

The University of British Columbia

FACULTY OF GRADUATE STUDIES

PROGRAMME OF THE  
FINAL ORAL EXAMINATION

FOR THE DEGREE OF  
DOCTOR OF PHILOSOPHY

of

NIZAM ABDURAHMAN

A.R.C.S.T., University of Strathclyde, Glasgow, Scotland  
M.Sc., University of British Columbia

WEDNESDAY, SEPTEMBER 13, at 3:30 p.m.

IN ROOM 225, CHEMISTRY BUILDING

COMMITTEE IN CHARGE

Chairman: B.N. Moys

|              |               |
|--------------|---------------|
| E. Piers     | G.G.S. Dutton |
| W. Cullen    | C.A. McDowell |
| J. Schaeffer | M. Smith      |

External Examiner: W.A. Ayer  
Department of Chemistry  
University of Alberta  
Edmonton, Alberta

Research Supervisor: J.P. Kutney

# SYNTHETIC STUDIES OF INDOLE ALKALOIDS

## ABSTRACT

Novel transannular cyclisation reactions of nine-membered ring compounds like quebrachamine, dihydrocleavamine and carbomethoxydihydrocleavamine, previously described in this laboratory, provide an attractive entry into the Aspidosperma, Vinca and Iboga alkaloids.

In this thesis two approaches to the synthesis of the nine-membered ring alkaloid, quebrachamine, are described.

The first section of this thesis discusses the synthesis of model compounds suitable for evaluating the acyloin condensation for the synthesis of this alkaloid. For this purpose, 3-carbomethoxypiperidine (98) was prepared by three different routes. In sequence (a), nicotinic acid (109) was methylated to give methyl nicotinate (110), which on catalytic hydrogenation yielded (98). In sequence (b), nicotinic acid was reduced in the presence of dilute aqueous ammonia and 5% rhodium on charcoal to provide nipecotic acid (111). Esterification with diazomethane provided the desired piperidine (98). In sequence (c), the desired material was prepared by an esterification reaction of nipecotic acid hydrochloride (111,a).

The formation of the intermediate arylhydrazone (108,a) was accomplished via a Japp-Klingemann reaction from diethyl  $\gamma$ -chloropropylmalonate (108) and benzene-diazonium chloride. The arylhydrazone (108,a) was then treated under the conditions of the Fischer indole synthesis to provide 2-carboethoxy-3-( $\beta$ -chloroethyl)-indole (97,a). Transesterification with methanol provided 2-carbomethoxy-3-( $\beta$ -chloroethyl)-indole (97,b). The piperidine derivative (98) was coupled with (97,a) and (97,b) to provide the coupling products (99,R=Et) and (99,R=Me). Attempted acyloin condensations of these latter compounds to provide the nine-membered ring compound

(100) are described.

The second section of this thesis describes a new total synthesis of (dl)-quebrachamine via a completely different sequence. Diethyl  $\gamma$ -benzyloxypropylethylmalonate (144) was prepared by the condensation between diethyl ethylmalonate and 1-chloro-3-benzyloxypropane (143.). Alkaline hydrolysis of (144) provided  $\gamma$ -benzyloxypropylethyl malonic acid (145), which was decarboxylated to give 2-( $\gamma$ -benzyloxypropyl)-butanoic acid (146). Esterification of (146) provided ethyl 2-( $\gamma$ -benzyloxypropyl)-butanoate (147), which by subsequent alkylation with triphenylmethyl sodium and ethyl bromoacetate gave ethyl  $\alpha$ -( $\gamma$ -benzyloxypropyl)- $\alpha$ -ethylsuccinate (148). Condensation of (148) with tryptamine provided N-[ $\beta$ -(3-indolyl)-ethyl]- $\alpha$ -( $\gamma$ -benzyloxypropyl)- $\alpha$ -ethylsuccinimide (123), which was reduced with lithium aluminum hydride to yield N-[ $\beta$ -(3-indolyl)-ethyl]-3-( $\gamma$ -benzyloxypropyl)-3-ethylpyrrolidine (124).

Thy uncyclised benzyl ether amine (124) was treated with an excess of mercuric acetate to provide a crude product which was immediately reduced with sodium borohydride to give a mixture of the isomeric cyclic benzyl ether amines (125). Catalytic debenzylation provided three separable aminoalcohols (164) A, B and C. The relatively abundant aminoalcohol B was converted to the quaternary ammonium salt (126) by treatment with methanesulfonyl chloride in pyridine. Ring cleavage of (126) with sodium and liquid ammonia yielded (dl)-quebrachamine (1).

## PUBLICATIONS

- . Abdurahman, D.A. Applegarth, G.G.S., Dutton, D. McLardy, K.E. Pierre and B.I. Stephenson, Hemicelluloses of Four Coniferous Trees, Tappi, 47, 812 (1964)
- . P. Kutney, N. Abdurahman, P. LeQuesne, E. Piers and I. Vlattas, A New Total Synthesis of (dl)-Quebrachamine and (dl)-Aspidospermidine. A General Entry into the Aspidosperma Alkaloids. J. Am. Chem. Soc. 88, 3656 (1966)

## GRADUATE STUDIES

field of Study: Chemistry

|   |   |
|---|---|
| Topics in Organic Chemistry                   | R. Bonnett<br>R. Stewart<br>J.P. Kutney |
| Topics in Physical Chemistry                  | J.A.R. Coope<br>R.F. Snider             |
| Topics in Inorganic Chemistry                 | N. Bartlett<br>W.R. Cullen<br>C. Willis |
| Carbohydrate Chemistry                        | L.D. Hayward<br>G.G.S. Dutton           |
| Physical Organic Chemistry                    | R. Stewart<br>R.E. Pincock              |
| Recent Synthetic Methods in Organic Chemistry | D.E. McGreer<br>W. McRae                |
| Seminar in Chemistry                          | J.P. Kutney                             |
| Organic Reaction Mechanism                    | R.E. Pincock                            |
| Heterocyclic Compounds                        | F. McCapra                              |
| Alkaloid Chemistry                            | J.P. Kutney                             |
| Isoprenoid Compounds                          | T. Money                                |
| Structure of Newer Natural Products           | T. Money                                |

Related Studies:

|                           |            |
|---------------------------|------------|
| Organic Medicine Products | T.H. Brown |
|---------------------------|------------|

SYNTHETIC STUDIES OF INDOLE ALKALOIDS

by

NIZAM ABDURAHMAN

A.R.C.S.T., University of Strathclyde, Glasgow, Scotland, 1958

M.Sc., University of British Columbia, 1962

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF  
THE REQUIREMENTS FOR THE DEGREE OF  
DOCTOR OF PHILOSOPHY

in the Department  
of  
Chemistry

We accept this thesis as conforming to the  
required standard

THE UNIVERSITY OF BRITISH COLUMBIA

JUNE, 1967

In presenting this thesis in partial fulfilment of the requirements  
for an advanced degree at the University of British Columbia, I agree  
that the Library shall make it freely available for reference and  
Study. I further agree that permission for extensive copying of this  
thesis for scholarly purposes may be granted by the Head of my  
Department or by his representatives. It is understood that copying  
or publication of this thesis for financial gain shall not be allowed  
without my written permission.

Department of Chemistry

The University of British Columbia  
Vancouver 8, Canada

Date 28th. Sept. 67'

### ABSTRACT

Novel transannular cyclisation reactions of nine-membered ring compounds like quebrachamine, dihydrocleavamine and carbomethoxydihydrocleavamine, previously described in this laboratory, provide an attractive entry into the Aspidosperma, Vinca and Iboga alkaloids.

In this thesis two approaches to the synthesis of the nine-membered ring alkaloid, quebrachamine, are described.

The first section of this thesis discusses the synthesis of model compounds suitable for evaluating the acyloin condensation for the synthesis of this alkaloid. For this purpose, 3-carbomethoxypiperidine (98) was prepared by three different routes. In sequence (a), nicotinic acid (109) was methylated to give methyl nicotinate (110), which on catalytic hydrogenation yielded (98). In sequence (b), nicotinic acid was reduced in the presence of dilute aqueous ammonia and 5% rhodium on charcoal to provide nipecotic acid (111). Esterification with diazomethane provided the desired piperidine (98). In sequence (c), the desired material was prepared by an esterification reaction of nipecotic acid hydrochloride (111,a).

The formation of the intermediate arylhydrazone (108,a) was accomplished via a Japp-Klingemann reaction from diethyl  $\gamma$ -chloropropylmalonate (108) and benzenediazonium chloride. The aryl<sup>y</sup>hydrazone (108,a) was then treated under the conditions

of the Fischer indole synthesis to provide 2-carboethoxy-3-( $\beta$ -chloroethyl)-indole (97,a). Transesterification with methanol provided 2-carbomethoxy-3-( $\beta$ -chloroethyl)-indole (97,b). The piperidine derivative (98) was coupled with (97,a) and (97,b) to provide the coupling products (99, R=Et) and (99, R=Me). Attempted acyloin condensations of these latter compounds to provide the nine-membered ring compound (100) are described.

The second section of this thesis describes a new total synthesis of (dl)-quebrachamine via a completely different sequence. Diethyl  $\delta$ -benzyloxypropyl ethylmalonate (144) was prepared by the condensation between diethyl ethylmalonate and 1-chloro-3-benzyloxypropane (143). Alkaline hydrolysis of (144) provided  $\delta$ -benzyloxypropyl ethyl malonic acid (145), which was decarboxylated to give 2-( $\delta$ -benzyloxypropyl)-butanoic acid (146). Esterification of (146) provided ethyl 2-( $\delta$ -benzyloxypropyl)-butanoate (147), which by subsequent alkylation with triphenylmethyl sodium and ethyl bromoacetate gave ethyl  $\alpha$ -( $\delta$ -benzyloxypropyl)- $\alpha$ -ethylsuccinate (148). Condensation of (148) with tryptamine provided N-[ $\beta$ -(3-indolyl)-ethyl]- $\alpha$ -( $\delta$ -benzyloxypropyl)- $\alpha$ -ethylsuccinimide (123), which was reduced with lithium aluminum hydride to yield N-[ $\beta$ -(3-indolyl)-ethyl]-3-( $\delta$ -benzyloxypropyl)-3-ethylpyrrolidine (124).

The uncyclised benzyl ether amine (124) was treated with an excess of mercuric acetate to provide a crude product which was immediately reduced with sodium borohydride to give a



mixture of the isomeric cyclic benzyl ether amines (125). Catalytic debenzylation provided three separable aminoalcohols (164) A, B and C. The relatively abundant aminoalcohol B was converted to the quaternary ammonium salt (126) by treatment with methanesulfonyl chloride in pyridine. Ring cleavage of (126) with sodium and liquid ammonia yielded (dl)-quebrachamine (1).

TABLE OF CONTENTS

|   | Page |
|---|------|
| TITLE PAGE.....   | i    |
| ABSTRACT.....   | ii   |
| TABLE OF CONTENTS.....                                      | v    |
| LIST OF FIGURES.....  | vii  |
| ACKNOWLEDGEMENTS.....                                       | x    |
| INTRODUCTION.....   | 1    |
| (i) Biogenesis.....   | 2    |
| (ii) Synthesis of Possible Biogenetic<br>Significance.....  | 18   |
| (iii) Previous Synthetic Approaches.....                    | 23   |
| DISCUSSION.....   | 32   |
| I. Scheme A.....  | 32   |
| (i) Synthesis of the Indole Moiety.....                     | 35   |
| (ii) Synthesis of the Piperidine Moiety.....                | 39   |
| (iii) Coupling Reactions.....                               | 41   |
| (iv) Acyloin Condensation.....                              | 46   |
| II. Scheme B.....   | 50   |
| (i) Synthesis of the Succinate Derivative.....              | 53   |
| (ii) Condensation with Tryptamine.....                      | 56   |
| (iii) Cyclisation via Bischler-Napieralski<br>Reaction..... | 57   |
| (iv) Reduction of the Imide.....                            | 60   |
| (v) Oxidative Cyclisation.....                              | 65   |

|   | Page |
|---|------|
| (vi) Debenzylation of the Benzyl Ether<br>with Boron Tribromide.....              | 70   |
| (vii) Quaternary Ammonium Salt Formation.....                                     | 70   |
| (viii) Ring Cleavage Reaction.....  | 71   |
| (ix) Debenzylation of the Benzyl Ether Amines<br>by Catalytic Hydrogenolysis..... | 71   |
| EXPERIMENTAL.....   | 81   |
| BIBLIOGRAPHY.....   | 115  |

LIST OF FIGURES

| Figure  | Page |
|---------|------|
| 1.....  | 4    |
| 2.....  | 4    |
| 3.....  | 6    |
| 4.....  | 8    |
| 5.....  | 9    |
| 6.....  | 10   |
| 7.....  | 12   |
| 8.....  | 12   |
| 9.....  | 13   |
| 10..... | 16   |
| 11..... | 17   |
| 12..... | 19   |
| 13..... | 21   |
| 14..... | 22   |
| 15..... | 22   |
| 16..... | 24   |
| 17..... | 26   |
| 18..... | 27   |
| 19..... | 28   |
| 20..... | 29   |
| 21..... | 30   |
| 22..... | 30   |
| 23..... | 31   |

| Figure  | Page |
|---------|------|
| 24..... | 33   |
| 25..... | 33   |
| 26..... | 34   |
| 27..... | 35   |
| 28..... | 36   |
| 29..... | 38   |
| 30..... | 40   |
| 31..... | 43   |
| 32..... | 44   |
| 33..... | 45   |
| 34..... | 49   |
| 35..... | 49   |
| 36..... | 51   |
| 37..... | 52   |
| 38..... | 53   |
| 39..... | 57   |
| 40..... | 59   |
| 41..... | 61   |
| 42..... | 62   |
| 43..... | 63   |
| 44..... | 66   |
| 45..... | 69   |
| 46..... | 72   |

| Figure  | Page |
|---------|------|
| 47..... | 74   |
| 48..... | 75   |
| 49..... | 76   |
| 50..... | 77   |
| 51..... | 79   |

### ACKNOWLEDGEMENTS

I wish to express my sincere appreciation to Professor J.P. Kutney for his excellent guidance and constant encouragement during the course of my research.

Thanks are also due to Dr. P. LeQuesne and Dr. E. Piers for their useful discussions.

Financial aid from the University of British Columbia and Chemcell (1963) Ltd. is very gratefully acknowledged.

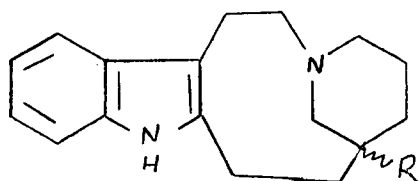
## INTRODUCTION

At the dawn of experimental organic chemistry just over a century and a half ago, Serturner isolated morphine from opium. Although he was not the first man to isolate morphine, he did recognise it to have basic properties, and referred to it as a "vegetable alkali". Meisner, in 1818, proposed that such "vegetable alkalis" should be called alkaloids. The noun became accepted and today the word generally denotes a basic, physiologically active nitrogen-containing natural product. Among the earliest known alkaloids are the indole alkaloids, and some five hundred of these bases have been obtained from about three hundred plants, mostly of the family Apocynaceae. They also occur to a lesser extent in the Asclepiadaceae, Loganiaceae and Rubiaceae families. More than three hundred structures have been elucidated and these are listed by Hesse in a recent compilation<sup>1</sup>.

This thesis is concerned with the chemistry of a selected group of indole alkaloids, viz., the Aspidospermine group, and with the biogenetic considerations arising from their chemistry. This group of alkaloids, whose basic carbon skeleton was not readily accounted for in earlier biosynthetic hypotheses, appears somewhat restricted in Nature, occurring principally in the genera *Aspidosperma*, *Kopsia*, *Pleiocarpa* and *Stemmadenia*. Quebrachamine(1), an alkaloid of this group, whose total synthesis is described in this thesis, is one of the most widely distributed. Although as an indole it is distinct from the majority of the



members of this group, which are dihydroindoles, its obvious relation to the others justifies its inclusion here. Earlier literature on quebrachamine (1) has been summarised<sup>2</sup>. Most important from a biogenetic point of view is the existence in nature of both optical enantiomers of quebrachamine (1).



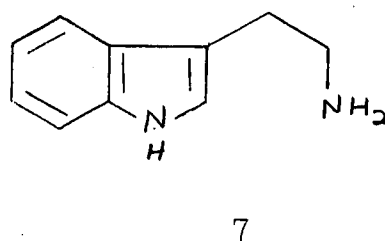
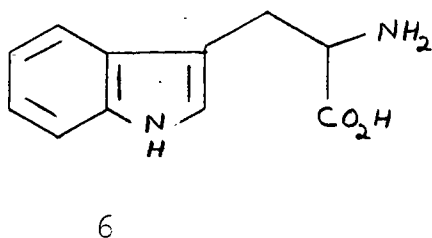
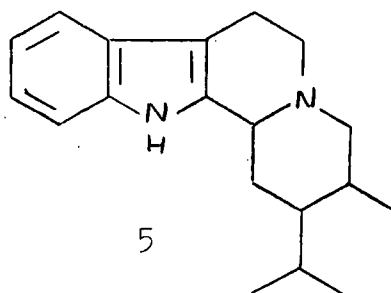
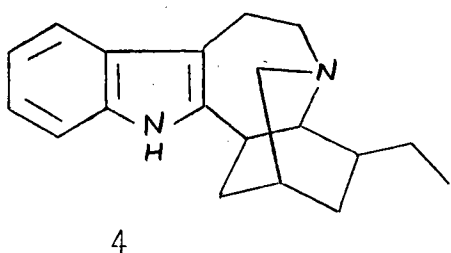
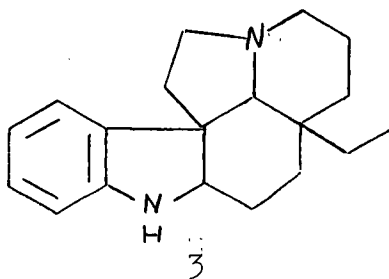
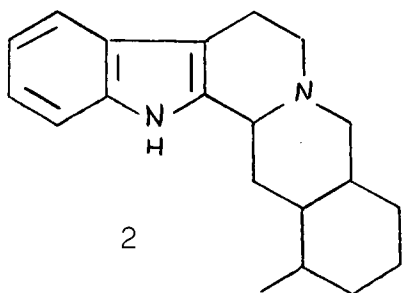
R =  $\alpha$ -ethyl, (+) isomer

R =  $\beta$ -ethyl, (-) isomer

(1)

#### (i) Biogenesis

Ever since the structures of alkaloids were first elucidated, organic chemists have speculated on their biosynthesis. Since the alkaloids of the Yohimbine (2), Aspidosperma (3), Iboga (4) and Corynanthe (5) types contain a common structural feature, the  $\beta$ -(2-aminoethyl)-indole group, it has been felt that tryptophan (6) or its decarboxylation product tryptamine (7) is the precursor of the aromatic portion of these molecules. In fact, labelling experiments have shown that DL-tryptophan-2-<sup>14</sup>C (8) is incorporated by Rauwolfia serpentina into ajmaline (9), serpentine (10) and reserpine (11)<sup>3,4</sup>, and by Vinca rosea into vindoline (12)<sup>5</sup>, figure 1. DL-Tryptophan-3-<sup>14</sup>C (13) was also incorporated by Tabernanthe iboga into ibogaine (14)<sup>6</sup>, figure 2. These experiments strongly suggest that all the indole and dihydroindole alkaloids which contain a  $\beta$ -(2-aminoethyl)-indole or  $\beta$ -(2-aminoethyl)-dihydroindole moiety are derived in part from tryptophan.



The biogenesis of the "non-tryptophan" aliphatic  $C_9$ - or  $C_{10}$ - portion of the molecule is less obvious than that of the aromatic portion. In total, four hypotheses have been advanced.

The first hypothesis (Barger-Hahn<sup>7,8,9</sup>) suggested that the skeleton of yohimbine (15) can be derived from tryptamine (7), dihydroxyphenylalanine (16) and formaldehyde or its  $C_1$ -equivalent. This proposal was particularly attractive since tryptamine undergoes condensation reaction with aldehydes under physiological conditions to yield carboline derivatives.

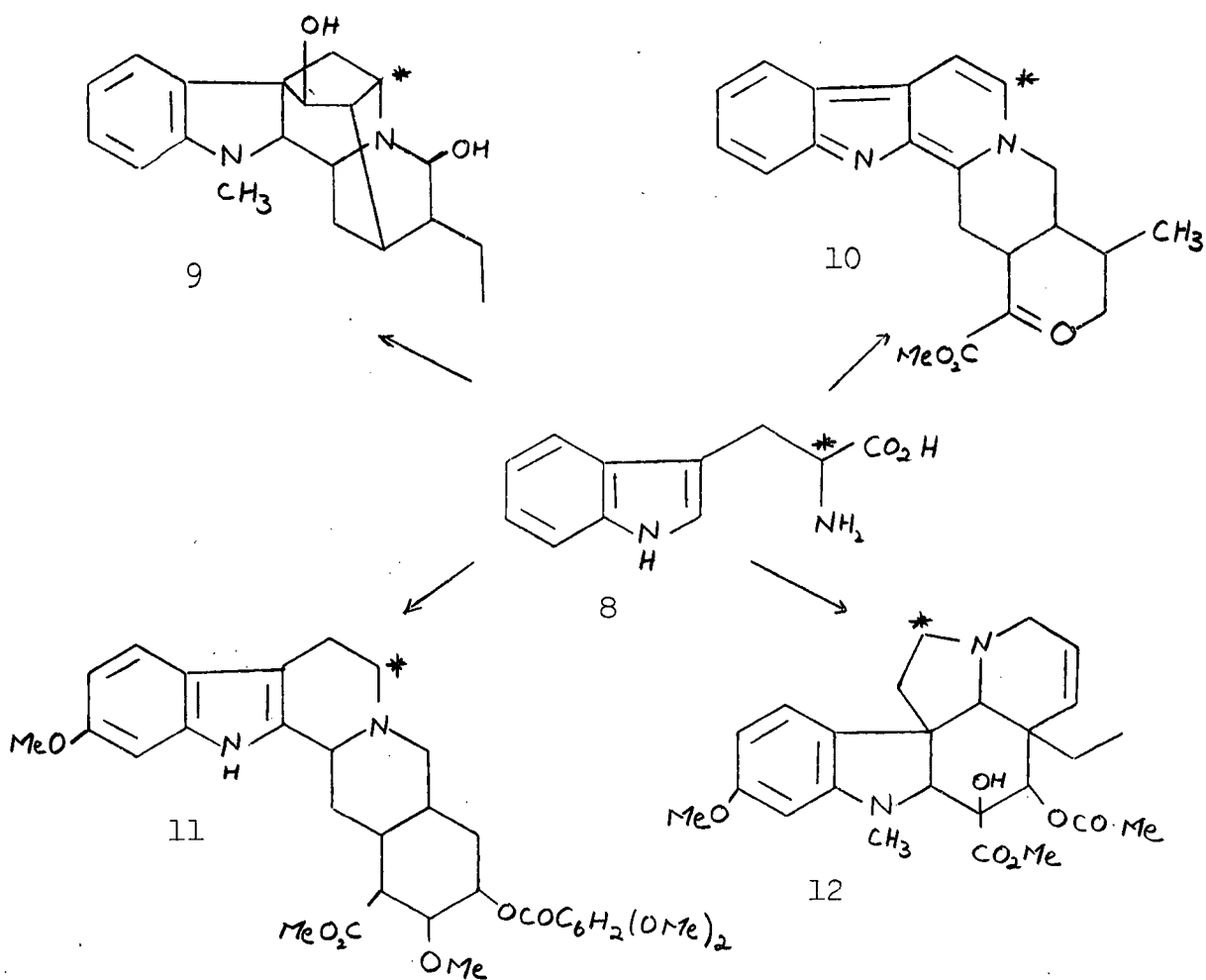


Figure 1. Incorporation of DL-Tryptophan-2-<sup>14</sup>C into Ajmaline, Serpentine, Reserpine, and Vindoline.

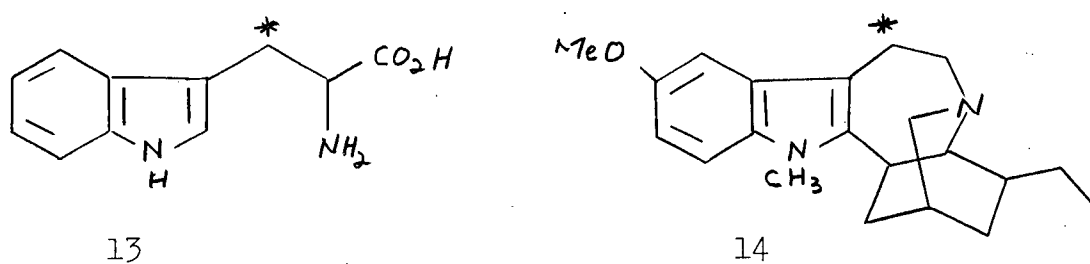


Figure 2. Incorporation of DL-Tryptophan-3-<sup>14</sup>C into Ibogaine.

The introduction of the carbomethoxy group was then postulated to lead to yohimbine (15). Robinson suggested that it was possible to account for the carbomethoxy group by expansion of the aromatic ring to a tropolone (17) which then collapses to a keto-acid or its ester<sup>10</sup>.

The Barger-Hahn hypothesis gained considerable support as a consequence of the attractive suggestion of Woodward<sup>11</sup>, that a related pathway involving the fission of the 3,4-dihydroxy-phenylalanine-derived ring E with the incorporation of a single acetate unit, could simply account for the origin of strychnine (18), figure 3. A valuable consequence of this postulate has been the successful biosynthetic anticipation of the subsequently determined structures of a number of other indole alkaloids, e.g. corynanthine (19) and ajmalicine (20), sarpagine (21)<sup>12</sup> and ajmaline (9)<sup>13</sup>.

The second hypothesis was proposed by Wenkert and Bringi<sup>14</sup> after they drew attention to the following limitations of the Barger-Hahn scheme: (a) it does not readily account for the predominantly aliphatic character of the indole alkaloids containing a carbocyclic ring E; (b) it is inconsistent with the observation that C-15 appears to possess a unique absolute configuration - the single exception being -akuammicine (22); (c) the postulate of the origin of the carbomethoxy group involving a tropolone intermediate is considered to be inadequate. Wenkert<sup>15</sup> then suggested that the non-tryptophan part is derived from carbohydrates via a pathway involving shikimic (23) and prephenic acids (24). The key step in Wenkert's "Prephenic Acid Hypothesis" (figure 4) is the rearrangement of prephenic

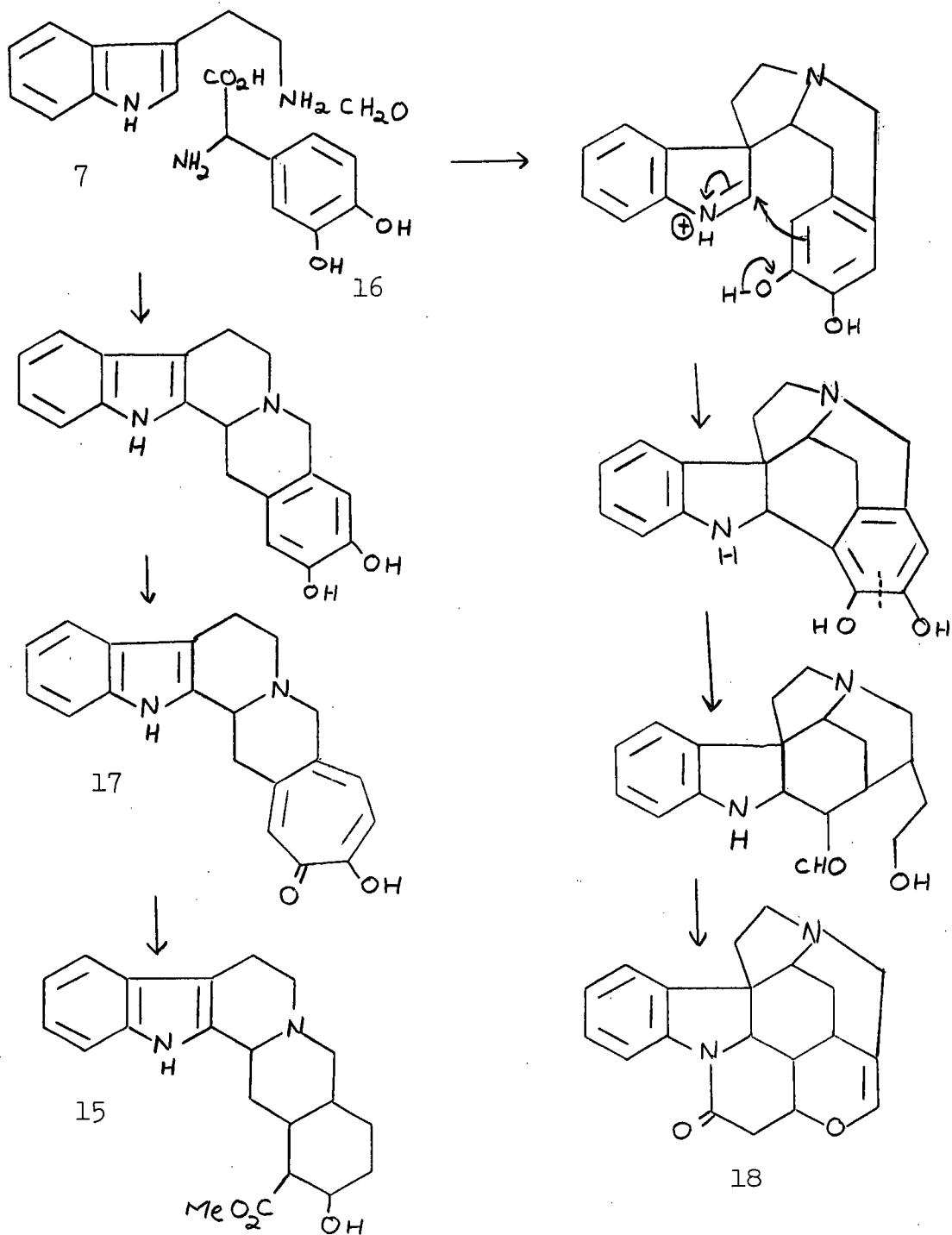
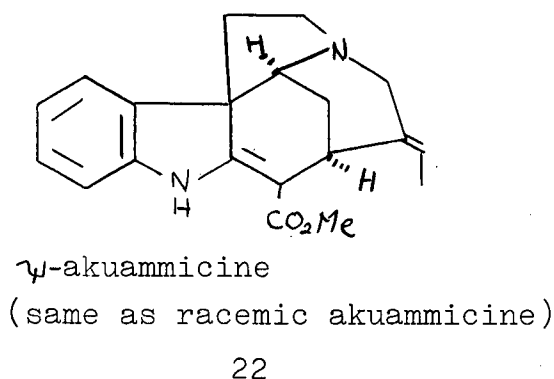
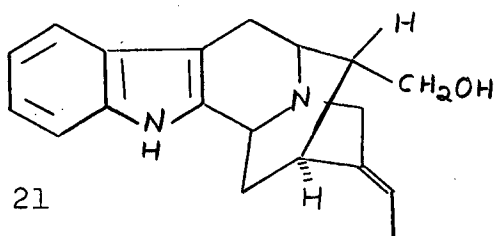
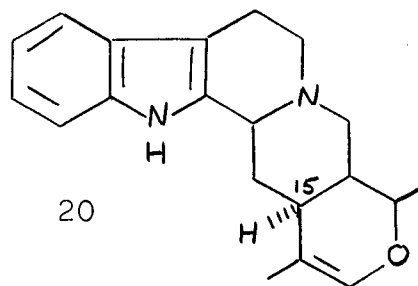
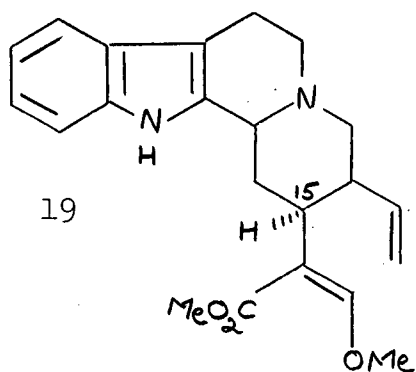


Figure 3. Barger-Hahn-Robinson-Woodward Hypothesis.



acid (24) by a 1,2-shift of the pyruvyl side chain with retention of configuration, followed by hydration and condensation with a C-1 equivalent which affords unit (25), readily discernible in yohimbine (15). Retro-aldolisation of the unit (25) yields the "seco-prephenate-formaldehyde" (SPF) unit (26) which on condensation with tryptamine yields the alkaloids corynantheine (19) and ajmalicine (20), sarpagine (21) and ajmaline (9), as outlined in figure 5. One of the attractive features of this scheme is that it accounts for the common stereochemistry of the C-15 position, where the hydrogen atom is in an  $\alpha$ -configuration.

The biosynthesis of the Strychnos bases and the structurally more complicated Iboga and Aspidosperma alkaloids are encompassed in this scheme. Condensation of the formylacetate group of (27)

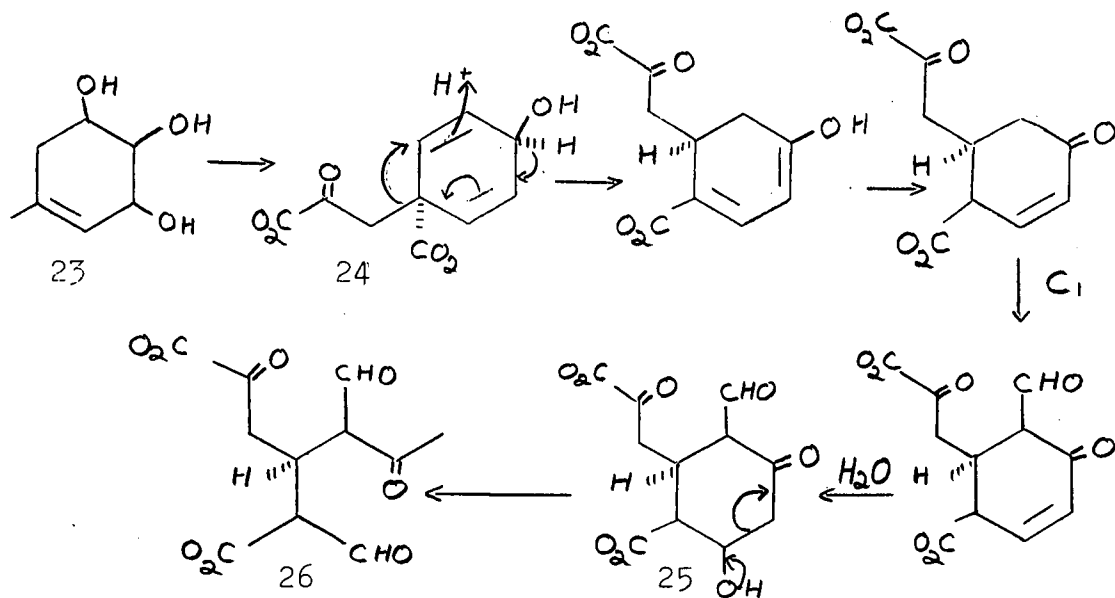


Figure 4. Wenkert's Prephenic Acid Hypothesis.

with the  $\alpha$ -position of the indole ring leads to the intermediate (28) which by a transannular cyclisation to the iminium ion could account for the formation of the strychnine skeleton. Retro-Michael condensation of the tryptamine-SPF complex (28) leads to (29) which can undergo conventional oxidation and reduction changes to give piperideines of varying states of oxidation, e.g. (30) and (31). Michael additions of these compounds to the  $\alpha\beta$ -unsaturated acid system would afford the nine-membered ring compounds (32) and (33), which closely resemble the skeletons of quebrachamine (1) and its structural isomer cleavamine (34) respectively. Transannular cyclisations of (32) and (33) lead to the Aspidosperma (35) and Iboga (36) skeleta respectively.

The third postulate, the "Monoterpenoid Hypothesis", was independently proposed by Wenkert<sup>15</sup> and Thomas<sup>16</sup>. These authors

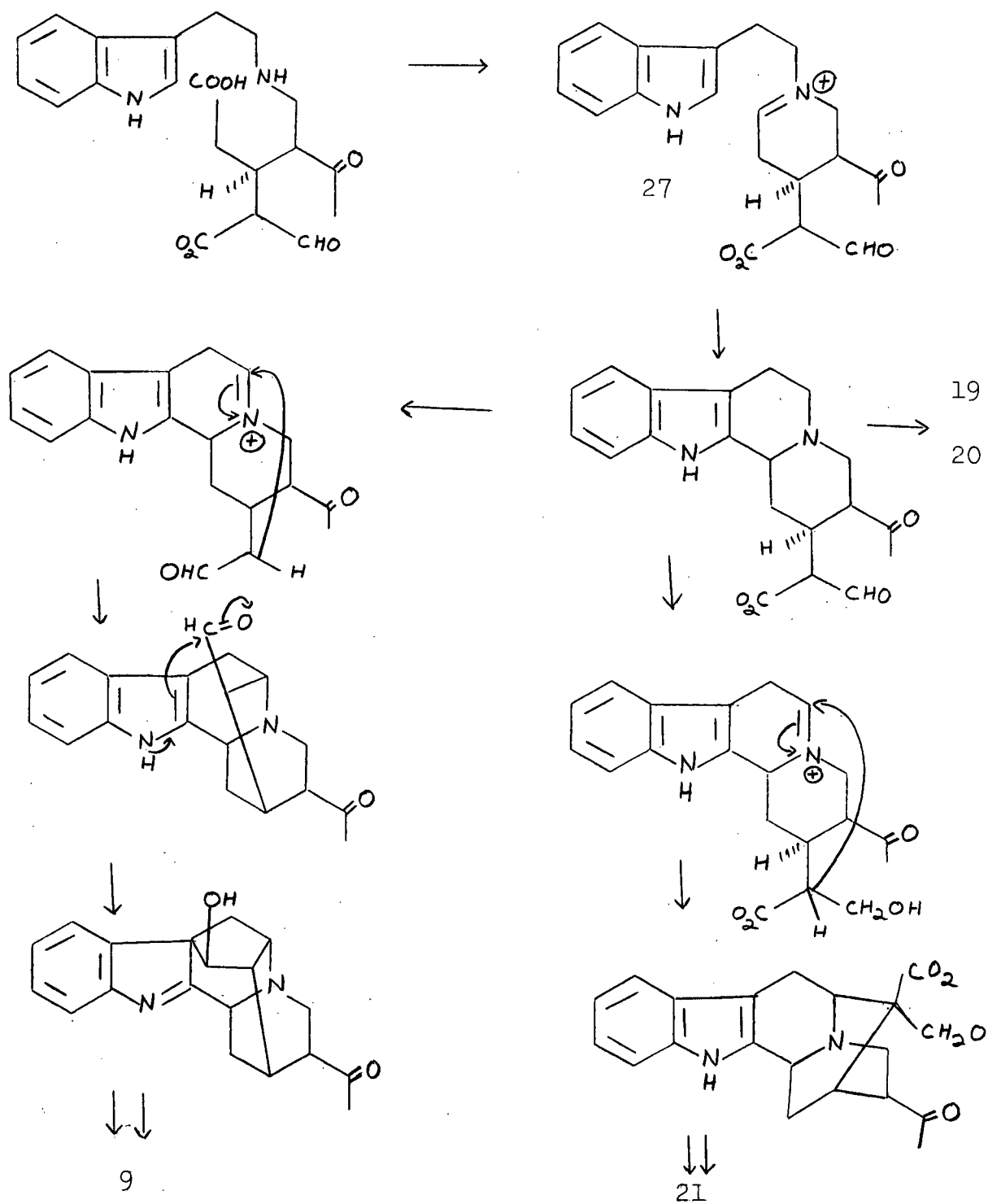


Figure 5. Incorporation of the SPF Unit into Corynantheine, Yohimbine, Ajmaline and Sarpagine.



