monochloramine (NH_2Cl), dichloramine ($NHCl_2$) and nitrogen trichloride, in synthetic organic chemistry has been discussed in two review articles (7,8).

MECHANISM

Although the decomposition of N-bromo and N-chloroamines in sulfuric acid received a fair amount of attention as a synthetic tool for the preparation of pyrrolidine derivatives during the period 1890 to 1940, no work was directed toward the elucidation of the mechanism of this reaction. The first step in this direction came about as a result of the work carried out by Wawzonek and Thelen, on the synthesis of N-methyl-granatinine (II) from N-chloro-N methyl-cyclooctylamine (I)(3).



I II

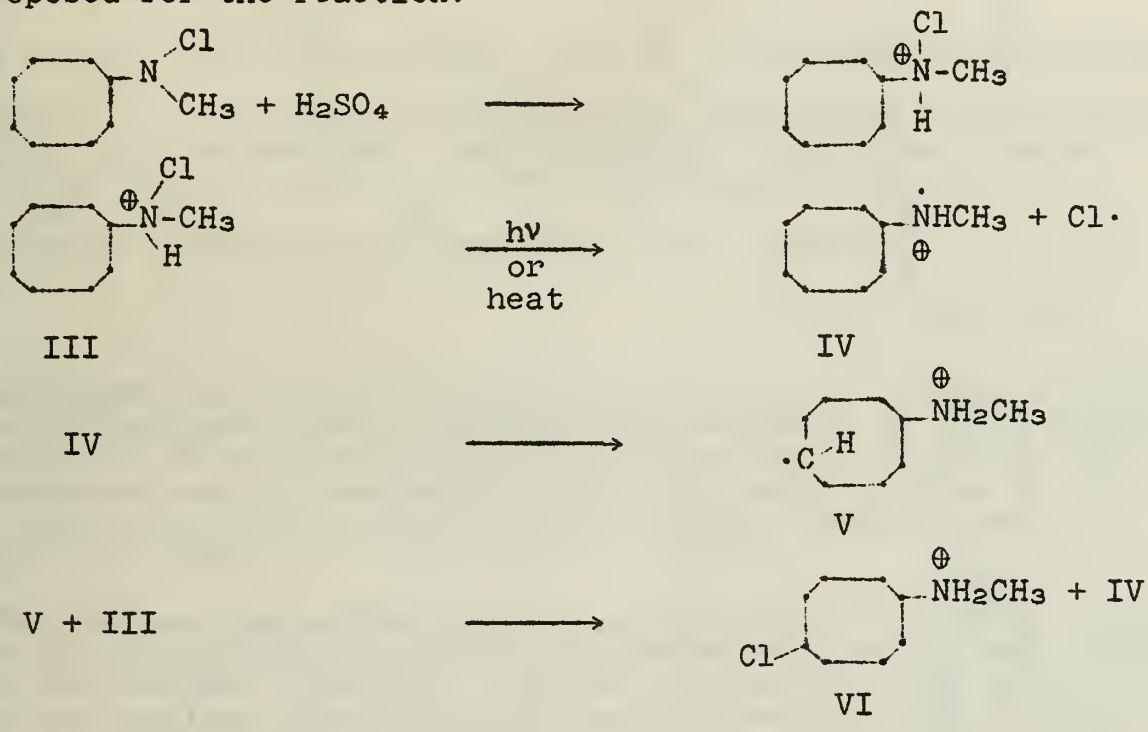
The following observations were made in a study of the above mentioned reaction:

1) The best yield of N-methylgranatinino (24%) was obtained when the reaction mixture was irradiated with ultraviolet light, in the presence of chlorine at 0-8°C.

2) When the reaction was carried out in complete darkness only a small amount (3%) of N-methylgranatinine was isolated.

3) Addition of hydrogen peroxide to the reaction mixture in the dark, resulted in an increased yield of N-methylgranatinine (12%).

On the basis of these data the following free radical chain mechanism was proposed for the reaction.



Homolytic cleavage of the chloroammonium salt (III) results in the formation of an aminium ion radical (IV). The aminium ion radical thus formed then abstracts a hydrogen from a sterically favored carbon atom and forms the alkyl free radical (V), which then may start a chain reaction and form the chlorocyclooctylamine salt. Treatment of compound VI with sodium hydroxide would then bring about cyclization to the observed N-methylgranatinine.

The effect of ultraviolet light has further been demonstrated for the cyclization of N-chlorodibutylamine to N-butylpyrrolidine (9). The chloroamine titer of a solution of N-chlorodibutylamine in 84% sulfuric acid remained constant in the absence of light, whereas one half of the chloroamine reacted within thirty-two minutes after irradiation with ultraviolet light was begun.

Further evidence in support of a free radical mechanism has been obtained by studying the effect of added reagents, known to act as free radical initiators and inhibitors (9). Addition of catalytic amounts of ferrous ammonium sulfate to a mixture of N-chlorodibutylamine in 85% sulfuric acid in the dark, brought about rapid disappearance of the chloroamine. This result can best be explained in terms of an oxidation-reduction process, in which the oxidizing species, N-chlorodibutylamine, is converted to an aminium ion radical and chloride ion.

$$Fe^{++} + (\underline{n}\text{-}C_4H_9)_2\text{-}\overset{\oplus}{N}HCl \longrightarrow Fe^{+++} + n\text{-}(C_4H_9)_2\text{-}\overset{\oplus}{N}\cdot_H + Cl^{\ominus}$$

This observation is in agreement with the findings of Johanneson, who observed that at pH-3 or less monochloramine acts as a good oxidizing agent (10).

When N-chlorodibutylamine was decomposed thermally in the presence of small amounts of iodine, N-butylpyrrolidine was obtained in a 15% yield as opposed to a 65% yield in the absence of iodine, under similar conditions and reaction time. The iodine breaks the radical chain reaction at the alkyl radical stage to form the less active iodine radical.

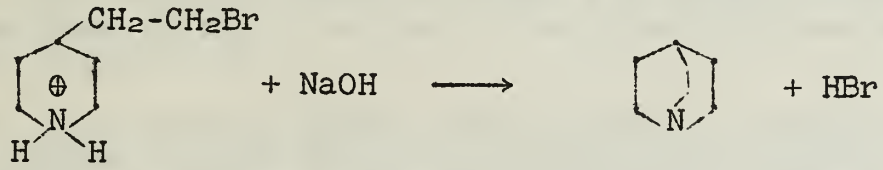
$$I_2 + \cdot CH_2\text{-}(CH_2)_3\text{-}\overset{\oplus}{N}H_2\text{-}\underline{n}\text{-}C_4H_9 \longrightarrow I\cdot + I\text{-}CH_2\text{-}(CH_2)_3\text{-}\overset{\oplus}{N}H_2\text{-}\underline{n}\text{-}C_4H_9$$

Oxygen and N-chlorodiethylamine were also found to be effective inhibitors of the reaction. Inhibition by N-chlorodiethylamine probably proceeds according to the following equation:

$$(C_2H_5)_2\text{-}\overset{\oplus}{N}HCl + \cdot CH_2\text{-}(CH_2)_3\text{-}\overset{\oplus}{N}H_2\text{-}\underline{n}\text{-}C_4H_9 \longrightarrow (C_2H_5)_2\text{-}\overset{\oplus}{N}H + Cl\text{-}(CH_2)_4\text{-}\overset{\oplus}{N}H_2\text{-}\underline{n}\text{-}C_4H_9$$

The diethylaminium ion radical does not have a sterically favorable carbon for hydrogen abstraction and thus serves as a "chain breaker". The inability of N-chlorodiethylamine to undergo cyclization had been demonstrated by irradiating a sulfuric acid solution of the amine. The chloroamine concentration remained constant over a period of one hour.

The proposed mechanism for the decomposition of N-chloroamines implies the formation of a chloroalkylamine salt as the end product of the free radical reaction. Indirect evidence for the formation of the intermediate alkyl chloride was obtained in a study carried out on the cyclization of N-chloro-4-ethylpiperidine (4). After irradiation with ultraviolet light, the solution was quickly adjusted to pH-9. In a short time the pH dropped to about 5. This was repeated several times before the solution remained constant at pH-9. This was interpreted as being evidence for the formation of the intermediate 4-(β-bromoethyl)-piperidine salt, which under the basic conditions was cyclizing to give the observed quinuclidine and hydrogen bromide.



4-(β-Iodoethyl)-piperidine is known to cyclize to quinuclidine in the presence of weak base (11).

Direct evidence for the formation of a chloroalkyl intermediate was obtained with the isolation of 4-chlorodibutylamine hydrochloride from irradiation of N-chlorodibutylamine in sulfuric acid (12). This compound was identical with respect to melting point and infrared spectra to 4-chlorodibutylamine hydrochloride prepared by another route. Both samples were converted by cold alkali into N-butyl-

pyrrolidine in a 64% yield. The intermediate 4-chlorodihexylammonium bisulfate arising from the irradiation of N-chlorodihexyl amine has also been isolated and characterized (17).

The possibility of a bisulfate or sulfate ester being the end product of the reaction was ruled out on the basis of an experiment in which N methyl-4-hydroxyamylamine was heated in sulfuric acid (9). No 1,2-dimethyl pyrrolidine could be detected on basification.

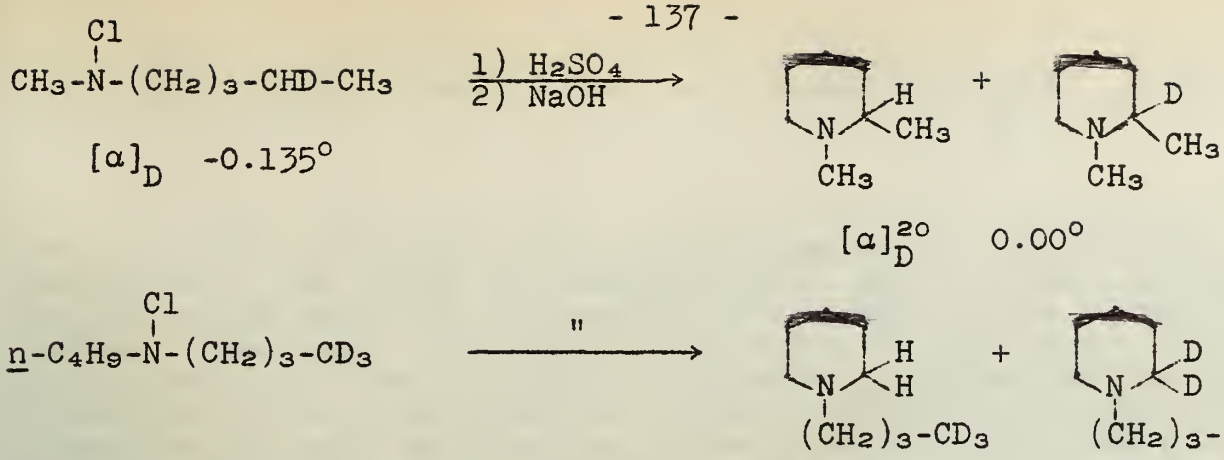
A noteworthy feature of the mechanism proposed by Wawzonek is that the species undergoing initial homolytic cleavage is not the chloroamine but rather the protonated form of the chloroamine. Chloroamines have been shown to have very high ka values (18) (9.5×10^{-2} for diethylchloroamine) in aqueous media, thus it is not inconceivable that some of the chloroamine could exist in the unprotonated form in sulfuric acid and this unprotonated species could then undergo homolytic cleavage. When N-chloro dibutylamine was heated in ethanol, dibutylamine, butylamine, N-butylbutyramide and ethyl glyoxal were the only products isolated. In acetic acid where the protonated species would be present in a negligible amount, decomposition again took place to give mainly dibutylamine. N-Butyl pyrrolidine was not formed in this reaction.

The decomposition of N-chlorodibutylamine has been carried out in acetic acid containing varying concentrations of sulfuric acid (9). The results of these experiments are summarized in the following table.

Conc. of N-chloro dibutylamine	Conc. of H_2SO_4 (N)	Half-life (min.)	Yield of N-butyl pyrrolidine (%)
0.255	0	2909	0
0.260	1	62	42
0.255	2	52	69
0.245	5	47	80

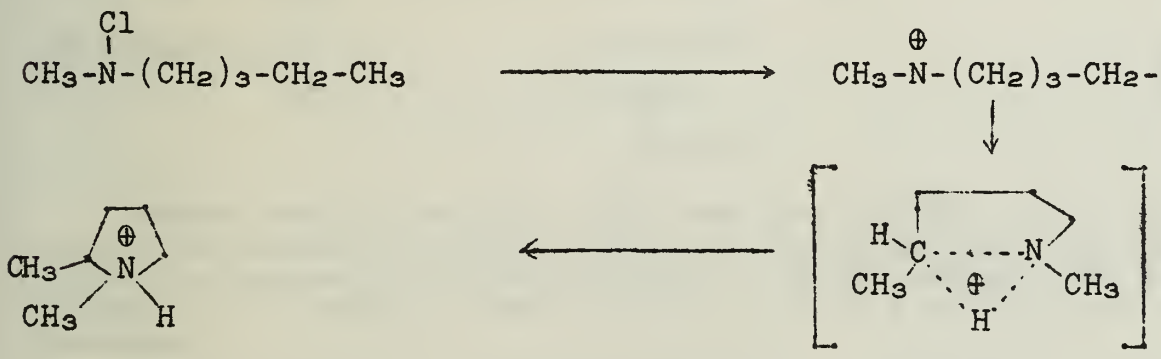
Thus all available evidence indicates that the presence of a strong acid is required for the process leading to the formation of the cyclic amine. That the species undergoing initial homolytic cleavage is the protonated form of the chloroamine may be questioned on the grounds that the evidence presented above would equally well apply if only the chain carrying steps required a protonated species. If this were the case initial cleavage of the free chloroamine would be a definite possibility.

In order to determine whether abstraction of hydrogen by aminium ion radical proceeded with an appreciable isotope effect, the two compounds, methylamylamine-4-d and dibutyl amine-4-d_3 were converted to their N-chloro derivatives and then subjected to thermal decomposition in sulfuric acid (9).



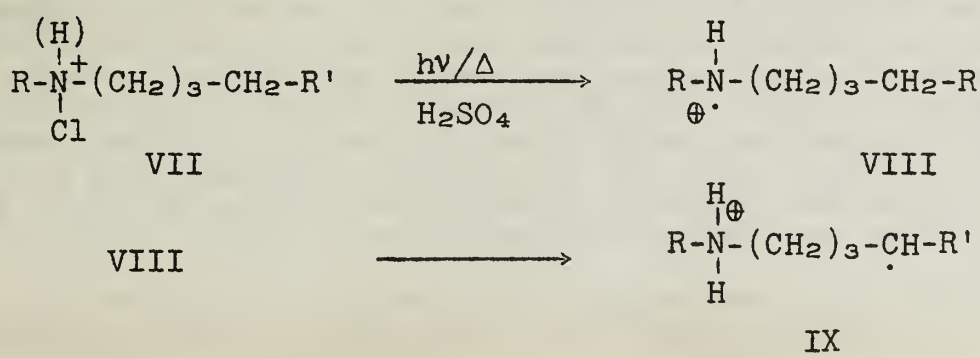
The isotope effect kH/kD for the first reaction was found to be 3.54, while the isotope effect for abstraction of the primary hydrogen, as is the case in the second reaction, was found to be in the order of 2.6. The maximum value of the deuterium isotope effect for the breaking of a C-H bond at 95° is close to 4.7. Thus breaking of the C-H bond appears to have proceeded to an appreciable extent in the transition state for the abstraction of hydrogen by aminium ion radical.

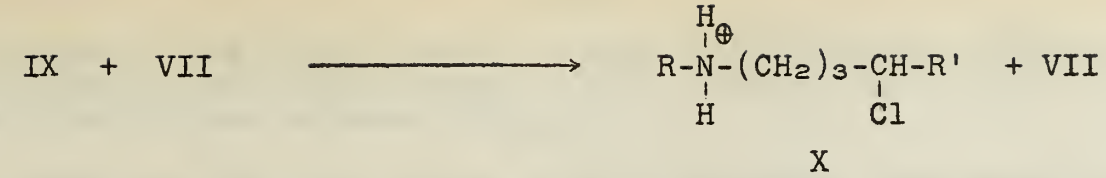
The cyclization of methylamylamine-4-d also served to demonstrate that racemization occurred at the δ carbon atom. The 1,2-dimethylpyrrolidine formed during the cyclization process was found to be optically inactive. It was felt that this was evidence against an ionic mechanism involving direct electrophilic attack of a cationic nitrogen species on carbon, since this might be expected to proceed with retention of configuration.



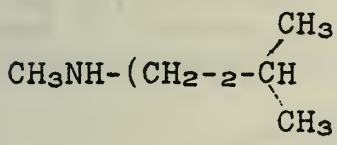
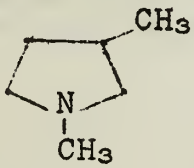
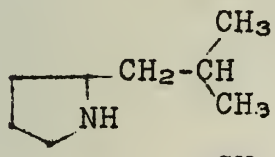
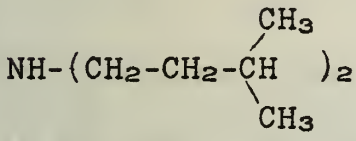
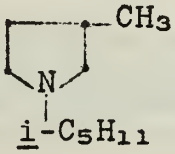
Cyclization of N-chlorodibutylamine in a mixture of 85% sulfuric acid -D_2O solution gave N-butyl pyrrolidine, which showed no absorption in the C-D stretching region of the infrared spectrum (5). These results indicate that abstraction of hydrogen by aminium ion radical is probably an irreversible process.

On the basis of available evidence the mechanism for the decomposition of N-chlorodialkylamines can be formulated as follows:





The ring size of the resulting tertiary amine will be directly dependent on the nature of intermediate X, which in turn is dependent on the second step, the abstraction of hydrogen by the aminium ion radical. Because of the fairly substantial isotope effect observed in the reaction it would appear reasonable to assume that in the transition state, the carbon atom will have appreciable free radical character and since abstraction is due to a positively charged species, the carbon atom might also have some positive character. Ease of hydrogen abstraction might then be expected to increase in the order primary < secondary < tertiary. When the maximum length of the alkyl group is four carbon atoms this is not the case however as can be seen in the following table:

Secondary Amine	Product	Reference
		14
		15
		16

These results indicate that the free energy of activation required for abstraction of a hydrogen from a carbon less than four positions removed from the nitrogen is much greater than the difference in energy between abstraction of a primary and a tertiary hydrogen.

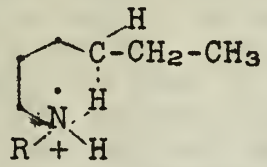
When compounds were studied in which the aminium ion radical was able to abstract either a primary, secondary or tertiary hydrogen from a carbon four position removed from the nitrogen, it was found that the hydrogens were removed in the order tertiary > secondary > primary (9). N-Chlorobutylamylamine gave N-butyl-2-methylpyrrolidine as the sole product. When N-chloroamylisohexylamine and N-chlorobutylisohexylamine were thermally decomposed in 85% sulfuric acid, hydrogen chloride was evolved. Basification of the reaction mixtures failed to give a tertiary amine product in both cases. It is believed that in the latter two cases the tertiary hydrogen was preferentially abstracted by the aminium ion to give the intermediate tertiary chloro compound, which then decomposed in sulfuric acid to give hydrogen chloride and an amine which could not cyclize to a tertiary amine. Evolution of hydrogen chloride was also noted when t-butyl chloride was subjected to the same conditions.

The energy of the transition state involving abstraction of hydrogen by aminium ion radical will be dependent on 1) the stability

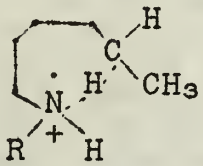
of the carbon free radical being formed, 2) the steric availability of the hydrogen to be abstracted, 3) the tendency to minimize non bonded interactions between hydrogens.

A study on the cyclization of ethylamylamine, methylhexylamine and dihexylamine has been carried out to determine the relative importance of the above mentioned factors, in the abstraction of hydrogen by aminium ion radical (17). Ethylamylamine gave 1-ethyl-2-methylpyrrolidine as the sole product, whereas methylhexylamine gave a mixture consisting of 80% 1-methyl-2-ethylpyrrolidine and 20% 1,2-dimethylpiperidine. Cyclization of dihexylamine resulted in a mixture consisting of 95.6% 1-hexyl-2-ethylpyrrolidine and 4.4% 1-hexyl-2-methylpiperidine.

In the case of amylamines it is believed that the factor controlling hydrogen abstraction from the fourth rather than the fifth carbon, is the formation of the secondary free radical. Abstraction of hydrogen from the fourth or fifth carbon in hexylamines should give radicals of similar stability. The preponderance of the pyrrolidine product indicates that a combination of factors 2) and 3) favors the six-membered ring transition state (XI) over the seven-membered one (XII).



XI



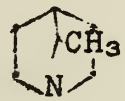
XII

The decreased yield of the piperidine product in changing R from methyl to the larger hexyl group has been attributed to a change in the configuration about the nitrogen, from a planar to a more tetrahedral structure, which would favor the six-membered ring transition state.

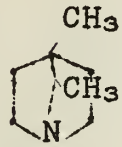
The formation of N-methylgranatinine from N-chloro N-methylcyclooctylamine can be explained by considering the non-bonded hydrogen interactions of the two possible transition states and also the steric availability of the hydrogens on the carbons four and five positions removed from the nitrogen. Non-bonded interactions would be less in the transition state leading to the formation of N-methylgranatinine. Models show that there would be better overlap in the transition state between nitrogen and the hydrogen five positions removed, than the one in which the nitrogen and hydrogen are four positions removed. Since the stability of the two radicals would be expected to be the same, the above mentioned steric factors appear to be the sole ones involved in the formation of N-methylgranatinine.

Studies carried out on the cyclization of N-chloro-4-ethylpiperidines have been reported to yield quinuclidines as the only tertiary amine products (4). The formation of the six membered ring in preference to the five membered ring was again attributed to steric factors. However other workers (19) have reported that the N-chloro derivatives of 4-ethyl piperidine and 4-methyl-4-ethylpiperidine, on treatment with sulfuric acid and ultraviolet light gave 7-methyl-1-azabicyclo-[1·2·2]heptane (XIII) and 4,7-dimethyl-1-azabicyclo-[1·2·2]heptane (XIV) respectively. These are the

the products resulting from abstraction of a secondary hydrogen rather than the primary hydrogen, as is the case in the formation of the quinuclidines.



XIII



XIV

Steric factors again appear to be the controlling ones in the conversion of N-chloro-N-methyl cyclohexylamine (XV) to 1,4-methyl-iminocyclohexane (XVI)(9).

XV

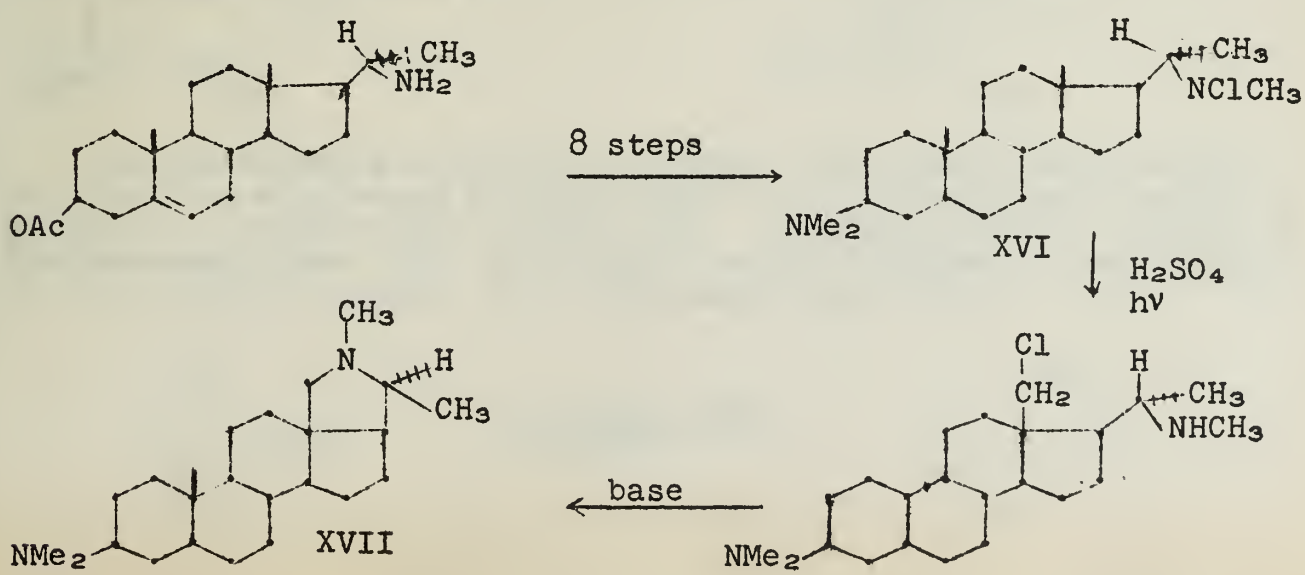
XVI

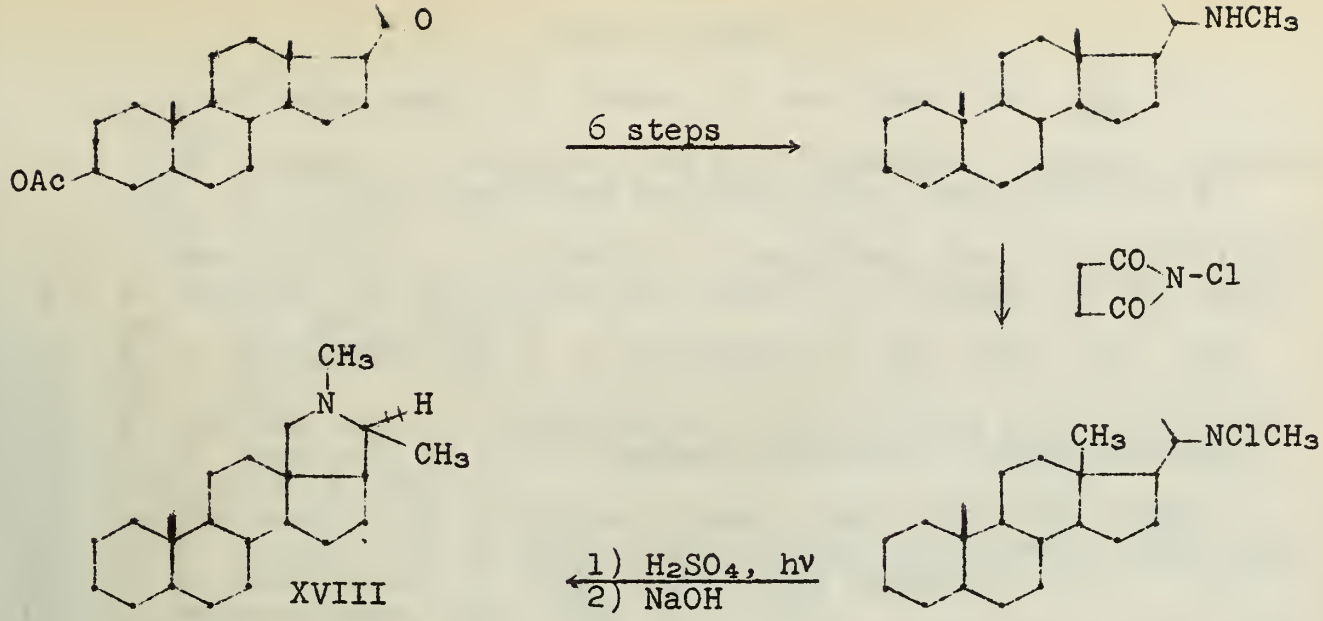
The half life for the decomposition of XV was 570 minutes as opposed to a half life of 10 minutes for the decomposition of N-chlorodibutylamine. Assuming that the aminium ion radical has a long enough life time in solution to take part in a chain terminating step, possibly by reaction with Cl· or Cl_2, the diminished rate of the above reaction can be explained in terms of the energy required to change the cyclohexane ring from a chair to a boat conformation plus the poor accessibility of the hydrogen atom.

USE OF N-CHLOROAMINES IN SYNTHESIS

A seminar given at M.I.T. tabulates the various pyrrolidine derivatives that have been synthesized using N-chloroamines (7).

Recently a considerable amount of work has been directed toward the synthesis of steroids containing functionality at the C_{18} angular methyl group. Known procedures for the introduction of functionality at C_{18} have been restricted to long total or partial synthesis of the steroid nucleus in question. Using the N-chloroamine reaction as the key step the alkaloids dihydroconessine XVII and conanine (XVIII) have been synthesized (20,21).

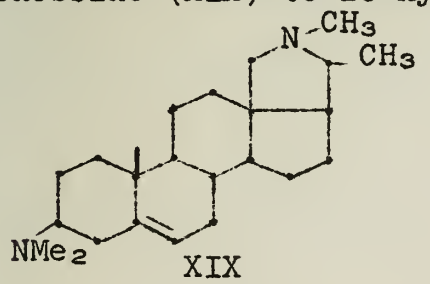




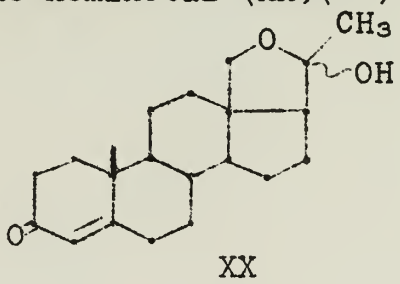
The unique feature of both syntheses is that the nitrogen function has been introduced at C_{18} directly, keeping the steroid nucleus intact throughout. The preferential abstraction of primary hydrogen is due to the steric inaccessibility of any of the secondary hydrogens.

In the synthesis of dihydroconessine evidence was obtained for the intermediate 18-chloro compound (XVI). The crude amine product obtained after irradiation and basification, formed an ether insoluble amine salt on heating, which on treatment with base gave dihydroconessine (XVII). The importance of the intermediate chloro-derivative (XVI) lies in that it has possibilities as a synthetic precursor to 18-oxygenated steroids.

That the final product of the cylization, the pyrollidine derivative, also has possibilities as a synthetic precursor to 18-oxygenated steroids has been demonstrated by the conversion of conessine (XIX) to 18-hydroxyprogesterone hemiketal (XX)(22).

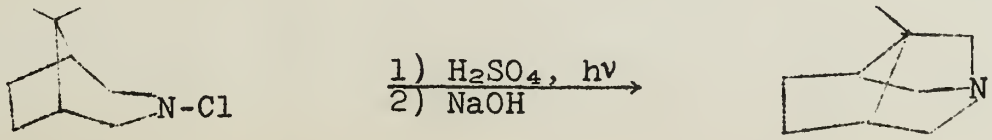


XIX

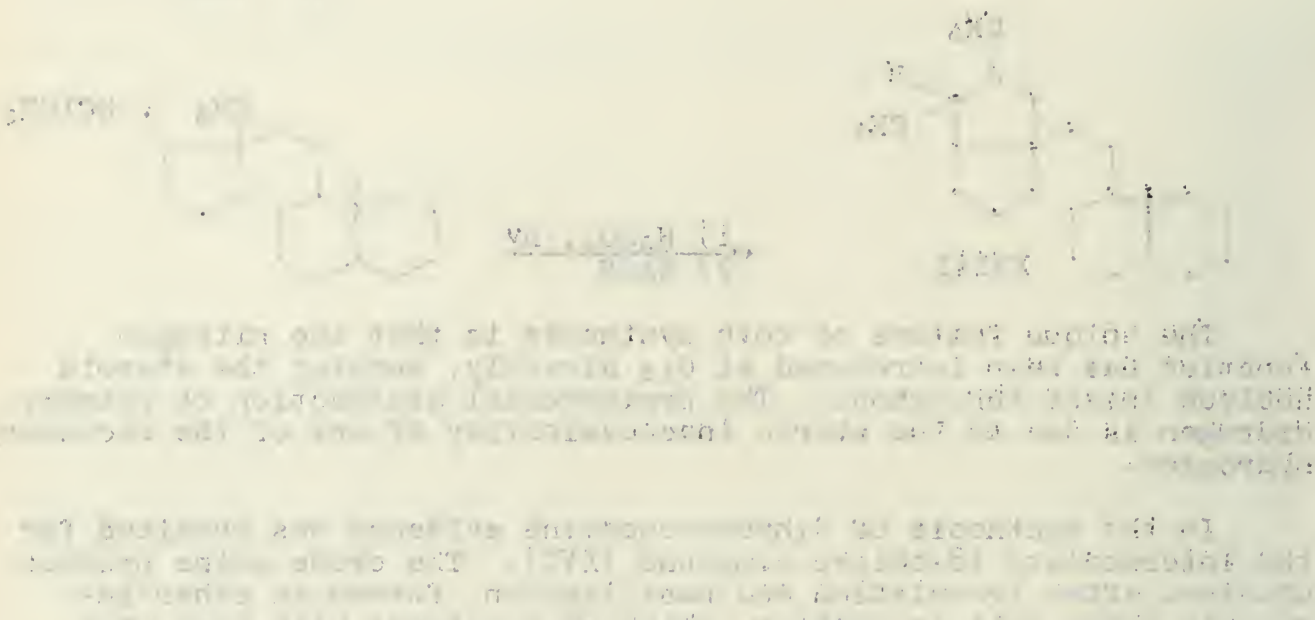


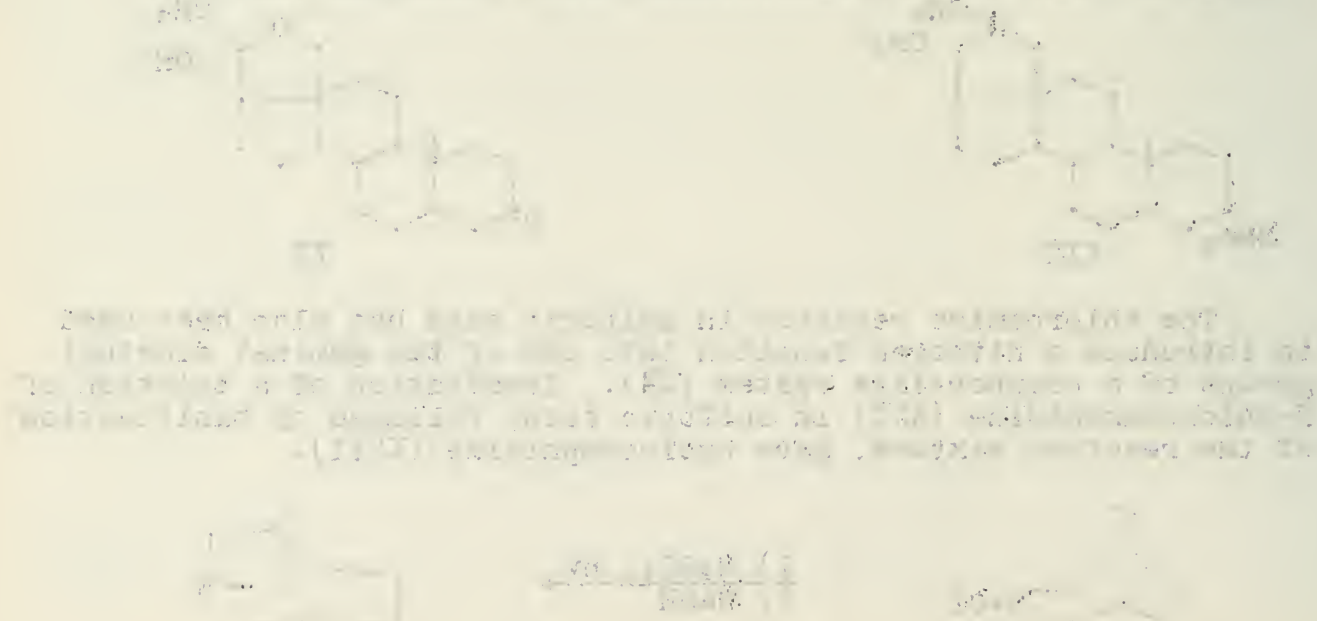
XX

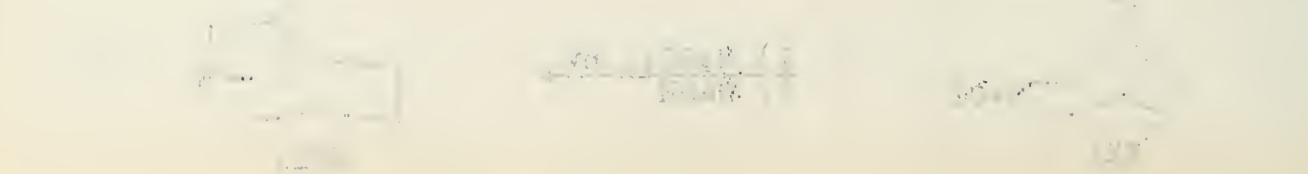
The chloroamine reaction in sulfuric acid has also been used to introduce a nitrogen function into one of the geminal dimethyl groups of a camphor-like system (23). Irradiation of a solution of N-chlorocamphidine (XXI) in sulfuric acid, followed by basification of the reaction mixture, gave cyclocamphidine (XXII).



XXI XXII







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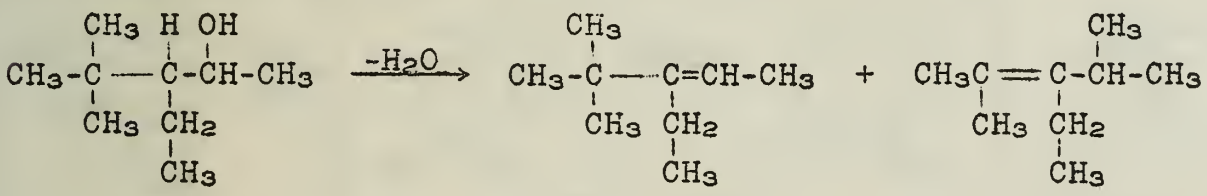
LONG RANGE MIGRATIONS IN ELECTRON DEFICIENT SYSTEMS

Reported by T. H. Kinstle April 21, 1960

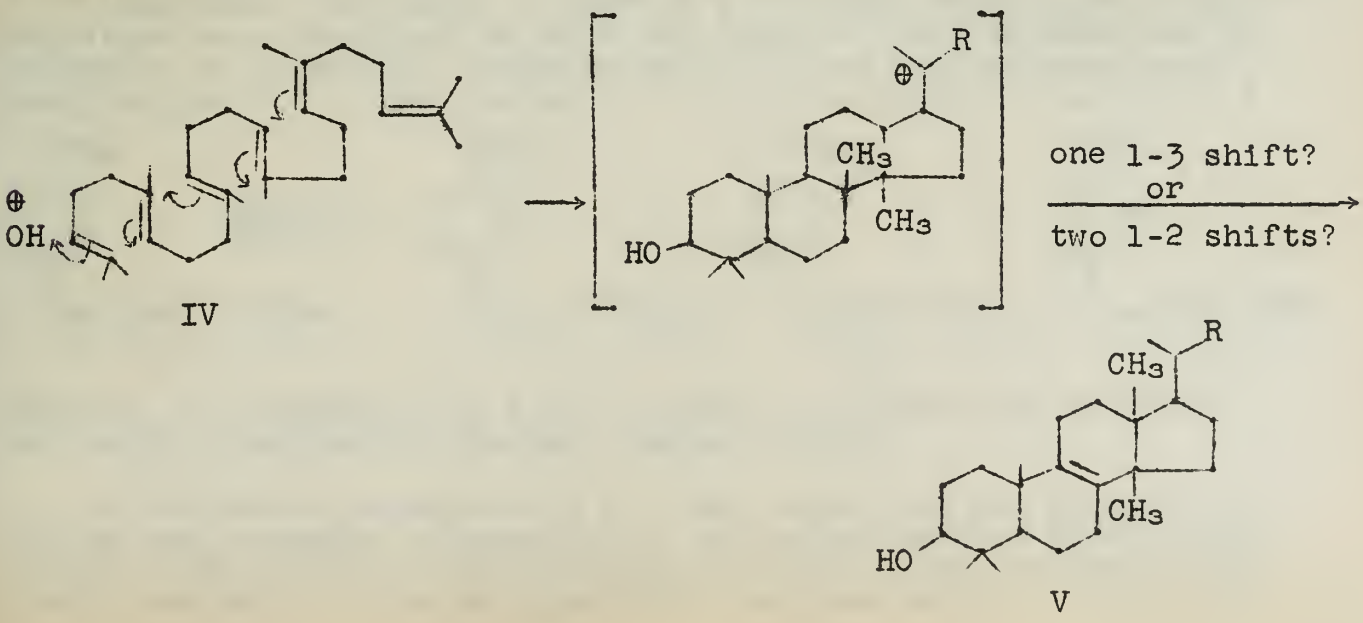
Numerous examples of 1-2 shifts in rearrangement reactions, beginning with Fittig's discovery of the pinacol-pinacolone transformation in 1860, led to the development of the "1-2 shift" concept as the underlying mechanism for organic molecular rearrangements. Many incorrect mechanisms were proposed for these shifts prior to the presently accepted hypothesis of Whitmore.[1] This concept has been shown to be capable of accommodating a large number and variety of molecular changes.[2] In fact, those rearrangements which cannot be rationalized in terms of a 1-2 shift, or a short sequence of such shifts, are of special significance. Recently, much work has been done on "non-Whitmore" type rearrangements. This seminar will be concerned with a review of successful and attempted migrations (of groups other than hydrogen) in systems containing an electron deficient carbon atom. Certain other types of 1-3 shifts are covered elsewhere[3].

