SEMINAR TOPICS

Summer Session, 1959

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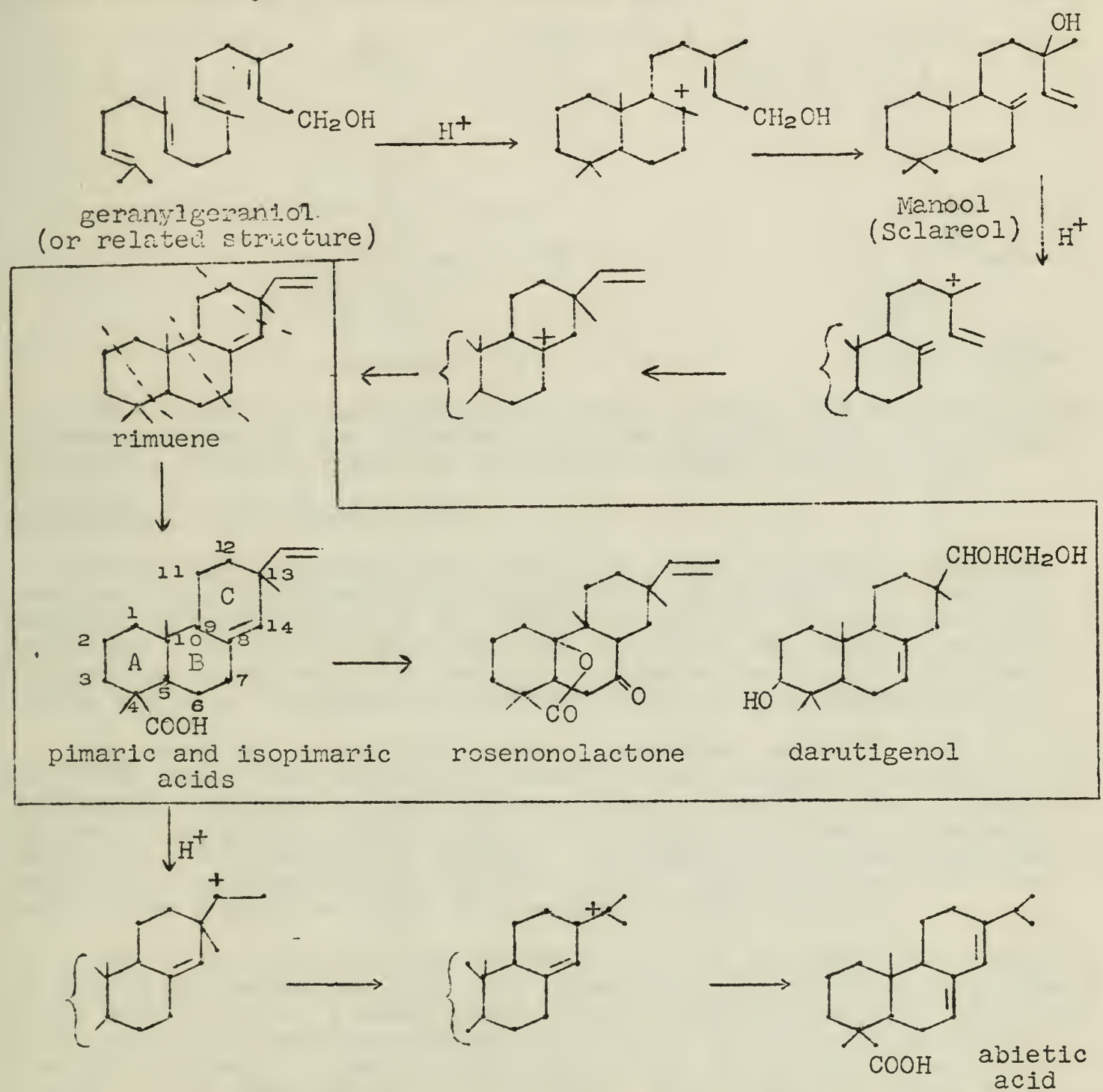
DITERPENES OF THE PIMARANE SERIES

Reported by J. R. Beck

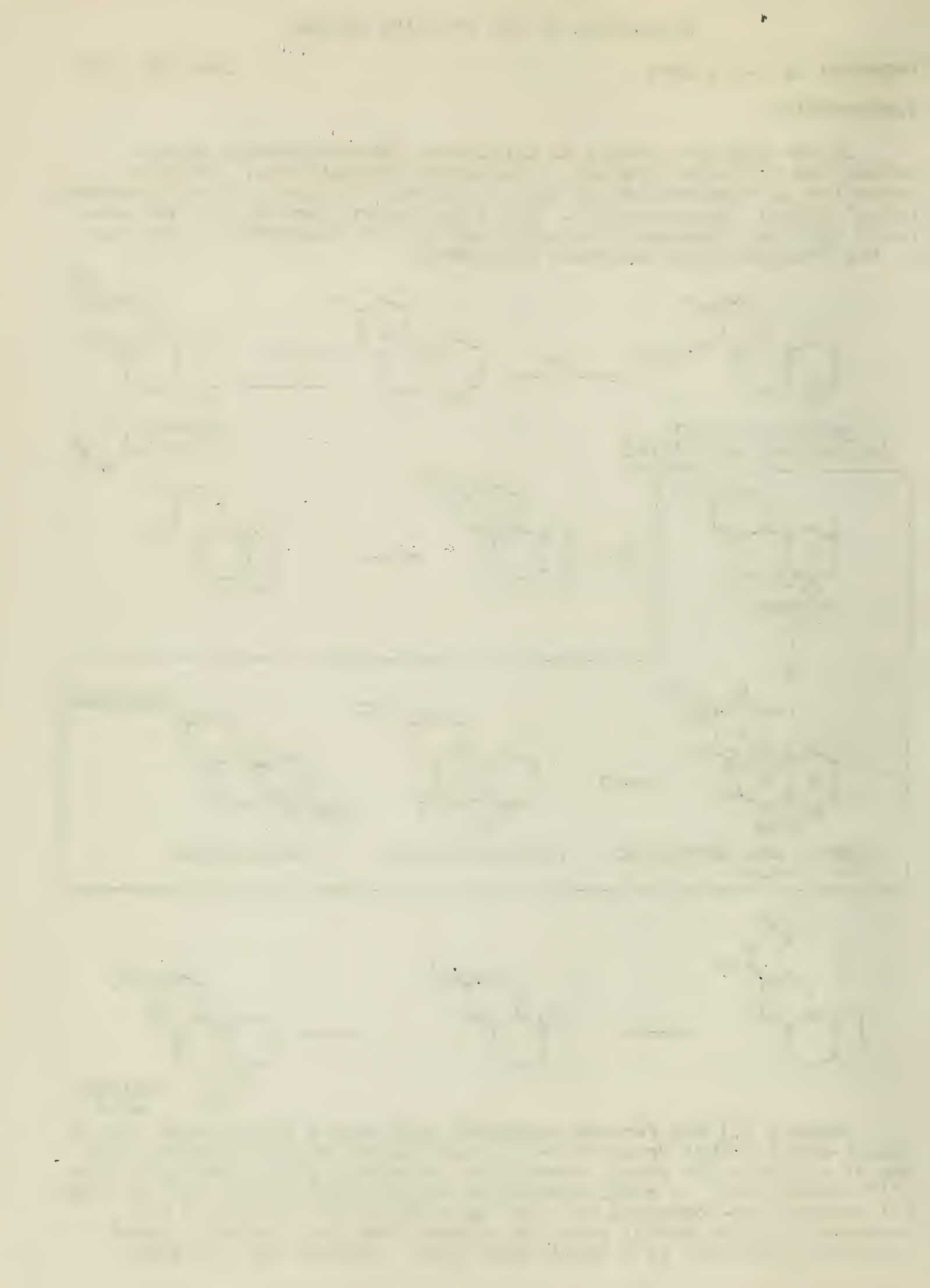
June 26, 1959

INTRODUCTION

In the pimarane series of diterpenes dehydrogenation always yields, as the major product, 1,7-dimethylphenanthrene. With the exception of rosenonolactone these compounds consist of four "isoprene units" linked "head-to-tail". For this reason, Ruzicka (1) has proposed that the pimarane diterpenes may well be biogenetic precursors of the tricarbocyclic abietane diterpenes.

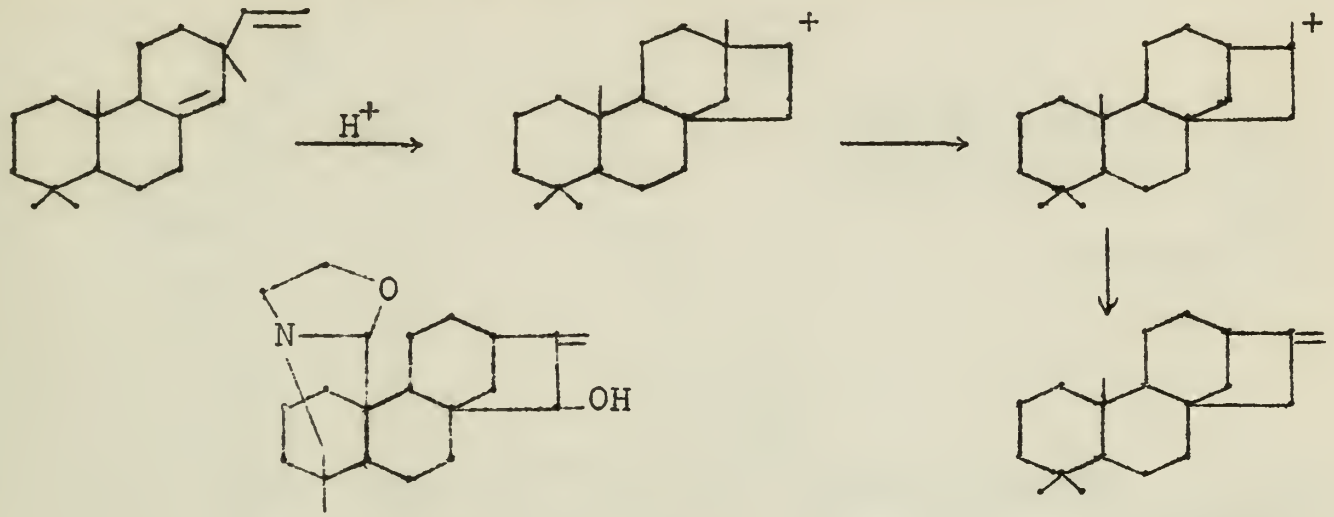


Wenkert (2) has further suggested that only a pimaradiene with a quasi-axial methyl group at C-13 could undergo methyl migration by way of a single low energy transition state with participation of the $\Delta^{8,14}$ double bond. A quasi-equatorial methyl group would make the overall process non-concerted and also more difficult because of the necessity for the methyl group to migrate from its favorable quasi-equatorial position to a quasi-axial atom. Wenkert has therefore



proposed that the natural occurring pimarane diterpenes must all possess quasi-equatorial methyl and quasi-axial vinyl groups at C-13 (since the opposite configuration should be enzymatically converted to the abietane diterpenes which occur in the same plant resins).

From this, the intermediacy of the pimaranes (quasi-axial vinyl group) was postulated in the biogenesis of the tetracarbocyclic diterpenes, e.g. phyllocladene (3,4,5) and the related Garrya alkaloids, e.g. veatchine (6), as well as the alkaloid atisine (7,8).



veatchine phyllocladene

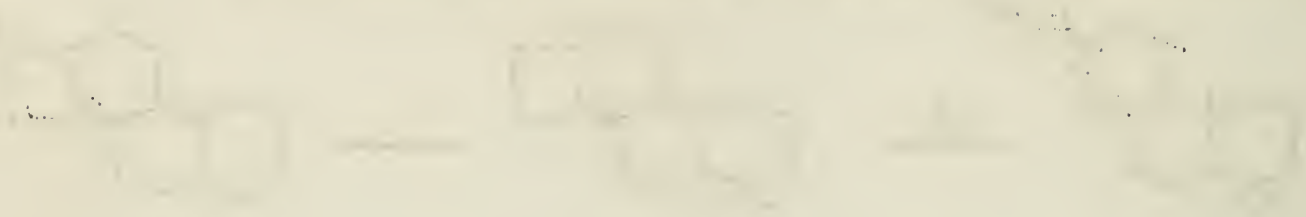
As a result of these proposals, much interest was focused on the stereochemistry of the pimaranes with the hope that this large group of natural products might all belong to a single steric group.

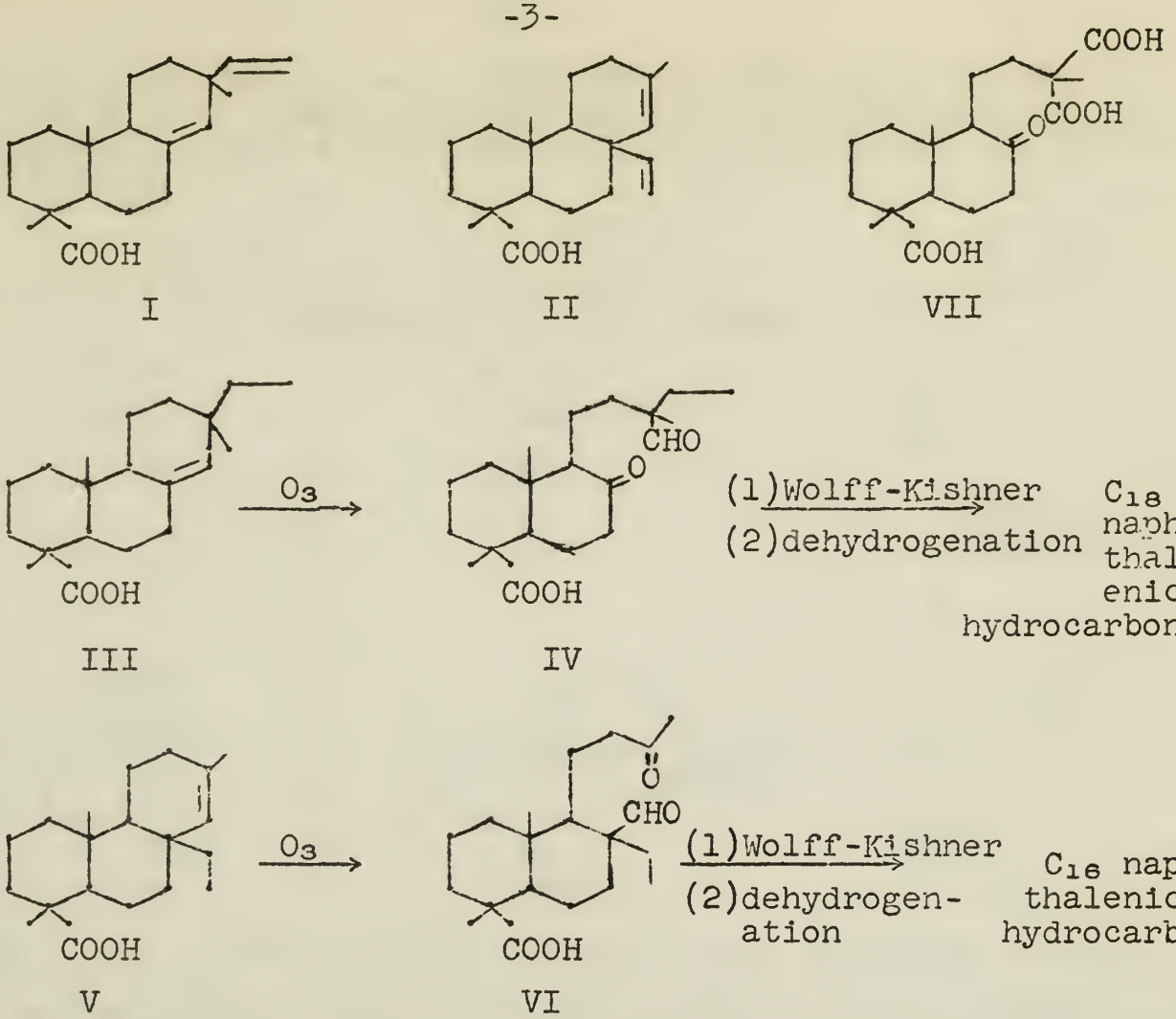
STRUCTURE OF THE PIMARIC ACIDS.

Early work concerning the structure proof of pimaric acid has been reviewed by Simonsen and Barton (9). As a result of chemical studies and application of the isoprene rule (1), Ruzicka and Sternbach (10) were able to show that the structure was either I or II. The authors preferred II primarily because no 1-methyl-7-ethylphenanthrene could be obtained by dehydrogenation of dihydropimaric acid.

By treating pimaric acid with concentrated sulfuric acid at -20 to -30°C, Fleck and Palkin (11) were able to recover a lactone in 25-30% yield. They attributed the formation of this lactone to migration of the C-ring double bond to the $\Delta^{8,9}$ position followed by lactonization at C-9 yielding a δ-lactone. Although their final assignment of structure was later proven incorrect (12), they concluded that the double bond migration could only occur with structure I.

That I actually was the correct structure was shown conclusively by Harris and Sanderson (13), who formulated that ozonolysis of the dihydro derivative of I would yield a keto aldehyde IV which could then be reduced and dehydrogenated to give a C_{18} naphthalenic hydrocarbon. Similar treatment of the dihydro derivative of II would give a C_{16} (or possibly C_{17}) naphthalenic hydrocarbon. The former was found to be the case and structure I was assigned to pimaric acid.





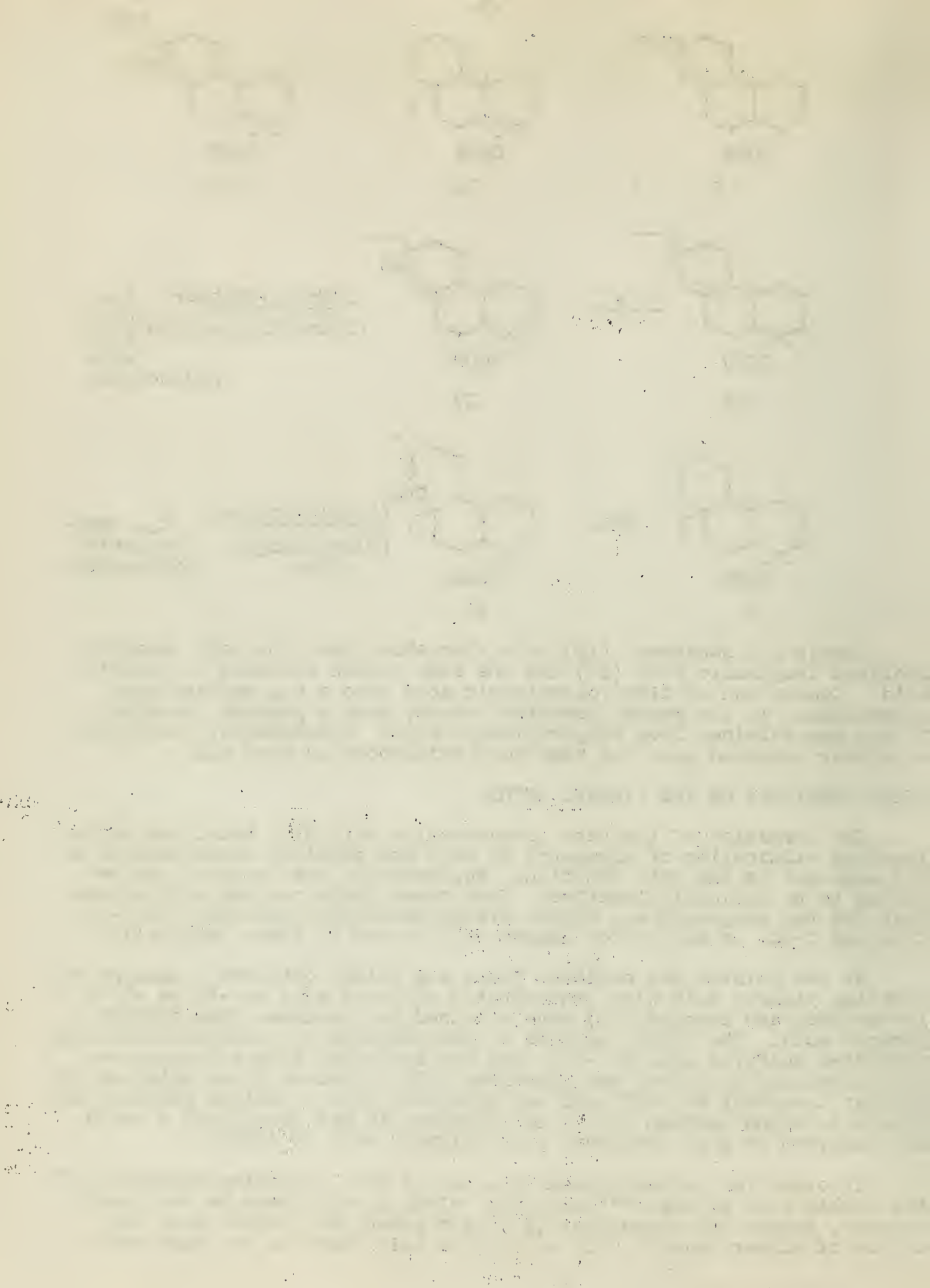
Harris and Sanderson (13) have also shown that the more recently isolated isopimaric acid (14) has the same carbon skeleton as pimaric acid. Conversion of dihydroisopimaric acid into a C_{18} naphthalenic hydrocarbon, in the manner described above, gave a product identical to the one obtained from dihydropimaric acid. Furthermore, ozonolysis of either compound gave the same keto tricarboxylic acid VII.

STEREOCHEMISTRY OF THE PIMARIC ACIDS.

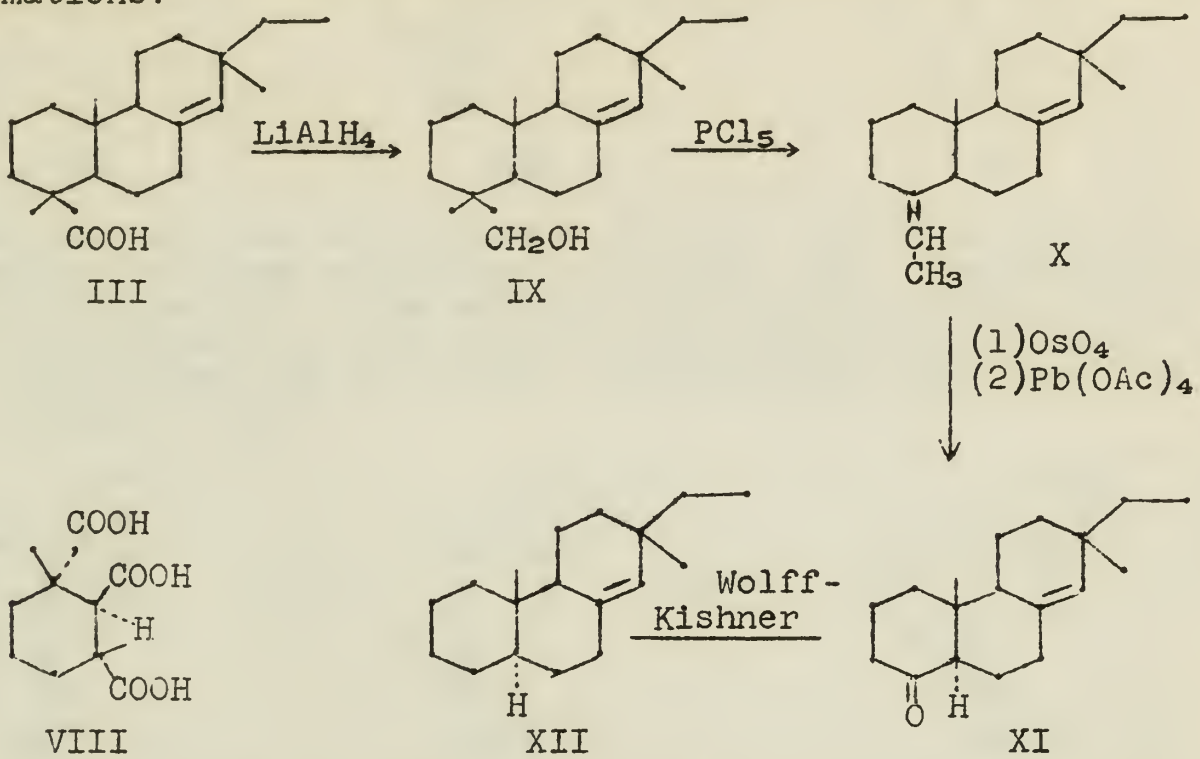
The formation of the keto tricarboxylic acid VII, mentioned above, involves elimination of asymmetry at C-13 and possibly isomerization at C-9 adjacent to the keto function. Furthermore, the compound was reported to be optically inactive. From these facts one can only assume that the two compounds are either stereochemically equivalent at C-4, C-5, and C-10, or are mirror images with regard to these centers (15).

As was pointed out earlier, Fleck and Palkin obtained a lactone by treating pimaric acid with concentrated sulfuric acid at -20 to -30°C. Le-Van-Thoi and Ourgaud (12) have obtained two lactones from dihydropimaric acid. The first, lactone A, was prepared by treatment with concentrated sulfuric acid at -5°C, and was identical with a lactone reported earlier by Harris and Sanderson (13). Lactone B was obtained by similar treatment at +20°C and was identical with a lactone reported by Hasselstrom and Hampton (16). In addition, it was found that A could be converted to B by treatment with sulfuric acid at +20°C.

In order for lactonization to occur at C-9, following migration of the double bond to the $\Delta^{8,9}$ position, rings A and B must be cis fused. However, Barton and Schmeidler (17) have shown that nitric acid oxidation of either abietic acid or pimaric acid leads to the same opti-



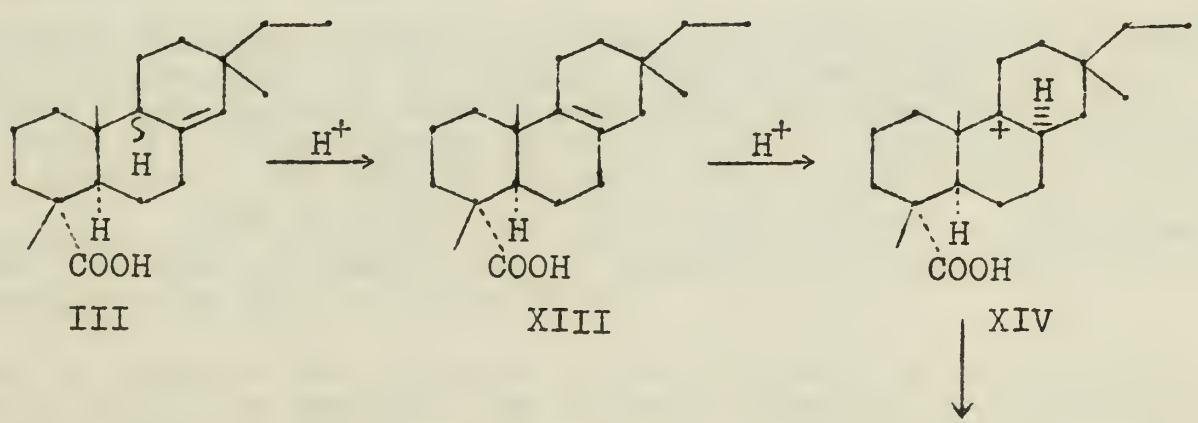
cally inactive tricarboxylic acid VIII, which indicates that the A/B ring fusion is in fact trans. Further evidence for the trans fusion has been obtained by Brossi and Jeger (18) who carried out the following transformations.

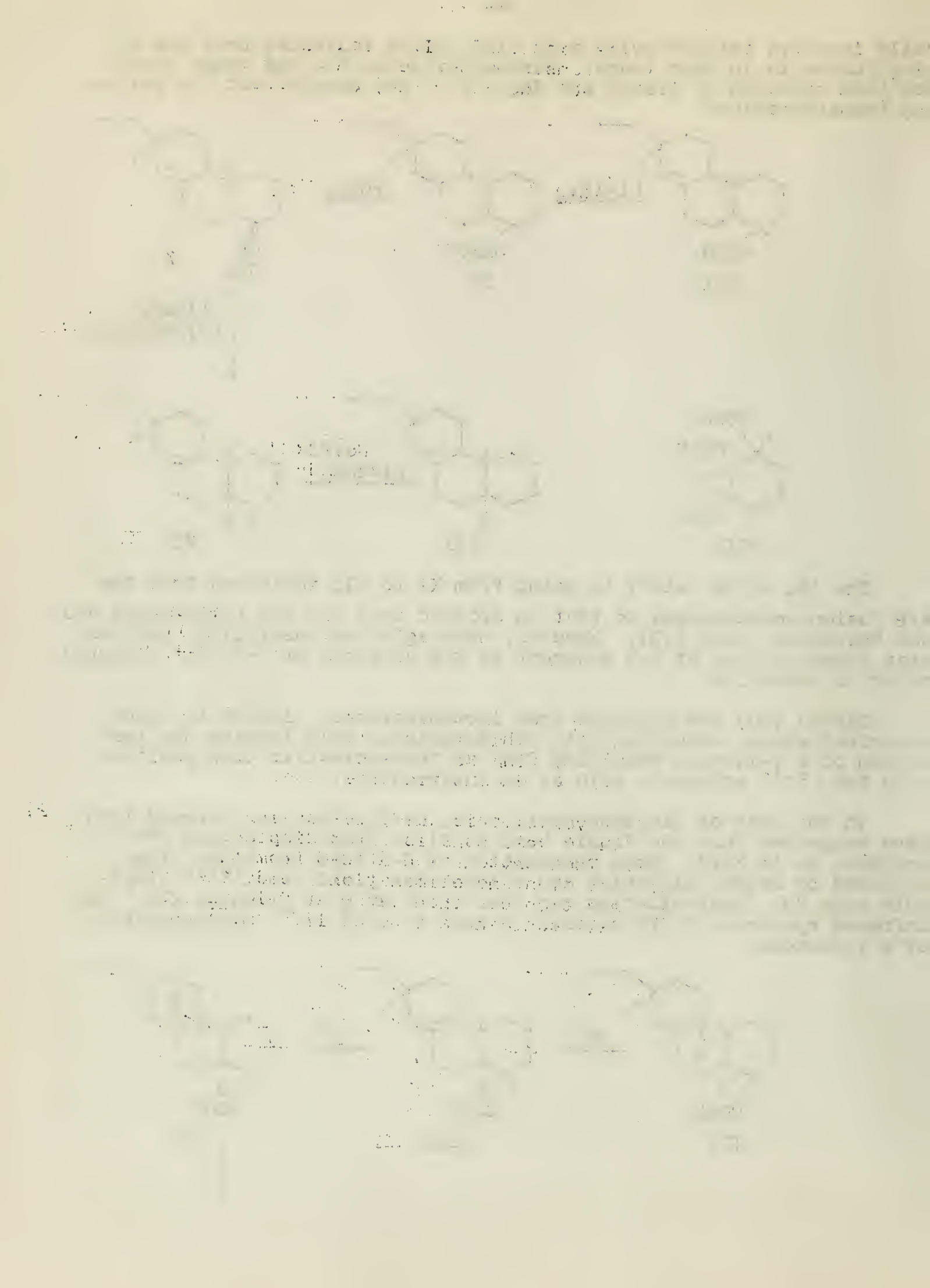


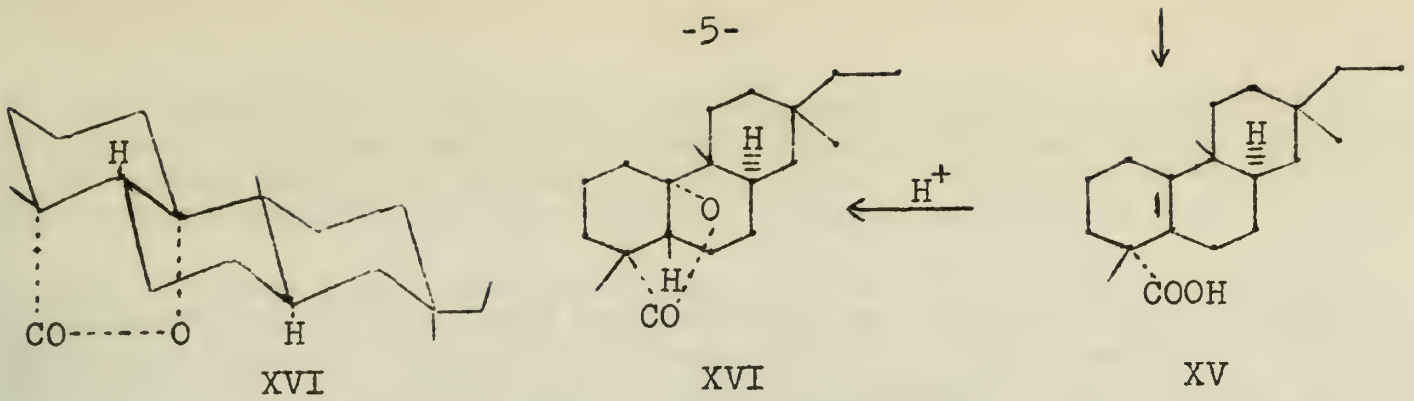
The ΔM_D value (+16°) in going from XI to XII indicated that the A/B fusion corresponded to that in abietic acid and the triterpenes and was therefore trans (19). However, here agin the possibility existed that isomerization at C-5 adjacent to the carbonyl at C-4, had occurred prior to reduction.

Barton (20) has proposed that lactonizations, similar to those described above, occurring with dihydroabietic acid involve the formation of a γ-lactone resulting from an intramolecular transposition with the $\Delta^{5,10}$ ethylenic acid as an intermediate.

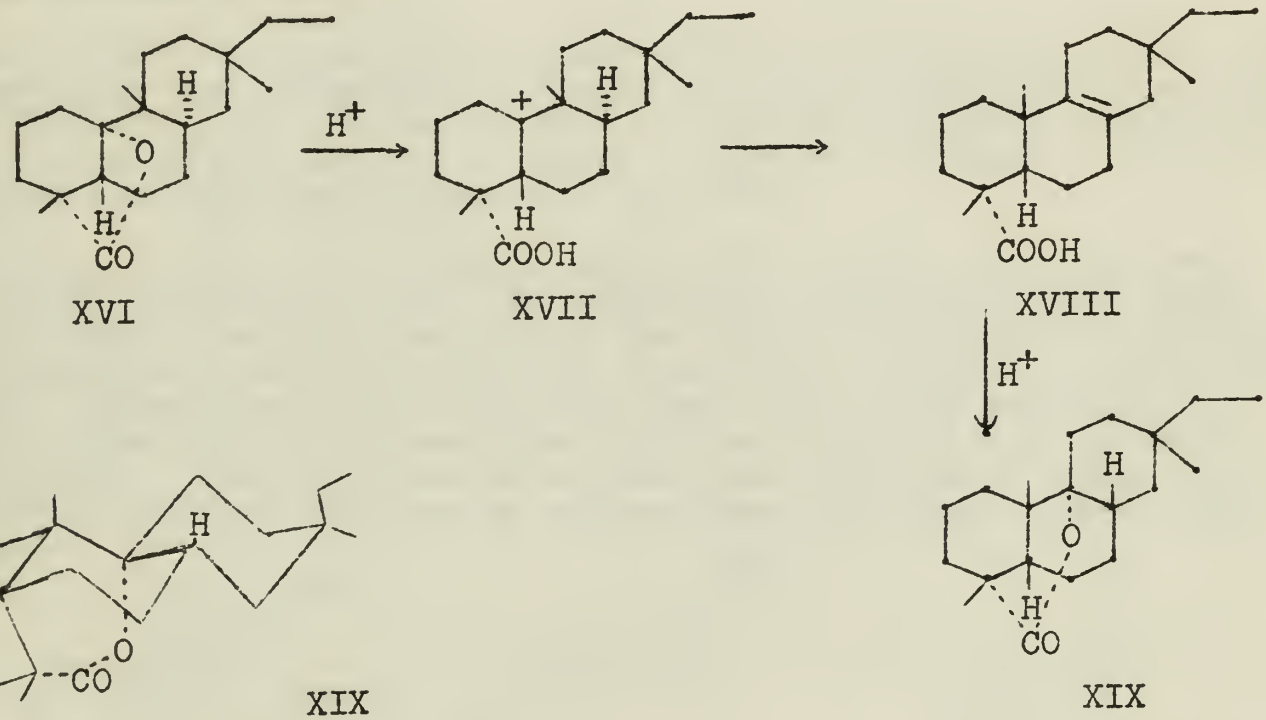
In the case of dihydropimaric acid, Le-Van-Thoi and Ourgaud (12) have suggested that the double bond is first displaced to the $\Delta^{8,9}$ position as in XIII. Then protonation at C-8 from the alpha side, followed by methyl migration and elimination yields the $\Delta^{5,10}$ ethylenic acid XV. Lactonization can then occur at C-10 yielding XVI. The infrared spectrum of XVI contains a band at 1778 cm.$^{-1}$ characteristic of a γ-lactone.







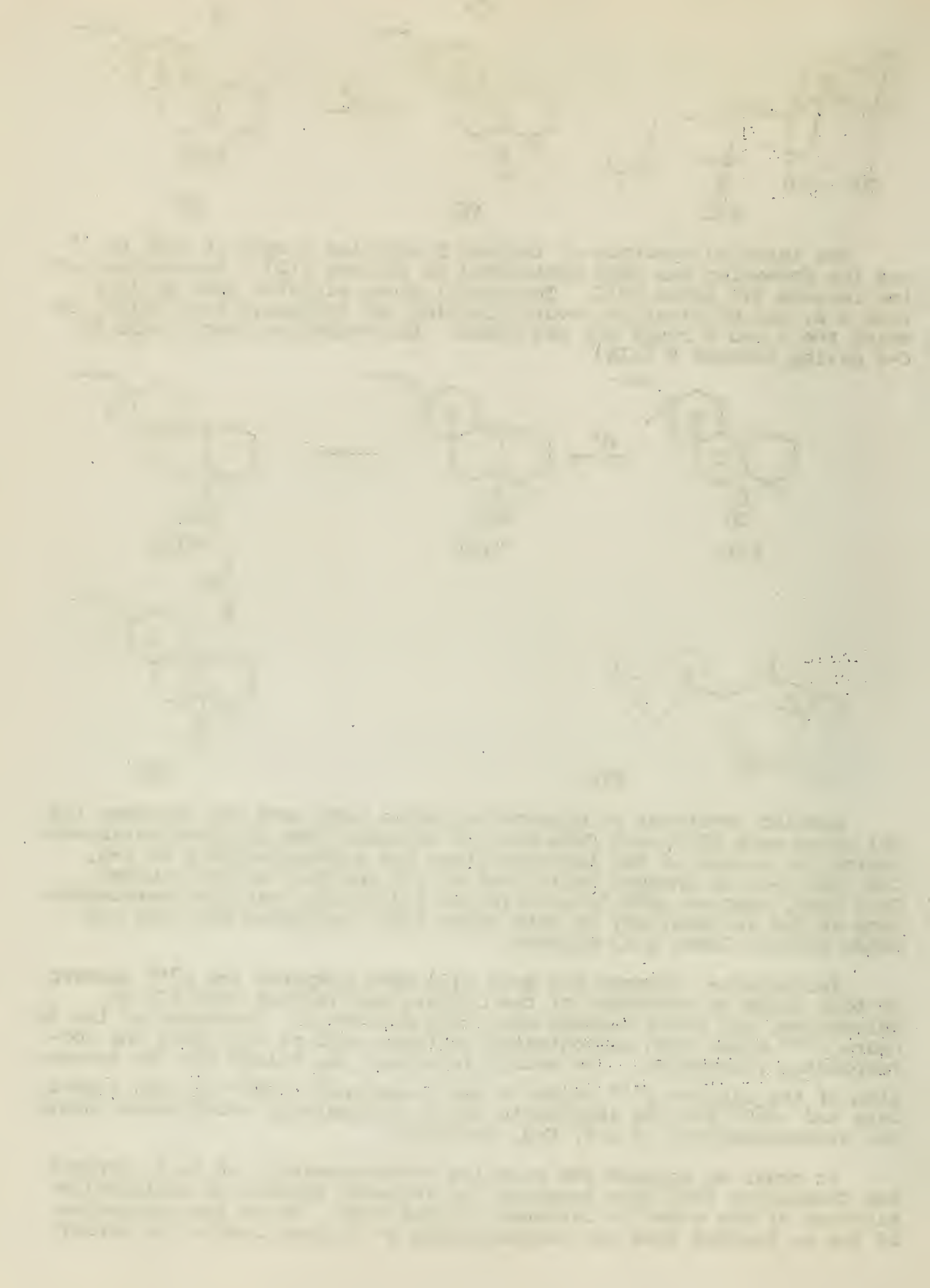
The infrared spectrum of lactone B contains a band at 1726 cm.$^{-1}$ and its formation has been postulated as follows (12). Protonation of the lactone XVI gives XVII. The methyl group migrates back to 10 β from 9 β, and elimination occurs yielding the ethylenic acid XVIII, in which the A and B rings are cis fused. Lactonization then occurs at C-9 giving lactone B (XIX).



Similar treatment of dihydroisopimaric acid gave two lactones (15, 21) which were different from the two obtained from dihydropimaric acid. During the course of the lactonizations the stereochemistry at C-5, C-9, and C-10 is changed while that at C-4 and C-13 is undisturbed. This fact, coupled with later evidence indicating that the stereochemistry at C-4 is identical in both cases (15), indicated that the two acids were at least C-13 epimers.

Furthermore, Edwards and Howe (15) have prepared the $\Delta^{8,9}$ isomers of both acids by treatment of the dihydro derivatives with HCl in chloroform, and these isomers were also different. Treatment of the dihydro $\Delta^{8,9}$ acids with concentrated sulfuric acid at -5°C gave the corresponding γ-lactones. The nearly identical ΔM_D values for the conversion of the dihydro $\Delta^{8,9}$ acids to the γ-lactones (-268° for the pimaric case and -260° for the isopimaric case) conclusively established identical stereochemistry at C-4, C-5, and C-10.

In order to compare the relative stereochemistry at C-13, Wenkert and Chamberlin (22) have examined the infrared spectra of equilibrium mixtures of the γ-and δ- lactones in each case. Since the conversion of the γ- lactone into the corresponding δ- lactone involves a confor-



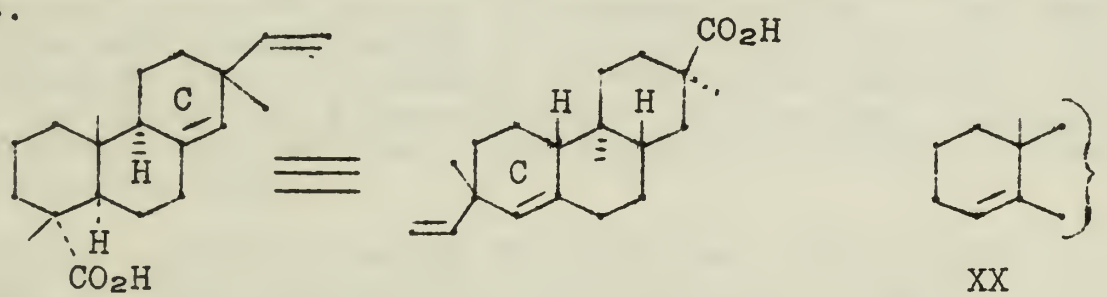
mational inversion at C-13, it would appear that the component with the highest γ-lactone content at equilibrium would be the one with the bulkier ethyl group in the beta (equatorial) position. These conclusions are independent of the original stereochemistry at C-9.

The authors found that equilibration of the γ-lactone (concentrated sulfuric acid at room temperature for 19 hours) from dihydropimaric acid gave a mixture containing 95.0 + 0.6% δ-lactone and 5.0 ± 0.6% γ-lactone. Similarly for the dihydroisōpimaric acid case, the mixture contained 96.4 ± 0.8% δ-lactone and 3.6 ± 0.8% γ-lactone.

From this they concluded that the vinyl group at C-13 is beta in pimaric acid and alpha in isopimaric acid. However, due to the very small differences involved, these conclusions are not entirely satisfactory in the light of the present status of quantitative infrared spectrum analysis.

Bruun (23,24) had reached the same conclusion from surface tension measurements but the assumption was made that the hydrogen atom at C-9 was alpha in both acids and the effect of the $\Delta^{8,14}$ double bond on the conformation of ring C was not included in the calculations. His conclusions are therefore not necessarily accurate.

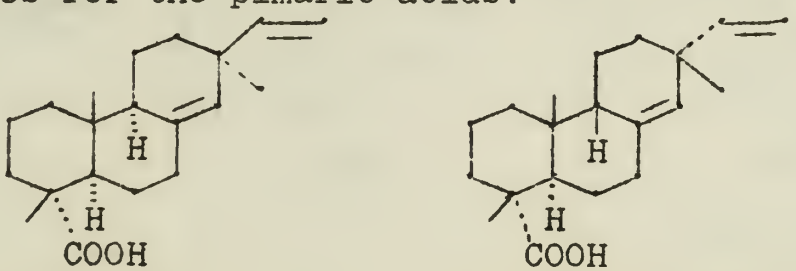
Green et al (25) have recently presented evidence that the two acids are also epimeric at C-9. Treatment of dihydroisopimaric acid with dilute HCl, under considerably milder conditions than were reported not to isomerize pimaric acid (26), led to the formation of the $\Delta^{8,9}$ derivative. From this it was concluded that the methyl group at C-10 and the hydrogen atom at C-9 must be trans in pimaric acid and cis in isopimaric acid. Hydrogenation data involving the pimaric acids and the sterically related Δ^4-steroid, cholest-4-ene XX also support this hypothesis.



XX

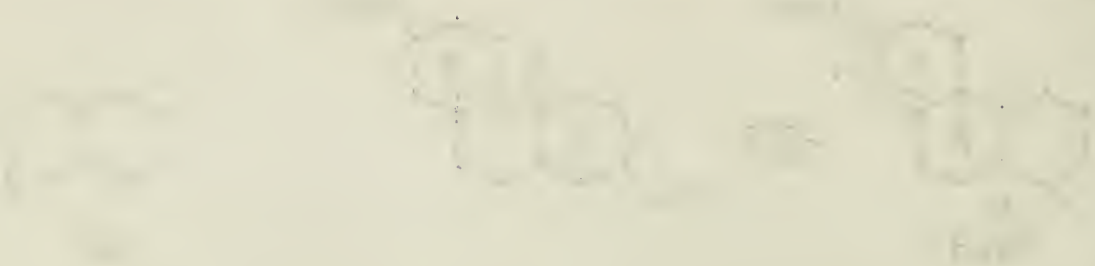
The ΔM_D for the hydrogenation of dihydropimaric acid was found to be +5° while that for cholest-4-ene was +149°. The corresponding value for dihydroisopimaric acid was found to be -89°.

On the basis of these findings, and applying the conclusions of Bruun (24,25) concerning C-13, Green et al have provisionally assigned the following structures for the pimaric acids.



pimaric acid isopimaric acid

In support of Green's conclusions concerning C-9 Bruun et al (27)



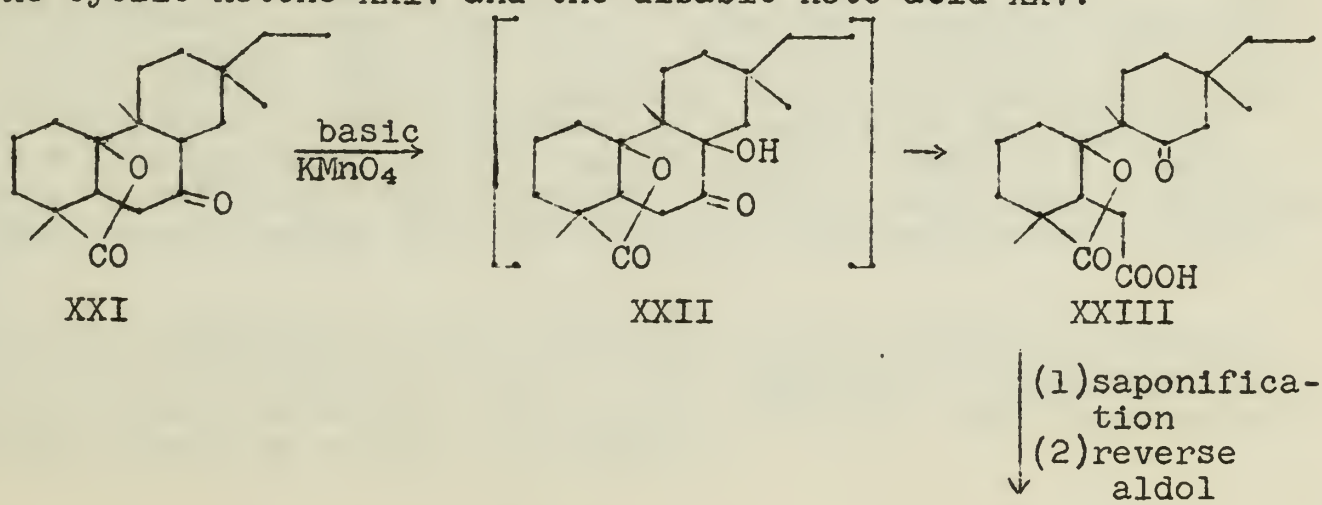
have recently stated that mass spectrographic evidence indicates that the two acids are indeed C-9 epimers. Edwards and Howe (15) are now attempting to eliminate asymmetry at C-13 by converting the vinyl group into a methyl group. Their findings should provide conclusive evidence as to whether or not the two acids are epimeric at C-9.

STRUCTURE OF ROSENONOLACTONE AND RIMUENE.

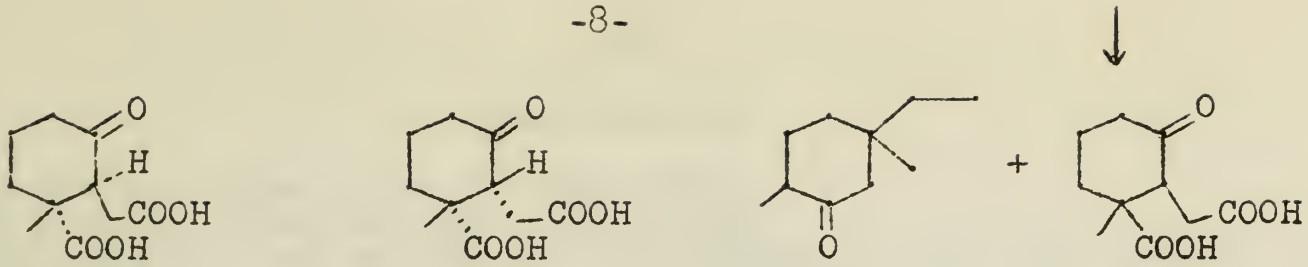
As was stated earlier, rosenonolactone differs structurally from the other members of the pimarane series in that it consists of four "isoprene units" arranged in an irregular manner (1), indicating either a different precursor or more likely a methyl migration during biogenesis. Ozonolysis of rosenonolactone yielded formaldehyde as in the case of the pimaric acids, and hydrogenation gave a dihydro derivative (28). The infrared spectrum contained a band at 1786 $cm.^{-1}$ indicating a γ-lactone and a band at 1724 $cm.^{-1}$ which was shown to be due to a six-membered cyclic ketone (29). Selenium dehydrogenation yielded 1,7-dimethylphenanthrene and 1,7-dimethyl-9-hydroxyphenanthrene, thus placing the keto function at C-7 (30). Treatment of rosenonolactone with 2N alcoholic HCl gave a mixture of that compound plus an isomer which was designated isorosenonolactone. The infrared spectrum of this compound contained bands at 1776 and 1712 $cm.^{-1}$, and it seemed probable that isomerization had occurred at C-8.

Treatment of dihydrorosenonolactone with basic permanganate gave rosoic acid with no overall change in C-methyl content. Mild alkaline hydrolysis of rosoic acid yielded a cyclic ketone $C_{10}H_{18}O$ plus a dibasic keto acid $C_{10}H_{18}O_5$. The cyclic ketone on treatment with nitric acid yielded 2-methyl-2-ethylsuccinic acid (although the amount obtained was insufficient for an optical rotation measurement). By analogy to the pimaric acids, it therefore appeared that the cyclic ketone was probably derived from the C-ring of rosenonolactone. Treatment of the cyclic ketone with ozone yielded a monobasic keto acid which gave a positive iodoform test, in contrast to the parent compound. It was therefore concluded that a transformation of the type, $-COCH(CH_3)- \longrightarrow -COOH + -CO(CH_3)$, had occurred. Consequently the cyclic ketone was assigned structure XXIV.

The overall reaction scheme proposed was that the action of basic permanganate on dihydrorosenonolactone XXI leads possibly to the formation of the 8-hydroxy derivative XXII, which then undergoes carbon-carbon bond cleavage giving the keto carboxy lactone XXIII. Saponification of the lactone followed by a reverse aldol-type condensation gives the cyclic ketone XXIV and the dibasic keto acid XXV.



XXI XXII XXIII



XXVa XXVb XXIV XXV

The dibasic keto acid XXV was obtained as a mixture of two diastereoisomers. One of the isomers was stable to acid and base and was therefore probably trans XXVa, while the second diastereomer could be isomerized to the first and was therefore cis XXVb. Consequently rings A and B must be trans fused in rosenonolactone.

Birch et al (31) have shown that the biological formation of rosenonolactone can be explained by precursors as outlined in the introduction, the difference being that a methyl group migrates from C-10 to C-9 during biogenesis, similar to a situation encountered in steroid biogenesis (32). This particular methyl migration and lactonization is remarkedly similar to the acid catalyzed γ-lactonizations of the pimaric acids. The methyl migration was shown by incorporating mevalonic lactone, labeled in the two position, into rosenonolactone. Degradation showed that the rosenonolactone was labeled at C-1, C-7, C-12, and at the methyl carbon on C-4. These conclusions were independently arrived at by Britt and Arigoni (33).

The structure of rimuene has been determined by Briggs et al (34). Hydrogenation of rimuene led to a dihydro derivative and under more vigorous conditions a tetrahydro derivative. The infrared spectrum contained a doublet at 1381 and 1368 cm.$^{-1}$ characteristic of gem-dimethyl groups. Dehydrogenation gave 1,7-dimethylphenanthrene and ozonolysis gave formaldehyde. Monoperphthalic acid oxidation of dihydrorimuene gave an oxide which upon treatment with methyl magnesium iodide yielded 1,2,8-trimethylphenanthrene, thus placing the second double bond at the $\Delta^{8,14}$ position as in the pimaric acids. It was therefore concluded that the structure of rimuene is as shown in the introduction. The synthesis of rimuene from the pimaric acids is now in progress (34).

CONCLUSION.

Since Wenkert's original proposal (2) of the intermediacy of the pimarane diterpenes in the biogenesis of the phyllocladene diterpenes and the related Garrya alkaloids and atisine, investigations (35,36), chiefly optical rotary dispersion studies, have shown that these compounds are antipodal to the pimaranes and steroids at the A/B ring fusion (C-5 hydrogen beta and C-10 methyl alpha). This fact coupled with the quite different stereochemistry of the pimaric acids indicates that several steric groups may be involved in the biogenesis of these compounds.

Since the completion of this abstract, a new pimarane diterpene, darutiginol, has been reported (37). This compound is unusual as it contains a hydroxyl function at C-3 and is antipodal (A/B ring fusion) to the other pimaranes and the triterpenes.

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MICROBIOLOGICAL REDUCTIONS OF DECALINDIONES

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INTRODUCTION

The practical significance of microbiological reactions for obtaining known steroid hormones (1) has led to numerous investigations of these reactions in the steroid series. The known factual material very impressively demonstrates the uniqueness of these reactions in regard to both stereoselectivity and product stereospecificity. In the case of microbiological reactions of steroids the stereospecificity is excellent in comparison to similar reactions carried out in vitro.

Quite recently Prelog and co-workers have been interested in microbiological reductions of decalindiones and other closely related systems (2-9). They have investigated several microorganisms; but, in particular, they have found two, Curvularia falcata (Tehon) Boedijn and Rhizopus nigricans Ehrenb., which displayed a low degree of stereoselectivity but a high degree of product stereospecificity. However, the former displayed a much higher degree of product stereospecificity than the latter and has been shown to react in a very definite steric course.

Several of the microorganisms investigated by Prelog and co-workers have been used in the steroid series. Curvularia falcata has been found to hydroxylate the 7α-position (10), Rhizopus nigricans has been used in the hydroxylation of either the 11α- or the 6β-position (11), and Streptomyces of the breed ETH. A 7747 brings about hydroxylation in the 16α-position (12).

The system used for the designation of absolute configurations at the various sites of asymmetry was that developed by Cahn, Ingold, and Prelog (13,14). This system involves three main rules. These are summarized below along with a few examples of their application.

I. Absolute Configuration Labels

If under the sequence and conversion rules, the center of asymmetry is a right-handed arrangement it is designated by an R, if it is a left-handed one it is designated by an S.

II. The Sequence Rule

The sequence rule in its very simplest form states that in the representation of an asymmetric atom the groups shall be arranged in the order of decreasing atomic numbers of the atoms bound to it. More often in organic chemistry at least two groups are bound to the asymmetric atom through carbon atoms. In this case the sequence rule has to be extended until there exists some difference between the groups.

Thus in (+)-amyl alcohol (Fig. I.), there are three methylene groups and a hydrogen atom bound to the asymmetric carbon atom. However, one of the methylene groups is bound to an oxygen atom, one is bound to a carbon atom, and the other is bound to a hydrogen atom. The differences in atomic numbers of these atoms gives the sequence as: $-CH_2OH > -CH_2-CH_3 > -CH_3 > -H$. Thus the asymmetric atom has the R configuration.

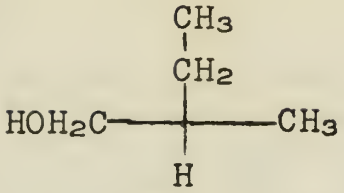


Fig. I

When a double bond is encountered the atom at its further end is considered to be duplicated. Thus in the case of $-CH=CH_2$, it is counted as $-\overset{C}{\underset{|}{C}}H-CH_2$. This means that an ethylenic linkage would have preference over any primary alkyl group but it would be subordinate to any secondary alkyl group.

III. The Conversion Rule

If four groups are in an assemblage Xabcd (Fig. II), the conversion rule states that their spatial pattern shall be described as left- or right-handed as the sequence a→b→c traces a left- or right-handed turn. A model of a steering wheel and its shaft is sometimes helpful in this matter. If the atom or group d is placed down the steering shaft; and a, b, and c are placed on the steering wheel, the result is shown in Fig. III. Since the sequence rule states the sequence as a→b→c, it is obvious that this is a right-handed arrangement and is designated R.

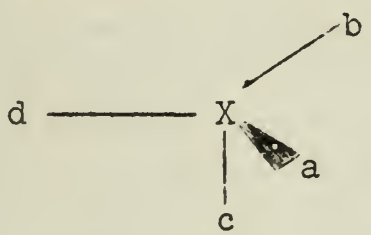


Fig. II

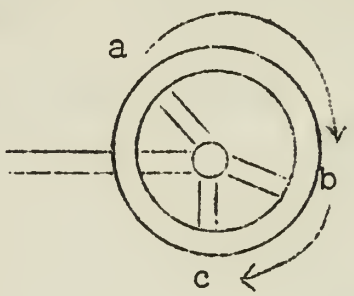


Fig. III

Another example is that of (+)-limonene, which is represented by the stereoformula given in Fig. IV. The sequence rule states $-\overset{Me}{\underset{|}{C}}=CH_2 > -CH_2-CH=\overset{Me}{\underset{|}{C}}- > -CH_2-CH_2- > -H$.

If the hydrogen atom at C-4 is placed down the steering shaft, the result is that (+)-limonene has the R configuration.

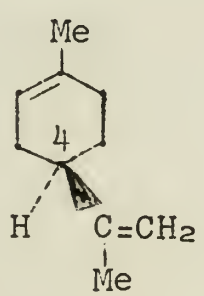


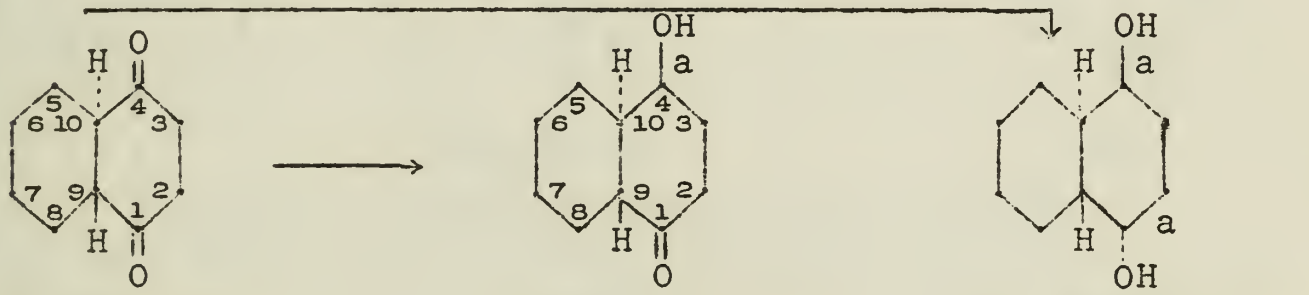
Fig. IV

MICROBIOLOGICAL REDUCTIONS

In experiments carried out on 1,4-decalindione both diastereomers were used (2). The trans-fused isomer has one racemic, enantiomorphic pair (I and II), while the cis isomer has one meso form (X) since it possesses a plane of symmetry. On the basis of preliminary investigations two microorganisms, Curvularia falcata and Rhizopus nigricans, were employed when the reductions were carried out on a preparative scale. It should also be pointed out that racemic, trans-1,4-decalindione was used as a reactant.

