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PART I: THE TOTAL SYNTHESIS OF d,l-
ELWESINE. PART II: THE APPLICATION OF
THE ISOXAZOLE NUCLEUS TO THE SYNTHESIS OF
SEMICORRINS.

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PART I:  THE TOTAL SYNTHESIS OF $d_1,l$-ELWESINE.

PART II: THE APPLICATION OF THE ISOXAZOLE NUCLEUS TO THE SYNTHESIS OF SEMICORRINS.

by

LOUIS E. DUPREE, JR.

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

DOCTOR OF PHILOSOPHY

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ABSTRACT

PART I : The Total Synthesis of d,l-Elwesine.

PART II : The Application of the Isoxazole Nucleus to the Synthesis of Semicorrins.

Louis E. DuPree Jr.

Part I describes the total synthesis of the racemic form of the naturally occurring crinine alkaloid elwesine (dihydrocrinine) [1] and the attempted synthesis of its hydroxy epimer d,l-dihydro-epi-crinine [2]. The synthetic sequence is summarized in Scheme I.

SCHEME I

\[
\begin{align*}
ArCH_2OH \rightarrow & \rightarrow ArCH_2CN \rightarrow ArCN \\
\rightarrow & \rightarrow ArCHO \rightarrow ArCN \\
& \rightarrow ArCN \\
& \rightarrow ArCN \\
& \rightarrow ArCN
\end{align*}
\]
Scheme I (Cont'd)

[1] α-OH
[2] β-OH

Part II describes the synthesis of isoxazole [3] and its conversion to Semicorrin E [4].
DEDICATION

TO ROSEMARY
ACKNOWLEDGEMENTS

I wish to express my thanks to Dr. R. V. Stevens for the invaluable guidance and encouragement without which the work described in this thesis would have been impossible to complete.

The financial assistance from the Rice Chemistry Department during my first year of graduate study is gratefully acknowledged.

I also wish to thank my wife Rosemary for her love, patience, and understanding during this sometimes difficult period.
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PART I

THE TOTAL SYNTHESIS OF d, l-ELWESINE
HISTORICAL REVIEW

Introduction:
The group of plants belonging to the family *Amaryllidaceae* have been known for sometime to be a rich source of a number of alkaloids. The development of sophisticated methods of separation and structure determination had, by 1966, permitted the isolation and characterization of well over one-hundred different alkaloids from this family\(^1\). This rapid proliferation over only a few years has necessitated subdivision of the family into groups of compounds based on specific structural features. Those alkaloids possessing the 5,10b-ethanophenanthridine nucleus [1] belong to the crinine family. The most recent edition of *The Alkaloids* lists thirty-five members of this family. As can be seen from

![Diagram](attachment:image.png)

[Diagram 1](attachment:image.png) [2] [3]

Diagram 1, a high percentage of the members of the crinine family have structures corresponding to the general structure [2]. It is readily apparent that development of a general synthetic method applicable to the synthesis of [2] could, with perhaps only minor modifications, constitute, a total synthesis of any one of the members of the crinine family of *Amaryllidaceae* alkaloids.

Before considering the present work toward the synthesis of
**Diagram 1**

R₁ = R₂ = H, Crinine
R₁ = R₂ = H, β-OH, epi-Crinine
R₁ = R₂ = H, dimethoxy instead of methylenedioxy, Martidine
R₁ = H, R₂ = CH₃, Bupanisine
R₁ = H, R₂ = CH₃, β-OH, epi-Bupanisine
R₁ = OMe, R₂ = Me, Bupanidrine
R₁ = R₂ = H, dihydro species, Elwesine
R₁ = OMe, R₂ = H, Powelline

R = H, Nerbowdine
R = Ac, Acetylnerbowdine

R₁ = R₂ = H, 11-Hydroxy-vittatine
R₁ = R₂ = R₃ = H, Vittatine
R₁ = Me, R₂ = H, R₃ = OH, Haemanthamine
R₁ = Me, R₂ = R₃ = OH, Hamanthidine
R₁ = Me, R₂ = R₃ = OH, dihydro species, Dihydrohamanthidine

Tubispacine
$R_1 = H, R_2 = OMe, Crinamide$  
$R_1 = H, R_2 = Ac, Bowdensine$  
$R_1 = Me, R_2 = OMe, Undulatine$  
$R_1 = R_2 = H, O, O$-$Deacetylelbowdensine$  

$R_1 = H, R_2 = Me, R_3 = OH, Ambelline$  
$R = H, Crinamine$  
$R = OH, 6$-$Hydroxy$-$crinamine$  

$R = H,$ Haemultine(?)  
$R = OMe, Fiancine(?)$  

$R = H, Powellamine(?)$  
Opt. Antipode - Cripaline

Flexamine  
Flexine  
Annapowine  
Kregaline  
Structure Unknown
elwesine (dihydrocrinine) [3], it is instructive to note the development of the structure of the parent compound crinine and to explore some of the previous methods of synthesis of the appropriately substituted 5,10b-ethanophenantridine nucleus. This enchantment with crinine is justified by the fact that elwesine was identified by comparison of its spectra to that of dihydrocrinine. Thus the structure proof and synthesis of crinine also became the structure proof and synthesis of elwesine.

Structure Proof:

Crinine was first isolated from two unidentified South African Crinum species by Mason[2]. Subsequent investigations have shown it to be present in the bulbs of several other members of the Amaryllidaceae family[1,3].

Initial work[4] disclosed that crinine had the same molecular formula ($C_{16}H_{17}NO_3$) and functionality, viz. one methylenedioxyphenyl group, one hydroxyl, and one aliphatic double bond, as the known alkaloid caranine

![Chemical structures](attachment:image.png)


This suggestion was quickly disproved by degradative evidence.
Unlike lycorine, crinine gave no identifiable products on Hofmann degradation and was quite stable to attempted dehydrogenation by palladium on charcoal at 200°. The easiest explanation for this inertness to dehydrogenation is the presence of a spiro ring system.

Using biogenetic considerations Wildman suggested that the basic crinine ring system was the 5,10b-ethanophenantridine system. He demonstrated the validity of this hypothesis in 1956. Crinine was catalytically reduced and then oxidized to dihydrooxocrinine. This material was converted to the deoxy compound crinane [7] by Wolff-Kishner conditions. The structure of [7] was then proved by the synthetic sequence shown in Diagram 2. The solution I.R. of (-)-crinane was identical to that of the synthetic material.

The ready oxidation of crinine by manganese dioxide was strongly suggestive of an allylic hydroxyl group. Knowing the structure of

---

**DIAGRAM 2**

Reagents: 1. Triton B/Acrylonitrile, 2. MeOH/HCl; 85% Hydrazine 3. HNO₂, 4. H₂/Pd; HCHO/HCl
crinane allows one to draw three possible structures, [8], [9], and [10], which encompass all the structural features of crinine. The correct structure was deduced from the experimental evidence shown in Diagram 4.

**DIAGRAM 4**

\[
\begin{align*}
& \xleftarrow{2} & \\
[12] & \xleftarrow{2} & [14] \\
& \xleftarrow{3} & \\
& \xrightarrow{2} & [15] \\
\end{align*}
\]

Although crinine itself was quite resistant to Hofmann degradation, oxocrinine [11], reacted as the methiodide, readily gave a 95% yield of oxocrininmethine [13]. This material was chemically and spectrally consistent with structure [13]. Oxocrininmethine was also optically inactive. Under similar conditions dihydrooxocrinine [12] yielded optically active dihydrocrininmethine [15]. Both [13] and [15] could be converted to the same optically inactive tetrahydrooxocrininmethine [14] by catalytic hydrogenation. Only if crinine is represented by structure [10] can this information be interpreted in a consistent manner.

The stereochemistry of the 5,10b-ethanophenanthridine nucleus was clarified in 1958 by Wildman and Fales\textsuperscript{6}. It is readily apparent that only two stereoisomers [16] and [17] are possible for members of the

\[
\text{[16]}\quad \text{[17]}
\]

of the crinine series. Sugimoto and Kugita\textsuperscript{7} favored [16] because Wildman\textsuperscript{5} had found that some of the crinine alkaloids had morphine-like pharmacological properties. However, further studies by Wildman and coworkers produced the physiologically inactive alkaloids haemantamine [18]\textsuperscript{8} and haemanthidine [23]\textsuperscript{9}, both of which possess the 5,10b-ethanophenanthridine nucleus. The structure of haemantamine had been established previously by the degradation/synthesis sequence shown in
Diagram 4.

**Diagram 4**

Reagents: 1. CrO\textsubscript{3}/pyridine, 2. t-BuOK/t-BuOH, 3. Ethyl glycinate 4. H\textsubscript{2}/Pd, 5. Aq. KOH


**Diagram 5**
Dihydrohaemanthamine [21] was treated with thionyl chloride followed by lithium aluminum hydride to give the desoxydihydro compound [22]. This material was identical in melting point and I.R. spectra to dihydrobuphanisine [24]. Optical rotation studies showed however that the two compounds were optical isomers. The well known fact that buphanisine [25] was the methyl ether of crinine further related crinine to the basic nucleus [17].

\[
\begin{align*}
[21] & \quad R_1 = \text{OH}, \quad R_2 = \text{H} \text{(no double bond)} \\
[22] & \quad R_1 = R_2 = \text{H} \text{(no double bond)} \\
[23] & \quad R_1 = R_2 = \text{OH} \\
[24] & \quad \text{No double bond} \\
[25] & \quad \\
\end{align*}
\]

This correspondence between haemanthamine, buphanisine, and crinine was also a key to clarifying the stereochemistry of the 3-hydroxyl group in crinine. The fact that oxocrine [11] was reduced to epi-crinine by sodium borohydride and lithium aluminum hydride lead Fales and Wildman to suggest that the epi compound possessed the more stable equitorial hydroxyl. This was verified by further work by Fales and Wildman and others.

Haemanthidine methiodide [26] is readily converted to tazettine [27] by the action of dilute alkali. Though this reaction has been known for sometime, it was not until 1969 that the mechanism was elucidated.
The structure and stereochemistry of [27] is based on degradative evidence from Taylor, Uyeo, and coworkers. Uyeo has further verified the cis relationship of the methoxy and aryl groups of tazettine with respect to ring C. This was done by synthesis of [29], a degradation product of tazettine. The interrelation of haemanthamine and haemanthidine has been done by Uyeo. Diacetoxy haemanthidine [30] was catalytically reduced to dihydrohaemanthamine acetate [31]. Tazettine was converted to epi-haemanthamine ([28] is the methiodide of epi-haemanthamine) by the action of lithium aluminum hydride followed by thionyl chloride in pyridine. Thus it is clear that haemanthamine must have the aryl and methoxyl groups cis with respect to the C ring. The structural
relationship previously seen between dihydrohaemanthamine [21] and
dihydrobuphanisine [24] require that the relative configuration of
crinine be written as [32].

\[
\begin{align*}
\text{[29]} & \quad \text{[30]} \quad R_1 = R_2 = OAc \\
\text{[31]} & \quad R_1 = OAc, \quad R_2 = H, \text{ No double bond}
\end{align*}
\]

The absolute configuration of the tazettine-crinine families had
been assigned by Taylor and Uyeo\textsuperscript{12} on the basis of Mills Rule\textsuperscript{17}. This
rule states that the 2-cyclohexenyl derivative [33] will possess a more
positive rotation than its epimer [34]. By this rule crinine would have

\[
\begin{align*}
\text{[33]} & \quad \text{[34]} \\
\text{[35]} & \quad \text{[36]}
\end{align*}
\]

the absolute configuration shown in [32]. Highe and Highe have now
verified this assignment by degradation to a compound of known absolute
configuration\textsuperscript{18}. The product of Hofmann degradation of dihydrotazettine
([27], no double bond) has recently been demonstrated to be [35]\textsuperscript{19}. The
12b-4a position of the double bond (rather than 1-12b) has also been
verified\(^1\). Exhaustive ozonization of [35] yielded (\(+\))-R-\(\beta\)-methoxy adipic acid [36].

ALKALOID BIOGENESIS:

During the 1950's many suggestions were made concerning the discrete steps in the biosynthesis of alkaloids, but it was not until 1960 that tracer studies were begun which clarified, to a certain extent, these synthetic sequences. Wildman\(^1\) has given an excellent review of this work and only a brief outline will be given here.

