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Syntheses of tryptamine bases

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SYNTHESES OF TRYPTAMINE BASES

by

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TABLE OF CONTENTS

INTRODUCTION

The methods which are used to synthesize the basic ring system of the numerous indole alkaloids are quite varied. Most of the synthetic routes are lengthy as a consequence of the presence of one or more centers of asymmetry in the natural products. However, certain wholly aromatic indole alkaloids lack these stumbling blocks. One of the alkaloids in this group is the compound flavopereirine.

This investigation is undertaken to develop a convenient, rapid synthesis of flavopereirine. Particular emphasis is to be placed on the feasibility of introducing catalytic dehydrogenation into the synthesis as a method of forming carbon-carbon bonds.

HISTORICAL REVIEW

The Chemistry of Flavopereirine

Introduction

In recent years much chemical interest has centered on the alkaloidal constituents of plant materials which have been used in folk medicine. Although this interest was stimulated by the discovery of reserpine in the roots of the Indian apocyanaceous plant Rauwolfia serpentina (1), it has extended both to examinations of new plant material and to re-examinations of previously studied materials.

According to the folk-lore of Brazil, the bark of the apocyanaceous tree Geissospermum vellosii has the power to relieve fevers. Although this bark had been previously studied (2), several groups of workers re-examined the extraction and separation of its alkaloidal constituents. In doing so, they discovered several new alkaloids, among them, flavopereirine.

Isolation

In their attempts to improve the isolation of alkaloids already known to be present in Geissospermum bark, as well as to analyze further the extracts of this bark, two independent groups of workers (3a, 3b, 4) found a new strongly basic orange-colored alkaloid in the bark of two Geissospermum varieties, G. vellosii and G. laeve. In addition, a third group of workers (5) independently isolated this substance as an impurity of a fraction containing the moderately basic alkaloids of the extract. The compound was named flavopereirine (3a) after its deep color and the popular Brazilian name -- "pao pereira" -- given to the tree.

The methods of all three groups were quite similar and can be summarized briefly as follows. From three to seven kilograms of finely ground bark of G. vellosii or G. laeve were extracted exhaustively with ethanol, either for a week in a soxhlet type of apparatus using 95% ethanol (4) or by leaching an alcoholic paste of the bark with fresh 70% ethanol until 60 liters of extract had been collected (3b).

Non-alkaloidal materials present in the extract could be largely removed either by allowing the extract to stand five days at 0°C. (4) (thus precipitating about one-half of the material originally extracted) or by evaporating the solvent and treating the residue with dilute sodium hydroxide solution for two days (5). Since later steps in the purification automatically eliminated such impurities, this could be omitted (3b).

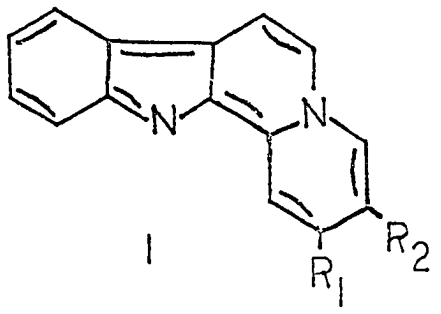
The solid material remaining after the extracting solvent had been evaporated (or after sodium hydroxide treatment) was dissolved in a weekly acidic aqueous solution — pH 3.5 to 4 — from which weak bases could be removed by continuous extraction for four days with ether (4). The moderately strong bases were then removed by adjusting the pH to 7 with saturated sodium hydroxide solution and extracting continuously for eleven days with ether, or by adjusting the pH to 8 - 9 with sodium carbonate and extracting first with ethyl acetate and then with chloroform (3b). Strong bases were recovered from the aqueous layer by making it strongly alkaline (pH 10 or greater) with sodium hydroxide and extracting continuously for seven days with ether (4) or four times with chloroform (3b). Flavopereirine was found largely in the latter extracts (3, 4) but was also present as a contaminant in the fraction of the moderately strong bases (5).

The strong bases could be fractionated further into two substances, flavopereirine and geissoschizoline (4). This was achieved by dissolving the strong bases in aqueous ethanol containing hydrochloric acid and precipitating the flavopereirine as the nitrate by addition of a saturated solution of sodium nitrate. Alternately, the hydrochlorides of the strong bases were treated with sodium hydroxide solution, extracted into chloroform and the dried chloroform solution passed through a column of alumina. Elution with chloroform which contained 0.5% to 2% of methanol produced flavopereirine, which was collected as the hydrochloride, decolorized with charcoal and crystallized as the perchlorate (3b). In the former procedure flavopereirine nitrate was reconverted to the free base which was chromatographed on alumina and isolated and characterized as the free base.

The yield of flavopereirine from 6.87 Kg. of G. vellosii bark was 2.1 g., 0.0306% (4) and of flavopereirine perchlorate from 6 Kg. of G. laeve bark, 1.17 g., 0.0102% (3b).

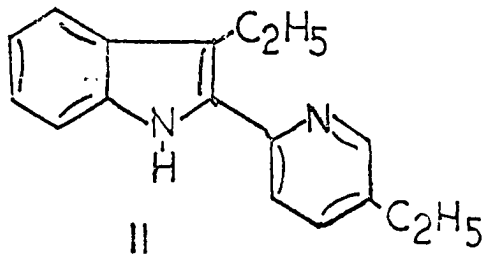
Determination of Structure

The structure of flavopereirine was determined simultaneously by the two groups of workers who isolated the compound. Janot, et al. (3a) based their proposed structure on two key pieces of evidence: the near identity of the ultraviolet absorption spectrum of flavopereirine to that of the known alkaloid sempervirine (IA) and the selenium-catalyzed high temperature degradation of flavopereirine to desethylalstyrine (II), a known compound which contained the same number of carbon and nitrogen atoms as flavoperpeirine. Hughes and Rapoport (6) uncovered and utilized the same two pieces of evidence. In addition they confirmed and extended the inferences



I

I	R_1	R_2
A	$-(CH_2)_4-$	
B	H	H
C	C_2H_5	C_2H_5
D	CH_3	C_2H_5
E	H	C_2H_5



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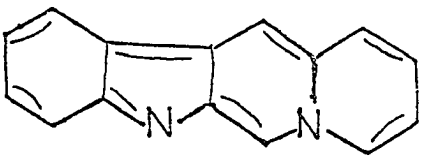

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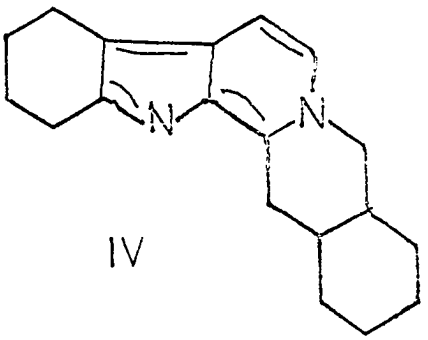

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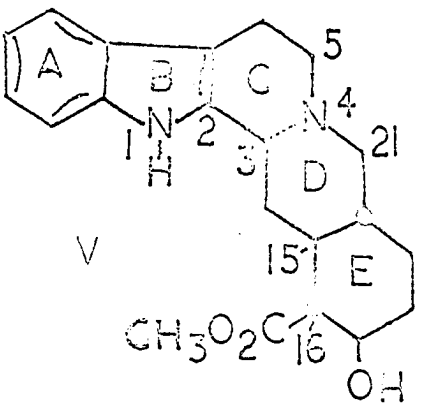
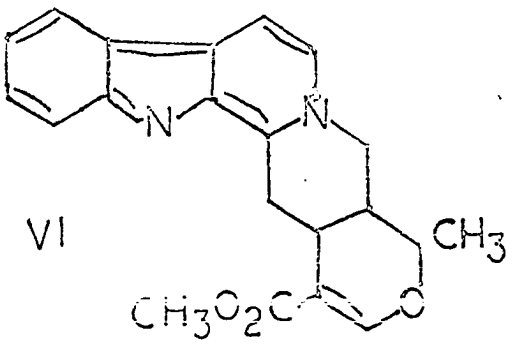


V



VI

drawn from flavopereirine's ultraviolet absorption by a series of catalytic reductions of the compound, and degraded desethylalstyrine to known compounds for a conclusive proof of its structure.

The formula of free flavopereirine is $C_{17}H_{14}N_2$. The fact that the molecular weight was 246 and not some multiple of it was indicated by the fact that the base sublimed readily at 200°C. and 0.1 mm. Hg pressure. It was demonstrated conclusively when flavopereirine was first synthesized (7). The free base was optically inactive and lacked N-methyl, N-ethyl and C-methyl groups.

Flavopereirine absorbs strongly in the ultraviolet, possessing a complex spectrum which is altered when a neutral or acidic solution is basified: λ max. ($\log\epsilon$) in acidic or neutral ethanol, 230mμ(4.40), 238 (4.43), 248 (4.39), 294 (4.14), 351 (4.25), 390 (4.14); in basic ethanol, 231mμ(4.44), 241 (4.38), 255 (4.23), 288 (2.47), 316 (4.17), 360 (4.34) (4). These spectra in acid and base are nearly identical with those of a host of compounds of the 12H-indolo[2,3-a]quinolizine type structure: 12H-indolo[2,3-a]quinolizine itself (IB) (8), flavocoryline (IC) (9), flavoserpentine (ID) (10), and sempervirine (IA) (4) among others. When considered together with the elemental analysis and the lack of a simple N-substituent, this spectral comparison indicated clearly that flavopereirine possessed either the indolo[2,3-a]quinolizine structure or a linear variation of it (III). In either case, all but two carbon atoms of the formula are accounted for by these analogies.

A series of catalytic reductions of flavopereirine at varying acidities located the C_2 group on ring D. Reduction over platinum in glacial acetic

acid introduced four moles of hydrogen after six days. The product exhibited ultraviolet absorption comparable to the octahydrosempervirine (IV) prepared from sempervirine under similar conditions, and was thus a pyrrolopyridine type of structure with rings A and D reduced. Reduction for eight hours over platinum in methanol, to which a trace of solid potassium hydroxide had been added (10 mg. per 3 g. of flavopereirine), generated two compounds. One, a hexahydro derivative, was tentatively classified as a pyrid [3,4-b]indole system on the basis of its ultraviolet spectrum; thus, ring D was both reduced and cleaved by hydrogenolysis. The other, a second octahydroflavopereirine showed ultraviolet absorption similar to the indolic absorption of β-yohimbine (V) and was therefore derived from flavopereirine by the reduction of rings C and D. Reduction over platinum for eight hours in methanol, to which an excess of solid potassium hydroxide had been added (pH above 10), introduced four atoms of hydrogen. Since the ultraviolet spectrum of this compound was comparable with those of alstonine (VI) and serpentine (VI), only ring D must have been reduced. The two octahydro products and the tetrahydro product had a C-methyl group, whereas the hexahydro product had two C-methyl groups. Since the Kuhn-Roth oxidation by which this was determined destroys methyl and ethyl groups attached to aromatic rings, the C_2 fragment must be attached to a reduced ring in each case. The only ring which was commonly reduced was ring D; this must be the ring to which the C_2 is attached. In addition, this fragment must be an ethyl group, since only the hydrogenolytically cleaved hexahydro compound possesses two C-methyl groups.

The mode of attachment of ring D to the norharmane skeleton as well as the exact location of the ethyl side chain were decided by selenium-

catalyzed degradation of flavopereirine. When flavopereirine itself was heated to 300°C. with selenium metal, the ultraviolet spectrum of the extract of the product mixture indicated the presence of a trace of alstyrine-like material. However, a mixture of the indolic actohydroflavopereirine and selenium metal evolved hydrogen selenide at 240°C. in the presence of tetrahydroquinoline (to reduce formation of the pyrid [3,4-b]indole compound) and produced the alstyrine-like substance in excellent yield: 70 mg. of oil from 75 mg. of substrate (3b). This compound's identity with desethylalstyrine was proved by its ultraviolet spectrum and the melting point and mixture melting point of its picrate (3b), and by comparison of its ultraviolet spectrum and the melting points of its picrate, styphnate and hydrochloride with comparable values for desethylstyrine recorded in the literature (4) (3b, 4, 11). This product clearly placed flavopereirine in the 12H-indolo[2,3-a]quinolizine structural family and firmly located the ethyl side chain in the 3-position of ring D. It also served to determine that the pyrid[3,4-b]indole harman-like compound isolated both from mildly basic hydrogenation and from catalytic dehydrogenation was in fact 1-(3'-methylpentyl)-9H-pyrid[3,4-b]indole.

In the absence of an authentic sample of desethylalstyrine for comparative purposes, Hughes and Rapoport (4) degraded their sample to prove its structure conclusively. Treatment of the picrate of desethylalstyrine yielded the free base which was reacted with hydrogen peroxide in acetic acid for one day at 20°C. These reagents attack the pyrrole ring of the indole portion of the molecule to produce the keto-amide o-(5-ethylpicolinoylamino)-propiophenone. This compound was then hydrolyzed by refluxing

four and one-half hours in 10N sulfuric acid to give two fragments: o-aminopropiophenone, identified by comparison of its melting point and the melting point of its benzoate with those values reported in the literature, and 5-ethylpicolinic acid, identified by comparison with an authentic synthetic sample.

Thus, a series of catalytic reductions and a catalytic dehydrogenation, along with a study of the major dehydrogenation product and the ultraviolet spectra of all compounds introduced in the analysis, proved the structure of flavopereirine to be 3-ethylindolo[2,3-a]quinolizine (IE).

Synthesis

Flavopereirine has been synthesized by four groups of workers, each employing a different synthetic route.

LeHir et al. (7) reacted tryptamine with ethyl 4-bromomethylhexanoate to obtain 1-[2-(3-indolyl)ethyl]-5-ethyl-2-piperidone, the key intermediate. The hexanoate was obtained by cyanoethylation of ethyl 2-ethylmalonate to give ethyl 2-ethyl-2-cyanoethylmalonate, followed by hydrolysis and decarboxylation to 2-ethyl-4-cyanobutyric acid and selective reduction of the diazomethane-produced ester of this acid with a potassium borohydride-lithium chloride reagent to 2-ethyl-2-cyanobutanol which on treatment with ethanolic hydrogen bromide underwent hydrolysis of the cyano group to a carboxyl function, esterification of the carboxyl and displacement of the hydroxyl group by bromide. Refluxing the resulting substituted hexanoate with tryptamine in absolute ethanol for seventy-two hours under nitrogen with added potassium carbonate and a trace of potassium iodide yielded the piperidone.

Refluxing this piperidone with phosphoryl chloride for three and one-half hours in benzene produced hexahydroflavopereirine, isolated as the perchlorate. The free base was dehydrogenated to flavopereirine, characterized as the perchlorate which was identical with the material isolated and characterized by these same workers (3b).

Prasad and Swan (8) formed 2-(4-ethoxybutyryl)-5-ethylpyridine by an inverse Grignard reaction between 2-cyano-5-ethylpyridine and 4-ethoxypropylmagnesium bromide and isolated the ketone after hydrolysis of the imino product with hydrochloric acid. This intermediate was refluxed in acetic acid under nitrogen with constant-boiling hydrobromic acid for conversion to 1-keto-1,2,3,4-tetrahydro-7-ethylquinolizinium bromide, the key intermediate.

Treatment of this quinolizinium salt with phenylhydrazine gave the phenylhydrazone which, under the conditions of the Fischer indole synthesis (refluxing in dry ethanolic hydrogen chloride) yielded 3-ethyl-6,7-dihydro-12H-indolo[2,3-a]quinolizinium chloride, isolated as the nitrate. This dihydro derivative of flavopereirine proved resistant to most attempts of dehydrogenation, but was converted readily to flavopereirine by heating the chloride salt for nine hours in glacial acetic acid with p-tetrachlorobenzoquinone. This synthesis produced the highest melting flavopereirine perchlorate recorded in the literature (331°C., dec.), although a sample of the compound isolated by Bejar *et al.* (3a) (m.p. 307-308°C.) melted almost as high (330°C.) in the hands of Prasad and Swan (8).

Thesing and Festag (12) obtained their key intermediate by reacting a quaternary salt of gramine with N-phenacyl-3-ethyl-pyridinium bromide,

formed by the reaction of phenacyl bromide with 3-ethylpyridine. Trimethylamine was displaced by the latter reagent from gramine methosulfate to yield benzoyl-(3-indolylmethyl-) (3-ethyl-1-pyridinium)-methane bromide which without isolation was hydrolyzed in warm methanolic potassium hydroxide to yield N-(2-indoylethyl)-3-ethylpyridinium bromide and benzoic acid.

Under the influence of Raney nickel in basic methanol, this pyridinium bromide took up two moles of hydrogen to form the tetrahydropyridine derivative which cyclized readily on standing for sixteen hours in hydrochloric acid solution. The oily octahydroflavopereirine product was undoubtedly a mixture of stereoisomers. Nonetheless, the indoloquinolizine mixture was readily dehydrogenated to flavopereirine, isolated and characterized as the perchlorate (m. p., 329°C.).

The synthesis of flavopereirine by H. Kaneko (13) follows in most respects that of Prasad and Swan (8). The difference lies in the first two steps: Kaneko utilized 5-ethyl-2-pyridinecarboxylic acid, first forming its acid chloride and then reacting this with 3-ethoxypropylcadmium Grignard reagent to obtain the 2-(4-ethoxybutyryl)-5-ethylpyridine of Prasad and Swan. This compound was converted to flavopereirine as described above.

The Dehydrogenation of Piperidine Rings

A variety of methods have been employed for the elimination of hydrogen from piperidine systems, ranging from the selective chemical reagents lead tetraacetate and mercuric acetate to high temperature

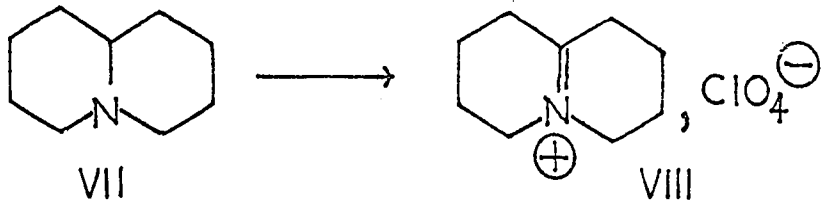
dehydrogenations catalyzed by palladium and selenium.

Chemical Dehydrogenation

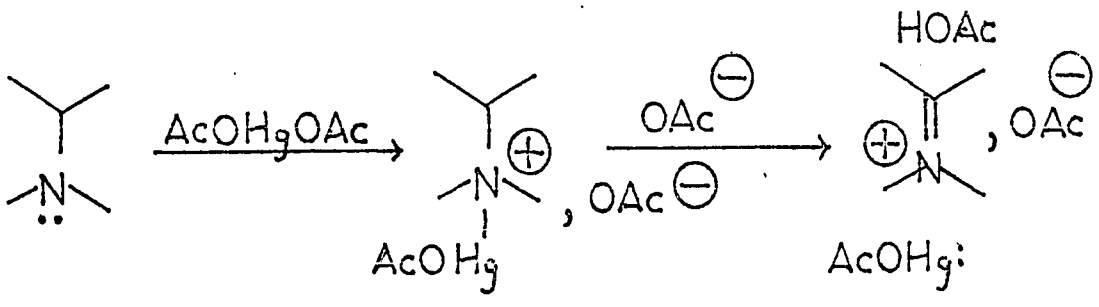
Mercuric acetate oxidation of piperidine rings has been the subject of an extensive continuing investigation by N. J. Leonard and his co-workers (14). It was found that quinolizidine (VII) was oxidized in five per-cent aqueous acetic acid by mercuric acetate to the quaternary dehydroquinolizidinium compound (VIII) isolated as the perchlorate (14a). The mechanism proposed at the time for this reaction is still invoked. It depicts an initial displacement of acetate ion from covalent mercuric acetate by the free electron pair of the nitrogen atom (IX to X) followed by elimination of acetic acid and mercury and subsequent oxidation of the latter to mercurous acetate by mercuric acetate (X to XI). The course of the reaction may be followed by observing the rate of precipitation of mercurous acetate, which is nearly quantitative in most cases.

The infrared spectrum of this and other compounds, such as the [4.3.0] and the [5.4.0] systems (XII and XIII), indicated that the preferred form of the products was the eneamine, with the newly-introduced unsaturation residing alpha-beta to the nitrogen, whereas the perchlorate salts existed entirely as the immonium salt (14b).

Such oxidation need not stop at the two-electron stage. Further oxidation depends on the nature of the starting compound, the amount of reagent added and the conditions of the reaction. Thus trans-1-methyldecahydroquinoline (XIV) was converted to the hydroxyoctahydroquinoline (XV) in fifty-four percent yield (14c), and 5-oxo-1-azabicyclo[4.4.0]

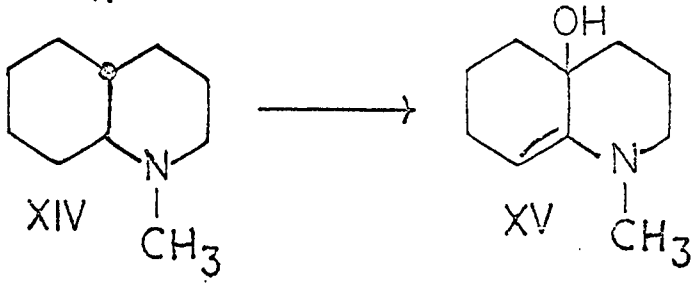


VII VIII

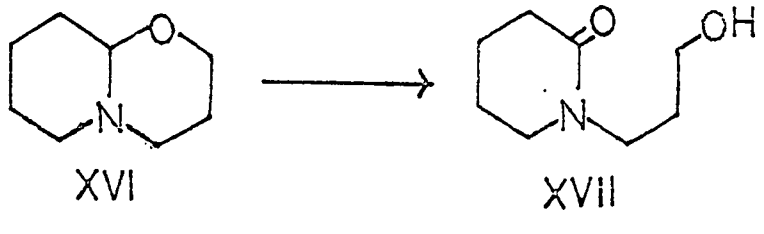


IX X XI

XII XIII



XIV XV



XVI XVII

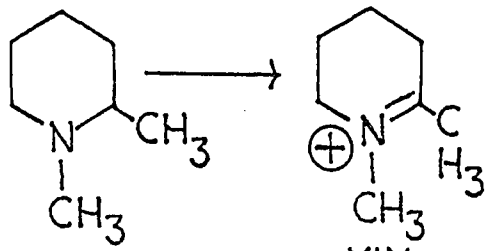
decane (XVI) was oxidized to 1-(3'-hydroxypropyl)-piperidone (XVII) in thirty-three percent yield (14d).

Studies on a number of unsymmetrical model compounds indicated that the imine products invariably had their double bonds in the most substituted positions (14e). Thus, N-alkylated mono-, di- and tri- substituted piperidines were converted to the corresponding 3,4,5,6-tetrahydropyridinium compounds (XVIII through XXIII). Absence of an alpha hydrogen on a given carbon atom prevented oxidation at that site (XXIV and XXVI).

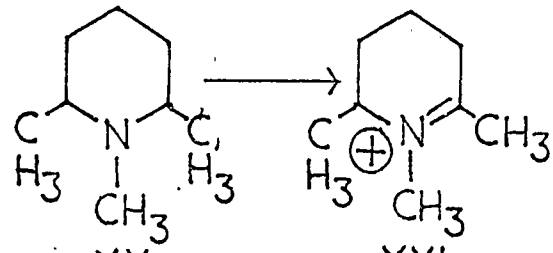
In an ingenious extension of this method, a series of 3-piperidinopropanols were cyclized oxidatively to the corresponding bicyclic tetrahydro-1,3-oxazines (14d) in yields ranging from 36 to 60 per cent. (XXVII to XXVIII, R & R' is hydrogen or methyl).

Although Leonard's studies of mercuric acetate oxidation are by far the most extensive, the reagent has been employed by many other investigators, usually as a method of introduction of the imino functional group. Thus the substituted tetrahydroisoquinoline (XXIX) was oxidized to the dihydroisoquinoline (XXX) in seventy-one per cent yield (15), and the benzo[a]quinolizine (XXXI) to the quinolizinium betaine (XXXII) quantitatively (16). Reminiscent of the latter are the oxidations of canadine (XXXIII) to berberine (XXXIV) (17) and of the yohimbene (XXXV) to 5,6-dihydrosempervirine (XXXVI) (18).