The results of these investigations are summarized in the following two charts:

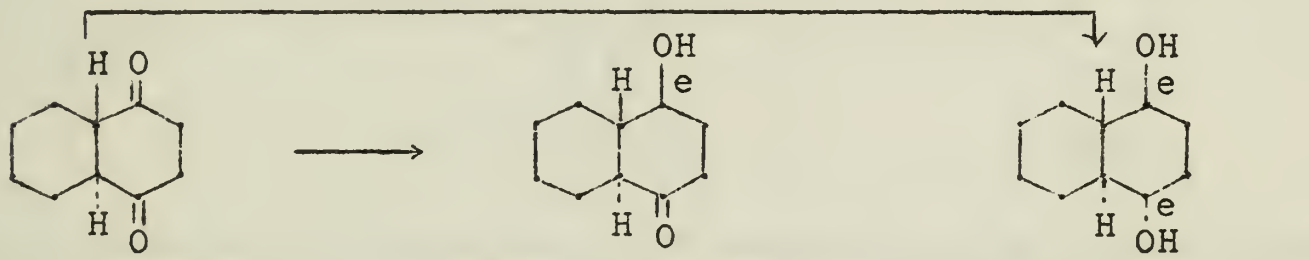
Chart I
Reductions with Curvularia falcata



I (-)-(9R)-trans

III (4S,9R)-trans
k* = 0.5

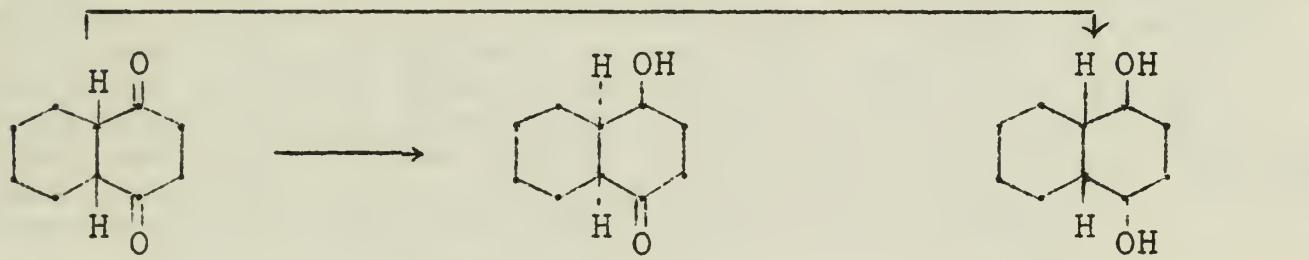
V(1S,4S,9R)-trans
k* = 6.0



II (+)-(9S)-trans

IV(4S,9S)-trans
k* = 0.25

VI(1S,4S,9S)-trans
k* = 1.1



X cis(meso)

XI(4S,9S)-cis

XIII(1S,4S,9R)-cis

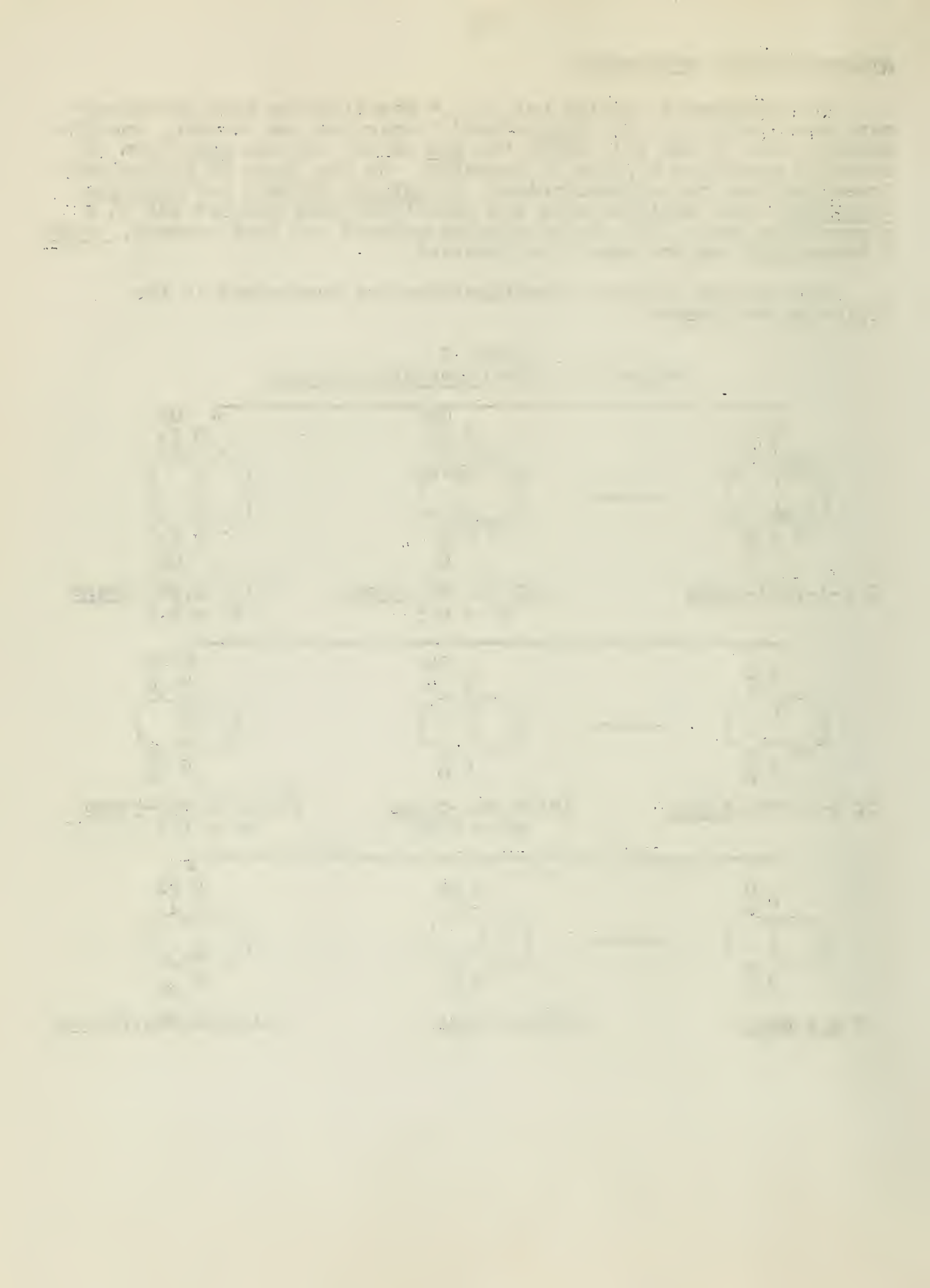
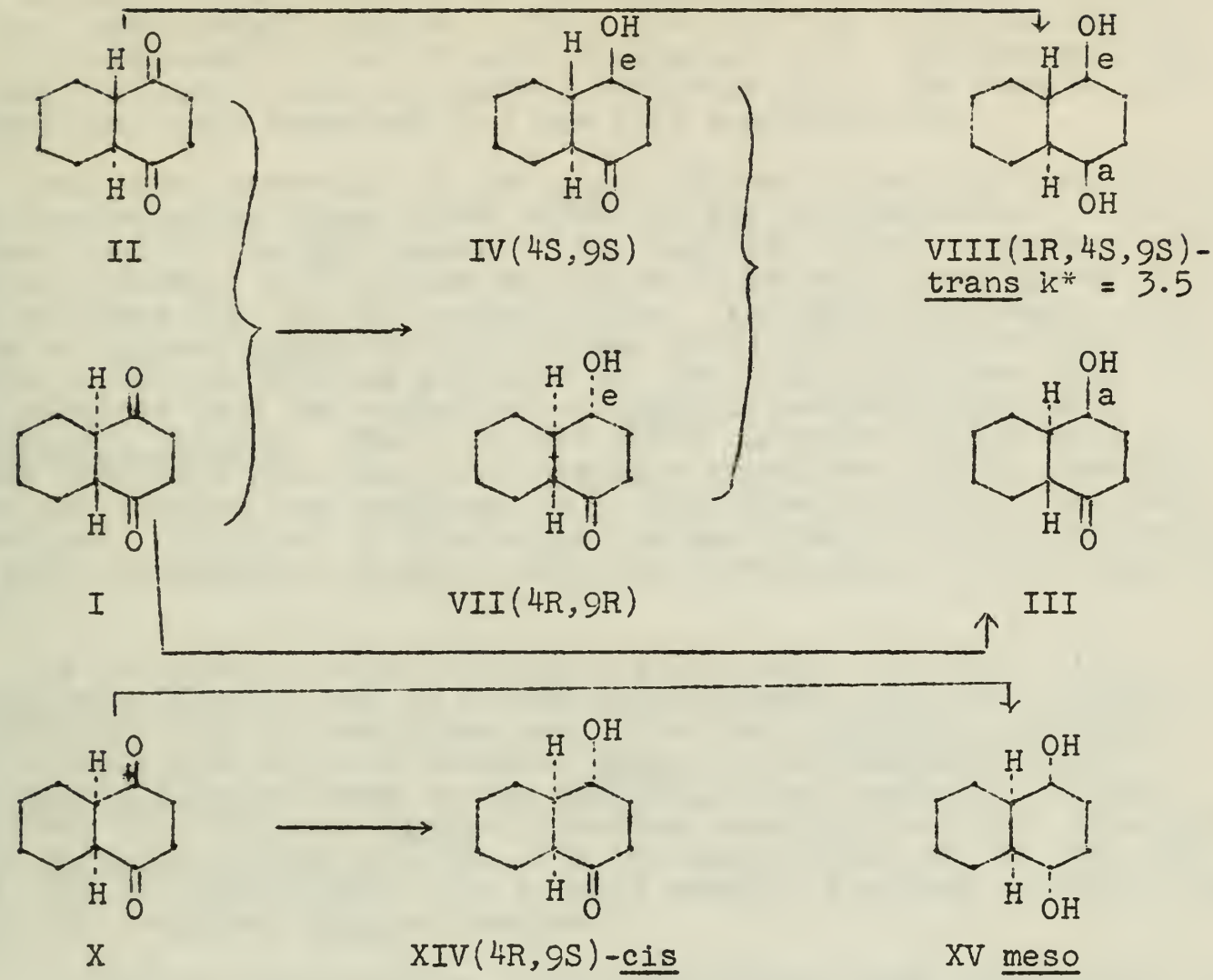


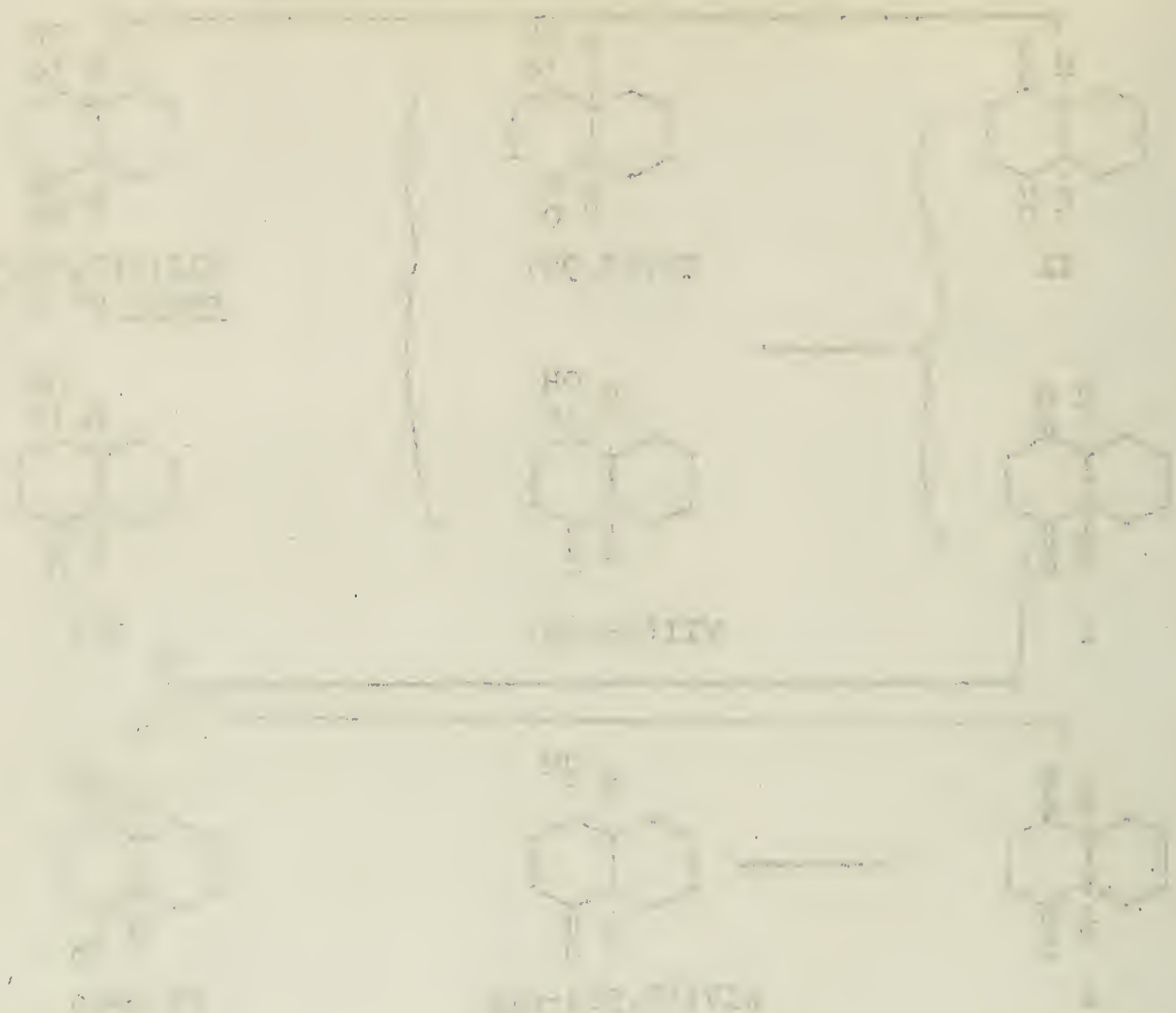
Chart II
Reductions with Rhizopus nigricans



The relative configurations of the resulting trans-hydroxyketones and diols were derived on the basis of their relative rates of oxidation, k*, with chromium (VI) oxide in glacial acetic acid (15) using 3β-cholestanol as the reference (k* = 1). For the determination of the absolute configuration of the enantiomers of trans-1,4-decalindione, optical rotary dispersion curves were important (16). On comparison of similarly constituted compounds (16) whose absolute configurations had been established in an unequivocal manner with the diketones I and II, the optical rotary dispersion curves revealed that the levorotary diketone must have the (9R) configuration, and that the dextrorotary diketone must have the (9S) configuration.

It should be pointed out that in the case of the trans-decalin derivatives the configuration at both ring junctures is "frozen" as well as the configuration of the neighboring carbon atoms (C-1 and C-4).

The absolute configurations of the hydroxyketones and the diols were then established on the basis of their oxidation products with chromium (VI) oxide in pyridine (17). For example compound III was converted by this reagent to the levorotary diketone (I) whose absolute configuration at C-9 had already been established as (9R). In addition, the hydroxyl group at C-4 in compound III was shown to be axial on the basis of its relative rate of oxidation with chromium



(VI) oxide in glacial acetic acid. Thus compound III must have the (4S, 9R) configuration. A very similar pattern was used to determine the absolute configurations of the remaining hydroxyketones and diols of the trans-decalin series. Also, the absolute configurations at C-4 in compounds III and IV were determined in an independent study of the atrolactic acid asymmetric synthesis (9). The results confirmed that both compounds had the (4S) configuration.

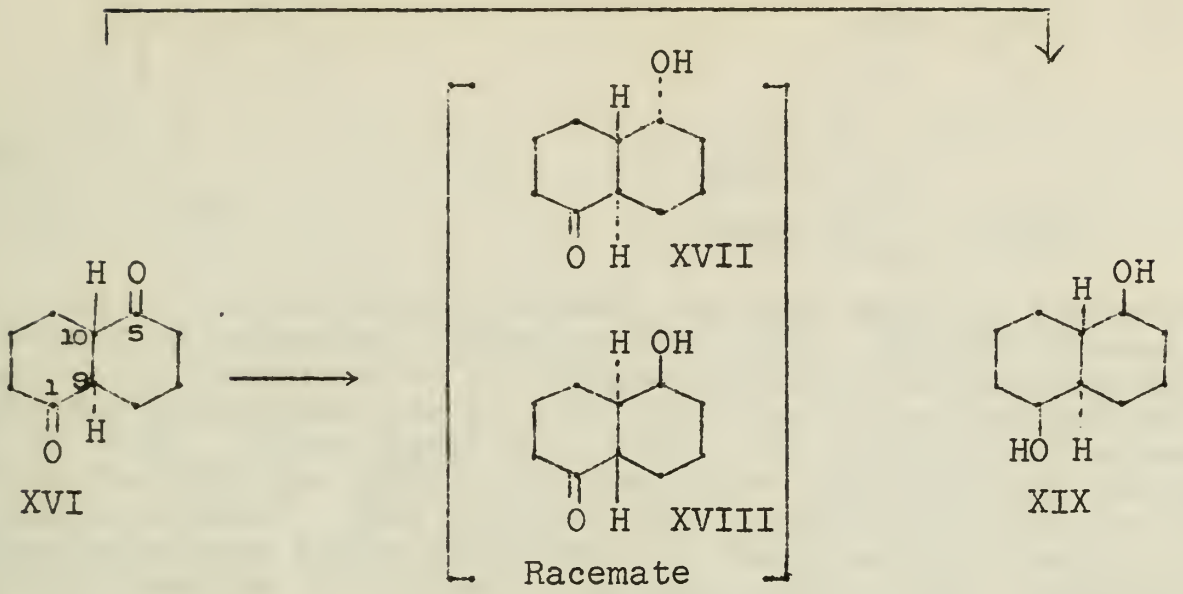
The easy conversion of the cis-4-hydroxy-1-decalone isomers into the corresponding trans forms served in the determination of the configurations of the cis isomers. For example, XI was converted into III by treatment with sodium methoxide in methanol, and therefore XI was assigned the (4S,9S) configuration. Analogous treatment of XIV gave an unknown trans-hydroxydecalone (VII) which had the same R_f value (0.68) and melting point as its (4S, 9S) enantiomer (IV) which was obtained from the reduction of trans-1,4-decalindione with Curvularia falcata. The IR of the solid racemate (IV and VII) was quite different from that of the single enantiomer (VII). However, when the spectra were measured in a chloroform solution, they were identical. This use of IR analysis proved itself to be quite useful in the determination of enantiomers in this series of investigations (18).

It is quite evident from the results that reductions with Curvularia falcata lead to a much higher degree of product stereospecificity than do analogous reductions with Rhizopus nigricans. For example reduction of racemic, trans-1,4-decalindione with Curvularia falcata leads to two optically pure products, (4S 9S)- and (4S, 9R)-4-hydroxy-trans-1-decalone, whereas analogous treatment with Rhizopus nigricans leads to a racemic mixture of the (4S, 9S)- and (4R, 9R)-enantiomers plus a small amount of almost optically pure (4S, 9R)-4-hydroxy-trans-1-decalone.

A similar investigation to that described above was carried out with both diastereomers of 1,5-decalindione (3). In this case, the trans-fused isomer has a single meso form, whereas the cis form has a racemic, enantiomorphic pair.

The results of this investigation using Curvularia falcata as the reducing agent were in excellent agreement with those obtained in the 1,4-decalindione series. Each carbonyl that was reduced gave rise to a new center of optical activity; the absolute configuration of which was S in each case. In the case of Rhizopus nigricans, however, racemic modifications were again found to be present. In addition a new microorganism, Streptomyces, was used as a reducing agent. In this case only the trans isomer of 1,5-decalindione was employed as a reactant. The results, summarized in Chart III, show that this microorganism also displayed a low degree of product stereospecificity.

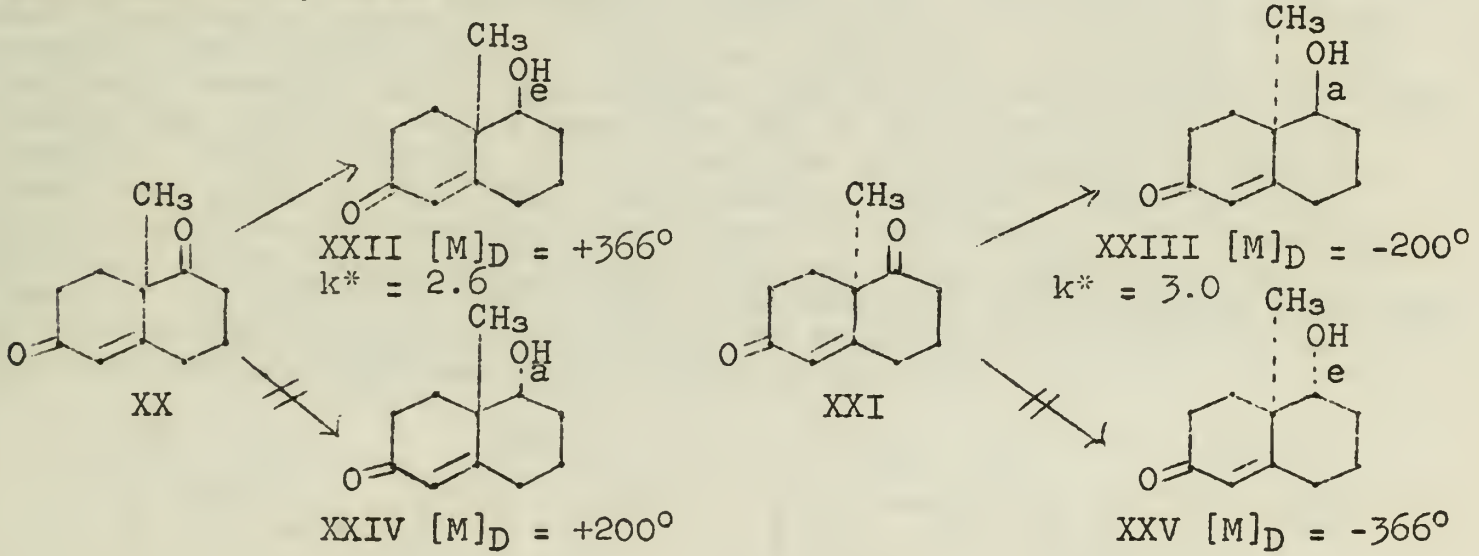
Chart III
Reductions with Streptomyces

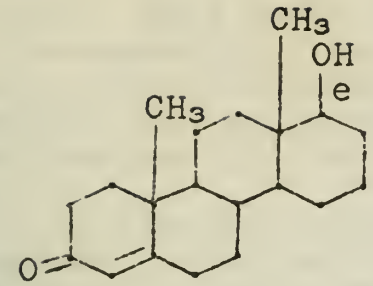


The constitutions and configurations of all the reduction products were determined by entirely analogous methods to those used in the 1,4-decalindione series.

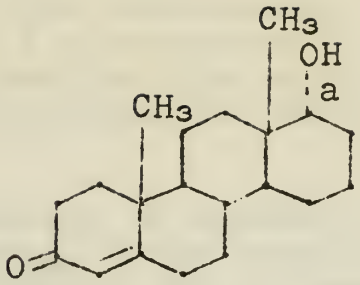
Reductions of compounds closely related to the decalindiones were also carried out using microorganisms. For example, the reduction of Δ^4-9-methyl-octalin-3,8-dione (XX and XXI) with Curvularia falcata gave approximately equal amounts of two diastereomers (4). From the IR and U.V. spectra it was determined that there were present an α,β-unsaturated carbonyl and a hydroxyl group. The similarity of configuration at C-8, and hence the dissimilarity at C-9, was shown by the oxidation of the two diastereomers with chromium (VI) oxide in pyridine. The dextrorotary hydroxyketone gave the dextrorotary diketone, and the levorotary hydroxyketone gave the levorotary diketone.

Thus the two hydroxyketones can be represented either by XXII and XXIII or by XXIV and XXV.





XXVI $[M]_D = +380^\circ$



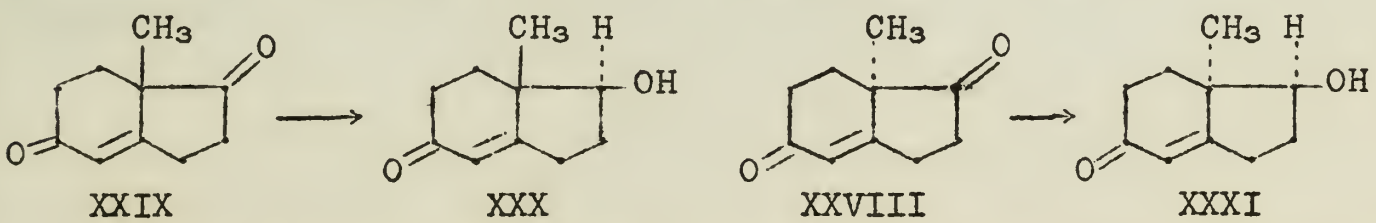
XXVII $[M]_D = +258^\circ$

In order to distinguish between the two pairs of structures, differences in molecular rotations were used. The difference between the molecular rotations of the diastereomers of the analogously constituted D-homosteroids is $+122^\circ$ (18), and that between XXII and XXIV is $+166^\circ$. Since these two values are in very good agreement, the formulas XXII and XXIII must therefore represent the two products which were obtained. The relative configurations of C-8 in both diastereomers were again determined by their relative rates of oxidation with chromium (VI) oxide in glacial acetic acid. The absolute configuration of C-8 in both cases was (8S).

Racemic Δ^4-9-methyl-octalin-3,8-dione was also treated with Aspergillus niger van T. (5). This microorganism showed itself to have no product stereospecificity, for it yielded all four possible isomers of Δ^4-9-methyl-8-hydroxy-3-octalone.

In each of the above cases a "latent" culture of the microorganism was used. A portion of the culture was centrifuged and was placed in a suspension with a buffered sugar solution. An alternative to this procedure was to use a rapidly growing culture. However, the use of a "latent" culture was found to be more practical, for the mass of the preserved microorganisms was more easily controllable, and the work-up of the reaction mixture was considerably easier.

Treatment of racemic $\Delta^{4,9}$-8-methylhexahydroindene-1,5-dione with a "latent" culture of Curvularia falcata gave levorotary $\Delta^{4,9}$-8-methylhexahydroindene-1,5-dione (XXVIII) and a dextrorotary $\Delta^{4,9}$-8-methyl-1-hydroxyhexahydro-5-indenone (XXX) (6). Isolation of the products revealed that approximately 80% of the dextrorotary diketone (XXIX) was reduced, while less than 5% of the levorotary diketone reacted. When a rapidly growing culture of Curvularia falcata was used, the yield of XXXI was approximately doubled. Nevertheless, this reaction represents the only case in this series of investigations in which Curvularia falcata displayed any stereoselective nature. In addition, the product stereospecificity obtained from this microorganism was still high since the absolute configuration at C-1 in both XXX and XXXI was again found to be (1S).

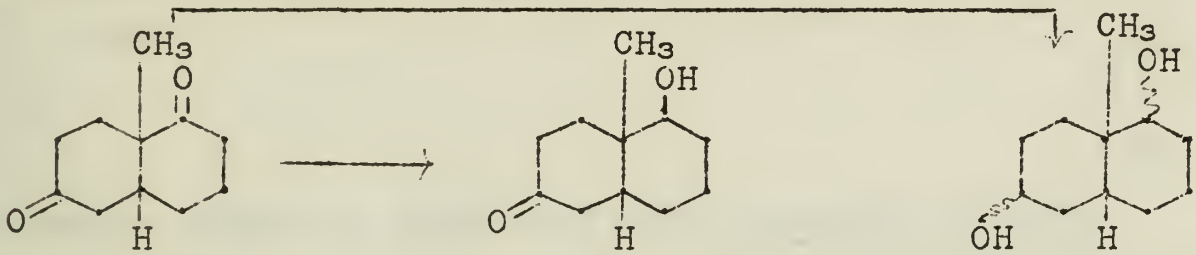


XXIX XXX XXVIII XXXI

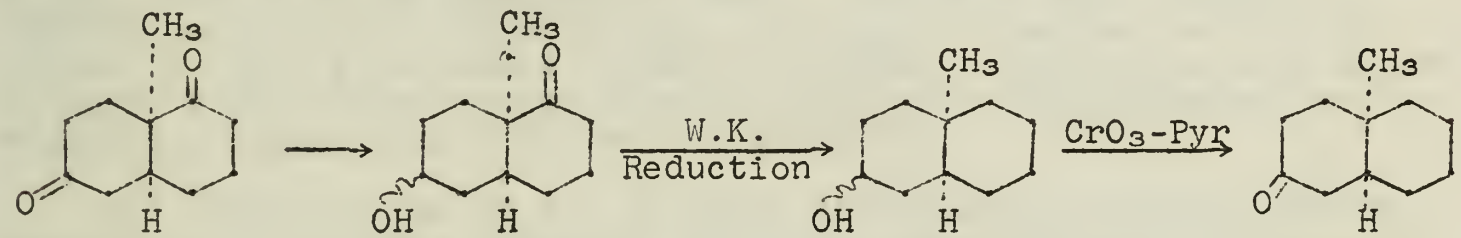
There is considerable difference in the rate of reaction between racemic $\Delta^{4,9}$-8-methylhexahydroindene-1,5-dione and racemic Δ^4-9-methyloctalin-3,8-dione, the former being reduced much slower than the

latter. This could be due to the fact that the carbonyl group is in a five-membered ring in one case and in a six-membered ring in the other. The difference has been determined for the reduction of cyclohexanone and cyclopentanone with sodium borohydride where k(cyclohexanone)/k(cyclopentanone) = 23 (19).

In another investigation, the reduction of racemic 9-methyl-cis-decalin-1, 6-dione with Rhizopus nigricans, a new type of stereoselectivity was observed (7). In the case of the (9S)-enantiomer of the saturated diketone, the carbonyl group at C-1 was reduced much faster than that at C-6, but in the case of the (9R)-enantiomer only the carbonyl group at C-6 was reduced.



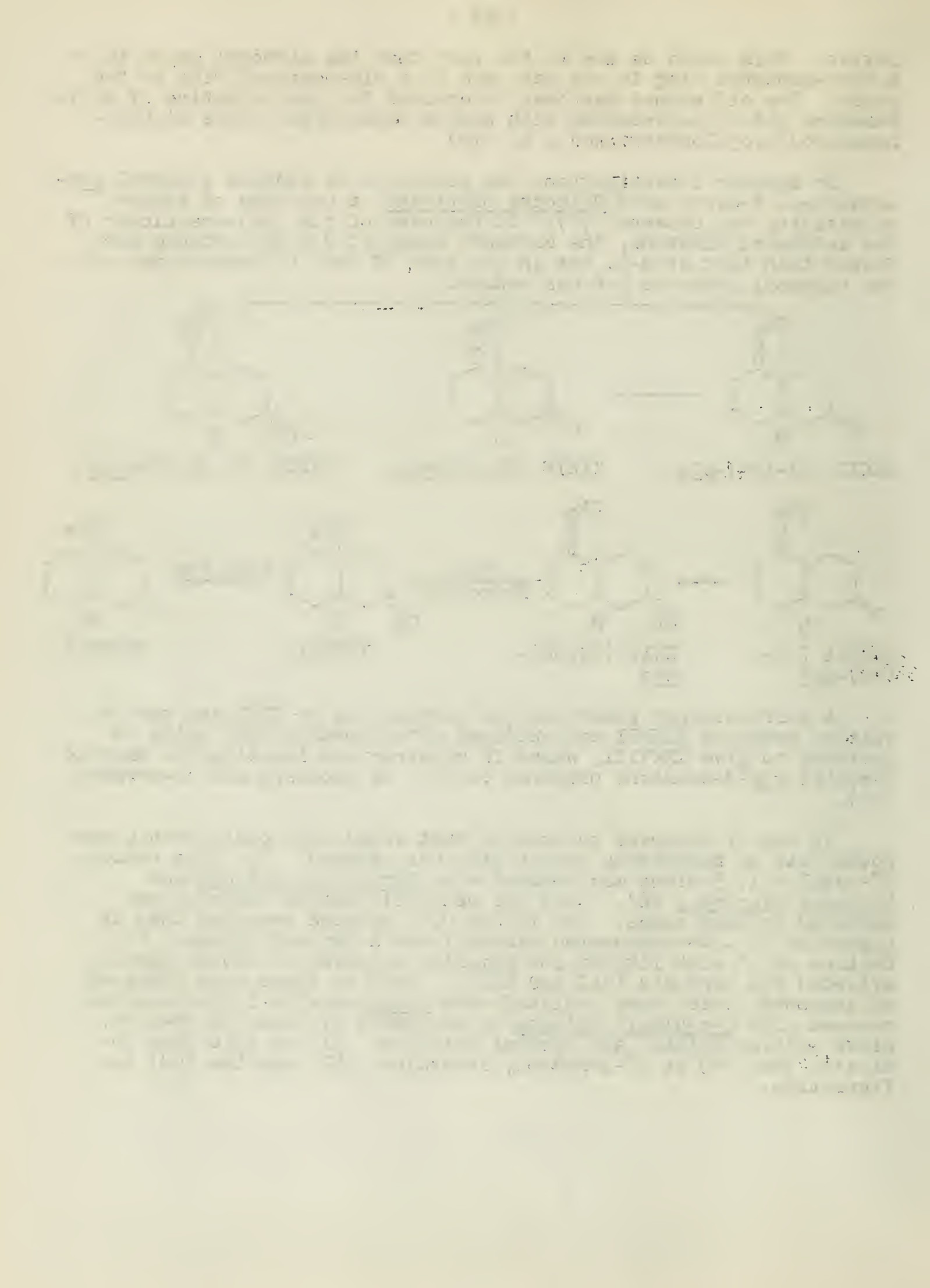
XXXII (+)-(9S)-cis XXXIV (1S,9S)-cis XXXVI (1ξ,6ξ,9S)-cis

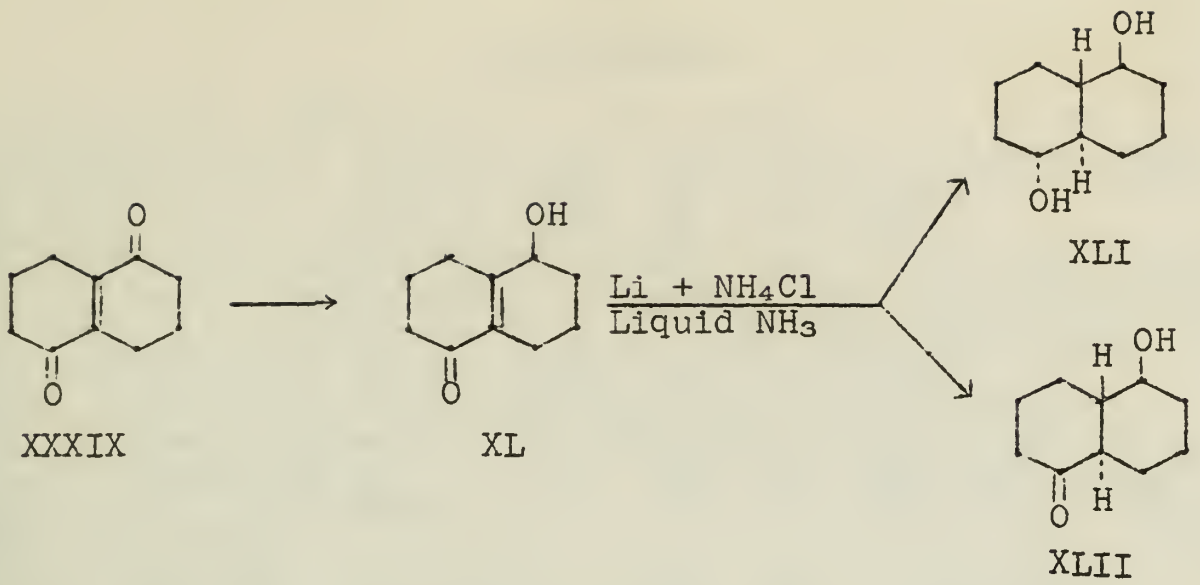


XXXIII (-)-(9R)-cis XXXV (6ξ,9R)-cis XXXVII XXXVIII

A Wolff-Kishner reduction was carried out on XXXV and the resulting compound XXXVII was oxidized with chromium (VI) oxide in pyridine to give XXXVIII, whose IR spectrum was identical to racemic 9-methyl-cis-3-decalone prepared earlier by Woodward and co-workers (20).

It was of interest to observe what would take place when a compound with no asymmetric carbon atom was reduced. For this reason, Δ^9-octalin-1, 5-dione was treated with Curvularia falcata and Rhizopus nigricans (8). Only one optically active compound was isolated in both cases. Its IR and U.V. spectra revealed that it possessed an α,β-unsaturated carbonyl and a hydroxyl group. Reduction of XL with lithium and ammonium chloride in liquid ammonia afforded two products (XLI and XLII). Both of these were identical to compounds which were isolated when trans-decalin-1, 5-dione was reduced with Curvularia falcata on the bases of their IR spectra, mixed melting points, and optical rotation. All of this data indicates that C-5 in Δ^9-5-hydroxy-1-octalone (XL) has the (5S) configuration.

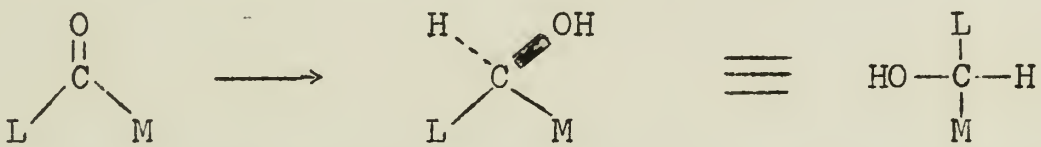




THE STERIC COURSE OF REDUCTIONS WITH CURVULARIA FALCATA

In consideration of the results, it is striking that Curvularia falcata and Rhizopus nigricans showed a similarly small degree of stereoselectivity in regard to cis and trans isomers as well as in regard to their enantiomers. They both showed, however, a high degree of product stereospecificity whereby Curvularia falcata marks out an especially simple steric course of reduction.

The steric course of all hitherto investigated microbiological reductions of carbonyl compounds employing Curvularia falcata as the reducing agent is pictured in the following scheme.



The symbols L(large) and M(medium) have the same signifigance as in the case of asymmetric syntheses in vitro, that is, they give the relative spatial requirement in the direct neighborhood of the reaction site(21).

In every case in which Curvularia falcata was employed as the reducing agent the spatial requirement played an essential role in the steric course of the reaction, for it imparted to every new site of asymmetry that arose from reduction the S configuration. The spatial requirement is also important in the case of asymmetric reductions in vitro, i.e., the Meerwein-Ponndorf reduction(21) and reductions employing the Grignard reagent (22).

These microbiological reductions are also of great practical importance, for they constitute a means for the separation of enantiomers in the series of compounds that were investigated (23).

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CALOPHYLLOLIDE

Reported by R. Z. Greenley July 6, 1959

INTRODUCTION

Calophyllum inophyllum is a tree found in certain tropical regions of Asia and Eastern Africa, Australia and Madagascar. A substance can be extracted from the nuts of the tree, the oil of which has been found useful in the treatment of lepers. (1) Because of this important usage, an attempt has been made to determine the structures of the compounds making up this substance.

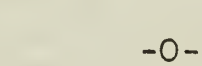
PRELIMINARY INVESTIGATIONS

The first investigators were able to isolate three compounds: two lactones, calophyllolide and inophyllolide, and an unsaturated acid, calophyllic acid. More recently, inophyllic acid has been isolated. (2)(3)(4)

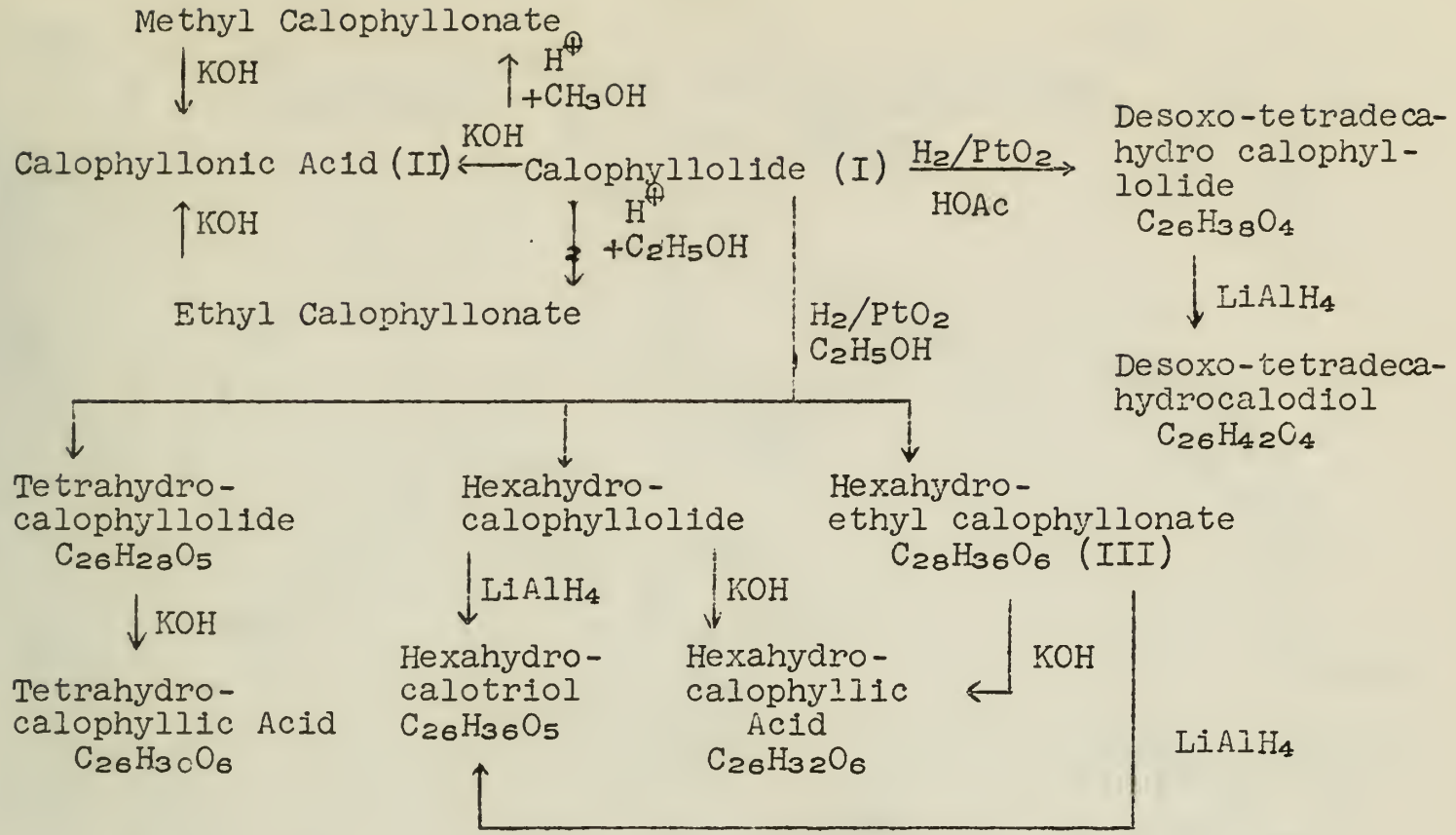
The lactonic function of calophyllolide is readily saponified and relactonizes upon heating. Calophyllolide, I, takes up three moles of hydrogen, and its corresponding acid takes up two moles. The infrared spectrum of this tetrahydro acid shows a conjugated phenyl group. (1)

When calophyllic acid, II, is heated, three neutral compounds are recovered. One is thought to be a decarboxylated product and the other two seem to be lactones. Alkaline fusion, ozonization, and permanganate or chromic acid oxidation of I and II give benzophenone and/or benzoic acid as products. Thus I and II were thought to be similar in structure. (5)

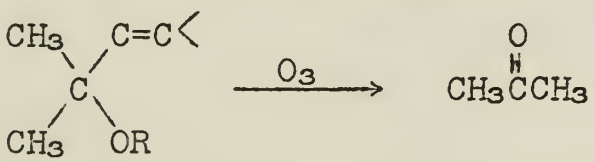
The empirical formula for calophyllolide was found to be $C_{26}H_{24}O_5$ which includes a methoxy function. The infrared spectrum of I shows a band at 1770 cm^{-1} (γ-lactone) and two bands at 1613 and 1600 cm^{-1} which are perhaps due to



Hydrolyses and reductions were also carried out according to the following scheme (6):

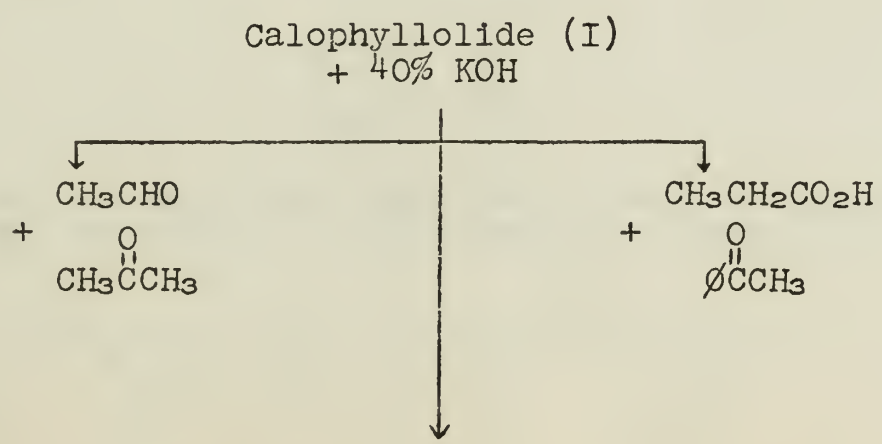


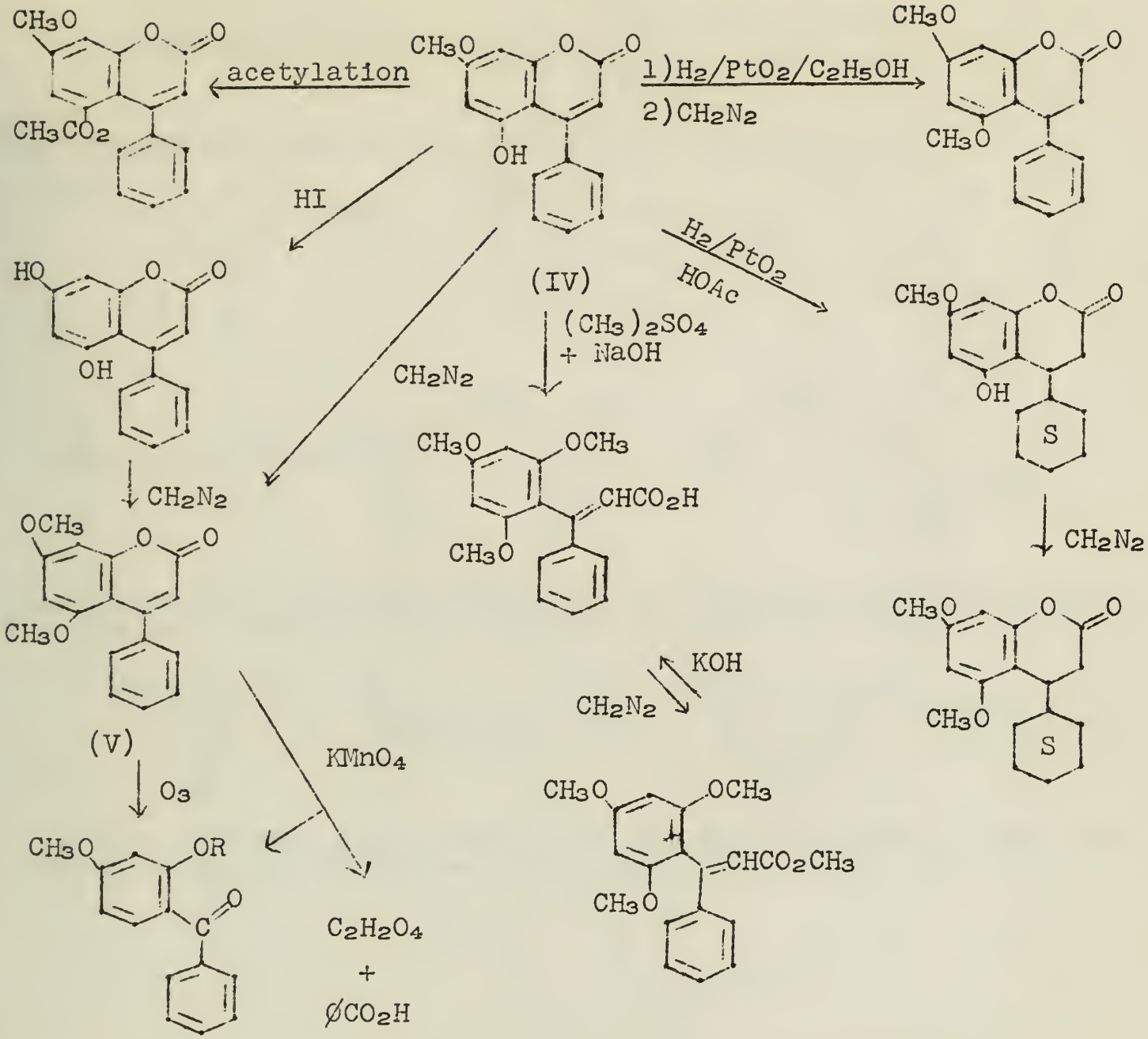
Ozonization of I gave acetone, acetaldehyde, and some unrecovered volatile materials. (6) It was later found that the acetaldehyde was due to a normal ozonization of an unsaturated chain (7), but the acetone is derived from an abnormal ozonization (8):



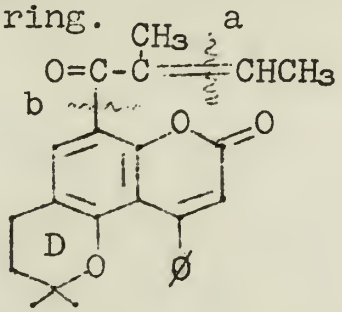
I was recovered unchanged from its reaction with lead tetra-acetate. But a reaction did occur with ethyl hexahydro-calophyllonate, III. The hexahydro-lactone was isolated, showing that lactonization will occur in an acidic medium. Ethyl cinnamate was also isolated, showing that a phenyl group is β to the lactonic carbonyl. (6) The Kuhn-Roth determination of C-methyl groups showed the existence of three such groups in I. (9)

BASIC DEGRADATION

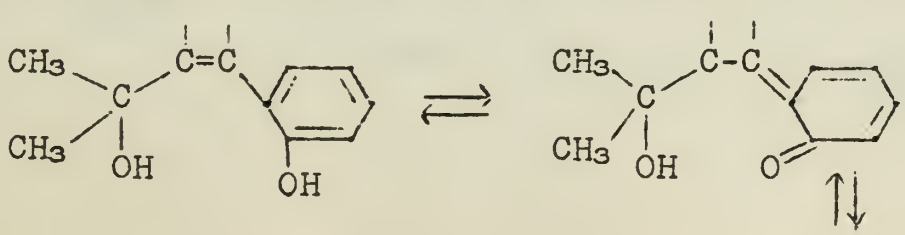


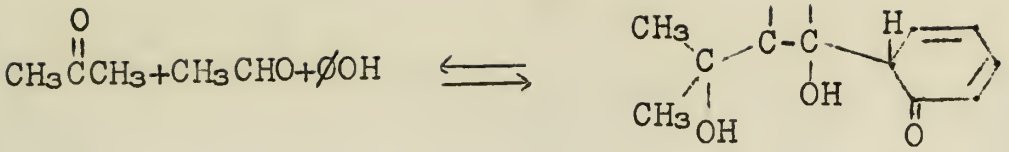


The acetaldehyde comes from a reverse Aldol (a) and the propionic acid comes from a scission at (b), which may be conditioned by the degradation of the "D" ring.

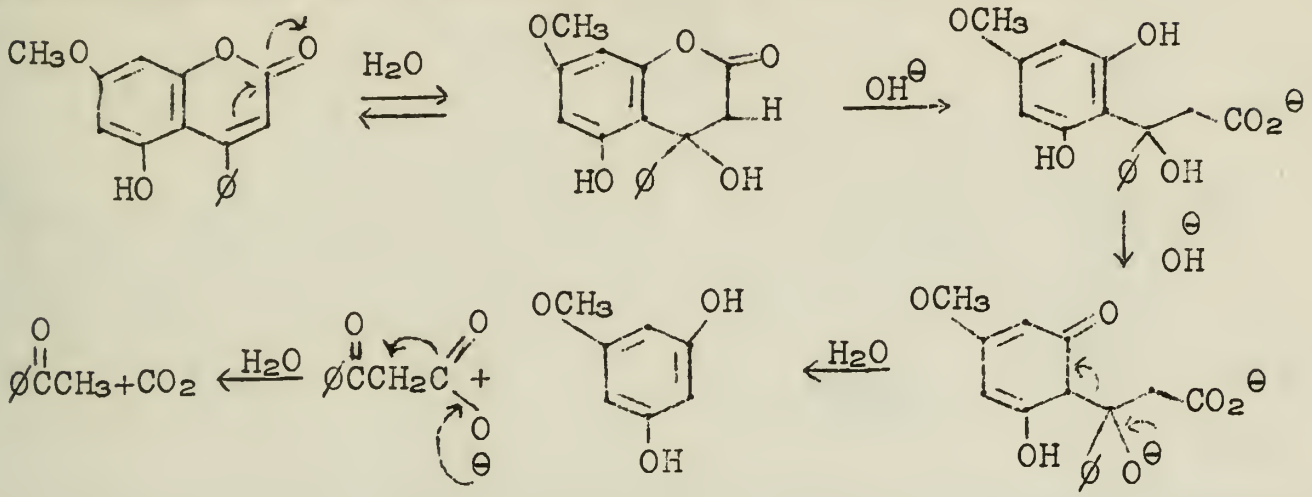


The acetone and acetaldehyde might be produced through a mechanism similar to the following, in the presence of base (17):

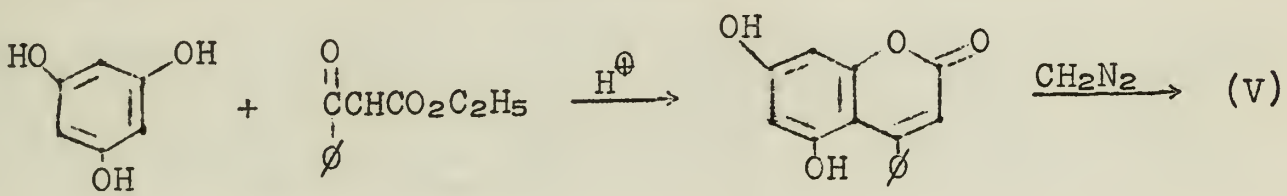




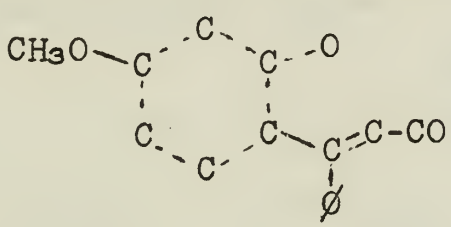
The acetophenone may be accounted for by this mechanism:



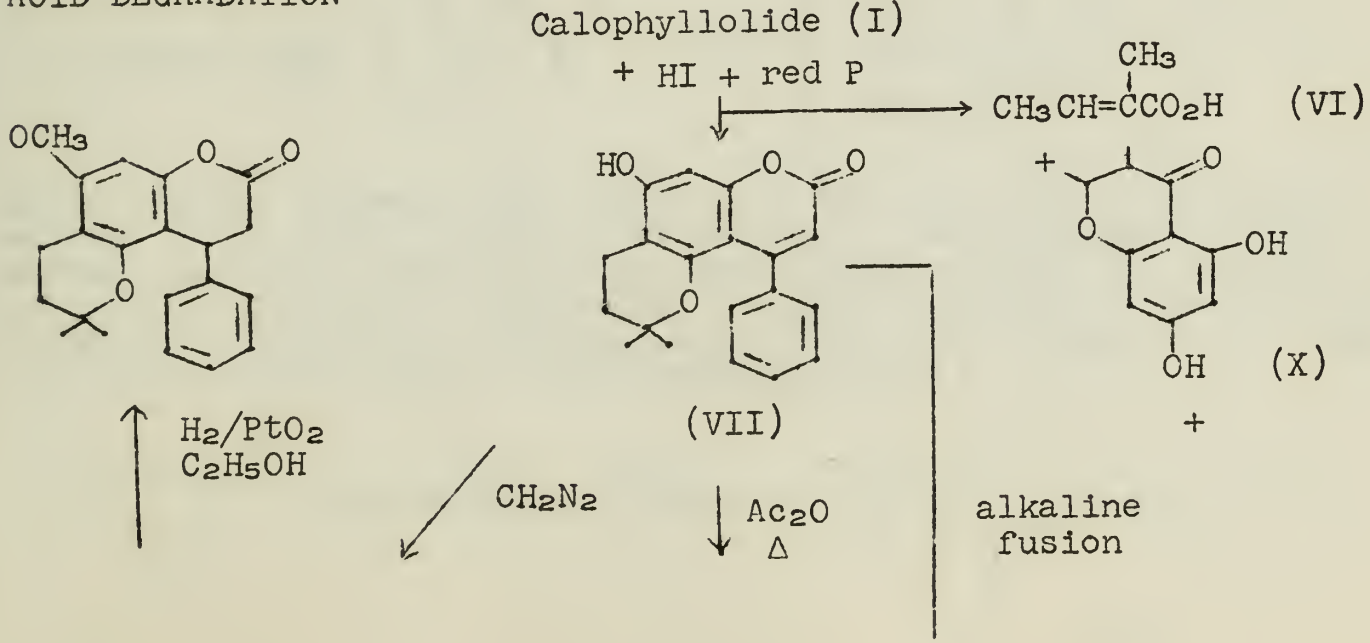
The 4-phenyl-5,7-dimethoxy coumarine, V, compares favorably in all of its physical properties with those of an authentic compound (9)(10):

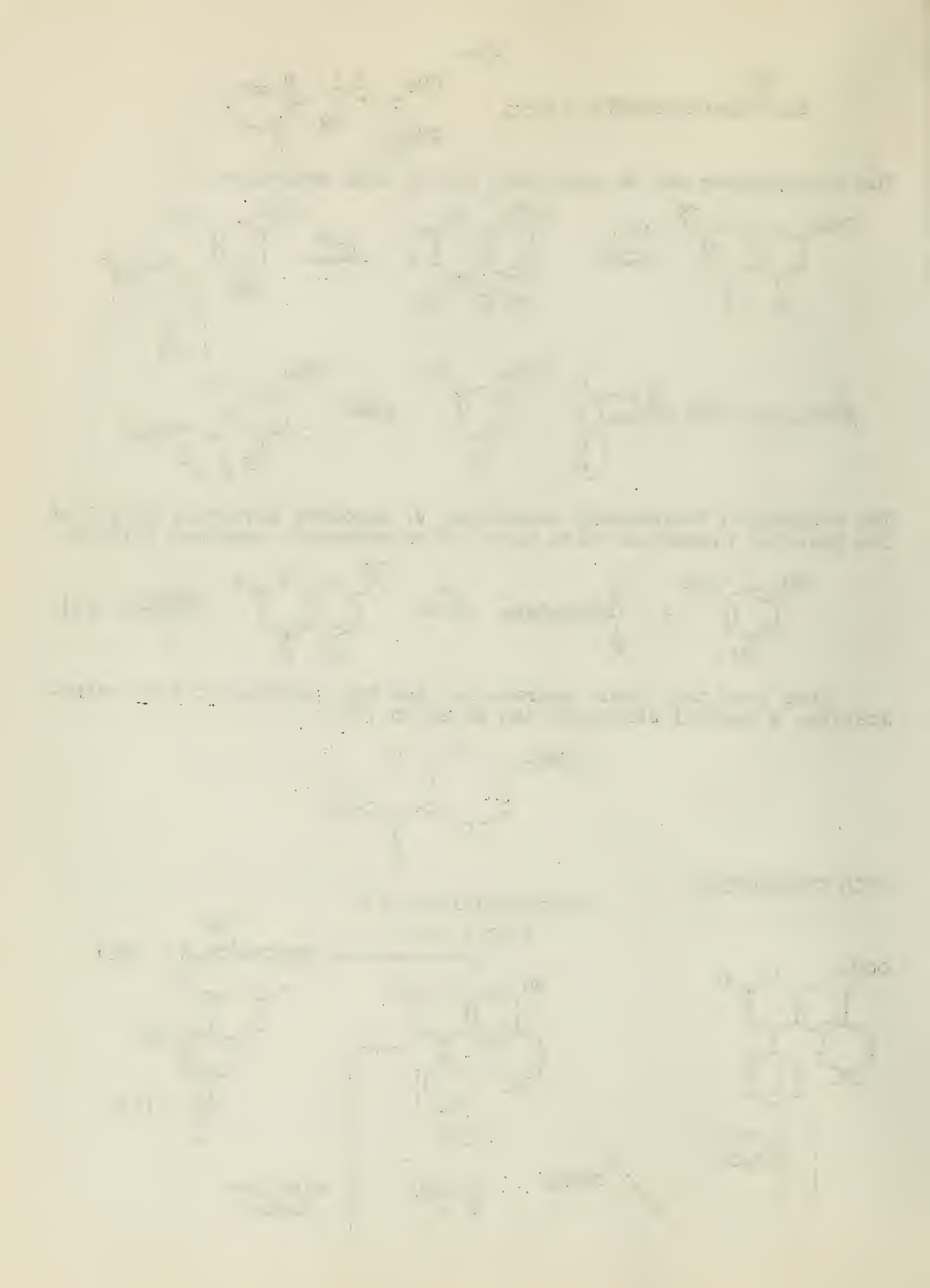


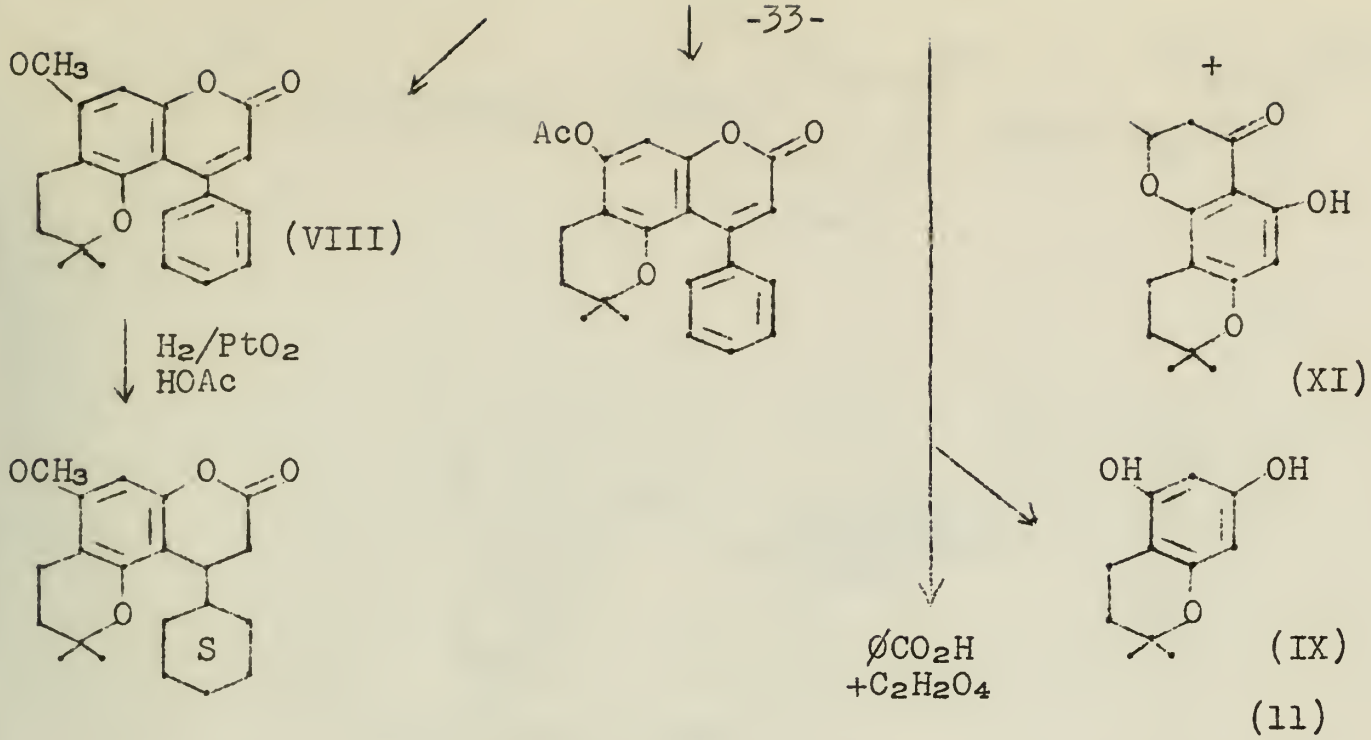
Thus from this basic degradation and the reaction of lead tetra-acetate, a partial structure can be shown (6):



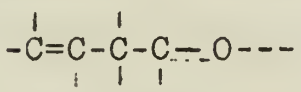
ACID DEGRADATION



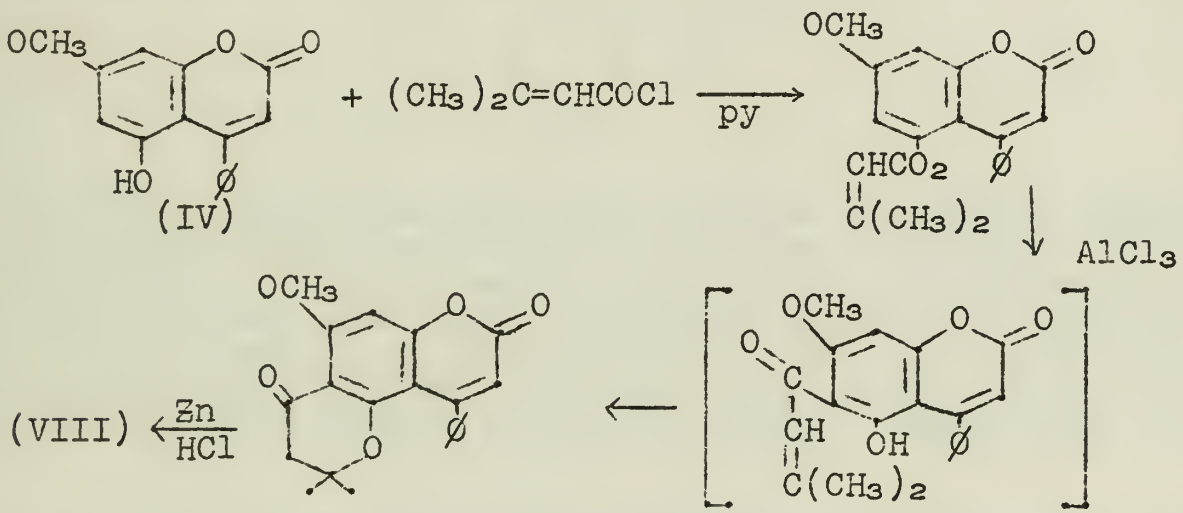




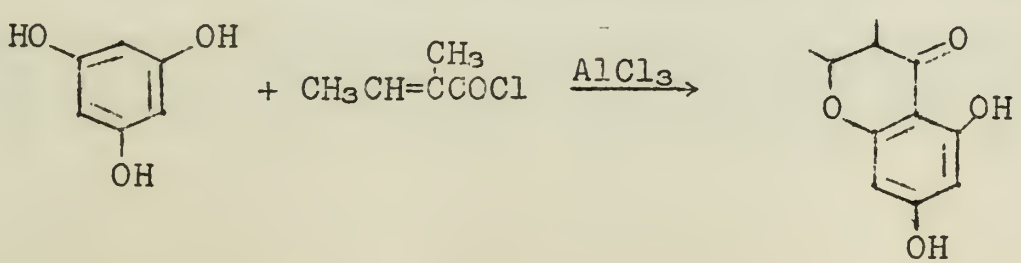
The tiglic acid, VI, is probably produced from this fragment:

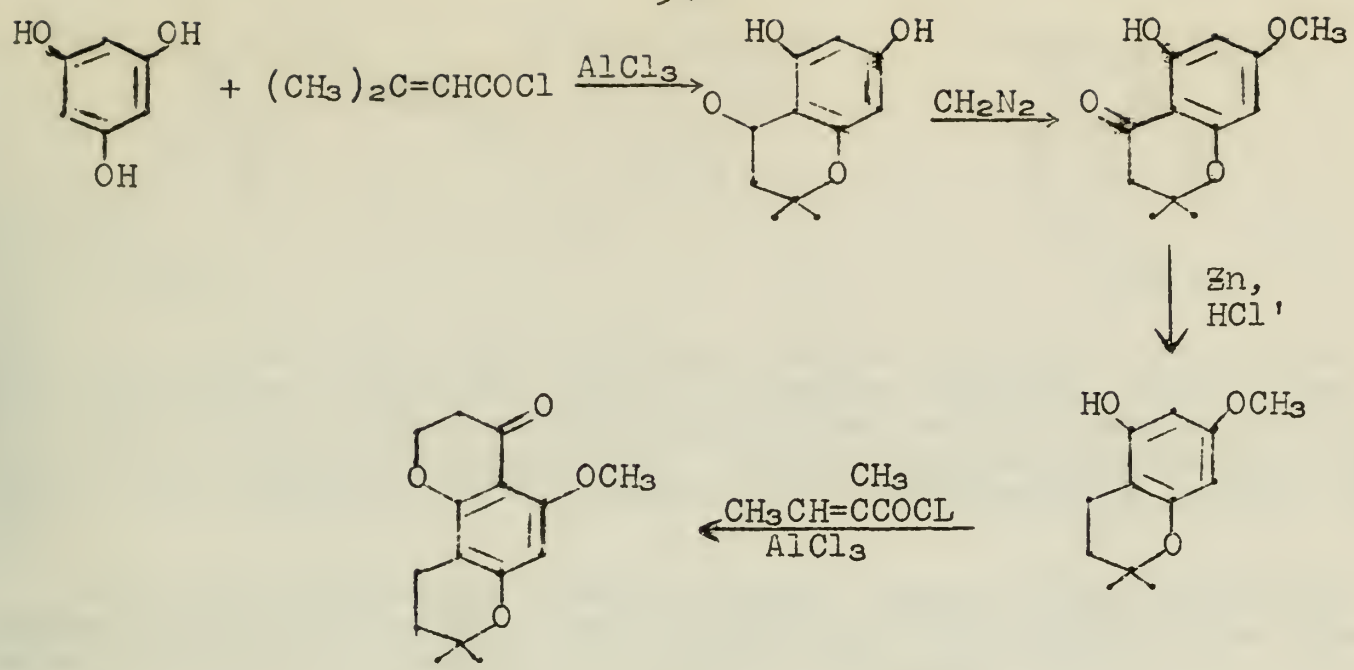


This same group is the parent for the acetaldehyde and the propionic acid found in the basic degradation. VII and VIII were partially characterized by their ultraviolet and infrared spectra, their ability to be saponified, and their failure to form carbonyl derivatives. VIII was then synthesized:



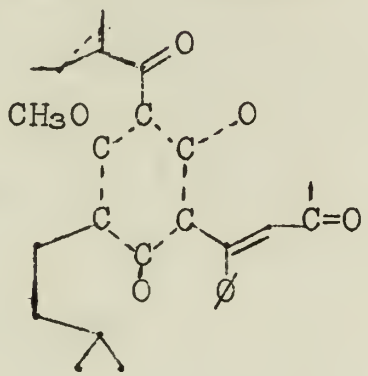
IX is a known compound and compared in all ways with an authentic sample. (11) X and XI were more difficult to characterize since neither infrared spectrum showed bands corresponding to hydroxyl and/or carbonyl because of chelation. But the spectrum of the acetate of X showed a conjugated carbonyl as did the methyl ether of XI. Both chromanones were readily synthesizable (6)(7):





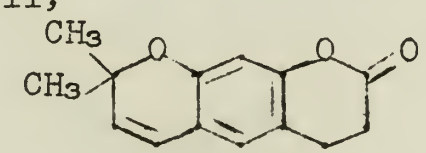
mono-methyl ether
of (XI)

We are now sure of more of the calophyllolide structure (6):



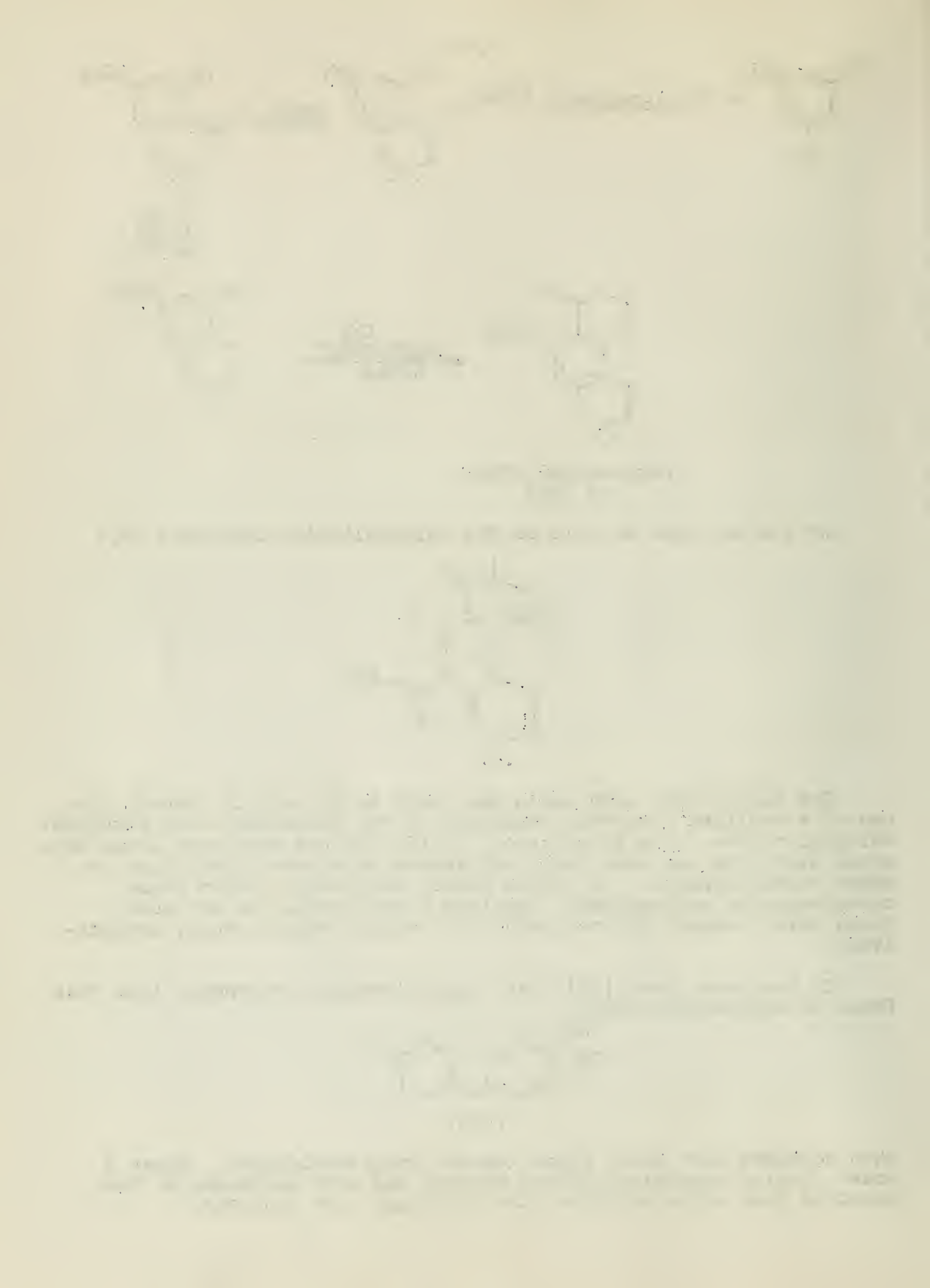
The tiglic acid side chain was found to be acyclic through the use of a modified Kuhn-Roth oxidation on the tetrahydro- and perhydro-calophyllolides. For this method, (6)(7)(12) the resultant acids were steam distilled and then their ethylamine salts were identified by paper chromatography. To effect better resolution, vapor phase chromatography was employed. Besides acetic acid, the two acids found were α-methyl butyric acid and β-methyl valeric acid, respectively.