Radioactive incorporation studies have confirmed the initial suggestion that p-phenylalanine and tyrosine are the universal precursors [37] of the Amaryllidaceae alkaloids. These studies also make it clear that phenylalanine is the A-ring precursor and it is only slowly, if at all, converted in vivo to the C-ring precursor tyrosine. The tyrosine moiety is known to be incorporated as tyramine [38]. Incorporation of

\[
\begin{align*}
\text{[37]} & \quad \begin{array}{c}
\text{OH} \\
\text{H}_2\text{N} \\
\text{COOH} \\
\text{H}_2\text{N} \\
\text{COOH}
\end{array} \\
\text{[38]} & \quad \begin{array}{c}
\text{OH} \\
\text{H}_2\text{N}
\end{array}
\end{align*}
\]

phenylalanine into the alkaloid molecule requires the loss of two carbons and the addition of two or more oxygens. The ready incorporation of cinnamic [39] and cafeic [40] acids and protocatechuic aldehyde [41] into the biogenetic pathway suggest the transformations shown in Diagram 7.
In 1957 Barton and Cohen\textsuperscript{15} proposed that compounds such as [42] could undergo oxidative coupling in the plant to form an intermediate dieneone [43] which could then self-condense in Michael fashion to give a crinine nucleus [44]. Support for this proposed route came from the
isolation of belladine ([42], R=Me). Conclusive proof came from incorporation studies using labeled norbelladine ([42], R=H). The norbelladine was found to be incorporated intact into the Amaryllidaceae alkaloid skeleton. One of the final biosynthetic steps is the formation of the methylenedioxy bridge. The incorporation of the benzylamine derivative [45] into haemanthamine suggests that the methylenedioxy bridge is formed by coupling a methoxyl with a hydroxyl group.

**DIAGRAM 9**

Synthetic Routes to Crinine Derivatives:

Several syntheses of crinine, dihydrocrinine, or compounds having the basic 5,10β-ethanophenantridine nucleus have been published. If a synthetic procedure is to have value it must possess some basic advantage over previous methods; improved yield, fewer steps, simplicity, or increased generality are all valid improvements. In order to emphasize the advantages of our synthetic method we shall examine some of these previous methods of synthesis.

Hendrickson, Foote, and Yoshimura²⁰ appear to have been the first group to synthesize the tetracyclic system by a method which incorporated some functionality in the C-ring. Their essentially classical procedure is shown in Diagram 10. This route allows preparation of the tetracyclic
molety in a reasonable number of steps in 15-20% yield and appears suitable for the preparation of the 11-hydroxy crinine alkaloids such
as haemanthamine. If this procedure is to be extended to known crinine alkaloids there are a few knotty problems which must be dealt with. The ability of the 6-hydroxyl group to form apo compounds such as [20] might require removal or blocking of this group. Whitlock and Smith²¹ found that compounds like [45] would rearrange to the correct crinine C-ring.

DIAGRAM 11

\[
\begin{array}{c}
\text{HO} \\
\text{O} \\
\text{O} \\
\text{N} \\
\text{[45]} \\
\end{array}
\xrightarrow{\text{HCl}}
\begin{array}{c}
\text{OH} \\
\text{O} \\
\text{N} \\
\text{35%} \\
\end{array}
\]

It is, however, not clear whether allylic oxidizing or halogenating reagents would attack the Hendrickson compound in the desired C₁ or C₃ position or the unusable C₂ or C₄ position. The double bond is a handle for injecting further functionality, but it is one of low utility.

Muxfeldt and coworkers²² have synthesized crinine itself using a rather neat utilization of the Claisen Rearrangement. Eschenmoser²³ had observed that allylic alcohols react with N,N-dimethyl acetamide diethyl acetal to give a product [46] which rearranges to the amide [47] with mild heating. The incorporation of this rearrangement into the total

DIAGRAM 12

\[
\begin{array}{c}
\text{OH} \\
\text{O} \\
\text{N(CH₃)₂} \\
\text{[46]} \\
\end{array}
\xrightarrow{\text{N(CH₃)₂}}
\begin{array}{c}
\text{N(CH₃)₂} \\
\text{[47]} \\
\end{array}
\]
Diagram 13

1. Triton B/Methyl Vinyl Ketone
2. Piperidine Acetate
3. Dil. NaOH

59% from [13.1]

1. NaBH₄
2. Acetamide acetal

45%

10% NaOH

40%

[13.5]

1. LiAlH₄
2. HCl/HCHO

70%

[32]
synthesis of crinine is shown in Diagram 13. The rearrangement is a clever way to form the ethano bridge, but unfortunately one takes a beating in the yield. The rearrangement not only gives a mixture of epimers [13.4], but over 50% of the isolated product is the unusable, but mechanistically interesting, diene [48]. The subsequent low yield 

![Chemical Structure](image)

on amide hydrolysis is because only one of the epimers of [13.4] will close to [13.5]. The final step is also an apparent weak point. Selenium dioxide hydroxylations usually give 40-60% yields, however in this case no yield is reported. Once again we have the problem of dealing with a double bond in the C-ring.

The only reported synthesis of the tetracyclic system which does not rely on a Pictet-Spengler type reaction to form the B-ring is from Uyeo and coworkers.\(^{24,25,26}\). This does not seem to be an advantageous departure. In general the sequence is long and the final steps are plagued by 40-50% yields. This method does, however, correctly place the oxygen functionality in the C-ring. Diagram 14 details the Uyeo route to dihydrocrinine.

The conversion of [14.4] to [14.5] was a non-specific Schmidt Reaction and both amides [14.5] and [14.6] were obtained in equal amounts. The rather low conversion of [14.5] to [14.7] is never commented on, but there is certainly the possibility that bromine preferentially
DIAGRAM 14

[14.1] \[ \text{CN} \] \[ \xrightarrow{1. \text{LiAlH}_4} \] \[ \text{CHO} \] \[ \xrightarrow{2. \text{Ac}_2\text{O/py}} \] (42%) [14.2] \[ \text{Ac} \] \[ \xrightarrow{1. \text{Wittig}} \] \[ \text{H}_2/\text{Pt} \] (61%) [14.3] \[ \text{EtOCO} \] \[ \xrightarrow{1. 25\% \text{NaOH}} \] \[ \text{Ac} \] \[ \xrightarrow{2. \text{Ac}_2\text{O/py}} \] \[ \text{PCl}_5/\text{SnCl}_4 \] (46%) [14.4] \[ \xrightarrow{3. \text{Sarratt Oxidn.}} \] [14.5] \[ + \] [14.6] \[ (33\% \text{ yield of each isomer}) \] [14.7] \[ \xrightarrow{1. \text{Br}_2} \] \[ \xrightarrow{2. \text{LiCl/DME}} \] (40%) [14.8] \[ \xrightarrow{\text{TsOH}} \] \[ \xrightarrow{\text{Ethylene glycol}} \] (53%)
attacked the electron rich aromatic system. The initial plan was to convert [14.7] to [14.8] by use of strong base, but all attempts were uniformly unsuccessful. Fortunately, when ketal formation was attempted on [14.7] not only did a ketal form, but the B-ring closed. The reduction of the amide carbonyl in [14.8] had to be done in two steps. The bridgehead nitrogen stops reduction at the carbinol amine stage and final reduction is achieved only when the hydroxyl is replaced by chloride.

Certainly the most interesting of the published procedures for obtaining derivatives of crinine is the total synthesis of d,l-crinine by Whitlock and Smith. The most crucial (and most novel) step in their synthesis is the formation, rearrangement, and reduction of the vinyl aziridine [49]. The rearrangement is carried out in a high boiling polar aprotic solvent (diglyme) and is iodide catalyzed. Whitlock and Smith
suggest an iodide addition/elimination mechanism. Incorporation of this

rearrangement into their synthetic sequence is shown in Diagram 18. A number of steps are worthy of comment. The reduction of [18.5] to [18.6] is surprisingly clean. The steric bulk of the aryl group is apparently overcome by a rather strong π bonding to the catalyst surface. As was noted previously, the bromination of [14.5] was effected in only moderate yield. However, in the Whitlock-Smith synthesis a similar bromination ([18.8] →[18.9]) went in quite good yield. Use of the amine hydrochloride
1. NaOEt/Diethyl Glutarate
2. HCl/MeOH

1. HCl/AcOH
2. H⁺/MeOH

(35% from Piperonyl cyanide)

1. PCl₃/CHCl₃
2. Aziridine/Et₃N (51%)

NaI/145° (55%)

[18.5] → [18.6] (76%)

[18.7] (5.5%)
apparently decreases the electronegativity of the electron rich aryl system sufficiently to allow ketone bromination to compete efficiently with aryl bromination.

The final step of the synthesis is a very neat allylic rearrangement. Goering had found that cyclohexenyl cations had a pronounced tendency to pick up nucleophiles in a pseudo-axial manner. Using this information Whitlock and Smith generated the cation of [18.10] by the use of aqueous
acid or solvolysis of the allylic tosylate. This cation picked up water to yield only one alcohol crinine. The only other products were from elimination to the diene.

Two recent synthetic procedures have utilized biogenetic-like steps to obtain the tetracyclic 5,10b-ethanophenanthridine skeleton. Franck and Lubs\(^{28}\) used the norbelladine derivative [50] (R=OMe) as their starting material. It should be noted that [50] is available by a nine-step
step synthesis starting from vanillin and 3,4-dihydroxy benzaldehyde. Phenolic coupling of the trifluoroacetamide of [50] \( R=\text{OMe} \) followed by hydrolysis of the amine and simultaneous ring closure yielded [52] \( R=\text{OMe} \) in 6% yield. Schwartz and Holton\(^{29} \) have used an almost identical route to obtain [52] \( R=\text{H} \). Using vanadylloxochloride as the phenolic oxidant, the yield of coupling reaction was raised to 37%; three times that obtained by Franck and Lubs.

RESULTS and DISCUSSION

Our interest in the synthesis of those \textit{Amaryllidaceae} alkaloids belonging to the crinine family was a logical extension of previous work in these laboratories. Earlier efforts to exploit the Cloke Rearrangement\(^{30} \) (Diagram 21) for the synthesis of naturally occurring materials had culminated in the two step synthesis of the pyridine alkaloids apoferro-
rosamine [56] and myosmine [57]\(^{31} \). This versatile rearrangement also allowed preparation of the \textit{Aizoaceae} alkaloid mesembrine [61] in five steps in fairly good yield\(^{32} \).

The extension of this work to the crinine alkaloid elwsine [76] and its epimer \textit{epi}-dihydrocrinine [77] became a necessity after the successful synthesis of mesembrine. The synthesis of elwsine was patterned after that
Reagents: 1. 2-Pyridyl Lithium, 2. 3-Pyridyl Lithium, 3. Cat. HCl/Δ
DIAGRAM 23 (CONT'D)


of mesembrine, but it was hoped that this study would provide improved methods of obtaining the requisite cyclopropylcarboxaldehydes so vital to this general pathway. The synthesis of elwesine as it was initially envisioned is shown below. Piperonyl cyanide [62] is converted to the cyclopropyl nitrile [63] which can be reduced either to the aldehyde [64] (Path B) or the imine [67] (Path A). Imine [67] could be rearranged to the Δ¹-pyrrrole [70] and possibly annelated to the tricyclic ketoamine [71]. Alternatively an imine [65] or [66] is formed from [64], the imine rearranged to the Δ²-pyrrrole [68] or [69], and the pyrrolidine annelated and dealkylated to yield [71]. Subsequent reduction of [71] to the epimeric alcohols [74] and [75] followed by Pictet-Spengler ring closure would yield elwesine and dihydro epi-crinine. Although the conversion of [63] to [67] saves a subsequent amine dealkylation, our lack of familiarity with annelations of the type [70]→[71] balanced this savings and no one route initially appeared to have a greater advantage.

The synthetic sequence formally begins with the known compound piperonyl cyanide [62], however, the preparation of this compound is worthy of note. The most economical route to [62] appeared to be conversion of commercially available piperonyl alcohol [78] to the chloride [79]
and effect a cyanide displacement. Several attempts to induce formation of [79] by the use of thionyl chloride/pyridine\(^{33,34}\) ended in failure. It was possible, however, to prepare [79] in quantitative yield by simply bubbling anhydrous HCl into a benzene solution of the alcohol\(^{35}\). Drying the benzene and removal of solvent gave material suitable for conversion to [62]. The chloride was taken up in reagent DMSO and the system flushed with nitrogen before addition of 1.5 equivalents of NaCN\(^{36}\). Reaction at 35-40° for a few hours yielded [62] in around 80% from [78]. It was noted that failure to flush the system with nitrogen and to use an inert atmosphere at all times substantially reduced the yield of [62].