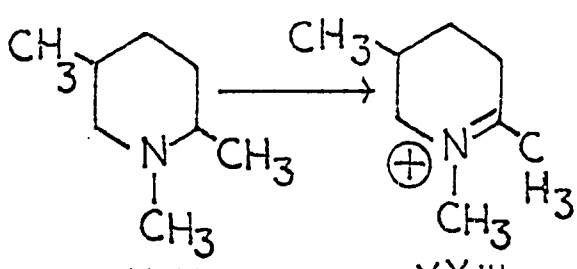
In an attempt to determine its structure, the involuted compound calycanthine (XXXVII) was oxidized to dehydrocalycanthine (XXXVIII) (19), whose structure was decided by hydrolyzing it to an amide alcohol and methylamine. Similarly, isorhynchophylline (XXXIX) was transformed to a



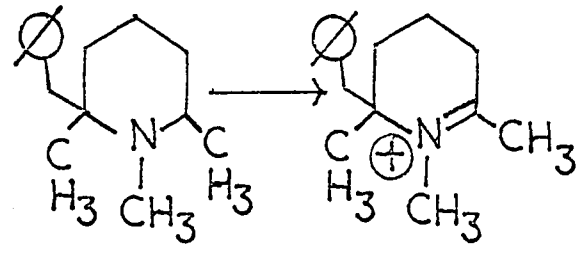
XVIII XIX



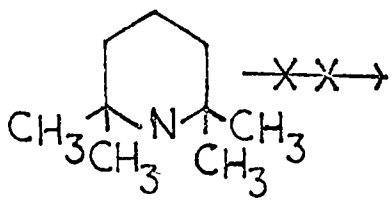
XX XXI



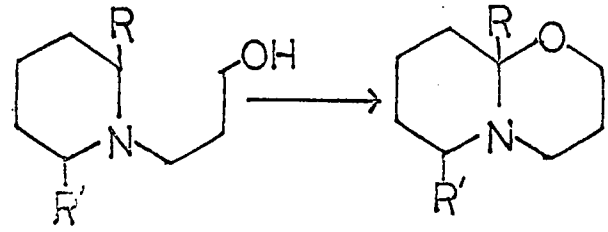
XXII XXIII



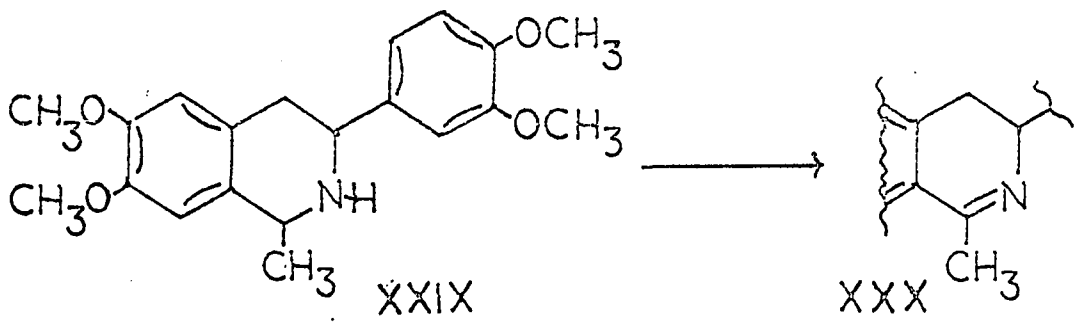
XXIV XXV



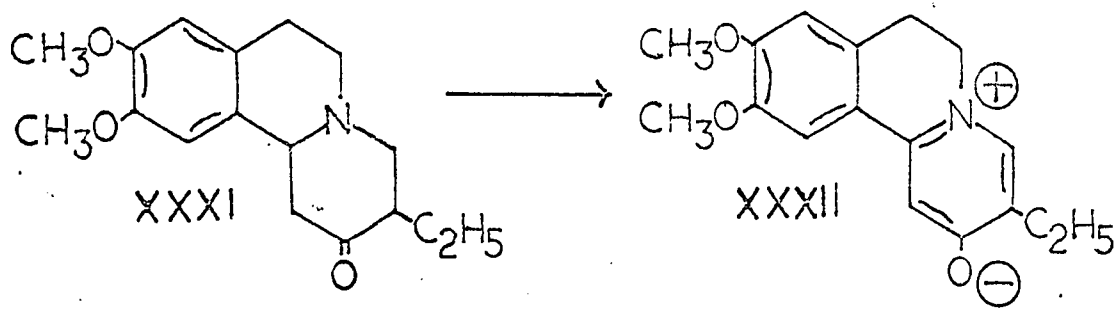
XXVI



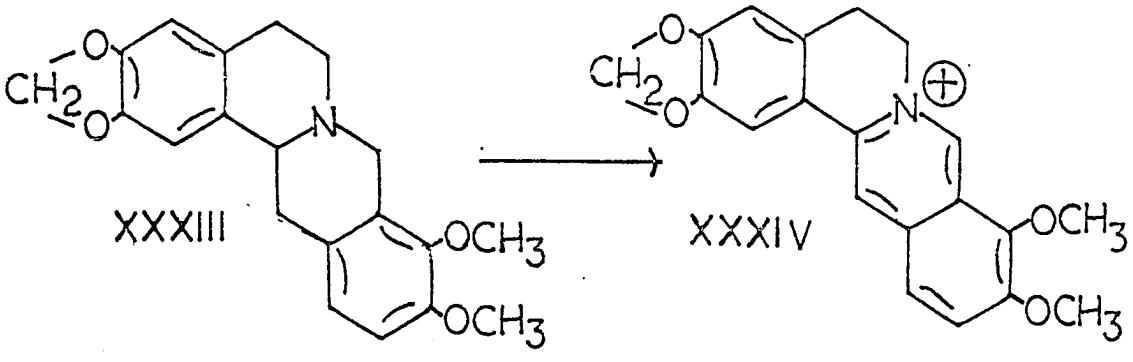
XXVII XXVIII



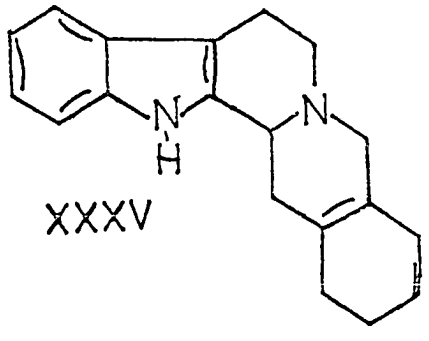
XXIX XXX



XXXI XXXII



XXXIII XXXIV



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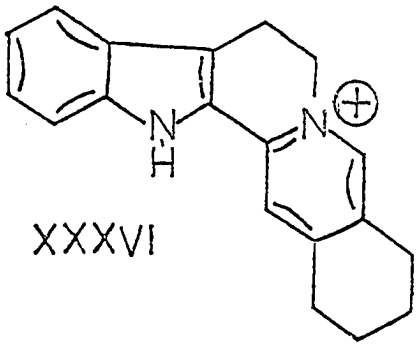

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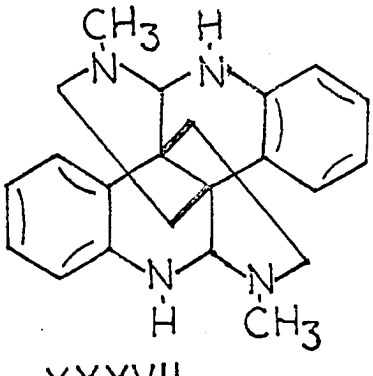

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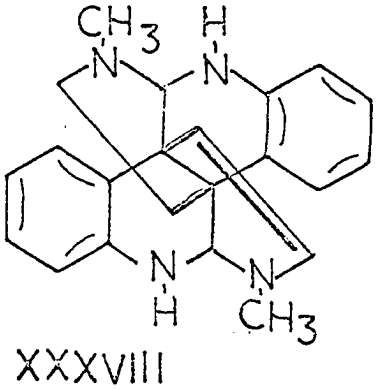
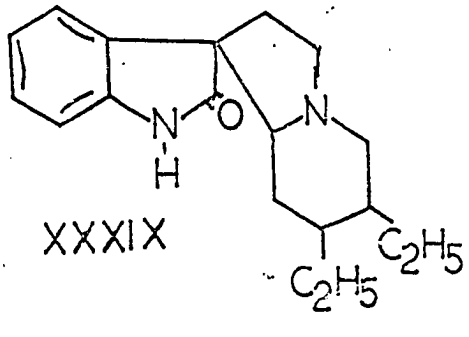
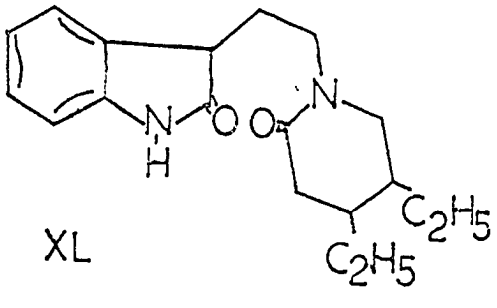


XXXVIII



XXXIX



XL

neutral dilactam which was assigned the probably structure (XL)(20). Oxidation of p,p'-di-(N-piperidino)-diethyl ketone (XLI) to the diamino dialdehyde (XLII) followed by cyclization *in situ* gave a ketone which could be reduced to sparteine (21).

A host of indole alkaloids have been converted to their 3-dehydro derivatives with this reagent. Included among these are corynanthine (XLIII) and alloyohimbine (XLIV)(22), a variety of reserpine compounds (e.g., XLV (23)), and yohimbone (XLVI)(18). In connection with the last compound, it is worth noting that 3-epialloyohimbone (XLVII) was unreactive toward the conditions which oxidized yohimbone (18).

Lead tetraacetate has seen slight use on piperidine ring systems, possibly because of the complex nature of the reaction or the lack of a sound mechanistic interpretation. In early studies of yohimbine (XLVIII) it was observed that either the didehydro or the tetradehydro product could be obtained (24) depending on the amount of reagent employed.

Relatives of yohimbine which have been transformed into the ring C tetradehydro derivatives include ψ-yohimbine (XLIX) and yohimbane (25), as well as alloyohimbine (XLIV)(26).

Oxides of chromium have been employed to convert piperidines to pyridines in excellent yields. Thus, from three grams of tryptophan, after base-catalyzed condensation with formaldehyde followed by a brief oxidation with boiling acetic acid-potassium dichromate solution, were isolated two grams of norharman (L)(27); the whole reaction sequence was carried out without isolation of intermediates. Similarly, tetrahydro-norycobyrinecarboxylic acid (LI) was converted to norycobyrine (LII)(28),

6-benzyl-5,6-dihydrophenanthridine to 6-benzoylphenanthridine (LIII)(29), and 4,5-dimethylacridane to the corresponding acridine (LIV)(30).

Chromic oxide heated in acetic acid was used to oxidize the suitable tetrahydroazafluorenone to ethyl 1-phenyl-3-methyl-4-azafluorenone-2-carboxylate (LV)(31) as well as the suitable dihydropyridine to 3,5-dicyano-2,6-dimethyl-4-o-nitrophenylpyridine (LVI)(32).

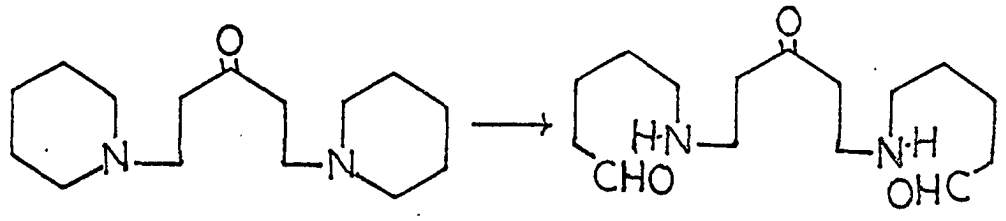
The use of miscellaneous reagents appears scattered throughout the chemical literature. For example, a number of quinones have been examined for their ability to dehydrogenate piperidine compounds; Barclay and Campbell (33) showed that chloranil was the reagent best suited to oxidize a number of reduced carbazoles.

Mercuric oxide in refluxing ethanol dehydrogenated 2-benzyl-1,2-dihydroquinoline to 2-benzylquinoline (34).

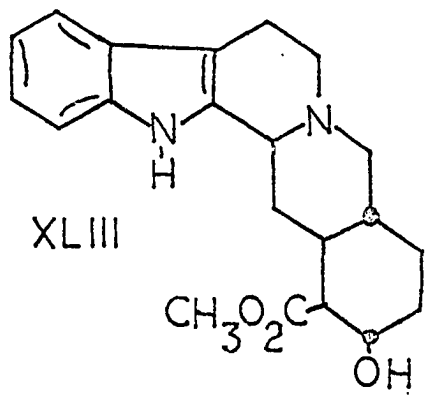
Ferric chloride appears to be well-suited for converting acridanes to their acridines both selectively and in good yields (35,36).

A mixture of iodine and potassium acetate in alcohol provides a smooth conversion of 1,2,3,4-tetrahydroisoquinoline to a mixture of 3,4-dihydroisoquinoline and isoquinoline (37) and of tetrahydroalstonilinol (LVII) to alstonilinol iodide (LVIII)(38).

Oxygen in the presence of sodium hydroxide is capable of oxidizing 1-amino-4-methylacridane to the corresponding acridine (LVIX)(39). Brief boiling with nitric acid converts the dihydropiperidine (LX) to diethyl 4,3'-quinolyl-2,6-dimethyl-3,5-pyridinedicarboxylate (40). One-half hour at 190°C. in the presence of nitrobenzene dehydrogenates the adduct of aminophenyllithium and isoquinoline to 1-(p-aminophenyl)-isoquinoline (LXI)(41).



XLI XLII



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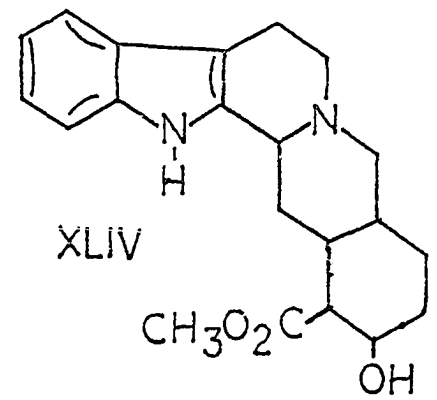
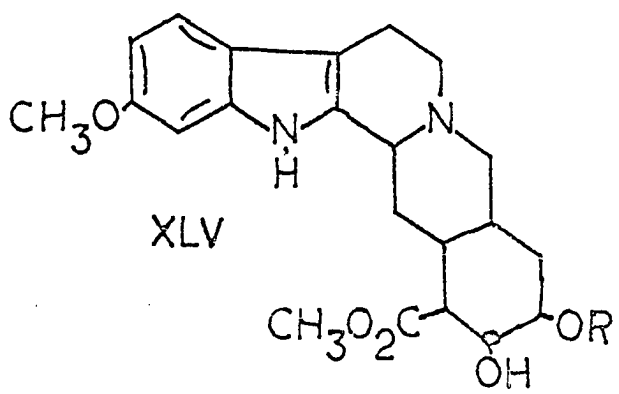
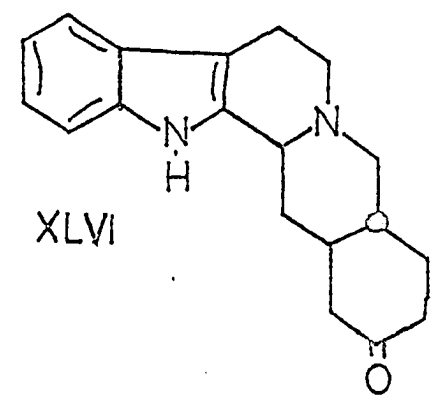


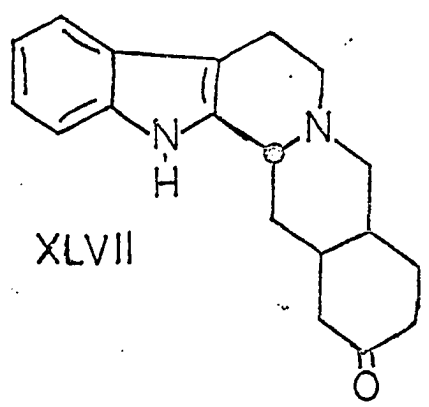
XLIV



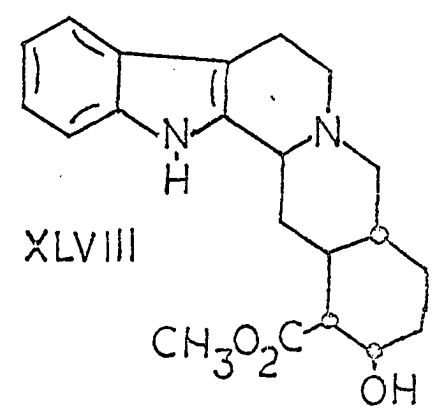
XLV



XLVI



XLVII



XLVIII

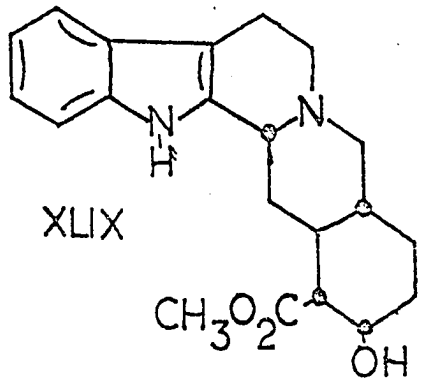
Refluxing for one minute in acetic acid with triphenylmethyl perchlorate oxidizes 1,2-dihydro-1,2-dimethyl-quinoline to the quinaldine methoperchlorate (LXII)(42).

Catalytic Dehydrogenation

Although the reactivity of the metals nickel, palladium and platinum as dehydrogenation catalysts is similar to that of the non-metals sulfur and selenium, there are enough similarities among the metals and sufficient differences between the two groups to merit discussing each group separately.

Within a given period the catalysts have often been used interchangeably by altering slightly temperature, time of reaction or ratio of catalyst to substrate.

Palladium, platinum and iridium can be used as reduction catalysts in the temperature range between 100 and 180°C. (43). Palladium begins to act as a dehydrogenation catalyst between 155 and 180°C., the other metals above 200°C. Whereas the piperidine ring is rapidly dehydrogenated above the lower temperature, the cyclohexane ring begins to lose hydrogen only above 280°C., and then more slowly than the piperidine ring (44). Thus the mechanism advanced for the catalytic dehydrogenation of cyclohexane, which involves an initial formation of cyclohexene followed by disproportionation to give cyclohexane and cyclohexadiene which disproportionates into cyclohexene and benzene (45), may not apply to piperidine ring systems. However, the concept that the geometry of the surface of the metal lattice determines the specificity of metal catalysts in affecting



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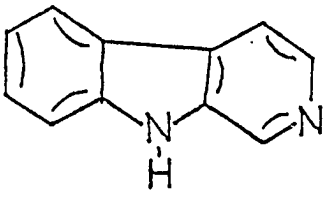
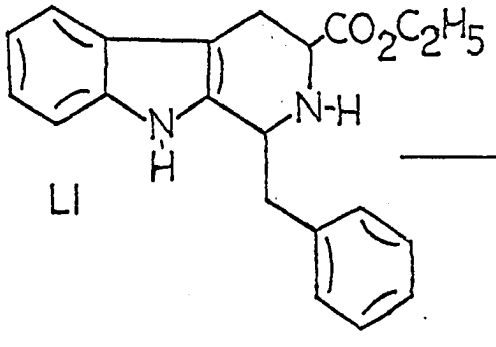
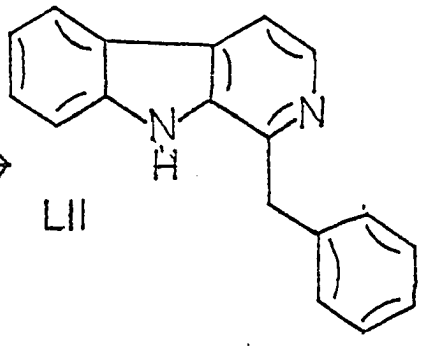


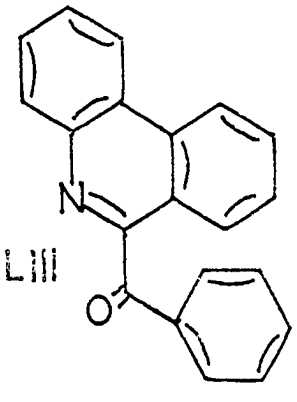
L



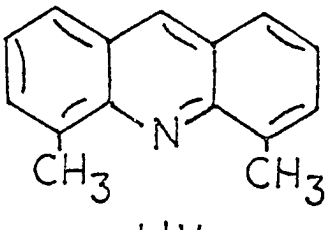
LI



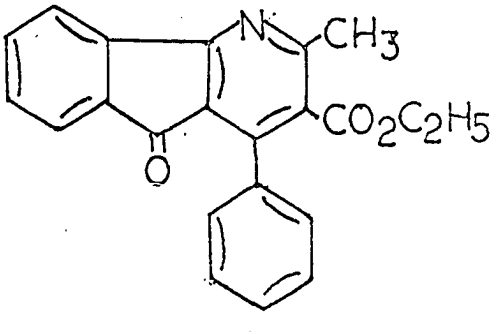
LII



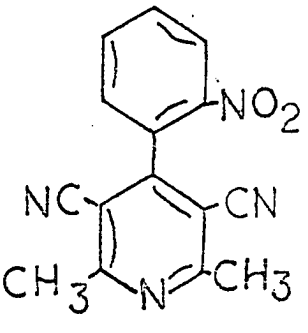
LIII



LIV



LV



LVI

alicyclic compounds (46) probably still holds true for heterocyclic compounds.

Piperidine itself can be dehydrogenated by palladium or platinum either as the free metals or supported on a variety of neutral materials (carbon, asbestos, silica gel, etc.) at temperatures ranging from 180° to 500°C. (47). By recycling the products, the commercial yields of pyridine from this reaction approach quantitative levels.

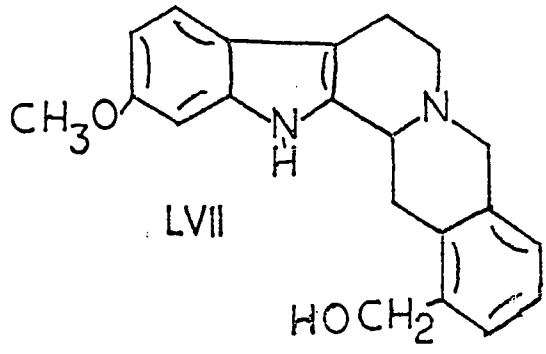
Substitution of the piperidine nucleus affects the course of dehydrogenation only if the substituents are on the nitrogen atom or geminally attached to one of the ring carbons. Thus, anabasine (LXIII), cicutine (LXIV), 2-phenylpiperidine and 4-phenyl-1,2,3,6-tetrahydropyridine (LXV) are dehydrogenated in the usual manner to their respective pyridines by silver acetate (48), palladium-on-carbon (49), platinum-on-asbestos (50) and palladium-on-alumina in refluxing nitrobenzene (51), respectively. But N-alkyl groups are eliminated, as from N-methylpiperidine (52) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (51), to yield the suitable norpyridine derivatives. And geminal substituents can affect the dehydrogenation in one of two ways. Either a concurrent elimination can lead to a norpyridine: a series of 1-benzyl-3,5-dimethyl-4-alkyl-4-hydroxypiperidines (in which the alkyl group could be ethyl, butyl or benzyl) was dehydrogenated over palladium at 240°C. to give the corresponding 4-alkyl-3,5-dimethylpyridines (53)(e.g., LXVI to LXVII). Dehydrogenation attempts may fail altogether: only starting material was recovered when 2-isopropyl-3,3-dimethylpiperidine was exposed to 40% palladium-on-carbon at 250°C. (52).

In an interesting series of dehydrogenations, Prelog and coworkers (54) found that several 1-methyl-3-acetyl-4-methylpiperidines rearranged on heating with selenium of palladium-on-carbon catalysts to yield 2,3,4-trimethylpyridine, whereas the corresponding alcohols merely lost methane to give 3-ethyl-4-methylpyridine (β-collidine)(i.e., LXVIII to LXXI).

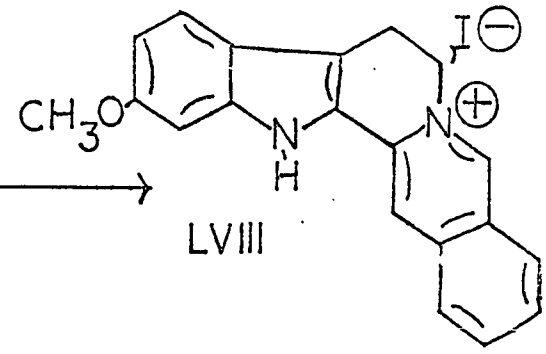
Where these alkyl substituents took the form of parts of a polycyclic ring system, ring fission can occur. Tropane (LXXII) when heated to 300°C. in the presence of palladium-on-asbestos yields the methylcycloheptenylamine (LXXIII)(55). And 1-azabicyclo[2.2.1]heptane (LXXIV) and quinuclidine (LXXV) when heated at 350°C. with palladium-on-carbon or selenium lose hydrogen smoothly to yield 4-picoline and 4-ethylpyridine respectively (56). However, under these same conditions a small amount of quinoline was the only well-defined product from the reaction of quinolizidine.

In contrast to this last observation 3H,4H-quinolizinium iodide or picrate (LXXVI) is converted readily, albeit in only fifteen percent yield, to the dehydroquinolizinium salt (57) by refluxing with 10% palladium-on-carbon in ethanol or butanol.

