STUDIES
IN STEROIDS AND ALKALOIDS
by
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Dipl. Chem. The University of Athens - Greece, 1959
M.Sc., The University of British Columbia, 1963.

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF THE
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DOCTOR OF PHILOSOPHY
in the Department
of
Chemistry

We accept this thesis as conforming to the
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THE UNIVERSITY OF BRITISH COLUMBIA
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FOR THE DEGREE OF

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of

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STUDIES IN STEROIDS AND ALKALOIDS

ABSTRACT

In part I of this thesis are described our studies in the area of aza steroids. These investigations involve chemical and spectroscopic studies of these compounds.

Lithium aluminum hydride reduction of \(3\beta\)-hydroxy-11-aza-5\(\alpha\),22\(\beta\)-spirost-8(9)-en-12-one (72) provides the enamine, (73), which upon subsequent conversion to its iminium salt, (75), and borohydride reduction yields 11-aza-5\(\alpha\),8\(\gamma\),9\(\alpha\),22\(\beta\)-spirostan-3\(\beta\)-ol (76). This reaction furnishes a convenient sequence for reduction of the 8,9-double bond in 11-aza steroid derivatives. Degradation of the sapogenin side chain then allows entry into 11-aza pregnane derivatives. The synthetic sequence provides the first examples of 11-aza steroid analogues in which ring C is six-membered and completely saturated.

A detailed discussion of the mass spectra of 6- and 11-aza steroid derivatives is presented.

In part II of this thesis is described our work which relates to a synthetic approach to the Iboga and Aspidosperma alkaloids. The first section involves the synthesis of 2-carbomethoxy-3-[\(\alpha\)-hydroxy-\(\beta\)-(3-carbomethoxy-N-piperidyl)-ethyl]-indole (78) and 3-\(\beta\)-(3-carbomethoxy-N-piperidyl)-ethyl]-indole-2-acetic acid methyl ester (93).

The Hoesch reaction was used for the synthesis of 2-carbomethoxy-3-chloroacetylindole (75) from 2-carbomethoxy-indole (74) and chloroacetonitrile. Treatment of 75 with 3-carbomethoxy piperidine (76) yielded 2-carbomethoxy-3-(3-carbomethoxy-N-piperidyl)-acetylindole (77). The latter was reduced with sodium borohydride or by catalytic hydrogenation with Raney nickel to 78. Prolonged hydrogenation of 77 or 78 with Raney nickel catalyst provided 2-carbomethoxy-3-[\(\alpha\)-hydroxy-\(\beta\)-(3-carbomethoxy-N-piperidyl)ethyl]-4,5,6,7-tetrahydroindole (79). Similarly 2-carbomethoxy-indole (74) was reduced to 2-carbomethoxy-4,5,6,7-tetrahydro-indole (80) by hydrogenation with platinum oxide catalyst.

The Hoesch reaction was also used for the synthesis of 3-chloroacetylindole-2-acetic acid methyl ester (89) from indole-2-acetic acid methyl ester (88) and chloroacetonitrile. Treatment of 89 with 3-carbomethoxy
piperdine (76) provided 3-(3-carbomethoxy-N-piperidyl)-acetylindole-2-acetic acid methyl ester (92). The latter substance was reduced with diborane to 93.

The second section provides the synthesis of 1,2,3,5,6,11,11b(ξ)-heptahydro-2ξ-(3-chloroprophyl)-2ξ-ethyl-3-oxo-indolo(2,3-g)indolizine (118). The fundamental reaction involved condensation of tryptamine with either ethyl α-keto-γ-(γ-benzylxypropyl)-γ-ethyl-glutarate (70b) or ethyl α-(γ-benzylxypropyl)-α-ethyl-succinate (70a). When glutarate 70b was condensed with tryptamine the amides 110 and 111 were obtained. On the other hand the succinate 70a reacted with tryptamine to afford the desired N-[β-(3-indolyl)-ethyl]-α-(γ-benzylxypropyl)-α-ethyl-succinimide (112). Treatment of the latter substance with boron tribromide yielded N-[β-(3-indolyl)-ethyl]-α-(3-hydroxypropyl)-α-ethyl-succinimide (115), which was subsequently converted to N-[β-(3-indolyl)-ethyl]-α-(3-chloropropyl)-α-ethyl-succinimide (116) with thionyl chloride. Cyclization of the latter substance with phosphorus pentoxide afforded 2,3,5,6,11-pentahydro-2ξ-(3-chloropropyl)-2ξ-ethyl-3-oxo-indolo(2,3-g) indolizine (117), which on hydrogenation with platinum oxide yielded 118.

The glutarate 70b and the succinate 70a involved in the above syntheses were obtained via a series of established reactions, starting from benzyl -chloropropyl ether (101).

GRADUATE STUDIES

Fields of Study: Chemistry

Topics in Physical Chemistry
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A. Rosenthal
PUBLICATIONS


Synthesis of 6-Aza Steroids. A Novel Class of Steroidal Sapogenin Analogues.

ABSTRACT

In part I of this thesis are described our studies in the area of aza steroids. These investigations involve chemical and spectroscopic studies of these compounds.

Lithium aluminum hydride reduction of 3β-hydroxy-11-aza-5α,22β-spirostan-8(9)-en-12-one (72) provides the enamine, (73), which upon subsequent conversion to its iminium salt, (75), and borohydride reduction yields 11-aza-5α,8β,9α,22β-spirostan-3β-ol (76). This reaction furnishes a convenient sequence for reduction of the 8,9-double bond in 11-aza steroid derivatives. Degradation of the sapogenin side chain then allows entry into 11-aza pregnane derivatives. The synthetic sequence provides the first examples of 11-aza steroid analogues in which ring C is six-membered and completely saturated.

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PART I

Studies in Aza Steroids
SECTION A

The synthesis of the 11-aza steroids

Introduction

In recent years there have been numerous investigations concerned with the effect of substituents attached to the normal steroid skeleton on the biological properties of these important substances. These investigations have brought forth the realization that very dramatic alterations in these properties are indeed encountered when such substituents as halogen, particularly fluorine, hydroxyl and methyl are placed at rather specific positions in the molecule.\(^1\)\(^-\)\(^3\) These steroidal derivatives still possess the basic steroid skeleton so that the nature of the molecule is not altered to a very significant extent. Our own interest in this area was directed toward the introduction of a hetero atom in the steroid skeleton. In particular, the substitution of a nitrogen atom may provide aza steroids which exhibit new types of biological activity. Dorfman et al. had reported some interesting findings in this regard.\(^4\) A more detailed discussion by Doorenbos indicated that aza steroids indeed provide a rich source of new drugs against certain diseases.\(^5\)

For example, the acetate derivatives of 17β-hydroxy-4-aza-androst-5-en-3-one (1) and 17β-hydroxy-17α-methyl-4-aza-androst-5-en-3-one (2) (Figure 1) exhibited androgenic activity equivalent to one seventh and one fifth that of testosterone by a chick comb injection test. The latter compound and 17β-hydroxy-4-aza-19-norandrosten-3-one (3) when injected on the chick's comb at a dose of 2 mg, inhibited the action of testosterone administered by subcutaneous injection.\(^4\) The compounds, N-methyl-4-aza-3β-methyl-5α-cholestane (4) and N,N-dimethyl-4-aza-3β-benzyl-5α-cholestane iodide (5)
Figure 1. Some Biologically Active Aza Steroids.
have been found to block the reduction of desmosterol to cholesterol during the biosynthesis of cholesterol.

\[
\begin{align*}
\text{Acetyl-coenzyme A} & \quad \rightarrow \quad \text{Acetoacetyl-coenzyme A} \\
\text{3-Hydroxy-3-methylglutaryl-coenzyme A} & \quad \rightarrow \quad \text{Mevalonic acid} \\
\text{Squalene} & \quad \rightarrow \quad \text{Lanosterol} \\
\text{Zymosterol} & \quad \rightarrow \quad \text{Desmosterol} \\
\text{Cholesterol} & \quad \rightarrow \\
\end{align*}
\]

Figure 2. Scheme Showing the Important Intermediates in the Biosynthesis of Cholesterol.

Counsell and co-workers have also discovered that a group of diaza derivatives of cholesterol apparently block the conversion of 3-hydroxy-3-methylglutaryl-coenzyme A into mevalonic acid. One of the most effective
compounds in this connection is 20,25-diazacholesterol (6). It is suggested that these substances which block the biosynthesis of cholesterol may be of clinical value for the treatment of the disease atherosclerosis, which is associated with abnormally high serum cholesterol levels.\(^5,6\)

Some aza steroids may also exert a marked increase in cholesterol biosynthesis. The most active of these are 3α-N-ethanolamino-cholestane (7) and N-phenyl-4-aza-5-cholestan-3-one (8). These derivatives are useful in deducing sclerotic lesions in laboratory animals without resorting to high levels of cholesterol in the diet.

Besides these properties aza steroids have been reported to possess anabolic, anti-bacterial, anti-fungal, hypotensive, coronary artery dilating, CNS stimulant, CNS depressant, neuromuscular blocking, anti-inflammatory, and androgenic activities.\(^6\)

The introduction of a nitrogen atom into the steroid nucleus has attracted the interests of chemists for some time. As a result of numerous investigations particularly during recent years, nitrogen atoms have been introduced into virtually every position on the steroid nucleus as well as in the side-chain.

An excellent literature survey on the various aza steroid syntheses is given by Djerassi\(^7\) whereas the side-chain introduction is given in reference 8. A review of the recent literature reveals that a considerable number of investigations have been carried out in the field of aza steroids. It would be pertinent to discuss this work briefly at this point of the thesis.

The Beckmann rearrangement has been utilized frequently in these syntheses and recently the oximes of a 1-keto steroid (9) and the corresponding 1-keto-A-nor derivative (12) were converted to the 1-aza-A-homo (10) or
the 1-aza analogue (13) possessing the conventional steroid skeleton. The 1,10-seco-1-cyano compounds 11 and 14 also obtained via abnormal rearrangement.\(^9\) (Figure 3).

Figure 3. Synthesis of 1-Aza and 1-Aza-A-homo Steroids.

The oxime of 5α-cholestan-2-one (15) on Beckmann rearrangement provided a mixture of 2- and 3-aza-A-homo lactams (16) and (17) which could be separated and reduced with lithium aluminum hydride to the corresponding 2- and 3-aza-A-homo-5α-cholestanes 18 and 19 respectively.\(^9\) On the other hand, the Beckmann rearrangement of the oxime of A-nor-5α-cholestan-2-one (20) provided an inseparable mixture of 2-aza-5α-cholestan-3-one (21) and 3-aza-5α-cholestan-2-one (22).\(^10\) The authors were able to separate the two products as their dichloro derivatives (23) and (24) and distinguish between them in their reactivity with collidine (Figure 4). The results concerning Beckmann
rearrangement of 2-keto steroids were in agreement with previous investigations on the 2-oximino-A-nor-5β-cholanate series.\textsuperscript{11}

Similarly the Beckmann rearrangement of the 5α-cholestan-3-one oxime (25) provided an inseparable mixture of the 3- and 4-aza-A-homo derivatives (26) and (27).\textsuperscript{12} On the other hand, Beckmann rearrangement of the oxime of a

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4}
\caption{Synthesis of Some 2- and 3-Aza Steroids.}
\end{figure}
Δ⁴-3-keto steroid (28) provided only the unsaturated lactam (29) which after catalytic hydrogenation and lithium aluminum hydride reduction gave the 3-aza-A-homo steroid analogue (30). In this particular case it was found that the yield of the lactam (29) was independent of the relative amounts of the syn and anti forms of the oxime present in the mixture at least under the particular conditions used for the Beckmann rearrangement (SOCl₂ in dioxane). These results indicated that the reaction product was not necessarily related configurationally to the starting oxime as may be expected from the mechanism of the Beckmann rearrangement (Figure 5).

The synthesis of a 3-aza equilenin derivative (33) has been recently accomplished via an intramolecular interconversion of 2-aminoequilenin-3,4-quinone (31) with peracetic acid and subsequent decarboxylation of the acid (32) with copper powder. The high physiological activity associated with some 4-aza steroid derivatives has stimulated an extensive research towards the synthesis of these compounds. Doorenbos and his coworkers have reported recently a number of 3- and 4- substituted 4-aza steroids. In this work intermediate keto acid (34) was cyclized with the appropriate amines to provide 4-hydroxy (35), 4-amino (36) and 4-alkylamino (37) steroid derivatives as well as other heterocyclic steroids which include nitrogen in the steroid skeleton (38). On the other hand, 3-alkyl- or 3-aryl-4-aza steroids (41) have been obtained from the reaction of the saturated lactam (39) and an appropriate Grignard reagent followed by subsequent hydrogenation of the resultant enamine (40) (Figure 7).

The synthesis of 5-aza-A-nor-B-homo and 5-aza-A-nor steroids (45) and (49) has been accomplished via a Beckmann rearrangement of the keto ester oximes (42) and (46), cyclization of the resulting lactams (43)
Figure 5. Synthesis of Some 3- and 4-Aza-A-homo Steroids.

Figure 6. Synthesis of 3-Aza-4-hydroxy Equilenin.
Figure 7. Synthesis of Some 3- and 4-Substituted 4-Aza Steroids.
and (47) with phosphorus oxychloride and subsequent reduction of the imides (44) and (48) (Figure 8).

Figure 8. Synthesis of Some 5-Aza Steroids.
A successful sequence leading to the synthesis of 6-aza steroids has been developed in our laboratory several years ago. This sequence as well as a similar one independently conceived by Jacobs and Brownfield provided the first general synthesis of ring B aza steroids. Other workers have also succeeded in the synthesis of 6-aza steroids by using a modified Curtius reaction. The elimination of the C-3 oxygen function during the course of the above sequences was a disadvantage for the synthesis of steroid derivatives in which such a function was to be retained. Knof was able to overcome this difficulty by reduction of the intermediate isocyanate in the Curtius reaction sequence. To support these results Knof suggested the existence of an equilibrium between the isocyanate and the lactone. The latter intermediate on catalytic hydrogenation or lithium aluminum hydride reduction leads to 52 and 53 respectively. (Figure 10).

The total synthesis of 6-aza steroids in the estrogenic series has been independently reported recently by three groups of workers. Burckhalter and Wattanabe were able to obtain the ketone from which the synthesis, involving several modifications of Johnson's classic equilenin synthesis led to dl-6-aza equilenin (Figure 11).

Another attractive approach to 6-aza equilenin and other 6-aza estrone derivatives has been independently reported (Figure 12).

The synthesis of 6-aza-B-homo steroids has been recently reported (Figure 13).

Another sequence involving the Beckmann rearrangement of a 7-keto oxime provided the 7a-aza-B-homo steroids (Figure 14).

The synthesis of the true 7-aza steroid system was accomplished by a Beckmann rearrangement of the 5β-B-nor-6-ketoxime (Figure 15).
Figure 9. Preparation of 6-Aza Steroids Using Ring Cleavage and Enol-lactam Ring Closure.
Figure 10. Synthesis of 6-Aza Steroids via a Modified Curtius Reaction.
Figure 11. Total Synthesis of dl-6-Aza Equilenin.
Figure 12. Total Synthesis of dl-6-Aza Equilenin and Other 6-Aza Estrone Derivatives.
Figure 13. Synthesis of 6-Aza-B-homo Steroids.

Figure 14. Synthesis of 7α-Aza-B-homo Steroids.
The total synthesis of aza steroids containing a nitrogen atom at a bridge head position has been recently reported. Clarkson\textsuperscript{36} has accomplished the synthesis of 8-aza estrone (62) and his synthetic sequence is summarized in Figure 16.
Meltzer et al.\textsuperscript{37} reported the formation of six diastereoisomers due to the development of C\textsubscript{9}, C\textsubscript{13}, and C\textsubscript{14} asymmetric centers in their synthetic approach to 8-aza estrone (63) (Figure 17).

Meyers et al.\textsuperscript{38} have developed a synthetic approach to both 8- and 9-aza steroidal analogues (64) and (65) (Figure 18).
Figure 17. Synthesis of 8-Aza Estrone Derivatives.

The synthesis of 13-aza-18-nor equilenin methyl ether (66) has been recently reported independently by two groups of workers.

The synthetic sequence by Kessar et al\textsuperscript{39} is given in Figure 19.

Birch and Subba Rao\textsuperscript{40} have developed a synthetic approach to 13-aza-18-nor as well as 13-aza-18-nor-D-homo equilenin methyl ether (66) and (67) (Figure 20).

Rakjit and Gut\textsuperscript{41} synthesized 17-aza pregnane derivatives (69) using the lactam (68) as starting material\textsuperscript{42} (Figure 21).
Figure 18. Synthesis of 8- and 9-Aza Steroids.
Figure 19. Synthesis of 13-Aza-18-nor Equilenin Methyl Ether.
With appropriate modifications of the above sequence and using the lactam 70 as starting material, 17-aza progesterone (71) was obtained (Figure 21).

Some diaza cholesterol derivatives and particularly 20,25-diaza-cholesterol (6) was found to be extremely potent inhibitor of cholesterol biosynthesis in laboratory animals. In an effort to obtain further insight as to the mode of action of this compound a series of cholesterol isosteres having only one nitrogen atom in the side chain was synthesized as shown in Figure 22.
Figure 21. Synthesis of Some 17-Aza Pregnan Derivatives.
Figure 22. Synthesis of Some Side Chain Aza Cholesterol Derivatives.
The above discussion has summarized the recent work in other laboratories on the synthesis of various aza steroids. I would now like to return to our investigations in this area.

I have already mentioned above that we had succeeded in developing a synthetic sequence for the introduction of a nitrogen function into ring B of the steroid skeleton. This work provided some of the first examples of 6-aza steroids in which the normal steroid skeleton was retained. We subsequently extended out studies to the synthesis of ring C-aza steroids and succeeded in preparing the first 11-aza derivative in the steroidal sapogenin series. The synthetic sequence is illustrated in Figure 23.

This part of the thesis describes the extension of this work to 11-aza pregnane derivatives.

Figure 23. Synthesis of 11-Aza Steroids via the Seco-keto Acid Method.
Discussion

The synthesis of 11-aza pregnane derivatives from the synthetic intermediate bearing the spiroketal side chain (72) required the investigations of two distinct reactions: (a) reduction of the 8,9 double bond to provide the saturated system in ring C and (b) degradation of the spiroketal side chain. Since the latter phase of this problem was expected to follow the well-known degradation of steroidal sapogenins to the pregnane series, initial consideration was given to part (a).

From previous results in our laboratory in the area of 6-aza steroids and those of other workers it was apparent that the hydride reduction of an enol lactam system could lead to either an enamine or imine function. We decided to investigate this possibility in the case of the 11-aza intermediate (72). Reduction of 72 with lithium aluminum hydride in refluxing tetrahydrofuran provided a new reaction product and the spectral properties of this material quickly established that the lactam had been reduced. The strong lactam absorption present in the infrared spectrum of 72 had disappeared and instead, a weak absorption at 6.13 μ characteristic of the enamine chromophore was evident.

The expected shift to 6.02 μ was also observed in the infrared spectrum of the hydrochloride salt of (73) in good agreement with published work on α,β-unsaturated amines. Furthermore, the characteristic absorption in the ultraviolet spectrum of the enol lactam (72) (λ max 255 μ) was also absent in the ultraviolet spectrum of the reduction product but now a new absorption at 236 μ was noted. This data was again in good agreement with the enamine chromophore which has been extensively investigated in the ultraviolet region by Leonard and co-workers. This evidence excludes the imine chromophore since the >C=N− grouping would not exhibit these spectral...
properties and we assign structure (73) to this reduction product. In spite of numerous attempts to obtain this enamine crystalline, we were unsuccessful and consequently characterized this compound as the acetate, (74).

It should be noted at this point that Engel and Rakhit$^{50}$ have reported a similar reduction and also postualte an enamine grouping although no spectral data is presented for the product obtained directly from the reduction. They also encountered difficulties in obtaining a crystalline product and report spectral data on the crystalline acetate derivative of the enamine.

Having obtained the $\Delta^{8,9}$-11-aza hecogenin derivative, (73) we then considered the reduction of the 8,9 double bond. It is well known from the normal steroid series that this double bond is particularly difficult to hydrogenate and the necessary conditions would almost certainly destroy the spiroketal system so that this method could not be seriously considered. It was felt that one way to eliminate this difficulty would be to convert the enamine, (73) into the iminium system, (75), and then subsequently reduce the latter by means of a hydride reagent. The conversion, $>\text{C=CH}_2< \rightarrow >\text{C=CH}<$, is well known from the work of Leonard on unsaturated amines$^{48,51}$ and strong support for the success of this reaction was already evident from the observed shift in the infrared spectrum of the salt derivative of 73. Indeed when the enamine, (73) was first treated with anhydrous hydrogen chloride and the resulting crude product was subjected to reduction with sodium borohydride, we obtained after chromatographic purification, the desired reduction product, (76) m.p. 211-212°C, as one of the crystalline substances from this reaction. Three other crystalline products were actually obtained from this reaction and the pertinent data is discussed below although further work is necessary before complete
Figure 24.
structural assignments can be made in these instances. The reduction product (76), exhibited the expected spectral properties in agreement with the assigned structure. The compound no longer showed any absorption in the ultraviolet spectrum and the enamine absorption in the infrared region was also absent. The characteristic spiroketal bands\textsuperscript{52,53} were still present in the fingerprint region of the infrared spectrum and therefore indicated that, as expected, the spiroketal system was still intact.

Nuclear magnetic resonance (NMR) spectroscopy also played an important role in providing confirmatory evidence for all the structures in this investigation. This was possible since in relation to another problem a detailed analysis of the NMR spectra of a large number of known steroidal sapogenins had been carried out\textsuperscript{54,55} and pertinent regions of the NMR spectra could be now assigned with certainty. It is necessary at this point to discuss briefly some of the relevant features of the previous work as they apply to the present study.

Dr. Kutney had previously shown that in the instance of saturated sapogenins, the low field region of the NMR spectra indicated only two sets of signals. One set was observed as a broad multiplet which showed two main broad signals in the region 200-210 c.p.s., which was attributed to $C_{26}$ protons of the spiroketal system and the other set at lower field (250-300 c.p.s.) was due to the lone proton at $C_{16}$ and the $C_3$ proton in the case of $C_3$-acetylated sapogenins. With this information on hand one could readily analyse the low field region of the NMR spectrum of 76.

As expected the $C_{16}$ proton appeared as a broad signal in the region, 245-280 c.p.s. The $C_{26}$ and $C_3$ proton signals were also clearly evident in the region 190-230 c.p.s. but in addition to these signals, new sets of lines appeared in the region 130-185 c.p.s. and these corresponded in area
to three additional protons. This region is normally completely devoid of any signals as shown by the spectra of numerous steroidal sapogenins and it was immediately obvious that these absorptions were due to protons on carbon atoms attached to the basic nitrogen atom (C₉ and C₁₂). This latter fact was confirmed when the NMR spectra of the crystalline monoacetate (77) and diacetate (78) were analyzed (See Figures 26 and 27). One would expect that in the former only the C₃ proton would be shifted downfield and indeed this was the case. The broad absorption signal in the 245-300 c.p.s. region integrated for two protons while the proton absorption in the 130-190 c.p.s. region remained essentially unchanged. In the case of the diacetate (78) it was now expected that the C₉ and C₁₂ protons would be shifted downfield as well. There was a general downfield shift of the signals in the 130-185 c.p.s. region and most important, this region now constituted an area due to only two protons. A new one-proton signal now appeared as a broad doublet at lower field (220-245 c.p.s.) and was attributed to the C₉ proton. The presence of the O-acetyl group in 77 was confirmed by a singlet at 117 c.p.s. Similarly the O-acetyl and N-acetyl groupings in 78 were confirmed by the singlets at 118 and 128 c.p.s. The proximity of the N-acetyl function to the C₁₉ angular methyl group could also be recognized by analysis of the high field region in the NMR spectra of 76 and 78. In the former, the two angular methyl groups were barely separated and were observed as two sharp lines at 53 and 55 c.p.s. respectively, whereas in the latter a larger separation was noted (47 and 58 c.p.s.) and, as expected, the C₁₉ signal now occurred at lower field. It was now clear that the sodium borohydride reduction had been successful.
Figure 26.
Figure 27.
Having assigned structure 76 to this reduction product, I would like to mention some data which has been obtained for the other three crystalline products (arbitrarily assigned as A, B and C isolated from this reaction. Mass spectrometry which became available to us after this project was essentially completed, has played a major role in providing structural evidence for these compounds. Although mass spectra are discussed in detail in the subsequent section of this thesis a brief mention of this data is necessary at this time.

First of all, the IR spectra of all three compounds indicated the characteristic absorption bands (980, 923, 900 and 865 cm\(^{-1}\)) for the spiro-ketal side chain. In confirmation of this result was the presence of a significant signal at m/e 139 in the mass spectra of these compounds - a feature characteristic of steroid sapogenins. Furthermore the IR spectra also indicated the presence of -NH and -OH groups in these compounds.

