THE TOTAL SYNTHESIS OF VERATRUM ALKALOIDS

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ABSTRACT

A general method for the total synthesis of Veratrum alkaloids is outlined and its application to the synthesis of 5α,6-dihydroveratramine described.

The condensation of 3β-acetoxy-5α-etiojerv-12(13)-en-17-one (80), a known compound available from the degradation of hecogenin or from total synthesis, with the lithio derivatives of appropriately substituted pyridines and subsequent elaboration of the coupled products is considered as a general scheme for synthesizing members of the Veratrum family.

2-Ethyl-5-methyl-3-hydroxypyridine (78) was chosen to provide the heterocyclic portion of 5α,6-dihydroveratramine (18). A synthesis of this material was achieved *via* 2-propionyl-4-methyl furan (122). Two independent routes were developed for the synthesis of 122 and these studies led to novel results on the electrophilic substitution of 3-methylfuran.

Condensation of the lithio derivative of the methyl ether of 78 with the steroidal enone (80) followed by acetylation gave a mixture of two compounds. These were characterized as 3β-acetoxy-23-methoxy-22,27-iminojerva-12(13),22,24,27-tetraen-17-ol (compound "A", 131) and 3β-acetoxy-23-methoxy-22,27-iminojerv-12(13),14(15),16(17),22,24,27-hexaene (compound "B", 132). Compound "A" was subsequently converted to a D-ring aromatic compound isomeric with 132 (compound "C", 134). The stereochemical implications of these results are described.

Methods for the reduction of the pyridine ring in 132 to the piperidine moiety present in 5α,6-dihydroveratramine are outlined. Catalytic hydrogenation of 132 in an acid-ethanol medium furnished 5α,6-dihydroveratramine which was identified by comparison with authentic sample. In view of the

known conversions, the present work completes the formal total syntheses of veratramine, jervine, 11-deoxojervine and veratrobasine.

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ACKNOWLEDGEMENTS

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INTRODUCTION

Veratrum alkaloids occupy a position of importance among the various groups of steroidal alkaloids mainly because of their largely modified steroidal skeleton and the pharmacological activity exhibited by some of the members. During the past decade significant contributions have been made regarding the chemistry and stereochemistry of several sub-groups among the Veratrum alkaloids. The general classification Veratrum alkaloids includes those alkaloids from the tribe Veratreae belonging to the Liliaceae family and specifically from the genera Veratrum, Zygadenus, Stenanthium and Schoenocaulon. Alkaloids of similar structure have also been shown to occur in the Fritillaria genus of the Liliaceae.

Reviews on various aspects of the chemistry of Veratrum alkaloids have been published by Fieser and Fieser,[1] Boit,[2] Narayanan[3] and Kupchan.[4] In addition, the occurrence of alkaloids in plants of the Veratreae, and the implication of the alkaloid occurrence and structure to the taxonomy of the Veratreae have been reviewed.[5] Also relationships between structure and hypotensive activity of Veratrum alkaloids and their semisynthetic derivatives have recently been reviewed by Kupchan and Flacke.[6] The division of the Veratrum alkaloids into the Jerveratrum and Ceveratrum groups as proposed by Fieser has now been generally accepted.[4]

The Jerveratrum alkamines contain only 1 to 3 atoms of oxygen and are

found in the unhydrolyzed plant extracts in part as the free alkamines and in part in combination with one molecule of D-glucose as glucoalkaloids. The Ceveratrum alkamines are highly hydroxylic and contain 7 to 9 atoms of oxygen. They usually occur esterified with various acids as ester alkaloids but are in some instances unconjugated; they have never been found as glycosides.

Crude extracts from Veratrum and related plants have been used for various medicinal purposes since the middle ages, and their use in the control of hypertension dates from a report by Baker[7] in 1859. Treatments in the second half of the nineteenth century employed crude extracts which gave erratic results and their usage was discontinued. During the late 1930's purified alkaloidal preparations became available and improved techniques led to the first crystalline alkaloidal preparation, protoveratrine which was shown to be a powerful hypotensive agent.[8,9]

Following pharmacological investigation by Krayer[10] this preparation was introduced into clinical use in the treatment of certain types of hypertension.[11] One of the limiting factors in the use of this drug is the narrow dosage range between hypotensive and emetic effects. The advent of the superior hypotensive compound reserpine has almost eliminated the use of the protoveratrines.

The Jerveratrum alkamine rubijervine (1), so named because of its red colour with sulfuric acid rather than a similarity to jervine, may be regarded as the simplest of the Veratrum alkaloids from a structural point of view. It possesses the normal C-27 steroid skeleton (e.g. cholesterol) and the E and F rings may formally be regarded as having been formed by

folding the normal cholesterol side chain around the nitrogen atom. Other Jerveratrum members veratramine (2), verarine (3), jervine (4) and veratrobasine (5) are characterized by the C-nor-D-homo ring skeleton which may formally be regarded as having originated by migration of the C-13, C-14 bond of a normal steroid to the C-12,C-14 position. Since it was our aim to provide a synthetic entry into the C-nor-D-homo Jerveratrum alkaloids, the structural elucidation of veratramine, verarine and jervine will now be briefly reviewed.

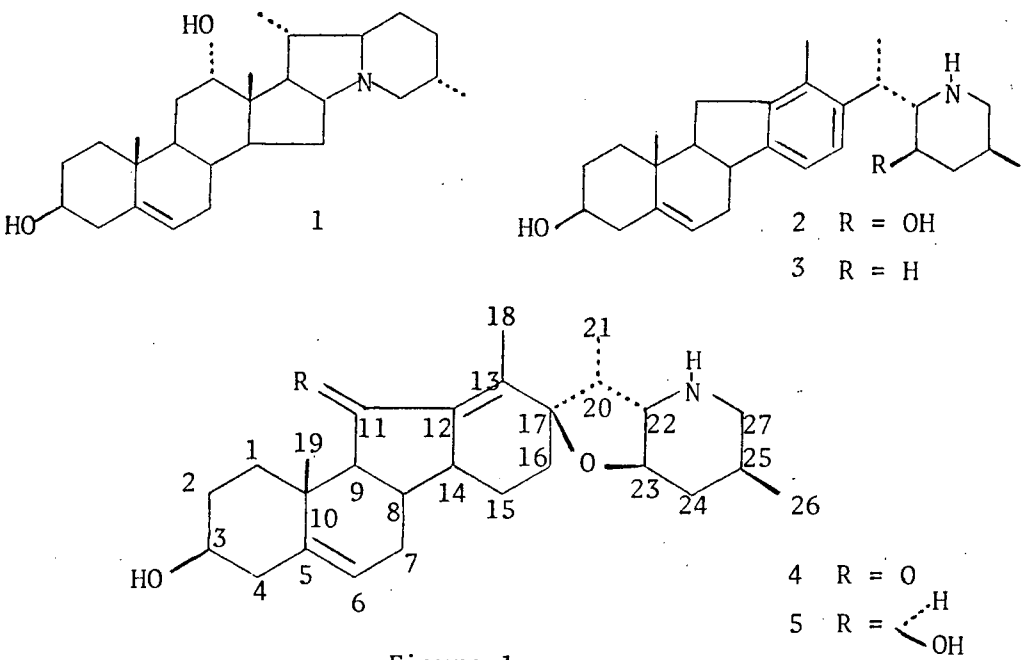


Figure 1

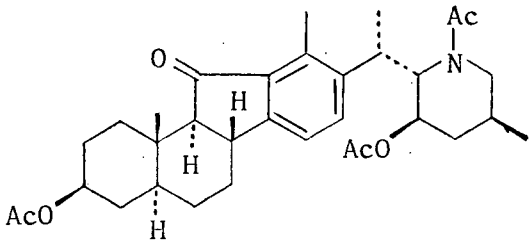
Fried and Klingsberg[12] proposed that the term "jervane" be adopted to represent the carbon skeleton of jervine (4) and the term "etiojervane" to represent the parent tetracyclic hydrocarbon. This proposal has been widely accepted and simplifies the nomenclature of these alkaloids. The

systematic steroid nomenclature for the "etiojervane" portion is 17-methyl-C-nor-D-homo-18-nor-5α,12α- androstane indicating the obvious advantages of the above proposal. The numbering scheme for these compounds is as indicated for jervine (4) in fig. 1. It has been proposed recently[13] that the term "cholojervane" be adopted for the 24 carbon skeleton which arises by the cleavage of the C-24, C-25 bond.

Both jervine (4) and veratramine (2) have been converted to the triacetyl-derivative (6) and jervine has been interrelated with hecogenin[14] (7) via compound 8. This suggested the 9α configuration for veratramine and further support for this assignment was obtained by conversion of hecogenin[15] and veratramine[16] to compound 9. Additional evidence for the 9α configuration was provided by Johnson[17] in a base catalysed equilibration study of compound 10 formed from N-acetyl-11-ketoveratramine (11). Treatment of the diketone 10 with methanolic potassium hydroxide effected partial conversion to a new compound. The n.m.r. spectrum of the diketone 10 showed a sharp signal attributed to the C-19 methyl at τ 8.81 which was superimposable on the corresponding signal in the synthetic trans compound 13. The equilibration mixture exhibited a new sharp signal at τ 8.45 which was superimposable on the corresponding C-19 methyl signal in the synthetic cis compound 12.

This work established the B/C trans junction for N-acetyl-11-keto-veratramine (11) which was related to veratramine by conversion to N-ethyl veratramine under conditions which allowed no epimerization at C-9.

The configuration of the piperidine moiety was first investigated by Sicher and Tichy.[18] Their studies, solely based on infrared spectra of pairs of isomeric pipecolinol derivatives 14 and 15, led to the conclusion



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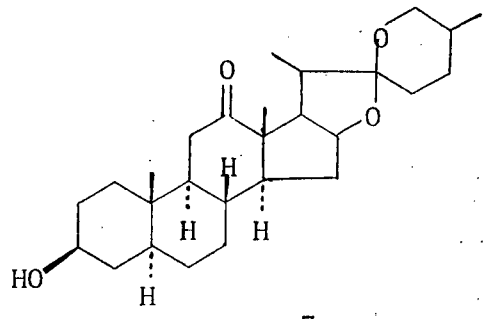

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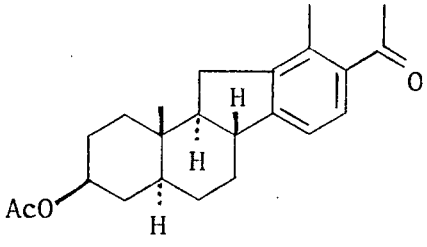

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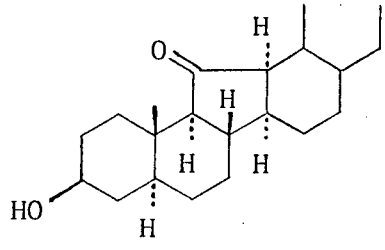

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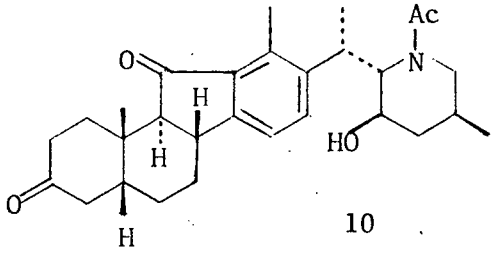

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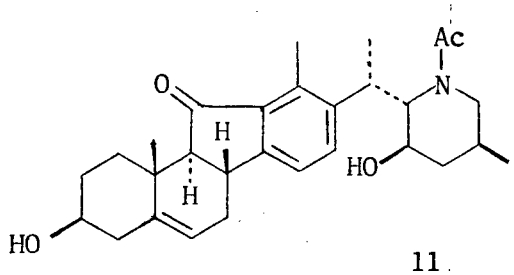

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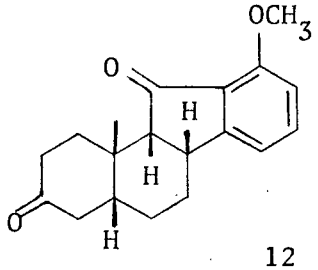

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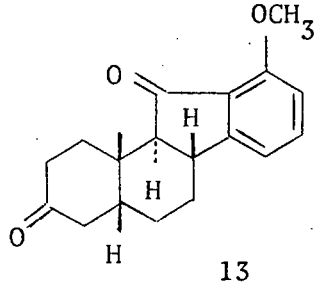

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Figure 2

that the arrangement of the alkyl side chain at C-22 and the C-23 hydroxyl is trans diequatorial. Subsequently it was proposed[19] that the C-26 methyl group belongs to the (S) series and occupied the β position. From these considerations the configuration of veratramine was assigned as in 16.

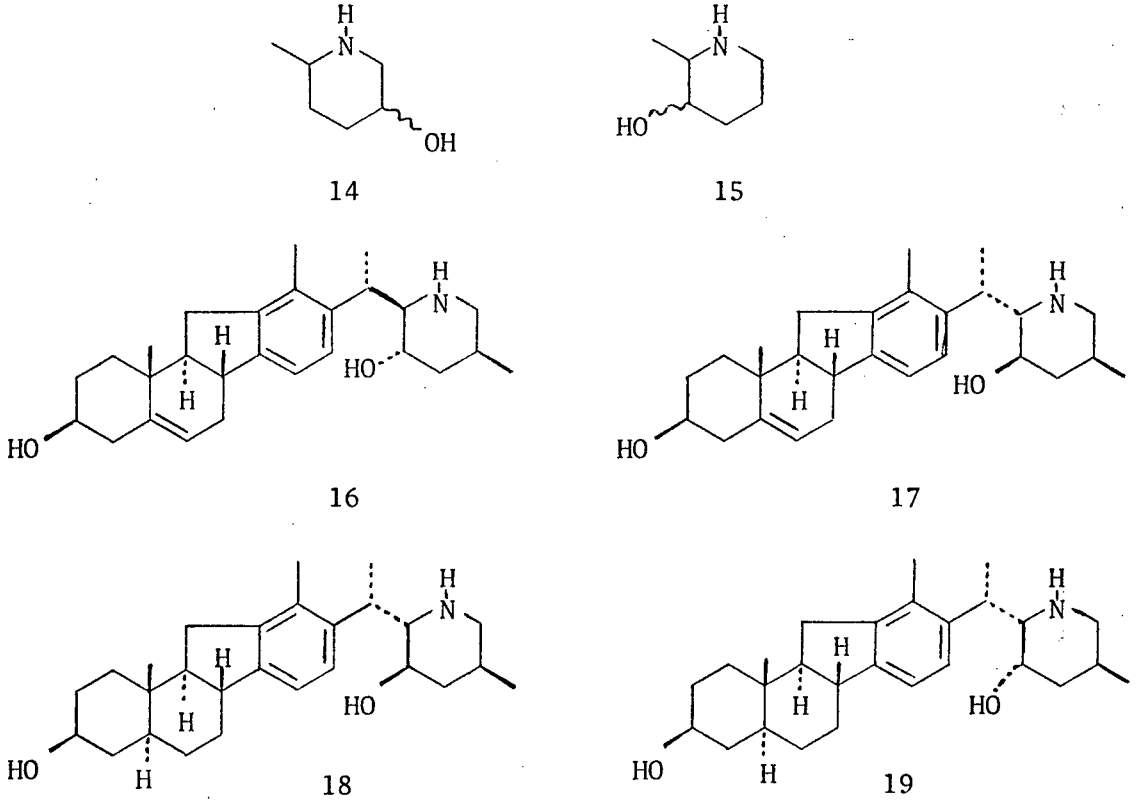
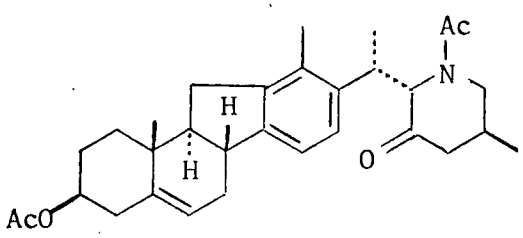


Figure 3

However a recent investigation by Johnson[20] has indicated that veratramine is correctly represented by 17 in which all the substituents on the piperidine are equatorial. Johnson prepared 5α,6-dihydroveratramine (18) and 5α,6-dihydro-23-isoveratramine (19) without epimerising the C-22 alkyl side chain. The iso compound must have the C-23 hydroxyl group in an axial orientation. This would be expected to cause a 12-13 Hz shift to lower field of the C-26 methyl signal if this group is also axially oriented.

The C-26 signal was shown to occur at τ 9.18 in both compounds 18 and 19 indicating that the C-26 methyl group is equatorial. Since this group occupies the β-configuration and the substituents at C-22 and C-23 are trans and equatorial, the correct assignment for veratramine is represented by 17. Earlier work by Augustine[21] and Masamune[22] involving equilibration studies on the keto amide of veratramine had supported the assignment of Sicher and Tichy[18]. Masamune studied the base catalyzed epimerization of 3,N-diacetyl-23-dehydroveratramine (20) which was originally postulated as having one of the alkyl groups on the piperidine moiety in an axial orientation. Treatment of 20 with methanolic potassium hydroxide gave a predominance of the C-22 isomeric compound in a ratio 10:1. This result was explained on the basis that epimerization at this position would lead to the piperidine ring being able to assume the more stable conformation with both groups equatorial.

Paulson and Todt[23,24] have shown that acylation of 2-methyl piperidine is accompanied by conformational inversion of the ring (methyl group axial) to relieve steric interaction between the equatorial methyl group and the amide carbonyl. The recent n.m.r. study by Johnson[20] supports this inversion of the piperidine ring in the N-benzoyl derivative of veratramine (21).



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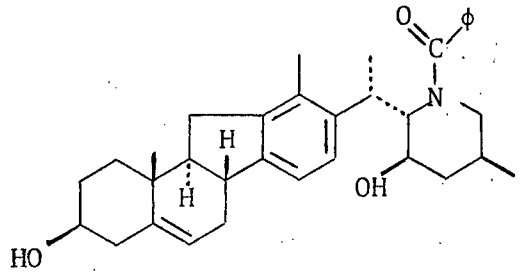

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The C-23 proton appears as a relatively sharp unresolved multiplet indicative of an axial hydroxyl whilst the signal assigned to the C-26 methyl group

now appears at τ 9.97. The downfield shift of the C-26 methyl group indicates a 1,3-diaxial relationship between the C-23 hydroxyl and C-26 methyl groups.

It therefore appears very probable that the ketoamide (20) exists preferentially in that conformation with the C-22 and C-25 substituents both axial. Epimerization to the C-22 iso compound occurs readily since this compound can exist in the conformation with the C-22 substituent axial and the C-26 methyl equatorial. These studies indicate that veratramine is correctly represented as 17 since the configurations at all centres except C-20 have been investigated. The configuration at C-20 was assigned originally on the basis of biogenetic analogy with other steroids. Conclusive evidence for the correctness of the stereochemical assignment at C-20 and other centres was obtained by the recent X-ray work[25] on veratrobasine (5) and the interrelation of these results to jervine, 11-deoxojervine, veratramine and verarine by Kupchan.[26]

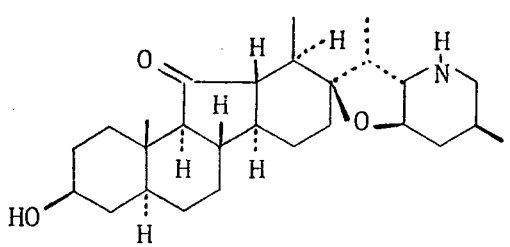
Earlier the configurations at C-22 and C-23 in jervine had been interrelated to those of veratramine and therefore the tetrahydrofuran ring in jervine must be attached to the piperidine ring in a trans manner. Degradation of jervine by Fried and Klingsberg[12] gave 8 which had been synthesized from hecogenin. The interrelation with veratramine gave additional support for the 9α configuration, whilst the configurations at all centres of 5,6,12,13-tetrahydrojervine (22)have been proposed by Wintersteiner and Moore.[27] The 12α configuration suggested for tetrahydrojervine in the above investigations has now been disproved and evidence has been advanced[28,29] to indicate the 12β configuration in this and the related compounds.

Under fragmentation conditions N-methyljervine gave 1,5-dimethyl-3-

piperidone which was then reduced to 1,3-dimethylpiperidine.[20] A synthesis of 1(3R)-dimethylpiperidine from D(+)-citronellal was carried out and the product shown to be the antipode of the compound from N-methyljervine. Consequently the absolute configuration at C-25 in jervine is (S) and the C-26 methyl group has the β-orientation. The recently revised configurations of the piperidine ring in veratramine also apply to jervine since the two compounds have been interrelated.

Recently Masamune has reinvestigated the problem of C-9 configuration in jervine and has provided conclusive evidence for the 9α configuration via the conversion of veratramine and "jervin-11β-ol" to the 5α,6-dihydro-derivative 23. At this time the configuration at C-17 and C-20 were assigned only by biogenetic analogy and not by direct evidence. The recent X-ray diffraction determination on veratrobasine has revealed that this compound is "jervin-11β-ol".[25] In the light of this work and the direct conversion of jervine to veratrobasine[26,62] the structure of jervine is correctly represented by 24 in which the ether bridge is β at both C-17 and C-23.

Verarine[31] has been shown to be 23-desoxyveratramine[22,31] and hence the configuration assigned to veratramine must necessarily apply to verarine (3).



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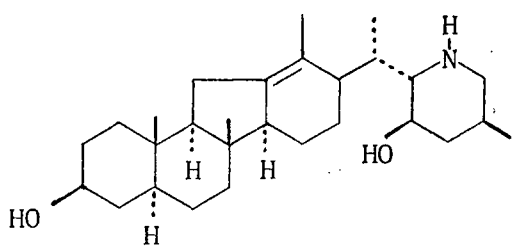

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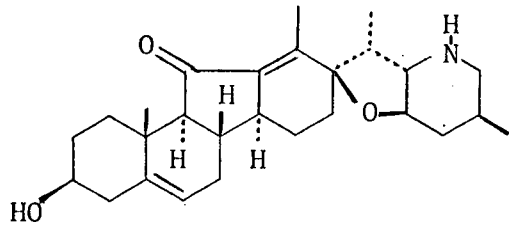

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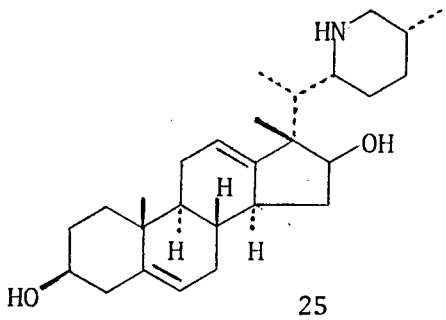
Two new Veratrum alkaloids veralkamine[32] (25) and veramine[33] (26) have recently been isolated and investigated by Tomko and Schreiber. These compounds have been shown to possess the unusual 17β-methyl-18-nor-17-iso-cholastane carbon skeleton as indicated in fig. 4. These compounds are unusual when compared with the known Jerveratrum alkaloids and closely resemble the spiroaminketal alkaloids solanidine and tomatidine. The above workers have further investigated these types of alkaloids.[34,35]



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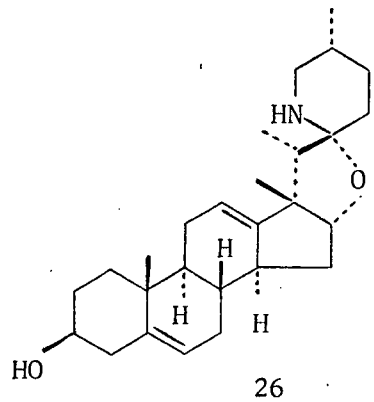

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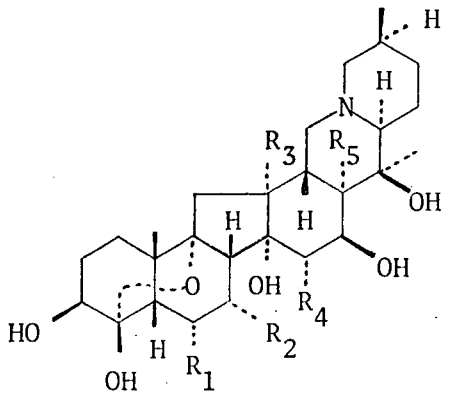
Figure 4

The Ceveratrum alkaloids are highly oxygenated and generally occur as esters. All have the cevanenucleus which is characterized by the C-nor-D-homo skeleton with an alternate folding of the side chain around the nitrogen atom. The commonly occurring alkamines are veracevine (27), germine (28), zygadenine (29), protoverine (30) and sabine (31) (fig. 5).