1-3 MIGRATIONS

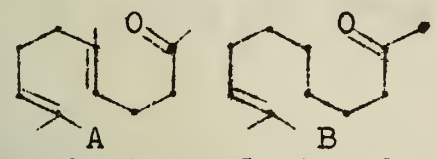
The earliest claims[5] of 1-3 alkyl migrations were not well proved and could be explained more easily by a series of 1-2 shifts. Mosher[6] has proposed a direct 1-3 migration of a methyl group to explain the formation of III from the dehydration of 3-ethyl-4, 4-dimethyl-2-pentanol (I). Although models show that this methyl group is quite close to the reaction center, this view must nevertheless be regarded with suspicion in light of evidence to be cited later.

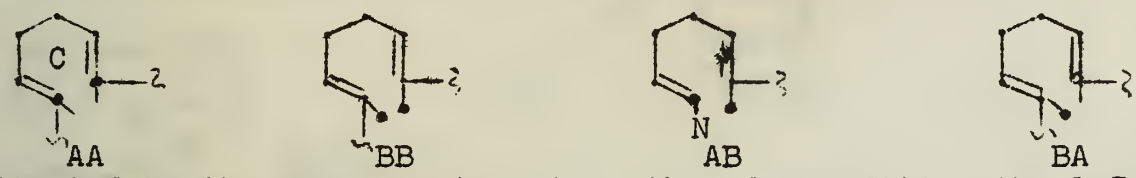


During the enzymatically catalyzed cyclization of squalene (IV) to lanosterol (V) there occurs a rearrangement of methyl groups that has often been rationalized in terms of a 1-3 migration. In a very elegant tracer experiment, Bloch[7] has determined which of these two



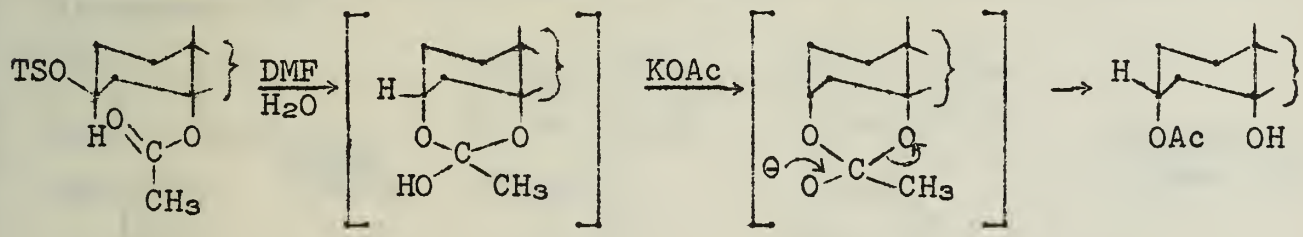
possibilities is correct. By synthesizing the ^{13}C labeled geranyl acetones A and B (—• designates the isotopic carbon), he could prepare the four labeled all-trans squalenes of partial structure AA, AB, BA, and BB. These squalenes were cyclized to lanosterol enzymatically and the lanosterol oxidized by Kuhn-Roth procedure to acetic acid residues. These acetic acid residues were further transformed to ethylene and the ^{13}C content of each of these ethylenes measured by mass spectrometry. It can be seen that the <u>only</u> path by which $^{13}CH_2{=}^{13}CH_2$ can be produced would be from squalene BA by successive 1-2 methyl migrations. Approximately the calculated amount of the doubly labeled ethylene was in-





dicated by the mass spectrometer, thus discrediting the 1-3 shift proposals.

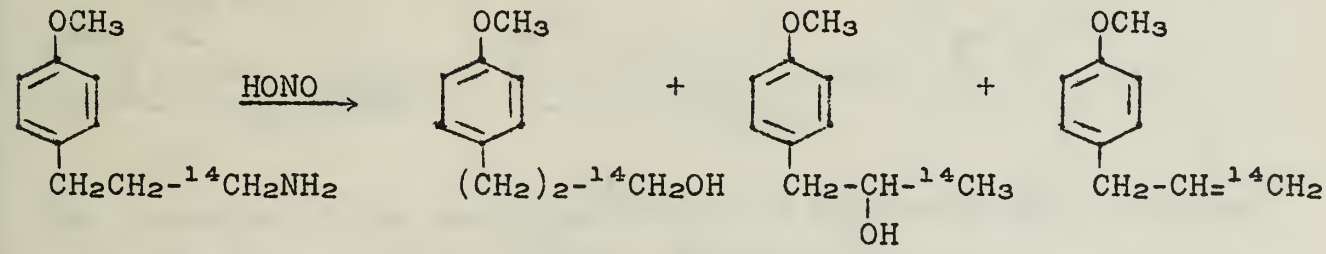
The acetate group is known to participate as a neighboring group in many carbonium ion reactions. In one of its interesting participations in the steroid series,[8] the 5α-acetate group in cholestan-3β-tosyloxy-5α-acetoxy-6-one (VI) migrates to carbon-3 during solvolysis in DMF, water, and added potassium acetate. Without the added potassium acetate, the product was the unrearranged 3β-ol-5α-acetate. Due to the rigidity of the steroid nucleus, the acetate group in this



VI

compound can approach the backside of the tosylate function, and formation of the cyclic ring intermediate provides the driving force for the reaction.

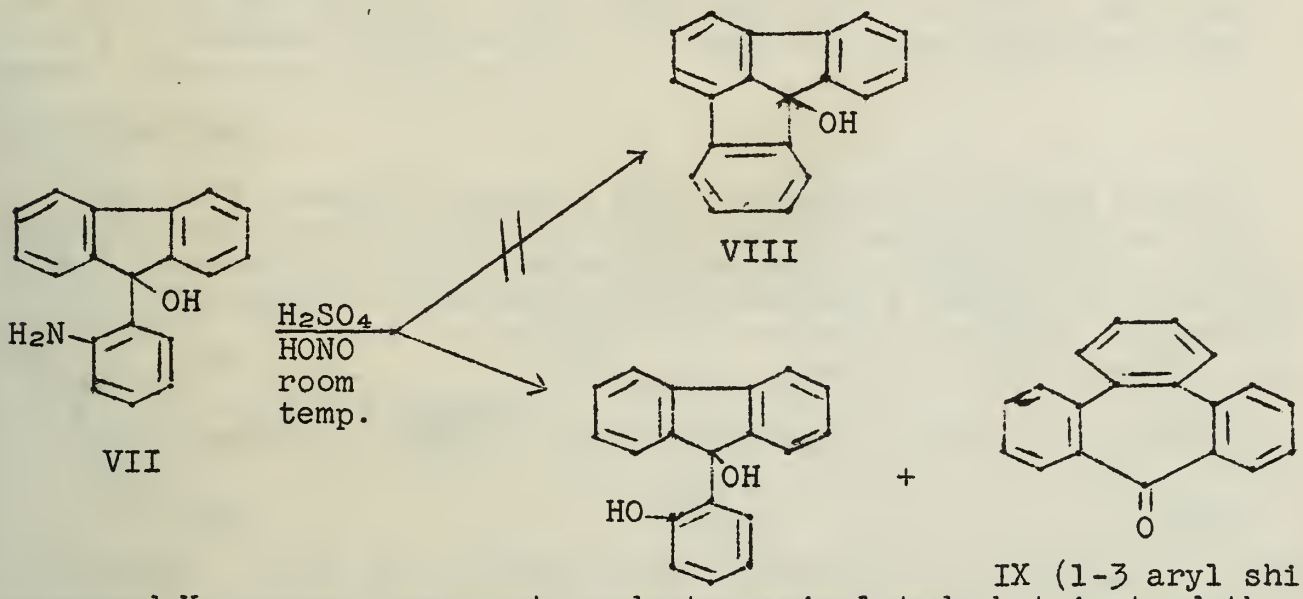
Experiments designed to observe a 1-3 aryl participation and migration were performed by Fort and Roberts,[9] who studied the deamination of 3-phenyl-1-propylamine-1-^{14}C and 3-<u>p</u>-methoxyphenyl-1-propylamine-1-^{14}C. The failure of benzyl or phenyl to migrate is



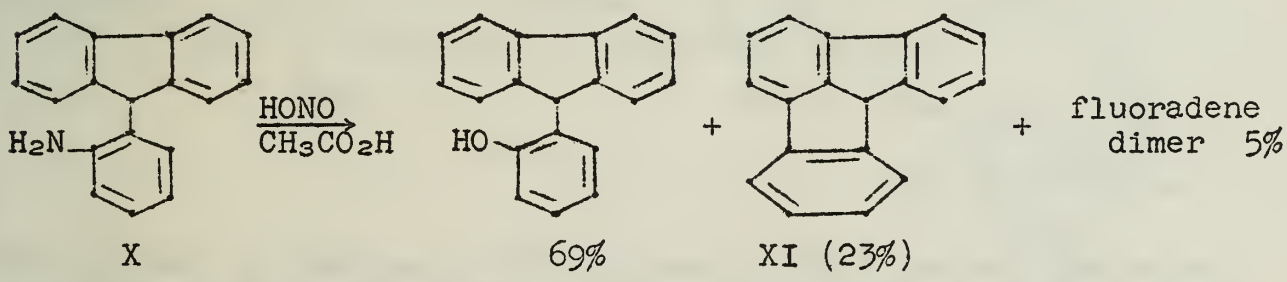
shown by no scrambling of the ^{14}C label. Further work by Fort[10] on 3-aryl-1-butylamine yielded similar results.

A successful example of a 1-3 aryl migration was discovered during the attempted preparation of an indenofluorene derivative[11] (VIII). The structure of the tribenzotropone (IX), formed in 24% yield, was proven by base degradation to <u>o</u>-terphenyl-2-carboxylic

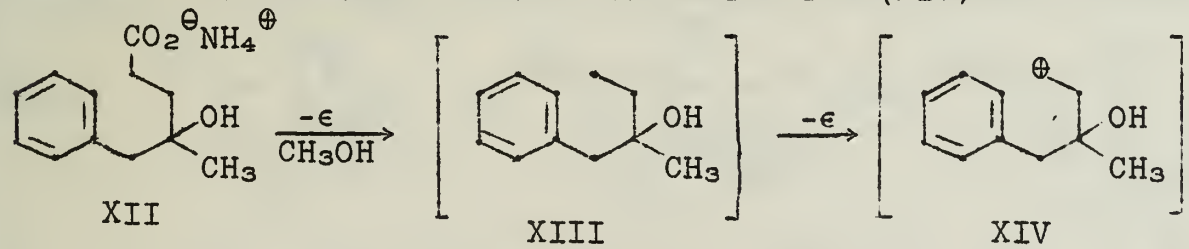
acid which was further dehydrated to 4-phenylfluorenone. An authentic sample of 4-phenylfluorenone was synthesized from fluorenone-4-carboxylic acid *via* a free radical phenylation. This rearrangement has been extended to other *o*-aminophenylcarbinols.[11a] Rapoport[12] has shown that this rearrangement is dependent upon the ability of the hydroxyl group at C-9 to stabilize the positive charge caused by the leaving aryl group. By repeating the reaction on the analogous



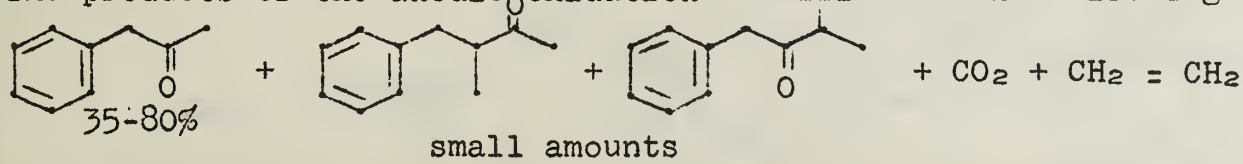
compound X, no rearrangement product was isolated, but instead the products included a 23% yield of the very interesting hydrocarbon fluoradene (XI).



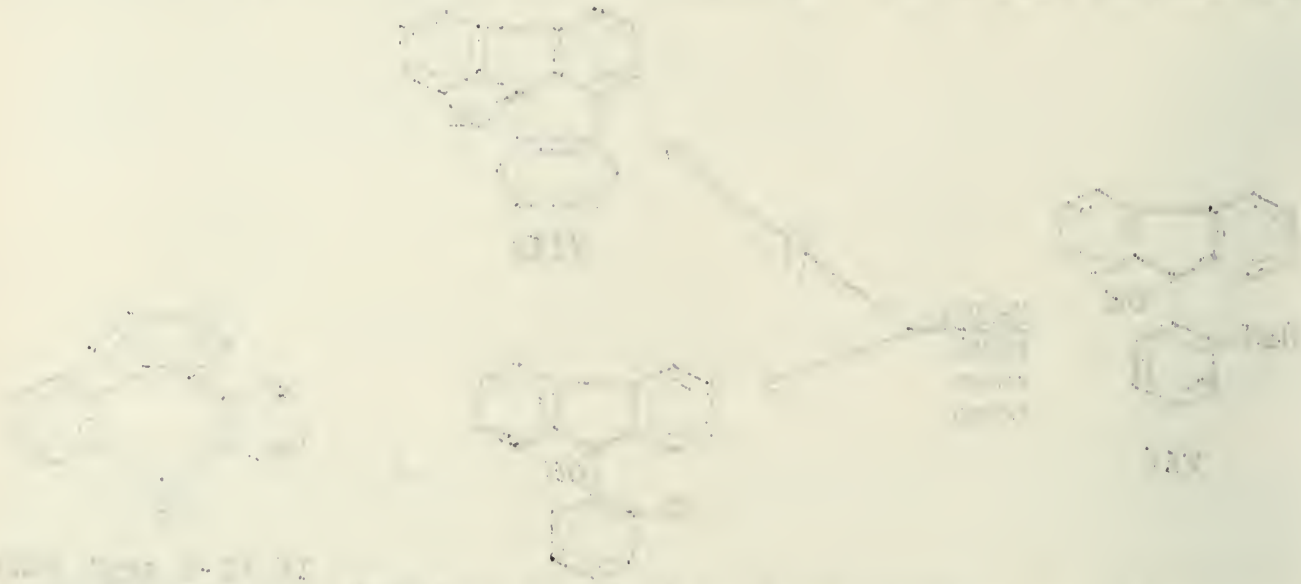
Work done by Bauld gives some evidence that 1-3 shifting is, in general, a very non-favored reaction. While working on the mechanism of electrolytic oxidative cleavage[13] of the C_β-C_γ bond in γ-hydroxy-acids, he proved that the intermediate radical formed by decarboxylation was further oxidized to a carbonium ion (XIV).[14]

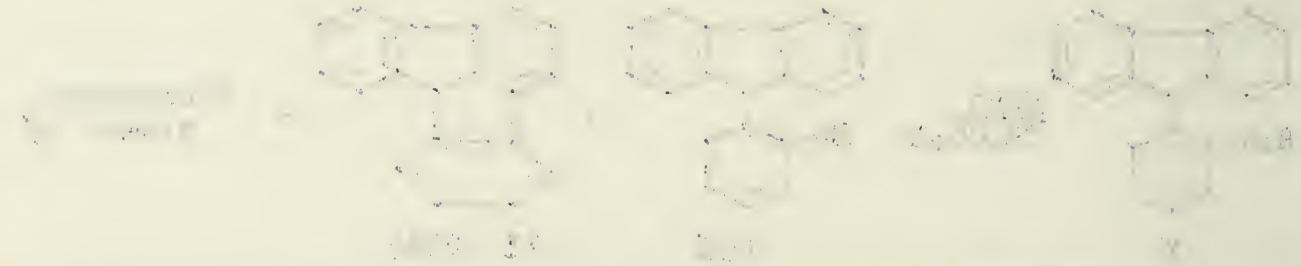


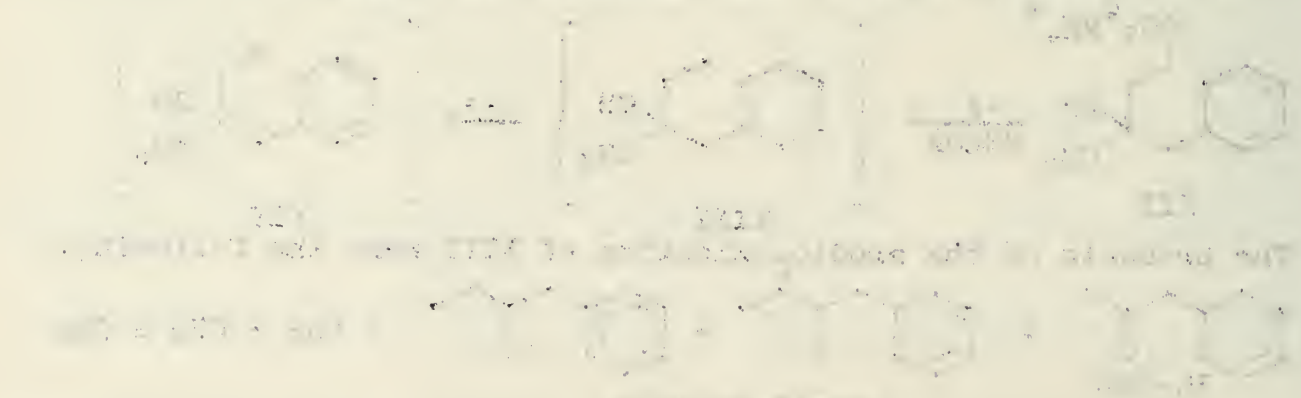
The products of the anodic oxidation of XIII were the following:



The carbonium ion (XIV) formed at the anode would be characterized by its freedom of commitment to solvent, and as such should be a somewhat "hot" carbonium ion. Thus, the complete lack of formation





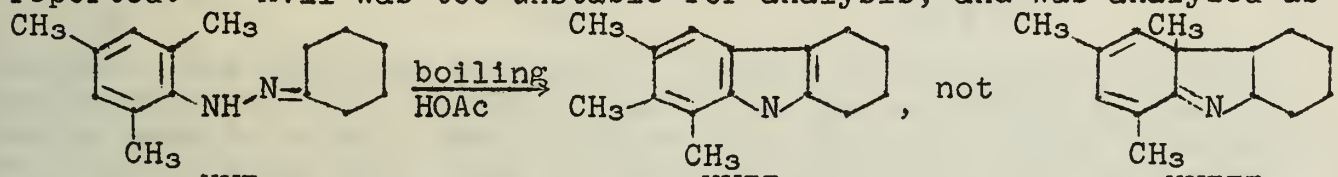


of XV, the product which would result from a benzyl group migration, despite the facts that: (1) the benzyl group would be a very good migrating group, (2) the carbonium ion formed after the benzyl shift would be the very stable conjugate acid of a ketone, and (3) the initial carbonium ion is very free, provides convincing evidence of the intrinsic inexpediency of 1-3 shifting. This leaves the probability that most long range migrations would be the result of relief of extreme steric strain or formation of a transition state with great electronic stabilization.

XV

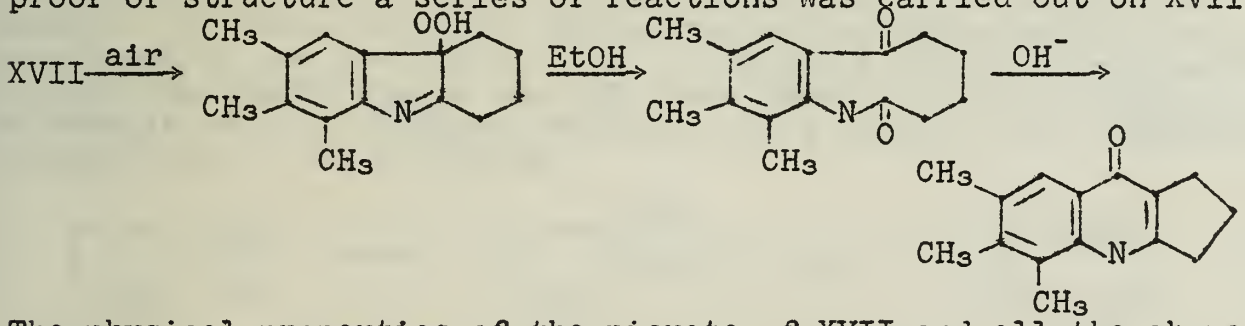
1-4 MIGRATIONS

Carlin[15] recently reported that the product isolated from a Fischer indole synthesis using cyclohexanone mesitylhydrazone (XVI) is 6,7,8-trimethyl-1,2,3,4-tetrahydrocarbazole (XVII) and not the 1,2,3,4-tetrahydro-6,8,12-trimethylisocarbazole (XVIII) as previously reported.[16] XVII was too unstable for analysis, and was analyzed as

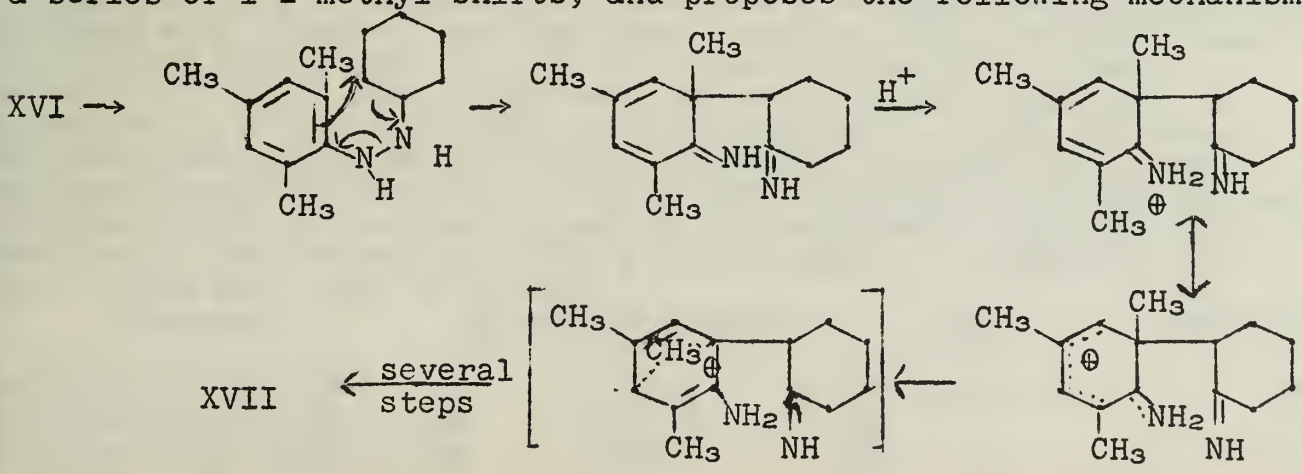


XVI XVII XVIII

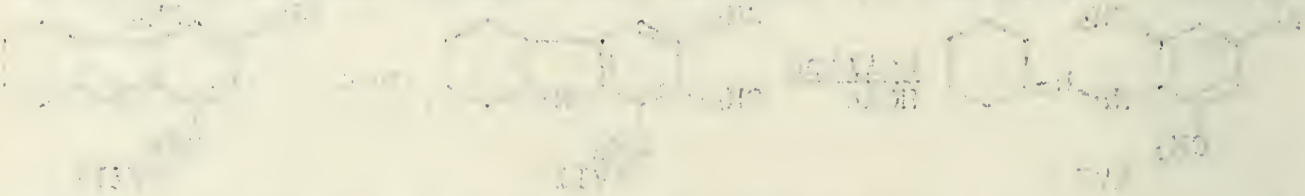
its picrate. XVII when treated with chloranil in xylene gave 1,2,3-trimethylcarbazole, identical to an authentic sample. As further proof of structure a series of reactions was carried out on XVII:

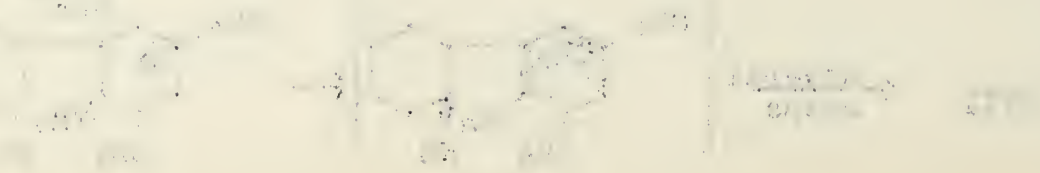


The physical properties of the picrate of XVII and all the above transformation products were identical with the corresponding compounds prepared <u>via</u> the Fischer synthesis from cyclohexanone hemimellitene-hydrazone. Carlin prefers to explain this reaction by a single 1-4 methyl migration through transition state XIX, instead of a series of 1-2 methyl shifts, and proposes the following mechanism:



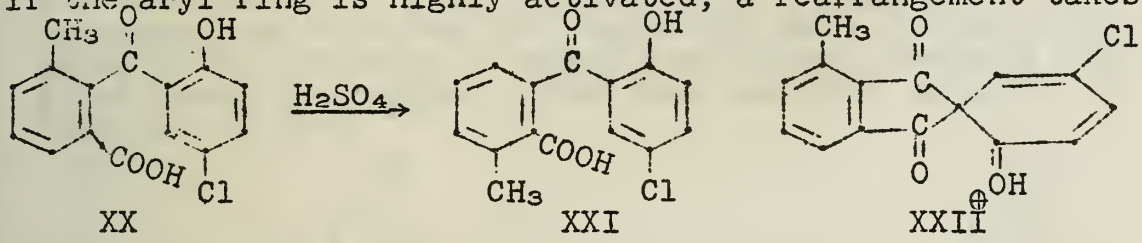
XIX



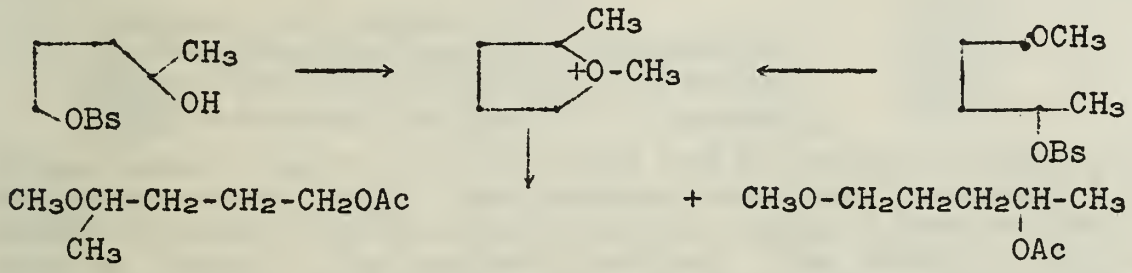


The isolation of this compound is surprising, since the reaction with the 2,6-dimethyl hydrazone gives a 1,4-dimethyl carbazole. The idea of the 1-4 methyl shift must initially be viewed with suspicion, since (1) the reaction has not been shown to be definitely intramolecular, (2) the methyl group would be moving to a position of large steric hindrance, and (3) the migration would be completely without analogy.

An example of a 1-4 aryl migration is that shown by Hayashi.[17] Usually the treatment of an o-benzoyl benzoic acid with H_2SO_4 results in the formation of an anthraquinone. But it has been found that if the aryl ring is highly activated, a rearrangement takes place



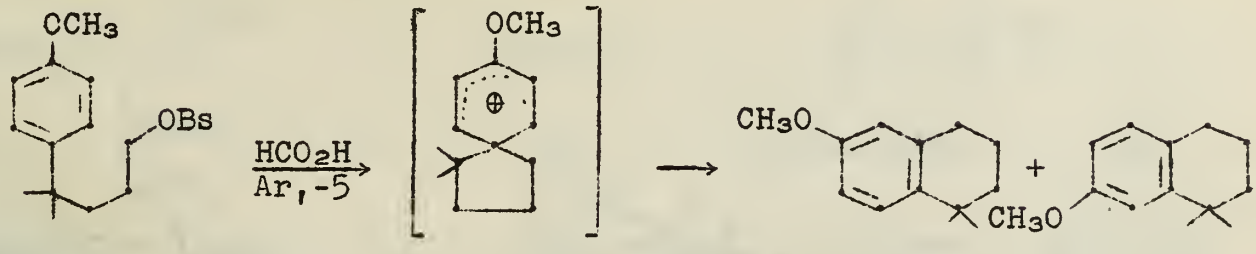
instead. The mechanism proposed[18] for this rearrangement involves the formation of the ion XXII, from which the rearranged product is easily seen to arise. Participation by neighboring groups placed 4 or 5 carbon atoms away from the reacting functional group are often known to form 5 or 6 membered onium rings. For a discussion of participating sulfur and nitrogen, see reference (19). Winstein[20] has studied participation by a neighboring methoxyl function placed 1 to 6 carbons away from a brosylate group during solvolysis reactions. He found that MeO- participation was important for ring size 5 and 6, but not for 3, 4 or 7. The rate of acetolysis at 75° of $CH_3O\text{-}CH_2\text{-}CH_2CH_2\text{-}CH_2OBs$ was 675 times that of n-butyl brosylate. An example of a 1-4 methoxyl migration as a result of an intermediate oxonium ring is the following:



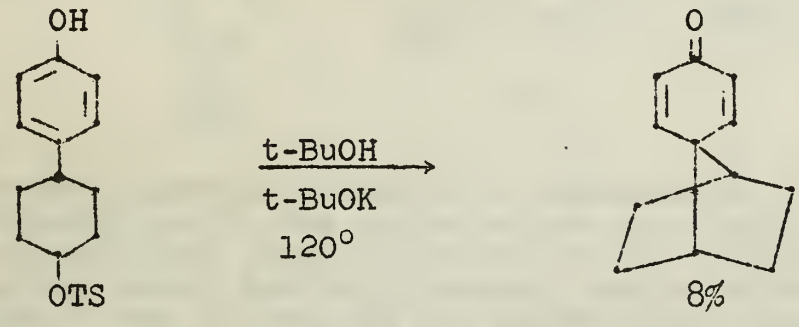
The same mixture of products was obtained from both starting materials. Winstein also observed that the o-MeO group in $(CH_3)_2\text{-}C(o\text{-}CH_3OC_6H_4)\text{-}CH_2\text{-}OTs$ can participate to form 3,3-dimethylcoumaran. Several workers[21,22,23,24] have shown that activated phenyl rings can, by either Ar_1-5 or Ar_2-6 or even Ar_1-6 participation, lead to intermediate spiro-carbonium ions which rearrange to tetralins or benzcycloheptanes. In the symbol Ar_1-5, the subscript, 1, refers to the position in the participating aryl group involved in the creation of the ring in the transition state and the number, 5, refers to the size of the ring that is formed.

Compound	Type Participation	% yield	Reference
$p\text{-}CH_3OC_6H_4(CH_2)_4\text{-}OBs$	Ar_1-5	54% (tetralin)	26
$o,p(CH_3O)_2C_6H_4\text{-}(CH_2)_4\text{-}OBs$	Ar_1-5	91% "	26
$m,m(CH_3O)_2C_6H_4\text{-}(CH_2)_4\text{-}OBs$	Ar_2-6	88% "	26
$o,p(CH_3O)_2C_6H_4\text{-}(CH_2)_5\text{-}OBs$	Ar_1-6	4.2%benzcycloheptane	24

The first example of a 1-4 aryl migration in this field was reported by Winstein and co-workers.



More recently, much work has been done on participation of a C-4 substituent in a cyclohexane ring. Proposals[25] of 1-4 bridged halonium ions have been put forth and the 1,4 epoxide has been isolated by treatment of trans-4-chloro-cyclohexanol with base.[26] A 1-4 phenyl participation has been shown by isolation of a novel tricyclic dienone.[27]

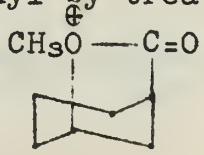


Noyce[28] has completed a tritium labeling study that completely confirmed his earlier postulate,[29] made on the basis of kinetic and product studies, of a symmetrical intermediate in the solvolysis of trans-4-methoxycyclohexyl p-toluensulfonate. By solvolysis of trans-4-methoxycyclohexyl-1-^{3}H tosylate in acetic acid at 75°, the following products were obtained:

4-Methoxycylcohexene-1-^{3}H	(XXIII)	66.4%
cis-4-Methoxycyclohexyl-1-^{3}H acetate	(XXIV)	9.6%
trans-4-Methoxycyclohexyl-1-^{3}H acetate	(XXV)	13.8%
trans-4-Methoxycyclohexyl-4-^{3}H acetate	(XXVI)	10.2%

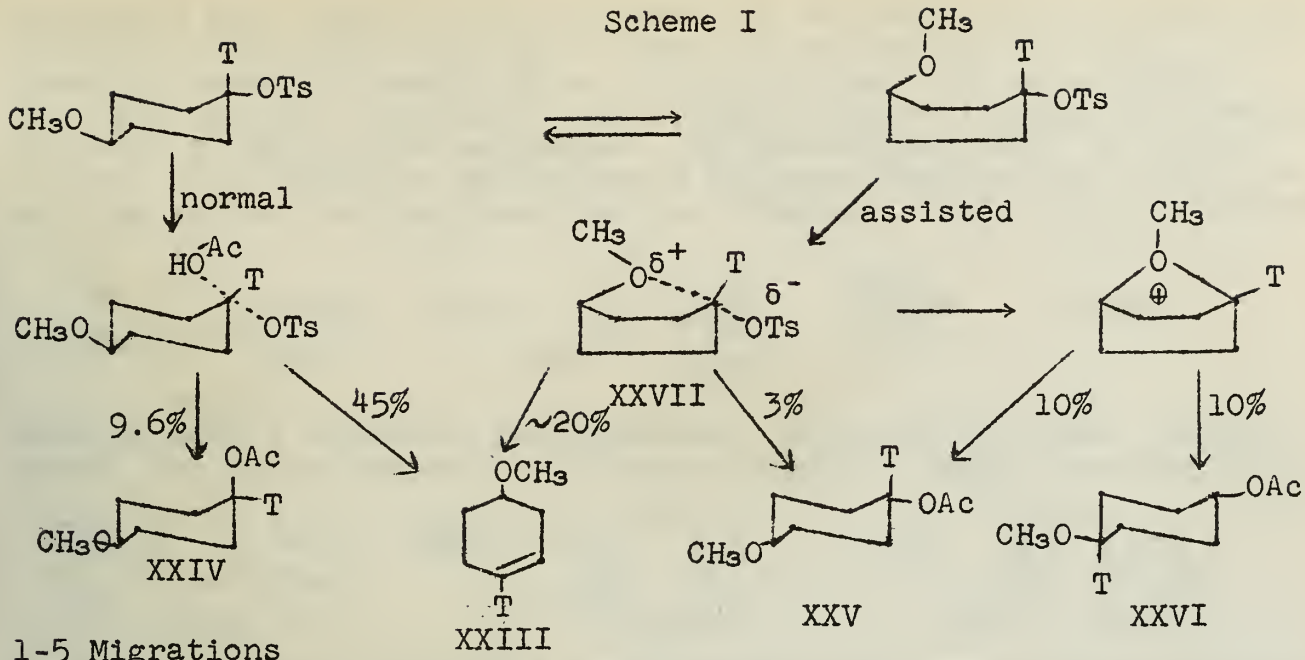
It was shown that no tritium label had migrated to the 2- or 6-positions of the ring. The previous rate data suggested a considerable amount of assisted reaction, meaning some of the olefin must be formed in the assisted pathway. The excess of XXV over XXVI, when both arise from the same symmetrical intermediate, plus the fact that the cyclohexene formed retains all its label, leads one to the conclusion that a further intermediate must be formed before the symmetrical oxonium bridge. Such an intermediate could be the ion pair XXVII, which could give olefin by the merged mechanism of Winstein. If one assumed that the unassisted elimination:substitution ratio of the trans-methoxycyclohexyl tosylate is the same as the cis isomer, then ~20% yield of olefin would arise by the merged mechanism. All these considerations lead to scheme I (T = tritium).

Noyce[30] has also effected a 1-4 migration of methoxyl by treating cis-3-methoxycyclohexanecarboxylic acid with thionyl chloride giving as reaction products methyl-3-cyclohexenyl-carboxylate and methyl trans-3-chlorocyclohexanecarboxylate. This reaction proceeds through the bridged oxonium ion XXVIII.



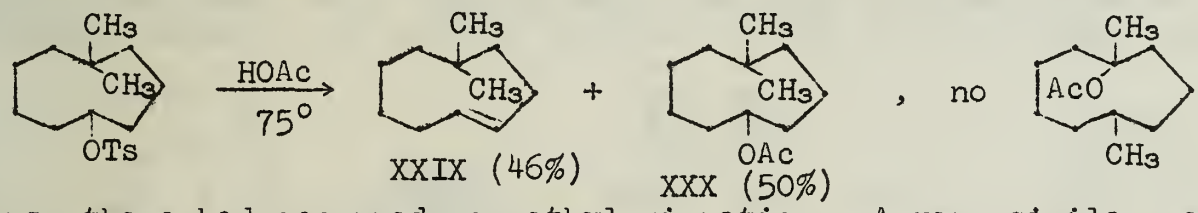
XXVIII

Scheme I

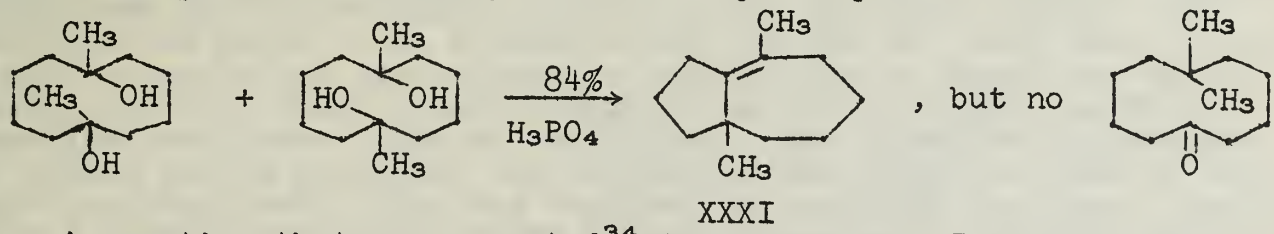


1-5 Migrations

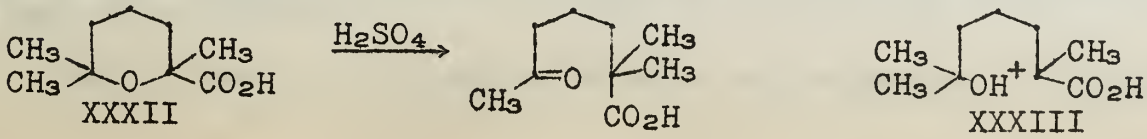
There have been numerous examples of transannular 1-5 or 1-6 migrations of hydride ion in the medium-sized ring field. One might expect these very strained rings to be good model systems for the migration of various alkyl and aryl groups. One such attempt was that of Blomquist,[31] who solvolyzed 5,5-dimethylcyclononyl tosylate in the hope of obtaining a 1-5 migration of methyl. The rate of solvolysis, however, was only one-half that of the unsubstituted cyclononyl tosylate. The method of analysis was quantitative IR, and within the limit of sensitivity (5%), the products were XXIX and XXX only.



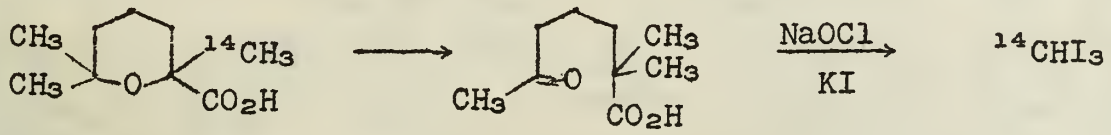
Thus, there had occurred no methyl migration. A very similar reaction was carried out[32] using 5,5-diphenylcyclononyl tosylate, the phenyl group being expected to participate more easily than methyl, but again no participation could be detected. In fact, the rate of acetolysis was only one-tenth that of the unsubstituted compound. The products were again the unrearranged olefin (71%) and acetate (20%). Another attempted methyl migration in a medium-sized ring was reported by Prelog[33] who attempted to carry out a transannular pinacol rearrangement. The product, however, was the bicyclic product XXXI.



A reaction that was reported[34] to involve a 1-5 methyl migration was the acid catalyzed rearrangement of cinenic acid (XXXII). The

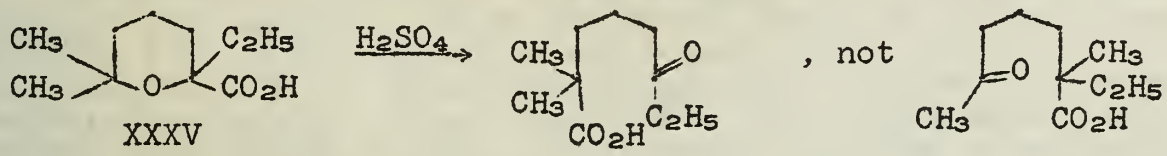


mechanism that remained unquestioned for 40 years was acid catalyzed opening of the ether linkage to form the carbonium ion XXXIII, followed by methyl migration from C-2 to C-6 and loss of a proton to form the ketone. Meinwald[35] has recently reinvestigated this reaction in order to verify its mechanism. By rearranging the ^{14}C labeled cinenic acid XXXIV and performing a haloform degradation on the resulting ketone, labeled iodoform was obtained. This reaction showed



XXXIV

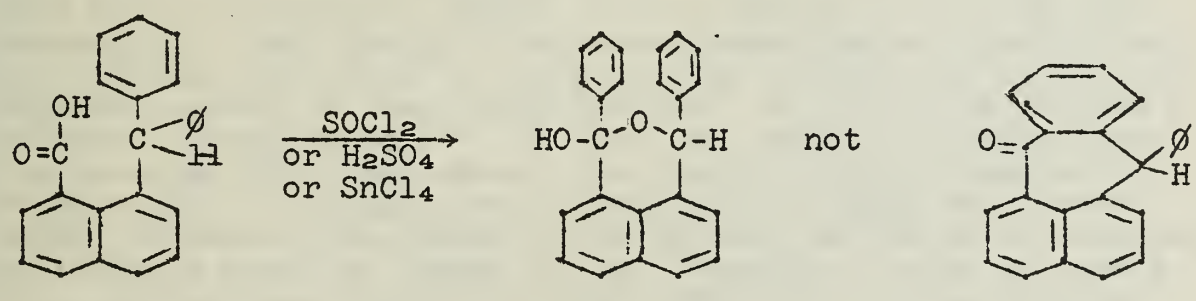
that no methyl migration had occurred. In order to obtain further proof, the rearrangement of XXXV was studied. Again a carboxyl group



XXXV

transfer is indicated, and a new mechanism has been proposed[36] which involves decarbonylation-recarbonylation.

