SYNTHETIC STUDIES OF INDOLE ALKALOIDS

by

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We accept this thesis as conforming to the
required standard

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Abstract

Two synthetic approaches to the Aspidosperma and Iboga classes of indole alkaloids are described.

Section A discusses a possible synthetic route to the nine-membered ring alkaloid quebrachamine (93a). Nicotinic acid (75) was reduced to nipecotic acid hydrochloride (76), which was esterified to yield methyl nipecotate (77). Attempted preparation of 3-carbomethoxy-3-ethylpiperidine (67) by alkylation of (77) or of its \( \rho \)-bromobenzamide derivative (78) was unsuccessful.

The substituted piperidine (67) was then prepared by another synthetic sequence. Alkylations of methyl cyanoacetate led to methyl 3-chloropropylethylcyanoacetate (83). Catalytic reduction of the latter nitrile to the corresponding amine allowed cyclization to 3-carbomethoxy-3-ethylpiperidine (67). Reaction of 67 with 2-carboethoxy-3-(\( \beta \)-chloroethyl)-indole (66) provided 2-carboethoxy-3-[\( \beta \)-(3-carbomethoxy-3-ethyl-N-piperidyl)-ethyl]-indole (68). Attempted acyloin condensation of the latter to a nine-membered ring compound (69) was unsuccessful and led only to hydrolysis products.

Section B describes the first total synthesis of the nine-membered ring compounds \( \xi \alpha \)- and \( \xi \beta \)- dihydrocleavamine (152) and (153), isomeric with quebrachamine. Conversion of 2-ethyl 1,3-propanediol (106) to the monobenzyl ether (107) followed treatment with thionyl chloride provided 3-benzyloxy-2-ethyl-
propyl chloride (108). Alkylation of malonic ester with the latter afforded diethyl 3-benzylxy-2-ethylpropylmalonate (109). A second alkylation of 109 with ethyl bromoacetate yielded diethyl 2-(2-benzylxymethylbutyl)-2-carboethoxysuccinate (113). Hydrolysis, decarboxylation and re-esterification of this triester provided the substituted succinic ester (71a) in high yield. The succinic ester (71a) was also prepared but in low yield by hydrolysis, decarboxylation and re-esterification of the malonic ester (109) followed by alkylation with ethyl iodoacetate.

Condensation of the succinic ester (71a) with tryptamine provided the succinimide (130) which was reduced with lithium aluminum hydride to the tertiary amine (131) in high yield. Mercuric acetate oxidation of the latter afforded a mixture of isomeric cyclized compounds, one of which was the desired benzyl ether 72a. Catalytic debenzylation yielded the corresponding aminoalcohol (149) which was converted to the quaternary mesylate (73a) by treatment with methanesulfonyl chloride. Reductive cleavage of 73a with sodium in liquid ammonia yielded 4α- and 4β- dihydrocleavamine.

The synthesis of the isomeric dihydrocleavamines coupled with other synthetic work provides a general entry into the Aspidosperma and Iboga alkaloids.
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INTRODUCTION

Nature has provided us with a vast array of organic compounds of varying degrees of complexity and interest. A large group of these compounds, known as alkaloids, have been of considerable interest, even since before the onset of science in the modern sense of the word. Alkaloids are nitrogenous bases that occur in plants, usually localized in the bark, roots, seeds or leaves. Certain alkaloids have long been known to have characteristic and profound effects on biological systems, and this observation undoubtedly has provided the stimulus to their examination in ever increasing detail.

The indole alkaloids constitute a large class of compounds ranging in complexity from simple derivatives such as psilocybin (1), the hallucinogenic principle of Mexican mushrooms, to intricate ring systems such as those found in strychnine (2), the well known poison.

Approximately six hundred indole alkaloids have been reported isolated to date, and structural determinations
carried out on some three hundred of them. Characterization of these compounds, as with most newer natural products has been immensely aided by modern scientific instrumentation. The use of such analytical tools as mass spectrometry and nuclear magnetic resonance spectroscopy has become standard practice as will be illustrated in the discussion section.

The study of the biosynthesis of the indole alkaloids has recently become a field of intensified interest. The elucidation of biochemical pathways has been determined almost exclusively by the use of radioactively labelled precursors and has led to remarkable progress.

The amino acid tryptophan (3) has a strong structural similarity to the indole alkaloids, and has long been felt to be the precursor to the indole portion of the molecule. Radioactively labelled tryptophan has now been shown by a variety of workers to be incorporated into serotonin (4), psilocybine (1), gramine (5), ajmaline (6), serpentine (7) and reserpine (8), as well as vindoline (9), ibogaine (10), vindolinine (11) and catharanthine (12). It is felt that tryptophan is decarboxylated to tryptamine which then undergoes condensation reactions.

In contrast to the general agreement of different workers with regard to the "tryptophan" portion of the indole alkaloids, the biogenetic origin of the "non-tryptophan" or C\textsubscript{9-10} unit (thickened bonds in structures below), has been the subject
of considerable controversy. A number of theories have been proposed for this portion of the alkaloids. Results within the last year or two, however, provide very strong evidence for a monoterpenoid origin. The monoterpenoid hypothesis was originally proposed by Thomas and Wenkert at about the same time on the basis of structural similarities among many monoterpenes and the C\(_{9-10}\) portion of the indole alkaloids. Mevalonic acid (16), an intermediate in terpene biosynthesis, has been shown to be incorporated into the C\(_{9-10}\) portion of vindoline (9), reserpine (8), serpentine (7), catharanthine (12), 1,2-dehydroaspidospermidine (14) and ajmalicine (13). Geraniol (17), itself a monoterpenoid, has been shown to be a precursor of ajmalicine, serpentine, catharanthine and vindoline. More recently, Battersby and co-workers have incorporated the monoterpenoid loganin (15) into the alkaloids ajmalicine, vindoline and catharanthine.

Degradation of the labelled alkaloids has led to the biogenetic scheme shown in Figure 1. Structures 18, 19 and 20 represent the C\(_{10}\) units of the Corynanthe, Iboga and
Aspidosperma groups of alkaloids respectively which together account for the majority of the indole alkaloids.

An alternate biogenetic scheme for the derivation of the non-tryptophan portion of the indole alkaloids was proposed by Wenkert at the same time as his monoterpene hypothesis (Figures 2). Rearrangement of prephenic acid (21), an intermediate in the biosynthesis of aromatic acids, with retention of configuration of the migrating pyruvate side chain, then hydration provides intermediate 22 whose structure is readily discernible in yohimbine (23). Condensation of formaldehyde
Figure 2. Incorporation of Wenkert's SPF unit into Corynantheine and Ajmaline type Alkaloids
with intermediate 22 followed by ring opening possibly by a retro-aldo mechanism leads to a "seco-prephenate-formaldehyde" (SPF) unit (24), a crucial intermediate which could be incorporated not only into corynantheine (25) and ajmalicine (13) alkaloids but also ajmaline (6) and sarpagine (26). An important feature of the prephenic acid proposal was that it accounted for the almost constant configuration observed at carbon-15 in the indole alkaloids.

Wenkert's SPF unit (24) contains the identical carbon skeleton, with the exception of one carbon atom, as that proposed in the monoterpene hypothesis (18). The subsequent condensations of the SPF unit proposed by Wenkert therefore could apply to this monoterpene intermediate at its appropriate oxidation level.

Wenkert extended his proposal to include the Aspidosperma and Iboga groups of bases (Figure 3). Condensation of the SPF unit with tryptamine was envisaged as being followed by a retro-Michael reaction providing the cleavage product 29. If this undergoes ordinary oxidation - reduction changes, piperideines of various states of oxidation are formed whose intramolecular Michael and Mannich reactions lead to the Aspidosperma (30) and Iboga-like (31) skeletons respectively.

The bond making and bond breaking processes depicted for the derivation of the Aspidosperma and Iboga alkaloids are not unlike those currently proposed in the monoterpene hypothesis described earlier (18→19 and 20). The use of
Figure 3.
transannular cyclizations involving iminium salt intermediates is particularly interesting since Kutney and co-workers have demonstrated that such reactions are chemically feasible and have led to partial syntheses of the Iboga and Aspidosperma-type skeletons. (See Figures 4 and 5.)

Dihydrocleavamine\textsuperscript{16} (32), available from the alkaloid catharanthine\textsuperscript{17} (33), was converted by mercuric acetate oxidation via the intermediate iminium salt (34), to 7-ethyl-5-desethyaspidospermidine\textsuperscript{18} (35). This reaction was then utilized to convert the naturally occurring alkaloid (-)-quebrachamine (36) to the known alkaloid (+)-aspidospermidine\textsuperscript{19} (37).

Application of the transannular cyclization to carbomethoxydihydrocleavamine provided both the Aspidosperma and Iboga-type skeletons\textsuperscript{20}. Oxidation of carbomethoxydihydrocleavamine (38) to the iminium salt (39), followed by transannular cyclization provided pseudo-vincadifformine (40) - a variation of the Aspidosperma skeleton. Alternately, oxidation in the same reaction mixture, to the iminium salt (41) followed by transannular cyclization provided the Iboga skeleton (42).

In the case of the iminium salt (41), the ethyl group at C\textsubscript{4} was epimerized via the enamine (43) with the result that the known Iboga alkaloid coronaridine and its C\textsubscript{4} epimer dihydrocatharanthine (42) were obtained.
Figure 4. Transannular Cyclizations Providing the Aspidosperma Skeleton
Fig. 5. Conversion of Carbomethoxydihydrocleavamine into the Aspidosperma and Iboga Skeletons
The transannular cyclization is thus seen to be a possible biosynthetic and a versatile synthetic entry into the Aspidosperma and Iboga alkaloids. A synthesis of the appropriate nine-membered ring compounds like quebrachamine, dihydrocleavamine, and carbomethoxydihydrocleavamine would exploit the value of the transannular cyclization to the utmost and afford total syntheses of large classes of alkaloids.

A variety of approaches to the synthesis of indole alkaloids has appeared in the literature. However, those pertinent to the work herein, that is of the Aspidosperma and Iboga groups, are relatively few.

A recent synthesis of desethyllybogamine via a fairly short route was reported by Huffman\(^2\) and provides a useful model (Figure 6). Epoxidation of 3-cyclohexene-1-carboxylate (44) with metachloroperbenzoic acid to a mixture of cis and trans epoxides (45), followed by reaction with tryptamine gave a mixture of amino alcohols. Cyclization of the amino alcohol (46) from the trans epoxide, by heating, provided the N-indolyl-ethylisoquinuclidone (47). Cyclization of the tosylate to the indole ring gave desethyllybogamine lactam (48) which was reduced to desethyllybogamine (49) in high yield.

Buchi et al\(^2\) were the first to report the total synthesis of an Iboga alkaloid to date\(^a\). The reaction sequence

\(^a\) The synthetic work contained in this thesis leading to dihydrocleavamine and subsequently to the Iboga alkaloids has now been published in Journal of the American Chemical Society 88, 4756 (1966).
involves the elaborate construction of the isoquinuclidine (50) via a crucial Hofmann rearrangement. Combination of 50 with β-indolylacetyl chloride gave the amide (51) which was converted through the series of reactions depicted in Figure 7. to (−)-ibogamine (52) and (±)-epiibogamine (53).

Figure 6.
Figure 7. Synthesis of (+)-Ibogamine and (+)-Epiibogamine
(b) Dicyclohexylcarbodiimide in dimethyl sulfoxide
Another recent investigation by Duc and Fetizon\textsuperscript{23} using an entirely different approach led to the synthesis of an ibogaine analogue (54) and is shown in Figure 8.

Stork\textsuperscript{24} reported the first successful total synthesis of dl-aspidospermine (57) and dl-quebrachamine (36) as shown in Figure 9. Fischer indole cyclization of the appropriately prepared phenylhydrazone (56) is the key step. More recently Ban\textsuperscript{25} and co-workers reported a total synthesis of aspidospermine again using the Fischer indole cyclization of intermediate 56 but of different stereochemistry. Kuehne\textsuperscript{26} also obtained the intermediate 55 which would lead to aspidospermine and quebrachamine.

An interesting route to the Aspidosperma and Hunteria alkaloids has been reported by Barton and Harley-Mason\textsuperscript{27} as illustrated in Figure 10. The formation of (\textsuperscript{\(\dagger\)})-3-methylaspidospermidine (60) from the intermediate (58) involves a boron trifluoride induced rearrangement, while treatment of 58 with osmium tetroxide and subsequent cleavage of the diol leads to (\textsuperscript{\(\dagger\)})-eburnamine (61).

As discussed earlier, the transannular cyclization of a nine-membered ring intermediate provides a synthetic route to a large number of alkaloids. Quebrachamine and dihydrocleavamine led to the Aspidosperma series while carbomethoxydihydrocleavamine led to the Iboga and Vinca classes. Similarly carbomethoxyquebrachamine (62) could be expected to provide
Figure 8
Figure 9. Total Synthesis of dl-Aspidospermine and dl-Quebrachamine
Figure 10. Synthesis of (\textsuperscript{+})-3-Methyldapidospermidine and (\textsuperscript{+})-Eburnamine
vincadifformine\textsuperscript{28} (63) a naturally occurring alkaloid.

A synthesis of quebrachamine, dihydrocleavamine and their corresponding carbomethoxy derivatives therefore appeared desirable. Furthermore, since quebrachamine and dihydrocleavamine are epimeric, it became of interest to examine whether a similar route to these compounds themselves was attainable, as such a route would constitute a fairly general synthesis of the aforementioned alkaloids.

In addition to the intrinsic value of the synthesis of dihydrocleavamine lies its consideration as a possible eventual means of entry to dimeric alkaloids, some of which are well known for their anti-leukemic properties. Vinblastine\textsuperscript{29} and vincristine\textsuperscript{30}, obtained from Vinca rosea Linn, have recently been shown by X-ray analysis\textsuperscript{31} to have the structures 64 and 65 respectively. This work confirmed the previous structural assignment based on chemical and spectroscopic evidence and most importantly provided the absolute configuration for this molecule.
(64) \( R_1 = \text{CO}_2\text{CH}_3, \)
\( R_2 = \text{CH}_3, \)
\( R_3 = \text{OCH}_3, \)
\( R_4 = \text{Ac}, \)
no CH\(_3\) at N\(_6\)!

(65) \( R_1 = \text{CO}_2\text{CH}_3, \)
\( R_2 = \text{CHO}, \)
\( R_3 = \text{OCH}_3, \)
\( R_4 = \text{Ac}, \)
no CH\(_3\) at N\(_6\)!
DISCUSSION

Two synthetic routes were examined and involved entirely different modes of generation of the all important nine-membered ring. For this reason the discussion has been divided into two sections, A and B, each dealing with the appropriate synthetic approach.

The initial route which was being designed for the compound quebrachamine is outlined in Figure 11 and utilized the well known acyloin condensation to form the nine-membered ring. The acyloin condensation is one of the few practicable methods available for generating medium size rings, where non-bonded interactions become an important consideration during the ring closure. This method failed to yield the desired compounds but it is appropriate to mention some of the chemistry which was involved.

The second route, applied to dihydrocleavamine and depicted in Figure 12, consisted in the generation of the nine-membered ring by cleavage of a bond common to a fused five- and six-membered ring (73a). This method was successful and resulted in the first total synthesis of dihydrocleavamine.

Additional work carried out concurrently in our laboratory by other workers and which involved the successful synthesis of quebrachamine by the second route described, as well as a successful conversion of dihydrocleavamine into carbomethoxy-dihydrocleavamine, will be mentioned at the end of the discussion.
Section A

The synthesis of the diester (68) desired for acyloin condensation was accomplished through the coupling of 2-carboethoxy-3(\(\beta\)-chloroethyl)-indole (66) with 3-carbomethoxy-3-ethylpiperidine (67). The synthesis of the substituted piperidine (67) itself involved two approaches. Initially it was thought that a simple carbon alkylation by standard procedures of the easily obtainable 3-carbomethoxy piperidine (77) (see Figure 13) would be possible, alkylation of disubstituted acetic esters being fairly well known\(^\text{32,33}\).

![Chemical Structure Diagram]

\[
R = O; \quad R' = \text{\(-\text{OH}\)}
\]

\[
\text{and/or} \quad R = \text{\(-\text{OH}\)}; \quad R' = O
\]

Figure 11
Nicotinic acid (75) was reduced to nipecotic acid hydrochloride (76) by the reported method of platinum oxide (Adams catalyst) in hydrochloric acid\(^{34}\). The crude product, after drying, exhibited no absorption in the ultraviolet region and was therefore esterified directly with absolute methanol and hydrochloric acid\(^ {35}\). The desired methyl nipecotate\(^ {36} \) (77) was thus prepared in 35% overall yield from nicotinic acid.
The piperidine ester (77) exhibited a sharp three proton singlet in the NMR spectrum at $\delta 6.30$ due to the methoxyl protons. The structural assignment was also supported by the presence of a strong absorption band in the infrared at 1725 cm$^{-1}$ due to the ester group and a broad absorption at 3250 cm$^{-1}$ (NH). Elemental analysis on the parent substance and on its crystalline p-bromobenzamide derivative (78) completed the characterization of this compound.

