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PART I: AN IMPROVED TOTAL SYNTHESIS OF
D,L-MESEMBRINE AND THE CONSTRUCTION OF THE
BASIC SKELETON OF SCELETIUM ALKALOID A4.
PART II: THE TOTAL SYNTHESIS OF D,L-ELWESINE.

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PART I: AN IMPROVED TOTAL SYNTHESIS OF \textit{D, L}-MESEMBRINE AND
THE CONSTRUCTION OF THE BASIC SKELETON OF SCELETIUM ALKALOID A₄

PART II: THE TOTAL SYNTHESIS OF \textit{D, L}-ELWESINE

by

PATRICIA M. LESKO

A THESIS SUBMITTED
IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

Thesis Director's signature:

[Signature]

Houston, Texas

May 1974
DEDICATION

This thesis is dedicated to the two people whose enthusiasm for teaching and for science lead me to pursue a career in chemistry; C.C. Bunds and R.B. Turner.
ACKNOWLEDGEMENTS

I am very pleased to thank Professor Stevens for the guidance and support which made this work possible. The receipt of National Science Foundation Graduate Fellowships for the years 1968-1972 is also gratefully acknowledged.

I am especially grateful to my friends and co-workers for their help, understanding, friendship and companionship during my years at Rice.
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PART I

An Improved Total Synthesis of \textit{d,l}-Mesembrine and the
Construction of the Basic Skeleton of Sceletium Alkaloid \textit{A$_4$}
INTRODUCTION

The mesembrine alkaloids are a group of nitrogen containing basic materials isolated from several plants belonging to the genus {	extit{Sceletium}} N.E. Brown (fam. Aizoaceae or Ficoidaceae)\textsuperscript{1} that are indigenous to Southern Africa. Pharmacological interest in these compounds stems from their discovery in a drug preparation used by the Bushmen of Namaqualand called "Channa" or "Kougoed."\textsuperscript{2} The drug, when chewed, is reported to have a narcotic effect resembling the effect of cocaine.\textsuperscript{3}

To date, alkaloids exhibiting two fundamental structure-types have been isolated from {	extit{Sceletium}} species, but there are a number of minor alkaloids that remain uncharacterized. The majority of the mesembrine alkaloids have an N-methyl-3a-(3',4'-dimethoxyphenyl)-cis-octahydroindole skeleton (1).

\[
\begin{align*}
\text{Ar} &= 3',4'-\text{dimethoxyphenyl} \\
\text{Mesembrine (2), mesembrenine (3), and mesembrinol (4), the major alkaloids isolated from } &\textit{Sceletium expansum, S. tortuosum, S. anatomicum, and S. namaquense}^2, \text{ all exhibit this basic framework,}
\end{align*}
\]
as do four recently elucidated constituents of *S. strictum*.\(^4\)

\[\text{Ar} = \begin{array}{c}
\text{OCH}_3 \\
\text{OCH}_3 \\
\end{array} \]

\[\begin{array}{ll}
3 \text{ mesembrenine} & 4 \text{ mesembrinol} \\
\end{array} \]

In 1970 three seco-mesembrine alkaloids were found in *S. joubertii*.\(^5\) The seco-mesembrine alkaloids are bicyclic compounds in which the C\textsubscript{7a}-N bond of the octahydroindole nucleus has been cleaved, and joubertiamine, dihydrojoubertiamine, and dehydrojoubertiamine belong to this class.

\[\begin{array}{llll}
\text{OH} & \text{OH} & \text{OH} \\
\text{CH}_3 \text{CH}_3 & \text{CH}_3 \text{CH}_3 & \text{CH}_3 \text{CH}_3 \\
\end{array} \]

joubertiamine dihydrojoubertiamine dehydrojoubertiamine

The second skeletal type is exemplified by a dibasic alkaloid, designated Sceletium A\textsubscript{4}, isolated from *S. namaquense* and *S. tortuosum*. The structure of Sceletium A\textsubscript{4} (5), which has a 2,3 disubstituted pyridine
ring fused to the cis-octahydroindole, was obtained in 1971 by direct method X-ray analysis. The following spectral data served to confirm the presence of a 3,4-disubstituted phenyl ring and a 2,3-disubstituted pyridine ring.

**PMR: (CDCl₃, TMS)**

δ = 2.34 3H, s (N-Me)
3.70 3H, s (O-Me)
3.77 3H, s (O-Me)
6.48-6.72 3H, mult (aromatic protons)
8.48, 7.56, 7.15 3H, AMX spin system (pyridine protons)

**IR: (KBr)**

λ = 1605 cm⁻¹
1582
1571
1520

**UV: (EtOH)**

λ_max (log ε_max) = 232 (3.84)
268 (3.59)
274 (3.61)
286 (3.47)

Sceletium A₄ had been isolated prior to this time, but in amounts that precluded a chemical structure determination. Hydrogenolysis of this base with palladium on charcoal results in its conversion to the corresponding seco-derivative tortuosamine (6), a
naturally occurring alkaloid also isolated from *S. tortuosum*.\(^2\)

In light of the professed narcotic and stimulatory effects of the drug "Channa", the structural similarity between Sceletium A\(_4\) and nicotine (7) cannot be overlooked.

![Structural formulae]

5, Sceletium A\(_4\)  7, nicotine

Several studies to test the effects of structural modifications on the toxicity of nicotine have been run. The conclusions were that both an intact pyrrolidine ring and the aromatic pyridine nucleus made definite contributions to this alkaloid's biological activity.\(^6d\) Biological activity has also been attributed to the 1-methyl-3a-aryl-octahydroindole nucleus, and these compounds have been claimed to be useful as ataractic agents.\(^6e\)
RESULTS AND DISCUSSION

During the past few years, as part of a study to develop general methods of alkaloid synthesis employing endocyclic enamines, workers in these laboratories have achieved efficient total syntheses of the alkaloids \textit{d,\textit{l}-mesembrine}\textsuperscript{7e} and \textit{d,\textit{l}-joubertiamine}\textsuperscript{7g} (refer to schemes 1 and 2). Key steps in the syntheses are the acid catalyzed, thermal rearrangement of a cyclopropyl imine (eg. \textit{10}) to an appropriately substituted \(\Delta^2\)-pyrroline (eg. \textit{11}), and the subsequent annelation of this \(\Delta^2\)-pyrroline with methyl vinyl ketone (MVK) yielding the \textit{cis}-octahydroindolone.

\begin{center}
\textbf{Scheme 1}
\end{center}

\begin{center}
\begin{tikzpicture}
\node (8) at (0,0) {\textbf{8}}; \\
\node (9) at (2,0) {\textbf{9}}; \\
\node (10) at (4,0) {\textbf{10}}; \\
\node (11) at (2,-2) {\textbf{11}}; \\
\node (2) at (0,-4) {\textbf{2}}; \\
\node (a) at (2,0) {a}; \\
\node (b) at (2,-2) {b}; \\
\node (c) at (4,-2) {c}; \\
\node (d) at (3,-4) {d}; \\
\node (e) at (0,-4) {e}; \\
\draw[->] (8) -- (9) node[midway,above] {\textit{a}}; \\
\draw[->] (9) -- (10) node[midway,above] {\textit{b}}; \\
\draw[->] (9) -- (2) node[midway,above] {\textit{c}}; \\
\draw[->] (9) -- (11) node[midway,above] {\textit{d}}; \\
\draw[->] (11) -- (2) node[midway,above] {\textit{e}}; \\
\end{tikzpicture}
\end{center}

\textit{d,\textit{l}-mesembrine}

\(\text{Ar} = 3,4\text{-dimethoxyphenyl}

reagents (% yield): a) \textit{n}-butyl lithium, 1,2-dibromoethane (24), 
b) Lithium aluminum hydride (38), c) methyl amine, \text{MgSO}_4 (91), 
d) \text{NH}_4 \text{Cl}, \Delta (76), e) \text{MVK} (56).\)
Scheme 2

\[
\begin{align*}
    &\text{Ar-CN} \xrightarrow{a} \text{Ar-CN} \xrightarrow{b} \text{Ar-CHO} \\
    &\text{Ar} \xrightarrow{e} \text{Ar} \xrightarrow{d} \text{Ar-CH-NCH}_3 \\
    &\text{CH}_3 \xrightarrow{f} \text{OH} \\
    &\text{CH}_3 \xrightarrow{g} \text{d,l joubertiane} \\
\end{align*}
\]

Ar = \text{p-methoxyphenyl}

reagents (% yield): a) LiNH\textsubscript{2}, DME, 1,2-dibromoethane (75),
b) diisobutylaluminum hydride (86), c) methyl amine, MgSO\textsubscript{4} (91),
d) NH\textsubscript{4}Cl, 140° (98), e) MVK (93), f) 1. methyl iodide, 2. hydroxide
(62), g) 48% HBr (80).

When the structures of Sceletium A\textsubscript{4} and tortuosamine were reported, the application of these synthetic principles to these pharmacologically interesting compounds was a logical extension of the above work. The synthesis of Sceletium A\textsubscript{4} can be represented formally as the annelation of 1-methyl-3-(3',4'-dimethoxyphenyl)-\textalpha\textsuperscript{2}-pyrrole (11) with 2-vinyl pyridine, to give the intermediate 12 (see scheme 3); this inter-
mediate would then be expected to rearomatize to the racemic alkaloid 5. Based on the previous experiences with MVK annelations, a cis fused ring system would be the expected result.

