NOVEL CHROMIUM CARBONYL COMPLEXES OF DIHYDROPYRIDINES
AND THEIR APPLICATION TO THE SYNTHESIS OF DEHYDROSECODINE

BY

VICENTE ERNESTO RIDAURA-SANZ
B.Sc., ITESM, Monterrey, Mexico, 1970

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF
THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
IN
THE FACULTY OF GRADUATE STUDIES
Department of Chemistry
University of British Columbia

We accept this thesis as conforming
to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA
August, 1979
© Vicente Ernesto Ridaura-Sanz, 1979
In presenting this thesis in partial fulfilment of the requirements for an advanced degree at the University of British Columbia, I agree that the Library shall make it freely available for reference and study. I further agree that permission for extensive copying of this thesis for scholarly purposes may be granted by the Head of my Department or by his representatives. It is understood that copying or publication of this thesis for financial gain shall not be allowed without my written permission.

Vicente Ernesto Ridaura-Sanz

Department of Chemistry

The University of British Columbia
2075 Wesbrook Place
Vancouver, Canada
V6T 1W5

Date August 21, 1979.
The work presented in this thesis is aimed at the total synthesis of 14,21-dehydrosecodine (1). This substance is an indole derivative with reactive substituents at position 2 (an acrylic ester segment) and 3 (a 1,6-dihydropyridine system). The stabilization of the latter involved the generation of chromium carbonyl complexes employing trisacetonitriletricarbonylchromium (0) as the reagent with appropriate synthetic indole derivatives.

In order to develop the required methodology for the preparation of the above complexes, the initial experiments employed simple dihydropyridine systems. Thus, when N-methyl-3-ethyl pyridinium iodide (41) was treated with NaBH₄ in a two-phase system (ether - water), N-methyl-3-ethyl-1,2-dihydropyridine (46) was obtained. When this compound was treated with the above complexing agent a mixture (ratio 1:2) of (N-methyl-3-ethyl-1,2-dihydropyridine) tricarbonylchromium (0) (43) and (N-methyl-3-ethyl-1,6-dihydropyridine) tricarbonylchromium (0) (44) was obtained. Thermal isomerization of this mixture in refluxing cyclohexane afforded a 1 : 1 ratio of (43) and (44). Liberation of the organic ligand could be achieved by stirring (43) and/or (44) with pyridine.
The above strategy was applied to the indole intermediate, N-(2-carbomethoxyethyltryptophyl)-3-ethylpyridinium perchlorate (36) but only a low yield (2%) of the desired chromium complexes was obtained. These results prompted a change in the original synthetic strategy and a new approach was initiated by other coworkers in this laboratory.

Some studies with the novel system (46) were conducted as they relate to position of alkylation. It was shown that (46) undergoes reaction with benzyl bromide to afford the 5-substituted derivative.
<table>
<thead>
<tr>
<th>TABLE OF CONTENTS</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>TITLE PAGE</td>
<td>i</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>ii</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>iv</td>
</tr>
<tr>
<td>LIST OF DIAGRAMS</td>
<td>v</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>ix</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>x</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>RESULTS AND DISCUSSION</td>
<td>38</td>
</tr>
<tr>
<td>CONCLUSIONS</td>
<td>119</td>
</tr>
<tr>
<td>EXPERIMENTAL</td>
<td>121</td>
</tr>
<tr>
<td>ADDENDUM</td>
<td>154</td>
</tr>
<tr>
<td>APPENDIX</td>
<td>157</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>158</td>
</tr>
<tr>
<td>Diagram</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>1</td>
<td>Some Indole Alkaloid Families</td>
</tr>
<tr>
<td>2</td>
<td>Early Postulations of the Biosynthesis of Indole Alkaloids</td>
</tr>
<tr>
<td>3</td>
<td>Wenkert-Thomas Hypothesis for the Biosynthesis of Indole Alkaloids</td>
</tr>
<tr>
<td>4</td>
<td>Loganin Biosynthesis</td>
</tr>
<tr>
<td>5</td>
<td>Role of Loganin in the Biosynthesis of Indole Alkaloids</td>
</tr>
<tr>
<td>6</td>
<td>Early Stage in the Biosynthesis of Indole Alkaloids</td>
</tr>
<tr>
<td>7</td>
<td>Biosynthesis of Akuammicine and Stemmadenine</td>
</tr>
<tr>
<td>8</td>
<td>Biosynthetical Postulate for the Formation of Aspidosperma-Type Alkaloids</td>
</tr>
<tr>
<td>9</td>
<td>Wenkert's Hypothesis for the Biosynthesis of Aspidosperma and Iboga-Type Alkaloids</td>
</tr>
<tr>
<td>10</td>
<td>Kutney's Transannular Cyclization of Indolic Nine-Membered Ring Systems</td>
</tr>
<tr>
<td>11</td>
<td>Kutney's Synthesis of Pseudovincadifformine and Dihydrocatharanthine by a Transannular Cyclization</td>
</tr>
<tr>
<td>12</td>
<td>Use of the Transannular Cyclization for the Synthesis of Catharanthine and Pseudocatharanthine</td>
</tr>
<tr>
<td>13</td>
<td>Feeding Experiments in <em>C. roseus</em></td>
</tr>
<tr>
<td>14</td>
<td>Feeding Experiments in <em>V. minor</em></td>
</tr>
<tr>
<td>15</td>
<td>Proposed Mechanism for the Conversion of Aspidosperma-Type Alkaloids into Iboga-Type</td>
</tr>
<tr>
<td>Diagram</td>
<td>Description</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>16</td>
<td>Role of Dehydrosecodine in the Biosynthesis of Indole Alkaloids</td>
</tr>
<tr>
<td>17</td>
<td>Secodine-Type Compounds Isolated from Natural Sources</td>
</tr>
<tr>
<td>18</td>
<td>Presecamine-Type Alkaloids and Their Chemistry</td>
</tr>
<tr>
<td>19</td>
<td>Incorporation of Secodine into Vindoline and Catharanthine</td>
</tr>
<tr>
<td>20</td>
<td>Scott's Thermal Rearrangement of Indole Alkaloids</td>
</tr>
<tr>
<td>21</td>
<td>14,21-Dehydrosecodine as an Intermediate in the Thermal Rearrangements of Indole Alkaloids</td>
</tr>
<tr>
<td>22</td>
<td>Trapping of the Dehydrosecodine Intermediates in the Thermal Rearrangements of Indole Alkaloids</td>
</tr>
<tr>
<td>23</td>
<td>14,21-Dehydrosecodine as an Intermediate in the Thermal Rearrangement of Catharanthine</td>
</tr>
<tr>
<td>24</td>
<td>Synthesis of Andraginine by Thermal Rearrangement of Indole Alkaloids</td>
</tr>
<tr>
<td>25</td>
<td>14,21-Dehydrosecodine</td>
</tr>
<tr>
<td>26</td>
<td>Ziegler's Synthesis of Minovine</td>
</tr>
<tr>
<td>27</td>
<td>Secodine Reactions</td>
</tr>
<tr>
<td>28</td>
<td>General Method for the Construction of the Acrylic Ester Segment</td>
</tr>
<tr>
<td>29</td>
<td>Methodology for the Synthesis of α-Methylene Lactones and Ziegler's Synthesis of 2-Indolyl-Acrylic Esters</td>
</tr>
<tr>
<td>30</td>
<td>Protection of α-Methylene Lactones</td>
</tr>
<tr>
<td>31</td>
<td>Isomeric Dihydropyridines</td>
</tr>
<tr>
<td>Diagram</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>32</td>
<td>Stable Dihydropyridines</td>
</tr>
<tr>
<td>33</td>
<td>Oxidation of Dihydropyridines</td>
</tr>
<tr>
<td>34</td>
<td>Some Dihydropyridine Reactions</td>
</tr>
<tr>
<td>35</td>
<td>Hantzsch Synthesis of Dihydropyridines</td>
</tr>
<tr>
<td>36</td>
<td>1,2-Dihydropyridines via Condensation Reactions</td>
</tr>
<tr>
<td>37</td>
<td>NaBH₄ Reduction of Pyridinium Salts</td>
</tr>
<tr>
<td>38</td>
<td>Orientation of the Nucleophilic Additions to Pyridinium Salts</td>
</tr>
<tr>
<td>39</td>
<td>Nucleophilic Reactions with Pyridinium Salts</td>
</tr>
<tr>
<td>40</td>
<td>Dihydropyridines from Other Heterocyclic Systems</td>
</tr>
<tr>
<td>41</td>
<td>Protection of Dihydropyridines</td>
</tr>
<tr>
<td>42</td>
<td>Scheme &quot;A&quot;: Synthesis of Dehydrosecodine</td>
</tr>
<tr>
<td>43</td>
<td>Scheme &quot;B&quot;: Synthesis of Dehydrosecodine</td>
</tr>
<tr>
<td>44</td>
<td>Formation of N-Methyl-3-ethyl Dihydropyidine Chromium Complexes</td>
</tr>
<tr>
<td>45</td>
<td>Overreduction of N-Methyl-3-ethylpyridinium with NaBH₄</td>
</tr>
<tr>
<td>46</td>
<td>Mass Fragmentation Pattern of N-Methyl-3-ethyl-1,2-dihydropyridine and Its Chromium Complex</td>
</tr>
<tr>
<td>47</td>
<td>Alkylation of N-methyl-3-ethyl-1,2-dihydropyridine</td>
</tr>
<tr>
<td>48</td>
<td>Alkylation of N,3,5-Trimethyl-1,2-dihydropyridine</td>
</tr>
<tr>
<td>49</td>
<td>Scheme for the Synthesis of 2-carboxymethyltryptophyl Chloride (65)</td>
</tr>
<tr>
<td>Diagram</td>
<td>Description</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>50</td>
<td>Intramolecular Condensation of N-(2-cyanomethyl-tryptophyl) Pyridinium</td>
</tr>
<tr>
<td>51</td>
<td>Scheme &quot;C&quot; for the Synthesis of 14,21-Dehydrosecodine (1)</td>
</tr>
<tr>
<td>52</td>
<td>Synthesis of (N-Benzyl-2-carbomethoxy-methylindolyl)-benzyl Ether (72)</td>
</tr>
<tr>
<td>53</td>
<td>Reduction of 2-N,N-Dimethylcarbox-amidoindole Derivatives with LiAlH₄</td>
</tr>
<tr>
<td>54</td>
<td>Homologation Reactions in Acetic Ester Derivatives</td>
</tr>
<tr>
<td>55</td>
<td>Complexation Reaction of N-(2-Carbomethoxymethyltryptophyl)-3-ethyl-1,2-dihydropyridine (37)</td>
</tr>
<tr>
<td>56</td>
<td>Synthesis of N-Benzyl-3,14-dehydrosecodine</td>
</tr>
<tr>
<td>57</td>
<td>Appendix: Numbering System of Indole Alkaloids</td>
</tr>
<tr>
<td>Figure</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Figure 1</td>
<td>NMR spectrum of (N-methyl-3-ethyl-1,2-dihydropyridine)tricarbonylchromium(0) complex (43) (C₆D₆)</td>
</tr>
<tr>
<td>Figure 2</td>
<td>NMR spectrum of (N-methyl-3-ethyl-1,6-dihydropyridine)tricarbonylchromium(0) complex (44) (C₆D₆)</td>
</tr>
<tr>
<td>Figure 3</td>
<td>Double resonance studies of complex 44 (C₆D₆)</td>
</tr>
<tr>
<td>Figure 4</td>
<td>NMR spectrum of (1,6-dihydropyridine)chromium complex 44 in CDCl₃</td>
</tr>
<tr>
<td>Figure 5</td>
<td>NMR spectrum of N-carbomethoxy-3-ethyl-1,2-dihydropyridine (49) (C₆D₆)</td>
</tr>
<tr>
<td>Figure 6</td>
<td>Double resonance studies of 49</td>
</tr>
<tr>
<td>Figure 7</td>
<td>NMR spectrum of N-methyl-3-ethyl-1,2-dihydropyridine (46) (C₆D₆)</td>
</tr>
<tr>
<td>Figure 8</td>
<td>NMR spectrum of N-methyl-3-ethyl-1,2-dihydropyridine (51) (C₆D₆)</td>
</tr>
<tr>
<td>Figure 9</td>
<td>NMR spectrum of (N-tryptophyl-3-ethyl-1,6-dihydropyridine)tricarbonylchromium(0) complex (59)</td>
</tr>
<tr>
<td>Figure 10</td>
<td>NMR spectrum of (N-tryptophyl-3-ethyl-1,2-dihydropyridine)tricarbonylchromium(0) complex (60)</td>
</tr>
</tbody>
</table>
ACKNOWLEDGEMENTS

The author wishes to thank Dr. James P. Kutney for his direction and unconditional help during the course of the present work. He would also like to thank other members of the research group for their helpful suggestions, especially Drs. R. Greenhouse and E. Jahngen, as well as Professor W.R. Cullen for various discussions during the early phases of this research.

Financial aid from CONACYT in 1971-72 is gratefully acknowledged, as is further financial support from the University of British Columbia in the form of a University Graduate Fellowship from 1974-76, and the U.B.C. Chemistry Department for a teaching assistantship.
INTRODUCTION

Biosynthesis of naturally occurring compounds is an area that has intrigued scientists for many years, leading to the postulation of several hypotheses for the formation of various families of compounds found in living systems, mainly in the plant kingdom. These hypotheses have been formulated to try and correlate, in a logical manner, the different compounds isolated from a particular plant that belongs to a specific family of substances (alkaloids, terpenes, etc.). This correlation is sometimes based on known chemical reactions and on other occasions enzymes are inexplicably bestowed with powerful and magical properties.

The biosyntheses of alkaloids belonging to the Yohimbé, Corynanthé, Strychnos, Aspidosperma and Iboga families (see Diagram 1), have been subject to a great deal of speculation and it was not until 1965 that some light was shed on this interesting problem. Since 1930 the tryptamine segment of this type of alkaloid was thought to be derived from tryptophan, but not until recently was this proven to be correct. Labelled tryptamine can also be incorporated into the major alkaloids of *Vinca* and other species, although in a less efficient manner than the previously mentioned aminoacid.
DIAGRAM 1
Some Indole Alkaloid Families

YOHIMBINE  
(Yohimbe Family)

AJMALICINE  
(Corynanthe Family)

AKUAMMICINE  
(Strychnos Family)

VINDOLINE  
(Aspidosperma Family)

CATHARANTHINE  
(Iboga Family)
Early postulations for the biosynthesis of the non-tryptamine portion of yohimbine invoked phenylalanine and formaldehyde as precursors. This idea was reinforced when Woodward suggested a related pathway for the formation of strychnine involving the fission of a 3,4-dihydroxy phenylalanine-derived ring E, with the incorporation of an acetate unit (Diagram 2).

**DIAGRAM 2**

Early Postulations of the Biosynthesis of Indole Alkaloids
With the isolation of new types of indole alkaloids possessing the C₀₋C₁₀ unit for the non-tryptamine moiety, Wenkert and Thomas noted that the previous hypothesis was limited as it did not readily account for the predominantly aliphatic character of these compounds, especially those containing a carbocyclic ring E. They proposed an alternative scheme based mainly on the similarity of the C₀₋C₁₀ segment of the indole alkaloids with several new glycosides, isolated at that time, known as iridoids and seco-iridoids. Rearrangement of these compounds before or after condensation with tryptamine, or the tryptamine precursor, gives the different indole alkaloids that have a C₀₋C₁₀ segment. This postulation is known as the Wenkert-Thomas Hypothesis and is summarized in Diagram 3.

The terpenoid character of these alkaloids was proven by the incorporation of labelled mevalonic acid and/or geraniol into vindoline. Scott conveniently divides the biosynthesis of terpenoid indole alkaloids and their interconversions into three phases. The early stage covers the development of a highly oxygenated and reactive glucoside (secologanin) and its conversion to vincoside (a). This is followed by the
DIAGRAM 3

Fenkert-Thomas Hypothesis for the Biosynthesis of Indole Alkaloids

IRIDOIDS

AJMALICINE

VINDOLINE

YOHIMBINE

AKUAMMICE

CATHARANTHINE
transformation of vincoside to Corynanthé and Strychnos alkaloids (b), and finally the development of the Aspidosperma and Iboga families (c).

a) FROM MEVALONATE TO VINCOSIDE - Thomas\textsuperscript{21} suggested in 1964 that the particular monoterpene precursor for a series of indole alkaloids might be the glucoside, loganin (see Diagram 4), which undergoes cleavage to secologanin (see Diagram 5) as part of the intermediary metabolism. Loganin has been found by radiochemical dilution in \textit{Catharanthus roseus}\textsuperscript{22} as well as in other plant species (\textit{Strychnos}, \textit{Rhaza}, \textit{Catharanthus}, etc.)\textsuperscript{1b}, where the terpenoid indole alkaloid is also present. Its biosynthesis is shown in Diagram 4.

The pathway between loganin and vincoside was elucidated as a result of the isolation of two new glucosides\textsuperscript{23,24}, foliamenthin and menthiafolin (Diagram 5). Hydrolysis of these two compounds, ring opening and methylation furnished secologanin which, in its [O-methyl-\textsuperscript{3H}]-labelled form, proved a good precursor for the three families of indole alkaloids\textsuperscript{25,26} (Corynanthé, Aspidosperma and Iboga). The conversion from loganin to
secologanin was visualized by Battersby via hydroxylation of the former compound to yield the as yet unisolated hydroxyloganin which is transformed to secologanin via a 1,3 fragmentation reaction (Diagram 5). Condensation in vitro of secologanin with tryptamine forms a separable mixture of vincoside and its three epimer isovincoside or strictosidine (see Diagram 5).
Role of Loganin in the Biosynthesis of Indole Alkaloids

LOGANIN

-Monoglucosylated-18-β-D-glucopyranosyl-"B"-3,16,17-trihydroxy-18-oxo-16,18-dimethyl-19-nor-1,2,3,4,9,9,10,10-octahydro-1H-carbazole-1-carboxylic acid"

HYDROXYLOGANIN

-Monoglucosylated-18-β-D-glucopyranosyl-"B"-3,16,17-trihydroxy-18-oxo-16,18-dimethyl-19-nor-1,2,3,4,9,9,10,10-octahydro-1H-carbazole-1-carboxylic acid"

SECOLOGANIN

-R = cyclohexyl carbonyl - = FOLIAMETHIN

-R = cyclohexyl OH carbonyl - = MENTHIAFOLIN

TRYPTAMINE

VINCOSIDE

ISOVINCOSIDE
The presence of secologanin, vincoside and isovincoside in C. roseus has been shown by radiochemical dilution analysis. Scott, studying germinating C. roseus seedlings, showed that vincoside is one of the first alkaloidal-type materials produced (24 hours).

b) FROM VINCOSIDE TO CORYNANTHE AND STRYCHNOS ALKALOIDS

As just mentioned, vincoside was reported as one of the first alkaloids produced in germinating C. roseus seedlings, however, two other Corynanthe alkaloids are formed at the same time (ajmalicine and corynantheine, see Diagram 6). In order to convert vincoside into the Corynanthe family a hydrolysis of the glucoside is necessary, followed by a cyclization of the resultant dialdehyde, as shown in Diagram 6. As can be see in the Diagram the stereochemistry of C\textsubscript{3} must be inverted when vincoside is transformed into the Corynanthe alkaloids. Feeding experiments using tritium at C-3 in vincoside and isovincoside showed that only the former compound was incorporated in ajmalicine. Any mechanism converting vincoside into the Corynanthe family must explain inversion at C-3 without loss of the label. One such possibility is shown at the bottom of Diagram 6.

It has been shown recently by using tissue
Early Stage in the Biosynthesis of Indole Alkaloids

VINCOSIDE

CH₂O₂C

R = H CORYNANTHEINE ALDEHYDE

R = CH₃ CORYNANTHEINE

AJMALICINE

GEISSOSCHIZINE
cultures that the previously mentioned feeding experiments are incorrect and that isovincoside is indeed the precursor for the Corynanthe alkaloids.