It was hoped that this ester (77) could be alkylated at the $\alpha$-carbon without alkylation on nitrogen by first irreversibly generating the carbanion with sodium hydride, followed by the addition of ethyl iodide.
ester to sodium hydride in toluene caused the evolution of gas and subsequent reaction with ethyl iodide was evident by the formation of a pale yellow precipitate. Purification of the product by distillation gave a clear colorless oil which, however, was indicated by its NMR spectrum to be the N-ethyl compound. The presence of an ethyl group was shown by the presence of a three proton triplet at $\tau$ 8.95 (-CH$_2$CH$_3$) and a quartet at $\tau$ 7.6 (-CH$_2$CH$_3$). The low chemical shift of the methyl and methylene protons strongly suggested that N-alkylation had occurred and this was subsequently verified when the desired compound was prepared by another route described later.

Since it was felt that the desired ester anion had been formed successfully with sodium hydride, prevention of N-alkylation could be accomplished by conversion of the basic amine to a neutral amide derivative. Subsequent hydrolysis could then lead to the desired piperidine (67) as shown in Figure 14.

The p-bromobenzamide derivative (78) prepared by standard techniques (p-bromobenzoylchloride in pyridine) was a beautifully crystalline solid. The infrared spectrum of the latter showed the presence of an ester carbonyl at 1730 cm$^{-1}$, an amide band at 1630 cm$^{-1}$ and no absorption in the NH (3200 - 3500 cm$^{-1}$) region. The NMR spectrum showed the methoxyl group as a sharp singlet at $\tau$ 6.3 and the aromatic
region contained a pair of doublets at \( \tau 2.4 \) and \( \tau 2.7 \) as expected for two non-equivalent pairs of protons.

![Chemical Structures](image)

**Figure 14**

Refluxing a mixture of the amide (78), sodium hydride (10% excess) and ethyl iodide (10% excess) in toluene caused the slow evolution of gas and the precipitation of a solid. The reaction product however was indicated by thin layer chromatography as being a mixture of at least four compounds. Alumina chromatography initially yielded a white crystalline compound identified as methyl \( p \)-bromobenzoate (80) by comparison with an authentic sample (mixed melting point
and superimposable infrared spectra). This compound was consistently formed in 40 to 50% yield. Careful chromatography also eventually led to the separation of two oils and a more polar amorphous solid. The major oil was obviously not the desired compound (79) as it exhibited absorption in the olefinic region of the NMR spectrum. The minor oil which was difficult to purify appeared to have the general spectral features expected for the desired product. Alkylation had occurred as evidenced by the presence of a three proton triplet at $\gamma 9.25$ for the methyl of an ethyl group. Two doublets integrating for four protons were present in the aromatic region at $\gamma 2.4$ and $\gamma 2.7$ and a methoxyl peak appeared at $\gamma 6.3$, although its integral was low. The carbonyl region of the infrared spectrum was almost identical to that of the starting amide (78) and exhibited absorption at 1725 cm$^{-1}$ and 1630 cm$^{-1}$. This compound was not completely characterized due to separation difficulties and low yield which also made it impracticable as a synthetic intermediate.

The amorphous solid which was obtained, as mentioned above, again showed an ethyl group likely present as a triplet. It appeared at $\gamma 8.9$ in the NMR spectrum. A methoxyl function was evident as a singlet at $\gamma 6.3$ and two aromatic doublets were again present. The integral in the 6.5 to $\gamma 8.5$ region however indicated a number of protons far in excess of the desired product. Ester and amide groups were indicated as being present by absorption in the infrared at 1725 cm$^{-1}$ and
1630 cm$^{-1}$. The polar nature of this material suggested it may be a dimeric or polymeric substance and the formation of methyl p-bromobenzoate in the absence of any external source of methoxide indicates that intermolecular condensations are not unlikely. The formation of methyl p-bromobenzoate can be rationalized by the type of mechanism indicated in Figure 15. Alternately the methoxide could arise from direct nucleophilic displacement by hydride ion.

Figure 15
Because of the difficulties encountered in the above route, the products were not examined further and another method of synthesis of the substituted piperidine (67) was examined. This approach proved to be successful and will be discussed presently.

A particularly convenient synthesis from cyanoacetic ester is shown in Figure 16 and had previously been reported for the preparation of 3-carboethoxy-3-phenylpiperidine\(^37\)\(^{86}\). The piperidine ring is generated in the final step through reduction of a nitrile group followed by cyclization of the resulting chloroamine.

Alkylation of methyl cyanoacetate (81) with ethyl iodide using sodium methoxide as base\(^38\) yielded a clear colorless oil upon distillation. This reaction product was shown by gas chromatography to be a mixture of three components and NMR indicated the presence of two different triplet methyl resonances around \(\gamma 9\). Fractional distillation on a spinning band column (25 to 30 theoretical plates) failed to separate the components which had a combined boiling range of four degrees. Separation of the major component which was estimated as 60% of the mixture was performed by gas chromatography on an Apiezon J column. This was easily identified as the desired alkylated compound (82) by its NMR spectrum. This spectrum showed a three proton triplet at \(\gamma 8.9\) (\(-\text{CH}_2\text{CH}_3\)) and a one proton triplet at \(\gamma 6.55\) for the hydrogen atom on the carbon\(\alpha\) to the carbomethoxy and cyano groups. The methoxyl protons appeared as a sharp three
proton singlet at \( \gamma 6.25 \). The presence of these functional groups was also supported by nitrile absorption at 2230 cm\(^{-1}\) and ester absorption at 1740 cm\(^{-1}\) in the infrared spectrum.

It is well known that dialkylation of cyanoacetic esters is an interfering side reaction and is more serious here than with malonic esters\(^{33}\). This is due to the greater acidity of cyanoacetic esters as compared to malonic esters.

The smallest component of the mixture, approximately 10%, was separated similarly and shown to be unreacted methyl cyanoacetate (infrared spectrum and thin layer chromatography).
The remaining component, representing about 30% was also separated in small quantities and again shown to have ester and nitrile absorption in the infrared. This compound was undoubtedly the dialkylated cyanoacetic ester as the NMR spectrum of the initial mixture had indicated two different triplet methyl groups.

The presence of a mixture inseparable by distillation at this point did not cause any particular difficulty in the subsequent step since methyl ethylcyanoacetate (82) was to be alkylated again with bromochloropropane. The introduction of this larger group now allowed separation of the desired dialkylated compound (83) by fractional distillation. The presence of methyl diethylcyanoacetate did not interfere since it could not be alkylated again and had a significantly lower boiling point than the desired methyl 3-chloropropylethylcyanoacetate (83). The presence of unreacted methyl cyanoacetate however could interfere if monoalkylated with bromochloropropane since the resulting compound would differ from the desired one merely by an ethyl group. Therefore, an excess of alkyl halide was used at this point to effect dialkylation of the methyl cyanoacetate since the resulting compound would contain two large alkyl groups and be considerably higher boiling than the desired compound. Indeed alkylation of the above mixture with bromochloropropane using this technique led to the preparation of 83 in 30% overall yield from methyl cyanoacetate.
The NMR spectrum of the chloride (83) was in good agreement with the assigned structure. It showed the presence of a methoxyl group at $\gamma 6.2$ (sharp three proton singlet) and the methyl protons of the ethyl group were revealed as a three proton triplet centered at $\gamma 8.95$. A distorted two proton triplet appeared at $\gamma 6.4$ due to the methylene adjacent to the chlorine atom. The infrared spectrum indicated an ester carbonyl at 1735 cm$^{-1}$ and a nitrile peak at 2220 cm$^{-1}$. Gas chromatographic examination of this material (Apiezon J column) indicated that it was virtually free of contamination by other alkylation products and an analytical sample prepared in this manner gave a positive Beilstein halogen test.

Reduction of the nitrile (83) to the amine with a large excess of palladium in methanolic hydrochloric acid followed by treatment with alkali provided the desired piperidine (67). The reduction of the nitrile did not go to completion, usually only 40 to 50% of the theoretical amount of hydrogen being consumed. Recovery of the unreacted nitrile (usually 50 to 60%) separated from the amine was accomplished by preferential extraction. The initial product of reduction was the salt (84) which was made basic and then allowed to stand for a period of a few days or warmed to produce the cyclic amine (67) as its hydrochloride salt. The latter then was converted to the free base by a second treatment with alkali.
Purification of 3-carbomethoxy-3-ethylpiperidine by vacuum distillation was usually accompanied by considerable decomposition so that small quantities necessary for structural and analytical data were obtained by gas chromatography (Apiezon J column). The pure compound exhibited a complex pattern in the NMR spectrum, important features being the presence of a sharp three proton singlet at \( \gamma^6.25 \) (\(-\text{COOCH}_3\)) and a three proton triplet centered at \( \gamma^9.2 \) (\(-\text{CH}_2\text{CH}_3\)). The infrared spectrum possessed a broad absorption band at 3250 cm\(^{-1}\) (NH) and a sharp peak at 1725 cm\(^{-1}\) (\(-\text{COOCH}_3\)).

Analytical and further structural evidence for this compound were provided from the 3,5-dinitrobenzamide derivative, which was obtained as a sharp melting, easily crystallized pale yellow compound which possessed characteristic spectral features. Two very prominent bands appeared in the carbonyl region of the infrared spectrum due to the methyl ester (1725 cm\(^{-1}\)) and the amide (1630 cm\(^{-1}\)) groups. An aromatic peak was also easily discernible at 3030 cm\(^{-1}\). A three proton triplet in the NMR spectrum at \( \gamma^9.25 \) provided evidence for the presence of an ethyl group and the methoxyl group appeared as a sharp three proton spike at \( \gamma^6.3 \). The aromatic region of the NMR consisted of a one proton triplet at \( \gamma^0.9 \) and a two proton doublet at \( \gamma^1.1 \). The low chemical shift of these aromatic protons is attributable to the presence of electron withdrawing substituents on the ring, the lower triplet being readily assigned to the proton between
the two nitro groups. The spectral and analytical data on
this derivative as well as the spectral data on the piperidine
itself suffice to establish the structure of the compound.

The final step in the sequence to provide the inter-
mediate (68) for acyloin condensation proceeded well.
Reaction of the piperidine (67) with 2-carboethoxy-3-
(5-chloroethyl)-indole (66) in a sealed tube at 160°C
provided the coupling product (68). The latter was purified
by column chromatography on alumina and was obtained as a
sharp melting colorless crystalline solid.

\[ \text{(66)} \quad + \quad \text{H}_{\text{N}} \quad \text{COOCH}_3 \quad \text{H} \quad \text{(67)} \quad \rightarrow \quad \text{N} \quad \text{COOCH} \quad \text{CH} \quad \text{(68)} \]

The infrared spectrum of the coupling product (68) was
characterized by intense bands at 1730 cm\(^{-1}\) and 1675 cm\(^{-1}\)
due to the methyl and conjugated ethyl ester carbonyl groups
respectively. A band at 3350 cm\(^{-1}\) was attributable to the
indole NH. The NMR spectrum again showed the presence of
two different ester groups, the methoxy group appearing as
a three proton singlet at \(\gamma 6.35\), and the ethyl group of the
ethyl ester appearing as a three proton triplet at \(\gamma 8.6\),
(-COOCH\(_2\) CH\(_3\)) and a two proton quartet at \(\gamma 5.57\) (-COOCH\(_2\) CH\(_3\)).
A second three proton triplet at $\gamma 9.2$ was readily assigned to the methyl of the ethyl group on the piperidine ring. The indole ring was shown by the aromatic absorption which appeared in the region $\gamma 2.2-3.0$ in the NMR spectrum and its typical absorption at 228 and 297 m$\mu$ in the ultraviolet spectrum.

Further structural evidence for compound 68 in addition to analytical data was provided by examination of its mass spectrum. The molecular ion peak at m/e 386 confirmed the molecular formula while an extremely intense peak at m/e 184 was dominant in the spectrum. From the extensive data available on the fragmentation of indole alkaloids$^{40}$, this peak can be attributed to the fragment (87) arising by simple cleavage of the bond $\beta$ to the piperidine nitrogen. Fragmentation of this type was also encountered in other compounds prepared in this work to be discussed later.
Having obtained the coupling product (68) it now became possible to study the acyloin condensation reaction to form the nine-membered ring. The acyloin condensation has been employed with spectacular success in the synthesis of medium sized rings\textsuperscript{41,42,43}. Yields obtained by other methods (e.g. Dieckmann, intermolecular alkylation, etc.) are satisfactory for five, six and seven membered rings, however, are poor for eight to fourteen membered rings and reach a minimum at ten. This is explained by the fact that non-bonded interactions become important in this range and reach a maximum in the ten-membered ring. Repulsive forces, therefore, hinder the approach of the two ends of the molecule which in itself is less likely as the chain length increases, resulting in a preponderance of polymerization over cyclization. The yields of cyclization by the acyloin method also reach a minimum at the ten-membered ring, but are still in a respectable range (usually about 50%). The success of the acyloin condensation is a result of the reaction occurring on the surface of the sodium metal. The ester is weakly adsorbed on the surface and since the sodium is dispersed as a fine sand, this becomes in effect, a reaction at high dilution, reducing intermolecular interaction and polymerization.

The method used for the acyloin condensation was that described by Leonard\textsuperscript{44} whereby a dilute solution of the diester was added to a vigorously stirred refluxing suspension of sodium in toluene. Initially a relatively low speed stirrer
was used for the reaction and the product was investigated by thin layer chromatography. Three compounds in about equal quantities and with $R_f$ values similar to the starting material could be seen on the chromatoplate in addition to a very polar substance. Separation of the three similar components was possible in small quantities by preparative thin layer chromatography on alumina. One of these compounds was shown to be identical to the starting diester (TLC and infrared comparison). The other two compounds exhibited infrared spectra which were remarkably similar to the starting compound and showed normal indole absorption in the ultraviolet region. The NMR spectrum of one of these indicated that the ethyl ester originally attached to the indole ring was absent but a new three proton signal was present at $\delta 6.05$ in addition to the methoxyl spike at $\delta 6.35$ observed in the starting compound. The other acyloin product, however, lacked the methoxyl signal at $\delta 6.35$ but now possessed a new triplet and quartet at slightly higher field than that observed for the ethyl ester function in the starting diester. It therefore was apparent that the starting unsymmetrical methyl ethyl ester had simply undergone ester exchange giving the dimethyl and diethyl esters respectively. One of these compounds was later shown to be identical to the authentic dimethyl ester$^{39}$ (thin layer chromatography).

The polar material was only examined in a preliminary manner at this point as only a small quantity was obtained.
Its infrared spectrum indicated that it was a carbonyl containing compound and the NMR spectrum indicated the presence of methyl and ethyl esters in the same region as observed for the starting diester. Their integrals, however, were quite low and a peak was present for approximately one proton at \( \gamma = 1.7 \).

Subsequent acyloin condensation attempts using a high speed stirring apparatus led to the formation of only the polar material. The latter was obtained in pure form by preparative thin layer chromatography on silica gel. This purified material contained carbonyl absorption in the infrared region, and a slightly shifted indole absorption was present in the ultraviolet region, with maxima now occurring at 225 and 295 m\(\mu\), compared to 227 and 298 m\(\mu\) for the starting diester. The NMR spectrum of this polar material retained the same general features as that observed in the crude material mentioned above although the entire spectrum was ill-defined. A mass spectrum indicated this was not the desired acyloin product as no significant peaks were present for the predicted molecular ion peak at m/e 312.

Acyloins may be oxidized to \( \alpha \)-diketones by treatment with chromium trioxide\(^{15} \). This material, however, could not be oxidized by this method without destruction of the indole chromophore. It was readily reduced by lithium aluminum hydride, so the crude acyloin product containing no unreacted diester was treated with this reagent. This reduced material
was purified by preparative thin layer chromatography on silica gel and exhibited no carbonyl absorption in the infrared region. The NMR spectrum possessed two very prominent singlets at $\gamma 5.35$ and $\gamma 6.5$, both integrating for approximately two protons. A third broad singlet at $\gamma 4.4$ was sensitive to concentration shifts and readily exchanged with deuterium oxide. This compound was therefore strongly suspected to be a diol and acetylation with acetic anhydride in pyridine was carried out. The NMR spectrum of the latter showed a downfield shift of $\gamma 0.57$ and $\gamma 0.50$ respectively for the two singlets mentioned above and indicated that the alcoholic functions were primary. The presence of acetate groups was also indicated by two sharp spikes at $\gamma 8.0$ in the NMR spectrum and carbonyl absorption at 1725 cm$^{-1}$ in the infrared spectrum.

The diacetate (88) prepared from the authentic dimethyl ester by a similar lithium aluminum hydride reduction and acetylation was found to be identical to the above diacetate obtained from the acyloin condensations (thin layer chromatography on silica gel, alumina, infrared and mass spectrometry). It is of interest to point out that the base peak in the mass spectrum occurred at m/e 198 and is attributable to the ion (89) which arises by fragmentation of the type suggested earlier for compound (68).
The polar nature of the acyloin condensation product and its ability to be reduced to an alcohol with lithium aluminum hydride indicated that it must have been an acid. This was confirmed as treatment of the acyloin product with diazomethane gave a mixture of two esters. One of these was identical (by thin layer chromatography) to the diester used for the acyloin condensation (68) while the other was identical to the authentic dimethyl ester. The products arising from the acyloin condensation reaction mixture were therefore merely the two acid-esters (90) and (91).
This explanation is consistent with the observed reactions and spectral data and although the diacid of compound 90 could also give the dimethyl ester on esterification with diazomethane it would be surprising if its polarity on thin layer chromatography would be such as to make it indistinguishable from the ester acids. The low integrals observed for the ester signals in the NMR spectrum of the acyloin product are also explicable in these terms. The peak at $\gamma'-1.7$ mentioned earlier could be attributed to the carboxyl proton.