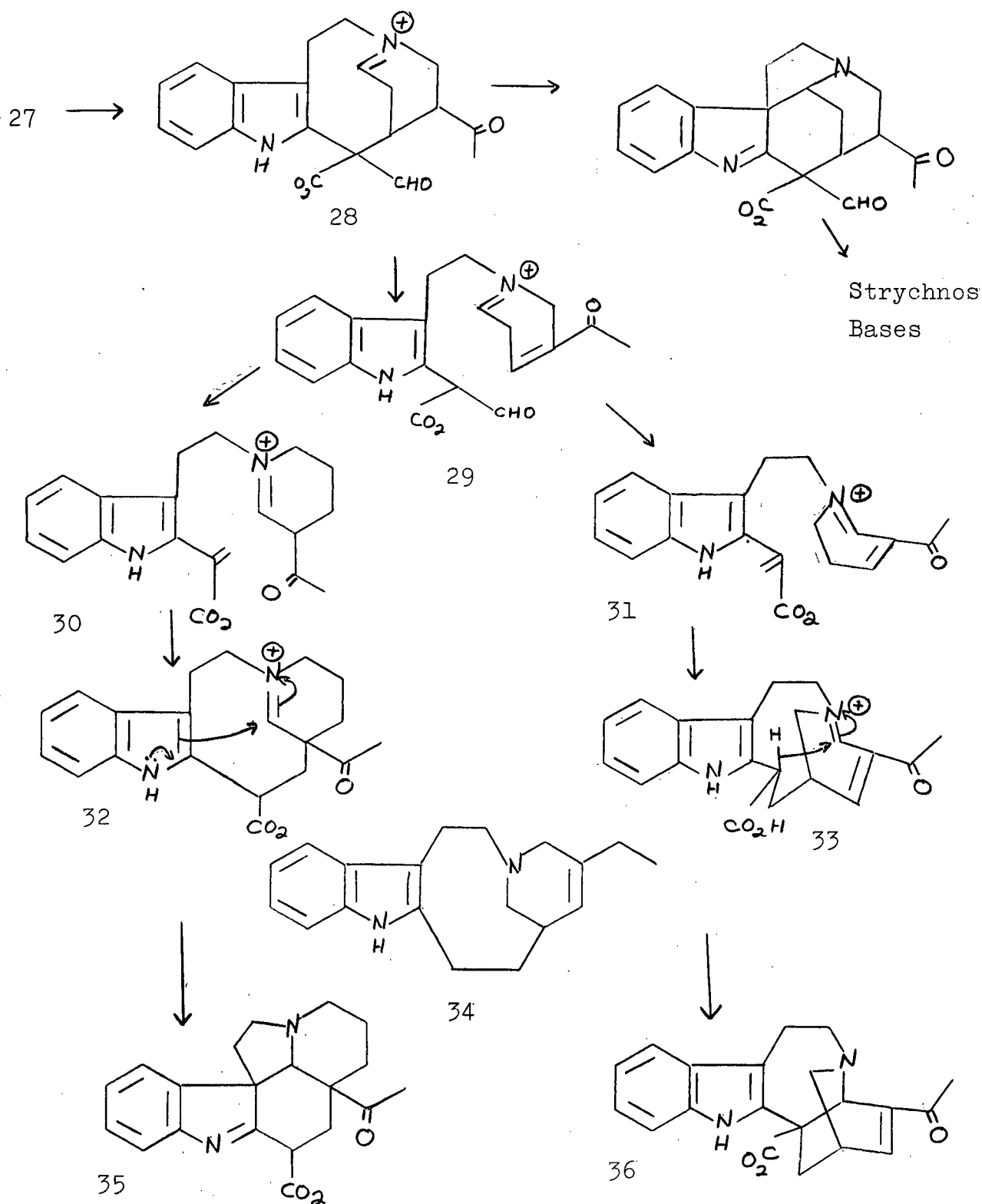
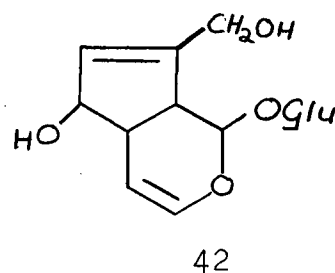
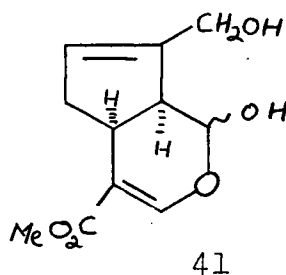
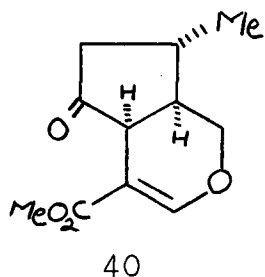
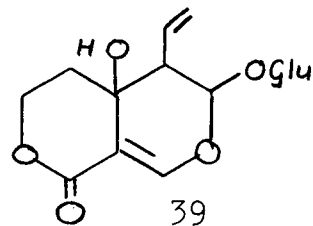
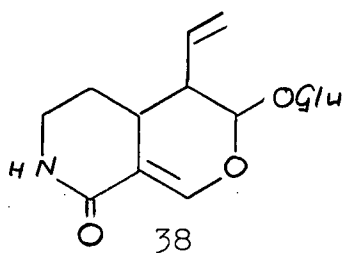
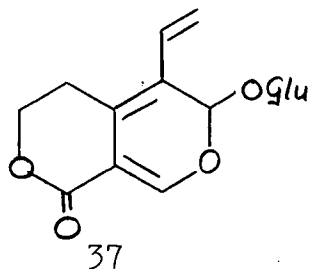


Figure 6. Incorporation of the SPF Unit into the Iboga and Aspidosperma Alkaloids.



noted that the non-alkaloidal glycosides, gentiopicrin (37), bakankosin (38) and swertiamarin (39) had structures which could be based on the SPF unit. It was also noted that cyclopentanoid monoterpenic glucosides, such as verbenalin (40), genipin (41) and aucubin (42), have the common carbon skeleton (43). Cleavage of the cyclopentane ring as indicated (figure 7) would give rise to the carbon skeleton of the SPF unit having the required stereochemistry at C-15 (equivalent to C-6 in 43) in the indole alkaloid. The formation of the more complicated *Aspidosperma* (3) and *Iboga* (4) skeleta could then follow the same course as suggested by the earlier prephenic acid theory (Figures 4, 5 and 6).

The fourth hypothesis to account for the origin of the non-tryptamine portion was put forward by Schlittler and Taylor<sup>17</sup>, figure 8. They suggested that three molecules of acetyl-coenzyme A condense to form a poly- $\beta$ -keto chain (45) which by further

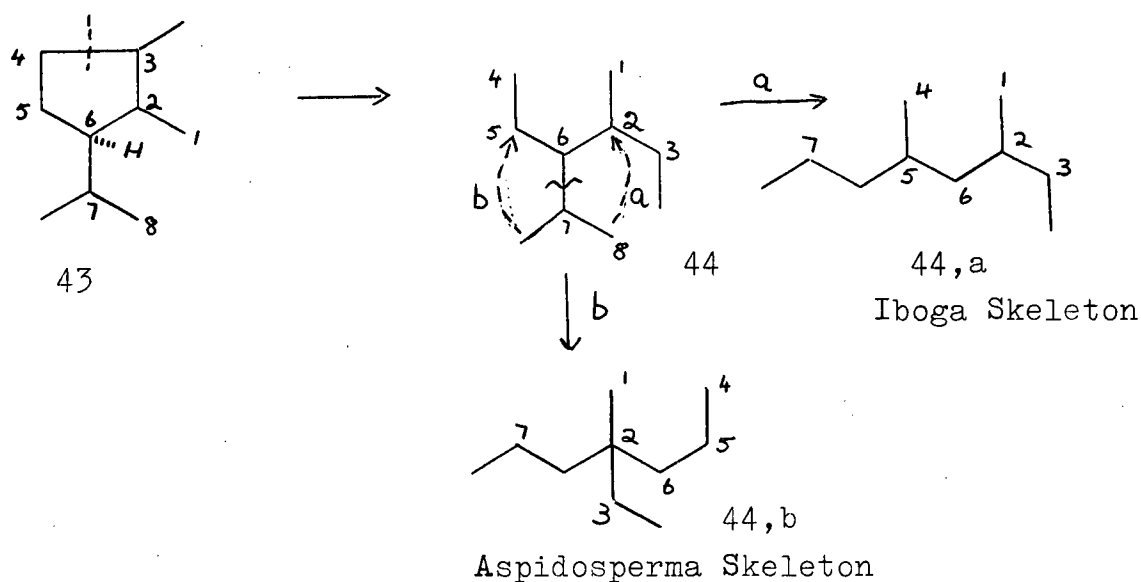


Figure 7. Wenkert-Thomas Monoterpene Hypothesis.

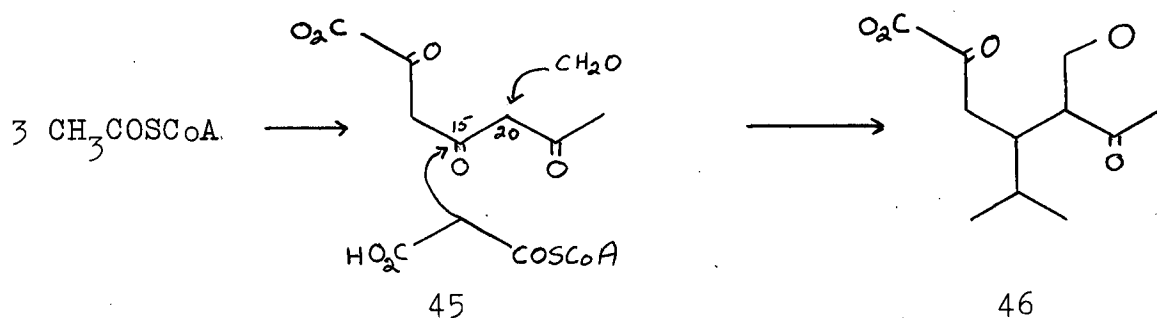
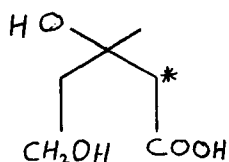
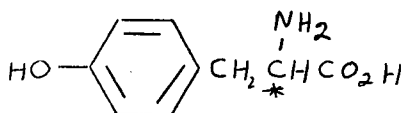


Figure 8. Schlittler-Taylor-Leete Hypothesis.

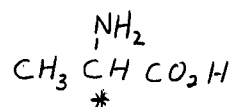
condensation with formaldehyde at C-20 and with malonyl-coenzyme A at C-15 forms an intermediate (46) very similar to Wenkert's SPF unit (26). This intermediate would then condense with tryptamine to give the various indole alkaloids in a manner similar to the latter part of Wenkert's hypothesis.



47



48



49

In order to decide between these hypotheses a great deal of work has been carried out using tracer techniques. Leete<sup>18</sup> reported that ajmaline (9) isolated from Rauwolfia serpentina plants which were fed with mevalonic-2-<sup>14</sup>C acid (47) or tyrosine-2-<sup>14</sup>C (48) - which is a known precursor of 3,4-dihydroxyphenylalanine (16) - was completely inactive. These results rendered unlikely the Woodward fission hypothesis and the monoterpene hypothesis. Alanine-2-<sup>14</sup>C (49) was also fed to test Wenkert's prephenic acid hypothesis on the assumption that pyruvate formed by transamination of alanine would be incorporated into the side chain of prephenic acid. However the actual precursor of the side chain of prephenic acid is phosphoenolpyruvate which is not readily formed from pyruvic acid in vivo. Thus no definite conclusion can be drawn from this latter finding. Leete<sup>18, 19</sup> also fed sodium acetate-1-<sup>14</sup>C to R. serpentina and found that half the total activity of ajmaline (9) was located at C-3 and C-19 and equally

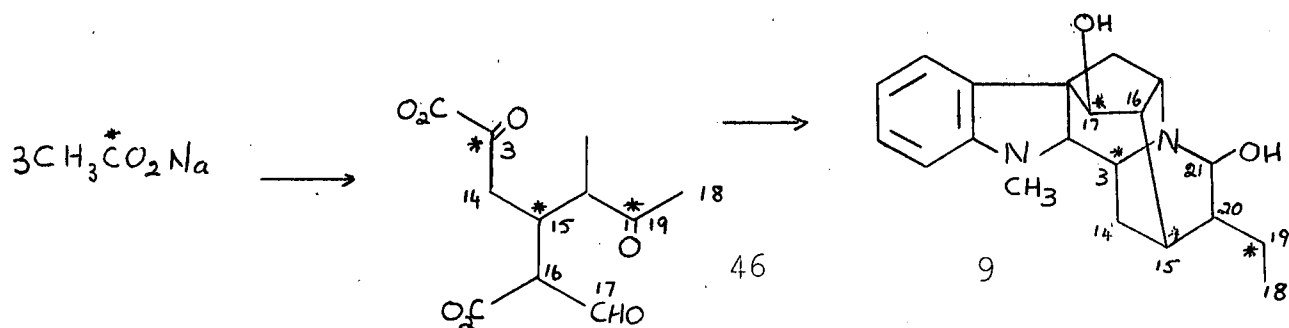


Figure 9. Incorporation of Acetate into Ajmaline.

distributed between these positions, figure 9. If it is assumed that the remaining half of the activity was shared between C-15 and C-17, then this would support the hypothesis of Taylor.

However, Battersby<sup>20</sup> also studied the biosynthesis of ajmaline (9) and obtained results in contrast to those of Leete. Leete<sup>21</sup> was later unable to reproduce his original results, but rather obtained results compatible with those of Battersby. These results would apparently exclude the "Schlitter-Taylor Hypothesis".

Since shikimic acid is the direct precursor of prephenic acid, Mothes<sup>22</sup> fed shikimic-U-<sup>14</sup>C acid (23) to Catharanthus roseus and isolated radioactive vindoline (12) and catharanthine (50). Over 90% of the total activity of vindoline (12) was located in the aromatic part of the indole nucleus. This would tend to disprove Wenkert's postulate that shikimic acid is the precursor of the non-aromatic portion.

It is well recognised that due caution must be exercised in the interpretation of negative results in incorporation studies. The success of feeding experiments depends on the choice of the plant, the age of the plant, the method of feeding and the ability of the labelled precursor to be absorbed into the plant and transported to the site of active synthesis. Since none of these biogenetic hypotheses has been unequivocally supported by adequate feeding experiments reinvestigations of these theories has become necessary.

The important discovery by Scott<sup>23, 24</sup>, that mevalonic-2-<sup>14</sup>C acid lactone (51) is incorporated into the Aspidosperma-type

alkaloid, vindoline (12) by Catharanthus roseus G. Don concentrated interest in the Wenkert-Thomas theory. Essentially identical, independent results have emerged from the work of Arigoni<sup>25</sup>, who fed sodium mevalonate-2-<sup>14</sup>C (46) to Vinca rosea Linn. Degradative studies showed that one quarter of the total activity in vindoline (12) was located at C-22. This finding is in agreement with the mevalonoid nature of the non-tryptamine portion. Scott, thus tentatively proposed the terpenoid pathway shown in figure 10, as a possible route to the Yohimbine (2) Aspidosperma (3) and Iboga (4) types.

Battersby<sup>26</sup> also showed that mevalonic-2-<sup>14</sup>C acid (54) was incorporated by Vinca rosea into vindoline (12) ajmalicine (20) and serpentine (10) and that the carbomethoxy groups (C-22) of ajmalicine (20) and catharanthine (50) had 24% and 23% of the total activity respectively. Kuhn-Roth degradation of catharanthine established that C-6, C-20 and C-21 were inactive, while 3-ethylpyridine obtained by palladium dehydrogenation had 48% of the total activity. Thus a partial assignment of radioactivity in catharanthine (50) can be made: C-22, 23%; C-1+C-18 by difference 29%; and 48% located at some point(s) in C-2, C-3, C-5 and C-19, figure 11. All these results are consistent with the Wenkert-Thomas scheme and eliminates the alternate scheme by Scott, which requires that 50% of the total activity be located at C-22 in the Iboga skeleton (50).

From these reports on the incorporation of mevalonic acid into ajmalicine (20), serpentine (10), catharanthine (50) and vindoline (12) workers felt that geraniol, which on current

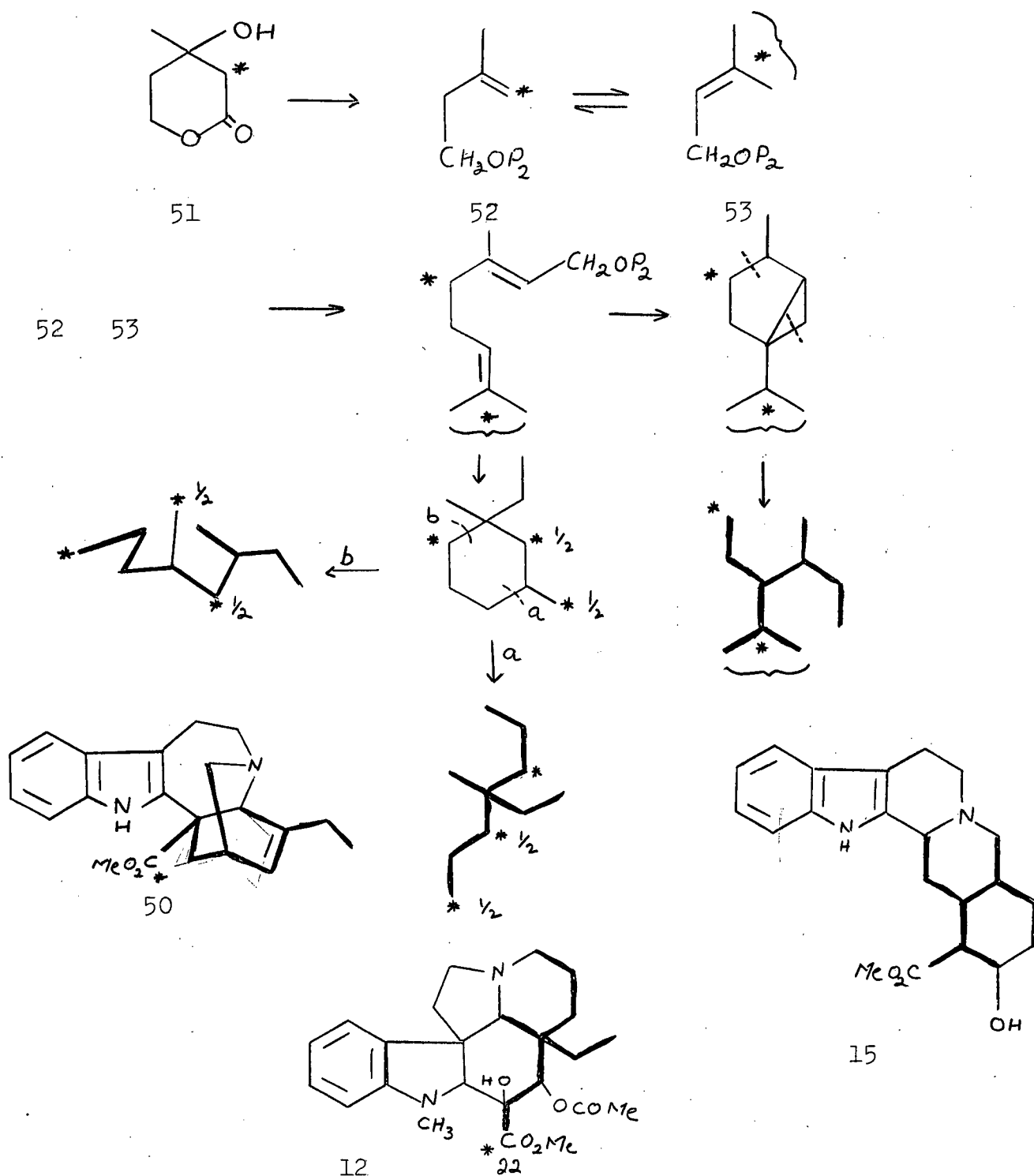


Figure 10. Mevalonate Incorporation Experiments by Scott and Arigoni.

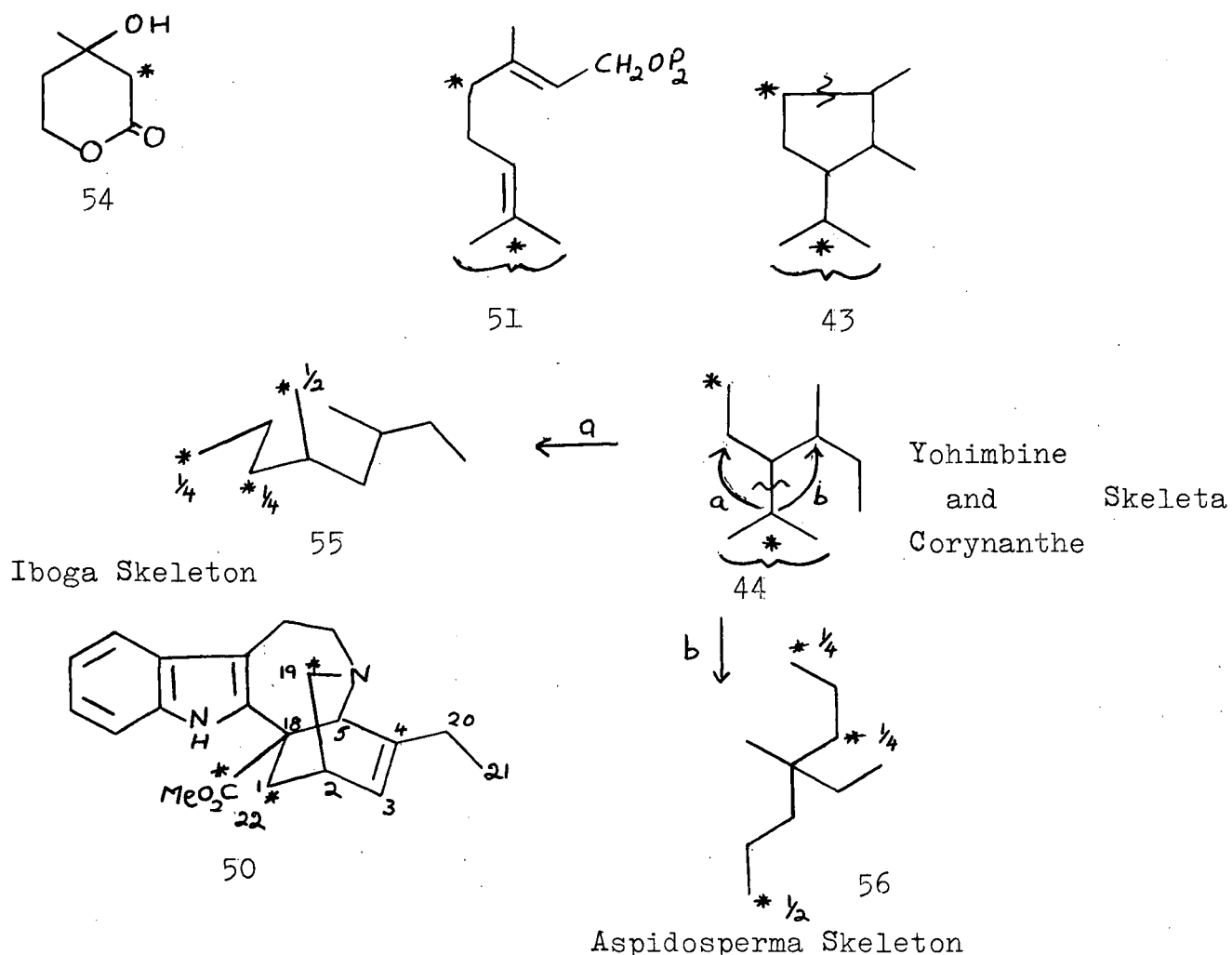


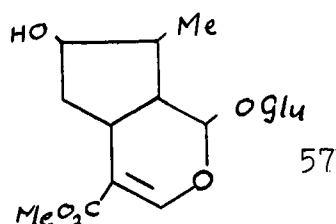
Figure 11. Mevalonate Incorporation Experiments by Battersby.

knowledge of isoprenoid biosynthesis should be a logical precursor for these alkaloids. In fact Battersby<sup>27, 28</sup>, Arigoni<sup>29</sup>, Scott<sup>30</sup> and their research groups independently discovered that geraniol (51) is a precursor of the non-tryptamine portion. The pattern of labelling found in ajmalicine (20) catharanthine (50) and vindoline (12) derived from geraniol-2-<sup>14</sup>C (51) was consistent with the formation of the intermediate cyclopentanoid monoterpene (43). Subsequent bond cleavage and rearrangements leads to the structures (44), (55) and (56) which represent the three alkaloidal families



indicated, figure 11. Further confirmation has recently been offered by Leete<sup>31</sup> who fed geraniol-3-<sup>14</sup>C to Vinca rosea and isolated catharanthine (50) and vindoline (12) with the label in the expected place.

The incorporation of mevalonic acid and geraniol strongly supports the suggestion that the indole alkaloids are formed from a cyclopentanoid monoterpene. In support of this idea Battersby<sup>32</sup> has shown that loganin (57), a known cyclopentanoid monoterpenoid, is incorporated into the Iboga (4), *Aspidosperma* (3) and *Corynanthe* (5) families.



## (ii) Syntheses of Possible Biogenetic Significance

Although the earlier stages of Wenkert's prephenic acid scheme have been replaced by the monoterpenoid hypothesis, the latter stages of the prephenic acid pathway remain an attractive basis for experimental work. In fact, considerable support for the latter part of this proposal can be found in the reactions of certain alkaloids.

For instance, in a chemical correlation<sup>33</sup> between condylocarpine (57) and akuammicine (58), carried out to verify the absolute configuration of the former (see figure 12), the transformation of condyfoline (59) to tubifoline (60) was postulated to occur through a reversible ring opening to the iminium salt (61). This intermediate then rearranges to (62) and is followed by a

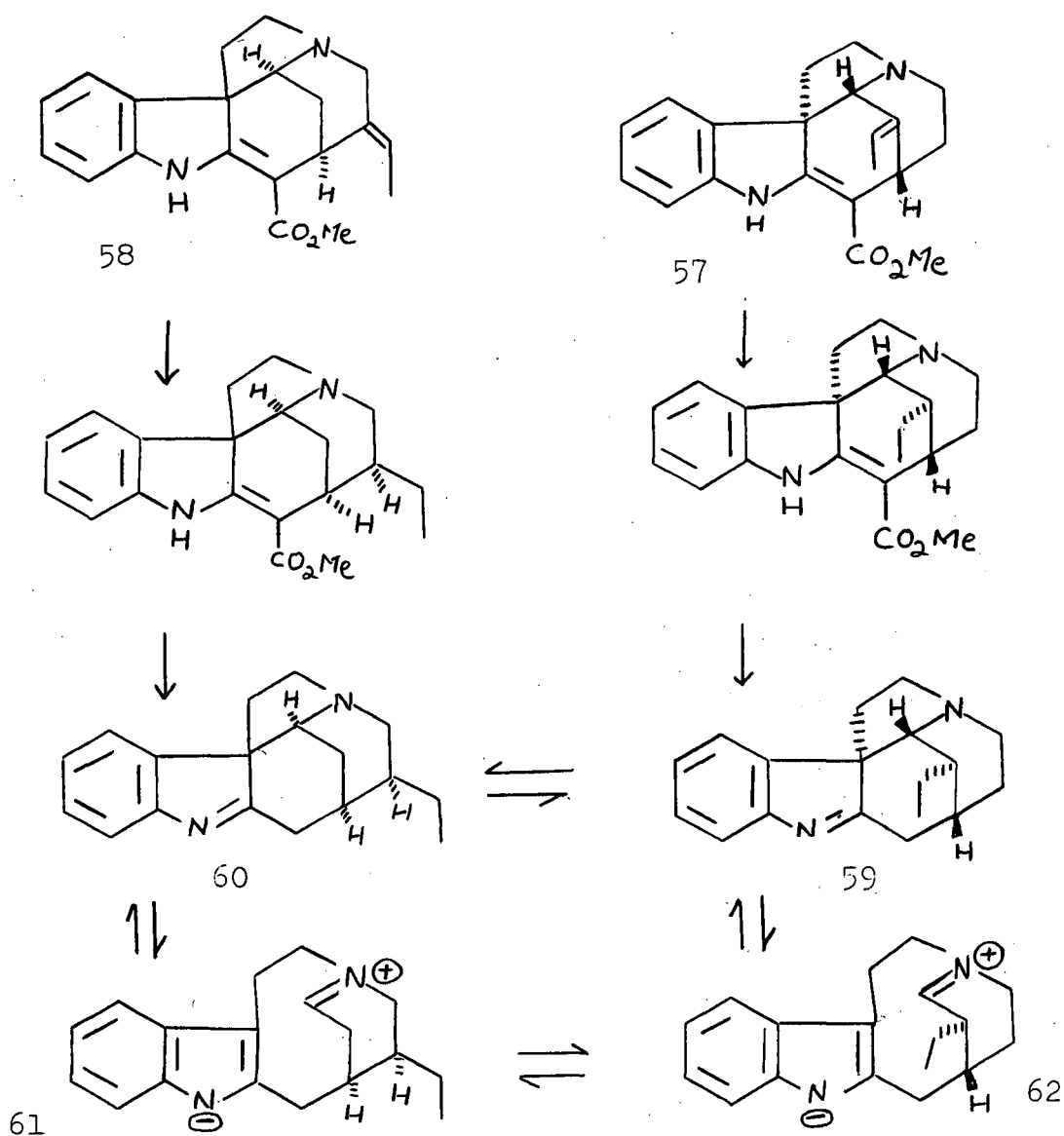


Figure 12. Correlation between Condyllocarpine and Akuammicine.

transannular cyclisation similar to that postulated in Wenkert's scheme, figure 6.

A great deal of attention has recently been focussed on transannular cyclisation processes similar to those postulated by Wenkert to account for the biogenetic formation of the *Aspidosperma* (32  $\rightarrow$  35) and *Iboga* (33  $\rightarrow$  36) skeleta. The first

laboratory realization of such a cyclisation to provide the Aspidosperma skeleton was reported by Kutney<sup>34</sup>. This sequence (figure 13) involves the mercuric acetate oxidation of dihydrocleavamine (63) to the ionic intermediate (64) which undergoes a transannular cyclisation reaction to give the indolenine (65). The final product (66) was obtained after hydride reduction of (65).

It then became apparent from the above results that carbomethoxydihydrocleavamine (67) could undergo cyclisations in an alternative sense and lead to Iboga- and Vinca-like systems. In fact, Kutney<sup>35, 36</sup> was able to show that the mercuric acetate oxidation of carbomethoxydihydrocleavamine (67) leads to the iminium intermediates (69) and (68) which via transannular cyclisation reactions generate the Iboga (70) and (71), and Vincadifformine-type (72) skeleta respectively. These results are summarised in figure 14. The isolation of both coronaridine (70) and dihydrocatharanthine (71) from the transannular cyclisation of (69) is not unexpected since this iminium intermediate could isomerise to an enamine bearing a double bond between the C-4 and C-5 positions.

Several interesting conclusions may be drawn from a consideration of the stereochemistry of these transannular cyclisations. It was felt that these reactions would proceed in a completely stereoselective manner since the folding of the nine-membered ring intermediates would necessarily provide rigid cyclisation products of unique stereochemistry. In fact, this has been borne out in the cyclisations of (-)-quebrachamine (1)

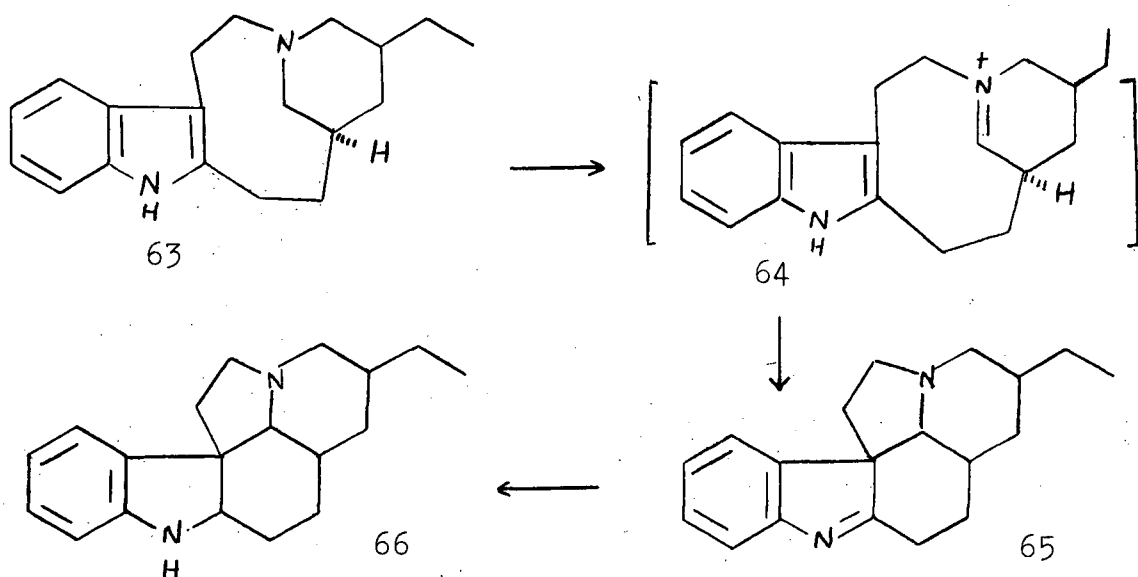


Figure 13. Transannular Cyclisation of Dihydrocleavamine.

to optically active (+)-aspidospermidine (72)<sup>37, 38, ,</sup>  
figure 15.

Since the absolute configuration of the lone asymmetric centre in cleavamine had been determined by x-ray analysis<sup>39</sup>, the absolute configuration at this centre remains the same in dihydrocleavamine (63). If, as is to be expected, the configuration of this position remains unaltered in the cyclisation process to provide the Iboga skeleton, the absolute configuration of this position in the Iboga alkaloids may be assigned. With this evidence there is only one conformation which allows the C-18 and C-5 to come into reasonable proximity for bond formation and in this conformation the C-2-19-N-bridge is  $\alpha$ -oriented. Thus the bridge in the rigid Iboga system will have an  $\alpha$ -orientation and not a  $\beta$ -orientation as suggested by previous workers. The correct absolute configuration<sup>40</sup>

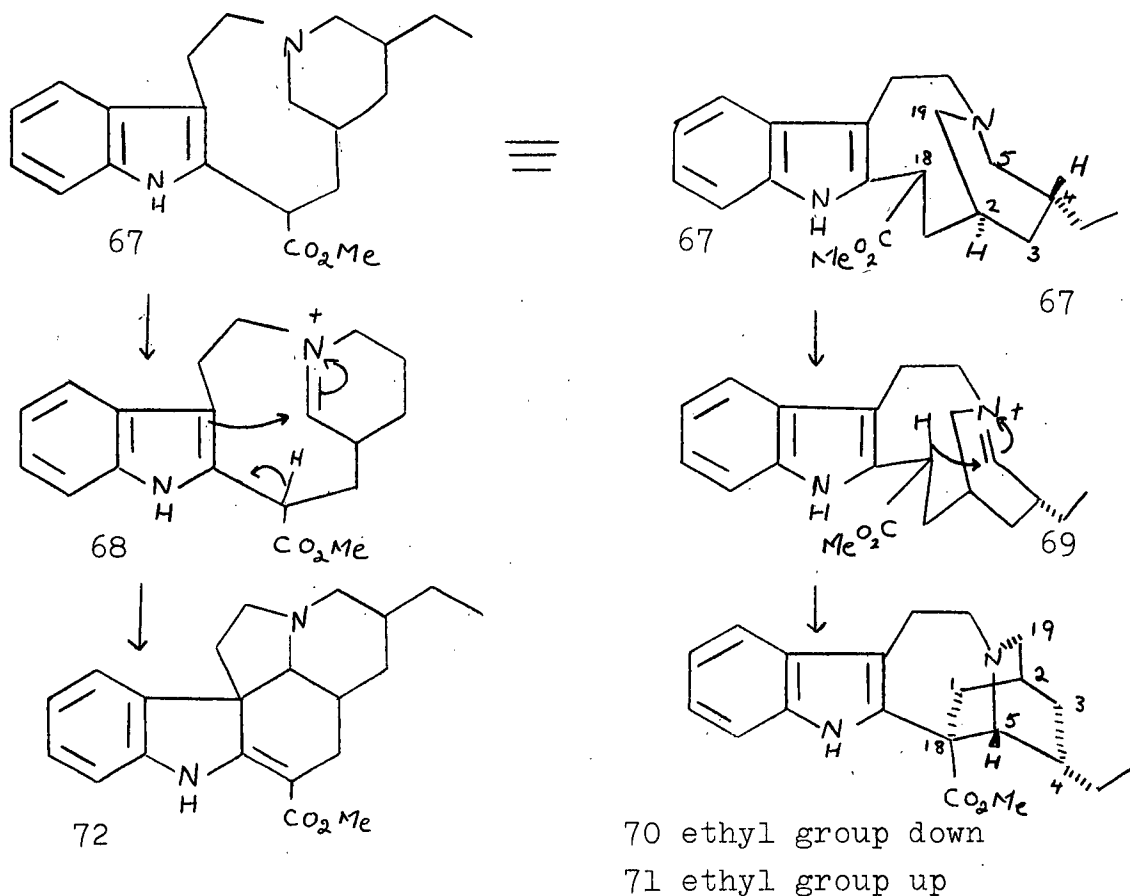


Figure 14. Transannular Cyclisation of Carbomethoxy-dihydrocleavamine.