The conversion of homoveratronitrile [58] to the cyclopropyl compound [60] had previously been accomplished in this laboratory using butyllithium to generate a dilitio salt [59] which reacted with excess ethylene dibromide to provide [60] in around 25% yield. A series of reactions were run in hopes of improving the yield of intermediate [63]. The results of this study are shown in Table 1. The dramatic enhancement

<table>
<thead>
<tr>
<th>BASE</th>
<th>SOLVENT</th>
<th>PRODUCT</th>
<th>YIELD</th>
</tr>
</thead>
<tbody>
<tr>
<td>t-BuOK</td>
<td>t-BuOH</td>
<td>Polymer</td>
<td>—</td>
</tr>
<tr>
<td>MeONa</td>
<td>Benzene</td>
<td>N.R.</td>
<td>&quot;Low&quot;</td>
</tr>
<tr>
<td>NaNH(_2)</td>
<td>Glyme</td>
<td>[63]</td>
<td>22%</td>
</tr>
<tr>
<td>NaH</td>
<td>Glyme</td>
<td>[63]</td>
<td>65-75%</td>
</tr>
<tr>
<td>LiNH(_2)</td>
<td>Glyme</td>
<td>[63]</td>
<td></td>
</tr>
</tbody>
</table>
of the yield by the use of lithium amide/glyme was one of the desired results of this study. In practice all reactants are combined in a jacketed reaction vessel and stirred 2-3 days at room temperature until all the starting nitrile is consumed. Interestingly enough, use of the jacketed reaction vessel with tap water passing through the jacket increased yields 10-15% over values found when using a standard round bottom flask.

With [63] in hand the decision of which pathway to follow was now made. It was decided to try direct conversion of [63] to the imine [67]. Attempts to reduce the nitrile to the alumino salt [80] by using 1/4 equivalent of LiAlH₄ followed by mild hydrolysis with sodium sulfate dehydrate were generally unsuccessful and poorly reproducible. Mixtures of amine [81], [63], and traces of imine [67] were the usual products.

\[ \text{DIAGRAM 26} \]

\[
\begin{align*}
\text{[63]} & \quad \xrightarrow{} \quad \text{[80]} & \quad \xrightarrow{} \quad \text{[67]} \\
\downarrow & \quad & \\
\text{[81]} & \quad \\
\end{align*}
\]

In one case I.R. indicated that a mixture of [67] and aldehyde [64] had
been formed. Treatment of this mixture with ammonia gave a mixture which I.R. suggested to be mostly [67]. However, ammonium chloride catalyzed rearrangement of this material gave no $^1\Delta$-pyrrole [70] absorption in the I.R. Use of Nagata's procedure$^{37}$ for reducing nitriles to imines with lithium aluminum diethoxy hydride yielded only [81] on several attempts. Apparently [80] is more labile to further reduction than is the nitrile.

At this point a procedure for the use of diisobutyl aluminum hydride (DIBAL) to reduce nitriles to aldehydes was found$^{38}$. Exploratory studies clearly indicated this to be a very useful reagent. The reduction apparently goes by formation of an alumino salt [82] which is stable toward further reduction under the mild reaction conditions (room temp./one hour). It appeared that the intermediate salt [82] might lend itself

**DIAGRAM 27**

\[
\text{RCN} \xrightarrow{\text{DIBAL}} \text{R} \equiv \text{N}_{\text{Al}(i-\text{Bu})_2}^+ \xrightarrow{\text{H}_2\text{O}^+} \text{RCHO}
\]

[82]

to a Cloke-like rearrangement and form the desired pyrrole [70].

**DIAGRAM 28**
Attempted rearrangement by thermal means gave only recovered [82] whereas heating with acid catalyst present yielded only gums and chars.

In view of these results and the easy availability of [64] it was decided to pursue route B. Use of DIBAL on a preparative scale was convenient and [64] could be obtained in 75-85% yields in a very clean reaction.

It now became necessary to choose which imine [68] or [69] to use. The numerous synthetic procedures for demethylation of tertiary amines plus our experience with similar compounds in the mesembrine series suggested that the methyl case should be investigated first. Reaction of [64] with methyl amine saturated benzene in the presence of anhydrous magnesium sulfate gave almost complete conversion to [65] after 2-3 days. The reaction was followed by the disappearance of the aldehyde band in the I.R. Analytic TLC was useless since the imine readily hydrolyzed on the plate. The imine could be obtained in analytic purity by direct distillation of the reaction mixture. This, rather than direct rearrangement of the crude imine, is the work-up of choice since the unreacted aldehyde is exceptionally difficult to remove from the pyrroline [68].

The rearrangement of [65] was quite straightforward. Using a catalytic amount of anhydrous HBr and a temperature of 140-150°, rearrangement could be effected in about an hour. The pyrroline is quite soluble in hexane and can be extracted out of the reaction leaving polymeric material behind. It should be noted that the yields reported for this and other members of the methyl series were not maximized, but even so were in the range of 35% for the conversion of [64] to [68].

The annelation of [68] to tricyclic ketoamine [72] was carried out by a procedure similar to that used in the synthesis of mesembrine.
It was found that unless the ethylene glycol solvent was thoroughly purged with nitrogen prior to reaction all that was produced was a highly reactive material which decomposed on standing or attempted chromatography.

All along we had planned to remove the methyl group and close the B-ring with a classic Pictet-Spengler reaction, but the intriguing possibility that the methyl group could be used to form the needed methylene bridge seemed worthy of investigation. Work by Leonard and Morrow suggested that the N-methyl group could be oxidized to the formal Pictet-Spengler intermediate [83] by the use of mercuric acetate.

However, experimental attempts and a later study by Leonard and Cook showed conclusively that N-substituted pyrrolidines did not react in this manner. Attempts to demethylate [72] using basic potassium ferricyanide in the manner of Perrine gave only recovered starting material. Attempted conversion of [72] to the known compound [84] was also unsuccessful. Reaction of [72] with chloromethyl methyl ether or formaldehyde gave no detectable amounts of anything resembling [84]. Our inability to either remove or modify the N-methyl group was annoying to say the least, but a private communication from Professor P. W. Jeffs indicated that this might be an impossible transformation. His group had spent
Reagents: 1. HCHO/HCl, 2. Chloromethyrmethyl ether.

considerable time and effort trying to demethylate mesembrine [61] and had been quite unsuccessful. This was a very strong impetus for our beginning an examination of the N-benzyl case.

The conversion of aldehyde [64] to the benzylinine [66] was without difficulty. Reaction of [64] with excess benzylamine in the presence of anhydrous magnesium sulfate gave distilled yields of [66] in the 80-90\%
range. When the rearrangement of cyclopropyl imine [66] was attempted using HBr catalysis as before the imine turned into a black tar within a few minutes. It was apparent that [66] was appreciably more reactive than the corresponding methylimine [65]. However, use of the milder acidic catalyst ammonium chloride smoothly effected rearrangement in around 70% isolated yield. As in the N-methyl case, extraction of the crude residue with boiling hexane appeared to be the work-up of choice. It should be noted that these $\Delta^2$-pyrrolines are only moderately stable compounds which darken slowly at room temperature but appear to be quite stable in the cold. They are difficult to get >95% pure and several recrystallizations and/or sublimations were necessary to obtain analytical purity.

Up to now no mention has been made of the mechanism of the Cloke Rearrangement. Although no formal mechanistic studies have been made, at least three mechanisms can be postulated which agree with experimental observations. In all cases studied to date, the rearrangement is acid catalyzed and cannot be induced by purely thermal means. It would appear then that the reactive species is some form of the protonated imine [85]. Further reaction could then take place by attack of halide as in

![Chemical Structure](image)

the opening of cyclopropyl ketones by mineral acid to give $\gamma$-halo ketones. Alternatively the cyclopropyl carbonium ion could collapse, either straightaway or by way of a cyclobutonium ion [86]. At the present
time there is no evidence to support any of these, or any other mechanism.

The annelation of [69] with methyl vinyl ketone was now attempted.
Several attempts using the same procedure that had been successful with pyrrolone [68] gave only complex mixtures of unstable materials which decomposed on attempted chromatography. Formation of [73] was successful only when an alternate procedure was used. The hydrochloride [87] of [69] was precipitated in dry ether and the gummy, solvent free salt taken up in acetonitrile. Refluxing with excess methyl vinyl ketone gave 55-65% yields of [73] after recrystallization from cyclohexane. A variety of solvent systems gave fairly pure recrystallized material, but only multiple sublimations gave the analytically pure substance.

It was anticipated that the ring closure in the annelation would be cis as in the mesembrine case. As one can see in [88] a cis closure gives maximum orbital overlap in the transition state. The mechanistic sequence postulated for the annelation is essentially the same as for the non-catalyzed case. Whether this is in fact correct is not known. It is also very unclear just what the effect of the added HCl is. It could be working to labilize the vinyl ketone toward Michael-type addition, but there is also the possibility that the pyrrolone hydrochloride is more stable toward reaction conditions than the free pyrrolone. If
equilibrium "A" is far to the left, as one would expect, self-reaction of the pyrrolidine would be very unfavorable while reaction with excess methyl vinyl ketone would be greatly enhanced. Analytical TLC of the
reaction during intermediate stages indicated the presence of one or more transient species. Compounds [89] and [90] have been proposed as likely structures for this intermediate, but evidence supporting this contention is shaky at best. A sample of pyrroline [69] was stirred 48 hours at room temperature in the presence of excess methyl vinyl ketone and the crude reaction examined by NMR. The spectrum is obviously that of a complex mixture, but the suggestion is that [89] is probably not present and [90] possibly could be.

The cis fused system of [73] is conformationally flexible and can exist as two distinct conformational isomers [91] and [92]. That the preferred conformation of the product is [91] is clearly shown by NMR spectroscopy. One expects a small non-equivalence in the benzylic methylene proton absorption due to the inherent asymmetry of its environment. The observation that these two protons show up as a pair of doublets at 3 and 4.086 suggests some special non-equivalence is present. Dreiding models clearly show that one of the benzylic protons (3σ) in [91] is quite close to the face of the methylenedioxyphenyl ring while
the other proton (4.086) points out into space. No such interaction is possible in [92]. This result is just the opposite of the findings of Jeffs\(^4\) in the structurally similar mesembrinol series [93]. Apparently

![Chemical Structure](image)

the substitution of a benzyl for a methyl group causes just enough steric interaction to favor [91] over [92].

With [73] in hand it appeared that elwesine was virtually synthesized. This was, unfortunately, far from the truth. The first attempt to debenzylate [73] to [71] was by a general procedure\(^5\); atmospheric hydrogenation of the amine hydrochloride over 10% palladium on charcoal. The product was a mixture of starting material and an oil having very polar TLC properties. This oil decomposed on attempted chromatography. We were encouraged however by the absence of benzylic protons in the NMR. The reaction was repeated under the same conditions and the crude product subjected to Pictet-Spengler conditions\(^3\). The resultant product shows up as a gross mixture on analytic TLC. Repetition of this sequence with slight variations in the Pictet-Spengler procedure gave essentially the same results. Similarly reaction of the crude reduction product under essentially neutral conditions\(^7\) gave a mixture
of polar compounds.

It became increasingly clear that something strange was going on. Since we were going to need it sooner or later it was decided to concentrate on obtaining a pure sample of the debenzylated material [71]. Repitition of the cleavage procedure yielded material which still contained the benzyl group. I.R. spectra quickly revealed that the carbonyl group had been reduced. We were at a loss to explain this result, but the thought was that perhaps the acid concentration was critical. To explore this possibility the hydrochloride of [73] was prepared and subjected to the debenzylation conditions. Once again an oil was obtained, but an NMR of the crude reaction showed removal of the benzyl group. It was decided to methylate this material (HCHO/HCOOH)$^{48}$ to the known compound [72]. A mixture of products were obtained, but none had spectral properties resembling [72]. Though the reason is obscure, it seems clear that the keto group is at least partially the cause of these difficulties.

Chemical methods of debenzylation were generally successful, but the ketone continued to complicate matters. Cyanogen bromide reacted with [73] to give mixtures of the debenzylated cyanamide [97] and the $\beta$-elimination product [98]. Ethyl chloroformate in refluxing benzene$^{49}$ gave clean conversion to the $\beta$-elimination product [100]. Conversion of [73] to the ketal [94] surpressed the $\beta$-elimination reaction and subsequent reaction of [94] with CNBr and ethyl chloroformate cleanly gave the debenzylated compounds [99] and [95] respectively. Unfortunately these two intermediates were not amenable to further conversion. It was hoped that acid hydrolysis of the cyanamide [99]$^{50}$ would lead to the ketoamide [96] by a route similar to that shown in Diagram 35. The product from this hydrolysis formed a purple oil when treated with
Reagents: 1. CNBr, 2. TsOH/Ethylene Glycol, 3. ClCOOEt, 4. 25% H₂SO₄, 5. POCl₃.

chloroform. It is known however that [96] is stable in chloroform. Basic hydrolysis of [99] stopped at the amide stage due to precipitation of the urea [101]. Addition of sufficient ethanol to maintain homogeneous conditions resulted in the formation of an intractable brown oil.

Attempted ring closure of the urethane [95] using phosphorous oxychloride was also unsuccessful. Refluxing benzene/POCl₃ gave only
recovered [95] while neat POCl₃ yielded polymeric material. Treatment of [95] at 10° with concentrated sulfuric acid gave gummy polymer after a few minutes.