Following Scott's sequential isolation of alkaloids from C. roseus seedlings it was found that corynantheine aldehyde, geissoschizine and a series of oxidized derivatives of the latter compound are isolated in a period of between 28 to 40 hours after germination (Diagram 7). Alkaloids belonging to the Strychnos family (preakuammicicine, akuammicine, stemmadenine) start to appear after a germination time of 40 to 50 hours.

Feeding experiments in C. roseus have shown geissoschizine to be a good precursor for akuammicine. This, together with the series of oxidized geissoschizine derivatives isolated in the same period (40-50 hours), led to the proposal of the sequence, shown in Diagram 7, for the conversion of the Corynanthe-type of alkaloids to the Strychnos family.

The sequence is a rationalization of the compound isolated and has not yet been proven. The only evidence that exists to support this claim at the moment is the positive
Biosynthesis of Akuammicine and Stemmadenine
incorporation of geissoschizine oxyindole into akuammicine.  

c) FORMATION OF ASPIDOSPERMA AND IBOGA-TYPE ALKALOIDS -

In the same time interval that preakuammicine, akuammicine and stemmadenine are formed, tabersonine, one of the Aspidosperma-type alkaloids, is also produced by C. roseus seedlings. If a sequential isolation of compounds, with respect to time, can give an idea of how molecules are formed, that means that tabersonine, could have stemmadenine or preakuammicine (both with a C_{10}-unit) as a precursor. For this to happen the bonds indicated as dotted lines in Diagram 8 must be broken to form an intermediate (named "intermediate A" as no functionality is shown at this point), which will cyclize as shown to give the Aspidosperma skeleton.

In 1962 Wenkert proposed a similar sequence for the formation of Aspidosperma and Iboga-type alkaloids. His sequences started with an oxidized form of stemmadenine to yield a compound that has the same structure as "intermediate A". Cyclization in the forms indicated in Diagram 9, will give compounds "B" and "C", which could be the precursors to the
quebrachamine and cleavamine-types of alkaloids, respectively. The latter family of compounds has not yet been isolated from any natural source, except in the form of bisindole alkaloids. A second cyclization of the nine-membered ring intermediates will furnish the Aspidosperma and Iboga alkaloids.

Investigating a general entry to the syntheses of Aspidosperma and Iboga-type alkaloids, Kutney studied the transannular cyclization reaction of indolic nine-membered ring systems, similar to the one proposed by Wenkert for the final stages of this kind of alkaloid (Diagram 9).
DIAGRAM 9

Wenkert's Hypothesis for the Biosynthesis of Aspidosperma and Iboga-Type Alkaloids

IBOGA FAMILY

ASPIDOSPERMA FAMILY

CLEAVAMINE FAMILY

QUEBRACHAMINE FAMILY

"C"

"B"
Kutney and collaborators started their study with simple systems using mercuric acetate to oxidize the piperidine ring forming an iminium salt, which then condensed with the indole. In this manner oxidation of 4β-dihydrocleavamine ("D") followed by a reduction with lithium aluminum hydride (LAH) of the resultant indolenine gave 7β-ethyl-5-desethyl aspidospermidine ("E"), as shown in Diagram 10. A similar reaction using (-) quebrachamine gave (+) aspidospermidine in good yield.  

**Diagram 10**

Kutney's Transannular Cyclization of Indolic Nine-Membered Ring Systems
When 18α-carbomethoxy dihydrocleavamine ("F") was used as starting material\textsuperscript{32,33} a mixture of three compounds was isolated. One of them was a compound with an Aspidosperma skeleton that was named pseudovincadifformine and whose formation follows reactions similar to those outlined in Diagram 10. The other two compounds were identified as coronaridine and dihydrocatharanthine, which belong to the Iboga family. These two compounds are obtained by a cyclization of the carbon α to the carbomethoxy with the other possible iminium salt that can be formed in the piperidine ring. Epimerization of the ethyl side chain can be explained by equilibration of the iminium salt with the corresponding enamine, as described in Diagram 11.

The same research group was interested to see if the introduction of a double bond in the piperidine ring affected the course of this transannular cyclization. They found that 18β-carbomethoxy cleavamine ("G"), when treated with mercuric acetate, gave a mixture of catharanthine plus pseudocatharanthine\textsuperscript{32,33}, a compound previously reported in the literature (Diagram 12).
Kutney's Synthesis of Pseudovincadifformine and Dihydro-catharanthine by a Transannular Cyclization
Now that Kutney et al proved that the transannular cyclization was a useful synthetic reaction, they wondered whether this reaction had any significance in the later stages of Aspidosperma and Iboga biosyntheses and if not, was there any relationship between the nine-membered ring compounds and the rigid cyclic systems (Iboga and Aspidosperma), as suggested by Wenkert? To answer this question a series of experiments
was carried out where derivatives of the quebrachamine and cleavamine-type alkaloids were fed to *C. roseus* under varying conditions. The isolated alkaloids (vindoline and catharanthine) were shown to contain little or no activity (Diagram 13).

This lack of incorporation could simply mean that there were some difficulties with permeability and/or transport of these high molecular weight substances to the site of biosynthesis, or that the cyclization reaction was of little biosynthetic significance.

To overcome the first difficulty tabersonine was fed to *C. roseus* and a positive incorporation was observed in vindoline and, most surprisingly, in catharanthine (last feeding experiment in Diagram 13). With this experiment it was demonstrated that there was no problem of permeability or transportation of the precursor. To be certain of the negative results obtained with the nine-membered ring precursors, biosynthetic studies were performed in another plant, *Vinca minor*, where alkaloids belonging to the quebrachamine and other Aspidosperma families are found. Labelled tryptophan was fed to this plant and the alkaloids, vincadine, vinca-minoreine (quebrachamine-type), minovine and vincadifformine
(aspidosperma-type), were isolated at different time intervals. If there was any biosynthetic relationship between these two families of alkaloids the ratio between
them (B/A) should increase or decrease with respect to
time. As can be seen in Diagram 14, the ratio B/A
remained relatively constant over a period of fourteen days.

DIAGRAM 14

Feeding Experiments in V. minor

\[
\begin{align*}
R = H & \quad \text{VINCADINE} \\
R = \text{CH}_3 & \quad \text{VINCAMINOREINE} \\
R = H & \quad \text{VINCADIIFORMINE} \\
R = \text{CH}_3 & \quad \text{MINOVINE}
\end{align*}
\]

<table>
<thead>
<tr>
<th>TIME</th>
<th>TOTAL % INCORPORATION</th>
<th>B/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 hours</td>
<td>0.003</td>
<td>0.057</td>
</tr>
<tr>
<td>1 day</td>
<td>0.015</td>
<td>0.24</td>
</tr>
<tr>
<td>2 days</td>
<td>0.01</td>
<td>0.21</td>
</tr>
<tr>
<td>4 days</td>
<td>0.01</td>
<td>0.22</td>
</tr>
<tr>
<td>7 days</td>
<td>0.009</td>
<td>0.13</td>
</tr>
<tr>
<td>14 days</td>
<td>0.003</td>
<td>0.06</td>
</tr>
</tbody>
</table>

The possibility of equilibration of these compounds in the
plant system (which could account for a constant B/A ratio)
was eliminated when it was shown\textsuperscript{35} that neither vinca-
minoreine nor minovine transfer any activity to each other
when they are separately incorporated into the plant over
a period of one week.

The conversion of tabersonine into catharanthine (last
experiment in Diagram 13), demands a considerable number
of transformations since the structural features of the
two alkaloid families are substantially different. A
possible pathway could be the one described in Diagram 15
(no functionality shown), where the bonds cleaved by dotted
lines break to provide an intermediate which possesses the
same structure as "intermediate A" in Diagram 8. By
cyclization in the manner indicated (probably via a con-
certed mechanism) the Iboga system will be formed.

In order to verify the functionality inherent in intermediate "A" it is
convenient to go back to Scott's feeding experiments\textsuperscript{4,20,28}
where stemmadenine was positively incorporated into vindol
line and catharanthine. Scott explains these conversions
(Diagram 16) by an isomerization of stemmadenine to a com-
pound that he named isostemmadenine (still not isolated
from natural sources). This compound then rearranges to
form "H", which is the protonated form of a 1,6-dihydro-
pyridine, named from this point on as dehydrosecodine.
The dihydropyridine can react as a diene with the double bond of the acrylic ester via an intra-molecular Diels-Alder to yield catharanthine, or it can react as an enamine that adds in a Michael manner to the acrylic ester to form compound "I". This substance will cyclize to form tabersonine, which is further transformed into vindoline, or it could remain in the ring-opened nine-membered ring form and be the precursor for the quebrachamine-type alkaloids. The
Role of Dehydrosecodine in the Biosynthesis of Indole Alkaloids

STEMMADENINE

DEHYDROSECODINE

"N"

Diels-Alder

Diels-Alder

CATHARANTHINE

TABERSONINE

VINCADINE

(quebrachamine-type)

VINDOLINE
formation of tabersonine from dehydrosecodine could also be visualized by an intra-molecular Diels-Alder\textsuperscript{37} reaction between the 2,3 double bond of the dihydropyridine and the diene formed by the indole and the acrylic ester.

The formation of tabersonine from dehydrosecodine is a reversible process on the basis of Kutney's biosynthetic work (see Diagram 14). The sequence presented in Diagram 16 is very similar to the one proposed by Wenkert in 1962\textsuperscript{13}, the main difference being that in the former the nine-membered ring intermediates are eliminated.

The instability of the dihydropyridine and the reactivity of the acrylic ester moiety makes the dehydrosecodine almost impossible to isolate from any plant system. However the following \textit{in vivo} evidence and results obtained in the laboratory indicate the certainty of the existence of such intermediates:

1. Compounds with the same skeleton as dehydrosecodine have been isolated from \textit{Razhya orientalis} by Smith\textsuperscript{38}. At the same time Battersby\textsuperscript{41} reported the isolation of a similar compound from \textit{C. roseus} shoots: 16,17-dihydrosecodine-17-ol (Diagram 17).

Working with the same plant Smith also isolated a
series of new dimeric alkaloids that were named pre-
secamines. Treatment of these compounds with 2N
hydrochloric acid gave the previously reported secamine
alkaloids. When the presecamines were heated a
series of secodine derivatives were obtained which, on
standing for two days at 0°C without solvent, returned
to a mixture of isomeric presecamines (Diagram 18).

2. Positive incorporation of secodine into vindoline and
catharanthine was found by Kutney and Scott.
Doubly labelled secodine with tritium in the ethyl side chain was incorporated intact, maintaining the same $^{14}\text{C}/\text{T}$ ratio. However, 62% of this label was lost when $^3\text{H}$ was present in the piperidine ring segment (Diagram 19).
What this suggested was that the piperidine had gone to a higher oxidation stage prior to forming vindoline and catharanthine, which was consistent with a dihydropyridine intermediate.

**Diagram 19**

Incorporation of Secodine into Vindoline and Catharanthine
3. In 1968 Scott reported that tabersonine, on heating with AcOH for 16 hours, gave (+) catharanthine and (+) pseudocatharanthine, and that stemmadenine, under the same conditions, gave a mixture of (+) tabersonine, (+) catharanthine and (+) pseudocatharanthine. He invoked the formation of dehydrosecodine as the intermediate for the products obtained. The existence of dehydrosecodine as an intermediate formed in the thermal rearrangement of alkaloids (aspidosperma, strychnos and iboga) was further proved in the following experiments.

a) When 19,20-dihydrostemmadenine acetate or 19,20-dihydropreakuammicine were heated over silica gel at 150°C for 45 minutes a mixture of pseudocatharanthine and dihydropseudocatharanthine was obtained. Scott explained this transformation by the series of reactions outlined in Diagram 20. Oxidation of the dihydrostemmadenine derivative to dihydropreakuammicine is an easy reaction and can be performed under several experimental conditions (best yields are obtained with PtO₂/O₂). By heating dihydropreakuammicine, the iminium salt "J" is formed which then transforms to the corresponding enamine "K". Via a retro-Michael reaction...
this substance gives the dihydropyridinium salt "L", which is actually the protonated form of a 1,2 dihydropyridine "M" (3,14 dehydrosecodine). By a Michael reaction and then cyclization with the indole ring, or directly by a Diels-Alder reaction, the dihydropyridine gives (+)pseudocatharanthine. The formation of the dihydro product is probably due to a disproportionation reaction between "L" and "M", which is a very common reaction for dihydropyridines.

When 19,20-dihydroprecondylocarpine acetate was treated under the same conditions, a mixture of (+) tabersonine and (+) vincadifformine was obtained as indicated in Diagram 21. In this case the isomeric dehydrosecodine "N" (14,21 dehydrosecodine) is formed.

b) i. Treating dihydropreakuammicine with methanol at 80°C for 15 minutes gave 15-methoxy-dihydropseudocatharanthine. This confirmed the existence of intermediate "L" (Diagram 22).

ii. Hydrogenation of stemmadenine acetate with PtO₂ as a catalyst gave 75% tetrahydrosecodine (Diagram 22).
Scott's Thermal Rearrangement of Indole Alkaloids

19,20-DIHYDROSTEMMADENINE ACETATE

\[ \xrightarrow{[0]} \]

19,20-DIHYDROPREAKUAMMICINE ACETATE

"K"

\[ \xrightarrow{\text{ }} \]

"J"

"L"

\[ \xrightarrow{\text{ }} \]

"M"

15,20-DIHYDRO PSEUDOCATHARANTHINE
DIAGRAM 21

14,21-Dehydrosecodine as an Intermediate in the Thermal Rearrangements of Indole Alkaloids

19,20-DIHYDROPRECONDYLOCARPINE ACETATE

(+) TABERSONINE

(+) VINCADIFFORMINE
Trapping of the Dehydrosecodine Intermediates in the Thermal Rearrangements of Indole Alkaloids

15-\textgamma\textendash\textEND SUBSTITUTED DIHYDRO-PSEUDOCATHARANTINE

STEMMADEINE ACETATE

TETRAHYDROSECODINE
c) When catharanthine was heated with methanol at 140°C the pyridinium salt "O" (Diagram 23) was formed in 50% yield\textsuperscript{48,49}. Again, a dehydroseco
dine intermediate was contemplated which, by a disproportionation reaction, produced the pyridinium salt. When the salt was heated at 175°C a mixture of 1-methyl-2-hydroxy-carbazole and 3-ethyl pyridine was formed. The same mixture was obtained when tabersonine was heated with xylene at 205°C.

\textbf{DIAGRAM 23}

\textit{14,21-Dehydrosecodine as an Intermediate in the Thermal Rearrangement of Catharanthine}
d) Finally, when precondylocarpine was heated in EtOAc a new pentacyclic alkaloid was obtained (Diagram 24)\textsuperscript{47}. Almost at the same time Potier\textsuperscript{48} reported the isolation of the same pentacyclic compound from \textit{Craspidospermum verticillatum}, naming it andragínine. If the thermal rearrangement is performed using methanol as solvent, then methoxy-dihydroandroginine is formed. Andragínine has also been thermally synthesized from $\Delta^{18}$-tabersonine\textsuperscript{49}.

As can be seen, dehydrosodecine is an important intermediate in the last stage of alkaloid biosynthesis as well as in the thermal rearrangements of some indolic alkaloids. Due to its instability it has not been isolated from any plant system or reaction mixture and there is only indirect evidence of its existence.

It was thought that the synthesis of dehydrosodecine would be helpful since it would allow us to ascertain the chemistry of this type of compound and, depending on the results obtained, could probably be used in biosynthetic studies.

Preliminary studies towards the synthesis of dehydrosodecine constitute the work reported in this thesis.
Synthesis of Andraginine by Thermal Rearrangement of Indole Alkaloids

\[ \text{Precondylocarpine} \rightarrow \text{Andraginine} \rightarrow \Delta^{18}-\text{Tabersonine} \rightarrow 15-\text{Methoxy-14,15-Dihydro-Andraginine} \]
RESULTS AND DISCUSSION

As mentioned in the introduction, the object of this work is the synthesis of 14,21 dehydrosecdine (1), which will be utilized in further studies of synthesis and biosynthesis of indole alkaloids.

Upon inspection of the molecule to be synthesized (Diagram 25) it is found that the 14,21 dehydrosecdine possesses two segments that are very reactive: 1) an acrylic ester derivative (segment A), and 2) an N-substituted 3-ethyl-1,6-dihydropyridine (segment B).

Due to the fact that these two segments are chemically very different, it is necessary to analyse them sufficiently (i.e. factors affecting stability, reactions, methods of preparation and protection, if any), in order to decide when they will be constructed within a synthetic scheme.
Acrylic Ester Segment

In general acrylic ester derivatives are very good Michael acceptors that react, in relatively mild conditions, with a variety of nucleophiles\textsuperscript{53}, including hydrides (NaBH\textsubscript{4}, LiAlH\textsubscript{4})\textsuperscript{54}, to yield the corresponding 1,4 adducts. Due to the fact that they possess a polarized double bond, acrylic esters have been utilized very successfully as dienophiles in Diels-Alder reactions\textsuperscript{55}.

In the case of a methyl 2-(2'-indolyl)-acrylate derivative (as in dehydrosecodine), an extra property is added to the system, that is, the double bond of the acrylic ester, in conjugation with that of the indole's pyrrole segment, makes a good system for Diels-Alder-like reactions. This property has been utilized by Ziegler\textsuperscript{56,57} in the total synthesis of minovine (4) (Diagram 26). For this particular case, the reaction could be explained directly by a Diels-Alder reaction or by an addition of the endocyclic enamine (2) to the 2-(2'-indolyl)-acrylic ester (3), followed by an intramolecular Mannich condensation, as shown in the Diagram. The diene formed between the indole and the acrylic ester is quite reactive and, as described in the introduction, dimerizes very easily yielding presecamine-type alkaloids\textsuperscript{38} (Diagram 27). In the same paper where this reaction is described, Smith reports that when the indolyl-acrylate system is kept in
Ziegler's Synthesis of Minovine

(±) Minovine 4
methanol, the 17-methoxy derivative (7 in Diagram 27) is formed.

**DIAGRAM 27**

Secodine Reactions

A general method for construction of the acrylic ester segment of the dehydrosecodine might be one in which a preformed \( \alpha \)-indolyl-acetic ester is converted directly via an "\( \alpha \)-methylenation sequence" into the desired 2-indolyl-acrylic ester (Diagram 28).
DIAGRAM 28

General Method for the Construction of the Acrylic Ester Segment

\[ \text{Diagram} \]

The methodology for this transformation is very similar to the one utilized for the synthesis of \( \alpha \)-methylene lactones, which has been reviewed by Grieco\(^5\). Analyzing his paper one can see that in general, the procedures utilized for the \( \alpha \)-methyleneation of lactones follow the two general routes outlined in Diagram 29.

In his synthesis of seco
dine Kutney\(^{35-37}\) used route A (\( x = \text{OH} \)) for the formation of the 2-indolyl-acrylic system. A different approach was taken by Ziegler in his synthesis of minovine. In this case an indole glyoxylic (8) ester is converted via a Wittig reaction into the acrylic ester derivative (9) as shown at the bottom of Diagram 29.
Methodology for the Synthesis of α-Methylene Lactones

Ziegler's Synthesis of 2-Indolyl-Acrylic Esters
As can be seen in the previous Diagram, the 1,4 adduct (10) is the same type of intermediate as that obtained in one of the routes described for the preparation of α-methylene lactones (Route A in Diagram 29). Therefore, a possibility in the synthesis of dehydrosecodine could be the preparation of an indolic compound containing the same features as (10), which would allow us to build the other sensitive segment of dehydrosecodine without any side reaction. Finally the acrylic segment could be formed at the last stage of the synthesis via a retro-Michael reaction, similar to the one outlined in Diagram 30.