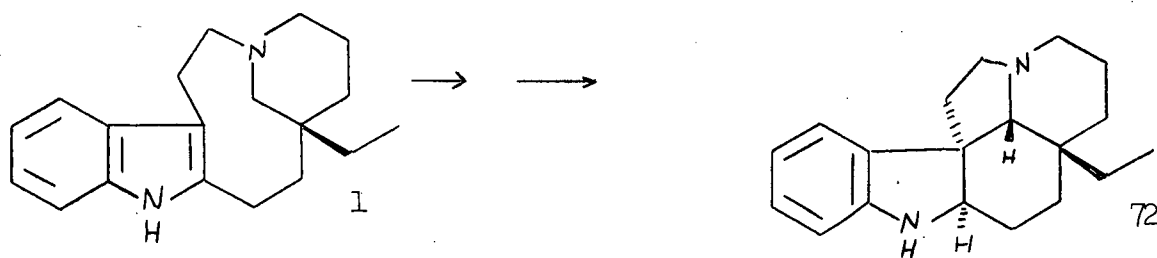


Figure 15. Transannular Cyclisation of (-)-Quebrachamine.

for the Iboga family is represented by structures (70) and (71).

Since all of these transannular cyclisations made possible the interconversion and interrelation of the important and

widespread groups of Vinca, Aspidosperma and Iboga alkaloids, considerable attention was then directed to the synthesis of compounds like quebrachamine (1), dihydrocleavamine (63) and carbomethoxydihydrocleavamine (67). It is particularly noteworthy in this connection that the bridgehead asymmetric centre in quebrachamine (1) dihydrocleavamine (63) and carbomethoxydihydrocleavamine (67) directs the steric course of the cyclisation products. Hence a synthetic scheme involving the transannular cyclisation as the penultimate step does not require special consideration of the stereochemistry of the intermediates in the sequence.

In this thesis the total synthesis of (dl)-quebrachamine (1) is described by a synthetic sequence which is completely general in its application to the preparation of nine-membered ring systems. In fact (dl)-dihydrocleavamine (63) has also been synthesised by an analogous sequence<sup>41, 52</sup>.

### (iii) Previous Synthetic Approaches

First of all it is appropriate to describe some recent work which presents successful synthesis of some Aspidosperma and Iboga alkaloids.

The first total synthesis of dl-aspidospermine (73) and (dl)-quebrachamine (1) was achieved by Stork<sup>42</sup>, figure 16. It is interesting to note that the tricyclic amide (75) in the Fischer indole synthesis with o-methoxyphenylhydrazine gave only indolic material showing that enolisation, even under equilibrating conditions, proceeds away from the ring junction. This is due to the fact that enolisation in the desired

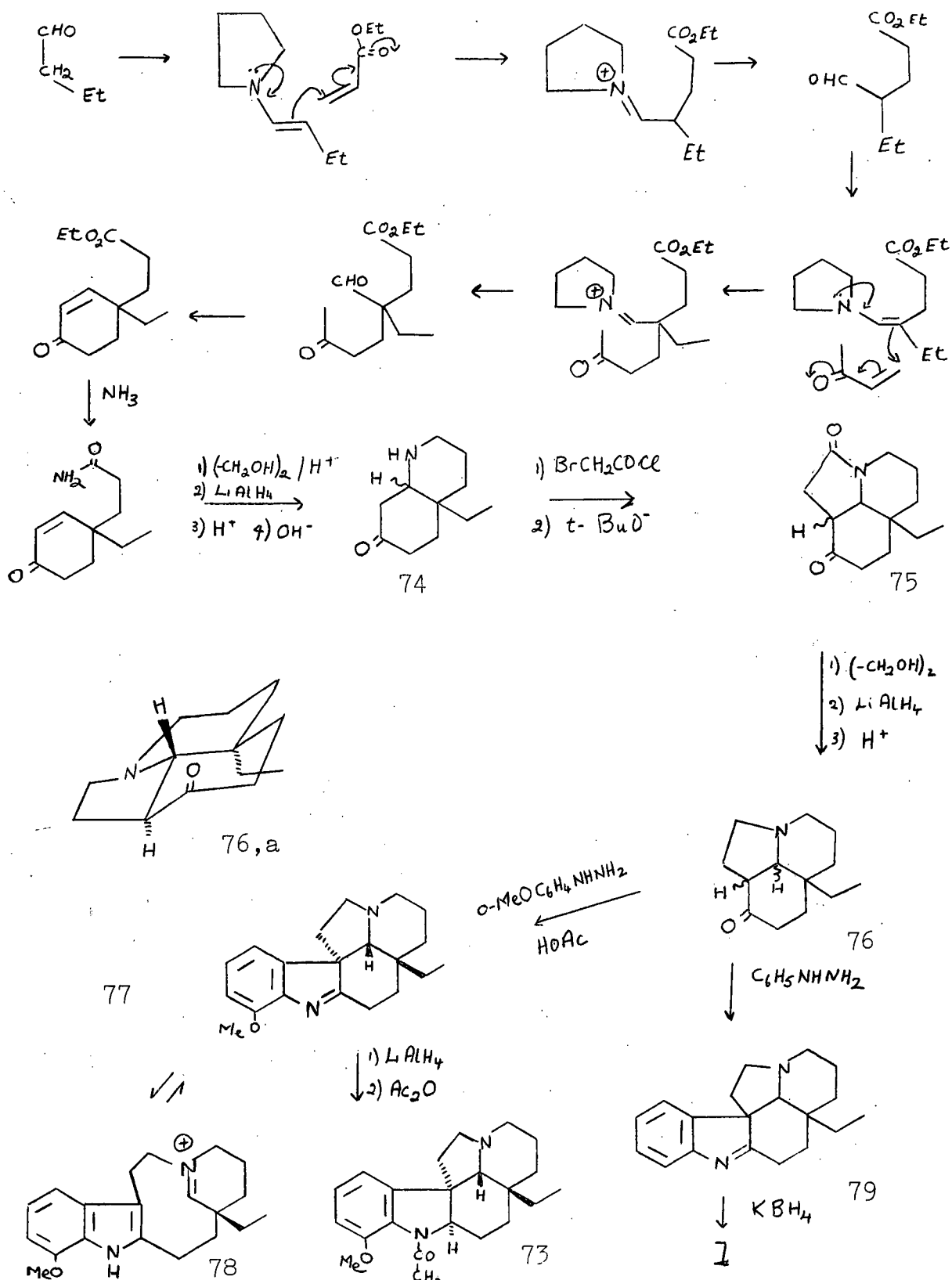


Figure 16. Stork's Synthesis of (dl)-Quebrachamine and (dl)-Aspidospermine.

direction would result in a strained five-membered ring containing three trigonal atoms. The product of reduction of this keto amide (75) contains only one trigonal atom, and the Fischer synthesis with this compound yielded an indolenine which was the dl-form of 1,2-dehydrodeacetylaspidospermine (77). The fact that this product had the correct stereochemistry derives from the equilibration of the asymmetric centres at C-12 and C-19 by the reversible conversion to (dl)-78 during the Fischer synthesis, (77) being the most stable isomer. Lithium aluminum hydride reduction of (77) introduces the hydrogen on the desired side of the molecule. Cyclisation of the phenylhydrazone of (76) leads to (79) which by reductive cleavage with potassium borohydride gives (dl)-quebrachamine (1).

Several possible routes toward the synthesis of aspidospermine (73) have been investigated by Ban<sup>43</sup>. One of these (figure 17) reached the intermediate (80) which has the same planar structure as the corresponding intermediate (74) of Stork's sequence. Although these differed stereochemically, Ban was able to prepare (dl)-aspidospermine (73) by subjecting (80) to the same sequence of reactions as those carried out in Stork's synthesis. This finding supports the equilibration  $(77) \rightleftharpoons (78)$  suggested by Stork.

In a recent communication Kuehne<sup>44</sup> describes the synthesis of the key tricyclic keto-amine (81 or 76) with stereochemistry (82a) and (82b) by a completely different route (figure 18) from that of Stork and Ban. The stereochemistry of Stork's and Ban's keto-amines are shown by (76a) and (81a).



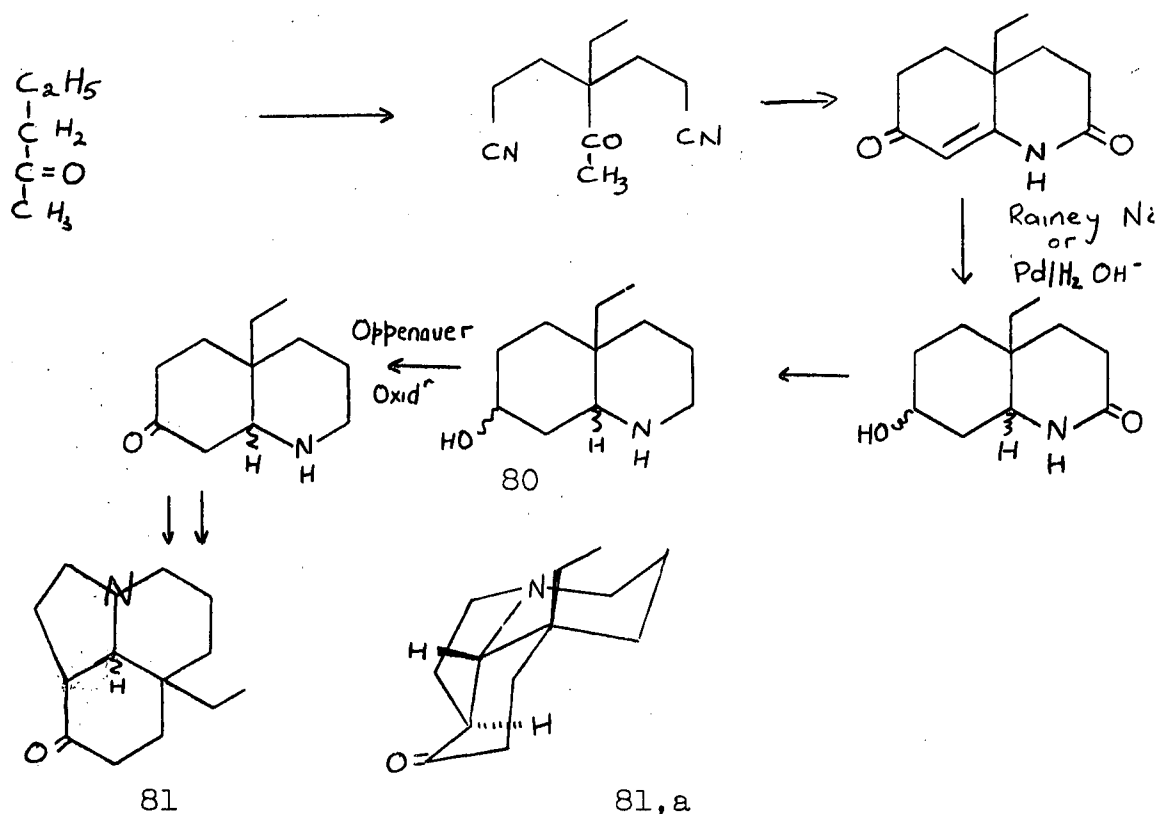


Figure 17. Ban's Synthesis of (dl)-Aspidospermine.

A successful, stereochemically controlled synthesis of the tetracyclic indole (83) by Salley<sup>45</sup> suggested a feasible pathway to the synthesis of the Iboga skeleton. The cis- and trans- fused C/D rings of (83) were constructed from the corresponding enedione (84) as outlined in figure 19. It is interesting to note that the cis-ketaloxime (85) rearranges spontaneously to the cis-lactamketal (86) whereas the trans-epimer rearranges more slowly. This is believed to be due to the coplanarity of the participating centres. The formation of the "isolactam" (87) during ring expansion has been excluded. Because the Beckmann rearrangement proceeds with anti-migration<sup>46</sup>, the structure of the two lactams (86) in retrospect, verified the anti-stereochemistry of both oximes (85).

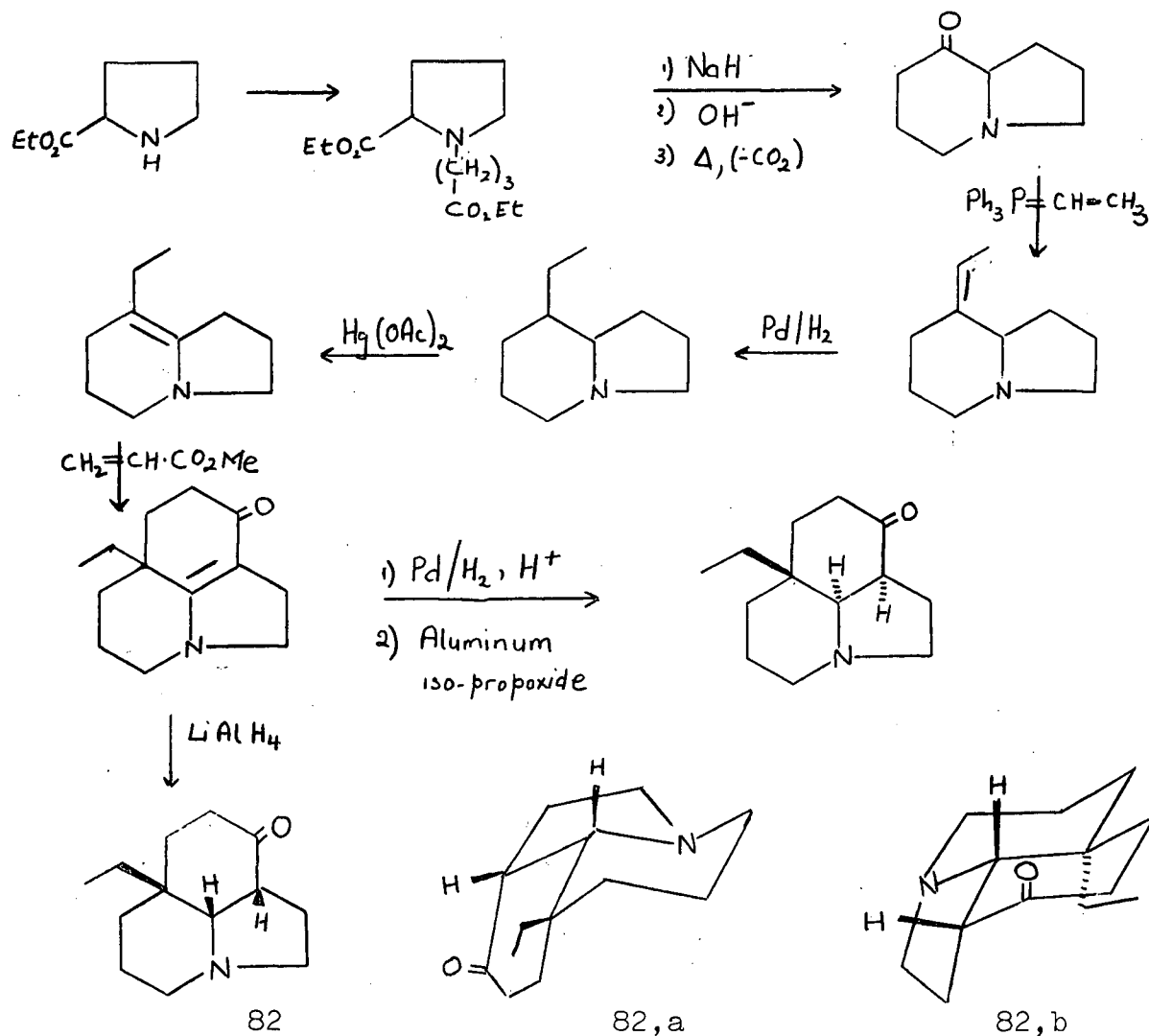


Figure 18. Kuehne's Synthesis of the Tricyclic Keto-Amine.

The first total synthesis of an Iboga alkaloid (dl)-ibogamine (88) and (dl)-epiibogamine (89) was accomplished by Buchi<sup>47</sup>. In the above mentioned synthesis the indole portion is fused via a Fischer indole synthesis, onto a suitable intermediate containing the rings C, D and E, figure 20.

Concurrently with Buchi's synthesis, Huffman<sup>48</sup> reported the synthesis of desethylibogamine (91). In addition to providing a new pathway to the Iboga skeleton, this synthesis

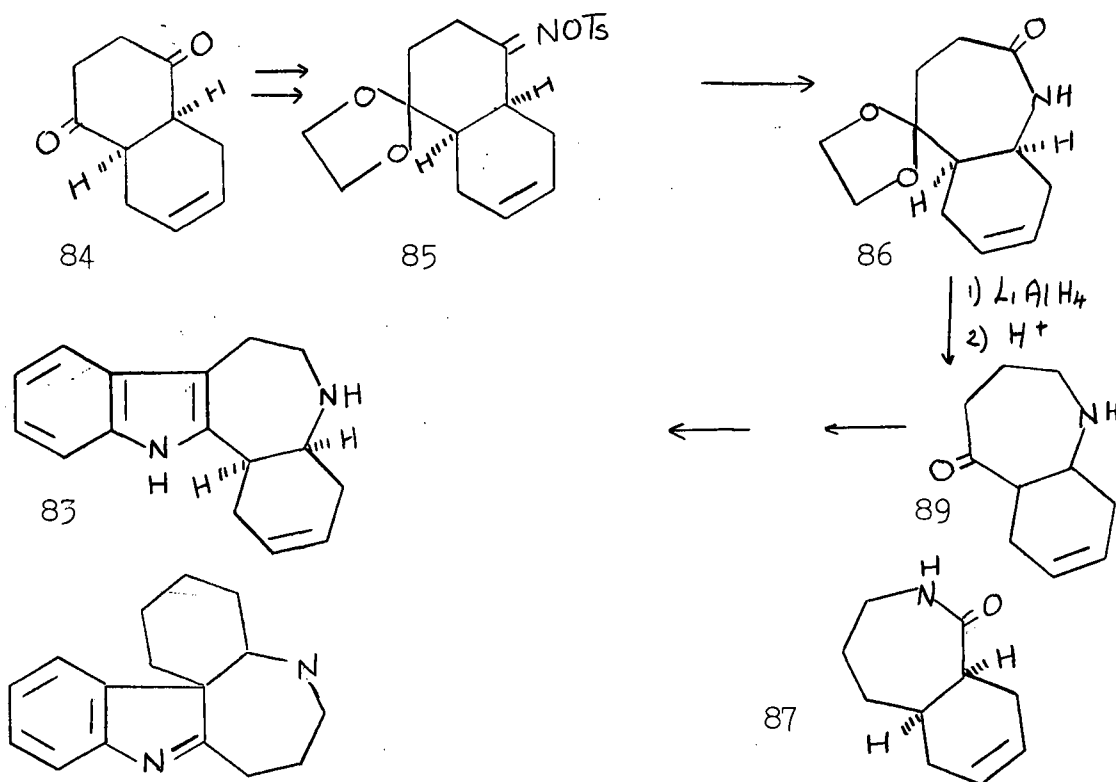
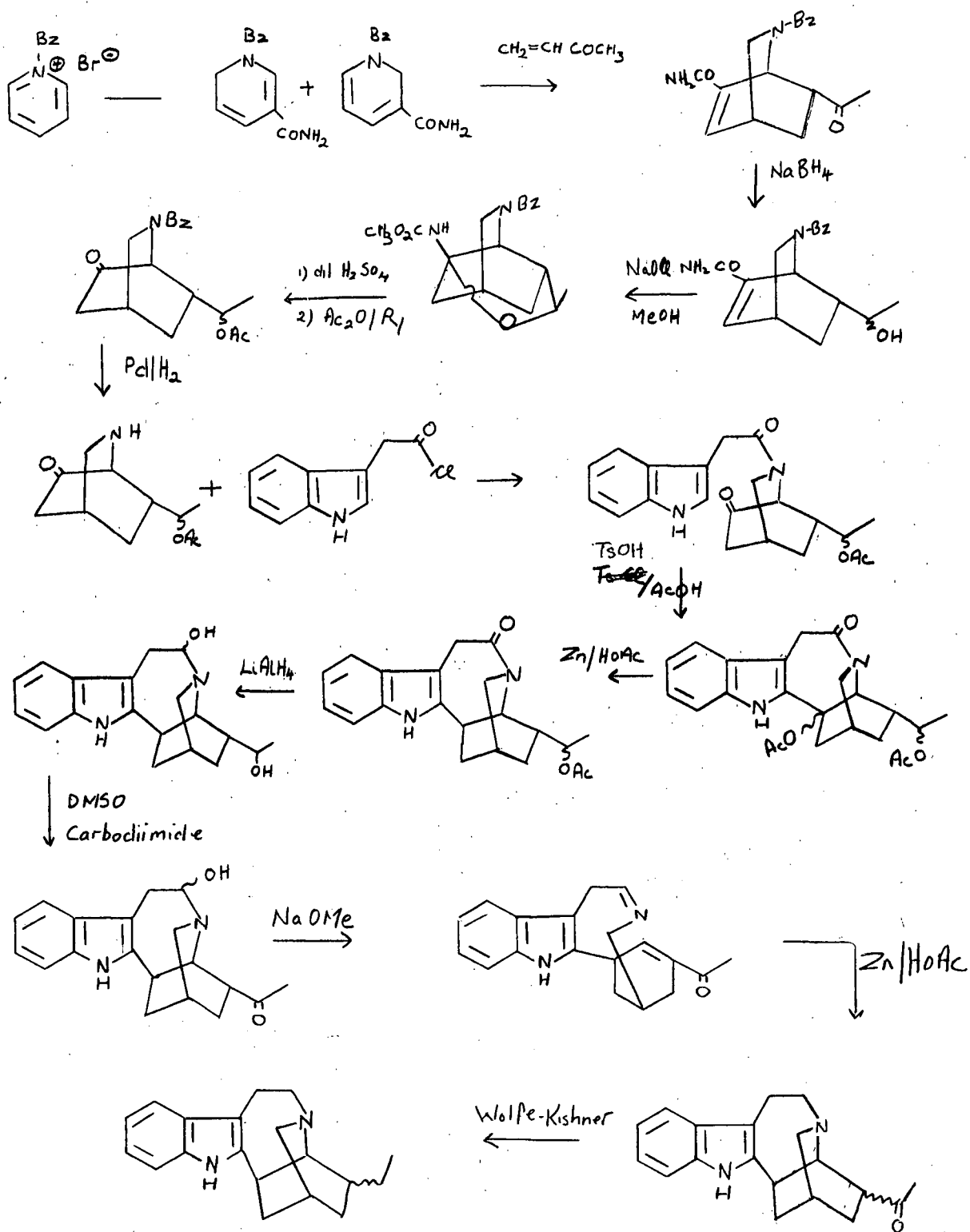


Figure 19. Salley's Approach to the Synthesis of the Iboga Skeleton.

constitutes a new preparation of isoquinuclidines, figure 21.

Recently Harley-Mason<sup>49</sup> synthesised (dl)-eburnamine (93) and (dl)-3-methylaspidospermine (94) from a common intermediate (95) which resembles the intermediate (44b) described in the Wenkert-Thomas hypothesis, figure 7. This sequence is summarised in figure 22.

Very shortly after our work was published<sup>50</sup>, Harley-Mason<sup>51</sup> reported the total synthesis of  $\alpha$ - and  $\beta$ - (dl)-dihydrocleavamine (63) by a sequence similar to ours. The formation of the  $\beta$ -carboline system was accomplished via a Pictet-Spengler<sup>52</sup> condensation of tryptamine and the aldehyde triester (96). His sequence is summarised in figure 23.



88, ethyl group up

89, ethyl group down

Figure 20. Buchi's Synthesis of (dl)-Ibogamine and (dl)-Epiibogamine.

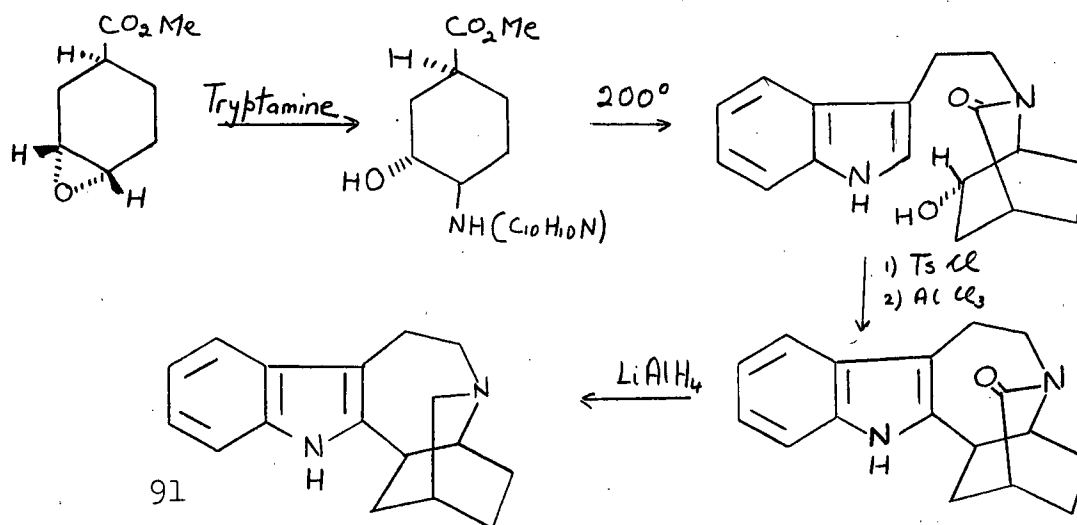


Figure 21. Huffman's Synthesis of Desethylbogamine.

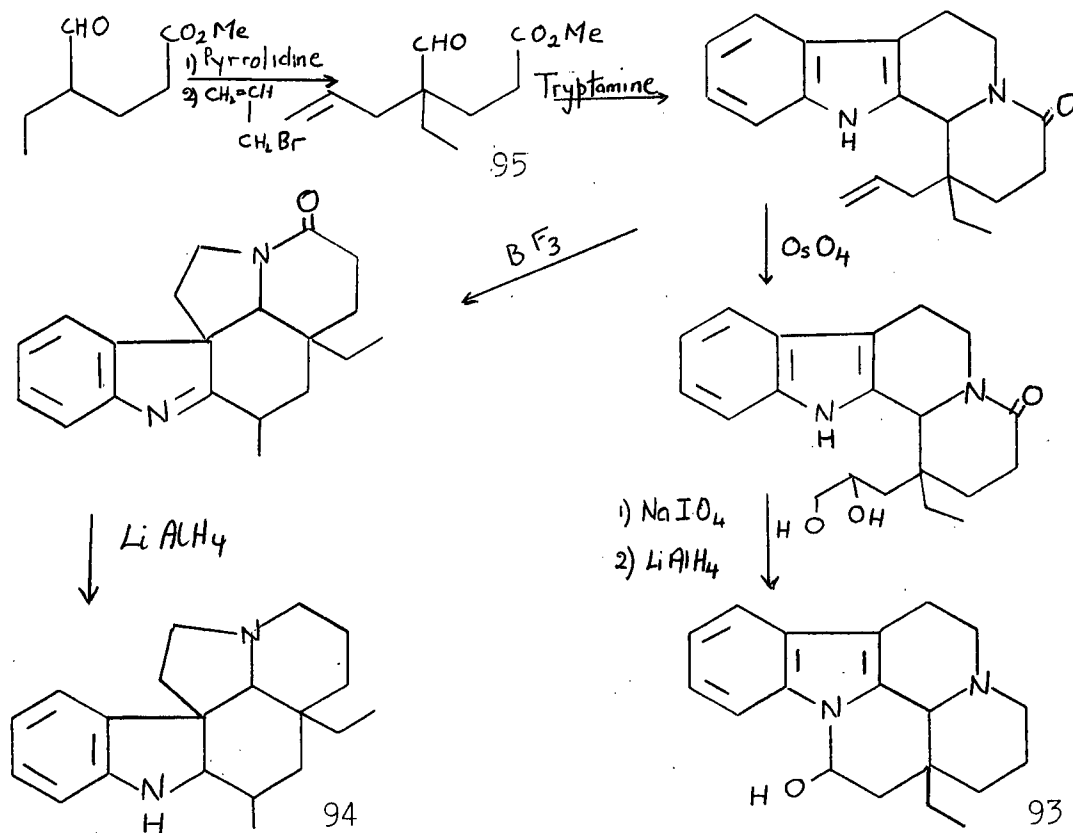
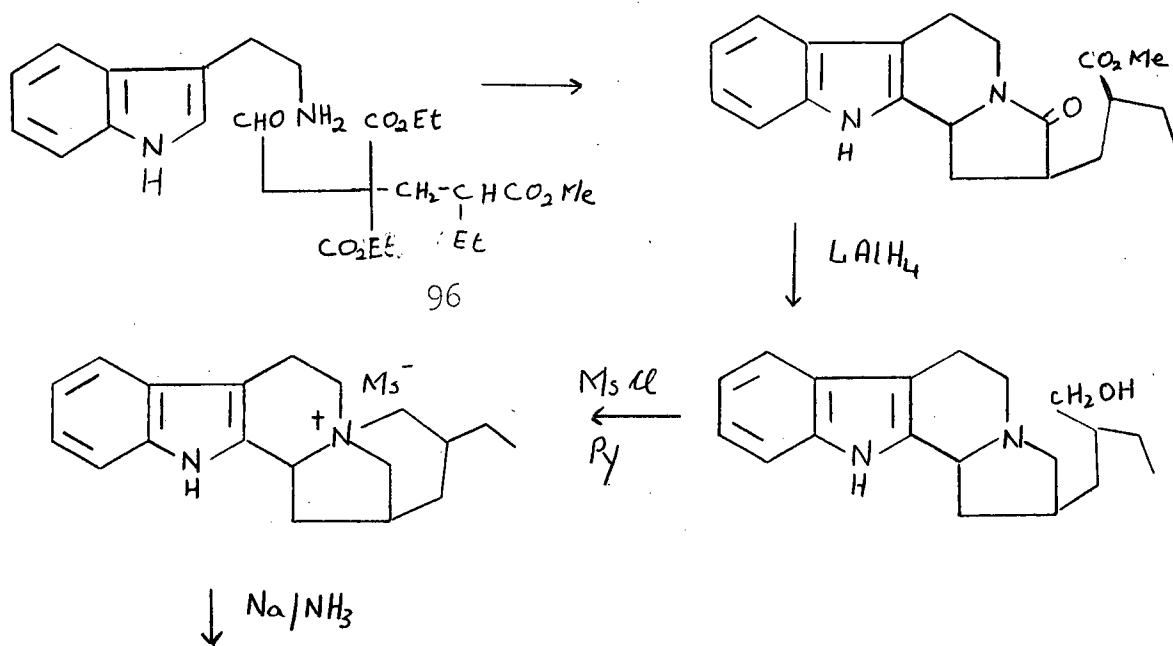


Figure 22. Harley-Mason's Synthesis of (dl)-Eburnamine and (dl)-3-Methylaspidospermine.



Dihydrocleavamine

Figure 23. Harley-Mason's Synthesis of  $\alpha$ - and  $\beta$ -(dl)-dihydrocleavamine.

## DISCUSSION

As already mentioned the transannular cyclisation reactions of nine-membered ring compounds like quebrachamine, dihydrocleavamine and their derivatives provide an attractive synthetic entry into the Aspidosperma, Vinca and Iboga series. In this thesis are described two approaches to the total synthesis of the nine-membered ring alkaloid, quebrachamine. In the first approach, which will be referred to as scheme A, a suitably substituted piperidine moiety is fused to a  $\beta$ -ethylindole derivative, and the formation of the nine-membered ring is envisaged as proceeding via an acyloin condensation, figure 24. In the other approach, scheme B, the nine-membered ring and the piperidine ring are generated simultaneously by a reductive ring cleavage, figure 25.

### I. Scheme A

The first step of this synthetic sequence involves the preparation of the indole derivative (97) and the piperidine derivative (98) which are coupled together to give the intermediate diester (99). Attempts to cyclise this ester under acyloin condensation<sup>53</sup> conditions to generate the nine-membered ring intermediate (100) are described.

It is first appropriate to discuss some preliminary investigations<sup>54,a</sup> in this laboratory which were directed toward the synthesis of intermediate like (99), viz., (104) and (107).

A Reissert synthesis, figure 26, was used to prepare 2-carbomethoxyindole (101), which was heated with

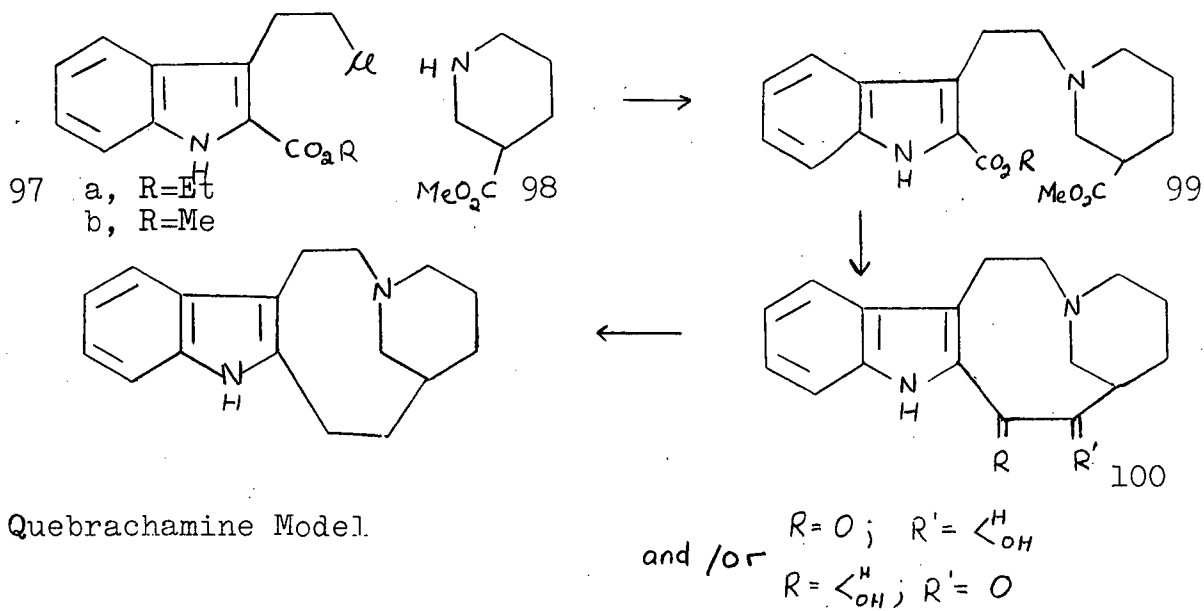


Figure 24. General Outline of Scheme A.

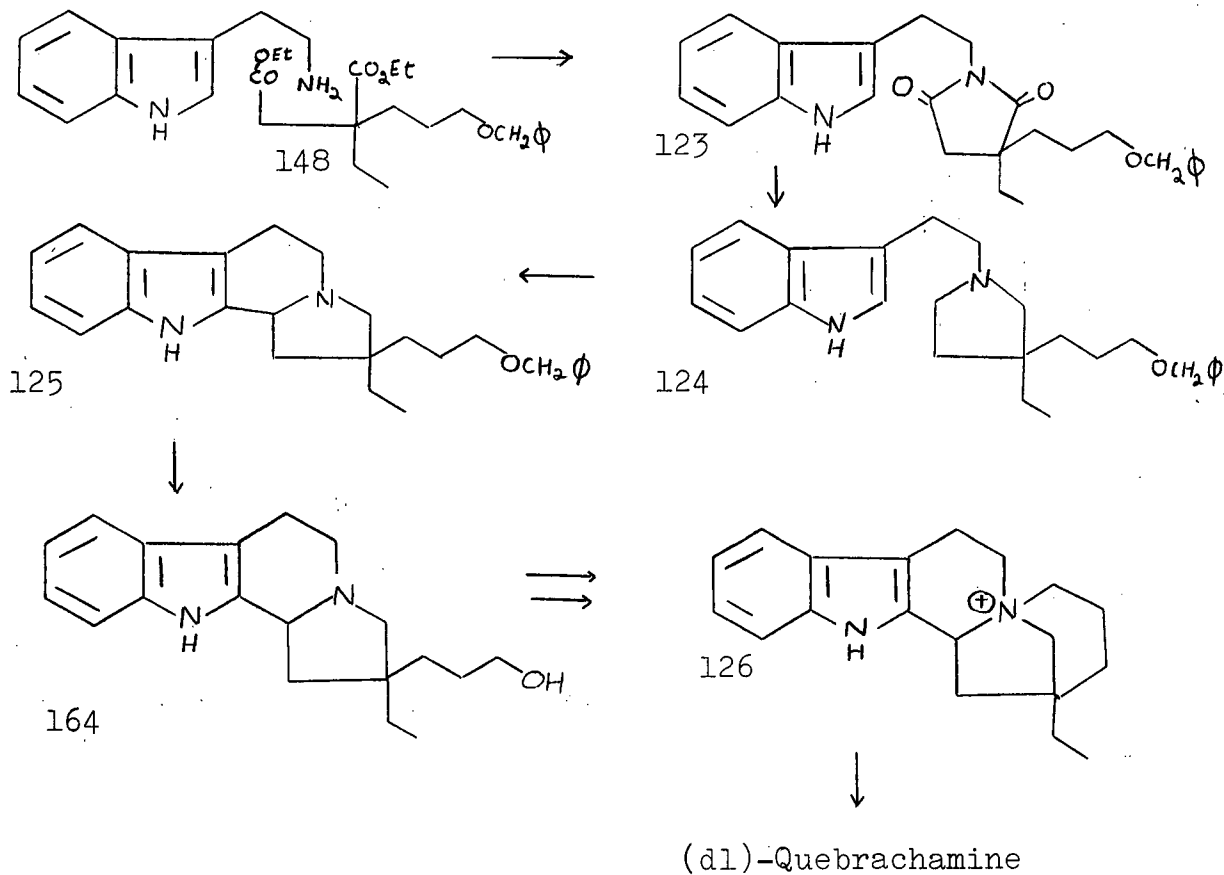


Figure 25. General Outline of Scheme B.



