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Dehydrogenation studies in the field of indole alkaloids

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DEHYDROGENATION STUDIES IN THE FIELD OF INDOLE ALKALOIDS

by

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Dean of Graduate College

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INTRODUCTION

Various methods of dehydrogenation have been used in the field of indole alkaloids but no concentrated effort has been made so far to generalize their preparative uses or to understand their stereochemical requirements. Information regarding the stereochemistry of reductive processes used for the regeneration of the alkaloids from their dehydro derivatives also has remained incomplete.

The purpose of this work is to explore dehydrogenation as a preparative and stereochemically diagnostic tool and to investigate the reduction of dehydro derivatives, with emphasis on the stereochemical consequences.

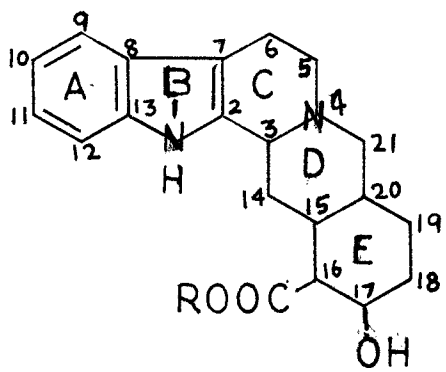
HISTORICAL

Methods of Dehydrogenation in the Field of Indole Alkaloids

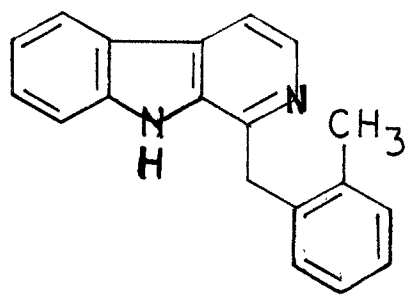
Various methods of dehydrogenation or oxidation have been used for the structure elucidation of indole alkaloids. Of all the hitherto existing methods of dehydrogenation, the following more important ones reveal pertinent information about the ring skeleta.

Use of selenium at high temperature

The earliest method used in the structure elucidation of indole alkaloids involved dehydrogenation with selenium at high temperature. Thus treated, yohimbine (I, R = CH_3) yielded yobyrine (II), tetrahydro-iso-yobyrine [tetrabyrine](III) and keto-yobyrine (IV) (1).

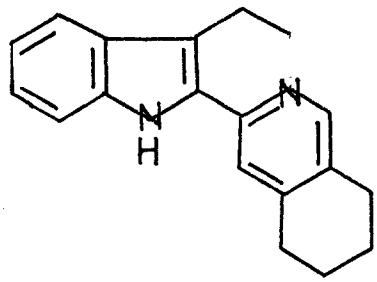


I

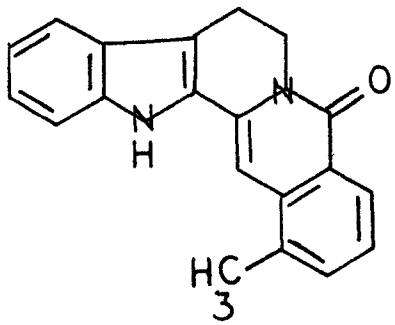


II

Dehydrogenation was also carried out with yohimbic acid (I, R = H) resulting in the same products (2). Other alkaloids possessing the same ring-skeleton I had also



III

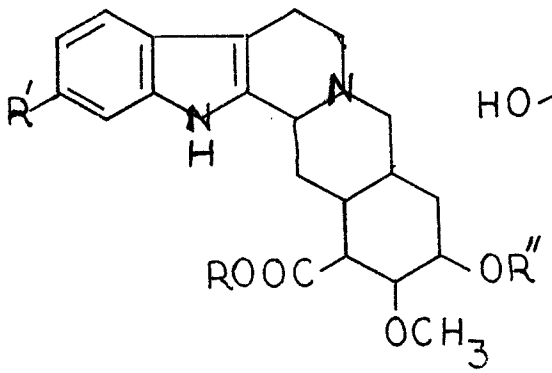


IV

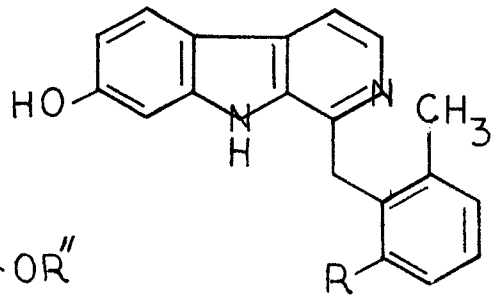
been reported to form the same dehydrogenation products. Thus pseudoyohimbine (3) and rauwolscine (4) yielded II, III and IV on selenium dehydrogenation. Janot and Goutarel (5) obtained II and III from α-yohimbine (rauwolscine) and corynanthine, and Schlittler and co-workers (6) reported the same compounds from 3-epi-α-yohimbine. Janot and co-workers (7) obtained II, III and IV from isorauhimbine by selenium dehydrogenation and assigned a yohimbine ring skeleton to this alkaloid. Similarly, Chatterjee and Bose (8) had shown that serpine lent itself to such characterization on selenium dehydrogenation.

Reserpic acid (V, R = R'' = H, R' = OCH_3) yielded yobyrine (II) and 7-hydroxyyobyrine (VI, R = H) on selenium dehydrogenation (9).

Methyl canescate (deserpidate) (V, R = CH_3, R' = R'' = H) on selenium dehydrogenation produced mostly yobyrine (II) (10).



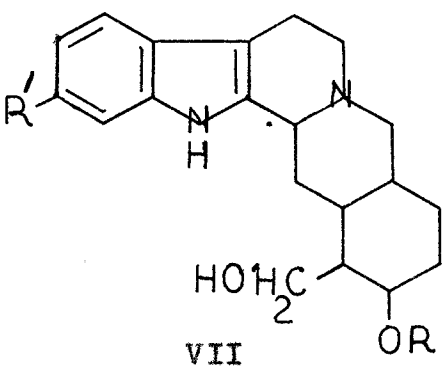
V



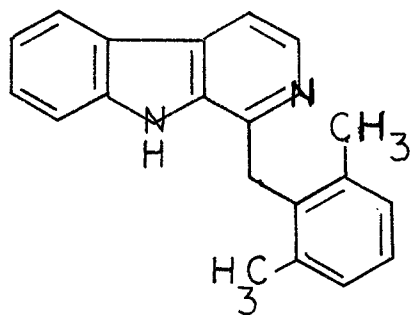
VI

Yohimbyl and rauwolscinyl alcohols (VII, R = R' = H) on selenium dehydrogenation yielded yobyrine (II) and methylyobyrine (VIII) (4, 11).

3-Epi-α-yohimbyl alcohol (VII, R = R' = H) also yielded VIII (6).



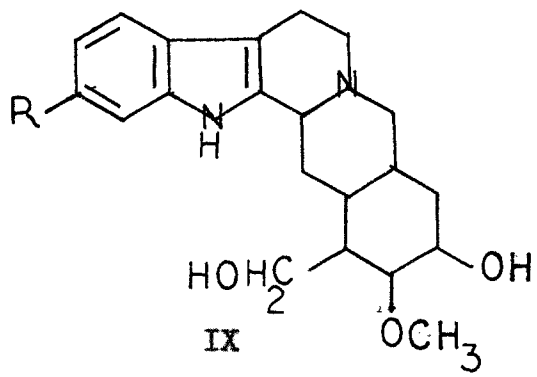
VII



VIII

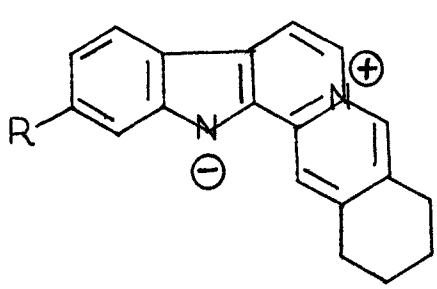
Deserpidinediol (IX, R = H) when subjected to this treatment produced methylyobyrine (VIII) (12). Similarly, reserpinediol (IX, R = OCH_3) or reserpinol (VII, R = CH_3,

R' = OCH_3) on dehydrogenation yielded 7-hydroxy methyl-yobyrine (VI, R = CH_3) (13).

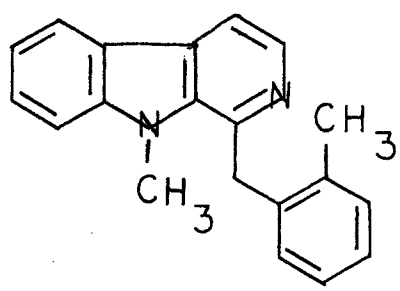


IX

Sempervirine (X, R = H) on dehydrogenation with selenium isomerised into yobyrine (14, 15, 16) and sempervirine methochloride on heating with selenium was converted into ind-N-methylyobyrine (XI) (17).



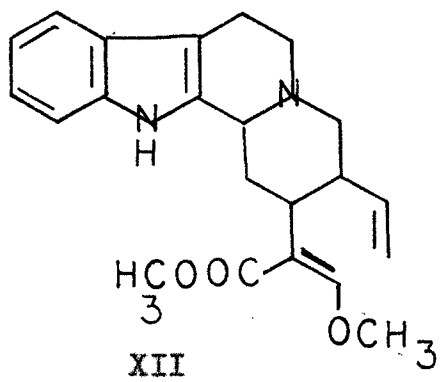
X



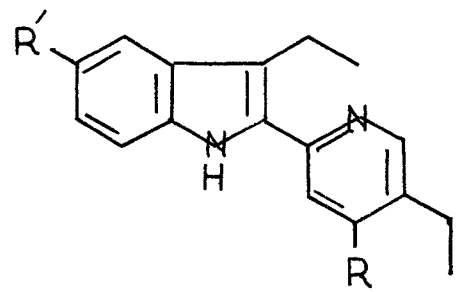
XI

Corynantheine (XII) on selenium dehydrogenation yielded corynanthyrine (now known as alstyrine) (XIII, R = Et, R' = H) (18). The same dehydrogenation carried out by Janot and Goutarel (19) gave desethyl alstyrine (XIII, R = R' = H) with

alstyrine (XIII, R = Et, R' = H). Corynantheidine, possessing



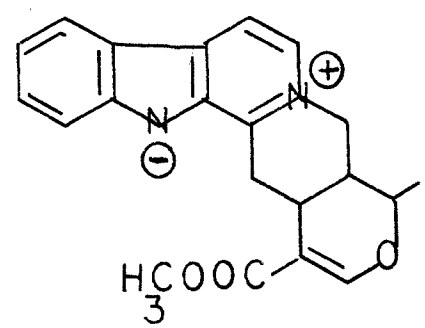
XII



XIII

the same ring skeleton as corynantheine (XII), on selenium dehydrogenation produced alstyrine (XIII, R = Et, R' = H) and desethylalstyrine (XIII, R = R' = H) (20).

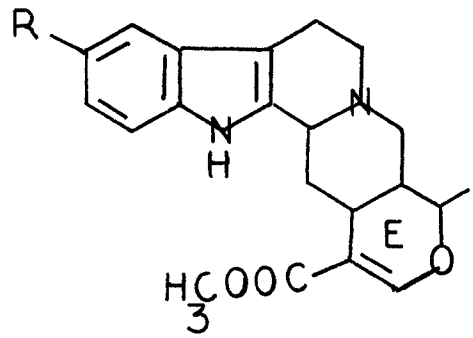
Both alstonine and serpentine (XIV) on selenium dehydrogenation yielded alstyrine (XIII, R = Et, R' = H) (21, 22).



XIV

Ajmalicine [also known as δ-yohimbine or py-tetrahydroserpentine (23)] (XV, R = H) has been dehydrogenated similarly to alstyrine (XIII, R = Et, R' = H) (24).

Akuammigine and mayumbine, stereoisomers of ajmalicine



XV

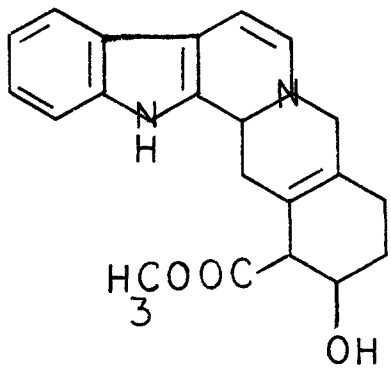
and serpentinine, an alkaloid of undecided structure, belonging to the family of ring E heterocycles, also yielded alstyrine on selenium dehydrogenation (25, 26, 27).

Aricine (XV, R = OCH_3) another ring E heterocyclic compound, yielded mainly a methoxydesethylalstyrine (XIII, R = H, R' = OCH_3) and some methoxyalstyrine (XIII, R = Et, R' = OCH_3) (28).

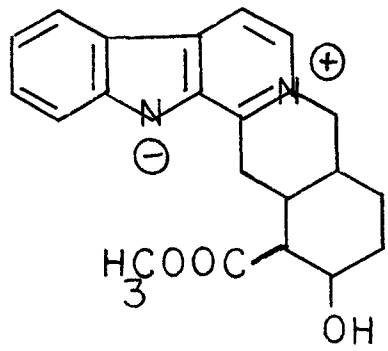
Use of lead tetraacetate for dehydrogenation

Hahn, Kappes and Ludewig (29) used lead tetraacetate for the oxidation of yohimbine (I) and reported the conversion of the base into tetradehydroyohimbine (XVI).

However, the structure XVI was later revised by Schwarz (30) in favor of XVII on careful analysis of ultraviolet spectra of various carbolines and their quaternary salts.

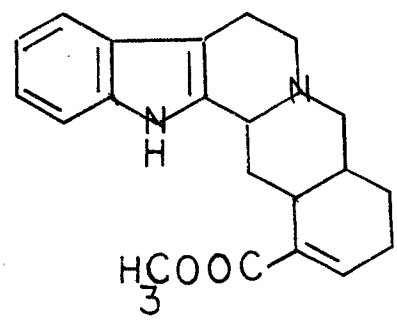


XVI



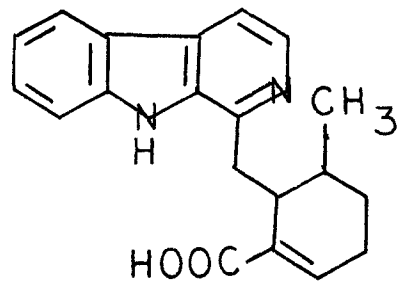
XVII

Witkop (31) reported the use of lead tetraacetate for the dehydrogenation of apo-yohimbine (XVIII) and obtained a



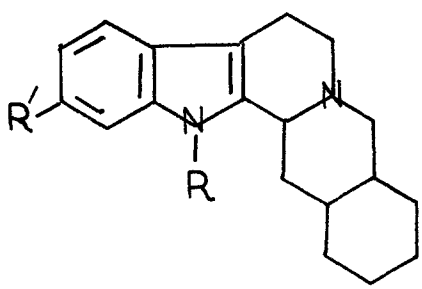
XVIII

dehydrogenated product. After hydrolysis this was claimed to be tetrahydroyobyrine carboxylic acid (XIX). Pseudo-yohimbine, an isomer of yohimbine, was also dehydrogenated using this reagent by Janot and co-workers (32), and tetra-dehydroyohimbine (XVII) was isolated. Both yohimbane and

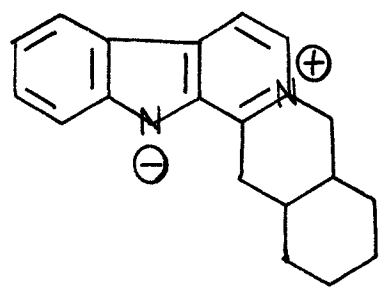


XIX

alloyohimbane (XX, R = R' = H) have been dehydrogenated by this method to yield the corresponding tetradehydro compounds (32,



XX

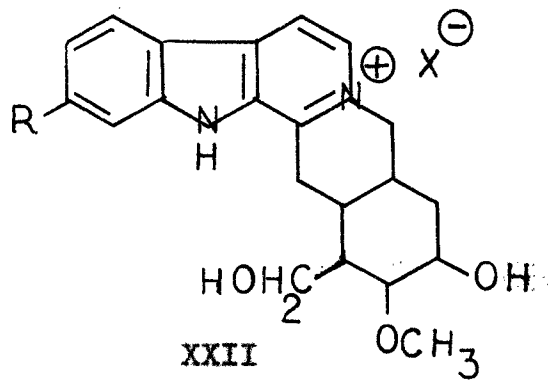


XXI

33). Ajmalicine (δ-yohimbine) (XV, R = H) was oxidized by this reagent to serpentine (XIV) (23). 3-Epi-α-yohimbine, stereoisomer of yohimbine (I), gave an isomer of tetradehydroyohimbine (XVII) (6).

Both deserpidinediol (IX, R = H) and reserpinediol (IX, R = OCH_3) have been converted to their corresponding tetradehydro products, (XXII, R = H) and (XXII, R = OCH_3),

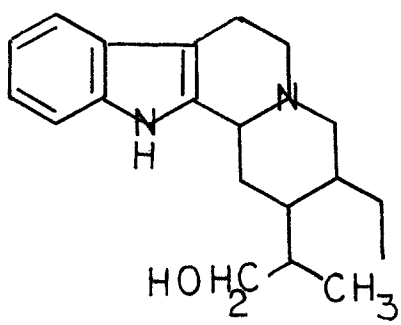
respectively (12).



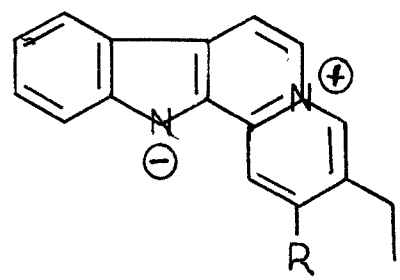
XXII

Use of palladium

Schwyzer (34) observed that using specially prepared 5% palladium on charcoal in the presence of acid at 280-300° tetrahydrodesmethoxycorynantheine alcohol (XXIII) dehydrogenated into a sempervirine type compound (XXIV, R = either CH_2CH_3 or $CH(CH_3)_2$).



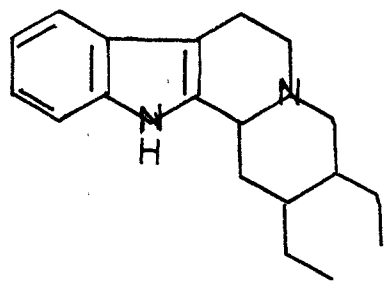
XXIII



XXIV

This dehydrogenation method was used by Janot and co-workers (35) for the dehydrogenation of stereoisomeric

dihydrocorynantheane and corynantheidane (XXV) to obtain XXIV (R = Et). When using ordinary 30% palladinised charcoal at 250-290° the same group of workers obtained only alstyrine (XIII, R = Et, R' = H) from the above compounds (19, 20).



