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# Chemical transformations in the field of indole alkaloids

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# CHEMICAL TRANSFORMATIONS IN THE FIELD OF INDOLE ALKALOIDS

by

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# INTRODUCTION

A number of current investigations in the area of alkaloid chemistry are concerned with the stereochemical nature of alkaloid structures. Although the use of X-ray and molecular rotation techniques have made possible the assignments of absolute configurations to a number of alkaloids, among them the indole alkaloid, yohimbine, it is nevertheless desirable to determine these configurations through chemical correlations with compounds of known absolute configuration.

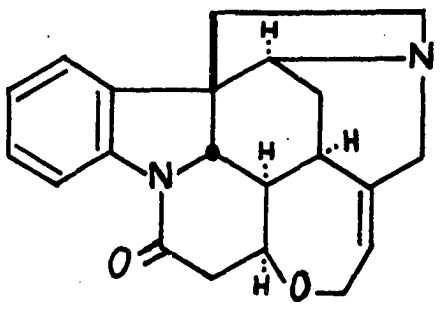
It is the purpose of this study to investigate the stereochemistry of some indole alkaloid systems by chemical means. Since the absolute configuration of 18,19-dihydrocorynantheane is known, it is to be employed as an intermediate in 1) the determination of the absolute configurations of ajmaline and its $C_{20}$ epimer, isoajmaline, and 2) correlation studies between the yohimbine and corynantheine series of indole alkaloids. Investigations are to be conducted on the $C_3$ epimerization of quaternary $N_b$-salts of yohimbines, and on the degradation of yohimbane to products of potential use in asymmetric syntheses of various alkaloid systems.

# HISTORICAL

Recent years have seen a tremendous growth of activity in the field of alkaloid chemistry. Compounds isolated as far back as the late 1800's and early 1900's have been under intense investigation. An incredibly large number of new alkaloids isolated during the last several decades are being studied for the first time.

It was once considered quite adequate in a chemical investigation of this scope to isolate a natural product, characterize it by functional group analyses and degradation studies, and then propose a reasonable structure for it. Due to recent advancements in chemical theory, techniques and instrumentation, no current study of an unknown substance is deemed complete unless there is an unequivocable proof of structure advanced by a total laboratory synthesis of the compound. In addition, complete determinations of the stereochemical configurations of all asymmetric centers, first the relative and then the absolute, are required before one can consider the investigation completed.

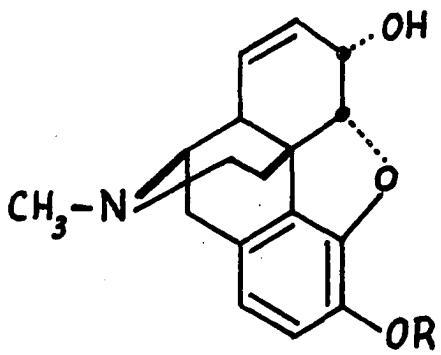
Notable accomplishments toward this final goal in a few of the areas of alkaloid investigations have been made within the last decade. In 1951, physical proof of the basic structure of strychnine (I) was provided by Robertson and Beevers (1) and by Bokhoven *et al.* (2) on the basis of X-ray analyses. The absolute configuration of (-) strychnine, as depicted in



I

I, was determined by further analyses of X-ray diffraction patterns by Peerdeman and reported in 1956 (3). While no chemical determination of the absolute configuration of this alkaloid has thus far been made, its total synthesis has been accomplished by Woodward and coworkers (4).

The scope and applications of the techniques of X-ray analyses have grown tremendously in recent years. Another area of study to which they have been applied with great success is the investigation of the morphine alkaloids. The basic structure of morphine (IIa) was first proposed by

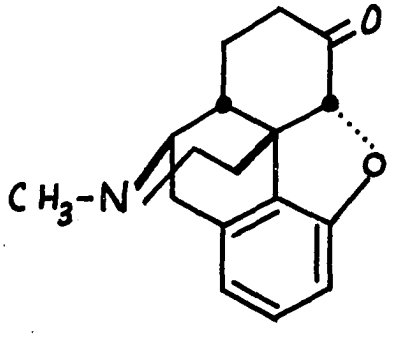


IIa: R = H

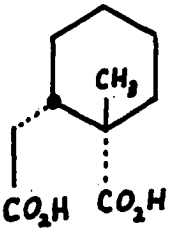
IIb: R = $CH_3$

Gulland and Robinson (5), but it was not conclusively proven correct until the total synthesis of the alkaloid was first reported in 1952 (6). In 1955, Mackay and Hodgkin reported the stereochemistry for morphine as depicted in IIa (7). Their assignments were made on the basis of X-ray analyses and confirmed the stereochemical assignments initially proposed by Rapoport and Payne (8). At about the same time, the stereochemistry of the closely related alkaloid codeine (IIb), determined also by X-ray studies, was reported by Lindsey and Barnes (9). This supported assignments made on the basis of earlier chemical studies.

The absolute configurations of the morphine alkaloids have been determined by both physical and chemical means. Bentley and Cardwell showed by optical rotation studies that the structure depicted in IIa and not its mirror image represents morphine (10). Chemical proof was provided by Kalvoda and coworkers who degraded dihydrocodeinone (III) to cis 2-methyl-2-carboxycyclohexaneacetic acid (IV) of known abso-



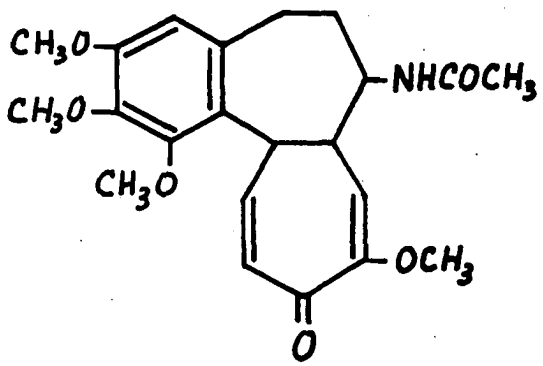

III



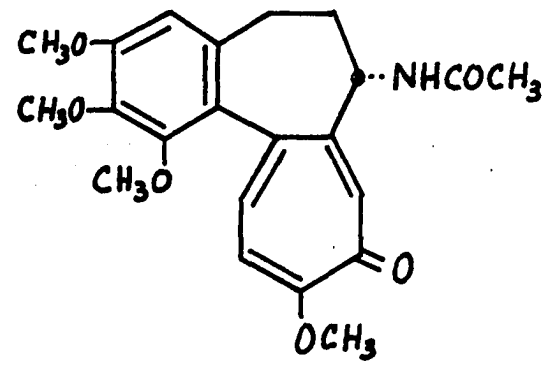

IV

lute configuration (11).

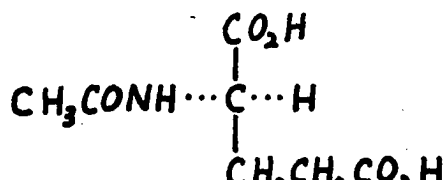
In 1955, the absolute configuration of the one asymmetric center in colchicine (Vb) was reported by Corrodi and Hardegger (12). Degradative oxidation of colchicine yielded N-acetyl-L-glutamic acid (VI) whose absolute configuration may be related to that of D-glyceraldehyde through the established correlation of the naturally-occurring amino acids with carbohydrates.




Va



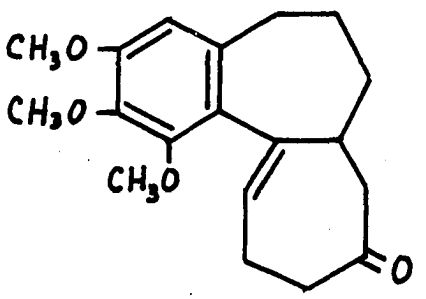

Vb




VI

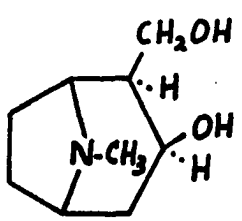
The basic structure shown in Va was proposed by Dewar (13). Further work prompted Cech and Santavy to propose the closely related structure Vb for the alkaloid (14). X-ray diffraction studies supported this second structure but did not remove all uncertainties concerning the positions of the ring C carbonyl and methoxyl groups (15). Conclusive

chemical proof of structure Vb for colchicine was provided by Loewenthal (16) with his recent reported synthesis of the ethylene ketal of VII, hexahydrodemethoxydesacetamidocolchicine, a degradation product of colchicine (17).

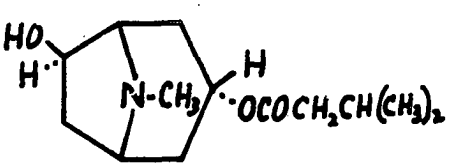


VII

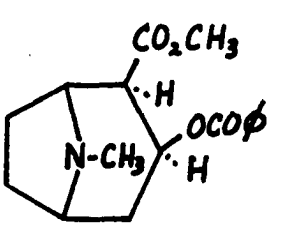
Much of the stereochemical work in the area of tropane alkaloids has been due to Fodor and coworkers. The absolute configuration of (-) ecgoninol (VIII), one of the many alkaloids studied, was determined through interpretation of rotational values of several derivatives (18). This was advanced in 1956 and was followed in 1957 by the absolute configuration of valeroidine (IX) which was determined by similar chemical



VIII



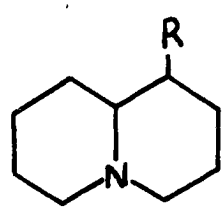
IX



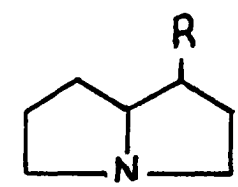
X

and physical means (19). The relative stereochemistry of an important tropane alkaloid, l-cocaine, was deduced by Fodor and coworkers in 1954 (20) and is represented by X. Due to the work of Hardegger and Ott, who correlated the alkaloid with L-glutamic acid of known configuration, the stereochemistry indicated in X was shown also to be the absolute configuration of l-cocaine (21).

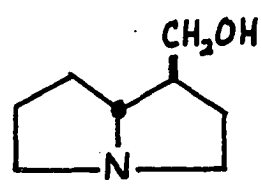
Absolute configurations of several lupin alkaloids have been investigated and reported within recent years. Comparisons and interpretation of molecular rotation differences of derivatives of quinolizidine alkaloids (XI) and corresponding ones in the pyrolizidine series (XII) enabled Leonard to deduce the absolute configuration of laburnine shown in XIII (22). In 1958, Warren and von Klemperer published the absolute configuration of the closely related alkaloid, (-) heliotridane (XIV) (23).



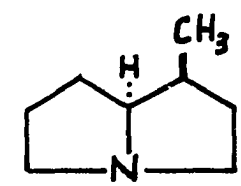

XI




XII

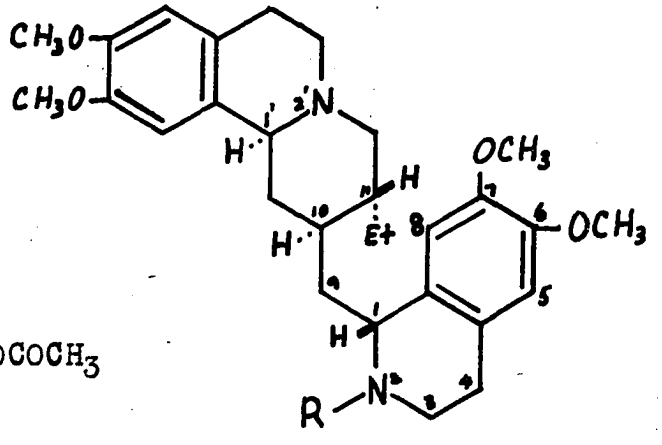



XIII




XIV

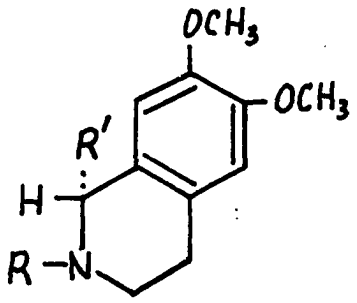
Among the most recent accomplishments made in the stereochemical investigations of alkaloid structures was the determination of the absolute configurations of the asymmetric centers in emetine. The assignments of the relative stereochemistry as shown in XVa were due largely to van Tamelen (24) and to Battersby (25, 26, 27). The absolute stereochemistry of $C_{1'}$, $C_{10}$ and $C_{11}$ of the benzoquinolizidine system was reported in 1959 by Battersby and Garratt on the basis of molecular rotation studies of various derivatives (28, 29). The configurations are as depicted in XVa. In 1960, the



XVa: R = H

XVb: R = $-OCOCH_3$

absolute stereochemistry of the remaining asymmetric center, $C_1$, was established by chemical means (30). N-acetylemetine (XVb) was first degraded down to the N-acetyl acid XVIa. The constitution of this levorotatory compound was proven by favorable comparisons with an authentic sample obtained by synthetic means through the known dextrorotatory amino-ester XVIb. The levorotatory enantiomer of this amino-ester and

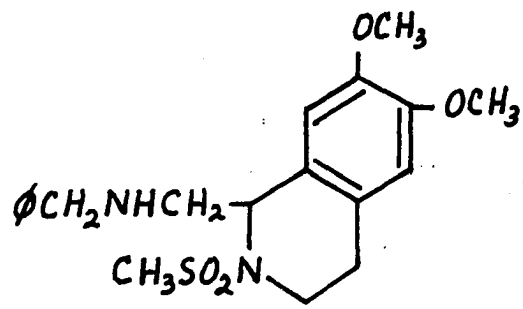


XVIa: R = $-\overset{O}{\overset{\|}{C}}-CH_3$; R' = $-CH_2CO_2H$

XVIb: R = H; R' = $-CH_2CO_2E+$

XVIc: R = H; R' = $-CH_2OH$

the closely related alkaloid, (+) calycotomine (XVIc), were both converted to common derivatives of the structure XVII (stereochemistry not indicated). These derivatives proved to be enantiomeric with one another. The absolute configuration of (+) calycotomine had been shown to be that depicted in



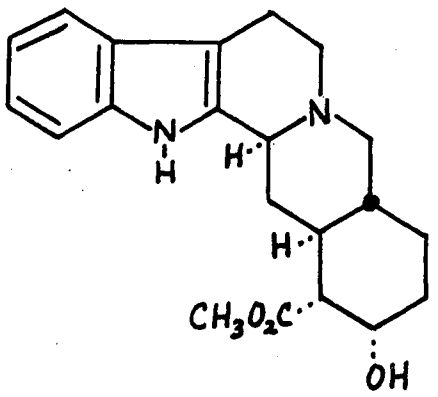
XVII

XVIc by correlation with the naturally occurring amino acids (31). Consequently, on the basis of the conversions described earlier, it could be concluded that the dextrorotatory enantiomer of the amino-ester (XVIb) and therefore the degradation product XVIa of N-acetylemetine both possess the absolute

stereochemistry of (+) calycotomine. The absolute configuration of $C_1$ of emetine as shown in XVa was thus proven.

During the last several decades, chemical activity in the vast field of indole alkaloids has perhaps been greater than in any other family of alkaloids. Investigations of all types from isolation and functional group studies to complete structural elucidations, syntheses and stereochemical determinations have expanded the amassed knowledge about this family exponentially within recent years.

Yohimbine (XVIII), the parent alkaloid of a major sub-

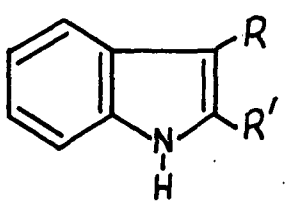


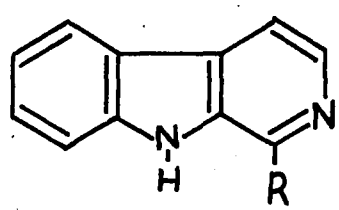

XVIII

family of the indole alkaloids, was isolated in the late 1800's, but it was not until the early 1900's that chemical investigations of the alkaloid were seriously undertaken. Functional group determinations were due to the efforts of Spiegel (32, 33, 34), Winzheimer (35), Schomer (36) and Hahn and Schuch (37) who showed the presence of a hydroxyl group,

a secondary and a tertiary nitrogen and a carbomethoxyl group in yohimbine.

In the late 1920's, investigators turned their efforts to elucidating the molecular skeleton of yohimbine. Soda lime distillation of the alkaloid (38, 39) and dry distillation of the corresponding free acid (40) both gave mixtures of indolic compounds later identified as skatol (XIXa) and 3-ethylindole (XIXb). Zinc dust or steam degradation (39) yielded, in addition, isoquinoline as a detectable product. Destructive distillation of the alkaloid afforded harman (XXa) and indolyl-2-carboxylic acid (XIXc) (41).



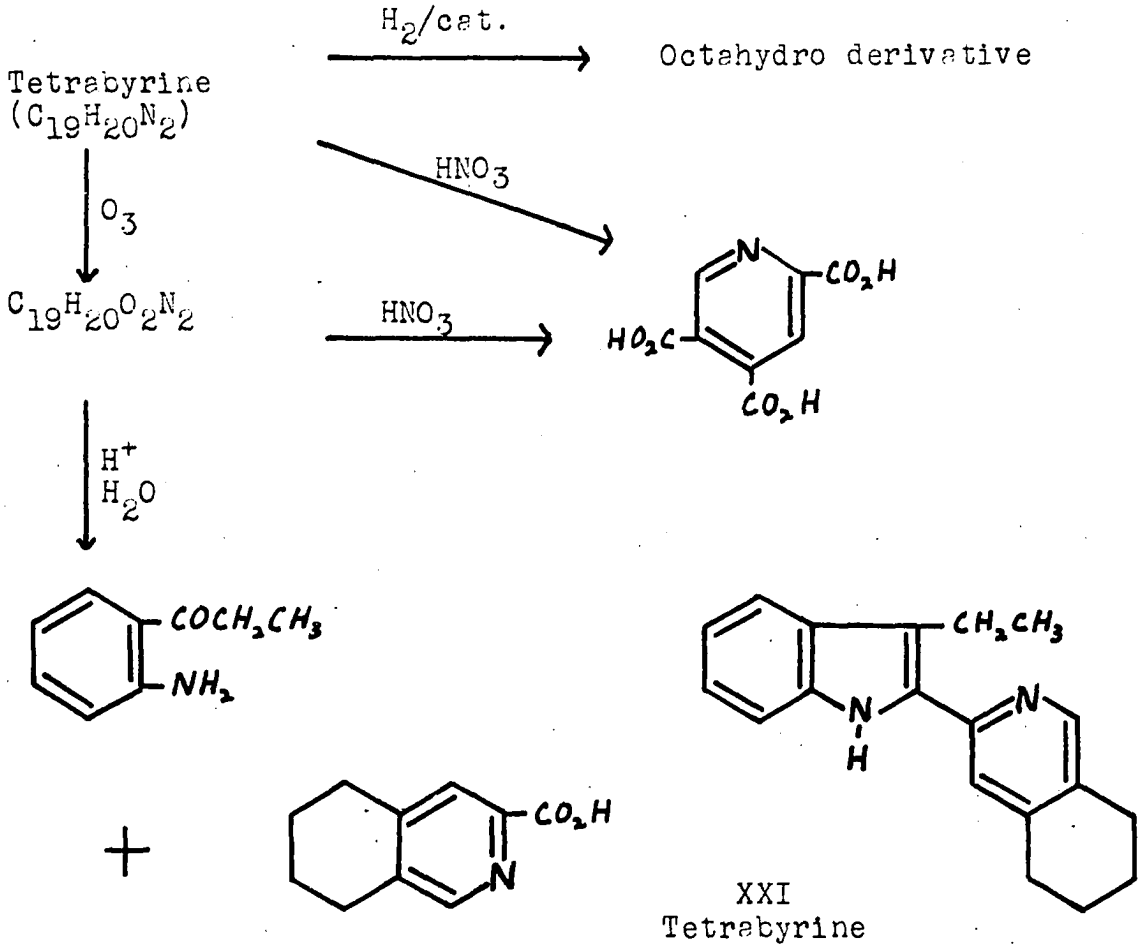




XIXa: R = $-CH_3$; R' = -H
XIXb: R = $-CH_2CH_3$; R' = -H
XIXc: R = -H; R' = $-CO_2H$

XXa: R = $-CH_3$
XXb: R = -H

A number of papers were published in the early 1930's on the selenium dehydrogenation of yohimbine and some of its derivatives (42, 43, 44, 45). Structure determinations of these dehydrogenation products and interpretations of these and other experimental results eventually paved the way for the complete structural determination of yohimbine.

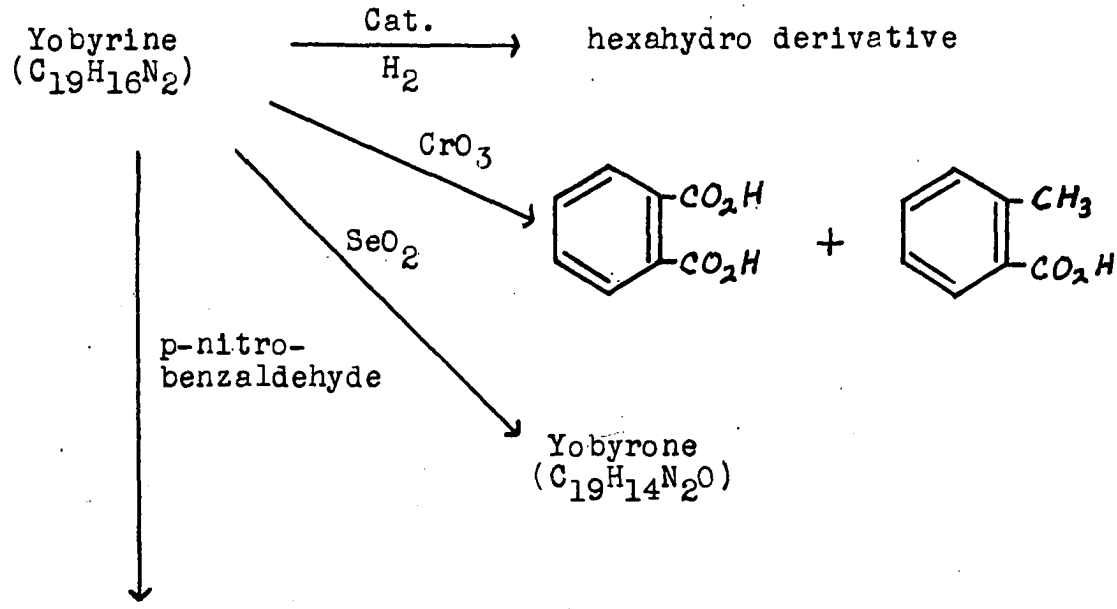
Selenium dehydrogenation of yohimbine yielded three separate products, tetrabyrine ($C_{19}H_{20}N_2$), yobyrine ($C_{19}H_{16}N_2$) and ketoyobyrine ($C_{20}H_{16}N_2O$). Further degradative studies on tetrabyrine, indicated in the following scheme, led to the proposal of structure XXI for this dehydrogenation product (45, 46, 47). Proof of structure was provided by a synthesis of the compound reported in 1948 by Julian and coworkers (48).