A very good system for studying new intramolecular rearrangements should be the 1,8-disubstituted napthalene system. The substituents in this sytem are held firmly in close proximity and there is very little electronic coupling of 1-8 positions <u>via</u> the napthalene nucleus as shown by electrophilic substitutions. Letsinger used this system to effect a 1-5 hydride transfer[37] and then extended the study to rearrangement of aryl and alkyl groups. By treating the 1-benzhydryl-8-napthoic acid (XXXVI) with a variety of Friedel-Crafts ring closure reagents, the product obtained in 90% yield was the naptho-

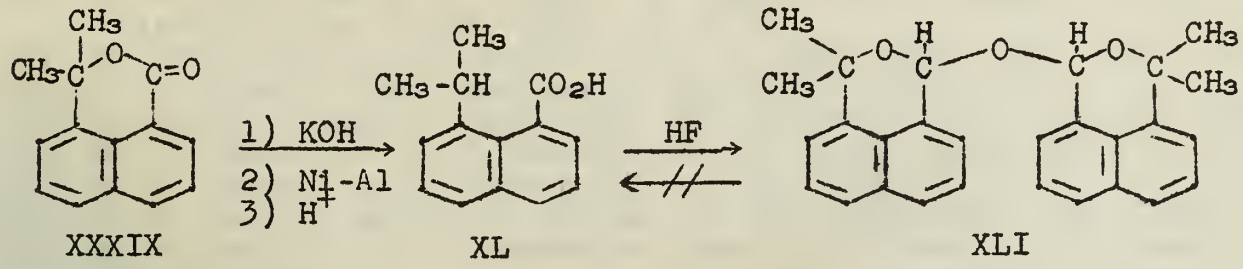


XXXVI XXXVII XXXVIII

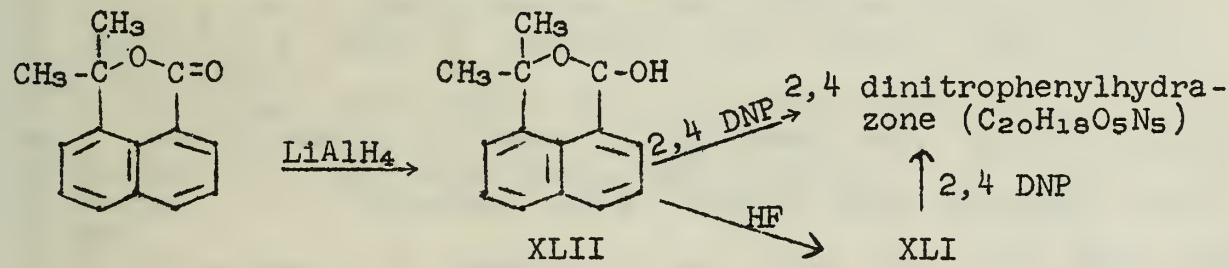
pyran derivative XXXVII, which is the result of a 1-5 aryl migration, and not the seven-membered ring ketone XXXVIII. The structure of XXXVII was proved by oxidation with CrO_3 to the known 1,8-dibenzoyl hapthalene and by reduction with $LiAlH_4$ to the known glycol. The reaction was shown to be intramolecular by the fact that $SnCl_4$ is not a good catalyst for intermolecular Friedel-Crafts reactions, having failed to bring about reaction between benzoyl chloride and triphenylmethane under vigorous conditions. The alternate possibility of attack by the acylonium ion complex at the <u>ortho</u> position of the participating phenyl ring was excluded by repeating the above reaction with a <u>p</u>-MeO substituent on the benzene rings and isolating only the <u>para</u>-substituted phenyl rings in the final product. If attack had been in the <u>ortho</u>-position, one ring in the product would have had a <u>meta</u>-substituent.

Having had such success with aryl rearrangements, Letsinger[38]

used this same type of system for a study of methyl rearrangements. The synthesis of 1-isopropyl-8-naphthoic acid (XL), though quite difficult, was achieved and this material was subjected to treatment with H_2SO_4 or HF. In either case, the only isolated product was the aldal structure XLI, in 67% yield. No methyl migration has occurred.



The proof of structure of XLI rested on the following data: (1) analysis for $C_{28}H_{26}O_3$, (2) no HO- or C=O bands in IR, C-O-C bands at 9.25, 9.37, 9.80 and 9.85 μ and a very strong band at 10.3 μ, (3) reaction with 2,4-dinitrophenylhydrazine to give a DNP with analysis $C_{20}H_{18}O_5N_5$. It was found that the lactone XXXIX could be reduced with $LiAlH_4$ to XLII. XLII formed a 2,4-DNP identical with that of XLI, and when treated with H_2SO_4, formed XLI. Oxidation of



XLI with CrO_3 gave back the lactone in good yield.

From all the reactions listed in this seminar, it is obvious that transfer of alkyl groups to a non-adjacent carbon atom is very difficult indeed, and fails to occur even in systems (1) in which such migration would be sterically favored[38] or (2) which involve a very reactive carbonium ion.[14] In fact, no completely unambiguous methyl migrations have been shown. No studies which attempted to observe migration of groups such as isopropyl or tert-butyl have been found, although such groups might be expected to be more capable of stabilizing a positive charge in the transition state of such a reaction. It has been shown[39] that the tert-butyl group migrates 25% of the time, the phenyl group 75%, in the semipinacolic deamination of 1-tert-butyl-2-amino-1-phenylethanol, while methyl, n-propyl, and isopropyl groups in the corresponding compounds, did not migrate at all.

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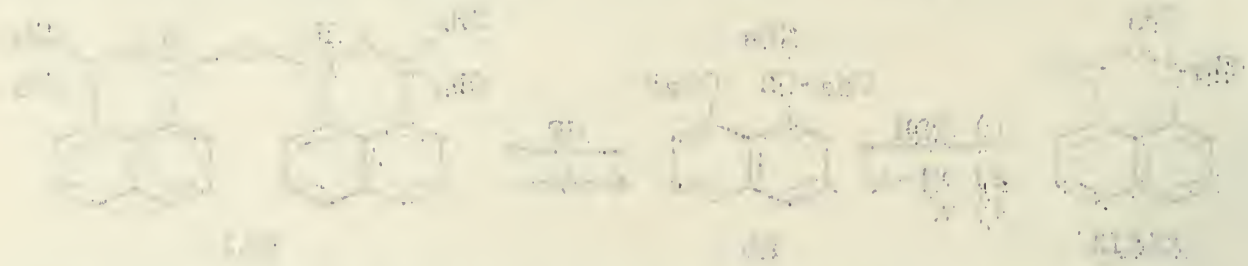

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MECHANISM OF ALLYLIC AND BENZYLIC NBS BROMINATIONS

Reported by J. C. Summers April 25, 1960

INTRODUCTION

A superior procedure employing N-bromosuccinimide (NBS) has been developed by Ziegler (1) for effecting allylic and benzylic brominations. Several excellent review articles (2-4) emphasizing these and other synthetic applications of N-bromosuccinimide have been published, but none of these deal extensively with the more recent advances concerning the mechanism of the reaction. The scope of this seminar will be limited primiarly to the mechanistic aspects of allylic and benzylic NBS brominations in relatively non-polar solvents.

ALLYLIC BROMINATION

In 1944, Bloomfield (5) suggested that allylic bromination of alkenes by NBS occurred by a radical chain mechanism. Since then Dauben and McCoy (6) have made a detailed study on the elucidation of the mechanism of a typical allylic bromination reaction carried out in a relatively non-polar solvent, the reaction of cyclohexene with NBS in carbon tetrachloride. Since the reaction time for a radical chain reaction would be expected to become longer as peroxides, light, and oxygen are excluded and since these environmental factors are present during a normal NBS reaction, the effect of these variables on the course and the time of complete reaction was investigated, and the results substantiated a radical chain process.

In the following table NBS brominations were carried out in the ratio of 0.1 mole NBS/0.15 mole cyclohexene/75 ml. carbon tetrachloride at the reflux temperature of carbon tetrachloride. The lower time limit in Table I indicates the last time at which a positive test for positive bromine was obtained with moistened starch-iodide paper and the upper limit the time for the first negative test. Tests were made on small samples removed from the reaction mixture. Runs made in the dark were made in a flask covered with black lacquer or a black cloth and the apparatus was set up in a dark hood. Analysis was accomplished by means of fractional distillation and by double bond determination, and results were corrected by comparison with a control run.

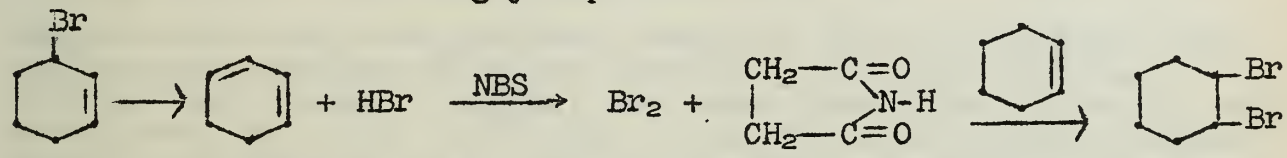
Table I

Effect of Environmental Factors on Reaction of NBS with Cyclohexene in Carbon Tetrachloride

Run	Oxygen[a]	Light	Time Min.	%Yield[b] 3-Bromo-cyclohexene	3,6-Dibromo-cyclohexene	1,2-Dibromo-cyclohexane
1	+	+	70-75	62	10	1
2	+	-	75-80	60	8[c]	-
3	-	+	105-130	55	13	4
4[d]	-	-	>660	40	8	15
5[e]	-	-	305-312	60	2	8
6[f]	-	-	300-360	22	11	37

a) In runs with an air atmosphere (+) the cyclohexene was 0.022M in peroxides; in runs with a nitrogen atmosphere (-) the cyclohexene was distilled from sodium in a nitrogen atmosphere directly into the reaction flask. b) Yields based on major distillation fractions without correction for intermediate fraction. c) Yield of 3,6-dibromo-cyclohexene by direct crystallization and isolation; yield of 1,2-dibromocyclohexane not determined. d) About 6% NBS remained at end of run; all other runs went to completion. e) Conducted in same manner as run 4 except that after 280 min. 2 ml. of stale cyclohexene (0.022 M in peroxide) was added. f) conducted in the same manner as run 4 except that 1 mole per cent. pyridine added initially.

Runs 1 and 2 indicated that ordinary diffuse light does not significantly contribute to the initiation of the NBS-cyclohexene reaction when 0.022 M peroxides are also present since similar reaction times were obtained when 2 was run in the dark and when 1 was run in diffuse light while both were subject to air and preformed peroxides. Runs 3 and 4 showed that normal diffuse light can initiate the reaction in the absence of peroxides and oxygen, but at a slower rate than 0.022 M peroxide. When access to light was additionally removed, the reaction still proceeded possibly due to thermal homolysis of bromine or NBS to yield bromine radicals or to slight traces of peroxides not removed from the system. As the reaction time increased due to the exclusion of environmental initiators, the yield of monoallylically brominated 3-bromocyclohexene decreased, that of diallylically brominated 3,6-dibromocyclohexene remained constant and that of 1,2-dibromocyclohexane, probably formed by bromine addition, increased. Thus the fundamental course of the reaction was not altered, but a side reaction became increasingly important.



3-Bromocyclohexene is known to undergo slow dehydrobromination under reaction conditions, and therefore the above reaction seems probable.

An interesting effect is produced in the NBS-cyclohexene reaction by an excess of oxygen. Whereas traces of oxygen help to initiate chains, an excess of oxygen retards bromination. Traces of oxygen probably react with cyclohexene to form cyclohexenyl hydroperoxide which aids the reaction by acting as an initiator. Retardation of the reaction can be explained by postulating that excess oxygen reacts with the cyclohexenyl radical to form -C=C-C-OO. faster than with NBS and that -C=C-C-OO· subsequently reacts with NBS slowly or not at all.

Further evidence for a radical chain mechanism was supplied by a study of the effect of modifiers on the NBS-cyclohexene reaction. Bromanil, picric acid > s-trinitrobenzene > iodine > m-dinitrobenzene > hydroquinone were found to be retarders and their effectiveness was found to be consonant with the inhibitor-retarder order for induced decomposition of benzoyl peroxide and for polymerization of compounds such as vinyl acetate and styrene while being variant from inhibitor-retarder order for autoxidations. (7,8,9,10) Since the effectiveness of these inhibitor-retarders in polymerizations decreases as the electron-accepting properties of the polymer radicals increase the relatively low retarding action of these

modifiers indicates that the retarders react with the electron accepting chain carriers, succinimidyl radicals, rather than with the electron donating cyclohexenyl radicals in allylic bromination reactions. (11,12) This reasoning is also in agreement with evidence that benzylic bromination of substituted toluenes by NBS is facilitated by electron-donating substituents and retarded by electron-accepting ones. Accelerating modifiers studied for the NBS-cyclohexene reaction may be divided into the following three groups: normal radical initiators, bromine producing groups, and amine groups. Azo-bis-isobutyronitrile, benzoyl peroxide, and cyclohexenyl hydroperoxide are among the modifers belonging to the first group. Bromine, hydrogen bromide, ethanol, water and thiophenol compose the second, and the third consists of triethylamine, pyridine and piperidine. It is noteworthy that with cyclohexene containing 0.022 M peroxide, triethylamine is the best accelerator of the modifiers mentioned. This is ascribed to amine induced homolytic decomposition of NBS and hydroperoxide. Tertiary amines might react with NBS by one or more of the following oxidation-reduction-displacement mechanisms (1), with a subsequent elimination (2) to yield vinylamines. (6,13,14)

$$(1)\quad (CH_3CH_2)_3N: + Br\text{-}N(COCH_2)_2 \rightarrow (CH_3CH_2)_3\overset{\oplus}{N}\cdot,\ Br^{\ominus} + \cdot N(COCH_2)_2$$

$$\downarrow$$

$$(CH_3CH_2)_3\overset{\oplus}{N}\cdot Br,\ :\overset{\ominus}{N}(COCH_2)_2 \rightarrow (CH_3CH_2)_3\overset{\oplus}{N}\cdot + Br\cdot + :\overset{\ominus}{N}(COCH_2)_2$$

$$(2)\quad (CH_3CH_2)_3\overset{\oplus}{N}\cdot + \cdot N(COCH_2)_2 \text{ or } Br\cdot$$

$$\longrightarrow (CH_3CH_2)_2\overset{\oplus}{N} = CHCH_3 + H\text{-}N(COCH_2)_2 \text{ or } HBr$$

$$\hookrightarrow (CH_3CH_2)_2N\text{-}CH = CH_2 + H^{\oplus}$$

Enamines have not been isolated from this type of reaction, but the expected enamine hydrolysis products, the corresponding aldehyde and secondary amine, have been identified. Also by using development of a blue color from 2,5-dichloro-3,6-dimethoxybenzoquinone and enamines as a test for enamine formation, it has been shown that NBS dehydrogenates triethylamine. 2,5-Dichloro-3-(2'-diethylaminovinyl)-6-methoxy-benzoquinone has been isolated from this type of reaction and is the source of the blue color. Braude and Waight (15) also showed that NBS reacts with triethylamine in the absence of cyclohexene in the ratio 1:2, possibly by the following equation:

$$2(CH_3CH_2)_3N + NBS \rightarrow (CH_3CH_2)_2NCH{=}CH_2 + (CH_3CH_2)_3\overset{\oplus}{N}H, Br^{\ominus} + HN(COCH_2)_2$$

which corresponds to the proposed scheme if tertiary amine reacts with the hydrogen bromide produced. Triethylamine hydrobromide has been isolated in 48% yield. The production of radicals as in the proposed mechanisms might be expected to accelerate allylic bromination by formation of succinimidyl radicals or radicals which can abstract an allylic hydrogen. The amine-induced homolytic decomposition of hydroperoxide leading to acceleration of allylic bromoination probably occurs as follows:

$$(3)\quad RO\text{-}OH + (CH_3CH_2)_3N: \longrightarrow (CH_3CH_2)_3\overset{\oplus}{N}\cdot + RO\cdot + OH^{\ominus}$$

In view of this evidence supporting a radical chain mechanism a mechanism similar to or identical with the following scheme is probable.

<u>Initiation</u>

(1a) $\text{In-In} \rightarrow 2\,\text{In}^{\bullet}$

(1b) $\text{In}^{\bullet} + (CH_2CO)_2N\text{-Br} \longrightarrow \text{In-Br} + (CH_2CO)_2N^{\bullet}$

(1c) $\text{In}^{\bullet} + \text{-C=C-C(H)-} \longrightarrow \text{In-H} + \text{-C=C-C}^{\bullet}\text{-}$

<u>Propagation</u>

(2a) $(CH_2CO)_2N^{\bullet} + \text{-C=C-C-} \rightarrow (CH_2CO)_2N\text{-H} + \text{-C=C-C}^{\bullet}\text{-}$

(2b) $\text{-C=C-C}^{\bullet}\text{-} + (CH_2CO)_2N\text{-Br} \rightarrow \text{-C=C-C(Br)-} + (CH_2CO)_2N^{\bullet}$

<u>Termination</u>

(3a) $(CH_2CO)_2N^{\bullet} + \text{-C=C-C}^{\bullet}\text{-} \rightarrow \text{-C=C-C(=N)-}(COCH_2)_2$

(3b) $\text{-C=C-C}^{\bullet}\text{-} + \text{-C}^{\bullet}\text{-C=C-} \longrightarrow \text{-C=C-C-C-C=C-}$

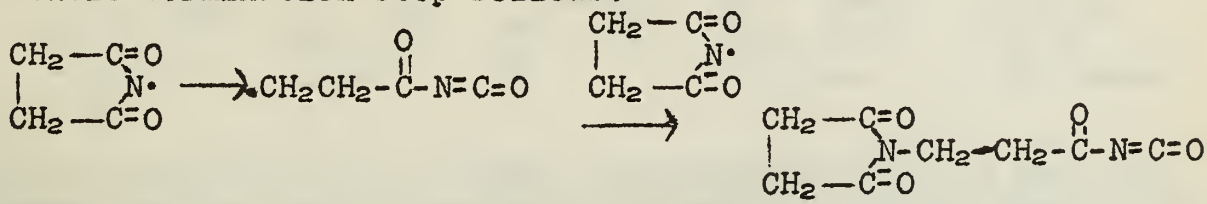
(3c) $(CH_2CO)_2N^{\bullet} + {}^{\bullet}N(COCH_2)_2 \longrightarrow$ inactive products

The above scheme is based on the kinetics of the NBS-cyclohexene reaction in benzene carried out in degassed systems at 20-40° and using azo-bis-isobutyronitrile as the initiator. (16) Initiation was found to occur by dissocation of the initiator (1a) to produce radicals that react with NBS (1b) or with alkene (1c). Initiation may occur by the following methods: (1) by thermal decomposition of added radical sources and allylic hydroperoxides present as impurities; (2) by thermal or photochemical homolysis of bromine present as an impurity; (3) by photolysis of NBS in diffuse light; (4) by oxidation-reduction-decomposition of hydroperoxides with NBS or added tertiary amines, or of NBS with tertiary amines; and (5) by thermal homolysis of NBS at elevated temperatures.

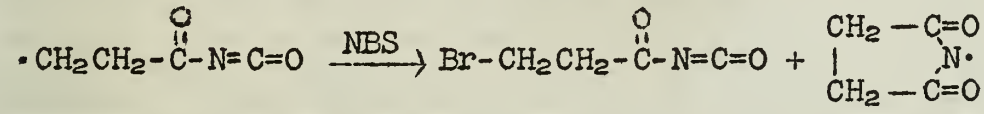
Steps (1b) and (1c) are about equally probable since estimated heats of reaction of various initiator fragments with NBS or with cyclohexene indicate that both types of reaction will be about equally exothermic. Credible propagation steps involve the abstraction of an allylic hydrogen by the succinimidyl radical and the reaction of an allylic radical with NBS as shown in steps (2a) and (2b) with (2a) being the slower step. The presumed chain carrier, the succinimidyl radical, should have electron-acceptor properties while the allylic radical should have electron-donator properties. Some substantiation to (2a) being the slower step is provided by the finding that electron-accepting chain terminators are only moderately effective retarders of the bromination. Further support is supplied by calculation of the heats of reaction while assuming that the more exothermic the reaction, the lower the energy of activation. Using $D((CH_2CO)_2N\text{-H})=74$, D(cyclohexenyl-H)=75, D(cyclohexenyl-Br)=47.5 and $D((CH_2CO)_2N\text{-Br})=44$ kcal. mole^{-1}, the predicted heats of reaction for steps (2a) and (2b) are + 1 and -3.5 kcal. mole^{-1}. (16)

The NBS-cyclohexene kinetic studies previously mentioned indicate that reaction (3c), the coupling of two succinimidyl

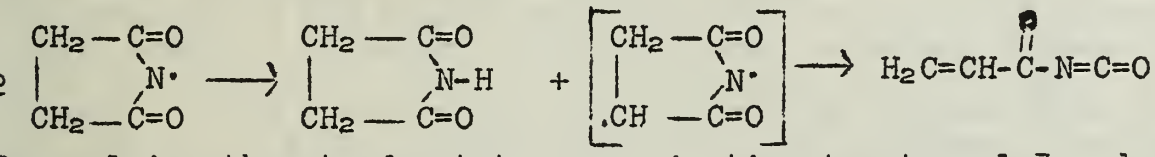
radicals rather than (3a), a combination of an allyl and a succinimidyl radical, or (3b), a combination of two allyl radicals, is the most likely termination step. A combination of two succinimidyl radicals to give bis-N-succinimidyl would seem to be a probable termination step. However, attempts to prepare bis-N-succinimidyl by other means have been unsuccessful. Another possible termination step follows:



Martin and Bartlett (17) have also suggested the following reaction of the intermediate radical.



The isolation of B-bromopropionyl isocyanate from many NBS reactions lends credence to the rearrangement of the succinimidyl radical. (18,19) However, an alternative explanation for the presence of B-bromopropionyl isocyanate involves the abstraction of a hydrogen from one succinimidyl radical by another to give succinimide and a diradical which rearranges to form acryl isocyanate. Subsequent reaction with hydrogen bromide would convert this to B-bromopropionyl isocyanate.

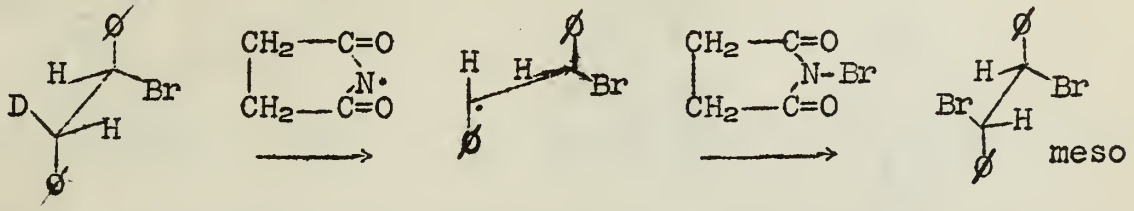


By applying the steady state approximation to steps 1-3 and assuming that the concentration of the initiator is relatively small (0.022 M) and the chain length is large (kinetically determined to be 2800), the derived rate law which corresponds with steps (1a), (1b) or (1c), (2a) and (2b) and (3c) becomes identical with $-d(NBS)/dt=k(NBS)^{0}(RH)(\text{Azo-bis-isobutyronitrile})^{1/2}$, the experimentally determined rate law. Still assuming that the concentration of the initiator is small and the chain length large, the derived rate laws with (3a) and (3b) the terminating steps are respectively $-d(NBS)/dt=k(NBS)^{1/2}(RH)^{1/2}(\text{Azo-bis-isobutyronitrile})^{1/2}$ and $-d(NBS)/dt=k(NBS)(RH)^{0}(\text{Azo-bis-isobutyronitrile})^{1/2}$.

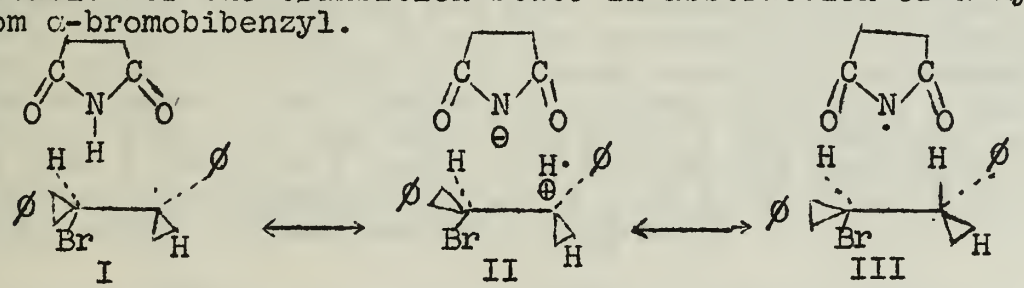
BENZYLIC BROMINATION

Benzylic bromination like allylic bromination is generally thought to proceed by a radical mechanism in non-polar solvents. Relative to the allylic case, a considerable amount of productive work has been done to elucidate the detailed mechanism of NBS benzylic bromination reactions, and in particular the stereochemical course of the reaction and the degree of freedom and the configuration of the intermediate radical. In studying the stereospecificity of the NBS bromination of bibenzyl and acenaphthene, where bromination of a carbon atom adjacent to an aromatic ring takes place, it has been found by Greene, Remers and Wilson (20) that after bromination of one methylene group, both the attack

of the succinimidyl radical on the hydrocarbon substrate and the subsequent attack of the resulting carbon radical on NBS are stereospecific. The erythro form of 1-bromo-2-deuterio-1,2-diphenyl ethane was brominated by NBS.



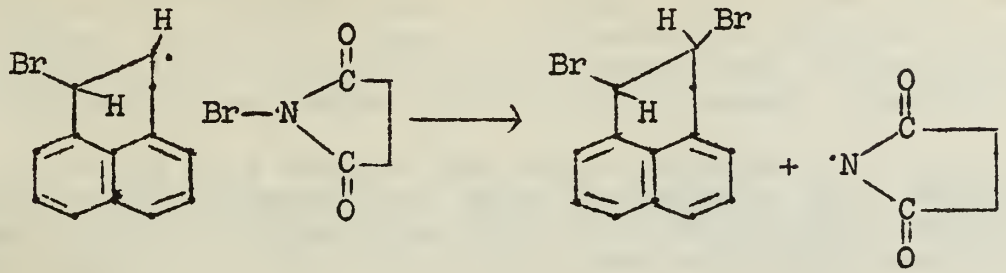
This bromination gave somewhat unexpected results in that the deuterium atom was predominantly extracted in preference to the hydrogen atom. Assuming that the preferred conformation of the substrate had the phenyl groups removed as far apart as possible, the deuterium extraction may be explained by steric and polar effects. In order for deuterium extraction to occur, the succinimidyl radical approaches between the phenyl and hydrogen groups whereas if the hydrogen atom is extracted, the radical must approach between the bulkier phenyl and bromine groups. A polar effect might be expected to be important since in an analogous case competitive brominations of m and p substituted toluenes with NBS gave a ρ of -1.55 when Hammett plots were made. (21) This is indicative of a considerable degree of positive character at carbon in the transition state. (22,23,24,25) A fair correlation was obtained with σ constants in the substituted toluene case but a much better straight line resulted when σ^+ values were plotted. (21,26,27) This might be expected if charge separation is involved in the transition state for the attack of N-succinimidyl radicals on benzyl hydrogen atoms. Although Hammett plots have not been made for the α-bromobibenzyl case, II might be expected to be a significant contributor to the resonance hybrid. In view of this the following contributing resonance forms are probable for the transition state in abstraction of a hydrogen from α-bromobibenzyl.



The subsequent radical extraction of a bromine atom from NBS is also a stereospecific reaction since the resulting dibromide is approximately 92% in the meso form. This again is explained by reasoning that the NBS molecule approaches the radical on its less sterically hindered side. The possibility that the intermediate radical retains an asymmetric configuration about its trivalent carbon atom exists, but this is generally unsupported. Also the possibility of initial formation of the dl-dibromide followed by conversion to the thermodynamically more stable meso isomer was considered and eliminated since the amount of meso isomer isolated was the same in both the presence and absence of added dl-dibromide when bibenzyl was allowed to react with NBS.

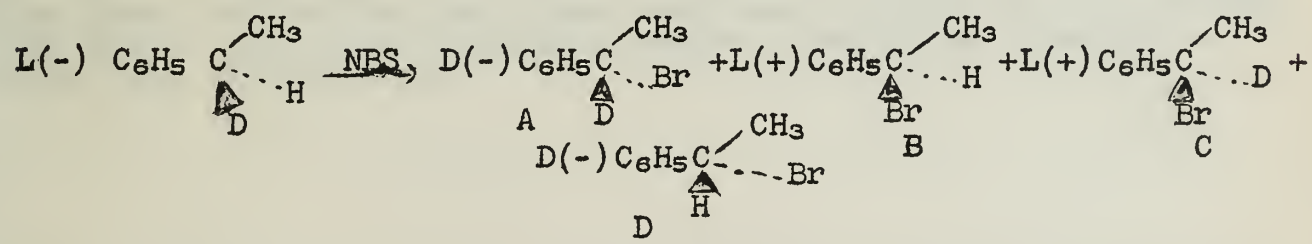
After initial NBS bromination in the fused acenaphthene molecule, subsequent reaction proceeds by hydrogen abstraction

and reaction of the resultant radical with NBS on the side opposite to the carbon-bromine bond already present.



The resultant 1,2-dibromoacenaphthene has been shown to have the trans structure by partial resolution, and thus the reaction occurred in a manner similar to that of the bibenzyl case.

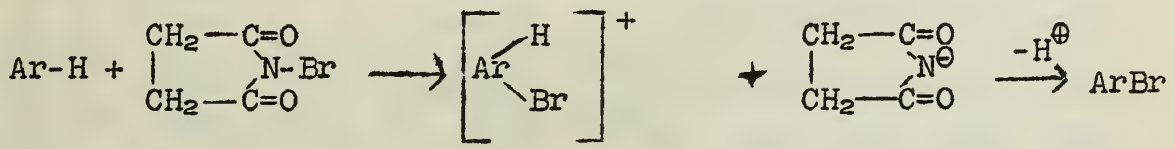
In order to more clearly elucidate the degree of freedom and the stereoconfiguration of the intermediate radical formed in bromination with NBS, the stereochemical course of the reaction between optically active (-)-α-deuterioethylbenzene and NBS to yield phenylmethylcarbinyl bromide with nearly complete racemization has been studied. (28) The possibility that the racemic product was formed during work-up conditions has been excluded since when optically active phenylmethylcarbinyl bromide was heated under reflux in carbon tetrachloride for twenty-five minutes, less than 2% racemization occurred. Additional evidence supporting only slight racemization was obtained when the bromination of ethylbenzene by NBS in refluxing carbon tetrachloride with benzoyl peroxide initiator was conducted in the presence of optically-active phenylmethylcarbinyl bromide. An 82% yield of phenylmethylcarbinyl bromide with $(\alpha)_D^{24}$ -0.020 ± 0.010° was obtained from L-(-)-α-deuterioethylbenzene with $(\alpha)_D^{23}$ -0.293° (41.6% optical purity) by NBS reaction. The isotope effect for the reaction was found to be 2.67 ± .04. Assuming that phenylmethylcarbinyl bromide and its alpha deuterio analog have the same specific rotations $(\alpha)_D^{20}$ 96.4°, the rotations of enantiomorphic bromide products expected by different substitution mechanisms may be estimated: (a) complete retention would give A and B in a ratio of 2.67:1.00 and have $(\alpha)_D$ -18.3°; (b) complete inversion would give C and D in a ratio of 2.67:1.00 and have $(\alpha)_D$ + 18.3°; and (c) complete racemization would give A, B, C and D in a ratio of 2.67 (A+C):1.00(B+D) and have $(\alpha)_D$ 0.0°.



Since the observed rotation of the phenylmethylcarbinyl bromide was $(\alpha)_D^{24}$=-0.020 ±.010°, no more than 0.11% (0.02/18.3) optical reactivity remained and the reaction thus occurred with nearly complete racemization. Since the product is optically stable, racemization must have occurred at an intermediate step in the substitution reaction, probably after an alpha hydrogen or deuterium atom was removed from the optically-active alpha deuterioethylbenzene by the succinimidyl radical with subsequent formation of the alpha

phenylethyl radical. Thus the radical must either be formed in a planar configuration or in a rapidly inverting trigonal pyramid configuration with inversion occurring faster than the reaction of the radical with NBS. Based on observed and expected rotational differences it is estimated that racemization of the radical occurred at least 600 times faster than its displacement reaction on NBS.

Although this seminar has been concerned with the free radical aspects of NBS brominations which predominate in a relatively non-polar solvent, it should be noted that under polar conditions an ionic reaction of the N-Br bond is competitively operative.



This ionic reaction may be illustrated by the use of propylene carbonate, a highly polar solvent, as the reaction medium for the NBS bromination of toluene. (29) NBS reactions were run with 0.1 mole NBS, 0.4 mole toluene, and 200 cc. propylene carbonate with 0.6 g. benzoyl peroxide and 0.1 g. chloranil being added as indicated. The reactions were warmed on a water-bath, and fractional distillation followed by vapor fractometer analysis was used to determine yields.

Table II

Bromination of Toluene in Propylene Carbonate

		% Yield		
Reagent	Added Substance	Benzylbromide	p-Bromotoluene	o-Bromotoluene
NBS	None	29.9	24.6	12.3
NBS	Benzoyl Peroxide	72.5	3.3	1.9
NBS	Chloranil	14.0	36.5	18.5
Br_2	None	0.0	40.7	22.7

The possibility that nuclear bromination occurred by bromine reaction, with production of bromine from NBS, can be minimized by examining the analogous bromination of fluorene. The nuclear substituted 2-bromofluorene may be obtained both by direct bromination and by NBS bromination, but the latter occurs at least twenty-five times faster than the former and thus obviates the possibility that NBS is just an intermediate source of molecular bromine in these ionic brominations.

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SECONDARY HYDROGEN ISOTOPE EFFECTS

Reported by R. Searle April 28, 1960

A secondary hydrogen isotope effect is an alteration in the rate of a reaction caused by substitution of deuterium or tritium for a hydrogen atom which is not detached in the rate-determining step of the reaction (1). Hydrogen isotope effects have been observed also in equilibrations in which an isotopically substituted C-H bond is not broken (Table II).

Possible origins for the secondary deuterium isotope effect on reaction rates which should be considered are the following: (a) Deuterium may differ sufficiently from protium in inductive ability to alter the vibrations, including the stretching vibration, of the bond being broken or formed in the transition state. (b) Activation may weaken or stiffen a number of bonds in the molecule. If isotopically substituted C-H bonds are altered upon activation, an isotope effect will be observed. C-H bonds can be weakened by hyperconjugation with a positively charged carbon or by inductive withdrawal of electrons from the C-H bond by a positively charged reaction center. C-H bonds close to the reaction center can be stiffened by steric interference with entering or leaving groups. It would not be surprising if (a) and (b) operate simultaneously.

The small magnitude of the effect makes a purely qualitative discussion of its origin unsatisfactory. It is necessary to adopt a semi-quantitative approach based on the absolute rate theory. The vibrational origin proposed in statement (b) is subject to quantitative treatment if simplifying approximations are made.

Consider a reaction: $A + B + C + \ldots \rightleftharpoons \ddagger \longrightarrow$ products.* Let the reactant, A, be isotopically substituted; let the subscript, D, signify the reactant bearing heavy hydrogen, and the subscript, H, signify the reactant bearing common hydrogen. ‡ is the symbol for the transition state. The rate constants for the reaction of A_H and its deuterated analogue, A_D, are given by the absolute rate theory:

$$k_H = K_H \frac{kT}{h} \frac{\frac{Q_H^{\ddagger}}{No}}{\frac{Q_{AH}}{No} \cdot \frac{Q_B}{No} \cdot \frac{Q_C}{No} \ldots} \quad ; \quad k_D = K_D \frac{kT}{h} \frac{\frac{Q_D^{\ddagger}}{No}}{\frac{Q_{AD}}{No} \cdot \frac{Q_B}{No} \cdot \frac{Q_C}{No} \ldots}$$

The isotope effect, k_H/k_D, is $K_H Q_H^{\ddagger} Q_D / K_D Q_D^{\ddagger} Q_H$. K is the transmission coefficient, and Q is a molar partition function. Q can be factored into a product of partition functions, each of which is related to a specific type of energy. $Q = Q_{translation} Q_{vibration} Q_{rotation} Q_{electronic} Q_{internal\ rotation} Q_{zero\text{-}point\ vibration}$. $Q_{electronic} = 1$ because the reactions under consideration do not involve excited electronic states and because the degeneracy of the ground state will be the same as that of the transition state. $Q_{translation}$, $Q_{rotation}$, and $Q_{internal\ rotation}$ are functions of the mass of the entire molecule — isotopic substitution will probably

* The calculation is adapted (2) from references 3 and 4.

change them insignificantly. It is assumed that the transmission coefficients are the same for the reaction of isotopic analogues. Under the harmonic oscillator approximation for the vibrational energies, the isotope effect, k_H/k_D, is

$$\prod_i \frac{(1-e^{\frac{-hV_{iD}^{\ddagger}}{kT}})(1-e^{\frac{-hV_{iH}}{kT}})}{(1-e^{\frac{-hV_{iH}^{\ddagger}}{kT}})(1-e^{\frac{-hV_{iD}}{kT}})} \; e^{\frac{h}{2kT}(V_{iD}^{\ddagger} + V_{iH} - V_{iH}^{\ddagger} - V_{iD})} \qquad \text{(eq. 1)}$$

The first factor is nearly one because excited vibrational states are largely frozen out at normal temperatures. The second factor is split into two parts yielding equation 2, in which i runs over all the C-H vibrations in A_H which become C-D vibrations in A_D; j runs over all the other vibrations of A. Equation 2 can be

$$\frac{k_H}{k_D} = \prod_i e^{\frac{h}{2kT}(V_{iD}^{\pm} + V_{iH} - V_{iH}^{\ddagger} - V_{iD})} \prod_j e^{\frac{h}{2kT}(V_{jD}^{\ddagger} + V_{jH} - V_{jH}^{\ddagger} - V_{jD})} \qquad \text{(eq. 2)}$$

simplified still further by use of the relationship $V_D = V_H/1.35$ (3):

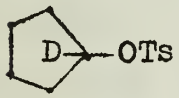
$$\frac{k_H}{k_D} = \exp\left\{\frac{0.187}{Tc}\sum_i (V_{iH} - V_{iH}^{\ddagger}) + \frac{h}{2kT}\sum_j (V_{jD}^{\ddagger} + V_{jH} - V_{jH}^{\ddagger} - V_{jD})\right\} \qquad \text{(eq. 3)}$$

The theoretical treatment of isotope effects has been more rigorously reported in a University of Illinois Organic Seminar on C^{14} isotope effects (5).

An aldehyde C-H bond may be used as a model of an alpha C-H bond in the transition state preceeding a carbonium ion intermediate or of an alpha C-H bond of the transition state of a displacement proceeding by the nucleophilic mechanism. In the two transition states the carbon atom is nearly sp^2 hybridized; the carbonyl carbon atom of the model may be expected to carry some positive charge (3). The aldehyde model is defective chiefly because too small a positive charge is localized on the carbon atom— prediction of an isotope effect deduced from it should be too small. Aldehyde C-H bonds adsorb in the infra-red at about 2800 cm^{-1} (stretching), 1350 cm^{-1} (in-plane bending), and 800 cm^{-1} (out-of-plane bending) (3). The alpha C-H bond of cyclopentyl tosylate adsorbs at 2890 cm^{-1}, and has two approximately degenerate modes of vibration at 1340 cm^{-1} (3). The isotope effect expected if only the stretching mode of the hydrogen substituted by deuterium is considered is 1.06 according to equation 3, and if only the most altered bending mode of this hydrogen is considered an isotope effect of 1.38 is predicted (3). The isotope effect found is 1.15 (Table I). It would be interesting to apply a similar calculation to the methyl esters of Table I since reverse isotope effects are observed.

