Synthetic Studies in the *Veratrum* Alkaloid Series. II.[1] The Total Synthesis of Verarine, Veratramine, Jervine, and Veratrobasine

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Coupling of 3β-acetoxy-5α-etiojerv-12(13)-en-17-one (**1**) with the lithio derivative of 2-ethyl-5-methylpyridine provides the crucial intermediate (**3**) for the subsequent elaboration to verarine. Aromatization of **3** to **4** and reduction of the latter provides a mixture from which *N*-acetyl-5α,6-dihydroverarine (**11**) was isolated. Subsequent introduction of the 5,6-double bond in the latter and removal of the *N*-acetate function completed the synthesis of verarine (**31**). In a similar sequence of reactions employing **1** and the lithio derivative of 2-ethyl-3-methoxy-5-methylpyridine, the resultant intermediate (**54**), was elaborated to 5α,6-dihydroveratramine (**56**). Due to known conversions of the latter to veratramine (**14**), jervine (**32**), veratrobasine (**33**), and 11-deoxojervine (**34**), the formal total synthesis of these natural products is complete.

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Le couplage de l'acétoxy-3β(5α)-étiojervène-12(13) one-17 (**1**) avec le dérivé lithié de l'éthyl-2 méthyl-5 pyridine fournit l'intermédiaire (**3**) crucial pour l'élaboration subséquente de la véranine. L'aromatisation de **3** en **4** et la réduction de ce dernier dérivé fournit un mélange duquel on peut isoler la *N*-acétyldihydro-5α,6 véranine (**11**). L'introduction subséquente d'une double liaison en position 5,6 et l'élimination de la fonction *N*-acétate, complète la synthèse de la véranine (**31**). Utilisant une séquence semblable de réactions faisant appel à **1** et au dérivé lithié de l'éthyl-2 méthoxy-3 méthyl-5 pyridine, on a obtenu l'intermédiaire (**54**) qui a été transformé en dihydro-5α,6 vératramine (**56**). En se basant sur le fait que ce dernier composé peut être transformé, à l'aide de séquences connues, en vératramine (**14**), en jervine (**32**), en vératrobasine (**33**) et en déoxo-11 jervine (**34**), on peut considérer que la synthèse totale formelle de ces produits naturels est maintenant complète. [Traduit par le journal]

In the previous publication (26) we described the total synthesis of various C-nor-D-homo steroidal analogs to be employed as intermediates in the synthesis of *Veratrum* alkaloids. We also outlined a synthetic plan which envisages the *Veratrum* skeleton as consisting of a C-nor-D-homo steroid or etiojervane portion to which is attached at the 17-position, an appropriate heterocyclic unit. We would now like to present the experiments which demonstrate the application of this plan to the total synthesis of the alkaloid verarine (**31**) (1, 2).

The structure of verarine reveals that the required heterocyclic unit attached to the steroid portion is a 2,5-disubstituted piperidine and it was felt that the latter is readily available from the appropriate pyridine by well known reduction methods. On this basis, the essential features of the synthetic plan, as outlined in Fig. 1, were to couple the pyridine system at C_{17} of the already available 3β-acetoxy-5α-etiojerv-12(13)-en-17-one (**1**)[1] and the resultant product **3** could, hopefully by aromatization of ring D (**4**) and subsequent reduction, lead to the desired 5,6-dihydroverarine (**5**, R = R′ = H) system. It should be noted here that *both* racemic and optically active forms of **1** are available from total synthesis, the former from our previous work (26, 27) and the latter from that of Sondheimer and co-workers (3) who presented a total synthesis of optically active hecogenin from isoandrosterone. For the purposes of the synthetic experiments discussed here we have employed optically active **1** obtained via degradation of hecogenin acetate as outlined in Part I of this series.[1]

To evaluate the feasibility of the approach

[1]For part I, see ref. 26. For preliminary reports on a portion of this work, see ref. 27.

[2]Revision received February 4, 1975.

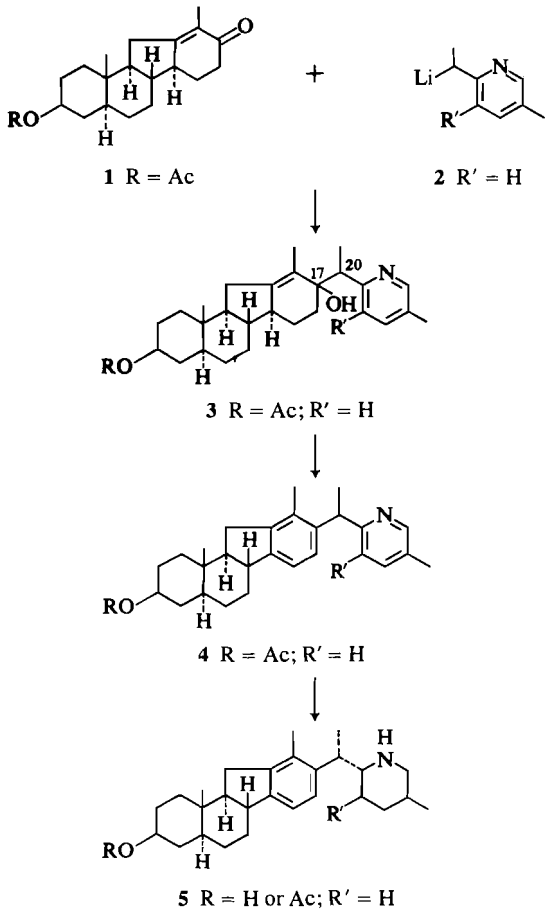
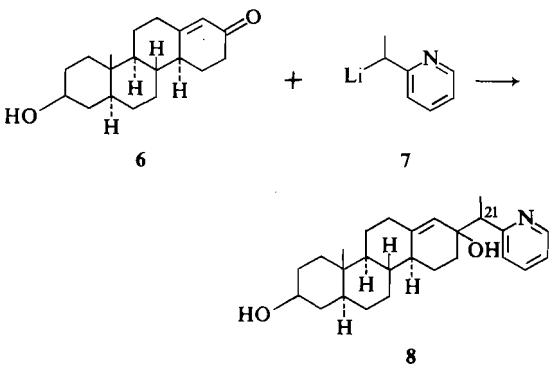


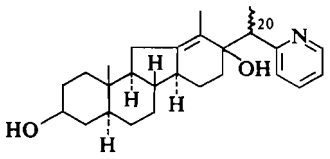
FIG. 1. General outline of synthetic plan for the synthesis of verarine (**31**).

presented in Fig. 1, the readily available (26, 27) hydrochrysene derivative **6** was utilized as the model substance and this was condensed with the lithio derivative of 2-ethylpyridine (**7**).



Addition of **6** to the red solution of 2-ethylpyridine and methyl lithium provided a reaction mixture which after chromatographic purification yielded the desired product. Its u.v. spectrum showed peaks at 257, 262, and 270 nm corresponding to the pyridine chromophore while the mass spectrum exhibited a peak at *m/e* 395 corresponding to the parent ion for compound **8**. The absence of a carbonyl peak in the i.r. supported the 1,2-addition of the organolithium derivative to the α,β-unsaturated carbonyl compound as opposed to any 1,4 addition.

This procedure was then extended to the reaction of **7** with 3β-acetoxy-5α-etiojerv-12(13)-en-17-one (**1**). Column chromatography of the products from this reaction gave primarily some material which appeared as one compound on t.l.c. The spectroscopic properties of the reaction product (λ_{max} 257, 262, and 269 nm; *m/e* 395) were again in accord with the desired coupling product although the n.m.r. spectrum (two doublets in the region τ 8.84) revealed that a mixture of two isomers, most likely epimeric at C_{20}, had been obtained (**9**).



These model studies indicated that the required attachment of a heterocyclic unit at C_{17} of the C-nor-D-homo compound could be achieved and our efforts turned to the consideration of substituted 2-ethylpyridines which would allow entry to the skeleton of some of the naturally occurring *Veratrum* alkaloids.