**Dihydropyridine Segment**

The reduction of the aromatic heterocycle pyridine can lead to several isomeric dihydro-and tetrahydro-pyridines, depending on the conditions used in the reaction. Dihydropyridines play an important role as reaction intermediates in the reaction of pyridine, e.g. in nucleophilic substitutions. They also represent ring systems of theoretical and biological importance.

In theory there can be five isomeric dihydropyridines (structures 11 - 15 in Diagram 31), but in fact most of the known dihydropyridines have either the 1,2 dihydro (11) or the
On the basis of the reactivity reported for the indolyl-acrylic segment, it is adviseable to form this at the last stage of the planned synthesis of dehydrosecodine. Otherwise, this segment could create several problems that would be difficult to overcome unless a way to protect this portion were utilized.

In his review Grieco points out that there have been several methods reported for the protection of α-methylene lactones. All of them utilize the high reactivity of this system towards nucleophiles, to form the corresponding 1,4 adducts (10). By a "retro-Michael" reaction the α-methylene unit is reestablished from the adduct, via a type of intermediate that depends on the nucleophile utilized (Diagram 30).

DIAGRAM 30
Protection of α-Methylene Lactones
1,4 dihydro structure (12). When a substituent (R), is present at position 2 or 3 of the pyridine ring, two isomeric dihydro structures (11) can arise, named 2-R (or 3-R)-1,2-dihydopyridine and 2-R (or 3-R)-1,6-dihydopyridine (structures 16 and 17, respectively, in Diagram 31).

DIAGRAM 31

Isomeric Dihydopyridines

11 1,2 Dihydro

12 1,4 Dihydro

13

14

15

16 3-R-1,2-Dihydro

17 3-R-1,6-Dihydro
There are scattered data available that indicate that the 1,4 dihydropyridine system is more stable than the 1,2 isomer. One example is the work by Traber and Karrer\textsuperscript{60}, which reports that 1,2 dihydropyridines are oxidized by silver ion at a faster rate than the 1,4 derivative. From equilibration studies of N-methyl-1,2-dihydropyridine, Fowler\textsuperscript{61} estimates that the 1,4 isomer of this system is more stable by a difference of 2.3 kcal/mole.

In general\textsuperscript{62} electron withdrawing substituents, capable of resonance interaction (COR, CO\textsubscript{2}R, CN, NO\textsubscript{2}) in the 3 and/or 5 position, stabilize dihydropyridines by extending the conjugation. Substituents in the same positions but that donate electrons by resonance (SC\textsubscript{6}H\textsubscript{5}, OC\textsubscript{6}H\textsubscript{5}) have a destabilizing effect. Alkyl substitution on nitrogen as well as in the 3 and 5 positions have the same destabilizing effect. A glucosyl substituent on the nitrogen appears to have a remarkable stabilizing influence. Polycyclic or otherwise highly substituted dihydropyridines seem to be less reactive, probably due to steric factors.

There are several patents\textsuperscript{63} that claim the use of stable, low toxicity dihydropyridines as antihypertensives and in the treatment of circulatory and cardiac disorders. The compounds
used consist of hindered 1,4 dihydropyridines with electron withdrawing groups on nitrogen as well as in the 3 and 5 positions (18 in Diagram 32). Another example of a stable dihydropyridine is the NADPH enzyme which is involved in several important biological oxido-reduction reactions. A part of this enzyme is constituted by an N-ribofuranosyl-1,4-dihydropyridine with an amide group at the 3 position (19 in Diagram 32).

DIAGRAM 32

Stable Dihydropyridines
In general dihydropyridines are very reactive intermediates which oxidize very easily. Eisner and Kuthan classify the oxidation of this type of compounds in three ways:

1) **Dehydrogenation**, where a one or two electron transfer takes place. There are a wide variety of oxidizing reagents that can cause this type of reaction: $\text{O}_2$, $S_8$, $\text{NO}_2$, $\text{HNO}_3$, $\text{H}_2\text{O}_2$, $\text{AgNO}_3$, $\text{I}_2$, $\text{Hg(OAc)}_2$, etc. Again, little work has been reported on the correlation between structure and ease of oxidation. The relative rates of dehydrogenation decrease with the substituents in the 3 position in the order: $\text{CONH}_2 > \text{CO}_2\text{Et} > \text{COCH}_3$, and with substituents at N in the order $\text{OCH}_2 > \text{Cl}_2\text{OCH}_2 > \text{OCH}_2$.

2) **Hydrogen Transfer**, where a hydrogen is transferred from a dihydropyridine to an acceptor, as a free radical or a hydride, the latter being the more common. For this reaction, several hydride acceptors have been utilized, for example: maleic acid, pyruvic acid, hexachloroacetone, $\alpha,\beta$-unsaturated ketones, etc.

3) **Disproportionation**, where the dihydropyridine, in acidic media, is both a donor and an acceptor of hydrogen.

These three modes of dihydropyridine oxidation are exemplified in Diagram 33.
DIAGRAM 33

Oxidation of Dihydropyridines

1) Dehydrogenation

\[
\text{Oxidation of Dihydropyridine} \rightarrow \text{Pyridine}
\]

Ref. 65

2) Hydrogen Transfer

\[
\text{Amine + Chlorosulfonic Acid} \rightarrow \text{Pyridine}
\]

Ref. 66

3) Disproportionation

\[
\text{Pyridine} \xrightarrow{\text{H}^+} \text{Pyridine} \quad \text{Pyridine} \xrightarrow{\text{Nucl.}} \text{Tars}
\]
Besides the disproportionation reaction, the protonated dihydropyridine (20) can be attacked by a variety of nucleophiles (Nucl.= H^−, Cl^−, MeO^−, CN^−, Ø5), or polymerized (see bottom of Diagram 33). This is one of the reasons why reactions using these sensitive compounds, yield, in general, several products and a fair amount of tars. However, there are examples where this reaction between derivatives of (20) and nucleophiles has been successfully utilized in the synthesis of indole alkaloids (see example in the upper part of Diagram 34).

Although dihydropyridines could be considered as diene-amines (homoannular type), and therefore should behave as such in functionality, there have not been any reports on C-alkylation (a typical reaction of diene-amines^67) of these pyridine derivatives^68. However, N-lithiated-1,2-dihydropyridine (21) has been successfully alkylated and functionalized with a wide variety of reagents (see bottom part of Diagram 34). The C versus N functionalization of these dihydropyridines depends upon the type of reagents used.

Some examples of Diels-Alder reactions between 1,2 dihydropyridines and several dienophiles (maleic anhydride^73, N-phenylmaleimide^74, methyl vinyl ketone^75,76 and acrylonitrile^76) have been reported. In all cases, the dihydropyridine...
DIAGRAM 34

Some Dihydropyridine Reactions

Ref. 69

Ref. 70

Ref. 71

Ref. 72
pyridine has been stabilized by electron-withdrawing groups (-CN, -CO₂R or -CONH₂).

Apart from one unsupported statement⁷⁷ that N-phenyl-1,2-dihydropyridine adds to dimethyl acetylene dicarboxylate in a Michael fashion, there are no reports of this type of reaction by dihydropyridines in the literature.

There are three main general synthetic routes for the preparation of dihydropyridines: a) cyclization of acyclic starting materials (Hantzsch synthesis); b) nucleophilic additions to pyridine and pyridinium salts and c), thermal rearrangement of other ring systems.

The original Hantzsch dihydropyridine synthesis consisted of the reaction between ethyl acetoacetate and an aldehyde in the presence of ammonia (or ammonium salt), yielding the 1,4 dihydropyridine (22) shown in Diagram 35. The aldehyde reacts with two molecules of the enamine formed between the β-keto ester and ammonia. Cyclization of the resulting molecule with elimination of ammonia gives the 1,4 dihydropyridine.

Several modifications to the Hantzsch synthesis have been reported (the use of β-diketone, β-ketonitriles, their enamine
Hantzsch's synthesis is a very versatile and high-yielding reaction, used mainly for the preparation of 1,4 dihydropyridines. There are few examples where a 1,2 dihydropyridine is formed instead. In general these compounds are produced when the aldehyde is substituted by a ketone or when the nitrogen source is a primary amine (Diagram 36). In these cases, it is more likely that a different mechanism prevails.

Nucleophilic attack on the pyridine ring is another efficient method of preparing dihydropyridines, especially if the more electrophilic pyridinium salt is employed. This last compound has electrophilic positions at the 2-, 4-, and 6- carbon
atoms. Of these, the 2- and 6- positions are the more positive ones, because of their proximity to the quaternary nitrogen, therefore a nucleophile should attack preferentially at these two positions. However, the steric and electronic factors resulting from the type and location of substituents, as well as the nature of the nucleophile, are the real factors that govern the orientation of a nucleophilic attack on a pyridinium salt.

Borohydride reduction of pyridinium salts yields unstable dihydropyridines which have been detected spectroscopically.
These dihydropyridines are usually reduced further to tetrahydropyridine, since the solvent protonates them and the resulting iminium salt is reduced to the tetrahydro derivative (Diagram 37). In order to stop the reaction at the dihydropyridine stage, large concentrations of alkali have to be used.

DIAGRAM 37

NaBH₄ Reduction of Pyridinium Salts

Ref. 80
Lyle and Anderson\textsuperscript{80} established that in the reduction of pyridinium salts with NaBH\textsubscript{4}: \(a\) the attack of the hydride ion will occur preferentially at the carbon adjacent to the nitrogen (positions 2 and 6) if steric interference does not occur; \(b\) this attack will not take place if these positions are substituted or, at least, the rate will be greatly reduced; and \(c\) large substituents near the point of potential attack will direct attack towards more distant positions (i.e.: sugar residues attached at the 1-position favor hydride addition at the 4-position).

The influence of the type of pyridine substituents on the site of attack of a particular nucleophile, is exemplified in Diagram 38. Thus, reduction of N-tryptophyl-3-ethyl-pyridinium bromide (23), with NaBH\textsubscript{4} yields the 1,2-dihydropyridine\textsuperscript{81} (24) exclusively, but when an electron withdrawing group is in the 3-position, a mixture of 1,2 and 1,6 dihydropyridines (25, 26) results, the latter being the more predominant\textsuperscript{75,76}. Two additional examples are given in Diagram 38, where a different nucleophile is utilized\textsuperscript{82}.

The reaction between pyridinium salts and Grignard reagents\textsuperscript{83} or lithium dialkycuprates\textsuperscript{84} is a good illustration of the influence of nature on the nucleophile. In the case of Grignard reagents, a 1,2-addition occurs, whereas in the case
DIAGRAM 38

Orientation of the Nucleophilic Additions to Pyridinium Salts

\[ \text{Diagram depicting nucleophilic additions to pyridinium salts.} \]
of the cuprate derivative, a 1,4-addition is observed (Diagram 30). The behavior of these two reagents is the same as that reported for α,β-unsaturated carbonyl compounds, which are typical analogs for pyridines or pyridinium salts.85

DIAGRAM 39

Nucleophilic Reactions with Pyridinium Salts

\[
\begin{align*}
\text{Pyridine} & \xrightarrow{\text{ClCO}_2R} \text{Pyridinium Salt} & & \xrightarrow{\text{MgCl}} \text{Alcohol Derivative} \\
\text{NaBH}_4 & \xrightarrow{\text{Solvent}} \text{Pyridine} + \text{Pyridine Derivative} \\
\text{Solvent: THF} & \rightarrow \text{mixture of 28 and 29} \\
\text{MeOH,} & \rightarrow \text{only 29}
\end{align*}
\]
Another factor that has a definitive influence on the orientation of the nucleophilic attack is the solvent used in the reaction. For instance, Fowler reports\textsuperscript{73} that when (27) (Diagram 39) is treated with NaBH\textsubscript{4} in THF, a mixture of 1,2- and 1,4-dihydropyridines is formed but, if the reaction is performed in dry methanol, only the 1,2-isomer is formed.

The synthesis of dihydropyridines via the thermal rearrangement of other heterocyclic systems is not as versatile as the methods previously discussed, but has the great advantage that it leads to a specific dihydropyridine (1,2- or 1,4-isomer), as shown in Diagram 40. The main problem with this method is the difficulty of synthesizing the appropriate ring systems.

There is only one report concerning the protection of dihydropyridines\textsuperscript{88}. In that study it was observed that when a pyridinium salt was reduced with NaBH\textsubscript{4} in the presence of hydrogen cyanide, substituted 6-cyano-1,2,5,6-tetrahydropyridines (30) are formed in high yield. Treatment of these compounds with base regenerates the dihydropyridine, probably via the mechanism outlined in Diagram 41.

In 1967 Öfele reported\textsuperscript{89} the preparation of stable (dihydropyridine) chromium tricarbonyl complexes from the unstable
Dihydropyridines from Other Heterocyclic Systems

Dihydropyridine and chromium hexacarbonyl (31 and 32 in Diagram 41). This type of reaction could be a good way to trap and protect these reactive intermediates if the chromium complexes are really stable under a wide variety of reaction conditions and, if there is a mild method available to disengage the dihydropyridine as a ligand. All these questions need answers in order to claim that the formation of the dihydropyridine chromium complexes is a good way to protect these compounds.
DIAGRAM 41

Protection of Dihydropyridines

\[ \text{R} \quad \text{NaBH}_4 \quad \text{R} \]

\[ \text{CN} \quad \text{CN}^- \quad \text{CN} \]

\[ \text{30} \]

\[ \text{CH} \quad \text{CH}_3 \quad \text{Cr(CO)}_6 \quad \text{CH}_3 \quad \text{CH}_3 \quad \text{Cr(CO)}_3 \quad \text{CH}_3 \quad \text{CH}_3 \quad \text{Cr(CO)}_3 \]

\[ \Delta \]

\[ \text{31} \]

\[ \text{32} \]

\[ \text{33} \]
Another stable dihydropyridine metal complex (33 in Diagram 41) has been reported, where a method for decomplexation is given. However, this type of compounds have little synthetic use since the dihydropyridine employed is already stable.

This brief introduction to acrylic ester and dihydropyridine chemistry provides a basis for outlining the possible synthetic strategies for the preparation of 14,21-dehydrosecodine (1). As already mentioned, this substance, possesses a 1,6-dihydropyridine with two alkyl substituents at position 1 and 3 of the pyridine ring (besides the acrylic ester moiety). These alkyl substituents do not stabilize the dihydropyridine system, which means that the molecule will be very reactive and unstable.

Two schemes were envisioned for the synthesis of 14,21-dihydropyridine: A) construction of a protected acrylic ester, followed by the generation of the dihydropyridine and finally the removal of the acrylic ester protection (Diagram 42), or alternatively B) formation of a protected or trapped dihydropyridine and subsequent generation of the acrylic ester function, and liberation of the pyridine derivative (Diagram 43).

The two schemes shown in the Diagrams rely on the reduction of a pyridinium salt with NaBH₄. It has been reported that
in these conditions N-indolyl-3-alkylpyridinium salts give exclusively 1,2-dihydropyridines (see Diagram 38). If this is the case for the system being studied, following scheme "A", or route "a" of Scheme "B", will lead directly to the preparation of the isomeric 3,14-dehydrosecodine (35).
Scheme "B": Synthesis of Dehydrosecodine

DIAGRAM 43

Route a

Route b

36

37

38

39

40

35

1
Since there are no reports on the direct preparation of N,3-dialkyl-1,6-dihydropyridines, the only alternative is to use the thermal isomerization of dihydropyridine chromium complexes (route "b" in Diagram 43) reported by Öfele\(^\text{89}\) (see Diagram 41), with the hope of finding an efficient and mild method for removing the ligand from these stable and novel complexes.

If the chromium complexes are to be used with the dual purpose of protection of dihydropyridines and a method for preparing the 1,6-isomer, the following questions have to be answered:

1) Can the (dihydropyridine) tricarbonyl chromium complex be formed?
2) Will the indole moiety interfere with the complex formation?
3) Does the thermal isomerization occur in the system without too much decomposition?
4) Are the chromium complexes stable in the reaction conditions used for the formation of the acrylic ester segment?
5) Finally, and most important, is there a mild method for liberating the dihydropyridines that will not destroy them?

In order to answer all these questions and to develop the required methodology, it was decided to start the investigation
using a simple model, before going into more complicated systems. The model had to resemble the dehydrosecodine structure, that is, it had to have two alkyl substituents at positions 1 and 3 of the pyridine and, in order to simplify the spectroscopic identification of the products (especially NMR), they had to be different. On this basis the N-methyl-3-ethylpyridinium system (41) was chosen as our model.

As mentioned previously, the use of a strong basic medium in the reaction of pyridinium salts with NaBH₄ retards the over-reduction of the dihydropyridines, enhancing their stability and allowing their isolation in some cases. Moreover, the use of a two-phase system (ether - water), in which the pyridinium salt is reduced in a basic aqueous layer and then extracted from the reducing medium into an organic layer as soon as the dihydropyridine is formed, further lessens the chances of overreduction. Initial work performed by A. Zanarotti* concentrated on the generation of the dihydropyridine with no attempt at isolation and characterization of the reactive intermediates.

After several experiments with negative results, it was found that when N-methyl-3-ethylpyridinium iodide (41) is reduced with NaBH₄ in a vigorously stirred mixture of ethyl ether,

*1971-1972 Postdoctoral Fellow with Dr. James P. Kutney
methanol and 2.1N sodium hydroxide solution under an inert atmosphere, the U.V. absorption of the starting material at 266 nm. disappears in five minutes and then shows a new maximum at 327 nm. (that decreases with time), which corresponds to a dihydropyridine.

Treatment of a benzene solution of crude dihydropyridine (obtained in the manner described), with Cr(CO)$_6$, did not yield any of the expected chromium complexes. However when added to dry, freshly prepared trisacetonitrile-tri-carbonylchromium(0), (42), under an oxygen-free atmosphere of dry nitrogen, a deep red solution was formed. After 30 minutes of stirring at room temperature, the U.V. spectrum of the reaction mixture showed no dihydropyridine absorption (327 nm.) and only a new maximum at 400 nm. was observed. By TLC the reaction mixture showed three coloured spots. The less polar one had a yellow coloration and was identical to the acetonitrile chromium complex; the other two spots were red and very close together. By repetitive TLC these two compounds were separated, showing that the predominant one was the least polar. Preparative TLC followed by crystallization from benzene - hexane allowed the isolation of these two red compounds.

The minor component (43) of the mixture presented a U.V.
maximum at 403 nm. and three carbonyl absorptions at 1830, 1860 and 1942 cm\(^{-1}\) in the I.R. spectrum. Elemental analysis and the low resolution mass spectrum (m/e 259 (M\(^+\))) were consistent for a (dihydropyridine) tricarbonylchromium complex. NMR\(^*\) signals at 0.7 (triplet for 3H; J = 7Hz), 1.74 (quartet for 2H; J = 7Hz) and 1.44 (singlet for 3H), revealed the presence of an ethyl side-chain and an N-methyl group, respectively. The NMR spectrum showed a pair of doublets at 2.28 and 2.36 for two hydrogens forming an AB system (J = 10Hz), as well as a series of olefinic protons in the form of a doublet at 4.47 for two hydrogens (J = 5Hz) and a triplet (or doublet of doublets) at 4.98 for one hydrogen (J = 5Hz), (Figure 1).

The signals in the olefinic region form a typical AX\(_2\) pattern for a \(\frac{J}{\nu_A-\nu_B} = 0.1\) \(^92\). In this particular case, two olefinic protons (X) have the same chemical shift and the same coupling constant (\(J_{AX}\)) to the third olefinic proton (A), and become "accidentally equivalent" \(^93\). In general, because of low symmetry, compounds whose spectra exhibit "accidental equivalence" would not generally preserve this in different solvents. In the case described compound 43 could not be run in any solvent other than benzene, because of severe sample decomposition.