Table I

$\left(\frac{k_{ROH}^{**}H_2O}{k_{AcOH}}\right)_y$	compound	solvent	temp.	k_H/k_D	rpd.	k_H/k_D per D atom	ref.
	CD_3I	H_2O	70.05	0.87	1%	0.96	6
300***	CD_3Br	"	79.94	0.90	1%	0.97	6
	CD_3Cl	"	89.94	0.92	1%	0.97	6
	CD_3ONO_2		100.00	0.92	1%	0.97	6

	CD_3OBs	CH_3OH	-	0.94	-	0.98	7
	$CD_3SO_3CH_3$	H_2O	60.07	0.96	-	0.99	6
	CD_3OTs	"	70.05	0.96	1%	0.99	6
	CD_3OBs	CH_3OH (CH_3O^-)*	-	0.96	-	0.99	7
	$CD_3SO_3CH_3$	H_2O	24.64	0.97	1%	0.99	6
	$CH_3CH_2CD_2Br$	H_2O	-	0.98	-	0.99	8
40	$(CH_3)_2CDBr$	C_2H_5OH ($C_2H_5O^-$)*		1.00	-	1.00	7
	$PhCH_2CD_2OTs$	HOAc (AcO^-)	75.25	1.17	2%	1.09	9
	p$CH_3PhCDClCH_3$	80%$(CH_3)_2CO$	37.6	1.11	1%	1.11	10
30	$PhCD_2OTs$	H_2O	50.0	1.25	2%	1.12	11
30	PhCHDOTs	"	50.0	1.12	3%	1.12	11
6	$(CH_3)_2CDOBs$	"	70.0	1.12	1.5%	1.12	11
		HOAc	50	1.15	1%	1.15	3

*S_N2 kinetics — all others S_N1

**reference 12

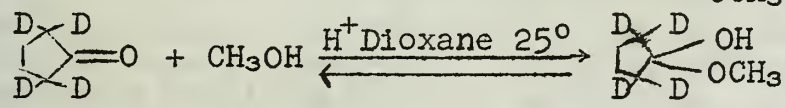
*** $(k_{ROH}/k_{HCOOH})y$

Unfortunately the small mass of the molecule makes it impossible to assign the vibrations to particular C-H bonds and probably invalidate the approximations involved in equation 3 as well. The uncomplicated vibrational argument would be unlikely to predict a reverse isotope effect, however. Since the observed isotope effect is much less than predicted for cyclopentyl-1-d tosylate, and is even less than one for several examples listed in Table I, it seems very probable that an effect opposing the simple bond weakening is operative.

Equation 3 does not apply in cases where isotopic substitution changes vibrational potentials. There is some evidence that substitution of deuterium for hydrogen does alter vibrational potentials in other parts of the molecule due to greater electron release from the C-D bond than from the C-H bond -- that is, there is an isotope effect on the inductive effect. The electronic dissimilarity of bonded deuterium and protium is demonstrated by the following observations: (a) H-D has a dipole moment of the order of 10^{-3}D(13). (b) The fluorine nmr spectra of n-heptafluoropropane-1-d and n-1,1,1,2,2,3,3-heptafluoropropane shows that the two 3-fluorines are 0.6 ± 0.05 ppm more shielded in the deuteride (14). Fluorine chemical shifts have been related to sigma constants (15). A shift of 0.6 ppm is roughly comparable to a change in sigma-meta of -0.1; this would imply an isotope effect of 0.45 for a solvolysis for which rho = -3 and a reduction in the acidity of benzoic acid of 20%. (c) The protons of toluene-α-d are more shielded than those of toluene by 0.015 ± 0.002 ppm (16). These effects are explained by the anharmonicity of the potential for the C-H vibration -- especially the stretching vibration (17,18,13). Since the C-D ground state vibrations are lower than those of C-H, a Morse potential, for instance, would predict a shorter equilibrium bond length for the isotopic species -- it follows that deuterium should be more electron-donating that hydrogen.

Secondary isotope effects have also been observed in equilibrations (Table II), and these observations are cited as evidence for an inductive source of the effects (18,21,22). However, there is probably sufficient loosening of C-H bonds in the product of at

Table II

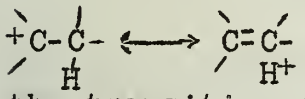
equilibrium	k_H/k_D	rpd.	ref.
$\underline{p}ClPhCDO \xrightleftharpoons{95\%\ H_2SO_4} \underline{p}ClPh\overset{+}{C}DOH$	1.005	0.6%	19
$\underline{p}(CH_3OPh)_2CDOH \xrightleftharpoons{95\%\ H_2SO_4} \underline{p}(CH_3OPh)_2\overset{+}{C}D$	1.18	1%	19
$Ph_2CDOH \xrightleftharpoons{95\%\ H_2SO_4} Ph_2\overset{+}{C}D$	1.32	0.5%	19
$(CD_3)_3BN(CH_3)_3 \xrightleftharpoons{65\text{-}95^\circ} (CD_3)_3B + (CH_3)_3N$	1.25	3%	20
$PhCD_2COOH \xrightleftharpoons{H_2O} PhCD_2COO^- + H_3O^+$	1.11_9	1.5%	21
$PhCD_2NH_2 \xrightleftharpoons{H_2O} PhCD_2NH_3^+ + OH^-$	0.87	-	22
$CD_3COCD_3 + CH_3OH \xrightleftharpoons{H^+\ Dioxane\ 25^\circ} (CD_3)_2C(OH)(OCH_3)$	1.29	9%	23
	1.51	6%	23

least some of the equilibrations of Table II to account for the effects (3). Comparison of the vibrational spectra of acetic acid vapor and acetic-d_3 acid vapor (24) with the vibrational spectra of water solutions of the corresponding acetates (25) by means of the first factor of equation 2, that is, disregarding any isotopic inductive effect on non-isotopically substituted bonds, leads to a prediction of 1.13/D atom for the isotope effect on the dissociation of the acid. The O-H stretching vibration occurs at 3546 cm^{-1} in acetic acid and at 3640 cm^{-1} in acetic-d_3 acid (24). The ratio of the squares of these vibrational frequencies is a measure of O-H bond strength in the two acids and therefore is a measure of inductive effects on the acid strength. The predicted isotope effect on the basis of induction alone is 1.03/D atom. The observed isotope effect on the dissociation of phenylacetic-d_2 acid is 1.05_9/D atom (21). The major contribution to the observed isotope effect probably originates from C-H bond weakening in the acetate although clearly no very convincing argument can be made on the basis of only one set of measurements.

An alternate explanation for the reverse isotope effect observed in the solvolyses of the methyl compounds in Table I is that steric interference of the hydrogen bending modes by the entering and leaving groups stiffens these vibrations (6). Any stiffening of C-H vibrations in the transition state will, according to equation 3, lead to a reverse isotope effect. There is a rough nonlinear inverse correlation between Winstein's sensitivity parameter, $(k_{ROH\text{-}H2O}/k_{RCOOH})y$ (12), and the size of the isotope effect (Table I). It is reasonable that the steric effect of entering and leaving groups would become more pronounced as the nucleophilic character of the solvolysis increases. Calculating backwards, it is found that a Hooke's Law constant of about 10^5 r^2 dyne cm^2 for each of three C-H bonds is required for the out-of-plane bending mode in order to account for the observed isotope effect in the methyl bromide solvolysis (6). Since Hooke's Law constants of 0.46(10^5) and 0.51 (10^5) r^2 dyne cm^2 are found for terminal methylene and 1.5(10^5) r^2 dyne cm^2 for aldehyde (6) the calculated constant is of reasonable magnitude.

The reverse isotope effect in the hydrolysis of benzylamine-1,1-d_2, 0.87 (22), can be attributed to steric crowding in the ion due to increased solvation and the increased covalency of the nitrogen.

Secondary isotope effects occuring in solvolyses because of deuteration in the beta positions or in alkyl groups modifying a phenyl substituent of an alpha position have been studied more extensively than alpha-hydrogen effects, a division of interest undoubtedly motivated by the need for experimental evidence concerning the chemical significance of hyperconjugation. Hyperconjugation can account for the observed rate retardations in two ways: (a) The resonance forms,



cause a reduction in the energy of the carbonium ion intermediate, and by Hammond's principle, of the transition state leading to the intermediate. The stabilization is purely electronic. It is necessary to postulate that deuterium participates less effectively in the stabilizing resonance than ordinary hydrogen, somewhat contrary to its proposed inductive function. (b) Hyperconjugation may weaken the C-H bonds of the beta position so that an isotope retardation occurs according to equation 3 (3). A reduction in the methylene bending frequencies is reasonable since this vibrational mode corresponds to motion along the pi hyperconjugative molecular orbital (figure 1) (3).

While no experiments have been devised to differentiate the electronic from the kinetic energy explanation, there is evidence for one or the other. Demonstration of hyperconjugation in a reactive and highly energetic species such as a carbonium ion implies nothing about its operation in ground state molecules (3); in fact there is considerable doubt about its significance in the latter (26).

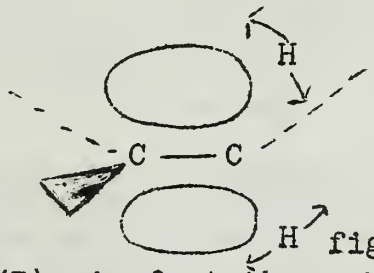


figure 1

A hyperconjugative origin for the beta secondary isotope effects is supported by the observation that a para-methyl-d_3 or a para-methyl-1,1-d_2 substituent leads to an isotope effect greater than one, whereas a meta-methyl-d_3 substituent leads to a reverse isotope effect in the solvolysis of benzhydryl or 1-phenylethyl chloride (10,27) (Table III).

Table III

compound	solvent	temp.	k_H/k_D	rpd.	k_H/k_D per D atom	ref.
mCD_3PhCHClCH$_3$	80% acetone	62.4	0.976	1.5%	0.992	10
mCD_3PhCHClCH$_3$	70% "	37.6	0.994	3%	0.998	10
pCH_3CD_2PhCHClPh	80% "	0.0	1.025	0.5%	1.012	27
pCD_3PhCHClPh	80% "	0.0	1.058	0.5%	1.016	27
pCD_3PhCHClCH$_3$	80% "	37.6	1.008	0.5%	1.003	10
pCH_3PhCHClCD$_3$	80% "	37.6	1.14	0.5%	1.05	10
pCH_3PhCDClCH$_3$	80% "	37.6	1.11	1%	1.11	10

pCHD_2PhCHClCH$_3$	HOAc	50.25	1.10	2%	1.05	10
pCH_3PhCHClCD$_3$	"	50.25	1.28	2%	1.09	10
pCHD_2PhCHClCH$_3$	"	65.30	1.07	2%	1.04	10
pCH_3PhCHClCD$_3$	"	65.30	1.17	2%	1.06	10

However, hyperconjugation does not need to be invoked because resonance structures (figure 2) could account for the effect if the close proximity of the positive charge to the methyl group caused loosening of the C-H bonds of the latter; the stabilization of the positive

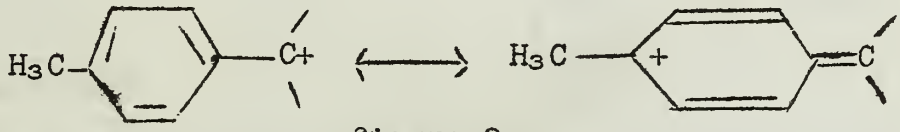


figure 2

charge by inductive release from the methyl group would not explain the effects as it would lead to an isotope effect less than one if consistant with the alpha effects discussed earlier.

Further evidence for hyperconjugation is that the rate of acetolysis and formolysis of 2-(p-methoxyphenyl)-ethyl-2,2-d_2 tosylate and 2,2-diphenylethyl-2-d tosylate (28) and the rate of formolysis of 2-phenylethyl-2,2-d_2 tosylate (1) are the same as for the corresponding undeuterated esters. Phenyl participation might be expected to destroy the orientation required for the empty pi orbital of the ion to overlap with the C-H sigma bond. Since the rates of solvolysis of 2-phenylethyl tosylate (1) and 2-pentyl tosylate (29) at the same termperature are of the same order of magnitude, it can be concluded, with the exception of the methoxy substituted compound, that the lack of an isotope effect for the phenylethyl tosylates cannot be attributed to a leveling effect.

In the examples in which direct comparison is possible, it is observed that beta hydrogen is nearly as effective in rate reduction as alpha hydrogen -- this suggest hyperconjugation. The isotope effect in the acetolysis of cyclopentyl-1-d tosylate is 1.15; under the same conditions the isotope effect on the acetolysis of cis and trans-cyclopentyl-2-d tosylate is 1.16 (3). In the hydrolysis of three isomers of n-propyl-d_2 bromide isotope effects of 0.98_0, 1.054, and 0.92 were found for the 1,1, the 2,2, and the 3,3 isomers (8). An explanation for this result is the following: (a) Inductive electron donation from the alpha position is opposed by steric stiffening of the C-H bending modes in the transition state. (b) Beta C-H bonds are loosened by hyperconjugation. (c) Llewellyn accounts for the low isotope effect at the gamma position by a steric effect (8). Comparison of the isotope effect for the solvolysis of 1-(p-methylphenyl)-ethyl-2,2,2-d_3 chloride, 1.05 (10), and 1-(p-methylphenyl)-ethyl-1-d chloride, 1.11 (10), also gives some support to this argument for hyperconjugative effects.

Solvation of the beta hydrogens has been used to rationalize the increase of isotope effect with decreasing dielectric constant of the solvent in the p-alkylbenzhydryl chlorides (Table IV)(27). Interaction with the solvent may stretch the C-H bond in the transition state. Such stretching weakens the bond in the transition state causing the observed isotope effect. Solvents of high dielectric strength more effectively dissipate the positive charges built up in the transition state thus reducing solvation at the beta

Table IV (27)

solvent	90% Ethanol	80% Acetone	70% Acetone	66.7% Acetone
dielectric constant	28.1	29.6	35.7	37.5
compound		isotope effect		
pCD_3PhCH_2ClPh	1.025	1.058	1.038	1.021
p$CH_3CD_2PhCHClPh$	1.009	1.025	1.019	1.012
p$(CH_3)_2CDPhCHClPh$	.998	1.006	-	-
p$(CH_3)_2CHCD_2PhCHClPh$	-	1.020	-	-

position. The result is the trend observed in Table IV(27). A more satisfactory explanation is that with solvents of low dielectric strength, the positive charge of the transition state for the carbonium ion is more localized, creating a greater electron demand at the positive center and thereby increasing bond weakening by hyperconjugation (3). Further evidence against specific solvation of beta hydrogens is offered by Streitwieser, who found identical isotope effects for the solvolysis of cyclopentyl-cis-2-d tosylate and cyclopneyl-trans-2-d tosylate, 1.16 at 50°(3). The type of solvent-hydrogen interaction proposed above should affect the trans more than the cis isomer.

Secondary hydrogen isotope effects have been observed in a number of other reactions. In examples in which the mechanism is established, the explanations already presented account for the effects satisfactorily.

Isotope effects of 0.93, 0.94, and 0.98/D atom have been found for the benzoylation of aniline-N-d_2, aniline-N,2,4,6-d_5, and aniline-2,4,6-d_3 at 25°(30). In the transition state for this reaction the "unbrella" vibrational mode of the aniline is probably changed to a bending vibration of higher frequency due to the steric effect of the entering group (30). The reverse isotope effect found for aniline-2,4,6-d_3 may be caused by an inductive effect; induction would increase the basicity of the amine nitrogen in all three examples (30). C-H or C-D bond stiffening due to loss of several resonance forms (figure 3) might also account for the effects.

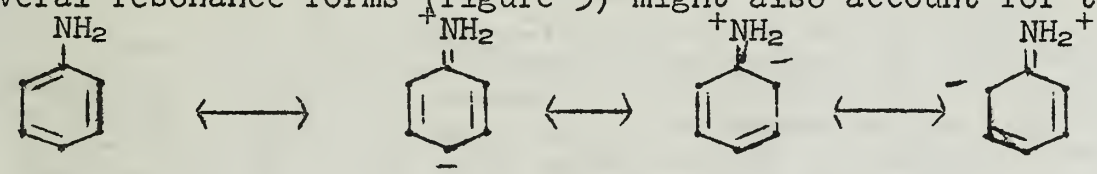


figure 3

The isotope effect in the acid catalyzed hydrolysis of a number of ketals in aqueous dioxane at 25°(Table V) may be caused by loosening of C-H or C-D bonds in the transition state by hyperconjugation with the positive center (figure 4) (31).

Table V (31)

compound	solvent	k_H/k_D (rpd. 1%)	$k_H/k_D/D$ at
$CH_3CD_2(CD_3)C(OC_2H_5)_2$	50% Dioxane	1.10	1.02
$(CD_3)_2C(OC_2H_5)_2$	50% "	1.10	1.02
$(CD_3)_2C(OC_2H_5)_2$	90% "	1.12	1.02
$(CH_3)_2CD(CD_3)C(OC_2H_5)_2$	90% "	1.11	1.03
$CH_3CD_2(CD_3)C(OC_2H_5)_2$	90% "	1.15	1.03
$PhOCD_2C(CD_3)(OC_2H_5)_2$	90% "	1.25	1.12

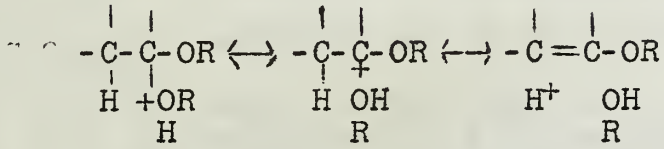


figure 4

Base catalyzed hydrolysis of methyl p-toluate-α-t shows an isotope effect of 1.04_9, whereas acid catalyzed hydrolysis in 100% sulfuric acid shows no isotope effect (32). The transition state for the base catalyzed reaction is represented in figure 5a. Induction from the para-methyl or para-methyl-t group would be expected to slow the base catalyzed hydrolysis. If tritium is a better electron donor than protium by the inductive process, an isotope effect greater than one is expected. Induction should accelerate the acid catalyzed hydrolysis, causing a reverse isotope effect. The reverse isotope effect may be opposed by hyperconjugative weakening of the C-T bond (figure 5b), if as Hodnett suggests, the reaction proceeds through an acylium ion (32).

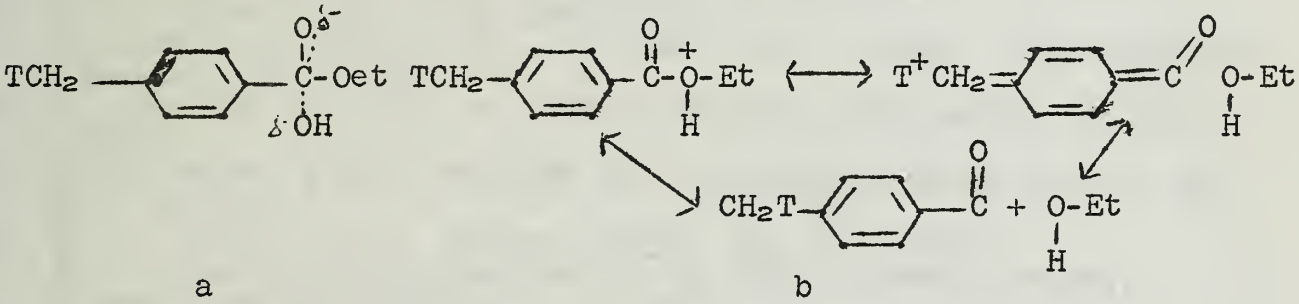


figure 5

Base and acid catalyzed enolization of cyclopentyl-2,2,5,5-d_4-phenyl ketone and acid catalyzed enolization of cyclohexyl-2,2,6,6-d_4-phenyl ketone show secondary isotope effects of 1.06, 1.06, and 1.10 (33). If the transition state resembles the enol product, C-H bond loosening at the beta carbons might be expected through hyperconjugation with the C-C double bond of the enol (33).

Reverse isotope effects of the order of 0.9 have been found in a number of reactions of 1,2-diphenylethene-1,2-d_2 (dideuterostilbene) (34). The reactions include additions and oxidations. If the hybridization of the ethylenic carbons approaches sp^3 in the transition state such an isotope effect would be expected due to stiffening of the deformation vibrations (34).

Secondary isotope effects have been reviewed by Lewis (35), Streitwieser (36), and Bell (37), and are the subject of an MIT Organic Seminar (38).

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DIARYLIODONIUM SALTS

Reported by J. E. Schultz May 2, 1960

The development of improved synthetic methods in the last few years has made diaryliodonium compounds readily available for use as reagents in synthesis and has opened up a new series of reactions for mechanistic study. Since the original synthesis of these compounds in 1894 (1), a fairly large number of reviews have been written on the subject (2,3,4,5,6,7). The purpose of this seminar is to discuss the recent studies of diaryliodonium salts and their uses in synthesis.

SYNTHESIS

There are five main routes to the synthesis of diaryl iodonium compounds (8,9).

1. Coupling of two aromatic compounds with iodyl sulfate in sulfuric acid:

$$4ARH + (IO)_2SO_4 + 3H_2SO_4 \longrightarrow 2Ar_2I^{\oplus} + 2H_3O^{\oplus} + 4H_2SO_4$$

This method gives only symmetrical diaryliodonium compounds with yields varying considerably for different substituents.

2. Coupling of two aromatic compounds with iodate in acetic acid-acetic anhydride-sulfuric acid:

$$2ARH + IO_3^{\ominus} + 2H_2SO_4 + 2Ac_2O \longrightarrow Ar_2I^{\oplus} + 2HSO_4^{\ominus} + 4AcOH + [O]$$

This reaction also yields only symmetrical compounds but produces some compounds that cannot be produced by reaction 1. Both reactions 1 and 2 have the disadvantage that only diaryliodonium bisulfites are produced. Other anions must be substituted by subsequent reactions.

3. Coupling of two aromatic compounds with iodine (III) acylates in the presence of an acid.

$$2ArH + I(OCOR)_3 + HX + Ar_2I^{\oplus}X^{\ominus} + 3RCOOH$$

This reaction is primarily used to produce symmetrical compounds which cannot be produced by method 1 or 2 (e.g. 4,4'-dimethoxydiphenyliodonium salts).

4. Condensation of an iodoso compound, an iodosodiacetyl, or an iodoxy compound with another aromatic compound in the presence of an acid.

$$ARIO + Ar'H + H_2SO_4 \longrightarrow ArI^{\oplus}Ar'HSO_3^{-} + H_2O$$
$$ARI(OAc)_2 + Ar'H + H_2SO_4 \longrightarrow ArI^{\oplus}Ar'HOSO_3^{-} + 2AcOH$$
$$ArIO_2 + Ar'H + H_2SO_4 \longrightarrow ArI^{\oplus}Ar'\ HOSO_3^{-} + H_2O + [O]$$

This reaction offers a method of preparing unsymmetrical diaryliodonium salts in yields up to 90 per cent depending upon the substituents.

5. Reactions of organometallic compounds with aryl iodoso dichlorides where the organometallic compounds include those of mercury,

$$R'M + RICl_2 \longrightarrow R'RI^{\oplus}Cl^{\ominus} + MCl$$

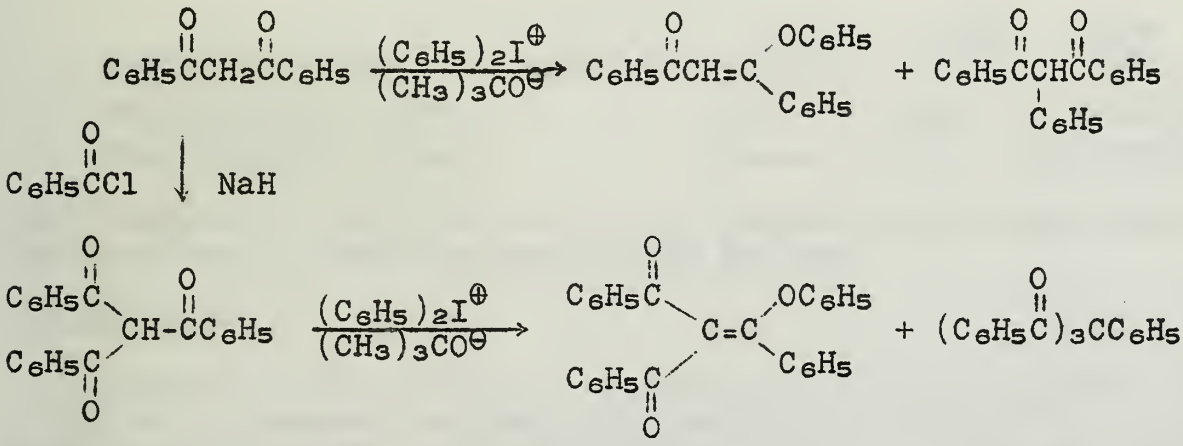
silver, tin, and magnesium. These reactions are useful in producing compounds which may not be readily available by other means (e.g. 2,2'-dinaphthyliodonium).

Syntheses of particular diaryliodonium salts bearing carboxyl, hydroxyl, alkoxyl and Amino groups have also been devised (10,11).

PHENYLATIONS

Diaryl iodonium compounds have their widest synthetic use in the phenylation of various anions, both organic and inorganic, such as benzoate, methoxide, phenoxide, sulfide, sulfhydryl, sulfite, p-toluenesulfinate, nitrite, and cyanide to list only a few (7,12, 13,14,14).

The phenylation products of several compounds have been studied by Beringer and coworkers (16). Of these, an interesting example is the phenylation of di- and tribenzoyl methane as shown below.



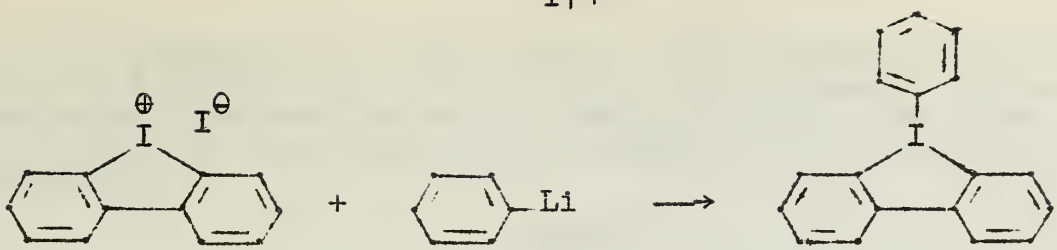
Both C-phenylation and O-phenylation is observed in many of these compounds.

This reaction has been extended to the phenylation of many organic compounds having reactive hydrogens such as malonic ester (17). It is found, however, that the reaction gives better yields and fewer competing reactions if the phenylation is restricted to compounds bearing only one active hydrogen. The mechanism of this reaction and related reactions is currently being investigated by Beringer and coworkers.

REACTIONS WITH ORGANOMETALLICS

At low temperatures aryliodosodichlorides react with aryllithium reagents to give diaryliodonium salts. More aryllithium reagent or grignard reagents convert the iodonium compounds to triaryl iodine which then may decompose by a radicalmechanism or may be decomposed by acid to yield iodonium salts and hydrocarbons (9).

An example of this is the reaction of 2,2'-biphenylyliodonium iodide with phenyl lithium



A typical example of the reaction with grignard reagents is the reaction of diphenyl iodonium iodide with ethyl grignard which yields iodobenzene, benzene, biphenyl, ethyl benzene, and ethyliodide. The variety of products may be explained on the basis that ethyldiphenyl iodine was formed and then decomposed at room temperature into free radicals which gave the observed products. This explanation is shown in the following reaction scheme:

$$C_2H_5MgX + (C_6H_5)_2I^+ X^\ominus \longrightarrow MgX_2 + (C_6H_5)_2IC_2H_5$$

$$\downarrow$$

$$C_6H_5I + C_2H_5$$

$$C_6H_5C_2H_5 + C_6H_5C_6H_5 + C_2H_5C_2H_5 \longleftarrow + C_2H_5\cdot + C_6H_5\cdot$$

$$CH_3\dot{C}HOCH_2CH_3 + C_6H_6 \longleftarrow C_6H_5\cdot + CH_3CH_2OCH_2CH_3$$

$$CH_3\dot{C}HOCH_2CH_3 + C_2H_5 \longleftarrow C_2H_5\cdot + CH_3CHOC_2CH_3$$

Small amounts of products were also observed which would arise from the coupling of phenyl radicals with solvent.

DECOMPOSITION

Thermal decomposition of diaryliodonium salts to yield substituted benzenes is one of the earliest reported reactions of these compounds and is the most useful method of identifying them (7). For symmetrical salts the reaction always proceeds as follows:

$$Ar_2I^\oplus X^\ominus \xrightarrow{\Delta} ArI + ArX$$

An early report suggested a free aryl carbonium ion mechanism for this reaction (7,12). However, there is considerable evidence that the reaction proceeds by a nucleophilic attack of the anion on the diaryliodonium cation producing the noted products. In 1936, Lucas showed that 2,2'-dimethyldiphenyl iodonium iodide yielded only 2-iodotoluene and concluded that the reaction was ionic rather than radical. Sandin and coworkers found that the decomposition of 4-methoxydiphenyliodonium halides proceeded with attachment of the halide ion to the unsubstituted ring and Beringer reported that the reaction of 2- and 3-nitrodiphenyliodonium bromide was much faster than the unsubstituted case and the products were only 2- and 3-nitrobromobenzene and iodobenzene (18). This evidence suggests that the reaction of many iodonium compounds proceeds via a nucleophilic attack of a base on the 1-position of the diphenyliodonium ion to yield iodobenzene and a phenyl derivative of the base.

Beringer and co-workers (19) investigated the kinetics of the decomposition of various symmetrical and unsymmetrical diaryliodonium salts in dimethylformamide. The reactions were followed to 90 per cent completion and found to be first order. The rate constants and activation parameters are summarized for the bromides in table I.

It is apparent from the data in table I that there is a significant substituent effect; electron withdrawing groups increasing and electron releasing groups retarding the rate. Such an effect would be characteristic of reactions involving attack of a nucleophile.

TABLE I

Substituent	k/k_o	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
3,3'-$(NO_2)_2$	2.0	31.1	10
H	1.0	31.6	10
4,4'-Cl_2	0.77	30.9	7
4,4'-$(t\text{-}Bu)_2$	0.42	31.6	8
4,4'-$(CH_3)_2$	0.38	31.9	9
4,4'-$(CH_3O)_2$	0.038	36.9	16

Because of the variation of $\Delta S^{\ddagger}$ one would not expect a Hammett σ-ρ relationship to hold. Actually, the correlation with the sigma constant is not at all good and only demonstrates the general trend. There is a somewhat better correlation with σ^{+}.

CATALYSIS AND INHIBITORS

About ten years after the discovery of iodonium salts, Buchner (20) reported that the decomposition of diphenyliodonium chloride and iodide was second order and the rate was strongly influenced by small quantities of acid, iodine, or base. Beringer and coworkers (18) found that reactions of these salts with chloride ion in water, dimethylformamide, and diethylene glycol was strongly catalyzed by addition of small amounts of copper salts. In the presence of cupric chloride in diethylene glycol, the reaction, as followed by the disappearance of chloride ion, showed a definite induction period. On the other hand, when cuprous chloride was used as the catalyst, no induction period was observed. The rate of disappearance of chloride ion in the region of the linear portions of the two curves was in close agreement. These workers concluded that the nucleophilic species in both cases was the $CuCl_2^{\ominus}$ ion which has also been proposed as the catalytic species in the Sandmeyer reaction (21) On the basis of studies of Edwards (22), which relate nucleophilicity and oxidation reduction potentials, the $CuCl_2^{\ominus}$ ion would be a better nucleophile than chloride ion. When the reaction medium was dimethylformamide or water, no induction period was observed. The lack of such an induction period was assumed to indicate that $CuCl_2^{\ominus}$ was not the only catalyzing species in the solution.

In order to investigate further the copper salt catalysis, Beringer (23) studied the kinetics of the hydrolysis and reaction with chloride ion both with and without catalysis. However it was immediately apparent that copper was not the only species which affected the rate. In the hydrolysis reaction, four effects were noted: 1) Small amounts of added sulfuric acid strongly inhibited the initial reaction, 2) the reaction was slower in the presence of chloride ion than in the presence of benzenesulfonate ion, 3) iodine retarded the rate, 4) changes in atmosphere had secondary effects on the rate. In the reaction of chloride ion: 1) Acid repressed the rate, 2) under an atmosphere of nitrogen the plots

curved upward, and 3) iodine increased the rate. No attempt was made to explain the action of iodine, but Beringer concluded that since the reaction was repressed by acid, this reaction must involve an intermediate whose formation is retarded by acid.

A possible reaction pattern to explain the above data would have to have the following characteristics: a) A base could convert the diphenyliodonium cation to a reactive intermediate; b) the concentration of this intermediate would be repressed by oxonium ions and chloride ions; c) this intermediate must give phenol by decomposing or reacting with water; and d) the intermediate must give chlorobenzene by reaction with chloride ion.

A possible reaction scheme would be:

$$C_6H_5I^{\oplus}C_6H_5 + nH_2O \underset{H^{\oplus}}{\overset{-H^{\oplus}}{\rightleftharpoons}} C_{12}H_9I\cdot(H_2O)n$$

$$C_{12}H_9I\cdot(H_2O)n + x^{\ominus} + H_2O \longrightarrow C_6H_5x + C_6H_5I + OH^{\ominus} + nH_2O$$

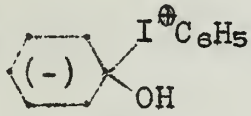
$$C_{12}H_9I\cdot(H_2O)n + (1-n)H_2O \longrightarrow C_6H_5OH + C_6H_5I$$

$$C_{12}H_9I\cdot(H_2O)n + BH \longrightarrow C_6H_5B + C_6H_5I + nH_2O$$

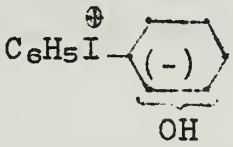
The composition of such an intermediate would be impossible to ascertain in water as a solvent, therefore one can speculate only as to its structure. The possible structures proposed by Beringer are I, II, III, in the case where n is equal to one and IV, V, and VI where n is equal to zero.

$(C_6H_5)_2IOH$

I



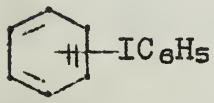
II



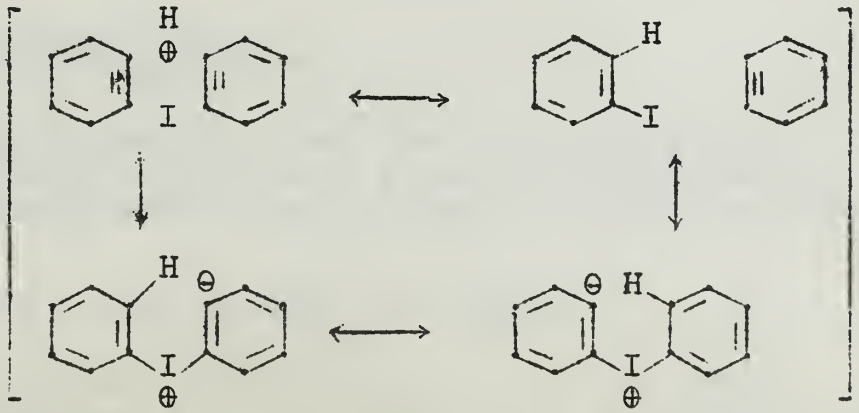
III

While structures I, II, and III may be visualized as intermediates in the formation of phenol, it seems improbable that any of these would be more susceptible to attack by chloride ion than the diphenyliodonium ion itself. For this reason, the intermediate is visualized as the conjugate base, $C_{12}H_9I\cdot$ However, this leads to a structural problem. Intermediates of the form IV and V are excluded by the observation of Caserio, Glusker, and Roberts (24) that the hydrolysis of 3-nitro-4'-methoxydiphenyliodonium cation gave only 3-nitrophenol and 4-methoxyphenol. The lack of isomers rules out any symmetrical structures. For this reason structure VI was proposed.

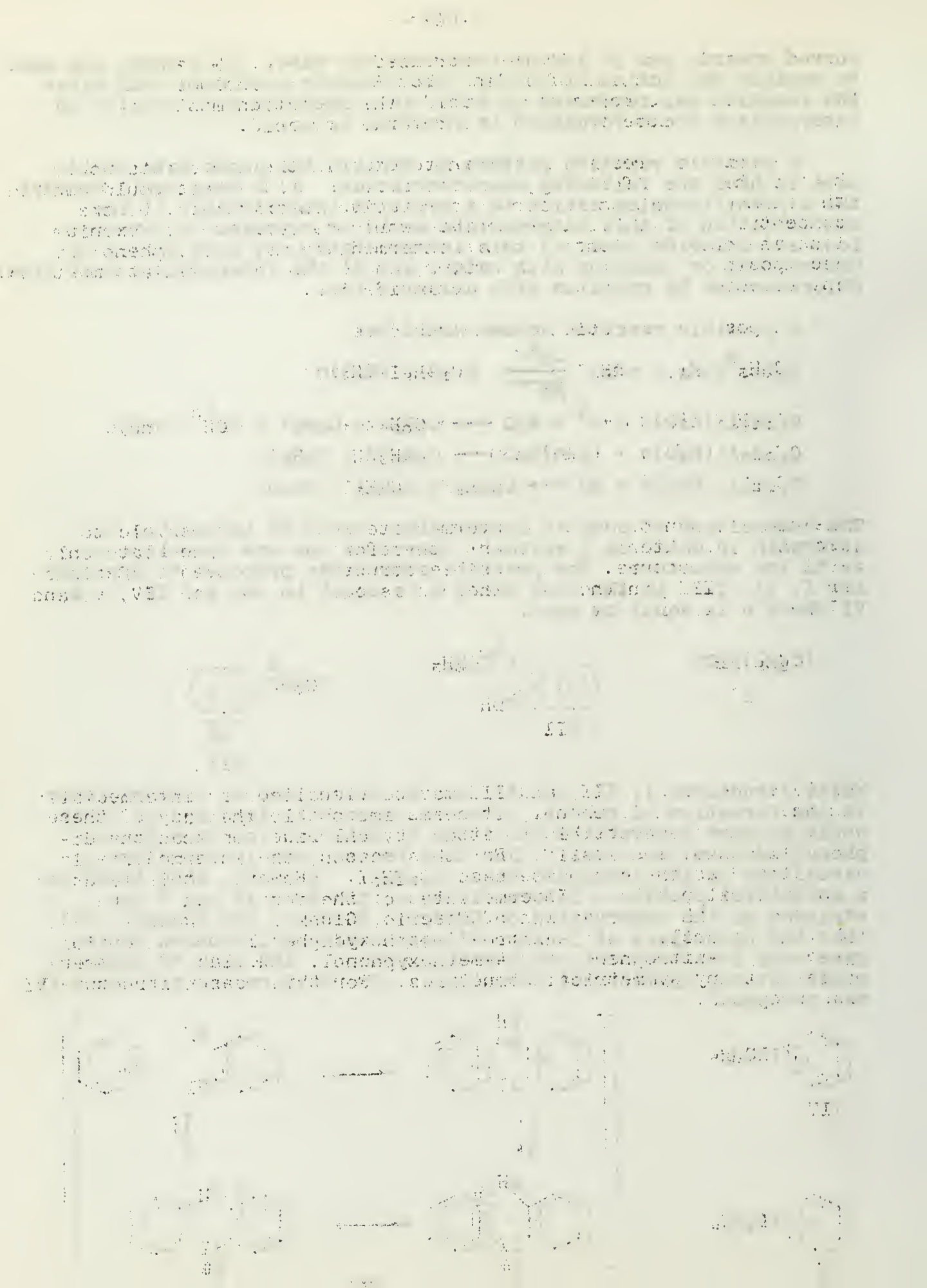
IV



V



VI



It must be realized that structure VI is only a working hypothesis and lacks any form of proof. Beringer has planned some additional work, including deuterium exchange to test this hypothesis.

Kinetic expressions were derived by Beringer from the following reaction sequence using the conjugate base $C_{12}H_9I$ as an intermediate which may or may not be solvated by water.

$$C_6H_5I^{\oplus}C_6H_5 + H_2O \underset{2}{\overset{1}{\rightleftharpoons}} C_{12}H_9I + H_3O^{\oplus}$$

$$C_6H_5I^{\oplus}C_6H_5 + OH^{\ominus} \underset{4}{\overset{3}{\rightleftharpoons}} C_{12}H_9I + H_2O$$

$$C_6H_5I^{\oplus}C_6H_5 + B \underset{9}{\overset{8}{\rightleftharpoons}} C_{12}H_9I + BH^{\oplus}$$

$$C_{12}H_9I + H_2O \xrightarrow{5} C_6H_5OH + C_6H_5I$$

$$C_{12}H_9I + OH^{\ominus} + H_2O \xrightarrow{6} C_6H_5OH + C_6H_5I + OH^{\ominus}$$

$$C_{12}H_9I + Cl^{\ominus} + H_2O \xrightarrow{7} C_6H_5Cl + C_6H_5I + OH^{\ominus}$$

Assuming that the concentration of the conjugate base is small and constant, a steady state approximation leads to the following expression for this concentration:

$$(1) \quad m = \frac{(k_1 + k_3[OH^-] + k_8[B])\ [C_6H_5I^{\oplus}C_6H_5]}{k_4 + k_5 + k_2[H_3O^+] + k_6\ [OH^-] + k_7[Cl^-] + k_9\ [BH^+]}$$

In the presence of a high concentration of strong base, the kinetic equation based on the above reaction scheme would reduce to:

$$(2) \quad -\frac{d[OH^{\ominus}]}{dt} = k_3[C_6H_5I^{\oplus}C_6H_5][OH^-]$$

which fits the data of Lewis and Stout (25) in their study of the reaction of hydroxide ion with diphenyl iodonium salts.