Methylation of 2,5-lutidine employing phenyl lithium and methyl iodide afforded the known (4) 2-ethyl-5-methylpyridine and this in the form of its lithium salt (**2**) was condensed with the etiojervene derivative (**1**). The resultant product mixture upon t.l.c. examination, revealed two major components with similar R_f values but attempts to separate these proved fruitless. Conversion to the C_3-acetate derivatives did allow purification of this mixture.

It is to be noted that the coupling reaction creates two new asymmetric centers and consequently there exists the possibility of obtaining

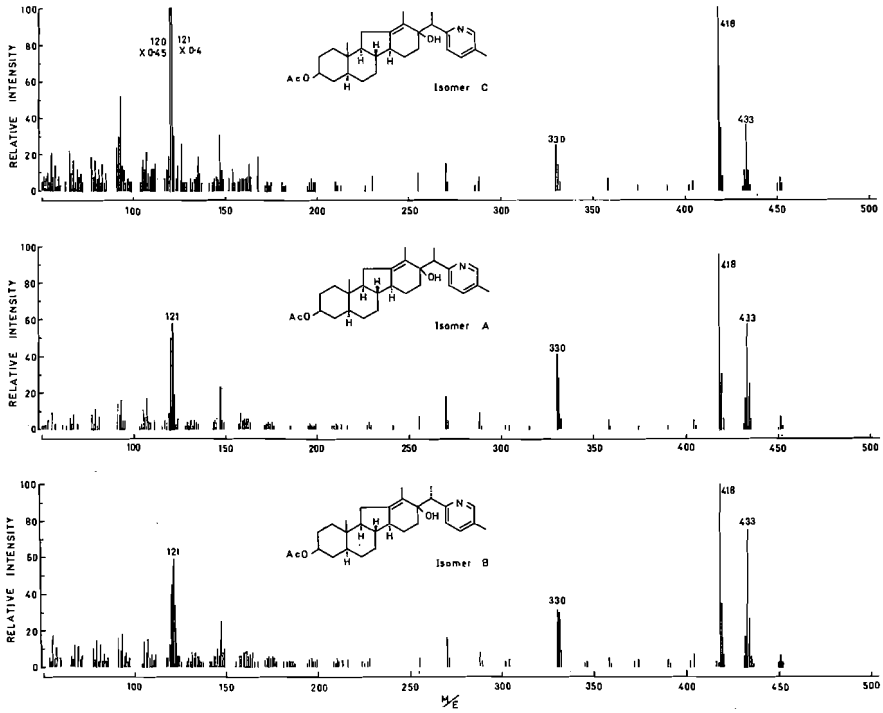


FIG. 2. Mass spectra of isomers **A**, **B**, and **C**.

four compounds possessing the gross structure **3** and differing in stereochemistry at C_{17} and/or C_{20}. All of these could be obtained in pure form.

One of the major components which could be obtained crystalline, m.p. 189–190°, was designated compound **A**. Spectral data allowed the assignment of structure **3** to this substance. Apart from the pyridine chromophore in the u.v., the n.m.r. spectrum was particularly instructive. A quartet occurring at τ 6.71 was assigned to the proton at C_{20} since a decoupling experiment showed this signal to be coupled to the C_{21} methyl doublet at τ 8.79. The C_{19} methyl signal appeared as a sharp three-proton singlet at τ 9.21. The pyridine protons were readily discernible in the aromatic region of the spectrum with a one-proton doublet at τ 2.82, $J = 8$ Hz, corresponding to $C_{23}H$ whereas $C_{24}H$ gave rise to two doublets at τ 2.52 ($J = 8$ and 2 Hz) and $C_{25}H$ appeared as a broad singlet at τ 1.67. The mass spectrum of **A** (Fig. 2) revealed the desired molecular ion (*m/e* 451) and expected fragmentation pattern.

Column chromatography of the mother liquors from the crystallization of compound **A** gave a second crystalline component, m.p. 191–192°, designated as compound **B** which also revealed spectral data in accord with structure **3**. The isomeric nature of **B** and **A** is seen from the close similarity in the mass (Fig. 2) and n.m.r. spectra of these compounds. In general the n.m.r. features already noted for **A** also appear in **B** although there are some differences in the chemical shifts. The largest differences are seen in the positions of the C_{18} and C_{21} methyl group signals and the pyridine protons (see Experimental).

Additional purification of chromatography fractions, obtained during isolation of **B** by means of preparative layer chromatography, allowed the isolation of two minor components, **C** and **D**, which constituted about 4 and 1% of the total product mixture. Neither of these could be induced to crystallize but satisfactory spectral data could also be accumulated for these substances and again the gross structure **3** could be assigned. At this stage of the investigations no assignments of stereochemistry at C_{17} and/or C_{21} could be made to these four coupling products but evidence in this direction was obtained during later studies as discussed below.

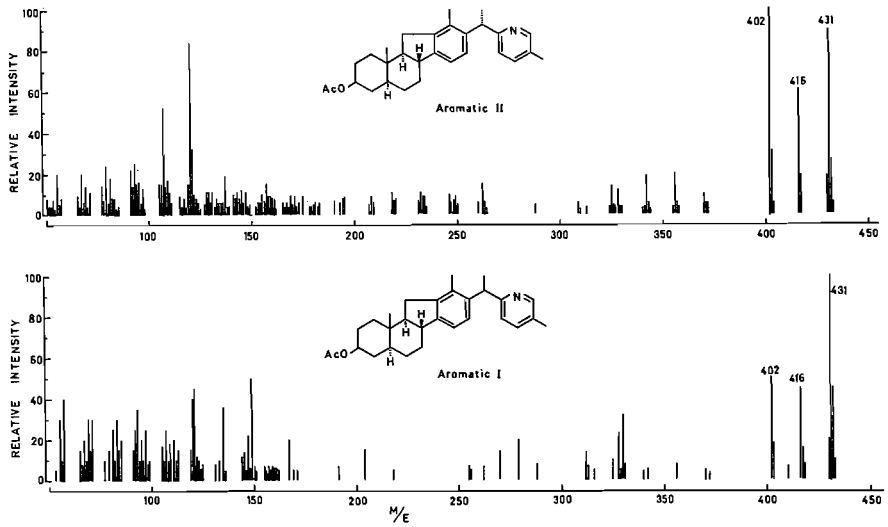


FIG. 3. Mass spectra of aromatic **I** and **II**.

The further extension of this sequence to the ring D aromatized series only involved the compounds **A** and **B** as the small amounts of **C** and **D** which were available precluded any useful reactions.

Compound **B** was ground with 10% palladized charcoal until the two substances were thoroughly mixed and then the powder was heated at 200° for 10 min. Examination of the reaction product mixture by t.l.c. indicated that compound **B** had been converted to a new compound possessing a similar R_f value. Separation by preparative layer chromatography indicated this new compound, which was designated 'aromatic **II**', had been produced in 80% yield. The u.v. spectrum showed no qualitative difference from that of compound **B** but the extinction coefficient at 270 nm increased from 4130 in the latter to 5400 in this compound. The mass spectrum exhibited a peak at *m/e* 431 corresponding to the molecular ion for a compound of structure **4**. The mass spectrum (Fig. 3) shows a completely different pattern to that observed with the series of compounds **A** to **D**. The n.m.r. spectrum was particularly useful in confirming that the desired ring **D** aromatization had occurred. The most significant feature is the appearance of a second pair of doublets in the downfield region of the spectrum corresponding to the expected AB system for the protons at C_{15} and C_{16}. In addition the broad three-proton singlet which corresponds to the C_{18} methyl in the starting material has disappeared but a new sharp singlet appears at τ 7.89 in the product in accord with the aromatization of ring **D**.

Isomer **A** was similarly treated with 10% Pd/C at 200° and the residue examined by t.l.c. Three compounds could be isolated in pure form by thick-layer chromatography. Two of these could be identified as the α,β-unsaturated ketone (**1**) and 2-ethyl-5-methylpyridine. The third compound which was formed in 25% yield appeared similar in properties to the aromatic compound from isomer **B** and was designated 'aromatic **I**'. The mass spectrum exhibited a peak at *m/e* 431 corresponding to the molecular ion for a compound of structure **4** and, in general, the fragmentation pattern was very similar to that of aromatic **II** (Fig. 3). This and other data suggested that these two aromatic substances were merely isomeric at C_{20} and support for this postulate came forth from further experiments as noted below.

