SYNTHETICAL EXPERIMENTS RELATED TO THE INDOLE ALKALOIDS

A THESIS

PRESENTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

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By

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CONTENTS

SUMMARY

A method for the preparation of 3-acetylindole has been developed whereby the formation of highly-coloured by-products during acetylation is prevented. The presence of vinyl acetate or styrene in the reaction mixture prevents oxidation by removal of dissolved oxygen from solution.

3-Acetylindole is known to exhibit many of the properties of aryl-alkyl ketones, but reacts with lithium aluminium hydride with the formation of 3-ethylindole. It has now been shown that 1-methyl-3-acetylindole does not yield 1-methyl-3-ethylindole on treatment with this reagent, and this difference in behaviour between the two compounds has been rationalised and an explanation provided.

Tertiary aromatic bases have been found to condense with 3-acetylindole in the presence of iodine with the formation of quaternary salts. Thus the use of isoquinoline in this reaction led to 2-(2-3'-indolyl-2-oxoethyl)isoquinolinium iodide, which on treatment with lithium aluminium hydride in tetrahydrofuran solution gave 5,7,8,13,13b,14-hexahydrobenz[g]indolo[2,3-a]quinolizine (hexadehydroyohimbane). This compound contains the essential skeleton of the alkaloids of the Yohimbine group.

Pentacyclic β-carbolines possessing ring E in a partially-reduced state have been found accessible through a similar reaction. 2-(2-3'-Indolyl-2-oxoethyl)-5,6,7,8-tetrahydroisoquinolinium iodide

reacted with lithium aluminium hydride yielding 1,2,3,4,5,7,8,13,13b,14-decahydrobenz[*g*]indolo[2,3-*a*]quinolizine. The ind-*N*-methyl-derivative of this substance was shown to be identical with the product from the sodium borohydride reduction of *N*-methylsempervirinium salts.

The course of the reaction of 1-(2-3'-indolyl-2-oxoethyl)-pyridinium iodides with lithium aluminium hydride has been found to depend upon the solvent employed. Thus the reduction of 3-ethyl-1-(2-3'-indolyl-2-oxoethyl)pyridinium iodide in ether solution led to 3-ethyl-1-(2-3'-indolylethyl)-Δ^3-piperideine, but in tetrahydrofuran the tetracyclic β-carboline 3-ethyl-1,4,6,7,12,12b-hexahydroindolo-[2,3-*a*]quinolizine was formed. This latter compound was converted in several steps to the alkaloid flavopereirine.

The results of a preliminary investigation into a second method of formation of the pentacyclic β-carboline ring system are recorded. Treatment of 2-(2-3'-indolylethyl)-1,2,3,4-tetrahydro-isoquinoline with mercuric acetate has given products which remain uncharacterised at this time.

This thesis incorporates no material previously submitted for a degree in any University, and no material previously published or written by another person except where due reference has been made.

(D.R. Liljegren)

ACKNOWLEDGEMENTS

I wish to express my appreciation of the stimulating guidance of Dr. K.T. Potts, to whom this project owes its inception.

I should also like to thank Professor G.M. Badger for his active interest in this work, and other members of this Department for helpful discussion. I thank also Dr. R.A. Jones for precise infrared spectral measurements (other than recorded from an Infracord), and Dr. T.H. Crawford of the University of Louisville, Kentucky, for the determination of nuclear magnetic resonance spectra.

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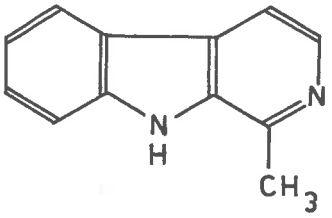
INTRODUCTION

The chemistry of the indole group of alkaloids has attracted a great deal of attention over past years. Some preliminary work on the subject was done prior to 1939 in an effort to establish the basic ring structure of many of the alkaloids, but most of the work of importance, particularly of synthetic nature, has taken place in the last two decades.

The interest in this field has been due in part to the pharmacological action of many of the natural bases, although the alkaloids of the indole group have found less medicinal use than, for example, the morphine-type alkaloids of the isoquinoline series. However, reserpine has been widely used in the treatment of hypertension due to its effect of lowering blood pressure by dilation of the intestinal blood vessels.[1] The tranquillising effect also associated with this drug has led to application to the treatment of mental illness. Yohimbine, the most pharmacologically active of the Yohimbé group, also produces a lowering of blood pressure, but its toxicity in paralysing respiration has severely restricted its application.

An example of degradative experiments designed to determine the structure of the Yohimbé alkaloids may be found in experiments performed with yohimbine. Among the first definite indications of the nuclear structure of this base was the discovery[2] that the distillation of yohimbine with zinc dust, or with steam at 300° in

the presence of alkali, yielded a base $C_{12}H_{10}N_2$. This compound was subsequently shown[3] to be harman (1), and the presence of the indole group in yohimbine was thus established. Hahn and his co-workers[4] found that yohimbine yielded a tetradehydroyohimbine under certain dehydrogenation conditions. This compound when boiled with potassium hydroxide in amyl alcohol gave harman and m-toluic acid (2). Selenium dehydrogenation of yohimbine at 300°



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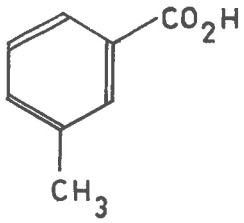
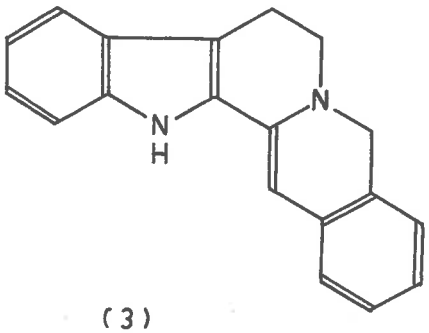


(2)

gave three compounds; yobyrine, "tetrahydroyobyrine" and ketoyobyrine.[5,6] Taking the degradation fragments into account, Barger and Scholz[6] proposed structure (3) for yobyrine, and regarded this as the basic ring structure of yohimbine. However, Witkop[7]



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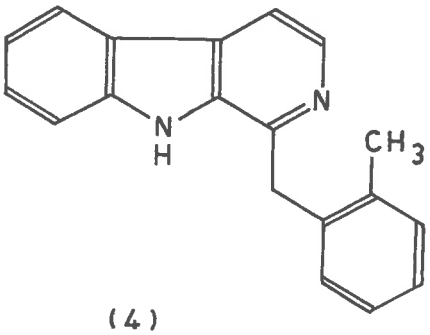
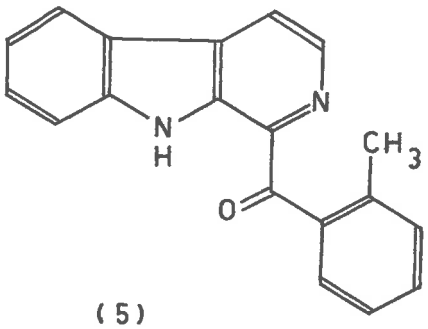


(4)

believed that as yobyrine behaved as an unreduced substance, its structure was more adequately represented by (4). This structure

accounts for the fact[8] that oxidation of yobyrine by sodium dichromate in acetic acid yielded phthalic acid, o-toluic acid, and yobyrone, which Witkop represented as (5).



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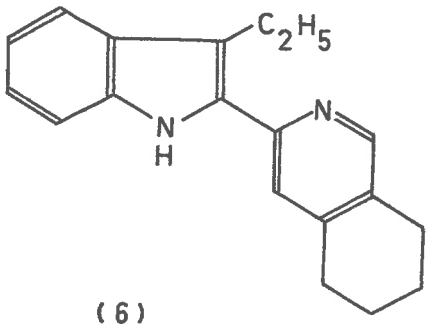
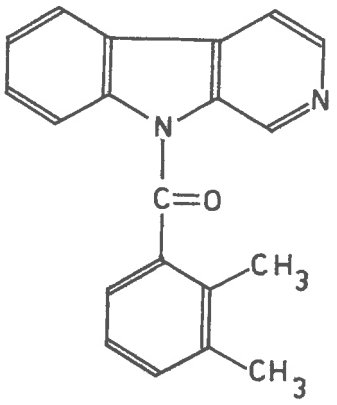


(6)

"Tetrahydroyobyrine" is a misnomer, and it was proposed[7,8] that structure (6) was correct for this compound. Ketoyobyrine, the third product from the selenium dehydrogenation of yohimbine, was first formulated at (7) by Witkop,[7] on the basis of the formation of norharman (8) and 2,3-dimethylbenzoic acid when subjected to basic hydrolysis. Clemo and Swan[9] subsequently proposed structure (9)



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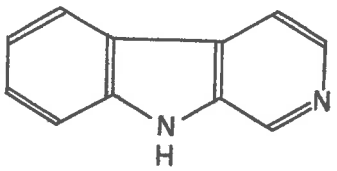
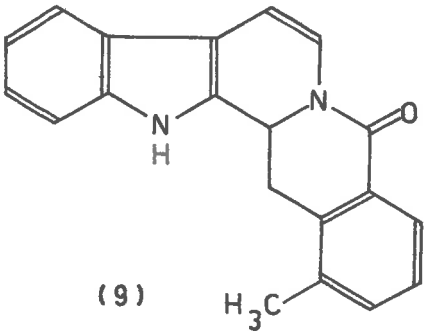


(8)

for ketoyobyrine, but this was disproved with the synthesis[10] of a compound (10) that appeared to be identical with the ketoyobyrine

derived from natural material.



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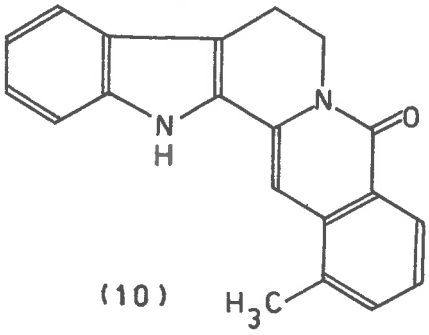
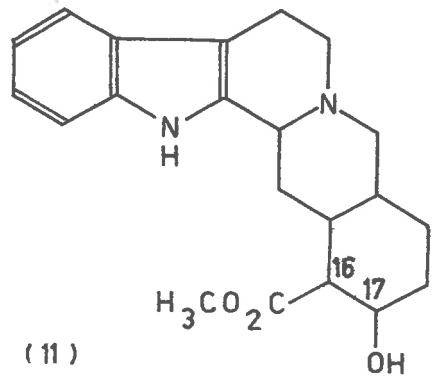


(10)

The location of the carbomethoxy-group in the yohimbine molecule was established by the isolation of m-toluic acid from the hydrolysis of the tetradehydroyohimbine described previously. It was placed at C-16 (see 11) and more recent work has agreed with this formulation. The evidence brought forward to support C-17 as the location of the hydroxyl group in yohimbine allowed structure (11) to be proposed for the alkaloid. Witkop[7] found that the Oppenauer oxidation of yohimbine yielded a ketone yohimbone, and in the light of his experimental evidence Witkop was able to propose structure (12) for the compound. This formulation, and therefore the nuclear structure and position of the hydroxyl group in yohimbine itself, was confirmed by the subsequent synthesis of yohimbone.[11]



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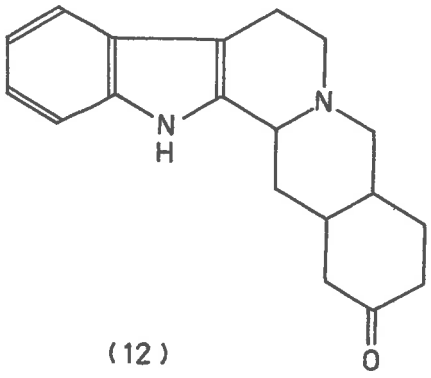
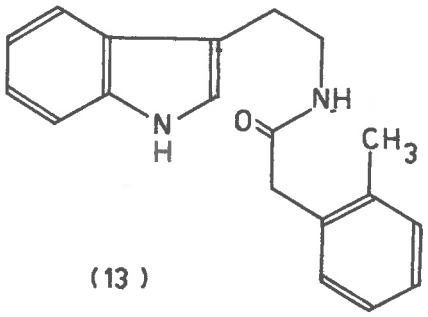


(12)

The structure of yobyrine (4) was soon confirmed by two independent syntheses.[12,13] o-Tolylacetic acid condensed with tryptamine to yield 3-[β-(o-tolylacetamido)ethyl]indole (13) which when subjected to ring closure with phosphorus pentoxide or phosphorus oxychloride gave the dihydroyobyrine (14). Dehydrogenation of (14) with palladium black gave yobyrine (4), identical with a sample obtained by the degradation of yohimbine.



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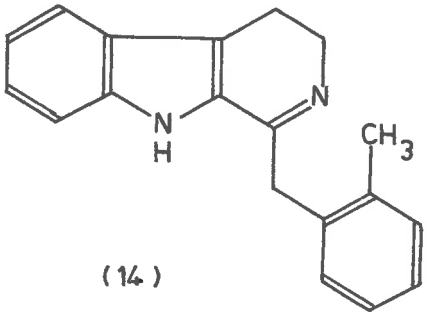
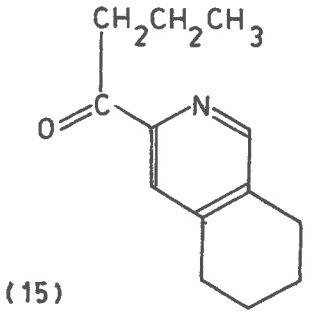


(14)

Julian[13] also provided confirmation of the proposed structure for "tetrahydroyobyrine" (6). 3-Carboxy-5,6,7,8-tetrahydroisoquinoline was treated with n-propyl-lithium, yielding 3-butyryl-5,6,7,8-tetrahydroisoquinoline (15). Formation of the phenylhydrazone

followed by ring closure under the conditions of the Fischer indole reaction gave "tetrahydroyobyrine" identical with a sample derived from natural material.



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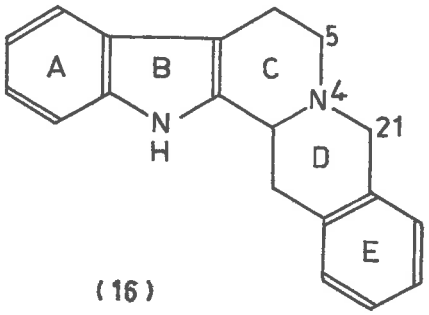
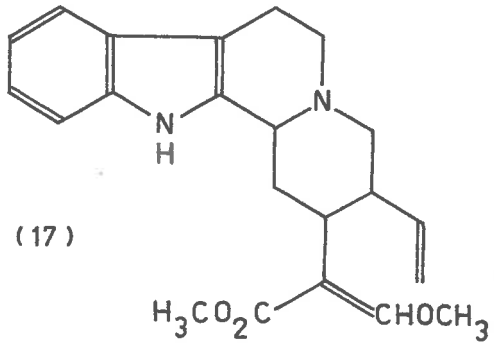


(16)

It was reported[12] at this time that the dehydrogenation of hexadehydroyohimbane (16) under vigorous conditions with palladium black yielded a mixture of bases, among which was yobyrine. The formation of the latter compound involves the fission of the N_4— C_{21} bond, with the aromatisation of ring C. This was taken as an indication of a possible pathway for the formation of yobyrine from yohimbine during selenium dehydrogenation. Similarly, in the formation of "tetrahydroyobyrine" from yohimbine, the N_4— C_5 bond breaks, enabling ring D to become aromatic.

The establishment of the structures of other alkaloids of the Yohimbé group proceeded concurrently with the work on yohimbine itself. Some, notably corynantheine (17), were found to be tetracyclic bases, and the position of substitution in ring D showed them to be closely related to yohimbine. The Alstonia group of

alkaloids was also studied at this time, and one of the main constituents, alstoniline, was assigned the pentacyclic structure (18). The syntheses of derivatives of the Alstonia alkaloids were later developed along similar lines to those designed more specifically for the Yohimbé bases.



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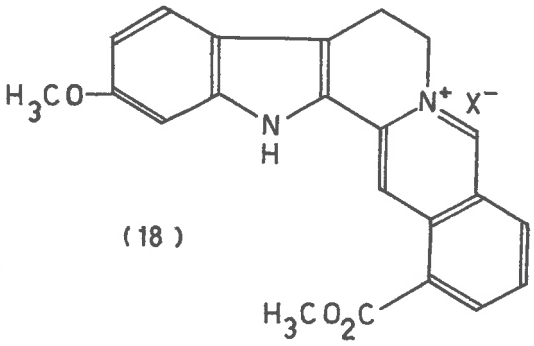
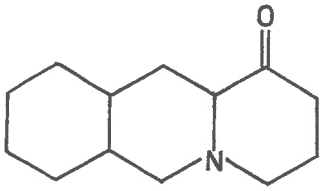


(18)

With the tetra- and pentacyclic nature of these alkaloids firmly established, attention was directed towards the synthesis of the basic ring systems. The most suitable of these was then, in some cases, applied to the preparation of the alkaloids themselves once the stereochemistry became known with certainty. The several theoretical methods for the build-up of the pentacyclic system have been quite fully investigated, and most are applicable to the synthesis of tetracyclic β-carboline systems.

The first synthetic method employed was the Fischer ring closure of the phenylhydrazones of suitable ketones such as (19). This involved the closure of ring B on to a completed C-D-E ring skeleton as in (20).



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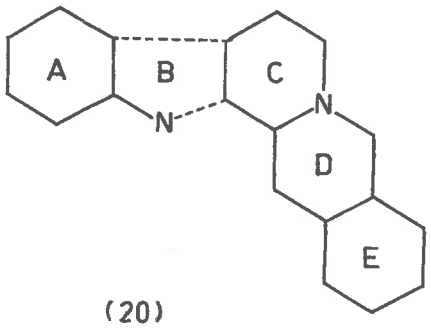
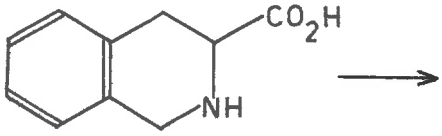


(20)

The pioneering work in this direction was the synthesis of 5,7,8,13,13b,14-hexadehydrobenz[g]indolo[2,3-a]quinolizine (16), hexadehydroyohimbane.[12] The ethyl ester of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (21) condensed with γ-bromopropyl cyanide to give ethyl 2-(γ-cyanopropyl)-1,2,3,4,-tetrahydroisoquinoline-3-carboxylate (22), which on treatment with hydrogen chloride in



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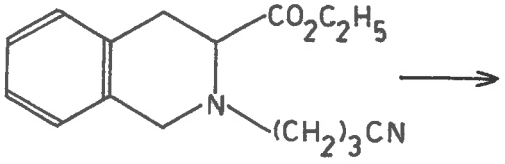

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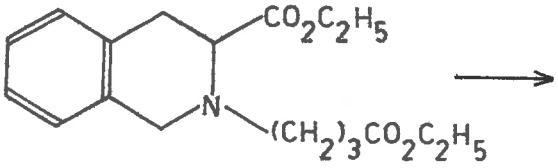

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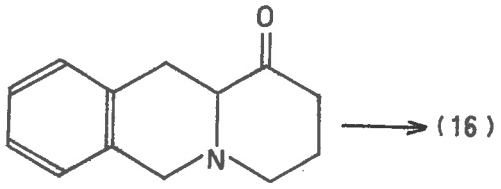
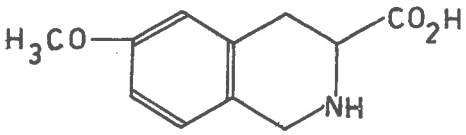


(24)

ethanol, yielded the diester (23). A Dieckmann condensation on (23) gave 1,3,4,6,11,11a-hexahydro-1-oxo-2H-benzo[b]quinolizine (24). The phenylhydrazone of this ketone readily underwent the Fischer indole reaction, producing hexadehydroyohimbane (16).

A direct application of this route was the synthesis of yohimbone via a dehydrogenated derivative of the ketone. By the use of 6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (25) in the above scheme, the methoxyhexadehydroyohimbane (26) was prepared.[11] When this was reduced under the conditions of the Birch



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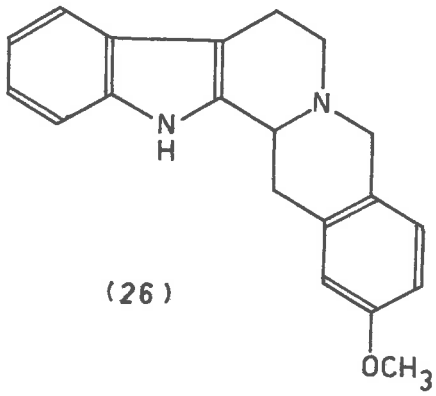
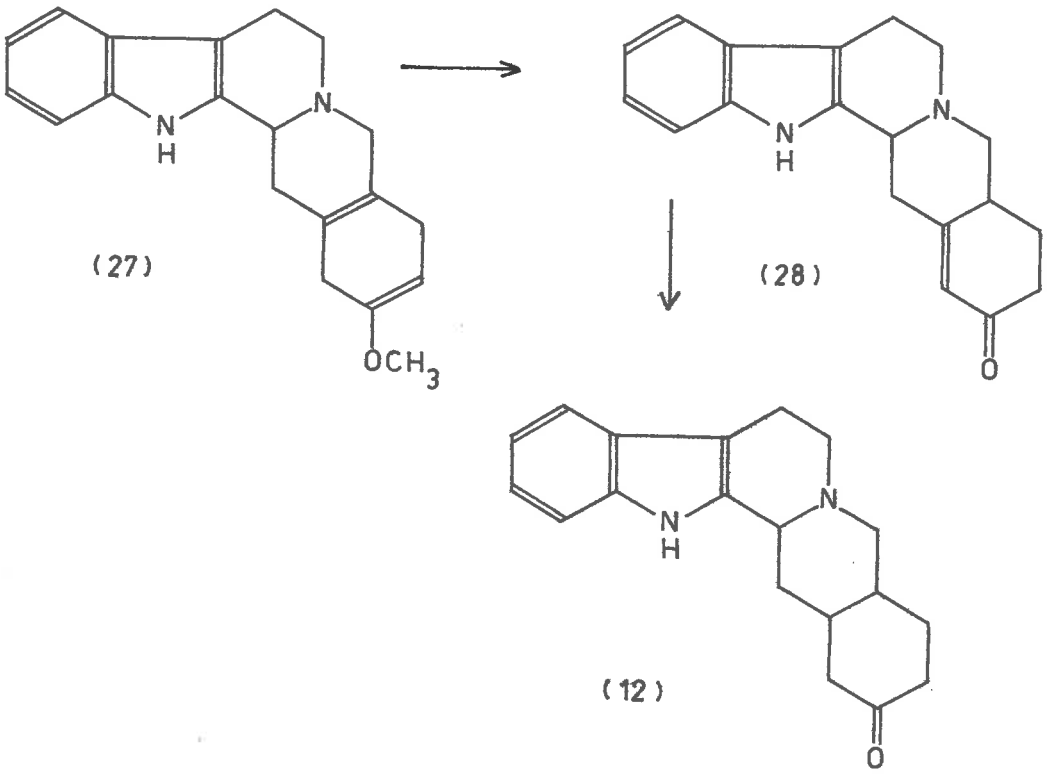
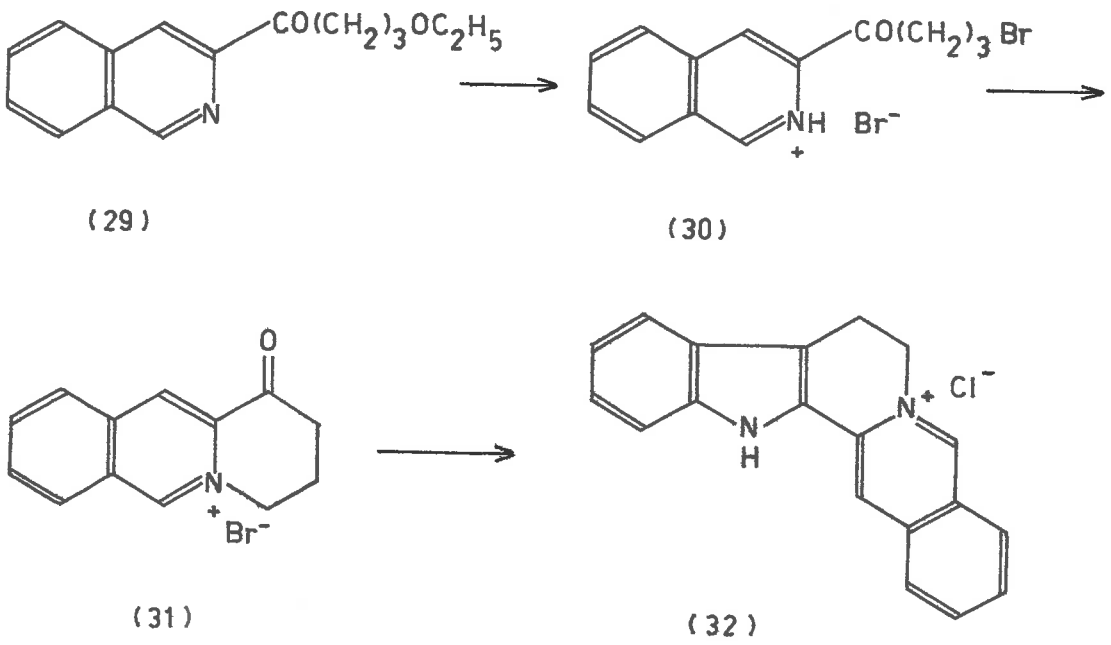


(26)

reduction, a compound which was assigned structure (27) was isolated. On treatment with methanolic hydrochloric acid (27) gave the unsaturated ketone (28) which, when reduced with Adams' catalyst under controlled conditions yielded yohimbone (12). This synthetic base was found to be identical with the sample obtained from the Oppenauer oxidation of yohimbine.

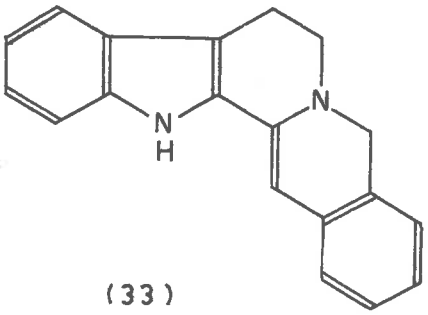


The Fischer indole method of ring closure was also used[14] for the synthesis of 7,8-dihydro-13H-benz[g]indolo[2,3-a]quinolizinium chloride (32). A different method of approach was needed to obtain the tricyclic ketone (31) required for the ring closure. 3-Cyanoisoquinoline condensed with 3-ethoxypropylmagnesium bromide, and acid hydrolysis of the intermediate gave 3-γ-ethoxybutyryliso-quinoline (29). The action of hydrogen bromide in acetic acid on (29) yielded a mixture of the bromide hydrobromide (30) and the cyclised product (31). A further amount of the ketone was obtained by the addition of base to a solution of (30). The phenylhydrazone of (31) underwent the Fischer indole reaction yielding the quinolizinium chloride (32).



(29) (30) (31) (32)

The alkaloid sempervirine is closely related to the base (32). Goutarel, Janot and Prelog[15] found that dehydrogenation of the alkaloid under a range of conditions yielded yobyrine and "tetrahydro-yobyrine", and stated that the basic ring system was therefore the same as that found in yohimbine. The presence of one active hydrogen atom was detected, and Prelog[16] proposed structure (33) for the alkaloid, with some reservation concerning the positions of the double bonds. Swan[17] immediately disproved this formulation by a synthesis of (33) <u>via</u> the cyclic lactam (34), the preparation of which will be described later. Further, it was found that (33), on reduction with Adams' catalyst in acetic acid, gave hexadehydro-yohimbane, whereas sempervirine did not react under the same conditions.



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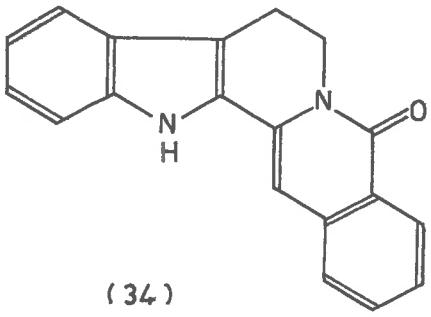
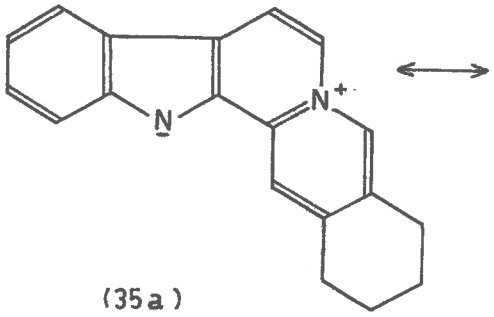
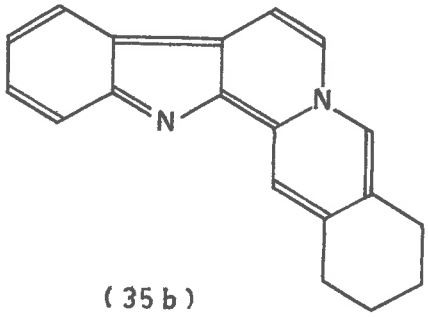


(34)

Bentley and Stevens[18] reasoned that as "tetrahydroyobyrine" was formed from sempervirine under relatively mild dehydrogenation conditions, then ring E of the base should exist in the reduced state, as in yohimbine. The expression (35a ⟷ 35b) was therefore proposed for sempervirine.



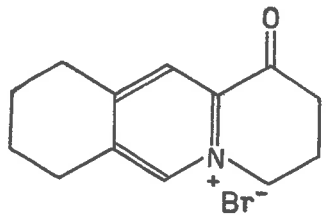
(35a)



(35b)

This structure for the alkaloid was soon proved by two syntheses of a different nature. The first was essentially the same as that used for the preparation of the 7,8-dihydro-13H-benz[g]-indolo[2,3-a]quinolizinium salts (32). 3-Cyano-5,6,7,8-tetrahydro-isoquinoline was converted in several steps[14] to the ketone (36). Fischer indole ring closure in the usual way yielded the salt (37)

which on dehydrogenation gave a product which was identical with an authentic sample of sempervirine.



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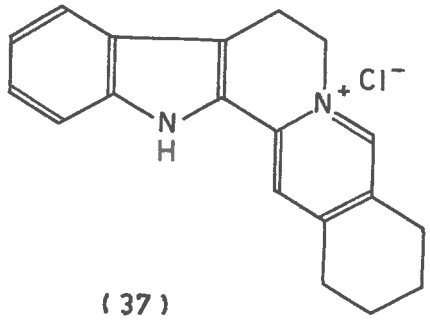
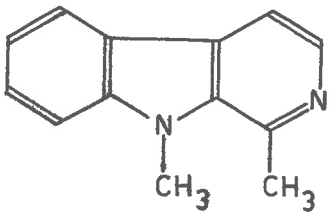


(37)

The synthesis of sempervirine methochloride[19] represented the first synthesis of the pentacyclic β-carboline system that did not require a final dehydrogenation step to aromatise rings C and D. The lithium derivative of N-methylharman (38) condensed with isopropoxymethylene cyclohexanone (39) to give salts of the methylsempervirinium cation (40) directly. This method of ring closure has not been applied to the preparation of the parent sempervirine salts.



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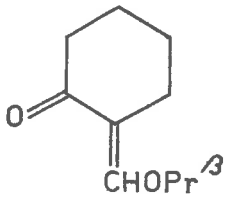

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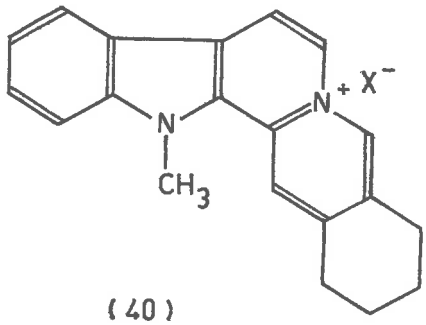
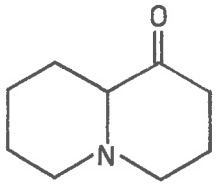


(40)

The tetracyclic β-carbolines have been successfully prepared using the Fischer indole synthesis. The methods are completely analogous to those of the pentacyclic β-carbolines. Thus, hexahydro-indolo[2,3-a]quinolizine (42) is produced[20] in good yield from the bicyclic ketone (41).



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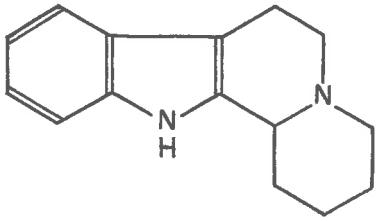
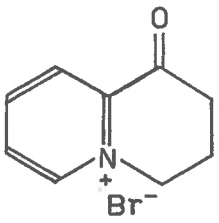
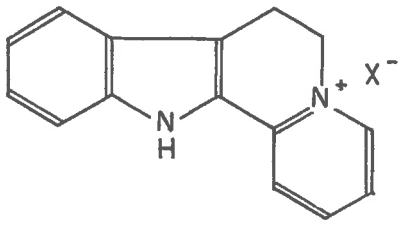


(42)

12H-Indolo[2,3-a]quinolizinium salts, the chromophore of sempervirine, were prepared simultaneously by three independent groups.[21,22,23] The three synthetic methods all used the Fischer indole ring closure of the phenylhydrazone of 1,2,3,4-tetrahydro-1-oxoquinolizinium bromide (43) to yield 6,7-dihydro-12H-indolo-[2,3-a]quinolizinium salts (44). Dehydrogenation of this compound with tetrachloro-o-benzoquinone,[21] or with acidified palladium on charcoal[22] gave the 12H-indolo[2,3-a]quinolizinium salts. The identity of (44) was confirmed by catalytic reduction to the hexahydro-derivative (42).

