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THE UNIVERSITY OF ALBERTA

STUDIES RELATED TO THE SYNTHESIS OF LYCOPODINE

BY

ARNOLD CLIFFORD SOPER

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR

THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

AUGUST, 1968

UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "Studies Related to the Synthesis of Lycopodine", submitted by ARNOLD CLIFFORD SOPER, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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August, 1968

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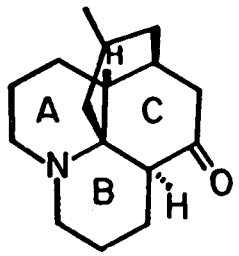
Especially, Dr. W.A. Ayer for the patient and excellent guidance which he always provided and for the wisdom and knowledge which he imparted to me.

ABSTRACT

Original samples of some Lycopodium alkaloids isolated by Manske and Marion were examined. L.9 was found to be a molecular complex made up of the known alkaloid lycopodine (2) and of O-acetyllofoline (80).



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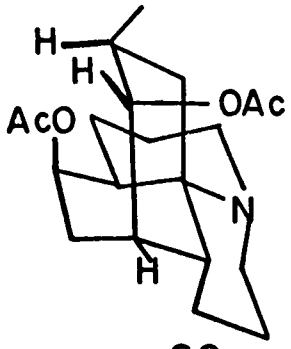

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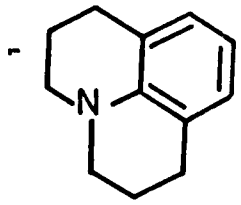
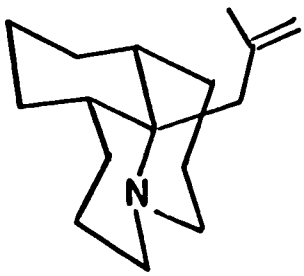


15

Studies related to the synthesis of lycopodine type alkaloids were carried out. Initially julolidine (15) was used as a model compound. Its reduction to an immonium salt was carried out and addition to C_{11} of the immonium salt was found to proceed readily. The substitution products were found to have cis-cis ring junctures (e.g. 102).



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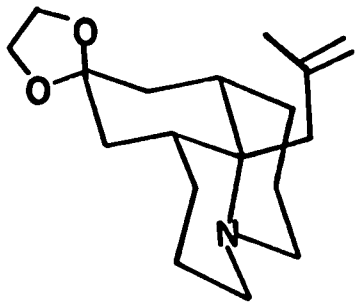

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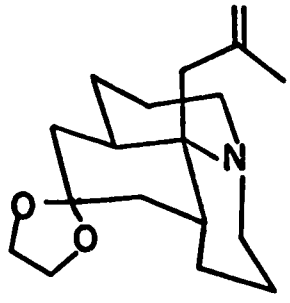
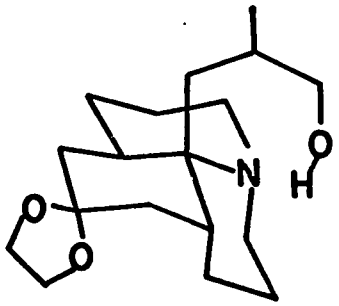


119

The synthetic study was extended to a more suitable system, 9-methoxyjulolidine (110). Reduction of this system followed by substitution at C_{11} resulted mainly in cis-cis ring junctions in the products (e.g., 115). A method of changing the stereochemistry of the products from cis-cis to the synthetically useful cis-trans system was developed.

A method for the formation of the fourth ring (D) in lycopodine type alkaloids was investigated. The method considered involved an internal aldol condensation in compound 152 to give 154. It was found that compound 152 could not be prepared at all readily, either by oxidation of 146 or by other methods investigated.



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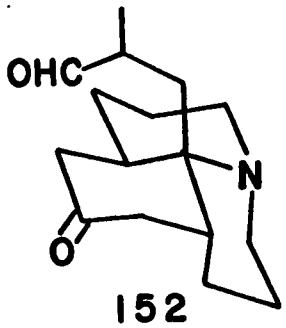

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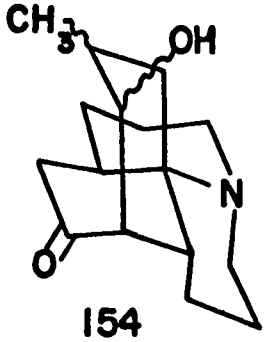

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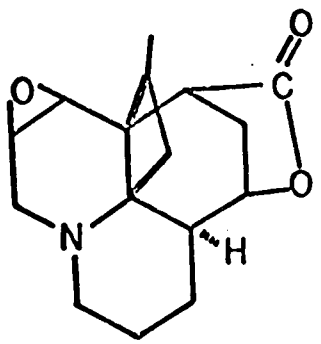
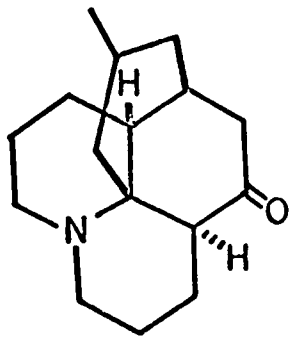
INTRODUCTION

The family of club mosses Lycopodiaceae are readily accessible plants which have proven to be rich in alkaloid content. Although the isolation of bases from various species of this family had been previously reported[1] it was not until the early 1940's that a systematic study of the alkaloidal content of the Lycopodiaceae was conducted. Then Manske and Marion[1] characterized no less than 35 bases in the period from 1942 to 1953. Some of these compounds were identified by name while most of them were simply referred to by symbol (e.g., L.13, L.20).

Annotinine (L.7) (1), first isolated from Lycopodium annotinum L.[2], was the first of these alkaloids to yield to structural studies.[3] The structure of this compound was confirmed by X-ray analysis.[4]



Annotinine
1



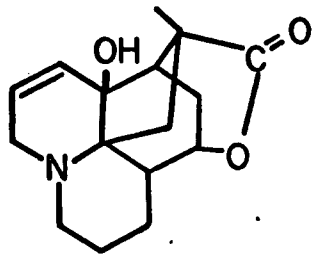
Lycopodine
2

In 1960, Lycopodine, the most widespread alkaloid found in the Lycopodiaceae, was assigned structure 2 by MacLean and Harrison.[5] Following the publication of this

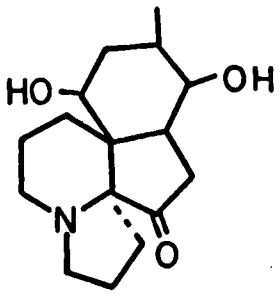
work a whole series of structures were elucidated many having a similar carbon skeleton to lycopodine as well as some differing substantially from that structure.[6] Some representatives of the various groups are shown in Chart I. Many of the advances achieved in the structural studies are due to the rapid development and perfection of methods of isolation as well as methods of structural analysis. Countercurrent extraction, thin layer chromatography (t.l.c.), elution chromatography and gas-liquid chromatography have all contributed greatly to the study of Lycopodium alkaloids. These methods have been of great use in the search for minor alkaloids and have allowed better separations of the crude alkaloids. This has led to the reinvestigation of several species of Lycopodiaceae.

The elucidation of structure of the alkaloids has equally been aided by the development of physical methods. Nuclear magnetic resonance has played a large part in this field of study (e.g., serratinine[11], Chart I) as have infrared and ultraviolet spectroscopy. The application of mass spectrometry has been of great value in the elucidation of the structures of the Lycopodium alkaloids. MacLean[12] examined the spectra of a variety of alkaloids having the lycopodine skeleton. Since then mass spectrometry has been used in virtually all structural

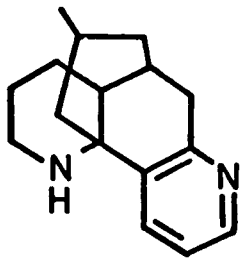
Chart I



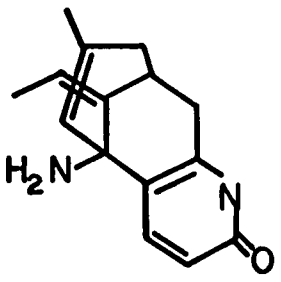
Annotine



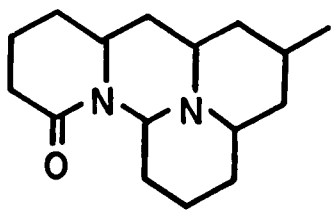
Serratinine



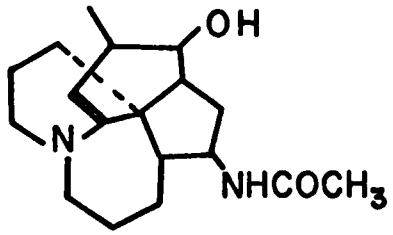
Lycodine



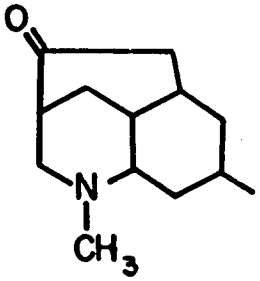
Selagine



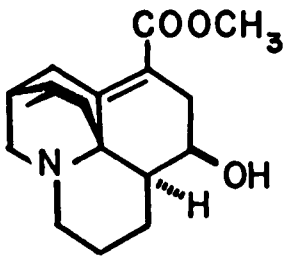
Cernuine



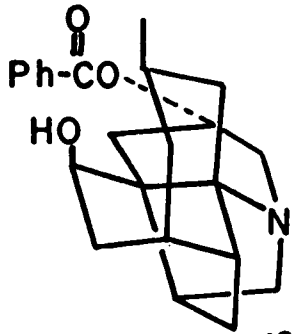
Serratinidine[7]



Luciduline[8]



Annopodine[9]



Alopecurine[10]

studies. A brief discussion of the spectra of some lycopodine type alkaloids is appropriate, since extensive use has been made of this method in the work described in this thesis.

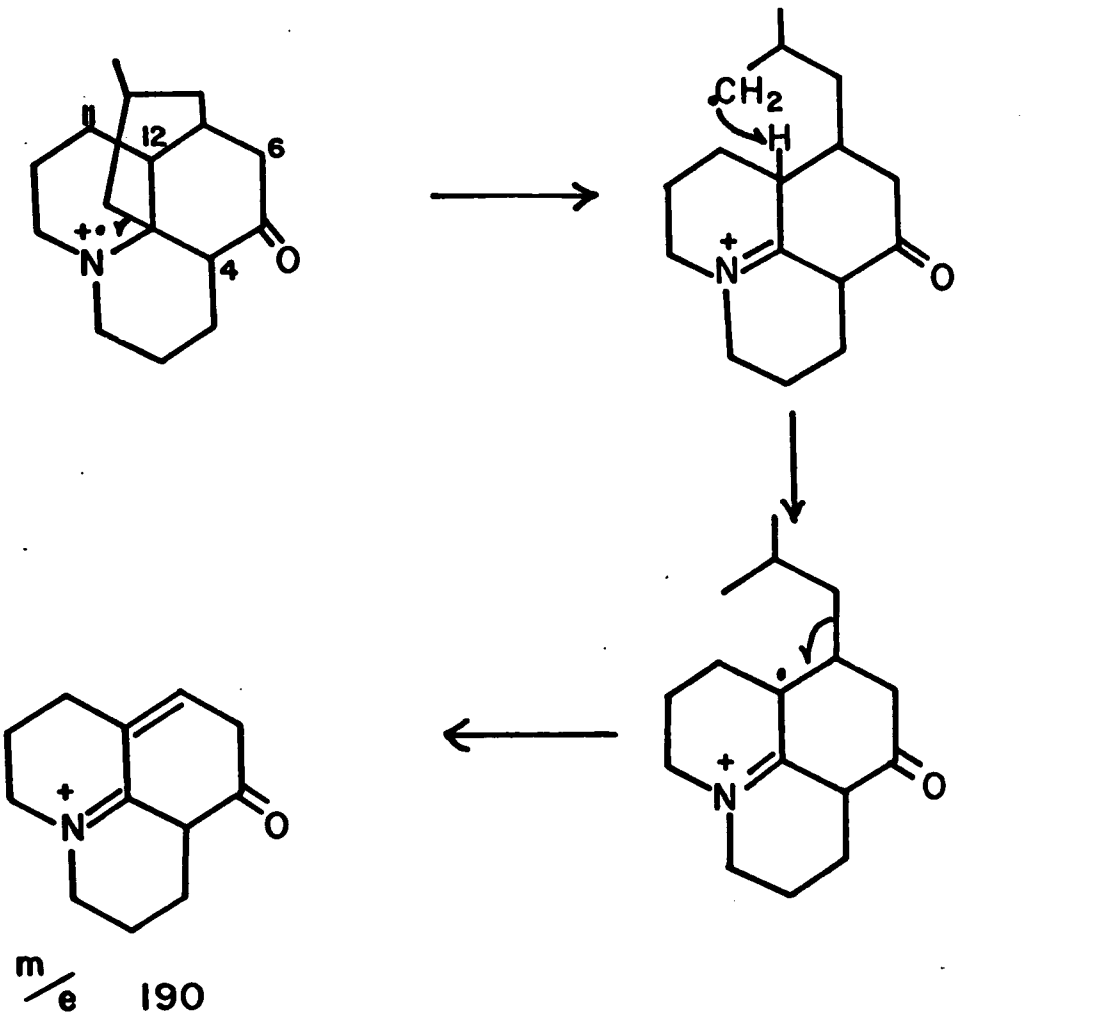
Upon electron impact lycopodine (2) shows prominent peaks at m/e 247 (M^+), 204 (M^+-43), 190 (M^+-57 base peak), 162 (M^+-85), and 134 (M^+-113). The fragmentation leading to the base peak involves the loss of the bridge as shown in Scheme I. It may be noted that this is a typical cyclohexylamine fragmentation route.[13]

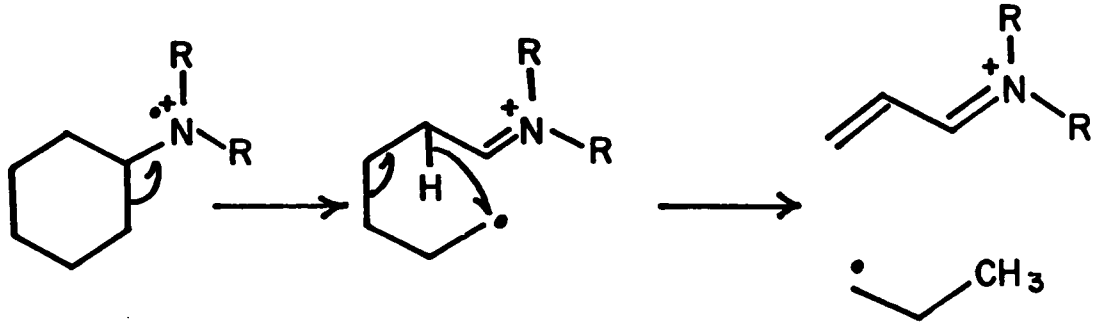
The hydrogen lost with the bridge is postulated to come from position 12 since deuterium introduced at C_6 and C_4 is not lost and acrifoline, which has a double bond between C_{11} and C_{12}, shows a very different fragmentation pattern.[12] An examination of the fragmentation pattern of annofoline[6] (3) will account for the M^+-43 fragment. The fragments showing m/e 162 (M^+-85) and m/e 134 (M^+-113) represent consecutive losses of 28 units from the base peak (m/e 190) and are no doubt due to losses of carbon monoxide and ethylene. The order in which these units are lost has not been determined.

Annofoline (3) shows major peaks at m/e 263 (M^+), 220 (M^+-43), 193 (M^+-70), 192 (M^+-71), 176 (M^+-87), 175 (M^+-88), 174 (M^+-89) and 146 (M^+-117).

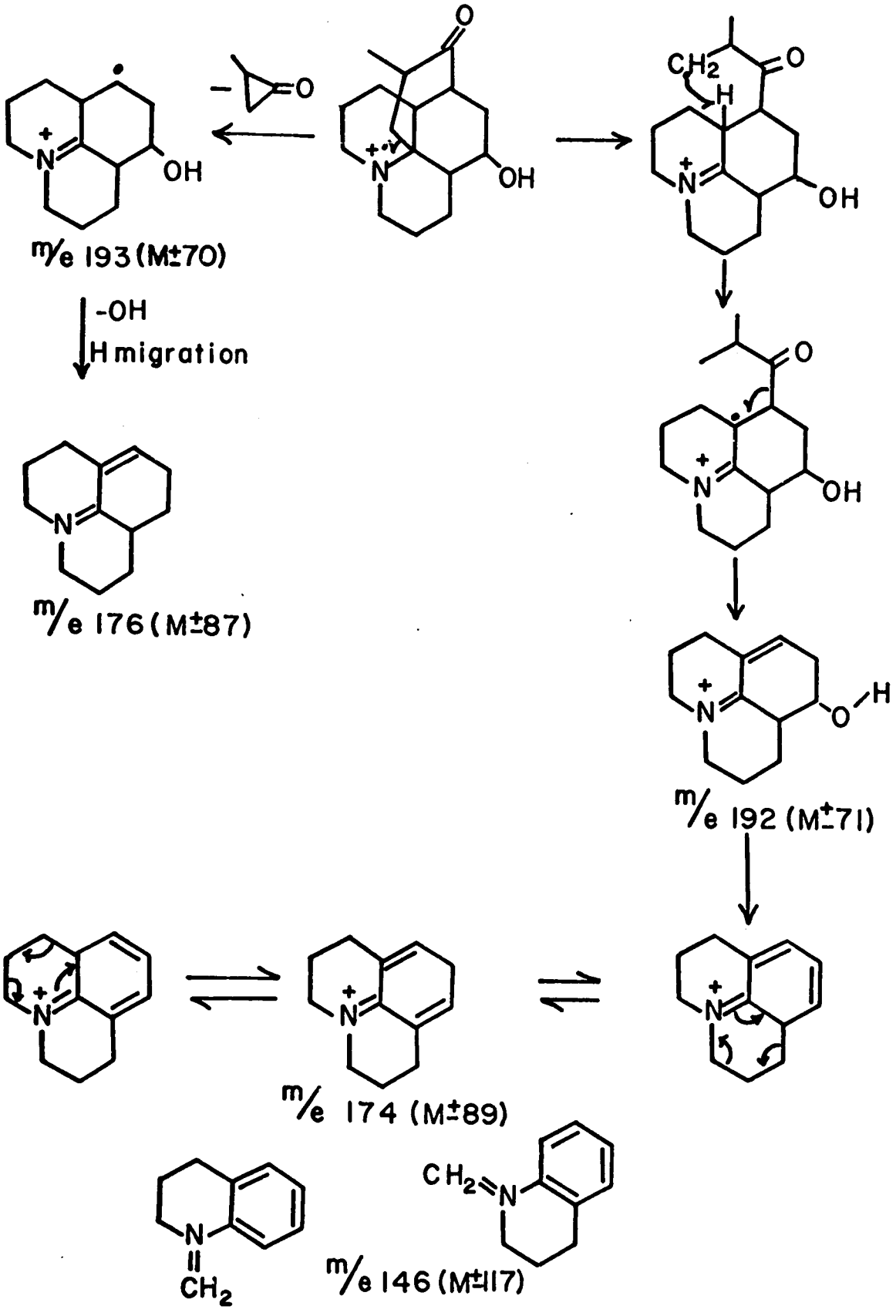
The fragmentation of annofoline (3) is accounted for in Scheme II.

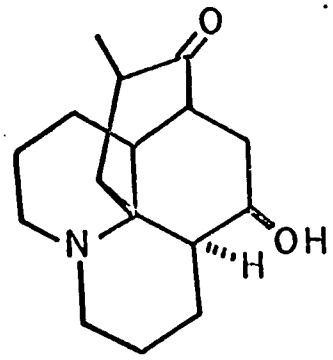
Scheme I





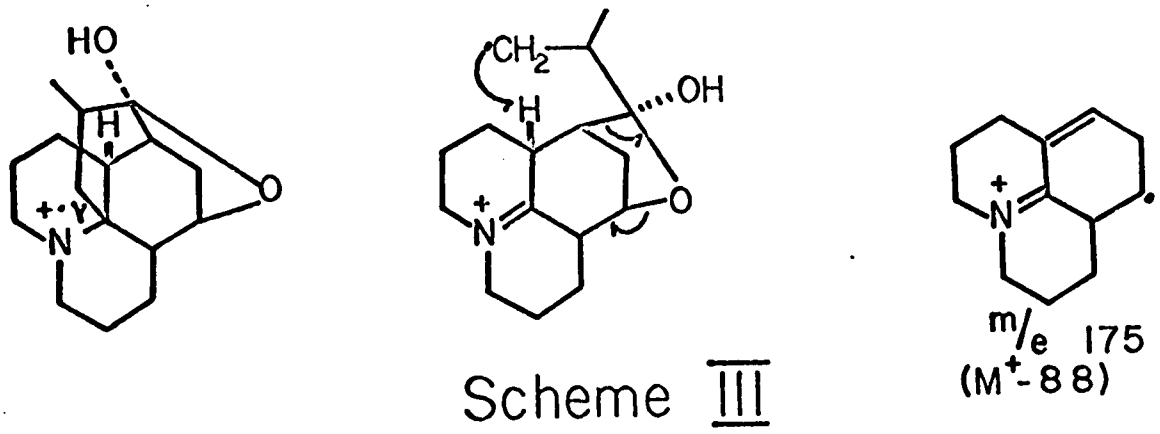
Scheme II


m/e 193 (M±70)
-OH
H migration
m/e 176 (M±87)
m/e 192 (M±71)
m/e 174 (M±89)
m/e 146 (M±117)



Annofoline
3

The peak at m/e 175 can be explained if one considers that annofoline (3) can exist in the hemiketal form shown[14] in Scheme III[12] which accounts for this peak. A metastable peak has been observed for this fragmentation.

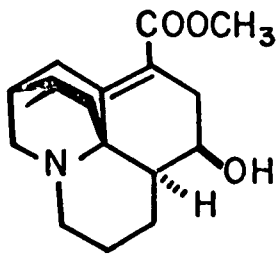


Scheme III

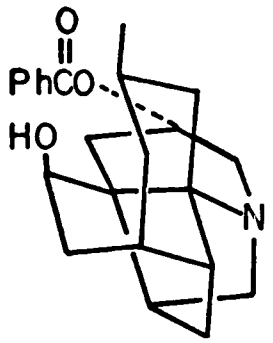
The M^+-43 peak, which is often found in Lycopodium alkaloids, has been shown by deuterium labeling to be due to the loss of part of the bridge.[12]

The amount of material available for structure studies is frequently limited. In examining the minor alkaloids of the Lycopodiaceae it was not infrequent that a problem was abandoned due to lack of material. X-ray crystallography

has proved valuable in such cases. Thus the structure of annopodine (4)[9] and alopecurine (5)[10] were determined by X-ray analysis. The fact that both these alkaloids have novel skeletons would probably have meant that larger amounts of material and much more time would have been necessary to determine the structures by classical methods.



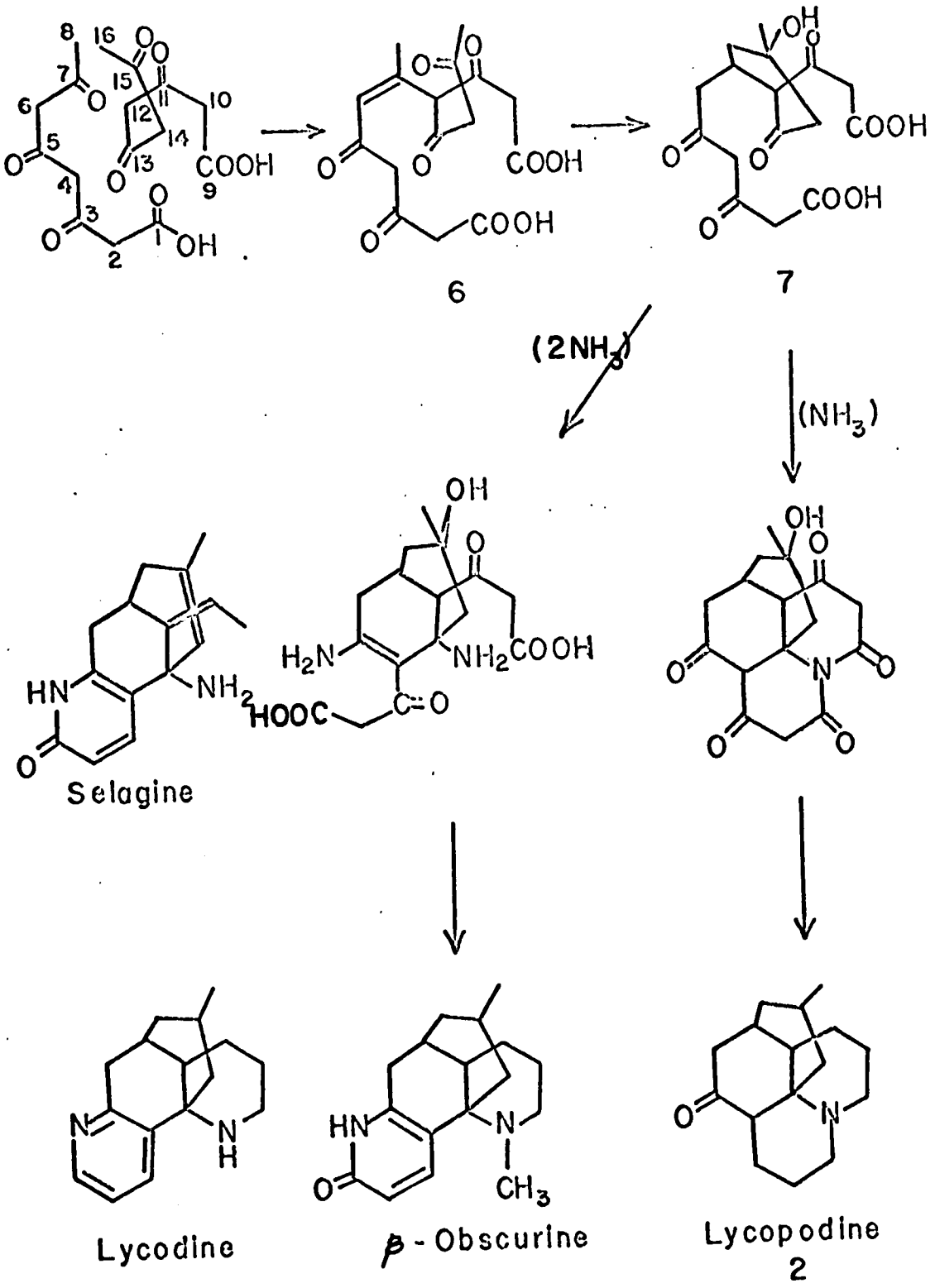
Annopodine
4



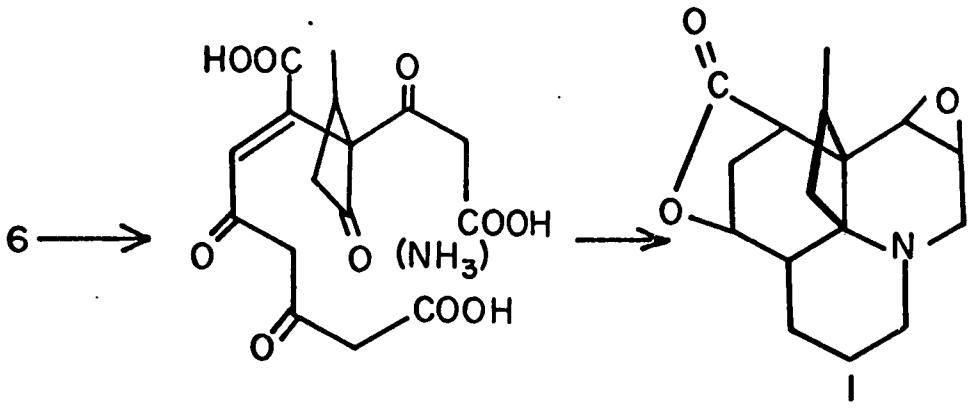
Alopecurine
5

The biogenetic origin of the Lycopodium alkaloids has been speculated on for quite some time. Conroy[15] proposed that the alkaloids might be formed from the condensation of two eight-carbon polyacetate chains. Two molecules of a 3,5,7-triketo octanoic acid equivalent account not only for the general construction of the alkaloids but also for many structural details. In the case of the mononitrogenous alkaloids one molecule of ammonia would be required while two would be incorporated in the dinitrogeneous group. A brief outline of this hypothesis leading to the then known alkaloid groups is given in Scheme IV.

Scheme IV



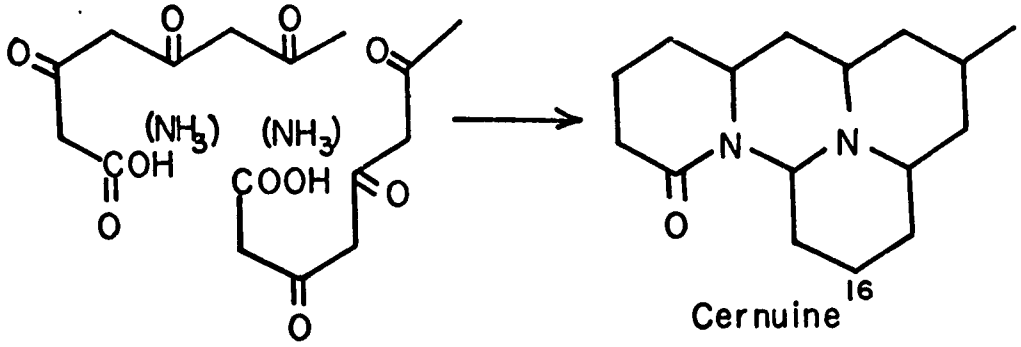
The route to annotinine (1) is a minor variant of the general pattern. In 6, Scheme IV, if carbon 8 is oxidized to a carboxyl group before formation of 7, no aldol condensation can occur at C-8. An alternative ring closure could occur at C_{12} forming a cyclobutane ring. The formation of annotinine then follows.

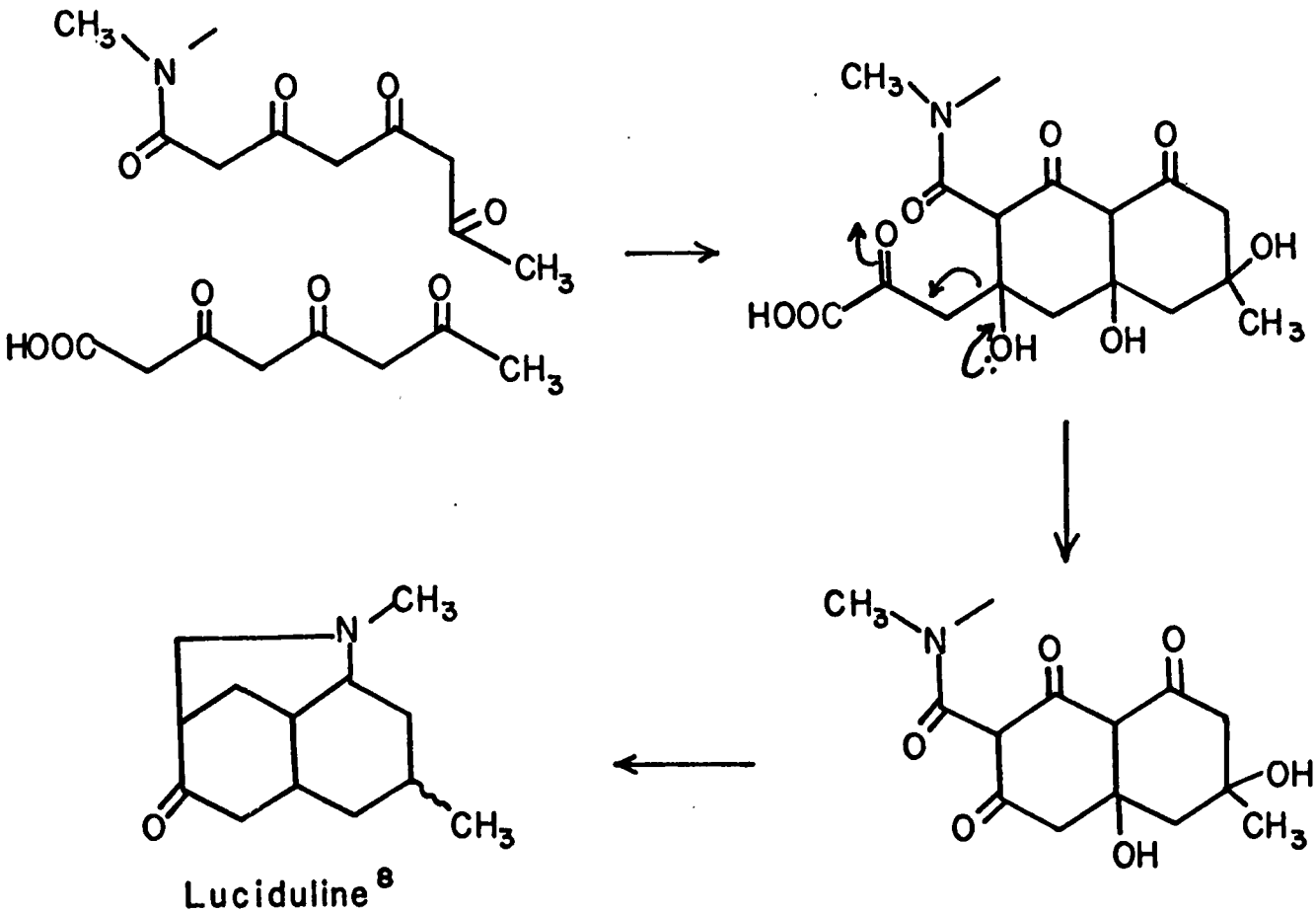


The hypothesis also accommodates the newly elucidated Lycopodium alkaloids having completely different skeletons. Two examples are given in Scheme V.

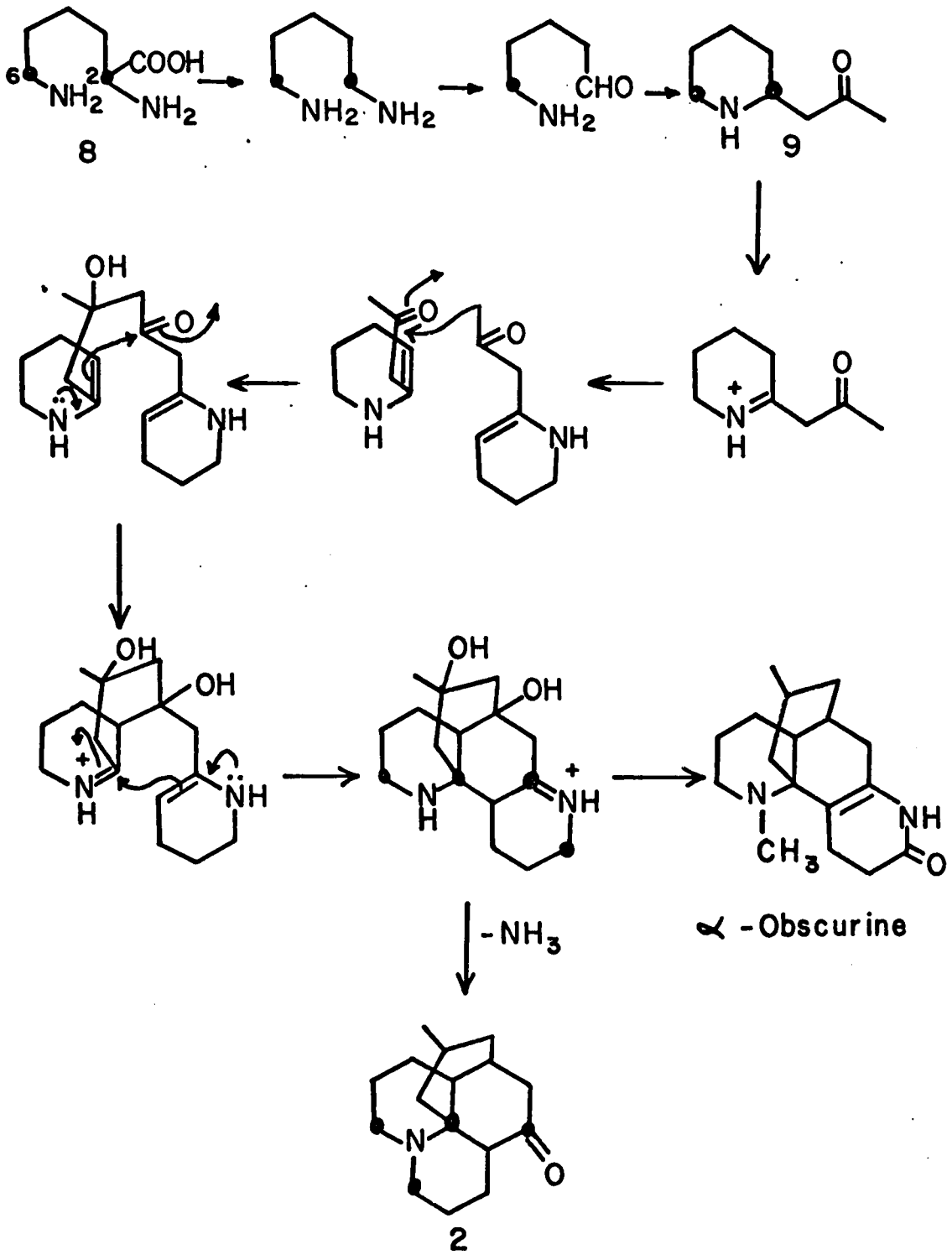
More recently MacLean and Spenser[17] conducted experiments in which lysine-2-^{14}C and lysine-6-^{14}C were separately administered to Lycopodium flabelliforme. In each case radioactive lycopodine (2) was isolated. One-fourth of the activity was found at the carbonyl carbon in both experiments. Further experiments led the authors to propose that lysine (8) serves as a precursor to lycopodine (2) via two isopelletierine units (9), Scheme VI. The fact that lysine-6-^{14}C is specifically incorporated into

Scheme V





Scheme VI


COOH
NH2
NH2
NH2
NH2
CHO
NH2
O
N
H
8
9
OH
O
N
H
NH
O
O
N
H
NH
O
+
N
H
OH
OH
+
N
H
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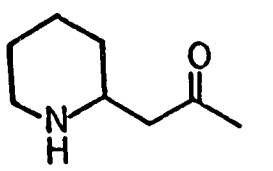
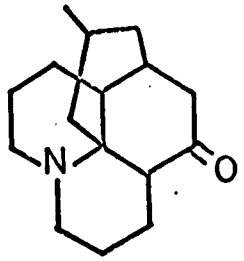
NH
O
-NH3
∝ -Obscurine
N
O
2



Isopelletierine

9



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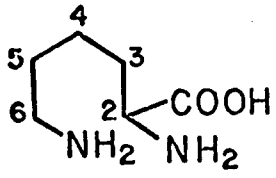
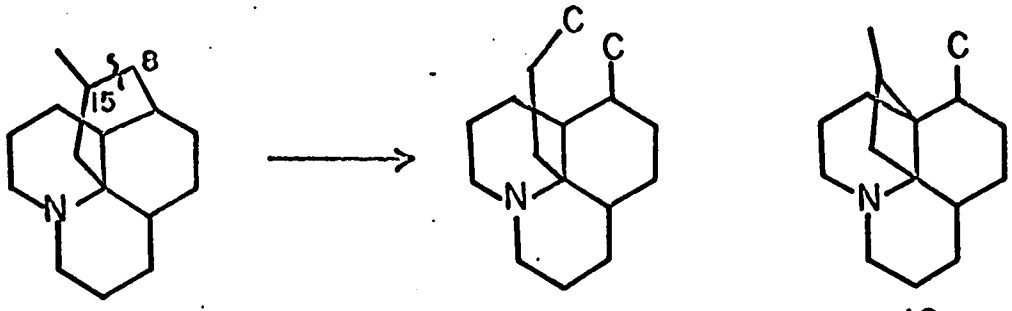


Lysine

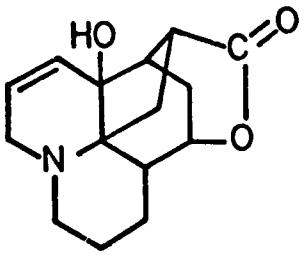
8

the piperidine ring of N-methylisopelletierine[17] lends further support to this hypothesis. Annotinine (1) can be accommodated in the scheme if one considers that lycopodine (2) or some related form may be a precursor.[18] Cleavage of the C_8 - C_{15} bond followed by recyclization could afford an annotinine system 10.



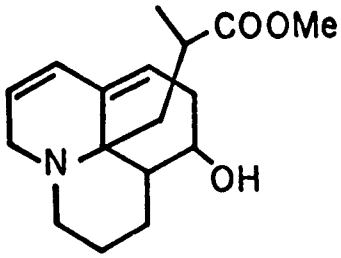
10

It has also been postulated that lyconnotine (11) and annotine (12) as well as serratinine (13) could arise from rearrangements of the lycopodine skeleton.[6]



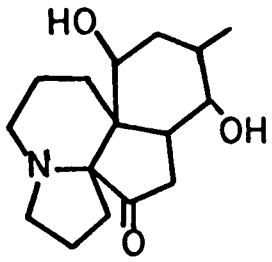
Annotinine

12



Lyconnotine

11



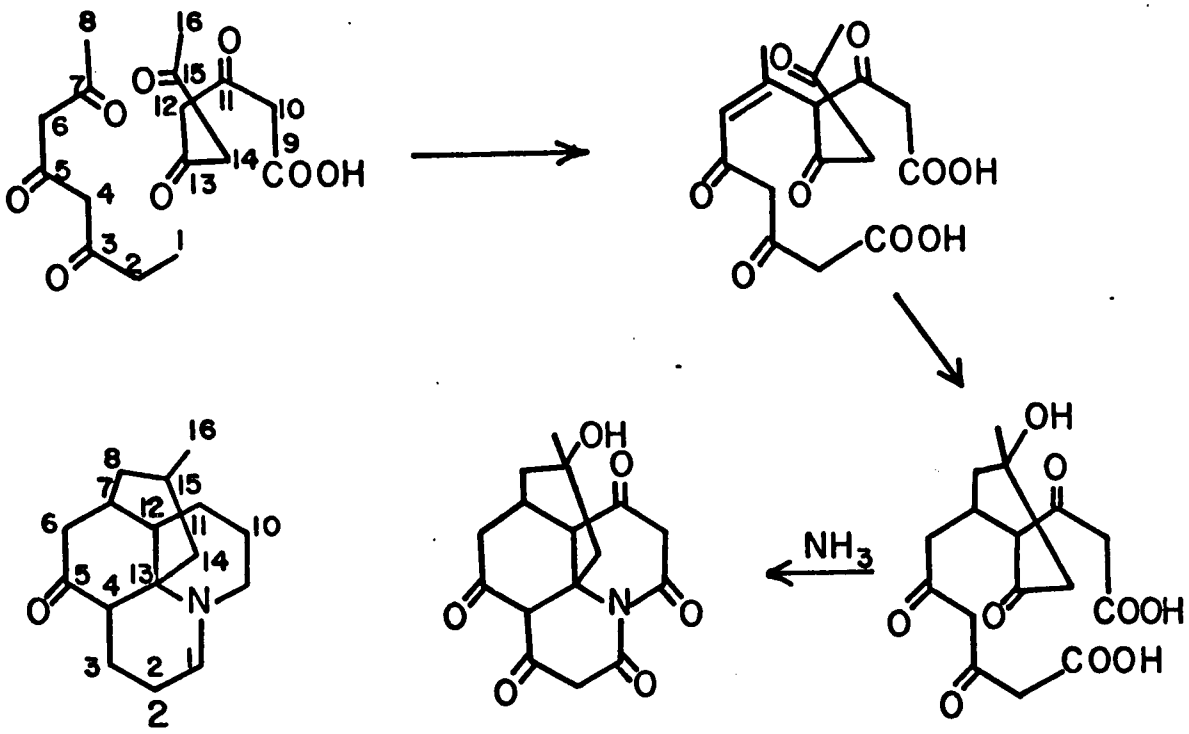
Serratinine

13

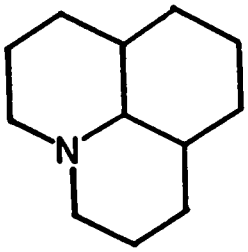
Since no experimental evidence has been presented to support the Conroy hypothesis its value would now appear dubious. However this hypothesis happens to coincide with the MacLean-Spenser hypothesis to the point that they cannot be distinguished on the basis of structure. A good example of this is presented in the newly examined alkaloid luciduline[8] (Scheme V).

Besides contributing to structure elucidation the polyacetate hypothesis of Conroy[14] is the origin of the numbering system used for these alkaloids. Thus the numbering of lycopodine (2) is made rational if one examines Scheme VII.

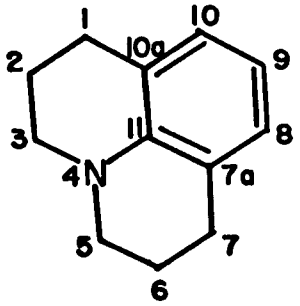
It may be pertinent to point out that many of the lycopodine alkaloids have a perhydrojulolidine (14) skeleton. This is simply a hexahydro derivative of julolidine (15) which has the numbering indicated.[19]



Scheme VII



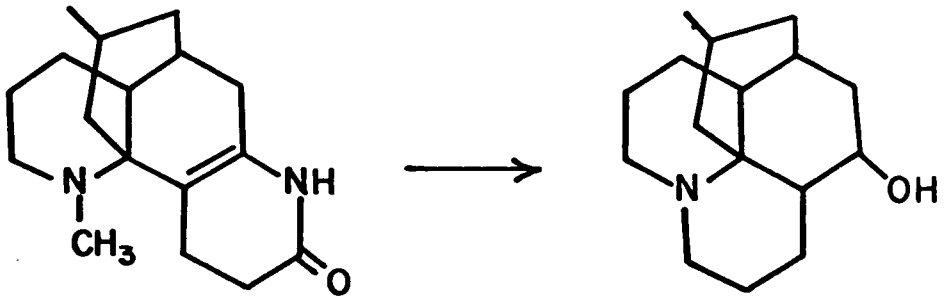
14



15

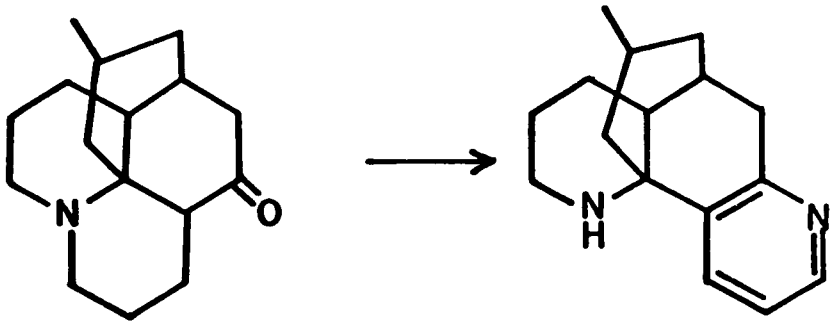
In the forthcoming discussion on synthesis, compounds in which the bridge (lycopodine $C_{13}C_7$) is not closed, shall be considered as julolidine (15) derivatives and shall be numbered accordingly.