The $\Delta^2$-pyrrole 11 required for this scheme is identical to the intermediate used for the synthesis of mesembrine, but since several of the transformations leading to 11 went in disappointingly low yields, its preparation was investigated further. In particular, a more efficient means was needed of effecting the alkylation of 3,4-dimethoxyphenyl acetonitrile (8) to give the cyclopropyl compound (9).
Earlier studies\textsuperscript{8} indicated that the intermediate in the alkylation is a dianion, and in agreement with this fact, generating the more covalent dilithio salts with lithium amide or n-butyllithium showed a distinct advantage over the use of other strong bases such as sodium hydride, sodium amide or dimethylsodium,\textsuperscript{9} in these cases where the alkoxy substituents on the phenyl ring resonance destabilize an anion. Nevertheless, even using lithium amide or n-butyllithium, the yields of 1-(3,4-dimethoxyphenyl)cyclopropyl cyanide (9) did not exceed 30%.

An alternative approach was suggested by the following sequence.\textsuperscript{10}

\[
\begin{align*}
\text{CN} + & \quad \begin{array}{c}
\text{Br} \\
\text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{Br}
\end{array} \\
\xrightarrow{\text{Bu}_4 \text{N}^+ \text{OH}^-} & \quad \begin{array}{c}
\text{CN} \\
\text{Br}
\end{array}
\end{align*}
\]

The reaction is carried out in a heterogeneous medium with benzyl cyanide and the alkylation agent in the organic phase, and the base, hydroxide, in the aqueous phase. The tetraalkyl ammonium ion is employed as a phase transfer catalyst, conducting anions to the organic phase.\textsuperscript{11}

A number of experiments were done using benzyl cyanide and an excess of 1,2-dibromoethane in methylene chloride as the organic phase and up to 15 equivalents of sodium hydroxide in the aqueous layer. The progress of the reaction was followed using pmr spectroscopy by comparing the cyclopropyl resonances of the product (mult, $\delta = 1.33, 1.58$) to the methylene resonance of the starting material (s, $\delta = 3.68$). At best, a 15% conversion was found. In order to
provide a better leaving group on the alkylating agent, the dimesylate of ethylene glycol was substituted for dibromoethane. On work up, large amounts of the mesylate of vinyl alcohol were found, indicating that the alkylating agent was being consumed far more readily in the elimination reaction, than in the desired alkylation. At this point attention was directed once again to lithium bases.

Since lithium amide is insoluble in organic solvents, it was reasoned that a strong, ether soluble base such as lithium diisopropylamide (LDA) might yield better results by providing a homogeneous reaction mixture. This prediction was verified as is shown in Table 1, where the results of experiments with LDA are summarized.

![Chemical Reaction Diagram]

**Table 1**

<table>
<thead>
<tr>
<th>Base</th>
<th>Equivalents of base</th>
<th>Solvent</th>
<th>X</th>
<th>Average % yield of 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiNH₂</td>
<td>8*</td>
<td>DME</td>
<td>Br</td>
<td>25</td>
</tr>
<tr>
<td>LDA</td>
<td>2.2</td>
<td>THF</td>
<td>Br</td>
<td>35</td>
</tr>
<tr>
<td>LDA</td>
<td>2.2</td>
<td>THF-HMPA</td>
<td>Br</td>
<td>55</td>
</tr>
<tr>
<td>LDA</td>
<td>2.3</td>
<td>THF-HMPA</td>
<td>Cl</td>
<td>70</td>
</tr>
</tbody>
</table>

* These conditions were found to be optimum in similar systems. 

The advantages of using hexamethylylphosphoric triamide (HMPA) as a cosolvent with THF for solubilizing dianions have been demonstrated now in a number of instances. As the 1,2-dibromoethane was added
to the reaction, a dark red color appeared, reminiscent of bromine. Based on this, 1,2-dichloroethane was substituted for the dibromide, and not only were the highest yields of cyclopropyl compound obtained, but the product also contained fewer impurities and crystalized spontaneously after workup and removal of solvent.

The next step, selective reduction of the nitrile \( \text{9} \) to the corresponding aldehyde, was conveniently carried out in 75% yield using diisobutyl aluminum hydride (DiBal-H). One difficulty that had been encountered in the alkylation step was finding a means of separating the cyclopropyl cyanide \( \text{9} \) from unreacted starting material \( \text{8} \). This separation became unnecessary when it was discovered that treatment of a mixture of alkylated and unalkylated cyanides with DiBal-H still resulted in the cyclopropyl carboxaldehyde \( \text{9a} \) as the only isolated product.

One final modification was made in the original procedure for preparing the \( \Delta^2 \)-pyrroline \( \text{11} \). The work up for the acid catalyzed, thermal rearrangement of \( \text{10} \) to \( \text{11} \) was considerably simplified by effecting the conversion with ammonium iodide in refluxing benzene, rather than neat, with ammonium chloride at 140°.\(^{13}\)

With this improved synthesis of pyrroline \( \text{11} \) now available, attention could be focused towards the addition of the remaining parts of the Sceletium \( A_4 \) molecule. There are numerous examples in the literature of nucleophilic additions to 2-vinyl-pyridines\(^{14}\), including the following reaction with the pyrrolidine enamine of cyclohexanone.\(^{14a}\)

For the case at hand (refer to scheme 3 on page 8), addition of the enamine \( \text{11} \) to 2-vinyl-pyridine would give a zwitterionic inter-
mediate 12, similar to the intermediate 14. However, since 12 cannot undergo a proton transfer to a neutral intermediate such as 15, there are two plausible alternative paths for the reaction to take; ring closure through the pyridine nucleus to 13 and/or collapse back to starting materials. The formation of 13 would require that the aromaticity of the pyridine ring be disrupted and it was anticipated that this might be a prohibitively high energy process. Freshly distilled 2-vinyl pyridine and the \(\Delta^2\)-pyrroline 11, or the hydrochloride salt of the pyrroline, were refluxed in diglyme for up to 96 hours, but in no instance was any material containing both the 3,4-dimethoxyphenyl and pyridyl moieties isolated.

By converting 2-vinyl pyridine to its N-oxide, the electron deficiency of the double bond is enhanced and this increases the tendency for nucleophilic agents to add in Michael fashion. 15 In
addition, because of resonance contributing forms such as 16b, the use of the N-oxide of 2-vinyl pyridine should make the ring closure from 16 to 17 more energetically favorable. Vinyl pyridine N-oxide was prepared via pyrolysis of 2(β-hydroxyethyl)pyridine-1-oxide and used directly in reactions with 11. Once again, the results were totally negative. Starting materials and their self-polymers were the only materials isolated.

An annelation, analogous to the one being attempted here, was reported by Ziegler as part of the total synthesis of the Aspidosperma
alkaloid minovine. Indolylacrylic ester 18 was condensed with the enamine 19 to afford the tetracyclic amino ester 20. With this result in mind, one further modification of the vinyl pyridine-enamine reaction was pursued.

A carbomethoxy substituent was added to the vinyl group to provide for additional resonance stabilization of the zwitterionic intermediate (compound 22, scheme 4), thereby increasing its lifetime over that of the unsubstituted zwitterionic intermediate 12. This stabilized intermediate might then stand a better chance of undergoing the desired cyclization to 25.

Methyl-α-(2-pyridyl)-acrylate (21) was prepared from 2-pyridine acetic acid hydrochloride (26) in the following fashion. Treating 26 with methanol and excess HCl at room temperature, overnight, gave a 92% yield of the ester 27. Direct α-hydroxymethylation was accomplished by first forming the enolate of 27 with lithium diisopropyl amide in THF at -78°, then warming the reaction mixture to -25° and passing formaldehyde vapors over the rapidly stirred solution. A 65% yield of crude 28 was obtained. While purifying this material via bulb-to-bulb distillation, spontaneous dehydration occurred and the acrylic ester 21 distilled over as a bright yellow oil. Subsequent
Scheme 4

\[
\text{Ar} \quad \text{CH}_3
\]

\[
\begin{align*}
\text{21} & \quad \text{DMF} \quad 170^\circ \\
\text{22} & \quad \text{conc.} \\
\text{23} & \quad \text{dilute} \\
\text{Ar} & = \quad \text{OCH}_3 \\
\text{OCH}_3
\end{align*}
\]
pyrrolyses were carried out in the presence of potassium hydrogen sulfate catalyst, and yields were in the range of 30 - 49%. Compound 21 absorbed in the ir at 1728 (α-β unsaturated ester), 1590, 1565, 1470 and 1433 cm⁻¹ (2-substituted pyridine). The pmr spectrum, taken in CDCl₃, exhibited a two proton singlet at δ 6.43 which was assigned to the terminal methylene group. The addition of a little methanol to the sample split this singlet into an AB quartet, the predicted pattern for a 1,1-disubstituted ethylene with nonequivalent substituents.

The acrylic ester 21 was stable for several hours in solution, but polymerized rapidly if neat, and was therefore used directly in reactions with the enamine 11. Stirring 11 and 21 in degassed dimethyl formamide (DMF) at 170° for 24 hours yielded, in addition to unreacted starting materials and self-polymers, a high melting (262-4°C) crystalline solid which displayed both ester and pyridine absorptions in the ir.
The pmr spectrum (CDCl₃) had four sharp singlets at δ = 3.96, 3.87, 3.68 and 2.81. A multiplet at δ 8.5, which is the region characteristic for pyridine protons on the carbons adjacent to nitrogen, integrated to two protons, based on each singlet representing one methyl group. The mass spectrum gave a parent ion at m/e = 555. These data are consistent with a 1:2 adduct of Δ²-pyrroline 11 and acrylic ester 21, as represented in structure 23. This result is very interesting because it provides the first concrete evidence that intermediate 22 is in fact formed. Nevertheless, it was discouraging that 22, a very hindered anion, would add to a second molecule of 21 in lieu of cyclizing to 25.