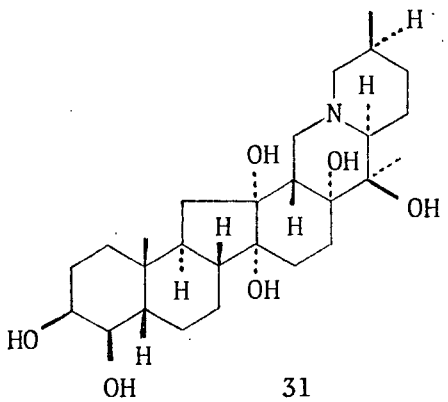


27 $R_1 = R_2 = R_4 = H$; $R_3 = R_5 = OH$

28 $R_1 = R_3 = R_5 = H$; $R_2 = R_4 = OH$

29 $R_1 = R_2 = R_3 = R_5 = H$; $R_4 = OH$

30 $R_3 = R_5 = H$; $R_1 = R_2 = R_4 = OH$



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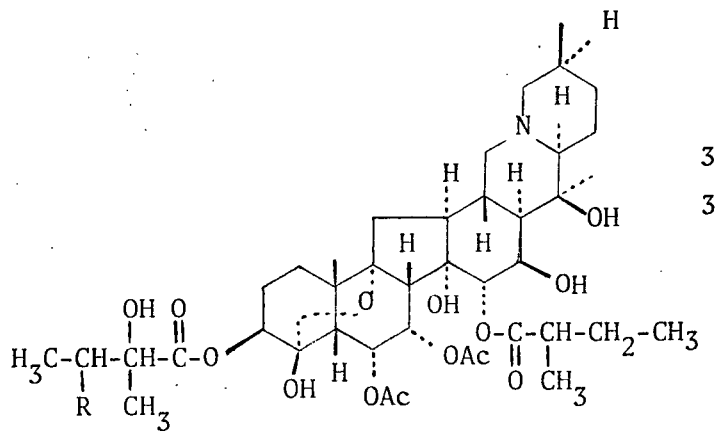


32 R = H

33 R = OH

Figure 5

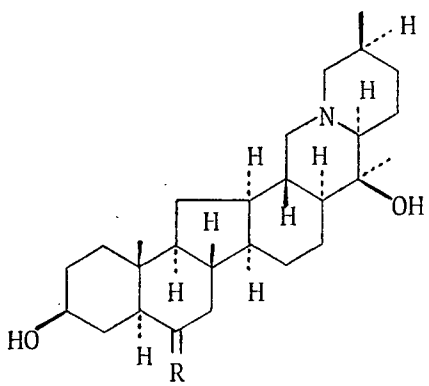
The protoverine esters A and B (32 and 33) have been investigated thoroughly. Structural studies on these compounds culminated in 1960 with the elucidation of the structure and configuration of the alkamine protoverine and the tetraesters protoveratrine A and protoveratrine B.[36] Protoveratrine A is a potent hypotensive agent with a narrow therapeutic dosage range whilst protoveratrine B is less active but the emetic side effects are not as pronounced. Structurally, the difference between these compounds is small and this prompted Kupchan to examine a number of protoveratrine derivatives with the aim of improving the therapeutic dosage range.[37] This study led to a number of generalisations concerning structure activity relationships for the protoveratrines but no radical improvement of the therapeutic dosage range.

The assignment of configurations at C-8, C-13, C-16, C-20 and C-22 in veracevine has been presented[38] and a subsequent X-ray study of veracevine hydroiodide has provided conclusive evidence for the configurational assignments of thirteen of the fourteen asymmetric centres[39] whilst evidence has been advanced to support the 20β configuration.[38]

Alkaloids of related structure have been isolated from plants of the Fritillaria genus of the Liliaceae family. The Fritillaria alkaloid verticine (34) was first isolated by Fukuda[40] from F. Verticillata Willd. var thunbergii Baker. The same alkaloid was isolated by Chou and Chen from F. roylei Hook and named peimine.[41] The identity of the two compounds was established by direct comparisons[42-45]. Structurally, verticine represents the simplest example of a compound having the cevan nucleus as found in the Ceveratrum alkaloids. A further alkaloid, fritillarine, was isolated in the above studies and has since been characterized as verticinone (35)

by mixed m.p. and infrared spectra comparison.[43] The assignments of the structure and configuration of verticine and verticinone have been based entirely on degradation studies, spectral data and biogenetic considerations.[43] Very recently an X-ray determination[46] has confirmed the correctness of the proposed structures for verticine and verticinone and established the absolute stereochemistry of these compounds.

An extensive n.m.r. study of members of the Ceveratrum group has been carried out.[47] The spectra of 37 alkaloids of this group were recorded and data for methyl group signals examined. The study provides additional support for the configuration of the C-27 methyl group and the effect of forming the D ring orthoacetate upon the stereochemistry of the D ring was examined.

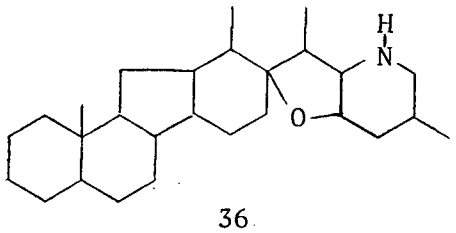


34 R = H, OH

35 R = O

Masamune[48] has examined the n.m.r. spectra of 65 derivatives of the Jerveratrum group of alkaloids. All the compounds contain the 22,27-imino-17,23-oxidojervane ring skeleton (36) and the data from the spectra is confined to the correlation of the chemical shifts of the methyl groups with changes in environment.

In the n.m.r. spectra of steroids[49] and triterpenoids[50] the long range shielding effects of various substituents on the chemical shift of the angular methyl protons have been shown to be additive. In order to examine



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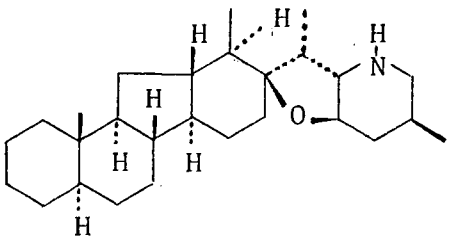

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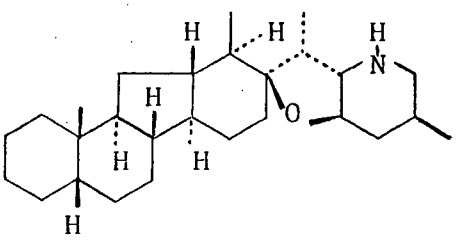

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both additivity and shielding effects in the 22,27-imino-17,23-oxidojervane skeleton, the compounds were divided into those derived from the A/B trans form (37) and those from the A/B cis series (38). The contributions due to various functional groups were obtained by pairing compounds which differ only by the group in question. Values calculated for the C-19 methyl protons using these contributions were in good agreement (within 0.02 τ) with the observed chemical shifts, indicating that the "principle of additivity" holds satisfactorily for the 19-methyl protons of these C-nor-D-homosteroidal alkaloids.

Masamune[51] and Johnson[52] have recently published the results of their independent investigations regarding the synthesis of some Veratrum alkaloids. Masamune has succeeded in synthesizing veratramine and jervine whilst

Johnson has synthesized veratramine. Both groups utilised 17-acetyl-5α-etiojerva-12,14,16-triene-3β-ol (-O-acetate) (8) as the source of the C-nor-D-homosteroid skeleton followed by elaboration of the 17-acetyl side chain to provide the heterocyclic portion to complete the Jerveratrum skeleton.

An outline of Masamune's synthetic approach is given in figure 6. In this sequence compound 8 was obtained by degradation of hecogenin and the piperidine portion is attached via an alkylation of the pyrrolidine enamine 46 with 45. This leads directly to an isomeric mixture of 3,N-diacetyl-5α,6-dihydro-23-dehydroveratramines (47) since the (S) configuration of the methyl group is established in 43. This isomeric mixture was compared with an authentic sample obtained from 5α,6-dihydroveratramine. The ether bridge between C-17 and C-23 was linked by a series of elegant steps including the formation of the important intermediate 22,27-iminojervan-13-(17)-ene-3β,23β-diol (49) which was identified by comparison with an authentic sample.

Epoxidation of this compound (49) gives 50 which undergoes cleavage of the epoxide and concommitant attack by the C-23 hydroxyl to give the desired ether bridge. Dehydration with thionyl chloride gave 3,N-diacetyl-11-deoxo-5α,6-dihydrojervine (52) which was compared with an authentic sample prepared from jervine in an unambiguous manner. The introduction of the 11-keto group unfortunately proceeds in a very low yield (1%), but it was possible to isolate 53 and complete the sequence to jervine as shown.
It should be noted that in view of the recent paper by Kupchan,[26] formulae 51-56 are indicated with the correct stereochemistry at C-17. Since hecogenin has been totally synthesized[53] this work represents in a formal sense, a total synthesis of veratramine and jervine.

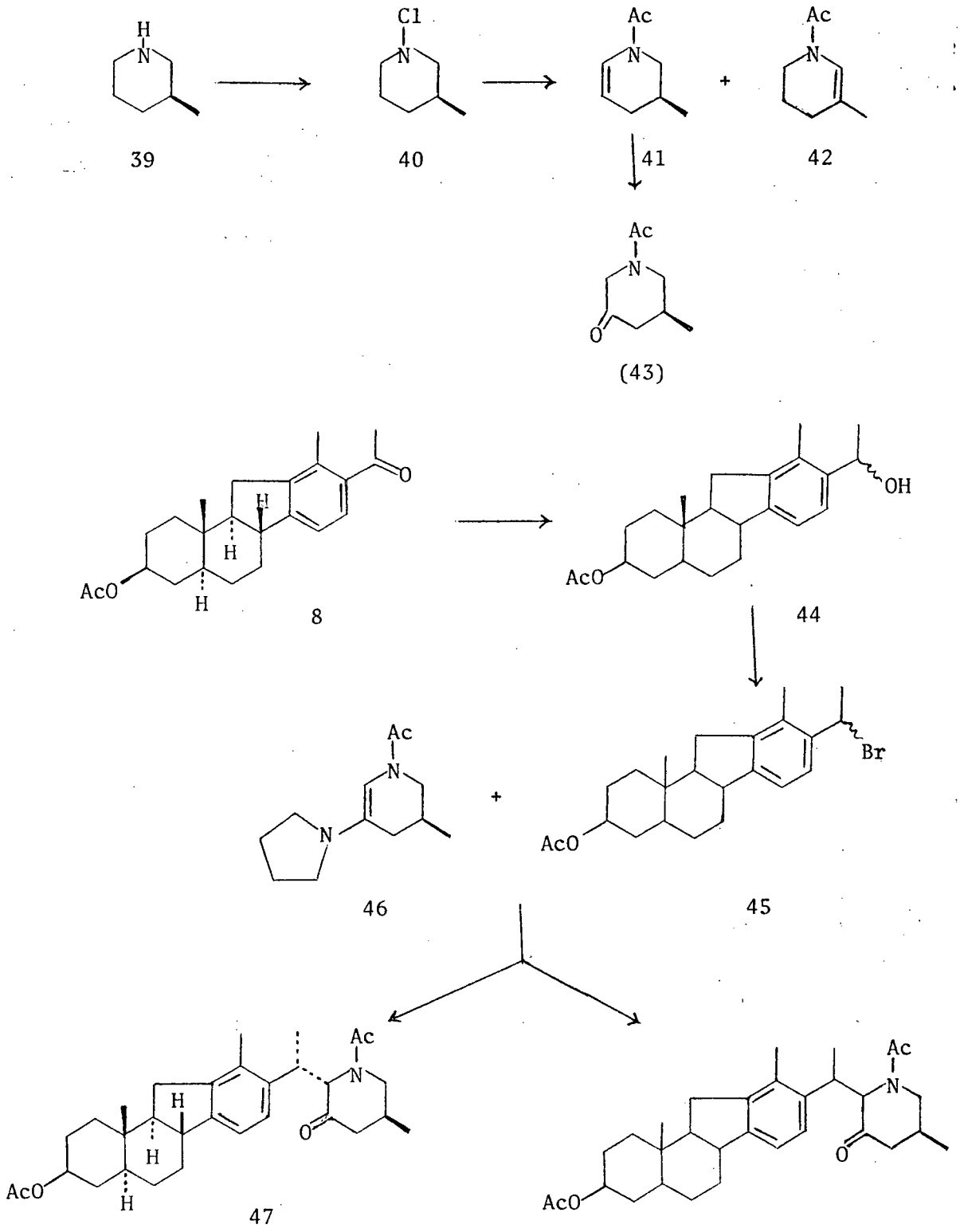


Figure 6: Masamune's synthesis of jervine[51]

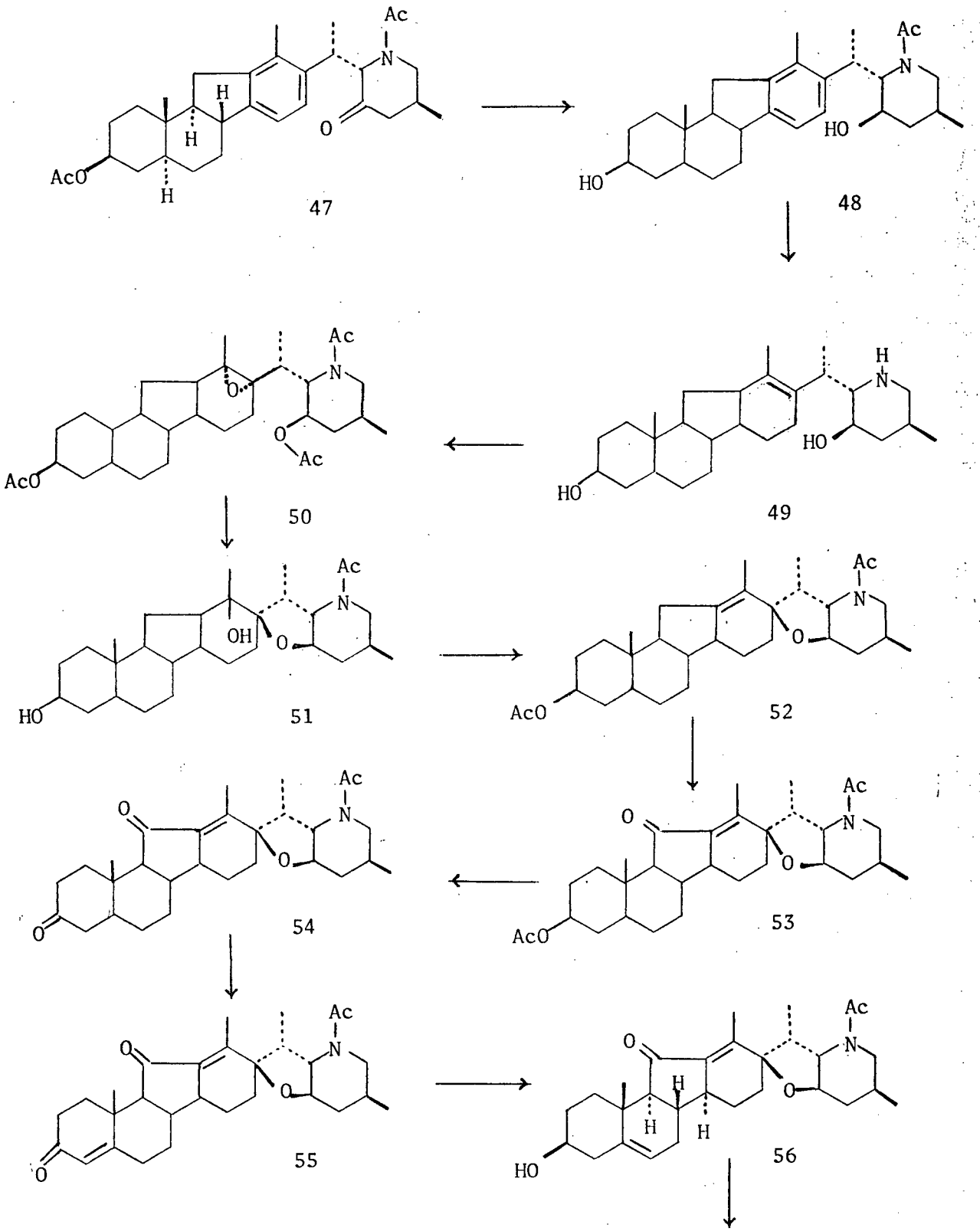


Figure 6 (continued)

The W.S. Johnson group also employed 17-acetyl-5α-etiojerva-12,14,16-trien-3β-ol (8) as the source of the C-nor-D-homo steroidal skeleton. This substance in turn was totally synthesized[54] from Hagemann's ester (57) as outlined in figure 7. The synthesis involves the use of a relay compound from veratramine for the conversion of 66 to 8. An alternate synthesis of 8 has also been published[55] recently by the same group by an extension of the hydrochrysene approach which they had investigated earlier.[56]

Figure 8 outlines the synthesis of veratramine from 17-acetyl-5α-etiojerva-12,14,16-trien-3β-ol (8) in which the piperidine ring is built up from the uncyclized compound 72 through 73 and 74 to yield a mixture of epimeric N-benzoyl-5α,6-dihydro-3,23-diketoveratramines (75) which was compared with an authentic sample prepared from veratramine. Introduction of the 5,6 double bond was achieved <u>via</u> formation of the Δ^4-3-ketone which was converted to the enol acetate. Reduction of this compound with sodium borohydride provided N-benzoyl veratramine which was debenzoylated to give veratramine. This synthesis represents a direct total synthesis of veratramine which can be extended to jervine employing procedures developed by the Masamune group.

About the same time these groups have investigated the total synthesis of Jerveratrum alkaloids, our own efforts in this direction led to the successful culmination in the total synthesis of verarine.[57] Our work represented part of a broader program of research directed to the design of completely general and yet relatively simple methods for the total synthesis of the Jerveratrum alkaloids potentially capable of extension to the more complex members and eventually to the Ceveratrum family. Since

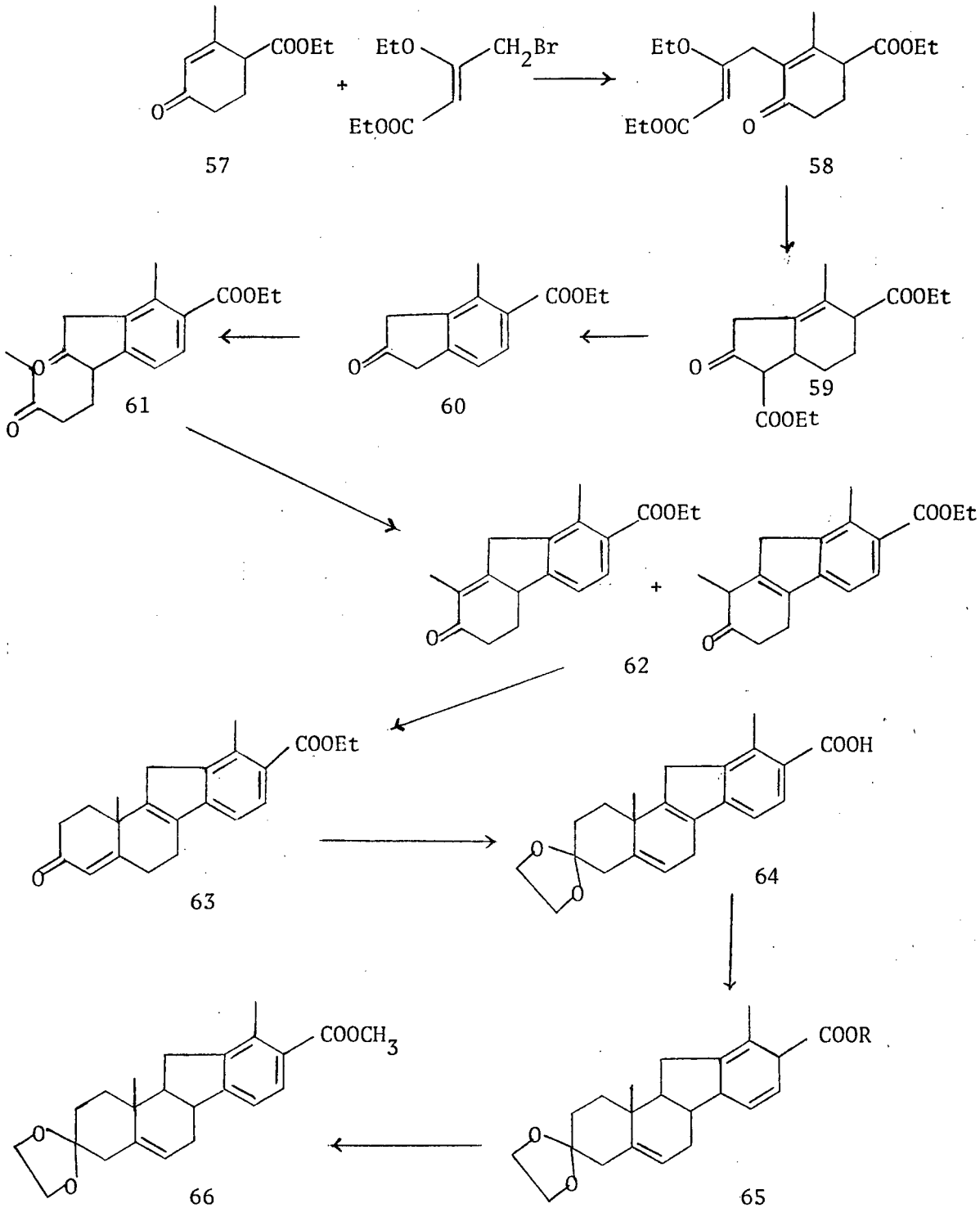


Figure 7: Johnson's synthesis of 17-acetyl-5α-etiojerva-12,14,16-trien-3β-ol (8)[54]

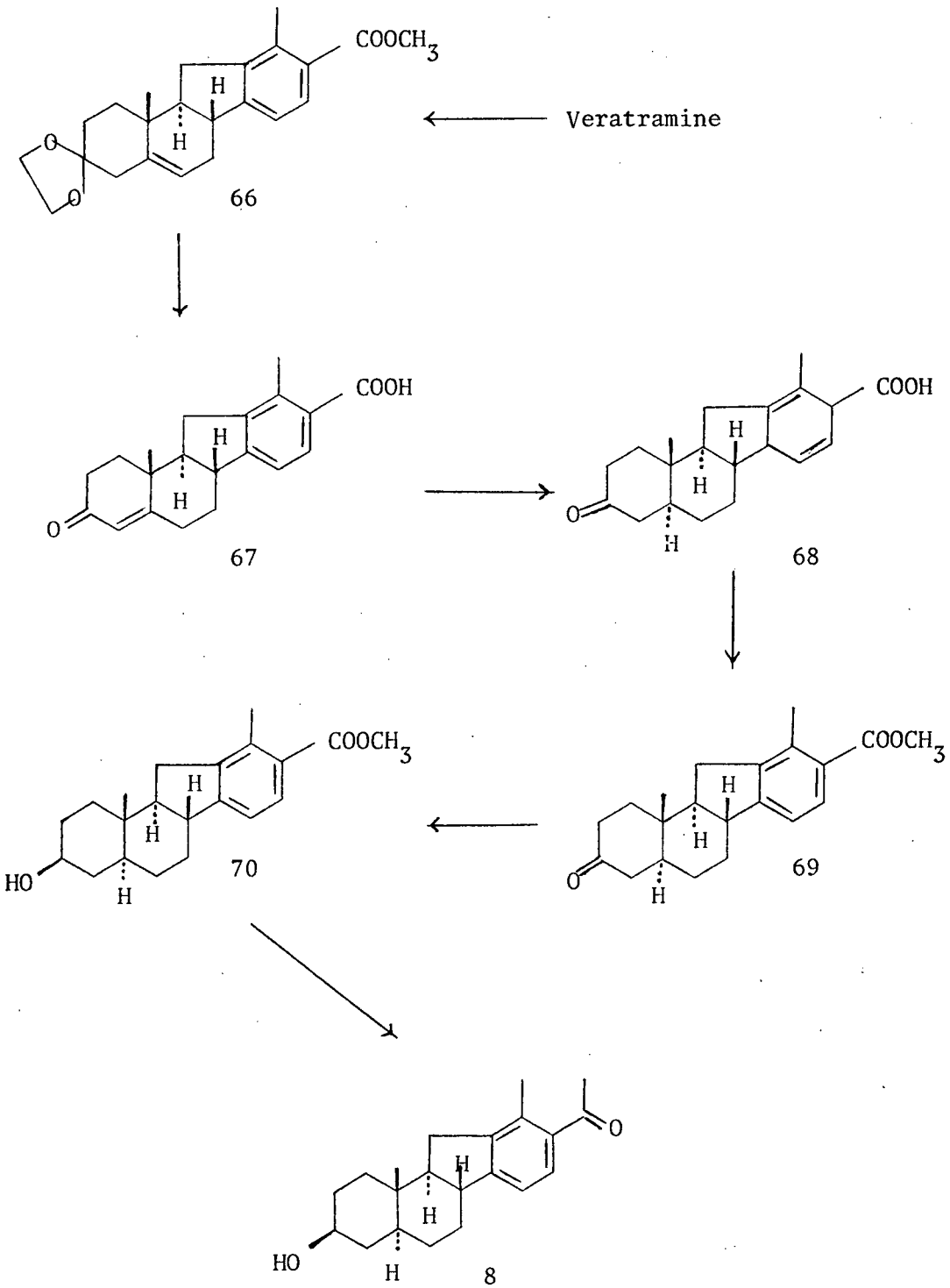


Figure 7 (continued)