The success encountered in debenzyllating the ketal [94] using ethyl chloroformate encouraged us to try a similar reaction which seemed to have a better chance of leading to ring closed keto-amide [96]. If phosgene could displace the benzyl group⁵³, the resulting carbamoyl chloride [102] should certainly be amenable to Friedel-Crafts acylation.
This quickly turned into one of the most confusing and frustrating series of reactions to be undertaken. An excess of phosgene was condensed in a dry flask under nitrogen and a benzene solution of [94] added dropwise. After 18 hours at reflux, TLC showed one component non-equivalent to starting material. Treatment of a benzene solution of the crude concentrated reaction with anhydrous aluminum chloride$^{54}$ produced no apparent change in the TLC of the reaction even after several hours at reflux. Extensive purification of the resulting complex mixture gave only two identifiable products. NMR analysis identified these as the ketone derived from hydrolysis of [94] and the β-elimination product [103]. This lactam is of course formed in the same manner as [98] and

[100] are; hydrolysis of the ketal followed by β-elimination. It was the inability to stop the hydrolysis of the ketal that doomed this
procedure. When the reaction was repeated with spectral analysis of the product from the phosgene treatment (before refluxing) it was quite clear that only [104] was present. In an effort to eliminate ketal hydrolysis the reaction was run under the most anhydrous conditions possible. The pre-purified nitrogen was passed through a Dehydrite tower, the phosgene was passed through 4A sieves and anhydrous potassium carbonate, and the benzene was dried over fresh sodium wire. Reaction as before gave a mixture of [104] and a previously unknown compound. Treatment of the crude reaction mixture with stannic chloride in benzene caused disappearance of this "new" compound and appearance of a second compound. Unfortunately when solvent was removed after a dilute acid workup only an insoluble polymer remained.

Attempted debenzylation of [94] and ring closure using chloromethyl methyl ether\textsuperscript{55} was also abortive. Treatment of the crude reaction with

DIAGRAM 37
with BF$_3$ gas after an initial reflux produced only a gummy mixture of several products. Attempted debenzylation of [73] with ethyl azodicarboxylate$^{56}$ gave only recovered [73].

The key to the removal of the benzyl group was found when [73] was reduced to a mixture of the epimeric alcohols [105] and [106] by the action of sodium borohydride in ethanol. The reaction is essentially quantitative yielding an approximately 3:1 mixture of axial to equatorial alcohol. The epimers are cleanly separable by preparative layer chromatography (see experimental). The identification of the two epimers is readily apparent from their NMR spectra. The non-equivalent benzyl protons are present in both epimers so the aryl-equatorial conformation is maintained. The orientation of the methine proton on the alcohol carbon with respect to its neighboring groups is shown by Newman projection in Diagram 38. One would expect the methine in [107] (the axial alcohol) to show up as a symmetric pentet. The epimer showing a 1-proton symmetric pentet at 3.98δ has been assigned the axial structure [105]. Rather happily this is the epimer which was obtained in highest yield. The equatorial nature of the aryl group is further verified by the splitting pattern of the methine proton adjacent to nitrogen. The NMR
spectra of the epimeric mesembrinols [93] and their acetates show a poorly resolved triplet for this proton in the region 2.79-2.85. The absence of any absorption in this region in the spectra of [105] and [106] is strongly suggestive that the methine proton is pseudo-axial as shown and not pseudo-equitorial as in the mesembrine series.

The I.R. spectrum of [106] is normal, showing both free and intermolecularly H-bonded hydroxyl absorption in fairly concentrated solution and only free O-H absorption in dilute solution. The I.R. of the axial alcohol [105] is anomalous. In concentrated solution only a broad hydroxyl absorption centered at ≈3250 cm⁻¹ (CHCl₃) is present. Dilution decreases the intensity of this band, but no free hydroxyl stretching is ever observed. This type of behavior is generally diagnostic of a case of intramolecular hydrogen bonding, but if structure [105] is correct this is impossible. The I.R. behavior was unchanged after sublimation at 140° and .3mm so the presence of water or alcohol of hydration was judged unlikely. Hanosek had observed similar behavior in the I.R. of [109]. He ascribed this behavior to a non-dissociating dimer [110] although he gives no real proof for the existence of [110]. To investigate the possibility that we might be dealing with some type of dimeric species, the molecular weight of [105] was determined by the freezing
point depression of a cyclohexane solution of [105]$^{58}$. The experimental value of 723 is in excellent agreement with the expected value of 722 for a dimer of [105]. Thus the I.R. behavior of [105] is the result of intermolecular hydrogen bonding in a non-dissociating dimer [111].

When [105] and [106] were subjected to a modification of the previously used debenzylolation procedure of Buchi$^{46}$ both compounds were cleanly debenzylated to the corresponding $2^o$ amine; [105]→[74], [106]→[75]. On several occasions it had been noted that hydrogen uptake was
very sluggish or did not occur at all. It was found that hydrogen uptake was always smooth and rapid if the amine hydrochloride was prepared first and a methanolic solution of this salt subjected to hydrogenolytic conditions. Isolation of the hydrochloride salt of [74] and [75] was quantitative in both cases.

Amine [74] (as the hydrochloride salt) was subjected to Pictet-Spengler cyclization conditions as given by Wildman. The product of this reaction was a yellow oil [112] which could not be induced to crystallize, nor did repeated chromatography yield a pure sample. The NMR of this sample was, however, very encouraging. The aryl multiplet had collapsed to a 2-proton singlet and a new 2-proton singlet had appeared in the region (≈4.76) where the methylene bridge was expected to be seen. A sample of this material was sent to Professor W. C. Wildman at Iowa State for comparison to an authentic sample. Unfortunately, the sample was too impure and the results were inconclusive. In an attempt to obtain a better yield
and/or a pure product, the ring closure conditions of Whitlock and Smith²¹ were tried. This reaction did indeed yield a crystalline product in good yield, but NMR and TLC quickly showed that the product was an entirely new compound [113]. In the case of [113] the aryl protons show up as two 1-proton singlets. Although no NMR of crinine or elwesine has been published, Wenkert⁹⁵ has published data on a number of similar Amaryllidaceae alkaloids. In all of the cases he studied the aryl protons appear as two 1-proton singlets.

When the hydrochloride salt of [74] was heated in an aq. formalin solution for 1 hr at 90° a mixture of two products was obtained. NMR immediately identified one of these as [113], but the other material [114] has remained unidentifed. It is not starting material, but the NMR spectrum shows that there are still three aryl protons present. The mass spectrum of this material gives the molecular ion as 275. This suggests that there was enough formic acid in the formalin (or formed during the reaction by air oxidation) to partially N-methylate [74].

Comparison of an I.R. of [113] with an I.R. of the naturally occurring compound dihydrocrinine (graciously supplied by Professor W. C. Wildman) showed the two compounds to be almost identical. Unfortunately the spectrum of the natural, optically active material had been taken as a KBr disc so it is not unexpected that racemic material would give a slightly different I.R. when taken in this manner.

Complete identification of [113] was obtained by oxidation to the ketone [12] which had been previously synthesized by Uyeo²⁶ and for which we had a solution spectrum (also supplied by Professor Wildman). Attempts to effect this oxidation using the Collins modification of the Sarett oxidation⁹⁶ produced only low yields of mixtures which contained
almost no carbonyl absorption in the I.R. Use of the Oppenauer oxidation as detailed by Wildman gave clean oxidation to material whose I.R. was identical in all respects to the spectrum of [12]. It is clear that [113] and d,l-elwesine [76] are one and the same.

The identity of [112] remains obscure, but the presence of only two aryl protons in the NMR spectrum certainly suggests that some reaction has taken place on the aromatic ring. Perhaps [112] is the result of ring closure in the alternate orientation [112a] or perhaps the reaction conditions are more conducive to hydroxymethylation [112b] than to cyclization.

With the completion of the synthesis of elwesine there remained two additional transformations which were required to "round things out". That is, the conversion of [75] to epi-elwesine [77] and, having now defined the proper debenzylation and ring closure conditions, it would be satisfying to be able to convert [73] directly to dihydroxocrinine [12]. Unfortunately these final attempts were unsuccessful. As was noted in the elwesine case the final ring closure [74]→[76] can give at least three products, depending on the reaction conditions. Although this cyclization has been quite reproducible in the synthesis of elwesine the identical conditions fail miserably in effecting the closure of
[71]--[12] or [75]--[77].

When N-benzyl amine [73] was subjected to the same debenzylation conditions used on the corresponding alcohols [105] and [106], NMR analysis showed clean debenzylation. An I.R. verified that the keto group was intact. However, when this material was subjected to the same cyclization conditions used on [74] a mixture of products were formed. Examination of the reaction by analytical TLC (silica gel) disclosed that [12] was not present in the mixture.

Treatment of 2° amine [75] (from 80mg of hydrochloride) with HCHO under these same conditions yielded 37mg of white solid. TLC showed this to be at least two different compounds, neither of them starting material. An NMR spectrum showed a two one-proton aryl absorption similar to that observed for elwesine and a three proton aryl multiplet characteristic of some uncyclized product. Attempted purification by preparative layer chromatography separated the "cyclized" material into two fractions (7mg of each isolated). As far as could be determined by NMR at this low concentration, both of these fractions contained the two one-proton aryl absorption. A lack of additional amounts of [71] or [75] forced termination of the investigation at this point. Clearly the Pictet-Spengler cyclization is very sensitive to reaction conditions when used on this type of system.
PART II

THE APPLICATION OF THE ISOXAZOLE NUCLEUS TO THE SYNTHESIS OF SEMICORRINS.
INTRODUCTION

Of necessity a new synthetic organic method must be developed on as simple a system as is possible but which will still demonstrate the utility of the method. The true test of any synthetic method, however, comes when the method is tested to its limit by application to the synthesis of a complex, polyfunctional molecule. Among the more formidable synthetic tasks recently undertaken by the organic chemist concerns the preparation of natural or model compounds based on the porphyrin [1] or corrin [2] ring system. The corrin ring is the nucleus of one of the most functionally formidable molecules known to organic chemistry vitamin B$_{12}$ [3]. Work toward the preparation of [3] is being actively pursued in several laboratories$^{59,60}$.

Almost all the published synthetic routes to corrin and porphyrin ring systems consist of stepwise approaches in which "semicorrins" [4] of appropriate substitution and oxidation level are coupled with a second semicorrin or semiporphyrin or subjected to two stepwise condensations with monocyclic elements.

The Eschenmoser research group has used all these methods to synthesize a number of model compounds in the corrin and porphyrin series.
The most important point to note about these compounds is the B-C ring system. In all cases it was formed from the same semicorrin [10].

Eschenmoser has devised two routes to [10]. Both of these begin with $\beta,\beta$-dimethyl levulinic acid [11]. The second route utilizes a rather novel thiocarbonyl oxidative coupling followed by desulfurization with maintenance of the integrity of the dimer. Mechanistically it is suggested that this reaction goes by way of an epi-sulfide [20].
DIAGRAM 2

[11] \( \xrightarrow{\text{NH}_3} \) [12] \( \xrightarrow{\Delta \ (70\%)} \) [12]

[13] \( \xrightarrow{\text{t-BuOH (81\%)}} \) [13] \( \xrightarrow{\text{hv (50\%)}} \) [14]

[15] \( \xrightarrow{\text{NH}_3/\text{MeOH (80\%)}} \) [15] \( \xrightarrow{\text{t-BuOK (80\%)}} \) [10]

[12] \( \xrightarrow{\text{KCN (90\%)}} \) [16] \( \xrightarrow{\text{P}_2\text{S}_5 (82\%)}} \) [17]
DIAGRAM 2 (Cont'd)

\[(\text{PhCO}_2)_2 \xrightarrow{[12]} \text{[18]} \xrightarrow{\text{Ph}_3\text{P}} (84\%) \xrightarrow{\text{t-BuOK}} (51\%) \xrightarrow{[10]} \text{[19]}\]

DIAGRAM 3

\[\text{[20]}\]
The importance of [10], which we have named Semicorrin E, prompted our exploration of alternate methods of synthesis of this strategic compound. The good stability of the isoxazole moiety [21] toward acid and base coupled with the ease of cleavage of the N-O bond to give vinylogous amides of the type [22] under mild catalytic hydrogenation conditions suggested the use of an isoxazole as a masking group for the

![Diagram 4](image)

initial structural manipulations involved in the synthesis of Semicorrin E.

Isoxazoles are obtainable by a number of synthetic routes, but one of the most gentle methods involves the condensation of a primary nitro compound with an acetylene in the presence of a dehydrating compound such as phenyl iso-cyanate and a catalytic amount of base. The reactive intermediate is a nitrile oxide [23] which adds across the acetylenic bond in a 1,3-dipolar manner. We reasoned that a structurally diverse isoxazole

![Diagram 5](image)
could be prepared and catalytically opened to an intermediate which was suitable for conversion to a semicorrin species. The proposed use of this method to obtain [14] is shown in Diagram 6. It was anticipated that

**DIAGRAM 6**

\[
\begin{align*}
\text{[24]} & \quad + \quad \text{[25]} \\
\rightarrow & \quad \text{[26]} \\
\end{align*}
\]

\[
\begin{align*}
\text{[27]} & \quad \xrightarrow{[H]} \quad \text{[14]} \\
\end{align*}
\]

vinylogous amide [27] would collapse to [14] spontaneously or with only gentle heating.