In the course of elucidating the structure of the presently known Lycopodium alkaloids many of these were correlated with one another.[6] Thus Ayer and co-workers[20] were able to convert α abscurine (16) to dihydrolycopodine (17) in five step sequence. At the same time Anet and Rao[21] converted lycopodine (2) to lycodine (18).



∝-Obscurine
16

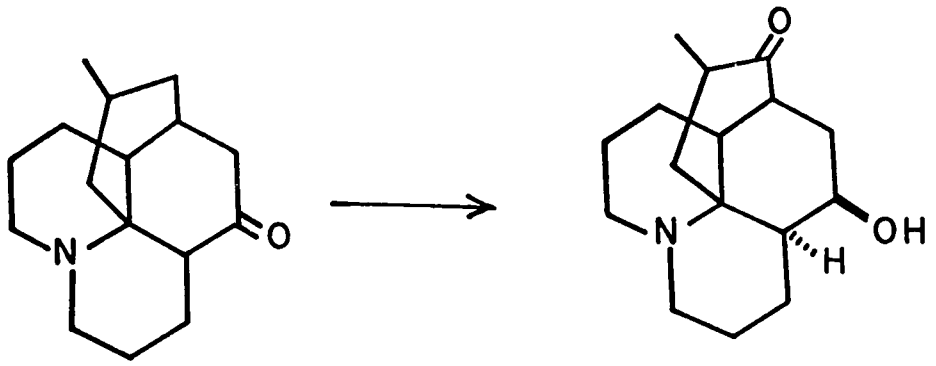
17



2

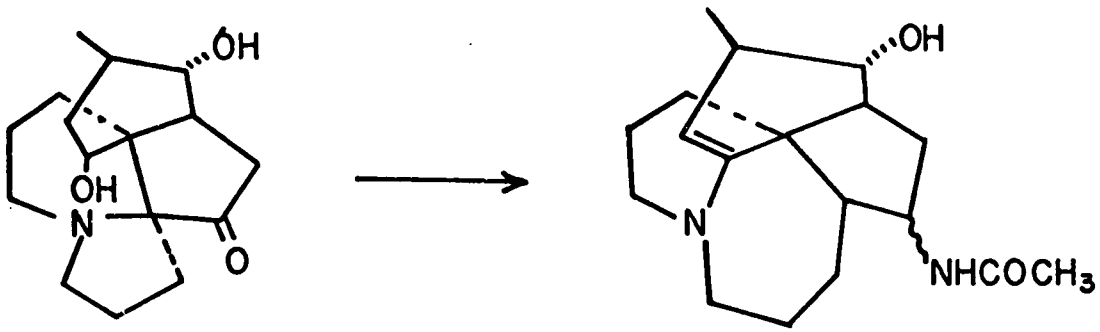
Lycodine
18

A few years later lycopodine (2) was converted to annofoline (3) by Ayer and co-workers.[22]



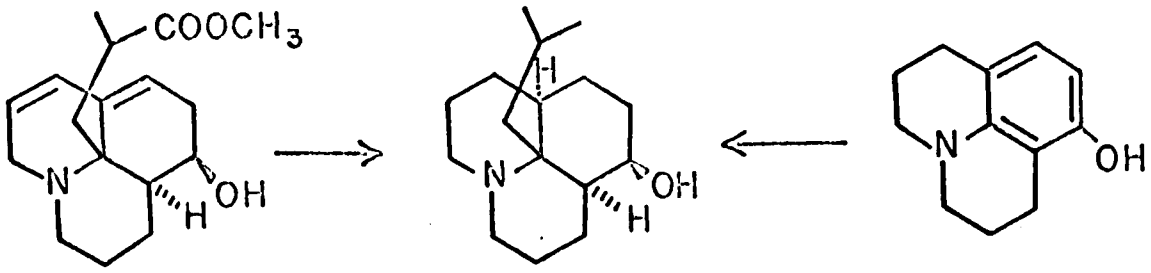
2 3

A correlation between serratinine (13) and serratinidine (19) was reported by Inubushi and co-workers in 1966.[7]

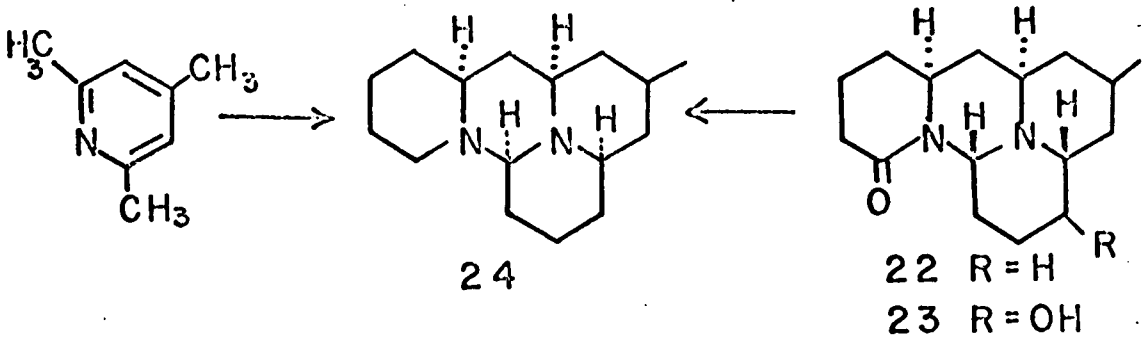


13 19

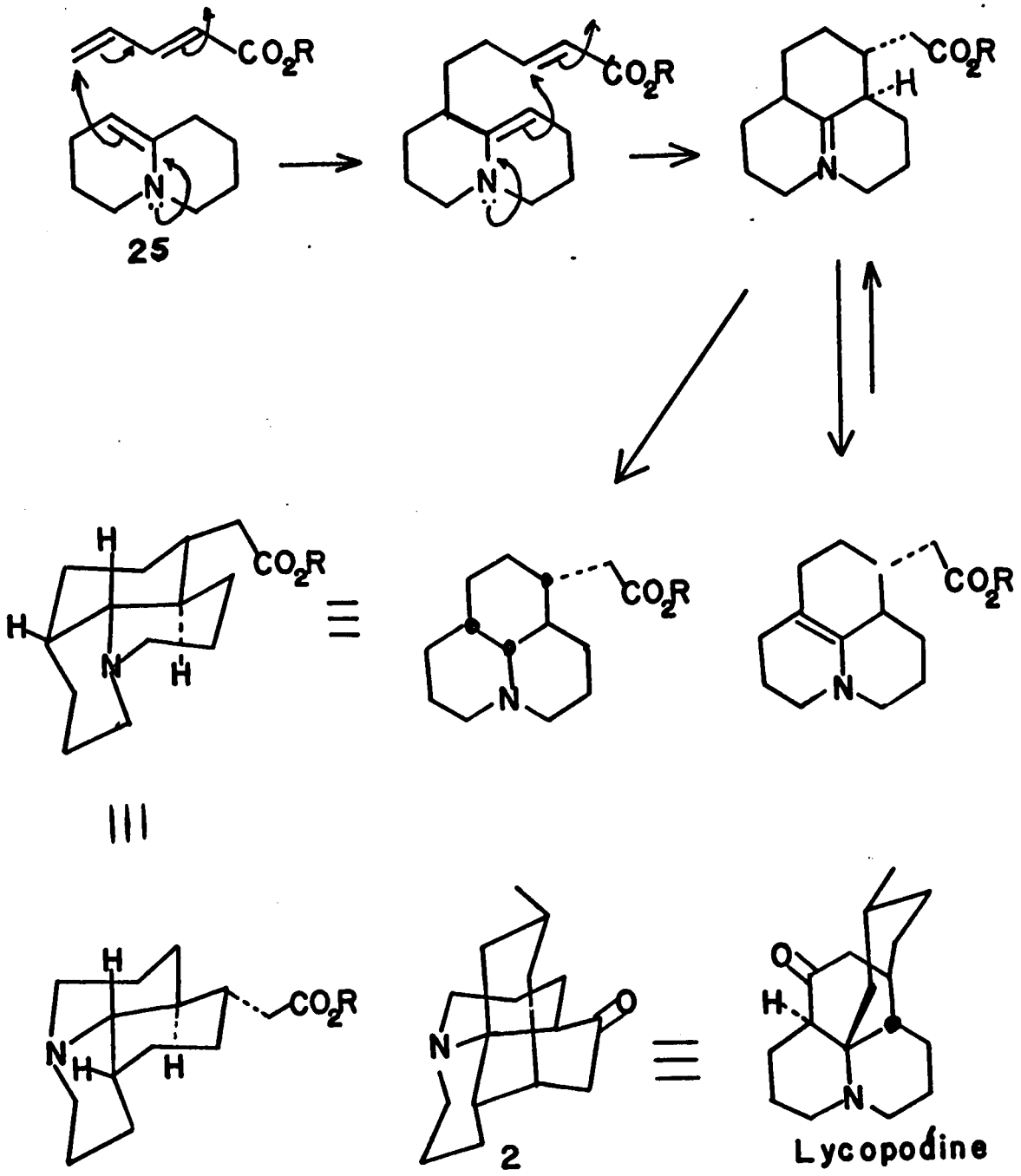
As well as making direct correlations between known alkaloids, some degradation products obtained in structural studies were independently synthesized. Weisner, Valenta and co-workers[23] proved the structure of lyconnotine (11) by synthesizing one of its degradation products (20) from 8-hydroxyjulolidine (21)



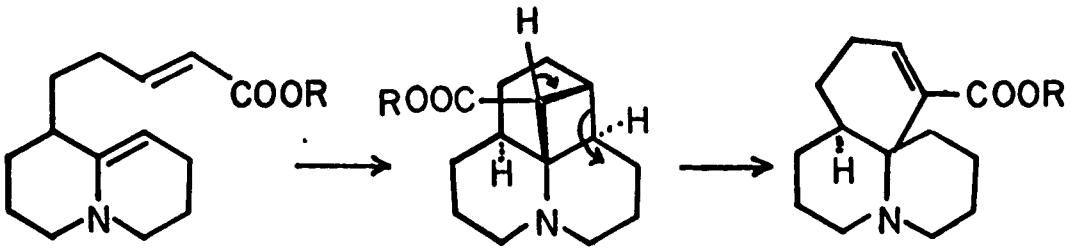
In the course of the structure elucidation of cernuine (22) and lycocernuine (23), Ayer and Piers[24] synthesized dihydrodeoxyepiallocernuine (24) which had been obtained from lycocernuine (23).[25,26]



Bohlmann and co-workers[27] were the first to report an attempted synthesis of lycopodine (2). They had found that dehydroquinolizidine (25) could easily undergo Michael additions, which were reported to lead to substituted julolidine derivatives.

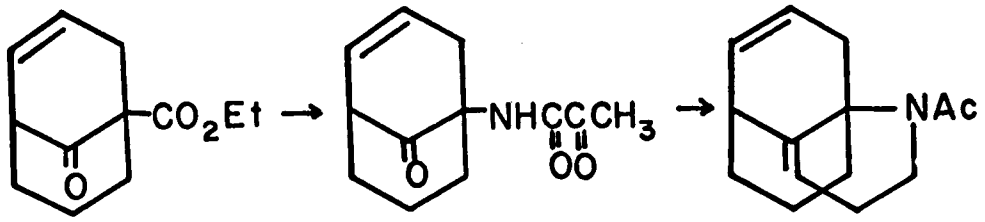

CO2R
H
N
25
2
Lycopodine
O

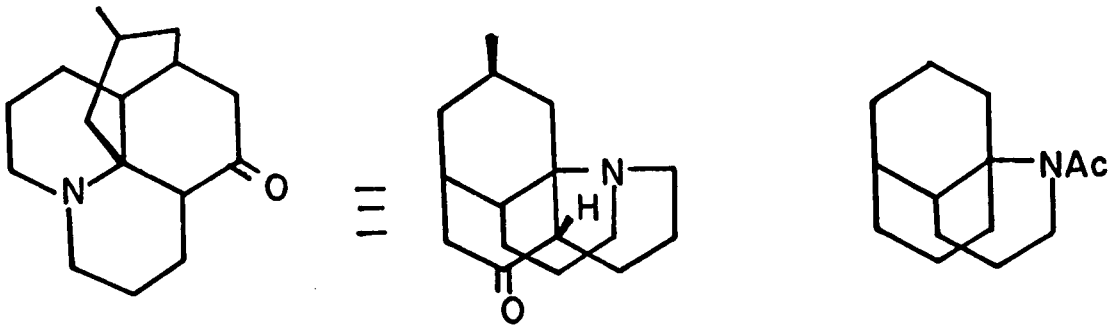
It was later[28] shown that this reaction, unlike that with methylvinylketone had not proceeded as indicated above but had instead given compound 26.



26

By elaboration of a preformed [3,3,1] nonane derivative Raphael and co-workers[29] hoped to be able to obtain lycopodine (2) or one of its derivatives. They report the synthesis of the N-acetyl-5-8a-propenoperhydroquinoline (27).



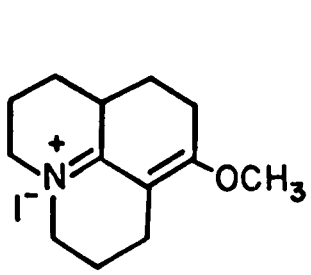


2 ≡ 2 27

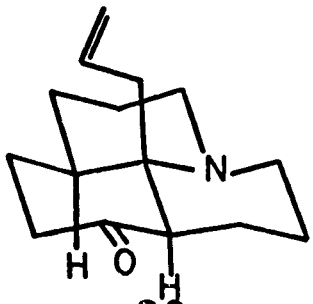
An approach similar to that used by Bohlmann, i.e., the elaboration of a perhydro julolidine system, was used by Wenkert and Stevens[30] in their attempted synthesis of lycopodine (2).

Wiesner and Valenta[31] were able to modify part of their synthesis of the degradation product 20 obtained from lyconnotine (11) to synthesize the tetracyclic system found in lycopodine (2).

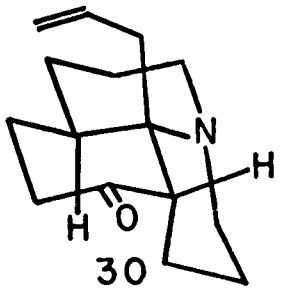
Treatment of the immonium salt 28 with excess allylmagnesium bromide followed by hydrolysis yielded the trans-trans ketone 29 which could be epimerized to the isomeric cis-trans ketone 30. Cyclization of compound 30 proceeded smoothly in 70% sulfuric acid yielding alcohol 31. Conversion to the bromo derivative followed by reduction using sodium amalgam afforded the tetracyclic compound 32. This structure differs from lycopodine (2) in that the C_{15} methyl and the keto group at C_5 are lacking.



28



29



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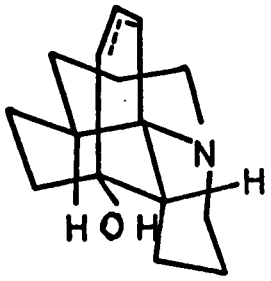

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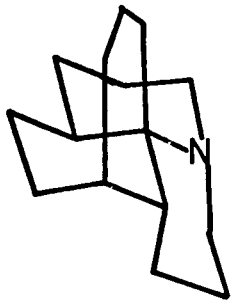
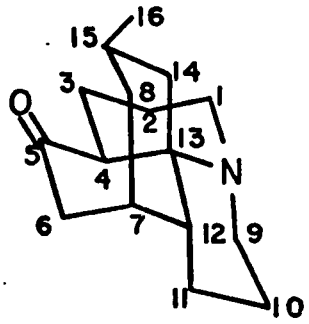
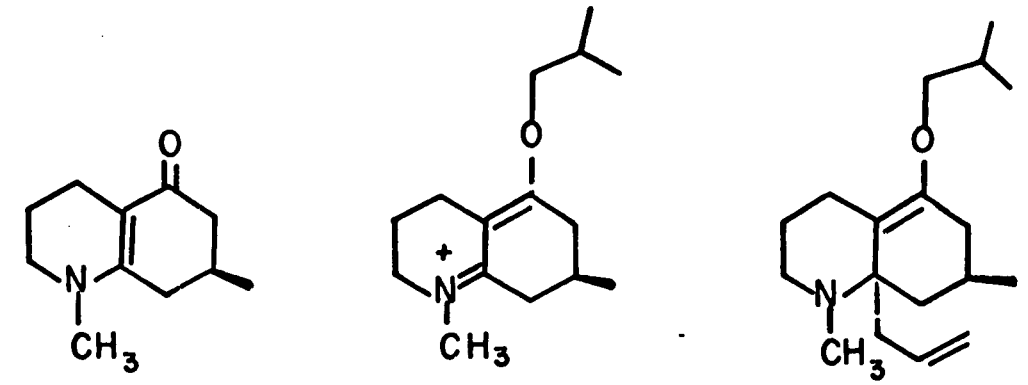


32

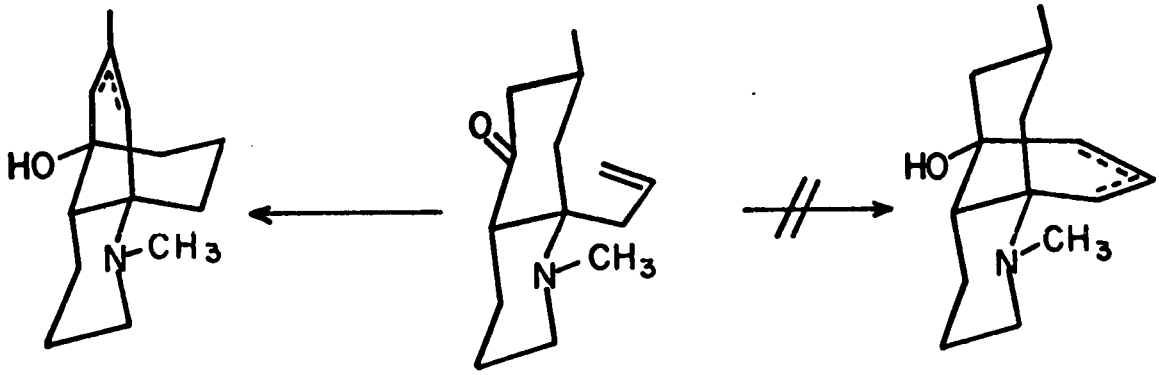


2

In the same paper[31] a modification of this synthesis was reported. 5-Methyl-1,3-cyclohexanedione was converted in three steps to compound 33 which on treatment with isopropyl iodide in refluxing benzene yielded compound 34. Reaction of 34 with allylmagnesium bromide yielded 35. Reaction of 35 with 75% sulfuric acid gave, via ketone 36, the tricyclic compound 37 which was shown to be different from the expected product 38. It would appear that 36 is initially formed but undergoes facile hydride transfer. Thus the route was abandoned.



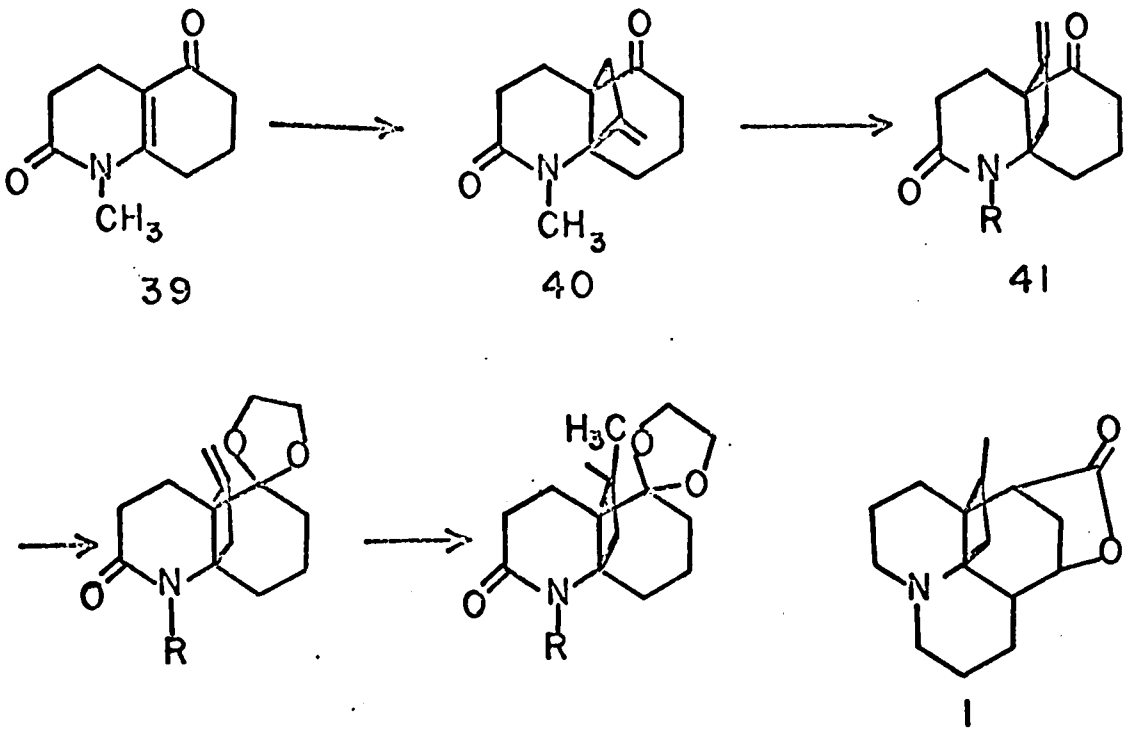
33 34 35



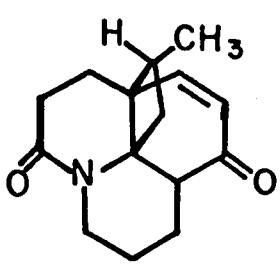
37 36 38

The research group at the University of New Brunswick then turned their attention to annotinine (1). In a series of four publications,[32,33,34,35] they report a synthetic sequence which eventually led to synthetic annotinine (1). The initial work consisted of studies designed for the construction of the cyclobutane ring. They found that the vinylogous amide 39, prepared in three steps from 1,3-cyclohexanedione, underwent photoaddition with allene yielding a mixture of 40 and 41. It was also found that if the methyl group was replaced by a bulkier group,

only one isomer, corresponding to 41, was obtained. Hydrogenation of the olefin was found to give one isomer, if the ketone was first ketalized.



The photochemical reaction was again employed in the preparation of 42, a compound which had been obtained from annotinine (1)[36]. The initial step involved condensation of 43 with acrylic acid to give 44 which on irradiation in the presence of allene yielded 45 in quantitative yield.



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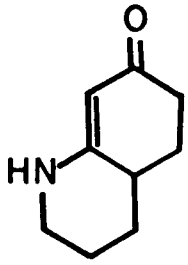
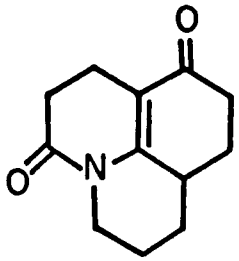
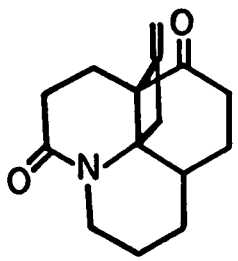


43

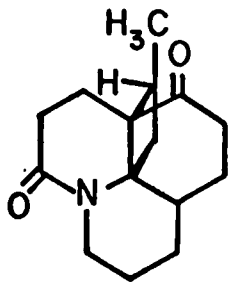


44

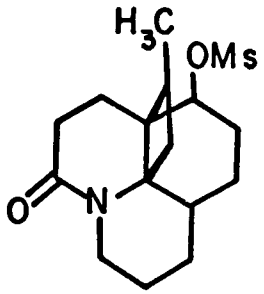


45

Ketalization, hydrogenation and hydrolysis yielded 46, which gave the mesylate 47 after reduction with sodium borohydride and reaction with mesyl chloride in pyridine. Elimination of the mesyl group was accomplished with difficulty by heating 47 in DMF with 3-4 moles of KCN. The product, 48, was then converted to 42 by oxidation with selenium dioxide in acetic acid, hydrolysis of the resulting acetate and oxidation with chromium trioxide-pyridine.



46



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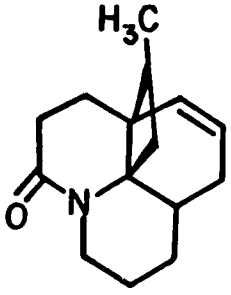
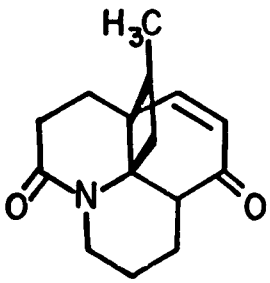


48

Compound 42 was then treated with KCN and NH_4Cl in DMF to yield a nitrile which was hydrolyzed to the corresponding carbomethoxy derivative 49. This compound has previously[36,37] been converted to compound 50 which now, on reaction with p-toluenesulfonic acid and DMF in benzene, yielded 51, an important degradation product[38] of annotinine (1).



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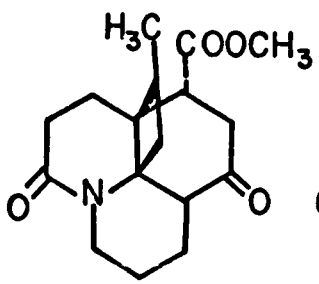

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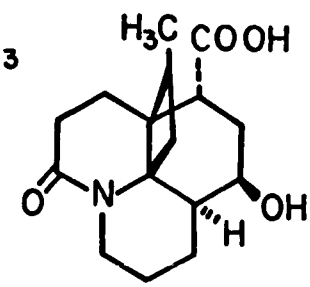
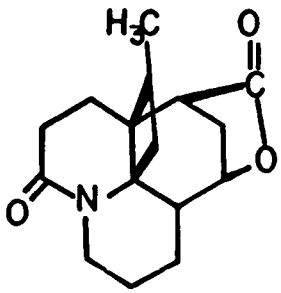


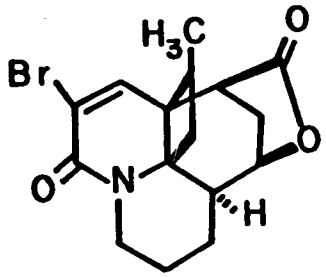
50



51

In the final paper of the series, annotinine (1) was obtained in four steps from 51. Reaction with NBS in the presence of light yielded 52 which was converted to the bromohydrin 53 by reaction in 10% HBr. Compound 53 was then converted to the epoxide 54 which had previously[39] been converted to annotinine (1).

This synthesis amounted to the first total synthesis of a Lycopodium alkaloid.



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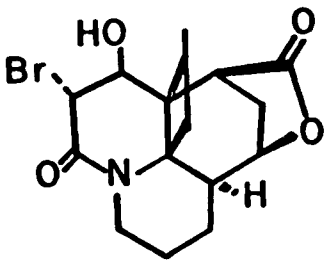
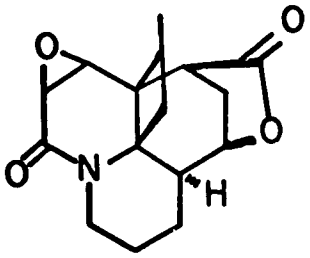
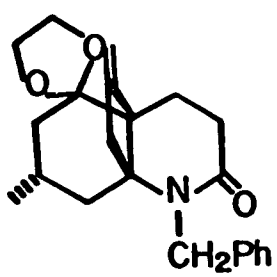


53



54

At the same time as the synthesis of annotinine (1) was reported,[35] Wiesner, Valenta and co-workers[40] reported the synthesis of epilycopodine (55).[41] Compound 56 was prepared following the method just described in the annotinine synthesis. Epoxidation using perbenzoic acid followed by $LiBH_4$ reduction yielded 57. Mild hydrolysis yielded the diketone 58 which was then allowed to stand in ethanolic NaOH.



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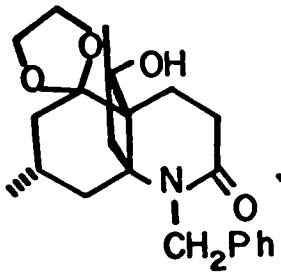

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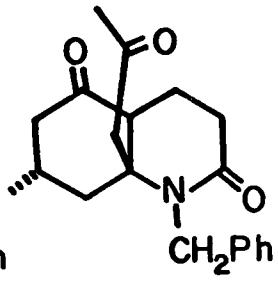

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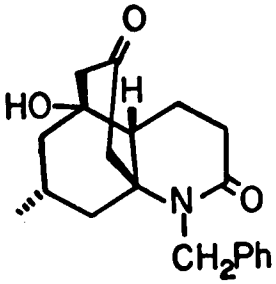
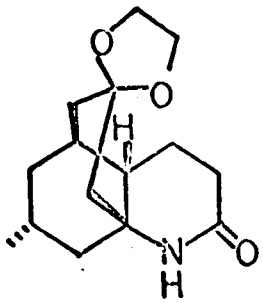


59

This resulted in the formation of 59. Treatment of the keto-alcohol 59 with phosphorous trichloride, followed

by ketalization and reaction with sodium in ammonia, yielded compound 60. The lactam was removed using lithium aluminum hydride, the ketone was regenerated by mild hydrolysis and the resulting compound was condensed with acrylyl chloride to give compound 61.



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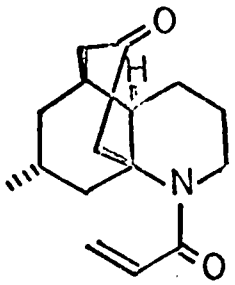
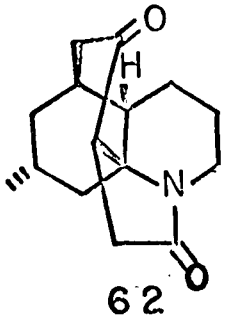
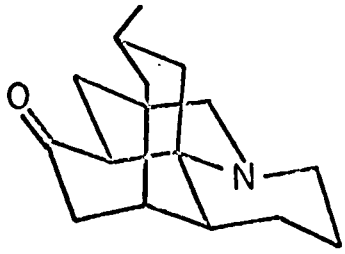


61



62

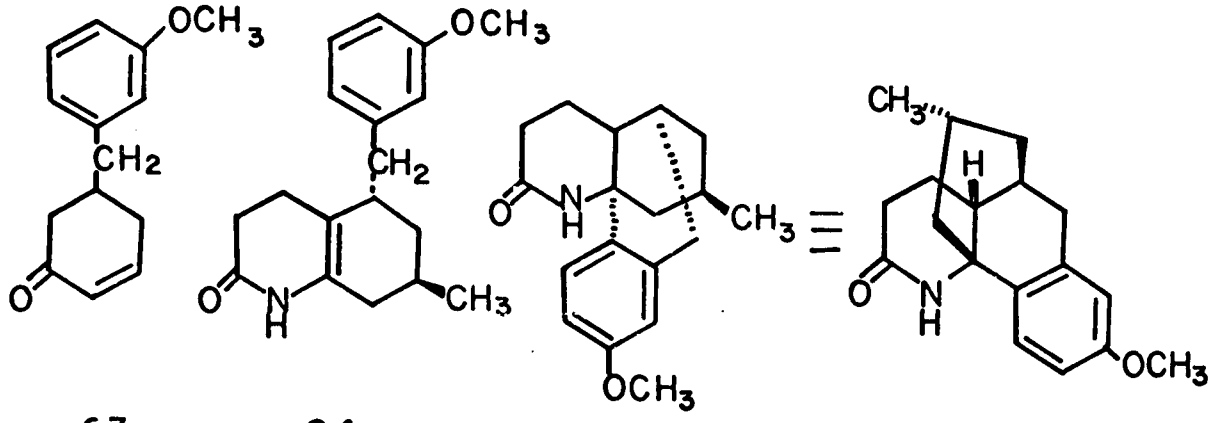


55

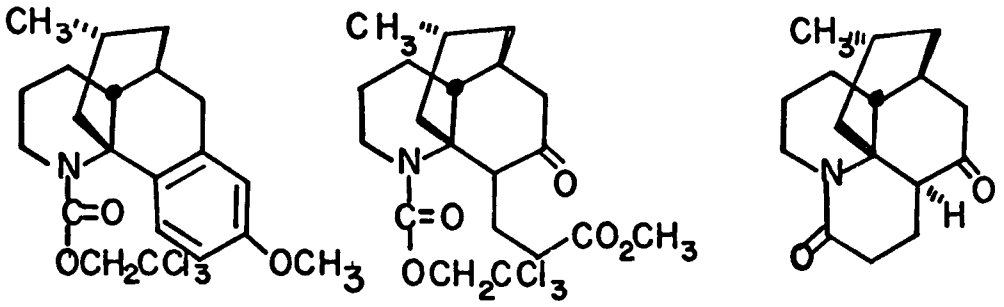
The fourth ring was formed by refluxing 61 in benzene with p-toluenesulfonic acid. The product 62 was then converted to epilycopodine (55) by reduction with $LiAlH_4$, followed by Jones oxidation. This compound had previously been prepared from lycodoline by Ayer and Iverach.[41]

In 1968, the synthesis of lycopodine (2) was simultaneously reported by Stork and co-workers[42] and by Ayer and co-workers.[43] Stork prepared compound 63 in four steps. This compound was then methylated using MeMgI and CuI_2 in ether after which it was condensed with acrylamide via the pyrrolidinenamine. This afforded compound 64. Cyclization with 1:1 80% phosphoric acid:formic acid gave 65 which was then converted in four steps to 66.

Ozonolysis followed by selenium dioxide oxidation and hydrolysis resulted in the formation of compound 67. Removal of the protecting group using zinc dust in methanol allowed formation of the fourth ring. Reduction of the resulting keto-lactam 68 followed by oxidation of the resulting alcohol using Jones reagent afforded dl-lycopodine (2).



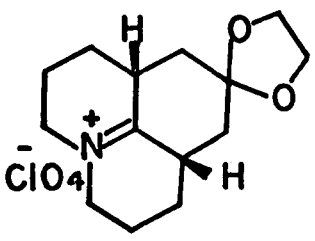
63 64 65



66 67 68

In the synthesis of lycopodine (2) described by Ayer and co-workers,[43] immonium salt 69 was reacted with the Grignard reagent prepared from 1-chloro-2-methyl-3-methoxypropane. The product, 70, a cis-cis-

perhydrojulolidine derivative, was isomerized to the desired cis-trans configuration in a four step sequence involving hydrolysis, bromination α to the ketone, dehydrobromination and lithium-ammonia reduction of the α,β-unsaturated ketone. The diasteriomeric mixture of ketones 71 was separated in the form of the alcohols which were obtained by ether cleavage with BBr_3. One of the alcohols 72 was acetylated, oxidized to the lactam, hydrolyzed to the alcohol-lactam, mesylated and ring closed to give 73.



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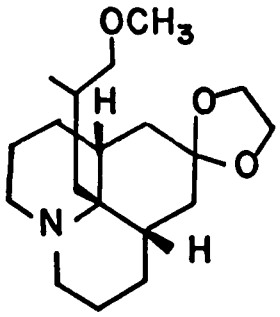

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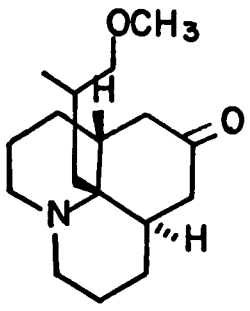

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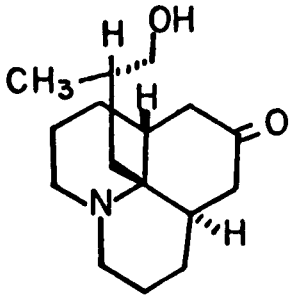

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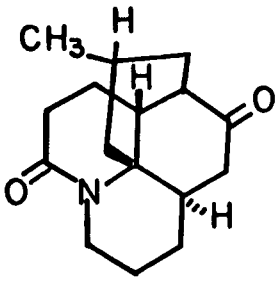

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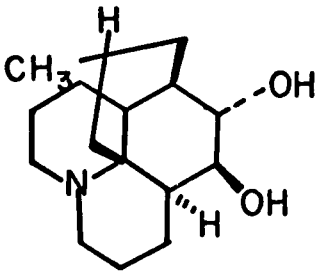
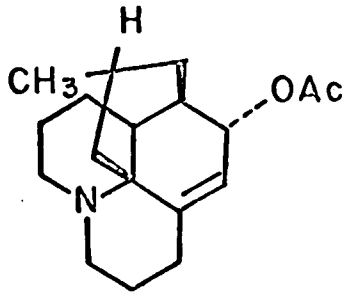


74

Compound 73 had been prepared from natural lycopodine (2) by the following method. Bromination, hydrolysis with sodium bicarbonate, and reduction with lithium aluminum hydride yielded compound 74.[44,45] Acetylation in acetic anhydride and pyridine, followed by dehydration with thionyl chloride and pyridine afforded 75. Hydrolysis, manganese dioxide oxidation and lithium-ammonia reduction yielded compound 76. This was then oxidized using permanganate to the keto-lactam 73. This natural relay was then reconverted to 76 by $LiAlH_4$ reduction, followed by Jones oxidation. Selenium dioxide oxidation of 76[44] yielded the known compound 77 which on Wolff-Kishner reduction gave lycopodine (2), anhydrodihydrolycopodine (78), also a naturally occurring alkaloid, and dihydrodeoxylycopodine (79).



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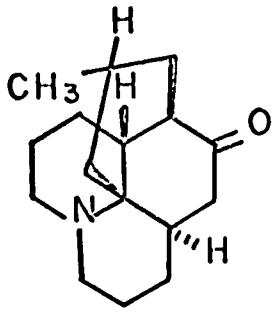

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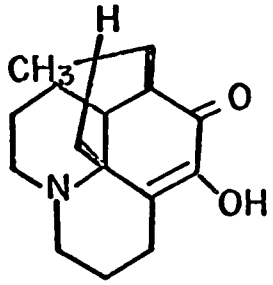

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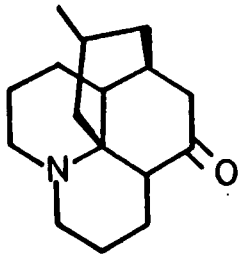

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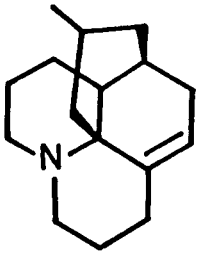

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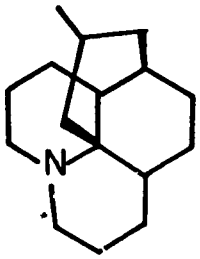
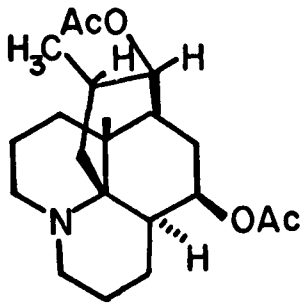


79

The two methods for the preparation of lycopodine (2) also represent in a formal sense the synthesis of many of the other Lycopodium alkaloids which have been synthesized from lycopodine (2).[6] The alkaloids having different skeletons from lycopodine (2) and annotinine (1) now represent interesting synthetic problems.

The work presented herein can be divided into three distinct problems. The first problem undertaken involved examination of some of the original samples of Lycopodium alkaloids isolated by Manske and Marion (see ref. 6). L.9[46] was thus identified as a mixture of lycopodine (2) and of O-acetyllofoline (80).

The second problem involved synthesizing model compounds which could be used in elaborating a synthetic route to lycopodine (2). This was associated mainly with investigating the formation of 11-substituted perhydrojulolidine compounds 81.



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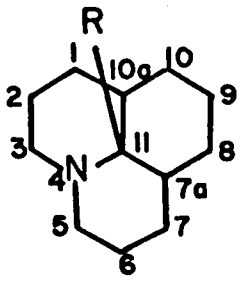

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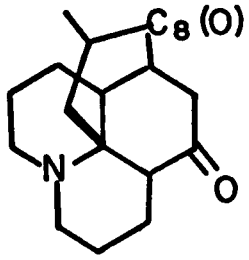


82

Finally the investigation of a synthetic route towards lycopodine (2) and some of its derivatives was carried out. This involved developing a method for the construction of substituted cis-trans-hexahydrojulolidines[47] and an attempt at the preparation of a C_8 oxygenated lycopodine derivative 82.

SECTION II. L.9 -DISCUSSION AND RESULTS

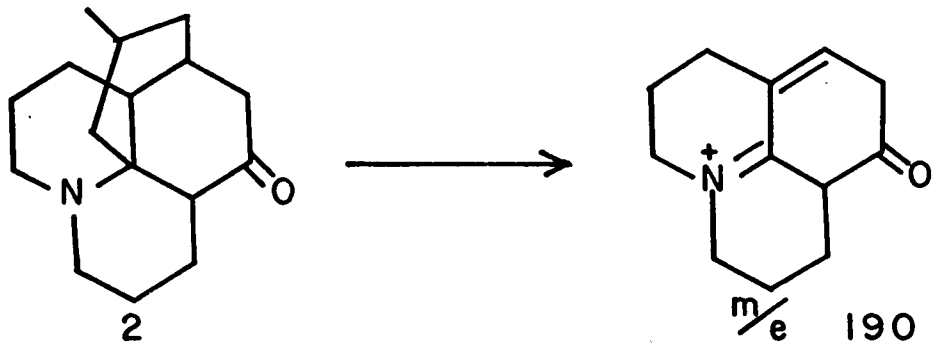
In 1943 Manske and Marion reported[2] the isolation of a basic substance having a melting point of 122° from Lycopodium annotinium L. This base, L.9, was thought to be a mixture. However, the authors preferred to consider it as one alkaloid until more evidence could be obtained. Dr. Manske kindly provided us with a sample of alkaloid L.9.

The infrared spectrum, Figure 1, was informative in that the presence of absorption bands at 1735, 1725, 1250 and 1230 cm^{-1} was indicative of O-acetyl groups. Another absorption, this one at 1698 cm^{-1}, led us to believe that a six membered ketone was also present.

Thin-layer chromatography (t.l.c.) over alumina ($CHCl_3$) revealed the presence of at least two components. The Rf values of a variety of available Lycopodium alkaloids were then measured and compared with the components of L.9. Lycopodine (2) was found to have the same Rf as the less polar component of L.9. When L.9 and lycopodine (2) were mixed only two spots were apparent on the alumina plate. Thus lycopodine (2) was presumed to be one of the components of L.9.

The mass spectrum of L.9, Figure 2, confirmed the presence of lycopodine (2) by showing peaks at m/e 247, 190, 162 and 134. The peak at m/e 247 corresponds to the parent peak for lycopodine (2), Figure 3, and fragment

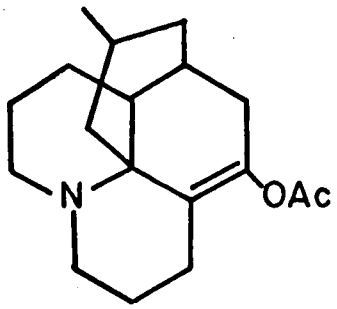
m/e 190 corresponds to M^+-57 which is due to the loss of the bridge ring,[12] 83.



The presence of peaks at m/e 162 and m/e 134 represent loss of ethylene and carbon monoxide from 83.

Other peaks in the mass spectrum of L.9 are at m/e 349, 290, 289, all of which were weak, and more intense peaks are found at m/e 234 and m/e 174.

Since the peak at m/e 349 is very small it was initially ignored and a compound from which fragments 289, and 174 could be obtained was considered. Two compounds which could show such a fragmentation pattern are lycopodine enol acetate (84) and anhydroisofawcettiine (85).



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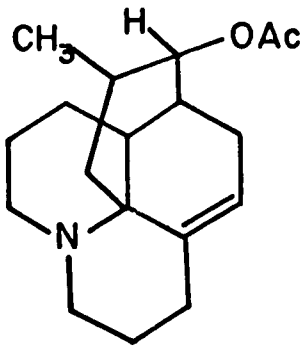

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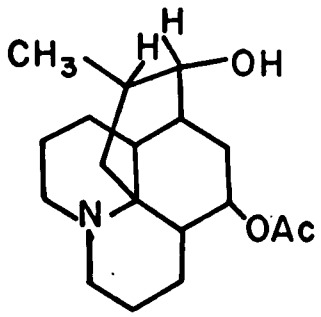
Loss of the bridge in 85 would show a fragment at m/e 174 while loss of the bridge in 84 plus loss of the acetate could also lead to a peak at m/e 174.

T.l.c. comparison of L.9 and lycopodine enol acetate revealed that the latter was not a component of L.9.

Anhydroisofawcettiine (85) was prepared in three steps from fawcettiine (86).



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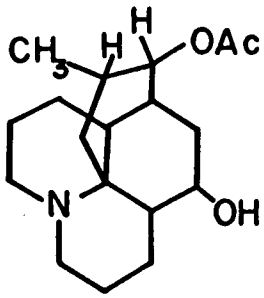

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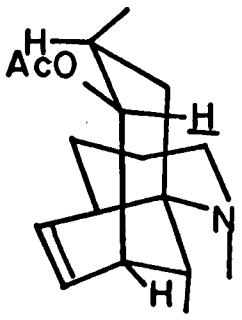

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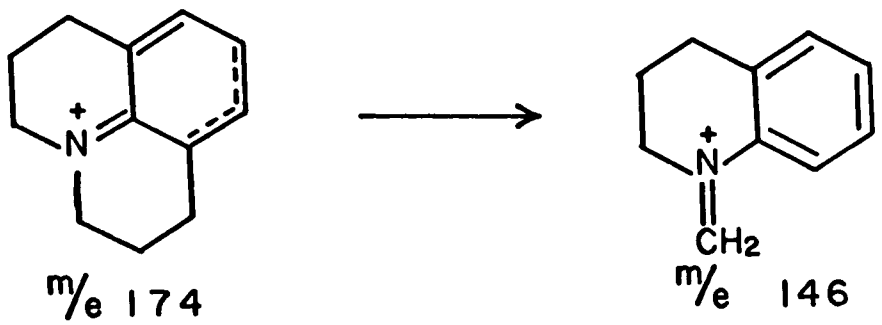
Fawcettiine (86) was first converted to deacetylfawcettiine by the method of Burnell.[48] Acetylation using pyridine-acetic anhydride yielded isofawcettiine[49] (87).

Treatment of the crude reaction product with thionyl chloride in benzene gave, after purification, anhydroisofawcettiine (85).