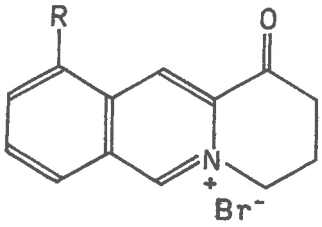


(43)

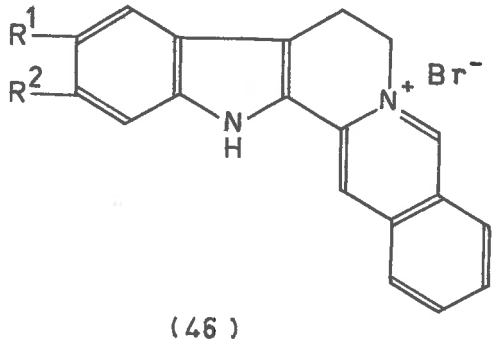


(44)

The structure assigned to alstoniline[24] (18) has been mentioned previously. In an effort to achieve a synthesis of this compound, Elderfield[23] proposed to cyclise the m-methoxyphenylhydrazone of the ketone (45), where R represents any function readily convertible to a carbomethoxy-group. However, to study the direction of the Fischer ring closure when substituted phenylhydrazones were used, the m-methoxy-, p-methoxy- and 3,4-dimethoxyphenylhydrazones of the ketone (45; R=H) were prepared. On cyclisation, these compounds yielded the 11-methoxy- (46; R^1=H, R^2=OCH_3), the 10-methoxy- (46; R^1=OCH_3, R^2=H), and the 10,11-dimethoxy- (46; R^1=R^2=OCH_3) β-carbolines respectively. These results are in agreement with those of Glover and Jones[22] who worked on a similar series. They justify the prediction of Ockenden and Schofield[25] that the introduction of electron-donating substituents into the 3-position of a phenylhydrazone should lead to the preponderance of the 6-substituted indole after cyclisation.



(45)

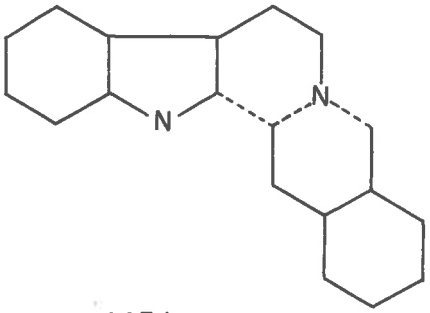


(46)

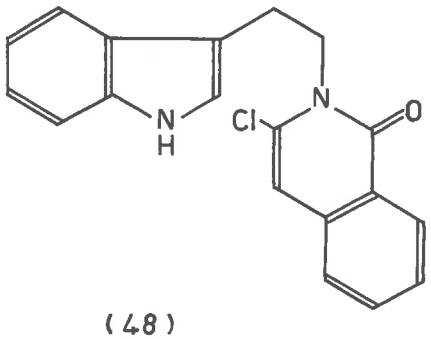
With the direction of the cyclisation firmly established, Elderfield turned to the synthesis of (45). However, although several

methods of attack on the problem were examined, none was found that would give a workable amount of the substituted ketone, and so this route to the synthesis of alstoniline was abandoned.

The second method of the construction of the pentacyclic β-carboline system involved the closure, more or less simultaneously, of rings C and D onto the pre-formed indole nucleus, as in (47). This involved a Bischler-Napieralski type of reaction on the product resulting from the condensation of tryptamine and derivatives of homophthalic acid.



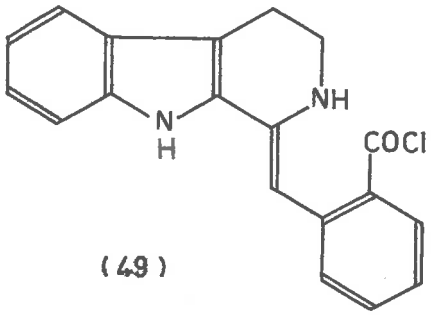
(47)



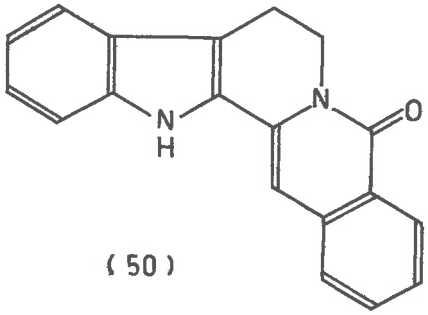
(48)

Clemo and Swan[12] condensed tryptamine with homophthalic acid, but the product, N-(2-3'-indolylethyl)homophthalimide, on treatment with phosphorus oxychloride, yielded a chlorine-containing compound which was formulated as (48). In the light of later evidence,[26] it seems possible that this structure is incorrect, and the compound is more likely to be (49). In any case, all attempts to cyclise this product to the lactam (50) failed. A slight modification in the reagents led to a measure of success. Tryptamine condensed with homophthalic anhydride to give N-(2-3'-indolylethyl)homophthalamic

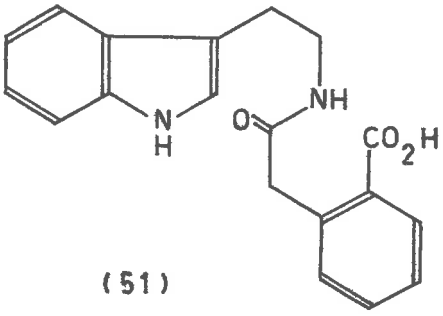
acid (51) which, on esterification and subsequent treatment with phosphorus oxychloride, gave a small amount of what proved to be the lactam (50). The yields of both the intermediate (51) and the cyclised lactam were later improved greatly.[9,27] The possibility that the reaction could have yielded the isomeric lactam (52) was not discounted, although this seemed unlikely from the physical characteristics of the compound. That the structure was, in fact, represented by (50) was proved[17] by the hydrogenolysis of the carbonyl group with lithium aluminium hydride and reduction with Adams' catalyst to yield hexadehydroyohimbane (16).



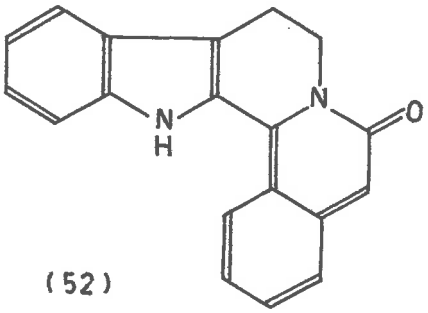
(49)



(50)



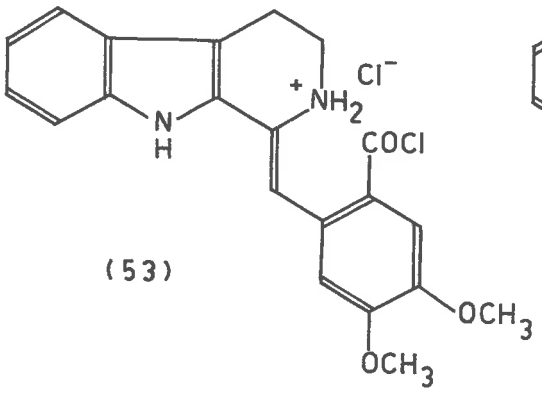
(51)



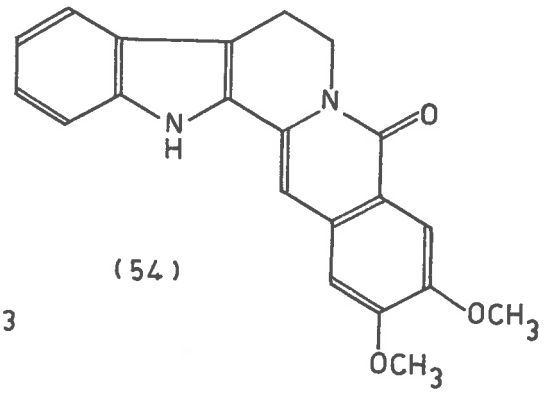
(52)

This cyclisation was soon applied[26] to the synthesis of substituted analogues of the lactam (50). Tryptamine condensed with 4,5-dimethoxyhomophthalic anhydride to give the substituted homophthal-

amic acid corresponding to (51). Esterification with diazomethane and treatment with phosphorus oxychloride yielded 1-(2-chlorocarbonyl-4,5-dimethoxybenzylidene)-1,2,3,4-tetrahydro-β-carboline (53). On the addition of sodium hydroxide, the acid chloride eliminated hydrogen chloride and ring closed to form the lactam (54). This represented one of the few cases in this series where the intermediate involved in the cyclisation was isolated and characterised.

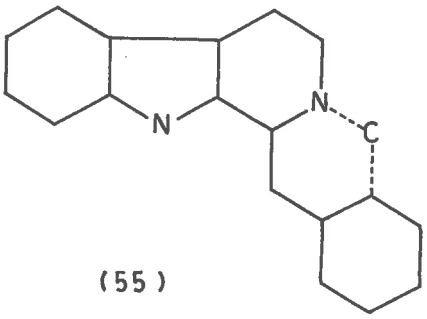


(53)



(54)

In 1935 Hahn and his co-workers[28] published a synthesis of the yohimbine skeleton that represented a tremendous early advance in the synthesis of the pentacyclic system. It involved the closure of ring D onto a pre-formed benzyl-β-carboline molecule (55). Tryptamine



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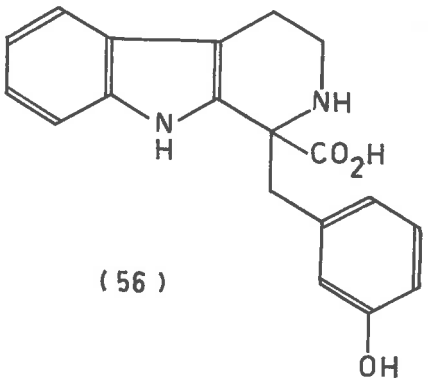

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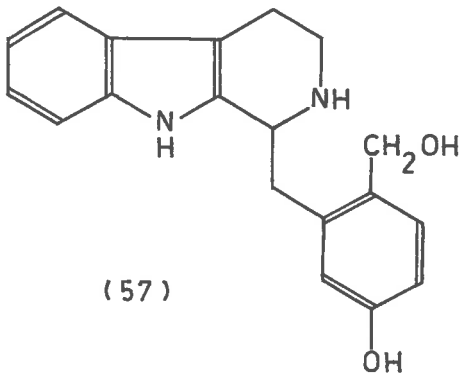
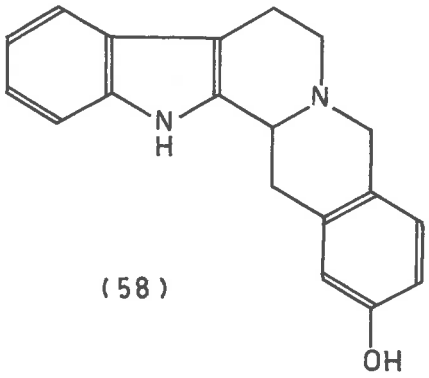


(57)

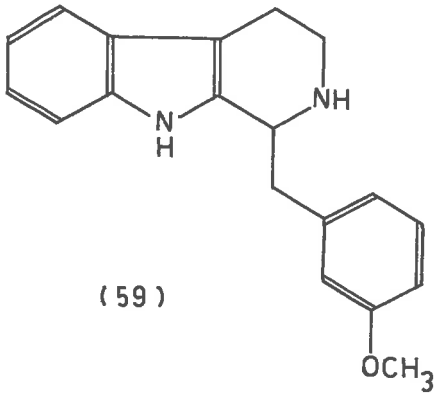


(58)

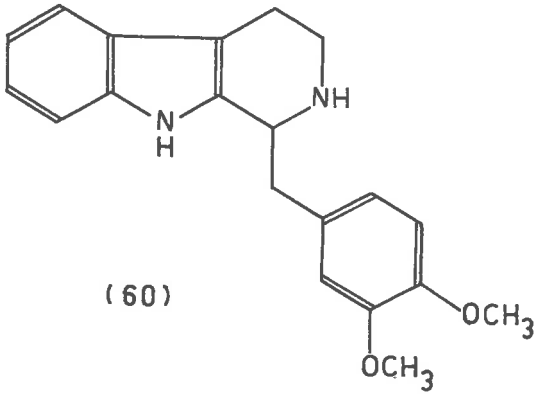
hydrochloride and m-hydroxyphenylpyruvic acid were condensed under so-called physiological conditions, at pH 4.2 and 25°, to give an 87% yield of 1-(m-hydroxybenzyl)-1,2,3,4-tetrahydro-β-carboline-1-carboxylic acid (56). Decarboxylation of this acid and treatment with aqueous formaldehyde was thought to give the 3-hydroxy-6-hydroxymethylbenzyl-β-carboline (57). The hexadehydroyohimbol (58) was obtained by treatment of aqueous solutions of (57) with ammonia or sodium carbonate. The yields of products in all stages of the reaction scheme were high. However, Hahn later reported[29] that the compound believed to have structure (57) was in reality a hydrated form of the pentacyclic hexadehydroyohimbol, but he presented evidence supporting the theory that the cyclisation could take place *via* an intermediate such as (57).

This method was subsequently applied to the synthesis of other hexadehydroyohimbanes substituted in ring E. The methoxy-derivative (26) was prepared[11] from the methoxybenzyl-β-carboline (59) and this was used as an intermediate in the synthesis of yohimbone. Potts and

Robinson[26] modified Hahn's experimental conditions, and found that heating (60) under reflux with aqueous formaldehyde produced an excellent yield of the corresponding dimethoxyhexadehydroyohimbane.

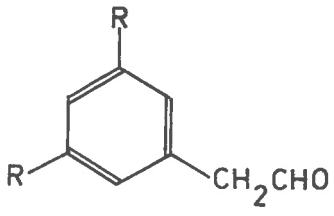


(59)



(60)

Although the main route to the benzyl-β-carboline system remains the condensation of tryptamine and substituted phenylpyruvic acids, the use of two other reagents is noted. Pleininger[30] found that tryptamine hydrochloride condensed with substituted phenylacetaldehydes (61) to give β-carbolines, but the yields of the base were low. 3-Methoxy-4-hydroxyphenylthiopyruvic acid (62) was also found[31] to react with tryptamine hydrochloride to give the benzyltetrahydro-β-carboline with the elimination of hydrogen sulphide and carbon dioxide.



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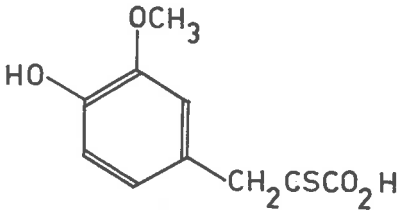
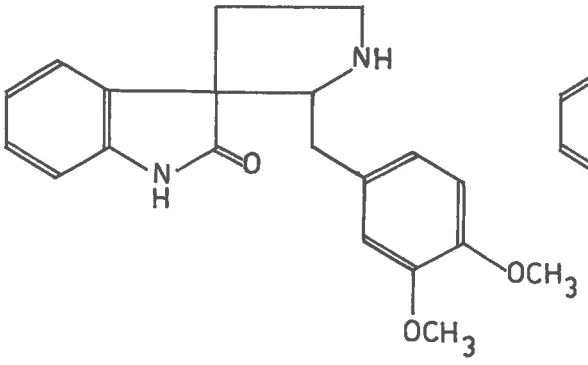
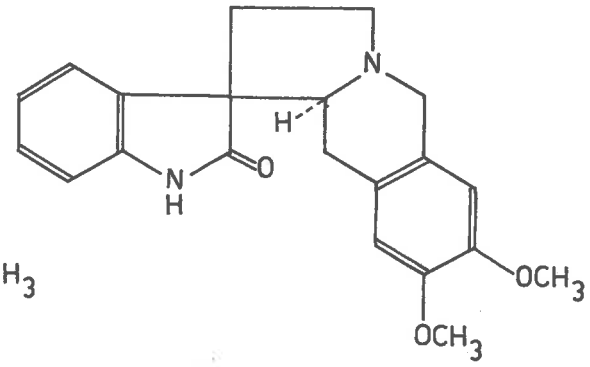


(62)

Recently a synthesis of derivatives of the Strychnos species under simulated physiological conditions was achieved.[55] 3,4-Dimethoxyphenylacetaldehyde and hydroxytryptamine were mixed in dilute aqueous solution at pH 6, and a 38% yield of the adduct (63) isolated. Treatment of (63) with aqueous formaldehyde gave the cyclised product (64). It was demonstrated that the relative stereochemistry of (63) was the same as that present in natural strychnine, a fact that has led to the proposal of an elegant biogenetic scheme for the strychnoid alkaloids.

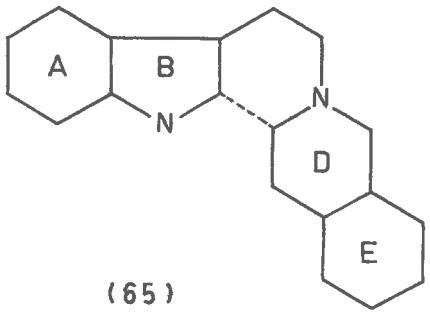


(63)

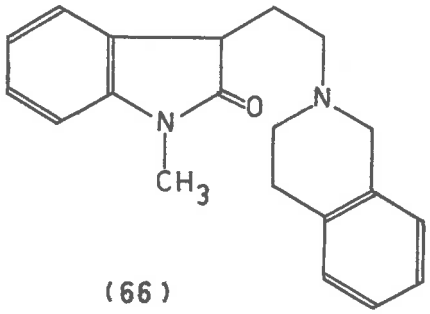


(64)

The pentacyclic β-carboline skeleton was found to be accessible by the closure of ring C onto the bridged A-B-D-E system (65). Julian and co-workers[32,33] purported that the dehydrogenation of 3-(N-tetrahydroisoquinolylethyl)-1-methyloxindole (66) with palladium black



(65)



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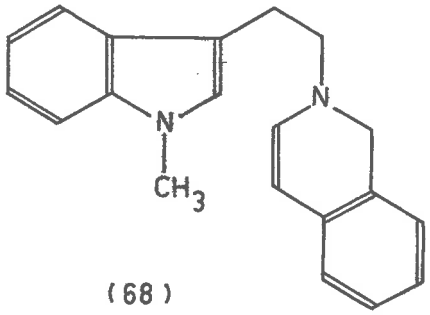
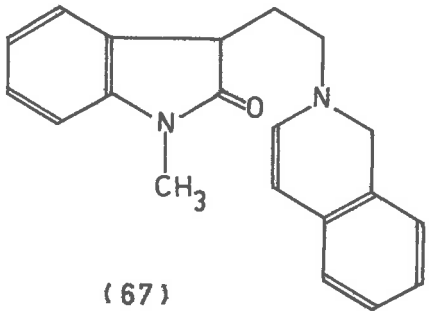


(68)



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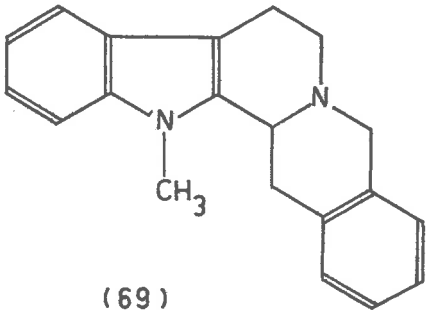
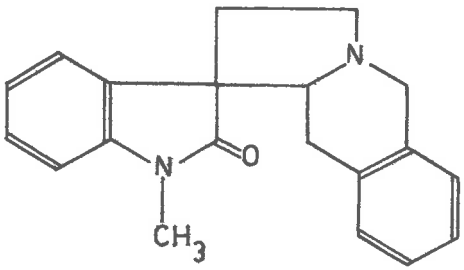


(69)

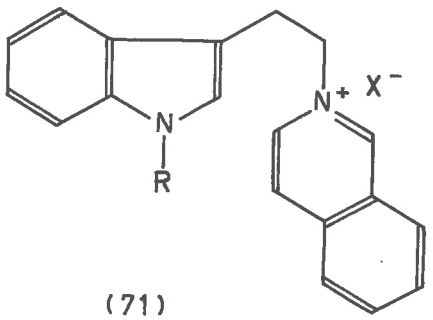


(70)

yielded the enamine (67). The evidence to support this statement was enlarged by the fact that treatment of (67) with lithium aluminium hydride, a substance known to reduce oxindoles to the parent indoles, gave N-methylhexadehydroyohimbane (69). The enamine (68) was supposed to be the intermediate in this transformation, and the cyclisation was considered to be spontaneous. Re-examination of the

physical and chemical characteristics of the supposed enamine (67) led Belleau[34] to propose the spiro-structure (70) as the true formulation for the compound. The smooth conversion of (70) to N-methylhexadehydroyohimbane was explained in terms of a reduction of the carbonyl group followed by an intramolecular rearrangement.

Although this work showed the term "reductive cyclisation", which had been applied to the above reaction sequence, to be erroneous, it brought forward a new method of approach to the yohimbine skeleton. The suggestion that (68) was an intermediate in the production of (69) was incorrect, but the exploitation of such an intermediate was considered possible. Potts and Robinson[26] showed that the treatment of 2-(2-3'-indolylethyl)isoquinolinium salts (71) with lithium aluminium hydride, and the isolation of the product using mineral acid, produced the pentacyclic hexadehydroyohimbane. The mechanism for this transformation will be discussed in detail in Chapter II, and it is sufficient at this stage to note that an intermediate similar to (68) was considered to be involved. The cyclisation was successful in the two cases shown (71; R=H, R=CH_3).



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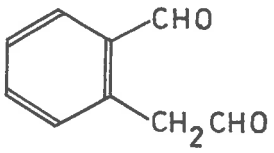
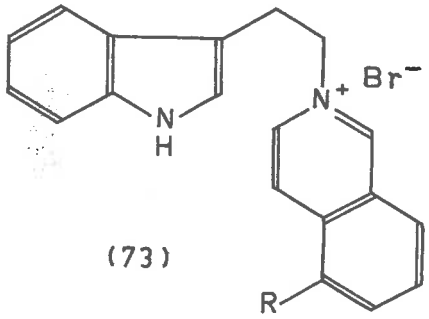


(72)

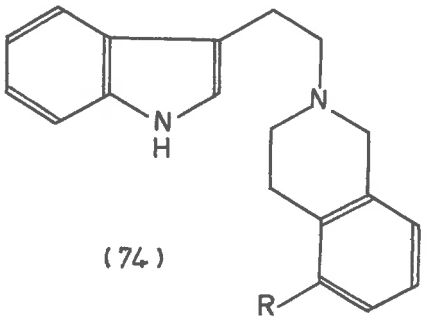
The indolylethylisoquinolinium salts were prepared by two methods. Tryptamine and homophthalaldehyde (72) condensed readily and gave the desired salts on the addition of the appropriate acid. An alternative synthesis was effected by the condensation of 2-3'-indolylethyl bromide with isoquinoline in benzene solution.

The effect of metal hydrides on salts of the type (71), but containing a substituted isoquinolinium system, was studied by Elderfield and Fischer.[35,36] Reduction of (73) with sodium borohydride in methanol yielded the substituted indolylethyltetrahydroisoquinolines (74). However, when ethanol was used as the solvent for the reduction of (73; R=CO_2CH_3), the carbomethoxy-group was also attacked to give (74; R=CH_2OH). When lithium aluminium hydride was



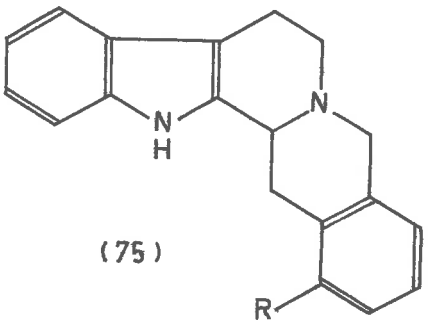
(73)

R= CN ; CO_2CH_3



(74)

R= CN ; CO_2CH_3



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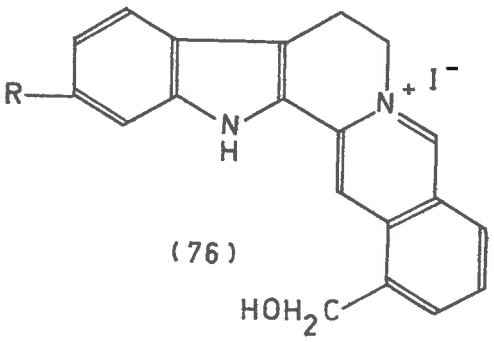


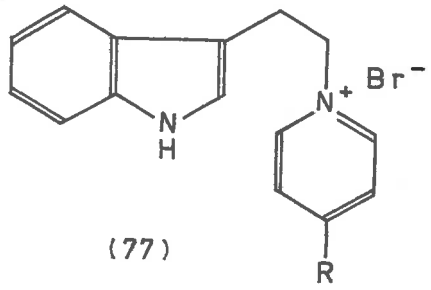
(76)

used as the reducing agent, the cyclised products corresponding to (75) were obtained. The reduction of (73; R=CO_2CH_3), and treatment with acid, yielded (75; R=CH_2OH), which was oxidised with iodine and potassium acetate to the quaternary salt (76; R=H).

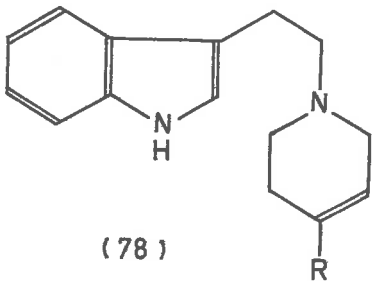
The success of the above reactions led Elderfield to undertake a synthesis of alstonilinol, a compound derived from the alkaloid alstoniline. 6-Methoxy-3-(2-bromoethyl)indole was prepared and condensed with 5-carbomethoxyisoquinoline. The product was treated with lithium aluminium hydride, and then dehydrogenated with iodine and potassium acetate yielding alstonilinol (76; R=OCH_3), identical with a sample prepared from natural alstoniline.

No report has yet appeared in the literature of the successful application of this method of ring closure to the preparation of the tetracyclic β-carbolines. The problem has been examined,[37] however. 1-(2-3'-Indolylethyl)pyridinium bromide (77; R=H) was treated separately with sodium borohydride and lithium aluminium hydride, but the product, the indolylethylpiperideine (78; R=H), was the same regardless of the reagent used. Noting this difference in the behaviour of the N-substituted pyridinium and isoquinolinium salts, Elderfield prepared a series of substituted pyridinium compounds (77; R= CH=CH.Ph, R=$CO_2C_2H_5$) in an effort to reproduce the electronic effect associated with the double bonds of the benzene ring in the case of the isoquinolinium salts. He hoped, in this way, to be able to prepare substituted tetracyclic β-carbolines. However, treatment

of these salts with sodium borohydride yielded the corresponding substituted piperideines as before. The use of lithium aluminium hydride gave oily products that could not be characterised.



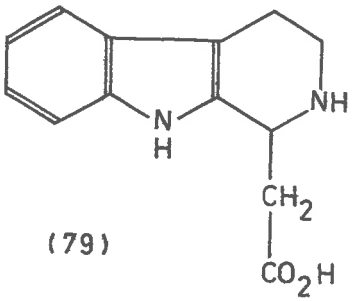
(77)



(78)

The importance of the tetracyclic β-carboline system, especially when the structures of corynantheine, serpentine[38] and certain of the Alstonia alkaloids are taken into account, was sufficient to warrant numerous efforts to establish a synthesis. Behind much of this work lay the hope that if ring D of the system could be prepared suitably substituted, then ring E, the most complex in many of the alkaloids, could be specifically added at a later stage.

Groves and Swan[39] obtained 1,2,3,4,6,7,12,12b-octahydro-2-ketoindolo[2,3-a]quinolizine (81; R=H) by an application of the Dieckmann reaction. Condensation of the ethyl ester of 1,2,3,4-tetrahydro-β-carboline-1-acetic acid (79) with ethyl acrylate yielded the diester (80). When this compound was subjected to a Dieckmann reaction, and the product hydrolysed with dilute acid, the keto-β-carboline (81; R=H) was obtained in good yield.



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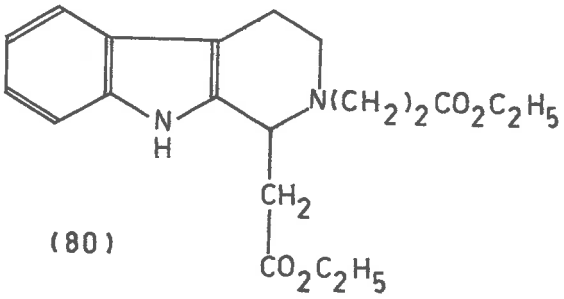

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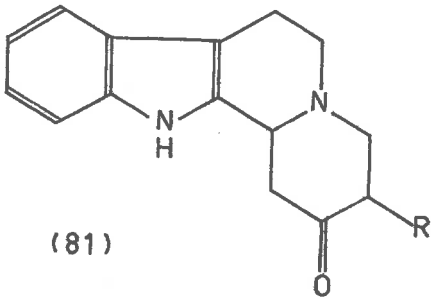
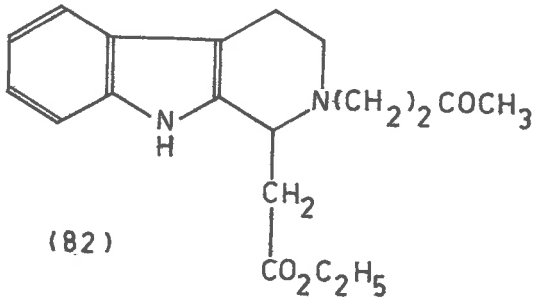


(81)

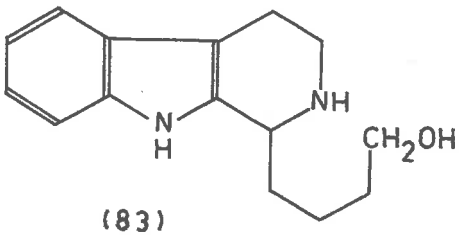


(82)

The synthesis of (81; R=CO.CH_3) was accomplished[40] by a modification of the above route. The ethyl ester of (79) underwent a Mannich reaction with acetone and formaldehyde to yield the ester (82) which ring closed under the conditions of the Dieckmann reaction to give the tetracycle (81; R=CO.CH_3). Neither this nor the parent compound were found to be suitable for the further construction of ring E to give a pentacyclic base, as ring D opened under very mild conditions.

The construction of ring D onto a completed A-B-C skeleton also allowed a ready synthesis[39] of 1,2,3,4-tetrahydro-12H-indolo-[2,3-a]quinolizinium bromide (85). 1-4'-Hydroxybutyl-1,2,3,4-tetrahydro-β-carboline (83) was dehydrogenated with palladium and

treated with hydrogen bromide to yield the bromide hydrobromide (84). The base liberated from this compound by the addition of one equivalent of sodium carbonate rapidly underwent internal quaternisation yielding (85).



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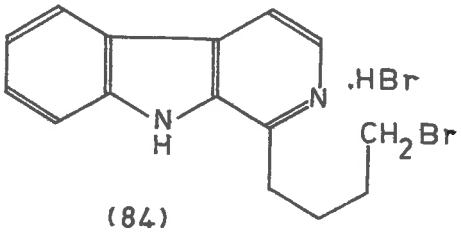

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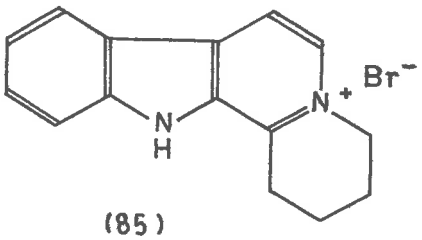

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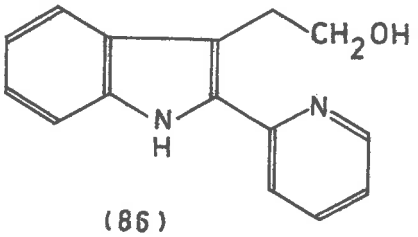
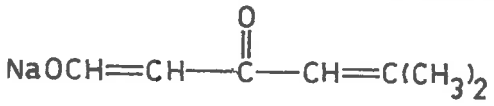


(86)

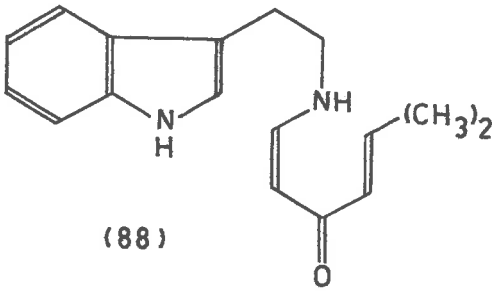
A method theoretically similar to the above enabled Sugasawa[41] to report the first β-carboline synthesis involving the closure of ring C from the 3-position of the indole with a 2-carbon chain. 2-(2'-Pyridyl)indole was converted in several steps to the alcohol (86). On treatment with phosphorus tribromide, 6,7-dihydro-12H-indolo[2,3-a]quinolizinium bromide (44; X=Br) was obtained. This compound was also prepared readily by Ban and Seo[42] who found that simply heating a mixture of 2-3'-indolylethyl bromide and 2-chloropyridine produced the bromide (44) in high yield.

The hydroxymethylene derivative (87) was found to be a useful intermediate in the formation of tetracyclic β-carbolines.[43] It condensed with tryptamine hydrochloride to give the unsaturated

base (88), and successive treatment with methanolic hydrogen chloride and sodium bicarbonate yielded the ketone (89).



(87)



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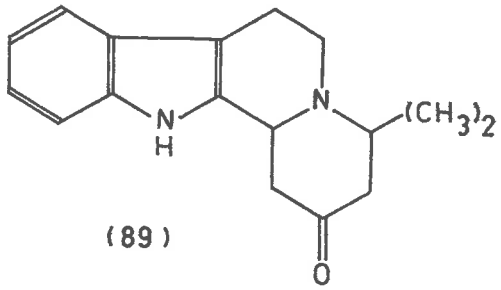
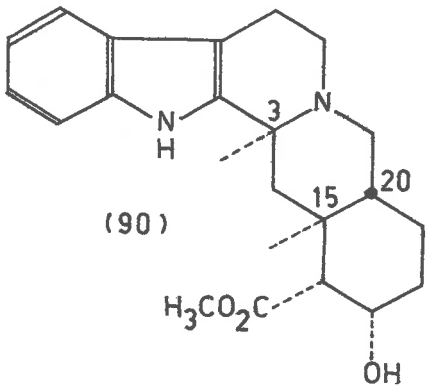


(89)

With the nuclear structure of yohimbine definitely established, attention was turned to the stereochemical problems associated with the molecule. It is not proposed to elaborate on how these problems were solved. However, the ways in which synthetic methods developed for the synthesis of the yohimbine skeleton were used to confirm the stereochemical assignments will be demonstrated.