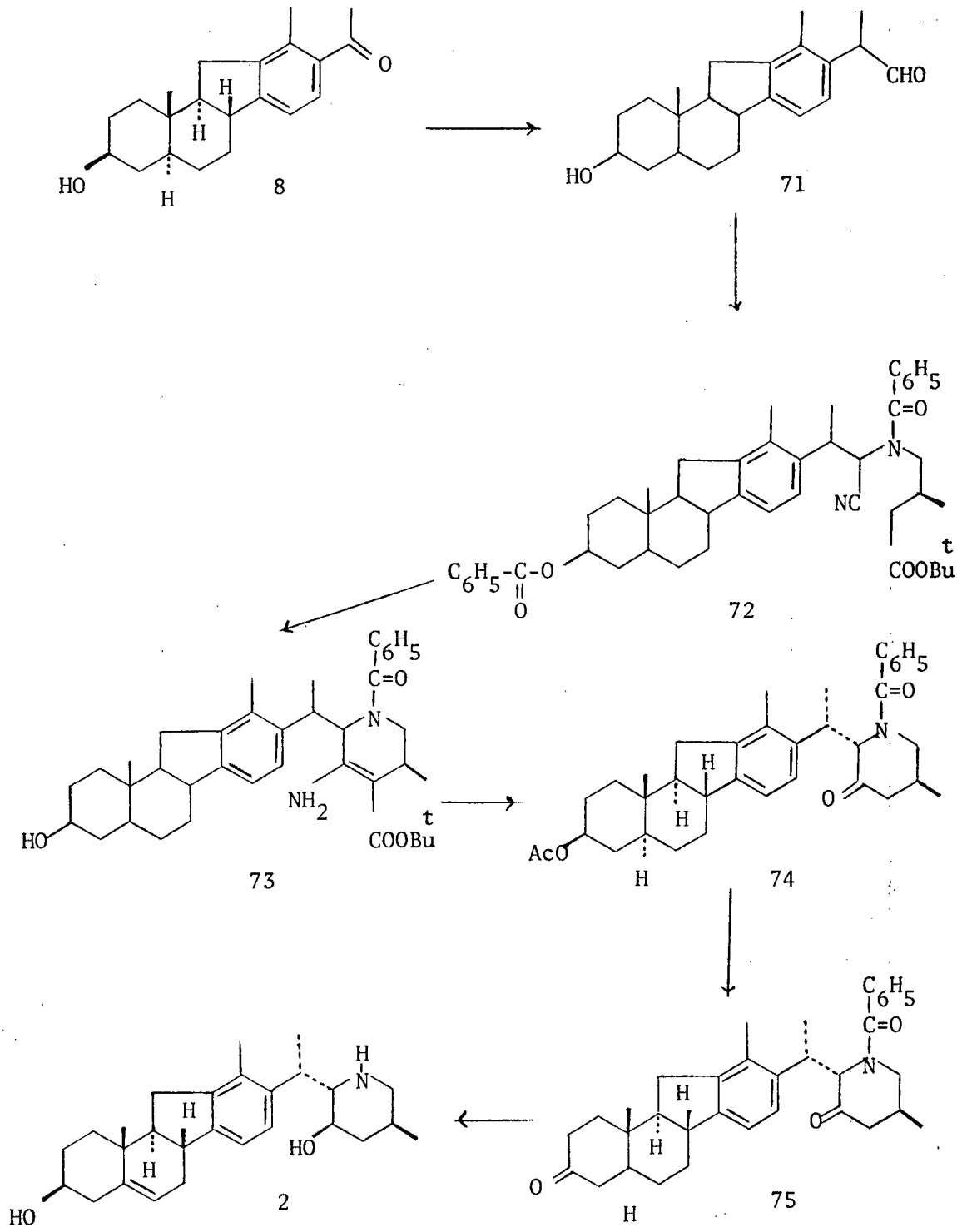


Figure 8: Johnson's synthesis of veratramine (2)[52]

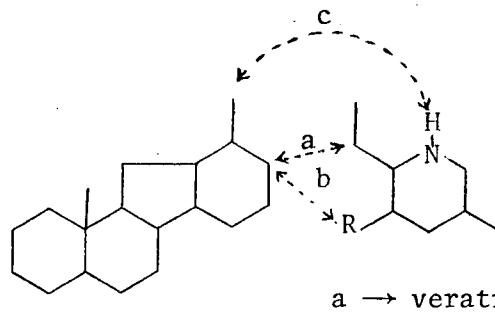
the total synthesis of verarine is intimately tied up with the synthesis of veratramine, which forms the subject matter of this thesis, it will be presented briefly in the discussion part of the thesis.

It is appropriate to add here that after this introduction has been completed, the IUPAC Commission on the Nomenclature of Organic Chemistry and IUPAC-IUB Commission on Biochemical Nomenclature have put forward a tentative set of rules for nomenclature of steroids.[58] According to these rules veratramine will be known as (22R,25S)-veratra-5,12,14,16-tetraenine-3β-ol. However, owing to the difficulties involved in naming some of the compounds as well as for the sake of uniformity, the original nomenclature due to Fried and Klingsberg[12] is retained throughout the thesis.

DISCUSSION

For the past several years, members of this laboratory have been engaged in active research directed to the design of a totally synthetic entry into the Veratrum alkaloids possessing the unique C-nor-D-homo-steroidal skeleton. The anatomy of these alkaloids revealed a basic unity in their build-up. All of them are constituted of two fundamental building blocks: 1) the C-nor-D-homosteroidal (etiojervane) portion and 2) a substituted piperidine. The Jerveratrum alkaloids can be further regarded as etiojervane substituted at C-17 by the piperidine moiety followed by subsequent elaboration. The Ceveratrum alkaloids can be considered as further cyclic analogues of the above members in that a cyclization of the C-13 methyl onto the nitrogen atom of the piperidine ring provides the quinolizidine system present in these alkaloids. Such a concept of the Veratrum alkaloids reveals itself in the results obtained by the selenium dehydrogenation[59,60] of members of the group, for example, veratramine (2) and jervine (4) (fig. 9).

Since we considered the Veratrum alkaloids as constituted of two common units viz, the etiojervane portion and the appropriately substituted piperidine, it was clear to us that it is possible to design methods of general application for the total synthesis of these compounds. Basically our



a → veratramine (2), verarine (3)

a + b → jervine (4), veratrobasine (5)

a + c → Cevane nucleus present in Ceveratrum alkaloids.

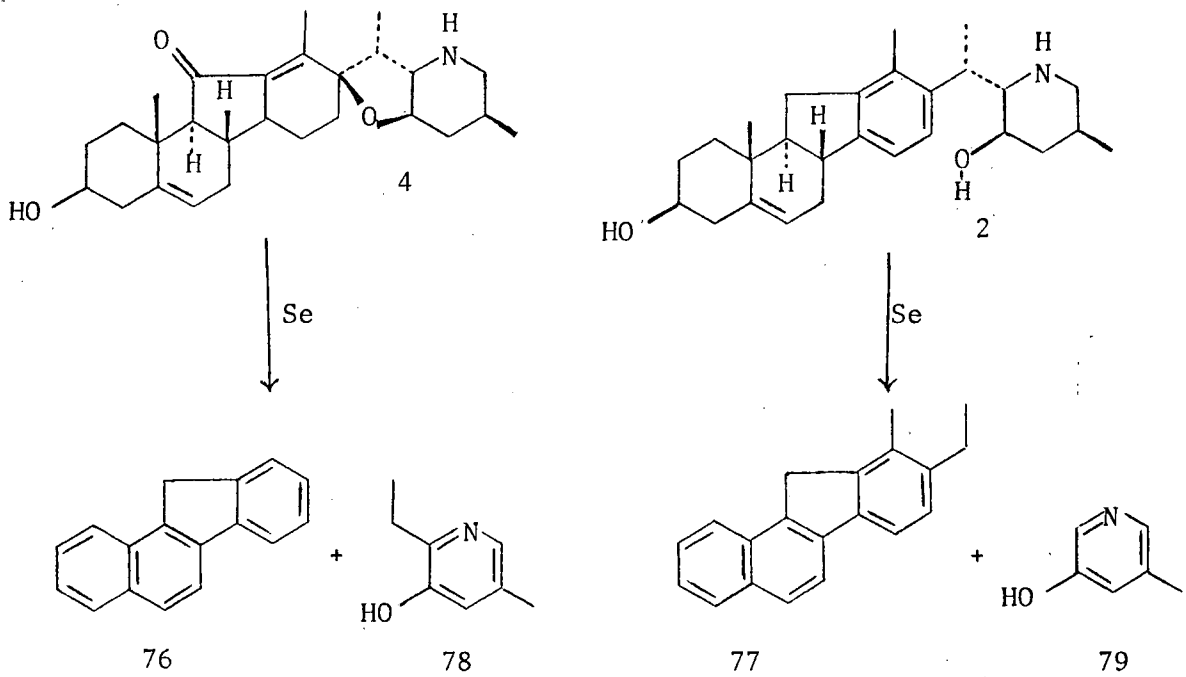


Figure 9: Selenium dehydrogenation of Veratrum alkaloids

approach consisted of synthesizing the steroidal portion and the heterocyclic unit separately and then coupling them in an appropriate manner to provide the desired skeleton. Further elaboration of the products resulting from such coupling was expected to afford the different alkaloids. The proposed scheme as exemplified by the synthetic scheme for veratramine (2) and verarine (3) is outlined in fig. 10, in which 3β-acetoxy-5α-etiojerv-12(13)-en-17-one (80) is reacted with the lithio derivative of the appropriately substituted pyridine (81a or b) to provide isomeric mixtures of compounds possessing the structure 82. Aromatization of ring D would provide compounds of type 83 differing only in configuration at C-20. A selective reduction of the pyridine to the piperidine system generates new asymmetric centres and would give rise to a mixture of isomers.

If all the possible isomers are obtained on selective hydrogenation, then one of these isomers should be identical with the 5α,6-dihydroalkaloids for which this sequence is designed. If R is hydrogen, then the isomeric 5α,6-dihydroverarines (84) will be obtained and in the instance where R is hydroxyl the sequence was expected to lead to an isomeric mixture of 5α,6-dihydroveratramines (85).

As an alternative to the hydrogenation of the pyridine ring leading to all the possible isomers, a sequential reduction of the pyridine ring to generate the desired isomer was thought to be feasible in the case of veratramine. The proposed scheme is outlined in fig. 11. The latter sequence, although somewhat lengthy, has the advantage that conversion of the substituted pyridine to the piperidine can be achieved stereoselectively.

As far as the total synthesis of the Jerveratrum alkaloids are considered, the total synthesis of 5α,6-dihydroveratramine ([18]) was a

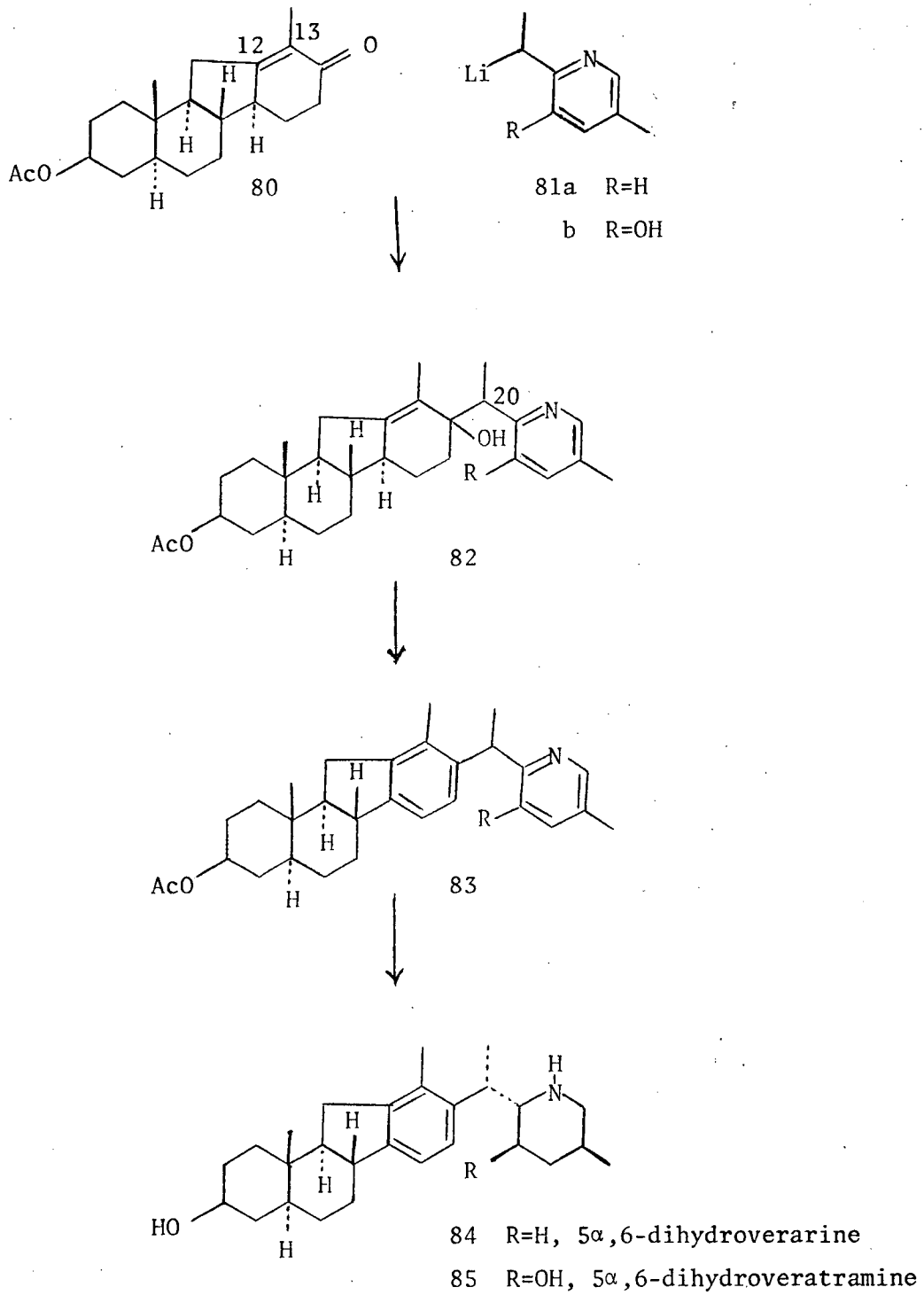


Figure 10: General scheme for the synthesis of simple Veratrum alkaloids

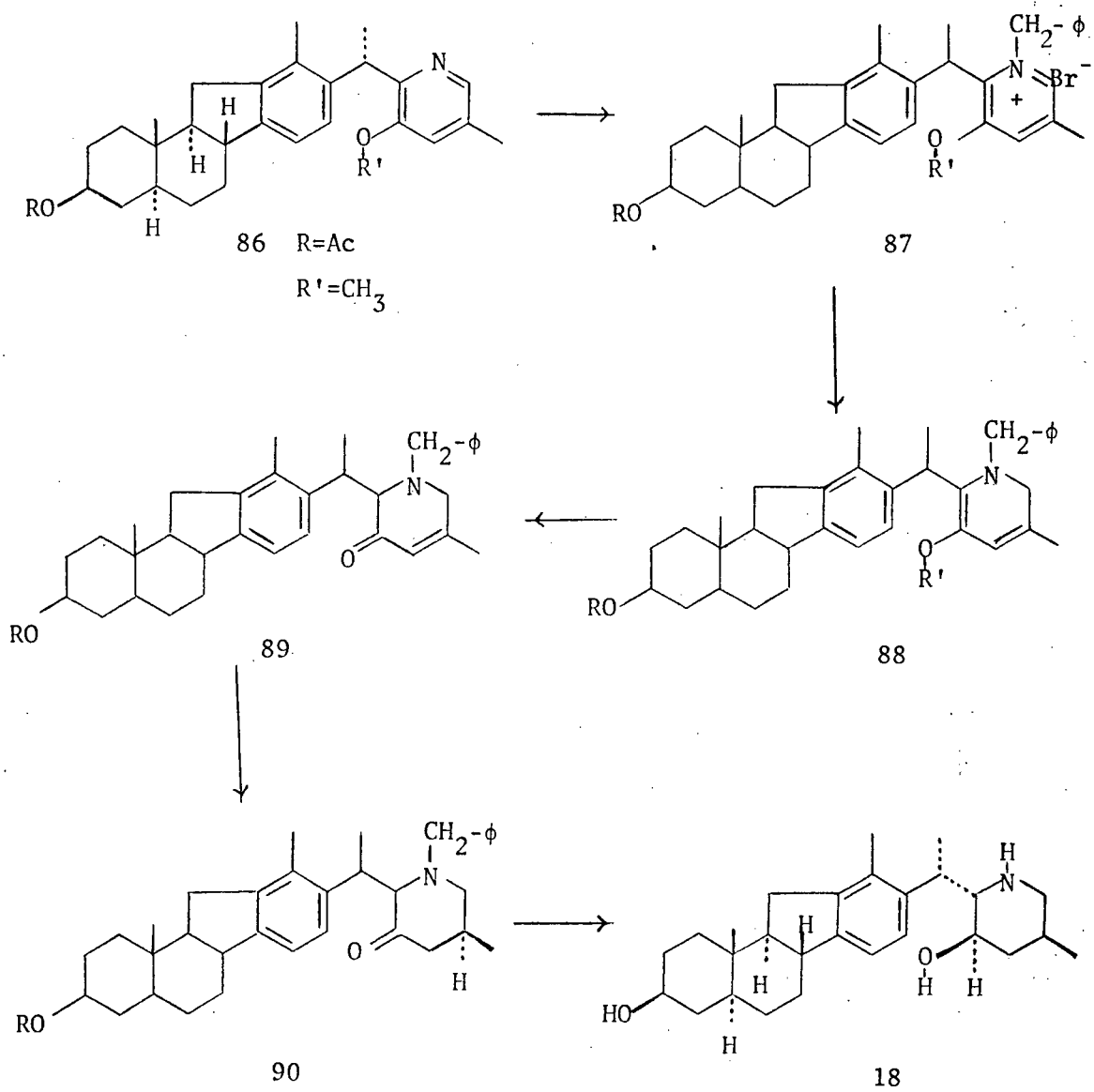


Figure 11: Stereoselective synthesis of 5α,6-dihydroveratramine (a proposal)

convenient goal, since this material has already been converted to veratramine,[52] jervine,[51] 11-deoxojervine[61] and veratrobasine.[26,62]

The steroidal moiety desired to provide the etiojervane portion was considered to be 3β-acetoxy-5α-etiojerv-12(13)-en-17-one (80). At about the same time the present work was initiated, a total synthesis of this compound was completed by other members in our laboratories[57] and is outlined in figures 12 and 13. This substance is also readily available from the degradation of hecogenin (112, R = H) by published procedures.[63,64] Since it was felt that the quantity of 3β-acetoxy-5α-etiojerv-12(13)-en-17-one (80) available from total synthesis would be insufficient to complete the synthesis of the various members of the Veratrum family we envisaged the use of optically active 3β-acetoxy-5α-etiojerv-12(13)-en-17-one (80) obtained by the degradation of hecogenin as a relay compound for further studies. This material, in optically active form, is also a totally synthetic compound since hecogenin has been synthesized[53] in another laboratory.

The procedure due to W.F. Johns[64] was employed in the degradation of hecogenin as outlined in fig. 14. This sequence, although somewhat lengthy, gives a reasonable yield of the desired 3β-acetoxy-5α-etiojerv-12(13)-en-17-one (80). A feature of this sequence which proved important in our totally synthetic approach was that the desired α,β-unsaturated ketone (80) was formed from the saturated ketone (111). A brief discussion of the chemistry involved in this latter conversion is now presented.

Attempts to prepare 3β-acetoxy-5α-etiojerv-12(13)-en-17-one (80) from compound 110 *via* alkylation of the enamine were unsuccessful. However, alkylation *via* the enolate anion of 110 led to compound 111 which was shown