When a solution of 21 was added slowly to a stirred solution of 11 in DMF at 170°C, a different product, homogeneous by tlc and isolated by preparative layer chromatography, was found. Initially this material showed no carbonyl absorption in the ir and its pmr spectrum had four sharp methyl singlets at δ = 3.83, 3.74, 3.63 and 2.38. However, it underwent rapid decomposition, which could be followed by the appearance of an ester carbonyl at 1735 cm⁻¹ in the ir spectrum, and by the decay of the methyl singlets in the pmr spectrum, accompanied by the appearance of a singlet at δ = 6.43 (where the resonance for the terminal methylene of acrylate 21 occurs). The mass spectrum had major peaks at m/e = 219 and 163, plus metastable peaks at 150 and 190.

Compound 24, which is similar to intermediates in the methyl vinyl ketone annelation of 11,⁷e is consistent with all the above observations and would be expected to readily fall apart to starting materials.

Despite exhaustive chromatographic separation and analysis of the
reaction mixtures, there was in no instance any indication that 5-carbomethoxy-Sceletium A₄ (25) was being produced. Consequently, a synthetic route wherein the pyridine moiety could be joined to an already existing octahydroindole skeleton was begun.

A recently reported one step, acid catalyzed synthesis of 2,3-disubstituted pyridines appeared well suited for preparing Sceletium A₄ directly from mesembrine. According to this procedure, heating an α-methylene ketone with β-amino acrolein (29)₂¹ results in the loss of two moles of water and cyclization to the pyridine.

\[
\begin{align*}
\text{(CH}_2\text{)}_n\text{C}^\text{CO} + \text{OHC}^\text{CH}^\text{H}_2\text{N}^\text{CH} & \rightarrow \text{(CH}_2\text{)}_n\text{C}^\text{N} \\
& \quad \text{H}_2\text{O}, \Delta
\end{align*}
\]

S· mesembrine (2) has a methylene on either side of the carbonyl, the possibility for the formation of two isomeric pyridines,
and Sceletium A₄ (5), is present. However early workers had found, that when the hydrochloride of mesembrine was recrystallized from ethanol, the salt of the enol ether 31, rather than that of mesembrine, was isolated.²⁰ Formation of the Δ⁵,⁶ enol ether 31 was indicated by the pmr spectrum, which showed the vinyl proton split into a doublet (δ = 5.30, 5.42). This suggested that 5 might be the major isomer resulting from the acid catalyzed reaction between mesembrine and β-amino acrolein.

Mesembrine (2) was prepared by MVK annelation of the hydrochloride salt of Δ²-pyrrole 11 in refluxing acetonitrile.⁷f,g This completes an improved total synthesis of d,l-mesembrine. The overall yield, starting from the nitrile 8, is 20%, compared to an overall yield of 3.6% that was obtained previously in these laboratories.⁷e

The treatment of mesembrine with β-amino acrolein in the presence of piperidinium acetate at 120° for 36 hours did indeed yield two products, 30 and 32, in a ratio of approximately 5:1. The separation of these materials from each other and from unreacted mesembrine was achieved after extensive chromatography on alumina followed by silica
gel preparative layer plates. The major isomer was shown to be compound 30, by comparison of its spectra (pmr, ir) with those of an authentic sample of Sceletium A₄. The salient features in the pmr spectrum of 30 are: three methyl singlets at δ = 2.42, 3.85 and 3.90, which correspond to the N-methyl and two O-methyl groups, respectively; a two proton singlet at δ = 3.05, assigned to the methylene protons on C-4 (see structure 1 for numbering of the octahydroindole skeleton); and a two proton multiplet at δ = 7.1 and a one proton multiplet at δ = 8.1 which were assigned to the pyridyl protons. For comparison, the spectral data for Sceletium A₄ are listed on page 4.

The quantities of the minor isomer 32 that were available precluded a positive identification, although the data obtained do suggest the identity of 32 and 5. In particular, the pmr spectrum has three singlets at δ = 3.86, 3.78 and 2.43, which are the relative spacings found for the singlets of Sceletium A₄. Other features of the spectrum were obscured by background noise.

The ß-amino acrolein reaction was also run on the hydrochloride salt of mesembrine. Although the reaction time was shortened and the overall yields of pyridine compounds were improved, the isomer 30 was still formed in great predominance over 32. Despite the fact that Sceletium A₄ may have been synthesized by this route, the yield was on the order of 2%, and with encouraging results from another approach, no further effort was expended.

Pyridines have also been synthesized using a structural isomer of ß-amino acrolein, acrylamide (33). The "aza-annelation" reaction, the reaction between acrylamide and the enamine of a ketone to form a dihydropyridone (34), was first described by Stork.
Conversion of dihydropyridones to pyridines has been carried out in conjunction with the elucidation of the structures of the *Lycopodium* alkaloids. In this family of alkaloids the dihydropyridone, pyridone and pyridine analogues are all natural products.

In 1971, Ninomiya reported that better yields of dihydropyridones could be obtained by using the imine of a ketone rather than the enamine. This variation of the aza-annelation reaction was therefore tried for the synthesis of *Sceletium A₄*. The benzylimine of mesembrine (35) was prepared in essentially quantitative yield by azeotropic removal of the water. All reactions with acrylamide were carried out in sealed tubes which were totally immersed in the heating bath, since the acrylamide would otherwise sublime away from the other
reactants; p-Toluene sulfonic acid (TsOH) was employed as the acid catalyst. As was the case with the amino-acrolein, two new compounds were produced in the reaction between imine $35$ and acrylamide. Mesembrine itself did not react under the conditions used. The mass spectrum of a mixture of the two materials gave a parent ion at m/e = 342, which is the expected molecular weight of the dihydropyridones $36$ and $37$. The formation of isomeric $36$ and $37$ was assumed to account for the two products indicated by tlc. Numerous attempts to separate these materials on alumina failed and separation was finally achieved on
silica gel preparative layer plates that had had the acidic sites neutralized by pretreatment with gaseous methylamine.

Both materials thus isolated exhibited an intense ir absorption at 1675 cm\(^{-1}\), characteristic of the unsaturated lactam moiety. The major was the dihydropyridone \textsuperscript{36}, once again corresponding to alkylation at C-5, rather than at C-7 as was desired. The direction of alkylation that is observed in both instances indicates that the reactions are controlled primarily by steric factors, since the adjacent pyrroolidine ring causes C-7 to be more hindered than C-5.

The pmr spectrum of the major product \textsuperscript{36} was quite similar to that of the pyridine \textsuperscript{30}. Pertinent features of the spectra are:

\begin{align*}
\text{PMR: (CDCl}_3, \text{TMS)} & \quad \text{IR: (CH}_2\text{Cl}_2) \\
\delta & = 2.23 \quad 3H, s \text{ (N-Me)} \quad \lambda = 3690 \text{ cm}^{-1} \\
3.20 & \quad 2H, s \text{ (C-4 protons)} \quad 3490 \\
3.90 & \quad 6H, s \text{ (O-Me)} \quad 1675 \\
6.43 & \quad 1H, \text{ broad s (N-H)} \quad 1512 \\
6.85 & \quad 3H, s \text{ (aromatic protons)}
\end{align*}

In light of an unambiguous synthesis of the dihydropyridone \textsuperscript{37}, which is described below, the minor product of the acrylamide reaction was not \textsuperscript{37}. It may be a double bond isomer of \textsuperscript{36}, however since the amount of this material available was very small, no further work was done on its structure elucidation.

Successful construction of the basic ring system of Sceletium A\(_4\) begins with the annelation of the \(\Delta^2\)-pyrroline \textsuperscript{11} with a substituted analogue of MVK, namely methyl-5-oxohept-6-enoate (38). This vinyl ketone is readily available from a Friedel-Crafts reaction between
ethylene and the half-acid chloride, half-ester of glutaric acid. The sequence of reactions leading to the dihydropyridone 37 is summarized in scheme 5.

Scheme 5

Ar = OCH₃

reagents: a) 1. HCl, Et₂O 2. CH₃CN, Δ, b) NH₃, MeOH, c) 1. KO-t-Bu, t-BuOH 2. trifluoroacetic acid.
The MVK annelation of 1-methyl-3-aryl-Δ²-pyrrolines has been used to great advantage in the synthesis of alkyloids. However there have been no previous examples of such annelations with other alkyl vinyl ketones, such as 38. The salt of enamine 11 is prepared by bubbling HCl gas through an ether solution, and then evaporating off the ether. This salt is air sensitive and must be kept under a vacuum or nitrogen at all times to prevent decomposition. Acetonitrile and the vinyl ketone 38 are added to the dry salt and the solution is refluxed for 48 hours. After workup and purification by chromatography on alumina, a 54% yield of keto ester 39 is obtained as a mixture of C-7 epimers. Approximately a fourth of the material is lost on the alumina column, presumably due to saponification of the ester to an acid.

The epimers of 39 could be cleanly separated by preparative layer chromatography on silica gel, but rapidly reverted back to the original mixture of epimers. The pmr spectrum showed that the octahydroindole ring juncture was cis, as was predicted. Trans-fused mesembrine has been synthesized and has a very characteristic pmr spectrum, which did not correlate with the materials obtained here.

The ir spectrum of 39 showed sharp absorptions at 1735 (ester) and 1710 cm⁻¹ (ketone), and the pmr spectrum had singlets at δ = 2.43(3H), 3.68(3H) and 3.93(6H).

The keto ester was dissolved in methanol and treated with a large excess of ammonia in a pressure vessel at room temperature for 24 hours. A mixture of a minimum of three diastereomers by tlc analysis of carbinolamides (40) was the sole product of this reaction. The ir
spectrum, taken in methylene chloride, had a very intense absorption at 1660 cm\(^{-1}\). Subsequent dehydration to the unsaturated amide 37 shifted this carbonyl absorption upfield to 1675 cm\(^{-1}\), as one would predict. The pmr spectrum of 40 was characterized by the absence of the ester methoxyl resonance and the presence of numerous N-methyl singlets.