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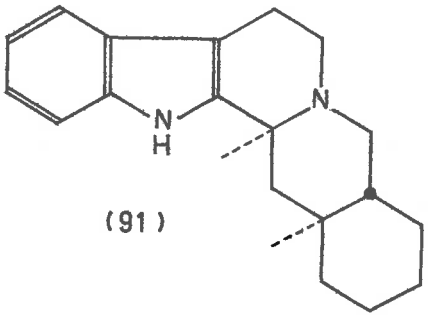


(91)

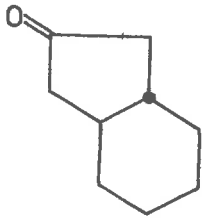
Yohimbane (91) was isolated from yohimbine (90) by Jost[44] in 1949, although of course he did not know the configuration of the

product. The process involved the Oppenauer oxidation of yohimbine, with loss of the carbomethoxy-group and production of yohimbone. Wolff-Kishner reduction of the ketone yielded the yohimbane (91). Under the conditions of the reactions it seemed improbable that any change would take place at the asymmetric centres C-3, C-15 or C-20, and it could be stated with certainty that the nature of the D/E ring junction would be the same in yohimbine and yohimbane.

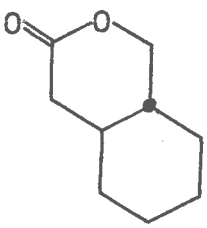
The assignment of the D/E ring junction in yohimbine as trans was based upon the isolation of an optically active N-methyl-trans-decahydroisoquinoline as one of the degradation products of the alkaloid. As the method for obtaining the isoquinoline involved both vigorous conditions and catalytic reduction of an intermediate of undetermined structure, it was not absolutely certain that the D/E junction had been left unchanged during the degradation. To resolve this doubt, and to prove conclusively the nature of the D/E junction in yohimbine, van Tamelen developed[45] a stereospecific synthesis of dl-yohimbane.

Perbenzoic acid oxidation of dl-trans-2-hydrindanone (92) yielded the lactone (93) which was converted into the bromoester (94) with ethanolic hydrogen bromide. The ester condensed with tryptamine to give the lactam (95) which was converted into the unsaturated base (96) with phosphorus oxychloride. Catalytic reduction of (96) gave dl-yohimbane in high yield, with no evidence of epimer formation. The sample was identical in all respects with

that derived from yohimbine.



(92)



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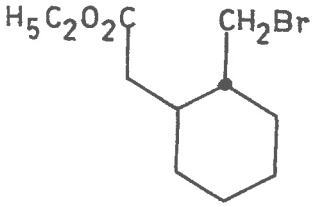

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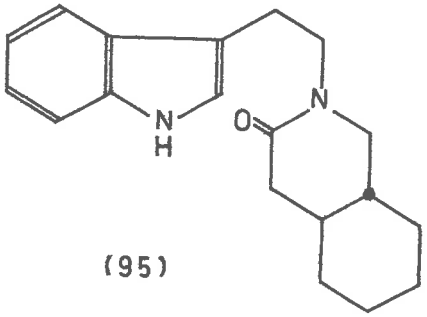

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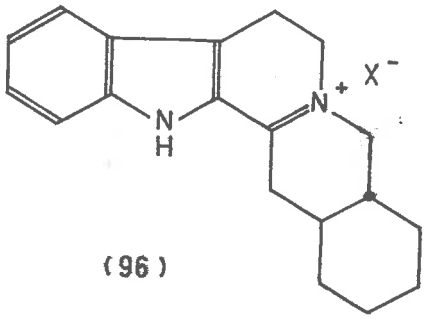
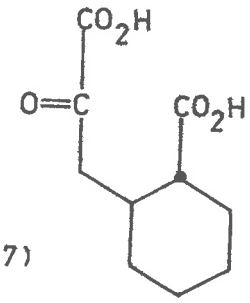


(96)

Corsano[46] also provided a synthesis of yohimbane by a different route. Tryptamine and trans-2-carboxycyclohexylpyruvic acid (97) were heated together in acetic acid to give the cyclic lactam (98) directly, and this compound yielded dl-yohimbane when treated with lithium aluminium hydride.



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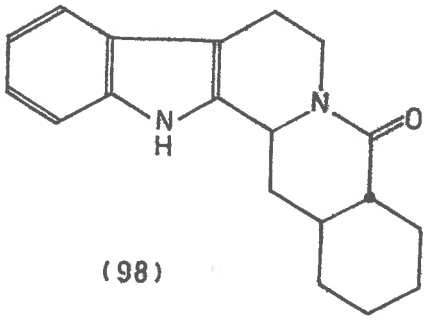
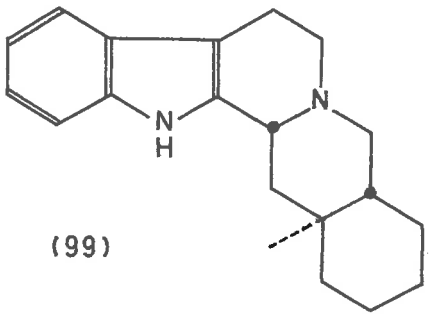


(98)

The presence of the C-3 epimer of yohimbane, epiyohimbane (99), in Nature was demonstrated by Goutarel and Janot and their co-workers.[47] ψ-Yohimbine and yohimbine both gave the same tetradehydroyohimbine (100) on treatment with lead tetra-acetate, and it was concluded that the two bases differed only in the configuration at position 3. Reduction of (100) under alkaline conditions yielded yohimbine, which is presumably the more stable isomer of the two. ψ-Yohimbine was therefore assigned the epiyohimbane skeleton (99).



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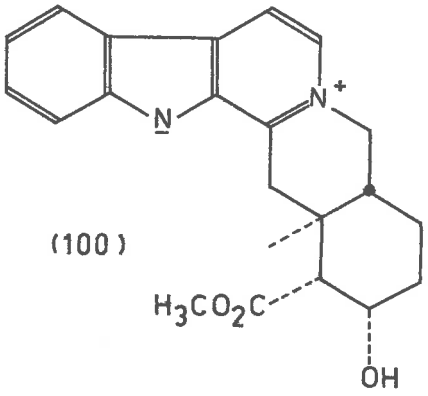
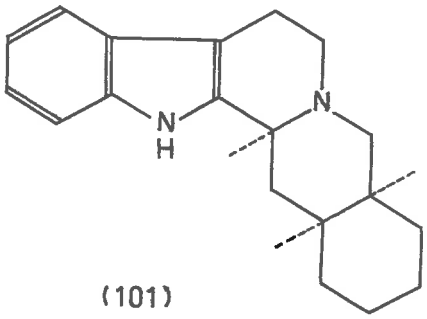


(100)

The two remaining members of the yohimbane group, alloyohimbane (101) and epialloyohimbane (102), differ from yohimbane and its C-3 epimer by possessing a D/E cis ring junction. Derivatives of the two systems are found among the alkaloids, but remarkably the epialloyohimbane skeleton was not noticed in Nature until after its synthesis had been reported.[48]



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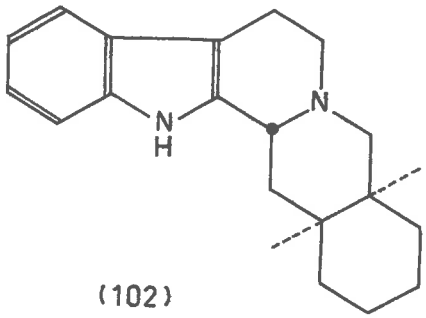
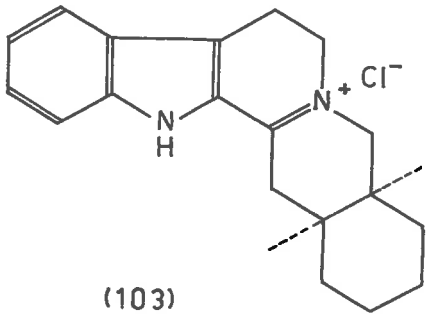


(102)

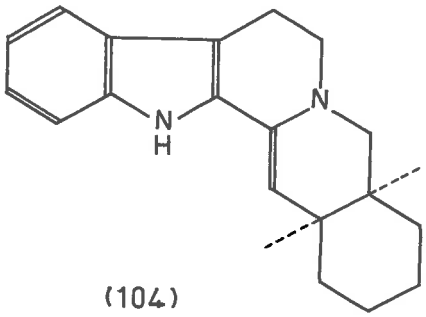
Alloyohimbine and α-yohimbine when submitted to Oppenauer oxidation yielded the same alloyohimbone, which on Wolff-Kishner reduction gave alloyohimbane (101). The identity of (101) was established[49] by comparison with the product resulting from the hydrogenation of sempervirine (35). A similar process of degradation showed epialloyohimbane to be the skeleton of epi-α-yohimbine.[50] The product of the final reduction was a mixture of (101) and (102), but it was shown that the alloyohimbane arose from the original epialloyohimbane by epimerisation under the alkaline conditions of the reaction.

The establishment of the configuration of the alkaloids mentioned above depended on the structure of the product obtained by the reduction of sempervirine. Whilst this had correctly been assigned as (101) the uncertainties attending the course of the hydrogenation made a separate stereospecific synthesis of alloyohimbane and epialloyohimbane desirable. Stork and Hill[51] achieved this by a method similar to that described earlier for the synthesis of yohimbane. Starting

from cis-2-hydrindanone the quaternary salt (103) was derived, which liberated the free base (104). Reduction with Adams' catalyst gave solely dl-alloyohimbane, whilst reduction with sodium/ethanol/liquid ammonia yielded dl-epialloyohimbane.

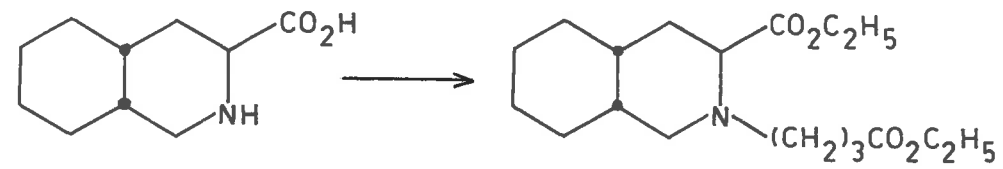


(103)

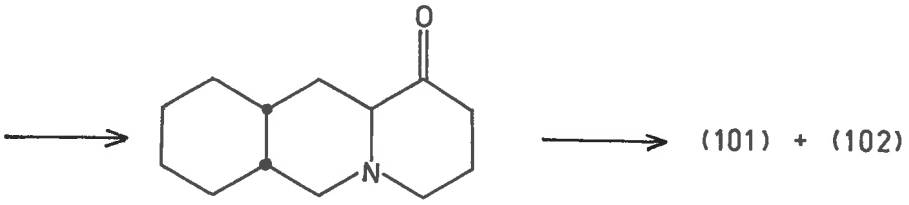


(104)

The Fischer indole method of ring closure developed by Swan[11,12] was also applied to the synthesis of the systems (101) and (102).[56] Ethyl γ-bromobutyrate was used to alkylate cis-decahydroisoquinoline-3-carboxylic acid (105), and the diester (106) was ring closed by an application of the Dieckmann reaction. Hydrolysis and decarboxylation yielded the tricyclic ketone (107). Treatment of the phenylhydrazone of (107) with hot ethanolic hydrogen chloride gave the desired pentacycles, and it was found that alloyohimbane predominated in the mixed product.



(105) (106)



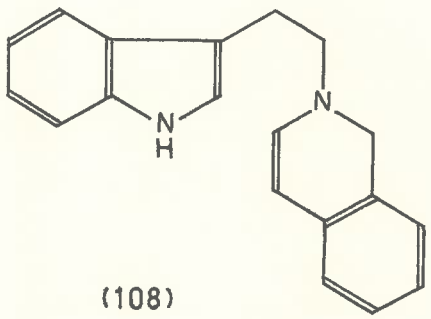
(107)

The natural culmination of the synthetic work reported here has been the laboratory preparations of several of the well-known indole alkaloids. These represent most notable successes, and examples may be found in the syntheses of yohimbine,[52] reserpine[53] and strychnine.[54]

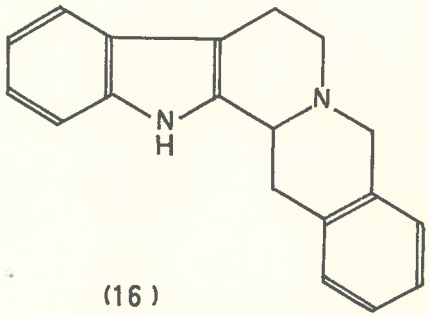
DISCUSSION

Many of the syntheses of tetra- and pentacyclic β-carbolines described in Chapter 1 are restricted in application due to the complex nature of the starting materials. Frequently a multi-step process is necessary to obtain the desired alkaloid or alkaloid derivative. The development of a ready synthesis of the indole alkaloid skeleton was therefore an attractive prospect.

The route chosen for investigation involved the closure of ring C onto the completed A-B-D-E system. This method of formation, involving the "reductive cyclisation" of 2-(2-3'-indolylethyl)isoquinolinium iodide to hexadehydroyohimbane (16) *via* the intermediate (108), has been previously studied,[26] and was described in Chapter 1. It was proposed to increase the availability of (16) by circumventing several of the steps necessary to obtain the enamine (108).



(108)



(16)

This was achieved by the condensation of 3-acetylindole with

iodine and isoquinoline to give the quaternary salt 2-(2-3'-indolyl-2-oxoethyl)isoquinolinium iodide, which was reduced by lithium aluminium hydride to the enamine (108). Cyclisation was effected with dilute mineral acid, and 5,7,8,13,13b,14-hexahydrobenz[g]indolo[2,3-a]quinolizine (hexadehydroyohimbane) obtained from indole in three steps with an overall yield of the order of 45%.

As large quantities of 3-acetylindole were required, available syntheses were evaluated. The most satisfactory method for the preparation of this compound appeared to be the basic hydrolysis of 1,3-diacetylindole which is available from the reaction of indole with a mixture of acetic acid and acetic anhydride.[57] However, under the conditions of the reaction, black tarry by-products are formed which complicate purification of the final product and so reduce the overall yield of pure 3-acetylindole.

The formation of coloured by-products was found to be eliminated when the acetic acid in the acetylation mixture was replaced by small quantities of vinyl acetate. In an initial experiment indole was heated under reflux with a mixture of acetic anhydride and vinyl acetate (92% : 8%) for 24 hours. Fractional crystallisation of the pale yellow product showed the presence of both 3-acetylindole and 1,3-diacetylindole. In subsequent reactions using an acetylation mixture containing 6% vinyl acetate and a reaction time of 15 to 20 hours, the crude product was treated

with alcoholic sodium hydroxide without further purification to obtain a maximum yield (ca. 67%) of the desired 3-acetylindole. The product also contained a small amount of 1,3'-indolyl-1,3"-indolylidene ethane (109), a compound also formed when indole is treated with a mixture of acetic acid and acetic anhydride.[57]

It was noticed that no indole remained unchanged once the reaction mixture became pale yellow, and using this fact as a guide, it was found possible to reduce the reaction time by reducing the amount of vinyl acetate in the acetylation mixture. Thus, when only 4% vinyl acetate was present, a good yield of 3-acetylindole was obtained after a reaction time of 8 hours (Table 1). However, when the mixture contained 10% of the ester the acetylation of the indole was inhibited to a large extent. After a reaction time of 50 hours the mixture was still colourless, and indole (ca. 85%) was recovered unchanged, with 1,3-diacetyl-indole being the only other product.

The presence of styrene (10%) during acetylation also prevented darkening of the reaction mixture, the yield of 3-acetyl-indole being comparable to that when vinyl acetate (6%) was employed (Table 1). A small amount of polystyrene was isolated as a by-product.

Table 1

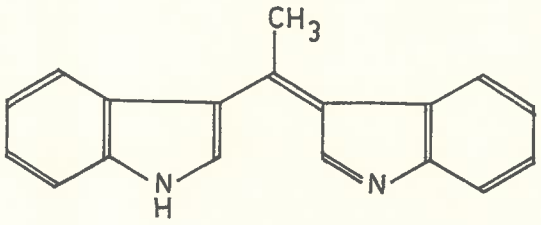
Acetylation of Indole

Acetic anhydride plus	Reaction time (hr.)	3-Acetylindole isolated
Vinyl acetate (6%)	15-20	67%
Vinyl acetate (4%)	8	61%
Vinyl acetate (10%)	50	15%
Styrene (10%)	24	67%

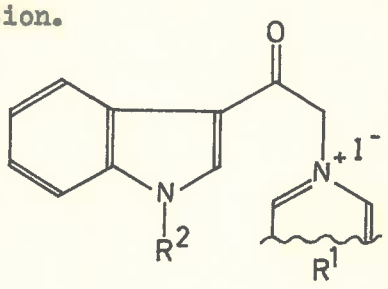
The reason for the prevention of the formation of coloured by-products by compounds containing the vinyl group most probably lies in the removal of oxygen from the solution. It has been demonstrated[58] that certain vinyl compounds undergo thermal polymerisation, and that peroxides are formed in the presence of oxygen. In an adequate supply of oxygen the formation of the peroxides, which are excellent polymerisation catalysts, is the preferred reaction. However, in solution the dissolved oxygen is quickly removed and the polymerisation of the remaining vinyl monomer aided by the peroxides formed. The small amount of polystyrene isolated may be accounted for in this way.

The inhibition of the acetylation reaction by increased amounts of vinyl acetate cannot be explained at this time. There was a drop of 4° in the temperature of the solution under reflux when

the acetylation mixture contained 10% vinyl acetate instead of 6%, but it is difficult to imagine such a small difference causing such a marked reduction in acetylation.



(109)

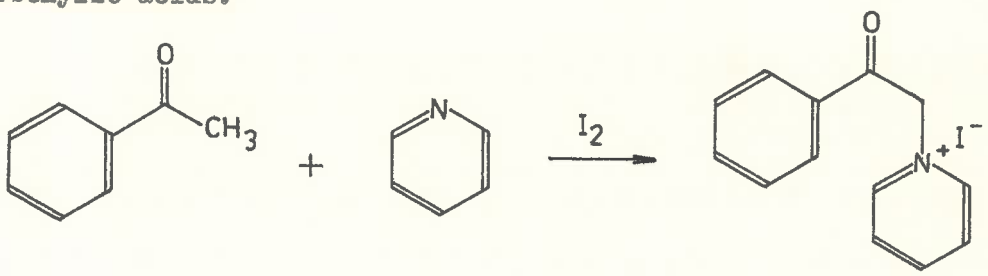


(110)

The next step in the synthesis of the pentacyclic β-carboline system was the preparation of salts of the type (110; R^1= isoquinoline, R^2=H, CH_3). This type of substituted indole, but containing the quaternary pyridinium nucleus, had previously been prepared by Sanna.[59] Iodoacetyl chloride reacted with indolyl magnesium iodide to give 3-(iodoacetyl)indole, which condensed with pyridine forming (110; R^1=pyridine, R^2=H). However, the low yield during the Grignard substitution rendered an improved synthesis of the iodides desirable, and they were found to be readily prepared in good yield from 3-acetylindole.

In many ways 3-acetylindole reacts as a typical methyl-aryl ketone. Thus it readily forms a phenylhydrazone,[60] an oxime,[61] a thiosemicarbazone,[62] and a Mannich base with paraformaldehyde and dimethylamine hydrochloride,[63] in an analogous manner to acetophenone. This compound has been shown to

condense with iodine and a tertiary aromatic base, for example pyridine, to form the quaternary salt (111). In a detailed study of this reaction, King and his co-workers have demonstrated its general application to compounds with a methyl ketone group directly attached to an aromatic nucleus.[64,65] The structures of the products were confirmed by comparison with authentic samples, and by alkaline cleavage to the corresponding aromatic carboxylic acids.



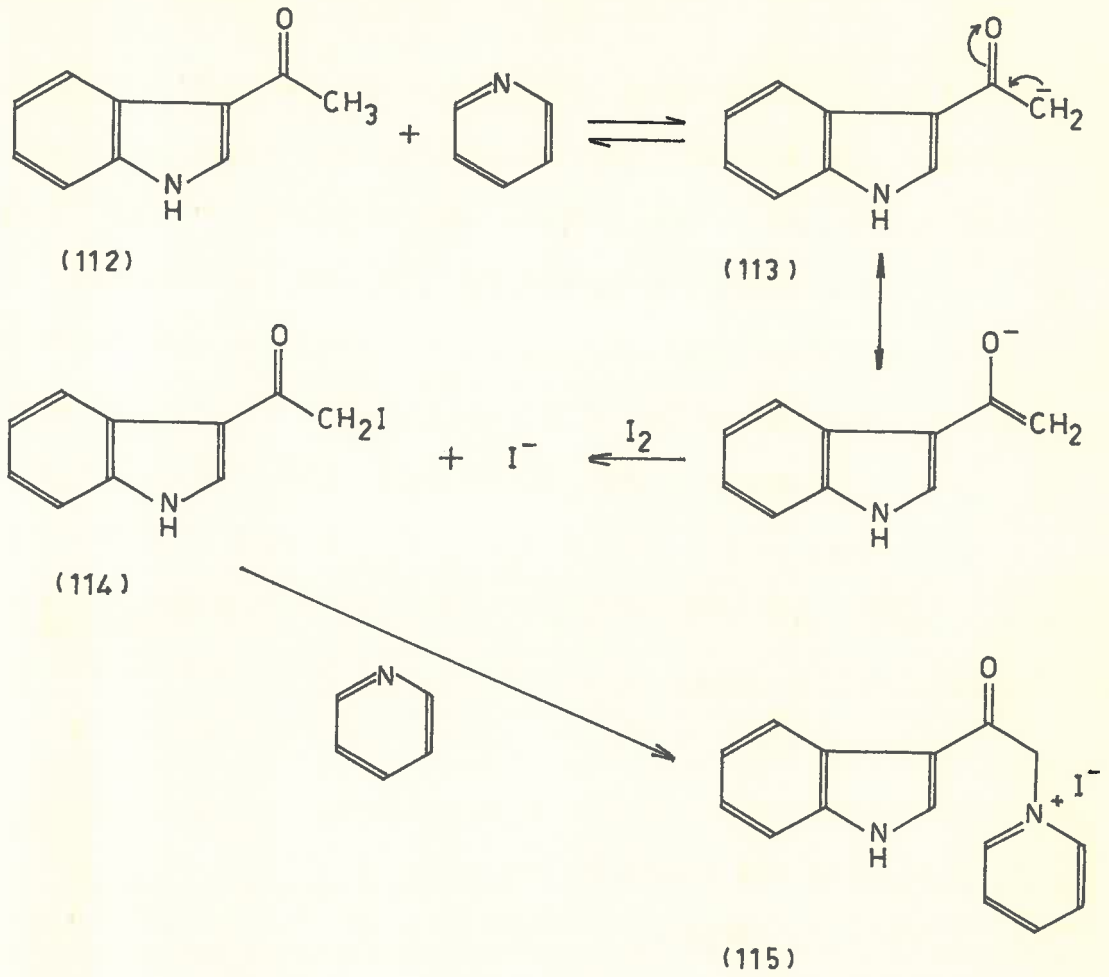
(111)

It was therefore expected that 3-acetylindole would react in a similar manner to form compounds that would have the required structure for use as intermediates in the synthesis of β-carbolines. This expectation was fulfilled and 3-acetylindole condensed with iodine and isoquinoline to form 2-(2-3'-indolyl-2-oxoethyl)isoquinolinium iodide (110; R^1=isoquinoline, R^2=H) in almost quantitative yield. Table 2 shows a list of corresponding salts formed from various aromatic bases. The iodide ion was readily exchanged for the perchlorate ion by treatment with 50% aqueous perchloric acid.

Table 2

Quaternary Iodide from:	Yield (%)	pK_a of base
Isoquinoline	94	5.14
Quinoline	53	4.94
Pyridine	68	5.23
3-Methylpyridine	64	5.82
3-Ethylpyridine	80	
3-Ethyl-4-methylpyridine	22	6.55
5,6,7,8-Tetrahydroisoquinoline	4	

The mechanism for the formation of these compounds most probably parallels that for the formation of 1-phenacylpyridinium iodide (111), which has been fully elucidated by Pearson.[66] The rate of reaction is independent of the concentration of iodine and depends upon the usual base-catalysed enolisation of the ketone. In the reaction between 3-acetylindole (112), iodine and pyridine the rate-determining step would be the abstraction of the proton to form the tautomeric carbanion (113) which would then react rapidly with iodine to give 3-(iodoacetyl)indole (114). Subsequent reaction of this compound with a second molecule of the base would give 1-(2-3'-indolyl-2-oxoethyl)pyridinium iodide (115).



(112)

(113)

(114)

(115)

On the basis of the above mechanism it is difficult to rationalise the vast difference in the percentage yields of products when different aromatic bases are used in the condensation. From an elementary consideration it might be expected that a stronger base would more readily promote carbanion formation by the ketone, which could then react further as explained. However, when 3-ethyl-4-methylpyridine was employed in the reaction a 22%

yield of the quaternary iodide was isolated, and the use of 5,6,7,8-tetrahydroisoquinoline gave only trace amounts of the corresponding salt. It is of interest at this stage to note that King[64,65] also reported a similar wide variation in the yield of condensed products in the acetophenone series (Table 3), although he offered no explanation for it.

Table 3

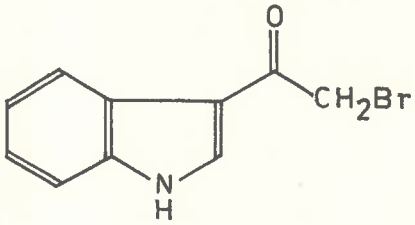
Iodide	Yield (%)
1-Phenacylpyridinium	88
1-Phenacyl-2-picolinium	24
1-Phenacyl-3-picolinium	56
1-Phenacyl-4-picolinium	12
2-Phenacylisoquinolinium	95
1-Phenacylquinolinium	43

From Tables 2 and 3 it would seem that poor yields of the expected iodides are obtained whenever an aromatic base containing an alkyl-substituent in either the 2- or the 4-position is employed in the reaction. In the author's opinion no effective conclusions can be drawn from the percentage yields quoted in these Tables. Isolation of pure products is rendered difficult by the presence of excess base, iodine, and the hydroiodide of the base

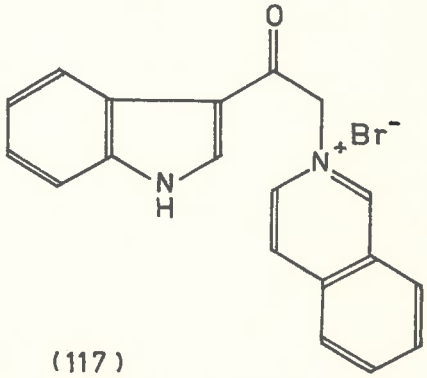
formed as a by-product of the reaction. It was frequently found necessary to triturate the black semi-crystalline tar with solvents in which the products were quite soluble in order to obtain an uncontaminated sample of the desired quaternary iodide. For example, during the preparation of 2-(2-3'-indolyl-2-oxoethyl)-5,6,7,8-tetrahydroisoquinolinium iodide the solid material obtained by extraction of the tar with boiling water could not be purified by further crystallisation, although an infrared spectrum indicated that it contained a large proportion of the condensed product. When the crude mixture was triturated with ethanol a homogeneous sample of the iodide was obtained, but in very low yield. It would therefore seem that the amount of product isolated and reported in Tables 2 and 3 has little relation to the amount actually formed during the reaction.

The structure of the quaternary iodides was proved by comparison with samples prepared by unambiguous routes. 3-(Bromoacetyl)indole (116) reacted readily with isoquinoline yielding 2-(2-3'-indolyl-2-oxoethyl)isoquinolinium bromide (117) which was converted into the iodide and compared with the sample prepared directly from 3-acetylindole. The structure of 3-ethyl-1-(2-3'-indolyl-2-oxoethyl)pyridinium iodide was also proved in this way. An authentic sample of 2-(2-3'-indolyl-2-oxoethyl)-5,6,7,8-tetrahydroisoquinolinium iodide was obtained from 3-(chloroacetyl)-indole. This compound, made by the Grignard method from indole

and chloroacetyl chloride, condensed with 5,6,7,8-tetrahydroisoquinoline and the anion was exchanged by treatment with aqueous potassium iodide.

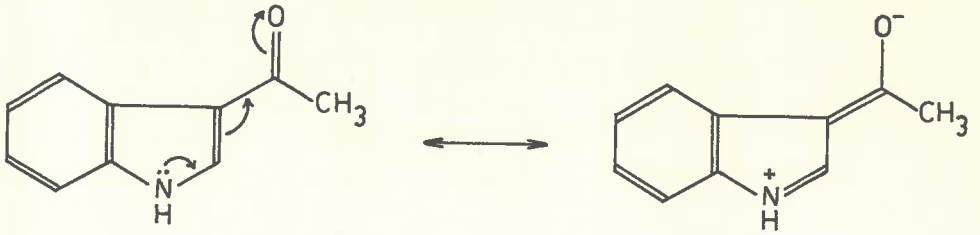


(116)



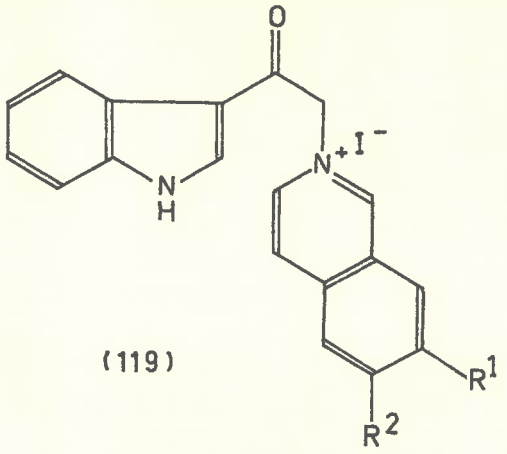
(117)

The formation of hexadehydroyohimbane from 2-(2-3'-indolylethyl)isoquinolinium salts (71; R=H) has been described in Chapter 1. The only difference between these salts and the iodide (119; R^1=R^2=H) is the presence of the keto group adjacent to the indole nucleus in the latter compound. It was found possible to remove this group using lithium aluminium hydride, a reagent known to reduce 3-acetylindole to 3-ethylindole and 3-formylindole to skatole.[83] It has been proposed that in this way 3-acetylindole reacts as a vinylogous amide showing a certain contribution to the resonance hybrid from the dipolar form (118). As the environment of the carbonyl group in (119) is the same as in 3-acetylindole it was expected that ready hydrogenolysis would occur on treatment with lithium aluminium hydride. This did,

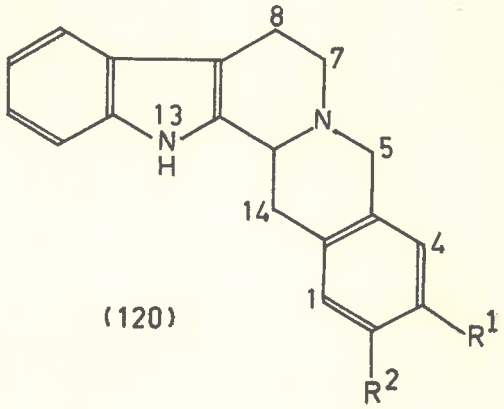


(112) (118)

in fact, proceed together with reduction of the quaternary isoquinolinium moiety to the 1,2-dihydro stage. On treatment of the reaction mixture with acid 5,7,8,13,13b,14-hexahydrobenz-[g]indolo[2,3-a]quinolizine (hexadehydroyohimbane) (120; R^1=R^2=H) was isolated in good yield. The reaction was shown to be independent of the nature of the anion as hexadehydroyohimbane was formed from both the iodide and perchlorate of (119; R^1=R^2=H) in approximately equivalent yields. The identity of the product was established by comparison with an authentic sample of hexadehydroyohimbane prepared from 2-(2-3'-indolylethyl)isoquinolinium iodide by the method of Potts and Robinson[26] (see Fig. 1). A second example of the formation of β-carbolines in this manner was provided by the synthesis of 2,3-dimethoxy-5,7,8,13,13b,14-hexahydrobenz[g]indolo[2,3-a]quinolizine (120; R^1=R^2=OCH_3) from the corresponding salt (119; R^1=R^2=OCH_3).



(119)



(120)

The mechanism for the formation of these pentacyclic compounds from the salts (119) is best considered in three stages: the reduction of the isoquinolinium moiety, the hydrogenolysis of the carbonyl group, and the final cyclisation. As will be demonstrated, it is probable that the steps occur in that order. Schmidt and Karrer[67] have reported that N-substituted isoquinolinium salts are rapidly reduced to the dihydro-compounds by lithium aluminium hydride at room temperature. The vigorous effervescence observed when salts of the type (119) are added to solutions of the hydride is probably associated with this reduction.