In view of the different extent of ring D aromatization encountered with isomers **A** and **B**, the relative stability of these two compounds was further investigated. The C_{17}—C_{20} bond cleavage, which occurs with isomer **A** under the conditions for the D ring aromatization, appears to be very facile since this cleavage also occurs slowly in methanol or ethanol. The cleavage is slightly enhanced when the compound is dissolved in 0.1 *N* methanolic potassium hydroxide. Isomer **A** is stable in dimethylformamide or benzene but is converted to 3β-acetoxy-5α-etiojerv-12(13)-en-

17-one and 2-ethyl-5-methylpyridine when dissolved in aqueous dimethylformamide containing potassium hydroxide (p*H* 9).

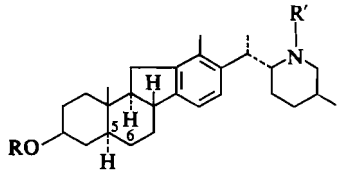
Isomer **B** is stable under the above conditions and shows no C_{17}—C_{20} bond cleavage. Dehydration of the tertiary alcohol appears to be the main process for both isomers **A** and **B** in acidic methanol solution.

Thus two compounds of structure **4** had been prepared and the selective reduction of the pyridine to a piperidine ring was investigated. One of these aromatic compounds should lead to an isomeric mixture of 5α,6-dihydroverarines while the other would lead to a mixture of isomers of similar structure but differing in configuration at C_{20} from the naturally occurring alkaloid verarine.

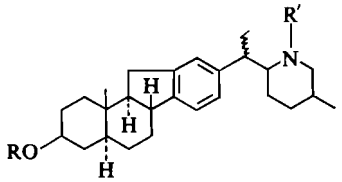
Catalytic reduction (5) of aromatic compound **II** provided a reaction mixture, which upon examination by t.l.c. indicated that four new compounds possessing very similar R_f values had been formed. These compounds, which were numbered **i** to **iv** in order of decreasing R_f values on silica gel, were separated by careful preparative layer chromatography. These compounds were suspected to be isomers of 3-*O*-acetyl-5α,6-dihydroverarine (**10**). However, preparation of a sample of this compound from verarine for comparison purposes is difficult since acetylation of verarine yields *N*-acetylverarine or 3-*O*,*N*-diacetylverarine.

None of the four compounds from the hydrogenation of aromatic compound **II** could be induced to crystallize but it was found from other investigations that *N*-acetyl-5α,6-dihydroverarine (**11**) crystallizes readily from an ethereal solution. Consequently it was decided to convert the four compounds obtained above to the *N*-acetyl derivatives (gross structure **12**) via acetylation to the 3-*O*,*N*-diacetates (**13**) followed by selective hydrolysis of the 3-acetoxyl group. The conversion to the respective diacetates was accomplished with acetic anhydride–pyridine (1:1) while hydrolysis of the 3-acetoxyl group was achieved with 0.1 *M* potassium hydroxide in methanol.

The appropriate verarine derivatives required for the above comparison were prepared from the more readily available alkaloid veratramine (**14**) essentially according to the scheme developed by Masamune (1) with modifications at appropriate stages (**14** → **15** → **16** → **17**).



10 R = Ac; R′ = H
11 R = H; R′ = Ac



12 R = H; R′ = Ac
13 R = R′ = Ac

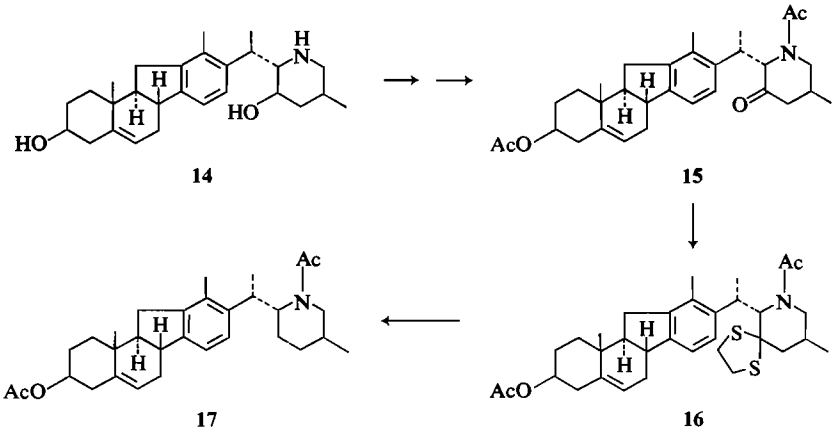
The diacetate **17** was identified by t.l.c. comparison with an authentic sample[3], melting point, rotation, mass spectrum, and n.m.r., all of which were in accord with the published data (6). Subsequent hydrolysis of the 3-acetoxyl compound gave *N*-acetylverarine.

Hydrogenation of the 5,6-double bond in veratramine employing Adams' catalyst in acetic acid had been reported to give mainly the 5α,6-dihydroveratramine (7). By analogy it was expected that the hydrogenation of the 5,6-double bond in 3-*O*,*N*-diacetylverarine (**17**) using these conditions would provide mainly the desired 3-*O*,*N*-diacetyl-5α,6-dihydroverarine. This hydrogenation was carried out and careful examination of the product by t.l.c. indicated that only one compound had been formed. However, a close examination of the n.m.r. spectrum particularly in the region τ 8.5–9.5 indicated that both the 5α and the 5β compounds had been formed.

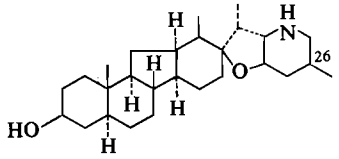
The n.m.r. spectrum of 3-*O*,*N*-diacetylverarine exhibited a three-proton doublet at τ 9.02 which was attributed to the C_{26} methyl while the C_{19} methyl appeared as a three-proton singlet at 8.85.

The n.m.r. spectrum of the hydrogenation product exhibited a sharp singlet at 8.92 and a doublet at 9.03. The upfield half of the doublet centered at 9.03 was, however, very intense and the integral of this doublet corresponded to 4.5 protons. From the excellent n.m.r. study of 22,27-

[3]We are grateful to Dr. J. Tomko, Slovak Academy of Sciences, Bratislava, Czechoslovakia, for a gift of this sample.



14 15 16 17



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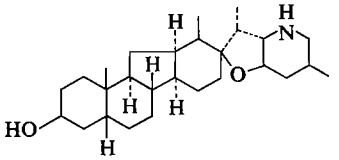

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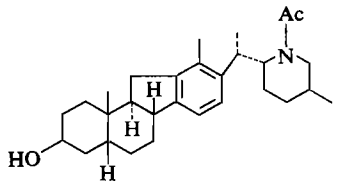

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imino-17,23-oxidojervane derivatives by Masamune *et al.* (8) one would expect the C_{19} methyl signal for the 5α compound to be at a higher field position than in the 5β compound. This difference is due to the shielding of the C_{19} methyl group by the ring A protons which are in close proximity in the 5α derivatives but removed to a large extent in the 5β derivatives. This effect has been noted in various steroids (9) where the stereochemistry of the molecule is fixed.

The difference in chemical shift between the singlet at 8.92 and the upfield half of the doublet due to the C_{26} methyl group was 13 Hz and it was informative to compare this difference with the C_{19} methyl resonances in compounds **18** and **19**.

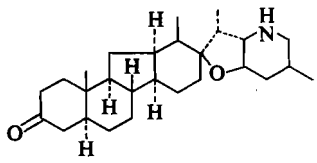
The n.m.r. spectra of these two compounds have been studied by Masamune *et al.* (8) who found the C_{19} methyl resonance in **18** to occur at τ 9.19 whilst in **19** the three proton-singlet is observed at τ 9.07, a separation of 12 Hz.

It therefore appeared that the hydrogenation of 3-*O*,*N*-diacetylverarine had given both the 5α and 5β compounds. In an attempt to obtain some separation of these two compounds and verify their existence the product was converted to the monoacetate by hydrolysis of the 3-acetoxyl group by means of 0.1 *N* potassium hydroxide in methanol. A t.l.c. examination of the resulting *N*-acetyl-5,6-dihydroverarines showed clearly that two compounds (**11** and **20**) were present. The n.m.r. spectra of the two compounds after separation by thick-layer chromatography, supported the analysis of the C_{19} methyl group positions outlined above.