The mass spectrum of A indicated that this substance was an isomer of 76 (at C\(_8\) and/or C\(_9\)) since it possessed a molecular ion peak at m/e 417 and a series of signals which were common to both 76 and A.

The mass spectra of B and C indicated molecular ion peaks at m/e 434 and also strong M-18 signal at m/e 416. This evidence suggested that an additional hydroxyl function was present in these compounds. Although an insufficient amount of B was available for NMR studies, the NMR spectrum of C indicated the characteristic signals of the C\(_{16}\) and C\(_{26}\) protons at 263 and 204 c.p.s. respectively. It was noted that signals due to five or six protons were also present in the region 120-190 c.p.s. These spectral properties allow us to make a tentative assignment of structure 83 to the compounds B and C with the difference between them being one of stereo-chemistry at the asymmetric centers C\(_8\) and/or C\(_9\). It is clear that further
work is necessary before any more definite conclusions can be reached. The conversion of the iminium intermediate 75 to structure 83 could arise by a simple hydrolysis of this intermediate to the amino-ketone 82 and subsequent reduction as shown in Figure 28.

The stereochemistry of the newly created asymmetric centers (C₈ and C₉) in (76) deserves some comment. Although it is clear that the evidence presented here does not rigorously establish these asymmetric centers, consideration of the conformational expressions for the intermediates involved does allow tentative assignments.

The initial process involving the conversion of the enamine, (73), to the iminium intermediate, (75), generates an asymmetric carbon atom C₈ and this should be considered presently. Conformational structures for both possibilities (8α and 8β) are shown in 84 and 85 respectively, since it is felt that approach of the hydrogen atom is probable from either side of the molecule. It is immediately obvious that in the 8α isomer, (84), ring B adopts the boat conformation and serious interactions exist between the "flagpole" hydrogen atoms at C₅ and C₈ and also between the 7β hydrogen and
the C₁₈ angular methyl group. On the other hand, in the 8β isomer, (85), ring B is not in a boat conformation and there are not severe interactions of the type encountered in 84. In fact the overall conformation of the molecule closely approximates that of the normal trans-anti-trans backbone of the natural steroids. If one is justified to consider that the conversion of 73 to 75 is a process which leads to equilibration, then the 8β isomer (85), is certainly the preferred structure. Consideration of the next step, namely the borohydride reduction of the iminium intermediate to the final product, (76), reveals that the approach of hydride from the 9α side in both 8α and 8β isomers is very much preferred. In both 84 and 85 the two angular methyl groups prevent effective approach from the β side of the molecule.

The stereochemistry of sodium borohydride reductions of certain preformed iminium slats has been studied by Bohlmann. In this work it was shown that attack of hydride occurred from the least hindered side of the molecule in its most stable conformer.

On the basis of our considerations and the above investigation, we postulate that the most likely stereochemistry at C₈ and C₉ in the reduction product, (76), and in all subsequent substances reported below is 8β, 9α so
that the normal steroid stereochemistry persists. Although this speculation does not provide absolute proof for these stereochemical centers, it is not possible to present any more rigorous data at this time since conclusive correlation to the conventional steroid system is not directly feasible.

Now that the enamine group had been reduced to a more stable system we then considered the well known degradation of the spiroketal side shain to $\Delta^{16}$-20-keto-pregnene derivatives.\(^{57}\) (See Figure 29).

![Figure 29](image)

When the reduction product, (76), was treated with acetic anhydride at 200° for ten hours, a brown oily product was obtained which, without further purification, was subjected to oxidation with chromium trioxide and the crude oily oxidation product was subjected to the action of aqueous potassium hydroxide at room temperature.

The final crude product was purified by chromatography on alumina to provide initially the expected 11-aza-pren-16-en-20-one derivativem (80). The spectral properties of this crystalline material were in agreement with structure (80). The infrared spectrum indicated three strong absorptions of
equal intensity at 5.78, 6.04 and 6.13 μ for the \(\text{O-acetyl,}^\Delta_{16}\text{20-keto and N-acetyl groupings. The conjugated ketone chromophore was further confirmed by the ultraviolet spectrum which showed an absorption at 325 μ. Finally the NMR spectrum (Figure 30) was again very instructive and completely confirmed the structural assignment. A broad, one-proton signal centered at 403 c.p.s. indicated the presence of the \(\text{C}_{16}\) olefinic hydrogen atom and a very sharp line at 135 c.p.s. due to three protons was easily assigned to the \(\text{C}_{21}\) methyl group. Indeed comparison of these signals with those observed in the NMR spectrum of \(\Delta^\Delta_{16}\text{-allopregnane-20-one which has the same system in ring D, showed excellent agreement.}^{58}\) The effect of the N-acetyl group on the two angular methyl protons was again clearly indicated since their signals are shifted to lower field (62 and 57 c.p.s.) relative to those observed in \(\Delta^\Delta_{16}\text{-allopregnane-20-one (52 and 48 c.p.s.). Finally the region 180-300 c.p.s, which is completely transparent in the spectrum of the allopregnane derivative indicates several sets of multiplets in the NMR spectrum of 80. The total area under these signals corresponds to four protons and apart from the lone proton at \(\text{C}_3\) which normally shows a broad multiplet in the region, 270-300 c.p.s., the remaining signals are obviously due to the \(\text{C}_9\) and \(\text{C}_{12}\) protons of this aza steroid derivative.

A second solid product was obtained in the later chromatographic fractions of the reaction mixture from the sapogenin side chain degradation. The spectral properties suggested immediately that it was merely the 3\(\beta\)-hydroxy-1\(\alpha\)-N-acetyl derivative, (79). The ultraviolet spectrum was identical with that observed for the diacetate, (80), but the infrared spectrum now indicated only two strong absorptions at 6.04 and 6.15 μ for the conjugated ketone and N-acetyl groups respectively. The structure 79 was conclusively established when acetylation of this compound provided the triacetate, (80).
Figure 30.
The final step in this sequence, namely the reduction of the 16,17-double bond was readily accomplished by catalytic hydrogenation. This reduction product indicated no absorption in the ultraviolet region and the infrared spectrum revealed three strong absorption bands at 5.79, 5.88 and 6.08 μ for the three carbonyl groups now present in the molecule. The NMR spectrum of this compound was also in agreement with the assigned structure, (81).
Conclusion

A synthesis of 11-aza steroids with the true steroid skeleton has been developed. This represents the first synthesis of an 11-aza steroid of the pregnane series. The sequence employs hecogenin acetate as starting material to provide the necessary intermediate 9,12-seco keto acid which cyclizes in the presence of ammonia to an enol lactam intermediate. Lithium aluminum hydride reduction of the enol lactam provides the corresponding enamine whose immonium salt can be reduced with sodium borohydride to an 11-aza steroidal sapogenin analogue. Degradation of the sapogenin side chain provides the 11-aza steroids possessing the acetyl side chain at C₁₇. These intermediates may possibly provide a convenient route to the adreno-cortical class as well.
Experimental

All melting points were determined on a Kofler apparatus and are uncorrected. The ultraviolet spectra were recorded in 95% ethyl alcohol on a Cary 14 recording spectrophotometer and the rotations were taken in 1% chloroform solutions. The infrared spectra were determined on a Perkin-Elmer Model 21 spectrophotometer. Analyses were performed by A. Bernhardt and his associates, Mulheim (Ruhr), Germany. The NMR spectra were taken in deuteriochloroform solutions on a Varian A60 instrument; the line positions or centers of multiplets are given in cycles per second (c.p.s.) scale with reference to tetramethylsilane as the internal standard. The multiplicity, and integrated area and type of protons are indicated in parentheses. Every molecular weight (M.W.) quoted was determined mass spectrometrically.

3β-Hydroxy-11-aza-5α,22β-spirost-8(9)-ene (73)

The enol lactam (72) (12.9 g) was dissolved in anhydrous tetrahydrofuran (1000 ml) and refluxed for 20 hours with lithium aluminum hydride (4 g) which was initially placed in a Soxhlet apparatus and gradually brought into the vessel by the refluxing solvent. The solvent was evaporated in vacuo and the residue decomposed cautiously by the addition of wet ethyl ether. The mixture was then treated with water, the ether layer separated and dried over anhydrous magnesium sulfate. Removal of the solvent provided a semi-solid product (10.6 g). This material was treated with ether (300 ml) and the white insoluble solid which remained undissolved was removed by filtration (5.5 g). Three recrystallizations of this material from ether provided a pure sample, m.p. 173-175° (block preheated to about 168°); [α]D22 -30°; infrared (KBr): 2.94 (broad), 6.11υ; no ultraviolet absorption. This material is very difficult to analyze and its structure is still in question.
The ethereal filtrate was then concentrated to yield (73) as an oil (5 g) which resisted all attempts to crystallize; infrared (Nujol): 2.94 (broad), 6.13 μ (1632 cm⁻¹, weak); infrared of HCl salt (Nujol): 6.02 μ (1660 cm⁻¹, weak); ultraviolet: λ_max 236 μ (alcohol); λ_max 272 μ (alcohol solution containing a few drops of concentrated hydrochloric acid).

The aqueous layer was extracted exhaustively with ether in a continuous extraction apparatus (12 hrs). The ether extract was dried over anhydrous magnesium sulfate and then concentrated in vacuo, to yield a further 1.5 g of (73).

3β-Acetoxy-N-acetyl-11-aza-5α,22-spirost-8(9)-ene (74)

The oily enamine, (73) (500 mg) was dissolved in pyridine (10 ml) and treated with acetic anhydride (20 ml). The mixture was allowed to stand at room temperature for 24 hours, after which time it was treated cautiously with water and extracted with ether. The ether extract was washed several times with water, then with 5% aqueous sodium bicarbonate solution and again with water. Filtration and removal of the solvent in vacuo provided an oil product (500 mg). This material was chromatographed on alumina (20 g, activity III). Elution with petroleum ether-benzene (1:3) and benzene yielded an oily material (200 mg). Final purification of this product was accomplished by preparative thin-layer chromatography (silica gel G, with chloroform-ethyl acetate (1:1) as developling medium, R_f = 0.65) and the analytical sample (50 mg) of 74 was obtained as an amorphous solid: [α]_D^22 + 56°; infrared (CHCl₃) 5.82, 6.15μ. Found: C, 71.81; H, 9.43; O, 16.41; N, 2.55. Calc. for C₃₀H₄₅O₅N: C, 72.11; H, 9.08; O, 16.01; N, 2.80
Sodium Borohydride Reduction of Enamine

The enamine, (73), (4.9 g) was dissolved in absolute methanol (500 ml) and hydrogen chloride gas was then passed through the solution until it was strongly acidic. The solvent was removed in vacuo and the reddish residue was taken up in absolute methanol (3000 ml). The resulting solution was treated with sodium borohydride (20 g) and the mixture then refluxed for five hours. The solvent was removed in vacuo and the residue dissolved in ether. The ether solution was first washed with water, then dried over anhydrous magnesium sulfate and finally concentrated in vacuo to provide a white solid (4.6 g). This material was dissolved in benzene and chromatographed on alumina (18 g, activity III). Elution with benzene chloroform (9:1) provided a crystalline material (312 mg) which upon recrystallization from ether-hexane yielded an analytical sample, m.p. 167-170°; [α]_D$^{22}$ -60°; infrared (KBr): 2.96 μ; no ultraviolet absorption. Found: C, 73.97; H, 10.31; O, 12.26; N, 3.57; M.W. 417. Further work is required before a definite structure can be assigned to this compound.

The desired product (1.42 g) was eluted from the column with benzene-chloroform (3:1). Three recrystallizations from benzene provided an analytical sample (1.3 g) of 11-aza-5α,8α, α,228-spirostan-3β-ol (76), m.p. 211-212°; [α]_D$^{22}$ -60°; infrared (KBr): 2.84 μ (sharp, NH), 2.94 μ (broad, OH); no ultraviolet absorption, NMR: 275-250 (broad multiplet, 1H, C_16 proton), 230-130 (complex pattern, 6H, C_3+C_9+C_12+C_26 protons), 58, 55, 53, 49, 44, (multiplet, 12H, C_16+C_19+C_21+C_27 methyl protons). Found: C, 74.56; H, 10.21; O, 11.40; N, 3.84; M.W. 417. Calc. for C_26H_43O_3N: C, 74.77; H, 10.38; O, 11.49; N, 3.35; M.W. 417.

Elution with benzene-chloroform (3:2) provide another crystalline compound (410 mg). Recrystallization from methylene chloride-hexane
yielded an analytical sample, m.p. 179-183°; \([\alpha]_D^{22} -100^\circ\); infrared (KBr):
5.90, 6.09\(\mu\); no ultraviolet absorption. Found: C, 69.61; H, 9.09; O, 17.72; N, 3.82; M.W. 434. Further work is required before a definite structure can be deduced for this compound.

Elution with benzene-chloroform (1:3) and finally with chloroform yielded the fourth crystalline compound (1.83 g). Three recrystallizations from methylene chloride-hexane provided the analytical sample, m.p. 227-228°; \([\alpha]_D^{22} -109^\circ\); infrared (KBr): 2.84\(\mu\) (sharp, NH), 2.94\(\mu\) (broad, OH); no ultraviolet absorption; NMR: 275-250 (broad multiplet, 1H, C\(_6\) proton), 230-225 (multiplet, 2H, C\(_{26}\) protons), 225-120 (complex pattern, approximately 5H) 60-37 (complex pattern, 11H, region of methyl protons). Found: C, 70.58, 70.40; H, 9.98, 9.76; O, 15.82, 16.38; N, 3.29; 3.83; M.W. 434.

**Acetylation of 76**

The alcohol, 76, (200 mg) was dissolved in pyridine (5 ml), treated with acetic anhydride (5 ml) and allowed to stand at room temperature for 24 hours. The reaction mixture was cautiously treated with water and then with ether. The ether solution was washed several times with water, then with 5% aqueous hydrochloric acid, water, and finally with 5% aqueous sodium carbonate solution. After drying over anhydrous magnesium sulfate, the solvent was removed in vacuo to provide an oily product (140 mg). This material was recrystallized twice from hexane to provide an analytical sample of the diacetate, (78) m.p. 195-198°; \([\alpha]_D^{22} -14^\circ\); infrared (KBr):
5.79, 6.07\(\mu\); NMR 300-250 (broad multiplet, 2H, C\(_3\)+C\(_{16}\) protons), 250-135 (complex pattern, 5H, C\(_3\)+C\(_{26}\)+C\(_{12}\) protons), 130 (singlet, 3H, N-C-CH\(_3\)), 117 (singlet, 3H, O-C-CH\(_3\)), 58, 55, 48, 44 (multiplet, 12H, C\(_{18}\)+C\(_{19}\)+C\(_{21}\)+C\(_{27}\) methyl protons). Found: C, 71.59; H, 9.23; O, 15.32; M.W. 501. Calc.
The hydrochloric acid washings were made basic with 10\% aqueous sodium hydroxide and the organic precipitate was extracted with ether. The ether solution was washed with water, dried over anhydrous magnesium sulfate and concentrated \textit{in vacuo} to provide a crystalline product (40 mg). Recrystallization of this compound from dichloromethane-hexane provided an analytical sample of the monoacetate, \((77)\), m.p. 210.213\(^\circ\); \([\alpha]_D^{22} -59^\circ\); infrared (KBr): 5.78; NMR: 300-250 (broad multiplet, 2H, C\(_3\)+C\(_{16}\) protons), 250-150 (complex \(0^\circ\) pattern, 5H, C\(_9\)+C\(_{26}\)+C\(_{12}\) protons), 117 (singlet, 3H, O-C-CH\(_3\)), 59, 55, 49, 44 (multiplet, 12H, C\(_{18}\)+C\(_{19}\)+C\(_{21}\)+C\(_{27}\) methyl protons). Found: C, 73.50; H, 9.97; N, 3.66. Calc. for C\(_{28}\)H\(_{45}\)O\(_4\)N: C, 73.16; H, 9.87; N, 3.05.

**Degradation of Sapogenin Side Chain**

The procedure used here was essentially that of Wall\(^\text{57}\) with slight modifications.

The alcohol, \((76)\), (4.2 g) was subjected to the action of acetic anhydride (60 ml) in a sealed tube at 200\(^\circ\)C for 11 hours. The reaction mixture was treated with methanol to destroy the excess anhydride and the solution was concentrated \textit{in vacuo} to yield a brownish oily residue. This residue was taken up in glacial acetic acid (100 ml) and the solution was cooled to 15\(^\circ\)C. To this cold solution, a solution of chromium trioxide (2 g) in 80\% acetic acid (16 ml) was added dropwise over a period of 20 minutes while the reaction temperature was kept at 15\(^\circ\)C. The mixture was allowed to stand at 22\(^\circ\)C for 15 hours, then treated with water to allow the organic material to precipitate. This precipitate was extracted with ether and the ether extract was washed successively with water, aqueous potassium carbonate and finally with water. After drying over anhydrous magnesium sulfate, the solvent was removed to provide a white amorphous
This material was dissolved in t-butyl alcohol (100 ml) and a solution of potassium hydroxide (1 g potassium hydroxide in 2 ml of H₂O was added. This mixture was stirred vigorously for 2.5 hours at room temperature. The reaction mixture was treated with ether (500 ml) and the solvent, after drying over anhydrous magnesium sulfate, yielded an amorphous product (2.7 g). This material was dissolved in a small amount of benzene and chromatographed on alumina (110 g, activity III). Elution with benzene-chloroform (4:1) yielded 3\(\delta\),11-diacetoxy-11-aza-5\(\alpha\)_,8\(\delta\),9\(\alpha\)-pregn-16-en-20-one (80) (850 mg), m.p. 185-188°; \([\alpha]_D^{22} +110°\); infrared (KBr): 5.78, 6.04, 6.13\(\mu\); ultraviolet: \(\lambda_{\text{max}}^{\text{max}}\) 235 \(\mu\) (log \(e\) 3.99); NMR: 404 (broad singlet, 1H, C\(_{16}\) proton), 300-250 (complex pattern, 2H, C\(_3\)+C\(_9\) protons), 250-180 (complex pattern, 2H, C\(_{12}\) protons), 135 (singlet, 3H, C\(_{21}\) methyl protons), 120 (singlet, 3H, N-C-CH\(_3\)), 117 (singlet, 3H, O-C-CH\(_3\)), 62 (singlet, 3H, C\(_{18}\) methyl protons), 57 (singlet, 3H, C\(_{18}\) methyl protons). Found: C, 71.98; H, 8.80; O, 15.35; N, 3.79; M.W. 401. Calc. for C\(_{24}\)H\(_{35}\)O\(_4\)N: C, 71.79; H, 8.79; O, 15.94; N, 3.49; M.W. 401.

Further elution with benzene-chloroform (2:3) provided a second product (1.1 g) which on two recrystallizations from ether yielded an analytical sample of the monoacetate, (79) m.p. 191-194°; infrared (KBr): 2.90, 6.04, 6.13\(\mu\); ultraviolet: \(\lambda_{\text{max}}^{\text{max}}\) 234 \(\mu\) (log \(e\) 3.92); NMR: 405 (broad singlet, 1H, C\(_{16}\) proton), 300-250 (complex pattern, 2H, C\(_3\)+C\(_9\) protons), 250-170 (complex pattern, 2H, C\(_{12}\) protons), 135 (singlet, 3H, C\(_{21}\) methyl protons), 119 (singlet, 3H, N-C-CH\(_3\)) 60 (singlet, 3H, C\(_{18}\) methyl protons), 56 (singlet, 3H, C\(_{19}\) methyl protons). Found: C, 73.26; H, 9.52; N, 4.41; M.W. 359. Calc. for C\(_{22}\)H\(_{33}\)O\(_3\)N: C, 73.50; H, 9.25; N, 3.90; M.W. 359.
Acetylation of (79)

The alcohol, (79), (50 mg) was dissolved in pyridine (1 ml) and treated with acetic anhydride (1 ml). After allowing to stand at room temperature for 24 hours, the mixture was cautiously treated with water and extracted with ether. The ethereal solution was washed successively with water, 5% aqueous sodium carbonate and finally with water and then dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo provided a crystalline product (50 mg) which was shown to be identical in every respect with 80.

Catalytic Reduction of (80)

The diacetate, (80), (70 mg) was dissolved in 95% ethanol (10 ml) and hydrogenated at room temperature and atmospheric pressure with 10% palladium on charcoal (30 mg). The catalyst was filtered and the ethanol was removed in vacuo to provide a crystalline product (70 mg). Three recrystallizations of this material from methylene chloride-hexane provided an analytical sample of 3β,11-diacetoxyl-11-aza-5α,8β,9α-pregnan-20-one, (81), m.p. 188-192°; [α]D^{22} +71°; infrared (KBr): 5.79, 5.88 and 6.08 μ; NMR: 130 (singlet, 3H, C21 methyl protons), 128 (singlet, 3H, N-CH3), 118 (singlet, 3H, O-C-CH3), 58 (singlet, 3H, C19 methyl protons), 42 (singlet, 3H, C18 methyl protons). Found: C, 71.55; H, 9.16; O, 15.23; N, 3.74; M.W. 403. Calc. for C24H37O4N: C, 71.43; H, 9.24; O, 15.86; N, 3.47; M.W. 403.
SECTION B

Mass spectra of 6-aza and 11-aza steroids

Introduction

Mass spectrometry has become a particularly effective physical method in the structural elucidation of natural products and in recent years a tremendous effort has been put forth on investigations with this technique. A number of excellent books on this subject have appeared from various laboratories but the one most pertinent to this discussion has been published by a Stanford University group. This book deals with the application of mass spectrometry to structure elucidation of natural products with special reference to steroids. In this work it is emphasized that the general fragmentation pattern of the steroid skeleton, upon electron impact, is highly susceptible to the directing influence of substituents. The ability of the substituent to stabilize a positive charge in the molecular ion as well as in the fragment ions, determine the degree of its influence on the fragmentation process. For example, nitrogen substituents as well as the ethylene ketal and aromatic functions stabilize the positive charge so effectively that they often have the ability to direct the fragmentation in a specific manner. In this way this influence often overcomes fission reactions promoted by other more common steroid substituents.

The marked effect of the nitrogen atom in directing the fragmentation process was well demonstrated from the numerous investigations in the alkaloid field. Also of relevance to this discussion was the examination of the mass spectra of a number of steroidal alkaloids and dimethyl amino steroid derivatives, in which the nitrogen function is connected in different ways to the steroid skeleton.
The successful synthesis of 6-aza and 11-aza steroids in our laboratory has furnished us with compounds in which the nitrogen atom is incorporated into the steroid skeleton. We considered it of considerable interest to examine the mass spectra of these compounds since such an investigation may not only provide some interesting fragmentation processes but will also allow us to extend this technique to other structural problems in aza steroids.
Discussion

For the sake of clarity this discussion will consider the mass spectra of 6-aza and 11-aza steroids in separate sections. It must be indicated at the outset that throughout this entire discussion, I present "mechanistic rationalizations" in an attempt to provide some insight into the possible modes of fragmentation and explain the appearance of significant peaks in the mass spectra. It must be emphasized that these postulates are by no means established but are mainly put forth as being reasonable on the basis of the extensive investigations of Djerassi and other researchers in this field.

A. The mass spectra of 6-aza-5\(\alpha\)-steroids

For studies in the 6-aza series, the mass spectra of 6-aza-5\(\alpha\)-cholestan (86) and 17\(\beta\)-hydroxy-6-aza-5\(\alpha\)-androstane (87) were first examined (Figure 31).

The 6-aza cholestan derivative (86) indicates significant peaks at m/e 538 (M-15), 344 (M-29), 330 (M-43) 316 (M-57), 302 (M-71), 164 and 124. Similarly the corresponding fragments in the androstane compound (87) are also present (m/e 262, 248, 234, 220, 206 164 and 124.

The M-15 peak is due to the loss of a methyl group, most probably the one at C\(_{19}\).

The most abundant M-57 fragment can be derived by homolytic cleavage of the C\(_{4}\)-C\(_{5}\) linkage to provide the primary radical II. The allilic C\(_{1}\)-C\(_{10}\) bond now cleaves to yield the radical III which in turn can lose a hydrogen atom to provide the fully conjugated ion IV (M-57).
On the other hand, homolysis of the C₅-C₁₀ linkage provides the tertiary radical V which can be the common precursor for the fragment ions occurring at m/e 344 and 248 (M-29), 330 and 234 (M-43) as well as 302 and 206 (M-71) in the spectra of 86 and 87 respectively. Loss of CH₃CH₂. (or CH₂=CH₂ plus one hydrogen) provides the M-29 fragment ion VI and its formation occurs only to a small extent. Transfer of a hydrogen atom from C₉ to C₁₀ provides an equally well stabilized tertiary radical VII which can give rise to the primary radical VIII by homolytic cleavage of the C₁-C₁₀ bond. The C₃–C₄ linkage is now activated and suffers homolysis to the allylic radical IX. The latter species loses one hydrogen atom to provide the fully conjugated M-43 ion X.