If (119) is regarded as containing a vinylogous amide system, a mechanism can be deduced for the hydrogenolysis of the carbonyl group. Paddock[68,69] has suggested that in solution lithium aluminium hydride furnishes the lithium cation and the alumino-hydride anion, the latter existing in equilibrium with aluminium hydride and the hydride ion. The first step in the reduction would

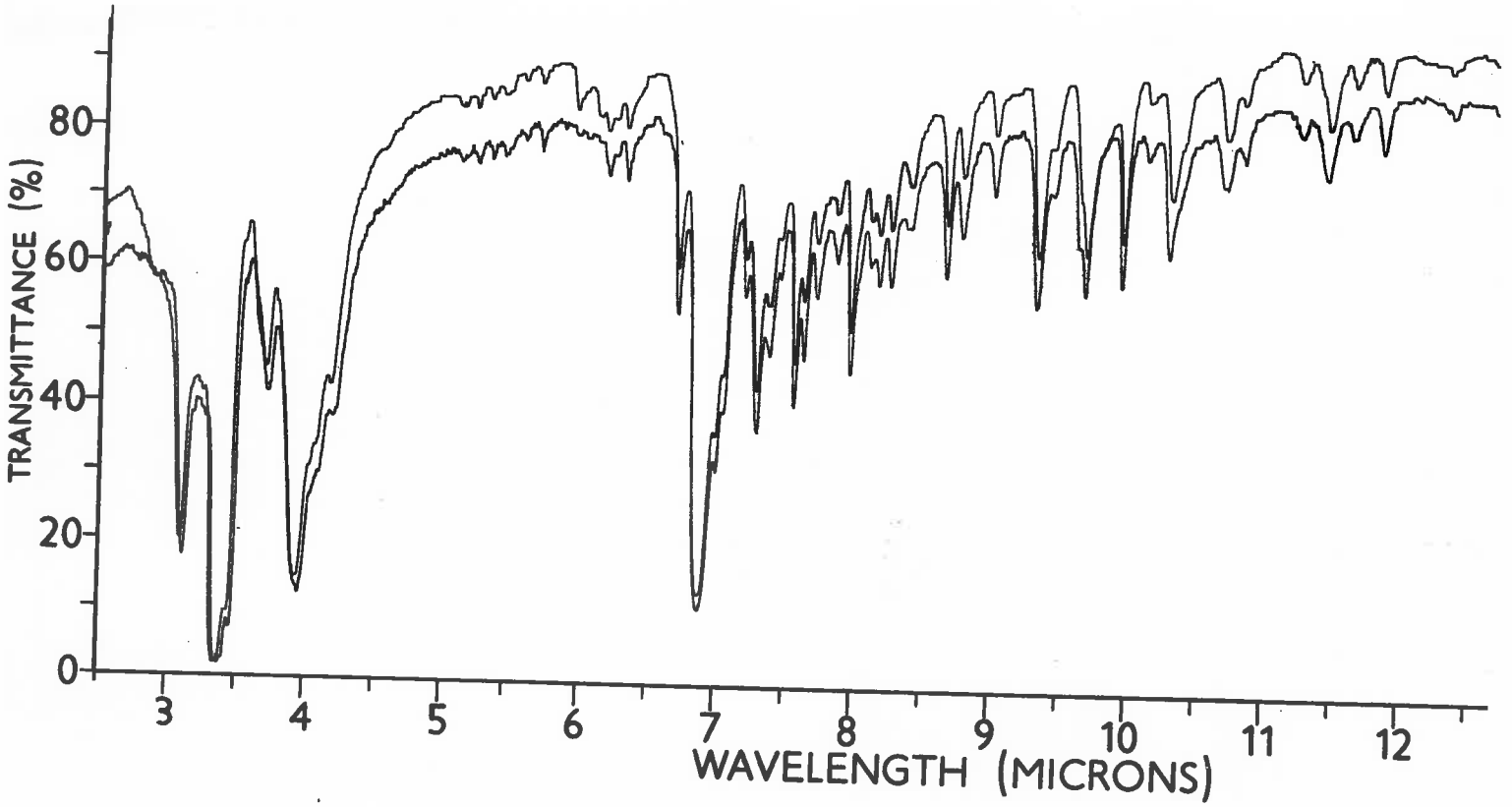
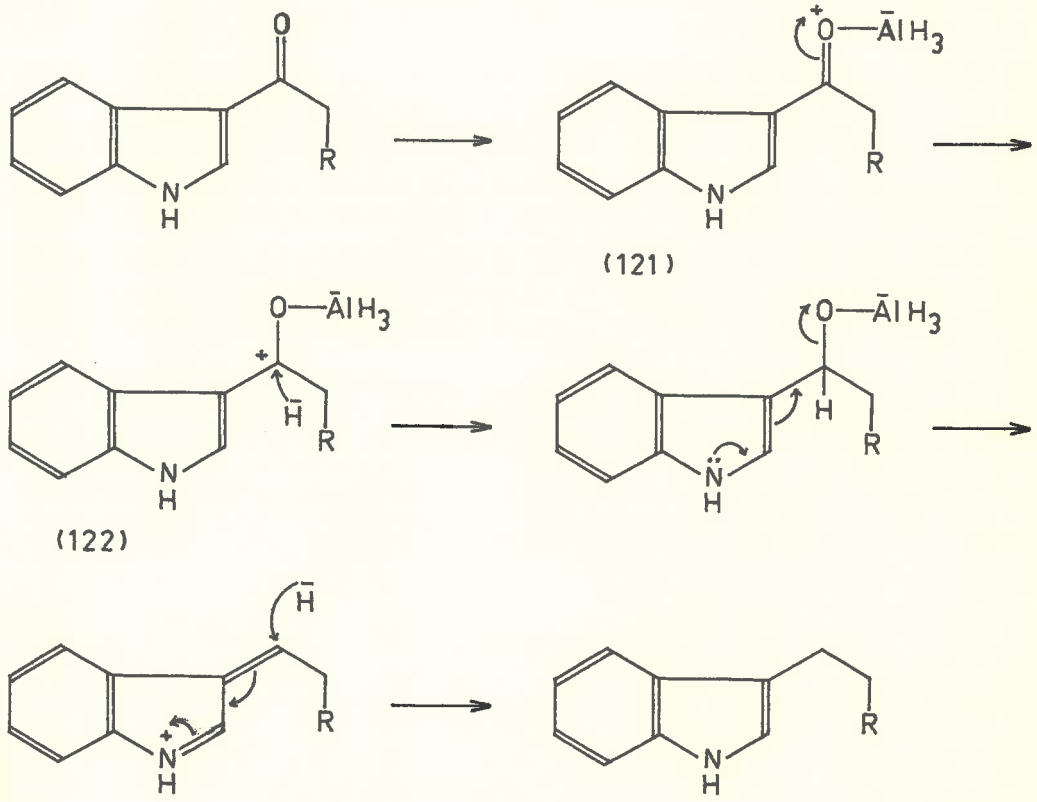


Fig. 1. Infrared absorption (Nujol mull) of 5,7,8,13,13b,14-hexahydro-benz[g]indolo[2,3-a]quinolizinium hydrochloride (120; R^1=R^2=H).

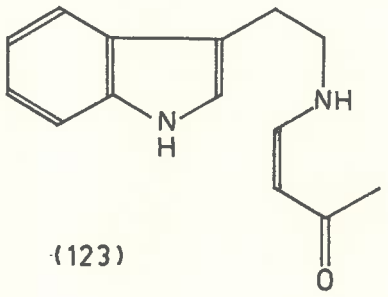
Upper - authentic

Lower - synthetic

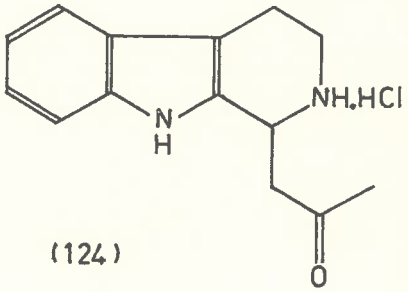
be the co-ordination of aluminium hydride with the oxygen of the carbonyl function to give (121) which would be followed by a shift of electrons associated with the carbon-oxygen double bond leading to (122). A hydride ion would then attack the positive centre and the lone electron pair associated with the nitrogen could then aid the fission of the carbon-oxygen bond. The attack of a second hydride ion would lead to the observed oxygen-free product. Such a pathway is an extension of that accepted for the reduction of amides by lithium aluminium hydride,[70] and as will be demonstrated at a later stage requires slight modification to account for the reduction of 1-methyl-3-acetylindole.



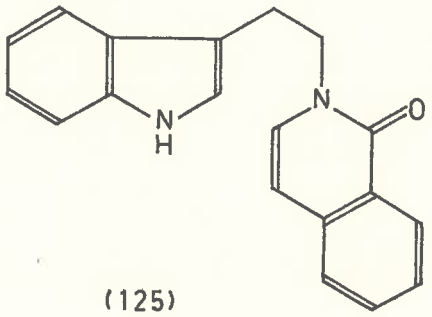
After the two reduction steps had proceeded to completion to give the intermediate (108), the excess of lithium aluminium hydride was decomposed with water, and the reaction mixture then treated with mineral acid. It is believed that ring closure with formation of the β-carboline system occurred at this stage. Supporting evidence for this view is provided by Schut[71] who found that treatment of the unsaturated ketone (123) with methanolic hydrogen chloride resulted in the formation of 1-(2-oxopropyl)-1,2,3,4-tetrahydro-β-carboline hydrochloride (124). Further, the cyclic lactam (125) was converted into hexadehydroyohimbane by reduction with lithium aluminium hydride followed by addition of mineral acid to the reaction mixture.[72] More directly, Huffman[73]



(123)

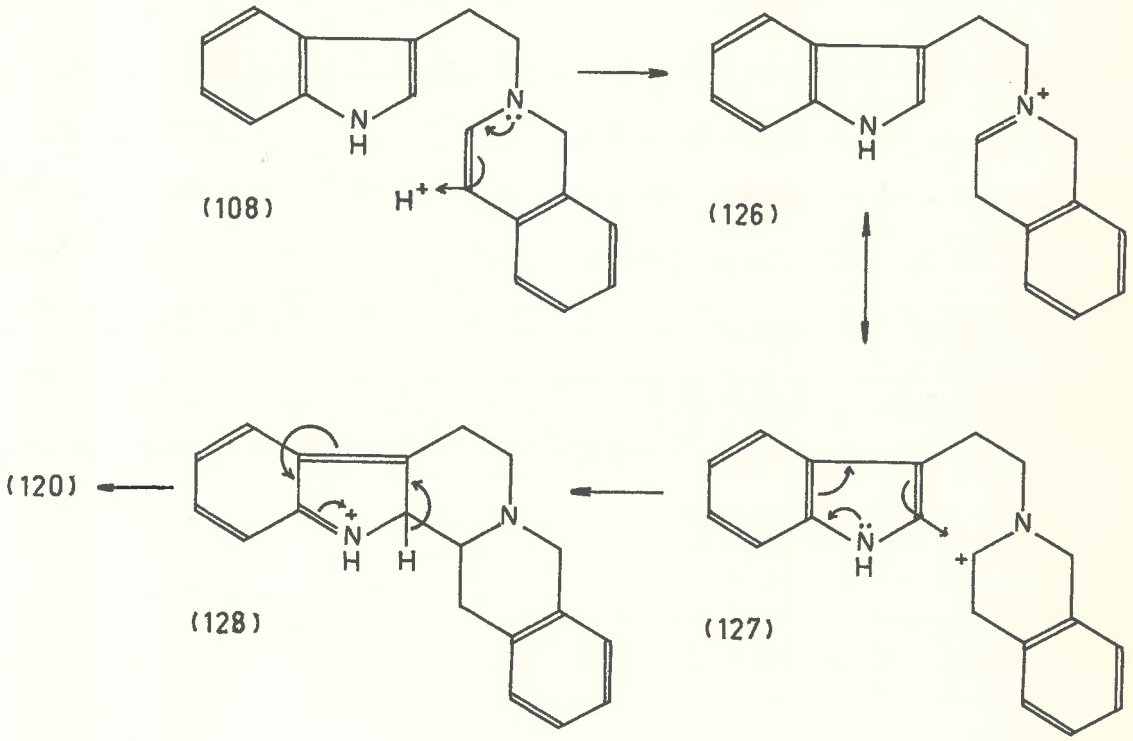


(124)



(125)

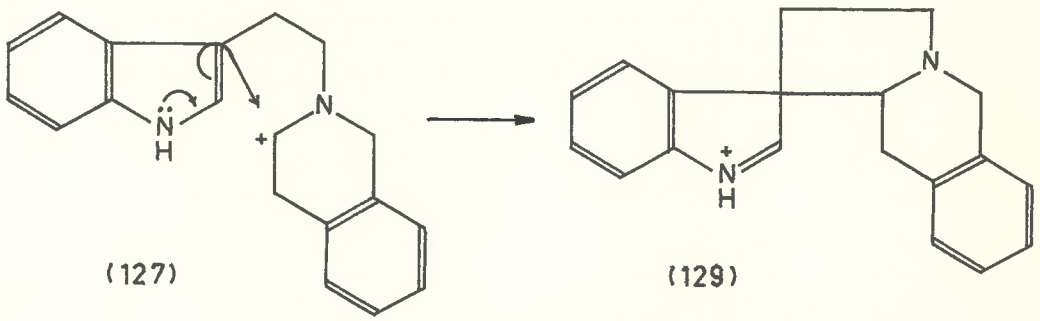
presented spectral evidence supporting the structure (108) as that of the intermediate before cyclisation. Immediately after the lithium aluminium hydride reduction of 2-(2-3'-indolylethyl)isoquinolinium bromide an unstable base was isolated. The ultraviolet spectrum of the sample was shown to be equivalent to that of a mixture of equal parts of skatole and 2-methyl-1,2-dihydroisoquinoline, which is what could be predicted for the compound (108). The addition of acid to solutions of (108) gave hexadehydroyohimbane.



If it is accepted that the addition of acid promotes the cyclisation step, there are still two routes by which it can

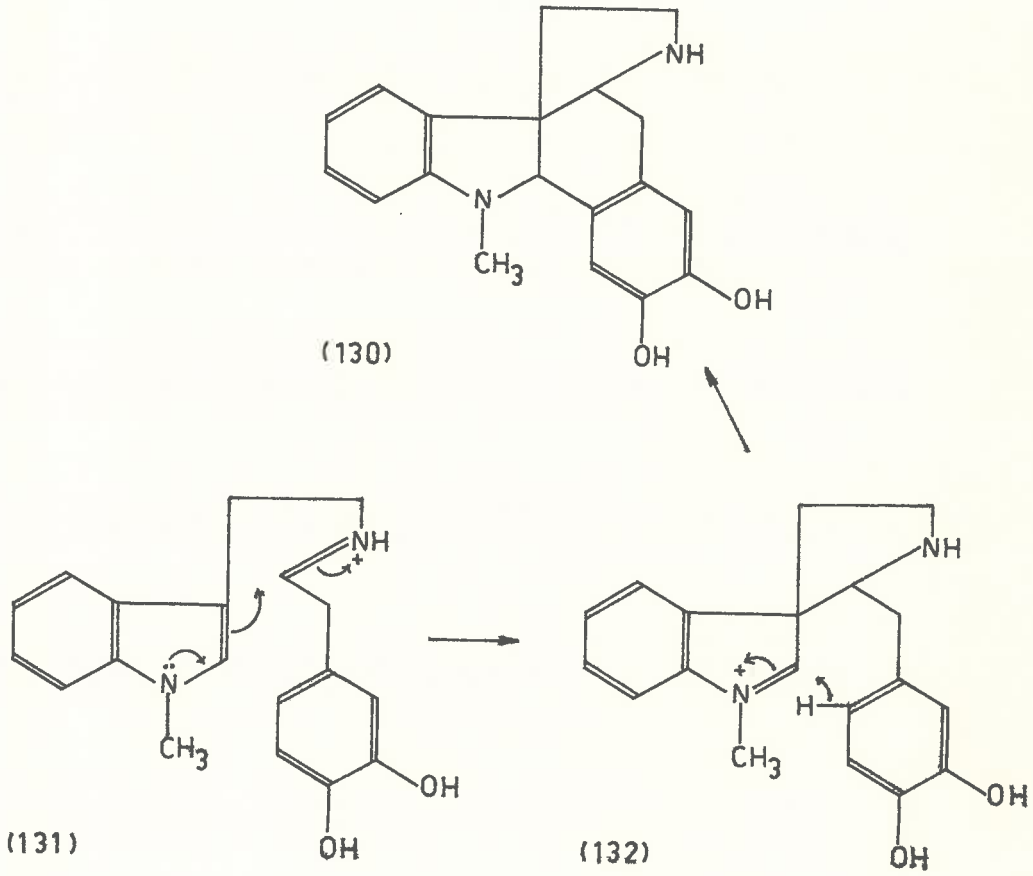
occur, and at present no decision can be made between them. The intermediate (108) is an α,β-unsaturated amine, and such systems are transformed into the quaternary salt form in the presence of acid.[74] Therefore (108) would be converted to (126) which is capable of resonance stabilisation (126 ⟷ 127). Ring closure may then occur to the α-position of the indole nucleus as in (128).

There is, however, some evidence to indicate that the above scheme may be an over-simplification of the actual course. Molecular orbital calculations show that the 3-position of the indole nucleus has a higher electron density than the 2-position,[75] and this is demonstrated by the chemical reactivity of indole towards cationic species. The resonance hybrid form (127) could therefore undergo cyclisation to form the spiro-compound (129) which could then rearrange to (120) during the process of isolation. This concept is supported by the work of Belleau[34] described in Chapter 1, p. 23, and the preferential migration of the tertiary carbon atom of the spiro-ring of (129) is in agreement with the relative migration tendencies of aliphatic groups.[76]

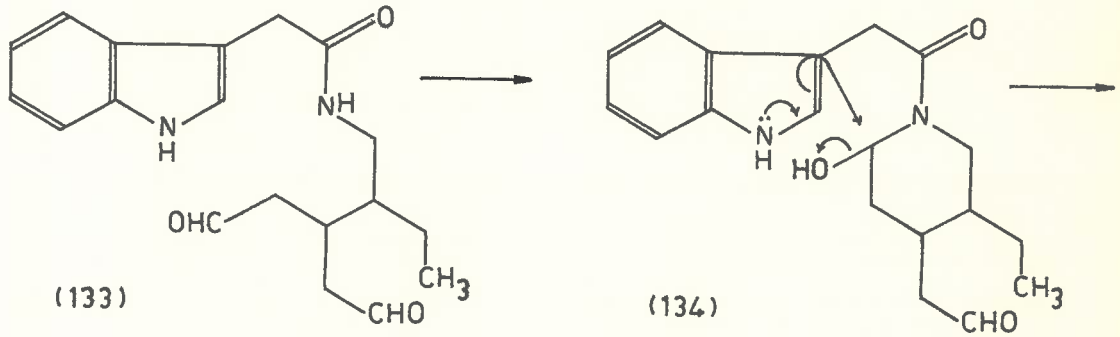


(127) (129)

There are two recently reported examples of cyclisation to the β-position of the indole ring to yield spiro-compounds that have been isolated. In both cases rearrangement is prevented by the presence of blocking substituents in the α-position. Harley-Mason and Waterfield[77] envisaged the formation of (130) as proceeding by a cyclisation of (131) to the spiro-compound (132) which can react further at the 4-position of the catechol ring to give (130).



In an elegant synthesis of a compound containing the essential skeleton of the strychnine-type alkaloids, van Tamelen[78] demonstrated the formation of (136) from the indole derivative (133) on gentle warming in aqueous solution with acetic acid and sodium acetate. It was proposed that the intermediate (134) underwent cyclisation to the β-position of the indole residue, and that this was immediately followed by the formation of ring C (135 ⟶ 136) before the spiro-compound (135) could rearrange.



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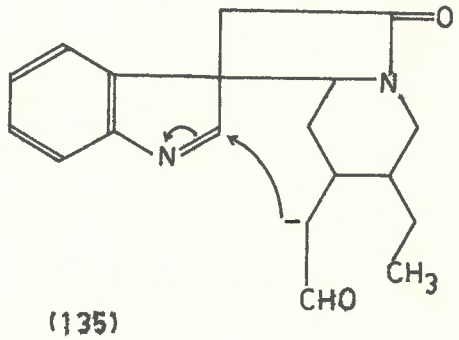
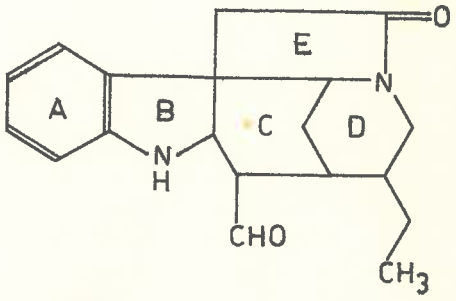
(134)

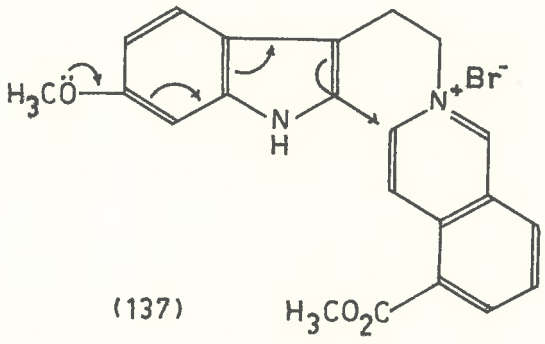


(135)



(136)

The majority of available evidence therefore seems to support the pathway (127) ⟶ (129) ⟶ (120), induced by the addition of acid to the intermediate (108), as the actual route of the cyclisation to form hexadehydroyohimbane. There is, however, one example of the formation of a pentacyclic β-carboline during a reaction of this type where no acid was necessary to promote the closure of ring C. The tetrahydroalstonilinol (138) was formed directly[36] by the lithium aluminium hydride reduction of the bromide (137). In this case the presence of the 6-methoxyl group would be expected to increase the electron density at the indole α-position as shown (137), and the cyclisation could be effected by some complex derived from the lithium aluminium hydride.



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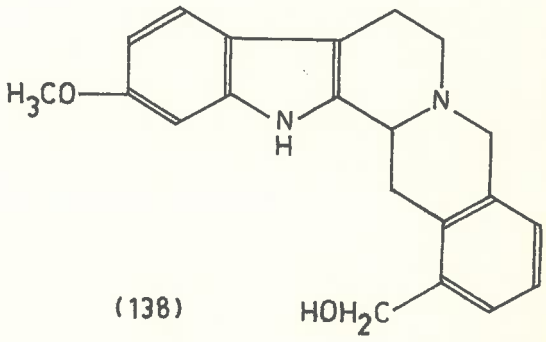
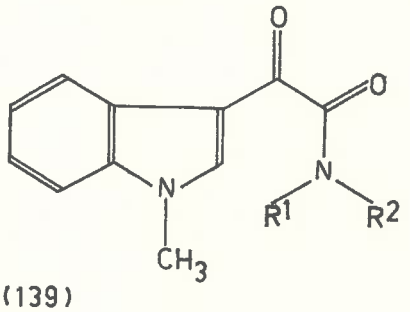


(138)

The formation of ind-N-methylhexadehydroyohimbane from the corresponding N-methyl-salt (110; R^1=isoquinoline, R^2=CH_3) was the next problem examined. However, it was impossible to

predict the probable course of the reaction with any degree of certainty, as there are conflicting reports in the literature concerning the lithium aluminium hydride reduction of compounds of the general formula (139). For example, Speeter[79] reports the lithium aluminium hydride reduction of (139; R^1=H, R^2=CH_3) as yielding the alcohol (140; R^1=H, R^2=CH_3), whereas Buzas and co-workers[80] found the treatment of (139; R^1=R^2=$CH_2C_6H_5$) with the same reagent to produce the oxygen-free base (141; R^1=R^2=$CH_2C_6H_5$). It has also been reported[81] that the hydride reduction of 1-methyl-3-indolylaldehydes gives the corresponding 1-methyl-3-hydroxymethylindoles.



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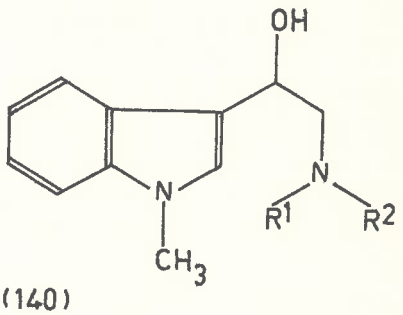

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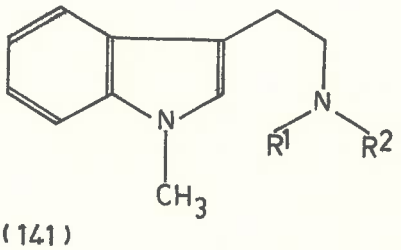
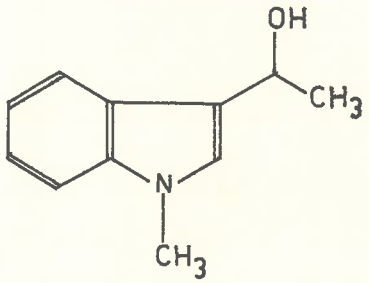


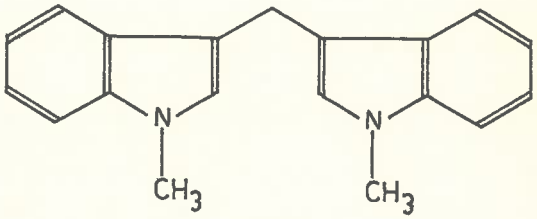
(141)

The lithium aluminium hydride reduction of 1-methyl-3-acetylindole was therefore examined in an attempt to determine the

conditions that would lead to 1-methyl-3-ethylindole. Immediately after isolation the product showed intense absorption in the infrared due to the presence of a hydroxyl group. This indicated a probable structure of (142), but no derivative of the alcoholic function could be obtained. On standing the crude product developed an odour of acetaldehyde, which was of interest as Leete[81] found that 1-methyl-3-hydroxymethylindole eliminated formaldehyde on boiling with water to form the diindolylmethane (143). A sample of the diindolylethane corresponding to (143) was prepared by methylation of authentic 1,1-di-3'-indolylethane, and compared with the compound isolated after the product of suspected structure (142) had been boiled with water. However, the two were different.



(142)

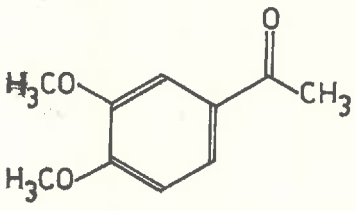


(143)

On attempted distillation of the original product the sample appeared to polymerise as it approached the boiling point. The resulting glass was purified and found to be identical with the sample obtained by boiling the alcohol with water. This product is formulated as poly-(1-methyl-3-vinylindole) on the

following grounds. The infrared spectrum of the sample showed a complete absence of absorption in the hydroxyl region, and analytical data agreed excellently with a molecular formula of $(C_{11}H_{11}N)_n$. The ultraviolet spectrum showed, in addition to peaks characteristic of the 1-methylindole residue, a broad shoulder at 2670 Å, and 1-methyl-3-vinylindoles have been found[82] to exhibit maxima in the region of 2650 Å. Further supporting evidence is provided by the behaviour of 3-hydroxymethylindole,[83] which resisted attempts to form a picrate or an acyl-derivative and polymerised on treatment with dilute acid.

This behaviour of 1-methyl-3-acetylindole on reduction with lithium aluminium hydride is typical of aryl-methyl ketones, as demonstrated by the results obtained when 3,4-dimethoxyacetophenone (144) was reduced in an analogous fashion. The infrared spectrum of the liquid product (145) showed absorption due to a hydroxyl group, and on distillation water was eliminated with the formation of the dimethoxystyrene (146), characterised as the dibromide. The sample (146) rapidly polymerised on standing to a rubbery mass.



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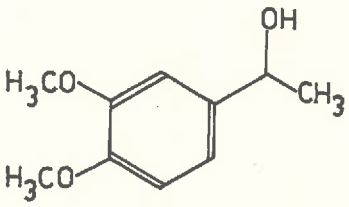
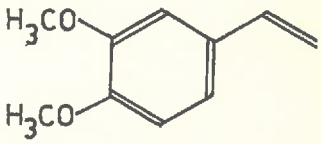


(145)



(146)

Mixtures of lithium aluminium hydride and aluminium chloride have been found to promote hydrogenolysis of certain ketones where the use of lithium aluminium hydride alone yields the alcohol.[84] Thus diphenylmethane was obtained from benzophenone and ethylbenzene from acetophenone. The yields of oxygen-free products are variable, and dependent upon the order of addition of reactants. By the use of this mixed reagent, 3,4-dimethoxyacetophenone has now been reduced to 3,4-dimethoxyethylbenzene, and 1-methyl-3-acetylindole to 1-methyl-3-ethylindole.

The reason for the difference in the behaviour of 3-acetylindole and 1-methyl-3-acetylindole towards lithium aluminium hydride is not at once apparent. In accounting for the hydrogenolysis which occurs with the former compound, the presence of the "vinylogous amide" system has been frequently mentioned. There must be some contribution to the resonance hybrid from the dipolar form (118), but the added inductive effect due to the N-methyl group in 1-methyl-3-acetylindole would be expected to increase this contribution. If this was the sole reason for the procedure of the hydrogenolysis reaction, then 1-methyl-3-ethylindole should readily form from 1-methyl-3-acetylindole on treatment with the hydride.

A study of the infrared spectra, and in particular the frequency of the carbonyl absorption, of the ketones shows that

structure (118) contributes very little to the resonance hybrid. The low carbonyl absorption frequency of 3-acetylindole in Nujol is due almost entirely to intermolecular hydrogen bonding as is shown in Table 4. The values obtained for 3-acetylindole and 1-methyl-3-acetylindole when the spectra were determined in carbon tetrachloride solution are in good agreement, and lie just below the range generally quoted for the carbonyl absorption of aryl-alkyl ketones.[85]

Table 4

Frequencies ($cm.^{-1}$) of absorption due to carbonyl groups[a]

	Nujol	CCl_4
3-Acetylindole	1617	
	1628 (sh)	1669[b]
1-Methyl-3-acetylindole	1646	1667[c]
3,4-Dimethoxyacetophenone	-	1688[c]

(a) measurements were made using a Grubb-Parsons Model S4 double-beam spectrometer

(b) saturated solution

(c) 5 mg./ml.

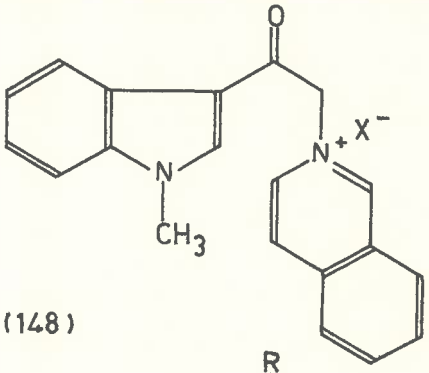
It is therefore proposed that the reactive species that promotes hydrogenolysis when 3-acetylindole is added to solutions of lithium aluminium hydride is the conjugate base (147), which would rapidly be formed. The presence of an ind-N-methyl group prevents anion formation and the lone electron pair associated with the nitrogen does not provide a sufficient driving force to break the carbon-oxygen bond.

(147)

With this more definite knowledge of the behaviour of 1-methyl-3-acetylindoles towards lithium aluminium hydride a series of reductions of the salt (148; X=I, ClO_4) was begun. Despite repeated attempts using the hydride alone or mixed with aluminium chloride no pure products could be isolated when tetrahydrofuran was employed as the solvent for the reaction. The experimental method was the same as that used for the synthesis of hexadehydroyohimbane, with the exception that after treatment of the reaction mixture with acid the basic products were isolated and chromatographed on alumina. Spectral evidence obtained from the brown oily products eluted from the column indicated that at least partial reduction of the carbonyl group had occurred,

but in no case could a sample or its derivative be obtained sufficiently pure to allow structural assignments to be made.

The reason for the failure of the reaction to yield pure isolable products is probably found in the increased possibility for the occurrence of side-reactions. If the reduction ceased at the stage represented by (149) cyclisation might be expected to occur on the addition of acid. However, as 1,3-dimethylindole is reduced to 1,3-dimethylindoline by lithium aluminium hydride,[86] the bases (150; R=H or OH) could conceivably be formed. This reduction of the 2,3-bond of the indole residue would preclude both the fission of the carbon-oxygen bond and the cyclisation to form ring C. The instability of the intermediate enamine (108) in the formation of hexadehydroyohimbane has previously been mentioned, and there is no doubt that compounds of type (150) would rapidly undergo extensive decomposition.



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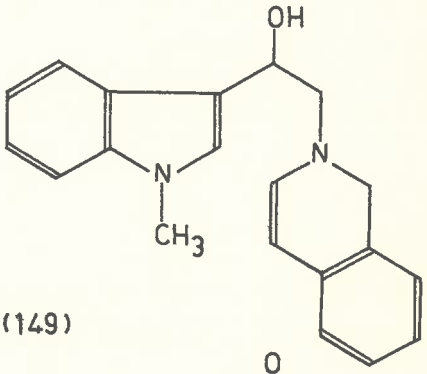
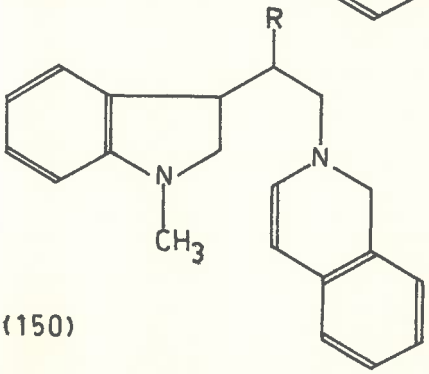


(149)



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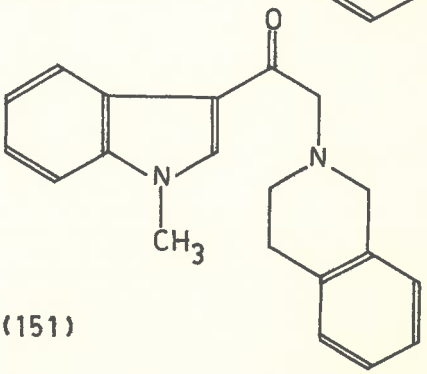

(151)

The reduction of (148; X=I) with a mixture of lithium aluminium hydride and aluminium chloride in tetrahydrofuran solution was further complicated by the fact that this solvent is known to be cleaved by the mixed reagent with the formation of n-butyl alcohol.[87] The hydrogenolysis of 1-methyl-3-acetylindole itself is not effected by this side reaction, probably because of the ready solubility of the starting material and the rapidity of the reaction. However, the salt (148; X=I) is only sparingly soluble in tetrahydrofuran and a much larger percentage of the reducing agent employed would be destroyed by attack on the solvent before reduction of the indole derivative could occur.

To eliminate this complicating factor dioxane, a solvent much more stable under the conditions of the reaction,[87] was used as a medium for the reduction. The iodide was found to be only sparingly soluble and the intermediate complex almost insoluble, so that at no stage was the reaction mixture homogeneous. Two experiments were performed, one with a reaction time of 5 hours and the other of 20 hours, and the products were the same in each case. The compound formed in greatest quantity was shown to be 2-(2-1'-methyl-3'-indolyl-2-oxoethyl)-1,2,3,4-tetrahydroisoquinoline (151). An authentic sample was prepared by the conversion of the iodide (148) to the corresponding chloride followed by reduction with Adams' catalyst in acetic acid, when 2 moles of hydrogen were rapidly absorbed.