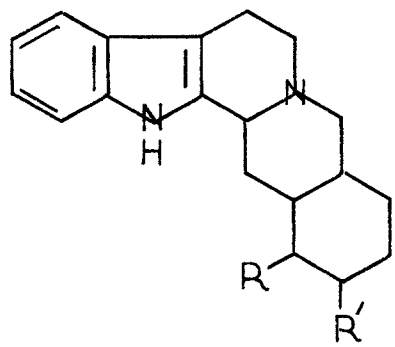
XXV

Similarly, whereas dehydrogenation with 5% palladium on charcoal in the presence of acid gave tetradehydroyohimbane (XXI) and sempervirine (X, R = H) from yohimbane and alloyohimbane (XX, R = R' = H) respectively (36), dehydrogenation in presence of ordinary palladinised charcoal yielded yobyrine (II) in both cases (37, 38). It was also reported yohimbine, corynanthine, pseudoyohimbine, alloyohimbine, α-yohimbine (I) all yielded yobyrine on being dehydrogenated with ordinary palladinised charcoal (38).

Karrer and co-workers (11) obtained yobyrine (II) from yohimbyl alcohol (VII) by dehydrogenation with an 8% palladium-charcoal catalyst at 290°.

Use of palladium in the presence of maleic acid

Majima and Murahashi (39) observed that yohimbic acid (I, R = H), desoxyyohimbic acid (XXVI, R = COOH, R' = H) and yohimbyl amine (XXVI, R = NH_2, R' = OH) when heated with palladium black in aqueous solution in presence of maleic acid, yellowish tetradehydro products were obtained.



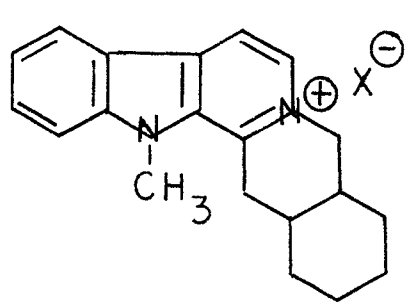
XXVI

This report lay dormant till 1955 when Wenkert and Liu (40) reported that alloyohimbane was dehydrogenated very easily by this method, while epialloyohimbane was not. Schlittler and co-workers (41) demonstrated quantitative dehydrogenation of reserpinediol (IX, R = OCH_3) to the corresponding tetradehydro product (XXII, R = OCH_3).

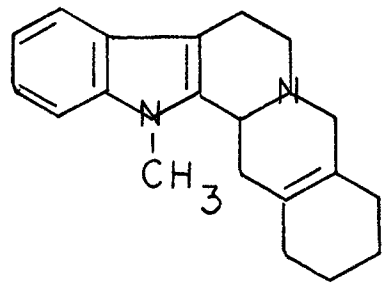
Use of molecular oxygen, ozone, and iodine

The catalytic autoxidation of N-methylyohimbane (XX, R = CH_3, R' = H) in glacial acetic acid with platinum catalyst and oxygen led to the formation of N-methyltetradehydroyohimbane (42) (XXVII).

Methylhexahydrosempervirine (XXVIII) and yohimbine



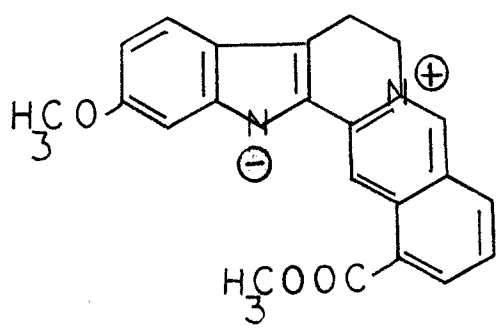
XXVII



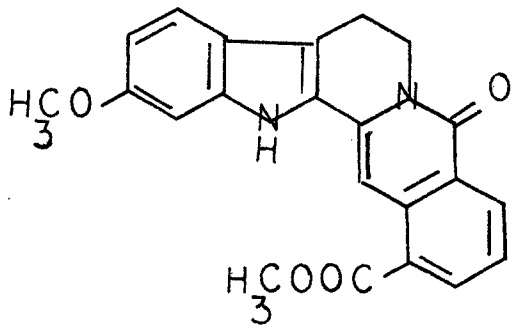
XXVIII

(I, R = CH_3) on similar oxidation gave products with green fluorescence, which were not completely characterized (42).

Alstoniline (XXIX) underwent oxidation to give alstoniline oxide (XXX) in the presence of platinum oxide and molec-



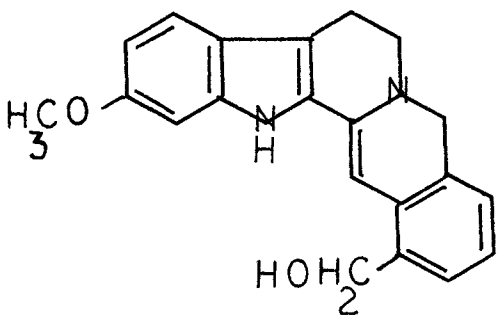
XXIX



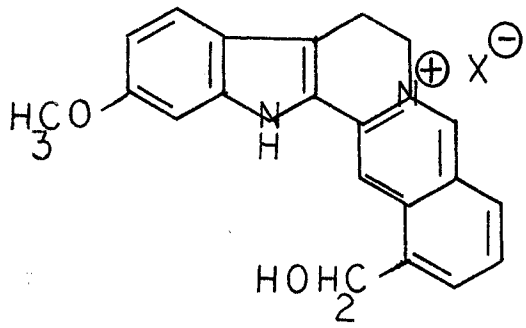
XXX

ular oxygen. The lithium aluminum hydride reduction product of alstoniline oxide (XXXI) could be oxidized to alstonilinol (XXXII) (43).

Ozonization of yohimbine (I), tetrahydroalstonine (XV, R = H, stereoisomer) and yohimbane (XXI, R = H) in 80% acetic

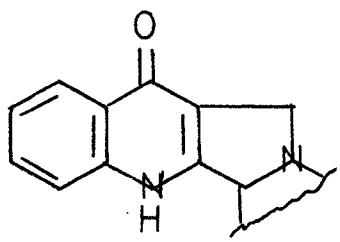


XXXI

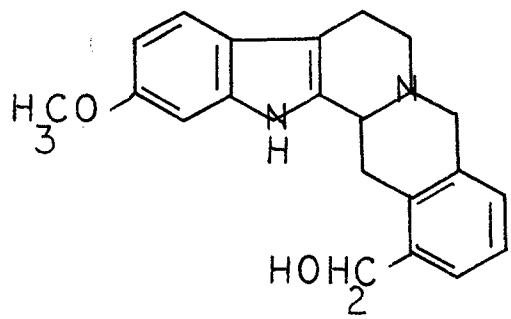


XXXII

acid and final work-up with bicarbonate yielded quinolones (partial structure XXXIII) (44, 45). Molecular iodine oxidized tetrahydroalostonilinol (XXXIV) to alostonilinol (XXXII) (43).



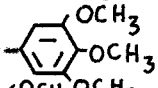
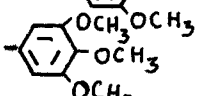
XXXIII

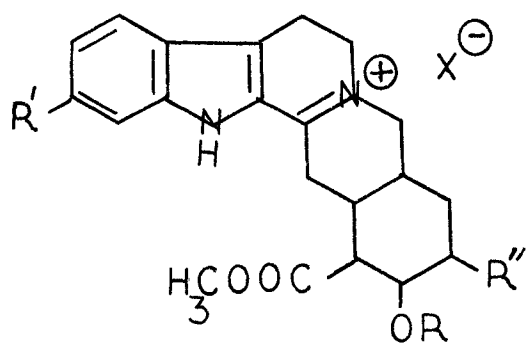


XXXIV

Use of mercuric acetate

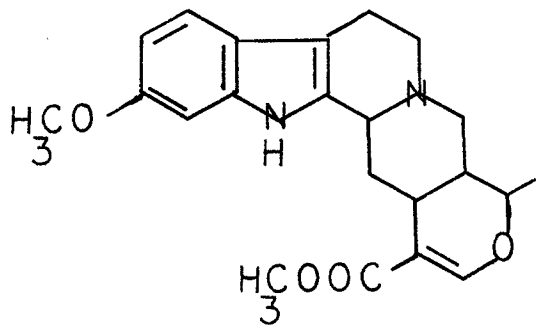
In 1927, Schomer (46) reported the dehydrogenation of yohimbine by mercuric acetate to an uncharacterized, colored substance. Recently Weisenborn and Diassi (47) have con-

ducted such dehydrogenations on yohimbine (I, R = CH_3), and other indole alkaloids, obtaining 3-dehydro products (XXXV, R = R' = R'' = H). To account for their observation that pseudo-yohimbine (I, R = CH_3), reserpine (V, R = CH_3 R' = OCH_3, R'' = CO- ), and deserpidine (V, R = CH_3 R' = HO R'' = CO- ) were unreactive under identical reaction conditions; they suggested that only compounds containing an axial hydrogen atom at C_3 would dehydrogenate with mercuric acetate.



XXXV

Djerassi and co-workers (48) have subjected tetraphylline, (XXXVI) isoreserpinine (XXXVI) and aricine (XV, R = OCH_3) to mercuric acetate dehydrogenation and also obtained the corresponding 3-dehydro derivatives.



XXXVI

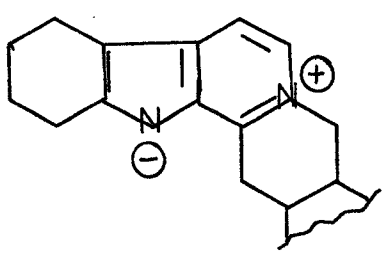
Methods of Reduction of the Anhydronium Bases and 3-Dehydro Compounds

Catalytic reduction

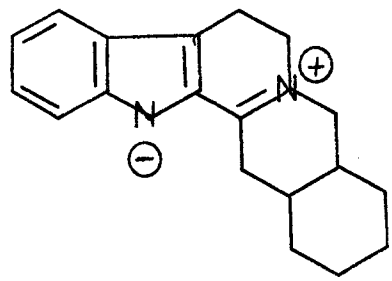
Alstonine (XIV) on reduction in absolute methanol with platinum oxide gave tetrahydroalstonine (XV, R = H) (49). The same compound was also obtained on hydrogenation at pH 10 (50). This indicated that in neutral or alkaline condition, the reduction of tetradehydro indole alkaloids led to the saturation of the pyridine moiety (ring C). Thus tetradehydroyohimbine (XVII) and serpentine (XIV) on reduction at pH 10 with platinum oxide gave yohimbine and ajmalicine, respectively (31, 51). Tetradehydroyohimbane and tetradehydroalloyohimbane (XXI) on hydrogenation at pH 10 yielded yohimbane and alloyohimbane (XX, R = H) respectively (32, 33). Sempervirine (X, R = H) underwent the same reduction yielding mostly d,l alloyohimbane and also a small amount of d,l

epialloyohimbane (stereoisomer of XX, R = R' = H) (40, 52). 11-Methoxysempervirine (X, R = OCH_3) on similar reduction produced d,l 11-methoxyalloyohimbane (XX, R = H, R' = OCH_3) (53).

Reduction of the tetradehydro compounds in glacial acetic acid with platinum was shown to produce hydrogenation of the benzenoid ring (ring A) (54, 55). Thus serpentine (XIV) and tetradehydroyohimbine (XVII) both yielded tetrahydro products with part structure (XXXVII), and sempervirine (XI, R = H), yielded an octahydro derivative which spectroscopically was shown to have the same chromophoric system (XXXVII).



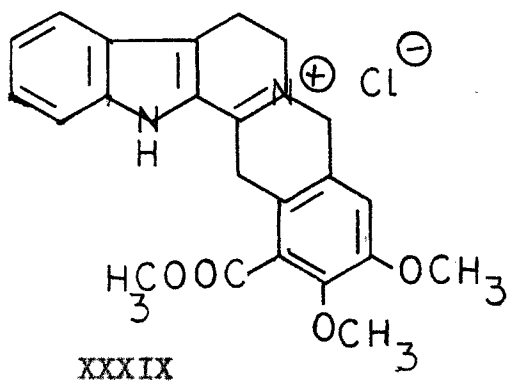
XXXVII



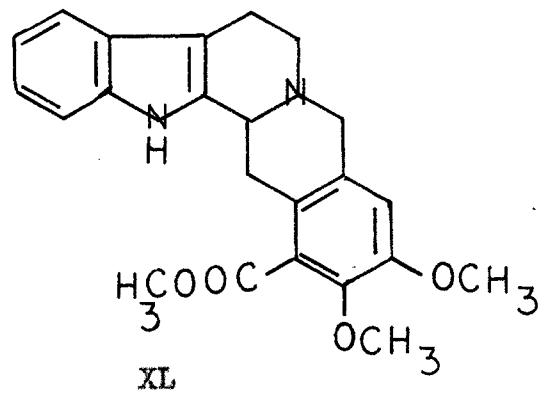
XXXVIII

d,l 3-Dehydroyohimbane and d,l 3-dehydroalloyohimbane (XXXVIII) suffered reduction in ethanol with platinum oxide to yield d,l yohimbane and d,l alloyohimbane (56, 57). 3-dehydroyohimbine on catalytic hydrogenation in methanol with platinum oxide regenerated yohimbine (47). The unsaturated base (XXXIX) was reduced with platinum in methanol

to the corresponding saturated base (XL) (58).



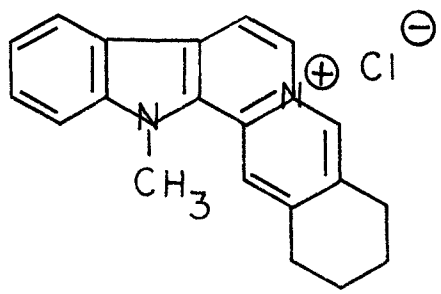
XXXIX



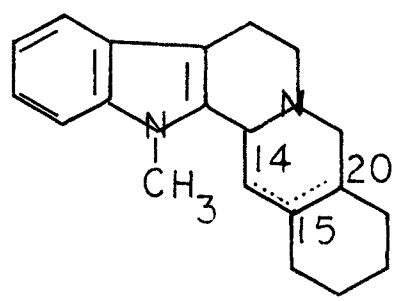
XL

Sodium borohydride reduction

Selectivity of sodium borohydride in the reduction of quaternary cyclic Schiff bases has been known for quite some time. Thus methylsempervirine chloride (XLI) on refluxing



XLI

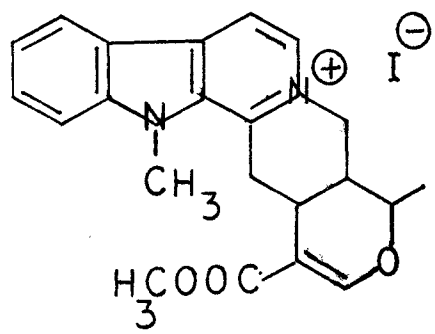


XLII

with sodium borohydride in methanol suffered reduction to ind-N-methyl- $\Delta^{14(15)}$ or $\Delta^{15(20)}$ yohimbene (XLII) (42).

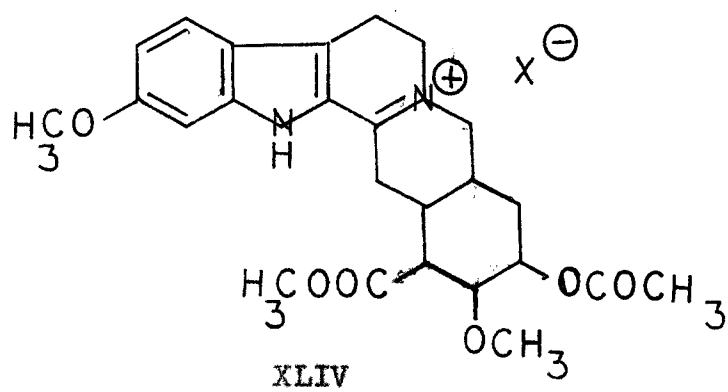
Tetradehydroreserpinediol (XXII, R = OCH_3) on reduction with sodium borohydride yielded 3-isoreserpinediol (stereo-

isomeric with IX, R = OCH_3), and similarly tetradehydrodeserpidinediol (IX, R = H) produced 3-isodeserpidinediol (12). Tetradehydroepi-α-yohimbine (XVII) under identical conditions generated α-yohimbine (6). Serpentine (XIV) has recently been reduced to ajmalicine by this method, (59) and N(ind)-methylserpentine iodide (XLIII) has also produced the corresponding py-tetrahydro compound (60).



XLIII

Woodward and co-workers (61) have reduced methyl 3-dehydroreserpate 18-acetate (XLIV) to methyl isoreserpate 18-acetate (V, R = CH_3, R' = OCH_3, R'' = $COCH_3$) using sodium



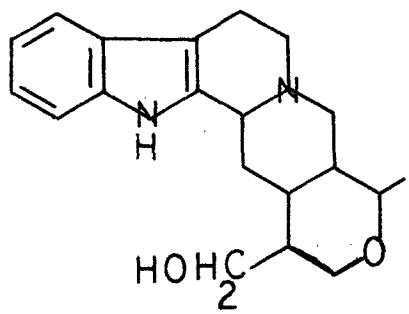
XLIV

borohydride. 3-Dehydrotetraphylline and 3-dehydroaricine perchlorate have also been reduced by sodium borohydride to regenerate tetraphylline (XXXVI) and aricine (XV, R = OCH_3) (48).

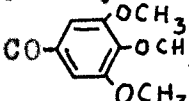
Miscellaneous reductive methods

3-dehydroalloyohimbane (XXXVIII) was reduced by Hill (62) using metallic tin and hydrochloric acid to obtain alloyohimbane (XX, R = R' = H). Stork and Hill (57) indicated that the same compound on reduction with sodium and alcohol in liquid ammonia yielded epi-alloyohimbane (XX, R = R' = H).

3-Dehydroyohimbine and 3-dehydro-α-yohimbine (XXXV, R = H, R' = H, R'' = H) on reduction with zinc and hydrochloric or glacial acetic acid yielded pseudoyohimbine and



XLV

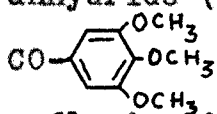
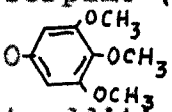
3-epi-α-yohimbine (I, R = CH_3) respectively. 3-Dehydroreserpine (XXXV, R = CH_3, R' = OCH_3, R'' = O - CO- ) and methyl 3-dehydroreserpate (XL, R = CH_3, R' = OCH_3, R'' = OH) produced reserpine and methyl reserpate (46), re-

spectively.

Serpentine (XIV) was reduced to py-tetrahydroserpentinol (XLV) with metallic sodium and butyl alcohol (54).

Acid-catalysed Equilibration at C_3

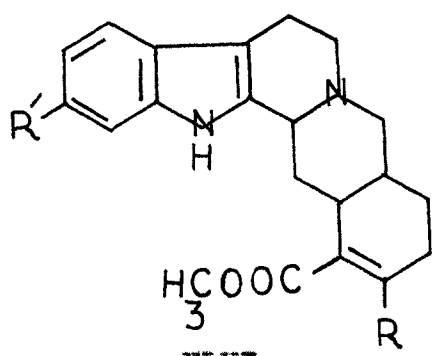
Wenkert and Liu (40) observed that concentrated hydrobromic-acetic acid treatment of either alloyohimbane or epialloyohimbane (both stereoisomers of XX, R = R' = H) led to a mixture in which the latter prevailed in the ratio of 3.6:1. When applied to 3-epi-α-yohimbine (I) this method allowed isolation of α-yohimbine alone from the equilibrated mixture (12). Huebner (63) observed that 11-methoxyalloyohimbane (X, R = OCH_3) by refluxing in acetic acid for two days yielded 11-methoxy-3-epialloyohimbane (X, R = OCH_3) as the major product.