In spite of great precautions which were taken to prevent simple hydrolysis of the diesters to the mono-acids 90 and 91, we were not successful in achieving the desired cyclization. Unfortunately we were only able to study the acyloin reaction with milligram quantities of starting diester and even minute traces of water (usually about 14 mg) were sufficient to cause the above hydrolysis. Rather that spend a good deal of time preparing large quantities of the desired diester we turned our attention to a completely different sequence which was being investigated concurrently in our laboratory. I would now like to discuss this work which led to the first total synthesis of dihydrocleavamine and constitutes section B of this thesis.
Section B

The key step in this sequence centres on the reductive cleavage of a particular bond common to a five and six-membered ring as shown below. If this cleavage is performed on the intermediate 73a, the nine-membered ring compound, dihydrocleavamine (74a) is generated. Similarly the intermediate 92a provides quebrachamine (93a). The corresponding carbomethoxy derivatives (73b and 92b) would give rise to carbomethoxydihydrocleavamine (74b) and carbomethoxyquebrachamine (vincadine) (93b) respectively.

\[
\begin{array}{c}
\text{(73a)} \quad R = R' = H, R'' = \text{Et} \\
\text{(92a)} \quad R = R' = H, R'' = \text{Et} \\
\text{(73b)} \quad R = \text{COOCH}_3, R' = H, R'' = \text{Et} \\
\text{(92b)} \quad R = \text{COOCH}_3, R' = \text{Et}, R'' = H
\end{array}
\]

The reductive cleavage of carbon-nitrogen bonds in quaternary ammonium salts is a well known reaction and is especially useful in the alkaloid field. A number of examples of its application to alkaloids of particular interest to this study have appeared recently in the literature and deserve comment. The cleavage is normally accomplished by the use of sodium or lithium in liquid ammonia. For example, the reduction of the quaternary iodide 94 to the ring opened compound (95) has been reported in 89% yield using
sodium in liquid ammonia.\(^{46}\)

\[
\begin{align*}
(94) & \quad \text{Reduction of the compound} \quad \text{by either sodium in liquid ammonia or lithium aluminum hydride gives a ten-membered ring compound} \quad \text{(97)}. \quad \text{This reaction and other similar cleavages reported by the same authors} \quad \text{are shown in Figure 17.}
\end{align*}
\]

\[
\begin{align*}
(96) & \quad \text{(97)}
\end{align*}
\]

A ring cleavage of the quaternary salt 98 to provide a ten-membered ring compound (99) has also been successfully carried out in our laboratory.\(^{49}\)
In a model study, designed for quebrachamine synthesis, Wenkert, et al.\cite{50} reported the conversion of 100 to 101 by means of lithium in liquid ammonia.

![Chemical diagram showing the conversion of 100 to 101](image)

It can be seen, therefore, that there was considerable precedent for this type of cleavage desired in the case of the quaternary salts (73a and b) and (92a and b). A study of a synthetic sequence leading to the compounds 73a and b and their possible cleavage to the appropriate nine-membered ring systems was therefore warranted. The work involved with this aspect constitutes the central portion of this thesis.

A promising route to the compounds 92a and b was currently under study in our laboratory and since these compounds are epimeric with 73a and b, an analogous sequence utilizing the appropriately modified intermediates was desirable. The underlying principle involved here was that the synthesis of the isomeric esters (71a, 102a) and (71b, 102b) followed by condensation with tryptamine would hopefully lead to intermediates which through a common series of subsequent reactions would eventually yield dihydrocleavamine, quebrachamine and their corresponding carbomethoxy derivatives.
A synthesis of the diesters 102a and b had already been achieved in our laboratory by the scheme depicted in Figure 18. An analogous synthesis of the diester 71a was now considered and this sequence is summarized in Figure 19.

Diethyl ethylmalonate (105) was reduced to 2-ethyl-1,3-propanediol (106) in 91% yield by means of lithium aluminum hydride in tetrahydrofuran. The diol was converted to the monobenzyl ether (107) by treatment with sodium in hot xylene followed by reaction with benzyl chloride (77% yield). The preferential formation of the monobenzyl ether was ensured by using a 3:1 molar ratio of the diol to the sodium metal. The resulting mixture of unreacted diol and monobenzyl ether was then separated by fractional distillation. The infrared spectrum of the desired benzyl ether possessed an absorption band at 3300 cm.−1 (OH) and characteristic aromatic C-H out of plane bending modes at 695 cm.−1 and 740 cm.−1 (also present in all other benzyl ethers reported subsequently). The NMR spectrum showed a five proton singlet at ν2.7 for the aromatic protons and a two proton singlet at ν5.5 for the benzyl methylene protons. These two singlets were also very characteristic for all the subsequent compounds containing the benzyl
Figure 18
ether moiety. The C-methyl group appeared as a three proton triplet centered at \( \gamma 9.1 \) while a four proton multiplet centered at \( \gamma 6.4 \) was attributed to the four methylene protons adjacent to an oxygen atom. A three proton multiplet in the region \( \gamma 8.0 \) to 8.9 could be assigned to the methine and two methylene protons attached directly to a carbon atom. The remaining sharp one proton singlet at \( \gamma 7.2 \) was identified as the hydroxyl proton as it completely disappeared upon addition of deuterium oxide to the solution and the spectrum taken again.

It was a distinctive feature of the compounds examined in this synthetic sequence that they all possessed extremely informative NMR spectra so considerable emphasis will be placed on this data during the discussion.

The ether-alcohol (107) was converted to the chloride (108) in 66% yield by treatment with thionyl chloride in \( \text{N, N-dimethylaniline}^{55} \). The resulting chloride (108) showed no infrared absorption in the hydroxyl region but the aromatic peaks mentioned above were present. The NMR spectrum lacked the hydroxyl proton peak observed in the starting ether-alcohol and the remainder of the spectrum was consistent with the assigned structure (108). The aromatic protons appeared again as a sharp five proton singlet at \( \gamma 2.7 \) and the benzyl methylene protons as a sharp two proton singlet at \( \gamma 5.5 \). A four proton multiplet centered at \( \gamma 6.45 \) was assigned to the four hydrogen atoms adjacent to the oxygen and chlorine atoms. The methyl protons of the ethyl group appeared as a three proton triplet
centered at \( \gamma 9.1 \), and the remaining three hydrogen atoms (one methine and two methylene) appeared as a multiplet in the region of \( \gamma 7.9 - 8.8 \).

Alkylation of diethyl malonate with the chloride (108) using sodium ethoxide as base\(^{56} \) provided diethyl 3-benzylxy-2-ethylpropylmalonate (109). The reaction was sluggish and consistent recoveries of 50% of unreacted halide were observed. This was easily separable from the much higher boiling alkylated malonic ester (109) and a yield of 89% was attained in the reaction. The infrared spectrum of the alkylation product showed strong carbonyl absorption at 1735 cm\(^{-1} \) due to the ester groups as well as the two familiar aromatic bands. Again the NMR spectrum (Figure 20) was invaluable in establishing the structure of this compound. The benzyl ether was again evident by the presence of a sharp five proton singlet at \( \gamma 2.65 \) and a two proton singlet at \( \gamma 5.5 \). A four proton quartet centered at \( \gamma 5.8 \) and a six proton triplet centered at \( \gamma 8.8 \) were readily assigned to the methylene and methyl protons of the ethyl ester groups respectively. A three proton multiplet which appeared at \( \gamma 6.55 \) could be easily analyzed since the two protons of the methylene next to the oxygen of the benzylxy group absorb in this region. The remaining proton resonating at this frequency was evidently the one attached to the carbon atom bearing the two carbo-ethoxy groups. This assignment is confirmed by comparison of this spectrum with the NMR spectrum of diethyl ethylmalonate.
Figure 20

Et COOEt

\[ \phi \text{CH}_2\text{OCH}_2\text{CHCH}_2\text{CH} \]

Figure 21

Et COOEt

\[ \phi \text{CH}_2\text{OCH}_2\text{CHCH}_2\text{CH}_2 \text{COOEt} \]
where the analogous proton appears at $\gamma 6.8$. A somewhat isolated two proton multiplet was apparent at $\gamma 8.05$ and was assigned to the two protons on the carbon atom between the carbon atoms bearing the ethyl group and the two carbomethoxy groups. This assignment was made on the basis of a NMR comparison with the monoester (112) in which it is absent and the triester (113) to be discussed later. Finally the methyl of the ethyl group appeared as a three proton triplet centered at $\gamma 9.15$.

Initially the route from this malonic ester to the substituted succinic ester (71a) (Figure 19) was investigated in a manner analogous to that for the conversion of the malonic ester (103) to the succinic ester (102a) shown in Figure 18. It was also hoped that this sequence would provide the $\alpha$-ketoglutaric ester (71b) (Figure 19) isomeric with the $\alpha$-ketoglutaric ester (102b) (Figure 18).

Indeed the synthesis of the succinic ester (71a) by first converting it to the substituted ester 112 and then alkylating with ethyl iodoacetate was successful. However the alternate route via the triester (113) to be discussed later was anticipated to proceed in better yield and this was subsequently verified.

Thus, hydrolysis of the substituted malonic ester (109) with aqueous potassium hydroxide provided the corresponding malonic acid (110) as a viscous oil. This compound could not be induced to crystallize but the spectral data were in accord with the assigned structure. The NMR spectrum indicated the
absence of the ethyl ester protons and a new absorption peak appeared at \( \gamma 1.0 \) integrating for two to three protons. The chemical shift is somewhat high for the expected position of the carboxyl protons; however, the presence of very broad absorption in the 3500 to 2400 cm\(^{-1}\) region of the infrared spectrum confirmed the presence of carboxylic acid functions.

Smooth decarboxylation to the monoacid (111) was effected by heating the viscous diacid for five hours at 120\(^\circ\)C. The resultant viscous oil was reesterified without purification by treatment with ethanol and sulfuric acid to provide the substituted ester 112 in 75\% overall yield. This monoester possessed carbonyl absorption at 1730 cm\(^{-1}\) in the infrared spectrum as well as the two usual aromatic bands. The NMR spectrum (Figure 21) possessed a sharp five proton singlet at \( \gamma 2.65 \) and a two proton singlet at \( \gamma 5.5 \) for the benzyl ether aromatic and methylene protons respectively. A two proton quartet centered at \( \gamma 5.85 \) along with a triplet centered at \( \gamma 8.75 \) indicated the presence of one ethyl ester group. The methylene protons on the carbon atom adjacent the benzyl ether oxygen appeared as a broad two proton doublet at \( \gamma 6.6 \) and a two proton multiplet at \( \gamma 7.65 \) could be attributed to the methylene protons on the carbon atom \( \alpha \) to the carbomethoxy group. The "malonic" proton on the carbon atom between the two carboethoxy groups observed in the spectrum of the malonic ester (109) had disappeared as had the two proton multiplet at \( \gamma 8.05 \) assigned earlier. This data is consistent with the
chemical shifts one would expect on removal of one of the carboethoxy groups. The usual three proton triplet centered at $\delta$ 9.1 for the methyl protons of the ethyl group was also evident on the spectrum.

Alkylation of substituted acetic esters using very strong bases such as triphenylmethyl sodium are fairly well known and were used successfully, as mentioned before, to prepare the substituted succinic (102a) and $\alpha$-ketoglutaric (102b) esters. The $\alpha$-ketoglutaric ester (71b) was of interest since Wenkert and co-workers\textsuperscript{50} had condensed ethyl $\alpha$-ketoglutarate (116) with tryptamine to provide the lactam (117). The analogous reaction on the substituted $\alpha$-ketoglutarate (71b) would have possibly provided a very convenient route to dihydrocleavamine.

\[
\begin{align*}
(70) & \\
(116) & \\
(117)
\end{align*}
\]

The enolate of the monoester (112) was easily generated with triphenylmethyl sodium in ether as evidenced by the almost instantaneous disappearance of the characteristic deep red color of the triphenylmethyl anion upon addition of the ester. When this addition was immediately followed by the addition of ethyl $\alpha$-bromopyruvate, precipitation of sodium bromide was virtually instantaneous. Analysis of the reaction mixture, however, led only to an 80 - 85% recovery of unreacted
monoester (112), and no bromopyruvate could be recovered. No desired alkylation product could be isolated and thin-layer and gas chromatographic examination of the crude product indicated no significant compounds other than starting material and triphenylmethane.

When the solution of the ester 112 and triphenylmethyl sodium were stirred for one hour before the addition of the bromopyruvate, a new compound was formed. This material was purified by column chromatography and proved to be extremely high boiling. The NMR spectrum indicated this was obviously not the desired α-ketoglutaric ester (71b) and appeared to be most probably the self condensation product. This would not be surprising since self-condensation of substituted acetic esters is the well known Claisen ester condensation and this is known to constitute the most serious side reaction in the alkylations of monosubstituted acetic esters. Attempted alkylation using the anion of dimethyl sulfoxide in dimethyl sulfoxide was also unsuccessful.

When ethyl iodoacetate was added immediately to the enolate of the ester 112, the reaction was again virtually instantaneous and sodium iodide precipitated. Analysis of the crude reaction product under conditions similar to that for the product of the bromopyruvate reaction (thin-layer and gas chromatography) clearly indicated the presence of a new minor compound but the major component was still the starting ester. The new product was separated and purified by column
chromatography on alumina, followed by distillation to provide a low yield of the succinic ester (71a). Gas chromatography on a 20% SE30 column effected further purification of a small quantity of this material for analytical and spectral data.

The diester (71a) possessed an absorption band in the carbonyl region of the infrared spectrum at 1730 cm\(^{-1}\) and the two familiar aromatic bands. The NMR spectrum (Figure 22) was again very informative. The benzyl ether was apparent from the five proton singlet at \(\tau\) 2.7 and the two proton singlet at \(\tau\) 5.5. Two almost superimposable quartets appeared at \(\tau\) 5.85 integrating for four protons and combined with a triplet centered at \(\tau\) 8.75 indicated the presence of two ethyl ester groups. The methylene protons on the carbon adjacent the oxygen of the benzyloxy function appear as a two proton multiplet at \(\tau\) 6.6, and the three protons on the carbon atoms \(\alpha\) to the two carboethoxy groups appear in the region of \(\tau\) 7.0 to 7.6. Again the methyl protons of the ethyl group appear as a three proton triplet centered at \(\tau\) 9.1.

The unsuccessful attempt at preparing the substituted \(\alpha\)-ketoglutaric ester (71b) and the low yield of the succinic ester (71a) by this alkylation technique was probably due to the fact that the anion of the monoester (112) was acting preferentially as a base, rather than a nucleophile. If the anion abstracts a proton from the \(\alpha\)-carbon of ethyl bromopyruvate and ethyl iodoacetate it would simply regenerate the ester.112 Since the preparation of the \(\alpha\)-ketoglutaric ester
Figure 22

\[
\text{Et} \quad \text{COOEt} \\
\text{OCH}_2\text{OCH}_2\text{CHCH}_2\text{CHCOOEt} \\
\text{CH}_2\text{COOEt}
\]

Figure 23

\[
\text{Et} \quad \text{COOEt} \\
\text{OCH}_2\text{OCH}_2\text{CHCH}_2\text{CH}_2\text{COOEt} \\
\text{COOEt}
\]
(7lb) was not successful by the simple alkylation discussed, the preparation of the succinic ester (71a) was examined by the more desirable route utilizing the triester 113.

The alkylation of the malonic ester (109) with ethyl bromoacetate using sodium ethoxide as base provided a fair yield of the triester (113) along with a good recovery of starting material. The use of sodium in ether in place of sodium ethoxide, however, provided an improved yield (60%) of the triester as well as some recovered malonic ester (30%). The triester was very high boiling (195 - 200°C at 0.25 mm.) and could be separated from the lower boiling malonic ester by fractional distillation.

The characteristic features in the infrared spectrum of the ester (113) were again the presence of ester carbonyl absorption at 1730 cm.\(^{-1}\) and the two usual aromatic bands. The NMR spectrum (Figure 23) shows a number of interesting features. The characteristic five proton singlet at \(\gamma 2.7\) and a two proton singlet at \(\gamma 5.55\) are the familiar benzyl aromatic and methylene protons respectively. A six proton multiplet centered at \(\gamma 5.85\) is due to the methylene protons of the ethyl esters and the two triplets at \(\gamma 8.75\) and 8.80 to the corresponding methyl protons. The chemical shift of the ester protons of the malonic ester would be expected to be slightly different from that of the newly introduced ester group because of the difference of an additional intervening carbon atom. The methylene protons on the carbon next to the benzyloxy group appear as a two
proton doublet at γ 6.7 and the additional peak observed in the malonic ester compound (109) (see Figure 20) due to the lone hydrogen atom on the carbon between the carboethoxy groups has disappeared. In addition, the two proton multiplet at γ 8.05 observed in the spectrum of the malonic ester (109) has shifted slightly down to γ 7.9. The chemical shift occurring upon the introduction of the additional ester function is therefore consistent with the earlier assignment of this multiplet to the two protons on the carbon atom between those bearing the ethyl and the two carboethoxy groups. It is also of interest that this multiplet is not present in the NMR spectrum of the substituted succinic ester (71a) (Figure 22). A new sharp two proton singlet which appeared at γ 6.95 was due to the methylene protons on the carbon atom adjacent to the newly introduced carboethoxy group. The methyl protons of the ethyl group again appeared as a three proton triplet at γ 9.15.