The survival of the carbonyl group during the mixed hydride reduction is not surprising when the insolubility of the intermediate complex is considered. The reduction of the isoquinoline moiety would proceed rapidly, and if this was followed by precipitation of the complex, further reaction would be prevented. There are many examples of labile groups remaining intact during attempted reduction with lithium aluminium hydride due to the insolubility of the intermediate complex in the solvent employed.[70]

Ind-N-methylhexadehydroyohimbane, although not formed in the above reactions, was found to be readily obtainable using a standard technique for the methylation of indoles.[88] Thus when methyl iodide was added to a solution of hexadehydroyohimbane and sodamide in liquid ammonia the ind-N-methyl-derivative was formed in quantitative yield.

With the completion of experiments directed towards a synthesis of the pentacyclic β-carbolines, attention was turned to the possible extension of the reactions to lead to the tetracyclic analogues. Mention was made in Chapter 1 of attempts to prepare these compounds by treatment of 1-(2-3'-indolylethyl)-pyridinium bromides (77) with lithium aluminium hydride. The only products isolated were the indolylethylpiperideines (78) in which the pyridinium ring of the starting material had been

reduced to the tetrahydro-stage.[37]

The preparation of the 1-(2-3'-indolyl-2-oxoethyl)-pyridinium salts required for this study has been described previously (see Table 2), and in initial experiments the parent compound (110; R^1=pyridine, R^2=H) was subjected to lithium aluminium hydride reduction in ether and tetrahydrofuran solutions.* The general procedure for the work-up of the reaction mixtures involved decomposition of the excess hydride and treatment of the solutions with dilute hydrochloric acid, followed by basification and chromatography of the crude base mixtures. Rather surprisingly different products were obtained when the reduction of 1-(2-3'-indolyl-2-oxoethyl)pyridinium iodide was carried out in ether and tetrahydrofuran. When ether was the solvent employed 1-(2-3'-indolylethyl)-Δ^3-piperideine (152; R=H) was isolated in 33% yield. This compound rapidly absorbed 1 mole of hydrogen when reduced with Adams' catalyst with the formation of 1-(2-3'-indolylethyl)piperidine, which was compared with authentic material. However, when the reduction was performed

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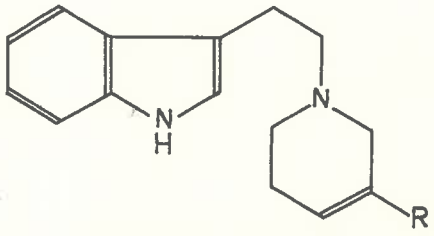
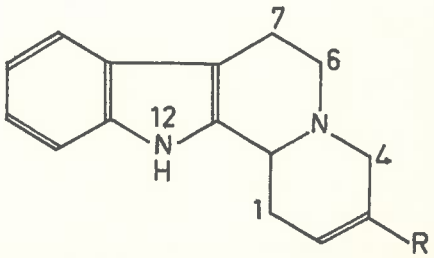
*Dr. R. Massy-Westropp has kindly informed the author of some results he obtained while working in collaboration with Professor E. Wenkert at Iowa State University. He was concerned with the lithium aluminium hydride reduction of 1-(2-3'-indolylethyl)-pyridinium salts in ether solution, and the results obtained show a close parallel to those reported in this text.

in tetrahydrofuran solution the tetracyclic β-carboline 1,4,6,7,12,12b-hexahydroindolo[2,3-a]quinolizine (153; R=H) was formed. Hydrogenation of this material gave 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine, a compound well characterised in the literature.



(152)



(153)

The yields of both (152; R=H) and (153; R=H) were found to vary with the length of reaction time (see Table 5). Thus the piperideine derivative was formed in 33% yield when the reaction was performed in ether solution for 6 hours, and in 40% yield when the reaction time was reduced to 3 hours. Similarly, with tetrahydrofuran as the solvent 44% of the β-carboline was isolated after $4\frac{1}{2}$ hours, and 56% after 2 hours. It is probable that a series of reactions would lead to conditions whereby greater amounts of the β-carboline could be isolated.

The positions of the double bonds in compounds (152; R=H) and (153; R=H) were not proved. The structures shown were formulated by analogy with products formed by similar reductions of substituted pyridinium salts where definite assignments could

be made. The use of nuclear magnetic resonance spectra for this purpose will be described later.

A similar variation in the course of the reaction was observed when 3-ethyl-1-(2-3'-indolyl-2-oxoethyl)pyridinium iodide was reduced by lithium aluminium hydride in ether and tetrahydrofuran solutions. When the former solvent was employed 3-ethyl-1-(2-3'-indolylethyl)-Δ^3-piperideine (152; R=C_2H_5) was isolated, together with a small amount of 3-ethyl-1,4,6,7,12,12b-hexahydroindolo[2,3-a]quinolizine (153; R=C_2H_5). The latter compound was the sole product when tetrahydrofuran was the solvent for the reaction. There was a small difference in the amounts of the β-carboline (153; R=C_2H_5) obtained on varying the reaction time, the yield rising from 48% to 52% on reducing the time from $4\frac{1}{2}$ to 2 hours. The results from these experiments are summarised in Table 5.

Both the piperideine (152; R=C_2H_5) and the β-carboline (153; R=C_2H_5) absorbed one mole of hydrogen on catalytic reduction demonstrating the presence of the isolated double bond. Proof of the structures assigned to these compounds was obtained from a study of their nuclear magnetic resonance spectra (see Fig. 2).*

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* The spectra were recorded from a Varian V-4302 Dual Purpose, 60 m.c. N.M.R. Spectrometer, and chemical shift values are reported in τ- units using tetramethylsilane (τ =10.00) as internal standard.

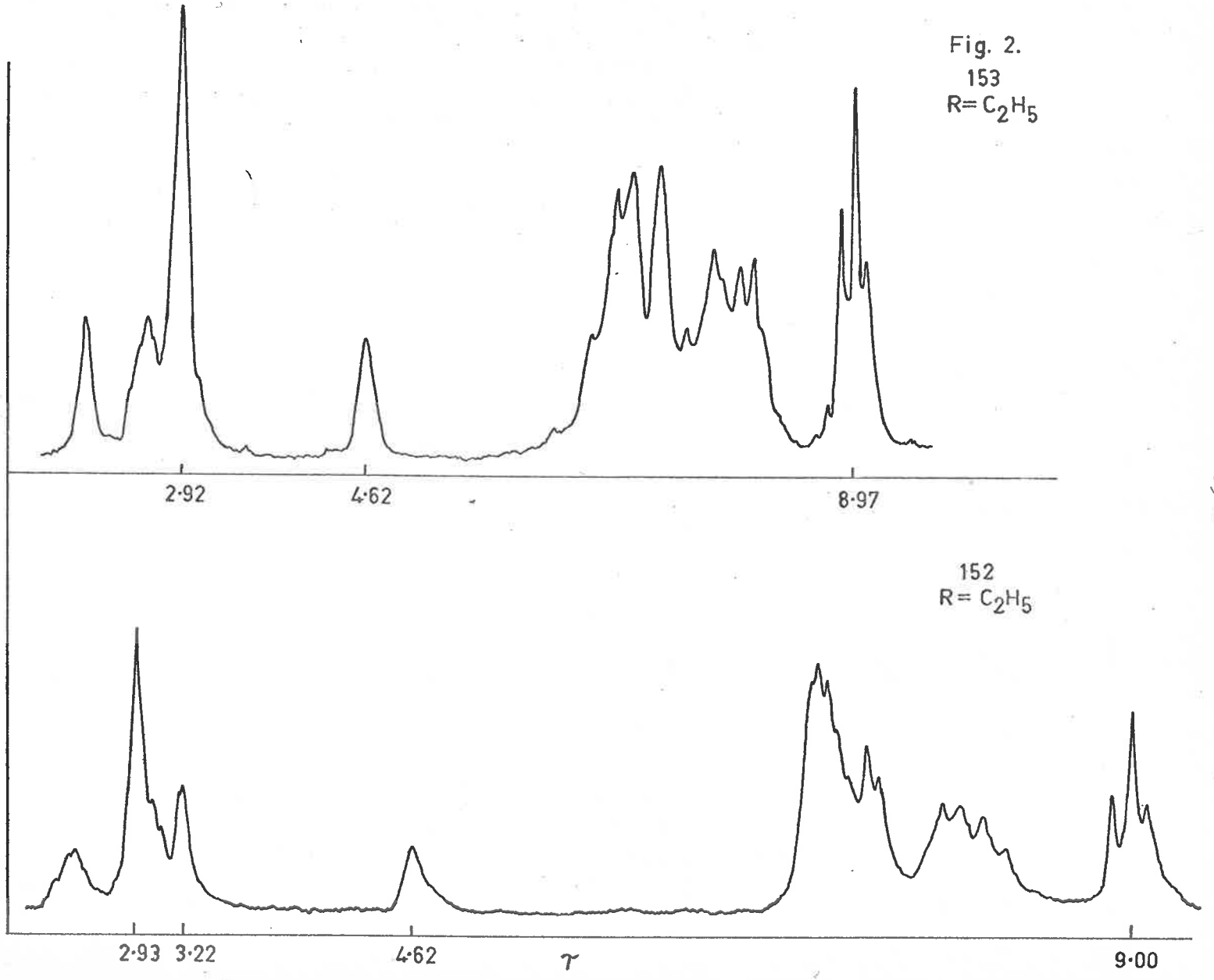


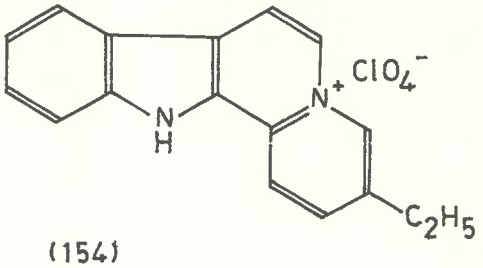
Fig. 2.

The presence of one olefinic proton was shown by the absorption at 4.62 τ in both cases, and the position of this absorption proved that the samples did not possess an α,β-unsaturated amine system (153; R=C_2H_5, but double bond from C-3 to C-4). In such cases the olefinic proton absorbs at much lower field.[89] In addition to the signal due to the aromatic protons present in both spectra, the piperideine (152; R=C_2H_5) showed absorption at 3.22 τ due to the indole α-proton. From studies on 3-methylindole Witkop and co-workers[90] report a τ-value of 3.20 for this absorption. The methylene regions of the spectra are complex and no definite assignments of bands to particular protons were made with the exception of the absorption at ca. 9.0 τ, due to the methyl group of the side-chain.

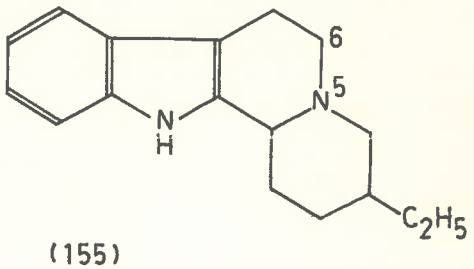
Table 5

Products from the Lithium Aluminium Hydride Reduction of 1-(2-3'-Indolyl-2-oxoethyl)pyridinium Iodides

Iodide from:	Solvent	Reaction Time (hr.)	Product (152)	Product (153)
Pyridine	Ether	6	33%	-
Pyridine	Ether	3	42%	-
Pyridine	T.H.F.	4 1/2	-	44%
Pyridine	T.H.F.	2	-	56%
3-Ethylpyridine	Ether	4	35%	5%
3-Ethylpyridine	T.H.F.	4 1/2	-	48%
3-Ethylpyridine	T.H.F.	2	-	52%



(154)



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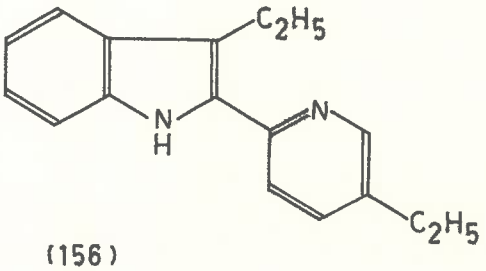
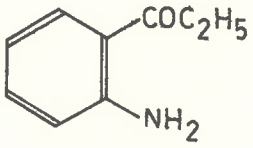


(156)



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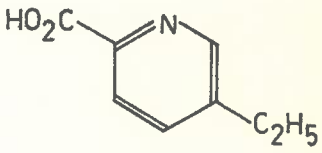
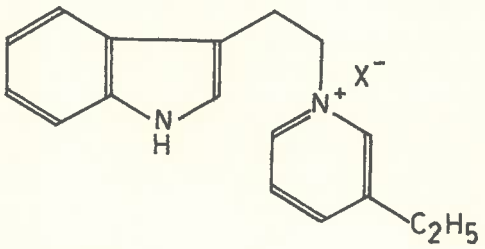


(158)

Additional proof of the orientation of (153; R=C_2H_5) was obtained by conversion to flavopereirine. This alkaloid, shown as the perchlorate (154), is present in Geissospermum laeve or vellosii, and the structure has been elucidated by degradation.[91,92] The ultraviolet absorption spectrum of the sample was found[91] to be similar to that of sempervirine (35), and it was concluded that both alkaloids must contain the indolo[2,3-a]quinolizine chromophore (see Chapter 1, p. 14). Catalytic hydrogenation of flavopereirine in methanol containing a trace of potassium hydroxide led to the octahydro-derivative (155) and selenium dehydrogenation of this compound yielded the desethylalstyrine (156) by fission of the N-5 to C-6 bond. When the alkaloid

itself was submitted to dehydrogenation in the presence of 1,2,3,4-tetrahydroisoquinoline a higher yield of (156) was obtained, which on oxidation and subsequent hydrolysis gave o-aminopropiophenone (157) and 5-ethylpicolinic acid (158). Flavopereirine perchlorate was therefore assigned the structure (154).

This formulation has since been proved by syntheses developed by several groups of workers.[21,93,94,95] Thesing and Festag[94] found that reduction of the salt (159) with Raney nickel produced the tetrahydro-derivative (160) which on treatment with acid gave octahydroflavopereirine (155). Dehydrogenation of this compound with palladium led directly to the alkaloid. An unambiguous synthesis of flavopereirine was provided by Prasad and Swan[21] by the use of 2-cyano-5-ethylpyridine in their preparation of



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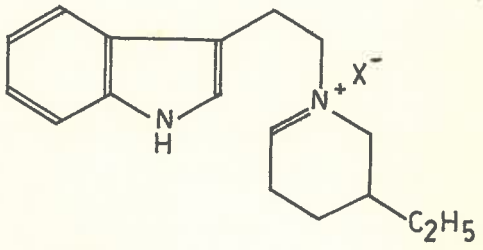

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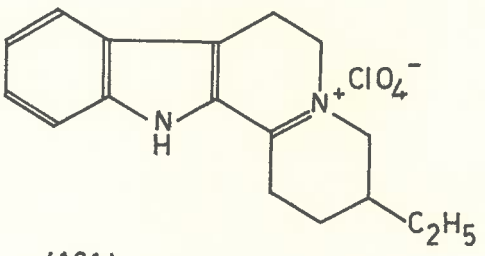


(161)

indolo[2,3-a]quinolizines by the Fischer indole method of ring-closure (Chapter 1, p. 14).

The conversion of the β-carboline (153; R=C_2H_5) to flavopereirine was accomplished by following established routes. The first step involved catalytic reduction to octahydroflavopereirine, followed by oxidation with mercuric acetate to 3-ethyl-1,2,3,4,6,7-hexahydro-12H-indolo[2,3-a]quinolizinium perchlorate (161). The infrared and ultraviolet absorption spectra were the same as those published for this compound by Janot.[93] Dehydrogenation of (161) with palladium on carbon catalyst gave flavopereirine, isolated as the perchlorate, identical with a sample of the alkaloid supplied by Professor Rapoport (Fig. 3).

With the nature of the products from the lithium aluminium hydride reduction of 1-(2-3'-indolyl-2-oxoethyl)pyridinium iodides (110; R^1=pyridine or 3-ethylpyridine, R^2=H) definitely established, it remains to explain the difference in the products obtained when the two solvents ether and tetrahydrofuran are employed. The hydrogenolysis of the carbonyl group is assumed to proceed *via* the mechanism discussed earlier (p. 48) and not to effect the reduction of the pyridinium ring. The lithium aluminium hydride reduction of pyridine alone or in ether solution is known to give unstable dihydro-derivatives,[96,97] but whether a 1,2- or a 1,4-attack of the reducing species is involved is uncertain.

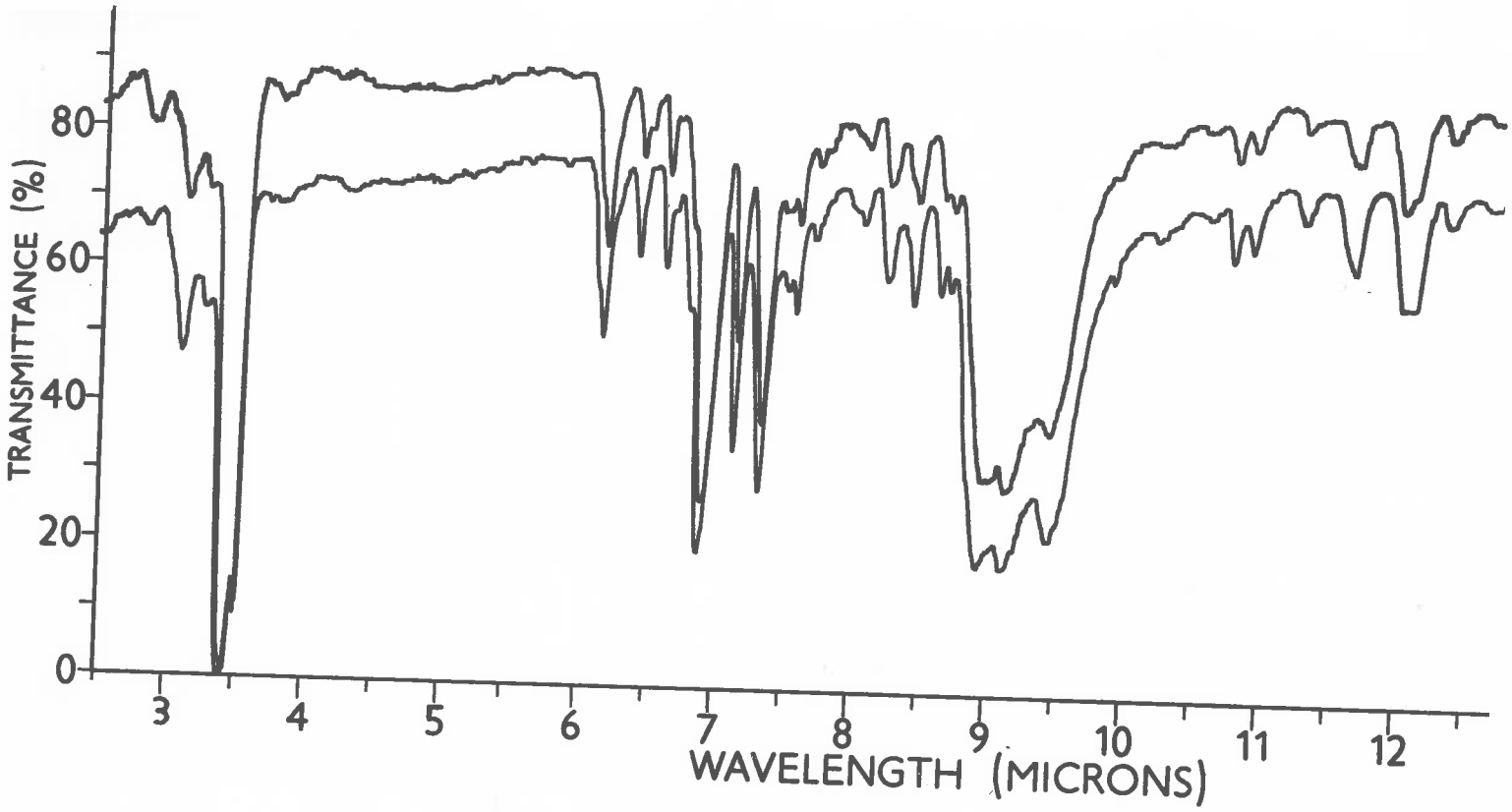


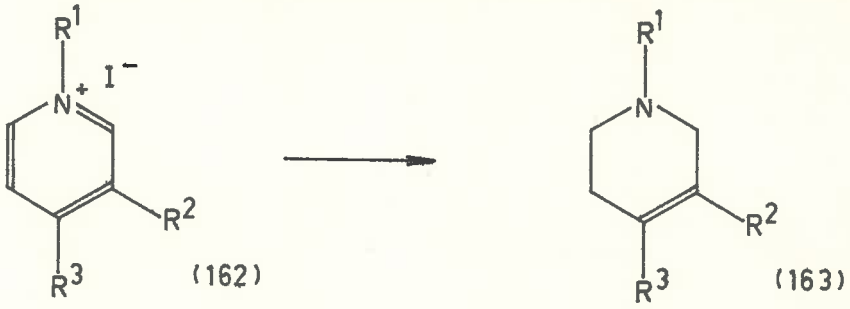
Fig. 3. Infrared absorption (Nujol mull)

of flavopereirine perchlorate.

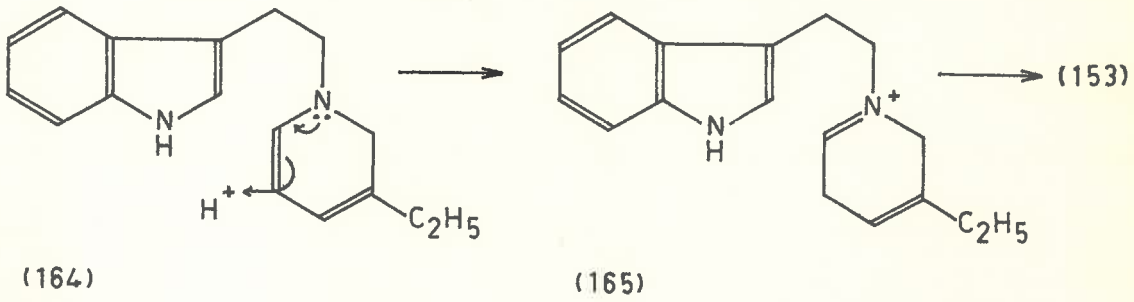
Upper - synthetic

Lower - authentic

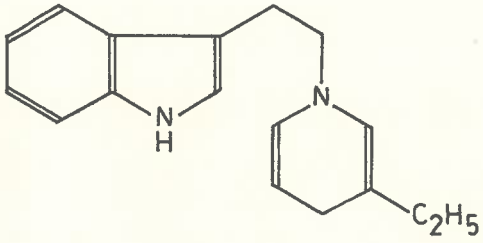
However, Ferles[98] has found that the reduction of quaternary pyridinium salts (162) by lithium aluminium hydride in a mixture of ether and chloroform leads to the Δ^3-piperideine derivatives (163).



It is now proposed that the above type of reduction proceeds by an initial 1,2-attack, or alternatively by a 1,4-attack with immediate rearrangement of the product to give a 1,2-dihydro-species. This may be demonstrated by considering the reduction of 3-ethyl-1-(2-3'-indolyl-2-oxoethyl)pyridinium iodide with lithium aluminium hydride in tetrahydrofuran solution. The formation of the β-carboline (153; R=C_2H_5) may be explained by the ring closure of the intermediate (164) by treatment with acid. This would proceed by an extension of the mechanism proposed (p. 52) for the formation of hexadehydroyohimbane. It is obvious that protonation of (164) must occur at the 5-position to give rise to the product isolated. Moreover, the structure (164) is the only one that



could lead to (153; R=C_2H_5). If a 1,4-dihydropyridinium intermediate (166) was involved cyclisation would be expected to give a mixture of (167) and (168). The ring closure of the alternative 1,2-dihydropyridinium intermediate (169) would, by protonation at the 3-position lead to (170), and at the 5-position to (171). No evidence was found for the presence of any of these compounds in the product from the reaction.



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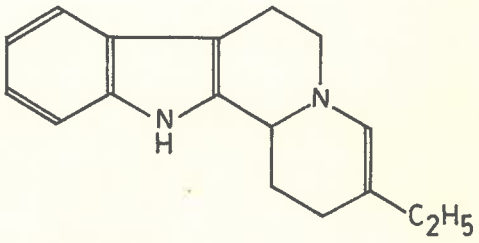

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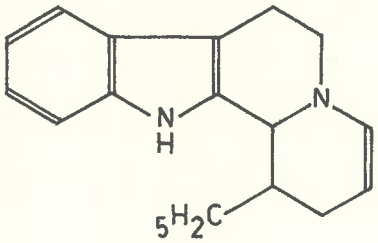

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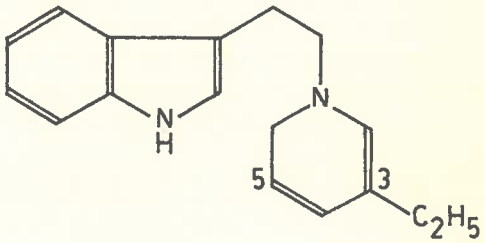

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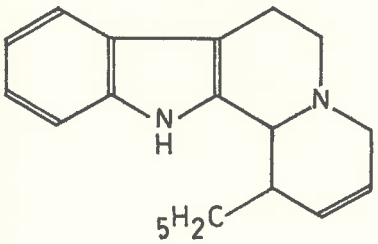

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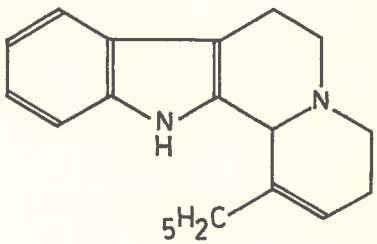
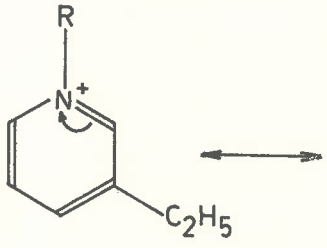


(171)

A more detailed account of the mechanism of the hydride addition may now be considered. The 1,2-attack proposed would be facilitated by the contributing resonance structure (173) and the product would be the complex (174). The formation of such a dative bond has been well established in organo-metallic chemistry. Bonitz[99] has demonstrated the existence of a 1:1 complex between aluminium alkyls and isoquinoline, and Ruff and Hawthorne[100] have described the preparation of 1:1 complexes between aluminium hydride and tertiary alkyl amines by treatment of the amine hydrochloride with lithium aluminium hydride. Fetter[101] has also shown that purely covalent aluminium-nitrogen bonds are



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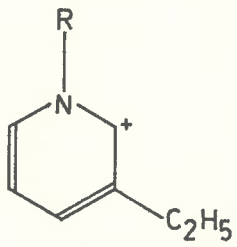
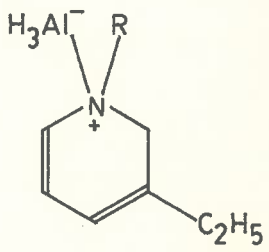


(173)



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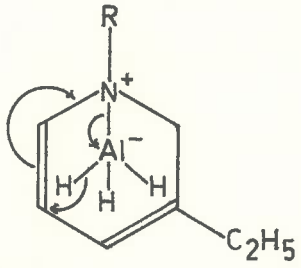

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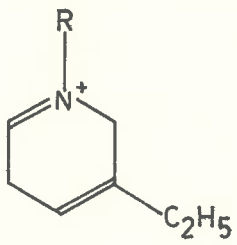

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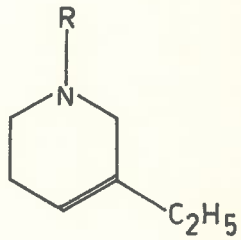


(176)

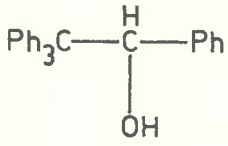
formed through a complex containing a dative bond, with subsequent elimination of a suitable species from the ion-pair.

It is possible that the intermediate (174) could then react as shown (174 → 175 → 176). The positively charged nitrogen atom in (174) would polarise the α,β-double bond and facilitate the intramolecular attack of hydride ion. The product (175) would then be further reduced by a process identical to that involved in the first step of the reaction.

The reason for the formation of the Δ^3-piperideine in ether and not in tetrahydrofuran solution is apparent from a consideration of the relative basicities of the two ethers. The heat of solvation of triethyl aluminium by tetrahydrofuran and ether has been determined as 14.0 and 11.2 kcal./mole respectively.[99] These values show that the former is the stronger base and can complex more readily with the aluminium species. Confirmation of this order is found in the results obtained by Brown[102] in a study of the complexes of boron trifluoride with ether and tetrahydrofuran. That between the fluoride and the cyclic ether was the more stable, and this was attributed to the rigidity of the ring system lessening the possibility of strain in the complex. Co-ordination of the aluminium hydride with the nitrogen atom of the reduced pyridinium ring (174) may therefore be expected to be complicated by co-ordination with the solvent employed. In ether solution most of the aluminium may complex with the nitrogen atom and

reduction could proceed to the tetrahydro-stage as explained above. The presence of the more basic tetrahydrofuran may well drastically reduce the amount of the intermediate (174) present in solution, and the dihydropyridinium species would then survive the reduction process.

There are many examples in the literature of reactions involving organo-metallic complexes proceeding by different routes in different solvents.[103] The reduction of the acid phthalate ester of benzpinacolyl alcohol (177) with lithium aluminium hydride in ether solution yielded the optically active alcohol. This has been employed as a preparative method since basic hydrolysis of the ester results in cleavage of the anion (178) to triphenyl methane and benzaldehyde.[104] However, the lithium aluminium hydride reduction of benzpinacolone (179) in pyridine solution gave triphenyl methane and benzyl alcohol <u>via</u> the alcohol (177).[105] The intermediate (180) containing the co-ordinated aluminium hydride is formed in both these reactions, but it has



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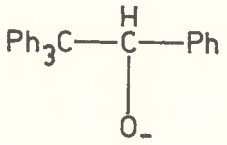

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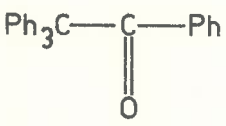

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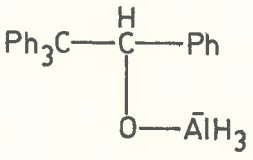
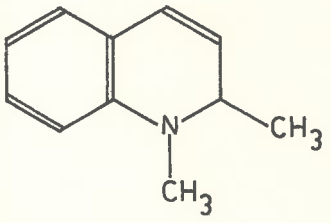


(180)

been proposed that the ether is insufficiently basic to remove the aluminium species from the alkoxide. The function of the pyridine is to remove the co-ordinated aluminium hydride leaving (178) which may then decompose with the liberation of the resonance-stabilised triphenylmethyl carbanion.[105]

In a recent publication Elderfield and Wark[106] have reported that the lithium aluminium hydride reduction of 1,2-dimethylquinolinium iodide in ether solution yielded a mixture of the dihydro- and tetrahydro-products (181) and (182). When tetrahydrofuran was used as the solvent the product consisted entirely of the dihydroquinoline (181). The formation of (182) was explained in terms of a prior attack of hydride at the 4-position to give (183), which is capable of further reduction in the accepted manner. If initial attack occurred at the 2-position to give (184) then the nitrogen atom could no longer



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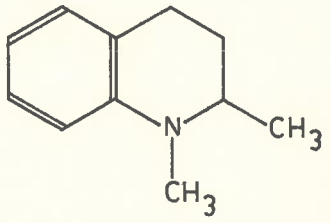

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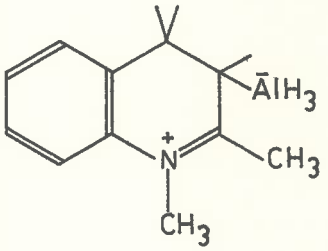

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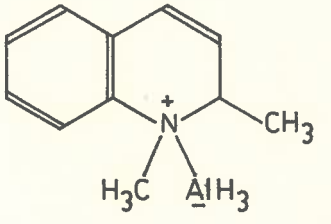
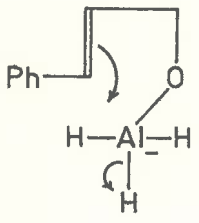


(184)

polarise the 3,4-double bond, and reduction to the tetrahydro-derivative would not occur. Whilst this mechanism accounts for the formation of the two products, it does not provide the reason for the different reaction course in ether and tetrahydrofuran.

The existence of cyclic intermediates has been invoked to account for apparently anomalous results obtained from some lithium aluminium hydride reductions. For example, although this reagent normally has no action on carbon-carbon double bonds it has been found[107] that cinnamaldehyde furnishes hydrocinnamyl alcohol on reduction in ether solution. The reaction occurs in two stages, with prior reduction of the carbonyl group followed by reduction of the double bond. The intermediate aluminium complex (185) could react as shown, and hydride addition to the β-carbon atom would lead to (186). Further reaction with another molecule of cinnamaldehyde would form the complex (187), considered by Brown[107] to be the intermediate immediately before hydrolysis. It would be of interest to perform this reaction in a solvent of greater basicity and to determine whether the reduction of the carbon-carbon double bond occurred.



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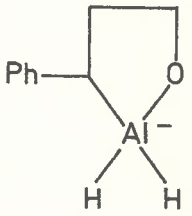

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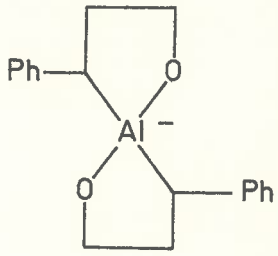
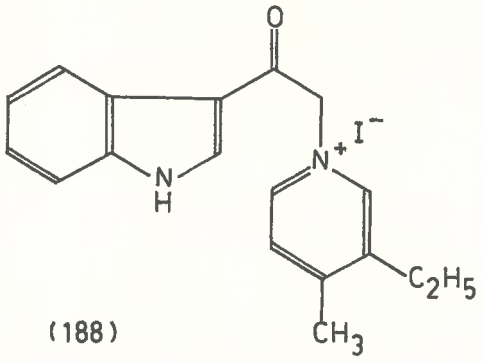


(187)

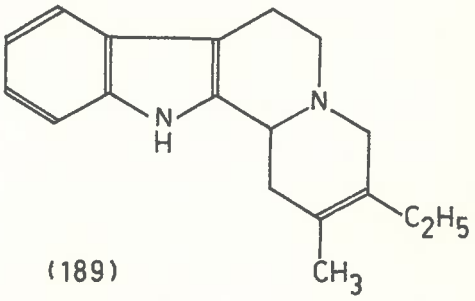
It is to be emphasised that the mechanism proposed for the lithium aluminium hydride reduction of quaternary pyridinium salts is of a speculative nature, and is perhaps premature without the support of additional experimental evidence. Whilst the concepts involved find support in the literature, and the idea of a quasi-cyclic intermediate may be likened to that proposed for some Grignard reactions[108] and aluminium alkoxide reductions,[109] no direct analogies can be drawn.