Additional support for the configurational differences at C_5 was evident from the C_3 proton signals (τ 5.97, narrow multiplet in **11**, equatorial H; 6.3–6.5, broad multiplet in **20**, axial H).

It was vital to provide additional data which establish more firmly the identity and stereochemistry of these compounds. The o.r.d. curves of 3-keto steroids with the 5α and 5β configuration have been extensively studied and Masamune *et al.* (8) have recorded the o.r.d. curves of compounds **21** and **22**. These latter substances provide a very good analogy with the compounds under consideration.

Compound **21** exhibits a strong positive Cotton



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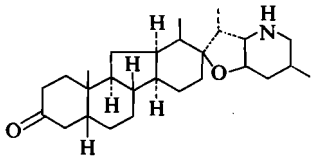
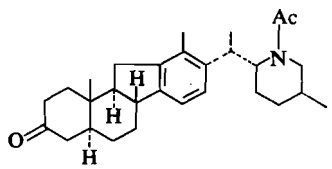


22

effect curve with values of $[\phi]_{304}^{peak}$ +2740° and $[\phi]_{265}^{trough}$ −1180° whereas **22** exhibits a negative Cotton effect curve with values of $[\phi]_{304}^{trough}$ +265° and $[\phi]_{265}^{peak}$ +2340°.

The hydrogenation products which had tentatively been assigned the 5α (**11**) and 5β (**20**) configurations were converted to the respective 3-keto compounds (**23** and **24**) using Jones' reagent as the oxidizing agent. The presence of the *N*-acetyl group tended to complicate the o.r.d. curves to some extent since it had a strong absorption at 230 nm but the absorption at 300 nm was not sufficient to affect the curve in this region. Compound **23** showed a strong positive Cotton effect curve with a peak at 305 nm while compound **24** showed only a very weak trough at 305 nm.

After this work had been completed, a publication (10) appeared in which the hydrogenation of veratramine employing Adams' catalyst in acetic acid has been more closely examined. Saito (7) had reported only the formation of the 5α-6,



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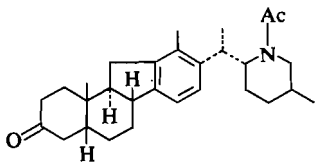

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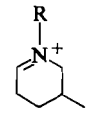


25 R = H
26 R = Ac

dihydroveratramine but the recent work indicates that a mixture of 5α,6-dihydroveratramine (41%) and 5β,6-dihydroveratramine (44%) is produced. It is interesting to note that these workers also distinguished the two compounds on the basis of the chemical shifts of the C_{19} methyl resonances in the n.m.r. spectra.

Having established the identity of the desired *N*-acetyl-5α,6-dihydroverarine (**11**) the comparison of this compound with the *N*-acetyl derivatives of the four compounds obtained from the hydrogenation of aromatic compound **2** was now undertaken. These crystalline acetates of compounds **i–iv** were compared in the usual manner (m.p., t.l.c., i.r., n.m.r., and mass spectra) with authentic **11**. It was established that **i**, *N*-acetate, was identical in every respect with **11** as prepared above.

Careful analysis of the mass spectra of all five compounds (**11** and **i–iv**) reveals an essentially identical fragmentation pattern with very intense peaks at *m/e* 140 and 98. Budzikiewicz (11) has examined the mass spectra of veratramine, *N*-acetylveratramine, and verarine and has postulated cleavage of the benzylic C_{20}—C_{22} bond which, in the present instance, would allow the fragments **25** and **26** to account for strong peaks at *m/e* 98 and 141, respectively.

Aromatic compound **I** which was obtained in 25% yield from isomer **A** was subjected to hydrogenation under the same conditions as applied to aromatic compound **II**. Examination of the product by t.l.c. indicated that four new compounds of similar R_f values had been formed. For the sake of convenience these were designated **v–viii** in order of decreasing R_f values on a thin-layer chromatoplate. These compounds were separated by thick-layer chromatography and then converted via the diacetates to the respective *N*-acetyl derivatives. A t.l.c. comparison of the four *N*-acetates with *N*-acetyl-5α,6-dihydroverarine (**11**) indicated that only compounds **v** and **vi** had a similar R_f value. Surprisingly none of these *N*-acetyl derivatives could be induced to crystallize from ether in contrast to *N*-acetyl-5α,6-dihy-

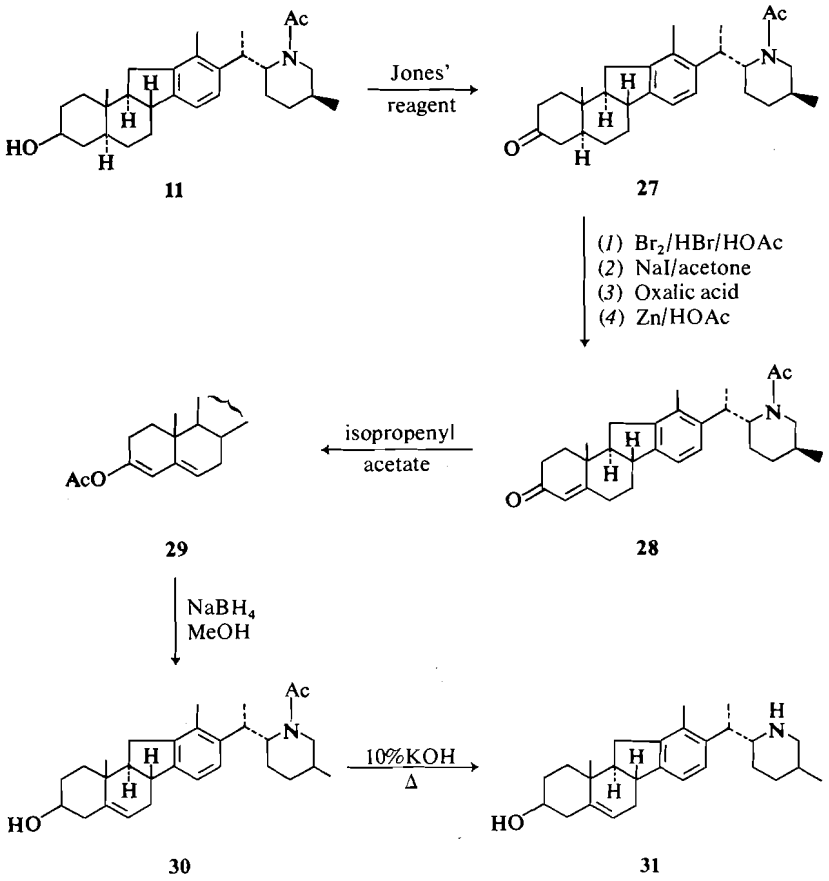


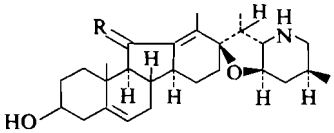
FIG. 4. Conversion of *N*-acetyl-5α,6-dihydroverarine (**11**) to verarine (**31**).

droverarine and the *N*-acetates of compounds **i–iv** which all crystallize very readily from this solvent. The mass spectra of the compounds **v–viii** exhibited a peak at *m/e* 437 corresponding to the molecular ion for *N*-acetyl-5α,6-dihydroverarine as well as prominent peaks at *m/e* 98 and 140.

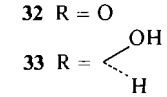
To complete the synthesis of verarine (**31**) it was necessary to introduce the 5,6-double bond and remove the *N*-acetate function in *N*-acetyl-5α,6-dihydroverarine (**11**). The steps involved in achieving these goals are outlined in Fig. 4. The procedure for introduction of the double bond is taken from the investigations of Evans *et al.* (12) in the cortisone series. A similar pathway has been employed by Johnson *et al.* (13) in the conversion of 23-*O*,*N*-dibenzoyl-5α,6-dihydroveratramine to veratramine.