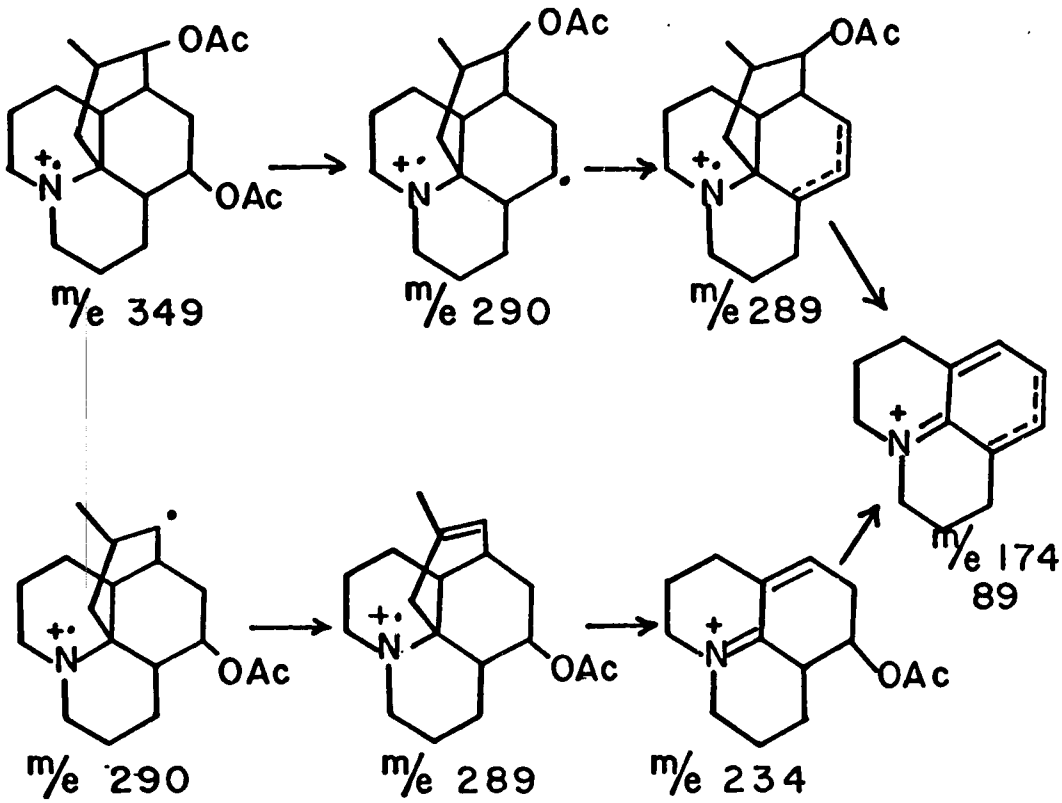
The infrared spectrum does not show double bond absorption. The n.m.r. and mass spectra were examined. The broad singlet found at τ4.55 was assigned to the olefinic hydrogen while the quartet at τ5.45 was assigned to the hydrogen on the carbon bearing the acetoxyl group. The coupling constants are in agreement with this, as can be seen in partial structure 88. The presence of the singlet methyl for the acetate group and of the doublet methyl at C_{15} are in accordance with this.

The mass spectrum confirms the molecular weight 289 (m/e 289) and its fragmentation is in accord with established principles.[12] Loss of acetate and acetic acid yield peaks at m/e 230 and m/e 229 respectively. Loss of the whole bridge leads to the base peak at m/e 174, 89. The peak at m/e 204 results from partial loss of the bridge.[12] The peak at m/e 146 follows from m/e 174.[12,50]



When anhydroisofawcettiine (85) was mixed with L.9 and analyzed on t.l.c., three spots appeared. This was sufficient to show that the second component of L.9 was not anhydroisofawcettiine (85).

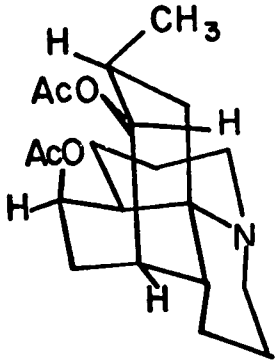
The mass spectrum of L.9 was reexamined and the peak at m/e 349 was taken into account. Loss of acetoxyl would account for the peak at m/e 290 while loss of acetic acid would account for the one at m/e 289. Loss of the bridge (including one acetoxyl group) would result in a peak at m/e 234. Loss of acetic acid would then account for a peak at m/e 174. This can be seen by examining Scheme VIII.



Scheme VIII

Base K, O-acetylfawcettiine (90), which has been isolated from Lycopodium fawcettii,[49] was prepared as described by Burnell.[49] This compound did not correspond to the second component of L.9 (t.l.c.).

The C_8 epimer of O-acetylfawcettiine (90), O-acetyllofoline (80) was prepared by the acetylation of lofoline (91)[51] in pyridine-acetic anhydride. The infrared and n.m.r. spectra are in accord with the structure. The hydrogen on C_8 is a triplet while that on the carbon bearing the other acetoxyl group is a multiplet. The mass spectrum, Figure 4,which shows peaks at m/e 349, 290, 234, 174, and 146 is in full agreement with Scheme VIII.



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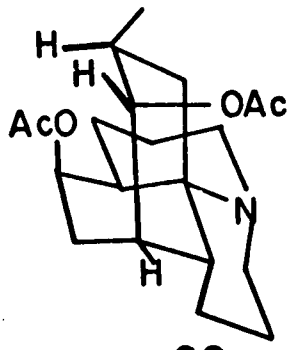

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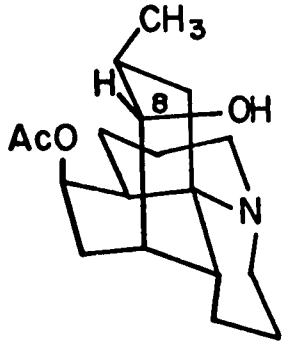


91

O-acetyllofoline (80) was found to be indistinguishable by t.l.c. from the compound of lower Rf in alkaloid L.9 .

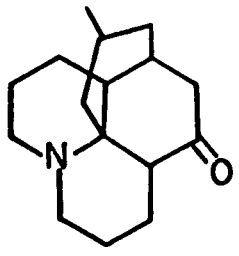
When a new sample of L.9 was eventually separated by chromatography, it was found that the components were indeed lycopodine (2) and O-acetyllofoline (80), these being present in approximately equal proportions.

Crystallization of a 1:1 mixture of lycopodine (2) and O-acetyllofoline (80) from hexane yielded crystalline material having a m.p. of 121-122° and which was shown to be identical with authentic "alkaloid L.9" by mixed melting point, infrared spectrum, and t.l.c. behavior. This "alkaloid" must then be a molecular complex of the two substances. Recrystallization of the complex from either hexane or ether did not alter the melting point.

Samples of L.26 and L.35, which were also provided by Dr. Manske, were examined by t.l.c. and infrared spectroscopy.

L.26 was found to have the same Rf as dihydrolycopodine (17). The infrared spectra were identical except for the appearance of a weak absorption band at 1540 cm^{-1}.

L.35 was found to be made up of two components (t.l.c.) The Rf values of these compounds were identical to those of lycopodine (2) and flabelliformine (92). When lycopodine, flabelliformine (92) and L.35 were mixed and analyzed by t.l.c., only two spots were apparent on the alumina plate.



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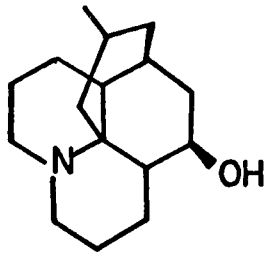

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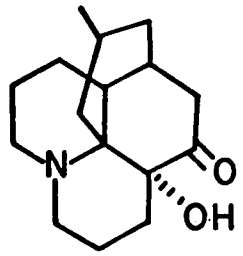

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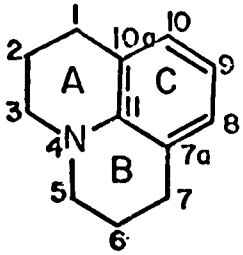
SECTION III. MODEL STUDIES OF JULOLIDINE

In examining the structue of lycopodine (2) and annotinine (1), as well as several other Lycopodium alkaloids it is possible to envisage the synthesis of these compounds by constructing a bridge from position 11 to position 10 or 10a in a modified tricyclic julolidine (15) type system. Julolidine (15) is the common name for 2,3,6,7-tetrahydro-1H,5H-benzo[ij] quinolizine.[19]



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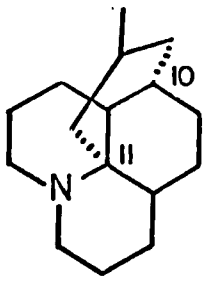
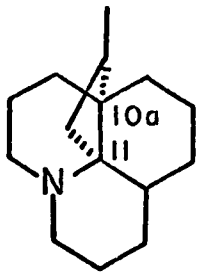
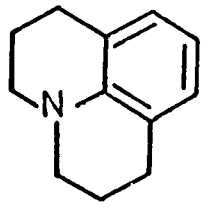




Our approach to the problem was to initially attach a group at positon 11 and then to devise a method of closing the final ring. The reaction of 3° immonium salts with nucleophilic reagents such as Grignard reagents, lithium alkyls etc. had been studied by Leonard[52] and by Schneider.[53] Leonard[54] had also reduced julolidine (15) to Δ^{10a}julolidine 93 which on treatment with perchloric acid yielded the immonium salt 94.



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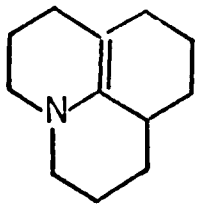

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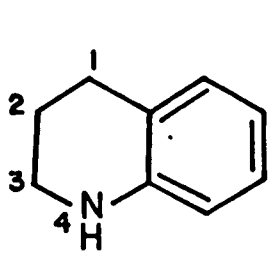
94

The same salt had been prepared by Bohlmann by mercuric acetate oxidation of a hexahydrojulolidine 14, followed by treatment with perchloric acid. Thus our approach was to prepare the immonium salt 94 and to study its reactivity toward a variety of reagents.

Julolidine (15) was prepared by a known method.[56] This involved refluxing 1,2,3,4-tetrahydroquinoline (95) in 1-bromo-3-chloropropane. The product obtained after purification by distillation had a melting point of 40° which is in agreement with the reported value.[57] The n.m.r. spectrum confirmed the structure by showing a quintet of 4 hydrogens at τ8.1(A) and two triplets of four hydrogens each at τ7.3 (B) and τ6.92(C) as well as a three hydrogen multiplet at τ3.52 (D), Figure 5.

Julolidine (15) was reduced with lithium in n-propylamine.[54] The enamine produced, 93, was immediately converted to the immonium salt 94 which had identical



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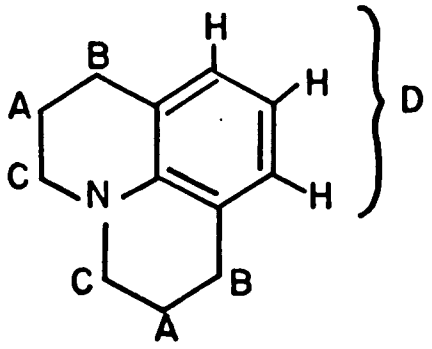

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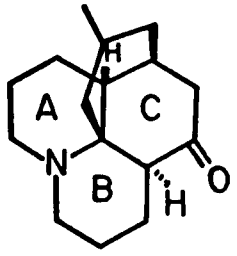
properties with that previously prepared.[54,55] The free base, some of which was regenerated from 94, exhibited the same properties as authentic material.[55]

Our main concern in these model studies was the stereochemistry of the product obtained by nucleophilic substitution of the immonium salt 94.

Lycopodine (2) has a cis A/C ring juncture and a trans B/C ring juncture. Thus the hexahydrojulolidine required is a cis-trans-hexahydrojulolidine 96. Reduction of 94 with



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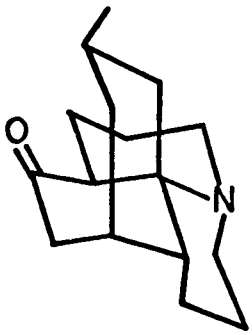

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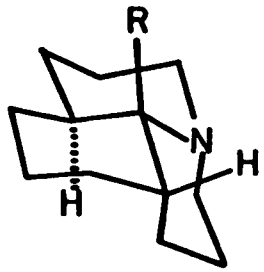
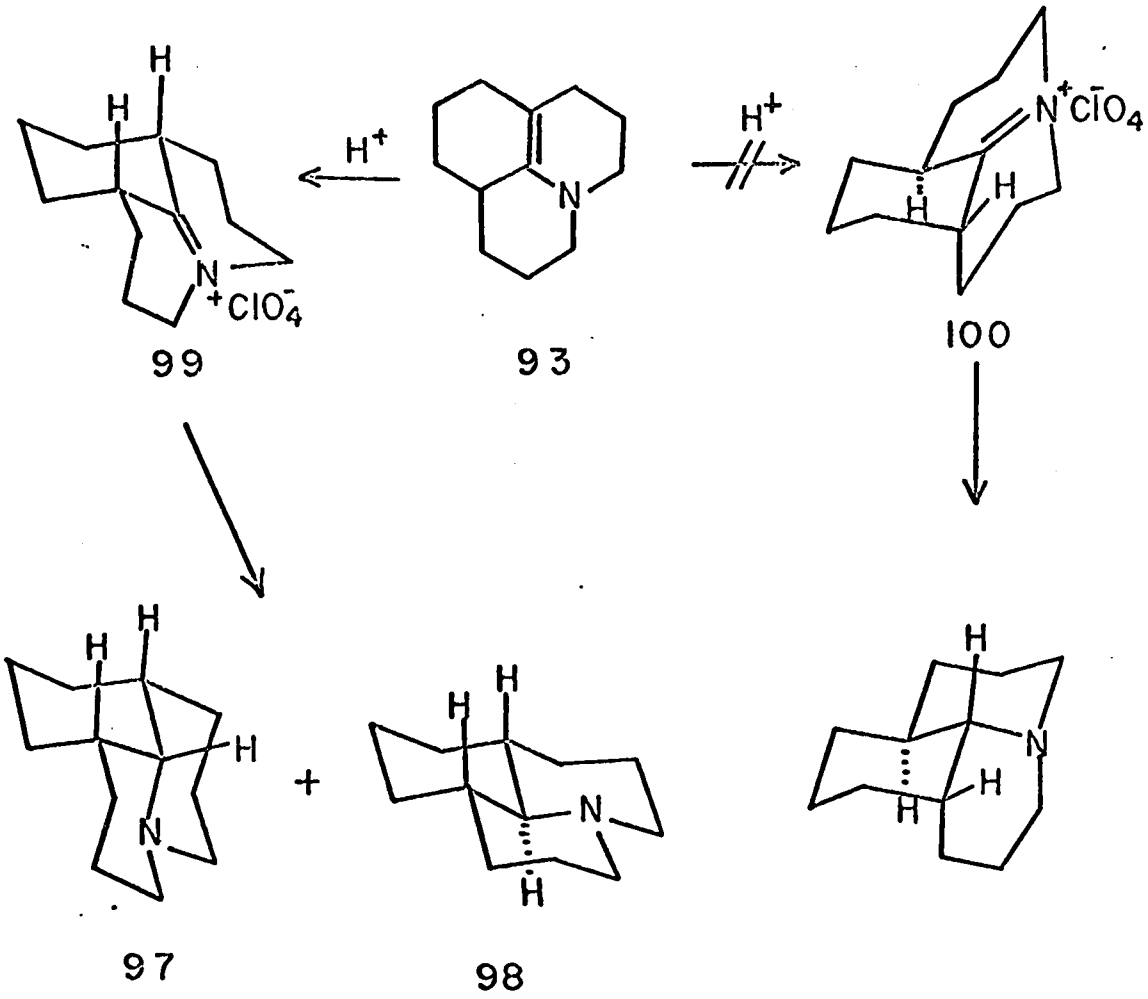


96

lithium aluminum hydride confirmed the findings of Bohlmann.[55]

Two hexahydrojulolidines are produced. These were separated and found to be cis-cis-hexahydrojulolidine 97 and trans-trans-hexahydrojulolidine 98. They were found to have superimposable infrared spectra to the ones prepared by Bohlmann, who also rigorously assigned their structures.[55]

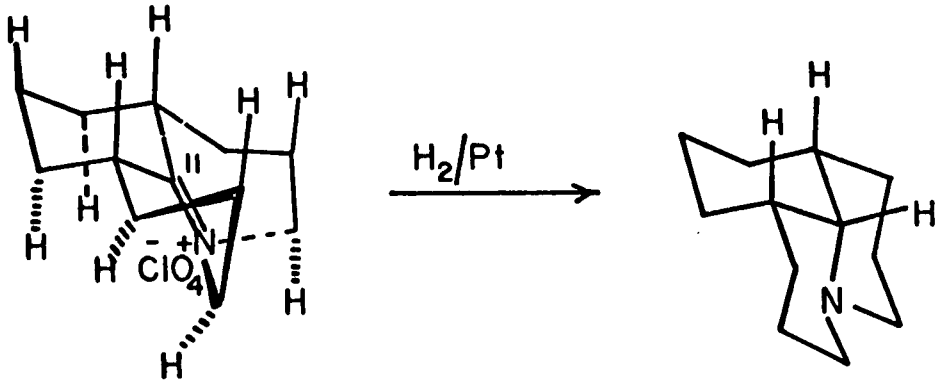


This meant that the immonium salt 94 had cis ring juncture hydrogens as in 99 and could not have had the stereochemistry as shown in 100. Dreiding models of the two possible immonium salts 99 and 100 clearly show that there is much

less strain in 99 than there is in 100. Structure 99 has one chair and two half-chairs while structure 100 has one chair and two half-boats. Thus 99 is certainly the favoured form of the immonium salt.

The reduction of the immonium salt 99 with lithium aluminum tri-tertiarybutoxyhydride gave the same result as $LiAlH_4$ reduction. The exact proportions of cis-cis to trans-trans product was not measured, however it appeared that a substantial amount of both was present.

Catalytic hydrogenation gave one product, cis-cis-hexahydrojulolidine 97. This was identified by its infrared spectrum[55], Figure 6, and by its picrate (m.p. 225)[55] as well as by the fact that it would not form a methiodide by refluxing with excess methyl iodide in anhydrous ether for 1 hour.[58] Examination of Dreiding models shows that carbon-11 is much closer to the "surface" of the molecule on the side of the C_{7a} and C_{10a} hydrogens than on the opposite side.

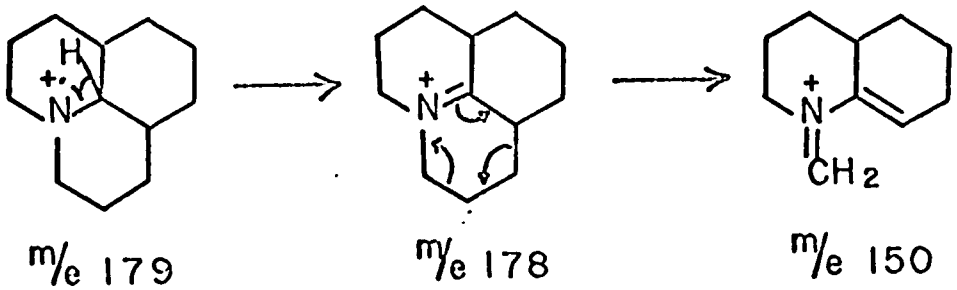


99 97

The addition of Grignard reagents to the immonium salt 99 was then investigated. Methallylmagnesium bromide, prepared in anhydrous ether, was allowed to react with a slurry of the immonium perchlorate. Upon workup only one product (t.l.c.) was obtained (m.p. 54°).

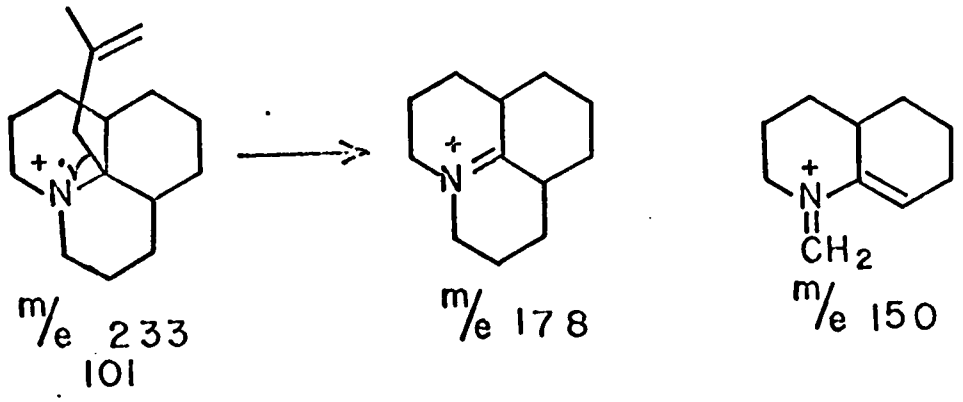
The product was identified as follows: the analysis of the perchlorate (m.p. 215-216°) indicated the addition of a methallyl group to the tetrahydrojulolidine portion, i.e., $C_{16}H_{27}N \cdot HClO_4$. The mass spectrum, Figure 7, of the free base has a peak at m/e 233 which corresponds to $C_{16}H_{27}N$. The base peak is found at m/e 178 (M^+-55, methallyl = 55) and prominent peaks appeared at m/e 176, 150, 149, and 148.

Cis-cis-hexahydrojulolidine 97 had shown prominent peaks in its mass spectrum, Figure 8, at m/e 179 (M^+), 178 (M^+-1, base peak) and 150 (M^+-29). This was explained as shown in Scheme IX.



Scheme IX

In the methallyl Grignard product a similar scheme could explain the prominent peaks if the compound is designated as 101. The fragmentation would then follow as in Scheme X. The other peaks m/e 176, 150, 149 and 148

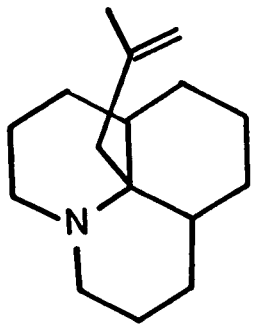


Scheme X

represent hydrogen losses from the various fragments.

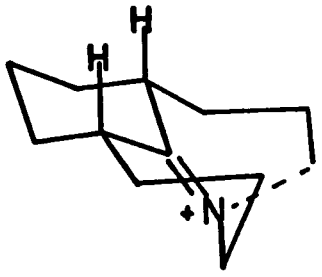
The n.m.r. spectrum shows two one proton singlets at τ5.17 and τ5.27 which were assigned to the olefinic methylene. A singlet at τ7.45, having the same integration as the τ5.22 signal, was assigned to the allylic methylene, while the singlet at τ8.16 was assigned to the allylic methyl group. The infrared spectrum, Figure 9, also shows the presence of an olefinic methylene with absorption at 3080, 1635 and 900 cm^{-1}.

On the basis of this spectral evidence, as well as by its mode of formation, the Grignard addition product was assigned structure 101.

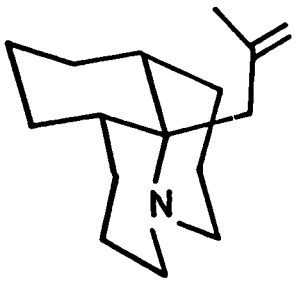


101

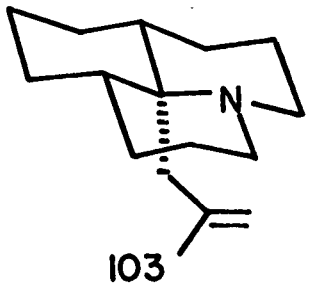
The stereochemistry of compound 101 was assigned as follows: the immonium salt had been assigned structure 99, a system which on Grignard addition at C_{11} could lead to two products, the cis-cis-, or the trans-trans-11-methallylhexahydrojulolidine, 102 and 103 respectively.



99



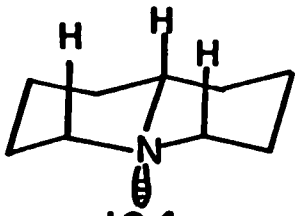
102



103

That the product was one of these two (and not the cis-trans isomer) was indicated by the fact that the infrared spectrum of the product showed moderately intense absorption between 2800 and 2700 cm^{-1}. Bohlmann[55,59] had shown that, when the lone pair of electrons on

nitrogen is trans diaxial to two or more hydrogens on carbons adjacent to the nitrogen, absorption occurs in the 2800 to 2700 cm^{-1} region. Thus trans-quinolizidines 104 show "Bohlmann" bands while cis-quinolizidines 105 do not.



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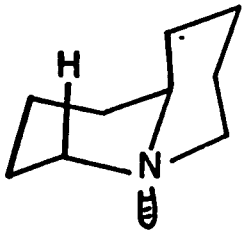

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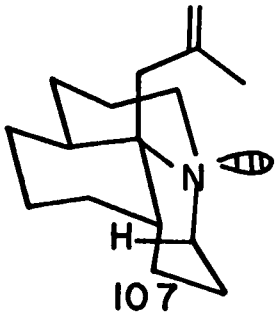
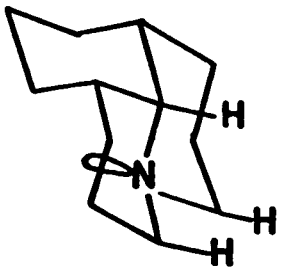
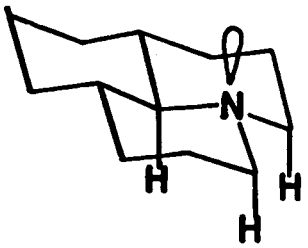


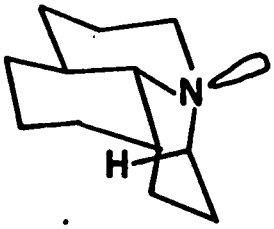
107



97



98

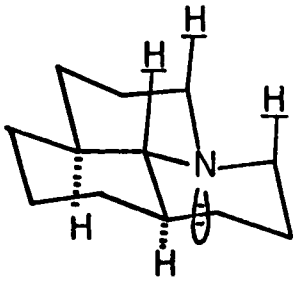


106

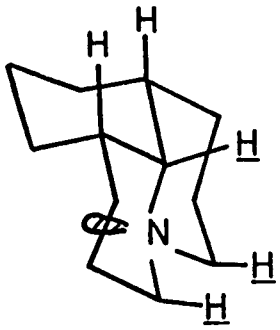
Of the three hexahydrojulolidine compounds 97, 98 and 106, only the cis-trans isomer 106 does not show these bands.[55] The product of Grignard addition cannot be the cis-trans isomer 107.

The product 101 was found not to react with methyl iodide in refluxing ether (1 hr, or 3 hr) or in

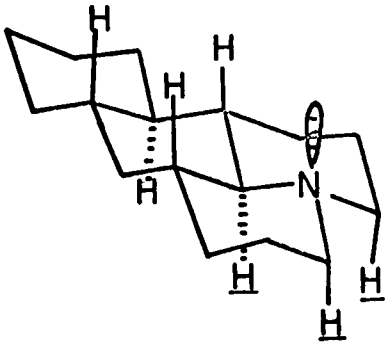
refluxing acetone. However, it did form in 95% ethanol. It had previously been shown that in the hexahydrojulolidine series the trans-trans isomer 98 formed a methiodide in refluxing ether (1 hr) while the cis-cis isomer 97 did not.[58] Furthermore methiodide formation of similar types of compounds has been extensively studied.[58,59] It has been found that trans-trans systems react approximately 30 times faster with methyl iodide than do the cis-cis systems, both of which show "Bohlmann" bands in the infrared. Examples of the rate constants measured at 35° are given in Chart II. The units of k are in L./mole/sec and are expressed as multiples of 10^4.



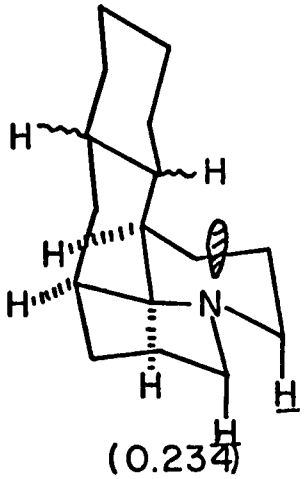
(10.74)



(0.267)



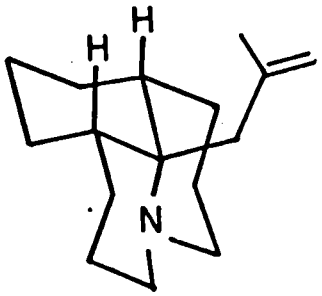
(9.77)



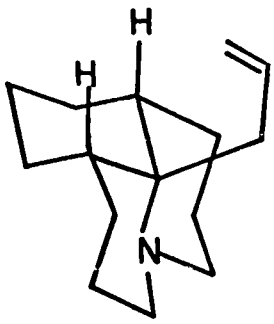
(0.234)

Chart II

On the basis of this evidence the Grignard product 101 was assigned the cis cis configuration 102.



102



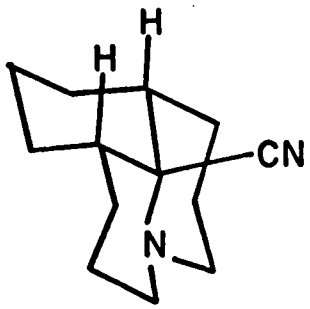
108

A similar preparation involving allylmagnesium bromide[61] was carried out. All the physical data as well as its chemical behavior were similar to those of 102. Because of this the product was assigned structure 108.

Immonium salt 99 was reacted with KCN following a method developed by Schneider.[53] This involved shaking KCN and the immonium salt in a 1:1 mixture of water and ether. A pure (t.l.c.) product (m.p. 78°) was obtained in 95% yield. The mass spectrum, the chemical analysis, the infrared spectrum, the n.m.r. spectrum and its failure to react with methyl iodide in refluxing ether (1 hr), were in agreement with the assigned structure 109.

This result, in view of the hydride reductions which had yielded two products, was rather unexpected.

These studies showed that a functional group could be attached to the C_{11} position of hexahydrojulolidine



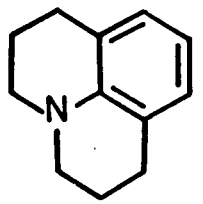
109

derivatives and that the product has the undesired cis-cis configuration. Such a system could then only be used if some method of changing the stereochemistry of the substitution products were available.

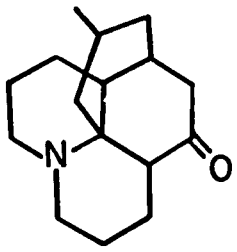
As this work was being carried out, a C_9 substituted julolidine system was being examined. This system shall be discussed in the next section.

9-METHOXYJULOLIDINE SYSTEM

While the studies on julolidine (15) were being carried out, similar types of reactions on a more elaborate system were examined.[62] This involved the preparation of a functionalized julolidine derivative which could potentially allow for the formation of the fourth ring in lycopodine (2). The derivative used is 9-methoxyjulolidine (110).



15



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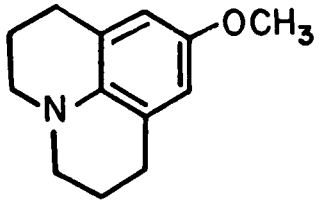
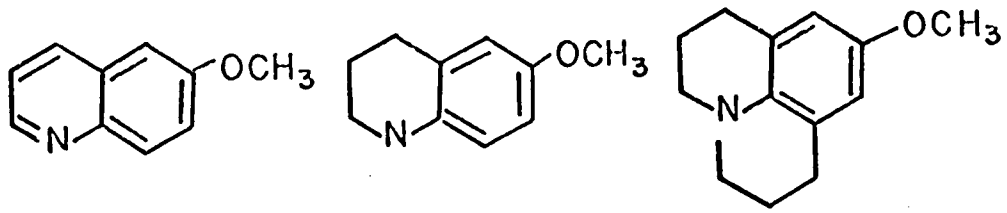


110

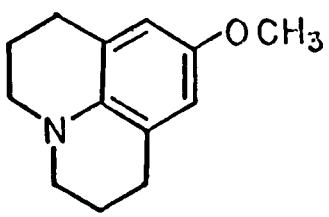
9-Methoxyjulolidine (110) is a readily available substance which can be synthesized in two steps from 6-methoxyquinoline (111). Hydrogenation of 111 at 50 p.s.i. for 24 hours using platinum oxide as catalyst led to 6-methoxy-1,2,3,4-tetrahydroquinoline (112), commonly called thalline.[63,64] Condensation of thalline (112) with 1-bromo-3-chloropropane[65] yielded 9-methoxyjulolidine (110).



111 112 110

Since julolidine (15) had also been prepared[65] using the double condensation of aniline and two moles of 1-bromo-3-chloropropane the synthesis of 9-methoxyjulolidine (110) was attempted in a similar way. p-Anisidine was heated with 1-bromo-3-chlorpropane under a variety of conditions. In all cases, t.l.c. indicated the presence of many products. Consequently the method was not pursued.

The method for the transformation of 9-methoxyjulolidine (110) to a suitable immonium salt was developed by Cooke.[62] This involves reduction of 110 using lithium in liquid ammonia and tert-butyl alcohol to the dihydro derivative 113. The unstable product is immediately dissolved in warm ethylene glycol which is then acidified using 70% perchloric acid. The ethylenedioxy immonium salt 114 which precipitates is purified by repeated digestion in methanol.



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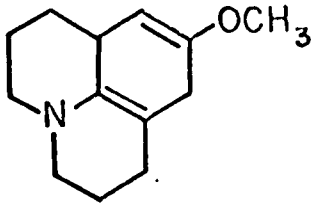
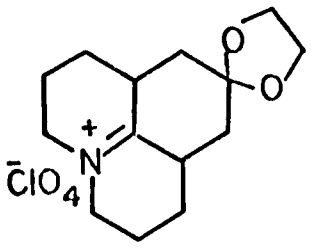


113



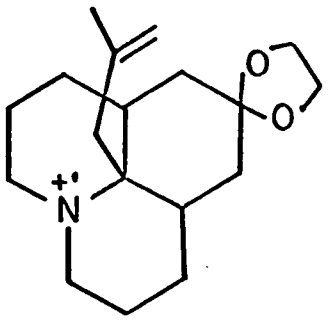
114

The purity of immonium salt 114 was of some concern. The analytical results[62] agree with the assigned formula $C_{14}H_{21}NO_2 \cdot HClO_4$. The infrared spectrum has absorptions at 1675 cm^{-1} corresponding to $\rangle C=N\langle^{+}$ [54] and at 1080 cm^{-1}, corresponding to the perchlorate band. The former absorption band however has a shoulder at 1660 cm^{-1}. Since many products were later obtained in its reaction with methallylmagnesium chloride the composition and stereochemistry of the immonium salt 114 will be discussed in more detail later.

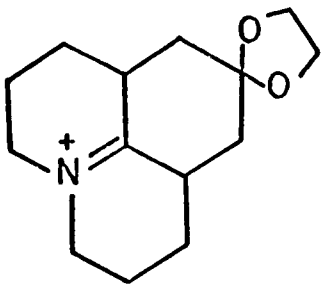
Tetrahydrofuran (THF) was found to be the most suitable solvent for the reaction of methallylmagnesium chloride with the immonium salt 114. The reaction using diethyl ether takes much more time to go to completion. Methallylmagnesium chloride is formed in approximately 8 hours by treating methallyl chloride with magnesium metal in dry THF. A slurry of immonium salt 114 is then

added to the Grignard reagent in THF and the mixture stirred under reflux for one hour. This reaction always yielded a mixture of products, anywhere from three to five, which were somewhat difficult to separate.

The main product was always 115. The compound melts at 59-61° and is homogeneous by g.c. and t.l.c. The infrared spectrum, Figure 10, shows the presence of the terminal methylene ($C=CH_2$) with absorptions at 3070, 1635, and 885 cm^{-1}. The n.m.r. confirms this; τ5.08, (1H, s), τ5.18, (1H, s) and τ8.12 (singlet, CH_3-C) and also indicates the presence of the ethylene ketal, τ6.09 (singlet, 4H, OCH_2CH_2O). The mass spectrum confirms the analytical result for $C_{18}H_{29}NO_2$: molecular weight 291, found, 291 and shows the base peak at m/e 236 (M^+-55) which corresponds to the loss of the methallyl group as indicated below.



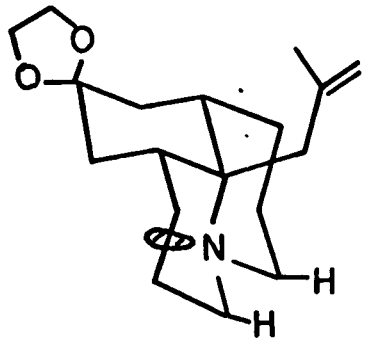
m/e 291 (M^+)



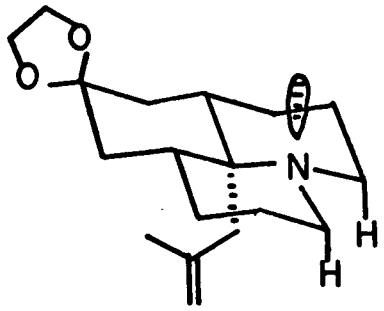
m/e 236 (M^+-55)

The infrared spectrum of 115, Figure 10, shows prominent "Bohlmann" bands which indicate the presence of either 115 or 116. Since the compound had been found to

be very sluggish in its reaction with methyl iodide[62] and by analogy with the results obtained in the 9-deoxyjulolidine series, it was assigned the cis-cis-configuration.

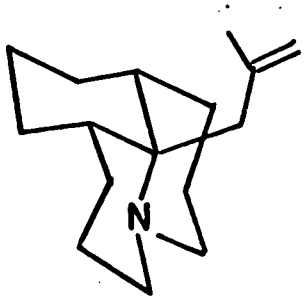


115

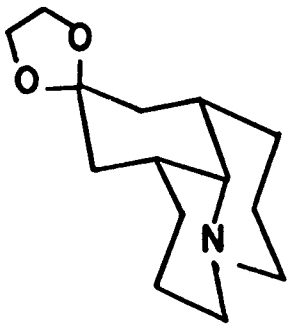


116

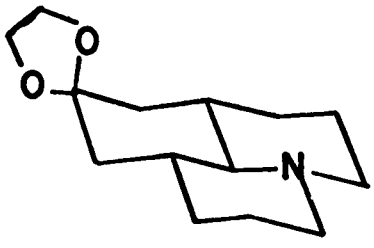
The other products obtained were found to vary greatly in yield as well as in relative proportion. The most common by-product was 102. The structural assignment is based on comparison with authentic material obtained in the model series.



102

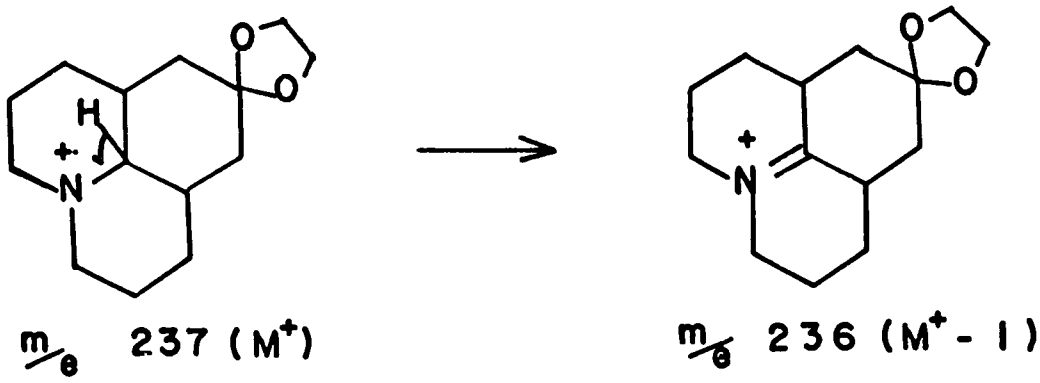


117



118

The other products which were fairly consistently obtained were isomeric compounds. The least polar of these has a melting point of 96-97° after sublimation. Its infrared spectrum shows strong "Bohlmann" bands (2800, 2770, 2740 cm^{-1}) and lacks double bond absorption. The n.m.r. spectrum shows the presence of the ethylene ketal (τ6.08, singlet, 4H, OCH_2CH_2O). The analysis agrees with the formula $C_{14}H_{23}NO_2$ and its molecular weight is 237 (mass spectrometry); calculated for $C_{14}H_{23}NO_2$, 237. The mass spectrum also shows the base peak at m/e 236 which is in accord with the fragmentation shown below.



m/e 237 (M^+) m/e 236 (M^+ - 1)

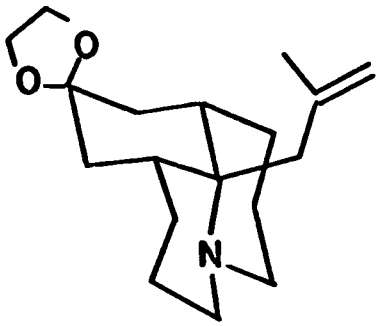
Its stereochemistry is based on the fact that it has spectral properties[62] identical with those of the product obtained by catalytic reduction of the immonium salt 114. The perchlorates[66] were also identical. Since catalytic hydrogenation of the immonium salt would be expected to occur from the least hindered side, the compound is assigned the cis-cis configuration 117. The fact that it is

eluted from alumina before its epimer (nitrogen more hindered) is in agreement with its assigned structure. It should, however, be pointed out that the compound obtained from the hydrogenation of immonium salt 114 has been reported to have a melting point of 161-164°.[62]

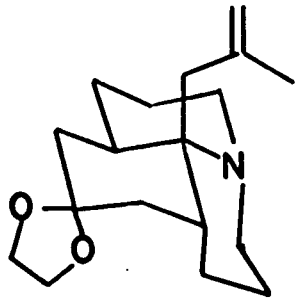
The most polar substance obtained in the Grignard reaction has an infrared spectrum completely different in the fingerprint region from that of 117 but it does show "Bohlmann" bands and fails to show double bond absorption. The n.m.r. shows the presence of the ethylene ketal (τ6.08, singlet, 4H) and the mass spectrum shows the parent peak at m/e 237 and the base peak at m/e 236 (M^+-1) as was the case in the epimeric compound 117. It was assigned the trans-trans configuration (118) since the compound does show "Bohlmann" bands in the infrared spectrum.

In some cases, upon careful chromatography of the Grignard addition products, a fifth compound, which closely followed 102, was isolated. A sample, shown to be homogeneous by g.c. and t.l.c., melted at 81-83°. Its infrared spectrum, Figure 11, shows absorption at 3070, 1635, and 885 cm^{-1} ($C{=}CH_2$), however it fails to show "Bohlmann" bands. The n.m.r. spectrum shows the presence of olefinic hydrogens (τ5.21, broad singlet, 2H) and of the ethylene ketal (τ6.11, apparent triplet, 4H). The mass spectrum has peaks at m/e 291 (M^+) and m/e 236 (base,

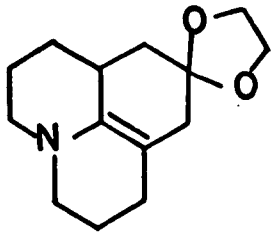
M^+-55) which corresponds to the loss of the methallyl group. The formula $C_{18}H_{29}NO_2$ was confirmed by high resolution mass spectrometry (m/e 291) and by analytical results. On this basis the compound was assigned structure 119. It was later shown that a sample, prepared by isomerization of the cis-cis-epimer 115, was completely identical with that obtained directly from the Grignard reaction.



115



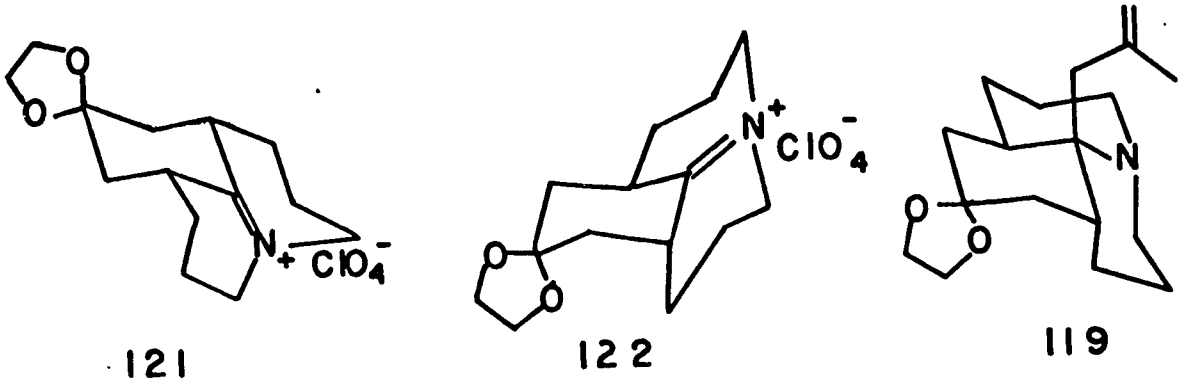
119



120

The yields of the minor products were variable. Compound 119 was the least often encountered and usually was obtained in low yield. On one occasion (see Experimental section) the starting enamine 120 and the products 102, 117 and 118 were the only materials isolated. On other occasions 115 was obtained in 85% yield. The description given in the experimental is one example in which all the products mentioned were isolated and in which the yield of 119 was the highest obtained.

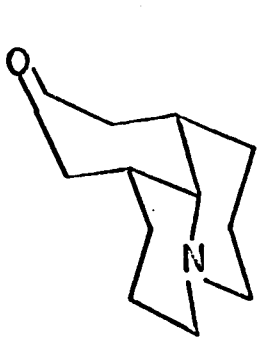
In view of the many products obtained, the stereochemistry of the immonium salt 114 had to be reconsidered. Two possible spacial arrangements can be assigned to this compound 121 (cis) and 122 (trans).



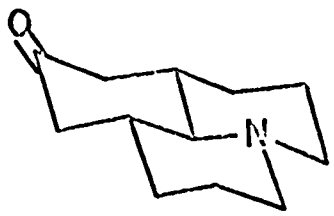
121 122 119

Since 9-ethylenedioxy-11-methallyl-cis-trans-hexahydrojulolidine (119) was obtained in certain cases of Grignard addition to immonium salt 114 it appeared that the immonium salt might be a mixture of 121 and 122. In order to clarify this point some reductions of the immonium salt 114 were carried out.