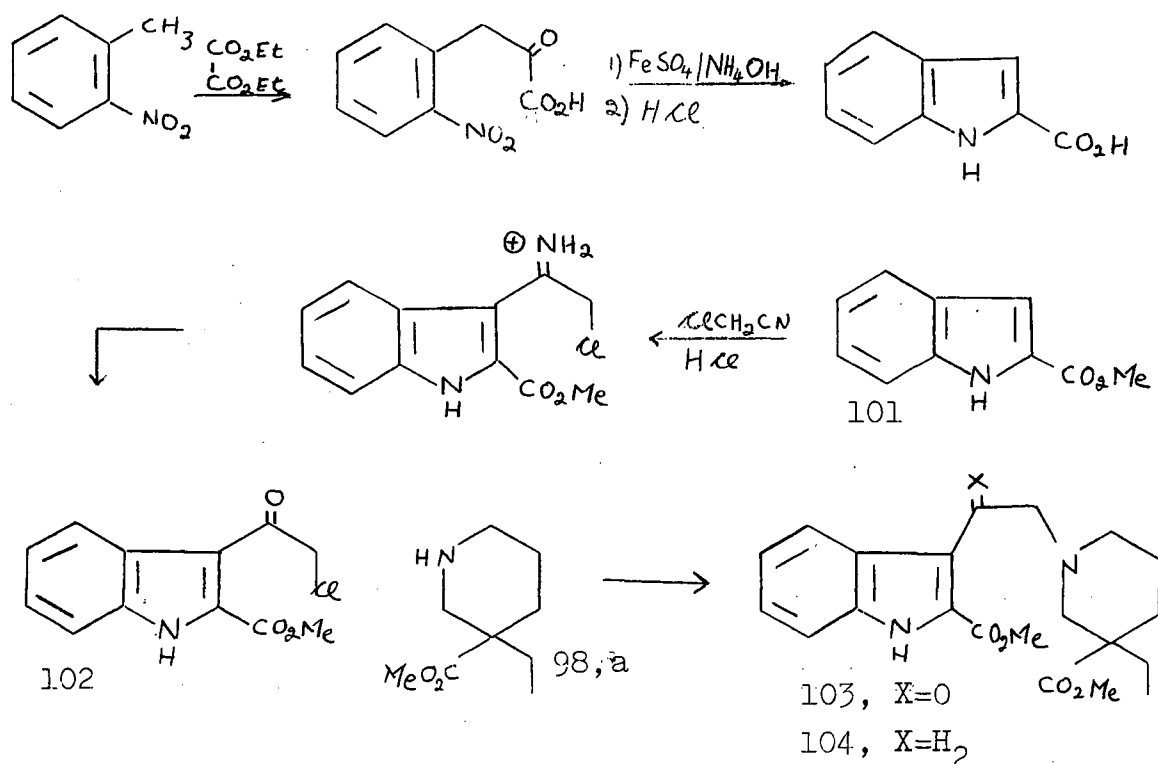


Figure 26.

chloroacetonitrile in a Hoesch reaction<sup>55</sup> to give 2-carbomethoxy-3-chloroacetylindole (102). Alkylation of this indole (102) with the piperidine (98,a) gave the expected diester ketone intermediate (103). Attempts to reduce this ketonic function catalytically or with metal hydrides to give the diester (104) required for acyloin condensation were unsuccessful.

A related intermediate (107) was sought as a desirable model to investigate the utility of Dieckmann-type cyclisation in this series. It's synthesis is outlined in figure 27. The indole-2-acetic acid prepared by the published procedure<sup>56</sup>, was subjected to a Hoesch reaction with chloroacetonitrile to give 3-chloroacetylindole-2-acetic acid methyl ester (105).

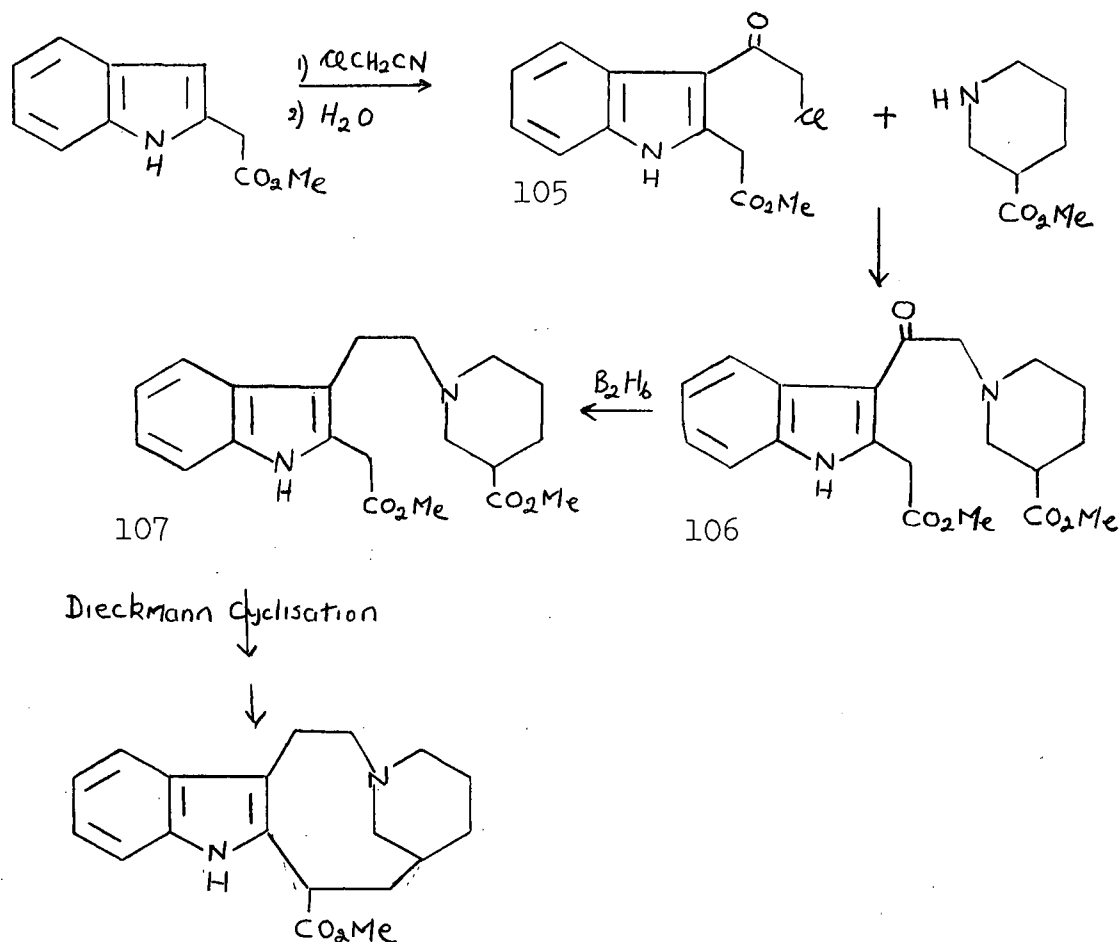


Figure 27.

Alkylation of this compound with 3-carbomethoxypiperidine (98) yielded the expected intermediate (106). Attempts to remove the ketonic oxygen function in (106) by conventional procedures were also unsuccessful in this case. However, the diester (107) was eventually obtained by the treatment of (106) with diborane in dry tetrahydrofuran at  $0^\circ\text{C}$ .

#### (i) Synthesis of the Indole Moiety

In view of the difficulty experienced in the removal of the oxygen function in the  $\beta$ -ethylindole side chain of (103),

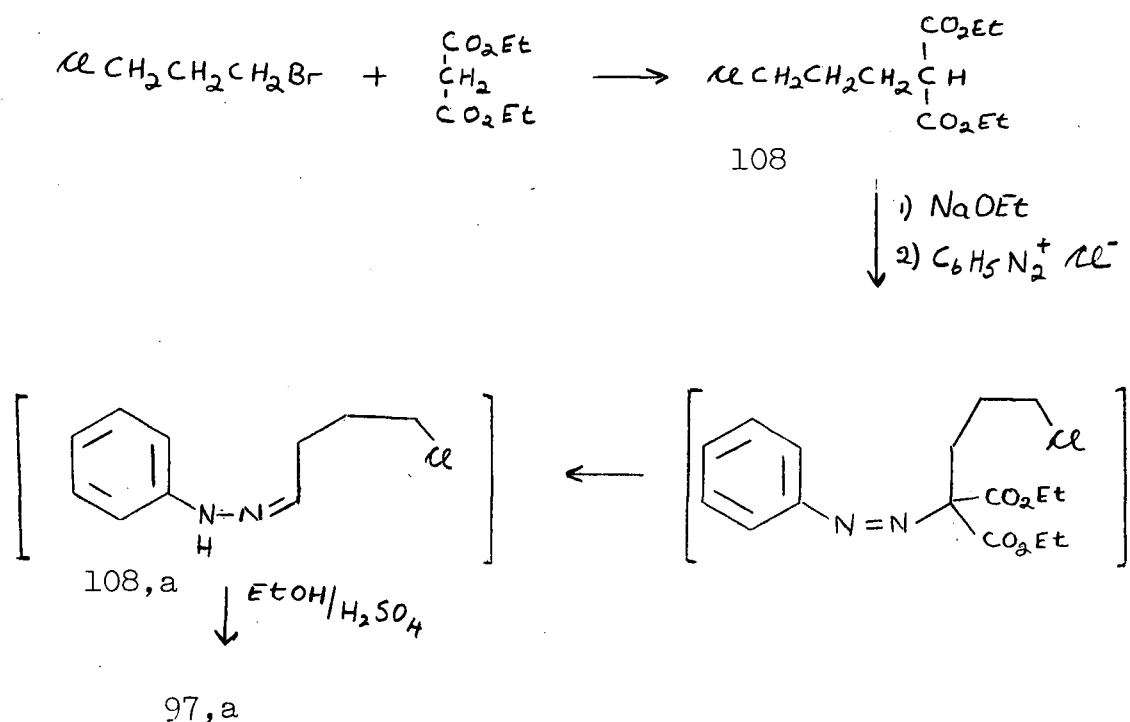


Figure 28. Synthesis of the Indole Moiety (97,a).

we turned our attention to the synthesis of 2-carboethoxy-3-( $\beta$ -chloroethyl)-indole (97,a). A convenient method for the preparation of esters of substituted indole-2-carboxylic acids is the Fischer indole<sup>57</sup> synthesis, which involves the cyclisation of an arylhydrazone of an  $\alpha$ -keto ester with a proton acid, or a Lewis acid as catalyst. The most convenient method for preparing arylhydrazones of  $\alpha$ -keto esters is the Japp-Klingeman reaction<sup>58</sup>. This process consists initially of an electrophilic attack of an aryldiazonium cation on the anionic carbon atom of an active methinyl compound to give an azo-intermediate. The latter compound, under the conditions of the coupling reaction ordinarily undergo hydrolysis with expulsion of one of the original carbon substituents to give

an arylhydrazone. Our approach to the preparation of (97,a) is outlined in figure 28.

The diethyl  $\gamma$ -chloropropylmalonate (108) was prepared<sup>59</sup> in a 70% yield by treating the monosodium salt of diethylmalonate with 1,3-chlorobromopropane. Attempted condensation of the sodium salt of (108) with benzene diazonium chloride<sup>60-62</sup> led to the recovery of the starting material (108). Since the lack of reaction may be due to the regeneration of the starting material in aqueous media we decided to carry out the Japp-Klingemann reaction under anhydrous conditions. For this purpose anhydrous benzene diazonium chloride<sup>63</sup> was reacted with an alcoholic solution of the sodium salt of (108) at 0°C. The reaction mixture was allowed to stand overnight in the refrigerator and the crude reaction product subjected to a Fischer indole synthesis using sulfuric acid as the catalyst. Purification of the reaction product by chromatography on aluminum resulted in a 50% recovery of the starting material (108) and also a new crystalline product whose elemental analysis suggested a formula,  $C_{13}H_{14}NO_2Cl$ . The ultraviolet spectrum showed the typical absorption of an indole-2-carboxylic ester ( $\lambda_{max}$  296 m $\mu$ ) while the infrared spectrum had sharp bands at 3250  $cm^{-1}$  ( $-NH$ ) and at 1670  $cm^{-1}$  ( $-COOEt$ ). The NMR spectrum (figure 29) showed the normal multiplet centred at  $\tau$ 2.60 for the aromatic protons on the indole nucleus, a two-proton quartet at  $\tau$ 5.54 ( $-COOCH_2CH_3$ ), a four proton multiplet at  $\tau$ 6.50 ( $-CH_2CH_2Cl$ ) and a three-proton triplet at  $\tau$ 8.60 ( $-COOCH_2CH_3$ ). These spectral data were in complete agreement with the structure (97,a).

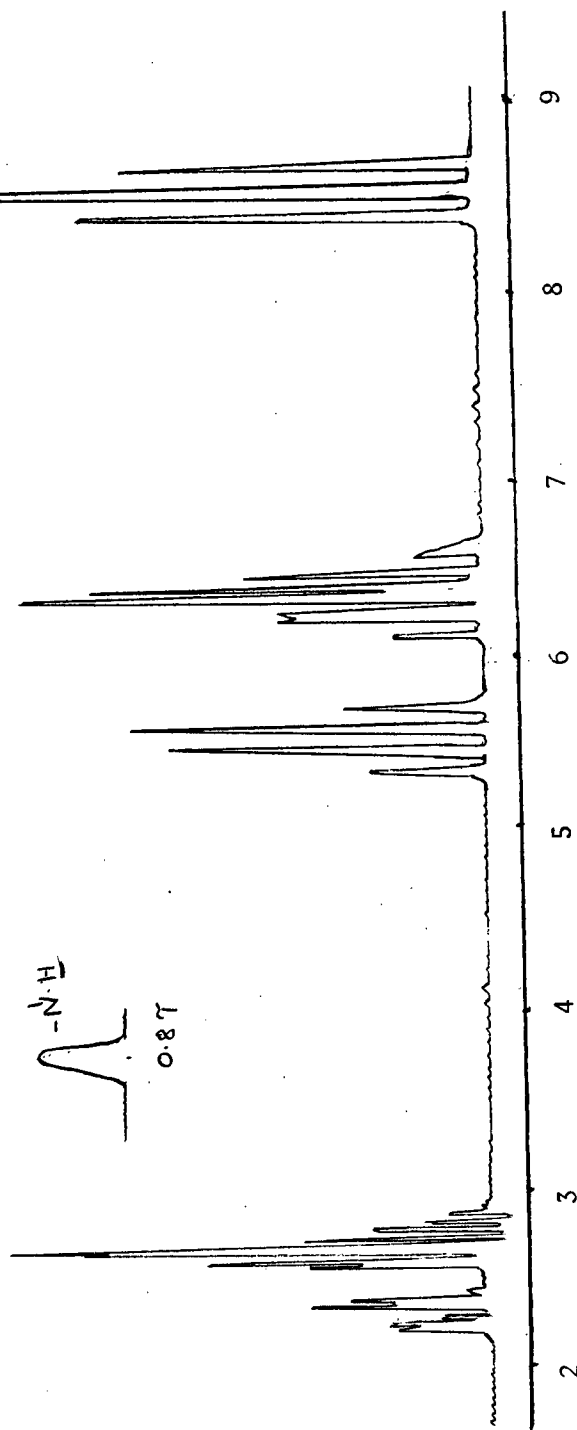
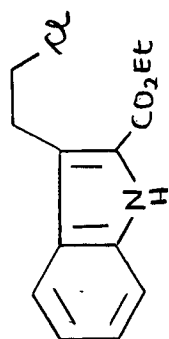


Figure 29

(ii) Synthesis of the Piperidine Moiety

Next we turned our attention to the synthesis of the piperidine derivative required for this sequence. Difficulties encountered by other investigators<sup>54, b</sup> in this laboratory in the preparation of 3-carbomethoxy-3-ethylpiperidine (98, a) led us to carry out model reactions with a readily available piperidine. As the model compound we selected 3-carbomethoxy-piperidine (98) which was synthesised by three different routes, as shown in figure 30.

In sequence (a), nicotinic acid (109) was converted to its ester by reaction with methanol and concentrated sulfuric acid<sup>64</sup>. However, the reduction of methyl nicotinate (110) with platinum oxide in glacial acetic acid<sup>65</sup> provided the desired methyl nipecotate (98) in a low yield, and we therefore sought methods of preparing nipecotic acid (111) which on esterification would yield the desired material.

A straight forward catalytic reduction (rhodium catalyst) of nicotinic acid uncomplicated by hydrogenolytic decarboxylation has been recently reported by Freifelder<sup>66</sup>. Following his procedure we prepared (sequence, b) nipecotic acid (111) in 80% yield and the latter on esterification with diazomethane gave two compounds, which could not be separated by chromatography or fractional distillation. The infrared spectrum of this mixture showed absorption bands at  $3230\text{ cm}^{-1}$  and  $1710\text{ cm}^{-1}$  corresponding to the ( $-\overset{|}{\text{NH}}$ ) and the ( $-\text{COOMe}$ ) groups respectively. The ultraviolet spectrum had no absorption above 230 m $\mu$ , suggesting that neight product arose from incomplete hydrogenation. Apart from the sharp singlet at  $\tau 6.40$  ( $-\text{COOCH}_3$ ) the NMR spectrum was complex.

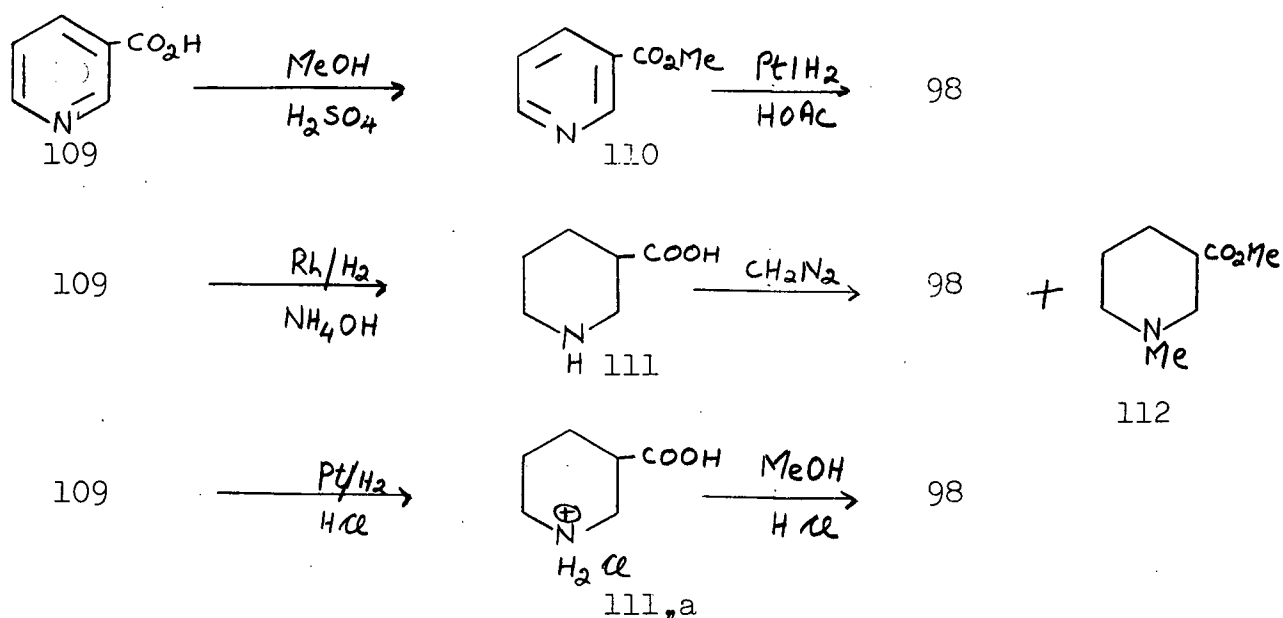


Figure 30. Synthesis of 3-Carbomethoxypiperidine.

At this time a crude sample of nipecotic acid hydrochloride (111,a) became available. Esterification with methanolic hydrogen chloride (sequence, c) gave a pure sample of 3-carbomethoxypiperidine (98), whose NMR spectrum was very similar to that of the mixture obtained above. The most outstanding difference was the absence of the sharp singlet at  $\tau 7.75$  in the spectrum of the pure sample. This signal could be assigned to the methyl protons of an N-methyl group. We thus felt that the other component of the mixture could be the N-methylated product (112), and being a tertiary amine its presence would not interfere with the coupling reaction. In fact, coupling reaction were carried out using the pure and the impure samples and in each case similar relative results were obtained.

### (iii) Coupling Reactions

Having completed the synthesis of the desired piperidine, we turned our attention to coupling it with the indole moiety (97,a). This could be accomplished by heating a solution of 2-carboethoxy-3-( $\beta$ -chloroethyl)-indole (97,a) and 3-carbomethoxypiperidine (98) in dry dioxane in a sealed tube for 12 hours at 160°C. Chromatography of the crude basic product yielded a crystalline compound whose elemental analysis suggested a formula  $C_{20}H_{26}N_2O_4$ . The infrared spectrum of this solid showed two carbonyl absorption bands at  $1710\text{ cm}^{-1}$  and  $1670\text{ cm}^{-1}$ . Similar bands appear in the infrared spectra of the starting materials (97,a) and (98). The ultraviolet spectrum ( $\lambda_{\text{max}}$  228 and 296 m $\mu$ ) was identical with that of the starting indole (97,a). The NMR spectrum (figure 31) showed a broad one-proton singlet at  $\tau 0.80$  (-NH), the normal four-proton multiplet centred at  $\tau 2.60$  for the aromatic protons on the indole nucleus, a two-proton quartet at  $\tau 5.50$  (-COOCH<sub>2</sub>CH<sub>3</sub>), a sharp three-proton singlet at  $\tau 6.03$  (-COOCH<sub>3</sub>) and a three-proton triplet at  $\tau 8.60$  (-COOCH<sub>2</sub>CH<sub>3</sub>). These spectral data are in complete accord with the proposed structure (99, R=Et).

During the investigation of the acyloin condensation itself, we found it necessary to prepare coupling products having similar ester functions attached to the indole and piperidine portions of the molecule, eg. 99, R=Me. This was done to eliminate difficulties due to ester exchange in the acyloin condensation (see later). For this purpose we prepared 2-carbomethoxy-3-( $\beta$ -chloroethyl)-indole by heating (97,a) with



a large excess of dry methanol in the presence of concentrated sulfuric acid. This reaction could be followed by observing the disappearance in the NMR spectrum of the high field triplet at  $\tau$ 8.60 due to the methyl protons of the ethyl ester. The methyl protons of the methyl ester appeared as a sharp singlet at  $\tau$ 6.06.

The coupling product (99, R=Me) was synthesised by the procedure described for the preparation of (99, R=Et). Although the ultraviolet and infrared spectra of these products were superimposable, they were clearly distinguishable by their NMR spectra, figures 31 and 32.

The crude coupling product could be separated into basic and non-basic fractions. The basic fraction contained the coupling product and the unreacted piperidine. Apart from the unreacted indole derivative, the non-basic fraction, in some instances contained a crystalline by-product. Elemental analysis suggested a formula,  $C_{11}H_9NO_2$ , which was confirmed by a mass spectrometric molecular weight (m/e 187). The ultraviolet spectrum was identical with that of the indole derivative (97,b), while the infrared spectrum contained a carbonyl absorption at  $1690\text{ cm}^{-1}$  characteristic of an  $\alpha\beta$ -unsaturated  $\delta$ -lactone, as well as indole NH absorption at  $3250\text{ cm}^{-1}$ . The NMR spectrum (figure 33) had a broad one-proton absorption at  $\tau$ 0.40 characteristic of the indole NH, the normal four-proton multiplet centred at  $\tau$ 2.60 for the aromatic protons on the indole nucleus, a two-proton triplet at  $\tau$ 5.36 ( $-\text{COOCH}_2\text{CH}_2-$ ) and a two-proton triplet at  $\tau$ 6.90 ( $-\text{COOCH}_2\text{CH}_2-$ ). That these

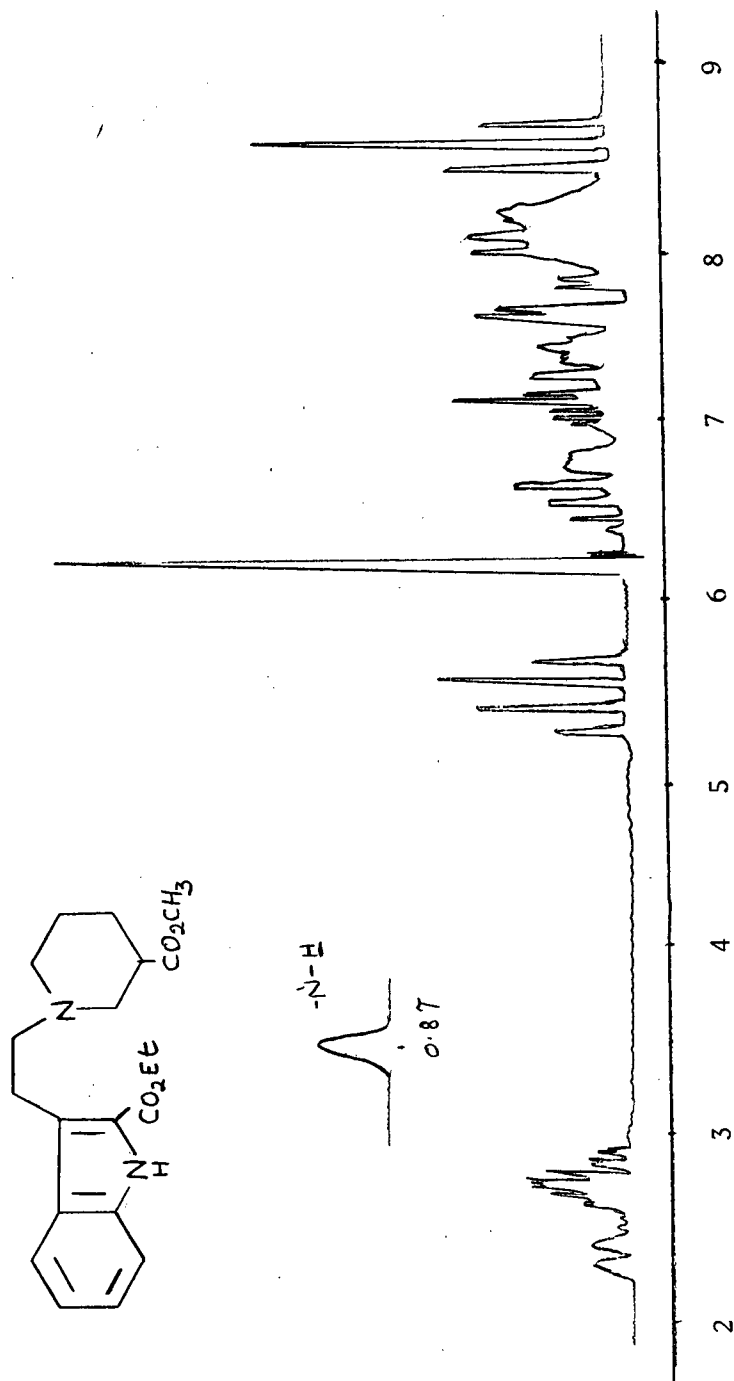


Figure 31

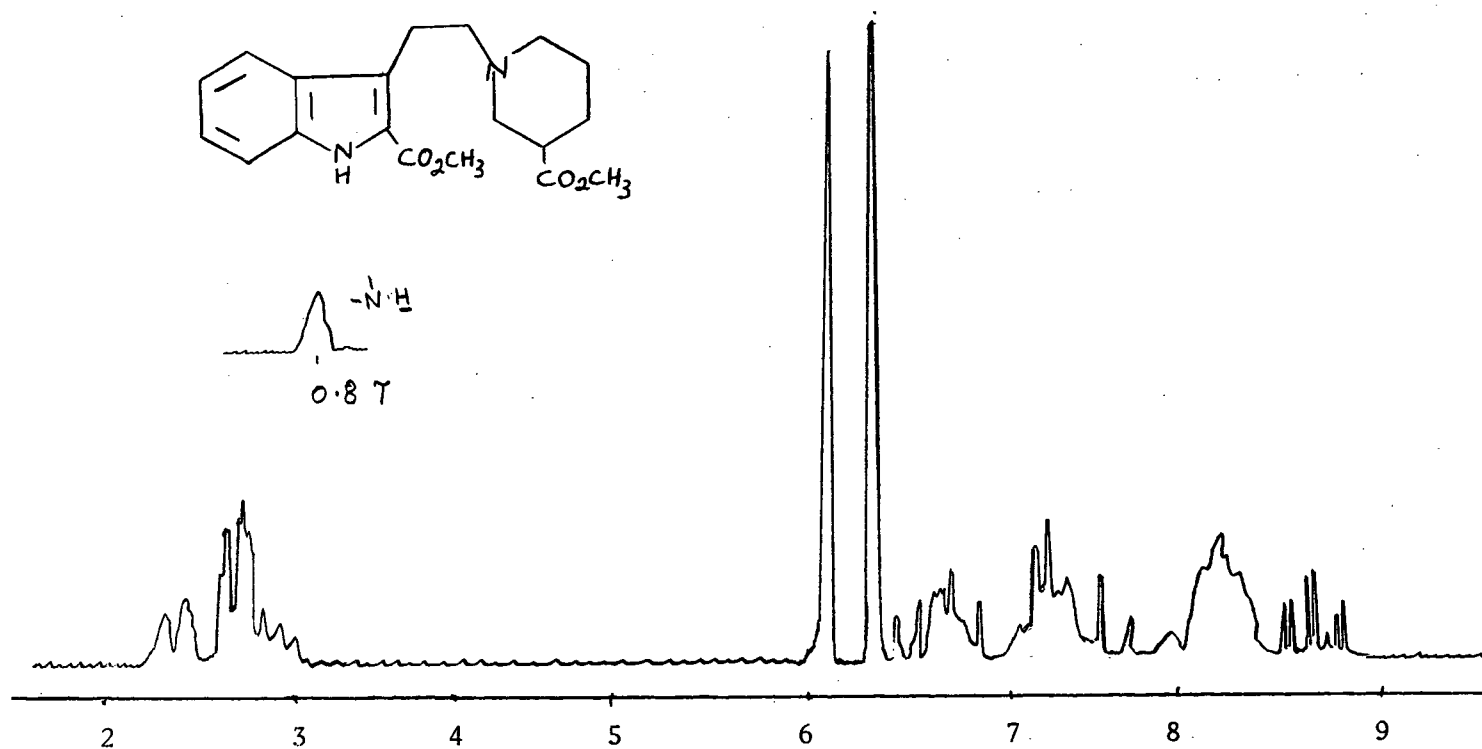


Figure 32

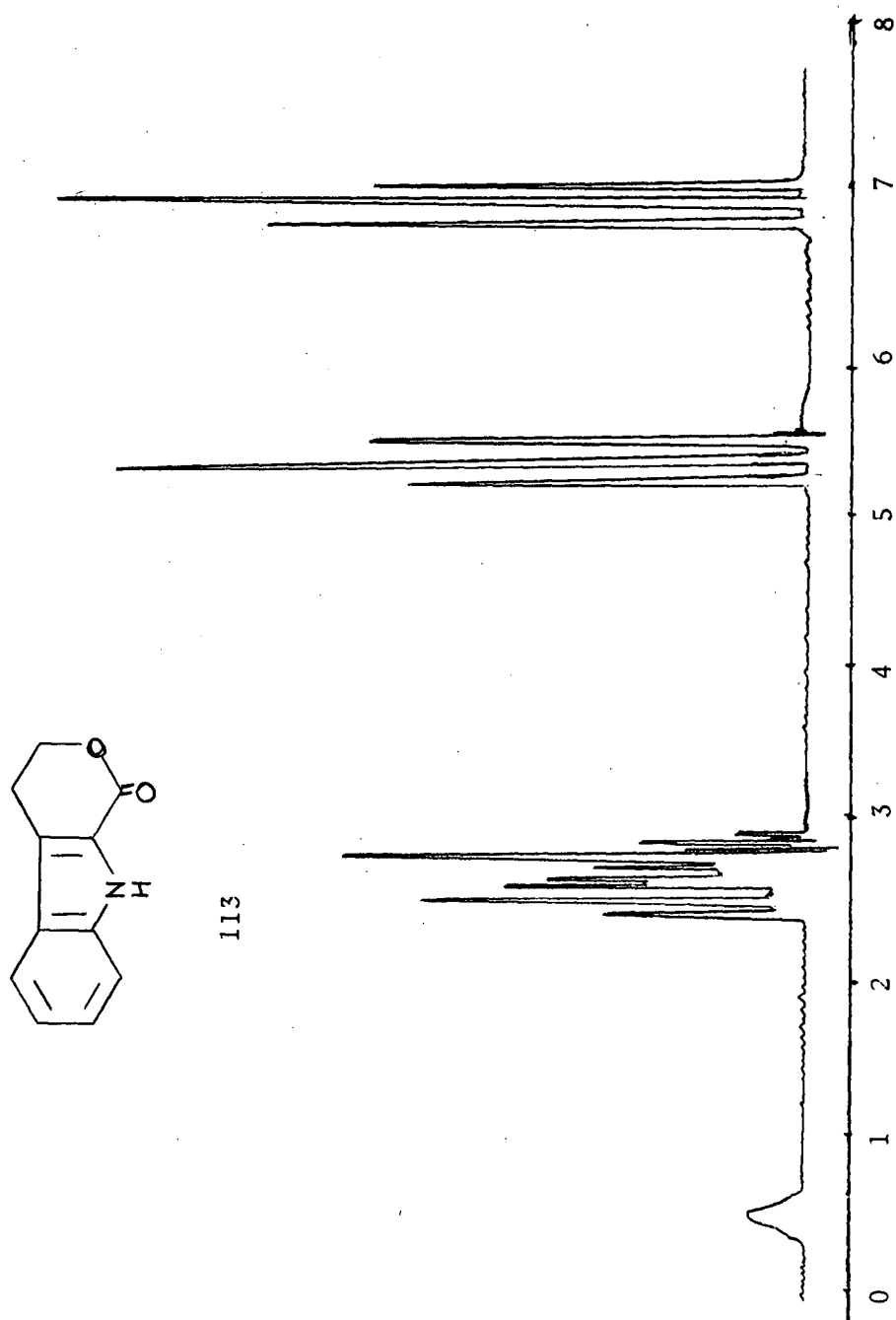


Figure 33

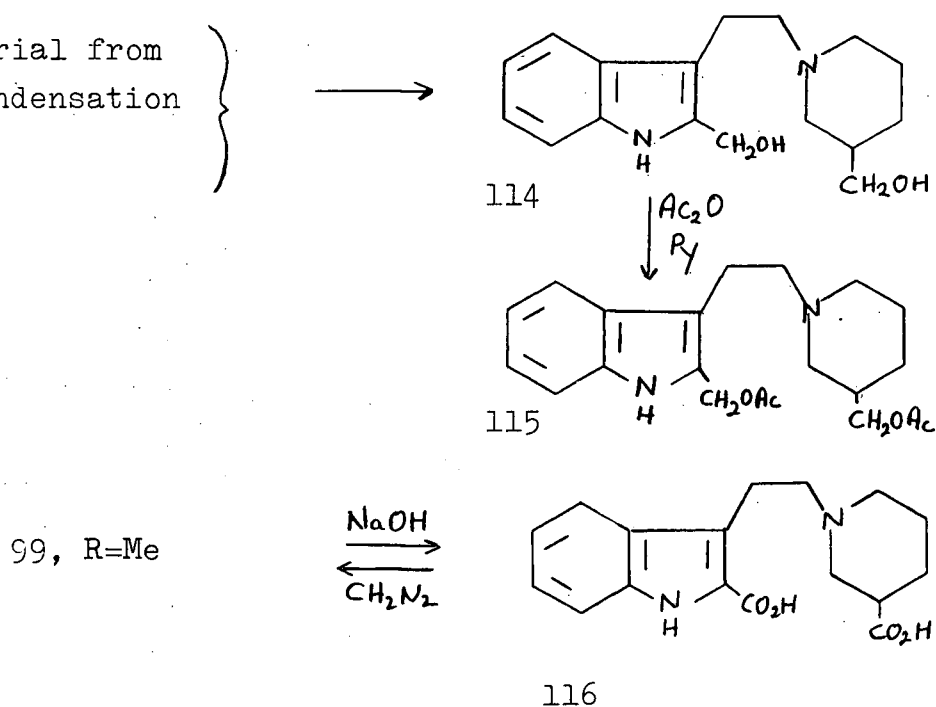
latter four protons are attached to adjacent carbon atoms was established by decoupling experiments. This evidence is in complete agreement with the structure (113).

(iv) Acyloin Condensation

Having prepared the necessary coupling products we next turned out attention to the acyloin condensation. Using the intermediate (99, R=Et), the acyloin condensation was carried out in the presence of sodium and refluxing toluene. The crude product, as shown by thin layer chromatography, contained three components having  $R_f$  values very similar to that of the starting material. These three components were separated by preparative thin layer chromatography. Although their infrared and ultraviolet spectra were very similar to that of the starting material, the NMR spectra suggested that the major component was unreacted starting material and that the other two components arose from ester exchange. To avoid complications resulting from ester exchange we decided to study the acyloin condensation with an intermediate having similar ester groups, namely, (99, R=Me). Purification of the crude acyloin condensation product yielded, in addition to unreacted starting material, a polar fraction which was mainly one component. Further characterisation of this compound by spectroscopic techniques <sup>was</sup> ~~were~~ unsuccessful.

In an attempt to characterise this polar material we felt it advantageous to remove the carbonyl function which would be present in the product of an acyloin condensation (see intermediate 100). Reduction with lithium aluminum

Polar Material from  
Acyloin Condensation  
Product



hydride in tetrahydrofuran provided a product whose ultraviolet spectrum ( $\lambda_{\text{max}}$  224, 276(sh), 284, 292 m $\mu$ ) was characteristic of a typical indole. The NMR spectrum contained the normal multiplet centred at  $\tau$ 2.60 due to the aromatic protons of the indole nucleus, a sharp two-proton singlet at  $\tau$ 5.42 characteristic of the methylene protons of a carbinol group attached to an aromatic system (cf. C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>OH at  $\tau$ 5.60) and a two proton doublet at  $\tau$ 6.65 ( $-\text{CHCH}_2\text{OH}$ ). Acetylation of this compound with acetic anhydride and pyridine yielded a diacetate whose NMR spectrum contained a two-proton singlet at  $\tau$ 4.80 and a two-proton doublet at  $\tau$ 6.05. This downfield shift of approximately 0.60 in the resonance of the  $\alpha$ -methylene protons

is in agreement with the acetylation shifts observed for primary alcohols<sup>67</sup>. This evidence strongly suggests that the compound arising from the reduction with lithium aluminum hydride is the diol (114) which on acetylation gives the diacetate (115). Additional evidence supporting this assignment was obtained by reducing the coupling product with lithium aluminum hydride to an alcohol which was identical with (114). Acetylation of this diol yielded the diacetate (115). These results show that the crude acyloin product is a mixture of unreacted starting material and its hydrolysis product(s).

One would expect this to be confirmed by re-esterification of the crude reaction with diazomethane to give starting material. Before pursuing this thought, it was necessary to establish that no complicated side reactions occurred on re-esterification of the hydrolysed coupling product with diazomethane. For this purpose we prepared the diacid (116) which was quantitatively reconverted to the coupling product (99, R=Me) by treatment with diazomethane, thus confirming that the only reaction occurring was o-methylation.