\(^*\)All chemical shift values will be given from here on in the \(\delta\) scale, which refers to tetramethylsilane as the internal standard.
FIGURE 1

NMR spectrum of (N-methyl-3-ethyl-1,2-dihydropyridine) tricarbonylchromium(0) complex (43) (C₆D₆)
This information leads to the conclusion that 43 is the (N-methyl-3-ethyl-1,2-dihydropyridine)tricarbonylchromium complex, where protons at 4, 5 and 6 (see Diagram 44) form the described AX\textsubscript{2} system (A = H\textsubscript{5}; X\textsubscript{2} = H\textsubscript{4}, H\textsubscript{6}) and the two hydrogens at position 2 give the AB quartet centered at \(\delta2.32\).

The major constituent (44) of the mixture of the two red compounds obtained in the complexation reaction has a maximum of 399 nm. by U.V. It also portrays three characteristic carbonyl signals by I.R., at 1825, 1860 and 1942 cm\(^{-1}\). Again, elemental analysis and low resolution mass spectrum (m/e 259 (M\textsuperscript{+})), are consistent for a dihydropyridine chromium complex.

Öfele reported\textsuperscript{89} that 1,4-dihydropyridines do not form complexes with chromium and the complexed 1,2-isomer has already been identified, therefore, compound 44 has to be the tricarbonylchromium complex, which possesses an N-methyl-4-ethyl-1,6-dihydropyridine as ligand. If this is true, then a downfield singlet in the NMR spectrum due to the olefinic proton at 2 (see Diagram 44), could be expected.

The NMR spectrum of 44 in deuterobenzene (Figure 2) showed a triplet at 1.12 (\(J = 7\text{Hz}\)) for three protons (\(-\text{CH\textsubscript{2}CH\textsubscript{3}}\)); and a singlet at 1.45 also for three protons (N-\textsubscript{CH\textsubscript{3}}). A complex
NMR spectrum of (N-methyl-3-ethyl-1,6-dihydropyridine) tricarbonylchromium(0) complex (44)(C₆D₆)
pattern is observed between 2.0 and 2.7, integrating for four hydrogens. The spectrum also shows a split triplet at 3.09, the expected singlet at 4.53 and a doublet ($J = 7$ Hz) at 4.83, all of which are integrated for one proton each.

The downfield doublet was assigned to $H_4$ and when doubly irradiated, only the triplet at 3.09 was affected (see Figure 3), allowing the assignation of this last signal to the hydrogen at position 5. Irradiation of this triplet caused $H_4$ to become a singlet. In any of these decoupling studies, the signals between 2.0 and 2.7 (which correspond to $H_{6,6}'$ and $-CH_2CH_3$) had a recognizable pattern, even when the methyl group at 1.12 was irradiated.

When the NMR spectrum was run using deuterochloroform as solvent (Figure 4), the methylene of the ethyl chain can be recognized as two quartets. When this solvent is used the $H_2$ and $H_4$ signals are reversed. The triplet due to $H_5$ is rapidly recognized but now forms what is probably an ABC system with $H_6$ and $H_6'$ (slightly simplified when the extra coupling with $H_4$ is eliminated) that has not been studied further.

The structures assigned to compounds 44 and 45 were confirmed by X-ray analysis.\textsuperscript{94,95} Although it has been reported\textsuperscript{89} that some isomerization of
Double resonance studies of complex 44 (C₆D₆)
NMR spectrum of (1,6-dihydropyridine) chromium complex

44 in CDCl₃
the dihydropyridines occurs during the complexation reaction, the fact that the predominant isomer obtained in this type of reaction was the 1,6-dihydropyridine, led to the conclusion that this pyridine derivative was also the predominant one in the reduction of the 3-ethyl pyridinium salt (41) with NaBH₄, which is contrary to expectations.

The only way to establish the degree of isomerization taking place in the system was to isolate and identify the products obtained in the reduction of the pyridinium salt or try to get some indirect information on the type of compounds formed.
This last alternative could be the overreduction of the N-methyl-3-ethyl pyridinium salt (41), since every isomeric dihydropyridine would lead to a different overreduced product (Diagram 45).

DIAGRAM 45

Overreduction of N-Methyl-3-ethylpyridinium with NaBH₄
Treatment of salt \( 41 \) with \( \text{NaBH}_4 \) in methanol gave a mixture of three compounds in a ratio of 15:2:1 by gas chromatography (G.C.). Using preparative G.C. purification the mixture's major component was isolated and identified as tetrahydropyridine \( 47 \), based on comparison of its spectroscopical data with data reported for that compound\(^9\).

The isolation of N-methyl-3-ethyl-3-piperideine (47) as the predominant product in the overreduction of the pyridinium salt \( 41 \) indicated that, contrary to expectations but in agreement with previously reported results\(^8\), the N-methyl-3-ethyl-1,2-dihydropyridine (46) is indeed formed during the reaction of salt \( 41 \) with \( \text{NaBH}_4 \), unless the tetrahydropyridine \( 48 \) rearranges during the reaction or the work-up, to form compound \( 47 \).

Since the fact that in the complexation reaction the predominant product contained a 1,6-dihydropyridine, but there was some evidence that the starting material for that particular reaction consisted mainly of the 1,2-isomer, was rather confusing, it was decided that a stable dihydropyridine would be prepared which, once purified and identified, could be transformed into the model system and later on be submitted to the complexation reaction. In order to do this, N-carbomethoxy-3-ethyl dihydropyridines were prepared, since it has been reported\(^7\).
that this type of substances are very stable, can be purified by column chromatography and when treated with LiAlH₄, give N-methyl dihydropyridines in high yield.

When 3-ethyl pyridine was treated in methanol with methyl chloroformate and NaBH₄ at -78°C, a single compound was obtained which, based on spectroscopic properties, was identified as N-carbomethoxy-3-ethyl-1,2-dihydropyridine (49).

Compound 49 has a U.V. maximum at 298 nm. and in the I.R. spectrum shows an absorption at 1700 cm⁻¹, that corresponds to the N-carbomethoxy group. The NMR spectrum shows typical signals for the ethyl chain, 1.07 triplet (J = 7); 2.03 quartet (J = 7); and a singlet at 3.75, due to the methoxy group. Signals at 4.21 (quartet; 2H; J = 1Hz); 5.02 (doublet of doublets; 1H; J = 6Hz); 5.52 (doublet; 1H; J = 6Hz) and 6.53 (broad doublet; 1H; J = 6Hz) were attributed to H₂,₂', H₅, H₄ and H₆, respectively, based on double resonance studies done with the molecule (Figures 5 and 6).

Around that time Dr. R. Greenhouse* was studying the reduction of the pyridinium salt 41 with NaBH₄ in the two-phase system. He found that if some precautions were taken (especially no

---

1973-1974 Postdoctoral Fellow for Dr. James P. Kutney
FIGURE 5

NMR spectrum of N-carbomethoxy-3-ethyl-1,2-dihydro-pyridine (49) (C₆D₆)
Double resonance studies of 49
exposure to air), a transparent, thick oil could be isolated from the organic layer after 5 minutes of reaction. This oil had a U.V. absorption maximum at 327 nm., that corresponds to a dihydropyridine. This was confirmed by mass spectroscopy, since this oil has a parent peak at 123 that corresponds to a molecular formula of $C_8H_{13}N$. The compound isolated in the reduction reaction was identified as N-methyl-3-ethyl-1,2-dihydropyridine (46) based on the NMR spectrum (Figure 7) and double resonance studies. As can be seen in the Figure, the NMR resembles the spectrum of N-carbomethoxy-3-ethyl-1,2-dihydropyridine (49), with the difference that the signals for $H_2$ and $H_6$ are higher field, which is to be expected when going from an N-carbomethoxy to an N-methyl group. Further confirmation of compound 46's structure was obtained when N-carbomethoxy-3-ethyl-1,2-dihydropyridine was treated with LiAlH$_4$ to yield a compound that has the same spectroscopic properties as compound 46 (see Diagram 46).

It is interesting to note that the 1,2- and 1,6-dihydropyridine chromium complexes have the same fragmentation pattern as the N-methyl-3-ethyl-1,2-dihydropyridine, once the elements of Cr(CO)$_3$ have been eliminated in the ionization chamber (Diagram 46).

Knowing that the reduction of N-methyl-3-ethyl-pyridinium iodide with NaBH$_4$ yielded only the 1,2-dihydropyridine isomer, it was
FIGURE 7

NMR spectrum of N-methyl-3-ethyl-1,2-dihydropyridine

(46) (C₆D₆)
DIAGRAM 46

Mass Fragmentation Pattern of N-Methyl-3-ethyl-1,2-dihydropyridine and Its Chromium Complex
obvious that the isomerization to the 1,6-derivative was occurring only during the complexation reaction. This reaction was repeated several times and it was observed that the ratio of the two isomers was not constant. This indicated that the degree of isomerization must depend on some experimental conditions that were not properly controlled.

When a solution of the 1,2- or 1,6-dihydropyridine chromium complex in cyclohexane was refluxed under inert atmosphere, a 1:1 mixture of the two isomers was obtained. The thermal isomerization was followed by NMR (iterative integration of the triplet at 4.98 due to $H_5$ of the 1,2 isomer, and the triplet at 3.98 for $H_5$ of the 1,6-derivative), and it was observed that the 1:1 ratio is obtained after refluxing the solution for 7 hours.

Using this thermal isomerization of the chromium complexes, the ratio of isomer obtained in the complexation reaction becomes a minor problem since, independently of which of the isomers predominates, it can always be converted into a 1:1 mixture.

The two chromium complexes decompose very slowly on exposure to air at room temperature (up to two weeks for total decomposition). They are soluble in most organic solvents but in pyridine or DMSO, they decompose very rapidly. The
same thing happens only to the 1,2-dihydropyridine complex when it is dissolved in halogenated solvents. They are very stable to basic media, decomposing rapidly in acidic ones. The dihydropyridine complexes do not react with NaBH₄ or sodium hydride, which are the reagents used in one of the methods for preparing acrylic esters.

Once the preparation of the dihydropyridine chromium complexes was achieved and their chemical and physical properties were known, the studies related to the liberation of the dihydropyridine from the complexes were initiated.

There are two general methods for disengagement of organic ligands from metal complexes: 1) oxidation of the complex or 2) substitution of the ligand for another one. For the dihydropyridine complexes, the first method has the disadvantage that the oxidant used for the metal will also oxidize the free dihydropyridine. The second method will not destroy it although the possibility exists that the dihydropyridine will isomerize whilst being freed.

When the (N-methyl-3-ethyl-1,2-dihydropyridine)triscarbonyl chromium complex was treated with triphenylphosphine or triphenylphosphite in cyclohexane, it was recovered intact after 24 hours of stirring at room temperature. When more
vigorous conditions were used (reflux), a 1:1 mixture of the two isomeric complexes was obtained. The U.V. spectrum of the reaction mixture did not show any absorption for the free dihydropyridine (327 nm.). However, when this complex was treated with pyridine in cyclohexane or N-pentane under nitrogen atmosphere, an orange compound precipitated out of the solution. After four hours of reaction the U.V. spectrum of the reaction mixture showed that some dihydropyridine was being liberated but a fair amount of starting material (400 nm.) was still present. After 24 hours of reaction the starting chromium complex was completely consumed. At this time, the reaction mixture was filtered and the solvent evaporated under reduced pressure, yielding an oil that, by NMR, was identical to N-methyl-3-ethyl-1,2-dihydropyridine (46), without contamination of any other compound except for some pyridine.

When the corresponding 1,6-dihydropyridine chromium complex was treated with pyridine in the manner described, N-methyl-3-ethyl-1,6-dihydropyridine (51) was obtained in high yield. This compound has a U.V. maximum at 332 nm.; the NMR (Figure 8) shows the triplet and quartet of the ethyl group at 1.02 and 1.98 respectively; the N-methyl group appears as a singlet at 1.98. Based on splitting patterns of the signals as well as on double resonance studies, the rest of the
NMR spectrum of N-methyl-3-ethyl-1',2-dihydropyridine
signals were assigned as follows: the doublet at 3.50 
(J = 4Hz) corresponds to H₆,6′; H₅ appears as a doublet 
of triplets at 5.18 (J₄,5 = 8Hz, J₅,6 = 4Hz); the signals 
for H₂ and H₄ are shown as a broad singlet and a doublet 
(J = 8Hz) at 5.52 and 5.58, respectively.

Once the necessary methodology for preparing and handling 
unstable dihydropyridines was known and, given the scattered 
information of the reactions of this type of compounds, it 
was important to study some of their chemical properties, 
especially those reactions that supposedly occur with dehydro­
secodine (1) during the biosynthesis of indole alkaloids.

Attempts to alkylate N-methyl-3-ethyl-1,2-dihydropyridine 
with allyl or benzyl bromide in benzene, followed by reductive 
work up (NaBH₄), yielded very complex reaction mixtures that 
could not be separated. One reason that so many products 
were encountered in these reactions is that the iminium salt 
(52) initially produced on alkylation (see Diagram 47) is 
itself an electrophile, capable of alkylating another dihydro­
pyridine. Modification of the reaction conditions such as 
addition of a diluted solution of dihydropyridine to a large 
excess of benzyl bromide, did not improve the results of the 
alkylation reaction.

In order to eliminate all undesired products it is necessary
to trap the iminium salt formed upon alkylation before it has a chance to react further. A similar system to the one used for the reduction of pyridinium salts to tetrahydro-pyridines could be used, where a large excess of NaBH$_4$ is added to the reaction mixture in order to reduce the pyridinium salt as well as the iminium salt produced by protonation of the resulting dihydropyridine (see Diagram 37). If these conditions were to be used there is a possibility of competition between alkylation versus protonation of the reactive diene-amine system. However this last process can be reduced if a large excess of alkylating reagent (benzyl bromide) and a two-phase system (ether - water) is used, given that the dihydropyridine will be present primarily in the organic phase, that is where the benzyl bromide is dissolved. Furthermore the same conditions (benzyl bromide added) used for the generation of dihydropyridines can be utilized (two-phase system consisting of aqueous sodium hydroxide, methanol, ether and NaBH$_4$ to which the pyridinium salt is added), eliminating the need for the isolation of these intermediates since the following sequence of events takes place (Diagram 47):

1. The pyridinium salt (41) enters the aqueous layer and is reduced to the corresponding dihydropyridine which is transferred to the organic layer.
2. The dihydropyridine is alkylated to give a water-soluble iminium salt (52) which leaves the ether layer.
3. In the water layer the salt 52 is reduced with borohydride, after which the tetrahydropyridine 54 thus formed is extracted into the ether.

4. The tetrahydropyridine 54 will either remain in the upper phase or be alkylated a second time with the remaining benzyl bromide to form a water soluble quaternary ammonium salt (53) which is then transferred to the lower aqueous phase.

When N-methyl-3-ethyl-pyridinium iodide was added to the two-phase system mentioned (ten-fold excess of benzyl bromide) a salt-type material (53) was isolated after three hours of reaction from the aqueous layer. This compound came from the 3-ethyl pyridine system since the ethyl chain could be recognized very easily in the NMR spectrum. Moreover, the presence of an olefinic proton at 5.71 and two sets of aromatic protons at 7.26 and 7.41 suggested a doubly benzylated tetrahydropyridine. The presence of a singlet at 4.53 for two hydrogens, as well as a downfield N-methyl signal (3.08) was the reason for allocating one of the benzyls to the nitrogen, forming a quaternary ammonium salt with the methyl group.

When the salt material obtained in the reaction described was treated with lithium propyl mercaptide in HMPA98 a
DIAGRAM 47

Alkylation of N-methyl-3-ethyl-1,2-dihydropyridine
selective N-debenzylation took place yielding an N-methyl tetrahydropyridine with a benzyl group still attached to the ring.

If dihydropyridines behaved as normal diene-amines a \( \beta \)-benzylation should take place which, after reduction, would give compound 54 (Diagram 47) but, being a homoannular system it may happen that a \( \delta \)-attack is preferred, in which case tetrahydropyridine 55 (Diagram 47) will be formed. The fact that the compound obtained in the debenzylation reaction shows only one olefinic proton in the NMR, rules out the possibility of a \( \delta \)-attack, in which case two olefinic hydrogens should be present.

When the alkylation reaction was done using only a two-fold excess of benzyl bromide a mixture of N-methyl-3-ethyl-5-benzyl-1,2,5,6-tetrahydropyridine (54; 10%) and its corresponding N-benzylated salt 53 (R = \( \mathcal{OCH}_2^- \); 20%) was obtained, plus a second quaternary ammonium salt that was identified as N-methyl-N-benzyl-4-ethyl-1,2,5,6-tetrahydro pyridinium salt (53, R = H; 50%), by direct comparison with an authentic sample obtained from the reaction between the tetrahydropyridine 47 and benzyl bromide. The yield of salt 53 (R = H) could be as high as 80% if a less reactive alkylation reagent
(benzyl chloride) was used.

It can be argued that the possibility of a δ-attack on the diene-amine system cannot be ruled out completely under the circumstances that in the particular model system used (N-methyl-3-ethyl), there is a substituent in that same position inhibiting (for steric reasons) the chance of such an alkylation.

To observe the influence that a substituent at the alkylation site could have on the alkylation of dihydropyridines, the reaction was repeated, using N-methyl-3,5-lutidinium iodide (56). In this case the only product isolated from the reaction mixture was N-methyl-3,5-dimethyl-5-benzyl-1,2,5,6-tetrahydropyridine (57 in Diagram 48) in about the same yield (48%) as the previous alkylation reaction.

The method described for the alkylation of dihydropyridines yields very clean, easy to work-up reaction mixtures, demonstrating that this type of system is alkylated in the β position even if there is an alkyl substituent at that position. All this indicates that the homoannularity of diene-amine does not induce abnormal behaviour for the alkylation of this functionality.
Some preliminary work on the Diels-Alder reaction of Dihydropyridines with acrylic derivatives was done by Dr. Greenhouse. He found that when N-methyl-3-ethyl-1,2-dihydropyridine was refluxed in the acrylonitrile the predominant product obtained was a 1:2 adduct of the dihydropyridine with two molecules of acrylonitrile. Small amounts of a 1:1 adduct that could correspond to the Diels-Alder product were also isolated. Neither of these two products were fully characterized since it was decided at this time to put aside the model system and continue with the research related to the synthesis of dehydrosecodine.

The next problem was to see if an indole side chain in the pyridine ring, interfered with the complexation reaction. To resolve this, N-tryptophyl-3-ethyl-pyridinium bromide (58), prepared from 3-ethyl-pyridine and tryptophyl bromide, 100,
was reduced with NaBH$_4$ in the same manner as the model compound. The UV spectrum of the ether layer after five minutes of reaction showed a maximum at 336 nm. that corresponded to the dihydropyridine, as well as the typical signals for the indole system (290, 283 and 220 nm.). When this ether solution was added to the dry trisacetonitriletricarbonyl chromium(0) complex, a red gum was isolated in 20% yield, by preparative TLC. This gum had UV (402, 290, 283 and 220 nm.), IR (1945, 1865 and 1830 cm$^{-1}$) and MS spectra (388 (M$^+$)) for C$_{20}$H$_{20}$N$_2$O$_3$Cr that were consistent for (N-tryptophyl-dihydropyridine)tricarbonylchromium complex. Although this compound showed only one spot by TLC, the NMR spectrum indicated that it consisted of a mixture of the two dihydropyridine isomers. Separation of the two isomers was achieved by preparative TLC using a solvent mixture of low polarity and repetitive developments at the cost of losing a lot of the material, due to sample decomposition.