Having completed the synthesis of the simplest member of the *Veratrum* series, it was decided to extend the above strategy to encompass some of the more oxygenated *Veratrum* alkaloids and 5α,6-dihydroveratramine (**56**) became the target compound. Since the latter had already been converted to veratramine (**14**) (13), jervine (**32**) (14, 15), veratrobasine (**33**) (15, 16), and 11-deoxojervine (**34**) (17), a synthesis of this intermediate represents in a formal sense the total synthesis of these natural products.

Analysis of the structure of veratramine, for

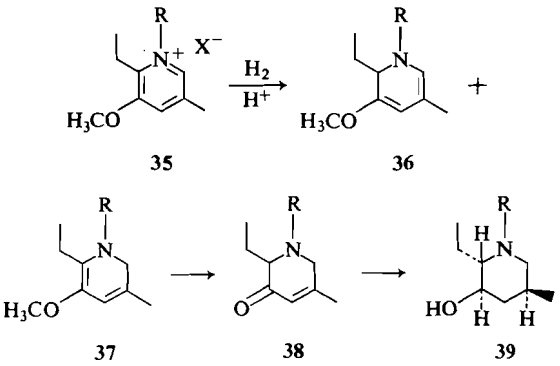


32 R = O

33 R = 

34 R = H_2

example, reveals that the substituents attached to the three chiral centers (C_{22}, C_{23}, and C_{25}) involving the piperidine ring are in equatorial orientations. It was thus felt that reduction of an appropriately substituted pyridinium system, under equilibrating conditions, should lead predominantly to the desired stereochemistry in the resultant product (see **35** → **36** + **37** → **38** → **39**).



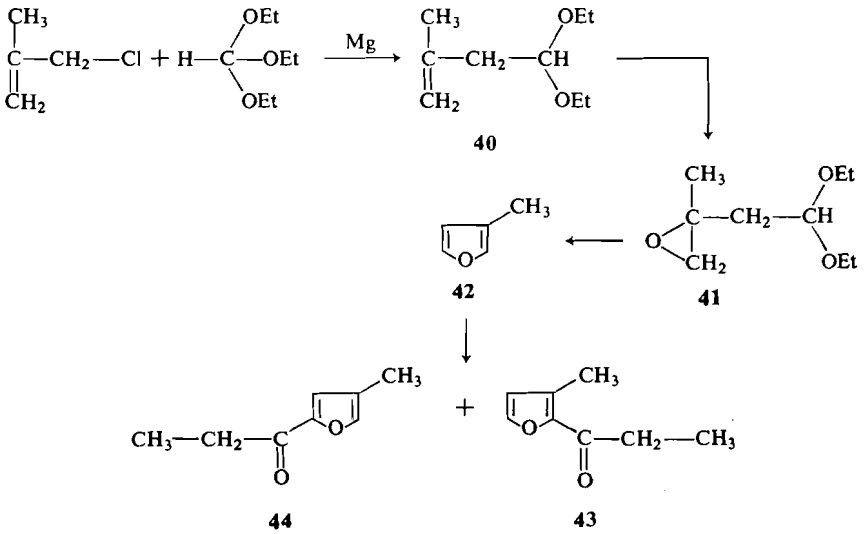
35 **36** **37** **38** **39**

The obvious heterocyclic unit required for achieving the synthesis in this direction was an unknown pyridine derivative, 2-ethyl-3-hydroxy-5-methylpyridine, and its synthesis was first considered. We chose an approach which made use of the reaction of furyl ketones with ammonia (18) since it seemed to be more direct and suitable for our purposes. In this connection we have developed two independent sequences for the synthesis of the desired pyridine. In effect, both sequences depend on the availability of crucial furan intermediates and therefore the synthesis of these substances was initially considered. Figures 5 and 6 outline the reactions involved in the preparation of these materials. Figure 5 reveals the preparation of 2-propionyl-4-methylfuran (**44**) via a Friedel–Crafts reaction on 3-methylfuran.

A survey of the literature at this time indicated that there had been no work on the Friedel–Crafts reaction of 3-methylfuran. In fact only limited data on the electrophilic substitution of 3-alkylfurans in general was available and the data indicated that the substitution takes place exclusively at the 2-position (19–21). 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 (**42**), was prepared according to the procedure of Cornforth (22, 23) as outlined in Fig. 5.

Reaction of 3-methylfuran with propionic anhydride and orthophosphoric acid as the catalyst at 60° provided a product which upon examination by v.p.c. indicated that it was a mixture of two compounds in the ratio 70:30. Separation of the mixture by means of preparative v.p.c. using a FFAP column allowed the isolation of 2-propionyl-3-methylfuran (**43**) and 2-propionyl-4-methylfuran (**44**).

It is noteworthy that indeed substitution takes place at both C_2 and C_5 positions of 3-methylfuran and this was the first demonstrated example of electrophilic substitution at the C_5 position of



40 **42** **41** **44** **43**

FIG. 5. Synthesis and propionylation of 3-methylfuran.

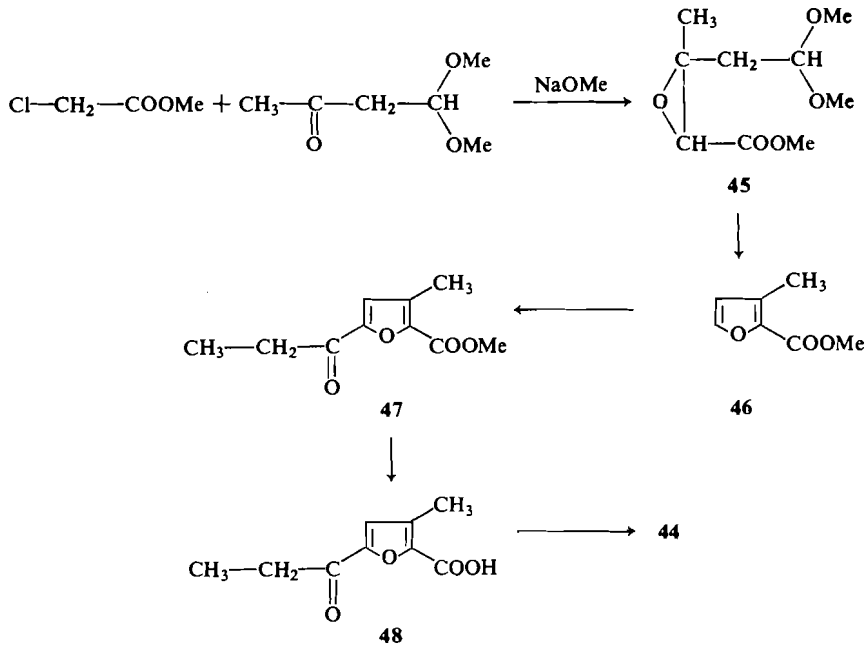


FIG. 6. Synthesis of 2-propionyl-4-methylfuran (**44**).

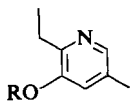
a 3-alkylfuran unsubstituted at the 2-position. Documented data indicate that only furans with electron-withdrawing substituents (*e.g.*, —COOR group) at C_3 can direct substitution to C_5 whereas the presence of electron-donating substituents invariably direct the substitution to C_2 (20). A more detailed investigation is now reported from our laboratory (24).

The difficulties encountered in the separation of the reaction mixture as well as the poor yield of the desired ketone **44** compelled us to discard the above sequence in favor of an alternate direct route to the preparation of this compound.

This latter route makes use of methyl 3-methyl-2-furoate (**46**) as the starting material. The preparation of this compound by a known procedure (25) and the subsequent reactions leading to 2-propionyl-4-methylfuran are schematically presented in Fig. 6.

The next stage in the synthesis was the conversion of 2-propionyl-4-methylfuran to 2-ethyl-3-hydroxy-5-methylpyridine (**49**). This conversion was effected by a known procedure (18). The resultant product (**49**) was crystalline and revealed spectral data in agreement with the assigned structure (λ_{max} 287 nm; τ 8.75, triplet, CH_3CH_2; 7.8, singlet, C_5—CH_3; 2.9 and 2.1, singlets, C_4 and C_6H).