It is possible for the nitrile oxide-acetylene addition to occur in two orientations, head to tail [28] or head to head [29]. The mechanistic details of dipolar additions are still very much a source of controversy\(^{66a,b}\). The only absolute conclusion one can draw from the numerous cases studied is that the orientation of 1,3-dipolar addition
in unsymmetric cases is determined by a delicate balance of steric and electronic effects. Fortunately there was considerable presidence for the addition of 1,3-dipolar species to terminal acetylenes in the desired head to tail manner\textsuperscript{67a,b}. Our case, with its large steric factors, was expected to enhance the desirability of head to tail coupling. In fact no head to head coupling product has ever been observed in this study.

RESULTS AND DISCUSSION

We anticipated that nitroester [24] would be obtainable by a Michael type addition of nitromethane to \( \beta,\beta \) dimethyl methyl acrylate in a manner similar to that of the nitromethane addition to mesityl oxide\textsuperscript{68}. Surprisingly, this and all other methods tried were a complete failure. The use of Triton B/DMSO\textsuperscript{73}, methoxide/methanol, ethoxide/ethanol, KOH/ethanol, and piperidine was tried at a variety of temperatures, but only starting material was recovered in all but two cases. When \( \beta,\beta \) dimethyl methyl acrylate was treated with excess Triton B in refluxing nitromethane in the manner of Leonard and Felly\textsuperscript{69}, something besides starting material was obtained. This substance was never identified, but was observed to spontaneously decompose when heated on the steam bath and to decompose on attempted chromatography.

Of necessity a more circuitous route was undertaken. Acetyl nitrate
was generated in situ and condensed iso-butylene added at -20° to yield the nitro-acetate [30] in around 65% yield.\textsuperscript{70a,b} Treatment of [30] with DIAGRAM 7

\[ \begin{align*}
\text{[30]} & \quad \text{[31]} \\
\text{[32]} R = \text{Et} & \quad \text{[34]} \\
\text{[33]} R = \text{Me} \\
\text{Reagents: 1. Et}_3\text{N/Ether, 2. (ROOC)}_2\text{CH}_2/\text{RONa} \\
\end{align*} \]

sodium nitrite in DMF gave a mixture of α,β and β,γ unsaturated nitro compounds [31] which was suitable for conversion to nitrodiester [32] or [33]. It was found that DMF was difficult to remove from [31] so triethylamine in diethylether was used as the elimination reagent.\textsuperscript{70a} This allowed preparation of [31] in better than 70% yields in high purity. Finally, Michael addition of malonic ester in the presence of catalytic alkoxide gave almost quantitative yields of [32] or [33]. Combination of all three steps without isolation of intermediates gave a 43% yield of [33]. It was obvious that sooner or later [33] was going to have to be decarbomethoxylated, so an attempt was made at this point to convert [32] to [34]. Use of the method used in the Organic
Synthesis preparation of pelagic acid\textsuperscript{72} gave no monoacid [34], but retro-Michael cleavage instead.

While working on another synthetic problem we had observed the Michael addition and cleavage of the cyclopropyl keto-ester [35] when an equivalent amount of methoxide was employed\textsuperscript{73}. If methyl acetoacetate

\begin{center}
\textbf{DIAGRAM 8}
\end{center}
and [31] would undergo a similar addition and cleavage we could avoid the decarbomethoxylation step completely and prepare [24] straightaway. When this reaction was attempted under the same conditions used on [35] (refluxing MeOH) there was no apparent reaction. Repetition of the reaction at room temperature gave a mixture containing one major product. NMR analysis of this material showed no absorption characteristic of the methylene protons adjacent to the nitro group (e4.56).

Preparation of the acetylenic ketone [25] also involved more difficulty than originally anticipated. Wentland had previously alkylated iso-propyl cyanide with propargyl bromide to give [36] using a modification of a procedure due to Compagnon and Miocquet. Reaction of [36] with methyl lithium at -76° gave [25] in only 5-10% yields from iso-

![Diagram]

Reagents: 1. LiNH$_2$/liq. NH$_3$, 2. MeLi/-76°/Ether

propyl cyanide. Besides the low yield the alkylation is difficult to scale up. One sequence which yielded 35 g of [36] required 2 liters of liquid NH$_3$. Substitution of commercial lithium amide in DMF as the reaction medium provided only a low yield of at least five compounds.

A suitable substitute for [36] would be the methyl ester [37]. This compound could be obtained in very low yield by reaction of 1-methyl-methyl propionate with trityllithium and propargyl chloride. Use of the
same procedure using 2,3-dichloro-propene-1 as the alkylation agent \(^{75}\) produced [38] in 62% yield. Several attempts to convert [38] to [37] by the dehydrohalogenation sequence of Caine and Tuiler\(^{76}\) gave no acetylenic material.

A much easier route to [25] would be simple propargylation of methyl-iso-propyl ketone [39], that is, if alkylation could be directed to the proper side. Use of an acid catalyst to generate the most stable enol and reaction with a propargyl species should yield the desired ketone [25]. Unfortunately [39] showed no reaction toward propargyl alcohol in the presence of boron trifluoride etherate \(^{77}\), BP\(_3\)-Et\(_2\)O and sulfuric acid, or sulfuric acid in refluxing benzene.

Alternatively, [39] could be blocked on the methyl side and then alkylated. Ireland and Marshall\(^{78}\) have used the thiobutyl group as an
easily removable blocking group for unsymmetrical ketones. Condensation of [39] with ethyl formate by the method of Johnson and Povlic̆79 produced [40] in better than 80% yield. This sodium salt was converted to

\[
\begin{align*}
\text{[39]} & \xrightarrow{1} \text{NaO} & \xrightarrow{2} \text{TsO} \\
\text{EtO}_2\text{CH} & & \text{[40]} & \text{[41]}
\end{align*}
\]

Reagents: 1. NaOEt, 2. TsCl/Pyridine, 3. BuSH/Pyridine,

tosylate [41] by the action of tosyl chloride in pyridine. Crude [41] was reacted immediately with butyl mercaptan in pyridine to realize a distilled yield of 44% of [42]. Subsequent attempts to alkylate [42] to [43] were quite unsuccessful. Treatment of [42] with \(\text{t-BuOK/t-BuOH}\) or trityllithium in glyme followed by addition of propargyl bromide gave only gross mixtures. On the other hand, \(\text{t-BuOK or NaH}\) in ether produced a very clean reaction between [42] and propargyl bromide. The product of this reaction possessed no vinyl protons (or acetylenic protons for that matter). This route was subsequently abandoned.

Meinwald and Ouderkirk80 had reported the conversion of 2-methyl-
cyclohexanone to 2,2-dimethyl-cyclohexanone by the use of sodium amide in ether followed by addition of methyl iodide. Use of their procedure with [39] and propargyl chloride gave a small amount of material showing no acetylenic C-H absorption in the I.R. Generation of the anion of [39] with trityllithium in THF and reaction with propargyl chloride gave a very complex mixture as shown by G.L.C. The first encouraging results were the result of using commercial LiNH$_2$ in DMF. The product consisted mostly of self-condensation products plus small amounts of both alkylation products. Since the ketone had been added to an excess of base, it was apparent that under these conditions anion formation was quite slow. The discovery that the sodium amide that had been used in the Meinwald procedure was quite inactive prompted re-examination of this reaction. Repetition of this procedure using freshly opened sodium amide did indeed yield [25] as the only high boiling material in the reaction. Unfortunately all attempts to reproduce this result on a preparative scale gave only polymeric material. The suggestion that lithium enolates favored the most substituted double bond form and our suspicion that propargyl bromide was responsible for the polymerization problem led us to try the alkylation using LiNH$_2$ in liquid ammonia as the base and propargyl chloride as the alkylating agent. Indeed a small amount of material could be isolated from this reaction, but it bore no resemblance to [25]. The possibility that the ammonia was in some way responsible for the polymerization problems was explored by generating the lithium salt of [39] in liquid ammonia and then evaporating the NH$_3$. The dry salt was taken up in DMSO and propargyl chloride added at 10°. This method gave distilled yields of [25] of around 25% and was quite easy to scale up.
With both starting materials available and suitable methods for obtaining more if necessary, we turned to the preparation of isoxazole \[44\]. The method of Bachman and Strom\[82\] had previously been used in this laboratory to generate nitrile oxide \[48\]\[43\]. Several attempts to generate \[46\] by this method gave only recovered \[32\]. After several initial failures, the method of Mukaiyama and Hoshino\[83\] was found to produce \[44\]. It was quite evident that this reaction went slowly or not at all unless the triethylamine catalyst was freshly distilled from calcium hydride immediately before addition to the reaction. Subsequent reactions provided \[44\] and \[45\] in around 15% yield. Initially the reaction was run by combining all reactants and allowing the reaction to
take place over several days. This procedure not only gave low yields, but the reaction mixture contained impurities which could not be removed from the isoxazole by repeated chromatography or molecular distillation. Both [44] and [45] are viscous, high boiling oils which could not be fractionally distilled or crystallized. Following Mukiyama's original procedure, [33] was added very slowly to a mixture of an excess of acetylenic ketone [25] and two equivalents of phenyl iso-cyanate. This procedure gave almost quantitative conversion to isoxazole [44]. An NMR of the crude product showed complete consumption of [33] and a very clean spectrum of [44]. An exact yield is difficult to determine due to the purification problems of the isoxazole and the tenacious manner with which it holds solvents, but 90-95% seems reasonable in light of the "crude" NMR. We had a moment of concern over the I.R. spectrum of [44] when three rather than the expected two carbonyl bands were observed. This is apparently a fairly common phenomenon of β-diesters. Felton and Orr have suggested that this splitting of the carbonyl peak is due to a symmetric and anti-symmetric coupling of the two C=O stretching vibrations or perhaps their resonance coupling to an overtone.

Much the same purification problem encountered with [44] and [45] was found in the synthesis of isoxazole [50]. This material was a

\[
\begin{align*}
\text{HC} &= \text{C} \quad \text{CN} \\
\text{H}_3\text{CO}_2\text{C} &\quad \text{C} \quad \text{N} \\
\text{H}_3\text{CO}_2\text{C} &\quad \text{[49]} \\
\text{H}_3\text{CO}_2\text{C} &\quad \text{[50]} \quad \text{R=CN} \\
\text{[51]} \quad \text{R=CONH}_2
\end{align*}
\]
perfect model to test a possible key reaction. One of the functionalities present in the vitamin B$_{12}$ semicorrin [53] is a propionamide side chain. We anticipated that Michael addition of acrylonitrile to [44] or [45] would be a suitable method of incorporating this moiety if the nitrile could be easily hydrolyzed. Treatment of [50] with 30% peroxide in 6N sodium hydroxide$^{85}$ gave clean hydrolysis to [51]. We were pleased to note
that [44] was recovered unchanged from these hydrolysis conditions. On the negative side, preliminary attempts to convert [44] to [52] have been unsuccessful. A general characteristic of nitrile oxides is their instability. They dimerize quite rapidly to the corresponding furoxan (1,2,5-oxadiazo-
ole-5-oxide) [54] even in dilute solution. Grundman and Datta have recently succeeded in preparing several highly hindered nitrile oxides (eg. [55]) which are stable at room temperature and distillable at high vacuum. Although [46] is fairly hindered, it was suspected that it would not be isolable. A few quantitative observations confirm this suspicion. Phenyl iso-cyanate, triethylamine, and [33] were combined and the reaction checked periodically by I.R. After .5 hr at room temperature the characteristic furoxan band at 1600 cm\(^{-1}\) was quite prominent. Storage of the reaction at 0\(^\circ\)seemed to stabilize the system and no further change in the I.R. was noted until the reaction was allowed to warm to room temperature. This stabilization was almost certainly a slowing down of nitrile oxide formation rather than an indication of the stability of [49]. Repeated chromatography failed to give a pure sample of [56], but the crude I.R. is quite definitive, showing the absence of nitro and
and iso-cyanate bands and a strong 1600 cm\(^{-1}\) absorption.