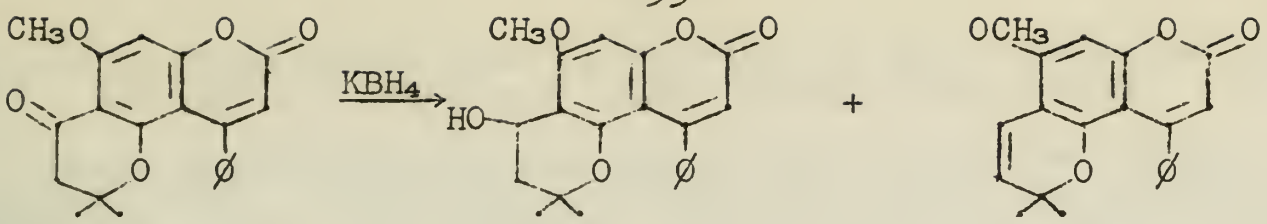
It has been shown (13) that a gem-dimethyl chromanene, like that found in xantholetin, XII,



(XII)

when degraded with base, gives acetone and acetaldehyde. Since I under similar conditions yields acetone and more acetaldehyde than expected from chain scission, the following test was made:

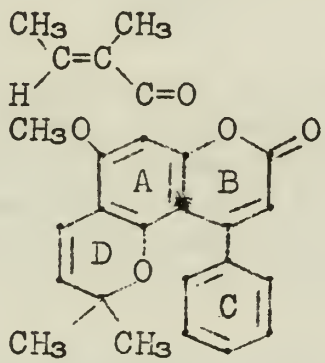




(VIII) (XIII)

XIII was degraded with 40% potassium hydroxide and the 2,4-dinitrophenylhydrazones were made from the volatile products. These were then identified as the corresponding derivatives of acetone and acetaldehyde by paper chromatography. Interestingly,no degradation takes place in the absence of the lactone or its corresponding hydroxy acid. (7)

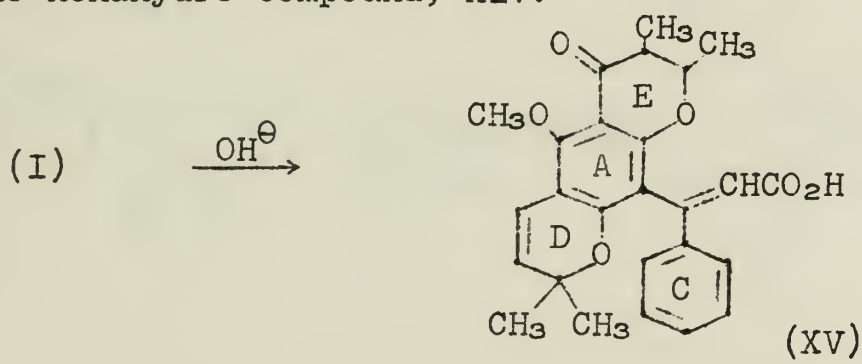
After this exhaustive chemical study, wherein each previously unknown degradation product was authentically synthesized, the complete structure of calophyllolide can be assigned (7):



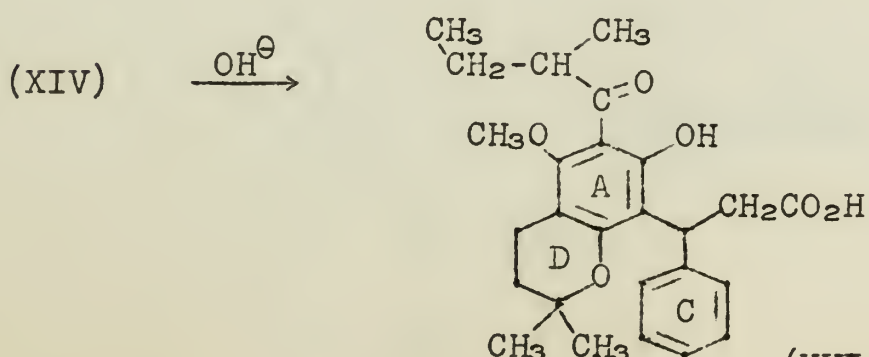
(I)

INOPHYLLOLIDE AND CALOPHYLLIC ACID

It was found that the saponification of I caused a secondary cyclization through a Michael condensation. But this is not possible for the hexahydro compound, XIV.



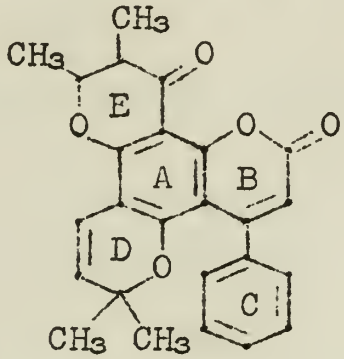
(XV) Calophyllonic acid



(XVI) Hexahydrocalophyllic acid

XV gave no acetaldehyde upon ozonization and gave a negative phenol test. XVI upon oxidation gave only α-methyl butyric acid.

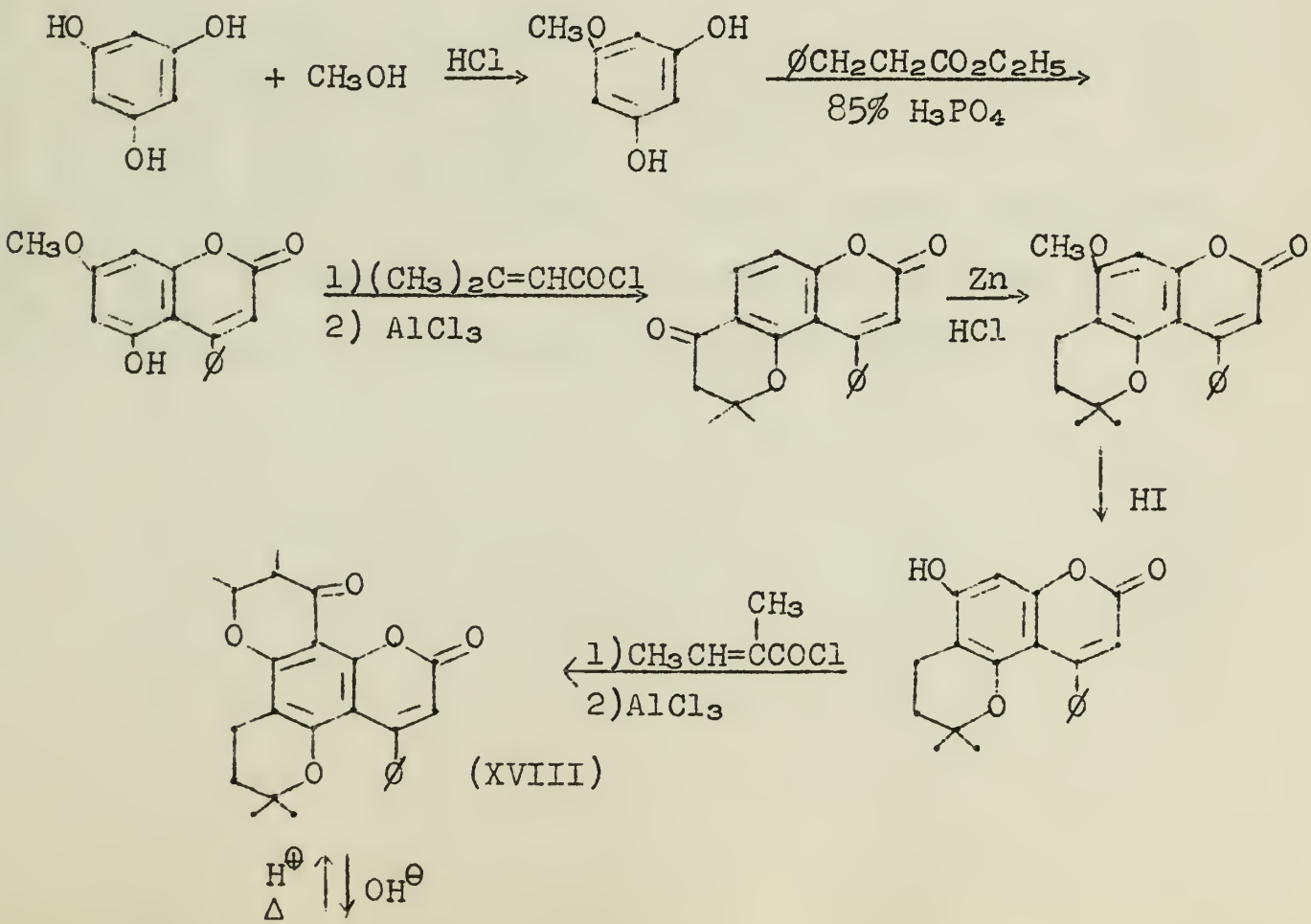
Basic demethylation of calophyllolide by ammonium chloride led to a racemic acid. Lactonization of this acid gave a new compound, inophyllolide, XVII. This compound contains no acyclic chain as shown by oxidation and ozonization studies, and was assigned the following structure:



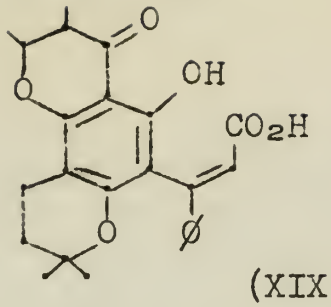
(XVII)

The formation of the "E" ring in the opposite direction was excluded on the basis of three different observations. (1.) The chelated hydroxy acid requires acid and a temperature of 150° to relactonize. (2) The reaction of diazomethane and methyl calophyllonate leads to a methoxy compound whose infrared spectrum shows a carbonyl band. (3) Natural calophyllic acid, $[\alpha] = -26.6°$, upon lactonization gives inophyllolide, $[\alpha] = -10.9°$.

The synthesis of dihydroinophyllolide, XVIII, and dihydrocalophyllic acid, XIX, was carried out in the following manner (7):

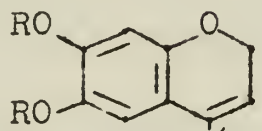


(XVIII)



(XIX)

Calophyllolide, inophyllolide, and dalbergin, XX, (14)



(XX)

are among the few naturally occuring 4-phenylcoumarines known.

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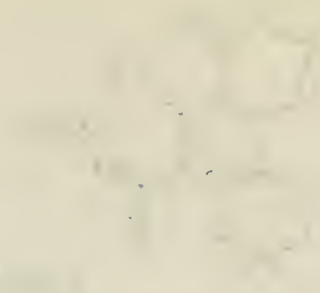
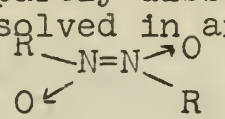


HALOGEN CONTAINING C-NITROSO-COMPOUNDS

Reported by W. E. Adcock July 13, 1959

INTRODUCTION

Few alkyl nitroso-compounds are monomeric under normal conditions and four main types may be distinguished: (a) Those which contain the >CH-NO group form colorless dimers or isomerize to the oxime >C=NOH. (b) Those which contain hydrogen and halogen on the α-carbon isomerize only slowly, but form colorless dimers. (c) Those which contain the nitroso-group attached to a tertiary carbon atom cannot isomerize, but yield colorless dimers [e.g. $(Me_3CNO)_2$]. The colorless dimers of (b) and (c) often partly dissociate to the blue monomer when heated or melted, or dissolved in an organic solvent, and their structure can be represented by  (d) The polyfluoronitroso-compounds, which do not form dimers under normal conditions.

The purpose of this seminar is to consider the synthesis, particularly photochemical, and some of the chemical properties of gem-halonitroso-(b) and polyfluoronitroso-compounds (d).

PREPARATION

Piloty (1) first prepared substituted chloro- and bromo-nitroso-compounds in high yields from the corresponding ketoximes:

$$(CH_3)_2\,C{=}N{-}OH + Br_2 \xrightarrow{\text{Pyridine}} (CH_3)_2\,C(NO)Br + HBr$$

Aldoximes react with an excess of halogen in a two-stage process with isomerization of the secondary nitroso-compound formed:

$$RCH{=}N{-}OH + X_2 \longrightarrow RCHX{-}NO + HX$$
$$RCHX{-}NO \longrightarrow RCX{=}NOH$$
$$RCX{=}NOH + X_2 \longrightarrow RCX_2NO + HX$$

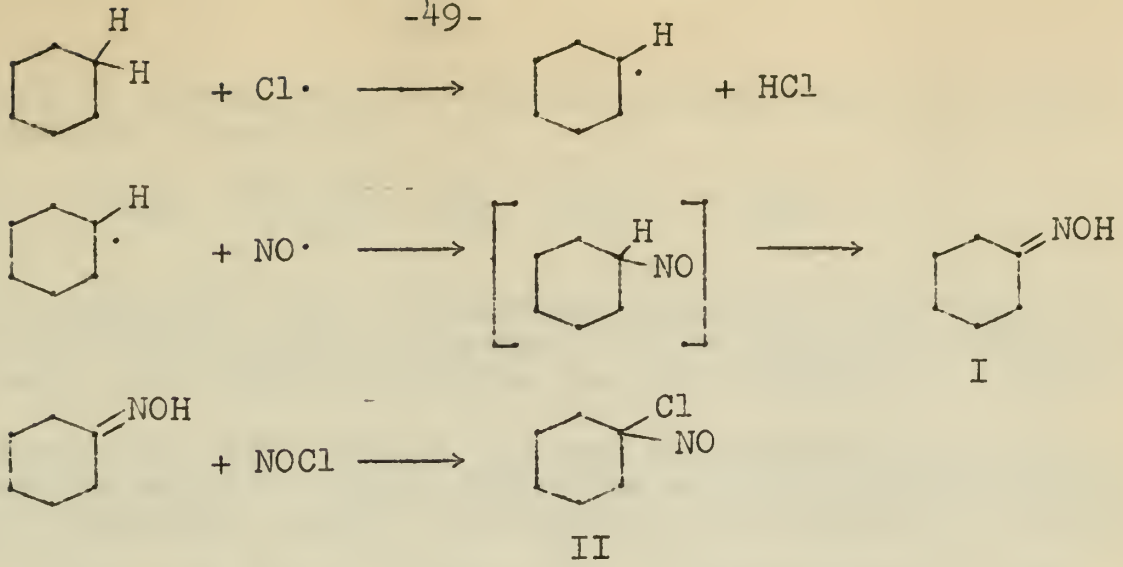
More recently (2), it was found that N-bromosuccinimide reacts with alicyclic ketoximes in aqueous sodium bicarbonate to give the blue bromonitroso-compounds.

The oximes have been found to react with nitrosyl chloride (3), giving low yields of chloronitroso-compounds:

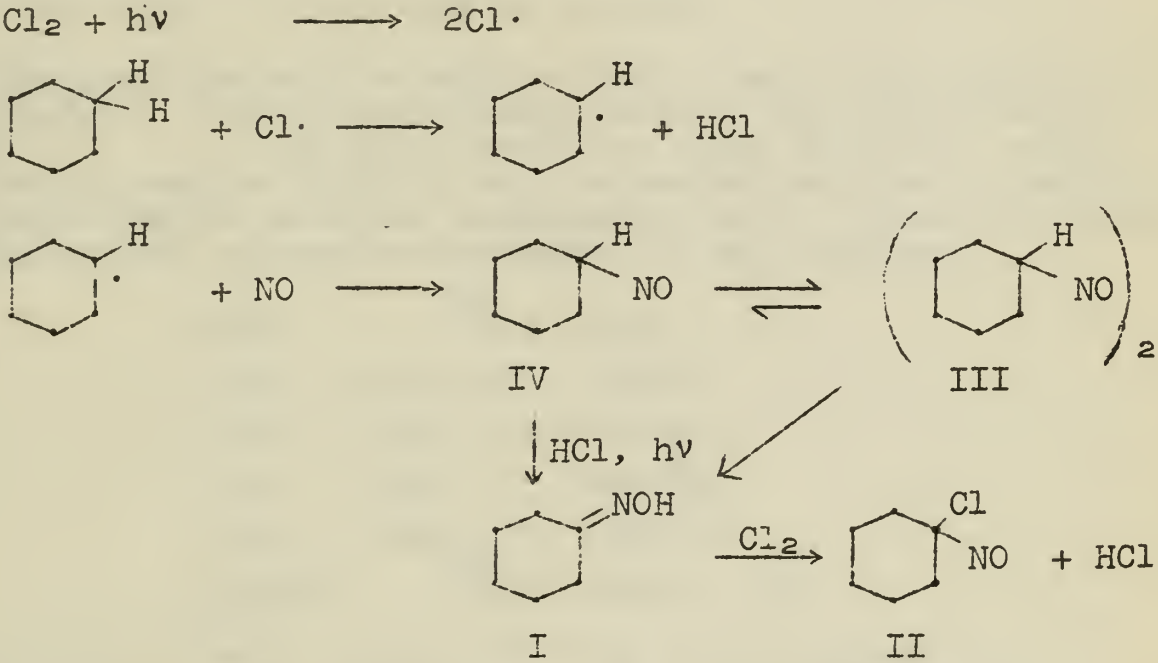
$$CH_3{-}CH{=}NOH + NOCl \longrightarrow CH_3{-}\overset{\displaystyle H}{\underset{\displaystyle Cl}{\overset{|}{\underset{|}{C}}}}{-}NO$$

Naylor and Anderson (4) have synthesized cyclohexanone oxime (I) in 71% yield by a photochemical reaction of nitrosyl chloride on cyclohexane. If a high concentration of nitrosyl chloride is maintained, gem-chloronitrosocyclohexane (II) may be obtained. The following mechanism has been suggested:

$$NOCl + h\nu \longrightarrow NO\cdot + Cl\cdot$$



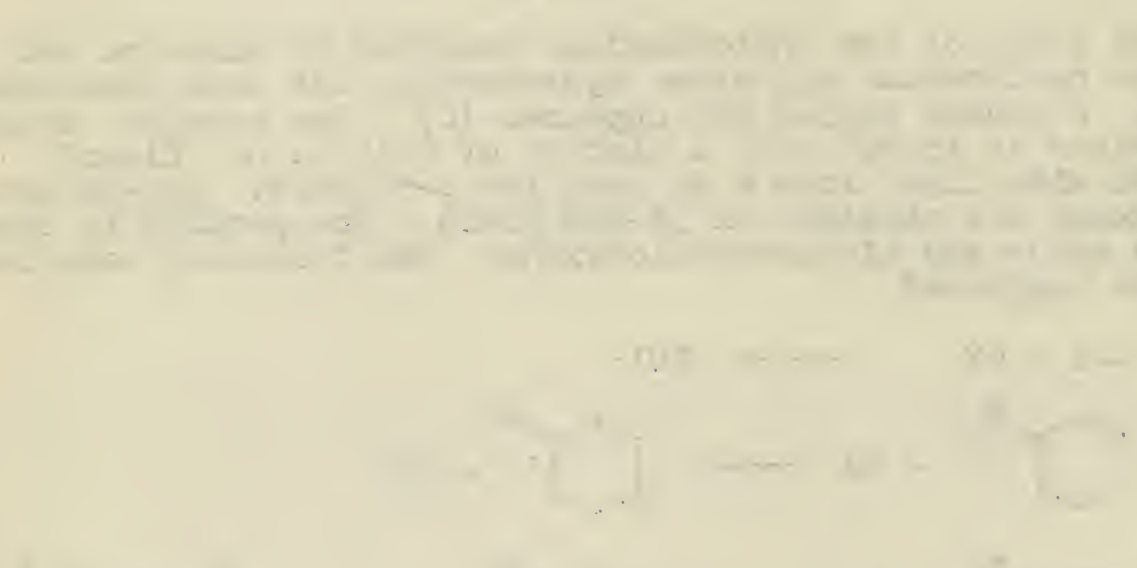
A detailed study of the photochemical reaction of chlorine and nitric oxide on cyclohexane and other hydrocarbons has been undertaken by Müller (5). A recent review has appeared (6). For example, cyclohexane was treated at 15-20° with a mixture of 0.17 l./hr. Cl_2 and 0.40 l./hr. NO with light from a Hg lamp for two hours. Gem-chloronitrosocyclohexane was obtained in 54-60% yield. The product is contaminated with mono- and dichlorocyclohexane. The following reaction scheme has been suggested:



Irradiation of the reaction mixture with NO : Cl_2 in a volume ratio of 8 : 1, respectively, yields 60% of the bisnitrosocyclohexane (III). Heating at 120° transforms the bisnitrosocylohexane to the oxime (I). A 2 : 1 volume ratio of NO : Cl_2 gives gem-chloronitrosocyclohexane (II. This could occur with the monomer (IV) being transformed in the presence of a catalytic amount of HCl and U.V. light to the isomeric oxime (I). The oxime reacts further with an excess of chlorine in a dark reaction to give gem-chloronitrosocyclohexane (II).

When n-heptane is treated with NO : Cl_2 in a volume ratio of 2 : 1 a 40% yield of x-chloro-x-nitroso-n-heptanes is isolated. Separation and characterization of the isomers has not been accomplished.

Trifluoronitrosomethane, a deep-blue monomeric gas, was first prepared by Ruff and Giese (7) by treatment of a silver cyanide-silver nitrate mixture with fluorine. Pure trifluoronitrosomethane has now



been obtained (8) by irradiation of trifluoroiodomethane and nitric oxide in the presence of mercury:

$$CF_3I \xrightarrow[110^\circ]{h\nu,\ Hg} CF_3\cdot \xrightarrow{NO} CF_3NO$$

Mercury plays an important role by removing iodine and reacting with any dinitrogen tetroxide which is present. In an experiment where mercury was not used, trifluoronitromethane was the predominant product.

A simple apparatus which avoids the use of pressure has been described by Haszeldine (9). Up to 0.25 mole of trifluoroiodomethane can be used per experiment giving a 38% yield of the nitroso-compound.

The above method has been extended (10) to homologues of CF_3I, yielding the blue compounds $CF_3(CF_2)_nNO$ where n = 1,2,3,4, or 6. This was made possible by the synthesis of the fluoroiodides in good yield from the corresponding fluorinated carboxylic acids (11). When a salt of trifluoroacetic acid, for example the lead or silver salt, is mixed with iodine and heated, simultaneous decarboxylation and iodination occurs, and the gaseous products are CO_2 and CF_3I. It has also been shown (12) that trifluoroiodomethane will undergo an addition polymerization with tetrafluoroethylene to give a polymer $CF_3(CF_2CF_2)_nI$ from which the compounds with n = 1-10 may be isolated.

Some breakdown of the perfluoroalkyl chain occurs (13) during the preparation of C_3F_7NO. Over-irradiation increases the breakdown and C_2F_5NO and CF_3NO are then formed in 4 and 2% yield, respectively. Perfluoro-n-hexane (27%) is also a product and the corresponding nitro-compounds can be detected spectroscopically. These products support the free-radical mechanism proposed for the reaction:

$$C_3F_7I \xrightarrow{h\nu} C_3F_7\cdot + I\cdot$$
$$C_3F_7\cdot + NO \longrightarrow C_3F_7NO$$
$$C_3F_7\cdot + C_3F_7\cdot \longrightarrow C_6F_{14}$$
$$C_3F_7\cdot + NO_2 \longrightarrow C_3F_7NO_2$$
$$C_3F_7\cdot + NO_2 \longrightarrow C_3F_7ONO$$
$$C_3F_7ONO \xrightarrow{h\nu} C_3F_7O\cdot + NO$$

The perfluoroalkoxyl radicals account for the chain degradation:

$$C_3F_7O\cdot \longrightarrow C_2F_5\cdot + COF_2 \longrightarrow \text{etc.}$$

The use of iodo-compounds can be avoided (14) by reaction of the silver salt of the corresponding carboxylic acid with nitrosyl chloride:

$$CF_3(CF_2)_nCO_2Ag \xrightarrow{NOCl} AgCl + CF_3(CF_2)_n\text{-}\overset{O}{\overset{\|}{C}}\text{-}ONO$$

$$CO_2 + CF_3(CF_2)NO_2 + CF_3(CF_2)_nNO \xleftarrow{\Delta}$$

The advantages of this method are that iodine, mercury, or ultraviolet light are avoided and that substantial quantities of the nitroso-compound can be prepared in a short time.

CHEMICAL PROPERTIES

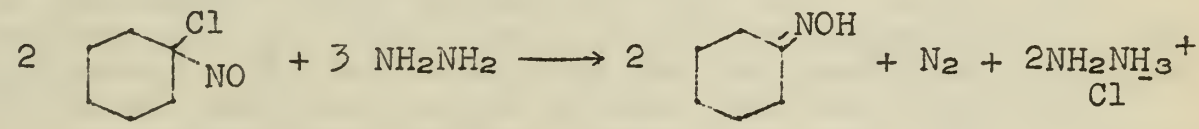
I OXIDATION

Treatment of the appropriate nitroso-compound with dimanganese heptoxide (explosive !), chromium (VI) oxide, or lead dioxide gave the compounds CF_3NO_2, $C_2F_5NO_2$, $C_3F_7NO_2$, and CF_2ClNO_2 (10). Reactions were carried out in sealed tubes. Yields of trifluoronitrosomethane were a follows: dimanganese heptoxide - 49% ; chromium (VI) oxide - 38% ; and lead dioxide - 32%. Carbon dioxide, silicon tetrafluoride, and carbonyl fluoride were by-products of the oxidation.

A method which was developed later (13) allows heptafluoronitropropane to be prepared in 75-80% yield by heating the nitroso-compound in oxygen.

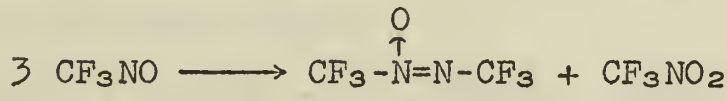
II REDUCTION

The gem-chloronitroso-derivatives of cycloalkanes yield the oxime by reduction of NO followed by elimination of HCl. Hydrazine in methanol (15) gives an 88% yield of the oxime:



Catalytic reduction (16) with platinum and hydrogen gives an 86% yield of cyclohexanone oxime. Reduction may also be accomplished with $LiAlH_4$ or $NaBH_4$, but with lower yields.

A disproportionation, or internal oxidation and reduction, occurs (17) when trifluoronitrosomethane is shaken with aqueous base or heated with active carbon:

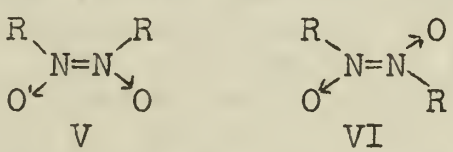


The structure of the hexafluoroazoxymethane was clearly confirmed by its infra-red spectrum. An analogous reaction was observed by Bamberger (18) for nitrosobenzene.

III DIMERIZATION

Structure of C-nitroso-dimers

The major details of the structure of dimeric nitroso-compounds have been solved and nitroso-alkane dimers in both cis (V) and trans (VI) forms have been prepared.



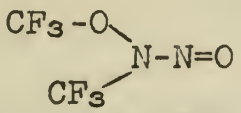
A recent review article summarizes the evidence (19).

Structure of the Trifluoronitrosomethane "Dimer"

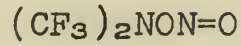
CF_3NO is completely stable in the dark, even after several years, but on exposure to light, particularly to U.V. light, the blue gas (b.p. - 87°) changes almost quantitatively into a brownish-red gas of a much higher boiling point (10°) (20). This compound is not a dimer of type (V) or (VI) since it is deeply colored and does not revert, at least

not completely, to the colored monomer upon heating or dissolving in a organic solvent. No known dimer is an exception to these facts.

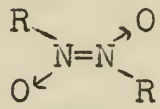
It was concluded that the "dimer" was (VII) or (VIII) and not analogous to (IX).



VII



VIII



IX

The infra-red spectrum of $C_2O_2N_2F_6$ (20) has no strong bands between 1750 and 1330 cm.$^{-1}$, the region shown to be characteristic of the nitrite group (21). A very strong doublet is observed at 1828,1802 cm.$^{-1}$ and this is an abnormally large shift from the usual nitrite vibrations (20).

Further spectroscopic studies on nitrosamines and nitrites (22) enable a much clearer distinction to be made between the two. The N=O group in a nitrosamine vapor absorbs at 1488 cm.$^{-1}$, and introduction of fluorine into the alkyl group shifts the absorption to 1550 cm.$^{-1}$ [$(CF_3CH_2)_2N$-N=O]. The N=O vibration for the perfluoro-compound (VII) can thus now be predicted to lie between 1560 and 1690 cm.$^{-1}$. The spectrum of trifluoronitrosomethane dimer shows only weak absorption in this region, but, as mentioned above, has a strong doublet at 1828, 1802 cm.$^{-1}$ Since alkyl nitrites absorb at 1675 cm.$^{-1}$, and the compound CF_3CH_2ON=O absorbs at 1736 cm.$^{-1}$, it is thus very probable that the 1828, 1802 cm.$^{-1}$ doublet is caused by an -ON=O system attached to a negative group, and this indicates $(CF_3)_2NON$=O as the structur for trifluoronitrosomethane dimer.

It was found that the equilibrium

$$RCH_2ONO + C_2H_5OH \rightleftharpoons RCH_2OH + C_2H_5ONO$$

lies well to the right when R = fluoroalkyl, and the ultraviolet spectrum of a fluoroalkyl nitrite in ethanol is thus essentially that of ethanolic ethyl nitrite and quite different from the spectrum of the fluoroalkyl nitrite as a vapor or as a solution in light petroleum.

The ultraviolet spectrum of a fluoroalkylnitrosamine is scarcely altered by change from vapor to solution in ethanol and is quite distinct from that of ethyl nitrite. Therefore, distinction between a nitrosamine and a nitrite each containing fluorine near to the -NNO or -ONO group can be made by observing if the spectrum remains virtually unchanged in ethanolic solution (fluoronitrosamine) or changes to that of ethyl nitrite (fluoronitrite). The spectrum of an ethanolic solution of $C_2O_2N_2F_6$ is identical with that of ethyl nitrite, indicating a fluoronitrite structure. The shift to the red of the main nitrite peak (vapor) observed for trifluoroethyl nitrite (22) is thus continued with O-nitrosobistrifluoromethylhydroxylamine (VIII): C_2H_5ONO 355 mμ; CF_3CH_2ONO 364 mμ; $(CF_3)_2NONO$ 374 mμ.

Chemical evidence (23) is shown by conversion of the nitrite into hydroxylamine:

$$(CF_3)_2NON=O + HCl\ aq. \rightleftharpoons (CF_3)_2NOH + NOCl$$

X

[illegible]

It [illegible] (VII) [illegible]

[illegible]

The Spiro- [illegible]
1730 and 1750 cm. [illegible]
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[illegible]

[illegible]

The structure of N,N-bistrifluorohydroxylamine (X) was proved by its reaction with phosphorous pentachloride to give the known bistrifluoromethylamine (XI).

$$(CF_3)_2NOH + PCl_5 \longrightarrow (CF_3)_2NCl + POCl_3 + HCl$$
$$(CF_3)_2NCl + HCl \longrightarrow (CF_3)_2NH + Cl_2$$
XI

This eliminates the alternate structure (VII) because $CF_3(CF_3O)NH$ would arise from the reaction

$$CF_3(CF_3O)N\text{-}N{=}O + HCl\ aq. \rightleftharpoons CF_3(CF_3O)NH + NOCl$$

and PCl_5 could not convert this compound into bistrifluoromethylamine (XI). Therefore, O-nitrosobistrifluoromethylhydroxylamine (VIII) is the correct structure for the dimer of trifluoronitrosomethane.

Free-radical Addition to a Nitroso-group

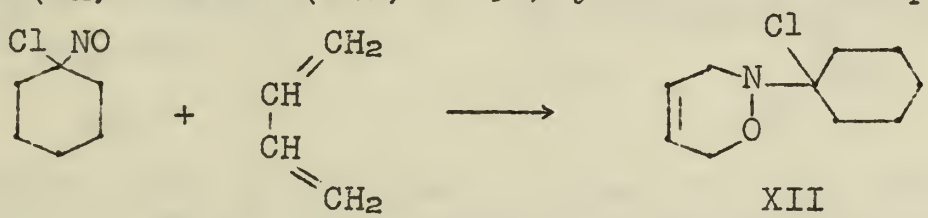
The elucidation of the structure of the trifluoronitrosamine "dimer" establishes the direction of free-radical addition (23) to a nitroso-group:

$$CF_3\text{-}NO \xrightarrow{h\nu} CF_3\cdot + NO$$
$$CF_3\cdot + CF_3NO \longrightarrow (CF_3)_2NO\cdot$$
$$(CF_3)_2NO\cdot + NO \longrightarrow (CF_3)_2NON{=}O$$
or
$$(CF_3)NO\cdot + CF_3NO \longrightarrow (CF_3)_2NON{=}O + CF_3\cdot \rightarrow \text{etc.}$$

The trifluoromethyl radical clearly attacks nitrogen in preference to oxygen.

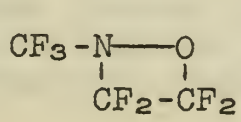
ADDITION REACTIONS

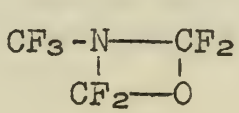
Chloronitroso-compounds will participate in the Diels-Alder reaction (24) yielding an oxazine ring structure. The synthesis of a 3,6-dihydro-1,2(2H)-oxazine (XII) in 90% yield is an example:

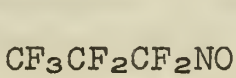


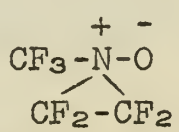
XII

Trifluoronitrosomethane combines slowly and quantitatively with tetrafluoroethylene (9) in the dark at room temperature to give 30-65% of a colorless gas (b.p. -6.8°) and 35-70% of an almost colorless viscous oil. The ratio of gas to oil can be controlled by choice of reaction temperature. Higher temperature favors the gas. The gas has a molecular formula of C_3ONF_7 and is unaffected by water, aqueous acid or alkali, or U.V. light. Possible structures have been suggested:

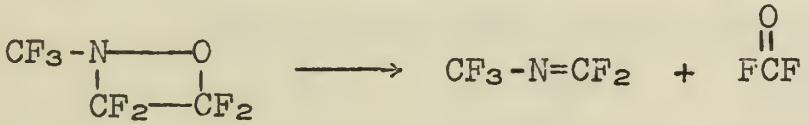

XIII


XIV


XV


XVI

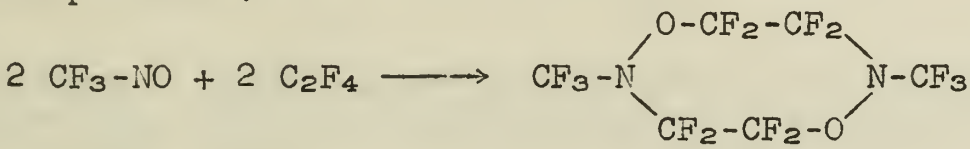
Heptafluoronitrosopropane (XV) can be eliminated since this is known (13) and is a deep blue gas which shows the characteristic N=O stretching vibration (1605 cm.$^{-1}$) in its infrared spectrum. Compound (XIV) is improbable as it would require fission of the C-C and N-O bonds in the starting materials. It is not probable that a three-membered ring of the type in (XVI) would be stable or that the coordinate $\overset{+}{\underset{}{N}}\text{-}\overset{-}{O}$ bond could be sufficiently non-polar to account for the low boiling point of -6.8°. Also, due to the decreased availability of the lone pair of electrons on the nitrogen atom, perfluoro-amines, such as $N(CF_3)_3$ are unable to form amine oxides. Support for structure (XIII) was given by its pyrolysis at 550° at low pressure in absence of air to yield equimolar quantities of carbonyl floride and perfluoro(methylenemethylamine) (XVII).



XVII

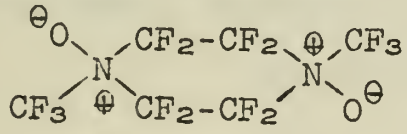
The infrared spectrum of (XVII) shows a strong band at 1808 cm.$^{-1}$, assigned to the C=N stretching vibration.

The oil has an empirical formula of C_3ONF_7, the same as perfluoro-2-methyl-1:2-oxazetidine (XIII). This eliminates the possibility that it is a tetrafluoroethylene polymer $-(CF_2\text{-}CF_2)_n-$. Since analytical data indicated a 1:1 ratio of CF_3NO and C_2F_4, the formation of cyclic compounds was possible:

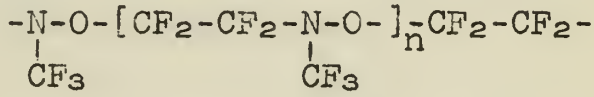


XVIII

This possibility was rejected since compounds with 8-, 12-, or 16-membered rings would be appreciably volatile. An amine oxide such as (XIX) would explain the 1:1 ratio of CF_3NO to C_2F_4 and the high boiling point could be attributed to the polar nature of the $\overset{+}{\underset{}{N}}\text{-}\overset{-}{O}$ bonds.



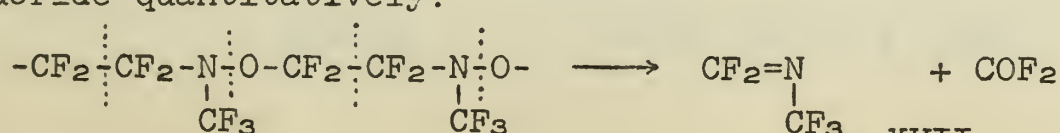
XIX



XX

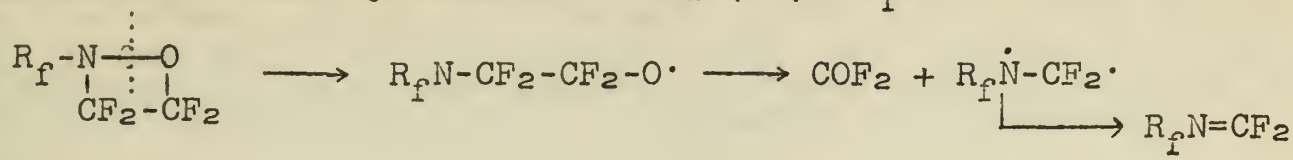
A third possibility for the oil was a polymer of type (XX) formed by copolymerization of tetrafluoroethylene and trifluoronitrosomethane. Distinction between (XIX) and (XX) was made on basis of a molecular-weight determination in perfluoromethylcyclohexane. The mean molecular weight was a least 7000 and possibly much higher. The oil is thus the polymer (XX). This appears to be the first example of an N=O group acting like a C=C in copolymerization, although it has been shown above that free-radical addition to N=O can occur.

When heated in a vacuum at 400° in absence of air, it yields equimolar amounts of perfluoro(methylenemethylamine) (XVII) and carbonyl fluoride quantitatively:

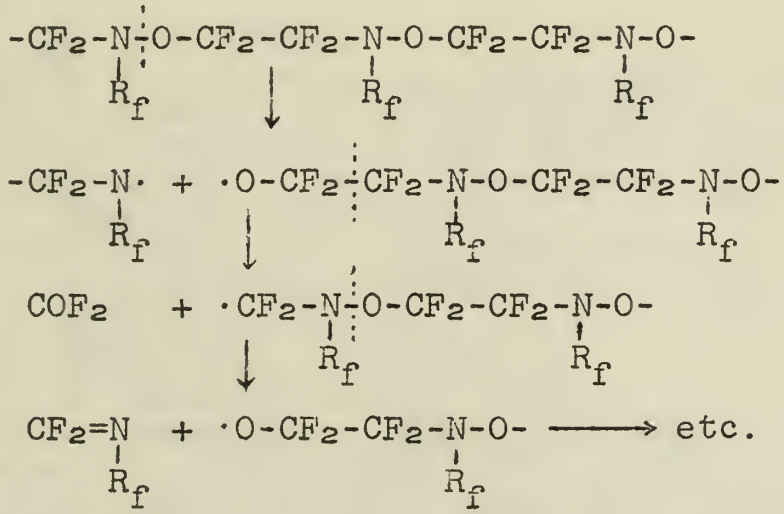


XVII

It seems very probable that the pyrolysis of the oxazetidine (XIII) (13) occurs by initial fission of the N-O bond to give the diradical (XXI). This radical is actually a perfluoroalkoxyl-radical which is known to readily eliminate COF_2 (25). R_f=fluoroalkyl



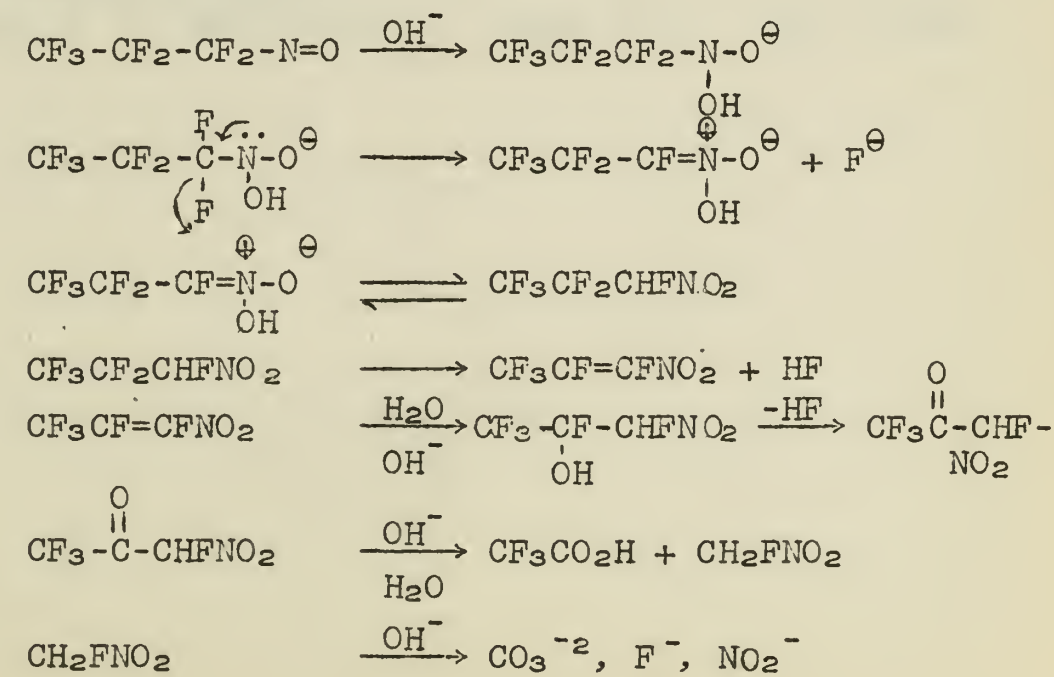
Pyrolysis of the polymer (XX), which proves its structure, may proceed by a similar mechanism (13):



The reaction of heptafluoronitrosopropane with 10% aqueous base (13) is interesting since it yields pentafluoropropionic and trifluoroacetic acid as main products as well as fluoride, nitrite, and carbonate:

$$C_3F_7NO \xrightarrow[H_2O]{OH^-} C_2F_5CO_2H + CF_3CO_2H$$

The following steps were suggested by Barr and Haszeldine (13) to explain the partial breakdown of the perfluoroalkyl group, which is normally extremely resistant to attack:



In this scheme nucleophilic attack on the nitrogen of the nitroso-group is followed by fluoride elimination. Rearrangement into hexafluoronitropropane is followed by elimination of hydrogen fluoride and base-catalyzed hydration of the resultant olefin to give the fluoronitro-ketone. In an alkaline medium this ketone would undergo hydrolytic cleavage to trifluoroacetic acid. The nucleophilic attack on the nitrogen of the nitroso-group is substantiated by the fact that heptafluoronitropropane is stable in a similar reaction medium.

****

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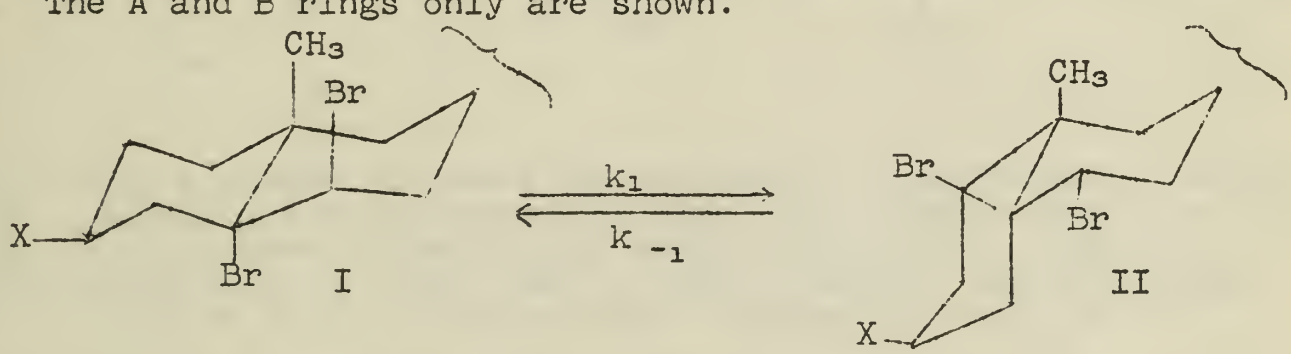
Diaxial-Diequatorial Rearrangements

Reported by W. G. Bentrude July 15, 1959

Many years ago Mauthner (1) discovered that ordinary cholestene dibromide formed from the ionic addition of bromine to Δ^5-cholestene underwent mutarotation when left in benzene or choloroform solution at room temperature. Later Bretschneider (2) showed the existence of two 5,6-dibromocholestane-3β-yl-benzoates. Both mutarotated in solution until equilibrium was attained. At equilibrium in benzene solution 79% of the higher-melting, stable isomer was found. In chloroform the percentage was 83.

That the mutarotation of dibromocholesterol and its esters actually involved conversion of the dibromide from a 5α,6β- to a 5β, 6α-configuration was demonstrated by Barton and Miller (3). The labile dibromide, formed by the addition of bromine to cholesterol, is 5α,6β-dibromocholestan-3β-ol. This assignment of configuration was suggested by comparison of molecular rotation data between the dibromo and the dichloro compounds and was confirmed chemically by treating the known α-oxide with hydrogen bromide to give 5α-hydroxy-6β-bromocholestan-3β-ol. This was oxidized to the corresponding 3-ketone and dehydrated to the 6β-bromo-Δ^4-cholestene-3-one. The oxidation and dehydrobromination of ordinary cholesterol dibromide afforded the identical ketone. Oxidation of the stable cholesterol dibromide followed by dehydrobromination gave 6α-bromo-Δ^4-cholesten-3-one. The choice between 5α,6α- and the 5β,6α-configuration was made by comparison of rates of dehydrohalogenation of the benzoates on treatment with alkali. In contrast to 5α,6β-dichlorocholestan-3β-yl benzoate, 5α,6α-dichlorocholestan-3β-yl benzoate, a cis-1,2-dihalide undergoes facile elimination of hydrogen chloride. But stable dibromocholesterol benzoate is attacked by alkali even more slowly than ordinary (5α,6β-) benzoate dibromide. Thus the (trans-) 5β,6α-configuration is assigned to the stable dibromide.

The mutarotation therefore involves the following interconversion. The A and B rings only are shown.



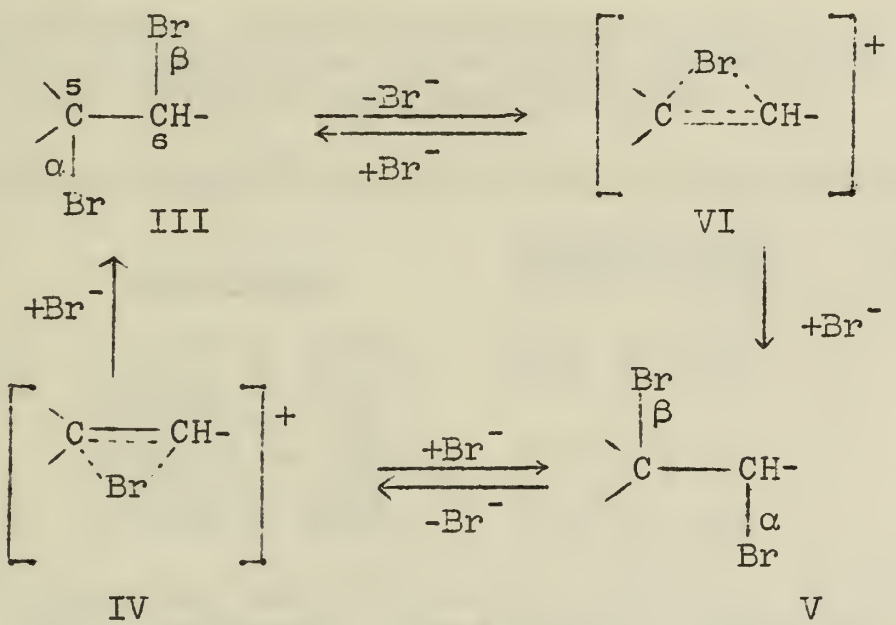
The driving force for such an interconversion is obviously of conformational origin. Relief of strain arises from conversion of the C-10 methyl from an orientation axial with respect to rings A and B (a_A,a_B) to an orientation equatorial to A and axial B, (e_A,e_B). The orientation of the 5-bromine changes from $a_A a_B$ to $a_A e_B$, and the 6-bromine atom from axial to equatorial. The latter also results in a decrease in interaction energy between the 6-bromine and the C-10 methyl group. Evidently these factors outweight the increase in repulsive nonbonded energy going from the trans-decalin to the cis-decalin conformation and the increase in dipolar interaction between the bromines as they move into positions equatorial to each other.

The presence of a 3β-substituent makes the isomerization energetically less favorable, since the substituent assumes an axial position which is also sterically involved with the equatorial 5β-bromine. The following data are of interest in this regard.

3β-substituent	% 5β,6α-dibromide at equilibrium in $CHCl_3$ at 40.0°C	conversion ratio	reference
H	>99	99	4
Br	10	0.11	5
Cl	13	0.15	5
OBz	80	4.0	5
OH	86	6.1	4

To a first approximation the position of equilibrium is seen to vary with the size of the 3β-substituent.

A mechanism for the mutarotation of the cholesterol dibromides, proposed by Barton and Miller, involved the β-bromonium ion, VI, as intermediate in the conversion of the labile isomer, III, to the stable isomer, V. As written the reverse would proceed through the α-bromonium ion, IV.

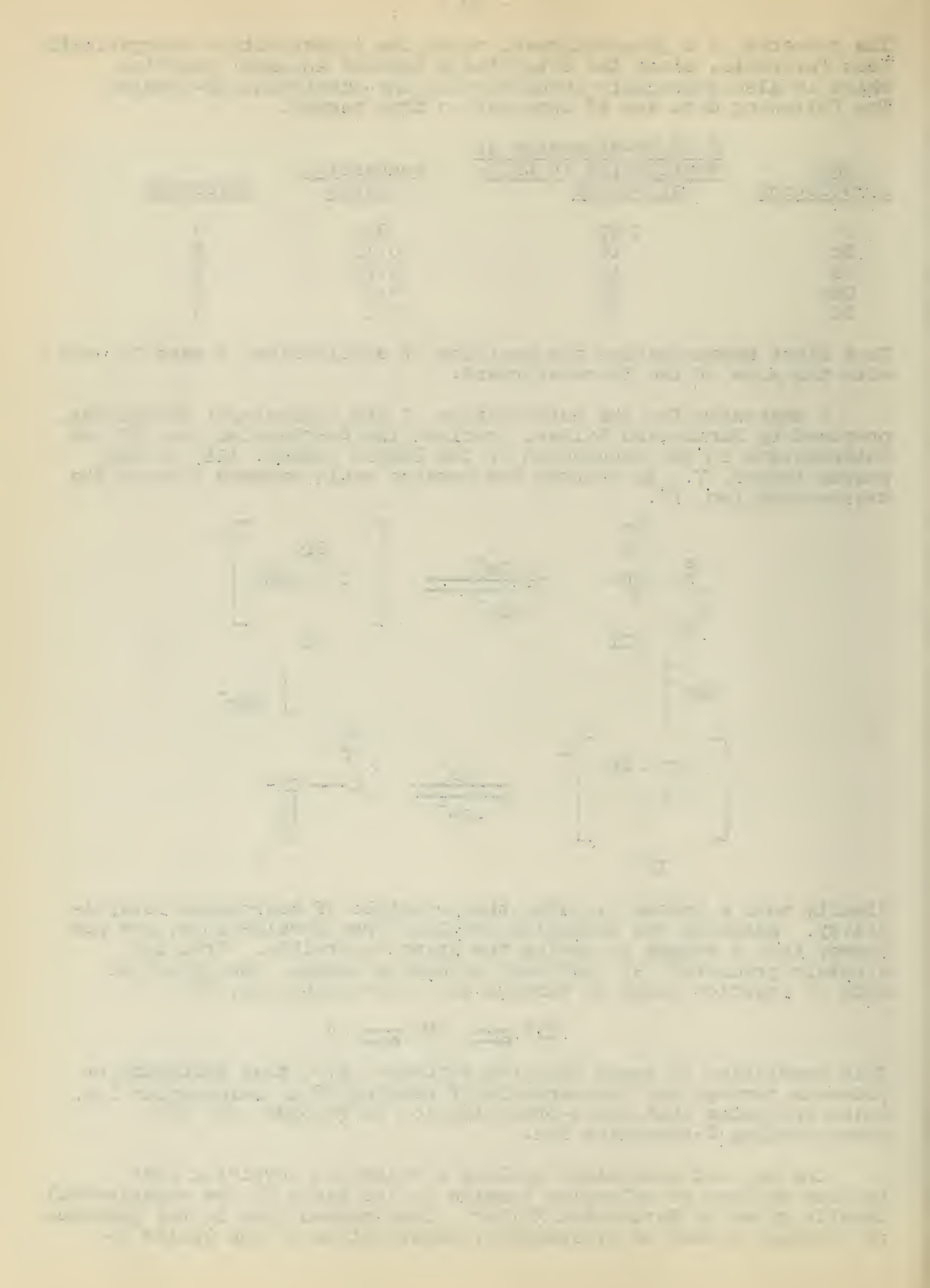


Clearly such a scheme violates the principle of microsopic reversibility. Assuming the mechanism involves free bromide ions, one may remedy such a scheme by making the steps reversible. Grob and Winstein predicted (4) that then in such a scheme, the principal mode of reaction would be through the α-bromonium ion, IV.

$$\text{III} \rightleftharpoons \text{IV} \rightleftharpoons \text{V}$$

This prediction is based upon the evidence (6,7) that halogenation proceeds through the non-Markonikoff opening of an α-bromonium ion, which indicates that the α-bromonium ion is favored over the corresponding β-bromonium ion.

One may not completely exclude a mechanism involving free bromine cations or molecular bromine on the basis of the experimental details given by Barton and Miller. They showed that in the presence of 30-molar excess of cyclohexene, mutarotation of the labile 5-



cholestene dibromide, the amount of stable dibromide formed was only 10 percent less than the amount formed in the presence of cyclohexane. However such a mechanism might still be possible if cyclohexene adds bromine at a rate 330 times less than Δ^5-cholestene.

Two indications that the process might be intramolecular were: (1) the high rate of mutarotation in inert solvent (8)(first order rate constant ca. 10^{-5} sec^{-1} in $CHCl_3$ at 25°); (2) the mutarotation of labile 5,6-dibromocholestane and 5,6-dibromocholesteryl benzoate (2) in competition with solvolysis in boiling ethanol. Such competition of external bromide with solvolysis is considered to be improbable under these conditions (9,10).

The mutarotation as represented by the conversion of I to II has been followed polarimetrically and shown to be first order (4). For the dibromocholestane series (X = H), k_1 was constant over a nine-fold variation of initial dibromide concentration (5). No catalysis by HBr was noted. A radical chain mechanism was ruled out because of the failure of added benzoyl peroxide or pyrochatechol to have any effect on the rate constant. The activation parameters for the mutarotation of 5,6-dibromocholestane in CCl_4 were determined to be: $E^{\ddagger}$ = 25.5 kcal./mole; ΔH = 24.9 kcal./mole; $\Delta S^{\ddagger}$ = -5.1 e. u.

The lower-melting, labile dibromocholestane is sensitive to solvolysis, and in competitive experiments between solvolysis and mutarotation, the following data were obtained.

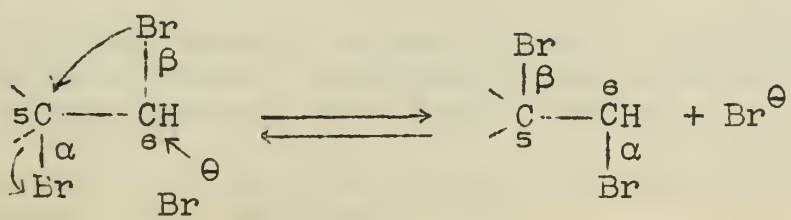
Solvolysis-mutarotation of 0.0471 M. Dibromocholestane[4]

Solvent	Added Salts	Polarimetric k sec^{-1} x 10^5	Solvolysis k sec^{-1} x 10^5
$CHCl_3$-AcOH 1:1	0.0467 M. NaOAc	(8.21 ± 0.18)	2.4
$CHCl_3$-AcOH 1:1	(0.0234 M. NaOAC) (0.0234 M. LiBr)	(8.8 ± 0.6)	2.4
$CHCl_3$-AcOH 1:1	(0.00934 M. NaOAc) (0.0374 M. LiBr)	8.59 ± .08	2.4
$CHCl_3$-AcOH 1:1	0.0468 M. NaOAc	8.00 ± 0.48	2.4

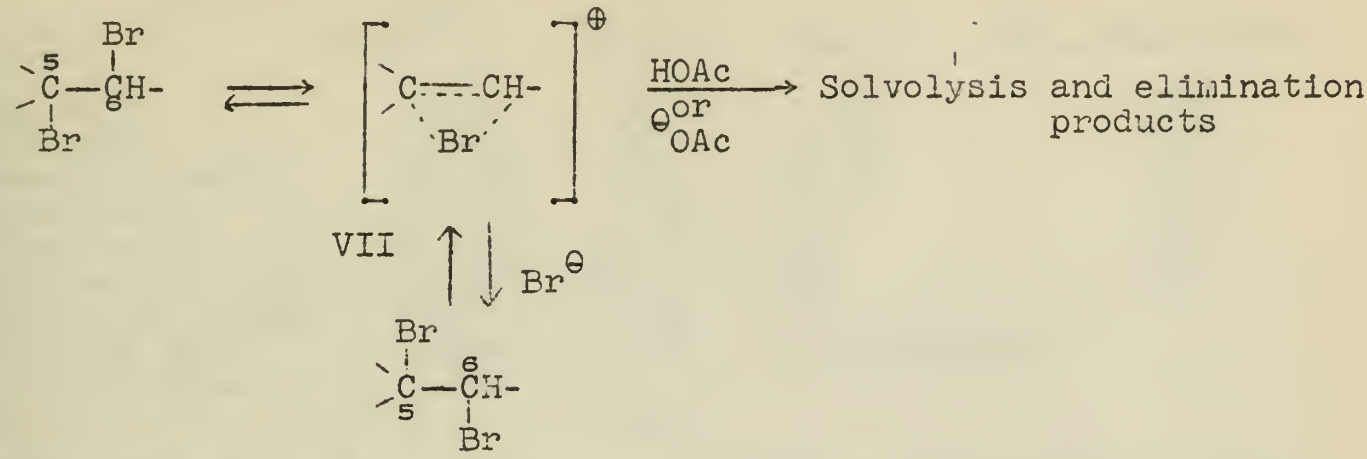
The solvolysis reaction was followed by titration of NaOAc. A plot of amount of perchlorate used versus time was identical for all ratios of salts added.