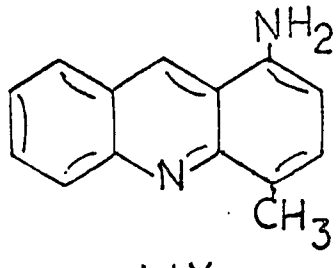
The quinoline nucleus appears to be more amenable to dehydrogenations. Bz-tetrahydroquinoline (LXXVII) is converted in eighty-five per cent, yield to quinoline in three hours over palladium-on-carbon at 300°C. (58), 6-methoxy-1,2,3,4-tetrahydroisoquinoline to the aromatic quinoline in ninety-five per cent yield in one hour at 200°C. in naphthalene over Raney nickel (59). However the reactivity of both decahydroquinoline and decahydroisoquinoline depends on the nature of the ring juncture. Supported on asbestos either platinum or palladium catalyzes the dehydrogenation of cis-decahydroquinoline to quinoline in two passes at 300°C.(60)



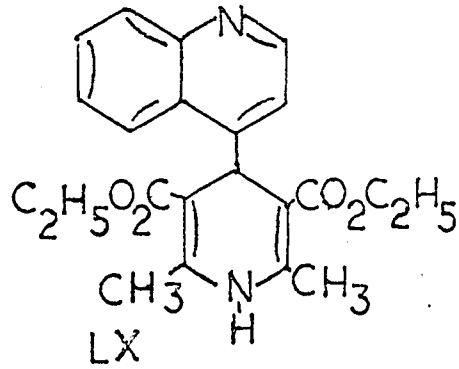
LVII



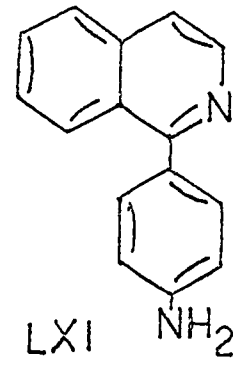
LVIII



LIX



LX



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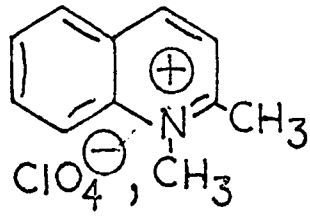

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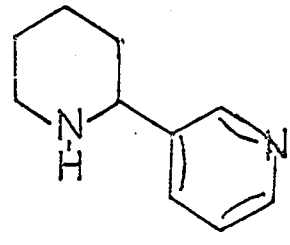

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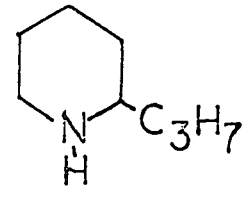
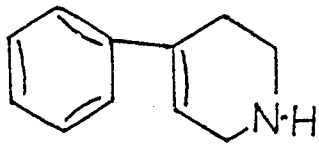
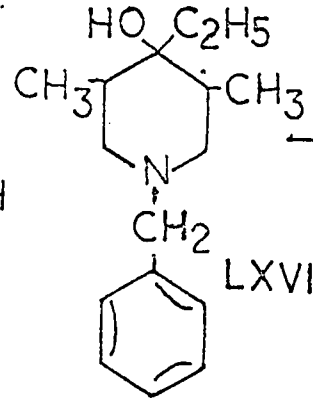


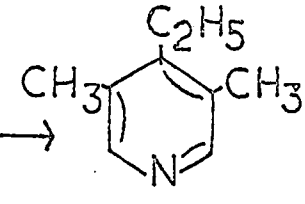
LXIV



LXV



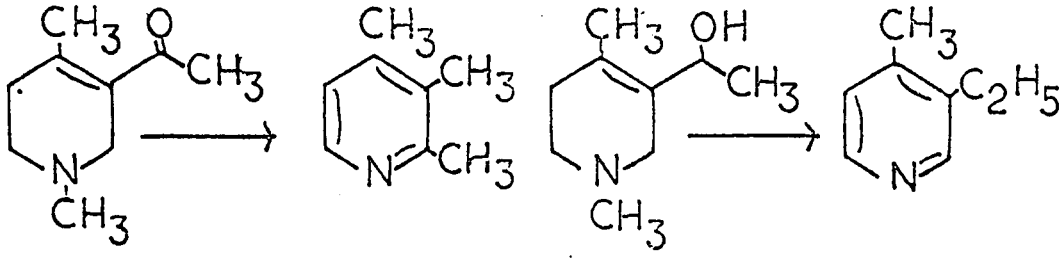
LXVI



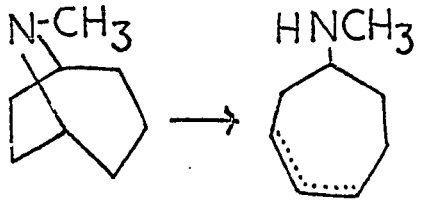
LXVII

although the yields are better with platinum. However, the palladium is unable to affect the trans compound (LXXVIII). In one pass the platinum catalyst produces no quinoline (LXXVIX), thirty per cent bz-tetrahydroquinoline (LXXX) plus starting material. Only after two passes over the platinum does quinoline appear in the product mixture (60). Methylation of the nitrogen atom does not alter the effect of the ring juncture but results in the appearance of N-methyl-py-tetrahydroquinoline (cairoline) (LXXXII) as the sole product (60); again the trans compound (LXXXI) is unaffected by the palladium catalyst. (Concurrent studies on the decalins indicated that platinum is 1.5 times as fast as palladium in dehydrogenating trans-decalin, and that dis-decalin reacts distinctly faster than trans-decalin (60).) These effects are reversed in the decahydroisoquinolines: the trans compound can be dehydrogenated to isoquinoline in three hours at 210°C. with a three-fold weight excess of palladium black catalyst, whereas the cis compound requires refluxing for forty-eight hours in tetralin with selenium and then is only dehydrogenated to bz-tetrahydroisoquinoline (61).

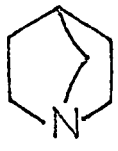
The addition of substituents to the isoquinoline nucleus produces no rational effect on the course of yield in dehydrogenation. Thus 6,7-dimethoxy-1-(3,4,5-trimethoxybenzyl)-3,4-dihydroisoquinoline is dehydrogenated in fifty per cent yield to (LXXXIII)(62); 6,7-dimethoxy-3,4-dihydroisoquinoline in eighty-two per cent to (LXXXIV)(63); 1-(2,3-dimethoxybenzyl)-5,6-diethoxy-3,4-dihydroisoquinoline in ninety per cent to (LXXXV)(64); 6,7-methylenedioxy-1-(3'-pyridyl)-3-methyliso-3,4-dihydroisoquinoline in "poor yield" to (LXXXVI)(65). All reactions were performed over various types of palladium.



LXVIII LXIX LXX LXXI

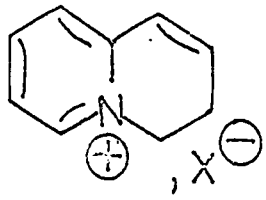


LXXI LXXII

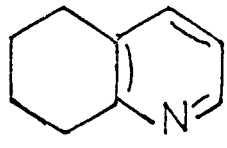


LXXIV

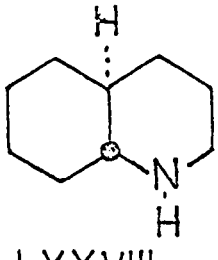
LXXV



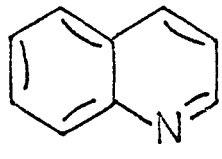
LXXVI



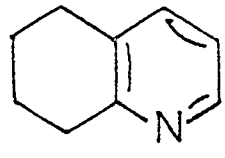
LXXVII



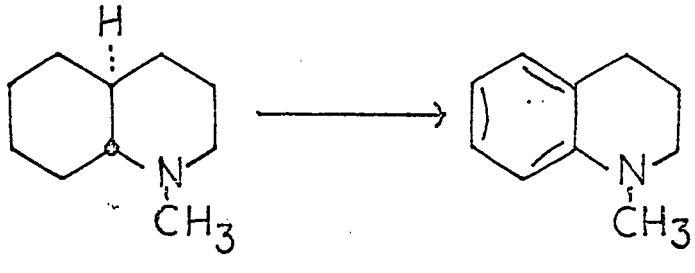
LXXVIII



LXXVIX



LXXX



LXXXI LXXXII

An inadvertant dehydrocyclization of an N-substituted tetrahydroisoquinoline was brought about when 1-methyl-3-[2-(1,2,3,4-tetrahydro-2-isoquinolyl)-ethyl]oxindol (LXXXVII) was heated with palladium for one hour at 200°C. in an attempt to obtain the 1,2-dihydro-derivative (66). The structure of the product of this reaction was subsequently postulated (67) and proved by synthesis (68) to be that of a spiro-oxindole (LXXXVIII).

The palladium-catalyzed dehydrogenation of the partially reduced acridines has been studied in detail by Masamune and Homma (68). The results of their study can be summarized as follows. At temperatures up to 200°C., rearrangement and disproportionation predominated. From the octahydro compounds, more of the pyridine form (LXXXIX) was formed than the tetrahydropyridine form (XC). At 250°C. the pyridine form was converted to dihydro and tetrahydro acridines to the extent of eighty percent. The cis and trans tetrahydropyridine forms (XC) were converted to the pyridine form: the dihydro and the tetrahydro acridines to about the same extent (about twenty percent of each type of product), the cis form proving to be somewhat more labile than the trans form. At 200°C. trans (XC) only isomerized to (LXXXIX), whereas cis (XC) isomerized to (LXXXIX) and also lost hydrogen to give some dihydro and tetrahydro compounds.

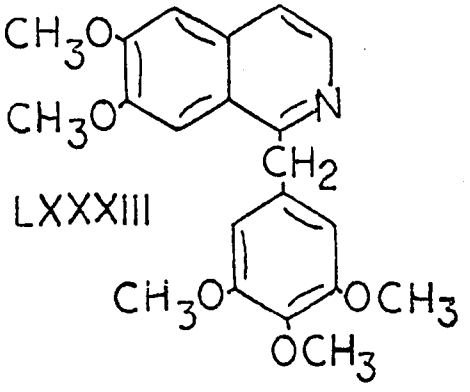
A number of other tricyclic and tetracyclic piperidine derivatives have been dehydrogenated with palladium. They include 9,10-dihydrophenanthridine (XCI), converted nearly quantitatively to phenanthridine (69) with palladium-on-carbon at 260°C., N-acetyl-tetrahydrocytisine (XCII), converted to N-acetylcytisine (XCIII) in four hours over palladium between 250 and 280°C. (70), 2.6-dimethyl-1,2,3,4-tetrahydroanthrazoline

(XCIV) oxidized in thirty percent yield to 2,6-dimethyl-1,5-anthrazoline by arsenic acid and palladium-on-carbon in water at 140°C. (71) (other hydrogen acceptors gave lower yields, e.g., five percent with maleic acid); and the hexahydro-6,12-diazachrysene (XCV), converted to caly-canine (XCVI), a degradation product of calycanthine (19).

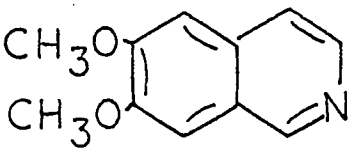
In contrast to the above use of palladium and arsenic acid, nickel-sodium arsenate was used in the last step of the synthesis of lysergic acid (XCVIII) which involved the conversion of an indoline to an indole group of a suitable precursor (XCVII)(72).

Catalytically induced dehydrogenations of polycyclic compounds (including indole alkaloids) have been undertaken to eliminate certain hydrogens selectively, as in dehydrogenations of smaller molecules or in degradations of the substances to simpler, recognizable fragments for structure determinations. In the former case selectivity is enhanced by milder conditions which can be made possible by the use of various hydrogen acceptors.

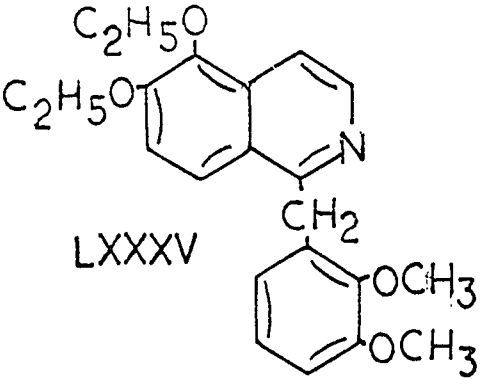
Majima and Murahashi (73) introduced maleic acid as a hydrogen acceptor in dehydrogenations catalyzed by palladium or platinum. The method was applied to the conversion of yohimbic acid (XCIX) to the ring C tetradehydro compound (C). Since its introduction, the most extensive use of palladium-maleic acid dehydrogenation has been made by Wenkert and Roychaudhuri (74) who oxidized twelve alkaloids and derivatives (such as 3-iso-ajmalicine(CI) and akuammigine (CII)) as part of a study of alkaloid stereochemistry. Other examples of the use of this method are the oxidation of N-methylcorynantheidane and N-methyl-dihydrocorynantheane (CII



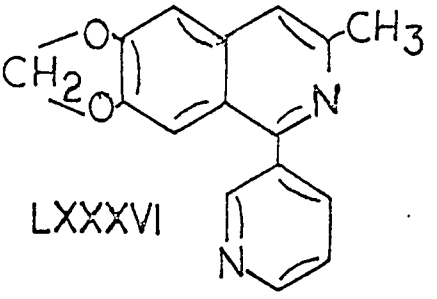
LXXXIII



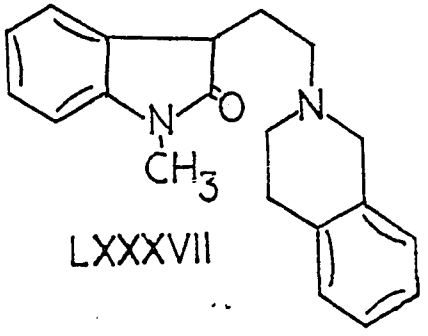
LXXXIV



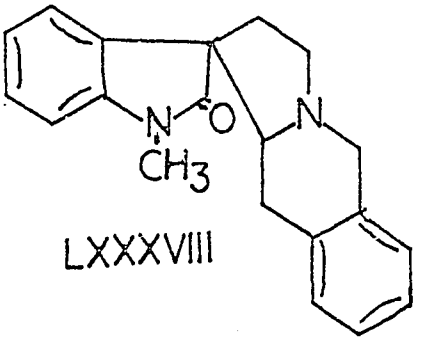
LXXXV



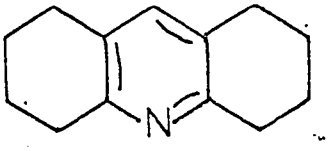
LXXXVI



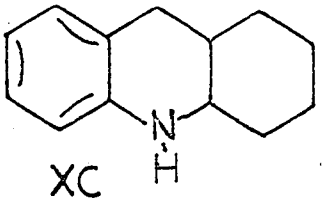
LXXXVII



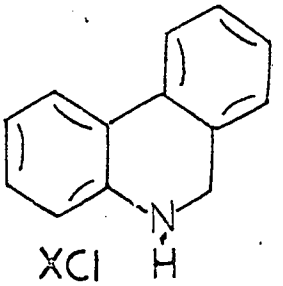
LXXXVIII



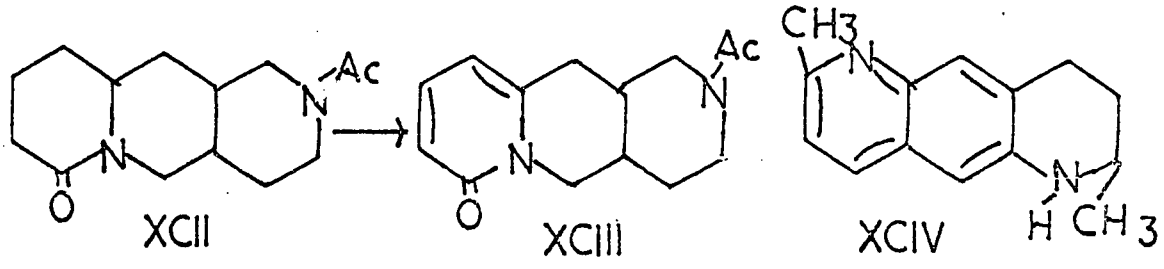
LXXXIX



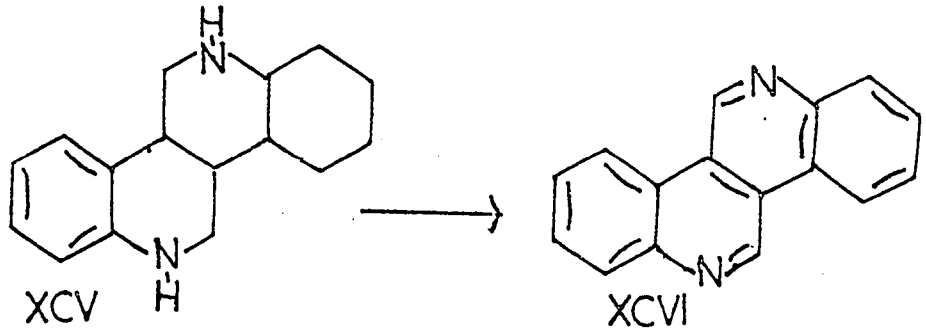
XC



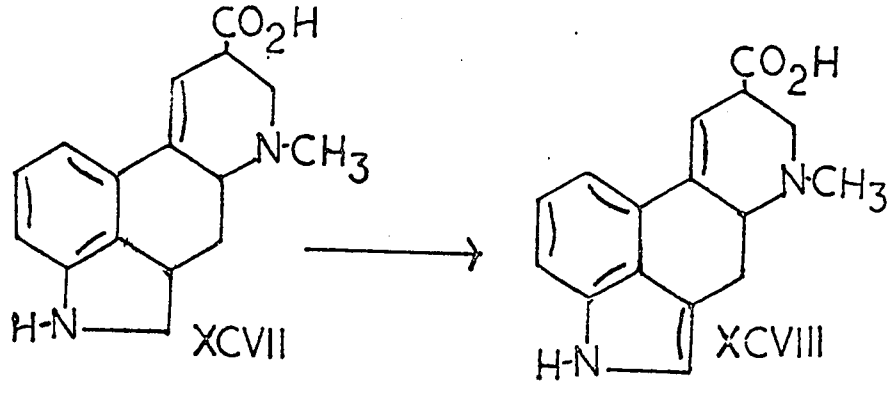
XCI



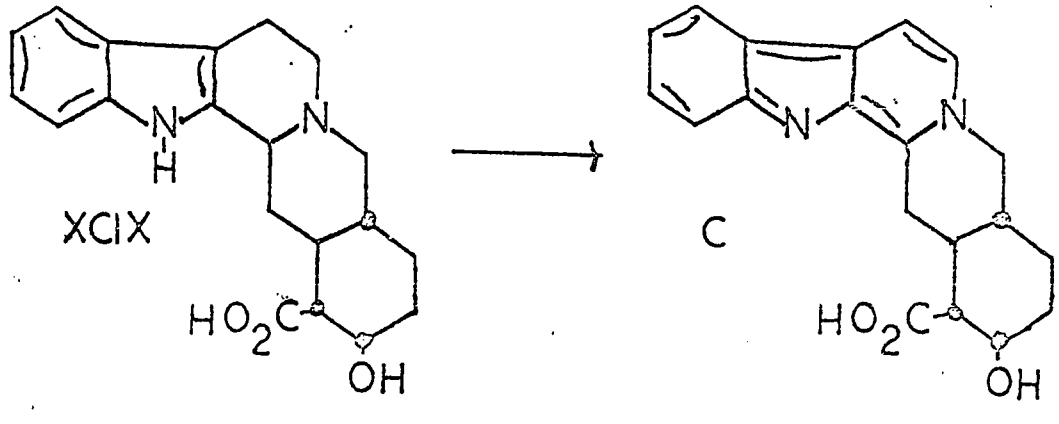
XCII XCIII XCIV



XCV XCVI



XCVII XCVIII



XCIX C

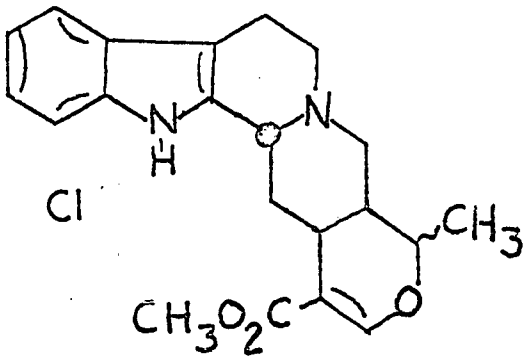
and CIV) to their tetradehydro derivatives (75) serpentinine (probable structure, (CV)) to a ring D tetradehydro compound (76) and ajmalicine (CVI) to the indoloquinolizinium compound flavoserpentine (CVII)(77).

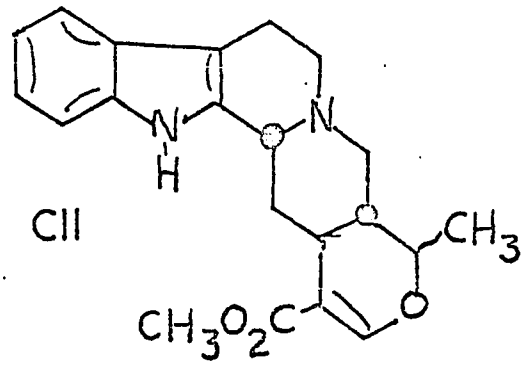
Witkop (78) employed oxygen as the hydrogen acceptor in the catalytic oxidation of N-methylyohimbane (CVIII) to the methyl-tetrahydrosempervirinium salt (CIX) but no further examples of this method have been recorded. Kobayashi (79) used cinnamic acid in acetic acid as the acceptor in an attempted synthesis of yobyrine (CX); the compound which he made (CXI) has since been shown not to be yobyrine (80).

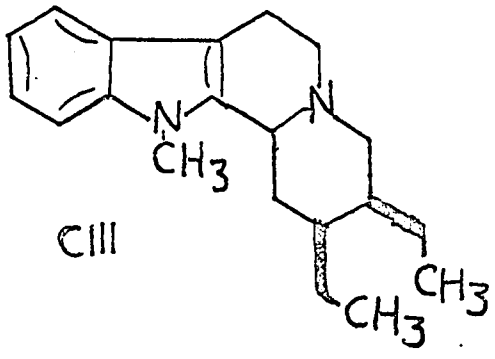
In an attempt to bridge the gap between the selectivity of the palladium-maleic acid reagent and the power of palladium itself, Kaneko (81,82) treated several compounds with palladium-on-carbon in refluxing para-cymene under carbon dioxide. Under these conditions, methyl reserpate (XLV,R=H) after five hours yielded 7-methoxyyobyrine (CXII) and py-tetradehydroreserpic acid lactone (CXIII) in a 7:1 ratio, yohimbine (XLVIII) after two hours yielded py-tetradehydroyohimbic acid (CXIV) as the sole product, and the quinolizinium chloride (CXV) after three hours yielded flavoserpentine (CVII).

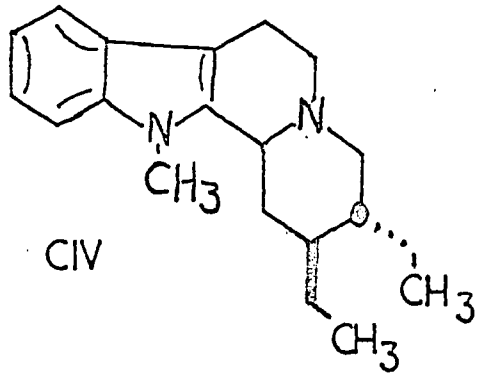
It was concluded that palladium-on-carbon in cymene is a milder reagent than palladium without solvent or than selenium, comparable in effect to lead tetraacetate, since after only two or three hours refluxing, rings D and E remain unaffected.