In acid solution, the rate equation in the presence of chloride ion becomes:

$$(3) \quad \frac{d[H_3O^+]}{dt} = \frac{k_1k_5[C_6H_5I^{\oplus}C_6H_5]}{k_4 + k_5 + k_2[H_3O^+] + k_7[Cl^-]}$$

which agrees with the experimental result that acid and chloride ion repress the rate. In the absence of initial acid or chloride ion the equation becomes:

$$(4) \quad \frac{d[H_3O^+]}{dt} = \frac{k_3k_5[C_6H_5I^{\oplus}C_6H_5]}{k_4 + k_5 + k_2[H_3O^+]}$$

which agrees with the observation that the rate falls off with increasing acid concentration but not in a simple proportionality. If chloride ion concentration is zero, equation (3) can be integrated to yield:

$$(5) \quad -[\frac{1}{k_2}\ (k_4 + k_5) + h + a]\ \ln\ (1-\frac{x}{a})\ -x = \frac{k_1k_5}{k_2}\ t$$

where h is the concentration of oxonium ion, a is the initial concentration of iodonium ion, and a-x is the amount of iodonium ion remaining at time t.

An approximation which casts 5 into a form more convenient for plotting involves dropping the first term in brackets, to give equation 6:

$$(6) \quad -[h + a] \ln \left(1 - \frac{x}{a}\right) - x = \frac{k_1 k_5}{k_2} t$$

Values of k_1k_5/k_2 for various runs are in fair agreement.

The reaction of chloride ion with diphenyliodonium ion in the presence of concentrated base leads to the expression:

$$(7) \quad -\frac{d[Cl^-]}{dt} = k_7 \, m[Cl^-]$$

where m is defined by equation 1. Substitution for m and a few appropriate assumptions leads to equation 8:

$$(8) \quad -\frac{d[Cl^-]}{dt} = \frac{k_7 k_8}{k_4+k_5} [B][C_6H_5I^{\oplus}C_6H_5][Cl^-]$$

which agrees with the observation that the reaction of iodonium salts with chloride ion in the presence of pyridine is apparently third order, obeying this rate law.

Finally, the kinetic expression for the reaction with chloride ion in acid is given by:

$$(9) \quad -\frac{d[Cl^-]}{dt} = \frac{k_1 k_7 [C_6H_5I^{\oplus}C_6H_5][Cl^-]}{k_4+k_5+k_2[H_3O^+]+k_7[Cl^-]}$$

which would explain why the initial reaction with chloride ion is retarded strongly acid.

However, these kinetic expressions do not explain the catalysis by copper salts. Therefore the hydrolysis of diphenyliodonium salts was studied in the presence of added cupric sulfate. Beringer observed that: 1) First order plots were not linear and the apparent first order rate constants decreased with the progress of the run. Second order plots were more nearly linear and showed no induction period, 2) acid depressed the initial rate, 3) first order rate constants taken early in the run at comparable, low acid concentrations showed that the initial first order rate constants were roughly proportional to the concentration of added cupric salt over a 500 fold range of catalyst concentration, 4) the reaction was fastest under hydrogen, intermediate under nitrogen and slowest under oxygen.

On the basis of these observations, one can propose catalysis either by Cu(I) or Cu(II) or both, Possible explanations of the catalytic effect are: a) A copper catalyzed decomposition of the conjugate base, $C_{12}H_9I$ (proposed as the intermediate in the uncatalyzed reaction; and b) formation and hydrolysis of some copper complex or complexes.

A reaction scheme following possibility (a) is:

$$C_{12}H_9I + H_2O + Cu^{++} \xrightarrow{5a} C_6H_5OH + C_6H_5I + Cu^{++}$$

If the reaction is neutral or acid, the rate expression reduces to:

$$(10)\quad \frac{d[H_3O^+]}{dt} = \frac{k_1k_5a[Cu^{++}][C_6H_5I^{\oplus}\ C_6H_5]}{k_2[H_3O^+] + k_5a\ [Cu^{++}]}$$

If k_2 is less than or equal k_5a, then as $[Cu^{++}]$ becomes large equation 10 approaches a first order expression, which would disagree with the observation that the first order rate constants are proportional to $[Cu^{++}]$. However, there is no evidence that k_5a is greater than k_2 so scheme (a) is ruled out only for this special case. This sort of catalysis by Cu(I) would lead to the same rate expression and would create the same problem.

If the reaction occurs according to (b), the following scheme will apply.

$$C_{12}H_{10}I^+ + Cu^{++} + H_2O \underset{11}{\overset{10}{\rightleftharpoons}} C_{12}H_9CuI^{++} + H_3O^+$$

$$C_{12}H_9CuI^{++} + H_2O \xrightarrow{12} C_6H_5OH + C_6H_5I + Cu^{++}$$

the kinetic form for this reaction is:

$$(11)\quad \frac{d[H_3O^+]}{dt} = \frac{k_{10}K_{11}[Cu^{++}][C_6H_5I^{\oplus}C_6H_5]}{k_{12} + k_{11}\ [H_3O^+]}$$

which is the same form as equation (3) and therefore reduces to the same integrated form (using the same assumptions for convenience):

$$(12)\quad -[h + a]\ \ln\ (1-\frac{x}{h}) - x = \frac{k_{10}k_{12}}{k_{11}}\ [Cu^{++}]\ t$$

Plots according to this equation are roughly linear and deviations could be attributed to the approximations made. Again [Cu(I)] could replace [CuII] in all the above expressions.

If the reaction is catalyzed by Cu(I) only as in the case of the reaction in dimethylene glycol, a possible reaction scheme is:

$$Cu^{++} + \text{reductant} \underset{b}{\overset{a}{\rightleftharpoons}} Cu(I) + \text{oxidant}$$

$$Cu(I) + 2H_2O \underset{d}{\overset{c}{\rightleftharpoons}} CuOH + H_3O^{\oplus}$$

$$C_6H_5I + C_6H_5 + CuOH \xrightarrow{e} C_6H_5OH + C_6H_5I + Cu(I)$$

The rate expression in this case becomes:

$$(13)\quad \frac{d[H_3O^+]}{dt} = ke[CuOH][C_6H_5I^{\oplus}C_6H_5] = \frac{kcke}{kd}\ \frac{[Cu^+][C_6H_5I^{\oplus}C_6H_5]}{[H_3O^+]}$$

This equation 13 is in good accord with many of the observed effects. It would explain repression by acid and oxygen and acceleration by hydrogen as inhibition or promotion of the formation of CuOH, the proposed attacking species. However this scheme does not explain why cupric ion is a catalyst, or, if it is not, why there is no induction period during which Cu(I) is formed as in the case of the reaction in diethylene glycol.

Roberts et al. (24) also studied the hydrolysis of diaryliodonium salts in 1:1 water-dioxane, water, and aqueous acetonitrile. They found that in the hydrolysis of 4-methoxydiphenyliodonium salts, 4-methyliodonium salts, and 3-nitro-4'-methoxy-

diphenyliodonium salts, all possible products were obtained in a ratio such that it was apparent that the reaction was remarkably insensitive to substituent effects, solvent effects, catalysts, and anions. It was also observed that acid depressed the rate of both the catalyzed and the uncatalyzed reaction when the catalyst was cupric ion. In order to determine what copper species was catalyzing the reaction, two experiments were performed. First, the kinetics of the reaction in the presence of Cu(I), formed in solution from a solution of cupric chloride reduced with acetone (26) with added acid were compared with the same reaction in the presence of cupric ion and added acid. It was observed that the reaction containing Cu(I) was not retarded by acid significantly whereas that containing cupric ion was retarded in the usual way. Second, a Cu(I) chelating agent, cuproin (2,2'-biquinoline) was added to the hydrolysis of an iodonium salt in aqueous ethanol in the presence of cupric chloride. A control experiment showed good first order kinetics while the rate of the reaction in the presence of cuproin was almost completely suppressed. These experiments leave very little doubt that the sole catalyst in these reactions is Cu(I). The only explanation for the apparent catalysis by cupric ion is that it is so rapidly reduced in the solution, that no induction period can be observed.

To account for the insensitivity of this reaction to substituents and solvent, Roberts proposed a radical mechanism for the hydrolysis of diaryliodonium salts as follows:

$$RI^{+}R + 2H_2O \rightleftharpoons R_2IOH + H_3O^{+}$$

$$R_2IOH \longrightarrow RI + \overline{R\cdot + \cdot OH}$$

$$\longrightarrow \overline{RI\cdot R + \cdot OH}$$

$$\longrightarrow \overline{(R\cdot + RI\cdot OH)}$$

The catalysis by cuprous ion is explained by:

$$RI^{+}R + Cu(I) \longrightarrow \overline{RI\cdot R + Cu(II)}$$

$$\overline{RI\cdot R + Cu(II)} + 2H_2O \longrightarrow RI + ROH + Cu(I) + H_3O^{+}$$

The lack of substituent effect observed by Roberts makes the mechanism proposed by Beringer an unlikely one. This mechanism involves some sort of nucleophilic attack. Whether it is on the proposed conjugate base VI or on any of the other proposed intermediates, one would expect some sort of substituent effect. The lack of any effect in hydrolysis is unexpected in view of the fact that the reaction with chloride ion shows a definite increase in rate with more electron withdrawing groups. The fact that the reaction with chloride is also catalyzed by copper salts and retarded by acid would lead one to believe that this reaction proceeded by a similar mechanism to hydrolysis. Since the work of Roberts involved only 3 substituents, it would be interesting to study the hydrolysis of a number of substituted diphenyliodonium salts to make sure that there is no substituent effect at all.

[illegible] possible products [illegible] leaves no [illegible] that [illegible] appears that the [illegible] remarkably [illegible] substituent effects, [illegible] catalysts [illegible] [illegible] to conserved that acid dependence [illegible] order of both [illegible] of the nucleophilic reaction when the reaction was [illegible] [illegible] be what copper species was causing [illegible] case [illegible] performed. First, the kinetics [illegible] the [illegible] of $Cu(I)$, formed in solution from a [illegible] [illegible] reacted with acetone in [illegible] added [illegible] same reaction in the presence of [illegible] [illegible] and [illegible]. It was observed that the reaction catalyzing [illegible] $Cu(I)$ [illegible] and significantly observes that reaction [illegible] [illegible] to the usual [illegible]. Second, [illegible] $Cu(I)$ [illegible] [illegible] has added to the [illegible] [illegible] with [illegible] ethanol in the presence [illegible] of [illegible] experiments showed good first order [illegible] [illegible] the rate of the reaction in the presence of copper [illegible] [illegible] apparently supposed. These experiments [illegible] [illegible] [illegible] that the sole catalyst in these reactions is $Cu(I)$. [illegible] [illegible] for the apparent catalysis by copper ion is that [illegible] [illegible] reduced in the solution, that no induction period [illegible] [illegible].

[illegible] for the necessarily of this reaction to substituents and [illegible], Roberts, proposed a radical mechanism for the type of [illegible] with as follows:

$$[illegible] + H_2O \longrightarrow R_2IOH + H_3O^+$$

$$[illegible] \longrightarrow [illegible] + [illegible]$$

$$[illegible] \longrightarrow [illegible]$$

$$[illegible] \longrightarrow [illegible]$$

The catalysis by [illegible] ion is explained by

$$[illegible] \longrightarrow [illegible]$$

$$[illegible] + 2H_2O \longrightarrow RI + ROH + [illegible] + H_3O^+$$

The [illegible] substituent effect observed by Roberts makes the mechanism proposed by [illegible] an unlikely one. This mechanism involves some sort of nucleophilic attack. Whether it is on the proposed [illegible] [illegible] [illegible] or on any of the other proposed intermediates, one would expect some sort of substituent effect. The lack of any effect is [illegible] in unexpected in view of the fact that the [illegible] with [illegible] ion among a detailed interest in [illegible] with more electron withdrawing groups. The fact that the reaction with chloride is [illegible] catalyzed by copper salts and promoted by acid would lead one to believe that this reaction proceeded by a mechanism [illegible] by hydrolysis. Since the work of Roberts involved only [illegible] substituents, it would be interesting to study the hydrolysis of a number of substituted diphenyliodonium salts to make sure that there is no substituent effect at all.

Another difficulty with Beringer's mechanism is that the catalysis by cuprous ion, which was proposed, does not fit the observation that acid fails to suppress the rate when cuprous ion is the catalyst. For this reason the proposed CuOH species cannot be the attacking species. On the basis of the observed data, it is clear that the mechanism proposed by Roberts more closely explains the observations.

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KINETICS AND MECHANISM OF AMINOLYSIS OF ESTERS

Reported by D. Tuleen May 9, 1960

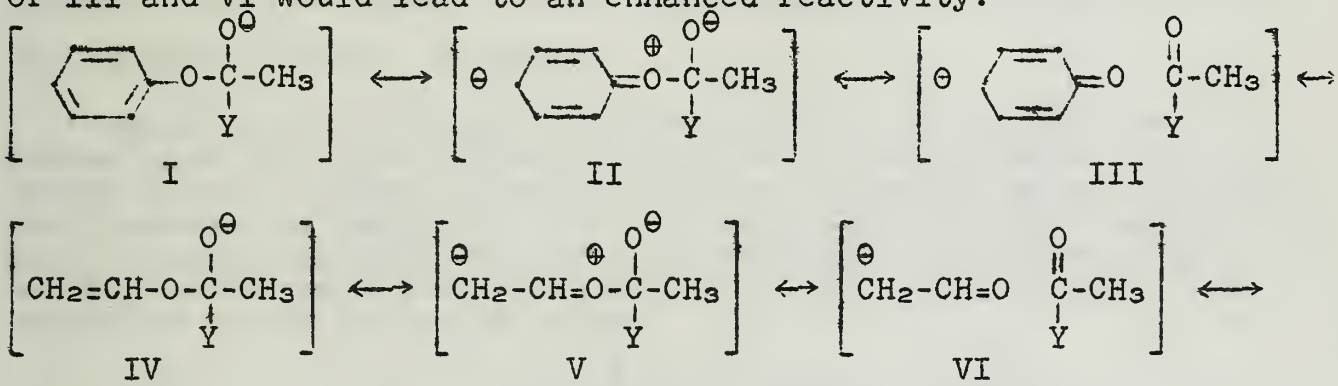
INTRODUCTION:

Mechanisms for the hydrolysis of esters have been well catalogue and reviewed.[1] The reversible reaction of esters with ammonia or amines to form amides necessarily involves acyl oxygen cleavage, and exhibits structural and substituent effects similar to those encountered in hydrolysis. Both reactions are accelerated by electron withdrawing groups and retarded by electron donors. Because of these similarities, aminolysis has often been assumed to be analogous to ester hydrolysis, and relatively few accurate kinetic and mechanistic studies of aminolysis have been carried out.

Studies of ammonolysis have established a relative reactivity series for the reaction of ammonia with acetates, CH_3COOR:[2,3]

R = phenyl > vinyl > methyl > benzyl > ethyl > n-propyl > n-butyl > s-butyl; t-butyl

Inductive effects explain this sequence. The rapid rate of phenyl and vinyl acetates can also be explained by resonance stabilization of the transition state. Structures such as II and V may be more important in a transition state than in the ester; the contribution of III and VI would lead to an enhanced reactivity.



Changes in the acid portion of the ester, due to its proximity to the reaction site, have a greater effect on reactivity. A relative reactivity sequence for the ammonolysis of methyl esters, $RCOOCH_3$, is the following:[2]

$RCOO^-$ = formate >> acetate > phenylacetate > propionate > benzoate > i-butyrate >> pivalate

This order is in agreement with both inductive and steric considerations. The significance of steric retardation can be demonstrated by Table I., which lists the relative rates for a portion of the above series.

Examination of substituent effects in the ammonolysis of substituted ethyl benzoates[4,5] has established the same relative reactivity that exists in hydrolysis,[6] and a Hammett plot of positive slope.

Table I

Ester	Rel. rate of ammonolysis
$CH_3-\overset{O}{\overset{\|\|}{C}}-OCH_3$	340
$CH_3-CH_2-\overset{O}{\overset{\|\|}{C}}-OCH_3$	192
$CH_3-\underset{\underset{CH_3}{\|}}{CH}-\overset{O}{\overset{\|\|}{C}}-OCH_3$	60
$CH_3-\underset{\underset{CH_3}{\|}}{\overset{CH_3}{\overset{\|}{C}}}\leftarrow\overset{O}{\overset{\|\|}{C}}-OCH_3$	1

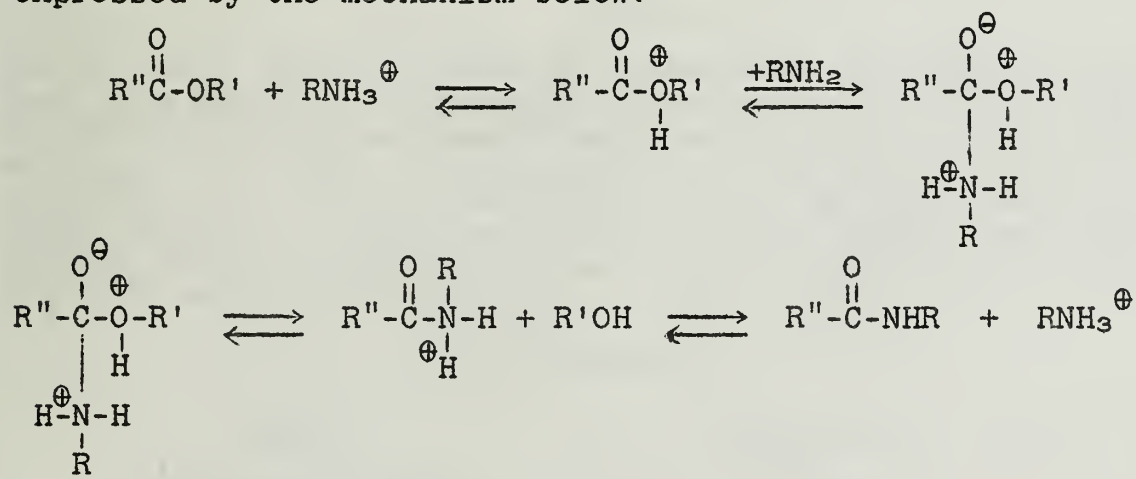
The rate of aminolysis is dependent also upon the nature of the amine. Alkyl substituents will increase the basicity of the amine, but will also increase the steric barrier toward nucleophilic attack. Aminolyses with primary amines display a relative reactivity sequence:[7]

Amine:	methyl	ethyl	n-butyl	n-propyl	i-butyl	ammonia	s-butyl
rel. rate:	100	13	12.4	10.3	5.1	1.6	0.27

Secondary amines react considerably less readily than do primary amines;[8] tertiary amines cannot react with esters to form amides.[9]

II. KINETIC STUDIES IN AMINES:

Ammonolysis of esters in liquid ammonia, and aminolysis in amines have been found to be pseudo first order in ester. The conjugate acids of these solvents, ammonium and amine salts, accelerate the formation of amide.[10,11,12] Although this catalysis has not been clearly distinguished from salt effects, it is conceivable that aminolysis in amine could parallel acid hydrolysis in water,[5] as expressed by the mechanism below:



III. SOLVENT EFFECTS:

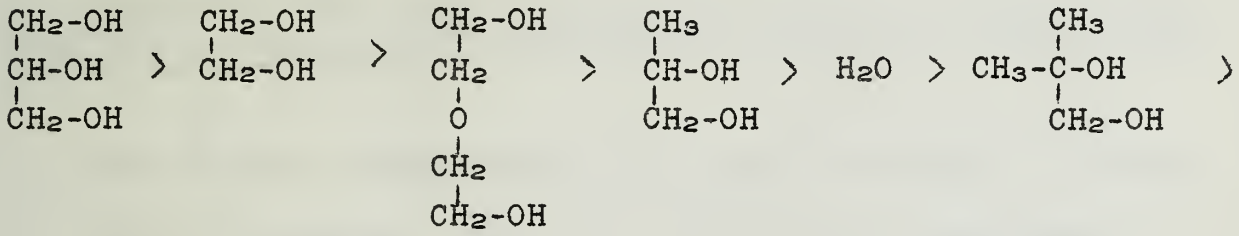
In general, simple esters will not react with ammonia or amines at a practical rate in the absence of catalysis. Glasoe, Scott and

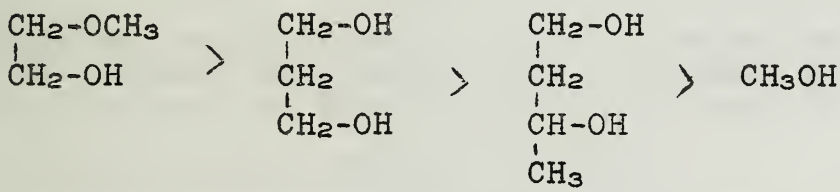
Audrieth[13] found that water increased the rate of aminolysis of ethyl phenylacetate in n-butyl amine. This effect can be explained by an equilibrium in which a small amount of the N-alkyl ammonium ion is formed:

$$RNH_2 + H_2O \rightleftharpoons RNH_3^{\oplus} + OH^{\ominus}$$

This explanation accounts for the observations that water catalysis is not as effective per mole as is catalysis by the amine salt and that catalysis by water occurs even beyond the point where the ratio of concentrations of water:amine exceeds unity.

Investigations of the catalytic effects of hydroxylated solvents other than water on aminolysis carried out by Miller, Day, and co-workers[14,15,16] led to a practical synthetic route for the preparation of amides under anhydrous conditions. The ammonolysis of methyl acetate in dioxane proceeds at a very slow rate. Kinetics were run on solutions containing water (10 M.), ester (0.7 M.), ammonia (2.5 M.), and added hydroxylated solvent (5 M.) in dioxane. The reaction was erroneously assumed to be second order, first order in amine and in ester, and yielded rate constants which fell off with time; these constants do, however, define a qualitative relative catalytic activity sequence of various solvents which is listed below. (Water was used in this study to achieve practical rates with added solvents whose catalytic effect is slight.)





The validity of a quantitative correlation of relative rates obtained from this sequence by subtracting the rate constant for ammonolysis in aqueous (10 M.) dioxane from rates of reactions with added solvent is doubtful. A quantitative correlation for a portion of this series can be obtained from kinetics of the ammonolysis of methyl acetate in anhydrous glycols. Here, again, the reaction was assumed to be second order; the relative rate constants listed in Table II were at 24 hours.

Table II

Solvent	Relative k (l. mole^{-1} hr.$^{-1}$)
ethylene glycol	1.0
diethylene glycol	0.68
propylene glycol	0.41
trimethylene glycol	0.05

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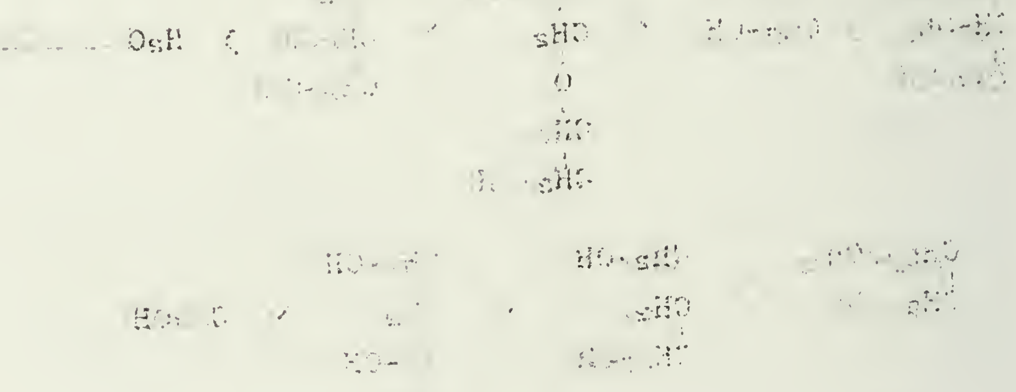

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Solvent	Dielectric [illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
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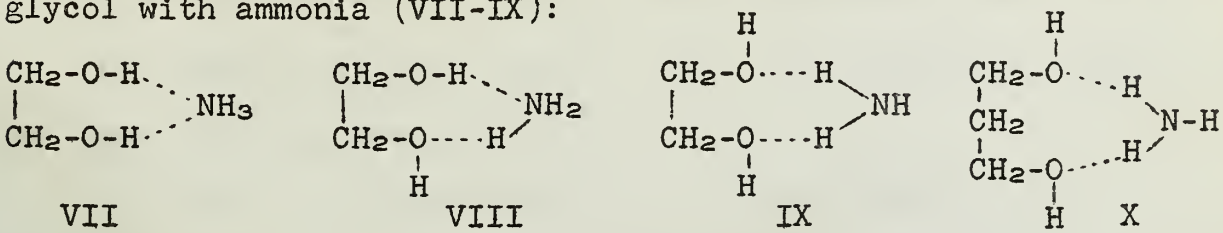
The catalytic effect of glycols may be due to a hydrogen bonded complex of solvent with amine, which increases the nucleophilicity of the attacking agent. The structure of this complex has not been proved, but, for purposes of discussion, a 1:1 complex will serve. There are three possible structures for a 1:1 complex of ethylene glycol with ammonia (VII-IX):



VII VIII IX X

Structure IX is the only one of these three which would account for an enhanced rate, as VII and VIII would tie up the unshared electron pair of nitrogen, reducing the nucleophilicity of the amine. The superior catalytic effect of 1,2 glycols to 1,3 glycols may be due to the relative stabilities of IX and X, supposing the seven membered ring to be more stable than the eight membered one. This interpretation is in agreement with spectroscopic data, which indicate that the favored ring size for cyclic structures involving hydrogen bonding is 6-7 members.[17] The superiority of 1,2 glycols also seems logical if one considers the amount of entropy needed to form the complex of the 1,3 glycol.

Watanabe feels that the catalytic effect of hydroxylated solvents is due to ester interchange, forming new esters which aminolyze more readily:[18]

$$CH_3-\overset{O}{\overset{\|}{C}}-OCH_3 + HOCH_2CH_2OH \rightleftharpoons CH_3-\overset{O}{\overset{\|}{C}}-OCH_2CH_2OH + CH_3OH$$

$$CH_3-\overset{O}{\overset{\|}{C}}-OCH_2CH_2OH + NH_3 \longrightarrow CH_3-\overset{O}{\overset{\|}{C}}-NH_2 + HOCH_2CH_2OH$$

It has been shown, however, that the ammonolysis of methyl acetate in the presence of ethylene glycol proceeds more readily than does the ammonolysis of β-hydroxy ethyl acetate.[14]

IV. EARLY KINETIC STUDIES IN ALCOHOL:

Experimentation on the kinetics of ammonolysis has established that the reaction deviates considerably from second order. Betts and Hammett[4] found the ammonolysis of methyl phenylacetate in methanol to be:

a) approximately 3/2 order in ammonia, as well as first order in ester,
b) accelerated by added methoxide, and
c) retarded by ammonium chloride in such a way that plots of the apparent second order rate coefficient vs. $1/(NH_4^+)$ were linear.

These effects can be explained by more than one mechanism, but the path most obvious to them was one which involved competing bimolecular rate determining steps in which the ester was attacked not only by ammonia, but also by the amide ion. Although the amide ion is present in low concentration, it is far more nucleophilic than ammonia.

(1) $NH_3 + NH_3 \rightleftharpoons NH_4^+ + NH_2^-$ Kam

(2) $NH_3 + CH_3OH \rightleftharpoons NH_4^+ + CH_3O^-$ K_B

(3) $C_6H_5\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}OCH_3 + NH_3 \longrightarrow C_6H_5\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH_2 + CH_3OH$ k_1

(4) $C_6H_5\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}OCH_3 + NH_2^{\ominus} \longrightarrow C_6H_5\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH_2 + CH_3O^{\ominus}$ k_2

The rate for such steps would be:

(5) $\text{rate} = k_1\ (\text{ester})(NH_3) + k_2\ (\text{ester})(NH_2^-)$

but from (1),

(6) $(NH_2^-) = \text{Kam}\ (NH_3)^2/(NH_4^+)$

so, (7) $\text{rate} = k_1\ (\text{ester})(NH_3) + k_2\text{Kam}\ (\text{ester})(NH_3)^2/(NH_4^+)$

and the specific rate, k_o, is the following:

(8) $k_o = k_1 + k_2\text{Kam}\ (NH_3)/(NH_4^+)$

Plots of this specific rate vs. $1/(NH_4^+)$ were linear at (NH_4^+) = 0.01 M. to 0.1 M., explaining the retardation by ammonium ion. Such plots yield k_2Kam from the slope; the intercept is the rate constant for the reaction of the ester with ammonia, k_1. In the absence of added ammonium ion, since $K_B \gg$ Kam,

(9) $(NH_4^+) = (CH_3O^-) = K_B^{1/2}(NH_3)^{1/2}$

(10) $\text{rate} = k_1\ (\text{Ester})(NH_3) + \dfrac{k_2\text{Kam}}{K_B^{1/2}}\ (\text{Ester})(NH_3)^{3/2}$

This explains the approximate 3/2 order in ammonia, and first order in ester which was observed. The specific rate, obtained from (10) is:

(11) $k_o = k_1 + \dfrac{k_2\text{Kam}}{K_B^{1/2}}\ (NH_3)^{1/2}$

A plot of this specific rate vs. $(NH_3)^{1/2}$ is linear, and K_B is determined from equations (8) and (11) to be 3.2×10^{-6}. Conductivit measurements place this value at 1.2×10^{-6}. However, from (9) and (11),

(12) $k_o = k_1 + \dfrac{k_2\text{Kam}}{K_B}\ (CH_3O^-)$

Using the previously determined k_2Kam and k_1, K_B may be calculated from this equation to be 6.3×10^{-5}. Thus, equation (12) accounts qualitatively for acceleration by methoxide ion, but lacks quantitative confirmation.

Watanabe and De Fonso[18] in the aminolysis of ethyl formate by n-butyl amine found a similar retardation by amine salt, which they demonstrated to be not a salt effect. They also observed strong catalysis by ethoxide ion, but were unable to correlate quantitatively its effect. They emphasized the possibility of other mechanisms, but found the best correlation of their data in terms of the mechanism of Betts and Hammett which has come to be generally accepted.

V. RECENT MECHANISTIC STUDIES:

The results of the previous investigators are also compatible with a mechanism involving general base catalysis:

$$(13)\quad R''COOR' + RNH_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R''COOR'\cdot RNH_2$$

$$(14)\quad R''COOR'\cdot RNH_2 \xrightarrow{k_2} R''CONHR + R'OH$$

$$(15)\quad R''COOR'\cdot RNH_2 + B \xrightarrow{k_3} R''CONHR + R'OH + B$$

Employing the steady-state approximation, the rate for such a process would be:

$$(16)\ \text{rate} = \left\{\frac{k_1k_2 + k_1k_3(B)}{k_{-1} + k_2 + k_3\ (B)}\right\} (R''COOR')(RNH_2)$$

and, if k_{-1} greatly exceeds both k_2 and k_3, the denominator is simplified to k_{-1}, and,

$$(17)\ \text{rate} = \frac{k_1k_2}{k_{-1}}(\text{Ester})(RNH_2) + \frac{k_1k_3}{k_{-1}}(\text{Ester})(RNH_2)\Sigma(B)$$

With alcohol as solvent, and the amine and the conjugate base of the alcohol as the bases, the rate becomes:

$$(18)\ \text{rate} = \frac{k_1k_2}{k_{-1}}(\text{Ester})(RNH_2) + \frac{k_1k_3'}{k_{-1}}(\text{Ester})(RNH_2)(R'O^-) + \frac{k_1k_3''}{k_{-1}}(\text{Ester})(RNH_2)^2$$

With no added amine salt, since $(R'O^-) = K_B{}^1/_2(RNH_2)^1/_2$, from (9), the rate becomes, writing $\frac{k_1k_3'}{k_{-1}} = kR'O^-$ and $k_1k_3''/k_{-1} = kRNH_2$:

$$(19)\ \text{rate} = \frac{k_1k_2}{k_{-1}}(\text{Ester})(RNH_2) + k_{R'O^-}K_B{}^1/_2(\text{Ester})(RNH_2)^3/_2 + k_{RNH_2}(\text{Ester})(RNH_2)^2$$

When amine salt is present, $(R'O^-) = K_B(RNH_2)/(RNH_3{}^+)$ from (2), and:

$$(20)\ \text{rate} = \frac{k_1k_2}{k_1}(\text{Ester})(RNH_2) + k_{R'O^-}K_B(\text{Ester})(RNH_2)^2/(RNH_3{}^+) + k_{RNH_2}(\text{Ester})(RNH_2)^2$$

Bunnett and Davis (19) studied the aminolysis of ethyl formate in ethanol by n-butyl amine. In excess amine the reaction was found to be pseudo first order in ester, with a rate constant, $k\psi$.

$$(21)\quad \text{rate} = k\psi(\text{Ester}) = \frac{k_1k_2}{k_{-1}}(\text{Ester})(RNH_2) + k_{R'O^-}K_B{}^1/_2(\text{Ester})(RNH_2)^3/_2 + k_{RNH_2}(\text{Ester})(RNH_2)^2$$

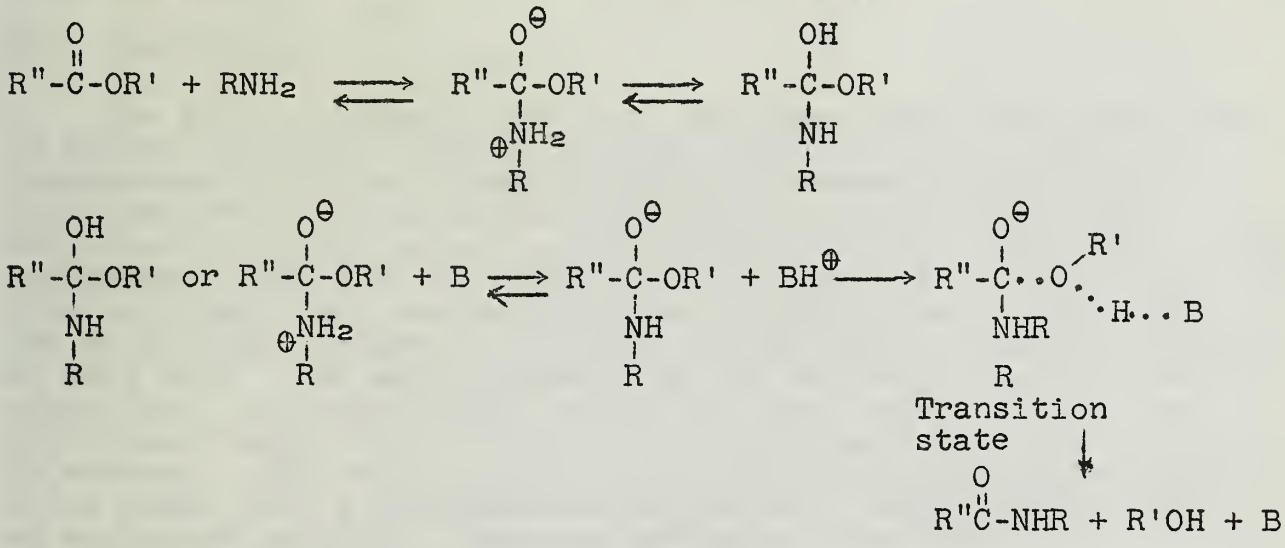
If the term first order in amine is neglected,

$$(22)\ \frac{k\psi}{(RNH_2)^3/_2} = k_{R'O^-}K_B{}^1/_2 + k_{RNH_2}(RNH_2)^1/_2$$

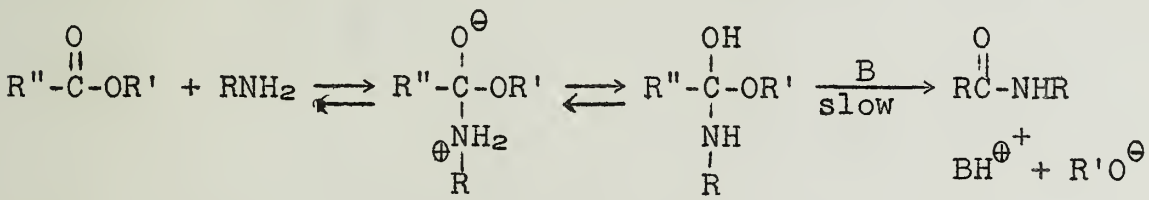
Variation in amine concentration from 0.1 to 1.0 molar at (Ester) = 0.01 M. yielded values for $k\psi$. A plot of $k\psi/(RNH_2)^3/_2$ vs.

$(RNH_2)^{1/2}$ was linear, resolving the catalyzed terms into terms three-halves and second order in amine, and confirming that in this medium, the uncatalyzed term, the term first order in amine, is of minor importance. Added ethoxide ion resulted in a decrease in the percentage yield of the aminolysis product, and formation of formate via a side reaction. The total pseudo first order rate coefficient was dissected into its components, coefficients k_A for amide formation, and k_F for formate production. A plot of k_A vs. (EtO^-) was linear, as is called for by equation (18). The addition of small amounts of n-butyl ammonium chloride at constant amine concentration had a moderate decelerating effect. The addition of RNH_3Cl should repress formation of ethoxide ion (2) and essentially eliminate the second term in (18) and (20). A gradual increase in rate coefficient with increasing salt concentration which was noted is presumably a positive salt effect on the term second order in amine in (18) and (20). A linear plot of $k\psi/(RNH_2)^2$ vs. (RNH_3^+) supports this interpretation.

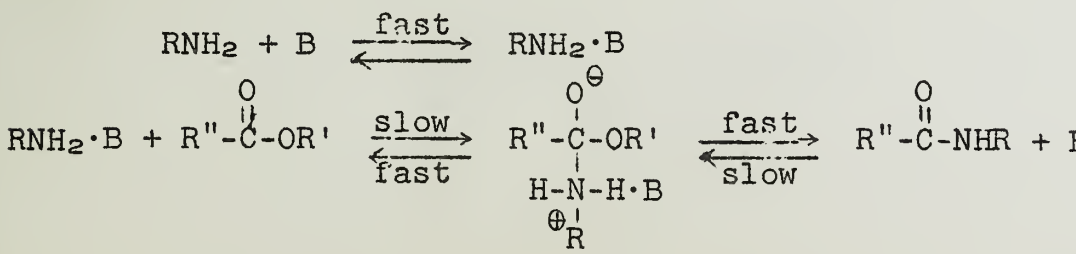
The rate law is not very specific as to what is the particular mechanism of this general base catalyzed reaction. The route which seems most consistent to Bunnett and Davis is:



The rate determining step as indicated by this mechanism seems most unlikely. A more likely mechanism would be the following:



It is also quite feasible that attack of the ester by a complex of amine and base is the slow step:



The insignificance of the uncatalyzed or solvent catalyzed term (k_1k_2/k_{-1}) x (Ester)(RNH_2) in the aminolysis of ethyl formate in ethanol would certainly not be expected to be noted in all cases. Either an increase in the basicity of the solvent or the use of an ester containing a better leaving group could make this term significant.

Experiments for establishing general base catalysis are usually designed to show that the rate is proportional to a series of catalytic constants times catalyst concentration at constant pH and ionic strength. A linear correlation, known as the Bronsted relationship, between the log of the rate constant and the log of the equilibrium constant of the base commonly exists.[20] Studies of the kinetics of aminolysis have usually shunned the use of water, to avoid possible hydrolysis complications.

A recent study[21] of the aminolysis of phenyl acetate has been made at constant ionic strength and controlled pH. It attempts to show a drastic variation in the type of catalysis exhibited by various amines. The conclusions of this study have not as yet been justified.

VI. CONCLUSION:

The work of Bunnett and Davis indicates that the aminolysis of esters is general base catalyzed. Their results cannot be interpreted in terms of the bimolecular mechanism previously accepted. The earlier mechanism does not provide for terms 3/2 and second order in amine in the absence of added amine salt. Both mechanisms agree that the addition of amine salt should effectively eliminate one term, the second terms in equations (7) and (20). The mechanisms disagree as to what should remain after elimination of this term. The earlier mechanism calls for an over-all second order term, k_1(Ester)(RNH_2), which has been shown to be of insignificant magnitude in the n-butyl aminolysis of ethyl formate in ethanol. The results of Bunnett and Davis show a term over-all third order with a superimposed salt effect, k_{RNH_2}(Ester)$(RNH_2)^2$ as explained earlier. These results make a mechanism with a bimolecular rate determining step untenable.

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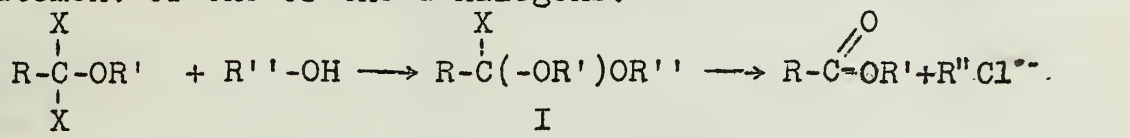
REACTIONS OF α,α-DIHALO ETHERS

Reported by C. G. Carlson May 12, 1960

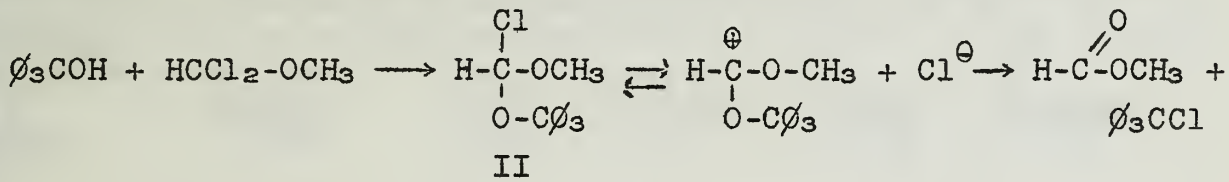
The reactions of α,α-dihalo ethers with alcohols, carboxylic acids, aldehydes and ketones have been proposed to involve the decomposition of an ortho ester analogue intermediate, I, formed by the replacement of one of the α-halogens.