One notes that isomerization predominates and the extent to whic dibromide is consumed by solvolysis and elimination is completely insensitive to the concentration of added acetate ion and bromide ion at constant ionic strength. The constancy of solvolysis and mutarotation rates with variation in bromide ion rules out the following:

(1) An S_N2'-type mechanism

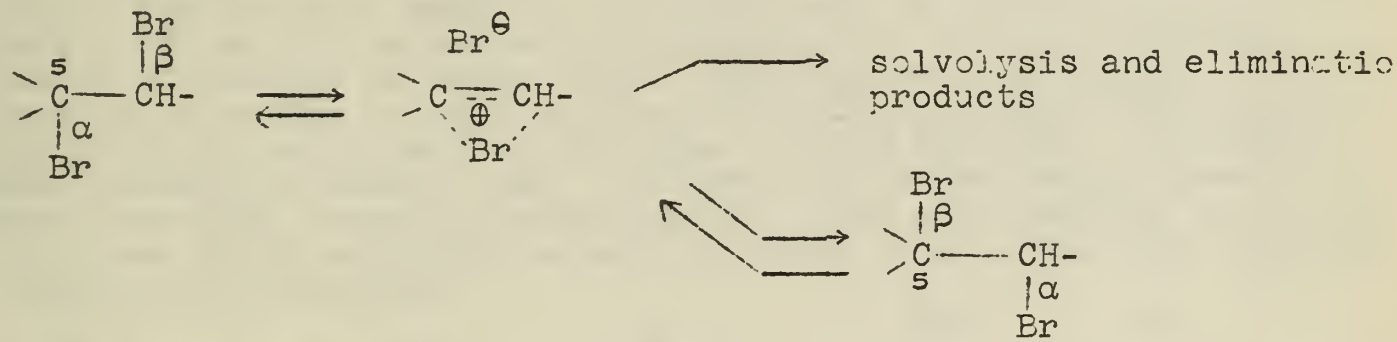


(2) A mechanism involving dissociation to a bromide ion and an intermediate bromonium ion, VII, which may react with free external bromide or, alternatively, with solvent.

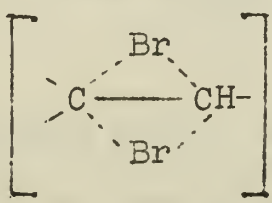


The important mode of isomerization is therefore an internal one.

The relative total rates of reaction in the various solvents at 40° C. are (5): heptane, 1 < CCl_4, 2.7 < C_6H_6, 5.3 < $C_6H_5NO_2$, 28 < $CHCl_3$, 86 < $CHCl_3$-AcOH (1:1), 115 < $CHCl_3$-C_2H_5CH (1:1), 284. These data on effect of solvent and the data on effect of added bromide ion and acetate ion are interpreted by Winstein and Grob to be most easily explained, at least in the better ionizing solvents, by means of an intermediate bromide-bromonium ion pair.

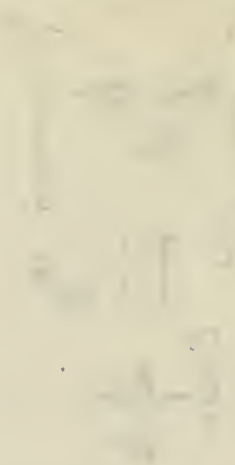


The fact that the rate of isomerization drops off only slowly in going to the inert solvents (1:1 $CHCl_3$-AcOH leads to reaction rate only three times that in $CHCl_3$) and that mutarotation in the poorly ionizing solvents is not catalyzed by traces of polar impurity are indications of the possibility that the nature of the intermediate changes gradually as the ionizing power of solvent decreases until in the poorest ionizing solvents an intermediate or transition state with negligible charge separation is involved. Both bromines would be essentially equivalent. This differs from the ion pair inter-



mediate in having less charge separation and more covalent character in the carbon-bromine bonds---ion-pairs and covalently bonded cyclic intermediates being extremes in a graded series.

The mutarotation of 5α,6β-dibromocholestane in benzene has been shown to be general acid catalyzed (11).



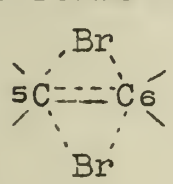
Acid Catalysis of the Mutarotation of 5α,6β-dibromocholestane

Catalyst	Conc. moles/kg.	k_f 10^6	k_c 10^6	Rel. pK_a in C_6H_6
Acetic acid	0.303	7.45	4.26	5.18
Benzoic acid	0.228	7.40	5.43	4.58
Chloroacetic acid	0.0443	8.21	47.6	2.90
Salicylic acid	0.0287	7.53	47.8	2.55
Dichloroacetic acid	0.0553	16.68	190	1.75
Trichloroacetic acid	0.0279	20.1	501	0.70
Piperidinium acetate	0.107	6.44	...	
Acetic acid and piperidine	0.626 0.181	7.64	3.38(acetic)	
None		6.16		

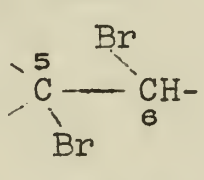
The data demonstrate clearly the existence of a general acid catalysi and the lack of important base catalysis. The catalysis was shown to approach first order in carboxylic acid, and k_c, the catalytic rate constant, was calculated from the equation

$$k_f = k_o + k_c[HA]$$

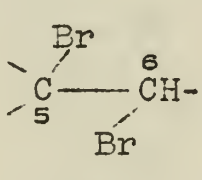
where k_o is the constant for mutarotation in the absence of added acid, and k_f is the observed rate constant in the presence of added acid. The Bronsted catalysis law (12), $\log k_c = x \log K_b + C$, was obeyed. The Bronsted catalytic coefficient, $-d(\log k_c)/d(pK_a)$, equals 0.486 at 44° which is even greater than that for the mutarotation of glucose in water (13). Acid may be functioning to decrease the electron density in the carbon-bromine bond being broken which would in turn increase the ease of bond breaking. Assuming a cyclic transition state, VIII for the uncatalyzed rearrangement in benzene which is probably intramolecular, the contribution from resonance forms VIIIc and VIIId should be about equal. The same applies to forms VIIIe and VIIIf.



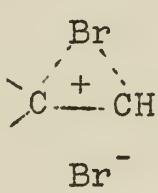
VIII



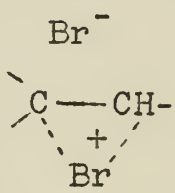
VIIIa



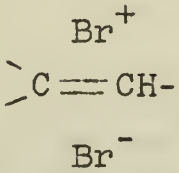
VIIIb



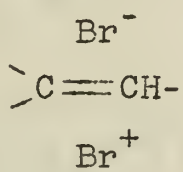
VIIIc



VIIId

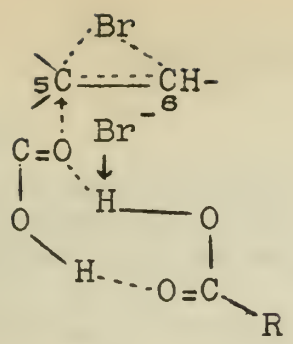


VIIIe

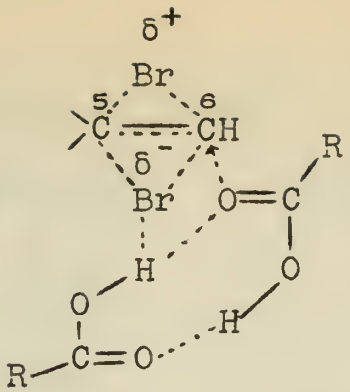


VIIIf

A transition state with little charge separation is probable. The function of the carboxylic acid is possibly two-fold: 1) Coordination with the partial negative charge on the α-bromine, 2) Coordination with the 5- or 6-carbon to stabilize the charge deficiency developing there in the transition state of the rate-determining step during mutarotation. These are demonstrated in the following structures. Coordination with the β-bromine is excluded by steric

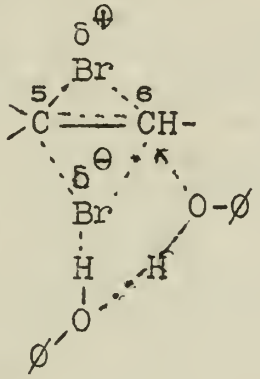


or

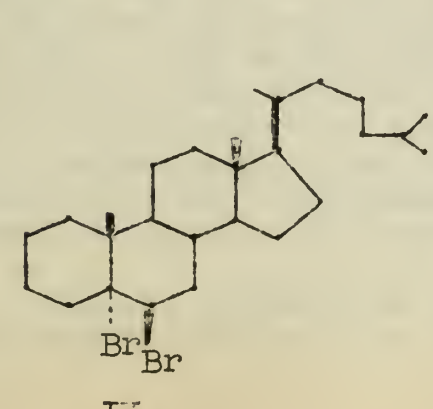


considerations. The molecularity in acid is probably two, since carboxylic acids exist predominately as dimers in nonpolar solvents[14]. Increased importance of structures VIIIc and VIIIe and concurrent lowering of the energy of the transition state results. In addition, the probability of ion pair formation is increased by the presence of acid even in catalytic amounts. The effect of added acetic acid on the rate of mutarotation on labile 2,3-dibromocholestane observed by Grob and Winstein[4] finds explanation is general acid catalysis. The increase in rate on addition of alcohol[4] is probably due to its actior as a nucleophile as well as the increase in dielectric constant from its addition.

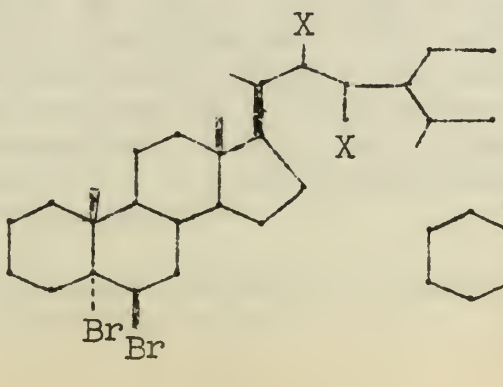
The mutarotation of 5α,6β-dibromocholestane is also catalyzed by various phenols. The order in phenol was not determined for the substituted phenols. The order in unsubstituted phenol is 1.68 which was interpreted by Kwart to signify the participation of two moles of phenol in the rate-determining transition state. Values of the pKa's for various phenols in benzene are not available, hence Bronated plots could not be made. Assuming the low value for order in phenol, 1.68, is caused by considerable monomolecular catalysis, then the bimolecular catalytic effect may be similar in action to that of the carboxylic acid dimers and be represented by



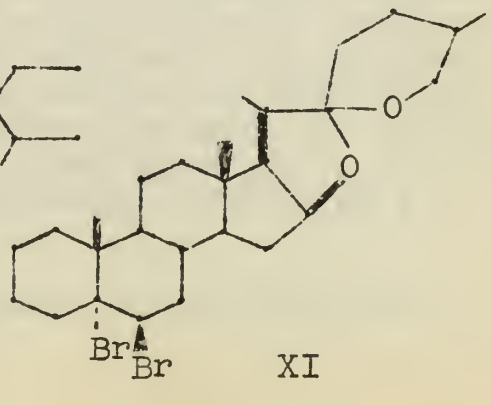
Evidence for possible so-called long range effects on the rates of mutarotation at the 5,6-position have been noted.[5,15] The following structures and data are instructive.



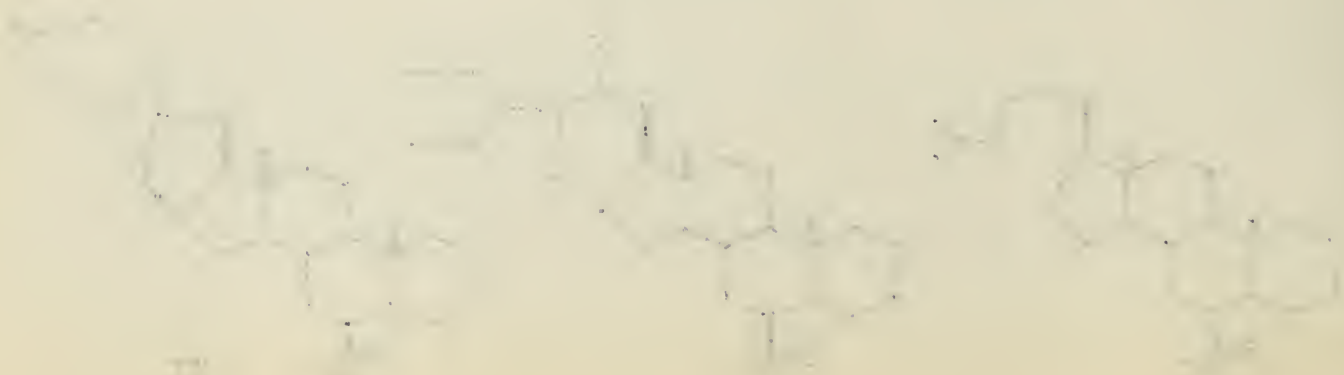
IV



V



XI



Relative Rates of Mutarotation in $CHCl_3$[5]

Dibromide	Rel. rate	Ea kcal./mole
5α;6β-dibromocholestane (IX)	1	20.4
5α;6β-dibromostigmastane (X; X = H)	1	20.4
5α;6β,22ξ,23ξ-tetrabromostigmastane (X; X = Br)	0.75	20.4
5α; 6β-dibromodeoxytigogenin (XI)	0.69	20.4

The isomerization in all cases was shown to be first order in dibromide and independent of initial concentration of dibromide. It was demonstrated that the decrease in rate of mutarotation of the tetrabromo compound can not be due to mutarotation in the side chain. The effect is evidently not due to the extra ethyl group in the side of the stigmastanes as dibromostigmastane mutarotated at the same rate as the dibromocholestane. The side chain of the 5α,6β-dibromodeoxytigogenin, XI, is more greatly modified and this modification results in a decrease in rate of mutarotation. There was no effect of traces of HBr on the side chain as shown by control experiments. Barton[15] estimates the maximum electrostatic effect of the 22 and 23-bromines to be no greater than 50 cal. in favor of mutarotation.

These effects must be explained either by the inductive effect of the bromine or oxygen atoms or by some "long range" effect arising from conformational distortion. The effects of modification of parts of the molecule remote to the reaction site on the reaction of benzaldehyde with some triterpenoid ketones to give benzylidene derivatives have been ascribed to long-range conformational strain.[16] In the ketone reactions, electrostatic and inductive effects have been excluded as possible explanations.

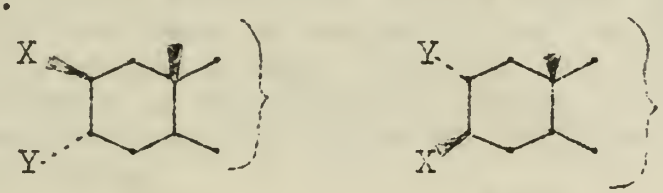
The proposal that a general diaxial-diequatortial rearrangement of an intramolecular type occurs not only at the 5,6-position but also at for example the 2,3-, 3,4- and 4,5-positions has been made by Barton.[18,17,19] That the mutarotation[22] on melting of the product of the addition of bromine to Δ^2- cholestene involves the isomerization of the 2β,3α-dibromide to the 2α,3β-dibromide was shown by Alt and Barton.[20] The evidence is the following. Addition of the halogen is generally accepted to be of the <u>trans</u> ionic type. The labile dibromide, m. p. 123-124° on melting rearranges to a more stable dibromide, m. p. 144-145°. The latter affords Δ^2-cholestene on debromination with zinc. The rearranged product is identical with the minor product of bromination as would be expected if they were the respective <u>trans</u> addition products. From the relative rates of debromination with zinc, the stable isomer is assigned the <u>trans</u>-2α,3β-configuration and the labile isomer the 2β,3α-configuration. Similarly it was shown that addition of chlorine to Δ^2-cholestene yields the 2β,3α-dichlorocholestene as major product which is transformed on melting to the 2α,3β-dichlorocholestene. The conversion of 2β-bromo-3α-chloro-cholestane to 3α-bromo-2β-chloro-cholestane was demonstrated.[20] The product of bromination of Δ^3 cholestene is shown to be the 3α,4β-isomer and to be isomerized to the 3β,4α-configuration. In all probability the isomerization of 4,5-dibromocholestene involves a diaxial-diequatorial rearrangement.[26]

Kinetic studies of the mutarotation of some 2,3-disubstituted cholestanes yielded the following data.

Rates of Rearrangement of Acyloxyhalogenocholestane Melts at 136°±1°[18]

Diaxial 2β,3α-disubstituted cholestane		$10^4 k$ (sec^{-1})
2β	3α	
Br	OBz	1.43
Br	p-$MeOC_6H_4CO_2$	3.55
Br	p-$NO_2C_6H_4CO_2$	1.13
Cl	OAc	0.0466
Br	OAc	1.07
I	OAc	8.04
Br	Br	1.49

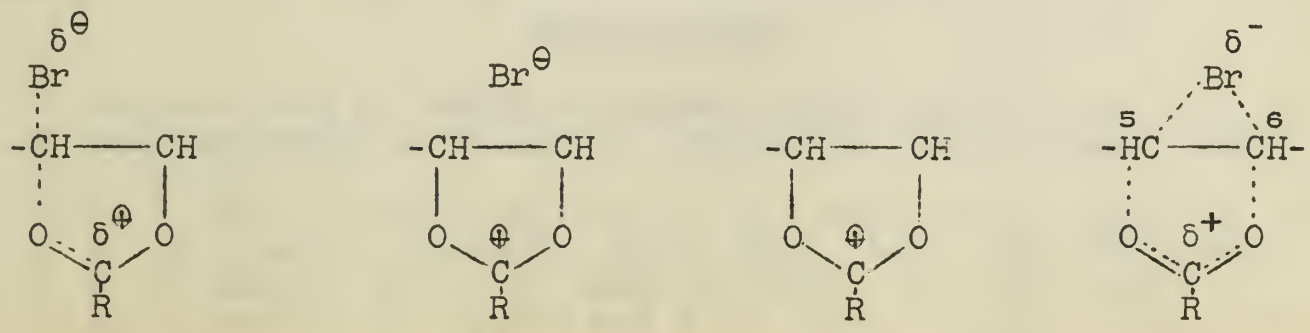
Good first order plots were obtained in all cases. The acetate, benzoate and substituted benzoate esters of 2β-halogenocholestane-3α-ol (XII; X = halogen, Y = acyloxy) were shown to rearrange on melting to the corresponding 3β-halogenocholestane 2α-yl esters (XIII; X = halogen, Y = acyloxy).



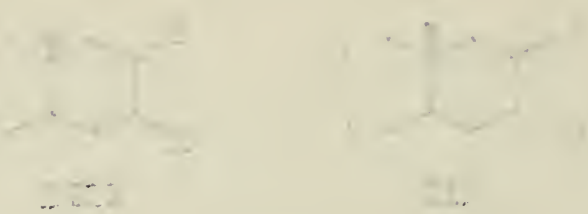
XII XIII

For example, heating the bromo-acetate (XII; X = Br, Y = OAc) at 136° transformed it smoothly into an isomer shown to be XIII (X = Br, Y = OAc) on the basis of the following evidence. Treatment with alkali gave 2α,3α-epoxycholestane indicating the product was a trans-halogenohydrin[23] substituted at positions 2 and 3. Secondly, hydrogenolysis of XIII furnished the known[24] 2α-acetoxycholestane.

A comparison of the rates of rearrangements of the halogeno-acetates shows that the relative rates parallel the relative polarizability of the halogens and the ease of rupture of the carbon-halogen bonds. The relative rates of mutarotation of the substituted benzoates indicate that electron donation is important in stabilization of the transition state. One may obtain a linear Hammett plot from the rate data of Barton only if σ^+ is used for the p-methoxy benzoate. (ρ=-0.55) These data support the postulation of a benzoyloxy-assisted ionization XIV to an ion pair XV which may then by internal return give rearranged diequatorial product. Alternately the ionization may lead to dissociation to free bromide and the stable bridged carbonium ion XVI which may react with external bromide to give the diequatorial product.



XIV XV XVI XVII



There seems to be no real reason to assume as Barton implies that the halogeno-benzoates and acetates are part of a series of diaxial-diequatorial rearrangements which proceed by an intramolecular mechanism through a transition state such as XVII directly to diequatorial products. The only real evidence for an intramolecular mechanism is for the 5,6-dibromo case in solution. Ion-pair formation and bridged-carbonium-ion formation would be more favorable with the 1,2-halogeno-esters than with the dibromo compounds. One may not rule out the possibility of intermediates in the reaction from the available data.

It is interesting to note the effect of variation of type of halogen on the relative ease of mutarotation of the various steroidal dihalides. Essentially complete conversion of the labile 2,3-dibromocholestane was effected by heating at 180° for 20 minutes[20], while the labile 2-chloro-3-bromocholestane required 2 hours of heating at 210-220°. Also, the unstable 3-acetate of cholesterol dibromide was converted to the stable isomer on heating at 117° for 20 minutes[25], but the corresponding dichloride was unchanged by heating at 123° for one hour. Again, the labile benzoate of cholesterol dibromide showed a tendency to mutarotate on standing in $CHCl_3$ solution, but the corresponding 5-bromo-6-chloro ester was stable under the same conditions.[6] Apparently the relative ease of mutarotation varies in the order dibromo>bromo-chloro>dichloro. This reflects the relative ability of the halogens to participate as neighboring groups and as nucleophiles. This variation also follows the order of relative ease of breaking of the carbon-halogen bonds.

Mutarotation appears to be easiest when one of the bromine-substituted carbons is the tertiary 5-carbon. All of the 5,6-dibromo-steroidal compounds mutarotate on standing in $CHCl_3$ at room temperature. Mauthner noted that whereas ordinary 4,5-dibromocholestane mutarotated at room temperature in $CHCl_3$[26], the 2,3-dibromocholestane did not[21]. Structures such as VIIIc and VIIId which can contribute to the transition state are of course favored by the presence of a tertiary carbon atom. 2β,3α-dibromo-3β-methylcholestane mutarotates in boiling (ca. 60°) $CHCl_3$ with a first order rate constant of about 4×10^{-6}. A crude extrapolation of this value to 136° and comparison with the rate for mutarotation of 2β,3α-dibromocholestane indicates a rate increase of about 10 may be attributed to the presence of the methyl group at carbon three. It is perhaps surprising that the rate of mutarotation of the 2,3-dibromo-3-methyl compound is slower than that of the 5,6-dibromide by a factor of about 100 at 60°. However, the decrease in entropy in going to a somewhat rigid transition state might be greater for the 2,3-dibromide than the 5,6-dibromide, since motion at the 5-position is so restricted in the ground state as compared to that at the 3-position.

****

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THE CURARE ALKALOIDS

Reported by P. Kiener July 3, 1959

INTRODUCTION

The curare, a generic term applied to arrow poisons by South American Indians, have been known for centuries. As early as 1641 (1), Acuña described the "deadly arrow poison". However, the first noteworthy report concerning the origin and preparation of the curare came from Alexander v. Humbold and after him by Robert Schomburg and Richard Schomburg (1).

The obtention of the poisons by the Indians consists of the extraction of different plants, mainly the barks, followed by evaporation of the water solution to a consistent syrup.

The first attempts to isolate the active components of the curare which have the effect of causing muscular paralysis, were made by Boussingault (1), followed by R. Boehm (2), but the results of these early works were very inaccurate. Boehm found that the types of containers used by the Indians to keep the curare led to a fairly good classification of the alkaloids involved (3). He distinguished three types of curare: a) tube, para or bamboo curare, b) pot curare and c) gourd or calabash curare.

The present seminar deals exclusively with the calabash curare alkaloids, which have only recently been successfully studied.

CALABASH CURARE (4)

The calabash curare is far more physiologically active and toxic that the pot or tube curare. While tube and pot curare contains alkaloids which are derivatives of isoquinoline and diisoquinoline types, the calabash alkaloids seem to be derivatives of indole types.

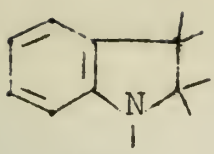
The structure proof of calabash alkaloids is very difficult because of the limited amount of crude material available, the low content in alkaloids and the great complexity of such products.

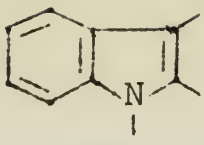
Today it is recognized that most of the alkaloids of calabash curare come from the bark of Strychnos species. The following plants have already been investigated and found to contain curare alkaloids:

1) Strychnos Mitscherlichii
2) " toxifera
3) " melinoniana
4) " guianensis
5) " diaboli

Refined techniques, mainly paper chromatography, have led Karrer and Schmid's school to isolate and characterize more than seventy alkaloids from calabash curare and Strychnos species. All seem to be indole derivatives.

According to their absorption spectra, degradation products and other properties Karrer (5) suggests a tentative classification based on eight chromophores:


XIV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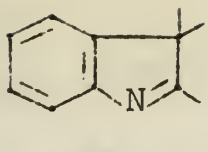
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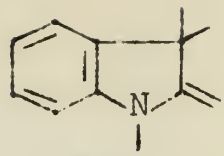
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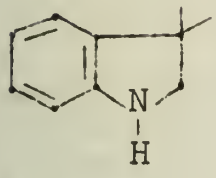
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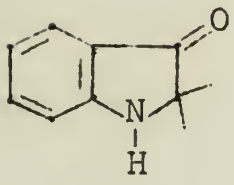
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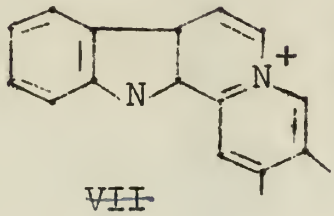
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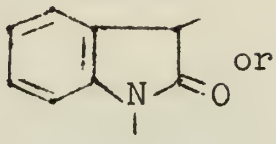
XX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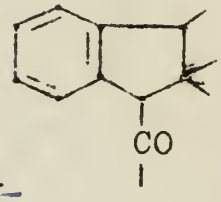

VIII
XXI

Calabash Curare Alkaloids (5-26)

Alkaloids	Type		From Str. Species
C-curarine I	XVI	$C_{40}H_{44-46}ON_4^{++}$	1
C-curarine II	XIV	$(C_{20}H_{23}N_2)_1^+$ or 2	
C-curarine III = C-Fluorocurarine		$C_{20}H_{23}ON_2^+$	1
C-toxiferine I = Toxiferin	XVII	$C_{40}H_{46-48}O_2N_4^{++}$	2
C-toxiferine II = C-Calebassine	XIV	$C_{40}H_{48-50}O_2N_4^{++}$	1
Toxiferine II = Strychnotoxine			2
C-dihydrotoxiferine I = Alkaloid K	XVII	$C_{40}H_{46-48}N_4^{++}$	
C-isodihydrotoxiferine		$(C_{20}H_{23}N_2)_1^+$ or 2	
C-alkaloid A	XIV	$C_{40}H_{48-50}O_4N_4^{++}$	1
B	XVIII	$C_{20}H_{25}ON_2^+$	1
C	XVIII		1
D	XVIII	$C_{40}H_{46}N_4O_2^{++}$	
E	XVI	$C_{40}H_{44-46}L_3N_4^{++}$	
F	XIV	$C_{20}H_{25}O_2N_2$	
G	XVI	$C_{20}H_{23}ON_2$	
H	XVII		
I	XIV	$C_{19}H_{23}N_2^+$ or $C_{20}H_{25}N_2^+$	1
J	XV	$C_{19}H_{21}N_2^+$	
L	XV		
M	XV		
O	XXI	$C_{20}H_{27}ON_2^+$	
P		$C_{20}H_{25}ON_2^+$	
C-alkaloid UB	XXI	$C_{19}H_{23}O_3N_2^+$	2
C-alkaloid Y	XIV		
C-alkaloid X	XIV		
C-calebassinine	XIV	$C_{19}H_{23}O_2N_2^+$	
C-fluorocurine	XIX	$C_{20}H_{25}O_2N_2^+$	2
C-fluorocurinine	XIX		1
C-mavacurine	XV	$C_{20}H_{25}ON_2^+$	2 and 3
C-xanthocurine	XXI	$C_{20}H_{21}ON_2^+$	
C-alkaloid 1	XIV		
2			
C-Guianine	XVI	$C_{21}H_{25}ON_2^+$ or $C_{20}H_{25}N_2^+$	4
Fedamazine	XXI		2

Caracurine I	XVIII		2
II	XVIII	$C_{38}H_{44}O_4N_4$	2
III	XVIII		2
IV			
V	XVI	$C_{38}H_{38}O_2N_4$	2
VI	XVII		2
VII	XIV	$C_{19}H_{22}O_2N_2$	2
VIII	XV		2
IX	XV		2
Nordihydrotoxiferine	XVII	$C_{38}H_{40-42}ON_4$	2
C-Alkaloid Q	XV	$(C_{22}H_{22}O_3N_3^+)_{1 \text{ or } 2}$	
C-Alkaloid R	XVIII	$(C_{21}H_{27}N_2O_2^+)_{1 \text{ or } 2}$	
C-Alkaloid S	XVII	$C_{19-20}H_{22-24}N_2^+$	
Pseudo-fluorocurine	XIX		
Croceocurine	XXI		
Kryptocurine	XV		
C-Alkaloid T = Lochnerin	XV		
Lochneram		$C_{21}H_{27}O_2N_2^+$	
Melinonine A		$C_{22}H_{27}O_3N_2^+$	3
MelinonineB	XV	$C_{20}H_{27}ON_2^+$	3
E	XX	$C_{20}H_{23-25}ON_2^+$	3
G	XX	$C_{17}H_{15}N_2^+$	3
Harman-chloromethyl	XV		3
Melinonine H		$C_{20}H_{21-23}ON_2^+$	3
J	XV		3
K			3
L		$C_{20}H_{26}O_4N_2$	3
Diaboline			5
Toxiferine III to XII (21) (purity doubtful)			

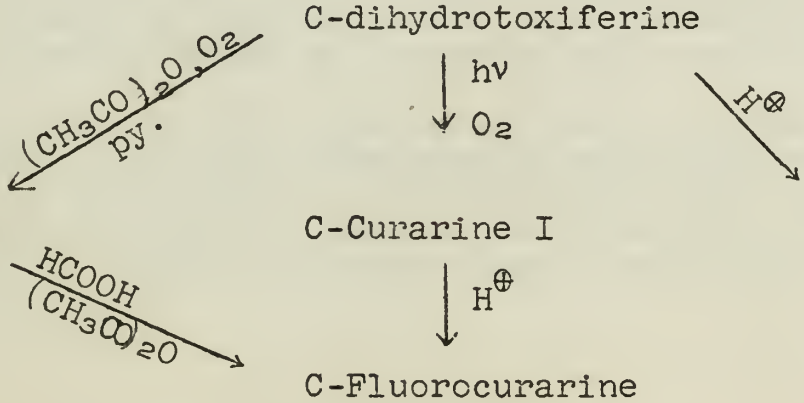
Several of the formulas are uncertain and may in fact be bimolecular.

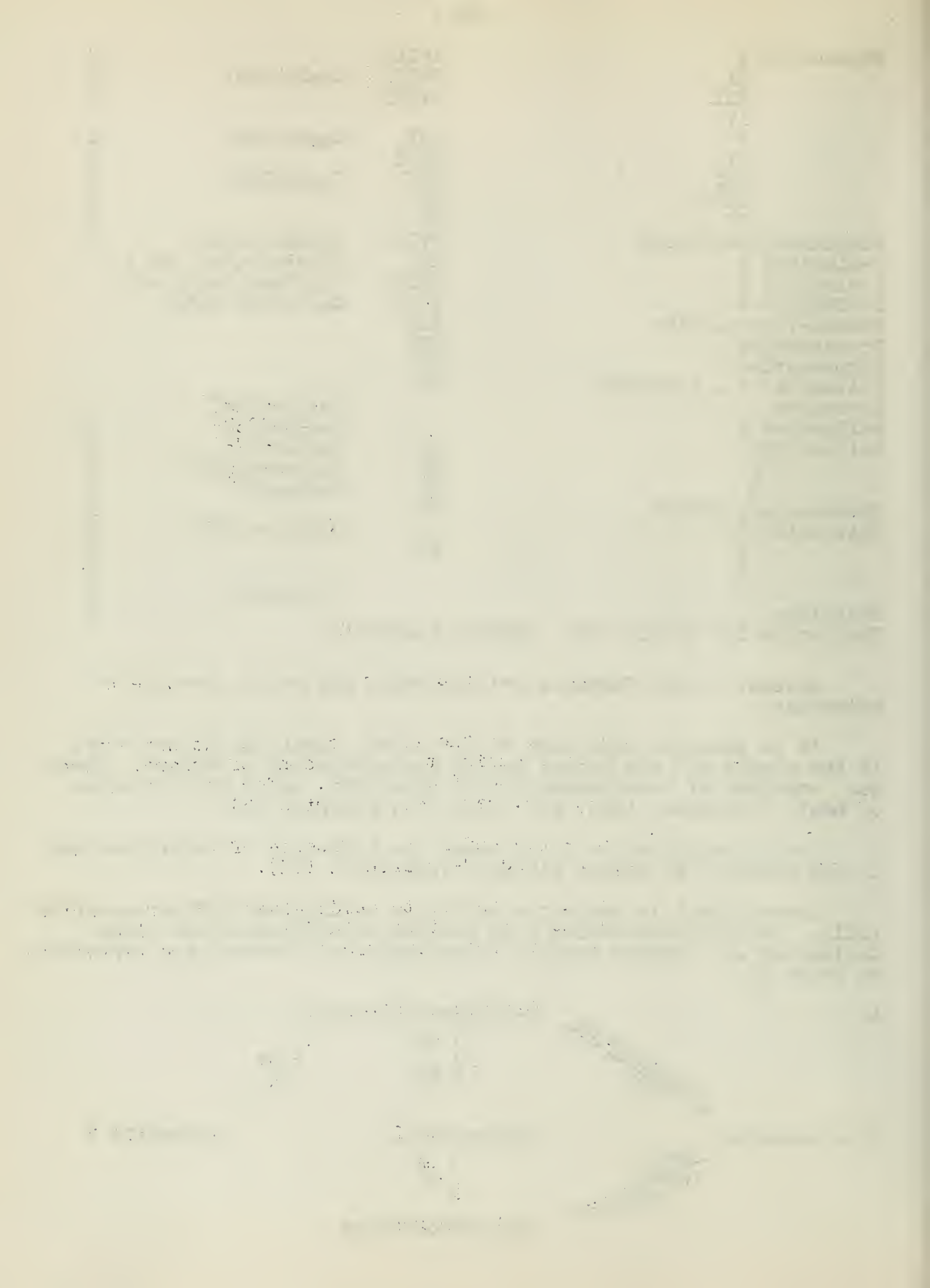
It is possible that some of the listed alkaloids do not exist in the plants but are formed during the processing of curare. Numerous examples of transformations of alkaloids, under the influence of heat, radiation, ions, etc. have been reported (5).

C-dihydrotoxiferine I (I) under the influence of radiations and in the presence of oxygen yields C-curarine I (II).

C-Curarine I in contact with dilute acids gives C-Fluorocurarine (III). C-dihydrotoxiferine I in contact with dilute acids gives C-Alkaloid D. Further typical transformations observed are represented below (5).

1.





2. Caracurin V

H^+ ⇅ Δ $C_{38}H_{38}O_2N_4$

Caracurin VA

$C_{38}H_{40}O_2N_4$

Caracurin II ← → Caracurin VII

3. Caracurin VI $\xrightarrow{H^+}$ C-Alkaloids B, C, and D.

RECENT DEVELOPMENT IN STRUCTURE PROOF OF C-ALKALOIDS

From the early work of Wieland up to recently, little was known on the structure of the calabash alkaloids.

Karrer has shown the bimolecular nature of several C-alkaloids (5).

Two C-alkaloids, melinonine F and melinonine A had been found identical with already known compounds. Melinonine F was identified as N-Harmanchloromethyl and melinonine A as tetrahydroalstonine-chloromethyl (22).

Structures had been proposed for two further alkaloids, mavacurin and fluorocurin (22). These structures had not been fully proven, but, however, they were in complete agreement with extensive chemical degradations and with the spectroscopic properties of these two alkaloids. The complete structures were formulated with the help of biogenetic considerations (27).

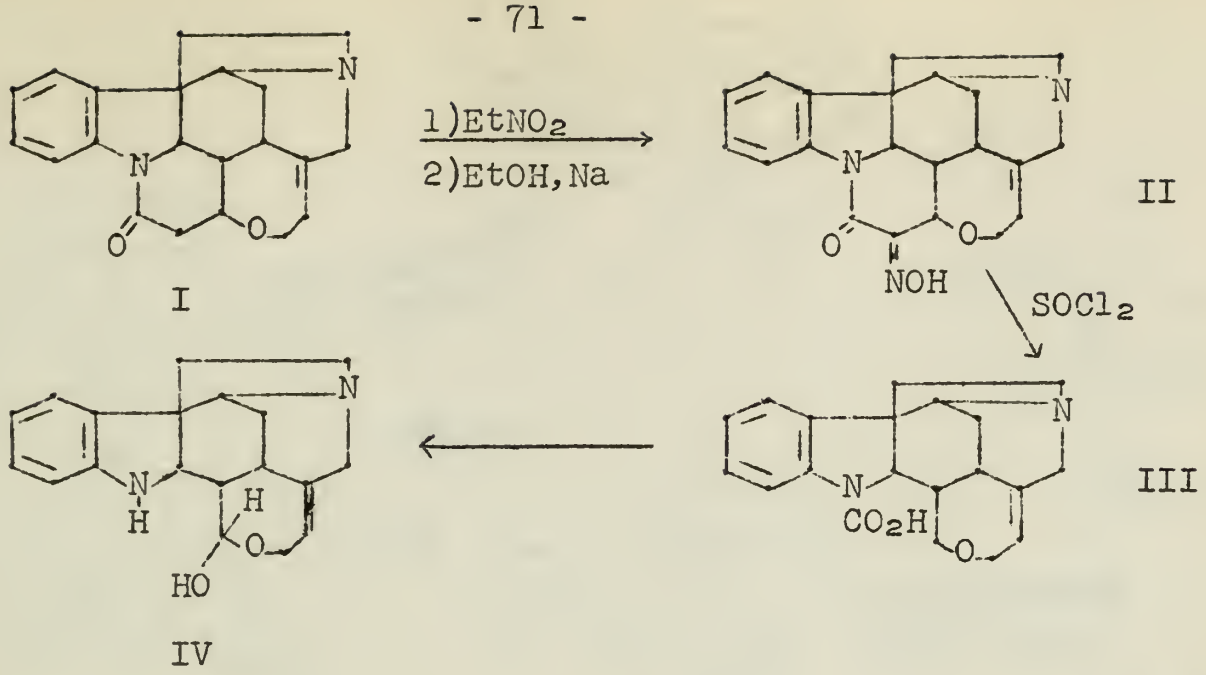
The indole fragment of the C-alkaloid was generally easily recognizable.

CALABASH ALKALOIDS RELATED TO STRYCHNINE TYPE

Recently, caracurine VII obtained from a Strychnos species of Venezuela was found to be identical with the Wieland-Gumlich aldehyde (28). The discovery of that identity has allowed tremendous progress in the determination of the structure of the curare alkaloids related to strychnine.

The structure of strychnine has been definitely determined by Robinson and Woodward, and is particularly certain since its complete synthesis has been achieved by Woodward and coworkers (29).

Strychnine (I) in the presence of ethyl nitrite forms an isonitroso compound (II) which when treated with thionyl chloride rearranges to form a carbamic acid derivative (III). This derivative in the presence of water and barium hydroxide is hydrolyzed and decarboxylated to yield an aldehyde base, called the Wieland-Gumlich aldehyde (IV)(30,31).



The identification of Curarine VII with the Wieland-Gumlich aldehyde was the first certain proof of the strychnine like structure of a curare alkaloids from Strychnos species.

Using the Wieland-Gumlich aldehyde as starting material several important alkaloids have now been synthesized.

C-Dihydrotoxiferine. (32)

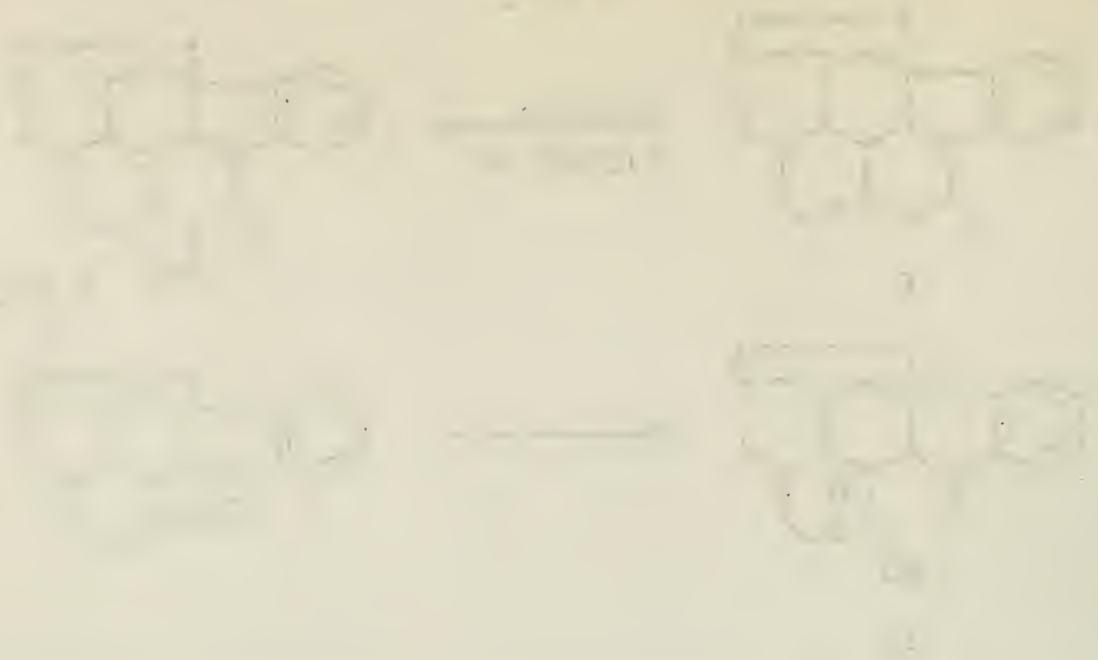
C-Dihydrotoxiferine (I), or simply dihydrotoxiferine isolated from calabash curare for the first time by Wieland and co-workers, counts among the most toxic C_{40} alkaloids. Dihydrotoxiferine has two $N_{(b)}$-CH_3. These methyl groups are easily removed to give nor-alkaloids. The ozonization of the alkaloid yields acetaldehyde. Extensive chemical degradations and spectroscopic properties show that dihydrotoxiferine posseses a methylene-indoline chromophore. In the same group are several other important alkaloids, C-toxiferine I, C-alkaloid H, iso-dihydrotoxiferine, C-alkaloid 2, caracurine Va and caracurine VI.

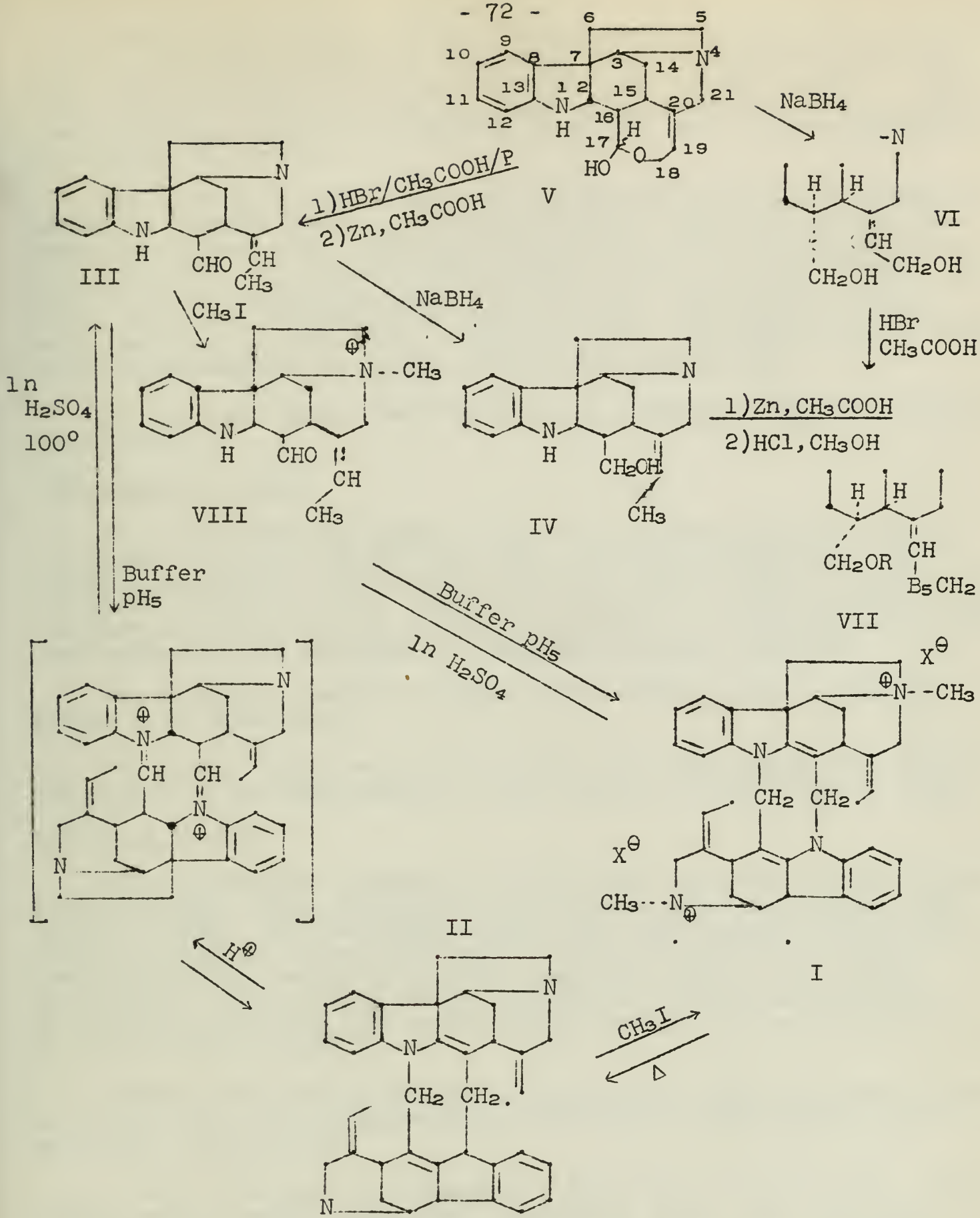
The following observations and interpretations were made by Karrer, Schmid and co-workers: Dihydrotoxiferine (I) submitted to high vacuum destillation yields nor-dihydrotoxiferine (II). The C_{38} alkaloid (II) heated for a short time with sulfuric acid gives among several products an aldehyde (III) as proved by its infrared spectrum (yield 40%). The aldehyde (III) was then reduced with sodium borohydride to the corresponding alcohol (IV).

An identical alcohol was obtained from the Wieland-Gumlich aldehyde by the following procedure:

The Wieland-Gumlich aldehyde (V) was reduced with sodium borohydride to a glycol (VI). Treatment of the glycol with hydrobromic acid in glacial acetic acid followed by debromination with zinc dust and acetic acid gave an O-acetate which after mild acid hydrolysis yielded the same alcohol (IV).

The infrared spectrum, specific rotation and mixed melting point of alcohol (IV) obtained from dihydrotoxiferine and from Wieland-Gumlich aldehyde proved their complete identity.

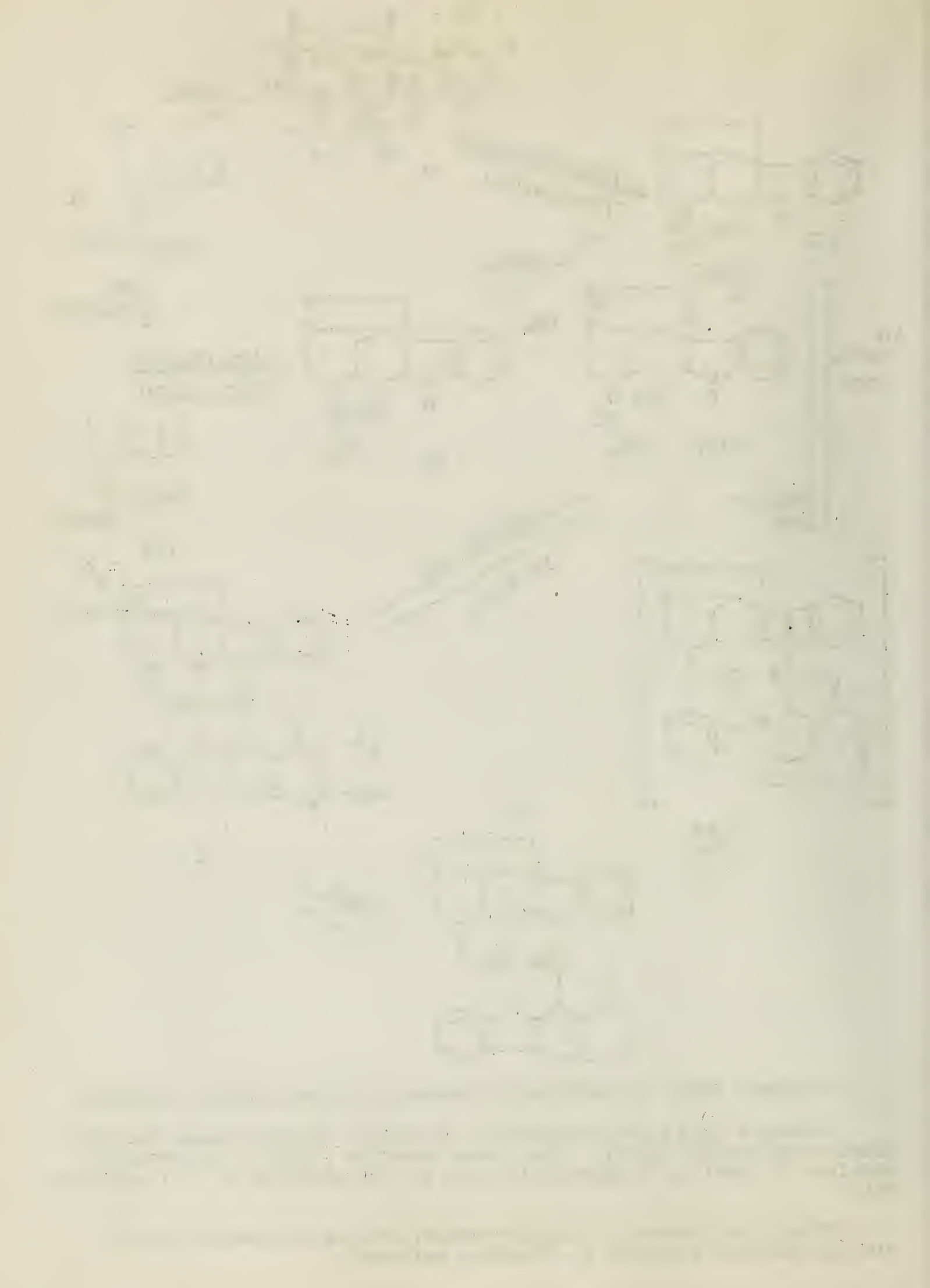




Aldehyde (III) is obviously 18-desoxy-Wieland-Gumlich aldehyde.

Aldehyde (III) in the presence of methyl iodide formed the hemi-dihydrotoxiferine (VIII). This same compound (VIII) is also easily obtained by heating dihydrotoxiferine in the presence of 1 N sulfuric acid.

Finally an isomer of dihydrotoxiferine was synthesized using Wieland-Gumlich aldehyde as starting material:



Aldehyde (V) heated with a mixture of hydrobromic acid, glacial acetic acid and phosphorous, then submitted to reduction with zinc dust, gave an impure 18-desoxy-aldehyde (III) (yield 10-14%). Addition of methyl iodide to the desoxy-aldehyde produced the $N_{(b)}$ metho-compound which heated in a buffered solution (pH = 5) gave an isomer of dihydrotoxiferine.

The synthetic product and the corresponding natural dihydrotoxiferine (I) showed identical infrared spectra, specific rotation and retention properties. The physiological activity of both alkaloids is also very similar. However the picrates proved to be different. The picrate of the synthetic product formed well crystallized needles which decomposed at 244-248°C. while that of the natural product formed plates of m.p. 182-185°C. Apparently this difference is the result of an isomerization, probably at the 19-20 double bond.

Attempts at mutual transformation by seeding of crystals remained unsuccessful.

C-Toxiferine I. (34)

In the presence of methyl iodide, the Wieland-Gumlich aldehyde (V) formed the metho-derivative (XIV). The chloromethylate (XIV) heated with glacial acetic acid and sodium acetate gave a mixture of C-toxiferine I dichloride (XIII) and caracurine V dichloromethyl (XV). The dichloromethyl (XV) is easily transformed to C-toxiferine I (XIII) when heated in the presence of a mild acid buffer solution.

The synthetic product and the corresponding natural alkaloid proved to be identical.

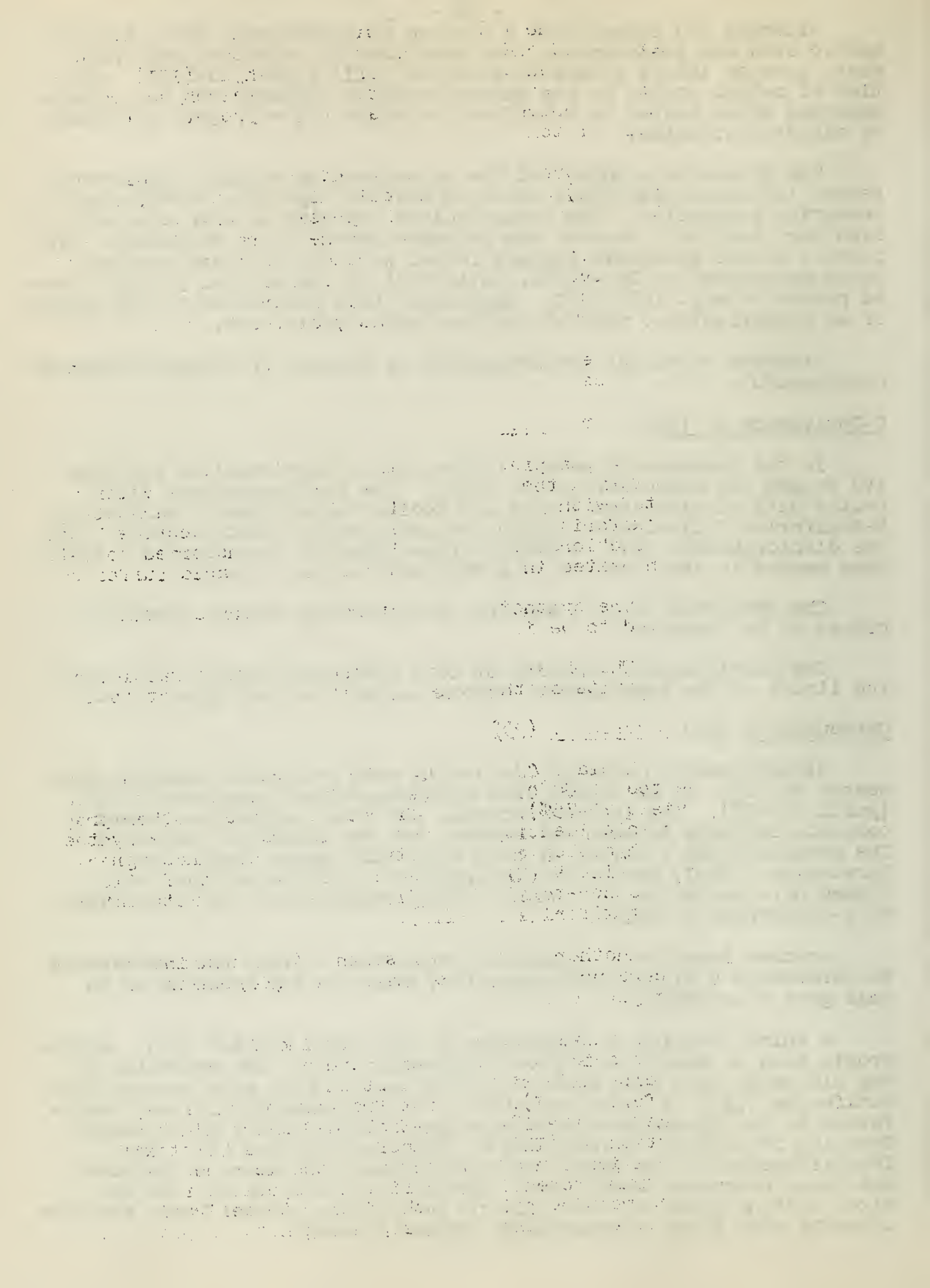
The physiological activity of both alkaloids agreed well within the limits of the experimental errors subject to that type of test.

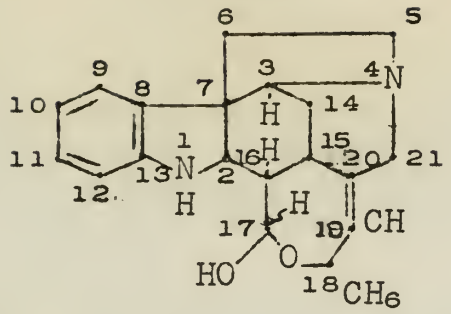
Caracurin V. (33)

Wieland-Gumlich aldehyde in acetic acid and sodium acetate when heated at 80°C. in an oxygen free atmosphere gave caracurine V (XII) (yield 70-75%). The infrared spectra and other properties proved a complete identity between the natural and the synthetic caracurin V. The physiological activity of both compounds agreed fairly well. Caracurine V (XII) heated in the presence of dilute sulfuric acid formed nor-toxiferine (XI) which through methylation was transformed to C-toxiferine I (XIII).

Another fraction of synthetic caracurine V (XII) was transformed to caracurine V dichloromethylate (XV) which in the presence of an acid gave C-toxiferine.

A third fraction of caracurine V (XII) when treated with hydrobromic acid in acetic acid gave a dibromide (XVI), the reduction of the dibromide with zinc dust in glacial acetic acid gave nor-dihydrotoxiferine (II). A first fraction of the nor-product (II) was transformed to the 18-desoxy-Wieland-Gumlich aldehyde (III) and a second fraction of (II) was transformed to dihydrotoxiferine (I). The identification of the three synthetic products by means of infrared spectrum, retention coefficient, specific rotation as well as the mixed melting point of the dipicrate derivatives proved their complete identity with their corresponding natural product.

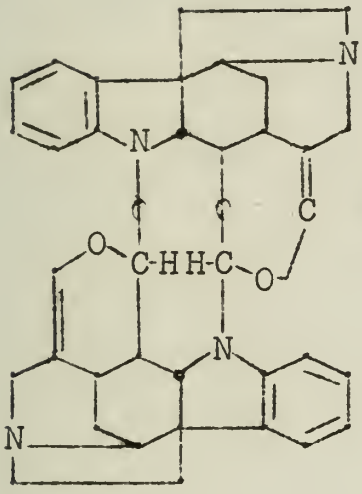




V

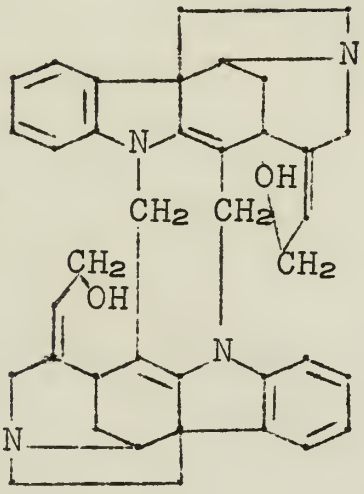
H_2SO_4 dil. ⇄ CH_3COOHg NaOAc

CH_3I

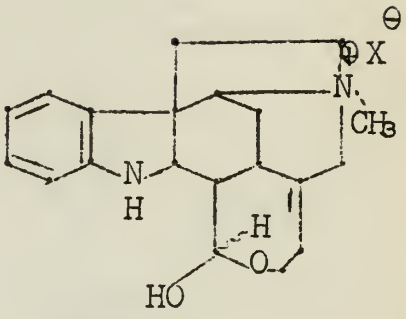


XII

H_2SO_4 dil. ⇄ Δ



XI



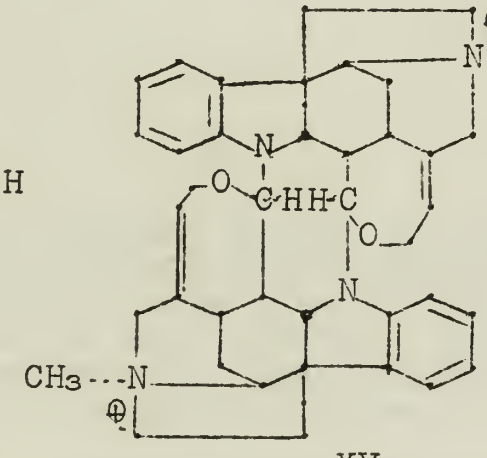
XIV

CH_3COOH NaOAc

CH_3I

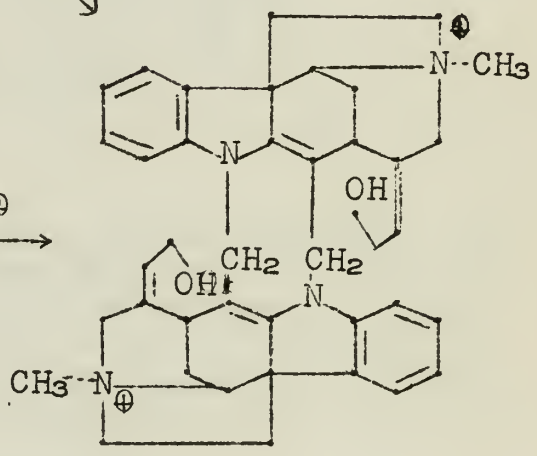
CH_3I

HBr CH_3COOH

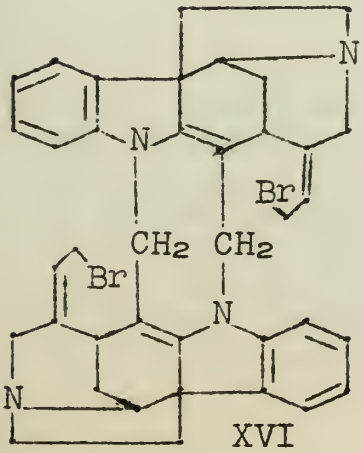


XV

$H^{\oplus}$



XIII



XVI

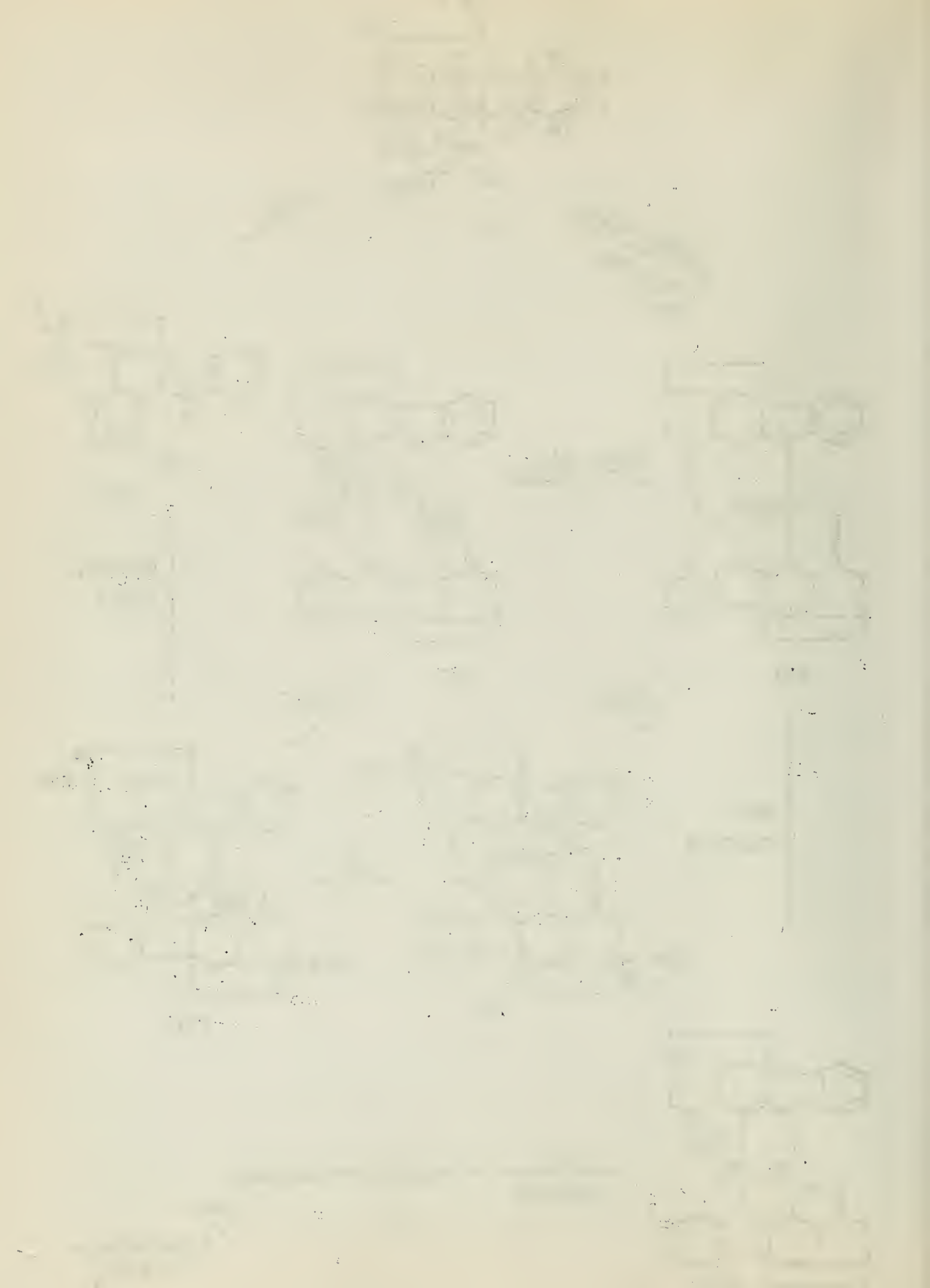
Zn / CH_3COOH → nor-dihydrotoxiferine

II

CH_3I

dihydrotoxi-ferine

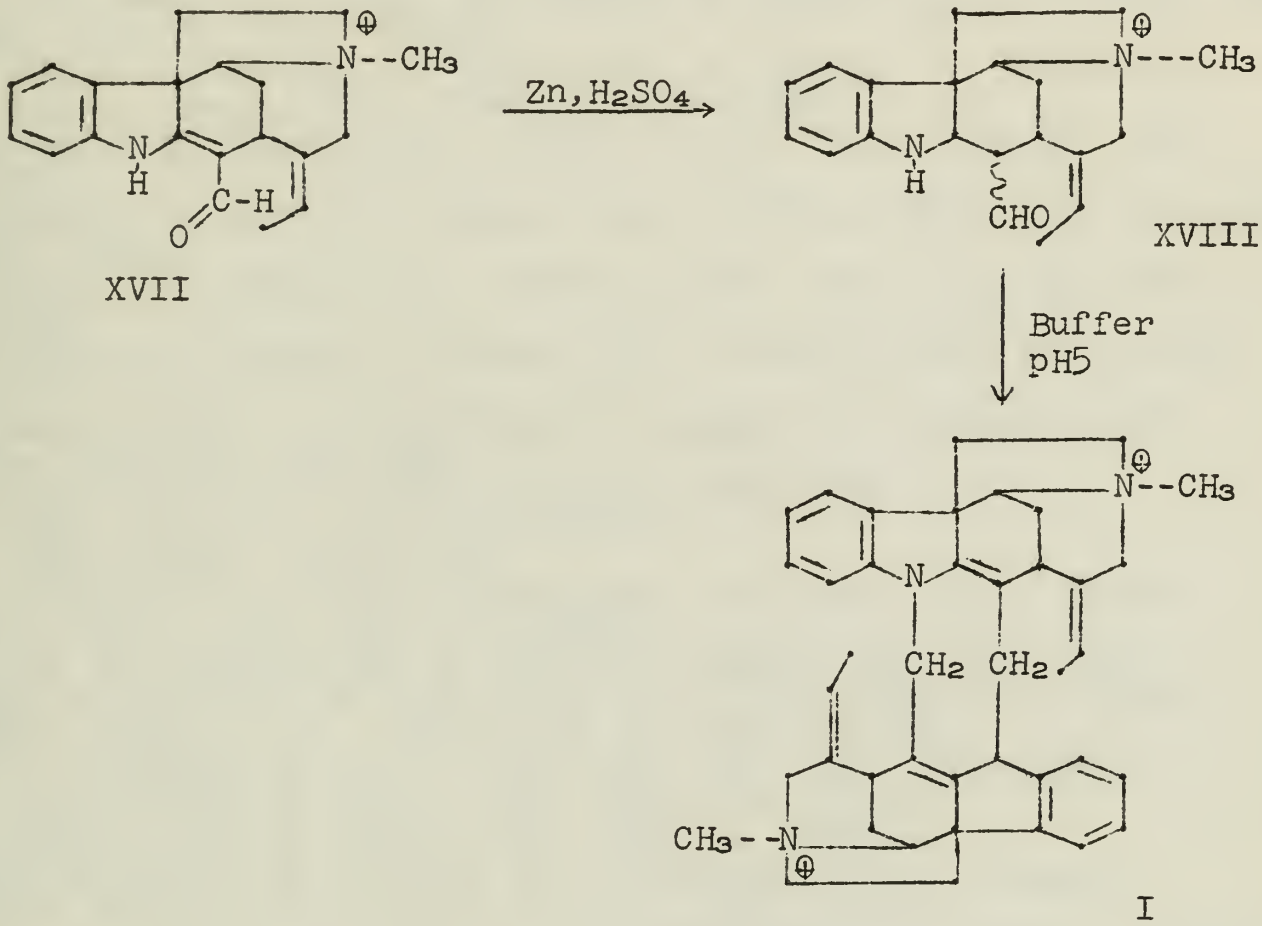
I



C-Fluorocurarine. (34)

Reduction of fluorocurarine chloride (XVII) with zinc and sulfuric acid gave an indoline type aldehyde as shown by ultraviolet spectrum. When heated in a buffered solution of pH 5, the aldehyde gave dihydrotoxiferine (I) which proved to be identical with the corresponding natural alkaloid.