The third facet in the development of the synthesis of β-carboline derivatives was to prepare pentacyclic compounds possessing rings D and E in the fully reduced state. One step of the planned sequence involved the usual lithium aluminium hydride reduction of the 5,6,7,8-tetrahydroisoquinolinium salt (190), which in effect is a 3,4-disubstituted pyridinium derivative. Before the lengthy synthesis of the tetrahydroisoquinoline was undertaken it was decided to study the behaviour of the salt (188), prepared from the readily available β-collidine, towards hydride reduction. When this was performed in the usual manner in tetrahydrofuran solution 2-methyl-3-ethyl-1,4,6,7,12,12b-hexahydroindolo[2,3-a]quinolizine (189) was obtained. The structure was assigned on the basis of analytical results, the absence of absorption due to olefinic protons or the α-proton of the indole residue in the nuclear magnetic resonance spectrum, and by analogy with the direction of the cyclisation described previously. It was

therefore reasonable to expect the reduction of the 5,6,7,8-tetrahydroisoquinolinium salt (190) to yield a similar product.

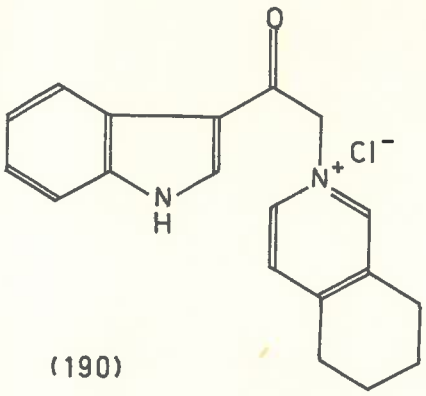


(188)



(189)

The poor yield from the condensation of 3-acetylindole, iodine, and 5,6,7,8-tetrahydroisoquinoline has been mentioned previously, and the necessary intermediate (190) was therefore prepared by the reaction of the base with 3-(chloroacetyl)indole. Reduction of (190) in tetrahydrofuran solution, followed by treatment with mineral acid afforded 1,2,3,4,5,7,8,13,13b,14-decahydrobenz[g]indolo[2,3-a]quinolizine (191; R=H). The physical characteristics of this compound agreed with those described in the literature,[110] and the structure was further proved by an examination of the nuclear magnetic resonance spectrum. As in the case of the base (189) there was no signal from an olefinic proton or from a proton attached to the α-position of the indole ring.



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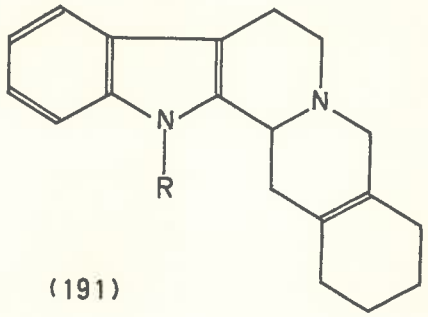
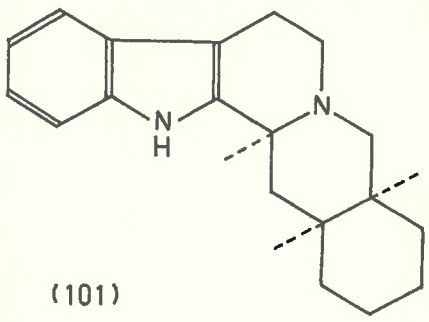
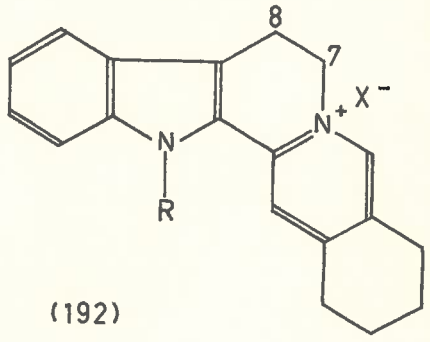


(191)

Attempts to reduce the isolated double bond of the β-carboline (191; R=H) were unsuccessful. Solutions of the base failed to absorb hydrogen when shaken with rhodium on carbon or a highly active platinum catalyst prepared by the method of Brown.[111] The starting material only was isolated after attempted reduction under the conditions used by Janot and co-workers[112] in the preparation of alloyohimbane (101) from sempervirine (192; R=H, double bond from C-7 to C-8). However the synthesis of (191; R=H) does constitute a synthesis of alloyohimbane as the former has been converted to the latter <u>via</u> the dihydrosempervirinium salt (192; R=H).[110]



(101)



(192)

The sodium borohydride reduction of N-methylsempervirinium salts (192; R=CH_3, double bond from C-7 to C-8) gives rise to a hexahydro-base which Witkop[113] has formulated as (191; R=CH_3). This structure was assigned from the fact that catalytic hydrogenation failed to reduce the product, and from a comparison of the pK_a value with those of model compounds. Methylation of (191; R=H) should therefore give a base identical with that obtained from the borohydride reduction. Treatment of the former compound with sodamide and methyl iodide in liquid ammonia yielded 1,2,3,4,5,7,8,-13,13b,14-decahydro-1'-methylbenz[g]indolo[2,3-a]quinolizine (191; R=CH_3) in quantitative yield. The infrared spectrum of the sample was identical with that published for the product from the reduction of the methylsempervirinium salt. A sample of the picrate of this compound, made available through the courtesy of Professor Witkop, was compared directly with the picrate of the synthetic base. There was no depression in the melting point on admixture of the two, and the infrared spectra were superimposable, (Fig. 4). Confirmation of the structure proposed by Witkop was therefore provided.

The instability of members of this series of compounds is worthy of mention. Without exception those β-carboline or Δ^3-piperideine derivatives containing an isolated double bond in ring D or at the junction of rings D and E rapidly decomposed in air and light. During crystallisation processes solutions obtained

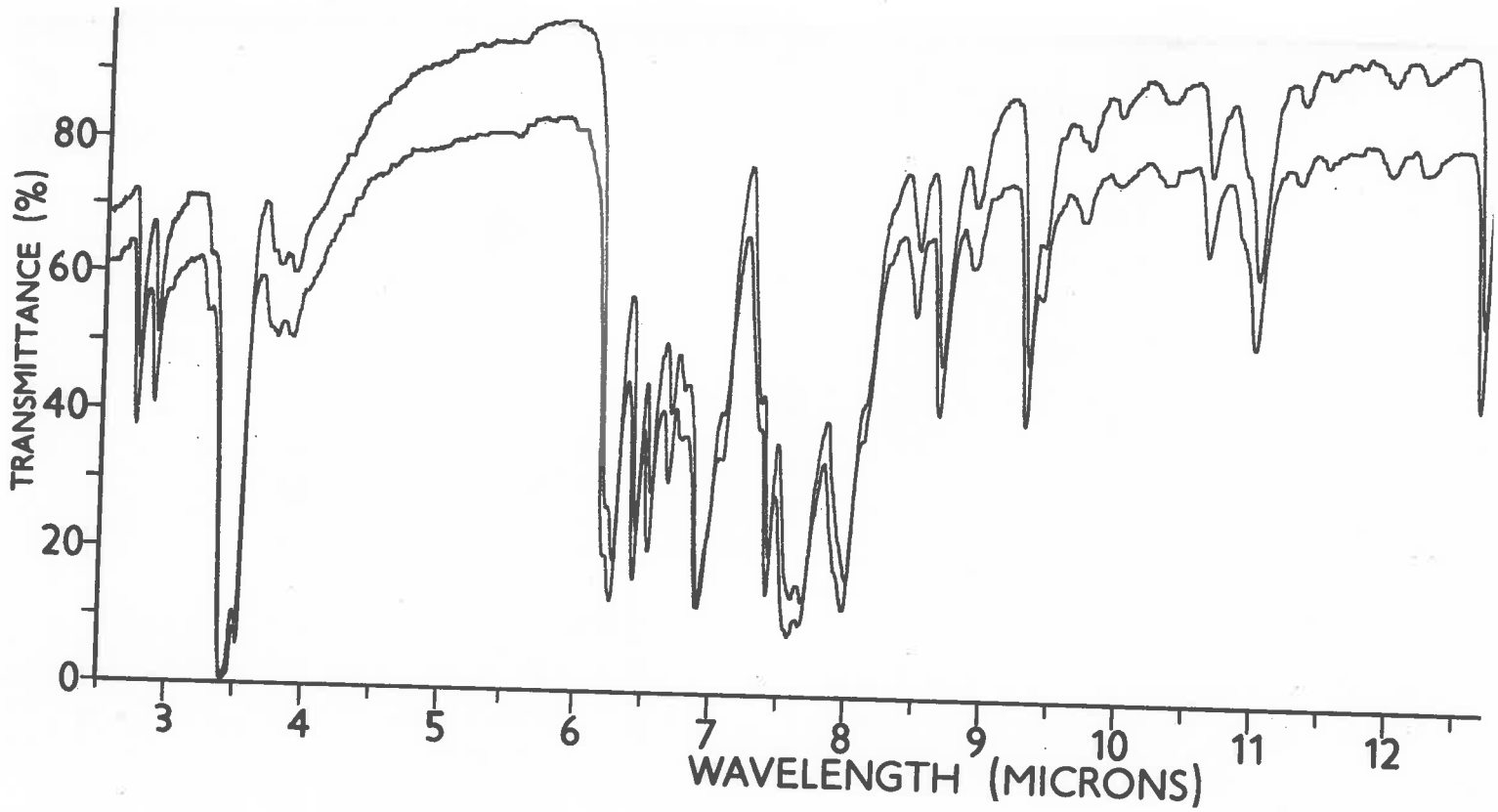


Fig. 4. Infrared absorption (Nujol mull) of 1,2,3,4,5,7,8,13,13b,14-decahydro-1'-methylbenz[g]indolo[2,3-a]quinolizinium picrate.

Upper - authentic

Lower - sample supplied by Professor Witkop

colourless after treatment with charcoal became yellow within a few minutes, and this effect was most noticable in hydrocarbon solvents. The difficulty experienced in obtaining correct analytical figures for the bases is illustrated by two separate analyses performed on 1,2,3,4,5,7,8,13,13b,14-decahydrobenz[g]-indolo[2,3-a]quinolizine (191; R=H). When the determination was carried out as soon as possible after isolation values in agreement with the theoretical were obtained, but a second determination performed on the sample one day later gave a figure for the carbon analysis 1.1% below the theoretical. This phenomenon is probably connected with an oxidative process involving the double bond, for when this was removed by reduction the bases were found to be stable and more easily purified.*

The synthesis of a number of β-carbolines containing a double bond in ring D permitted a study of their infrared spectra; in particular the region 2700-2800 cm.$^{-1}$ Wenkert[110] has suggested that the presence of absorption between these limits can be used to identify the configuration of the hydrogen atom at C-12b in yohimbine-type alkaloids or their derivatives (see 193). Thus it was proposed that compounds possessing an α-hydrogen atom at

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* This observation is supported by the results obtained by Dr. R. Massy-Westropp (see footnote p. 66).

C-12b exhibited two peaks of medium intensity in this region. Subsequently it has been shown from studies in the quinolizidine series that the ability to exhibit these peaks is associated with the presence of at least two α-hydrogen atoms trans-coplanar to the electron pair of the bridgehead nitrogen.[114] Further examination of the infrared spectra of derivatives in the reserpine series has led Rosen[115] to suggest that Wenkert's original proposal should be modified to "all compounds possessing in their stable conformations axial hydrogen atoms at C-12b exhibit two or more peaks or distinct shoulders between 2700 and 2900 $cm.^{-1}$ ..... whereas those containing equatorial hydrogen atoms at C-12b do not".

Compounds of general formula (193) have been shown to give rise to two bands in the above region (Table 6), and it is therefore concluded that an axial hydrogen atom is present at C-12b in all cases. The preferred conformation of the molecules would appear to be as represented in (194), and not as in (195) where the hydrogen atom at C-12b is equatorial. The reasons for this preference are that in (194) rings C and D are trans-fused and the indole residue is equatorial to ring D. In the absence of further substitution about the ring, trans-fused quinolizidines are reported to be energetically preferred over the cis-fused system,[114,116] and Stork and Hill[51] have suggested that the most

Table 6

Infrared Absorption in the 2700–2800 $cm.^{-1}$

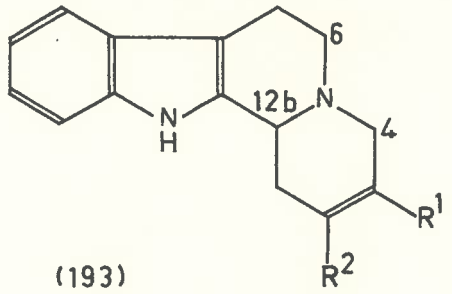
Region of Compounds of General Formula (193).[a]

	CCl_4		H.C.B.D.[b]	
5,7,8,13,13b,14-Hexahydrobenz[g]indolo[2,3-a]-quinolizine (120; $R^1=R^2=H$)	2807	2758	2786	2730
5,7,8,13,13b,14-Hexahydro-1'-methylbenz[g]-indolo[2,3-a]quinolizine	2807	2758		
6,7-Dimethoxy-5,7,8,13,13b,14-hexahydrobenz[g]-indolo[2,3-a]quinolizine (120; $R^1=R^2=OCH_3$)[c]	–		2778	2728
1,2,3,4,5,7,8,13,13b,14-Decahydrobenz[g]indolo-[2,3-a]quinolizine (191; R=H)	2795	2737		
3-Ethyl-1,4,6,7,12,12b-hexahydroindolo[2,3-a]-quinolizine (153; $R=C_2H_5$)	2795	2735		

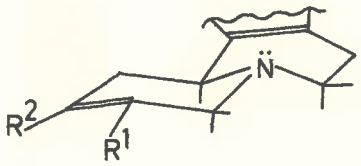
(a) measurements were made using a Grubb-Parsons Model S4 double-beam spectrometer

(b) hexachlorobutadiene mull (c) insoluble in carbon tetrachloride

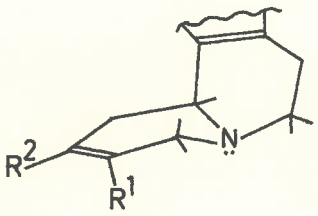
stable conformations in the alloyohimbane series are those where the indole residue is equatorial to ring D.



(193)



(194)

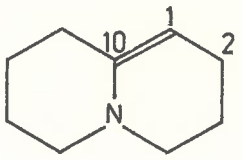


(195)

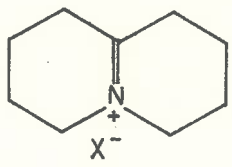
The synthetic pathway described in this text represents one of the most convenient methods of obtaining compounds possessing the yohimbine skeleton, and there exists considerable possibility for its application to the preparation of the indole alkaloids themselves.

A second method of formation of the pentacyclic β-carboline ring system has been subjected to preliminary investigation. Once again the key intermediate in the planned reaction sequence is the enamine (108).

Mercuric acetate has often been employed as an oxidising agent during organic syntheses. Of particular relevance to this particular project is its action on quinolizidines and N-substituted piperidines. Leonard and his co-workers[117] found that treatment of quinolizidine itself with mercuric acetate in dilute acetic acid led to the introduction of α,β-unsaturation with the formation of $\Delta^{1(10)}$-dehydroquinolizidine (196). In accordance with the behaviour of enamine systems the salt (197) was formed on the addition of acid. In an analogous fashion N-substituted piperidines underwent dehydrogenation to give Δ^{2}-piperideine derivatives.[118]



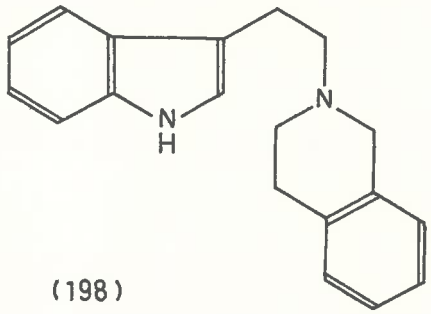
(196)



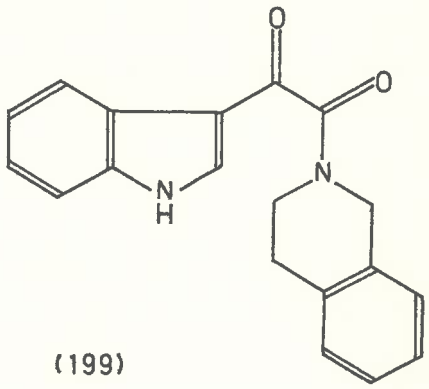
(197)

When the above facts were taken into account it was thought possible that treatment of 2-(2-3'-indolylethyl)-1,2,3,4-tetrahydro-isoquinoline (198) with mercuric acetate could produce the enamine (108) by α,β-dehydrogenation. It was hoped that cyclisation to

hexadehydroyohimbane under the acidic conditions of the reaction would occur immediately following the formation of (108).



(198)



(199)

The starting material for the reaction, the base (198), has been prepared by the lithium aluminium hydride reduction of the dioxo-compound (199), which was formed by the reaction of 1,2,3,4-tetrahydroisoquinoline with indole-3-glyoxalyl chloride.[73] The yields of both these products were greatly improved by the use of different solvents for the reactions. In particular the reduction has been reported to yield 39% of the base (198) when performed in ether solution, but this has been increased to 90% by the use of tetrahydrofuran as solvent.

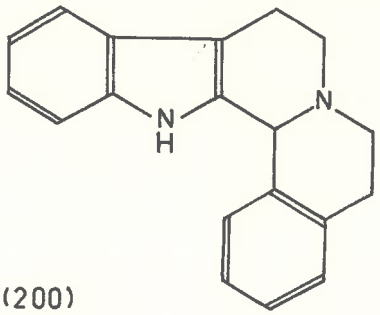
The reaction of 2-(2-3'-indolylethyl)-1,2,3,4-tetrahydro-isoquinoline ($C_{19}H_{20}N_2$) with mercuric acetate in dilute acetic acid has given two products. That formed in greatest quantity was a colourless hydrated base, "compound A" $C_{19}H_{18}N_2.H_2O$, and the other was a bright red base, "compound B" $C_{19}H_{14}N_2$, which formed

a yellow hydrochloride in ethanol solution. The former compound was not hexadehydroyohimbane. The two substances must be closely related, for when "A" was heated it lost solvent slowly above 100° and finally melted with decomposition to give "B". Unlike the starting material neither product gave any colour when boiled with Ehrlich's reagent, indicating that the α-position of the indole ring must be substituted.

The ultraviolet spectrum of "compound A" is very similar to that of the starting material and it can therefore be stated with certainty that there are no external double bonds conjugated with the indole residue. This is supported by the infrared spectrum which showed only very weak absorption in the 1620 $cm.^{-1}$ region due to the aromatic systems.

Treatment of "compound A" with iodine and potassium acetate gave a quaternary iodide, "compound C" $C_{19}H_{17}N_2I$. This supports the idea suggested by the result of the Ehrlich colour test - that "compound A" is a pentacyclic β-carboline derivative - as the reaction is characteristic of this class of compound. The iodide was readily converted to the corresponding chloride which on catalytic reduction absorbed one mole of hydrogen with the regeneration of "compound A".

The assignment of definite structures to "A", "B" and "C" cannot be attempted at this stage and must await the accumulation



(200)

of further data. The possibility that "A" may be a derivative of the base (200) will be examined further.

EXPERIMENTAL

Unless otherwise stated melting points were determined in capillaries, and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Infracord spectrometer. Ultraviolet spectra were recorded for solutions in 95% ethanol from an Optica CF4 spectrophotometer. Microanalyses were performed by the C.S.I.R.O. Microanalytical Laboratory, Melbourne.

3-Acetylindole.- (A) Indole (5.0 g.), acetic anhydride (45 ml.) and vinyl acetate (4 ml.) were heated together under reflux for 24 hr. The solvent was removed under reduced pressure and ice added to the oily product. The yellow oil that separated was washed several times with water, and after this had been decanted, a little ethanol was added. The cream solid product (2.8 g.) was collected and crystallised from benzene. The first crop of colourless needles had m.p. 143-145° (c.f. 1,3-diacetylindole m.p. 150-151°), and the second crop had m.p. 185-187° (c.f. 3-acetylindole m.p. 190-191°). Infrared spectra of the two samples indicated that the first crop of crystals was almost pure 1,3-diacetylindole, and the second crop mainly 3-acetylindole. The yield of acetylated product isolated was low, as a considerable amount dissolved in the ethanol during trituration.

(B) Indole (5 g.), acetic anhydride (45 ml.) and vinyl acetate (2 ml.) were heated together under reflux for 8 hr. Most of the solvent was distilled from the golden-yellow solution, and the last traces were removed under vacuum at 100° to yield a yellow crystalline product. Aqueous sodium hydroxide (2N, 20 ml.) and ethanol (50 ml.) were added and the mixture stirred for a few minutes until no more solid appeared to dissolve. On standing for more than about 3-4 min. the basic solution rapidly became dark brown. The crystalline solid residue was collected (0.94 g.) and crystallised from acetone as small straw-coloured rhombs, m.p. 243-244°. It was identified as 1,3'-indolyl-1,3"-indolyl-idine-ethane by mixed m.p. determination and comparison of its infrared spectrum with that of an authentic sample.[57] 3-Acetyl-indole was precipitated from the filtrate by the addition of water. It crystallised from ethyl acetate (charcoal) as pale fawn columns (4.1 g., 61%), m.p. 190-191° (lit.[57] m.p. 190-191°). Further crystallisation from a large volume of benzene yielded colourless needles, m.p. 190-191°.

(C) Indole (17.5 g.), acetic anhydride (160 ml.) and vinyl acetate (10 ml.) were heated together under reflux for 15-20 hr., after which time the solution attained a golden-yellow colour. The solvent was removed as in (B) above, and the yellow crystalline residue treated with aqueous sodium hydroxide (2 N, 70 ml.) and ethanol (140 ml.). 1,3'-Indolyl-1,3"-indolylidine-ethane (3.68 g.)

was collected and characterised by comparison of its infrared spectrum with that of an authentic sample. Addition of water to the filtrate precipitated 3-acetylindole as a fawn powder. Crystallisation from ethyl acetate (charcoal) yielded pale fawn columns (15.8 g., 67%) m.p. 190-191°.

(D) Indole (17.5 g.), acetic anhydride (160 ml.) and vinyl acetate (17.5 ml.) were heated together under reflux for 50 hr. After this time the solution was still almost colourless, and had not become yellow as indicated in (C). The solvent was removed under reduced pressure and the semicrystalline residue extracted with light petroleum (b.p. 40-60°). On cooling the extract indole (14.6 g.) was recovered. A second crystallisation from light petroleum yielded colourless plates of indole, m.p. and mixed m.p. 51-52°. The crystalline residue from this extraction was shown to be 1,3-diacetylindole by comparison of its infrared spectrum with that of an authentic sample.

(E) Indole (5 g.), acetic anhydride (45 ml.) and styrene (5 ml.) were heated together under reflux for 24 hr. After removal of the solvent from the yellow solution aqueous sodium hydroxide (2N, 15 ml.) and ethanol (40 ml.) were added. The majority of the solid dissolved, but 1.3 g. of insoluble material remained. This was extracted with a little warm benzene, treated with charcoal, and polystyrene precipitated by the addition of methanol.

After further purification by partial precipitation from benzene solution, the infrared spectrum was found to be identical with that of an authentic sample. The residue from the benzene extract was identified as 1,3'-indolyl-1,3''-indolylidine-ethane by comparison of infrared spectra. Addition of water to the original basic extract precipitated 3-acetylindole as a fawn powder that crystallised from ethyl acetate as very pale fawn columns (4.53 g., 67%) m.p. 190-191°.

2-(2-3'-Indolyl-2-oxoethyl)isoquinolinium Iodide.- 3-Acetylindole (1.6 g., 0.01 mole) and isoquinoline (3.87 g., 0.03 mole) were warmed together on a water-bath. Iodine (2.5 g., 0.01 mole) was added and the mixture heated on a steam-bath for 45 min. until, when cooled, there was no iodine apparent in the bottom of the flask. The solid product was washed with a small amount of water to remove isoquinoline hydroiodide and excess isoquinoline. Trituration with ethanol precipitated the crude 2-(2-3'-indolyl-2-oxoethyl)isoquinolinium iodide, (3.91 g., 94%) as a fawn microcrystalline powder, m.p. 265-268° (decomp.). Crystallisation from water yielded the iodide as fine, pale yellow needles, m.p. 270-272° (decomp.) (Found: C, 54.8; H, 3.8; N, 6.5. $C_{19}H_{15}N_2OI$ requires C, 55.1; H, 3.7; N, 6.8%).

The perchlorate was prepared by the addition of 50% aqueous perchloric acid to a hot aqueous solution of the iodide. It separated from aqueous dimethylformamide as colourless needles,

m.p. 276-277° (decomp.) (Found: C, 58.5; H, 4.1; N, 6.7. $C_{19}H_{15}N_2O_5Cl$ requires C, 59.0; H, 4.2; N, 7.2%).

2-(2-3'-Indolyl-2-oxoethyl)isoquinolinium Bromide.- 3-(Bromoacetyl)indole[117] (0.48 g., 0.002 mole) and isoquinoline (0.78 g., 0.006 mole) were mixed together and warmed on a water-bath for 2-3 min. The solid product was triturated with ethanol (5 ml.) and the colourless powder collected and washed with ether. The bromide crystallised from water as small fawn irregular prisms, m.p. 297-299° (decomp.) with previous darkening (Found: C, 62.0; H, 4.1; N, 7.9. $C_{19}H_{15}N_2OBr$ requires C, 62.2; H, 4.1; N, 7.6%).

Conversion into the iodide. A sample of the bromide was dissolved in hot water and an aqueous solution of potassium iodide added. The precipitated 2-(2-3'-indolyl-2-oxoethyl)isoquinolinium iodide was collected and crystallised from water as pale yellow needles, m.p. 269-271° (decomp.). There was no depression in the m.p. on admixture with a sample of the iodide prepared by the above method, and the infrared spectra of the two samples were identical in every respect.

1-(2-3'-Indolyl-2-oxoethyl)quinolinium Iodide.- 3-Acetylindole (1.6 g., 0.01 mole), quinoline (3.87 g., 0.03 mole) and iodine (2.5 g., 0.01 mole) were heated together on a steam-bath for 45 min. After cooling, the green-black tar was washed with water (50 ml.) and hot ether (4 x 50 ml.). Ethanol (50 ml.) was added, and on rubbing a brown powder (1.4 g., m.p. 225-227°)

separated. The addition of light petroleum (b.p. 40-60°) to the mother-liquor gave a further 0.8 g. of this product. Crystallisation from ethanol (charcoal) and then from water yielded the iodide as fine yellow needles, m.p. 247-249° (decomp.) (Found: C, 54.8; H, 3.8; N, 6.4. $C_{19}H_{15}N_2OI$ requires C, 55.1; H, 3.7; N, 6.8%).

2-(2-1'-Methyl-3'-indolyl-2-oxoethyl)isoquinolinium Iodide.- 1-Methyl-3-acetylindole (4.2 g., 0.024 mole) and isoquinoline (9.3 g., 0.072 mole) were warmed together on a water-bath to effect solution, and iodine (6.0 g., 0.024 mole) added. The mixture was heated on a steam-bath for 45 min. and then cooled. A little ethanol was added and, on rubbing, the product solidified. Several crystallisations from water yielded 2-(2-1'-methyl-3'-indolyl-2-oxoethyl)isoquinolinium iodide as fine, pale yellow needles (5.8 g., 56%), m.p. 255-256° (decomp.) with previous darkening (Found: C, 56.0; H, 3.8; N, 6.5. $C_{20}H_{17}N_2OI$ requires C, 56.1; H, 4.0; N, 6.5%).

The perchlorate, prepared in the above manner, crystallised from acetone as colourless needles, m.p. 243-244° (decomp.) (Found: C, 60.0; H, 4.4; N, 6.7. $C_{20}H_{17}N_2O_5Cl$ requires C, 59.9; H, 4.3; N, 7.0%).

1-(2-3'-Indolyl-2-oxoethyl)pyridinium Iodide.- This salt was prepared as above from 3-acetylindole (2.4 g., 0.015 mole), pyridine (3.6 g., 0.045 mole) and iodine (3.75 g., 0.015 mole). Trituration of the crude product with water yielded the crude iodide,

and several crystallisations from water yielded yellow needles (4.0 g., 68%), m.p. 254-255° (decomp.) (lit.[59] m.p. 238°).

The perchlorate separated from water as cream needles, m.p. 229-231° (decomp.) (Found: C, 53.7; H, 3.9; N, 7.9. $C_{15}H_{13}N_2O_5Cl$ requires C, 53.5; H, 3.9; N, 8.1%).

1-(2-3'-Indolyl-2-oxoethyl)-3-methylpyridinium Iodide.- 3-Acetylindole (1.6 g., 0.01 mole) and 3-picoline (2.82 g., 0.03 mole) were warmed together on a water-bath, and iodine (2.5 g., 0.01 mole) added. The mixture was heated on a steam-bath for 50 min., and on cooling, a black viscous tar was formed. Ethanol (50 ml.) was added and a fawn microcrystalline powder (2.3 g., 64%) was collected, m.p. 249-250° (decomp.). Crystallisation from water gave the iodide as pale pink needles, m.p. 266-267° (decomp.) (Found: C, 51.2; H, 4.1; N, 6.8. $C_{16}H_{15}N_2OI$ requires C, 50.8; H, 4.0; N, 7.4%).

The perchlorate crystallised from water as long colourless needles, m.p. 249-250° (Found: C, 54.9; H, 4.4; N, 7.8. $C_{16}H_{15}N_2O_5Cl$ requires C, 54.8; H, 4.3; N, 8.0%).

3-Ethyl-1-(2-3'-indolyl-2-oxoethyl)-4-methylpyridinium Iodide.- The use of 3-ethyl-4-methylpyridine in the above condensation yielded the corresponding iodide (2.7 g., 22%) on concentration of an ethanolic solution of the crude products. Crystallisation from water yielded fine, pale fawn needles, m.p. 260-262° (decomp.) (Found: C, 53.1; H, 4.7; N, 6.6. $C_{18}H_{19}N_2OI$ requires C, 53.2;

H, 4.7; N, 6.9%).

The perchlorate separated from acetone as small colourless needles, m.p. 264-265° (decomp.) with previous darkening (Found: C, 57.6; H, 5.3; N, 7.1. $C_{18}H_{19}N_2O_5Cl$ requires C, 57.1; H, 5.1; N, 7.4%).

3-Ethyl-1-(2-3'-indolyl-2-oxoethyl)pyridinium Iodide.- 3-Ethylpyridine[118] (2.8 g., 0.03 mole) and 3-acetylindole (1.6 g., 0.01 mole) were warmed together on a water-bath. Iodine (2.54 g., 0.01 mole) was added, and the mixture heated at 95-100°. The product began to crystallise after several minutes, and heating was continued for 1 hr. The solid product was triturated with ethanol (ca. 20 ml.) and a cream powder collected. 3-Ethyl-1-(2-3'-indolyl-2-oxoethyl)pyridinium iodide (3.1 g., 80%) crystallised from water as a mixture of fawn plates and needles, m.p. 257° (decomp.) with darkening from 248°. Both of these crystalline forms of the iodide separated from ethanol as fine colourless needles, m.p. 260-262° (decomp.) with darkening from 255° (Found: C, 52.0; H, 4.5; N, 7.2. $C_{17}H_{17}N_2OI$ requires C, 52.1; H, 4.4; N, 7.1%). Solutions of the iodide in ethanol gradually became deep yellow on standing at room temperature for several hours.

3-Ethyl-1-(2-3'-indolyl-2-oxoethyl)pyridinium Bromide.- A mixture of 3-(bromoacetyl)indole (0.48 g., 0.002 mole) and 3-ethylpyridine (0.28 g., 0.003 mole) was gently warmed on a water-bath for a few minutes. The solid product was rubbed with

a little ethanol and the colourless powder that precipitated was collected and washed with ether. 3-Ethyl-1-(2-3'-indolyl-2-oxoethyl)pyridinium bromide separated from water as colourless needles, m.p. 268-271° (decomp.) (Found: C, 58.7; H, 4.7; N, 8.2. $C_{17}H_{17}N_2OBr$ requires C, 59.1; H, 5.0; N, 8.2%).

Conversion into the iodide. The addition of an aqueous solution of potassium iodide to a solution of the bromide in hot water produced an immediate precipitate of 3-ethyl-1-(2-3'-indolyl-2-oxoethyl)pyridinium iodide that crystallised from water as colourless needles, m.p. and mixed m.p. 259-261° (decomp.) with a sample prepared as above.

2-(2-3'-Indolyl-2-oxoethyl)-5,6,7,8-tetrahydroisoquinolinium Chloride.- (A) 3-(Chloroacetyl)indole[119] (200 mg.) was added to 5,6,7,8-tetrahydroisoquinoline[120] (150 mg.) in benzene (ca. 40 ml.) and the mixture heated under gentle reflux for 2½ hr. The solvent was removed under reduced pressure and the semi-crystalline residue rubbed with a little ethanol to give a colourless powder (190 mg.), m.p. ca. 190° (decomp.). The powder was extracted with hot chloroform, and on cooling the extract deposited 3-(chloroacetyl)indole as colourless needles, m.p. 215-217° (decomp.) with previous darkening. The pale yellow crystalline residue after the chloroform extract had m.p. 250-258° (decomp.).