The crude acyloin product on treatment with diazomethane gave a mixture of compounds. One of these had the same  $R_f$  value as that of the coupling product (99, R=Me). Therefore we can conclude that the crude acyloin product is a mixture of starting material, components resulting from its hydrolysis and some other materials, which have not yet been fully characterised. On account of the low yields and difficulties in purifying the acyloin condensation product we proceeded

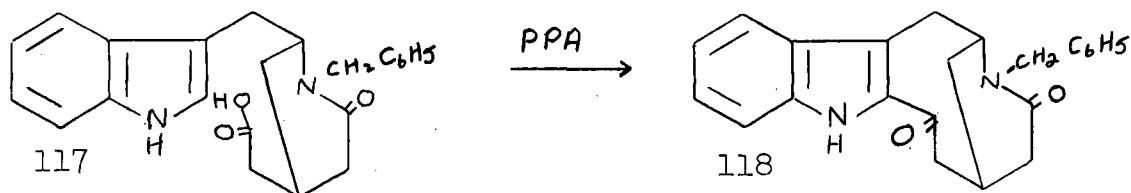


Figure 34. Yamada's Cyclisation to Provide the Eight-membered Ring Intermediate (118).

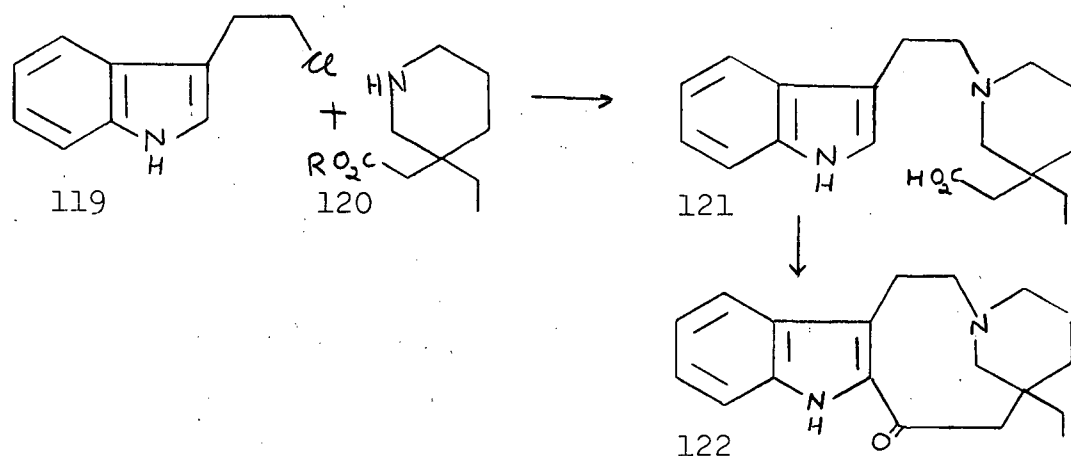


Figure 35. Possible Extension to Our Sequence A.

investigate the second of the two major approaches, scheme B.

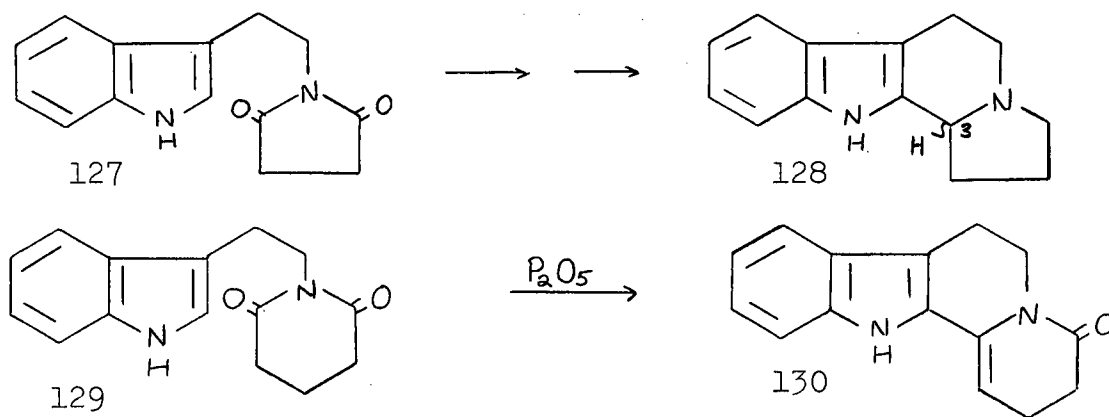
In the light of the present discussion on the formation of the nine-membered ring it is interesting to mention the recent findings of Yamada<sup>68</sup> who synthesised the carbon skeleton of the 2-acylindole alkaloids. The crucial step in this synthesis is the intramolecular cyclisation of (117) in the presence of polyphosphoric acid to give the eight-membered ring intermediate (118), figure 34. A very attractive extension of our work would be to prepare a suitably substituted piperidine (120) which on coupling with an indole derivative like (119) would provide the intermediate (121). Cyclisation according to Yamada's procedure should give the nine-membered ring intermediate (122), figure 35.



## II. Scheme B

The crucial steps of this approach are outlined in figure 25. Before discussing our experimental results in detail it is appropriate to review briefly the experimental results of other workers since these provided some encouragement for the possible success of an attractive and general approach to the synthesis of nine-membered rings.

The first crucial step is the formation of the indolopyrrocoline derivative (125). Although there are no examples of the formation of this system by the cyclodehydration of an N-[ $\beta$ -(3-indolyl)-ethyl]-succinimide (127), cyclodehydrations of amides, as in the Bischler-Napieralski synthesis, is well known<sup>69</sup>. Wenkert<sup>70</sup> was unable to cyclise the imide (127) to the indolopyrrocoline system (128) with phosphorus oxychloride, which has been generally the reagent of choice. Morrison<sup>71</sup> also found that the cyclisation of N-[ $\beta$ -(3-indolyl)ethyl]-glutarimide (129) under similar conditions was unsuccessful. However when phosphorus pentoxide was used Morrison was able to isolate the desired ene-lactam (130) in a 31% yield.



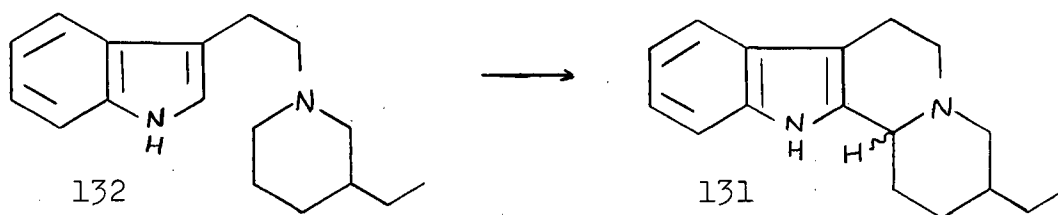
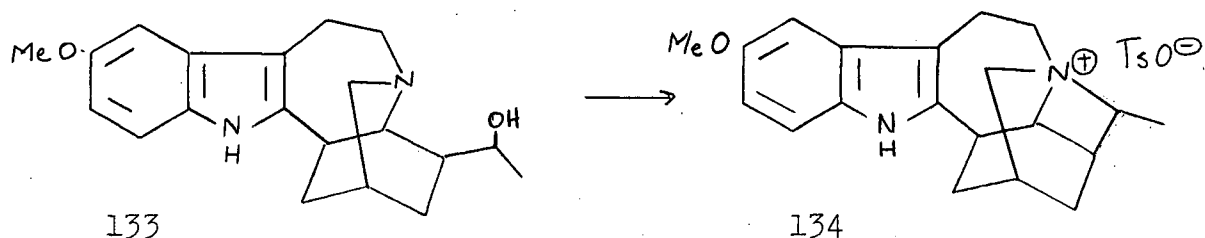


Figure 36. Wenkert's Synthesis of Octahydroflavopereirine.

An alternate approach to the synthesis of the indolopyrrocoline derivative (125) is based on the oxidative cyclisation of the intermediate amine (124) which is readily prepared by lithium aluminum hydride reduction of the intermediate (123). The synthesis of indole alkaloids of the tetrahydrocarboline type by oxidative or reductive cyclisations from 2,3-seco precursors has been recently reported<sup>72, 73</sup>. Of particular interest to our sequence is Wenkert's<sup>73</sup> synthesis of octahydroflavopereirines (131) by the mercuric acetate oxidation of N-[β-(3-indolyl)-ethyl]-3-ethylpiperidine (132), see figure 36.

The formation of quaternary ammonium salts of the type (126) in the indole alkaloid series is well-known. For instance, in an attempted preparation of the o-tosylate of iboxygaine (133), the tosylate readily underwent an internal cyclisation and only the ionic tosylate of the quaternary compound (134) could be isolated<sup>74</sup>. An example which bears a close relationship



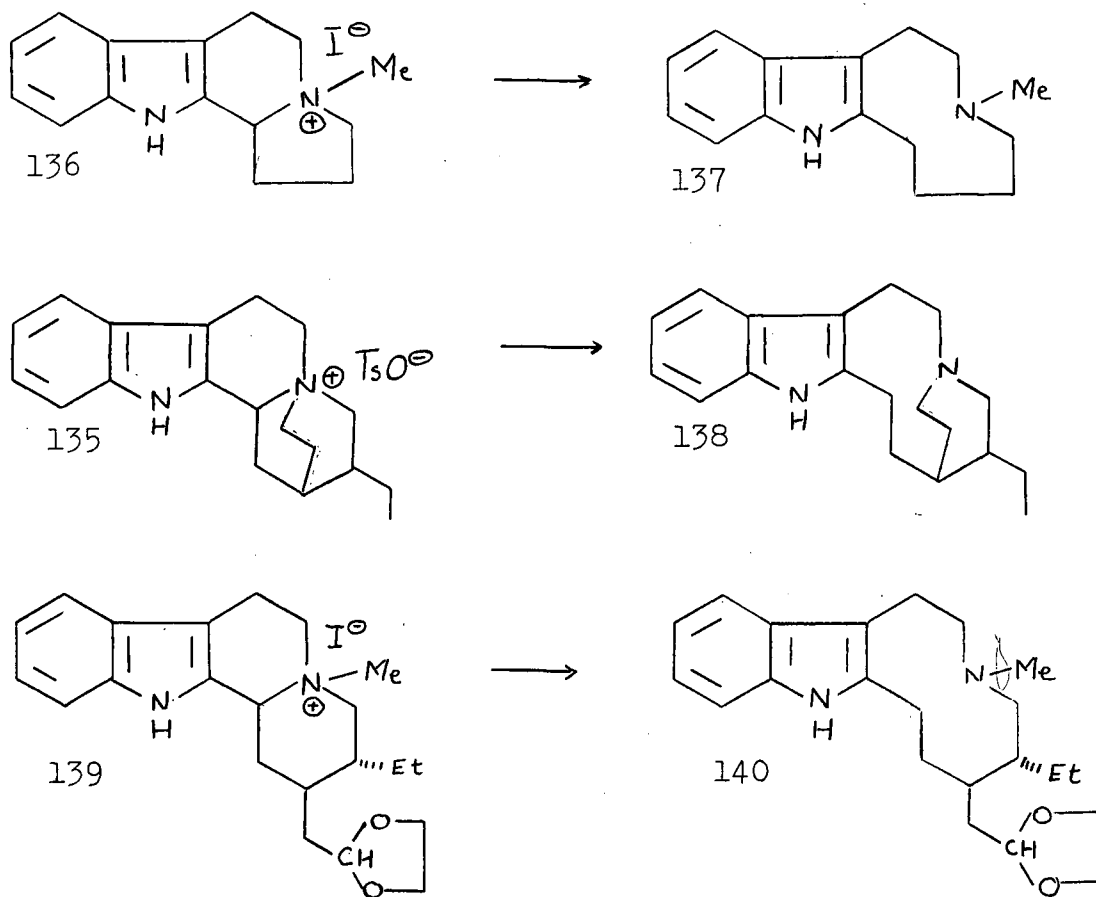


Figure 37.

to our intermediate is the quaternary salt (115) prepared by Dolby<sup>75</sup>.

Reductive cleavage of a C-N bond in a quaternary ammonium salt, which is probably the most important reaction in our sequence has also been used in the alkaloid field. Examples closely related to our sequence can be found in the formation of a nine-membered system (137) by means of a lithium-ammonia<sup>70</sup> reduction of the intermediate (136), and the lithium aluminum hydride reduction of the quaternary ammonium salt (135).

Additional evidence to support the generality of this reaction

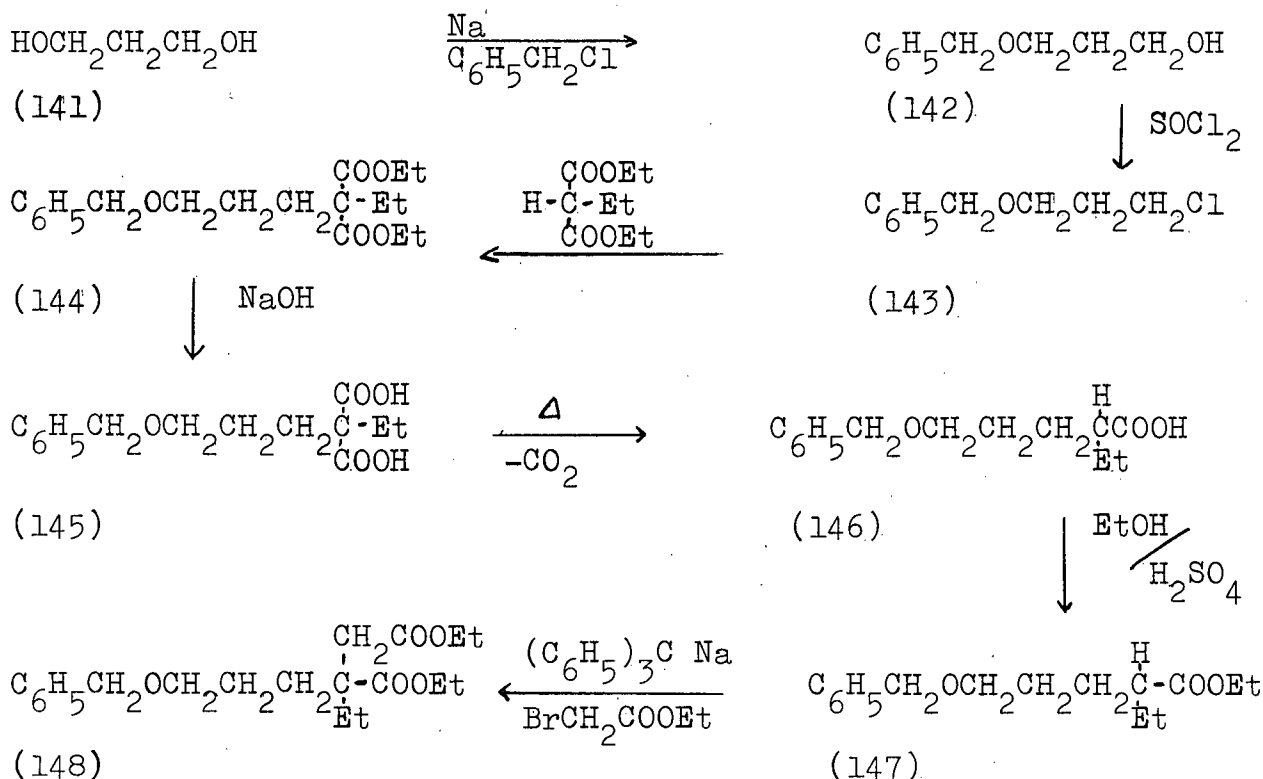


Figure 38. Synthesis of the Succinate Derivative (148).

comes from recent investigations<sup>76</sup> in our laboratory, in which the methiodide of dihydrocorynanthealethylene acetal (139) is reduced in the presence of sodium and liquid ammonia, to give the compound (140), see figure 37.

#### (i) Synthesis of the Succinate Derivative

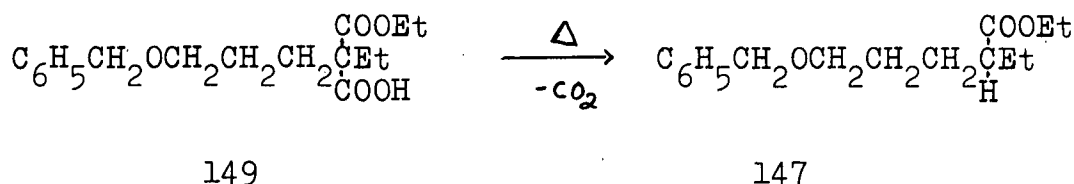
We will now turn our discussion to the synthesis of the diethyl succinate derivative required for the condensation with tryptamine. The successful sequence leading to this compound is outlined in figure 38. Since this work has already been presented in a previous thesis<sup>54,a</sup> it will not be necessary to discuss it in great detail.

$\gamma$ -Benzyloxypropanol (142) was prepared<sup>77</sup> in 65% yield by condensing the monosodium salt of propane-1,3-diol (141) with

benzyl chloride. The treatment of (142) with thionyl chloride gave 1-chloro-3-benzyloxypropane<sup>78</sup> (143) in 80% yield, and this compound on alkylation with diethyl ethylmalonate yielded diethyl  $\gamma$ -benzyloxypropylethylmalonate (144) in 47% yield. The most characteristic features of the NMR spectrum of (144) are, a five-proton singlet at  $\tau$ 2.75 due to the aromatic protons, a two-proton singlet at  $\tau$ 5.56 due to the benzyl methylene, a two-proton triplet at  $\tau$ 6.58 arising from the propyl methylene adjacent to the ether oxygen, a four-proton quartet at  $\tau$ 5.86 and a six-proton triplet at  $\tau$ 8.82 due to the two ethyl ester groups, and finally a three-proton triplet at  $\tau$ 9.20 due to the methyl protons of the ethyl substituent. The resonances at 2.75, 5.56 and  $\tau$ 6.58 in this compound due to the benzyloxypropyl group, are at similar positions in subsequent compounds containing this group, and will not be specifically mentioned in each case.

Hydrolysis of (144) with potassium hydroxide gave the crystalline  $\gamma$ -benzyloxypropylethyl malonic acid (145). The NMR spectrum no longer contained the quartet at  $\tau$ 5.86 and the triplet at  $\tau$ 8.82 due to the ethyl ester groups, but contained a new sharp singlet at  $\tau$ -1.50 assignable to the two carboxylic acid protons. The mother liquors from the crystallisation of (145) contained two polar compounds, as shown by thin layer chromatography. One of these had an  $R_f$  value identical to that of the diacid (145). The NMR spectrum of this mixture (quartet at  $\tau$ 5.82 and a triplet at  $\tau$ 8.80) suggested that the other component was the monoester derivative (149).

This suggestion was confirmed when (149) was decarboxylated to give ethyl 2-( $\gamma$ -benzyloxypropyl)-butanoate (147) identical with the material prepared in a subsequent reaction.



$\gamma$ -Benzyloxypropylethyl malonic acid (145) was smoothly decarboxylated at 160°C to provide the 2-( $\gamma$ -benzyloxypropyl)-butanoic acid (146), which was used for subsequent reaction without further purification.

The crude acid (146) was esterified with ethanol and sulfuric acid to provide ethyl 2-( $\gamma$ -benzyloxypropyl)-butanoate (147). In addition to the absorptions arising from the presence of the benzyloxypropyl group, the NMR spectrum showed the presence of a one-proton multiplet at  $\tau$  7.80 due to the tertiary proton ( $-\overset{\text{H}}{\text{C}}\text{COOEt}$ ), a two-proton quartet at  $\tau$  5.95 and a three-proton triplet at  $\tau$  8.85 due to the ethyl ester function.

The monoester (147) was alkylated with  $\alpha$ -bromoethyl acetate in the presence of triphenylmethyl sodium to give the desired succinate derivative (148) in 40% yield. The purity of (148) was most conveniently assessed by vapor phase chromatography; the succinate (148) having a longer retention time (3x that of the monoester, 147). The NMR spectrum showed a new sharp two-proton singlet at  $\tau$  7.40 due to the methylene

protons ( $-\overset{|}{\text{C}}\text{CH}_2\text{COOEt}$ ). The two ester groups were not magnetically equivalent giving rise to two quartets and two triplets at  $\tau$ 5.92 and  $\tau$ 8.82 respectively.

Attempts to prepare (148) using methylsulfinyl carbanion<sup>81</sup> as the base resulted in the total recovery of the starting material (147)

(ii) Condensation with Tryptamine

Having the required succinate derivative at hand we next considered the condensation with tryptamine. Indeed we were able to obtain the imide (123) by refluxing a mixture of tryptamine and the succinate ester (148) for 48 hr. in diethylene glycol monoethyl ether. The crude imide (123) was purified by chromatography on alumina and in spite of numerous attempts it resisted crystallisation from a variety of solvents. Elemental analysis suggested a formula,  $\text{C}_{26}\text{H}_{30}\text{N}_2\text{O}_3$ , which was supported by the molecular ion peak ( $m/e$  418), figure 40, in the mass spectrum. The ultraviolet spectrum showed the typical absorption of an indole ( $\lambda_{\text{max}}$  224, 275(sh), 282, 290  $\mu$ ), and the infrared spectrum showed two carbonyl absorption bands at  $1760\text{ cm}^{-1}$  (weak) and  $1690\text{ cm}^{-1}$  (strong) which are characteristic of the succinimide system<sup>79</sup>. In addition to the benzyloxypropyl group the NMR spectrum showed a one-proton doublet at  $\tau$ 3.60 due to the  $\alpha$ -proton on the indole nucleus<sup>80</sup>, two triplets at  $\tau$ 6.18 and  $\tau$ 7.00 arising from the ethylene bridge, a two-proton singlet at  $\tau$ 7.60 due to the methylene of the succinimide moiety and finally a three-proton triplet at  $\tau$ 9.26 due to the methyl protons of the ethyl substituent.

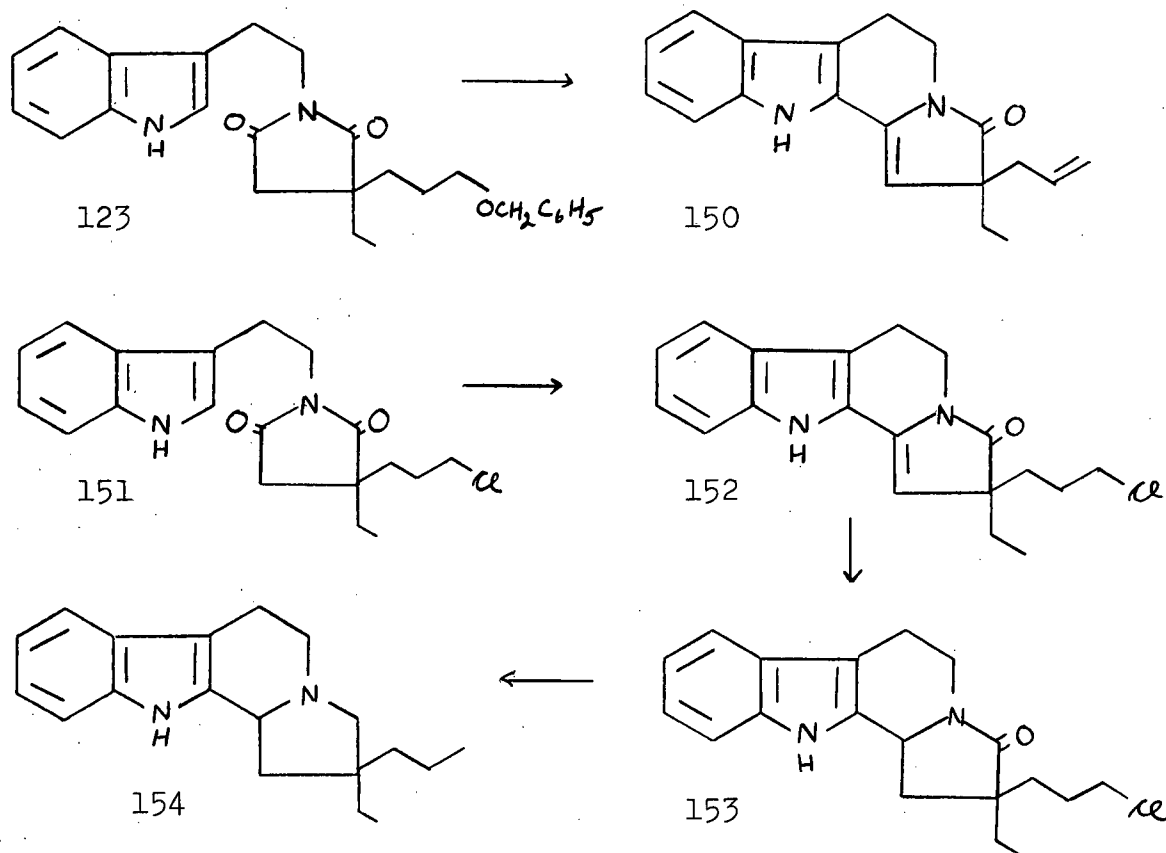


Figure 39.

(iii) Cyclisation via Bischler-Napieralski Reaction

The next step in the sequence involved the cyclisation of the succinimide ring onto the  $\alpha$ -position of the indole nucleus. For this purpose the Bischler-Napieralski reaction was first considered. Following the experimental conditions described by Morrison<sup>71</sup>, the cyclisation of the imide (123) to provide the desired ene-lactam (150) was accompanied by the loss of the benzyloxy group to give a terminal double bond. This product, which was obtained in poor yield (5%) would require subsequent hydration of the terminal olefinic double bond to enable the quaternary ammonium salt to be finally formed.



In a concurrent investigation (figure 39) the  $\gamma$ -chloro-propyl analogue of the imide (151), which would not be expected to undergo elimination under Bischler-Napieralski conditions was employed. The chloro compound was cyclised under the same conditions to provide the desired intermediate (152) in 18% yield. This was smoothly reduced with platinum oxide in acetic acid to the chlorolactam (153). However, reduction of this lactam with lithium aluminum hydride was accompanied by the hydrogenolysis of the chlorine group. Since this reaction product (154) no longer possessed any functionality in the propyl side chain, it too was impractical for our synthesis.

With these experimental facts in hand we considered the cyclisation of the imide (123) using milder conditions. For this purpose we reduced the reaction time and changed the solvent from xylene to toluene. Treatment of the imide (123) under these conditions provided an amorphous yellow solid (10%) whose ultraviolet spectrum ( $\lambda_{\text{max}}$  224, 313, 326 m $\mu$ ;  $\lambda_{\text{max}}^{\text{HCl}}$  395 m $\mu$ ) was in perfect agreement with that reported<sup>71</sup> for compound (130). The mass spectrum (figure 40) had a molecular ion peak (m/e 310) which corresponds to the molecular formula,  $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_2$ , and a strong peak at (M-18) corresponding to the loss of water. These spectral properties are in agreement with the structure (155) which now possesses the suitably functionalised propyl side chain. Due to its susceptibility to air oxidation, the crude cyclisation product was hydrogenated using platinum oxide in acetic acid. The indolic ultraviolet spectrum of this crude hydrogenation product indicated that the double bond of the

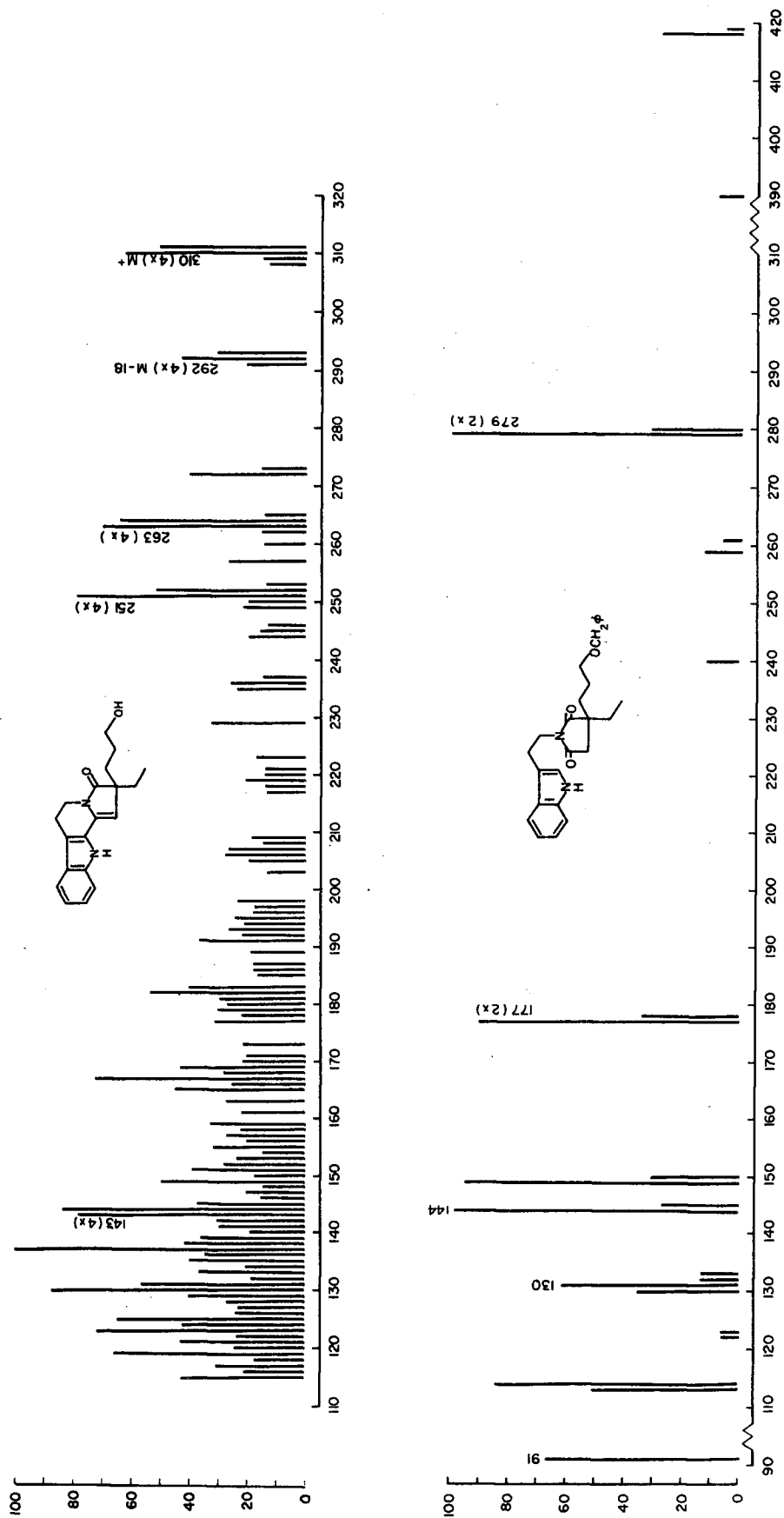
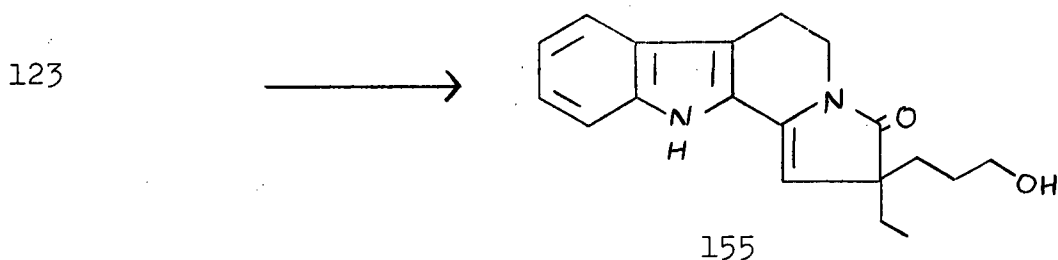


Figure 40

lactam ring had been saturated. A complete separation of the products of hydrogenation was unsuccessful and the low yields of these reactions caused us to consider the alternate route to the formation of the indolopyrrocoline system.



In order to study the alternate approach it was first necessary to investigate methods of reducing the imide (123) to the benzyl ether amine (124).

#### (iv) Reduction of the Imide (123)

The imide (123) was reduced with lithium aluminum hydride under mild conditions to provide the desired benzyl ether amine (124) as a clear oil which resisted crystallisation. The ultraviolet spectrum was that of a normal indole, while the infrared spectrum lacked the characteristic imide absorption. The NMR spectrum (figure 41) showed the presence of the benzyloxypropyl group, a one-proton doublet at  $\tau$ 3.22 due to the  $\alpha$ -hydrogen on the indole nucleus and a two-proton singlet at  $\tau$ 7.59 ( $\text{N}-\text{CH}_2-\text{C}$ ). The molecular formula,  $\text{C}_{26}\text{H}_{34}\text{N}_2\text{O}$ , was established by high-resolution mass spectrometry, which provided the value 390.269 (calculated value 390.267). The mass spectrum (figure 43) also revealed the expected fragmentation to provide the base peak

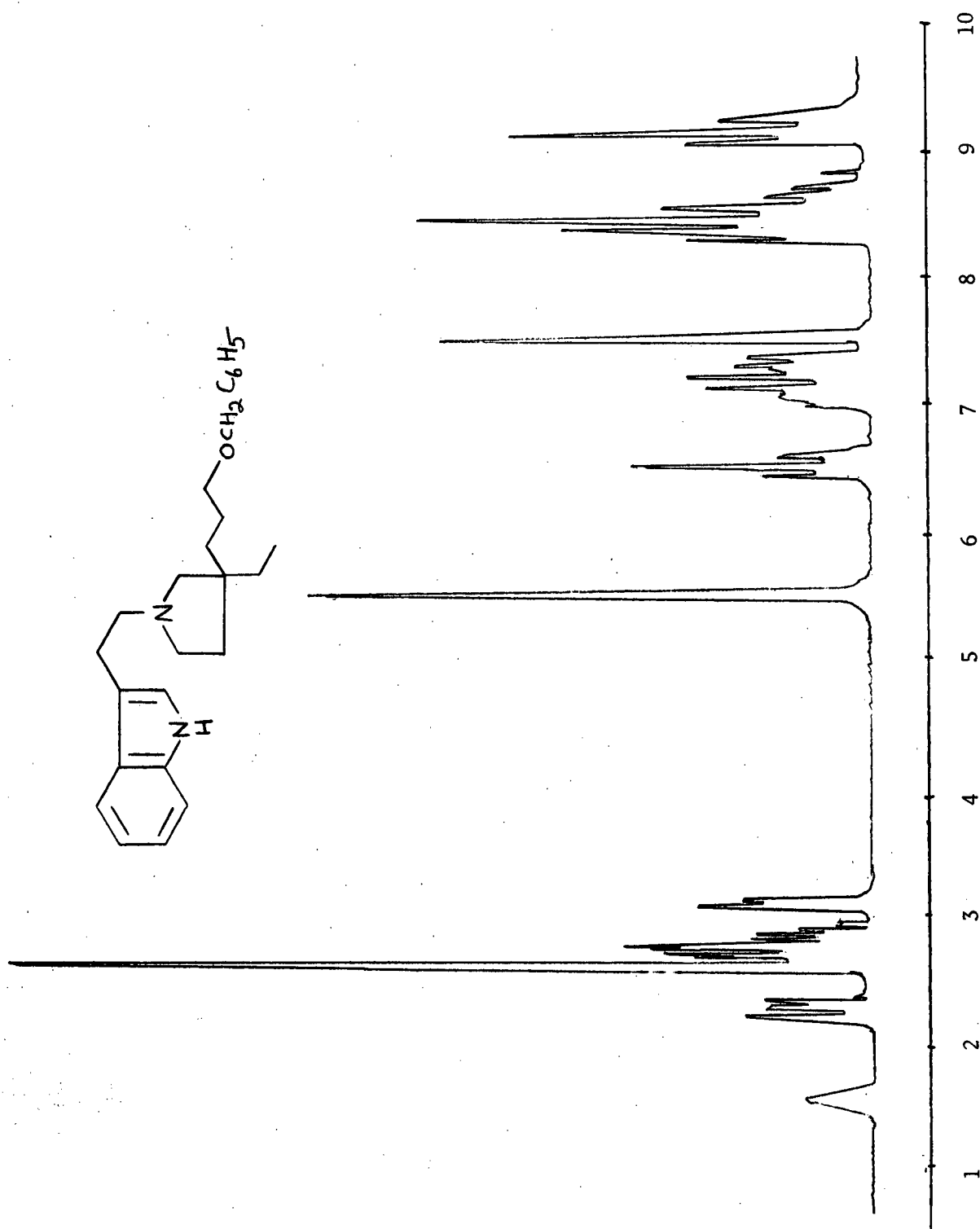


Figure 41

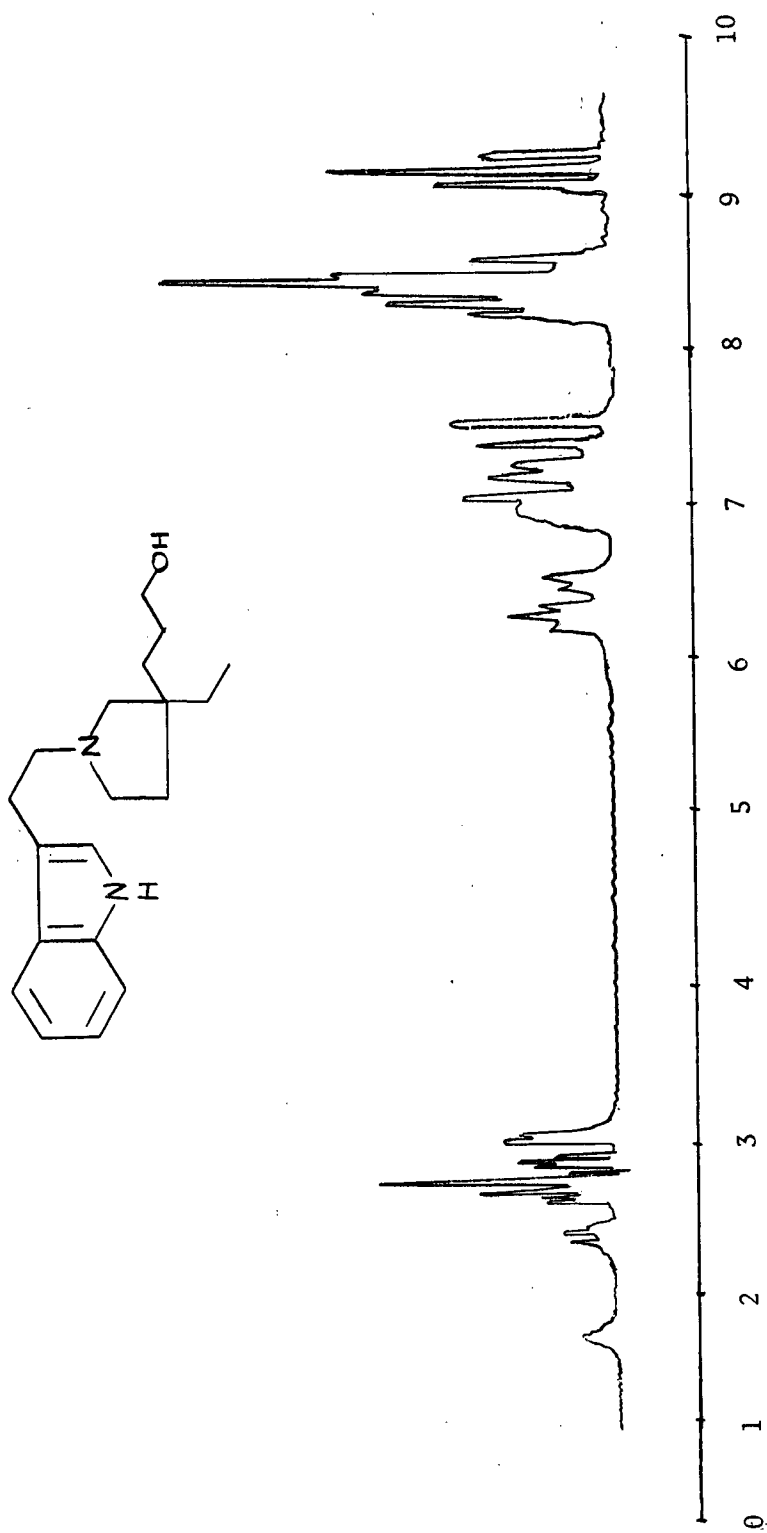
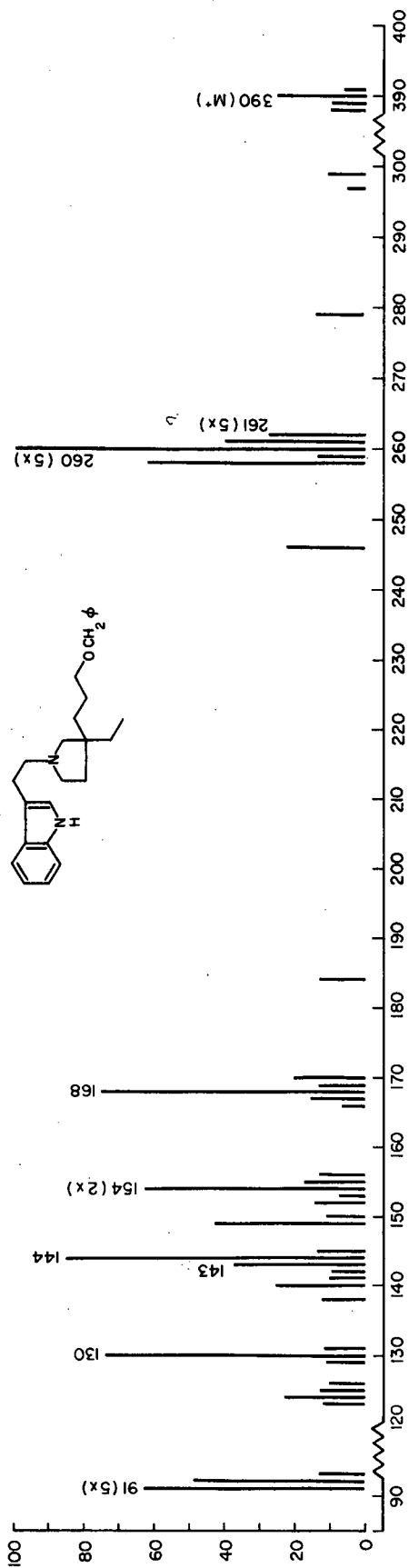