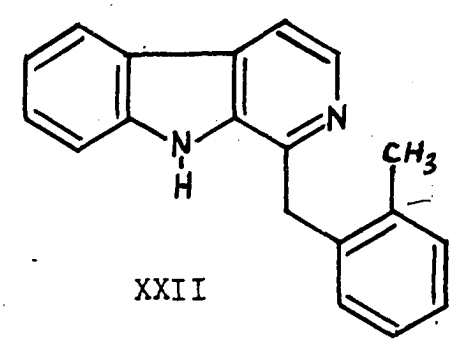



XXI
Tetrabyrine

The structure of yobyrine (XXII) was arrived at through much the same sequence of degradative steps, as illustrated in

the following scheme (49, 46). Two independent syntheses later proved XXII to be correct for yobyrine (50, 48).




XXII

Yobyrine

The third selenium dehydrogenation product, ketoyobyrine, was a non-basic compound in contrast to the other two products. Upon treatment with potassium hydroxide in amyl alcohol, norharman (XXb) and 2,3-dimethylbenzoic acid were formed in one instance (45) and norharman and 1,2,3-tricarboxybenzene in another (51). The structure XXIV proposed for ketoyobyrine

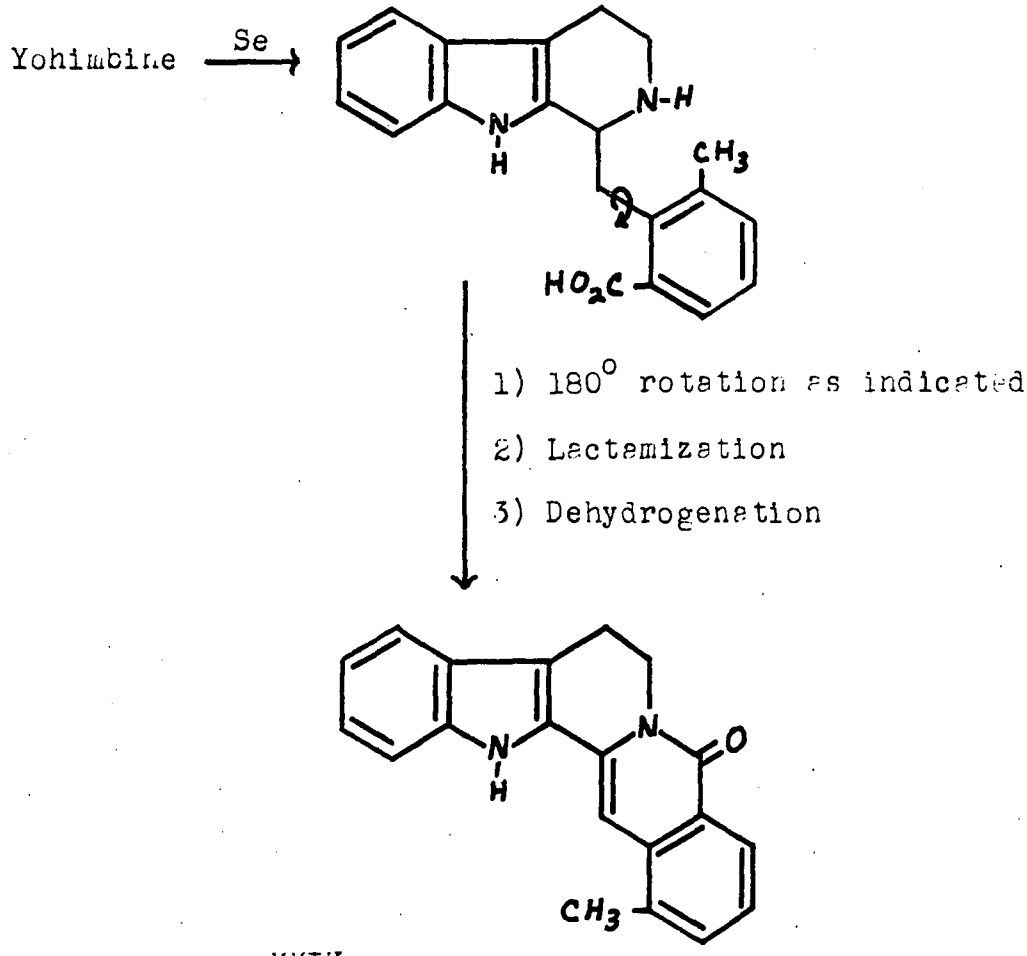
(51, 52, 53, 54) was subsequently shown to be correct by synthetic means (55, 56).

The structure determinations of these three products appeared to confirm the basic skeletal structure XXIII proposed for yohimbine by Scholz in 1935 (47). Remaining then were the assignments of the hydroxyl and carbomethoxyl groups.

In 1934, Majima and Murahashi reported the oxidation of yohimbine with palladium-black and maleic acid to a ring C-tetradehydro derivative (57). This compound, also prepared by lead tetraacetate oxidation of yohimbine, could be further degraded by treatment with potassium hydroxide in amyl alcohol to harman (XXa) and m-toluic acid (58). Interpretation of these results led to the tentative assignment of $C_{16}$ as the point of attachment of the carbomethoxyl group. This assignment was made on the assumptions that $C_{14}$ of yohimbine and the harmane methyl carbon were one and the same and that $C_{21}$ of yohimbine appeared as the methyl group in m-toluic acid. This therefore suggested that the carbomethoxyl group of yohimbine, appearing as the carboxyl group in the isolated m-toluic acid, was attached to $C_{16}$ in the original alkaloid. Although this assignment is now known to be correct, it was not unequivocable at the time, since the possibility of a $C_{18}$ attachment instead could not be eliminated.

Confirmation of the $C_{16}$ attachment was provided by the synthesis and proof of structure of ketoyobyrine, one of the

selenium dehydrogenation products of yohimbine. A brief account of this work has been made earlier. The formation of ketoyobyrine (XXIV) was postulated to proceed through the following steps (52).




XXIV

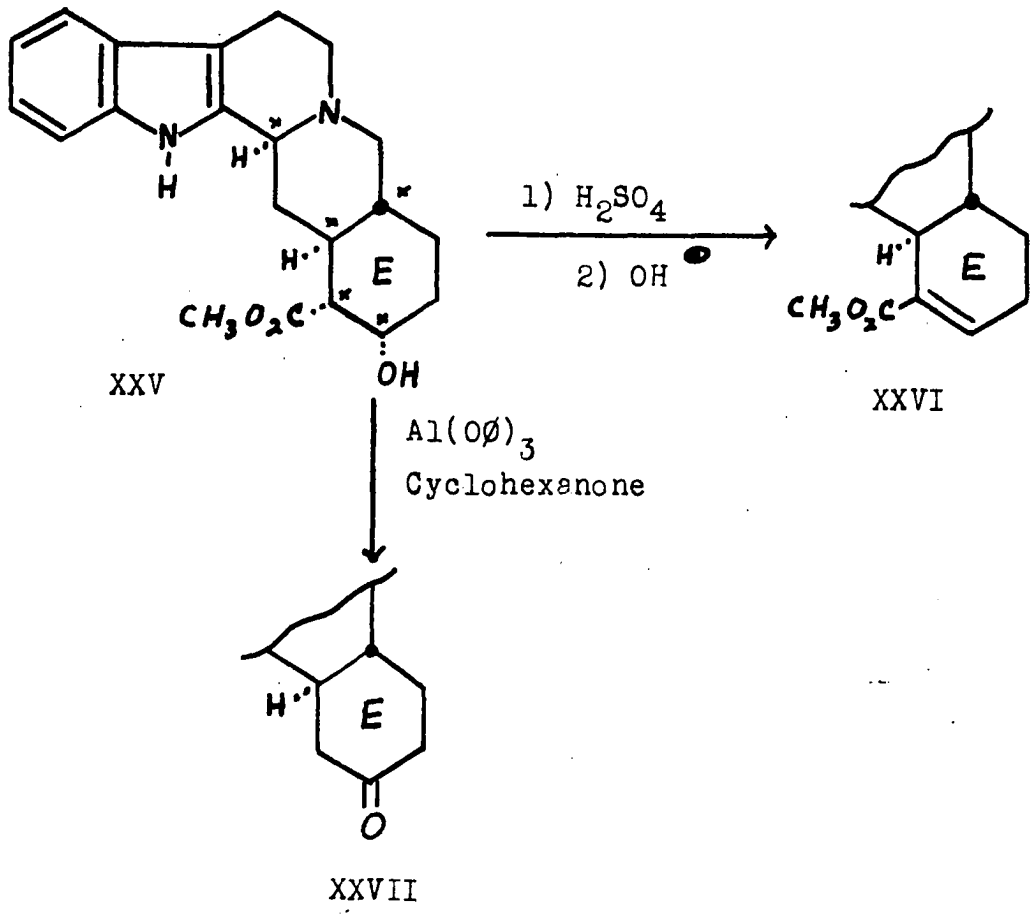
Ketoyobyrine

Proof of its structure by synthesis (56, 55) furthermore confirmed the assignment of $C_{16}$ as the point of attachment for the carbomethoxyl group of yohimbine.

Barger and Field showed that treatment of yohimbine with cold concentrated sulfuric acid yielded a sulfuric acid ester. Upon subsequent treatment with base, this ester lost the elements of sulfuric acid and yielded a product which was named apoyohimbine (XXVI) (38). The product differed from yohimbine only by the elements of water. Later, Witkop showed that treatment of yohimbine with aluminum phenoxide and cyclohexanone in xylene not only oxidized the hydroxyl group of the alkaloid to a ketonic group but also effected a hydrolysis and decarboxylation of the carbomethoxyl group (49) to yield the compound yohimbone (XXVII). The facile decarboxylation indicated that the original hydroxyl group was beta to the carbomethoxyl group and hence was attached to $C_{17}$. The complete basic structure of yohimbine was therefore determined to be XXV, and the various reactions just described are represented in the scheme shown on the following page.

Yohimbine possesses five asymmetric carbon atoms--$C_3$, $C_{15}$, $C_{16}$, $C_{17}$ and $C_{20}$. These are indicated by asterisks in XXV. Stereochemical determinations of these five centers constituted the next phase of work in yohimbine chemistry. The investigations of several groups, and especially those of Janot and coworkers, led to the assignment of the relative stereochemistry as shown in XXV (60).

Much of the investigation undertaken on this stereochemical problem was conducted not only on yohimbine itself

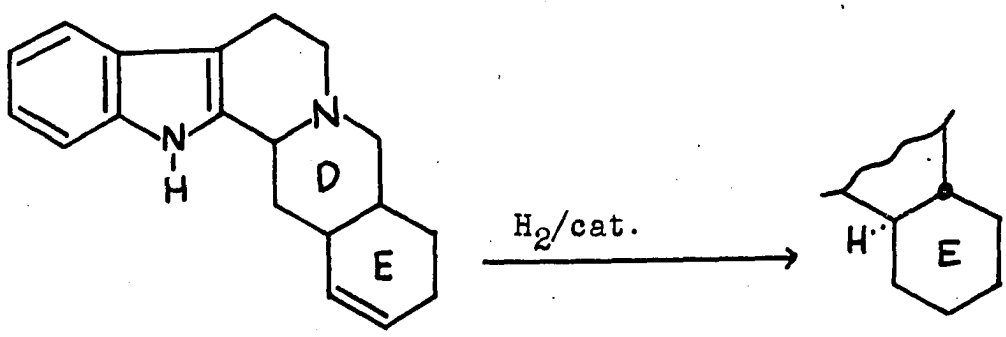



XXV XXVI XXVII

but also on a number of stereoisomers of the alkaloid which had become known to alkaloid chemists since the yohimbine studies were first begun. The structure determinations of these compounds followed very closely the degradative steps used to deduce the structure of yohimbine. A detailed discussion of the former will therefore not be included here, although appropriate literature references will be given wherever necessary.

A potassium hydroxide treatment of the sulfuric ester

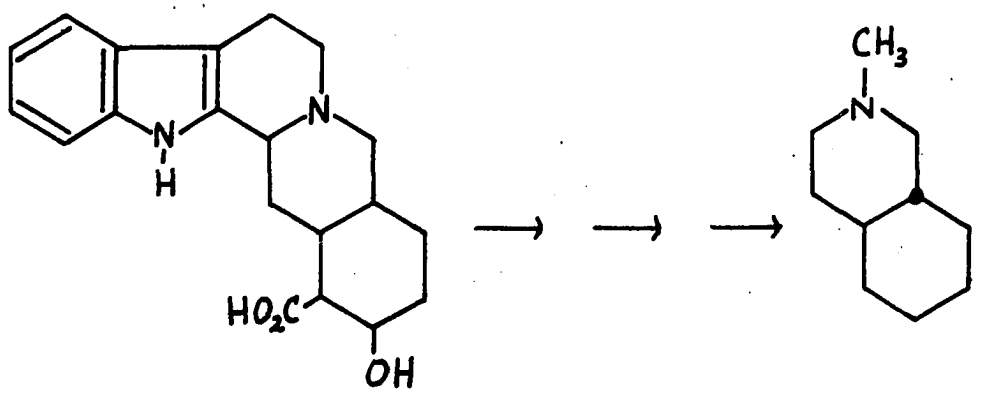
of corynanthine, a stereoisomer of yohimbine (62), in a manner similar to the reaction which had converted yohimbine to apoyohimbine (59), effected not only a dehydration, as in the case of the yohimbine derivative, but also a decarboxylation (60). The product so formed, apocorynanthol (XXVIII), could be catalytically hydrogenated to yohimbane (XXIX), the Wolff-Kishner reduction product of yohimbone (XXVII). Since the loss of the sulfuric ester group proceeds by a trans elimination, these experimental observations suggested that in yohimbine the $C_{16}$ hydrogen and the $C_{17}$ hydroxyl were trans to each other, and in corynanthine, the $C_{16}$ carbomethoxyl and the $C_{17}$ hydroxyl were trans to each other. The observed easier saponification of yohimbine suggested that its carbomethoxyl group occupied an equatorial position. Furthermore, it was observed by Janot and Goutarel (61) that acid hydrol-




XXVIII XXIX

ysis of corynanthine gave corynanthic acid, but that basic hydrolysis yielded the epimeric yohimbic acid, identical with that prepared by basic hydrolysis of yohimbine. This suggested a base equilibration of the carboxyl group in corynanthic acid to the more stable equatorial conformation present in yohimbic acid. These investigations thus revealed that a cis relationship existed between the $C_{16}$ carbomethoxyl group and the $C_{17}$ hydroxyl group in yohimbine, with the former occupying an equatorial conformation and the latter an axial one. Furthermore it was also determined that yohimbine and corynanthine were epimeric at only one center, $C_{16}$.

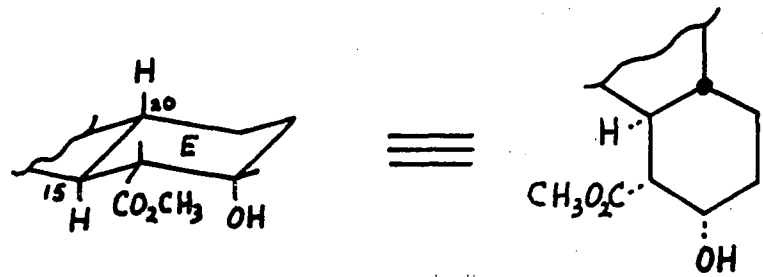
Through degradations of yohimbic acid (XXX) to an N-methylisoquinoline (XXXI), Witkop showed by comparison of this product with one of known configuration that the two rings were trans-fused (63). Since none of the degradative steps carried out on yohimbic acid were believed to involve or




XXX XXXI

alter any of the ring junction carbons, it was concluded that in yohimbine, the D/E ring junction was also trans.

The experimental observations thus far discussed allow the following partial representations (XXXII) to be made for yohimbine, showing the relative steric configurations of four of the five asymmetric centers. Further studies by Witkop on

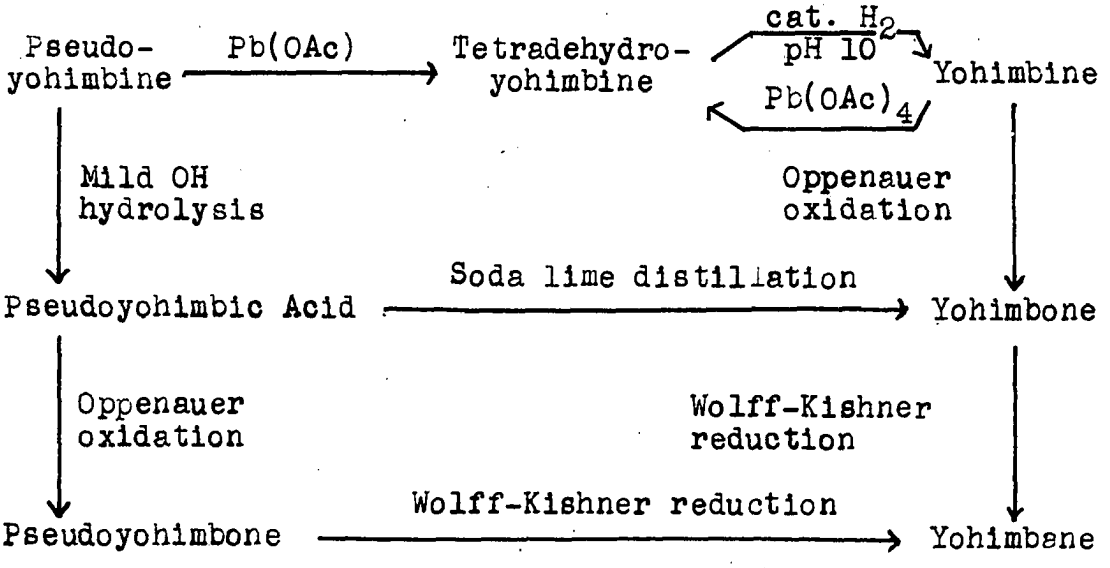



XXXII

yohimbol, the Meerwein-Ponndorf reduction product of yohimbone, confirmed these relative configurational assignments (49). The one remaining asymmetric center to be discussed is $C_3$.

Investigations undertaken by Janot and coworkers on pseudoyohimbine, another stereoisomer of yohimbine (64), gave information concerning the $C_3$ stereochemistry in yohimbine. Treatment of pseudoyohimbine with lead tetraacetate gave a ring-C tetradehydro derivative which was identical in all respects with that obtained by the same reaction steps from yohimbine (60). Since $C_3$ was the only asymmetric center involved in the oxidation, it could be deduced that yohimbine and pseudoyohimbine were epimeric

only at $C_3$. The assumption that the $C_3$ configuration in yohimbine was the more stable of the two was made on the observation that catalytic reduction at pH 10 of the tetrahydro derivative from either alkaloid regenerated yohimbine in good yields. This stability was further illustrated by other reactions outlined in the following scheme. Since



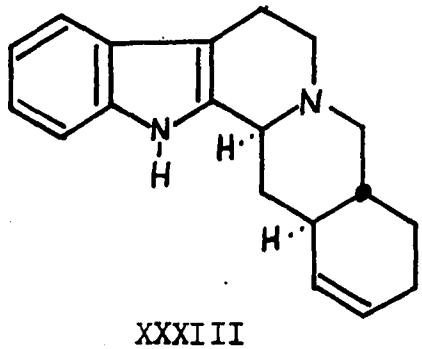

the hydrogen at $C_3$ is the most acidic ring junction hydrogen, it might be expected to epimerize under strongly basic conditions, such as those present in soda-lime distillations and Wolff-Kishner reductions, to the most stable configuration, if this is not already present. The epimerizations of the pseudoyohimbine derivatives (pseudoyohimbic acid and pseudoyohimbone) to the yohimbine derivatives (yohimbone and yohimbane, respectively) lend credence to the assignment of the more stable $C_3$ configuration to yohimbine. From steric

considerations, the structure bearing the greatest number of equatorial substituent bonds would be the most stable. For a system with a trans D/E ring junction, the most stable $C_3$ configuration then would be the one in which the hydrogen occupied an axial position and the $C_2$-$C_3$ bond an equatorial one. The relative configurations of all the asymmetric centers in yohimbine were thus determined and are as illustrated in XVIII (60, 65).

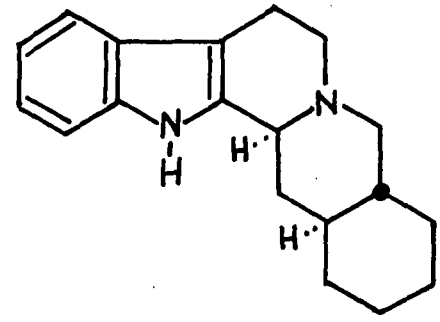
Proof of the relative stereochemistry of the ring junction carbon atoms, $C_3$, $C_{15}$ and $C_{20}$, as shown in XVIII, was provided by van Tamelen and coworkers in their stereospecific synthesis of dl-yohimbane, the Wolff-Kishner reduction product of yohimbone (66). This was soon followed by the total synthesis of d-pseudoyohimbine in 1958 (67). Since the epimerization of pseudoyohimbine to yohimbine had previously been reported (60, 68), this work also constituted a formal total synthesis of yohimbine. Another synthesis of the alkaloid, using yohimbone as the starting material, has been reported by Aksanova and Preobrazhenskii (69). Since the total synthesis of yohimbone has been accomplished (70), the Russian synthesis may also be regarded as a total synthesis of yohimbine.