The triester (113) was hydrolyzed with potassium hydroxide to the corresponding triacid (114), obtained as a non-crystalline viscous oil. NMR data on the latter indicated complete removal of the ethyl ester groups and a three proton broad singlet appeared in the expected region (γ 0.4) for the carboxyl hydrogen atoms.

Decarboxylation of the above triacid to the succinic acid derivative (115) was effected by heating the triacid at 165-170°C for a period of 3½ hours. The resultant brown viscous acid was esterified by treatment with ethanol and
sulfuric acid to provide the desired succinic ester (71a) in an overall yield of 78% from the triester. The succinic ester prepared in this manner was identical by infrared and NMR spectroscopic comparison as well as by gas chromatography to that prepared by the alkylation of the substituted ester 112 with ethyl iodoacetate.

When the succinic ester from either of the described synthetic routes was subjected to careful gas chromatographic analysis an interesting phenomenon was observed. An analytically pure sample appeared almost as one peak except for the presence of a slight shoulder when examined on a SE30 (20%) column at 260°C (Figure 24). This shoulder became more pronounced at 245°C. Examination using a FFAP (20%) column showed the presence of two peaks at 265°C more effectively and this was much more pronounced at 245°C (Figure 25). Collection and reinjection of this material produced the same peak ratios indicating the compound was not being altered by the gas chromatographic procedure. While this material satisfied all the necessary criteria to support the structure (71a) and appeared as one compound by thin-layer chromatography, the presence of two diastereoisomers was expected since the compound possessed two asymmetric centres (see Figure 26). Since these asymmetric centres would ultimately appear at the two asymmetric centres of dihydrocleavamine (74a, Fig. 26 indicated by the asterisks), their demonstration in the succinic esters should be reflected by the synthesis of the two known isomeric dihydrocleavamines (as will be shown later).
Figure 24

Figure 25

Figure 26
Because of the high degree of success in the synthesis of the succinic ester (71a) via the triester (113), a brief attempt was made at an analogous synthesis of the aldehydo-ester (120) via alkylation of the malonic ester (109) with bromoacetaldehyde diethylacetal (118). The product (119) could possibly then be decarboxylated and the aldehyde group regenerated.

\[
\begin{align*}
\text{Et COOEt} & \quad \text{OEt} \\
\phi\text{CH}_2\text{OCH}_2\text{CHCH}_2\text{CH} & \quad +\text{BrCH}_2\text{CH} \\
\text{COOEt} & \quad \text{OEt} \\
(109) & \quad (118) \\
\rightarrow & \quad \rightarrow \\
\phi\text{CH}_2\text{OCH}_2\text{CHCH}_2\text{CH}_2\text{CH(OEt)}_2 & \quad \text{Et COOEt} \\
(119) & \quad \\
\rightarrow & \quad \\
\phi\text{CH}_2\text{OCH}_2\text{CHCH}_2\text{CHCOOEt} & \quad \text{Et}
\end{align*}
\]

(120)

The condensation of aldehydo-esters with tryptamine is a well known and valuable synthetic route. Its importance lies in the fact that the aldehyde group reacts preferentially before the ester group with the tryptamine and can, therefore, be used to direct the position of the alkyl side chain in the resultant lactam. For example, the aldehydo-ester 121 condenses with tryptamine to yield the cyclization product (122) which has been a synthetic intermediate in the synthesis of certain Hunteria and Aspidosperma alkaloid ring systems.²⁷
Similarly compound (123) has been condensed with tryptamine to provide the cyclization product $^6$ (124).

Unfortunately bromoacetaldehyde diethyl acetal failed to react with the malonic ester (109) under the conditions successful for the alkylation with ethyl bromoacetate. This acetal is apparently relatively inert $^{64,65}$, and this made it unsuitable as an alkylating agent in this case.

We, therefore, proceeded to the condensation of the succinic ester (71a) with tryptamine as the analogous condensation with the isomeric ester (102a) to provide the imide (125) had recently been successful in our laboratory $^{51}$, and its cyclization to the indole nucleus was currently being investigated. The results of these particular cyclization studies $^{66}$ are shown in Figure 27.

Thus the condensations of the succinic ester (71a) with tryptamine at 190 - 200°C provided the desired imide (130,
Figure 27
Figure 28) in 77% yield. The crude imide was purified by column chromatography on alumina and remained as a light brown non-crystalline gum. It was possible, however, to distill small quantities of this imide for analytical data.

The imide lent itself to a straightforward structural analysis due to the presence of certain very characteristic spectroscopic features. The compound possessed a typical indole absorption in the ultraviolet region ($\lambda_{\text{max}}$ 222, 274 (sh), 283, 291 µ). In addition to absorption band at 3320 cm$^{-1}$ (NH) in the infrared spectrum there appeared sharp bands at 1755 cm$^{-1}$ (medium intensity) and 1685 cm$^{-1}$ (strong), which are characteristic of a five-membered ring imide. The NMR spectrum (Figure 29) exhibited a one proton singlet at $\gamma$ 1.9 (NH) and a nine-proton multiplet centered at $\gamma$ 2.7 due to the aromatic protons of the benzene rings. The $\alpha$-proton on the heterocyclic ring of the moiety appeared as a one proton doublet at $\gamma$ 3.0. The benzyl methylene protons appeared as usual as a two proton singlet at $\gamma$ 5.55. A two proton triplet at $\gamma$ 6.2 was assigned to the methylene protons on the carbon atom adjacent the imide nitrogen, and forming part of the ethylene bridge to the indole ring. The two protons on the carbon atom adjacent to the oxygen of the benzyloxy group appeared as a multiplet at $\gamma$ 6.65 and a three proton triplet appeared at $\gamma$ 9.15 for the methyl protons of the ethyl group.

The mass spectrum of the succinimide (Figure 30) provided further structural evidence. The molecular ion peak was
Figure 28
indicated as being the desired value of 418 and the spectrum was dominated by peaks at m/e 143, 130 and 91. The peaks at m/e 143 and 130 are the characteristic indole fragments of the type (135) and (136) respectively commonly observed in many simple indole alkaloids. The peak at m/e 91 is undoubtedly due to the cleavage of the benzyl group and subsequent production of the tropylilum ion (137).

Studies in our laboratory had by this time established that the isomeric imide (125) could be cyclized in low yield via Bischler - Napieralski reaction but during the course of this reaction the benzyl group was lost and the product isolated was the enol lactam (126). Although loss of the benzyl ether moiety could be avoided by cyclization of the chloride (127), subsequent reduction of the lactam (129) with lithium aluminum hydride resulted also in loss of the chlorine group. Although alternatives were possibly available to preclude this difficulty another approach to the cyclization of the five-membered ring to the indole nucleus was now thought more advantageous. Studies by Wenkert and Wickberg had shown that N-\[\beta-(3-indolyl)-ethyl\] -piperidines could be cyclized onto the indole nucleus by treatment with mercuric acetate or other oxidizing agents. For example oxidation of the amine (138) with mercuric acetate provided a good yield of the cyclized product (140). Similar oxidation of (139) led to a mixture of the isomeric products (141a,b).
The imide (130) was reduced with lithium aluminum hydride in tetrahydrofuran to the tertiary amine (131, see Figure 28) in 95% yield.

The crude amine was purified by column chromatography on alumina and was obtained as a light brown gum. Small quantities of this compound, as with the imide, were readily distillable under reduced pressure and yielded a clear colorless glass.

The infrared spectrum of the amine exhibited no absorption in the carbonyl region indicating the imide function had been removed and the ultraviolet spectrum was that of a normal indole. In addition to the chemical analysis the
the molecular formula was established by high resolution mass
spectrometry as C_{26}H_{31}N_2O (Found: 390.267; Calc. 390.267). The mass spectrum (Figure 31) was dominated by a very intense peak at m/e 260 which could be attributed to the simple fragmentation of the parent molecule to the ion 142. This fragmentation mode is analogous to that observed for the coupling product (68) mentioned earlier. The presence of the benzyl ether was again indicated, as in the imide, by a strong peak at m/e 91.

\[ \begin{align*}
    \text{(131)} & \quad \text{NMR} \\
    \text{OCH}_2\text{O} & \quad \text{(142)}
\end{align*} \]

It now became important to locate accurately in the NMR spectrum the chemical shift of the proton on the carbon atom \(\alpha\) to the nitrogen of the indole ring. Its presence or absence in the reaction products from the mercuric acetate oxidation would be a measure of the success of the cyclization to the amines (134, Figure 28). Fortunately, this proton is usually located at slightly higher field than the other aromatic protons of the indole ring, as shown by the analysis of simple indoles and tryptamines. These studies have demonstrated that this proton usually appears in the range of 3.0 - 3.4 depending on concentration and is coupled to the proton on
the indole nitrogen atom.

Indeed, examination of the NMR spectrum of this amine taken at 100 Mc/s (Figure 32) showed that this proton was located at \( \tau 3.11 \) as a doublet. Addition of deuterium oxide caused this doublet to collapse to a singlet (Figure 32) demonstrating the coupling mentioned above. The remainder of the aromatic protons appeared as a nine proton multiplet centered at \( \tau 2.75 \) and the proton on the nitrogen atom of the indole nucleus appeared at \( \tau 1.55 \) as a broad singlet. The benzyl methylene protons appeared as a two proton singlet at \( \tau 5.55 \) and the methylene protons on the carbon atom adjacent the benzyloxy function appeared as a two proton doublet at \( \tau 6.70 \). A three proton triplet at \( \tau 9.15 \) was again due to the methyl protons of the ethyl group.

It was now possible to study the mercuric acetate oxidation and cyclization of this amine. Preliminary investigations indicated that a convenient method of following the reaction was through further oxidation of the already cyclized product (13\( \frac{1}{4} \)) to the iminium salt 133 (see Figure 28). This type of oxidation, which was also observed by Wenkert and Wickberg\(^{70} \) in the case of the compounds 138 and 139, provided a compound with a characteristic chromophore which absorbed at 352 mu in the ultraviolet region. This oxidation product was then easily reduced with sodium borohydride to the desired cyclization product (13\( \frac{1}{4} \)). The addition of dilute sodium hydroxide to a solution of the oxidation product 133 caused a
disappearance of the absorption maximum at 352 μ and the appearance of two new maxima at 310 and 322 μ (see Figure 33). This spectral shift is indicative of an imine-enamine shift, as indicated in Figure 34 and observed in similar compounds.\textsuperscript{75}

Initially considerable difficulties were encountered in this reaction with mercuric acetate. Oxidation, cyclization and re-oxidation were indicated by the ultraviolet spectrum as being only partial. Yields were fairly low (15 - 20%) and the complete separation of cyclized products from uncyclized starting material was virtually impossible on a practical scale. In fact, it was very fortunate that among the mixture of cyclized products one could always differentiate the uncyclized amine and the cyclized amines by thin-layer chromatography. Antimony pentachloride in carbon tetrachloride as a spray reagent produced a characteristic green colour with the cyclized compounds while the uncyclized amine gave a light brown colour.

A more careful examination of this reaction indicated that the chromophoric system in the reaction mixture which had an absorption maximum at 352 μ rapidly degenerated during the filtration and other manipulations required during the work-up. Exposure of a fairly concentrated solution of the iminium salt (133) to air during the work-up led to virtually no cyclization products and only recovered starting material. Consequently, the reaction procedures were performed under an atmosphere of purified nitrogen using dilute solutions with...
Figure 33

Figure 34
the result that an overall 37% yield of cyclized products was obtained.

Thin-layer chromatography indicated that a complex mixture of cyclization products was at hand. Careful column chromatography on alumina failed to separate any significant quantities of pure compounds, however, a combination of column chromatography followed by preparative thin-layer chromatography on alumina and/or silica gel led to the eventual separation of small quantities of four compounds. These were designated A, B, C and C' on the basis of their Rf values. A fifth very minor cyclized amine D could not be separated even by this combination of techniques. The mass spectra of all four compounds were examined and in the case of the major products (B and C) sufficient material was obtained pure to allow examination of their NMR spectra (100 Mc/s).

The mass spectra of all these compounds (Figure 35) were very similar and much different from that observed for the uncyclized amine (131). A number of peaks present in their fragmentation patterns are present in alkaloids of the tetrahydro-β-carboline type, e.g. ajmalicine (13) and yohimbine (23). A strong m+1 peak which appeared in the spectra of all four compounds also appears in the alkaloids ajmalicine and yohimbine and has been demonstrated as partially arising from the ion 144 (Figure 36). A series of significant peaks then appeared at m/e 156, 169, 170 and 184 which have been shown in the case of the alkaloids mentioned, to arise from the indole
portion of the molecule. Deuteration studies have established that the likely fragments contributing to these peaks are those shown in Figure 36. The presence of the benzyl ether moiety was indicated by the presence of peaks at m/e 297 (m-91) and m/e 91 (tropylium ion). The indolic nature of all four compounds was further shown by their typical indole absorption in the ultraviolet region (λmax 225, 274 (sh), 283, 291 μm).

High resolution mass spectrometry established that three of these benzyl ethers possessed the molecular formula C26H32N2O (Found: A, 388.251; B, 388.252; C, 388.252; Calc: 388.251). The fourth ether (C') isolated was also indicated by its mass spectrum as having a molecular weight of 388.

While these mass spectrometric results established that the cyclization had in fact occurred to produce a mixture of isomeric products, there remained the question of the location of the benzyloxypropyl side chain on the five-membered ring. As indicated by structure 132 (Figure 28), there were two iminium salts which could be considered as possibly cyclizing to the indole nucleus. A third iminium salt could also be formed in the reaction mixture in which the double bond was
Figure 36
exocyclic to the five-membered ring. However, even if the formation of the latter was realized its cyclization would lead to a highly unfavorable four-membered ring. Therefore, of the two possible cyclization products derivable from this reaction (72a and 145), only one (72a) would ultimately lead to dihydrocleavamine. Although Wenkert and Wickberg\(^7\) had observed the formation of both possible cyclization products 141a and b in the cyclization of \(N-[3-(3\text{-indolyl})\text{-ethyl}]-\text{piperidines} (139)\), it had been hoped that the increased steric effects created by the proximity of the side chain to the indole portion of the molecule would minimize or preclude the formation of isomer 145.

![Diagram of 72a and 145](image)

The two major cyclized benzyl ethers (B and C) were examined by NMR spectroscopy (100 Mc/s) and the spectra obtained are shown in Figure 37 and 38 respectively. Radical differences were immediately apparent in the spectra of these two compounds, the most outstanding of which was the aromatic region. Ether C which was obtained in slightly greater amount than ether B in this reaction, exhibited a nine proton multiplet in the region \(7.25\) to \(3.1\) (see Figure 38). The characteristic one proton
doublet at $\tau 3.11$ in the uncyclized amine due to the $\alpha$-proton on the indole nucleus was now absent. By contrast, some of the aromatic peaks in the NMR spectrum of ether B (Figure 37) were located at higher field, in the region $\tau 3.0$ to 3.5. Although the mass spectral evidence had already established that ether B was in fact a cyclized compound, the absence of the $\alpha$-proton on the indole nucleus was also completely confirmed by a deuteration experiment. Exchange of the proton on the indole nitrogen atom with deuterium caused no change in the aromatic region of the spectrum. The reason for this dramatic upfield shift in the aromatic region of the NMR spectrum of ether B became apparent upon examination of other features of the two spectra. The proton on the nitrogen atom of the indole nucleus was located at $\tau 0.50$ in the spectrum of ether B while in ether C it appeared at $\tau 1.80$. The methylene protons of the benzyloxy group were located as two proton singlets at $\tau 5.30$ and 5.60 in the spectra of ethers B and C respectively. The downfield shift of the benzyloxy methylene protons in the spectrum of ether B relative to ether C revealed the most important feature of these spectra. A doublet was present at $\tau 5.60$ in the spectrum of ether B which integrated for approximately one proton. The spectrum of ether C possessed a broad multiplet integrating for approximately one proton in the region $\tau 5.7$. This was partially obscured, however, by the methylene singlet of the benzyloxy group. NMR studies of indole alkaloids of the tetrahydro-$\beta$-carboline type have shown that the C-3
proton may be located as low as $\nu 5.5$ depending on the conformation of the molecule. In the case of the compound 146 this proton appears as a multiplet in the region $\nu 5.8$ to 6.0$^5_0$.