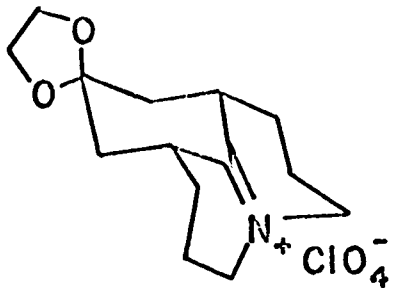
Catalytic reduction[62] of 114 had yielded one product which because of its infrared spectrum (Bohlmann bands) and by analogy to the experiments carried out on the model compounds was assigned the cis-cis-configuration. Lithium aluminum hydride reductions[67] of the immonium salt 114 yielded two products, which were isolated as the ketones, after hydrolysis of the ketal grouping. Both ketones show "Bohlmann" bands. These compounds must be assigned structures 123 and 124.



123



124



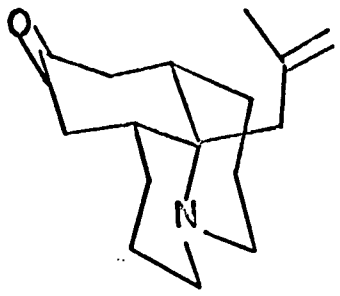
121

Since the cis-trans isomer was not obtained it was concluded that the salt did not contain significant amounts of 122 and was in fact the cis-isomer 121.

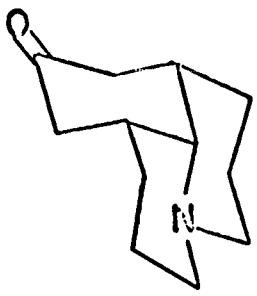
Examination of the ethylene glycol-perchloric acid mother liquors showed only the presence of $\Delta^{7a(11)}$-9-ethylenedioxyhexahydrojulolidine (120) and of unchanged 9-methoxyjulolidine (110). Repeated recrystallization of immonium salt 114 from anhydrous acetone failed to alter its infrared spectrum.

The formation of the cis-trans isomer 119 is difficult to explain as are the reactions leading to the other by-products. Since not all batches of immonium salt 114 were prepared in precisely the same way and since not all were tested for purity, it is possible that the by-products arise from impurities in the immonium salt. Compounds 117 and 118 may, of course, arise by reduction of 114 by the Grignard reagent.

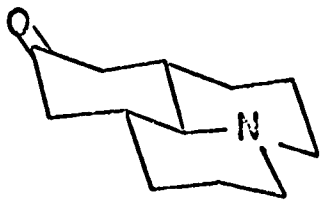
Since difficulties were initially encountered in the separation of the Grignard products, chromatography of the crude product after acid hydrolysis was attempted. This led to the isolation of three compounds, 125, 123 and 124 in that order.



125

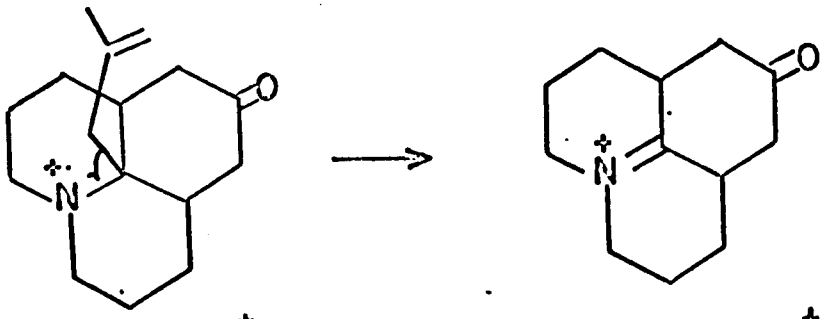


123



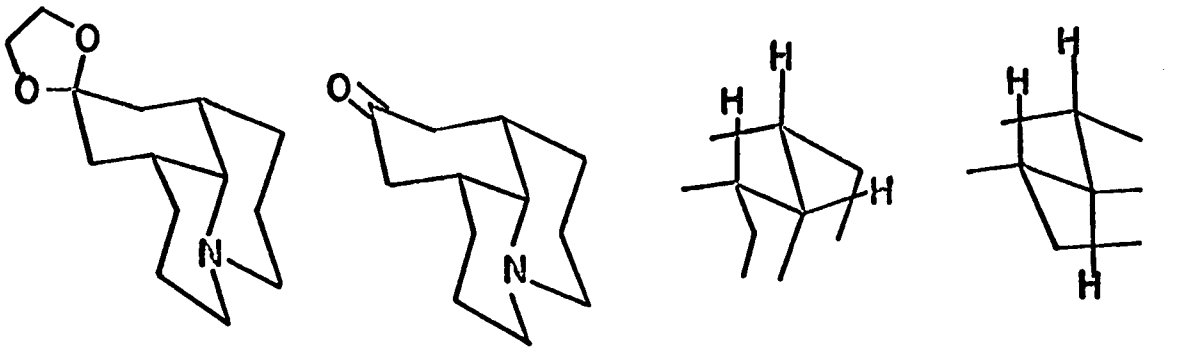
124

Other compounds were present (t.l.c.) but none of these were obtained in pure form. The main product 125 has a melting point of 75-76° and was homogeneous by t.l.c. It shows "Bohlmann" bands in the infrared as well as double bond absorption (3050, 1630, and 895 cm^{-1}) and ketone absorption (1710 cm^{-1}). The n.m.r. shows the presence of the olefinic hydrogens (τ5.17 1H, s, τ5.27, 1H, s) and the mass spectrum gives a parent peak at m/e 247, with the base peak at m/e 192 (M^+-55). The mass spectral data agrees with the assigned structure. This compound is identical in every respect to the compound obtained on hydrolysis of 115.



m/e 247 (M^+) m/e 192 ($M^+ - 55$)

The other two compounds, 123 and 124 were correlated with other compounds. When compound 117 was hydrolyzed in dilute HCl-methanol a ketone was obtained. This ketone has structure 123. This was confirmed by its n.m.r. which shows the methine hydrogen as an apparent triplet at τ6.82.

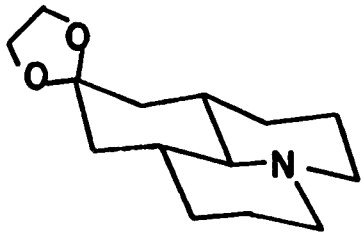


117 123 cis-cis trans-trans

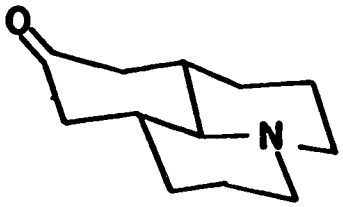
Since the compound obtained in the chromatography of the hydrolyzed crude Grignard product was identical with the above, it was also assigned structure 123.

The third compound obtained in this chromatography was assigned the trans-trans configuration because it possesses

"Bohlmann" bands in its infrared but has no side chain at carbon 11. Furthermore it can be presumed that 124 arose from 118.

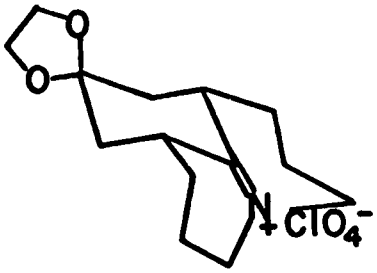


118

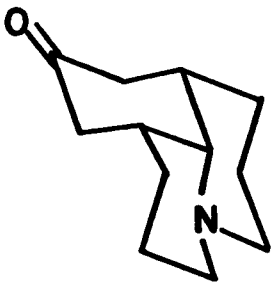


124

It should be noted that these two compounds have infrared spectra superimposable on those obtained after hydrolysis of the $LiAlH_4$ reduction products[67] of immonium salt 121.



121



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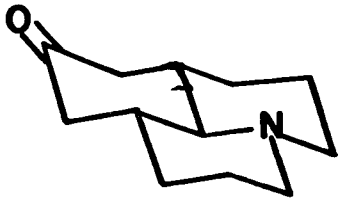
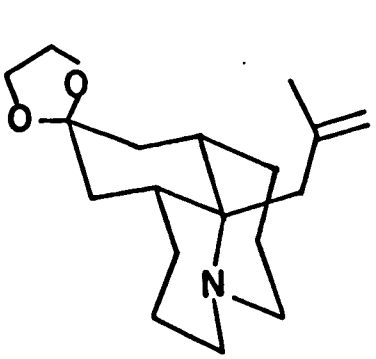


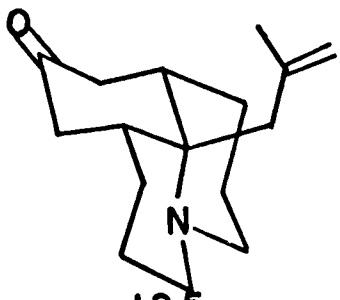
124

Separation of the products, after hydrolysis, proved equally difficult. After much experimenting it was possible to obtain complete separation of the products before hydrolysis of the mixture (see Experimental).

The major product obtained from the reaction of methallylmagnesium bromide and immonium salt 121 was 115 which was easily converted to compound 125 by hydrolysis.



115



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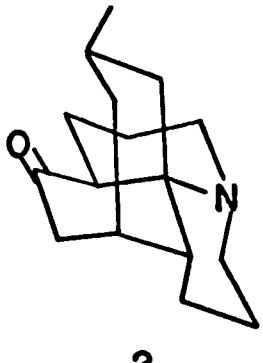
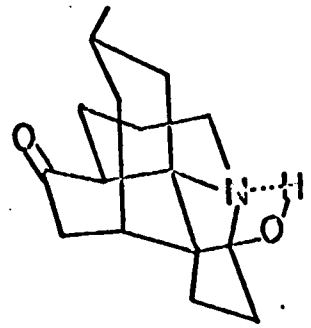


2

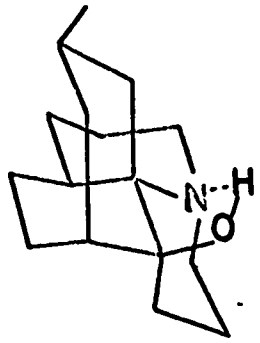
This compound 125 has a cis-cis ring juncture and cannot be cyclized to form the fourth ring in lycopodine (2). A method which would change a cis-cis-julolidine to a cis-trans-julolidine had to be devised.

Lycodoline, L.8, (126)[68] had previously been converted to desoxolycodoline (127) which on dehydration with P_2O_5 had yielded anhydrodesoxolycodoline (128). This compound, 128, has "Bohlmann" bands in its infrared spectrum as does its reduction product 129 while its precursors 127 and 126 do not. This then represents a conversion from a cis-trans-julolidine system to a trans-trans one.

On this basis, it appeared possible that the introduction of a double bond at one of the ring junctures of 125 would lead to inversion of the system, as indicated below:



126



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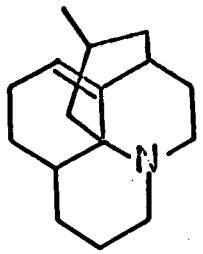
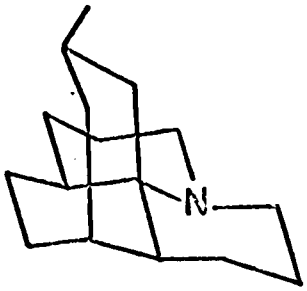
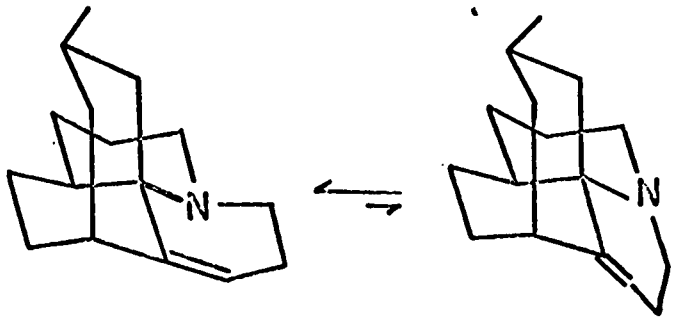


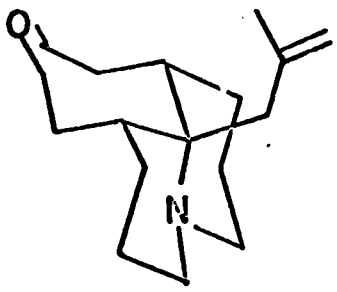
128



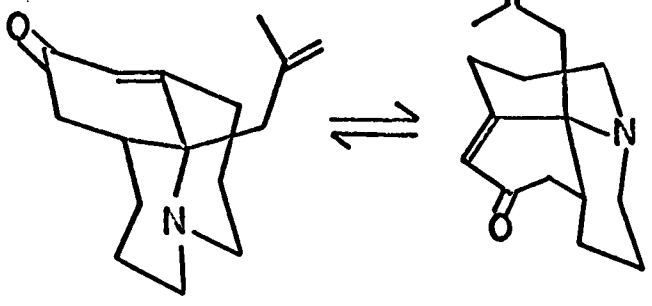
129



128b 128a



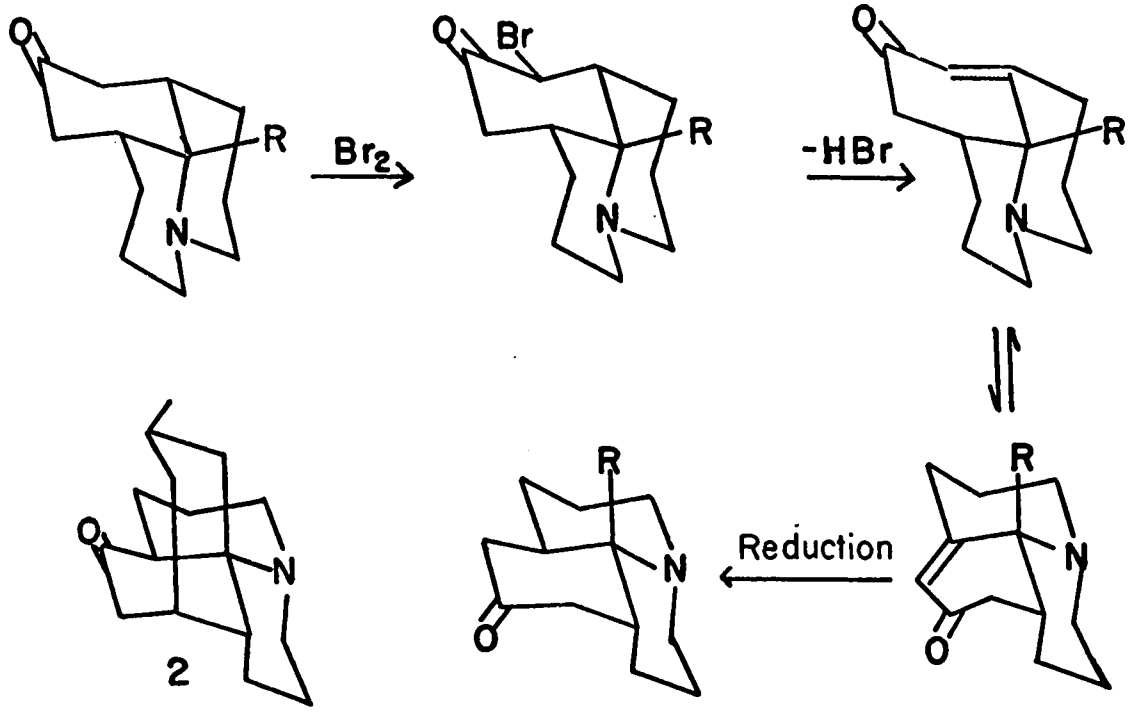
125



130 131

Examination of Dreiding models shows that inversion of the nitrogen and transformation of the resultant boat into a new chair form with simultaneous transformtion of the unsaturated ring from one half-chair form to the other half-chair in 130 leads to 131 and vice versa. Conformer 131 also seems to be more favoured.

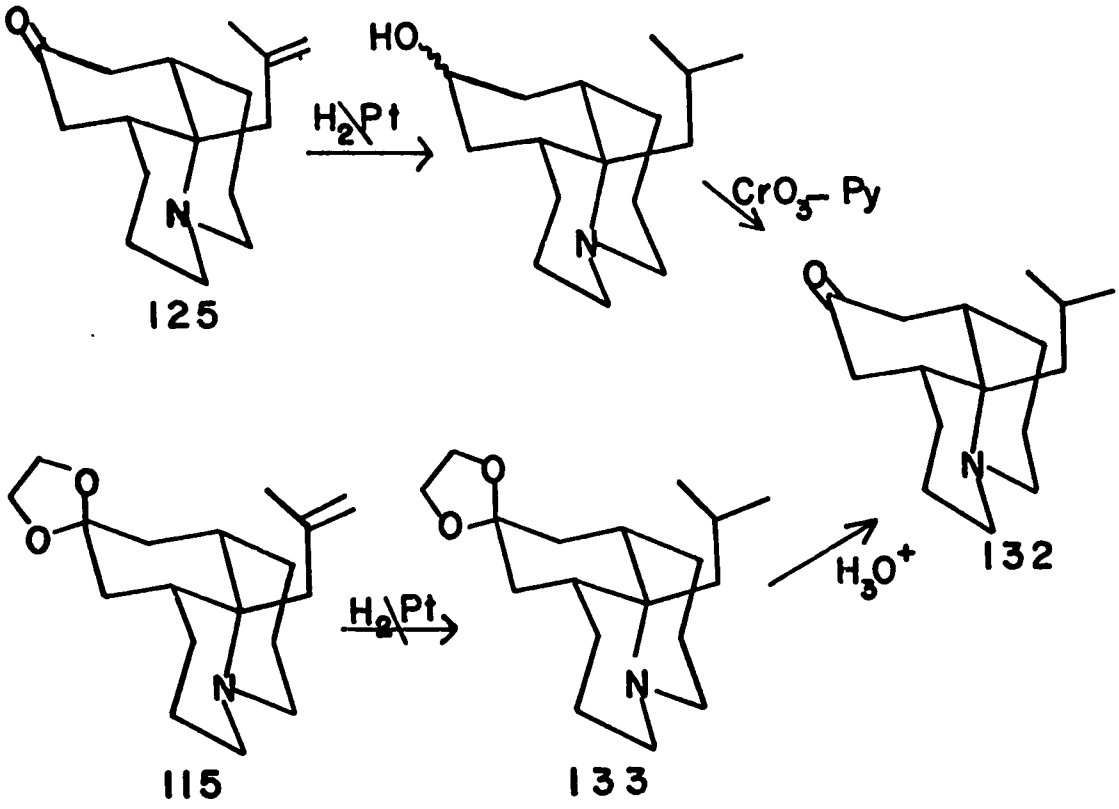
A synthetic route which would result in introduction of the required double bond is given in Scheme XI.



Scheme XI

According to Scheme XI, the cis-cis to cis-trans conversion requires a keto group or a potential keto grouping at position 9 in the 11-substituted-cis-cis-hexahydrojulolidines. Two compounds, 115 and 125 which have this requirement have already been described.

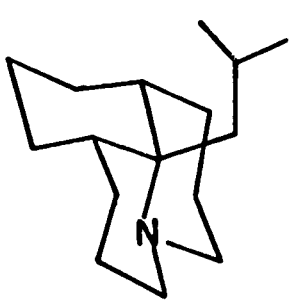
In order to keep the system as simple as possible the methallyl group was converted to the isopropyl group as in 132. Compounds 115 and 125 were thus converted to 132 as shown in Scheme XII.



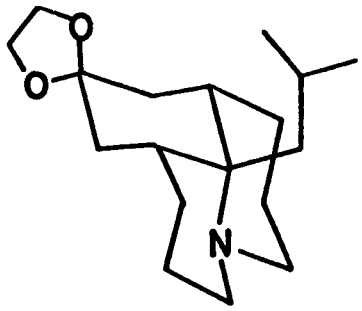
Scheme XII

9-Keto-11-isobutyl-cis-cis-hexahydrojulolidine (132) was more easily obtained by treatment of immonium salt 121 with isobutylmagnesium bromide followed by hydrolysis of the appropriate product (133). This particular Grignard reaction yielded many products only two of which were identified. The first shows "Bohlmann" bands in the i.r.,

no ethylene ketal (n.m.r.) and a molecular weight of 235 (mass spectrometry). This data agrees with the assignment of structure 134. The other product was 133. It was identical with authentic material.[62] Its characteristics are; m.p. 48°; i.r. 2800, 2770, 2750 cm^{-1}; n.m.r., τ6.07 (singlet, 4H), τ9.01 (doublet, J =.6 cps, 6H); mass spectrum, m/e 293 (M^+) and m/e 236 (M^+-57, isobutyl = 57). Hydrolysis of 133 gave 132 which has an identical infrared spectrum to that of a previously prepared sample.[62]



134

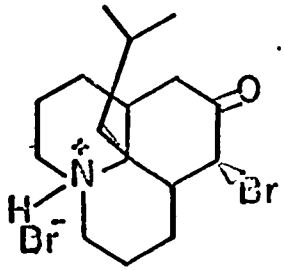


133

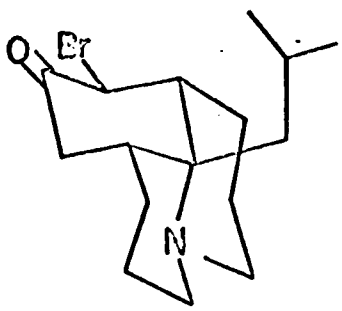
At this point compound 132 was made available to us by three closely related routes. We then proceeded to carry out the intended inversion (Scheme XI) which we hoped would lead us to a cis-trans-hexahydrojulolidine derivative.

9-Keto-11-isobutyl-cis-cis hexahydrojulolidine (132) was firstly converted to its crystalline hydrobromide (from acetone, m.p. 220 dec). Bromination[44] by the addition of one equivalent of bromine to a chloroform solution of the hydrobromide salt yielded the crystalline bromoketone

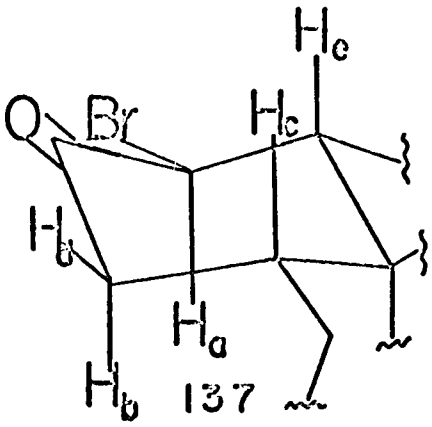
hydrobromide 135. The equatorial nature of the bromine is shown by the shift (+25 cm^{-1}) of the carbonyl absorption in the infrared spectrum of the product (from 1710 cm^{-1} in 132 to 1735 cm^{-1} in 135 and 136).



135



136

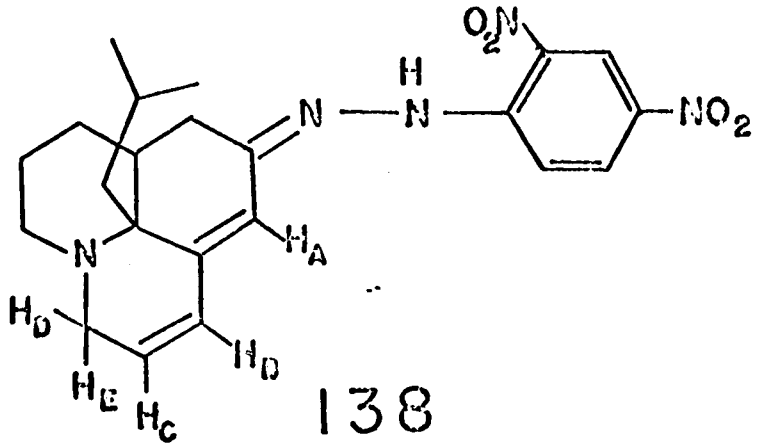


137

This was confirmed by examination of the n.m.r. spectrum of the free base 136. This shows a one proton doublet at τ4.68 (Jae = 12 cps) assigned to Ha in 137, a triplet at τ6.65 (Jbc = Jbd = 12-13 cps) assigned to Hb, and a 6-proton doublet (J = 6 cps) at τ9.05.

Elimination of hydrogen bromide was initially attempted by formation of the 2,4-dinitrophenylhydrazone[69] of the bromoketone hydrobromide 135. Treatment of 135 with 2,4-dinitrophenylhydrazine in acetic acid yielded a red solid which appeared to consist of two components (t.l.c.). A small amount of one of the components was obtained in pure form by chromatography. Its ultraviolet spectrum indicates that it is not an α,β-unsaturated 2,4-dinitrophenylhydrazone but rather an α,β,γ,δ-unsaturated 2,4-dinitrophenylhydrazone ($\lambda_{max}^{Et_2O}$ 396 mμ).

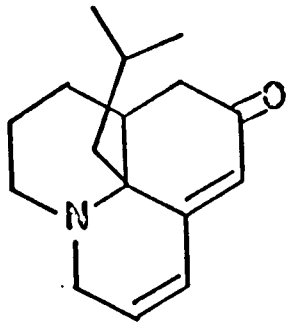
This was confirmed by its n.m.r. spectrum.



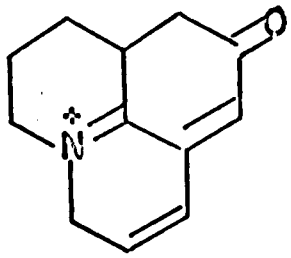
138

It shows: H_A, τ3.88, singlet; H_B, τ3.76, quartet (J_{BC} = 10 cps, $J_{allylic}$ = 2.5 cps); H_C, τ4.08, octet (J_{BC} = 10 cps, J_{CD} = 5 cps, J_{CE} = 3 cps); H_D, τ6.9, quartet (J_{DE} = 20 cps, J_{DC} = 5 cps); H_E τ6.05, doublet (J_{DE} = 20 cps).

Some of the 2,4-dinitrophenylhydrazone 138 was hydrolyzed using acetone, HCl and stannous chloride.[70] After purification of the crude product a small amount of semi-solid was obtained which was mainly one component as shown by t.l.c. The infrared spectrum shows a low frequency carbonyl (1660 cm^{-1}) and two weaker absorptions at 1610 and 1580 cm^{-1}. The ultraviolet spectrum shows a maximum at 285 mμ, while the mass spectrum fails to show a parent peak but does show the base peak at m/e 188. On this basis the compound was assigned structure 139. Such an assignment would account for the ultraviolet maximum (calculated 280 mμ)[71] and also for the mass spectral fragment at m/e 188 which corresponds to the loss of the isobutyl group.

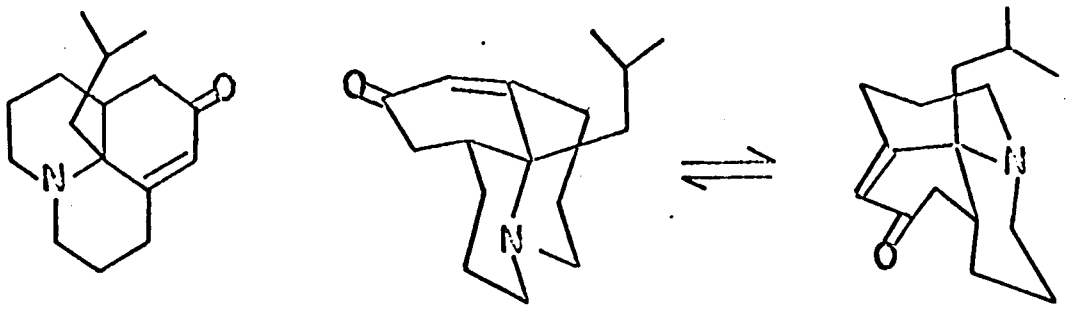


139



m/e 188 (M^+-57)

Other methods of dehydrobromination were attempted.[72,73,74,75] Of the various procedures investigated, the one described by Green and Long[75] was the most successful. This involves refluxing the bromoketone hydrobromide 135 in acetic acid with two equivalents of freshly prepared semicarbazine,[76] followed by exchange of the resulting semicarbazone with pyruvic acid in aqueous acetic acid. The product, after chromatography, was an oil (31% from 135) which shows absorption in the infrared at 1675 and 1615 cm^{-1}. There are no "Bohlmann" bands (2700-2800 cm^{-1}) in this spectrum. The ultraviolet spectrum shows a maximum at 242 mμ (calculated 244 mμ).[71] The n.m.r. shows a signal at τ4.15 (doublet, J = 1.5 cps, allylic coupling) and the mass spectrum has a parent peak at m/e 247, with a base peak at m/e 190 (M^+-57). On this basis, the compound was assigned structure 140.

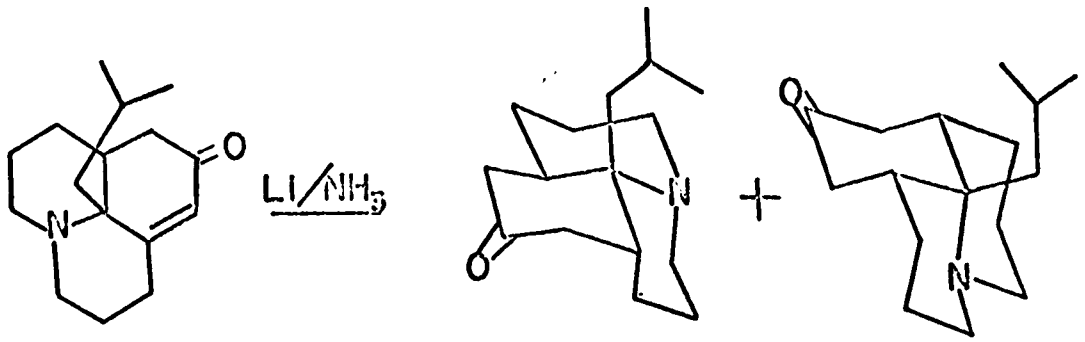


140 140a 140b

The α,β-unsaturated ketone 140 which can exist in two forms (140 a and 140b) seems, judging from the lack of "Bohlmann" bands, to exist predominantly in the form 140b.

Reduction of the α,β-unsaturated ketone 140 using lithium in liquid ammonia yielded 2 components. The first of these compounds (55%) has a m.p. 90°. Its infrared spectrum lacks Bohlmann bands. The mass spectrum is virtually identical with that of 9-keto-11-isobutyl-cis-cis-hexahydrojulolidine 132 (m/e 249 (M^+), 192 (base, M^+-57)). This compound was thus assigned structure 141. The other compound isolated from the crude reduction product was the cis-cis isomer 132.

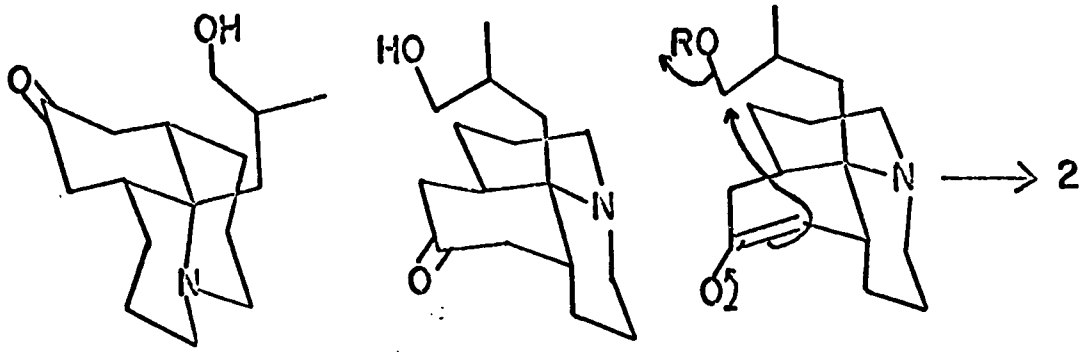
Compound 119, occasionally obtained as a minor product in the reaction of methallylmagnesium bromide with immonium salt 114, was hydrogenated and hydrolyzed to the ketone. This ketone was found to be identical (t.l.c., i.r., mass spectrometry) with 9-keto-11-isobutyl-cis-trans-hexahydrojulolidine 141 prepared by bromination,



140 141 132

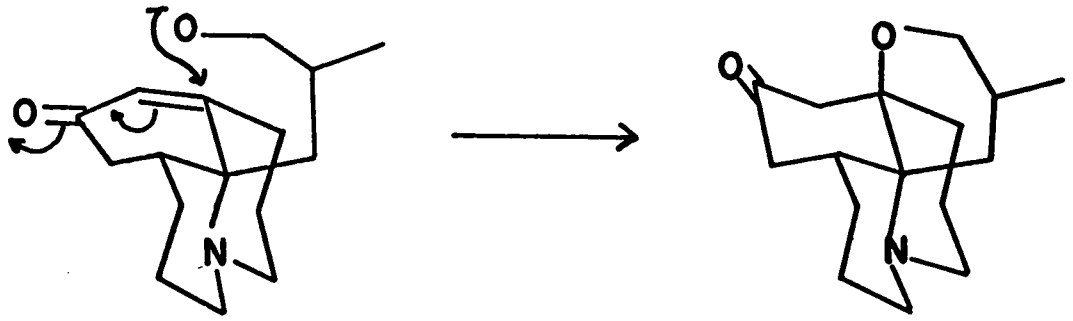
dehydrobromination and reduction of its epimer 132.

Now that a cis-cis julolidine system had been converted to the corresponding cis-trans system, as found in lycopodine (2), a compound, modified in such a way as to permit formation of the fourth ring, was necessary. A compound considered very suitable for this was the hydroxyketone 142. This compound, on epimerization, would lead to the diasteriomeric alcohols 143 which if properly treated could lead to lycopodine (2).

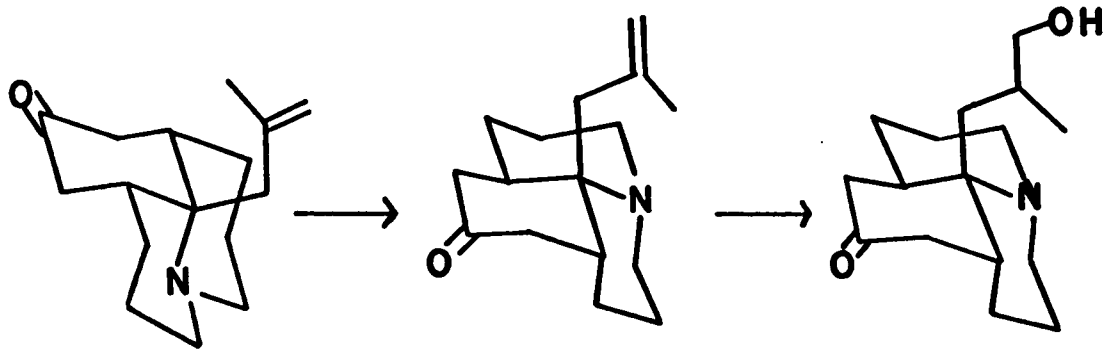


142 143

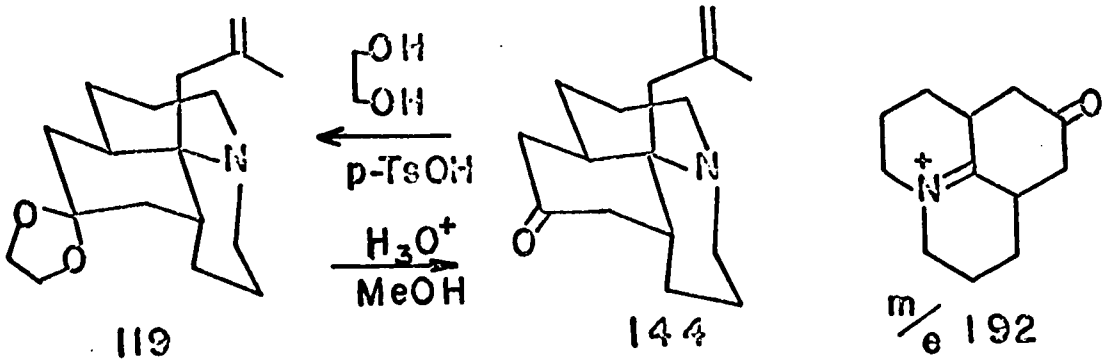
This sequence was investigated by W.R. Bowman in these laboratories[66] and was beset with difficulties, the major one involving the addition of the oxygen function to the double bond in the α,β-unsaturated ketone during the attempted transformation of the cis-cis compound to the cis-trans compound.



It was therefore decided to isomerize 125 to 144 before introducing the hydroxyl group.



Epimerization of 125 to 144 was achieved in the same way as in the isobutyl series. Bromination (HBr, Br_2, 0°, $CHCl_3$), dehydrobromination (semicarbazide, acetic acid, pyruvic acid, H_2O) and reduction (Li/NH_3) yielded 144. This compound shows olefinic absorption in the infrared (3070, 1645 and 895 cm^{-1}), a ketonic carbonyl (1717 cm^{-1}) and no "Bohlmann" bands. The mass spectrum confirms its molecular weight and shows the expected base peak at m/e 192. This compound is identical with the hydrolysis product of the minor Grignard product which has been assigned structure 119.

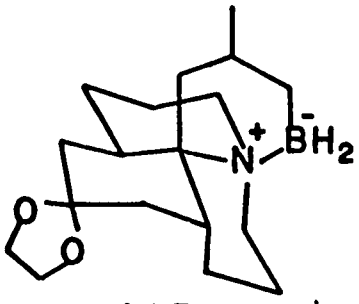


The product of epimerization, 144, was converted to the ethylene ketal derivative 119 in order to carry out a hydroboration reaction. Refluxing 144 in benzene with p-toluenesulfonic acid and ethylene glycol for 24 hours yielded a crystalline material which from its analytical and spectral properties was assigned structure 119. It is identical with the minor product occasionally obtained

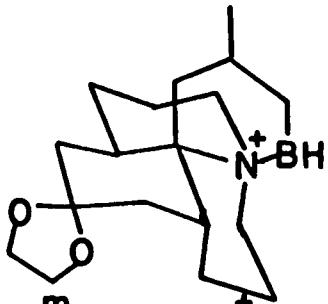
directly from the Grignard reaction.

Treatment of 119 with diborane in THF followed by the addition of ice, 3N NaOH and 30% H_2O_2 yielded four products. The least polar (t.l.c.) of these was a crystalline solid which shows B-H stretching in the infrared spectrum Figure 12, (2350 cm^{-1}). The n.m.r. spectrum indicates the presence of the ethylene ketal function (τ6.12, apparent triplet, 4H). The mass spectrum shows peaks at m/e 305 (parent), m/e 304 (base, M^+-1) and m/e 236 (M^+-69). The exact mass of the peak at m/e 305 is 305.2526, corresponding to $C_{18}H_{32}NO_2{}^{11}B$ while the m/e 304 peak is 304.2448 corresponding to $C_{18}H_{31}NO_2{}^{11}B$. On the basis of the evidence presented and due to its method of preparation the compound was assigned structure 145. The presence of the base peak in the mass spectrum (M^+-1)[77] and the fact that the compound is not reduced by propionic acid[78] is in agreement with this structure. Since monoalkylboranes of this type have been found to show infrared absorption between 2500 and 2600 cm^{-1}, while the same compounds, when complexed with tri-alkylamines absorb in the region 2200-2400 cm^{-1}, compound 145 (i.r. 2350 cm^{-1}) most likely exists in the cyclic form.

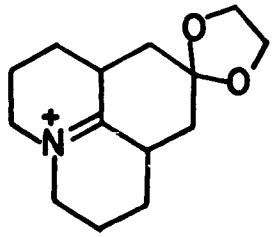
The next two compounds were the diasteriomeric alcohols 146. The spectral characteristics were in agreement with the assigned structures. Of interest is the -O-H stretching



145

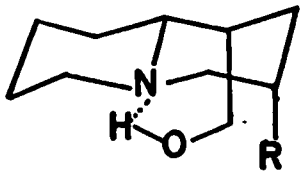


m/e 304 ($M^+ - 1$)



m/e 236

band which in this case appears at 3140 cm^{-1} and is extremely broad, Figure 13. This has been observed in other compounds (e.g., 147)[27] in which hydrogen bonding between an amine and an alcohol results in a cyclic structure.



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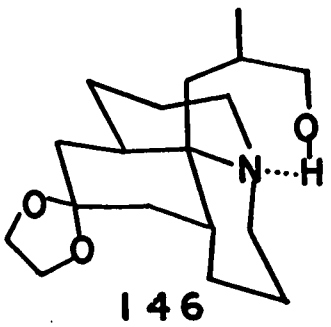
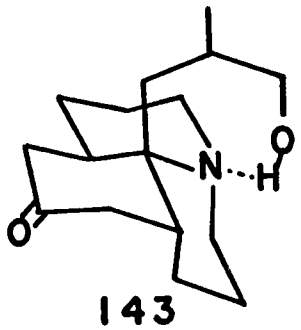


146



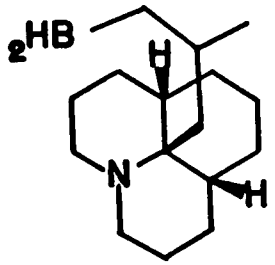
143

The fourth compound obtained in the hydroboration reaction was not identified. Its infrared spectrum shows no O-H absorption and no "Bohlmann" bands. The n.m.r. does show the presence of the ethylene ketal. The mass spectrum shows peaks at m/e 394, 393, 236 (base peak), 174 and 146. When hydrolyzed in dilute acid, a solid is obtained which now shows a carbonyl group in the i.r.,

(1710 cm^{-1}) and the mass spectrum has peaks up to m/e 360 (M.S.2) while the mass spectrum (MS9, direct probe) shows peaks up to m/e 829. This data was not sufficient to assign a structure to "X".

Oxidation of compound 145 was achieved with difficulty. When 145 was heated overnight at 70° with 30% hydrogen peroxide and 3N NaOH in dioxane some starting material was recovered in addition to some of the alcohols 146 and compound "X".

It is interesting to note that a similar type of boron containing compound had been obtained by treatment of 11-methallyl-cis-cis-hexahydrojulolidine (102) with diborane in THF followed by the addition of 3N NaOH and 30% H_2O_2. Two substances which could easily be separated were obtained. The least polar (t.l.c.) of these was a solid which shows B-H stretching bands (2340 and 2270 cm^{-1}). The molecular weight was determined by osmometry and found to be 243. The mass spectrum shows the parent peak at m/e 247 and the base peak at m/e 246. The exact mass of fragment 246 was 246.2394 which corresponds to $C_{16}H_{29}N^{11}B$. On this basis the compound was assigned structure 148. Because it shows no "Bohlmann" bands in its infrared spectrum and shows B-H stretching bands as low as 2340 and 2270 cm^{-1},[79] it most likely exists in the cyclic form 149. The other product of hydroboration was the expected alcohol 150.



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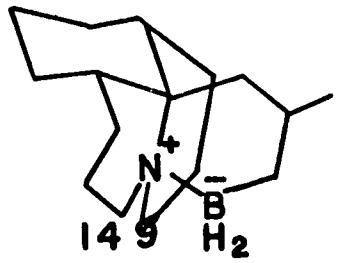

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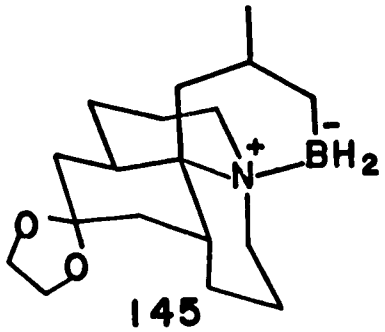
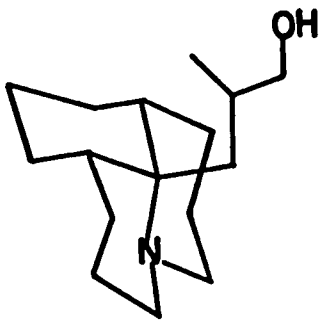
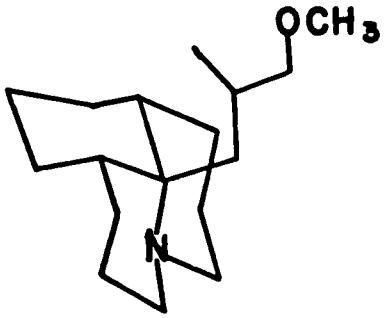


145

In contrast to compound 145, which does not appear to be strained, compound 149 oxidizes readily in 3N NaOH, 30% H_2O_2 and dioxane at room temperature. Alcohol 150 is the only product. This alcohol is also produced when compound 151, obtained by W.R. Bowman,[66] is treated with BBr_3.



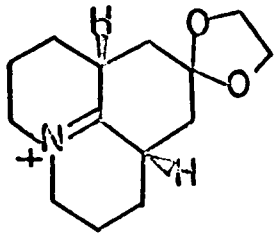
150



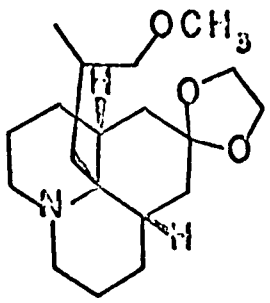
151

While this work was being carried out a more suitable method of preparing 143 was developed.[66] This involved the reaction of the Grignard reagent from 1-chloro-3-methoxy-2-methylpropane with the immonium salt 69. Epimerization of the Grignard product 70 to 71 and cleavage of the ether

function in 71 using BBr_3 led to 142 in reasonable yield. This route was the one which eventually led to lycopodine (2)[42] (see Introduction).



69



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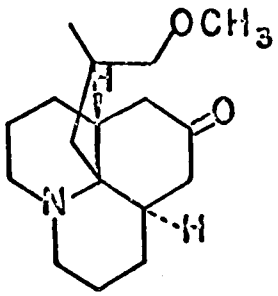
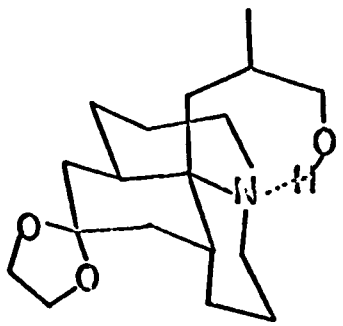


71

At this stage we decided to explore a route to these alkaloids involving the side chain aldehyde 152. Simultaneously other workers were investigating the internal alkylation sequence previously discussed. The simplest approach was to oxidize compound 146 to the corresponding aldehyde 153 which on hydrolysis would yield keto-aldehyde 152. An internal aldol condensation could then form the fourth ring as in 154. The expected product from such an



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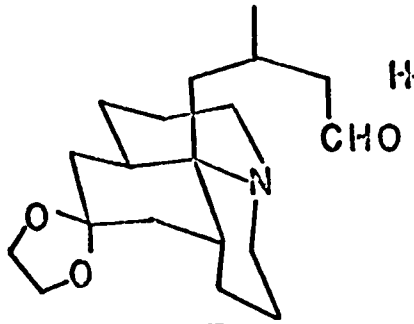

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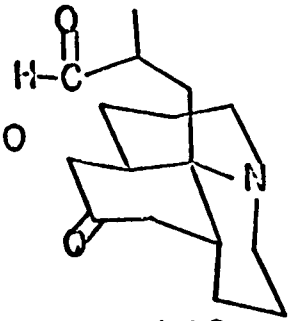

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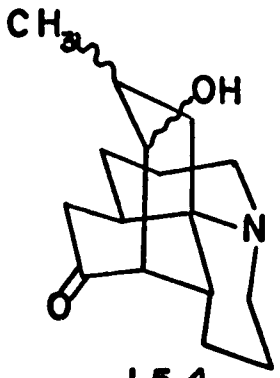

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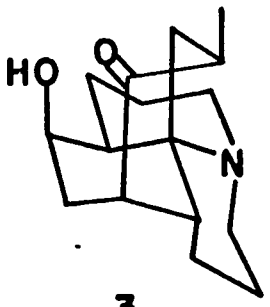
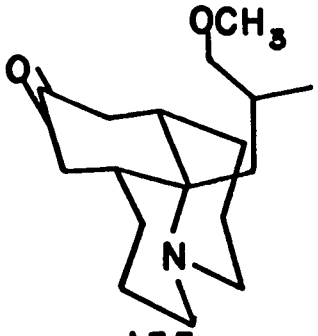


3

aldol condensation would be oxygenated at C_8. This would then be closely related to the alkaloid annofoline (3).