Dehydration of the carbinolamide was achieved by refluxing 40 for two hours with one equivalent of potassium-t-butoxide in t-butyll alcohol.\(^{30}\) The material was completely dehydrated, evidenced by the shift of the carbonyl absorption in the ir, but two compounds were present, ostensibly the double bond isomers 37 and 41. These were stirred with trifluoroacetic acid (TFA) for one hour at room temperature, which resulted in a single compound, 37, homogeneous by tlc and having one sharp N-methyl singlet in the pmr spectrum.\(^{31}\) A high resolution mass spectrum gave a measured mass of 342.1972, which corresponds to the molecular formula C\(_{20}\)H\(_{26}\)N\(_2\)O\(_3\). Other spectral data for compound 37 are:

\[ \begin{align*}
\text{PMR (CDCl}_3, \text{TMS):} & \quad \text{IR (CH}_2\text{Cl}_2): \\
\delta = 2.50 & \quad \lambda = 3420 \text{ cm}^{-1} \\
3H, s (N-Me) & \quad 3.91 \quad 6H, s (O-Me) \\
6.80 & \quad 1585 (sh 1600) \\
3H, s (aromatic protons) & \quad 1510 \\
7.55 \quad 1H, broad s (N-H) & \quad 1675 \\
\end{align*} \]
Although this work does not complete the total synthesis of Sceletium \( A_4 \), it does provide a high yield pathway to the basic skeleton of this alkaloid. And, as was mentioned in connection with the *Lycopodium* alkaloids, procedures for the conversion of unsaturated lactams such as \( 37 \) to the corresponding pyridines have already been developed. It may be found, as the structures of other minor alkaloids from *Sceletium* species\(^2\) are elucidated, that compounds having the pyridine ring in these other oxidation states also occur naturally in the plant, along the biosynthetic pathway to Sceletium \( A_4 \).
PART II

The Total Synthesis of \textit{d,l}-Elwesine
INTRODUCTION

The structural similarity between mesembrine (2) and Amaryllidaceae alkaloids of the crinine group, which incorporate the 5,10b-ethanophenantridine nucleus (43), has been frequently observed. The

\[
\begin{align*}
\text{mesembrine} & \equiv \\
\end{align*}
\]

\[
\begin{align*}
\text{crinine} & \equiv \\
\end{align*}
\]

biogenetic pathway of the crinine-type Amaryllidaceae alkaloids has been well established.\(^{32}\) However the biosynthetic affinities of these two classes are not yet clear. Two amino acid precursors, phenylalanine (44) and tyrosine (45), supply the necessary carbons for the A ring and C ring, respectively. The intermediacy of a norbelladine-type compound was demonstrated by the incorporation of intact norbelld
ladine (46) into the *Amaryllidaceae* alkaloid skeleton.

\[
\begin{align*}
\text{H}_2\text{N}-\text{COOH} & \quad 44 \\
\text{H}_2\text{N}-\text{COOH} & \quad 45 \\
\text{OR} & \quad 46, \text{norbelladine} \\
(R=H) & \\
\text{OR} & \quad 47 \\
\text{RO} & \quad 48
\end{align*}
\]

Similarly, in the biogenisis of mesembrine (2) the precursors are the amino acids phenylalanine and tyrosine, the aromatic ring being derived exclusively from phenylalanine and the perhydroindole moiety coming exclusively from tyrosine.\(^{33}\) It was of interest to ascertain whether a crinine type intermediate (48) might be a precursor of mesembrine. Tritium labeling experiments have shown that this is not the case, and also have excluded the norbelladine system from the biogenisis of mesembrine.\(^{34}\)

At least 35 alkaloids that are closely related in structure to crinine (42) are known, and the synthesis of one of these bases was a
logical extension of previous work in these laboratories to develop general principles of alkaloid synthesis. A large percentage of these crinine related alkaloids have the general structure \(49\), therefore the particular compound chosen as a synthetic target was elwesine (dihydrocrinine) \((50)\), a minor alkaloid of *Galanthus elwesii* Hook f.\(^{35}\)

\[\text{elwesine} \quad \text{3-epi-elwesine}\]

The basic skeleton of elwesine was first constructed by Dr. L. E. DuPree, Jr., in conjunction with a total synthesis of \(d,l\)-3-epi-elwesine \((51)\).\(^{44}\) The series of reactions leading to epi-elwesine is depicted in scheme 6. Although the synthesis was designed as an approach to \(d,l\)-elwesine, the final product, an alcohol, did not correlate with an authentic sample of optically active elwesine\(^{37}\) when a comparison of the solution ir spectra and tlc behavior was made. However Oppenauer oxidation of this alcohol yielded the known dihydro-
Scheme 6

1.  

2.  

3.  

4.  

5.  

6.  

7.  

8.  

3-epi-elwesine

Ar = 3,4-methylenedioxyphenyl

reagents: 1) BrCH₂CH₂Br, LiNH₂, DME, 2) DiBal-H, 3) benzylamine, MgSO₄, 4) NH₄Cl, Δ, 5) MVK, 6) NaBH₄, 7) Pd-C/ H₂, 8) CH₂O, HCl, MeOH
oxocrinine (60), which is also the product from the Oppenauer oxidation of elwesine. This confirmed the fact that the C-3 epimeric alcohol had been obtained instead of elwesine.

The difficulty arose from an erroneous assignment of stereochemistry at C-3 for the two alcohols, 58a and 58b, resulting from the sodium borohydride (NaBH₄) reduction of ketone 57 (refer to scheme 6). The false assignment was due to an unusual conformational equilibrium that has been observed for 3a-aryl-octahydroindole derivatives, but which was unknown at the time that epi-elwesine was being synthesized. In order to unambiguously establish the structures of 58a and 58b, as well as their preferred ground state conformations in solution, the spectroscopic studies described below were undertaken.
RESULTS AND DISCUSSION\textsuperscript{36b}

The ketone 57 was prepared essentially according to procedures developed by Dr. DuPree, utilizing the acid catalyzed thermal rearrangement of cyclopropyl imines to $\Delta^2$-pyrrolines and the methyl vinyl ketone annelation of endocyclic enamines; two reactions that have proven quite important in the synthesis of alkaloids.\textsuperscript{7,28} The cyclopropyl cyanide (53) was obtained in 71\% yield from 3,4-methylenedioxyphenylacetonitrile (52) using the LDA-HMPA method described in part I of this thesis. Selective reduction of 53 to the aldehyde 54 with diisobutyl aluminum hydride (DiBal-H) was achieved in yields of 75-85\% and the benzylimine 55 was prepared in 85\% yield by stirring a mixture of aldehyde 54 and benzylamine over CaCl$_2$. The rearrangement to the enamine 56 employed NH$_4$Cl as the acid catalyst, and a 60\% yield of crystalline $\Delta^2$-pyrroline resulted. Pyrroline 56 was converted to its hydrochloride salt, which was refluxed with MVK in acetonitrile to give, after chromatography on silica gel, a 60\% yield of the N-benzylamino-ketone 57.

The reduction of the amino ketone 57 produced a mixture of two epimeric alcohols, 58a and 58b. The conversion of 58b to epi-elwesine
and spectroscopic studies (see below) indicated that 58a was the compound required for the synthesis of elwesine. The data on the reduction of 57 is summarized in Table 2.

**TABLE 2**

<table>
<thead>
<tr>
<th>reducing agent</th>
<th>overall yield</th>
<th>% 58a</th>
<th>% 58b</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaBH₄</td>
<td>93%</td>
<td>28</td>
<td>72</td>
</tr>
<tr>
<td>H₂/PtO₂,i-PrOH</td>
<td>96%</td>
<td>89</td>
<td>11</td>
</tr>
</tbody>
</table>

Thus the sodium borohydride (NaBH₄) reduction gave an unfavorable product ratio. An alternative method, which was found to yield primarily 58a, was a Pt catalyzed reduction, done in a Parr bomb with isopropyl alcohol as solvent and an initial hydrogen pressure of 42 psi.

Aminoalcohol 58a was converted to the hydrochloride salt and debenzylated in quantitative yield using a 10% palladium on carbon catalyst in methanol and one atmosphere of hydrogen pressure. It is interesting to note that no debenzylation was observed with the PtO₂ catalyst, and that the attempted debenzylation of aminoketone 57 resulted in a β-elimination to the unsaturated ketone 61.

The debenzylated aminoalcohol 59a was converted to d,1-elwesine (50) in 61% yield by means of a Pictet-Spengler cyclization, thus completing the stereoselective synthesis in eight steps. The structure was confirmed by the superimposable solution infrared spectra and identical tlc behavior of the synthetic elwesine and an authentic sample of optically active elwesine. Compound 50 was also converted
to dihydrooxocrinine (60) with fluorenone and potassium t-butoxide in benzene.\textsuperscript{40}

It became apparent, as the work on the synthesis of elwesine progressed, that a very interesting conformational equilibrium exists in the solutions of bicyclic intermediates 57, 58 and 59. It has now been demonstrated,\textsuperscript{4,41} that mesembrine (2) and the epimeric mesembrinols 62a and 62b, as well as the acetates 62c and 62d, adopt conformations wherein the bulky aryl substituent has an axial configuration. Since this result is not what one would predict on the basis of the general precepts of conformational analysis,\textsuperscript{42} it prompted a similar analysis for compounds 57, 58 and 59.