By NMR (Figure 9) the less polar dihydropyridine complex (59) of the N-tryptophyl series was identified as the 1,6-isomer since it presented the same signal pattern between 63 and 5 for the protons at 2, 4 and 5 of the pyridine ring as the same isomer (43) of the N-methyl series (compare Figures 2 and 9). As in this last compound, compound 59 also presented
NMR spectrum of (N-tryptophyl-3-ethyl-1,6-dihydropyridine) tricarbonyl-chromium(0) complex (59)
a complex pattern for the two hydrogens at position 6 and the methylene of the ethyl side chain, that was even more difficult to recognize because of the presence of signals for the ethylene part of the tryptophyl group.

The NMR spectrum of the (N-tryptophyl-3-ethyl-1,2-dihydropyridine)tricarbonylchromium complex (60) (Figure 10) shows some dissimilarities when compared with the spectrum of the 1,2-dihydropyridine complex (44) obtained from the N-methyl pyridinium salt. These differences are:

1. H\textsubscript{2} and H\textsubscript{4} are no longer "accidentally equivalent" as with the N-methyl derivatives; they appear now as a distorted triplet at 4.68.

2. The AB quartet present in the N-methyl series for the two protons at position 2 of the pyridine ring, becomes a broad singlet at 2.68 in the N-tryptophyl derivative.

This last change is an indication that the conformation of the tryptophyl moiety of this complex is such that the indole part, together with the chromium, forms a type of "sandwich" with the dihydropyridine located between the two parts. The same phenomenon must occur with the N-
FIGURE 10

NMR spectrum of (N-tryptophyl-3-ethyl-1,2-dihydropyridine) tricarbonyl-chromium(0) complex (60)
tryptophyl-1,6-dihydropyridine chromium complex, although the evidence is not as clear as in the case just discussed.

The results obtained up to now answer positively all the questions related to the use of the chromium complexes as a method for trapping and protecting dihydropyridines. In spite of not having optimized the complexation reactions, it was decided to move on to the synthesis of dehydrosecodine, as outlined in Diagram 43 (route b), and try to increase the yield of the complexation reaction in this series. In order to obtain the pyridinium salt 36, the indolyl chloride 65 (Diagram 49) or tosylate 67 must be prepared. There are several methods reported in the literature for the preparation of this type of compounds, however the one reported by Wenkert is the most convenient because it is a high yielding sequence of reactions (Diagram 49) that can easily be scaled up without too many complications.

The required starting material (2-carboxytryptophol lactone 61) used for the synthesis of chloride 65, was prepared from δ-butyrolactone following the work reported by Plieninger. The lactone 61 was opened with dimethylamine in methanol at room temperature to give the corresponding carboxyamido-tryptophol derivative 62. By reduction of this amide
Scheme for the Synthesis of 2-Carbomethoxy-methyltryptophyl Chloride (65)
with LiAlH$_4$, followed by treatment with methyl iodide, the quaternary ammonium salt 63 was obtained in 67% overall yield from lactone 61. Reaction of the methiodide 63 with potassium cyanide in refluxing acetonitrile gave a high yield (90%) of the nitrile 64. Treatment of this material with a saturated solution of hydrogen chloride in methanol converts the nitrile functionality into a carbomethoxy group and the alcohol into the chloride 65, after stirring the solution at room temperature for three days. To try to speed up this reaction the solution was heated, but this resulted in a mixture of compounds 65 and 66.

Condensation of 65 at 80°C with 3-ethyl pyridine gave the corresponding N-tryptophyl pyridinium salt 36, isolated as the perchlorate salt after a quick purification by column chromatography (Alumina grade V). Salt 36 can also be obtained from the spiro-compound 66 and a mixture of 3-ethyl pyridine and its hydrochloride salt. In this case, the hydrogen chloride present in the reaction mixture opens the cyclopropyl ring to yield the tryptophyl derivative 65, which then reacts with the pyridine to form the salt.

Before proceeding with the sequence of reactions portrayed in Diagram 43, some studies had to be done in relation to the
reaction conditions to be used for the generation of the dihydropyridine 37 (Diagram 43) since there were literature precedents\textsuperscript{105} that established that similar pyridinium salts under mild alkaline conditions (NaHCO\textsubscript{3}) form dihydropyridines via an intramolecular condensation (Diagram 50).

**DIAGRAM 50**  
Intramolecular Condensation of N-(2-cyanomethyl-tryptophyl) pyridinium

The possibility of a similar condensation to the one just described had to be studied for the pyridinium derivative 36 because in the two-phase system used for the generation of the dihydropyridine, strong alkaline conditions are employed in order to prevent the formation of tetrahydropyridines. The U.V. spectrum of the pyridinium salt 36 shows the absorption maxima corresponding to the indole moiety (219, 280 and 289 nm.) plus the absorption for the pyridinium part
at 265 nm. Upon addition of a 2N solution of sodium hydroxide to the U.V. cell, the spectrum remained unchanged even after a period of 30 minutes. However, when some crystals of NaBH\(_4\) were added, the maximum due to the pyridinium segment disappeared in about ten minutes and a new absorption at 327 nm. (dihydropyridine) was then observed. This qualitative experiment quickly gives an indication that, if the intramolecular condensation takes place, it occurs at a slower rate than the reduction of the pyridinium system.

With this information on hand a complexation experiment was set using the two-phase system for the generation of the dihydropyridine and then the normal procedure for the formation of the chromium complexes. The results obtained were not very good since, besides the expected red coloured compounds, the TLC showed several spots as well as a fair amount of baseline material. The purification of the reaction mixture was aimed at the isolation of the dihydropyridine complexes only. After several separations by column chromatography and preparative TLC, a few milligrams of the desired red material were isolated. The NMR spectrum of this material was complex, indicating a mixture of at least two isomeric dihydropyridine complexes. The IR and low resolution mass spectra were consistent with the desired type of dihydropyridine chromium complexes.
Several modifications to the complexation technique were tried with essentially the same results. The mixture of dihydropyridine complexes isolated from all these experiments were combined and the separation of the two isomers was done using preparative TLC. As in the case of the N-tryptophyl dihydropyridine series, there was severe decomposition of the sample and no clean separation of the complexes was achieved. Still, the less polar component of the mixture was pure enough to identify it as the 1,6-dihydropyridine complex (40 in Diagram 43) based on the characteristic splitting pattern that this kind of isomer presents in the NMR spectrum: doublet and a singlet in the region between δ4.5 and 5.00 for the hydrogen at position 2 and 4 and a triplet around 4.2 for the hydrogen at 5. The U.V. spectrum of the other red compound isolated from the mixture had the indole absorption, plus one at 401 nm. that corresponded to a dihydropyridine chromium complex. It was assumed that this complex had the 1,2-dihydropyridine as ligand (39, Diagram 43) although a positive identification could not be done due to the small amount isolated (less than 2 mg.).

The low yield obtained in the complexation reaction, considering that the acrylic segment still had to be built, was one of the reasons for which the synthetic scheme was changed. The new scheme chosen was a combination of the one outlined
in Diagram 42 and the one followed up to now, that is, half construction of the acrylic ester (34) moiety followed by the preparation of the dihydropyridine chromium complexes and finally formation of the acrylic ester and liberation of the dihydropyridine from the chromium complex. These last two reactions could be done stepwise or perhaps be performed at the same time. In this way, even if the complexation reaction yield is still low it is almost at the end of the synthesis (Diagram 51).

**DIAGRAM 51**

Scheme "C" for the Synthesis of 14,21-Dehydrosecodine (1)
For this new approach to the synthesis of 14,21-dehydro-secodine it was necessary to answer two questions:

1. Which substrate is the most appropriate to do the homologation reaction of the acetic ester derivative (introduction of a \(-\text{CH}_2\text{-X}\) unit, refer to Diagram 24, route A), and

2. What kind of building unit (nature of X) was most useful for the partial synthesis of the acrylic ester.

From the compounds already synthesized, three of them could be utilized as substrates for the homologation: 2-cyano-methyl tryptophol (64), 2-carbomethoxymethyl tryptophyl chloride (65), and the pyridinium salt 36. This last compound was disregarded because of solubility problems. The possible use of the chloro-ester 65 was also eliminated because previous experience with this compound\(^{102}\) has shown that under strong basic conditions it is converted into the spiro-cyclopropyl-indole derivative 66.

The cyano derivative 64, besides the active methylene group, has two acidic hydrogens (\(\text{>NH}, \text{-OH}\)) that perhaps could interfere with the homologation reaction. To eliminate this possibility, these two positions were protected as the benzyl
derivatives, as shown in Diagram 52.

When the indole lactone 61 was treated with potassium hydride in HMPA, the N-benzyl derivative 68 was obtained in 70\% yield after purification by column chromatography. Opening the lactone with dimethylamine yielded the amide 69, which, upon treatment with benzyl bromide in the same conditions mentioned before, gave the dibenzyl amide 70. This compound can also be obtained from N,N-dimethyl-2-carboxamido-tryptophol (62 in Diagram 49) using two equivalents of potassium hydride and benzyl bromide, however, the product obtained in this way is not as pure as when the method described earlier is employed.

**DIAGRAM 52**

*Synthesis of (N-Benzyl-2-carbomethoxymethyl-indolyl)-benzyl Ether (72)*
Treatment of compound 70 with LiAlH₄ followed by direct treatment, without purification, of the resulting dimethyl amine derivative (7₃ in Diagram 53), with a large excess of methyl iodide gave the corresponding methiodide salt in only 40% yield. Reaction of this salt with potassium cyanide in refluxing acetonitrile gave a high yield of the nitrile 71 which was solvolysed to the methyl ester 72 in 70% yield.

Reinvestigation of reduction of the amide group with LiAlH₄ indicated that a mixture of two compounds was obtained possessing the same polarity on the TLC plate. One of them reacted with methyl iodide to give the methiodide salt previously described but the other remained in the reaction mixture. After removal of the salt, this compound was isolated and identified as (N-benzyl-2-carbinol-tryptophyl)-benzyl ether 7₄ (Diagram 53). Contrary to what happened in the reduction of the amide 6₂ (Diagram 49), that yielded only the amine derivative, the amide in 7₀ was reduced to the corresponding alcohol and amine. These two compounds were separated by preparative TLC and fully characterized. By iterative integration of the NMR spectrum signals for the methylene of the benzyl groups attached to the indole nitrogen, it was found that the alcohol 7₄ was the predominant product of this reduction reaction by a ratio of 6:1.
DIAGRAM 53

Reduction of 2-N,N-Dimethylcarboxamidoindole Derivatives with LiAlH₄

70 R = CH₂φ
69 R = H

73 R = CH₂φ  R' = N(CH₃)₂
74 R = CH₂φ  R' = OH
75 R = H  R' = N(CH₃)₂
76 R' = CH₂φ  R' = H

77

R = H or CH₂φ

78

79

80 R = N(Et)₂
81 R = OH
It has been reported in the literature\textsuperscript{106} that the reduction of amides with LiAlH\textsubscript{4} preferentially yields the corresponding amine but, depending on steric and electronic factors, as well as on the nature of the reducing agent, the alcohol or a mixture of this and the amine, is obtained instead.

For the case under discussion, there is an amide that behaves normally (62) but when the hydroxy group and the nitrogen of the indole of this molecule are benzylated (70), the amide functionality behaves differently. Of the two modifications done with compound 62 the one most likely to be responsible for the abnormal behaviour of the amide group in 70, is the one that affects the indole nucleus (N-benzyl-\textit{ation}). If this assumption is correct the amide 69 (Diagram 53) would give a mixture of alcohol and amine. Treatment of this amide in the same manner as the two previous compounds resulted in a high yield conversion to the amine 75 exclusively.

With all these results on hand it was clear, although not understood, that what was affecting the reduction of the amide was whether a free alcohol was present in the molecule or not. It was realized that if the free alcohol was present it would react very rapidly with LiAlH\textsubscript{4} forming an aluminate derivative that could be considered as changing the nature of the reducing agent, reacting with the amide group in an inter- or intra-molecular fashion. If this is what really
occurs in the reduction of this type of amides, then there is a possibility that when the dibenzylated amide 70 is treated with a similar type of reducing agent, the dibenzylated amine 73 will be formed preferentially. When 70 was added to a solution of LiAlH$_4$ in anhydrous THF, previously treated with one equivalent of n-butanol, a mixture of alcohol 74 and the amine 73 was again obtained but now, this last compound was the predominant one by an 8:1 ratio.

To complete the studies of the reduction of this type of amide it was necessary to prepare a derivative of 62 (Diagram 42) where the nitrogen of the indole is free and the alcohol is protected as the benzyl ether (2-((N,N-dimethyl carboxamido)-tryptophyl-benzyl ether). This compound was more difficult to synthesize than expected, since when 62 was treated with only one equivalent of benzyl bromide in basic conditions, the N-benzyl, free alcohol, dimethyl amide 69 was formed exclusively. No other type of approach for the preparation of the desired benzyl ether was attempted and the synthesis of this compound was eventually abandoned.

Searching for another amide that would fail to give the normal reduction product, it was thought that perhaps compound 77 would give a mixture of alcohol and amine, when treated with LiAlH$_4$. However, this was not the case, since in both series
(R = H or R = benzyl), the N,N-dimethyl amine 78 was the only product isolated from the reaction mixture. The only tertiary amide that has been reported in the literature that has an abnormal behaviour when reduced with this type of hydride is the N,N-diethylbenzamide \( (79) \)
\(^{107} \) that yields a 1:1 mixture of benzyl alcohol (81) and diethylbenzyl amine (80). This amide was converted exclusively to the amine 80 when treated with LiAlH\(_4\)–n-BuOH (one equivalent) in the same conditions.

A type of amide (70) was accidentally found that has very peculiar chemical properties, not only in the reduction with LiAlH\(_4\) but also when it is reduced with diborane\(^{106} \). In this case a mixture of the dimethyl amine derivative 73 and the fully reduced product 76 was obtained in a 3:1 ratio.

Once the problem in the reduction of amide 70 was solved, the yield in the formation of the amine 73-methiodide salt was increased up to 80%, just by treating the crude product from the reduction with an excess of methyl iodide. Attempts to incorporate the reduction by-product, alcohol 74, into the synthesis of the dibenzyl nitrile 71 by treating the corresponding benzoate or p-bitrobenzoate with potassium cyanide failed, mainly due to the formation of
several reaction products that made this approach unattractive.

Coming back to the original problem of forming a partially synthesized acrylic ester, two methods were studied where the ester 72 was used as the substrate, instead of the nitrile 71, as originally planned. The first method was the synthesis of the enamine 85 (Diagram 54) which could be converted to a protected acrylic ester-type substance, upon reduction with cyanoborohydride, to the corresponding amine, or it could remain as such and be transformed into the acrylic ester segment, once the chromium complexes were formed. The other method investigated was the formylation of 72 to form the enol 87. In this case the enol functionality must remain as such and be protected as methyl enol ether (or some other type of protection), because:

1. the free enol is reduced with NaBH$_4$ and this will interfere with the reduction of the pyridinium salt;

2. the reduction of the enol to the corresponding alcohol will interfere with the formation of the pyridinium salt since, once the benzyl groups are removed, a molecule with two primary alcohols will be obtained and it will be difficult to functionalize only one of them.
Homologation Reactions in Acetic Ester Derivatives

82 \[ \text{CO}_2\text{CH}_3 \] \[ \text{CO}_2\text{CH}_3 \] \[ \text{CO}_2\text{CH}_3 \]

83

84

85 \[ X = (Z)\text{N}(\text{CH}_3)_2 \]

86 \[ X = \text{H} \]

87 \[ X = \text{OH} \]

88 \[ X = R = \text{OH} \]

89 \[ X = (Z)\text{OCH}_3 \quad R = \text{OH} \]

90 \[ X = (Z)\text{OCH}_3 \quad R = \text{OTs} \]

91 \[ X = (E)\text{OCH}_3 \quad R = \text{OH} \]

92 \[ X = (E)\text{OCH}_3 \quad R = \text{OTs} \]

93 \[ X = (E)\text{OCH}_3 \quad R = \text{N} \]
In the literature it was reported that active methylene could be transformed into enamine derivatives when treated with the complex formed between dimethyl formamide and dimethyl sulphate (DMF-DMS complex), under strongly basic conditions. To check if this method could be used for the preparation of the enamine, the methyl ester of 2-phenyl-acetic acid (82) was chosen as the model compound. When 82 was treated first with lithium or potassium di-isopropyl amide and later with the DMF-DMS complex, the enamine 83 was formed in high yield. Treatment of this compound with sodium cyanoborohydride under slightly acidic conditions, gave the dimethyl amine derivative which, once converted into the corresponding methiodide, was treated with sodium bicarbonate to yield methyl atropate (84) in almost quantitative yield.

When the methyl ester 72 (Diagram 52) was treated with the DMF-DMS complex in the manner described in the previous paragraph, enamine 85 was formed in 30% yield (78% based on recovered starting material).

The vinylic hydrogen of the compound enamine system was at 7.71, which compares very closely to the reported value (7.69) for the (Z)-configuration of a very similar compound: methyl (Z)-2(2-(3-methyl)indoly1)-3-N,N-dimethylaminoacrylate. The vinylic proton for the (E) isomer of this derivative appears at δ7.9.
Treatment of 85 with cyanoborohydride gave a mixture of two compounds that had very different Rf values by TLC. The most polar compound was difficult to isolate in a pure form since, on standing at room temperature, it is converted into the other component present in the reaction mixture. This last substance was identified as the acrylic ester 86, which was surprisingly very stable. Once this compound was fully characterized it was possible, from the NMR of the crude reaction mixture, to determine the structure of the polar component as the corresponding amine derivative (85 with no double bond in the acrylic segment), by subtracting the signals due to 86. This amine derivative spontaneously loses the elements of dimethyl amine to form the acrylic derivative 86.

The stability observed in 86 was the main factor for deciding to retain the N-benzyl group in the indole ring as this would be beneficial during the synthesis of dehydroscecodidine.

The anion prepared from ester 72 and potassium di-isopropylamide was allowed to react with methyl formate at room temperature to furnish the enol 87, which on hydrogenolysis gave 88. Methylation of this compound with diazomethane produced a mixture of two methylated substances (89 and 91) in a 2:1
ratio, that were separated by preparative TLC.

By calculations using the substituent coefficients for the chemical shift of olefinic protons\textsuperscript{110}, the vinylic proton in the (Z)-isomer 89 was expected to be at higher fields (calculated value: 7.16) than the same proton in the (E)-isomer (calculated value: 7.38). The minor component of the mixture was identified as the (Z)-isomer 89, since the olefinic proton in this product was at higher field (6.52) than in the major component (7.69) to which an (E)-configuration was assigned.
Due to time limitations the synthesis of 14,21-dehydrosecodine was not completed, however, the following results obtained from the work presented here, provided alternatives and a basis for further research.

1. The dihydropyridine chromium complexes provided a good method for protecting this sensitive type of substances.

2. The thermal isomerization of the dihydropyridine complexes, in conjunction with the mild method found for the liberation of the dihydropyridine ligand, makes this type of compounds synthetically useful because it facilitates the preparation of dihydropyridine isomers, which would otherwise be difficult to prepare.

3. Although the yields were from low to moderate, the complexation reaction took place when more elaborate dihydropyridines were used (i.e. N-tryptophyl dihydropyridine derivatives).

4. Based on the low yields obtained in the complexation of the dihydropyridine 37 (Diagram 43) a new approach for the synthesis of 14,21 dehydrosecodine was begun (Diagram 51).
5. Although the sequence of reactions outlined in Diagram 51 was not finished, three important results were obtained:

A) A method was found to correct the problem in the LiAlH₄ reduction of tertiary amides when they failed to give the corresponding amine.

B) An efficient method for the preparation of acrylic esters was found via the homologation of an acetic ester segment, using the complex formed between dimethyl formamide and dimethyl sulphate.