This transformation was considered to prove the structure postulated by Karrer, which had been formulated with the help of biogenetic considerations. (27)



Conclusion:

The progress realized during the last years in the chemistry of the calabash-curare alkaloids has permitted the synthesis of several of them. It has been shown also that the structure of most of these alkaloids are very closely related. Therefore it can be anticipated that within a few years, in spite of the enormous complexity of the calabash curare, the structure of most of its alkaloids will be proven.

****

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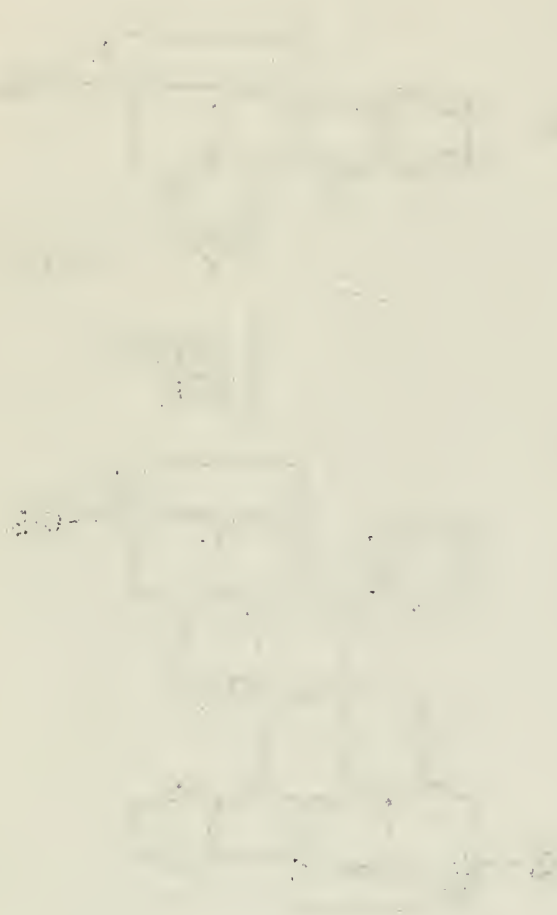

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USE OF MASS SPECTROMETRY IN STRUCTURAL PROBLEMS

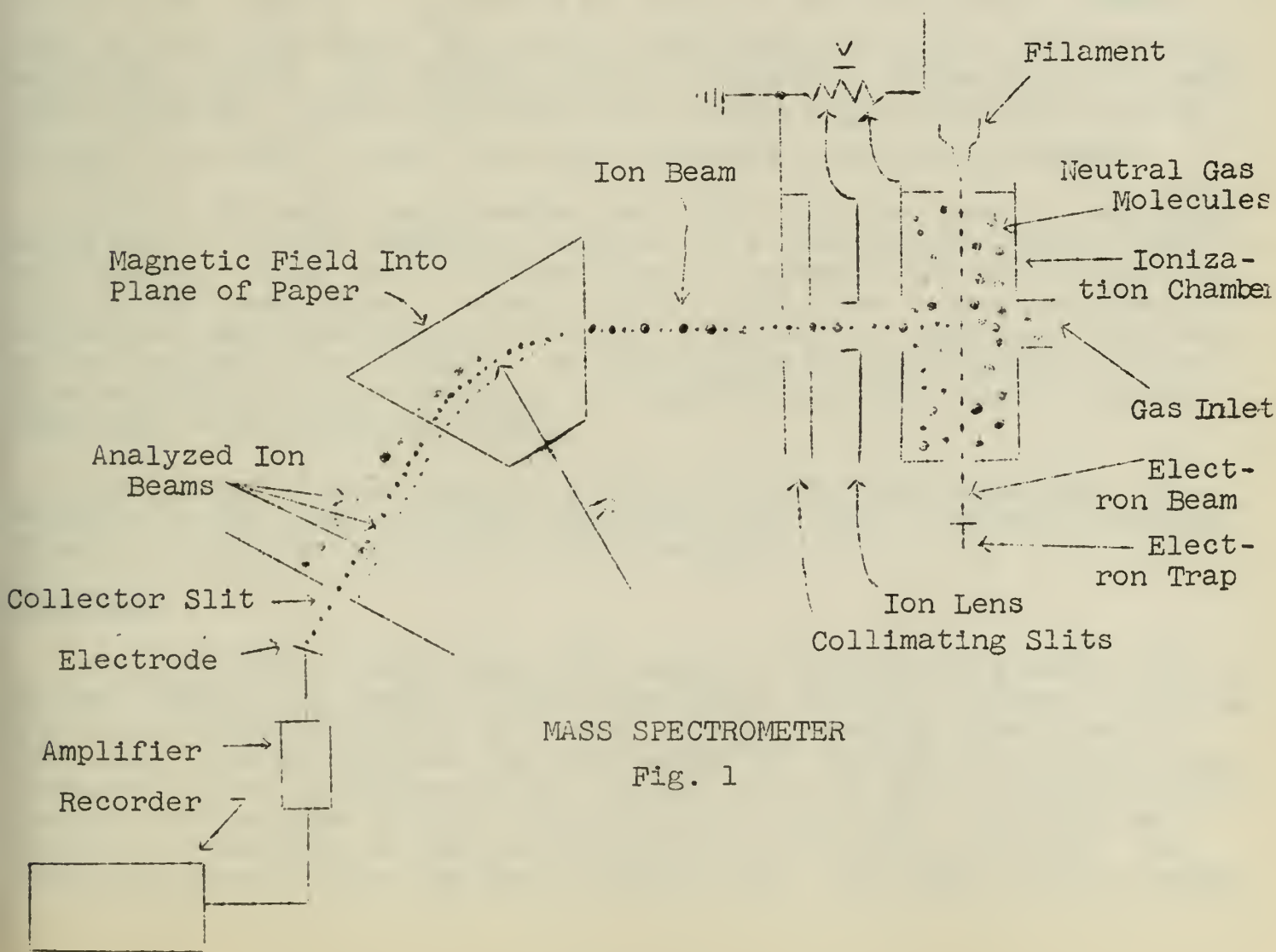
Reported by J. C. Hill July 17, 1959

INTRODUCTION

When the mass spectrometer (1) was first developed, it was used mainly by physicists. In recent years it has become increasingly useful in broader fields of application and today is widely employed in chemical analysis, kinetic and tracer work, and in the study of patterns of molecular ionization and dissociation; all of great interest to chemists.

MASS SPECTROMETER

The mass spectrometer (Fig. 1) is an instrument which separates out ions of the same mass to charge ratio (m/e) from an ion beam containing many different ionic species and measures the relative abundance of these particles. The ion beam is formed by admitting neutral gas molecules into the ionization chamber of the mass spectrometer at very low pressure ($\sim 10^{-7}$ mm) and bombarding them with an electron beam with an energy from 10 to 100 electron volts. The low pressures are especially needed outside of the ionization chamber to minimize the scattering of ions by collisions with residual gas molecules. The bom-



MASS SPECTROMETER

Fig. 1

bardment produces positively charged particles (cations), negatively charged particles (anions) and neutral fragments (atoms or radicals). A potential difference (V) accelerates the positive ions uniformly through an entrance slit and collimating slits into the mass spectrometer proper. Once inside the mass spectrometer proper, the beam comes under the influence of a magnetic field (H), directed perpindicular to the plane of the paper, which bends it into a circular path. The radius of the path (R) is described by

$$R = \left(\frac{2mV}{eH^2}\right)^{1/2}$$

The radius of the path depends upon the ratio of the mass of the cations to their charge (m/e); thus the combined action of the electric and magnetic fields sorts the ions. The dimensions of the mass spectrometer chamber are such that only particles describing a certain radius (R) will pass through the collector slit and be recorded by the ion collector electrode beyond it. These particles produce a weak current in the electrode which is amplified and then recorded either manually or mechanically. This current produced is a measure of the abundance of the ions. Rearranging the equation for the radius of the path

$$(m/e) = \frac{R^2H^2}{2V}$$

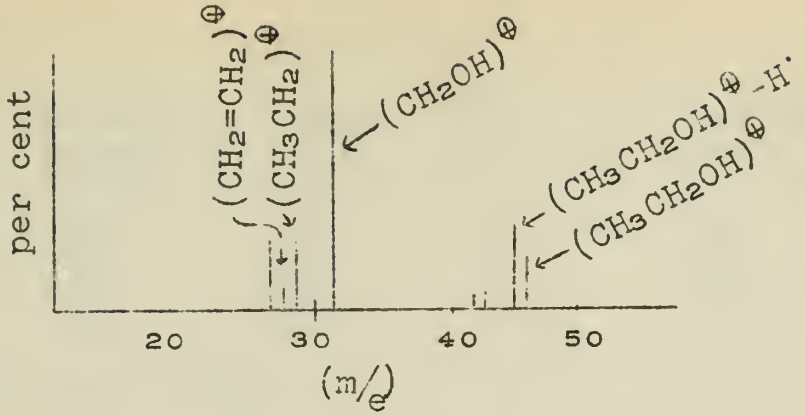
Thus we see that the (m/e) value of the ions collected will depend upon R, which is fixed, as well as the applied electric (V) and magnetic (H) fields. By varying either H (magnetic scanning) or V (voltage scanning), ions of different and known (m/e) value are focussed on the exit slit in turn, and thus the mass spectrum is scanned.

Since the mass spectrometer was first put into use, it has been modified in several respects, leading to a considerable improvement in performance. Much work has been done to increase the mass range and improve the resolution. Ryhage (2) describes how he has modified a commercial mass spectrometer to obtain spectra on compounds with molecular weights of up to 619. He uses a heated inlet system to introduce samples of low volatility. A complete spectrum may be run on less than a milligram of sample.

New types of mass spectrometers have also been developed. An example is the time of flight instrument (3) used in kinetic studies. These will not be discussed in this seminar.

SPECTRUM:

The spectrum shown in Fig. 2 for example, is that of ethanol (4). It was obtained by using 70 volt electrons, ionizing current of 10 μa., ion source temperature of 250°C and voltage scanning from mass 17. The small peak at (m/e) 46 is the "molecular" or "parent" peak which corresponds to the molecular weight of the molecule being studied and is present in the mass spectra of nearly all compounds. The peak at (m/e) 45 corresponds to the parent peak minus a hydrogen atom. The strongest peak in the spectrum is called the "base peak" and is taken



as 100%. In the above spectrum, the peak at (m/e) 31 is the base peak and it arises from cleavage of the carbon-carbon bond beta to the hydroxyl group. Beta cleavage is characteristic for alcohols, amines, ethers, mercaptans and other electron releasing groups. The weak pea at (m/e) 29 probably arises from the $CH_3CH_2^{\oplus}$ ion. In all alcohols there is a peak corresponding to parent peak minus eighteen mass unit and in this case probably arises from a $CH_2=CH_2^{\oplus}$ ion. There are also smaller peaks of a few percent of the base peak which will not be dis cussed. Some of these arise from C^{13}. This isotope of carbon has a natural abundance of about 1% and can be detected easily in the spectrum of a simple molecule like methane (5).

TYPES OF CLEAVAGE

A few general statements can be made on the type of cleavage tha may be expected in various organic molecules (4, 6, 7, 8, 9, 10, 11, 12, 13). Peaks corresponding to carbonium ions which are stabilized by resonance or hyperconjugation are large. Halogen, nitro and almos all carbonyl-type groups tend to weaken the alpha bond for cleavage b electron impact. This does not apparently extend to all electron-attracting groups as some, like nitriles, tend to break at the beta bond. As mentioned previously, electron releasing groups typically cause cleavage at the beta bond.

LOW ENERGY STUDIES:

When a molecule enters the ionization chamber and is hit by the electron beam, it may either be ionized as a whole or ionized and fragmented. Fragmentation almost invariably occurs; at least to some extent, at the normal energy of the electron beam of 50-100 electron volts, giving rise to "cracking" patterns, but can be minimized at lo electron energies (~10 electron volts), which is useful in molecular weight determination and also side chain determination in steroids an related compounds.

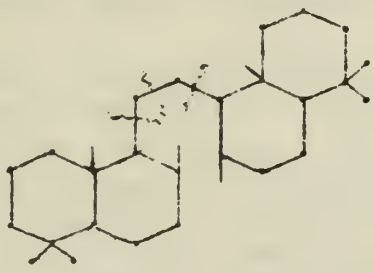
Low energy studies (9-15 ev) were recently used by Reed (14) for determining molecular weights and in some cases the number of carbon atoms in the side chain of steroids and triterpenoids (Table 1). The side chain and fragments of it are probably produced either by the heating of the sample or by a combination of this with the low energy electron beam. In favorable cases the ring skeleton is not ruptured by these conditions and confusion between the ions corresponding to fragments of the chain (terminating in a mass corresponding to a complete side chain) and others derived from the nucleus or the nucleus plus remnants of the side chain is unlikely. The lower series will no in general correspond to an alkyl chain of more than ten carbon atoms whereas in the steroid and triterpenoid fields, the nucleus contains

Table 1

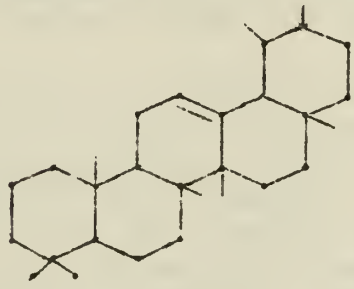
Compound	Molecular Weight Found	Calc.	Side Chain Found	Calc.
Cholestane	372	372	110	113
Ergostane	386	386	123	127
Stigmastanone	413	414	137	141
Lanost-9(11)-ene	413	412	-	-

at least fourteen carbon atoms.

In an earlier note (15), Reed and deMayo showed how tetracyclic triterpenoids as α-onocerane (I) can be easily distinguished from the pentacyclic members like α-amyrene (II). (Table 2).



I



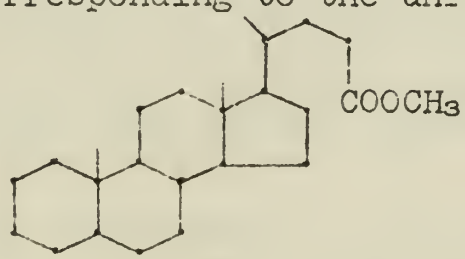
II

Table 2

Compound	Molecular Weight Found	Calc.	Side Chain Found	Calc.
α-Onocerane	413.2	414.7	188, 205, 224	193,207,22
α-Amyrene	411.0	410.7	none	none

For substances such as α-amyrene which lack a side chain, there is virtually no spectrum until the electron beam energy is ~18 electron volts, when a spectrum of the electron-induced dissociation appears. This spectrum has ions corresponding to nearly all mass numbers for an intergral number of carbon atoms with the appropriate number of hydrogens. Reed has made some generalizations on the bonds in fused ring systems which should break preferentially.

Other work of this type has been reported (16) although conditions for obtaining the mass spectra were not indicated. The mass spectra of the methyl esters of the bile acids exhibit several characteristic features. The methyl ester of cholanic acid (III) shows an intense peak at ($m/_e$) 374 corresponding to the unfragmented ionized



III

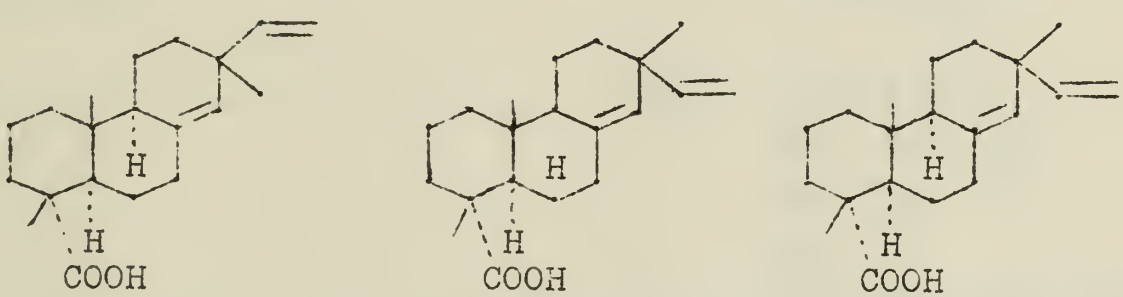
molecule $C_{25}H_{42}O_2^{\oplus}$. This peak is the largest in the spectrum. When the sterol nucleus carries one or more hydroxyl groups the molecular peaks are either very small or absent because the hydroxyl groups are easily eliminated as water with the formation of double bonds. The side chain is also readily split off and in the mass spectrum there occurs a peak corresponding to the ionized unsaturated nucleus. For methyl esters of monohydroxycholanic acids such as 3-hydroxycholanic acid this peak occurs at ($m/_e$) 257. For 3,7,12-trihydroxycholanic acid the "nuclear peak" is at ($m/_e$) 253. For a saturated bile acid the nuclear peak thus indicates the number of hydroxyl groups present in the sterol ring.

If the ring system contains both hydroxyl groups and double bonds, the nuclear peak indicates their sum. Thus stigmasterol and β-sitosterol, which both have one hydroxyl group and one double bond in the ring system, give a characteristic nuclear peak at ($m/_e$) 255.

In some recent work done on natural products (17), a compound wa isolated whose hydrogenated derivative showed a molecular peak at ($m/_e$) 430 in its mass spectrum. Other data indicated a triterpenoid with the formula ($C_{30}H_{54}O$). The mass spectrum also showed a peak at ($m/_e$) 299 which indicates a steroid nucleus with five methyl groups. This peak also showed that the compound was a tetracyclic and not a pentacyclic triterpenoid. This aided in identifying the compound as tetrahydrodommaradienol.

MOLECULAR STRUCTURE.

Using a modified mass spectrometer (2) with high energy electron Bruun (18) was able to obtain information regarding the structural relations between dextropimaric acid (IV), isodextropimaric acid (V) and cryptopimaric acid (VI). The mass spectrum of the methyl ester



of (VI) is strikingly similar to that of the methyl ester of (IV). The methyl ester of (V) gives a quite different mass spectrum. These results were interpreted as showing that (IV) and (VI) can be structurally different only with regard to the methyl and vinyl groups attached to C-7, and that (IV) and (V) must be different with regard to the geometry of the ring system. The stereochemical difference at C-7 has recently been confirmed (19) and it follows that the acids are stereochemically different both at C-7 and C-13.

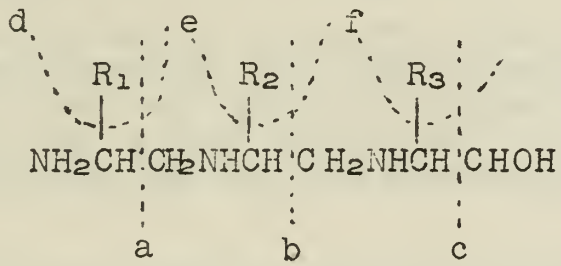
An interesting structure determination was reported by Buchi (20) He had obtained a ketone that had given a negative iodoform test and would take up three deuteriums. All chemical tests indicated that it was not a methyl ketone. The mass spectrum of the ketone showed an intense peak at ($m/_e$) 43 corresponding to a $CH_3CO^{\oplus}$ ion. The spectrum of the trideuterated ketone showed a high intensity peak at ($m/_e$) 46 a

demanded by a $CD_3CO^{\oplus}$ ion. Investigation of the mass spectra also showed that deuterium was introduced only on the methyl groups becaus both the deuterated and undeuterated ketones showed peaks at (m/e) 165 corresponding to the molecule minus the methyl ketone group. They also showed peaks at (m/e) 208 and (m/e) 211 respectively. In contrast to the chemical evidence which indicated the absence of an acetyl group, the mass spectrum confirmed its presence.

A recent communication (21) has appeared on the application of mass spectrometry to the determination of amino acid sequence in peptides.

The mass spectra of several polyamino alcohols obtained by reducing small peptides with lithium aluminum hydride have been investigated. The reasons for reducing the peptides are the polyamino-alcohols show greater volatility which is an important factor in mass spectrometry and cleavage of the carbon-carbon bond alpha to the amin group yields valuable information.

A general example of the important peaks for a triamino alcohol obtained from a tripeptide are given below.

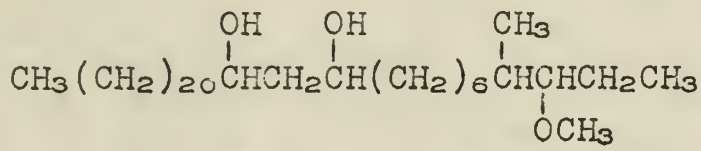


Point of Cleavage	Peak observed at (m/e)
a	$R_1 + 29$
a	$R_2 + R_3 + 115$
b	$R_1 + R_2 + 71$
b	$R_3 + 73$
c	$R_1 + R_2 + R_3 + 113$
c	31
d	$M-R_1$
e	$M-R_2$
f	$M-R_3$

There are also many more peaks in the complex spectrum which further aid in the interpretation. There is no appreciable parent peak at M, but there is one at M+1. Since this peak depends on the pressure and focussing conditions, it is very easily located since its intensity relative to the others varies when these conditions are changed.

The structures of the fragments were checked by comparing the mass spectra of the triamino alcohols obtained by the reduction of N-acetyl-leucyl-alanyl-prolyl-ethyl ester and N-acetyl-glycyl-phenyl-alanyl-ethyl ester with lithium aluminum hydride and lithium aluminum deuteride respectively. The spectra of the two pairs showed the expected shifts in mass numbers by two units.

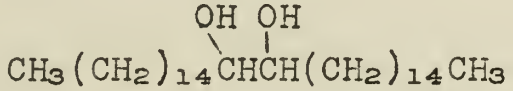
The structure of phthiocerol (VII) was determined by Ryhage and workers (22) by comparing its mass spectrum to mass spectra of related compounds. The structure of the carbon skeleton was determined



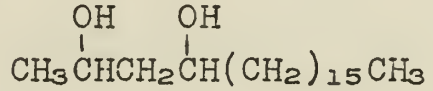
VII

by studying the mass spectrum of the parent hydrocarbon, phthiocerane It showed a small parent peak at (m/e) 492 corresponding to $C_{35}H_{72}^{\oplus}$ unfragmented molecular ion, and very strong peaks at (m/e) 449 and (m/e) 421 corresponding to $C_{32}H_{65}^{\oplus}$ and $C_{30}H_{61}^{\oplus}$ respectively, arising from cleavage on either side of the tertiary carbon atom in position 4.

Comparison of the mass spectra of 16,17-dihydroxydotriacontane (VIII) and 2,4-dihydroxyeicosane (IX) with the spectrum of phthiocerol indicated the presence of the hydroxyl groups in positions 22 and 24.

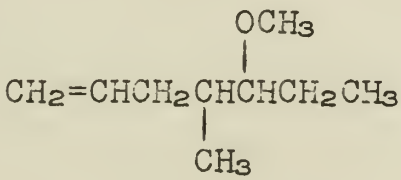


VIII



IX

The position of the methoxyl group had previously been inferred from mass-spectrometric and x-ray data (23) to occupy the 3-position. This was confirmed by a mass-spectrometric study of 3-methoxy-4-methylheptene-6 (X). The spectrum of this molecule, like that of



X

phthiocerol shows an intense peak at (m/e) 73 arising from cleavage between carbon atoms 3 and 4.

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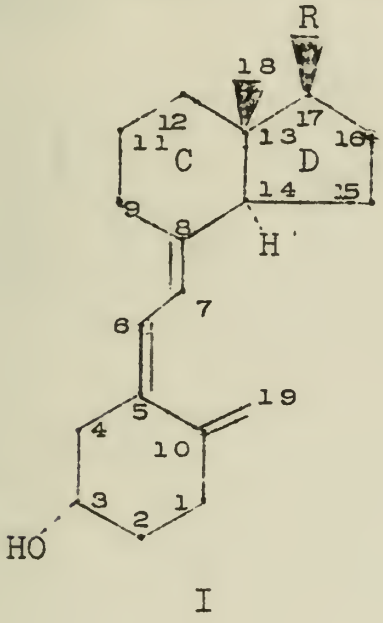
SYNTHESES IN THE VITAMIN D SERIES

Reported By D. L. DeVries July 20, 1959

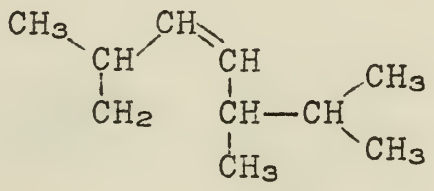
INTRODUCTION

There are two common forms of vitamin D, both of which are available naturally and one of which is prepared commercially by irradiation of its steroid precursor. They are vitamin D_2 (Ia) and vitamin D_3 (Ib) which derive from ergosterol (1) and 7-dehydrocholesterol (2) respectively. The irradiation of 22-dihydroergosterol (3,4) yields vitamin D_4 (Ic) which is more potent biologically than vitamin D_2 and nearly as active as vitamin D_3. Irradiated 7-dehydrositosterol gives a substance with high antirachitic activity called vitamin D_5 (Id). Other less active D-vitamins have been obtained by irradiation of various steroid precursors. Only vitamin D_3 has been reported to be synthesized chemically with one irradiation step which has been clearly defined.

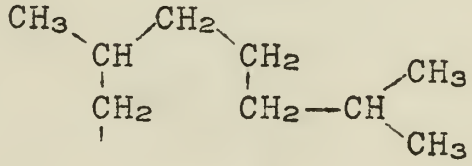


I

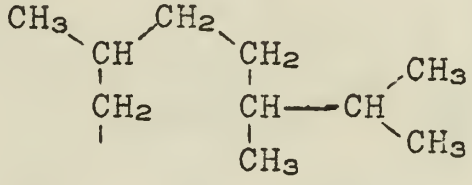
Ia. R = C_9H_{17};



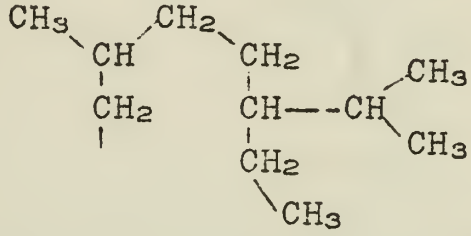
Ib. R = C_8H_{17};



Ic. R = C_9H_{19};



Id. R = $C_{10}H_{21}$;



STRUCTURE OF VITAMIN D

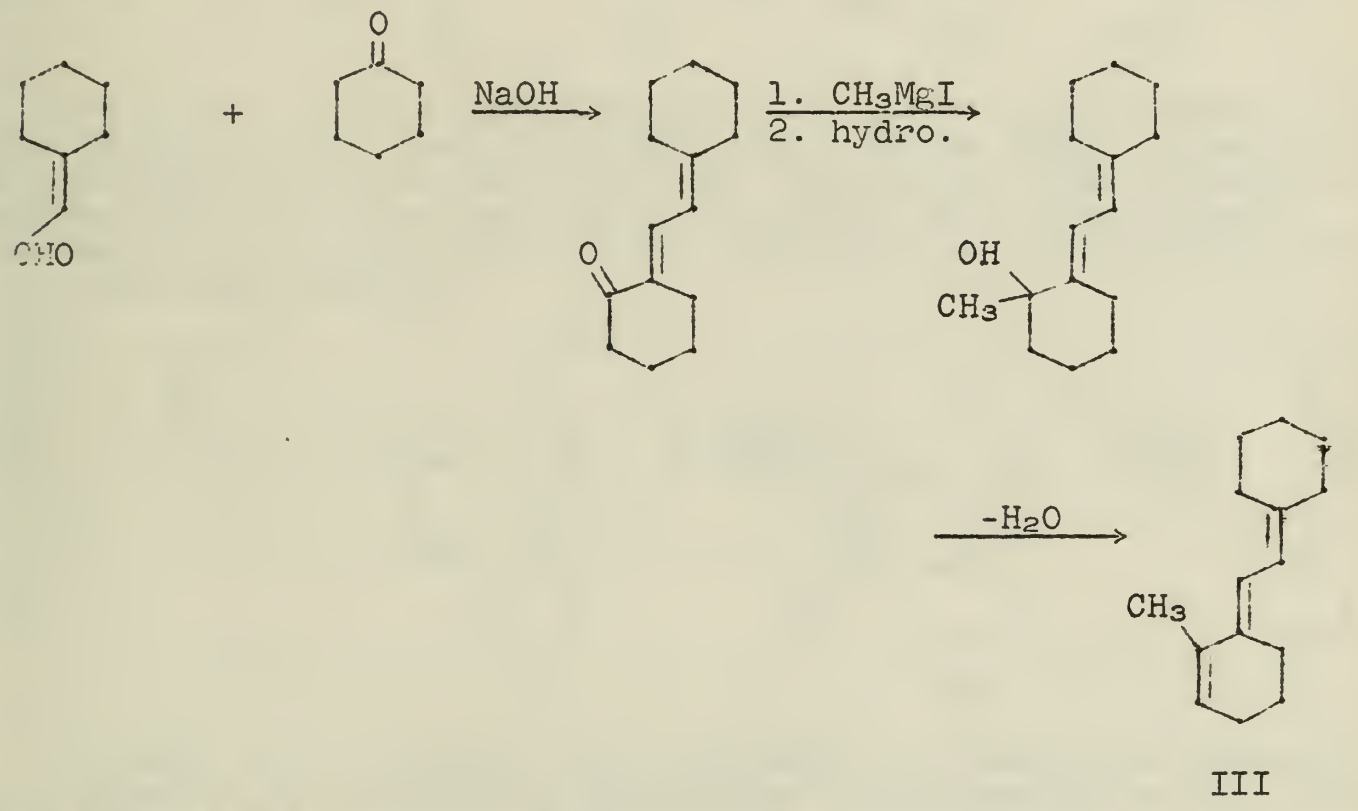
The structure of vitamin D_2, except for the geometrical detail, was established about 1935 through a series of degradations carried out by Windaus (7) and Heilbron (8). Evidence for the geometry (9) of vitamin D was first provided by a two-dimensional crystallographic analysis of the 4-iodo-5-nitrobenzoate, from which Crowfoot and Dunitz deduced the "cis"-5-"trans"-7-structure (I). Three dimensional electron density calculations (10) have been carried out and they confirm structure I.

SYNTHESES OF MODEL SYSTEMS

The synthesis of vitamin D proved to be relatively difficult. All three double bonds in the conjugated system of vitamin D are

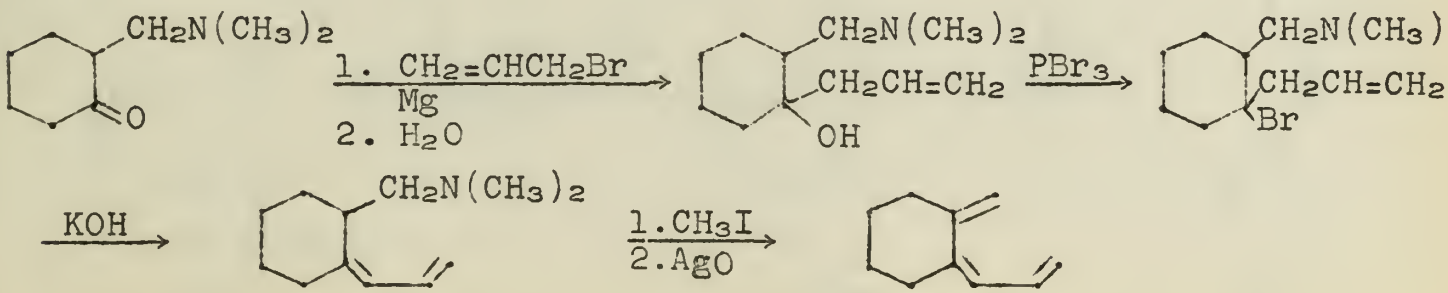
semicyclic to cyclohexane rings and have therefore a relatively high energy content. Attempts to introduce the double bonds by elimination reactions, subject to Saytzeff-type control, generally resulted in the formation of endocyclic double bonds and not the desired exocyclic ones. The Wittig olefin synthesis (11), which is exceptionally well suited for the construction of semicyclic double bonds, provided the key to advances in vitamin D synthesis. Other major synthetic problems were the syntheses of the building blocks for the A ring and the intrinsically unstable trans C/D ring system.

Shortly after the structure of vitamin D had been published, Dimroth (12) reported the aldol condensation of cyclohexylideneacetaldehyde (II) with cyclohexanone, followed by an attempt to replace the carbonyl oxygen with a methylene group by way of a Grignard reagent and elimination of water. His primary product proved to be the triene III with the double bond introduced into the ring. This result was verified by Aldersley and Burkhardt (13) who carried out a similar experiment, substituting 4-hydroxycyclohexanone for cyclohexanone.

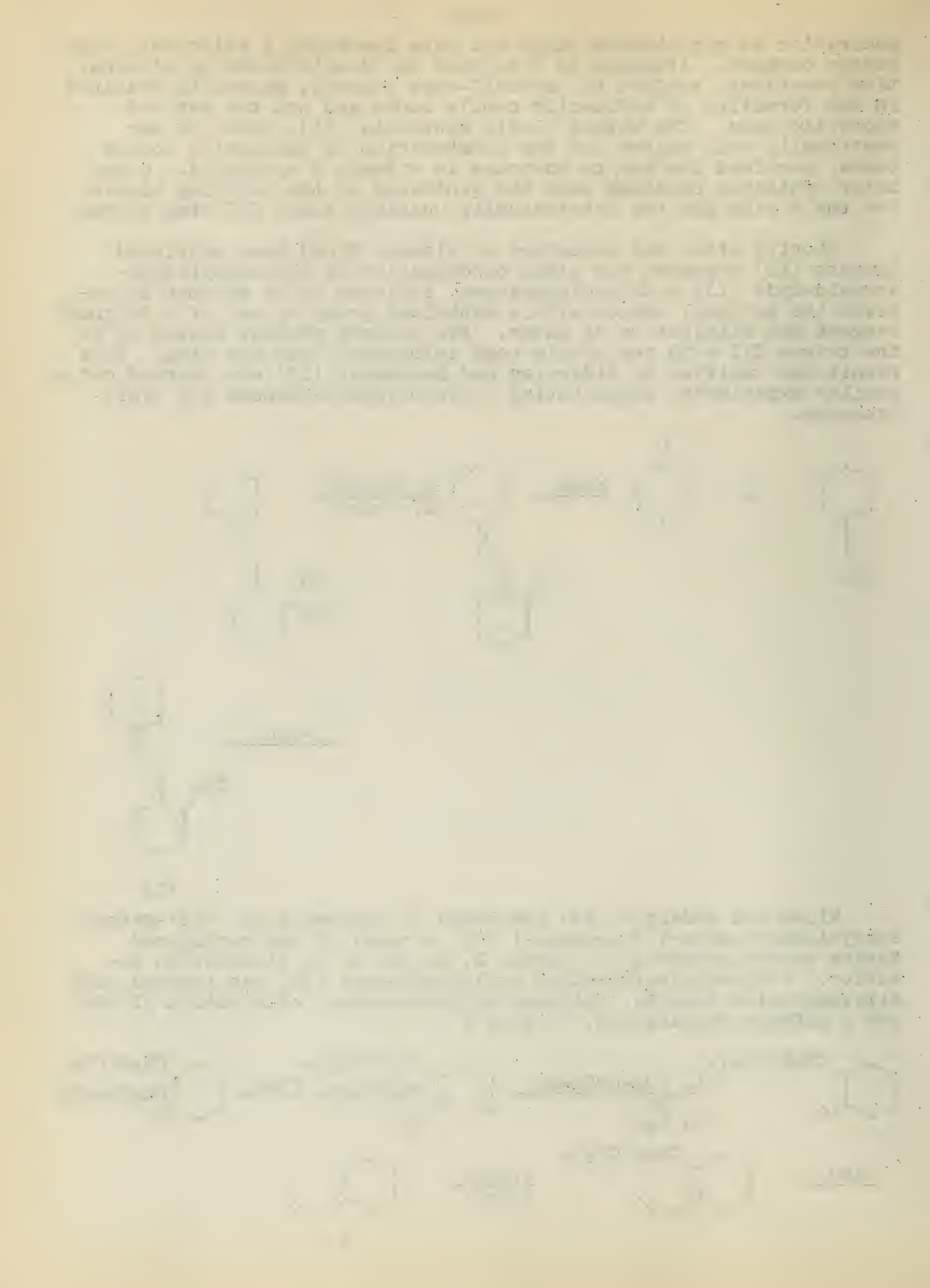


III

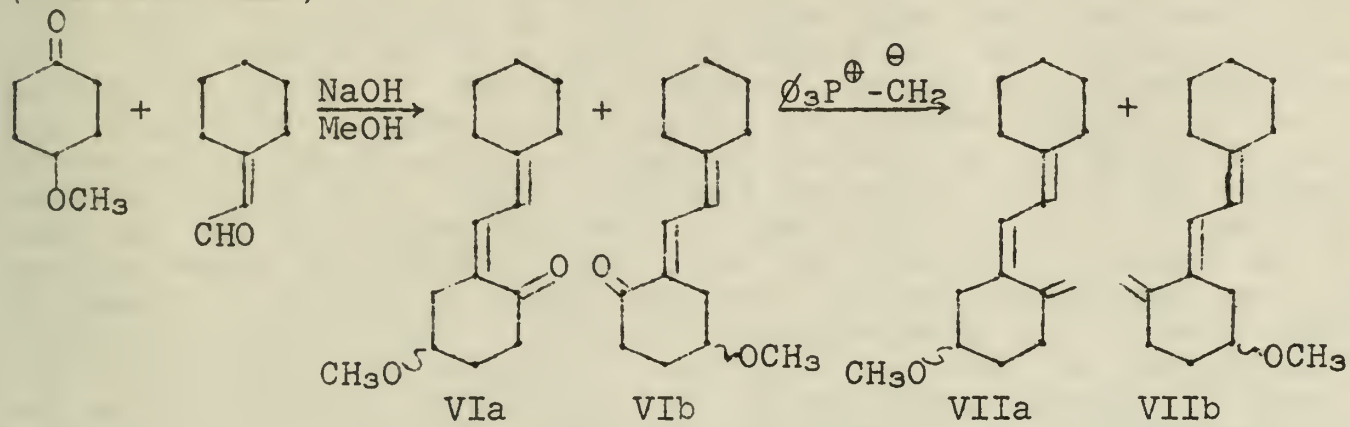
Milas and Anderson (14) succeeded in synthesizing 3-[2'-methylenecyclohexylidene-1']-propene-1 (V), a model of the conjugated triene system existing in vitamin D, by way of an elimination reaction. 2-Dimethylaminomethyl cyclohexanone-1 (IV) was treated with allylmagnesium bromide, followed by bromination, elimination of HBr, and a Hofmann degradation, to give V.



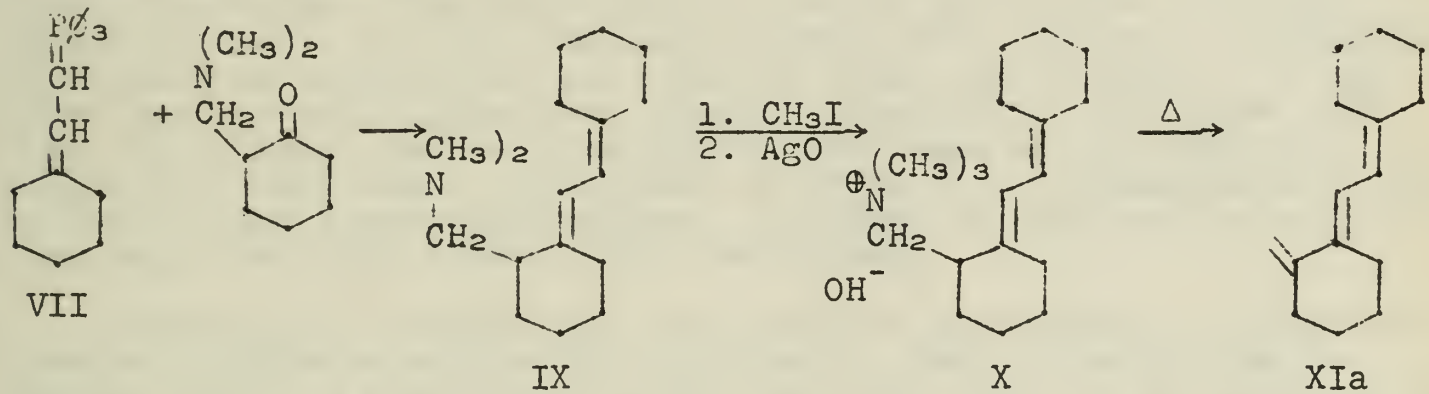
V



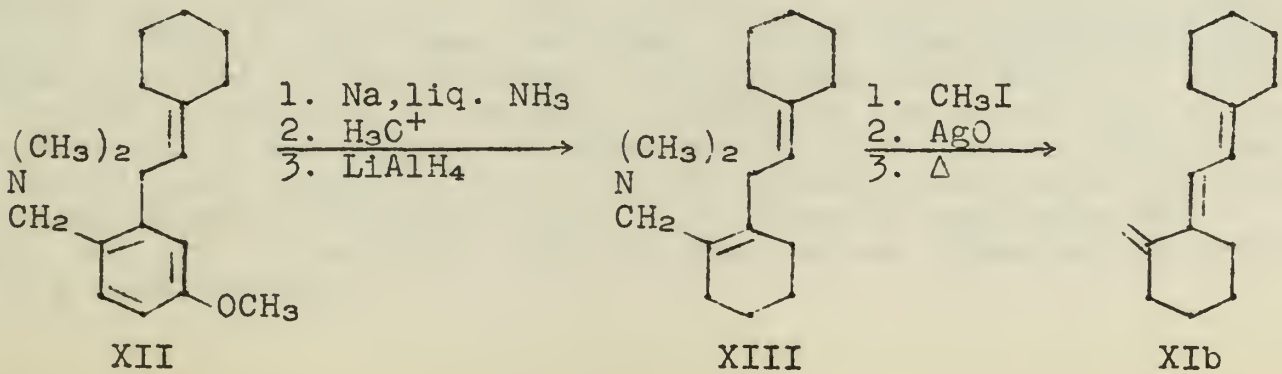
The latter method was found to be impractical for the synthesis of vitamins D_2 or D_3 so Miles and co-workers carried out another model reaction (15) with a Wittig reagent which they hoped would find application in the synthesis of vitamin D. They condensed cyclohexylideneacetaldehyde with 4-methoxycyclohexanone to give the ketone VI, which was presumably a mixture of cis and trans isomers (VIa and VIb). These reacted with triphenylphosphinemethylene to give cis and trans 1-cyclohexylidene-2[5'-methoxy-2'-methylenecyclohexylidene-1']-ethane (VIIa and VIIb).

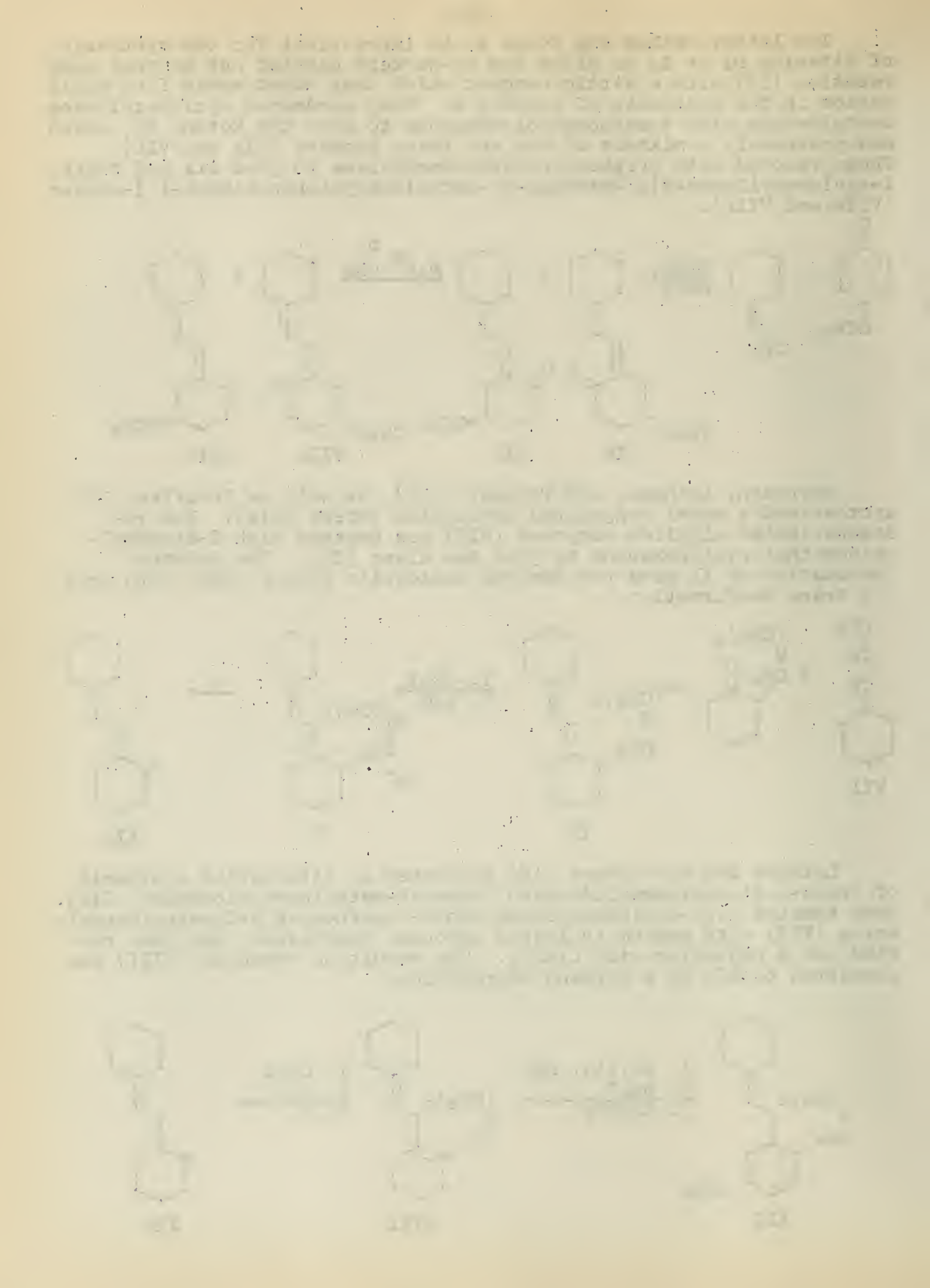


Harrison, Lythgoe, and Trippett (16), as well as Inhoffen (17), synthesized a model conjugated semicyclic triene (XIa). The $\gamma\gamma$-disubstituted allylide compound (VII) was reacted with 2-dimethylaminomethyl cyclohexanone to give the diene (IX). The Hofmann degradation of IX gave the desired semicyclic triene (XIa) with only the trans conformation.



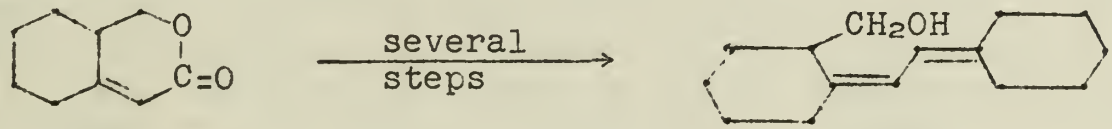
Lythgoe and co-workers (18) published an alternative synthesis of trans-1,2'-cyclohexylideneethylidene-2-methylenecyclohexane (XIb). They treated 2,2'-cyclohexylidene-ethyl-4-methoxy-N,N-dimethylbenzylamine (XII) with sodium in liquid ammonia, hydrolyzed, and then carried out a reduction with $LiAlH_4$. The resulting compound (XIII) was converted to XIb by a Hofmann degradation.





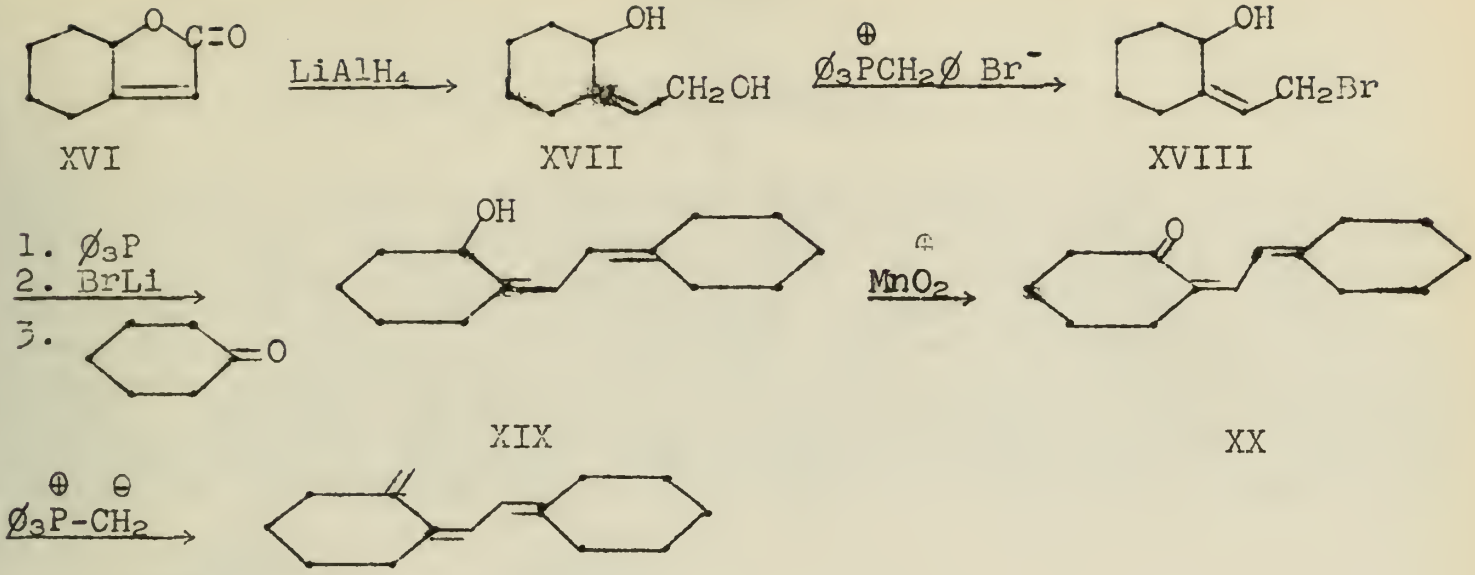
Attempts to prepare the conjugated triene system existing in vitamin D by allowing cyclohexylideneethylenetriphenyl phosphine to react with 2-dimethylaminomethylcyclohexanone as performed by Harrison (16) and by Inhoffen (17) are reported to give only the trans isomer. Milas and Priesing (19) claim to have synthesized a model triene with the cis configuration. They had previously prepared VIa and VIb by condensing cyclohexylideneacetaldehyde with 4-methoxycyclohexanone in the presence of base and converted VIa and VIb to VIIa and VIIb by treatment with triphenylphosphinemethylene. Upon closer examination of their product they reported the isolation of a 14% yield of the cis compound (VIIa) and the presence of an undetermined amount of the trans isomer. It was felt that Harrison and Inhoffen's failure to obtain the cis isomer was due to the steric hindrance of the dimethylamino group present on the 2-dimethylaminomethylcyclohexanone. Milas reported the isolation of the compound with the cis structure assigned on the basis of its U.V. and I.R. spectra which he compared with those of vitamin D_3. Milas was unable to observe a change in either the U.V. absorption maximum or in the extinction coefficient of a solution containing his dienone (VIa and VIb) when treated with iodine. He concluded that he very probably had an equilibrium mixture of the cis and trans isomers or that iodine fails to cause an observable change in the configuration of α,β-unsaturated carbonyl compounds. After comparing the U.V. spectrum of Milas' cis compound (VIIa) (λ_{max}265; ϵ = 23,200) with the spectra of model compounds of known structure, Inhoffen and Irmscher (20) pointed out that the U.V. absorption maximum should be 4-6 mμ lower and the molecular extinction coefficient should also be lower if what was thought to be VIIa were to be assigned the cis configuration. They also noted that iodine is known to aid cis → trans isomerizations. If only the trans isomer (VIb) existed, no isomerization would be expected as was noted by Milas and Priesing. On the other hand, when Inhoffen and Irmscher irradiated the dienone with U.V. light, they observed simultaneous decreases in the molecular extinction coefficient (indicative of trans → cis isomerization) and in the dienone absorption maximum. Inhoffen is inclined to believe that only the trans isomer (VIb) was formed.

Harrison and Lythgoe (21) were able to demonstrate a non-photochemical synthesis of a model cis triene. They converted the δ-lactone (XIV) in good yield to the cis diene (XV) but all attempts to convert it into a semicyclic conjugated triene failed. Instead they

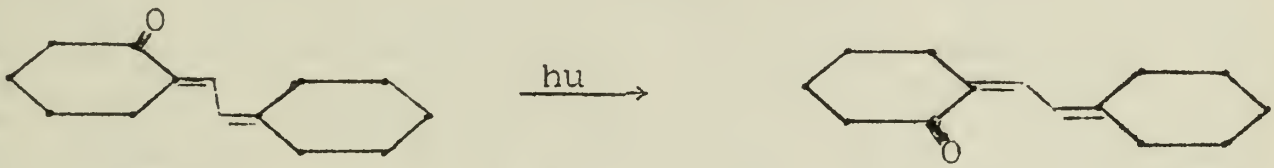


XIV XV

obtained the γ-lactone (XVI) and treated it with $LiAlH_4$ to obtain the diol (XVII), which upon treatment with triphenylbenzylphosphonium bromide gave the monosubstituted bromine compound (XVIII). XVIII was readily converted to the dienol (XIX) by treatment with triphenylphosphine and butyllithium followed by the addition of cyclohexanone. The dienol upon oxidation gave the cis dienone (XX) which could be converted to the conjugated model cis triene by employing the Wittig reagent. The double bond in the lactone appeared to retain its cis configuration.



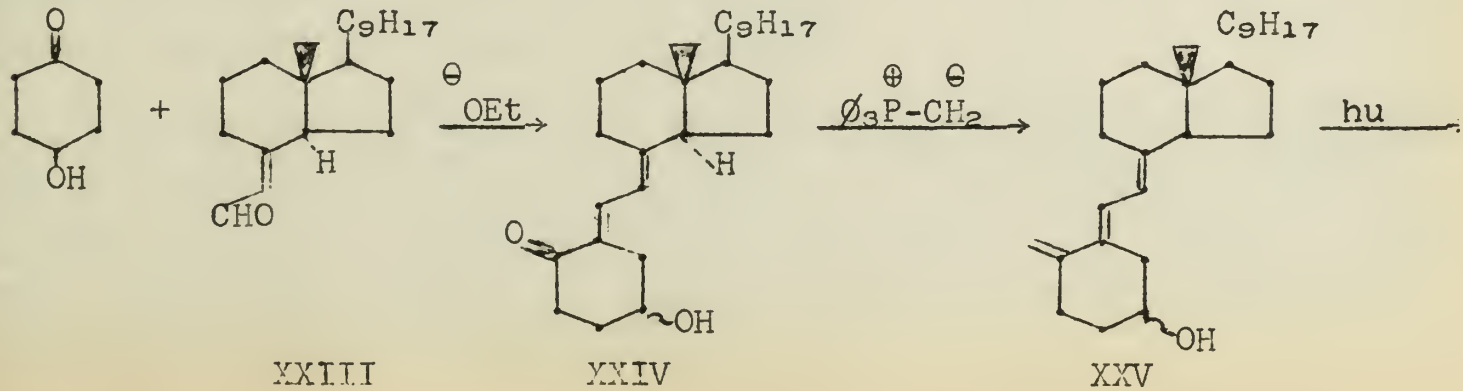
The model system syntheses accomplished their purpose of developing methods for the aldol condensation, the introduction of the exocyclic double bond via the Wittig reagent, and the photochemical conversion of the "trans" to the "cis" compounds. The ultraviolet irradiation method of converting trans into cis αβ-unsaturated ketones was well-known. Harrison and Lythgoe (22) showed that XXI could be convert ed to XXII by this method. These methods were later employed in the more difficult task of synthesizing vitamin D_3. In the actual synthesi of vitamin D_3, the Wittig reaction to replace the carbonyl oxygen with a methylene group preceded the irradiation step.