An examination of this scheme indicated that there might be advantages over the scheme used in the synthesis of lycopodine (2) itself.[66] Five of the main intermediates obtained in this synthesis are shown in Chart III.

Chart III



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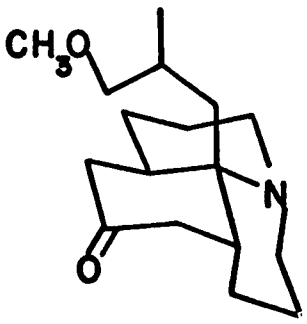
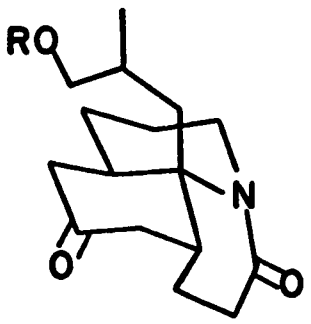
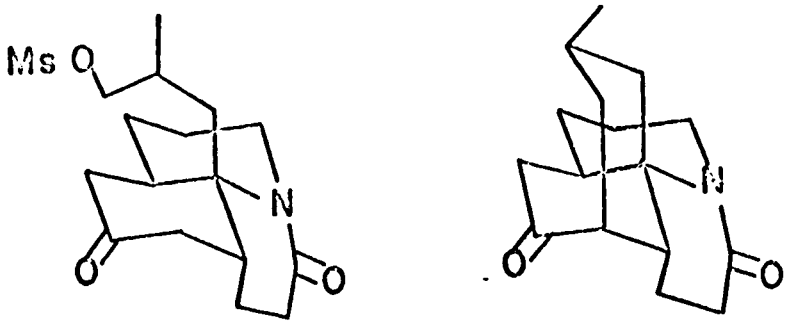


156



157

Chart III (con't)

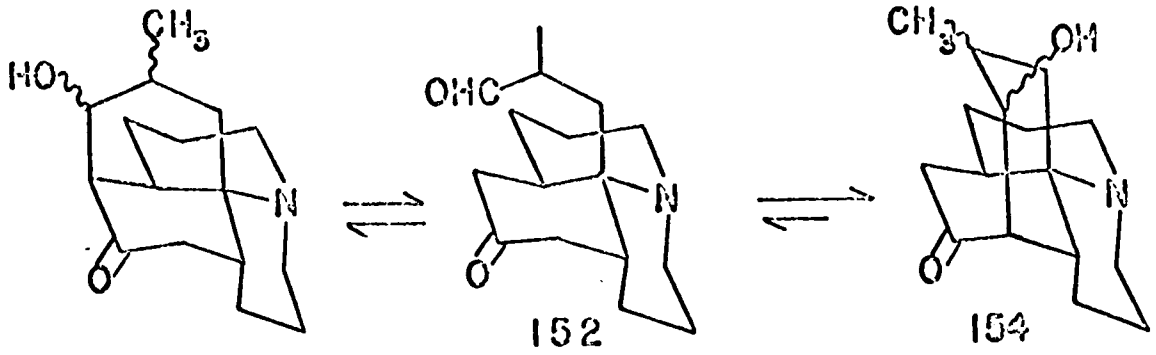


158 159

In converting compound 155 to compound 156 the symmetry of the molecule is lost so that 156 represents a diasteriomeric pair of compounds. One diasteriomer led to lycopodine (2) while the other yielded an epimer of lycopodine. The diasteriomers had to be separated as the alcohols, one of which then could not be utulize for the synthesis of lycopodine (2) itself. It had also been shown that attempts to change the methoxyl group in 156 to a better leaving group led to ring closure on nitrogen. To avoid this the nitrogen had to be protected in the form of the lactam 157. The ring closure of 158 to 159 was also of some concern in that closure could occur in two positions. Since the process is presumably kinetically controlled, it would be impossible to manipulate the proper ring closure.

Aldol condensation of 152 would avoid these problems. The nitrogen need not be protected, the asymmetric center could easily be equilibrated before ring closure or after by oxidation of the aldol product 154 and thermodynamic

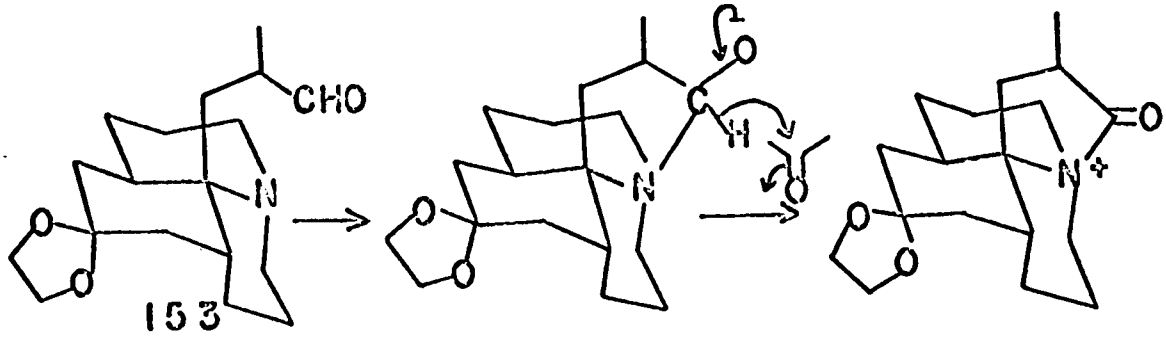
control should favour ring closure in the desired direction in that fewer interactions are present in this isomer.



The problem, at this point, involved finding a suitable way of oxidizing the cis-trans-ethylene ketal-alcohol 146 to the corresponding aldehyde 153. The oxidation of primary alcohols to aldehydes has been found to be rather difficult,[80] especially when the molecule being oxidized contains acid-labile protecting groups. The compound that we wished to oxidize not only contained an acid-labile ethylene ketal but also a tertiary nitrogen. This meant that the oxidation had to be carried out in a neutral or basic medium. A suitable method for the oxidation of nitrogen-containing alcohols in a basic medium is the modified Oppenauer oxidation developed by Warnhoff.[81] This involves reacting the alcohol in benzene with potassium tert-butoxide and using 9-fluorenone as the hydride acceptor. This method was used to oxidize

11-[3-hydroxy-2-methyl-1-propyl]-cis-cis-hexahydrojulolidine (150) to the corresponding aldehyde. The aldehyde which was obtained in 65% yield after purification shows all the spectral features of the expected aldehyde (i.r., 2700 cm^{-1}; 1730 cm^{-1}; n.m.r., τ0.61, doublet, J = 3 cps, 1H, CH-CHO).

A similar reaction carried out on the cis-trans ethylene ketal-alcohol 146 led only to the recovery of 25% of the starting material. Several other attempts yielded even less starting material. This was rather unexpected in that normally the Oppenauer oxidation does not proceed past the aldehyde stage. However, because of the participation of the nitrogen in the hydroboration step and because of the unusual -OH bonding in that product (3140 cm^{-1}) it was felt that the nitrogen might be involved in the further oxidation of the aldehyde as shown in Scheme XIII

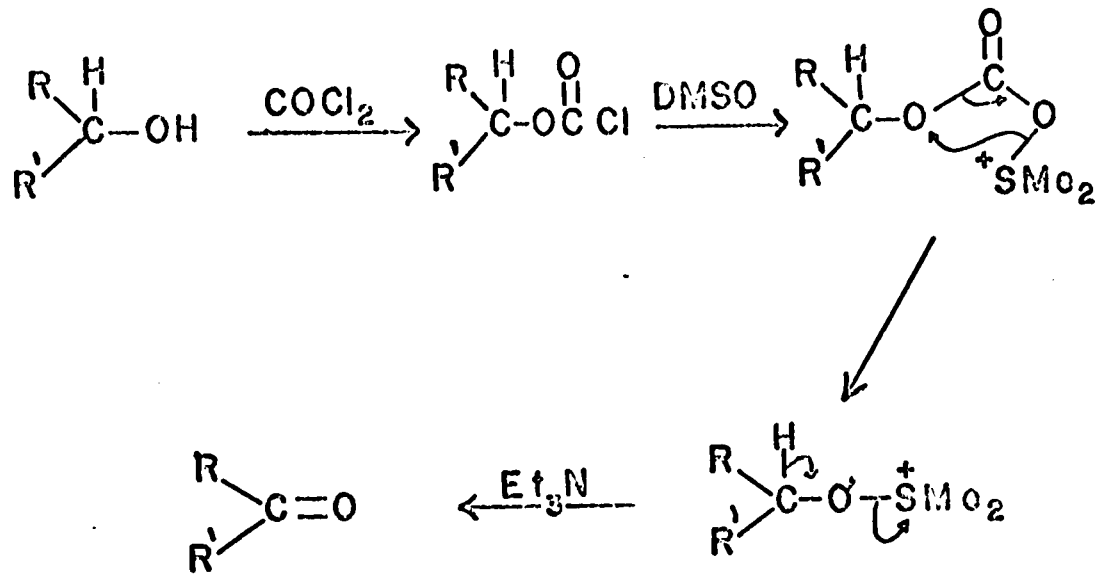


Scheme XIII

In the hope that aluminum triisopropoxide might tie up the lone pair of electrons on nitrogen by complexing, an Oppenauer oxidation using freshly prepared aluminum triisopropoxide[82] and cyclohexanone in refluxing toluene[83] was carried out. The crude product obtained from this reaction did not show an aldehyde proton in the n.m.r.

Oxidation using chromium trioxide and pyridine (Sarett reagent) either gave back starting material or yielded intractable material.

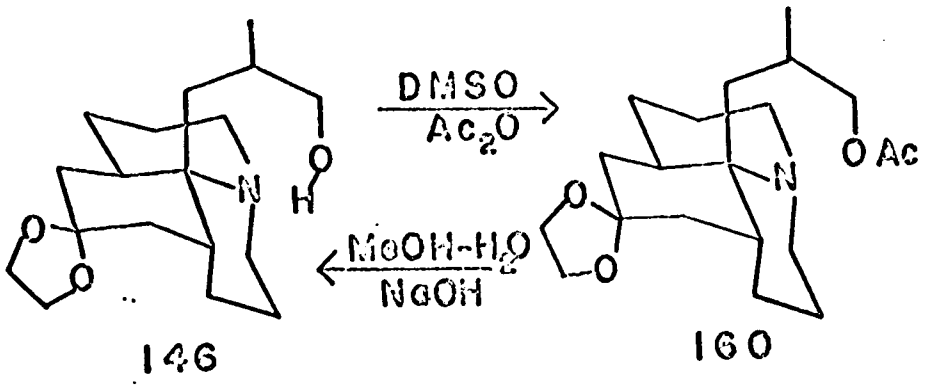
The Barton method of oxidation[84] was attempted next. This reaction requires the formation of the chloroformate from the alcohol which is then reacted with dimethylsulfoxide. The dimethylsulfoxonium salt, which is obtained after rearrangement, is converted to the aldehyde or ketone by the addition of a slight excess of triethylamine. The outline of the reaction is shown in Scheme XIV. Using this method, the recovery of basic product amounted to as much as 35%. The crude product usually showed a carbonyl (1730 cm^{-1}) in the infrared spectrum although the relative absorbance varied greatly. The less polar components (two) show infrared absorptions at 2800 (broad, weak), 2700 (broad, weak) and 1735 cm^{-1}, Figure 14. "Bohlmann" bands are not observed in the infrared spectrum. The n.m.r. does show



Scheme XIV

a signal at τ0.25 (doublet, J = 1.5 cps) and one at τ6.38 (singlet) but the ratios of these peaks is 1:5.5 instead of the required 1:4. The yield of what is believed to be the desired aldehyde did not exceed 5%, and could not be improved even after considerable experimentation.

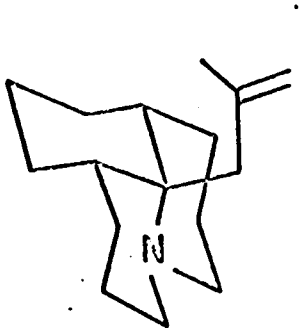
Oxidation using dimethylsulfoxide and acetic anhydride[85] was next attempted. This reaction gave a product (50%) which appeared to be made up of the diasteriomeric acetates 160 of the starting alcohols (i.r. 1735 and 1230 cm^{-1}, mass spectrum M^+ at m/e 351). This was confirmed when the product was hydrolyzed in aqueous NaOH-methanol to give the starting alcohols 146.



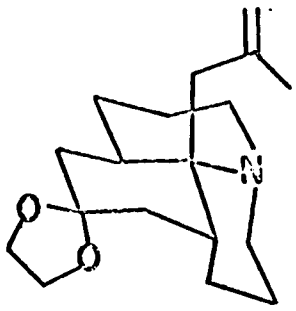
146 160

Dicyclohexylcarbodiimide and dimethylsulfoxide[86] have been found to be useful in the oxidation of alcohols, especially oxidations in which a virtually neutral medium is required. Two variants of this reaction[87,88] were attempted. Essentially no basic material was recovered when alcohols 146 were caused to react with dimethylsulfoxide (excess), dicylohexylcarbodiimide (3 equivalents), pyridine (3 equivalents) and trifluoroacetic acid (1.5 equivalents) in benzene at room temperature for 9 hours. A similar reaction using dimethylsulfoxide, dicyclohexylcarbodiimide and phosphoric acid led to a low recovery of basic materials. These products usually included what was thought to be unchanged starting material (t.l.c., O-H bonding in the i.r.). No separation could be accomplished. On one occasion a product was isolated which showed the characteristics of an aldehyde (i.r. 2700, 1735 cm^{-1}). Hydrolysis of this substance failed to alter its infrared spectrum. Careful examination of this

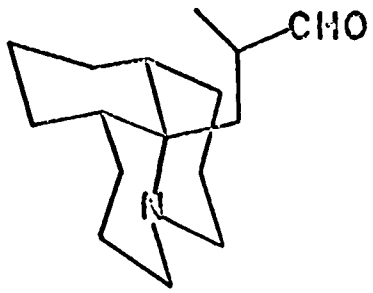
product showed it to be identical with 11-[2-methyl-3-oxo-1-propyl]-cis-cis-hexahydrojulolidine (161). Examination of the sample of 119 used in this case showed that 11-methallyl-cis-cis-hexahydrojulolidine (102) had been present as an impurity before the hydroboration step.



102

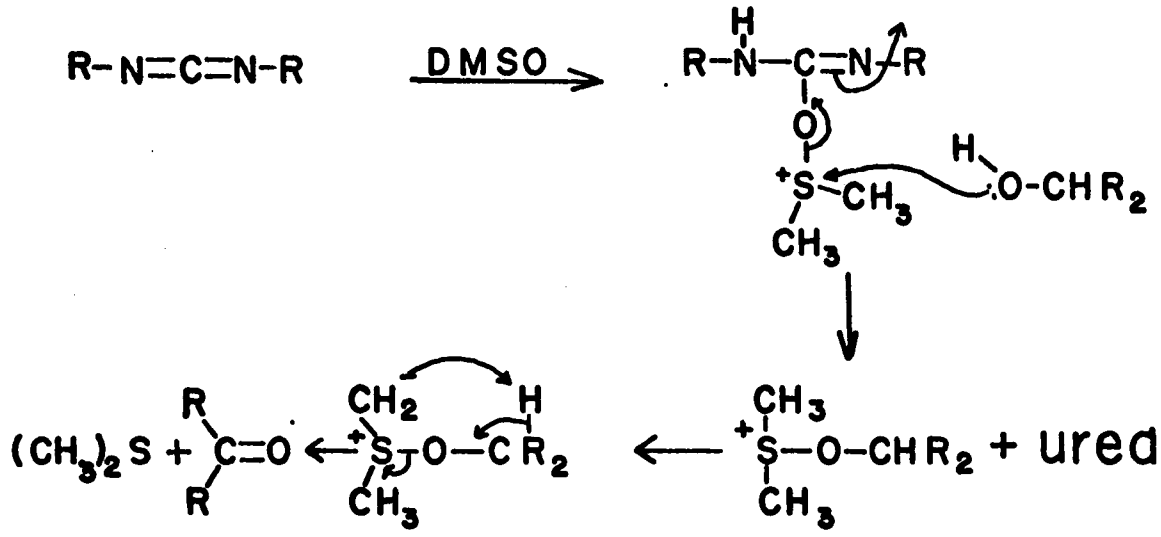


119

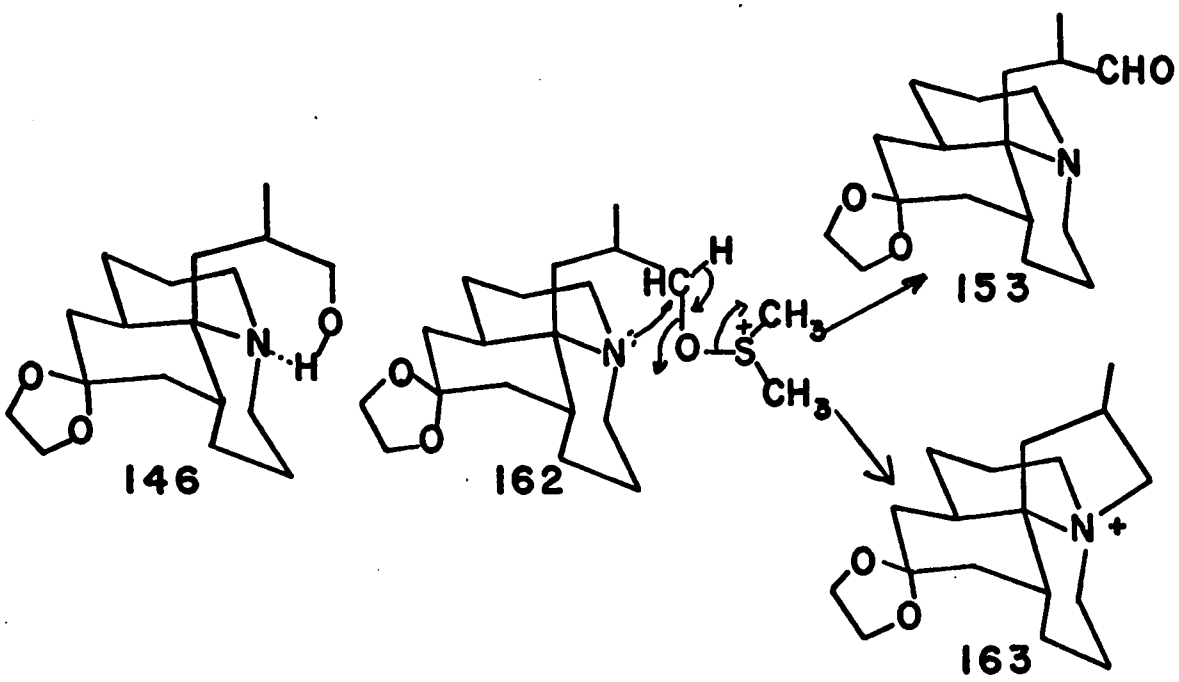


161

This result quite clearly indicates that in the Moffatt oxidations[87,88], the cis-trans alcohol is lost while the cis-cis system behaves normally. The loss of the cis-trans material may be explained on the basis of the mechanism of the dicyclohexylcarbodiimide-dimethylsulfoxide oxidation,[86] Scheme XV. Alcohols 146, when converted to the dimethylsulfoxonium salt 162 can react in two ways. Removal of an α-hydrogen and elimination of dimethylsulfoxide would lead to the desired aldehyde 153 while displacement of dimethylsulfoxide by the nitrogen lone pair of electrons would lead to the quaternary salt. 163. Since compounds similar to 146 had been found to cyclize on nitrogen when the alcohol function was changed to a good leaving group (e.g., tosylate[66]), it is not


R-N=C=N-R
DMSO
R-N-C=N-R
H
O
+S
CH3
CH3
H
O-CHR2
(CH3)2S + C=O
R
R
CH2
H
+S
O-CR2
CH3
+S-O-CHR2 + ured
CH3
CH3

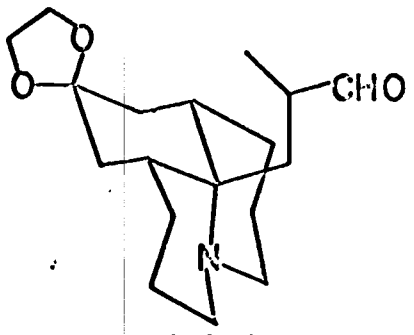
Scheme XV


CHO
N
O
O
153
146
N
H
O
O
162
HC
H
N
O
+S
CH3
CH3
N+
O
O
163

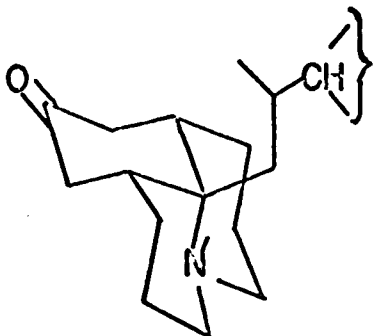
unwarranted to assume that the same is happening in this case.

The lead tetraacetate-pyridine oxidation[89] was also attempted. The products obtained corresponded to the acetates previously isolated in the dimethylsulfoxide-acetic anhydride oxidation. In addition, some starting material was recovered.

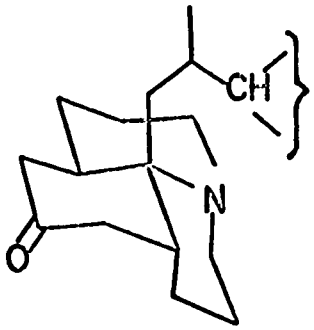
Since all attempts at oxidation of 146 were fruitless, it was decided to carry out the oxidation before epimerization. This would involve formation of the aldehyde 164 which would then have to be selectively protected in order to carry out the epimerization from a cis-cis system 165 to a cis-trans one 166.



164

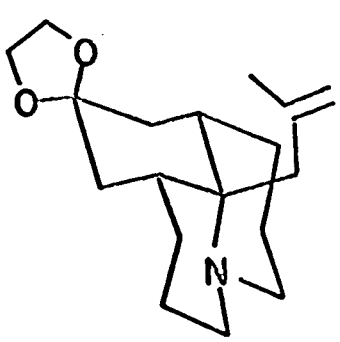


165



166

The preparation of aldehyde 164 proceeded smoothly. Treatment of 115 with diborane in THF followed by the addition of 3N NaOH and 30% H_2O_2 afforded the known alcohol 167[66] in 95% yield. Oxidation using the Warnhoff modification of the Oppenauer method gave aldehyde 164 in 81% yield. The alcohol 167 shows O-H stretching in the



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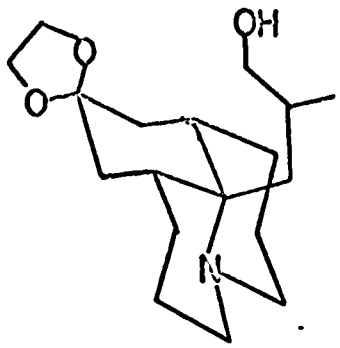
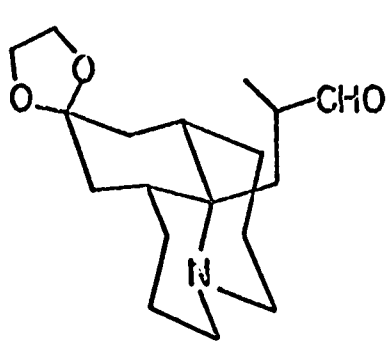


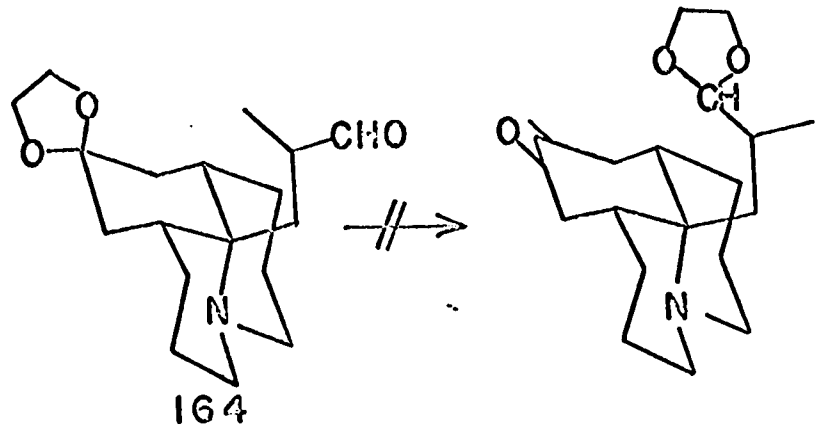
167



164

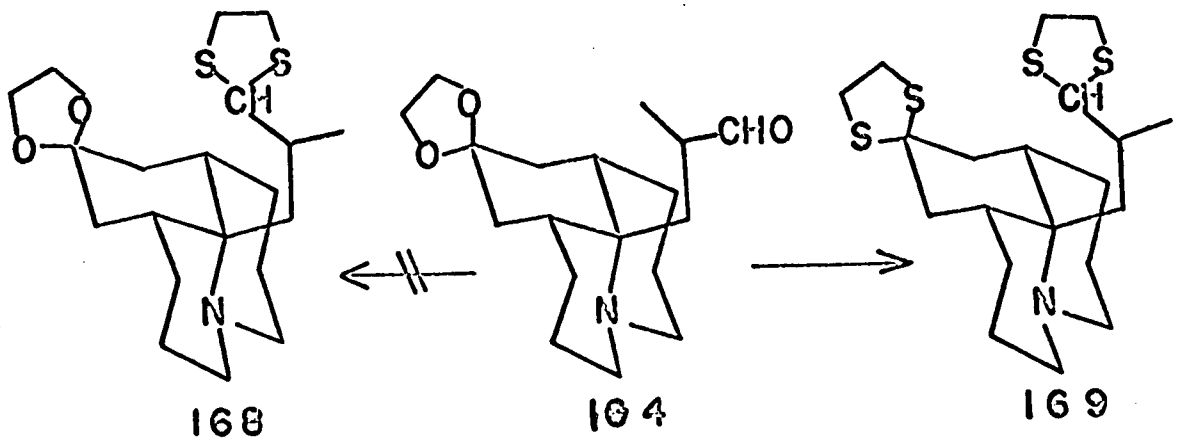
infrared spectrum at 3620 and 3480 cm^{-1}. The infrared spectrum of the aldehyde 164 shows "Bohlmann" bands and aldehyde absorption at 2700 and 1735 cm^{-1}. The aldehydic proton is found at τ0.37 (doublet, J = 2 cps) in the n.m.r. The mass spectrum shows the required parent peak (m/e 307) and the base peak is as expected (m/e 236).

Attempted ketal-aldehyde to ketone-acetal exchanges[90] failed to yield a single product. Heating 164 with p-toluenesulfonic acid in benzene gave a mixture of products which by mass spectrometry seemed to include all the four possible combinations, keto-aldehyde, keto-acetal, ketal-aldehyde and ketal-acetal. Attempted separations failed.



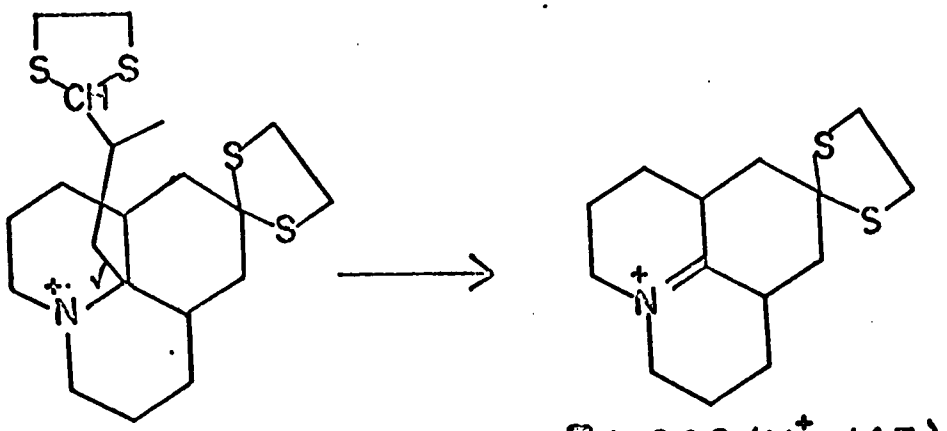
164

A selective preparation of the ethylene ketal-ethylene thioacetal 168 seemed to offer good potential.[91,92] The treatment of aldehyde 164 with 1 equivalent of ethanedithiol in dry benzene with HCl as a catalyst gave a mixture of compounds. The use of two equivalents of ethanedithiol resulted in the formation of the ethylene thioacetal-ethylene thioketal 169.

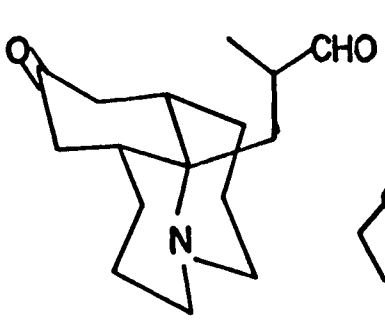


168 164 169

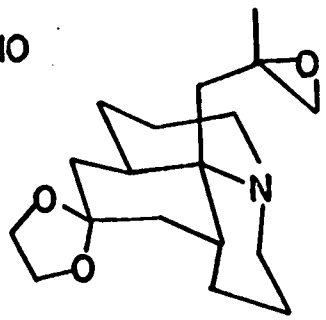
Compound 169 was identified by means of its i.r. (no carbonyl absorption), n.m.r (τ5.28, doublet, J = 4.5 cps, $CH\overset{S}{\underset{S}{}}$; τ6.72, singlet, 4H and τ6.78, singlet 4H); and mass spectrum (M^+ at m/e 415 corresponds to the required $C_{20}H_{33}S_4N$, base peak m/e 268).



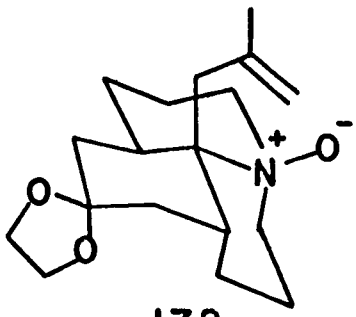
The ethylenedioxy-aldehyde 164 was converted to the keto-aldehyde 170. Attempts at selective formation of the ethylene acetal failed. Since the type of selectivity required could not be achieved, attention was again focussed on the cis-trans series of compounds. The formation of an epoxide[93] in the side chain was considered worthwhile in that it could possibly act in the sense of a leaving group and could also be made to undergo an acid-catalyzed rearrangement to the carbonyl compound, in this case to the desired aldehyde. Preparation of epoxide 171 was investigated. Treatment of 9-ethylenedioxy-11-methallyl-cis-trans-hexahydrojulolidine (119) with m-chloroperbenzoic acid yielded an intractable gum. The same reaction, using p-nitroperbenzoic acid[95] yielded the N-oxide 172.



170



171

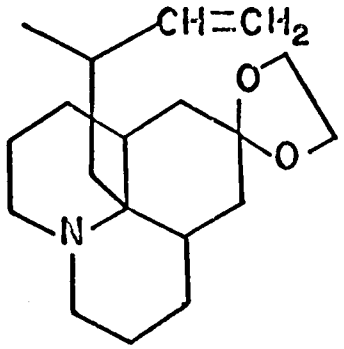


172

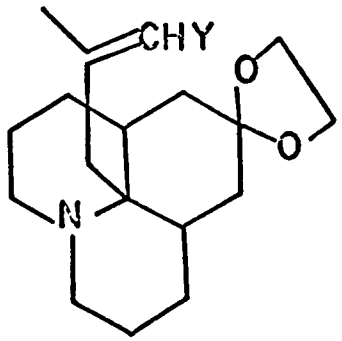
The scheme leading to C_8 oxygenated lycopodine derivatives depended mainly on the availability of keto-aldehyde 152. Direct oxidation of alcohols 146 to the ethylene ketal-aldehyde 153 was not successful. Attempts to convert a cis-cis-julolidine derivative having a suitable oxidized carbon in the side chain to the cis-trans-system had to be abandoned due to our inability to protect the oxidized carbon in the side chain. Finally, the formation of epoxide 171 which would have the necessary function for the required synthesis was also unsuccessful.

One of the objects of this approach was to circumvent the need for protection of the nitrogen atom in the molecule. It appears however, that the nitrogen does participate in the attempted oxidation of the alcohol to the aldehyde. Since the aldehyde 152 still represents an attractive intermediate for the synthesis of the 8-oxygenated Lycopodium alkaloids, it is interesting to consider alternate modes for its preparation. The

addition of a side chain which already contains C_8 at the required oxidation level seems to be an attractive possibility. The addition of the Grignard reagent from 3-methyl-4-halo-1-butene to give 173 is a possibility. Cleavage of the double bond would lead to the desired aldehyde. The side chain involved here should behave like the methallyl side chain which did not interfere in the epimerization of the cis-cis to the cis-trans system. Another possibility is a compound of type 174, where Y is a group such as alkoxyl or halogen. Since this group must be stable to gentle acid hydrolysis (i.e., less susceptible to hydrolysis than the ethylene ketal group) the enol ether does not seem appropriate. The vinyl halide (174, Y = halogen) seems a more attractive possibility, although it may suffer from the fact that it does not hydrolyze readily enough. The Grignard reaction of 1,3-dichloro-2-methyl-1-propene with the immonium salt 121 is currently under investigation in these laboratories.



173



174

EXPERIMENTAL: GENERAL

Special Instruments and Services

Most of the i.r., u.v., n.m.r. and mass spectral data were obtained by the technical services personnel of this Department.

Nuclear magnetic resonance spectra were measured using a Varian Associates Model A-60 spectrometer or a Varian Associates Model HR-100 spectrometer with tetramethylsilane as an internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 421 dual grating infrared spectrophotometer, on a Perkin-Elmer Model 337 grating infrared spectrophotometer or on a Perkin-Elmer Model 700 infrared spectrophotometer. Ultraviolet spectra were recorded on a Perkin-Elmer Model 202 Ultraviolet-Visible Spectrophotometer. Mass spectra were recorded on an A.E.I. Model MS-2H or on an A.E.I. Model MS-9.

Melting points were determined on a Fisher-Johns melting point apparatus and on a Microscope Heating Stage 350 by Leitz and are uncorrected.

Microanalyses are by F. Pascher, Bonn, Germany; C. Daesle, Montreal, Canada; Schwarzkopf Microanalytical Laboratory, Woodside, New York, U.S.A. and Mrs. D. Mahlow of this Department.

Alumina used for chromatography was "Aluminium Oxide for Chromatographic Adsorption Analysis" supplied by The British Drug Houses Ltd., (BDH) unless otherwise stated. CAMAG Aluminium Oxide was used for thin-layer chromatography.

Skelly B refers to Skelly Oil Company light petroleum b.p. 62-70°.

SECTION V. EXPERIMENTAL:L.9

Deacetylfawcettiine

Fawcettiine (440 mg, 1.43 mmole) was dissolved in methanol (50 ml) to which was added 1:1 methanol:5N NaOH (35 ml). After 19 hours, the mixture was diluted with water, basified with dilute ammonium hydroxide and extracted with chloroform (3 x 25 ml). The chloroform extracts were combined, dried ($MgSO_4$) and evaporated. 355 mg of white solid (m.p. 206° dec) was obtained. The infrared spectrum (nujol) shows no absorption between 2800 and 1460 cm^{-1}. Hydrogen bonded OH absorption appears at 3450 cm^{-1}. The product was homogeneous by t.l.c.

Anhydroisofawcettiine

Deacetylfawcettiine (200 mg, 0.75 mmole), recrystallized from acetone, was dissolved in pyridine (15 ml) and acetic anhydride (15 ml). The reaction mixture was left standing at 0°C for 24 hours. Removal of the pyridine and acetic anhydride left 300 mg of dark gum. This gum was not characterized but did appear homogeneous by t.l.c.

The crude material was dissolved in benzene (25 ml) and thionyl chloride (1 ml) was added. After four hours at room temperature the solution was evaporated to dryness. The residue was taken up in water (20 ml), basified with

ammonium hydroxide and the alkaline solution extracted with chloroform (3 x 25 ml). The chloroform extracts were combined, dried ($MgSO_4$) and evaporated. The oil which remained was filtered through alumina (Woelm, Grade 1, 6 g). 201 mg (93%) of light coloured oil was recovered. The oil was shown by t.l.c. to be homogeneous. The infrared spectrum (CCl_4) shows absorption at 1725 and 1230 cm^{-1}. The n.m.r. ($CDCl_3$) shows a broad singlet at τ4.55 (1H), a quartet at τ5.45 (1H, J = 12cps, J = 5 cps) and a singlet at 7.97 (3H) and a doublet (J = 7 cps) at τ9.1 (3H). The mass spectrum shows a parent peak at m/e 289 and the base peak at m/e 174. Other prominent peaks appear at m/e 230, 229, 204 and 146.

The methiodide prepared in methanol and recrystallized from acetone-ether has a m.p. 256-258°.

Base K

Fawcettiine (228 mg, 0.74 mmole) was dissolved in pyridine (20 ml) and acetic anhydride (20 ml). The solution was kept at room temperature for 24 hours. The solvent was removed and the residue was filtered through alumina. (Woelm, Grade I, 10 g). 179 mg (70%) of homogeneous material was obtained. This crystallized and shows m.p. 116-117°. The infrared spectrum (nujol) shows absorption at 1725 cm^{-1} and a doublet at 1240 cm^{-1}. This is in agreement with the values obtained by Burnell.[48]

O-Acetyllofoline

Lofoline (0.22 g, 0.72 mmole) was dissolved in 1:1 acetic anhydride-pyridine (30 ml) and the solution was kept at room temperature for 48 hours. After removal of the solvent, the oily residue was dissolved in chloroform and filtered through alumina (8 g). Evaporation of the solvent left a colourless viscous oil (0.22 g, 87%) which showed a single spot on t.l.c. A sample was purified by evaporative distillation under reduced pressure.

Calcd. for $C_{20}H_{31}O_4N$: molecular weight, 349. Found: molecular weight (mass spectrometry) 349. The infrared spectrum ($CHCl_3$) shows absorption at 1720-1730, and 1225 cm^{-1}. The nuclear magnetic resonance spectrum (CCl_4) shows signals at τ4.92 (1H, triplet, C<u>H</u>OAc), τ5.25 (1H, mult., C<u>H</u>OAc), τ7.96 and τ8.02 (6H, two OCOC<u>H</u>$_3$) and at τ9.12 (3H, doublet, CHC<u>H</u>$_3$).

A sample of the base in acetone was converted to the perchlorate by the addition of perchloric acid. After recrystallization from acetone-ether, the salt melts at 272-273° (dec). The infrared spectrum (nujol) shows bands at 3040, 1737, 1722, and 1235 cm^{-1}. The mass spectrum shows a parent peak at m/e 349 and the base peak at m/e 174. Other important peaks are found at m/e 290, 234 and 146.

Anal. Calcd. for $C_{20}H_{31}O_4N \cdot HClO_4$: C, 53.40; H, 7.17; N, 3.11%. Found: C, 53.30; H. 7.06; N, 2.95%.

Chromatography of L-9

L-9 (105 mg) was chromatographed on alumina (Woelm, Grade I. 4 g). Elution with Skelly B-benzene (1:1, 500 ml) yielded 38 mg of lycopodine, as identified by infrared spectroscopy and t.l.c. A mixed fraction (10 mg) was obtained on elution with benzene (75 ml). Elution with benzene-ether (1:1, 125 ml) afforded 54 mg of O-acetyllofoline identified by infrared spectroscopy and t.l.c.

L.9

(a) A sample supplied by Dr. R.H. Manske melted at 121-122°. The infrared spectrum (nujol) shows absorption at 1735, 1725, 1698, 1250 and 1230 cm^{-1}. The mass spectrum shows peaks at m/e 349, 290, 289, 247, 234, 190, 174, 162 and 134.

A hydroperchlorate was also supplied. Samples of this derivative melts at 260-265°.

(b) O-Acetyllofoline (84 mg) and lycopodine (60 mg) were dissolved in a minimum volume of hot hexane. On cooling, colourless crystals (110 mg), m.p. 121-122°, separated. The same melting point was obtained after recrystallizations from either hexane or anhydrous ether. The material was identical by mixed melting point, infrared spectrum and t.l.c. behavior with an authentic sample of alkaloid L.9.

SECTION V. EXPERIMENTAL: THE MODEL COMPOUNDS

Preparation of Julolidine

1,2,3,4-Tetrahydroquinoline (66.5 g, 0.5 mole) was dissolved in 1-bromo-3-chloropropane (400 g). The solution was refluxed for 20 hours. Concentrated HCl (60 ml) and water (600 ml) were added and the excess 1-bromo-3-chloropropane was removed by steam distillation. The residue was basified with 40% NaOH (125 ml) and extracted with two portions of ether (125 ml each). The ether extracts were combined, washed with 150 ml of water and dried with NaOH pellets. The ether was evaporated and the residue distilled under vacuum. b.p. 125-130° at 3 mm; yield 70.5 g, (82%) of colourless viscous oil. The infrared spectrum (CCl_4) shows prominent bands at 3080, 3040, 3020, 2940-2780, 1590, 1485, 1455, 795, 740, 725 cm^{-1}. The n.m.r. spectrum (CCl_4) shows signals at τ8.07 (quintet), τ7.28 (triplet), τ6.93 (triplet) and at τ3.52 (multiplet). These signals were in a ratio of 4:4:4:3.

Reduction of Julolidine

Julolidine (32.8 g, 0.19 mole) was dissolved in n-propylamine (300 ml). Lithium (13.88 g, 2 mole) was added and the mixture was stirred for 12 hours. The excess lithium was removed and the n-propylamine was removed by distillation. The crude residue was covered with ether and solid ammonium chloride was added in small portions. When most of the solid had disappeared, water (100 ml)

was added cautiously. The layers were separated and the water layer was extracted 4 times with ether. The ether layers were combined and 1:1 70% $HClO_4$:EtOH was added until the solution was acid to Congo Red indicator paper. The solid mass was cooled and filtered. The precipitate was then recrystallized twice from 95% ethanol.

Yield 25.1 g, 45%, m.p. 280 (dec). The infrared spectrum ($CHCl_3$ and nujol) shows absorption at 2950, 2870, 1665, 1080 cm^{-1}.

Anal. Calcd. for $C_{12}H_{20}NO_4Cl$: C, 51.98, H, 7.22 N, 5.05. Found: C, 52.26, 52.31; H, 7.06, 7.09; N, 5.19%.

7a, 8,9,10,10a-Tetrahydrojulolidinium perchlorate (447 mg. 1.5 mmole) was dissolved in water which was then basified using conc. ammonium hydroxide. The basic mixture was extracted 3 times with ether. The ether extracts were combined, dried ($MgSO_4$) and concentrated. The residue was distilled at 110°-112°/4mm. 200 mg (70% yield) of colourless oil was obtained. The infrared spectrum (CCl_4) shows absorption at 2930, 2860, 2830, 2770, and 1640 cm^{-1}.

The n.m.r. (CCl_4) shows two broad signals at τ7.3 and τ8.2 with a relative intensity of 6:16 (required 5:14). The mass spectrum shows a parent peak at m/e 177 and the base peak at m/e 176. Other prominent peaks are found at m/e 149, 148, and 134.

Catalytic Reduction of 7a,8,9,10,10a-Tetrahydrojulolidinium perchlorate.

7a,8,9,10,10a-Tetrahydrojulolidinium perchlorate (1.030 g, 3.7 mmole) was dissolved in 95% ethanol (75 ml) and was hydrogenated at 1 atm using PtO_2 (100 mg) as catalyst. When the uptake of H_2 had ceased, the Pt was filtered off and the ethanol evaporated to 5-10 mls. Upon cooling crystals were formed. These were filtered off and washed with 1:1 petroleum ether:ether. 834 mg was obtained (81%) m.p. 255 (dec).

The infrared spectrum shows absorption at 3120 ($^{+}_{N}$-H) and 1100 cm^{-1}. The absorption band at 1665 cm^{-1} has disappeared.

Lithium Aluminum Hydride Reduction

7a,8,9,10,10a-Tetrahydrojulolidinium perchlorate (500 mg, 1.8 mmole) was added to a slurry of lithium aluminum hydride (140 mg, 3.6 mmole) in anhydrous ether (25 ml). The mixture was refluxed for 2 hours and was then left to stand overnight. The excess lithium aluminum hydride was destroyed using methanol. 40% NaOH was added and the resulting mixture was extracted three times with ether. The ether extracts were combined, dried ($MgSO_4$) and concentrated. 308 mg of oil was obtained (94%).

T.l.c. indicated the presence of two substances.

Lithium Aluminum Tri-tertiarybutoxyhydride Reduction

7a,8,9,10,10a-Tetrahydrojulolidinium perchlorate (500 mg, 1.8 mmole) was mixed with tetrahydrofuran (20 ml, distilled from LAH). To the slurry was added lithium aluminum tri-tertiarybutoxyhydride (843 mg, 3.92 mmole) in anhydrous ether (20 ml). The mixture was refluxed for 36 hours, after which it was cooled and dil. ammonium hydroxide was added. The precipitate was filtered off and the layers were separated. The aqueous layer was extracted three more times with ether. The organic layers were combined, dried ($MgSO_4$) and evaporated. 304 mg (93%) of oil was obtained. T.l.c. indicated the presence of two components.

The products showed identical t.l.c. behavior to the products obtained by lithium aluminum hydride reduction.

Separation of Hydride Reduction Products

The substances obtained by reduction of 7a,8,9,10,10a-tetrahydrojulolidinium perchlorate using lithium aluminum hydride and lithium aluminum tri-tertiary-butoxyhydride were combined and chromatographed on alumina. Elution with Skelly B (12 x 25 ml) and with 5% ether-Skelly B (4 x 25 ml) yielded 189 mg of oil which showed one spot on t.l.c. The infrared spectrum is identical with that

assigned to cis-cis-hexahydrojulolidine by Bohlmann.[55]

Elution with 50% ether-Skelly B (5 x 25 ml) and 75% ether-Skelly B (3 x 25 ml) yielded 122 mg of oil showing 2 spots on t.l.c.