(B) 5,6,7,8-Tetrahydroisoquinoline (2.7 g., 0.02 mole) and 3-(chloroacetyl)indole (1.7 g., 0.009 mole) were mixed together

in a flask protected by a drying-tube and warmed on a water-bath. A pale pink solution was formed, and after 1-2 min. the reaction mixture solidified to a cream mass. Trituration with ethanol (6-7 ml.) yielded a colourless powder, m.p. 269-270°. 2-(2-3'-Indolyl-2-oxoethyl)-5,6,7,8-tetrahydroisoquinolinium chloride (2.9 g., quant.) crystallised from methanol as colourless plates, m.p. 270-272° (decomp.) (Found: C, 69.3; H, 6.1; N, 8.7. $C_{19}H_{19}N_2OCl$ requires C, 69.8; H, 5.9; N, 8.6%).

Conversion into the iodide. A sample of the chloride was dissolved in hot water and a saturated aqueous solution of potassium iodide added. The precipitated 2-(2-3'-indolyl-2-oxoethyl)-5,6,7,8-tetrahydroisoquinolinium iodide was collected and crystallised from water as cream needles, m.p. 249-251° (decomp.). There was no depression in the m.p. on admixture with a sample of the iodide prepared by the method below, and the infrared spectra of the two were identical.

2-(2-3'-Indolyl-2-oxoethyl)-5,6,7,8-tetrahydroisoquinolinium Iodide.- (A) 3-Acetylindole (0.8 g., 0.005 mole) and 5,6,7,8-tetrahydroisoquinoline (2.0 g., 0.015 mole) were heated together on a steam-bath with iodine (1.25 g., 0.005 mole) for 40 min. The cooled melt was extracted with boiling water (charcoal) and on cooling a yellow oil was deposited. The mother-liquor was decanted and when the oil was rubbed with a little ethanol a pale yellow powder precipitated. 2-(2-3'-Indolyl-2-oxoethyl)-5,6,7,8-

tetrahydroisoquinolinium iodide (85 mg., 4%) crystallised from water as fine cream needles, m.p. 251-252° (decomp.) (Found: C, 54.7; H, 4.6; N, 6.8. $C_{19}H_{19}N_2OI$ requires C, 54.6; H, 4.6; N, 6.7%).

(B) 3-Acetylindole (2.3 g., 0.014 mole), 5,6,7,8-tetrahydroisoquinoline (5.8 g., 0.043 mole) and iodine (3.6 g., 0.028 mole) were heated together as in (A). The tar was extracted with boiling water and the solvent removed leaving a yellow semi-crystalline oil (9.9 g.). Further crystallisation from water yielded a colourless powder, m.p. ca. 160°, that could not be purified further. Comparison of the infrared spectrum of the sample with that of the iodide from (A) indicated the presence of the latter in the mixture.

2-(2-3',4'-Dimethoxyphenyl-2-oxoethyl)isoquinolinium Iodide.- 3,4-Dimethoxyacetophenone[121] (14.4 g., 0.08 mole) and isoquinoline (31 g., 0.18 mole) were warmed together on a water-bath. Iodine (20 g., 0.08 mole) was added, and the mixture heated on a steam-bath for 45 min. The cooled, semi-solid product was washed with water and ether, and then extracted with several portions of hot ethanol. After concentration and cooling, the iodide was deposited as pale yellow needles (5.7 g., 16%), m.p. 215-218° (decomp.) with previous darkening. Crystallisation from water yielded fine yellow needles, m.p. 223-225° (decomp.) (Found: C, 50.5; H, 4.4

N, 2.9; OCH_3, 13.7. $C_{19}H_{18}NO_3I.1H_2O$ requires C, 50.3; H, 4.5; N, 3.1; OCH_3, 13.7%). The molecule of water of crystallisation was not removed after heating to 100°/0.1 mm. for 10 hr.

Reduction of 2-(2-3'-Indolyl-2-oxoethyl)isoquinolinium Iodide in Ether Solution.- The powdered salt (0.1 g., 0.00025 mole) was added to lithium aluminium hydride (0.03 g., 0.00075 mole) suspended in dry ether (50 ml.). An immediate intense green fluorescence was observed. The mixture was heated under reflux for 2 hr., cooled in an ice-bath, and the complex and excess hydride decomposed by the careful addition of water. Dilute hydrochloric acid (10 ml.) was added, the mixture shaken for several minutes, and the aqueous layer separated and stored in a refrigerator. The orange-yellow oil that was deposited solidified on scratching to a yellow powder (37 mg., m.p. 265-275° decomp.). The crude hydrochloride thus obtained was dissolved in a little hot water and the solution basified with sodium hydroxide (10% aqueous). Ether extraction (2 x 25 ml.) followed by evaporation of the solvent yielded the crude base as a yellow oil. The infrared spectrum, determined in chloroform solution, exhibited an absorption band at 1720 $cm.^{-1}$

5,7,8,13,13b,14-Hexahydrobenz[g]indolo[2,3-a]quinolizine (120; R^1=R^2=H).- (A) Method of Potts and Robinson.[26] 2-(2-3'-Indolyl-ethyl)isoquinolinium iodide (6.0 g., 0.012 mole) was added in portions to lithium aluminium hydride (3.0 g., 0.08 mole) suspended in dry

tetrahydrofuran (500 ml.) and the mixture heated under reflux for 2 hr. The fluorescent solution was cooled, and the excess hydride carefully decomposed with water. An excess of dilute hydrochloric acid was added, the yellow solution filtered, and the majority of the tetrahydrofuran removed under reduced pressure on a warm water-bath. An oily product separated as the tetrahydrofuran was removed, and on cooling and scratching this solidified to a yellow powder. Repeated crystallisation from methanol (charcoal) yielded the hydrochloride of 5,7,8,13,13b,14-hexahydrobenz[g]indolo-[2,3-a]quinolizine as fine colourless needles, m.p. 295-297° (decomp.).

The free base was obtained by the addition of solid sodium hydroxide to an aqueous solution of the hydrochloride. The colourless precipitate was collected, washed with a little water, and dried. The sample separated from aqueous methanol as colourless needles, m.p. 194-195°.

(B) Finely powdered 2-(2-3'-indolyl-2-oxoethyl)isoquinolinium iodide (0.9 g., 0.0022 mole) was added in small portions to lithium aluminium hydride (0.5 g., 0.013 mole) in dry tetrahydrofuran (ca. 70 ml.). The fluorescent mixture was heated under reflux for $4\frac{1}{2}$ hr., cooled in an ice-bath, and the excess hydride decomposed by the careful addition of water. On acidification with dilute hydrochloric acid the pale yellow colour of the solution was

intensified. Most of the tetrahydrofuran was evaporated under reduced pressure on a water-bath, and on cooling an orange powder was deposited, m.p. 275-278°. Successive crystallisation from methanol (charcoal) yielded fine colourless needles of 5,7,8,13,13b,14-hexahydrobenz[g]indolo[2,3-a]quinolizinium hydrochloride (0.47 g., 69%), m.p. 295-297° (decomp. in vacuo) (Potts and Robinson[26] report m.p. 288-289° for this compound). The m.p. was not depressed on admixture with an authentic sample (Found: C, 73.4; H, 6.5; N, 8.6. Calc. for $C_{19}H_{19}N_2Cl$: C, 73.4; H, 6.2; N, 9.0%).

The free base was obtained by the addition of solid sodium hydroxide to a solution of the hydrochloride (80 mg.) in hot water (20 ml.). The precipitate was collected and dried (76 mg., m.p. 194°). Crystallisation from aqueous methanol yielded cream needles, m.p. 193-195° with previous darkening (lit.[12] m.p. 196-197°). The mixed m.p. with an authentic sample showed no depression (Found: C, 82.9; H, 6.7; N, 9.9. Calc. for $C_{19}H_{18}N_2$: C, 83.2; H, 6.6; N, 9.9%).

The infrared spectra of both the hydrochloride and the free base were identical with those of authentic specimens.

(C) Finely powdered 2-(2-3'-indolyl-2-oxoethyl)isoquinolinium perchlorate (1.0 g., 0.003 mole) was added to a solution of lithium aluminium hydride (0.5 g., 0.013 mole) in tetrahydrofuran

(100 ml.). Effervescence occurred with dissolution of the salt and the formation of a yellow colour and green fluorescence. The mixture was heated under gentle reflux for 4 hr., cooled in an ice-bath, and the excess hydride decomposed with water. The solution was acidified with perchloric acid, and the tetrahydrofuran removed under reduced pressure on a water-bath. The precipitated yellow semi-solid was dissolved in water, basified with aqueous sodium hydroxide solution, and the resultant cream powder collected. 5,7,8,13,13b,14-Hexahydrobenz[g]indolo-[2,3-a]quinolizine (0.45 g., 65%) crystallised from aqueous methanol as colourless needles, m.p. 194-196°. The melting point on admixture with an authentic sample obtained as in (A) was 194-196°.

6,7-Dimethoxy-2-(2-3'-indolyl-2-oxoethyl)isoquinolinium Bromide.- 6,7-Dimethoxyisoquinoline[122] (1.6 g., 0.0078 mole) and 3-(bromoacetyl)indole (1.8 g., 0.0075 mole) were mixed and heated on a steam-bath for 5 min. The reaction mixture quickly solidified and on cooling and trituration with methanol (5 ml.) a colourless powder was precipitated. 6,7-Dimethoxy-2-(2-3'-indolyl-2-oxoethyl)-isoquinolinium bromide (1.32 g., 40%) crystallised from methanol as clusters of small colourless needles, m.p. 237-239° (decomp.) (Found: C, 57.8; H, 4.7; N, 6.1. $C_{21}H_{19}N_2O_3Br.CH_3OH$ requires C, 57.5; H, 5.0; N, 6.1%). A band at 3500 $cm.^{-1}$ in the infrared

spectrum confirmed the presence of the molecule of methanol of crystallisation.

2,3-Dimethoxy-5,7,8,13,13b,14-hexahydrobenz[g]indolo[2,3-a]-quinolizine (120; $R^1=R^2=OCH_3$).- Dried, powdered 6,7-dimethoxy-2-(2-3'-indolyl-2-oxoethyl)isoquinolinium bromide (1.0 g., 0.0023 mole) was added in small portions to a solution of lithium aluminium hydride (0.6 g., 0.016 mole) in dry tetrahydrofuran (100 ml.). Marked effervescence occurred with dissolution of the salt and formation of a pale green solution with a green fluorescence. The mixture was stirred and heated under reflux for $3^1/2$ hr. in an atmosphere of nitrogen. Hydrated sodium sulphate was added to the cooled reaction mixture, the precipitated inorganic material removed by filtration under nitrogen, and the pale yellow filtrate treated with dilute hydrochloric acid (ca. 50 ml.). The volume of the solution was reduced by heating on a water-bath, and on cooling a fawn crystalline solid was deposited, m.p. 273-275°. 2,3-Dimethoxy-5,7,8,13,13b,14-hexahydrobenz[g]indolo[2,3-a]-quinolizinium hydrochloride (0.74 g., 85%) separated from methanol as colourless plates, m.p. 275-276° (lit.[26] m.p. 276°). There was no depression in the m.p. on admixture with an authentic sample of the hydrochloride[26] and the infrared spectra of the two samples were superimposable.

The free base was obtained by the addition of aqueous sodium hydroxide to an aqueous solution of the hydrochloride. The

precipitated solid crystallised from anisole as small colourless needles, m.p. 294-296° with no depression on admixture with an authentic sample of the base.

Reduction of 1-Methyl-3-acetylindole with Lithium Aluminium Hydride. Poly-(1-methyl-3-vinylindole).- 1-Methyl-3-acetylindole (6.0 g., 0.03 mole) was added to a solution of lithium aluminium hydride (4.0 g., 0.11 mole) in dry tetrahydrofuran (300 ml.) and the solution heated under reflux for $4\frac{1}{2}$ hr. Water was added to the cooled solution to decompose the complex and excess hydride, and the mixture was then extracted with ether and the extract dried over sodium sulphate. The solvent was removed to yield the product as a pale yellow oil (6 g.). An infrared spectrum of the crude sample showed intense broad absorption at 3400 $cm.^{-1}$ Attempts to form a derivative of the alcoholic function using freshly prepared 3,5-dinitrobenzoyl chloride gave 3,5-dinitrobenzoic acid as the only isolable crystalline product.

The crude product, which had an odour of acetaldehyde, was extracted with cold water. The addition of Brady's reagent to the extract gave a yellow precipitate of acetaldehyde 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 168°, which had an infrared spectrum identical with that of an authentic sample. The residue from the cold water extraction was divided into two portions. The first was boiled with water for 24 hr., and on

cooling, a brown solid material, m.p. 70-80°, was deposited. An infrared spectrum of the sample showed a complete absence of absorption in the 3400 $cm.^{-1}$ region. The compound was purified by filtration through a column of neutral alumina in benzene solution. Evaporation of the solvent gave a colourless glass that could not be obtained crystalline.

An attempt was made to distill the second portion of the residue from the cold water extraction. However, as the sample appeared to be reaching the b.p., polymerisation occurred with the formation of a brown glass. Purification was effected by filtration through a column of neutral alumina in benzene solution, and the product had an infrared spectrum identical with that of the product obtained by boiling with water for 24 hr. Poly-(1-methyl-3-vinylindole) distilled (free flame, high vacuum) as a colourless glass (Found: C, 84.0; H, 6.9; N, 8.8. $(C_{11}H_{11}N)_n$ requires C, 84.0; H, 7.1; N, 8.9%). Light absorption: $\lambda_{max.}$ 2290, 2670 (broad shoulder), 2930 (log ε 4.76, 4.07, 4.18), $\lambda_{min.}$ 2530 Å (log ε 3.92). The infrared spectrum was similar to, but not identical with, that of 1,1-di-(N-methyl-3'-indolyl)-ethane.

1,1-Di-(N-methyl-3'-indolyl)ethane.- (A) Sodium (46 mg.) was added to liquid ammonia (30 ml.) containing a crystal of ferric nitrate. 1,1-Di-3'-indolylethane[57] (470 mg.) was added, and after 5 min., methyl iodide (300 mg.) was added dropwise to

the stirred mixture. Whilst stirring was continued the mixture was allowed to stand at room temperature until the ammonia had evaporated. Water was added, and ether extraction (3 x 50 ml.) gave the product (520 mg., quant.) as a pale yellow oil. Purification was effected by passage through a column of Woelm neutral alumina (activity 1), eluting with benzene. The product, obtained as a colourless glass soluble in light petroleum, could not be induced to crystallise. The infrared spectrum was identical with that of the product obtained in (B) below.

(B) N-Methylindole (6 g.), paraldehyde (1.2 g.) and zinc chloride (1.5 g.) were heated together on a steam-bath for 4 hr. The black tar was extracted with hot benzene, treated with charcoal, and the solvent removed to yield 1,1-di-(N-methyl-3'-indolyl)ethane as a pale yellow glass (5.8 g., 87%). Decomposition to a black oil occurred slowly in the presence of air and light. After purification as above, the product was distilled (free flame/vac.) (Found: C, 83.1; H, 6.9; N, 9.9. $C_{20}H_{20}N_2$ requires C, 83.3; H, 7.0; N, 9.7%). Light absorption $\lambda_{max.}$ 2290, 2940 (log ϵ 4.70, 3.98), $\lambda_{min.}$ 2560 Å (log ϵ 3.64).

Reduction of 3,4-Dimethoxyacetophenone with Lithium Aluminium Hydride.- 3,4-Dimethoxyacetophenone (7.2 g., 0.04 mole) was added in small portions to a suspension of lithium aluminium hydride (2.3 g., 0.06 mole) in dry tetrahydrofuran (150 ml.),

with marked effervescence occurring. The mixture was heated under gentle reflux for 4 hr., cooled in an ice-bath, and the excess hydride decomposed by the dropwise addition of water. A further amount of water was added (150 ml.) and the mixture filtered. The filtrate was extracted with ether (3 x 200 ml.), the extract dried over sodium sulphate, and the solvent removed. The colourless liquid residue (6.6 g.) exhibited strong absorption in the hydroxyl region of the infrared spectrum. The product was distilled (118-120°/0.5 mm.) and an infrared spectrum of the distillate determined. The intensity of the band in the hydroxyl region decreased markedly, and absorption characteristic of a conjugated vinyl group appeared at 1625(s), 1440(s), 987(s), 1305(m), and 1830(w) cm.$^{-1}$ The distillate, consisting mainly of 3,4-dimethoxyvinylbenzene, was dissolved in carbon tetrachloride and treated with a dilute solution of bromine in carbon tetrachloride until the colour persisted. The solution was concentrated, and on cooling a precipitate separated. 3,4-Dimethoxy-1-(1,2-dibromoethyl)benzene crystallised from light petroleum (b.p. 40-60°) as clusters of colourless needles, m.p. 97-98° (Quelet and Calcagni[123] report m.p. 98° for this compound). 3,4-Dimethoxyvinylbenzene polymerised to a colourless rubbery mass on standing in air.

Reduction of 1-Methyl-3-acetylindole with a Mixture of Lithium Aluminium Hydride and Aluminium Chloride.- A solution of

1-methyl-3-acetylindole (1.7 g., 0.01 mole) and aluminium chloride (2.68 g., 0.02 mole) in dry tetrahydrofuran (100 ml.) was added, over a period of 30 min., to a stirred solution of lithium aluminium hydride (0.4 g., 0.01 mole) and aluminium chloride (1.0 g., 0.0075 mole) in tetrahydrofuran (50 ml.). An immediate blue fluorescence was produced, and the mixture was heated under gentle reflux for 4 hr. The complex was decomposed by treating the cooled solution with hydrated sodium sulphate, and then with water. The filtered solution was extracted with ether and the extract dried overnight with sodium sulphate. Evaporation of the solvent yielded 1.4 g. of a fluorescent liquid, and the infrared spectrum of the crude sample showed no absorption due to a hydroxyl group. The oil (1.2 g.) was distilled and 1-methyl-3-ethylindole (1.0 g., 74%) collected, b.p. 74-76°/0.3-0.4 mm. $n^{20}D$ 1.5808 (Snyder et al.[124] report fluorescent oil, b.p. 95-96°/0.6 mm. $n^{20}D$ 1.5806). The picrate, formed in ethanol, crystallised from a small volume of ethanol as long red needles, m.p. 97-98° (lit.[124] m.p. 96-97°).

Reduction of 3,4-Dimethoxyacetophenone with a Mixture of Lithium Aluminium Hydride and Aluminium Chloride.- A solution of 3,4-dimethoxyacetophenone (3.6 g., 0.02 mole) and aluminium chloride (5.4 g., 0.04 mole) in dry tetrahydrofuran (100 ml.) was added, over a period of 30 min., to a stirred solution of lithium aluminium hydride (0.8 g., 0.02 mole) and aluminium

chloride (2.0 g., 0.015 mole) in tetrahydrofuran (50 ml.). The mixture was heated under gentle reflux for 4 hr., cooled in an ice-bath, and the complex and excess hydride decomposed by the careful addition of hydrated sodium sulphate. Water was added, the mixture filtered, and the filtrate extracted with ether. After drying overnight over sodium sulphate the solvent was removed, yielding 3.2 g. of a colourless oil. The infrared spectrum of this crude sample showed a small absorption band in the hydroxyl region. Distillation of 3 g. of the oil yielded 3,4-dimethoxyethylbenzene (2.6 g., 87%) b.p. 122-124°/15 mm., that was shown (infrared spectrum, analysis) to be contaminated with a trace amount of 1-(3,4-dimethoxyphenyl)-1-hydroxyethane. Distillation from sodium produced a pure sample of 3,4-dimethoxyethylbenzene, b.p. 122-124°/15 mm. (Barger and Silberschmidt[125] report b.p. 110-112°/9 mm.) (Found: C, 72.3; H, 8.7; O, 19.1. Calc. for $C_{10}H_{14}O_2$: C, 72.3; H, 8.5; O, 19.3%).

Reduction of 2-(2-1'-Methyl-3'-indolyl-2-oxoethyl)isoquinolinium Iodide with Lithium Aluminium Hydride in Tetrahydrofuran Solution.- The dried, powdered salt (3.6 g., 0.008 mole) was added portionwise to a solution of lithium aluminium hydride (1.9 g., 0.05 mole) in tetrahydrofuran (150 ml.) with the immediate formation of a yellow-coloured solution with a blue fluorescence. The mixture was heated under reflux for 18 hr., cooled, and the excess hydride decomposed by the addition of water. Acidification

with dilute hydrochloric acid and concentration of the solution under reduced pressure precipitated a red-brown gum that did not solidify on contact with a variety of organic solvents.

A sample of the crude salt mixture was dissolved in aqueous methanol, the solution basified by the addition of solid potassium hydroxide, and the precipitated fawn powder collected and dried. An infrared spectrum of the product (chloroform solution) showed absorption at 3450, 1650 and 1600 cm.,$^{-1}$ and ethanolic solutions became red when boiled with Ehrlich's reagent. The basic mixture rapidly decomposed to a dark brown oil on exposure to air. Chromatography of a sample of the product on Woelm neutral alumina and elution with a 1:1 mixture of benzene/light petroleum (b.p. 60-80°) produced a succession of brown oils that could not be induced to crystallise or form crystalline derivatives. Spectral determinations (infrared, ultraviolet) indicated that the fractions were very impure.

The above reaction was repeated many times varying the amount of lithium aluminium hydride present in the mixture and the length of the reaction time. In all cases it was found impossible to isolate any pure products or derivatives of products.

Reduction of 2-(2-1'-Methyl-3'-indolyl-2-oxoethyl)isoquinolinium Iodide with a Mixture of Lithium Aluminium Hydride and Aluminium Chloride in Tetrahydrofuran Solution.- A solution of the iodide (1.29 g., 0.003 mole) and aluminium chloride (0.8 g., 0.006 mole)

in tetrahydrofuran (50 ml.) was added over a period of 30 min. to a stirred solution of lithium aluminium hydride (0.19 g., 0.005 mole) and aluminium chloride (0.54 g., 0.004 mole) in tetrahydrofuran (50 ml.) under an atmosphere of dry nitrogen. The solution was stirred and heated under gentle reflux for $4\frac{1}{2}$ hr., cooled, and the complex decomposed with hydrated sodium sulphate. Water was added, the inorganic salts removed by filtration, and the filtrate extracted with ether. Dilute hydrochloric acid was added to the extract and the mixture shaken for 30 min. with gentle warming. The acidic layer was separated, basified with ammonium hydroxide, and extracted with ether. The extract was dried over sodium sulphate and the solvent removed to yield a brown oil. An infrared spectrum of the sample (chloroform solution) showed strong absorption at 1720 $cm.^{-1}$ Chromatography of the product on Woelm neutral alumina and elution with a 1:1 mixture of benzene/light petroleum (b.p. 60-80°) produced a succession of brown oils that could not be purified further.

Reduction of 2-(2-1'-Methyl-3'-indolyl-2-oxoethyl)iso-quinolinium Iodide with a Mixture of Lithium Aluminium Hydride and Aluminium Chloride in Dioxane Solution.- (A) A suspension of the iodide (3.87 g., 0.009 mole) and aluminium chloride (2.4 g., 0.018 mole) in dioxane (100 ml.) was added over a period of 30 min. to a stirred solution of lithium aluminium hydride

(0.8 g., 0.021 mole) and aluminium chloride (1.62 g., 0.012 mole) in dioxane (200 ml.). As stirring was continued at 60-65° for 5 hr. under an atmosphere of nitrogen a yellow-brown gummy precipitate was formed. Hydrated sodium sulphate was added to the cooled mixture, and after decomposition of the excess hydride was complete the inorganic salts were removed by filtration under nitrogen. The filtrate was acidified with dilute hydrochloric acid, warmed on a water-bath for 30 min., and allowed to cool to room temperature. The solution was basified with ammonium hydroxide, extracted with ether and the extract dried over sodium sulphate. Removal of the solvent left an orange-brown glassy residue that was adsorbed onto alumina (activity 4, 90 g.). Elution with light petroleum (b.p. 60-80°) gave a pale yellow oil (440 mg.) that rapidly decomposed to a brown mass on exposure to air. The sample was not obtained crystalline and formed an oily picrate that could not be induced to solidify despite trituration and attempted crystallisation from a variety of solvents. Its identity remains unknown.

Development of the column with a 1:1 mixture of benzene/light petroleum (b.p. 60-80°) yielded 2-(2-1'-methyl-3'-indolyl-2-oxoethyl)-1,2,3,4-tetrahydroisoquinoline (0.73 g., 27%) that crystallised from benzene as fine colourless needles, m.p. 162-164°. The m.p. was undepressed on admixture with an authentic

sample, and the infrared spectra of the two were superimposable.

Further elution with a 4:1 mixture of benzene/ether gave a brown oil (480 mg.) that could not be characterised.

(B) The above reaction was repeated under identical conditions but employing a reaction time of 18 hr. The basic mixture was isolated and purified as above and infrared spectra determined on the fractions from the column. The products were judged to be identical to those from (A) and were formed in similar amounts.

2-(2-1'-Methyl-3'-indolyl-2-oxoethyl)-1,2,3,4-tetrahydroisoquinoline (151).- 2-(2-1'-Methyl-3'-indolyl-2-oxoethyl)isoquinolinium iodide (500 mg.) dissolved in a mixture of ethanol (350 ml.) and water (180 ml.) was heated under reflux with silver chloride (ca. 4 g.) for 18 hr. The cooled solution was filtered and the solvent removed from the filtrate under reduced pressure. The residue was dissolved in a small volume of methanol, treated with charcoal and filtered. The addition of ether to the filtrate precipitated 2-(2-1'-methyl-3'-indolyl-2-oxoethyl)isoquinolinium chloride as clusters of cream needles, m.p. 277-281° (decomp.).

Platinum oxide (19 mg.) was suspended in acetic acid (10 ml.) and reduced and saturated with hydrogen. The chloride (27.1 mg.) was introduced and hydrogen (4.07 ml.) was absorbed over 30 min. (calculated absorption for reduction of 2 double bonds 3.90 ml./774 mm./17°). The catalyst was removed and the colourless

filtrate evaporated to dryness under reduced pressure. Water was added to dissolve the residue, the solution basified with ammonium hydroxide and extracted with ether. Removal of the solvent from the dried extract gave a colourless crystalline residue. 2-(2-1'-Methyl-3'-indolyl-2-oxoethyl)-1,2,3,4-tetrahydroisoquinoline crystallised from benzene as small colourless needles, m.p. 162-164° (Found: C, 78.8; H, 6.6; N, 9.1. $C_{20}H_{20}N_2O$ requires C, 78.9; H, 6.6; N, 9.2%). Light absorption: $\lambda_{max.}$ 2470, 3030 (log ε 4.29, 4.26), $\lambda_{min.}$ 2330, 2750 Å (log ε 3.99, 4.04).

5,7,8,13,13b,14-Hexahydro-1'-methylbenz[g]indolo[2,3-a]-quinolizine.- Powdered 5,7,8,13,13b,14-hexahydrobenz[g]indolo-[2,3-a]quinolizine (450 mg.) was added to a stirred solution of sodamide in liquid ammonia (from 41 gm. of sodium in ca. 40 ml. of liquid ammonia). After 5 min. methyl iodide (300 mg.) was added, and the mixture stirred at room temperature until all the ammonia had evaporated. Water was added and the product collected (450 mg., m.p. 121-123°). Crystallisation from methanol yielded colourless plates, m.p. 135° (lit.[33] m.p. 135°) (Found: C, 83.6; H, 7.3; N, 9.7. Calc. for $C_{20}H_{20}N_2$: C, 83.3; H, 7.0; N, 9.7%). Light absorption: $\lambda_{max.}$ 2280, 2890 (log ε 4.23, 3.95), $\lambda_{min.}$ 2530 Å (log ε 3.48). The picrate formed in ethanol and crystallised from methanol as small yellow needles, m.p. 208° (decomp.) (lit.[26] m.p. 208-209° decomp.).

Reduction of 1-(2-3'-Indolyl-2-oxoethyl)pyridinium Iodide with Lithium Aluminium Hydride in Ether Solution. 1-(2-3'-Indolylethyl)-Δ^3-piperideine (152; R=H).- (A) The dried powdered salt (400 mg.) was added to a suspension of lithium aluminium hydride (200 mg.) in dry ether (150 ml.). A stream of dry nitrogen was passed into the reaction vessel and the mixture was stirred at room temperature for 4 1/2 hr. Hydrated sodium sulphate was cautiously added to decompose the excess hydride, the mixture filtered, and the ethereal filtrate treated with dilute hydrochloric acid. The ether was evaporated on a water-bath and the acid decanted from the precipitated gum. The product was dissolved in hot water, the solution basified with ammonium hydroxide and extracted with ether. After drying the extract over sodium sulphate the solvent was removed to yield a pale yellow oil that could not be induced to crystallise. The product was dissolved in a little ethanol and a saturated solution of picric acid in ethanol added. Crystallisation of the precipitate from ethanol yielded the picrate of 1-(2-3'-indolylethyl)-Δ^3-piperideine as orange needles, m.p. 174-175° (Found: C, 54.9; H, 4.7; N, 15.1. $C_{21}H_{21}N_5O_7$ requires C, 55.4; H, 4.7; N, 15.4%).

(B) 1-(2-3'-Indolyl-2-oxoethyl)pyridinium iodide (2.7 g., 0.0075 mole) was added portionwise over a period of 30 min. to a stirred solution of lithium aluminium hydride (1.0 g., 0.025 mole)

in anhydrous ether (ca. 200 ml.), whilst a stream of dry nitrogen was passed into the reaction vessel. The mixture was heated under gentle reflux for 6 hr., and as the reaction progressed the yellow starting material dissolved and a flocculant white substance was precipitated. At the end of the reaction time the excess hydride was decomposed by the addition of hydrated sodium sulphate, and the precipitated inorganic material removed by filtration under nitrogen. The ethereal filtrate was pale green with a blue fluorescence. Dilute hydrochloric acid was added with the immediate precipitation of a yellow gum. The ether was evaporated by gentle warming on a water-bath and the acidic solution was allowed to stand for 2 hr. Basification with aqueous potassium hydroxide solution precipitated the bases, which were extracted into ether and the extract dried over sodium sulphate. The yellow oil obtained on removal of the solvent was adsorbed onto 8 g. neutral alumina, which was then added to a column of Woelm neutral alumina (activity 4, 65 g.). Elution with a 1:1 mixture of benzene/light petroleum (b.p. 60-80°) yielded a pale yellow crystalline material. 1-(2-3'-Indolyl)-Δ^3-piperideine (0.52 g., 33%) crystallised from hexane as colourless needles, m.p. 152-153° (Elderfield *et al.*[37] report m.p. 152-153°) (Found: C, 79.5; H, 8.1; N, 12.4. Calc. for $C_{15}H_{18}N_2$: C, 79.6; H, 8.0; N, 12.4%). The mixed m.p. of this sample with 1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine was 114-116°. Further

development of the column with benzene and a mixture of benzene/ether (4:1) yielded a few mgs. of yellow oily material that could not be characterised.

(C) 1-(2-3'-Indolyl-2-oxoethyl)pyridinium iodide (1.35 g., 0.0038 mole) and lithium aluminium hydride (0.5 g., 0.0125 mole) were mixed together in ethereal solution as in (B) above. The mixture was heated under reflux for 3 hr., cooled, and treated with hydrated sodium sulphate. The suspension was filtered and the ethereal filtrate treated with dilute hydrochloric acid. The precipitated semi-solid was dissolved in a mixture of tetrahydrofuran and water and the solution basified with aqueous potassium hydroxide. Extraction with ether and evaporation of the solvent gave a yellow oil that was adsorbed onto alumina (5 g.) and added to a column of Woelm neutral alumina (activity 4, 40 g.). Elution with a 1:1 mixture of benzene/light petroleum (b.p. 60-80°) yielded 1-(2-3'-indolylethyl)-Δ^3-piperideine (0.332 g., 40%), which crystallised from hexane as colourless needles, m.p. 151-153°. The m.p. was not depressed on admixture with a sample of the product from (B) above.

Hydrogenation of 1-(2-3'-Indolylethyl)-Δ^3-piperideine.- Platinum oxide (15.4 mg.), suspended in absolute alcohol (10 ml.), was reduced and saturated with hydrogen. 1-(2-3'-Indolylethyl)-Δ^3-piperideine (30.0 mg.) was added and hydrogen (3.12 ml.) was absorbed over a period of 20 min. (theoretical absorption for one

double bond is 3.21 ml./760 mm./19°C). The solution was filtered and the solvent removed under reduced pressure leaving a colourless crystalline residue. 1-(2-3'-Indolylethyl)piperidine separated from hexane as small colourless needles, m.p. 149-150°; mixed m.p. with an authentic sample, 149-151°.

1-(1,2-Dioxo-2-3'-indolylethyl)piperidine.- 3-Indoleglyoxylyl chloride (4.15 g., 0.02 mole) was suspended in methylethyl ketone (60 ml.) and piperidine (4.2 g., 0.05 mole) added slowly to the stirred mixture. The temperature of the reaction mixture rose, and heating was continued at 50° for 30 min. after all the piperidine had been added. The precipitated piperidine hydrochloride was filtered (3.0 g.) and the filtrate washed with saturated sodium bicarbonate solution. The organic layer was separated, washed with water, and dried over sodium sulphate. Removal of the solvent under reduced pressure and crystallisation of the product from ethanol (charcoal) produced pale yellow needles of 1-(1,2-dioxo-2-3'-indolylethyl)piperidine (3.0 g., 66%). Further crystallisation from ethanol yielded fine colourless needles, m.p. 180-181° (Found: C, 70.2; H, 6.2; N, 10.8. $C_{15}H_{16}N_2O_2$ requires C, 70.3; H, 6.3; N, 10.9%).

1-(2-3'-Indolylethyl)piperidine.- 1-(1,2-Dioxo-2-3'-indolylethyl)piperidine (2.0 g., 0.0078 mole) dissolved in dry tetrahydrofuran (50 ml.) was added slowly to lithium aluminium

hydride (1.0 g., 0.026 mole) suspended in dry tetrahydrofuran (80 ml.). The mixture was heated under reflux for 10 hr., cooled in an ice-bath, and the excess hydride decomposed by the dropwise addition of water. The mixture was made basic with sodium hydroxide solution (4 N), the inorganic material removed, and the tetrahydrofuran layer separated from the aqueous layer. After drying over sodium sulphate the solvent was removed under reduced pressure on a water-bath, leaving a pale pink crystalline residue. 1-(2-3'-Indolylethyl)piperidine (1.3 g., 74%) separated from benzene/hexane as fine colourless needles, m.p. 148-149° (Elderfield et al.[37] report a m.p. of 151-152° for this compound).