Furthermore a hydrogen transfer from C₈ to C₁₀ in V can generate the tertiary radical XI. Homolysis of the C₉-C₁₀ bond will provide the secondary
radical XII which could then cleave at C₃-C₄ to afford the allylic radical XIII. The latter intermediate would lose one hydrogen atom at C₇ to provide the stable substituted dihydro pyridinium ion XIV (M-71).

Another fragmentation process which is expected in this system, can be initiated by the cleavage of the C₇-C₈ linkage to generate the secondary radical XV.

\[ \text{XVIII} \rightarrow \text{XV} \rightarrow \text{XVI} \]

In fact it is felt that the fragment occurring at m/3 124 is possibly due to this type of fragmentation. Homolytic cleavage of the C₉-C₁₀ bond in XV would provide the tertiary radical XVI, which loses the C₅ hydrogen atom to afford the conjugated immonium ion XVII (m/3 124).

Another common signal (m/e 164) in the mass spectra of 86 and 87 is possibly derived by the homolytic cleavage of the C₈-C₁₄ and C₁₂-C₁₃ bonds to the fragment XVIII.

The spectrum of the cholestane analogue (86) also indicates a signal at m/e 288 which can be attributed to the loss of C₆H₁₃. from the molecular ion and we believe that this represents cleavage of the C₂₀-C₂₂ bond in the side chain.
The N-benzyl-6-aza steroids indicate a very similar fragmentation pattern but of course with the additional presence of a number of signals due to the presence of the benzyl group. For example the mass spectra of the N-benzyl-6-aza-5\(\alpha\)-cholestane (88), 17\(\beta\)-hydroxy-N-benzyl-6-aza-5\(\alpha\)-androstan (89) and 20\(\beta\)-hydroxy-N-benzyl-6-aza-5\(\beta\)-pregnane (90) possess a common peak (m/e 91) due to the fragment C\(_7\)H\(_7\)\(^+\). Also the significant M-77 and M-91 fragments which occur at m/e 387, 289, 318 and 373, 275, 304 in the three spectra respectively are due to the loss of a phenyl (C\(_6\)H\(_5\)\(^-\)) or benzyl (C\(_6\)H\(_5\)CH\(_2\)\(^-\)) moiety from the molecular ion. It is to be noted that these peaks are absent in the spectra of the parent 6-aza compound. Again, the most abundant peak (besides the molecular ion peak) in the spectra of these compounds is the one corresponding to the M-57 fragment.

The fragments XVII and XVIII which were expected to appear at m/e 214 (124 + 90) and 254 (164 + 90) are no longer present in the spectra of these compounds. This is not too surprising when one considers the low abundance of these fragments in the spectra of the parent 6-aza steroids and the competing strong fragmentation which may be expected across the N-benzyl bond in the N-benzyl-6-aza homologues.

The spectrum of the pregnane analogue (90) also indicates a signal at m/e 350 which can be attributed to the loss of CH\(_3\)CH\(_2\)O\(^-\) from the molecular ion presumably due to the cleavage of the C\(_{17}\)-C\(_{20}\) bond in the side chain.

It is pertinent at this point to discuss briefly some recently published work\(^{60}\) on the mass spectra of cyclic amines such as piperidine. Due to the rigidity of the tetracyclic system of the 6-aza steroids, many of the mechanistic interpretations for the principal ions observed in the mass spectrum of piperidine cannot be applied directly to our series but some comparisons are certainly of interest. Three fragments which are
Figure 34.

Relative Intensity

- 91
- 373 (M-91)
- 379 (M-85)
- 387 (M-77)
- 393 (M-71)
- 407 (M-57)
- 421 (M-43)
- 435 (M-29)
- 449 (M-15)
- 464 M⁺
Figure 35.

Relative Intensity

0  2  4  6  8  10  12  14  16  18  20

0  0  0  0  0  0  0  0  0  0  0

100

150

200

250

300

350

275 (M-91)

289 (M-77)

295 (M-71)

309 (M-57)

323 (M-43)

337 (M-29)

348 (M-18)

351 (M-15)

366 M^+
Figure 36.

Relative Intensity

Charge - Relative Intensity

304 (M-91)  \( \times 6.3 \)

318 (M-77)  \( \times 6.3 \)

324 (M-71)  \( \times 1.5 \)

338 (M-57)  \( \times 5.3 \)

350 (M-45)  \( \times 2.1 \)

366 (M-29)  \( \times 1.8 \)

380 (M-15)  \( \times 7,395, M^+ \)

m/e

- 65 -
observed in the spectrum of piperidine at m/e 84 (XIX) (M-1), 56 (XX) and 30 (XXI) are of some relevance since they arise via fragmentation processes which are possible in the above compounds.

In the spectra of 6-aza steroids the fragments corresponding to XIX and XX can be represented by XXII and XVII. The fragment XXII (M-1) is considerably less abundant than the corresponding one (XIX) in the spectrum of piperidine. As it was mentioned in the above discussion the signal m/e 124 in the spectra of compounds 85 and 86 was attributed to fragment XVII. Obviously, no conclusive indication can be drawn for the formation of the fragment XXI (m/e 30) from the mass spectra of the aza steroids since this region is too complicated.
B. The mass spectra of 6-aza-5α-7-one steroids

The presence of a carbonyl group at the C7 position of the 6-aza steroid skeleton has a dramatic effect on the fragmentation pattern of these compounds (Figure 37). The mass spectra of these compounds reveal several significant differences when compared to those discussed in the preceding section. These are: a) a very strong molecular ion peak as well as intense M-1 and M-2 peaks; b) considerable variation in the fragmentation process and c) the significant fragments retain the A and B rings of the molecule and arise from cleavage of bonds in rings C and D. The fragmentation of ring A occurs to a minor extent in this series.

Evidence in support of the retention of ring A and B in these fragments is provided from several separate sets of results: a) the fact that the occurrence of these fragments is independent of the nature of the side chain at C17; b) the fragmentation of the enol lactams (to be discussed
later) which possess an additional double bond at C\textsubscript{4}-C\textsubscript{5} indicates, as expected, that these fragments now occur at m/e values which are lower by two units and c) the fragmentation of the N-benzyl-6-aza-7-one derivatives provides fragment ions at m/e values which are higher by ninety units.

I will attempt to provide possible mechanisms for the formation of these fragments which occur at m/e 166, 179, 192, 206, 220 etc. in the spectra which were obtained.

The formation of the m/e 166 fragment (XXIII) could be visualized as arising through the homolysis of the C\textsubscript{8}-C\textsubscript{14} and C\textsubscript{9}-C\textsubscript{11} as shown in the following scheme. However, in view of some very recent work\textsuperscript{66,67} the suggested hydrogen transfer may not occur because of the large interatomic distance between the hydrogen at C-15 and the oxygen atom at C-7. Perhaps this fragment arises via homolytic cleavage of the C\textsubscript{8}-C\textsubscript{14} bond.

\[ \text{XXIII} \]

The fragment XXVII (m/e 179) and XXIX (m/e 192) may be formed from the ion radical XXV which arises by a hydrogen transfer from C\textsubscript{9} to C\textsubscript{8} in the enol form XXIV of the molecular ion and subsequent homolysis of the
C\textsubscript{8}-C\textsubscript{14} bond to provide the radical XXVI. The latter species by cleavage of the C\textsubscript{11}-C\textsubscript{12} bond provides the fragment XXVII. On the other hand, homolysis of the C\textsubscript{12}-C\textsubscript{13} bond provides the radical XXVIII which loses one hydrogen to give the conjugated immonium ion XXIX.

A possible rationalization for the formation of the other fragment utilizes a cleavage of the C\textsubscript{13}-C\textsubscript{14} linkage to generate the species XXX which can be the intermediate for a number of fragment ions. This intermediate can lose the tertiary hydrogen at C\textsubscript{17} to provide the ion XXXI and further homolysis of the allylic C\textsubscript{15}-C\textsubscript{16} and C\textsubscript{11}-C\textsubscript{12} linkages gives the immonium ion XXXII (m/e 206).

If the intermediate XXX cleaves at the C\textsubscript{11}-C\textsubscript{12} position it will provide the radical XXXIII which may proceed to the ion XXXIV (m/e 220) by the indicated pathway.
Another fragment of the same mass as XXXIV can be formed from XXX through an analogous sequence of intermediates. Homolysis of the \( C_{16}C_{17} \) bond in XXX provides the radical XXXV which by hydrogen transfer from \( C_9 \) to \( C_{16} \) generates the tertiary allylic radical XXXVI. Cleavage of the \( C_{11}-C_{12} \) bond in the latter species provides a conjugated immonium ion at \( m/e \) 220.

If hydrogen transfer from \( C_{15} \) to \( C_{13} \) takes place in XXX, and subsequent fission of the \( C_{16}-C_{17} \) bond occurs, the species XXXVII is formed
and this intermediate can be the precursor for a number of fragments as shown in the scheme below. Homolysis of the C₁₂-C₁₃ bond provides the allylic radical XXXVIII (m/e 233), which can lose one hydrogen atom to afford the conjugated ion XXXIX (m/e 232). If cleavage of the C₁₂-C₁₃ bond takes place with simultaneous hydrogen atom transfer from the C₁₇ substituent R (R= -C₆H₁₇ or -OH) to C₁₂, the immonium ion XL is obtained (m/e 234).

The formation of the fragments at m/e 232, 233, 234 can be also visualized through another fragmentation process. Fission of the C₁₄-C₁₅ bond in XXIV provide the intermediate radical XLI which upon hydrogen atom transfer from the C₁₇ substituent R (R= -C₆H₁₇ or -OH) to C₁₅ and subsequent cleavage of the C₁₃-C₁₇ bond generates the allylic radical XLII (m/e 233). This latter species could lose one hydrogen atom to provide
the fragment ion XXXIX. If the cleavage of the C_{13}-C_{17} bond takes place with simultaneous hydrogen transfer from C_{16} to C_{13} in XLI the fragment ion XLIII arises (m/e 324).

The abundant fragment XLIV (m/e 274) can be formed by homolytic cleavage of the C_{17} -R(R= C_8H_{17} , -OH) bond in the intermediate XXX.

In an analogous fashion rationalizations in the formation of the significant fragments occurring at m/e 246 (XLV), 247 (XLVI), 248 (XLVII) and 260 (XLVIII) are presented in the scheme below.
There are rather intense peaks due to M-28, M-29 and M-43 fragment ions in the spectra of these compounds and these can be attributed to the loss of CO, CHO and CO plus \( \cdot \text{CH}_3 \) from the molecular ion respectively.

The mass spectra of 91 and 92 possess relatively strong signals at m/e 292 and 196 respectively. These signals differ from the corresponding molecular ions by 95 mass units and therefore, their formation can be considered as being derived by loss of the elements of ring A.

The formation of this M-95 fragment can be visualized by cleavage
of the C₉-C₁₀ bond in the molecular ion XXIV to provide the tertiary radical XLIX, subsequent fission of the C₅-N bond and a hydrogen transfer from C₄ to N via a four-membered cyclic transition state.

The above mechanistic interpretation for the formation of the M-95 fragment is in great agreement with the main fragmentation of aliphatic amines as described in a recent publication.⁶¹

Other characteristic peaks in the spectra of these compounds are the M-15 for the loss of -CH₃ from the molecular ion, M-18 for the loss of water, M-33 for the loss of H₂O and CH₃ in the androstane analogue, (92) and a significant signal at M-85 for the loss of C₆H₁₃ from the side chain in the cholestane derivative, (91).

It is now of considerable interest to compare the mass spectral results obtained in the N-benzyl compounds 93, 94 and 95 with those discussed above. The abundant fragments which were mentioned above were postulated as resulting from cleavage of the bonds in ring C and D. Such a suggestion would receive support if the significant fragments in the
Figure 40.

Relative Intensity

- 228
- 256
- 269
- 282
- 296
- 310
- 322
- 342
- 364
- 372
- 386 (M-91) x 5.3
- 392 (M-85) x 3.4
- 400 (M-77) x 2.6
- 434 (M-43)
- 449 (M-28)
- 462 (M-15) x 1.5
- 477M⁺ x 13
- 477M⁺ x 4.8
Figure 41.

Relative Intensity

- 91
- 256
- 282
- 286
- 290 (M-91)
- 296
- 304 (M-77)
- 322
- 324
- 336
- 351
- 364
- 366 (M-15)
- x1.9 x4.3
- 381 M^+
N-benzyl series were now occurring at m/e values which were higher by 90 mass units. This situation would of course prevail only if fragmentation in rings C and D occurred prior to any significant loss of the benzyl group. Indeed inspection of the mass spectra, as for example in the case of compound 93, reveals that this is the case - the peaks now occur at m/e 256 (166 + 90), 269 (179 + 90), 282 (192 + 90) etc. Although the abundance of these fragments is not very high it must be recognized that in general, the intensity of all peaks relative to the molecular ion signal is considerably lower in these spectra than in those of compounds 91 and 92.

As in the case of the N-benzyl compounds 88, 89 and 90, the mass spectra of the N-benzyl-6-aza-7-one analogues 93, 94 and 95 indicate the presence of fragments at m/e 91, m/e 386, 290, 360 (M-91) and m/e 400, 304, 374 (M-77) respectively which are due to the presence of the benzyl group.

Again the peaks due to the fragments M-18 and M-33 are present in the spectrum of 94 whereas the spectrum of 93 indicates the signal due to the loss of \( \cdot \text{C}_6\text{H}_{13} \) from the side chain, while that of 95 reveals a M-87 \( \text{H} \) fragment due to the loss of the side chain (\( \text{CH}_3\text{-C-OAC} \)).

I would like now to discuss briefly at this point the work published by Djerassi et al\(^\text{62}\) on the mass spectra of lactams such as 2-piperidone. These results have some relevance to our work in the mass spectra of 6-aza-5\( \alpha \)-7-one steroids, since they provide evidence for the fragmentation patterns on simple lactam systems. However, only the arguments which are pertinent here will be presented.

In the mass spectrum of 2-piperidone a peak at m/e 71 (LII or LIII, M-28) is noted and is believed to arise from the loss of ethylene rather than carbon monoxide from the molecular ion L or LI. This conclusion is based on the unobserved shift of the peak at m/e 71 to m/e 73 in the
3,3-dideuterio compound.

If this type of fragmentation occurred in compounds 91 and 92, the fragments LIV or LV which correspond to LII or LIII would appear at m/e 139. However, the spectra of these aza steroids do not possess a significant signal at this point (m/e 139). On the other hand, the relatively intense signals due to M-28 fragments (which are also observed in the spectra of the N-benzyl analogues 93, 94 and 95) are probably due to the loss of carbon monoxide or ethylene which could be expelled from another part of the molecule. Further work with deuterium-labelled compounds would be necessary before any distinction could be made between the two alternatives.

For the mechanistic interpretation of the formation of the fragment at m/e 70 (M-29) three mechanisms were postulated and are shown below. These workers showed with deuterium labelling that mechanism 1 predominates in the formation of this fragment. In the case of the 6-aza-7-one steroids, mechanism 1 cannot provide a fragment analogous to LVI and therefore no information can be obtained from the spectra of these compounds as far as
Mechanism 1

Mechanism 2

Mechanism 3

mechanism 1 is concerned.

On the other hand, mechanism 2 could provide the fragment LIX of mass 138. The mass spectra of compounds 6 and 7 possess no signal at m/e 138

and this is in good agreement with Djerassi's results which indicated fragment LVII contributes only 2% to the composition of the fragment occurring at m/e 70.

Finally, the mass spectra of compounds 91 and 92 (and the N-benzyl compounds 93, 94 and 95) indicate signals due to M-29 fragments. These results provide some support for mechanism 3, which could generate the fragment LX. It is interesting to indicate here that the intensity ratio of the signals due to the M-28 and M-29 fragments is reverse to the one observed in the spectrum of 2-piperidone.
C. The mass spectra of Δ^4-6-aza-7-one steroids

The previous discussion has provided rather lengthy explanations for a variety of fragments in which rings A and B are retained. Consequently, it is immediately obvious that if such species are significant in the fragmentation of the enol lactams, they must occur at m/e values which are lower by 2 mass units. Indeed this situation is evident since the mass spectra of 6-aza-4-cholestene-7-one (96) and 17β-hydroxy-6-aza-4-androstene-7-one (97) indicate a number of common signals at m/e 164, 177, 190, 204, 218, 230, 232, 244, 245, 246, 258 and 272 due to the Δ^4 analogues of the fragments discussed in the case of the 6-aza-7-one compounds (91) and (92). The relatively abundant M-28, M-29 and M-43 fragments are again probably due to the loss of CO, CHO and CO plus CH₃ respectively.
Figure 44.
The abundant M-95 fragment present in the spectra of the 6-aza-7-one steroids is no longer present in the spectra of the $\Delta^4$ compounds, (96) and (97). This is to be expected since the postulated mechanistic interpretation for the formation of this fragment in the case of 6-aza-7-one steroids, cannot be applied in the case of the $\Delta^4$ analogues.

In the case of the N-benzyl-$\Delta^4$-6-aza-7-one steroids the expected signals at m/e 244 (164 + 90), 267 (177 + 90), 280 (190 + 90), etc. due to the fragmentation in ring C and D are very weak. The most intense peak, besides the molecular ion signal, is now due to the M-28 fragment and is probably due to the loss of CO from the molecular ion. Similarly the M-29 and M-43 fragment are relatively abundant in the spectra of these compounds and they are again probably due to the loss of CHO and CO plus CH$_3$ respectively.

On the other hand, the N-benzyl-$\Delta^4$-6-aza steroids indicate three very characteristic signals at m/e 198, 199 and 200 with the most intense peak occurring at m/e 199. The formation of the corresponding fragments LXI (m/e 198), LXII, (m/e 199) and LXIII (m/e 200) can be visualized via the following scheme.

If such a fragmentation was taking place in this series of compounds, one would expect that the spectra of the $\Delta^4$-6-aza steroids would possess signals at m/e 108 (198-90), 109, (199-90) and 110 (200-90). Inspection of this region in the spectrum of 97 reveals clearly that this is actually the case.

The relatively intense signals at m/e 171 and 184 are also very characteristic in the spectra of the N-benzyl-$\Delta^4$-6-aza-7-one series.
It has been mentioned in the previous discussion that the presence of the N-benzyl group in the 6-aza and 6-aza-7-one series is associated with the formation of fragments such as C$_7$H$_7^+$ (m/e 91), M-77 and M-91 due to the loss of C$_6$H$_5^-$ and C$_7$H$_7^-$ from the corresponding molecular ions respectively. Therefore, one would expect the formation of the above fragments in the N-benzyl-$\Delta^+$-6-aza-7-one series as well. Although the C$_7$H$_7^+$ fragment does appear as indicated by a very strong signal at m/e 91 in the spectra of the latter series, signals due to fragment ions corresponding to M-77 and M-91 are no longer present in these spectra.

In order to provide an explanation of the absence of the above signals is necessary to comment on the fragmentation responsible for the formation of the fragment ions represented by C$_7$H$_7^+$, M-91 and M-77. It is well known that a benzyl bond is easily cleaved to provide the benzyl ion
LXIV in which the positive charge is stabilized by resonance. Meyerson has shown that this fragment is present rather as a tropilium ion (LXV) (m/e 91).

On the other hand, the ability of a nitrogen atom to stabilize a positive charge similarly can favor a fragmentation across the N-CH$_2$ or NCH$_2$ bonds to provide the M-91 and M-77 fragments and the stable radicals C$_6$H$_5$CH$_2$ and C$_6$H$_5$ respectively. The fact that these fragments are not present implies that the above mechanism is either not operative to any significant extent in these compounds, or else the species so generated are immediately fragmented further before they can be recorded in the mass
spectrometer. We feel that a more preferable explanation lies in an alternate mechanism (already postulated previously for the formation of the fragment LXI, LXII and LXIII) in which we suggest that a fission of the N-C=O bond occurs in the initial stages preferentially to the C-CH₂⁺ or NCH₂-⁺ cleavage respectively.

The pregnane derivatives 95 and 100 indicate three very characteristic signals at m/e 149, 279 and 261 (M-90 in 95), 359 (M-90 in 100), which are probably due to the nature of the side chain in these compounds.

The mass spectra of Δ⁴-6-aza-7-one steroids, as in the case of the 6-aza-7-one series, provide an analogous comparison of results with respect to the formation of the signals at m/e 71 and 72 in the mass spectrum of 2-piperidone. The intensity of the signals corresponding to the M-28 fragment in the mass spectra at the Δ⁴-6-aza-7-one steroids (and particularly in the case of their N-benzyl analogues) is relatively higher than the one observed in the spectra of the 6-aza-7-one series. We feel that, the loss of ethylene via a retro-Diels Alder reaction in the former compounds may contribute significantly to the intensity of these signals.

It is also interesting to emphasize at this point the similarity of the mechanistic interpretation postulated above for the formation of the intense signals at m/e 198 (LXI), 199 (LXII) and 200 (LXIII) in the spectra of the N-benzyl derivatives 98, 99 and 100 (m/e 108, 109, and 110 in the spectrum of 96) and the one postulated for the formation of the most
intense signal at m/e 30 in the spectrum of 2-piperidone.

\[ \text{H}_2N\text{CH}_2=+\text{NH}_2 \quad \text{m/e} 30 \]

D. The mass spectra of the 11-aza steroids

For the studies of the mass spectra of the 11-aza series we first examine the spectra of the compounds 79, 81 and 80 (Figure 49). The compounds 79 and 80 indicate a series of common significant peaks at m/e 176, 190, 202, 203, 204, 206, 218, 216, 230, 232, 245, 249 and 262. On the other hand, compound 81 indicates an analogous series of signals which differ from those of 79 and 80 by only two mass units (m/e 178, 192, 204, 205, 206, 208, 218, 220, 232, 234, 247, 251 and 264). Therefore, it becomes obvious
Figure 50.

Relative Intensity

- 359 M^+
- 341 (M-18)
- 326 (M-33)
- 249
- 232
- 218
- 204
- 203
- 190, x1.8
- 176
- 162

m/e
250
300
350
400
500
600
700
800
900
1000
Figure 52.

Relative Intensity

m/e

149
162
176
190
203
218
232
245
249
298
316
326 (M-75) x 2.2
241 (M-60) x 3.1
242 (M-59) x 2
358 (M-43)
386 (M-15)
401 x 1.8 M^+
Figure 53.

Relative Intensity

m/e

0  40  80  120  160  200  240  280  320  360  400  440

126  148  162  176  218  220  234  246  248  260  262  274  276  288  290 x 2.5  303  345  374  399 (M-18)  402 (M-15)  417 M^+ x 1.7
from the above comparison that ring A or part of ring A is not present in
the above fragments since the substituents at C₃ do not alter the mass of
these fragments. On the other hand, these species must retain ring D since
the positions at which they occur are dependent on the functionality in this
ring. The mass spectra of compounds 76 and 78 are in further support of
this conclusion. If we accept the above postulate one would expect to
observe that the corresponding fragment ions in the spectra of the latter
compounds must shift by the appropriate values. In compound 78 the peaks
should occur at m/e values which are higher by 98 units due to the presence
of the sapogenin side chain. Indeed the spectrum of this compound does
possess signals at m/e 276, 290, 302 (weak), 303, 304 (weak), 316 (weak),
318 (weak), 330 (weak), 332 and 345. On the other hand, the spectrum of
76 which bears no N-acetyl function (42 mass units) indicates a series of
signals at m/e 220, 234, 248, 260, 261 (weak), 262, 264 (weak), 274, 276,
290 and 303. These values differ as expected by 56 mass units (98-42 = 56)
from those of compound 81 and by 42 mass units from those of compound 78.
The latter observation also indicates clearly the presence of the nitrogen
function in these fragment ions. It is therefore, reasonable to conclude
that the fragmentation responsible for these signals occurs via homolysis
of bonds involving rings B and/or C.

The m/e values recorded in parentheses in the following discussion
are taken from the spectrum of compound 81, unless otherwise stated.

A reasonable postulate for the fragmentation responsible for the
generation of the most of the above fragments can be visualized as shown
in the scheme below. Homolytic cleavage of the C₉-C₁₀ bond in the ion
radical LXVII which may fragment in two different ways. For instance,
cleavage of the C₅-C₆ bond in the latter generates the primary radical
LXVIII which by loss of a hydrogen atom is converted to the fragment LXIX (m/e 247). The latter species by loss of a methyl radical provides the less abundant fragment LXX (m/e 232).

On the other hand, homolysis of the C₅-C₇ bond in LXVII generates the primary radical LXXI which by loss of a hydrogen atom is converted to the highly abundant conjugated ion LXXII (m/e 234). This fragment can generate another conjugated fragment ion LXXIII (m/e 218) by loss of a methyl group and a hydrogen atom as shown below.