Isomerization of methyl reserpate (V, R = CH_3, R' = OCH_3, R'' = H) to methyl 3-isoreserpate 18-acetate (V, R = CH_3, R' = OCH_3, R'' = $COCH_3$) was effected by refluxing with acetic anhydride (12). Reserpine (V, R = CH_3, R' = OCH_3, R'' = ) was smoothly isomerized to 3-isoreserpine by refluxing in acetic anhydride (12) whereas refluxing in acetic acid gave an equilibrium mixture containing 20 per cent reserpine and 80 per cent 3-isoreserpine (64). Deserpidine (V, R = CH_3, R' = H, R'' = ) was unaffected by refluxing acetic acid but addition of p-toluenesulfonic acid brought about epimerization to an

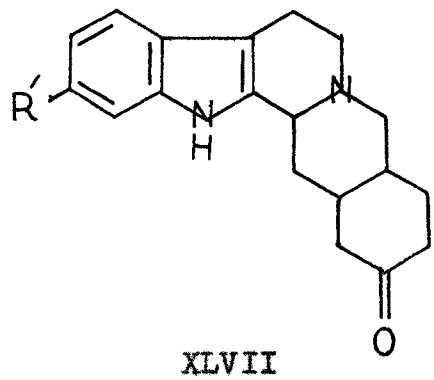
equilibrium mixture containing 20 per cent deserpidine and 80 per cent 3-isodeserpidine (64).

Refluxing in collidine containing p-toluenesulfonic acid had also the same isomerizing effect (12). Reserpinol (VII, R' = OCH_3, R = CH_3) was transformed to 3-isoreserpinol, and methyl reserpate (V, R = CH_3, R' = OCH_3, R'' = H) yielded methyl 3-isoreserpate (12).

Methyl 3-isoanhydroreserpate (XLVI, R = R' = OCH_3) on being refluxed with dilute hydrochloric acid gave rise to 11-methoxyalloyohimbone and 11-methoxy-3-epialloyohimbone (XLVII, R' = OCH_3) in a 2:3 ratio (52).



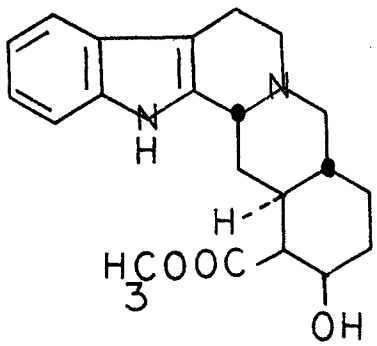
XLVI



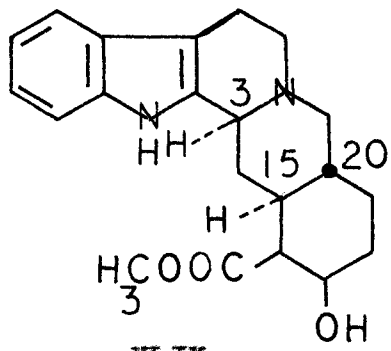
XLVII

DISCUSSION

The stereochemistry of yohimbine and several of its isomers was derived by Janot and co-workers (32) utilizing methods of conformational analysis. Pseudoyohimbine (XLVIII) and yohimbine (XLIX) when dehydrogenated with lead tetra-acetate lose their asymmetric center at C_3 and yield the same tetradehydroyohimbine (XVII) (32). Catalytic reduction



XLVIII

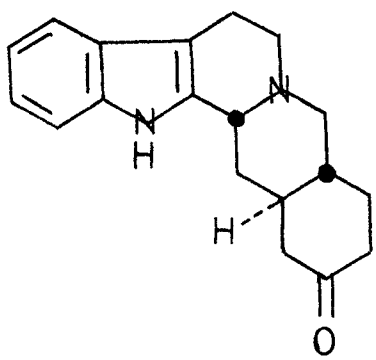


XLIX

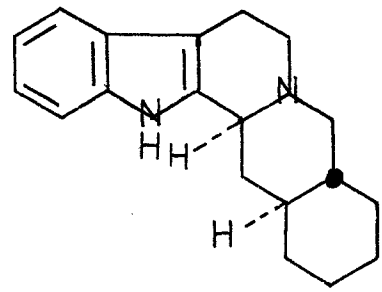
of tetradehydroyohimbine at pH 10 regenerated yohimbine which is presumably the more stable isomer, and therefore contains the greater number of equatorial carbon-carbon bonds making all the hydrogen atoms at the bridgeheads C_3, C_{15} and C_{20} axial as indicated in XLIX. This will be called the normal configuration.

Pseudoyohimbine (XLVIII) upon Oppenauer oxidation yields pseudoyohimbone (L) and the latter, when treated according to the Huang-Minlon variant of the Wolff-Kishner reduction method, is converted into yohimbane (LI) (32). The same yohimbane is

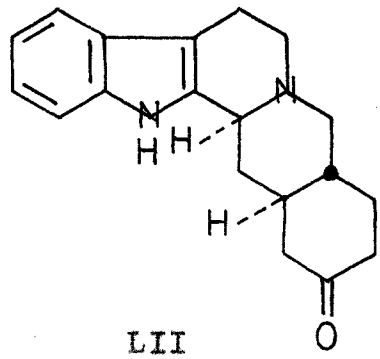
obtained by identical reduction of yohimbone (LII) (65). Tetradehydroyohimbane (XXI) on catalytic hydrogenation at pH 10 yielded only yohimbane (LI). The stereochemistry of the D/E ring-juncture indicated in LI was further proved by the synthesis of d,l yohimbane (56).



L

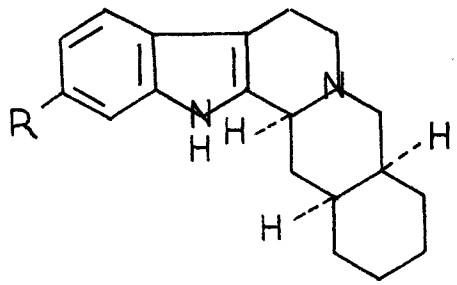


LI

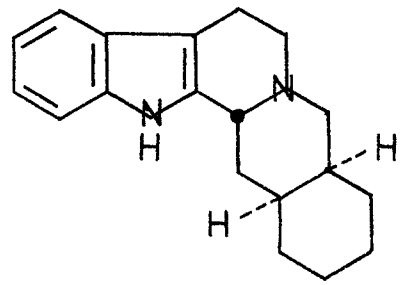


LII

Sempervirine (X) on hydrogenation at pH 10 yielded mostly d,l alloyohimbane (LIII, R = H) and a small amount of epialloyohimbane (LIV) (40). This observation is consistent with the assumption that the product is a syn-cis system and that alloyohimbane and epialloyohimbane are of



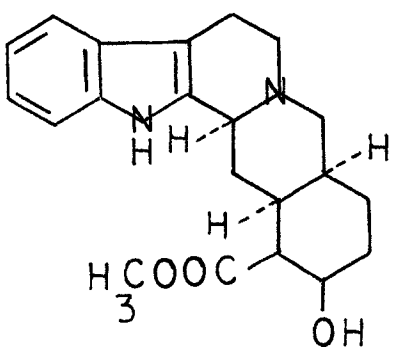
LIII



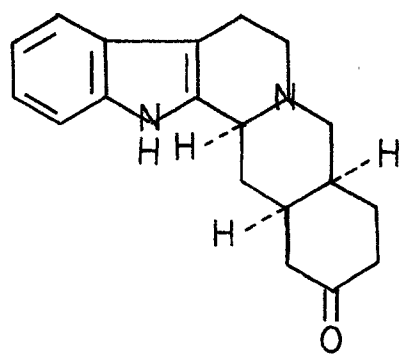
LIV

comparable energy content.

Both alloyohimbine (LV) and α-yohimbine (LV) on Oppenauer oxidation produced alloyohimbone (LVI), which on Wolff-Kishner reduction gave alloyohimbane (LIII, R = H) (33). Hydrogenation of tetradehydroalloyohimbane (LVII) at pH 10 yielded only alloyohimbane (LIII, R = H) (35).

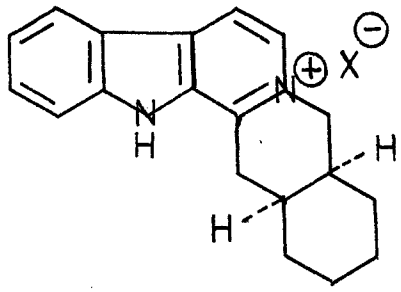


LV



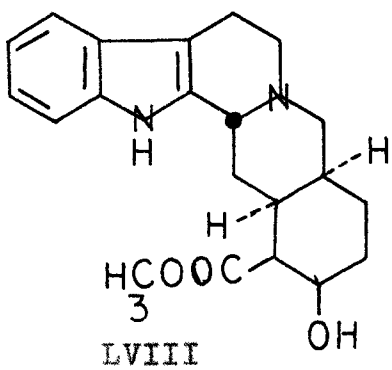
LVI

3-Epi-α-yohimbine (LVIII) on Oppenauer oxidation has yielded 3-epialloyohimbone (LIX) (6). The latter on Wolff-Kishner reduction produced a mixture of epialloyohimbane

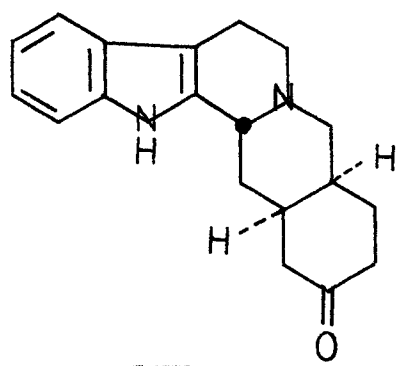


LVII

(LIV) and alloyohimbane (LIII, R = H) (6), which also points out the similarity of energy content of these two compounds. Total syntheses of d,l alloyohimbane and d,l epialloyohimbane confirmed the D/E cis ring-juncture (57).



LVIII



LIX

Perhaps, one could conclude from the above results that regeneration of the asymmetric center at C_3 by catalytic hydrogenation at pH 10, like the reduction of ketones to the alkanes by the Wolff-Kishner method, leads to products consisting predominantly, if not exclusively, of the more stable

isomer, viz. C_3-H (α). However, a complete investigation of the stereochemistry of reduction of tetradehydro products by various methods with stoichiometric details, wherever pertinent, was considered worthwhile for the following reasons:

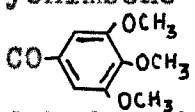
(1) to obtain further insight into the mode of reduction,

(2) to explore the possibilities of general diagnostic value of the methods of reduction for stereochemical problems.

To accomplish this, it was necessary to prepare a large number of tetradehydro compounds from the saturated alkaloids or their derivatives. Among the methods which have been used before, lead tetraacetate oxidation was considered first. The deleterious effect of this reagent towards compounds like yohimbone (31) limits its usefulness. Use of palladium on charcoal in the presence of acid at high temperature would also have been a poor choice because of low yield and simultaneous destruction of asymmetric centers at C_{15} and C_{20} along with the one at C_3 in some cases (35, 36).

Finally, use of palladium in the presence of maleic acid under refluxing conditions was found to be the most suitable method for ring C dehydrogenation. This method has previously been used for the preparation of tetradehydro compounds and the yields were fairly high (39). The original method used by Majima and Murahashi (39) was adopted without modification. Thus the free amine was dissolved in aqueous maleic acid solution, the latter stirred and refluxed with palladium

black. The anhydronium bases obtained on dehydrogenation were precipitated in some cases by the addition of ammonia to the cooled aqueous solution. These were very highly colored and generally unstable substances. Consequently their nitrate or perchlorate salts were prepared by dissolving the free bases in dilute acetic acid and precipitating the salts by the addition of aqueous saturated solutions of ammonium nitrate or potassium perchlorate. The same precipitation could be effected from the original acidic aqueous solutions. The yields ranged from 45 to 75%. The ultraviolet spectra* of these compounds showed maximum absorption at 253 mμ (log ε 4.3), 307 mμ (log ε 4.15), 361 mμ (log ε 3.7) characteristic of the cations of anhydronium bases of this type (30).

By the above procedure yohimbane and alloyohimbane have been converted to their corresponding tetradehydro derivatives. Yohimbine, α-yohimbine and yohimbyl alcohol have also yielded tetradehydro compounds. Compounds containing various types of substituents in ring E like ajmalicine (XV), yohimbone (LII) and deserpidine (V, R = CH_3, R' = H, R'' = ) have been transformed into serpentine, tetradehydroyohimbone and tetradehydrodeserpidine, respectively. Apoyohimbine (XVIII) has also been subjected to this dehydrogenation. Spectroscopic examination of the reaction product

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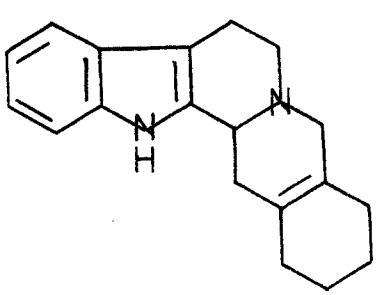
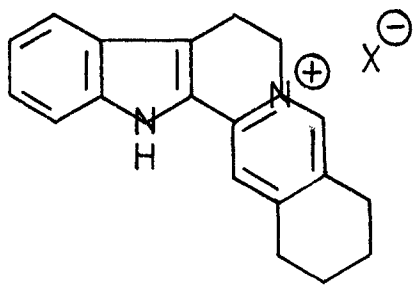
*See spectra section for all the spectra reported in discussion.

indicated that it belonged to the regular tetradehydro class of compounds, thus excluding the possibility of its being a tetrahydroyobyrine derivative as suggested by Witkop (31).

However, d,l $\Delta^{15(20)}$ yohimbene (LX), obtained by sodium borohydride reduction of sempervirine (vide infra), was converted by this method of dehydrogenation into 5,6-dihydrosempervirine (LXI). Structure LXI was assigned on the basis of the ultraviolet spectrum of this compound which showed maxima of 223 mμ (log ε 4.58), 320 mμ (log ε 4.33) and a minimum at 276 mμ (log ε 3.85). Ultraviolet spectra of tetrabyrine (III) and alstyrine (XIII, R = Et, R' = H) show a maximum at 321 mμ (log ε 4.36) and a minimum at 274 mμ (log ε 3.67), with a shoulder off 230 mμ (log ε 4.5) (66, 18), which presumably are characteristic properties of a simple indole nucleus conjugated with a pyridine moiety.

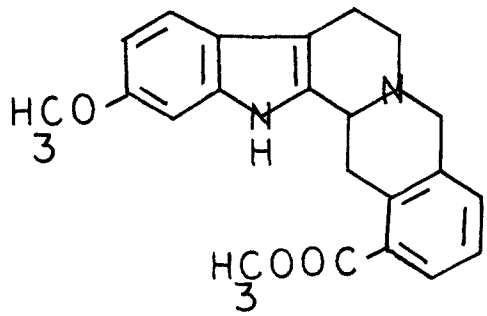


LX

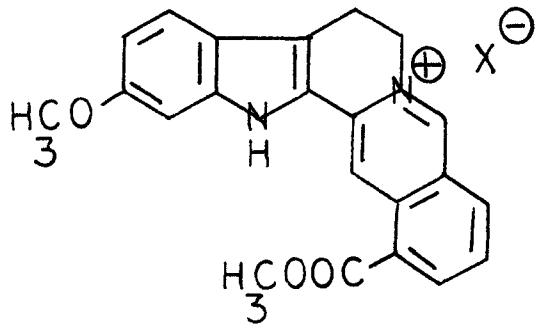


LXI

Elderfield (67) has indicated that tetrahydroalstoniline (LXII) has been converted to alstoniline (LXIII) by palladium-maleic acid treatment.

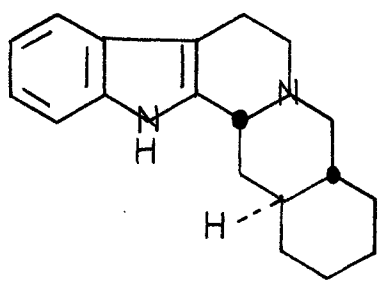


LXII



LXIII

Catalytic hydrogenation of tetradehydroyohimbane at pH 10 with platinum and careful chromatographic work-up of the reduction products allowed only isolation of yohimbane (LI). Pseudoyohimbane (LXIV) which possesses an axial C_2 - C_3 bond is at least 2.4 kcal less stable than yohimbane on the basis of empirical values obtained for perhydroanthracenes (68). Through Linstead's brilliant research in Hill (62, p. 42) the stages determining the configuration of the products in catalytic hydrogenation have been established. These are:



LXIV

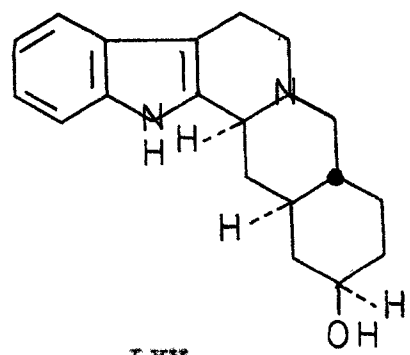
(1) adsorption of the molecule on the surface of the catalyst,

(2) addition of hydrogen in cis-syn fashion to the rear. Presumably in the reduction of tetradehydroyohimbane the configuration of the transition state after adsorption lies close to yohimbane, causing reduction at C_3 to occur preferentially from the axial side. This implies that hydrogenations of unhindered systems are only susceptible to secondary steric effects and dependent on the conformation of the transition state.

Catalytic hydrogenation of 5,6-dihydrosempervirine (LXI) at pH 10 yielded alloyohimbane (LIII, R = H). Sempervirine (X, R = H) under the same conditions has been shown to yield alloyohimbane (LIII, R = H) and appreciable amounts of epialloyohimbane (LIV) (40). However, in the reduction of tetradehydroalloyohimbane by catalytic method at pH 10 with platinum and chromatography of the reaction product, only a slight trace of epialloyohimbane (LIV) was obtained as side-product. Whereas in the reduction of sempervirine which is essentially a planar molecule, the small difference in energy between alloyohimbane and epialloyohimbane makes production of a perceptible amount of epialloyohimbane feasible (40), the reduction of tetradehydroalloyohimbane possibly tends to follow mainly syn-cis addition across $\rangle C_3 = \overset{\oplus}{N}\langle$ for primary steric reasons. A D/E cis ring juncture forces the incoming hydrogen to approach from the side of the bridgehead hydrogens

at C_{15} and C_{20}. Furthermore, since Wenkert and Liu (40) have shown isomerization of alloyohimbane under alkaline treatment yields a mixture containing 4% of the isomerized amine, it is possible, although less likely, that at pH 10 such isomerization might take place after reduction, and give rise to the observed amount of epialloyohimbane.

Reduction of tetradehydroyohimbone at pH 10 with platinum yielded epiyohimbol (LXV) (31). This product was identical in every respect with the compound obtained by lithium aluminum hydride reduction of yohimbone. Barton (69)



LXV

has pointed out that the reduction of unhindered ketones by lithium aluminum hydride always yields the thermodynamically stable, equatorial isomers. Thus, like 3-keto steroids, reduction of yohimbone should give the equatorial alcohol. It can now be concluded that epiyohimbol (LXV), obtained by catalytic hydrogenation of tetradehydroyohimbone and also by Meerwein-Ponndorf reduction of yohimbone (LII) (31), possesses an equatorial hydroxyl group.