C) Based on the remarkable stability found for the 2-(N-benzyl-indolyl)-acrylic derivative 86 (Diagram 54), the goal of this work has changed and is now aimed at preparing the N-benzyl-14,21-dehydrosecodine, since the stability added when the nitrogen of the indole ring is protected will help in the synthesis and chemical behaviour studies of this important biological intermediate.
Melting points were determined on a Kofler block and are uncorrected. Ultraviolet (UV) spectra were recorded on a Cary 15 spectrophotometer in ethanol solution. The wavelengths of absorption maxima are reported in nanometers (nm) with log ε values in parentheses. Infrared (IR) spectra were measured on a Perkin Elmer model 710 or 457 spectrophotometer in chloroform solution. The absorption maxima are reported in wavenumbers (cm⁻¹), calibrated with respect to the absorption band of polystyrene at 1601 cm⁻¹. Proton magnetic resonance (^1Hmr) spectra were measured in deuterochloroform (CDCl₃) solution at ambient temperature on either a Varian HA-100 or XL-100 spectrometer. Chemical shift values are given in the δ (ppm) scale relative to tetramethylsilane (TMS) used as internal standard. The integrated peak areas, signal multiplicities and proton assignments are given in parentheses. Low resolution mass spectra (MS) were determined on either an AEI-MS-902 or an Atlas CH-4B spectrometer. High resolution mass spectra were measured on an AEI-MS-902 instrument. Microanalyses were carried out by Mr. P. Borda of the Microanalytical Laboratory, University of British Columbia.

Thin-layer chromatography (TLC) utilized Merck silica gel G
(according to Stahl) containing 2% fluorescent indicator. For preparative layer chromatography (PLC), plates (20 x 20 or 20 x 60 cm) of 1 mm thickness were used. Visualization was effected by viewing under ultraviolet light and/or by colour reaction with ceric sulphate spray reagent. Column chromatography utilized Merck silica gel 60 (70-230 mesh) or Merck aluminum oxide 90 (neutral).

As a matter of routine, all reagents and solvents were recrystallized or distilled before use.

All the indole derivatives were named as derived from tryptophol (2-(3-indolyl)-ethanol) following Wenkert's system100,103.

All the work presented in this section was done by the author unless otherwise stated.

**N-Methyl-3-ethyl-pyridinium Iodide (41)** (From Greenhouse's 1974 research report)

64 g of 3-ethylpyridine and 90 g of methyl iodide are each dissolved in dry iso-propanol and then mixed at room temperature. The solution, protected from moisture, is allowed
to stand at room temperature overnight. The alcohol is removed under reduced pressure and the solid residue washed well with ether to remove any excess methyl iodide. The salt is then recrystallized from acetone to give 130 g of the methiodide 41 in 88% yield; mp: 91-92°C; UV $\lambda_{\text{max}}$: 219 (4.24), 266 (3.72); $^1$Hmr $\delta$: 1.4 (3H, t, J = 7.5 Hz, -CH$_2$CH$_3$), 3.00 (2H, q, J = 7.5 Hz, -CH$_2$CH$_3$), 4.68 (3H, s, N-CH$_3$), 8.15 (1H, dd, J = 6 Hz, J = 7 Hz, C(5)-H), 8.54 (1H, d, J = 7 Hz, C(4)-H), 9.2 (1H, d, J = 6 Hz, C(6)-H), 9.35 (1H, s, C(2)-H). Analysis calculated for C$_8$H$_{12}$NI: C 38.58, H 4.86, N 5.62; found: C 38.39, H 5.00, N 5.83.

(N-Methyl-3-ethyl-1,2-dihydropyridine)tricarbonylchromium(0) and (N-Methyl-3-ethyl-1,6-dihydropyridine)tricarbonylchromium(0) Complexes (43 and 44)

1. Formation of trisacetonitriletricarbonylchromium(0) (42)$^{91}$: A solution of 15 g of Cr(CO)$_6$ in 250 ml of freshly distilled acetonitrile is refluxed under an inert atmosphere for two to three days until no carbonyl absorption, due to starting material, is observed in the IR spectrum (1990 cm$^{-1}$). The excess acetonitrile is eliminated under reduced pressure and the yellow precipitate obtained is immediately used in the complexation reaction. IR $\nu_{\text{max}}$: 1940, 1895, 1835. Caution:
it has been reported\(^9\) that this complex ignites on exposure to air.

2. Generation of N-methyl-3-ethyl-1,2-dihydropyridine (46)

(From Greenhouse's report): To a mixture of 20 ml of a 2.1 N solution of sodium hydroxide in water and 80 ml Et\(_2\)O, 2.5 g of NaBH\(_4\) were added. The mixture was vigorously stirred under a nitrogen atmosphere for 10 min and then a solution of 15 g of the methiodide 41 in 20 ml of methanol was added. After 5 min of reaction, the aqueous layer was removed with a syringe and the ether solution was briefly washed with 10 ml of 2.1 N sodium hydroxide by vigorous stirring. The water layer was removed and the ether layer dried under nitrogen on anhydrous sodium sulphate with a pellet or two of sodium hydroxide added. The ether was filtered and the drying agent washed well with ether. The combined ether solutions were evaporated at room temperature under reduced pressure to give 6.2 g of a nearly colourless oil (82% yield). UV \(\lambda_{\text{max}}\): 327; \(^1\)Hmr (C\(_6\)D\(_6\)) \(\delta\): 1.00 (3H, t, J = 7 Hz, -CH\(_2\)CH\(_3\)), 1.88 (2H, q, J = 7 Hz, -CH\(_2\)CH\(_3\)), 2.27 (3H, s, N-CH\(_3\)), 3.58 (2H, s, C(2)-H\(_2\)), 4.74 (1H, dd, J = 7 Hz, J ca 7 Hz, C(5)-H), 5.73 (2H, m, superimposed doublets, one of them with J = 7 Hz, C(6)-H and C(4)-H); MS m/e: 67, 94, 96, 107, 108, 122 (100%), 123 (M\(^+\)). High resolution
molecular weight determination, calculated for C₈H₁₃N: 123.1047; found: 123.1041.

3. Complexation reaction (from Zanarotti's report):

The dihydropyridine obtained in the previous experiment, was taken up in 30 ml of benzene and added to the acetonitrile complex 42 prepared as described earlier, all this under an inert atmosphere. The addition immediately produced a deep red coloured solution which did not show dihydropyridine absorption (λ_max = 327) after 30 min of stirring at room temperature, but a maximum was observed at 400 nm. At this time the TLC (benzene - hexane, 1:1) showed three coloured spots. The less polar one was yellow, decomposed very rapidly on exposure to air, and was identified as the acetonitrile complex. The other two spots were red and very close together. The complexation reaction mixture was concentrated to a small volume and chromatographed on silica gel (1.5 Kg). After the yellow band of the unreacted acetonitrile chromium complex was eluted with a mixture of benzene-petroleum ether (1:1), 5.3 g of the two red compounds were eluted with benzene. A small portion of this mixture (70 mg) was separated by preparative TLC (benzene - petroleum ether, 1:1; developed twice), yielding 15 mg of the less polar component and 9 mg of the other one. This last compound was
recrystallized from benzene-hexane and identified as the (N-methyl-3-ethyl-1,2-dihydropyridine)tricarbonylchromium (0) complex (43) based on its spectroscopic properties. mp: 97-98°C; UV λ_max: 403 (3.64); IR ν_max: 1942, 1860, 1830; \(^1\)Hmr (C\(_6\)D\(_6\)) δ: 0.70 (3H, t, J = 7 Hz, -CH\(_2\)CH\(_3\)), 1.45 (3H, s, N-CH\(_3\)), 1.60 (2H, q, J = 7 Hz, -CH\(_2\)CH\(_3\)), 2.34 (2H, AB system, J = 10 Hz, ((2)-H\(_2\))), 4.50 (2H, br.d. J = 5 Hz, C(4)-H and C(6)-H), 5.00 (1H, t, J = 5 Hz, C(5)-H); MS m/e: 94, 107, 122 (100%), 123, 259 (M\(^+\)). Analysis calculated for C\(_{11}\)H\(_{13}\)NO\(_3\)Cr: C 50.90, H 5.05, N 5.40; found: C 51.04, H 4.95, N 5.46.

The major component of the reaction mixture obtained in the complexation reaction was identified as a chromiumtricarbonyl complex but now possessed an N-methyl-3-ethyl-1,6-dihydropyridine as ligand (44). Recrystallization of 44 from benzene-hexane gave red prisms that had mp: 68°C; UV λ_max: 399 (3.67); IR ν_max: 1942, 1860, 1825; \(^1\)Hmr (C\(_6\)D\(_6\)) δ: 1.12 (3H, t, J = 7 Hz, -CH\(_2\)CH\(_3\)), 1.45 (3H, s, N-CH\(_3\)), 2.0-2.7 (4H, m, -CH\(_2\)CH\(_3\) and C(6)-H\(_2\)), 3.09 (1H, distorted t, J = 7 Hz, C(5)-H), 4.58 (1H, s, C(2)-H), 4.83 (1H, br.d. J = 7 Hz, C(4)-H); (CDCl\(_3\)) δ: 1.40 (3H, t, J = 7 Hz, -CH\(_2\)CH\(_3\)), 2.39 (3H, s, N-CH\(_3\)), 2.73 (2H, m, -CH\(_2\)CH\(_3\)), 3.7-3.45 (2H, m C(6)-H\(_2\)), 6.29 (1H, br.d. J = 7 Hz, C(4)-H), 5.40 (1H, hr.s. C(2)-H); MS m/e: 94, 107,
122 (100%), 123, 259 (M+). Analysis calculated for 

\[ \text{C}_{11}\text{H}_{13}\text{NO}_2\text{Cr}: \text{C} \ 50.90, \ \text{H} \ 5.05, \ \text{N} \ 5.40; \text{ found: C} \ 50.81, \ \text{H} \ 5.26, \ \text{N} \ 5.16. \]

4. Thermal isomerization of the dihydropyridine chromium complexes: 70 mg of a mixture of complexes 43 and 44 (this last one being predominant) were dissolved in 15 ml of cyclohexane and refluxed for 6 h under a nitrogen atmosphere. In this manner a 1:1 ratio was obtained based on the integration of the signal in the NMR for the hydrogen at position 5 ((C\textsubscript{6}D\textsubscript{6}) 5.01 in 43 and 3.02 for complex 44).

\textit{N-Methyl-3-ethyl-1,2,5,6-tetrahydropyridine (47) (From Greenhouse's research report)}

\textit{N-Methyl-3-ethylpyridinium iodide (0.250 g) was dissolved in methanol (15 ml) and treated with sodium borohydride (0.250 g) added in small portions with stirring. After 20 min the solution was diluted with 3N solution of HCl and extracted with ether. The aqueous layer was basified with solid sodium hydroxide and extracted with methylene chloride. The organic layer was dried with anhydrous sodium sulphate and evaporated to yield 0.036 g (29%) of a nearly colourless oil. Gas liquid chromatography (GLC) using a 30% carbowax (10 ft long,
at a temperature of 120°C with a flow of 10 ml/7 sec) indicated that this oil consisted of a mixture of three substances in a 15:2:1 ratio. By preparative VPC the major component of this mixture was isolated. IR $\nu_{\text{max}}$: 2960, 2780, 1460, 840; $^1\text{Hmr}$ $\delta$: 0.95 (3H, t, $J = 7$ Hz, $-\text{CH}_2\text{CH}_3$); 2.20 (3H, s, $-\text{N-CH}_3$), 2.5-1.7 (6H, m, C(5)−H, C(6)−H and $-\text{CH}_2\text{CH}_3$), 2.65 (2H, bs, C(2)−H$_2$), 5.33 (1H, m, C(4)−H); MS m/e: 67, 81, 82, 94, 96 (100%), 110, 124, 125(M$^+$). High resolution molecular weight determination, calculated for C$_8$H$_{15}$N: 125.1204; found: 125.1225.

**N-Carbomethoxy-3-ethyl-1,2-dihydropyridine (49)**

Methyl chloroformate (1.89 g) in 3 ml of anhydrous ether was added at −78°C to a mixture of 0.8 g of NaBH$_4$ and 2.14 g of 3-ethylpyridine in 20 ml of absolute methanol. The rate of addition was controlled so that the reaction temperature did not exceed −69°C. Two hours after the addition was completed, the reaction mixture was poured into ice-water and extracted with ether. The ether layer was worked up in the usual manner and concentrated. The light yellow oil obtained was filtered over a column containing 100 g of basic alumina to yield 1.6 g of the dihydropyridine 49; UV $\lambda_{\text{max}}$: 298; IR $\nu_{\text{max}}$: 1700; $^1\text{Hmr}$ $\delta$: 1.07 (3H, t, $J = 6.5$ Hz, $-\text{CH}_2\text{CH}_3$), 2.03 (2H, q,
J = 6.5 Hz, -CH₂CH₃, 3.75 (3H, s, N-CH₃), 4.21 (2H, d, J = 1 Hz, C(2)-H₂), 5.02 (1H, dd, J = 6 Hz, J = 6.5 Hz, C(5)-H), 5.52 (1H, bd, J = 6 Hz, C(4)-H).

N-Methyl-3-ethyl-1,6-dihydropyridine (51)

0.185 ml of pyridine were added to a solution of 150 mg of chromium complex 44 in 12.5 ml of n-pentane (ratio 44 to pyridine, 1:4). The reaction was stirred at room temperature and followed by UV. After 24 h of reaction an abundant precipitate had formed and the UV spectrum showed very small amounts of complex 44 (399 nm). The precipitate was filtered and the solvent evaporated under reduced pressure to give a pale orange oil (72% yield); UV λ_{max}: 332; ¹Hmr δ: 1.02 (3H, t, J = 7 Hz, -CH₂CH₃), 1.98 (2H, q, J = 7 Hz, -CH₂CH₃), 2.24 (3H, s, N-CH₃), 3.50 (1H, d, J = 4 Hz, C(6)-H₂), 5.18 (1H, dt, J = 4 Hz, J = 8 Hz, C(5)-H), 5.52 (1H, s, C(2)-H).

N-Methyl-3-ethyl-5-benzyl-1,2,5,6-tetrahydropyridine (54)

(From Greenhouse's research report)

Pyridinium salt 41 (1.00 g) was added all at once to a mixture of sodium borohydride (0.385 g) and benzyl bromide (4.75 ml) in 2.1N sodium hydroxide (6 ml), methanol (6 ml) and ether
(40 ml), and vigorously stirred for 20 h. Ether (100 ml) was added and the mixture was acidified with 2.5N hydrochloric acid. The two layers were separated and the aqueous one was further extracted with two portions of ether and evaporated to dryness, to give 1.316 g of a light yellow solid (53, R = \( \text{CH}_2\text{O} \)).

\[ ^1\text{Hmr} (\text{CDCl}_3-\text{DMSO-d}_5) : 1.10 (3\text{H}, \text{t}, J = 8 \text{ Hz}, -\text{CH}_2\text{CH}_3), \]
\[ 2.11 (2\text{H}, \text{q}, J = 8 \text{ Hz}, -\text{CH}_2\text{CH}_3), \]
\[ 2.79 (2\text{H}, \text{apparent triplet, C(5)-CH}_2\text{O}), \]
\[ 3.08 (3\text{H}, \text{s, N-CH}_3), \]
\[ 3.20-2.85 (1\text{H}, \text{m, C(5)-H}), \]
\[ 3.44 (2\text{H}, \text{apparent triplet, C(6)-H}_2), \]
\[ 3.86 (2\text{H}, "\text{AB quartet"}, J_{\text{AB}} = 16 \text{ Hz, C(2)-H}_2), \]
\[ 4.53 (2\text{H}, \text{s, N-CH}_2\text{O}), \]
\[ 5.71 (1\text{H}, \text{br.s., C(4)-H}), \]
\[ 7.41 \text{ and } 7.26 (10\text{H, two singlets, aromatic}). \]

Dry HMPA (10 ml) and lithium hydride (0.25 g) were added to the salt 53. The suspension was deoxygenated at water aspirator pressure and placed under nitrogen while cooling to 0°C. Propane thiol (1.15 ml) was added all at once with stirring. The reaction mixture was brought to room temperature and stirred for 20 h and poured onto a mixture of ice and 2.5 HCl solution and extracted with ether. The aqueous layer was basified and extracted with ether to yield 0.75 g of 54 as the hydrochloride salt. Purification of the free salt by column chromatography gave 0.49 g of 54 (48% from 41);

\[ ^1\text{Hmr} (\text{C}_6\text{D}_6) \delta: 0.91 (3\text{H}, \text{t}, J = 7 \text{ Hz, -CH}_2\text{CH}_3), \]
\[ 1.83 (2\text{H}, \text{q}, J = 7 \text{ Hz, -CH}_2\text{CH}_3), \]
\[ 2.10 (3\text{H}, \text{s, N-CH}_3), \]
\[ 2.90-1.95 (7\text{H, m proton at C(2), C(5) and C(6)}), \]
\[ 5.34 (1\text{H, br.s. C(4)-H}), \]
7.09 (5H, s, aromatic); MS m/e: 42, 44, 91, 115, 123, 124,
128, 129, 138, 143 (100%), 144, 157, 186, 200, 215 (M+).

High resolution molecular weight determination, calculated

N,3,5-Trimethyl-5-benzyl-1,2,5,6-tetrahydropyridine (57)

When 3 g of N-methyl-3,5-lutidinium iodide (56) was treated
with benzyl bromide in the same way as described in the previous
experiment, 1.92 g of the hydrochloride salt of 57 were
isolated. Purification by column chromatography yielded
1.1 g of 57 (48%); bp: 79-81°C (hot box distillation);
IR v max: 1600, 1500, 1465, 1455, 740, 705; ¹Hmr δ: 0.86 (3H, s, C(5)-CH₃),
1.61 (3H, s, C(3)-CH₃), 2.11 (2H, "AB quartet",
J = 11 Hz, C(6)-H₂), 2.28 (3H, s, N-CH₃), 2.63 (2H, s,
C(5)-CH₂₀), 2.71 (2H, "AB quartet", J = 12 Hz, C(2)-H₂), 5.11
(1H, s, C(4)-H), 7.15 (5H, m, aromatic); MS m/e: 157 (100%),
172, 215 (M⁺). Analysis calculated for C₁₅H₂₁N: C 83.67,
H 9.83; found: C 83.90, H 9.95.

(N-Tryptophyl-3-ethyl-1,6-dihydropyridine)tricarbonylchromium(0)
and (N-Tryptophyl-3-ethyl-1,2-dihydropyridine)tricarbonyl-
chromium(0) Complexes (59 and 60)
N-Tryptophyl-3-ethylpyridinium bromide\textsuperscript{100} (58) (0.5 g) was added to a mixture of ether (25 ml), 2.1N solution of sodium hydroxide (3 ml), methanol (1 ml) and sodium borohydride (60 mg), and stirred for 20 min. At this time, besides the indole absorption (220, 274, 282, 289), the UV spectrum showed the typical band for a dihydropyridine (336). The ether layer was separated, washed with 2.1 N sodium hydroxide and added to dry trisacetonitriletricarbonylchromium(0) (42) (≈2 g), and stirred under a nitrogen atmosphere for 12 h. The reaction mixture was filtered and evaporated to dryness under reduced pressure and the product obtained was purified by preparative TLC (petroleum ether - ethyl acetate, 6:4), to give 109 mg (20%) of red compound that showed a single spot on the TLC (same system as before). The NMR spectrum indicated that this compound was a mixture of at least two compounds. Using a less polar solvent (petroleum ether - ethyl acetate, 85:15) and repetitive development of the plates (four times) two red compounds were isolated. The less polar compound (7 mg) was identified as the dihydropyridine chromium complex \textsuperscript{59} based on its spectroscopical properties; UV $\lambda_{\text{max}}$: 219, 272, 278, 288, 397; IR $\nu_{\text{max}}$: 3480, 1950, 1870, 1835; $^1$Hmr (C\textsubscript{6}D\textsubscript{6}) $\delta$: 1.04 (3H, t, $J = 7 \text{ Hz}$, $-\text{CH}_2\text{-CH}_3$), 3.19 (1H, br. distorted t, apparent $J = 7 \text{ Hz}$, C(5)-H), 4.86 (1H, br.s. C(2)-H), 4.90 (1H, d, $J = 7 \text{ Hz}$, C(4)-H), 6.31 (1H, br.s.,}
indole-C(2)-H), 7.1-7.6 (4H, m, aromatic-H₄); MS m/e: 52, 122 (100%), 130, 144, 252, 304, 388 (M⁺).