Reduction of 1-(2-3'-Indolyl-2-oxoethyl)pyridinium Iodide with Lithium Aluminium Hydride in Tetrahydrofuran Solution. 1,4,6,7,12,12b-Hexahydroindolo[2,3-a]quinolizine (153; R=H).- (A) The dried powdered salt (2.7 g., 0.0075 mole) was added portionwise over a period of 15 min. to a stirred solution of lithium aluminium hydride (1.0 g., 0.025 mole) in tetrahydrofuran (ca. 150 ml.). Marked effervescence occurred, and the solution developed a pale green colour with a green fluorescence. A stream of dry nitrogen was passed into the reaction vessel, and the mixture was heated under reflux with stirring for $4^1/_2$ hr. The mixture was cooled to room temperature and the excess hydride and the complex decomposed by the addition of hydrated sodium sulphate. The inorganic salts were removed by filtration under nitrogen, and

the pale yellow filtrate acidified with dilute hydrochloric acid (ca. 100 ml.). The solution was concentrated by the evaporation of some of the tetrahydrofuran (water-bath; normal pressure), cooled, and basified with ammonium hydroxide. Extraction with ether and removal of the solvent yielded a pale yellow semi-crystalline oil (1.4 g.) that was adsorbed onto neutral alumina (10 g.) and transferred to the top of a column of Woelm neutral alumina (activity 4, 80 g.). The column was developed with a 1:1 mixture of benzene/light petroleum (b.p. 60-80°) and the first 2000 ml. of eluent were evaporated to give pale yellow crystals, m.p. 143-145°. 1,4,6,7,12,12b-Hexahydroindolo[2,3-a]quinolizine (0.73 g., 44%) crystallised from hexane or light petroleum (b.p. 60-80°) as clusters of thick colourless plates, m.p. 147-148° (Found: C, 79.7; H, 7.2; N, 12.6. $C_{15}H_{16}N_2$ requires C, 80.3; H, 7.2; N, 12.5%). Light absorption: $\lambda_{max.}$ 2260, 2830, 2910 (log ϵ 4.61, 3.92, 3.84), $\lambda_{min.}$ 2470, 2890 Å (log ϵ 3.30, 3.81). The crystalline base or its solutions in hydrocarbon or alcoholic solvents rapidly changed from colourless to pale yellow-green in the presence of air and light.

The picrate, formed in ethanol, crystallised from aqueous methanol as clusters of orange needles, m.p. 119-121° (Found: C, 53.7; H, 4.5; N, 15.1. $C_{21}H_{19}N_5O_7 \cdot 1H_2O$ requires C, 53.5; H, 4.5; N, 14.9%).

Further development of the column with a 4:1 mixture of benzene/ether gave 43 mg. of a yellow oil that would not form a crystalline derivative. Continuous extraction of the alumina in a Soxhlet apparatus with boiling hexane for 3 days gave 7 mg. of a semi-crystalline oil that was not identified.

(B) 1-(2-3'-Indolyl-2-oxoethyl)pyridinium iodide (1.7 g., 0.0047 mole) and lithium aluminium hydride (0.6 g., 0.015 mole) were mixed together in tetrahydrofuran (ca. 120 ml.) as in (A) and heated under reflux for 2 hr. After decomposition of the excess hydride and removal of the inorganic salts in the usual way the solution was acidified with dilute hydrochloric acid and warmed on a water-bath for 30 min. The solution was cooled, basified with aqueous potassium hydroxide, and extracted with tetrahydrofuran (3 x 60 ml.). The extract was dried and the solvent removed leaving a brown gum. This was adsorbed onto alumina (8 g.) and transferred to the top of a column of Woelm neutral alumina (activity 4, 50 g.). Elution with a 1:1 mixture of benzene/light petroleum (b.p. 60-80°) yielded 1,4,6,7,12,12b-hexahydroindolo-[2,3-a]quinolizine (0.58 g., 56%), m.p. 144-146°. Further development of the column with benzene and a 4:1 mixture of benzene/ether gave 55 mg. of a yellow oil that could not be induced to crystallise or form a crystalline derivative.

Hydrogenation of 1,4,6,7,12,12b-Hexahydroindolo[2,3-a]-quinolizine.- Adams' catalyst (20 mg.) was suspended in ethanol

(10 ml.) and saturated with hydrogen. The base (40 mg.) was added, and hydrogen (4.6 ml.) was absorbed over a period of 10 min. (theoretical absorption for one double bond 4.4 ml./764 mm./ 20°C). The solution was filtered to remove the catalyst and evaporated to dryness, leaving a colourless residue. 1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-a]quinolizine separated from hexane as small colourless prisms, m.p. 152-153° (lit.[42] m.p. 152-153°) (Found: C, 79.3; H, 8.1. Calc. for $C_{15}H_{18}N_2$: C, 79.6; H, 8.0%). The mixed m.p. of the product with 1-(2-3'-indolylethyl)piperidine was 119-121° (Elderfield *et al.*[37] report 120-121° for this mixed m.p.).

Reduction of 3-Ethyl-1-(2-3'-indolyl-2-oxoethyl)pyridinium Iodide with Lithium Aluminium Hydride in Ether Solution. 3-Ethyl-1-(2-3'-indolylethyl)-Δ^3-piperideine (152; R=C_2H_5).- Dried, powdered 3-ethyl-1-(2-3'-indolyl-2-oxoethyl)pyridinium iodide (3.44 g., 0.0087 mole) was added to a stirred solution of lithium aluminium hydride (1.2 g., 0.03 mole) in ether (300 ml.) under an atmosphere of dry nitrogen. The pale green mixture was heated under reflux for 3 hr., cooled, and the excess hydride decomposed by the addition of hydrated sodium sulphate. The mixture was filtered under nitrogen and the colourless ethereal filtrate treated with dilute hydrochloric acid, with the immediate precipitation of a yellow gum. The ether was removed by warming on a water-bath and a little tetrahydrofuran was added to dissolve the organic salts. The solution was basified with aqueous potassium hydroxide and

extracted with several portions of tetrahydrofuran. The extract was dried, the solvent removed, and the oily product adsorbed onto alumina (10 g.). This was transferred to the top of a column of Woelm neutral alumina (activity 4, 100 g.) and eluted with a 1:4 mixture of benzene/light petroleum (b.p. 60-80°). The first two fractions (800 ml.) contained 3-ethyl-1,4,6,7,12,12b-hexahydroindolo[2,3-a]quinolizine (0.111 g., 5%), m.p. 143-145°. The m.p. was not depressed on admixture with an authentic sample of the base. Further development of the column with a 1:1 mixture of benzene/light petroleum (b.p. 60-80°) gave pale yellow crystalline material, m.p. 117-120°. 3-Ethyl-1-(2-3'-indolylethyl)-Δ^3-piperideine (0.879 g., 40%) crystallised from a colourless solution in hexane as pale yellow irregular prisms, m.p. 121-123° (Found: N, 10.9. $C_{17}H_{22}N_2$ requires N, 11.0%).

The picrate was formed by the addition of a saturated solution of picric acid in ethanol to a dilute solution of the base in methanol. It separated as orange-red needles, m.p. 155-157°, and successive crystallisation from methanol raised this value to 165-167° (Found: C, 57.0; H, 5.3; N, 14.1. $C_{23}H_{25}N_5O_7$ requires C, 57.1; H, 5.2; N, 14.5%).

Hydrogenation of 3-Ethyl-1-(2-3'-indolylethyl)-Δ^3-piperideine.- Palladium on carbon (20%, 20 mg.) was suspended in ethanol (10 ml.) and saturated with hydrogen. The unsaturated base (37.4 mg.) was added, and hydrogen (3.84 ml.) was absorbed over a period of 4 hr.

(theoretical absorption for one double bond 3.63 ml./760 mm./22°C). The catalyst was removed by filtration and the solvent removed from the filtrate leaving a colourless oil. The base was very soluble in hexane and light petroleum (b.p. 40-60°) and could not be obtained crystalline. Light absorption: $\lambda_{max.}$ 2230, 2830, 2920. $\lambda_{min.}$ 2440, 2890 Å.

The picrate of 3-ethyl-1-(2-3'-indolylethyl)piperidine, formed in ethanol, crystallised from methanol-water as fine orange needles, m.p. 127-128° (Found: C, 56.8; H, 5.6; N, 14.2. $C_{23}H_{27}N_5O_7$ requires C, 56.9; H, 5.6; N, 14.4%).

Reduction of 3-Ethyl-1-(2-3'-indolyl-2-oxoethyl)pyridinium Iodide with Lithium Aluminium Hydride in Tetrahydrofuran Solution. 3-Ethyl-1,4,6,7,12,12b-hexahydroindolo[2,3-a]quinolizine (153; R=C_2H_5).- (A) The finely powdered iodide (2.94 g., 0.0075 mole) was added in small portions over a period of 15 min. to a stirred solution of lithium aluminium hydride (1.0 g., 0.025 mole) in tetrahydrofuran (ca. 150 ml.). Marked effervescence occurred, and the solution became pale green with a green fluorescence. Stirring was continued and the solution was heated under reflux for $4^1/_2$ hr. in an atmosphere of dry nitrogen. Hydrated sodium sulphate was added to the cooled solution, and after the decomposition of the excess hydride was complete, the precipitated inorganic salts were removed. The filtrate was acidified with dilute hydrochloric acid

and the volume of the solution reduced by evaporation (water-bath) as a stream of nitrogen was bubbled through. The pale yellow solution was basified with ammonium hydroxide, extracted with several portions of ether, and the extract dried over sodium sulphate. Removal of the solvent yielded a yellow fluorescent glass (1.65 g.) which was adsorbed onto alumina (10 g.) and transferred to the top of a column of Woelm neutral alumina (activity 4, 100 g.). Elution with a 1:1 mixture of benzene/light petroleum (b.p. 60-80°) gave a crystalline material, m.p. 143-145°. 3-Ethyl-1,4,6,7,12,12b-hexahydroindolo[2,3-a]quinolizine (0.897 g., 48%) separated from hexane as colourless plates, m.p. 146-148°, or from aqueous methanol as colourless needles, m.p. 153-155° (Found: C, 80.2; H, 7.9; N, 11.4. $C_{17}H_{20}N_2$ requires C, 80.9; H, 8.0; N, 11.1%). The crystalline base or its solutions rapidly became yellow on exposure to air and light. Light absorption: $\lambda_{max.}$ 2260, 2830, 2910(sh) (log ϵ 4.52, 3.83, 3.75), $\lambda_{min.}$ 2450 Å (log ϵ 3.17).

The picrate, formed in ethanol, crystallised from ethanol/light petroleum (b.p. 40-60°) as small yellow needles, m.p. 184-186° (decomp.) (Found: C, 56.9; H, 4.4; N, 14.5. $C_{23}H_{23}N_5O_7$ requires C, 57.4; H, 4.8; N, 14.6%).

(B) A mixture of 3-ethyl-1-(2-3'-indolyl-2-oxoethyl)pyridinium iodide (5.88 g., 0.015 mole) and lithium aluminium hydride (2.0 g., 0.05 mole) in tetrahydrofuran (ca. 300 ml.) was heated under reflux

for 2 hr. Isolation of the product was accomplished in a manner identical to (A) above. 3-Ethyl-1,4,6,7,12,12b-hexahydroindolo-[2,3-a]quinolizine (1.32 g., 52%) crystallised from hexane as colourless plates, m.p. 146-148°.

Hydrogenation of 3-Ethyl-1,4,6,7,12,12b-hexahydroindolo-[2,3-a]quinolizine.- Adams' catalyst (10 mg.), suspended in ethanol (10 ml.), was reduced and saturated with hydrogen. The unsaturated base (25.2 mg.) was added, and hydrogen (2.42 ml.) was absorbed over a period of 80 min. (theoretical absorption for one double bond 2.36 ml./770 mm./18.5°C). The solution was evaporated to dryness leaving a colourless residue of 3-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (octahydroflavopereirine) that could not be obtained crystalline (Thesing and Festag[94] report an oil; Hughes and Rapoport[91] report m.p. 163-164°).

The picrate was prepared in ethanol and crystallised from methanol as small irregular orange prisms, m.p. 208-210° (decomp.) alone and when mixed with authentic octahydroflavopereirine picrate kindly donated by Dr. J. Thesing. The infrared spectra of the two samples were superimposable.

Mercuric Acetate Oxidation of 3-Ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine. 3-Ethyl-1,2,3,4,6,7-hexahydro-12H-indolo[2,3-a]quinolizinium Perchlorate (161).- Octahydroflavopereirine (65 mg., 0.00026 mole) was dissolved in 5% acetic acid (6 ml.) and mercuric acetate (0.32 g., 0.001 mole) added. The

mixture was heated at 78° for $2^1/_2$ hr. whilst a stream of nitrogen was bubbled through. After standing overnight the mixture was filtered to remove precipitated mercurous acetate (80 mg.) which was washed with a little 5% acetic acid. The yellow filtrate was heated to boiling, saturated with hydrogen sulphide, and a little concentrated hydrochloric acid added to coagulate the precipitate. The black mercuric sulphide was removed by filtration through a pad of Celite and the filtrate treated with a saturated aqueous solution of potassium perchlorate. The precipitated 3-ethyl-1,2,3,4,6,7-hexahydro-12H-indolo[2,3-a]quinolizinium perchlorate was collected, and crystallised from methanol as small yellow prisms, m.p. 218-220° (hot-stage) (lit.[93] m.p. 221-223°) (Found: C, 58.4; H, 6.0; N, 7.7. Calc. for $C_{17}H_{21}N_2O_4Cl$: C, 57.9; H, 6.0; N, 7.9%). The infrared spectrum of the sample was identical in every respect with that published by Le Hir et al.[93] Light absorption: $\lambda_{max.}$ 2470, 3520 (log ε 4.01, 4.31), $\lambda_{min.}$ 2350, 2760 Å (log ε 3.91, 3.19).

3-Ethyl-12H-indolo[2,3-a]quinolizinium Perchlorate (Flavopereirine Perchlorate) (154).- 3-Ethyl-1,2,3,4,6,7-hexahydro-12H-indolo[2,3-a]quinolizinium perchlorate (300 mg.) was mixed with palladium on carbon (10%, 700 mg.) and placed in a small flask. The flask was heated in a metal-bath to 280° over a period of 5 min. under reduced pressure (1 mm.). The tarry product was extracted several times with boiling methanol, filtered,

and the solvent removed leaving a brown residue. Extraction with acetic acid gave a pale yellow solution, and on the addition of a saturated aqueous solution of potassium perchlorate, a pale yellow precipitate was obtained (45 mg., m.p. 290-295° decomp.). Repeated crystallisation from methanol yielded flavopereirine perchlorate as pale yellow needles, m.p. 318-320° (decomp.) (hot-stage). The m.p. of an authentic sample of flavopereirine perchlorate supplied by Professor Rapoport was 320-321° (decomp.) under the same conditions, and there was no depression in the m.p. on admixture of the two samples. Light absorption: $\lambda_{max.}$ 2360, 2950, 3500, 3900 (log ϵ 4,48, 4.21, 4.36, 4.22), $\lambda_{min.}$ 2730, 3090, 3810 Å (logϵ 4.10, 4.14, 4.18). The infrared spectra of the synthetic and the authentic samples of the perchlorate were superimposable.

Reduction of 3-Ethyl-1-(2-3'-indolyl-2-oxoethyl)-4-methyl-pyridinium Iodide with Lithium Aluminium Hydride in Tetrahydrofuran Solution. 2-Methyl-3-ethyl-1,4,6,7,12,12b-hexahydroindolo[2,3-a]-quinolizine (189).- (A) The finely powdered iodide (1.2 g., 0.003 mole) was added to a solution of lithium aluminium hydride (0.7 g., 0.018 mole) in dry tetrahydrofuran (100 ml.) and the mixture heated under reflux for $3^1/_2$ hr. After cooling the reaction mixture water was cautiously added to decompose the excess hydride, Treatment with dilute hydrochloric acid gave yellow solution containing grey suspended inorganic material. The mixture was

filtered and tetrahydrofuran removed from the filtrate at 30-40° under reduced pressure. As the solution concentrated a yellow powder separated that was collected by filtration. Further concentration of the mother-liquor precipitated a yellow oil that solidified on standing. 2-Methyl-3-ethyl-1,4,6,7,12,12b-hexahydroindolo[2,3-a]quinolizium hydroiodide (0.695 g., 61%) crystallised from methanol as colourless needles, m.p. 296-298° (decomp.) (Found: C, 54.8; H, 5.8; N, 7.1. $C_{18}H_{23}N_2I$ requires C, 54.8; H, 5.8; N, 7.1%). A solution of the salt in ethanol gave no colour with Ehrlich's reagent on prolonged warming.

The free base was prepared by the addition of ammonium hydroxide to an aqueous solution of the hydroiodide. It separated from aqueous methanol as colourless needles, m.p. 171-173° (Found: C, 80.7; H, 8.3; N, 10.5. $C_{18}H_{22}N_2$ requires C, 81.2; H, 8.3; N, 10.5%). Light absorption: $\lambda_{max.}$ 2260, 2820, 2900 (log ϵ 4.39, 3.92, 3.83), $\lambda_{min.}$ 2470, 2880 Å (log ϵ 3.34, 3.82). Colourless solutions of the base rapidly became yellow on standing.

(B) 3-Ethyl-1-(2-3'-indolyl-2-oxoethyl)-4-methylpyridinium iodide (2.66 g., 0.0064 mole) was added to a solution of lithium aluminium hydride (0.88 g., 0.022 mole) in tetrahydrofuran (ca. 150 ml.) under an atmosphere of dry nitrogen. The salt dissolved with effervescence to give a yellow-green solution with a green fluorescence that was heated under reflux for 3 hr. Hydrated sodium sulphate was added to the cooled reaction mixture and the

precipitated inorganic salts were removed by filtration under nitrogen. The filtrate was acidified with dilute hydrochloric acid and the volume of the solution reduced by heating on a water-bath. On cooling colourless crystals of 2-methyl-3-ethyl-1,4,6,7,12,12b-hexahydroindolo[2,3-a]quinolizinium hydrochloride (0.85 g., 43%) were deposited. The salt crystallised from methanol as long colourless needles, m.p. 281-282° with frothing (Found: N, 9.0. $C_{18}H_{23}N_2Cl$ requires N, 9.3%).

The acidic mother-liquor was basified with aqueous potassium hydroxide and extracted with ether. The extract was dried over sodium sulphate and the solvent removed to give a brown oil that was adsorbed onto neutral alumina (5 g.) and transferred to the top of a column of Woelm neutral alumina (activity 4, 40 g.). The column was developed with a 1:1 mixture of benzene/light petroleum (b.p. 60-80°) and the first 300 ml. of eluent contained 2-methyl-3-ethyl-1,4,6,7,12,12b-hexahydroindolo[2,3-a]quinolizine (325 mg., 18%). The base separated from aqueous methanol as colourless needles, m.p. 171-172°.

Further development of the column with a 4:1 mixture of benzene/ether gave 170 mg. of a brown oil that could not be induced to crystallise or form a crystalline picrate or hydrochloride.

Lithium Aluminium Hydride Reduction of 2-(2-3'-Indolyl-2-oxoethyl)-5,6,7,8-tetrahydroisoquinolinium Chloride in Tetrahydrofuran Solution. 1,2,3,4,5,7,8,13,13b,14-Decahydrobenz[g]indolo-

[2,3-a]quinolizine (191; R=H).- Lithium aluminium hydride (1.0 g., 0.025 mole) was suspended in dry tetrahydrofuran (ca. 150 ml.) and the dried powdered chloride (2.4 g., 0.0076 mole) added in small portions. Vigorous effervescence occurred and a yellow-green solution with an intense pale green fluorescence was formed. The mixture was stirred and heated under gentle reflux for 3 hr. whilst a stream of dry nitrogen was passed through the reaction vessel. Hydrated sodium sulphate was added to the cooled reaction mixture, and the precipitated inorganic salts removed by filtration under nitrogen. The colourless filtrate became pale yellow on the addition of dilute hydrochloric acid (ca. 50 ml.). The volume of the solution was reduced by evaporation (water-bath) and the cooled concentrate was basified with aqueous potassium hydroxide. Extraction with ether and removal of the solvent gave a brown oily product that was adsorbed onto alumina (10 g.) and transferred to the top of a column of Woelm neutral alumin (activity 4, 80 g.). The column was eluted with a 1:1 mixture of benzene/light petroleum (b.p. 60-80°) and 200 ml. fractions were taken. Fractions 2, 3 and 4 were combined and on removal of the solvent a pale yellow crystalline residue was obtained. 1,2,3,4,5,7,8,13,13b,14-decahydrobenz[g]indolo[2,3-a]-quinolizine (1.42 g., 67%) separated from benzene or aqueous methanol as colourless needles, m.p. 196-197° with darkening (lit.[110] m.p. 196-197°)(Found: C, 81.6; H, 7.9; N, 10.2. One

day later: C, 80.9; H, 8.0. Calc. for $C_{19}H_{22}N_2$: C, 82.0; H, 8.0; N, 10.1%). The base or its solutions rapidly became yellow on exposure to air and light.

The picrate, formed in ethanol, separated from aqueous methanol as fine yellow needles, m.p. 178-180° (decomp.) with previous darkening (Found: C, 59.5; H, 5.1; N, 13.6. $C_{25}H_{25}N_5O_7$ requires C, 59.2; H, 5.0; N, 13.8%).

Further development of the column with a 4:1 mixture of benzene/ether gave a small amount of a brown oily material that could not be characterised.

1,2,3,4,5,7,8,13,13b,14-Decahydro-1'-methylbenz[g]indolo-[2,3-a]quinolizine (191; R=CH_3).- Liquid ammonia (ca. 15 ml.) was distilled from sodium and collected in a small flask immersed in a dry-ice/ethanol bath. A crystal of ferric nitrate was added, followed by sodium (22 mg.). The mixture was stirred for several min., 1,2,3,4,5,7,8,13,13b,14-decahydrobenz[g]indolo[2,3-a]quinolizine (225 mg.) added, and after a further 10 min. methyl iodide (150 mg.) was introduced. Stirring was continued at room temperature until all the ammonia had evaporated, and then water was added and the product collected (230 mg., m.p. 112-115°). 1,2,3,4,5,7,8,13,13b,14-Decahydro-1'-methylbenz[g]indolo[2,3-a]quinolizine crystallised from aqueous methanol as fine colourless needles, m.p. 137-138° (lit.[113] m.p. 137-139°) (Found: C, 81.9; H, 7.9; N, 9.7. Calc. for $C_{20}H_{24}N_2$: C, 82.1; H, 8.3; N, 9.6%). The infrared spectrum

of the base was identical in every respect with that published by Witkop.[113]

The picrate was prepared by the addition of a saturated ethanolic solution of picric acid to a dilute solution of the base in methanol. It crystallised from methanol as yellow needles, m.p. 182-185° (lit.[113] m.p. 188-192°) (Found: C, 58.5; H, 5.4; N, 13.0. Calc. for $C_{26}H_{27}N_5O_7.CH_3OH$: C, 58.6; H, 5.6; N, 12.7%). The m.p. of the picrate was not depressed on admixture with an authentic sample provided by Professor Witkop, and the infrared spectra of the two samples were identical.

Attempted Hydrogenation of 1,2,3,4,5,7,8,13,13b,14-Decahydrobenz[g]indolo[2,3-a]quinolizine.- (A) Rhodium on carbon catalyst (5%, 5 mg.) (Baker platinum division, Engelhard Industries Ltd.) was suspended in ethanol (10 ml.) and saturated with hydrogen. The base (11.1 mg.) was added but no hydrogen was absorbed over a period of 3 hr.

(B) 1,2,3,4,5,7,8,13,13b,14-Decahydrobenz[g]indolo[2,3-a]-quinolizine (22 mg.) was dissolved in absolute methanol (10 ml.) and the pH of the solution adjusted to 10 with 10% aqueous potassium hydroxide solution. Adams' catalyst (10 mg.) was added and the mixture hydrogenated (room temp., 4 atmos.) for 1 hr. The suspension was filtered and the solvent removed from the filtrate under reduced pressure. Water and ammonium hydroxide were added and the colourless precipitate collected and washed with water. The

product crystallised from methanol as colourless needles, m.p. 195-197°. There was no depression in the m.p. on admixture with a sample of the starting material.

(C) Aqueous chloroplatinic acid (2M, 1 ml.) was placed in a hydrogenation flask with ethanol (30 ml.). The vessel was flushed with nitrogen and the catalyst generated by the addition of a solution of sodium borohydride in ethanol (10M, 5 ml.). The excess borohydride was decomposed with hydrochloric acid (6M, 4 ml.) and the flask was then sealed. The catalyst was saturated with hydrogen and the base (355 mg.) dissolved in ethanol (5 ml.) injected with a hypodermic syringe. No hydrogen uptake was apparent during several hr., and the starting material was recovered, m.p. and mixed m.p. 195-196° after crystallisation from methanol.

2-(1,2-Dioxo-2-3'-indolylethyl)-1,2,3,4-tetrahydroisoquinoline.- 1,2,3,4-Tetrahydroisoquinoline (20 g., 0.15 mole) was added slowly to a suspension of 3-indoleglyoxylyl chloride (12.45 g., 0.06 mole) in methylethyl ketone (180 ml.). The temperature of the mixture rose to 40°, and after the addition of the tetrahydroisoquinoline had been completed, the temperature was raised to 50° and maintained for 30 min. The precipitated tetrahydroisoquinoline hydrochloride was collected (5.2 g.) and the filtrate washed with saturated sodium bicarbonate solution, and then with water. The organic layer was dried over sodium sulphate and the solvent removed under reduced pressure to yield a pale yellow crystalline

mass. 2-(1,2-Dioxo-2-3'-indolylethyl)-1,2,3,4-tetrahydroisoquinoline (10.6 g., 59%) crystallised from ethanol as colourless needles, m.p. 187-188° (lit.[73] m.p. 189-190°) (Found: C, 74.6; H, 5.2. Calc. for $C_{19}H_{16}N_2O_2$: C, 75.0; H, 5.3%).

2-(2-3'-Indolylethyl)-1,2,3,4-tetrahydroisoquinoline.- 2-(1,2-Dioxo-2-3'-indolylethyl)-1,2,3,4-tetrahydroisoquinoline (3.45 g., 0.013 mole) dissolved in tetrahydrofuran (40 ml.) was added dropwise over 15 min. to a suspension of lithium aluminium hydride (2.5 g., 0.06 mole) in tetrahydrofuran (80 ml.). The green mixture was heated under reflux for 15 hr., cooled in an ice-bath, and the excess hydride decomposed with water. The mixture was basified with sodium hydroxide solution (2N) and the inorganic material removed. The organic layer of the filtrate was separated and dried over sodium sulphate. Evaporation of the solvent under reduced pressure on a water-bath yielded a colourless crystalline product (2.67 g., 90%). 2-(2-3'-Indolylethyl)-1,2,3,4-tetrahydroisoquinoline separated from benzene solution as colourless irregular rhombs, m.p. 123-124° (lit.[73] m.p. 121-122°) (Found: C, 82.1; H, 7.2; N, 10.1. Calc. for $C_{19}H_{20}N_2$: C, 82.6; H, 7.3; N, 10.1%). The base produced a purple colour with Ehrlich's reagent after warming for 5 min. on a hot water-bath.

The hydrochloride, precipitated from benzene solution with a stream of hydrogen chloride, crystallised from methanol/ether as colourless irregular prisms, m.p. 204-205°.

The picrate, formed in ethanol, separated from acetone as a bright orange microcrystalline powder, m.p. 171-172° (Potts and Robinson[26] report m.p. 171°).

Mercuric Acetate Oxidation of 2-(2-3'-Indolylethyl)-1,2,3,4-tetrahydroisoquinoline.- Mercuric acetate (58.6 g., 0.18 mole) and 2-(2-3'-indolylethyl)-1,2,3,4-tetrahydroisoquinoline (10.4 g., 0.038 mole) were dissolved in acetic acid (5%, 340 ml.) and heated at 80-85° for 2 hr. whilst a stream of nitrogen was passed through the mixture. The precipitated mercury and mercurous acetate (ca. 18 g.) were removed by filtration and the filtrate saturated with hydrogen sulphide. A little concentrated hydrochloric acid was added to coagulate the mercuric sulphide and the mixture filtered through a pad of Celite. The black residue was extracted continuously with ethanol for 80 hr., the volume of the extract reduced, poured into ammonium hydroxide and extracted with ether. A portion of the acidic filtrate was treated with a saturated aqueous solution of potassium perchlorate, but no precipitate was obtained. The remainder was basified with ammonium hydroxide and extracted with ether. The two extracts were combined, dried over sodium sulphate and the solvent removed to give a red-brown waxy residue (7.2 g.). A portion (5 g.) of this material was adsorbed onto alumina and transferred to the top of a column of Woelm neutral alumina (activity 4, 150 g.). The column was developed with light petroleum (b.p. 60-80°) and 450 mg. of a brown oil was obtained that rapidly

decomposed on exposure to air. This compound could not be induced to crystallise or form a crystalline picrate.

Elution with a (1:1) mixture of benzene/light petroleum (b.p. 60-80°) give 3.23 g. of a pale yellow crystalline material. "Compound A" crystallised from methanol as long colourless needles which on heating lost solvent from ca. 100-120° and finally melted with decomposition at 168-170° (Found: C, 78.2; H, 6.7; N, 9.6. $C_{19}H_{18}N_2.H_2O$ requires C, 78.1; H, 6.9; N, 9.6%). Light absorption: $\lambda_{max.}$ 2270, 2760(sh), 2830, 2910(sh) (log ε 4.30, 3.85, 3.87, 3.80), $\lambda_{min.}$ 2490 Å (log ε 3.43). The main absorption in the infrared (chloroform solution) occurred at 3660, 3500, 3010, 2960, 2870, 1450, 1280, 1140, 1090 and 1020 $cm.^{-1}$ The base gave no colour on prolonged heating with Ehrlich's reagent.

The picrate, formed in ethanol, crystallised from that solvent as clusters of pale yellow rods, m.p. 184-186° (decomp.) with previous darkening (Found: C, 59.4; H, 4.5; N, 13.7. $C_{19}H_{18}N_2.C_6H_3N_3O_7$ requires C, 59.6; H, 4.2; N, 13.9%).

Further development of the column with benzene/ether (4:1) gave 430 mg. of bright red crystals. "Compound B" separated from benzene/light petroleum (b.p. 40-60°) as red plates, m.p. 211-213° (Found: C, 84.2; H, 5.2; N, 10.4. $C_{19}H_{14}N_2$ requires C, 84.4; H, 5.2; N, 10.4%). Light absorption: $\lambda_{max.}$ 2780, 3190(sh), 3330, 3620, 3990, 4760 (log ε 4.31, 4.22, 4.30, 3.79, 3.77, 3.11), $\lambda_{min.}$ 2570, 3020, 3500, 3770, 4360 (log ε 4.07, 4.04, 3.74, 3.63, 3.01).

Infrared absorption (chloroform solution) occurred at 3100(sh), 3000, 2960, 1620, 1480, 1330, 1250 and 1120 cm.$^{-1}$ Ethanolic solutions of "compound B" became pale yellow on the addition of hydrochloric acid, but no change in colour was produced by boiling with Ehrlich's reagent.

Conversion of "Compound A" to "Compound B".- A sample of "A" was placed in a flask and heated at 180° for 30 min. The red glass produced dissolved in benzene and on the addition of light petroleum (b.p. 40-60°) red plates of "compound B" separated, m.p. 210-212°. There was no depression in the m.p. on admixture with the sample of "B" obtained above, and the infrared spectra of the two were superimposable.

Oxidation of "Compound A".- Potassium acetate (10.5 g., 0.11 mole) and iodine (5.1 g., 0.04 mole) were warmed together in ethanol (150 ml.) and added to "compound A" (1.05 g., 0.036 mole) dissolved in ethanol (30 ml.). The mixture was warmed on a water-bath for 10 min., cooled, and the precipitate collected and washed with a little cold ethanol. The material was suspended in hot water and sulphur dioxide bubbled through for a few seconds. The yellow product was collected and washed with cold water and ethanol. "Compound C" (1.3 g., 90%) separated from ethanol as orange-yellow prisms, m.p. 294-295° (Found: C, 57.0; H, 4.2; N, 6.6. $C_{19}H_{17}N_2I$ requires C, 57.0; H, 4.3; N, 7.0%). Light absorption: $\lambda_{max.}$ 2570, 2800(sh), 3000, 3320, 3850 (log ε 3.91, 3.91, 3.94, 3.90,

4.16), $\lambda_{min.}$ 2460, 2710, 3230, 3440 Å (log ε 3.79, 3.87, 3.87, 3.84). The main peaks in the infrared spectrum (hexachlorobutadiene mull) occurred at 3150, 1590, 1520, 1430, 1330, 1300, 770, 760, 740 and 715 $cm.^{-1}$

Reduction of "Compound C".- The above iodide (0.48 g.) was added to a suspension of freshly prepared silver chloride (ca. 5 g.) in ethanol (350 ml.) and water (180 ml.), and the mixture heated under reflux for 12 hr. The inorganic material was removed by filtration and the solvent removed from the filtrate under reduced pressure. The chloride crystallised from methanol-ether as yellow needles, m.p. 278-280°.

Platinum oxide (24 mg.) suspended in acetic acid (10 ml.) was reduced and saturated with hydrogen. The chloride (30.4 mg.) was introduced and 1 mole of hydrogen (2.52 ml.) was absorbed in 30 min. (calculated 1 mole absorption 2.30 ml./774 mm./17°). The catalyst was removed by filtration, the filtrate evaporated under reduced pressure, and the residue dissolved in water. Basification and ether extraction yielded "compound A", obtained from methanol as colourless needles that exhibited the same characteristics on melting as described previously. The infrared spectrum of the sample was identical with that of authentic "compound A".

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