Elution with 75% ether (2 x 25 ml), ether (4 x 25 ml) yielded 156 mg of oil which showed one spot on t.l.c. The infrared spectrum was identical with that assigned to trans-trans-hexahydrojulolidine by Bohlmann.[55]

Hexahydrojulolidine

Hexahydrojulolidinium perchlorate (356 mg, 1.3 mmole) was dissolved in water (5 ml). The solution was basified with conc. ammonium hydroxide and was extracted 3 times with a total of 15 ml of ether. The ether extracts were combined, dried ($MgSO_4$) and evaporated. 209 mg of oil remained (87%). The oil was distilled at 80°/1.2 mm.

The infrared spectrum ($CHCl_3$) shows absorption at 2930, 2810, 2780, 2690 cm^{-1}. The n.m.r. spectrum (CCl_4) shows two groups of hydrogen signals one centered at τ7.35 and the other stretching from τ7.9 to τ9.0. The relative intensity is about 1:10. The mass spectrum shows pertinent peaks at m/e 179 (parent), m/e 178 (base), and m/e 150.

Picrate Formation.

The picrate was prepared in ether and was recrystallized from ethanol, m.p. 225°dec. (reported m.p. 226°).[58]

Attempted Methiodide Formation

Hexahydrojulolidine (65.2 mg, 0.363 mmole) was dissolved in anhydrous ether. Methyl iodide (3 ml) was added and the solution was refluxed for 1 hour. The solvent was evaporated leaving 69 mg of oil. The infrared spectrum ($CHCl_3$) shows absorption at 3010 (CH_3I), 2800, 2760, 2680 (Bohlmann Bands) cm^{-1}.

Methallyl Grignard Addition

In a 500 ml, three-necked flask fitted with a ground-glass stirrer, reflux condenser, and addition funnel, was placed magnesium (0.63 g, 0.026 g-atom). The entire system was flamed out while it was being flushed with dry nitrogen. All subsequent operations were carried out under nitrogen.

The magnesium was covered with anhydrous ether (75 ml) and a solution of 3-chloro-2-methylpropene (2.34 g, 0.026 mole) in ether (25 ml) was added to the magnesium over 6 hours. The mixture was stirred and refluxed for an additional 8 hours.

7a,8,9,10,10a-Tetrahydrojulolidinium perchlorate (3.60 g, 0.013 mole) was added through a powder funnel. The mixture was stirred and refluxed for 6 hours. It was cooled and 50 ml of saturated aqueous ammonium chloride solution was added. The layers were separated and the ether layer was washed twice with 50 ml of water.

To the combined aqueous layers was added 50 ml of saturated sodium fluoride in water. The precipitate was centrifuged and the supernatant liquid was basified with 40% aqueous sodium hydroxide. The basic solution was then extracted with ether.

The combined ether layers were dried over $MgSO_4$. Removal of the ether afforded 2.48 g (81%) of oil which eventually crystallized. Continuous extraction of the aqueous layers yielded 112 mg of yellow oil.

The major product was homogeneous on t.l.c. and had a boiling point of 135°/1.5 mm. It could be recrystallized from ethanol, white plates, m.p. 54°. The infrared spectrum ($CHCl_3$) shows absorption at 3080, 2940, 2870, 2820, 2780, 2690, 1635, 900 cm^{-1}. The n.m.r. (CCl_4) shows a signal at τ5.17 (s, 1H), τ5.27 (s,1H), one at τ7.45, (s, 2H) and one at τ8.16 (s, 3H), The mass spectrum shows a small parent peak at m/e 233 and has a base peak at m/e 178. Other prominent peaks are at m/e 176, 150, 149, 148 and 134.

The perchlorate was formed in ether by the addition of 1:1 EtOH:70% $HClO_4$ to pH 3 and was recrystallized to 95% ethanol, m.p. 215-216. The infrared shows bands at 3125, 2930, 2860, 1633, 1100, 1055, and 915 cm^{-1}.

Anal. Calcd. for $C_{16}H_{28}NO_4Cl$; C, 57.66; H, 8.41; N, 4.31%
Found: C, 57.37, 57.51; H, 8.46, 8.31; N. 4.31%

The minor substance obtained by continuous extraction was more polar on t.l.c. and formed a perchlorate which melted with decomposition at 280°. The infrared spectrum was identical to that of the starting immonium salt.

Methiodide of 11-methallyl-cis-cis-hexahydrojulolidine

11-methallyl-cis-cis-hexahydrojulolidine (49 mg) was dissolved in anhydrous ether (15 ml) to which was added methyl iodide (.25 ml). The solution was refluxed for 1 hour after which time the solvent was pumped off. 47 mg of oil remained. This has an infrared spectrum identical to that of the starting material.

Similar attempts were made using ether as solvent and refluxing for three hours. This gave back starting material. One hour reflux in acetone also gave back starting material.

11-Methallyl-cis-cis-hexahydrojulolidine (32 mg) was dissolved in 10 ml of 95% ethanol to which was added .3 ml of methyl iodide. The solution was refluxed for 3 hours after which it was concentrated to 1 ml. The concentrated solution produced needle-like crystals on cooling (40 mg). m.p. 219-222°. The infrared spectrum (nujol) shows bands at 2920, 2850, 2795, 2740, 2720, 1642, and 918 cm^{-1}.

Allyl Grignard Addition

In a 500 ml, three-necked flask equipped with a ground-glass stirrer, reflux condenser and addition funnel was

placed magnesium metal (.63 gm, 0.026 g-atom). The entire system was flamed out while it was being flushed with dry nitrogen. All subsequent operations were carried out under nitrogen.

The magnesium was covered with 75 ml of anhydrous ether and a solution of allyl bromide (3.04 gm, 0.025 mole) in anhydrous ether (75 ml) was added to the magnesium. After 3 hours all the magnesium had disappeared and a white suspension was left behind.

7a,8,9,10,10a-Tetrahydrojulolidinium perchlorate (3.60 gm, 0.013 mole) was added through a powder funnel. The mixture was then stirred and refluxed overnight. The resulting solution was cooled and water (100 ml) was added. The suspension was continuously extracted with ether for 24 hours. The ether was then dried ($MgSO_4$) and evaporated. 2.00 gm of crystalline material was obtained, 70% yield. T.l.c. showed the presence of 1 component, m.p. recryst./EtOH 52.5°. The infrared spectrum ($CHCl_3$) shows absorption bands at 3070, 2920, 2860, 2810, 2770, 1630, 910 cm^{-1}. The n.m.r. (CCl_4) spectrum shows 3 olefinic protons.

The perchlorate was formed by the addition of 1:1 EtOH 70% $HClO_4$ to an ether solution of the product. This was recrystallized from ethanol, m.p. 240 (dec). The infrared spectrum shows bands at 3110, 2920, 2850, 1642, 1100, 1050 cm^{-1}.

Methiodide of 11-allyl-cis-cis-hexahydrojulolidine

11-allyl-cis-cis-hexahydrojulolidine (39 mg) was dissolved in anhydrous ether (15 ml) to which was added methyliodide (.3 ml). The solution was refluxed for one hour and the solvent evaporated off. 40 mg of oil was recovered. This shows an infrared spectrum identical with that of the starting material.

Refluxing for 3 hours also yielded starting material.

Cyanide Addition

7a,8,9,10,10a-tetrahydrojulolidinium perchlorate (2.8 g, .01 mole) was slurried in water (75 ml). To the slurry was added KCN (2 g. .03 mole) and ether (75 ml). The flask was sealed and shaken for 6 hours. The layers were separated and the aqueous layer was extracted four times with ether. The ether extracts were combined, dried ($MgSO_4$) and evaporated. 1.936 gm (95%) of crystalline material was obtained. Some of the material was sublimed. It had m.p. 78° and appeared as one spot on t.l.c. The infrared spectrum (nujol and $CHCl_3$) shows absorption at 2940, 2860, 2810, 2770, 2670, and 2210 cm^{-1}. The n.m.r. spectrum (CCl_4) shows only two signals, one at τ7.5 (4H) and one at τ8.5 (16H). The mass spectrum shows a small parent peak at m/e 204 and a base peak at m/e 177. Other prominent peaks are at m/e 178, 150 and 149.

Anal. Calcd. for $C_{13}H_{20}N_2$; C, 76.47; H, 9.80; N, 13.72% Found: C, 76.40, 76.31; H, 9.98, 10.09; N. 13.64%

Attempted Methiodide Formation

11-cyano-cis-cis-hexahydrojulolidine (52 mg) was dissolved in anhydrous ether (20 ml). To the solution was added methyl iodide (.4 ml). The solution was refluxed for 1 hour. The solvent was evaporated leaving 58 mg of solid in the flask. This substance had an infrared spectrum identical to that of the starting material.

Isomerization

11-methallyl-cis-cis-hexahydrojulolidinium perchlorate (498 mg, 1.5 mmole) was refluxed in 10% aqueous perchloric acid (20 ml) for 24 hours. The solution was cooled and the crystals filtered off. These crystals were recrystallized from 1:1 ethyl acetate:ethanol. 276 mg was recovered (55% recovery), m.p. 237° (dec). The infrared spectrum (nujol) shows bands at 3110, 2920, 2850, 1660, 1635, 1100 and 1050 cm^{-1}.

Anal. Calcd. for $C_{16}H_{28}NO_4Cl$: C, 57.66; H, 8.41; N, 4.20% Found: C, 57.74, 57.55; H, 8.34, 8.27; N, 4.00%

The mother liquors from the isomerization reaction were basified using dilute ammonium hydroxide. The suspension was extracted three times with ether. The ether extracts were combined, dried ($MgSO_4$) and evaporated.

White crystalline material (113 mg) was obtained. This substance shows infrared absorption ($CHCl_3$) at 3070, 2930, 2855, 2810, 2770, 1660, and 1632. The n.m.r. spectrum ($CDCl_3$) shows a singlet at τ4.45, and a doublet at τ5.22 of relative intensity 5:4.

SECTION V. EXPERIMENTAL: 9-METHOXYJULOLIDINE

Preparation of 6-methoxy-1,2,3,4-tetrahydroquinoline. (Thalline).

Freshly distilled 6-methoxyquinoline (93.95 g, 0.59 mole) was dissolved in methanol (400 ml). To the solution was added PtO_2 (9.4 g). The mixture was hydrogenated at 50 psi for 24 hours. The Pt was filtered off and the methanol evaporated. The crude product was then fractionally distilled, b.p. 115-125 at 1.2 mm. Yield 96.5 g, 90%. The infrared spectrum shows absorption at 3410, 3000, 2950, 2830, 1510, 1255, 885 and 810 cm^{-1}. The n.m.r. spectrum ($CDCl_3$) shows signals at τ8.12 (2H, quin.), τ7.28 (2H, t) τ6.82 (2H, t), τ6.38 (1H, s), τ6.32 (3H, s) and 3H signals from τ3.32 to τ3.74. The n.m,r. is identical with that shown in the Varian Catalog (266).[64]

Preparation of 9-methoxyjulolidine

Freshly distilled 6-methoxy-1,2,3,4-tetrahydroquinoline (60 g, .37 mole) was dissolved in 1-bromo-3-chloropropane (500 ml) and the solution was refluxed for 18 hours. Dilute HCl (10%, 1000 ml) was added to the solid-containing brown mixture. The excess 1-bromo-3-chloropropane was steam distilled out and the residue was cooled. The residue was basified using conc. ammonium hydroxide and the alkaline mixture was extracted with two litres of ether. The ether solution was dried ($MgSO_4$) and concentrated. The residue was distilled under vacuum. The fraction

boiling between 140 and 150° at 3 mm was collected. 61 g, 81%. The infrared spectrum (CCl_4) shows absorption at 2995, 2940, 2840, 2770, 1600, 1480 and 1195 cm^{-1}. The n.m.r. spectrum ($CDCl_3$) shows signals at τ8.08 (4H, quintet J = 5 1/2 cps), τ7.3 (4H, triplet J = 6 cps), τ7.01 (4H, triplet J = 5 1/2 cps), τ6.34 (3H, singlet) and τ3.62 (2H, singlet).

Attempted Preparation of 9-Methoxyjulolidine from p-anisidine

Freshly recrystallized (petroleum ether-ether) p-anisidine (25 g, .2 mole) was dissolved in 1-bromo-3-chloropropane (75 ml) and the resulting solution was refluxed for 24 hours. The reaction mixture was then cooled and acidified with HCl (100 ml - 20%). To the acidic mixture was added water (500 ml) and the excess 1-bromo-3-chloropropane was removed by steam distillation. The residue was washed with chloroform and the aqueous layer was basified with bicarbonate solution. The resulting pink suspension was extracted four times with ether. The ether extracts were combined, dried ($MgSO_4$), and evaporated. A dark oil, 16.55 g, remained. T.l.c. showed the presence of at least 7 components.

A preparation in which solid Na_2CO_3 was added to the reaction mixture lead to an oily product which by t.l.c. appeared to be made up of at least 6 components.

9-Ethylenedioxy-$\Delta^{4(11)}$tetrahydrojulolidinium perchlorate.

9-methoxyjulolidine (23 g, 0.113 mole) was dissolved in ether (50 ml) and the solution was filtered. The clear filtrate was added to freshly distilled liquid ammonia (1200 ml) contained in a 3 l three-necked flask equipped with a dry ice condenser, a mechanical stirrer and a 500 ml dropping funnel. Freshly cleaned lithium metal (3.2 g, 0.46 mole) was added in small portions to the stirred solution. The resulting blue solution was stirred for 40 minutes during which time tertiary-butyl alcohol (200 ml) in ether (100 ml) was added dropwise. The solution was stirred for an additional 10 minutes after which the reaction was quenched with solid ammonium chloride. The ammonia was evaporated and 500 ml of water was added. The layers were separated and the aqueous layer was extracted with ether (4 x 100 ml). The ether layers were combined, dried ($MgSO_4$) and concentrated. The remaining oil was added to hot ethylene glycol (300 ml). The oily mixture was rapidly stirred and slowly acidified using 70% $HClO_4$. After it was stirred and heated for 1/2 hr the solution turned into a solid mass. The slurry was cooled and filtered. The precipitate was boiled in methanol (150 ml), cooled and filtered. 17 g of white solid was obtained (45% yield). The infrared spectrum (nujol) shows absorption at 1675 cm^{-1}, with a shoulder at 1660 cm^{-1}, and at 1080 cm^{-1}.

Reaction of methallylmagnesium chloride and 9-ethylenedioxy-7a,8,10,10a-tetrahydrojulolidinium perchlorate in THF.

Magnesium metal (5.7 g, 0.24 mole) was added to a three-necked 1000 ml round bottom flask containing a magnetic stirrer and equipped with a condenser, drying tubes and a dropping funnel. The whole apparatus was flame dried and dry tetrahydrofuran (200 ml, distilled from LAH) was added. Freshly distilled methallyl chloride (10.8 g, 0.12 mole) dissolved in dry tetrahydrofuran (100 ml, distilled from LAH) was added dropwise to the stirred, refluxing mixture over a two hour period.

After 6 hours, during which time most of the magnesium dissolved, 9-ethylenedioxy-7a,8,10,10a-tetrahydrojulolidinium perchlorate (20 g, 0.06 mole) was added. It dissolved immediately. After 1 hour the flask was cooled and the solids were filtered. Water (300 ml) was added and the magnesium hydroxide was removed using a celite filter pad. The mixture was made more strongly basic using conc. ammonium hydroxide and the layers were separated. The aqueous layer was extracted four times with ether (total 300 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated. 16.14 g of oil was obtained. Thin layer chromatography (4:1 benzene:ether) indicated the presence of at least 5 components. The oil was then chromatographed on 500 gm of alumina (BDH).

Elution with Skelly B (300 ml) yielded a mixture (3.905 g) made up of three components (t.l.c.). This was later rechromatographed.

Further elution with Skelly B (22.5 l), followed by elution with Skelly B - 5% benzene (2500 ml), Skelly B-10% benzene (2500) and Skelly B-50% benzene (1000 ml) yielded 7.324 g of white crystalline material. This substance which was homogeneous on gas-liquid chromatography (5 ft x 0.25 in. silicone (Fluoro) QF1, 190°) and on t.l.c. (4:1 benzene-ether) has: m.p. 59-61°; $\nu_{max}^{CCl_4}$ 3070 ($=C\langle^{H}_{H}$); 2800, 2780, 2750, 2680 (Bohlmann bands); 1635 cm^{-1} (C=C); 1350, 1145, 1080, 1050, 945; 885 ($C=C\langle^{H}_{H}$): n.m.r. spectrum ($CDCl_3$), τ5.08, (1H, s) and τ5.18, (1H, s), due to terminal methylene, τ6.09 (singlet, 4H) due to the ethylene ketal): τ8.12 (singlet), m/e 291 (M^+), m/e 236 (M^+-55, base peak).

Anal. Calcd. for $C_{18}H_{29}NO_2$: C, 74.22; H, 9.96; N, 4.81% Found: C, 74.31; H, 9.97; N, 4.75%

Elution with more Skelly B-50% benzene (1000 ml) yielded 0.447 g of solid which was shown to be made up of 2 components by t.l.c. (1:1 benzene-ether), As well, Skelly B-50% benzene (500 ml) yielded 341 mg of solid material which was shown to be homogeneous by t.l.c. (1:1 benzene:ether).

This substance has m.p. 96-97°; infrared absorption (CCl_4) at 2800, 2770, 2740 cm^{-1} (Bohlmann bands) and no absorption due to the methallyl group at 3070, 1665 and 885 cm^{-1}; n.m.r. spectrum ($CDCl_3$) shows a signal at τ6.08 (singlet 4H) due to the ethylene ketal, and one at τ7.22 (doublet, J 13 cps, 2H); mass spectrum, m/e 237 (M^+), m/e 236 (M^+-1, base peak).

Anal. Calcd. for $C_{14}H_{23}NO_2$; C, 70.88; H, 9.70; N, 5.90% Found, C, 70.68; H, 9.69; N. 5.78%

Elution with ether (200 ml) gave 230 mg of solid showing 2 spots on t.l.c. Further elution with ether (500 ml) gave 430 mg of solid material which was shown to be one component by t.l.c. This material shows infrared absorption (CCl_4) at 2920, 2800, 2750, 2670 cm^{-1} (Bohlmann bands) and no absorption due to $C=CH_2$ (3070, 1665, 885 cm^{-1}). The n.m.r. spectrum ($CDCl_3$) shows a signal at τ6.08 and a broad doublet at τ7.12, (J = 15 cps). The mass spectrum shows peaks at m/e 237 (M^+), m/e 236 (M^+-1, base peak).

The forerun obtained in the chromatography was dissolved in ether (150 ml) to which was added alumina (20 g, BDH). The solvent was evaporated and the alumina pumped dry. Ths alumina was added to the top of an alumina column (150 g, BDH) prepared in Skelly B.

Elution with Skelly B (500 ml) yielded 0.473 g of oil which was homogeneous by vapor phase chromatography

(5 fl x 0.25 in silicone (fluoro) QF1, 190°) and by t.l.c. (benzene). This material shows the following spectral features: infrared absorption (CCl_4); 3070, 1635, 890 cm^{-1} ($C=CH_2$), 2810, 2770, 2700 cm^{-1} (Bohlmann bands): n.m.r. ($CDCl_3$); τ5.12, (1H,s), τ5.24, (1H,s), no signal for the ethylene ketal: mass spectrum; small m/e 233 (M^+), m/e 178 (M^+-55, base peak).

This material was identical with an authentic sample.

Further elution with Skelly B (8000 ml) yielded 1.530 g of crystalline material m.p. 81-83°, which was homogeneous by g.l.c. (5 fl x 0.25 in. silicon (fluoro) QF1, 190°) and by t.l.c. (benzene). This material also appeared to be less polar (higher Rf) than the previously eluted material when run on t.l.c. (alumina, benzene).

Infrared absorptions (CCl_4) appear at 3070, 1635, 885 cm^{-1} ($C=CH_2$); n.m.r. ($CDCl_3$) signals occur at τ5.21 (broad singlet) and at τ6.11 (apparent triplet) in a ratio of 1:2 thus indicating the presence of ($C=CH_2$) and of ($-O-CH_2CH_2-O-$): the mass spectrum has peaks at m/e 291 (M^+), m/e 236 (M^+-55, base peak). Exact mass: Calc. for $C_{18}H_{29}NO_2$, 291.2198: Found 291.2197.

Anal. Calcd. for $C_{18}H_{29}NO_2$: C, 74.22; H, 9.96; N, 4.81% Found. C, 73.96; H, 10.15; N, 4.76%

Elution with ether (500 ml) gave 330 mg of oil which was shown by g.l.c. (5ft x 0.25 in. silicone (fluoro) QF1, 190°) and by t.l.c. (alumina, benzene) to be made

up of two components.

Further elution with ether yielded 396 mg of crystalline material which was shown by g.l.c. (5 ft x 0.25 in silicone (fluoro) QF1, 190°) and by t.l.c (alumina, benzene: ether 1:1) as well as by spectral properties (i.r., n.m.r.) to be identical to the major component (9-ethylenedioxy-11-methallyl-cis-cis-hexahydrojulolidine) already characterized.

Reaction of methallylmagnesium chloride and 9-ethylenedioxy-7a,8,10,10a-tetrahydrojulolidinium perchlorate in ether.

Dry magnesium turnings (1.38 g, 0.056 mole) were placed in a three-necked flask to which was fitted a condenser with a drying tube, a stirrer, and a dropping funnel with a nitrogen gas inlet. The whole apparatus was flame dried during which dry (H_2SO_4) nitrogen gas was passed through the system. After cooling, the magnesium was covered with anhydrous ether (75 ml) and to this was added, dropwise methallyl chloride (5.2 gm, 0.058 mole) in ether (75 ml) over a four hour period. The white suspension was vigorously stirred for 24 hours after which time most of the magnesium had disappeared. 9-Ethylenedioxy-$\Delta^{4(11)}$-hexahydrojulolidinium perchlorate (8.76 g, .026 mole) was added directly to the Grignard suspension.

Aliquots (10 ml) were removed at various times. These aliquots were treated with water and extracted with

ether. The ether extracts were combined, dried ($MgSO_4$) and evaporated. The free bases thus obtained were examined by n.m.r. The signals at τ5.12 and τ6.05 were found to be in the ratio 1:2 after 5 days. Thus the reaction was considered complete.

Water (200 ml) was then added to the reaction mixture. The layers were separated and the basic aqueous layer was extracted 3 more times with ether. The ether layers were combined, dried ($MgSO_4$) and evaporated . 1.91 g of material remained. Continuous extraction of the aqueous layer failed to yield any substantial amount of product.

The product eventually gave brownish white crystals, m.p. 59-65°. Careful examination of the t.l.c. showed three components of very similar Rf. The infrared spectrum (CCl_4) shows absorption bands at 3070, 2870, 2810, 2770 and 1630 cm^{-1}. On some occasions as many as 5 products were obtained.

The same products were obtained by forming the Grignard reagent in ether (24 hrs) and then replacing the ether with dry (LAH) tetrahydrofuran before adding the immonium salt. The Grignard addition was faster (8 hours) and the yields were better. A more satisfactory procedure was to do the whole reaction in tetrahydrofuran.

Hydrolysis of Crude Methallyl Grignard Product

The oily product (3.315 g) obtained by reaction of methallylmagnesium chloride with 9-ethylenedioxy-7a,8,10,10a-tetrahydrojulolidinium perchlorate was dissolved in 5% HCl (50 ml) and the yellow solution was refluxed for 4 hours. The reaction mixture was cooled, basified with dil. ammonium hydroxide and extracted with ether (total 200 ml). The ether extracts were combined, dried ($MgSO_4$) and concentrated. 3.15 g of brown oil was obtained. This oil was made up of at least 4 components (t.l.c.).

The product was chromatographed on alumina (90 g, BDH). Elution with Skelly B (1000 ml) and with Skelly B-10% benzene (1000 ml) yielded 668 mg of oil which showed two spots on t.l.c. Elution with benzene (700 ml) afforded 1138 mg of crystalline material. This has m.p. 75-76° and shows infrared absorption (CCl_4) at 3050, 2920, 2850, 2780, 2750, 1710, 1630 and 895 cm^{-1}. The n.m.r. ($CDCl_3$) shows signals at τ5.14 (1H,s), τ5.22(1H,s) as well as many unresolved signals along with a singlet at τ8.18. The mass spectrum shows a parent peak at m/e 247 and a base peak at m/e 192.

Further elution with benzene (400 ml) yielded 57 mg of oil made up of two components (t.l.c.). Further elution with benzene (900 ml) yielded 110 mg of solid which has infrared absorption (CCl_4) at 2920, 2870, 2840, 2750, 2720, 2680, 2660, and 1710 cm^{-1}. The infrared

spectrum is identical with one obtained by P. Smith in the reduction studies on the immonium salt.[67]

Elution with benzene-10% ether (200 ml) gave 343 mg of a two component (t.l.c.) mixture. Further elution with benzene-10% ether (800 ml) afforded 205 mg of solid material. This shows infrared absorption (CCl_4) at 2930, 2850, 2780, 2740, 2680, 2670, and at 1710 cm^{-1}. The infrared spectrum is identical with one obtained by P. Smith in the reduction studies on the immonium salt.[67]

Reaction of isobutylmagnesium bromide with 9-ethylenedioxy-7a,8,10,10a-tetrahydrojulolidinium perchlorate.

Magnesium (1.11 g, 0.045 m) was placed in a three-necked 500 ml round bottom flask equipped with a condenser, drying tubes, a mechanical stirrer and a dropping funnel. The whole apparatus was flame dried and dry tetrahydrofuran (50 ml, distilled from LAH) was added. To the stirred refluxing mixture was added isobutyl bromide (6.1 g, 0.045 mole) in dry tetrahydrofuran (50 ml, distilled from LAH) over a two hour period. Refluxing and stirring was continued for four more hours.

9-Ethylenedioxy-7a,8,10,10a-tetrahydrojulolidinium perchlorate (7.62 g, 0.023 mole) was added through a powder funnel. The reaction mixture was then refluxed and stirred for 3 hours. After cooling, water (200 ml) was added. The precipitate which formed was filtered using a celite filter pad. The alkaline solution was then

extracted with ether (total 200 ml). The extracts were combined, dried ($MgSO_4$) and evaporated. 3.36 g of oil remained. T.l.c. (alumina, 1:1 benzene:ether) showed this to be made up of four components two of which seemed to predominate.

The product was chromatographed on alumina (120 g, BDH). Elution with Skelly B (1200 ml) afforded 673 mg of oil which appeared as 1 spot on t.l.c.(alumina, 1:1 benzene:ether). The infrared spectrum (CCl_4) shows absorption at 2800, 2760, 2680 cm^{-1} (Bohlmann bands) and at 1350 cm^{-1} (isopropyl). The n.m.r. spectrum ($CDCl_3$) shows a strong signal at τ9.0 (doublet, J = 5 cps). The mass spectrum shows a peak at m/e 235 (parent) and a base peak at m/e 178.

Elution with more Skelly B (2000 ml) yielded 495 mg of a mixture of compounds (t.l.c.).

Elution with Skelly B-50% benzene (60 ml) yielded 940 mg of semi-crystalline material. A sublimed sample melted at 48°. The infrared spectrum (CCL_4) shows absorption at 2800, 2770, 2750 cm^{-1} (Bohlmann bands). The n.m.r. ($CDCl_3$) shows signals at τ6.07 (singlet) and τ9.01 (doublet J = 6 cps). The mass spectrum shows a small parent peak at m/e 293 and a base peak at m/e 236. This material was identical with that prepared by Cooke.[62]

Elution with benzene yielded an oil which was made up of three compounds (t.l.c.).

9-Keto-cis-cis-hexahydrojulolidine

9-Ethylenedioxy-cis-cis-hexahydrojulolidine (900 mg, 3.8 mmole) was dissolved in methanol (20 ml) to which solution was added water (50 ml) and conc. hydrochloric acid (15 ml). The solution was stirred overnight then was basified using saturated Na_2CO_3. The white suspension was extracted with ether (6 x 25 ml). The ether extracts were combined, dried ($MgSO_4$) and evaporated. 425 mg (56%) of solid material remained. This material was homogeneous by t.l.c. The infrared spectrum shows (CCl_4) absorptions at 2850, 2795, 2750, 2730, 2690, 2675 and 1710 cm^{-1}. The n.m.r. spectrum shows a one hydrogen signal at τ6.83 (apparent triplet) and a series of unresolved peaks between τ7.0 and τ8.8. The spectral properties of this compound agree with those obtained by P. Smith of one compound obtained in the hydrolysis of the "hydride" reduction product of the immonium salt.[67]

9-Ethylenedioxy-11-isobutyl-cis-cis-hexahydrojulolidine.

9-Ethylenedioxy-11-methallyl-cis-cis-hexahydrojulolidine (2.625 g, 9.0 mmole) was dissolved in methanol (75 ml) and platinum oxide (250 mg) was added. The mixture was hydrogenated in a Parr apparatus at 50 psi for 20 hours. The platinum was filtered and the methanol evaporated. 2.639 g of slightly coloured oil remained. The oil was homogeneous by t.l.c. and had a slightly higher Rf than

the starting material. The infrared spectrum (CCl_4) is identical to that of the same substance prepared by G.A. Cooke.[62]

9-Hydroxy-11-isobutyl-cis-cis-hexahydrojulolidine

9-Keto-11-methallyl-cis-cis-hexahydrojulolidine (0.985 g, 4 mmole) was dissolved in methanol (50 ml) to which was added PtO_2 (.153 g). The mixture was subjected to 25 psi H_2 for 20 hours in a Parr hydrogenator. At the end of this period the yellow solution was filtered and the solvent removed. 1.021 g of amorphous solid remained. This material was filtered through a column of alumina (10 g, BDH) using ether as eluant. 874 mg of yellow crystals were recovered (85%). The infrared spectrum (CCl_4) shows absorption bands at 3610, 2790, 2760 and 1108 cm^{-1}. A broad singlet at τ5.9 appears in the n.m.r. (CCl_4).

Oxidation of 9-Hydroxy-11-isobutyl-cis-cis-hexahydrojulolidine.

9-Hydroxy-11-isobutyl-cis-cis-hexahydrojulolidine (636 mg, 2.5 mmole) was dissolved in 95% acetic acid (25 ml). This solution was added to a solution of CrO_3

(738 mg, 7.4 mmole) in 95% acetic acid (25 ml). The reddish solution was stirred at room temperature for 36 hours. The solvent was then evaporated, leaving a dark oil. This oil was basified with dilute ammonium hydroxide and the resulting suspension was extracted with ether (6 x 25 ml). The ether extracts were combined, dried ($MgSO_4$) and concentrated. 330 mg of amber oil was obtained (52%). The infrared spectrum (CCl_4) shows absorptions at 2920, 2850, 2800, 2760 and 1700 cm^{-1} and is identical to the spectrum of authentic 9-keto-11-isobutyl-cis-cis-hexahydrojulolidine.[62]

9-Keto-11-isobutyl-cis-cis-hexahydrojulolidine.

9-Ethylenedioxy-11-isobutyl-cis-cis-hexahydrojulolidine (388 mg, 1.32 mmole) was dissolved in methanol (20 ml). To the yellow solution was added 20% HCl (25 ml). The solution was stirred for 24 hours after which time it was basified using saturated Na_2CO_3 solution. The white suspension was extracted with ether (4 x 25 ml). The ether extracts were combined, dried ($MgSO_4$) and concentrated. 303 mg (91%) of yellow oil remained. This oil later crystallized. The infrared spectrum (CCl_4) with absorptions at 2850, 2800, 2760 and 1710 cm^{-1} was identical to that of an authentic sample of 9-keto-11-isobutyl-cis-cis-hexahydrojulolidine.

8α-Bromo-9-keto-11-isobutyl-cis-cis-hexahydrojulolidine hydrobromide.

9-Keto-11-isobutyl-cis-cis-hexahydrojulolidine (2.05 g, 8.4 mmole) was dissolved in acetone (50 ml) and acidified using 48% aqueous HBr. White crystalline material soon separated. The suspension was cooled and filtered This yielded 2.414 gm of white crystals (87%), m.p. 220° (dec). The infrared spectrum (nujol) shows absorption at 2690, 2660, 2580, and 1710 cm^{-1}.

9-Keto-11-isobutyl-cis-cis-hexahydrojulolidine hydrobromide (2.054 g, 6.2 mmole) was dissolved in 25 ml of chloroform. The solution was saturated with gaseous HBr and to the solution was added bromine (0.992 g, 6.2 mmole) in chloroform (25 ml) dropwise over a 30 minute period. Stirring was continued for 1 hour after which the solvent was removed. A light brown oil remained which, upon the addition of a few drops of acetone, crystallized. A total of 2.115 g (82%) of white crystals was obtained, m.p. 215-218°. These show infrared absorption (nujol) at 2660, 2590, and 1725 cm^{-1}.

Some of the above material was converted to the free base. The infrared spectrum (CCl_4) shows absorptions at 2860, 2800, 2760, and 1735 cm^{-1}. The n.m.r. spectrum ($CDCl_3$) shows signals at τ4.68 (doublet, J = 12 cps) and at τ6.65 (triplet J = 12-13 cps) as well as a large doublet at τ9.05.

2,4-Dinitrophenylhydrazone of 8-bromo-9-keto-11-isobutyl-cis-cis-hexahydrojulolidine.

8-Bromo-9-keto-11-isobutyl-cis-cis-hexahydrojulolidine hydrobromide (735 mg) was dissolved in hot acetic acid (20 ml). 2,4-Dinitrophenylhydrazine (396 mg) in acetic acid (20 ml) was added. The solution was refluxed under an atmosphere of nitrogen for 1 hour. The solution was cooled and diluted with water (50 ml). Basification with ice cold conc. ammonium hydroxide caused the separation of a red solid which was filtered off. Extraction of the mother liquors with chloroform (3 x 25 ml) yielded more of the same material (identical t.l.c. behavior). The total product (443 mg) was chromatographed on alumina. Elution with Skelly B-5% benzene (500 ml) yielded 116 mg of red solid which shows the following properties: t.l.c. indicated the presence of two components: the infrared spectrum ($CHCl_3$) shows absorption at 3310, 3100, 1620, 1600, 1500 and 1340 cm^{-1}: the ultraviolet spectrum (Et_2O) shows a maximum at 396 mμ: the n.m.r. spectrum ($CDCl_3$) shows signals at τ9.0 (singlet, 3H), τ8.93 (singlet, 3H), τ6.92 (quartet, J = 5 cps, J = 20 cps, 1H), τ6.07 (doublet J = 20 cps, 1H), τ4.08, (octet, 1H), τ3.76 (quartet, J = 10 cps, J = 2.5 cps) τ3.88 (singlet, 1H) and some aromatic signals between τ1.4 to τ2.2.

Elution with 25% benzene-Skelly B (875 ml) yielded 41 mg of red solid which was homogeneous by t.l.c. and

has the same t.l.c. behavior as the more polar component in the first fraction. This compound has a m.p. 193-195° dec. The sample was used for n.m.r. decoupling experiments.

Elution with various other solvents yielded complicated mixtures (t.l.c.).

Hydrolysis of the 2,4-dinitrophenylhydrazone of 8-bromo-9-keto-11-isobutyl-cis-cis-hexahydrojulolidine hydrobromide.

A mixture of the 2,4-dinitrophenylhydrazones obtained in the previous reaction (108 mg) was dissolved in acetone (25 ml). To the solution was added conc. HCl (0.6 ml). The reaction mixture was then refluxed for 1/2 hour during which time the colour changed from bright red to orange. After cooling stannous chloride (0.65 g) in conc. HCl (2.6 ml) was added as well as water (4 ml). This reaction mixture was refluxed for 3/4 of an hour.

Upon cooling, the solution was diluted with water (20 ml) and basified with dilute ammonium hydroxide. The alkaline mixture was extracted with ether (4 x 25 ml) and the extracts were combined, dried ($MgSO_4$) and evaporated. 41 mg of coloured material was obtained. The t.l.c. showed many brightly coloured polar components. I_2 and Dragendorf's reagent showed the presence of 1 non-coloured, non-polar component.

The crude product was filtered through alumina using benzene as solvent. 13 mg of a semisolid was obtained. This was nearly homogeneous on t.l.c. The infrared spectrum (CCl_4) shows absorption at 3020 (benzene), 2810, 2790, 1660, 1610, and 1580 cm^{-1}. The ultraviolet shows a maximum (EtOH) at 285 mμ which shifted to 275 mμ on the addition of a small amount of acid. The mass spectrum shows no parent peak. The base peak is at m/e 188.

Preparation of Semicarbazine

Semicarbazide hydrochloride (5.5 g, 0.050 mole) was mixed with anhydrous NaOAc (4.5 g, 0.055 mole). The solid mixture was ground in a mortar and boiled in absolute ethanol (50 ml) for 15 minutes. The hot slurry was filtered and the filtrate cooled. 2.21 g (60%) of white crystalline material (m.p. 96°) was obtained.

Dehydrobromination of 8-bromo-9-keto-11-isobutyl-cis-cis-hexahydrojulolidinium hydrobromide.

8-Bromo-9-keto-11-isobutyl-cis-cis-hexahydro-julolidine hydrobromide (328 mg, .8 mmole) was dissolved in glacial acetic acid (7 ml). Solid, freshly recrystallized semicarbazine (120 mg, 1.6 mmole) was added. Carbon dioxide gas was bubbled through the solution which was refluxed for 8 minutes. To the hot solution was added pyruvic acid (0.5 ml) and water (0.4 ml). The solution

was then refluxed for 20 minutes during which time CO_2 was continuously bubbled through the solution. After cooling, the solution was basified with conc. ammonium hydroxide and extracted with ether (5 x 25 ml). The ether extracts were combined, dried ($MgSO_4$) and concentrated. 167 mg of brownish oil was obtained.

The crude product was chromatographed on alumina (10 g. BDH). The first fractions contained 3 components (875 ml Skelly B, 1275 ml Skelly B-5% benzene, and 250 ml Skelly B-20% benzene). Further elution with Skelly B-20% benzene (2000 ml) yielded 61 mg (31%) of oil which appeared as one component on t.l.c. (ether). The infrared spectrum (CCl_4) shows absorption at 2860, 2800, 1675, and 1615 cm^{-1}. The ultraviolet spectrum shows a maximum at 242 mμ (ε9,000). The n.m.r. spectrum shows a signal at τ4.15 (doublet, J ~ 1.5 cps, allylic coupling). The mass spectrum shows a parent peak at m/e 247 and the base peak at m/e 190.

Preparation of 9-Keto-11-isobutyl-cis-trans-hexahydro julolidine.

9-Keto-11-isobutyl-Δ^{7a}-hexahydrojulolidine (48 mg, 0.2 mmole) was dissolved in anhydrous ether (20 ml). The ether solution was added to freshly distilled ammonia (40 ml). The solution was stirred using a magnetic stirrer and a very small piece of freshly cleaned lithium metal was added. The resulting blue solution was stirred

for 10 minutes after which time just enough solid ammonium chloride was added to remove the blue colour. The ammonia was evaporated and water (50 ml) was added. The layers were separated and the aqueous layer was extracted with ether (4 x 20 ml). The ether extracts were combined, dried ($MgSO_4$) and evaporated. 43 mg of crystalline material was obtained. This was made up of two components by t.l.c. (1:1 benzene:Skelly B).

The crude product was filtered through alumina (1.2 g, BDH) using Skelly B. The major product (least polar by t.l.c.) was completely removed from the column after 525 ml. 26 mg (55%) of white crystals was obtained m.p. 90°. The infrared spectrum (CCl_4) shows absorptions at 2855, 2800(w), and 1710 cm^{-1}. This spectrum was completely different (no Bohlmann bands!) to that of the isomer 9-keto-11-isobutyl-cis-cis-hexahydrojulolidine. The mass spectrum shows a parent peak at m/e 249 and a base peak at m/e 192.

Hydrogenation of 9-ethylenedioxy-11-methallyl-cis-trans-hexahydrojulolidine.

9-Ethylenedioxy-11-methallyl-cis-trans-hexahydrojulolidine (70 mg, 0.2 mmole) was dissolved in methanol (15 ml). Platinum oxide (16 mg) was added and the mixture was subjected to 1 atm of hydrogen at room temperature. When hydrogen uptake had stopped, the platinum

was filtered off and the methanol was evaporated. 66 mg (91%) of product was obtained. The product was homogeneous by t.l.c. (benzene:ether, 1:1) and of higher Rf (less polar) than the starting material. The infrared spectrum (CCl_4) does not show Bohlmann bands or olefinic absorption.

Hydrolysis of 9-Ethylenedioxy-11-isobutyl-cis-trans-hexahydrojulolidine

9-Ethylenedioxy-11-isobutyl-cis-trans-hexahydrojulolidine (60 mg, .2 mmole) was dissolved in methanol (10 ml). To this solution was added hydrochloric acid (22 ml, 10%). The reaction mixture was refluxed for 3 hours, after which it was cooled and basified with saturated aqueous sodium carbonate. The alkaline solution was extracted with ether (4 x 15 ml) and the ether extracts were combined, dried ($MgSO_4$) and evaporated. 41 mg of crystalline material, m.p. 90°, was obtained. The infrared spectrum (CCl_4) is identical with that of 9-keto-11-isobutyl-cis-trans-hexahydrojulolidine prepared by isomerization of the cis-cis isomer.

Preparation of 9-keto-11-methallyl-cis-cis-hexahydrojulolidine.

9-Ethylenedioxy-11-methallyl-cis-cis-hexahydrojulolidine (5.725 g, 0.02 mole) was dissolved in methanol (25 ml). HCl (100 ml, 10%) was added and the solution was stirred overnight. Basification with dilute ammonium hydroxide

yielded a white suspension which was extracted with ether (4 x 50 ml). The ether extracts were combined, dried ($MgSO_4$) and evaporated. 4.269 g (86%) of white crystalline material was obtained. This had a melting point, after sublimation, of 75-76° and was homogeneous by t.l.c. The infrared spectrum (CCl_4) shows absorptions at 3070, 2940, 2870, 2810, 2770, 1710, 1640 and 895 cm^{-1}. This i.r. was identical to that of a similar sample of 9-keto-11-methallyl-cis-cis-hexahydrojulolidine obtained by chromatography of the hydrolysed crude "Grignard" product. The mass spectrum shows a small parent peak at m/e 247 and a base peak at m/e 192.

Anal. Calcd. for $C_{16}H_{25}NO$: C, 77.73; H, 10.12; N. 5.66% Found, C, 77.64; H, 10.11, N. 5.42%

Hydrobromide

9-Keto-11-methallyl-cis-cis-hexahydrojulolidine (4.26 g, .017 mole) was dissolved in acetone (25 ml). The clear solution was acidified with constant boiling HBr. After cooling, the white precipitate was filtered off. 4.70 g was obtained, m.p. 234°. The infrared absorption (nujol) occurs at 2910, 2700, 1715, 1638 and 900 cm^{-1}.

Anal. Calcd. $C_{16}H_{26}NOBr$: C, 58.53; H, 7.93; N, 4.27% Found. C, 58.57; H, 7.92; N, 4.02%

Preparation of 8-bromo-9-keto-11-methallyl-cis-cis-hexahydrojulolidine

9-Keto-11-methallyl-cis-cis-hexahydrojulolidine hydrobromide (457 mg, 1.4 mmole) was dissolved in chloroform (20 ml). Chloroform (1 ml) saturated with hydrogen bromide gas was added. The solution was cooled to 0° and bromine (224 mg, 1.4 mmole) in chloroform (25 ml) was added to the stirred solution over a half hour period. The chloroform was then evaporated leaving a gum which crystallized upon the addition of a few drops of acetone. 596 mg of white crystalline material was obtained, m.p. 185-190°. The infrared spectrum (nujol) shows absorption at 2700, 2760, 2680, 1735, and 1640 cm^{-1}.

The infrared spectrum (CCl_4) of the free base shows absorption at 3065, 2930, 2870, 2810, 2765, 1740, 1640 and 900 cm^{-1}.

Generally the bromoketone-hydrobromide was dehydrobrominated directly without purification.

Dehydrobromination of 8-bromo-9-keto-11-methallyl-cis-cis-hexahydrojulolidine hydrobromide.

Crude 8-bromo-9-keto-11-methallyl-cis-cis-hexahydrojulolidine hydrobromide (6.1 g, 0.015 mole) was dissolved in hot acetic acid (30 ml) through which solution was continuously bubbled CO_2. The solution was refluxed and freshly recrystallized semicarbazine (2.68 g, 0.032 mole)

in acetic acid (10 ml) was added. The reaction mixture was refluxed for 6 minutes. Pyruvic acid (20 ml, 1:1 by weight, pyruvic acid:water) and water (10 ml) were added. Refluxing under an atmosphere of CO_2 was continued for 20 minutes. The solution was cooled in ice and was basified with ice cold conc. ammonium hydroxide. The pink suspension was extracted with ether (4 x 50 ml). The ether extracts were combined, dried ($MgSO_4$) and concentrated 2.68 g of brown semi-solid was obtained. The t.l.c. of this material indicated the presence of two major non-polar substances as well as many minor polar substances. The product was filtered through a column of alumina (15 g) using benzene as eluant. 1.9 g of semi-solid was recovered. This appeared to be made up of only two components (t.l.c.).

Part of the above product (500 mg) was chromatographed on alumina (30 g). Elution with Skelly-B 3% benzene (14 x 100 ml) afforded 65 mg of solid material which was made up of at least 2 components (t.l.c.) Further elution with Skelly B-3% benzene (26 x 100 ml) yielded 93 mg of solid (m.p. 75°) which had identical spectral properties with those of 9-keto-11-methallyl-cis-cis-hexahydrojulolidine. Elution with Skelly B-20% benzene yielded 42 mg of solid material which appeared to be made up of two components (t.l.c.). Further elution with Skelly B-20% benzene (28 x 100 ml) yielded 81 mg of semisolid which was homogeneous on t.l.c. The infrared

spectrum (CCl_4) shows absorption at 3070, 2930, 2850, 2810, 1680, 1640, 1620, and 895 cm^{-1}. The ultraviolet spectrum (MeOH) shows a maximum at 246 mμ. The n.m.r. ($CDCl_3$) shows signals at τ4.18 (doublet, J = 7 cps, 1H), τ5.18 (doublet J = 7 cps, 2H) and τ8.2 (singlet, 3H).

Further elution yielded a mixture of compounds.