Considering the size of the 3,4-substituents in \([56]\) one might ask whether formation of a 1,2,4-oxadiazole-4-oxide \([57]\) might be a favored pathway. The published spectra of both the 1,2,5 and 1,2,4 systems formed from terephthalonitrile oxide show only minor differences in peak shapes. Comparison of our spectra to those of Fujimoto plus Grundman's observation\(^88\) that even highly hindered mesitonitrile oxide \([58]\) forms furoxan \([59]\) leaves little doubt that \([56]\) is the dimeric species.
Studies in this\textsuperscript{43,91} and other laboratories had shown that the isoxazole N-O bond could be opened by catalytic hydrogenation under several sets of conditions. Interestingly enough, it appeared that each isoxazole studied was unique in that it would reduce cleanly with only one catalytic system and was inert to or overreduced by other systems. Isoxazole [44] was no exception. Use of 10\% palladium on charcoal in triethylamine/ethyl acetate under the same conditions used by Wentland\textsuperscript{43} to convert \([60]\) to \([61]\) gave only recovered \([44]\)\textsuperscript{90}. Hydrogenation of \([62]\) over Adam's catalyst in methanol had cleanly opened \([62]\) to \([63]\)\textsuperscript{91,92}, but \([44]\) was totally inert to these conditions. When hydrogenation was attempted using Raney nickle in methanol at 45 psig, a solid was obtained whose spectral characteristics suggested that a large amount of overreduction had taken place; no methyl ketone, isoxazole, or vinyl protons were seen in the NMR spectrum. Slightly encouraged by this result, the reaction was repeated at atmospheric pressure\textsuperscript{93}. This
procedure cleanly opened [44] to [64] which closed to [65] under the reaction conditions. Amide [65] is structurally quite similar to

\[ \text{DIAGRAM 19} \]

Eschenmoser's compound [14], but spectrally there are strong differences. The I.R. of [14] shows three distinct carbonyl bands at 1750, 1705, and 1665 cm\(^{-1}\) and a UV max at 283nm (log \( \varepsilon = 4.3 \)). Compound [65] shows only a single broad carbonyl band and a UV max at 242nm (log \( \varepsilon = 3.6 \)). The strongest proof for the validity of structure [65] is the vinyl proton singlet at 5.39\( \delta \) and a broad N-H absorption at 10.55\( \delta \) in the NMR. These values are in excellent agreement with Eschenmoser's values of 5.31 and 10.56. We would like to suggest that the anomalous I.R. and UV behavior of [65] is due to the carbomethoxy group. The presence of this group next to a gem-dimethyl group probably distorts the amide ring enough to destroy some of the conjugation and thus lower the UV max. The best proof for the validity of structure [65] comes from the work described below. When the offending carbomethoxy group is removed from [44] and the
resultant monoacid [67] hydrogenated, compound [14] is obtained.

Preparation of [14] was achieved by first hydrolyzing [44] to the
diacid [66] with methanolic KOH. The crude diacid was taken up in toluene
and heated at 100° for 2 hours to effect clean decarboxylation to the
monoacid [67]. This monoacid presented a purification problem
similar to that encountered in the case of the isoxazole [44]. Monoacid
[67] is a viscous, high boiling oil which holds solvents quite ten-
aciously. The solvents can be removed by molecular distillation, but the
acid suffers some decomposition in the process and no appreciable pur-
ification is otherwise effected. Column or preparative layer chrom-
matography do not seem to particularly enhance the purity of [67] either.
Fortunately [67] is obtained from the hydrolysis/decarboxylation
sequence in a very pure state so it was not really necessary to worry a
great deal about further purification.

Attempts to form a solid derivative of [67] were very exasperating.
The ketone function would not form a 2,4-dinitrophenylhydrazone, an
adduct was formed with phenyl hydrazine, but repeated recrystallizations
did not improve the initially wide melting range. The oxime apparently
never formed and attempts to form an anilide gave only tarry residues.
A suitable derivative was formed by the addition product of [67] and
cyclohexyl amine. Sublimation of this adduct and then recrystallization
gave sharply melting needles.

When [67] was hydrogenated under the same conditions (1 atm, 25°)
as used for converting [44] to [65] a white solid was obtained which,
after purification by preparative layer chromatography, showed all the
spectral details (UV, IR, NMR) of known compound [14]. It is still
rather surprising to us that vinylogous amide [68], the proposed inter-
mediate, would condense with the acid moiety at room temperature.

DIAGRAM 20

An NMR of the crude reaction indicated an 80-90% conversion to [14], but purification by preparative layer chromatography gave only a 44% yield of moderately pure [14]. This rather large disparity between the NMR yield and the observed yield has not been adequately explained. Perhaps the slightly acidic silica gel is in some way detrimental to [14] and there is some decomposition on the plate.

The conversion of [14] to Semicorrin E [10] was essentially by the
method of Eschenmoser as shown in Diagram 2. Although Eschenmoser's procedure is quite vague, the conversion of [14]→[15]→[10] was found to be quite straightforward and was effected with little difficulty (see experimental). Our yields are somewhat lower than those found by Eschenmoser and coworkers, but since he does not comment on the source of his yield values (crude, recrystallized, from instrumental analysis, etc.) it is impossible to compare the two sets of values.
EXPERIMENTAL

Infrared spectra were obtained on a Beckman IR-8 spectrometer. UV spectra were taken on a Bausch and Lomb Spectronic 505 spectrometer in 95% ethanol solution. NMR spectra were recorded on a Varian A-56/60a spectrometer using tetramethyldisilane as internal standard. Mass spectra were taken on a Consolidated Electrodynamics Corp. 21-110 high resolution mass spectrometer. Melting points and boiling points are uncorrected. Microanalyses were done by the Elek Microanalytical Laboratory, Torrance, California. Preparative layer chromatography operations employed Brinkmann precoated 20 x 20 cm plates of silica gel F-254, 2 mm thick.

PART I:

Piperonyl Chloride [79]. Piperonyl alcohol (Aldrich), 30 g (.197 mole), was dissolved in 200 ml of warm, dry reag. benzene. The solution was cooled to 10° in an ice bath and saturated with anhyd. HCl gas. The temperature was maintained at 10° or below. After saturation was complete the reaction was allowed to come to room temperature. The benzene layer was decanted and dried over anhyd. MgSO₄. A residual haze was removed with Norit-A. Removal of solvent and excess HCl under reduced pressure gave a cloudy oil which solidified to fine white needles on cooling to -76°, mp 22.5-23° (lit. 23°)³⁵. The yield was essentially quantitative.

Homopiperonyl Nitrile [62].

a.) From [79]. Piperonyl chloride, 13.8 g (.082 mole), is dissolved in 60 ml reagent DMSO and 1.5 equivalents of NaCN are added. (Note: For reactions using more than 25 g of chloride the NaCN should be added portionwise to avoid side reactions.) The system is flushed with N₂ and warmed to 40° with stirring. After 4 hr 120 ml H₂O are added and
the resultant solution extracted continuously for 24 hr with CHCl₃. The orange extract was dried over anhyd. MgSO₄, filtered, concentrated, and vacuum distilled to give 10.4 g (79%) of water white oil bp 104-106 @ .11 mm. On standing the oil slowly solidified to clear plates mp 38.5-40°. One recrystallization from cyclohexane-toluene (98:2) gave a white powder mp 39.0-39.5° (lit. 42°)⁹⁸; ir (neat) 2250 cm⁻¹; nmr (CCl₄) 3.53δ (s, 2H), 5.85δ (s, 2H), 6.66δ (s, 3H).

b.) From Piperonyl Alcohol. Piperonyl alcohol, 58.7 g (.386 mole), was converted to the chloride as before. The crude [79] was treated as in (a.) to give 46.3 g (74.5%) of [62]. Repetition on 50 g of alcohol gave 43 g (81.2%) of [62].

1-(3,4-Methylenedioxyphenyl)-cyclopropanecarbonitrile [63]. The general method of synthesis is as follows. X g of [62], X g LiNH₂ (Alpha Inorganics, freshly opened bottle), 2X ml ethylene dibromide, and 10X ml dry glycine are combined in any order in an oven dried jacketed reaction vessel equipped with N₂ system and a mechanical stirrer. Tap water is passed through the jacket. The reaction can be followed by TLC or by the color change from the initial light tan to the final dark brown. Solvent is removed under reduced pressure and water added cautiously to the residue. The resulting emulsion is extracted 3X with CH₂Cl₂. Drying the extract over anhyd. Na₂SO₄ and removal of solvent yields a red-black oil. Distillation yields reasonably pure [63], bp 120°@.2 mm, mp 69-70°. Two recrystallizations from pet ether gave the analytic sample (needles) mp 74.75-75.5°. Sublimation at 80° and .2 mm is also a suitable purification method. Use of this general procedure on 10 g (.053 mole), 13.5 (.07 mole), and 43g (.23 mole) of [62] gave
72%, 65% and 63% yields respectively. I.R. (CHCl₃, page 103) 2200 cm⁻¹; NMR (CDCl₃, page 113) 1.44 (s, 9H); 5.98 (s, 2H); 6.76 (s, 3H).

Analytical: Calc. for C₁₁H₁₉O₂N; C, 70.58%; H, 4.85%; N, 7.48%. Found; C, 70.66%; H, 5.02%; N, 7.33%.

1-(3,4-Methylenedioxyphenyl)-cyclopropanecarboxaldehyde [64].

Nitrile [63], 10 g (.054 mole), is taken up in 100 ml sodium dried reagent benzene. This solution is added to a jacketed reaction vessel equipped with N₂ blanket, dropping funnel, and a magnetic stirrer. Tap water is passed through the jacket. Diisobutylaluminum hydride (1.25 equivalents, Texas Alkyls, 15% solution in toluene) is added dropwise. The slightly yellow solution is stirred one hour after addition is complete. The reaction mixture is cautiously poured into 5% H₂SO₄ (foams!). The two phase mixture is stirred vigorously for one hour and the layers separated. The aqueous layer is extracted three times with ether, the organic fractions are combined, dried over anhyd. MgSO₄, and the solvent removed under reduced pressure. The residual oil is taken up in the minimum amount of hot cyclohexane. Cooling the solution gives 8 g (78.5%) of aldehyde mp 62.5-63.5°. Recrystallization from hexane/cyclohexane gave the analytic sample mp 63.5-65°; 2,4-dinitrophenylhydrazone mp 232-232.5°.

Other preparations using 1, 6.2, 5, and 32 g of nitrile gave respective yields of 60, 52, 56, and 86%. I.R. (CCl₄, page 103) 1715 cm⁻¹; NMR (CCl₄, page 113) 1.24 (t, 2H); 1.41 (t, 2H), 5.88 (s, 2H), 6.66 (s, 3H), 9.36 (s, 1H).

Analytical: Calc. for C₁₁H₁₀O₃; C, 69.47%; H, 5.30%. Found; C, 69.67%; H, 5.46%.
1-(3,4-Methylenedioxyphenyl)-N-methyl-cyclopropanecarboxaldehydeimine

[65]. Aldehyde [64], 1.2 g (.0063 mole), was taken up in 150 ml dry, reagent benzene and the solution saturated at 5° with anhyd. methylamine. After saturation was complete the reaction was allowed to stir 3 days at room temperature in the presence of 1 g anhyd. MgSO₄. The reaction is followed by I.R. Filtration and removal of solvent gives a yellow oil which is short path distilled to yield 810 mg (63%) of water white oil bp 105.5-106.5° @ .45mm. Within the limits of the NMR this is pure imine and is submitted for analysis as is. I.R. (film, page 104) 1663 cm⁻¹ (C=N); NMR (CDCl₃, page 114) 1.16δ (symm. multiplet, 4H), 3.25 (d, 3H), 5.84δ (s, 2H), 6.68-6.88 (m, 3H), 7.47δ (quartet, 1H); Mass Spec. M⁺=203. Analytical: Calc. for C₁₂H₁₃O₁₂N: C, 70.92%; H, 6.45%. Found; C, 70.89%; H, 6.46%.

1-(3,4-Methylenedioxyphenyl)-N-benzyl-cyclopropanecarboxaldehydeimine

[66]. Aldehyde [64], 7.75g (.048 mole), was dissolved in 50 ml of sodium dried benzene. This solution was treated with 10 ml reag. benzylamine and 5g anhyd. CaCl₂. After stirring at room temperature for 12 hr an I.R. showed no carbonyl absorption. The slurry was filtered through a fritted glass funnel and solvent removed to give a yellow oil. Excess benzylamine was removed with the vacuum pump. Short path distillation yielded 10.4g (92%) of water white oil bp 168-170 @ .1mm. An analytical sample was prepared by sublimation at 110° and .4mm (needles) mp 67-67.5°. Sublimation seems to be the best method of purification. Preparations using 1, 1, 1.3, and 28g of aldehyde gave respective yields of 80.5, 72, 73, and 89.5%. I.R. (film, page 105) 1655 cm⁻¹ (C=N); NMR (CDCl₃, page 115) 1.22δ (m, 4H), 4.5δ (d, 2H), 5.89δ (s, 2H), 6.7-6.85δ (m, 3H), 7.25δ (s, 5H), 7.98
(t, 1H); Mass Spec. M⁺=279.

Analytical: Calc. for C₁₈H₁₇O₂N; C, 77.40%; H, 6.13%. Found: C, 77.60%; H, 6.11%.