Although little mechanistic work has been done, the paths of these reactions can be discussed, by comparison with other reactions in which a compound of type I is either a reactant, or thought to be an intermediate.

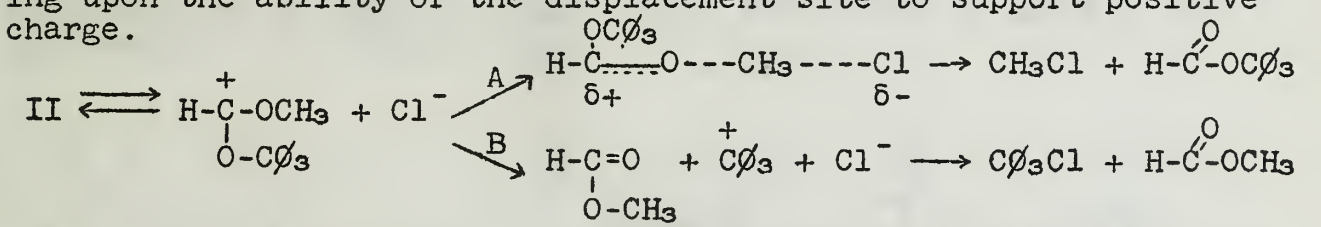
Reaction of α,α-Dihalo ethers with Alcohols

When an arylcarbinol was mixed with a small excess of dichloromethyl methyl ether in the presence of 0.1% $ZnCl_2$, a good yield of the corresponding arylcarbinylhalide (benzylchloride 69%, diphenylmethylchloride 84%, tritylchloride 94%) along with methylformate, was obtained.[1] It was proposed that the reaction involved intermediate II. It is further suggested that II then dissociates, and the observed products result from a chloride ion attack on the carbonium ion.



The formation of II is not unreasonable, since the displacement of the halogen in α-halo ethers by nucleophilic reagents is well known.[2] The dissociation of II would be facilitated by the stability of the dialkoxyl carbonium ion. For comparison, the ionic dissociation of II would seem to be more facile than the first-order ethanolysis of chloromethyl methyl ether to form ethoxymethyl methyl ether in various ethanol- diethyl ether solvent mixtures,[3] since in the latter case, a carbonium ion stabilized by only one alkoxyl group is formed.

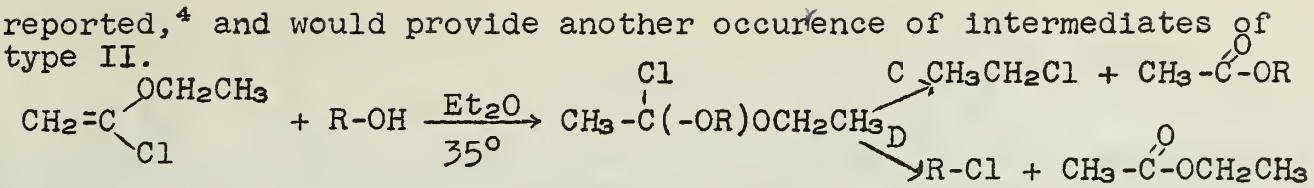
The last step would be displacement by chloride ion at either the methyl or benzylic carbon. The nature of the displacement could be best described as Lim with varying degrees of N character, depending upon the ability of the displacement site to support positive charge.



The observed products indicate that the rate along Lim path B, is faster than that along path A, which would be expected to have more N character for the particular substituents shown.

The reaction of 1-chlorovinyl ethyl ether with alcohols has been

reported,[4] and would provide another occurence of intermediates of type II.



R	% Yield $CH_3-\overset{O}{\overset{\|\|}{C}}-OR$ (path C)	% Yield RCl (path D)
benzyl	21	52
cyclohexyl	56	-
trityl	-	69
phenyl	40	-

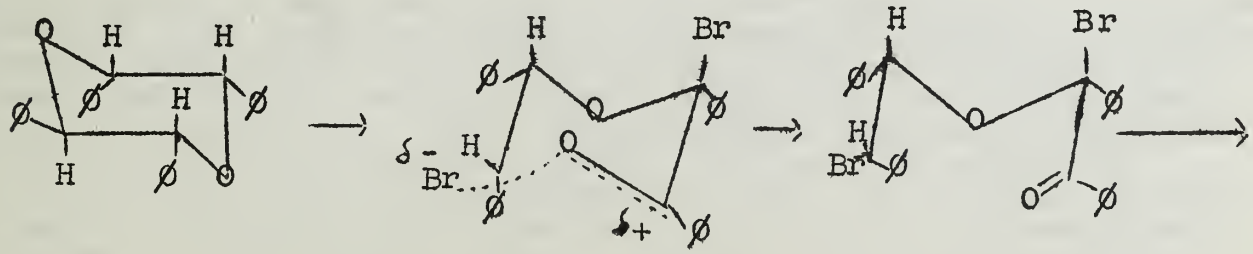
Again, products arising from the most facile Lim attack are observed.

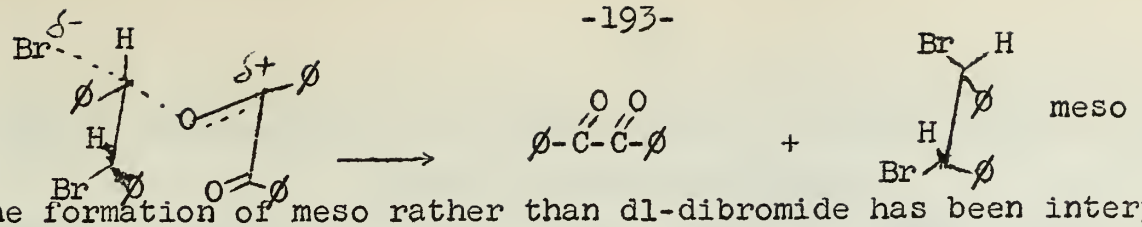
More qualitative results have been reported on the reaction of 1,2-dichlorovinyl ethyl ether with various alkyl (R=isoamyl, heptyl and menthyl) alcohols where path C was found to predominate, and little ethylchloroacetate (path D) was reported in each case. Also, methanol reportedly gave both paths C and D, while phenol gave path D products only.[5] The value of these results is limited because the reaction conditions are not reported in detail, but they may give an indication of the selectivity of the chloride ion attack on a di-alkoxyl carbonium ion. The displacements at primary alkyl sites would have some N character, and thus steric effects would become operative, explaining the preference of attack at ethyl compared to longer chain alkyl groups. The following relative second-order rates of replacement of primary iodide by phenoxide ion in ethanol at 42.5° show the same trend,[6] and are perhaps mechanistically similar to the backside attack of chloride ion.

R	methyl	ethyl	n-propyl	n-butyl	n-heptyl
relative rate	4.84	1.00	0.4	0.39	0.35

1,2,2-Trichlorovinyldiethylamine has been found to react with sec-butyl alcohol at 40°-50° to give sec-butylchloride (81%), and N,N-diethyl-2,2-dichloroacetamide (92%).[7] The reaction was proposed to proceed by a path analogous to the reaction of a 1-chlorovinyl-ether and an alcohol. Good evidence is provided for backside attack of chloride ion, since, when d-sec-butylalcohol (α_D+13.89) was used, l-sec-butylchloride (84%) (α_D-31.05) of opposite configuration[8] was obtained, with an estimated maximum racemization of 8%.[7]

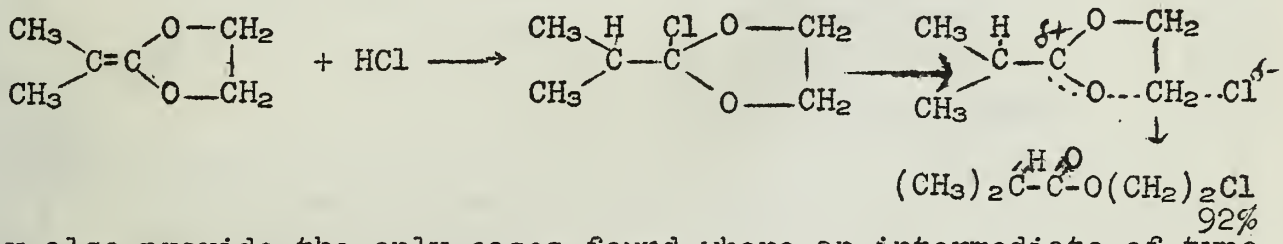
It has also been observed that 2,3-dibromo-2,3,5,6-tetraphenyl-p-dioxane obtained from the bromination of cis-2,3,5,6-tetraphenyl-p-dioxene, rearranged to benzil and meso stilbenedibromide,[9] which is what would be expected from a backside attack of bromide ion on the intermediate carbonium ion.



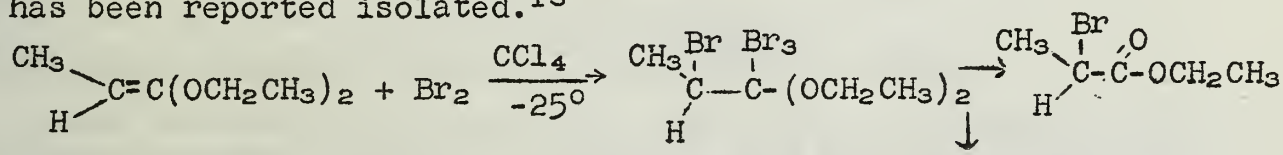


The formation of meso rather than dl-dibromide has been interpreted[10] as indicating a series of two Sni reactions. However, any conclusions must be drawn with caution since under various conditions dl-stilbenedibromide will equilibrate to the meso compound.[11]

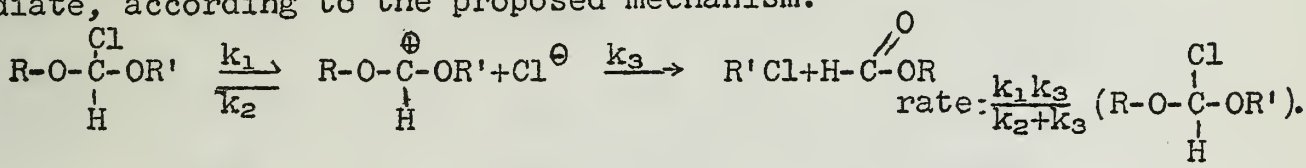
The reactions of a halogen or halogen acid with a ketene acetal provide another route to an intermediate of type II.[12]



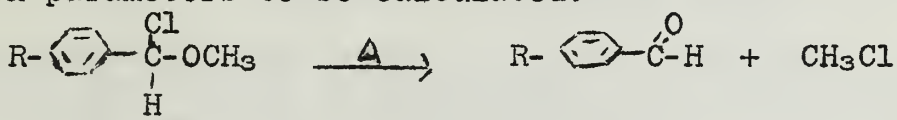
They also provide the only cases found where an intermediate of type II has been reported isolated.[13]



The kinetic order of the displacement reaction undergone by intermediate II would be expected to be first order in the intermediate, according to the proposed mechanism.



A reaction which would be mechanistically similar is the thermal decomposition of α-methoxybenzylchloride to give methyl chloride and benzaldehyde, since upon dissociation, a chloride ion and a carbonium ion, stabilized by a methoxyl group, are formed. The decomposition showed first order kinetics, and reported half-times for p-substituted-α-methoxybenzylchlorides at different temperatures enable activation parameters to be calculated.[14]

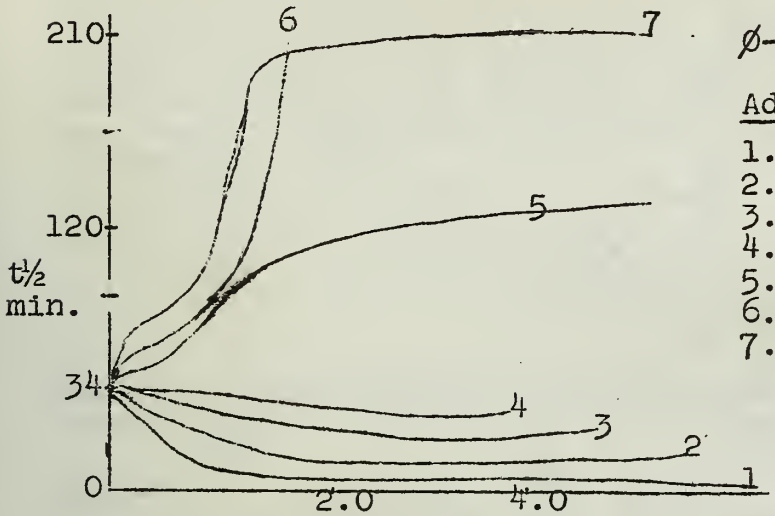


R	NO_2	Cl	H	CH_3	OCH_3	
$t_{1/2}$ @ 120°, minutes	400	94	34	14	1	no solvent
Δ H‡ k.cal./mole	21	28	20	21	17	
Δ S‡ e.u.	-26	-4	-25	-21	-25	

The reaction at 120° was found to follow σ^+ fairly well, with a rho of -1.85. The positive charge in the transition state is probably greater than indicated by the rho value, since the methoxyl group could stabilize the positive charge making the role of the para substituents smaller. Also, an appreciable solvent effect on the reaction rate was found (see graph). The solvent could also stabilize the charge in the transition state, and account for the negative entropy of activation by being frozen by the separated charges in the transition state. The data of the decomposition are in agreement with a mechanism involving dissociation to a

chloride ion and carbonium ion, and as such lend support to a similar mechanism for the decomposition of intermediates of type II.

Effect of added Substances



$$\phi\text{-}\underset{Cl}{\overset{H}{C}}\text{-}OCH_3 \xrightarrow{120^\circ} \phi\text{-}\overset{O}{\overset{\|}{C}}\text{-}H + CH_3Cl$$

Additive	Dielectric Constant (20°).[15]
1. sym-tetrachloroethane	(8)
2. benzaldehyde	(17)
3. benzonitrile	(26)
4. nitrobenzene	(36)
5. bromobenzene	(5.5)
6. xylene	(2.6)
7. di-n-pentyl ether	(2.3)

Reaction of α,α-Dihalo ethers with Carboxylic acids.

The reaction of an α,α-dihalo ether with a carboxylic acid yields the corresponding acid chloride, and has been suggested[1,16] to involve the decomposition of an intermediate 1-chloro-1-alkoxylester III. The following mechanism can be written.

$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}OH + R'\text{-}CCl_2\text{-}OCH_2R' \longrightarrow HCl\uparrow + R'\text{-}\underset{O\text{-}CH_2R'}{\overset{Cl}{C}}\text{-}O\text{-}\overset{O}{\overset{\|}{C}}\text{-}R \quad \text{III}$$

$$\text{III} \rightleftharpoons R'\text{-}\overset{\oplus}{C}(O\text{-}\underset{\underset{O}{\|}}{C}\text{-}R)\text{-}O\text{-}CH_2R' + Cl^{\ominus}$$

$$\xrightarrow{A} R\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}\overset{O}{\overset{\|}{C}}\text{-}R + R'\text{-}CH_2Cl$$

$$\xrightarrow{B} R\text{-}\overset{O}{\overset{\|}{C}}\text{-}Cl + R\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}CH_2R'$$

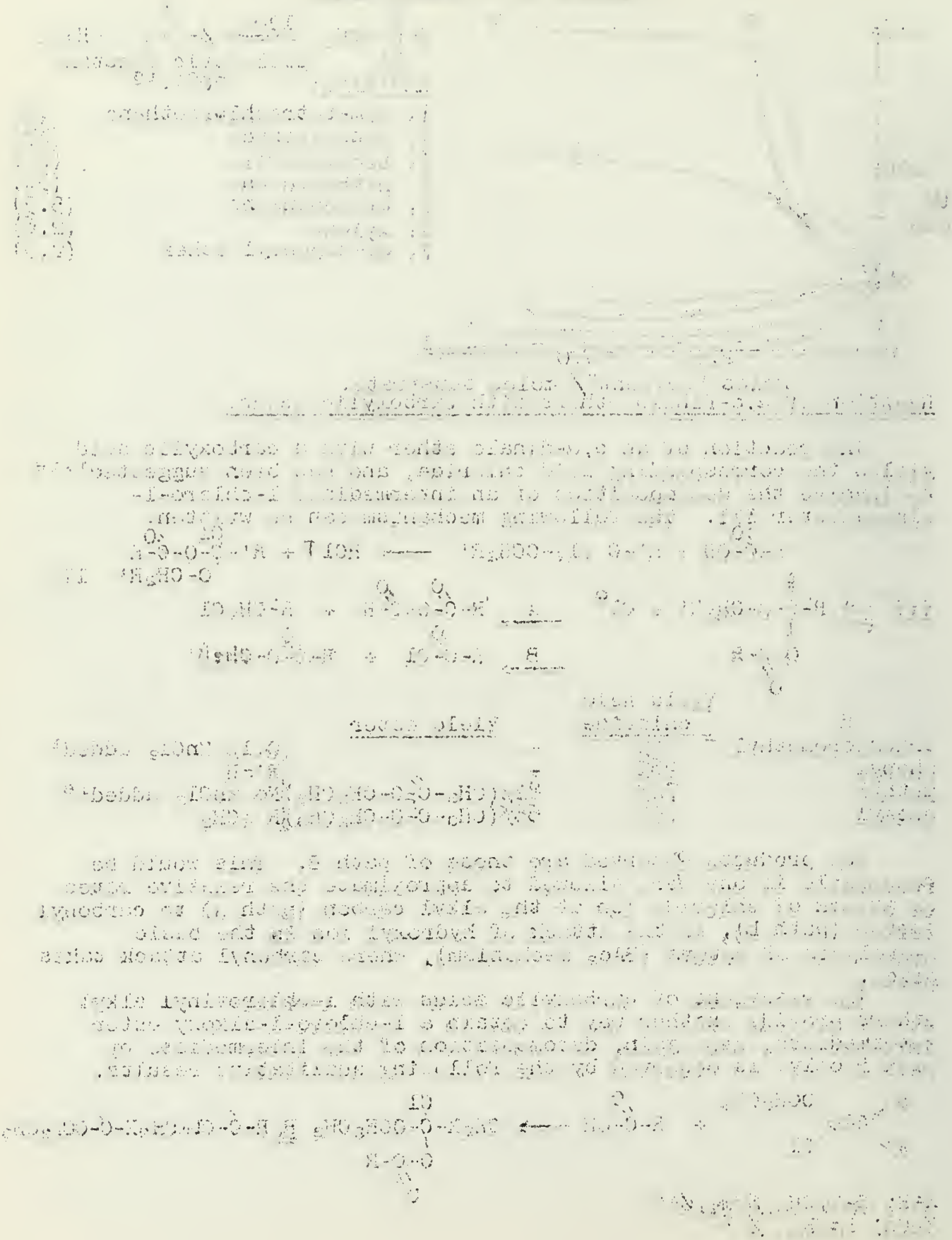
R	Yield Acid chloride	Yield ester	
trichloromethyl	88%	-	0.1% $ZnCl_2$ added[1]
phenyl	96%	-	R'=H
methyl	72%	82% ($CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}CH_2CH_3$)	No $ZnCl_2$ added[16]
phenyl	85%	68% ($CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}CH_2CH_3$)	R'=CH_3

The products observed are those of path B. This would be reasonable if one were allowed to approximate the relative rates of attack of chloride ion at the alkyl carbon (path A) to carbonyl carbon (path B), to the attack of hydroxyl ion in the basic hydrolysis of esters (BAc_2 mechanism), where carbonyl attack takes place.

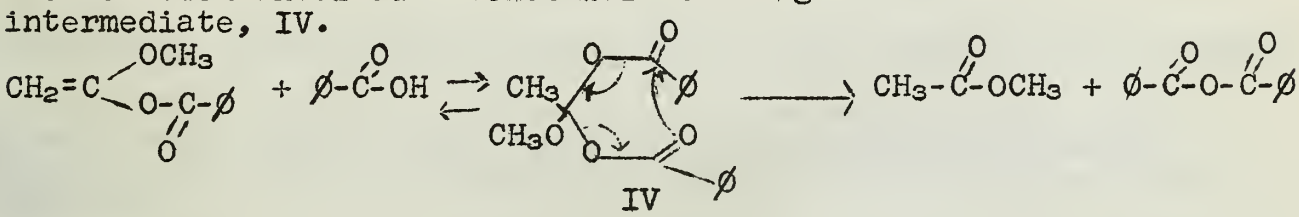
The reactions of carboxylic acids with 1-chlorovinyl alkyl ethers provide another way to obtain a 1-chloro-1-alkoxy ester intermediate, and again, decomposition of the intermediate by path B only, is observed by the following qualitative results.

$$\begin{matrix} H \\ X \end{matrix}\!\!>C=C<\!\!\begin{matrix} OCH_2CH_3 \\ Cl \end{matrix} + R\text{-}\overset{O}{\overset{\|}{C}}\text{-}OH \longrightarrow CH_2X\text{-}\underset{\underset{O}{\|}}{\overset{Cl}{C}}(O\text{-}C\text{-}R)\text{-}OCH_2CH_3 \xrightarrow{B} R\text{-}\overset{O}{\overset{\|}{C}}\text{-}Cl + CH_2X\text{-}\overset{O}{\overset{\|}{C}}\text{-}OCH_2CH_3$$

X=H; R=H, CH_3, ϕCH_2, ϕ[18]
X=Cl; R=CH_3, ϕ[5]

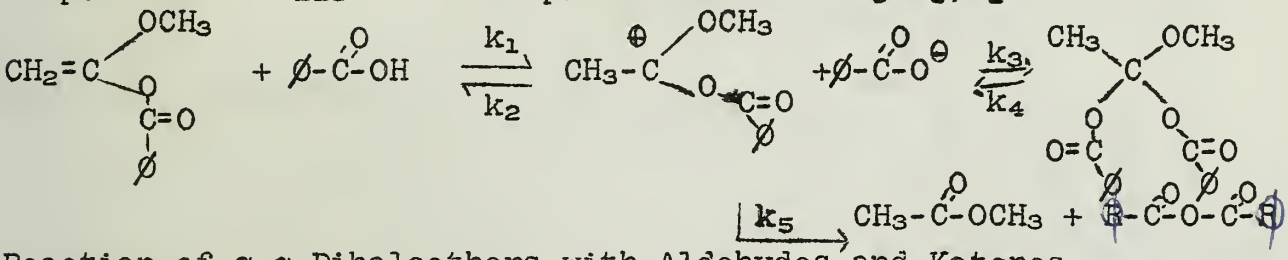


The reaction of 1-methoxyvinyl benzoate with benzoic acid to form methyl acetate and benzoic anhydride would be suspected to proceed by a mechanism similar to that proposed for the decomposition of intermediate III. When oxygen labelled benzoic acid (1.26 atom % O^{18} per oxygen) was mixed with four molar equivalents of unlabelled 1-methoxyvinylbenzoate, methyl acetate with 0.59 atom % O^{18} per oxygen, in the carbonyl oxygen was obtained.[19] The high activity in the ester carbonyl oxygen led to the conclusion that the reaction involved a molecular rearrangement of a diester intermediate, IV.



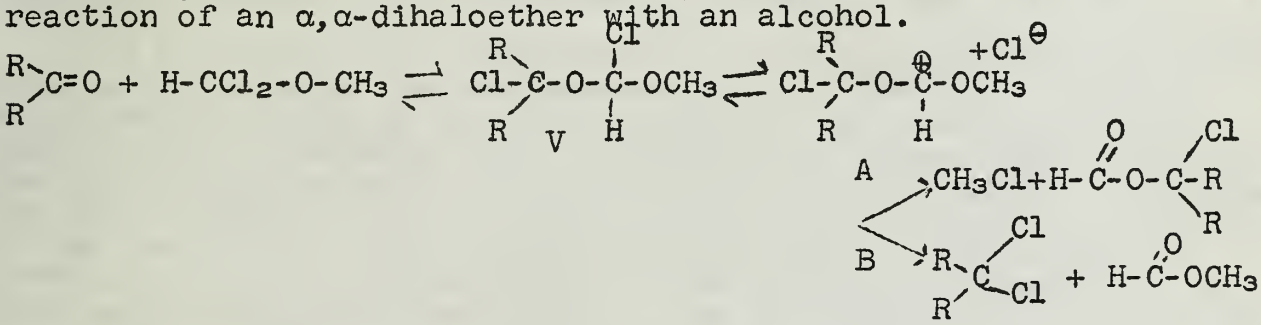
IV

However, these results are in agreement with a path similar to decomposition of III with the provisions that $k_3 > k_5 > k_2$.



Reaction of α,α-Dihaloethers with Aldehydes and Ketones.

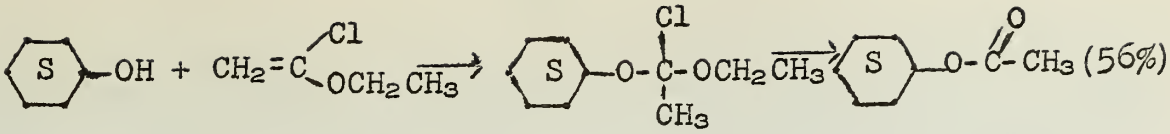
Dichloromethyl methyl ether was shown to react with aldehydes and ketones in the presence of 0.1% $ZnCl_2$ to form gem-dichloro compounds.[1] The reaction can be formulated involving an intermediate V, similar to II which was proposed to be involved in the reaction of an α,α-dihaloether with an alcohol.



Starting material	Product	% Yield
1. benzaldehyde	α,α-dichlorotoluene	97%
2. benzophenone	diphenyldichloromethane	90%
3. acetone	2,2-dichloropropane	65%
4. cyclohexanone	1-chlorocyclohexene	73%
5. acetophenone	1-chlorostyrene	74%

The predominance of path B could be explained by the Lim nature of the final displacement by chloride ion, since path B involves displacement on an arylcarbinyl or secondary carbon, path A, a methyl group.

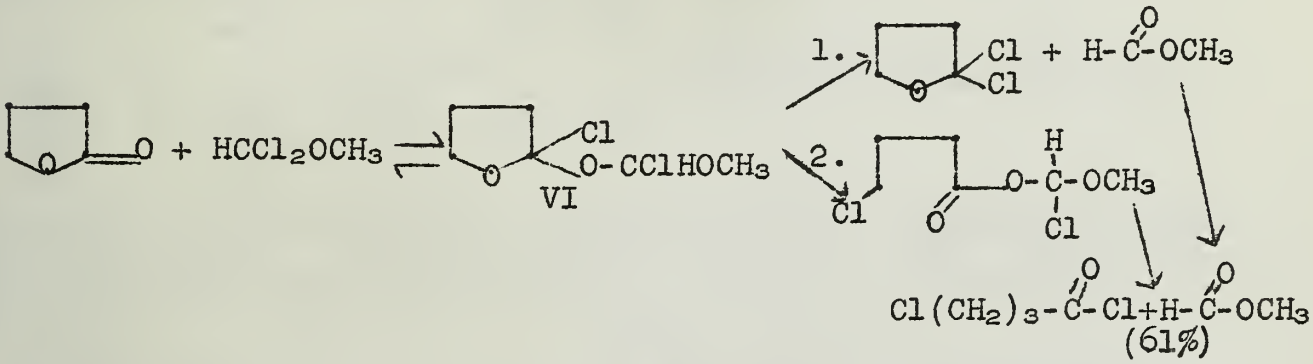
Previously, it had been mentioned that in refluxing diethyl ether, 1-chlorovinyl ethyl ether reacted with cyclohexyl alcohol to form cyclohexyl acetate in 56% yield, which would indicate a predominance of attack at the ethyl carbon.



In case four above, there is a predominance of chloride ion attack at chlorocyclohexyl, rather than methyl. In general, the rate of displacement in Lim reactions is increased by an alpha halogen,[20,21] and would explain this apparent change in the site of chloride ion attack.

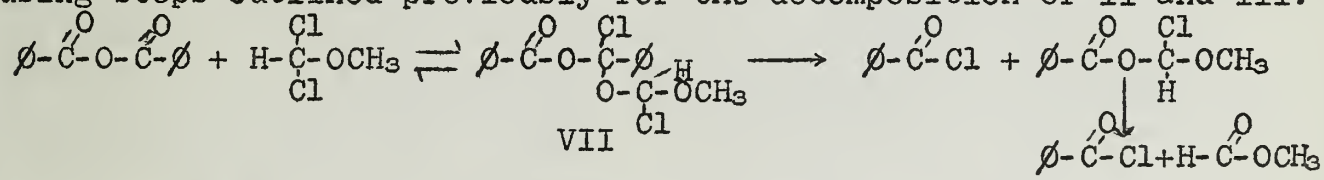
Reaction of Dichloromethyl methyl ether with Anhydrides and Lactones.

In the only case studied, α,α-dichloromethyl methyl ether reacted with butyrolactone to yield α-chlorobutyrylchloride.[1] The reaction could be formulated as follows using steps outlined previously.



Assuming the reaction involves the intermediate diether VI, there are two probable ways the intermediate could decompose to form the observed products. Path two could be favored, since it would initially involve a tertiary alkoxyl carbonium ion.

The reaction of α,α-dichloromethyl methyl ether with anhydrides gives good yields of the corresponding acid chlorides. Using a slight molar excess of the dihalo ether in the presence of 0.1% $ZnCl_2$, benzoic anhydride gave a 98% yield of benzoylchloride, while succinic anhydride gave succinoylchloride in 96% yield.[1] Mechanisms for these reactions can be written incorporating first the addition of the elements of dichloromethyl methyl ether to the anhydride carbonyl, and then decomposition of the resulting intermediate VII, using steps outlined previously for the decomposition of II and III.

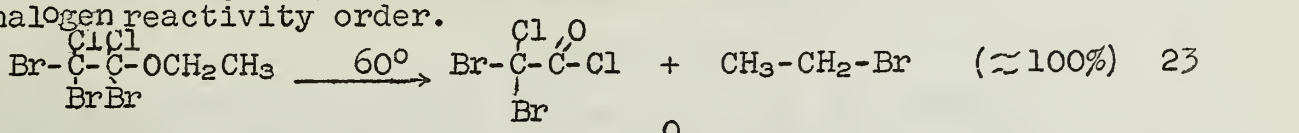


However, if the reaction involved intermediate VII, there are several paths for subsequent decomposition and one cannot say with assurance which would be the more probable. The path shown above, using benzoic anhydride as an example, was chosen because it involves dissociation to a stabilized carbonium ion and attack at carbonyl which was shown previously to appear faster than chloride attack at an alkyl carbon.

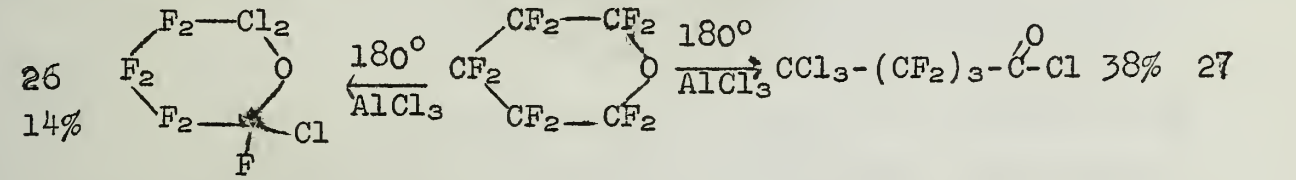
Thermal Reaction of α,α-Dihalo Ethers

The thermal reaction of α,α-dihalo ethers to form alkyl halides and ~~aldehydes~~ acid halides has not been studied in detail. However, it

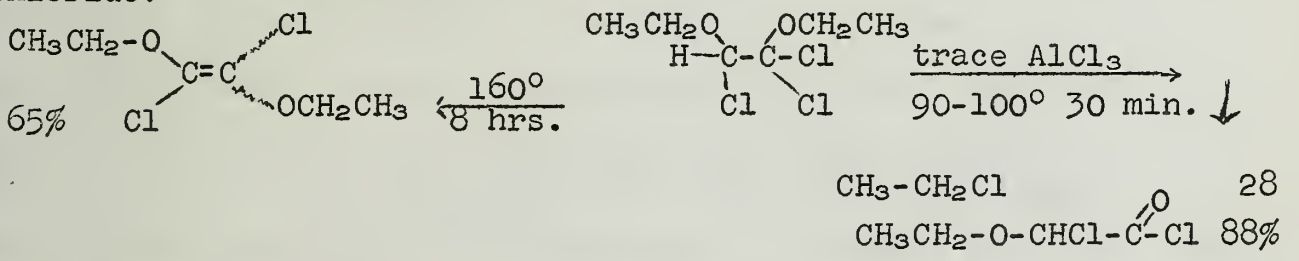
is known that halogen migration follows the order iodo > bromo > chloro > fluoro. This is partly deduced from the fact that chloro- and bromo-dimethyl ether are stable at room temperature, whereas iodomethyl methyl ether gives formaldehyde and methyl iodide.[22] The following competition experiments provide the rest of the halogen reactivity order.



Perfluoro ethers are thermally very stable and react only under very stringent conditions (800° over sodium fluoride pellets).[25] In the presence of aluminum chloride, perfluoro ethers do split, after prior α-substitution has taken place.



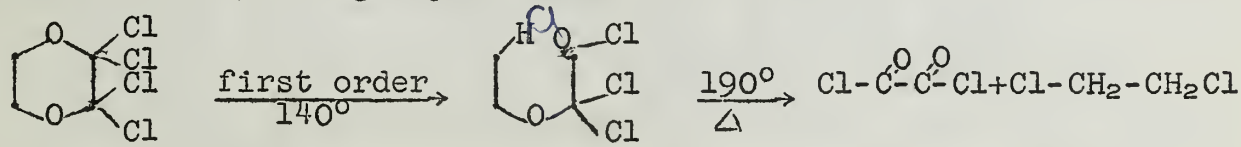
α,α-Dihalo ethers with beta-hydrogens thermally dehydrohalogenate to vinyl ethers. In the presence of $AlCl_3$, at lower temperatures, the otherwise stable ether gives an alkyl halide and an acid chloride.



On the other hand, 1-halovinyl ethers react readily with halogen acids to give α,α-dihaloethers and no alkylhalide or acid chloride. For example, hydrogen bromide and 1-bromovinyl ethyl ether in refluxing diethyl ether gave α,α-dibromoethyl ethyl ether (62%).[29]

The action of aluminum chloride could be interpreted as assisting the abstraction of an α-halogen, thus lowering the reaction temperature required, and keeping the hydrogen chloride in solution allowing a reversal of any reaction to form vinyl ether. In this way the concentration of the intermediate halo alkoxyl carbonium ion available for reaction to the alkyl halide and acid chloride, is greater.

Few kinetics have been run on the thermal decomposition of α,α-dihaloethers to acid chlorides. The decomposition of 2,2,3,3-tetrachloro-p-dioxane has been shown to involve two steps, the rate of the first step being reported first-order.[30]



Also, tetrachloroethylene oxide decomposes to trichloroacetyl chloride in a first order reaction.[31]

The order of reactivity of the halogens, and the catalytic action of aluminum chloride are consistant with a mechanism involving formation of a carbonium ion, followed by attack of the halide on the alkyl carbon.

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HYDROBORATION

Reported by N. S. Rajan May 16, 1960

The term "hydroboration" has been recently applied to the addition of borane or substituted borane to unsaturated compounds, in analogy with hydrohalogenation. The resulting compounds, generally known as organoboranes, readily undergo oxidation to give the corresponding alcohols. No special equipment is needed and the reaction conditions are mild. Moreover working with diborane poses no hazard since the reagent is not handled directly. The organoboranes also exhibit interesting isomerization under certain conditions, opening a new synthetic method for many compounds. This seminar mainly deals with the organoboranes derived from olefins and substituted olefins, with particular reference to their preparation, important reactions and their usefulness as intermediates in synthesis.

The addition of a B-H compound to a carbon-carbon double bond is quite a general reaction (1). Addition of diborane to the carbon-oxygen double bond has long been known (2), and addition to C≡N has been recently discovered (3):

$$\text{C=C} + \text{H-B}\langle \longrightarrow \text{H-C-C-B}\langle$$

$$\text{C=O} + \text{H-B}\langle \longrightarrow \text{H-C-O-B}\langle$$

$$\text{-C}\equiv\text{N} + \text{H-B}\langle \longrightarrow \text{H-C=N-B}\langle$$

Earlier workers used diborane and aluminum borohydride for the preparation of organoboranes (4,5,6). These reactions were either carried out at elevated temperatures or required long reaction times. Later it was found that a mixture of sodium borohydride and aluminum chloride in ether solutions converts olefin almost quantitatively and rapidly into organoboranes at room temperature (7). Also diborane in ether solution, and sodium borohydride in the presence of boron trifluoride readily transform olefins into organoboranes. These methods are quite convenient for the preparation of organoboranes, and offer considerable promise to synthetic routes.

The amount of hydride available to an olefin is estimated from the quantity of hydrogen evolved on hydrolysing the active hydride left over after the reaction. The quantity of reagent is expressed in terms of the concentration of the available hydride as indicated by the hydrogen evolved on hydrolysis. Thus 1 M sodium borohydride is 4 M in hydride and 1 M aluminum borohydride is 12 M in hydride.

EXPERIMENTAL METHODS:

Several convenient methods are available for the preparation of organoboranes, of which the following are most useful:

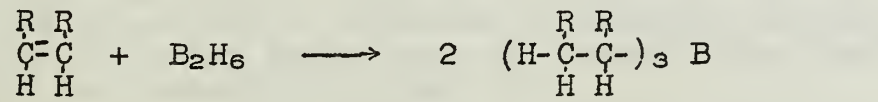
(1) Use of Diborane in ether solutions:

The reaction of diborane with olefins can be represented as:

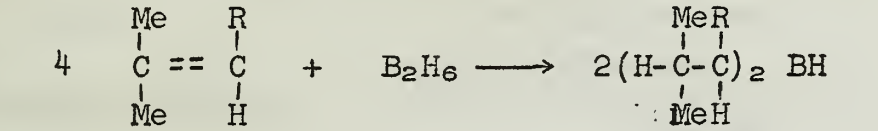
$$6 \quad RCH{=}CH_2 + B_2H_6 \longrightarrow 2(RCH_2CH_2\text{-})_3B$$

Diborane is passed into a solution of the olefin in ether at room temperature in an atmosphere of nitrogen to form the corresponding trialkylborane quantitatively. Tetrahydrofuran is commonly used as the solvent since diborane is highly soluble in it, favoring complete utilization of the gas. An advantage of this method is that no byproducts or inorganic salts are formed in the reaction.

In the case of a great majority of olefins the reaction proceeds to the complete utilization of active hydrogen in the diborane molecule:



However, trisubstituted olefins, such as 2-methyl-2-butene and 2,4,4-trimethyl-2-pentene, appear to react at room temperature to utilize only two-thirds of the active hydrogen, yielding a dialkylborane or its dimer as the reaction product (8):



With tetra-substituted olefins the reaction seems to stop at the monoalkylborane stage:

A typical experiment for the hydroboration of olefins using diborane consists in passing diborane (about 20% excess), generated from sodium borohydride and boron trifluoride etherate, over a period of 30 minutes into a solution of the olefin dissolved in tetrahydrofuran (or diglyme) at room temperature. The exit to the reaction vessel is connected to a wash-bottle containing acetone, which converts any diborane escaping from the reaction vessel into diisopropoxyborane. The reaction mixture is allowed to stand for another 30 minutes and ethylene glycol is added to convert residual hydride into hydrogen. Diborane not absorbed in the reaction vessel is determined by titrating the acetone wash solution (after hydrolysis) for boric acid. These two measurements yield the hydride not used by the olefin and by difference the hydride utilized is estimated. The results of some typical experiments for the synthesis of trialkylboranes are given in Table I.

TABLE I

Olefin	Solvent	Reaction product	Yield (%)
1-hexene	DG	tri-n-hexylborane	91
2-hexene	DG	tri-sec-hexylborane	92
1-octene	DG	tri-n-octylborane	90
1-decene	THF	tri-n-decylborane	84
cyclohexene	THF	tricyclohexylborane	86
cyclopentene	THF	tricyclopentylborane	79

DG = Diglyme; THF = Tetrahydrofuran

(2) Use of Sodium Borohydride-Boron trifluoride in ether solution:

This method consists in treating a solution of olefin and sodium borohydride in diglyme with boron trifluoride etherate in diglyme solution. The reaction can be represented by the following equation:

$$12\ RCH{=}CH_2 + 3NaBH_4 + 4BF_3 \longrightarrow 4\ (RCH_2CH_2\text{-})_3\ B + 3NaBF_4$$

Diborane, first formed between $NaBH_4$ and BF_3 is retained as an addition complex, $NaBH_4.BH_3$, in excess of sodium borohydride (9), which then reacts with the olefin to form the trialkylborane. This procedure has the obvious advantage over the previous one in avoiding the generation of diborane separately, but inorganic salts and occasionally other byproducts are formed. The results of some experiments are presented in Table II.