While the desired cyclized benzyl ether C (72a) was expected to exhibit a one proton multiplet for the proton at C-3, the undesired cyclization product (145) was expected to show a doublet; one of the protons at C-14 now having been replaced by the benzyloxypropyl side chain. It appeared, therefore, on the basis of this NMR spectral data, that the undesirable cyclization product 145 was in fact being obtained, although in slightly lower yield than the desired product 72a. The upfield shift of the aromatic protons of the indole nucleus observed in the spectrum of ether B may be attributed to the proximity of the benzyloxy group. Molecular models of the compound 145 show that the benzene ring of the benzyloxy group may be easily located directly beneath the indole nucleus. Such an arrangement could cause a shielding of the indole aromatic protons and also lead to the differences in the chemical shifts of the indole (N) and the benzyloxy methylene protons observed in these two compounds. A similar orientation
of the benzyloxy group with respect to the indole nucleus in the case of ether C is shown by molecular models to be very unlikely.

It now became evident that a separation of the desired cyclization products from the undesired compounds was required as epimeric compounds with the structure $1_{45}$ would not yield dihydrocleavamine. However, separation of compounds epimeric at C-3 and at the position of the ethyl group in $72a$ would be unnecessary since the asymmetry at C-3 is lost during the cleavage reaction in the final stages of the synthesis while the synthesis of both dihydrocleavamines epimeric at the position of the ethyl group, would be a desirable feature.

Since separation of the various benzyl ethers was not feasible on a scale suitable for continued synthetic work, the mixture of the cyclized and uncyclized ethers was converted to the corresponding alcohols.

Removal of the benzyl ether group in a mixture of the above compounds was accomplished in 85% yield by catalytic hydrogenolysis using palladium on charcoal in glacial acetic acid. Thin-layer chromatography of the reaction mixture indicated the presence of five cyclized compounds again by their characteristic color reaction with antimony pentachloride, as well as the uncyclized amino alcohol. The alcohols had a greater variation in Rf values than the corresponding benzyl ethers and the major alcohol designated C, was readily separated by column chromatography on alumina.
This alcohol was obtained as an amorphous solid and was indicated as being the desired compound by its spectral characteristics.

High resolution mass spectrometry established that the molecular formula was \( \text{C}_{19}\text{H}_{26}\text{N}_2\text{O} \) (Found: 298.203; Calc: 298.205). The mass spectrum (see Figure 39) possessed significant peaks at \( M-1 \) (297), \( m/e \) 184, 170, 169 and 156, also observed in the mass spectra of the benzyl ethers. However, the strong peak at \( m/e \) 91 observed in the spectra of the benzyl ethers was lacking. The ultraviolet absorption was that of a normal indole and the infrared spectrum in chloroform possessed absorption in the hydroxyl region (3100 - 3600 cm\(^{-1}\)) in addition to the sharp spike at 3350 cm\(^{-1}\) (NH). The 100 Mc/s NMR spectrum (Figure 40) indicated that the benzyl group had been removed as the aromatic region now consisted of a four proton multiplet centered at \( \gamma 2.85 \) and the two proton singlet of the benzyloxy methylene group originally observed in the region \( \gamma 5.3 \) to 5.7 had disappeared. The removal of this latter signal in the NMR spectrum now clearly revealed a broad one proton multiplet at \( \gamma 5.78 \) ascribed to the C-3 proton. That this signal was not simply the hydroxylic proton was shown through deuterium exchange, which produced no effect on this peak. The methylene protons of the primary alcohol group were present as a broad singlet at \( \gamma 6.61 \) and the methyl protons of the ethyl group appeared as a distorted triplet centered at \( \gamma 9.16 \).
Figure 39

Relative Intensity

Alcohol C

Relative Intensity

Alcohol B

Same as B'

R = H, R, CH, CH, OH

m = 298
The alcohol C was established as being derived from the ether C in a separate experiment. A small quantity of ether C was purified by the chromatographic procedures described earlier and hydrogenolyzed under the identical conditions. The resultant alcohol obtained was shown by thin layer chromatography to be identical to alcohol C obtained from the hydrogenolysis of the ether mixture, and different from all other isomeric alcohols obtained.

Small quantities of three additional isomeric cyclized amino alcohols were obtained by a combination of column chromatography followed by preparative thin-layer chromatography on silica gel. The alcohol designated B was formed in slightly less quantity than alcohol C and was suspected as having been derived from ether B. High resolution mass spectrometry provided the molecular formula \( \text{C}_{19}\text{H}_{26}\text{N}_2\text{O} \) (Found: 298.205; Calc. 298.205). The fragmentation pattern in the mass spectrum (see Figure 39) was similar to that of alcohol C and the ultraviolet spectrum was again that of a normal indole. The NMR spectrum (Figure 41) consisted of a four proton multiplet in the region \( \gamma 2.5 \) to 3.15 and no longer possessed the two proton singlet of the benzyloxy methylene group at \( \gamma 5.3 \). The removal of the benzyl group was thus seen to be accompanied by a downfield shift of the protons which were located at \( \gamma 3.15 \) to 3.5 in the benzylic ether. This shift is, therefore, in accord with the earlier suggestion that the protons of the indole nucleus were shielded to some extent by the benzyloxy
Figure 41
An isolated one proton doublet was present at $\gamma 5.72$ which was ascribed to the C-3 proton of the undesired cyclized amino alcohol. Again this signal was not affected by exchange with deuterium oxide. The methyl protons of the ethyl group as usual appeared as a three proton triplet at $\gamma 9.15$. The NMR spectrum of this compound, therefore, supported the earlier proposal that cyclization was occurring during the mercuric acetate reaction to provide both the desired cyclization product (72a) and the undesired product (145).

The remaining two isomeric amino alcohols which were obtained pure were also indicated as possessing the molecular formula $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}$ by the found values 298.205 and 298.204 (Calc. 298.205). Their mass spectra (see Figure 39) were essentially the same as that of the alcohols B and C and both exhibited normal indole ultraviolet absorption. Insufficient quantities of these isomers were obtained in a pure state for NMR analysis.

The conversion of the alcohol 149 to the quaternary salt (73a) desired for ring cleavage was now examined. Spontaneous intramolecular quaternization had been observed during the elucidation of the structure of reserpine and a similar reaction had been recently reported in the literature. N. Yoneda and co-workers in the synthesis of compounds containing the sarpagine ring system (148) had achieved the final ring formation through tosylation of the alcohol 147.
An analogous conversion of the alcohol 149 to the quaternary salt was carried out via the intermediate mesylates. Treatment of compound 149 with methansulfonyl chloride in pyridine at 0°C. provided an ether insoluble material, possibly the salt 150, which was treated with ammonia to ensure the presence of the free base (151). Thin-layer chromatographic examination of the reaction product at this time indicated complete absence of the starting alcohol and the presence of two new green spots, one at the base line and one less polar than the starting alcohol. This product possessed an essentially normal indole absorption in the ultraviolet region. Upon standing for a period of a few days the less polar spot gradually faded with the appearance of a stronger spot at the base line of the thin-layer chromatographic plate. The quaternary salt (73a) would be expected to be a very polar compound so this material was subjected to reduction with sodium in liquid ammonia47. Examination of the crude product by thin-layer chromatography indicated the presence of three compounds, two of which were identical in colour and Rf to the authentic samples of the two isomeric dihydrocleavamines.
Unfortunately the third component of the mixture had a very similar Rf value to the two dihydrocleavamines although it was readily distinguishable by its colour. Careful alumina chromatography of the total product provided a pure compound which was identical to authentic 4α-dihydrocleavamine (153) by thin-layer chromatography on both alumina and silica gel with respect to Rf and colour reactions obtained with a variety of spray reagents. A mass spectrum of this synthetic compound was superimposable with the mass spectrum of an authentic sample obtained from natural sources.
Preparative thin-layer chromatography of the remaining mixture of compounds afforded another pure compound which was identical to an authentic sample of 4β-dihydrocleavamine (152) by thin-layer chromatography on alumina and silica gel with a variety of spray reagents. The mass spectrum of this compound was identical to that of authentic 4β-dihydrocleavamine.

The successful route described here for the synthesis of the dihydrocleavamines has also been applied to quebrachamine (93a) by other workers in our laboratory and has been recently published. The condensation of the isomeric succinic ester derivative (102a) with tryptamine and subsequent analogous conversions to the quaternary mesylate (92a) followed by reduction to quebrachamine has demonstrated that this is in fact a general route to the quebrachamine and dihydrocleavamine series.

The successful conversion of 4β-dihydrocleavamine to carbomethoxydihydrocleavamine has also been accomplished in our laboratory and will now be mentioned briefly. Oxidation of 4β-dihydrocleavamine (152) with t-butyl hypochlorite provided the chloroindolenine (154) which was reacted with potassium cyanide to provide a cyanodihydrocleavamine (155). The latter compound, on treatment with methanolic hydrochloric acid provided carbomethoxy-4β-dihydrocleavamine (156) identical in all respects with an authentic sample. An analogous conversion of quebrachamine to vincadine is currently under study.
It can be seen, therefore, that the synthetic route described in Section B is not only a general route to dihydrocleavamine and quebrachamine but coupled with the introduction of a carbomethoxy group as well as the previous transannular cyclization studies completes a general entry into the Iboga, Aspidosperma and Vinca alkaloids. The use of various methoxylated tryptamines in this synthetic sequence would provide a route to alkaloids such as voacangin (157) and pyrifolidin (158).

Shortly after this synthesis of $\alpha$- and $\beta$-dihydrocleavamine and the corresponding $\alpha$-$\beta$-carbomethoxydihydrocleavamine had been published, a second synthesis of the two isomeric
dihydrocleavamines appeared\textsuperscript{83}.
Experimental - Part A

Melting points were determined on a Kofler block and are uncorrected. The ultraviolet (UV) spectra were recorded in 95% ethanol on a Cary 11 recording spectrophotometer, and the infrared (IR) spectra were taken on Perkin-Elmer Model 21 and Model 137 spectrometers. Nuclear magnetic resonance (NMR) spectra were recorded in deuteriochloroform at 60 megacycles per second (unless otherwise indicated) on a Varian A60 instrument and the chemical shifts are given in the Tiers \( \tau \) scale with reference to tetramethylsilane as the internal standard. Gas chromatography was performed on a Wilkins Aerograph Autoprep, Model A-700. Mass spectra were recorded on an Atlas CH-4 mass spectrometer and high resolution molecular weight determinations were determined on an AEI MS-9 mass spectrometer. Analysis were carried out by Dr. A. Bernhardt, Mulheim (Ruhr), Germany, Miss C. Jenkins and Mr. P. Borda of the microanalytical laboratory, the University of British Columbia. Silica Gel G and Woelm alumina containing electronic phosphor were used for thin-layer chromatography and Shawinigan alumina deactivated with 3 ml. of 10% acetic acid per 100 g. (unless otherwise indicated) was used for column chromatography.

**Nipotec acid hydrochloride (76)**

Nicotinic acid (20.0 g., 0.163 mole) was dissolved in IN hydrochloric acid and hydrogenated in the presence of platinum oxide (1.46 g.) at 1.5 atmospheres pressure until the uptake
of hydrogen had ceased (approximately 3 hours). The catalyst was removed by filtration, barium hydroxide (73 g.) was added, and any resulting piperidine was steam distilled. The residue of the steam distillation was treated with an exact amount of sulfuric acid to neutralize the excess base and the resultant barium sulfate removed by filtration. Evaporation of the filtrate provided nipecotic acid hydrochloride (23.4 g., 87%) mp. 242-244° (Lit. 239°) as a white solid. This crude acid possessed no ultraviolet absorption and was used directly for the preparation of methyl nipecotate.

Methyl nipecotate (77)

Crude nipecotic acid hydrochloride (20 g.) prepared by the reduction of nicotinic acid, was covered with a 5% by weight solution of hydrogen chloride in absolute methanol (160 ml.) and the mixture refluxed for 10-12 hours. The resulting solution was concentrated in vacuo to approximately 60 ml., cooled in an ice-bath and diluted with ether. This cooled solution was quickly transferred to a separatory funnel and shaken with a 30% sodium hydroxide solution. The aqueous alkaline layer was extracted with two additional portions of ether, the extracts being combined with the original ether layer and dried over anhydrous sodium sulfate. The ether and most of the remaining alcohol was evaporated and the residual yellow oil distilled under reduced pressure to provide methyl nipecotate (6.7 g., 35% yield from nicotinic acid) as a clear colorless oil, b.p. 53-54°/0.7 mm. (Lit. 82-84°/6 mm.).
Infrared (film): 1725 (\(-\text{COOCH}_3\)), 3250 (\(-\text{NH}\)) cm\(^{-1}\). NMR signals: 6.3 (singlet, 3H, \(-\text{OCH}_3\)). Found: C, 58.61; H, 9.25; N, 9.95. Calc. for C\(_7\)H\(_{13}\)O\(_2\)N: C, 58.72; H, 9.15; N, 9.78.

**Methyl nipecotate p-bromobenzamide (78)**

A mixture of methyl nipecotate (1.0 g., 7.0 m. mols), p-bromobenzoyl chloride (2.2 g., 0.010 mols) and pyridine (15 ml.) brought into solution by slight warming and allowed to stand at room temperature for 24 hours. The solution was then concentrated in vacuo to approximately 5 ml., then poured into ice-cold dilute ammonium hydroxide (30 ml.) with rapid stirring. The resultant white precipitate was removed by filtration, washed with water and air dried. Recrystallization of this material from methanol-water provided the pure amide as colorless platelets, mp. 109.5-110.0°C.

Infrared (KBr): 1730 (\(-\text{COOCH}_3\)), 1630 (\(-\text{CN}\)) cm\(^{-1}\). Ultraviolet, \(\lambda_{max} (\log e)\): 228 (4.11) m\(\mu\). NMR signals: 2.4 (doublet, 2H, aromatic), 2.7 (doublet, 2H, aromatic), 6.3 (singlet, 3H, \(-\text{OCH}_3\)). Found: C, 51.70; H, 5.10; N, 4.23; O, 14.66; Br, 24.70. Calc. for C\(_{14}\)H\(_{16}\)O\(_2\)NBr: C, 51.55; H, 4.95; N, 4.30; O, 14.71; Br, 24.80.

**Methyl ethylcyanoacetate (82)**

To a solution of sodium (7.1 g., 0.308 mols) in absolute methanol (125 ml.) was added a solution of methyl cyanoacetate (30 g., 0.304 mols) in absolute methanol (125 ml.). The reaction mixture was cooled with stirring in an ice-bath
during the addition. The resultant solution was allowed to warm to room temperature, stirred for 10 minutes, then ethyl iodide (51.0 g, 0.327 mols) added dropwise. The reaction flask was cooled intermittently during this addition, as considerable heat was evolved. The mixture was then stirred at room temperature for a further 1.5 hours, after which time it was nearly neutral to litmus. Most of the methanol was removed by distillation and the residual dark red mixture of liquid and sodium iodide transferred to a separatory funnel. Ice water, containing a few ml. of concentrated hydrochloric acid was added, and the mixture extracted three times with ether. The ether extracts were combined, washed with cold water to neutrality and dried over anhydrous sodium sulfate. Evaporation of the ether provided an orange oil which was distilled under reduced pressure to give a clear colorless oil (31 g) bp. 110-118°C/38 mm. NMR signals: 8.9 and 9.0 (two triplets, -CH₂CH₃).

This product was shown by gas chromatography (detailed conditions below) as being a mixture of three components, the major (60%) being the desired methyl ethylcyanoacetate.

Small quantities of the methyl ethylcyanoacetate were separated by gas chromatography on an analytical 20% Apiezon J column (45/60 Chrom W, 5' x 1/4", column temperature 110°C, helium flow rate 90 ml/min.). Infrared (film): 1740 (-COOCH₃), 2230 (-C≡N) cm⁻¹. NMR signals: 6.25 (singlet, 3H, -OCH₃), 8.9 (triplet, 3H, -CH₂CH₃), 6.55 (triplet, 1H, NC-CH₃COOCH₃).

Similar isolation of the smallest component of the mixture (10%) allowed its identification as unreacted methyl cyanoacetate (superimposable infrared spectra and thin-layer chromatographic properties - silica gel, benzene).

The third component of the mixture (30%) was also isolated in small quantity. Infrared (film): 1740 (–COOCH₃), 2230 (–C≡N) cm⁻¹.

Methyl 3-chloropropylethylcyanoacetate (83)

To a solution of sodium (15.6 g., 0.680 moles) in absolute methanol (350 ml.) was added a mixture of methyl ethylcyanoacetate, methyl cyanoacetate and methyl diethylcyanoacetate as obtained in the above experiment (101 g., containing approximately 0.58 moles of material which can be alkylated) with stirring. After approximately 15 minutes, 1-bromo-3-chloropropane (186 g., 1.18 moles) was added dropwise. The resultant mixture was warmed only slightly until the initial heat of reaction had subsided, then refluxed for 2 hours after which time the solution was neutral to litmus. The methanol was largely removed in vacuo and the residual mixture of solid and orange oil transferred to a separatory funnel. Cold water containing a few ml. of concentrated hydrochloric acid was added and the oil which separated taken up in ether. The aqueous layer was extracted twice more with ether, the extracts combined, washed with water to neutrality and dried over
anhydrous sodium sulfate. Concentration of the ether solution gave an orange oil which was distilled at 5 mm. pressure through a 15 cm. Vigreux column. The first fraction, b.p. 35-40°C was recovered bromochloropropane followed by a mixture of methyl diethlycyanoacetate (identical by gas chromatography to that obtained by alkylation of methyl cyanoacetate with ethyl iodide above) and methyl 3-chloropropyl-ethylcyanoacetate (50 g.) boiling in the range 82-140°C (mostly 82-95°C). Pure methyl 3-chloropropylethylcyanoacetate then was obtained (60 g., 30% overall yield from methyl cyanoacetate) as a clear colorless oil bp 140-148°C (mostly 144-147°C). An analytical sample was obtained by gas chromatography on an Apiezon J column (45/60 Chrom. W, 5' x \frac{1}{4}" column temperature 210°C, helium pressure 50 psi.) Infrared (film): 1735 (-COOCH3), 2220 (-CN) cm.-1. NMR signals: 6.2 (singlet, 3H, -OCH3), 8.95 (triplet, 3H, -CH2CH3), 6.4 (distorted triplet, 2H, -CH2Cl). Found: C, 52.64; H, 7.10; N, 6.56. Calc. for C9H14NO2Cl: C, 53.13; H, 6.93; N, 6.88.