In 1953, Klyne showed through molecular rotation studies that the relative stereochemistry depicted in XVIII is also the absolute configuration of naturally occurring yohimbine

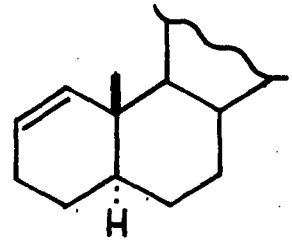
in terms of the D-glyceraldehyde convention (71). Comparison of the $[\overline{M}]_D$ of apocorynanthol ($-522^o$) (XXXIII) and of yohimbane ($-230^o$) (XXXIV) showed that the rotation contribution of the ring E double bond was $-292^o$. The corresponding double bond in ring A of steroids with known absolute configuration (XXXV) has been shown to contribute a positive rotation (72). Therefore the absolute configurations of apocorynanthol and of yohimbane are as indicated in XXXIII and XXXIV respectively.



XXXIII



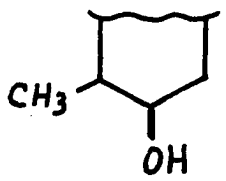
XXXIV



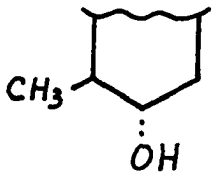
XXXV

Due to the relative stereochemistry of the $C_{16}$ carbomethoxyl and $C_{17}$ hydroxyl groups to the rest of the molecule, it was then also possible to assign them absolute configurations on the basis of this work. Further proof of an

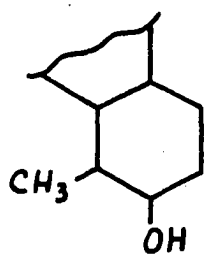
α-orientation for the $C_{17}$ hydroxyl group, and consequently an α-carbomethoxyl orientation, was provided shortly thereafter by further investigations of Klyne and Stokes (73). They conducted molecular rotation studies on a number of different cyclohexanols, and observed that the rotation contribution of the hydroxyl group in a structure with the configuration XXXVI was negative, and that of a hydroxyl in a structure of configuration XXXVII was positive. The observation was made that the $\Delta[M]_D$ between 16-methylyohimbane




XXXVI




XXXVII

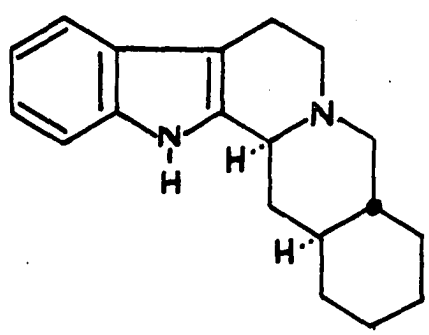



XXXVIII

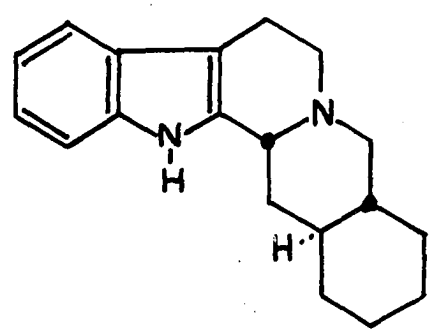
($[M]_D$-168°) and 16-methylyohimbol ($[M]_D$~0°) (XXXVIII-stereochemistry not indicated) was +168°. This positive contribution due to the hydroxyl group led Klyne and Stokes to assign an α-absolute configuration to the yohimbine $C_{17}$ hydroxyl and consequently an α-configuration also to the $C_{16}$-carbomethoxyl. These results confirmed their earlier assignment of XVIII as the correct absolute representation of (+) yohimbine.

While molecular rotation studies provided a pathway for

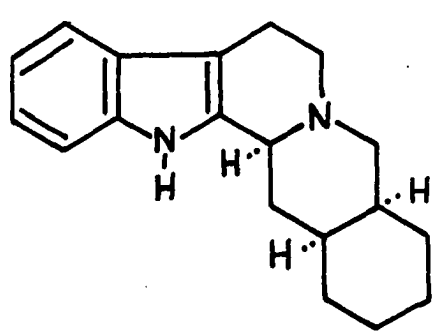
the eventual determination of the absolute configuration of yohimbine, this was not the sole area of investigation toward the determination of the stereochemical nature of the three asymmetric centers common to most of the yohimbe bases--$C_3$, $C_{15}$ and $C_{20}$. It became possible to establish four subclasses for these indolic alkaloids on the basis of the relative stereochemistry of these centers. The "normal" series is represented by yohimbane (XXXIX) whose formation from yohimbine has been discussed earlier. The second series, the "pseudo" series, is represented by pseudoyohimbane (XL),



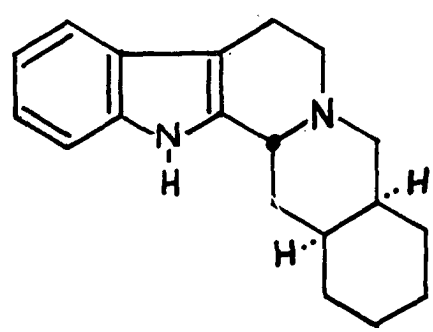
XXXIX



XL

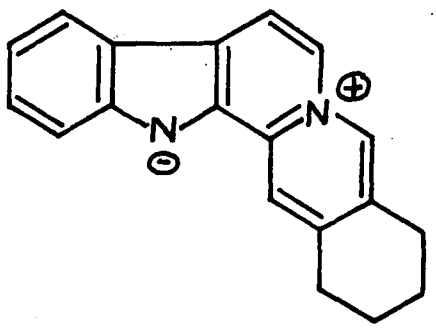


XLI



XLII

the $C_3$ epimer of yohimbane. This compound has been prepared by Wenkert and Roychaudhuri by zinc and acetic acid reduction of 3,4-dehydroyohimbane (74). The relationship between the parent compounds, yohimbine and pseudoyohimbine, has also been determined experimentally and has been discussed already. Alloyohimbane, the parent compound of the "allo" series, is represented by XLI. This stereoisomer possesses a cis D/E ring junction and has been prepared by catalytic hydrogenation of sempervirine (XLIII) (75, 76), and by chemical transformations of alloyohimbine, the $C_{20}$ stereoisomer of yohimbine (77). The stereochemistry assigned to alloyohimbane as



XLIII

depicted in XLI has recently been proven correct by the stereospecific synthesis of the racemic compound by Stork and Hill (78, 79). The representations in XLI also depict the correct absolute configurations of all asymmetric centers as determined by molecular rotation differences (80). The $C_3$ epimer of alloyohimbane is represented by XLII and serves as the model for the fourth series, the "epiallo" series. The

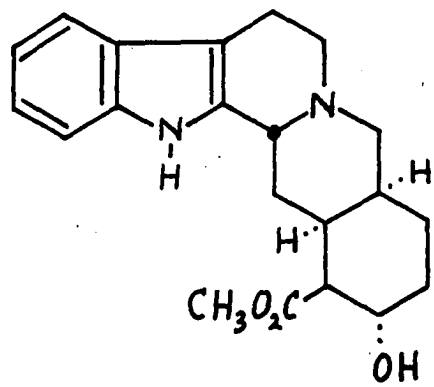
compound has been obtained as a minor product in the catalytic hydrogenation of sempervirine (75, 76) and by Raney nickel desulfurization of the ethylene thioketal of 3-epialloyohimbone, the Oppenauer oxidation product of 3-epialloyohimbine (81).

A number of investigators have been concerned with 1) the classification of yohimbé alkaloids into one of these several sub-groups, 2) the correlation of one series with another by physical or chemical means, and 3) the chemical determinations of the absolute stereochemistry of representative members of each class. Notable accomplishments have been made by Wenkert in the development of procedures useful in these areas.

In 1956 Wenkert and Roychaudhuri reported an infra-red method for the determination of $C_3$-hydrogen configurations of yohimbé alkaloids (74). They observed that compounds in the "normal" and "allo" series showed several distinct peaks on the longer wavelength side of the main C-H peak at 3.46 $\mu$ in the infra-red region. In comparison to this, compounds belonging to the "pseudo" and "epiallo" series showed only slight shoulders in this region. By means of this physical method, it was thus possible to distinguish $\alpha$-oriented $C_3$ hydrogens, as found in "normal" and "allo" compounds, from $\beta$-oriented hydrogens, characteristically found in "pseudo" and "epiallo" compounds. Applications of this analytical procedure enabled these investigators to confirm the stereo-

chemical assignments made to a number of indole alkaloids and also to assign $C_3$ configurations to a number of other alkaloids with unknown stereochemistry at this center.

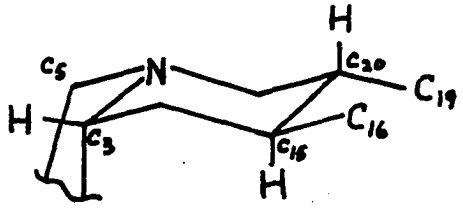
Development of several oxidation-reduction procedures by Wenkert and Roychaudhuri have made possible other means for facile determinations of alkaloid stereochemistry. One of these methods utilized the rates of ring-C dehydrogenations as a means for determining the stereochemistry at $C_3$ (82, 83). The oxidation system employed was palladium-black and maleic acid. "Epiallo" compounds such as epialloyohimbane and 3-epi-$\alpha$-yohimbine (XLIV) were observed to oxidize at an appreciably lower rate than the corresponding "pseudo" compounds such as



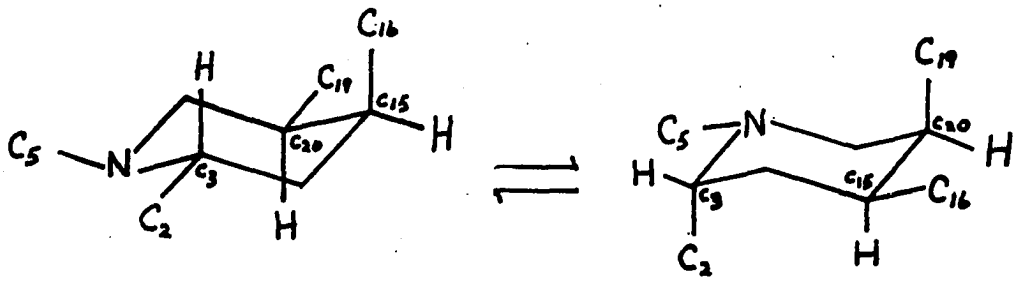

XLIV

pseudoyohimbane and pseudoyohimbine. Since it is reasonable to assume that the degree of accessibility of the $C_3$-hydrogen to the catalytic surface governs the rate of oxidation, these experimental findings are in accord with the presence of a $\beta$ $C_3$ hydrogen in the "pseudo" series which is less sterically

hindered than the corresponding hydrogen in the "epiallo" series. This can be illustrated by the following conformational diagrams. Application of this method thus makes




XLV "Pseudo"



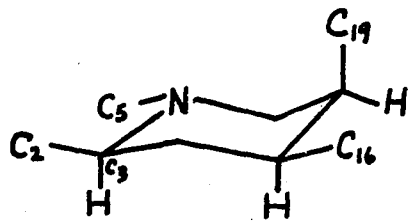

XLVIa "Epiallo" XLVIb

possible the distinction between these two series of indole alkaloids.

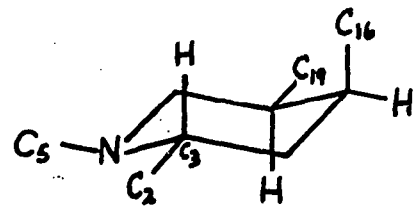
Reductions of ring-C didehydro and tetradehydro derivatives were also utilized by Wenkert as further diagnostic procedures for stereochemical determinations. The 3,4-dehydro systems, best prepared by mercuric acetate oxidation of the corresponding alkaloids, were reduced either catalytically over platinum oxide or with sodium borohydride in methanol (83, 84). Analyses of the products revealed that only

"normal" or "allo" compounds were formed, e.g. yohimbane and alloyohimbane from the corresponding 3,4-dehydro derivatives. Similar reductions of the 3,4,5,6-tetradehydro derivatives, with sodium borohydride or by catalytic means at pH 10, regenerated "normal" products solely from those tetradehydro compounds with trans D/E ring junctions. For those compounds with cis D/E ring junctions, regeneration of the "allo" compounds predominated over the "epiallo" among the products.

The mercuric acetate oxidation of ring C of indole alkaloids was proposed by Welsenborn and Diassi as a means for distinguishing "normal" and "allo" compounds, which undergo the oxidation easily, from "pseudo" and "epiallo" compounds, which do not (85). The supposition was made that this reaction was useful for detecting an axial from an equatorial $C_3$ hydrogen since it was believed that the former was necessary for the oxidation to occur. However, as pointed out by Wenkert, this does not sufficiently explain the observed experimental results since both "allo" and "epiallo" systems may possess conformations with axial $C_3$ hydrogens as illustrated in the following diagrams (84, 86). The diagrams also suggest that




XLVII "Allo"



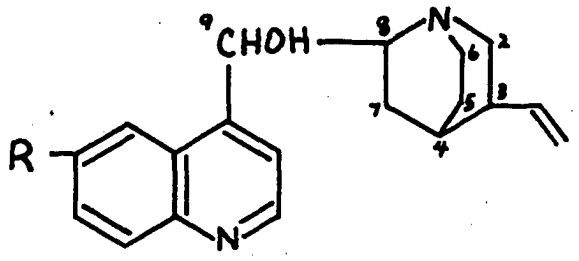

XLVIII "Epiallo"

steric interference due to ring E constituents may explain the non-reactivity of the "epiallo" system toward mercuric acetate.

Due to the development of these classification procedures, it has been possible to categorize a large number of indole alkaloids into one of these four stereochemical classes. The determination of the absolute configuration of yohimbine by physical means, as elaborated earlier, has further enabled alkaloid chemists to assign absolute configurations to all alkaloids which have been stereochemically related to it.

In spite of these significant accomplishments in alkaloid chemistry, there nevertheless still remains the desirability of proving or determining absolute configurations by chemical rather than physical methods. Reference has already been made to some accomplishments of this sort in families other than the indole alkaloids. One study which has made possible the recent chemical determination of the absolute stereochemistry of several indole alkaloids was the elucidation of the configurations of the cinchona alkaloids.

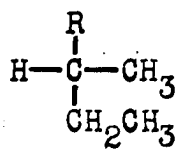
In 1944, Prelog and Zalan reported the absolute configurations of the three asymmetric centers on the quinuclidine unit of the cinchona alkaloids, (+) cinchonine (XLIXa), (-) quinine (XLIXb) and two stereoisomers, (-) cinchonidine and (+) quinidine respectively (87). Degradation of




XLIXa: R = H

XLIXb: R = $-OCH_3$

cinchonine by reactions which did not affect the stereochemistry at $C_3$ and $C_4$ ultimately yielded an optically active hydrocarbon, 3-methyl-4-ethylhexane, $[\alpha]_D^{18}$ -12°, in which carbons 3 and 4 corresponded to $C_3$ and $C_4$ of the original cinchonine molecule. On the basis of work done by Levene and Marker (88, 89), the asymmetric center of this hexane degradation product was assigned the configuration La in terms of the D-glyceraldehyde convention. Confirmation of this assignment was made by converting (-) methylethylacetic acid (Lb) of known configuration to a 3-methyl-4-ethylhexane with



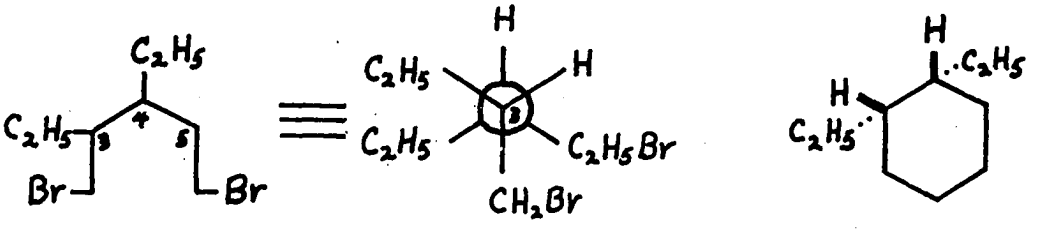

La: R = $-CH(CH_2CH_3)_2$

Lb: R = $-CO_2H$

levorotatory powers which was identical to the cinchonine degradation product (90). By these means, the absolute configuration of $C_3$ in cinchonine was established.

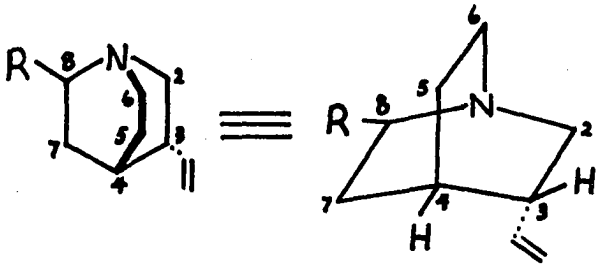
To determine next the configuration of $C_4$, use was made

of (+) 3-bromomethyl-4 (β-bromoethyl)hexane (LIa), an intermediate in the degradation of cinchonine just discussed. This intermediate was converted by mild controlled reactions to a 1,2-diethylcyclohexane which showed no optical activity. Neither of the two asymmetric centers in the starting compound was believed affected in the conversion, and it could be concluded that the dibromo starting material possessed the "erythro" configuration, as illustrated by LIb. This accounted for the formation of this "meso" diethylcyclohexane (LII)

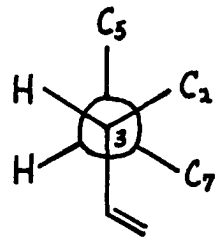



LIa LIb LII

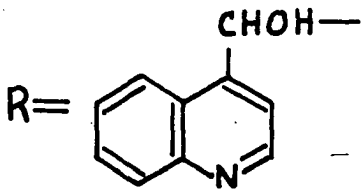
as a degradation product. The determination of this cis relationship between the two ethyl groups provided proof for the assignment of an endo configuration to the $C_3$-vinyl group of cinchonine as depicted in LIIIa and LIIIb (stereochemistry of $C_8$ unassigned). Only with the endo configuration at $C_3$ was it possible by the sequence of degradative steps employed in the study to obtain a product in which the ethyl groups, derived from the $C_3$-vinyl group and the $C_4$-$C_7$-$C_8$ carbon chain, were cis to one another. This is best illustrated by use of the Newman projection diagram LIIIc.



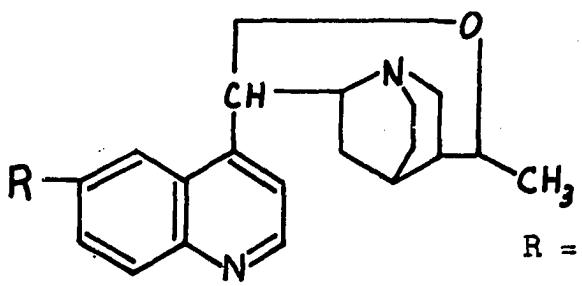
LIIIa LIIIb



LIIIc



The stereochemistry of the remaining asymmetric center, $C_8$, on the quinuclidine nucleus of cinchonine may be such that the $C_8$-$C_9$ bond is cis to the $C_3$-vinyl group and hence also endo, or trans to the $C_3$-vinyl group and hence exo. To assign correctly the $C_8$ stereochemistry, it was only necessary to interpret the experimental observations that only the dextrorotatory alkaloids, cinchonine and quinidine, formed ethers of the type shown in LIV when exposed to acids (91, 92). Since ethers of this structure could be formed only if the

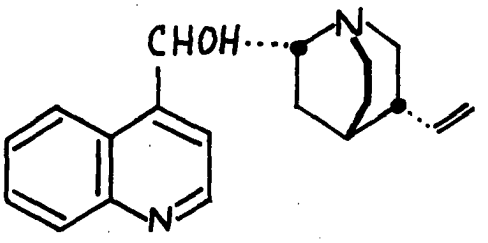


LIV

R = -H (cinchonine derivative)

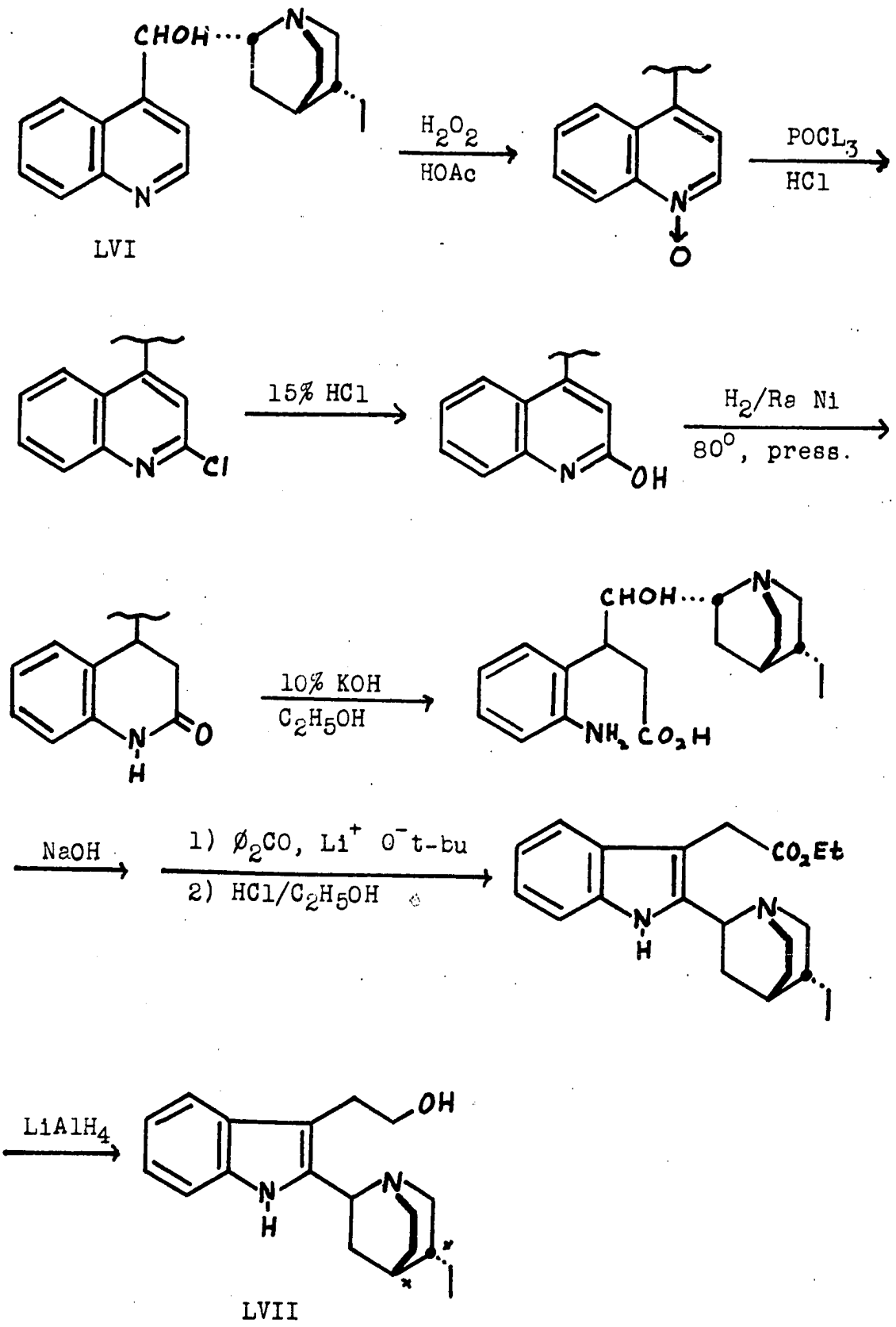
R = $-OCH_3$ (quinidine derivative)

$C_3$ and $C_8$ substituents were cis to each other, and since it has been determined that the $C_3$-vinyl group possesses an endo configuration, the configuration at $C_8$ must be that one in which the $C_8$-$C_9$ bond is also endo to the quinuclidine bridge. The absolute configurations of the three quinuclidine asymmetric centers in cinchonine may thus be represented as in LV.