Reduction of serpentine (XIV) by the above method yields only ajmalicine (XV, R = H). This indicates a syn relation of the C_3 and C_{15} hydrogen atoms. Thus, only a normal or allo configuration can be assigned to ajmalicine.

Sodium borohydride reduction of tetradehydroyohimbane yielded yohimbane (LI) exclusively. d,l Tetradehydroalloyohimbane yielded only alloyohimbane. As observed by Chatterjee and Talapatra (59), reduction of serpentine by this method gave only ajmalicine. Sodium borohydride reduction of tetradehydroyohimbone produced epiyohimbol (LXIV), identical with the compound prepared previously by other reduction methods.

Thus, reduction by sodium borohydride follows the same pattern as catalytic hydrogenation in base to yield the more stable normal or allo derivatives. Since the tetradehydro compounds obtained from derivatives of reserpine and deserpidine on sodium borohydride reduction gave rise to 3-iso compounds (12), these alkaloids could be classified only as pseudo or epiallo compounds.

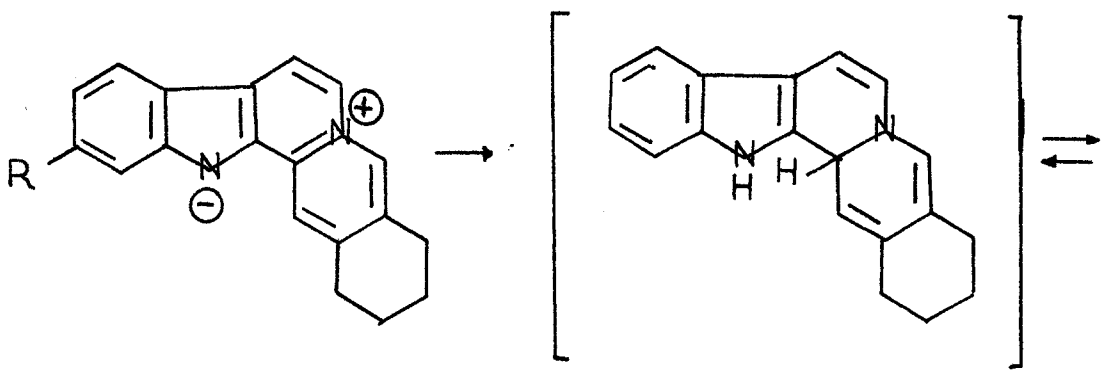
Reduction of sempervirine (X, R = H) by sodium borohydride gave a colorless base $C_{19}H_{22}N_2$. An ultraviolet spectrum showed maxima at 225 mμ (log ε 4.52), 282 mμ (log ε 3.88) and 290 mμ (log ε 2.80) like those of alloyohimbane (LIII, R = H). This excluded the possibility of its being a 3-dehydro ($\Delta^{3(4)}$ or $\Delta^{3(14)}$) compound. The stability of this compound towards acid further eliminates $\Delta^{3(14)}$ or $\Delta^{20(21)}$

cases.

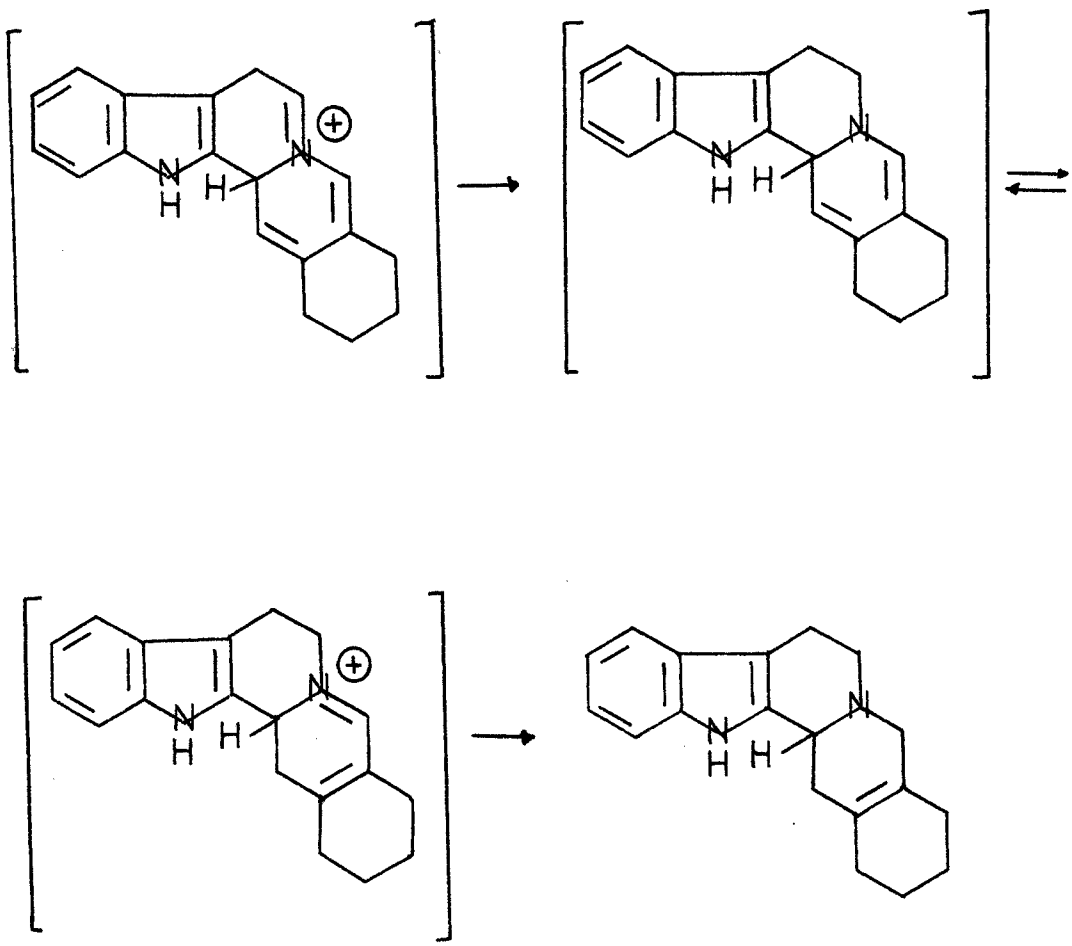
Furthermore, Witkop's (42) methylhexahydrosempervirine, obtained by sodium borohydride reduction of methylsempervirine chloride must be an analogue of this compound. Failure of methylhexahydrosempervirine to undergo catalytic hydrogenation favored it to be a $\Delta^{15(20)}$ compound, since in contrast with a $\Delta^{14(15)}$ compound, the tetrasubstituted nature of the double bond in $\Delta^{15(20)}$ compound might cause this inertness (42).

Finally, lack of isomerization when refluxed in hydrobromic acid-acetic acid mixture provided strong evidence in favor of its being $\Delta^{15(20)}$ yohimbene (LX).

The reduction probably assumed the following pathway:



X, R = H



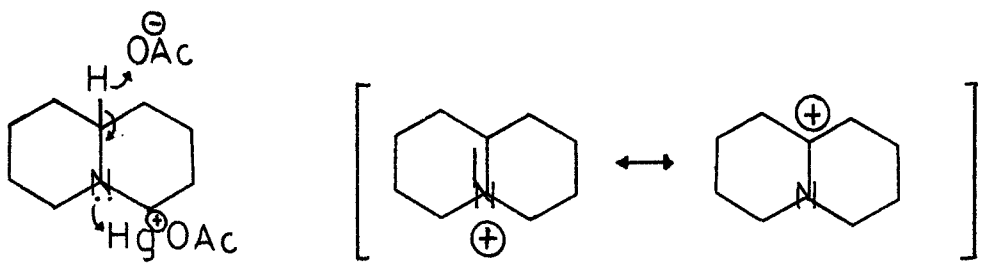
LX

5,6-Dihydrosempervirine (LXI) (vide supra) is reduced by sodium borohydride to the same yohimbene.

During the total syntheses of d,l yohimbane (LI) and d,l alloyohimbane (LIII, R = H), the last asymmetric center at C_3 was introduced via the reduction of corresponding 3-dehydro compounds (56, 57). In this connection, a complete investigation of the different methods of reduction on different 3-dehydro derivatives seemed necessary for the con-

struction of a general stereochemical pattern.

For this purpose, syntheses of a number of 3-dehydro compounds became essential. Among the methods known, use of mercuric acetate was selected because of its well-known oxidation of general amines and alkaloids to imines or their analogues. Leonard and his co-workers (71) have oxidized a large number of cyclic tertiary amines to their immonium salts. The reaction has been proposed to follow the mechanism portrayed below:

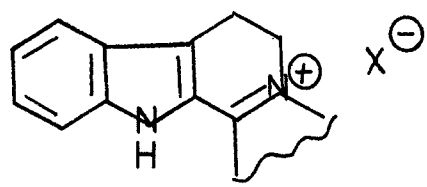


LXVI

Thus quinolizidine (LXVI) on oxidation with mercuric acetate in acetic acid yields its corresponding immonium salt.

When yohimbine (XLVIII), yohimbone (L), yohimbane (LII), d,l alloyohimbane (LIII, R = H) and ajmalicine (XV, R = H) were subjected to mercuric acetate oxidation, yellow 3-dehydro products (LXVII part structure) were obtained. Their spectra distinguished them readily from their precursors as well as from tetradehydro products. The infrared spectra in nujol exhibited characteristic 1625, 1570 and 1540 cm^{-1} peaks,

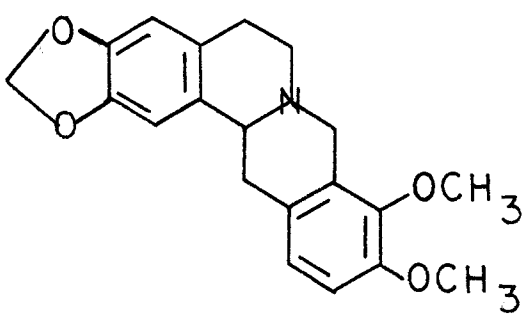
while the ultraviolet spectra showed maximum absorption at 248 mμ (log ε 4.10) and 353 m (log ε 4.41) and minimum absorption at 232 mμ (log ε 3.96) and 278 mμ (log ε 2.88).



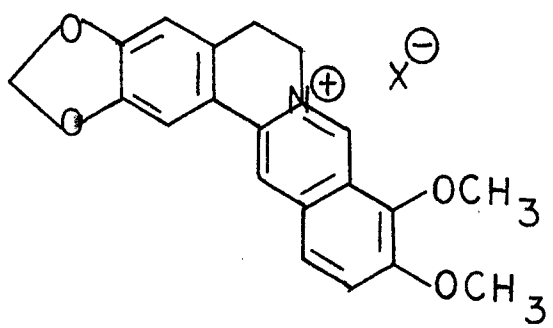
LXVII

Because of its additional chromophore in ring E 3-dehydro ajmalicine showed a slight deviation in its ultraviolet absorption curve.

$\Delta^{15(20)}$ Yohimbene on mercuric acetate dehydrogenation yielded 5,6-dihydrosempervirine (LXI). This is perhaps analogous to the transformation of canadine (LXVIII) to berberine (LXIX) by mercuric acetate as reported by Gadamer (72).

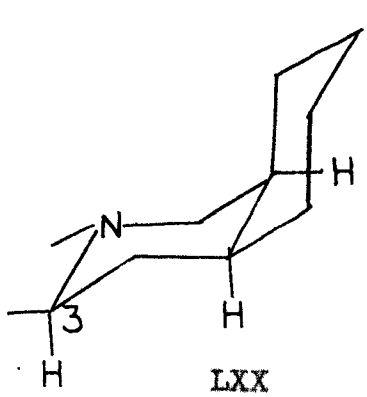


LXVIII

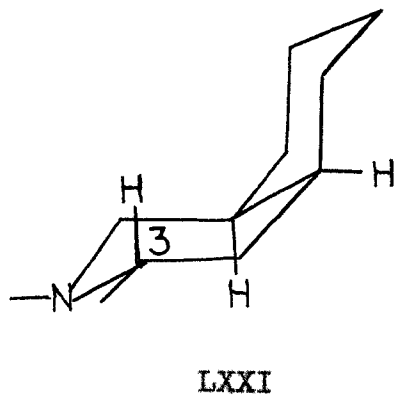


LXIX

d,l Epialloyohimbane (LIV) and epialloyohimbone (LIX) yielded no appreciable dehydro product, even under forcing conditions. The reason for this inertness is not immediately obvious, although it must be inextricably associated with the steric requirements of the transition complex of the mercuric acetate reaction. In similar dehydrogenation studies Weisenborn and Diassi (47) discovered that in 2 hour runs normal and allo compounds undergo the oxidation, while pseudo and epiallo systems do not, and ascribed this phenomenon to the necessary availability of an axial C_3-H bond in order to accomodate a coplanar transition state in the reaction mechanism originally proposed by Leonard (71). While this argument satisfies the behaviour of the conformationally unequivocal normal and pseudo compounds, it appears somewhat ambiguous for the allo and epiallo substances one of whose two all-chair, C/D trans conformation (LXX - allo, LXXI - epiallo) always possesses an axial C_3 - hydrogen atom (40).

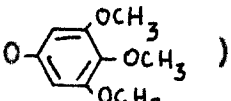
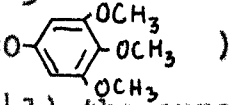


LXX



LXXI

Whereas, admittedly, in such unreactive compounds as reser-

pine (V, R = CH_3, R' = OCH_3, R'' = ), methyl reserpate, (V, R = CH_3, R' = OCH_3, R'' = H) and deserpidine (V, R = CH_3, R' = OCH_3, R'' = ) this conformation is the less favorable one (40, 41) the opposite is the case with the essentially inert d,l epialloyohimbane and epialloyohimbone. In conclusion, the mechanism of the mercuric acetate oxidation requires further study before its stereochemical implication can be fully understood.

All 3-dehydro products reverted back to their precursors on sodium borohydride reduction as well as on catalytic hydrogenation. During the syntheses of d,l yohimbane (56), d,l alloyohimbane (57) and reserpine (61) the same stereochemical consequences have been observed (cf. historical section) by other workers.

The formation of d,l alloyohimbane from its dehydro derivative during catalytic reduction was predictable on steric grounds, i.e., adsorption on the catalyst's surface, and hence hydrogen transfer to C_3, would have been expected to proceed preferentially on the side of the C_{15} and C_{20} hydrogen atoms.

The exclusive formation of yohimbane and yohimbine in the absence of their pseudo epimers, appears, at first glance, to be an anomaly, in view of the accepted concept of cis addition of hydrogen to $\rangle C = \overset{\oplus}{N}\langle$ and absence of any steric interference during this addition. This unambiguous case of catalytic hydrogenation under thermodynamic control

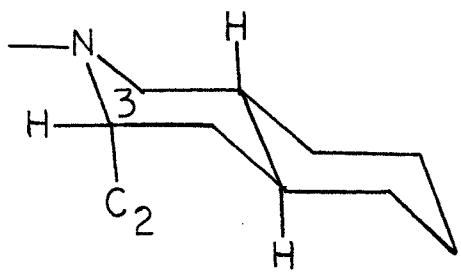
strongly suggests that the reduction of the immonium linkage takes place unsymmetrically via the transfer of a hydride, or its equivalent, to C_3, instead of the usual H_2 transposition onto both atoms attached to a double bond simultaneously. This has been stated in slightly different terms by van Tamelen (56).

The production of both normal and pseudo systems on hydrogenation, followed by a rapid catalyst-induced epimerization of the pseudo product, was excluded as an alternative explanation, since pseudoyohimbine (XLVIII) was recovered unchanged after being subjected to catalytic hydrogenating conditions.

Since ajmalicine (XV, R = H) can possess the stereochemistry of only a normal or allo compound, because of its relationship to serpentine (vide supra) its hydrogenative regeneration from its 3-dehydro product was expected. Tetraphylline (XXXVI) and aricine (XV, R = OCH_3) have been similarly classified as normal or allo products by Djerassi (48).

Wenkert and Liu (40) observed in 1955 that palladium dehydrogenation in aqueous maleic acid solution readily affected alloyohimbane (LIII, R = H) but not epialloyohimbane (LIV). Assuming that adsorption of the molecule on the catalyst surface is the first stage in dehydrogenation, this difference in reactivity can be easily explained on the basis of steric difficulties in the adsorption of epialloyohimbane, resulting in the lack of accessibility of C_3-H atom towards

the "active spots" on the catalyst. A close examination of the conformations LXX and LXXI of alloyohimbane and epiallo-yohimbane will bear evidence to this contention. Whereas epiallo substances offer this type of conformational deficiency towards the requirements of catalytic dehydrogenation, inspection of the conformation of pseudoyohimbane (LXXII) reveals the absence of such difficulties, since the D/E trans ring juncture produces a nearly planar molecule.



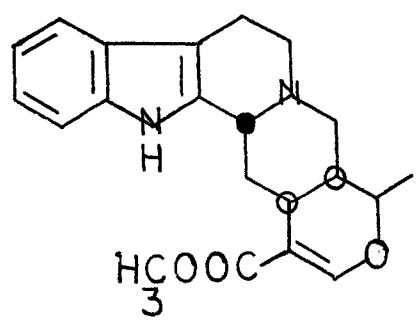
LXXII

Under the above circumstances it seemed extremely worthwhile to investigate the possibility of using the palladium-maleic acid method of catalytic dehydrogenation as a stereochemically diagnostic tool.

In order to translate this proposal into action, a large number of epiallo and pseudo compounds were to be made available. Whereas epiallo compounds were found to be more accessible and readily available through commercial sources, pseudo compounds proved more difficult to obtain.

Weisenborn and Diassi (47) have made pseudoyohimbine

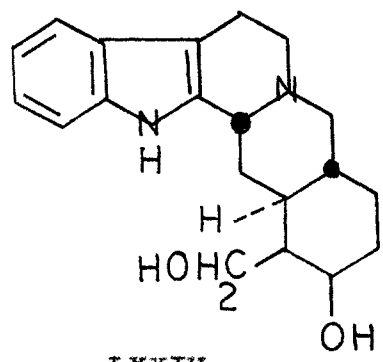
(XLVIII) by zinc and hydrochloric acid reduction of 3-dehydroyohimbine. In our hands, a 2 hour reduction of 3-dehydroyohimbine with zinc and glacial acetic acid under refluxing condition yielded a mixture of yohimbine (XLIX) and pseudo yohimbine (XLVIII) which was separated by chromatography over alumina. Using the same method, pseudoyohimbane (LXIV) and yohimbane (LI) were obtained from 3-dehydroyohimbane. The preparation of pseudoyohimbane not only makes available the fourth and last, till now unknown, isomer of yohimbane, but also constitutes a total synthesis of the same in view of its derivation from yohimbane and the formation of the latter from totally synthetic yohimbone (73). Pseudoyohimbone (L) and yohimbone (LII) were obtained from 3-dehydroyohimbone. This constitutes a total synthesis of pseudoyohimbone (L) due to its derivation from totally synthetic yohimbone (LII) (73). 3-isoajmalicine (LXXIII) was also prepared from 3-dehydro ajmalicine.