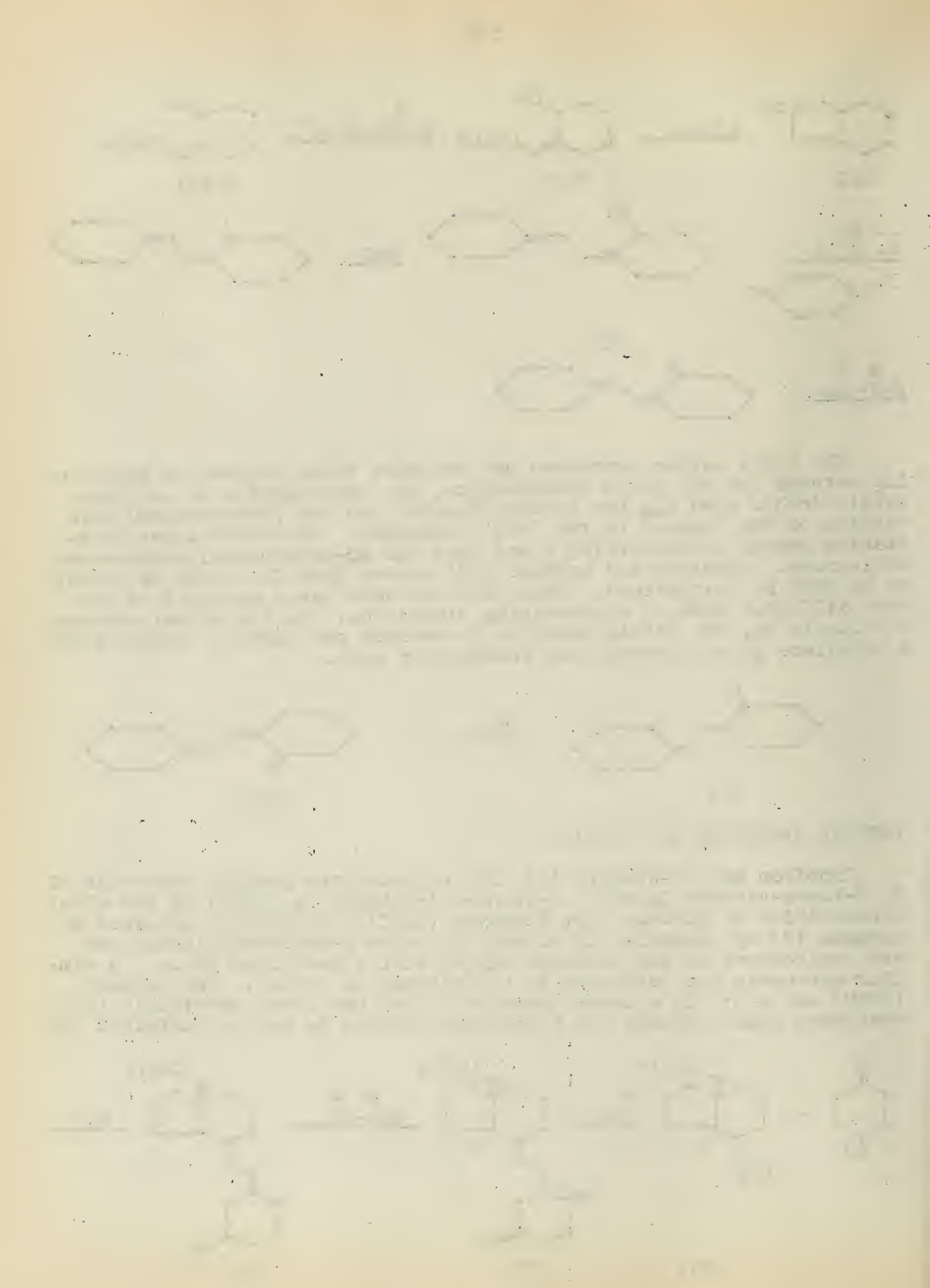
XXI XXII

PARTIAL SYNTHESIS OF VITAMIN D

Inhoffen and co-workers (23, 24) reported the partial synthesis of 5, 6-trans-vitamin D_2 and 5,6-trans-epi-vitamin D_2 (XXIV) by the aldol condensation of Windaus C_{21} aldehyde (XXIII) (originally obtained by Windaus (7) by oxidation of vitamin D_2) with p-hydroxycyclohexanone and replacement of the carbonyl oxygen with a methylene group. A similar synthesis was performed in the vitamin D_3 series. The product (XXIV) was a 1:1 C_3 epimeric mixture. They had found previously (25) that they could convert the 5,6-trans-vitamins D_2 and D_3 (obtained (26

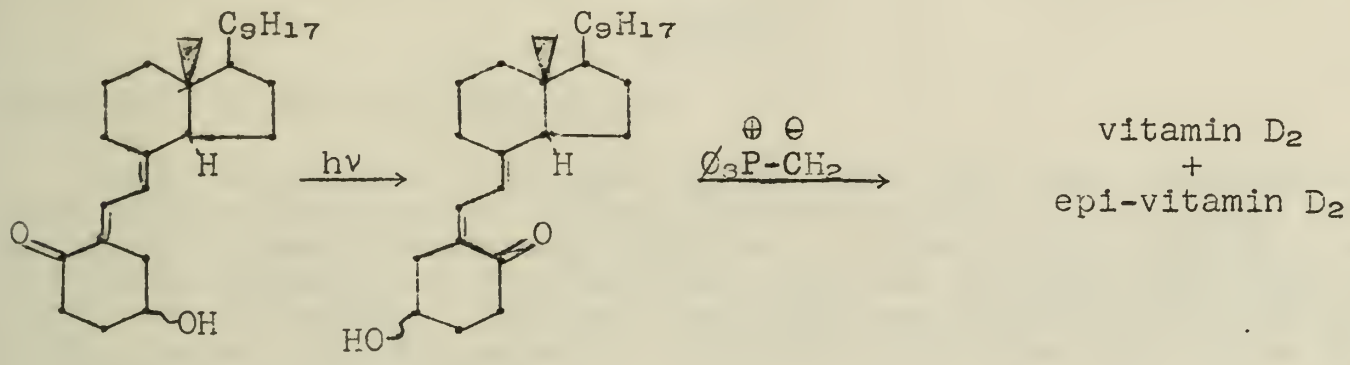


XXIII XXIV XXV



→ vitamin D_2 + epi-vitamin D_2

from natural vitamin D by treatment with iodine) to the 5,6-cis-vitamins D_2 and D_3, respectively, by irradiating them with glass-filtered U.V. light obtained from a mercury lamp. If non-filtered light is use the resulting cis isomer is destroyed. They reported the partial synthesis of vitamins D_2 and D_3 since they had previously shown that 5,6-trans-vitamins D_2 and D_3 gave the natural cis structures when irradiated. Harrison and Lythgoe (22) used the dienone (XXIV) and reverse the steps used by Inhoffen. They irradiated XXIV with U.V. light to obtain the cis dienone (XXVI), which was a C_3 epimeric mixture. XXVI

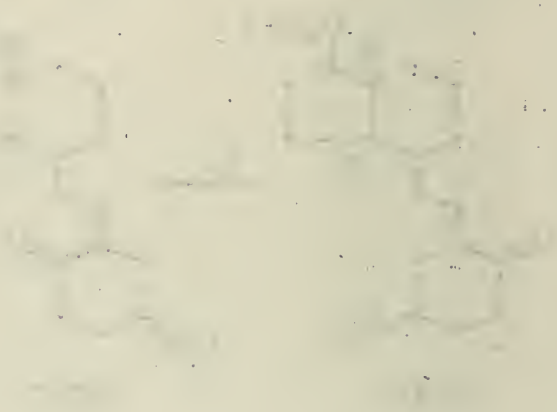


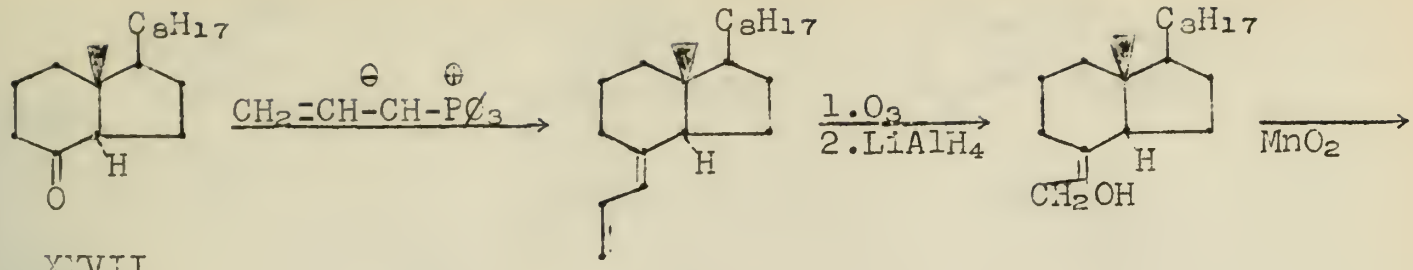
XXIV XXVI

was converted to vitamin D_2 and epi-vitamin D_2 (C_3 hydroxyl group is β) by treatment with triphenyl phosphinemethylene. The 3,5-dinitrobenzoate esters allowed separation of the epimeric mixture of vitamin D_2. They reported a 3:1 ratio of epi-vitamin D_2 to vitamin D_2 in the mixture. They also claimed that they were the first to partially synthesize vitamin D_2 on the basis that Inhoffen may not have isolated 5,6-trans-vitamin D_2 at all but only obtained 5,6-trans-epi-vitamin D_2 Inhoffen and his colleagues responded (27,28) by showing by means of optical rotations that in their epimeric mixture which they isolated as crystalline material, the ratio of trans-vitamin D_2 to trans-epi-vitamin D_2 was 13:87. The mixture was irradiated to obtain a certain quantity of natural vitamin D_2. They also maintained that the isolation of the natural vitamin D_2 and epi-vitamin D_2 in a 1:3 ratio by Lythgoe did not mean that the epimers originally existed in that ratio They indicated that Harrison and Lythgoe had discarded part of their epimeric mixture of the dienolone (XXIV) during chromatography, leavin a mixture which resulted in unequal proportions of the esters. Also what Lythgoe considered to be epi-vitamin D_2 was a 1:1 mixture of natural and epi-vitamin D_2.

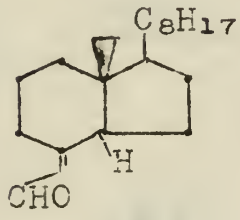
PARTIAL SYNTHESIS OF WINDAUS' C_{21} ALDEHYDE

Inhoffen and co-workers (29) made an advance towards the total synthesis of vitamin D when they converted the ketone (XXVII) (obtained (7) as a degradative product of vitamin D_3) to the aldehyde (XXVIII) through a series of reactions including treatment with the ylid of all bromide, addition of ozone, reduction with $LiAlH_4$, and oxidation with MnO_2. XXVIII was shown to be identical with the aldehyde obtainable from vitamin D_3 by direct oxidation.





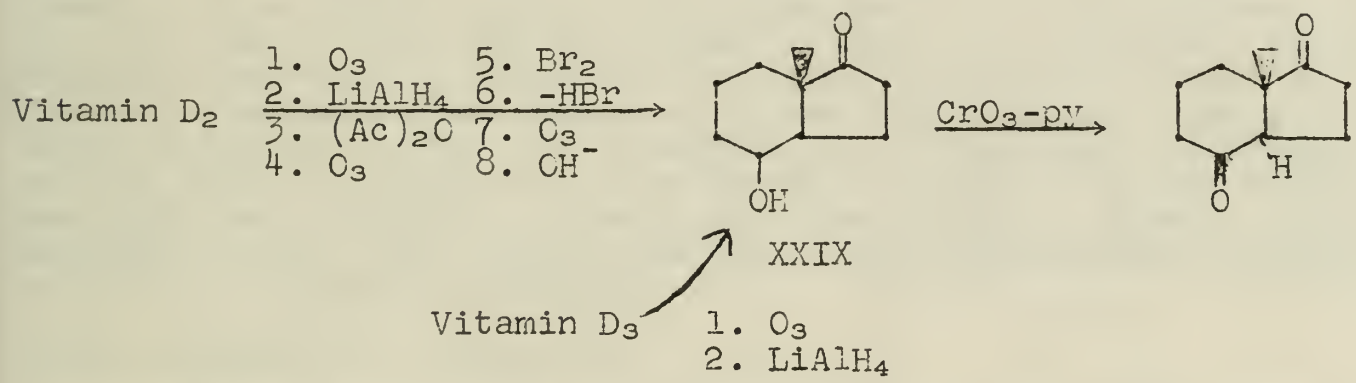
XXVII



XXVIII

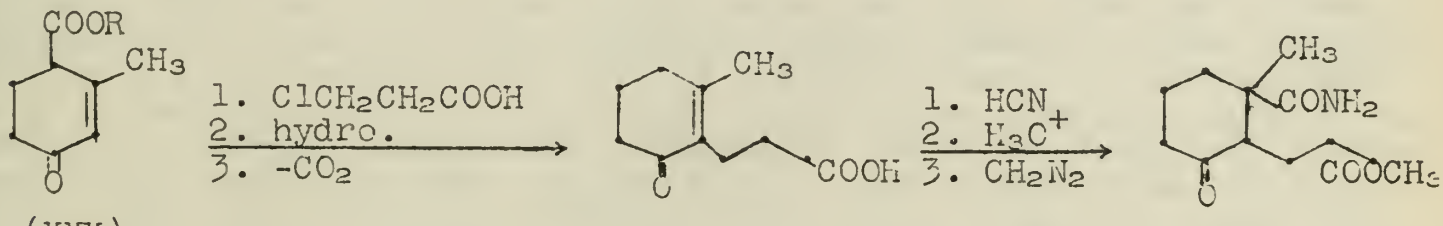
SYNTHESIS OF THE C/D RING SYSTEM

Inhoffen and his colleagues synthesized the trans hydrindane C/D ring system which exists in the vitamin D series. First they obtained (30,31) 8-methyl-trans-hydrindan-4-ol-1-one (XXIX) through a several step degradation of vitamin D_2 and also through a two step degradation of vitamin D_3. The two resulting compounds were identical in either case. Careful oxidation of XXIX with chromic acid gave 8-methyl-trans-hydrindan-1,4-dione.

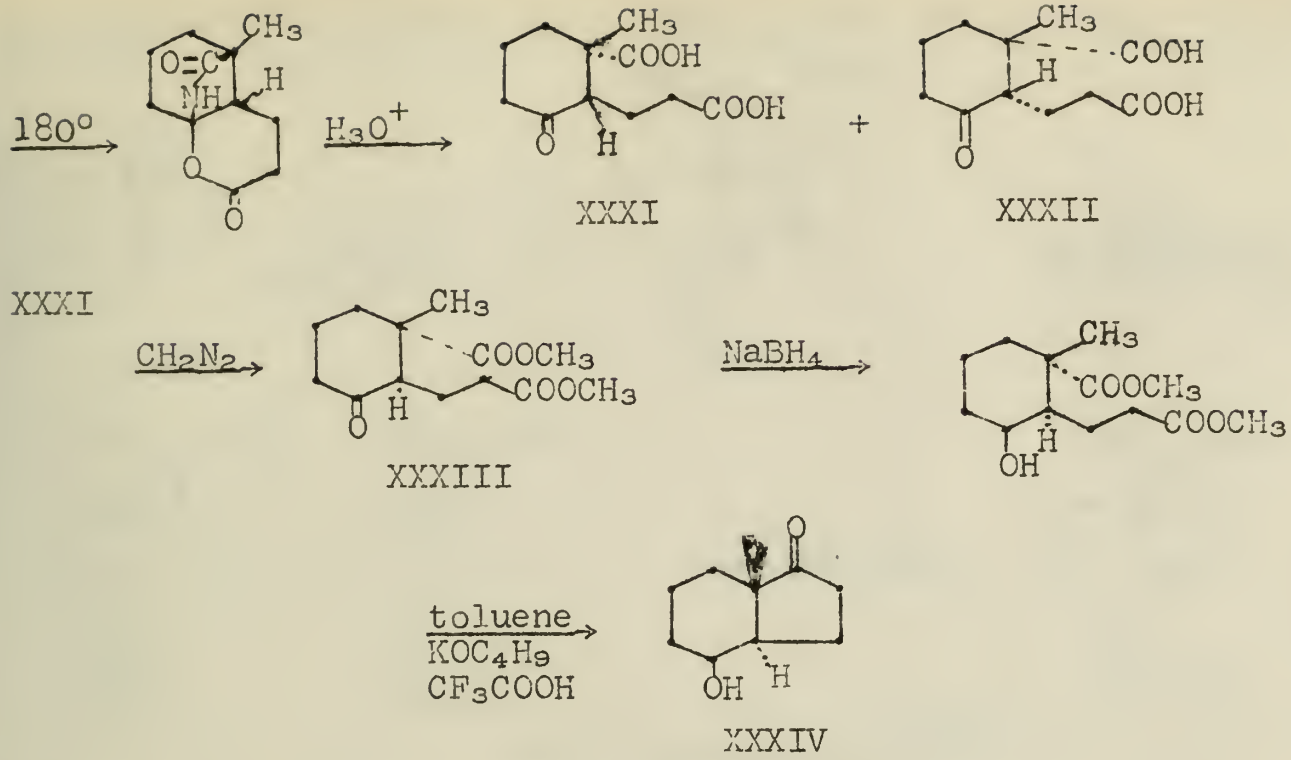


XXIX

Inhoffen and Kramer (32) synthesized some hydrindane derivatives via the Diels-Alder reaction but they never saw application in the vitamin synthesis. Inhoffen and co-workers (33,34) succeeded in synthesizing (+) and (-)-8-methyl-trans-hydrindan-4-ol-1-one beginning with the Hagemann ester (XXX) and proceeding through the steps listed.



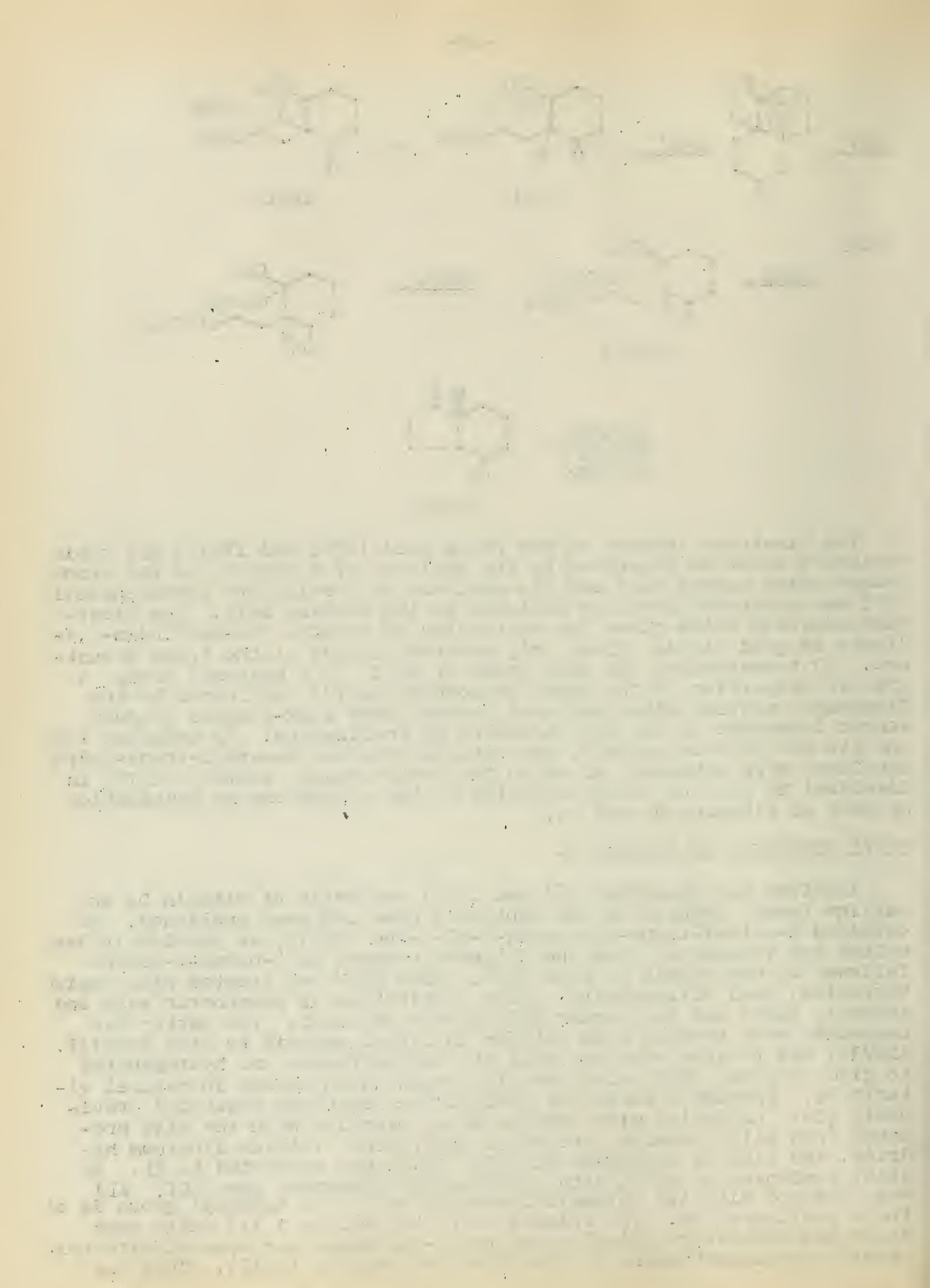
(XXX)



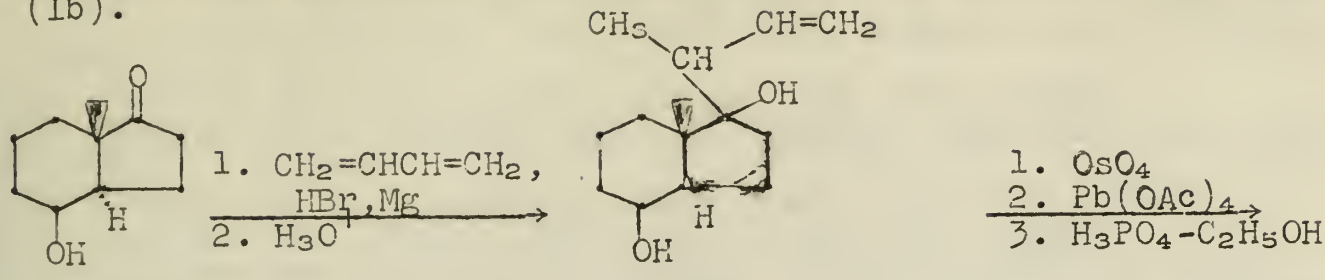
The cis-trans isomers of the Prinz acid (XXXI and XXXII) and their antipodes could be separated by the addition of a crystal of the trans isomer which caused XXXI and its antipode to precipitate preferentially. XXXI was separated from its antipode as its brucine salt. The Dieckmann reaction which gives the energetically favored cis-hydrindan-1,4-diones in good yields, gives only moderate yields of the trans structure. By transforming the keto group of XXXI to a hydroxyl group, a greater proportion of the trans structure (XXXIV) was formed by the Dieckmann reaction since the once formed trans ring-closure product cannot isomerize to the cis structure by enolization. By treating XXXI and its antipode separately, two optically active 8-methyl-trans-hydrindanolones were obtained, of which the dextrorotary isomer (XXXIV) is identical in all its characteristics to the corresponding degradation product of vitamins D_2 and D_3.

TOTAL SYNTHESIS OF VITAMIN D_3

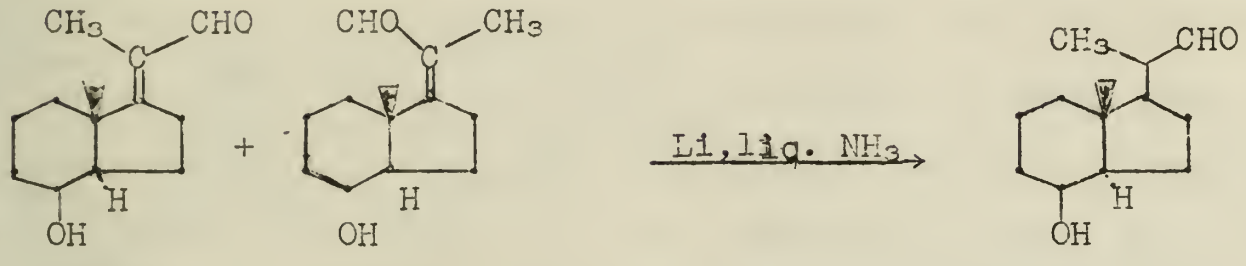
Inhoffen has described (6) the total synthesis of Vitamin D_3 in outline form. Details of the synthesis have not been published. He obtained 8-methyl-trans-hydrindan-4-ol-1-one (XXXIV) as previously described and treated it with the Grignard reagent of 4-brome-1-butene followed by hydrolysis to give XXXV. When XXXV was treated with osmium tetroxide, lead tetraacetate, and a combination of phosphoric acid and ethanol, XXXVI and its isomer XXXVII were obtained. The latter two compounds were treated with lithium in liquid ammonia to give XXXVIII. XXXVIII was treated with the ylid of 3-methylbutane and hydrogenated to give compound XXXIX with the side chain which exists in natural vitamin D_3. Through a series of consecutive reactions described previously (29), oxidation with chromic acid, reaction with the ylid prepared from allyl bromide, treatment with ozone, lithium aluminum hydride, and finally manganese dioxide, XXXIX was converted to XL. An aldol condensation of XL with p-hydroxycyclohexanone gave XLI. XLI was obtained with its epimeric isomer in which the hydroxyl group is of the α configuration. The epimers which existed in a 1:1 ratio were separated chromatographically and the β-dienolone was treated with triphenylphosphinemethylene to give trans-vitamin D_3 (XLII). XLII was



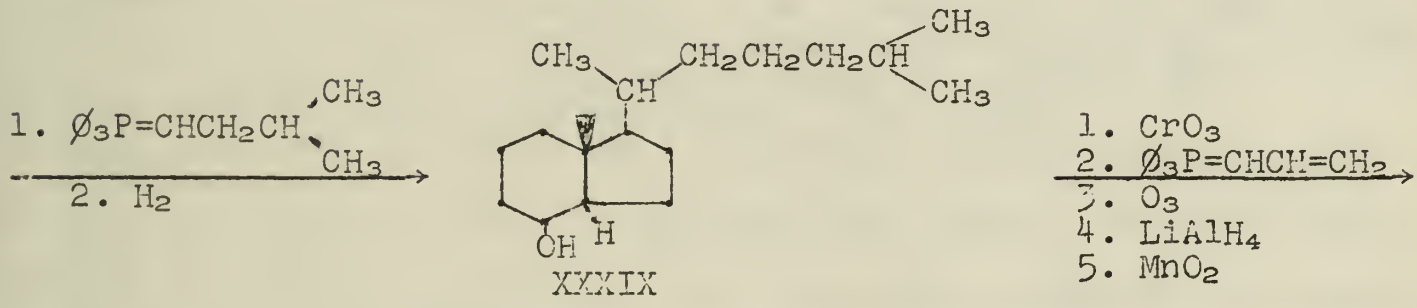
irradiated with filtered U.V. light to give the natural cis vitamin D_3 (Ib).



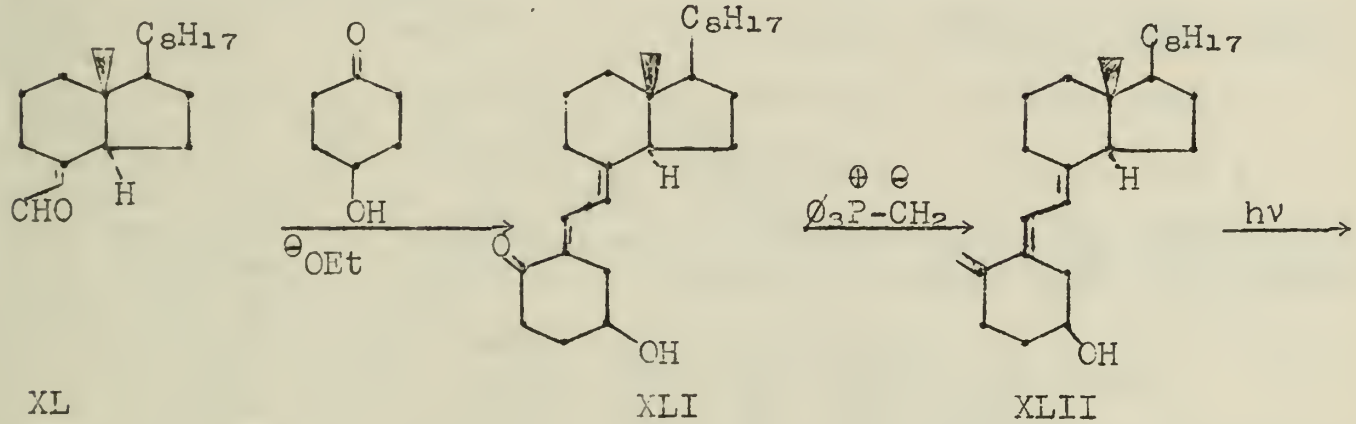
XXXIV XXXV



XXXVI XXXVII XXXVIII



XXXIX



XL XLI XLII

→ vitamin D_3 (Ib)

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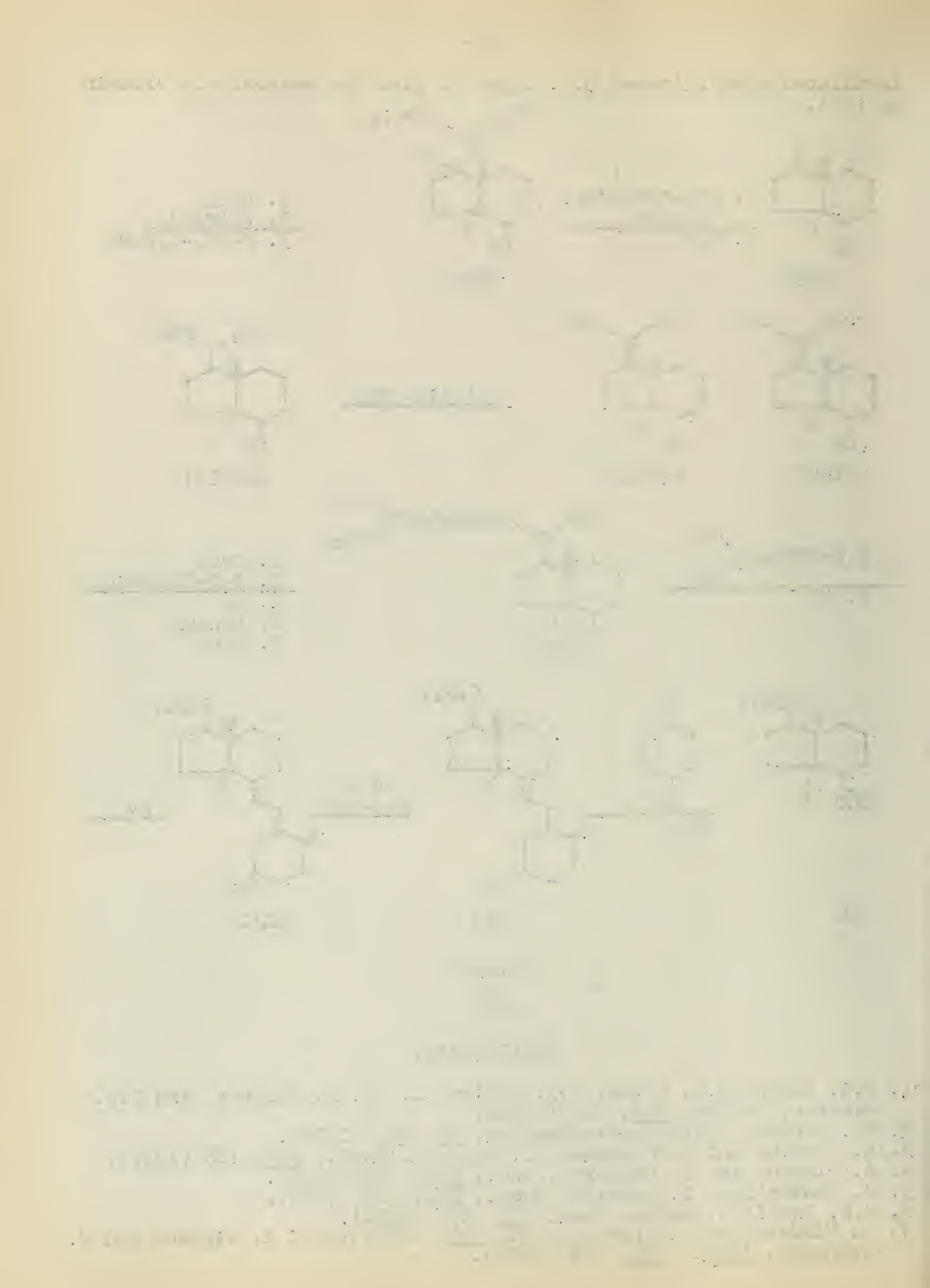

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MECHANISMS OF SUBSTITUTION REACTIONS IN OCTAHEDRAL COMPLEXES

Reported by A. J. Bollero July 22, 1959

INTRODUCTION

The mechanisms of substitution reactions in carbon compounds are postulated to be primarily of two types, the familiar S_n1, dissociation reaction, and S_n2, displacement reaction. First order kinetics and racemization are considered characteristic for reactions which proceed by the S_n1 mechanism while second order kinetics and stereochemical specificity are associated with the S_n2 process. It will be seen that substitutions in octahedral complexes do not follow these conditions and indeed the problem of determining the mechanism of a reaction is quite difficult.

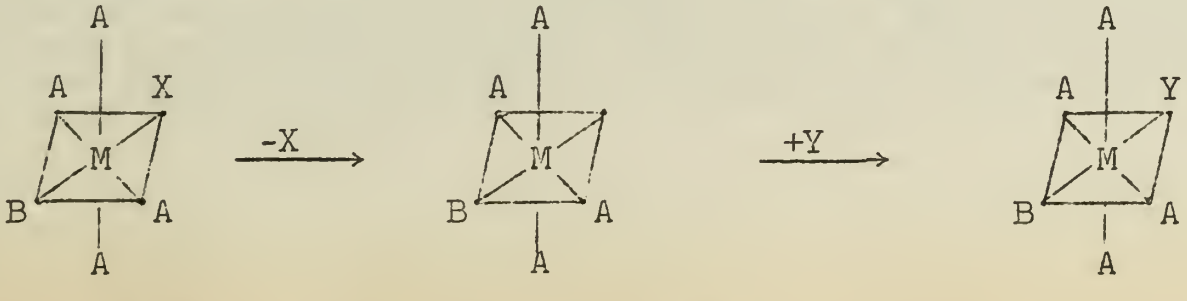
Several methods are available for attempting the solution of the type of mechanism under which substitution is occurring. Detection in some manner of the intermediate of reduced coordination number is the best diagnosis of the S_n1 mechanism. However, this approach can be misleading since detection of the intermediate may be impossible due to a short life. Dependence of the rate of reaction on the incoming ligand should indicate an S_n2 mechanism, but this may not be true for all ranges of concentration. S_n1 and S_n2 mechanisms should give rise to quite different stereochemical results, however it is not necessary that they do so, nor can the expected stereochemistry in each case be predicted before hand without further assumptions. Recently the use of crystal field theory has been suggested as a means of determining the mechanism of a reaction (1).

A survey of the literature of octahedral substitutions suggests that some sort of duality of mechanism, which might well be a coexistence of the bimolecular and unimolecular mechanisms of nucleophilic substitutions, is general.

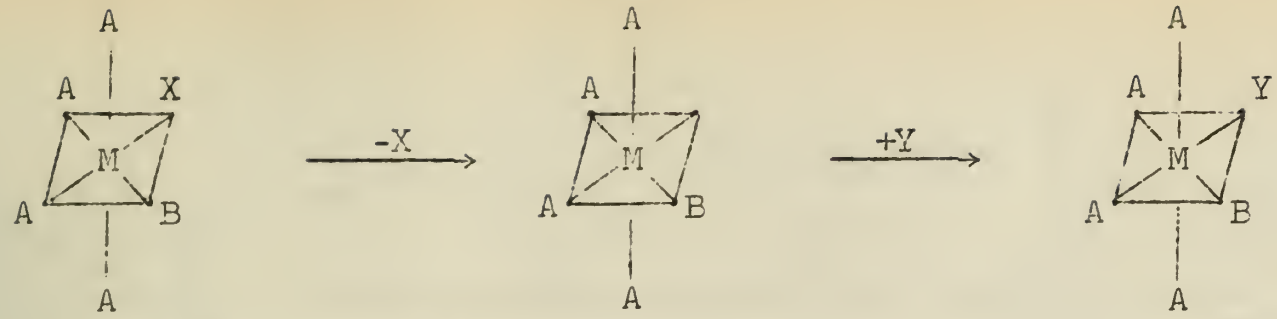
STEREOCHEMICAL BASIS OF REACTION MECHANSIM

Dissociation (S_n1) mechanism. The dissociation mechanism for an octahedral complex requires the formation of a five-coordinated intermediate. This intermediate can exist in one of two forms: a tetragonal pyramid or trigonal bipyramid (2,3,4). These two structures appear to be the most plausible ones because (a) stable compounds of such structures are known, (b) these structures can be derived from the octahedron with little atomic motion, while intermediates of the planar and pentagonal pyramid type need not be considered as these structures generally cannot be achieved without excessive rearrangement (4).

It is apparent that the reaction of either a cis- or trans-compound through a tetragonal pyramid intermediate can take place without rearrangement.

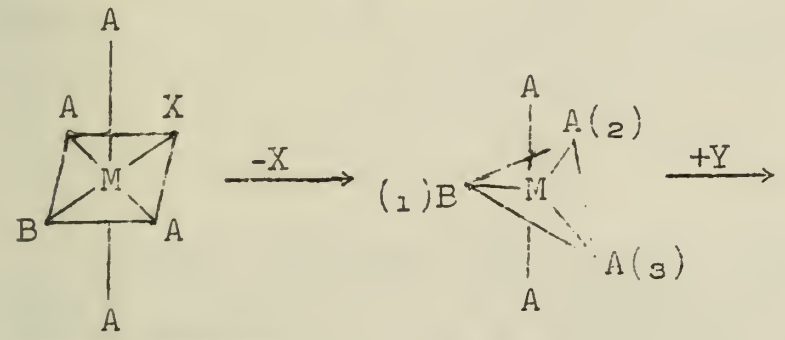


trans-isomer---one position of attack---trans-product



cis-isomer-----one position of attack-------cis-product

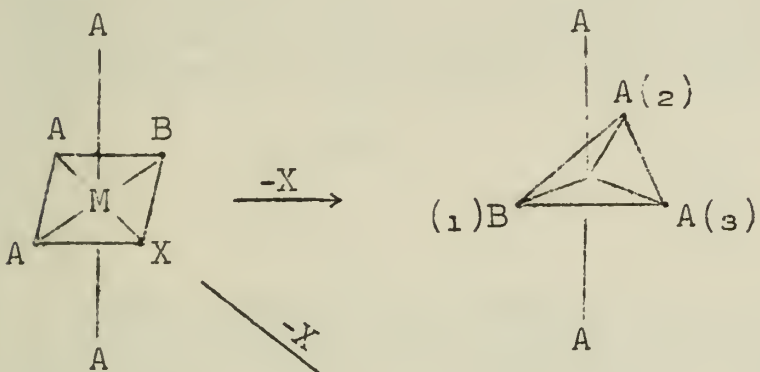
Reactions of cis- and trans- compounds by way of a trigonal bipyramid intermediate may lead to rearrangement.



2 cis- (<1,2 and <1,3) products

1 trans- (<2,3) product

trans-isomer

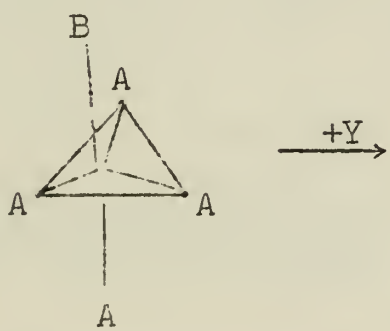


2 cis- (<1,2 and <1,3) products

1 trans- (<2,3) product

cis-isomer

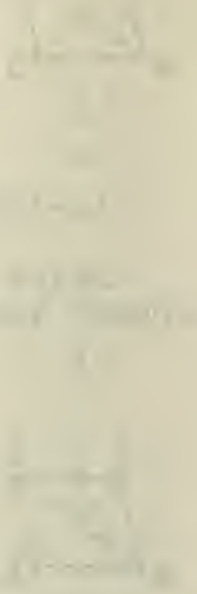
-X

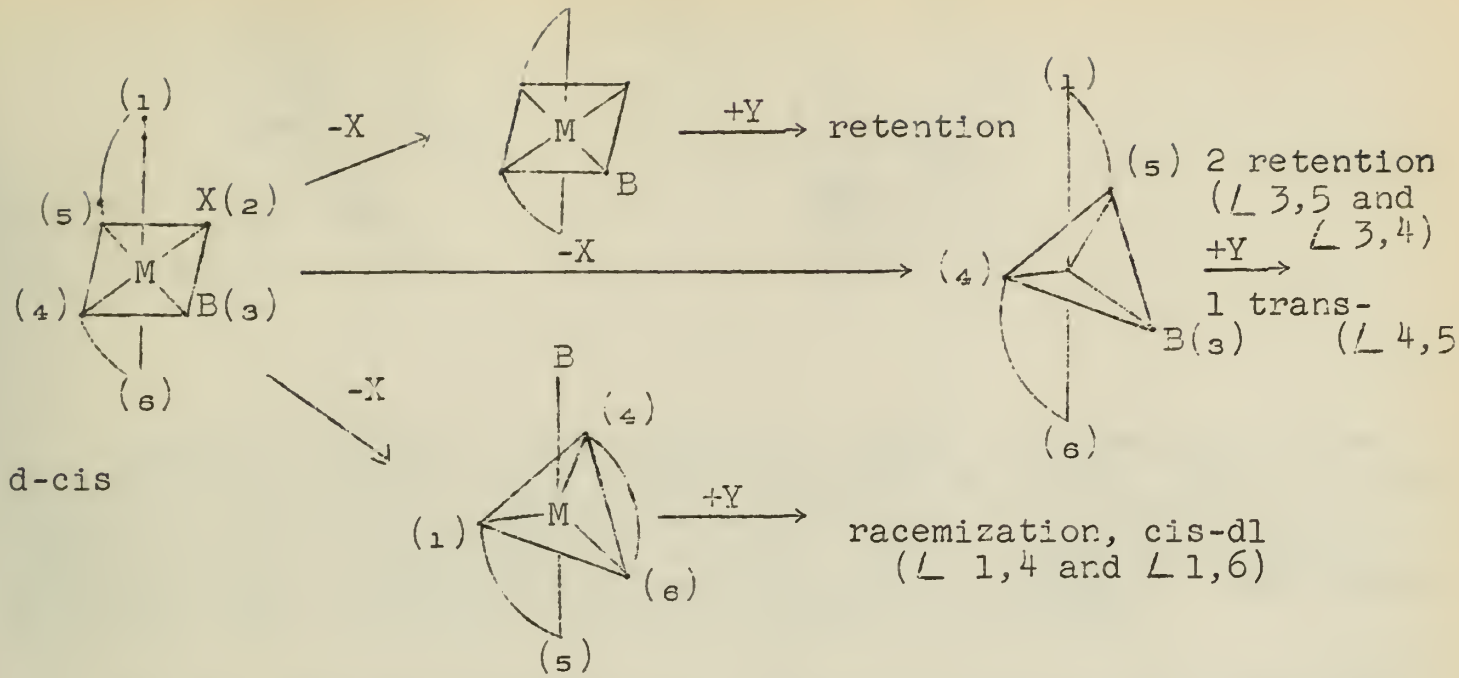


1 cis-product

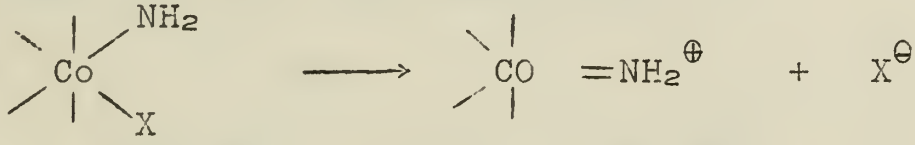
In using these approaches the assumption that the incoming group enters the activation complex at the most accessible positions, namely in the trigonal plane, can be made (5).

Considering the study of optically active complexes of the type cis-$Co(en)_2AX$ we can apply the same treatment as that used above in the case of geometrical isomers. For an S_n1 process inversion cannot take place; only retention of configuration and/or loss of optical activity can occur.

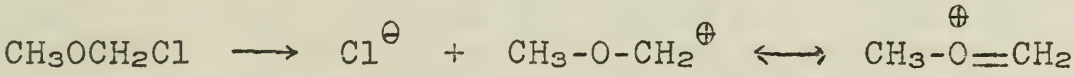




In all complexes that contain an amino group with an unshared pair of electrons, it is proposed that the increased rate of dissociation observed is due to π-bonding--the partial transfer of p orbital electrons on the ligand atom toward the central atom (6). Such π-bonding where the unshared electrons of the amino group move toward the Co helps to displace the halide ion and to stabilize the 5-coordinated intermediate after the loss of the halide ion.



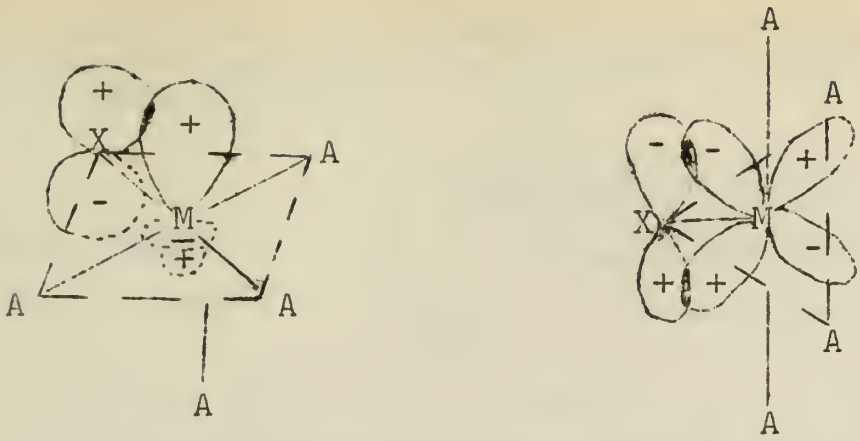
The situation is similar to that encountered in organic chemistr in explaining the high reactivity of α-halo ethers. The accepted explanation for this reactivity is that a resonance structure involving π-bonding from the oxygen atom's unshared electron pairs stabilizes the carbonium ion.



The tetragonal pyramid intermediate formed has 4 ligands located in a plane and the 5th is situated normal to that plane. No change in orbital hybridization need be involved in the formation of this intermediate.

In the trigonal bipyramid intermediate three ligands lie in a central plane with one ligand below this plane. The trigonal plane would involve $(S + d_{z^2})$ (p_x) (p_y) hybrid orbitals which are directed toward the apices of an equilateral triangle and the orbitals normal to the plane would be $(S + d_{z^2})$ (p_z) hybrids, leaving the $d_{x^2-y^2}$ orbital vacant which consists of four lobes in the trigonal plane directed towards the corners of a square.

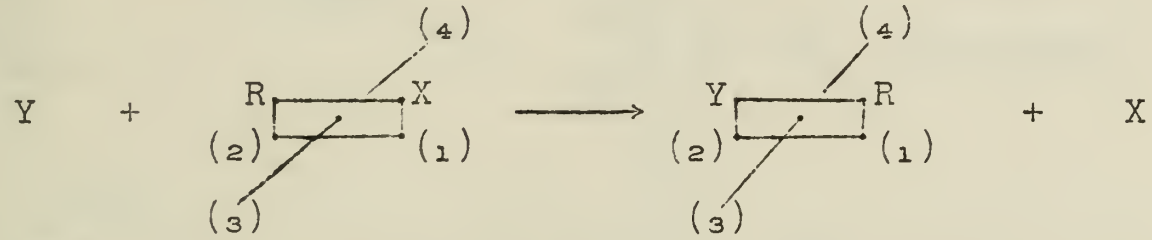
The criterion for π-bonding then is a suitable matching of the vacant Co orbital with the p orbital of the ligand which contains the free electron pair. The orbitals must be oriented so that lobes of the same sign can overlap (7).



Since the +lobes in the tetragonal pyramid do overlap some π-bonding will occur but only a weak bond will be formed. This overlap can only occur for a p orbital of a ligand which is located in a position cis- to the vacant Co orbital. For a ligand in a trans-position, the p orbital must always be directed normal to the vacant Co orbital and therefore could not overlap it properly.

In the trigonal bipyramid both the positive and negative lobes are well matched for good overlap. Thus the trigonal bipyramid can undergo reasonably strong π-bonding.

Displacement(S_n2) mechanism. A hypothesis which has been suggested for bimolecular reactions by Brown, Ingold, and Nyholm is that d-l conversions and cis-trans changes are essentially of the same type and that either can arise in an octahedral system as a result of what they call edge-displacement (8).

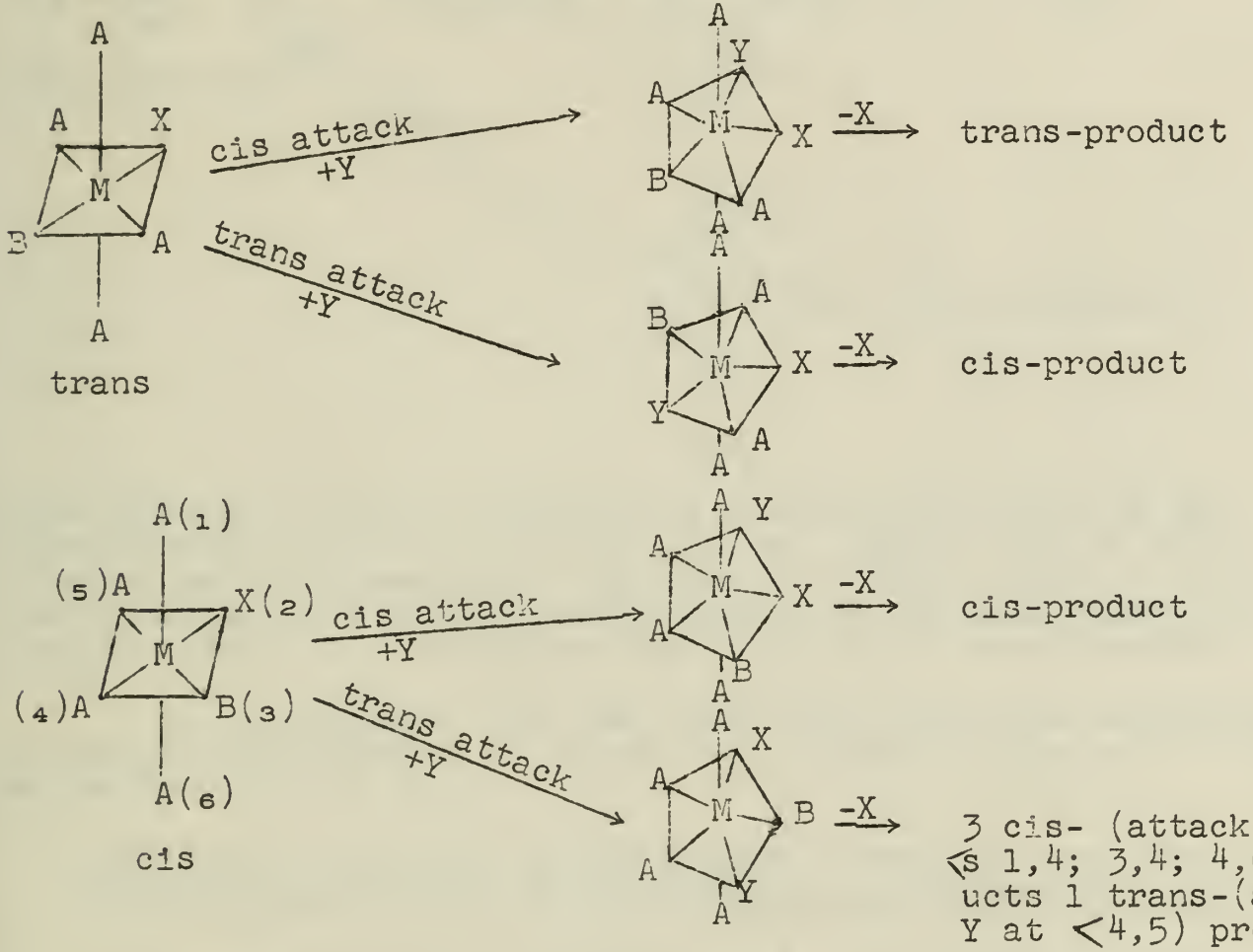


The observation and description of this change depends, not on the groups Y, R, and X, but on the position of some unaffected group A, whose relation to the replaced and replacing groups X and Y is denoted by the prefixes d and l, or cis and trans. If A is at (1) the process is cis $\longrightarrow$ trans, if at (2) it is trans $\longrightarrow$ cis, and if at (3) or (4) either d $\longrightarrow$l or l $\longrightarrow$d. While any observed stereo change can be understood as an edge-displacement an observed absence does not always imply the absence of an edge-displacement. If the groups in (1) and (2) and likewise those in positions (3) and (4), can be superposed either on the other by a rotation of the molecule, then in the represented substitution with edge-displacement, a cis-factor will give a cis-product, chemically identical with that which would be given by substitution without edge-displacement. Similarly, if the positions (1) and (3) and the positions (2) and (4) are identically coupled, as by ethylenediamine molecules, then there is retention of configuration (d $\rightarrow$d or l $\rightarrow$l) during substitution just as there is without edge-displacement. The two processes do yield different results for reactions of trans-MA_4BX. In this case substitution with edge-displacement must yield a cis-product, whereas substitution without edge-displacement gives the corresponding trans-isomer.

The relation of stereo-change to edge-displacement and non-edge-displacement processes for a complex of the type MA_4BX is given in the following table (8).

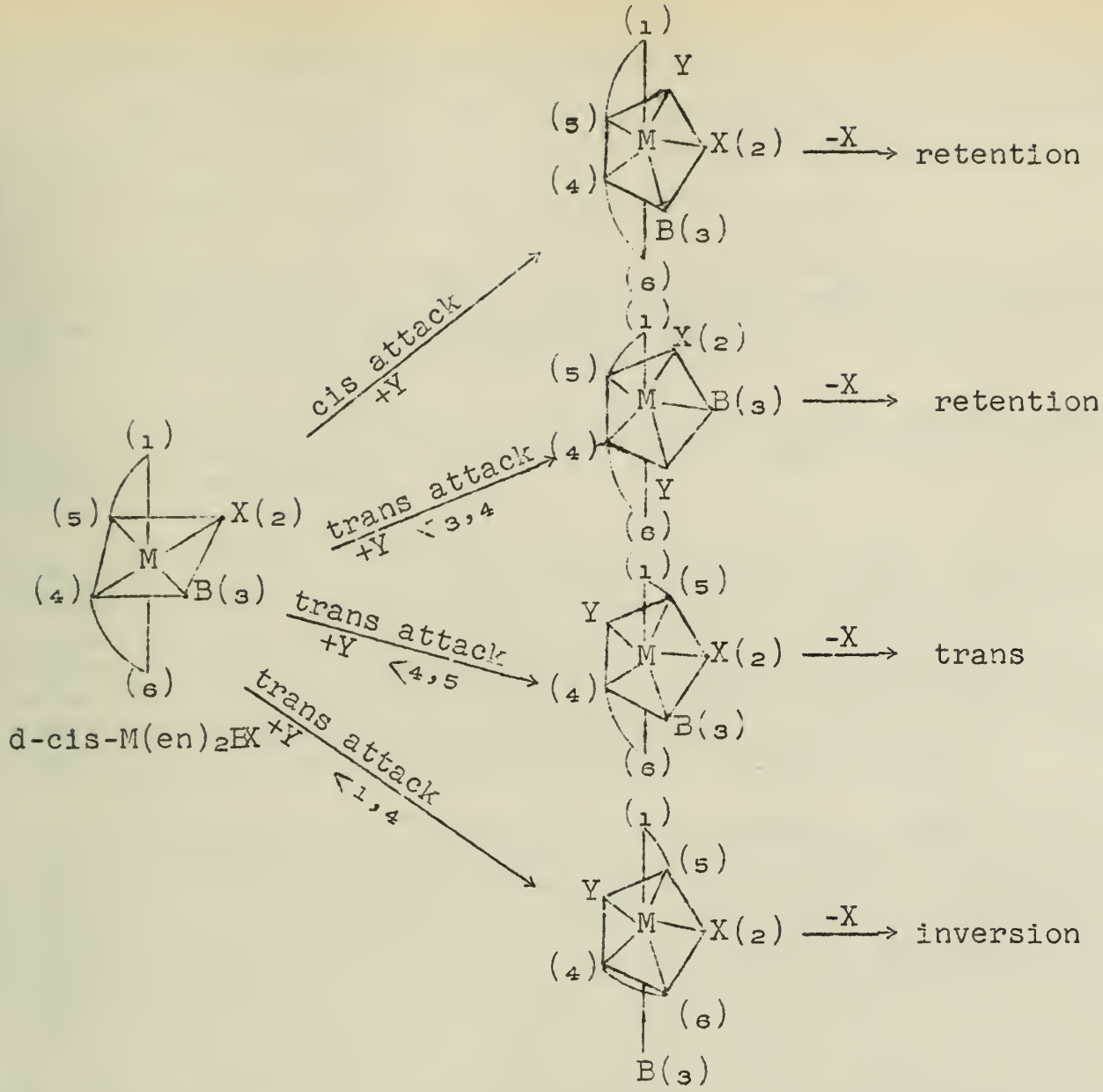
Substitution with edge-displacement		Substitution without edge-displacement		
Stereo change		No Stereo change		
cis⟷trans	d⟷l	d⟷d l⟷l	cis⟷cis	trans⟷trans
Substitution with edge-displacement				

According to Basolo, Pearson, and co-workers (4) substitution by means of a displacement mechanism requires the intermediate formation of a seven-coordinated complex. The seven-coordinated intermediate may be formed either by an approach of the entering group towards a position adjacent to that of the departing ligand (cis- or front side attack) or towards a position opposite from that of the departing ligand (trans or backside attack)(5).



A cis-attack produces no net rearrangement; but a trans-attack gives a mixture of cis- and trans-isomers with the cis-isomer whereas the trans-isomer yields only a cis-product.

The use of the pentagonal bipyramid for reaction intermediate may also be applied to optically active octahedral complexes to predict the products resulting from a S_n2 reaction mechanism.



Trans-approach allows inversion of configuration with an S_n2 mechanism as compared to an S_n1 process. Since none of the 7-coordinated are symmetrical the loss of optical rotation is due to the formation of a trans-product and/or to the same extent of reaction through the two intermediates that lead to cis-enantiomorphs.

It is apparent from the table given that the stereochemistry of the reaction product is often not in itself diagnostic of the mechanism involved (5).

Statistical Amounts (%) of Isomeric Products Predicted For Different Mechanisms of Substitution in Octahedral Complexes

Reactant	Dissociation (S_n1)				Displacement (S_n2)			
	Tetragonal Pyramid		Trigonal Bipyramid		cis-attack		trans-attack	
	cis	trans	cis	trans	cis	trans	cis	trans
trans-MA_4BX	0	100	66.6	33.3	0	100	100	0
Cis-MA_4BX	100	0	83.3	16.6	100	0	75	25
D-$M(en)_2BX$	D-100	0	D-33.3	16.6	D-100	0	D-33.3	33.3
		DL-50					L-33.3	

MECHANISM OF ACID HYDROLYSIS REACTIONS

The substitution reaction most extensively studied by kinetic methods is the aquation or acid hydrolysis reaction.

$$MA_5X^n + H_2O \longrightarrow MA_5H_2O^{n+1} + X^-$$

An appreciable amount of data is available on the rates of hydrolysis reactions (9,10). These studies, made in aqueous solutions, give a linear plot for first-order kinetics, but give no information as to the molecularity of the reactions.

The way in which the rate constant is affected by various change in the nature of the complex ion is expected to give information about the mechanism.

For example, increasing chelation slows down the rate of acid hydrolysis (11). Since the central cation becomes less available for attack by water as the amount of chelation becomes greater, the observed decrease in rate would suggest an S_n2 mechanism. In complexes where the central atom is virtually completely shielded the S_n2 mechanism would be excluded. However, the fact that these complexes react only slightly slower than the less hindered ones is perhaps the most direct piece of evidence against an S_n2 process.

Another series of complexes whose rates of aquation have been studied are those of the type $Co(AA)_2Cl_2^{+1}$ where AA is a diamine which has been substituted both on C and N (12). Progressive substitution of methyl groups on the carbon atoms of ethylenediamine produces a continuous increase in the rates of aquation of the corresponding complexes and when substitution is complete as for the tetramethylethylenediamine complex, the aquation is too rapid to measure even at low temperatures. This would seem to rule out a displacement or S_n2, mechanism since a decrease in rate is usually observed for reactions of this type as the reaction center becomes less accessible. The increasing rate would be expected if the activated complex were pentacoordinated as in a dissociation mechanism.

As the alkyl chain length of N-alkyl substituted ethylenediamines is increased the rate of aquation increases.

On the basis of experimental data available (5) it appears that acid hydrolysis reactions proceed without stereochange. These observations of extensive retention of configuration tentatively suggest that substitution proceeds either by an S_n1 process through a tetragonal pyramid intermediate or by an S_n2 mechanism with a cis-attack. In terms of the edge-displacement theory, the results suggest that the reactions occur primarily without edge-displacement. From kinetic observations the S_n1 mechanism seems to predominate for acid hydrolysis. Since these reactions proceed generally with retention of configuration it follows that for the most part the five-coordinated intermediate must have a tetragonal pyramid structure.

MECHANISMS OF BASE HYDROLYSIS REACTIONS

The one category of substitution reactions in Co(III) complexes which appears to be accompanied by extensive rearrangement is that of base hydrolysis. The stereochemical observation most diagnostic of the reaction process is that which occurs during the reaction of the

trans-isomer. A trans-factor yields a trans-product unless the reaction takes place either through a trigonal bipyramid intermediate which gives largely a cis-product or a trans-displacement giving entirely a cis-product. In base hydrolysis reactions of trans-$Co(en)_2BX$, large quantities of cis-$Co(en)_2B(OH)$ are found. These results indicate a different mechanism from that of acid hydrolysis for which trans-reactants yield largely trans-products.

Ingold (9) assumes that base hydrolysis reactions are bimolecular S_n2, and accounts for the large amount of cis-product on the basis of an edge-displacement mechanism. If this were completely an edge-displacement, the product would be 100% cis. However, since some trans is obtained, unlike bimolecular substitutions on tetrahedral carbon, which are known to produce practically exclusive inversion, these substitutions on octahedral Co lead predominately, but not exclusively to edge-displacement. One immediate objection to this interpretation is the assumption that these reactions are bimolecular, whereas kinetic studies suggest that the reactions are of a S_n1CB type (substitution, nucleophilic, unimolecular, conjugate base) (13,14,21)

$$Co(NH_3)_5Cl^{++} + OH^- \xrightleftharpoons{fast} Co(NH_3)_4NH_2Cl^{+} + H_2O$$
$$Co(NH_3)_4NH_2Cl \xrightarrow{slow} Co(NH_3)_4NH_2^{++} + Cl^-$$
$$Co(NH_3)_4NH_2^{++} + H_2O \xrightarrow{fast} Co(NH_3)_4NH_2(H_2O)^{++}$$
$$Co(NH_3)_4NH_2(H_2O)^{++} \xrightarrow{fast} Co(NH_3)_5OH^{++}$$

This explanation of the observed stereo change for the base hydrolysis of trans-$Co(en)_2BX$ is in agreement with both the S_n1CB mechanism indicated by kinetic studies and the formation of small amounts of trans-product along with the cis-isomer. It also is in agreement with the observation that a cis-isomer yields a larger amount of cis-product than does the same trans-starting material.

This mechanism was challenged by Ingold and Asperger (15) since it requires that the rate with different reagents should run parallel to their proton-affinity, whereas the rates observed showed no kind of parallelism to base strength. In answer to this Pearson, Meeker, and Basolo, (16) state that the replacement, in cations such as trans-dichlorobis (ethylenediamine) cobalt(III), of the bis(ethylenediamine) by either tetrapyridyl or bis-$\alpha\alpha$-dipyridyl residues, leads to an easy aquation. It is inferred that the absence of N-bound H in these aromatic complexes has excluded the normal mechanism of alkaline hydrolysis, thus leaving aquation in control. The high rates, especially those found in the dipyridyl complexes, point clearly to a promoted aquation, i.e. to a mechanism facilitated, rather than to one excluded, by the bond properties of the aromatic groups. This is explained on the basis that the facilitated aquation is a unimolecular solvolysis as of a diphenylmethyl halide, and that it is facilitated for a like reason, in other words, the aromatic electrons are conjugated with the electrons of the breaking bond. In the matter of formal conjugation, the replacement of an ethylene diamine ligand in a chloro-cobalt (III) complex by two pyridyl ligands is like passing from a cyclopentyl halide to a diphenylmethyl halide, a change which gives greatly increased prominence to unimolecular reactions.

An exception to this S_n1CB mechanism is the basic hydrolysis of trans-$Co(en)_2NO_2Cl^+$ which yields 96% of the trans-hydroxo isomer (12,17) This result can be explained if there is an inhibition of nucleophilic attack adjacent to the nitro group and hence an orientation of attack

in an opposite position (15). Such a stereospecific approach may result from steric and/or polarization effects of the nitro ligand. Since this group is expected to π-bond with a pair of the d electrons on Co(III) it follows that the electron density near the nitro group will be large and thus nucleophilic attack adjacent to it is very slow However, the same polarization of Co will oppose heterolysis of the departing halogen: as always in bimolecular nucleophilic substitution, the question of whether a polar substituent will accelerate or retard reaction depends on a balance of opposing effects, in particular on whether the importation of electrons by the substituting agent needs only a smaller, or is conditional on a larger, simultaneous release of electrons toward the departing group. Both sorts of balance are found in bimolecular nucleophilic substitution on carbon. In these substitutions on Co, the electron release is slightly the more important of the two processes of electron transfer which are involved in the formation of the transition state. The case is analogous to bimolecular nucleophilic substitutions of benzyl and of allyl halides by anions.

This picture of orientation in bimolecular substitution by anions at octahedral Co suggests the existence of two broad classes of orienting groups. Cyano and carbonyl groups are likely to exhibit tendencies similar to that of the nitro-group, towards the promotion of substitution, remotely from the orienting group and thus with predominately retention of configuration when a trans group is displaced. Halogeno-, azido-, and aquo- groups are likely to resemble isothiocyanato- and ammino- (10) groups in not restricting substitution in their neighborhood, thereby allowing substitution to proceed with extensive stereo-change, and, when a trans-group is displaced, with predominating stereo-change.

REACTIONS IN NON-AQUEOUS SOLVENTS

Brown and Ingold (18) have investigated the kinetics of substitution of a chloro group in cis-$Co(en)_2Cl_2^+$ by several anions in the solvent methyl alcohol using polarimetric, spectroscopic, chemical, and radiochemical methods. The substitutions by NO_3^-, $*Cl^-$, Br^-, and NCS^- proceed by an S_n1 mechanism as the rates obtained were found to be independent of the concentration of the entering anion. The rate-determining step in all cases is the rate of formation of the five-coordinated intermediate,

$$Co(en)_2Cl_2^+ \underset{-Cl}{\overset{slow}{\rightleftharpoons}} Co(en)_2Cl^{++} \xrightarrow[+X]{fast} Co(en)_2ClX^+$$

Other observations--rate of loss of optical activity equal to rate of reaction and mass retardation observed--further support this mechanism.

Three anionic reagents, NO_2^-, N_3^-, and CH_3O^- react much more rapidly and roughly according to a second-order law. Thus it is suggested that they proceed by an S_n2 mechanism.

The methoxide reaction in methanol is very likely the analog of the hydroxide ion reaction in water, namely an S_n1CB type mechanism (19). The high rates obtained for the basic anions may be due to methanolysis in unbuffered systems producing the methoxide ion, for example; $N_3^- + CH_3OH \longrightarrow HN_3 + OCH_3^-$

A plausible explanation for the fact that the order with respect to the anion approaches zero at high concentrations is that ion-pairs

are formed which react more rapidly than the original complex ion. The equation which is given for mechanisms in which the first step is a rapid reversible formation of an ion-pair is:(20)

$$Co(en)_2Cl_2^+ + X^- \rightleftharpoons Co(en)_2Cl_2^+ , X^-$$

and the slow step may be either of three reactions; a dissociation reaction of the ion pair (S_n1IP);

$$Co(en)_2Cl_2^+ , X^- \xrightarrow{slow} Co(en)_2Cl^{++} , X^- + Cl^-$$
$$Co(en)_2Cl^{++} , X^- \xrightarrow{fast} Co(en)_2ClX^+$$

a displacement reaction of the ion-pair (S_n2IP);

$$Co(en)_2Cl_2^+ , X^- \xrightarrow{slow} Co(en)_2ClX^+ + Cl^-$$

or a displacement reaction of the free ions (S_n2).