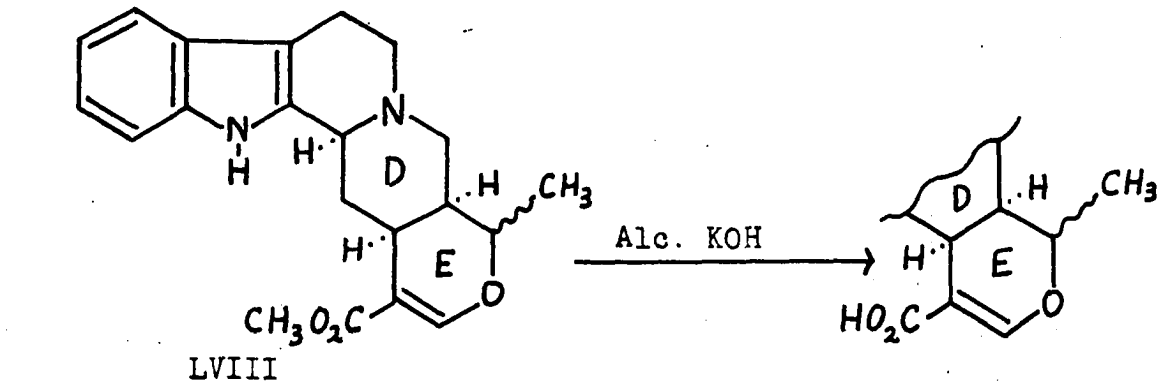

LV

The years 1958 and 1959 brought further significant contributions to the growing knowledge of absolute configurations of alkaloids through chemical determinations from Ochiai and coworkers in Japan and Wenkert and coworkers in this country. In the notable work briefly summarized in the scheme on the following page, Ochiai and Ishikawa carried out the conversion of dihydrocinchonine (LVI) to dihydrocinchonamine (LVII), thereby successfully relating by chemical means the cinchonine family with one of the indole alkaloid families (93, 94). The product was identical with dihydrocinchonamine in melting point, infra-red and ultra-violet spectra. Due to the earlier work of Prelog on the absolute configurations of $C_3$ and $C_4$ of cinchonine (87), it became possible through this work by

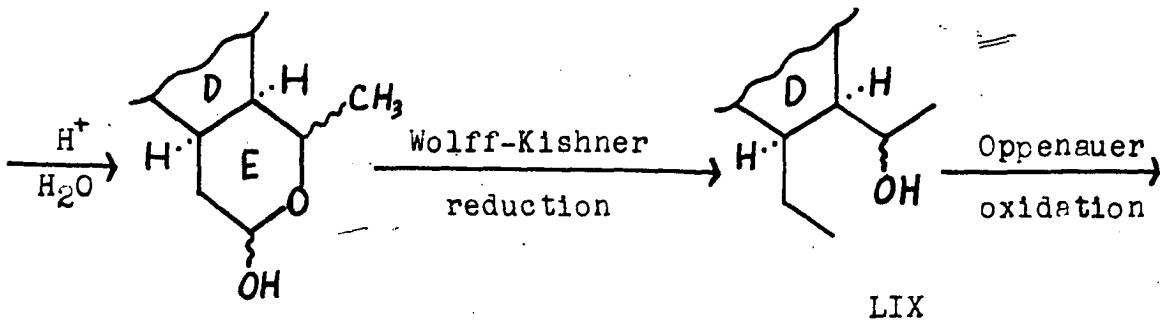

CHOH
N
$H_2O_2$
HOAc
$POCl_3$
HCl
O
LVI
15% HCl
Cl
OH
$H_2$/Ra Ni
80°, press.
10% KOH
$C_2H_5OH$
$NH_2$ $CO_2H$
NaOH
1) $\phi_2CO$, $Li^+$ $O^-$t-bu
2) HCl/$C_2H_5OH$
$CO_2Et$
$LiAlH_4$
LVII

Ochiai to assign absolute configurations to two of the asymmetric carbons of the quinuclidine component of dihydrocinchonamine, as designated by asterisks in LVII. Due to the stringent conditions of the Oppenauer oxidation employed in the conversion, it is not possible to assign a conclusive absolute configuration to the $C_8$-hydrogen in dihydrocinchonamine, although one might expect it to equilibrate to the most stable configuration. This would be the one depicted in LVII in which the hydrogen was $\alpha$ and endo and the indole unit $\beta$ and exo. The synthesis of the un-reduced naturally occurring alkaloid, (+) cinchonamine, has been reported by Chen and coworkers (95, 96).

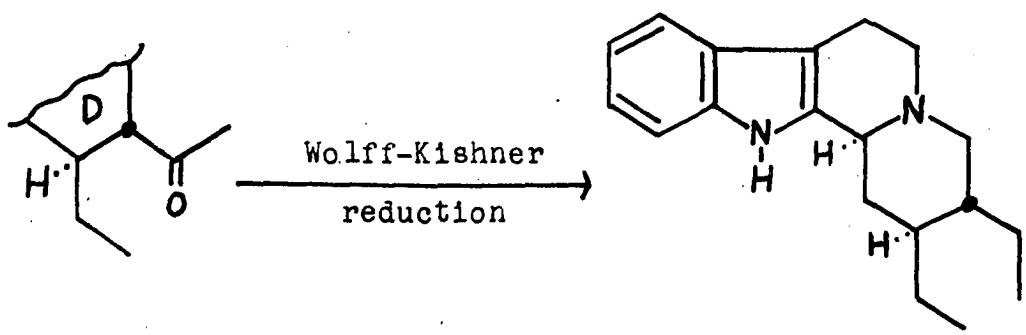
The correlations accomplished by Ochiai made it possible for Wenkert and Bringi to chemically relate the cinchona bases with the yohimbe bases shortly thereafter. Correlation between the two indole alkaloids, ajmalicine (LVIII) and corynantheine (LXII), was accomplished first by the series of reactions illustrated on the following page (97, 98). In conducting the Oppenauer oxidation on the alcohol LIX, an equilibration occurs under the strongly basic conditions to produce the most stable configuration at $C_{20}$ for the ketonic product LX. Since the $C_3$ hydrogen is the most acidic of the three ring junction hydrogens, it should also be possible to epimerize it if necessary under the basic conditions of the Oppenauer oxidation to give the most stable configuration, that shown in LXI. The final degradation product, LXI, was




LVIII



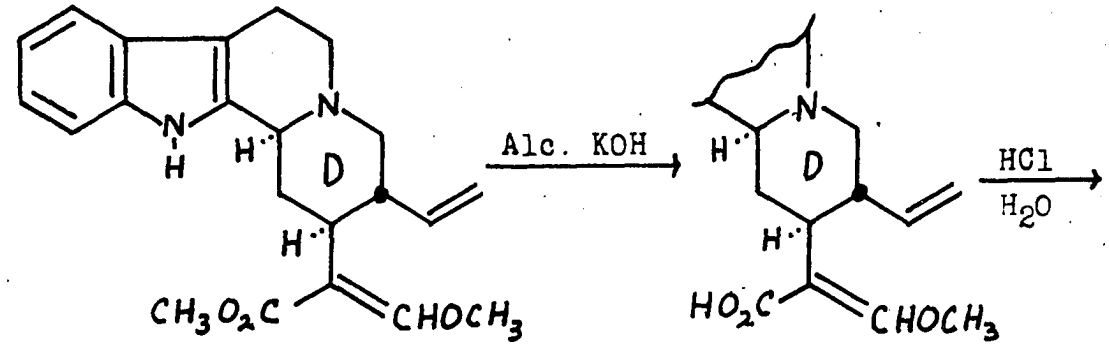

LIX



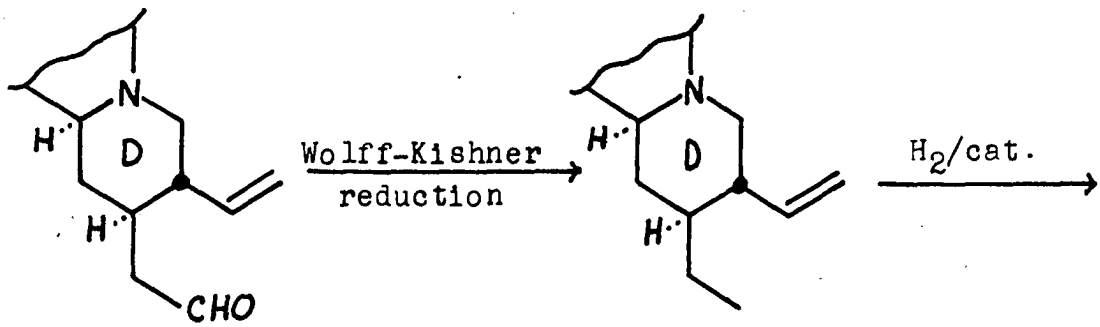

LX LXI

identical in its melting point, specific rotation and infrared spectrum with 18,19-dihydrocorynanthean (LXIV), the degradation product of corynantheine (LXII) obtained through a similar sequence of reactions by Janot and Goutarel (99,

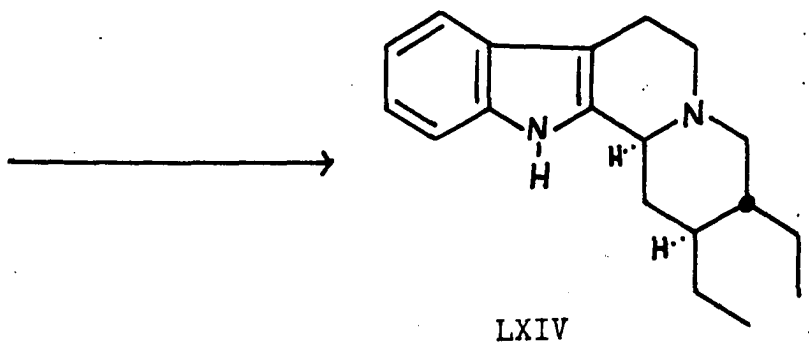
100, 101). The degradative scheme is given below.




LXII




LXIII

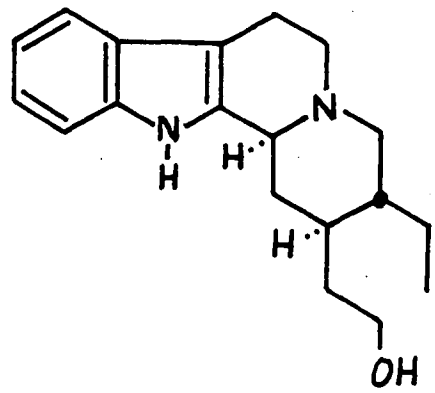


LXIV

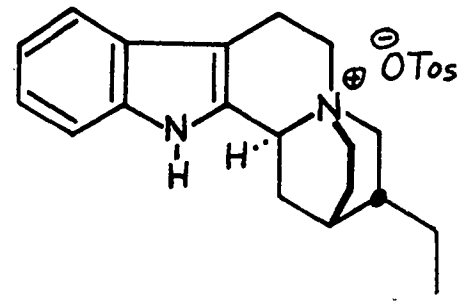
Having thus correlated these two systems of indole alkaloids, Wenkert and Bringi then proceeded to determine the absolute configurations of ajmalicine and corynantheine by chemical correlation of the latter with dihydrocinchonamine,

the absolute configuration of which had been determined by Ochiai (93, 94).

18,19-Dihydrocorynantheol (LXV), prepared by lithium aluminum hydride reduction of 18,19-dihydrocorynantheal (LXIII with vinyl group reduced) (102), was treated with tosyl chloride in pyridine (97, 98). The tosylate thus formed was then heated in refluxing dimethylformamide to yield the quanternary




LXV

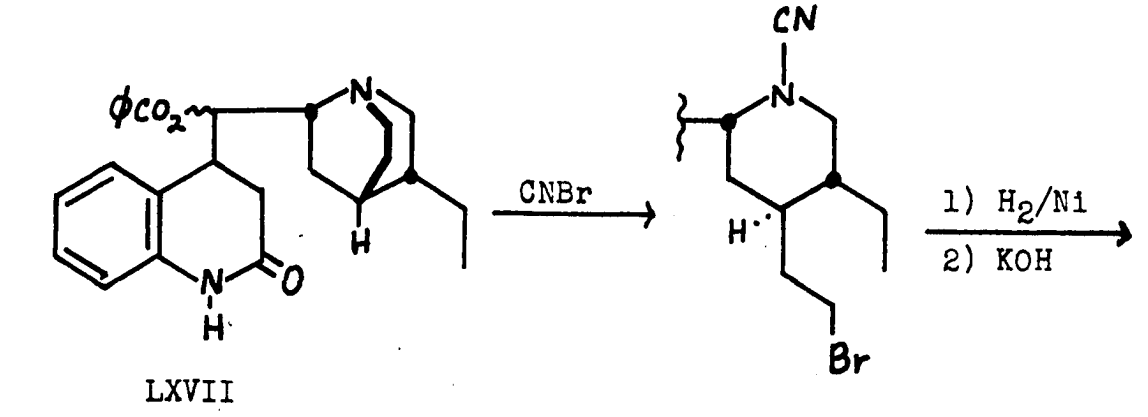



LXVI

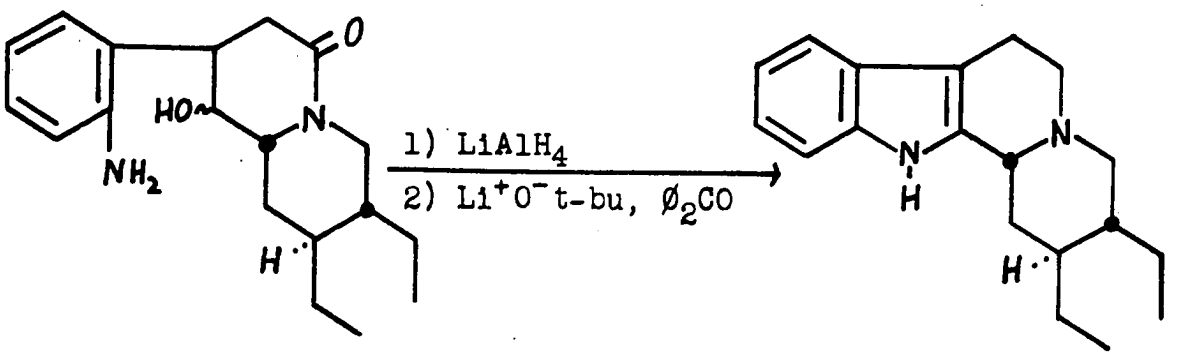
ammonium tosylate salt LXVI. Similar treatment of dihydrocinchonamine (LVII) with tosyl chloride in pyridine yielded a quaternary ammonium chloride which could be converted to the tosylate salt by treatment with silver tosylate. This tosylate salt was identical in all respects (melting point, specific rotation and infra-red spectrum) with the salt obtained from 18,19-dihydrocorynantheol. Due to the work of Ochiai and Ishikawa on the dihydrocinchonamine configuration (LVII) as described earlier, it was possible through these

correlations of Wenkert and Bringi to show that the stereochemistry of ajmalicine and corynantheine as depicted in LVIII and LXII respectively is in effect also the correct absolute stereochemistry of each alkaloid. The total synthesis of d,l-ajmalicine has recently been reported by van Tamelen and Placeway (103).

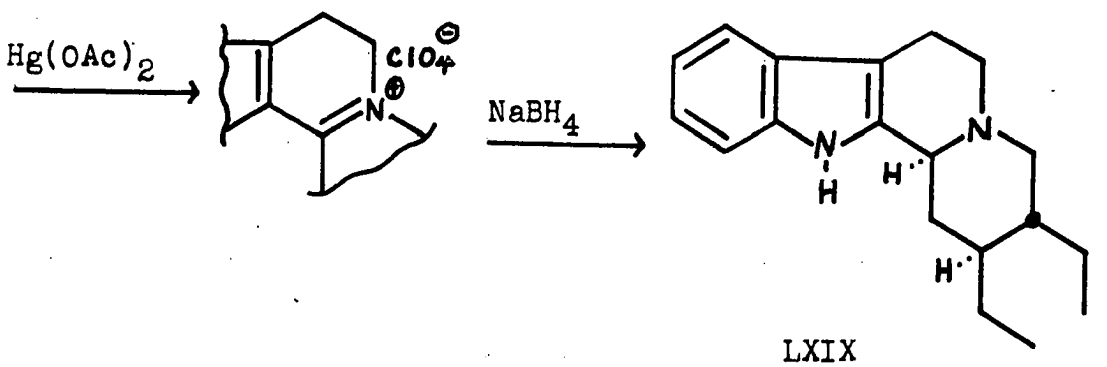
The same conclusion regarding the configuration of corynantheine was reached by Ochiai and Ishikawa by an independent study in which cinchonine was converted into 18,19-dihydrocorynantheane (104, 105). Starting material for their study was the 9-benzoyl derivative (LXVII) of an intermediate in their earlier conversion of dihydrocinchonine to dihydrocinchonamine (a discussion and reaction scheme of this conversion have been given earlier). The reaction sequence to which this 9-benzoyl derivative was exposed is represented by the scheme shown on the following page. The initial product, LXVIII, was shown to be 3-epi-18,19-dihydrocorynanthean on the basis of its infra-red spectrum and its reluctance to undergo oxidation with mercuric acetate under the normal reaction conditions. Treatment under more stringent conditions gave a 3,4-didehydro derivative which produced, upon reduction with sodium borohydride, a compound (LXIX) that was identical in melting point, specific rotation and infra-red spectrum to authentic 18,19-dihydrocorynantheane. It is not readily obvious why the 3-epi compound appeared




LXVII




LXVIII




LXIX

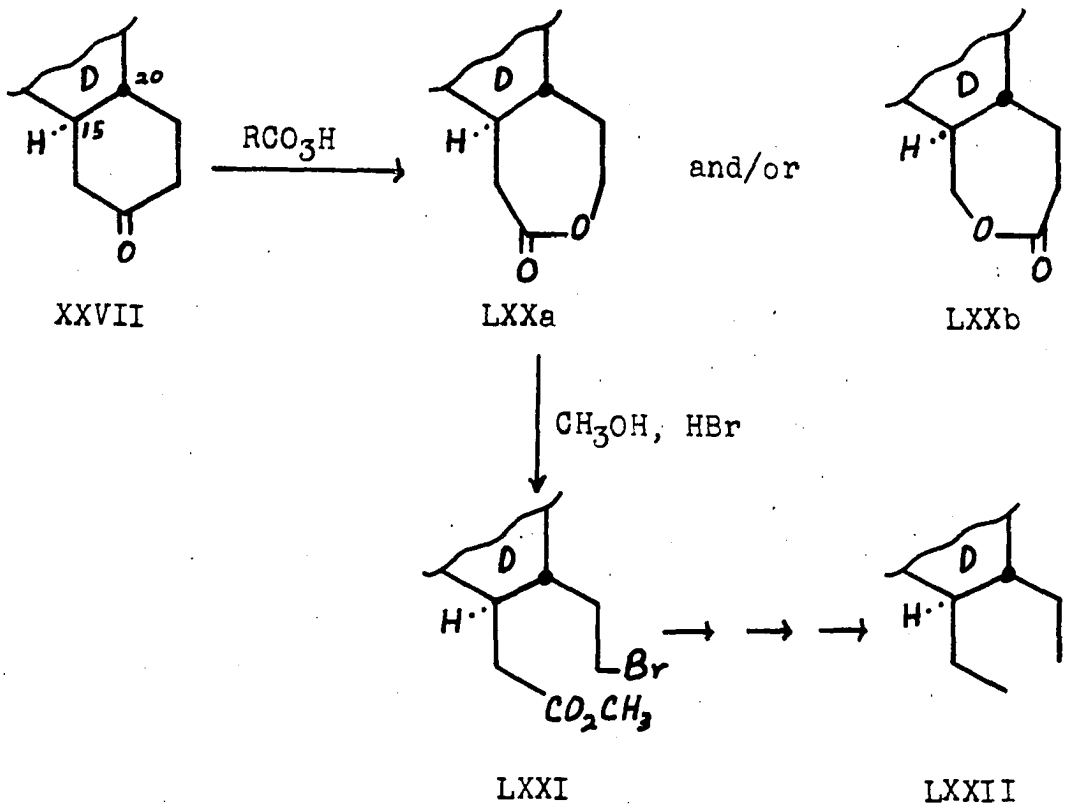
as the initial product rather than the more stable "normal" diastereomer possessing an $\alpha$ $C_3$-hydrogen. One would have expected an equilibration to take place to the most stable epimer during the stringent Oppenauer oxidation step in the reaction sequence.