LXXIII

Pseudoyohimbyl alcohol (LXXIV) was made by the lithium

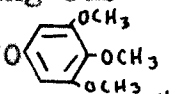
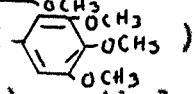
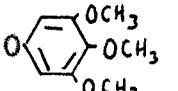
aluminum hydride reduction of pseudoyohimbine (XLVIII).



LXXIV

During the course of the identification studies of the above compounds, the occasion arose often to inspect the infrared spectra of chloroform solutions of various pairs of C_3 epimers. It became apparent that the 3.4 - 3.7μ region of the C-H stretching vibration can be used to identify unmistakably the stereo configuration of the hydrogen atom at C_3 of the alkaloids or their derivatives. Thus all compounds possessing an α-hydrogen at C_3, i.e. normal and allo products such as yohimbine (XLIX), d,l alloyohimbane (LIII, R = H) and ajmalicine (XV, R = H), exhibit two or more distinct and characteristic peaks of medium intensity on the high-wavelength side of the major 3.46μ band. However, those compounds containing a C_3-H β -orientation, i.e. pseudo or epiallo products such as pseudoyohimbine (XLVIII), d,l epialloyohimbane (LIV) and 3-isoajmalicine (LXXIII) show merely

shoulders on the high wavelength side of the main peak*. Pseudoyohimbane (LXIV) and pseudoyohimbone (L) were thus identified as the C_3 epimers of the normal compounds.

On the basis of the above spectrophotometric method, the following compounds are normal or allo systems: yohimbine (XLIX), yohimbone (LII), yohimbane (LI), β-yohimbine (stereoisomer of XLIX), coryanthine (stereoisomer of XLIX), alloyohimbine (LV), rauwolscine (stereoisomer of LV), 11-methoxyalloyohimbane and its racemate (LIII, R = OCH_3), methyl isoreserpate (V, R = CH_3, R' = OCH_3, R'' = H), corynantheine (XII), ajmalicine (XV, R = H), tetrahydroalstonine (XV, R = H, stereoisomeric with ajmalicine) while the succeeding substances: reserpine (V, R = CH_3, R' = OCH_3, R'' = CO ) rescinnamine (V, R = CH_3, R' = OCH_3, R'' = COCH = CH ) deserpidine (V, R = CH_3, R' = H, R'' = CO ), methyl reserpate (V, R = CH_3, R' = OCH_3, R'' = H), 3-epi-α-yohimbine (LVIII), pseudoyohimbine (XLVIII) and pseudoyohimbane (LXIV) belong to the pseudo or epiallo series. The configurational assignment of these ninteen compounds is in complete accord with their previously designated stereochemistry (74, 75, 76).

Infrared analysis suggested that the formerly proposed pseudo structure for serpine (8) and epiallo formula for methyl 18-desoxydeserpidate (LXXV) require reasignment into the normal or allo series. Hochstein's (77) finding that

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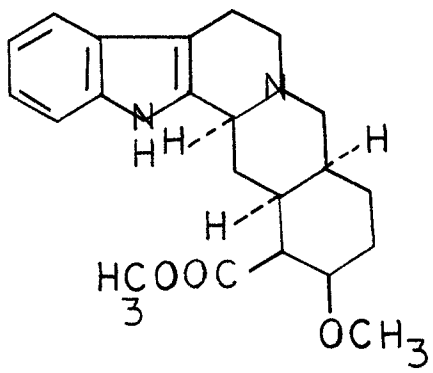
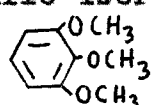
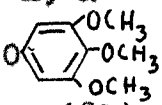
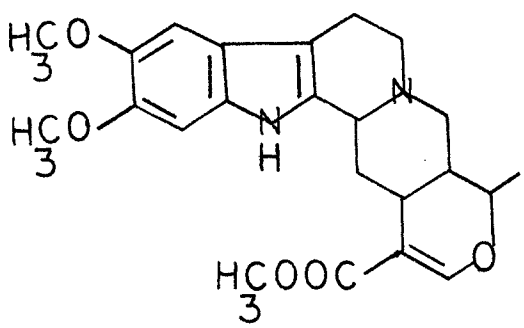
*See spectra section for these and other infrared spectra.



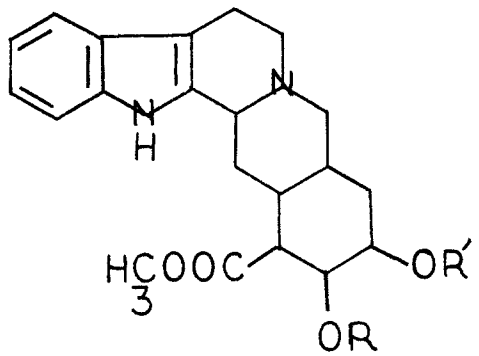
LXXV

serpine is a mixture of yohimbine and rauwolscine and Huebner's (78) success in proving by chemical means that the above deserpidine derivative possesses the allo configuration indicate the power of this method.

Finally, the new analytical method permits the classification of fifteen alkaloids of unknown configuration. Aricine (XV, R = OCH_3), tetraphylline (XXXVI), reserpinine (Stereoisomer of XXXVI), mayumbine (stereoisomer of ajmalicine XV, R = H), isoreserpiline (LXXVI), raumitorine (stereoisomer of aricine XV, R = OCH_3) and corynantheidine (XII) belong to the normal or allo series, while isorauhimbine (I) (7), raunescine (LXXVII, R = H, R' = CO ) (79), isoraunescine (LXXVII, R = CO  , R' = H) (79), raujemidine (80), pseudoreserpine (81) isoreserpinine (XXXVI), reserpiline (stereoisomer of isoreserpiline, LXXVI) and akuammigine (stereoisomer of ajmalicine XV, R = H) are part of the pseudo or epiallo series of alkaloids.



LXXVI



LXXVII

Djerassi and co-workers (48) and Diassi (82) have confirmed the above assigmment for aricine, tetraphylline, reserpinine, isoreserpinine by mercuric acetate oxidation, followed by reduction. The similarity of the infrared spectra of isorauhimbine and 3-epi-α-yohimbine indicate that they may possibly be different crystalline forms of the same substance (64).

Whereas acid-catalysed equilibration experiments have been used to determine the relative stability of various allo and epiallo systems (see historical section) and also to obtain the epimer from easily available allo sources (63, 75), no investigations have so far been made in the normal-pseudo series.

In the present work, hydrobromic acid-acetic acid treatment of pseudoyohimbine (XLVIII) under refluxing conditions for 2-hours followed by diazomethane treatment of the reaction mixture yielded only yohimbine (XLIX). This result was

not unexpected since conformational analysis indicated that yohimbine possesses the more favored conformation and thus should be more stable (74).

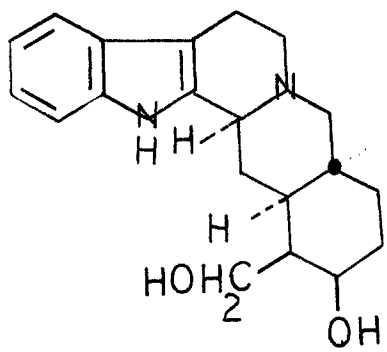
Epialloyohimbane (LIV) was prepared from alloyohimbane (LIII, R = H) using the above method.

With the availability of various epiallo and pseudo compounds, the study of comparative rates of dehydrogenation of various systems by palladium-maleic acid was undertaken. Since all the tetradehydro compounds have characteristic ultraviolet spectra quite distinct from their precursors, use of the spectral characteristics of the reaction mixtures was made as a criterion of progress of the reaction. A set of calibration curves were made by studying the ultraviolet spectra of solutions containing varying amounts of tetradehydroyohimbine and yohimbine along with fumaric acid, recognizing the latter to be the preponderant conversion product of maleic acid under the conditions of the dehydrogenation. A direct comparison with the ultraviolet spectrum of any reaction mixture was then used to assess the percentage of dehydrogenation.

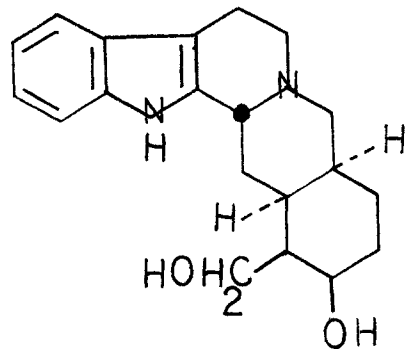
The following set of compounds were used for the study of comparative dehydrogenation rates:

(1) yohimbine (XLIX), pseudoyohimbine (XLVII), α-yohimbine (LV), 3-epi-α-yohimbine (LVIII)

(2) yohimbyl alcohol (LXXVIII), pseudoyohimbyl alcohol (LXXII), 3-epi-α-yohimbyl alcohol (LXXIX).



LXXVIII



LXXIX

(3) yohimbane (LI), pseudoyohimbane (LXII), alloyohimbane (LIII, R = H), epialloyohimbane (LIV).

Time used for refluxing was 4 hours for this set of experiments.

In another series of experiments, using 8 hours as the refluxing period, the following compounds were tested:

(1) yohimbine (XLIX), pseudoyohimbine (XLVIII), α-yohimbine (LV) and 3-epi-α-yohimbine (LVIII).

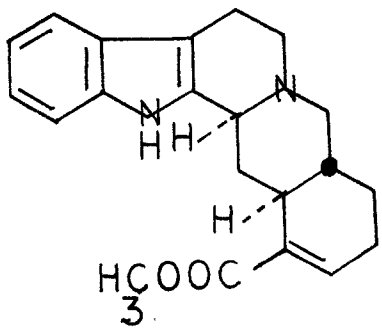
(2) pseudoyohimbyl alcohol (LXXII), 3-epi- -yohimbyl alcohol (LXXIX).

(3) apo-yohimbine (LXXX), apo-α-yohimbine (LXXXI), apo-3-epi-α-yohimbine (LXXXII) (79) and epialloyohimbane (LIV).

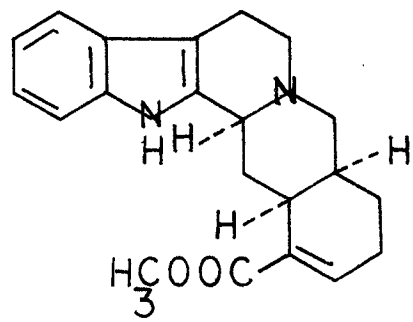
The apo-compounds provide suitable models for the ring E heterocyclic ajmalicine type compounds.

Examination of the results reveal that the dehydrogenation of epiallo compounds proceed at a rate appreciably lower

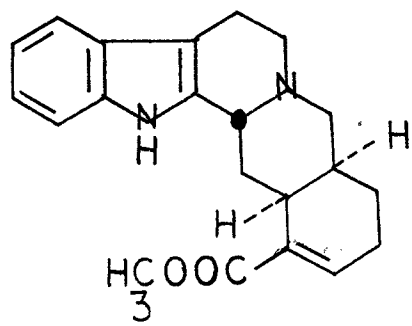
than that of their pseudo analogues and also the corresponding normal or allo compounds.



LXXX

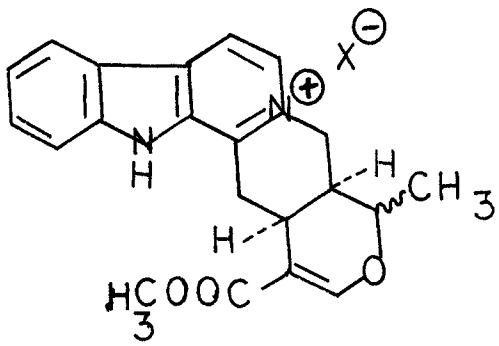


LXXXI

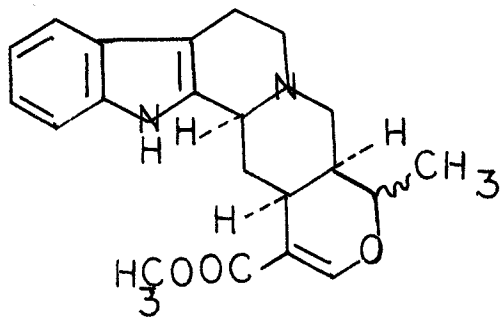


LXXXII

The infrared method classified 3-isoajmalicine and akuammigine as pseudo or epiallo systems. When these compounds were tested by the dehydrogenation method described above, they proved to be epiallo and pseudo structures, respectively. Consequently, serpentine possesses the stereoformula LXXXIII, while ajmalicine is its allo derivative LXXXIV. The same stereochemistry has been recently suggested

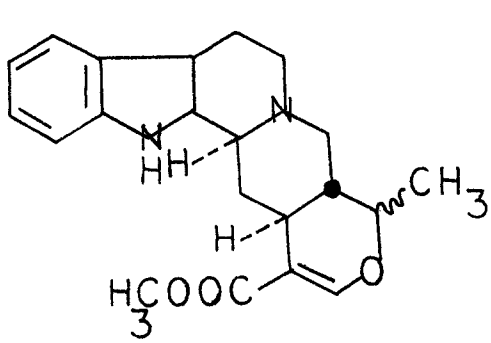


LXXXIII

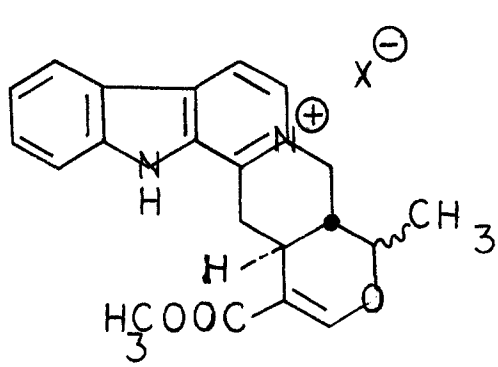


LXXXIV

by another group of workers (59) on the basis of the unreliable evidence of the inertness of the ring E enol ether toward 2:4 dinitrophenyl hydrazine. Since the oxidation product of akuammigine, isolated as perchlorate, was identical with alstonine perchlorate (21, 45, 83) akuammigine can now be considered as 3-isotetrahydroalstonine, tetrahydroalstonine as having a normal configuration (LXXXV) and alstonine consisting of structure (LXXXVI).



LXXXV



LXXXVI

SPECTRA

All infrared absorption spectra were recorded using a Baird Double Beam infrared spectrophotometer. Ultraviolet spectra were run in 95% ethanol using a Beckman model DU quartz spectrophotometer. Special thanks are due the Institute for Atomic Research, Iowa State College, for the use of the infrared spectrophotometer.

Figure 1. Ultraviolet spectra.

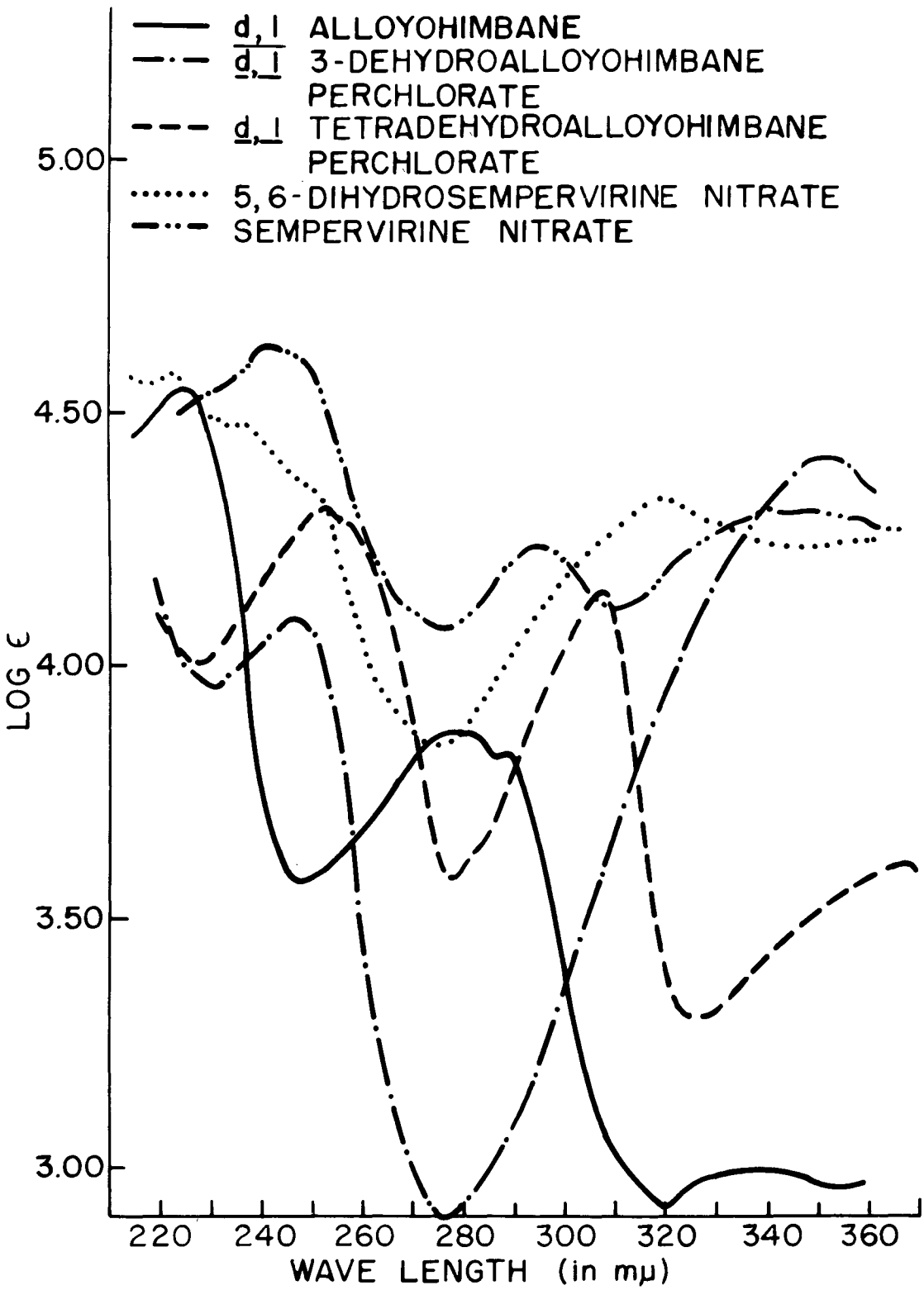

d,l ALLOYOHIMBANE
d,l 3-DEHYDROALLOYOHIMBANE PERCHLORATE
d,l TETRADEHYDROALLOYOHIMBANE PERCHLORATE
5,6-DIHYDROSEMPERVIRINE NITRATE
SEMPERVIRINE NITRATE
LOG ε
5.00
4.50
4.00
3.50
3.00
220
240
260
280
300
320
340
360
WAVE LENGTH (in mμ)

Figure 2. Ultraviolet spectra.