In our initial studies on the coupling of the substituted pyridine with the steroidal enone, it was decided to use the lithio derivative of 2-ethyl-3-*O*-benzyl-5-methylpyridine (**50**). This compound was prepared by heating a solution of 2-ethyl-3-hydroxy-5-methylpyridine in aqueous



49 R = H
50 R = $CH_2C_6H_5$
51 R = CH_3

sodium hydroxide with benzyl chloride. However these investigations were unsuccessful and hence we discarded the use of the *O*-benzyl ether in favor of the corresponding *O*-methyl ether (**51**) which was readily available from the reaction of **49** with diazomethane.

Thus with the desired steroidal enone, 3β-acetoxy-5α-etiojerv-12(13)-en-17-one (**1**), and the appropriately substituted pyridine, 2-ethyl-3-methoxy-5-methylpyridine (**51**), 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 (**56**) is

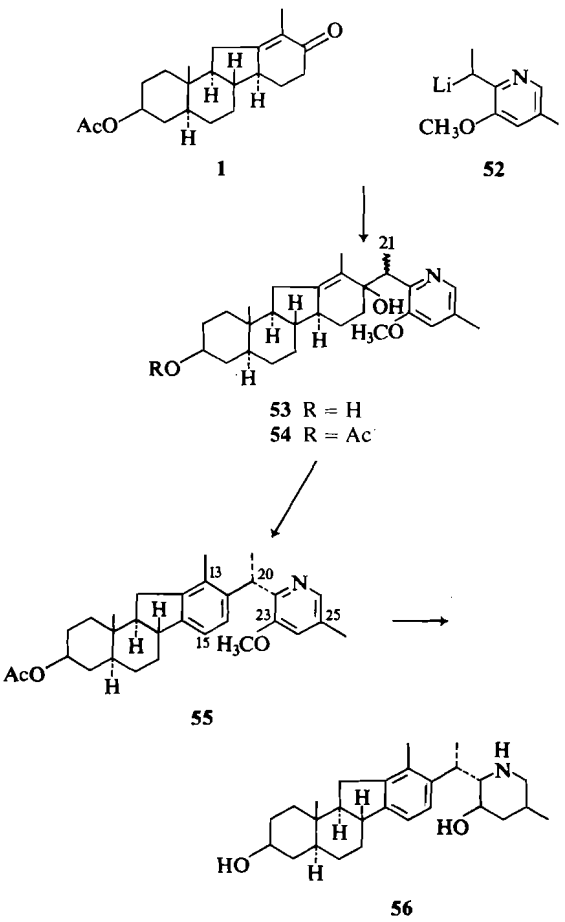


FIG. 7. Synthesis of 5α,6-dihydroveratramine (**56**).

shown in Fig. 7 and follows the strategy outlined previously.

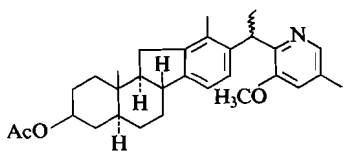
Coupling of the lithio derivative **52** and **1** provided a reaction product which in the u.v. spectrum (λ_{max} 283 nm) showed a pyridine chromophore while the mass spectrum exhibited a peak at *m/e* 439 corresponding to the parent ion for a substance bearing the gross structure **53**.

That the material obtained above, 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 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 **E** while the less polar one is designated as compound **F**.

Examination of compound **E** revealed the following spectral data. The u.v. spectrum showed a peak of 283 nm with a shoulder at 225 nm indicative of the pyridine chromophore while the mass spectrum exhibited the parent peak at *m/e* 463 which indicated that dehydration of the coupled product (**54**) has occurred in the mass spectrometer. The n.m.r. spectrum of **E** 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) and 2.0 (C_{27}H).

The u.v. spectrum of compound **F** was similar to that of **E** while the mass spectrum exhibited the parent peak at *m/e* 461 corresponding to an ion which accounts for the loss of 20 units from the desired compound of gross structure **54**. In the n.m.r. spectrum, the C_{18} methyl signal was shifted downfield (τ 7.7) and was in the position expected for a methyl group on an aromatic ring. Further evidence in support of aromatization of ring D came from an examination of the low field (τ 4–2) region in the spectrum where, in



57

addition to the pyridine proton signals, an AB quartet centered at τ 3.05 was noted. 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).

Since the above spectral data was consistent for the structure **57**, it was clear that compound **F** arises via dehydration of the C_{17} hydroxyl function in the condensation product (**53**) followed by aromatization of the resulting diene.

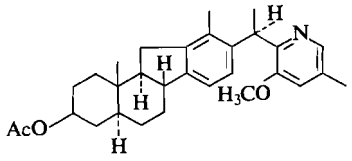
It can be seen from Fig. 7 that the coupling reaction generates two chiral centers and consequently there exists the possibility of obtaining four compounds possessing structure **53**. However in our studies only two compounds could be isolated and characterized.

The above results suggest that the coupling reaction afforded a mixture of alcohols of gross structure **53** and that one of them fortuitously 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 chromatographic 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 directly 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 the low field AB quartet noted earlier. The results of the experiment allowed us to conclude that one of the two alcohols undergoes dehydration and aromatization to **F** (**57**) during the acetylation step.

In our subsequent studies we have been able to convert the alcohol acetate **54** (compound **E**) to an aromatic compound isomeric with **F**. In a typical experiment, compound **E** was reacted with palladized charcoal at 200° and three compounds, the α,β-unsaturated ketone **1**, 2-ethyl-3-methoxy-5-methoxypyridine (**52**), and a new substance designated as compound **G**, were isolated in a pure state. The spectral properties of **G** were remarkably similar to those of **F** and it was clear that these compounds were diastereoisomeric at C_{20}, the chiral center created during the coupling reaction.

Since in subsequent experiments the aromatic compound **F** gave rise to compounds in the natural series, the stereochemistry at C_{20} in this compound is known and is indicated in **55**. This leads to the conclusion that compound **G** is the C_{20} epimer of **F** and has the stereochemistry as indicated in **58**.



58

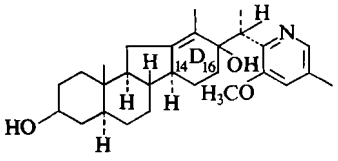
After having established that the condensation product of 2-ethyl-3-methoxy-5-methylpyridine and 3β-acetoxy-5α-etiojerv-12(13)-en-17-one is a mixture of epimeric alcohols **53** and that one of these alcohols undergoes dehydration and aromatization to give compound **F** during the subsequent work-up, 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. We wish to emphasize that we are unable at this time to distinguish clearly between several alternative explanations.

It is clear that several important factors must be considered in proposing any stereochemical assignments to the condensation products possessing the gross structure **53**. (*i*) 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. (*ii*) 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 molecular models quickly revealed that no distinct preference for either approach is apparent. In other words, one would expect the epimers at C_{17} as the most likely course of events. In the explanation given below we 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

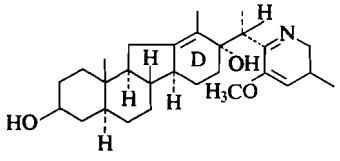
particular stereochemistry chosen for C_{20} was the one which is present in the natural *Veratrum* series. The reasons for the latter choice are two-fold: (*a*) there is a minimal interaction between the various groups on ring D and the heterocyclic portion when this stereochemistry is considered and (*b*) one of the above condensation products leads to 5α,6-dihydroveratramine.

Once a tentative assignment of the stereochemistry at C_{20} in the condensation products is advanced one is 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.

If we consider the 'axial' alcohol (**58***a*) and its possible conversion to the ring D aromatic derivative (**55**) 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 **55**.

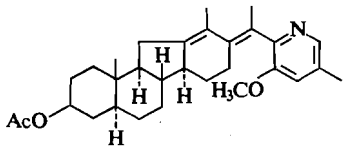


58*a*



69

On the other hand, examination of molecular models for the 'equatorial' alcohol (**69**) 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 the C_{18} and C_{21} methyl groups and an increase in nonbonded 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 provide the necessary energy. Dehydration in this event will lead to a diene **70**, which via



70

double bond rearrangement and aromatization would provide the aromatic compound **57**. Obviously such a process can lead to epimerization at C_{20}. In fact the aromatic compound (**G**) isolated in this reaction is isomeric with compound **F** and must therefore be its C_{20} epimer (*i.e.* **58**).