3-Carbomethoxy-3-ethylpiperidine (67)

Methyl 3-chloropropylethylcyanoacetate (8.0 g., 0.0393 moles) was added over 1 hour to a stirred suspension of Pd (8.0 g., 10% on charcoal) in absolute methanol (100 ml.) to which 5N hydrochloric acid in absolute methanol (20 ml.) had been added. Stirring at room temperature was continued for 24 hours at which time approximately 1100 ml. of hydrogen
(55-60% of the theoretical amount) had been consumed and uptake had essentially ceased. The catalyst was removed by filtration and the filtrate evaporated to a small volume. Ether and water were added, the mixture transferred to a separatory funnel and the layers separated. The aqueous acidic layer was extracted once more with ether, the ether extracts combined and washed once with water, the water wash being added to the original aqueous layer. The ether layer was dried over anhydrous sodium sulfate and later combined with that obtained from the reduction of another 8 g. (83). These were evaporated to give essentially pure recovered nitrile (9.0 g., 56% recovery).

The aqueous acidic layer was then made strongly basic by the addition of ice-cold 30% sodium hydroxide solution and extracted three times with ether. The basic ether extracts were combined, dried rapidly over anhydrous sodium sulfate and evaporated to yield a pale yellow oil (approximately 3 g.) which was allowed to stand for 2 days. This oil upon standing became increasingly viscous and after 2 days was ether insoluble. This conversion could also be accomplished by heating the oil briefly on a steam bath. Ether and a small amount of water was added to the materials obtained in this manner from two reductions (8.0 g. of nitrile having been used in each experiment) followed by cold 30% sodium hydroxide. The resultant mixtures were combined in a separatory funnel and the layers separated. The aqueous layer was then extracted
with two additional portions of ether and the combined extracts were dried over anhydrous sodium sulfate. Evaporation of the solvent gave the desired piperidine (4.8 g., 82% crude yield) as a pale yellow oil possessing a characteristic piperidine odour. This material was used without further purification for the reaction with 2-carboethoxy-3-((p-chloroethyl)-indole (66). Vacuum distillation of a small amount (200 mg.) of this compound at 150° (bath temperature) at 0.1 mm. provided a sample for the preparation of the 3,5-dinitrobenzamide derivative (85). Further purification of the distilled material was effected by gas chromatography on an Apiezon J column (45/60 Chrom W. 5' x 1/4", column temperature 150°, helium flow rate 90 ml/min.). Infrared (film): 1725 (-COOCH₃), 3250 (NH) cm⁻¹. NMR signals: 6.25 (singlet, 3H, -OCH₃), 9.2 (triplet, 3H, -CH₂OCH₃). Repeated elemental analysis (five determinations) gave unsatisfactory results for carbon and hydrogen. 3-Carbomethoxy-3-ethylpiperidine-3, 5-dinitrobenzamide (85)

The reagent 3,5-dinitrobenzoyl chloride was freshly prepared as follows: 3,5-dinitrobenzoic acid (14.0 mg., 0.66 m. mols) and phosphorus pentachloride (14.5 mg., 0.70 m. moles) were warmed gently on a flame in a small test-tube until the reaction was initiated. After the reaction was complete and the resultant liquid cooled, a few ml. of petroleum ether (30-60°) was added in order to precipitate 3,5-dinitrobenzoyl chloride. The petroleum ether was removed
with a pipet and the 3,5-dinitrobenzoyl chloride washed twice more with petroleum ether to remove traces of phosphorus oxychloride. 3-Carbomethoxy-3-ethylpiperidine (90 mg., 0.53 m. mols) was added and after the initial reaction had subsided the mixture was warmed gently in the steam bath for 5 minutes. The product was dissolved in ether and washed successively with 5% hydrochloric acid, water, 5% sodium hydroxide, and finally water. Since the product tended to crystallize from ether, the solvent was evaporated directly to yield a crystalline residue which was recrystallized once from methanol to provide the pure amide as pale yellow needles, mp. 122.0-122.5°.

Infrared (KBr): 1725 (-COOCH₃), 1630 (-CN-), 3030 (aromatic) cm⁻¹. Ultraviolet, λ max (logε): 230 (4.30) μ. NMR signals: 6.3 (singlet, 3H, -OCH₃), 9.25 (triplet, 3H, -CH₂CH₃), 0.9 (triplet, 1H, aromatic), 1.4 (doublet, 2H, aromatic). Found: C, 52.65; H, 5.44; N, 11.48; O, 30.74. Calc. for C₁₆H₁₉O₇N₃: C, 52.60; H, 5.24; N, 11.50; O, 30.66.

2-Carbethoxy-3-[β-(3-carbomethoxy-3-ethyl-N-piperidyl)-ethyl]-indole (65)

2-Carbethoxy-3-(β-chloroethyl)-indole (66) (2.0 g., 8.0 m mols) and 3-carbomethoxy-3-ethylpiperidine (2.8 g., 16.4 m mols) in dioxane (25 ml.) were heated in a thick-walled sealed tube in a pressure bomb for 20 hours at 160°, the tube having been saturated with dry nitrogen before sealing. After cooling to room temperature the tube was opened, the dioxane solution decanted from the gummy, insoluble material and evaporated. The gummy residue remaining in the tube was combined with this
reaction product by thoroughly washing the tube with ether and water. The resultant mixture was acidified by the addition of concentrated hydrochloric acid and shaken in a separatory funnel. The layers were separated and the ether layer was dried over anhydrous magnesium sulfate and concentrated to give essentially pure unreacted starting indolic ester (1.2 g., 60% recovery).

The above aqueous layer was washed with a small amount of ether (discarded), then made basic by the careful addition of solid potassium carbonate, saturated with sodium chloride, and extracted three times with ether. The ether extracts were combined, washed with a small amount of water and dried over anhydrous magnesium sulfate. Evaporation of the ether gave a basic fraction (1.6 g.) which by thin-layer chromatography (alumina, chloroform, potassium permanganate spray) showed mainly one spot. This material was chromatographed on alumina (120 g.) and elution with benzene-ether (3:1) yielded the desired compound (1.0 g.). The later fractions of this chromatography contained a slightly more polar compound which could be removed by rechromatography. Crystallization of the pure product from pet. ether (60-80°) gave very pale orange crystals, mp. 104-106°, recrystallization of which provided an analytical sample as colorless prisms mp. 105.5-106.5°.

Infrared (KBr): 1730 (-COOCH₃), 1675 (-COOEt), 3350 (NH) cm⁻¹.
Ultraviolet; λ max (log ε): 229 (4.35), 298 (4.24) mμ.
NMR signals: 0.92 (broad singlet, 1H, NH), 2.2-3.0 (multiplets,
-107-

4H, aromatic), 5.57 (quartet, 2H, -OCH₂CH₃), 6.35 (singlet, 3H), 8.6 (triplet, -OCH₂CH₃), 9.2 (triplet, 3H, -CH₂CH₃).

Mass spectrum M.W. 386, base peak m/e 184. Found: C, 68.38; H, 7.77; N, 7.40; O, 16.63. Calc. for C₂₂H₃₀N₂O₄: C, 68.37; H, 7.82; N, 7.25; O, 16.56.

Attempted Acyloin Condensation of the Diester (68)

Toluene which had been freshly distilled from sodium was again distilled from sodium under dry nitrogen into a three-necked reaction vessel equipped with a high speed stirrer and a dilution chamber attached to a condenser. The toluene collected in the reaction flask was then continuously distilled through the dilution chamber to remove water from the apparatus (continued for ½ hour). Freshly cut sodium (90 mg.) was added to the reaction flask containing the refluxing toluene (30-40 ml.) and the diester 68 (300 mg., 0.78 m moles) added through the dilution chamber containing toluene (approximately 50 ml.) over a period of ¼ hours while the sodium suspension was being stirred at 4000-5000 rpm. After the addition of the diester was complete the mixture was refluxed with stirring for an additional 2½ hours. The reaction mixture was cooled in an ice-bath and glacial acetic acid added until the mixture was neutral to litmus. The precipitated material was removed by filtration, washed with ether and the combined filtrate and washings then dried over anhydrous sodium sulfate. The residue was then washed well with chloroform and the chloroform solution was dried over anhydrous sodium sulfate. Evaporation of the toluene-ether and chloroform fractions provided brown gums (85 mg. and 205 mg. respectively) which were
indicated by thin-layer chromatography (alumina, benzene ethyl acetate (5:1), and silica gel, methanol) as containing essentially the same material and no starting diester. Preparative thin-layer chromatography on silica gel (0.5 mm., methanol) on a portion of the combined products afforded a polar product (60% recovery) as an amorphous solid, one spot by thin-layer chromatography. Infrared (CHCl₃): 1720 cm⁻¹ (carbonyl). Ultraviolet, λmax: 225, 295 m. NMR signals: 6.0 (broad multiplet, 1-1.5H), 6.40 (broad singlet, 1.5H).

**Lithium Aluminum Hydride Reduction of the Acyloin Product**

The crude acyloin product (175 mg.) was dissolved in dry tetrahydrofuran (10 ml.) and added to a suspension of lithium aluminium hydride (175 mg.) in dry tetrahydrofuran (18 ml.). The resulting mixture was refluxed for 2½ hours, then cooled in an ice-salt bath and the excess lithium aluminium hydride destroyed by the careful addition of ice-water. Chloroform was added and the mixture filtered through Celite which in turn was washed well with chloroform. The combined filtrate and washings were dried over anhydrous potassium carbonate, then evaporated to yield a brown oil (155 mg.). A portion of this material (108 mg.) was purified by preparative thin layer chromatography on silica gel plates (20 x 20 cm., 0.5 mm., ethyl acetate:methanol, 2:1) to provide a purified product (50 mg.). This was again purified by the same process to yield a pure product (40 mg.). Infrared (CHCl₃): no carbonyl. Ultraviolet;λmax: 225, 272 (sh), 284, 292 m. NMR signals: 0.90 (singlet, 1H, -NH), 2.4-3.1 (multiplet, 4H, aromatic), 4.40 (broad singlet subject to concentration
shifts and exchanged by deuterium oxide, -OH), 5.35 (singlet, 2H), 6.45 (broad singlet, 2H), 9.25 (triplet, 3H, -CH2CH3).

**Acetylation of the Alcohol Obtained from Reduction of the Acyloin Product**

The alcohol obtained as described above (13 mg.) was treated with anhydrous pyridine (0.5 ml.) and acetic anhydride (0.05 ml.) and the mixture warmed to near reflux for 1 hour. The pyridine was evaporated under a stream of nitrogen, the residue dissolved in chloroform and dried over anhydrous potassium carbonate. Evaporation of the solvent provided a dark brown gum. NMR signals: 2.13-3.0 (aromatic), 4.78 (singlet), 5.95 (singlet), 8.0 (two singlets, -COCH3), 9.20 (triplet, 3H, -CH2CH3). This material was purified by preparative thin-layer chromatography on silica gel (20 x 20 cm., 0.5 mm., benzene:ethyl acetate, 1:1) to provide a light brown gum (9 mg.). Infrared (film): 3300 (-NH), 1725 (-OCOCH3) cm⁻¹. Ultraviolet, λmax: 224, 273 284, 292.5 mμ. Mass spectrum: base peak m/e 198.

**2-Hydroxymethyl-3[β-(3-ethyl-3-hydroxymethyl-N-piperidyl)-ethyl]-indole diacetate (58)**

This compound was prepared from authentic 2-carbomethoxy-3[β-(3-carbomethoxy-3-ethyl-N-piperidyl)-ethyl]-indole by reduction and acetylation in the identical manner to that described above for the acyloin condensation product. The diacetate obtained was identical to that described above (infrared, mass spectra, thin-layer chromatography - silica gel, benzene - ethyl acetate, 1:1, alumina, benzene - ethyl
Esterification of the Acyloin Condensation Product

The crude acyloin condensation product (20 mg.) was dissolved in chloroform (0.5 ml.) and diazomethane in ether (2 ml., approximately 0.4 M) was added (effervescence). After standing for one hour with occasional shaking the solvent was evaporated under a stream of nitrogen and a further solution of diazomethane in ether (2 ml.) was added directly to the oily residue. After one hour the product was investigated by thin-layer chromatography (aluminum, benzene - ethyl acetate, 5:1) and shown to contain both 2-carboethoxy-3-\(\beta-(3\text{-carbomethoxy-3-ethyl-N-piperidyl})\)-ethyl \(\beta\)-indole and the corresponding dimethyl ester by comparison with authentic samples.
2-Ethyl-1,3-propanediol (106)

To a stirred suspension of lithium aluminum hydride (30 g., 0.79 moles) in dry tetrahydrofuran (750 ml) under dry nitrogen, was added over a period of 45 minutes a solution of diethyl ethylmalonate (91+ g., 0.50 moles) in dry tetrahydrofuran (250 ml). The resulting mixture was refluxed with stirring under dry nitrogen for 6 hours. The reaction mixture was then cooled to 0-5° in an ice-salt bath and cold water added carefully to destroy excess lithium aluminum hydride. After having been allowed to come to room temperature and to stand for 10-15 minutes the mixture was filtered through Celite to remove inorganic material. The precipitate was washed well with hot tetrahydrofuran and the combined filtrate and washings were concentrated by vacuum distillation. The resultant viscous oil was taken up in fresh tetrahydrofuran and dried over anhydrous magnesium sulfate. The oil obtained by evaporation of the tetrahydrofuran was distilled under reduced pressure to provide 2-ethyl-1,3-propanediol (47.5 g., 91% yield) as a clear colorless oil, bp. 92-94°/0.7 mm. (Lit. 53 87°/0.5 mm.). Infrared (film): 3300 cm.\(^{-1}\) (-OH), no carbonyl absorption.

3-Benzyl oxy-2-ethylpropanol (107)

Freshly cut sodium (1.06 g., 0.046 moles) was added in small pieces to a hot (115-120°) stirred solution of 2-ethyl-1,3-propanediol (14.4 g., 0.138 moles) in dry xylene (6 ml), the temperature being maintained by removing or applying the
heat source as required. When all the sodium had reacted (45 min.) benzyl chloride (6.5 g., 0.051 moles) was added drop-wise, the temperature again maintained as above. The resulting mixture was stirred at 120° for 1 hour, then allowed to cool to room temperature and filtered to remove the sodium chloride (2.69 g.). The filtrate was concentrated in vacuo and the resultant viscous yellow oil distilled under nitrogen and at reduced pressure through a spiral tantalum distillation column (5 mm. x 33 cm.), equipped with heating jacket. After removal of the xylene, unreacted 2-ethyl-1,3-propanediol (9.1 g.), bp. 102-108°/2 mm. was first obtained, followed by 3-benzyloxy-2-ethylpropanol (6.88 g., 77% yield), as a clear colorless oil, bp. 130-133°/2 mm. Infrared (film): 3300 (OH), 740, 695 (aromatic) cm.⁻¹. NMR signals: 2.70 (singlet, 5H, aromatic), 5.50 (singlet, 2H, C₆H₅CH₂O⁻), 6.4 (multiplet, 4H, C₆H₅CH₂OCH₂⁻, and HOCH₂⁻), 7.2 (singlet, 1H, -OH), 8.0-8.9 (multiplets, 3H, -CHCH₂CH₃), 9.1 (triplet, 3H, -CH₂CH₃).

Found: C, 74.01; H, 9.58; O, 16.60. Calc. for C₁₇H₁₈O₂:
C, 74.19, H, 9.34, O, 16.47

3-Benzylloxy-2-ethylpropyl chloride (108)

Thionyl chloride (18.5 g., 0.155 moles) was added drop-wise to a stirred mixture of 3-benzyloxy-2-ethylpropanol (107) (29.0 g., 0.150 moles) and N,N-dimethylaniline (20.0 g., 0.165 moles), the temperature being maintained below 45° by cooling in an ice-bath. The resultant mixture was stirred for ½ hour at 45° then poured into dilute hydrochloric acid
contained in a separatory funnel. The heavy oil which separated was removed with chloroform, washed once with dilute hydrochloric acid to remove any N,N-dimethylaniline, then washed with several portions of water until neutral to litmus paper. The chloroform solution was dried over anhydrous sodium sulfate and the pale yellow oil resulting on evaporation of the chloroform was distilled under reduced pressure to yield 3-benzyloxy-2-ethylpropyl chloride (21.0 g., 66% yield) as a clear colorless oil, bp. 88-90°/0.3mm. Infrared (film): 735, 695 (aromatic) cm⁻¹. NMR signals: 2.70 (singlet, 5H, aromatic), 5.50 (singlet, 2H, C6H5CH2O-), 6.45 (multiplet, 4H, C6H5CH2OCH2- and ClCH2-), 7.9-8.8 (multiplet, 3H, -CHCH2CH3), 9.10 (triplet, 3H, -CH2CH3). Found: C, 67.39; H, 8.10. Calc. for C12H17OCl: C, 67.75; H, 8.06.