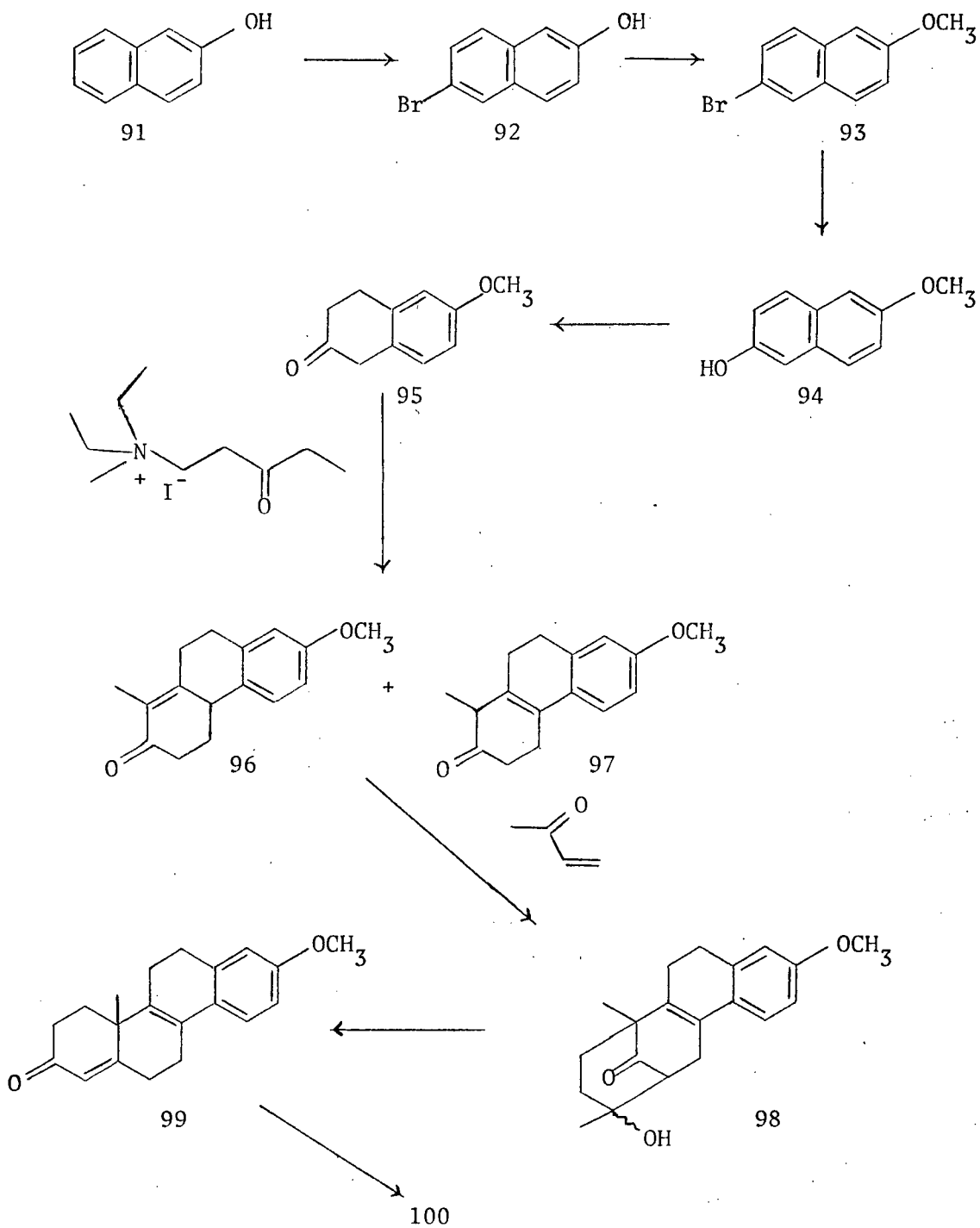


Figure 12: Kutney's synthesis of 3β-acetoxyetiojerv-12(13)-en-17-one

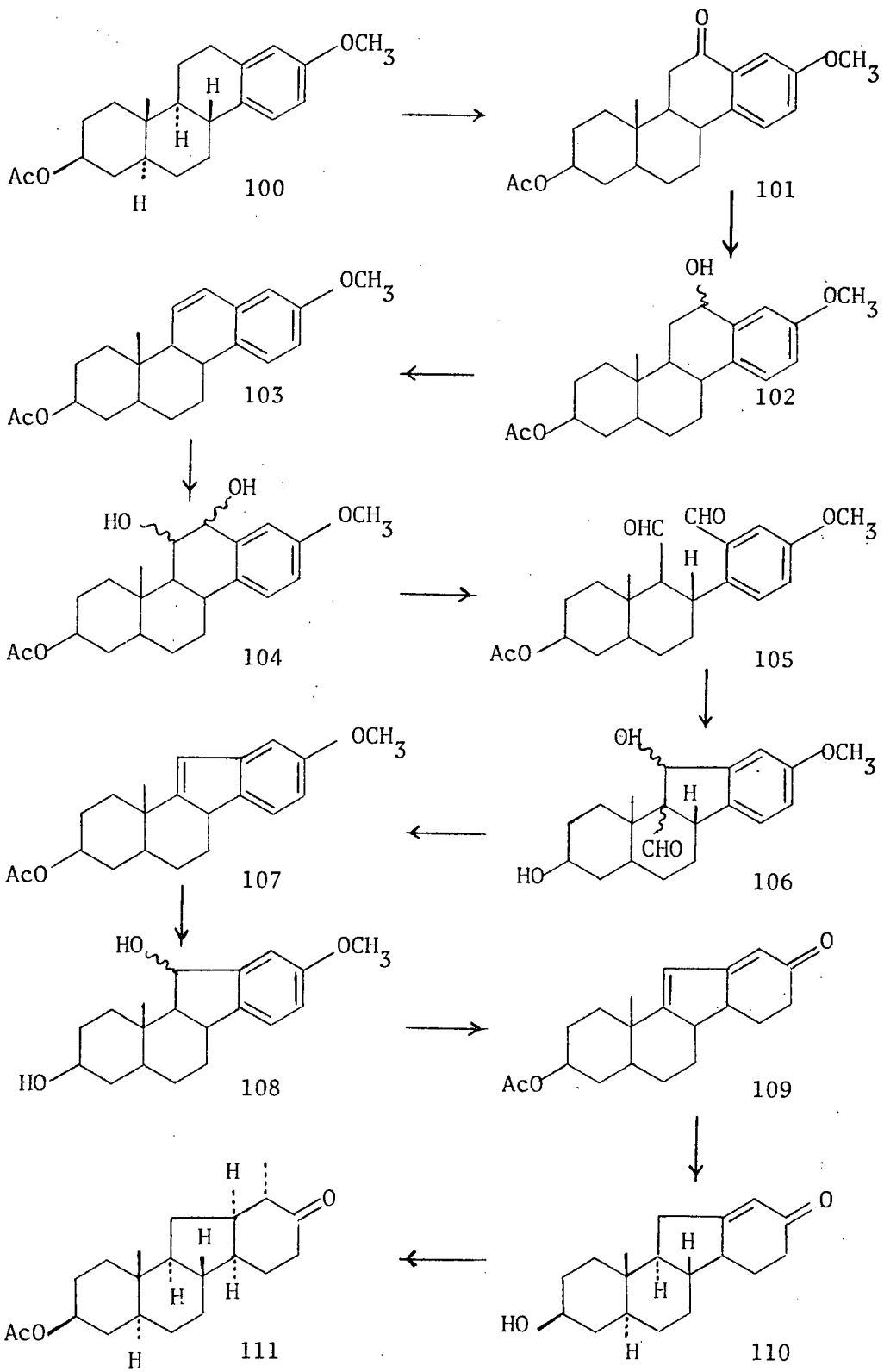


Figure 13: Kutney's synthesis of 3β-acetoxyetiojerv-12(13)-en-17-one (Continued)

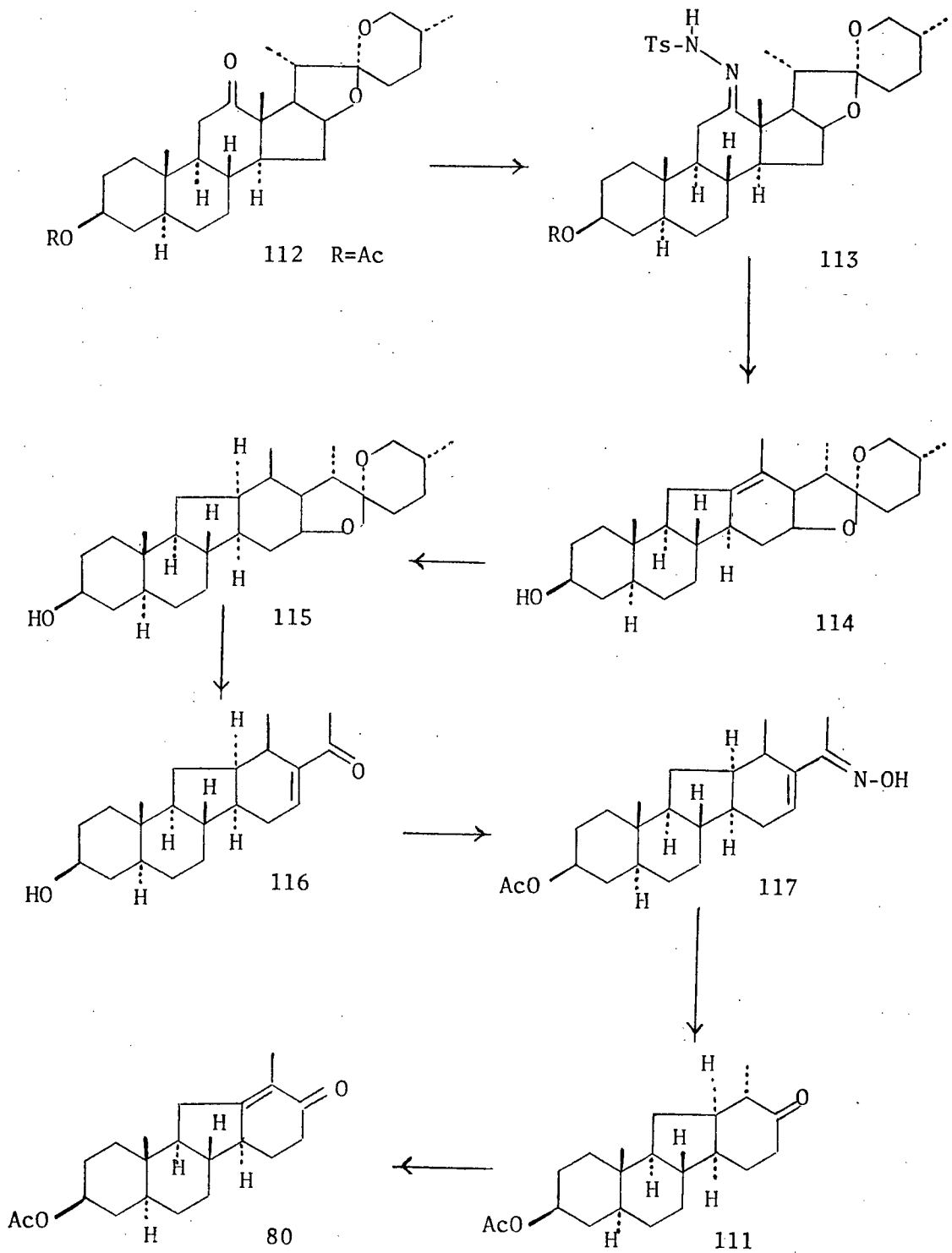


Figure 14: Preparation of 3β-acetoxyetiojerv-12(13)-en-17-one from hecogenin

to be structurally identical with the saturated ketone 111 obtained in the degradation of hecogenin (fig. 14). This compound (111) provides the point of linkage between the use of the relay compound from hecogenin and the totally synthetic substance obtained by the sequence outlined in figures 12 and 13.

After having selected the appropriate steroidal intermediate (80) to provide the etiojervane portion of the Veratrum alkaloids, we turned our attention to the heterocyclic unit potentially capable of generating the piperidine moiety of these compounds. The main purpose of the present work was to synthesize veratramine (2) and other Jerveratrum alkaloids possessing a C-23 oxygen function. Hence a logical selection of the heterocyclic unit required for this purpose was 2-ethyl-5-methyl-3-hydroxy-pyridine (78) or its derivatives. This compound has already been reported in the literature[60] since it was obtained by the selenium dehydrogenation of jervine (4). However, its structure was assigned only on the basis of its ultraviolet spectrum and colour reactions. Therefore the synthesis of this material had to be considered for the dual purpose of establishing its structure as well as for its use in our proposed total synthesis of vertramine (2) as outlined in fig. 10.

At this point it is appropriate to mention that in the proposed synthetic scheme (fig. 10), the heterocyclic unit required to complete the total synthesis of verarine, which is 23-desoxyveratramine, is obviously 2-ethyl-5-methylpyridine. The synthesis of verarine using this substance formed part of a broader program of our research. This was undertaken simultaneously by Dr. John Cable in our laboratories and has been completed successfully.[57]

In connection with the synthesis of 2-ethyl-5-methyl-3-hydroxypyridine (78), several alternatives could be considered. We chose an approach which made use of the reaction of furyl ketones with ammonia[65] since it seemed to be more direct and suitable for our purpose. In this connection we have developed two independent sequences for the synthesis of the desired pyridine (78). In effect, both sequences depend on the availability of crucial furan intermediates and therefore the synthesis of these substances was initially considered. Figures 15 and 16 outline the reactions involved in the preparation of these materials. Figure 15 reveals the preparation of 2-propionyl-4-methyl furan (122) via a Friedel-Crafts reaction on 3-methyl-furan.

A survey of the literature indicated that there has been no work on the Friedel-Crafts reaction of 3-methylfuran. In fact there has been very little work on the electrophilic substitution of 3-alkylfurans in general and all the available data indicated that the substitution takes place exclusively at the 2-position.[66-68] However, we did not rule out the possibility of substitution at the 5-position and hence decided to investigate this further. The desired starting material, 3-methylfuran (120) was prepared according to the procedure of Cornforth[69] as outlined in fig. 15. Thus the reactive halide, 2-methylallyl chloride on reaction with ethyl orthoformate in presence of magnesium afforded 3-methylbut-3-enal diethylacetal[70] (118). Treatment of this substance with m-chloroperbenzoic acid gave rise to 3,4-epoxy-3-methylbutanal diethylacetal[70] (119). This epoxyacetal without purification was heated with 0.1 N sulphuric acid and the resulting mixture of 3-methylfuran and ethanol was distilled. The resulting distillate was washed with half saturated aqueous calcium chloride solution followed by

saturated ammonium chloride solution and distilled after drying. The product, 3-methylfuran,distilled at 65-65.5°[69].

Reaction of 3-methylfuran with propionic anhydride and orthophosphoric acid as the catalyst at 60° provided a dark brown oil which upon distillation afforded a fragrant liquid, b.p. 135-40°/25 mm. Examination of this substance by v.p.c. indicated that it was a mixture of two compounds in the ratio 70:30. The separation of the mixture by distillation procedures was found to be very inefficient. Hence the two components of the mixture were separated by preparative v.p.c. using a FFAP column. The two compounds thus obtained were characterized as 2-propionyl-3-methylfuran (121) and 2-propionyl-4-methylfuran (122). The low field region (τ 4- τ2) of the n.m.r. spectra (figures 17 and 18) of these compounds was quite revealing. Thus the one proton doublets at τ 3.65 (J = 2.5 Hz) and τ 2.65 were readily assigned to C-4 and C-5 protons in compound 121 while the one-proton singlets at τ 3.05 and τ 2.7 were evident for C-3 and C-5 protons in compound 122.

It is noteworthy that indeed substitution takes place at both C-2 and C-5 positions of 3-methylfuran. To our knowledge this is the first demonstrated example of electrophilic substitution at the C-5 position of a 3-alkylfuran unsubstituted at the 2-position. Documented data indicate that only furans with electron-withdrawing substituents (e.g., -COOR group) at C-3 can direct substitution to C-5 while the presence of electron-donating substituents invariably direct the substitution to C-2.[71]

The difficulties encountered in the separation of the reaction mixture as well as the poor yield of the desired ketone 122 compelled us to discard the above sequence in favour of an alternate direct route to the preparation of this compound.

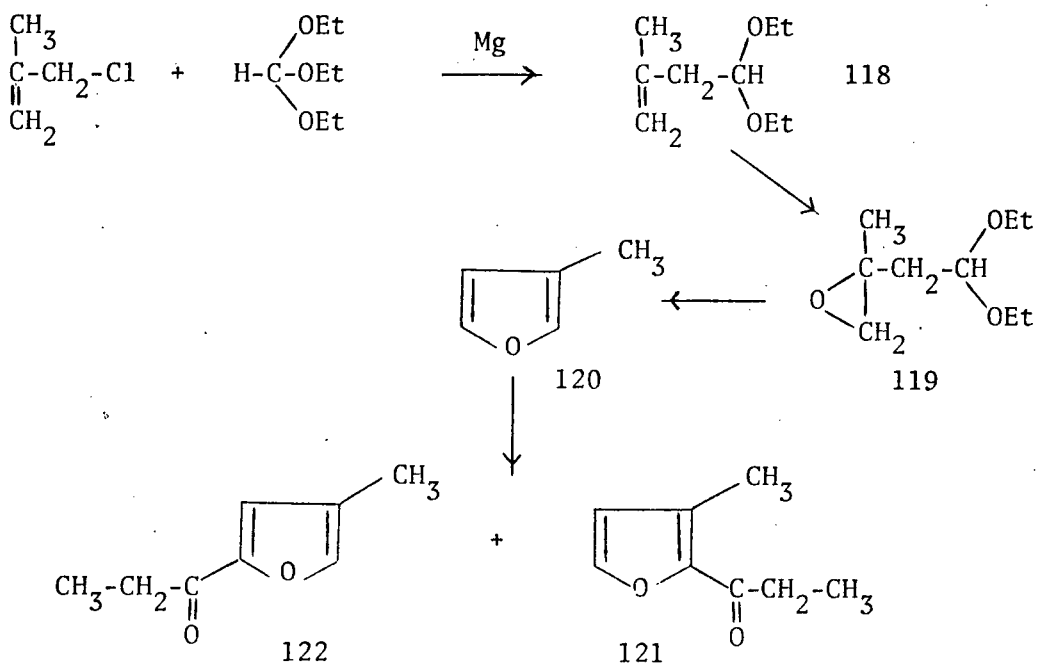


Figure 15: Preparation and propionylation of 3-methylfuran

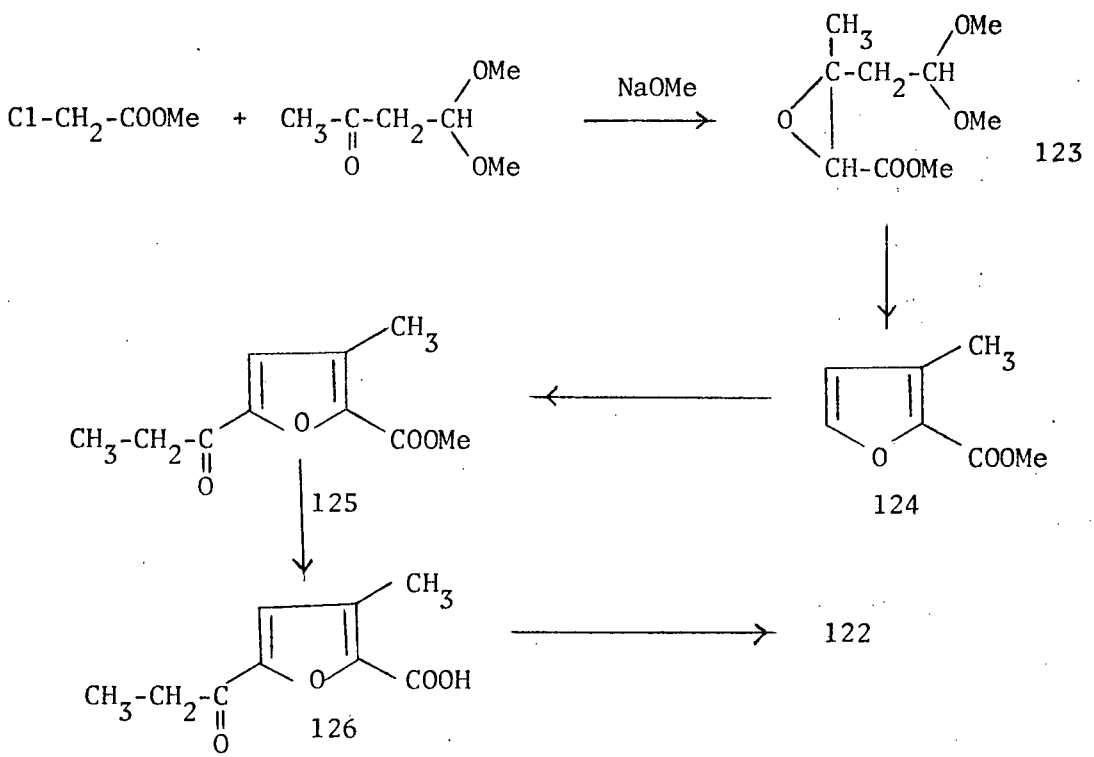


Figure 16: Synthesis of 2-propionyl-4-methylfuran

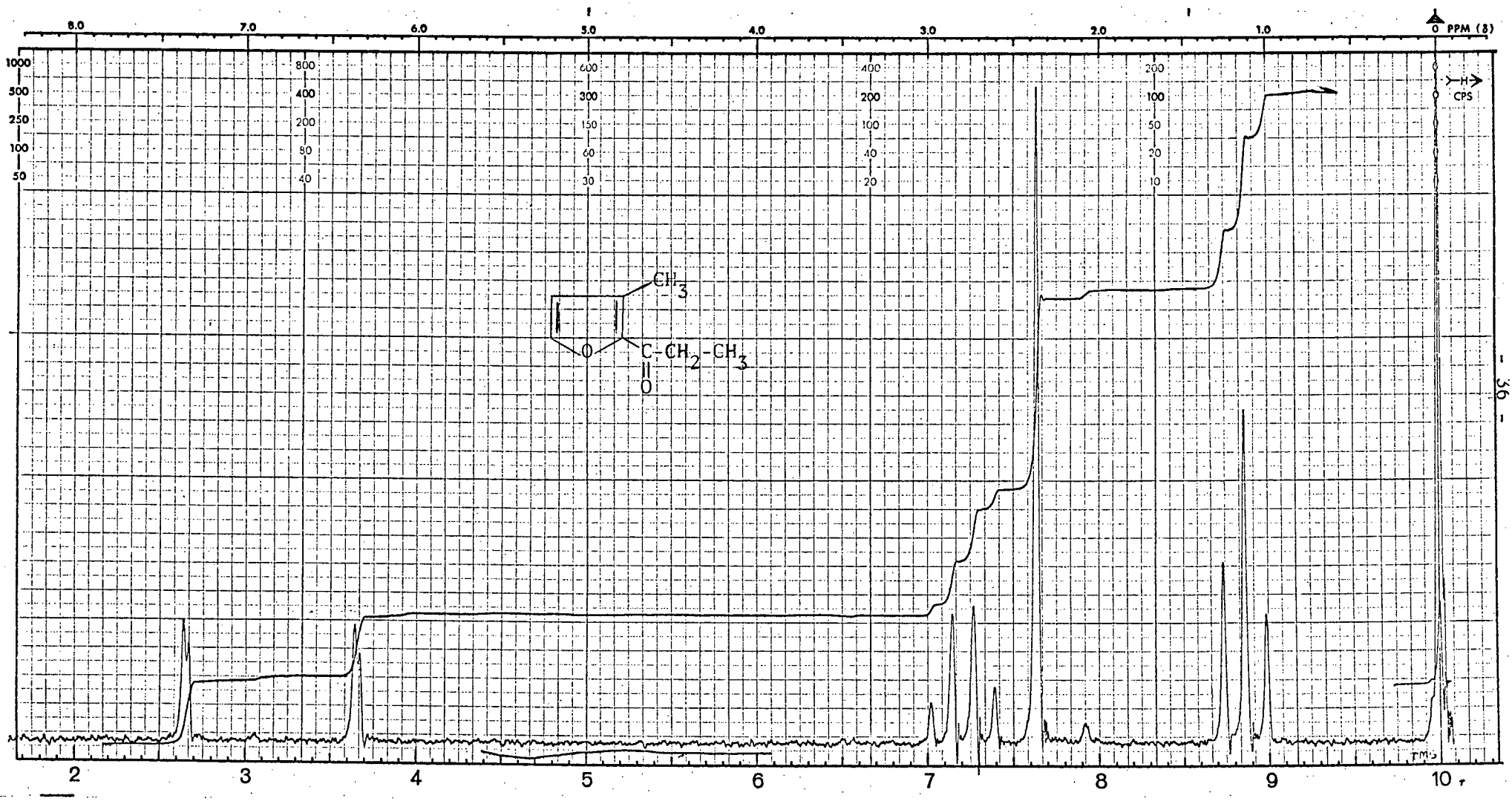


Figure 17. N.m.r. spectrum of 121

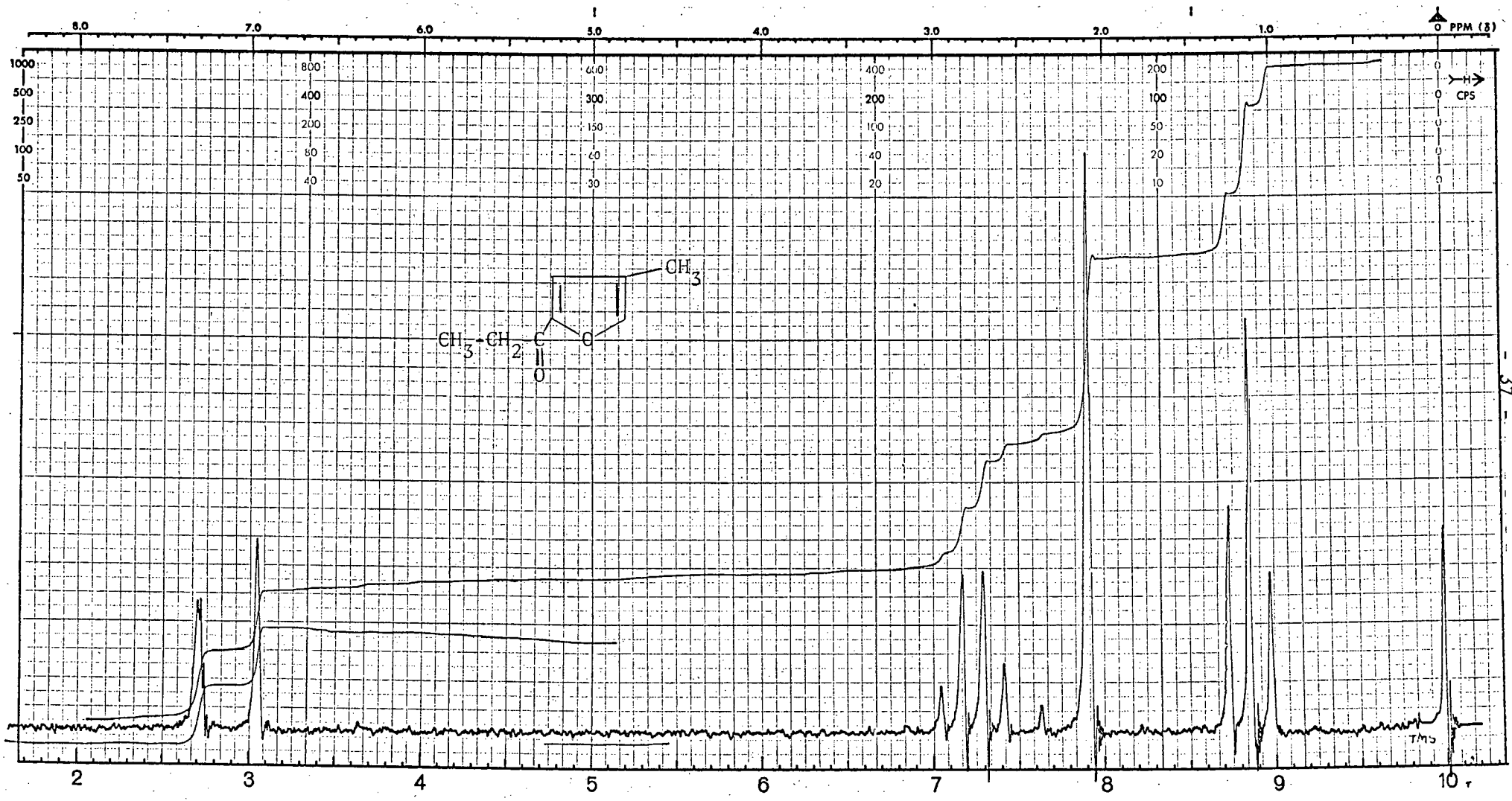


Figure 18. N.m.r. spectrum of 122

This latter route makes use of methyl-3-methyl-2-furoate (124) as the starting material. The preparation of this compound by a known procedure[72] and the subsequent reactions leading to 2-propionyl-4-methylfuran (122) are schematically presented in fig. 16. The reaction of 4,4-dimethoxy-2-butanone with methylchloroacetate in the presence of sodium methoxide afforded the epoxyester (123) without difficulty. The essentially pure epoxyester thus obtained was subjected to pyrolysis and the resulting methanol was distilled off continuously. The residual semi-solid mass was distilled and the fraction boiling at 72-78°/8 mm was found to be the desired methyl-3-methyl-2-furoate[72] (124). This latter compound was then subjected to a Friedel-Crafts reaction with propionic anhydride at 65° to provide the expected product (125). Spectral data on the purified substance quickly revealed the presence of the propionyl group (infrared, ~1700 cm^{-1}; n.m.r., three proton methyl triplet at τ 8.8 and two proton methylene quartet at 7.2). The n.m.r. spectrum is reproduced in fig. 19.