Furthermore homolysis of the activated C₇-C₈ bond in LXVII provides the allylic radical LXXIV from which loss of a methyl group with simultaneous hydrogen transfer from C₁₄ to C₁₃ generates the fragment LXXV (m/e 204). A simple loss of the C₁₄ hydrogen atom from LXXIV would yield the fragment LXXVI (m/e 220). This fragment ions LXXVII (m/e 205) and LXXVIII (m/e 206) can be derived from LXXVI as shown in the scheme.

A further series of fragments can be derived from the intermediate LXVII by homolysis of the activated C₈-C₁₄ bond followed by hydrogen transfer from C₁₂ to C₉ to provide the secondary radical LXXIX. Further fragmentation of the latter at the C₆-C₇ linkage generates the ion LXXX (m/e 208). The fragment LXXXI (m/e 192) can be obtained from LXXX by cleavage of the C₁₃-C₁₈ bond and subsequent loss of the C₁₄ hydrogen atom.

Another abundant pair of fragments LXXXIII (m/e 208) and LXXXIV (m/e 178) are probably derived from a common ion radical LXXXII which is formed as shown. Loss of a hydrogen atom from C₁₇ in LXXXII provides the conjugated ion LXXXIII (m/e 178) while loss of the C₂₁ methyl group generates the fragment LXXXIV (m/e 164). It is interesting to indicate here that in the case of C₁₆-C₁₇ dehydro analogues 79 and 80 the fragment LXXXV (m/e 162) arising via the above postulated fragmentation is much more
abundant than the fragment LXXXIV (m/e 164) in the dihydro series. This situation is possibly due to the fact that the C_{16}-C_{17} double bond in the former compounds is able to provide an aromatic bicyclic system.

It is of further interest to emphasize at this point that the intensity of the signals due to the fragment ions discussed above, with the exception of those at m/e 345 and 303 is considerably lower in the spectrum of compound 78. Similarly an analogous difference in the intensity of signals (with the exception of the one at m/e 290) is observed in the mass spectrum of compound 76 and those of 79, 81 and 80. It is not possible at this time to provide any conclusive explanation for the high intensity of the signals at m/e 345, 303 in the spectrum of compound 78 and at m/e 290 in the one of 76 but it is suggested they are perhaps due to the fragments LXXXVI (as LXIX in 81), LXXXVII (as LXXVII in 81) and (LXXXVIII (as LXXII in 81) respectively.

The important signal at m/e 139 (LXXXIX) common in compounds 76 and 78 is due to the fragmentation of the spiroketal side chain and is a characteristic feature in the mass spectra of sapogenins.\textsuperscript{59}
The signals at m/e 274, 288, 303 and 345 in the spectrum of compound 76 can be derived via a fragmentation process of the spiroketal side chain as shown below.\textsuperscript{59}
The abundant fragment M-60 (XC) and M-75 (XC-CH₃⁺) in the spectra of compounds 81, 80 and 78 are very reminiscent of the spectrum of cholestan-3β-ol acetate⁵⁸ and are due to the loss of CH₃COOH and CH₃COOH plus a methyl group from the molecular ion. In the case of compound 81 the corresponding signals occur at m/e 341 and 326 respectively. The metastable peak at m/e 313 (which is also present in the spectrum of compound 80 at m/e 312) strongly supports the relationship between those two fragments. The subsequent retro-Diels-Alder reaction which would normally provide the fragment XCI is apparently not occurring in our system since there is no signal corresponding to this fragment in compounds 81, 80 and 78. On the other hand, the compounds 79, 81 and 80 and 78 indicate signals at m/e 316, 360, 358 and 458 (M-43) respectively, which are due to the loss of the CH₃CO₂ group of the N-acetyl function from the molecular ion.

The M-33 fragment (m/e 326) in the spectrum of compound 79 is accordingly due to the loss of water plus a methyl group. The signal at m/e 341 (M-18) is also relatively strong in the spectrum of this compound and it is due to the loss of water.

In connection with the mass spectra of the 6-aza steroids it is pertinent to discuss briefly at this point the work reported recently⁶⁴
the mass spectra of 6-aza-equilenin (101) and 6-aza-14(β)-isoequilenin (102). The synthesis of these compounds is briefly described in the introduction part of section A in this thesis.32

The fragmentation of these compounds is closely related with the one of equilenin and 14(β)-isoequilenin which has been described in detail by Djerassi et al.65 In other words, the presence of hetero atom in these compounds does not provide a significant difference in the fragmentation pattern since this atom is part of a stable aromatic system. The spectra of compounds 101 and 102 indicate common signals at m/e 281 (M+) 266 (M-15) 225 and 210. Furthermore, the C/D trans isomer (101) indicates significant signals at m/e 238 and 212. The formation of the latter signals in the C/D trans isomer is attributed to stereochemically dependent processes. The examination of the mass spectra of 14,15-d2-azaequilenin (103) provided evidence for the plausible structures of these ions and for possible fragmentation pathways leading to their formation as shown below.
Experimental

The mass spectra of the compounds 78, 76 and 80 were obtained with a MS 9 mass spectrometer using a direct insertion probe. The samples were introduced directly into the mass spectrometer (MS 9) ion source and evaporated into the ionization region from the end of the sample probe situated only a few millimeters away. The ionizing energy was maintained at 70 e.v.

The rest of the mass spectra were obtained with an Atlas CH4 mass spectrometer using the direct insertion technique. The ionizing energy was maintained at 70 e.v.
REFERENCES


47. Part of this work was presented at the Symposium on Heterocyclic Steroids, Abstracts, 147th Meeting of the Am. Chem. Soc., P. 18M, April (1964).


PART II

Studies in the Alkaloid Field
Introduction

Of a large number of nitrogen bases occurring in Nature, a considerable portion contain the indole nucleus. A wide category of these compounds is the well known and very important family of so-called "Indole alkaloids", which have so far been isolated from upwards of twenty five genera of plants and trees. They include many important and widely used alkaloids, such as the ergot bases, valuable as oxytocic drugs in childbirth; strychnine, valuable as a general tonic and also employed as a vermin killer; yohimbine used in veterinary medicine as an aphrodisiac; the extracts of Rauwolfia serpentina Benth used in India for several purposes, chiefly as a sedative, etc.

The pharmacological properties of all these plant extracts have stimulated chemical investigations into the structures of the alkaloidal constituents, and so far the structures of approximately three hundred indole alkaloids have been completely elucidated.¹

Besides the isolation of alkaloids and the chemical elucidation of their structure a considerable effort has been contributed to the total or partial synthesis of these substances. In many of these instances investigators have even tried to follow synthetic schemes in the laboratory which could possibly bear some relationship to the pathways utilized by Nature. Although a good deal of work still remains to be carried out in the area of alkaloid biosynthesis, a considerable amount of information is already available from experiments with radioactive tracers.²

It has long been suspected that tryptophan (1) is the important amino acid which serves as the building unit for the indole alkaloids.³ Recent tracer experiments have provided con-
formation of this postulate. It is generally felt that after decarboxylation, is converted into tryptamine (2) which just like phenethylamine, is capable of undergoing a whole series of condensation reactions. (See Figure 1).

For example, serotonin (5-hydroxytryptamine) (4), one of the more important naturally occurring indolylalkylamines is produced by hydroxylation of tryptophan (1) to 5-hydroxytryptophan (3) and subsequent decarboxylation. Tryptamine itself cannot be hydroxylated. Psilocybine (5), a phosphoric ester derivative of N,N-dimethyl-4-hydroxytryptamine, is
the active constituent of the Mexican hallucinogenic fungi of the genus "Psilocybe". It is interesting to note that it is one of the few 4-hydroxy indole analogues actually isolated in Nature.

There are various hypotheses advanced for the biosynthesis of the "non-tryptophan" portion of the more complex indole alkaloids. We will concern ourselves here with only those postulates which are relevant to this thesis.

Wenkert in 1962, elaborated an elegant scheme involving prephenic acid (9) incorporation into the non-tryptophan portion of several classes of indole alkaloids. (Figure 2).

Rearrangement of prephenic acid (9) by a 1,2- shift of the pyruvate residue, with retention of configuration, followed by hydration affords a unit (10) readily discernible in yohimbine (12). Condensation of the above with a formaldehyde equivalent and retro-aldolisation then yields a "seco-prephenate-formaldehyde" (SPF) group (11) that can condense with tryptamine to eventually yield alkaloids typified by corynantheine (13) ajmalicine (14) sarpagine (15) and ajmaline (16).

According to Wenkert the role of the SPF unit (11) in the biosynthesis of corynantheine (13) and related alkaloids may be visualized as shown in Figure 3. Formation of a SPF-tryptamine complex (18) is followed by a Mannich-type condensation at the α-position of the indole system to give (19) which can then undergo appropriate modifications to yield the various series known in Nature.

The prephenic acid hypothesis also provides a comprehensive scheme for the biosynthesis of Strychnos and Iboga alkaloids and has the additional merit of encompassing the Aspidosperma series.

The strychinine group (22) evolves from the tryptamine-SPF complex
Figure 2.
Figure 3. Incorporation of SPF Unit in Corynantheine and Related Alkaloids.
(20) as shown in Figure 4.

**Figure 4. Incorporation of the SPF Unit in the Strychnos Type Alkaloids.**

Attack of the formyl acetate residue in the intermediate at the α-position of the indole portion provides the iminium ion (21), which bears an obvious resemblance to the known alkaloid stemmadenine (23). A transannular cyclisation then provides the strychinine precursor (22).

The relationship between tryptamine and the SPF unit in alkaloids
Figure 5. Biogenetic Incorporation of the SPF Unit in the Aspidosperma and Iboga Type Alkaloids.
of the Aspidosperma and Iboga type is not readily discernible. It is evident that these alkaloids arise from rearranged SPF units. The crucial rearrangement can be seen as proceeding via a retro-Michael reaction intermediate (24) (See Figure 5) and involves an activated hydrogen atom on a carbon atom α to either the iminium system or the acetyl group, with resultant cleavage of the SPF unit. The cleavage product (24) could be modified by unexceptional reactions to give either an Aspidosperma (25) or an Iboga (28) precursor. These compounds could then undergo a parallel series of reactions: Michael additions to the αβ-unsaturated acid systems would afford the nine-membered ring compounds (26) and (29), which could then, by transannular cyclisations, yield the Aspidosperma and Iboga skeleta (27) and (30) respectively.

There is as yet no direct proof of Wenkert's hypothesis and various researchers have been critical of its value in alkaloid biosynthesis. The hypothesis does, however, stimulate further investigations into some of the reactions proposed and recently some interesting work has been done with respect to the following equilibrium which is implied in the biosynthetic scheme.
Figure 6. Correlation of the Configuration of Akuammicine with that of Condylocarpine.
A recent study of this equilibrium was involved in the interconversion of an alkaloid of the akuammicine type and an alkaloid of the aspidospermatine series. The interconversion was carried out to verify the absolute configuration of the alkaloid condylocarpine (32) which had been assigned on the basis of a comparison of its optical rotation with that of akuammicine (31) whose configuration had been previously determined. The results of this work are summarized in Figure 6. The equilibrium between condyfoline (34) tubifoline (33) and the 20-epimer of condyfoline (36) could be accomplished by heating condyfoline under vacuo or under basic conditions but not under acidic conditions.

The transformation of condyfoline to tubifoline is postulated to occur as shown in Figure 7.
It is felt that the critical step $A + B$ may involve abstraction of a proton by base as shown below.

\[ \begin{array}{c}
\text{(a)} \\
\text{(b)}
\end{array} \]

The formation of the 20-epimer (36) of condyfoline undoubtedly involves an imine-enamine tautomerization of $A$ prior to the transannular cyclization step (Figure 7).

The biogentic significance of this work is that it predicts that the antipodal relationship between the alkaloids of the akuammachine and those of the aspidospermatine type, merely arises from appropriate oxidative cyclizations of a common precursor. In support of this contention both condyfoline and tubifoline give the same indole (35) on treatment with potassium borohydride in methanol.

Some other recent work which has relevance to Wenkert's ionic intermediate appears from a series of investigations by Kutney et al. This research provided the first laboratory realization of the transannular cyclization process, and established that such a reaction may be of considerable utility in the synthesis of complex indole alkaloids. It is appropriate at this point to discuss this work briefly since it has a direct bearing on the reasons for the syntheses which were carried out and which are described in this thesis.

In order to evaluate the feasibility of the transannular cyclization reaction, investigations in our laboratory were initiated and dihydrocleavamine (38), readily available from other research work on alkaloids from Vinca rosea linn, was utilized as the starting material. It was realized at that time that any successful results with this
compound could be extended to the natural Aspidosperma series, since the ring system present in dihydrocleavamine is identical with that already known in the Aspidosperma alkaloid quebrachamine (41). Indeed it was possible to convert the former to an Aspidosperma skeleton (40) as shown in Figure 8.

Figure 8. Synthesis of Aspidospermine Skeleton from Dihydrocleavamine.
In subsequent work another successful series of reactions was carried out in which carbomethoxydihydrocleavamine (42) reacted as above with mercuric acetate to provide an iminium intermediate. Cyclization of the latter gave a vincadifformine-type skeleton (46) as the major product (Figure 9). The latter compound by reduction with zinc in sulfuric acid gave (47) which, in turn, on treatment with hydrochloric acid and then reduction with lithium aluminum hydride, gave an Aspidosperma-type skeleton (48). The latter product differed from the previous compound (40) only in stereochemistry.

In the most recent paper it was demonstrated that a further possibility exists for the transannular cyclization process. The intermediate reaction product with the $\mathrm{>N=C_S<}$ grouping leads to the Iboga skeleton and in this manner, coronaridine and dihydrocatharanthine were synthesized (See Figure 9). The absolute configuration of the Iboga alkaloids as proposed previously by various workers is incorrect. The correct stereo formula is given in structure 44. Since all of these transannular cyclizations made possible the interconversion and interrelation of the important and widespread groups of Vinca, Aspidosperma, and Iboga alkaloids, considerable attention was then directed toward the preparation of dihydrocleavamine, carbomethoxy dihydrocleavamine and quebrachamine since these "key" compounds provide the route to the total synthesis of these various classes of alkaloids.

Before proceeding to our own work it is appropriate to review briefly at this point some very recent work which presents successful syntheses of some Aspidosperma and Iboga alkaloids.

The first successful synthesis of dl-aspidospermine and dl-quebrachamine by Stork is shown in Figure 10. The stereochemistry of the
Figure 9. Synthesis of Vincadifformine Skeleton from Carbomethoxy-dihydro cleavamine.
various bicyclic and tricyclic intermediates which are described in
Stork's work is left open at this point. This stereochemical ambiguity
is not significant since the indolenine (51) is formed under conditions
which would lead to equilibration at the two centers C-12 and C-19 via
a reverse Mannich reaction as shown below.

The most stable relative arrangement of the three asymmetric centers of
(51) would thus be expected to result, regardless of the stereochemistry
of the intermediates or the detailed course of the indolenine cyclization
process. There are good conformational arguments that this most stable
arrangement should coincide with that of dehydroaspidospermine.

Ban et al\textsuperscript{14} have also investigated several possible routes for the
synthesis of dl-aspidospermine. One of their approaches reached the
intermediate 54 (See Figure 11) which has the same planar structure as
the corresponding one of Stork's synthesis. Physicochemical properties of
this intermediate are quite different from those reported by Stork and
this suggested that these compounds are diastereoisomeric. Ban carries
through his synthetic sequence with intermediate 54 and indeed
succeeds in achieving a synthesis of dl-aspidospermine.
Figure 10. Synthesis of dl-Aspidospermine
Figure 11.
Figure 12. Synthesis of (+)-Eburnamine and (+)-3-Methyl Aspidospermidine.
Figure 13. Synthesis of (+)-Ibogamine and (+)-Epiibogamine.
The stereochemical assignments of the common intermediates in the Stork and Ban sequences were obtained from the NMR spectra of the lactam (50). The conformations 55 and 56 were postulated to Ban's and Stork's lactam respectively. The fact that dl-aspidospermine is synthesized from either 55 or 56 supports the existence of the equilibrium 51a ⇄ 51b, postulated above and the stereospecific reduction of the most stable stereoisomer of the indolenine (51) with lithium aluminum hydride.

An elegant synthetic path leading to Hunteria and Aspidosperma alkaloids was recently reported by Barton and Harley-Mason. Figure 12 indicates their synthetic sequence leading to (±)-eburnamine (59) and (±)-3-methyl aspidospermidine (60).

A total synthesis of the Iboga skeleton has been also reported recently. Buchi et al have achieved a total synthesis of (±)-ibogamine (61) and (±)-epiibogamine (62) and their work is summarized in Figure 13.

Huffman et al have also reported the synthesis of desethyl ibogamine (63) and this sequence is summarized in Figure 14.

![Figure 14. Synthesis of Desethyl Ibogamine.](image-url)
Discussion

As already mentioned in the introduction, the transannular cyclization of the appropriate nine-membered ring intermediate provided an attractive synthetic entry into a wide variety of indole and dihydroindole alkaloids. Consequently, it was now desirable to develop a synthetic pathway to these "key" intermediates for the proposed total syntheses of these natural products.

We have investigated in a preliminary manner, two synthetic approaches to the nine-membered ring system. For a matter of convenience, the discussion of this part of the thesis will be divided into two sections, A and B, corresponding to the two synthetic approaches, whose projected plans are outlined in Figures 15 and 16 respectively.

Section A.

In this synthetic sequence the initial step requires the formation of an appropriate diester (66a or b) which through subsequent reduction of the keto function and cyclization could generate the desired nine-membered ring intermediates 67 and 68. Section A outlines our investigations directed at the synthesis of the necessary indole units (64a and b), the alkylation reactions with the piperidine unit and finally reduction of the keto function in the product, (66). In our initial phases, 3-carbomethoxy piperidine (76), easily available from other work in our laboratory was used for study of various reaction conditions. Although it does not lead to the desired intermediates (67) or (68) it did enable us to develop the necessary experimental conditions which could then be applied to reaction with appropriate piperidine moiety, (65).
Figure 15.

Figure 16.
There are many well-known reactions which provide a synthetic entry into the indole nucleus.\textsuperscript{18-22} Of the various alternatives we chose to utilize the Reissert synthesis which is well suited for the preparation of indole derivatives possessing carboxyl or carbomethoxy groups at the α-position.\textsuperscript{23-24}

The known synthesis of 2-carbomethoxy-indole via the Reissert reaction is outlined in Figure 17.\textsuperscript{24}

In order to introduce a suitably reactive side chain at the 3-position of the methyl ester 74 we considered the Hoesch synthesis\textsuperscript{25} which is well known in the indole chemistry. This method which proceeds via electrophilic attack at the β-position, is well suited for the preparation of indole derivatives bearing side chains with ketonic functions.\textsuperscript{26} Therefore the ester 74 was treated with chloroacetonitrile and hydrogen chloride gas in dry chloroform as solvent in a sealed tube at 50°C. Although the more common Hoesch conditions employ absolute ether as solvent, our compound 74 was only slightly soluble in this solvent. The crude semi-crystalline solid obtained from this reaction was purified by chromatography on alumina to provide a colourless crystalline material (m.p. 147.5-148.5°C) in 30% yield.

The spectral properties of this substance were very instructive and served to establish the expected structure (75) for this compound. For example the NMR spectrum indicated the normal multiplet centered at 2.65 τ for the aromatic protons of the indole nucleus, a two-proton singlet at 4.98 τ (–C\textsubscript{2}H\textsubscript{5}Cl) and a three-proton singlet at 5.98 τ for the ester methyl protons. The infrared spectrum of the Hoesch product showed a very sharp band at 2.98 μ (>NH) and two carbonyl bands at 5.82μ and 6.0μ in complete agreement with the assigned structure. Finally the ultraviolet absorption
Figure 17.

Figure 18.
at 220, 249 and 318 μ, was distinctly different from that of the starting indole.

The Hoesch product (75) was subsequently reacted with three mole equivalents of the piperidine derivative (76) to provide a viscous oily material. This latter substance was purified by chromatography on neutral alumina and crystallized from an ether-hexane mixture to provide a crystalline product, m.p. 121-125°C. The NMR spectrum of the latter showed the normal multiplet due to four aromatic protons at 2.6 τ, two three-proton singlets at 6.08 and 6.4 τ due to the ester methyl protons of the indole and piperidine moieties respectively, and a two-proton broad doublet at 6.2 τ (–CCH₂N<). The infrared spectrum with a sharp band at 3.1μ (>NH) and two carbonyl bands at 5.78μ (strong) and 6.15μ was in complete agreement with the presence of two carboxy methoxy groups and the keto function as expected in the desired reaction product. Finally the ultraviolet spectrum with maxima at 220, 248 and 314 μ indicated a similarity to the indole 75. Indeed the spectral data was sufficiently instructive to assign the structure 77 to this compound.

The next obvious step in the sequence was to remove the carbonyl function from the two-carbon bridge in 77 and thereby obtain the intermediate necessary for the cyclization studies to generate the nine-membered ring. Therefore this compound was treated with sodium borohydride in methanol to provide an amorphous solid, which was purified by thin layer chromatography on alumina. In spite of numerous attempts to obtain this compound crystalline we were unsuccessful and therefore characterization of this product was done on the amorphous solid. We assigned the structure 78 to this compound on the basis of the following spectral data. The NMR spectrum showed the normal aromatic proton absorption at 2.65 τ, two three-
proton singlets at 6.25 and 6.45 \( \tau \) \( (2 \times -\text{C-OCH}_3) \) and a one-proton broad quartet centered at 4.4 \( \tau \) \( (-\text{C-C}) \). The carbonyl absorption due to the keto group in the infrared spectrum of 77 had now disappeared and a broad absorption band 2.95 \( \mu \) indicated the presence of a new hydroxyl group in this compound. Furthermore in this compound the strong broad carbonyl absorption band at 5.85 \( \mu \) was in agreement with the presence of two carbomethoxy groups already evident from the NMR spectrum. Finally the ultraviolet spectrum of this compound had an absorption pattern \( (\lambda_{\text{max}} 229 \text{ and } 298 \text{ \mu}) \) very different from that of 77 but very similar to the one of 2-carbomethoxy-indole (74) \( (\lambda_{\text{max}} 218 \text{ and } 294 \text{ \mu}) \).

The removal of the alcoholic group and generation of the intermediate possessing a \( -\text{CH}_2\text{CH}_2- \) bridge between the indole and piperidine moiety was now necessary. We considered that dehydration of the alcohol 78 could provide the corresponding enamine \((\text{R-CH}=\text{CH-N}<)\) which on reduction would yield the desired compound. The success of the dehydration could be ascertained by ultraviolet spectroscopy since the enamine chromophore will exhibit a characteristic absorption. However, in spite of numerous attempts we were unable to obtain the desired enamine.

We next considered catalytic hydrogenation of the keto function since it was possible that the expected alcohol might suffer hydrogenolysis and thereby yield the desired compound. This keto compound 77 on catalytic hydrogenation with Raney Nickel as catalyst smoothly absorbed one mole of hydrogen to provide an amorphous solid, which was shown to be identical to 78 on the basis of NMR, IR and thin layer chromatography comparison.

Prolonged hydrogenation of 77 or 78 under similar hydrogenation conditions lead to the same product, which also remained as an amorphous solid in spite of numerous attempts at crystallization of this material.
The NMR spectrum of this compound showed no aromatic proton absorption, a broad one-proton peak at 1.35 τ (H-N<) a one-proton multiplet centered at 4.85 τ (-CHCH2-N) and two three-proton singlets at 6.29 and 6.48 τ, indicating the presence of two ester methyl groups in this compound. The infrared spectrum showed absorption bands at 2.9 (sharp -NH) and 3.0 μ (broad -OH) and a doublet in the carbonyl region at 5.6 and 6.0 μ. The ultraviolet spectrum of this compound had a strong maximum at 290 μ an absorption which is characteristic for a 2-carbomethoxy-3,4,5-trialkyl-pyrrole system.

In order to draw additional information about the structure of this reduction product we subjected 2-carbomethoxy-indole (74) to catalytic hydrogenation with platinum oxide in ethanol in the presence of a trace of concentrated hydrochloric acid. When one mole of hydrogen was absorbed (at a rather slow rate) the hydrogenation was interrupted. The reaction provided a mixture of starting material and a new hydrogenation product in an approximate ratio of 2:1. Thin layer chromatography purification and crystallization from aqueous methanol gave an analytical sample of this product (m.p. 156-157°C). Elemental analysis was in agreement with the molecular formula C10H13O2N and spectroscopic data allowed us to assign structure 80 to this compound. The NMR spectrum showed the absence of the normal aromatic proton multiplet, the presence of a one-proton doublet at 3.52 τ due to the β-proton of the pyrrole system, a three-proton singlet at 6.27 τ (-OCH3) and two sets of four-proton multiplets centered at 7.5 and 8.25 τ due to the protons of the cyclohexene ring. The infrared spectrum showed a sharp band at 3.02 μ (>NH) and a strong carbonyl absorption at 6.0 μ. The ultraviolet spectrum showed a strong absorption at 287 μ which is again characteristic of a 2-carbomethoxy-pyrrole
Considering the similarities in the NMR, IR and UV spectra of 80 and the hydrogenation product of 77 or 78 we assigned the structure 79 to the latter compound.