Figure 42

UNCYCLISED BENZYL ETHER AMINE



UNCYCLISED AMINOALCOHOL

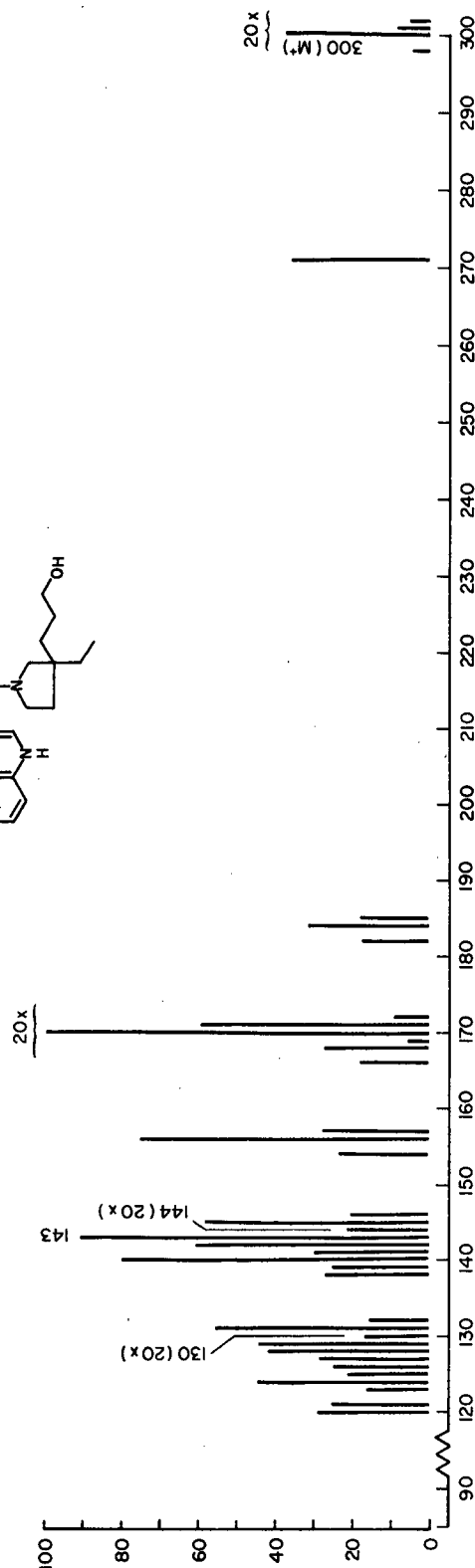
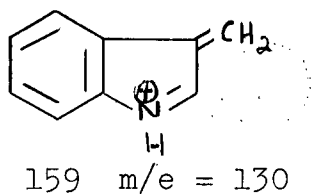
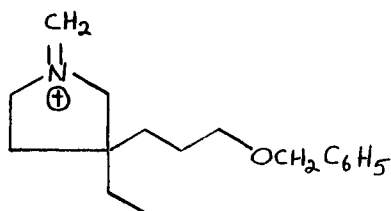
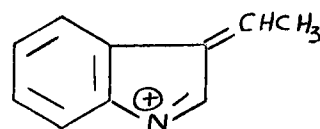
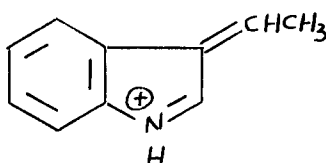
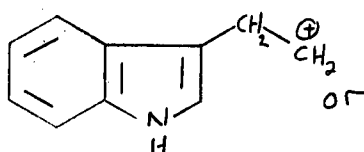
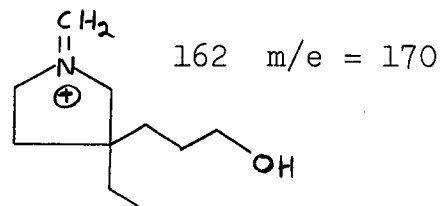
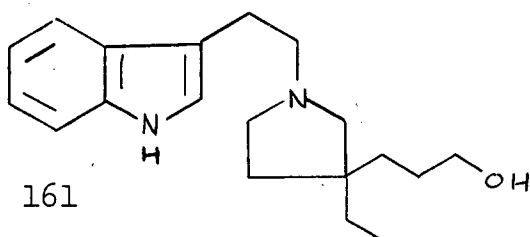


Figure 43



at  $m/e$  260 due to the stable ion (156). The peaks at  $m/e$  144, 143 and 130, assigned to the fragments (157, 158 and 159, respectively) are due to the indole nucleus<sup>82</sup>. The peak at  $m/e$  91 is due to the tropylium ion (160) which originates from the benzyl group.

During the investigations of the reduction of the imide, it was noted that treatment with lithium aluminum hydride under vigorous conditions led to hydrogenolysis of the benzyl

group. The ultraviolet spectrum of this aminoalcohol (161) had a typical indole absorption pattern, while the NMR spectrum (figure 42) lacked the absorptions due to the benzyl group. The new two-proton triplet at  $\tau$ 6.40 is due to the methylene protons of the primary alcohol and the broad one-proton singlet at  $\tau$ 6.80 was assigned to the hydroxyl proton on the basis of its disappearance on addition of  $D_2O$ . Deuterium exchange also caused the doublet at  $\tau$ 3.05 due to the  $\alpha$ -proton on the indole nucleus collapses to a singlet. It is noteworthy that in contrast to the NMR spectrum (figure 41) of the uncyclised benzyl ether, the amine (161) shows non-equivalence for the methylene protons ( $-N-CH_2-C-$ ).

The mass spectrum (figure 43) showed a molecular ion peak ( $m/e$  300) in agreement with the empirical formula,  $C_{19}H_{28}N_2O$ , and the expected fragmentation to a base peak at  $m/e$  170 due to the stable fragment (162). The presence of peaks at  $m/e$  144, 143 and 130 due to the indole nucleus were also noted.

#### (v) Oxidative Cyclisation

Having prepared the benzyl ether amine (124) we now turned to the preparation of the intermediate (125). In view of the recent applications of mercuric acetate in the oxidative transannular cyclisations in this laboratory<sup>34-37</sup> and by Wenkert<sup>73</sup> it was considered an appropriate reagent for our purpose. It was fortunate that the mercuric acetate-induced conversion of (124) to (125) led further to the overoxidised product (163). The formation of this latter substance made it possible to follow the progress of the reaction by observing



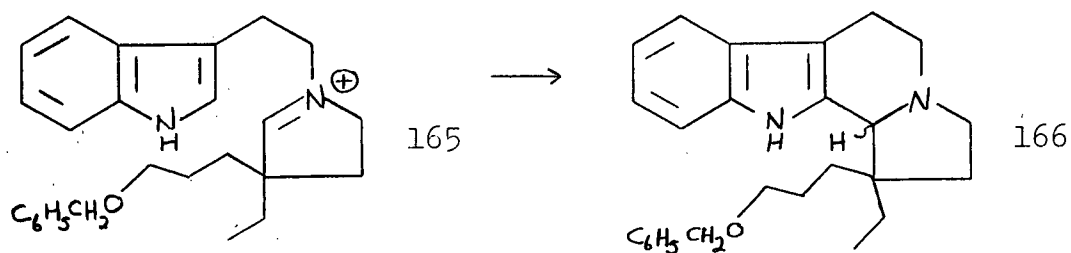
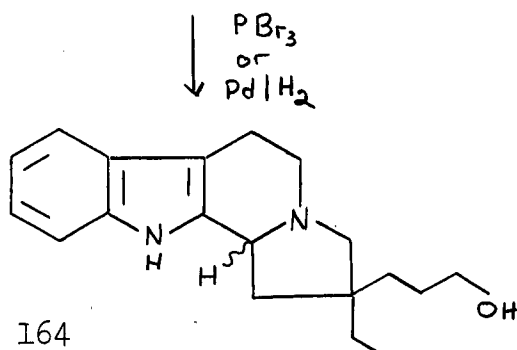
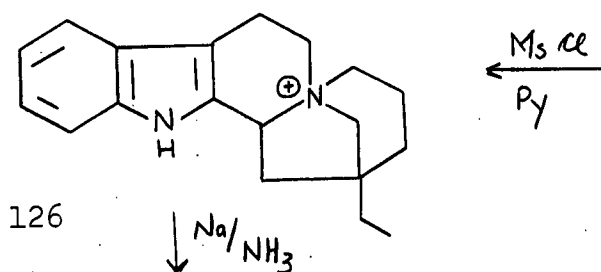
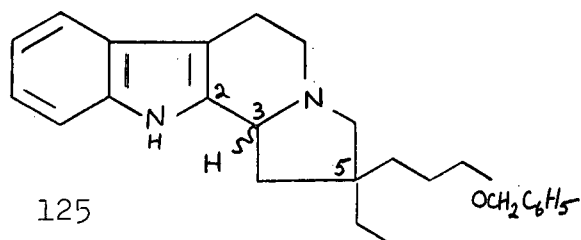
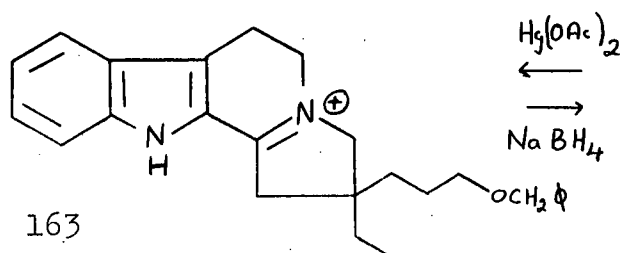
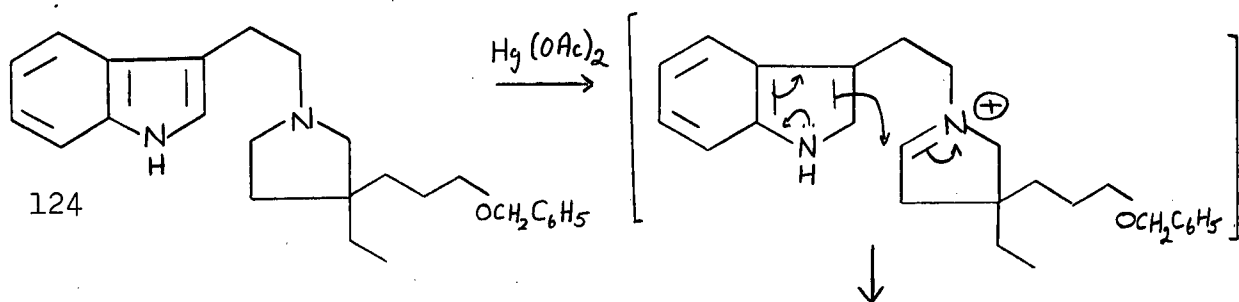


Figure 44.

the appearance of a new absorption ( $\lambda_{\text{max}}$  353 m $\mu$ ) in the ultraviolet spectrum.

Optimum yields of the cyclised materials were obtained when (a), the oxidation was allowed to proceed at room temperature for 12 hours before refluxing and (b), the crude products of the oxidation were immediately reduced with sodium borohydride. Molecular models suggest that this latter reduction would probably proceed in a non-stereospecific manner since there was no apparent preference for either  $\alpha$  or  $\beta$  approach of the reducing agent.

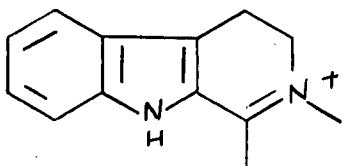
Although there are three directions in which the oxidation can occur, only the two endocyclic iminium ions would lead to cyclised products. One would expect the cyclisation of the iminium salt (165) to occur to a lesser extent since it would give rise to the sterically less favored structure (166), figure 44.

A great deal of difficulty was encountered in the attempted separation of the crude mixture of stereoisomeric components resulting from the cyclisation reaction. In fact, we were not successful in achieving complete resolution of this mixture and the spectral data quoted were obtained on a mixture of components. The major fractions contained three components whose  $R_f$  values, by thin layer chromatography, were very similar to each other and to that of the starting material (124). A partial separation of the least polar component from the other two was accompanied by large losses of material. Even in this instance it was still impure and completely definitive spectral

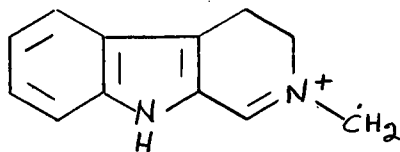
data could not be obtained. However, spectral data on the remaining mixture containing the two more polar components gave valuable information and it is therefore presented in detail. The ultraviolet spectrum exhibited a normal indole absorption while the NMR spectrum showed that the benzyloxy group was still present and that the doublet at  $\tau$ 3.20 due to the  $\alpha$ -proton on the indole ring was absent. This indicates that the mixture did not contain any uncyclised material. Furthermore, the appearance of a sharp singlet at  $\tau$ 8.04 ( $\text{N-CH}_2\text{-C}$ ) indicated that at least one of the components in this mixture must represent the desired cyclic structure (125). The alternate cyclisation product (166) would exhibit a multiplet for the methylene protons attached to the basic nitrogen.

The mass spectrum suggested a molecular ion at  $m/e$  388 whose accurate mass in the high-resolution mass spectrum was 388.251 (calculated for  $\text{C}_{26}\text{H}_{32}\text{N}_2\text{O}$ , 388.251). This latter result supported the above NMR data and suggested that these inseparable components were isomeric cyclic products. The most diagnostic peaks in the mass spectrum were found at  $m/e$  184, 170, 169, and 156. These four peaks, attributable to fragments (167-171, figure 45) have been shown to be associated with a substituted tetrahydro- $\beta$ -carboline system,<sup>82</sup> and could thus only arise from compounds having a cyclic structure.

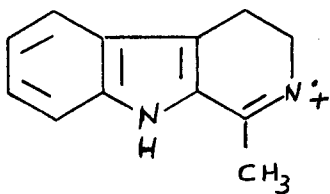
Although the above experimental problem was not completely overcome, we felt that it would not be necessary to separate the expected cyclic products since (a), the asymmetric centre at C-3 (see 125) would be destroyed in the final ring opening



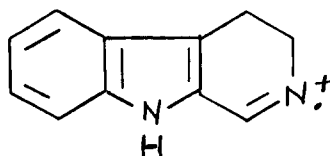
167 M-1



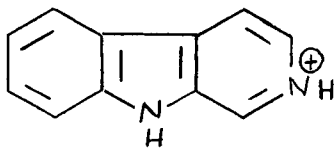
168 m/e = 184



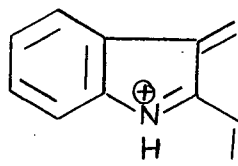
168 m/e = 184



169 m/e = 170



170 m/e = 169



171 m/e = 156

Figure 45. Fragments arising from a Substituted Tetrahydro- $\beta$ -carboline System.

reaction to give quebrachamine and (b), the asymmetric centre at C-5 merely determines which optical isomer of quebrachamine is formed, as quebrachamine possesses only one asymmetric centre.

Although the above spectral data provides no more than strong suggestive evidence for the presence of three cyclic products, conclusive results come forth from our subsequent debenzylation experiments where we were able to isolate three isomeric alcohols.

(vi) Debenzylation of the Benzyl Ether Amines (125) with BBr<sub>3</sub>

In our initial investigations the benzyl group was removed by brief treatment with boron tribromide<sup>83</sup> to provide a solid amorphous mixture of cyclised aminoalcohols. The ultraviolet spectrum of the latter showed a typical indole absorption, while the NMR spectrum indicated a complete absence of benzyl ether proton signals. The mass spectrum showed a molecular ion at m/e 298, and the usual peaks associated with a substituted tetrahydro- $\beta$ -carboline derivative (vide supra). It was on this mixture of cyclic aminoalcohols that we initially investigated the latter steps of the sequence as indicated below.

(vii) Quaternary Ammonium Salt Formation

Precedent for the formation of quaternary salts by intramolecular nucleophilic displacement of a tosyloxy group exists in the literature<sup>74, 87</sup>. Repeated attempts to prepare the tosylate ester of the mixture of aminoalcohols was unsuccessful. However, on treatment with methanesulfonyl chloride in pyridine at 0°C, the initially formed mesylate

ester proceeded to quaternise spontaneously to provide a water soluble salt. The water solution was concentrated to dryness to give the salt as an amorphous powder. The ultraviolet spectrum of this material possessed essentially a normal indole absorption.

(viii) Ring Cleavage Reaction

The ultimate step of the synthesis is a ring cleavage of the above mentioned quaternary salt. Reduction with sodium and liquid ammonia provided the desired (dl)-quebrachamine (1), which was identical in all respects with the natural material (thin layer chromatography, superimposable infrared spectra, mass spectra, see figure 46).

The formation of quebrachamine verifies, in retrospect, that at least one of the isomeric benzyl ether amines has the desired structure (125), and also that the aminoalcohol and the quaternary salt arising from (125) must possess the structures (164) and (126) respectively.

Although the synthesis of (dl)-quebrachamine was formally completed, it was clearly desirable to obtain some further information on the later steps of the sequence. For this purpose, we reinvestigated the debenzylation experiments in the hope that a separation of the cyclised components could be achieved at the alcohol stage.

(ix) Debenzylation of the Benzyl Ether Amines (125) by Catalytic Hydrogenolysis

Another debenzylation technique was considered since it might

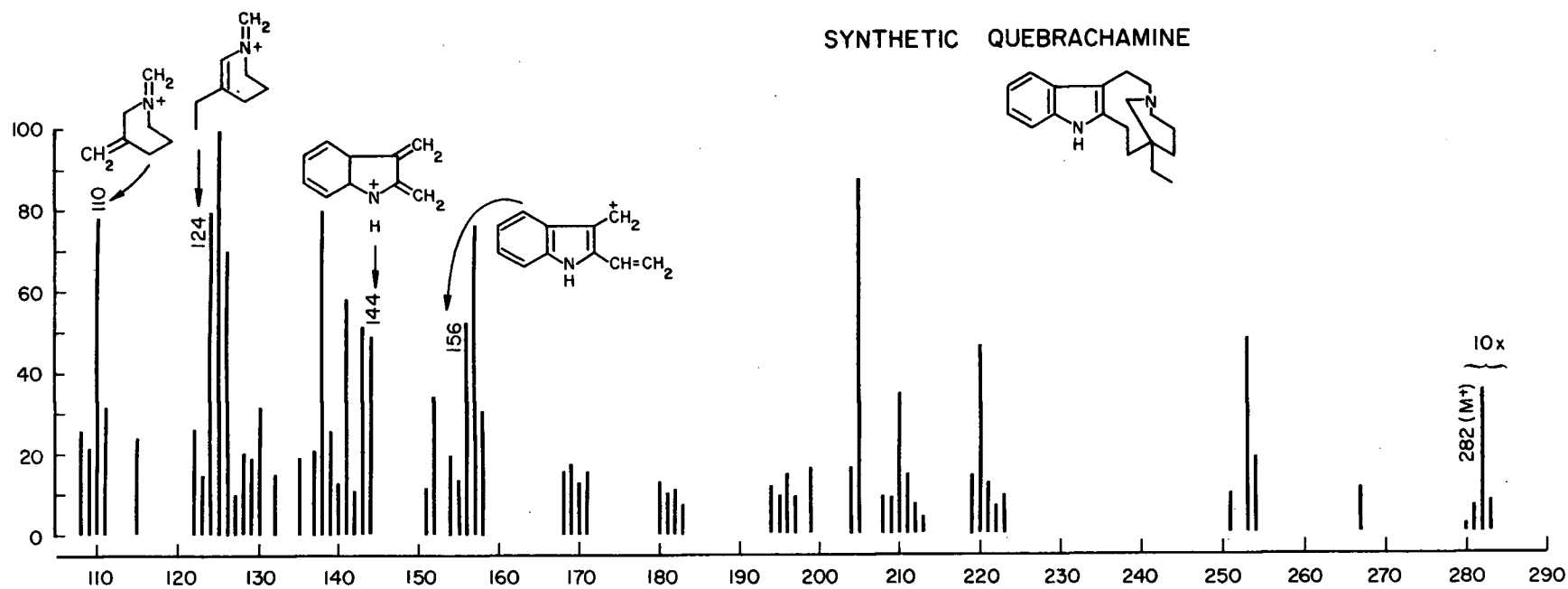


Figure 46

possibly lead to a less complex mixture of products. Catalytic hydrogenolysis using palladium on charcoal in glacial acetic acid<sup>84, 85</sup> was attempted, and indeed gave purer products. Removal of the benzyl group was again evident from the spectral data and chromatographic characteristics of the reaction products. By careful column chromatography we were able to separate three alcohols, referred to as A, B, and C in order of increasing polarity. Whilst alcohol C was obtained as a greenish gum, alcohols A and B were crystalline.

These three compounds showed identical indole ultraviolet absorption spectra, while the mass spectra (see figure 47) all contained a molecular ion peak at  $m/e$  298, and peaks at 297, 184, 170, 169 and 156. These latter four fragments have been observed in the mass spectrum of the benzyl ether amines and their significance has already been discussed. High resolution mass spectrometry established that these three aminoalcohols each possessed the molecular formula  $C_{19}H_{26}N_2O$  (Found: A, 298.204; B, 298.205 ; C, 298.206 ; Calc. 298.205).

The NMR spectra (figures 48-50) indicated that the benzyl group had been removed, and also that these compounds all lacked the absorption due to the  $\alpha$ -proton on the indole nucleus (cf. NMR spectrum of uncyclised aminoalcohol, figure 42). Aminoalcohol B, which appeared to be the major component, showed a two-proton singlet at  $\tau$ 8.00 which we believe, as already mentioned previously, could only arise from a compound having cyclised in the desired sense. Since we have already shown that these latter substances must be cyclic products this result



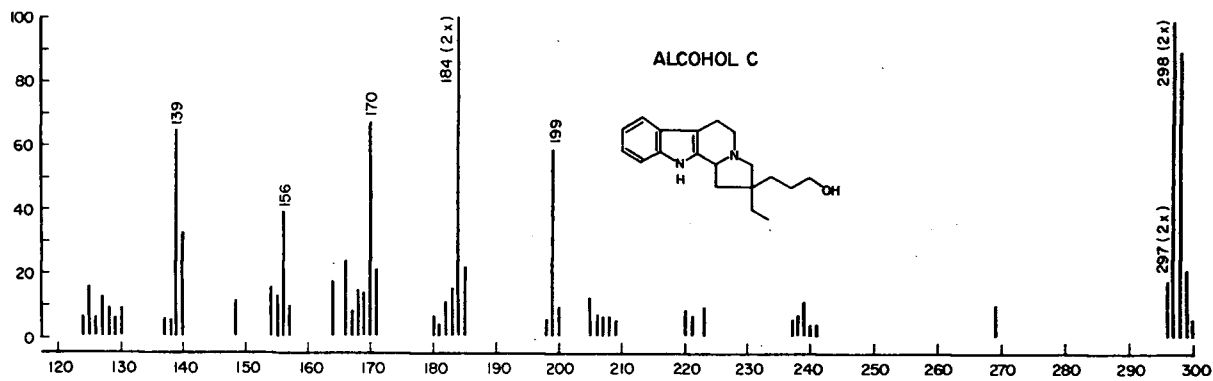
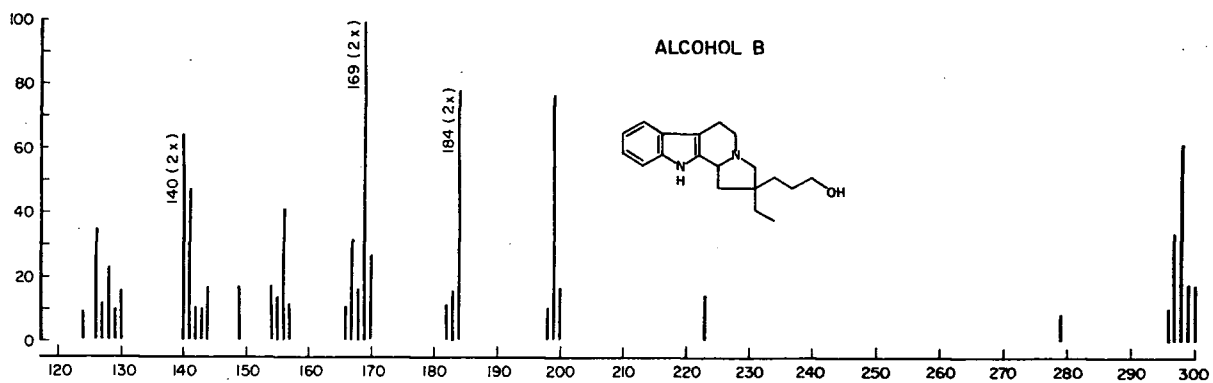
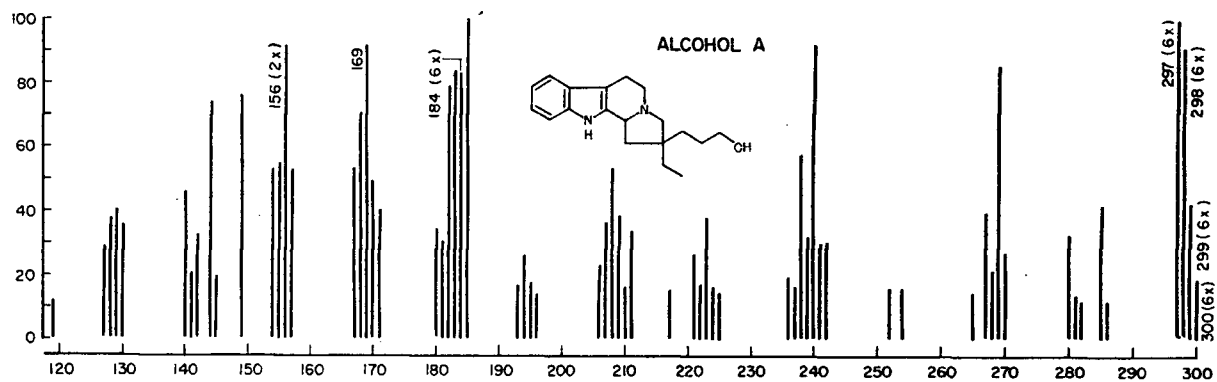


Figure 47

ALCOHOL A

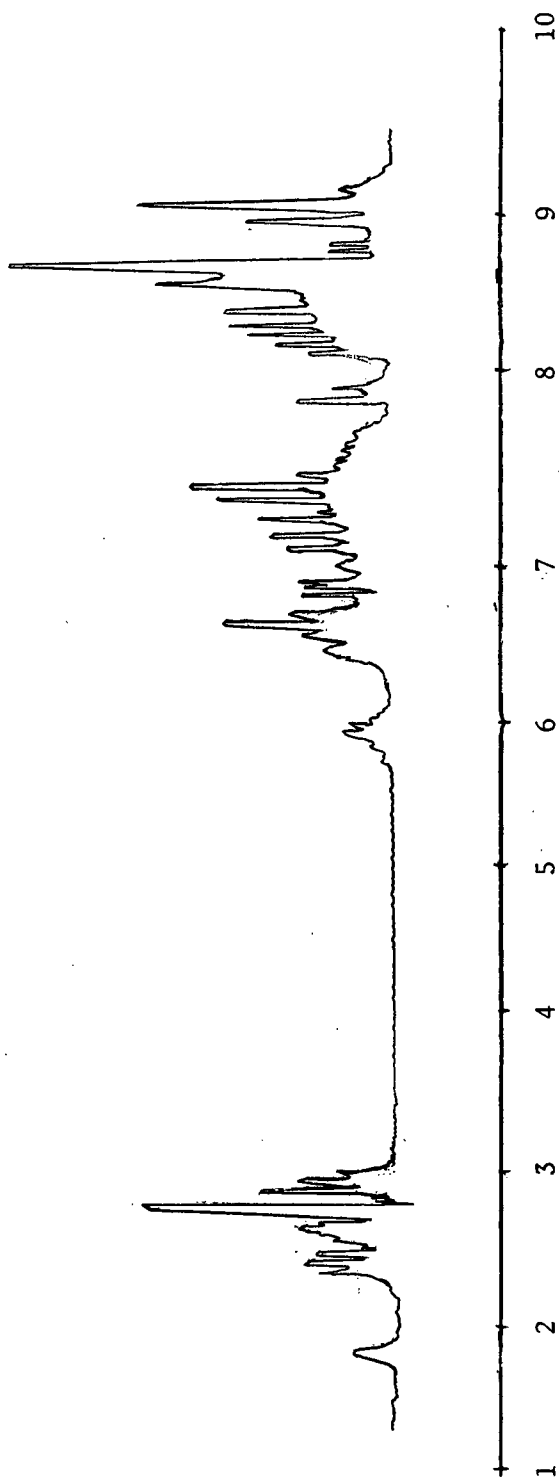


Figure 48

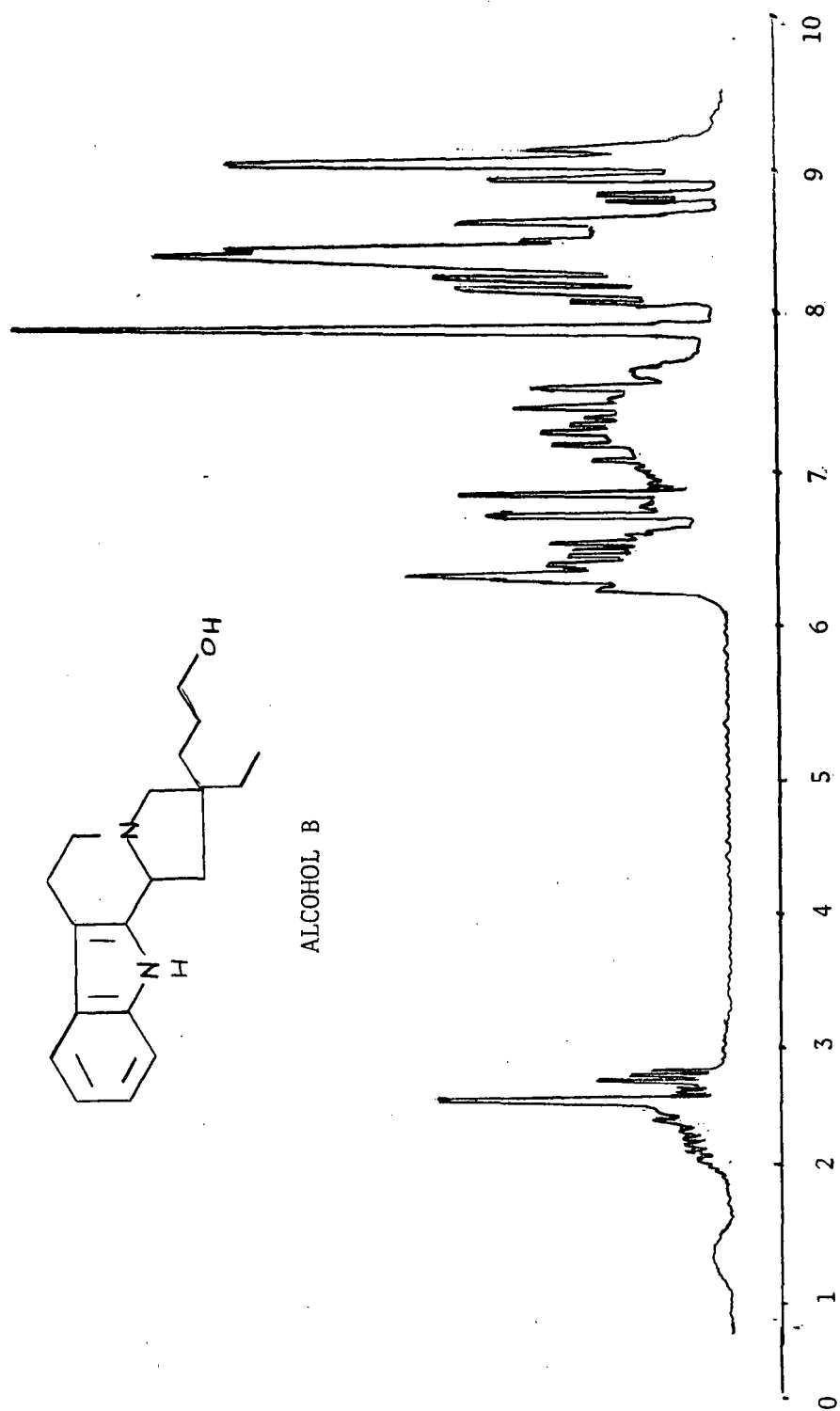


Figure 49

ALCOHOL C

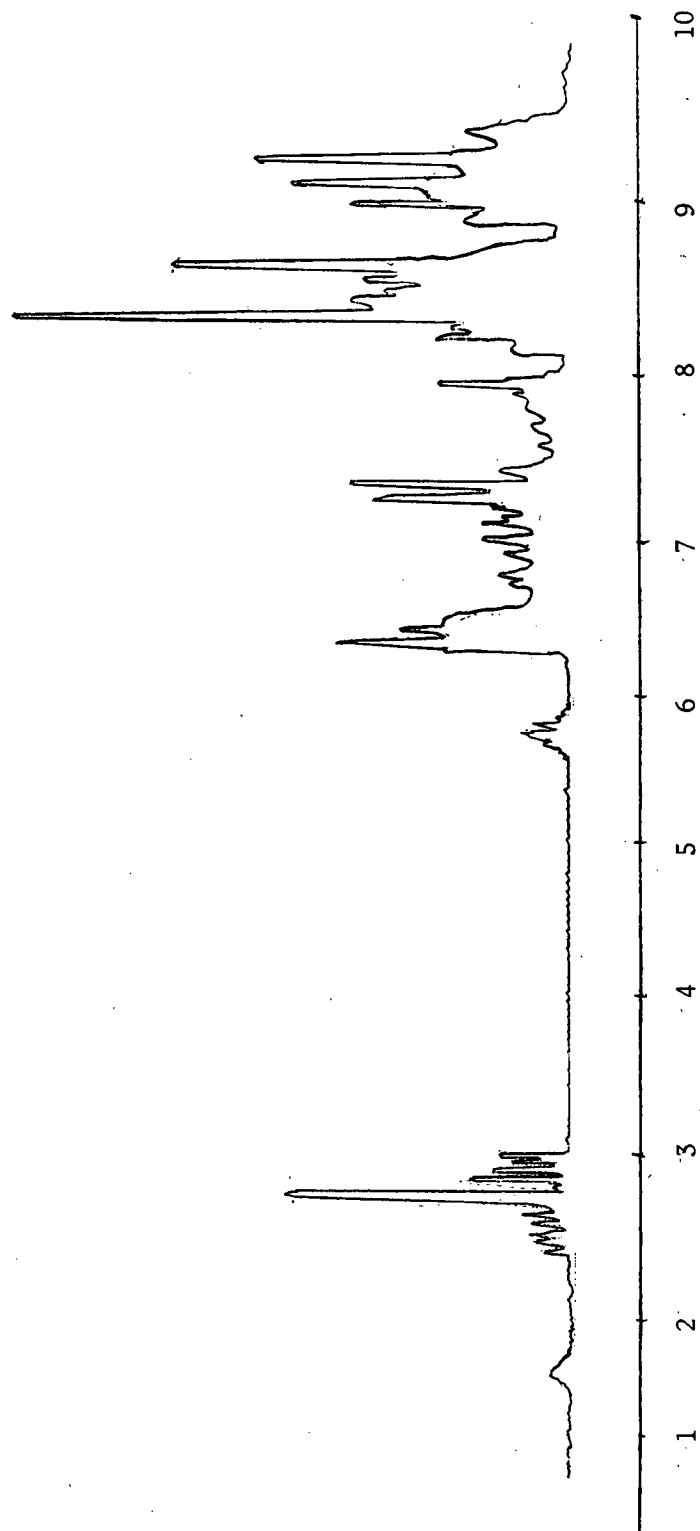


Figure 50

suggests that either A or C have this signal shifted upfield or else that they possess an undesirable cyclic system.