The ketoester (125) was hydrolyzed with aqueous sodium hydroxide solution and the resulting acid (126) which precipitated on acidification of the alkaline hydrolysate was filtered and dried. Decarboxylation of the latter by means of copper and quinoline provided 2-propionyl-4-methylfuran (122) which exhibited the spectral data as described earlier.

The next stage in the synthesis was the conversion of 2-propionyl-4-methylfuran (122) to 2-ethyl-5-methyl-3-hydroxypyridine (78). This conversion was effected by a known procedure.[65] The ketone (122) was treated with 11 N aqueous ammonia in a sealed tube at 160-170° for 18 hrs. The resulting reaction product was distilled in vacuo and a pale yellow oily liquid (b.p. 140°/0.3-0.5 mm) which was collected, crystallized instantaneously.

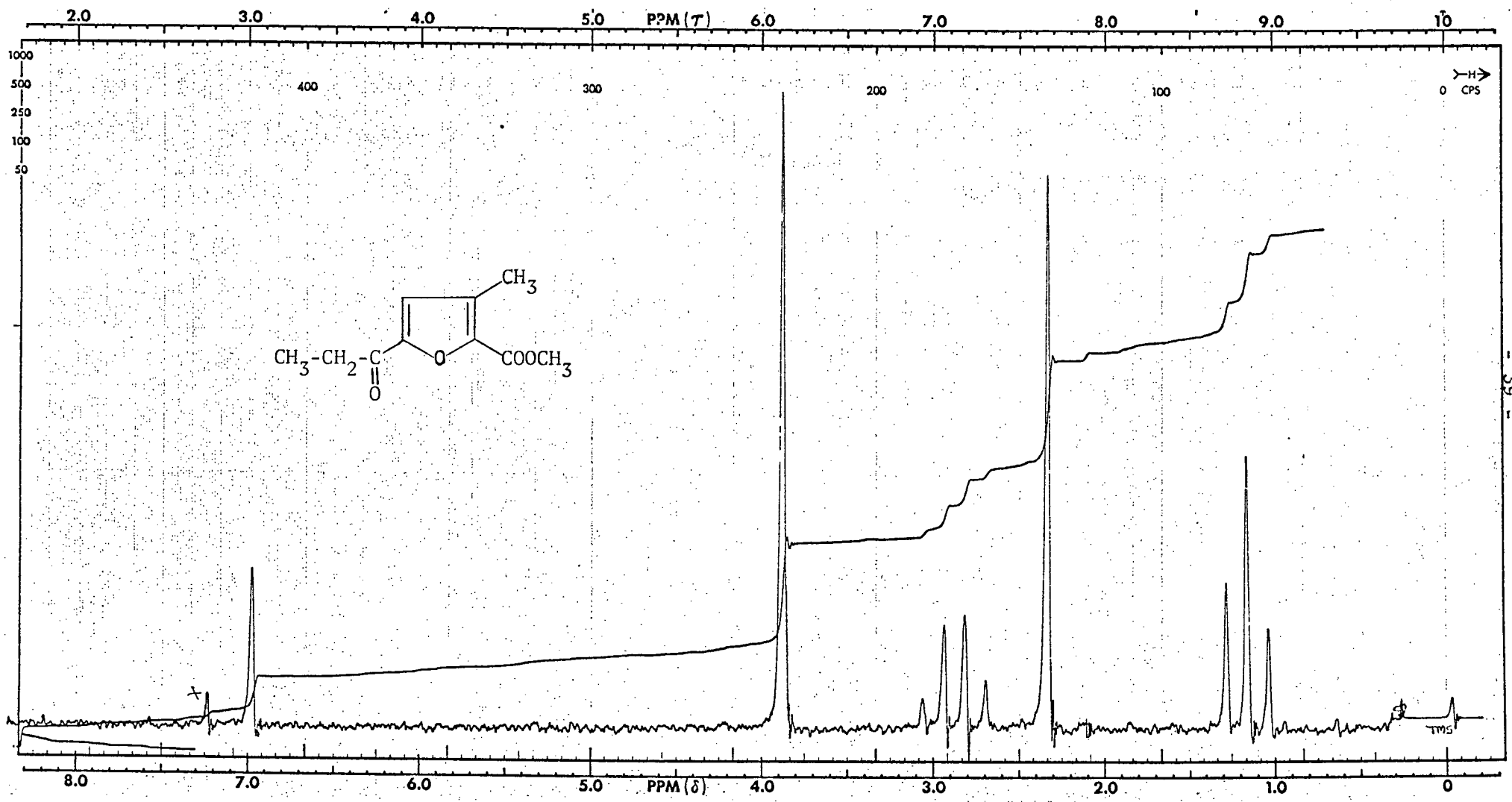
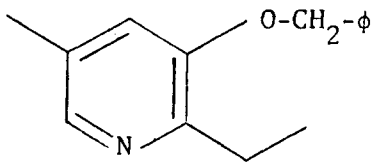


Figure 19. N.m.r. spectrum of 125

This substance on recrystallization from chloroform afforded shining prisms, m.p. 145-47°, (lit.[60] m.p. 143-144°). The ultraviolet spectrum with maxima at 287 mμ and 225 (sh) was characteristic of a 3-hydroxypyridine. The n.m.r. spectrum of the compound with signals at τ 8.75 (3H, triplet, $\underline{CH_3}$-CH_2), 7.8 (3H, singlet, C-5-CH_3), 7.1 (2H, quartet, $\underline{CH_2}$-CH_3), 2.9 (1H, singlet, C-4-H), 2.1 (1H, singlet, C-6-H), 1.0 (1H, unresolved multiplet, C-3-OH) was in complete agreement with the assigned structure (78).

In our initial studies on the coupling of the substituted pyridine with the steroidal enone (80), it was decided to use the lithioderivative of 2-ethyl-3-O-benzyl-5-methylpyridine (127). This compound was prepared by heating a solution of 2-ethyl-5-methyl-3-hydroxypyridine (78) in aqueous



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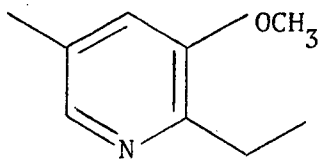


128

sodium hydroxide with benzyl chloride. However investigations on the condensation of this compound with the ketone 80 performed by Dr. J. Cable in our laboratories were unsuccessful and hence we discarded the use of the O-benzyl ether (127) and the corresponding O-methyl ether (128) was used instead.

The conversion of 2-ethyl-5-methyl-3-hydroxypyridine (78) to its O-methyl derivative (128) was achieved by treatment of an aqueous methanolic solution of this substance with ethereal diazomethane[73] at -10°. The n.m.r. spectrum of this substance is reproduced in fig. 20. Apart from the above-mentioned signals, it shows the replacement of the -OH proton in 78 by the

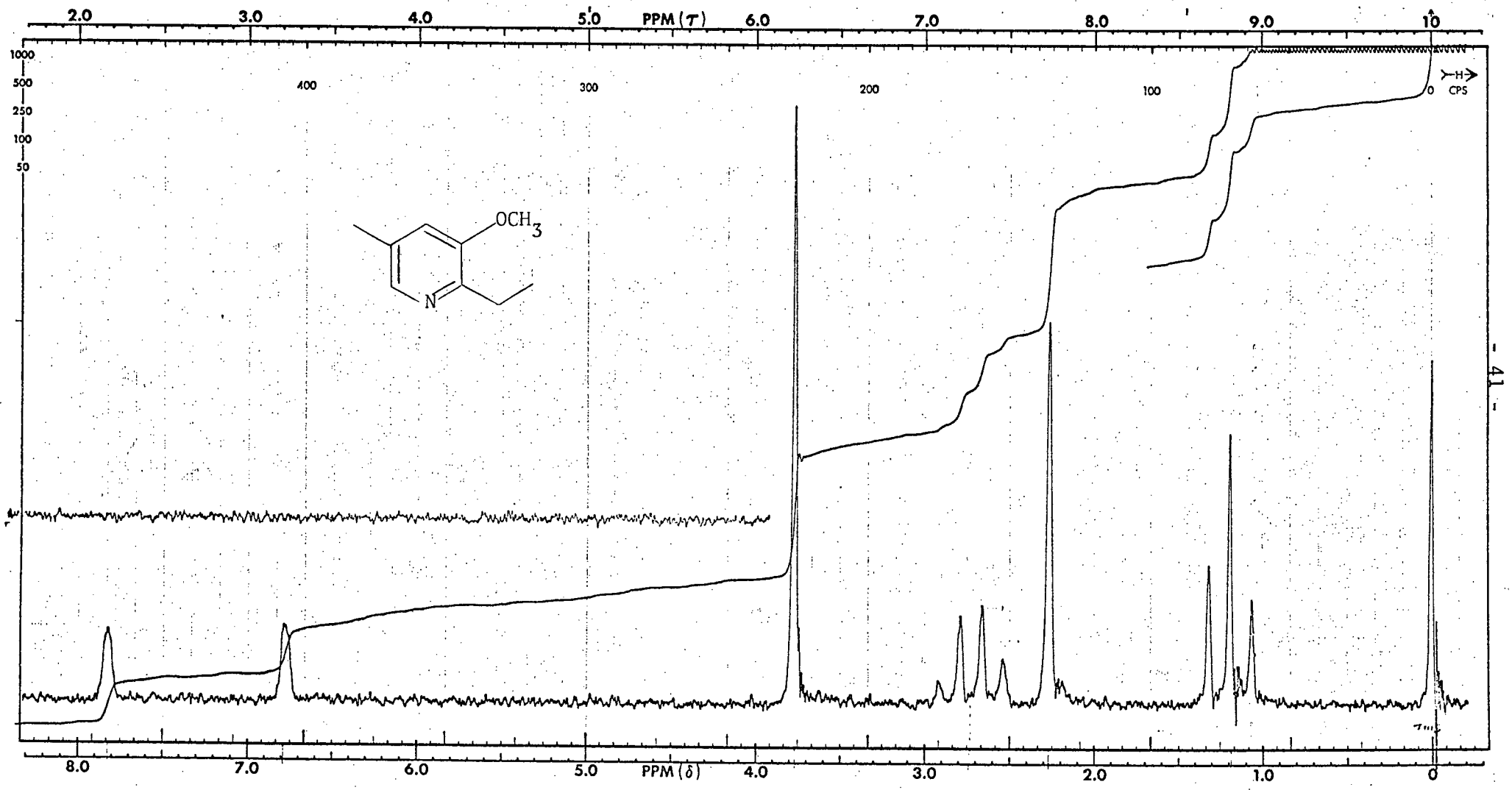


Figure 20. N.m.r. spectrum of 128

CH_3-group (singlet at~τ 6.3).

Thus with the desired steroidal enone, 3β-acetoxy-5α-etiojerv-12(13)-en-17-one (80) and the appropriately substituted pyridine, 2-ethyl-3-methoxy-5-methyl pyridine (128) in hand, the stage was set for the coupling reaction of these units. The actual reaction sequence employed for the synthesis of 5α,6-dihydroveratramine (18) is shown in fig. 21 and follows the proposal in fig. 10.

Addition of methyllithium to a solution of 2-ethyl-3-methoxy-5-methylpyridine in anhydrous refluxing tetrahydrofuran led to the development of a deep red colour presumably due to the anion (129). To this solution 3β-acetoxy-5α-etiojerv-12(13)-en-17-one (80) was added until the colour faded. Heating was continued for a short period and the reaction was quenched with saturated ammonium chloride solution. Examination of the ether extract by t.l.c. showed the presence of a new compound. This product was separated by column chromatography on alumina and obtained crystalline from ether. The ultraviolet spectrum showed a peak at 283 mμ indicative of the pyridine chromophore while the mass spectrum exhibited a peak at m/e 439 corresponding to the parent ion for a substance bearing the gross structure 130.

That the above material obtained, although homogeneous on t.l.c., was a mixture of two compounds was indicated by the n.m.r. spectrum which exhibited two sharp singlets at τ 6.21 and 6.24 due to the presence of two methoxyl groups. Two doublets were also seen at τ 8.81 and 8.84 which were probably due to the C-21 methyl group in each of the two compounds. Attempts at the separation of this mixture by chromatographic techniques

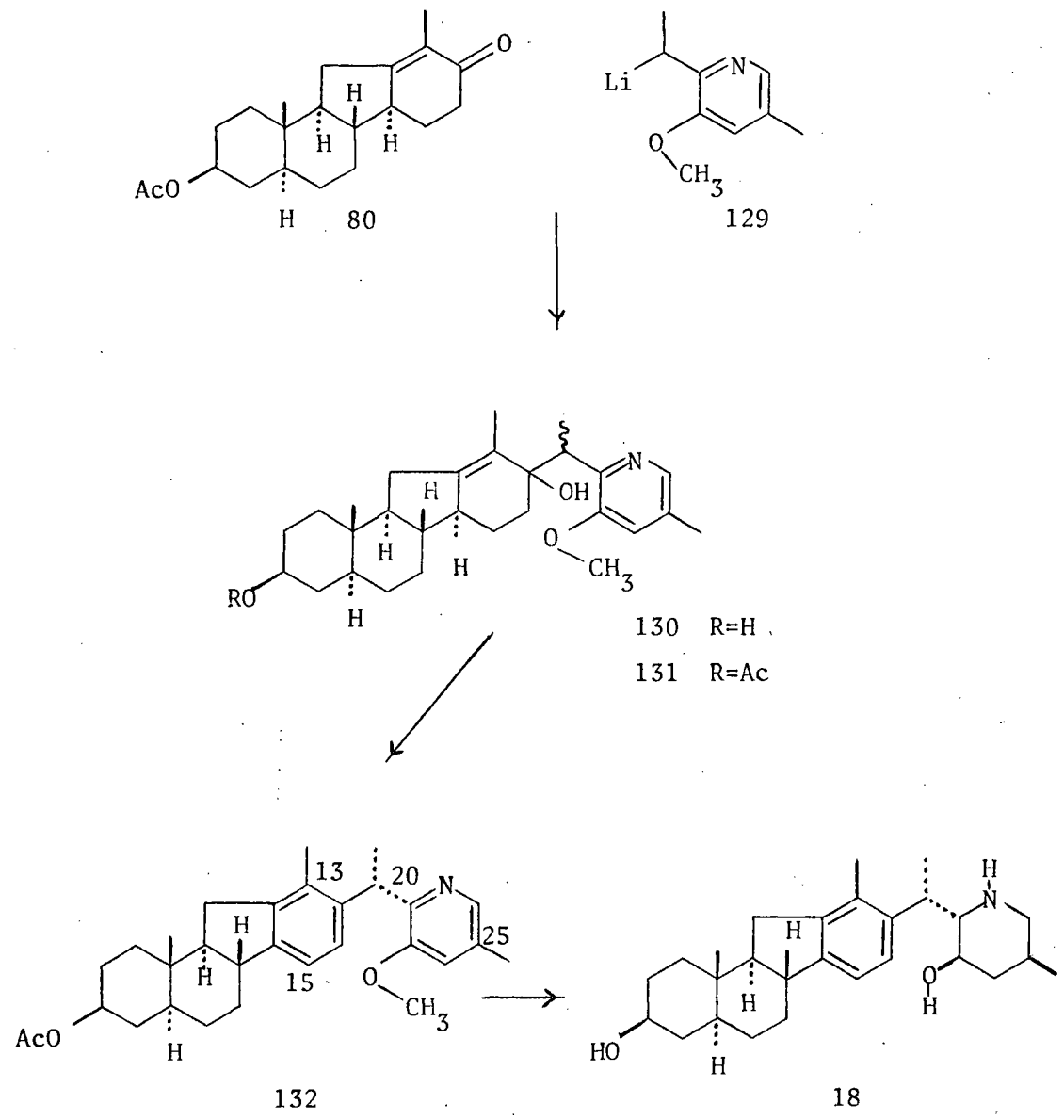


Figure 21: Synthesis of 5α,6-dihydroveratramine

were unsuccessful since both the compounds had identical R_f values on t.l.c. in numerous solvent systems.

In an attempt to achieve separation of these two compounds the mixture was subjected to acetylation by means of acetic anhydride and pyridine. The resulting reaction mixture on t.l.c. examination showed the presence of two compounds possessing very different R_f values. These were separated by column chromatography on alumina. For the sake of discussion the more polar compound is referred to as compound "A" while the less polar one is designated as compound "B".

The examination of compound "A" revealed the following facts: the ultraviolet spectrum showed a peak at 283 mμ with a shoulder at 225 indicative of the pyridine chromophore. The mass spectrum exhibited the parent peak at m/e 463 which indicated that dehydration of the coupled product (131) has occurred in the mass spectrometer. Confirmation of this result was obtained from the elemental analysis and spectral data of compound "A". For example, the infrared spectrum showed the presence of a hydroxyl group (3280 cm^{-1}) whereas the n.m.r. spectrum (fig. 23) is in complete accord with the proposed structure (131) for compound "A". The latter spectrum was particularly instructive and a detailed analysis was carried out. Thus a sharp singlet at τ 9.22 with a three proton integral was assigned to the C-19 methyl resonance. The doublet at 8.82 was attributed to the C-21 methyl protons, which were coupled with the C-20 proton, $J_{20,21}$ = 7.0 Hz. The sharp singlets at τ 8.79, 8.0 and 7.7 were due to C-18 methyl, C-3 acetate and C-26 methyl protons respectively while the three proton signal at 6.22 was easily recognized as due to the C-23 methoxyl protons. The protons on the pyridine ring appeared as sharp singlets at τ 3.08 (C-24 H)

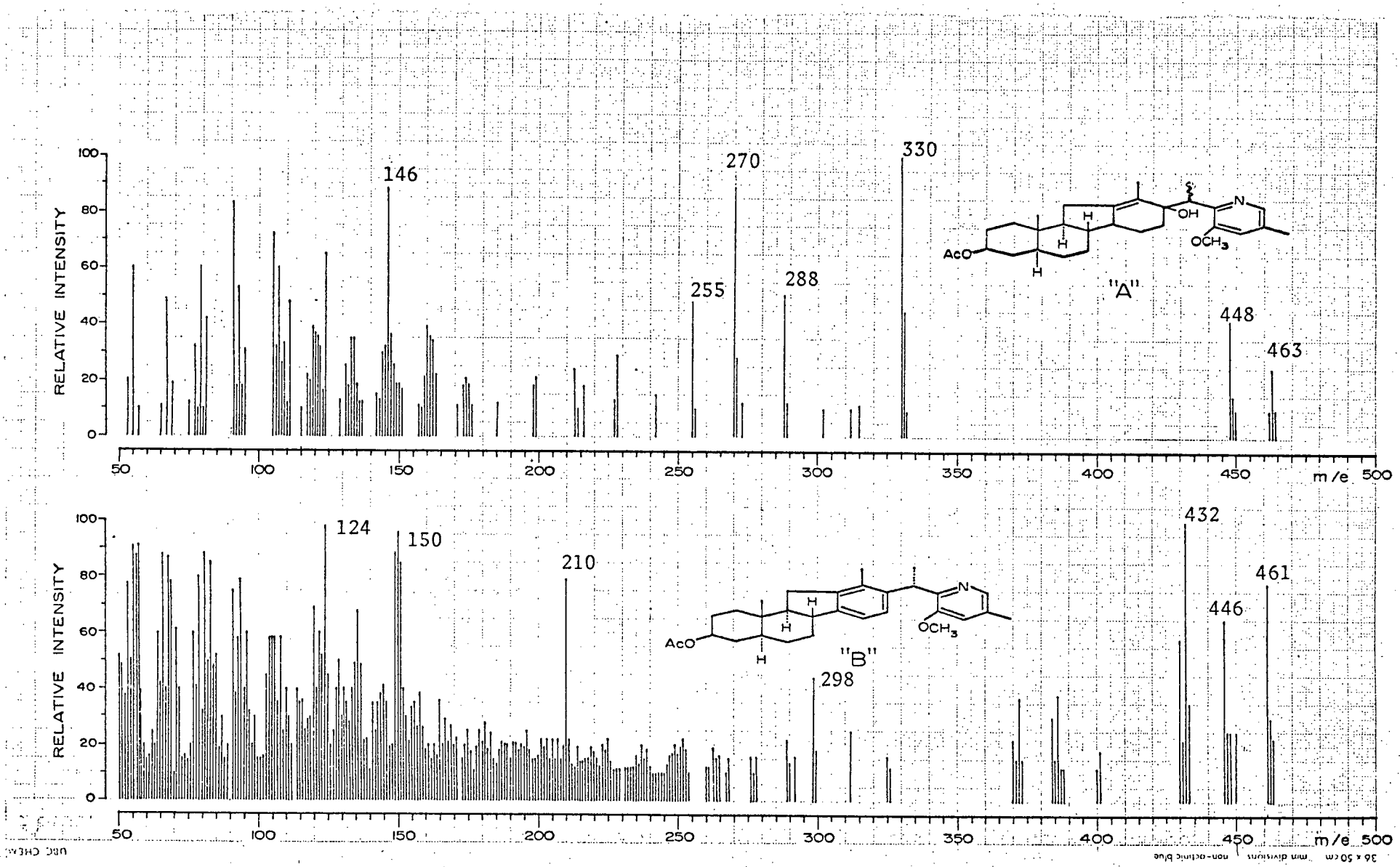
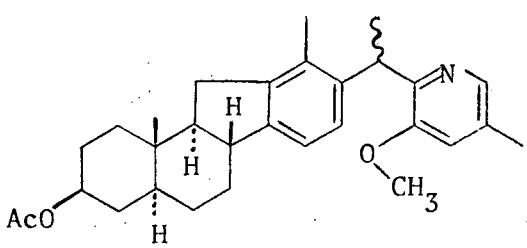


Figure 22. Mass spectra of 131 and 132.

and 2.0 (C-27 H). Finally the assignment of the molecular formula for the desired material (131) was further corroborated by high resolution mass spectrometry (found: 463.308; calc: 463.308).