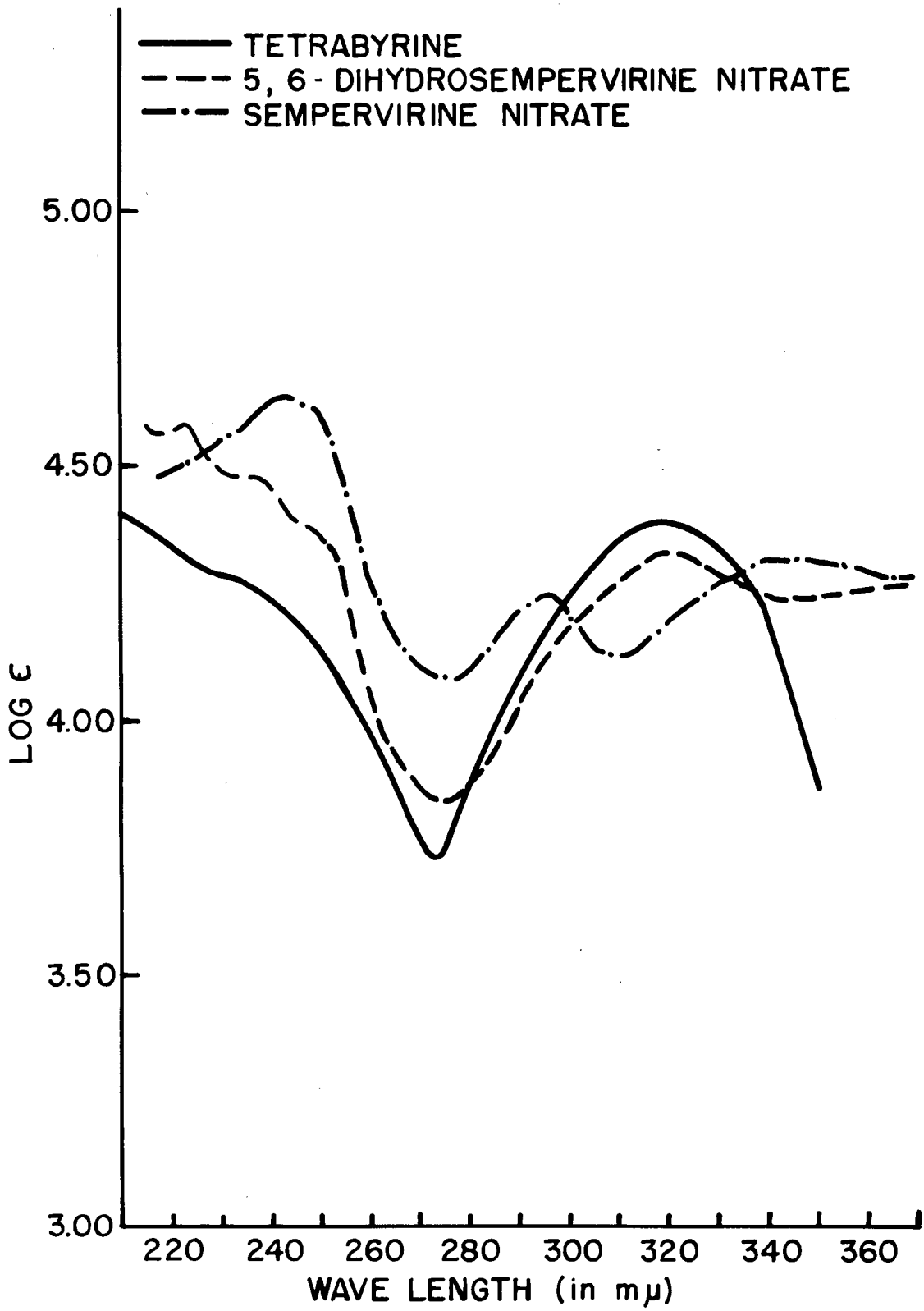

TETRABYRINE
5, 6 - DIHYDROSEMPERVIRINE NITRATE
SEMPERVIRINE NITRATE
5.00
4.50
4.00
3.50
3.00
LOG ε
220
240
260
280
300
320
340
360
WAVE LENGTH (in mμ)

Figure 3. Ultraviolet spectra.

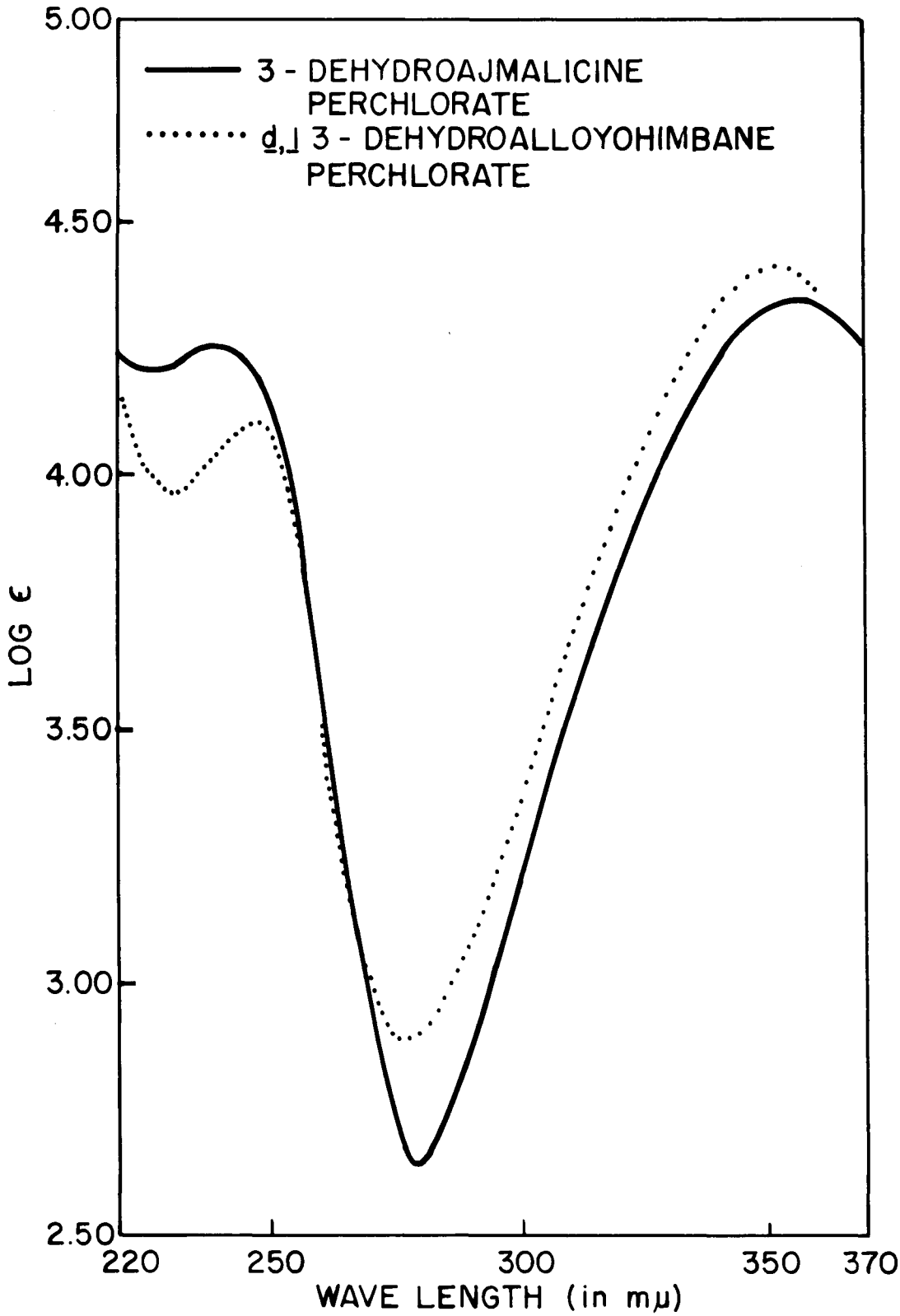
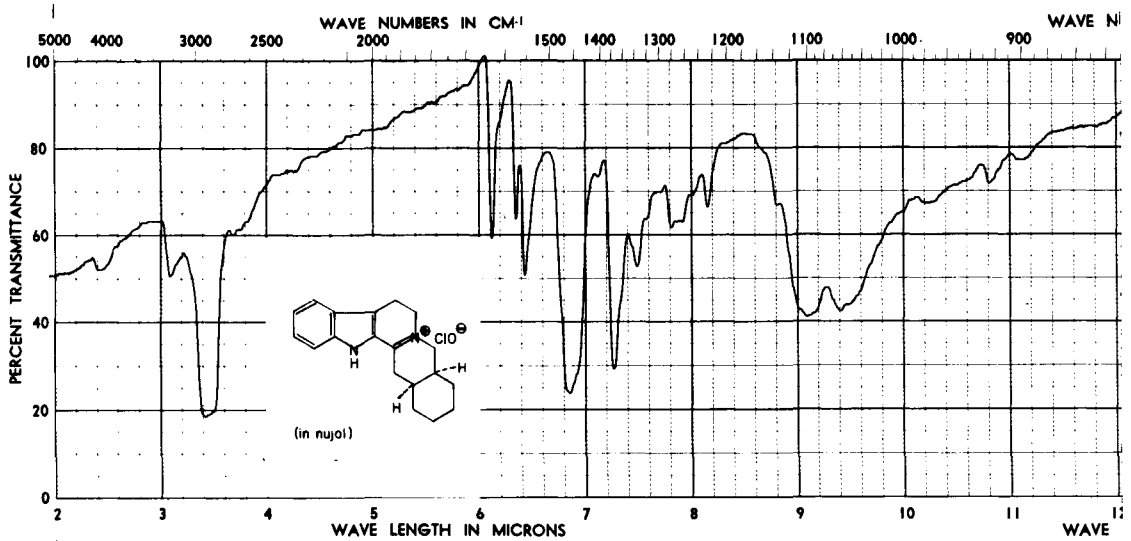
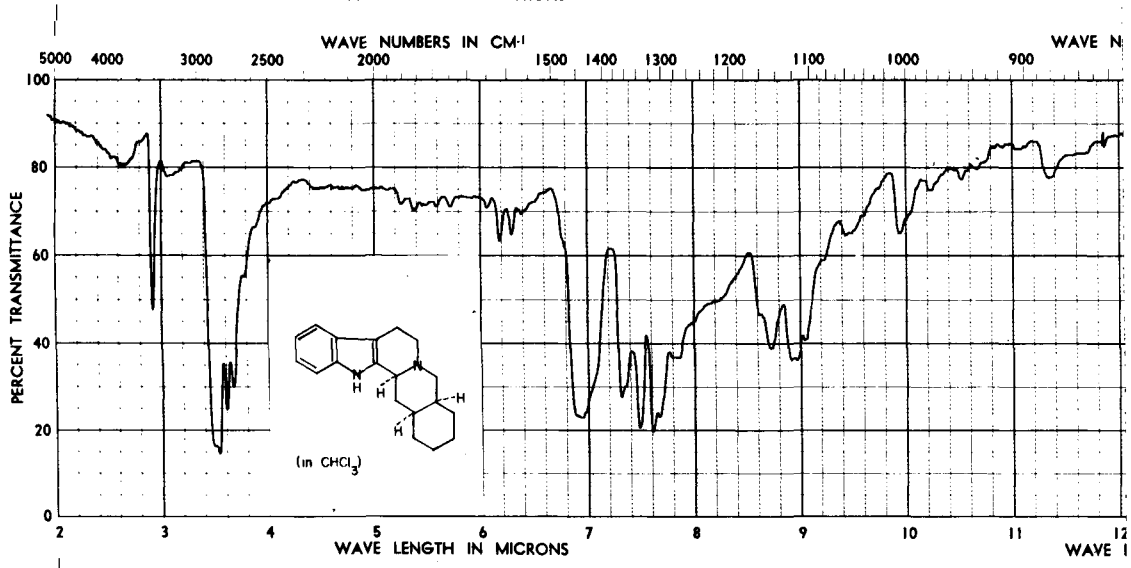

5.00
4.50
4.00
3.50
3.00
2.50
LOG ε
3 - DEHYDROAJMALICINE PERCHLORATE
d,l 3 - DEHYDROALLOYOHIMBANE PERCHLORATE
220
250
300
350
370
WAVE LENGTH (in mμ)

Figure 4. Infrared spectra.


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
PERCENT TRANSMITTANCE
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11
WAVE LENGTH IN MICRONS
(in nujol)


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
PERCENT TRANSMITTANCE
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11
WAVE LENGTH IN MICRONS
(in CHCl3)

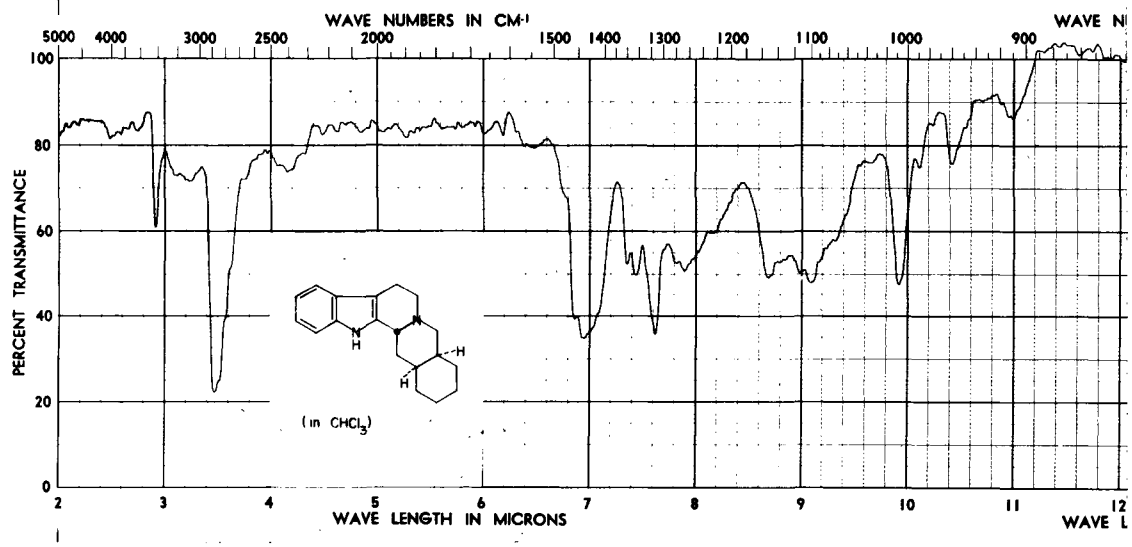

WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
PERCENT TRANSMITTANCE
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11
WAVE LENGTH IN MICRONS
(in CHCl3)

Figure 5. Infrared spectra.

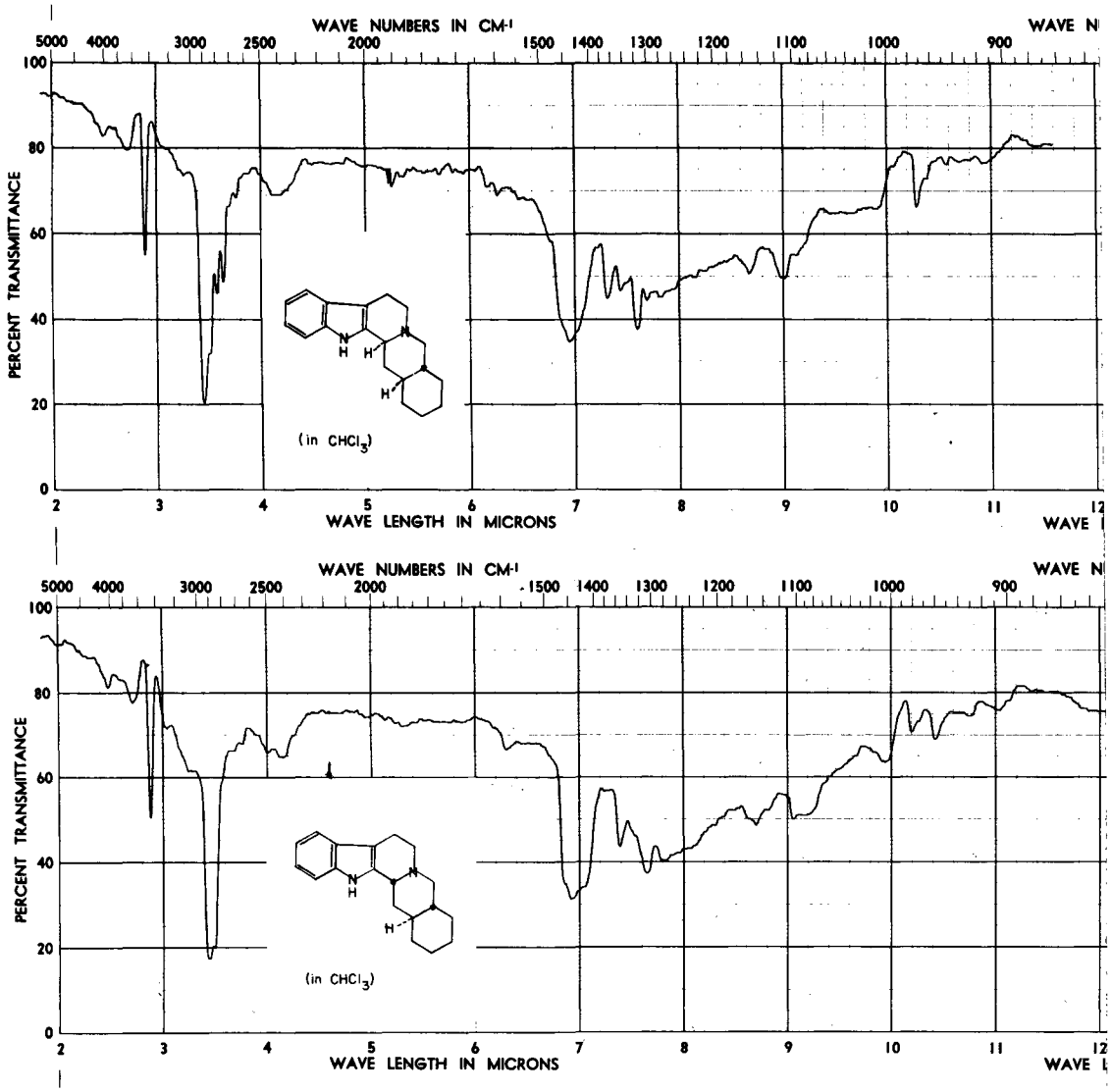

WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
PERCENT TRANSMITTANCE
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS
(in CHCl3)
WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
PERCENT TRANSMITTANCE
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS
(in CHCl3)

Figure 6. Infrared spectra.