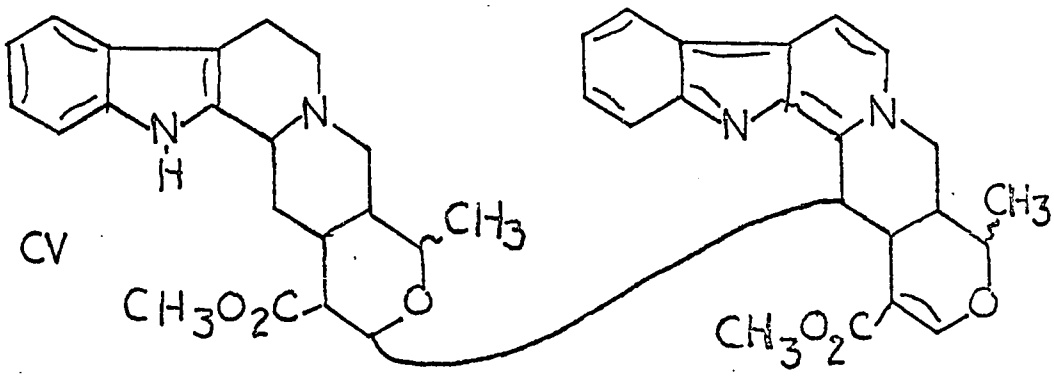
However, brief treatment with acidic palladium can produce similar results. In addition, the stereochemistry of the substrate can be employed in directing the course of the dehydrogenation. Thus, although

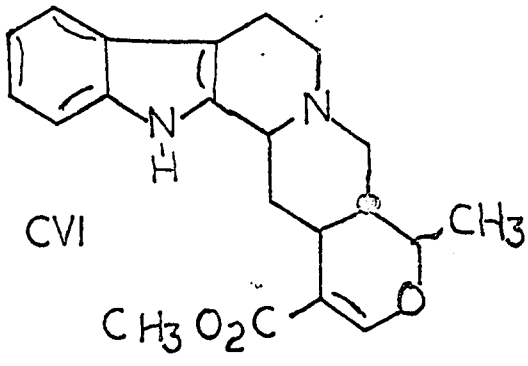

CI
N
H
N
CH3
CH3O2C
O

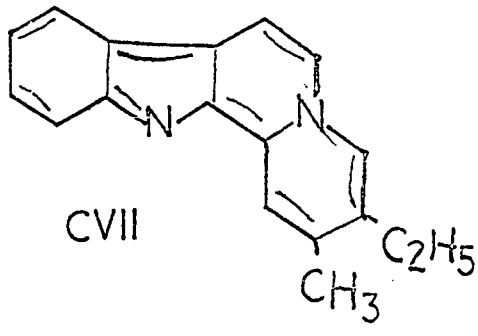

CII
N
H
N
CH3
CH3O2C
O


CIII
N
CH3
N
CH3
CH3


CIV
N
CH3
N
CH3
CH3


CV
N
H
N
CH3
CH3O2C
O
N
N
CH3
CH3O2C
O

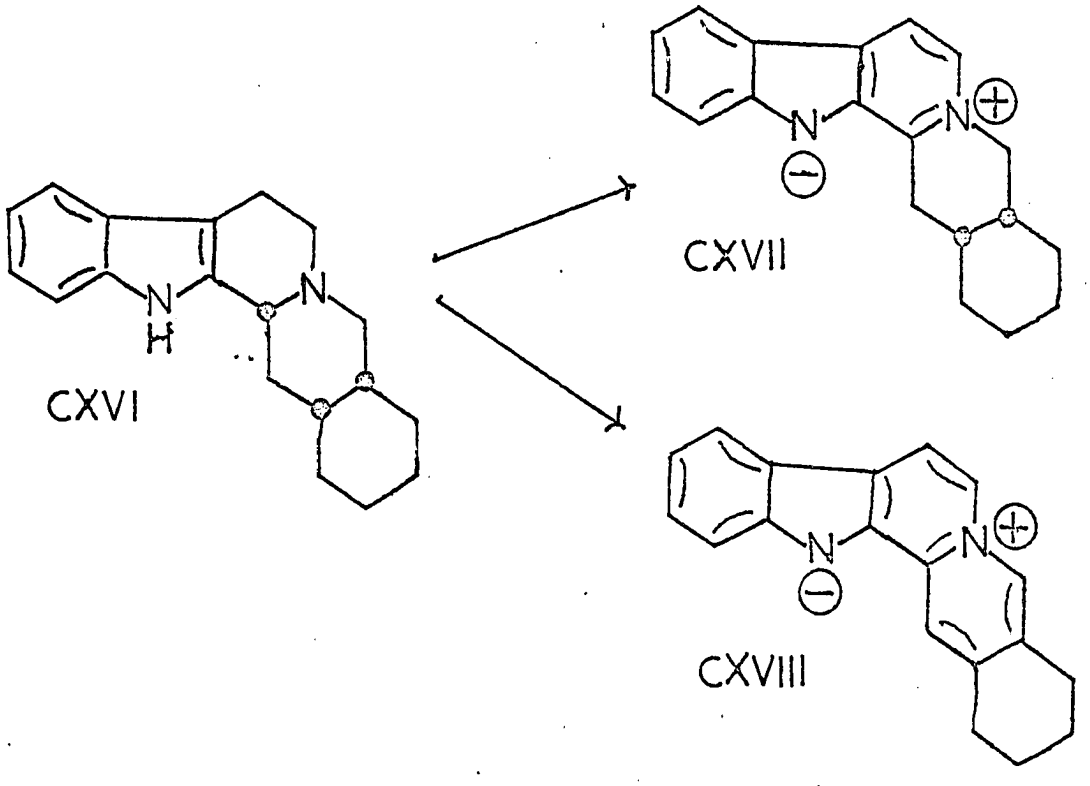

CVI
N
H
N
CH3
CH3O2C
O

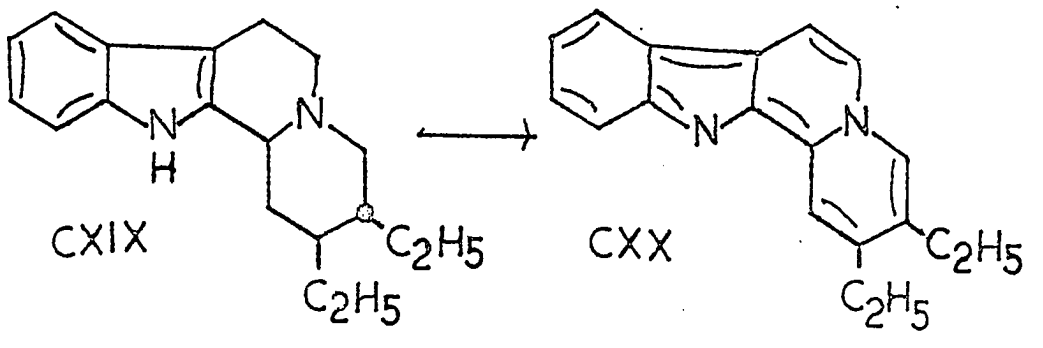

CVII
N
N
C2H5
CH3

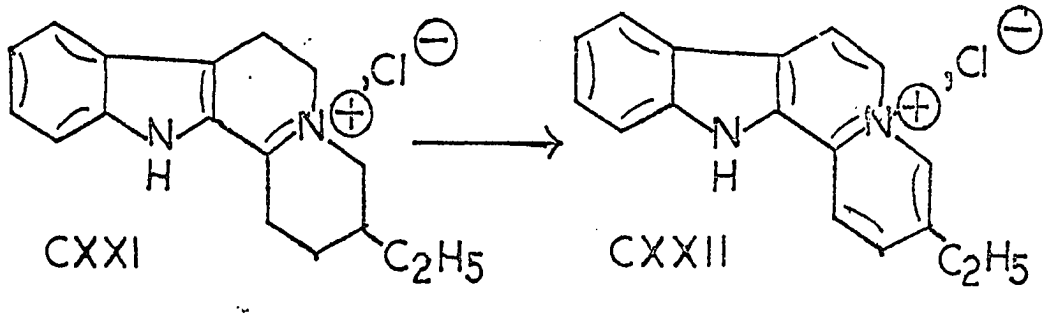
lead tetraacetate takes both yohimbane (CVIII) and alloyohimbane (CXVI) to their ring C tetradehydro derivatives (CIX and CXVII), treatment with acidified palladium for six minutes at 280°C. removed the hydrogens only from ring C of yohimbane CVIII) but from both ring C and ring D of alloyohimbane (CXVI), producing sempervirine (CXVIII)(83). Treatment of both compounds with neutral palladium produced yobyrine (CX)(83). In accordance with Witkop's observation (61) that cis decahydroisoquinolines are more readily dehydrogenated than the trans isomers, these results were adduced as proof of the stereochemistry of the two substances.

Acidic palladium (or neutral palladium employed with the amine hydrochloride) has also been used to produce flavocoryline (CXX) from both corynantheidane and dihydrocorynantheane (both CXIX)(84), and flavopereirine (CXXII) from the hexahydro precursor (CXXI) (7,8,12).

The use of neutral palladium catalysts on free base substrates seems invariably to lead to degradation in addition to dehydrogenation. Both corynantheidane and dihydrocorynantheane (CXXIII) are degraded to alstyrine (CXXIV)(9) as are dihydrodesoxydecarbomethoxygeissoschizine (CXXVI)(85) and desoxyajmaline (CXXV)(86). Desoxydihydroajmaline (CXXVII) is split to give a mixture of N-methylharmane (CXXVIII), ajarmine (CXXIX) and ajmyrine (CXXX)(87) by palladium-on-carbon at 250°C. — relatively mild conditions. Demethoxy-tetrahydrocorynantheine alcohol (CXXXI) is degraded to flavocorynanthyrine (CXXXII)(88,9). Serpentinine (CV) can be split and degraded to give desethyl alstyrine (CXXXIII)(89). Commenting on the fact that four isomeric yohimbines (type-structure XLVIII) were degraded over palladium-on-carbon to give high yields of yobyrine (CX), LeMen concluded


CXVI
CXVII
CXVIII


CXIX
CXX
C_2H_5
C_2H_5


CXXI
CXXII
C_2H_5
Cl

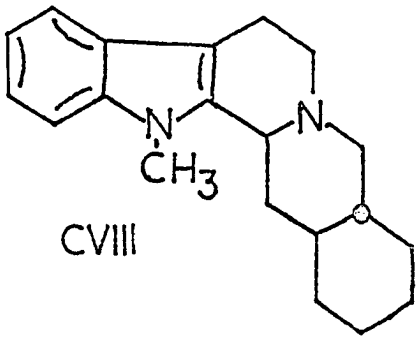
(90) that hydrogenated indole-cyclohexane-pyridocolines underwent ring C cleavage whereas hydrogenated dialkylpyridocolones underwent cleavage of ring D.

One instance of the use of thallous oxide as a dehydrogenating agent is recorded in the chemical literature. In this study yohimbic acid (XCIX) was converted to chanodesoxy-yohimbol by means of thallous oxide at 300°C. (CXXXIV)(91).

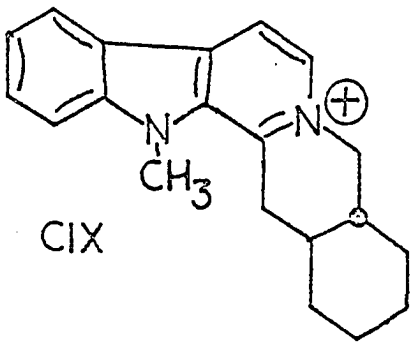
Neither of the metalloids selenium and sulfur is a catalyst since reaction intermediates or products including the metalloids can be isolated from reactions in which they are employed. Classically, however, they are discussed together with the noble metal catalysts because their effect on substrates is quite similar to the effect of the catalysts.

Simple piperidine rings have seldom been dehydrogenated with either sulfur or selenium. A variety of dihydropyridine esters (e.g., N-methyl-dihydro-γ-phenyl-lutidine-dicarboxylic esters, CXXXV) have been dehydrogenated to the corresponding des-N-alkyl pyridines (92) using sulfur at 215°C. Under similar conditions, a number of poly-substituted piperidines and hydroxypiperidines (e.g., 2,6-diphenylpiperidine) were dehydrogenated to their pyridines in yields of eighty-five to ninety-nine percent (93).

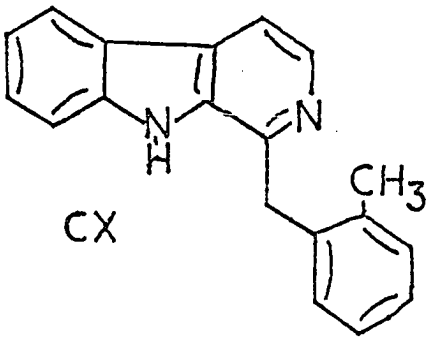
An interesting case of rearrangement during dehydrogenation was recorded by Prelog et al. (94). When 1-methyl-3-acetylpiperidine was treated with selenium at 300°C. in a sealed tube, the abnormal product 2.3-dimethylpyridine was isolated as the picrate. To show that this product was not simply due to a migration of the N-methyl, the starting material was reduced under the Wolff-Kishner conditions and the resulting



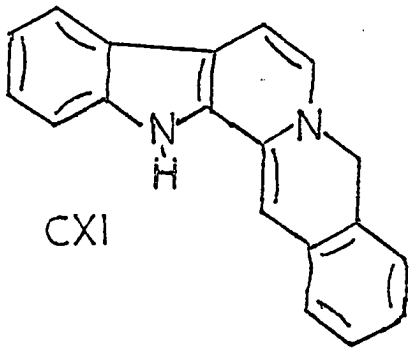
CVIII



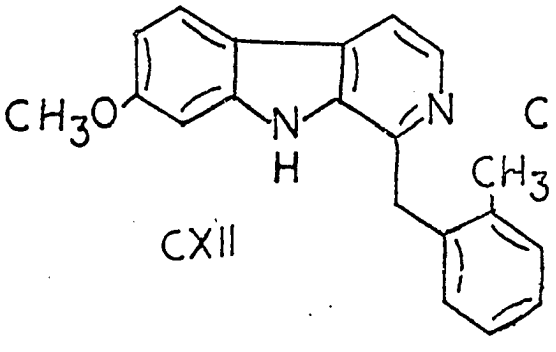
CIX



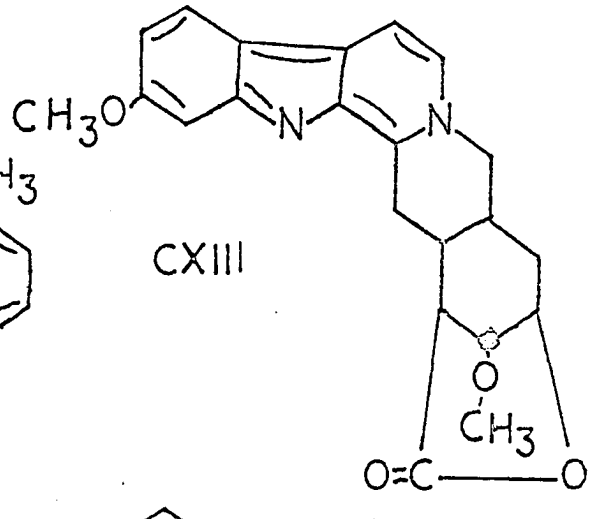
CX



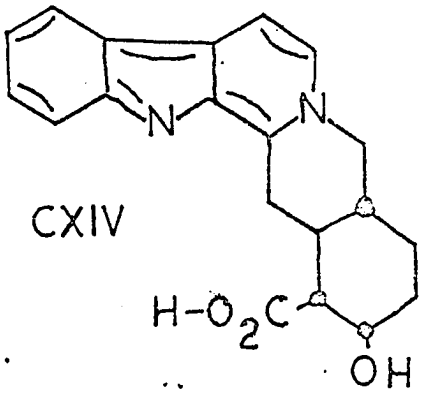
CXI



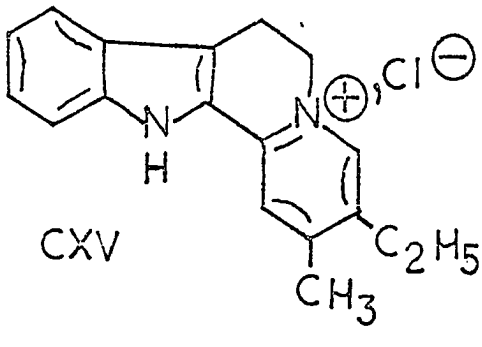
CXII



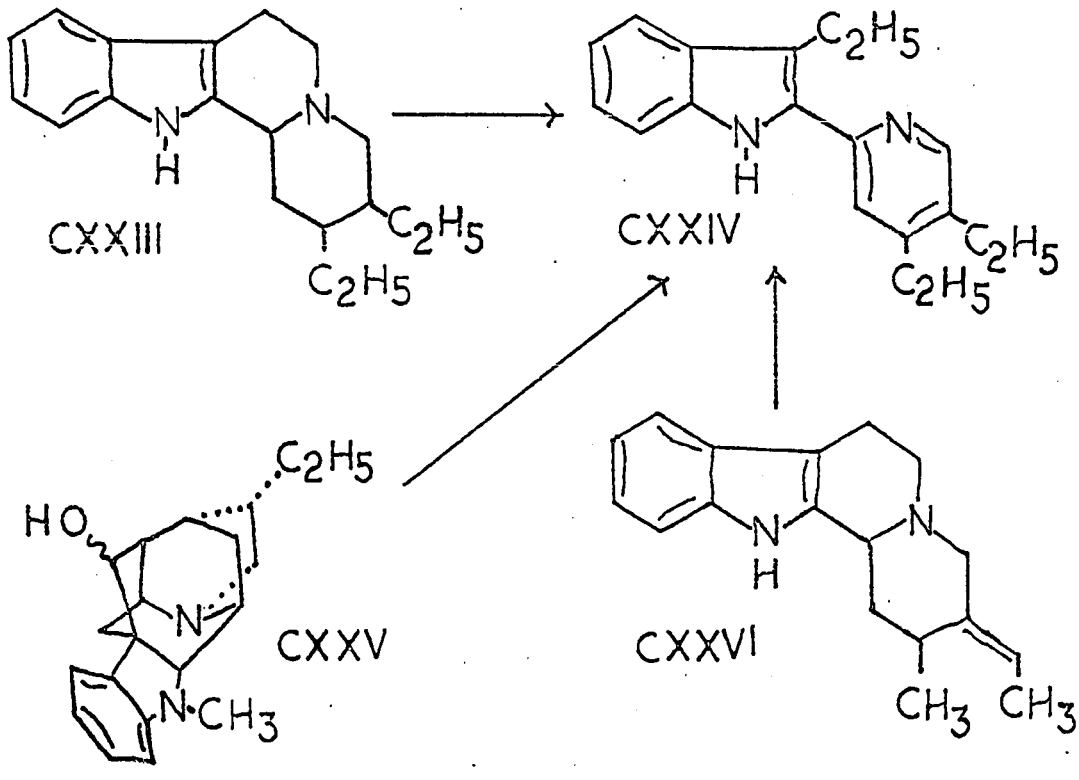
CXIII

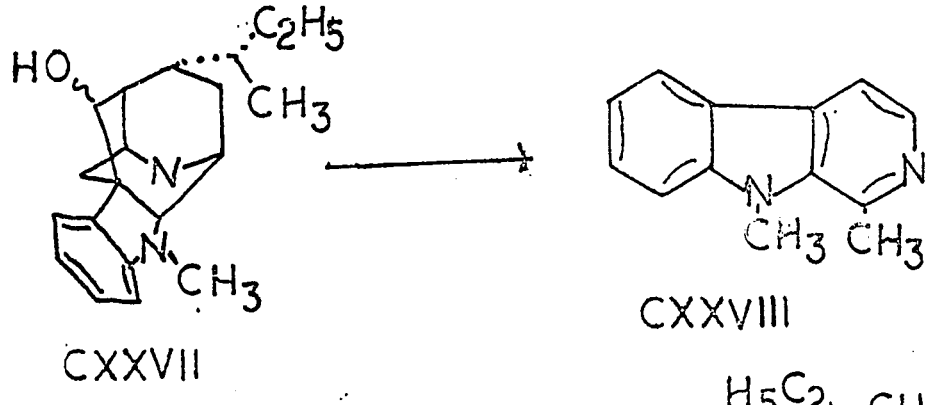


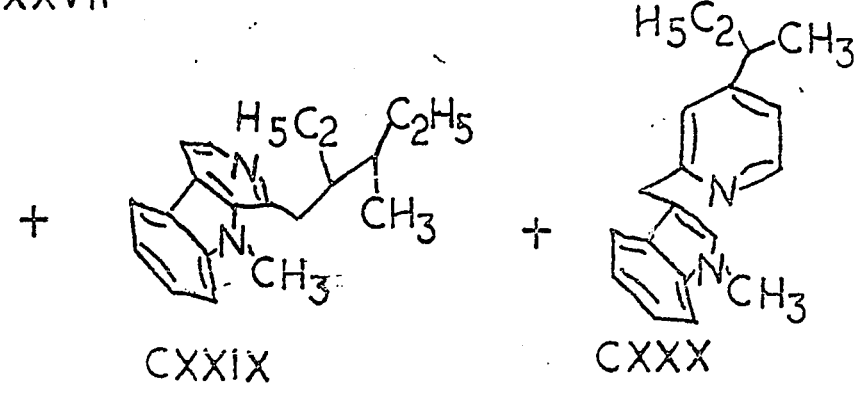
CXIV



CXV


CXXIII
CXXIV
CXXV
CXXVI

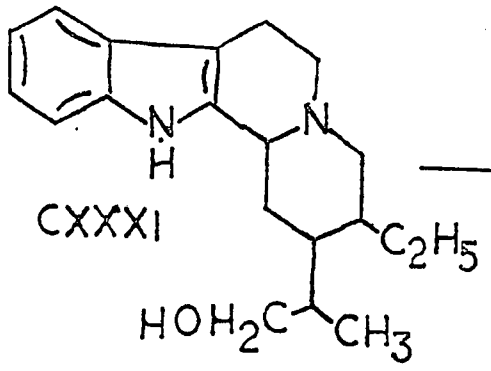

CXXVII
CXXVIII


CXXIX
CXXX

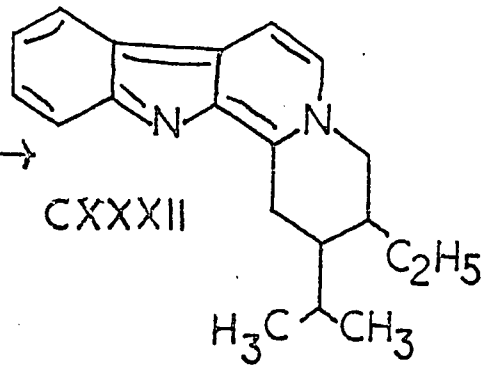
1-methyl-e-ethylpiperidine subjected to an identical dehydrogenation treatment. The product in this case was 3-ethylpyridine, characterized as the picrate. The mechanism depicted for this rearrangement is a modification of the Lipp reaction (95). In this reaction, a 1,3-disubstituted tetrahydropyridine rearranges and hydrolyzes in aqueous acid (CXXXVI to CXXXVII), then condenses with formaldehyde and recyclizes in a Mannich reaction (CXXXVII to CXXXIX). The reverse of such a sequence would be autocatalytic. Loss of the alpha proton (CXXIX to CXL) followed by hydrolysis (by traces of water initially present or formed by concurrent dehydration) leads to the ketone-aldehyde (CXLI) which can rearrange and cyclize to the quaternary tetrahydropyridinium ion (CXLII). Reduction, demethylation and dehydrogenation of this intermediate could give the observed product (CXLIII).

Selenium was also effective in dehydrogenating trans-decahydro-6-methylquinoline and alpha-methyl-octahydroindole to the respective quinoline and indole (96).

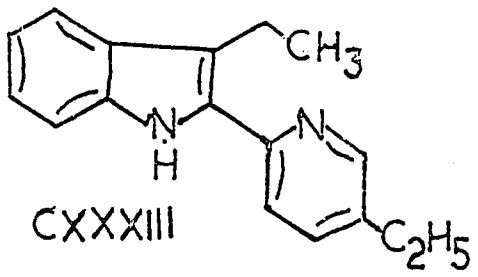
A large number of alkaloids which contain the nor-harmane nucleus (L) have been subjected to selenium dehydrogenation. In fact, this reaction is generally used as a diagnostic tool in structure determinations. If a given alkaloid yields yobyrine (CX) or a related compound, it is considered to have a yohimbine-type (XLVIII) skeleton. If an alkaloid yields alstyrine (CXXIV) or a related compound, it is felt to have an ajmalicine-type (e.g., 3-iso-ajmalicine, CI) skeleton. Thus, the following isomers of yohimbine yielded yobyrine when heated with selenium between 250 and 300°C.: yohimbine (97), ∝-yohimbine (rauwolscine, corynanthidine)(98,99),



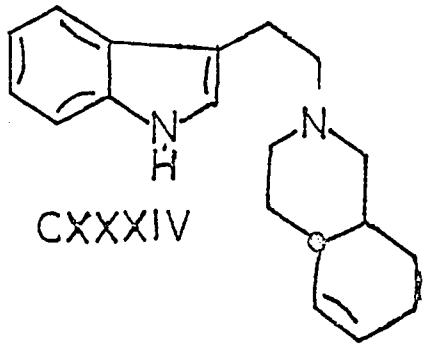
CXXXI



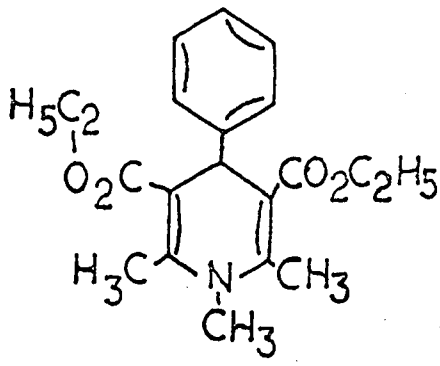
CXXXII



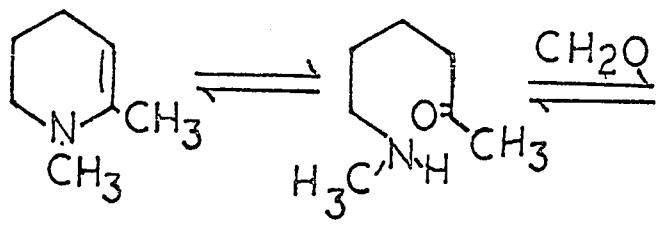
CXXXIII



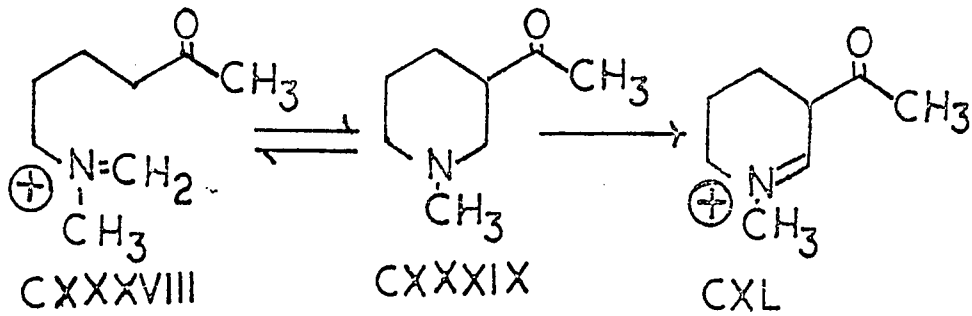
CXXXIV



CXXXV



CXXXVI CXXXVII



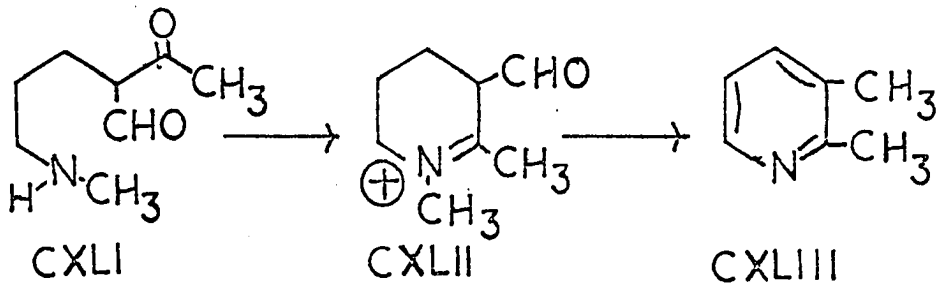
CXXXVIII CXXXIX CXL

β-yohimbine (26,100), ψ-yohimbine (25), 3-epi-α-yohimbine (isorauhimbine) (101,102), corynanthine (103). Yohimbyl alcohol (CXLIV)(104) and deserpidinediol (CXLVI, R=H)(105) both yield methyl-yobyrine (CXLVA) on selenium dehydrogenation due to the fact that the carboxyl group at C-16 has been reduced, and thus can no longer be lost through decarboxylation. Similarly, reserpinediol (CXLVI, R=OMe) yields the methoxylated methyl-yobyrine (CXLVB)(106). Sempervirine (IA) on heating with selenium yields N-methylyobyrine (CXLVA, NH=NMe)(107).