The conformational equilibria in question are depicted in scheme 7.
Pmr spectroscopy is a well established tool for determining preferred ground state conformations of molecules in solution.\textsuperscript{41a,43}

The distinction between an axial and an equatorial secondary alcohol in an epimeric pair has been made on the basis of the relative chemical shifts and/or the band widths at half height, $W_{\text{1}/2}$, of the methine hydrogen signals. The $W_{\text{1}/2}$ parameter is particularly used in lieu of coupling constants when the methine protons are poorly resolved multiplets. Typically, an equatorial proton of this type exhibits a $W_{\text{1}/2}$ of 5-10 Hz, whereas the corresponding axial proton has a value of 15-30 Hz.\textsuperscript{43}

It was first necessary to assign specific pmr resonances to the conformationally diagnostic hydrogens on C\textsubscript{6} and C\textsubscript{7a}. A one proton triplet at $\delta$ 3.22 was readily assigned to the C\textsubscript{7a} proton of aminoketone 57, although the chemical shift is a bit lower than the average chemical shift of a methine hydrogen adjacent to an amine substituent.\textsuperscript{44}
The apparent coupling constant, $J_{app}$, of this triplet is 3.5 Hz, indicating that the proton is probably equatorial, and if so, that the cis aryl group is axial. Thus the preferred ground state conformation of ketone 57 is shown by the left hand structure in the equilibrium of scheme 7, in agreement with similar results obtained for mesembrine.

When 57 was reduced to the amino-alcohols 58a and 58b, the C$_{7a}$ hydrogen resonance became obscured by various methylene signals and it was not possible to obtain a $W_{1/2}$ value. However new one proton resonances appear at $\delta$ 4.11 and 4.02 in the spectra of 58a and 58b respectively. These could be tentatively assigned to the C$_6$ methine protons, but evidence to support the assignment was desired.

The use of lanthanide shift reagents, such as tris(dipivalomethanato)europium (III), (Eu-resolve), has found considerable application in the simplification and interpretation of nmr spectra. It is possible, for instance, to calculate the magnitude of the downfield shift, $\Delta$Eu, for the various protons of cyclohexanols as a linear function of the relative concentrations of sample and Eu-resolve. Using the $\Delta$Eu values obtained for cyclohexanol, the expected shifts for the C$_6$ methine protons were calculated for samples of 58a and 58b and compared with the observed shifts of the resonances at $\delta$ 4.11 and 4.02. Table 3 shows that the calculated and observed values are in fairly good agreement. The $W_{1/2}$ value for the methine proton of amino-alcohol 58b increased from 8Hz to 20 Hz on addition of Eu-resolve, implying that a change of conformation probably accompanied the complexing with the shift reagent.
<table>
<thead>
<tr>
<th>Compound</th>
<th>initial δ</th>
<th>Amount of compound</th>
<th>Amount of Eu-resolve</th>
<th>Δ Eu calculated</th>
<th>Δ Eu observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>58a</td>
<td>4.11</td>
<td>150 mg</td>
<td>51 mg</td>
<td>-5 ppm</td>
<td>-4.5 ppm</td>
</tr>
<tr>
<td>58b</td>
<td>4.02</td>
<td>70</td>
<td>10</td>
<td>-2.15</td>
<td>-2.4</td>
</tr>
<tr>
<td>58b</td>
<td>4.02</td>
<td>70</td>
<td>23</td>
<td>-4.8</td>
<td>-6</td>
</tr>
</tbody>
</table>

It was felt that the shift reagent data was too ambiguous. Unambiguous determination of pmr signals corresponding to the C6 hydrogens resulted from the preparation of the monodeuterated amino-alcohols 58c and 58d. Ketone 57 was reduced with sodium borodeuteride (NaBD₄) to give a 1:2 mixture of 58c and 58d. After chromatographic separation, the pmr spectra of the deuterated and undeuterated materials were identical in all respects, except for the absence of signals at δ 4.11 and 4.02. Compounds 58c and 58d were debenzylated as before to give the amino ketones 59c and 59d, thus allowing for positive assignment of the C6 and C7a hydrogen resonances for these compounds also. All the pertinent pmr data for compounds 57, 58 and 59 is listed in table 4.

**TABLE 4**

<table>
<thead>
<tr>
<th>PMR DATA (CDCl₃, TMS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>57</td>
</tr>
<tr>
<td>58a</td>
</tr>
<tr>
<td>58b</td>
</tr>
<tr>
<td>59a</td>
</tr>
<tr>
<td>59b</td>
</tr>
</tbody>
</table>
Regardless of the substituent on the nitrogen, the data in table 4 demonstrates that in every case studied, the preferred ground state conformation is the one in which the $C_{7a}$ proton is equatorial and the adjacent aryl substituent is axial (the left hand conformation in scheme 7). As required for the synthesis of elwesine, amino alcohol 58a is identified conclusively to be the isomer having the aryl and hydroxyl groups cis with respect to each other.

Inspection of the hydroxyl stretching region in the ir spectra of amino alcohols 58a and 58b was also very informative. The spectra were taken in tetrachloroethylene (TCE), a solvent that is transparent in the region between 2000 and 4000 cm$^{-1}$. The ir spectrum of 58a exhibits a free hydroxyl stretching band at 3620 cm$^{-1}$ (sharp) and a hydrogen bonded hydroxyl band at 3500 cm$^{-1}$ (broad). At low concentrations, below 0.025M, only the band at 3620 cm$^{-1}$ remains, as is generally true when the hydrogen bonding is intermolecular.

Intramolecular hydrogen bonding is structurally precluded for 58a, and only possible for the particular conformation of 58b that has the aryl, amine and hydroxyl substituents all axial with respect to the cyclohexane ring. The ir spectrum of 58b has but one hydroxyl stretching band, located at 3325 cm$^{-1}$ and characteristic of a strongly hydrogen bonded species; no free hydroxyl band appears, even at concentrations as low as 0.0083 M, strongly suggesting intramolecular hydrogen bonding.

Conclusive evidence in support of intramolecular hydrogen bonding was obtained by the method of successive dilution.$^{47}$ A plot of molar absorptivity at $\lambda = 3330$ cm$^{-1}$ vs. the concentration of the ir solution
was made. The nonzero value obtained for molar absorptivity when the concentration is extrapolated to zero proves that the hydrogen bonding is intramolecular rather than intermolecular in the case of alcohol 58b (see graph below); thus confirming the all axial conformational assignment.

Molar Absorptivity vs Concentration for Alcohol 58b Measured at \( \lambda = 3330 \text{ cm}^{-1} \).
EXPERIMENTAL

Infrared spectra were obtained on a Beckman IR-8 spectrophotometer. Proton magnetic resonance spectra were recorded on a 60 MHz Varian A-56/60 spectrometer. Unless otherwise noted all pmr's were run in CDCl₃ containing TMS as an internal standard, at a sweep width of 500 Hz. Preparative and thin layer chromatography was run on Brinkmann precoated silica gel F-245 plates. Melting and boiling points are uncorrected.

\[ \text{CH}_3\text{O}-\text{CH}≡\text{CN} \rightarrow \text{CH}_3\text{O}-\text{CH}≡\text{CN} \]

The reaction was run in a 250 ml 3 neck round bottom flask with cone drive stirrer, constant pressure addition funnel, rubber septum inlet and N₂ blanket. The flask was charged with 100 ml of dry THF and diisopropyl amine (8.7 ml, 62 mmol) and cooled to 0°C. n-Butyl lithium (61.5 mmol, 2.2 M in hexane) was added dropwise and stirring was continued for 20 min at 0°C. The solution was cooled to -78°C, hexamethyl phosphoric triamide (HMPA, 12.8 ml, 74 mmol) was added, and after an additional 20 min at -78°C, 3,4-dimethoxyphenyl acetonitrile (8) (4.3 gm, 24.3 mmol) in THF was added dropwise. The cold bath was removed and stirring continued for 20 min, while the temperature rose to about -20°C. The 1,2-dichloroethane (10 ml, 127 mmol) was added dropwise and the reaction mixture turned yellow-green. The reaction flask was resubmerged in the dry ice/acetone bath and stirred overnight while gradually warming to room temperature.

Work up: The THF was removed on a rotary evaporator, water was added to the residue, which was then extracted 3 times with ether. The
combined ether extracts were dried over MgSO₄, the solvent was removed, and the remaining material was put under vacuum to remove traces of dichloroethane. The product was contaminated with HMPA, which was removed by dissolving in 9:1 ether/hexane and washing with water. Performing the initial extraction with 9:1 ether/hexane instead of ether still left HMPA in the product. Sublimation (100°C, 0.2 mm Hg) and recrystallization from hexane yielded 3.86 gm of a crystalline solid, consisting of 88% of the cyclopropyl cyanide 9 and 12% of the starting material 8, or a 70% yield of the alkylated product. The solid could be used directly in the next reaction or separated from starting material by recrystallization from 95% ethanol. pmr δ 6.80 (mult, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 1.48 (sym mult, 4H). Calcd for C₁₂H₁₃NO₂: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.92; H, 6.59; N, 7.11.

A 1 l 3NHB flask with magnetic stirrer, reflux condenser, and constant pressure addition funnel was flame dried, put under a N₂ blanket and charged with 300 ml of Na dried benzene and 3,4-dimethoxyphenyl cyclopropyl cyanide 9 (11.6 gm, 57.1 mmol). Diisobutylaluminum hydride (DiBal-H, 10.2 gm, 12.8 ml, 71.5 mmol, 1.25 equiv) was transferred to the addition funnel and added slowly, dropwise. The solution turned yellow and was stirred 1 hr at room temperature.