It is significant to call attention to the fact that all configurational determinations to date in the field of indole alkaloids indicate that one center, $C_{15}$, of all the possible asymmetric centers present in these alkaloids, possesses the same $\alpha$-configuration for its hydrogen atom in all alkaloids thus far investigated. This unique characteristic, pointed out by Wenkert (97, 98, 106), has been incorporated by the same as an important factor in the proposal of a theory of indole alkaloid biosynthesis (98).

# DISCUSSION

As part of an investigation of the stereochemistry of indole alkaloids, it became desirable to correlate chemically the ring-E carbocyclic compounds such as yohimbine (XVIII), possessing trans D/E ring junctions, with the 17,18-seco (ring-E open) or the ring-E heterocyclic compounds, represented respectively by corynantheine (LXII) and ajmalicine (LVIII). Previous work in this area of investigation has already made possible the correlations between 1) the D/E cis and the D/E trans carbocyclic yohimbe bases, represented by 3-epi-α-yohimbine (XLIV) and yohimbine (XVIII) (106) and 2) between the 17,18-seco and the ring-E heterocyclic bases, represented by corynantheine and ajmalicine (97, 98).

The most expedient procedure for relating the ring-E carbocyclic series with the ring-E open and heterocyclic series appeared to be the peracid oxidation of yohimbone (XXVII) to a lactone (LXXa or LXXb) which could then be cleaved to yield a ring-E open intermediate. The preferred lactone (LXXa), upon treatment with methanolic hydrogen bromide, was expected to yield the intermediate LXXI which could subsequently be converted to a 15,20-diethyl compound (LXXII). Comparison of this product with 18,19-dihydrocorynantheane (LXIV), which has been prepared from both ajmalicine and corynantheine (97, 98, 99, 100, 101) would then effect a correlation between these classes of indole bases.



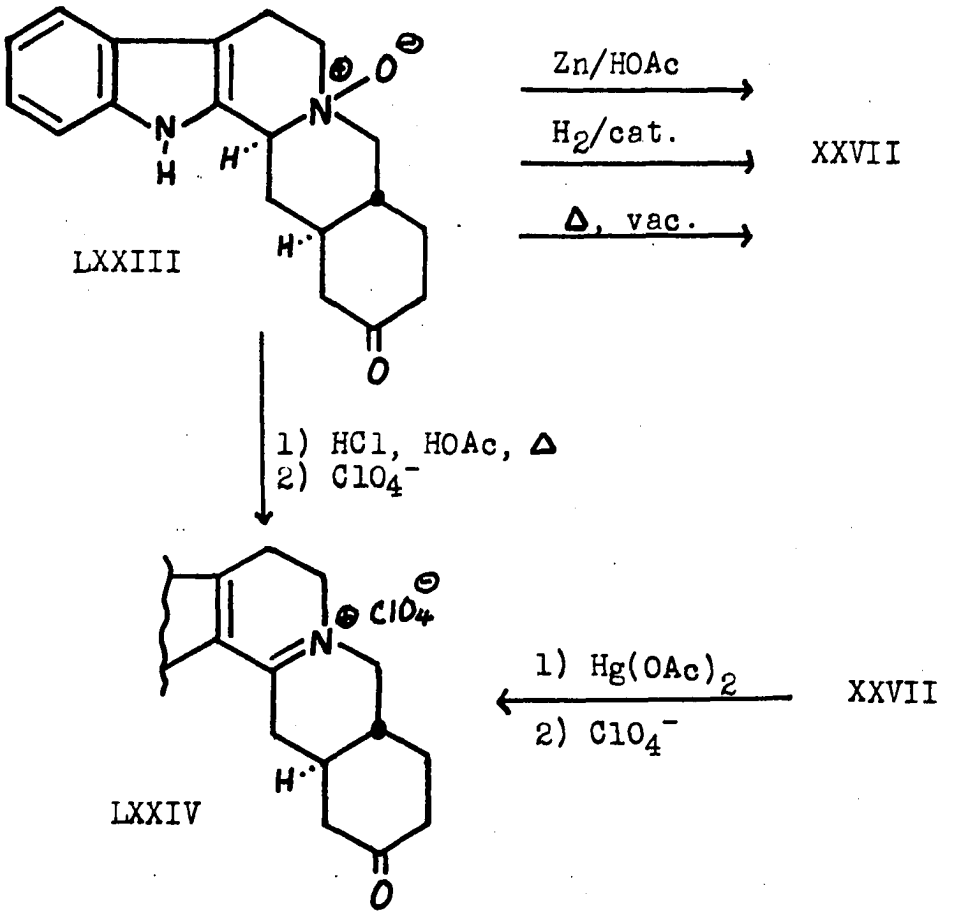

XXVII LXXa LXXb

LXXI LXXII

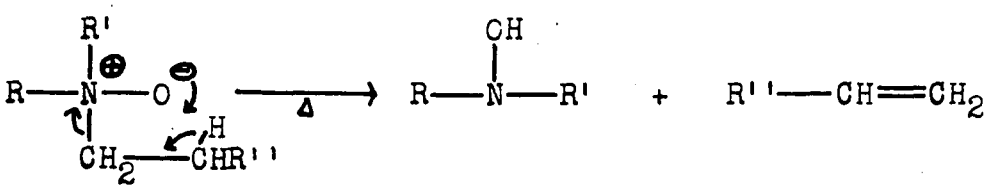
Emmons had shown that ketones may be oxidized in good yield to esters by trifluoroperacetic acid (107). The acidic medium which may be employed in this reaction made this procedure particularly attractive as the method of choice for conducting the desired oxidation of yohimbone. It was hoped that the formation of an $N_b$-salt by the interaction of the alkaloid with the trifluoroacetic acid present in the reaction mixture would prevent the formation of the $N_b$-oxide and allow the ring-E lactone formation to proceed preferentially. However, exposure of yohimbone to a trifluoroperacetic acid/

trifluoroacetic acid system gave only dark mixtures from which no recognizable organic products could be isolated.

It became necessary then to employ a more conventional oxidizing agent, such as perbenzoic acid. Treatment of yohimbone in chloroform with an equimolar quantity of perbenzoic acid, also in chloroform, gave a gelatinous precipitate which did not appear to be the desired lactone on the basis of solubility behavior and infra-red spectrum. Analysis of its picrate salt as well as results of several degradative studies which will be discussed presently revealed it to be yohimbone N-oxide (LXXIII).



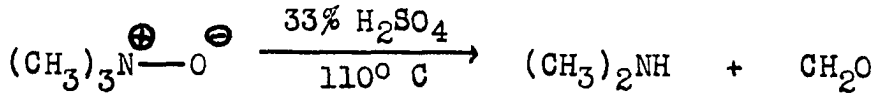
Reduction of the oxide by chemical or catalytic means regenerated yohimbone (XXVII). Exposure to a flash-pyrolysis/sublimation also yielded yohimbone. Although Cope and co-workers showed in 1949 that aliphatic amine oxides containing available $\beta$-hydrogens undergo elimination upon pyrolyses to yield olefins and substituted hydroxylamines (108), later



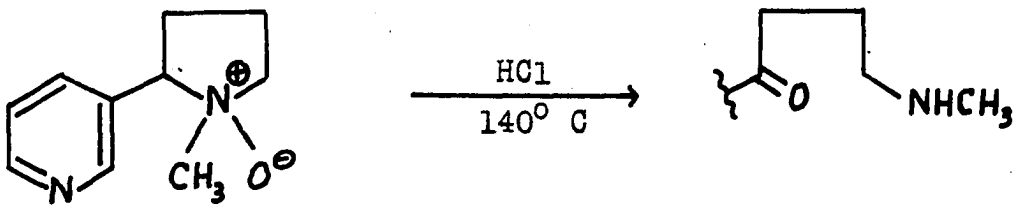
work showed that six-membered heterocyclic tertiary amine oxides are resistant to this cleavage process (109). Pyrolysis of N-methylpiperidine oxide, for example, gave N-methylpiperidine and piperidine as identifiable products. Failure of this oxide to undergo $\beta$-elimination was attributed to the inability of the required planar transition state to form in the six-membered heterocyclic strcuture. Similarly, in yohimbone N-oxide, this five-membered planar transition state cannot be formed to allow interaction of the N-oxide oxygen with any of the available hydrogens on the three $\beta$ carbons, $C_6$, $C_{14}$ and $C_{20}$. Consequently, no elimination products were formed.

With a hydrochloric acid/acetic acid treatment, the N-oxide was converted to a dehydro derivative of yohimbone (LXXIV) which compared favorably with the 3,4-dehydro product

formed by mercuric acetate oxidation of yohimbone. It has been shown that more stringent acidic treatments of amine oxides, for example, trimethylamine oxide (LXXV) and nicotine N-oxide (LXXVI), yielded isolable products containing secondary amine and carbonyl functional groups (110). The formation of the 3,4-dehydro product in the case of yohimbone

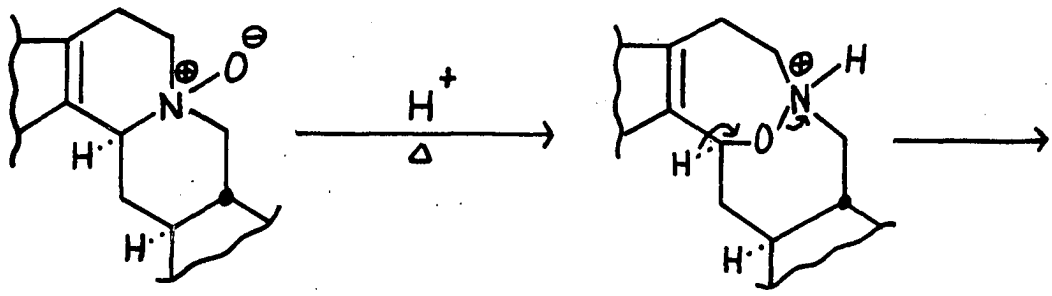



LXXV

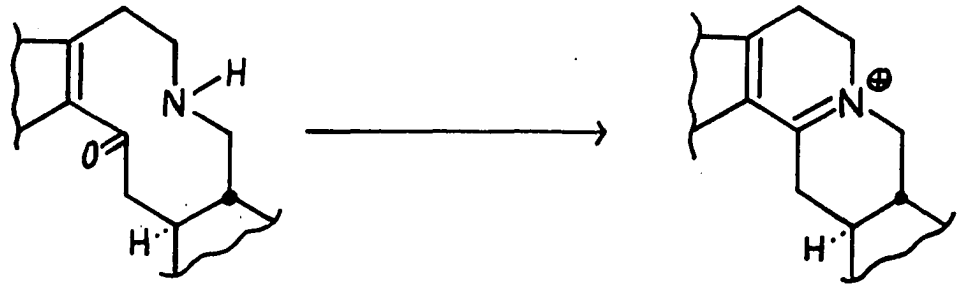



LXXVI

N-oxide may possibly be explained by the formation of the intermediate LXXVIIb containing a carbonyl group and a secondary amine group as parts of a ten-membered ring. Subsequent transannullar condensation between these two functional groups would then lead to the final product, LXXIV.

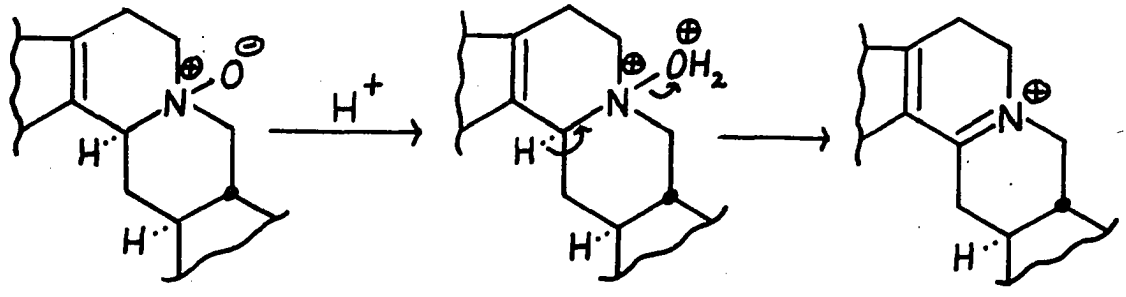


LXXIII LXXVIIa

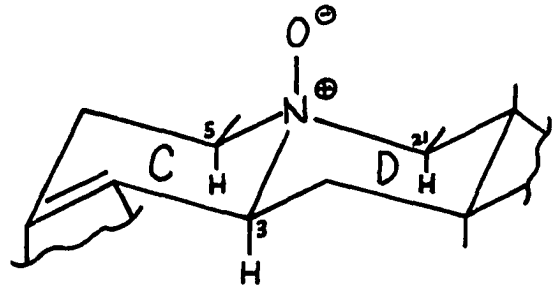


LXXVIIb LXXIV

Another pathway which may be proposed for the formation of the 3,4-dehydro product involves a simple elimination mechanism illustrated in the following scheme. This mechanism



is especially plausible since the N-O bond is most likely $\beta$-oriented (LXXVIII) and hence <u>trans</u> diaxially disposed toward the $C_3$ hydrogen atom--the most favorable configuration for elimination.

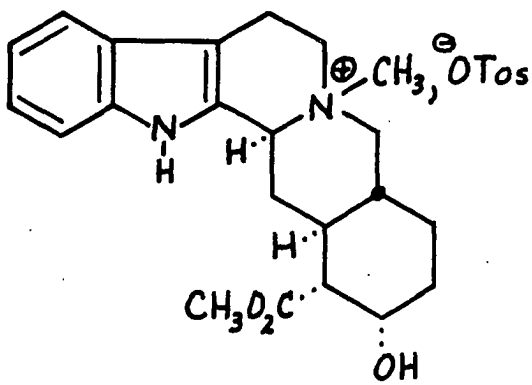



LXXVIII

It became important at this point, in connection with the stereochemical nature of $C_3$, to determine whether or not the $C_3$ hydrogen of Yohimbé alkaloids could be epimerized in the derivatives possessing quaternized $N_b$ atoms. In their work on the correlation of dihydrocinchonamine (LVII) with corynantheine (LXII), Wenkert and Bringi prepared the quaternary ammonium tosylate salt LXVI as a common intermediate from both alkaloids (97, 98). While they had made no comments regarding the stereochemistry of $C_3$ ($C_8$ of the cinchona alkaloids) in this compound, Augustine (111) assumed that an $\alpha$ configuration of the $C_3$ hydrogen had been implied and contested the validity of this configuration. He argued that the asymmetric center in question may be epimerized under the experimental conditions employed in the preparation of the

tosylate salt (LXVI), the key intermediate in the corynantheine/dihydrocinchonamine correlation. Consequently, he claimed that one cannot assign correctly the $C_3$ configuration on the basis of these studies alone.

To test the Augustine argument, the metho-p-toluenesulfonate salts of both yohimbine and pseudoyohimbine (LXXIXa and LXXIXb respectively) were prepared by treatment of the

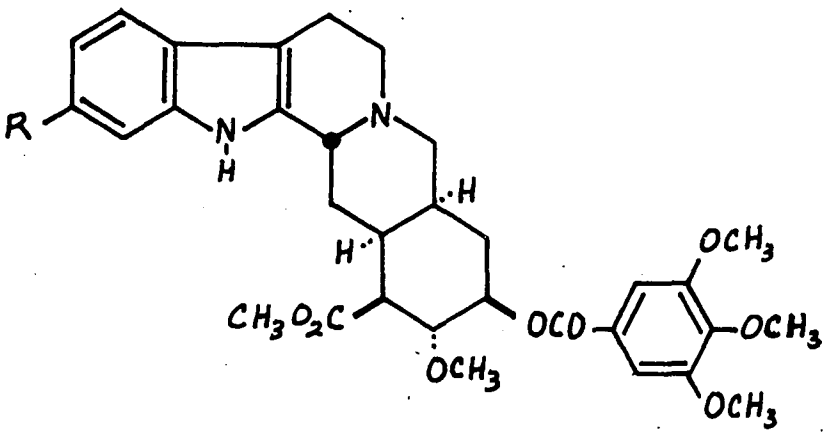



LXXIXa: as shown

LXXIXb: $C_3$-H $\beta$

alkaloids with methyl p-toluenesulfonate in dry benzene. The yohimbine derivative was found to be hygroscopic in the impure state and could not be recrystallized in media containing large amounts of hydroxylic solvents. The salts thus prepared were exposed to refluxing acetic acid. Work-up of both reaction mixtures gave back starting materials in nearly quantitative recovery. Wenkert and Roychaudhuri have shown that exposure of pseudoyohimbine to a refluxing hydrobromic acid-acetic acid mixture effected a $C_3$ epimerization to yohimbine (83). Much work has also been done in the field

of D/E cis alkaloid systems, notably in the reserpine family (112). Acetic acid treatment of reserpine (LXXXa) or its $C_3$ epimer, 3-isoreserpine, gave in either case an equilibrium mixture containing 20% reserpine and 80% 3-isoreserpine. Ring-A demethoxy analogues, such as deserpidine (LXXXb) and its $C_3$ epimer, epimerized more difficultly under similar conditions. Wenkert has also shown that hydrobromic acid-acetic




LXXXa: R = $-OCH_3$

LXXXb: R = -H

acid equilibration of either alloyohimbane (XLI) or its $C_3$ epimer, epialloyohimbane (XLII), leads to an equilibrium mixture containing 78% epialloyohimbane (86). It appears therefore that $C_3$ epimerizations of indole alkaloids with D/E cis ring junctions are a function of ring E substituents. In spite of the evidences just cited for the epimerizations of both D/E cis and D/E trans indole alkaloid systems in acidic

media, it is worthy to note that no epimerizations were detected when the prepared metho-p-toluenesulfonate salts were exposed to refluxing acetic acid.

In conducting the quaternization reactions to form the desired tosylate salt, LXVI, needed for their correlation studies, Wenkert and Bringi employed a pyridine medium under refrigerated conditions (97). In order to prove or disprove Augustine's suggestion that $C_3$ is epimerizable under these conditions, the methotosylate salts of yohimbine and pseudoyohimbine were exposed to pyridine at room temperature for several hours. Upon work-up of the reaction mixtures, starting material was recovered in both instances. Refluxing the salts in pyridine also did not effect epimerization in either case. These studies therefore demonstrated that Augustine's suggestion regarding $C_3$ epimerizations was incorrect.

Since the attempted peracid oxidation of yohimbone to a ring E lactone, which has been discussed earlier, could not be readily accomplished, a second sequence of reactions was undertaken to cleave ring E and to convert it into desired intermediates for the eventual preparation of the 15,20-diethyl compound LXXII. It had been shown by Wenkert and Bringi* that yohimbone may be converted to a compound

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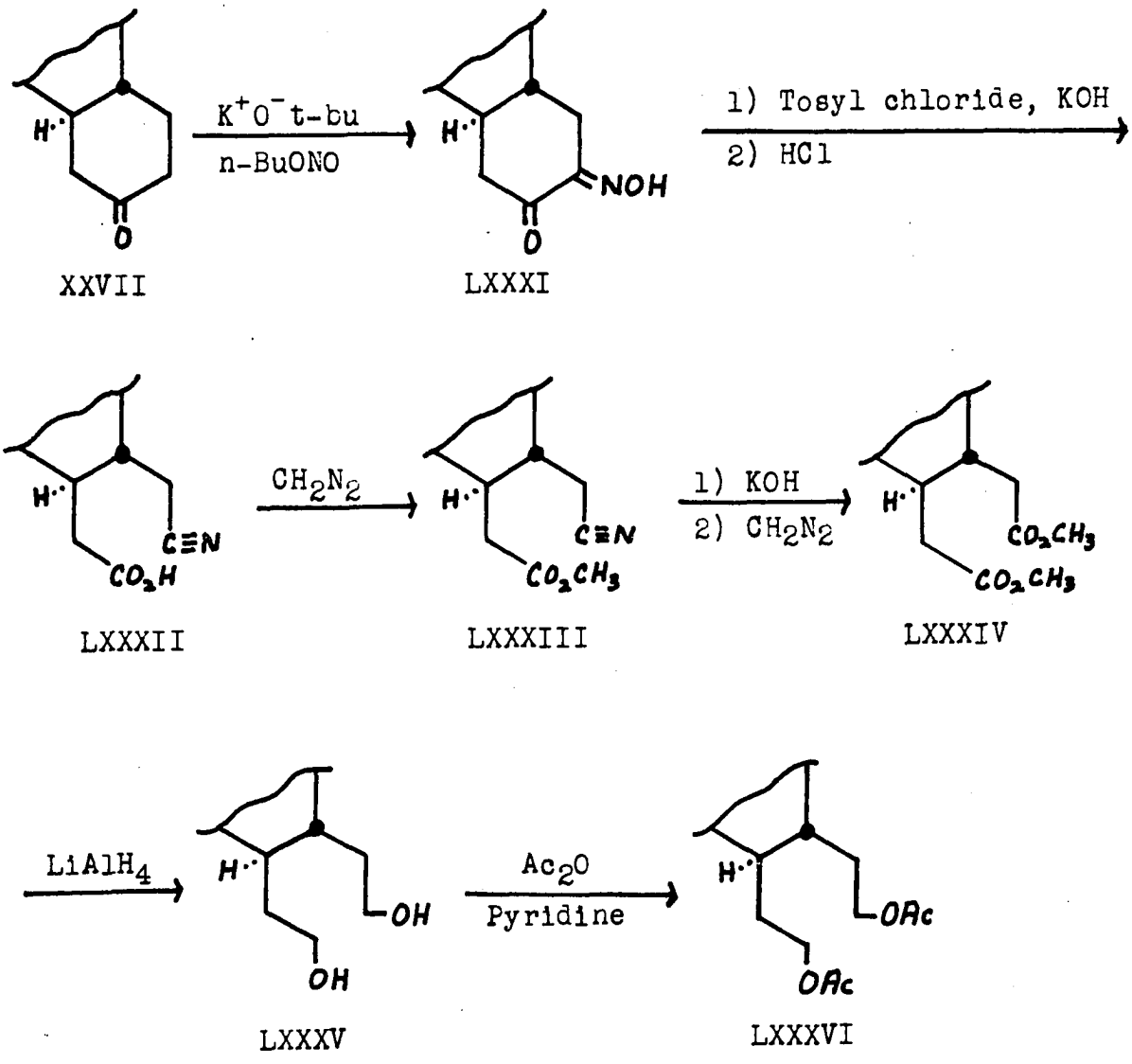
*Ernest Wenkert and N. V. Bringi, Iowa State University of Science and Technology, Ames, Iowa. Private communication. 1957.