During the course of these investigations the synthesis of β-(2-carbomethoxy-3-indolyl)ethylchloride (81) was achieved in our laboratory, as shown in Figure 19.

This compound was then successfully coupled with the piperidine derivative 65 to provide one of the desired synthetic intermediates 82. Since this
sequence proceeded without difficulty, the synthetic approach as discussed above was abandoned.

We now turned our attention to the synthesis of intermediate 66b which was also desirable for our work. Indole-2-acetic acid (87) necessary for the synthesis of the indole moiety was obtained according to a published sequence\textsuperscript{32} which is shown in Figure 20.

\begin{align*}
\begin{array}{c}
\text{N} \quad \text{CO}_2\text{H} \\
\text{H} \quad \text{H}
\end{array}
& \xrightarrow{\text{SOCl}_2} \\
\begin{array}{c}
\text{N} \quad \text{COCl} \\
\text{H} \quad \text{H}
\end{array}
& \xrightarrow{\text{HN(CH}_3)_2} \\
\begin{array}{c}
\text{N} \quad \text{CON(CH}_3)_2 \\
\text{H} \quad \text{H}
\end{array}
& \xrightarrow{\text{LiAlH}_4} \\
\begin{array}{c}
\text{N} \quad \text{CH}_2\text{CN} \\
\text{H} \quad \text{H}
\end{array}
& \xrightarrow{\text{KCN}} \\
\begin{array}{c}
\text{N} \quad \text{CH}_2\text{N(CH}_3)_2 \\
\text{H} \quad \text{H}
\end{array}
& \xleftarrow{\text{I\text{CH}_3}} \\
\begin{array}{c}
\text{N} \quad \text{CH}_2\text{N(CH}_3)_2 \\
\text{H} \quad \text{H}
\end{array}
& \xrightarrow{\text{KOH}} \\
\begin{array}{c}
\text{N} \quad \text{CH}_2\text{COOH} \\
\text{H} \quad \text{H}
\end{array}
& \xrightarrow{\text{CH}_2\text{N}_2}
\end{align*}

Figure 20.
The acid (87), on treatment with diazomethane provided indole-2-acetic acid methyl ester (88) as a nicely crystalline material. The NMR spectrum of the ester showed the normal aromatic proton absorption centered at 2.8 \( \tau \), a one-proton singlet at 3.84 \( \tau \) (\( \beta \)-proton), a two-proton singlet at 6.37 \( \tau \) (-CH\(_2\)-O\( \text{Me} \)) and a three-proton singlet at 6.41 \( \tau \) (-O-CH\(_3\)). The infrared spectrum showed a sharp peak at 3.01\( \mu \) (\( >\text{NH} \)) and the expected carbonyl band at 5.85\( \mu \). The ultraviolet spectrum was very characteristic of a normal indole system with maxima at 218, 272 and 289\( \mu \).

The Hoesch synthesis was now also used successfully in order to introduce the necessary carbon chain at the \( \beta \)-position of the indole ring. When the ester 88 was treated with chloroacetonitrile and dry hydrogen chloride, using anhydrous ether as solvent 3-chloroacetylindole-2-acetic acid methyl ester (89) was obtained as a nicely crystalline material in 70% yield (Figure 21).

A comparison of the spectral properties of the Hoesch product 89 with those mentioned above for the starting ester immediately established its structure. The infrared spectrum showed a sharp band at 3.0\( \mu \) (\( >\text{NH} \)) and two carbonyl absorptions at 5.79 \( \mu \) (-CO\( \text{CH}_3 \)) and 6.2\( \mu \) (-CH\(_2\)-Cl). The ultraviolet spectrum showed a very different absorption pattern (\( \lambda_{\text{max}} \) 214, 244, 267 and 309\( \mu \)) from the normal indole absorption of the ester 88. Finally the NMR spectrum showed the absence of the one-proton singlet at 3.84 \( \tau \) present in the spectrum of 88 due to the \( \beta \)-hydrogen on the indole ring. There were instead two new two-proton singlet at 5.3 and 5.8 \( \tau \) now present in the spectrum of 89. We attributed the two-proton singlet at 5.3 \( \tau \) to the methylene protons of the chloroacetyl side chain (-CH\(_2\)-Cl) whereas the other new two-proton singlet at 5.8 \( \tau \) must be due to the methylene protons of the ester side chain (-CH\(_2\)-CO\( \text{OCH}_3 \)) which have shifted
Figure 21.
downfield upon introduction of the $\beta$-substituent.

This assignment was confirmed when the NMR spectrum of the corresponding 3-acetyl derivative (90) was investigated. This latter compound was prepared in two different ways. The first sequence utilized catalytic hydrogenation of 89 with Raney nickel as catalyst at room temperature and atmospheric pressure. The reaction proceeded very rapidly under these conditions and it was interrupted when the hydrogen uptake became very slow. The product was obtained from the reaction mixture as a crystalline material. It was recrystallized from a mixture of ether-dichloromethane to provide an analytical sample (m.p. 128-131°C).

The Hoesch reaction was also used for the synthesis of the acetyl compound (90). However, in this case the reaction between indole-2-acetic acid methyl ester (88) and acetonitrile provided only a very small yield of the desired product. The infrared spectra of the latter showed two carbonyl bands at 5.66 and 6.1 $\mu$ and the ultraviolet spectrum was identical with that of compound (89) ($\lambda_{\text{max}}$ 215, 243, 272 and 303 $\mu$). The NMR spectrum showed the normal aromatic multiplet centered at 2.8 $\tau$, one two-proton singlet at 5.71 $\tau$ and a three-proton singlet at 6.33 (-OCH$_3$). The two-proton singlet at 5.3 $\tau$ present in the spectrum of 89 had now disappeared and a new three-proton singlet was present at 7.4 $\tau$ (H-$\text{CH}_3$).

We had now accomplished the synthesis of the desired indole moiety and the next step was to consider the coupling reaction with the piperidine unit. Consequently the compound 80 was treated with three mole equivalents of the piperidine derivative (76) and the resultant gummy basic reaction product which was obtained could be purified by thin layer chromatography on alumina. In spite of numerous attempts at crystallization, this substance remained as an amorphous solid. The most characteristic features in the
NMR spectrum of this compound were, the aromatic proton multiplet centered at 2.7 \( \tau \), two two-proton singlets at 5.67 and 6.17 \( \tau \) and two three-proton singlets at 6.3 and 6.46 \( \tau \) (2 x -COCH\(_3\)). If we assign the two-proton singlet at 5.67 to the methylene protons attached to the indole moiety (-CH\(_2\)COOCH\(_3\)) since there would be expected to absorb at approximately the same position as the corresponding protons of the compounds 89 and 90, then the two proton singlet at 6.17 \( \tau \) is clearly due to the methylene protons attached to the basic nitrogen atom of the piperidine portion of the molecule (-C-CH\(_2\)-N-). The chemical shift of the methylene protons from 5.3 in the chloro compound 89 to 6.17 \( \tau \) in the amine (92) is in agreement with several examples known in the literature, where this chemical shift is of the order of about 60 cycles/sec. The infrared spectrum showed a strong carbonyl absorption at 5.77\( \mu \) due to the presence of the two carbomethoxy groups and a weaker band at 6.1\( \mu \) for the keto group. The ultraviolet spectrum has an absorption pattern similar to the one of compounds 89 and 90 (\( \lambda_{\text{max}} \) 214, 243, 268, and 303 \( \mu\)). On the basis of this data we assigned the structure 92 to this compound (See Figure 20).

The next reaction which was necessary for our studies involved the reduction of the ketone group and hopefully, subsequent hydrogenolysis of the resulting alcoholic function so as to provide complete removal of the oxygen atom at this position. An analogous hydrogenolysis of an oxygen function very similar to ours has been reported recently. (Figure 21a) The compound 90 easily available from 89, was chosen as a model for these catalytic hydrogenation studies. Hydrogenation of 90 with platinum oxide in methanol and concentrated hydrochloric acid (1%), afforded a viscous oily substance which was purified by thin layer chromatography. The NMR spectrum of this product was very instructive and allowed us to
assign structure 91 to this compound. The aromatic proton multiplet was centered at 2.85 \( \tau \), but significantly the two-proton singlet due to the methylene group of the acetate moiety was shifted from 5.62 \( \tau \) (NMR spectrum of 90) to 6.28 \( \tau \). This chemical shift is in agreement with the corresponding situation present in the NMR spectrum of the indole-2-methyl acetate (88). The three-proton singlet of the ester methyl protons appeared as expected at 6.31 \( \tau \) but the three-proton singlet at 7.4 \( \tau \) which was present in the NMR spectrum of 90 had now disappeared. However, a new signal characteristic of an ethyl group was now present in the spectrum of the reduction product (a two-proton quartet centered at 7.38 \( \tau \) and a three-proton triplet centered at 8.8 \( \tau \)). The infrared spectrum of this substance showed a sharp band at 2.9\( \mu \) (\( >\text{NH} \)) and only one carbonyl absorption at 5.8\( \mu \). Furthermore, the ultraviolet spectrum showed the normal indole absorption pattern (\( \lambda_{\text{max}} \), 225, 276(sh), 285 and 293 \( \mu \)).

It was now clear that the reduction and hydrogenolysis had proceeded successfully and we turned our studies to the analogous sequence with the coupling product (92). Unfortunately when the coupling product was subjected to the above hydrogenation conditions, no reduction was observed. Under prolonged hydrogenation with a higher concentration of hydrochloric
acid, the coupling product was reduced to a compound which showed only one
three-proton singlet (-OCH₃) in the NMR spectrum and one carbonyl absorption
at 5.8μ in the IR spectrum. This indicates that under more drastic conditions
the keto function as well as one carbomethoxy group, presumably the one
which is part of the indole moiety were reduced. In spite of many attempts,
we were unable to find optimum hydrogenation conditions for the reduction
of the keto function preferentially to the carbomethoxy group. Sodium
borohydride was the next reducing reagent to be considered in our study.
The ester 90 was extremely reactive towards this reagent and even at 0°C
the reduction product indicated no carbonyl absorption in the infrared
spectrum. Similar results were also observed with the compound 92 where
the keto function and one carbomethoxy group were simultaneously reduced
with this reagent.

It therefore became necessary for us to study the reduction of the
keto function with a mild reducing reagent. When compound 90 was treated
with diborane in dry tetrahydrofuran at 0°C, a mixture of two compounds was
obtained, and these were separated by thin layer chromatography on alumina.
The major and less polar component of the mixture was found to be identical
with 91 by thin layer chromatography and IR spectra comparison. The minor
and more polar compound showed no carbonyl absorption in the infrared
spectrum which indicated that both carbonyl functions had been reduced in
this particular product.

It was now apparent that diborane could effectively reduce the keto
function preferentially to the carbomethoxy group. Therefore we subse­
quently treated the coupling product (92) with diborane under the above
reaction conditions and an amorphous solid product was obtained. The
latter substance which now showed no carbonyl absorption at 6.2μ in the
infrared spectrum did exhibit a new unexpected strong absorption band at 4.3 which was attributed to a boron-carbon stretching frequency. This absorption band indicated that this product was still in the form of a boron complex. In fact when this amorphous solid was treated with concentrated sulfuric acid in dry dioxane a mixture containing mainly two components was obtained. The infrared spectrum of the latter material now showed no absorption band at 4.3\(\mu\). The major and less polar component of the mixture was separated as a gummy substance by thin layer chromatography on alumina. The spectral properties of this compound were in excellent agreement with the assigned structure 93. The NMR spectrum showed the normal aromatic proton multiplet centered at 2.8 \(\tau\) while two three-proton singlets at 6.26 and 6.3 \(\tau\) indicated the presence of two carbomethoxy groups in this compound.

There was only one two-proton singlet present in the spectrum at 6.2 \(\tau\) and this was obviously due to the methylene protons of the methyl acetate moiety. This chemical shift was in agreement with that of the corresponding protons in the NMR spectra of indol-2-acetic acid methyl ester (80) and 3-ethylindole-2-acetic acid methyl ester (91).

The reduction product (93) was rather sensitive to air oxidation and was difficult to characterize in a satisfactory manner. Additional data was obtained from its hydrochloride salt which was also isolated as an amorphous solid. The infrared spectrum of this derivative showed a carbonyl absorption band at 5.79\(\mu\) and the ultraviolet spectrum with its typical indole absorption (\(\lambda_{\text{max}}\) 222, 275(sh), 283 and 292 \(\mu\)) was in agreement with the proposed structure (93).

We now hope that the above outlined sequence which leads successfully to the model intermediate 93 would be applicable in the synthesis of the desired diesters 95 and 66b. Dieckman cyclization of these compounds
could provide the necessary nine-membered ring intermediates of the Iboga (96) and Aspidosperma (67) type alkaloids (See Figure 22). Unfortunately, the necessary piperidines 65 and 94, whose syntheses were being investigated independently by other coworkers\textsuperscript{35} in our laboratory, were not available to us at this time and therefore we were forced to postpone our investigations in this direction.

In the meantime, we decided to consider our approach from an entirely different synthetic aspect and the results from this latter investigation are outlined in detail in the next section of this thesis.
Section B

An alternative approach to the synthesis of a medium-sized ring system utilizes a reaction in which an appropriate ring bond is cleaved to provide the desired nine-membered ring intermediate. Before turning to the specific sequence which was proposed for our purposes, it is necessary to review briefly the literature which is relevant and which supports the feasibility of the crucial "bond-cleavage" reaction which is illustrated below in the postulated synthetic pathway.

The reductive cleavage of C-N bond in a quaternary ammonium salt dates back to the work of Emde. This reaction now well-known as the Emde degradation has been used quite extensively in the alkaloid field and examples from the tetrahydroquinoline and isoquinoline series are cited below. 36, 37

![Chemical structures](image)

Figure 23.

This type of reductive fission was subsequently accomplished with sodium in liquid ammonia 38, 39 (Figure 24). An extension of the latter conditions to the indole alkaloids is shown in some degradation studies of the Rauwalfia alkaloids 40 (Figure 24).
More recently Wenkert et al. have reported the synthesis of a nine-membered ring system (98) by means of lithium in liquid ammonia reduction of the intermediate 97 (Figure 25).

Additional evidence which supports the generality of such a reaction comes from some very recent work in our laboratory. In these investigations, Birch reduction conditions or the use of lithium aluminium hydride has met with success. One example of this is given here (Figure 26).

A closely related sequence in the indole series has been also reported recently (Figure 27).
On the basis of the above results it became immediately apparent that the formation of quebrachamine or its derivatives would result from a reductive cleavage of the intermediate 73a and b.

The following discussion in this section of the thesis presents our investigations which are concerned with the synthesis of these compounds. The proposed sequence for this synthesis is outlined in Figure 29. Condensation of tryptamin with an appropriately substituted glutarate (70b)
and succinate (70a) via a Pictet-Spengler or Bischler-Napieralski cyclization could provide the necessary indolo-indolizine derivatives 71a and 71b. The tosyl or chloro derivatives of the latter substance could then undergo intramolecular cyclization to afford the desired intermediates 73a and 73b.

**Figure 29.**

Before proceeding to the reactions outlined above it is necessary to describe the syntheses of the ethyl α-ethyl-α-(γ-benzyloxypropyl)-α-keto-glutarate (70b) and ethyl α-ethyl-α-(γ-benzyloxypropyl)-succinate (70a) which are summarized in Figure 30.

Trimethylene glycol (99) was treated with one mole equivalent of sodium metal and the resulting sodium salt was reacted with benzyl chloride to provide γ-benzyloxypropanol (100). The latter compound (100) was
Figure 30.
subsequently reacted with thionyl chloride in the presence of N,N-dimethyl aniline to provide the benzyl-chloropropyl ether^{45}(101) in 83% yield. Alkylation of diethyl malonate with the latter provided the ethyl γ-benzyloxy malonate^{46}(102) in 77% yield. The latter compound was then alkylated with ethyl iodide to provide ethyl γ-benzyloxypropylethyl malonate (103). The latter compound was also obtained by alkylation of the diethyl ethyl malonate with the ether 101.

It may be appropriate at this point to discuss some of the spectral properties of the alkylation products. The infrared spectrum of compound 103 showed a carbonyl absorption band at 5.81μ. The most characteristic feature of the NMR spectrum of 103 (See Figure 32) was the new three-proton triplet at 9.2 τ due to the methyl protons of the additional ethyl group in this compound. The one-proton triplet at 6.6 τ (−C−CH−C−) in the NMR spectrum of 102 (Figure 31) was no longer present in the spectrum of 103.

The presence of the benzyloxy propyl function in the above mentioned compounds as well as in the compounds in the following discussion was clearly depicted in the NMR spectra by a five-proton aromatic singlet at 2.65 τ, a two proton singlet at 5.48 τ due to the benzyl methylene and a two-proton triplet at 6.47 τ due to the propyl methylene protons attached to the ether oxygen atom.

Hydrolysis of 103 with potassium hydroxide provided γ-benzyloxypropylethyl malonic acid (104) as a nice crystalline material (m.p. 117-120°C). The infrared of this acid showed a doublet in the carbonyl region at 5.74 (weak) and 5.89 (strong) μ.

The NMR spectrum (See Figure 33) was also in agreement with the structure of this compound.
Figure 31.

Figure 32.
Figure 33:

Figure 34:
The decarboxylation of 104 was accomplished smoothly at 140-150°C, to provide α-(γ-benzyloxypropyl)butyric acid (105) as a colorless viscous oil which was characterized without further purification.

The acid 105 was esterified with diazomethane or ethanol to provide the esters 106a and b as colorless viscous oils. Both compounds showed a carbonyl absorption band at 5.19μ in the infrared spectrum. The NMR spectra (See Figure 35, 36) showed a new one-proton multiplet at 7.8  τ due to the tertiary α-proton (CH-COOR) or the butyrate moiety which was generated from the decarboxylation reaction.

We had now achieved the syntheses of the desired methyl and ethyl α-(γ-benzyloxypropyl)butyrates 106a and b, which on subsequent alkylation could provide the succinates 107 and 70a as shown in Figure 30.

It is well known that sodium triphenyl methane is a strong base and capable of forming the enolate of an aliphatic ester. This enolate can then be alkylated with an alkyl halide.

The enolates of 106a and b were indeed formed when these esters were treated with sodium triphenyl methane in dry ether as solvent. Subsequent reaction of these intermediates with the corresponding methyl and ethyl bromo acetates, provide the desired methyl and ethyl succinates 107 and (70a). In both cases the reaction product was chromatographed on neutral alumina, and both succinates were eluted with benzene. Vacuum distillation provided these compounds as colorless oils.

Both compounds 107 and 70a showed a strong carbonyl absorption band at 5.8μ in the infrared spectra. The most characteristic features of the NMR spectra of these esters (See Figures 37, 38) were the absence of the one-proton multiplet at 7.8  τ present in the spectra of 106a and b and the presence of a two-proton singlet at 7.4  τ due to the methylene protons of
**Figure 35.**

```
COOCH₃
φCH₂OCH₂CH₂CH₂C CH₂CH₃
 H
```

**Figure 36.**

```
COOEt
φCH₂OCH₂CH₂CH₂C CH₂CH₃
 H
```
the newly introduced acetate unit. The spectrum of 107 shows two three-proton singlets at 6.4 and 6.46 ppm due to the two non-equivalent carbomethoxy groups present in this compound. Similarly the spectrum of 70a shows a four-proton octet centered at 5.87 ppm and a six-proton sextet centered at 8.79 ppm due to the two non-equivalent carboethoxy groups present in this compound.

The ethyl keto glutarate (70b) was similarly prepared from the ester (106b) using ethyl bromo pyruvate as the alkylating agent. This compound was obtained from the reaction mixture as a colorless oil, after chromatography from neutral alumina followed by vacuum distillation.

The infrared spectrum of this compound showed only one strong carbonyl absorption band at 5.8 μm. The NMR spectrum (See Figure 39) showed a four-proton quartet at 5.88 ppm and a six-proton triplet at 6.6 ppm due to the two carboethoxy groups present in this compound. The new methylene proton of the pyruvate unit give rise to a symmetrical quartet centered at 7.09 ppm which indicated the non-equivalence of these particular protons.

The striking difference in the behavior of the methylene protons of the acetate and pyruvate units of the compounds 70a and 70b in the NMR spectra must be discussed briefly at this point.

The protons of a methylene group adjacent to a center of molecular asymmetry can become magnetically non-equivalent and display AB-type splitting pattern in the NMR spectra. The existence of preferred conformations of the methylene group with respect to the asymmetric center has generally been considered necessary for magnetic non-equivalence. Another important factor contributing to magnetic non-equivalence is the intrinsic asymmetry of the molecule.48
Figure 37.

```
COOCH₃
φCH₂OCH₂CH₂CH₂C₂H₂CH₃
COOCH₃
```

Figure 38.

```
COOEt
φCH₂OCH₂CH₂CH₂C₂H₂CH₃
CH₂
COOEt
```
Figure 39.
The three staggered conformations of 70a which are pertinent to this discussion are I, II and III. If we assume that protons Ha and Hb are not equivalent in each of the above conformations, one would expect that they will give rise to an AB spectrum. However, in order to be consistent with the NMR spectrum of 70a in which these protons give rise to a singlet we can consider the two alternative possibilities which follow: a) the methylene protons are "accidentally" equivalent in each of the three conformations and therefore they will give rise to an A2 spectrum or b) we may also assume that the alkyl groups, \( \phi CH_2OCH_2CH_2CH_2-(R) \) and \( CH_3 CH_2-(Et) \) have a similar effect on the methylene protons or in other words, the compound 70a which possesses an asymmetric center behaves similarly to the system \( R'-CH_2-CR_2R'' \) (where \( R'' \) is a very different substituent from \( R \)). The methylene protons Ha and Hb will then be equivalent in conformation I. Similarly when the interconversion between II and III is rapid and these two conformations are equally populated, the methylene protons will experience the same average shielding and therefore, will become equivalent. On this basis the shielding of the methylene group will then be the arithmetic mean of the three environments and the spectrum will be of the A2 type.
If we now examine the conformations of compound 70b whose NMR spectrum indicates that the methylene protons are non-equivalent then the above conditions cannot prevail. Clearly the introduction of the pyruvate unit which bears an α-keto carbomethoxy system must play some role in creating the non-equivalence of the methylene protons. Whether this situation is derived from the intrinsic asymmetry of the molecule or a decrease in the rate of interconversion of the various conformations is not known at the present time. Let us briefly consider these two possibilities, in this case. If rapid interconversion does indeed occur and an equal population of the individual conformations is obtained then obviously, the non-equivalence of the protons Hα and Hβ must arise from the intrinsic asymmetry of the molecule 70b. On the other hand, the α-keto carbomethoxy system can also introduce additional steric and electronic repulsions in the molecule and thereby prevent a very rapid interconversion from one conformation to another so that unequal populations of these conformations are obtained. Furthermore, the methylene protons will become non-equivalent
providing that the environments of the $H_a$ and $H_b$ are not identical in conformations we consider for this molecule. If we accept as in the case of 70a, that the substituents $R$ and $Et$ have similar effects on protons $H_a$ and $H_b$ then only conformation $V$ and $VI$ will give rise to the non-equivalence of these protons. Since the latter alternative implies a) an equal effect of $R$ and $Et$ and b) restricted rotation and thereby prefered conformations for this molecule I feel that intrinsic asymmetry plays the major role in providing the non-equivalence of the methylene protons in compound 70b.

The difference of the chemical shifts ($\delta H_a - \delta H_b$) of $H_a$ and $H_b$ in the NMR spectrum of 70b was calculated $13$ cycles per second $^{49}$ (c.p.s.)

We were now ready to study the condensation of the ethyl keto glutarate 70b with tryptamine via a Pictet-Spengler $^{50}$ type of cyclization. Wenkert et al $^{41}$ were able to obtain the compound 108 by refluxing tryptamine hydrochloride with ethyl $\alpha$-keto glutarate in ethanol for 60 hours.

![Chemical Structures](image-url)

Figure 40.
When the ethyl keto glutarate 70b was reacted with tryptamine hydrochloride under Wenkert's conditions, a mixture of neutral compounds was obtained. The major component of this mixture was separated by preparative thin layer chromatography. The ultraviolet spectrum of this component showed an absorption pattern characteristic of an indole system and the infrared spectrum indicated the presence of an amide carbonyl. However, the complexity of the NMR spectrum indicated that this compound was still a mixture of at least two components. In fact, we were able to separate two compounds from this mixture by a subsequent and more careful thin layer chromatographic purification. For the sake of convenience, the less polar compound obtained was labelled as compound A whereas the more polar one was labelled as B. Compound A remained as gummy material in spite of numerous attempts to obtain it in crystalline form. On the other hand, compound B was crystallized from ether-hexane (m.p. 90-96°).