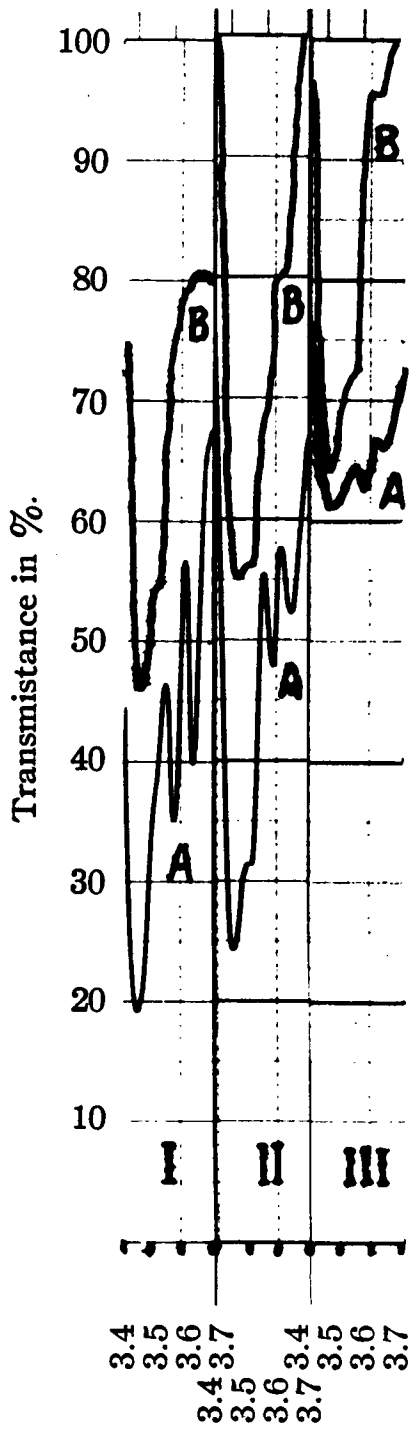
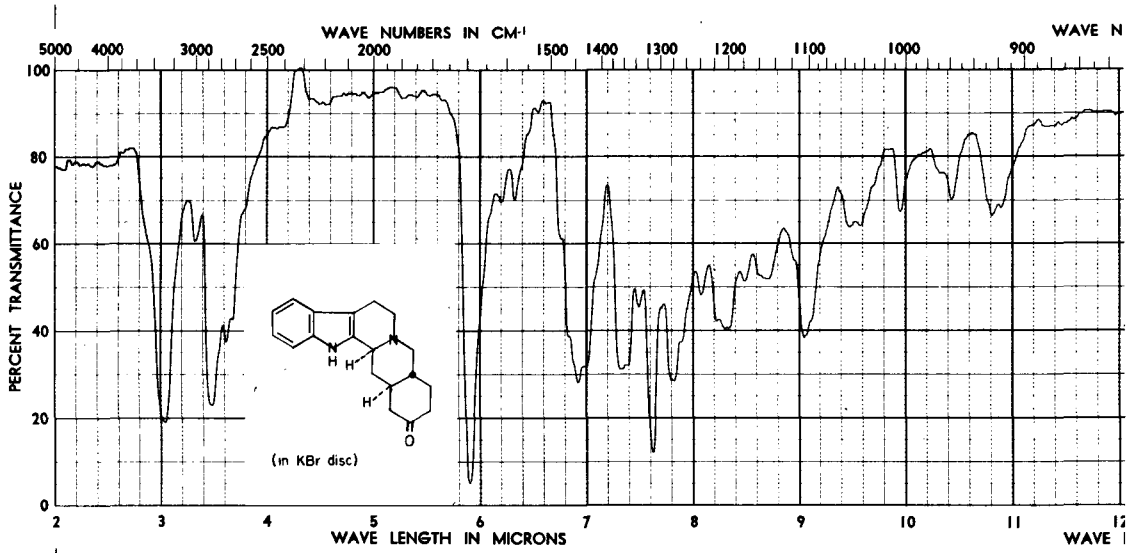
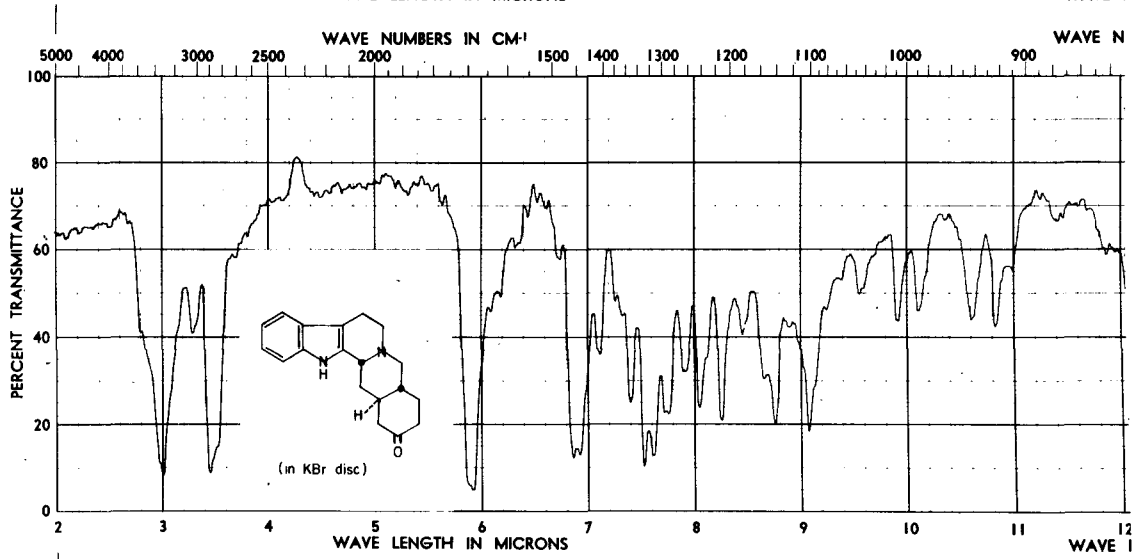
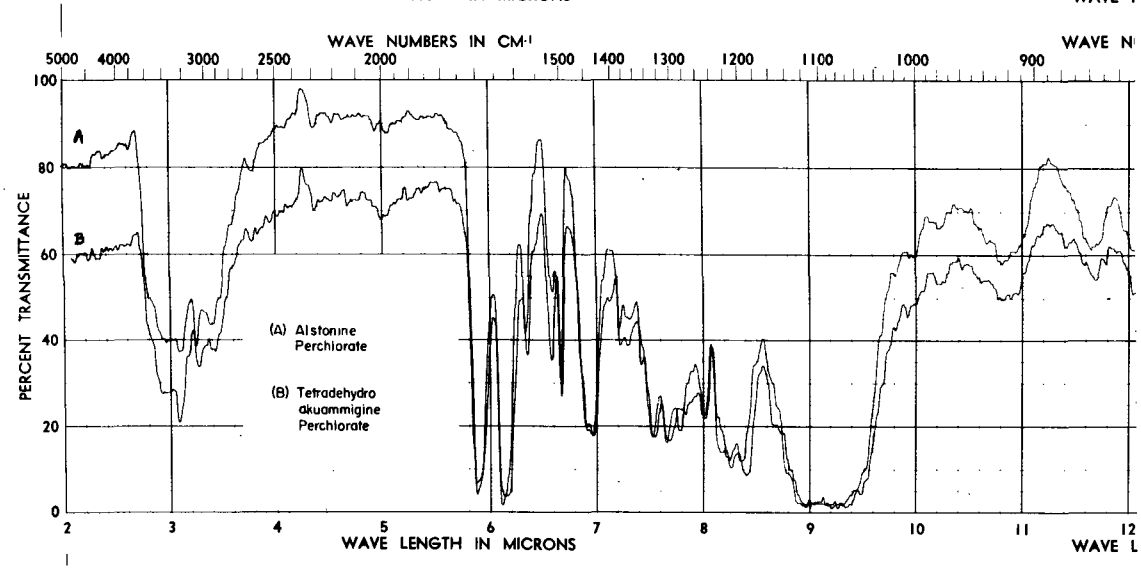

100
90
80
70
60
50
40
30
20
10
Transmistance in %.
B
B
B
A
A
A
I
II
III
3.4
3.5
3.6
3.7
3.4
3.5
3.6
3.7
3.4
3.5
3.6
3.7
Wave length in μ.

Figure 7. Infrared spectra.


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
PERCENT TRANSMITTANCE
100 80 60 40 20 0
(in KBr disc)
2 3 4 5 6 7 8 9 10 11
WAVE LENGTH IN MICRONS


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
PERCENT TRANSMITTANCE
100 80 60 40 20 0
(in KBr disc)
2 3 4 5 6 7 8 9 10 11
WAVE LENGTH IN MICRONS


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
PERCENT TRANSMITTANCE
100 80 60 40 20 0
A
B
(A) Alstonine Perchlorate
(B) Tetradehydro akuammigine Perchlorate
2 3 4 5 6 7 8 9 10 11
WAVE LENGTH IN MICRONS

EXPERIMENTAL

All melting points are uncorrected. Ultraviolet spectra were measured in 95% ethanol solution with a Beckman model DU quartz spectrophotometer. Microanalyses were carried out by Dr. L. Dorfman of Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

Adsorbent for Chromatography

Activated alumina, 80-200 mesh was allowed to stand with ethyl acetate for 24 hours, then washed with water and methanol, and dried at 100° for 24 hours.

Catalytic Reduction of Sempervirine (X, R = H) at pH 10

To 2.0 g. (6 mmoles) of sempervirine nitrate, dissolved in 30 ml. of methanol, 200 mg. of platinum oxide was added. 2.8 ml. of 2 N methanolic potassium hydroxide solution was then quickly added before hydrogenating the mixture overnight at 57 pounds per square inch pressure. The suspension was filtered and the crystallized residue was dissolved in hot methanol. The methanolic solution was evaporated to a small volume and allowed to crystallize. 400 mg. of yellowish white needles of d,l alloyohimbane (LIII, R = H) m.p. 148-150° were obtained. On concentration of the mother liquor 420 mg. of crystals of crude alloyohimbane m.p. 137-138° were also obtained. A 50% crude yield was attained. d,l Alloyohimbane

had a m.p. 148-150°.

Ultraviolet spectrum. (Figure 1). λmax. 225 mμ (log ε 4.55), 282 mμ (log ε 3.89) and 290 mμ (log ε 3.83); λmin. 250 mμ (log ε 3.59).

Infrared spectrum. (Figure 4).

d,l $\Delta^{15,(20)}$ Yohimbene (LX)

1.76 g. (5.3 mmoles) of sempervirine nitrate was dissolved in 20 ml. of methanol, and 1.5 g. (39 mmoles) of sodium borohydride was carefully added in several portions. The mixture was refluxed for 2 hours. The methanol was removed in vacuo, the residue was triturated with water, and the aqueous suspension was extracted with chloroform. The chloroform extract, after drying over anhydrous sodium sulfate and evaporation, left a yellowish brown residue.

The residue was taken up in petroleum ether-ether (1:1) and chromatographed on alumina. Using petroleum ether-ether (1:1) as eluent, 700 mg. (43%) of d,l $\Delta^{15(20)}$ yohimbene m.p. 190° was obtained. On recrystallization in methanol 500 mg. of material, m.p. 196-197°, was isolated. An analytical sample (m.p. 196-197°) was obtained after recrystallization in methanol two more times.

Anal. Calcd. for $C_{19}H_{22}N_2$:

C, 81.97; H, 7.97; N, 10.06;

Found: C, 81.57; H, 7.72; N, 9.93.

Ultraviolet spectrum. λmax. 225 mμ (log ε 4.55),

282 mμ (log ε 3.89) and 290 mμ (log ε 3.80); λmin. 250 mμ (log ε 3.38).

Dehydrogenation of d,l $\Delta^{15(20)}$ Yohimbene (LX)

By palladium maleic acid

200 mg. (0.7 mmoles) of d,l $\Delta^{15(20)}$ yohimbene was dissolved in 25 ml. of water with 400 mg. of maleic acid. 100 mg. of palladium black was added. The solution was stirred and refluxed overnight (10 hours). The mixture turned yellow after a few minutes.

The solution was filtered while hot, and the orange yellow filtrate was made basic with ammonia. The precipitated base was filtered and dissolved in 20 ml. of 5% aqueous acetic acid. Aqueous saturated ammonium nitrate solution was added, and the orange yellow nitrate of 5,6-dihydrosempervirine (LXI) was filtered. 100 mg. (41%) of crude nitrate was isolated. The crude material was recrystallized from methanol, giving material m.p. 278-280°. An analytical sample was recrystallized three more times in methanol and dried in vacuo at 60°, m.p. 305-306°.

Anal. Calcd. for $C_{19}H_{19}N_3O_3$:

C, 67.64; H, 5.68; N, 12.46;

Found: C, 68.06; H, 5.60; N, 12.27.

Ultraviolet spectrum (Figures 1 and 2). λmax. 223 mμ (log ε 4.58) and 320 mμ (log ε 4.33); λmin. 276 mμ (log ε 3.85).

By mercuric acetate

65 mg. (0.23 mmoles) of d,l $\Delta^{15(20)}$ yohimbene and 500 mg. (1.57 mmoles) of mercuric acetate was heated in 15 ml. of 5% aqueous acetic acid at 60° for four hours under nitrogen. At the end of dehydrogenation, 70 mg. (58% of the theoretical amount) of mercurous acetate was recovered on filtration. The filtrate was heated to boiling, and excess mercuric salts were removed as sulfides by the introduction of hydrogen sulfide. After separation of the sulfides, the perchlorate salt of the dehydro compound was precipitated by the addition of aqueous saturated potassium perchlorate. Recrystallization in methanol gave 17 mg. (19.5%) of orange-red crystals of 5,6-dihydrosempervirine (LXI) perchlorate, m.p. 308-309°.

The perchlorate salt was dissolved in methanol and 5% aqueous acetic acid, and the nitrate salt was precipitated by the addition of aqueous saturated ammonium nitrate solution. The precipitated nitrate was recrystallized in methanol to yield red needles of 5,6-dihydrosempervirine (LXI) nitrate, m.p. 305-306°, which was shown by mixed melting point and ultraviolet spectrum to be identical with 5,6-dihydrosempervirine nitrate obtained in the palladium-maleic acid dehydrogenation.

Reduction of 5,6-Dihydrosempervirine (LXI)

Catalytic hydrogenation

410 mg. (1.2 mmoles) of 5,6-dihydrosempervirine (LXI)

nitrate was dissolved in 30 ml. methanol. The pH was adjusted to 10 by the addition of 1 ml. of 2N methanolic potassium hydroxide. 125 mg. of platinum oxide was then added, and hydrogenation was carried out under 57 pounds per square inch of hydrogen for 6 hours.

The suspension was filtered, and the solvent of the filtrate was evaporated under vacuum. The residue on crystallization in methanol gave 135 mg. (40%) of crude alloyohimbane m.p. 141-143.5°. On further recrystallization in methanol, this yielded 80 mg. of material, m.p. 144-145° identical in all respects with d,l alloyohimbane (LIII, R = H) as indicated by mixed melting point and infrared spectrum.

Reduction by sodium borohydride

210 mg. (0.6 mmoles) of 5,6-dihydrosempervirine nitrate was dissolved in methanol and 300 mg. of sodium borohydride (8 mmoles) was added. The mixture was refluxed for two hours. Methanol was removed in vacuo, the residue was triturated with water and extracted with chloroform. After washing with water and aqueous saturated sodium chloride solution and drying over anhydrous sodium sulfate, the chloroform extract was evaporated in vacuo. The residue on crystallization in methanol gave 65 mg. of d,l $\Delta^{15(20)}$yohimbene (LX), m.p. 194-195°, as identified by mixed melting point and infrared spectrum.

Yohimbone (LII)

Yohimbone (LII) was produced by Oppenauer oxidation of yohimbine as reported by Witkop (31).

Yohimbane (LI)

Yohimbane (LI) was prepared by the Huang Minlon variant of the Wolff-Kishner reduction of yohimbone (LII) as reported by Janot and co-workers (32).

Dehydrogenation of Indole Alkaloids by the Palladium-Maleic Acid Method

In a typical run, 1 mmole of the amine was dissolved in water with 5 mmoles of maleic acid. Palladium black equal in weight to 0.5 mmole of the amine was added. The mixture was refluxed for 8 hours and then filtered while hot. On cooling and adding aqueous perchloric acid (70%), the perchlorate of the tetradehydro compound was obtained. In certain cases, the base was precipitated initially by adding concentrated ammonia, and the nitrate or perchlorate salt of the base was obtained by dissolving the free base in 5% aqueous acetic acid and adding saturated aqueous ammonium nitrate or potassium perchlorate solutions. The precipitated salt of the tetradehydro compound was filtered and crystallized in methanol.

d,l Alloyohimbane (LIII) gave a 49% yield of d,l tetra-

dehydroalloyohimbane perchlorate, yellow needles melting at 207-208°.

Anal. Calcd. for $C_{19}H_{21}N_2ClO_4$:
C, 60.54; H, 5.58; N, 7.44;
Found: C, 60.54; H, 5.83; N. 7.34.

Ultraviolet spectrum. (Figure 1). λmax. 253 mμ (log ε 4.31), 307 mμ (log ε 4.15) and 367 mμ (log ε 3.61); λmin. 228 mμ (log ε 4.01), 278 mμ (log ε 3.58) and 325 mμ (log ε 3.30).

Yohimbane (LI) yielded tetradehydroyohimbane nitrate (51%), yellow needles melting at 259-260°. $[\alpha]_D^{27}$ = + 120° (methanol).

Anal. Calcd. for $C_{19}H_{21}N_3O_3$:
C, 67.24; H, 6.24; N, 12.38;
Found: C, 67.51; H, 6.37; N, 12.14.

Yohimbone (LII) led to a 63% yield of tetradehydro yohimbone nitrate, rosy granules melting at 275-277°. $[\alpha]_D^{27}$ = + 92.6° (methanol).

Anal. Calcd. for $C_{19}H_{19}N_3O_4 \cdot CH_3OH$:
C, 62.32; H, 6.01; N, 10.90;
Found: 62.41; H, 5.91; N, 10.96 .

Yohimbine (XLIX) and pseudoyohimbine (XLVIII) gave tetradehydroyohimbine perchlorate in 74 and 64% yields respectively. The product consisted of colorless needles melting at 200-201°. $[\alpha]_D^{27}$ = + 181° (methanol).

Anal. Calcd. for $C_{21}H_{23}O_7N_2Cl.\ CH_3OH$:

C, 54.71; H, 5.64; N, 5.80;

Found: C, 54.64; H, 5.30; N, 5.96.

α-Yohimbine yielded tetradehydro α-yohimbine perchlorate (44%) cream colored needles melting at 250-251°. $[\alpha]_D^{27}$ = +99.4° (methanol).

Anal. Calcd. for $C_{21}H_{23}O_7N_2Cl.\ CH_3OH$:

C, 54.71; H, 5.64;

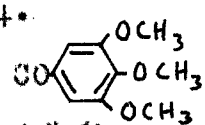
Found: C, 54.4 ; H, 5.45.

Yohimbyl alcohol (LXXVIII) yielded tetradehydroyohimbyl alcohol perchlorate (40%), cream colored needles melting at 250-251°. $[\alpha]_D^{27}$ = +145.4° (methanol).

Anal. Calcd. for $C_{20}H_{23}NO_6Cl.\ CH_3OH$:

C, 55.43; H, 5.98; N, 6.16;

Found: C, 55.32; H, 5.92; N, 6.54.

Deserpidine (V, R = CH_3, R' = H, R'' = ) yielded tetradehydrodeserpidine perchlorate (54%), yellowish green needles melting at 190-192°. $[\alpha]_D^{27}$ = −189° (methanol).

Anal. Calcd. for $C_{32}H_{34}N_2O_8.HClO_4$:

C, 56.92; H, 5.23; N, 4.15;

Found: C, 56.66; H, 5.67; N, 4.27.

Ajmalicine (LXXXIV) yielded serpentine nitrate (43%), m.p. 161-163°, as identified by melting point, mixed melting point, ultraviolet spectrum and infrared spectrum.