Work up: An aqueous solution of 5% sulfuric acid (300 ml) was added dropwise. The first few mls were added very cautiously because of foaming. After stirring 3 hrs at ambient temperature the layers were separated and the aqueous layer extracted with ether. The combined organic layers were
washed once with water and dried over Na$_2$SO$_4$. After removal of the solvent, the material was sublimed (90°, 0.5 mm Hg) to yield 8.83 gm (75%) of the 3,4-dimethoxyphenyl cyclopropyl carboxaldehyde 9a. ir (KBr) 1711 cm$^{-1}$; pmr $\delta$ 9.33 (s, 1H), 6.72 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H), 1.32 (sym mult, 4H). Calcd for C$_{12}$H$_{14}$O$_3$: C, 69.89; H, 6.84. Found: C, 69.93; H, 6.78.

The procedure is that of M.P. Wentland. A 500 ml RB flask was flame dried, put under N$_2$ and charged with dry benzene (250 ml), 3,4-dimethoxyphenyl cyclopropane carboxaldehyde (9a) (8.1 gm, 39.4 mmol), and anhydrous MgSO$_4$ (8 gm). Gaseous methyl amine was bubbled through to saturate the benzene solution, which was then stirred 24 hrs.

Work up: The solution was filtered, the benzene was removed on a rotary evaporator, and the residual oil distilled (bp 123-127°, 1.0 mm Hg). The carboxaldehyde 10 (7.74 gm, 35.4 mmol, 90% yield) was collected as a clear liquid. ir (film) 1662 cm$^{-1}$; pmr $\delta$ 7.56 (q, 1H, $J$= 1.3 Hz), 6.82 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 3.21 (d, 3H, $J$= 1.3 Hz), 1.18 (sym mult, 4H). Calcd for C$_{13}$H$_{17}$NO$_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.46; H, 7.85; N, 6.42.

A 50 ml RB flask with reflux condenser and magnetic stirrer was flame dried and
put under N₂. Dry benzene (25 ml), carboxaldehyde 10 (1.76 gm, 8.05 mmol) and NH₄I (1 gm) were added, then stirred and refluxed for 5 hrs. The course of the reaction was monitored by tlc (silica gel, ether eluent). After 5 hrs the benzene solution was cooled, separated from the gummy orange residue, and stripped of solvent. The yellow oil that remained was extracted twice with boiling hexane. Removal of the hexane gave 1-methyl-3(3′,4′-dimethoxyphenyl)Δ²-pyrrole (11) (1.31 gm, 6 mmol, 74.5% yield) as a yellow oil that crystallized when triturated. The off-white crystals of Δ²-pyrrole could be further purified by recrystallization from hexane, and were stored in the cold under nitrogen. ir (CHCl₃) 1619 cm⁻¹; pmr δ 6.73 (mult, 3H), 6.27 (mult, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 2.62 (s, 3H). Calcd for C₁₃H₁₇NO₂: C, 71.21; H, 7.81. Found: C, 71.50; H, 7.78.

The hydrochloride salt of Δ²-pyrrole 11 (971 mg, 4.4 mmol) was prepared by dissolving the pyrrole in dry ether, under N₂, and passing HCl gas over the stirred solution. The white salt, which precipitated from ether, was extremely sensitive to air, rapidly turning black if it was exposed.

The ether was removed under partial vacuum, and the apparatus (100 ml 3NRB flask with reflux condenser) put under N₂ again. Acetonitrile (50 ml, dried over mol. sieves) and freshly distilled methyl vinyl ketone (MVK, 2ml, 24.5 mmol) were added and the solution was refluxed for 9 hrs.

Work up: The cooled reaction mixture was poured into aqueous hydro-

11 2 d,l-mesembrine
chloric acid (150 ml, 5%), washed twice with ether (discarded), neutral-
ized with KOH pellets, and extracted twice with ether. The combined 
ether extracts were washed with brine and dried over K₂CO₃. The solvent 
was removed under vacuum to give a reddish oil. Column chromatography 
(Act II alumina, ether eluent) provided 650 mg (2.25 mmol, 51% yield) 
of d₅₁-mesembrine (2), a pale yellow oil. ir (film) 1719 cm⁻¹; pmr(CDCl₃) 
δ 6.90 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H), 3.32 (s, 3H); ms 289 (M⁺).

26 27

The reaction was run in a 
500 ml 2NBR flask with magnetic 
stirrer, HCl inlet and drying 
tube. The hydrochloride salt of 
2-pyridine acetic acid (26) (8 gm, 46.5 mmol) was dissolved in 100 ml 
of methanol, cooled to 0° in an ice bath and saturated with HCl gas. The 
cold bath was removed and the reaction was stirred at room temperature 
overnight.

Work up: After the methanol was removed on a rotary evaporator, a 
slurry of Na₂CO₃ and water was added to the residue until foaming ceased. 
The ester was extracted into methylene chloride, dried over K₂CO₃, freed 
of solvent, and distilled using a Kūgelrohr (oven T = 90°C, P = 2.5 mmHg). 
Methyl-2-pyridine acetate (6.45 gm, 42.8 mmol, 92% yield) was collected as 
a pale yellow liquid. ir (film) 1735 cm⁻¹; pmr δ 8.4 (mult, 1H), 7.25 
(mult, 3H), 3.75 (s, 2H), 3.50 (s, 3H).
and a N₂ blanket was charged with 100 ml of dry THF and diisopropyl amine (3.3 ml, 2.4 gm, 23.8 mmol), then cooled to 0°. n-Butyl lithium (11 ml, 2.2 M in hexane) was added dropwise, and the reaction mixture was stirred an additional 30 min at 0°. After cooling the reaction flask to -78°, methyl-2-pyridine acetate (27) (3 gm, 19.9 mmol) was added. The reaction mixture turned red initially, but after 5 min was yellow. After 30 min at -78°, the solution was warmed to -30°. Paraformaldehyde (1.2 gm, 0.4 mol) was decomposed with a microburner and the vapors were passed over the well-stirred reaction medium in a N₂ train. Stirring was continued 40 min.

Work up: The reaction was quenched with aqueous HCl (50 ml, 10%). The aqueous solution was washed with CH₂Cl₂, neutralized with NaHCO₃, extracted with CH₂Cl₂, and the organic layer was dried over K₂CO₃. Removal of the solvent gave α(2-pyridyl) β-hydroxypropionic acid, methyl ester (28) (2.343 gm, 65% yield) as a yellow glass. Further purification of this hydroxyester was not attempted, since distillation lead to the desired acrylic ester 21. Salient spectral features of compound 28 are: ir (film) 1730 cm⁻¹; pmr δ 8.4 (mult, 1H), 7.3 (mult, 3H), 3.7 (mult, 3H).

β-Hydroxy ester 28 (705 mg, 3.9 mmol) and KHSO₄ (600 mg) were placed in a Kügelrohr distillation apparatus and put under vacuum (0.2 mmHg). The oven was heated to 180°C and the ester was pyrolyzed for 45 min, while the collection bulbs were cooled with acetone soaked cotton.
Methyl-α(2-pyridyl)acrylate (21) (312 mg, 1.91 mmol, 49% yield) was collected as a viscous, bright yellow liquid, that polymerized rapidly unless it was kept in solution. ir (film) 1725, 1587, 1568, 1470, 1432 cm⁻¹; pmr δ 8.1 (mult, 1H), 7.4 (mult, 3H), 6.43 (s, 2H), 3.83 (s, 3H). This material had to be prepared immediately prior to use.

A solution of the Δ²-pyrroline 11 (120 mg, 0.5 mmol) and the acrylic ester 21 (150 mg, 1 mmol) in dry DMF was heated 24 hrs at 150⁰C under N₂. After cooling, ethyl acetate was added and the solution was decolorized with Act III alumina. All the solvent was removed in vacuo (16 hrs). When ethyl acetate was added to the residue, a white solid precipitated. This octahydroindole 23 was recrystallized from EtOAc to yield 7 mg (0.1 mmol, 2% yield) of solid, having a melting point of 262-264⁰C. ir (KBr) 1735, 1590, 1517, 1460 cm⁻¹; pmr δ 8.5 (mult, 2H), 7.4 (mult, 9H), 3.96 (s, 3H), 3.87 (s, 3H), 3.68 (s, 3H), 2.81 (s, 3H); ms 555 (M⁺), 514, 486 (M - CO₂CH₃), 355, 219.

A solution of the Δ²-pyrroline 11 (200 mg, 0.91 mmol) in 5 ml dry, degassed DMF was heated
to 150°C. The methyl acrylate 21 (150 mg, 1.0 mmol) in 5 ml DMF was added dropwise over several hours, then the reaction was kept at 150°C for 8 hrs, and 100°C for another 12 hrs. The solvent was removed from the orange solution in vacuo, and when EtOAc was added there was no precipitate (cf- the preparation of 23).

A silica gel preparative layer plate, EtOAc eluent, separated starting materials from a yellow band, R_f = .1. The material from this band was purified on a second plate, eluting with methanol, which resulted in one major band, R_f = .5. The material isolated in this way was very unstable, and its decomposition was accelerated by CHCl_3. ir (film) 1730 (weak, but increasing with time), 1665, 1630, 1590, 1445 cm⁻¹; pmr δ 6.72 (s, 3H), 3.83 (s, 3H), 3.74 (s, 3H), 3.63 (s, 3H), 2.38 (s, 3H). These signals decayed rapidly, while a singlet at δ 6.43 appeared (cf- ester 21). ms 219, 163, and metastable peaks at 190, 150. This evidence strongly suggests, but is not conclusive for structure 24.

\[
\begin{align*}
\text{Ar} & \quad + \quad \text{NH}_2\text{CHCH}_2\text{CHO} \\
\text{2} & \quad \rightarrow \quad \text{Ar} \\
\text{30} & \quad + \quad \text{Cmpd 32}
\end{align*}
\]

A 10 ml RB flask with reflux condenser, stirring bar and a N₂ blanket was charged with mesembrine (2) (159 mg, 0.55 mmol), β-amino acrolein (126 mg, 1.8 mmol), 150 μl of 1-ethyl-piperidine and a catalytic amount of piperidinium acetate. Enough ethyl-piperidine was used that it would not all be retained on the condenser coils. The very viscous mixture was stirred and heated at 120°C for 36 hrs. The progress of the reaction was
followed by observing diminution of the mesembrine carbonyl band in the ir spectrum (1717 cm\(^{-1}\)). After cooling, benzene was added to the black glass, and the solution was filtered to remove a black precipitate.