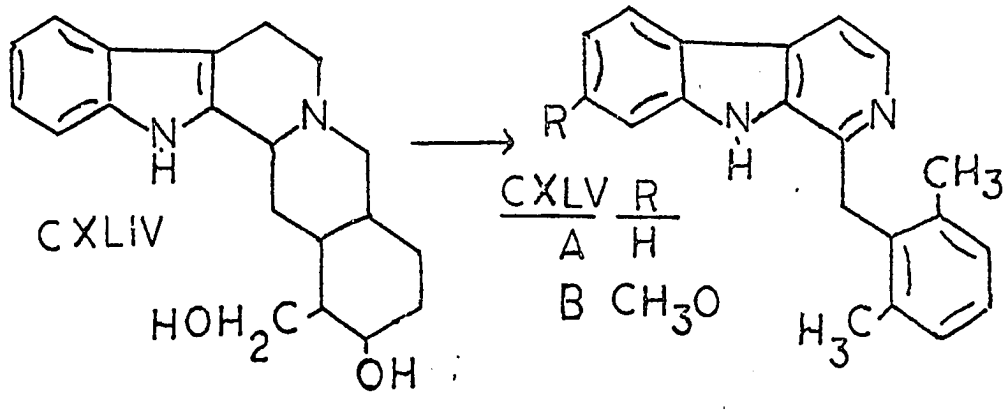
In addition to forming yobyrine on dehydrogenation, the yohimbine isomers also generally produce a small amount of keto-yobyrine (CXLVII). The mechanism underlying this observation is thought (102) to involve an initial cleavage of ring D between N-4 and C-21, followed by rotation of ring D to place the methyl group at the C-16 position and the carboxyl group at the C-21 position. If this mechanism is valid, the formation of keto-yobyrine therefore places the carboxyl group unequivocally at C-16 of the parent alkaloid.

Ring E heterocyclic indole alkaloids such as ajmalicine (CXLVIIIA) (δ-yohimbine, raubasine, tetrahydroserpentine) and ring E seco indole bases, such as corynantheine (CXLVIIIB) undergo cleavage of ring C on dehydrogenation to form alstyrine (CXXIV). Examples of such compounds are ajmalicine (108); mayumbine (109); alstonine (110); tetrahydro-alstonine (111); serpentine (112); aricine (113); akuammigine (114); serpentinine (115); corynantheine (116,117); tetrahydrodesmethoxycorynantheine alcohol (118); and dihydrodemethoxy-iso-geissospermine (85).

In addition, flavopereirine (IE) has been converted to desethylalstyrine (II) in excellent yield by boiling with selenium in

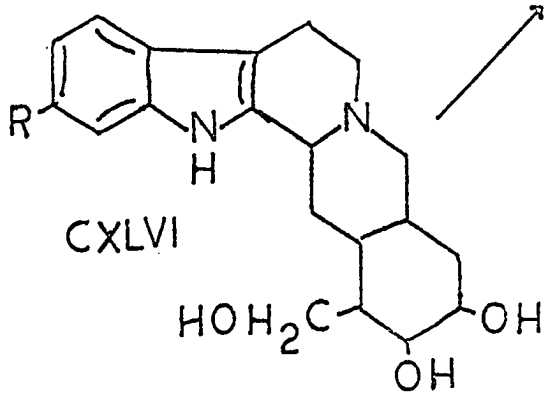


CXLI CXLII CXLIII

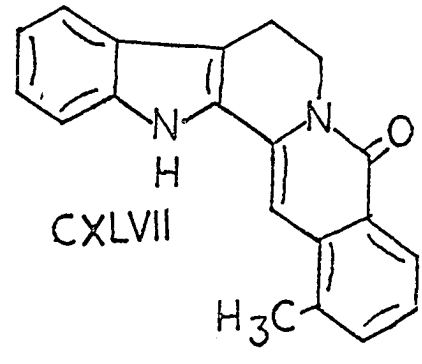


CXLIV

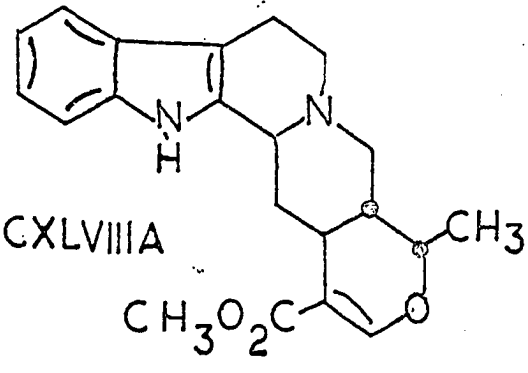
CXLV R
A H
B CH_3O



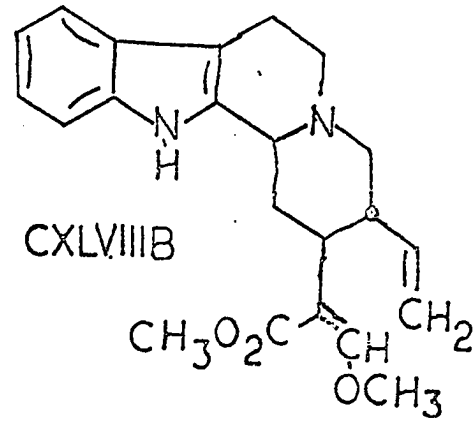
CXLVI



CXLVII



CXLVIIIA



CXLVIIIB

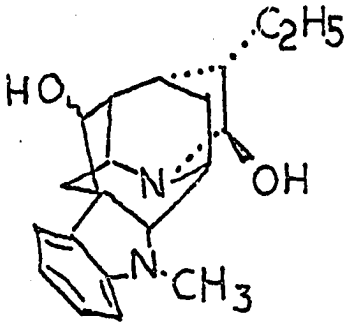
tetrahydroquinoline (6), ajmaline (CXLIX) to 9-methylharmane (CL) over selenium at 300°C. (119), and cryptolepine (CLI) to quindoline (CLII) under the same conditions (120).

Catalytic Formation of Carbon-Carbon Bonds by Dehydrogenation

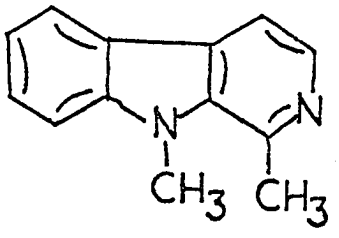
Although much study has gone into the mechanisms and yields of catalytic cyclodehydrogenation reactions, most of it involves hydrocarbons in operations on an industrial scale. Few studies involving a directed synthesis of carbon-carbon bonds have been reported.

When heptane was dehydrogenated at 475°C., both heptene and toluene are formed (121). The amount of heptene remained fairly constant whereas the amount of toluene increased with longer exposure to the catalyst.

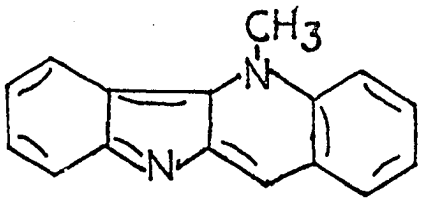
3-(2-Pyridyl)-1-propanol (CLIII) was converted to pyrrocoline (CLIV) in fifty percent yield by refluxing with palladium-on-carbon (122). The tetrahydro-dibenzophenanthrene (CLV) was cyclized and aromatized by refluxing with palladium-on-carbon, to give 1,12-benzoperylene (CLVI) in ninety-five percent yield (123). The related series of compounds diphenylmethane (CLVII), dicyclohexylmethane (CLVIII), dibenzyl (CLIX), dicyclohexylamine (CLX) and diphenylamine (CLXI) was subjected to platinum-on-carbon at 300°C. (124). Each member of the series yielded a corresponding cyclo-aromatic product (CLXII to CLXIV) in unspecified yields. Under these same conditions 1,3-diphenylpropane failed to cyclize (125). Below 300°C. dibenzyl also failed to cyclize. The yield of carbazole (CLXIV) from the aromatic precursor (CLXI) was lower than that from the saturated one (CLX) (124).



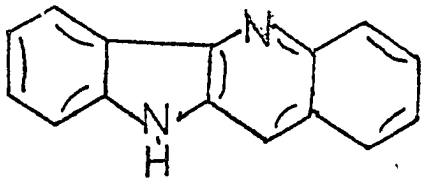
CXLIX



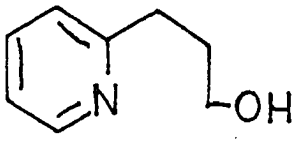
CL



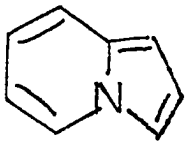
CLI



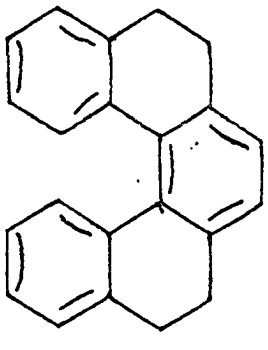
CLII



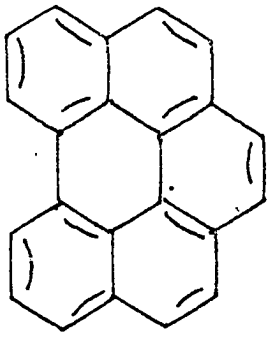
CLIII



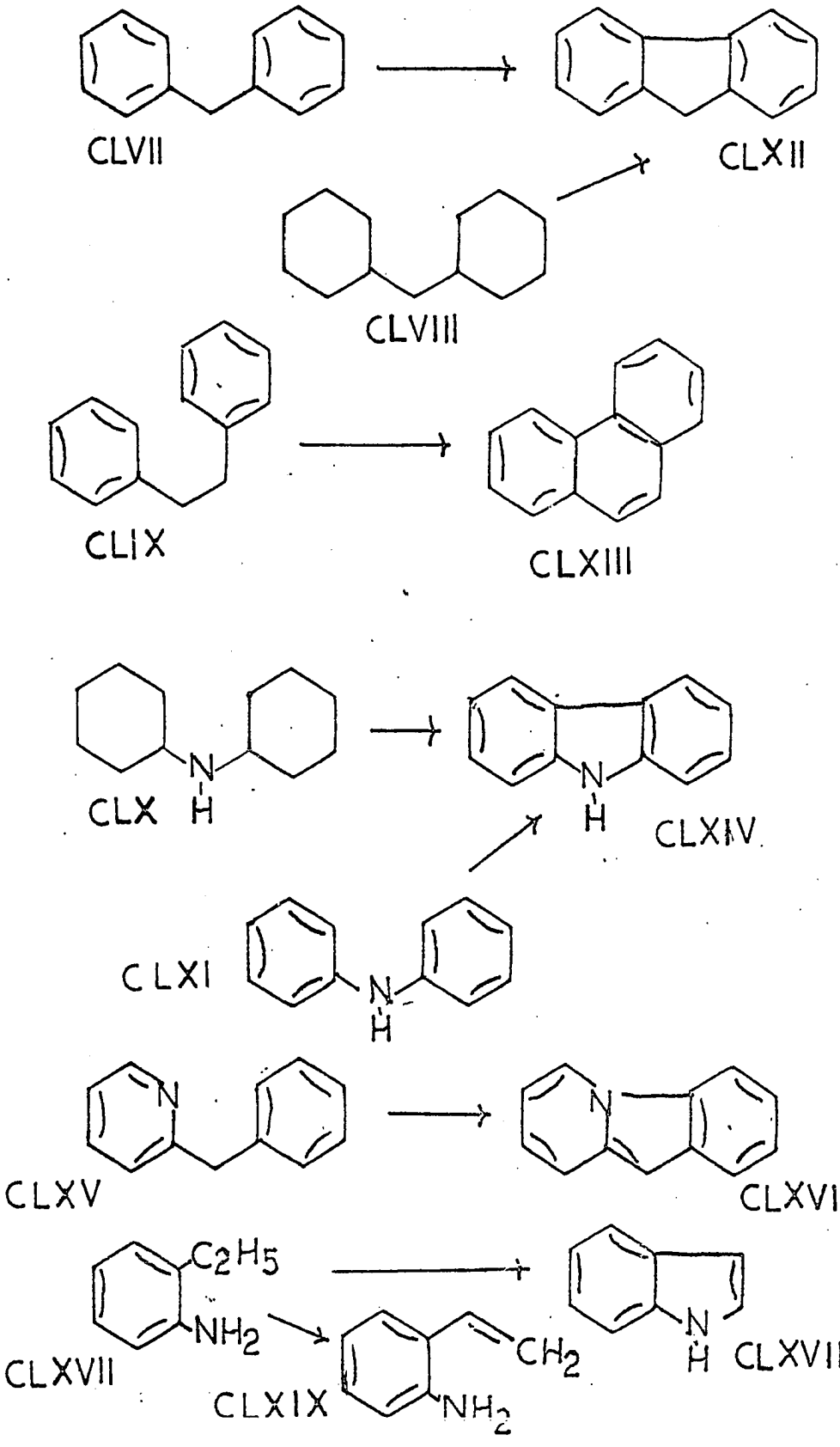
CLIV

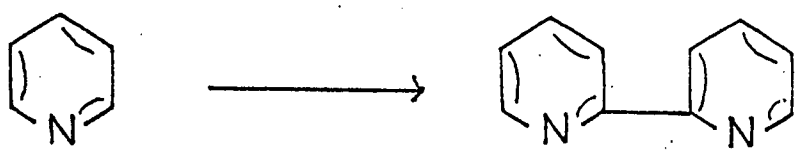


CLV

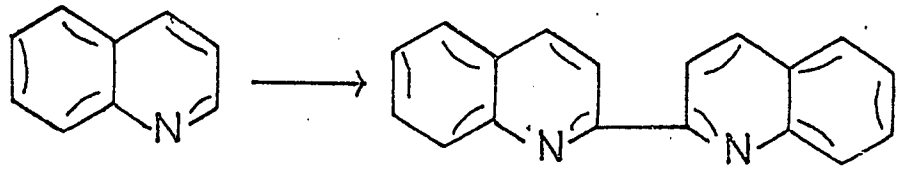


CLVI

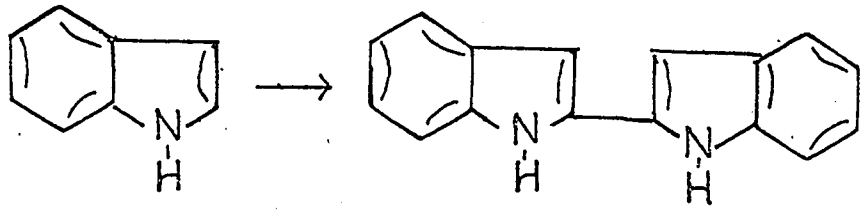

CLVII
CLXII
CLVIII
CLIX
CLXIII
CLX
H
CLXIV
CLXI
CLXV
CLXVI
C_2H_5
NH_2
CLXVII
CH_2
CLXIX
NH_2
CLXVIII



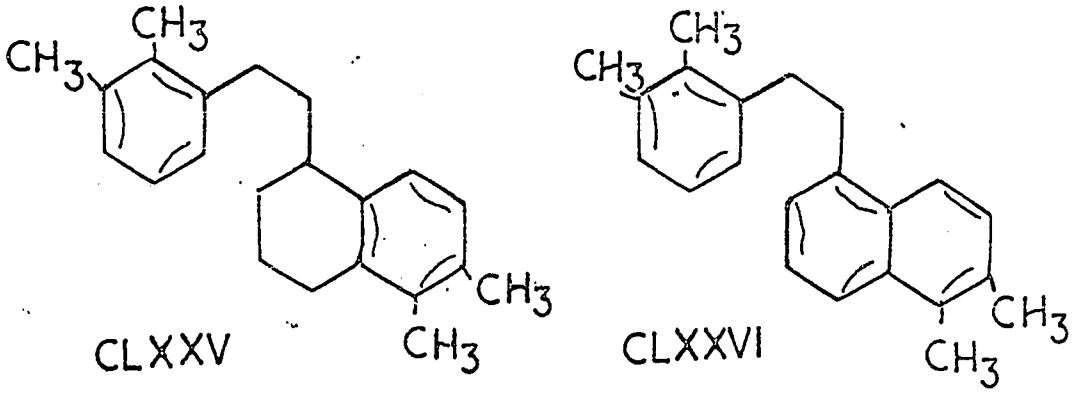
CLXX CLXXII



CLXXI CLXXIII



CLXVIII CLXXIV



CLXXV CLXXVI

2-Benzylpyridine (CLXV) was cyclized to the azafluorene (CLXVI) at 580°C. over copper turnings prereduced with hydrogen at 300°C. (126). Similarly, 2-ethylaniline (CLXVII) at 670°C. is cyclized to indole (CLXIII) over prereduced copper chromite-on-carbon in thirty-two percent yield (127), whereas at 560°C. 2-vinylaniline (CLXIX) is produced in sixty-five percent yield.

When the heterocycles pyridine (CLXX), quinoline (CLXXI) and indole (CLXVIII) were subjected to catalytic dehydrogenation (nickel-on-alumina at 320°C. for the first two, sulfur at 120°C. for the third) the corresponding dimers 2,2'-dipyridyl (CLXXII)(128), 2,2'-diquinolyl (CLXXIII) (129), and 3,3'-diindolyl (CLXXIV)(130) were formed in about fifteen percent yield.

In contrast to the above examples, the tetrahydro compound (CLXXV) gave only dehydrogenated product (1-(2,3-dimethylphenyl)-2-(1,2-dimethyl-5-naphthyl)-ethane, CLXXVI) on treatment with palladium-on-carbon at 370°C. (131).

EXPERIMENTAL

Melting points were determined on a Kofler melting point apparatus.

"Alumina" refers to commercial Al_2O_3 which was treated for two days with ethyl acetate, filtered, washed with water and methanol, and dried twenty-four hours under an infrared lamp.

"Cellulose" refers to Whatman cellulose powder ("Standard Grade").

Nitrogen gas was prepared from commercial tank gas by the method of Fieser (132, p. 299).

A Perkin-Elmer model 21 spectrophotometer, a Beckman model DK-2 spectrophotometer and a Varian Associates spectrometer recorded the infrared, ultraviolet and nuclear magnetic resonance spectra, respectively.

Synthesis of N-[β-(3-indolyl-)ethyl-]piperidine

The synthesis of Dr. B. Wickberg (Postdoctoral Fellow, Iowa State University, Ames, Iowa. Syntheses of indole bases. 1960) was followed.

Synthesis of Ethyl Indoleacetate

Indoleacetic acid (17.5 g., 0.1 mole) was dissolved in commercial absolute ethanol (100 ml.), 3 ml. concentrated sulfuric acid added and the solution refluxed overnight with partial azeotropic removal of water.

The cooled solution was neutralized with aqueous sodium bicarbonate and evaporated under vacuum to a small volume. The organic material was extracted into ether, the ethereal layer dried over anhydrous potassium carbonate, the mixture filtered and the ether distilled. The remaining

oil (15.8 g., 78% yield) was distilled under 0.5 mm. Hg pressure, the fraction distilling at 155-160°C. collected, chilled in Dry Ice until crystals appeared in the glassy product, and refrigerated until entirely crystalline. The resulting crystals melted 40-41°C. A sample for analysis was recrystallized from benzene.

Anal. Calcd. for $C_{12}H_{13}O_2N$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.89; H, 5.98; N, 6.86.

Unreacted indoleacetic acid (0.53 g.) was recovered by acidifying the sodium bicarbonate solution with dilute aqueous hydrochloric acid. Based on 17 g. of starting material, the yield of crystalline product (16.7 g.) was 82%.

Hitherto this compound had not been isolated as a crystalline solid.

Synthesis of Methyl Indoleacetate

Indoleacetic acid (5 g., 0.028 mole) was dissolved in 50 ml. of commercial absolute methanol and dry hydrogen chloride gas bubbled into the reaction vessel for twenty seconds. The flask was stoppered and allowed to stand overnight at room temperature.

After standing, the solvent and hydrogen chloride were removed under vacuum and the remaining oil dissolved in ether. This ether solution was washed until neutral with aqueous sodium bicarbonate solution, then with water, dried over anhydrous sodium sulfate and filtered. The ether was removed from the filtrate under vacuum and the residual oil used without further purification for the synthesis of the amide.

On repetition of this procedure, the oily product was distilled through Hickman-type still at 0.5 mm. Hg pressure and a bath temperature of 210°C. The distillate showed a refractive index of 1.5843 at 21.5°C. and a carbonyl absorption maximum (in chloroform) at 5.75μ. Based on the recovery of 0.2 g. of starting material, the yield of ester (3.2 g.) from 5 g. indoleacetic acid was 62%.

Synthesis of 3-Indoleacetyl Piperidine

Methyl indoleacetate from the preceeding step was dissolved in 25 ml. of piperidine dried over sodium hydroxide and the solution refluxed overnight under nitrogen.

The mixture was concentrated under vacuum on the steam bath, chloroform added and the solution extracted with dilute aqueous hydrochloric acid. The chloroform layer was washed with dilute aqueous sodium bicarbonate solution until neutral, then with water, dried over anhydrous sodium sulfate, filtered, and the solvent removed under vacuum. The product was an oil possessing amide carbonyl absorption at 6.08μ (in chloroform). The yield was 4.83 g., 71% from indoleacetic acid. All attempts at crystallization failed and it was reduced directly to the amine.

Synthesis of N-[β-(3-indolyl-)ethyl-]piperidine

3-Indoleacetyl piperidine (4.83 g., 0.02 mole) was dissolved in 200 ml. tetrahydrofuran (stored over sodium wire and distilled over lithium aluminum hydride directly into the reaction vessel) in a flame-dried apparatus under nitrogen. To this solution 2 g. (0.053 mole) of lithium aluminum

hydride was added and the mixture refluxed with stirring under nitrogen for four hours.

Excess hydride was destroyed by careful addition of a sodium sulfate-water slurry to the cooled reaction mixture, the mixture filtered and the filter cake washed with ether. The mixture of solvents was evaporated under vacuum from the product and ether added. This ethereal solution was washed with water and extracted with 1.5 N aqueous hydrochloric acid. The acidic layer was back-extracted once with ether, then neutralized with solid sodium bicarbonate followed by dilute sodium hydroxide solution. The liquid was then decanted from the precipitated solids and the solids washed with water until neutral.

The yield of dried solid was 2.86 g. (62%), m.p. 147-150°C. Crystallization from ethanol-water raised the melting point slightly to 148-150°C.

A sample of the solid was sublimed at 1 mm. Hg pressure and 140°C. bath temperature. It was identical in melting point (151-153°C.) and infrared spectrum (in chloroform) with an authentic sample of N-[β-(3-indolyl-)ethyl-]piperidine. A mixture of the two materials melted at 151-153°C.

Syntheses of 12H-Indolo[2,3-a]quinolizine Compounds

Synthesis of 5-Hydroxypentanal

The method of G. F. Woods, Jr. (134) was followed. The product boiling at 54°C. and 3 mm. Hg pressure was used. It exhibited an infrared absorption maximum at 2.75 μ and no maxima between 4.5 and 6.5 μ (in CCl_4).