Preparation of 9-keto-11-methallyl-cis-trans-hexahydro julolidine

The crude mixture (650 mg) obtained from the dehydrobromination of 8-bromo-9-keto-11-methallyl-cis-cis-hexahydrojulolidine was dissolved in ether (50 ml) The solution was added to freshly distilled ammonia (100 ml). The ammonia solution was stirred with a mechanical stirrer and small pieces of lithium metal were added until the solution remained blue. After 8 minutes enough solid ammonium chloride was added in small portions to cause the loss of the blue colour. The ammonia was then evaporated and water (100 ml) was added. The layers were separated and the aqueous layer was extracted with ether (3 x 25 ml). The ether extracts were combined, dried ($MgSO_4$) and evaporated. 510 mg of solid material was obtained. This was shown by t.l.c. to be made up of two components.

The product was chromatographed on alumina (15 g, BDH).

Elution with n-pentane (1000 ml) yielded 202 mg of crystalline material. The infrared spectrum (CCl_4) shows absorption at 3070, 2920, 2860, 1715, 1645, and 895 cm^{-1}. The mass spectrum shows a parent peak at m/e 247 and has the base peak at m/e 192.

Elution with n-pentane-25% benzene (800 ml) afforded 289 mg of crystalline material which was identical in every respect to 9-keto-11-methallyl-cis-cis-hexahydrojulolidine.

9-Keto-11-methallyl-cis-trans-hexahydrojulolidine.

9-Ethylenedioxy-11-methallyl-cis-trans-hexahydrojulolidine (56 mg, 0.19 mmole) was dissolved in methanol (5 ml) and to this solution was added hydrochloric acid (10 ml, 10%). The solution was refluxed overnight. The resulting light yellow solution was cooled, basified with dilute ammonium hydroxide and extracted with ether (4 x 20 ml). The ether extracts were combined, dried ($MgSO_4$) and evaporated. 41 mg (86%) of solid remained. This was shown to be homogeneous by t.l.c. and to have the same Rf and spectral properties as that of an authentic sample prepared by isomerization of the cis-cis isomer.

9-Ethylenedioxy-11-methallyl-cis-trans-hexahydrojulolidine

9-Keto-11-methallyl-cis-trans-hexahydrojulolidine (93 mg, .38 mmole) obtained from a lithium ammonia reduction of Δ^{7a}-9-keto-11-methallyl-hexahydrojulolidine

was dissolved in benzene (30 ml) to which was then added p-toluenesulfonic acid monohydrate (116 mg, 0.6 mmole) as well as ethylene glycol (.4 ml). The mixture was refluxed for 24 hours and the water removed by means of a water separator. The reaction mixture was cooled, basified with 10% NaOH and was extracted with ether (3 x 20 ml). The ether extracts were combined, dried ($MgSO_4$) and evaporated. 98 mg of oil which later crystallized was obtained (m.p. 82°). T.l.c. indicated the presence of only one compound. The infrared spectrum (CCl_4) shows absorption at 3070, 2920, 2860, 2800, 1645, and 890 cm^{-1}. The n.m.r. shows a signal at τ5.21 (singlet, 2H) and one at τ6.10 (apparent triplet, 4H). There is also a sharp singlet at τ8.08. The mass spectrum shows a weak parent peak at m/e 291 and prominent peaks at m/e 236 and m/e 178.

Anal. Calcd. for $C_{29}H_{29}NO_2$: C, 74.22; H, 9.96, N. 4.81%
Found. C, 73.94; H, 9.93; N, 4.86%

This material was identical in all respects with a sample obtained directly from the Grignard reaction.

Hydroboration of 9-Ethylenedioxy-11-Methallyl-cis-trans-hexahydrojulolidine.

9-Ethylenedioxy-11-methallyl-cis-trans-hexahydrojulolidine (4.637 g, 16 mmole) was dissolved in tetrahydrofuran (25 ml, distilled from LAH). B_2H_6, produced in dry diglyme (25 ml, distilled from CaH_2) by the dropwise

addition of $BF_3 \cdot Et_2O$ (9 ml, excess) to $NaBH_4$ (1.2 gm, 32 mmole) dissolved in dry diglyme (10 ml), was carried by N_2 gas into the THF solution. Once the generation of the B_2H_6 was over, the THF solution was sealed and stirred for 3 hours. The excess B_2H_6 was then cautiously decomposed with ice and 3N NaOH (50 ml) and dioxane (20 ml) were added. To the solution was carefully added 30% H_2O_2 (50 ml). The mixture was stirred and kept overnight at 60°. The alkaline solution was then extracted with chloroform (4 x 50 ml). The chloroform extracts were combined, dried ($MgSO_4$) and evaporated. 4.629 g of semi-solid material consisting of four components, (t.l.c.) was obtained. This was chromatographed on alumina (150 g, BDH).

Elution with Skelly B (1200 ml) gave white crystalline material, 2.042 g; 1 spot on t.l.c.; m.p. 167°. The infrared spectrum shows absorption at 2350 cm^{-1} (B-H), no characteristic "Bohlmann" bands and no -O-H absorption. The n.m.r. ($CDCl_3$) shows signals at τ6.12 (apparent triplet, 4H, $-OCH_2CH_2-O$) and at τ9.05 (doublet, J = 10 cps, 3H, $\underline{CH}_3-CH-$). The mass spectrum shows strong peaks at m/e 305 (parent peak), m/e 304 (base peak, M^+-1) and m/e 236 (M^+-69). The exact mass of the peaks m/e 305 and m/e 304 was found to be 305.2526 corresponding to $C_{18}H_{32}NO_2{}^{11}B$ and 304.2448 corresponding to $C_{18}H_{31}NO_2{}^{11}B$.

Anal. Calcd. for $C_{18}H_{32}NO_2B$: 71.29; H, 10.56; N, 4.62; B. 2.97% Found: C, 70.52, 70.45; H, 10.48, 10.76; B, 3.59%

Elution with Skelly B-benzene, benzene, benzene-ether, and ether gave an oil which slowly crystallized, 1.193 g; m.p. 90-105°; t.l.c. 2 spots. Infrared absorption (CCl_4) bands appear at 3140 cm^{-1} and at 3540 cm^{-1}. The n.m.r. spectrum ($CDCl_3$) shows signals at τ6.08 (apparent triplet, 4H, $-OCH_2CH_2-O-$) and at τ9.10 (doublet). The mass spectrum does not show a parent peak but shows a base peak at m/e 236.

Anal. Calcd. for $C_{18}H_{31}NO_3$: C, 69.90; H, 10.03; N, 4.53% Found: C, 69.57, 69.27; H, 9.73, 9.64; N, 4.35%

Elution with chloroform yielded 1.305 g of coloured oil, which was homogeneous on t.l.c. The infrared spectrum (CCl_4) shows strong absorption in the 2900 cm^{-1} region and between 1250 and 1450 cm^{-1}. The n.m.r. spectrum (CCl_4) shows the presence of the ethylene ketal function (singlet at 6.18). The mass spectrum shows the base peak at m/e 236 and prominent peaks at m/e 395, 394, 349, 293, 192, 174, and 146. This compound was designated as "X".

Oxidation of the Boron Containing Compound 145

9-Ethylenedioxy-11-[3-bora-2-methyl-1-propyl]-*cis* - *trans*-hexahydrojulolidine (3.05 g, 10 mmole) was mixed with 3N NaOH (50 ml), 30% H_2O_2 (50 ml) and dioxane (50 ml).

The mixture was stirred at 70° overnight. The solution was then cooled and extracted with ether (4 x 50 ml). The ether extracts were combined, dried ($MgSO_4$) and evaporated. 2.5 g of semi-solid was obtained. This was chromatographed on alumina (80 g, BDH).

Elution with Skelly B (1600 ml) and Skelly B-5% benzene (1200 ml) gave 425 mg of starting material.

Elution with Skelly B-5% ether (1400 ml), Skelly B-10% ether (2000 ml), Skelly B-50% ether (400 ml), afforded 1.054 g of 9-ethylenedioxy-11-[3-hydroxy-2-methyl-1-propyl]-cis-trans-hexahydrojulolidine as identified by t.l.c. and i.r.

Elution with chloroform gave 813 mg of a very polar substance (t.l.c., 5% MeOH-$CHCl_3$) which showed identical t.l.c. behavior and infrared spectrum to that obtained directly in the hydroboration reaction ("X").

Attempted Hydrolysis of the Boron Compound 145

9-Ethylenedioxy-11-[3-bora-2-methyl-1-propyl]-cis-trans-hexahydrojulolidine (50 mg) was dissolved in propionic acid (15 ml) and the solution was refluxed for 2 1/2 hours. Water (100 ml) was added and the solution was basified to pH 11 using conc. ammonium hydroxide. The alkaline solution was extracted with ether (3 x 25 ml). The extracts were combined, dried ($MgSO_4$) and evaporated. 45 mg of starting material was recovered.

Hydrolysis of Compound "X"

The polar compound obtained in the hydroboration reaction (2.8 g) was dissolved in methanol (20 ml). Aqueous HCl (100 ml, 10%) was added. The resulting yellow solution was stirred at room temperature for 16 hours. It was then cooled and basified to pH 11 using 3N NaOH. The alkaline solution was extracted with $CHCl_3$ (4 x 50 ml). The chloroform extracts were combined, dried ($MgSO_4$) and evaporated. A yellow oil remained. The infrared spectrum (CCl_4) of the homogeneous (t.l.c.) oil shows a carbonyl absorption at 1710 cm^{-1} as well as strong absorption in the 1250 to 1450 cm^{-1} region. The mass spectrum (MS2) of this product shows prominent peaks at m/e 192 (base peaks), 236, 267, 281, 241, and at 355. The n.m.r. shows loss of the ethylene ketal function.

The oil crystallized on the addition of acetone. 1.928 g was obtained, m.p. 220-223. The mass spectrum (MS-9, direct probe) shows strong peaks at m/e 825, 633, 577, 276, 193, 192 (base), 178, and 164.

Anal. Found: C, 68.66, 67.79; H, 9.35, 9.38.

Hydroboration of 11-methallyl-cis-cis-hexahydrojulolidine.

11-Methallyl-cis-cis-hexahydrojulolidine (1.475 g, 6.3 mmole) was dissolved in tetrahydrofuran (distilled from $LiAlH_4$, 20 ml). Diborane, produced in diglyme (distilled from CaH_2, 25 ml) by the dropwise addition of

freshly distilled $BF_3 \cdot Et_2O$ (10 ml) in diglyme (distilled from CaH_2, 10 ml) to $NaBH_4$ (1.47 g, 63 mmole) was carried by N_2 gas to the tetrahydrofuran solution. After generation of the diborane (2 hr) the reaction flask was sealed and left at room temperature for 12 hours. The excess diborane was destroyed by adding ice very cautiously to the cold THF solution. This was followed by the addition of hydrogen peroxide (35 ml-30%) and sodium hydroxide (35 ml-3N), all carried out at 0°. The reaction mixture was then stirred at room temperature for 3 hours. The solution was then diluted with water (100 ml) and extracted with ether, (4 x 50 ml). The ether extracts were combined, dried ($MgSO_4$) and evaporated. 1.415 g of oil was obtained. Two components were present in this material.(t.l.c.).

The crude product was chromatographed on alumina (40 g, BDH).

Elution with Skelly B yielded 547 mg of homogeneous material (m.p. 55°). This substance shows infrared absorption ($CHCl_3$) at 2990, 2950, 2870, 2810, 2340, and 2270 cm^{-1}. The mass spectrum shows the parent peak at m/e 247, the base peak at m/e 246 and some prominent peaks at m/e 220, 205, 178, 173 and 172.

The peak at m/e 246 was found to be 246.2394 corresponding to $[C_{16}H_{29}N^{11}B]^+$ which has a calculated value 246.2393. A molecular weight determination (osmometry) indicated 243.

Elution with ether yielded 704 mg of oil. The t.l.c. indicated the presence of one component. The infrared spectrum ($CHCl_3$) shows absorption at 3630, 3450, 2940, 2870, 2820, 2770, and 1025 cm^{-1}.

Oxidation of the alkyl borane 149 from 11-methallyl-cis-cis-hexahydrojulolidine .

The borane 149 (107 mg, 0.43 mmole) was dissolved in tetrahydrofuran (12 ml) to which was added hydrogen peroxide (30%, 12 ml) and sodium hydroxide (3N, 12 ml). The reaction mixture was stirred at room temperature for 20 hours. The mixture was diluted with water (50 ml) and extracted with ether (4 x 25 ml). The ether extracts were combined, dried ($MgSO_4$) and evaporated. 104 mg of starting material was obtained.

The same reaction was carried out using dioxane as solvent. This yielded 103 mg (95%) of oil which has an identical infrared spectrum and t.l.c. behavior to the compound obtained in the ether cleavage of 11-[3-methoxy-2-methyl-1-propyl]-cis-cis-hexahydrojulolidine.

11-[3-Hydroxy-2-methyl-1-propyl]-cis-cis-hexahydrojulolidine

11-[3-Methoxy-2-methyl-1-propyl]-cis-cis-hexahydrojulolidine (808 mg) was dissovled in methylene chloride (25 ml). BBr_3 (33% in CH_2Cl_2, 25 ml) was added dropwise to the stirred solution. The solution was stirred overnight after which diethyl ether was added

dropwise until visible reaction no longer took place. Water was added in a similar manner. Ammonium hydroxide (20%) was added until a clear mixture was obtained. The layers were then separated and the aqueous layer was extracted with methylene chloride (3 x 25 ml). The organic layers were combined, dried ($MgSO_4$) and evaporated. 559 mg of oil was obtained. T.l.c. indicated the presence of 1 component. The infrared spectrum ($CHCl_3$) is identical to that of the same compound obtained by hydroboration of 11-methallyl-cis-cis-hexahydrojulolidine.

Oxidation of 11-[3-hydroxy-2-methyl-1-propyl]-cis-cis-hexahydrojulolidine.

11-[3-hydroxy-2-methyl-1-propyl]-cis-cis-hexahydrojulolidine (135 mg, 0.54 mmole) and potassium tertiary-butoxide (148 mg, 1.3 mmole) were dissolved in benzene (40 ml). To the solution, through which nitrogen was continuously bubbled, was added fluorenone (456 mg, 2.5 mmole). The mixture, which turned from green to brown in a few minutes, was stirred at room temperature for 2 1/2 hours. To the reaction mixture was then added water (40 ml) and benzene (40 ml). The layers were separated and the aqueous layer was extracted with ether (3 x 20 ml). The combined organic layers were washed once with water then extracted with hydrochloric acid (5%, 4 x 20 ml). The acid extracts were combined and basified with sodium hydroxide (3N).

The alkaline mixture was extracted with ether (4 x 25 ml). The ether extracts were combined, dried ($MgSO_4$) and concentrated. 104 mg of light oil remained. This was shown by t.l.c. to be made up of two components.

The crude product was filtered through alumina (3 g, BDH). The first two fractions (25 ml each, benzene -10% ether) contained only the less polar component, 89 mg, 65% yield. The infrared spectrum (CCl_4) shows absorption at 2930, 2870, 2810, 2770, 2700 and 1730 cm^{-1}. The n.m.r. ($CDCl_3$) shows a signal at τ0.42 (doublet, J = 3 cps, 1H CH-CHO).

Modified Oppenauer Oxidation of 9-ethylenedioxy-11-[3-hydroxy-2-methyl-1-propyl]-cis-trans-hexahydrojulolidine.

9-Ethylenedioxy-11-[3-hydroxy-2-methyl-1-propyl]-cis-trans-hexahydrojulolidine (97 mg, 0.3 mmole) was dissolved in benzene (20 ml). To the ice cold solution was added potassium tertiarybutoxide (97 mg) and fluorenone (303 mg, 1.6 mmole). Nitrogen was continuously bubbled through the solution which was stirred for 2 hours at 0°. Water (30 ml) was added and the layers were separated. The aqueous layer was extracted three times with ether (3 x 25 ml). The organic layers were combined and extracted four times with 10% HCl (4 x 20 ml). The acidic extracts were immediately basified with conc. ammonium hydroxide. The alkaline solution was then extracted with ether

(3 x 20 ml). The ether extracts were combined, dried ($MgSO_4$) and evaporated. 28 mg of starting material was recovered.

Oppenauer Oxidation of 9-ethylenedioxy-11-[3-hydroxy-2-methyl-1-propyl]-cis-trans-hexahydrojulolidine.

9-Ethylenedioxy-11-[3-hydroxy-2-methyl-1-propyl]-cis-trans-hexahydrojulolidine (120 mg, .39 mmole) was dissolved in toluene (20 ml). Freshly prepared aluminum tri-isopropoxide (212 mg, 1 mmole) was added as well as 2 ml of cyclohexanone. The reaction mixture was refluxed for 3 hours. The solution was cooled and extracted with cold 10% HCl (4 x 15 ml). The HCl extracts were immediately poured into an excess of cold 3N ammonium hydroxide. The basic solution was then extracted with chloroform (4 x 15 ml). The chloroform extracts were combined, dried ($MgSO_4$) and evaporated. 117 mg of oil was obtained. This oil showed several spots on a t.l.c. plate. The infrared spectrum ($CHCl_3$) shows absorption at 3590, 3400 (broad), 2930, 2860, and 1710 cm^{-1}. The n.m.r. ($CDCl_3$) shows a signal at τ4.85 (singlet) but no aldehydic proton signal. Another sharp signal appears at τ6.05. The rest of the spectrum is not clearly defined. The mass spectrum shows a great variety of peaks, the strongest being at m/e 83. Other peaks are present at m/e 291, 236, 192, 150, 100, 99, 98, 86, 81, 71, and 67. The peaks above m/e 100

are much weaker than those below. A sample was sublimed. The oil obtained showed the same infrared spectrum as the crude product.

Sarett Oxidation of 9-ethylenedioxy-11-[3-hydroxy-2-methyl-1-propyl]-cis-trans-hexahydrojulolidine.

9-Ethylenedioxy-11-[3-hydroxy-2-methyl-1-propyl]-cis-trans-hexahydrojulolidine (58 mg, 0.19 mmole) was dissolved in pyridine (8 ml). The solution was added to a reagent made from CrO_3 (126 mg, .13 mmole) and pyridine (1 ml). The resulting reaction mixture was stirred at 0° for 3 hours. The solution was diluted with methylene chloride (30 ml) and was filtered through alumina (2 g, Activity III). 47 mg of starting material was obtained.

The above reaction was carried out on 41 mg of the alcohol (0.13 mmole) using CrO_3 (88 mg, 0.09 mmole) in pyridine at room temperature overnight. Similar workup gave 25 mg of a multicomponent (t.l.c.) oil which still contained starting material (t.l.c. and i.r.).

CrO_3-pyridine oxidation at room temperature for 2 hours followed by reaction at 100° for 1 hour gave, from 41 mg of starting alcohol, 17 mg of a multicomponent oil. This was not examined further than by infrared ($CHCl_3$) which shows strong O-H bonding and a series of weak absorptions from 1730 to 1630 cm^{-1}.

Barton Oxidation of 9-ethylenedioxy-11-[3-hydroxy-2-methyl-1-propyl]-cis-trans-hexahydrojulolidine.

9-Ethylenedioxy-11-[3-hydroxy-2-methyl-1-propyl]-cis-trans-hexahydrojulolidine (691 mg, 2.23 mmole) was dissolved in 1:1 ether:dichloromethane (20 ml). Ether, saturated with phosgene, was added in excess. The solvent was evaporated, leaving a white foam. The infrared spectrum ($CHCl_3$) of this foam shows broad absorption at 3350 and 2500 cm^{-1} and a strong sharp band at 1865 cm^{-1} (chloroçarbonate).

The semi-solid was dissolved in dimethylsulfoxide (distilled from CaH_2, 10 ml) and the solution was stirred for 20 minutes. Triethylamine (3 ml) was added and the mixture was stirred for 1 hour. After the addition of of sodium bicarbonate (10%, 50 ml) the solution was extracted with Skelly B (5 x 25 ml). The extracts were combined, dried ($MgSO_4$) and evaporated. 256 mg of oil was obtained. This oil contained at least 6 components (t.l.c.). The infrared spectrum (CCl_4) of the crude did show the presence of a carbonyl (1730 cm^{-1} weak).

Chromatography on alumina yielded three fractions. The first (Skelly B-50% benzene, 120ml) amounted to 26 mg and showed the presence of an aldehyde in its infrared spectrum. It was not homogeneous (2 components) by t.l.c. The infrared spectrum (CCl_4, weak) shows absorptions at 2950, 2930, 2870, 2850, 2800 (broad, weak), 2700 (broad, weak)

and at 1735 cm^{-1}. The n.m.r. shows two signals of interest, one, a doublet (J = 1.5 cps) at τ0.25 and what appeared to be three very sharp singlets at τ6.38. The ratio of these two signals was 1 to 5.5.

The second fraction contained at least four components (39 mg) and was not investigated further. The last fraction (ether-chloroform, 50%) contained 144 mg of starting material (i.r., t.l.c.).

The above reaction was carried out on ten different occasions using anywhere from 40 mg to 800 mg of starting material. In all cases recovery of basic material was small (30%) and most of this was starting material. In all cases the infrared indicated the presence of a carbonyl but this compound could not be isolated in pure form.

DMSO-Ac_2O Oxidation of 9-ethylenedioxy-11-[3-hydroxy-2-methyl-1-propyl]-cis-trans-hexahydrojulolidine.

9-Ethylenedioxy-11-[3-hydroxy-2-methyl-1-propyl]-cis-trans-hexahydrojuloline (480 mg, 1.55 mmole) was mixed with DMSO (5 ml, distilled from CaH_2) and acetic anhydride (3 ml). The reaction mixture was stirred overnight after which ice and water (20 ml) were added. The aqueous slurry was basified with ammonium hydroxide and extracted four times with ether (100 ml). The ether extracts were combined, dried ($MgSO_4$) and evaporated. 390 mg of dark oily solid was obtained. This was shown

to be mainly one component by t.l.c. The main component was collected after filtration through alumina. 260 mg of solid which appeared to be made up of two components of very similar Rf (t.l.c.) was obtained. The infrared spectrum (CCl_4) has no "Bohlmann" bands but does show absorption at 1735 and 1230 cm^{-1}. The mass spectrum shows a parent peak at m/e 351 and a base peak at m/e 150. Other prominent peaks appeared at m/e 236 and m/e 178.

Hydrolysis of 9-ethylenedioxy-11-[3-acetoxy-2-methyl-1-propyl]-cis-trans-hexahydrojulolidine.

9-Ethylenedioxy-11- [3-acetoxy-2-methyl-1-propyl]-cis-trans-hexahydrojulolidine (200 mg) was dissolved in methanol (5 ml) to which was added 3N NaOH (20 ml). The reaction mixture was stirred at room temperature overnight. The basic mixture was then extracted with ether (3 x 25 ml). The ether extracts were combined, dried ($MgSO_4$) and evaporated. 168 mg of solid material was obtained. The product was dissolved in 1:1 benzene:ether (20 ml) and filtered through alumina. 104 mg of solid was recovered. This material has an identical infrared spectrum with that of 9-ethylenedioxy-11-[3-hydroxy-2-methyl-1-propyl]-cis-trans-hexahydrojulolidine.

DMSO-DCC TFA Py Oxidation of 9-ethylenedioxy-11-[3-hydroxy-2-methyl-1-propyl]-cis-trans-hexahydrojulolidine.

9-Ethylenedioxy-11-[3-hydroxy-2-methyl-1-propyl]-cis-trans-hexahydrojulolidine (320 mg, 1.03 mmole) was

dissolved in benzene (3 ml). To the solution was added DMSO (3 ml, distilled from CaH_2) as well as pyridine (0.09 ml, 3.6 mmole) and trifluoroacetic acid (0.045 ml, 1.8 mmole). Dicyclohexylcarbodiimide (750 mg, 3.6 mmole) was added to the solution. The reaction flask was stoppered and left standing at room temperature for 9 hours. Ether (25 ml) and oxalic acid (330 mg) in methanol (4 ml) were added. The mixture was stirred overnight and filtered. The filtrate was extracted with 5% bicarbonate (3 x 20 ml) and twice with water. The ether was dried ($MgSO_4$) and evaporated. 262 mg of oil containing crystals were obtained. This product was made up of several components including starting material (t.l.c.). The infrared spectrum (CCl_4) shows weak OH absorptions (3640, 3150 cm^{-1}) as well as absorptions at 2930, 2850, 2120 (strong), 1735 (weak) and 1650 cm^{-1} .

Separation by chromatography on alumina gave two main fractions. The first had a very strong i.r. absorption band at 2120 cm^{-1} and the second main component showed absorption at 3430, 1650, and 1510 cm^{-1}.

<u>H_3PO_4-DCC Oxidation of 9-ethylenedioxy-11-[3-hydroxy-2-methyl-1-propyl]-cis-trans-hexahydrojulolidine</u>.

9-Ethylenedioxy-11-[3-hydroxy-2-methyl-1-propyl]-<u>cis-trans</u>-hexahydrojulolidine (571 mg, 1.8 mmole) was dissolved in freshly dried dimethylsulfoxide (2.5 ml)

containing dicyclohexylcarbodiimide (1.117 g, 5.5 mmole) and anhydrous phosphoric acid (4.5 ml of a 1M solution in DMSO). The reaction vessel was sealed and stirred for 14 hours. Water (10 ml), ether (10 ml) and H_3PO_4 (2.7 ml of a 1M H_3PO_4 in DMSO solution) were added. After stirring for 20 minutes, the precipitate was filtered off. The layers of the filtrate were separated and the aqueous layer was extracted again with ether. The water layer was basified with lithium hydroxide and was extracted again with ether (3 x 25 ml). All the ether extracts were combined, dried ($MgSO_4$) and evaporated. 174 mg of oil was obtained. T.l.c. showed the presence of at least four components. The infrared spectrum (CCl_4) shows a weak O-H absorption at 3640 cm^{-1} with hydrogen bonded hydroxyl from 3500 cm^{-1} to 3050 cm^{-1}, also very weak. Other absorption is found at 2930, 2860, 2800, 2770, 2700, 2120, 1735, 1680, and 1640 cm^{-1}.

The product was acid-base extracted. 124 mg of basic oil was recovered. This showed mainly 1 spot on t.l.c. The infrared spectrum still shows weak OH absorptions as well as absorptions at 2800, 2770 (Bohlmann bands), 2700 and 1735 cm^{-1}. The product was filtered through alumina. 87 mg of oil was recovered. The mass spectrum shows four small peaks at m/e 307, 308, 309, 310 as well as more intense peaks at m/e 248, 236, 179, 178 (base), 176 and 150 .

Hydrolysis of H_3PO_4-DCC Oxidation Product

The product obtained from the H_3PO_4-DCC oxidation was dissolved in methanol (2 ml) and 10% HCl (30 ml) was added. The solution was then stirred overnight. Basification using 3N NaOH was followed by extraction with chloroform (4 x 20 ml). The extracts were combined, dried ($MgSO_4$) and evaporated. 67 mg of oil remained.

The infrared spectrum (CCl_4) of the homogeneous oil (t.l.c.) shows absorption at 2930, 2850, 2800, 2770, 2700 and 1735 cm^{-1}. The n.m.r. ($CDCl_3$) shows a proton at τ0.27 doublet J = 4 cps. The mass spectrum shows peaks at m/e 249, 192, and 178 (base peak).

The product was found to be identical with an authentic sample of 11-[2-methyl-3-oxo-1-propyl]-cis-cis-hexahydrojulolidine.

Lead Tetraacetate Oxidation of 9-ethylenedioxy-11-[3-hydroxy-2-methyl-1-propyl]-cis-trans-hexahydrojulolidine.

9-Ethylenedioxy-11-[3-hydroxy-2-methyl-1-propyl]-cis-trans-hexahydrojulolidine (182 mg, .59 mmole) was dissolved in pyridine (10 ml). Lead tetraacetate (289 mg, .65 mmole) was added. The pyridine solution turned red immediately and became homogenous after fifteen minutes. The flask was sealed and the solution was stirred for 20 hours. The pyridine was removed and the residue was taken up in saturated $NaHCO_3$ (35 ml). The solution was extracted

four times with ether (4 x 20 ml). The ether layers were combined, dried ($MgSO_4$) and evaporated. 109 mg of dark oil remained. The infrared spectrum (CCl_4) shows absorption at 3640, 3150 (broad), 2950, 2870, 1780, 1745, and 1225 cm^{-1}. The n.m.r. shows a singlet at τ6.05, a singlet at τ7.95 and a doublet at τ6.51. T.l.c. showed the presence of some starting material (same Rf) as well as components of the same Rf as the acetates of the starting alcohols.

Modification of the Oppenauer Oxidation of 9-keto-11-[3-hydroxy-2-methyl-1-propyl]-cis-trans-hexahydrojulolidine.

9-Keto-11-[3-hydroxy-2-methyl-1-propyl]-cis-trans-hexahydrojulolidine (60 mg, 0.23 mmole) was dissolved in benzene (20 ml). Potassium tertiarybutoxide (67 mg, 0.6 mmole) was added and N_2 gas was bubbled through the solution. After cooling to 0°, 9-fluorenone (207 mg, 1.15 mmole) was added and stirring was continued for 2 1/2 hours. Ice water (20 ml) was added and the layers were separated. The benzene layer was extracted with 10% HCl (4 x 25 ml). Each acidic extract was poured into a solution of sodium bicarbonate (10%). The bicarbonate layer was made more basic using 3N NaOH and this basic solution was extracted with $CHCl_3$ (4 x 25 ml). The chloroform extracts were combined, dried ($MgSO_4$) and evaporated. 38 mg of crystalline material was recovered. This showed two spots on t.l.c. and has an infrared

spectrum identical with that of the starting material.

Hydroboration of 9-Ethylenedioxy-11-methallyl-cis-cis-hexahydrojulolidine.

9-Ethylendioxy-11-methallyl-cis-cis-hexahydrojulolidine (4.98 g, 17.1 mmole) was dissolved in dry tetrahydrofuran (distilled from LAH, 50 ml). Into this solution was bubbled a stream of nitrogen gas carrying B_2H_6 prepared in diglyme (distilled from $LiAlH_4$) by the addition of a solution of boron trifluoride-etherate (9 ml) in diglyme (20 ml) to diglyme (30 ml) containing $NaBH_4$ (1.3 g, 34 mmole). After addition of the diborane the flask was sealed and the solution stirred for 3 hours. The excess B_2H_6 was then cautiously destroyed with ice, and 3N NaOH (50 ml) was added followed by 30% H_2O_2 (50 ml), the latter dropwise over a one hour period. The mixture was stirred overnight and then extracted four times with ether (4 x 50 ml). The ether extracts were combined, dried ($MgSO_4$) and evaporated. A white oil (5.18 g, 95%) was obtained, The oil eventually crystallized, m.p. 110-112°.

T.l.c showed the presence of 1 substance only. The infrared spectrum (CCl_4) shows absorptions at 3630, 3480, 2920, 2860, 2800, 2870, 2840, and 2670 cm^{-1}. It fails to show the double bond absorptions at 3070, 1635, and 885 cm^{-1}. The mass spectrum shows a peak at m/e 309 (parent), one at m/e 308, and the base peak at m/e 236.

9-Ethylenedioxy-11-[2-methyl-3-oxo-1-propyl]-cis-cis-hexahydrojulolidine.

9-Ethylenedioxy-11-[3-hydroxy-2-methyl-1-propyl]-cis-cis-hexahydrojulolidine (5 g, 16.2 mmole) and potassium tertiarybutoxide (4.5 g, 41 mmole) were mixed in dry benzene (100 ml). The mixture was stirred with a magnetic stirrer and N_2 was bubbled through. 9-Fluorenone (14.5 g, 81 mmole) was added. The solution, which turned brown very quickly, was stirred at room temperature for three hours. Water (100 ml) was added and the layers were separated. The benzene layer was washed once with water (100 ml) then was extracted with 7% HCl (3 x 25 ml). The acid extract was immediately poured into cold 10% NaOH (100 ml). The alkaline mixture was then extracted with chloroform (4 x 25 ml). The chloroform extracts were combined, dried ($MgSO_4$) and evaporated. 4.1 g (81%) of oil remained. T.l.c. showed the presence of four components, one being the major product and the other three being minor impurities. The major product was obtained by filtering a solution of the crude product through alumina.

The infrared spectrum (CCl_4) shows absorption bands at 2920, 2850, 2800, 2750, 2700, and 1740 cm^{-1}. The n.m.r. spectrum ($CDCl_3$) shows signals at τ0.37 (doublet, J = 2 cps, 1H, CH-CHO) and at τ6.08 (singlet, 4H, $-OCH_2CH_2O-$).

The mass spectrum shows peaks at m/e 307 (M^+), m/e 306, 305, and 236.

Ketal Exchange

9-Ethylenedioxy-11-[2-methyl-3-oxo-1-propyl]-cis-cis-hexahydrojulolidine (750 mg, 2.4 mmole) was dissolved in dry benzene (25 ml). To the solution was added p-toluenesulfonic acid monohydrate (522 mg, 2.8 mmole). The solution was refluxed for 3 hours at which point the water was removed using a water separator. The benzene solution was extracted with 3N NaOH (25 ml) and with water (25 ml). The aqueous layers were combined and extracted with ether (3 x 25 ml). The ether extracts were combined with the benzene layer and the resulting solution was dried ($MgSO_4$) and evaporated. 696 mg of oil was obtained. The infrared spectrum of this oil still shows the presence of the aldehyde function by absorptions at 2700 and 1740 cm^{-1}. T.l.c. indicated the presence of at least two substances.

The above reaction was repeated. However refluxing was allowed to continue for 24 hours. The product obtained was made up of at least 3 components (t.l.c.) and shows infrared absorption at 1719 cm^{-1} (exact measurement). The mass spectrum shows strong peaks at m/e 351 (M^+), 350, 306, 236 (base peak), and 192.

The above product (516 mg) was dissolved in benzene (20 ml) to which was added p-TsOH·H_2O (611 mg) and 1 ml of

water. The mixture was refluxed for 15 hours and worked up as described above. 441 mg of oil was obtained. The infrared spectrum (CCl_4) shows carbonyls at 1740 and 1690 cm^{-1}. The mass spectrum shows peaks at m/e 351, 350, 320, 305, 275, 236 (base), 192, 190, 174, and 146.

Attempted Thioacetal Preparation.

9-Ethylenedioxy-11-[2-methyl-3-oxo-1-propyl]-cis-cis-hexahydrojulolidine (100 mg) was dissolved in dry benzene (25 ml). The solution was saturated with dry HCl and ethanedithiol (1 drop) was added. The solution was stirred under reflux for 2 hours. The water was removed using a water separator. The remaining benzene solution was washed twice with sodium bicarbonate, dried ($MgSO_4$) and evaporated. 92 mg of oil was obtained. This oil showed many spots on t.l.c. The infrared spectrum (CCl_4) shows absorption at 1735 cm^{-1}.

9-Ethylenedioxy-11-[2-methyl-3-oxo-1-propyl]-cis-cis-hexahydrojulolidine (136 mg) was dissolved in benzene (5 ml). The solution was acidifed with dry HCl and ethanedithiol (1 ml) was added. The solution was stirred overnight at room temperature. Benzene (25 ml) was added and the solution was washed twice with saturated $NaHCO_3$. The aqueous layers were extracted with ether (3 x 25 ml) and the organic phases were combined. After being dried ($MgSO_4$) and evaporated, the combined extracts yielded 114 mg

of oil which eventually crystallized. This was shown to be homogeneous by t.l.c.

The infrared (CCl_4) shows absorption at 2930, 2870, 2800 and 2870 cm^{-1}. The n.m.r. spectrum ($CDCl_3$) shows signals at τ5.30 (doublet, J = 4.5 cps, 1H, CH-CH$\overset{S}{\underset{S}{\diagup}}$), a signal at τ6.75 (singlet, 4H, -S-CH_2CH_2-S), and one at τ6.81 (singlet, 4H, S-CH_2CH_2-S). The mass spectrum shows peaks at m/e 416, 415, 414, 326, 284, 270, 269, 268 (base), 267, 266, 256, 240, 208, 175, 149, and 146.

9-Ethylenedioxy-11-[2-methyl-3-oxo-1-propyl]-<u>cis</u>-<u>cis</u>-hexahydrojulolidine (114 mg, 0.27 mmole) was dissolved in benzene (10 ml). HCl was bubbled through and ethanedithiol (26 mg, 0.27 mmole) in benzene solution (0.72 ml of a 25 ml solution containing 0.898 g of ethanedithiol) was added. After 2 hours the reaction mixture was washed twice with saturated $NaHCO_3$. The aqueous layers were combined, made more basic, and extracted with ether (3 x 25 ml). All the organic phases were combined, dried ($MgSO_4$) and evaporated. 98 mg of oil remained. This still showed a substantial aldehyde carbonyl in the infrared spectrum (CCl_4) at 1735 cm^{-1}. There were at least 3 compounds present (t.l.c.).

A similar experiment was carried out using 2 equivalents of ethanedithiol with a reaction time of 3 hours. The product obtained eventually crystallized. No carbonyl absorption appears in the infrared spectrum (CCl_4). The n.m.r. showed the following signals: τ5.28 (doublet

J = 4.5 cps, 1H, CH-CH$\langle^{S}_{S}$); τ6.72 (singlet, 4H, S-CH_2CH_2-S) and τ6.78 (singlet, 4H, S-CH_2CH_2-S).

Hydrolysis of 9-Ethylenedioxy-11-[2-methyl-3-oxo-1-propyl] cis-cis-hexahydrojulolidine.

9-Ethylenedioxy-11-[2-methyl-3-oxo-1-propyl]-cis-cis hexahydrojulolidine (682 mg) was dissolved in methanol (5 ml). To the methanol solution was added 10% HCl (100 ml). The resulting solution was stirred overnight at room temperature. The solution was then basified with 3N NaOH and extracted with chloroform (4 x 25 ml). The chloroform extracts were combined, dried ($MgSO_4$) and evaporated. 558 mg of dark oil remained. This showed many impurities on t.l.c. These were removed by chromatography.

The infrared spectrum (CCl_4) shows absorptions at 2940, 2870, 2810, 2798, 2700 and 1720 cm^{-1}. The mass spectrum shows a parent peak at m/e 263. The base peak is found at m/e 192.

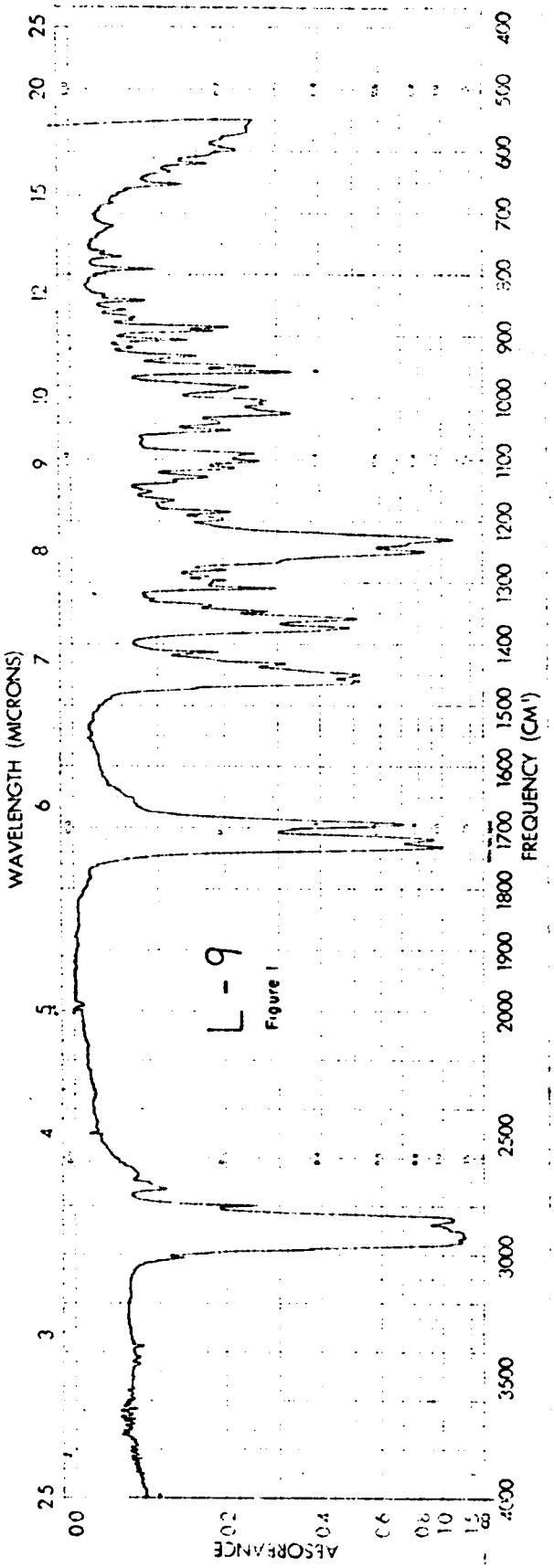
Attempted Epoxide Formation

9-Ethylenedioxy-11-methallyl-cis-trans-hexahydrojulolidine (100 mg) was dissolved in chloroform (25 ml). m-Chloroperbenzoic acid (155 mg) was dissolved in chloroform (25 ml). The solutions were cooled to 0° and the m-chloroperbenzoic acid solution was added dropwise to the other solution. The reaction mixture was continuously

stirred and allowed to reach room temperature after 6 hours. After a total reaction time of 24 hours the solution was washed with sodium bisulfite solution (2 x 15 ml, 10%) and then with sodium bicarbonate (3 x 20 ml, 10%). The chloroform was dried ($MgSO_4$) and evaporated. 10 mg of gum was recovered. T.l.c. showed the presence of a large number of components.

9-Ethylenedioxy-11-methallyl-cis-trans-hexahydrojulolidine (388 mg, 1.33 mmole) was dissolved in benzene (50 ml). p-Nitroperbenzoic acid (291 mg, 1.6 mmole) was added. The solution was kept at room temperature for 4 days. It was then extracted with saturated aqueous sodium bicarbonate (4 x 10 ml). The benzene was dried ($MgSO_4$) and evaporated. 159 mg of starting material was recovered.