Chromatography on alumina (Act II, 6 gm, 9:1 benzene/ethyl acetate eluent) yielded: 1) unreacted mesembrine (53 mg, 33.5%), 2) compound 32, and 3) the pyridine compound 30. Separation was not complete, necessitating further purification on preparative layer plates (silica gel, 1:1:1 ether/methanol/chloroform eluent, R\(_f\) of 32 = .45, R\(_f\) of 30 = .39). The ratio of the amounts of 30:32 obtained was approximately 5:1 and the overall yield of these two compounds, after purification, was 13 mg (.04 mmol, 11%), based on unrecovered mesembrine (2).

Salient spectral data on pyridine 30: ir (film) 1585, 1514, 1442, 800 cm\(^{-1}\); pmr (CDCl\(_3\)) \(\delta\) 8.3 (mul, 1H), 6.70 (mul, 3H), 3.80 (s, 3H), 3.74 (s, 3H), 3.05 (s, 2H), 2.41 (s, 3H); ms 324 (M\(^+\)), 309 (M\(^+\) - CH\(_3\)), 281, 266, 232, 219.

Spectral data on cmpd 32 (= cmpd 5?): ir (CH\(_2\)Cl\(_2\)) 1585, 1512, 1450, 800 cm\(^{-1}\); pmr (CDCl\(_3\)) singlets at \(\delta\) 3.86, 3.78, 2.43, multiplet at \(\delta\) 6.67. Other signals were obscured by background noise. Despite the extensive chromatography, the material was contaminated with an impurity, and the amount in hand was so small that positive identification was precluded.

An identical reaction was run on the hydrochloride salt of mesembrine, with all other variables the same. Qualitatively a better yield of pyridine compounds was obtained in a shorter time, however the ratio of compounds 32:30 was unchanged, and quantitative studies were not done.
A 25 ml RB flask was equipped with a Dean-Stark trap and a reflux condenser. Mesembrine (2) (220 mg, 0.765 mmol), benzyl amine (100 µl, 1.0 mmol) and 25 ml of benzene were refluxed overnight under N₂, as water was removed by azeotropic distillation. The benzene was removed on a rotary evaporator, and the last traces were removed in vacuo to give the benzyl imine 35 (264 mg, 0.7 mmol, 91.5% yield), a viscous yellow oil. IR (film) 1665 cm⁻¹; PMR δ 7.33 (s, 5H), 6.9 (mult, 3H), 3.88 (s, 6H), 2.38 (s, 3H).

The reaction was carried out in a sealed tube. Benzyl imine 35 (264 mg, 0.7 mmol), reagent acrylamide (200 mg, 2.82 mmol) and a catalytic amount of anhydrous p-toluenesulfonic acid were sealed under vacuum in a tube with a small magnetic stirring bar. The tube was totally submerged in an oil bath, and heated at 85⁰C for 24 hrs, then at 130⁰C for 45 min. Once the temperature of the bath reached 80⁰C, the reaction mixture was fluid enough to stir.

Work up: The tube was cooled, opened, and the contents were dissolved in CH₂Cl₂, washed with aqueous NaHCO₃, and dried over K₂CO₃. The dihydropyridone 36 was separated from starting materials by preparative layer chromatography (silica gel, 1:1 MeOH/ether eluent, Rf = 0.05-.4). Attempted further purification by column chromatography on alumina was
not successful. Compound 36 was obtained pure as follows. A silica preparative layer plate was impregnated with gaseous methyl amine, then heated to remove any MeNH₂ not chemisorbed on the plate. Elution with 7:3 ether/MeOH gave clean separation of 36 (17 mg, 0.05 mmol, 7.1% yield). ir (CH₂Cl₂) 3690, 3490, 1675, 1630, 1512 cm⁻¹; pmr δ 6.88 (s, 3H), 6.45 (broad s, 1H), 3.9 (s, 6H), 3.21 (s, 2H), 2.25 (s, 3H); ms 342 (M⁺), 327 (M - Me), 219.

The solvent-free hydrochloride salt of Δ²-pyrroline 11 (290 mg, 1.33 mmol) was prepared as described previously for the synthesis of mesembrine (2). This salt was suspended in dry acetonitrile (25 ml), methyl-5-oxo-hept-6-enoate (38) (0.6 ml, 4 mmol) was added, and the reaction mixture was refluxed 48 hrs.

Work up: The solvent was removed on a rotary evaporator, benzene was added, and the solution was extracted with dilute aqueous HCl. The aqueous layer was neutralized with NaHCO₃, and extracted with CH₂Cl₂. The organic extracts were combined and dried over K₂CO₃. After removal of the solvent, the residual oil was purified by chromatography on Act II alumina. The material balance for each chromatography was very poor. About 25% of the material adhered to the column even after elution with MeOH, strongly suggesting that the ester was being saponified to an acid. Ketoester 39 (270 mg, 0.72 mmol, 54% yield) was obtained as a mixture of C7 isomers. ir (film) 1735, 1710, 1513 cm⁻¹; pmr major singlets were at δ 6.9, 3.93,
3.68, 3.43. Since a mixture of isomers is involved, refer to the actual
spectrum. ms 375 (M⁺), 344 (M - OCH₃), 302 (M - C₃H₆O₂), 219.

The ketoester 39 (227 mg, .605 mmol) was dissolved in dry
MeOH (5 ml), and put in a pressure
vessel with a stirring bar, and
cooled to -78º. Approximately
5 ml of dry liquid ammonia were condensed in the pressure vessel. The
flask was sealed and brought to room temperature, and the contents were
stirred until homogeneous. After 18 hrs, the flask was again cooled to
-78º, opened, and allowed to warm up very slowly. Excess ammonia and
MeOH were evaporated, leaving a yellow foam (230 mg, essentially quanti-
tative yield). Tlc (silica gel, MeOH eluent) indicated a minimum of
three diastereomers were present. The foam recrystallized from benzene-
pentane as a white solid (mp 110-116ºC, with softening at 105º). ir
(CH₂Cl₂) 1665 cm⁻¹; pmr δ 6.95 (mult, 3H), 3.86 (s, 6H), the rest of
the spectrum integrates to 19 H; ms 360 (M⁺), 342 (M - H₂O), 327, 251,
221, 219.

The carbinolamide 40 (50 mg,
0.14 mmol) and t-butanol (10 ml)
were placed in a 25 ml 2NRE flask
equipped with a reflux condenser
and N₂ blanket. Potassium t-but-
oxide (20 mg, 0.18 mmol) was added and the mixture was refluxed for 2.5 hrs, cooled and poured into water. The aqueous solution was extracted with CH₂Cl₂, acidified with HCl, neutralized with NaHCO₃ and extracted a second time with CH₂Cl₂. The combined CH₂Cl₂ layers were dried over K₂CO₃ and evaporated to dryness. Tlc (silica gel, MeOH eluent) and ir indicated that dehydration had occurred, but that more than one isomer was present. This mixture of isomers was stirred in trifluoroacetic acid (TFA, 3 ml) under N₂ for 1 hr. Removal of the excess TFA, dissolution of the residue in CH₂Cl₂, washing with aqueous NaHCO₃, drying over K₂CO₃ and removal of the solvent yielded the dihydropyridone 37 (35 mg, 0.1 mmol, 73% yield), homogeneous on tlc. ir (CH₂Cl₂) 3420, 1675, 1588, 1511 cm⁻¹; pmr δ 7.52 (broad s, 1H), 6.80 (s, 3H), 3.92 (s, 6H), 2.5 (s, 3H). There were no olefinic protons. High resolution ms: Parent ion calcd for C₂₀H₂₆N₂O₃; 342.1943. Found; 342.1972.

The procedure was identical to that used for preparing the analogous 3,4-dimethoxyphenyl-cyclopropyl cyanide (9). The following quantities were used: 3,4-methylenedioxyphenyl-acetonitrile (52) (4 gm, 24.8 mmol), diisopropyl amine (8.7 ml, 62 mmol), n-butyl lithium (61.5 mmol, 2.2 M in hexane), HMPA (12.8 ml, 74 mmol), and 1,2-dichloroethane (10 ml, 127 mmol).

The yield of cyclopropyl compound 53 was 3.28 gm (71%) as a white solid, mp 74.5-75.5°C, after recrystallization from hexane. pmr δ 6.7
(s, 3H), 5.9 (s, 2H), 1.44 (sym mult, 4H). Calcd for C_{11}H_{9}NO_{2}: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.66; H, 5.02; N, 7.33.

The cyclopropyl cyanide 53 (10gm, 54 mmol) was dissolved in 100 ml of dry benzene in a 250 ml flask with N_{2} atmosphere, constant pressure addition funnel and magnetic stirrer. Diisobutylaluminum hydride (1.25 equivalents) was added dropwise with stirring, and the stirring was continued for an additional hour. The mixture was cautiously poured into 5% aqueous H_{2}SO_{4} (300 ml), the layers were separated and the aqueous phase was extracted with ether. The combined organic phases were dried (MgSO_{4}), and freed of solvent.