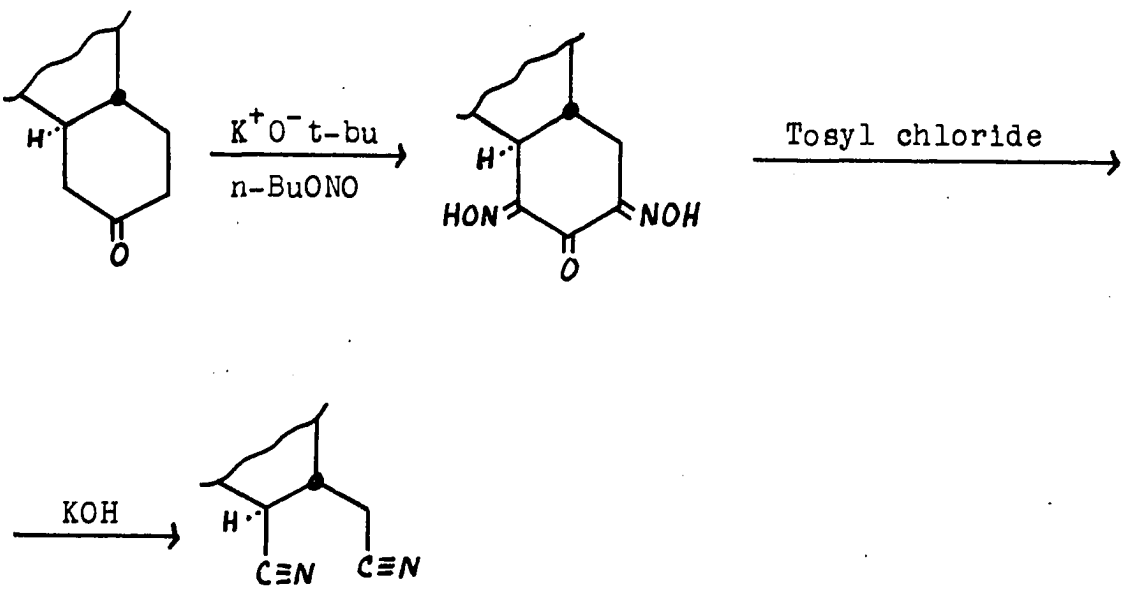
believed to be the diacetate derivative LXXXVI by the sequence of reactions illustrated in the following scheme. These con-




versions were re-conducted with the hope of improving the experimental procedure and obtaining a sufficient yield of the diacetate for further conversions toward the desired product.

The only intermediates isolated during the reaction

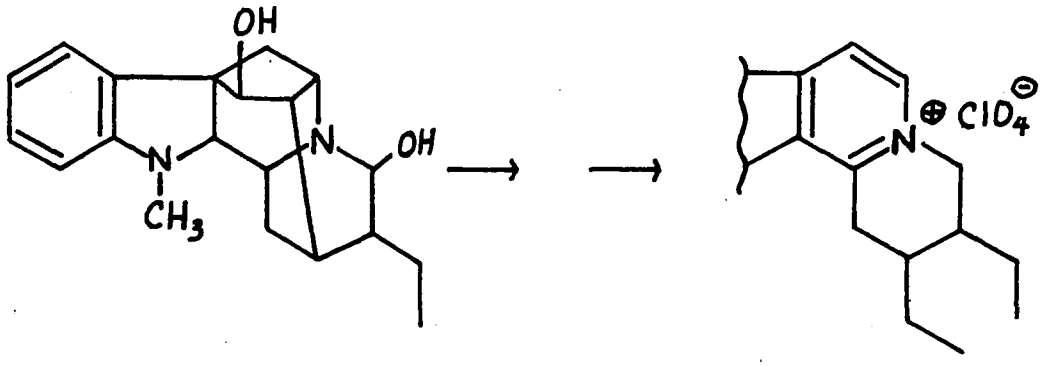
sequence, and for which yields could therefore be calculated, were LXXXIII (25% yield from XXVII), LXXXIV (89% yield from LXXXIII), LXXXV (80% yield from LXXXIV) and LXXXVI (26% yield from LXXXV). The first three major steps of the sequence appeared to be the most critical. It was not possible to determine which, if any one, of these three steps was the most difficult to accomplish in good yield since the intermediate products were not isolated. Experimental considerations indicated that the nitrosation reaction was the most critical, since slight alterations of the optimum experimental conditions found for this step resulted in drastic yield reductions of LXXXV. Minor amounts of a dicyano by-product (LXXXVII), formed through a dinitrosation reaction on




LXXXVII

yohimbone, could be removed from the potassium salt of LXXXII by chloroform extraction before regeneration of LXXXII with hydrochloric acid. Analyses of LXXXIII and LXXXVI, as reported in the Experimental section, were obtained but did not quite agree within the accepted limits. Time did not permit further work to be done beyond this point.

Due to the efforts of Bartlett and Taylor,* ajmaline (LXXXVIII) and its C-ethyl epimer, isoajmaline, were converted by a series of reactions to a tetracyclic derivative of the structure LXXXIX. Since the absolute stereochemistry of a closely related compound, 18,19-dihydrocorynantheane




LXXXVIII LXXXIX

(LXIV), had previously been determined by Wenkert and Bringi (97, 98), it was highly desirable to convert it into a compound of the structure shown by LXXXIX and thus determine the

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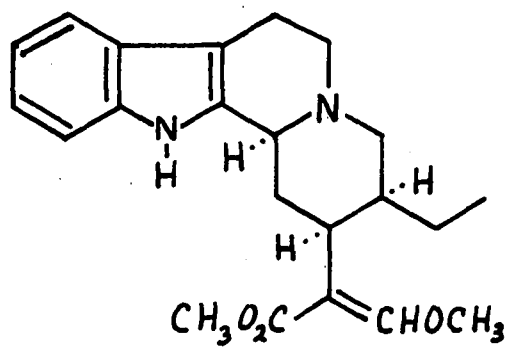
*M. F. Bartlett and W. I. Taylor, CIBA Pharmaceutical Products, Inc., Summit, New Jersey. Private communication. 1960.

absolute stereochemistry of ajmaline and isoajmaline.

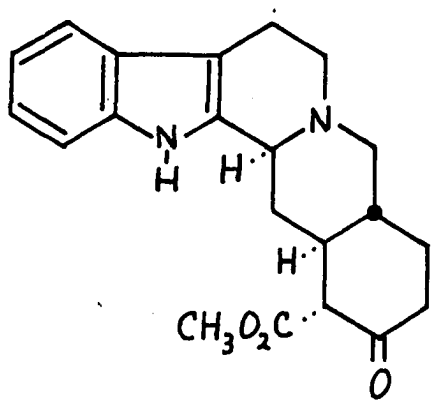
The required modifications of 18,19-dihydrocorynantheane were 1) oxidation of ring C to the tetradehydro state and 2) introduction of a methyl group on $N_a$, the indole nitrogen atom. The desired materials for this study were 18,19-dihydrocorynantheane, derivable from corynantheine or ajmalicine (97, 98, 99, 100, 101), and corynantheidane, its $C_{20}$ epimer, derivable from corynantheidine (XC) (113).




XC

Due to the greater availability of ajmalicine, this was selected over corynantheine as the source of 18,19-dihydrocorynantheane. The general sequence of reactions used for this conversion was reported by Wenkert and Bringi (97, 98) and has already been mentioned. Modification of several of the reaction steps enabled better yields to be obtained for some intermediates in the present study. Kimoto and coworkers have shown that conducting an Oppenauer oxidation on yohimbine in benzene rather than in xylene, as initially performed by

Witkop (49), yielded yohimbinone (XCI) instead of yohimbone (XXVII), the ordinary Oppenauer oxidation product (114). It was thought that application of this milder version of the



XCI

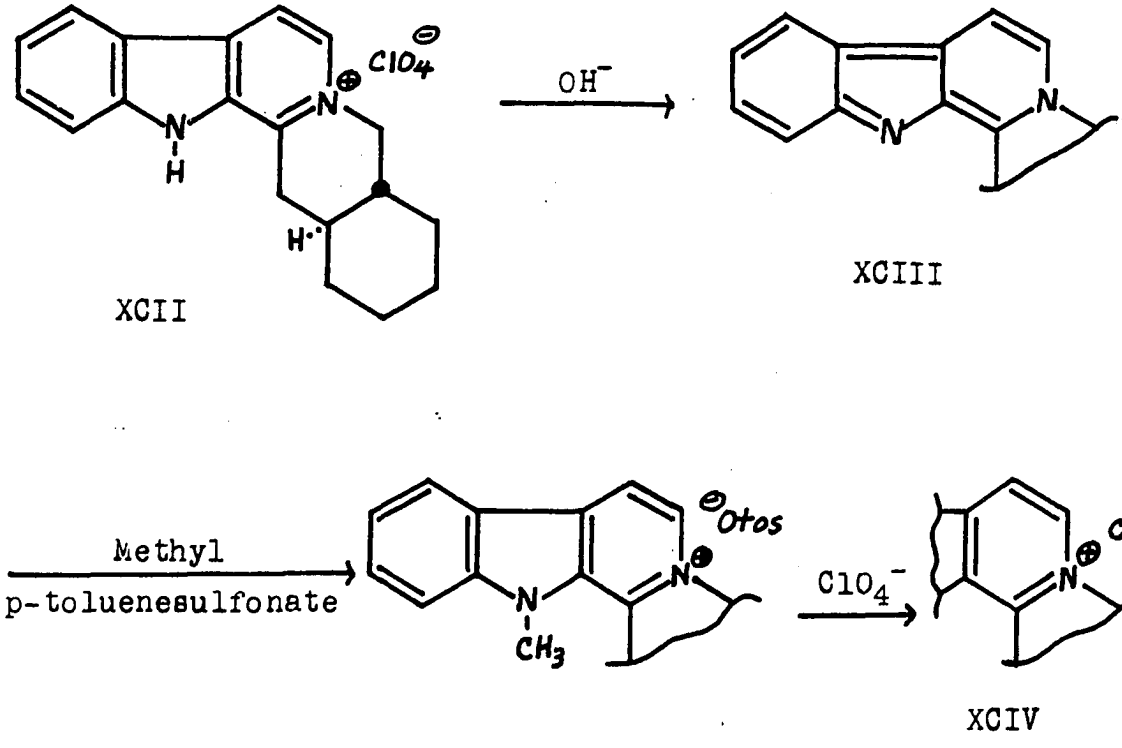
Oppenauer reaction to the oxidation of ajmaliciol (LIX) to the ketone (LX) would increase the yield of the latter, which at best had been only 37% of the theoretical when xylene had been used as solvent (98). The new reaction conditions improved the over-all yield of ketone to 74% and led to recovery of unreacted alcohol for re-use in more oxidation reactions. The ketonic product (LX) was susceptible to air decomposition and was best stored under nitrogen until needed. Reducing the reaction time for the Wolff-Kishner reduction to which this ketone was next exposed also enabled better yields of the diethyl product to be obtained.

Corynantheidane, the other compound desired for this investigation, was prepared from corynantheidine (XC)

according to the procedure reported by Janot et al. (113).

Palladium-black/maleic acid oxidations of 18,19-dihydrocorynantheane and corynantheidane were conducted according to the procedure developed by Majima and Murahashi (57) and applied with much success by Wenkert and Roychaudhuri (83). The ring C tetradehydro derivatives were obtained as their perchlorate salts in reasonably good yields.

Attempts were next made to introduce the $N_a$-methyl group into these derivatives. The 3,4,5,6-tetradehydro derivative of yohimbane (XCII), also prepared by a palladium-black/maleic acid oxidation, was used as a model for the proposed reaction




XCII XCIII XCIV

sequence. The free anhydronium base XCIII was liberated by treatment of XCII in methanol with 10% sodium hydroxide solution. Ether extraction of the basic mixture and vacuum removal of the ether solvent gave the free base as a yellow solid. This was then treated with methyl p-toluenesulfonate in dry benzene to yield a product which, upon treatment in a methanolic solution with perchloric acid gave the yellow perchlorate salt of $N_a$-methyl-3,4,5,6-tetradehydroyohimbane (XCIV). Application of this reaction sequence to the ring-C tetradehydro derivatives of 18,19-dihydrocorynantheane and corynantheidane gave, on first trial, an unidentified product and later, intermediates which rapidly decomposed.

The next approach taken to the problem was the introduction first of the $N_a$-methyl group into 18,19-dihydrocorynantheane and corynantheidane, followed then by ring-C dehydrogenation. The method used for the $N_a$-methylation was a modification of that used by Witkop for the preparation of $N_a$-methylyohimbane (115). Yohimbane was again employed as the model for these conversions. Treatment of the alkaloid with potassium in dry benzene gave the $N_a$-potassio salt which was treated with excess methyl iodide. The precipitate which formed was a mixture of potassium iodide and the methiodide salt of $N_a$-methylyohimbane. It had previously been shown by Karrer and Schmid (116) and by Schlittler and Hohl (117) that quaternary ammonium chlorides of indole alkaloids upon

exposure to high vacuum pyrolyses regenerated the parent alkaloid in reasonably good yield. Application of this procedure to the potassium iodide-methiodide salt mixture obtained in the methylation reaction just described gave a 62% yield of $N_a$-methylyohimbane. Similar methylation and pyrolysis reactions were conducted on 18,19-dihydrocorynantheane and corynantheidane. The $N_a$-methyl derivative of the former was obtained as a crystalline product in 58% yield. The corresponding derivative of the latter, however, was an oil at room temperature and was isolated as its perchlorate salt in about 76% yield.

The final step in the desired conversion was the ring-C oxidation of the prepared $N_a$-methyl derivatives. This was accomplished by means of the palladium-black/maleic acid system already described. The 3,4,5,6-tetradehydro products, as their perchlorate salts, were then compared by melting point, mixed melting point, specific rotation and infra-red spectrum with the derivatives prepared by Bartlett and Taylor from ajmaline and isoajmaline.* $N_a$-methyl-3,4,5,6-tetradehydro-18,19-dihydrocorynantheane perchlorate (XCVa) was found to be identical in all respects with the derivative obtained from isoajmaline, d-trans-2,3-diethyl-1,2,3,4-tetra-

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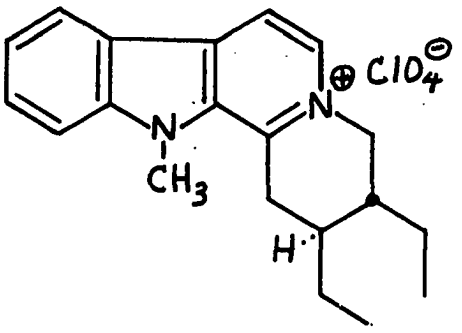
*M. F. Bartlett and W. I. Taylor, CIBA Pharmaceutical Products, Inc., Summit, New Jersey. Private communication. 1960.

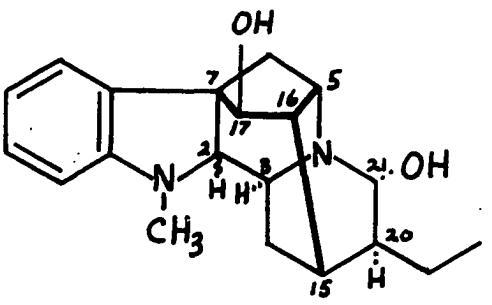


XCVa: as shown

XCVb: $C_{20}$-H $\alpha$

hydro-12-methylindolo [2,3,a] quinolizinium perchlorate. By similar comparisons of physical constants, $N_a$-methyl-3,4,5,6-tetradehydrocorynantheidane perchlorate (XCVb) was found identical with 1-cis-2,3-diethyl-1,2,3,4-tetrahydro-12-methyl-indolo-[2,3,a] quinolizinium perchlorate obtained from ajmaline.

These correlations indicate that the absolute configurations of ajmaline and isoajmaline at $C_3$, $C_{15}$ and $C_{20}$ are as depicted in XCVIa and XCVIb respectively. Furthermore, the stereochemistry of $C_5$, $C_7$ and $C_{16}$ is fixed as shown in XCVIa



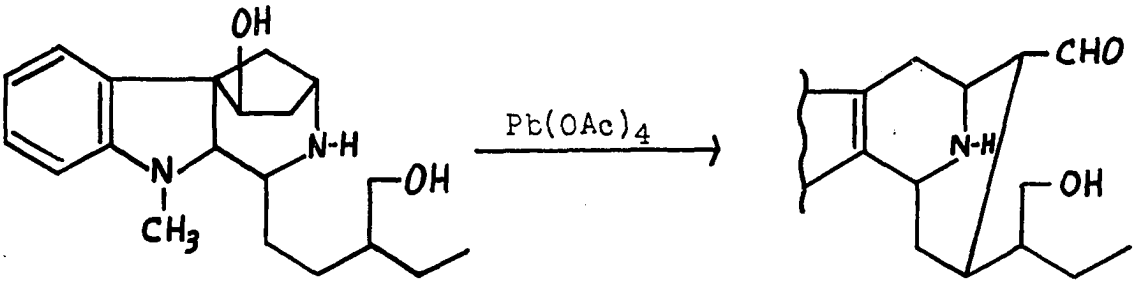
XCVIa: as shown

XCVIb: $C_{20}$-H and $C_{21}$-OH $\beta$

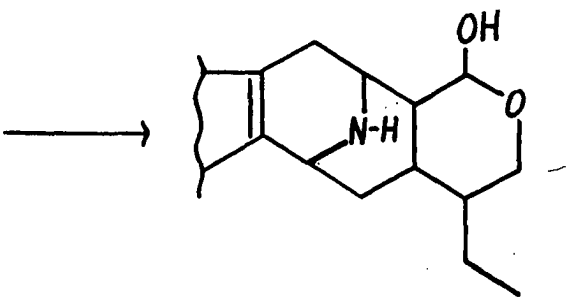
and XCVIb, once the configuration of $C_{15}$ has been established.

No data from the present study or previous investigations has a bearing on the stereochemistry of $C_2$. The orientation shown for the $C_{17}$ hydroxyl group is assigned on the basis of earlier investigations on ajmaline and related compounds. In 1957 Gorman *et al.* (118) reported the isolation of sandwicine from two Rauwolfia species, *R. sandwicensis* A.DC. and *R. mauiensis* Sherff. Investigations of its physical and chemical properties strongly suggested a basic structure very similar to that of ajmaline (LXXXVIII).

Sandwicine, upon sodium borohydride reduction, yielded a dihydro derivative similar to the derivative XCVII (stereochemistry not implied) obtained from ajmaline by a similar reduction (119). Lead tetraacetate oxidation of both the derivative obtained from sandwicine and that obtained from ajmaline gave the identical compound, the hemiacetal XCIX, formed through the initial formation of XCVIII followed by immediate cyclization to the hemiacetal. The formation of identical oxidation products suggested that dihydrosandwicine and dihydroajmaline were isomeric at $C_{17}$, the only center affected in the lead tetraacetate treatment. This also suggested that the parent alkaloids, sandwicine and ajmaline, were epimeric at $C_{17}$, although the possibility of $C_{21}$ isomerism cannot be ruled out completely.