Another interesting difference which is noted in the NMR spectra is the presence of a one-proton multiplet at low field in A ( $\tau$ 5.90) and C ( $\tau$ 5.80), but the absence of this signal in B. This signal may be assigned to the  $C_3$ -H proton and its chemical shift may be dependent on the stereochemistry and thereby the conformation of the aminoalcohol in question. Wenkert<sup>73</sup> has suggested that the broad one-proton multiplet at  $\tau$ 5.80-6.00 in the NMR spectrum of compound (128) is characteristic of  $C_3$ -H in a cis-pyrrocoline configuration. He also points out that in compound (131) the  $C_3$ -H resonance can vary from  $\tau$ 6.80 (axial) to  $\tau$ 5.54 (equatorial).

The above data was clearly consistent with cyclic structures for alcohols A, B and C and it was now necessary to try and assign definitive structures for these compounds. It is noted that structure (164), which leads to quebrachamine, contains two asymmetric centers and theoretically four stereoisomers (2 dl pairs) are possible. One might therefore expect that two of the above alcohols (each being a dl pair) may possess the gross structure (164). In fact, we were able to convert the relatively abundant alcohol B to (dl)-quebrachamine by the mesylation-reduction sequence, thus indicating that at least this alcohol has the desired structure. Due to insufficient quantities of the alcohols A and C we were unable to pursue further chemical investigations on these isomers at this time. We hope that this latter question will be clarified in subsequent investigations in our laboratory.

In a concurrent investigation in our laboratory, (dl)-dihydrocleavamine (63) was synthesised<sup>86</sup> by the sequence outlined in figure 51. It is to be noted that this pathway parallels the synthetic scheme outlined for quebrachamine and establishes the generality of this approach for the synthesis of nine-membered ring intermediates.

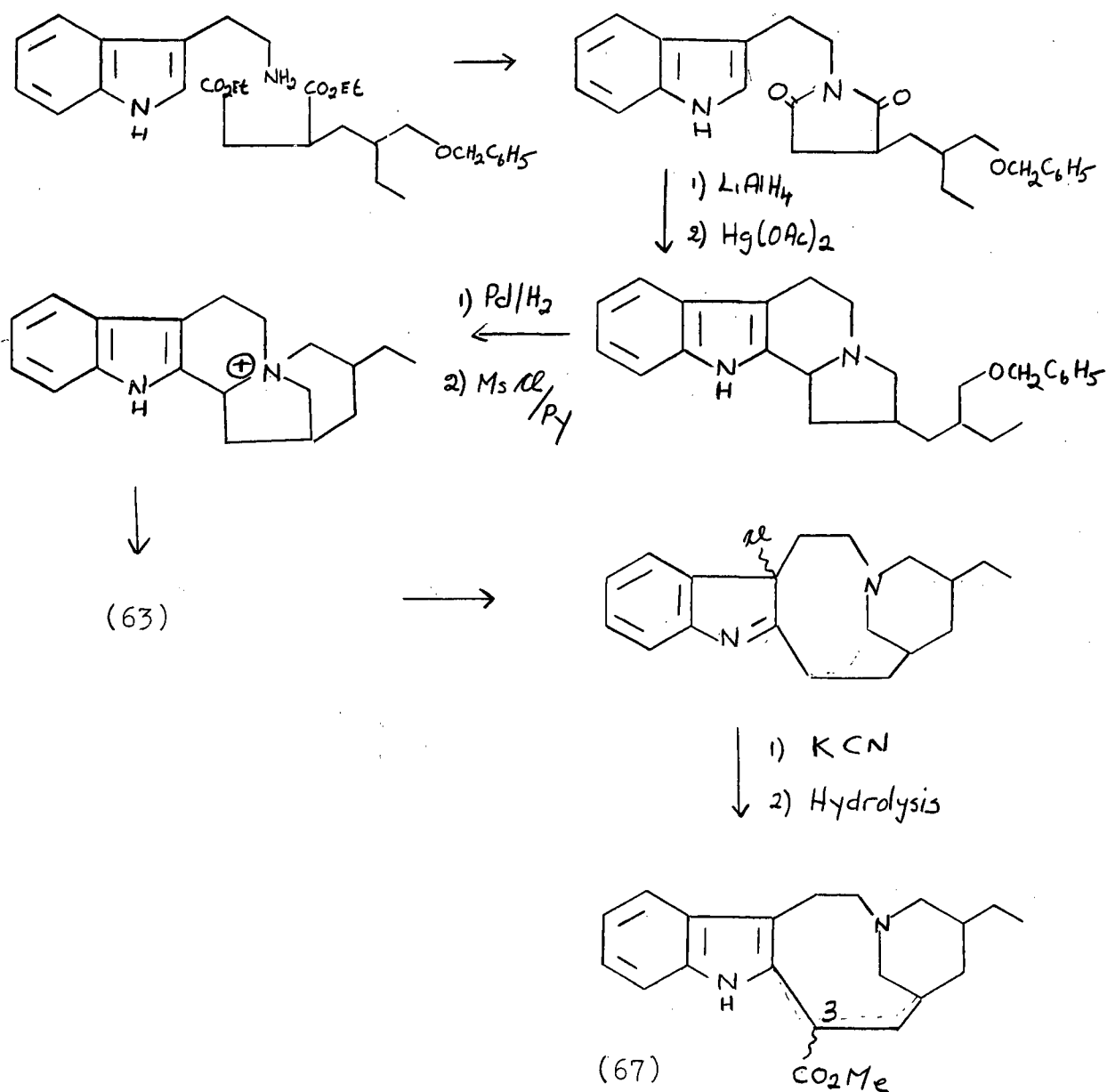
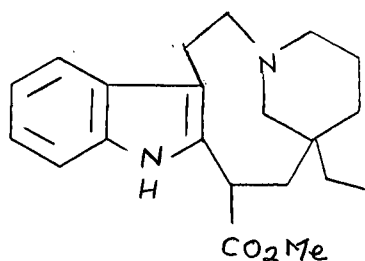


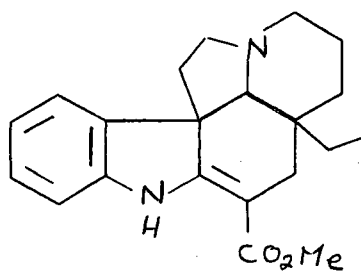
Figure 51. Synthesis of Dihydrocleavamine and Carbomethoxy-dihydrocleavamine.

An important extension of the cleavamine sequence involved the introduction of the ester group at C<sub>3</sub> to complete the total synthesis of carbomethoxy dihydrocleavamine (67). In view of previous work<sup>36</sup> this extension also completes the total synthesis of (dl)-coronaridine (70) and (dl)-dihydrocatharanthine (71).

It is now of great interest to investigate the similar introduction of a carbomethoxy group at C<sub>3</sub> of the quebrachamine molecule. This work would complete the total synthesis of a known Vinca alkaloid, vincadine (172) and since the latter would obviously undergo transannular cyclization<sup>35, 36</sup> to another alkaloid, vincadiformine (173), its potential in the total synthesis of a whole series of Vinca alkaloids is now apparent. Some of these investigations are now underway in our laboratory.



(172)



(173)

## EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. The ultraviolet (UV) spectra were recorded in methanol on a Cary 11 recording spectrophotometer, and the infrared (IR) spectra were taken on a Perkin Elmer Infracord. Nuclear magnetic resonance (NMR) spectra were recorded in deuteriochloroform at 60 megacycles/sec. (unless otherwise stated) on a Varian A60 instrument; the line positions or centres of multiplets are given in the Tiers  $\tau$  scale with reference to tetramethylsilane as internal standard; the multiplicity, and integrated area and type of protons are indicated in parentheses. Silica Gel G and Woelm alumina were used for thin layer chromatography; the type of absorbent and the solvent system used for development are given in parentheses. The alumina used for column chromatography was Shawinigan reagent grade deactivated with 3% of 10% aqueous acetic acid (unless otherwise stated). Analyses were performed by Dr. A. Bernhardt and associates, Mulheim (Ruhr), Germany and by Mr. P. Borda, the Microanalytical Laboratory, University of British Columbia. Mass spectra were determined using an Atlas CH-4 mass spectrometer, while high resolution molecular weight determinations were carried out on AEI MS-9 instrument.

### Scheme A Experimental Section

#### Methyl nicotinate (110)

To a solution of nicotinic acid (109) (123 g, 1 mole) in



dry methanol (310 ml), was added concentrated sulfuric acid (155 ml), and the mixture refluxed for 3 hr. Part of the methanol was distilled (200 ml) and the rest of the reaction mixture poured into ice-water. The mixture was extracted with chloroform and the chloroform extract washed with water, 5% sodium bicarbonate solution, and water again, and then dried over anhydrous magnesium sulfate. The chloroform was removed under reduced pressure and the resulting crude oil (130 g) distilled to give the desired material (115 g, 84%), bp 65°/1 mm, (lit<sup>64</sup>, 118.5°/25 mm).

#### Nipecotic acid (111)

A suspension of 24.6 g (0.2 mole) of nicotinic acid (109) in water (200 ml) was treated with 15N ammonia (40 ml) and hydrogenated in the presence of 9.0 g of 5% rhodium on carbon at room temperature and 2 atmospheres pressure. Hydrogenation was continued until the UV spectrum showed no absorption above 240 mμ. The reaction mixture was filtered through Celite and the filtrate was concentrated to dryness under reduced pressure. To ensure complete removal of water the residue was treated with anhydrous benzene and reconcentrated. The yield of the crude product (20 g, 80%), mp 254-260°, (lit<sup>66</sup>, mp 260-61°).

#### 3-Carbomethoxypiperidine (98)

(a) A solution of methyl nicotinate (110) (23.5 g, 0.17 mole) in dry methanol (80 ml) and glacial acetic acid (20 ml) was hydrogenated in the presence of platinum oxide (0.39 g) and

under 1.3-3 atmospheres pressure. After the uptake of hydrogen had ceased the catalyst was removed by filtration through Celite, and the filtrate was concentrated under reduced pressure below  $50^{\circ}$ . The resulting mixture was cooled in ice and concentrated potassium hydroxide (40%) added slowly, until the mixture was just alkaline. During this addition, care was taken to keep the temperature of the mixture below  $5^{\circ}$ . The free base was extracted with ether and the ether extract washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude oil (18 g) was distilled to give the desired material (5 g, 20%), bp  $70-75^{\circ}/1$  mm, (lit<sup>65</sup>,  $102-107^{\circ}/5$  mm). Infrared (film): 3230 ( $-\overset{|}{\text{NH}}$ ), 1710 ( $-\text{COOCH}_3$ )  $\text{cm}^{-1}$ . NMR signals: 6.40 (singlet, 3H,  $-\text{COOCH}_3$ ), 8.26 (singlet, 1H,  $-\overset{|}{\text{NH}}$ ).

(b) The crude nipecotic acid (111) (20 g) obtained as described above was suspended in dry methanol (10 ml) and the resultant mixture was cooled in an ice bath. Ethereal diazomethane was added slowly until a yellow color persisted. The reaction flask was then removed from the ice bath and held at room temperature for 6 hr. Removal of the solvent under reduced pressure provided a pale yellow syrup which was purified by distillation (15 g, bp  $65-7^{\circ}/2$  mm). Thin layer chromatography (alumina, ethyl acetate) indicated two major components. Purification by chromatography on Woelm alumina activity I was unsuccessful. Fractional distillation using a Nester-Faust 450x6 mm spinning band column gave a forerun (8.8 g, bp  $45^{\circ}/0.1$  mm)

which on examination by thin layer chromatography (alumina, ethyl acetate) was enriched in the undesired material (113). The later fractions (combined weight, 3.0 g, bp  $37^{\circ}/0.1$  mm) was shown by thin layer chromatography (alumina, ethyl acetate) to contain mainly the desired material (98). Infrared (film): 3230 ( $-\text{NH}$ ), 1710 ( $-\text{COOCH}_3$ )  $\text{cm}^{-1}$ . Ultraviolet spectrum: no absorption above 230 mu. NMR signals: 6.40 (singlet,  $-\text{COOCH}_3$ ), 7.80 (singlet,  $-\text{NCH}_3$ ), 8.26 (singlet,  $-\text{NH}$ ).

(c) Nipecotic acid hydrochloride (111,a) (8 g, 0.05 mole) was mixed with 80 ml of 5% methanolic hydrogen chloride and the resulting solution was refluxed for 12 hr. The solvent was removed under reduced pressure and the resulting solid treated with ice cold concentrated sodium hydroxide (30%). The free base was extracted with ether and the ether extract washed with saturated sodium chloride solution, dried over magnesium sulfate and then concentrated under reduced pressure. The resulting green liquid was distilled to give the desired material (98) as a clear liquid (3.6 g, 52%, bp  $50^{\circ}/1$  mm). Infrared (film): 3230 ( $-\text{NH}$ ) and 1710 ( $-\text{COOCH}_3$ )  $\text{cm}^{-1}$ . NMR signals: 6.40 (singlet, 3H,  $-\text{COOCH}_3$ ), 8.26 (singlet, 1H,  $-\text{NH}$ ).

#### Diethyl $\gamma$ -chloropropylmalonate (108)

A solution of diethyl malonate (130 g, 0.81 mole) and 1,3-chlorobromopropane (130 g, 0.82 mole) in anhydrous ether (200 ml) was added in one portion to a solution of sodium ethoxide (52.5 g, 0.75 mole) in dry ethanol (250 ml). The reaction mixture was maintained at  $35^{\circ}$  for 4 hr and then

allowed to stand at room temperature for 24 hr. The reaction mixture was poured into water (600 ml) and extracted with ether. The ether extract was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting oil was distilled to give the desired material (118 g, 70%), bp 80°/0.2 mm, (lit<sup>59</sup>, bp 142°/10 mm). Infrared (film): 1730 ( $-\text{COOCH}_2\text{CH}_3$ )  $\text{cm}^{-1}$ . NMR signals: 5.75 (quartet, 4H, 2x- $\text{COOCH}_2\text{CH}_3$ ), 6.56 (triplet, 2H,  $-\text{CH}_2\text{CH}_2\text{Cl}$ ), 6.75 [triplet, 1H,  $-\text{CH}_2\text{CH}(\text{COOCH}_2\text{CH}_3)_2$ ], 8.10 (multiplet, 4H,  $\text{ClCH}_2\text{CH}_2\text{CH}_2-$ ), 8.80 (triplet, 6H, 2x $\text{COOCH}_2\text{CH}_3$ ).

#### Benzenediazonium chloride

Aniline hydrochloride (10 g, 0.076 mole) was suspended in a mixture of glacial acetic acid (60 ml) and dry, peroxide-free dioxan (60 ml). The mixture was cooled in an ice-salt bath and isoamyl nitrite (10 g, 0.084 mole) was added slowly, the temperature being held below 5°. After the addition was complete the mixture was stirred for 30 min during which the solid suspension dissolved. Dry dioxan (300 ml) or dry ethyl ether (300 ml) was added in one portion and the white precipitate of benzenediazonium chloride was collected, washed with fresh solvent and dried in a desiccator. (Yield 9.5 g), (lit<sup>63</sup>).

#### 2-Carboethoxy-3-( $\beta$ -chloroethyl)-indole (97.a)

To a sodium ethoxide solution prepared by dissolving sodium (1.65 g, 0.0715 mole) in dry ethanol (200 ml), was added

diethyl  $\gamma$ -chloropropylmalonate (17.0 g, 0.0715 mole), and the mixture stirred for 30 min at room temperature. After cooling this solution in an ice-salt bath the benzenediazonium chloride was added in small portions in order to keep the temperature below 5°. The reaction mixture was allowed to stand in the refrigerator for 12 hr and then poured into water (200 ml). The dark red oil which separated was collected and the aqueous layer extracted with ether. The oil was combined with the ether extracts and the resulting solution was washed with water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude reaction product (19.0 g) was immediately subjected to the Fischer indole synthesis described below.

The material obtained above was dissolved in dry ethanol (150 ml) containing concentrated sulfuric acid (20 ml) and the mixture refluxed for 12 hr. After cooling to room temperature to reaction mixture was poured onto ice and the resulting mixture extracted with chloroform. The chloroform extract was washed several times with water, then with sodium bicarbonate solution, and again with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude dark oil (15 g) was purified by chromatography over alumina (750 g). Unreacted starting material (108) was eluted with benzene as a clear oil (6 g), while the desired material was eluted with chloroform, and obtained as a white solid. Recrystallisation from chloroform/petroleum ether

(60-80°) gave white needles (3.0 g, 26%), mp 125-132°. Infrared (nujol mull): 3250 ( $\text{-NH}$ ) and 1670 ( $\text{-COOCH}_2\text{CH}_3$ )  $\text{cm}^{-1}$ . Ultraviolet;  $\lambda_{\text{max}}$  ( $\log \epsilon$ ): 229 (4.40), 296 (4.27)  $\mu$ . NMR signals: 0.75 (broad singlet, 1H,  $\text{-NH}$ ), 2.60 (multiplet, 4H, aromatic), 5.54 (quartet, 2H,  $\text{-COOCH}_2\text{CH}_3$ ), 6.50 (multiplet, 4H,  $\text{-CH}_2\text{CH}_2\text{Cl}$ ) and 8.60 (triplet, 3H,  $\text{-COOCH}_2\text{CH}_3$ ). Found: C, 62.07; H, 5.53; N, 5.60; O, 12.64; Cl, 14.08. Calc. for  $\text{C}_{13}\text{H}_{14}\text{O}_2\text{NCl}$ : C, 62.03; H, 5.57; N, 5.57; O, 12.75; Cl, 14.12.

2-Carbomethoxy-3-( $\beta$ -chloroethyl)-indole (97,b)

2-Carboethoxy-3-( $\beta$ -chloroethyl)-indole (1.22 g, 4.9 mmole) was dissolved in dry methanol (300 ml) containing concentrated sulfuric acid (5 ml), and the mixture refluxed for 24 hr. Part of the methanol was distilled (100 ml) and the rest of the reaction mixture was poured onto crushed ice (500 g). After careful neutralisation with sodium bicarbonate the aqueous mixture was extracted with chloroform. The chloroform extract was washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a white solid. Crystallisation from light petroleum (60-80°)/ethyl ether gave white needles (1.0 g, 87%), mp 125-132°. Infrared (nujol mull): 3250 ( $\text{-NH}$ ), 1670 ( $\text{-COOCH}_3$ )  $\text{cm}^{-1}$ . Ultraviolet;  $\lambda_{\text{max}}$  ( $\log \epsilon$ ): 228 (4.26), 296 (4.30)  $\mu$ . NMR signals: 0.75 (broad singlet, 1H,  $\text{-NH}$ ), 2.60 (multiplet, 4H, aromatic), 6.06 (singlet, 3H,  $\text{-COOCH}_3$ ) and 6.40 (multiplet, 4H,  $\text{-CH}_2\text{CH}_2\text{Cl}$ ). Found: C, 60.64; H, 5.10; N, 5.89; O, 13.61 and Cl, 14.84. Calc. for

$C_{12}H_{12}NO_2Cl$ : C, 60.62; H, 5.04; N, 5.88; O, 13.44 and Cl, 14.91.

### Coupling reactions

#### (a) Coupling product (99, R=Et)

A solution of 2-carboethoxy-3-( $\beta$ -chloroethyl)-indole (97,a) 500 mg, 2 mmole) and 3-carbomethoxypiperidine (98) (600 mg, 4.2 mmole) in freshly distilled dry dioxane (15 ml) was sealed in a Carius tube. The tube was then transferred to a metal container and heated at  $160^\circ$  for 14 hr. After cooling, the reaction mixture was poured into dilute hydrochlorine acid (120 ml) and the acidic solution extracted with ether. The ether extract was washed with aqueous sodium bicarbonate and water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Examination by thin layer chromatography (alumina, chloroform) and NMR indicated that this crude product was unreacted starting material (97,a).

The aqueous acidic solution was basified with 15N ammonia and extracted with ether. The ether extract was thoroughly washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude solid (500 mg) was purified by chromatography on alumina (25 g). The desired material was eluted with chloroform and obtained as a white solid, which was recrystallised from petroleum ether ( $60-80^\circ$ )/ether or petroleum ether ( $60-80^\circ$ )/ chloroform as needles (250 mg, 60% based on unrecovered starting material (97,a) , mp  $103-5^\circ$ . Infrared (nujol mull):  $3250$  ( $-\dot{N}H$ ),  $1710$  ( $-COOCH_3$ ) and  $1670$  ( $-COOCH_2CH_3$ )  $cm^{-1}$ . Ultraviolet;

$\lambda_{\max}$  ( $\log \epsilon$ ): 228 (4.41) 296 (4.31)  $\mu$ . NMR signals: 0.80 (broad singlet, 1H,  $-\overset{|}{\text{NH}}$ ), 2.60 (multiplet, 4H, aromatic), 5.50 (quartet, 2H,  $-\text{COOCH}_2\text{CH}_3$ ), 6.30 (singlet, 3H,  $-\text{COOCH}_3$ ) and 8.60 (triplet, 3H,  $-\text{COOCH}_2\text{CH}_3$ ). Found: C, 66.89; H, 7.40; N, 7.77; O, 17.81. Calc. for  $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_4$ : C, 67.00; H, 7.31; N, 7.82; O, 17.85.

(b) Coupling product (99, R=Me)

The coupling reaction between (97,b) and (98) was carried out as described above. Crystallisation from petroleum ether (60-80°)/chloroform yielded white needles (50%), mp 109°. Infrared (nujol mull): 3250 ( $-\overset{|}{\text{NH}}$ ), 1720 ( $-\text{COOCH}_3$ ) and 1670 ( $-\text{COOCH}_3$ )  $\text{cm}^{-1}$ . Ultraviolet;  $\lambda_{\max}$  ( $\log \epsilon$ ): 229 (4.34), 296 (4.23)  $\mu$ . NMR signals: 0.80 (broad singlet, 1H,  $-\overset{|}{\text{NH}}$ ), 2.60 (multiplet, 4H, aromatic), 6.10 (singlet, 3H,  $-\text{COOCH}_3$ ), 6.32 (singlet, 3H,  $-\text{COOCH}_3$ ). Mass spectrum: MW 344, base peak m/e 156. Calc. MW: 344. Found: C, 65.88; H, 7.14; N, 8.03; O, 18.70. Calc. for  $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_4$ : C, 66.26; H, 7.02; N, 8.13; O, 18.58.

In some instances the ether extract of the aqueous acidic layer contained an additional product, which could be separated from the unreacted starting indole (97,b) by chromatography on alumina. This product (113) was eluted with chloroform containing 1% methanol and obtained as a white solid which could be crystallised from chloroform as white needles, mp 199-201°. Infrared (nujol mull): 3250 ( $-\overset{|}{\text{NH}}$ ) and 1690 ( $-\text{COOCH}_2-$ )  $\text{cm}^{-1}$ . Ultraviolet,  $\lambda_{\max}$  ( $\log \epsilon$ ): 230 (4.36),



296 (4.24) mu. NMR signals: 0.4 (singlet, 1H,  $-\overset{1}{\text{NH}}$ ), 2.60 (multiplet, 4H, aromatic), 5.36 (triplet, 2H,  $-\text{COOCH}_2\text{CH}_2-$ ) and 6.90 (triplet, 2H,  $-\text{COOCH}_2\text{CH}_2-$ ). Mass spectrum: MW 187, base peak m/e 187. Calc. MW: 187. Found: C, 70.48; H, 4.67; N, 7.39; O, 17.24. Calc. for  $\text{C}_{11}\text{H}_9\text{NO}_2$ : C, 70.58; H, 4.85; N, 7.48; O, 17.09.

Attempted Acyloin Condensation Using Intermediate 99, R=Me

The acyloin condensations were all run in a special apparatus. The reaction mixture was contained in a three-necked 250 ml Morton flask fitted with a high speed stirrer, a nitrogen inlet and a high dilution apparatus, as described by Leonard<sup>86</sup>. Prior to the start of the reaction, the apparatus was flame dried while a stream of purified nitrogen was passed through. Toluene was distilled from sodium into the reaction flask until it was three-quarters full. Part of the solvent was redistilled from the Morton flask and the condensate removed via a condenser at the top of the high dilution apparatus. Any remaining water was thus removed azeotropically from the apparatus. Following cooling, sodium (0.5 g) was introduced into the reaction flask and the solvent heated to vigorous reflux as the mixture was stirred at high speed (6000 rpm). The coupling product (99, R=Me, 1 g) was dissolved in anhydrous toluene (25 ml) and introduced into the dilution chamber over a period of 4 hr. When addition was completed refluxing was continued for an additional 2 hr. The flask and its contents were cooled and an

equivalent amount of glacial acetic acid added. Stirring was continued until all the sodium had been destroyed. The solid material was removed by filtration and washed with toluene, ether and chloroform. The combined toluene filtrate and toluene washings were concentrated under reduced pressure to yield a brown gum (500 mg) which crystallised on standing. This material was identified as unreacted starting material (99, R=Me). The ether and chloroform extracts upon examination by thin layer chromatography (silica, chloroform:methanol, 4:1) were shown to contain one major polar component and two very minor components. Infrared ( $\text{CHCl}_3$ ): 3220 ( $\text{-NH}$ ), 1700 (carbonyl)  $\text{cm}^{-1}$ . Ultraviolet spectrum,  $\lambda_{\text{max}}$ : 228, 296 m $\mu$ . NMR signals: although the spectrum was poorly resolved it did show a singlet at  $\tau$ 1.6 ( $\text{-NH}$ ) and a multiplet at  $\tau$ 2.70 characteristic of the aromatic protons.

Attempted Acyloin Condensation Using Intermediate 99, R=Et

The intermediate (99, R=Et) (500 mg) was subjected to the acyloin condensation as described above. The toluene soluble product (340 mg) on examination by thin layer chromatography (silica, ethyl acetate) was found to contain three components, which we will designate 1, 2 and 3 in order of increasing polarity. Preparative thin layer chromatography on silica gel (0.5 mm, ethyl acetate) provided homogeneous samples of these components.

Compound 1: Infrared (film): 3320 ( $\text{-NH}$ ), 1710 (saturated ester), 1680 (sh, aromatic ester)  $\text{cm}^{-1}$ . Ultraviolet spectrum,  $\lambda_{\text{max}}$ : 228, 296 m $\mu$ . NMR signals: 0.68 (singlet,  $\text{-NH}$ ), 2.65 (multiplet,

aromatic), 5.60 (quartet,  $-\text{COOCH}_2\text{CH}_3$ ), 5.86 (quartet,  $-\text{CHCOOCH}_2\text{CH}_3$ ), 8.75 (sextet,  $2x-\text{OCH}_2\text{CH}_3$ ). This product appeared to be the diethyl ester.

Compound 2: Infrared (film): 3320 ( $-\text{NH}$ ), 1715 (saturated ester), 1680 (sh, aromatic ester)  $\text{cm}^{-1}$ . Ultraviolet spectrum,  $\lambda_{\text{max}}$ : 228, 296  $\mu$ . NMR signals: 0.50 (singlet,  $-\text{NH}$ ), 2.65 (multiplet, aromatic), 6.08 (singlet,  $-\text{COOCH}_3$ ), 6.32 (singlet,  $-\text{COOCH}_3$ ).

$R_f$  value by thin layer chromatography (silica, ethyl acetate) identical with coupling product (99, R=Me).

Compound 3: Infrared (film): 3320 ( $-\text{NH}$ ), 1710 (saturated ester), 1675 (sh, aromatic ester)  $\text{cm}^{-1}$ . Ultraviolet spectrum,  $\lambda_{\text{max}}$ : 324, 296  $\mu$ . NMR signals: 1.0 (singlet,  $-\text{NH}$ ), 2.60 (multiplet, aromatic), 5.50 (quartet,  $-\text{COOCH}_2\text{CH}_3$ ) 6.30 (singlet,  $-\text{COOCH}_3$ ), 8.60 (triplet,  $-\text{COOCH}_2\text{CH}_3$ ).  $R_f$  value by thin layer chromatography (silica, ethyl acetate) was identical with starting material (99, R=Et).

#### Diol (114)

The coupling product (99, R=Me) (50 mg) was dissolved in anhydrous tetrahydrofuran (5 ml) and added to a suspension of lithium aluminum hydride (50 mg) in tetrahydrofuran (10 ml). The resulting mixture was refluxed for 2 hr, and the excess lithium hydride destroyed by the careful addition of moist tetrahydrofuran. The solid material was removed by filtration and the residue washed with chloroform. The combined filtrate and washings were dried over anhydrous sodium sulfate and the solvent removed under reduced pressure to give diol (35 mg),

which was one spot on thin layer chromatography (silica, chloroform: methanol, 4:1). Infrared ( $\text{CHCl}_3$ ): 3250 (broad,  $-\text{NH}$ ), no carbonyl. Ultraviolet,  $\lambda_{\text{max}}$ : 225, 276(sh), 284, 292 mu. NMR signals: 0.75 (singlet, 1H,  $-\text{NH}$ ), 2.60 (multiplet, 4H, aromatic) 5.10 (broad, 2H,  $2x-\text{OH}$  - assigned on the basis of deuterium exchange), 5.45 (singlet, 2H, indole- $\text{CH}_2\text{OH}$ ), 6.70 (doublet, 2H,  $-\text{CHCH}_2\text{OH}$ ). Mass spectrum: MW 288, base peak m/e 128. Calc. for  $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_2$ : MW 288.

#### Diacetate (115)

The diol (35 mg) obtained above was dissolved in a mixture of pyridine (1.5 ml) and acetic anhydride (1.5 ml) and the resulting solution was allowed to stand at room temperature for 12 hr. Anhydrous potassium carbonate was added and the resulting mixture filtered. The filtrate was concentrated under reduced pressure to provide the diacetate (115) as a clear colorless glass (43 mg). Examination by thin layer chromatography (alumina, chloroform) showed that this product was essentially one spot. Infrared ( $\text{CHCl}_3$ ): 3400 ( $-\text{NH}$ ), 1725 (carbonyl)  $\text{cm}^{-1}$ . Ultraviolet spectrum,  $\lambda_{\text{max}}$  225, 276(sh), 283, 292 mu. NMR signals: 1.5 (broad singlet, 1H,  $-\text{NH}$ ), 2.60 (multiplet, 4H, aromatic), 4.76 (singlet, 2H, indole- $\text{CH}_2\text{OAc}$ ), 6.05 (doublet, 2H,  $-\text{CHCH}_2\text{OAc}$ ), 8.0 (singlet, 6H,  $2x-\text{OCH}_3$ ).

#### Diacid (116)

The coupling product (30 mg) was mixed with 2 ml of 10% aqueous sodium hydroxide and the resulting mixture refluxed

for 12 hr. Upon cooling, an equivalent amount of glacial acetic acid was added and resulting mixture concentrated to dryness under reduced pressure. The solid residue was treated with warm chloroform (3 ml). The chloroform soluble material (18 mg) on examination by thin layer chromatography (silica, chloroform:methanol 1:1) was shown to contain one very polar spot. Ultraviolet spectrum,  $\lambda_{\text{max}}$ : 223(sh), 293 mu. NMR signals: 2.60 (multiplet, aromatic), no signals due to the methyl ester functions. The rest of the NMR spectrum was ill-defined.

#### Treatment of Diacid (116) with Diazomethane

The crude diacid (116) (18 mg) obtained above was suspended in dry ethyl ether (10 ml) and the resulting mixture cooled in an ice bath. Ethereal diazomethane added slowly until the yellow color persisted. The reaction flask was then removed from the ice bath and held at room temperature for 6 hr. Removal of the solvent under reduced pressure yielded a pale yellow glass (18 mg) which on examination by thin layer chromatography (alumina, chloroform) was essentially one component whose  $R_f$  value was identical with the coupling production (99, R=Me). Infrared (nujol mull): 3225 ( $-\overset{|}{\text{NH}}$ ), 1695 (broad carbonyl)  $\text{cm}^{-1}$ . Ultraviolet spectrum,  $\lambda_{\text{max}}$ : 228, 296 mu. NMR signals: 0.75 (broad singlet, 1H,  $-\overset{|}{\text{NH}}$ ), 2.60 (multiplet, 4H, aromatic), 6.10 (singlet, 3H,  $-\text{COOCH}_3$ ), 6.32 (singlet, 3H,  $-\text{COOCH}_3$ ).

Treatment of the Acyloin Product with Lithium Aluminum Hydride

The polar material (20 mg) obtained from the attempted acyloin condensation of compound (99, R=Me) was treated with lithium aluminum hydride by the procedure described above. The crude product (17 mg), which was essentially one spot on thin layer chromatography, (silica, chloroform:methanol 4:1) had an  $R_f$  value identical with the diol (114). Infrared ( $\text{CHCl}_3$ ): 3230 (broad, -OH), no carbonyl. Ultraviolet,  $\lambda_{\text{max}}$ : 224, 276(sh), 284, 292 m $\mu$ . NMR signals: 0.75 (singlet, 1H, -NH), 2.60 (multiplet, 4H, aromatic), 5.42 (broad singlet, 4H, indole-CH<sub>2</sub>OH and -CHCH<sub>2</sub>OH), 6.65 (broad singlet, 2H, -CHCH<sub>2</sub>OH). Mass spectrum: MW 288, base peak m/e 128. Calc for  $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_2$ , MW: 288.

Treatment of Reduced Acyloin Product with Acetic Anhydride in Pyridine

The reduced acyloin product (17 mg) was acetylated by the procedure described above. The crude product (21 mg) on examination by thin layer chromatography (alumina, chloroform) was essentially one spot, whose  $R_f$  value was identical with that of the diacetate (115). Infrared ( $\text{CHCl}_3$ ): 3350 (-NH), 1725 (carbonyl)  $\text{cm}^{-1}$ . Ultraviolet spectrum,  $\lambda_{\text{max}}$ : 225, 276(sh), 283, 292 m $\mu$ . NMR signals: 1.50 (broad singlet, 1H, -NH), 2.60 (multiplet, 4H, aromatic), 4.75 (singlet, 2H, indole-CH<sub>2</sub>OAc), 6.05 (doublet, 2H, -CHCH<sub>2</sub>OAc), 8.00 (singlet, 6H, 2x-OCH<sub>3</sub>).

Diazomethane Treatment of Acyloin Product

The polar material (20 mg) obtained from the attempted

acyloin condensation of compound (99, R=Me) was dissolved in anhydrous ether and treated with an excess of diazomethane in ether at 0°C. The solution was allowed to stand at room temperature for 6 hr, and the excess diazomethane destroyed by addition of water. The ether layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product, on examination by thin layer chromatography, contained three components, one of which had an  $R_f$  value identical to the coupling product 99, R=Me.

#### Scheme B Experimental Section

##### $\gamma$ -Benzyloxy propand (142)

Sodium (50 g, 2.18 mole) was added in small portions to a hot (115°-120°), vigorously stirred solution of trimethylene glycol (500 g, 6.6 mole) in dry xylene (200 ml). After all the sodium had dissolved, benzylchloride (300 g, 2.38 mole) was slowly added with stirring the hot (120°) solution over a period of 2 hr. The reaction mixture was heated for an additional 1 hr and then cooled to room temperature. The precipitated sodium chloride was removed by filtration and washed with benzene. The combined filtrate and washings were concentrated under reduced pressure to provide a clear liquid (600 g), which was fractionated through a 1 ft. Vigreux column. After a fore-run of trimethylene glycol (345 g), bp 80-85°/2 mm, the  $\gamma$ -benzyloxy propanol (243 g, 65%) distilled as a clear colorless oil, bp 95-100°/1-2 mm, (lit<sup>77</sup>, 145-150°/13 mm), NMR signals (neat): 2.76 (singlet, 5H, aromatic),

5.59 (singlet, 1H,  $-\text{OH}$ ), 5.65 (singlet, 2H,  $\text{C}_6\text{H}_5\text{CH}_2\text{O}-$ ), 6.35 (triplet, 2H,  $-\text{CH}_2\text{OH}$ ), 6.51 (triplet, 2H,  $\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2\text{CH}_2-$ ), 8.21 (quintet, 2H,  $-\text{OCH}_2\text{CH}_2\text{CH}_2\text{OH}$ ).

Benzyl  $\gamma$ -chloropropyl ether (143)

Thionyl chloride (190 g, 1.5 mole) was added to a mixture  $\gamma$ -benzyloxy propanol (234 g, 1.4 mole) and dimethylaniline (200 g) at such a rate as to keep the temperature below  $60^\circ$ . After completing the addition, which took 3 hr, the reaction was allowed to proceed for an additional hour. The mixture was then poured into hydrochloric acid (10%, 500 ml) and extracted with chloroform. The chloroform extract was washed with water, sodium bicarbonate solution, and with saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting dark oil was distilled through a 1 ft. Vigreux column to provide the desired material (200 g, 80%) as a colorless oil, bp  $95-100^\circ/1$  mm, (lit<sup>78</sup>,  $129^\circ/16$  mm). NMR signals (neat): 2.72 (singlet, 5H, aromatic), 5.72 (singlet, 2H,  $\text{C}_6\text{H}_5\text{CH}_2\text{O}-$ ), 6.57 (triplet, 2H,  $\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2\text{CH}_2-$ ), 6.65 (triplet, 2H,  $-\text{CH}_2\text{CH}_2\text{Cl}$ ), 8.30 (quintet, 2H,  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl}$ ).

Diethyl  $\gamma$ -benzyloxypropylethyl malonate (144).