Both compounds showed an identical ultraviolet absorption pattern characteristic of an indole system, ($\lambda_{\text{max}}$ 223, 275(sh) 284 and 292 μ). The infrared spectra of both compounds showed a sharp band at 2.79μ (>NH) and two carbonyl absorptions at 5.82 and 5.9μ corresponding to the presence of ester and amide functions respectively. The NMR spectra of both compounds were almost identical (See Figures 41 and 42). The aromatic proton region integrated for 9 protons. The one-proton doublet at 3.05 τ normally due to the α-position of the indole moiety indicated that no cyclization had occurred. The two-proton singlet at 5.53 τ was due to the presence of the benzyloxy methylene protons while the two-proton quartet centered at 5.8 τ and the three-proton triplet centered at 8.78 τ in the spectrum of compound A (the corresponding values for compound B appeared at 5.9 and 8.87 τ respectively) indicated the presence of one carboethoxy group which was in
agreement with the infrared spectrum. The methylene protons of the pyruvate unit gave rise again to a quartet centered at 7.0 $\tau$ in compound A and at 7.1 $\tau$ in compound B.

From the above spectral properties of the compounds A and B along with the analytical results obtained for the crystalline compound B, we assigned the structures 110 and 111 to either A or B. Furthermore, in the previous discussion concerning the non equivalence of the methylene protons

$\text{CH}_2\text{COCO}_2\text{Et}$ in the pyruvate 70b, we came to the conclusion that the $\alpha$-keto carbomethoxy group (C-C-O Et) was mainly responsible for the non-equivalence of these protons. One therefore expects that the difference in the chemical shifts of $\text{Ha}$ and $\text{Hb}$ ($\delta\text{Ha}-\delta\text{Hb}$) in 110 will be very similar to the one in the glutarate 70b, since the methylene substituent $\text{C}-\text{C-0 Et}$ is common in both compounds. On the other hand, the value of $\delta\text{Ha}-\delta\text{Hb}$ is expected to be different in 70b and 111 due to the different nature of the methylene substituent in 111 (C-C-NH-). The value $\delta\text{Ha}-\delta\text{Hb}$ was calculated 13 and 14.5 c.p.s. in compounds A and B respectively ($\delta\text{Ha}-\delta\text{Hb} = 13$ c.p.s. in compound 70b). However, we tentatively assigned the structures 110 and 111 to A and B respectively, although further work will be necessary in order to establish unambiguously the structure of these compounds.

The mixture of compounds A and B was also obtained when equivalent amounts of tryptamine and the keto glutarate 70b were heated in ethanol in a sealed tube at 120° or when refluxed in benzene for several hours.

The above results indicated that the keto glutarate 70b failed to follow the normal Pictet-Spengler type of cyclization with tryptamine. Although the reason for the failure of this reaction is unknown, it is felt that steric hindrance created by the two substitutents adjacent to the pyruvate carbonyl group may be responsible. Instead, reaction at
either end of the keto glutarate molecule with tryptamine provided the amides 110 and 111.

We now turned our attention to the condensation of the succinate 70a with tryptamine. We felt that the initial formation of an imide (112) could subsequently lead to the indole-indolizine intermediate (113) via Bischler-Napieralski cyclization reaction. In the following reactions the ethyl succinate 70a was used, for it was more easily available in our laboratory.

Indeed we were able to obtain the imide 112 by refluxing a mixture of tryptamine and 70a in diethylene glycol monoethyl ether as solvent for 44 hours. The imide (112) was isolated as a gummy material from the reaction mixture by chromatography on alumina. In spite of numerous attempts this product failed to crystallize.

The spectral properties were in excellent agreement with the structure 112 for this compound. The molecular ion peak (m/e 418) in the mass spectrum supported the molecular formula C_{26}H_{36}O_{3}N_{2}. The NMR spectrum (See Figure 44) showed a broad one-proton singlet at 1.0 τ (>NH), a nine-proton aromatic multiplet centered at 2.7 τ, and a one-proton doublet at 3.06 τ due to the α-proton of the indole system. The absorption due to nine aromatic protons and the two-proton singlet at 5.58 τ was in agreement with the presence of the benzyloxy group in this compound. Two two-proton triplets centered at 6.25 and τ were due to the ethylene bridge of the tryptamine moiety while the two-proton triplet centered at 6.68 τ was readily assigned to the methylene protons on the carbon atom attached to the ether oxygen atom (-CH_{2}O). Finally the two-proton singlet at 7.6 τ could be easily attributed to the methylene of the succinimide moiety.
Figure 43.
The infrared spectrum of this compound showed a sharp peak at 2.86\(\mu\) (>NH) and two carbonyl absorption bands at 5.67 (weak) and 5.91 (strong) \(\mu\). The latter absorption pattern is a very characteristic feature of a succinimide system.\(^{55}\) Furthermore, this compound gave typical indole ultraviolet absorption spectrum (\(\lambda_{\text{max}}\) 221, 275(sh), 283 and 291 \(\mu\)).

Although Wenkert et al\(^{41}\) were unable to cyclize N-[\(\beta\)-(3-indolyl)ethyl]-succinimide (120), Morrison and Cetenko have recently succeeded in accomplishing the cyclization of the N-[\(\beta\)-(3-indolyl)ethyl]glutarimide (121) to provide the indoloquinolizine system 122 by the use of phosphorus pentoxide in refluxing xylene.\(^{59}\) (Figure 45).

![Figure 45](image)

When we subjected the imide 112 to the above cyclization conditions we obtained among other products a compound in approximately 5% yield, whose spectral properties were in excellent agreement with those reported\(^{52}\) for the compound 122.

The ultraviolet spectrum of the former compound showed absorption maxima at 223(sh), 229, 314 and 327 \(\mu\) which is in good agreement with the absorption pattern reported for 122 (\(\lambda_{\text{max}}\) 220(sh) 232, 308 and 319 \(\mu\)). In the presence of a strong acid e.g. concentrated hydrochloric acid a new strong absorption peak appeared at 388 \(\mu\) (compound 122 exhibited \(\lambda_{\text{max}}\) 395 \(\mu\)).
The infrared (in KBr) of the cyclization product showed two carbonyl absorptions at 5.95 and 6.05 μ (compound 122 $\gamma_{max}$ 6.0 and 6.1 μ) and a sharp band at 3.05 μ (>NH). The NMR spectrum, which was obtained from a small amount of this product indicated that the benzyl group was no longer present since the aromatic proton multiplet now integrated for approximately four protons and the two-proton singlet due to the benzylic methylene was no longer present in this spectrum. On the other hand, approximately four protons were present in the olefinic region of the NMR spectrum.

The mass spectrum of the above compound showed the molecular ion peak at m/e 192 and this corresponded to the molecular formula C$_{19}$H$_{20}$ON$_2$. On the basis of the above data we assigned the structure 114 to this compound.

It was now obvious that we had succeeded in accomplishing the cyclization of the imide although the loss of the benzyloxy group and the small yield of the desired product made this particular reaction impractical for our synthesis.

In order to avoid the undesirable side reaction which could also be responsible for the low yield of the product we decided to replace the benzyloxy group with a substituent which could be stable under the cyclization conditions. A halogen atom appeared to be the most obvious substituent on the basis of our synthetic approach.

Consequently we modified our synthetic sequence to allow for this substitution. The benzyl ether function present in 112 was cleaved smoothly with boron tribromide or trichloride, to provide the corresponding alcohol (115). The cleavage of an ether with boron trihalides involves the formation of an intermediate oxonium ion complex from which, a carbonium ion intermediate is formed by rupture of C-O bond. In the benzyl ether 112 the benzyl carbonium ion will be resonance stabilized and therefore the
alcohol 115 was exclusively obtained.

The infrared spectrum of 115 showed a sharp band at 2.87\(\mu\) (>NH) which overlapped with a broad band at 2.95 (-OH) and also two carbonyl peaks at 5.66 (weak) and 6.1\(\mu\) characteristic of the presence of the succinimide chromophore.

The NMR spectrum (Figure 46) showed a multiplet of four aromatic protons centered at 2.7 \(\tau\) while the two-proton singlet of the benzyloxy methylene normally appearing at 5.48 \(\tau\) was no longer present. Another indication that the ether cleavage to the expected alcohol 115 had occurred was provided by the shift of the methylene protons attached to the oxygen function (-CH\(_2\)O) from 6.47 in the ether to 6.58 \(\tau\) in the alcohol. Finally a one-proton singlet at 6.75 \(\tau\) was assigned to the hydroxyl proton on the basis of the disappearance of this NMR peak on addition of D\(_2\)O to the sample.

The mass spectrum of this compound indicated a molecular ion peak at m/e 328 which was in agreement with the molecular formula C\(_{19}\)H\(_{24}\)O\(_3\)N\(_2\). As expected the ultraviolet spectrum still showed a typical indole absorption spectrum (\(\lambda_{\text{max}} 222, 275(\text{sh}), 283\) and 292 \(\mu\)) and thereby eliminated any change in this portion of the molecule.

Reaction of the alcohol 115 with thionyl chloride and pyridine in an ether-benzene solvent system, provided a mixture of products from which the chloro compound 116 was obtained as a gummy material by chromatography from neutral alumina. This compound remained as a gum in spite of the numerous attempts to obtain it in crystalline form.

The mass spectrum showed a molecular ion peak (m/e 346) which was in excellent agreement with the empirical formula C\(_{19}\)H\(_{23}\)O\(_2\)N\(_2\)Cl.
The infrared spectrum of this substance showed a sharp band at 2.87\textmu (\textgt{NH}) and the characteristic carbonyl bands [5.67 (weak) and 6.1 (strong)] chromophore for the succinimide.

The NMR spectrum (Figure 47) indicated very clearly that the replacement of the hydroxyl group by the chlorine function had occurred. In particular the absence of the hydroxyl proton peak which was present at 6.75 \tau in the spectrum of the alcohol and chemical shift of the methylene protons attached to the hydroxyl group from 6.58 to 6.68 \tau in the corresponding chloro compound 116 should be noted. In addition the ultraviolet spectrum indicated again the typical indole absorption pattern ($\lambda_{max}$ 223, 275(sh), 283 and 292 \textmu).

When the chlorocompound 116 was subjected to the same cyclization conditions as in the case of compound 112, we obtained among other products a substance (in 18\% yield), which indicated the desired ultraviolet and infrared spectral properties for the expected enol lactam 117. In our attempt to find more optimum cyclization conditions it was realized that the yield of this product was slightly improved when the reflux period was reduced from five to one and a half hours. The product 117 was obtained from the reaction mixture as an amorphous solid after chromatography on neutral alumina. This compound could not be obtained crystalline and it was characterized as an amorphous powder.

The infrared spectrum of this compound showed a sharp band at 3.04\textmu (\textgt{NH}) and a carbonyl at 5.93 and 6.04\textmu.

The ultraviolet spectrum showed absorption maxima at 223(sh), 229, 283(sh), 303(sh), 313 and 326 \textmu. When a drop of concentrated hydrochloric acid was added to the above solution a new peak appeared at 387 \textmu while the intensity of the peaks at 313 and 326 \textmu was reduced considerably.
These spectral properties are again in good agreement with the ones reported for the compound 122.

The NMR spectrum was also very instructive and in excellent agreement with the structure 117 assigned to this compound (Figure 48). This spectrum showed a broad one-proton-singlet at 1.6 τ (≥NH), a four-proton aromatic multiplet centered at 2.7 τ and a sharp one-proton singlet at 6.64 τ due to the olefinic proton at C₃. Furthermore two two-proton triplets centered at 6.15 and 6.96 τ due to the C₅ and C₆ methylene protons a two-proton triplet at 6.59 τ due to the -CH₂Cl group, a six-proton multiplet centered at 8.2 τ (-CH₂CH₂CH₂Cl and -CH₂CH₃) and a three-proton triplet at 9.3 τ (-CH₂CH₃) were clearly evident in the spectrum. Finally a one-proton doublet at 3.0 τ (β-proton of the indole) and the two proton singlet at 7.6 τ (methylene protons of the succinimide moiety) present in the spectra of 112, 115 and 116 were no longer present in the spectrum of the cyclization product.

The final piece of evidence in support of the cyclization product was obtained from the mass spectrum of this compound which showed a molecular ion peak at m/e 328 corresponding to the empirical formula C₁₉H₂₁ON₂Cl.

Hydrogenation of 117 with PtO₂ in acetic acid provided a substance which on purification by chromatography from neutral alumina provided a crystalline material (m.p. 148-156°). This material showed two spots on thin layer chromatoplates (alumina) when the latter was developed several times with benzene as eluant.

The mass spectrum of this mixture indicated a molecular ion peak (m/e 329) corresponding to the empirical formula C₁₉H₂₃N₂Cl. We were able to separate small amounts of the two compounds by careful preparative thin layer chromatography. Both of these substances showed molecular ion peaks
at m/e 329 in their mass spectra and it was clear that they were isomeric.

The infrared spectrum of the mixture indicated an amide absorption at 5.99 μ and the ultraviolet spectrum exhibited a typical indole absorption pattern ($\lambda_{\text{max}}$ 224, 275(sh), 283 and 290 μ).

On the basis of the above spectral properties it was obvious that the hydrogenation of 117 had provided the two expected stereo isomers at the newly created asymmetric center 11b.

The reduction of the lactam carbonyl was accomplished by refluxing the above mixture 118 with lithium aluminum hydride in tetrahydrofuran for 24 hours. The reduction product was again a mixture of two components. We were able to separate these compounds in small amounts by careful preparative thin layer chromatography. Both components of this mixture indicated a molecular ion peak at m/e 282 in their mass spectra - a value which corresponded to the molecular formula C$_{19}$H$_{26}$N$_2$. Other features of the spectrum were also in support of the fact that not only was the lactam carbonyl successfully reduced but unfortunately, the halogen had been lost. Although further work will be required, there appears little doubt that the structure of 119 is the correct one for these reduction products. It would appear that the two compounds are merely isomeric compounds.

It is therefore necessary at this point to develop milder conditions for the reduction of the lactam so that the chlorine group will remain unaffected. A possible alternative which is being considered at present is to obtain the thiolactam (120) by treating the lactam 118 with phosphorous pentasulfide and subsequent reduction of the latter with Raney nickel (Figure 49). The procedure has been recently employed in a synthesis of the alkaloid vincamine. $^{54}$
Another approach to the reduction of this carbonyl function could be the reduction of the enol lactam 117 with lithium aluminum hydride since this compound is expected to reduce under milder conditions than the lactam 118. It is hoped that the conditions would be sufficiently mild to prevent hydrogenolysis of the C-Cl bond. Subsequent reduction of the iminium salt 122 with sodium borohydride could lead to the desired cyclic product 121. The subsequent cyclization of the latter could provide the necessary intermediate, 73a. The above alternatives are now under investigation in our laboratory.
In conclusion, I would like to say that the synthetic sequence leading to the intermediate 73a is nearly complete. As was already mentioned above on several occasions, the small amounts of materials which were available or the gummy nature of some of the reaction products prevented complete characterization of some of the compounds. In particular, analytical data are lacking in some instances and will be obtained when a subsequent repetition of the above investigations on a larger scale will be carried out.
Experimental

Melting points were determined on a Kofler block and are uncorrected. The ultraviolet (UV) spectra were recorded in 95% ethanol on Cary 11 recording spectrometer, and the infrared (IR) spectra were taken on Perkin-Elmer Model 21 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded at 60 magacycles/sec on a Varian A60 instrument; the line positions or centers of multiplets are given in the Tiers scale with reference to tetramethylsilane as the internal standard; the multiplicity, and integrated area and type of protons are indicated in parentheses. Silica gel G and Woelm alumina were used for thin layer chromatoplates; the type of absorbent and the solvent system for developing the thin layer chromatoplates are given in parentheses. The alumina used for column chromatography was Shawinigan reagent grade deactivated with 3% of 10% aqueous acetic acid. Analyses were performed by Dr. A. Bernhardt and his associates, Mulheim (Ruhr), Germany and by the Microanalytical Laboratory, University of British Columbia. Every molecular weight (MW) quoted was determined mass spectrometrically with an Atlas CH-4 mass spectrometer.

2-Carbomethoxy-3-chloroacetyl indole (75)

Dry 2-carbomethoxy-indole (74) (5.644 g, 0.0032 mole) was placed in a thick-walled glass tube and treated with dry chloroform (200 ml), and dry chloroacetonitrile (50 ml, 0.756 mole).

Dry hydrogen chloride gas was bubbled into the mixture, cooled to 0°C, over a period of 2 hours. After this time the reaction was cooled to -78° (dry ice-acetone) and hydrogen chloride passed in for another 10 minutes at which point a yellow solid had formed in the reaction mixture. The tube was the sealed and the reaction mixture was kept at 50° for 11 hours. After this period the tube was slowly cooled to -78°,
then opened carefully and allowed to come to room temperature. The precipitate was filtered, washed with ice-cold chloroform (2 x 25 ml) and the combined filtrate and washings were kept aside as they contained mainly starting material. The deep yellow amorphous solid was dried under vacuum and then treated with water (50 ml) to affect hydrolysis of the iminium salt. The salt dissolved instantly, but on hydrolysis to the corresponding ketone an insoluble solid compound formed. The precipitate was filtered and subsequently extracted several times with boiling chloroform. The combined chloroform extracts were washed once with water and dried over anhydrous magnesium sulfate. Removal of the solvent afforded a light yellow semicyrstalline product (5.278 g). An additional 0.396 g of this product was obtained from treatment of the initial aqueous filtrate with ammonia gas and removal of the yellow solid which was precipitated during this treatment. The crude product (5.674 g) was chromatographed from alumina.

Initial elution with benzene-chloroform (1:1) gave starting material (1.023 g), but further elution with the same solvent gave the desired compound, (75) (1.76 g, 31% yield), m.p. 147.5-148.5°. Ultraviolet: \( \lambda_{\text{max}} \) 249 (4.11), 318 (4.10) μ. Infrared (CHCl\(_3\)): 2.98 (>NH), 5.80 (-COOCH\(_3\)), 6.0 (-CH\(_2\)-), 6.58 (aromatic) μ. NMR signals ((CD\(_3\))\(_2\)CO): 2.65 (multiplet, 4H, aromatic), 4.98 (singlet, 2H, -CH\(_2\)Cl), 5.98 (singlet, 3H, CH\(_3\)OC-). Found: C, 57.10; H, 4.11; O, 18.97; N, 5.73; Cl, 14.07. Calc. for C\(_{12}\)H\(_{10}\)O\(_3\)NCl: C, 57.24; H, 4.01; O, 19.07; N, 5.56; Cl, 14.11.

2-carbomethoxy-3-(3-carbomethoxy-N-piperidyl)-acetylindole (77)

Well powdered 2-carbomethoxy-3-chloroacetyl indole (75) (300 mg, 0.0012 mole) was thoroughly mixed with 3-carbomethoxy piperidine (76)
(500 mg, 0.0035 mole). The mixture was warmed slightly from time to time in a steam bath, until a clear viscous solution was obtained. To this viscous solution, ethyl ether (30 ml) and water (30 ml) were added and the mixture was shaken until the viscous oil was distributed between the aqueous and the ether layer. The ether layer was separated, washed once with water and dried over anhydrous magnesium sulfate. The ether was removed by distillation under vacuum to provide a viscous oil (519 mg). This material was chromatographed from alumina (15 g). The desired material (77) (270 mg) was eluted with benzene-ethyl ether (9-1) as an amorphous solid. Crystallization of this material from dichloromethane-ethyl ether provided and analytical sample m.p. 121-125°. Yield 60%.

Infrared (KBr): 3.1 (>NH), 5.78 (-COCH₃), 6.1 (CCH₂-N<) μ. Ultraviolet λmax 220 (4.412), 248 (4.155), 314 (4.074) μ. NMR signals (CDCl₃): 2.6 (multiplet, 4H, aromatic), 6.08 (singlet, 3H, -COCH₃), 6.4 (singlet, 3H, -COCH₃), 6.2 (broad doublet, 2H, -CH₂-N<) . Found: C, 63.49; H, 6.54, O, 22.98; N, 6.96. Calc. for C₁₉H₂₂O₅N₂: C, 63.68; H, 6.19; O, 22.32; N, 7.82.

2-carbomethoxy-3-[α-hydroxy-8-(3-carbomethoxy-N-piperidyl)ethyl]-indole (78)

The compound 77 (250 mg, 0.0007 mole) was dissolved in absolute methanol (50 ml) and sodium borohydride (400 mg, 0.01 mole) was added to this solution. The mixture was stirred for 4 hours at room temperature. The methanol was removed by distillation under vacuum and the residue was shaken with a mixture of water (30 ml) and ethyl ether (30 ml) until the residue was distributed between the aqueous and the ether layer. The ether layer was washed once with water and dried over anhydrous magnesium sulfate. The ether was removed by distillation under vacuum to provide an amorphous white solid (200 mg), which showed only one spot on thin layer chromato-
graphy (alumina, benzene-chloroform 1:1). This material, in spite of the numerous attempts, resisted crystallization. To prepare an analytical sample, this material was further purified by preparative thin layer chromatography (alumina, benzene-chloroform 1:1). The compound was eluted from the alumina with dry methanol. Yield 80%. Infrared (KBr): 2.95 (-OH, >NH), 5.85 (2 x -COCH₃) μ. Ultraviolet: λ_max 229 (4.39), 298 (4.272) μ. NMR signals (CDCl₃): 2.65 (multiplet, 4H, aromatic), 6.25 (singlet, 3H, -COCH₃), 6.45 (singlet, 3H, -COCH₃), 4.4 (broad quartet, 1H, -CH-CH₂-).

Found: C, 63.26; H, 6.86; O, 22.99, N, 6.90. Calc. for C₁₉H₂₁O₅N₂:
C, 63.32; H, 6.71; O, 22.2; N, 7.77.

Raney nickel hydrogenation of 77

The compound 77 (100 mg) was dissolved in 95% ethanol (30 ml) and hydrogenated over Raney nickel catalyst at room temperature and atmospheric pressure, for 1 1/2 hours. The catalyst was filtered and the ethanol was removed with distillation under vacuum. Preparative thin layer chromatography (alumina, benzene-chloroform 1:1) of the residue provided an amorphous white solid (80 mg). This material was found to be identical to 78 by thin layer chromatography, NMR and IR spectra comparison. Yield 84%.

2-carbomethoxy-3-[α-hydroxy-β-(3-carbomethoxy-N-piperidyl)-ethyl]-4,5,6,7-tetrahydro-indole (79)

a) Raney nickel hydrogenation of 77

The compound 77 (100 mg) was dissolved in 95% ethanol (30 ml) and hydrogenated over Raney nickel catalyst at room temperature and atmospheric pressure, for a period of 20 hours. The catalyst was filtered and the ethanol was removed by distillation under vacuum. Preparative thin layer chromatography (alumina benzene-chloroform 1:4) of the residue provided an
amorphous, white solid (65 mg) which, in spite of numerous attempts resisted crystallization. Yield 64%. Infrared (CHCl₃): 2.9 (>NH), 3(-OH), 5.6 (COCH₃ of the piperidine moiety), 6 (COCH₃ of the indole moiety) μ.


b) Raney nickel hydrogenation of 78

The compound 78 (100 mg) was dissolved in 95% ethanol (30 ml) and hydrogenated over Raney nickel catalyst at room temperature and atmospheric pressure for a period of 20 hours. The catalyst was filtered and the ethanol was removed by distillation under vacuum. Preparative thin layer chromatography (alumina, benzene-chloroform 1:4) of the residue provided the major component as a white amorphous solid (60 mg). This compound was found to be identical to 79 by thin layer chromatography (alumina, benzene-chloroform 1:4), IR and NMR spectra comparison.

2-carbomethoxy-4,5,6,7-tetrahydro-indole (80)

2-carbomethoxy-indole(74) (175 mg, 0.001 mole) was dissolved in 1% of concentrated hydrochloric acid in methanol solution (30 ml) and hydrogenated over Adams catalyst at room temperature and atmospheric pressure. When 1 mole of hydrogen was absorbed (in a period of approximately 6 hours), the hydrogenation was interrupted. The catalyst was filtered and approximately 25 ml of methanol was removed by vacuum distillation. The remained mixture was taken in ethyl ether (50 ml). The ether solution was washed once with water and dried over anhydrous magnesium sulfate. The ether was removed by distillation under vacuum to provide a white semicrystalline
solid. Preparative thin layer chromatography (silica gel, chloroform) of this solid provided starting material (95 mg) and the product 80 (50 mg). The latter was recrystallized from aqueous methanol m.p. 156-157°. Infrared (KBr): 3.02 (>NH), 6.0 (COCH₃)μ. Ultraviolet: λmax 287 (4.253) μ. NMR signals (CDCl₃): 3.52 (doublet, 1H, B-proton of the pyrrole), 6.27 (singlet 3H, COCH₃), 7.5 (multiplet, 4H), 8.25 (multiplet, 4H) μ. Found: C, 66.55; H, 7.68; O, 18.06; N, 7.86. Calc. for C₁₀H₁₃O₂N: C, 67.02; H, 7.31; O, 17.85; N, 7.82.