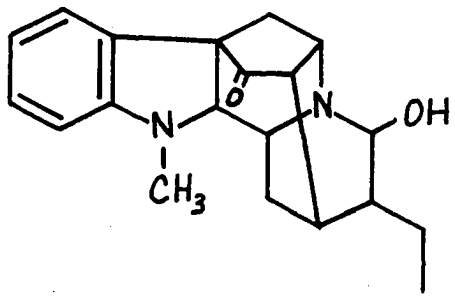



XCVII XCVIII

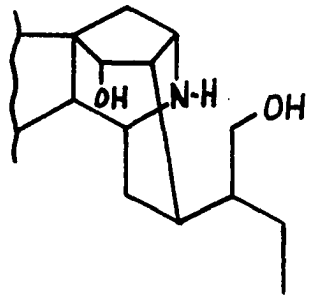



XCIX

Ajmalidine, an alkaloid first isolated by Pakrashi et al. (120) was shown to possess the structure C by spectral analyses (121). Sodium borohydride reduction of this alkaloid gave a tetrahydro derivative which was identical with dihydrosandwicine. Since the reduction of the cyclopentanone ring proceeds by attack of the reducing agent from the least hindered side, in this case, from the top side, this results in the formation of a hydroxyl group oriented downward, cis to the $C_{15}$-$C_{16}$ bond. This is illustrated in CI, a partial structure of dihydrosandwicine. Due to the determination



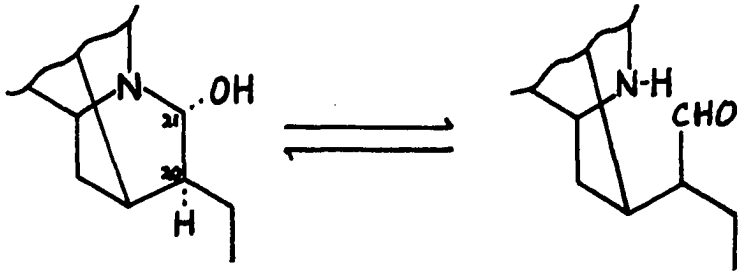

C




CI

earlier of the relationship between sandwicine and ajmaline, these additional data suggest that the $C_{17}$ hydroxyl in ajmaline is oriented above the five-membered ring, trans to the $C_{15}$-$C_{16}$ bond, as depicted in XCVIa.

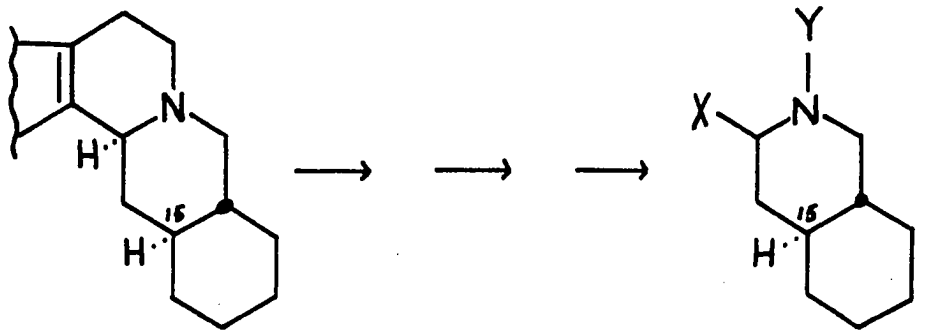
Due to possible equilibration through the acyclic amino aldehyde form CIII, the carbinol amine hydroxyl group at $C_{21}$ of ajmaline can assume the most stable orientation, which would be expected to be trans to the adjacent $C_{20}$ ethyl substituent. This is shown in CII (absolute configurations not




CII CIII

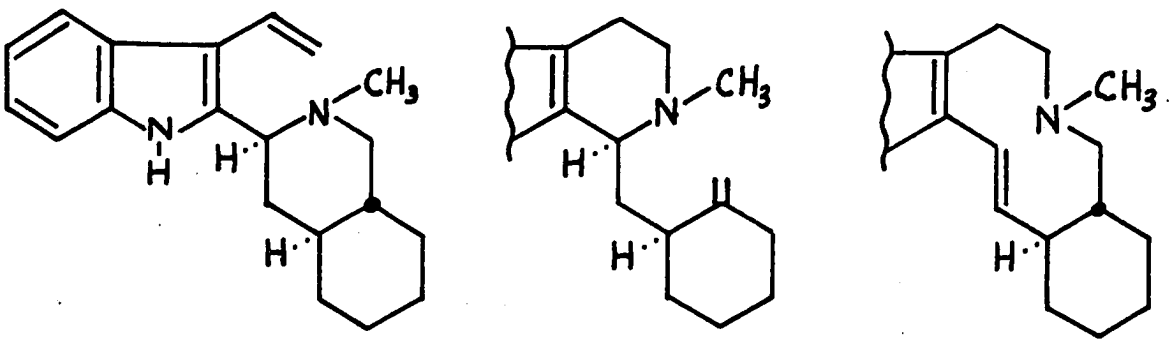
implied). Since the present absolute configuration studies have shown that the $C_{20}$ hydrogen is $\alpha$-oriented in ajmaline, the $C_{21}$ hydroxyl group must be $\alpha$-oriented also to place it in the more stable trans relationship with the $\beta$-oriented ethyl group at $C_{20}$. In like fashion, the $C_{21}$ hydroxyl group in isoajmaline occupies a $\beta$-orientation, trans to the $C_{20}$ ethyl group which was found to be $\alpha$-oriented in the present study. These assignments are depicted in XCVIa and XCVIb, the absolute representations of ajmaline and isoajmaline, respectively.

Most previous determinations of the stereochemistry of indole alkaloids have revealed a common $\alpha$ orientation of their $C_{15}$ hydrogens. A possible means for further proving the uniqueness of this configuration in yet unstudied indole alkaloids would be the introduction of a unit containing this asymmetric center into the alkaloid structures through synthetic processes. Since the absolute configuration of yohimbine (XVIII) had already been determined by physical means (71), an attempt was made toward degrading yohimbane (XXIX), a derivative of yohimbine, to a substituted isoquinoline (CIV) containing the asymmetric $C_{15}$ of the original alkaloid. Appropriate synthetic applications of this unit would make possible the determinations of the absolute configurations of other alkaloids at this and related asymmetric centers.



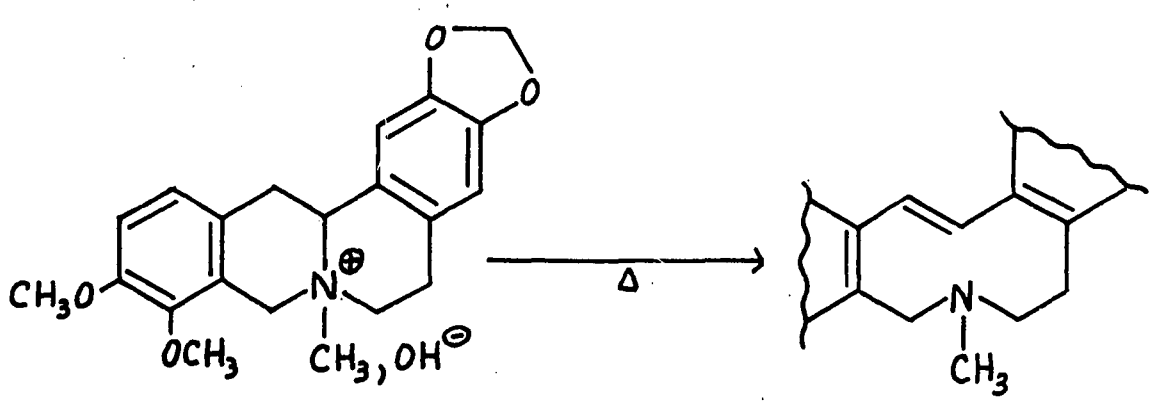
XXIX CIV

Quaternization of $N_b$ followed by a Hofmann elimination reaction were considered as first steps toward the preparation of the desired isoquinoline unit from yohimbane. Of the three possible elimination products which could form (CV, CVI, CVII), the first was considered the most useful for further



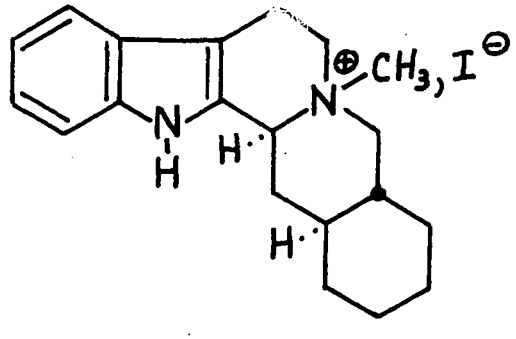
CV CVI CVII

degradative work. Pyman has shown that similar treatment of tetrahydroberberine methohydroxide (CVIII) yields the derivative CIX containing a ten-membered ring comparable to CVII (123).



CVIII CIX

Treatment of yohimbane with methyl iodide in dry benzene gave the corresponding $N_b$-methiodide, CX, which was converted



CX

to the methohydroxide by treatment with silver hydroxide. The product was isolated and used without further purification. Exposure to vacuum pyrolysis converted it into a low melting solid which upon catalytic hydrogenation gave a white solid which could not be purified by crystallization to a sharply

melting compound. Purification by chromatography gave two oily fractions and two solids, the first solid being eluted with 10% Skelly B in benzene and with pure benzene itself, and the second solid being eluted with 20% ether in benzene. Time permitted the identification of only the last of these fractions. Crystallization in methanol gave white needles which showed no depression of melting point upon admixture with authentic yohimbane. Experimental observations indicate that at least one Hofmann elimination product was formed in the pyrolysis reaction, but until the remaining chromatographic fractions are identified, it is not possible to determine which of the possible products (CV, CVI, CVII) was actually formed.

# EXPERIMENTAL

The solvents used in this study were of the ordinary commercial grade and were used without further purification. The alumina used for chromatographic separations and purifications was first treated with ethyl acetate, washed with water and methanol, and then activated by heating for 12 hours at 115°C before being employed.

Infra-red spectra were taken with a Perkin-Elmer Model 21 Infra-red Spectrophotometer and a Perkin-Elmer Model 137 Infracord Spectrophotometer. A Cary Model 14 Recording Spectrophotometer was used for the recording of ultraviolet spectra. All melting points were determined on a calibrated Kofler micro-hot stage melting point apparatus. Microanalyses were done by Mr. L. Dorfmann, CIBA Pharmaceutical Products, Inc., Summit, New Jersey; Drs. Weiler and Strauss, Microanalytical Laboratory, Oxford, England; and Dr. A. Bernhardt, Max Planck Institute, Mülheim (Ruhr), Germany.

## Preparation and Chemical Investigations of Yohimbone N-Oxide

### Preparation of perbenzoic acid

The procedure used for this preparation was given by Braun (123).

Preparation of standard sodium thiosulfate solution

Procedures used were based on those described by Diehl and Smith (124).

A stock thiosulfate solution was prepared by dissolving 5 g. of sodium thiosulfate pentahydrate and 50 mg. of sodium carbonate in sufficient distilled water to make 100 ml. of solution. This solution was standardized by the following general procedure. Weighed samples of potassium iodate (in the range of 20-40 mg.) were each dissolved in 15 ml. of distilled water. To the solutions were added 0.6 g. of potassium iodide and 2 ml. of a 1:10 diluted solution of hydrochloric acid. The liberated iodine in each solution was then titrated with the prepared thiosulfate solution, using a starch indicator to intensify the end point. The normality of the sodium thiosulfate solution was determined by the relationship:

$$N = \frac{\text{wt. of } KIO_3 \text{ sample}}{(\text{ml. of thiosulfate solution used})(\text{meq.wt. of } KIO_3)}$$

Standardization of the perbenzoic acid solution

To a mixture composed of 50 ml. of distilled water, 5 ml. of glacial acetic acid and 5 ml. of chloroform was added 0.5 ml. of the prepared perbenzoic acid solution. The mixture was well agitated, and the liberated iodine was titrated with standard thiosulfate solution. Three such determinations were made, and the concentration of the perbenzoic acid

solution was calculated utilizing the information given by Braun (123) that 1 ml. of 0.1 N thiosulfate solution is equivalent to 0.0069 g. of perbenzoic acid.

Preparation of yohimbone N-oxide

To a solution of 250 mg. ($8.5 \times 10^{-4}$ m.) of yohimbone in 25 ml. of chloroform were added 117 mg. ($8.5 \times 10^{-4}$ m.) of perbenzoic acid in chloroform. The exact volume of peracid solution used was dependent upon its concentration as determined by the previously described standardization procedure. The resulting reaction mixture was placed under refrigeration in a stoppered flask. After several hours, the formation of a thick gel was observed. The reaction was allowed to proceed overnight under refrigerated conditions. The absence of unreacted peracid was indicated by a negative test with starch-iodide paper. The gel was broken up into smaller fragments, and these were collected by suction filtration. The collected cake of material was pressed dry of solvent, washed with cold chloroform, and dried by suction. The hard solid remaining could be pulverized into a light tan powder and weighed 235 mg. ($7.6 \times 10^{-4}$ m., 89.4% yield). It appeared to melt sharply around 187°C. Recrystallization in methanol gave a white amorphous solid melting at 185-186.5°C. The picrate salt of the product was prepared by treating a hot saturated solution of 25 mg. ($8.1 \times 10^{-5}$ m.) of the N-oxide in 95%

ethanol with an equal volume of a saturated solution of picric acid in 95% ethanol. The resulting solution was boiled for one minute and was then allowed to stand at room temperature overnight. The yellow solid which crystallized in small clusters out of solution was collected by filtration and washed with cold 95% ethanol. This crude product weighed 30 mg. ($5.6 \times 10^{-5}$ m., 69% yield) and melted at 195-200°C. Recrystallization in 95% ethanol yielded yellow needles melting at 198-200°C. An analytical sample, dried at 100°C and 1 mm. pressure for 12 hours, gave a melting point of 200-2°C dec.

Analysis: Calculated for $C_{25}H_{25}N_5O_9 \cdot C_2H_5OH$: C = 55.38; H = 5.34; N = 11.96. Found: C = 55.39; H = 5.54; N = 12.21.

Reduction of yohimbone N-oxide

Zinc and acetic acid method Activation of zinc powder for use in the reduction was performed in the following manner. Six g. of zinc powder were stirred in 15 ml. of 2% hydrochloric acid solution for a few minutes. The zinc was then collected by suction filtration and washed successively with 15 ml. of 2% hydrochloric acid solution, 45 ml. of distilled water, 20 ml. of 95% ethanol and 10 ml. of absolute ether. The activated powder was dried at 115°C for several hours and was kept in a stoppered bottle until needed.

Forty mg. ($1.3 \times 10^{-4}$ m.) of yohimbone N-oxide were

dissolved in 10 ml. of glacial acetic acid. To this solution were added 120 mg. of activated zinc powder, and the mixture was heated on a steam bath for 20 minutes with frequent agitation. After being cooled to room temperature, the reaction mixture was neutralized with saturated sodium bicarbonate solution and then basified with ammonia. The basic aqueous solution was extracted with chloroform, the organic extract dried over anhydrous sodium sulfate, the drying agent removed by filtration, and the filtrate evaporated to dryness. The tan solid residue was crystallized in methanol, giving white silken needles melting at 306-7°C. Admixture with authentic yohimbone did not depress the melting point.

Catalytic hydrogenation method To a solution of 50 mg. ($1.6 \times 10^{-4}$ m.) of yohimbone N-oxide in 95% ethanol, contained in a hydrogenation flask, was added 10 mg. of 5% palladium on charcoal catalyst. Hydrogenation was allowed to proceed at room temperature and atmospheric pressure for 5 1/2 hours until no further uptake of hydrogen was observed. The catalyst was removed by filtration, and the filtrate was evaporated to dryness in vacuo, leaving a brown solid residue. Crystallization in methanol with Norit purification gave white silken needles melting at 305-6°C. Admixture with authentic yohimbone did not cause a depression of the melting point.

Reaction of yohimbone N-oxide with hydrochloric acid

Five hundred mg. ($1.6 \times 10^{-3}$ m.) of yohimbone N-oxide were dissolved in 5 ml. of glacial acetic acid, and to this solution were then added 2.5 ml. of concentrated hydrochloric acid. The reaction mixture was heated under nitrogen for one hour in a boiling water bath. Most of the solvent was then removed by heating in vacuo, and the residual concentrated liquid was diluted with water and basified with ammonia. The heavy precipitate which formed was taken back into solution with acetic acid, and the acidic solution was treated with saturated potassium perchlorate solution. A light yellow precipitate formed and was collected by suction filtration, washed with cold water, and dried. This crude product, weighing 110 mg. ($2.8 \times 10^{-4}$ m., 17.5% yield) and melting at 265-270°C, was recrystallized in methanol to yield feathery needles with a melting point of 272-3°C. Its ultraviolet spectrum taken in 95% ethanol showed maxima at 355 mμ (log ε 4.3) and 247 mμ (log ε 3.7). These data compared favorably with those of 3-dehydroyohimbone perchlorate prepared by the mercuric acetate oxidation of yohimbone according to the procedure described by Wenkert and Roychaudhuri (84).

Pyrolysis of yohimbone N-oxide

A sublimation apparatus containing 15 mg. of yohimbone N-oxide under 1 mm. pressure was immersed in a Wood metal

bath which had been preheated to 185°C. The temperature was slowly raised to 200°C during which time a light tan solid collected on the acetone/dry ice-cooled finger. This sublimate weighed 4 mg. and melted at 260-5°C. Chromatography on alumina of 11 mg. of this material (obtained from a total of 40 mg. of amine oxide exposed to this pyrolysis reaction) gave 3.6 mg. of a white solid upon elution with 75% ether in benzene and removal of solvent.

Similar chromatographic treatment of the 20 mg. of residual material remaining after the above pyrolysis reactions yielded 10 mg. of a white solid melting at 272-5°C. Crystallization in methanol of both chromatographic products gave in each case white needles melting at 305-6°C. Admixture with authentic yohimbone did not depress the melting point of either sample.

## Studies of the Methyl p-Toluenesulfonate Salts of Yohimbine and Ψ-Yohimbine

### Preparation of methyl p-toluenesulfonate

The reagent was prepared from p-toluenesulfonyl chloride and methanol according to the procedure given by Roos *et al.* (125).

### Preparation of pseudoyohimbine metho-p-toluenesulfonate

One gram ($2.8 \times 10^{-3}$ m.) of pseudoyohimbine was dissolved in 25 ml. of dry benzene. To this were added 550 mg.

($2.9 \times 10^{-3}$ m.) of methyl p-toluenesulfonate, and the resulting solution was refluxed under nitrogen and in the absence of moisture for about 3 hours. The precipitate which formed was collected by suction filtration, washed with dry benzene, and dried by suction. Weight of the crude product was 1.12 g. ($2.1 \times 10^{-3}$ m., 75% yield). This was crystallized in ethanol/ethyl acetate to yield white platelets, m.p. 283-4°C.

Analyses: Calculated for $C_{29}H_{36}O_6N_2S$: C = 64.42; H = 6.751; N = 5.18. Found: C = 64.16; H = 6.81; N = 5.15.

Preparation of yohimbine metho-p-toluenesulfonate

Treatment of 1 g. of yohimbine with 550 mg. of methyl p-toluenesulfonate was conducted according to the procedure described above. The product (975 mg., 64% yield) tended to be hydroscopic in the impure state. It was best crystallized from ethyl acetate and a minimum of methanol, yielding white platelets melting at 218-220°C.

Analysis: Calculated for $C_{29}H_{36}O_6N_2S$: C = 64.42; H = 6.71; N = 5.18. Found: C = 64.77; H = 6.95; N = 5.12.

Equilibration studies

Fifty mg. of yohimbine metho-p-toluenesulfonate were refluxed in 2 ml. of glacial acetic acid for 1 hour. Removal of the solvent *in vacuo* gave a residue which was crystallized in methanol/ethyl acetate. The purified compound melted at

217-19°C and showed no melting point depression when mixed with starting material. Recovery of material was nearly quantitative. Fifty mg. of pseudoyohimbine metho-p-toluenesulfonate were treated in similar fashion. The crude product, weighing 45 mg., gave white platelets, m.p. 283-5°C, upon crystallization. This melting point was not depressed upon admixture with starting material.

Exposure of 50 mg. of each quaternary salt to 2 ml. of dry pyridine at room temperature overnight, followed by removal of solvent *in vacuo*, yielded material which upon recrystallization was again identified as starting material in each case. Even exposure to refluxing pyridine did not effect epimerization in either system.

## Preparation of some Ring C-Dehydrogenated Indole Alkaloid Derivatives

### Preparation of 3,4,5,6-tetradehydroyohimbane perchlorate

Le Hir *et al.* have reported the preparation of this compound by treatment of yohimbane with lead tetraacetate and with acidic palladium on charcoal (126). The procedure used in this study was based on a palladium-black/maleic acid oxidation method described by Wenkert and Roychaudhuri (83).

A 200 mg. sample of yohimbane ($7.1 \times 10^{-4}$ m.) was added to an aqueous solution of 450 mg. ($3.9 \times 10^{-3}$ m.) of recrystallized maleic acid. To this were added 100 mg. of

palladium-black catalyst, and the mixture was heated on a steam bath for 8 hours with occasional stirring. The hot reaction mixture was filtered, cooled to room temperature, and treated with sufficient perchloric acid to cause complete precipitation of product. The precipitate, weighing 245 mg. ($6.5 \times 10^{-4}$ m., 92% yield), was crystallized in methanol to give yellow needles, m.p. 250-1°C. Reported melting point for 3,4,5,6-tetradehydroyohimbane perchlorate was 252°C (126). The product showed ultraviolet absorption maxima in 95% ethanol at 208 mμ, 252 mμ, 307 mμ, and 361 mμ, characteristic of ring C-tetradehydro derivatives of indole alkaloids (83).

Preparation of 3,4,5,6-tetradehydro-18,19-dihydrocorynantheane perchlorate

18,19-Dihydrocorynantheane This compound was initially prepared from ajmalicine by the sequence of steps reported by Wenkert and Bringi (98). Results were comparable to those reported in the publication. The modifications reported below were subsequently used to improve the experimental procedure and yield in the Oppenauer oxidation of ajmaliciol. These modifications involving milder reaction conditions were based on a procedure reported by Kimoto et al. (114).

To a solution of 75 mg. ($2.5 \times 10^{-4}$ m.) of ajmaliciol in 6 ml. of dry benzene were added 4 ml. of freshly distilled cyclohexanone and 0.5 g. of aluminum phenoxide. The resulting mixture was refluxed under a dry nitrogen atmosphere for 8

hours at 115-120°C bath temperature. It was then cooled and extracted with 2N sulfuric acid. The acidic solution was washed with small amounts of ether and then basified with ammonia. The resulting precipitate was extracted with ether, and the ethereal solution was dried over anhydrous magnesium sulfate and evaporated in vacuo under nitrogen. Chromatography on alumina of the resulting residue gave, upon elution with 1:2 benzene-ether, 31 mg. ($1.04 \times 10^{-4}$ m.) of 18,19-dihydro-19-corynantheone, identified by melting point and infra-red spectrum. The observed melting point was 223-5°C; reported melting point was 225-7°C (98). Further elution of the column with 9:1 ether-methanol gave 32 mg. ($1.07 \times 10^{-4}$ m.) of ajmaliciol, identified by infra-red spectrum. This was again used in subsequent oxidations. The yield of ketone obtained was 74%, based on the amount of alcohol actually undergoing reaction.