1-Methyl-3-(3,4-methylenedioxyphenyl)-2-pyrroline [68].

a.) From the cyclopropane-carboxaldehyde [64]. The aldehyde [64], 3.2g (.017 mole), was converted to [65] as in a.). The resulting crude imine was treated with a catalytic amount of anhyd. HBr and heated 1 hr at 155° under a N₂ blanket. Extraction of the cooled residue with boiling hexane and removal of solvent gave a yellow solid. Sublimation, 60° @ .1mm, yielded 1.43g of pyrroline contaminated with aldehyde. Passage through a
short silica gel column (benzene eluent) yields 1.06g of [68] (31%) of better than 95% purity.

1-Benzyl-3-(3,4-methylenedioxyphenyl)-2-pyrrole [69]. N-benzyl aldimine [66], 1.4g (.5X10^-2 mole), was heated 5 hrs under N_2 in the presence of a catalytic amount of NH_4Cl. The reaction was followed by I.R. as in the preparation of [68]. The resulting orange oil was extracted with boiling hexane. Cooling this solution gave 1.0g (71.5%) of off white powder. Two sublimations, 100° @ .3mm, gave the analytical sample mp 62.5-63.0°. Repetition on 1.0 and 33.2g (1g NH_4Cl used in latter case) scales gave respective yields of 60 and 80%. I.R. (TCE, page 105) 1618 cm^-1 (C=C-N); NMR (TCE, page 115) 2.5-3.46 (m, 4H), 3.99s (s, 2H), 5.516 (t, 1H), 5.866 (s, 2H), 6.56-6.766 (m, 3H), 7.336 (s, 5H); Mass Spec. M^+ = 279.

Analytical: Calc. for C_{18}H_{17}O_{2}N; C, 77.40%; H, 6.13%. Found; C, 77.52%; H, 6.31%.

N-methyl-6-oxo-3a-(3',4'-methylenedioxyphenyl)-cis-octahydroindole [72]. N-methyl pyrrole [68], 519mg (2.55X10^-3 mole), was taken up in 25ml of reagent grade ethylene glycol which had been purged with N_2. Freshly distilled methyl vinyl ketone (2ml) is added to the solution at room temperature. The solution is heated at 60° for 3 hrs under N_2. The temperature is then raised to 120° and held there for 3 hrs. The reaction is cooled and two volumes of water are added. Extraction with ether, drying over anhyd. MgSO_4, and concentration under reduced pressure gave 760mg of yellow-brown oil. Purification by preparative layer chromatography (EtOAc) yielded 310mg of [72]. An NMR of this yellow oil was
identical, except for the absorptions associated with the aryl moiety, to an NMR of an authentic sample of d,1-masembrine [61]43. I.R. (CHCl₃, page 106) 1725 cm⁻¹; NMR (CDCl₃, page 114) 2.0-3.36 (m, 11H), 2.456 (s, 3H), 6.078 (s, 2H), 6.9-7.25 (m, 3H).

N-benzyl-6-oxo-3a-(3',4'-methylenedioxyphenyl)-cis-octahydroindole [73]. N-benzyl pyrroline [69], 10g (.036 mole), is taken up in anhyd. ethyl ether and the hydrochloride salt precipitated with anhyd. HCl. The ether is removed on the Rotovap and the gummy salt taken up in 400ml of acetonitrile (dried over 4A sieves). An excess (10ml) of freshly distilled methyl vinyl ketone is added and the yellow solution refluxed for 9 hrs under N₂. The solution is cooled and poured into two volumes of 5% HCl. This solution is washed once with ether and then basified with solid KOH. The cloudy aq. phase is extracted three times with 100ml of ether. The combined ether extracts are washed once with brine, dried over anhyd. MgSO₄, and concentrated under reduced pressure to give 7.7g (61.5%) of white solid mp 98-99.5° with softening at 94°. Recrystallization from cyclohexane and a little benzene gives good quality material, but analytical purity could be achieved only by multiple sublimations.

Triple sublimed material (120° @ .2mm) had mp 98.5-101°. Use of this procedure on .2g, .2g, and .24g of [69] had previously given respective yields of 45.5, 67.3, and 56.0%. I.R. (TCE, page 106) 1725 cm⁻¹; NMR (TCE, page 115) 1.8-3.25 (m, 11H), 2.986 (d, 1H, J=12cps), 4.066 (d, 1H, J=12cps), 5.856 (s, 2H), 6.65-6.856 (m, 3H), 7.126 (s, 5H); Mass Spec. M⁺=349.

Analytical: Calc. for C₂₂H₂₃O₃N; C, 75.62%; H, 6.63%. Found; C, 75.62%; H, 6.85%.
N-benzyl-6-hydroxy-3a-(3',4'-methylenedioxyphenyl)-cis-octahydroindole [105] and [106]. N-benzyl ketone [73], 2.12g (.006 mole), was taken up in 200ml of abs. EtOH. This solution was treated with 1g (.025 mole) of NaBH₄ and stirred 24 hrs at 25°. At this time TLC showed complete consumption of [73]. The reaction was diluted with 400ml of H₂O and the cloudy solution extracted three times with 100ml portions of ether. The ether solution was dried over anhyd. MgSO₄ and solvent removed under reduced pressure to give 1.99g (93.5%) of a gum. A 400mg sample of this material was purified by preparative layer chromatography (1:1 CHCl₃/ether) to yield 260mg of axial alcohol [105] and 100mg of equitorial alcohol [106]. Trituration of [105] with ether induced crystallization. One recrystallization from ether gave transparent cubes mp 105-106°. The equitorial alcohol [106] crystallized on removal of solvent. One recrystallization from ether and drying (60° @ .4mm) in an Abderhalden pistol gave the analytical sample mp 135.5-136°.

Spectral and analytical data for [105]: I.R. (CHCl₃, page 107) 3250 cm⁻¹ (OH, broad); NMR (CDCl₃, page 116) 1.0-2.66 (m, 10H), 2.8-3.35 (m, 2H), 3.126 (d, 1H, J=12.5cps), 3.966 (poorly resolved pentet, 1H, J=2cps), 4.396 (d, 1H, J=12.5cps), 5.866 (s, 2H), 6.7-6.856 (m, 3H), 7.256 (s, 5H); Mass Spec. M⁺=351; a picrate (yellow powder from 95% EtOH) mp 229-231° was submitted for combustion analysis, calc. for C₂₈H₂₈O₁₀N₄, C, 57.93%, H, 4.86%; found, C, 58.28%, H, 4.94%.

Spectral and analytical data for [106]: I.R. (CHCl₃, page 107) 3615 and 3430 cm⁻¹ (free and bound OH); NMR (CDCl₃, page 116) 1.0-2.56 (m, 10H), 2.7-3.26 (m, 2H), 3.136 (d, 1H, J=13cps), 3.8-4.356 (m, 1H), 4.176 (d, 1H, J=13cps), 5.876 (s, 2H), 6.7-6.856 (m, 3H), 7.256 (s, 5H); Mass Spec. M⁺=351; calc. for C₂₂H₂₅O₃N, C, 75.19%, H, 7.17%; found, C, 74.83%,
H, 7.21%.

6α-Hydroxy-3a-(methylenedioxyphenyl)-cis-octahydroindole [74].

The method is a slight modification of that of Buchi.\(^{46}\) N-benzyl alcohol [105], 150mg (43×10\(^{-3}\) mole), is taken up in anhyd. ethyl ether and the hydrochloride salt precipitated with anhyd. HCl. Excess HCl and ether are removed under reduced pressure and the dry salt taken up in anhyd. MeOH. Hydrogenation at 1 atm over 10% Pd on charcoal ceased after 8.6ml (9.6 theory) of \(\text{H}_2\) had been taken up. Filtration and removal of solvent gave 124mg (100%) of the amine hydrochloride. One recrystallization from MeOH-THF gives a white powder mp 246-251.5° in a vacuum sealed capillary. The free amine was recrystallized from benzene/ether and sublimed (110° @ .45mm) to give the analytical sample as a powder mp 179-180° in a vacuum sealed capillary. I.R. (KBr, page 108) 3400 (broad), 3330 (sharp), and 3040 cm\(^{-1}\) (broad); NMR (D\(_2\)O, HCl salt, page 117) 1.5-2.56 (m, 8H), 3.2-3.86 (m, 2H), 3.9-4.356 (m, 2H), 4.616 (s, HDO), 5.945 (s, 2H), 6.85-7.056 (m, 3H); Mass Spec. M\(^+\)=261.

Analytical: Calc. for C\(_{15}\)H\(_{19}\)O\(_3\)N; C, 68.94%; H, 7.33%. Found; C, 68.59%; H, 7.62%.

6β-Hydroxy-3a-(methylenedioxyphenyl)-cis-octahydroindole [75].

The debenzylation of N-benzyl alcohol [106] to [75] is achieved by the same procedure as used in the preparation of [74]. The yield of amine hydrochloride was quantitative. The HCl salt was recrystallized three times from MeOH/ether and dried (60° @ .4mm) in an Abderhalden pistol to give the analytic sample as a white powder mp 241.5-242.0°(d) in a vacuum sealed capillary. An NMR of this material revealed that 1/4 mole
of methanol of crystallization was present. The free amine was recrystal-
лизed from benzene/ether and sublimed twice (90° @ .3mm) to give an
amorphous powder mp 154-156.5°. I.R. (KBr, page 108) 3380 (b), 3290 (s),
and 3040 cm⁻¹ (b); NMR (D₂O, HCl salt, page 116) 1.4-2.66 (m, 8H), 3.418
(s, 7H, CH₃OH), 3.526 (broad triplet, 2H), 4.05-4.456 (m, 2H), 4.618
(HDO, s) 5.966 (s, 2H), 6.9-7.16 (m, 3H); Mass Spec. M⁺=261.
Analytical: Calc. for C₁₅H₂₀O₃NCl. ½CH₃OH; C, 59.89%; H, 6.92%. Found;
C, 59.78%; H, 7.02%.

d₁₁-Elwesine [76]. The procedure is essentially that of Whitlock
and Smith ²¹. The hydrochloride salt of [74], 234mg (.79X10⁻³ mole), was
converted to the free amine. The amine was taken up in 10ml of anhyd.
methanol and 10ml of 36% formalin solution was added. After 5 minutes
20ml of 8N HCl was added and the reaction allowed to stand 2 hr at 25°.
The reaction was diluted with 25ml of H₂O and extracted twice with 20ml
portions of ether. The aq. phase was basicified with solid KOH and the
cloudy solution extracted three times with 50ml portions of CHCl₃. The
organic extracts were combined, dried over anhyd. K₂CO₃, and solvent
removed under reduced pressure to give 275mg of white solid. Recrystal-
lization from benzene/cyclohexane yields 139mg (65%) of a white
powder mp 184-188° from two crops. Drying (60° @ .4mm) in an Abderhalden
pistol (elwesine holds benzene quite tenaciously) raises the melting
point to 187-0-188.5° with softening at 185°. I.R. (KBr, page 109)
3420(b), 3220(b), 1500, 1485, 1370, 1335, 1320, 1240, 1095, 1080, 1040,
1005, and 940 cm⁻¹; NMR (CDCl₃, page 117) 1.0-3.96 (m, 13H), 3.706 (d,
1H, J=16), 4.346 (d, 1H, J=16cps), 5.826 (s, 2H), 6.406 (s, 1H), 6.635
(s, 1H); Mass Spec. M⁺=273.
Positive identification was obtained by conversion of [76] to the known compound dl-dihydrooxocrinine. dl-E1wesine, 75mg (0.27X10^-3 mole), was dissolved in 10ml of reagent benzene and subjected to Oppenauer oxidation according to the directions of Wildman. Sublimation (110° @ .2mm) of the crude reaction gave 36mg of solid which was recrystallized from benzene/ether to give irregular transparent plates 20mg, mp 171.5-174.5° (lit. 26 171-173°). The I.R. was identical in all respects to that of an authentic sample as supplied by Professor W. C. Wildman. I.R. (CHCl₃, page 109) 1705, 1493, 1473, 1445, 1420, 1360, 1322, 1313, 1300, 1275, 1150, 1120, 1080, 1030, 990, 960, 928, 860, and 845 cm⁻¹; NMR (CDCl₃, page 117) 1.65-3.70δ (m, 11H), 3.74δ (d, 1H, J=16cps), 4.35δ (d, 1H, J=16cps), 5.85δ (s, 2H), 6.43δ (s, 1H), 6.65δ (s, 1H); Mass Spec. M⁺=271.