Akuammigine yielded alstonine perchlorate (42%), m.p. 247-248°, $[\alpha]_D^{25}$ = +152° (methanol), as identified by com-

parison of its melting point, rotation and infrared spectrum (Figure 7), with those of authentic material. The latter was obtained by dissolving alstonine hydrochloride in 5% aqueous acetic acid and precipitating the perchlorate by the addition aqueous perchloric acid (70%). Alstonine hydrochloride was obtained from P. A. Diassi of The Squibb Institute for Medical Research, New Brunswick, New Jersey.

Catalytic Hydrogenation of Tetradehydro Compounds

3 mmoles of tetradehydro compound, as its nitrate or perchlorate salt, were dissolved in 60 ml. methanol and 2 ml. of 2N methanolic potassium hydroxide was added. 250 mg. of platinum oxide was added, and the mixture was hydrogenated under 57 pounds per square inch of hydrogen overnight. The solution was filtered, and the yellow filtrate was neutralized with 2N methanolic hydrochloric acid. The solvent was evaporated, and the residue was dissolved in water and the base precipitated with ammonia. The precipitate was filtered, washed free of ammonia with water and crystallized in methanol.

The crystalline bases were characterized by melting point, mixed melting point and infrared spectra.

Tetradehydroyohimbane nitrate gave yohimbane (LI), m.p. 204-205° in 48% yield.

d,l Tetradehydroalloyohimbane perchlorate gave d,l alloyohimbane (LIII), m.p. 147-148° in 54% yield. The mother

liquor on evaporation and chromatography over alumina using 1:1 petroleum ether-ether as solvent and eluent yielded d,l epialloyohimbane (0.4%) m.p. 194-195°; mixed melting point with an authentic sample of d,l epialloyohimbane (m.p. 187-188°) 184-185°.

Serpentine nitrate (LXXXIII) produced ajmalicine (LXXXIV), m.p. 249-250°, in 63% yield.

Tetradehydroyohimbone nitrate gave epiyohimbol (LXV), m.p. 257-258°, in 75% yield. Mixed melting point with epiyohimbol, m.p. 262-263°, prepared by the lithium aluminum hydride reduction of yohimbone (LII) (vide infra), was undepressed. The infrared spectra of both compounds were identical.

Reduction of Yohimbone (LII) by Lithium Aluminum Hydride

To a slurry of 200 mg. of lithium aluminum hydride in 25 ml. of purified anhydrous tetrahydrofuran , a solution of 500 mg. of yohimbone in 50 ml. tetrahydrofuran was added dropwise. The mixture was refluxed overnight. The reaction mixture was then cooled and decomposed by dropwise addition of aqueous saturated sodium sulfate solution. The solid mass was washed with ether, and the combined ether-tetrahydrofuran solution was dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was crystallized in methanol. 75 mg. (15%) of epiyohimbol (LXV), m.p. 262-263°, was obtained as fine needles. An additional 125 mg. (25%) of epiyohimbol, m.p. 254-255°, was obtained from the mother

liquor as identified by mixed melting point and infrared spectrum.

Reduction of Tetradehydro Compounds by Sodium Borohydride

0.8 mmole of the tetradehydro compound, as the perchlorate or nitrate salt, was dissolved in 30 ml. methanol, and 500 mg. (13 mmoles) of sodium borohydride was added. The mixture was refluxed for 2 hours. The solvent was evaporated in vacuo, and the residue was triturated with 10 ml. water. The suspension was extracted with chloroform. The solution was washed and dried over anhydrous sodium sulfate. On evaporation and recrystallization of the residue in methanol, the following bases, identified by their melting points, mixed melting points and infrared spectra were obtained:

yohimbane (LI), m.p. 204-205°, in 38% yield,
d,l alloyohimbane (LII), m.p. 145-146°, in 58% yield,
ajmalicine (LXXXI), m.p. 253-254°, in 50% yield,
yohimbine (XLIX), m.p. 230-231°, in 20% yield.
Epiyohimbol (LXV), m.p. 256-257° was obtained in 47% yield from tetradehydroyohimbone nitrate.

Dehydrogenation of Indole Alkaloids by Mercuric Acetate

A mixture of amine and mercuric acetate (1:4 mole) in 5% aqueous acetic acid was heated at 60-90° for two hours. The precipitated mercurous acetate (average 75% yield) was filtered and the filtrate heated to boiling and saturated

with hydrogen sulfide gas. A small amount of concentrated hydrochloric acid was added to the cooled solution and the latter heated until the black mercuric sulfide had coagulated and separated. The mixture was filtered, and the filtrate was treated with a saturated solution of potassium perchlorate. The resulting percipitate was filtered and recrystallized in methanol.

d,l alloyohimbane (LIII) yielded d,l 3-dehydroalloyohimbane perchlorate (23%), yellow rods melting at 227-228°.

Anal. Calcd. for $C_{19}H_{23}O_4N_2Cl$:

C, 60.23; H, 6.12; N, 7.39;

Found: C, 60.42; H, 6.25; N, 7.08.

Ultraviolet spectrum (Figures 1 and 3). λmax. 248 mμ (log ϵ 4.10) and 353 mμ (log ϵ 4.41); λmin. 232 mμ (log ϵ 3.96) and 278 mμ (log ϵ 2.88).

The infrared spectra (in nujol) showed the following characteristic peaks: 3230 (w), 1625 (m), 1570 (m) and 1540 (m) cm^{-1} (Figure 4).

Yohimbane (LI) yielded 74% of 3-dehydroyohimbane perchlorate, yellow needles, m.p. 273-274°, $[\alpha]_D^{28} = +98.3°$ (methanol).

Anal. Calcd. for $C_{19}H_{23}O_4N_2Cl$:

C, 60.23; H, 6.12; N, 7.39;

Found: C, 60.30; H, 6.37; N, 7.36.

Yohimbine (XLIX) yielded 3-dehydroyohimbine perchlorate (75%), yellow needles, m.p. 205-206°, $[\alpha]_D^{28} = +132°$ (metha-

nol) as identified by mixed melting point and infrared spectra with an authentic sample prepared by Weisenborn and Diassi (47).

Yohimbone (LII) yielded 3-dehydroyohimbone perchlorate (54%), yellow granules, m.p. 181-182°, $[\alpha]_D^{28} = +114°$ (methanol).

Anal. Calcd. for $C_{19}H_{21}O_5N_2Cl \cdot 2CH_3OH$:
C, 55.17; H, 6.39; N, 6.13;
Found: C, 54.84; H, 6.55; N, 5.82.

Ajmalicine (LXXXIV) yielded 3-dehydroajmalicine perchlorate (61%), yellow needles, m.p. 264-265°, $[\alpha]_D^{28} = +75.6°$ (methanol).

Anal. Calcd. for $C_{21}H_{23}O_7N_2Cl$:
C, 55.93; H, 5.14; N, 6.22;
Found: C, 55.90; H, 5.48; N, 6.33.

Ultraviolet spectrum (Figure 3). λmax. 240 mμ (log ϵ 4.25) and 356 mμ (log ϵ 4.34); λmin. 228 mμ (log ϵ 4.20) and 280 mμ (log ϵ 2.6).

Mercuric acetate oxidation of d,l epialloyohimbane yielded no mercurous acetate, even after 22 hours. The isolated perchlorate showed an ultraviolet spectrum corresponding to approximately a 10% conversion to dehydro product. Liberation of the free amine by ammonia yielded merely starting material, as indicated by melting point, mixed melting point, and ultraviolet spectrum.

Mercuric acetate oxidation of epialloyohimbone (LIX)

yielded no mercurous acetate, even after 8 hours. The ultraviolet spectrum of the crude mercury-free perchlorate showed no appreciable dehydrogenation.

Reduction of the 3-Dehydro Products

Sodium borohydride reduction

A mixture of the 3-dehydro perchlorate and a 25 molar excess of sodium borohydride in methanol was refluxed for three hours. The solvent was removed under vacuum, the residue treated with water and extracted with chloroform. The organic solution was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. On evaporation of the solvent a glass remained, which on recrystallization from methanol yielded yohimbane (LI), m.p. 204-205°, d,l alloyohimbane (LIII, R = H), m.p. 145-146°, and ajmalicine (LXXIX), m.p. 253-254°, from their corresponding dehydro products, as identified by melting points, mixed melting points and infrared spectra. The yields ranged from 40-90%.

Catalytic hydrogenation

A mixture of the 3-dehydro perchlorate and 10% (by weight) of platinum oxide catalyst in methanol were hydrogenated at 57 lb. pressure until hydrogen uptake had ceased. After filtration of the catalyst the solution was concentrated to a small volume, diluted with water and the free

base precipitated by adding ammonia. The precipitate was filtered, washed with water and crystallized from methanol, yielding yohimbane (LI), m.p. 204-205°, d,l alloyohimbane (LIII, R = H), m.p. 145-146°, yohimbine (XLIX), m.p. 232-234°, and ajmalicine (LXXXIV), m.p. 253-254°, from their corresponding 3-dehydro products, as identified by melting point, mixed melting point and infrared spectra.

The yields ranged from 52-91%.

Reduction in zinc and glacial acetic acid

To a solution of the 3-dehydro compound, as perchlorate salt, in glacial acetic acid, (a small amount of methanol was added in some cases to effect solution) a large excess of zinc dust (five times by weight in excess of weight of the 3-dehydro compound) was added. The suspension was refluxed for 2 hours. The mixture was filtered and most of the acetic acid was removed in vacuo. The residue was dissolved in aqueous methanol and basified with concentrated ammonia. The precipitated base was exhaustively extracted by chloroform. Chloroform extract washed, dried, and evaporated. The residue on chromatography yielded the bases from their corresponding 3-dehydro products.

Using chloroform as eluent on alumina, pseudoyohimbine (XLVIII), m.p. 277-278°, and yohimbine (XLIX), m.p. 234-235° were obtained in 11% and 7% yields respectively, as identified by melting points, mixed melting points and infrared

spectra.

Using benzene-ether (1:1) as the eluent pair on alumina, yohimbane (LI), m.p. 204-205°, was obtained in 6% yield as identified by melting point, mixed melting point and infrared spectrum (Figure 5) and pseudoyohimbane (LXIV), m.p. 95-96°, was obtained in 11% yield, $[\alpha]_D^{27} = +62°$ (Ethanol).

Anal. Calcd. for $C_{19}H_{24}N_2$:

C, 81.37; H, 8.63; N, 9.99.

Found: C, 81.32; H, 8.57; N, 9.59.

Infrared spectrum (Figure 5) shows differences in C-H stretching and fingerprint region with yohimbane.

By the use of benzene and benzene-ether (80:20) as eluents on alumina, 3-isoajmalicine (LXXIII) m.p. 193-194°, $[\alpha]_D^{27} = -122°$ (pyridine),

Anal. Calcd. for $C_{21}H_{24}O_3N_2$:

C, 71.55; H, 6.86; N, 7.95;

Found: C, 71.39; H, 6.96; N, 7.79.

and ajmalicine, m.p. 256-257°, as identified by melting point, mixed melting point, and infrared spectrum, were obtained in 18% and 13% yields, respectively.

Using benzene-ether (70:30) and ether-benzene (70:30) as eluents on alumina, yohimbone (LII), m.p. 305-306° and pseudoyohimbone (L) m.p. 270-273°, $[\alpha]_D^{25} = -24°$ (pyridine) were obtained in 13% and 7% yields, respectively, as identified by melting point, infrared spectra (Figure 7), and optical rotation.

Infrared spectra of yohimbine (XLIX) and pseudoyohimbine (XLVIII), ajmalicine (LXXXI) and 3-isoajmalicine (LXXIII) in chloroform showed differences in the C-H stretching region (3.4-3.7μ) (Figure 6).

Attempted Isomerization of Pseudoyohimbine (XLVIII) on Platinum in the Presence of Hydrogen

50 mg. of pseudoyohimbine were dissolved in 25 ml. methanol and 15 mg. of platinum oxide was added. The mixture was shaken at 57 pounds per square inch for three hours under hydrogen. The solution was filtered from platinum. The solvent was removed and the residue was crystallized in alcohol. 30 mg. of pseudoyohimbine m.p. 272-273° was recovered, and identified by melting point, mixed melting point and infrared spectrum.

Acid-catalyzed Equilibration of d,l Alloyohimbane (LIII)

500 mg. (1.8 mmoles) of d,l alloyohimbane were refluxed with 10 ml. of 48% hydrobromic acid and 10 ml. of glacial acetic acid. Most of the acid was then removed in vacuo. 50 ml. of water was added. The white precipitate was dissolved in methanol, diluted with water, and made alkaline with concentrated ammonia. The aqueous filtrate was also made alkaline with ammonia. Both the suspensions were exhaustively extracted with ether. Ether extract washed with water and aqueous saturated sodium chloride solution and

dried over anhydrous sodium sulfate. On evaporation and chromatography of the residue on 40 g. of alumina using absolute ether:petroleum ether (1:1) as eluent and final recrystallization of the residue in methanol, 110 mg. (22%) of d,l alloyohimbane, m.p. 150-151°, and 125 mg. (25%) of d,l epialloyohimbane, m.p. 187-188°, were obtained. The products were identified by melting point, mixed melting point and infrared spectra (Figure 4).

Acid-catalyzed Equilibration of Pseudoyohimbine (XLVIII)

200 mg. (0.57 mmoles) of pseudoyohimbine were refluxed with 5 ml. of 48% hydrobromic acid and 5 ml. of glacial acetic acid for 3 hours. Most of the acid was later removed in vacuo. The residue was dissolved in methanol and treated with an excess of ethereal diazomethane solution. The mixture was allowed to stand for 10 minutes. The solvent was evaporated in vacuo and the residue chromatographed on 20 g. of alumina. Chloroform eluted an oil which crystallized in ethanol to give 34 mg. (17%) of yohimbine (XLIX), m.p. 236-237°, as identified by melting point, mixed melting point and infrared spectrum.

Reduction of Pseudoyohimbine (XLVIII)
by Lithium Aluminum Hydride

To 150 mg. of lithium aluminum hydride in 10 ml. purified sodium-dry tetrahydrofuran, 300 mg. of pseudoyohimbine

in 10 ml. ether and 10 ml. of tetrahydrofuran were added. The mixture was refluxed gently for 6 hours. After cooling, the reaction mixture was decomposed by the addition of aqueous saturated sodium sulfate solution drop by drop. The mixture was filtered and the filtrate evaporated in vacuo. The residue was chromatographed on 20 g. of alumina. Elution with chloroform containing 5% methanol yielded an oil which was dissolved in 5% aqueous acetic acid and 70% perchloric acid was added to precipitate the perchlorate salt. Recrystallization from methanol yielded 165 mg. (46%) of pseudoyohimbyl alcohol (LXXVIII) as the perchlorate salt m.p. 290-291°.

Anal. Calcd. for $C_{20}H_{27}O_6N_2Cl$:
C, 56.27; H, 6.38; N, 6.56;
Found: C, 56.33; H, 6.49; N, 6.46.

Comparison with yohimbyl alcohol (LXXVIII) perchlorate, m.p. 280-281°, by mixed melting point and infrared spectrum proved them to be different.

Ultraviolet Analysis of the Reaction Mixtures from Palladium-maleic Acid Dehydrogenations

A series of solutions were prepared in 0.44% aqueous fumaric acid containing yohimbine and tetradehydroyohimbine perchlorate in the following molar ratios:

	Yohimbine	Tetradehydroyohimbine Perchlorate
No. 1.	100	0
No. 2.	80	20
No. 3.	60	40
No. 4.	40	60
No. 5.	20	80
No. 6.	0	100

Ultraviolet spectra (220-370 mμ) of these solutions were run using distilled water as the blank and the results were graphed.

Compounds used for dehydrogenation experiments

Amines. Besides the amines which are described elsewhere in the experimental section, the following bases were obtained from Ciba Pharmaceutical Products, Inc., Summit, N. J.

α-yohimbine (LV), m.p. 230-233° (d).

3-epi-α-yohimbine (LVIII), m.p. 127-131° (d).

yohimbyl alcohol (LXXVIII), m.p. 165°.

3-epi-α-yohimbyl alcohol (LXXIX), m.p. 228-231° (d).

apo-yohimbine (LXXX), m.p. 218-224°.

apo-α-yohimbine (LXXXI), m.p. 200-202°.

apo-3-epi-α-yohimbine (LXXXII), m.p. 260-268°.

Akuammigine, m.p. 113° was obtained from Sir Robert Robinson and Dr. K. Aghoramurthy, Oxford, England.

Maleic acid. Commercial maleic acid was recrystallized several times from acetone to give a pure sample, m.p. 131°.

Palladium black. The samples were obtained from American Platinum Works, Newark, N. J.

In a typical dehydrogenation run used to diagnose the extent of dehydrogenation, 0.05 mmole of the amine was dissolved in 8 ml. of 0.44% aqueous maleic acid solution 15 mg. of palladium black was added to this solution and the mixture was stirred and refluxed. Different batches of catalyst were used in different runs.

After refluxing, the solution was filtered from palladium black. The cooled solution was then diluted to 10 ml. with water and 0.4 ml. of the latter was further diluted to 100 ml. to give a final concentration of 2×10^{-5} moles/liter on the basis of free amine.

The ultraviolet spectra of the solutions were graphed and the curves were compared directly with the curves obtained from known yohimbine-tetradehydroyohimbine mixtures. On the basis of the height of the peaks at 248 mμ, 305 mμ and 365 mμ, the percentage of dehydrogenation was decided.

4 hour runs with palladium black (no. 1)

The following results were obtained using 4 hour reflux period:

	Percentage of dehydrogenation
A.	
yohimbine	95%
pseudoyohimbine	95%
α-yohimbine	95%

		Percentage of dehydrogenation
	3-epi-α-yohimbine	20%
B.		
	yohimbyl alcohol	70%
	pseudoyohimbyl alcohol	90%
	3-epi-α-yohimbyl alcohol	70%
C.		
	yohimbane	65%
	pseudoyohimbane	50%
	alloyohimbane	45%
	epi-alloyohimbane	45%

8 hour runs with palladium black (no. 2)

The following results were obtained using 8 hour reflux period:

		Percentage of dehydrogenation
A.		
	yohimbine	90%
	pseudoyohimbine	90%
	α-yohimbine	90%
	3-epi-α-yohimbine	80%
B.		
	pseudoyohimbyl alcohol	90%
	3-epi-α-yohimbyl alcohol	65%
C.		
	apo-yohimbine	80%
	apo-α-yohimbine	80%
	apo-3-epi-α-yohimbine	30%
	epialloyohimbane	40%

	Percentage of dehydrogenation
D.	
ajmalicine	80%
akuammigine	90%
3-isoajmalicine	0%

SUMMARY

Two methods of dehydrogenation have been used for the oxidation of variously ring E-substituted yohimbine- and ajmalicine-type indole alkaloids.

The first method, palladium-maleic acid dehydrogenation, produces ring C tetradehydro compounds and can be used for differentiating pseudo compounds from epiallo compounds. The second method, mercuric acetate oxidation, produces 3-dehydro compounds.

By the use of the first method the stereochemistry of several indole alkaloids was elucidated.

Infrared spectra in the C-H stretching region (3.4-3.7μ) have been used for differentiating between C_3 epimers of indole alkaloids.

Structures were proposed for several new compounds derived by oxidation or reduction of indole alkaloids or their derivatives.

The stereochemistry of various reduction methods was discussed.

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