The ketone thus obtained was exposed to a Wolff-Kishner reduction as described by Wenkert and Bringi. An improvement in yield from 42% to 62% could be accomplished by reducing the reaction time from 4 hours to 3 1/4 hours.

Ring C dehydrogenation of 18,19-dihydrocorynantheane - Palladium-black and maleic acid oxidation of 18,19-dihydrocorynantheane was carried out according to the general procedure described earlier for the preparation of 3,4,5,6-tetradehydroyohimbane. Quantities used were 10 mg.

($3.5 \times 10^{-5}$ m.) of 18,19-dihydrocorynantheane, 20 mg. ($1.7 \times 10^{-4}$ m.) of maleic acid, and 5 mg. of palladium-black catalyst. Addition of perchloric acid to the filtered reaction solution gave 6 mg. ($1.6 \times 10^{-5}$ m., 46% yield) of 3,4,5,6-tetradehydro-18,19-dihydrocorynantheane perchlorate which was purified by recrystallization in methanol. Yellow needles melting at 203-5°C were obtained.

Analyses: Calculated for $C_{19}H_{23}N_2ClO_4$: C = 60.23; H = 6.12; N = 7.40. Found: C = 59.94; H = 6.39; N = 7.20.

Preparation of 3,4,5,6-tetradehydrocorynantheidane perchlorate

Corynantheidane was prepared from corynantheidine acetonide according to procedures reported by Janot et al. (113). Oxidation of this product with palladium-black and maleic acid following the procedure described above for the similar oxidation of 18,19-dihydrocorynantheane gave the tetradehydro derivative as the perchlorate salt in 75% yield. Melting point of the recrystallized (methanol) product was 221-2°C.

Analysis: Calculated for $C_{19}H_{23}N_2ClO_4$: C = 60.23; H = 6.12; N = 7.40. Found: C = 60.63; H = 6.21; N = 7.00.

## $N_a$-Methylations of some Indole Alkaloids

Preparation of $N_a$-methylyohimbane

Modifications of a procedure described by Witkop for the $N_a$-methylation of yohimbane were employed for methylations in

this investigation (115).

To a solution of 60 mg. ($2.1 \times 10^{-4}$ m.) of yohimbane in 4 ml. of dry benzene were added 10 mg. ($2.6 \times 10^{-4}$ m.) of potassium metal. The mixture was stirred under reflux in a dry nitrogen atmosphere for several hours until the potassium metal was consumed. The resulting suspension was cooled to room temperature and treated with excess methyl iodide dissolved in dry benzene. The reaction mixture was stirred overnight, and the precipitate of KI and $N_a$-methylyohimbane methiodide which formed in the reaction flask was then collected and dried. Forty mg. of this mixture (total weight - 120 mg.), when heated in vacuo under sublimation conditions in an oil bath at 280-300°C, gave a solid sublimate which melted at 178-9°C after crystallization in methanol. The melting point reported by Witkop for $N_a$-methylyohimbane was 179°C. Total yield of product obtained by pyrolysis of the 120 mg. of crude reaction precipitate was 38 mg. ($1.3 \times 10^{-4}$ m., 62% based on the amount of yohimbane used).

Treatment of the pyrolysis/sublimation product with excess methyl iodide in dry benzene yielded the corresponding methiodide salt, m.p. 287-8°C. Reported melting point for $N_a$-methylyohimbane methiodide was 288-9°C (115). Exposure of this methiodide salt to pyrolysis/sublimation at 280-300°C again afforded $N_a$-methylyohimbane.

Preparation of $N_a$-methyl-18,19-dihydrocorynantheane

Following the procedure described above, 10 mg. ($3.5 \times 10^{-5}$ m.) of 18,19-dihydrocorynantheane in 4 ml. of dry benzene were treated with 6 mg. ($1.5 \times 10^{-4}$ m.) of potassium metal. Addition of two 0.5-ml. quantities of methyl iodide at 45 minute intervals to the resulting suspension of potassium salts gave after 15 hours 20 mg. of a white precipitate. Pyrolysis of this material under sublimation conditions at 300-340°C gave 6 mg. ($2.03 \times 10^{-5}$ m., 58% based on 18,19-dihydrocorynantheane) of crystalline sublimate which was crystallized in aqueous methanol to yield purified $N_a$-methyl-18,19-dihydrocorynantheane, m.p. 109-110.5°C, $[\alpha]_D$-22° (methanol).

Analysis: Calculated for $C_{20}H_{28}N_2$: C = 81.03; H = 9.52; N = 9.45. Found: C = 79.71; H = 9.52; N = 9.24.

Preparation of $N_a$-methylcorynantheidane perchlorate

In similar fashion, addition of 20 mg. ($5.1 \times 10^{-4}$ m.) of potassium to a solution of 60 mg. ($2.1 \times 10^{-4}$ m.) of corynantheidane in 5 ml. of dry benzene gave a suspension to which were added three 1-ml. quantities of methyl iodide at 2 hour intervals. After a total of 8 hours reaction time the white precipitate of KI and $N_a$-methylcorynantheidane methiodide weighing 127 mg. was collected. Fifty mg. of this mix-

ture were flash-pyrolyzed and sublimed *in vacuo* at 280-320°C. The oily sublimate ($N_a$-methylcorynantheidane) was dissolved in a slightly warm 5% acetic acid solution. The acidic solution was cooled to room temperature and treated with a few drops of perchloric acid. The pale yellow precipitate which formed weighed 25 mg. ($6.3 \times 10^{-5}$ m., *ca*, 76% yield based on corynantheidane) and was crystallized in methanol to yield fine granular crystals, m.p. 208.5-210°C.

Analysis: Calculated for $C_{20}H_{29}N_2ClO_4 \cdot CH_3OH$: C = 57.78; H = 7.89. Found: C = 57.54; H = 7.48.

## Preparation of $N_a$-Methyl-3,4,5,6-Tetradehydro Derivatives of some Indole Alkaloids

### Preparation of $N_a$-methyl-3,4,5,6-tetradehydroyohimbane perchlorate

*From 3,4,5,6-tetradehydroyohimbane perchlorate* Twenty mg. ($5.3 \times 10^{-5}$ m.) of 3,4,5,6-tetradehydroyohimbane perchlorate (preparation described earlier) were dissolved in a small amount of methanol and treated with a few drops of 10% sodium hydroxide solution. The resulting deep yellow solution was diluted with water until a precipitate began to form, and it was then extracted with ether. The ethereal extract was dried over anhydrous magnesium sulfate and evaporated *in vacuo*. The solid residue that remained was dissolved in dry benzene and treated with 2 drops of methyl p-toluenesulfonate. The solution was refluxed in the absence of moisture for 3 hours.

The precipitate which formed (believed to be $N_a$-methyl-3,4,5,6-tetradehydroyohimbane p-toluenesulfonate) was collected by filtration (9 mg., 37%, m.p. 205°C), dissolved in a minimum of methanol, and treated with perchloric acid. The precipitate of $N_a$-methyl-3,4,5,6-tetradehydroyohimbane perchlorate was filtered and crystallized in methanol to yield yellow crystals melting at 250-1°C. This same compound was also obtained by passing a methanolic solution of the p-toluenesulfonate salt through a column of Amberlite CG-45 Type I resin which had been converted to the perchlorate form. The filtrate obtained was concentrated to yield the perchlorate salt of $N_a$-methyl-3,4,5,6-tetradehydroyohimbane, m.p. 250-1°C.

Analysis: Calculated for $C_{20}H_{23}N_2ClO_4$: C = 59.64; H = 6.43; N = 6.62. Found: C = 59.37; H = 6.24; N = 6.58.

From $N_a$-methylyohimbane A mixture of 20 mg. ($6.8 \times 10^{-5}$ m.) of $N_a$-methylyohimbane, 10 mg. of palladium-black catalyst, and an aqueous solution of 40 mg. ($3.4 \times 10^{-4}$ m.) of maleic acid was heated on a steam bath overnight with continuous stirring. Filtration of the hot mixture followed by addition of perchloric acid to the cooled filtrate gave 26 mg. ($6.7 \times 10^{-5}$ m., 97% yield) of the corresponding tetradehydro perchlorate derivative, melting point 250-1°C after recrystallization in methanol. This product was identical with $N_a$-methyl-3,4,5,6-tetradehydroyohimbane perchlorate

prepared previously by the action of methyl p-toluenesulfonate on 3,4,5,6-tetradehydroyohimbane.

Preparation of $N_a$-methyl-3,4,5,6-tetradehydro-18,19-dihydrocorynantheane perchlorate

Five mg. ($1.7 \times 10^{-5}$ m.) of $N_a$-methyl-18,19-dihydrocorynantheane, 10 mg. ($8.6 \times 10^{-5}$ m.) of maleic acid, and 4 mg. of palladium-black in 5 ml. of water were heated on a steam bath with continuous stirring for 13 1/2 hours. Immediate filtration followed by addition of perchloric acid to the cooled solution gave 4 mg. ($1.02 \times 10^{-5}$ m., 60% yield) of $N_a$-methyl-3,4,5,6-tetradehydro-18,19-dihydrocorynantheane perchlorate. This showed a melting point of 198-200°C and $[\alpha]_D$+15° (methanol) after crystallization from aqueous methanol. Its infra-red spectrum in potassium bromide was identical with that of d-trans-2,3-diethyl-1,2,3,4-tetrahydro-12-methylindolo-[2,3-a] quinolizinium perchlorate obtained from isoajmaline. Mixed melting point determination of the two compounds showed no depression.

Preparation of $N_a$-methyl-3,4,5,6-tetradehydrocorynantheidane perchlorate

Thirty mg. of the potassium iodide-methiodide salt mixture isolated in the $N_a$-methylation reaction on corynantheidane (described earlier) were flash-pyrolyzed and sublimed *in vacuo* at 300-340°C. The oily sublimate was dissolved

directly in 95% ethanol, and the resulting solution was added to an aqueous solution of 60 mg. ($5.2 \times 10^{-4}$ m.) of maleic acid to which 20 mg. of palladium-black were also added. The mixture was stirred and heated on a steam bath for 16 hours. The solution was filtered hot, and the filtrate plus hot water washings were condensed to remove most of the ethanol. The condensed solution was cooled and treated with perchloric acid to yield 13 mg. ($3.3 \times 10^{-5}$ m., ca. 66% yield based on initial amount of corynantheidane used) of a pale yellow precipitate, $N_a$-methyl-3,4,5,6-tetradehydrocorynantheidane perchlorate. Crystallization in aqueous methanol gave flakes melting at 212-4°C, $[\alpha]_D$-27° (methanol). The infra-red spectrum in potassium bromide of the compound was identical with that of *l*-cis-2,3-diethyl-1,2,3,4-tetrahydro-12-methylindolo [2,3-a]-quinolizinium perchlorate obtained from ajmaline.* Mixed melting point determination of the two compounds showed no depression.

## Degradation Studies on Yohimbone

### Preparation of trans-2-carbomethoxymethyl-3-cyanomethyl-1,2,3,4-tetrahydro-12H-indolo [2,3-a] quinolizine

A solution of potassium t-butoxide was prepared by dis-

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*M. F. Bartlett and W. I. Taylor, CIBA Pharmaceutical Products, Inc., Summit, New Jersey. Private communication. 1959.

solving 82 mg. ($2.1 \times 10^{-3}$ m.) of potassium metal in 25 ml. of t-butyl alcohol under a dry nitrogen atmosphere. To this solution were added 300 mg. ($1.02 \times 10^{-3}$ m.) of yohimbone, dried at 100°C and 2 mm. pressure for 12 hours. The resulting suspension was stirred under a dry nitrogen atmosphere with a magnetic stirrer and was immersed in an oil bath maintained at 78°C. A 0.2 ml. ($1.7 \times 10^{-3}$ m.) quantity of n-butyl nitrite, recently prepared according to the procedure by Vogel (127) and stored under refrigeration, was added through a calibrated pipette whose tip was immersed below the surface of the reaction mixture. A brown coloration developed in the reaction flask, and the suspended yohimbone was observed to go into solution. The reaction was allowed to proceed, under dry nitrogen and with stirring, for exactly one minute at 78°C and for four hours at room temperature. Solvent was then removed *in vacuo* under nitrogen, and the resulting brown frothy residue was dissolved in 20 ml. of 1:1 acetone-water solution containing 2 g. of potassium hydroxide. A clear brown two-layer system developed. To this were added 250 mg. ($1.3 \times 10^{-3}$ m.) of recrystallized p-toluenesulfonyl chloride, and the resulting mixture was stirred at room temperature for 2 hours. An equal volume of water was then added, and the diluted solution was extracted with chloroform. The aqueous layer, combined with several aqueous washings of the chloroform layer, was acidified with concentrated hydrochloric acid.

The white precipitate that formed was extracted into n-butanol and the butanol solvent then removed by distillation *in vacuo* under nitrogen. Complete and rapid removal of solvent was facilitated by external heating. The residue remaining was dissolved in a minimum of methanol and treated with a freshly-distilled ethereal solution of diazomethane prepared from 2 g. of N-methyl-N-nitrosourea (128). The methylation was allowed to proceed for 1 hour in a stoppered flask under refrigeration with occasional swirling. The solvent was then removed from the cloudy solution *in vacuo* under nitrogen. The dark residue was basified with ammonia and extracted with chloroform. The chloroform solution was dried over anhydrous magnesium sulfate, filtered, and evaporated *in vacuo* under nitrogen. Chromatography on alumina of the resulting residue gave upon elution with benzene 84 mg. ($2.5 \times 10^{-4}$ m., 25% yield) of crude product. Crystallization in methanol gave white needles melting at 248-9°C. An analytical sample dried at room temperature and 1 mm. pressure for 15 hours gave a melting point of 251-252.5°C. The infra-red spectrum of the product showed peaks at 4.5 $\mu$ (-CN) and 5.8 $\mu$ ($-CO_2CH_3$).

Analysis: Calculated for $C_{20}H_{23}O_2N_3$: C = 71.19; H = 6.87; N = 12.45. Found: C = 70.50; H = 6.97; N = 12.45.

Preparation of trans-2,3-diacetoxyethyl-1,2,3,4-tetrahydro-12H-indolo [2,3-a] quinolizine

A solution was prepared of 195 mg. ($3.5 \times 10^{-3}$ m.) of potassium hydroxide in 9.1 ml. of ethylene glycol and 0.65 ml. of water. To this were added 130 mg. ($3.86 \times 10^{-4}$ m.) of the derivative prepared in the preceding reaction sequence. The resulting mixture was refluxed under nitrogen for 3 1/2 hours. Most of the solvent was then removed by distillation *in vacuo* under nitrogen. Dilution of the remaining slurry with water, followed by acidification with concentrated hydrochloric acid, gave a white precipitate which was extracted into n-butanol. Removal of the n-butanol by distillation *in vacuo* under nitrogen yielded a residue which was taken up in a minimum of methanol and treated with a freshly-distilled ethereal solution of diazomethane. Preparation of this reagent was referred to in the preceding section. After refrigeration for one hour with occasional swirling, in a stoppered flask, the methylation solution was evaporated *in vacuo* under nitrogen and the residue dried in a vacuum dessicator. The material was then chromatographed on alumina. Elution with ether gave, after vacuum removal of solvent under nitrogen, an oil which gave a peak at 5.75$\mu$ in the infra-red region but no 4.5$\mu$ peak. This diester, weighing 121 mg. ($3.27 \times 10^{-4}$ m., 89% yield), was dissolved in 35 ml. of dry tetrahydrofuran which was freshly distilled from lithium

aluminum hydride. To the resulting solution were added 520 mg. ($1.4 \times 10^{-2}$ m.) of lithium aluminum hydride, and the mixture was refluxed under dry nitrogen for 4 hours. Moist sodium sulfate was added in small amounts to hydrolyze excess reducing agent. The insoluble inorganic salts were removed by filtration, and the filtrate was evaporated *in vacuo*. The diol derivative was obtained as an oil weighing 82 mg. ($2.6 \times 10^{-4}$ m., 80% yield from the diester, 67% yield from the initial starting compound). This oil was dissolved in 3.5 ml. of acetic anhydride and 3.5 ml. of pyridine. The acetylation was allowed to proceed with stirring at room temperature overnight. Excess acetic anhydride was then hydrolyzed by addition of pieces of ice to the continuously-stirred reaction mixture. The resulting solution was basified with ammonia, and the precipitate which formed was taken up in chloroform. Removal of the solvent *in vacuo* under nitrogen, after magnesium sulfate drying, gave a glass which yielded a white solid upon trituration with methanol. Crystallization of this crude product in methanol gave 27.4 mg. of white needles ($6.9 \times 10^{-5}$ m., 26.5% yield from the diol; 18% yield from initial starting compound). A second crystallization gave needles melting at 102-3°C. An analytical sample dried at 78°C and 1 mm. pressure for five hours gave the following analysis.

Analysis: Calculated for $C_{23}H_{30}N$: C = 69.32; H = 7.59; N = 7.04. Found: C = 69.99; H = 8.19; N = 6.70.

## Hofmann Degradation of Yohimbane $N_b$-methohydroxide

### Preparation of yohimbane $N_b$-methiodide

A dry benzene solution of 336 mg. ($1.2 \times 10^{-3}$ m.) of yohimbane was heated to boiling with excess methyl iodide and allowed to cool to room temperature. The thick gelatinous material which had begun to form shortly after the reagents were mixed was then collected by suction filtration, washed with dry benzene and dried by suction. The solid thus obtained weighed 504 mg. ($1.19 \times 10^{-3}$ m., 99% yield) and was crystallized in absolute methanol to yield the pure methiodide salt melting at 254-6°C.

### Preparation of yohimbane $N_b$-methohydroxide

A solution of 200 mg. ($4.74 \times 10^{-4}$ m.) of yohimbane $N_b$-methiodide in hot water containing a little methanol was treated with 120 mg. of moist silver oxide (prepared from silver nitrate and 10% sodium hydroxide solutions). The mixture was stirred vigorously with a magnetic stirrer for 5 minutes at 110° (bath temperature). The light brown precipitate was removed by suction filtration of the hot mixture through a Celite mat. The mat was washed with warm water, and the combined aqueous filtrate was evaporated to dryness by means of a dry air stream directed onto the surface of the solution. Evaporation was facilitated by immersion in a warm

water bath. Upon scratching, the viscous residual oil crystallized into a white solid. After final drying in a vacuum dessicator, this product weighed 124 mg. ($3.97 \times 10^{-4}$ m., 84% yield) and melted at 165-7°C.

Hofmann degradation of yohimbane $N_b$-methohydroxide

The methohydroxide prepared as described above was used without further purification. A 103 mg. sample ($3.3 \times 10^{-4}$ m.) was pyrolyzed in a sublimation apparatus at 180-195°C and 0.25 mm. pressure. The sublimate, collected in two crops, had a total weight of 68 mg. and a melting point of 58-62°C. Its crude ultraviolet spectrum in 95% ethanol showed maxima at 227 mμ, 263 mμ and 282 mμ.

Catalytic hydrogenation of the Hofmann degradation product

A micro-hydrogenation apparatus was used for the catalytic reduction of the Hofmann elimination product. In one bulb of the hydrogenation flask were placed 106 mg. of the elimination product, dissolved in ethyl acetate. Into the other bulb were placed 25 mg. of 5% palladium-charcoal catalyst suspended in ethyl acetate. The catalyst suspension was pre-reduced before the solution of the organic sample was added to it. Reduction was allowed to proceed at 20° under a slight positive pressure of hydrogen gas. When no further uptake of hydrogen was observed, the reaction mixture was

removed and filtered. The filtrate was evaporated *in vacuo* yielding 101 mg. of a glass. Crystallization in methanol gave a white solid for which a good melting point range was not obtained. The product showed absorption maxima in the ultraviolet region at 226 mμ and 282 mμ.

Further purification was attempted through chromatography on alumina. Upon elution with Skelly B, 26 mg. of an oil were obtained. Successive elutions with 40, 50, 60 and 70% benzene in Skelly B gave a second oil, total weight 22 mg. With 90% benzene in Skelly B and with benzene itself, 18 mg. of a white solid were obtained. A second white solid (9 mg.) was obtained upon elution with 20% ether in benzene. Crystallization in methanol of this latter solid gave white needles melting at 198-200°C. Admixture with authentic yohimbane did not depress the melting point. The remaining fractions were not identified further.

## SUMMARY

It has been shown in a study of chemical correlations with 18,19-dihydrocorynantheane (of known absolute configuration) and its $C_{20}$ epimer, corynantheidane, that the $C_3$, $C_{15}$ and $C_{20}$ hydrogens in ajmaline possess an $\alpha$ orientation. Isoajmaline was shown to possess $C_3$- and $C_{15}$-$\alpha$ hydrogens, but a $\beta$-oriented $C_{20}$ hydrogen. On the basis of this determination, it was possible to assign an absolute configuration also to three other centers in these two alkaloids, $C_{16}$, $C_{17}$ and $C_{21}$.

Epimerization studies of the metho-p-toluenesulfonate salts of yohimbine and pseudoyohimbine revealed that the $C_3$ hydrogen in both series was un-epimerizable under the influence of acetic acid or pyridine.

One reaction sequence attempted for the correlation of the yohimbine and corynantheine series yielded yohimbone N-oxide as a product. It was characterized and its chemistry investigated. A second scheme produced an intermediate, trans-2,3-diacetoxyethyl-1,2,3,4-tetrahydro-12H-indolo [2,3-a]-quinolizine.

A Hofmann reaction on yohimbane methohydroxide and catalytic hydrogenation gave yohimbane and a mixture of unidentified oils.

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