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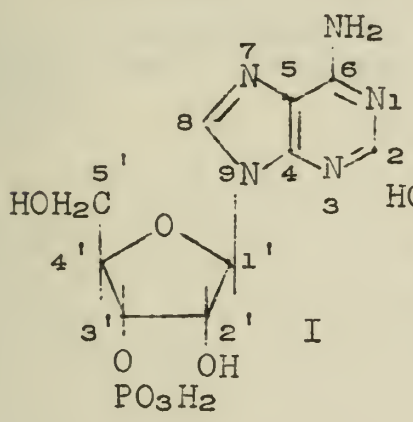
SYNTHESES OF NUCLEOTIDES

Reported by D. M. Paisley July 27, 1959

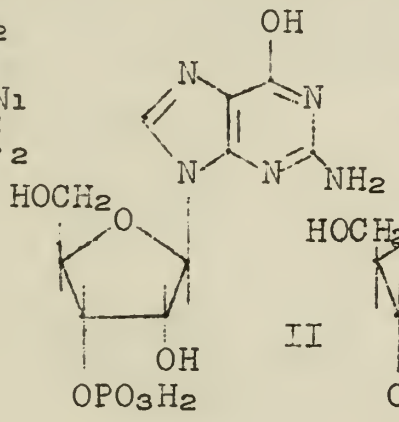
INTRODUCTION

Nucleotides include many compounds of central importance in the chemistry of the living cell. A nucleotide, or nucleoside phosphate, is a compound containing a phosphorylated sugar N-glycosidically linked to a heterocyclic base. The enzymatic or basic hydrolysis of yeast nucleic acid (1) yields the four most common nucleotides:



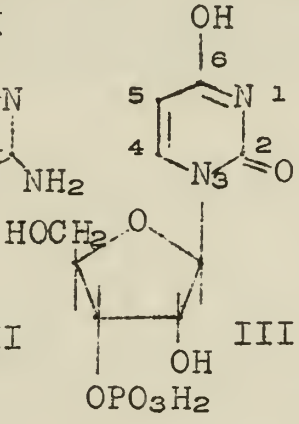
I

adenylic acid (base = adenine) (adenosine-3' phosphoric acid)



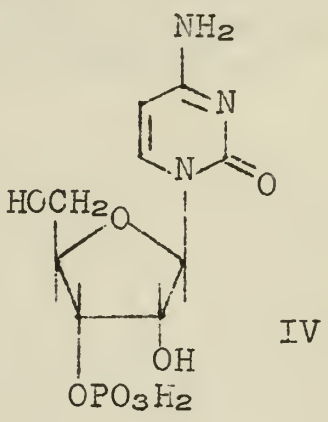
II

guanylic acid (base = guanine) (guanosine-3' phosphoric acid)



III

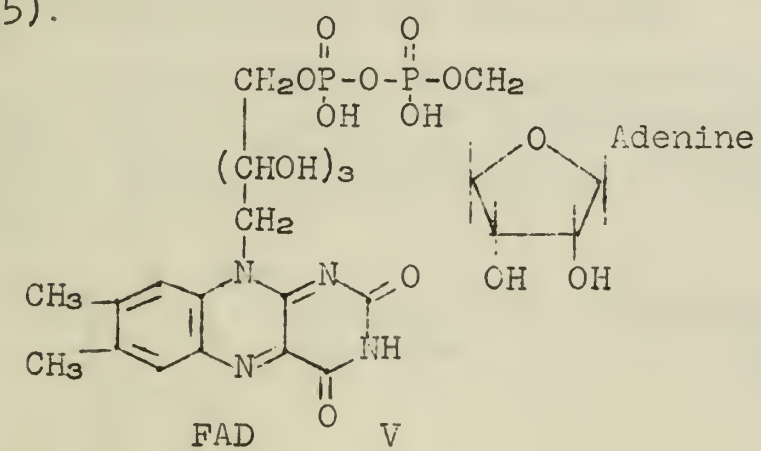
uridylic acid (base = uracil) (uridine-3' phosphoric acid)



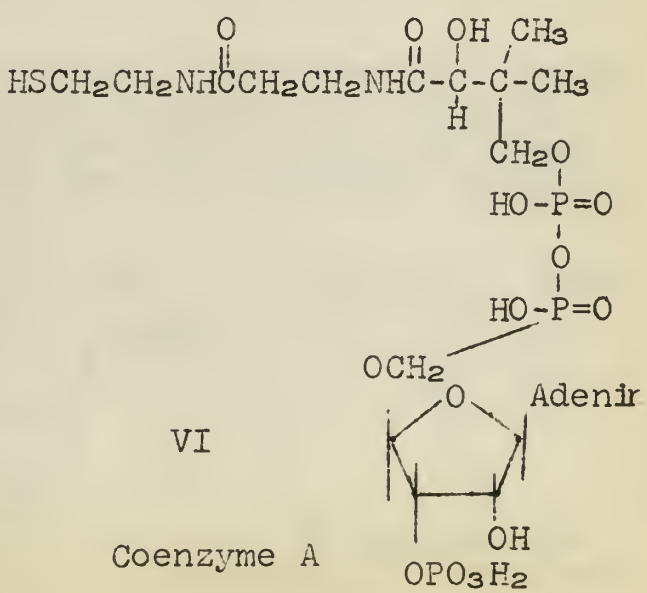
IV

cytidylic acid (base = cytosine) (cytidine-3' phosphoric acid)

The nucleotide coenzymes are characterized by the presence of at least one simple nucleotide residue and include such compounds as flavin adenine dinucleotide (FAD) (V), a hydrogen acceptor in aerobic dehydrogenases (2); Coenzyme A (VI), biochemically active with certain condensing enzymes, in the transfer of acetyl groups, and in fatty acid synthesis and oxidation (3); di- and triphosphopyridine nucleotides (DPN and TPN) (VII, VIII), which function as hydrogen acceptors in biological reduction-oxidation systems (4); and adenosin di- and triphosphate (ADP and ATP) (IX, X), which participate in the reversible phosphorylation of many important metabolic intermediates (5).

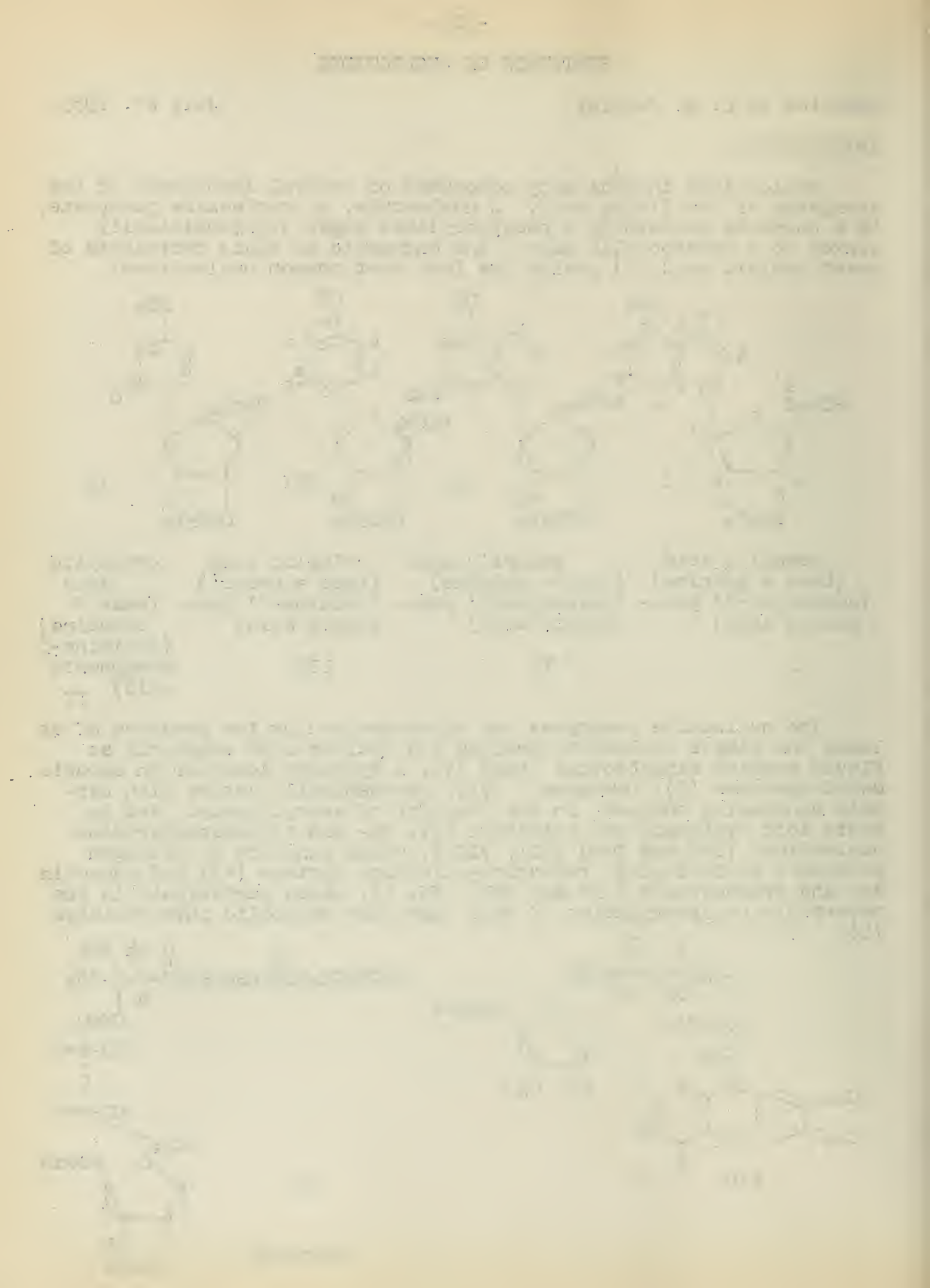


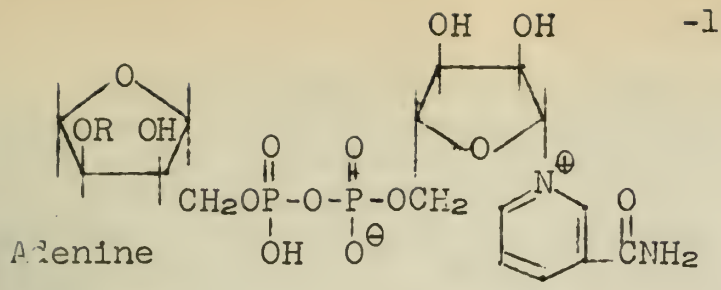
FAD V



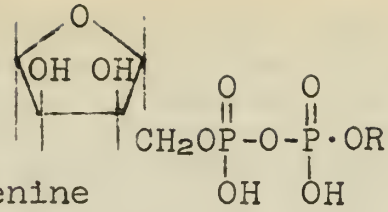
VI

Coenzyme A



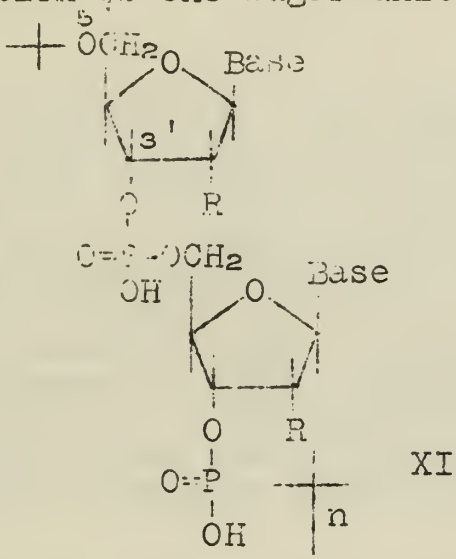


VII DPN, R=H
VIII TPN, R=PO_3H_2



IX ADP, R=H
X ATP, R=PO_3H_2

Ribonucleic acid (RNA or PNA) (6) and deoxyribonucleic acid (DNA (6) are polynucleotides (XI) joined by phosphate ester linkages involving the 3' position of one sugar unit and the 5' position of another.



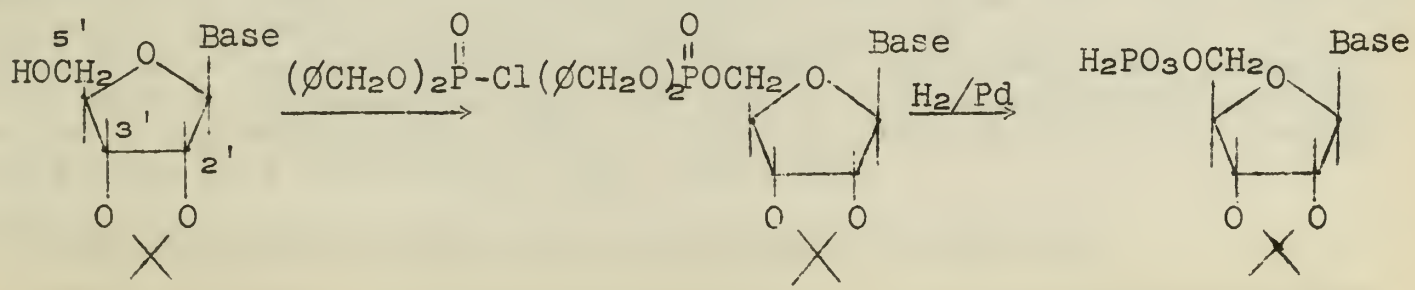
XI

RNA, R=OH; Base=adenine, guanine, cytosine, and uracil
DNA, R=H; Base=adenine, guanine, cytosine, methylcytosine and thymine

Organic phosphates and pyrophosphates are of common occurence in nature (7), but only recently has extensive work been done on their laboratory synthesis. Given the structures of the nucleosides, there are two main problems encountered in the synthesis of nucleotides: 1) phosphorylation of the nucleosides; 2) synthesis of the nucleotide coenzymes by A) formation of monoesters of pyro- and triphosphoric acid and B) formation of unsymmetrical diesters linked through phosphate and pyrophosphate bonds.

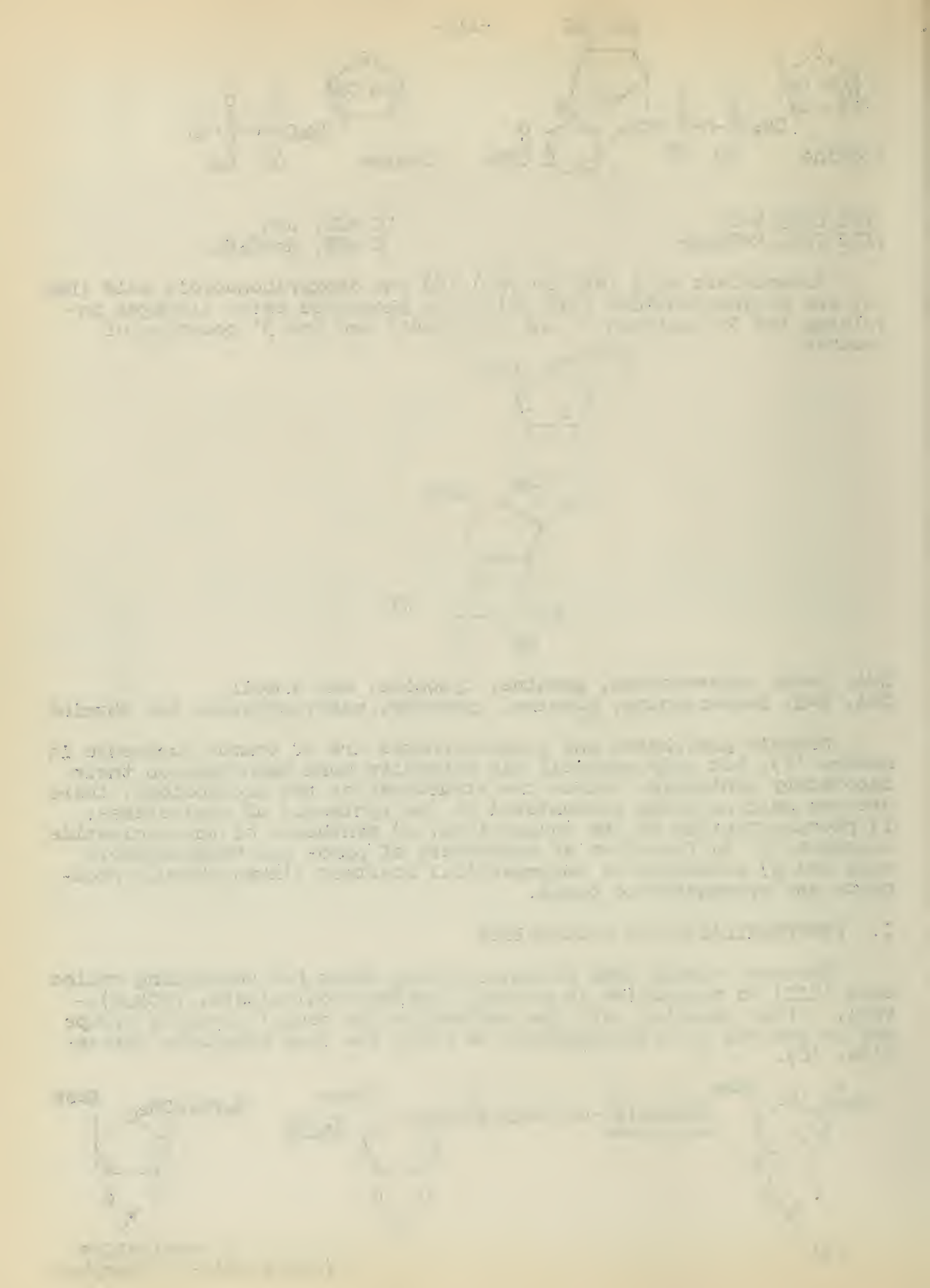
I. PHOSPHORYLATION OF NUCLEOSIDES

The most widely used phosphorylating agent for converting nucleoside (XII) to nucleotide is dibenzyl phosphorochloridate, $(\phi CH_2O)_2$-POCl. After reaction with the nucleoside the benzyl blocking groups may be removed by hydrogenolysis to yield the free phosphate derivative, (8).

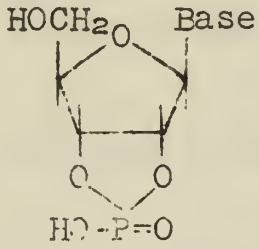


XII

5'-nucleotide
(nucleoside-5' phosphat

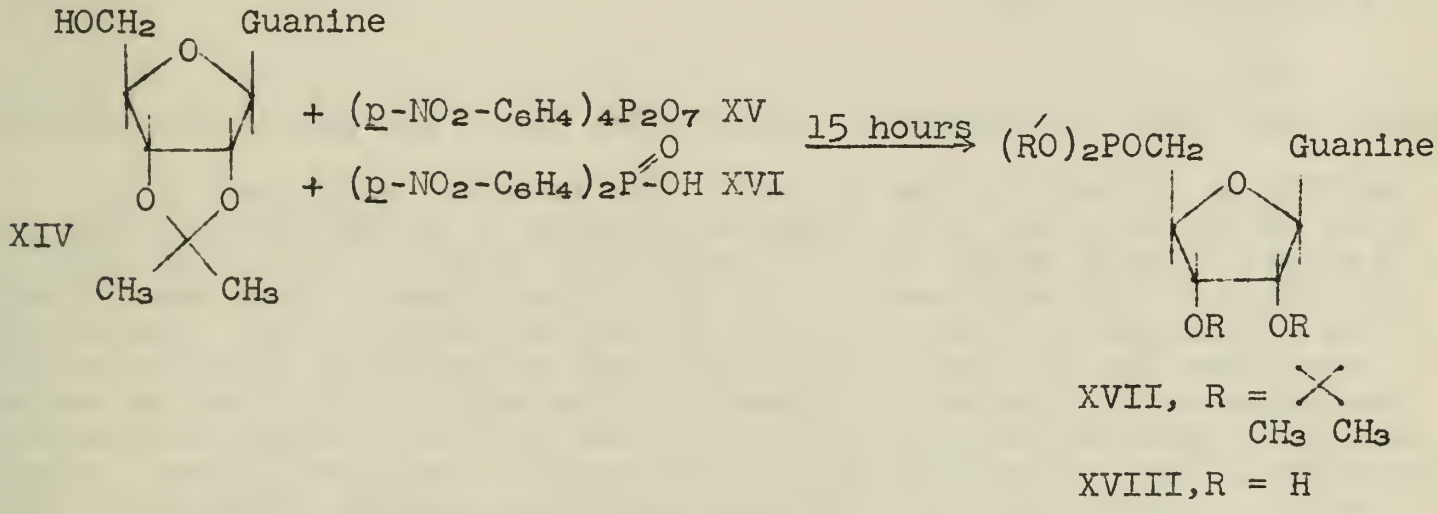


Of the three possible sites for phosphorylation, the 5' position may be selectively phosphorylated after blocking the 2'- and 3'-hydroxyls by formation of the cyclic ketal of acetone (9). Attempts to synthesize individual 2'- or 3'-ribonucleotides by phosphorylatio of the ribonucleoside derivatives fail because of phosphoryl migration between the 2'- and 3'- positions which always leads to an equilibrium mixture of 2'- and 3'-phosphate by way of a cyclic intermediate (XIII) (10).



XIII

Although highly satisfactory syntheses of a number of nucleoside 5' phosphates have been recorded (11), previous attempts at the phosphorylation of guanosine derivatives have not been successful. The 5'-hydroxyl group in 2',3'-O-isopropylidine guanosine (XIV) is uniquely inert and resists phosphorylation by dibenzylphosphorochloridate, although a 20% yield was realized with phosphorus oxychloride (12). Recent work by Khorana (11) showed that tetra-p-nitrophenyl pyrophosphate (XV) reacts with (XIV) in the presence of an equivalent amount of di-p-nitrophenyl hydrogen phosphate (XVI) to provide a quantitative yield of 2',3'-O-isopropylidine guanosine 5'-di-p-nitrophenyl phosphate (XVII) from which the protecting groups may be easil removed. Guanosine-5' phosphate (XVIII) was then isolated in 70% yield.



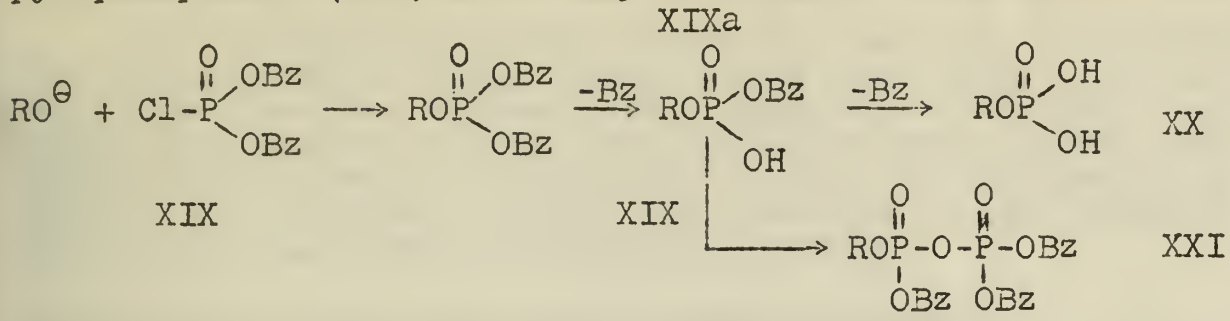
II. SYNTHESIS OF NUCLEOTIDE COENZYMES

The syntheses of nucleotide coenzymes have been the object of intensive study in recent years. These substances function in association with specific proteins, or apoenzymes, the complete enzymatic system being composed of the combination apoenzyme plus coenzyme (13) All known nucleotide coenzymes belong to one of two classes: 1) monoesters of polyphosphoric acid in which the esterifying group is a nucleoside derivative, e.g., ATP (X), and 2) unsymmetrical P^1P^2-diesters of pyrophosphoric acid in which at least one of the esterifying groups is a nucleoside, e.g., DPN (VII).

Phosphorochloridate Method for Pyrophosphate Synthesis

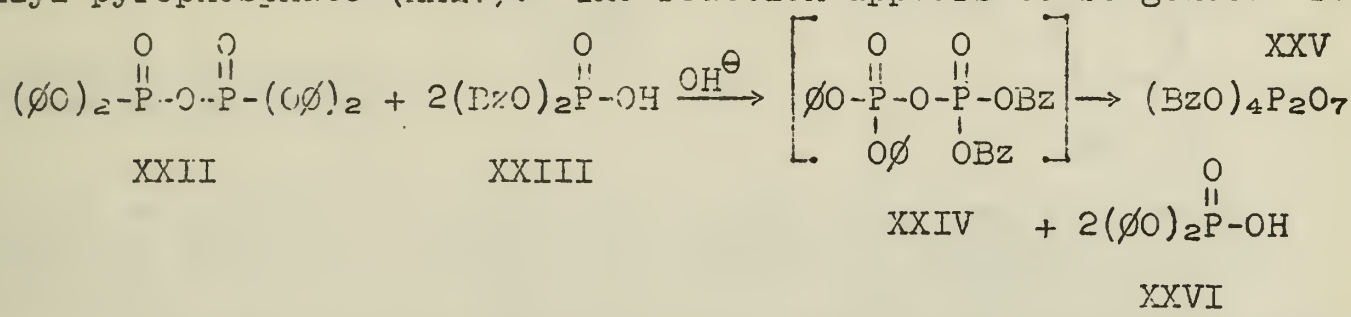
The simplest and most direct route to pyrophosphates is the reaction between dibenzylphosphorochloridate (XIX) and the salt of a

phosphodiester (XIX a) (14). Monoesters of both phosphoric (XX) and pyrophosphoric (XXI) acids may be formed. This method was used in the



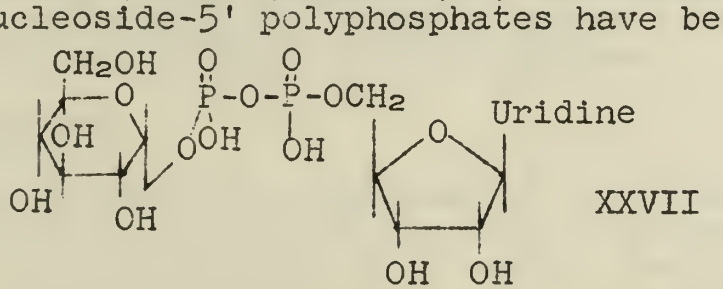
first total synthesis of ADP, although only fair yields were realized (15).

Fully esterified pyrophosphates are very labile compounds, readily phosphorylating amines and alcohols and undergoing exchange reactions with other anions. For example, tetraphenylpyrophosphate (XXII) reacts rapidly with dibenzyl phosphoric acid (XXIII) in the presence of base to give tetrabenzyl pyrophosphate (XXV) and diphenyl phosphoric acid (XXVI) (16). This reaction is a two stage process, the intermediate product being the unsymmetrical ester P^1-diphenyl P^2-dibenzyl pyrophosphate (XXIV). The reaction appears to be general for

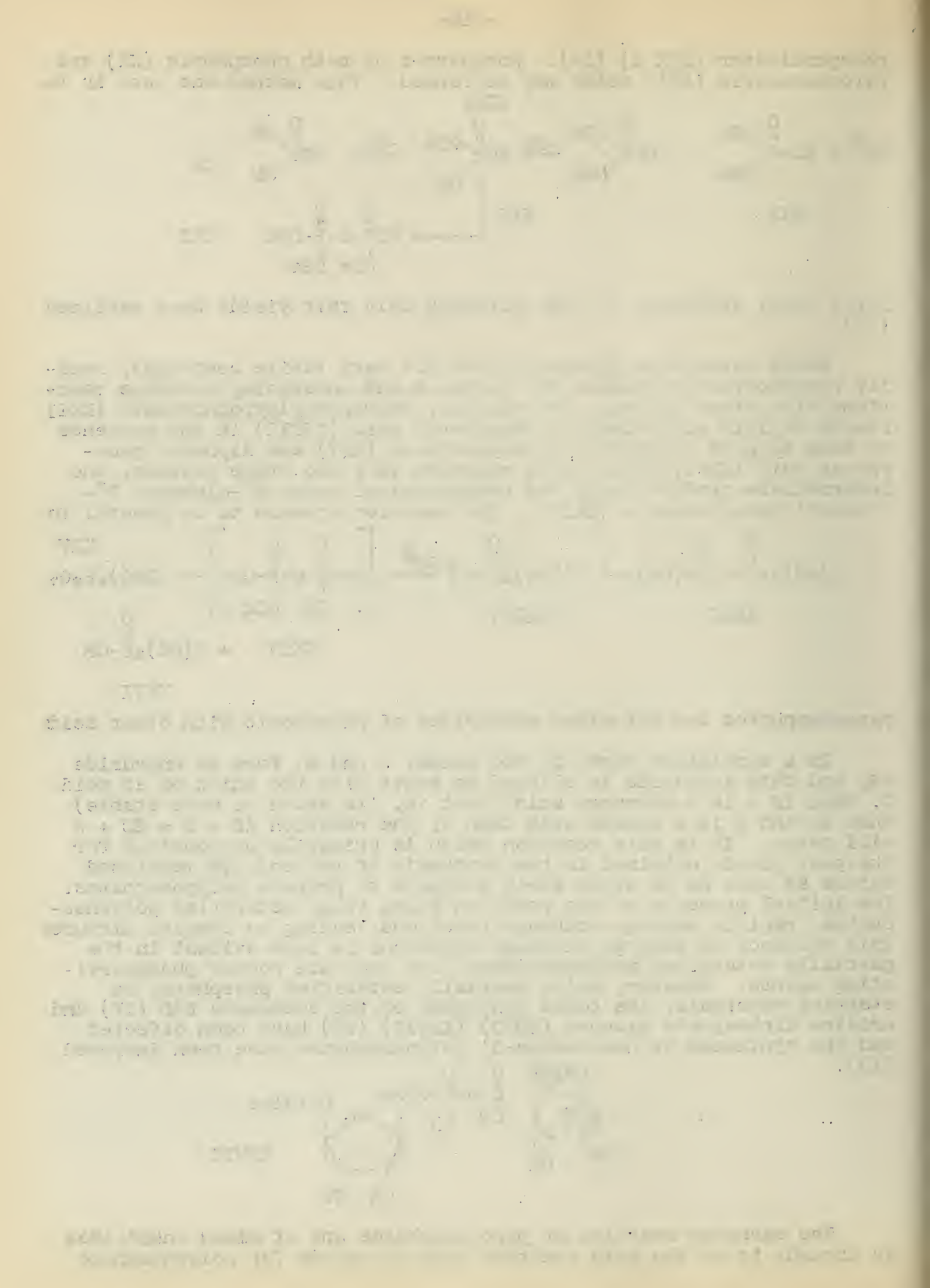


pyrophosphates and for mixed anhydrides of phosphoric with other acids

In a simplified form, if two acids, A and B, form an anhydride AB, and this anhydride is allowed to react with the anion of an acid C, then if A is a stronger acid (that is, its anion is more stable) than B, and C is a weaker acid than A, the reaction AB + C → BC + A will occur. It is this reaction which is primarily responsible for the poor yields obtained in the synthesis of ADP and ATP mentioned before as well as in other early attempts to prepare polyphosphates. The initial products of the reaction being fully esterified polyphosphates rapidly undergo exchange reactions leading to complex mixtures This tendency to undergo exchange reactions is less evident in the partially esterified polyphosphates, but they are poorer phosphorylating agents. However, using partially esterified phosphates as starting materials, the total syntheses of the coenzymes FAD (17) and uridine diphosphate glucose (UDPG) (XXVII) (18) have been effected and the syntheses of nucleoside-5' polyphosphates have been improved (19).



The exchange reaction of pyrophosphates and of mixed anhydrides is thought to be the main reaction used in nature for polyphosphate

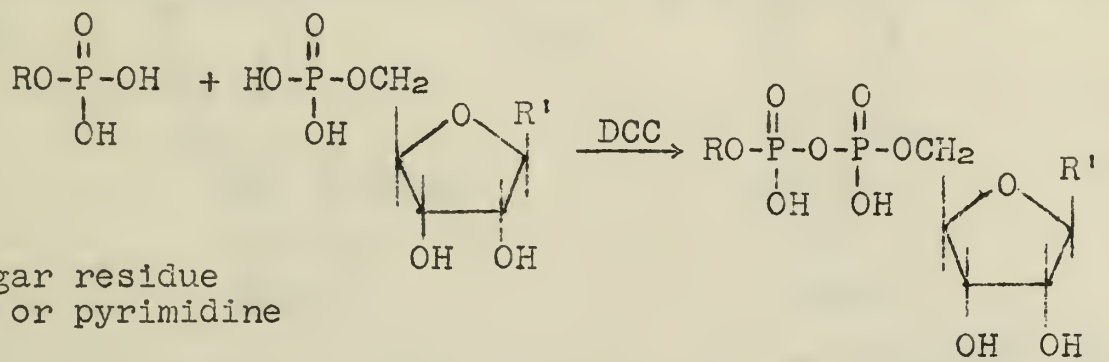


synthesis. The enzymatic synthesis of FAD from riboflavin phosphate and ATP is clearly a reaction of this type (20).

The phosphorochloridate route also has the disadvantages that the sugar hydroxyl groups must be protected when nucleoside phosphorochloroidates are employed and nonhydroxylic solvents must be used since phosphorochloridates react readily with alcohols and with water Thus there has been a search for reagents for synthesizing pyrophosphates from phosphates which might be used in the presence of water and without the need for protecting groups.

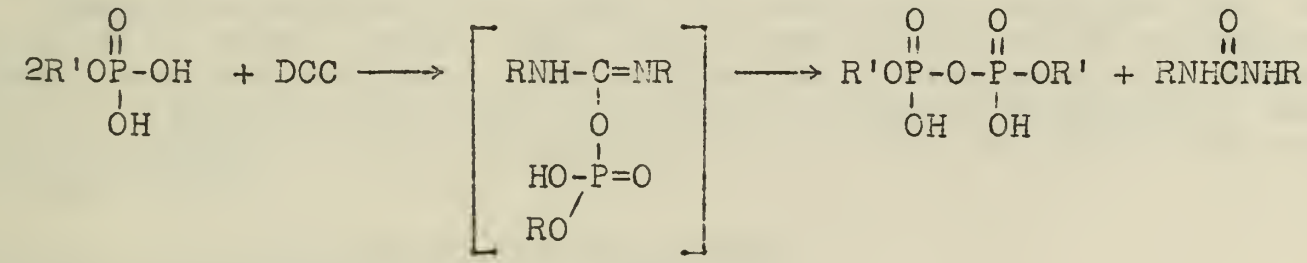
Carbodiimide Method for Pyrophosphate Synthesis

The dialkyl and diaryl carbodiimides (21) (RN = C = NR), of whic the dicyclohexyl (R = C_6H_{11}) (DCC) has been most commonly used, react with mono- and diesters of phosphoric acid to yield respectively di- and tetraesters of pyrophosphoric acid. Both polar and nonpolar



R=H or sugar residue
R'=purine or pyrimidine

media may be used and if excess DCC is used water may be present. The reaction appears to involve the addition of phosphate to the carbodiimide to give an intermediate of the type (XXVIII) which is then attacked by phosphate anion to give a pyrophosphate and the dialkyl urea. The overall reaction is very rapid and cannot be stopped

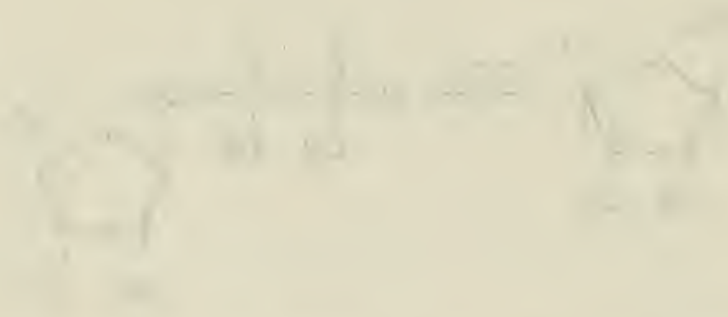


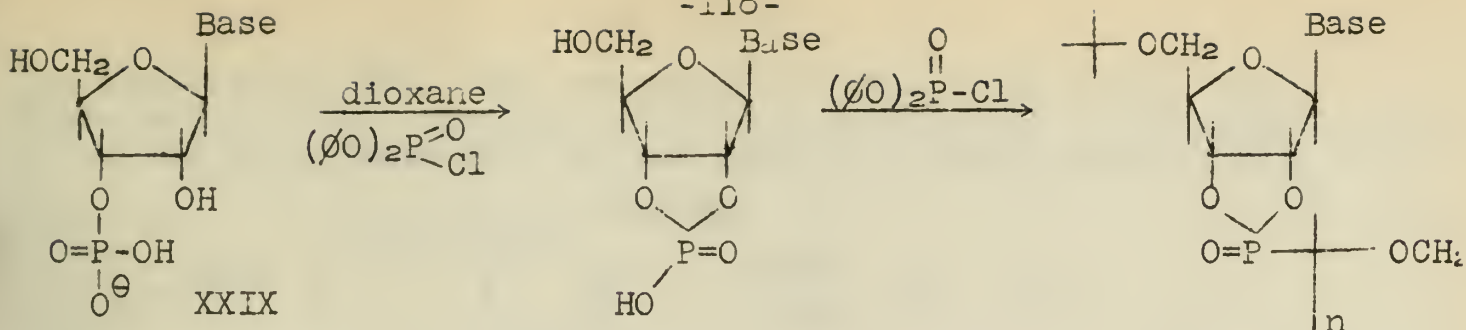
XXVIII

at the ψ-urea (XXVIII) stage; as a result, although the reaction is excellent for the synthesis of symmetrical pyrophosphates it usually lacks specificity in synthesizing unsymmetrical pyrophosphates of the nucleotide coenzyme type since treatment of a mixture of two different phosphates with a carbodiimide normally gives a mixture of all possible symmetrical and unsymmetrical pyrophosphates.

Synthesis of Polynucleotides

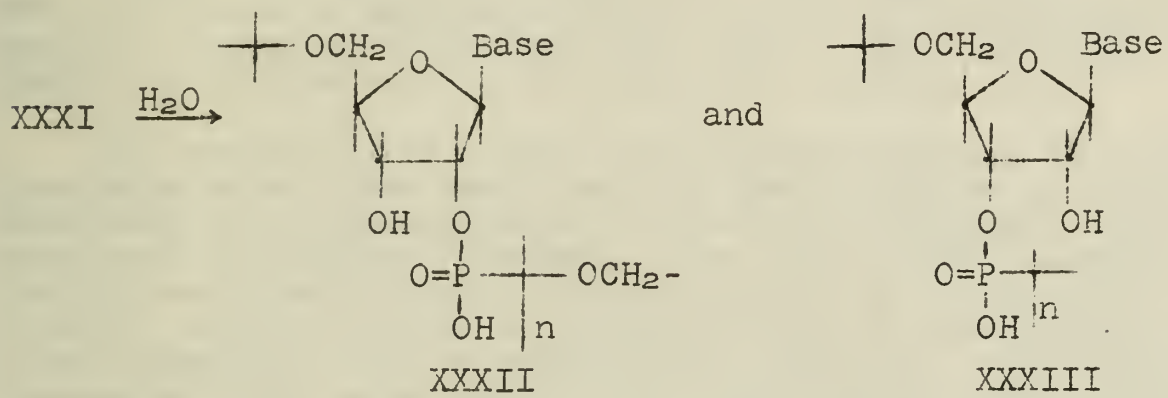
Michelson (22) has reported the preparation of a synthetic RNA, a polymer of ribonucleoside 2'- or 3'-phosphates. The nucleotides are easily converted to the nucleoside 2',3'-cyclic phosphate (XXX) by treating their tri-n-octylammonium salt (XXIX) with diphenylphosphorochloridate and tri-n-butylamine in anhydrous dioxane for one hour at room temperature. Further addition of diphenylphosphorochloridate





(or 2'-phosphate) XXIX XXX XXXI

to a concentrated solution of the nucleoside cyclic phosphate then caused rapid polymerization to yield (XXXI), which is hydrolyzed to the 2',5'-linked polymer (XXXII) and the 3',5'-linked polymer (XXXIII)



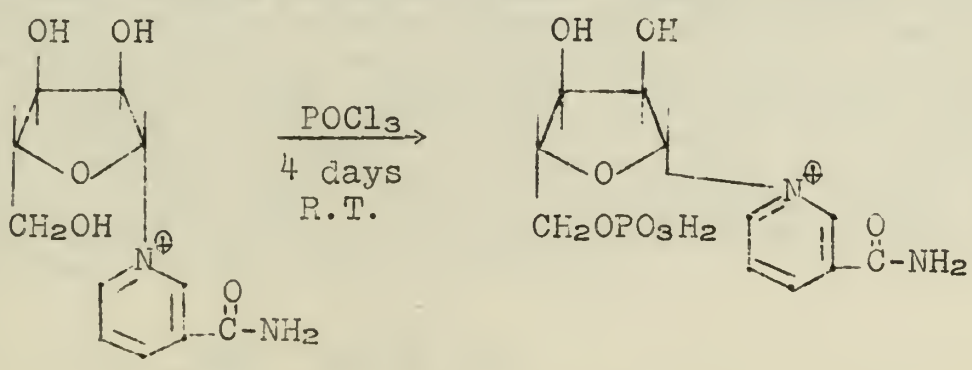
XXXII XXXIII

Polyadenylic acid, polyguanylic acid, and polyuridylic acid were prepared by this method, as were copolymers of the four major mono-ribonucleotides used in varying proportions. The copolymers, synthetic ribonucleic acids, were similar in several respects to yeast nucleic acid (23). The average chain length was 10-12 with the molecular species varying from six to twenty nucleotide units.

Chemical syntheses of a number of nucleotide coenzymes have been attempted in recent years. Both phosphorochloridate and carbodiimide methods have been employed, but neither has proved generally satisfactory. Exceptions are the syntheses of cytidine diphosphate choline (P^1cytidine-5'-P^2-choline pyrophosphate) (24) and of DPN by the carbodiimide method.

Synthesis of Diphosphopyridine Nucleotide

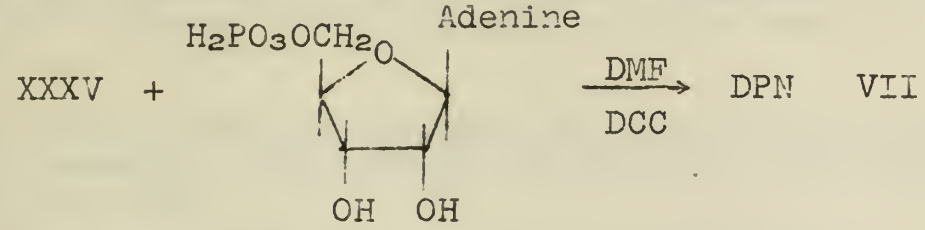
Nicotinamide nucleoside (XXXIV), which was prepared previously by Todd (25), was converted by phosphorylation with phosphoryl chloride to its 5'-phosphate (nicotinamide nucleotide) (XXXV). The nucleo-



XXXIV XXXV

tide was then condensed in DMF solution with adenosine-5' phosphate in

the presence of DCC. DPN was formed in about 50% yield, with diadenosine 5'-pyrophosphate and di-(nicotinamide nucleoside-5') pyro phosphate being separated by ion exchange chromatography (26).



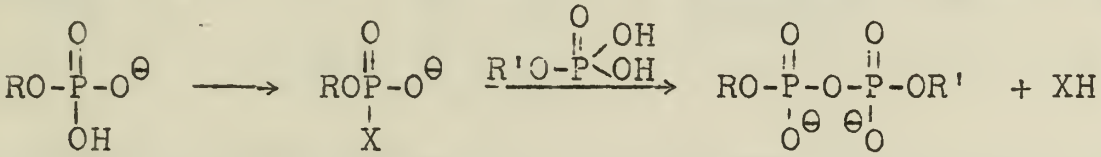
Synthesis of Triphosphopyridine Nucleotide

Using a procedure analogous to that used for the synthesis of DPN, a mixture of adenosine-2',5' and -3',5' diphosphates gave a product containing about 15% TPN (VIII), thus achieving the first non enzymatic synthesis of this important coenzyme (26).

The carbodiimide method for the condensation of unprotected phosphate esters has been used for the synthesis of a number of nucleoside-5' polyphosphates, nucleotide coenzymes, and related compounds of biological interest. The experimental conditions for effecting condensation have varied greatly with different nucleotides, however, and the yields of desired products have seldom been good. Other reagents, such as ketenimine, cyanamide, and the dialkylcyanamides (27), were studied but they shared with the carbodiimides the disadvantage of producing mixtures of products when applied to unsymmetrical pyrophosphate synthesis.

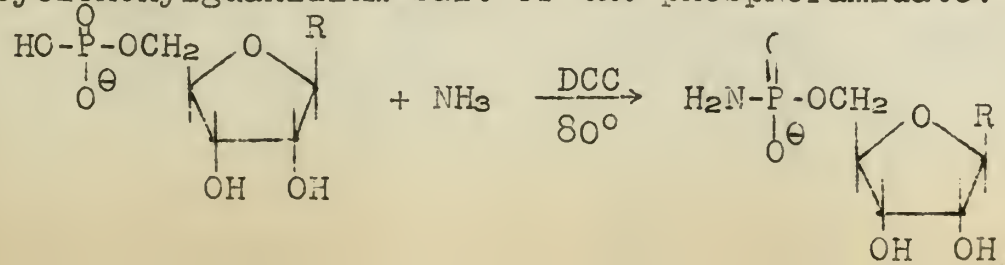
Phosphoramidate Method for Synthesizing Unsymmetrical Pyrophosphates

The specific synthesis of unsymmetrical pyrophosphates using phosphoramidic acid (XXXVI) (X=NH_2) and its derivatives has recently been investigated with great success by Khorana and his coworkers (28)

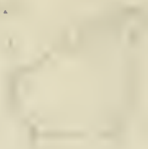


XXXVI

If one of the reactants is converted to a derivative of the general type (XXXVI), the P-X linkage being highly reactive and the phosphorous atom being rendered electrophilic, then pyrophosphate synthesis can be effected through anionic attack (phosphorolysis) on (XXXVI) by phosphoric acid or another phosphomonoester. The nucleoside-5' phosphoramidates (XXVII), key intermediates in the unsymmetrical pyrophosphate synthesis, were synthesized in 80-90% yield by a one-step reaction in which the nucleoside-5' phosphate is treated with ammonia in the presence of DCC in a solvent system of formamide-water-t-butyl alcohol at 80° (29). The dicyclohexylurea formed is further modified by excess ammonia, the final product being the dicyclohexylguanidium salt of the phosphoramidate.



XXXVII



Synthesis of ADP and UDP

The reaction between adenosine-5' phosphoramidate (XXXVII, R= adenine) and excess 85% H_3PO_4 in o-chlorophenol at 0° for three hours yields ADP in about 50% yield with no side reactions being observed (29).

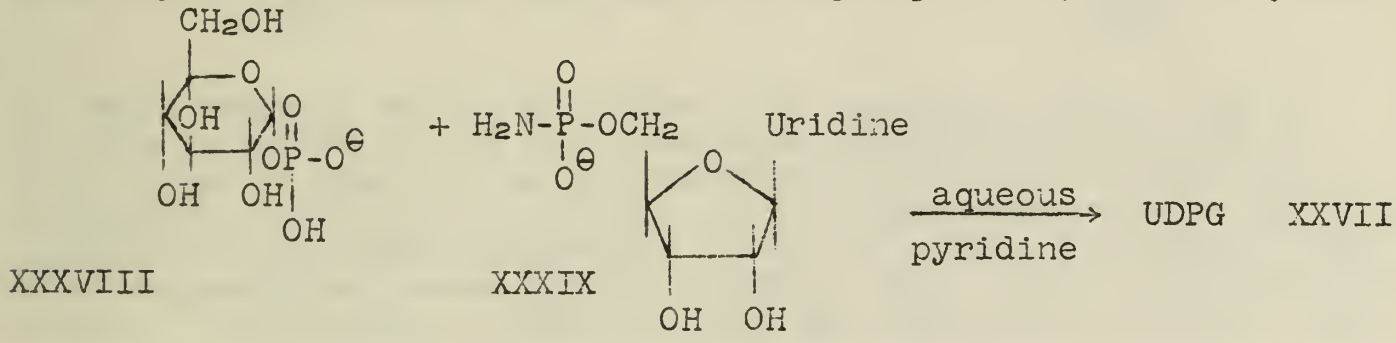
The dicyclohexylguanidinium salt of uridine-5' phosphoramidate (XXXVII, R=uracil) was reacted for one hour with 85% H_3PO_4 to form UDP in 50% yield (30).

The synthesis of cytidine-5' phosphoramidate, guanosine-5' phosphoramidate, their corresponding diphosphates and studies on nucleoside-5' triphosphate synthesis by the amidate procedure are to be reported in the near future.

Synthesis of UDPG and FAD

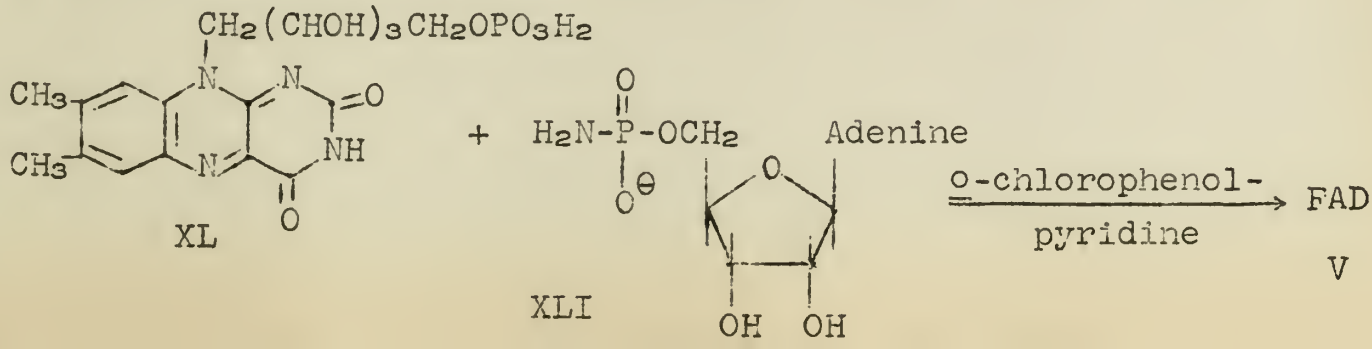
The phosphoramidate method has been used to synthesize two nucleotide coenzymes, UDPG and FAD (31). These two compounds, which have been the foci of much previous synthetic work, were considered to provide stringent tests of the superiority of the phosphoramidate method over the existing ones.

An excess of the mono-(trioctylammonium) salt of α-glucose-1-phosphate (XXXVIII) was reacted with dicyclohexylguanidinium uridine-5' phosphoramidate (XXXIX) in aqueous pyridine at room temperature for four days. The desired UDPG was the major product, with only small



amounts of uridine-5' phosphate and of the symmetrical pyrophosphates being present. A 59% yield was reported after purification, the material being completely biologically active (32). This procedure should also be applicable to the synthesis of related compounds, e.g., uriding diphosphate glactose and uridine diphosphate acetylglucosamine

The synthesis of FAD was effected by mixing an excess of riboflavin-5' phosphate (FMN) (XL) with dicyclohexylguanidinium adenosine-5' phosphoramidate (XLI) in an o-chlorophenol-anhydrous pyridine solvent system for four days at room temperature. The reaction products were separated on a diethylaminoethyl (DEAE) cellulose column, FAD being isolated in 40% yield.

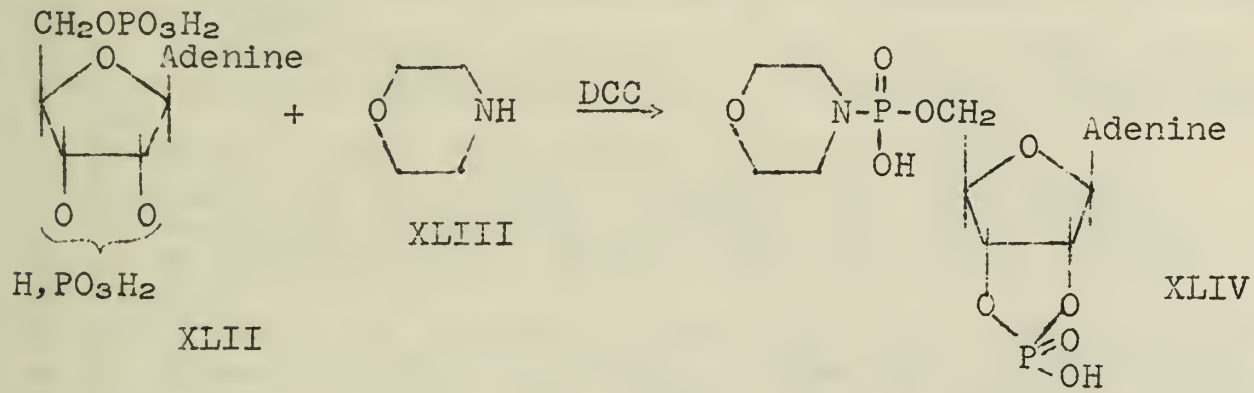


Synthesis of Coenzyme A

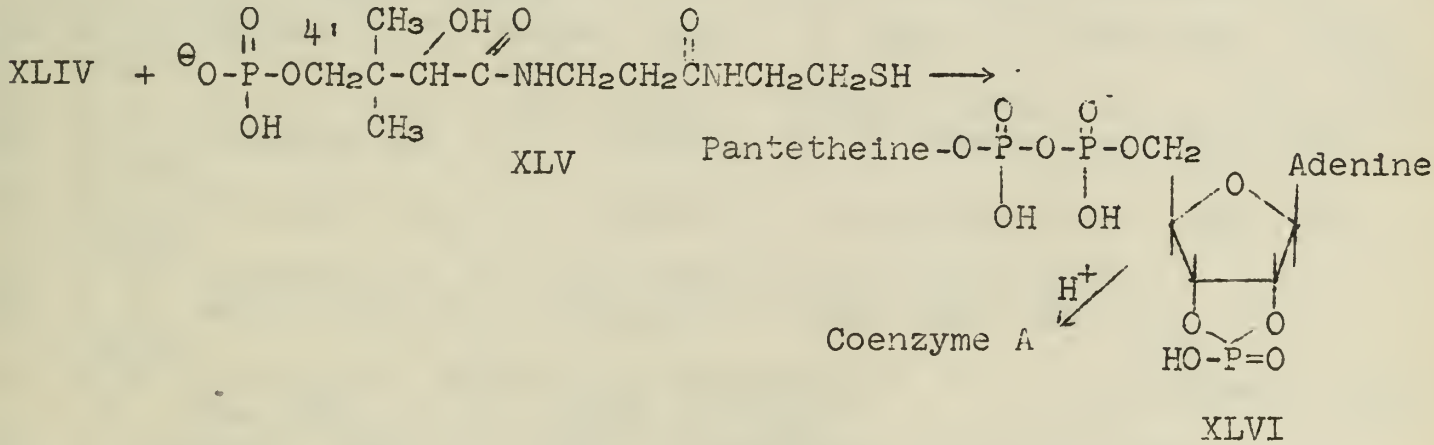
Since its discovery (33), Coenzyme A (VII) has been the center of intensive chemical and biochemical research. The substance is now known to occupy an important position as a mediator of biosynthetic reactions.

In a recent preliminary communication (34), Moffatt and Khorana record the total synthesis of this complex molecule. The basic approach used to synthesize the pyrophosphate bond is that used in the synthesis of UDPG and FAD. However, nucleoside phosphoromorpholidate (as XLIV), because of their greater reactivity and solubility in organic solvents, were reported to be superior to phosphoramidates and were used in their place.

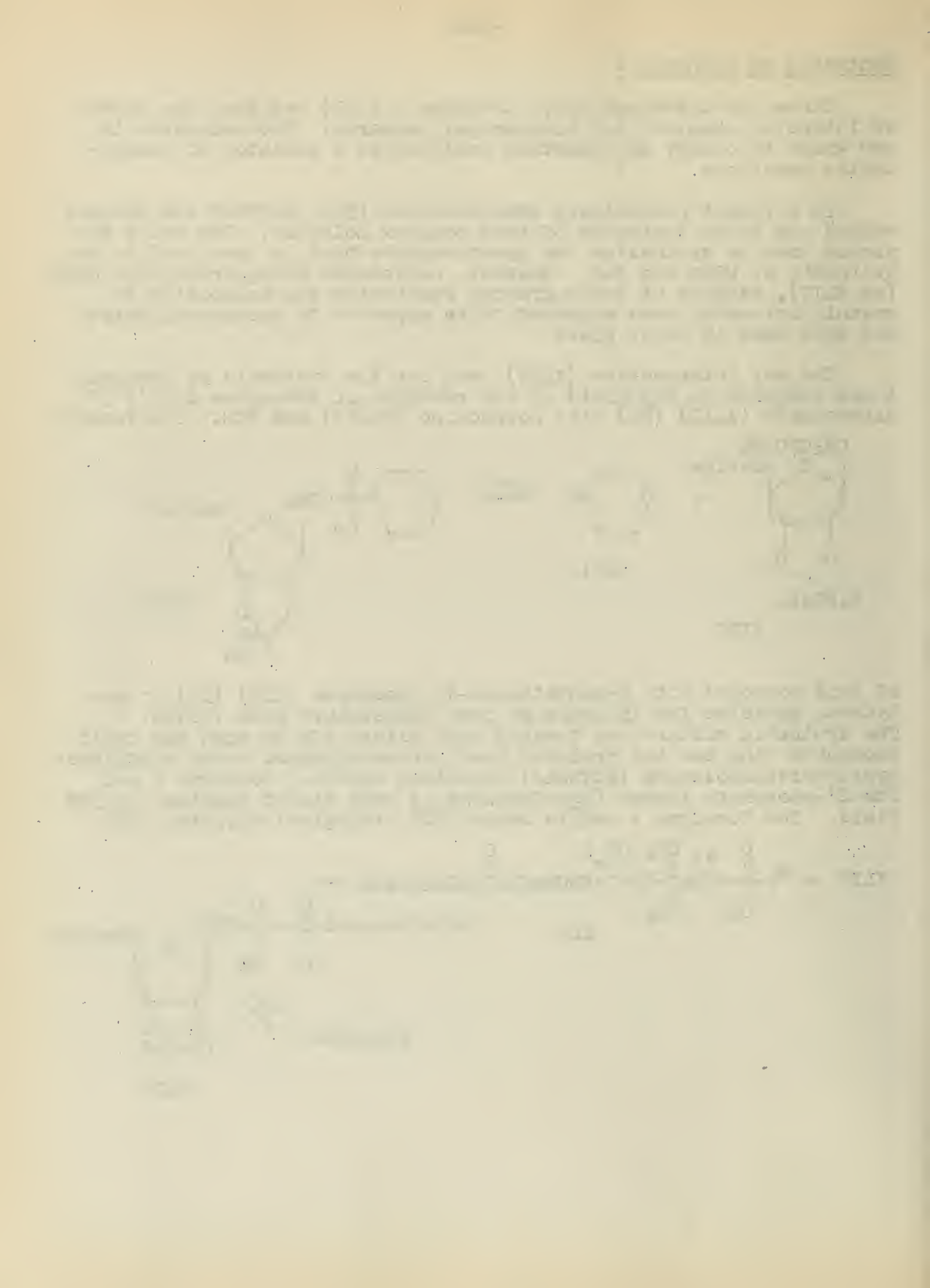
The key intermediate (XLIV) used for the synthesis of Coenzyme A was prepared in 98% yield by the reaction of adenosine-2'(3')-5' diphosphate (XLII) (35) with morpholine (XLIII) and DCC. The reactio



of this compound with D-pantetheine-4' phosphate (XLV) (36) in anhydrous pyridine for 15 hours at room temperature gave (XLVI). The synthetic mixture was treated with dilute HCl to open the cyclic phosphate ring and the products then chromatographed on an epichlorohydrintriethanolamine (ECTEOLA) cellulose column. Coenzyme A and its 2'-phosphate isomer (iso-Coenzyme A) were eluted together in 50% yield. The Coenzyme A sample showed 86% biological activity (37).



XLVI



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CONFORMATION ANALYSIS OF BICYCLO (2.2.1)HEPTANE ALCOHOLS

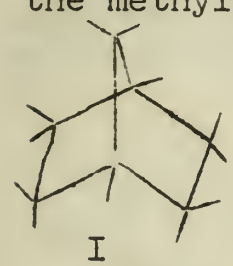
Reported by M. J. Konz August 3, 1959

THE BICYCLO(2.2.1)HEPTANE RING SYSTEM

The present seminar will deal essentially with the determination of the configuration of the bicyclo(2.2.1)heptane-2-ols.

A consideration of a model of bicyclo(2.2.1)heptane (I) shows two important effects caused by the 1,4 methylene bridge. One effect is that hydrogen atoms in "axial" (endo) and "equatorial" (exo) are eclipsed. Subsequently, when a hydrogen is replaced by a larger substituent, there should be non-bonded steric interaction. However the larger interaction should be between the endo substituents. Steric interaction between exo groups and methylene hydrogens would appear to be negligible. Thus, β-norborneol (II) should be more stable than its endo isomer, α-norborneol (III)(1). But when the bridge is substituted, as in borneol (IV) and isoborneol (V), the stability should be reversed due to the interaction between the cis bridge methyl and the exo hydroxyl group. The second effect is the deformation of the valence angle caused by the bridging. Essentially, a substituent at the bridge head is deflected and alters the properties of a hydroxyl group in an exo position as degree of association and saponification velocities. Undoubtedly, the best chemical evidence for this is the work by Kuusinen and Lampinen (2). Exo-2-oxyapocamphane-1-carboxylic formed with chloral the chloralid (VI) and a small amount of a tricyclene acid. On the other hand, under the same conditions, the endo-oxy acid remained unchanged. With acetone, the exo-2,10-camphanediol and exo-10-oxyfenchol formed the acetals (VII) and (VIII). Again, the endo diols did not react. However p-nitrobenzaldehyde reacted with both endo and exo diols forming the corresponding acetals. But of these the endo-2,10-camphanediol (IX) and endo-10-oxyfenchol (X) was easier to hydrolyze than the repective exo acetals, suggesting more ring strain in the endo compounds.

This situation cna be explained by a deformation in the valence angles in the exo compounds showing the distortion brought about by the methylene bridge.



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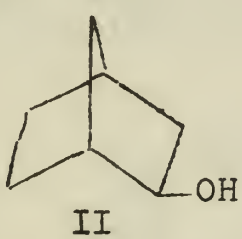

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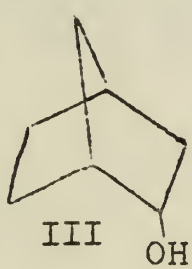

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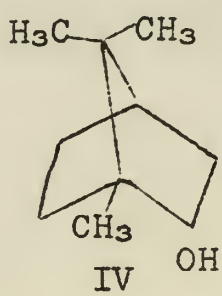

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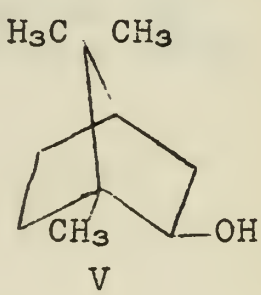

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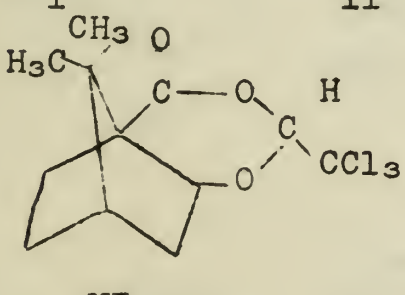

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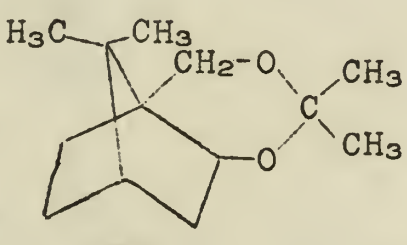

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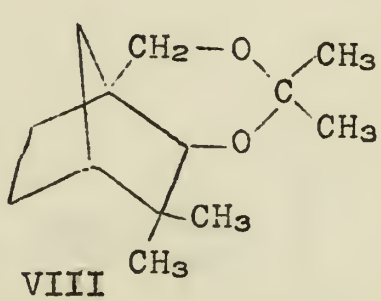

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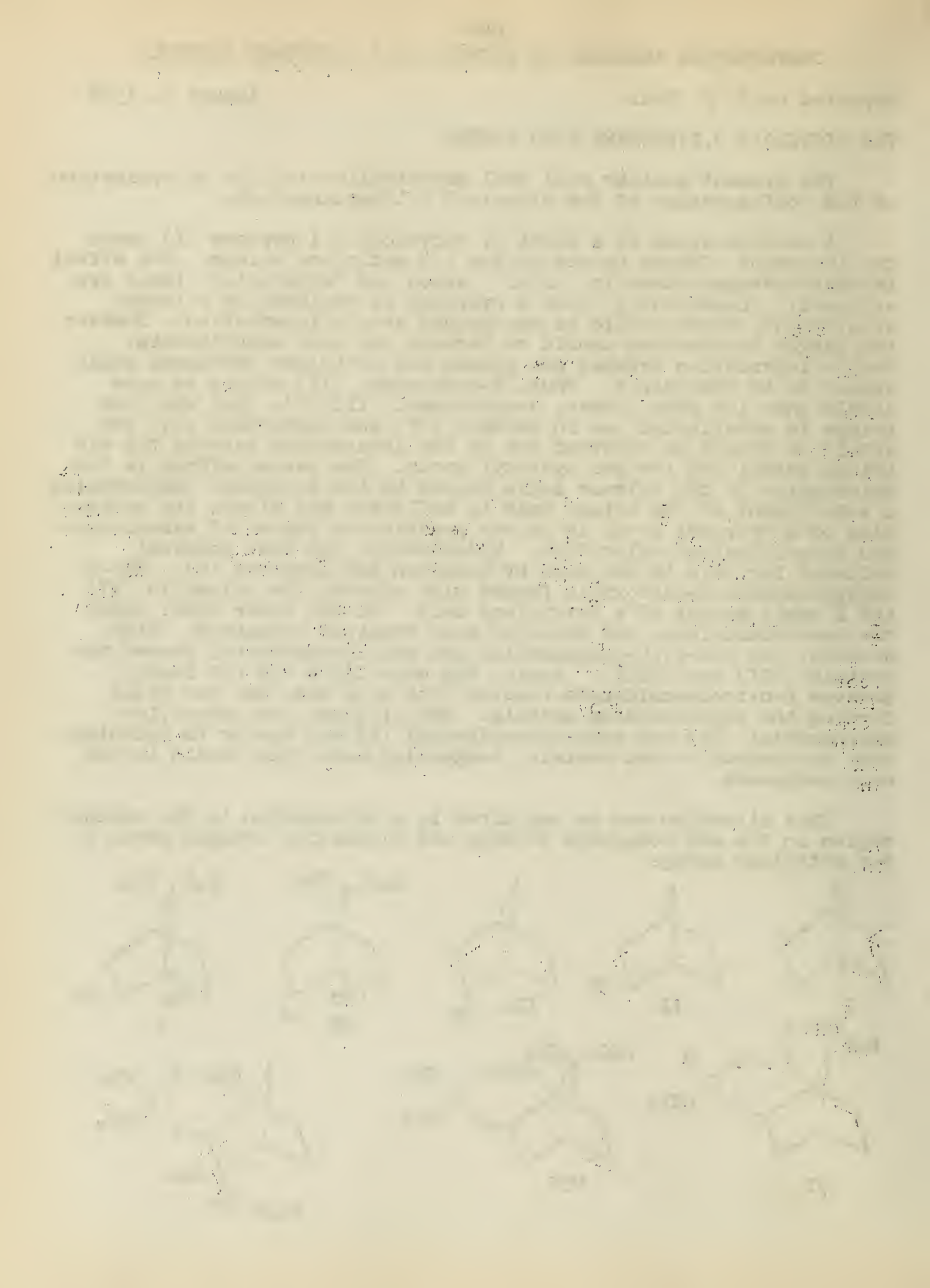

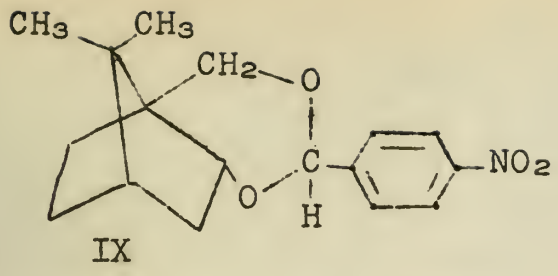

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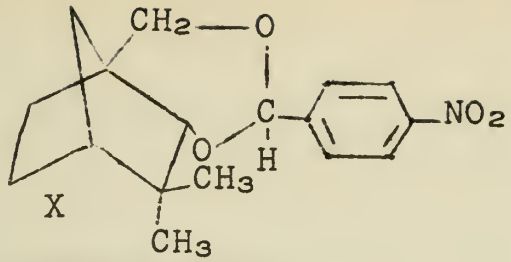


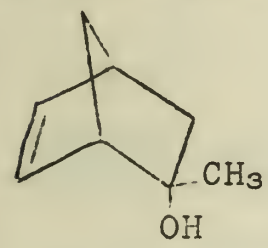
X

CHEMICAL MEANS OF DETERMINATION OF CONFIGURATION

Use of cyclic derivatives:

A first general method consists of oxidizing the alcohol to the corresponding hydroxy-cyclopentane-1,3-dicarboxylic acid and then attempt at formation of a lactone. Two examples in the literature are the 2-CH_3 norborneols and the fenchols.