PART II:

4,4-Dimethyl-5-oxo-hexyne-1 [25].

a.) From Methyl-iso-Propyl Ketone. Approximately 500ml of commercial anhyd. ammonia is condensed into a flame dried flask equipped with mechanical stirrer, N₂ blanket, dry ice condenser, and a gas inlet. Lithium amide is generated using 6.94g (1 mole) of freshly cut Li and a catalytic amount of anhyd. ferric chloride. Methyl-iso-propyl ketone, 86g (1 mole, dried over 4A sieves) is added dropwise to the refluxing slurry. The reaction is stirred 2 hrs and the ammonia is allowed to vaporize. The dry salt is warmed to 50° and the vessel flushed with N₂ to remove as much residual ammonia as possible. Approximately 400ml of anhyd. DMSO is added and the black slurry cooled to 10°. Propargyl chloride, 82g (1.1 mole), is added at such a rate that the temperature can be main-
tained at less than 15° (this is somewhat difficult in the early stages of addition). After addition is complete the reaction is allowed to come to room temperature and stirring continued for an additional 6 hrs. The reaction is poured into 1 liter of water and acidified with AcOH. The reaction is extracted with three 150ml portions of benzene. The benzene extracts are washed with brine, dried over anhyd. MgSO₄, and concentrated to about 200ml on the rotary evaporator. This residue is flash distilled to give 50-60ml of a DMSO-propargyl chloride-product mixture. One gram of hydroquinone is added to this solution and it is distilled through a short vigreux column at water pump vacuum. Ketone [25] is obtained as a water white liquid bp 74-76° @ 34mm, 26.7g (21.5%). An additional 10g of material was collected which was shown by G.C. to be a 7:3 mixture of [25] and DMSO. Total yield of [25] 27%. The ketone formed a,4-di-nitrophenyl hydrazone mp 112-112.5° (yellow plates from 95% EtOH) which was submitted for combustion analysis. I.R. (neat, page 110) 3300, 2110, and 1710 cm⁻¹; NMR (CDCl₃, page 118) 1.25δ (s, 6H), 2.0δ (t, 1H), 2.2δ (s, 3H), 2.4δ (d, 2H).

Analytical: Calc. for C₁₄H₁₆O₄N₄: C, 55.26%; H, 5.30%. Found: C, 55.15%; H, 5.54%.

b.) From 4,4-Dimethyl-4-cyano-butyne-[⁴³,⁷⁴]. A 250ml three-neck flask is equipped with magnetic stirrer, septum cap, condenser, dropping funnel, and N₂ inlet. The apparatus is oven dried at 110° and cooled under a stream of N₂. Methyl lithium, 83ml of 1.66M ether solution (.138 mole), was syringed into the flask. The flask was cooled to -76° in a dry ice-acetone bath and 6.9g (.065 mole) of nitrile added dropwise. After addition is complete the reaction is allowed to warm to room temperature and stirred one additional hour. A 1:1 mixture of 15% H₂SO₄ and EtOH is
added until pH 2 is reached and the reaction stirred 2 hrs. One-hundred ml of water are added and the reaction extracted three times with 100ml portions of ether. The ether extracts are washed with brine, dried over anhyd. \( \text{MgSO}_4 \), and concentrated at 25° on the rotary evaporator to give a yellow liquid. Distillation yields 5.9g (74%) of water white oil. This material is identified as pure [25] by comparison of I.R. and NMR spectra.

3-(1',1'-Dimethyl-2',2'-dicarbomethoxyethyl)-5-(2''-2''-dimethyl-3''-oxobutyl)-isoxazole [44]. Acetylenic ketone [25], 4g (.032 mole) and phenyl isocyanate, 3.1g (.026 mole), were combined in 5ml of dry, reagent benzene and placed under a nitrogen atmosphere. Nitro diester [33], 3g (.013 mole), and 2ml of Et₃N (distilled from CaH₂ immediately before addition) were taken up in 50ml of dry, reagent benzene. This solution was added dropwise to the mixture of [25] and phenyl isocyanate at a rate of ~1ml/hr. The reaction was stirred for 24 hrs after completion of addition. The precipitated urea is removed by filtration and the reaction concentrated under reduced pressure. Excess [25] is recovered by distillation and the pot residue is taken up in CHCl₃, washed with water and filtered to give a brown oil. Passage through a silica gel column removes the brown coloration. The resultant solution is concentrated, filtered, and stripped of all solvent to give 4.7g of clear orange oil (theory 4.37g). An NMR of this oil shows it to be quite pure [44] with urea and some other minor contaminant(s) present. Based on this NMR further purification was deemed unnecessary. An analytic sample was prepared by preparative layer chromatography (cyclohexane/ethyl acetate). I.R.(film, page 110) 1760, 1735, 1708, and 1600 cm⁻¹; NMR (CDCl₃, page 118) 1.2δ (s, 6H), 1.52δ (s, 6H), 2.16δ (s, 3H), 2.95δ (s,2H), 3.68δ (s,
6H), 3.92δ (s, 1H), 5.93δ (s, 1H); Mass Spec. M⁺=339, also peaks at 308 and 296.

Analytical: Calc. for C₁₇H₂₅O₂N; C, 60.16%; H, 7.42%. Found; C, 59.86%; H, 7.52%.

3-(1',1'-Dimethyl-2'-carboxyethyl)-5-(2''',2''''-dimethyl-3'''''-oxobuty1)-isoxazole [67]. Dicarbomethoxy isoxazole [44] from the previous synthesis, 3.05g (9x10⁻³ mole), was refluxed 4 hrs under N₂ in a solution of 30ml MeOH and 5g KOH. The reaction is cooled and diluted with 70ml H₂O. This solution is extracted twice with ether and then acidified with conc HCl. The resultant emulsion is extracted continuously for 18 hrs with CHCl₃. The CHCl₃ extract is dried over anhyd. MgSO₄ and concentrated on the rotary evaporator to give 2.07g of a viscous, brown oil which NMR analysis identifies as a very clean mixture of diacid [66] and monoacid [67]. Toluene is added to the oil and the mixture heated at 100° for 2 hrs under N₂ with vigorous stirring. The cooled solution is shaken with the minimum amount of 10% NaOH necessary to give a basic solution and the aq. phase extracted twice with ether. The aq. solution is concentrated on the rotary evaporator to the semi-solid salt. This salt is neutralized with the minimum amount of 15% HCl and the resulting emulsion extracted three times with 50ml portions of CHCl₃. The CHCl₃ extracts are dried over anhyd. MgSO₄ and concentrated under reduced pressure to give 1.75g of orange oil (73%) which NMR analysis shows to be very good [67] suitable for further conversion. A solid derivative was prepared in the following manner. An ether solution of [67] was treated with excess cyclohexylamine and all volatiles removed under reduced pressure. The adduct was sublimed (120° @ .45mm) to give a waxy solid. Three recryst-
tallizations from CHCl₃/ether gave white needles mp 112.0-112.5°. The methyl ester of [67], isolated as a side product of hydrolysis/decarboxylation or prepared by reesterification of [67], was easily purified by preparative layer chromatography (1:1 hexane/ethyl acetate). A sample of this ester (Mass Spec. M⁺=281) was submitted for combustion analysis. I.R. (film, page 111) 3200(b), 1725(sh), 1705, and 1600 cm⁻¹; NMR (ester, CDCls, page 113) 1.205 (s, 6H), 1.425 (s, 6H), 2.175 (s, 3H), 2.666 (s, 2H), 2.966 (s, 2H), 3.626 (s, 3H), 5.906 (s, 1H); NMR (acid, CDCls, page 118) 1.186 (s, 6H), 1.416 (s, 6H), 2.146 (s, 3H), 2.646 (s, 2H), 2.926 (s, 2H), 5.856 (s, 1H), 7.986 (s, 1H).

Analytical: Calc. for C₁₅H₂₃O₄N: C, 64.04%; H, 8.24%. Found; C, 63.98%; H, 8.37%.

Lactam Diketone [14]. Isoxazole monoacid [67], 1.03g (3.85 X 10⁻³ mole), is taken up in 10ml of anhyd. MeOH. A spatula of #28 Raney Nickle catalyst is added and the slurry hydrogenated at 1 atm and 25°. Hydrogen uptake was rapid and the reaction was terminated after 92ml (86 theory) of H₂ had been absorbed. The reaction was flushed with N₂ and stirred overnight. The pale green reaction is treated with H₂S and filtered.

Concentration of the filtrate gives a gray-green gum which NMR analysis shows to be 80-90% lactam. Purification by preparative layer chromatography (6:4 hexane/ethyl acetate) yields 437mg (44%) of an oil which solidifies to off-white crystals mp 101-106° when triturated with ether. A portion of this material was recrystallized from benzene/ether to give white crystals mp 114.5-115.3° (lit. 62 109°). All spectral data was in agreement with the published values 62. I.R. (CHCl₃, page 111) 3300, 1750, 1705, 1660, 1585 cm⁻¹; UV, 203(3.87), 282(4.31); NMR (CDCl₃, page 119) 1.206 (s, 6H), 1.315 (s, 6H), 2.165 (s, 3H), 2.296 (s, 2H), 2.745 (s,
2H), 5.30δ (s, 1H), 10.45δ (broad sing., 1H); Mass Spec. M+ = 251.

**Carbinol Amine** [15]. The procedure is essentially that of Eschenmoser 62. Lactam diketone [14], 350mg (1.39 × 10^{-3} mole), was taken up in 15ml of anhyd. MeOH and an approximately equal amount of commercial anhyd. ammonia condensed into the flask under N₂. The reaction yellows slightly. The reaction is allowed to warm to room temperature and when NH₃ evolution has become quite slow the flask is tightly stoppered. After 4 days at 25° (a previous small scale experiment showed that 3 days 62 did not give complete reaction) the solvent and excess NH₃ are evaporated under a stream of N₂ or dry air to give a creamy white solid which NMR analysis showed to be ~80% [15] and no more than a trace of [14]. Recrystallization from ether/benzene gave 150mg of white solid mp 151-152.5°. Two more recrystallizations with drying under vacuum at 25° ([15] seems to be fairly heat sensitive) gave clusters of fat needles mp 169-171° in a vacuum sealed capillary (lit. 62 161°). All spectral data was in good agreement with the published values 62. I.R. (CHCl₃, page 112) 3600, 1735(sh), 1720, 1650, 1595 cm⁻¹; UV, 204(4.18), 284(3.99), 347(4.38); NMR (CDCl₃, page 119) 1.02δ (3H, s), 1.10δ (s, 3H), 1.30δ (s, 6H), 1.39δ (s, 3H), 2.32δ (d, 1H, J=16cps), 2.35δ (s, 2H), 2.71δ (d, 1H, J=16cps), 4.95δ (s, 1H), 5.90δ (s, 2H); Mass Spec. M+ = 250.

**Semicorrin E** [10]. The procedure is essentially that of Eschenmoser 59. Carbinol amine [15], 70mg (.28 × 10^{-3} mole), is taken up in 10ml of dry t-BuOH (from 4A sieves), and placed under an N₂ blanket. Potassium t-butoxide in t-BuOH, 6ml of a stock solution made from 100mg K in 50ml t-BuOH (~.31 × 10^{-3} mole), was syringed into the reaction
vessel and the reaction brought to a gentle reflux. After a few minutes at reflux the reaction turns yellow. After 2.5 hrs the reaction is poured into water and extracted with ether. The ether extracts are dried over anhyd. Na₂SO₄ and solvent removed under reduced pressure to give 58mg (89%) of a pale yellow solid which NMR analysis shows to be 80-85% pure Semicorrin E. Three recrystallizations from CH₂Cl₂/hexane and one from hexane with drying under vacuum at 25° gave fine, white needles mp 152.5-154° with sintering at 142° (lit. 59 159°). All spectral data was in good agreement with the published values 62. I.R. (CHCl₃, page 112) 3160, 1740(sh), 1720, 1640, 1595 cm⁻¹; UV, 207(4.13), 220(sh, 4.08), 252 (3.93), 261 (3.95), 272 (3.93), 323(4.16), ~337(sh, 4.14), ~371(sh, 3.92); NMR (CDCl₃, page 119) 1.186 (s, 6H), 1.335 (s, 6H), 2.386 (s, 2H), 2.596 (s, 2H), 4.515 (s, 1H), 5.035 (s, 1H), 5.065 (s, 1H); Mass Spec. M⁺=232, also a peak at 218.

2-Carbomethoxy lactam diketone [65]. Dicarbomethoxy isoxazole [44], 100mg (.286 X 10⁻³ mole), was hydrogenated in the same manner as [14]. After 20 hrs the reaction was filtered, poured into brine, and extracted with three 25ml portions of ether. The ether solution was treated with H₂S, filtered, dried over anhyd. MgSO₄, and solvent removed under reduced pressure. The residue was purified by preparative layer chromatography (3:1 cyclohexane/ethyl acetate). The fastest moving major fraction yielded 20mg of material whose spectra are in complete accord with the assigned structure. I.R. (CHCl₃, page 120) 3350, 1785, 1715, 1600 cm⁻¹; UV, 242(3.6); NMR (CDCl₃, page 120) all singlets, 1.215(6H), 1.256(3H), 1.416(3H), 2.215(3H), 2.805(2H), 3.256(1H), 3.756(3H), 5.376 (1H), ~10.56(broad, 1H).
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