Diethyl 3-benzyloxy-2-ethylpropylmalonate (109)

Freshly cut sodium (3.68 g., 0.16 moles) was added in small pieces to absolute ethanol (75 ml) with stirring. The solution of sodium ethoxide was allowed to cool to about 50° then diethyl malonate (37 g., 0.23 moles) was added over a 10 minute period. The resulting solution was heated to reflux and 3-benzyloxy-2-ethylpropyl chloride (32.5 g., 0.153 moles) added dropwise over a 3 hour period, after which time the mixture was refluxed for a further 20 hours. Most of the ethanol was removed by distillation, then the cooled mixture of sodium chloride and oil poured into cold water containing acetic acid (10 ml). The layers were separated and the
aqueous layer extracted three times with ether. The separated oil and ether extracts were combined and washed once with water, twice with a 10% sodium bicarbonate solution and finally once with a saturated sodium chloride solution. After drying over anhydrous sodium sulfate and evaporation of the solvent, a viscous yellow oil was obtained. This product was distilled at reduced pressure to yield, in the initial fractions, unreacted diethyl malonate, then 3-benzyloxy-2-ethylpropyl chloride (16.8 g., 52% recovery) and finally diethyl 3-benzyloxy-2-ethylpropyl malonate (22 g., 89% yield based on recovered starting material) as a pale yellow oil bp. 155-160°/0.3 mm. Infrared (film): 1735 (-COOEt), 690, 735 (aromatic) cm.\(^{-1}\). NMR signals: 2.65 (singlet, 5H, aromatic), 5.50 (singlet, 2H, \(\text{C}_6\text{H}_5\text{CH}_2^0\)), 5.80 (quartet, 4H, \(-\text{OCH}_2\text{CH}_3\)), 6.55 (multiplet, 3H, \(\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2^-\) and \(-\text{CH(COOEt)}_2\)), 8.05 (multiplet, 2H, \(-\text{CH}_2\text{CH(COOEt)}_2\)), 8.8 (triplet, \(-\text{OCH}_2\text{CH}_3\)), 9.15 (triplet, 3H, \(-\text{CHCH}_2\text{CH}_3\)). Found: C, 68.17; H, 8.5. Calc. for \(\text{C}_{19}\text{H}_{28}\text{O}_5\); C, 67.83; H, 8.39.

3-Benzylxloxy-2-ethylpropylmalonic acid (110)

To a cold stirred solution of potassium hydroxide (5.9 g.) in water (9 ml) and ethanol (1 ml) was added diethyl 3-benzyloxy-2-ethylpropylmalonate (109) (9.0 g., 0.0268 moles) over 1½ hours. The mixture was then stirred with cooling in an ice bath, for four hours, then allowed to stand at room temperature overnight. The resultant yellow solution was extracted twice with ether, then cooled in an ice-bath, diluted with water
(10 ml) and ether (20 ml) and made strongly acidic (to Congo red paper) by the careful addition of concentrated hydrochloric acid. The layers were separated and the aqueous acidic layer extracted twice with ether. The combined ether extracts were washed twice with water, once with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of the solvent provided an extremely viscous oil which did not crystallize upon standing or upon trituration with various solvents. Infrared (film): 3500-2400, 1710 (-COOH) cm⁻¹. NMR signals: 1.0 (broad singlet, 2H, -COOH), 2.61 (singlet, 5H, aromatic), 5.49 (singlet, 2H, C₆H₅CH₂O⁻), 9.11 (triplet, 3H, -CH₂CH₃).

4-Benzylloxymethylhexanoic acid (111)

The crude malonic acid (110) (approximately 7.5 g.) was heated in an oil bath at 120° for 5 hours and the resulting light brown viscous oil which could not be induced to crystallize was not purified further. Infrared (film): 1710 (-COOH) cm⁻¹. NMR signals: -0.6 (broad singlet, 1H, -COOH), 2.65 (singlet, 5H, aromatic), 5.50 (singlet, 2H, C₆H₅CH₂O⁻), 6.60 (doublet, 2H, C₆H₅CH₂OCH₂⁻), 7.6 (multiplet, 2H, -CH₂COOH), 9.11 (triplet, 3H, -CH₂CH₃).

Ethyl 4-benzylloxymethylhexanoate (112)

The crude acid (111) (approximately 5 g.) was dissolved in anhydrous ethanol (20 ml) containing concentrated sulfuric acid (1 ml) and the solution refluxed for 1½ hours. The resulting solution was allowed to cool then poured into cold
water and extracted twice with ether. The combined extracts were washed successively with water, 5% sodium bicarbonate and saturated sodium chloride solutions, then dried over anhydrous sodium sulfate. The ether was evaporated and the residual yellow oil distilled under reduced pressure to provide ethyl 4-benzyloxyethylhexanoate (5.3 g., 75% yield from the malonic ester 109) as a clear colorless oil, bp. 122-128°/0.6 mm. Infrared (film): 1730 (-COOEt), 735, 695 (aromatic) cm. 

NMR signals: 2.65 (singlet, 5H, aromatic), 5.50 (singlet, 2H, C6H5CH2O-), 5.85 (quartet, 2H, -OCH2CH3), 6.60 (broad doublet, 2H, C6H5CH2OCH2-), 7.65 (multiplet, 2H, -CH2COOEt), 8.75 (triplet, -OCH2CH3), 9.10 (triplet, 3H, -CHCH2CH3). Found: C, 72.34; H, 9.27; O, 18.54. Calc. for C16H24O3: C, 72.69; H, 9.15, O, 18.16.

Preparation of Triphenylmethyl sodium

Sodium (3 g.) in dry xylene (10 ml) was warmed carefully with a flame until it melted. The flask was flushed with dry nitrogen and mercury (200 g.) added very cautiously to the melted sodium. The resultant mixture was allowed to cool to room temperature under nitrogen and the supernatant xylene decanted. Anhydrous ether (50 ml) and triphenylmethyl chloride (11 g.) was added, the flask well stoppered, then shaken for 6 hours. The resultant dark red solution of triphenylmethyl sodium was then diluted with anhydrous ether (80 ml) and maintained well sealed. The solution was transferred under dry nitrogen to a buret for a measured addition to the reaction
flask and for standardization by titration with acid\(^{84}\). The concentration as determined by this method on various occasions was 0.18-0.22 N.

**Diethyl 2-(2-benzylloxymethylbutyl)-succinate (71a)**

An ether solution of 0.22 N triphenylmethyl sodium (86.5 ml, 0.019 moles) was quickly run into a round bottomed flask that had been flushed with dry nitrogen. The ester (112) (5.0 g., 0.019 moles) was immediately added and the solution stirred for 2 minutes. Ethyl iodoacetate (4.05 g., 0.019 moles) was then added dropwise and the resultant mixture stirred for \(\frac{1}{2}\) hour at room temperature. Glacial acetic acid (2.5 ml) was added to remove any excess bases, the mixture filtered to remove sodium iodide and the filtrate dried over anhydrous sodium sulfate. The ether was evaporated and the residual light brown oil chromatographed on alumina (750 g.). Triphenylmethane was initially eluted with petroleum ether-benzene (4:1). The unreacted starting ester (2.5 g.) was removed with petroleum ether-benzene (2:1) and (1:1) but was contaminated with small amounts of triphenylcarbinol. A mixture of unreacted starting material and product (1.6 g.) was then eluted with benzene, again contaminated with a small amount of triphenylcarbinol which crystallized from the mixture. This ester mixture was separated from the triphenylcarbinol by means of a pipet and rechromatographed on alumina (96 g.). Careful elution with petroleum ether-benzene (3:1) provided starting material in the initial fractions, followed by the desired product. Further purification by vacuum
distillation (130-180°, bath temperature/0.1 mm) yielded the desired succinic ester (38.0 mg.) as a clear colorless oil. Gas chromatography on a 20% SE 30 analytical column (60/80 Chrom W, 10 x 1/4" column temp. 230°, helium flow rate 90 ml/min.) provided an analytical sample. Infrared (film): 1730 (-COOEt), 735, 690 (aromatic) cm.-1. NMR signals: 2.70 (singlet, 5H, aromatic), 5.50 (singlet, 2H, C_6H_5CH_2O-) 5.85 (two quartets, 4H, -OCH_2CH_3), 6.60 (multiplet, 2H, C_6H_5CH_2OCH_2-), 7.05 (multiplet, 1H, -CHCOOEt), 7.4 (multiplet, 2H, -CH_2COOEt), 8.75 (triplet, -OCH_2CH_3), 9.1 (triplet, 3H, -CHCH_2CH_3). Found: C, 68.42; H, 8.79. Calc. for C_20H_30O_5: C, 68.54; H, 8.63. Detailed gas chromatographic examination was performed on an analytical 20% SE 30 column (60/80 Chrom W), 10 x 1/4", helium flow rate 100 ml/min., column temperature 245° and 260°C., also on 20% FFAP (60/80 Chrom W), 10 x 1/4", helium flow rate 100 ml/min., column temperature 245° and 265°.

Diethyl 2-(2-benzylxoxymethylbutyl)-2-carboethoxysuccinate (113)

Freshly cut sodium (1.71 g., 0.075 moles) was added to dry xylene in a round bottomed 3-necked flask equipped with an external stirring motor. The xylene was heated until the sodium melted and the stirrer turned on and off a few times to disperse the sodium as a fine sand. The xylene was allowed to cool to room temperature and a large portion was decanted. Anhydrous ether was added and decanted from the sodium a few times to remove the remaining xylene. The sodium sand was finally covered with anhydrous ether (100 ml). The malonic
ester (109) (25 g., 0.075 moles) was added and the mixture refluxed for 3 hours at which time evolution of hydrogen had ceased and all the sodium had disappeared. Ethyl bromoacetate (12.7 g., 0.076 moles) was carefully added dropwise to the pale green solution of the malonate salt and the resulting solution stirred at room temperature for \( \frac{1}{2} \) hour, then refluxed for 1 hour. The reaction mixture was poured into cold water containing a small amount of acetic acid, and the layers separated. The aqueous layer was extracted twice further with ether, the combined extracts washed once with water, then dried over anhydrous sodium sulfate. The ether was evaporated and the remaining yellow viscous oil distilled under reduced pressure using a Claisen head well wrapped with glass wool. Initially a mixture of unreacted starting malonic ester and the triester (14.5 g.) distilling in the range 140°-190°/0.2 mm. was obtained. An estimate by NMR spectroscopy revealed the triester and malonic ester were in a ratio of 2:1. The subsequent fraction of the distillation contained pure desired triester (10.9 g.) bp. 190-200°/0.2 mm. Redistillation of the lower boiling fraction when combined with other reaction products provided additional triester. The overall yield was 78% based on recovered starting material. Infrared (film): 1730 (\(-\text{COOEt}\)), 695, 730 (aromatic) cm.\(^{-1}\). NMR signals: 2.70 (singlet, 5H, aromatic), 5.55 (singlet, 2H, \(\text{C}_6\text{H}_5\text{CH}_2\text{O}^-\)), 5.85 (multiplet, 6H, \(-\text{OCH}_2\text{CH}_3\)), 6.7 (doublet, 2H, \(\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2^-\)) 6.95 (singlet,
2H, -CH₂COOEt), 7.9 (multiplet, 2H -CH₂C(COOEt)₂), 8.75, 8.80 (two triplets, -OCH₂CH₃), 9.15 (triplet, 3H, CH₂CH₃).

Found: C, 65.06; H, 7.95. Calc. for C₂₃H₃₄O₇: C, 65.38, H, 8.11.

2-(2-Benzylloxymethylbutyl)-2-carboxysuccinic acid (114)

A mixture of the triester (113) (11.5 g., 0.0273 moles) and a 25% solution of potassium hydroxide (0.0905 moles) in 95% ethanol was refluxed for 5 hours. The alcohol was distilled and the residue taken up in water and extracted twice with ether. The aqueous alkaline solution was cooled in an ice-bath and made strongly acidic (to Congo red paper) by the careful addition of concentrated hydrochloric acid. The resultant mixture was extracted twice with ether, the extracts combined and washed twice with water, then dried over anhydrous sodium sulfate. Evaporation of the ether gave a very viscous light brown oil which did not crystallize upon standing or upon trituration with various solvents. Infrared (film): 1715 (-COOH) cm⁻¹. NMR signals: -0.4 (broad singlet, 3H, -COOH), 2.69 (singlet, 5H, aromatic), 5.55 (singlet, 2H, C₆H₅CH₂O⁻), 6.7 (broad doublet, 2H, C₆H₅CH₂OCH₂⁻), 6.85 (broad singlet, 2H, -CH₂COOH), 8.0 (multiplet, 2H, -CHCH₂C(COOH)₂), 9.2 (triplet, 3H, -CH₂CH₃).

2-(2-Benzylloxymethylbutyl)-succinic acid (115)

The crude triacid (114) obtained above (approximately 9 g.) was heated at 165-170° for a period of 3 hours. The crude product was refluxed in a 20% aqueous solution of potassium
hydroxide (2.5 moles), to remove any anhydride, (2-3 hours or until a clear solution was obtained). The aqueous solution was then cooled in an ice bath, made strongly acidic (to Congo red paper) by the careful addition of concentrated hydrochloric acid, and extracted three times with ether. The combined extracts were washed twice with water, dried over anhydrous sodium sulfate, and evaporated to provide the crude succinic acid as a mixture of crystals and viscous oil.

Infrared (film): 1700 (-COOH), 740, 695 (aromatic) cm⁻¹.

NMR signals: 1.05 (broad singlet, -COOH), 2.70 (singlet, 5H, aromatic), 5.50 (singlet, 2H, C₆H₅CH₂OCH₂⁻), 6.60 (multiplet, 2H, C₆H₅CH₂OCH₂⁻), 7.3 (very broad multiplet, 3H, -CH₂COOH, -CH₃COOH), 9.15 (triplet, 3H, -CH₂CH₃).

Diethyl 2-(2-benzyloxymethylbutyl)-succinate (71a)

The crude succinic acid (115) (approximately 7 g.) was dissolved in absolute ethanol (20 ml) containing concentrated sulfuric acid (1 ml) and refluxed for 1½ hours. The resultant solution was cooled and poured into cold water and extracted twice with ether. The combined extracts were washed twice with water, once with 5% sodium bicarbonate solution, and once with water, then dried over anhydrous sodium sulfate. Evaporation of the ether provided a light yellow oil which was distilled under reduced pressure (bath temp. 135-165°/0.5 mm) to provide the pure succinic ester (7.44 g., 78% yield from the triester 113) as a clear colorless oil. Spectral and gas chromatographic properties of this succinic ester
derivative were identical to those for the compound obtained by the alternate route as described earlier.

$N-[\beta-(3\text{-Indolyl})\text{-ethyl}]-3-(2\text{-benzyloxymethylbutyl})-\text{succinimide (130)}$

Tryptamine hydrochloride (5 g.) was suspended in 5% sodium hydroxide solution in a separatory funnel and shaken three times with ether to extract the free base. The combined extracts were washed three times with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent provided the crystalline tryptamine mp. 116-117° (Lit. 116°).

A mixture of tryptamine (3.1 g., 0.0194 moles), tryptamine hydrochloride (150 mg.) and the succinic ester (71a) (2.2 g., 0.0063 moles) was refluxed in freshly distilled 2-(2-Ethoxyethoxy)-ethanol (30 ml, bp. 190-200°C) for 50 hours under dry nitrogen. The resultant mixture was then allowed to cool to room temperature, taken up in ether and washed three times with water, five times with 10% acetic acid to remove tryptamine and three times with water. The green ethereal solution was dried over anhydrous sodium sulfate and evaporated to give a dark brown gum (approximately 3.1 g.). This material was chromatographed on alumina (175 g.) and the desired imide eluted with benzene and benzene-ether (4:1) as a light brown gum (2.02 g. - dried to constant weight, 77% yield). A small quantity of this material was distilled under vacuum to provide an analytical sample as an almost colorless light brown glass bp. 260-270°/0.005 mm (bath temp.).
Infrared (Nujol): 3320 (NH), 1755 (medium), 1685 (strong) (imide) 740 and 695 (aromatic) cm.\(^{-1}\). Ultraviolet, \(\lambda_{\text{max}}\) (log \(\varepsilon\)): 222 (4.57), 283 (3.79) m\(\mu\). NMR signals: 1.9 (broad singlet, 1H, NH), 2.7 (multiplet, 9H, aromatic), 3.00 (doublet, 1H, \(\alpha\)-proton of indole), 5.55 (singlet, 2H, \(\text{C}_6\text{H}_5\text{CH}_2\text{O}\text{-})\), 6.20 (triplet, 2H, \(-\text{CH}_2\text{N}\)), 6.65 (multiplet, 2H, \(\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_3\)\)), 9.15 (triplet, 3H, \(-\text{CH}_2\text{CH}_3\)). Mass spectrum: M.W. 418; main peaks: m/e 144, 143, 130, 91. Found: C, 74.81; H, 7.40; N, 6.52. Calc. for \(\text{C}_{26}\text{H}_{30}\text{N}_2\text{O}_3\): C, 74.61; H, 7.23; N, 6.69.