The ultraviolet spectrum of compound "B" was similar to that of "A" and showed maxima at 283 mμ and 225 mμ (sh). The mass spectrum exhibited the parent peak at m/e 461 corresponding to a molecular ion which accounts for the loss of 20 units from the desired compound of gross structure 131. The n.m.r. spectrum is reproduced in fig. 24. A first order analysis of the spectrum was carried out and the following assignments were made. A sharp singlet at τ 9.08 integrating for three protons was assigned to the C-19 methyl resonance. The doublet occurring at τ 8.45 was assigned to the C-21 methyl group which was coupled with the C-20 proton, ($J_{20,21}$ = 7.0 Hz). The singlet at τ 7.7 integrating for six protons was due to the C-26 and C-18 methyl groups, the latter now being situated on an aromatic ring. This result is in agreement with the absence of the signal at τ 8.79 present in the spectrum of compound "A" and unequivocally assigned to the C-18 methyl protons in this compound. Further proof for the correctness of such an



133

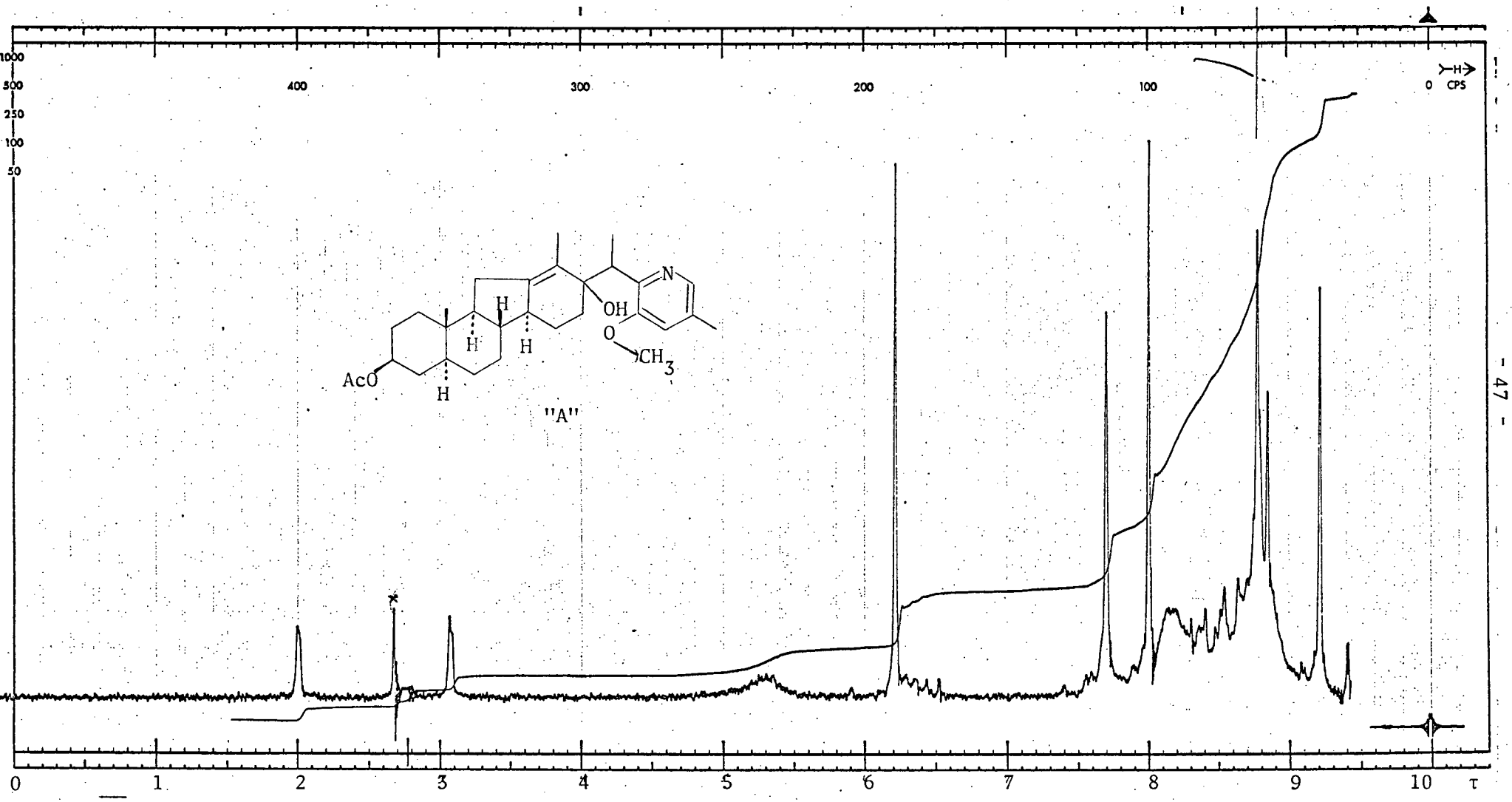


Figure 23. N.m.r. spectrum of compound "A" (131)

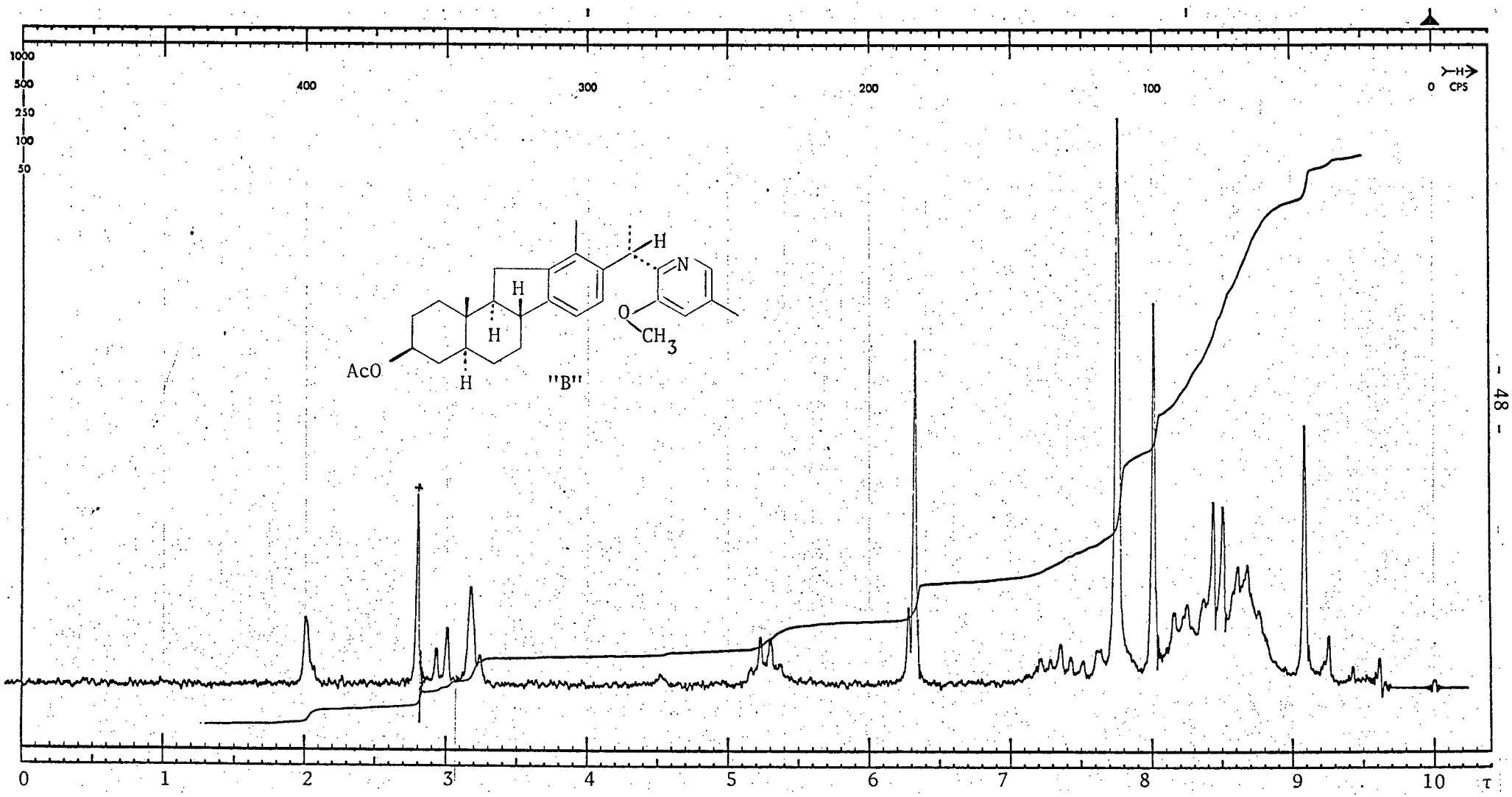


Figure 24. N.m.r. spectrum of compound "B" (132)

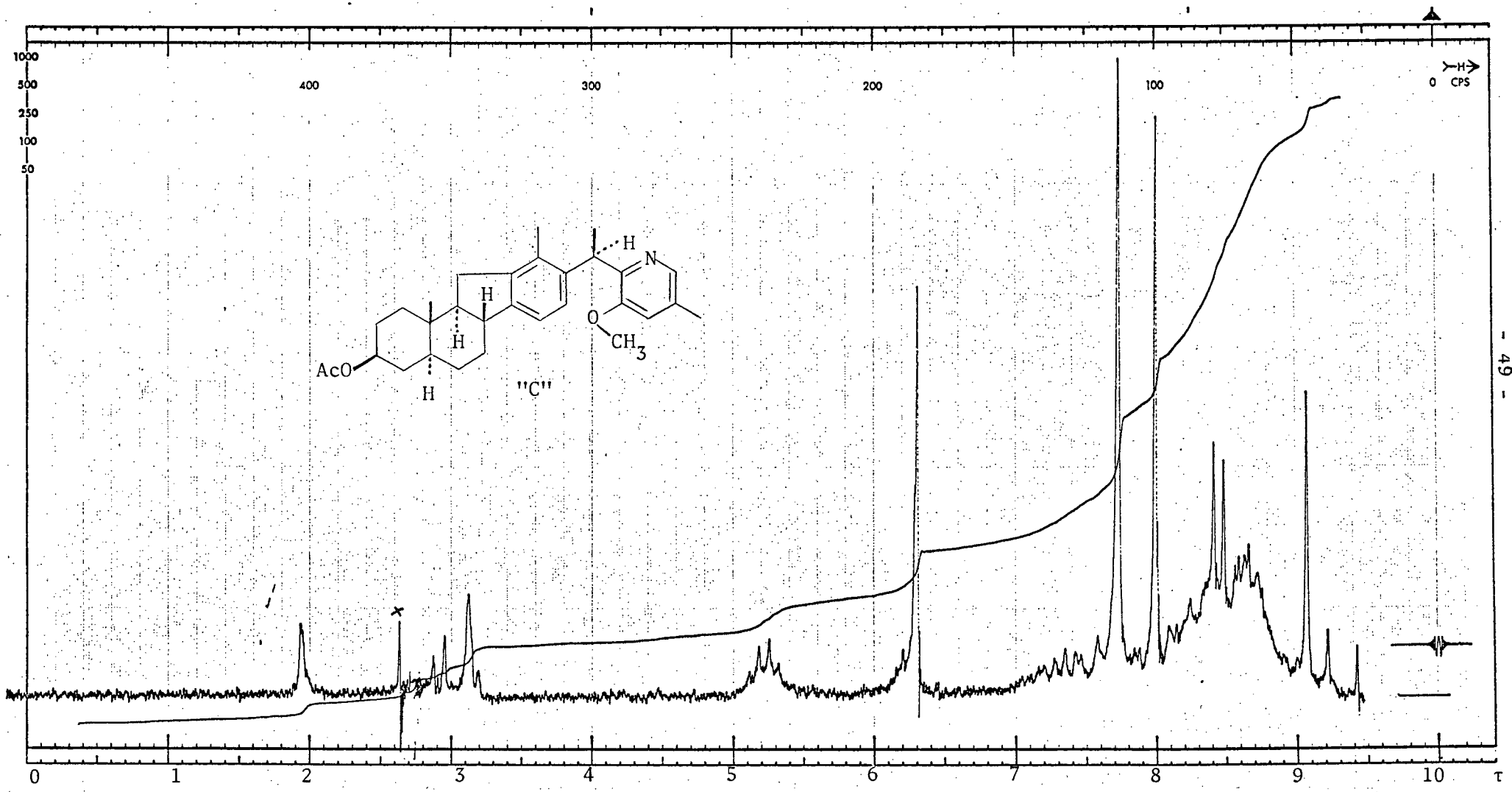


Figure 25. N.m.r. spectrum of compound "C" (134)

assignment came from the examination of the low field (τ 4-2) region of the spectrum. Only two one-proton singlets were expected in this region for a compound of structure 131. However this region of the spectrum exhibited an AB quartet centered at τ 3.05. This signal is clearly due to the C-15 and C-16 protons in a ring D aromatic compound with the expected large ortho coupling (J = 7 Hz). The acetate protons at C-3 and the C-23 methoxyl protons appeared as sharp singlets at τ 8.0 and 6.3 respectively. The pyridine protons were descernible as singlets at 3.16 (C-24 H) and 2.0 (C-27 H).

Since the above spectral data was consistent for the ring D aromatic structure 133, it was clear that compound "B" arises via dehydration of the C-17 hydroxyl function in the condensation product (130) followed by aromatization of the resulting diene. Further support for structure 133 came from the mass spectrum with parent peak at m/e 461 and the absence of a hydroxyl absorption in the infrared spectrum. The molecular formula, $C_{30}H_{39}NO_3$ was corroborated by high resolution mass spectrometry (calc: 461.293; found: 461.291).

It can be seen from fig. 21 that the coupling reaction generates two asymmetric centres and consequently there exists the possibility of obtaining four compounds possessing structure 130. However in our studies we have isolated only two compounds and did not recognize the presence of any more.

The above results suggest that the coupling reaction probably afforded a mixture of alcohols of gross structure 130 and that one of them fortuitiously underwent dehydration followed by aromatization during the subsequent work-up. There existed the possibility of this sequence of reactions occurring either during acetylation of the reaction mixture or during the chromato-

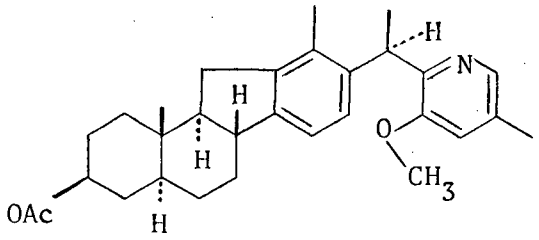
graphic separation on alumina.

We set out to explore this phenomenon by monitoring a typical experiment by n.m.r. spectroscopy. The product obtained in the coupling reaction was subjected to acetylation with acetic anhydride and pyridine at room temperature. After allowing the reaction mixture to stand overnight followed by the usual work-up, the n.m.r. spectrum of this material displayed an AB quartet in the low field region which was attributed to C-15 and C-16 protons in a ring D aromatized compound. The results of the experiment allowed us to conclude that one of the two alcohols under the influence of pyridine and acetic anhydride underwent dehydration leading to a cyclohexadiene system which probably aromatized instantaneously to give a ring D aromatic compound (compound "B", structure 133).

In our subsequent studies we have been able to convert the alcohol 131 (compound "A") to an aromatic compound isomeric with "B". In a typical experiment, compound "A" was ground with 10% palladized charcoal until the two substances were thoroughly mixed and then the powder was heated at 200° for 10 minutes under nitrogen. Examination of the reaction product by t.l.c. indicated the presence of a new compound with R_f value similar to that of "B". Besides this new compound we were able to recognize the presence of two other compounds. All the three compounds were obtained in a pure state by preparative t.l.c. and two of these were identified as the α,β-unsaturated ketone (80) and 2-ethyl-3-methoxy-5-methylpyridine (128). The third compound which was formed in 25% yield showed a colour reaction with antimony pentachloride on developing the chromatoplate, similar to that obtained with compound "B". This material is designated as compound

"C". The mass spectrum exhibited a peak at m/e 461 corresponding to the molecular ion for a compound of structure 133. The n.m.r. spectrum is reproduced in fig. 25 and is remarkably similar to that of compound "B". The three proton singlet due to the C-19 methyl group appears at τ 9.07, while the doublet at τ 8.4 integrating for three protons is assigned to the C-21 methyl group. The three proton singlet at τ 8.79 assigned to the C-18 methyl in compound "A" has now disappeared and the singlet at τ 7.74 integrating for six protons is attributed to be due to an overlapping of the signals due to C-18 methyl and C-26 methyl groups. This result is in accord with the aromatization of ring D. The aromatic region of the spectrum is similar to that of "B". An AB quartet centred at τ 3.0 was attributed to C-15 H and C-16 H (J = 7.0 Hz), whilst the singlets at τ 3.1 and 1.92 were assigned to the C-24 and C-27 protons respectively. The molecular formula of compound "C" was confirmed by high resolution mass spectrometry as being that of compound "B". The compounds "B" and "C" contain only one new asymmetric centre (C-20) when compared with 3β-acetoxy-5α-etiojerv-12(13)-en-17-one. The introduction of the asymmetric centre at C-20 would therefore be expected to give rise to two diastereomers and this is therefore the difference between the two aromatic compounds "B" and "C".

Since the aromatic compound "B" gave rise to compounds in the natural series, the stereochemistry at C-20 in this compound is known and is indicated in 132. This leads to the conclusion that compound "C" is the C-20 epimer of "B" and has the stereochemistry as indicated in 134.



134

After having established that the condensation product of 2-ethyl-3-methoxy-5-methylpyridine and 3β-acetoxy-5α-etiojerv-12(13)-en-17-one is a mixture of epimeric alcohols (130) and that one of these alcohols undergoes dehydration and aromatization to give compound "B" during the subsequent work-up, we set out to assign the stereochemistry of the condensation products. One of the several rational interpretations of the results is advanced in the following paragraphs. I wish to emphasize that we are unable at this time to clearly distinguish between several alternative explanations.

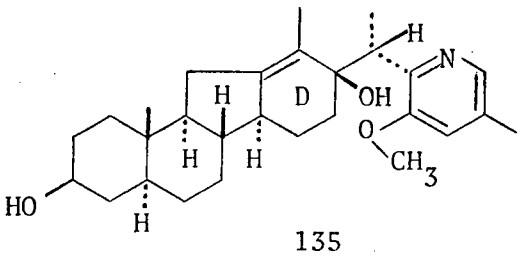
It is clear that several important factors must be considered in advancing any stereochemical assignments to the condensation products possessing the gross structure, 130. These are: 1) Is the stereochemistry at C-20 determined during the approach of the anion to form the C-17, C-20 bond or is the product composition a result of equilibration after the initial reaction has occurred? It is well known that protons adjacent to a pyridine ring (as at C-20) are readily removed by strong base. 2) Is the approach of the anion equally favorable from the "equatorial" and "axial" sides of the molecule since this factor determines the stereochemistry at C-17? With regard to the latter an investigation of the molecular models

quickly revealed that no distinct preference for either approach is apparent. In other words, one would expect that epimers at C-17 is the most likely course of events. In the explanation given below I have assumed that such is the case, i.e., the two condensation products differ in stereochemistry at C-17 but not at C-20. In actual fact the discussion below indicates that the results obtained are explicable, regardless whether a definite stereochemistry is initially assigned to C-20 in the condensation products. For the sake of clarity the particular stereochemistry chosen for C-20 was the one which is present in the natural Veratrum series. The reasons for the latter choice are twofold: a) there is a minimal interaction between the various groups on ring D and the heterocyclic portion when this stereochemistry is considered and b) one of the above condensation products leads to 5α,6-dihydroveratramine.

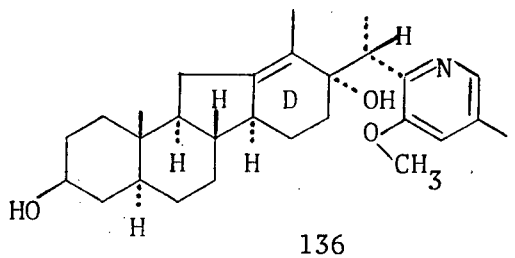
Once we have made a tentative assignment of the stereochemistry at C-20 in the condensation products we were left with the task of advancing a reasonable explanation for the difference in the stability of the alcohols and the observed facile dehydration followed by aromatization in one case as opposed to the sluggishness in the other. An acceptable explanation for the difference in their behaviour is given in the following paragraphs. Here again, it should be emphasized that there can be alternate explanations, but the one chosen appears to be the most reasonable one.

If we consider the "axial" alcohol (135) and its possible conversion to the ring D aromatic derivative (132) it is clear that the allylic hydroxyl can undergo 1,4-elimination making use of the C-14 proton, or alternatively a 1,2-elimination involving the α-(axial) proton at C-16 is

also a feasible process. Either of these eliminations would yield a highly strained cyclohexadiene system (with regard to ring D) which would be expected to aromatize rapidly to yield a compound of structure 132.

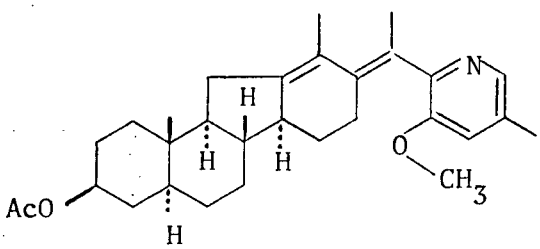


135



136

On the other hand, examination of molecular models for the "equatorial" alcohol (136) reveals that in this compound there are no ring D protons which are trans and coplanar to the hydroxyl group. The desired stereochemistry for the elimination can be attained at C-20 by rotation around the C-17, C-20 bond, but such a process leads to an eclipsing of C-18 and C-21 methyl groups and an increase in non-bonded interactions between ring D (particularly C-16) and the substituents on the heterocyclic ring. Hence the sluggishness of this alcohol to dehydrate may be related to the energy required to force the molecule into this sterically unfavorable conformation. The higher temperature (200°) as noted above, under which this alcohol converts to a substance possessing an aromatic D ring would then



137

provide the necessary energy. Dehydration in this event will lead to a diene 137, which via double bond rearrangement and aromatization would provide the aromatic compound 133. Obviously such a process can lead to epimerization at C-20. In fact the aromatic compound ("C") isolated in this reaction is isomeric with compound "B" and must therefore be its C-20 epimer (i.e. 134). It is to be noted that the various other asymmetric centres involving rings A, B, and C cannot be altered during the above reactions. On this basis it is clear that these centres are identical in both compounds "B" and "C".

After obtaining the D ring aromatized compound, our next objective was to find suitable methods to reduce the pyridine ring to the piperidine moiety present in veratramine (2). The ready availability of compound "B" (132) prompted us to undertake such studies initially with this compound. Although a selective hydrogenation of the pyridine ring[74] was the obvious choice, such an operation was expected to give a mixture of stereoisomers. Hence we considered a stepwise reduction of the pyridine ring (see fig. 11). In order to explore the feasibility of this scheme we used 2-ethyl-3-methoxy-5-methylpyridine itself as a model and the sequence of reactions outlined in fig. 26 was carried out.

The reaction of 2-ethyl-3-methoxy-5-methylpyridine (128) provided the salt, 138 without difficulty. This compound without further purification was dissolved in water and treated with a mixture of aqueous potassium carbonate and sodium borohydride at 0°.[75,76] T.l.c. examination of the reaction mixture showed the presence of two components of similar R_f values and the spectral data (ν_{max}: 1650, 1600, 725 cm^{-1} (-C=C-C=C-), λ_{max}: 260,

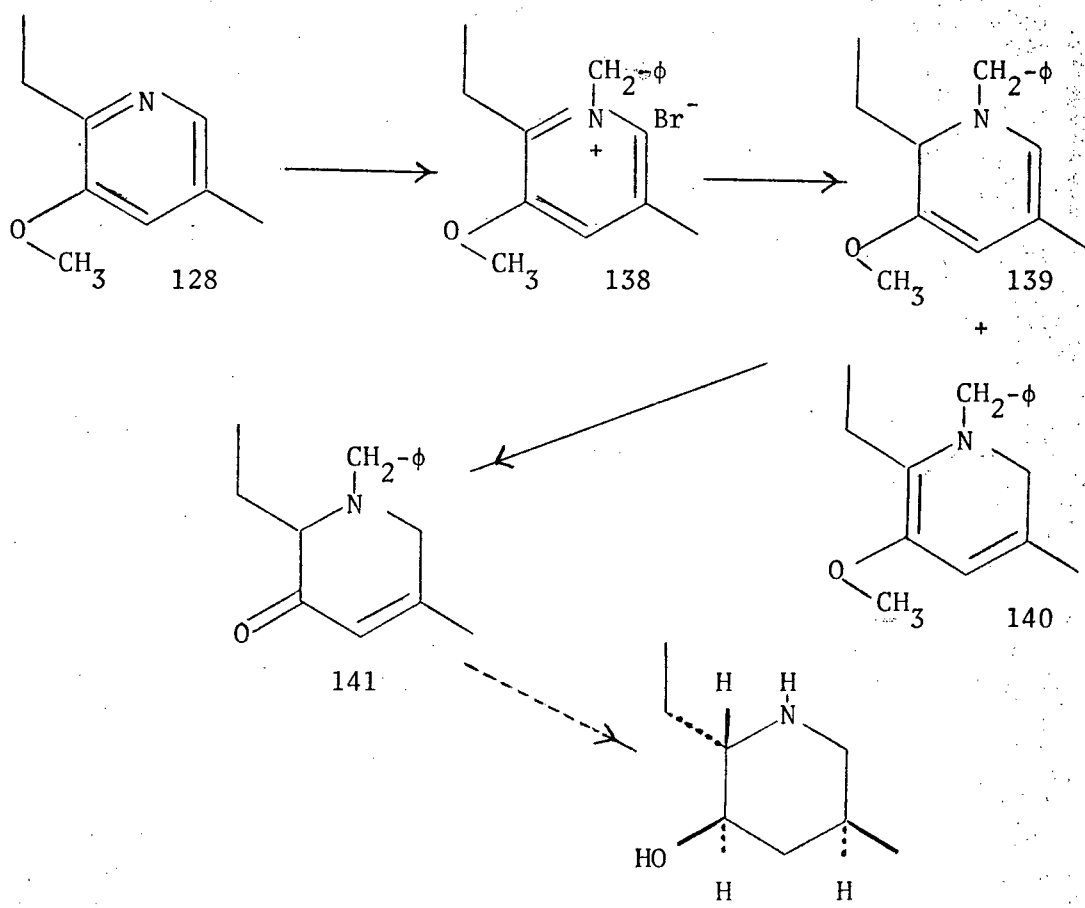


Figure 26: Stepwise reduction of 2-ethyl-3-methoxy-5-methylpyridine

227, 215 (sh) mμ) suggested tentative structures 139 and 140. This suggestion was supported by the fact that the product mixture was found to be extremely unstable and rearomatization to the starting pyridine was facile. No attempt was therefore made to separate these components. The reaction mixture thus obtained on treatment with hydrochloric acid afforded a mixture of two compounds which were separated by t.l.c. The less polar compound was found to be the pyridine derivative, 128, while the second component was assigned the structure 141 on the basis of its spectral data (ν_{max}: 1680 cm^{-1} (=C-C=O); λ_{max}: 335 (sh), 300, 225 (sh).