Synthesis of 1,2,3,4-Tetrahydro-12H-indolo/2,3-a/- quinolizinium Salts

Except for the purification of product on a cellulose column, the preparation of the hydrobromide salt followed the procedure of Groves and Swan (135).

A mixture of 5-hydroxypentanal (1 g., 0.01 mole) and tryptamine hydrochloride (1 g., 0.0051 mole) in 20 ml. of water was stirred under nitrogen for two days at a bath temperature of 44°C.

The reaction mixture was cooled, basified with 10% aqueous sodium hydroxide solution and extracted with ether. The ether extract was dried over anhydrous potassium carbonate, filtered and the ether evaporated under vacuum.

The residual material was dissolved in methanol and treated with anhydrous hydrogen chloride gas. After the addition of palladium-on-charcoal (5%, 2 g.) and further treatment with hydrogen chloride, the mixture was freed of methanol under vacuum. The reaction mixture was flushed with nitrogen and heated under nitrogen at 200°C. for six minutes and cooled. This dehydrogenation mixture was extracted overnight with boiling methanol, and the solvent removed from the extract under vacuum.

To the resultant gum, 25 ml. of 48% aqueous hydrobromic acid was added and the mixture refluxed forty minutes.

This reaction mixture was freed of water and excess hydrobromic acid and under vacuum on the steam bath and the tarry residue dissolved in chloroform and a small amount of methanol. The mixture was made strongly basic by the addition of 10% aqueous sodium hydroxide solution and extracted with chloroform until no further yellow color appeared in the

chloroform layer. The combined chloroform extracts were washed once with water and dried over anhydrous potassium carbonate. These extracts were filtered and glacial acetic acid was added dropwise until no further color change occurred. Solvent and excess acetic acid were removed under vacuum.

The residue was taken up in a small volume of dry chloroform and chromatographed on a column of 15 g. of cellulose which had been slurried in dry chloroform with 5.6 ml. of 0.05 M aqueous acetic acid. Fifty ml. fractions were collected and to each beaker a few ml. of approximately 2N aqueous hydrobromic acid solution were added to prevent air oxidation of free bases.

Tars were eluted with wet Skellysolve B-chloroform. Elution with wet chloroform-n-butanol (4:1, v:v) and evaporation of the solvent and excess hydrobromic acid yielded pale yellow needles. Crystals of fraction 31 melted 278-281°C. The literature value for the melting point of 1,2,3,4-tetrahydro-12H-indolo[2,3-a]quinolizinium bromide (135) is 280°C. (dec.). A test amount of the perchlorate salt, formed in glacial acetic acid containing 10% of 70% perchloric acid melted at 233-235°C. After three recrystallizations from ethanol it melted at 241-246°C.

Crystals from fractions 30 to 32 were combined and recrystallized from methanol-acetone: m.p. 283-284°C., yield 43.0 mg.

Solids from fractions 25 to 29 were combined, converted to the perchlorate as above and recrystallized from n-propanol: m.p. 235-237°C., yield 26.8 mg. Total yield of tetrahydroquinolizinium salts, 4.5% (based on 1 g. of tryptamine hydrochloride).

An analytical sample of the perchlorate was recrystallized from water (using decolorizing charcoal) and then from n-propanol. After drying overnight under high vacuum at 80°C. it melted at 242-247°C.

I. R. Spectrum (KBr pellet): Figure 1.

U. V. Spectrum (95% ethanol), λmax. (log E): 252 mμ (4.53), 306 (4.27), 365 (3.65).

Anal. Calcd. for $C_{15}H_{15}O_4ClN_2$: C, 55.82; H, 4.69; N, 8.68. Found: C, 55.74; H, 4.78; N, 8.75.

Synthesis of 12H-Indolo[2,3-a]quinolizinium Salts

1,2,3,4-Tetrahydro-12H-indolo[2,3-a]quinolizinium bromide (9.9 mg., 32.7 micromoles) was intimately mixed with 20 mg. 5% palladium-on-charcoal catalyst which had been washed with dilute aqueous hydrobromic acid, then water, and dried. The mixture was heated for nine minutes under nitrogen at 300°C.

The resulting mixture was cooled and extracted repeatedly with methanol to which a few drops of glacial acetic acid were added, until the extracts remained colorless. The extracts were combined and evaporated under vacuum, whereupon crystals melting at 267-272°C. formed. The mixed residue was taken up in a small volume of chloroform and chromatographed on a column of 4 g. of cellulose which had been slurried in dry chloroform with 1.3 ml. of a 0.05M aqueous acetic acid solution. Dilute aqueous hydrobromic acid was added to each fraction as it was collected to prevent air oxidation of free bases.

Elution with wet chloroform-n-butanol (5:1 by volume) yielded less than one milligram of solid: m. p. of picrate, 250-252°C. (literature

value of m. p. of 12H-indolo[2,3-a]quinolizinium picrate, 252-253°C. (8)).

Synthesis of 1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-a]quinolizine

1,2,3,4-Tetrahydro-12H-indolo[2,3-a]quinolizinium bromide (11.1 mg., 36.7 micromoles) was mixed with sodium borohydride (36 mg., approximately 4 milli-equivalents) in 5 ml. methanol. The mixture was allowed to stand at room temperature two and one-half hours.

On removing solvent under vacuum, dissolving the residue in a mixture of chloroform and aqueous sodium hydroxide, washing the chloroform layer with water and drying over anhydrous potassium carbonate, filtering and removing solvent, crystals were obtained from methanol which melted 280-295°C. This crystalline material was combined with its mother liquors, the solvent removed under vacuum and the combined material reduced again in methanol-water using a gross excess of sodium borohydride. The reduction mixture was refluxed for two hours after addition of all sodium borohydride, cooled, and solvents removed under vacuum. Treatment of the gummy residue with chloroform-aqueous sodium hydroxide, followed by washing, drying, filtering and evaporating solvent as above yielded a solid melting over a wide range (125-140°C.). Sublimation of this solid raised its melting point range to 138-148°C. and crystallization from Skellysolve B raised it to 149-151°C. Its mixed melting point with an authentic sample of the octahydroquinolizine compound was 149-151°C. The infrared spectrum (in chloroform) of this material was identical with that of the authentic compound. The literature value of the melting point of this compound as given by several groups of workers (135,136,8) falls between 149 and 153°C. Yield: 3.2 mg., 38.6%.

Investigations of Dehydrogenations Catalyzed by Palladium-on-Charcoal

The feasibility of using palladium-catalyzed dehydrogenation as a method of ring-closure as well as the optimum conditions for the reaction were investigated in a series of one milligram runs. The following description is of typical runs.

Preliminary Dehydrogenations of N-[β-(3-indolyl-)ethyl-]piperidine

N-[β-(3-indolyl-)ethyl-]piperidine (10 mg.) was dissolved in 10 ml. of ether and one ml. aliquots of this solution were transferred quantitatively into micro-cones by the use of ether. The appropriate catalyst was added (approximately 1 mg. of palladium black or 2 mg. of 5% palladium-on-charcoal) and the two substances mixed intimately. A drop of methanol was added and anhydrous hydrogen chloride gas was bubbled through the pasty mass.

The resulting mixture was stripped of solvent, blanketed in an atmosphere of dry nitrogen from a hypodermic needle and heated in a Wood's metal bath according to the following scheme:

Run	Time, min.	Temperature, °C.	Catalyst
1	12	255-260	Pd
2	25	255-260	Pd
3	14	295-305	Pd
4	25	295-305	Pd
5	12	255-260	Pd/C

Run	Time, min.	Temperature, °C.	Catalyst
6	25	255-260	Pd/C
7	14	295-305	Pd/C
8	25	295-305	Pd/C

Each sample was allowed to cool under nitrogen. The reaction mixture was transferred to a 10 ml. volumetric flask with the aid of 95% ethanol, a drop of 6N aqueous hydrochloric acid solution added, and the flask filled to the mark with 95% ethanol.

These flasks were allowed to stand for at least one hour. The contents of each was decanted in turn into a U. V. spectrophotometer cell and the absorption measured in the region of 200 mμ to 420 mμ.

The results are shown in figure 2.

The results of the preliminary dehydrogenation studies are tabulated below. The relative absorption values are most significant within a single series. Between two series, two runs employing similar conditions, one from each series, should be used as the basis for comparison; slight differences in weights between different series prevent exact comparisons.

Series A

Amount of substrate: 1 mg.

Catalyst: 5% Pd/C., approx. 3 mg.

Temperature: 300-305°C.

Treatment: Runs 1-3: free base, commercial untreated catalyst

Runs 4-6: substrate and catalyst treated with anhydrous HCl gas

Atmosphere: nitrogen

Run	Time, min.	Relative Absorption at 306 mμ	345 mμ	366 mμ	388 mμ
1	2	0.39	0.12	0.14	0.9
2	4	0.125	0.1	0.09	0.07
3	8	0.37	0.17	0.17	0.14
4	1	0.20	0.06	0.04	0.02
5	4	0.32	0.29	0.2	0.22
6	8	0.61	0.87	0.66	0.65

Series B

Substrate, Catalyst, Temperature: as in Series A

Treatment: anhydrous HCl gas added to all samples

Atmosphere: air

Run	Time, min.	Relative Absorption at 306 mμ	345 mμ	366 mμ	388 mμ
1	6	0.01	0.01	0.0	0.0
2	7	0.02	0.01	0.0	0.0
3	9	0.02	0.01	0.0	0.0
4	19	0.01	0.0	0.0	0.0

Series C

Substrate, Catalyst, Temperature, Treatment: as in Series B

Atmosphere: nitrogen

Extraction: Runs 1-4: glacial acetic overnight, centrifuge, decant, remove solvent.

Runs 5-8: glacial acetic acid plus a drop of benzene for two hours, centrifuge, decant, remove solvents.

Run	Time, min.	Relative Absorption at 306 mμ	345 mμ	366 mμ	388 mμ
1	6	0.03	0.01	0.01	0.0
2	7	0.10	0.14	0.10	0.10
3	8	0.20	0.29	0.21	0.20
4	10	0.20	0.29	0.21	0.21
5	8	0.29	0.36	0.27	0.25
6	10	0.34	0.42	0.31	0.29
7	12	0.42	0.52	0.38	0.36
8	21	0.27	0.32	0.23	0.22

Series D

Substrate: 3 mg.

Catalyst: Runs 1-4: 5% Pd/C, approx. 2 mg.

Runs 5-8: Pd black, approx. 1 mg.

Treatment: 1 mg. K_2CO_3 added

Run	Time, min.	°C. Temp.	Relative Absorption at 306 mμ	345 mμ	366 mμ	388 mμ
1	12	260	0.23	0.25	0.20	0.18
2	24	260	0.22	0.20	0.17	0.14

Run	Time, min.	°C. Temp.	Relative Absorption at 306 mμ	345 mμ	366 mμ	388 mμ
3	12	300	0.06	0.05	0.04	0.03
4	24	300	0.12	0.05	0.04	0.03
5	12	260	0.15	0.05	0.03	0.02
6	24	260	0.16	0.06	0.04	0.02
7	12	300	0.08	0.03	0.02	0.0
8	24	300	0.06	0.02	0.01	0.0

(Note: quantities of white vapor were evolved in all runs of Series D; the spectra of runs 5 and 6 were identical with that of the starting material; run 6 showed three-fourths of the 280 mm. absorption of run 5.)

Series E

Amount of Substrate: 1 mg.

Catalyst: 5% Pd/C. approx. 2 mg.

Treatment: 1 drop 6N HCl

Atmosphere: nitrogen

Run	Time, min.	°C. Temp.	Relative Absorption at 306 mμ	345 mμ	366 mμ	388 mμ
1	12	240	0.80	0.96	0.48	0.36
2	24	240	0.64	0.28	0.24	0.16
3	36	240	0.64	0.36	0.33	0.24
4	12	270	1.04	0.60	0.56	0.40
5	24	270	0.44	0.31	0.28	0.19

Run	Time, min.	°C. Temp.	306 mμ	345 mμ	366 mμ	388 mμ
6	36	270	0.84	0.38	0.31	0.27
7	12	300	0.25	0.29	0.24	0.20
8	24	300	0.95	0.86	0.70	0.64
9	36	300	0.78	0.80	0.63	0.57

Large-Scale Dehydrogenation of N-[β-(3-indolyl-)ethyl-]piperidine

N-[β-(3-indolyl-)ethyl-]piperidine (500 mg., 1.77 mmoles.) was dissolved in a minimum amount of methanol and anhydrous hydrogen chloride gas passed into the solution until it was saturated. The palladium-on-charcoal catalyst (5%, 1 g.) was added cautiously. (Note: methanol ignited spontaneously several times as the catalyst was poured into the flask; other solvents which did not ignite — ether, chloroform — were less desirable because of the lower solubility of the substrate or hydrogen chloride in these.) After evaporation of the solvent under vacuum, the flask was purged with dry nitrogen for several minutes. A constant pressure of nitrogen was then maintained over the contents of the flask while it was immersed in a Wood's metal bath heated between 295-305°C. Strong evolution of vapor occurred between four and eight minutes of heating. The flask was heated for twenty minutes.

The flask was cooled under nitrogen and its contents transferred to an extraction thimble. The solids were extracted continuously for

eighteen hours with commercial anhydrous methanol to which a few ml. of glacial acetic acid had been added.

Solvents were removed under vacuum from the resulting yellow extract and the residue treated with a mixture of 10% aqueous sodium hydroxide and chloroform. The aqueous layer was extracted repeatedly with chloroform until the lower layer remained colorless. The chloroform extracts were combined, washed once with water, dried over anhydrous potassium carbonate and filtered. Glacial acetic acid was added to the filtrate, and the solvent and excess acetic acid evaporated under vacuum on the steam bath. (All operations on the mixture of free bases were carried out as quickly as possible to prevent air oxidation of the tetrahydro compound.

The residual yellow mixture of gum and crystals was taken up in a minimum amount of chloroform and chromatographed on a column of 33 g. of cellulose which had been slurried in chloroform with 11 ml. of a solution of glacial acetic acid in water (1% by volume). Fifty ml. fractions were collected. As each fraction was collected, it was treated with a few ml. of dilute aqueous hydrochloric acid to prevent air oxidation of the bases.

The column was eluted with a series of wet solvents, starting with Skellysolve B, then Skellysolve B-chloroform and pure chloroform, until the tars had been eluted. Then a series of chloroform-n-butanol solvents, saturated with water and containing increasing amounts of n-butanol was employed. Chloroform-n-butanol (2.5:1, v:v) eluted solid material in fractions 34 to 37 and 43 to 68.

Fractions 34 to 37 showed the ultraviolet absorption characteristic of tetrahydroquinolizinium salts. The fractions were combined, the wash

solvent (methanol) evaporated, and the perchlorate salt formed by the addition of water, a few drops of glacial acetic acid and dropwise 10% aqueous sodium perchlorate solution until precipitation was complete. Crystallization of the resulting precipitate from aqueous ethanol gave cream-colored crystals melting 242-246°C. A mixture with an authentic sample of 1,2,3,4-tetrahydro-12H-indolo[2,3-a]quinolizinium perchlorate melted at 241-246°C. Ultraviolet and infrared absorption curves were identical.

Fractions 43 to 68 showed the ultraviolet absorption characteristic of the wholly aromatized quinolizine ring system. These fractions were combined with methanol, the solvent evaporated to a small volume, and the solution divided into two parts. One half was treated dropwise with a saturated solution of picric acid in methanol until precipitation was complete, and the crystals filtered. Crystallization from absolute ethanol gave crystals melting at 248-251°C., unchanged by admixture with authentic crystals of 12H-indolo[2,3-a]quinolizinium picrate. The second half was heated and ether added to the cloud-point. Cooling overnight produced long needles, which were filtered from the mother liquors and dried under vacuum at 80°C. for three hours, m. p. 291-296°C. (dec.) The literature value for the melting point of 12H-indolo[2,3-a]quinolizinium chloride is 295°C. (dec.)(8). The ultraviolet spectrum of the hydrochloride in 95% ethanol was identical with that recorded in the literature: λmax. (logϵ): 244 mμ (4.43), 294 (4.18), 345 (4.27), 388 (4.10)(8).

The yield of recrystallized tetrahydro perchlorate was 48 mg., 8.4%; of recrystallized picrate: 20.9 mg., 4.67%; of recrystallized hydrochloride, 10.3 mg., 4.05%; total yield of cyclized material, 17.1%.

Large-Scale Dehydrogenation of 1-[β-(3-indolyl-)ethyl-]3-ethylpiperidine

1-[β-(3-Indolyl-)ethyl-]3-ethylpiperidine (m. p. 112-113-5°C.) was dehydrogenated over 5% palladium-on-charcoal catalyst using the same amounts of substrate and catalyst and the same conditions as were employed in the previous procedure.

The cooled reaction flask was washed once with benzene to remove a tarry sublimate. The dry solids were then extracted continuously overnight with commercial anhydrous methanol with several ml. of glacial acetic acid added. Solvents were removed from the resulting fluorescent yellow solution under vacuum and the residue dissolved in a mixture of chloroform and 3N aqueous potassium hydroxide. The deep orange lower layer was separated and the aqueous layer extracted exhaustively with chloroform. After the combined organic extracts were washed, dried over anhydrous sodium sulfate and filtered, glacial acetic acid was added dropwise until the bright orange color was discharged.

Solvent and excess acetic acid were removed under vacuum with gentle heating and the residue transferred with a minimum volume of chloroform to a chromatographic column prepared from 33 g. of cellulose and 11 ml. of dilute aqueous acetic acid solution (1% by volume) slurried together in dry chloroform. Fifty ml. fractions were collected and treated with dilute aqueous hydrochloric acid to prevent air oxidation of the tetrahydro bases.

The column was eluted with 50 ml. of wet chloroform to remove tars, followed by a wet chloroform-butanol (5:1, v:v) mixture. Solvents were

evaporated on a steam plate. Solid material appeared on evaporation of fractions 2 through 10.

Fractions 2 through 5 possessed ultraviolet absorption comparable with that recorded for tetrahydroflavopereirine (6). Test amounts of perchlorate formed from them melted at 217-220°C. (fractions 2 and 3) and 225-228°C. (fractions 4 and 5); the literature value for the melting point of tetrahydroflavopereirine perchlorate is 220-222°C. (6). Fractions 2 through 5 were combined, the wash methanol evaporated, the residue dissolved in hot water and the perchlorate salt formed by dropwise addition of 10% aqueous sodium perchlorate. Two recrystallizations from absolute ethanol gave crystals melting 219-222°C., unchanged by admixture with authentic crystals of tetrahydrofalvopereirine. The infrared absorption spectrum (KBr pellet) was identical with that of authentic tetrahydroflavopereirine. The ultraviolet spectrum (95% ethanol) of these crystals was identical with that recorded in the literature: λmax. (log ϵ): 253mμ(4.51), 307 (4.33), 367 (3.63)(6). Yield of recrystallized perchlorate: 30.9 mg., 8.8%.

Fraction 6 showed complex ultraviolet absorption indicative of a roughly equimolar mixture of tetrahydro and fully aromatic compounds. Formation of the perchlorate as above and recrystallization from isopropanol(with charcoaling) gave crystals melting from 175°C. to above 280°C. The amount of recrystallized material, 3.1 mg., was not considered sufficient to warrant further separation.

Fractions 7 through 10 exhibited the ultraviolet absorption characteristic of the wholly aromatic flavopereirine system. However test

samples of the perchlorate salt melted between 230 and 310°C. The literature values for the melting point of natural and synthetic flavopereirine perchlorate range from 308°C. (3b) through 316-317°C. (6) to 330-331°C. (135). The infrared spectra of repeatedly recrystallized samples showed slight differences when compared with the infrared absorption spectrum of an authentic sample of flavopereirine perchlorate.

Fractions 7 through 10 were combined and the salts converted to the free bases with 3N aqueous potassium hydroxide. The bright orange solids were dissolved and extracted into chloroform. The chloroform extracts were combined, washed and dried over anhydrous sodium sulfate. After filtration and addition of glacial acetic acid, the solvent and excess acetic acid were evaporated and the residue transferred to the same column used in the initial fractionation, using a minimum amount of chloroform.

Fifty ml. fractions were collected during the chromatography and dilute hydrochloric acid added. Solvents were evaporated on a steam plate and the residue of each fraction transferred to a test tube with a small amount of water. The presence of ammonium base was determined by the addition of an excess of 10% aqueous sodium perchlorate solution.

Wet chloroform was used to elute fractions 1 through 38, and wet chloroform-n-butanol to elute fractions 39 through 46 (9:1, v:v) and 47 through 56 (5:1, v:v).

The cream-colored precipitates formed in fractions 9 through 34 showed ultraviolet absorption spectra characteristic of the flavopereirine system. However, when the mixtures were combined and filtered and the solids recrystallized from isopropyl alcohol the resulting crystals melted

rather sharply between 238-242°C. Recrystallization from isopropyl-alcohol-isopropyl ether mixtures raised this to 246-252°C. An authentic speciman of iso-tetrahydroflavopereirine perchlorate melted partly at 217°C., largely at 248-254°C. A mixture of the two substances melted at 246-252°C. The infrared (KBr pellet) and ultraviolet (95% ethanol) spectra of the substances were identical.

U. V. Spectrum: λ max. (log ϵ): 207mμ(4.40), 252 (4.48), 307 (4.34), 368 (3.70).

I. R. Spectrum: figure 1.

Yield of recrystallized perchlorate: 8.4 mg., 2.4%.

The precipitates formed in fractions 40 through 49 also showed the characteristic flavopereirine ultraviolet absorption pattern. The combined precipitates were recrystallized from isopropyl alcohol and then water, m. p. 320-325°C. Comparison of this melting point with an authentic specimen of flavopereirine proved difficult because the melting point of the authentic material varied with the solvent of crystallization and method of drying. Invariably it was above the literature value of 316-317°C. (6) for this particular source. A sample of each was recrystallized from water and dried overnight at 80°C., 1 mm. Hg pressure; the mixture melted at 323-327°C. The infrared spectra (in KBr pellets) were identical. The ultraviolet spectrum (in 95% ethanol) was identical with that recorded in the literature (6): λ max. (log ϵ): 230 mμ (4.40), 238 (4.43), 248 (4.39), 294 (4.14), 351 (4.24), 390 (4.14). Yield of recrystallized perchlorate, 2.3 mg. (0.66%). Total yield of cyclized material: 12%.

Other Compounds Used in This Study

Sufficient 1-[β-(3-indolyl-)ethyl-]3-ethylpiperidine to carry out the large-scale dehydrogenation was donated by Dr. Börje Wickberg. Dr. Wickberg also made available authentic samples of 1,2,3,4,6,7,12,12b-octahydroindolo-[2,3-a]quinolizine and iso-tetrahydroflavopereirine perchlorate for purposes of comparison.

Samples of flavopereirine perchlorate and tetrahydroflavopereirine perchlorate were obtained from Professor Henry Rapoport.

Attempted Synthesis of Flavoserpentine

Synthesis of 3-Ethyl-4-methylpiperidine

The reduction of 3-ethyl-4-methylpyridine was attempted. No uptake of hydrogen was observed on exposing the compound to atmospheric-pressure hydrogen in the presence of platinum or Raney nickel (W-2) in acidic, neutral or basic aqueous or alcoholic solutions; to low-pressure hydrogen in the presence of platinum in aqueous hydrochloric acid, glacial acetic acid or methanolic potassium hydroxide. Erratic uptake of hydrogen was observed under 2000 p.s.i. of hydrogen between 100 and 200°C. in the presence of Raney nickel (W-2) in cyclohexane solution.

Attempts to isolate piperidines from those runs in which hydrogen uptake occurred were unsuccessful. Infrared spectra of the reaction products remaining after solvent was removed under vacuum showed only small amounts of N-H absorption.

Synthesis of Indolylacetyl Chloride

The method of Shaw et al. (137) was employed, using 10 g. of indoleacetic acid. Yield of combined crops of acyl chloride, 3.6 g., 32.6%; m. p. of second crop, 59-65°C.

Reaction of Indolylacetyl Chloride With Reduction Mixtures

In several experiments an attempt was made to separate any piperidines present in the reaction mixture by reacting the entire reduction mixture directly with indolylacetyl chloride. The method of Shaw et al. (137) was used, substituting dropwise addition of the reduction mixture under nitrogen to the solution of the acyl chloride for the introduction of ammonia gas.

After warming to room temperature overnight, the mixture of products was freed of solvent under vacuum, dissolved in ether, washed with aqueous sodium bicarbonate solution and water until neutral, dried over sodium sulfate and filtered.

Because of previous difficulties in crystallizing other compounds of this series, each reaction mixture was taken through the entire reaction sequence of reduction and dehydrogenation and an attempt made to isolate flavoserpentine.

Reduction of Reaction Mixtures

The neutral fraction from each condensation was reduced with a fourfold molar excess of lithium aluminum hydride (on the basis of complete

reduction of the pyridine and complete conversion to the amide) in refluxing tetrahydrofuran purified just before use.

The reduction mixture was treated with a slurry of sodium sulfate in water to decompose excess hydride and extracted with chloroform or methylene chloride. Solvents were removed from the extract under vacuum, the residue dissolved in chloroform, dried over anhydrous sodium sulfate, filtered and freed of solvent under vacuum.