The other compound obtained from the TLC plates (4 mg) was identified as N-tryptophyl-3-ethyl-1,2-dihydropyridine chromium complex 60; UV λₘₐₓ: 220, 285, 290, 400; IR νₘₐₓ: 3480, 1945, 1855, 1830; ¹Hmr (C₆D₆) δ: 0.77 (3H, t, J = 7 Hz, -CH₂CH₃), 1.83 (2H, q, J = 7 Hz, -CH₂CH₃), 2.38 (4H, br.s. -CH₂CH₂-), 2.62 (2H, s, C(2)-H₂), 4.0-4.8 (2H, m, C(4)-H and C(6)-H), 4.90 (1H, t, J = 5.0 Hz, C(5)-H), 6.24 (1H, br.s. indole-C(2)-H), 7.0-7.6 (4H, m, aromatic-H₄).

2-Carboxytryptophol Lactone (61)¹⁰³

1. α-Ethoxalyl-γ-butyrolactone: In a 3 liter round-bottomed flask, equipped with an efficient condenser, a mixture of 69 g of finely cut sodium, 2 l of anhydrous ether, and one third of a mixture of 258 g of γ-butyrolactone and 438 g of diethyloxalate, was stirred mechanically. The reaction started upon addition of 1 ml of methanol and warming the reaction mixture. After a short time the reaction became violent and the warm bath was removed and replaced by an ice-water bath. The remaining two thirds of the γ-butyrolactone/diethyloxalate mixture was added over a two hour period, and
the mixture stirred until no more sodium was left. The ether was then distilled and the precipitate obtained was dissolved in 1 l of ice-water. Upon acidification with sulphuric acid, a thick oil separated out of solution. The mixture was then extracted with ether (3 x 1 l) and the combined ether layers were dried over anhydrous sodium sulphate. The ether was eliminated under reduced pressure, leaving approximately 300 ml of a very dense, brownish oil. This oil was distilled to yield 190 g (34%) of a colourless oil. Bp: 119-120°C at 10⁻² mm of Hg; UV λmax: 280 (3.77), 315 (3.59); IR νmax (neat oil): 3400, 1770, 1740, 1700, 1640; ¹Hmr δ: 1.39 (3H, t, J = 7 Hz, -CH₂CH₃), 3.23 (2H, t, J = 7.5 Hz, C(β)-H₂), 4.38 (2H, q, J = 7 Hz, -CH₂CH₃), 4.5 (2H, t, J = 7.5 Hz, C(γ)-H₂); MS m/e: 95, 113 (100%), 186 (M⁺). Analysis calculated for C₈H₁₀O₅: C 51.61, H 5.41; found: C 51.53, H 5.60.

2. α-Phenylhydrazono-δ-valerolactone: 191.4 g of α-ethoxalyl-γ-butyrolactone were suspended in 500 ml of a 2N solution of HCl and refluxed until no more CO₂ came out of the condenser (3 h). After cooling the solution at room temperature 85 g of sodium acetate and a solution of 115 g of phenylhydrazine in 16 ml of glacial acetic acid were added. The reaction mixture was heated at 80°C for half an hour and
diluted with 1 l of a 7M solution of HCl to yield a yellow precipitate, which was filtered off and recrystallized from hot methyl alcohol to yield 70 g (28%) of pure yellow crystals. 120 g of brownish crystals were obtained when the mother liquors were evaporated to dryness; mp: 189-190°C; UV $\lambda_{\text{max}}$: 230 (4.29), 284 (3.98), 292 (4.10), 333 (4.62); IR $\nu_{\text{max}}$: 3250, 1690, 1500, 750; $^1$Hmr (DMSO-d$_6$) $\delta$: 2.00 (2H, m, C(γ)-H$_2$), 2.63 (2H, t, J = 7 Hz, C(β)-H$_2$), 3.32 (1H, s, NH), 4.30 (2H, t, J = 5 Hz, C( )-H$_2$), 6.8-7.5 (5H, m, aromatic protons); MS m/e: 65, 91, 93, 205 (M$^+$, 100%). Analysis calculated for C$_{11}$H$_{12}$N$_2$O$_2$: C 64.69, H 5.92, N 13.72; found: C 64.95, H 5.83, N 13.71.

3. Indole lactone 61: The phenylhydrazone obtained in the previous experiment (50 g) was suspended in 250 ml of glacial acetic acid and a stream of hydrogen chloride was bubbled over a period of 20 min. The reaction mixture was then refluxed for 10 min and diluted with 1.2 l of water. The white precipitate formed was filtered off, washed with water and recrystallized from methanol - acetone to yield 39 g (85%) of the lactone 61 as long white needles. Mp: 194-196°C; UV $\lambda_{\text{max}}$: 227 (4.31), 296 (4.25); IR $\nu_{\text{max}}$: 3460, 1700; $^1$Hmr $\delta$: 3.16 (2H, t, J = 6 Hz, -CH$_2$CH$_2$O-), 4.72 (2H, t, J = 6 Hz, -CH$_2$CH$_2$O-), 6.9-7.8 (4H, m, aromatic-
N,N-Dimethyl-2-carboxamidotryptophol (62)

The indole lactone 61 (30 g) and excess dimethyl amine were stirred in dry methanol at room temperature until no absorption at 1700 cm⁻¹ (lactone) was observed in the IR spectrum (≈ 48 h). The solvent was removed under reduced pressure and the residue crystallized from acetone - benzene to give 32 g of the amide 62 (87.5%). Mp: 125-126°C; UV λ max: 218 (4.75), 289 (4.31); IR ν max: 3460, 3200, 1600; ¹Hmr δ: 3.04 (6H, s, -N(CH₃)₂), 3.11 (2H, t, J = 6 Hz, -CH₂CH₂OH), 4.0 (2H, t, J = 6 Hz, -CH₂CH₂OH), 5.92 (1H, s, D₂O exchangeable, -CH₂CH₂OH), 6.6-7.8 (4H, m, aromatic-H₄), 9.6 (1H, br. s, N-H); MS m/e: 128, 158, 202 (100%), 232 (M⁺). High resolution molecular weight determination, calculated for C₁₁H₉NO₂: 232.1211; found: 232.1214.

2-Dimethylaminomethyltryptophol-methiodide (63)

1. 2-Dimethylaminomethyltryptophol: A solution of the amide 62 (32 g) in dry tetrahydrofuran (200 ml) was added slowly to a suspension of lithium aluminum hydride (30 g) in
dry tetrahydrofuran (750 ml) at 0°C under a nitrogen atmosphere. The mixture was heated under reflux for about 5 h, cooled, and quenched with saturated sodium sulphate solution. The mixture was filtered and the solids were washed with hot ethyl acetate (ca 2 l). The filtrate was evaporated to dryness and the residue recrystallized from ethyl acetate to give 2-dimethylaminomethyltryptophol (24.3 g, 84%). Mp: 140-142°C; UV $\lambda_{\text{max}}$: 222 (4.61), 274 (3.91), 281 (3.95), 290 (3.88); IR $\nu_{\text{max}}$: 3470, 3400-3000; $^1$Hmr $\delta$: 2.2 (6H, s, $-N(CH_3)_2$), 3.01 (2H, t, J = 6 Hz, $-CH_2CH_2OH$), 3.49 (2H, s, $-CH_2N(CH_3)_2$), 3.84 (2H, t, J = 6 Hz, $-CH_2CH_2OH$), 4.29 (1H, br.s, $-CH_2CH_2OH$), 6.9-7.7 (4H, m, aromatic-$H_4$), 8.7 (1H, br.s, N-H); MS m/e: 115, 130, 132, 143, 144 (100%), 173, 174, 218 ($M^+$). Analysis calculated for C$_{13}$H$_{18}$N$_2$O: C 71.53, H 8.31, N 12.83; found: C 71.39, H 8.15, N 12.79.

2. Methiodide 63: Iodomethane (27.2 g) in ethyl acetate (40 ml) was added to an ethyl acetate solution (700 ml) of the dimethyl amine obtained in the previous section (24 g). The mixture was stirred at ambient temperature for 45 min then at 50°C for 1 h. The mixture was cooled and the precipitate collected by filtration. Recrystallization from ethanol yielded 35.7 g of the methiodide 63 (90.2%). Mp: 162-165°C; UV $\lambda_{\text{max}}$: 218 (4.72), 273 (4.02, 286 (3.93), 296 (3.68);
IR $\nu_{max}$: 3410, 3280; $^1$Hmr ($CDCl_3$-DMSO-d$_6$) $\delta$: 3.13 (2H, t, $J$ = 6 Hz, $-\text{CH}_2\text{CH}_2\text{OH}$), 3.28 (9H, s, $-\text{N(CH}_3)_3$), 3.80 (2H, m, $-\text{CH}_2\text{CH}_2\text{OH}$), 4.20 (1H, t, $J$ = 6 Hz, $-\text{CH}_2\text{CH}_2\text{OH}$), 4.96 (2H, s, $-\text{CH}_2\text{N(CH}_3)_3$), 6.9-7.8 (4H, m, aromatic-$H_4$), 10.84 (1H, s, N-H).

2-Cyanomethyltryptophol (64)
A mixture of 40 g of the methiodide 63 and 30 g of potassium cyanide was heated in refluxing acetonitrile (1 l) for 18 h under a nitrogen atmosphere. The reaction mixture was cooled and filtered. The filtrate was evaporated and the residue filtered through a short column of alumina (grade III) with dichloromethane (500 ml) and then with ethyl acetate (1 l), to yield 20 g of a pale yellow gum that solidified with time. Recrystallization from benzene gave 18.5 g of 2-cyanomethyltryptophol (64) (87%). Mp: 106-107°C; UV $\lambda_{max}$: 220 (4.58), 272 (3.89), 279 (3.90), 289 (3.79). IR $\nu_{max}$: 3680, 3620, 3460, 2400; $^1$Hmr $\delta$: 1.66 (1H, s, $-\text{CH}_2\text{CH}_2\text{OH}$), 2.90 (2H, t, $J$ = 6 Hz, $-\text{CH}_2\text{CH}_2\text{OH}$), 3.81 (2H, t, $J$ = 6 Hz, $-\text{CH}_2\text{CH}_2\text{OH}$), 3.84 (2H, s, $-\text{CH}_2\text{CN}$), 6.9-7.7 (4H, aromatic-$H_4$), 8.29 (1H, br.s, N-H). MS m/e: 64, 77, 115, 142, 169 (100%), 182, 200 ($M^+$). Analysis calculated for C$_{12}$H$_{12}$N$_2$O: C 71.98, H 6.04, N 13.99; found: C 72.10, H 6.20, N 13.74.
All inorganic salts (KI and KCN) obtained in this reaction were dissolved in water and treated with saturated solution of ferrous sulphate (with a small amount of ferric sulphate) to destroy excess potassium cyanide.

2-Carbomethoxymethyltryptophyl Chloride (65)
An ice-cold solution of 20 g of hydroxynitrile 64 and 4 ml of water in 400 ml of methanol was saturated with hydrogen chloride gas. After stirring at room temperature for 48 h the solution was taken to dryness under vacuum and the residue treated with a saturated solution of sodium bicarbonate (250 ml) and extracted with methylene chloride. The extracts were washed with water, brine and dried over anhydrous sodium sulphate. The solvent was removed and the residual oil obtained (19.4 g) was purified by column chromatography (600 g of silica gel, petroleum ether - ethyl acetate) to yield 8.8 g of 65 as a pale yellow gum that solidified when kept overnight in the freezer. The analytical sample was prepared by sublimation at 80°C and 10⁻² mm of Hg. Mp: 59-60°C; UV λ_max: 221 (4.58), 274 (3.90), 281 (3.91), 289 (3.86); IR v_max: 3480, 1730; ¹Hmr δ: 3.19 (2H, t, J = 7.5 Hz, -CH₂CH₂Cl), 3.72 (2H, t, J = 7.5 Hz, -CH₂CH₂Cl), 3.77 (3H, s, -OCH₃), 3.85 (2H, s, -CH₂CO₂CH₃), 7.0-7.7 (4H, m, aromatic-H₄), 8.61 (1H, br.s, N-H); MS m/e: 142, 143, 156, 192, 202 (100%), 251 (M⁺), 253
(M$^+$+2). Analysis calculated for C$_{13}$H$_{13}$NO$_2$Cl: C 62.03, H 5.61, N 5.56; found: C 62.11, H 5.78, N 5.57.

**N-(2-Carbomethoxymethyltryptophyl)-3-ethyl-pyridinium Perchlorate (36)**

The chloroester 65 (5.14 g) and freshly distilled 3-ethyl-pyridine (15 ml) were heated at 82°C for 18 h. The solution was cooled and diluted with ether. The ether was decanted and the residula oil chromatographed on alumina (grade V) with ethyl acetate. Evaporation of the eluate gave 4.5 g of a thick oil which was dissolved in water (100 ml). A saturated solution of sodium perchlorate (25 ml) was added and the precipitate formed collected by filtration. Recrystallization from methanol gave 3.85g(44%) of the perchlorate salt 36. Mp: 140-141.5°C; UV $\lambda_{\text{max}}$: 219 (4.56), 265 (4.01), 271 (3.98), 280 (3.91), 289 (3.83); IR $\nu_{\text{max}}$: 3350, 1740; $^1$Hmr (CDCl$_3$-DMSO-d$_6$) $\delta$: 1.01 (3H, t, J = 8 Hz, -CH$_2$CH$_3$), 2.60 (2H, q, J = 8 Hz, -CH$_2$CH$_3$), 3.40 (2H, t, J = 6.5 Hz, -CH$_2$CH$_2$Py$^+$), 3.74 (3H, s, -OCH$_3$), 3.83 (2H, s, -CH$_2$CO$_2$CH$_3$), 4.81 (2H, t, J = 6.5 Hz, -CH$_2$CH$_2$Py$^+$), 6.7-7.5 (4H, m, aromatic-H$_4$), 7.79 (1H, dd, J = 8 Hz, J = 6 Hz, pyridine-C(5)-H), 8.19 (1H, d, J = 8 Hz, pyridine-C(4)-H), 8.46 (1H, s, pyridine-C(2)-H), 8.70 (1H, d, J = 6Hz, pyridine-C(6)-H), 10.77 (1H, br.s, N-H).
Analysis calculated for C$_{20}$H$_{23}$N$_2$O$_6$Cl: C 56.81, H 5.48, N 6.65; found: C 56.61, H 5.30, N 6.63.

{N-(2-Carbomethoxymethyltryptophyl)-3-ethyl-1,6-dihydropyridine}tricarbonylchromium(0) Complex (40)

Using the procedure described for the formation of the chromium complexes 59 and 60, 1.2 g of the salt 36 gave 35 mg of a mixture of 39 and 40 (2.6%). The mixture was separated by preparative TLC to yield 6 mg of the less polar component that was identified as chromium complex 40; UV $\lambda_{\text{max}}$: 220, 273, 281, 290, 398; $^1$Hmr $\delta$: 1.02 (t, $J = 8$ Hz, -CH$_2$CH$_3$), 3.1 (distorted t, $J = 6$ Hz, pyridine-C(5)-H), 3.24 (s, -CH$_2$CO$_2$CH$_3$), 3.37 (s, -OCH$_3$), 4.84 (br.s, pyridine-C(2)-H), 4.86 (d, $J = 6$ Hz, pyridine-C(4)-H); MS m/e: 52, 122 (100%), 202, 220, 324, 344, 460 (M$^+$).

The other component (2 mg) of the mixture obtained in the complexation reaction was still impure and it was assumed that it corresponded to complex 39.

N-Benzyl-2-carboxytryptophol Lactone (68)

A solution of the lactone 61 (18.7 g) in HMPA (40 ml) and
tetrahydrofuran (30 ml) was added slowly to a suspension of potassium hydride (40 ml of 23% suspension) in HMPA (40 ml) and tetrahydrofuran (500 ml) at 0-5°C and stirring maintained at this temperature for 30 min then at ambient temperature for 2 h. The mixture was cooled in ice and excess hydride destroyed by the addition of alumina (grade III, 200 g) and the mixture stirred for 45 min. The solids were removed by filtration and the filtrate concentrated in vacuo. The oil obtained in this way was purified by column chromatography (800 g silica gel) to yield 22.6 g of a solid which upon crystallization from ethyl acetate-hexane gave 19.9 g of the lactone \( \underline{68} \) (67%). Mp: 109-109.5°C; UV \( \lambda_{\text{max}} \): 232 (4.64), 297 (4.55); IR \( \nu_{\text{max}} \): 1710; \(^1\)Hmr \( \delta \): 3.08 (2H, t, J = 6 Hz, -CH\(_2\)CH\(_2\)O-), 4.56 (2H, t, J = 6 Hz, -CH\(_2\)CH\(_2\)O-), 5.76 (2H, s, NCH\(_2\))0), 7.0-7.7 (9H, m, aromatic-H\(_9\)); MS m/e: 91 (100%), 277 (M\(^+\)). Analysis calculated for C\(_{18}\)H\(_{15}\)NO\(_2\): C 77.96, H 5.45, N 5.05; found: C 77.92, H 5.56, N 5.00.

N-Benzyl-2-dimethylcarboxamido-tryptophol (69)
As described before for the preparation of the amide \( \underline{62} \), \( \underline{68} \) gave a 91% yield of amide \( \underline{69} \) which was recrystallized from methanol - hexane. Mp: 93.5-94°C; UV \( \lambda_{\text{max}} \): 215 (4.91), 287 (4.31); IR \( \nu_{\text{max}} \): 3280, 1630, 740-710; \(^1\)Hmr \( \delta \): 2.52 (3H,
(N-Benzyl-2-dimethylcarboxamido-tryptophyl)-benzyl Ether (70)

As described for the preparation of 68, 69 gave a 91% yield of the amide 70 as a thick gum. UV $\lambda_{max}$: 215 (4.55), 287 (3.97); IR $\nu_{max}$: 1630, 745, 700; $^1$Hmr $\delta$: 2.44 (3H, br. s, $-N(\text{CH}_3)_2$), 2.89 (3H, br. s, $-N(\text{CH}_3)_2$), 3.04 (2H, t, $J = 7$ Hz, $-\text{CH}_2\text{CH}_2\text{O}$), 3.69 (2H, t, $J = 7$ Hz, $-\text{CH}_2\text{CH}_2\text{O}$), 4.47 (2H, s, $-\text{OCH}_2\text{O}$), 5.28 (2H, s, NCH$_2$O), 6.9-7.7 (17H, m, aromatic-$H_{17}$); MS m/e: 91 (100%), 149, 291, 412 (M$^+$). High resolution molecular weight determination, calculated for C$_{27}$H$_{28}$N$_2$O$_2$: 412.2151; found: 412.2159.