The above results clearly attested to the validity of the scheme as outlined in fig. 11. However, in practice, this approach failed completely when applied to our synthetic compound, 132. The dihydropyridine derivative obtained in this case was found to be extremely unstable and hence we discarded this approach.

Although we were aware that hydrogenation of the pyridine ring could lead to various isomers, such a course was chosen in the absence of better alternatives. Compound "B" (132) when subjected to hydrogenation in ethanol at pressures ranging from 40-65 p.s.i. did not undergo any change. However, it was found that this substance undergoes hydrogenation in an acid-alcohol medium. A solution of 132 in 95% ethanol containing 2% hydrochloric acid was subjected a hydrogen atmosphere of 62.5 p.s.i. in the presence of Adam's catalyst (PtO_2). T.l.c. examination of the reaction product revealed the presence of three major compounds along with trace amounts of several other components. One of the major compounds had the same R_f value as 5α,6-dihydroveratramine. Indeed, separation of the mixture afforded an 18% yield of 5α,6-dihydroveratramine (18), identical with the natural sample prepared by the hydrogenation of Veratramine.[30,77] The synthetic and natural substances possessed superimposable infrared spectra (see fig. 27) and no depression of melting point was observed in a melting point determination. The two other compounds isolated in the hydrogenation experiment were found to be extremely unstable and the limited quantities of these available prevented any meaningful investigation. However, a preliminary inspection of the n.m.r. spectra of the impure compounds revealed that in both instances the pyridine ring was only partially reduced (to the dihydro or tetrahydropyridine stage) while the methoxyl group was still intact.

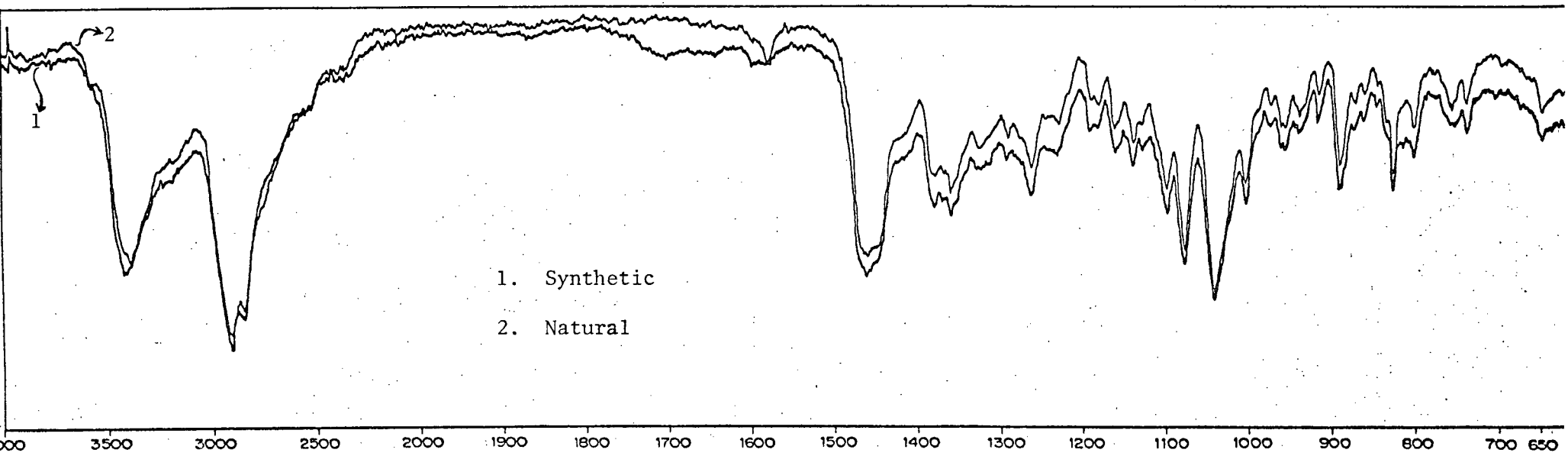


Figure 27. Infrared spectra of 5α,6-dihydroveratramine (synthetic and natural).

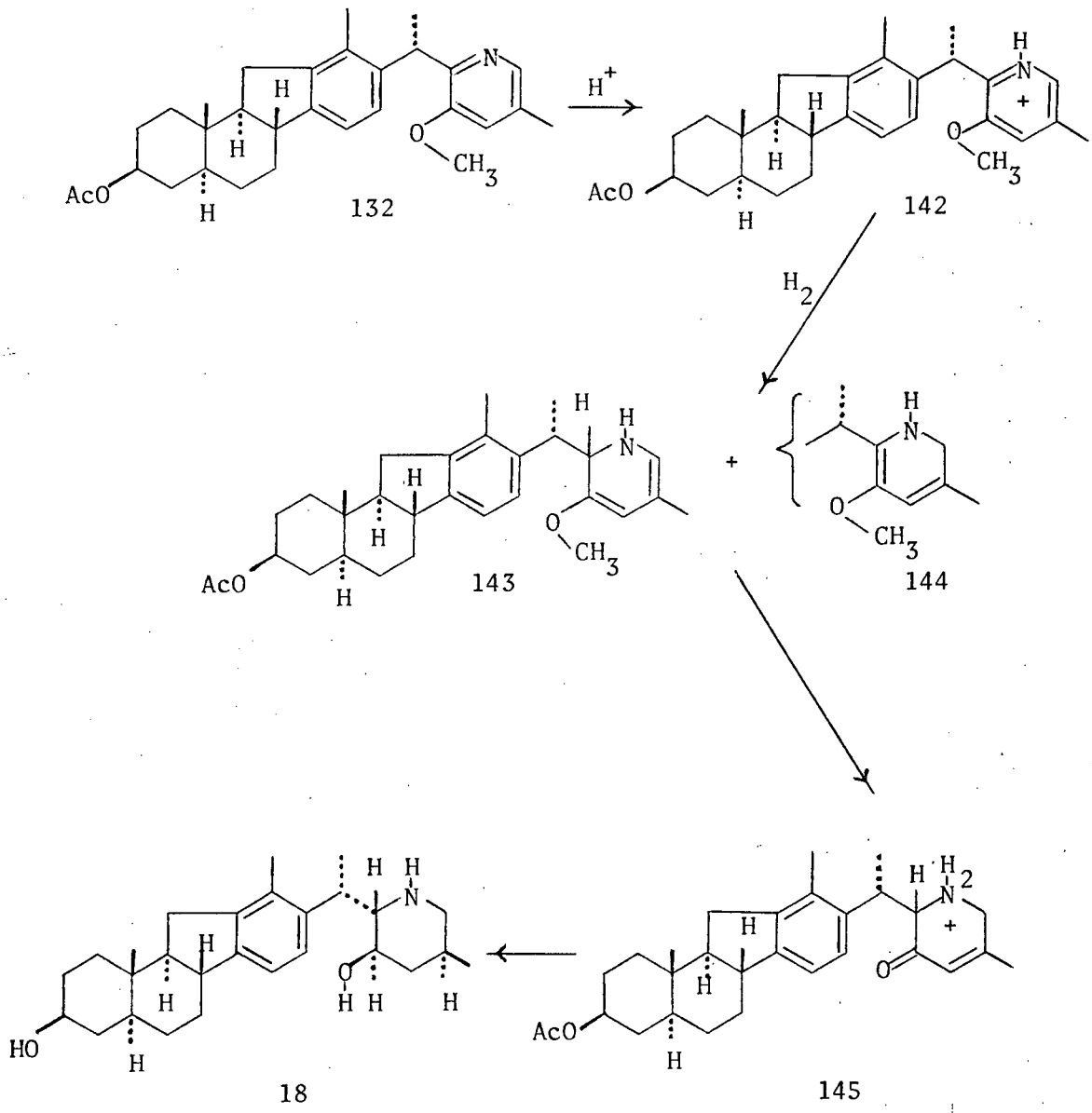


Figure 28: Possible intermediates in the hydrogenation of compound "B" (132)

The intermediates involved in the conversion of 132 to 5α,6-dihydroveratramine (18) cannot be detailed with certainty since no isolation of them was feasible. However, since the substituents at the three asymmetric centres (C-22, C-23 and C-25) in veratramine are in the most stable equatorial orientation, it was expected that the overall conversion involving equilibrating conditions would be feasible. A rationalization of the results is provided in fig. 28.

Protonation of the pyridine ring in 132 followed by initial attack of hydrogen on the pyridinium salt (142) may lead to either one or both of the dihydropyridines (143 and 144). Acidic hydrolysis of either of these intermediates would be expected to provide at least in part the α,β-unsaturated ketone (145). Further hydrogenation of the latter leads to the final product in which all the substituents are equatorial.

As mentioned earlier the synthesis of 5α,6-dihydroveratramine (18) was sufficient for our purpose because this material has already been converted to veratramine[52] (2), jervine[51] (4), veratrobasine[26,62] (5) and 11-deoxojervine.[61] Thus the present work represents in a formal sense the total synthesis of the above mentioned compounds.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Ultraviolet (U.V.) spectra were recorded in methanol on a Cary 11 recording spectrophotometer. Infrared (I.R.) spectra were obtained on a Perkin Elmer model 21 or 457 spectrophotometer. Nuclear magnetic resonance (n.m.r.) spectra were determined at 60 Hz on a Varian A-60 spectrometer and at 100 MHz on a Varian HA-100 spectrometer using carbon tetrachloride, deuteriochloroform or methanol-d_4 solutions with tetramethylsilane as internal standard. The chemical shifts are recorded in the Tiers τ scale. The types of protons, integrated area, multiplicity and spin coupling constant J (in Hz) are indicated in parentheses. Specific rotations ($[\alpha]_D$) were determined in chloroform solution at 20° on an O.C. Rudolph and Sons No. 219 polarimeter using a one decimeter cell. Mass spectra were recorded on an Atlas CH-4 or Associated Electrical Industries MS-9 spectrometer, high resolution measurements being determined on the latter instrument. Vapour phase chromatography (v.p.c.) was done on an Aerograph Autoprep model A-700 instrument using a FFAP column (20% FFAP on chromosorb W 1/4" x 10' s.s. column) or a S.E.-30 column (20% S.E. 30 on 60/80 chromosorb W 1/4" x 10' s.s. column). Silica gel G and Woelm neutral alumina containing 2% electronic phosphor were used in preparing thin layer chromatoplates and Woelm neutral alumina deactivated by the addition of 6% water or Shawinigan

alumina deactivated by the addition of 3% of 10% aqueous acetic acid solution was used for column chromatography. Elemental analyses were performed by Mr. P. Borda of the Microanalytical Laboratory, University of British Columbia.

Synthesis of 3β-Acetoxy-5α-etiojerv-12(13)-en-17-one (80)

Throughout the entire project this compound occupied a position of importance, since it provided the etiojervane portion of the Veratrum alkaloids. It is not a commercially available material but was prepared from hecogenin acetate[78] employing degradation procedures well documented by W.F. Johns.[64] Details of the quantities used and the yields of the various intermediates obtained in this work are given below. Special mention is made of modifications in the experimental procedure wherever applied. Any additional data obtained for the characterization of the intermediates in the degradation is also included.

Hecogenin p-toluenesulfonylhydrazone (113)

A solution of hecogenin acetate (112, (400 g)) in glacial acetic acid on treatment with p-toluenesulfonylhydrazine hydrochloride as outlined by Hirschmann et al[79] afforded hecogenin p-toluenesulfonylhydrazone (560 g). The product was essentially pure and was subjected to the next reaction without further purification.

13-Methyl-C-nor-D-homo-18-nor-5α,22α-spirost-12(13)-en-3β-ol (114)

A solution of hecogenin p-toluenesulfonylhydrazone (560 g) in potassium hydroxide/ethylene glycol was heated under nitrogen as described by W.F. Johns.[64] The product was purified by crystallization from aqueous

ethanol. Colorless shining needles, m.p. 108-111° (lit. m.p. 108-118°). N.m.r. signals: 9.28 (singlet, 3H, C-19 CH_3), 9.24 (doublet, $J_{25,26}$ = 6, 3H, C-26 CH_3), 8.91 (doublet, $J_{21,20}$ = 6, 3H, C-21 CH_3), 8.40 (broad singlet, 3H, C-18 CH_3). Mass spectrum: M.W. 414; base peak m/e 300; main peaks, m/e 414, 271, 263.

3β-Acetoxy-5α,13-methyl-C-nor-D-homo-18-nor-22α-spirostane (115)

13-Methyl-C-nor-D-homo-18-nor-5α,22α-spirost-12(13)-en-3β-ol acetate (280 g) which had been prepared by treatment of the olefin-3β-ol (114) with pyridine-acetic anhydride overnight was hydrogenated in acetic acid over 5% rhodium on alumina as outlined by W.F. Johns. The product was readily obtained crystalline from methanol, needles, m.p. 170-173° (220 g) (lit. m.p. 173-177°). N.m.r. signals: 9.20 (singlet, 3H, C-19 CH_3), 8.01 (singlet, 3H, CH_3-CO-). Mass spectrum: M.W. 458; base peak; m/e 342.

17-Acetyl-5α,13β-etiojerv-16-en-3β-ol (116)

The hydrogenation product (115, 110 g) was subjected to ring opening by octanoic anhydride, oxidation with chromic acid and elimination employing potassium hydroxide in t-butanol, according to the procedures outlined by W.F. Johns. Chromatography of the product on alumina (2Kg, Act. III[80]) eluting with 20% chloroform in benzene gave 17-acetyl-5α,13β-etiojerv-16-en-3β-ol (34 g) which was crystallized from acetone/petroleum ether. M.p. 162-165° (lit. m.p. 164-168°). N.m.r. signals: 9.22 (singlet, 3H, C-19 CH_3), 9.19 (doublet, $J_{18,13}$ = 7.0, 3H, C-18 CH_3), 7.0 (quintet 1H, C-13H), 3.1 (two doublets, $J_{16,15}$ = 3.0, $J_{16',15}$ = 7.5, 1H, C-16 H).

Conversion to 17-acetyl-5α,13β-etiojerv-16-en-3β-ol acetate was accomplished by dissolving the product in acetic anhydride/pyridine (1:1)

and allowing the solution to stand at 20° for 12 hours. Recrystallization of the product from acetone/petroleum ether gave needles (34.2 g), m.p. 143-144°.

17-Acetyl-5α,13β-etiojerv-16-en-3β-ol acetate-20-oxime (117)

A solution of 17-acetyl-5α,13β-etiojerv-16-en-3β-ol acetate (33 g) in pyridine was treated with hydroxylamine hydrochloride according to the procedure of W.F. Johns. The product was purified by crystallization from acetone. Needles (33.5 g), m.p. 200-202° (lit. 205-210°). N.m.r. signals: 9.18 (singlet, 3H, C-19 CH_3), 9.07 (doublet, $J_{18,13}$ = 7.0, 3H, C-18 CH_3), 8.0 (singlet, 6H, CH_3-CO- and CH_3-C=N-), 7.03 (quintet, 1H, C-16H). Mass spectrum: M.W. 373; base peak m/e 358; main peaks m/e 373, 296,255.

3β-Acetoxy-5α-etiojervan-17-one (111)

A solution of 17-acetyl-5α,13β-etiojerv-16-en-3β-ol acetate-20-oxime (33.0 g) in pyridine (400 ml) was treated with phosphorus oxychloride.[64] The product obtained after pouring the reaction mixture into aqueous hydrochloric acid at 60° was filtered, dried and chromatographed on alumina (700 g, act. III). Elution with 15% chloroform in benzene gave pure 3β-acetoxy-5α-etiojervan-17-one (24.8 g) which was crystallized from methanol/water giving colourless needles, m.p. 169-170° (lit. m.p. 175-177°); $[\alpha]_D$ +122° (lit. +123°). N.m.r. signals: 9.21 (singlet, 3H, C-19 CH_3), 9.05 (doublet, $J_{18,13}$ = 6.0, C-18 CH_3), 8.06 (singlet, 3H, CH_3-CO-). Mass spectrum: M.W. 332; base peak, m/e 272; main peaks m/e 332, 257, 200.

3β-Acetoxyetiojerv-12(13)-en-17-one (80)

Bromination of 3β-acetoxy-5α-etiojervan-17-one (111) followed by dehydrobromination as outlined by W.F. Johns[64] afforded 3β-acetoxy-5α-etiojerv-12(13)-en-17-one (80), m.p. 165°. N.m.r. signals: 9.18 (singlet, 3H, C-19 CH_3), 8.31 (singlet, 3H, C-18 CH_3), 8.01 (singlet, 3H, CH_3-CO-). Mass spectrum: M.W. 330; base peak m/e 330; main peaks, m/e 288, 272, 270,255.

Synthesis of 2-Ethyl-5-methyl-3-hydroxypyridine (78)

Since the heterocyclic unit required to complete the total synthesis of simple Jerveratrum alkaloids has been 2-ethyl-5-methyl-3-hydroxypyridine (78) or its derivatives, a synthesis of this material was important. This compound is not commercially available and has not been synthesized before. Hence we developed a synthesis of this compound involving furan intermediates and the details of the various experiments in the synthetic sequence are given below.

Methylbut-3-enal diethylacetal (118)

This was prepared according to the procedure of Cornforth and Firth.[70] Triethyl orthoformate (45 g) and magnesium (17.5 g) were stirred and heated at 60°. 2-Methylallyl chloride (24.5 g) was then added gradually (about 2.5 hr.) and the reaction mixture left overnight. The flask was cooled in ice and saturated aqueous ammonium chloride (20 ml) was added dropwise until the mixture set solid; the cake was filtered and washed well with ether. The filtrate on work-up afforded the acetal (118, 19 g), b.p. 60-61°/20 mm. (lit.[70] b.p. 60°/19 mm). The compound was found to be pure by v.p.c. examination using a FFAP column. ν_{max} (film): 1600 cm^{-1} ($\rangle C=CH_2$), 1100-1000 cm^{-1}, 880 cm^{-1} (acetal).

N.m.r. signals: 8.85 (triplet, 6H, 2x $\underline{CH_3}$-CH_2), 8.25 (singlet, 3H, C-2CH_3), 7.7 (doublet, J = 6.0, 2H, C-3 CH_2), 6.5 (multiplet, 4H, CH_2's of -O-CH_2-CH_3), 5.4 (triplet, 1H, C-4 H), 5.2 (singlet, 2H, $\underline{CH_2}$=C<).

3,4-Epoxy-3-methylbutanal diethylacetal (119)

A solution of 3-methylbut-3-enal diethylacetal (118, 6.6 g) in anhydrous ether (10 ml) was cooled in ice and treated gradually with a solution of m-chloroperbenzoic acid (9 g) in ether (30 ml). The reaction mixture was then allowed to warm up and kept at 30° by occasional cooling until the reaction subsided. Next day the reaction mixture was washed repeatedly with saturated sodium bicarbonate solution until the whole of m-chlorobenzoic acid was removed. The ether layer was separated and dried over magnesium sulfate. The solvent was removed under reduced pressure and distillation of the residual liquid afforded the epoxide (119) as a colourless oil (4.1 g), b.p. 82-86°/18 mm. (lit. b.p. 83-84°/17 mm.). The compound was found to be homogeneous by v.p.c. examination. ν_{max} (film): 1000, 950, 800 cm^{-1} (characteristic bands for epoxide). N.m.r. signals: 8.85 (triplet, 6 protons, 2x $\underline{CH_3}$-CH_2-O-), 8.7 (singlet, 3H, C-3 CH_3), 8.2 (doublet, J = 7.0, 2H, C-2 CH_2), 7.5 (AB quartet, $J_{A,B}$ = 5.5, 2H, $\underline{CH_2}$—C(O)-), 6.5 (multiplet, 4H, $\underline{CH_2}$'s of -O-CH_2-CH_3), 5.4 (triplet, 1H, C-1 H).

3-Methylfuran (120)

A mixture of 3,4-epoxy-3-methylbutanal diethylacetal (119, 5.0 g) and 0.1 N sulfuric acid (500 ml) were heated under a fractionating column for 3 hr., the methylfuran and ethanol being removed intermittently by distillation. The distillate was washed once with half-saturated aqueous calcium chloride (10 ml) and twice with saturated aqueous ammonium chloride,

dried over sodium and redistilled to give pure 3-methylfuran (1.1 g). B.p. 65-66° (lit.[69] b.p. 65-65.5°). ν_{max} (chloroform): 1500, 1200, 890 cm^{-1} (characteristic bands for furans); n.m.r. signals: 8.0 (singlet, 3H, C-3 CH_3), 3.85 (singlet, 1H, C-4 H), 2.87 (broad singlet, 1H, C-2 H), 2.75 (broad singlet, 1H, C-5 H).

Propionylation of 3-methylfuran

3-Methylfuran (1 g) and propionic anhydride (1.6 g) were mixed and two drops of orthophosphoric acid (85%) was added to it. The mixture was stirred vigorously and the heat generated was removed by cooling. Gradually the reaction mixture acquired a dark red colour. It was then heated to 60-65° and maintained at this temperature for 2 hr. The reaction mixture was then cooled and stirred with water (2 ml) for 1 hr. The dark organic layer was separated and again stirred with saturated sodium carbonate solution (5 ml) for 24 hr. It was then washed thoroughly with water, extracted with ether (2 x 5 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residual reddish brown oil obtained was distilled in vacuo in a hot box. A colourless fragrant liquid (0.5 g) was collected, b.p. 125-30°/25 mm. Infrared spectrum (film) of the product showed double carbonyl absorption (~ 1700 cm^{-1}). Examination of this material by v.p.c. using a FFAP column (172°) indicated that it was a mixture of two compounds in the ratio 70:30, with retention times 1.8 and 2.8 minutes respectively. These were separated by v.p.c. using a FFAP column (172°). The major component was characterized as 2-propionyl-3-methylfuran (121), b.p. 77-80°/5 mm. ν_{max} (film): 1670 (=C-C=O), 1505 (=C-O- of furan), 881 (most characteristic of furans) cm^{-1}. λ_{max}: 278, 230 mμ

N.m.r. signals: 8.85 (triplet, 3H, $\underline{CH_3}$-CH_2-), 7.65 (singlet, 3H, C-3 CH_3), 7.2 (quartet, 2H, -CO-$\underline{CH_2}$-CH_3), 3.65 (doublet, $J_{4,5}$ = 2.5, 1H, C-4 H), 2.65 (doublet, $J_{4,5}$ = 2.5, C-5 H). Mass spectrum: M.W. 138; base peak, m/e 109; main peak, 138. Found: C, 69.71; H, 7.27, Calcd. for $C_8H_{10}O_2$: C, 69.56; H, 7.24.