The residual oil was recrystallized from cyclohexane to give 85% of the aldehyde 54. mp 60.5-61.5°C; ir (CCl_{4}) 1715 cm^{-1}; pmr δ 9.3 (s, 1H), 6.66 (s, 3H), 5.88 (s, 2H), 1.41 (t, 2H), 1.24 (t, 2H). Calcd for C_{11}H_{10}O_{3}: C, 69.47; H, 5.30. Found: C, 69.67; H, 5.46.

The aldehyde 54 (7.4 gm, 39 mmol) and benzyl amine (10 ml) were dissolved in 50 ml dry benzene, and 5 gm of anhydrous CaCl_{2} were added to the stirred solution. The reaction was followed by observing the disappearance of the aldehyde carbonyl in the ir (1715 cm^{-1}).
After 12 hrs the solution was filtered, the solvent was removed and excess benzyl amine was evaporated in vacuo. Distillation (bp 160-165°, 0.1 mm Hg) gave 8.42 gm of the aldimine 55 (78% yield) as a clear oil that crystallized on standing. ir (film) 1655 cm⁻¹; pmr (CCl₄) δ 7.9 (t, 1H), 7.25 (s, 5H), 6.75 (mult, 3H), 5.89 (s, 2H), 4.5 (d, 2H), 1.22 (mult, 4H). Calcd for C₁₆H₁₇NO₂: C, 77.40; H, 6.13. Found: C, 77.60; H, 6.11.

The aldimine 55 and a catalytic amount of NH₄Cl were stirred and heated at 135° under a N₂ atmosphere. The reaction was followed by observing the disappearance of the imine absorption in the ir (1655 cm⁻¹). After 5 hrs, the resulting orange oil was extracted with boiling hexane, from which the Δ²-pyrroline 56 precipitated on cooling. A 70-80% yield of solid, mp 62.5-63°, was obtained after sublimation (100° C, 0.3 mm Hg). pmr (TCE) δ 7.33 (s, 5H), 6.6 (mult, 3H), 5.86 (s, 2H), 5.51 (t, 1H), 3.99 (s, 2H), 2.5-3.4 (m, 4H). Calcd for C₁₆H₁₇NO₂: C, 77.40; H, 6.13. Found: C, 77.52; H, 6.31.
The hydrochloride salt of 3-pyrroline 56 was prepared in ether from pyrroline 56 (1.8 gm, 6.5 mmol) and anhydrous HCl gas. The ether was removed in vacuo, the residue was dissolved in 80 ml dry acetonitrile, and freshly distilled methyl vinyl ketone (MVK, 2 ml, 2.3 gm, 33 mmol) was added. The solution was refluxed for 9 hrs under a N₂ atmosphere. Upon cooling, the reaction mixture was poured into 2 volumes of dilute HCl, washed with ether, basified with KOH, and extracted 3 times with ether. The combined ether extracts were washed with brine, dried over MgSO₄, and the solvent was removed. Chromatography on silica gel (3:1 benzene/hexane eluent) gave 1.39 gm (62% yield) of amino ketone 57, as a colorless solid, mp 98-99.5°C. ir (TCE) 1725 cm⁻¹; pmr δ 7.3 (s, 5H), 6.9-6.8 (mult, 3H), 5.89 (s, 2H), 4.07, 3.09 (AB pair, 2H, J = 13 Hz), 3.22 (t, 1H, J_app = 3.5 Hz), 3.1-1.75 (mult, 10 H). Calcd for C₂₂H₂₃NO₃: C, 75.62; H, 6.63. Found: C, 75.62; H, 6.85.

A: Reduction with PtO₂ catalyst

The amino ketone 57 (2.38 gm) was reduced in 200 ml of i-propyl
alcohol employing a PtO₂ catalyst and an initial hydrogen pressure of 42 psi in a Paar hydrogenator. After 48 hrs, the catalyst was removed and the filtrate was freed of solvent, leaving 2.3 gm of a white solid (96% yield) whose tlc revealed that it was cleanly a mixture of the two epimeric amino alcohols 58a and 58b. These isomers were separated by chromatography on silica gel (1:39 ether/benzene eluent), yielding 1.79 gm 58a and 0.23 gm 58b, or a product ratio of 8:1.

58a: mp (ether) 135.5-136°; pmr δ 7.28 (s, 5H), 6.93-6.73 (m, 3H), 5.87 (s, 2H), 4.17 (d, 1H, J = 13 Hz), 4.11 (m, 1H, W½ = 18 Hz), 3.17 (d, 1H, J = 13 Hz), 2.7-3.2 (m, 2H), 2.5-1.0 (m, 10H). Calcd for C₂₂H₂₅NO₃: C, 75.19; H, 7.17. Found: C, 74.83; H, 7.21.

58b: mp 105-106°; pmr δ 7.3 (s, 5H), 6.77-6.95 (m, 3H), 5.93 (s, 2H), 4.45 & 3.28 (AB pair, 2H, J = 13 Hz), 4.02 (m, 1H, W½ = 8 Hz), 3.35-2.86 (m, 2H), 2.63-1.18 (m, 10H); ms 351 (M⁺).

![Chemical Structures](image)

57 → 58c + 58d

B: Reduction with sodium borodeuteride

Amino ketone 57 (287 mg, 0.82 mmol), 27 ml of absolute ethanol and solium borodeuteride (150 mg, 3.6 mmol) were stirred 2 hrs at room temperature. After the addition of water, the solution was extracted with ether. The ether extracts were dried (MgSO₄) and the solvent was removed in vacuo to give 280 mg of a mixture of isomers 58c and 58d. Column
chromatography yielded a 2:1 ratio in favor of isomer 58d. The pmr of 58c was identical to that of 58a, except for the absence of the 1H multiplet at δ 4.11. The pmr of 58d was identical to that of 58b, except it lacked the 1H multiplet at δ 4.02.

![Chemical structures]

The alcohol 58a was dissolved in dry ether and the hydrochloride salt was precipitated with HCl gas. The solvent and excess HCl were removed in vacuo, and the dry salt was dissolved in MeOH. Hydrogenation at room temperature and 1 atm H₂ pressure over 10% Pd/C catalyst was continued until H₂ uptake ceased. Filtration and removal of the solvent gave a quantitative yield of essentially pure amino alcohol hydrochloride (59a). mp (HCl salt) 241.5-242.0; pmr (free base) δ 6.97-6.77 (m, 3H), 5.92 (s, 2H), 4.00 (m, 1H, W₁ = 21 Hz), 3.69 (t, 1H, W₂ = 10 Hz), 3.31-2.85 (m, 2H), 2.6 (concentration dependent, s, 2H), 2.28-1.22 (mult, 8H). Calcd for C₁₅H₂₀NO₃Cl·½CH₃OH: C, 59.89; H, 6.92. Found: C, 59.78; H, 7.02.

In a similar manner, debenzylolation of 58c yielded 59c. mp (free base) 154-156.0; pmr was identical to that of 59a, except for the δ 4.00 resonance.
The same procedure as was employed for the debenzylolation of 58a provided a quantitative yield of the hydrochloride salt of 59b. mp (HCl salt) 246-251.5°C; mp (free base) 179-180°C; pmr (free base) δ 6.92-6.65 (m, 3H), 5.88 (s, 2H), 4.4 (conc. dependent, s, 2H), 3.97 (t, 1H, J₂₃ = 8 Hz), 3.71 (m, 1H, J₂₃ = 7.8 Hz), 3.33-2.85 (m, 2H), 2.6-1.05 (m, 8H). Calcd for C₁₅H₁₉NO₃: C, 68.94; H, 7.33. Found: C, 68.59; H, 7.62.

Similarly, debenzylolation of 58d gave 59d. mp 171-174°C. pmr lacked only the δ 3.97 resonance of the spectrum of 59b.

The amino alcohol 59a was freed from its hydrochloride salt (234 mg, 0.79 mmol) by dissolution in water, addition of 3M NaOH, and extraction of the precipitated free base with ether. The ether was removed and the base dissolved in 5 ml MeOH, to which 2.4 ml of 37% formalin was added. After 10 min of stirring at room temperature, the mixture was poured into 80 ml of 6N HCl and stirred overnight. The slightly yellow solution was treated with charcoal, neutralized with conc. NH₄OH, and extracted 3 times with CHCl₃. The combined organic extracts were washed with water and dried over Na₂SO₄.
Removal of the solvent provided 130 mg (61% yield) of white crystalline \textit{d,l}-elwesine, mp 269-270°C. pmr δ 6.74 (s, 1H), 6.45 (s, 1H), 5.88 (s, 2H), 4.38-3.74 (AB quartet, 2H, J = 16.5 Hz), 4.22 (s, 1H, \(\nu^2 = 7\) Hz), 3.57-1.2 (mult, 11 H), 3.38 (mult, 1H, \(\nu^2 = 13\) Hz). The solution IR spectra of synthetic \textit{d,l}- and authentic, optically active elwesine were superimposable in every aspect.
LITERATURE REFERENCES

1. These plants were originally and erroneously classified as belonging to the genus *Mesembryanthemum* Dill, hence the designation, mesembrine alkaloids.


23. 60 MHz pmr and ir spectra of an authentic sample of Sceletium A₄ were kindly provided by Professor P.W. Jeffs, Duke University.
31. I would like to thank J.M. Fitzpatrick for suggesting this reagent.
    228, 519 (1971).
   b. This work has been published; see reference 7f.
37. Authentic samples of optically active elwesine and dihydrodxocrinine were kindly provided by Professor W.C. Wildman.


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