Now that the desired D ring aromatized compound had been obtained, it was essential to find suitable methods to reduce the pyridine ring to the appropriately functionalized piperidine moeity present in veratramine. For this purpose catalytic hydrogenation was selected as the method of choice. Compound **F** 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 (Pt as catalyst). Thin-layer chromatography 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 (**56**), identical with the natural sample prepared by the hydrogenation of veratramine (7, 10) (i.r., n.m.r., mass spectra, mixture m.p.).

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.

As mentioned earlier, the synthesis of 5α,6-dihydroveratramine was sufficient for our purpose because this material has already been converted to veratramine (**14**), jervine (**32**), veratrobasine (**33**), and 11-deoxojervine (**34**).

Experimental

All details concerning spectral measurements, chromatographic separations, etc., are described in part I of this series.

18-Nor-C-homo-26-nor-22,27-iminojerva-12α(13),22,24,27-tetraene-3β,17-diol (8)

An ether solution of 1.88 *M* methyl lithium (1.0 ml) was added to anhydrous tetrahydrofuran (4 ml) in a round-bottom flask which had been flame dried and flushed with dry nitrogen. A tetrahydrofuran solution of 2.0 *M* 2-ethylpyridine (1 ml) was added immediately and the mixture refluxed under nitrogen for 30 min. During this time the solution developed a deep red color. After the period of reflux the α,β-unsaturated ketone (**6**) in the form of a fine powder was added slowly until the color faded (120 mg) and the reaction mixture refluxed for a further 30 min while the flask was still under nitrogen. Water was then added cautiously to destroy any alkyl lithium remaining and the resulting mixture diluted with ether (10 ml). The organic phase was separated and washed with water (4 × 10 ml), before drying over anhydrous sodium sulfate. Evaporation of the ether gave a light oil (100 mg) which appeared as one major and several minor components when examined by thin-layer chromatography. The major component was obtained pure by preparative thin-layer chromatography on Woelm neutral alumina (20 × 20 cm, 0.4 mm, 2% methanol in chloroform). Spectral data indicated this was the desired condensation product (**8**) although the n.m.r. indicates the material is probably a mixture of two isomers; i.r.: 6.3, 6.4 (pyridine), 3.1 μ (hydroxyl); u.v.: λ_{max}: 257 (3.55), 262 (3.58), 270 nm (3.45); n.m.r.: 9.26 (angular methyl, 3H, singlet), 8.8, 8.75 (two overlapping doublets due to the presence of two isomers in the product (CH_3—C—H, J=7 Hz, 3H), 6.53 (CH_3CH, 1H, J = 7 Hz, quartet), 5.1 (C_{13}, 1H, singlet), 2.0, 3.0 (pyridine, 3H, multiplet), 1.5 (pyridine, 1H, multiplet).

26-Nor-22,27-iminojerva-12(13),22,24,27-tetraene-3β,17-diol (9)

An ether solution of 1.88 *M* methyl lithium (1.0 ml) was added to anhydrous tetrahydrofuran in a dry round-bottom flask under nitrogen. A solution of 2-ethylpyridine (1.0 ml of 2.0 *M*) in tetrahydrofuran was added immediately and the mixture refluxed for 30 min during which time a deep red color developed. Addition of 3β-acetoxy 5α-etiojerv-12(13)en-17-one (**1**) in the form of a finely ground dry solid was continued until the color faded (90 mg added) and the mixture stirred for a further 30 min, while the flask was still under nitrogen. Water was added to quench the reaction and the mixture diluted with ether (10 ml). The organic phase was separated and then washed with water (4 × 10 ml) before drying over anhydrous sodium sulfate. Examination of the ethereal extract by thin-layer chromatography indicated one major component which appeared as a bright yellow spot when the chromatoplate was developed with 1:1 antimony pentachloride – carbon tetrachloride (1:1) spray reagent. Column chromatography on alumina (Shawinigan, activity III, 25 g) eluting with benzene–chloroform (4:1) enabled purification of this component which was crystallized from benzene–ether as needles (42 mg), m.p. 204–206°; i.r. ($CHCl_3$): 6.30, 6.41 μ (pyridine); u.v.: λ_{max} 257sh, 262.5 (3.58), 269sh nm; n.m.r.: 9.26 (angular methyl, 3H, singlet), 8.84 (C_{21} methyl, 3H, $J_{20,21}$ = 7 Hz, doublet), 8.26 (C_{18} methyl, 3H, singlet), 2.8 (pyridine, 2H, multiplet), 2.34 (pyridine, 1H, multiplet), 1.5 (pyridine, 1H, multiplet) mass spectrometry: *m/e* 395 (M^+), prominent peaks at *m/e* 377, 362, 288.

Anal. Calcd. for $C_{26}H_{37}O_2N$: C, 78.94; H, 9.43; N, 3.54. Found: C, 78.85;, H, 9.50; N, 3.50.

2-Ethyl-5-methylpyridine

An anhydrous ether solution (250 ml) of bromobenzene (31.4 g, 0.2 mol) was added slowly to a dry round-bottom flask which had been flushed with nitrogen and which contained lithium wire (2.8 g, 0.4 mol). When the lithium had largely dissolved an ethereal solution (100 ml) of 2,5-lutidine (21 g, 0.2 mol) was added and the mixture refluxed for 30 min, during which time a deep red color developed in the solution. Methyl iodide (14.2 g, 0.1 mol) in ether (40 ml) was added slowly to this red solution over a period of 15 min and the mixture stirred for 10 min. The excess lithium and phenyl lithium were removed by the careful addition of water (100 ml) to the reaction mixture while the flask was still under nitrogen. A further 200 ml of water was then added and the organic phase separated, and washed with water (2 × 50 ml). The ethereal solution was reduced in volume to 40 ml by use of a rotary evaporator. This 40 ml was then carefully distilled at a pressure of 10 mm, employing a spinning band column. The first fraction, distilling at 50–55° was shown by n.m.r. to be recovered 2,5-lutidine whereas that distilling at 62–63° was shown to be 2-ethyl-5-methylpyridine; i.r. (film): 6.3, 6.4, 6.8, 7.02 μ; u.v.: λ_{max} 265sh (3.54), 269 (3.60), 276 nm (3.48); n.m.r.: 8.70 (CH_3CH_2, 3H, J = 7.5 Hz, triplet), 7.72 (CH_3—C, 3H, singlet), 7.20 (CH_2CH_3, 2H, J = 7.5 Hz, quartet), 2.93 (C_3, 1H, $J_{3,4}$ = 8 Hz, doublet), 2.59 (C_4, 1H, $J_{4,3}$ = 8.0 and $J_{4,6}$ = 2.0 Hz, two doublets), 1.63 (C_6, 1H, $J_{6,4}$ = 2.0 Hz, doublet). Picrate derivative from acetone, m.p. 143–144° (lit. (7) m.p. 144°).

3β-Acetoxy-22,27-iminojerva-12(13),22,24,27-tetraene-17-ol (3)

A 2.05 *M* ethereal solution of methyl lithium (25 ml, 0.051 mol) was added to a flame dried round-bottom flask containing anhydrous tetrahydrofuran (40 ml) under nitrogen. A mixture of anhydrous tetrahydrofuran (10 ml) and 2-ethyl-5-methylpyridine (6 g, 0.05 mol) was added immediately and the reaction mixture refluxed for 1½ h. During this period a deep red color developed in the solution. A faint pink color persisted after 3β-acetoxy-5α-etiojerv-12-en-17-one (**1**) (2.0 g, 0.006 mol) was added as a fine powder to the cooled solution and the mixture stirred for 10 min. Water (50 ml) was added cautiously to the reaction mixture while still under nitrogen, followed by ether (50 ml) prior to separation of the organic and

aqueous phases. The organic phase was washed with water (3 × 25 ml) and then dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* gave a light oil (2.3 g) which appeared to consist of two new components when examined by thin-layer chromatography. Attempts to obtain these compounds in a pure state were unsuccessful. However a small scale investigation indicated that the compounds could be separated more readily as the C_3 acetates rather than as the C_3 alcohols which were formed in the reaction.