To a solution of sodium ethoxide (70 g, 1 mole) in absolute ethanol (500 ml) was added ethyl diethyl malonate (190 g, 1 mole). The solution was heated to reflux and benzyl  $\gamma$ -chloropropyl ether (185 g, 1 mole) added over a period of 1/2 hr. Refluxing



was continued for 10 hr and the reaction mixture was then stirred at room temperature for a further 10 hr. Most of the ethanol was removed by distillation, and water added to dissolve the inorganic salts. The layers were acidified with glacial acetic acid and separated. The aqueous layer was extracted with ether. The oil and ether extracts were combined, washed with water, sodium bicarbonate solution, and saturated sodium chloride solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude liquid (320 g) was distilled to give the desired material (163 g, 46%) as a clear colorless oil, bp 140-150°/0.1 mm. NMR signals: 2.75 (singlet, 5H, aromatic), 5.56 (singlet, 2H  $\text{C}_6\text{H}_5\text{CH}_2\text{O}-$ ), 5.86 (quartet, 4H,  $2x-\text{OCH}_2\text{CH}_3$ ), 6.58 (triplet, 2H,  $\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2-$ ), 8.00 (multiplet, 6H,  $-\text{OCH}_2\text{CH}_2\text{CH}_2\overset{|}{\text{C}}\text{CH}_2\text{CH}_3$ ), 8.82 (triplet, 6H,  $2x-\text{OCH}_2\text{CH}_3$ ), 9.20 (triplet, 3H,  $-\text{CH}_2\text{CH}_3$ ). (cf. lit<sup>54,a</sup>).

$\delta$ -Benxyloxypropylethyl malonic acid (145)

A mixture of intermediate (144) (163 g, 0.5 mole), potassium hydroxide (108 g), water (200 ml) and ethanol (50 ml) was warmed to 40° for 10 hr and then allowed to stir for a further 10 hr at room temperature. The alkaline solution was extracted with ether to remove any starting material (5.0 g). The aqueous layer was acidified with concentrated hydrochloric acid using Congo red as indicator and the oil that separated was collected. The aqueous layer was extracted

with ether and the combined ether extracts and oil washed with water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting oil was diluted with warm ether, and hexane added until the solution was opalescent. Upon cooling the desired acid (145) separated as a white crystalline solid (70 g, 50%), mp 117-120°, NMR signals: -1.5 (singlet, 2H, 2x-COOH), 2.70 (singlet, 5H, aromatic), 5.47 (singlet, 2H, C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>O-), 6.50 (triplet, 2H, C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>OCH<sub>2</sub>-), 7.8-8.8 (multiplet, 6H, -OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 9.12 (triplet, 3H, -CH<sub>2</sub>CH<sub>3</sub>). (cf. lit<sup>54,a</sup>).

Examination of the mother liquors by thin layer chromatography (silica, chloroform) indicated the presence of another compound in addition to the foregoing diacid (145). The NMR spectrum showed the presence of an ethyl ester function (quartet at  $\tau$ 5.95 and triplet at  $\tau$ 8.85) and a carboxylic acid proton (singlet at  $\tau$ -1.6). The structure (149) was assigned on this basis, and was confirmed by decarboxylation to yield ethyl 2-( $\gamma$ -benzyloxypropyl)-butanoate (147), see below experiment (b).

#### 2-( $\gamma$ -Benzyloxypropyl)-butanoic acid (146)

Ethyl  $\gamma$ -benzyloxypropyl malonic acid (67 g, 0.25 mole) was heated at 160°. The evolution of carbon dioxide ceased after 6 hr. The product, a yellow viscous oil (54 g) was used for subsequent reaction without further purification. NMR signals: -1.6 (singlet, 1H, -COOH), 2.71 (singlet, 5H,

aromatic), 5.55 (singlet, 2H,  $\text{C}_6\text{H}_5\text{CH}_2\text{O}-$ ), 6.56 (triplet, 2H,  $\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2\text{CH}_2-$ ), 7.65 (multiplet, 1H,  $-\text{CHCO}_2\text{H}$ ), 8.45 (multiplet, 6H,  $-\text{OCH}_2\text{CH}_2\text{CH}_2\text{CCH}_2\text{CH}_3$ ), 9.11 (triplet, 3H,  $-\text{CH}_2\text{CH}_3$ ).  
(cf. lit<sup>54,a</sup>)

Ethyl 2-( $\gamma$ -benzyloxypropyl)-butanoate (147)

(a) A solution of 2-( $\gamma$ -benzyloxypropyl)-butanoic acid (146) (54 g, 0.23 mole) in absolute ethanol (1 litre) and concentrated sulfuric acid (8 ml) was refluxed for 10 hr. Part of the ethanol (800 ml) was removed by distillation and the rest of the reaction mixture was poured into ice water. The resulting mixture was extracted with ether. The ether extract was washed with water, 5% sodium carbonate solution, and with water again, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting liquid was distilled under reduced pressure to afford the desired material (50 g, 81%) as a clear oil, bp  $135^\circ/1.5$  mm. Gas chromatography, performed on a Wilkins Aerograph Autoprep, Model A-700, using a 20% SE 30 analytical column (60/80 Chrom W, 10' x  $\frac{1}{4}$ " column temperature 260, helium flow rate 100 ml/min), retention time 5 mins. NMR signals: 2.75 (singlet, 5H, aromatic), 5.58 (singlet, 2H,  $\text{C}_6\text{H}_5\text{CH}_2\text{O}-$ ), 5.95 (quartet, 2H,  $-\text{OCH}_2\text{CH}_3$ ), 6.61 (triplet, 2H,  $\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2\text{CH}_2-$ ), 7.75 (multiplet, 1H,  $-\text{CHCOOC}_2\text{H}_5$ ), 8.40 (multiplet, 6H,  $-\text{OCH}_2\text{CH}_2\text{CH}_2\text{CCH}_2\text{CH}_3$ ), 8.85 (triplet, 3H,  $-\text{OCH}_2\text{CH}_3$ ), 9.15 (triplet, 3H,  $-\text{CH}_2\text{CH}_3$ ). (cf. lit<sup>54,a</sup>).

(b) The mother liquors (60 g) obtained from the crystallisation of the diacid (145) were decarboxylated as described above. The crude product, by thin layer chromatography (silica, chloroform), contained a highly polar component and a non-polar component whose  $R_f$  value was identical with that of (147). Without further purification the crude product was esterified by the above procedure. The final product of reaction (40 g) was identical in all respects with (147).

#### Preparation of triphenyl methyl sodium

Sodium (3 g) was placed in a 250 ml ground glass stoppered bottle and covered with xylene (10 ml). The xylene was heated on an open flame until the sodium melted. The flame was extinguished and while a steady stream of nitrogen was passed through the bottle, mercury (200 g) was slowly added. After cooling the amalgam to room temperature the excess xylene was removed by means of a pipette and triphenyl methyl chloride (11 g) and anhydrous ether (50 ml) added. The bottle was stoppered with a well greased stopper which in turn was securely wired to the bottle. After vigorous shaking for 6 hr the solution attained the dark red color of triphenyl methyl sodium. A further 80 ml of anhydrous ether was added and shaking continued for 1/2 hr.

The concentration of triphenyl methyl sodium (approximately 0.2 mole/litre) was determined by titration with 0.1N sulfuric

acid using methyl orange as indicator.

Ethyl  $\alpha$ -( $\gamma$ -benzyloxypropyl)- $\alpha$ -ethylsuccinate (148)

(a) Using Triphenyl Methyl Sodium

An ethereal solution (200 ml, 0.0485 mole) of triphenyl methyl sodium was added to a 500 ml flask which had been filled with nitrogen and fitted with a dropping funnel containing the monoester (147). The monoester was added over a period of 15 mins and the solution allowed to stir at room temperature for 1.5 hr. Ethyl bromoacetate (12.8 g, 0.0485 mole) was slowly added through the dropping funnel at such a rate as to keep the ether from refluxing. After the addition was completed (15 mins) the mixture was stirred for 30 mins at room temperature. The reaction mixture was then treated with water (100 ml) and the ether layer collected, washed with fresh water, dried over anhydrous magnesium sulfate, and concentrated. The resulting oil was diluted with a small quantity of benzene and allowed to stand until most of the triphenyl methane had crystallised. The triphenyl methane was removed by filtration and the filtrate chromatographed through alumina (1100 g). The triphenyl methane which remained in the filtrate was eluted with petroleum ether (65-110<sup>o</sup>), while the unreacted starting monoester (147) was eluted with petroleum ether (65-110<sup>o</sup>)/benzene (1:1) (7.8 g). The desired succinate derivative (148) was eluted with benzene as a yellow oil, which was

subsequently purified by molecular distillation (2.80 g, 42% based on unrecovered starting material) to provide a clear viscous oil, bp 180-200°/0.1 mm. Gas chromatography, performed on a Wilkins Aerograph Autoprep, Model A-700, using a 20% SE 30 analytical column (60/80 Chrom W, 10' x 1/4" column temperature 260, helium flow rate 100 ml/min), retention time 15 mins. NMR signals: 2.72 (singlet, 5H, aromatic), 5.56 (singlet, 2H, C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>O-), 5.92 (octet, 4H, 2x-OCH<sub>2</sub>CH<sub>3</sub>), 6.60 (triplet, 2H, C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>-), 7.4 (singlet, 2H, -CH<sub>2</sub>COOEt), 8.32 (multiplet, 6H, -OCH<sub>2</sub>CH<sub>2</sub> $\overset{|}{\underset{|}{\text{C}}}$ CH<sub>2</sub>CH<sub>3</sub>), 8.82 (sextet, 6H, 2x-CH<sub>2</sub>CH<sub>3</sub>), 9.18 (triplet, 3H, -CH<sub>2</sub>CH<sub>3</sub>). (cf. lit<sup>54,2</sup>).

(b) Using Methylsulfinyl Carbanion

Sodium hydride (1.0 g, 0.20 mole, 50% mineral oil dispersion: Metal Hydrides, Inc.) was placed in a 2-necked flask and washed with dry petroleum ether (3x) and decanted to remove the mineral oil. Dimethyl sulfoxide (distilled from calcium hydride, bp 64°/4 mm) was added and the mixture heated to 70-75° until the evolution of hydrogen ceased.

The monoester (5.28 g, 0.02 mole) (147) and a small amount of triphenyl methane as indicator were dissolved in anhydrous ether (250 ml) and placed in a 3-necked flask fitted with a nitrogen inlet, drying tube and a syringe cap. The methylsulfinyl carbanion was introduced into this mixture through the syringe cap using a hypodermic syringe until the

red color of triphenyl methyl sodium persisted. Ethyl bromoacetate (3.24 g, 0.02 mole) was added over a period of 15 mins and the mixture stirred for a further 15 mins. After this time a thick precipitate had formed. The reaction mixture was then poured into water and the ether layer separated, washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product contained a quantitative yield of unreacted monoester (147).

N-[ $\beta$ -(3-Indolyl)-ethyl]- $\alpha$ -(8-benzyloxypropyl)- $\alpha$ -ethylsuccinimide  
(123)

A suspension of tryptamine hydrochloride (6.1 g, 0.0312 mole) in a mixture of water (100 ml) and ether (200 ml) was basified with 10% sodium hydroxide solution. The ether extract, which contained the free base, was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. A solution of the succinate derivative (2.5 g, 0.00715 mole) and tryptamine hydrochloride (152 mg) in freshly distilled 2-(2-ethoxyethoxyethanol) (75 ml) was added to the tryptamine residue. The mixture was heated to reflux and 10 ml of the solvent was distilled to remove the last traces of water. Refluxing was continued for 48 hr under an atmosphere of purified nitrogen. After cooling, the reaction mixture was poured into water and the aqueous solution extracted with ether. The ether extract was washed with

water, 10% acetic acid solution, water, 5% sodium bicarbonate solution, and finally with saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude reaction product, a dark brown oil (4.1 g), was purified by chromatography on alumina (300 g). The desired imide (123) was eluted with benzene/chloroform (1:1) as a clear slightly brown gum (2.5 g, 86%). An analytical sample was prepared by molecular distillation (290°/0.05 mm). Infrared (film): 3325 ( $\text{-NH}$ ), 1760 (weak) and 1690 (strong) (imide), 750 and 700 (aromatic)  $\text{cm}^{-1}$ . Ultraviolet,  $\lambda_{\text{max}}$  (log  $\epsilon$ ): 224 (4.23), 275 (sh, 3.64), 282 (3.68), 290 (3.62)  $\mu$ . NMR signals: 1.48 (broad singlet, 1H,  $\text{-NH}$ ), 2.70 (multiplet, 9H, aromatic), 3.06 (doublet, 1H,  $\alpha$ -proton of the indole), 5.60 (singlet, 2H,  $\text{C}_6\text{H}_5\text{CH}_2\text{O-}$ ), 6.13 (triplet, 2H,  $\text{-CH}_2\text{CH}_2\text{N-}$ ), 6.66 (triplet, 2H,  $\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2\text{CH}_2\text{-}$ ), 7.00 (triplet, 2H,  $\text{-CH}_2\text{CH}_2\text{N-}$ ), 7.60 (singlet, 2H,  $\text{-CH}_2\text{CN-}$ ), 8.55 (multiplet, 6H,  $\text{-OCH}_2\text{CH}_2\text{CH}_2\text{C(=O)CH}_2\text{CH}_3$ ), 9.26 (triplet, 3H,  $\text{-CH}_2\text{CH}_3$ ). Mass spectrum: MW 418; main peaks: m/e 144, 143, 130, 91. Found: C, 74.45; H, 7.17; N, 7.07. Calc. for  $\text{C}_{26}\text{H}_{30}\text{N}_2\text{O}_3$ : C, 74.61; H, 7.01; N, 6.69.

#### Bischler-Napieralski Cyclisation of Imide (123)

A solution of the imide (118 mg) in dry toluene (75 ml) was placed in a 3-necked flask fitted with a nitrogen inlet and condenser. The toluene was heated to reflux and approximately 10 ml distilled to remove the last traces of



moisture. With a steady stream of nitrogen passing through the apparatus phosphorus pentoxide (approximately 0.9 g) was added in three equal portions over a period of 45 mins. After refluxing for a further 30 mins, the reaction was cooled to room temperature and the toluene decanted. The brown precipitate was treated with ice-water and then made strongly alkaline with concentrated potassium hydroxide. The basic solution was extracted with chloroform and the chloroform extract washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a brown gum (49 mg).

Purification by chromatography on alumina provided a yellow amorphous solid (15 mg). Further purification by thin layer chromatography (alumina, chloroform) afforded a yellow amorphous solid (10 mg), to which we assigned structure (155). Ultraviolet,  $\lambda_{\max}$ : 224, 313, 326 m $\mu$ ,  $\lambda_{\max}^{\text{HCl}}$  395 m $\mu$ . Mass spectrum: MW 310; main peaks: m/e 282 (M-18), 263, 251, 143 and 130.

N-[ $\beta$ -(3-Indolyl)-ethyl-3-( $\gamma$ -hydroxypropyl)-3-ethylpyrrolidine (161)]

To a solution of the imide (110 mg, 0.262 mmole) in dry tetrahydrofuran (20 ml) was added lithium aluminum hydride (400 mg) and the resulting mixture was refluxed for 10 hr and then allowed to stand at room temperature for 12 hr. The excess lithium aluminum hydride was destroyed by addition of moist tetrahydrofuran and the solid hydroxide salts removed by filtration and the residue washed with fresh tetrahydrofuran.

The combined filtrate and washings were poured into water and the resulting mixture was extracted with chloroform. The chloroform extract was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue (90 mg) was chromatographed on alumina (10 g). The desired material was eluted with benzene/chloroform (1:4) as a clear greenish gum (64 mg, 82%). An analytical sample was prepared by molecular distillation (220/0.1 mm). Infrared (film): 3222 (-OH), 750 (aromatic)  $\text{cm}^{-1}$ . Ultraviolet,  $\lambda_{\text{max}}$  (log  $\epsilon$ ); 221 (4.30), 274 (sh, 3.56), 282 (3.59), 290 (3.53). NMR signals (100 Mc/s), 1.75 (broad singlet, 1H,  $-\text{NH}$ ), 2.70 (multiplet, 4H, aromatic), 3.05 (doublet, 1H,  $\alpha$ -proton on indole nucleus), 6.40 (triplet, 2H,  $-\text{CH}_2\text{CH}_2\text{OH}$ ), 6.60 (broad singlet, 1H,  $-\text{CH}_2\text{OH}$  - disappears on treatment with  $\text{D}_2\text{O}$ ), 7.35 (multiplet, 8H,  $-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)_2$ ), 8.52 (multiplet, 8H,  $-\text{CH}_2-\text{C}(\text{CH}_2\text{CH}_2\text{CH}_2\text{OH})_2$ ), 9.16 (triplet, 3H,  $-\text{CH}_2\text{CH}_3$ ). Mass spectrum: MW 300; main peaks: m/e 170 (base peak), 156, 144, 130. Found: C, 75.96; H, 9.34; N, 9.29. Calc. for  $\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}$ : C, 76.00; H, 9.33; N, 9.33.

N-[ $\beta$ -(3-Indolyl)-ethyl -3-( $\delta$ -benzyloxypropyl)-3-ethylpyrrolidine (124)]

To a solution of the imide (4.6 g, 11 mmole) in dry tetrahydrofuran (500 ml) was added lithium aluminum hydride (4.6 g, 120 mmole) and the resulting mixture was stirred at room temperature for 12 hr and then refluxed for 4 hr. The

reaction mixture was worked up as described above. The crude reaction product (4.5 g) was purified by chromatography on alumina (300 g). The desired benzyl ether amine (124) was eluted with benzene-chloroform (9:1) as a light brown viscous oil (3.50 g, 81%). The analytical sample was prepared by molecular distillation  $280^{\circ}/0.05$  mm. Infrared (neat): 3200 ( $\text{-NH}$ ), 740 and 695 (aromatic)  $\text{cm}^{-1}$ . Ultraviolet spectrum,  $\lambda_{\text{max}}$  (log  $\epsilon$ ): 224 (4.27), 275 (sh, 3.63), 282 (3.66), 290 (3.61)  $\mu$ . NMR signals (100 Mc/s): 1.6 (broad singlet, 1H,  $\text{-NH}$ ), 2.68 (multiplet, 8H, aromatic), 3.22 (doublet, 1H,  $\alpha$ -proton on indole nucleus), 5.58 (singlet, 2H,  $\text{C}_6\text{H}_5\text{CH}_2\text{O-}$ ), 6.50 (triplet, 2H,  $\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2\text{CH}_2\text{-}$ ), 7.25 (multiplet, 6H,  $\text{-CH}_2\text{CH}_2\text{NCH}_2\text{-CH}_2\text{-}$ ), 7.59 (singlet, 2H,  $\text{-NCH}_2\text{C-}$ ), 8.50 (multiplet, 8H,  $\text{-CH}_2\text{CCH}_2\text{CH}_2\text{-}$ ), 9.20 (triplet, 3H,  $\text{-CH}_2\text{CH}_3$ ). Mass spectrum: base peak  $m/e$  260, strong  $m/e$  91. Found: C, 79.76; H, 8.97; N, 7.02. Calc. for  $\text{C}_{26}\text{H}_{34}\text{N}_2\text{O}$ : C, 79.96; H, 8.77; N, 7.17. Molecular wt. 390.269. (Calc. 390.267).

#### Mercuric Acetate Oxidation of Benzyl Ether Amine (124)

The benzyl ether amine (124) (1.0 g, 2.5 mmole) was dissolved in anhydrous methanol (400 ml) containing mercuric acetate (8.0 g, 25 mmole) and glacial acetic acid (15 ml). The mixture was stirred under an atmosphere of nitrogen at room temperature for 12 hr. and then refluxed for approximately 4 hr. The progress of the reaction was followed by removing small aliquots of the reaction mixture, bubbling hydrogen sulfide

through as described later, and observing the development of the light absorption maximum at 353 m $\mu$ . The reaction mixture was allowed to cool and the mercurous acetate (2.7 g, 5.2 mmoles) was filtered off. The filtrate was warmed to 50° and hydrogen sulfide was bubbled through for 10 min to destroy the mercury complex. The precipitated mercury sulfides were filtered off, and the filtrate immediately treated with sodium borohydride until the light absorption maximum at 353 m $\mu$  had completely disappeared. Part of the methanol (200 ml) was distilled and the rest of the reaction mixture poured into water. The aqueous solution was extracted with chloroform and the chloroform extract washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure to provide a brown viscous oil (836 mg). Complete resolution of all the products of the reaction by chromatography on alumina was not successful. The major fractions, eluted with benzene/chloroform (1:1), contained three components (125) (300 mg) whose  $R_f$  values, as shown by thin layer chromatography (alumina, ethyl acetate:chloroform 2:1) were very similar to each other and to that of the starting material (124). By repeated chromatography on alumina the least polar component could be partially removed from the others.

The following spectral data were recorded on a mixture of the two more polar components. Infrared (neat): 3220 ( $\text{-NH}$ ), 735 and 695 (aromatic)  $\text{cm}^{-1}$ . Ultraviolet spectrum,  $\lambda_{\text{max}}$ : 224, 275 (sh), 283, 291 m $\mu$ . NMR signals (100 Mc/s): 2.75 (multiplet,

9H, aromatic), 5.58 (singlet, 2H,  $\text{C}_6\text{H}_5\text{CH}_2\text{O}-$ ), 5.90 (multiplet,  $\text{C}_3-\text{H}$ ), 6.60 (triplet, 2H,  $\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2\text{CH}_2-$ ), 8.04 (singlet,  $-\text{NCH}_2-\text{C}-$ ), 9.20 (multiplet,  $-\text{CH}_2\text{CH}_3$ ). Mass spectrum; main peaks: m/e 198, 184, 170, 169, 156, 154, 140. Molecular wt. 388.251. Calc. for  $\text{C}_{26}\text{H}_{32}\text{N}_2\text{O}$ : 388.251. Attempts to obtain a sample for combustion analysis by molecular distillation led to extensive decomposition, as shown by UV spectra and thin layer chromatography.

### Debenzylation of the Cyclised Benzyl Ether Amines (125)

#### (a) Using Boron Tribromide

A mixture of the cyclised benzyl ether amines obtained as described above (90 mg) was dissolved in dichloromethane (5 ml) and the solution cooled to  $0^\circ$ . Boron tribromide (10 drops) was added slowly, the temperature being held at  $0^\circ\text{C}$ . The reaction was stirred vigorously for 10 min and then poured into 20% potassium hydroxide solution (15 ml). The resulting mixture was thoroughly extracted with dichloromethane. The dichloromethane extract was washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to provide a yellow-green glass (70 mg). Chromatography on alumina (50 g) and elution with chloroform/methanol (20:1) provided an amorphous yellow solid (50 mg) which according to thin layer chromatography (alumina, chloroform:methanol 20:1) was a mixture of products. Ultraviolet spectrum,  $\lambda_{\text{max}}$ : 225, 283, 292 m $\mu$ . NMR signals: 2.80 (multiplet, aromatic), no  $\alpha$ -proton absorption at 3.10, 9.20 (triplet,  $-\text{CH}_2\text{CH}_3$ ). A small sample of this mixture was

separated by thin layer chromatography on alumina to provide a pure sample of the major component. Mass spectrum; main peaks:  $m/e$  184, 170, 169, 156. Molecular weight: 298.204. Calc. for  $C_{19}H_{26}N_2O$ : 298.205.

(b) By Catalytic Hydrogenolysis

The mixture of cyclised benzyl ether amines (125) (110 mg) obtained as described above and 10% palladium on charcoal (110 mg) in glacial acetic acid (10 ml) were stirred in an atmosphere of hydrogen until the uptake of hydrogen ceased. The catalyst was removed by filtration through Celite and the filtrate diluted with water (50 ml) and neutralised with solid sodium carbonate. The resulting mixture was extracted with chloroform and the chloroform extract was washed with water and with saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure to provide the crude alcohols (164) as a green viscous glass (65 mg). The crude product was purified by chromatography on alumina (10 g). Elution with chloroform/methanol (99:1) provided three pure alcohols which will be designated A, B, and C in order of increasing polarity.

Alcohol A; 10 mg, 14%, on addition of dichloromethane crystallised as white plates, mp 168-170°. Ultraviolet spectra,  $\lambda_{max}$  (log  $\epsilon$ ): 225 (4.32), 275 (sh, 3.68), 283 (3.70), 290 (3.61)  $\mu$ . NMR signals (100 Mc/s): 2.05 (broad singlet, 1H,  $-NH$ ), 2.75 (multiplet, 4H, aromatic), 5.90 (multiplet, 1H,  $C_3-H$ ), 6.55

(triplet,  $-\text{CH}_2\text{OH}$ ), 9.18 (triplet, 3H,  $-\text{CH}_2\text{CH}_3$ ). Mass spectrum; main peaks: m/e 297 (M-1), 184, 170, 169, 156. Molecular weight: 298.204. Calc. for  $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}$ : 298.205.

Alcohol B: 20 mg, 24%, on addition of dichloromethane crystallised as white needles, mp  $180-5^\circ$ . Ultraviolet,  $\lambda_{\text{max}}$  (log  $\epsilon$ ): 223 (4.26), 274 (sh, 3.65), 283 (3.68), 291 (3.62)  $\mu$ . NMR signals (100 Mc/s): 1.80 (broad singlet, 1H,  $-\text{NH}$ ), 2.75 (multiplet, 4H, aromatic), 6.40 (triplet,  $-\text{CH}_2\text{OH}$ ), 8.00 (singlet, 2H,  $-\text{NCH}_2\text{C}^-$ ), 9.16 (triplet, 3H,  $-\text{CH}_2\text{CH}_3$ ). Mass spectrum; main peaks: 297 (M-1), 199, 170, 169, 156, 140. Molecular weight: 298.205. Calc. for  $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}$ : 298.205.

Alcohol C: green amorphous solid (14 mg, 17%). Ultraviolet spectrum,  $\lambda_{\text{max}}$  (log  $\epsilon$ ): 225 (4.33), 275 (sh, 3.67), 283 (3.70), 291 (3.63)  $\mu$ . NMR signals (100 Mc/s): 1.60 (broad singlet, 1H,  $-\text{NH}$ ), 2.75 (multiplet, 4H, aromatic), 5.80 (multiplet, 1H,  $\text{C}_3\text{-H}$ ), 6.40 (triplet,  $-\text{CH}_2\text{OH}$ ). Mass spectrum; main peaks: m/e 297 (M-1), 199, 184, 170, 169, 156, 140, 139. Molecular weight: 298.206. Calc. for  $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}$ : 298.205.

#### Mesylation of the Cyclised Aminoalcohols (164)

(a) The mixture of cyclised aminoalcohols (164) (100 mg) obtained from the debenzylolation experiment (a) (see above) was dissolved in dry pyridine (2 ml) and the solution cooled to  $0^\circ$ . Methanesulfonyl chloride (200 mg) was added slowly and the resulting mixture was allowed to stand in the refrigerator for 24 hrs, after which time the solution was dark wine red.

The reaction mixture was poured into 2N ammonia (20 ml) and the resulting mixture was extracted with ether. The ether extract was washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to provide a light brown foam (12 mg). The ultraviolet spectrum ( $\lambda_{\text{max}}$ : 258, 262, 268 m $\mu$ ) lacked the characteristic absorptions of an indole but showed the presence of a pyridine. The aqueous layer was concentrated to dryness, and the last traces of water removed by azeotropic distillation with benzene and xylene. The resulting powdery white residue (126) had an indolic ultraviolet spectrum ( $\lambda_{\text{max}}$ : 220, 280, 289 m $\mu$ ) with a shoulder at 270 m $\mu$  probably due to pyridine salts.

(b) The cyclised aminoalcohol B (34 mg) was mesylated by the above procedure, and the desired material (126) was obtained from the water extract. Ultraviolet spectrum,  $\lambda_{\text{max}}$ : 220, 280, 289 m $\mu$  - with a shoulder at 270 m $\mu$  ascribed to pyridine salts.

#### Reductive Ring Cleavage Reaction

(a) The quaternary salt (126) obtained from the mesylation experiment (a) was dissolved in anhydrous ethanol (2 ml) and transferred to a 3-necked flask fitted with a dry ice condenser and an ammonia inlet. After condensing approximately 30 ml of liquid ammonia into the flask, small quantities (50 mg each) of freshly cut sodium were added



until after the final addition the blue color persisted for 20 mins. Ammonium chloride was added and the ammonia allowed to evaporate. The residue was treated with water and extracted with ether. The ether extract was washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue, a light green gum (32 mg) was chromatographed on alumina (Woelm, activity I, 3 g). (dl)-Quebrachamine (1) (5 mg, 6% - based on mixture of cyclised aminoalcohols) was eluted with dichloromethane: ether 20:1. The infrared spectrum (Perkin Elmer Double Beam Model 21, chloroform) of this material was superimposable on that of natural (-)-quebrachamine. Ultraviolet spectrum,  $\lambda_{\max}$  (log  $\epsilon$ ): 228 (4.40), 285 (3.83), 292 (3.81) m $\mu$ . Mass spectrum: MW 282; main peaks: m/e 253, 210, 156, 144, 143, 138, 124, 110. These properties were identical with those of an authentic sample of (-)-quebrachamine. Additional evidence came from thin layer chromatography using several systems - silica gel, chloroform:ethyl acetate 1:1; alumina, benzene. Spray reagent: antimony pentachloride - purple spot, ceric sulfate - green-grey spot.

(b) The quaternary salt obtained from mesylation experiment (b) was reduced by a procedure identical with that described above to provide (dl)-quebrachamine (1.5 mg, 5% - based on uncyclised aminoalcohol B).

Bibliography

1. M. Hesse, "Indolalkaloide", Springer-Verlag, Berlin-Göttingen-Heidelberg, 1964.
2. R.H.F. Manske, "The Alkaloids", Vols. 1-8, Academic Press, New York, 1950-1965.
3. E. Leete, Chem. and Ind., 692(1960).
4. E..Leete, J. Am. Chem. Soc., 82, 6338(1960).
5. E. Leete, A. Ahmad and I. Kompis, J. Am. Chem. Soc., 87, 4168(1965).
6. E. Leete, Tetrahedron Letters, 23, 1449(1964).
7. G. Barger and C. Scholz, Helv. Chim. Acta, 16, 1343(1933).
8. G. Hahn and H. Ludwig, Ber., 67, 203(1934).
9. G. Hahn and H. Werner, Liebigs Ann. Chem., 520, 123(1935).
10. R. Robinson, "The Structural Relations of Natural Products", Claredon Press, Oxford, 1955.
11. R.W. Woodward, Nature, 162, 155(1948).
12. L.D. Antonaccio, N.A. Pereira, B. Gilbert, H. Vorbrueggen, H. Budzikiewicz, J.M. Wilson, L.J. Durham and C. Djerassi, J. Am. Chem. Soc., 84, 2161(1962); Pure and Applied Chemistry, 6, 575(1963).
13. R.B. Woodward, Angew. Chemie, 68, 13(1956).
14. E. Wenkert and N.V. Bringi, J. Am. Chem. Soc., 81, 1474(1959).
15. E. Wenkert, J. Am. Chem. Soc., 84, 98(1962).
16. R. Thomas, Tetrahedron Letters, 544(1961).
17. E. Schlittler and W.I. Taylor, Experientia, 16, 244(1960).
18. E. Leete, S. Ghosal and P.N. Edwards, J.Am. Chem. Soc., 84, 1068(1962).

19. E. Leete and S. Ghosal, Tetrahedron Letters, 1179(1962).
20. A.R. Battersby, R. Binks, W. Laurie, G.V. Parry and B.R. Webster, Proc. Chem. Soc., 369(1963).
21. E. Leete, A. Ahmad and I. Kompis, J. Am. Chem. Soc., 87, 4168(1965).
22. K. Stolle, D. Groger and K. Mothes, Chem. and Ind., 2065(1965).
23. A.I. Scott, F. McCapra, T. Money and I.G. Wright, Chem. Comm., 537(1965).
24. A.I. Scott, F. McCapra, T. Money and I.G. Wright, Proc. Nat. Acad. Sci. U.S.A., 53, 901(1965).
25. D. Arigoni and H. Goeygel, Chem. Comm., 538(1965).
26. A.R. Battersby, R.T. Brown, R.S. Kapil, A.O. Plunkett and T.B. Taylor, Chem. Comm., 46(1966).
27. A.R. Battersby, R.T. Brown, J.A. Knight, J.A. Martin and A. O. Plunkett, Chem. Comm., 346(1966).
28. A.R. Battersby, R.T. Brown, R.S. Kapil, J.A. Knight, J.A. Martin and A.O. Plunkett, Chem. Comm., 888(1966).
29. P. Loew, H. Goeygel and D. Arigoni, Chem. Comm., 347(1966).
30. E.S. Hall, F. McCapra, T. Money, K. Fukumoto, J.R. Hanson, B.C. Mootoo, G.T. Phillips and A.I. Scott, Chem. Comm., 348(1966).
31. E. Leete and S. Ueda, Tetrahedron Letters, 4915(1966).
32. A.R. Battersby, R.T. Brown, R.S. Kapil, J.A. Martin and A.O. Plunkett, Chem. Comm., 890(1966).
33. D. Schumann and H. Schmid, Helv., 46, 1996(1963).
34. J.P. Kutney and E. Piers, J. Am. Chem. Soc., 86, 953(1964).

35. J.P. Kutney, E. Piers and R.T. Brown, J. Am. Chem. Soc., 86, 2286(1964).
36. J.P. Kutney, E. Piers and R.T. Brown, J. Am. Chem. Soc., 86, 2287(1964).
37. J.P. Kutney, E. Piers and R.T. Brown, Lloydia, 27, 447(1964).
38. B.W. Bycroft, D. Schumann, M.B. Patel and H. Schmid, Helv. Chim. Acta, 47, 1147(1964).
39. J.P. Kutney, J. Trotter, T. Tabata, A. Kerigan and N. Camerman, Chem. Ind., 648(1963).
40. J.P. Kutney, R.T. Brown and E. Piers, Can. J. Chem., 44, 638(1966).
41. J.P. Kutney, W.C. Cretney, P. LeQuesne, B. McKague and E. Piers, J. Am. Chem. Soc., 88, 4756(1966).
42. E. Stork and J.E. Dolfini, J. Am. Chem. Soc., 85, 2872(1963).
43. Y. Ban, Y. Sato, I. Inoue, M. Nogai, T. Oishi, M. Terashima, O. Yonemitsu and Y. Kamoka, Tetrahedron Letters, 2261(1965).
44. M. Kuehne and C. Bayha, Tetrahedron Letters, 1311(1966).
45. S. Salley, Tetrahedron Letters, 2443(1964).
46. L.G. Donaruma and W.Z. Holdt, Org. Rea., Vol. 11, ed. by A.C. Cope et al., pp. 4-14, John Wiley and Sons, Inc., New York and London (1960).
47. G. Buchi, D.L. Coffen, K. Kocsis, P.E. Sonnet and F.E. Ziegler, J. Am. Chem. Soc., 87, 2073(1965); *ibid.*, 88, 3099(1966).
48. J.W. Huffman, C.B.S. Rao and T. Kamiya, J. Am. Chem. Soc., 87, 2288(1965). J. Org. Chem., 32, 697 (1967).
49. J.E.D. Barton and J. Harley-Mason, Chem. Comm., 14, 298(1965).

50. J.P. Kutney, N. Abdurahman, P. LeQuesne, E. Piers and I. Vlattas, J. Am. Chem. Soc., 88, 3656(1966).
51. J. Harley-Mason, Atta-ur-Rahman and J.A. Beisler, Chem. Comm., 20, 743(1966).
52. W. Whaley and T. Govindachari, Organic Reactions, Vol. 6, pp. 151.
53. K.T. Finley, Chem. Rev., 64, 573(1964).
54. (a) I. Vlattas, Ph.D. Thesis. (b) B. McKague, Ph.D. Thesis.
55. R. Adams, Organic Reactions, Vol. V, pp. 387-411.
56. W. Schindler, Helv. Chim. Acta, 40, 2156(1957).
57. R. Robinson, Chem. Rev., 63, 373(1963).
58. R. Phillips, Organic Reactions, Vol. X, p. 143.
59. T.A. Favorskaya and I.P. Yakovlev, Zhur. Obsheei Khim., 22, 113(1952). C.A., 46, 11119(1952).
60. M. Faurel, Bull. Soc. Chem., 324(1902).
61. . Hughes, . Lions and . Ritchie, J. Proc. Roy. Soc., N.S. Wales, 72, 209(1938). C.A., 33, 6837(1939).
62. V.V. Feofilaktov, Akad. Nauk S.S.S.R. Inst. Org. Kim. Sintezy Org. Soedinenii, Sbornik, 2, 103(1952). C.A., 48, 666(1954)
63. W. Smith and C.E. Waring, J. Am. Chem. Soc., 64, 469(1942).
64. R. Revine and J.K. Sneed, J. Am. Chem. Soc., 73, 5616(1951).
65. R. Adams, J. Am. Chem. Soc., 49, 1307(1927).
66. M. Freifelder, J. Org. Chem., 28, 1135(1963).
67. L.M. Jackman, "Applications of NMR Spectroscopy in Organic Chemistry", Pergamon Press, 1959.

68. S. Yamada and T. Shioiri, Tetrahedron Letters, 4, 351(1967).
69. W. Whaley and T. Govindachari, Organic Reactions, Vol. VI, pp. 74.
70. E. Wenkert, S. Gariatt and K.G. Dave, Can. J. Chem., 44, 489(1964).
71. G. Morrison, W. Cetenka and J. Shavel, Jr., J. Org. Chem., 29, 2771(1964).
72. E. Wenkert and B. Wickberg, J. Am. Chem. Soc., 84, 4914(1962).
73. E. Wenkert and B. Wickbert, J. Am. Chem. Soc., 87, 1580(1962).
74. R. Goutarel, F. Percheron, M.-M. Janot, Compt. Rend., 246, 279(1958).
75. L.J. Dolby and S. Sakai, J. Am. Chem. Soc., 86, 1890(1964).
76. E. Piers and T. Inaba, unpublished results.
77. L. Smith and J. Spring, J. Am. Chem. Soc., 65, 1271(1943).
78. G. Bennett and A.L. Hock, J. Chem. Soc., 128, 472(1927).
79. The Sadtler Spec-Finder, Research Laboratories, Fifteen/Seventeen Vine Street, Philadelphia 2, Pennsylvania, Spectra No., 19268-19277.
80. L. Cohen, J. Daly, H. Kny and B. Witkop, J. Am. Chem. Soc., 82, 2184(1960).
81. E. Corey and M. Chaykovsky, J. Am. Chem. Soc., 87, 1345(1965).
82. H. Budzikiewics, C. Djerassi and D.H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry", Vol. 1, Holden-Day, Inc., San Francisco, Calif., 1964.
83. R.D. Yossefyeh and Y. Mazur, Chem. and Ind., 609(1963).
84. H. Meerwein, Houben-Weyl, Methoden der Organischen Chemie, VI/3 (1965) pp. 169.

- 85. R. Adams, Organic Reactions, Vol. VII, pp. 269.
- 86. J.P. Kutney, W. Cretney, P. LeQuesne, B. McKague and E. Piers,  
J. Am. Chem. Soc., 88, 4756(1966).
- 87. N. Yoneda, Chem. Pharm. Bull., 13, 1231(1965).
- 88. N.J. Leonard, R.C. Fox and M. Oki, J. Am. Chem. Soc., 76,  
5708(1954).