Indole-2-carboxylic acid dimethylamide (83)

To a stirred suspension of indole-2-carboxylic acid (31 g, 0.19 mole) in absolute benzene (500 ml), kept under a slow stream of nitrogen, was added thionyl chloride (50 ml), over a period of 1 hour. The mixture was then warmed to 45-50° and kept at this temperature for 1 1/2 hours, whereupon the acid went completely into solution. In order to remove excess thionyl chloride, 1/3 of the resulting solution was removed by distillation under reduced pressure. After dilution of the remainder with benzene (200 ml) the solution was slowly added dropwise, to a stirred solution of dimethylamine in benzene. The resulting mixture was treated with cold water (100 ml) in order to dissolve the dimethylamine hydrochloride, thoroughly stirred, and filtered. The solid was dried and crystallized from ethanol, producing the dimethylamide (30 g, 83%) m.p. 182-184°. Lit.: m.p. 180-182°.

2-Dimethylaminomethylindole (84)

To a stirred suspension of lithium aluminum hydride (28 g, 0.74 mole) in dry tetrahydrofuran (500 ml), a solution of indole-2-carboxylic acid dimethyl amide (56 g, 0.3 mole) in tetrahydrofuran (600 ml) was added
slowly over a period of 2 hours. After completion of the addition, the reaction mixture was stirred under an atmosphere of dry nitrogen at 45-50° for 5 hours, cooled to -10°, and treated cautiously with water to destroy excess hydride. The inorganic salts were separated by filtration and washed thoroughly with fresh volumes of tetrahydrofuran. The combined washings and filtrate were evaporated under reduced pressure. The residual oil was treated with ice-cold dilute (2N) aqueous sodium hydroxide solution (150 ml), and extracted thrice with ether. The combined ether extracts were washed twice with water and dried over anhydrous sodium sulfate. Removal of the ether with vacuum distillation produced a viscous oil which was distilled under vacuum, affording a clear liquid (48.5 g, 93%) which after some time in the cold, crystallized. A small amount was recrystallized from pet. ether (b.p. 60-80°) affording colorless blocks. B.p. 104-107°/0.1 mm (Lit. b.p. 118-120°/0.3 mm) m.p. 59-61° (Lit. 60-61°).

2-dimethylaminomethylindole methiodide (85)

To a stirred solution of 2-dimethylaminomethylindole (17.4 g, 0.1 mole) in dry ethyl ether (100 ml) a solution of methyl iodide (15.6 g, 0.11 mole) in dry ethyl ether (50 ml) was added dropwise. The quaternary salt came out of solution as a white crystalline solid. After complete addition of the methyl iodide, the reaction mixture was stirred over-night at room temperature. The ether was decanted from the solid and the residue was dried under vacuum affording a white crystalline solid (31 g). This material turned to a gummy oil when exposed to the open atmosphere and therefore it was kept under vacuum in a desiccator. The material was used for the next reaction step without further purification, since repeated attempts to crystallize from various solvents failed.
Indole-2-acetonitrile (86)

A solution of 2-dimethylaminomethylindole methiodide (18 g, 0.057 mole) and potassium cyanide (12 g, 0.185 mole) in absolute methanol (500 ml) was refluxed, with stirring, under an atmosphere of nitrogen, for 20 hours. After this time, approximately 350 ml of methanol was distilled and the residue poured into ice-water. The resulting mixture was extracted thrice with ether, the combined ether extracts were washed with ice-cold water, and then dried over anhydrous sodium sulfate. Removal of the ether produced a dark brown solid (9 g) which was chromatographed over alumina (500 g). The desired compound was eluted from the column with benzene-ether (9:1) which on recrystallization from ether-pet. ether (b.p. 60-80°) afforded white plates (4.5 g 56%) m.p. 95-97.5° (Lit. m.p. 96-98°).

Indole-2-acetic acid (87)

A solution of indole-2-acetonitrile (400 mg, 2.56 m.mole) in 95% ethanol (5 ml) was added to a solution of potassium hydroxide (410 mg, 7.3 m.mole) in water (2 ml). The resulting mixture was refluxed with stirring under an atmosphere of nitrogen for 45 hours. The solution was diluted with water (10 ml) and the ethanol removed under vacuum. The resulting aqueous solution was washed twice with ether, and then carefully acidified with concentrated hydrochloric acid. The mixture was extracted twice with ether, the ether extracts were combined, washed once with water, and dried over anhydrous sodium sulfate. Evaporation of the ether afforded a crude brown product (440 mg, 98% crude yield). The infrared spectrum was nearly identical to that of indole-2-acetic acid, reproduced by Schindler.32
Indole-2-acetic acid, methyl ester (88)

To a stirred solution of crude indole-2-acetic acid (420 mg) in anhydrous ether (10 ml) kept in an ice-water bath, a solution of diazomethane in ether-ethanol was added until the yellow color of the diazomethane persisted. The resulting solution was allowed to stand for 30 minutes and the solvent was evaporated in a stream of nitrogen, affording crude product (436 mg). The crude product was passed through a short column of alumina (10 g) using benzene-ether (1:1) as eluant. Evaporation gave pale yellow crystals (327 mg) which upon crystallization from ether-pentane afforded colorless blocks (296 mg) m.p. 74-75°. Infrared (Nujol): 3.06 (>NH), 5.85 (-COCH₃) μ. Ultraviolet: λ max 218, 272, 289 μ. NMR signals (CDCl₃): 2.55-3.35 (multiplet, 4H, aromatic), 3.84 (singlet, 1H, β-proton of the indole), 6.67 (singlet, 2H, -CH₂ COOCH₃), 6.41 (singlet, 3H, -CH₂ COOCH₃). Found: C, 69.40; H, 6.22; N, 7.65. Calc. for C₁₁H₁₁O₂N: C, 69.82; H, 5.86; O, 16.91; N, 7.40.

3-chloroacetylindole-2-acetic acid methyl ester (89)

Indole-2-acetic acid methyl ester (88) (1 g, 0.0053 mole) was dissolved in dry ether (7 ml) and chloroacetonitrile (8 ml) was added to this solution. The mixture was cooled to 0° and dry hydrogen chloride was passed through the solution for approximately 3 hours. At the end of this time a heavy white precipitate was formed, and the reaction mixture allowed to stay at 0° for another 2 hours. The precipitate was filtered and washed twice with dry ether. This precipitate was treated with water (100 ml) to affect hydrolysis of the iminium salt. The salt dissolved instantly, but on hydrolysis to the corresponding ketone yielded an insoluble solid compound. This solid was filtered and washed twice with water and then extracted three times with chloroform. The combined chloroform
extracts were washed twice with water and dried over anhydrous magnesium sulfate. Evaporation of chloroform under vacuum afforded a white semi-crystalline material. This material was passed through a short alumina column (25 g) using chloroform as eluant. Evaporation of the chloroform afforded a nice crystalline material (880 mg, 62%). A small amount of this material was recrystallized from dichloromethane-ethyl ether to provide an analytical sample m.p. 142-144°C. Infrared (KBr): 3.0 (>-NH), 5.79 (-COCH₃), 6.2 (-CCH₂Cl) μ. Ultraviolet: λ_max 214 (4.523), 244 (4.147), 267 (3.9555), 309 (4.048) μ. NMR signals ((CD₃)₂CO): 2.15-3.10 (multiplet, 4H, aromatic), 5.3 (singlet, 2H, -C-CH₂C₃), 5.8 (singlet, 2H, -CH₂COOCH₃), 6.4 (singlet, 3H, -CH₂COOCH₃). Found: C, 58.62; H, 4.75; O, 17.81; N, 5.42; Cl, 13.24. Calc. for C₁₃H₁₂O₃NCl: C, 58.76; H, 4.55; O, 18.07; N, 5.27; Cl, 13.35.

3-acetylindole-2-acetic acid methyl ester (90)

3-chloroacetylindole-2-acetic acid methyl ester (89) (71 mg) was dissolved in 95% ethanol (30 ml) and hydrogenated over Raney Nickel catalyst at room temperature and atmospheric pressure. After a period of 30 minutes the uptake of hydrogen became very slow and the reaction was interrupted. The catalyst was removed by filtration and the ethanol was distilled under vacuum. The residue was taken with dichloromethane, and the insoluble inorganic salts initially present in the ethanolic solution were filtered. The filtrate was concentrated down to provide a crystalline material (60 mg, 96%). This was recrystallized from ethyl ether-dichloromethane to provide an analytical sample m.p. 128-131°. Infrared (KBr): 3.16 (NH), 5.66 (-COCH₃), 6.1 (-C-CH₃) μ. Ultraviolet: λ_max 215 (4.442), 243 (4.114), 272 (3.882), 303 (3.954) μ. NMR signals (CDCl₃): 2.8 (multiplet, 4H, aromatic), 5.71 (singlet, 2H, -CH₂COOCH₃), 6.33 (singlet,
3-(3-carbomethoxy-N-piperidyl)-acetylindole-2-acetic acid methyl ester (92)

Well powdered 3-chloroacetylindole-2-acetic acid methyl ester (89) (380 mg, 0.0014 mole) was mixed with 3-carbomethoxy piperidine (76) (840 mg, 0.0059 mole). The mixture was warmed slightly from time to time in a steam bath, until a clear solution was obtained. This reaction mixture was allowed to stay overnight at room temperature. At the end of this time water (50 ml) and ethyl ether (50 ml) were added and the mixture was shaken until the viscous oil was distributed between the aqueous and the ether layer. The ether layer was washed once with water and dried over anhydrous magnesium sulfate. The ether was removed by vacuum distillation to afford a gummy material (672 mg). This material was passed through a short silica gel column (6 g) using chloroform as eluant. The chloroform was removed by vacuum distillation to afford a gummy material (500 mg, 93%). This material, in spite of numerous attempts resisted crystallization. For analytical purposes part of this material was further purified by preparative thin layer chromatography (alumina, chloroform) to afford an amorphous solid. Infrared (KBr): 3.12 (>NH), 5.77 (2 x -COCH₃), 6.1 (-CCH₂N) u. Ultraviolet: λmax 214 (4.604), 243 (4.266), 268 (4.066), 303 (4.14) μ. NMR signals (CDCl₃): 2.7 (multiplet, 4H, aromatic), 5.67 (singlet, 2H, -CH₂COOCH₃), 6.17 (singlet, 2H, -CCH₂N<), 6.3 (singlet, 3H, -COCH₃), 6.46 (singlet, 3H, COCH₃). Found: C, 64.21; H, 6.72; O, 22.84; N, 6.92. Calc. for C₂₀H₂₄O₅N₂: C, 64.5; H, 6.5; O, 21.48; N, 7.52.
3-ethylindole-2-acetic acid methyl ester (91)

(a) By catalytic hydrogenation of 90.

A solution of 3-acetylindole-2-acetic acid methyl ester (90) (225 mg) in 1% hydrochloric acid in methanol (15 ml) was hydrogenated over Adams catalyst at room temperature and atmospheric pressure. After a period of 30 minutes, when approximately 2 moles of hydrogen had been absorbed, the reaction was interrupted. The catalyst was filtered and the methanol was removed by vacuum distillation. The residue was taken with ethyl ether, and the ether extract was washed twice with water and dried over anhydrous magnesium sulfate. Removal of the ether afforded an oily material (170 mg). Preparative thin layer chromatography (silica gel, chloroform-ethylacetate 1:1) of this substance provided the hydrogenation product (91) (front running material) as a viscous oil (100 mg) and starting material (50 mg).

Infrared (liq. film): 2.9 (>NH), 5.8 (COCH₃) μ. Ultraviolet: λ max 225, 276(sh), 285, 293 μ. NMR signals (CDCl₃): 2.85 (multiplet, 4H, aromatic), 6.28 (singlet, 2H, -CH₂COOCH₃), 6.31 (singlet, 3H, -CH₂COOCH₃), 7.38 (quartet, 2H, -CH₂CH₃), 8.8 (triplet, 3H, -CH₂CH₃) τ.

(b) By diborane reduction of (90)

A solution of 3-acetylindole-2-acetic acid methyl ester (90) (50 mg, 0.0002 mole) in dry tetrahydrofuran (10 ml) was cooled at 0° and diborane, generated from boron trifluoride etherate (2 ml) in diglyme (8 ml) and sodium borohydride (500 mg) in diglyme (15 ml), was passed through the solution for a period of 1 1/2 hours. The reaction mixture was allowed to stay at 0° for another 30 minutes. The excess of diborane was destroyed with water and the mixture was extracted with ether. The ether extract was washed with water and dried over anhydrous magnesium sulfate. The
ether was removed by vacuum distillation to provide a clear viscous oily material, which turned yellow in contact with the air. Preparative thin layer chromatography (silica gel, chloroform-ethyl acetate 1:1) of this material provided the desired product 91. (Front running compound, 20 mg, 42%).

3-[8-(3-carbomethoxy-N-piperidyl)-ethyl]-indole-2-acetic acid methyl ester (93)

The coupling product 92 (200 mg, 0.00054 mole) was dissolved in dry tetrahydrofuran and the solution cooled to 0°. Diborane, generated from boron trifluoride etherate (3 ml) in diglyme (15 ml), and sodium borohydride (1 g) in diglyme (15 ml), was passed through the cold solution for a period of 3 hours. Dilute (10%) acetic acid (10 ml) was then added slowly to the reaction mixture. The resulted solution was allowed to stay at room temperature for ten minutes and subsequently extracted twice with ether. The combined ether extracts were washed once with 5% potassium carbonate solution, twice with water and dried over anhydrous magnesium sulfate. Removal of the ether afforded an amorphous yellowish solid (160 mg). This solid was dissolved in dry dioxane (5 ml) and a mixture of concentrated sulfuric acid (0.2 ml) in dioxane (10 ml) were added to the above solution. The mixture was shaken well and allowed to stay at room temperature for 15 minutes. The sulfuric acid was neutralized with 10% sodium bicarbonate, ethyl ether (50 ml) was then added to the dioxane solution and the mixture was washed several times with water to remove the dioxane. The ether solution was dried over anhydrous magnesium sulfate and the ether was removed with vacuum distillation to provide a gummy material (150 mg). Preparative thin layer chromatography (alumina, chloroform-ethyl acetate 1:1) of this
material afforded the desired reduction product (93) (Front running material, 60 mg, 28%). This compound, in spite of numerous attempts, resisted crystallization. NMR signals (CDCl₃): 2.8 (multiplet, 4H, aromatic), 6.2 (singlet, 2H, -CH₂COOCH₃), 6.26 (singlet, 3H, -COCH₃), 6.3 (singlet, 3H, -COCH₃). This compound was further characterized as an amorphous hydrochloride, which was prepared by passing dry hydrogen chloride through an ether solution of the product 93 and subsequent removal of the ether under vacuum to dryness. Infrared (KBr): 5.79 (2 x -COCH₃) μ. Ultraviolet: 222 (4.3), 275 (sh), 283 (3.7), 2.92 (3.664) μ. Found: C, 60.90; H, 7.33; O, 16.04; N, 5.85. Calc. for C₂₀H₂₇O₇N₂Cl: C, 60.83; H, 6.89; O, 16.2; N, 7.09.

γ-Benzyloxy propanol (100)

Sodium (25 g, 1.08 moles) was added in portions to a hot (115-120°) and vigorously stirred solution of trimethyleneglycol (240 g, freshly distilled, b.p. 115-119°/9 mm) in dry xylene (100 ml). External heating was not necessary until near the end of the reaction. Benzyl chloride (150 g) was slowly added with stirring to the hot (120°) solution of the sodium derivative. The mixture was heated (120°) and stirred for 1 hour, after all the benzyl bromide had been added. The mixture was cooled to room temperature and the precipitate was removed by filtration. The filtrate was distilled under reduce pressure through a distillation column. After a fore-run of xylene and dibenzyloxypropane the γ-benzyloxy propanol (125 g, 69%, Lit. 73%), boiled at 109-110°/8 mm) (Lit. 145-150°/13 mm). NMR signals (neat): 2.76 (singlet, 5H, aromatic), 5.59 (singlet, 1H, -OH), 5.65 (singlet, 2H, C₆H₅CH₂OH-,), 6.35 (triplet, 2H, -CH₂OH), 6.51 (triplet, 2H, 4CH₂O CH₂-), 8.21 (quintet, 2H, -OCH₂CH₂CH₂OH) τ.
Benzyl γ-chloropropyl ether (101)

Thionyl chloride (120 g) was added drop by drop to a mixture of γ-benzyloxy propanol (100) (160 g) and N-dimethyl aniline (130 g). The temperature of the reaction mixture was kept below 60° during the addition of the thionyl chloride. After all the thionyl chloride was added the reaction mixture was allowed to stay at 60° for another 1/2 hour. At the end of this time the reaction mixture was poured into excess of dilute hydrochloric acid, and the heavy oil which separated was extracted with chloroform. The chloroform extract was washed with dilute hydrochloric acid to remove the dimethylaniline, then with water and dried over anhydrous sodium sulfate. The solvent was evaporated and the oil was distilled. Benzyl-γ-chloropropyl ether was at once obtained (150 g, 81%, Lit. 83%) as a colorless oil b.p. 95-100°/1 mm (Lit. 129°/16 mm). NMR signal (neat): 2.72 (singlet, 5H, aromatic), 5.72 (singlet, 2H, \( \phi CH_{2}O \)), 6.57 (triplet, 2H, \( \phi CH OCH_{2} \)), 6.65 (triplet, 2H, -CH\(^2\)Cl), 8.2 (quintet, 2H, -CH\(^2\)CH\(^2\)CH\(^2\)) τ.

Ethyl γ-benzyloxypropyl malonate (102)

A solution of sodium (68 g, 2.96 gram atoms) in absolute alcohol (1250 ml) was made in a five liter three-necked flask. The solution was cooled and treated with ethyl malonate (675 g, 4.23 moles). The suspension was refluxed and stirred while benzyl-γ-chloropropyl ether (101) (520 g, 2.82 moles) was added over a period of 3 hours, and then the stirring and refluxing were continued for 21 hours. Most of the alcohol was removed by distillation, the residue cooled and water added to dissolve the inorganic salt. The layers were acidified with glacial acetic acid and separated. The water layer was extracted thrice with ether. Oil and extracts were combined, washed once with water, twice with 10% sodium
bicarbonate, once with saturated sodium chloride solution and finally
dried over anhydrous sodium sulfate. The product distilling at 150-160°/1
mm (Lit. 193-200°/4 mm) weighed 580 g (76%, Lit. 77%). NMR signals (neat):
2.71 (singlet, 5H, aromatic), 5.59 (singlet, 2H, \( \text{C}_6\text{H}_5\text{CH}_2\text{O}^- \)), 5.9 (quartet,
4H, 2xO\text{CH}_2\text{CH}_3), 6.6 (two triplets, 3H, \( \text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2- \) and \(-\text{C}-\text{CH}-\text{C}^- \)), 8.2 (multi-
plet, 4H, \(-\text{OCH}_2\text{CH}_2\text{CH}_2\text{C} \)), 8.86 (triplet, 6H, 2x-\text{OCH}_2\text{CH}_3) \( \tau \).

Ethyl \( \gamma \)-benzyloxypropylethyl malonate (103)

(a) Alkylation of 102 with ethyl iodide

A solution of sodium (13 g, 0.56 gram atoms) in absolute ethanol
(200 ml) was made in a one liter three-necked flask. The solution was
cooled and treated with ethyl \( \gamma \)-benzyloxypropyl malonate (102) (134.5 g,
0.43 ml). The mixture was heated to boil and then allowed to cool to 60°.
Ethyl iodide (6 g, 0.64 mole) was then added slowly with stirring. After
all the ethyl iodide was added, the stirring was continued for 10 hours
at 60°. The most of the ethanol was removed by distillation, the mixture
was allowed to cool to room temperature, water added and acidified with
glacial acetic acid. The mixture was extracted twice with ether and the
combined ether extracts were washed once with water, twice with 10% of
sodium bicarbonate solution, once with concentrated sodium chloride
solution and finally dried over anhydrous magnesium sulfate. The ether
was evaporated and the remained oil was distilled under reduced pressure.
The product was distilled at 220-222°/1.5 mm and weighed 123 g. (84%).
Infrared (liq. film): 5.81 \((-\text{COCH}_3 \ \mu \). NMR signals (neat): 2.72 (singlet,
5H, aromatic), 5.6 (singlet, 2H, \( \text{C}_6\text{H}_5\text{CH}_2\text{O}^- \)), 5.88 (quartet 4H, 2x-\text{OCH}_2\text{CH}_3),
6.6 (triplet, 2H, \( \text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2- \)), 8.2 (multiplet, 6H, \(-\text{OCH}_2\text{CH}_2\text{CH}_2\text{CCH}_2\text{CH}_3 \)),
8.85 (triplet, 6H, 2x\text{OCH}_2\text{CH}_3), 9.2 (triplet, 3H, \(-\text{CH}_2\text{CH}_3 \)) \( \tau \). Found:
(b). Alkylation of ethyl diethyl malonate with 101

A solution of sodium (11.2 g, 0.48 moles) in absolute ethyl alcohol (205 ml) was made in a one liter three-necked flask. The solution was cooled and treated with ethyl diethyl malonate (90 g, 0.48 mole). The mixture was heated to boil and benzyl γ-chloropropyl ether (101) (88 g, 0.48 mole) was added in a period of 1/2 hour with continuous stirring of the reaction mixture. The refluxing and stirring were continued for 10 hours. At the end of this time, part of the ethanol was distilled (180 ml), the mixture was cooled to room temperature and water (300 ml) was added. The mixture was acidified with glacial acetic acid and extracted twice with ether. The combined ether extracts were washed twice with 10% of sodium bicarbonate, once with saturated sodium chloride and dried over anhydrous magnesium sulfate. The ether was evaporated to afford 150 ml of a heavy oil, which was distilled under vacuum. The desired material (103) boiled at 150-170°/0.02 mm and weighed 90 g (56%).

γ-benzyloxypropylethyl malonic acid (104)

To a stirred solution of potassium hydroxide (90 g) in water (140 ml), ethanol (35 ml) and ethyl γ-benzyloxypropylethyl malonate (103) (112 g) were added. The mixture was heated (60°) with stirring for 15 hours. The ethanol was evaporated in a steam bath and the alkaline solution was washed twice with ether (the ether washings were discarded). Water (100 ml) was then added, the mixture was acidified to Congo red with concentrated hydrochloric acid and extracted three times with ether. The combined ether extracts were washed twice with water, once with saturated sodium
chloride and dried over anhydrous magnesium sulfate. The ether was evaporated and the viscous oily residue was crystallized from n-hexane-ether to provide colorless blocks (91 g, 97%), m.p. 117-120°. Infrared (KBr): 5.74 (weak), 5.89 (strong). NMR signals (CDCl₃): -0.5 (broad singlet, 2H, 2x-COOH), 2.65 (singlet, 5H, aromatic), 5.48 (singlet, 2H, C₆H₅CH₂O-), 6.47 (triplet, 2H, C₆H₅CH₂OCH₂-), 7.8-8.8 (multiplet, 6H, -OCH₂CH₂CH₂CCH₂-), 9.12 (triplet, 3H, -OCH₂CH₃). Found: C, 64.14; H, 7.12; O, 28.62. Calc. for C₁₅H₂₀O₅: C, 64.27; H, 7.19; O, 28.54.

2-(γ-benzyloxypropyl)-butanoic acid (105)

The diacid (104) (41.85 g) was heated at 140-150° for 5 hours (the evolution of carbon dioxide ceased at the end of this time). The product, a yellowish viscous oil, was used for the subsequent reactions without further purification. Infrared (liq. film): 5.87 (-COH), 2.8-3.7 (broad, -OH absorption). NMR signals (CDCl₃): -0.6 (singlet, 1H, -COOH), 2.71 (singlet 5H, aromatic), 5.55 (singlet, 2H, C₆H₅CH₂O-), 6.56 (triplet, 2H, C₆H₅CH₂OCH₂-), 7.65 (multiplet, 1H, CHCOOH), 8.45 (multiplet, 6H, -OCH₂CH₂CH₂CCH₂CCH₂-), 9.11 (triplet, 3H, CHCH₂CH₃).