Dehydrogenation of Reduction Mixtures

Because at least one of the products (flavoserpentine) of dehydrogenation would be easy to recognize if the reaction sequence had succeeded, this procedure was decided on as a simple diagnostic tool. A portion of the oil remaining after the reduction was heated under nitrogen for twelve minutes at 300°C. in the presence of twice its weight of 10% palladium-on-charcoal after treatment with anhydrous hydrogen chloride gas. After cooling under nitrogen, the reaction mixture was extracted overnight with methanol containing a few ml. of glacial acetic acid. The extracting solvent was removed under vacuum.

After one such sequence, employing 233 mg. of oil, a mixture of crystals and gum remained. Transformation of a portion of this mixture to the picrate and crystallization from ethanol produced crystals melting 287-290°C. undepressed on admixture with authentic flavoserpentine. The ultraviolet spectrum of the mixture showed peaks which could be attributed to a mixture tetrahydro and fully aromatic quinolizines.

This mixture was treated with chloroform and dilute aqueous potassium

solution, and the aqueous layer extracted exhaustively with chloroform until colorless. The extracts were combined, washed with water, dried over sodium sulfate, filtered, glacial acetic acid added to discharge the deep orange color, and the solution evaporated under vacuum.

Chromatography of the resulting mixture on a column of 33 g. of cellulose which had been slurried with 11 ml. of 1% aqueous acetic acid separated the mixture into fractions evidencing the ultraviolet absorption of the tetrahydro compound (11 through 17) and of the aromatic compound (20 through 23) upon elution with a mixture of wet chloroform-n-butanol (8/1, v/v). Fractions 20 through 24 were combined, converted to the perchlorate salt, and crystallized from water. The quantity of crystals was insufficient for a satisfactory Nujol infrared spectrum, but the position and relative heights of those peaks which could be observed agreed exactly with those of flavoserpentine perchlorate.

Reaction of Phenyllithium with 3-Ethyl-4-methylpyridine

Lithium wire (4 g., 0.58 g. atom, cut into short lengths) and sodium-dried ether (10 ml.) were treated with a few ml. of a solution of bromobenzene (40 g., 0.255 mole) in ether (200 ml., sodium-dried) under nitrogen in a flame-dried apparatus and the attached stirrer started. When refluxing had begun, the remainder of the bromobenzene was added dropwise at such a rate as to maintain gentle boiling. Total addition time was about two hours.

To the above solution was added dropwise a 3-ethyl-4-methylpyridine (24 g., 0.2 mole, redistilled commercial product, stored over sodium

hydroxide pellets) in ether (50 ml., sodium-dried) over a period of fifteen minutes under nitrogen with stirring.

The resulting deep red solution was poured through a bit of coarse glass wool into a 1 liter flask containing 200 g. of crushed solid carbon dioxide. The mixture was shaken and an additional 200 g. of carbon dioxide added. The excess carbon dioxide was allowed to evaporate from the yellow solution and the ether removed under vacuum without heating.

The above solids were dissolved in commercial anhydrous methanol and the solution cooled to -20°C. in a Dewar flask containing crushed solid carbon dioxide. Commercial anhydrous methanol, chilled to -20°C., was added portion-wise and the mixture saturated at this temperature with anhydrous hydrogen chloride gas. The rate of addition was such that the temperature of the reaction mixture did not rise above -5°C. After exhaustive saturation of the mixture with anhydrous hydrogen chloride gas, it was allowed to stand overnight at room temperature.

Solvents were removed under vacuum from the reaction mixture and chloroform solid potassium carbonate and water added. This mixture was heated for one hour below the reflux temperature, filtered, and the solvent removed under vacuum. The resulting gum was distilled under approximately 1 mm. Hg pressure; fraction 1 boiled below 100°C., 1.35 g.; fraction 2 boiled between 110 and 140°C., 3 g.; fraction 3 boiled between 140 and 145°C., 7.55 g. On distillation under 0.5 mm. Hg pressure fraction 3 boiled between 86 and 90°C. Vapor phase chromatography of arbitrary cuts from this distillation contained approximately the same complex mixture, showing two major and at least five minor peaks in the

chromatogram. The same complex mixture was eluted with Skellysolve B from an alumina column.

Fraction 3 gave a copious yellow picrate from saturated methanolic picric acid. Recrystallization from the minimum volume of 95% ethanol gave crystals melting 204.5 to 206.5°C. Total yield of picrate, 0.76 g. A portion of the picrate was converted to free base with sodium hydroxide solution, extracted into chloroform, dried over sodium sulfate, filtered and the solvent removed under vacuum with heating. Nuclear magnetic resonance and infrared spectra were recorded for the residual material.

I. R. Spectrum (CCl_4): figure 1.

N. M. R. Spectrum (15% in CCl_4, c.p.s. relative to tetramethylsilane): figure 3.

Anal. Calcd for $C_{20}H_{18}N_4O_7$: C, 56.34; H, 4.25; N, 13.14. Found: C, 55.80; H, 4.13; N, 13.60.

Dehydrogenation of Ajmalicine

Commercial tetrahydroserpentine (ajmalicine) (104 mg., 0.296 mmole.) was mixed with palladium-on-charcoal (200 mg. of 5%) and treated with two ml. methanol and a drop of 12M aqueous hydrochloric acid. The mixture was evaporated to dryness under vacuum with heating, the vessel flushed with nitrogen and heated under nitrogen at atmospheric pressure at 300°C. for twenty-three minutes.

After cooling under nitrogen, the resulting mixture was extracted continuously overnight with methanol containing a few ml. of glacial acetic acid. The extract was evaporated under vacuum leaving a mixture

of yellow hygroscopic crystals and gum. The mixture was converted to the free bases with aqueous sodium hydroxide solution and extracted with chloroform. This solution was washed with water, dried over anhydrous sodium sulfate powder, filtered, treated with glacial acetic acid, and evaporated under vacuum. The resulting gum was transferred to a column of cellulose (33 g.) which had been slurried with dilute aqueous acetic acid (11 ml., 1%, v/v) and the column eluted with wet chloroform (seven 50 ml. fractions) rollowed by wet chloroform-n-butanol (4/1, v/v) (nineteen fractions). Each fraction was treated with a few ml. of dilute aqueous hydrochloric acid before the solvents were evaporated. Crystals formed from fractions 10 through 27; the ultraviolet spectrum of these fractions was identical with that of the indolo[2,3-a]quinolizinium chromophore. The total weight of crystals: 53.9 mg.; yield, 63.6%.

Crystals of the hydrochloride from fraction 15 did not melt below 350°C., but darkened above 309°C. The picrate formed from this fraction melted 293-295°C. after recrystallization from ethanol. The literature value for the melting point of flavoserpentine picrate is 291°. The perchlorate from fraction 17, recrystallized from water, melted 307-309°C. The literature value (10) for the melting point of flavoserpentine perchlorate is 308°C.

Catalytic Reduction of Flavoserpentine

Ajmalicine (200 mg., 0.568 mmole.) was dehydrogenated, the dehydrogenation mixture extracted, the extraction mixture evaporated as described above.

The product mixture was dissolved in commercial absolute methanol (approximately 30 ml.) and platinum oxide (113 mg.) and potassium hydroxide (two pellets) added and this mixture immediately reduced at 55.5 p.s.i. for forty-eight hours.

The reaction mixture was filtered, the filtrate treated with hydrochloric acid, and an attempt made to partition the products according to their basicity after the methanol had been replaced with ether. When the strongly basic compounds (obtained by chloroform extraction of the solution when basified above pH 10 with sodium hydroxide solution) formed a broadly-melting perchlorate on treatment with glacial acetic acid and sodium perchlorate solution (44.6 mg. after one crystallization from methanol-water) this approach was abandoned. All extracts and crystals were recombined, basified with aqueous potassium hydroxide solution, and the bases extracted into chloroform. The chloroform extracts were combined, washed with water, dried over powdered anhydrous sodium sulfate, filtered, treated with glacial acetic acid in excess and solvents and excess acid removed under vacuum.

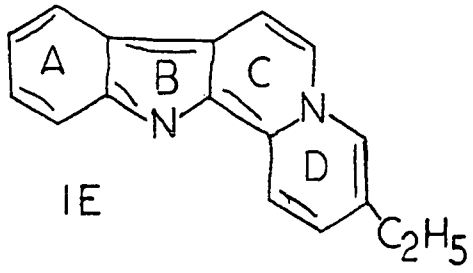
The residue was chromatographed on a column of cellulose (33 g.) which had been slurried with dilute aqueous acetic acid (11 ml. of a 1% solution by volume). Elution with wet chloroform followed by treatment with aqueous hydrochloric acid produced crystals in fractions 3 through 5. The perchlorate was formed and recrystallized from iso-propanol-iso-propyl ether, and melted over a wide range: 155-162°C. An analytical sample, recrystallized from water and dried under vacuum at 80°C. overnight, showed no change in melting point. Total yield of recrystallized

perchlorate, 22.5 mg., 10.9% from ajmalicine.

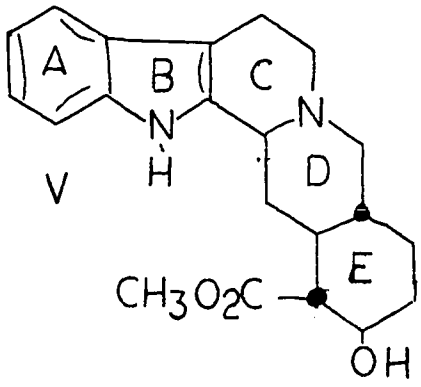
Anal. Calcd. for $C_{18}H_{21}N_2ClO_4$: C, 59.25; H, 5.80; N, 7.68. Found: C, 59.69; H, 5.87; N, 7.56.

DISCUSSION

The synthesis of the indole alkaloid ring skeleton of such molecules as flavopereirine (IE) and β-yohimbine (V)

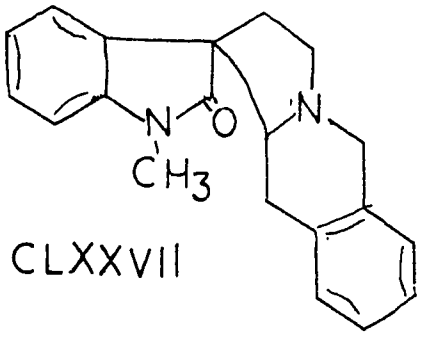


IE



V

can be approached in many ways. The most flexible approach involves the construction of ring C (c.f. β-yohimbine (V)) at the end of the synthesis, as the four syntheses of flavopereirine previously cited (pp. 9-11) demonstrate. When this investigation was undertaken, no convenient method of synthesizing the basic indole alkaloid skeleton by cyclization of ring C had been described. However, the accidental synthesis by Julian et al. (66) of the spiro system (CLXXVII) related to oxindole alkaloids appeared promising.

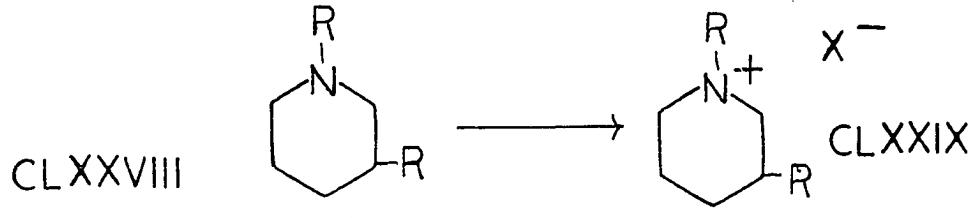


CLXXVII

If an oxidative formation of ring C along the lines of Julian's

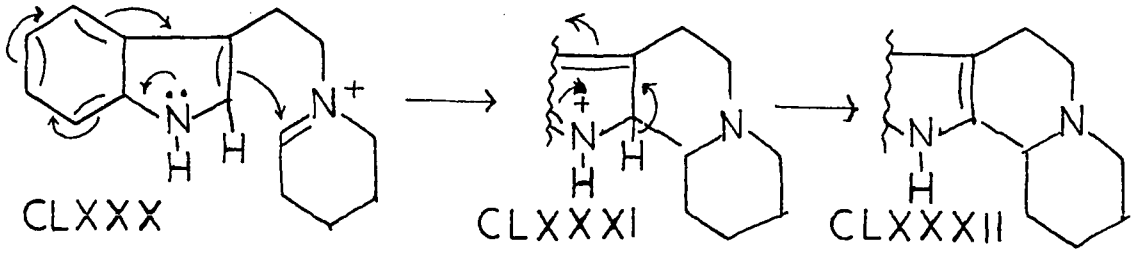
synthesis could be achieved, it would offer several advantages. First, the necessary starting materials would be relatively easy to obtain. Many substituted piperidines or tetrahydroisoquinolines are available commercially, or their syntheses may be achieved by well-known methods; e.g. indoleacetic esters can be bought and indoleacetyl chloride can be made readily. Second, the combination of one of these latter reactants with the necessary amine to form an amide and the hydride reduction of the amide to the required amine are both standard organic reactions. Third, the dehydrogenative ring closure, if feasible, might be a quick and straightforward reaction. Provided that mixtures of products resulting from the dehydrogenation could be separated, the above sequence would then represent a facile method of preparing the indole alkaloid skeleton. In situations where the yield of product was not critical (such as an attempt to prove the structure of a new compound by synthesis) it would provide a useful addition to the methods already at hand for such a synthesis.

The proposed cyclization could be postulated to proceed in the following reaction sequence. In the temperature range usually employed for palladium-catalyzed dehydrogenations - 200-300°C. - and under acidic conditions, the piperidine ring would be expected to lose hydrogen, yielding a tetrahydropyridinium salt (CLXXVIII to CLXXIX). There are ample



analogies for the addition of a nucleophile to such a system, e.g., the synthesis of flavopereirine by Thesing and Festag (12). The alpha

position of the indole nucleus represents such an internal nucleophile (CLXXX to CLXXXI). Elimination of the hydrogen at C-2 would restore the indole nucleus (CLXXXI to CLXXXII).



CLXXX CLXXXI CLXXXII

Since the resulting tetracyclic system is still susceptible to dehydrogenation, ring C or ring C and D dehydro compounds might be expected. The extent of such dehydrogenation would depend both on the nature of the new ring system and on the conditions employed for the reaction.

As a preliminary study several items had to be determined experimentally. First, what were the optimum conditions for cyclization. Second, what was the level of dehydrogenation of the product (or products). Third, could the level of dehydrogenation (or the ratio of the products) be altered by varying the reaction conditions. Fourth, if the reaction gave a mixture of products, how could they be separated from each other.

With palladium-charcoal as catalyst, the temperature range between 200 and 300°C. seemed the most promising: high enough for dehydrogenation to occur but low enough to avoid extensive decomposition of starting material or products, such as the elimination of the N-alkyl substituents. The experience of Schwyzer (88) LeHir et al. (83) and others indicated that the combination of acidic palladium-on-carbon and the amine salt was more selective and milder than neutral catalyst and the free amine. Supported palladium gave reaction mixtures more readily handled and extracted than did the metal itself. In addition, it was commercially

available in consistent quality.

The extent of cyclization was determined by means of ultraviolet spectroscopy of the reaction mixtures. Each of the possible cyclization products absorbed strongly in the ultraviolet and showed a complex pattern of absorption maxima strikingly different from that of each of the other products and of starting material. This made it possible to run a large number of probe reactions on milligram scale, suspend each probe mixture in ethanol in a volumetric flask, decant the solvent and record its ultraviolet absorption spectrum. Examination of the relative absorption was made at several wavelengths.

A typical series of probes would be run in the following manner. The model compound, 3-(2-piperidineothyl)-indole, was weighed out (close to 10 mg.), dissolved to 10 ml. volume in a suitable solvent (chloroform, ether, methanol), and aliquots (1 ml.) transferred to test tubes. The solvent was removed by gentle heating, and the residue transferred with a drop or two of solvent to a micro cone. After an approximate amount of catalyst had been added, either a base was added or the mixture was treated with a stream of dry hydrogen chloride gas. Any remaining solvent was removed and the micro cone was flushed with nitrogen. While a steady flow of gas was maintained over the reaction misture, the cone was inserted in Wood's metal bath preheated to the desired temperature, and the mixture allowed to react. Thereafter the cone was removed and allowed to cool.

The contents of each vessel were then carefully scraped and flushed with 95% ethanol into a 10 ml. volumetric flask and diluted to the mark. To reaction mixtures which had been run under basic conditions, a drop of

concentrated hydrochloric acid was added before dilution. The flasks were allowed to stand at least an hour before ultraviolet spectra were recorded. In view of the high-intensity ultraviolet absorption of all products less than 10% yield of cyclization product could be observed in the extracts. In addition, an estimate of the nature of the product mixture could be made with some accuracy.

The initial probes were performed for varying times (one to twelve minutes) under nitrogen both with and without hydrogen chloride treatment at a temperature of about 300°C. The ultraviolet spectra of the extracts showed the appearance of the quinolizine chromophore after about eight minutes and an increase in its concentration up to twelve minutes.

Small scale studies were continued to determine the effect of varying the amount of catalyst, of adding base, of performing the reaction in air, of extending the reaction time and of lowering the reaction temperature. The results of these studies may be summarized as follows. Both palladium-black and palladium-on-charcoal worked equally well; the amount of palladium deposited on the charcoal - whether 5% or 10% - seemed to be immaterial. Varying the ratio of catalyst to substrate from two to three (by weight) did not affect the results. Since the reaction mixtures in which palladium-on-charcoal were employed were more free flowing than those employing palladium black, the former was used regularly.

The extracts of several reactions performed in air showed only weak but complex absorption in the ultraviolet. Probably only cyclization had occurred and had been replaced or followed by catalyzed oxidation of starting material or products. Subsequent reactions were performed in an

atmosphere of nitrogen gas.

Schwyzer (88) determined that acid-washed palladium-on-charcoal was preferable to untreated catalyst, showing that yields were more reproducible and generally higher. In our hands, the extracts of several probes in which solid potassium carbonate had been added to the reaction mixtures to give a known amount of base, evidenced no absorption in the ultraviolet which could be attributed to cyclized products. Large amounts of white vapor were evolved when these mixtures were first inserted into the metal bath, which undoubtedly arose from sublimation of starting material. All subsequent runs were performed after the starting materials in solution had been treated with anhydrous hydrogen chloride gas. In addition to converting the free base substrate to the amine hydrochloride, this effectively neutralized any residual basicity of the charcoal catalyst support.

The effect of temperature and time were investigated next. At 240 or 270°C. there was a non-linear decrease in the ultraviolet absorption of the products at 345, 366 and 388 mμ, which indicated that the concentration of both undehydrogenated and aromatic cyclization products decreased as the reaction time was extended from twelve to thirty-six minutes. In contrast to this, heating at 300°C. produced an increase in absorption at these wavelengths (and by inference an increase in cyclized product) between twelve and twenty-four minutes, followed by a decrease after this time.

The cause of this behavior may be associated with the competition between the various amine salts for the active sites of the catalyst, but

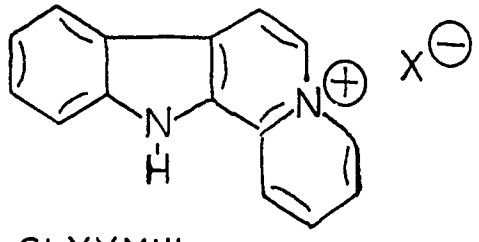
would require an extended kinetic study for full interpretation. However, it was apparent that whatever products were formed below about 300°C. were destroyed on continued heating, and either the initial products or the decomposition products prevented formation of more cyclization products. Only after most of the starting material had been cyclized and dehydrogenated, did the rate of decomposition of product appear to surpass that of formation of product.

The optimum conditions for the formation of cyclized products (regardless of state of further oxidation) therefore appeared to be the following: palladium-on-charcoal catalyst (5-10%), employed under nitrogen at a temperature of about 300°C. for twelve to twenty-four minutes after treatment of catalyst and starting material with dry hydrogen chloride or hydrochloric acid. These conditions were then utilized in large-scale dehydrogenations of 3-(2-piperidinoethyl)-indole and of 3-[2-(3'-ethyl)-piperidinoethyl]-indole.

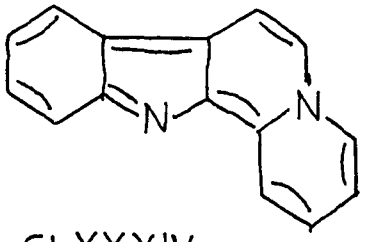
The piperidinoethyl compound was dehydrogenated in quantities of 100 to 500 mg. Separation of products from the catalyst was achieved by extraction of the mixture overnight with methanol to which acetic acid had been added to desorb the polar materials from the surface of the charcoal. In some experiments the mixture and reaction vessel were first washed with benzene to remove tars. Since the subsequent chromatography accomplished the same end, this wash was later omitted.

When the extraction solvents were evaporated, a mixture of gum and crystals, which melted over a wide range, remained. Attempts to purify the crystals by recrystallization only raised the melting range, but did

not narrow it. It appeared that a mixture of related products, rather than a single product contaminated by degradation products, was at hand. The mixture of chlorides was subjected to column partition chromatography using cellulose-water ("buffered" with dilute acetic acid) as the stationary phase and mixtures of wet petroleum ether and chloroform as the mobile phase. In order to avoid a double series of eluted peaks due to a mixture of acetate and chloride anions, the mixture of chloride salts was converted to the acetate salts by treatment with aqueous strong alkali and chloroform. Strong base converts the quinolizinium salts (CLXXXIII) to the free



CLXXXIII



CLXXXIV

bases (CLXXXIV) which were extracted into chloroform. After the chloroform layers were combined, washed with water to remove chloride ions and remaining strong base, dried and filtered, the organic bases were converted to the quinolizinium acetate salts by the addition of glacial acetic acid. The bases were deeply orange colored, while the salts had a light yellow color. Thus the addition of the correct amount of acid could be achieved by dropwise addition until a color change occurred.

The resulting mixture of acetates was added to the top of the cellulose column and the column eluted with various wet solvents. Regardless of the concentration of acetic acid in the stationary phase, tars were

consistently eluted with wet petroleum ether. In addition, any non-volatized decomposition products were undboutedly separated at this point. Thus, in keeping with the observations (c.f., 51) that N-substituted piperidines lose the N-alkyl group on catalytic dehydrogenation, it was expected that a certain amount of starting material would be converted to the pyridine and some indolic product: 3-ethylindole, skatole or indole. This would account for the white fumes and pink sublimate observed in even the acidic dehydrogenations, as well as for the strong odor of skatole.

Elution with wet petroleum ether-chloroform mixtures or with wet chloroform did not remove solid materials from the columns which contained less than about 0.5% acetic acid. In these cases, mixtures of n-butanol and chloroform, saturated with water, were used. The amount of butanol varied with the nature of the mixture and the amount of acetic acid in the stationary phase, but generally ranged between 10% and 50%. Elution with higher percentages of butanol seldom removed any solid material.

However, if the concentration of acetic acid was increased to about 1% (by volume) crystalline solids could be recovered on elution with wet chloroform. Apparently both partition and adsorption were occurring on the column, and the presence of more acetic acid decreased the extent of adsorption. Since the eluting solvents were not saturated with the mixture that made up the stationary phase, the acetic acid was gradually leached off the column. Thus, when the product mixture from the dehydrogenation of the ethylpiperidine derivative was first chromatographed, the solids were rapidly eluted by 500 ml. of wet 5:1 chloroform. When fractions 7 through 10 were rechromatographed on the same column, n-butanol,

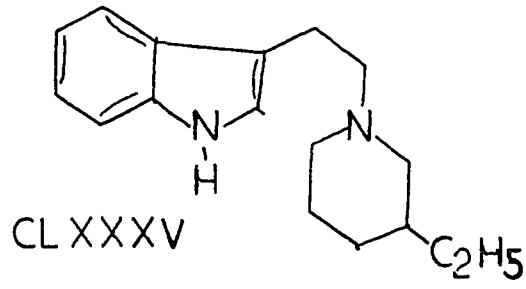
nearly two liters of wet chloroform and a liter of chloroform-n-butanol were required to elute all solid material.

Using a suitable combination of eluting solvents with a compatible concentration of acetic acid in the stationary phase, it was possible to separate the dehydrogenation product mixture into two crystalline substances, each possessing distinct ultraviolet and infrared absorption spectra and different, moderately sharp melting points (as perchlorates). The material which was consistently eluted first proved to be identical in all respects with a sample of 1,2,3,4-tetrahydro-12H-indolo[2,3-a]-quinolizinium perchlorate, and the material eluted later with a sample of 12H-indolo[2,3-a]quinolizinium picrate (see later discussion concerning the synthesis of authentic samples of these compounds).

The tarry initial fractions from the chromatography did not yield solid material with hydrochloric acid, perchloric acid or picric acid. Had any octahydroquinolizine survived the dehydrogenation, it would have appeared in these fractions. Since the initial small-scale reactions as well as the large-scale runs were directed toward forming and isolating the anhydronium salts of this system, these fractions were not investigated further. However, the ready formation of the dehydrogenated tetracycles indicated that any unoxidized cyclized material present in the product mixture would have arisen near the end of the heating period. At best, it would have represented only a small percentage of the total cyclized product.