TABLE II

Reactions of representative olefins with $NaBH_4$+BF_3 in diglyme solution:

Olefin	Trialkylborane	Yield (%)
1-octene	tri-n-octylborane	82-85%
2,4,4-trimethyl-1-pentene	tri-2,4,4-trimethylpentyl-borane	85%
cyclohexene	tricyclohexylborane	90%
cyclopentene	tricyclopentylborane	90%

(3) Use of $NaBH_4$ - $AlCl_3$ mixture in ether solutions (7):

Hydroboration using sodium borohydride - aluminum chloride mixture can be carried out either by using excess of the reagent or by using excess of the olefin. When using excess of the reagent, a solution of the reagent (3 $NaBH_4$ + $AlCl_3$) in diglyme is treated with about 50% of the olefin corresponding to the available hydride for about three hours at room temperature or about one hour at 75°C. the addition of the hydride is estimated by measuring the loss of active hydride from the solution on hydrolysis.

The use of excess olefin provides information both as to the ability of the reagent to react with the olefin and with regard to the number of hydrides in the reagent capable of reacting with it. A typical reaction consists in using a mixture of 3 mmoles of $NaBH_4$, 1 mmole of $AlCl_3$ and 24 mmoles of olefin and allowing the reaction to proceed for three hours at room temperature or one hour at 75°C. The amount of hydride used is estimated as before. The results of some experiments are given in Table III.

TABLE III

Reaction of excess olefin (24 mmoles) with $NaBH_4$(3 mmoles) - $AlCl_3$ (1 mmole) mixture in diglyme solution:

Olefin	Temp (°C)	Time (hours)	Amount of Hydride used
1-octene	25	1	9.1
	25	3	9.4
1-hexene	25	1	8.9
	25	3	9.4
1-pentene	75	1/2	8.2
2-pentene	75	1/2	8.3
Styrene	25	1	8.0
	25	3	9.2
	75	1	8.6

Olefin	Temp (°C)	Time (hours)	Amount of hydride used
2,4,4-trimethyl-1-pentene	25	1	8.9
	25	3	9.1
2,4,4-trimethyl-2-pentene	25	3	5.5
	75	1/2	6.7
	75	1	6.6
cyclohexene	25	1	11.7
	25	3	12.1
cyclopentene	25	1	7.1
	25	3	7.9
	75	1	8.6

The results indicate that most olefins can utilize only 9 out of the 12 active hydrides present in the reagent. These results are also confirmed by passing gaseous olefins (ethylene and propylene) into the reagent through a sintered glass disc. From the amount of hydride used, the reaction indicating the formation of trialkylborane from most olefins can be represented as:

$$9\ RCH{=}CH_2 + 3NaBH_4 + AlCl_3 \longrightarrow 3(RCH_2CH_2\text{-})_3B + NaCl + AlH_3$$

This method has the advantage of being useful for the large scale preparation of organoboranes. It suffers from the disadvantage that only 75% of the active hydride is used and that inorganic salts and other byproducts are formed in the reaction.

(4) Use of Aluminum borohydride in ether solution (7):

Solutions of aluminum borohydride in ether or diglyme react readily with olefins. Here also only 9 out of the 12 active hydrides are used up indicating the formation of the trialkylborane and aluminum hydride:

$$9\ RCH{=}CH_2 + Al(BH_4)_3 \longrightarrow 3(RCH_2CH_2\text{-})_3 + AlH_3$$

In carrying out a reaction, the olefin is added over a period of 1 hour to an excess of the reagent in a flask under a nitrogen atmosphere. After allowing the contents to stand for 3 hours at room temperature, the flask is warmed on a steam-cone for 1/2 hour to complete the reaction and the solvent removed by distillation in vacuum. A solid residue is obtained from which the organoborane is recovered by rapid distillation in vacuum. Some experimental results are given in Table IV.

TABLE IV

Olefin	Product	Yield (%)
1-octene	tri-n-octylborane	83
1-hexene	tri-n-hexylborane	88
1-pentene	tri-n-amylborane	88
2-pentene	tri-2-amylborane	82
styrene	tri-2-phenylethylborane	83
α-methylstyrene	tri-2-phenylpropylborane	80
cyclohexene	tricyclohexylborane	74
cyclopentene	tricyclopentylborane	79

The above experiments also confirm that freshly prepared aluminum hydride, presumably formed in the reaction, fails to add to typical olefins at room temperature.

Olefins can also be hydroborated at high temperatures

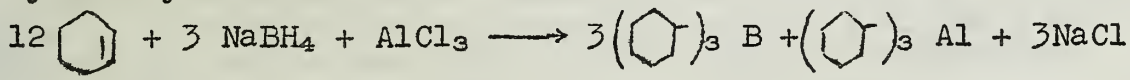
(100-200°C) by using pyridine-diborane or trialkylamineborane (10). These reactions presumably proceed through a partial dissociation of the addition compounds into their components. The trialkylborane formed undergoes isomerization under these conditions very often.

Hydroboration takes place readily with substituted olefins such as allyl ethyl ether, allyl chloride (11) and cinnamic acid. If the substituent itself is reducible, hydroboration is accompanied by reduction.

REACTIONS AND MECHANISMS:

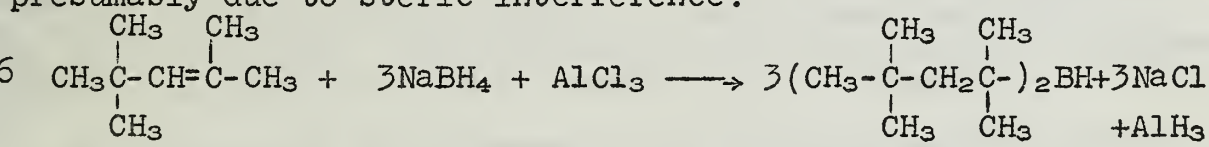
As already indicated the reaction of sodium borohydride-aluminum chloride mixture with most olefins involves only 9 out of the 12 active hydrides, the remaining three being locked up as AlH_3 indicate that the latter fails to add to typical olefins at room temperature.

However, cyclohexene differs from the above in that all the 12 active hydrides in the reagent are consumed, while cyclopentene behaves normally. This indicates that cyclohexene reacts further to form tricyclohexylaluminum in solution, in addition to tricyclohexylborane:



This observation by Brown and coworkers (7) constrasts with the results of Ziegler (12), who studied the reaction of cyclopentene and cyclohexene with diethylaluminumhydride and found that cyclohexene was considerably less reactive than cyclopentene.

The utilization of only 6 out of the 12 active hydrides in the case of 2,4,4-trimethyl-2-pentene and 2-methyl-2-butene indicates the formation of the dialkyl-rather than the trialkylborane and is presumably due to steric interference:



The large steric requirement of the olefin in these compounds probably renders the completion of the final stage relatively slow and difficult.

Hydroboration of olefins with diborane is markedly catalyzed by ethers (1). It is therefore possible that ether functions to dissociate the diborane to some extent, producing a moderate concentration of a more reactive intermediate, borane etherate, in the reaction mixture. It is also probable that similar ether complexes play an important role in the $NaBH_4$ - $AlCl_3$ reactions.

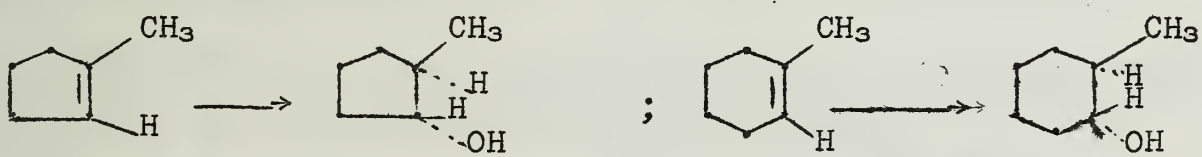
Hydroboration followed by oxidation results in an anti-Markownikoff hydration of olefins. This is indicated by the oxidation products of the organoboranes obtained from terminal olefins. These organoboranes, on oxidation with alkaline hydrogen peroxide, give mainly the corresponding primary alcohols (about 95%) with only a minor amount of the isomeric alcohol (5%). Even in the case of an internal olefin (2-methyl-2-butene) addition occurs to give an anit-Markownikoff product (3-methyl-2-butanol). In Table V are

listed the oxidation products of organoboranes obtained from several olefins.

TABLE V

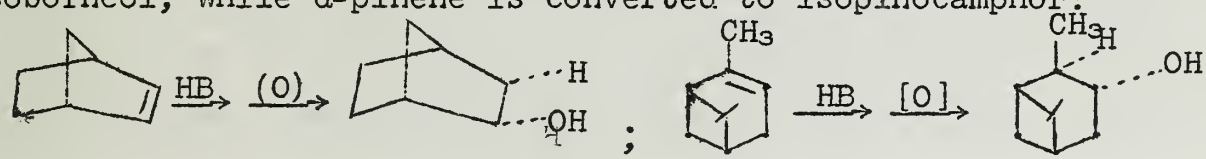
Olefin	Alcohol	Boiling point °C	P mm	Yield %
1-hexene	1-hexanol	156	745	90
1-octene	1-octanol	192	740	90
	2-octanol	180	740	10
1-pentene	1-pentanol	136	742	95 (infrared)
	2-pentanol			5 (infrared)
styrene	2-phenylethanol	104	14	81
2-pentene	2-pentanol			63 (infrared)
	3-pentanol			37 (infrared)
α-methylstyrene	2-phenylpropanol	110	14	90
1,1-diphenyl-ethylene	2,2-diphenyl-ethanol	192	20	86
t-butylethylene	3,3-dimethyl-1-butanol	140	741	67
2-methyl-2-butene	3-methyl-2-butanol	110	742	59
cyclohexene	cyclohexanol	159	750	90
cyclopentene	cyclopentanol	140	740	80

It is noteworthy that hydroboration followed by oxidation of cyclic olefins proceeds stereospecifically to add the H and OH of water to the double bond with overall cis-stereochemistry:



In the above two cases, cis-hydration results in the formatation of the thermodynamically more stable isomer. With 1,2-dimethylcyclopentene and 1,2-dimethylcyclohexene, cis-hydration would result in the less stable isomers, cis-1,2-dimethylcyclopentanol and cis-1,2-dimethylcyclohexanol, but even these are formed in more than 95% yield. The cis nature of the hydration is confirmed by the cholesterols obtained from Δ^3 and Δ^4 cholestenes (13,14).

In addition to the stereospecific nature, hydration takes place from the less hindered side of the double bond. This is confirmed from the studies on norbornene, which is converted into isoborneol, while α-pinene is converted to isopinocamphor:



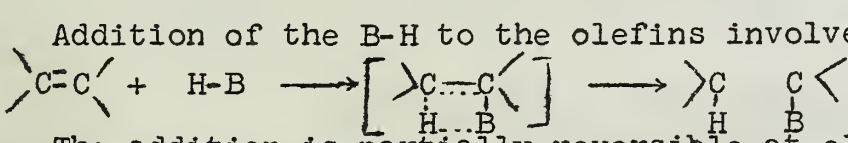
ISOMERIZATION REACTIONS:

The hydroboration of 2-pentene in diglyme solution yields the corresponding tri-sec-pentylborane, which on oxidation with alkaline H_2O_2, gives an equimolar mixture of 2- and 3-pentanol (infrared analysis). On the other hand, if the organoborane is first heated under reflux for 4 hours and then oxidized, the product is essentially 1-pentanol. These results indicate that the boron atom is 50% in 2- and 50% in 3-positions after the hydroboration stage and easily moves over to the 1-position on refluxing. This

This is confirmed by a similar observation by Hennion and coworkers (15), who found that tri-sec-butylborane, when heated under reflux in ether solvent for 20 hours, was converted into tri-n-butylborane. The isomerization proceeds with special ease in ether solvents.

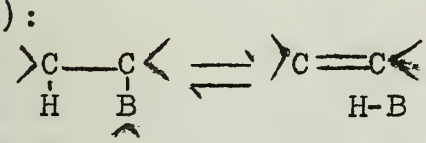
The following mechanism involving a series of eliminations and additions is proposed by Brown (16):

Addition of the B-H to the olefins involves a 4-center addition



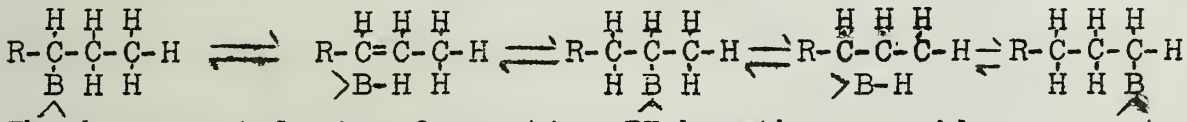
I

The addition is partially reversible at elevated temperatures (17):



II

The isomerization of the boron atom from an internal position to the terminal position of a carbon chain can be formulated as a succession of such eliminations and additions:



III

The known catalysis of reaction II by ether provides support for this mechanism.

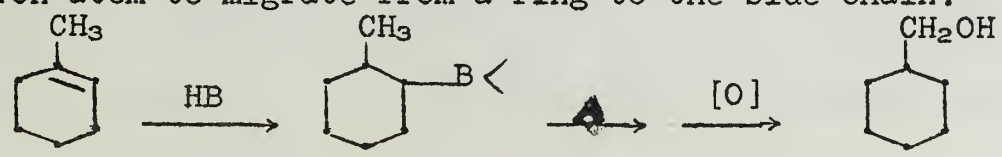
The preference of the terminal position for the boron atom is presumably due to the decreased steric interaction in that position as well as the electronically favored situation.

If the successive elimination and addition mechanism were correct, an added olefin under the conditions of isomerization should bring about the displacement of that formed in the elimination stage producing a new organoborane. This was indeed observed when tri-n-pentylborane was treated with 1-hexene, 1-octene and 1-decene under reflux to obtain tri-n-hexyl-, tri-n-octyl and tri-n-decylborane in 90% yields (3,18).

In contrast to the ease with which straight chain terminal olefins replace one another, the corresponding reaction of 2,4,4-trimethyl-1-pentene is relatively more sluggish, proceeding only to 60% completion in 12 hours. It is apparent that the methyl branch in the 2-position markedly reduces the ability of the olefin to participate in the reaction, probably due to steric hindrance. This is further confirmed by the sluggish isomerization observed with pyridine- and 4-picolineboranes (19).

Recently isomerizations of organoboranes containing quaternary carbon atoms and cycloalkane rings have been reported (20).

The hydroboration product of 1-methylcyclohexene after 6 hours at 160°C yields 50% cyclohexylmethanol, showing the ability of the boron atom to migrate from a ring to the side chain:



These results can be summed up thus: (1) the boron atom can migrate past a single branch; (2) it moves to the least hindered position and (3) it is capable of migrating from a ring position to the side chain in cyclic compounds.

HYDROBORATION AS A SYNTHETIC TOOL:

1. It has been mentioned that organoboranes are rapidly and quantitatively converted by alkaline hydrogen peroxide to the corresponding alcohols. Consequently, hydroboration followed by oxidation provides a convenient route for the anti-Markownikoff hydration of double bonds.

$$RCH{=}CH_2 \xrightarrow{HB} \xrightarrow{[O]} RCH_2CH_2OH$$
$$(H_3C)_2C{=}CH{-}CH_3 \xrightarrow{HB} \xrightarrow{[O]} (H_3C)_2\ CH{-}CH(OH)\ CH_3$$

2. The ready isomerization of trialkylboranes to place the B-atom in the terminal position provides a simple method of converting internal olefins to primary alcohols. Also, since the isomerized trialkylboranes readily undergo displacement with other olefins it is possible to convert the organoborane into the corresponding olefin and a new organoborane derived from the added olefin.

$$CH_3CH_2CH{=}CHCH_3 \xrightarrow{HB} CH_3CH_2CH_2{-}\underset{B<}{CH}{-}CH_3 \xrightarrow{\Delta} \xrightarrow{[O]} CH_3CH_2CH_2CH_2CH_2OH$$

$$CH_3CH_2CH_2CH_2\underset{B<}{CH_2} + CH_3CH_2CH_2CH_2CH{=}CH_2 \xrightarrow{\Delta} CH_3CH_2CH_2CH_2CH_2\underset{B<}{CH_2} + CH_3CH_2CH_2CH{=}CH_2 \quad (90\%)$$

3. Internal acetylenes undergo partial hydroboration, and the products are converted by acetic acid into cis-olefins of very high purity. Terminal acetylenes may be hydroborated by R_2BH to form the monohydroboration product. Oxidation of this yields the aldehyde, providing a convenient anti-Markownikoff hydration of terminal acetylenes (22). Dienes can be partially hydroborated to the corresponding unsaturated alcohols (23).

$$3\ RC{\equiv}CR + 1/2\ B_2H_6 \xrightarrow{0^\circ} \left(\begin{matrix} R{-}C{-}H \\ R{-}C{-} \end{matrix}\right)_3 B \xrightarrow[0^\circ]{HOAc} 3\ \begin{matrix} R{-}C{-}H \\ R{-}C{-}H \end{matrix}$$

$$n{-}C_4H_9{-}C{\equiv}CH + R_2BH \longrightarrow nC_4H_9CH{=}CH{\cdot}BR_2$$
$$\xrightarrow{HOAc} nC_4H_9CH{=}CH_2 \qquad \xrightarrow{H_2O_2} n\ C_4H_9CHO$$

4. Mono- and di-alkylboranes, formed by the addition of diborane (excess) to olefins can be readily hydrolyzed to the corresponding boronic and borinic acids respectively (25):

Alkylboronic acids undergo coupling with ammoniacal silver nitrate in excellent yield (26):

$$\underset{\text{1-butane-boronic acid}}{2\ CH_3CH_2CH_2CH_2B(OH)_2} \xrightarrow{Ag(NH_3)_2^+} \underset{\text{n-octane}}{CH_3(CH_2)_6CH_3}$$

Thus hydroboration provides a convenient synthetic route for the conversion

$$2\ RCH{=}CH_2 \longrightarrow R\ CH_2CH_2CH_2CH_2R$$

5. Organoboranes readily react with carboxylic acids at elevated temperatures to give the corresponding alkanes, thereby providing a simple noncatalytic hydrogenation of double bonds (27):

6. Cyclic olefins undergo CIJ-addition providing a useful method for preparing stereochemically pure alcohols (24):

(trans-2-p-anisyl-2-butene) $\xrightarrow{HB}\ \xrightarrow{[O]}$ (crythro-3-p-anisyl-2-butanol)

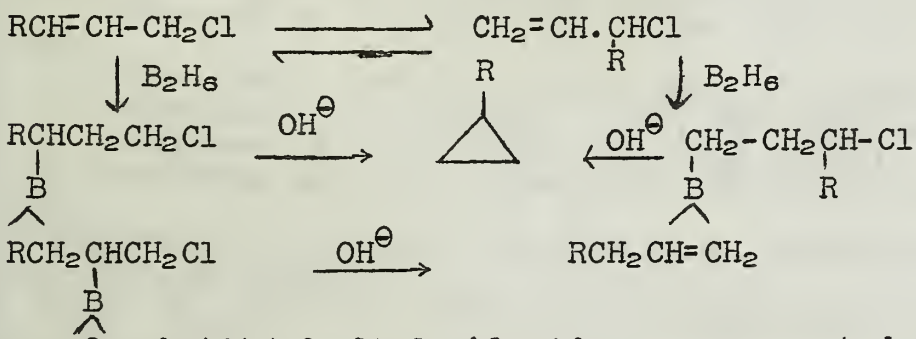
cis-2-p-anisyl-2-butene $\xrightarrow{HB}\ \xrightarrow{[O]}$ threo-3-p-anisyl-2-butanol 72%

7. Organoboranes, obtained by the addition of diborane to allyl chloride (in ether solutions), are converted into cyclopropanes on basic hydrolysis (11):

$$6\ CH_2{=}CH\ CH_2Cl + B_2H_6 \xrightarrow[25^\circ]{\text{Ether}} \underset{36\%}{2(Cl.CH_2CH_2CH_2)_3B}$$

$$(ClCH_2CH_2CH_2)_3B + 3OH^\ominus \xrightarrow[\text{NaOH}]{\text{aqueous}} \underset{90\text{-}95\%}{3\triangle} + B(OH)_3 + 3Cl^\ominus$$

The use of α- or γ- substituted allyl chloride would have led to the formation of a mixture of substituted cyclopropane and the isomeric olefin (30):

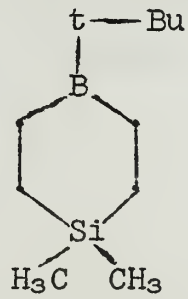


However, β-substituted allyl chlorides are converted into the corresponding substituted cyclopropane, without any olefin being formed (30):

R=H (43% yield)
=CH_3 (71%)
=$CH_3CH_2CH_2$ (61%)
=C_6H_5 (55%)
=$C_6H_5CH_2$ (45%)

Thus hydroboration can be used as an intermediate step for the synthesis of substituted cyclopropanes.

8. Organoboranes can also be used to synthesize interesting heterocyclic compounds. Thus dimethyl divinylsilane is found to react smoothly with tri-methylamine-t-butylborane to give 1-boro-1-t-butyl-4,4-dimethyl-4-silacyclohexane (29):



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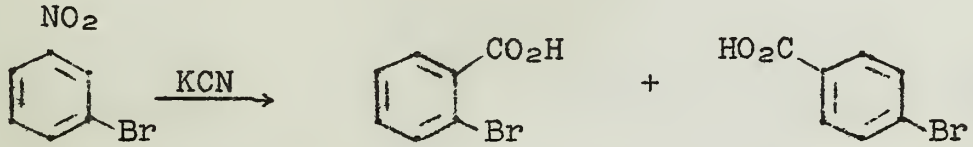
THE VON RICHTER REACTION

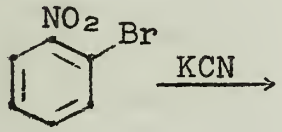
Reported by J. R. Fox May 19, 1960

The von Richter reaction was accidently discovered in 1871 when von Richter was attempting to prepare nitrobenzoic acids by treatment of bromonitrobenzenes with KCN in alcohol (1). Instead of the expected nitrobenzonitriles, von Richter obtained products which, when they were identified in 1875 (2), indicated that the following reactions had taken place:

1 

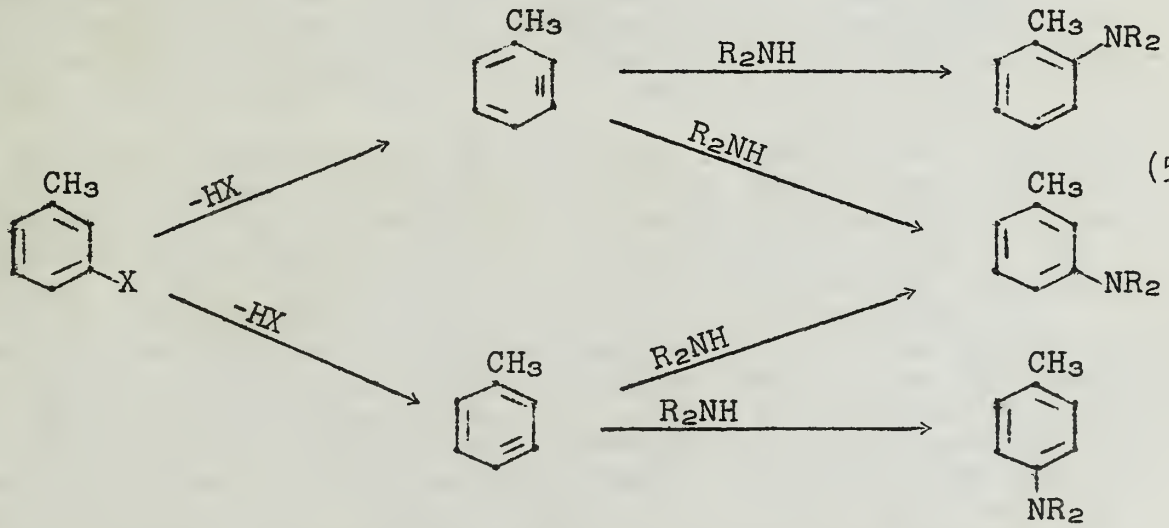
2 

~ 40% Trace

3 

No acidic products

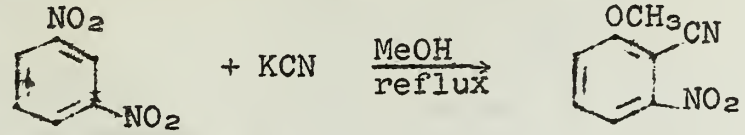
The von Richter reaction thus results in replacement of a nitro group by hydrogen and replacement of hydrogen by a carboxyl group, the carboxyl group occupying a position other than that vacated by the nitro group. Bunnett and Zahler (3) have chosen to call this type of reaction "cine substitution". By far the largest number of cine substitutions involving nucleophilic attack on an aromatic ring proceed via benzyne intermediates (equation 4) and Bunnett claims that the mechanism of the von Richter reaction is the only other known mechanism which accounts for cine substitution in nucleophilic substitution reactions on aromatic rings (4).

4 

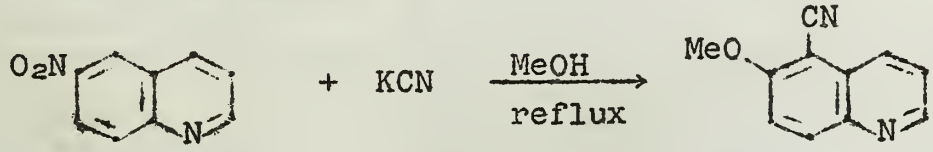
(5)

The von Richter reaction does not result in displacement of halogen, the displacement of halogen from aromatic rings by alkali cyanides being rare (3). Such displacements ordinarily require the use of copper compounds as in the Rosenmund-von Braun nitrile synthesis (6). The reactions of m-dinitrobenzene and 6-nitroquinoline

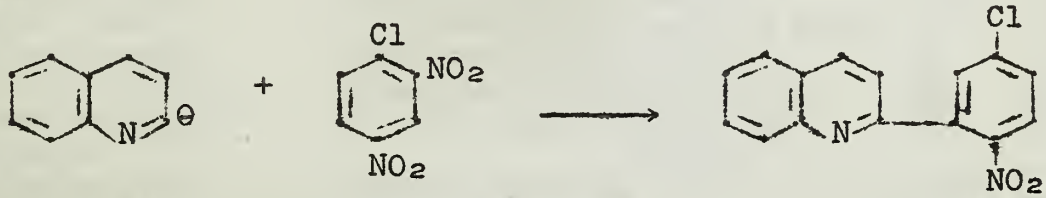
with KCN should not be considered von Richter reactions since they lead to products quite different from the benzoic acids obtained in von Richter reactions (see equations 5 and 6). On the other hand, the reaction of the 2-quinoyl anion with 2,4-dinitrochlorobenzene shows a marked similarity to the von Richter reaction (equation 7).

5 

(7)

6 

(8)

7 

(9)

The von Richter reaction is not limited to bromonitrobenzenes; the corresponding chloro and iodo derivatives react similarly. In addition, some other types of nitrobenzene derivatives undergo the reaction as well. On the other hand, there are a number of nitrobenzene derivatives which either fail to react or else give products other than benzoic acids (equations 5 and 6, for example), and Bunnett's claim (10) that the von Richter reaction is general for aromatic nitro compounds would seem to be an exaggeration. Table I contains a list of a few representative von Richter reactions. For a comprehensive list of the von Richter reactions which have been attempted, the papers of Bunnett and coworkers should be consulted (11,12,15).

At best, yields in the von Richter reaction are low, 40% being exceptional and yields of less than 20% being normal. As a result, the reaction is of little preparative value except in the few cases where a compound which is difficult to prepare by other means is obtained in one step from readily obtained starting materials. An example of such a case might be the preparation of 2-bromo-3-methylbenzoic acid in 13% yield from 3-bromo-4-methylnitrobenzene.

As would be expected in a nucleophilic substitution, yields in the von Richter reaction are dependent on the substituents on the ring. Bunnett (15) has attempted to correlate yields with the sum of the Hammett sigma values bearing on the position ortho to the nitro group. A plot of this sum versus the logarithm of the yield gave Bunnett a rather wide scattering of points from which he suggests that the yields are maximum when the sum of the sigma values (not including the sigma for the nitro group) bearing on the position ortho to the nitro group is about 0.37. There are so many exceptions to the above statement that it should not be taken as a general rule. p-Fluoronitrobenzene ($\sigma = 0.34$), for example, fails to give any m-fluorobenzoic acid while m-nitrotoluene ($\sigma = -0.17$) gives o-toluic acid in 19% yield. One significant conclusion can be drawn from this work, however. When the sum of the sigmas bearing on the position ortho to the nitro group is less than -0.2, the reaction does not occur and all or most of the starting material can be recovered. If the sum of the sigmas is greater than 0.6, a reaction occurs but

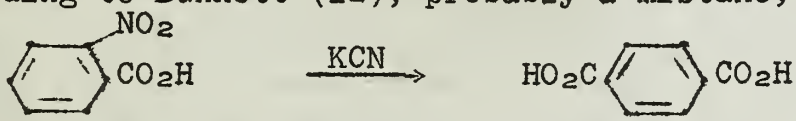
TABLE I

Starting Material	Product	Yield	Ref.
m-chloronitrobenzene	o-chlorobenzoic acid	-	(1)
m-iodonitrobenzene	o-iodobenzoic acid	-	(1)
	p-iodobenzoic acid	-	
2-nitro-4-bromotoluene	m-toluic acid	-	(2)
3-nitro-4-bromotoluene	no acid product	0%	(2)
2,4,6-tribromonitrobenzene	no acid product	0%	(2)
"o-nitrobenzoic acid"	terephthalic acid	-	(13)
m-nitrobenzenesulfonic acid	o-sulfobenzoic acid	15%	(14)
	p-sulfobenzoic acid	15%	
m-nitrotoluene	o-toluic acid	19%	(15)
p-phenylnitrobenzene	m-phenylbenzoic acid	0.5%	(15)
p-nitrobenzoic acid	1,3-benzenedicarboxylic acid	5%	(15)
p-phenoxynitrobenzene	m-phenoxybenzoic acid	6%	(15)
p-thiophenoxynitrobenzene	m-thiophenoxybenzoic acid	5%	(15)
m-trifluoromethylnitrobenzene	p-trifluoromethylbenzoic acid	8%	(15)
p-benzoylnitrobenzene	m-benzoylbenzoic acid	0.3%	(15)
β-nitronaphthalene	α-naphthoic acid	13%	(15)
p-nitrodimethylaniline	no acid product	0%	(15)
p-fluoronitrobenzene	no acid product	0%	(15)
m-nitroacetophenone	no acid product	0%	(15)
4-nitropyridine	no acid product	0%	(15)
2,3-dibromonitrobenzene	3,4-dibromobenzoic acid	1%	(11
3,4-dibromonitrobenzene	2,3-dibromobenzoic acid	16%	(11)
2,6-dibromonitrobenzene	no acid product	0%	(11)
2,4-dibromonitrobenzene	3,5-dibromobenzoic acid	2%	(11)
3,5-dibromonitrobenzene	2,4-dibromobenzoic acid	18%	(11)
2,5-dibromonitrobenzene	2,5-dibromobenzoic acid	7%	(11)
o-bromonitrobenzene	m-bromobenzoic acid	2%	(11)

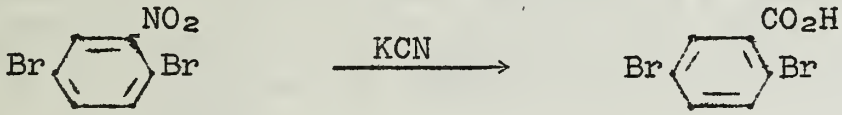
none of the expected benzoic acid is obtained. Instead, tars are formed and little or no starting material can be recovered. This observation is in agreement with what one would expect from a nucleophilic substitution reaction. Substituents that supply electrons (negative sigmas) would inhibit attack by cyanide while substituents that withdraw electrons (positive sigmas) would accelerate such attack. In the case of substituents with large sigma values, the product of attack by cyanide evidently takes a course leading to tars rather than to the desired products. With the possible exception of 3,4-dibromonitrobenzene ($\Sigma\sigma = 0.62$) there are no examples of compounds having total sigma values outside the range -0.2 to +0.6 which undergo the von Richter reaction. There are, however, cases in which total sigma values are within this range but in which reaction fails. p-Fluoronitrobenzene has already been mentioned. In addition, 3-bromo-4-fluoronitrobenzene ($\Sigma\sigma = 0.57$) fails to give any of the expected 2-bromo-3-fluoro- or 3-fluoro-4-bromobenzoic acid. Instead, these compounds produce acidic tars, and in the case of p-fluoronitrobenzene a small amount of p-nitrophenetole. In both cases no starting material could be recovered, indicating that, as expected from the sigma values, the nitro compound was consumed. m-Nitroacetophenone ($\sigma = 0.52$) also produces only tars while p-nitrobenzophenone (here the sigma for the acetyl group, 0.31, is considered) gives a yield of only 0.3% m-benzoylbenzoic acid with no recovery of starting material. One further point concerning

yields should be made. A consideration of the six dibromonitrobenzenes in Table I shows that when both positions ortho to the nitro group are occupied the reaction does not take place. If one of these positions is occupied the reaction takes place but with a low yield (1-7%) whereas when both positions are empty the reaction takes place in moderate yield (16-18%). It is also interesting to note that in this series of compounds the largest yields of product are accompanied by the largest amounts of tar. 2,6-Dibromonitrobenzene, which gives no acidic product, produces no tar, and starting material has been recovered in 93% yield (11).

In all of the von Richter reactions studied the carboxyl group appears to occupy a position ortho to that vacated by the nitro group. Schiff's (13) report of the reaction of o-nitrobenzoic acid (equation 8) is, according to Bunnett (12), probably a mistake, the reaction

8 

actually having been carried out with m-nitrobenzoic acid. Since there are no other clear cut examples of the carboxyl group entering a position meta to that vacated by the nitro group, Bunnett's conclusion seems reasonable. Unfortunately, a repeat of this reaction has not been reported. There are of course cases in which either ortho or para substitution could be assumed (m-bromonitrobenzene giving o-bromobenzoic acid) and in the case of 2,4-dibromonitrobenzene entry of the carboxyl group into any of the four nonbrominated positions would give the observed product (see equation 9). However,

9 

since only ortho substitution is applicable in all cases it appears to be the most reasonable. Exclusive ortho attack is also indicated in equations 5 and 6 (but not in 7).

In the case of halonitrobenzenes it should be noted that the carboxyl group occupies a position ortho not only to the position vacated by the nitro group but where possible, ortho to the halogen atom as well. 2-Bromo-4-nitrotoluene for example gives a 13% yield of 2-bromo-3-methylbenzoic acid rather than 3-methyl-4-bromobenzoic acid. m-Bromonitrobenzene gives a 40% yield of o-bromobenzoic acid and only a trace of the para isomer while the corresponding chloro derivative gives only chlorobenzoic acid. As expected, β-nitronaphthalene gives α-naphthoic acid rather than the β acid. On the other hand, m-nitrotrifluoromethylbenzene and m-nitroanisole give p-trifluoromethylbenzoic acid and p-methoxybenzoic acid (12) respectively, indicating that the carboxyl group entered ortho to the nitro group but para to the trifluoromethyl and methoxy groups. m-Nitrobenzenesulfonic acid apparently undergoes attack both ortho and para to the sulfonic acid group, giving 15% yields of both the o- and p-sulfobenzoic acids. The reaction of 2-nitro-4-bromotoluene is interesting since it gives m-toluic acid with elimination of the bromo as well as the nitro group.

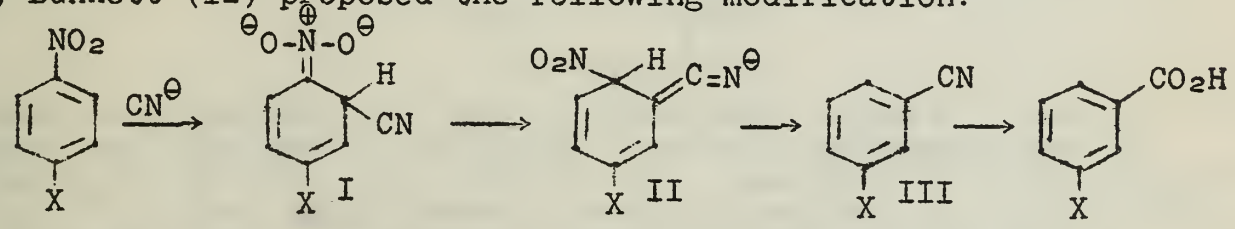
Von Richter's procedure for carrying out the reaction consisted of treating the nitro compound with two equivalents of KCN in an "alcoholic" solvent at temperatures of 180-200° C. for periods of

3-5 hours. The reactions were run in sealed tubes (1). Holleman (14), in his work with m-nitrobenzenesulfonic acid treated the potassium salt of the acid with a refluxing aqueous solution of KCN. Bunnett (12) has observed that under the sealed tube conditions yields in the von Richter reaction are independent of temperature in the range 155-195° and that yields are not increased by heating for more than one hours. Until 1950 the high temperatures obtained by use of sealed tube conditions was considered necessary for the reaction. The observation that β-nitronaphthalene reacted very rapidly under the sealed tube conditions (11) led Bunnett to the use of refluxing solvents for running the reaction. For the most part the use of refluxing solvents gives better yields than does the use of sealed tubes although reaction times are greater. Some compounds, however, require the high temperatures obtained with sealed tubes and thus high boiling solvents are necessary in order to use the refluxing technique. Benzoic acid, for example, is obtained in 21% yield from nitrobenzene using refluxing ethylene glycol as solvent. The use of 48% ethanol at 160° gives a 10% yield, while in refluxing 48% ethanol the reaction does not go at all. A large excess of cyanide ion is also necessary for optimum yields. Two equivalents of KCN in refluxing 90% and 95% ethylene glycol convert p-bromonitrobenzene to m-bromobenzoic acid in 10% yield (20% yield in 50% ethanol under sealed tube conditions) and starting material may be recovered. The use of 12 equivalents of KCN under the same conditions resultsin a 16% yield but in this case no starting material can be recovered (12).

In an effort to perfect the conditions of the von Richter reaction, Bunnett has conducted the reaction in a variety of solvents (11). In general, alcohols give better yields than pyridine, dioxane, benzene, or acetonitrile; and of the alcohols tried, ethanol gives the best yields. Mixtures of ethanol and water give better yields than 95% or 100% thanol.

Von Richter proposed a mechanism for the reaction in 1875 (8) and in 1904 Lobry de Bruyn and Van Geuns proposed another (7). In 1950, Bunnett (12) proposed the following modification:

10

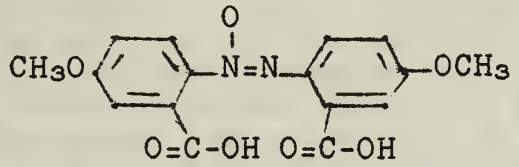


All of these early mechanisms proposed the hydrolysis of a nitrile as the product forming step.

Until 1954 no effort was made to verify the above mechanisms. The first such work was aimed at determining whether the conversion of I into III (equation 10) involves an inter- or intramolecular hydrogen shift. In two independent experiments, 4-chloronitrobenzene deuterated in the 2- and 6-positions and containing an average of 1.02 and 0.99 deuterium atoms per molecule of the nitrobenzene produced m-chlorobenzoic acid containing respectively, 0.42 and 0.38 deuterium atoms per molecule of acid. An intermolecular hydrogen transfer is therefore indicated. The reaction of nitrobenzene using D_2O and C_2H_5OD as solvent produced benzoic acid containing 0.72 atoms of deuterium per molecule of benzoic acid after equilibration with water. It is therefore concluded that the hydrogen that replaces the nitro group comes from the solvent (11).

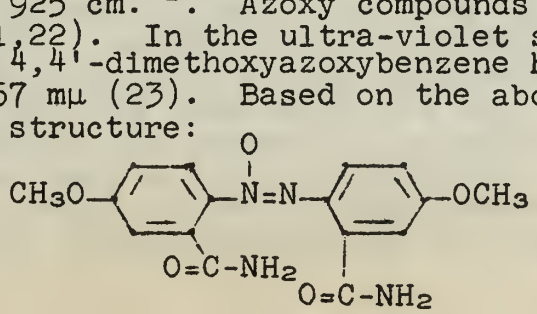
Formation of tars invariably accompanies von Richter reactions. Bunnett has separated the tar formed in the reaction of p-chloronitrobenzene in 48% ethanol into three fractions (11). Fraction 1 is soluble in hot water, fraction 2 is insoluble in water but soluble in ethanol, and fraction 3 is insoluble in both water and ethanol. The three fractions are various shades of brown and are acidic as shown by their solubility in dilute alkali. Fraction 2 was titrated potentiometrically and although the curves obtained did not show sharp breaks, neutral equivalents of 232 and 236 g. were estimated. The infra-red spectrum of fraction 2 shows only one well defined peak which occurs at 6.00μ and is the same as the peak shown by m-chlorobenzoic acid at 6.00μ. Qualititative analysis of fraction 2 indicates substantial amounts of chlorine and nitrogen are present. Based on the above evidence Bunnett has concluded the amorphous by-products obtained in this reaction are mixtures of polymeric carboxylic materials, that the carboxyl groups originate from the cyanide ion, and that the introduction of the carboxyl group and the formation of bonds between monomer units has not involved the loss of appreciable quantities of chlorine or nitrogen.