A mixture of 2-CH_3 dehydronorborneols was obtained by the addition of isopropenyl acetate to cyclopentadiene (3). The mixture was then separated by means of the hydrogen phthalic acid esters. The two isomers were separately treated with permanganate (4) and each was shown to form a cis dicarboxylic acid by anhydride formation. The dicarboxylic acid (XIII) formed from XI gave upon heating a γ lactone (XV) while the dicarboxylic acid (XIV) from XII did not form a lactone. Since the two substituents must be cis to each other for lactone formation, the alcohol, which also predominated in the diene synthesis, must have an endo configuration and the other alcohol an exo configuration.



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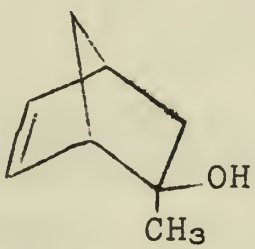

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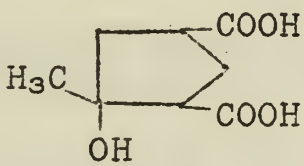

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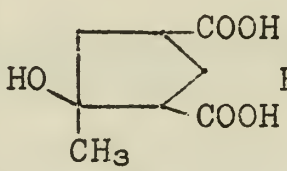

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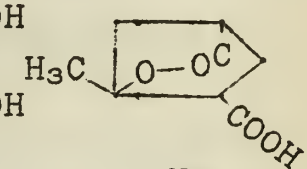
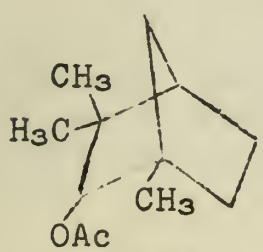


XV

Similarly, the configurations of α- and β-fenchol (XVI, XVII) were ascertained (fig. 1). Again, the acid derived from the endo alcohol formed the lactone, but in this case a β lactone was formed.



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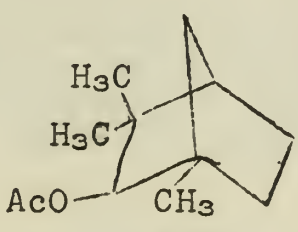

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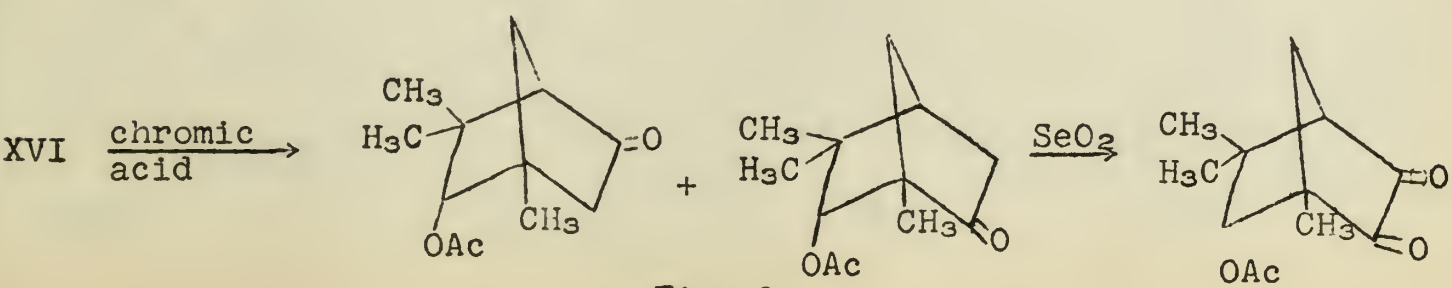
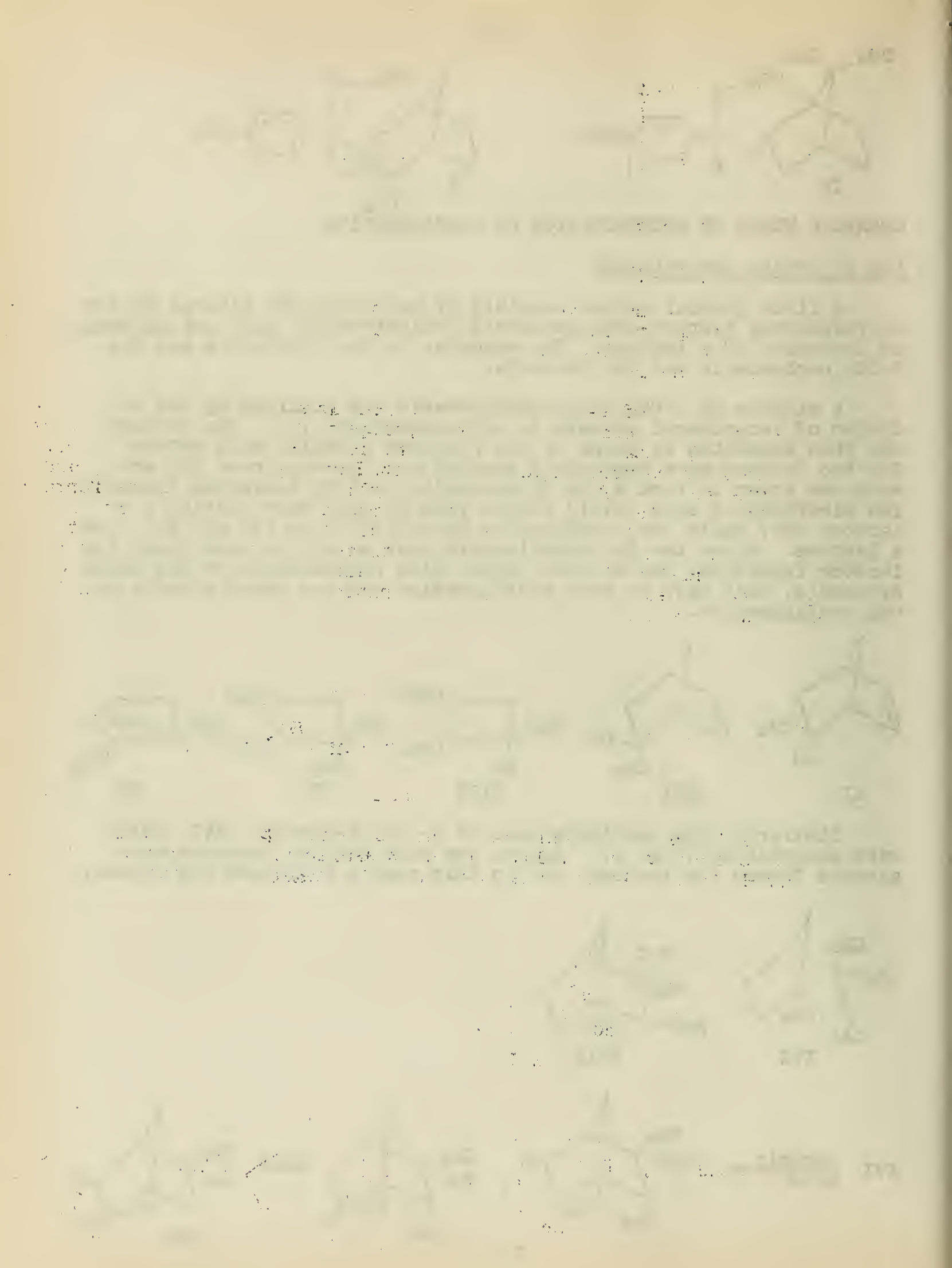
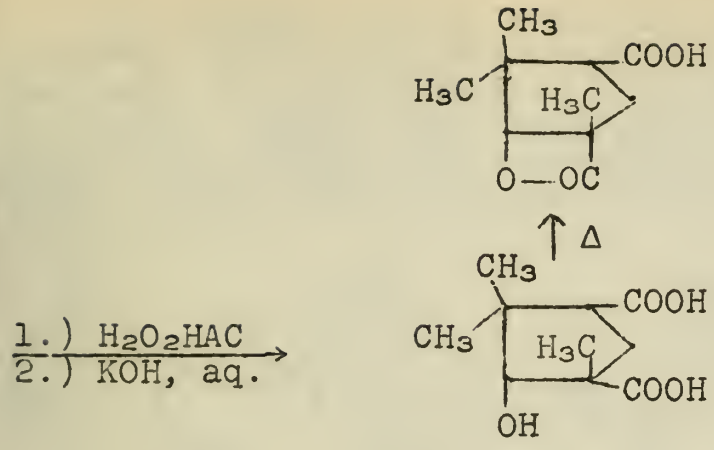


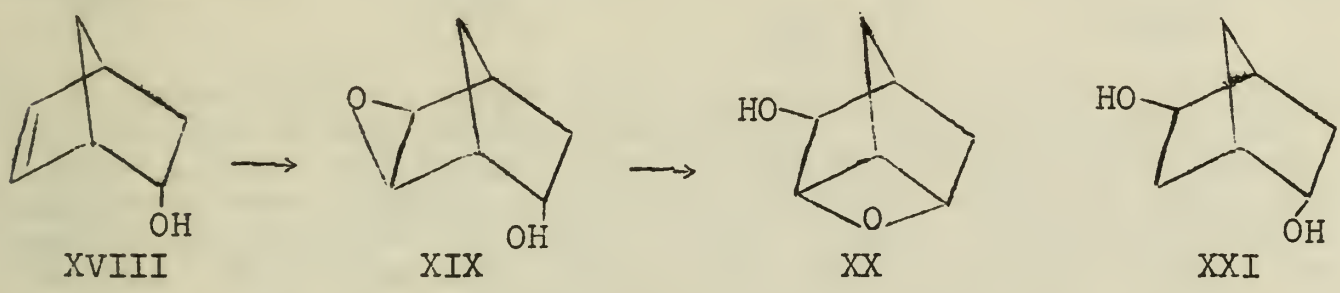
Fig. 1





The configuration of isoborneol has also been established by a lactonization as described in many text books.

Henbest (5) has definitely established the configuration of α-norborneol, not by lactonization but by treatment of XVIII with perbenzoic acid to form the epoxide XIX. This was identical with that formed from the acetate of XVIII. The epoxide XIX was then treated with potassium tert-butoxide to form XX. Both XIX and XX gave the same diol XXI upon reduction with $LiAlH_4$, thus confirming the endo configuration.

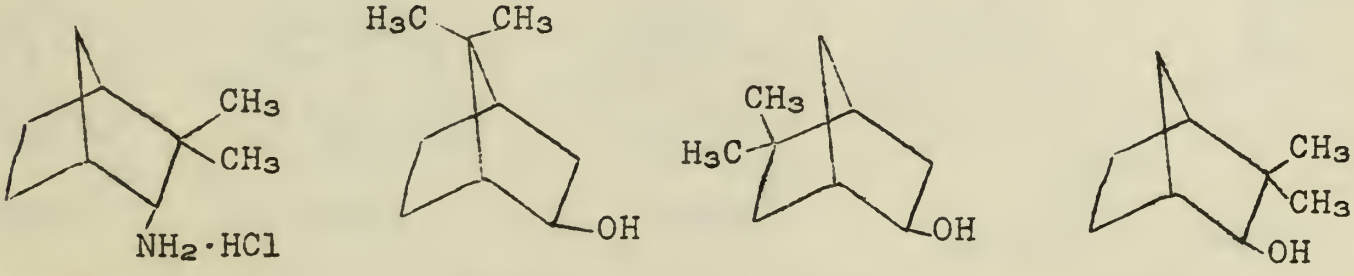


XVIII XIX XX XXI

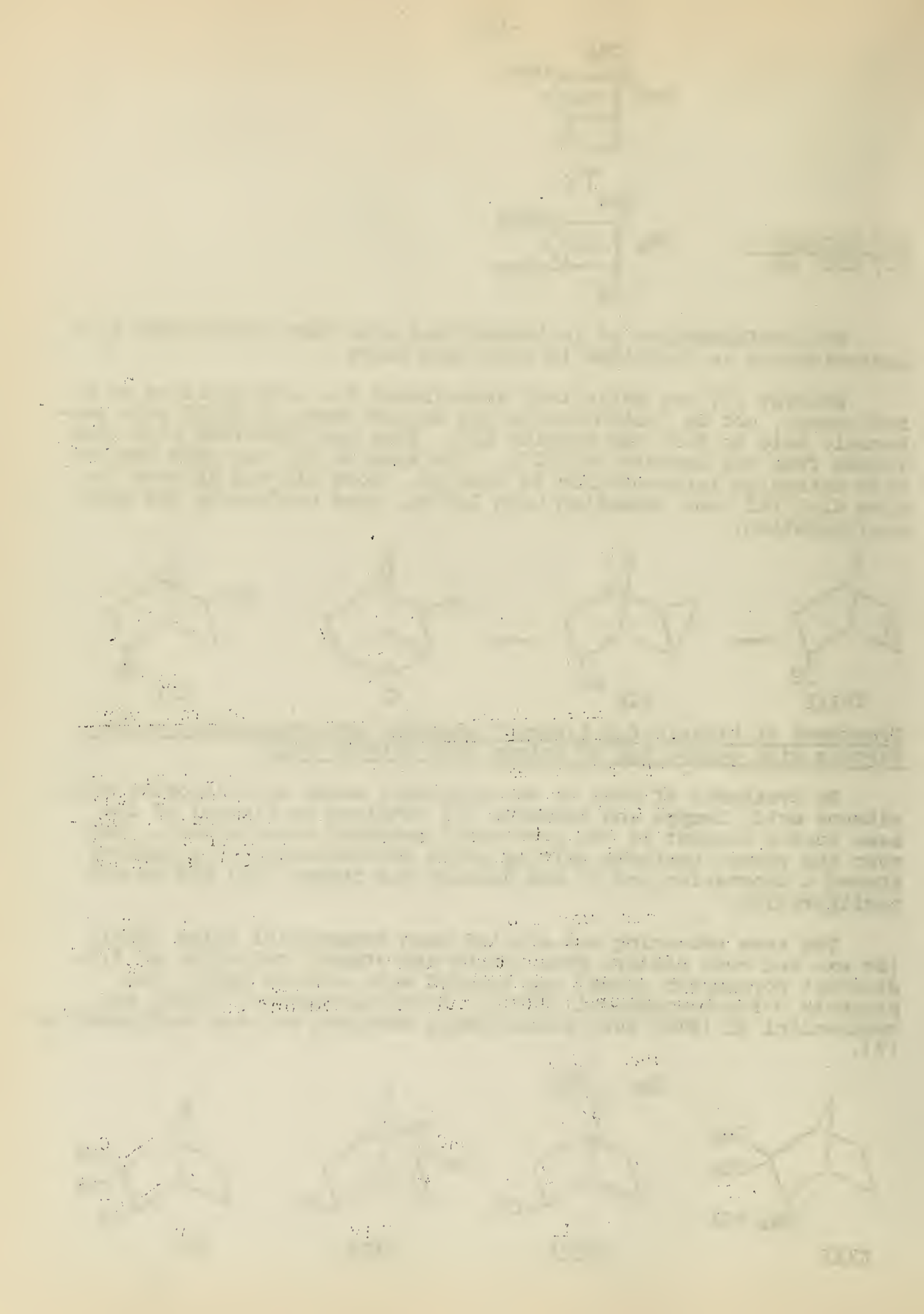
Treatment of bicyclo(2.2.1)heptyl alcohols and unsaturated hydrocarbons with acids, and of amines with nitrous acid:

By treatment of endo or exo norbornyl amine hydrochloride with nitrous acid, Komppa and Beckmann (6) obtained an alcohol of the same carbon content as the previously prepared α-norborneol. However the phenyl urethane melting point determination of a mixture showed a depression and it was assumed the isomer (II) had an exo configuration.

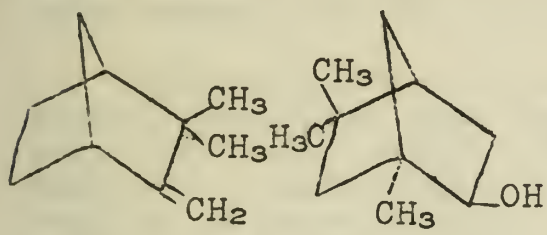
The same reasoning was applied when camphenilyl amine (XXII) (an exo and endo mixture from sodium and ethanol reduction of 3,3-dimethyl norcamphor oxime) was treated with nitrous acid. The products α-fenchocamphorol (XXIII), β-fenchocamphorol (XXIV) and camphenilol II (XXV) were subsequently assigned and exo configuration (7).



XXII XXIII XXIV XXV

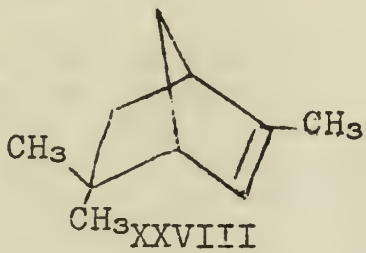


In analogy to the formation of isoborneol by treatment of camphene (XXVI) with acetic-sulfuric acid solution (8,9), other alcohols have been assigned a similar configuration. For example, α-isofenchol (XXVII) was obtained from γ-fenchene (XXVIII) (10), 1-CH_3 norborneol (XXIX) from norcamphene (XXX) (11), and α- and β-santenols (XXXI, XXXII) from endo and exo isosantene (XXXIII, XXXIV) (12).



XXVI

XXVII



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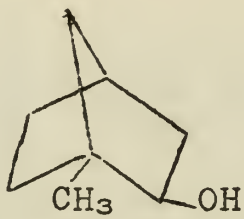

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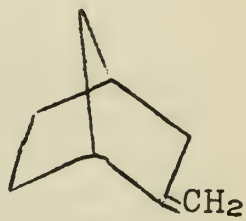

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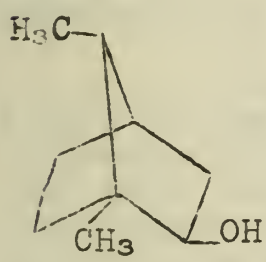

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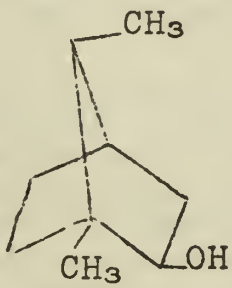

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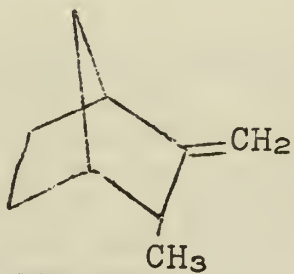

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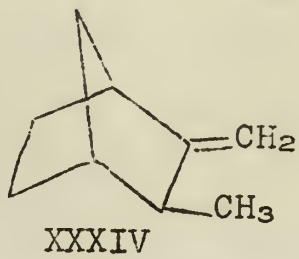
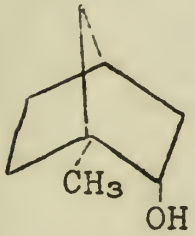


XXXIV

H. Toivonen (13) has shown that concentrated nitric acid oxidizes the endo alcohol to the ketone, and converts the exo isomer to the nitrate ester. The known optically inactive isomer pair borneol and isoborneol were treated at room temperature. From the endo isomer, camphor was isolated and from the exo isomer a nitric acid ester was obtained. The ester was reduced with Devarda's alloy (Al,Cu,Zn) in alcoholic potassium hydroxide to yield the original alcohol. Alkaline hydrolysis however gave the hydrocarbon camphene (XXVI). The 1-CH_3 norborneols (XXIX, XXXV) (14) were treated in the same manner and the results were the same, thus they were assigned an exo and endo configuration.

Optically active α- and β-isofenchol (XXXVI, XXXVII), α- and β-fenchol (XVI, XVII), and β-fenchenhydrate (XXXVIII) were similarly treated. Ketones were formed from β-isofenchol and α-fenchol, and nitrate esters from α-isofenchol, β-fenchol and β-fenchenhydrate. In each case, reduction of the esters gave α-isofenchol. Alkaline hydrolysis of the α-isofenchol and β-fenchol esters gave the same product, β-fenchenhydrate. Since there is formation of one single nitrate ester from the three alcohols, it is certainly pointing to a cyclopropyl intermediate or to cyclopropane like non-classical ion.



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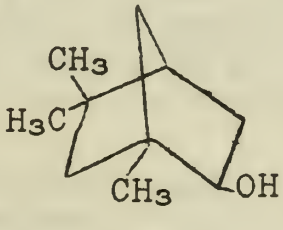

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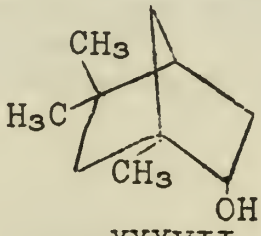

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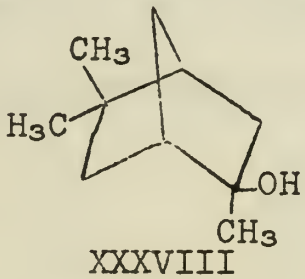
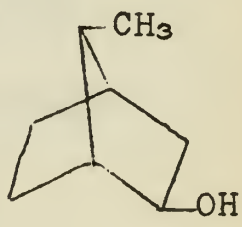


XXXVIII



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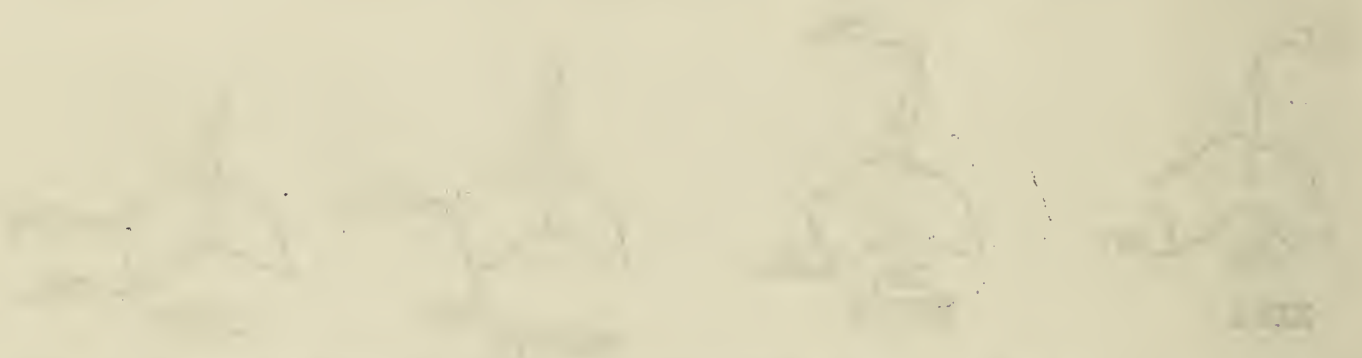


Solvolysis, saponification, catalytic reduction, equilibration:

These topics are considered together because each illustrates the effect of the ring structure and methyl substituents upon the chemistry of the alcohols. From the illustrations, one may be able to conclude the configuration and possibly extend these methods to other members of this series.

The classical work of Winstein's (15) and Robert's (17,18) schools has shown that the exo halides or substituted benzoates are solvolyzed more rapidly than their endo isomers. This has been the basis of a considerable amount of rationalization in terms of intervention of non-classical ions as discussed in recent textbooks (19). The alcohols obtained on solvolysis are identical with those obtained by hydration of olefins or nitrous acid deamination, pointing to a similarity in the last stages of the mechanisms involved (16).

Since the saponification rates seem to be dependent on accessibility to the functional group, any steric effects caused by substituents in the molecules should be evident. In the norborneols (II, III) (20), which contain no large substituents, the endo hydroxy group should be more hindered than in an exo position and consequently should be saponified at a slower rate. The experimental evidence, Table I, indicates there is very little difference between the isomers and a conclusion can't be made with certainty. The effect of methyl groups at the bridgehead and on the bridge methylene carbon atom should however have more of an influence. As was shown previously, there is a deformation of the valence angle caused by the 1,4 bridge. Therefore a methyl group at the bridgehead should have somewhat of a shielding effect on an exo hydroxyl function. Models indicate a similar protective influence by a methyl group on the bridge methylene carbon atom which is cis to the exo hydroxyl group. Thus it would appear, endo 1-CH_3 norborneol would be saponified at a faster rate than the exo isomer and slower than norborneol itself. The same would be expected of cis-7-CH_3 norborneol (XXXIX) (isosposantenol). The steric effect is further seen in isoborneol and borneol.

Alder and Stein (21) conducted an investigation of catalytic reduction of carbonyl groups in bicyclo(2.2.1)heptanones. From their studies, they concluded hydrogen addition was exo in the unsubstituted ring structure. By this method, α-norborneol was obtained (6) from norcamphor using platinum in acetic acid.

TABLE I

Saponification rate constants of acid phthalic esters (k, liter·mole^{-1}·min.$^{-1}$) and degree of association of alcohols expressed as percent molecular wgt. elevation (0.06 mol./100 g. benzene)

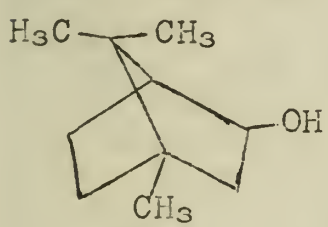
	$k_{40} \cdot 10^2$	Deg. of Assos.
α-norborneol (endo).....	5.8	56
β-norborneol (exo).....	5.6	58
exo-3-CH_3-norborneol (endo).....	5.3	59
5,5-dimethyl-norborneol..... (iso β-fenchocamphorol)	3.5	54
1-CH_3-norborneol (endo).....	2.1	43
1,7,7-trimethyl-norborneol (endo). (Borneol)	1.45	44

cis-7-CH_3-norborneol (exo).... (Isoaposantenol)	1.1	41
endo-3-CH_3-norborneol (endo)..	0.62	25
1-CH_3-norborneol (exo).....	0.59	32
3,3-dimethyl-norborneol (endo) (Camphenilol II)	0.47	33
1,3,3-trimethyl-norborneol (endo) (α-fenchol)	0.10	19
1,7,7-trimethyl-norborneol (exo) (Isoborneol)	0.074	24

Later Vavon and Peignier (23) investigated the camphor series and concluded that if the ketone is sterically hindered more "cis" isomer would result from the catalytic reduction. Thus isoborneol was obtained from camphor, epi-isoborneol (XXXX) from epicamphor (24), and 3,5-cycloisoborneol (XXXXII) from cyclocamphanol (26).

This same steric control was observed in reduction of the carbonyl groups with $LiAlH_4$ (26).

Equilibration experiments have been attempted to determine the more stable isomer and thus indirectly the configuration (25). From the controlled catalytic reduction and from reduction with sodium and ethanol, the isomeric alcohols of camphor, epi-camphor, and cyclocamphanone were produced. It was found sodium and ethanol had no effect on the proposed endo isomers but those from catalytic reduction were isomerized to the endo isomer. Thus it is seen, substitution on the bridge methylene carbon atom causes the exo isomer to be less stable than the endo isomer (XXXXI, XXXXIII).



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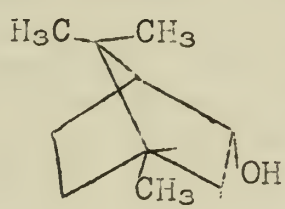

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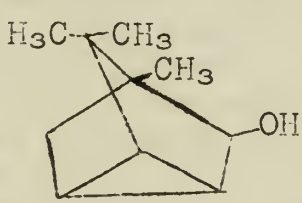

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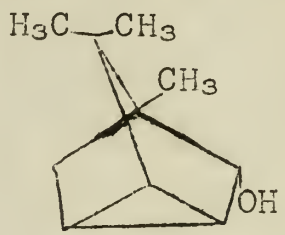


XXXXIII

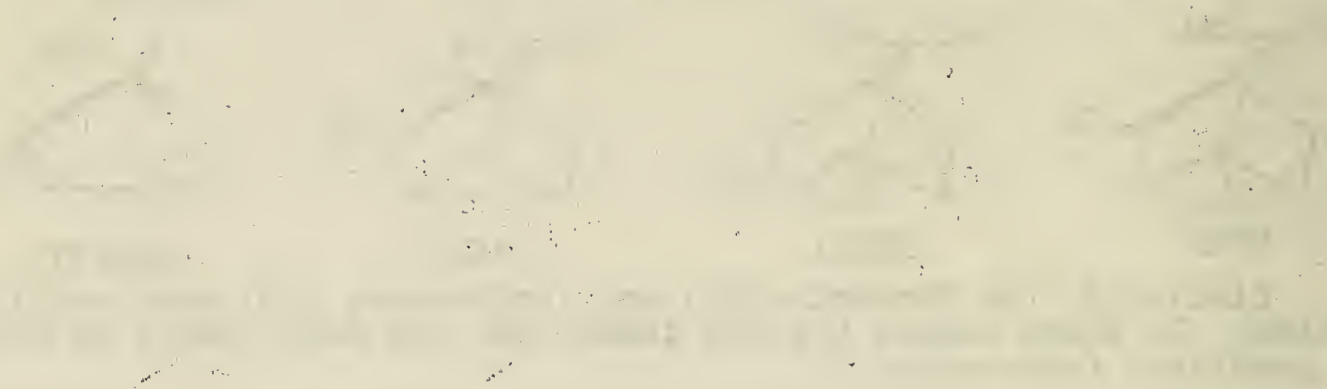
Similarly, the fenchols (27) and isofenchols (28) were equilibrated. In these cases. the exo isomer was the most stable as would be predicted from models.

Alkaline reduction:

In the examples through out the abstract, the reduction of the ketone with sodium and ethanol gave predominanty the endo or "axial" alcohol. The reduction of fenchone gave a ratio of 9 to 1 of α- to β-fenchol (26), and in epicamphor (24), the exo isomer was barely detectable. It is interesting that in chair form cyclohexanes, the equatorial hydroxyl predominates on alkaline reduction and is the more stable isomer. However, in the bicyclo (2.2.1)-heptanones, reduction gave the endo isomer and the stability seems to be dependent on the substituents in the ring structure.

The Diene synthesis:

The condensation of cyclopentadienes with methyl acrylates and vinyl acetates (12,22,31,32,33,34) have resulted in the theory that the functional group is in the endo position.



These condensations do not give in the majority cases sterically pure product. That of cyclopentadiene and vinyl acetate has been shown by infrared analysis to be 75.3% endo dehydronorborneol acetate and 24.7% of the other isomer (35). The only instance where no exo isomer has been reported was in the synthesis of borneol and epiborneol (32).

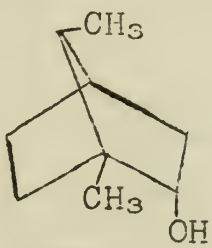
In one case, Mälkönen and Toivonen (36) have shown the synthesis of 2-CH_3 dehydronorborneol acetate was temperature dependent. The higher the temperature the more exo acetate was formed. This may be the case of others and therefore it is doubtful whether this is a reliable method for determination of configuration.

PHYSICAL MEANS OF DETERMINATION OF CONFIGURATION

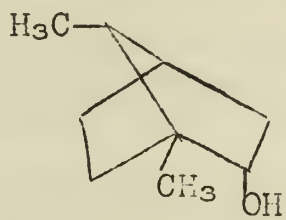
Percent molecular weight elevation:

The degree of association, as in saponification velocities, is dependent on the structure of the molecule. The same considerations should be applicable here as discussed previously. The experimental evidence (Table I) shows that saponification velocities and cryoscopic data parallel each other.

Further examples of the structual effects are observed in the santenols (12). Due to the shielding effect of the bridge methyl group cis to the exo hydroxyl and to the bridge head methyl group of β-santenol (XXXII), it would be predicted this alcohol should behave cryoscopically the same as isoborneol. Similarly, β-santenol alcohol (XXXXIV) should approximate that of borneol. But due to the trans position of the methyl group on the methylene carbon atom in α-santenol (XXXI) and α-santenol alcohol (XXXXV), the degree of association should be higher than β-santenol and β-santenol alcohol. Further the degree of association of α-santenol alcohol would be expected to be higher than α-santenol due to the protective influence of the 1-CH_3 substituent. This last effect has also been noted in α-isofenchol (XXXVI) and these two alcohols should have approximately the same value. The experimental values in Table II substantiate the predicted effects upon the exo and endo isomers and add validity to the assigned configurations.



XXXXIV



XXXXV

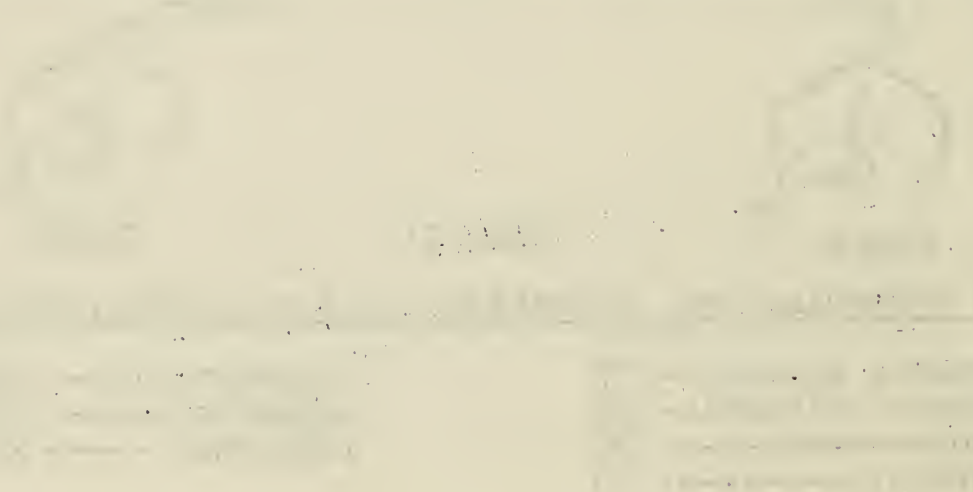
TABLE II

Percent Molecular Wgt. Elevation (0.05 mol./100g. benzene)

α-santenol alcohol--	37	α-isofenchol---	30
β-santenol alcohol--	36	β-santenol-----	20.5
borneol----------	36	isoborneol-----	20
α-santenol---------	30		

Mass Spectrometry:

Biemann and Seibel (37) have investigated the application of mass spectrometry to determination of configuration. Their results indicated a difference in abundance of M^+ ion in secondary alcohol isomers.



The peak was more intense in the less crowded epimer. The results of exo and endo norborneol were inconclusive but that of borneol and isoborneol showed the effect of steric hindrance on the stability of the M^+ ion (Table III).

TABLE III

Secondary Alcohol	Abund. of M^+ (M-18)	Secondary Acetate	Abund. of M^+ (M-60)
Borneol	0.17 1.47	Borneol	0.31 5.08
Isoborneol	0.14 2.41	Isoborneol	0.04 5.94

Infrared analysis:

The infrared data has been limited to the determination of intramolecular hydrogen bonding of the dimethyl esters of 5-hydroxycyclopentane-1,3-cis-dicarboxylic acids (35,38) as 5-hydroxy-iso-fencho acid of borneol, 5-hydroxy-isofencho acid of D-α-fenchol, 5-hydroxy-norcamphoric acid, 5-hydroxy-camphoric acid of isoborneol, and 5-hydroxy-isofencho acid of L-β-fenchol. The results show a similarity in absorption of bonded and free hydroxyl and in k values (equation 1) when the acids are derived from the parent compound of the same configuration. The hydrogen bonded hydroxyl (chelate formation) of the cis dicarboxylic acids showed a strong absorption in the bonded -OH region and a weak absorption in the free -OH region. Also, the k values of the bonded -OH remained constant over the concentration range investigated. However, the k values couldn't be determined precisely for the free -OH region. This constancy indicated the cis relationship of the two groups. The trans acids show absorption in the bonded and free -OH region but the k values are not constant. As the concentration is decreased, the value of the free -OH increases and that of the bonded undergoes a decrease. This effect is attributed to association of the molecules and therefore indicates a trans relation between the hydroxy and carboxyl groups.

$$\log_{10} \frac{P}{P_o} = -kc$$

c= conc., in moles per liter
k= molar extinction times layer thickness of the sample in the cell
$P \neq P_o$= intensities of solvent and solution measured by galvanometer deflection

Equation I

Summary is in Table IV: saponification velocities (sapon.), molecular weight elevation (assoc.), Diels-Alder (D.A.), catalytic reduction (cat.), acidic solutions (hydrat.), conc. nitric acid (n.a.), solvolysis (sol.), equilibration (equil.), lactonization (lact.), alkaline reduction (alk. red.), deamination (deam.), infrared (I.R.).

TABLE IV

Bicyclo(2.2.1)heptanol	Config.	Method (ref.)
α-norborneol	endo	D.A.(34),deam.(6),sol.(15,17,
β-norborneol	exo	18),n.a.(14),I.R.(35),assoc.(20).
2-CH_3 norborneol	endo	D.A.(33),assoc.(31),
2-CH_3 norborneol	exo	lact.(3). equil. (18)
3-CH_3(exo) norborneol	endo	D.A.(31),alk.red.(31),
3-CH_3(endo) norborneol	endo	assoc.(31),sapon.(20).

α-fenchocamphorol	endo	deam.(22),alk.red.(23),
iso-α-fenchocamphorol	exo	assoc.(31).
β-fenchocamphorol	endo	alk.red.(7),assoc.(22),deam.
iso-β-fenchocamphorol	exo	(11),hydrat.(7),sapon.(20).
camphenilol II	endo	alk.red.(26),sapon.(20),
camphenilol I	exo	assoc.(22).
β-isofenchol	endo	hydrat.(22),cat.(23),assoc.(22),
α-isofenchol	exo	n.a.(13),alk.red.(26), equil.(28).
α-fenchol	endo	alk.red.(23),cat.(23,sapon.(20)
β-fenchol	exo	n.a.(13),equil.(27),I.R.(38).
3,5-cycloborneol	endo	alk.red.(25),cat.(25),
3,5-cycloisoborneol	exo	equil.(25).
borneol	endo	D.A.(24),assoc.(22),sapon.(20), equil.(25),hydrat.(8,9),cat. (23,24),n.a.(13),sol.(15),I.R.
isoborneol	exo	(38),lact.(39).

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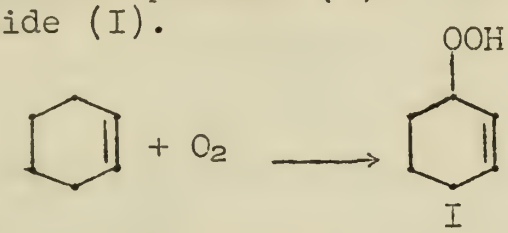
RECENT WORK ON AUTOXIDATION OF UNSATURATED HYDROCARBONS

Reported by J. Witt August 5, 1959

INTRODUCTION

The most common reaction that occurs when an olefin is oxidized by oxygen is the abstraction of an allylic hydrogen atom giving a hydroperoxide as the final product (1). For example, cyclohexene gives the hydroperoxide (I).



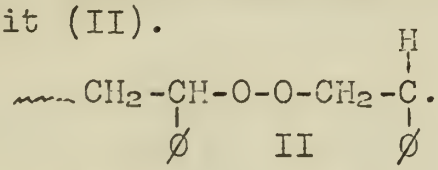
I

Autoxidations of this type have been reviewed by Bolland (2) and Bateman (3).

Instead of abstracting a hydrogen and thus yielding the hydroperoxide, the peroxy radical may add to the double bond. Recently, Mayo and Russell have studied substances with reactive double bonds and found that the peroxy radical adds to the double bond and gives a polymeric peroxide. Cleavage of the double bond to give carbonyl compounds and epoxide formation are other reactions which occur. This seminar will deal with materials such as these in which the main product is not the hydroperoxide.

AUTOXIDATION OF STYRENE

Mayo has studied the autoxidation of styrene both in the presence and absence of initiators (4,5). It was found that the free radical autoxidation takes two courses, the formation of styrene polyperoxide and cleavage to benzaldehyde and formaldehyde. The two reactions proceed by a common intermediate, a free radical which ends in a styrene unit (II).



II

The amount of styrene cleaved to the aldehydes and the composition of the polyperoxide are dependent upon the oxygen pressure. In addition to the polyperoxide and aldehydes, styrene oxide is also formed. It is assumed to be another primary oxidation product because it is formed in only trace amounts when styrene polyperoxide is decomposed.

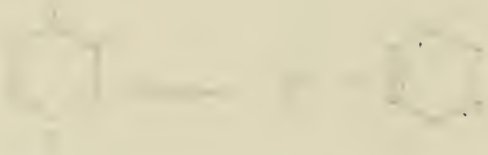
The rate of oxidation when initiated by α,α'-azodiisobutyronitril (ADBN) near a pressure of one atmosphere of oxygen follows the kinetic expression below.

$$-\frac{d(O_2)}{dt}=k(C_8H_8)\ (ADBN)^{\frac{1}{2}}$$

The rate is independent of oxygen pressure. In the absence of an added initiator the rate law is as follows.

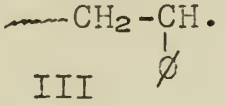
$$-\frac{d(O_2)}{dt}=k(C_8H_8)^{1.4}(O_2)^{0.4}$$

This shows that oxygen participates in the thermal oxidation initiation. This rate is 38 times faster than the rate of initiation for



the thermal polymerization when oxygen is not present. Temperature studies on the rate show that the overall activation energies for the thermal and initiated oxidations of styrene are 23.0 and 25.4 kcal./mole, respectively.

The usual autoxidation mechanism for olefins needs only to be changed by substitution of an addition for a transfer step to fit the case. M and M· represent styrene and the styrene radical (III) in the general mechanism below.



III

ADBN $\longrightarrow$	Indirectly 2M·	(1)
M+O_2 $\longrightarrow$	MO_2·	(1a)
M·+O_2 $\longrightarrow$	MO_2·	(2)
MO_2·+M $\longrightarrow$	M·	(3)
2MO_2· $\longrightarrow$	Non-radical products	(4)

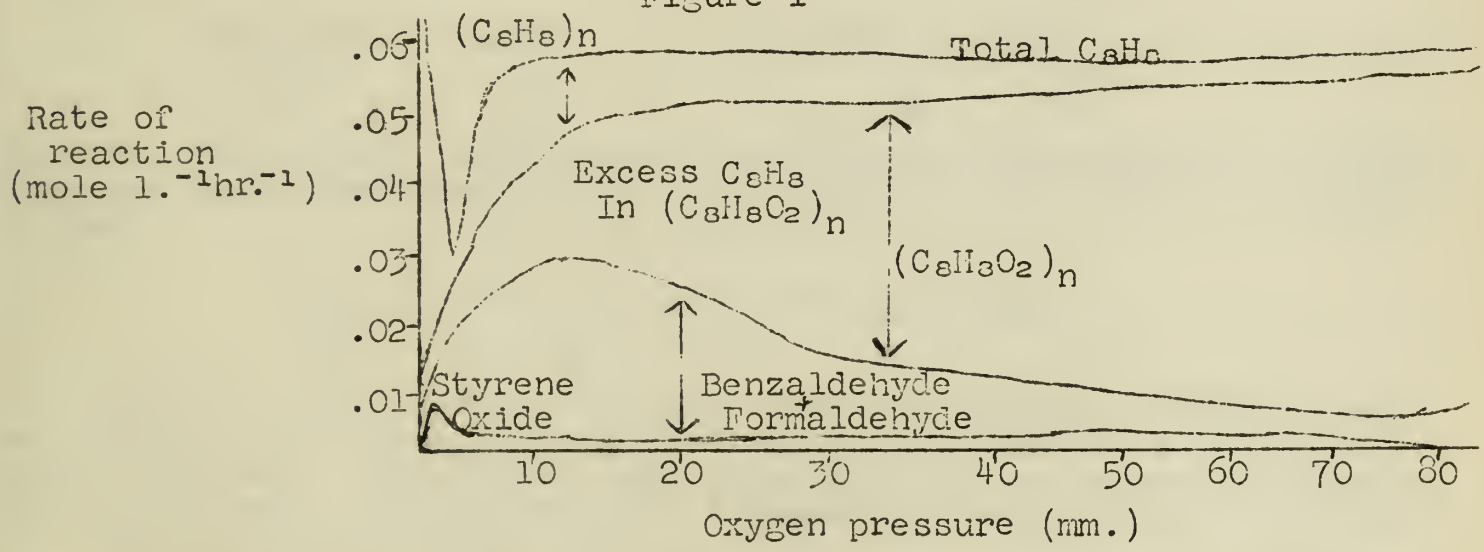
The kinetics follow (1) and (2-4) for the α,α'-azodiisobutyronitrile initiated reaction. The kinetics of (1a) and (2-4) for the thermally initiated reaction would require the following rate law,

$$-\frac{d(O_2)}{dt} = k(C_8H_8)^{1.5}(O_2)^{0.5}$$

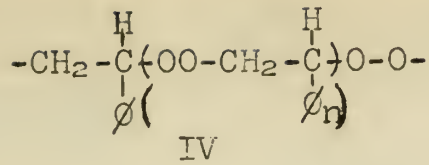
which is approximately the one obtained.

As the oxygen pressure decreases, the rates of formation of aldehydes and styrene oxide increase and reach their maxima below 20 mm. of oxygen and the composition of the polymer changes from the polyperoxide to polystyrene. The rates of formation of the various products and oxygen pressures are summarized in Figure 1.

Figure 1



Styrene radicals will react at the rate of a thousand steps per second in the absence of oxygen and their concentration is 10^{-7}M. At one atmosphere of oxygen, oxygen is 10^6 times as reactive as styrene but its concentration is 0.0071 M. Therefore, a styrene radical will react 900 times faster with oxygen than it will with a styrene molecule. The resulting peroxide radical will then usually react with a molecule of styrene and the net result is the formation of a polyperoxide with the following structure (IV).



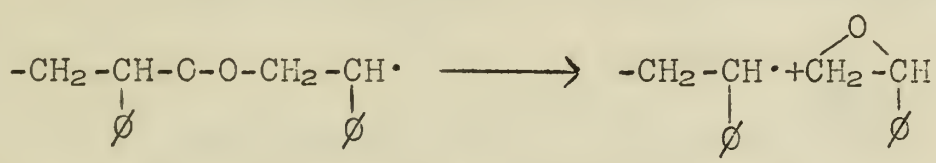
IV

The composition of the polyperoxide formed is dependent upon the oxygen pressure. The average composition at 50° and 10 mm. pressure is $(C_8H_8)_{1.5}O_2$ and goes to a limit of $C_8H_8O_2$ at high pressures. The relative reactivities of styrene and oxygen with the styrene radical can be determined from the amounts of styrene and oxygen in the polyperoxide. It was found that at the same concentration oxygen would react 2-3 X 10^5 times as fast as styrene with the styrene radical. The polyperoxide does not contain only oxygen and styrene units but ether and methylene units are also present. The evidence for the ether links comes from peroxide determinations, infrared, and formaldehyde balances.

Peroxide formation is some 17 times as fast as aldehyde formation at 760 mm. of oxygen but the rates are nearly equal at 25 mm. The fact that aldehyde yields are increased at lower oxygen pressures shows that the formation of aldehydes is due to a reaction of growing chains which end in styrene radicals. This type of intermediate is probably the only one which increases in concentration as the oxygen pressure decreases.

This intermediate is also responsible for the formation of polyperoxide and, therefore, for all of the oxygen absorption. A maximum of 56% of the reacting oxygen appears as aldehydes at 5 mm. and a maximum of 25% of the oxygen appears as styrene oxide at 0.5-1.0 mm.

The styrene radicals have a lifetime of only 10^{-6} seconds before they react with oxygen but this is sufficient for 0.3% of these radicals to rearrange to alkoxy radicals and styrene oxide as shown below.



Each of these alkoxy radicals will then rapidly depolymerize to benzaldehyde and formaldehyde before any reaction with styrene or oxygen occurs.

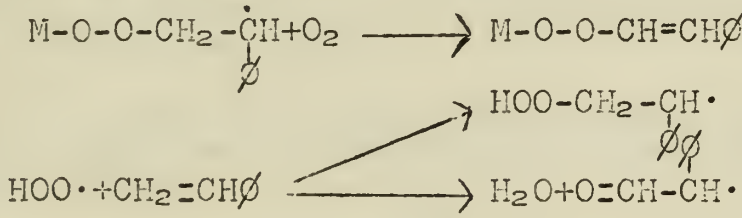
However, Walling feels that the step for epoxide formation may be difficult to reconcile with the maximum in yield at a particular oxygen pressure. The epoxide may also arise from a polar reaction of the olefin and a hydroperoxide in a manner analogous to the reaction of a peracid and an olefin (6).

When the oxygen pressure is reduced, the styrene radicals have a longer life and, therefore, there is a greater chance for them to react with styrene or to rearrange and depolymerize. These reactions replace more and more of the copolymerization with oxygen at lower pressures. At pressures above 10 mm. the reaction of peroxide radicals with styrene is rate determining. Below 10 mm. the life of the styrene radical increases and the peroxide radical concentration decreases. Reaction of the unlike radicals becomes more important and

finally produces a sharp minimum in the reaction rate of styrene below 1 mm. At 1 mm. the rates of reaction of the styrene radical with styrene and with oxygen and of the peroxide radical with styrene are all approximately equal.

The rates and proportion of epoxidation to styrene oxide and cleavage to the aldehydes are related to the concentration of the styrene radical. The amount of reacting oxygen that appears as cleavage products is approximately inversely proportional to the oxygen pressure down to 50 mm. A small amount of cleavage (2-3%) occurs at very high oxygen pressures and apparently does not involve styrene radicals. The ratio of the rates of cleavage and epoxidation, R_c/R_e, is a simple, nearly linear function. As this includes pressures at which both R_c and R_e pass through different maxima, and three different termination reactions apply, this relationship of the two rates is important. It suggests that if R_c is dependent upon $(O_2)^{-1}$, as found at one atmosphere, then R_e is proportional to $(O_2)^{-2}$. The mechanism mentioned earlier which postulates epoxide arising from styrene radicals is consistent with all the data. Epoxide formation is then followed by the cleavage of the alkoxy radicals to the aldehydes. Cleavage apparently still follows epoxide formation at high pressures even though the amount of epoxide formed is too small to observe.

The polyperoxide formed at 50° and one atmosphere approaches the limit of $C_8H_8O_2$ and has a molecular weight of approximately 3,000-4,000. About 560 molecules of styrene and oxygen react per molecule of initiator decomposed and the polyperoxide averages $(C_8H_8O_2)_n$ where n is 22-30. Therefore, the molecular chain must terminate by some chain transfer mechanism. Hydroxyl and carbonyl end groups have been identified but not sufficiently to determine the actual chain transfer mechanism and there is probably more than one occurring. The following chain transfer is plausible.



Neither accumulating benzaldehyde nor the process forming benzaldehyde can have more than a minor part in determining the molecular weight of the polymer.

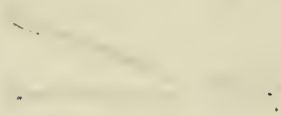
In the absence of oxygen styrene polymerizes to polystyrene and the following termination is known to apply.

$$2M\cdot \longrightarrow \text{Non-radical products}$$

The peroxy radicals which react relatively slowly with styrene are present in the largest amounts and are responsible for the termination of the kinetic chains. The rate of reaction of styrene passes through a sharp minimum between 0.5 and 1.0 mm. of oxygen, which can be associated with the following termination step.

$$M\cdot + MO_2\cdot \longrightarrow \text{Non-radical products}$$

Over the range of 0.5 - 4 mm. of oxygen the rate of oxygen reacting is proportional to the square root of the oxygen concentration which is required by the above termination. The reaction rate is nearly inde-



pendent of the oxygen pressure above pressures of 20 mm. The main product is the polyperoxide and the following termination has been established from the kinetics of the reaction.

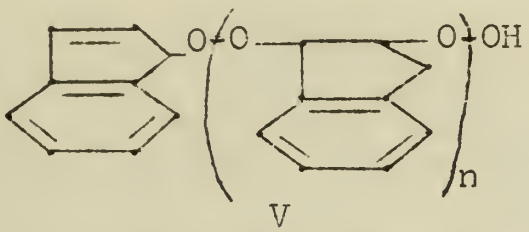
$$2MO_2\cdot \longrightarrow \text{Non-radical products}$$

AUTOXIDATION OF α-METHYLSTYRENE

The autoxidation of α-methylstyrene has also been studied by Mayo (7). The autoxidation leads to the same type of products as obtained from styrene, polyperoxide, acetophenone, formaldehyde, and epoxide. The main difference is the absence of homopolymerization of α-methylstyrene; this essentially eliminates the presence of excess α-methylstyrene units in the polymer.

AUTOXIDATION OF INDENE

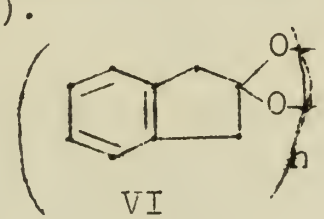
Autoxidation may lead to a polyperoxide or to abstraction of a hydrogen and formation of the hydroperoxide. Both of these reactions are possible with indene and both the hydroperoxide and the polyperoxide might be expected. Autoxidation of indene would then be expected to yield the following type of product (V).



V

Gutman (8,9,10) studied the reaction and concluded that both polyindene and indene polyperoxide are formed concurrently and that oxygen will accelerate the polymerization of indene to form polyindene containing only two atoms of oxygen per molecule. These results are difficult to explain if the polymerization and autoxidation proceed by a free radical mechanism.

Hock (11,12,13) postulated that the polymeric oxygen-containing compound was not a copolymer of indene and oxygen but possessed the following structure (VI).

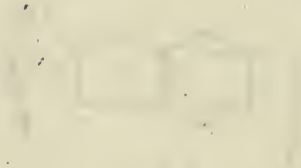


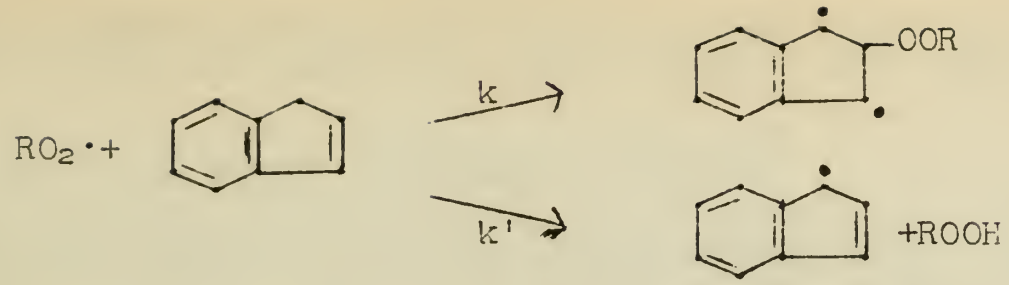
VI

The only evidence that the polymeric peroxides are cyclic trimeric and hexameric 2-indanone peroxides is analysis and reduction with Zn and HCl to 2-indanone in 15% yield.

Russell (14,15) has since studied the reaction in more detail and found that in the presence and absence of initiators, peroxides with a variety of physical properties are produced. Analysis, molecular weight, and chemical properties indicate that the products of the oxidation may be described by the general formula (V).

The degree of polymerization averages less than ten indicating that a chain transfer reaction is competing with the polymer-forming reaction. Considering the following processes,



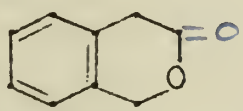


an approximate value of 4 to 1 is obtained for k/k' from the distribution of molecular weights if it is assumed that all of the chain transfer occurs by abstraction of a hydrogen atom. This ratio predicts that about 5% of the oxygen should be found as monomeric indenyl hydroperoxide.

The structure of the polymeric peroxide (V) is not as simple as shown. Olefinic unsaturation equivalent to what was expected was found but the hydroperoxide content was lower than the one unit per molecule. The infrared spectrum shows the presence of hydroxyl and carbonyl groups and it seems likely that these functions are chain endings in some of the molecules.

Reduction of the peroxide with lithium aluminum hydride (16) produces nearly one-half equivalent of hydrogen and destroys one-half equivalent of lithium aluminum hydride per peroxide link. The products are mainly cis- and trans-indene glycol, supporting the linear and not the cyclic polymer. Indene glycols are converted to 2-indanone on treatment with dilute acid. This fact renders Hock's argument for the cyclic compound doubtful. The glycols obtained contained nearly equal amounts of the cis and trans isomers. This indicates that the addition of a peroxy radical and an oxygen molecule to the double bond has a very low stereospecificity.

Hock and Russell both report the isolation of 3-isochromanone (VII) on treating polymeric indene peroxide with strong base, followed by acidification.



VII

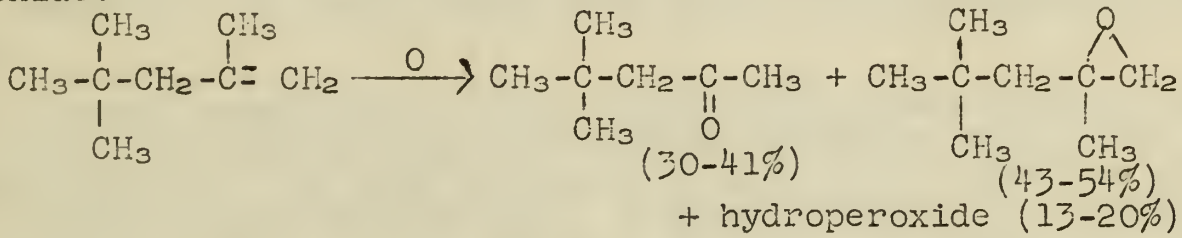
Russell feels that it would be difficult to postulate a reaction forming 3-isochromanone from the cyclic polymer but that it is not a surprising product from the reaction of base with the linear polymer. This would also substantiate Russell's claim that the polymer is linear.

There is evidence that end groups other than hydroperoxide and indenyl are present and these chain endings could be formed by a variety of methods: 1) The decomposition of hydroperoxide end groups, 2) Chain transfer, 3) Chain termination, and 4) Degradation of high molecular weight indene peroxide. The decomposition of hydroperoxide end groups to give carbonyl or hydroxyl groups should result in the formation of water which was not found. The chain termination is not important since the kinetic chain length is much greater than the degree of polymerization. The data show that forty chain transfer reactions occur for each chain termination. Degradation of the polyperoxide may be excluded as the degree of polymerization does not decrease significantly with an increase in the degree of oxidation.

Therefore, it seems probably that the end groups other than indenyl and hydroperoxide are formed in a chain transfer reaction of some type.

ATUOXIDATION OF ALIPHATIC UNSATURATED COMPOUNDS

It is generally considered that most aliphatic unsaturated hydrocarbons give 60-100% of allylic hydroperoxides as the result of autoxidation. However, Gasson (17) and Mayo (18) both report that the oxidation of α-diisobutylene, 2,4,4-trimethyl-1-pentene, at 140° gives epoxide and ketone as the major products and only a small amount of hydroperoxide.



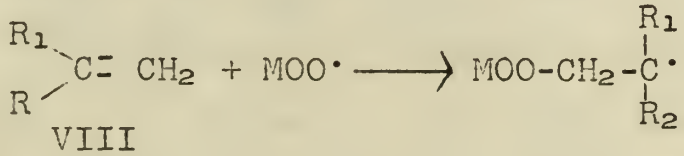
The formation of epoxides and cleavage products has also been reported for a number of other compounds such as hexenes (19), α-pinene (20), mesityl oxide (21), and oleic acid (22). Glycols which presumably arise from the hydrolysis of the epoxide were obtained from cyclohexene (19), oleic acid (23), and isobutylene (24).

The rate of oxidation of α-diisobutylene is nearly independent of oxygen pressure above 10 mm. but decreases below this pressure. The proportion of products obtained is constant over the entire pressure range. At temperatures lower than 140° the reaction is slower but the same products are formed. The chain lengths are about ten at 60° and about thirty at 100°.

EFFECT OF STRUCTURE ON RATE AND PRODUCTS

The structure of the olefin will determine whether the propagation step occurs by abstraction of an allylic hydrogen atom or by addition of a peroxide radical to the double bond. Some correlations between structure and the autoxidation products can be made (25). Addition instead of hydrogen transfer occurs predominately when a phenyl, vinyl, or nitrile group is attached to the unsaturated carbon atom. Addition is also favored when the unsaturated compound is a 1,1-dialkylethylene.

Most hydrocarbons with one to four alkyl groups on the doubly bound carbon atoms give hydroperoxides as the major product but epoxide and cleavage products are formed in small amounts. But 1,1-disubstituted ethylenes are generally more active in the addition of radicals than are 1-, 1,2-, 1,1,2-, or 1,1,2,2- substituted ethylenes. Therefore, olefins of type (VIII) would give the most addition and least abstraction of hydrogen atoms.



VIII

This has been found to be true in the case of α-diisobutylene (17,18) and 2-methyl-1-nonene (26).

With styrene and α-methylstyrene the monomers are resonance—

stabilized and their life must be prolonged by reducing the oxygen pressure to observe much epoxide formation. When β-peroxy radicals are not stabilized by resonance, the rearrangement to epoxide occurs so rapidly that it is unaffected by oxygen pressures below 120 mm. at 100°. It is possible that oxygen pressures above atmospheric will retard formation of epoxide and permit further growth of the radical chain. To obtain rearrangement to epoxide, the concentration of the monomer radical must be increased by lowering the oxygen pressure.

Compounds with an unreactive double bond but with no reactive hydrogen such as vinyl acetate and vinylidene chloride undergo the addition reaction, but more slowly than usual and give mostly polyperoxide.

The relative reactivity of the double bond toward radicals is the main factor in determining the relative oxidation rate of an unsaturated compound. The rate-determining step is the addition of the peroxide radical to the double bond. A 2-substituent in a 1-substituted ethylene will usually decrease the ease of attack by a radical on the double bond. However, a smaller or opposite effect is observed if a polar effect is enhanced by the 2-substituent. A β-methyl group decreases only slightly the reactivity of the styrene double bond but a β-bromine decreases the reactivity substantially. This is in accord with the idea that the peroxide radical is an electron acceptor and prefers to react with electron-rich double bonds. The oxidation rates of a number of unsaturated compounds are given in Table I.

TABLE I

Compound	R_o*	100k*
α-Methylstyrene	0.113	1.58
Indene	.081	0.97
Styrene	.061	.71
β-Methylstyrene	.027	.37
1,1-diphenylethylene	.018	.31
Allylbenzene	.0059	.079
β-Bromostyrene	< .0001	< .001

R_o is rate of oxygen absorption
k is rate of oxygen absorption/ molar concentration of pure monomer
* mole $l.^{-1}$ $hour^{-1}$

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