Methyl 2-(γ-benzyloxypropyl)-butanoate (106a)

The viscous oily acid (105) was dissolved in dry ethyl ether (50 ml) and the mixture was cooled to 0°. A solution of diazomethane in ether-ethanol was added to the above solution until the yellow color of the diazomethane persisted. The ether was evaporated in a stream of nitrogen and the resulted oil was distilled under reduced pressure to afford a colorless oil (28 g, 75%) b.p. 180-186°/1.2 mm. Infrared (liq. film): 5.19 (-COCH₃). NMR signals (neat): 2.75 (singlet, 5H, aromatic), 5.67 (singlet, 2H, C₆H₅CH₂O-), 6.67 (triplet, 2H, C₆H₅CH₂OCH₂-).
6.5 (singlet, 3H, \text{-OCH}_3), 7.8 (multiplet, 1H, CHCOOCH_3), 8.5 (multiplet, 6H, \text{-OCH}_2CH_2CH_2\text{CCH}_2CH_3), 9.2 (triplet, 3H, C-\text{CH}_2\text{CH}_3) \tau. \text{ Found: } C, 71.76; H, 8.48; O, 19.76. \text{ Calc. for } C_{15}H_{22}O_3: \text{ C, 71.97; H, 8.86; O, 19.17.}

**Ethyl 2-(\gamma\text{-benzyloxypropyl})-butanoate(106b)**

To a solution of 2-(\gamma\text{-benzyloxypropyl})-butyric acid (105) (14.9 g) in absolute ethanol (250 ml), concentrated sulfuric acid (2 ml) was added, and the mixture was refluxed for 6 hours. Part of the ethanol was distilled (150 ml) and the rest of the reaction mixture was poured into ice-water. The mixture was extracted twice with ether and the combined ether extracts were washed once with water, once with 5% sodium bicarbonate solution, once again with water and dried over anhydrous magnesium sulfate. The ether was evaporated and the resulted oil was distilled under reduced pressure to afford the ethyl ester (106b) (12.8 g, 76%) as colorless oil. b.p. 156-159°/0.25 mm. Infrared (liq film): 5.8 (\text{COC}_2\text{H}_5) \nu. NMR signals (neat): 2.73 (singlet, 5H, aromatic), 5.6 (singlet, 2H, C_6\text{H}_5\text{CH}_2O-), 5.95 (quartet, 2H, \text{-OCH}_2\text{CH}_3), 6.61 (triplet, 2H, C_6\text{H}_5\text{CH}_2\text{OCH}_2-) 7.75 (multiplet, 1H, \text{CHCOOC}_2\text{H}_5), 8.4 (multiplet, 6H, O\text{CH}_2\text{CH}_2\text{CH}_2\text{CCH}_2\text{CH}_3), 8.85 (triplet, 3H, \text{-OCH}_2\text{CH}_3), 9.15 (triplet, 3H, C-\text{CH}_2\text{CH}_3) \tau. \text{ Found: } C, 73.16; H, 8.99; O, 17.85. \text{ Calc. for } C_{16}H_{24}O_3: C, 72.69; H, 9.15; O, 18.16.

**Preparation of sodium triphenyl methane**

Sodium (3 g) covered with dry xylene was carefully melted with free flame. To this melted sodium, kept under a dry nitrogen atmosphere, mercury (200 g) was slowly added. The remained xylene was decanded and the amalgam allowed to cool to room temperature. To the cold amalgam, ethyl ether (50 ml) and triphenyl methyl chloride (11 g) were added and the mixture was shaken vigorously for 6 hours. At the end of this time
another 80 ml of dry ether were added, the mixture was shaken well and allowed to rest for 5 to 6 hours. The dark-red ether solution was then transferred into the reaction flask with caution, under a dry nitrogen atmosphere. The concentration of this solution was approximately 0.2 mole/lit.

**Methyl α-(y-benzyloxypropyl)-α-ethyl-succinate (107)**

To an ether solution of sodium triphenyl methane (0.03 mole) the ester 106a (7.5 g, 0.03 mole) was added and the mixture was stirred at room temperature for 1/2 hour. At the end of this time, methyl bromoacetate (5 g, 0.03 mole) was slowly added and the mixture was stirred for another 15 minutes. The reaction mixture was then treated with water (50 ml) and the layers were separated. The ether layer was washed once with water and dried over anhydrous magnesium sulfate. Removal of the ether afforded a yellowish viscous oil. To this oily residue, benzene (10 ml) was added and the mixture allowed to rest until most of the triphenyl methane had crystallized. The triphenyl methane was filtered and the filtrate was chromatographed from alumina (200 g). The triphenyl methane which remained in the filtrate was eluted with benzene-pt. ether (30-60°) (1:1) and it was followed by the unreacted ester 106a (2.5 g). Finally the desired product (107) was eluted with benzene as yellowish viscous oil and it was further purified by vacuum distillation (bath temperature 200-220°/1mm, 3.6 g, 37%).

Infrared (liq. film): 5.8 (2xCOCH₃) µ. NMR signals (CDCl₃): 2.74 (singlet, 5H, aromatic), 5.56 (singlet, 2H, C₆H₅CH₂O-), 6.4 (singlet, 3H, -OCH₃) 6.46 (singlet, 3H, -OCH₃), 6.6 (triplet, 2H, C₆H₅CH₂OCH₂-), 7.4 (singlet, 2H, -CH₂COOCH₃) 8.32 (multiplet, 6H, OCH₂CH₂CH₂CCH₂CH₃) 9.2 (triplet, 3H, C-CH₂CH₃) τ. Found: C, 67.27; H, 7.74; O, 24.99. Calc. for C₁₈H₂₆O₅:
Ethyl α-(α-benzylxypropyl)-α-ethyl-succinate (70 a)

To an ether solution of sodium triphenyl methane (0.019 mole) the ethyl ester 106b (5 g, 0.019 mole) was added and the mixture was stirred for 1 1/2 hours at room temperature. Ethyl bromoacetate (3.2 g, 0.019 mole) was then slowly added and the mixture was further stirred for another 10 minutes. The reaction mixture was subsequently treated with water (50 ml) and the layers were separated. The ether layer was washed twice with water and dried over anhydrous magnesium sulfate. Removal of the ether provided a yellowish viscous oil. To this oil, benzene (10 ml) was added and the mixture allowed to rest until most of the triphenyl methane had crystallized. The triphenyl methane was filtered and the filtrate was chromatographed from alumina (200 g). The triphenyl methane which remained in the filtrate was first eluted with benzene-pet. ether (30-60°) (1:1) and it was followed by the unreacted ester 106b (2.3 g). The desired material (70a) was eluted with benzene as a yellowish viscous oil and it was further purified by vacuum distillation (bath temperature 200-220°/1 mm 1.93 g, 20%). Infrared (liq. film): 5.8 (-COC₂H₅) μ. NMR signals: (CDCl₃) 2.75 (singlet, 5H, aromatic), 5.57 (singlet, 2H, C₆H₅CH₂O-), 5.87 (octet, 4H, 2x-OCH₂CH₃), 6.6 (triplet, 2H, C₆H₅CH₂OCH₂-), 7.4 (singlet, 2H, -CH₂COOC₂H₅), 8.4 (multiplet, 6H, OCH₂CH₂CH₂CH₂CH₃), 8.79 (sextet, 6H, 2x-OCH₂CH₃), 9.2 (triplet, 3H, C-CH₂CH₃). Found: C, 68.47; H, 8.55; O, 22.99. Calc. for C₂₀H₃₀O₅: C, 68.54; H, 8.63; O, 22.83.
Ethyl α-keto-γ-(γ-benzyloxypropyl)-γ-ethyl-glutarate (70b)

To an ether solution of sodium triphenyl methane (0.018 mole), the ester 106b (4.9 g, 0.018 mole) was added and the mixture was stirred for 1 1/2 hours at room temperature. Ethyl bromopyruvate (3.63 g, 0.018 mole) was then slowly added and the mixture was further stirred for another 10 minutes. The reaction mixture was subsequently treated with water (50 ml) and the layers were separated. The ether layer was washed once with water and dried over anhydrous magnesium sulfate. Removal of the ether afforded a yellowish viscous oil, which was diluted with benzene (10 ml) and allowed to rest until most of the triphenyl methane had crystallized. The triphenyl methane was filtered and the filtrate was chromatographed from alumina (200 g). The triphenyl methane which remained in the filtrate was first eluted with benzene-pet. ether (30-60°) (1:1) and it was followed by the unreacted ester 106b. The desired product (70b) was eluted with benzene as a yellowish viscous oil and it was further purified by vacuum distillation (bath temperature 210-230°/ 1 mm, 1.4 g, 23%). Infrared (liq. film): 5.8 (-CCOEt, -COOEt) μ. NMR signals: (CDCl₃): 2.73 (singlet, 5H, aromatic), 5.57 (singlet, 2H, C₆H₅CH₂O-), 5.88 (quartet, 4H, 2x-OCH₂CH₃), 6.6 (triplet, 2H, C₆H₅CH₂OCH₂-), 7.09 (quartet, 2H, -CH₂COOC₂H₅), 8.35 (multiplet, 6H, OCH₂CH₂CH₂OCH₂CH₃), 9.25 (triplet, 3H, C-CH₂CH₃) τ.

Condensation of the keto glutarate (70b) with tryptamine hydrochloride

A mixture of the keto glutarate (70b) (240 mg, 0.006 mole) and tryptamine hydrochloride (70 mg, 0.00026 mole) in absolute ethanol (2 ml) was refluxed for 60 hours under a nitrogen atmosphere. The ethanol was
evaporated under vacuum and the residue was treated with an ether-water mixture until it was distributed between the two layers. The ether layer was washed with water, dried over anhydrous magnesium sulfate. Removal of the ether provided an oily material (250 mg) which showed three spots on thin layer chromatography (silica gel, chloroform). This mixture was chromatographed from alumina (20 g). The unreacted keto glutarate (70b) (100 mg) was eluted with benzene and it was followed by an oily substance (20 mg) which indicated no ultraviolet absorption corresponding to an indole chromophore. Finally, a gummy material (40 mg) was eluted with benzene-ether (9:1). This latter material showed two spots on thin layer chromatography (alumina, chloroform-ethyl acetate 9:1) when the plate was developed three times in this solvent system. Infrared (CHCl₃): 2.79 (sharp, >NH), 5.92 μ. Ultraviolet: 233, 275(sh), 284, 292 μμ. Further information about this material are given in the following experiment.

Condensation of the keto glutarate 70b with tryptamine

Tryptamien hydrochloride (400 mg, 0.0013 mole) was dissolved in water. The solution was basified with sodium bicarbonate solution and the free base was extracted with ether. The ether extract was dried over anhydrous magnesium sulfate and the ether was removed under vacuum. The triptamine residue was dissolved in absolute ethanol (20 ml) and keto glutarate (70b) (500 mg, 0.0032 mole) was added to this solution. The mixture was heated (120°) in a sealed tube for 20 hours. The solution was cooled to room temperature, the ethanol was removed under vacuum and the residue was taken with ether. The ether solution was washed once with 5% hydrochloric acid solution, once with water and dried over anhydrous magnesium sulfate. Removal of the ether afforded a gummy material (650 mg). This material
showed two spots on thin layer chromatography (alumina, chloroform-ethyl acetate 9:1) when the plate was developed three times in this solvent system. Thin layer chromatography, IR and UV spectra indicated that the above mixture was identical with the one obtained from the reaction of ketoglutarate (70b) with tryptamine hydrochloride as it is described in the previous experiment. Preparative thin layer chromatography (alumina, chloroform-ethyl acetate 9:1) of the reaction mixture (450 mg) - the plate was developed 5 times in the above solvent system - afforded the less polar material (A) (196 mg) and the more polar one (B) (164 mg) as gummy substances. The compound B was crystallized from n-hexane-ether to provide an analytical sample, m.p. 90-96°. Compound A, in spite of numerous attempts, resisted crystallization.

**Compound A.** Infrared (CHCl₃): 2.79 (sharp, >NH) 5.81, 5.93 μ. Ultraviolet: λ max 223, 275(sh), 284 and 292 μ. NMR signals (CDCl₃): 1.7 (singlet, 1H, >NH), 2.7 (multiplet, 9H, aromatic), 3.05 (doublet, 1H, α-proton of the indole), 5.53 (singlet, 2H, C₆H₅CH₂O-), 5.8 (quartet, 2H, -OCH₂CH₃), 6.5 (multiplet, 6H, -CH₂CH₂N< and C₆H₅CH₂OCH₂-), 7.0 (quartet, 2H, -CH₂COCO-), 8.26 (multiplet, 6H, -OCH₂CH₂CH₂CH₂CH₃), 8.78 (triplet, 3H, -OCH₂CH₃), 9.18 (triplet, 3H, C-CH₂CH₃) t.

**Compound B.** Infrared (CHCl₃): 2.78 (sharp, >NH) 5.8, 9.2 μ. Ultraviolet: λ max 223, 275(sh), 284 and 292 μ. NMR signals (CDCl₃): 1.7 (singlet, 1H, >NH), 2.75 (multiplet, 9H, aromatic), 3.02 (broad singlet, 1H, β-proton of the indole), 5.6 (singlet, 2H, C₆H₅CH₂O-), 5.9 (quartet, 2H, -OCH₂CH₃), 6.6 (multiplet, 6H, -CH₂CH₂-N< and C₆H₅CH₂OCH₂-), 7.1 (quartet, 2H, -CH₂COCO-), 8.35 (multiplet, 6H, OCH₂CH₂CH₂CH₂CH₃), 8.8 (triplet, 3H, -OCH₂CH₃), 9.15 (triplet, 3H, C-CH₂CH₃) t. Found: C, 69.75; H, 7.32; O, 16.98; N, 6.02. Calc. from C₂₉H₃₆O₅N₂: C, 70.11; H, 7.37; O, 16.24;
The structures 110 and 111 has been tentatively assigned to the compounds A and B respectively as it is described in the foregoing discussion of this thesis.

**N-[8-(3-indolyl)-ethyl]-α-(γ-benzyloxypropyl)-α-ethyl-succinimide (112)**

Tryptamine hydrochloride (10 g, 0.033 mole) was dissolved in water, the aqueous solution was basified with 20% sodium bicarbonate solution and the tryptamine base was extracted with ether. The ether extract was washed once with water, dried over anhydrous magnesium sulfate and the ether was removed under vacuum. To the crystalline residue, a solution of ethyl succinate (70a) (4.8 g, 0.013 mole) in freshly distilled diethylene glycol monoethyl ether (60 ml) was added and 20 ml of solvent was subsequently distilled in order to azeotrope traces of water from the mixture. Tryptamine hydrochloride (300 mg) was then added and the mixture was refluxed for 40 hours in a nitrogen atmosphere. The reaction mixture was allowed to cool to room temperature and diluted with ethyl ether (200 ml). The ether solution was washed 5 times with water, twice with 10% glacial acetic acid solution once with 5% sodium bicarbonate solution, once again with water and dried over anhydrous magnesium sulfate. The ether was removed and the brown residue was chromatographed from alumina (500 g). The desired product (112) was eluted with benzene-chloroform (9:1) as a gummy material (3.9 g, 69%). This compound, in spite of numerous attempts, resisted crystallization. Infrared(CHCl₃): 2.86 (>NH), 5.67 weak, 5.91 (strong) µ. Ultraviolet: λ max 221, 275(sh) 283, 291 μ. NMR signals (CDCl₃): 1.0 (singlet, 1H, >NH), 2.7 (multiplet, 9H, aromatic), 3.06 (doublet, 1H, β-proton of the indole), 5.58 (singlet, 2H, C₆H₅CH₂O-), 6.25 (triplet, 2H, -CH₂CH₂N), 7.0 (triplet, 2H, -CH₂CH₂N<),...
6.68 (triplet, 2H, C_6H_5CH_2OCH_2-), 7.6 (singlet, 2H, C-CH_2-C-), 8.5
(multiplet, 6H, -OCH_2CH_2CH_2CCH_2CH_3), 9.27 (triplet, 3H, C-CH_2CH_3) \tau; MW, 418. Calc. for C_{26}H_{30}O_3N_2: MW, 418.

**Bischler-Napieraski cyclization of the imide (112)**

The benzyl-imide (112) (230 mg) was dissolved in dry xylene (35 ml) in a 50 ml three-necked round bottom flask. From above solution, xylene (10 ml) was removed by distillation in order to azeotrope traces of water. To the stirred refluxing solution, phosphorous pentoxide (approximately 1.5 g) was added in three portions (500 mg) over a period of 45 minutes under a dry nitrogen atmosphere. The refluxing and stirring was further continued for another 2 hours. The reaction mixture was allowed to cool to room temperature, the xylene was decanted and the brown precipitate was washed twice with ether. (The xylene and the ether washings were discarded). The brown precipitate was treated with ice-water (50 ml), the mixture was made strongly alkaline with concentrated potassium hydroxide and extracted 5 times with ether. The combined ether extracts were washed once with water and dried over anhydrous magnesium sulfate. Removal of the ether afforded an amorphous yellowish solid (130 mg), which was subsequently chromatographed from alumina. Elution with benzene afforded a yellowish amorphous solid (20 mg) which was further purified by preparative thin layer chromatography (alumina, benzene-chloroform 1:1). The recovered white amorphous solid (10 mg) indicated the following spectral properties. Infrared CHCl_3: 3.95, 6.05 (weak) µ. Ultraviolet: \lambda_{max} 223(sh), 229, 314, 327 mµ. Found: MW, 292. Calc. for C_{19}H_{20}O_2: MW. 292.

**N-[β-(3-indolyl)-ethyl]-α-(3-hydroxypropyl)-α-ethyl-succinimide (115)**

To an ice-cold solution of the imide (112) (3.95 g) in dry dichloro-
methane (25 ml), boron tribromide (3 ml) was added and the mixture was allowed to stay at 0° for 10 minutes. At the end of this time ethyl ether (100 ml) was added and the resulted mixture was subsequently treated with ice-cold water. The layers were separated and the ether layer was washed once with water and dried over anhydrous magnesium sulfate. Removal of the solvent afforded a yellowish gummy residue (3.7 g) which was chromatographed from alumina (100 g). The desired alcohol (115) was eluted with benzene-chloroform (1:4) as a colorless gummy material (2 g, 65%). This material, in spite of numerous attempts, resisted crystallization. Infrared (CHCl₃): 2.87 (˃NH), 2.95 (OH), 5.66 (weak), 6.1 μ. Ultraviolet: λmax 222, 275(sh), 283, 292, μ. NMR signals (CDCl₃): 1.47 (singlet, 1H, ˃NH), 2.7 (multiplet, 4H, aromatic), 3.06 (doublet, 1H, β-proton of the indole), 6.17 (triplet, 2H, -CH₂CH₂N<), 6.95 (triplet, 2H, -CH₂CH₂N<), 6.58 (triplet, 2H, HOCH₂-), 6.75 (singlet, 1H, HOCH₂-), 7.61 (singlet, 2H, C-CH₂-), 8.5 (multiplet, 6H, -OCH₂CH₂CH₂CH₂CH₃), 9.28 (triplet, 3H, C-CH₂CH₃).


N-[β-(3-indolyl)-ethyl-α-(3-chloropropyl)-α-ethyl-succinimide (116)]

To an ice-cold solution of the alcohol 115 (2 g) in dry ether (50 ml), a mixture of thionyl chloride (10 ml), dry pyridine (10 ml) and dry ether (25 ml) was slowly added with stirring. The reaction mixture was subsequently stirred for 15 hours at room temperature. At the end of this time benzene (25 ml) was added and the mixture was refluxed for 3 hours. The reaction mixture was subsequently cooled to 0° and the thionyl chloride was destroyed with ice-cold water. The organic layer was washed twice with water and dried over anhydrous magnesium sulfate. Removal of the solvent afforded a gummy residue (1.8 g) which was subsequently chromato-
graphed from alumina (100 g). The desired chloride (116) was eluted with benzene as a colorless gummy substance (0.87 g, 41%), which resisted crystallization. Unreacted starting material (290 mg) was eluted with chloroform. Infrared (CHCl₃): 2.87 (>NH), 5.67 (weak), 6.1 μ. Ultraviolet: λₘₐₓ 223, 275 (sh), 283, 292 μ. NMR signal (CDCl₃): 1.85 (singlet, 1H, >NH), 2.7 (multiplet, 4H, aromatic), 3.0 (doublet, 1H, β-proton of the indole), 6.15 (triplet, 2H, -CH₂CH₂N<), 6.93 (triplet, 2H, -CH₂CH₂N<) (triplet, 2H, -CH₂Cl), 7.59 (singlet, 2H, (C-CH₃C), 8.5 (multiplet, 6H, -OCH₂CH₂CH₂CCH₂CH₃), 9.25 (triplet, 3H, C-CH₂CH₃). Found: MW, 346. Calc. for C₁₉H₂₃O₂N₂Cl: MW, 346.5.

2,3,5,6,11-pentahydro-2ɛ(3-chloropropyl)-2ɛ-ethyl-3-oxo-indolo(2,3-g)-indolizine (117)

The chloro-imide 116 (120 mg) was dissolved in dry xylene (35 ml) in a three-necked round bottom flask. From the above solution, xylene (10 ml) was removed by distillation in order to azeotrope traces of water. To the stirred, boiling solution, phosphorous pentoxide (1.5 g) was added in three portions (500 mg) over a period of 20 minutes and under a dry nitrogen atmosphere. The mixture was further stirred and refluxed for 1 hour, and subsequently cooled to 0°. The xylene was decanted and the brown solid was washed twice with dry ether (the xylene and the ether washings were discarded). The brown solid was treated with ice-cold water (30 ml) and the mixture was made strongly basic with concentrated potassium hydroxide. The resulted emulsion was extracted 5 times with ether. The combined ether extracts were washed once with water and dried over anhydrous magnesium sulfate. Removal of the ether afforded a brownish amorphous solid.

The above procedure was repeated 5 times, using each time 120 mg of
the chloro-imide 116. The products of the above five reactions were combined (450 mg) and chromatographed from alumina (40 g). The desired product (117) was eluted with benzene as a yellowish amorphous solid (104 mg, 18.5%), which, in spite of numerous attempts, resisted crystallization. Infrared: (KBr) : 3.04 (>NH), 5.93, 6.04 μ. Ultraviolet: \( \lambda_{\text{max}} \) 223(sh), 229 (4.653), 303(sh) (4.375), 313 (4.481), 327 (4.38) μ. \( \lambda_{\text{max}} \) EtOH, HCl) 220, 230(sh), 303(sh), 314, 327, 387 μ. NMR signals (CDCl₃): 1.6 (singlet, 1H, >NH), 2.7 (multiplet, 4H, aromatic), 4.64 (singlet, 1H, C₁ olefinic proton), 6.15 (triplet, 2H, C₅ methylene), 6.96 (triplet, 2H, C₆ methylene), 6.59 (triplet, 2H, -CH₂Cl), 8.2 (multiplet, 6H, OCH₂CH₂CH₂CCH₂CH₃), 9.3 (triplet, 3H, C-CH₂CH₃). Found: C, 68.88; H, 6.58; N, 8.3; Cl, 10.11; MW, 328. Calc. for C₁₉H₂₁O₇NCl: C, 69.4; H, 6.43; O, 4.86; N, 8.52; Cl, 10.87; MW, 328.5.

1,2,3,5,6,11,11b(\( \xi \))-heptahydro-\( \xi \)-(3-chloropropyl)-2\( \xi \)-ethyl-3-oxo-indolo-(2,3-g)indolizine (118)

A solution of enol lactan 117 (60 mg) in glacial acetic acid was hydrogenated over Adams catalyst at room temperature and atmospheric pressure until the hydrogen uptake ceased. The catalyst was filtered, the filtrate was diluted with chloroform and the mixture was carefully treated with 20% potassium bicarbonate solution. The chloroform layer was washed once with water and dried over anhydrous magnesium sulfate. Removal of the chloroform provided an amorphous white solid which was subsequently chromatographed from alumina (80 mg). Elution with benzene provided a crystalline compound (40 mg), which was recrystallized from n-hexane-dichloromethane, m.p. 148-156°C. Thin layer chromatophagy (alumina, benzene 1:1) of this material indicated two distinct spots.
when the plate was developed 5 times. Infrared (KBr): 5.99 (>N-C-) μ.
Ultraviolet: λ_{max} 224, 275(sh), 283, 290 μm. Found: C, 67.94; H, 6.71;
N, 8.04; Cl, 9.69; MW, 329. Calc. for C_{19}H_{23}ON_{2}Cl: C, 68.96; H, 7.00;
O, 4.83; N, 8.46; Cl, 10.72; MW, 330.5.

The two components in the above mixture were effectively separated
by preparative thin layer chromatography (alumina, benzene) when the plate
was developed 5 times. Both components indicated very similar IR (λ_{max}
CHCl₃, 5.95) and UV (λ_{max} 224, 275(sh), 283, 290 μm) spectra and MW, 329.

**Lithium aluminium hydride reduction of 118**

A mixture of the two isomers of the amide 118 (20 mg) was treated
with lithium aluminum hydride in dry tetrahydrofuran with refluxing for
24 hours. The excess hydride was destroyed with water and the inorganic
salts were filtered. The filtrate was diluted with ether, the mixture was
washed 3 times with water and dried over anhydrous magnesium sulfate.
Removal of the ether provided an amorphous solid (15 mg) which showed two
spots on thin layer chromatography (alumina, benzene) when the plate was
developed 5 times. Ultraviolet: λ_{max} 225, 275(sh), 283, 290 μm.

The two components were separated by preparative thin layer chromato-
graphy (alumina, benzene) when the plate was developed 5 times. Both
components indicated MW, 282. Calc. for C_{19}H_{16}N_{2} MW, 282.
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