The aqueous washings were extracted with chloroform (3 x 25 ml). The chloroform layers were combined, dried ($MgSO_4$) and evaporated. 150 mg of solid material was recovered. This substance was nearly homogeneous (t.l.c.) and was very polar (t.l.c., alumina, $CHCl_3$). The infrared spectrum shows absorption at 1640 cm^{-1}. The mass spectrum has a parent peak at m/e 307 and the base peak at m/e 236. There is also a peak at m/e 291. The spectral properties are those expected for the N-oxide.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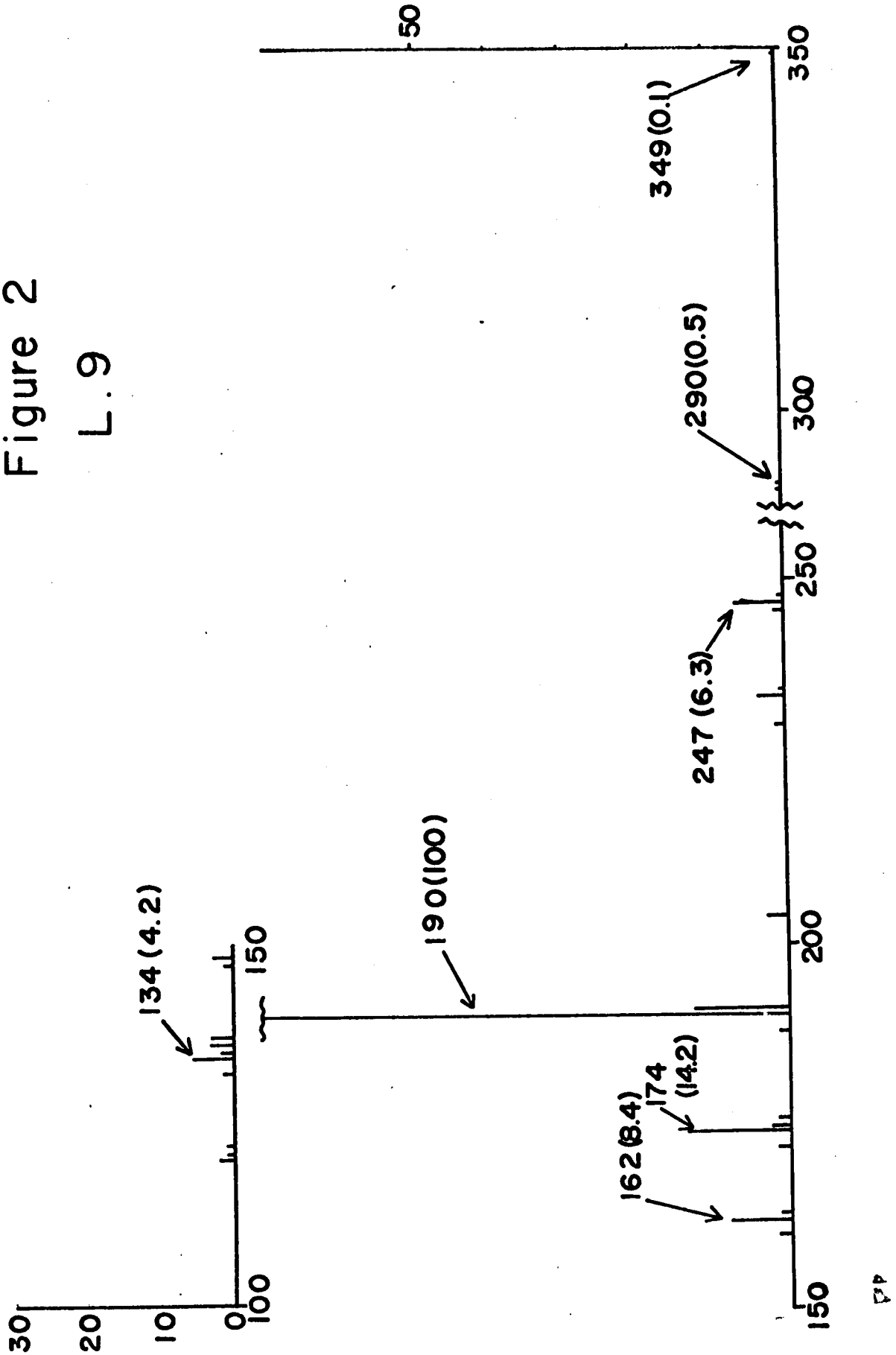
FREQUENCY (CM⁻¹)
ABSORBANCE
L-9
Figure 1

Figure 2

L.9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20
10
0
100
150
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190(100)
200
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50
150
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174
(14.2)

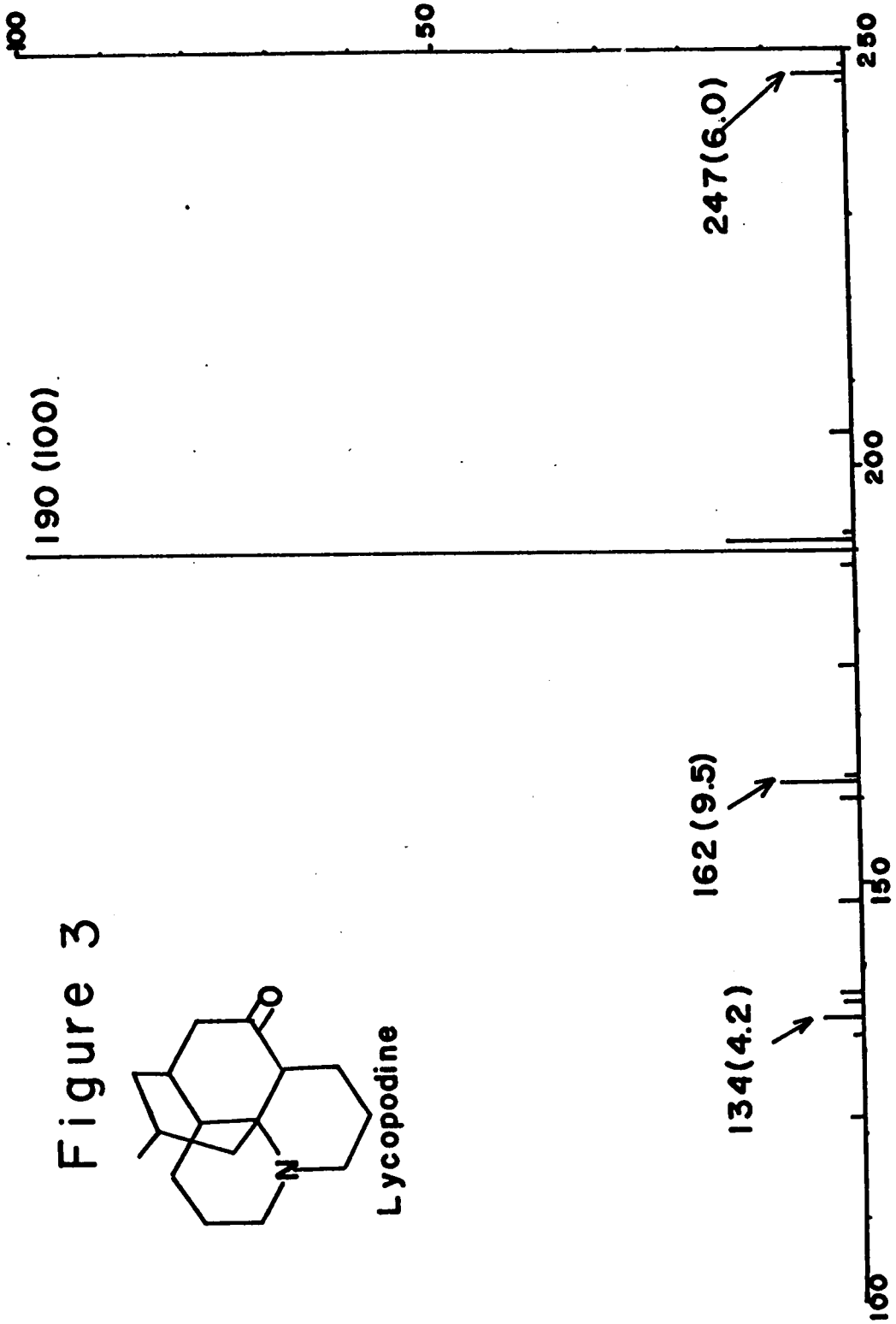
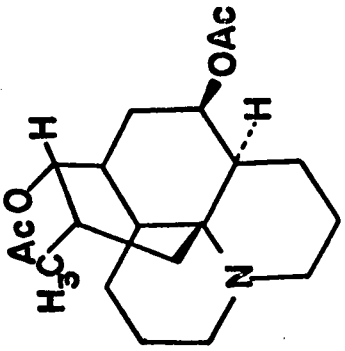


Figure 3

Lycopodine

Figure 4



O-acetyllofoline

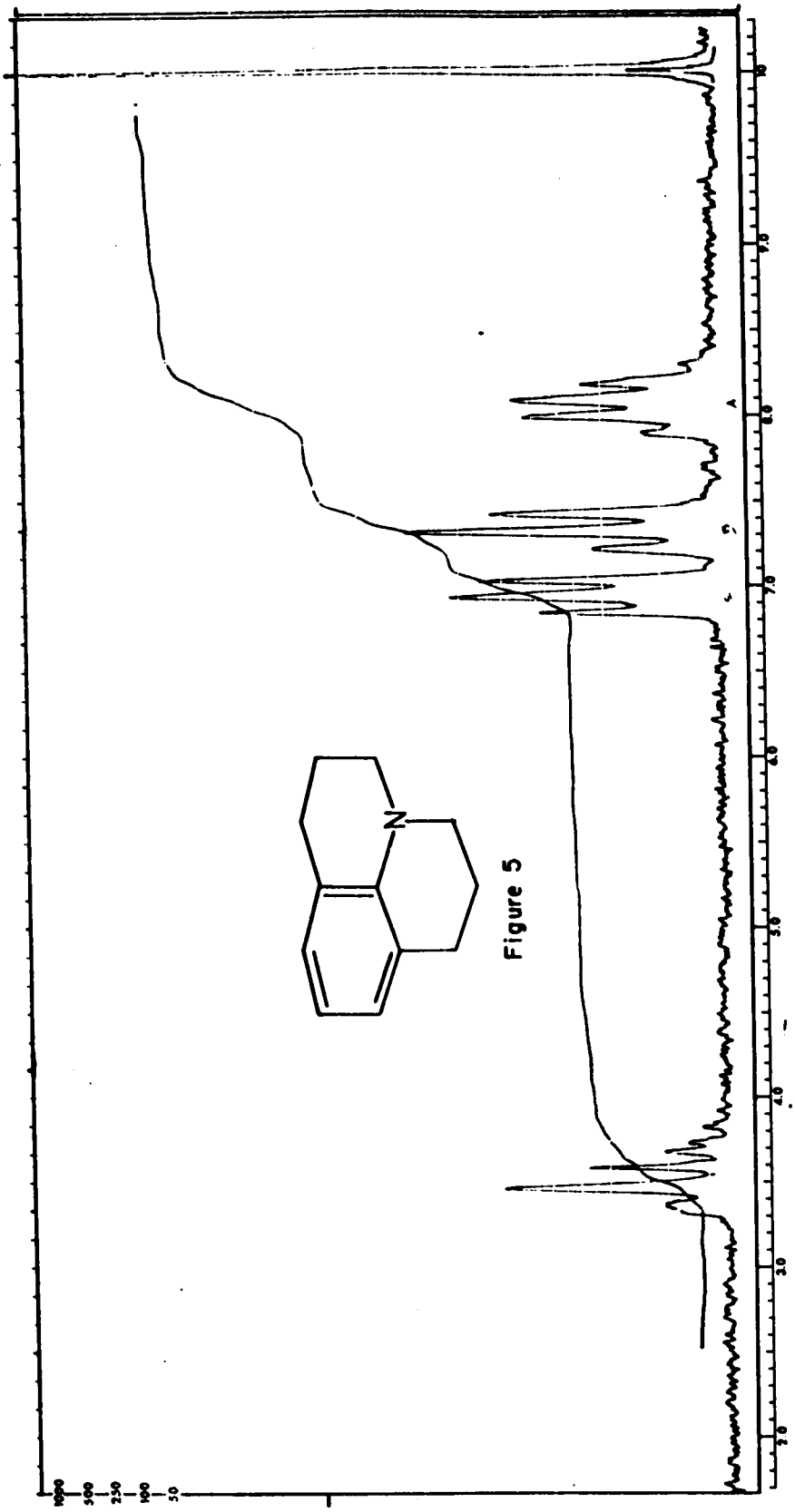
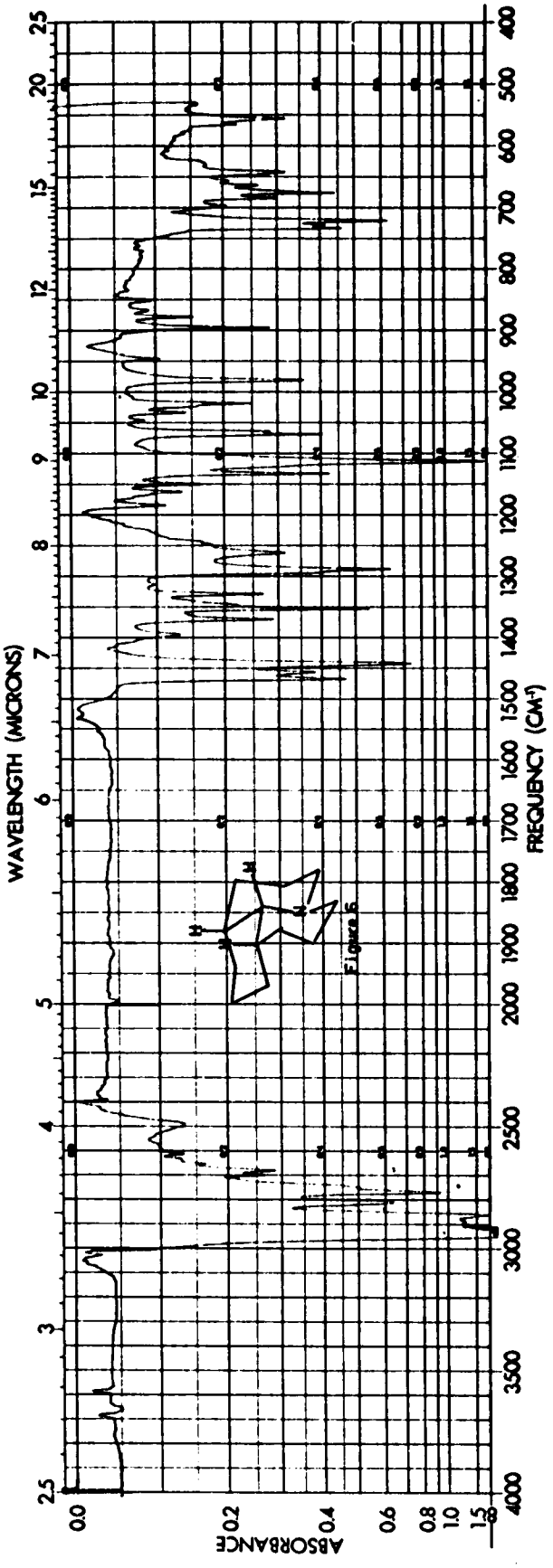


Figure 5


WAVELENGTH (MICRONS)
FREQUENCY (CM⁻¹)
ABSORBANCE
Figure 6

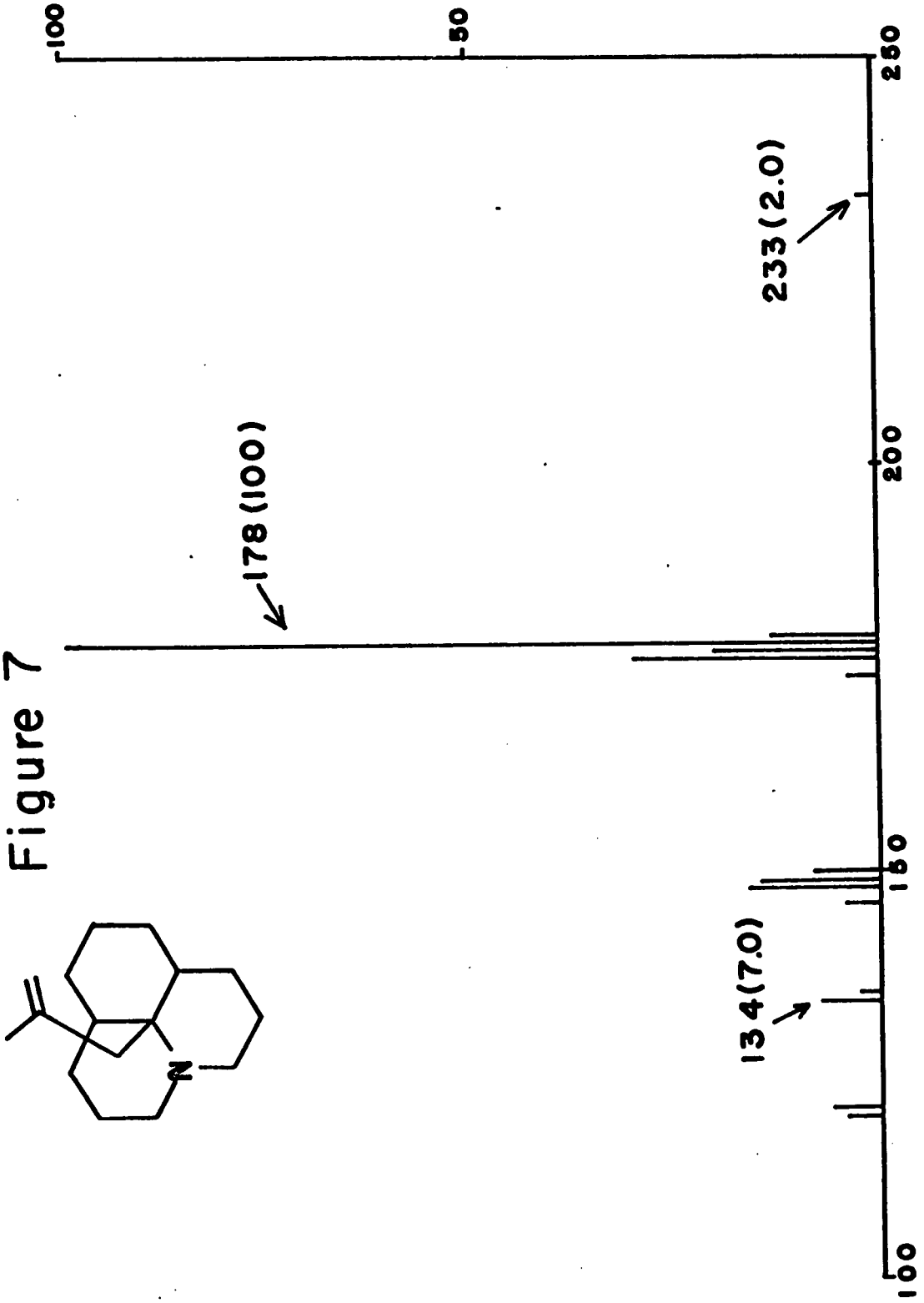


Figure 7

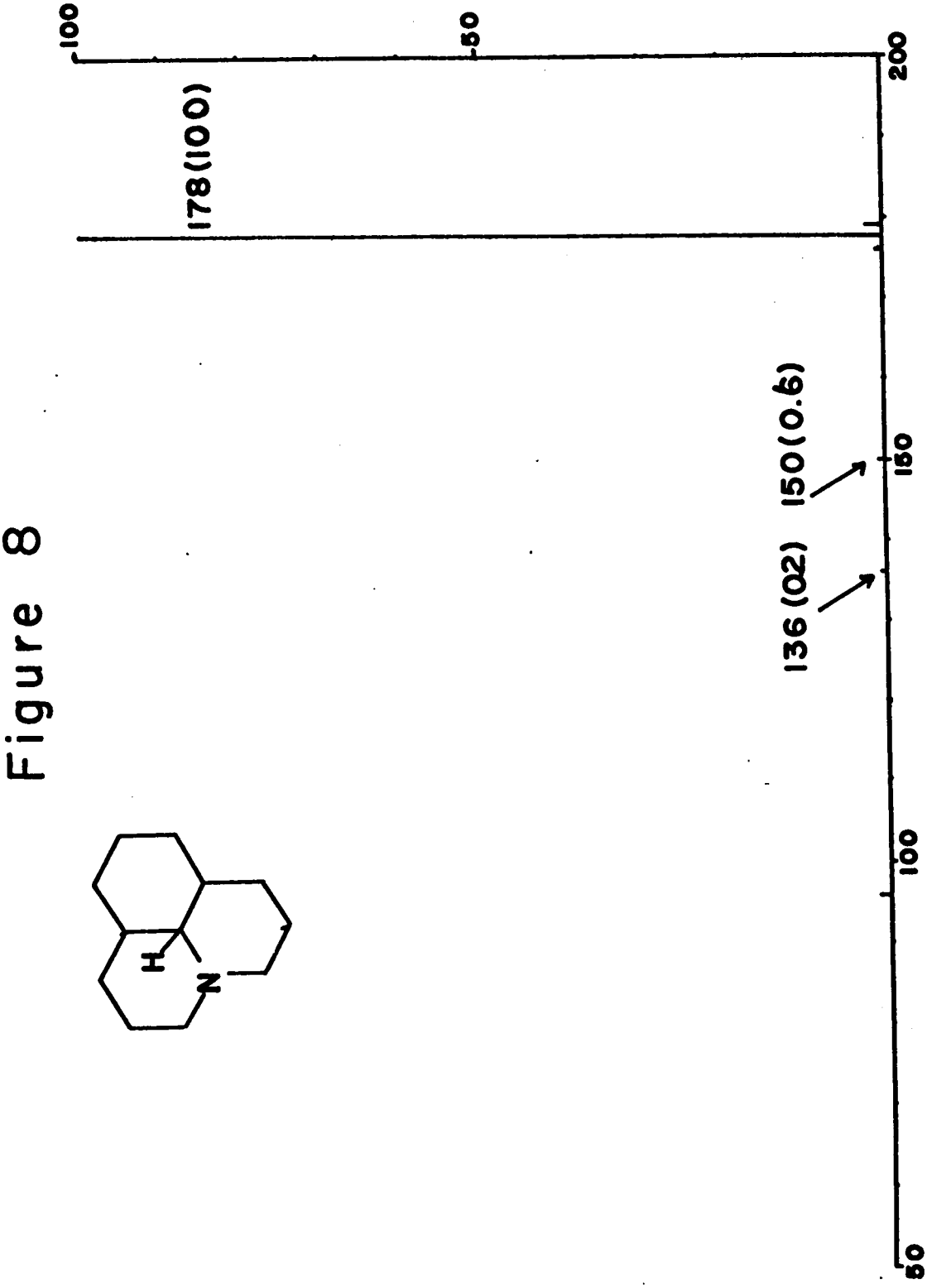
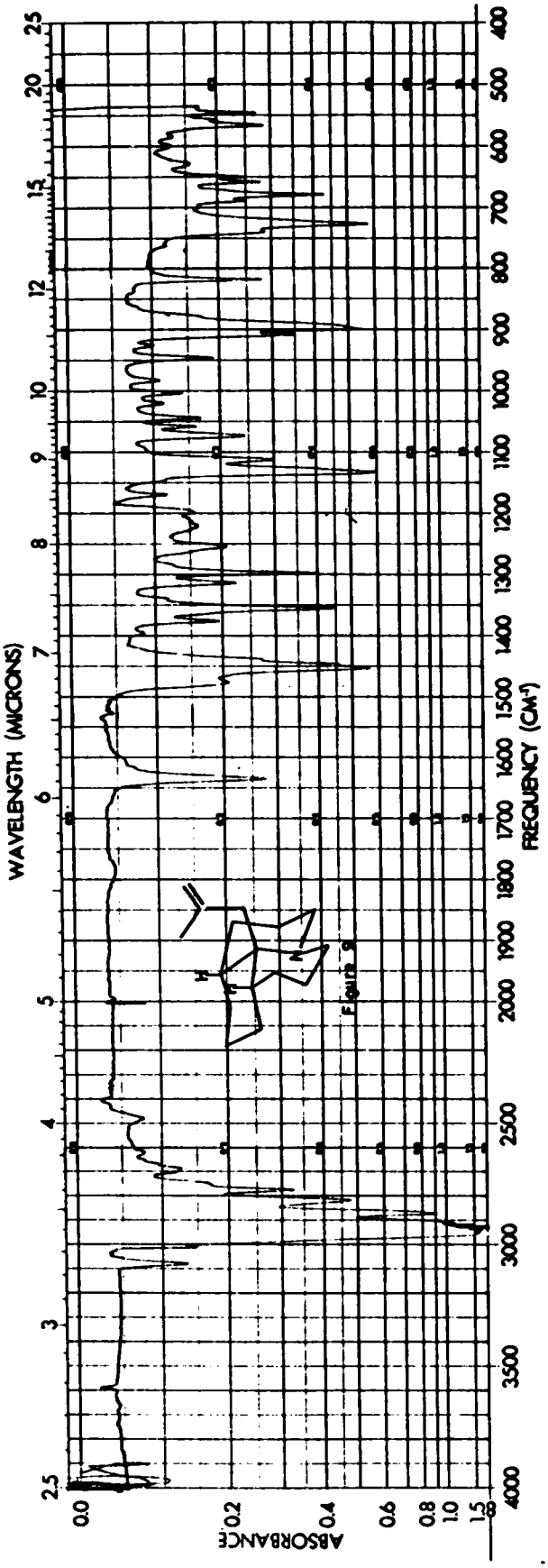
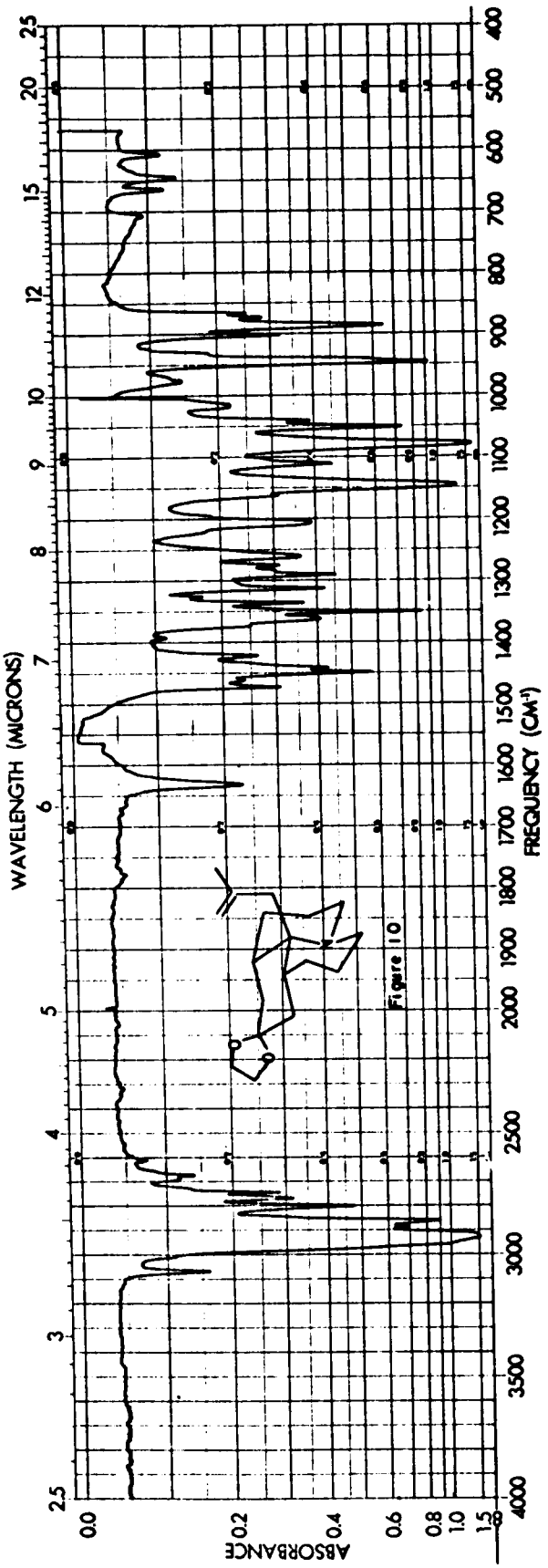
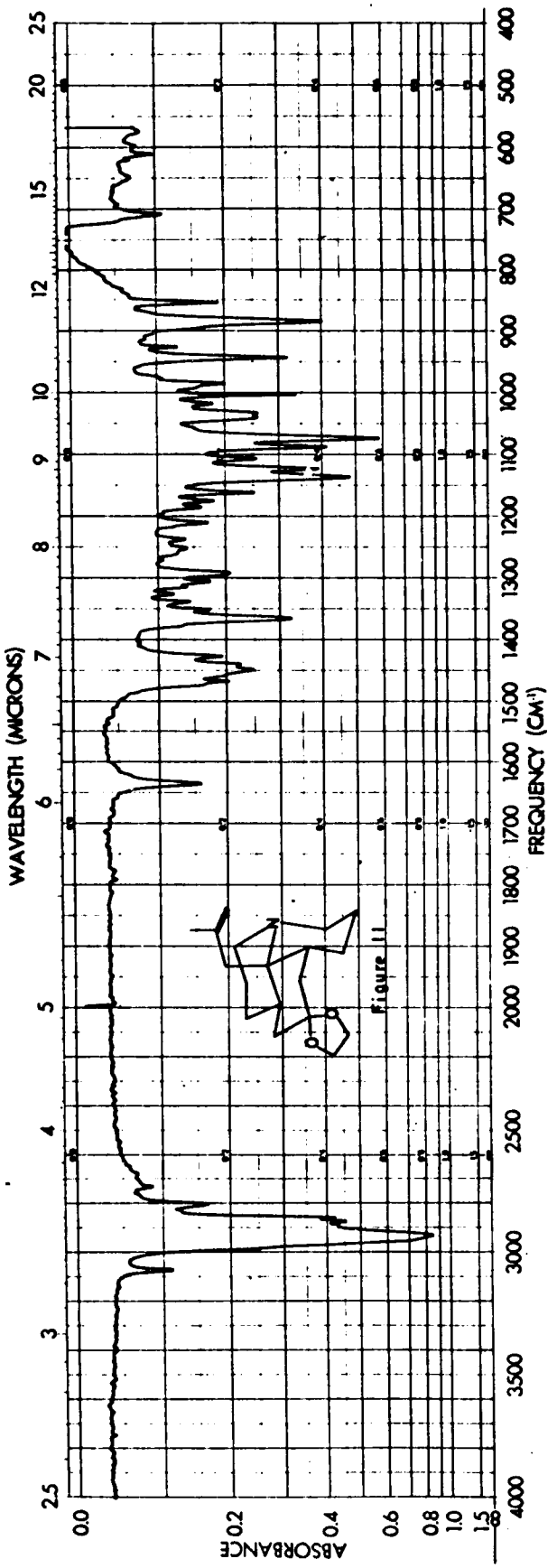
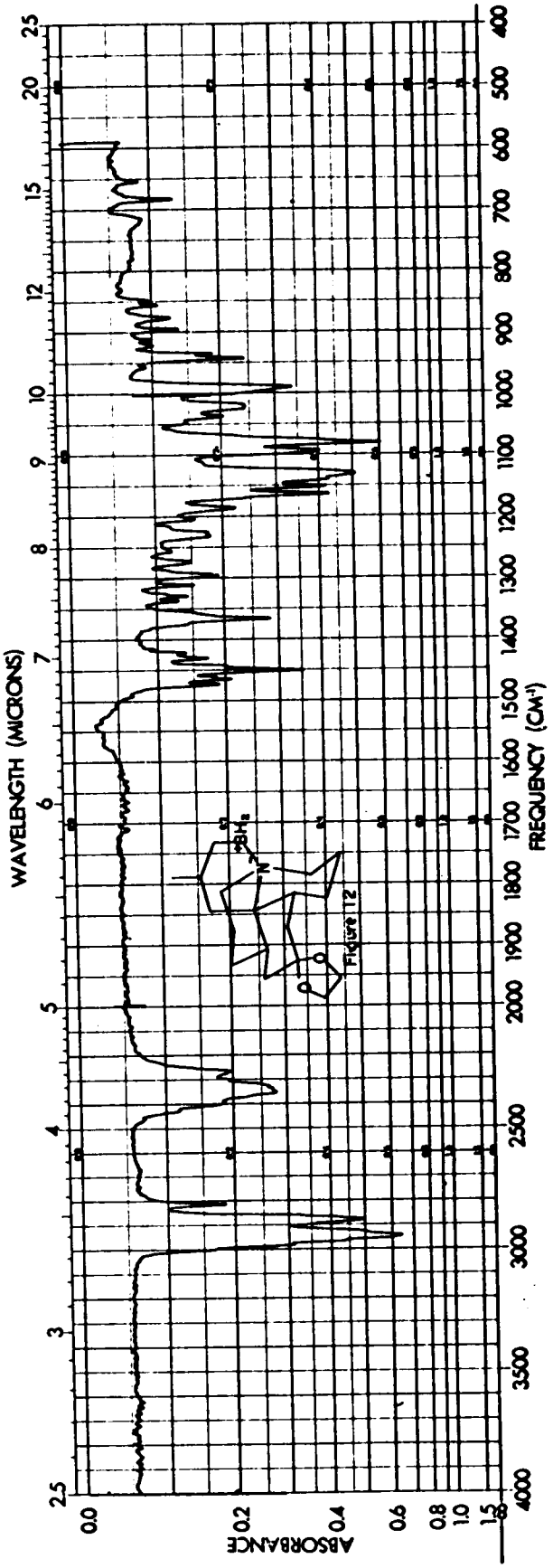


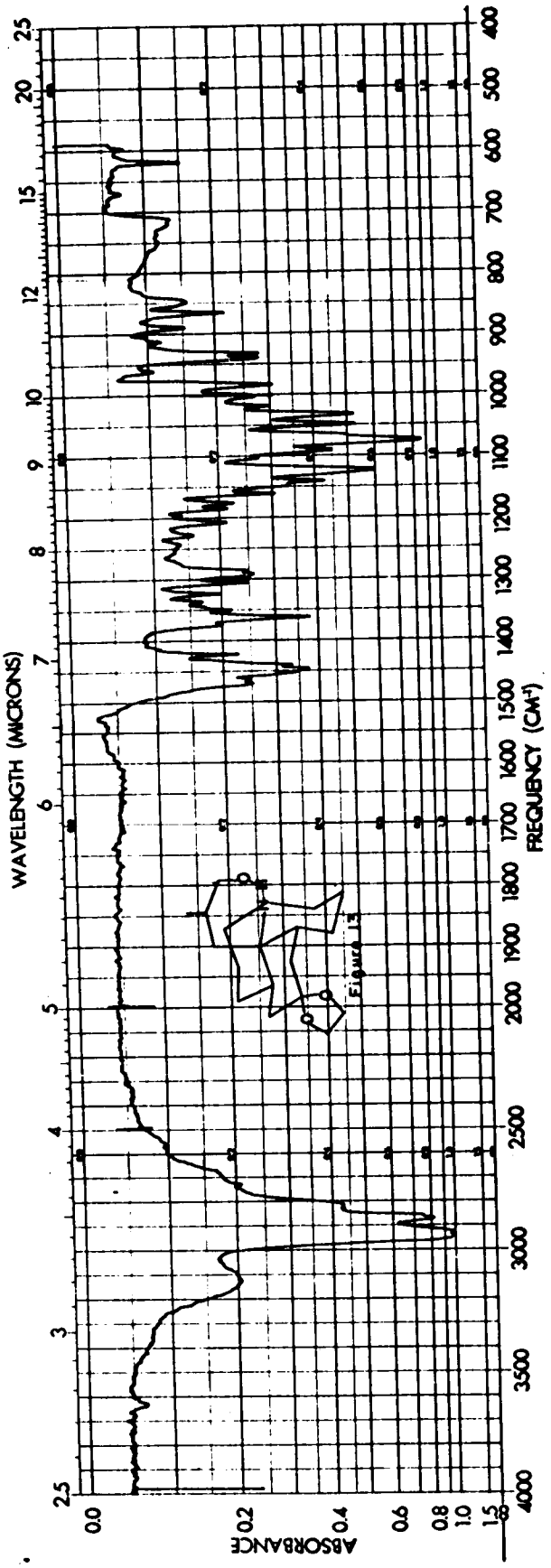
Figure 8

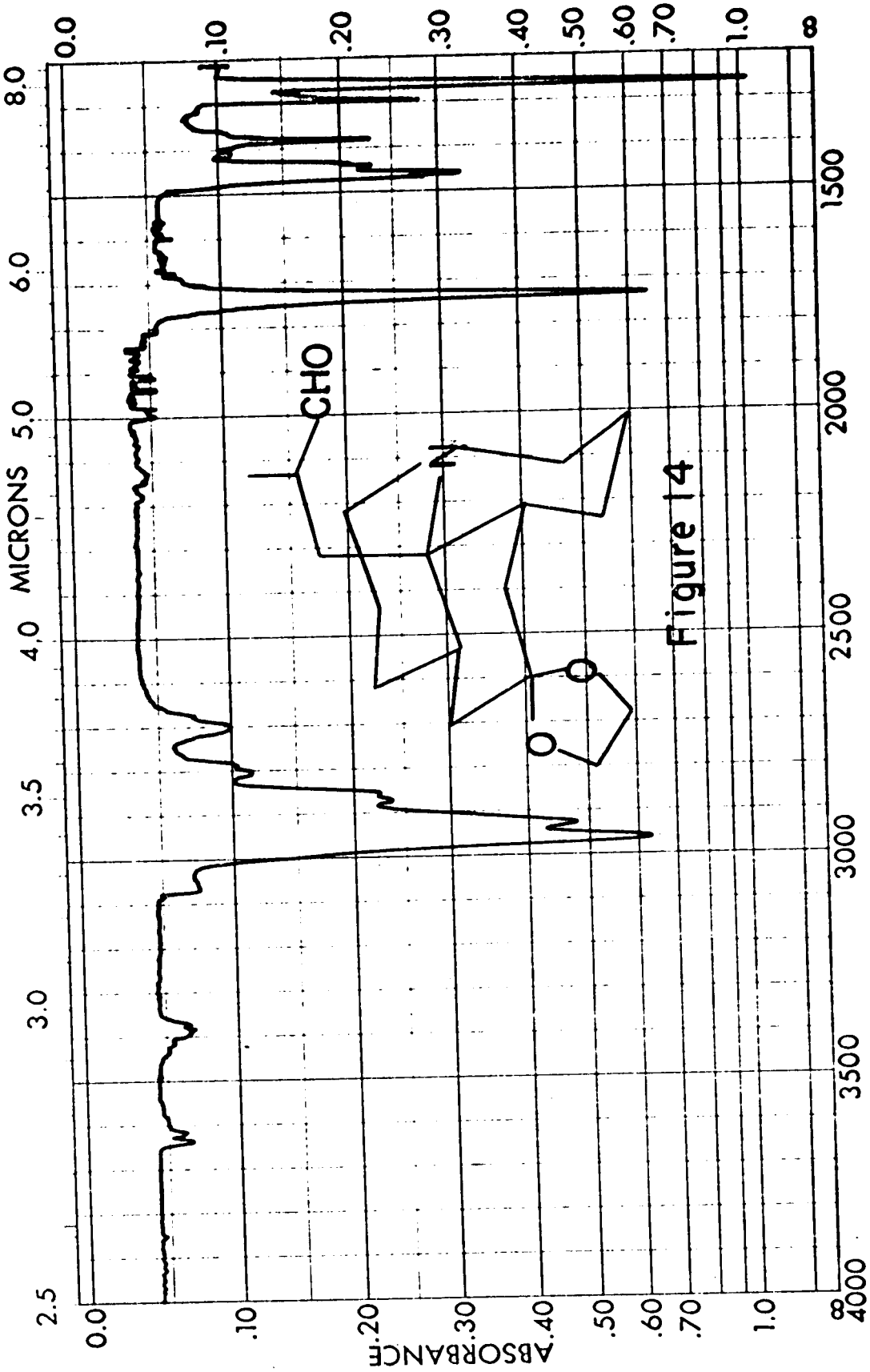

WAVELENGTH (MICRONS)
FREQUENCY (CM⁻¹)
ABSORBANCE
2.5
3
4
5
6
7
8
9
10
12
15
20
25
4000
3500
3000
2500
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
0.0
0.2
0.4
0.6
0.8
1.0
1.5
2.0
H
N
Figure 9


WAVELENGTH (MICRONS)
FREQUENCY (CM⁻¹)
ABSORBANCE
Figure 10


WAVELENGTH (MICRONS)
FREQUENCY (CM⁻¹)
ABSORBANCE
Figure 11


WAVELENGTH (MICRONS)
FREQUENCY (CM⁻¹)
ABSORBANCE
Figure 12


WAVELENGTH (MICRONS)
FREQUENCY (CM⁻¹)
ABSORBANCE
Figure 13


CHO
N
O
O
MICRONS
ABSORBANCE
Figure 14

BIBLIOGRAPHY

1. R.H.F. Manske. "Alkaloids" 5, 295 (1955).
2. R.H.F. Manske and L. Marion. Can. J. Res., B,21, 92 (1943).
3. K. Wiesner, W.A. Ayer, L.R. Fowler and Z. Valenta. Chem. and Ind. (London), 564 (1957).
4. M. Przybylska and L. Marion. Can. J. Chem., 35, 1075 (1957).
5. W.A. Harrison and D.B. MacLean. Chem. and Ind. (London), 261 (1960).
6. D.B. MacLean, in "The Alkaloids, Chemistry and Physiology", Vol. X, R.H.F. Manske, Ed., Academic Press Inc., New York, 1968.
7. B. Yasui, H, Ishii, T. Harayama and Y. Inubushi, Tetrahedron Letters, 3967 (1966).
8. W.A. Ayer, N. Masaki and D.S. Nkunika. Can. J. Chem., in press.
9. W.A. Ayer, G.G. Iverach, J.K. Jenkins and N. Masaki. Tetrahedron Letters, in press.
10. W.A. Ayer. 51st Chemical Institute of Canada Conference, Vancouver, 1968.
11. Y. Inubushi, H. Ishii, B. Yasui, M. Hashimoto and T. Harayana. Tetrahedron Letters, 1537 (1966).
12. D.B. MacLean. Can. J. Chem., 41, 2654 (1963).

13. Z. Pelah, M.A. Kielczewski, J.M. Wilson, M. Ohashi, H. Budzkiewicz, and C. Djerassi. J. Amer. Chem. Soc., 85, 2470 (1963).

14. F.A.L. Anet and N.H. Khan. Chem. and Ind. (London), 1238 (1960).

15. H. Conroy.. Tetrahedron Letters, 10, 34 (1960).

16. W.A. Ayer, J.K. Jenkins and S. Valverde-Lopez. Tetrahedron Letters, 2201 (1964).

17. R.N. Gupta, M. Castillo, D.B. MacLean, I.D. Spenser and J.T. Wrobel. J. Amer. Chem. Soc., 90, 1360 (1968).

18. K. Wiesner. Fortsch. Chem. Org. Naturstoffe, 20, 271 (1962).

19. A.M. Patterson, L.T. Capell, and D.F. Walker. The Ring Index, American Chemical Society, Washington, 1960, 2nd Edition, p. 452, Ring System 3493.

20. W.A. Ayer, J.A. Berezowsky and G.G. Iverach. Tetrahedron, 18, 567 (1962).

21. F.A.L. Anet and M.V. Rao. Tetrahedron Letters, 20, 9 (1960).

22. W.A. Ayer, D.A. Law, K. Piers. Tetrahedron Letters, 40, 2959 (1964).

23. Z. Valenta, P. Deslongchamps, R.A. Ellison, K. Wiesner. J. Amer. Chem. Soc., 86, 2533 (1964).

24. W.A. Ayer and K. Piers. Can. J. Chem., 45, 451 (1967).

25. W.A. Ayer, J. K. Jenkins, S. Valverde-Lopez and R.H. Burnell. Can. J. Chem., 45, 433 (1967).

26. W.A. Ayer, J.K. Jenkins, K. Piers and S. Valverde-Lopez. Can. J. Chem., 45, 445 (1967).

27. F. Bohlmann and O. Schmidt. Chem. Ber., 97, 1354 (1964).

28. F. Bohlmann, D. Schumann, and O. Schmidt. Chem. Ber., 99, 1652 (1966).

29. E. Colvin, J. Martin, W. Parker, and R.A. Raphael. Chem. Commun., 596 (1966).

30. R.V. Stevens, Ph.D. Thesis, Indiana University (1966).

31. H. Dugas, R.A. Ellison, Z. Valenta, K. Wiesner and C.M. Wong. Tetrahedron Letters, 1279 (1965).

32. E.H.W. Böhme, Z. Valenta and K. Wiesner. Tetrahedron Letters, 2441 (1965).

33. K. Wiesner, I. Jirkovsky, M. Fishman and C.J. Williams. Tetrahedron Letters, 1523 (1967).

34. K. Wiesner and I. Jirkovsky. Tetrahedron Letters, 2077 (1967).

35. K. Wiesner and L. Poon, Tetrahedron Letters, 4937 (1967).

36. K. Wiesner, Z. Valenta, W.A. Ayer, L.R. Fowler and T.E. Francis, Tetrahedron, 4, 87 (1958).

37. Z. Valenta, F.W. Stonner, C. Bankiewicz and K. Wiesner, J. Amer. Chem. Soc., 78, 2867 (1956).

38. D.B. MacLean and H.C.Prime. Can. J. Chem., 31, 543 (1953).

39. E.E. Betts and D.B. MacLean, Can. J. Chem., 35, 211 (1957).

40. H. Dugas, M.E. Hazenburg, Z. Valenta and K. Wiesner. Tetrahedron Letters, 4931 (1967).

41. W.A. Ayer, and G.G. Iverach, Can. J. Chem., 42, 2514 (1964).

42. G. Stork, R.A. Kretchmer and R.H. Schlessinger. J. Amer. Chem. Soc., 90, 1647 (1968).

43. W.A. Ayer, W.R. Bowman, T.C. Joseph and P. Smith. J. Amer. Chem. Soc., 90, 1648 (1968).

44. W.A. Ayer and D.A. Law. Can. J. Chem., 40, 2088 (1962).

45. W.A. Ayer, J.A. Berezowsky and D.A. Law, Can. J. Chem., 41, 6490 (1963).

46. W.A. Ayer, A.N. Hogg and A.C. Soper. Can. J. Chem., 42, 949 (1964).

47. W.A. Ayer, W.R. Bowman, G.A. Cooke and A.C. Soper. Tetrahedron Letters, 2021 (1966).

48. R.H. Burnell, B.S. Mootoo and D.R. Taylor. Can. J. Chem., 38, 1927 (1960).

49. R.H. Burnell, B.S. Mootoo and D.R. Taylor, Tetrahedron, 15, 173 (1961).

50. D.A. Law. Ph.D. Thesis, University of Alberta, 1963.

51. F.A.L. Anet. Tetrahedron Letters, 20, 13 (1960).

52. N.J. Leonard and A.S. Hay. J. Amer. Chem. Soc., 78, 1984 (1956).

53. W. Schneider and H. Götz. Ann. der Chemie, 653, 85 (1962).

54. N.J. Leonard, C.K. Steinhardt and C. Lee. J. Org. Chem., 4027 (1962).

55. F. Bohlmann and Christian Arndt. Chem. Ber., 91, 2167 (1958).

56. D.B. Glass and A. Weissberger. Org. Syn., 26, 40 (1946).

57. Heilbron and Bunbury. "Dictionary of Organic Compounds, Eyre and Spottiswoode, London, 1953. Vol. 4, p. 139.

58. K. Tsuda and S. Saeki, Chem. and Pharm. Bull. (Japan), 6, 391 (1958).

59. F. Bohlmann, Chem. Ber., 91, 2157 (1958).

60. S. Saeki, Chem. and Pharm. Bull. (Japan), 9, 226 (1961).

61. M.S. Kharasch and C.F. Fuchs. J. Org. Chem., 9, 364 (1944).

62. G.A. Cooke. Ph.D. Thesis, University of Alberta, 1964.

63. Heilbron and Bunbury, "Dictionary of Organic Compounds, Eyre and Spottiswoode, 1953. Vol. 4, p. 401.

64. N.S. Bhacca, L.F. Johnson, J.N. Shoolery. High Resolution NMR Spectra Catalog, Varian Associates, Palo Alto. #266.

65. G. Pinkus. Ber. 25, 2798 (1892).

66. W.R. Bowman. Ph.D. Thesis, University of Alberta. 1968.

67. P. Smith. Private Communication.

68. W.A. Ayer and G.G. Iverach. Tetrahedron Letters, 87 1962.

69. C. Djerassi, J. Amer. Chem. Soc., 71, 1003 (1949).

70. J. Demaecker and R.H. Martin, Nature, 173, 266 (1966).

71. A.I. Scott. "Interpretation of Ultraviolet Spectra of Natural Products" The MacMillan Company, New York, 1964.

72. W.F. McGuckin and E.C. Kendell, J. Amer. Chem. Soc., 74, 5811 (1952).

73. R.P. Holyez, J. Amer. Chem. Soc., 75, 4432 (1953).

74. J.A. Marshall and N.H. Anderson, J. Org. Chem., 31, 667 (1966).

75. G.F.H. Green and A.G. Long, J. Chem. Soc., 2532, 1961.

76. L. Gatterman. "Laboratory Methods of Organic Chemistry" MacMillan and Co. Ltd., London, 1948. p. 134.

77. R.M. Adams, F.D. Poholsky. Inorg. Chem., 2, 640 (1963).

78. F.A. Davis, M.J.S. Dewar, and R. Jones. J. Amer. Chem. Soc., 90, 706 (1968).

79. H.C. Brown. "Hydroboration", New York, W.A.Benjamin, 1962.

80. J. Carnduff, Quarterly Reviews, 169 (1966).

81. E.W. Warnhoff and C.M.M. Halls, Can. J. Chem., 43, 3311 (1965).

82. Vogel. "Practical Organic Chemistry", Longmans, Green and Co. London, p. 883.

83. G.G. Iverach. Ph.D. Thesis, University of Alberta, 1964.

84. D.H.R. Barton, B.J. Garner and R.H. Wrightman, J. Chem. Soc., 1855 (1964).

85. J.D. Albright and L. Goldman. J. Amer. Chem. Soc., 4214 (1965).

86. W.W. Epstein and F.W. Sweat. Chem. Reviews, 67, 247 (1967).

87. K.E. Pfitzner and S. Moffatt. J. Amer. Chem. Soc., 87, 5661 (1965).

88. K.E. Pfitzner and S. Moffatt. J. Amer. Chem. Soc., 5670 (1965).

89. R.E. Partch. Tetrahedron Letters, 3071 (1964).

90. W.S. Johnson, D.S. Allen, Jr., R.R. Hindersinn, G.N. Sausen and R. Pappo. J. Amer. Chem. Soc., 84, 2181 (1962).

91. R.A. Baxter, G.T. Newbolt, F.S. Spring, J. Chem. Soc., 370 (1947).

92. P.H. Griswold, Jr., and J. English, Jr., J. Amer. Chem. Soc., 67, 2039 (1945).

93. R.E. Parker and N.S. Isaac, Chem. Rev., 59, 737 (1959).

94. M. Velkas. Bull. Soc. chim., 1401 (1959).

95. B.M. Lynch and K.H. Pausacher, J. Chem. Soc., 1525 (1955).