Reduction of Amide 70

1. A solution of the amide (70) (1.65 g) in dry tetrahydrofuran (10 ml) was added slowly to a suspension of lithium
aluminum hydride (230 mg) in dry tetrahydrofuran (10 ml) at 0°C under nitrogen. The mixture was stirred at ambient temperature for 4 h, cooled, and excess hydride destroyed with Na₂SO₄·10H₂O. The solids were removed by filtration and the filtrate concentrated in vacuo. Chromatography on silica gel afforded: N-benzyl-2-dimethylaminomethyl-tryptophyl-benzyl ether (73) (150 mg, 9.5%); UV λ_max: 225, 277, 285 and 296; IR ν_max: 1470, 1450, 1360, 740, 700; ¹_Hmr δ: 2.11 (6H, s, -N(CH₃)₂), 3.09 (2H, t, H = 8 Hz, -CH₂CH₂O-), 3.19 (2H, s, -CH₂N(CH₃)₂), 3.67 (2H, t, J = 8 Hz, -CH₂CH₂O-), 4.48 (2H, s, -OCH₂Ø), 5.5 (2H, s, -NCH₂Ø), 6.8-7.7 (14H, m, aromatic-H₁₄); MS m/e: 91 (100%), 232, 262, 352, 353, 354, 398 (M⁺). High resolution molecular weight determination, calculated for C₂₇H₃₀N₂O: 398.2358; found: 398.2387; and (N-benzyl-2-carbinol-tryptophyl)-benzyl ether (74) (850 mg, 67%); UV λ_max: 225 (4.52), 279 (3.87), 286 (3.88), 297 (3.81); IR ν_max: 3400, 740, 700; ¹_Hmr δ: 2.82 (H, br. s, -CH₂OH), 3.06 (2H, t, J = 6 Hz, -CH₂CH₂O), 3.66 (2H, t, J = 6 Hz, -CH₂CH₂O-), 4.38 (2H, s, -OCH₂Ø), 4.54 (2H, s, -CH₂OH), 5.35 (2H, s, NCH₂Ø), 6.8-7.6 (14H, m, aromatic-H₁₄); MS m/e: 91, 250 (100%), 371 (M⁺). High resolution molecular weight determination calculated for C₂₄H₂₅NO₂: 371.1885; found: 371.1906.

2. n-Butanol (8.4 ml) was added, over a period of 15 min
to a suspension of lithium aluminum hydride (3.5 g) in dry tetrahydrofuran (60 ml) at 0-5°C under nitrogen and the mixture stirred at ambient temperature for 1 h. A solution of the amide 70 (7.4 g) in dry tetrahydrofuran (100 ml) was added and the mixture stirred at ambient temperature for 4 h. Work-up as described above gave a mixture of 73 and 74 (6.5 g, ratio 8:1 by $^1$Hmr).

3. A solution of borane-tetrahydrofuran (1.5 ml of 1N solution) was added to the amide 70 (250 mg) in dry tetrahydrofuran (50 ml) at 0-5°C under a nitrogen atmosphere. The solution was refluxed for 1 h, diluted with triethylamine (1 ml), and reflux continued for 2 h. The mixture was cooled and concentrated in vacuo. The residue was dissolved in ethyl acetate, washed with 1N ammonium hydroxide solution, water, brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. Chromatography on silica gel gave the amine 73 (140 mg, 58%) and a less polar compound (50 mg, 23%) that was identified as (N-benzyl-2-methyl-tryptophyl)-benzyl ether (76); UV $\lambda_{max}$: 225, 276, 284, 292; IR $\nu_{max}$: 1470, 1460, 1365, 740, 700; $^1$Hmr $\delta$: 2.24 (3H, s, indole-C(2)-CH$_3$), 3.07 (2H, t, J = 7.5 Hz, -CH$_2$CH$_2$O-), 3.67 (2H, t, J = 7.5 Hz, -CH$_2$CH$_2$O-), 4.10 (2H, s, -OCH$_2$O), 5.22 (2H, s, -NCH$_2$O), 6.7-7.6 (14H, m, aromatic-H$_{14}$); MS m/e: 91, 234 (100%), 355 (M$^+$).
resolution molecular weight determination, calculated for C\(_{25}H_{25}NO\): 355.1936; found: 355.1941.

(N-Benzyl-2-cyanomethyl-tryptophyl)-benzyl Ether (71)

1. Methiodide of 73: The crude product obtained in the reduction of 70 with LiAlH\(_4\)-nBuOH was stirred in ethyl acetate with iodomethane for 18 h. The solid was collected by filtration and recrystallized from methanol - ethyl acetate to give the methiodide of 73 in 82% yield. Mp: 143-145.5°C (decomposition); UV \(\lambda_{\text{max}}\): 220 (4.68), 276 (4.01), 292 (3.89), 304 (3.71); IR \(\nu_{\text{max}}\): 1400, 1200, 1100, 1030, 860, 730, 690; \(^1\)H NMR (CDCl\(_3\)-DMSO-d\(_6\)) \(\delta\): 3.24 (11H, br. s, -N(CH\(_3\)_3 and \(\text{CH}_2\text{CH}_2\text{O}-\)), 3.81 (2H, t, J = 6.5 Hz, -\(\text{CH}_2\text{CH}_2\text{O}-\)), 4.46 (2H, s, -OCH\(_2\phi\)), 5.01 (wH, s, -CH\(_2\)N(CH\(_3\)_3)), 5.67 (2H, s, NCH\(_2\phi\)), 6.7=7.8 (14H, m, aromatic-H\(_4\)). Analysis calculated for C\(_{28}H_{33}N_2O\): C 62.22, H 6.15, N 5.18; found: C 62.21, H 6.30, N 5.12.

2. Nitrile 71: The methiodide of 73 (18.5 g) and potassium cyanide (10 g) were stirred in refluxing acetonitrile (500 ml) for ca. 40 h. The mixture was cooled and filtered. The filtrate was washed with water (twice), brine (twice), dried, and concentrated in vacuo. Chromatography of the residue provided the nitrile 71 (10.6 g, 82%) as a thick gum.
UV $\lambda_{\text{max}}$: 222 (4.59), 275 (3.93), 283 (3.93), 295 (3.84); IR $\nu_{\text{max}}$: 2250, 740, 700; $^1$Hmr $\delta$: 3.04 (2H, t, J = 6.5 Hz, -CH$_2$CH$_2$O-), 3.66 (2H, t, J = 6.5 Hz, -CH$_2$CH$_2$O-), 3.69 (2H, s, -CH$_2$CN), 4.44 (2H, s, -OCH$_2$O), 5.40 (2H, s, NCH$_2$O), 6.8-7.7 (14H, m, aromatic-H$_{14}$); MS m/e: 91 (100%), 289, 380 ($M^+$). High resolution molecular weight determination calculated for C$_{26}$H$_{24}$N$_2$O: 380.1887; found: 380.1909.

(N-Benzyl-2-carbomethoxymethyl-tryptophyl)-benzyl Ether (72)

A solution of the nitrile 71 (14.4 g) in dry methanol (400 ml) and water (4 ml), cooled to ca. 0°C, was saturated with hydrogen chloride and then stirred for 72 h at room temperature. The solvent was partitioned between saturated sodium bicarbonate and dichloromethane. The organic layer was washed with water, brine, dried over sodium sulphate and evaporated. Purification of the residue by column chromatography afforded the ester 72 (10.5 g, 67%). UV $\lambda_{\text{max}}$: 224 (4.53), 277 (3.87), 287 (3.90), 295 (3.81); IR $\nu_{\text{max}}$: 1735, 740, 700; $^1$Hmr $\delta$: 3.09 (2H, t, J = 7 Hz, -CH$_2$CH$_2$O-), 3.43 (3H, s, -OCH$_3$), 3.68 (2H, t, J = 7 Hz, -CH$_2$CH$_2$O-), 3.71 (2H, s, -CO$_2$CH$_3$), 4.48 (2H, s, -OCH$_2$O), 5.38 (2H, s, NCH$_2$O), 6.8-7.7 (14H, m, aromatic-H$_{14}$); MS m/e: 91 (100%), 292, 312, 413 ($M^+$). High resolution molecular weight determination calculated for C$_{27}$H$_{27}$NO$_3$: 
Enamine 85

A solution of the ester 72 (160 mg) in dry tetrahydrofuran (2 ml) was added to a solution of lithium diisopropylamide (0.84 mmol) in tetrahydrofuran (10 ml) and HMPA (0.13 ml) at -78°C under a nitrogen atmosphere. The solution was stirred at -78°C for 15 min then allowed to attain 0°C. The adduct of dimethylformamide and dimethyl sulphate (1:1, 1 g)108 was added and the mixture stirred at 0°C for 2 h. The mixture was diluted with water and extracted with ethyl acetate. The extract was washed with water, brine, dried (Na₂SO₄), and evaporated. Chromatography on silica gel gave 72 (68 mg) together with the enamine (85) (30%), which can be recrystallized from methanol. Mp: 112-113°C;

UV \( \lambda_{\text{max}} \): 224, 281; IR \( \nu_{\text{max}} \): 1665, 1600; \(^1\)Hmr \( \delta \): 2.42 (6H, br.s, -N(CH\(_3\))\(_2\)), 2.92 (2H, m, -CH\(_2\)CH\(_2\)O-), 3.33 (3H, s, -CO\(_2\)CH\(_3\)), 3.64 (2H, m, -CH\(_2\)CH\(_2\)O-), 4.48 (2H, s, -OCH\(_2\)Ø), 5.12 (2H, AB system, J = 16 Hz, NCH\(_2\)Ø), 7.0-7.7 (14H, m, aromatic-H\(_{14}\)); 7.71 (1H, s, C = C(H)N(CH\(_3\))\(_2\); MS m/e: 91, 256, 316, 347, 468 (M\(^+\), 100%). Analysis calculated for C\(_{30}\)H\(_{32}\)N\(_2\)O\(_3\): C 76.90, H 6.88, N 5.98; found: C 76.69, H 6.97, N 6.25.
Acrylic Ester 86

Glacial acetic acid (8 drops) was added to a solution of the enamine 85 (50 mg) and sodium cyanoborohydride (50 mg) in methanol and tetrahydrofuran (1:1, 8 ml) and the mixture stirred under a nitrogen atmosphere for 18 h. The mixture was evaporated and the residue partitioned between saturated sodium bicarbonate solution and ethyl acetate. The extract was washed with water, brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue consisted of a mixture of two compounds that were separated by preparative TLC (silica gel; petroleum ether - ethyl acetate 1:4). The less polar compound (16 mg, 37%) was identified as the acrylic ester 86; Mp: 87-89°C; UV $\lambda_{max}$: 223, 276; IR $\nu_{max}$: 1720, 1615; $^1$Hmr $\delta$: 3.05 (2H, t, J = 7.5 Hz, CH$_2$CH$_2$O$-$), 3.52 (3H, s, -CO$_2$CH$_3$), 3.72 (2H, t, J = 7.5 Hz, -CH$_2$CH$_2$O$-$), 4.53 (2H, s, -OCH$_2$O), 5.20 (2H s, NCH$_2$O), 5.89 (1H, d, J = 2 Hz, C = CH$_3$), 6.75 (1H, d, J = 2 Hz, C = CH$_2$), 7.0-7.8 (14H, m, aromatic-H$_{14}$); MS m/e: 91, 304 (100%), 425 (M$^+$). Analysis calculated for C$_{28}$H$_{27}$NO$_3$: C 79.03, H 6.50, N 3.29; found: C 78.21, H 6.50, N 3.21.

The other component of the mixture (8 mg) was not fully characterized due to its instability. The structure corresponding to the reduced enamine was tentatively assigned. $^1$Hmr $\delta$: 2.03 (s, -N(CH$_3$)$_2$), 3.41 (s, -CO$_2$CH$_3$), 4.52 (s, -OCH$_2$O), 5.38 (s, NCH$_2$O), 6.8-7.6 (aromatic protons).
Enol 87

Potassium diisopropylamide was prepared at -30 to 0°C from potassium hydride (5.5 ml of 20% dispersion in oil) and diisopropylamine (10 ml) in dry tetrahydrofuran (50 ml) and dry HMPA (5 ml). A solution of 32 (3.0 g) in dry tetrahydrofuran (10 ml) was added at -30°C. The mixture was stirred at this temperature for 15 min, at ambient temperature for 1 h, then cooled to -30°C. Dry methyl formate (50 ml) was added and the mixture stirred at ambient temperature for 18 h and diluted with water (100 ml), ethyl acetate (250 ml), and 1N HCl (100 ml). The organic layer was washed with (Na₂SO₄), and concentrated in vacuo. Chromatography on silica gel gave the crude enol 87 (2.6 g) as a pale yellow crystalline solid, satisfactory for use in further reactions. Recrystallization from methanol gave pure 87 (2.1 g, 65%); mp: 88-90°C; UV λ<sub>max</sub>: 225 (4.45), 275 (4.17), 286 (4.12), 295 (4.01); IR ν<sub>max</sub>: 3500-3000, 1665, 1605; ¹Hmr δ: 2.95 (2H, t, J = 7 Hz, pCH₂CH₂O⁻), 3.35 (3H, s, -OCH₃), 3.64 (2H, t, J = 7 Hz, -CH₂CH₂O⁻), 4.46 (2H, s, -OCH₂Ø), 5.11 (2H, s, NCH₂Ø), 6.8-7.8 (16H, m, aromatic protons); MS m/e: 91 (100%), 288, 289, 290, 320, 441 (M⁺). Analysis calculated for C₂₈H₂₇NO₄: C 76.17, H 6.16, N 3.17; found: C 76.16, H 6.0, N 3.35.
Enol 88

The enol 87 (52 mg) and 10% Pd/C catalyst (11 mg) were stirred in methanol (5 ml) under one atmosphere of hydrogen at ambient temperature for 9 h. The mixture was filtered through Celite and the filtrate concentrated in vacuo. Chromatography on silica gel gave 87 (12 mg) and 88 (28 mg, 67%) as a clear gum. UV $\lambda_{\text{max}}$: 225, 276; IR $\nu_{\text{max}}$: 3700-3200, 1665, 1610; $^1$Hmr $\delta$: 2.88 (2H, poorly resolved triplet, $-\text{CH}_2\text{CH}_2\text{O}$), 3.36 (3H, br. s, $-\text{OCH}_3$), 3.72 (2H, poorly resolved triplet, $-\text{CH}_2\text{CH}_2\text{O}$), 5.11 (2H, br. s, $\text{NCH}_2\text{O}$), 6.4-7.7 (aromatic protons); MS m/e: 91 (100%), 288, 289, 292, 319, 320, 251 (M$^+$).

Methyl Enol Ethers 89 and 91

Excess ethereal diazomethane was added at 0-5°C to a solution of 88 (55 mg) in ethyl acetate (2 ml). The solution was kept at this temperature for 12 h. Excess reagent and solvent were removed by passage of nitrogen. Chromatography of the residue provided 88 (16 mg) together with ethers 89 and 91. These two compounds were separated by preparative TLC (silica gel, petroleum ether – ethyl acetate 3:2, developed four times). The least polar was the major component of the mixture and was identified (E) enol ether 91, based on the
calculated chemical shift for the vinylic proton (vide infra).

UV $\lambda_{\text{max}}$: 226 (4.56), 288 (3.86); IR $\nu_{\text{max}}$: 3660, 3600, 3560, 1700, 1630; $^1\text{Hmr} \delta$: 1.85 (1H, br. s, -CH$_2$OH), 2.93 (2H, t, J = 6 Hz, -CH$_2$CH$_2$OH), 3.57 (3H, s, -CO$_2$CH$_3$), 3.69 (3H, s, =C(H)OCH$_3$), 4.86 (2H, t, J = 6 Hz, -CH$_2$CH$_2$OH), 5.16 (2H, s, NCH$_2$Ø), 7.0-7.6 (9H, m, aromatic-H$_9$), 7.69 (1H, s, =C(H)OCH$_3$); MS m/e: 91, 334 (100%), 365 (M$^+$). High resolution molecular weight determination calculated for C$_{22}$H$_{23}$NO$_4$: 365.1627; found: 365.1627.

The other compound isolated (6 mg, 10.5%) was identified as the Z-isomer of the methyl enol ether (89). UV $\lambda_{\text{max}}$: 226 (4.56), 289 (3.89); IR $\nu_{\text{max}}$: 3550, 1710, 1630; $^1\text{Hmr} \delta$: 1.7 (1H, br. s, -CH$_2$OH), 3.05 (2H, t, J = 6 Hz, -CH$_2$CH$_2$OH), 3.51 (3H, s, -CO$_2$CH$_3$), 3.79 (3H, s, =C(H)OCH$_3$), 3.88 (2H, t, J = 6 Hz, -CH$_2$CH$_2$OH), 5.24 (2H, s, NCH$_2$Ø), 6.52 (1H, s, =C(H)OCH$_3$), 6.9-7.8 (9H, m, aromatic-H$_9$); MS m/e: 91, 334 (100%), 365 (M$^+$). High resolution molecular weight determination calculated for C$_{22}$H$_{23}$NO$_4$: 365.1627; found: 365.1628.

Chemical shift calculation for the vinyl proton in 89 and 91110:

(Z)isomer:  
\[
\begin{align*}
\text{Aromatic} & \quad \text{H} \\
\text{CH}_3\text{O}_2\text{C} & \quad \text{OCH}_3
\end{align*}
\]

(E)isomer:  
\[
\begin{align*}
\text{Aromatic} & \quad \text{OCH}_3 \\
\text{CH}_3\text{O}_2\text{C} & \quad \text{H}
\end{align*}
\]
<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base:</td>
<td>5.28</td>
<td>Base:</td>
<td>5.28</td>
</tr>
<tr>
<td>gem OR:</td>
<td>1.18</td>
<td>gem OR:</td>
<td>1.18</td>
</tr>
<tr>
<td>cis Aromatic</td>
<td>0.37</td>
<td>trans Aromatic</td>
<td>-0.1</td>
</tr>
<tr>
<td>trans CO$_2$R(conj.)</td>
<td>0.33</td>
<td>cis CO$_2$R(conj.)</td>
<td>1.02</td>
</tr>
<tr>
<td></td>
<td>7.16</td>
<td></td>
<td>7.38</td>
</tr>
</tbody>
</table>
The work presented in this thesis was finished in May 1976. Since that time, several important advances have been obtained by Dr. Kutney's group, based on the findings presented here:

The use of enol ethers $\text{89}$ and $\text{91}$ was not as helpful as was thought, since with time, this compound dimerizes to a substance not yet identified. These compounds are also very resistant to hydrolysis$^{111}$. This led to the reinvestigation of the complexation reaction, and it was found that flash chromatography of the reaction mixture obtained in the complexation reaction, using degassed florisil and degassed solvents (methylene chloride and THF), definitely improved the yield of the dihydropyridine complexes$^{112}$. It was also found that when the dihydropyridine $\text{37}$ was used a mixture of three chromium complexes was formed$^{112}$ (Diagram 55).

Finally, the synthesis of N-benzyl 3,14-dehydrosecodine has already been completed, using the sequence of reactions described in Diagram 56.
Complexation Reaction of N-(2-Carbomethoxymethyl-tryptophyl)-3-ethyl-1,2-dihydropyridine (37)
Synthesis of N-Benzyl-3,14-dehydrosecodine

\[
\begin{align*}
\text{R} & = \text{CH}_2\text{C}_6\text{H}_5 \\
\text{pyridine 50}^\circ\text{C} & \rightarrow \\
& \begin{bmatrix}
\text{N} & \text{C} \\
\text{R} & \text{CO}_2\text{CH}_3 \\
\end{bmatrix}
\end{align*}
\]
DIAGRAM 57

Numbering System of Indole Alkaloids\textsuperscript{113}
REFERENCES

1. For excellent reviews of the biosyntheses of indole alkaloids see:


30. A.I. Scott, "Cell-Free Biosynthesis of Natural Products from Tissue Cultures of Higher Plants", at the Fifth International Symposium on Natural Products, Monterrey, N.L., Mexico (1978).


59. For excellent reviews on the chemistry of dihydropyridines see:


   c) Japan Kokai 73-99,181 (C.A. 80:95749g).


77. R.M. Acheson, P.A. Tasker, unpublished results, see Ref. 584 in Eisner and Kuthan review.


110. Chapter 3-3 in Ref. 93.