\(\text{N=}[\varepsilon-(3\text{-Indolyl})\text{-ethyl}]\text{-3-(2-benzylxoxymethylbutyl)}\text{-pyrrolidine (131)}\)

The imide (130) (925 mg, 2.21 m moles) in dry tetrahydrofuran (25 ml) was added to a stirred suspension of lithium aluminum hydride (250 mg, 6.60 m moles) in dry tetrahydrofuran (25 ml), and the resulting mixture refluxed with stirring under dry nitrogen for 8\(\frac{1}{2}\) hours. The reduction product was then cooled in cold water and the excess lithium aluminum hydride destroyed by the careful addition of cold wet tetrahydrofuran. The mixture was allowed to warm to room temperature and after allowing to stand for a few minutes it was filtered through Celite to remove inorganic salts. The Celite was then washed well with hot tetrahydrofuran and the combined filtrate and washings were dried over anhydrous sodium sulfate. Evaporation of the solvent yielded the crude amine (925 mg) as a pale yellow oil. Chromatography of this material on alumina
(50 g.) and elution with benzene and benzene-ether (4:1) provided the pure amine (815 mg. - dried to constant weight, 95% yield) as a very pale yellow gum which gradually darkened upon standing. Vacuum distillation of a small quantity provided an analytical sample bp. 240-250° (bath temp.)/0.005 mm. as a clear colorless glass. Infrared (neat): 3350 (NH), 735 and 695 (aromatic) cm.⁻¹. Ultraviolet, λmax (log ε): 222 (4.56), 283 (3.80) μ. NMR signals (100 Mc/s): 1.55 (broad singlet, 1H, NH), 2.75 (multiplet, 9H, aromatic), 3.11 (doublet, 1H, α-proton of indole - collapses to singlet upon addition of D₂O), 5.55 (singlet, 2H, C₆H₅CH₂O⁻), 6.70 (doublet, 2H, C₆H₅CH₂OCH₂⁻), 9.15 (triplet, 3H, -CH₂CH⁻). Mass spectrum: base peak m/e 260, strong m/e 91. Found: C, 80.02; H, 8.82; N, 7.35. Calc. for C₂₆H₃₄N₂O: C, 79.95; H, 8.78; N, 7.17. Molecular wt. 390.267 (Calc. 390.267).

Mercuric Acetate Oxidation of the Amine (131)

Mercuric acetate (3.40 g., 0.0107 moles) and the amine 131 (500 mg., 1.28 m moles) were refluxed in anhydrous methanol (260 ml) containing glacial acetic acid (7.5 ml) for 4½ hours under highly purified nitrogen ("L" grade, Canadian Liquid Air Ltd.) The reaction was followed by periodically treating an aliquot of the mixture with hydrogen sulfide gas and observing the development of the absorption peak of the supernatant, at 353 μ. The resultant greenish-yellow mixture was allowed to cool and filtered through a sintered glass disc (medium porosity), into a 3-necked round bottomed
flask, to remove the mercurous acetate (1.18 g., 1.8 moles). The filtrate was warmed to approximately 50°, a flow of purified nitrogen being continuously passed through one neck of the flask, then hydrogen sulfide gas bubbled into the solution for 15 minutes to destroy mercury complexes. The resultant precipitate of mercury sulfides was removed by filtration, under a nitrogen atmosphere through another sintered glass disc as described above except that Celite was used as a filter aid and a high vacuum (oil pump) was employed to aid filtration.

It is important to emphasize that optimum yields in this reaction are obtained only if the entire operation described above is conducted under an inert atmosphere. For this purpose, an apparatus consisting of a series of three-necked flasks interconnected by bent adapters, which already contained the sintered glass discs, was used. In this manner, addition of reagents, filtration, etc., could be conveniently carried out under an atmosphere of dry nitrogen.

Sodium borohydride (2.2 g.) was immediately added to the filtrate and the solution stirred under nitrogen for 4 hours after which time the absorption peak at 353 m\(\mu\) had completely disappeared. The solution was then concentrated to approximately 20 ml and partitioned between chloroform and water. The aqueous layer was extracted twice more with chloroform, the extracts combined and washed twice with water, twice with 5% sodium hydroxide solution and twice more with
water. After drying over anhydrous sodium sulfate, the chloroform was evaporated to yield a brown gum (430 mg) which was chromatographed on alumina (20 g.). Elution with benzene:ether (4:1 and 1:1) removed a mixture of the cyclized benzyl ethers of increasing polarity and these were designated A, B, C, C' (C and C' were indistinguishable by thin layer chromatography on alumina) and D as well as uncyclized starting material (total 175 mg). Initially a mixture of isomers A and B was obtained, followed by mixtures of isomers B, C, C' and a small amount of un cyclized material. Elution with methanol yielded an additional mixture of isomers C, C' and D along with some polar material (total 160 mg) which was re-chromatographed to give additional isomers C, C' and D (35 mg.). The total weight of the cyclized product was 210 mg (yield 37% based on an estimate by thin-layer chromatography of 20% un cyclized material being present). This total mixture was used for the preparation of the corresponding alcohols. Small quantities of pure benzyl ethers were obtained by preparative thin-layer chromatography (as described below) of the partially separated mixtures obtained above by column chromatography.

A mixture of one of the minor isomers A and one of the major isomers B (16 mg) were spotted on a thin-layer chromatoplate (alumina, 20 x 20 cm., 0.3 mm thickness) and developed in benzene:ethyl acetate (2.5:1). The developed plate was examined under ultraviolet light while still wet,
and the bands corresponding to isomers A and B scraped off and extracted separately with methanol. The extracts were filtered through a sintered glass disc, washing well with methanol and the filtrates evaporated to dryness. The resultant residues were taken up in anhydrous ether and removed from any alumina by means of a pipet. Evaporation of the ether solutions provided pure isomer A (3 mg) as a mixture of crystals and gum. Ultraviolet, $\lambda_{\text{max}}$: 226, 274 (sh), 283, 291 m$\mu$. Molecular weight 388.251. Calc. for $C_{26}H_{32}N_2O$: 388.251 and pure isomer B (9 mg), as a pale green glass.

Infrared (film): 3240 (–NH), 740 and 695 (aromatic) cm$^{-1}$. Ultraviolet, $\lambda_{\text{max}}$: 226, 275 (sh), 283, 291 m$\mu$. NMR signals (100 Mc/s): 0.50 (singlet, 1H, –NH), 2.5–3.5 (multiplet, aromatic), 5.30 (singlet, 2H, C$_6$H$_5$CH$_2$O-), 5.60 (broad doublet approximately 1H, C-3H), 6.32 (quartet, C$_6$H$_5$CH$_2$OCH$_2$-), 9.10 (triplet, –CH$_2$CH$_3$). Molecular weight: 388.252.

The fractions as obtained in the above column chromatography and which appeared initially to be a pure ether C were found by thin layer chromatography on silica gel (methanol) to contain another minor isomer now designated C'. A mixture of these two isomers (30 mg) was separated by preparative thin-layer chromatography on silica gel (20 x 20 cm, 0.3 mm, methanol). The bands were separated as described above to provide the pure major isomer C (13 mg) as a clear pale green glass. Infrared (film): 3300 (–NH), 740 and 695 (aromatic) cm$^{-1}$. Ultraviolet, $\lambda_{\text{max}}$: 225, 273 (sh), 282, 290 m$\mu$. 
NMR signals (100 Mc/s): 1.80 (singlet, 1H, -NH), 2.5-3.1 (multiplet, 9H, aromatic), no doublet at 3.11, 5.60 (singlet, 2H, C\textsubscript{6}H\textsubscript{5}CH\textsubscript{2}O\textsuperscript{-}), 5.75 (broad multiplet, 1H, C-3H), 6.8 (doublet, C\textsubscript{6}H\textsubscript{5}-CH\textsubscript{2}OCH\textsubscript{2}H\textsubscript{2}-), 9.25 (triplet, 3H, -CH\textsubscript{2}CH\textsubscript{3}). Molecular weight: 388.252 and pure isomer C' (3 mg) as a clear pale green glass. Ultraviolet, \textit{\lambda}_{\text{max}} 225, 275 (sh), 282.5, 290.5 m\mu. Molecular weight 388.

**Hydrogenolysis of the Mixture of Cyclized Benzyl Ethers**

A mixture of the benzyl ethers obtained as described above (235 mg) and palladium (235 mg, 10% on charcoal) in glacial acetic acid (25 ml) was stirred under an atmosphere of hydrogen for 3\(\frac{1}{2}\) hours after which time the uptake had essentially ceased (approximately 80% of the theoretical amount consumed). The catalyst was removed by filtration and the acetic acid evaporated \textit{in vacuo}. The residual gum was taken up in chloroform, the latter washed with 5% sodium hydroxide solution, then twice with water and finally dried over anhydrous sodium sulfate. Evaporation of the chloroform yielded a pale orange gum (165 mg) which by thin-layer chromatography (alumina, ethyl acetate, antimony pentachloride in carbon tetrachloride, 1:1 as spray reagent) showed the presence of unreacted benzyl ethers as well as a mixture of more polar green spots and one polar brown spot. The crude product was chromatographed on alumina (10 g, deactivated with 0.5 ml, 10% acetic acid). Elution with benzene: ethyl ether (1:1) removed the unreacted benzyl ethers (65 mg, 28% recovery). Ether:methanol (99:1) removed a mixture of the
alcohols designated A and B (21 mg) and ether:methanol (98.2) removed a mixture of alcohols B and B' (5 mg). Continued elution with ether:methanol (98.2 and 95.5) removed a further mixture of alcohols B, B' and the uncyclized amino alcohol (49 mg). The uncyclized amino alcohol was identical by thin-layer chromatography to that prepared by hydrogenolysis of a small amount of uncyclized benzyl ether. Elution with ether:methanol (95:5 to 9:1) then removed the major pure cyclized alcohol C (26 mg) as an amorphous white solid while elution with ether:methanol (4:1) removed residual alcohol C (6 mg). Although a very minor alcohol designated D was observed in thin-layer chromatography of the crude product as being more polar than C, this material was not recovered from the column. The total weight of the amino alcohols (107 mg) represented an 83% yield. Rechromatography of the mixture of cyclized alcohols B, B' and the uncyclized amino alcohol allowed complete separation of these cyclized alcohols from the uncyclized alcohols.

Alcohol C. Infrared (CHCl₃): 3500, 3350, 3150 (-NH and -OH) cm⁻¹. Ultraviolet, λ max: 225, 273 (sh), 282, 290 m.μ. NMR signals (100 Mc/s): 0.40 (-NH), 2.5-3.0 (multiplet, 4H, aromatic), 5.78 (multiplet, 1H, C-3H), 6.61 (broad singlet, -CH₂OH), 9.18 (distorted triplet, 3H, -CH₂CH₃). Molecular weight: 298.203. Calc. for C₁₉H₂₆N₂O: 298.205.

Preparative thin-layer chromatography of a mixture of alcohols A and B (30 mg) on silica gel (20 x 20 cm., 0.3 mm,
methanol) was performed. The bands removed from the plate were extracted with methanol and filtered. Evaporation of the filtrate provided residues which were taken up in chloroform to remove any silica gel and the solvent evaporated again to yield pure alcohol A (9 mg) and pure alcohol B (16 mg) both as white amorphous solids. Preparative thin-layer chromatography on a mixture of alcohols B and B' (11 mg) using the same conditions provided an additional quantity of pure alcohol B (5 mg) and pure alcohol B' (2 mg) as amorphous solids.

Alcohol A. Ultraviolet, $\lambda_{\text{max}}$: 226, 273 (sh), 282.5, 290.5 nm. Molecular weight: 298.205.

Alcohol B. Infrared (CHCl$_3$): 3400, 3330, 3200 (-NH and -OH) cm$^{-1}$. Ultraviolet, $\lambda_{\text{max}}$: 226, 274 (sh), 283, 291 nm. NMR signals (100 Mc/s): 2.50-3.15 (multiplet, approximately 4H, aromatic), 5.72 (doublet, 0.7H, C-3H), 9.15 (triplet, -CH$_2$CH$_3$). Molecular weight: 298.205.

Alcohol B'. Ultraviolet, $\lambda_{\text{max}}$: 226, 274 (sh), 282.5, 290.5 nm. Molecular weight: 298.204.

**Hydrogenolysis of Cyclized Benzyl Ether C**

The ether C (8 mg) obtained pure by preparative thin-layer chromatography as described earlier was treated with palladium catalyst according to the procedure used above for the isomeric mixture. The product obtained (5 mg) was identical by thin-layer chromatography (alumina, ethyl acetate, silica gel, methanol) to alcohol C isolated from the hydrogenolysis of the mixture of ethers and different from the isomeric alcohols A,
Mesylation of Alcohol C

A solution of the alcohol C (43 mg) in dry pyridine (0.3 ml, distilled from potassium hydroxide) was cooled in an ice bath and added to ice-cold methanesulfonyl chloride (120 mg) in a small test-tube. The resultant light orange solution was allowed to stand in a refrigerator for 16 hours after which time the solution was dark red. The majority of the pyridine was evaporated under a stream of nitrogen with the aid of slight warming, and the last traces finally removed on an oil pump. The gummy red residue was washed twice with anhydrous ether, treated with water (0.5 ml) which appeared to partially dissolve the product, and washed twice further with benzene. Ammonium hydroxide (1 ml, 6N) was added and the aqueous mixture extracted thoroughly with chloroform (until the color of the extract was only pale yellow). The resultant dark red chloroform was dried quickly over anhydrous sodium sulfate and evaporated to provide a dark red gum (60 mg). Thin-layer chromatography (alumina, ethyl acetate, antimony pentachloride spray) showed the complete absence of the starting alcohol (Rf 0.25-0.30) and the presence of a less polar green spot (Rf 0.70) as well as a green spot on the base line. Ultraviolet, \( \lambda_{\text{max}} \): 226, 282, 289 \( \text{nm} \) (shoulder at 273 distorted, probably due to presence of pyridine). This product was allowed to stand in a vacuum dessicator for 4 days after which time it was very hygroscopic and thin-layer chromatography indicated a considerable increase in intensity of the base line spot relative
to the spot which was less polar than the starting alcohol.
Refluxing the material in chloroform for a few minutes did not noticeably alter the relative quantities of these two spots so this material was used for the following reduction.

Reduction of the Quaternary Mesylate (73a)

The mesylate obtained as described above (30 mg) was placed in a round bottom three-necked flask equipped with a dry ice trap and an ammonia inlet. (This operation was carried out as rapidly as possible but the amorphous mesylate turned gummy very quickly). Ammonia (5 ml) was run into the flask and sodium (50 mg) added to the suspension. The resulting blue solution was stirred for 20 minutes then quenched with ammonium chloride. The ammonia was allowed to evaporate and the residue partitioned between chloroform and water. The layers were separated and the chloroform layer washed three times with water and dried over anhydrous sodium sulfate. Evaporation of the chloroform provided a brown residue (20 mg). Chromatography of this material on alumina (1.0 g) and elution with benzene removed the major product (8 mg) which by thin-layer chromatography on silica gel (chloroform:ethyl acetate, 1:1, antimony pentachloride) contained both $4\alpha$- and $4\beta$-dihydrocleavamine as well as a third component which had an $R_f$ value intermediate between the two cleavamine derivatives.

The above procedure was repeated on the remaining mesylate (28 mg) to yield an additional identical mixture (7 mg). The combined products (15 mg) were chromatographed on
alumina (10 g., Woelm). Elution with ether yielded pure $\Lambda$-dihydrocleavamine (1 mg) which was identical to an authentic sample (mass spectrometry, thin-layer chromatography on several systems - silica gel, chloroform:ethyl acetate 1:1, antimony pentachloride and 1% ceric ammonium sulfate in 85% phosphoric acid as spray reagents; alumina, petroleum ether:benzene 4:1, same spray reagents). Continued elution with ether removed a mixture of the three compounds (8 mg) which was then further purified.

Preparative thin-layer chromatography on silica gel (20 x 20 cm., 0.3 mm, chloroform:ethyl acetate 1:1) was performed on this mixture. As the bands corresponding to $\Lambda$\beta-dihydrocleavamine and the unknown compound occurring between the two dihydrocleavamines overlapped extensively, only the very top portion of the desired band was removed and extracted with methanol. Extraction of the residue upon removal of the methanol, with chloroform and evaporation of the solvent provided pure $\Lambda$\beta-dihydrocleavamine (1 mg) which was identical to an authentic sample (mass spectrometry, thin-layer chromatography in several systems - silica gel, chloroform:ethyl acetate 1:1, and alumina, petroleum ether:benzene 4:1, using sprays mentioned above).

The overall yield of the two dihydrocleavamines from the alcohol C was estimated to be 17% by thin-layer chromatographic examination of the mixture of the three compounds obtained from the metal ammonia reduction.
Bibliography