The second component was characterized as 2-propionyl-4-methylfuran (122), b.p. 78-82°/5 mm. ν_{max}(film): 1675, 1505, 880 cm^{-1}. λ_{max}: 280, 230. N.m.r. signals: 8.85 (triplet, 3H, $\underline{CH_3}$-CH_2-), 7.9 (singlet, 3H, C-4 CH_3), 7.2 (quartet, 2H, -CO-$\underline{CH_2}$-CH_3), 3.05 (singlet, 1H, C-3 H), 2.75 (broad singlet, 1H, C-5 H). Mass spectrum: M.W. 138, base peak, m/e 109; main peak, m/e 138. Found: C, 69.68; H, 7.26. Calcd. for $C_8H_{10}O_2$: C, 69.56; H, 7.24.

Methyl-5,5-dimethoxy-3-methyl-2,3-epoxypentanoate (123)

This compound was prepared according to the procedure due to Burness[72] and the experimental details are as follows: A mixture of 4,4-dimethoxy-2-butanone (61.0 g, 0.5 mole), methyl chloroacetate (87.0 g, 0.8 mole) and anhydrous ether (400 ml) was placed in a 1 l. 3-necked flask. The solution was cooled in ice-salt bath to -10°. Freshly prepared sodium methoxide (43.0 g, 0.8 mole) was gradually added to the stirred solution at such a rate that a temperature below -5° was maintained (about 1.5 hr.). The mixture was stirred for an additional 2 hr. and then allowed to come to room temperature overnight. It was cooled again to 0° and made slightly acidic by the addition of a solution of acetic acid (5 ml in 75 ml. water). The ether was decanted and the residual slurry was further extracted (3 x 100 ml ether). The combined ether solutions were washed free of acid with saturated

sodium bicarbonate solution and finally with saturated sodium chloride solution. It was then dried over magnesium sulphate. Removal of the solvent under reduced pressure afforded a near quantitative yield of the crude glycidic ester (95.0 g) b.p. 110-120°/8 mm. (lit. b.p. 113-122°/8 mm.). The material thus obtained was found to be essentially pure (v.p.c.) and was used in the following experiment without further purification.

Methyl-3-methyl-2-furoate (124)

Methyl-3-methyl-2-furoate was prepared according to a known procedure[72] and the details are as follows: The crude glycidic ester prepared as described above was placed in a 250 ml flask which was attached to a 50 cm Vigreux column and heated in an oil bath. When the temperature reached about 120°, methanol began to distil. Heating was continued until the distillation of methanol ceased. The crude methyl-3-methyl-2-furoate thus obtained was distilled under reduced pressure b.p. 72-78°/8 mm. The ester (46.0 g) collected in the receiver as a colourless crystalline solid, m.p. 35°. Shining prisms from ethanol, m.p. 36° (lit. m.p. 36.5°-37°). ν_{max} (chloroform): 1725 ($COOCH_3$), 880 cm^{-1} (characteristic of furan). λ_{max}: 252 mμ. N.m.r. signals: 7.65 (singlet, 3H, C-3 CH_3), 6.2 (singlet, 3H, $-COOCH_3$), 3.68 (doublet, J = 2.0, 1H, C-4 H), 2.6 (doublet, J = 2.0, 1H, C-5 H). Mass spectrum: M.W. 128.

Methyl-3-methyl-5-propionyl-2-furoate (125)

Methyl-3-methyl-2-furoate (25.6 g, 0.2 mole) was dissolved in propionic anhydride (75 ml) and orthophorphoric acid (7.0 g) was added to it with vigorous stirring. The heat generated was removed by cooling with ice. The reaction mixture was then stirred at 65-70° for 48 hr. It was then

cooled and stirred into water. The dark brown organic layer was extracted with chloroform and the chloroform extract was washed with bicarbonate solution until neutral to litmus and dried over sodium sulphate. The solvent was distilled off under reduced pressure. The unreacted starting materials were removed by distillation in vacuo and the semi-solid residue was distilled using solid distillation apparatus at 120°/0.3-4 mm. A pale yellow crystalline material was collected in the receiver (23.5 g), m.p. 109-111°. It was recrystallized from aqueous ethanol (70%), colourless shining needles, m.p. 113-114°. ν_{max} (chloroform): 1745 (-COOR), 1700 cm^{-1} ($\rangle C=O$). λ_{max}: 280, 285 (sh), 212 mμ. N.m.r. signals: 8.8 (triplet, 3H, $-CH_2-\underline{CH_3}$), 7.65 (singlet, 3H, C-3 CH_3), 7.2 (quartet, 2H, $-CO-\underline{CH_2}-$), 6.1 (singlet, 3H, $-COOCH_3$), 3.0 (singlet, 1H, C-5 H). Mass spectrum: M.W. 196; base peak, m/e 167, main peaks, m/e 196, 167, 138, 123, 109. Found: C, 61.01; H, 5.97. Calcd. for $C_{10}H_{12}O_4$: C, 61.22; H, 6.12.

3-Methyl-5-propionyl-2-furoic acid (126)

A solution of methyl-3-methyl-5-propionyl-2-furoate (125, 9.8 g) in aqueous sodium hydroxide (10%, 100 ml) was heated under reflux for 1.5 hr. The solution was then cooled and acidified with concentrated hydrochloric acid and stirred for a few minutes. The product which separated as a brown granular solid was collected by filtration. It was washed with a little ice-cold water and dried in vacuo. Crystallization from methanol afforded pale yellow shining prisms (7.6 g), m.p. 179-181°. The compound was found to be pure by t.l.c. examination. ν_{max} (chloroform): 2700-2500 (-COOH), 1765 (-$\underline{C}$OOH), 1700 cm^{-1} ($\rangle C=O$). λ_{max}: 282, 212 mμ. N.m.r. signals: 8.8 (triplet, 3H, $\underline{CH_3}-CH_2-$), 7.6 (singlet, 3H, C-3 CH_3), 7.0 (quartet, 2H,

-CH_2-CO-), 2.85 (singlet, 1H, C-4 H), -0.2 (singlet, 1H, -COOH). Mass spectrum: M.W. 182; base peak m/e 137. Found: C, 59.21; H, 5.50. Calcd. for $C_9H_{10}O_4$: C, 59.33; H, 5.49.

2-Propionyl-4-methylfuran (122)

A mixture of 3-methyl-5-propionyl-2-furoic acid (9.1 g, 0.05 mole), anhydrous quinoline (20 ml) and powdered copper (2.0 g) was heated at 200-210° under nitrogen atmosphere for 3 hr. The evolution of carbon dioxide ceased by this time and the reaction mixture was extracted with chloroform (50 ml). The chloroform extract was filtered to remove the copper powder and washed successively with 1 N hydrochloric acid (3 x 50 ml) and water (100 ml) and finally with sodium bicarbonate solution until neutral to litmus. It was then dried over sodium sulphate and the solvent was distilled off under reduced pressure. The residual dark oil was distilled using a short fractionating column. The fraction boiling at 78-82°/5 mm. was collected as a colourless fragrant liquid (5.4 g). Examination of the compound by t.l.c. and v.p.c. indicated that it was pure. The physical and spectral data of the compound were identical with those of 122 obtained by the propionylation of 3-methylfuran.

2-Ethyl-5-methyl-3-hydroxypyridine (78)

2-Propionyl-4-methylfuran (122, 1.0 g) and aqueous ammonia (11 N, 25 ml) were heated in a sealed tube for 20 hr.[65] The reaction mixture was filtered off the residual solid matter and the filtrate was evaporated to dryness under a stream of nitrogen. The residue was extracted with chloroform and dried. The solvent was removed under reduced pressure and the dark brown semi-solid residue distilled 150°/0.3-5 mm. in a hot box. A small quantity of pale yellow liquid collected in the receiver soon

solidified into shining prisms (202 mg), m.p. 140-144°. Crystallization from chloroform provided an analytical sample, colourless shining prisms, m.p. 145-147° (lit.[60] m.p. 143-144°). ν_{max} (chloroform): 3215 (hydroxyl), 1590 (pyridine) cm^{-1}. λ_{max} (log ε): 287 (3.95), 225 (sh) mμ. N.m.r. signals: 8.75 (triplet, 3H, CH_3-CH_2-), 7.8 (singlet, 3H, C-5 CH_3), 7.1 (quartet, 2H, -CH_2-CH_3), 2.9 (singlet, 1H, C-4 H), 2.1 (singlet, 1H, C-6 H), 1.0 (multiplet, 1H, C-3 OH). Mass spectrum: M.W.: 137, base peak m/e 121; main peaks m/e 136, 94, 93. Found: C, 70.11; H, 8.10. Calcd. for $C_8H_{11}NO$: C, 70.07; H, 8.02.

This experiment was repeated several times to obtain sufficient quantity of the 3-hydroxypyridine (78) required for subsequent studies.

2-Ethyl-3-O-benzyl-5-methylpyridine (127)

2-Ethyl-5-methyl-3-hydroxypyridine (274 mg, 0.002 mole) was dissolved in aqueous sodium hydroxide (5%, 10 ml) and benzyl chloride (240 mg, 0.002 mole) was added to it. The mixture was heated at 100° for 2.5 hr. During this time the benzyl chloride gradually dissolved and a pale yellow oil separated in the flask. The reaction mixture was cooled and extracted with chloroform (2 x 10 ml). The chloroform extract was washed with water until neutral to litmus and dried over sodium sulphate. The residual oil obtained after the removal of the solvent was distilled in vacuo. A colourless oil collected in the receiver (228 mg), b.p. 118-120°/0.4-5 mm. Thin layer chromatography on alumina indicated that the compound was pure. The spectral data of the compound agreed with the structure 127. ν_{max} (film): 1595 (pyridine),1270, 1050 (ether) cm^{-1}. λ_{max}: 285, 225 (sh) mμ. N.m.r. signals: 8.8 (triplet, 3H, CH_3-CH_2-), 7.75 (singlet, 3H, C-5 CH_3), 7.2

(quartet, 2H, -$\underline{CH_2}$-CH_3), 5.0 (singlet, 2H, -O-$\underline{CH_2}$-C_6H_5), 3.15 (singlet, 1H, C-4 H), 2.65 (singlet, 5H, $\underline{C_6H_5}$-CH_2-O-), 2.1 (singlet, 1H, C-6 H).

2-Ethyl-3-methoxy-5-methylpyridine (128)

A solution of 2-ethyl-5-methyl-3-hydroxypyridine (2.74 g, 0.02 mole) in methanol (40 ml) containing 10% water was chilled in an ice-salt bath. To this was added a solution of diazomethane[73,81] (4.2 g, 0.1 mole) in ether (175 ml) with constant swirling, from a dropping funnel, the stem of which projected below the surface of the liquid. A brisk effervescence accompanied the addition which was interrupted several times in order to boil off the accumulated ether. The latter procedure serves to keep the polarity of the solution at a maximum. After being allowed to stand overnight, the methanolic solution was acidified with hydrochloric acid and most of the ether and methanol removed by concentration on the steam bath. The resulting syrup was diluted with water and the solution exhausted with ether. It was then alkalized with sodium hydroxide pellets and again extracted with ether (3 x 100 ml). This second extract was dried over potassium carbonate, the ether removed by distillation and the residual oil distilled in vacuo. The product (2.01 g) was a colourless oil, b.p. 100°/10 mm.

Some of the starting material was recoverable by the following procedure: The alkaline solution after exhaustion with ether was neutralized and evaporated to dryness followed by extraction with chloroform. Removal of the chloroform afforded a dark brown solid (480 mg) which was identified as 2-ethyl-5-methyl-3-hydroxypyridine (78).

The methyl ether was characterized as follows: ν_{max} (film); 1598, 1560 (pyridine), 1265, 1050 (ether) cm^{-1}. λ_{max} (log ε): 283 (3.86), 2.25 (sh) mμ.

N.m.r. signals: 8.8 (triplet, 3H, $C\underline{H}_3$-CH_2-), 7.7 (singlet, 3H, C-5 CH_3), 7.25 (quartet, 2H, -$C\underline{H}_2$-CH_3), 6.25 (singlet, 3H, -OCH_3), 3.2 (singlet, 1H, C-4 H), 2.15 (singlet, 1H, C-6 H). Found: C, 71.47; H, 8.64: Calcd. for $C_9H_{13}NO$: C, 71.52; H, 8.60.

23-Methoxy-22,27-iminojerva-12(13),22,24,27-tetraene-3β,17-diol(s) (130)

An ether solution (7.0 ml) of 2.0 M methyl lithium was added to anhydrous tetrahydrofuran (50 ml) in a dry round bottom flask which had been flushed with nitrogen. A solution of 2.0 M 2-ethyl-3-methoxy-5-methylpyridine (6.9 ml) was added immediately and the mixture refluxed for 1 hr. A deep red colour slowly developed in the solution. It was then cooled and 3β-acetoxy-5α-etiojerv-12(13)-en-17-one (80) was added as a fine powder until the colour faded (800 mg). The mixture was stirred under reflux for a period of 20 min. Saturated ammonium chloride solution (20 ml) was added cautiously while the mixture was still under nitrogen. Ether (50 ml) was added to the reaction mixture and the organic phase washed with water prior to drying over sodium sulphate. Evaporation of the solvent in vacuo gave a pale yellow oil (1.1 g) which appeared primarily as one spot when examined by thin-layer chromatography (Canary yellow spot when the chromatoplate is developed with antimony pentachloride-carbon tetrachloride spray reagent). Column chromatography on alumina (55 g, act. III) eluting with 50% ligroin in benzene removed the unreacted pyridine (128). Continued elution with benzene removed the unreacted enone (80). The desired condensation product was eluted with 5% chloroform in benzene. Evaporation of the solvent afforded 23-methoxy-22,27-iminojerva-12(13),22,24,27-tetraene-3β,17-diol(s) as a pale yellow oil which crystallized from 5% chloroform in ether (700 mg),

m.p. 209-214°. The spectral data indicated that the product is a mixture of two compounds of gross structure 130. ν_{max} (chloroform): 3275 (hydroxyl), 1595 (pyridine) cm^{-1}. λ_{max} (log ε): 283.5 (3.86) mμ. N.m.r. signals: 9.22 (singlet, 3H, C-19 CH_3), 8.84, 8.81 (two overlapping doublets $J_{20,21}$ = 7.0, 3H, C-21 CH_3), 6.24, 6.21 (two singlets, 3H, $-OCH_3$), 3.10 (singlet, 1H, C-24 H), 2.04 (singlet, 1H, C-27 H). Mass spectrum: M.W. 421; base peak m/e 406; main peaks m/e 421, 288.

Acetylation of 23-methoxy-22,27-iminojerva-12(13),22,24,27-tetraene-3β,17-diols (130)

A mixture of acetic anhydride and pyridine (1:1, 5 ml) was added to the condensation product (130, 390 mg) obtained in the above experiment and left overnight at room temperature. The solution was then poured into crushed ice and the resultant oil was extracted with ether (3 x 20 ml). The combined ether extracts were washed with saturated sodium bicarbonate solution and several times with water before drying over sodium sulphate. The solvent was distilled off in vacuo when a pale yellow semi-solid residue (330 mg) was obtained. T.l.c. examination of the product revealed the presence of two compounds with very different R_f values. The less polar compound appeared as an orange yellow spot when the chromatoplate was developed with antimony pentachloride reagent, whilst the second component appeared as a canary yellow spot. This product-mixture of acetates was separated by column chromatography on alumina (30 g, act. III). Elution with benzene afforded the less polar compound (designated as compound "B") in essentially pure state (125 mg). Further elution with 5% chloroform afforded the second component (designated as compound "A"), (191 mg).

An analytical sample of "A" was prepared by crystallization from 5% chloroform in ether. Colourless shining prisms were obtained, m.p. 181-182°. Investigations on compound "A" indicated that it has the structure 131, as expected. ν_{max}^{KBr}: 3280 (hydroxyl), 1712 (acetate), 1600 and 1565 (pyridine) cm^{-1}; λ_{max} (log ε): 284 (3.86) mμ. N.m.r. signals: 9.22 (singlet, 3H, C-19, CH_3), 8.82 (doublet, $J_{20,21}$ = 7.0, 3H, C-21 CH_3), 8.79 (singlet, 3H, C-18 CH_3), 8.0 (singlet, 3H, $OCOCH_3$), 7.7 (singlet, 3H, C-26 CH_3), 6.22 (singlet, 3H, OCH_3), 3.90 (broad multiplet, disappears on D_2O addition, 1H, C-17 OH), 3.08 (singlet, 1H, C-24 H), 2.0 (singlet, 1H, C-27 H). Mass spectrum: M.W. 463; base peak m/e 330; main peaks m/e 448, 288, 255, 146. High resolution mass spectrum. Found: 463.308. Calcd. for $C_{30}H_{43}NO_4$ ($-H_2O$): 463.308. Anal. Found: C, 74.65; H, 8.97. Calcd. for $C_{30}H_{43}NO_4$: C, 74.84; H, 8.94.

Compound "B" on the other hand could not be induced to crystallize. An analytical sample of this material was prepared by subliming a small amount of "B" at 170°/0.2 mm., when a colourless glassy solid was obtained. The spectral and analytical data for this compound was consistent with a structure, 132. ν_{max}^{KBr}: 1715 (acetate), 1595, and 1565 (pyridine) cm^{-1}. λ_{max} (log ε): 283.5 (4.03). N.m.r. signals: 9.08 (singlet, 3H, C-19 CH_3), 8.45 (doublet, $J_{20,21}$ = 7.0, 3H, C-21 CH_3), 8.0 (singlet, 3H, $OCOCH_3$), 7.7 (singlet, 6H, C-18 CH_3 and C-26 CH_3), 6.3 (singlet, 3H, C-23 OCH_3), 3.05 (AB quartet, $J_{15,16}$ = 7.0, 2H, C-15 H and C-16 H), 3.16 (singlet, 1H, C-24 H), 2.0 (singlet, 1H, C-27 H). Mass spectrum: M.W. 461; base peak m/e 432; main peaks m/e 461, 446, 298, 150. High resolution mass spectrum found: 461.291. Calcd. for $C_{30}H_{39}NO_3$: 461.293. Anal. Found: C, 77.78; H, 8.47. Calcd. for $C_{30}H_{39}NO_3$: C, 78.09; H, 8.45.

3β-Acetoxy-23-methoxy-22,27-iminojerv-12(13),14(15),16(17),22,24,27-hexaene: Compound "C"

Compound "A" (131, 150 mg) was thoroughly ground with 10% palladized charcoal (37 mg) until a homogeneous powder was obtained. This powder was heated at 200° under nitrogen for seven minutes and the resultant solid residue washed several times with chloroform. Thin-layer chromatography of the chloroform extract indicated that the product contained three major components and these were separated on preparative thin-layer plates (20 x 20 cm; 0.4 mm., chloroform). One of these three components was shown to be 2-ethyl-3-methoxy-5-methylpyridine (128) by n.m.r. The second band on extraction yielded a light oil which crystallized from acetone-petroleum ether as needles, m.p. 167°. This compound was identified as 3β-acetoxy-5α-etiojerv-12(13)-en-17-one (80) by its ultraviolet spectrum and mixed m.p. with an authentic sample. The third component which appeared as a light orange yellow spot when the chromatoplate was developed with antimony pentachloride-carbon tetrachloride reagent was extracted to yield a light oil which could not be induced to crystallize. An analytical sample of this compound, designated as compound "C" was obtained as a clear glass after sublimation at 170°/0.1 mm. Spectral data indicated that this compound possessed structure 133. ν_{max}^{KBr}: 1712 (acetate), 1595, 1565 (pyridine) cm^{-1}. λ_{max} (log ε): 283.5 (4.04). N.m.r. signals: 9.07 (singlet, 3H, C-19 CH_3), 8.4 (doublet, $J_{20,21}$ = 7.0, C-21 CH_3), 8.0 (singlet, 3H, $OCOCH_3$), 7.74 (singlet, 6H, C-18 CH_3 and C-26 CH_3), 6.3 (singlet, 3H, OCH_3), 3.0 (AB quartet, $J_{15,16}$ = 8.0, C-15 H and C-16 H), 3.1 (singlet, 1H, C-24 H), 1.92 (singlet, 1H, C-27 H). Mass spectrum: M.W. 461; base peak

m/e 432; main peaks m/e 461, 446, 298, 150. High resolution mass spectrum, found: 461.293; calcd. for $C_{30}H_{39}NO_3$: 461.293. Anal. found: C, 77.80; H, 8.46. Calcd. for $C_{30}H_{39}NO_3$: C, 78.09; H, 8.45.

N-Benzyl-2-ethyl-3-methoxy-5-methylpyridinium bromide (138)

Benzyl bromide (250 mg, 0.0015 mole) was added to a solution of 2-ethyl-3-methoxy-5-methylpyridine (151 mg, 0.001 mole) in benzene (15 ml) and the mixture refluxed for 12 hr. The colourless crystals separated were filtered, washed with benzene and dried (255 mg), m.p. 198-201°. λ_{max}: 293, 228 (sh), 212 (sh).

Sodium borohydride reduction[75,76] of N-benzyl-2-ethyl-3-methoxy-5-methyl-pyridinium bromide

The pyridinium salt (138, 161 mg) was dissolved in water (5 ml) and cooled in an ice-salt bath. A solution of sodium borohydride (22 mg) and sodium carbonate (110 mg) in water (3 ml) was added to it slowly while stirring. The mixture was kept stirred for 10 min. and then extracted with chloroform (3 x 10 ml). The combined extracts were dried and evaporated to give a pale yellow oil (110 mg). T.l.c. examination of the product showed the presence of two compounds in approximately equal amounts. This material was discerned to be a mixture of the dihydropyridines 139 and 140. ν_{max}: 1650, 1600, 725 cm^{-1} (-C=C-C=C-). λ_{max}: 260, 227, 215 (sh).

N-Benzyl-3-methyl-6-ethyl-5-oxo-Δ^3-tetrahydropyridine (141)

The mixture of dihydropyridines (100 mg) obtained in the above experiment, without further purification was dissolved in 12 N hydrochloric acid (1 ml) and stirred under nitrogen at 0° for 75 min. The acid was neutralized

with sodium bicarbonate solution and the product extracted with chloroform (3 x 5 ml). The chloroform extract was dried and evaporated *in vacuo* when a light red oil was obtained (85 mg). T.l.c. examination of this material showed the presence of two compounds. These were separated by preparative t.l.c. on neutral alumina (20 x 20 cm, 0.4 mm, chloroform). The less polar compound (20 mg) was characterized as 141 on the basis of its spectral data. ν_{max} (film): 1680 cm^{-1} (=C-C=O). λ_{max}: 335 (sh), 300, 225 (sh).

The second component (55 mg) was characterized as 2-ethyl-3-methoxy-5-methylpyridine (128) on the basis of its n.m.r. and infrared spectra (superimposable with those of an authentic sample.)

5α,6-Dihydroveratramine (18)

A solution of compound "B" (45 mg) in 95% ethanol (10 ml) containing 2% of 12 N hydrochloric acid was stirred with Adam's catalyst (PtO_2, 20 mg) at 20° for 18 hr. The mixture was filtered to remove the catalyst which was carefully washed with additional ethanol (5 ml). The combined extracts were neutralized with sodium bicarbonate solution and then reduced the volume to 2 ml *in vacuo*. It was diluted with water and extracted with chloroform (3 x 10 ml) prior to drying over sodium sulphate. Thin-layer chromatography on silica gel G (6% methanol in chloroform) revealed the presence of three major compounds. The two less polar components had similar R_f values, whilst the third compound had R_f value identical with that of 5α,6-dihydroveratramine. Besides these three compounds, there were several other compounds present in the product-mixture in trace amounts. The three major components were separated by preparative thin-layer chromatography on neutral alumina (20 x 20 cm, 0.4 mm., 3% methanol in chloroform,

plates developed three times). Extraction of the bands followed by the usual work-up afforded the two less polar compounds as pale yellow oils. The third compound with R_f value corresponding to that of 5α,6-dihydroveratramine was obtained crystalline from 5% methanol in chloroform. Colourless fluffy crystals (8 mg), m.p. 198°. This material was characterized as 5α,6-dihydroveratramine; undepressed m.p. and superimposable infrared spectrum with an authentic sample[30,77] were obtained.

The two less polar components obtained (17 mg and 13 mg respectively) were found to be very unstable and hence no detailed investigation of these was carried out. A preliminary examination of the n.m.r. spectra revealed that the pyridine ring was only partially reduced in both the compounds (signals at 3.8 and 4.2) whilst the 23-methoxyl group was intact (signal at 6.3).

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