Neutral by-products are also obtained in the von Richter reaction. The reaction of 100 g. of p-nitroanisole and 400 g. of KCN in 1 l. of refluxing 48% ethanol produced 20 g. of a neutral yellow material, A, melting with decomposition at 230-234°C. and having an empirical formula $C_{16}H_{16}N_4O_6$. No m-anisic acid was formed. A was reduced with iron and NH_4Cl in aqueous ethanol to give a colorless basic compound, B, melting at 103° and having an empirical formula $C_8H_{10}N_2O_2$. B was shown to be 2-amino-5-methoxybenzamide by conversion to 2-chloro-5-methoxybenzoic acid, melting at 169-170° (lit. m.p. 172.5-173°(17)), 2-bromo-5-methoxybenzoic acid melting at 159-160° (lit. m.p. 160°(17)), and to 3-methoxybenzamide, melting at 131-132° (lit. m.p. 133-134° (18)). Alkaline hydrolysis of A produced ammonia and a yellow acid, C, melting with decompositions at 222-229°. C had a neutral equivalent of 174 g. and an empirical formula $C_{16}H_{14}N_2O_7$. C was proved to have the structure shown



C

by unequivocal synthesis in the following way. Methyl 3-chlorobenzoate was nitrated to give methyl 2-nitro-5-chlorobenzoate, D, melting at 45-47° (lit. m.p. 48.5° (19)). Reaction of D with KOH and MeOH gave 2-nitro-5-methoxybenzoic acid, E, melting at 133-135° (lit. m.p. 132-133° (20)). Reaction of E with glucose and KOH gave a compound with melting point and infra-red spectrum identical to that of C. Treatment of E with PCl_5 and then NH_4OH gave F, melting at 154° and having an empirical formula $C_8H_8N_2O_4$. Treatment of F with iron and NH_4Cl gave a compound whose melting point and infra-red spectrum were identical to those of B. The infra-red spectrum of A showed absorption at about 1600, 1570, and 1300 cm.$^{-1}$, with a weak absorption about 925 cm.$^{-1}$. Azoxy compounds are known to absorb in these regions (21,22). In the ultra-violet spectrum, λ_{max} occurs at 354 mμ. λ_{max} for 4,4'-dimethoxyazoxybenzene has been reported to occur at about 357 mμ (23). Based on the above evidence, A is assigned the following structure:



A

Although nitriles and amides had never been detected in von Richter reactions, it was assumed that they were quantitatively hydrolyzed to acids under the sealed tube conditions (11). The discovery that β-nitronaphthalene was converted to α-naphthoic acid in 13% yield by refluxing with KCN and 48% ethanol for 4 hours however created some doubt as to the possibility of quantitative hydrolysis of nitriles under these mild conditions. The reaction of β-nitronaphthalene and KCN was stopped after $1^1/_2$ hours and produced a 6% yield of α-naphthoic acid. The neutral materials were chromatographed and produced 15% starting material but no nitrile or amide. If any α-naphthonitrile was formed it therefore must have hydrolyzed very rapidly to form acid. To test this possibility 1 g. of α-naphthonitrile and 1 g. of KCN in 20 cc. of 48% ethanol were refluxed for 4 hours. No acid was produced and 90% of the α-naphthonitrile was recovered. The possibility that nitrite ion (a product of the reaction) catalyzes such hydrolysis was ruled out when it was observed that a mixture of 1 g. of α-naphthonitrile, 1 g. of KCN, and 0.5 g. of $NaNO_2$ in 20 cc. of 48% ethanol resulted in quantitative recovery of starting material after 4 hours of refluxing. The possibility that some unknown product of the von Richter reaction catalyzes the hydrolysis of α-naphthonitrile can also be ruled out. A mixture of 2 g. of β-nitronaphthalene, 1 g. of α-naphthonitrile, and 1.7 g. of KCN in 40 cc. of 48% ethanol was refluxed for 4 hours and produced only 0.22 g. (11%, the normal yield) of α-naphthoic acid. It is therefore concluded that α-naphthonitrile is not an intermediate (10). A similar search for the nitrile intermediate in the sealed tube reaction of p-chloronitrobenzene was also fruitless. A tube containing 1.70 g. of p-chloronitrobenzene, 0.80 g. of m-chlorobenzonitrile, 5.00 g. of KCN, and 25 cc. of 48% ethanol was heated at 147° for 40 minutes along with an identical tube which did not contain the added nitrile. The tube containing nitrile produced a 47% yield (based on nitrile) of m-chlorobenzamide and 0.62 g. of m-chlorobenzoic acid. In another experiment 1.5 g. of m-chlorobenzonitrile, 2.6 g. of KCN, and 75 cc. of 48% ethanol were heated for 40 minutes in a sealed tube at 150°. Thirty-three percent of the starting material was recovered along with a 17% yield of m-chlorobenzoic acid. The remaining 50% of the material was not investigated, but in view of the previous observation probably contained a considerable amount of m-chlorobenzamide. When this same reaction was carried out with 0.90 g. of $NaNO_2$ added, a 69% yield of m-chlorobenzamide but no nitrile or acid was obtained. It therefore appears that although m-chlorobenzonitrile is extensively hydrolyzed under the sealed tube conditions of the reaction, the principal product of the hydrolysis is m-chlorobenzamide, not m-chlorobenzoic acid. Since amides have not been detected in von Richter reactions, it is concluded that nitriles are not intermediates.

The unlikely possibility that a nitrohalobenzonitrile is an intermediate in the von Richter reaction can be ruled out since 2-nitro-4-chlorobenzonitrile, when treated with KCN in 48% ethanol at 150° for 1 hour gave none of the required p-chlorobenzoic acid. Formate ion, which is a product of the hydrolysis of cyanide ion (24) has also been ruled out as an active agent in the reaction. A mixture of p-chloronitrobenzene, formic acid, and NH_4OH was heated in a sealed tube at 150°, but 95% of the p-chloronitrobenzene was recovered (10). The possibility that nitrosobenzene is an intermediate in the reaction has also been ruled out (11). Bunnett reacted nitrosobenzene with KCN in 48% ethanol in a sealed tube. A small amount of azobenzene but no benzoic acid was obtained. When 75% dioxane was used as solvent a small amount of azoxybenzene but no benzoic acid was formed. While nitrosobenzenes may not be intermediates in the

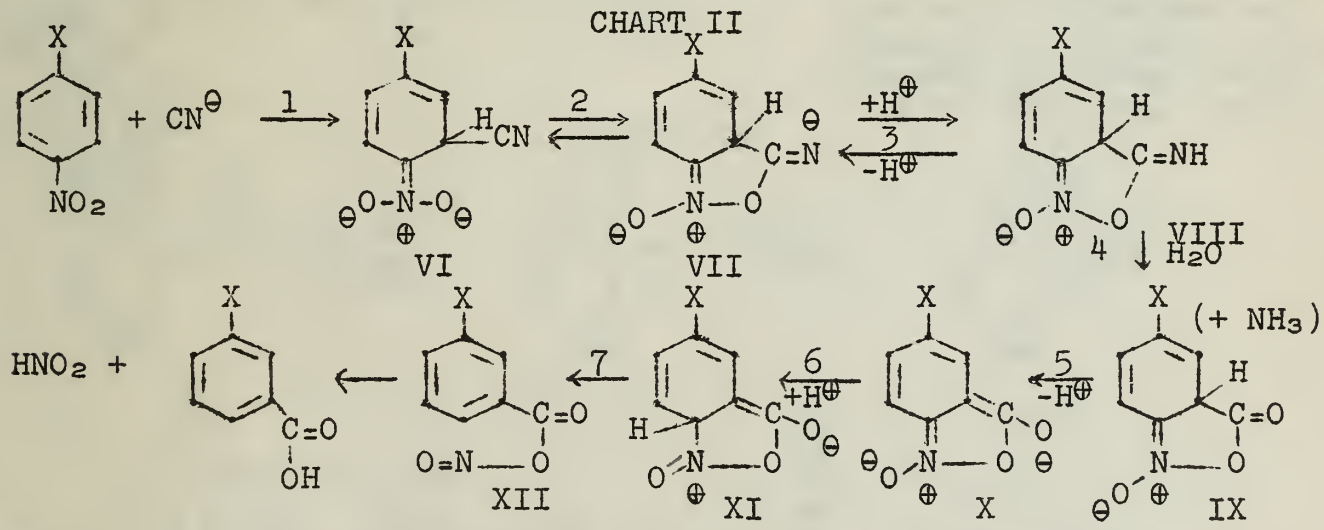
formation of benzoic acids, there is a possibility that they are involved in the formation of by-products. Bisulfite ion is known to reduce aromatic nitro compounds to nitroso compounds (25). Bunnett has observed that when Na_2SO_3 is added to von Richter reactions the reactions are inhibited and large quantities of tar are formed (11).

In view of the above observations, a suitable mechanism for the von Richter reaction must account for the following:

a. NH_3 and NO_2^- are produced in the reaction.
b. When starting material is recovered, it is free of isomers.
c. The carboxyl group takes a position ortho to that vacated by the nitro group.
d. Compounds with a substituent ortho to the nitro group react slowly if at all.
e. Hydrogen from the solvent is incorporated in the product.
f. Products are not formed by hydrolysis of nitriles or amides.
g. Substituents prohibit the reaction if the sum of the sigma values (exclusive of the sigma value for the nitro group) bearing on the position ortho to the nitro group is less than -0.2. When the sum is greater than 0.6, starting material is consumed but none of the desired product is formed.

Bunnett has proposed the mechanism shown in Chart II to account for the above observations (10). Step 1 involves attack by cyanide ion at the electron deficient position ortho to the nitro group. Such attack would be expected to be aided by substituents that withdraw electrons from this position and retarded by substituents supplying electrons to this position. The nitro group also withdraws electrons from this position as long as it is permitted to lie in the plane of

CHART II



the ring. A bulky substituent in one of the ortho positions would therefore be expected to retard attack by cyanide not only because of the statistical factor but through steric inhibition of resonance as well. Steps 2 and 3 are analogous to the base catalyzed addition of alcohols to nitriles to form imino esters (equation 11)(26). Species

11 $$RC{\equiv}N + R'O^{\ominus} \rightleftharpoons RC(=N^{\ominus})OR'$$

VIII might be expected to react analogously to imino esters which have been shown to decompose in aqueous acid to ammonia and esters (27). In base, imino esters decompose to produce alcohols and nitriles in

steps analogous to the reverse of steps 2 and 3. Although the medium in von Richter reactions is slightly basic, the formation of even small amounts of ammonia could reasonably be expected to provide the driving force for the conversion of VIII into IX. Steps 5 and 6 account for exchange of hydrogen with solvent and step 7 is analogous to the final step in a nucleophilic displacement. The acid nitrite XII would be expected to hydrolyze rapidly and would account for the formation of nitrite ion. It has been suggested that the unfavorable effect of strongly electron attracting groups is caused by over-stabilization of X. Other species in the reaction would then have time to react with X with the possible formation of the observed tars (10).

The first step of Bunnett's mechanism is perhaps the most questionable since it does not explain why cyanide attacks only the ortho position. A possible explanation is that para attack by cyanide does occur but that exclusive ortho attack is observed in the expected products because step 2 is capable of removing only the ortho adduct. If such is the case, step 1 of Bunnett's mechanism should be considered a reversible step. Another possibility is that para attack by cyanide results in the formation of some of the unidentified by-products. Considering m-bromonitrobenzene, if the para adduct, XIII, were to eliminate hydroxide ion, the resulting compound would be a bromonitrosobenzonitrile which might conceivably be involved in the formation of the azoxy by-products observed in the reaction. Elimination of hydride ion from XIII is unlikely since hydride ion is known to be a poor leaving group (3). Were it to occur, reduction by the hydride ion might also lead to azoxy or other reduced by-products. In the case of p-bromonitrobenzene the adduct formed by para attack of cyanide might reasonably be expected to eliminate bromide ion. If this were to happen the nitronitrile formed must react rapidly

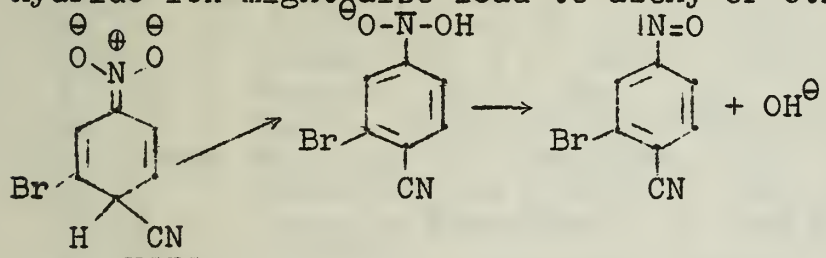
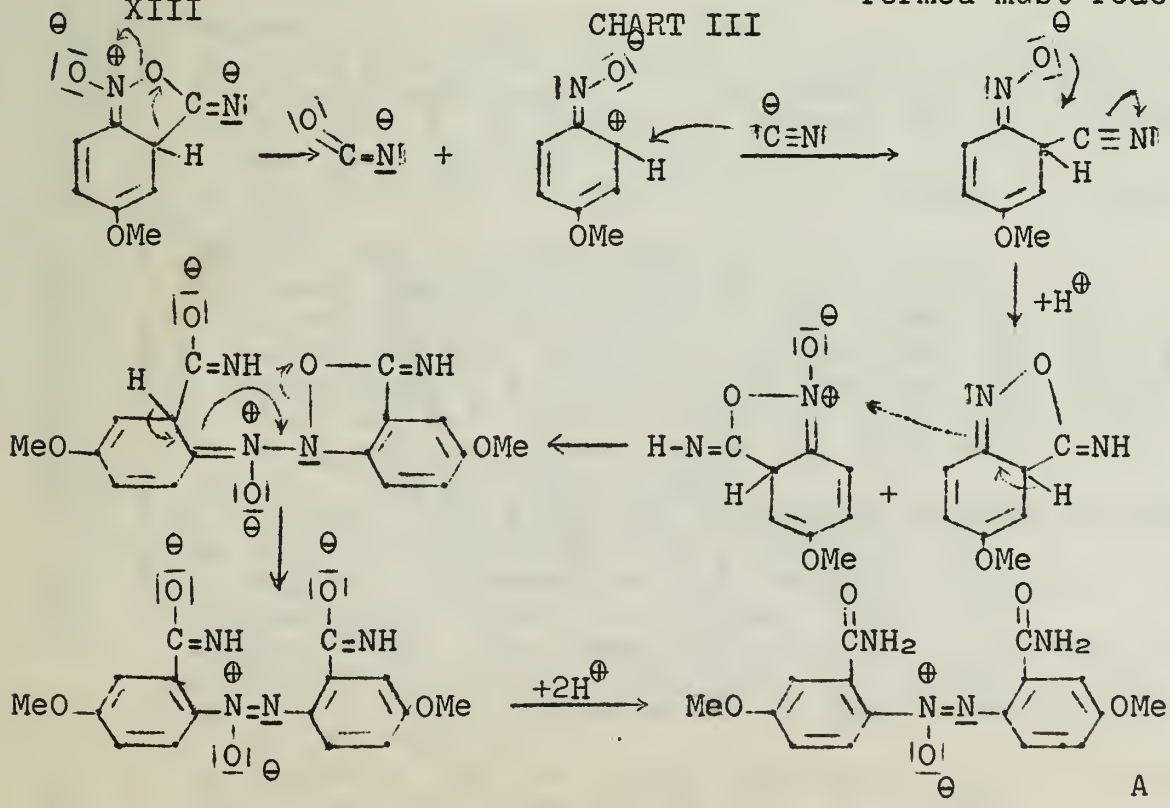


CHART III



to form by-products since nitriles have not been detected in von Richter reaction mixtures. Although these two possibilities are somewhat questionable, they cannot, nor can the possibility of para attack by cyanide, be ruled out until the identity of all products obtained in the von Richter reaction has been established.

Recent work of Samuel (28) supports the mechanism proposed by Bunnett. By using ethanol and O^{18} enriched water as solvent in the von Richter reaction Samuel has observed that in the benzoic acids obtained, only one of the oxygen atoms comes from the water. The other oxygen must therefore have come from the nitro group and the possibility of hydrolysis of a nitrile can be ruled out. Samuel's work also indicates that step 8 of Bunnett's mechanism involves rupture of the N-O bond.

It has been known for many years that certain nitro compounds are reduced to azoxy compounds by KCN. Although they have not isolated it, Lobry de Bruyn and Van Geuns (7) have stated that cyanate ion is also formed but that it is hydrolyzed to ammonia and carbon dioxide which are observed in such reactions. Assuming that cyanate ion is the product of such a reduction, the formation of by-product A above might proceed by way of the mechanism shown in Chart III. Such a mechanism would be in agreement with the observation that tar formation generally accompanies product formation.

By way of comparison it is interesting to note that the mechanism proposed by Bunnett is similar in many ways to the mechanism proposed by McEwen and Cobb for the acid catalyzed decomposition of Reissert compounds (29).

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THERMAL INITIATION OF THE POLYMERIZATION OF STYRENE

Reported by E. H. Drew May 26, 1960

INTRODUCTION

The thermal polymerization of styrene proceeds by a radical chain process involving initiation, propagation, chain transfer, and termination.[7] The most interesting step mechanistically is initiation. In order to understand the development of the various mechanisms proposed for this step, one must be familiar with the general characteristics of the polymerization. These characteristics are listed as follows: 1) The average molecular weight of the polymer formed remains approximately constant throughout the course of the reaction.[6-8] 2) The rate of polymerization is independent of the concentration of monomer for concentrations as low as 0.14M and in most cases independent of solvent.[2] 3) The rates of growth and reaction of styrene type radicals are independent of chain length.[12] 4) Over-all second or 5/2 order rate constants have been observed in the presence of solvents,[2] and pseudo zero order over-all rate constants in their absence.[3] 5) Solvents, depending upon their chain transfer constant, reduce the molecular weight of the polymer and, with the exception of bromobenzene[2] and chlorobenzene,[14] are incorporated into the resulting polymer.

The thermal polymerization of styrene is usually studied at low percentage conversion of monomer, up to 25%, in order to rule out the possibility of the termination and propagation steps becoming diffusion-controlled at high viscosities in the absence of solvent. This phenomenon has been reported by Vaughan[15] and Fujii[16] who found that the rate of termination decreased and the degree of polymerization increased at monomer conversions above 25%; however, Walling[13] failed to notice any change at these high conversions.

The kinetics of the polymerization have been followed by dilatometer contractions,[18] vapor pressure,[13] and ultraviolet absorption.[11] In using dilatometer contractions, one calibrates volume contractions with density of known mixtures of polystyrene in styrene and compares these with actual runs to determine the mole fraction of monomer converted. Degree of polymerization has been determined from number average molecular weights. These molecular weights have been determined from viscosity measurements, osmotic pressure, and freezing point depression. The molecular weight of the polymer varies according to the method used; however, a good correlation between viscosity and osmotic pressure molecular weights was found by Mayo et al[3] for conversions below 12%. Molecular weights determined cryoscopically were somewhat lower.[2] The variations indicate a broad molecular weight distribution.

Mayo et al[3] have reviewed the over-all rate constants reported in the literature for the bulk thermal polymerization of styrene at 60°. These pseudo zero order rate constants are 0.0072, 0.0089, 0.0082, and 0.0067 moles/l hr.

BIMOLECULAR INITIATION

The first mechanism consistant with experimental observations was proposed by P. J. Flory[7] in 1937. He proposed that active centers (radicals) could only be formed or destroyed in pairs. Utilizing this concept, the following reaction scheme is written

where M is monomer, M_n is a polymer molecule of n units, and $M\cdot, M_n\cdot$ are radicals.

		Rate	
(1)	$M + M \xrightarrow{k_i} 2M\cdot$	$2k_i[M]^2$	Initiation
(2)	$M_n\cdot + M \xrightarrow{k_p} M_n\cdot + 1$	$k_p[M_n\cdot][M]$	Propagation
(3)	$M_n + M \xrightarrow{k_{tr}} M_n + M\cdot$	$k_{tr}[M_n\cdot][M]$	Chain transfer
(4)	$M_n\cdot + M_m\cdot \xrightarrow{kt} M_{n+m}$ or M_m+M_n	$2k_t[M_n\cdot]2$	Termination

In step (1) the two radicals produced could be on the same molecule.

Assuming that monoradicals are produced, the specific rate constants can be determined from catalytic polymerizations. The initiation step in this case would consist of (1) and (1a).

(1a) $[\text{Initiator}] \xrightarrow{kd} 2R.$

The rate of initiation would be

$$Ri = 2\ kdf[\text{Init}] + 2ki[M]^2$$

where f is the fraction of radical pairs starting chains. Assuming that kinetic chains are long, monomer concentration is constant, and a steady state is obtained; the following expression can be derived:

$$\left(\frac{-dM}{dt}\right)^2 = R_p^2 = \left[\frac{k_p^2[M]^2}{k_t}\right]\left[kdf[\text{Init}] + ki(M)^2\right]$$

Another relationships exists for R_p. Where $\bar{P}_n$ is the number average degree of polymerization and C_m is the chain transfer constant k_{tr}/k_p, assuming termination by coupling,[3,4]

$$\frac{1}{\bar{P}_n} = \frac{kdf[\text{Init}]}{R_p} + Cm.$$

If $\bar{P}_n$ and R_p are studied as a function of initiator concentration, k_p^2/k_t, k_df, and k_{tr}/kp can be determined.

Using α-azo-bis-isobutyronitrile as a catalyst, f was found to be approximately one, and k_d could be determined by measuring the decomposition of this initiator. This value was obtained without any assumption about termination; however, it agreed with the value obtained using the above equation which assumed termination by coupling.

By the rotating sector method, the lifetime of the kinetic chain T_s can be found. The ratio R_pT_s/M is equal to $k_p/2k_t$[30]. Combining this relationship with the others mentioned above, the individual rate constants can be found. At 60° these are

$k_p = 176$ l/mole sec[4] $\qquad 2k_t = 7.2\text{x}10^7$ l/mole sec[4]

$k_{tr} = 1.05 \times 10^{-2}$ l/mole sec $\qquad k_i = 2.15 \times 10^{-12}$ l/mole sec.

Bamford and Dewar[1] have determined the individual rate constants by another method. From changes in intrinsic viscosity of a photopolymerization during and after irradiation and knowledge of the molecular weight of the polymer, they were able to calculate the rate constants. Since their derivations assumed termination occurred by disproportionation, their validity has been questioned.[4]

From the Arrhenius equation, Flory determined the over-all activation energy for a thermal and photopolymerization. Assuming the same sequence of reactions holds for both polymerizations and photoinitiation requires only a small amount of energy, the activation energy for the thermal initiation can be calculated from the difference between their over-all activation energys. E_1 was found to be 32 kcal.

Using dissociation energies of 75 kcal. for C-C, 95 kcal. for C-H, and 60 kcal. for opening C=C, Flory[7] calculated that a first order initiation and a bimolecular process producing two monoradicals would require too much energy. A bimolecular process producing a biradical which could grow on both ends would require $\Delta H < 29$ kcal. approximately the amount observed.

$$2\ CH_2 = CH\text{-}\phi \longrightarrow \phi\dot{C}H\text{-}CH_2\text{-}CH_2\text{-}\dot{C}H\text{-}\phi \quad (I)$$

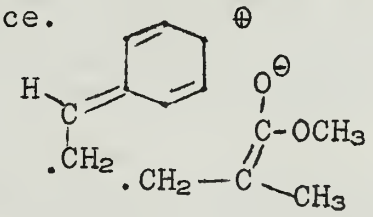
If the above process was reversible, initiation would be third order and ΔH was calculated to be less than 35 kcal.

$$2\ CH_2 = CH\text{-}\phi \rightleftharpoons \phi\text{-}\dot{C}H\text{-}CH_2\text{-}CH_2\text{-}\dot{C}H\text{-}\phi$$

$$CH_2{=}CH\text{-}\phi + \phi\text{-}\dot{C}H\text{-}CH_2\text{-}CH_2\text{-}\dot{C}H\text{-}\phi \longrightarrow \phi\text{-}\dot{C}H\text{-}CH_2\text{-}CH_2\text{-}\underset{\phi}{CH}\text{-}CH_2\text{-}\dot{C}H\text{-}\phi$$

Flory was unable to distinguish between the two initiation steps, but he favored (I) as the structure of the dimer biradical since it is stabilized and would require less activation energy for its formation. Staudinger's[6] work seems to support the argument that stabilization of the radical produced lowers the activation energy for its formation. He found that the ease of polymerization of olefins decreased in the order $C_6H_5\text{-}CH{=}CH_2 > CH_2{=}C(CH_3)_2 > CH_2{=}CH\text{-}CH_3 > CH_2{=}CH_2$. Since propagation, chain transfer, and termination are taken to be bimolecular and the over-all rate constant was second order,[2,13] most authors also assumed that initiation was second order.[18]

Walling[17] has compared the thermal initiation rate constants for pure styrene, 2.15×10^{-12} l/mole sec., and pure methyl methacrylate, 1.9×10^{-15} l./mole sec., with the initation rate constant for the two when they are mixed, 6×10^{-12}. He attributes the increase in the initiation constant to a polar effect in the transition state when cross initiation takes place.



A polar effect could also explain why k_i for styrene is greater than k_i for methyl methacrylate because a styrene molecule could have either positive or negative character from resonance.

Evidence for the existance of a diradical has been obtained by Melville and Watson[19] and by Kern and Feuerstein[20] both of whom isolated a two to one adduct of styrene and benzoquinone when this inhibitor was present during thermal polymerization.

Russell and Tobolsky[25] have compared the rate of disappearance of two inhibitors, 2,2 diphenylpicrylhydrazyl (DPPH) and benzoquinone, with the rate of thermal initiation of styrene in their absence and found the ratios to be

$$\frac{\text{Rate DPPH}}{\text{Rate th. in.}} = 85 \qquad \frac{\text{Rate Bzo}}{\text{Rate th. in.}} = 61 \text{ at } 60^\circ$$

These ratios were unity when catalysts were used as initiators. Since neither of these inhibitors were found to act as initiators, they concluded that biradicals are formed very rapid in the initiation step and most of them undergo self-termination to form small rings.

Haward[21] raised one the first objections to the diradical theory. He calculated, using Kuhn's statistical model of the polymer chain, that diradicals would prefer self-termination over bimolecular terminatinn. For a styrene diradical of molecular weight 10^4, the ratio of self-termination to bimolecular termination would be 165, 1650, and 16500 for diradical concentrations of 10^{-6}, 10^{-7}, and 10^{-8}, mole/l. respectively at 25°. This objection was supported by Mayo et al[3], who found that at 60° where the over-all rate constant is 0.0072 mole/l./hr., a diradical of 10,000 styrene units would have a root mean square distance between its ends of about 1050 A° as determined from light scattering data of a molecule of this length while the distant between individual radicals would be about 14,000 A° as determined from the propagation constant. Again, self-termination would be favored if diradicals are formed. In order to test these objections, Russell and Tobolsky[23] compared the polymerization of methyl methacrylate by the photodecomposition of 0.014M butyl disulfide which produces two monoradicals and 0.02M 1,4,5-oxadithiacycloheptane which produces a diradical. It was found that the efficiency of initiation of long chain polymers by photolysis of 1,4,5-oxadithiacycloheptane was less than 1% of that of butyl disulfide. Most of the diradicals produced underwent cyclization. It was also noticed that in the irradiated solution, the absorption of the S-S linkage dropped 16% during the reaction, indicating that some of the diradicals produced reacted with at least one molecule of monomer.

Zimm and Bragg[24] concurred that the high polymer formed in the thermal polymerization of styrene could not be produced from biradicals growing on both ends. They suggested that biradicals are produced in the initiation step, but only biradical chains of degree less than ten could then transfer with monomer producing monoradicals which carry on propogation while the larger biradicals cyclize. If biradicals of degree less than ten carry out this process at 60°, they calculate that 84% of the growing radicals present at one time will be monoradicals, and 71% of the monomer will be contained in the high polymer while 29% will consist of low molecular weight rings.

It was also thought that photoinitiated polymerization of styrene produced biradicals; however, Johnson and Tobolsky[22] showed that photoinitiation produced monoradicals. Using the relationship between $\bar{P}_n$ and R_p mentioned before, they plotted $1/\bar{P}_n$ as a function of R_p for a catalyzed and photoinitiated polymerization and obtained the same straight line. Since the catalyzed polymerization produces monoradicals and diradicals would give a different plot than monoradicals, they concluded that photoiniation produces monoradicals. They also suggested that possibly monoradicals could likewise be produced in the thermal initiated polymerization but had no evidence to substantiate it.

TERMOLECULAR INITIATION

When styrene was polymerized in chlorobenzene and bromobenzene, a low molecular weight product was isolated which did not contain any chlorine or bromine. Due to this uniqueness, Mayo[2] carried out extensive studies using bromobenzene as a solvent.

Polymerizations were carried out at 158°, and high and low molecular weight fractions were isolated. The high molecular weight fraction was dissolved in benzene and precipitated with methanol for purification. The low molecular weight fraction comprised about 2% of the total polymer at initial styrene concentrations of 1M; however, this percentage increases to 25% upon dilution to 0.05M concentration. Over a concentration range of 0.05M to 1.6M styrene, the rate of formation of high polymer appeared to be 5/2 order at 158°. He calculated the over-all rate constants from the following equations assuming second, 5/2 or third order where M and M_o are the initial and final concentrations of styrene in moles/l. and t is in seconds:

$$k_2 t = \frac{1}{[M]} - \frac{1}{[M]_o}$$

$$1.5 k_{5/2} t = \frac{1}{[M]^{\frac{3}{2}}} - \frac{1}{[M]_o^{\frac{3}{2}}}$$

$$2 k_3 t = \frac{1}{[M]^2} - \frac{1}{[M]_o^2} .$$

The rate constant for the formation of the high or low polymer is obtained by multiplying that fraction of total polymer produced times the over-all 5/2 order rate constant.

Exp	[Styrene]	Time hr.	%yield	Over-all rate k x 10^6 (L / H) k_2	$k_{5/2}$	k_3	%Low	Mol.Wt.	k x 10^6 Low	High
20	all	0.176	13.96	33.9	12.8	4.83	1.56	L	0.53	12.5
								H 116,000		
37	1.61	1.02	16.69	33.9	28.1	23.7	1.73	L	0.58	
								H 50,200		27.5
35	0.406	4.02	10.66	17.6	28.3	46.1	2.71	L 361	0.47	
								H 14,360		27.5
33	0.103	40.0	10.73	7.28	23.6	75.3	13.7	L 306	1.00	
								H 4,460		20.6
30	0.051	160.	15.28	5.67	25.0	119	24.9	L 356	1.36	
								H 1549		18.6

At 60°, for concentrations above 1M the formation of high polymer was closer to second order and above 0.4M the rate could be expressed as either 5/2 or second order. Since at 158° the rate of formation of high polymer is 5/2 order, a third order initiation is required. Using Matheson rate constants,[4] Mayo calculated the third order initiation rate constant.

$$k_{3i} = 1.32 \times 10^6 \exp(-28900/RT)$$

It was found that the high molecular weight polymer contained approximately 0.72 to 0.79 C=C per molecule while the low molecular weight fraction contained 0.50 to 0.63 C=C per molecule. Distillation of the low weight fraction yielded 20 weight % dimer and 50 weight % trimer. Mayo concluded that the high and low molecular weight fractions arose from different processes. He proposed that the low molecular weight fraction comes from the formation of a

biradical or from a nonradical interaction producing a saturated dimer or a trimer with some unsaturation. The high molecular weight fraction comes from a termolecular initiation step producing two monoradicals.

$$3\ C_6H_5\text{-}CH{=}CH_2 \longrightarrow H_3C\text{-}\overset{H}{\underset{\cdot}{C}}\text{-}C_6H_5 + H_3C\text{-}\underset{C_6H_5}{C}{=}CH\text{-}\overset{\cdot}{C}H\text{-}C_6H_5$$

This process would occur within the observed activation energy of 32 kcal. since the number of double bonds lost and single bonds formed is the same as in Flory's diradical formation. The above structure for the unsaturated monoradical is preferred by Mayo only because there is conjugation and resonance stabilization. Hiatt[29] has suggested that this radical would be too stable to account for the observed rate, therefore the alternate structure would be more favorable.

$$C_6H_5\text{-}\overset{\cdot}{C}H\text{-}CH_2\text{-}CH{=}CH\text{-}C_6H_5$$

Zimm and Bragg's proposal of diradical chain transfer with monomer must be reexamined in the light of Mayo's work. If one assumes that in the bulk polymerization of styrene the number of moles of low polymer formed corresponds to the number of biradicals generated, (7×10^{-5} at 60°) then even in ten propagation steps per radical only 10 C_m, where C_m is the chain transfer constant for styrene monomer, ($10 \times 6 \times 10^{-5}$) of these will be converted to monoradicals by transfer, much less than the number of moles of high polymer formed (2.54×10^{-6}) some of which came from transfer with monomer during prolonged growth of monoradicals. Thus biradicals are inadequate as a source of monoradicals in the absence of solvent. Since the over-all rate constant remains approximately constant from solvent to solvent, it appears that this transfer of biradicals also is not important in the presence of solvent.

Burnett and Loan[28] have criticized Mayo's work because he assumed that radicals produced by transfer were not capable of terminating and propagating chains and possibly re-initiating the polymerization process. A radical formed by chain transfer may react with a reactant molecule to restart a chain, with another of its own kind, or with a chain carrier. Taking these possibilities into consideration, they have derived a rate expression which has been simplified by Hiatt.[29]

The following notation is used: M is any monomer molecule; M· is any polymer radical; S is solvent; S· is any solvent radical.

1.			nM	$\xrightarrow{k_1}$	$2M\cdot$
2.	$M\cdot$	+	M	$\xrightarrow{k_2}$	$M\cdot$
3.	$M\cdot$	+	S	$\xrightarrow{k_3}$	$S\cdot$ + Polymer
4.	$S\cdot$	+	M	$\xrightarrow{k_4}$	$M\cdot$
5.			$2M\cdot$	$\xrightarrow{k_5}$	Polymer
6.	$S\cdot$	+	$M\cdot$	$\xrightarrow{k_6}$	Polymer
7.			$2S\cdot$	$\xrightarrow{k_7}$	Dimer

Since kinetic chains are long, (2) uses the most monomer and

$$-\frac{dM}{dt} = k_2\ M\ M\cdot$$

Assuming a steady state is obtained and chain transfer occurs many times per initiation,

$$\frac{dM^{\cdot}}{dt} = \frac{dS^{\cdot}}{dt} = 0$$

$$k_3\ SM^{\cdot} = k_4\ MS^{\cdot}$$

Solving for $M^{\cdot}$ and substituting into the rate expression gives

$$-\frac{dM}{dt} = k_2 M \frac{(k_i\ M^n)^{\frac{1}{2}}}{[k_5 + (2k_6 k_3/k_4)S/M + k_7(k_3/k_4)^2 S^2/M^2]^{\frac{1}{2}}}$$

Therefore, the reaction order in monomer will be dependent on the values of the termination constants, on k_3/k_4, and on the relative concentration of monomer and solvent. Burnett and Loan conclude that the over-all order of the thermal polymerization of styrene in bromobenzene should lie between 2 and 3 increasing with dilution. They claim that a point by point determination of reaction order from Mayo's data indicates a change from 2.0 to 2.8 in going from high concentration of monomer to low. Thus an over-all 5/2 order is wrong and a termolecular initiation is not necessary.

Hiatt and Bartlett[11] studied the polymerization in ethyl thioglycolate, which has a chain transfer constant of 58 at 60°. The reaction product isolated was the one-to-one adduct, ethyl β-phenyl ethylthioglycolate. The normal polymerization reaction (2) would thus be insignificant. Using the Burnett-Loan sequence of reaction, the rate of disappearance of mercaptan would be

$$-\frac{dS}{dt} = k_3 S \left[\frac{k_1\ M^n}{k_5 + (2k_6\ k_3/k_4)S/M + k_7(k_3 S/k_4 M)^2}\right]^{\frac{1}{2}}$$

In this case S stands for ethyl thioglycolate.

Rates were determined by iodine titer of remaining mercaptan in 90% acetic acid. Runs were carried out at 80°, 140.0°, and 100.9° while the ratio of mercaptan to styrene was varied from 0.08 to 250. The possibility of mercaptan participating in initiation was excluded because the ratio of $R/Ri^{\frac{1}{2}}$, where $R = -\frac{dS}{dt}$ and Ri is the rate of initiation, is the same in a run catalyzed by 2,2'-azo-bis-isobutyronitrile as in the thermal run with the initial proportions of styrene and mercaptan being the same. The ratio $R/(Ri^{\frac{1}{2}}S)$, by the preceding equation, is equal to

$$\frac{k_3}{[k_5 + 2k_6\ k_3/k_4 + k_7(k_3/k_4)^2]^{\frac{1}{2}}}$$

when S/M is unity. This constant was determined from the catalyzed run with S/M = 1 as 9.6 moles$^{-\frac{1}{2}}$ liter$^{-\frac{1}{2}}$ hr.$^{-\frac{1}{2}}$ at 80°. Knowing this constant, S, and R, the rate of thermal initiation $Ri = k_1 M^n$ can be solved for. This rate is compared with that calculated assuming bimolecular and termolecular initiation.

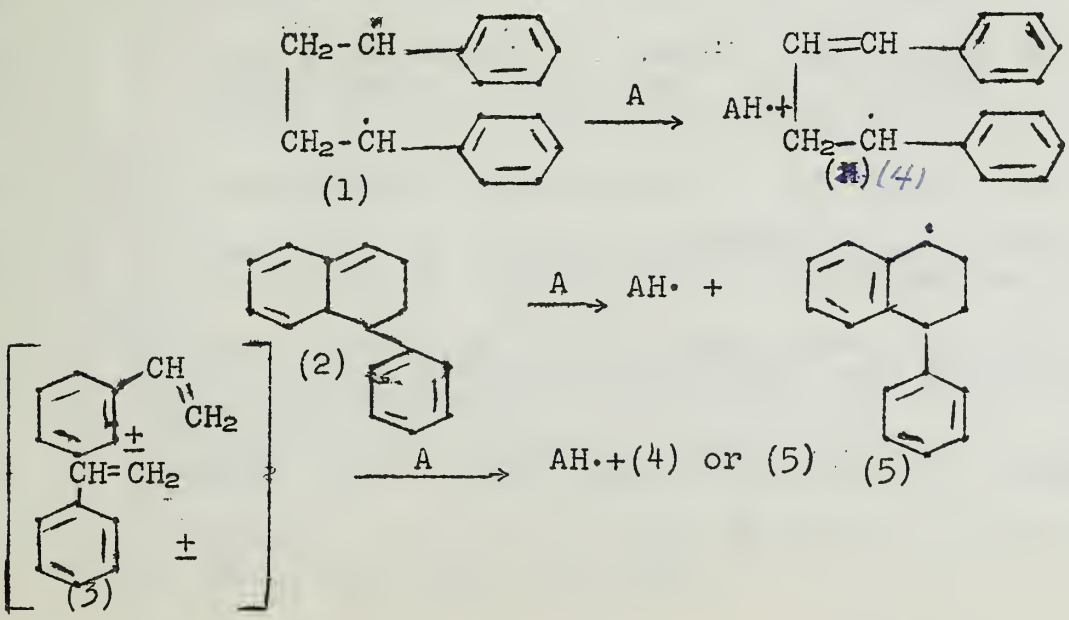
Time hr.	S moles/l.	M moles/l.	$\frac{-dS}{dt}$ mole/l.	Moles/l. hr.x10^7 Exp. Ri	Calc. Ri_3	Calc. Ri_2
0	3.70	4.66				
18	3.50	4.46	0.0244	5.3	7.0	15.9
43	3.00	3.96	.0188	4.3	4.9	12.5
67	2.58	3.54	.0135	3.0	3.6	10.1
91	2.31	3.27	.0099	2.0	2.7	8.5
139	1.84	2.84	.0071	1.6	1.8	6.3

These data support a third order initiation. Further evidence for a third order initiation was obtained when the initial concentrations of styrene and mercaptan were the same. Under these conditions the rate expression can be integrated to yield

$$\frac{1}{S^{\frac{n}{2}}} = At$$

where "A" is a constant. A plot of $1/S^{\frac{n}{2}} = 1/M^{\frac{n}{2}}$ vs time gave a straight line for n=3 but not for n=2. Runs with initial S/M ratios varying from 0.44 to 1.64 and final S/M ratios from 0.08 to 2.47, were satisfied by the expression $-dS/dt = AM^{\frac{3}{2}}S$. No correlation was found with $MS^{\frac{3}{2}}$ or $M^{\frac{1}{2}}S^2$ over this range which would be expected if one or two molecules of solvent were participating in initiation. The constant "A" remained constant over this range of S/M ratios. If steps (6) or (7) were dominant "A" would be expected to change when S/M changed. This means that termination is by reaction of two styrene type radicals, and Burnett and Loan's objection to Mayo's work is satisfied if this manner of termination is also dominant in bromobenzene.

Hiatt and Bartlett propose that the third order initiation occurs by two styrene molecules reversibly forming a complex which then reacts with a third styrene molecule which acts as a hydrogen acceptor producing two monoradicals. Three possibilities for the complex are given;



where (1) is a Flory diradical, (2) is a Diels-Alder type complex, and (3) is a charge transfer complex. Since the non reversible step requires that the complex act as a hydrogen donor, structure (1) is not favorable since it would be expected to be able to accept as well as donate a hydrogen. There is a possibility that other molecules may act as the hydrogen acceptor in initiation. Since the inhibitors studied by Russell and Tobolsky[25] are good hydrogen acceptors, they might participate in initiation and this would explain their rapid disappearance compared to the rate of thermal initiation.

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