The dehydrogenations of the ethylpiperidine compound (CLXXXV) and separation of products and the product isolation were performed in the

same manner. In all the attempts, the tetrahydroquinolizine which was

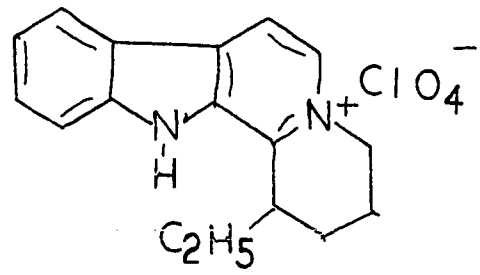


CLXXXV

identical with tetrahydroflavopereirine separated readily and cleanly from the other substances present. However, the quinolizine compound which showed properties nearly identical with those of flavopereirine remained elusively impure through repeated recrystallizations.

Since the ultraviolet spectra of fractions 6 through 8 from one preparation showed decreasing amounts of the tetrahydroquinolizinium chromophore, it was assumed that the impurity was simply tetrahydroflavopereirine. Purification was then attempted by rechromatographing the combined later fractions on the same column of cellulose used for the initial separation. This resulted in an impressively sharp separation of the mixture into two Gaussian-type peaks. The initially eluted material exhibited an ultraviolet spectrum nearly identical with that of tetrahydroflavopereirine, but its perchlorate melted fairly sharply 30°C. higher than that of tetrahydroflavopereirine. The infrared spectra of the two materials were nearly identical. However, the physical properties of this new material were identical with those of iso-tetrahydroflavoperpeirine perchlorate (CLXXXVI). A mixture with an authentic sample of this compound showed no change in melting point.

CLXXXVI

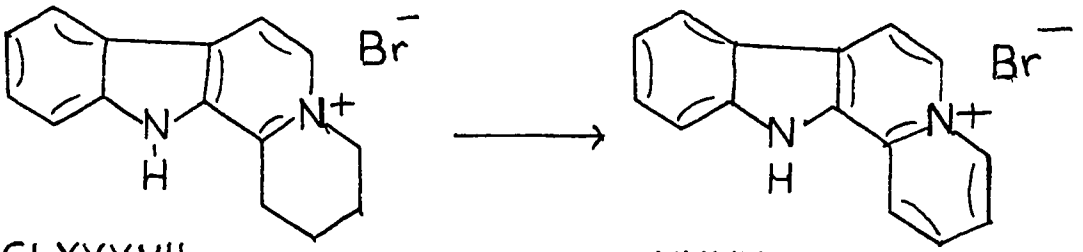


The material eluted at the end, now freed of the isotetrahydro compound, proved to be identical in all respects with authentic flavopereirine.

The yield of the isoflavopereirine systems was lower (no isoflavopereirine itself was isolated) than that of the flavopereirine systems. Presumably the ethyl group offers enough steric hindrance in the first step of the oxidative cyclization, the dehydrogenation of the piperidine nucleus to a tetrahydropyridinium salt, to cause this dehydrogenation to proceed preponderantly in the direction away from the ethyl group.

It was noteworthy that no isoflavopereirine was isolated. Either none had been formed or only small amounts had been present in fraction 6, which had not been investigated further. However, tetrahydroisoflavopereirine is reported (133) to be far more difficultly dehydrogenatible than tetrahydroflavopereirine. Undoubtedly, the transition state of the dehydrogenation of ring D would require high activation energy because of the necessity of placing the ethyl side chain into a position planar or nearly co-planar with the incipient fully aromatic system, a condition which would lead to a highly unfavorable steric repulsion of the peri ethyl and indole NH substituents.

In addition to the oxidative cyclizations, the described method of dehydrogenation and purification was also employed on a tetracyclic and a pentacyclic indolic system. A sample of the tetrahydroquinolizinium bromide (CLXXXVII) was dehydrogenated to provide authentic 12H-indolo-[2,3-a]quinolizinium bromide (CLXXXVIII) isolated and employed as the



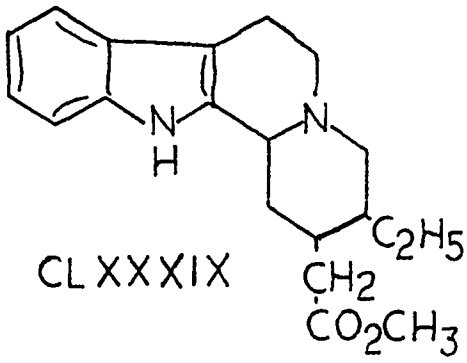
CLXXXVII CLXXXVIII

picrate. Ajmalicine (CXLVIIIA) was dehydrogenated to flavoserpentine (ID), a methylated homologue of flavopereirine. Although this sequence had been reported previously (77), the yields under these new conditions were considerably higher than under the reported conditions.

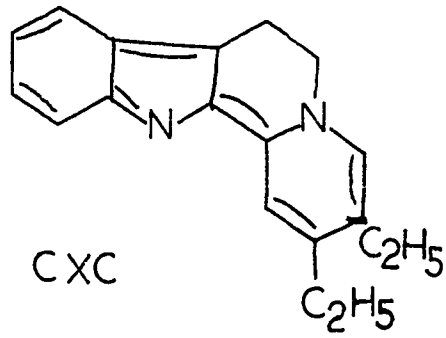
Other compounds used in this study were either synthesized by known methods with only slight modifications, or obtained as gifts. Thus, 1,2,3,4-tetrahydro-12H-indolo[2,3-a]quinolizinium perchlorate was prepared by the method of Groves and Swan (135) without isolation of intermediates, but employing a cellulose column for the final separation step. 3-(2-Piperidinoethyl)-indole has been prepared in a number of ways. The sequence developed by Dr. B. Wickberg (133) was used.

In addition to the dehydrogenation of the piperidino and the ethylpiperidino compounds discussed above, the dehydrogenation of two other compounds, the methyl and carbomethoxymethyl homologues of the ethylpiperidino compound, had been planned. Use of the former compound was

intended to lead to a novel synthesis of flavoserpentine (ID), and of the latter to a derivative of the dihydrocorynantheane-corynantheidane type of structure (CLXXXIX). In each case, the first step of the projected



CLXXXIX

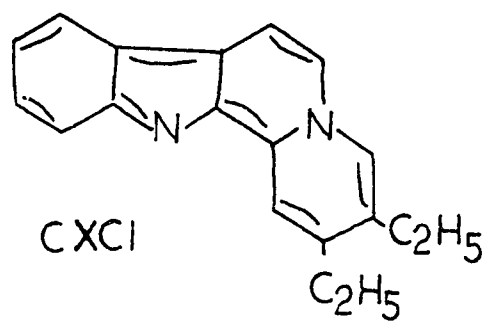


CXC

synthetic sequence failed or proved erratic.

The initial step in the synthesis of flavoserpentine was to have been the catalytic reduction of 3-ethyl-4-methylpyridine to the piperidine. Although this compound had been reduced by sodium in butanol (137), it was hoped that the cis-hydrogenated piperidine could be obtained catalytically. However, all attempts to reduce the pyridine failed; only under 2,000 p.s.i. of hydrogen using Raney nickel in hexane at a temperature between 100 and 180°C. was hydrogen taken up. But this was not a reproducible experience. In this one case, the mixture containing some piperidine, was reacted with indoleacetyl chloride in an attempt to form the amide. Without isolation of intermediates, the resulting oil was reduced with lithium aluminum hydride and dehydrogenated under the usual conditions. A small amount of material, exhibiting a comparable infrared spectrum (in Nujol, as the perchlorate) and identical melting point (as the picrate) with the infrared spectrum and melting point of the flavoserpentine derivatives, could be isolated. Further attempts of this synthesis failed.

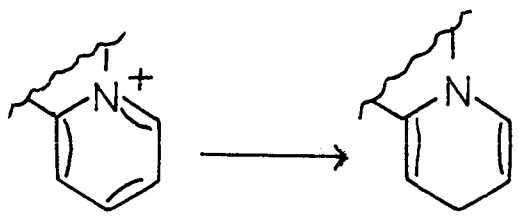
Although the recalcitrance of this simple system toward reduction is puzzling, a similar observation was recorded by Prasad and Swan (8) who reported the resistance of the diethyldihydroquinoizine system (CXC) to reduction in acetic acid over platinum. Further analogy can be found in the fact that flavoserpentine was far more difficult to reduce in our hands (using catalyst in a strongly basic solution) than the similar compounds sempervirine (Ia) and flavopereirine (Ie). The reported times required to reduce these compounds are twenty minutes (138) and one hour (6) respectively. However, when flavoserpentine was reduced under 50 p.s.i. pressure over platinum in strongly basic methanol, aliquots removed after one hour, twelve hours, and twenty-four hours still exhibited ultraviolet absorption spectra characteristic of complex mixtures of the various reduction products of this system. Only after forty-eight hours did the ultraviolet absorption approach that of a single compound — the tetrahydro system (CXCI). But attempts to purify the product by simple



CXCI

crystallization or a series of extractions from an increasingly basic aqueous solution nonetheless failed. Chromatography on cellulose produced a compound of reasonably sharp melting point which, on the basis of its ultraviolet spectrum and elemental analysis, was considered to be the tetrahydroflavoserpentine (CXCI), or a mixture of the cis and trans

stereoisomers. Although catalytic reduction is generally considered to yield cis products, the pyridine system presents a plausible exception to this rule. The initial reduction can lead to a dihydropyridine system (CXCII to CXCIII) which is capable of undergoing reduction from either



CXCII CXCIII

side of the ring. Although the preferential reduction would occur from the side of the smaller substituent, the proton, a ratio of trans:cis of 1:4 or 1:3 is not inconceivable. Separation of such a mixture could prove difficult by the methods employed.

The attempted synthesis of the carbomethoxymethylflavopereirine met with similar difficulties. The initial step here was to have been the carbonation of 3-ethyl-4-methylpyridine. The reaction of alpha or gamma methylated pyridines with phenyl lithium followed by addition of the methylpyridyl anion to carbon dioxide is a well known sequence. Following treatment with anhydrous methanolic hydrogen chloride, the ester is isolated. However, when 3-ethyl-4-methylpyridine was employed as the starting material, the isolated oil showed less than 5% ester formation by infrared analysis. The only substance which could be isolated (other than recovered starting material) proved to be condensation product of phenyl lithium with the pyridine.

This new compound was isolated, purified and analyzed as its picrate,

and converted to the free base for infrared and nuclear magnetic resonance analyses.

A number of similar additions of the phenyl radical to pyridine nuclei have been reported by Abramovitch and coworkers (139). For example, phenyl lithium reacts with 3-methylpyridine to form phenylated product in forty-two percent yield. The product is a mixture of nineteen parts 2-phenyl-3-methylpyridine and one part 2-phenyl-5-methylpyridine. Nicotine reacts to form equal amounts of the 2-substituted and the 6-substituted compound in thirty-four percent yield. However, both 3-aminopyridine and 3-methoxypyridine react with phenyl lithium to form solely the 2,3-disubstituted pyridine (140). The tendency of 3-substituted pyridines to undergo substitution at C-2 is not rationalized by these workers. However, this tendency together with the possibility of coordination between the free electron pair on the 3-substituent and the lithium is used to explain the exclusive formation of 2,3-disubstituted pyridines in the latter cases. The formation of equal amounts of 2-substituted and 6-substituted material from nicotine is ascribed to the bulkiness of the N-methyl-tetrahydropyrrole ring which hinders the approach of the phenyl lithium reagent.

By analogy with this work, the phenyl group of the product formed from phenyl lithium and 3-ethyl-4-methylpyridine is tentatively assigned to the 2-position. The nuclear magnetic resonance (figure 3) spectrum exhibits a sharp single-proton absorption at a delta of 9.05 which may be assigned to the proton in the system C_6H_5-C-N=C<u>H</u>. However, the peaks between 433 c.p.s. are not readily assigned to individual protons. It is therefore not

possible to decide whether the product is 2-phenyl-3-ethyl-4-methylpyridine (which possesses a vicinal pair of protons on C-5 and C-6) or 2-phenyl-4-methyl-5-ethylpyridine (which possesses single protons on C-3 and C-6).

Abramovitch et al. (139) cite several phenylation reactions from which the amount of phenylated products isolated was far less than the amounts isolated from his reaction conditions. The explanation given is that stringent conditions (refluxing in toluene for seven hours) are required for lithium to be eliminated from the addition product formed from the pyridine and phenyl lithium. This would account for the low yield of phenylated product obtained from the reaction of phenyl lithium with 3-ethyl-4-methyl-pyridine, since this reaction was performed at 35°C. for one hour.

Figure 1. Infrared Spectra

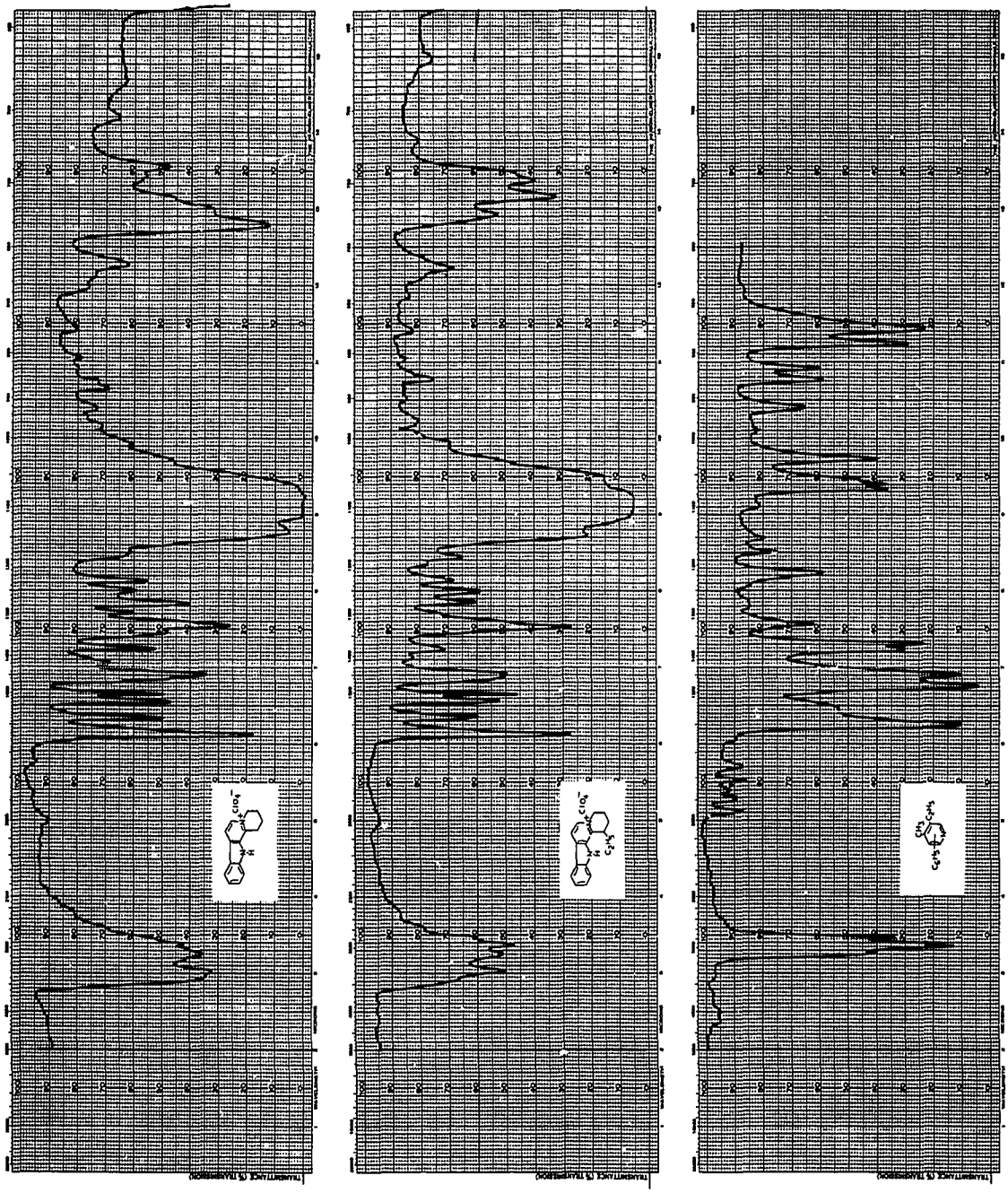


Figure 2. Ultraviolet Spectra of Preliminary Runs

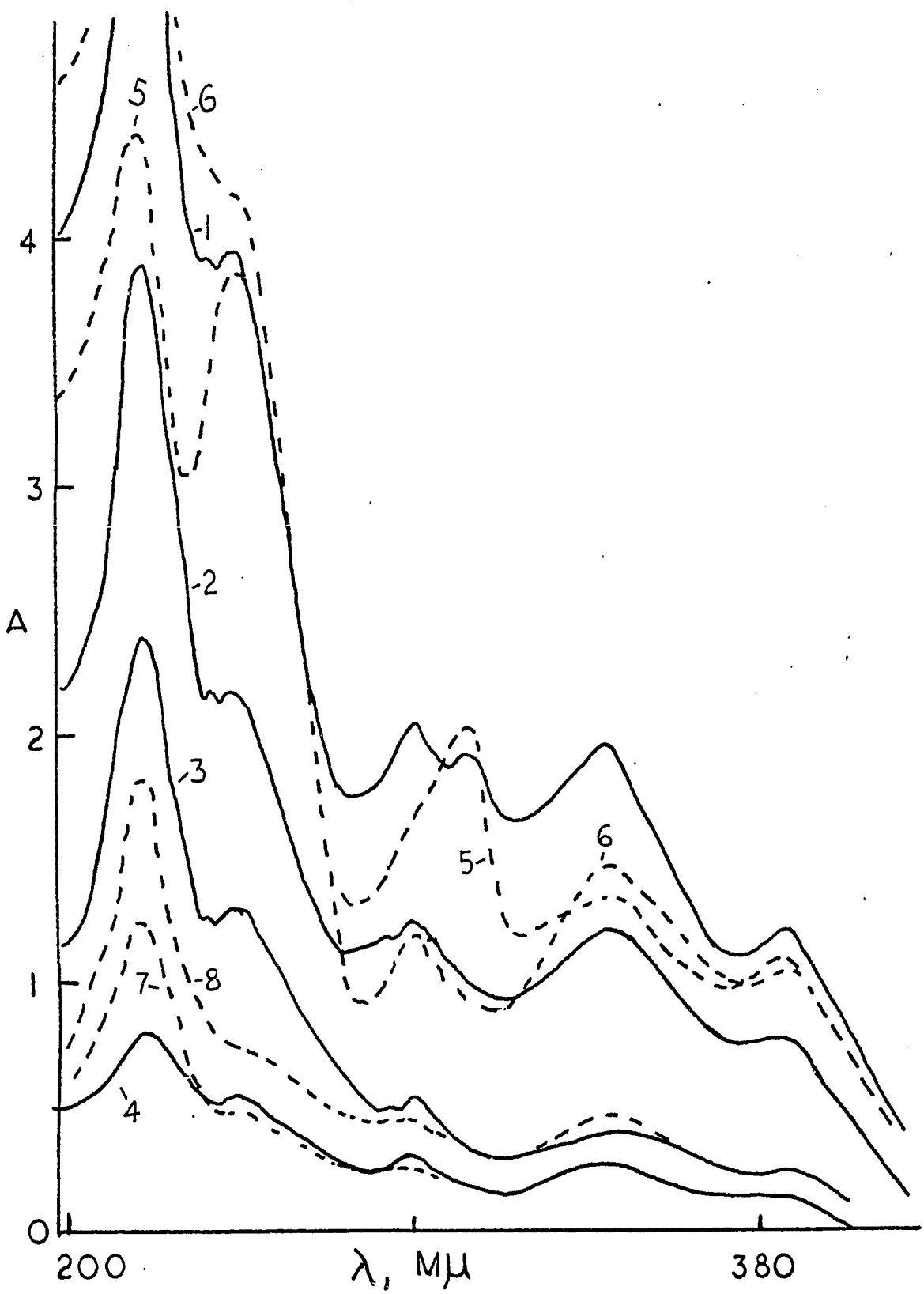
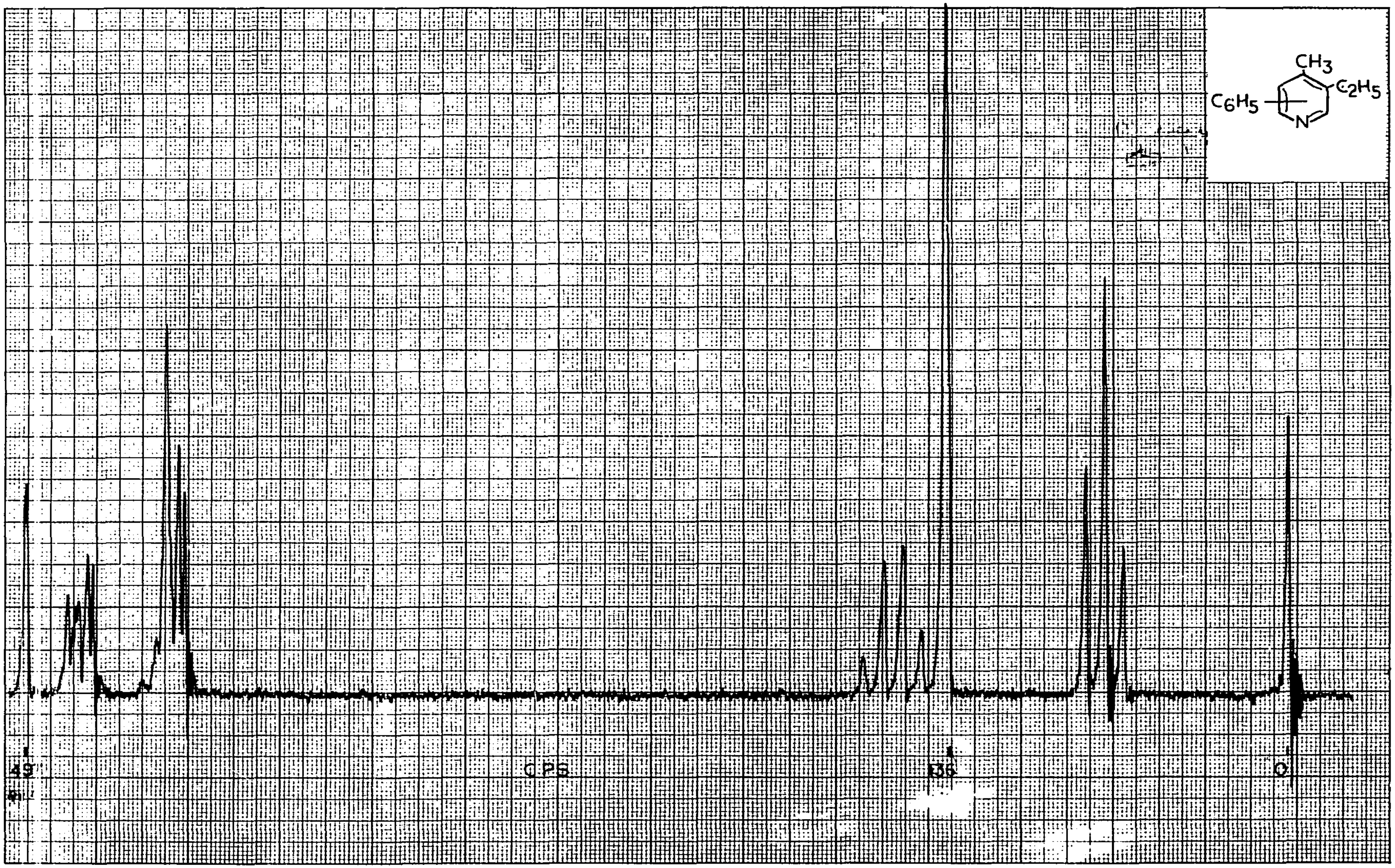

5
6
1
2
3
4
5-1
6
7
8
A
0
1
2
3
4
200
λ, Mμ
380

Figure 3. Nuclear Magnetic Resonance Spectrum


CH3
C6H5
C2H5
N
49
CPS
136
0

SUMMARY

A study was undertaken of the use of palladium-catalyzed dehydrogenation in forming carbon-carbon bonds as a tool of indole alkaloid synthesis.

Methyl indoleacetate was reacted with piperidine to form indoleacetyl piperidine. This was reduced to yield N-[β-(3-indolyl-)ethyl-]piperidine.

N-[β-(3-indolyl-)ethyl-]piperidine was dehydrogenated to yield 1,2,3,4-tetrahydro-12H-indolo[2,3-a]quinolizinium chloride and 12H-indolo-[2,3-a]quinolizinium chloride.

1-[β-(3-indolyl-)ethyl-]3-ethylpiperidine was dehydrogenated to yield flavopereirine, tetrahydroflavopereirine and iso-tetrahydroflavoperpeirine.

Ajmalicine was dehydrogenated to produce flavoserpentine. Flavoserpentine was reduced to yield tetrahydroflavoserpentine.

3-Ethyl-4-methylpyridine failed to take hydrogen in the presence of platinum in hydrochloric acid, acetic acid or potassium hydroxide solution.

3-Ethyl-4-methylpyridine reacted with phenyl lithium to yield a phenylated 3-ethyl-4-methylpyridine.

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