Conversion to the C_3 acetates was achieved by dissolving the crude product from the reaction in acetic anhydride – pyridine (1:1, 20 ml) and allowing the solution to stand at room temperature for 12 h. The solution was then poured onto crushed ice and the resultant flocculant solid extracted into ether. The combined ethereal extracts were washed with saturated aqueous sodium hydrogen carbonate solution and then several times with water before drying over anhydrous sodium sulfate. The volume of the ethereal solution was reduced *in vacuo* to 20 ml and then allowed to stand whereupon colorless needles were deposited, m.p. 187–189° (370 mg). Examination of the crystals by thin-layer chromatography indicated only one compound was present and recrystallization from ether gave an analytical sample, m.p. 189–190°. This compound was designated **A** and the physical and spectral data are in accord with structure **3**; i.r. ($CHCl_3$): 5.83 (OAc) 6.25, 6.37 (pyridine) μ; u.v.: λ_{max} 270 nm (3.61); $[\alpha]_D$ +83° (*c*, 1.24); n.m.r.: 9.21 (angular methyl, 3H, singlet), 8.79 (C_{21} methyl, 3H, $J_{21,20}$ = 7.0 Hz, doublet), 8.40 (C_{18} methyl, 3H, singlet), 8.01 (acetate, 3H, singlet), 7.70 (C_{26} methyl, 3H, singlet), 6.71 (C_{20}H, 1H, $J_{20,21}$ = 7.0 Hz, quartet), 3.89 (OH, 1H, broad multiplet, disappears on D_2O addition), 2.82 (C_{23}, 1H, $J_{23,24}$ = 8 Hz, doublet), 2.52 (C_{24}, 1H, $J_{24,23}$ = 8 and $J_{24,27}$ = 2 Hz, two doublets), 1.67 (C_{27}, 1H, $J_{27,24}$ = 2 Hz, doublet); mass spectrometry: *m/e* 451 (M^+), prominent peaks at *m/e* 433, 330, 147, and 121.

Anal. Calcd. for $C_{29}H_{41}O_3N$: C, 77.12; H, 9.15; O, 10.63; N, 3.10. Found: C, 76.92; H, 8.95; O, 10.46; N, 3.21.

Examination by thin-layer chromatography of the mother liquors from the crystallization of compound **A** indicated the presence of a further compound of similar color reaction when sprayed with antimony pentachloride – carbon tetrachloride reagent. These mother liquors were combined and chromatographed on alumina (60 g, activity III). Elution with benzene yielded unreacted 2-ethyl-5-methylpyridine initially, while further elution provided an additional compound (350 mg) which was obtained crystalline from a small volume of ether, m.p. 190–192°. Recrystallization from acetone – petroleum ether gave an analytical sample (250 mg), m.p. 190–192°. This compound was designated compound **B** and was slightly less polar than compound **A** on a silica gel chromatoplate developed with 2% methanol in chloroform; i.r. ($CHCl_3$): 5.83 (OAc), 6.25, 6.37 (pyridine) μ, u.v.: λ_{max} 265sh (3.57), 270 (3.61), 276sh nm (3.51); $[\alpha]_D$ −126° (*c*, 1.26); n.m.r.: 9.23 (angular methyl, 3H, singlet), 8.88 (C_{21} methyl, 3H, $J_{20,21}$ = 7.0 Hz, doublet), 8.28 (C_{18} methyl, 3H, singlet), 8.02 (CH_3CO, 3H, singlet), 7.72 (C_{26} methyl, 3H, singlet), 6.71 (C_{20}, 1H, $J_{20,21}$ = 7.0 Hz, quartet), 4.20 (OH, 1H, broad signal, disappears on D_2O addition), 2.92 (C_{23}, 1H, $J_{23,24}$ = 8.0 Hz, doublet), 2.70 (C_{24}, 1H, $J_{24,23}$ = 8 and $J_{24,27}$ = 2.0 Hz), 1.75 (C_{27}, 1H, $J_{27,24}$ = 2.0 Hz, doublet); mass spectrometry: *m/e* 451 (M^+), prominent peaks at *m/e* 433, 418, 330, 147, and 121.

Anal. Calcd. for $C_{29}H_{41}O_3N$: C, 77.12; H, 9.15; N, 3.10. Found: C, 77.19; H, 9.21; N, 3.19.

Elution with 20% ether in benzene gave additional compound **A** (150 mg) while two fractions appeared to contain two further compounds of similar reaction to the spray reagent when examined by thin-layer chromatography. Separation by preparative layer chromatography (20 × 20 cm, 0.3 mm, 1% methanol in chloroform, chromatoplate developed twice) yielded 35 mg and 8 mg of these compounds which were designated **C** and **D**, respectively. Compound **C** could not be induced to crystallize and an analytical sample was prepared by sublimation at 190°/0.1 mm which gave a clear glass. The spectral data were consistent with this compound being isomeric with **A** and **B**; i.r.: 5.8 (—OAc), 6.25, 6.39 (pyridine) μ; u.v.: λ_{max} 270 nm (3.60); n.m.r.: 9.26 (angular methyl, 3H, singlet), 8.77 (C_{21} methyl, 3H, $J_{21,20}$ = 7.02 Hz, doublet), 8.43 (C_{18} methyl, 3H, broad singlet), 8.01 (CH_3CO, 3H, singlet), 7.73 (C_{26} methyl, 3H, singlet), 6.90 (C_{20}H, 1H, $J_{20,21}$ = 7.0 Hz, quartet), 2.97 (C_{23}, 1H, $J_{23,24}$ = 8.0 Hz, doublet), 2.65 (C_{24}, 1H, $J_{24,23}$ = 8.0 and $J_{24,27}$ = 2.0 Hz, two doublets), 1.72 (C_{27}H, 1H, $J_{27,24}$ = 2.0 Hz, doublet); mass spectrometry: *m/e* 451 (M^+), prominent peaks at *m/e* 433, 418, 330, and 120.

Anal. Calcd. for $C_{29}H_{41}O_3N$: C, 77.12; H, 9.15. Found: C, 77.05; H, 9.33.

Compound **D** could not be induced to crystallize but the n.m.r. and mass spectrum indicate this compound is probably isomeric with the three characterized above; i.r. ($CHCl_3$): 5.83 (OAc), 6.25, 6.37 (pyridine) μ; u.v.: λ_{max} 270 nm (3.62); n.m.r. 9.21 (angular methyl, 3H, singlet), 8.63 (C_{21} methyl, 3H, $J_{21,20}$ = 7.0 Hz, doublet), 8.27 (C_{18} methyl, 3H, singlet), 8.01 (CH_3CO, 3H, singlet), 7.74 (C_{26} methyl, 3H, singlet), 6.89 (C_{20}, 1H, $J_{20,21}$ = 7.0 Hz, quartet), 3.08 (C_{23}, 1H, $J_{23,24}$ = 8.0 Hz, doublet), 2.62 (C_{24}, 1H, $J_{24,23}$ = 8.0 and $J_{24,27}$ = 2.0 Hz, two doublets), 1.70 (C_{27}, 1H, $J_{27,24}$ = 2.0 Hz, doublet); mass spectrometry: *m/e* 451 (M^+), prominent peaks at *m/e* 433, 418, and 121.

3β-Acetoxy-22,27-iminojerv-12(13),14(15),16,22,24,27-hexaene (4)

Aromatic I

Compound **A** (118 mg) was thoroughly ground with 10% palladized charcoal (30 mg) until a homogeneous powder was obtained. This powder was heated at 200° for 7 min and the resultant solid residue washed several times with chloroform. Thin-layer chromatography of the chloroform extract indicated the product contained three major components and these were separated by preparative layer chromatography (20 × 20 cm, 0.4 mm, 2% methanol in chloroform). One of these three components was shown to be 2-ethyl-5-methylpyridine by n.m.r. The band which exhibited a strong fluorescence when the chromatoplate was viewed under u.v. light was extracted and 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 (**1**) by its u.v. spectrum and by mixture melting point with an authentic sample. The third compound which appeared as a light orange spot when the chromatoplate was sprayed 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 which was designated aromatic **1** was obtained as a clear glass after sublimation at 185°/0.1 mm. Spectral data indicated this compound possessed structure **4**; i.r.: 5.82, 6.26, 6.39 μ; u.v.: λ_{max} 265sh, 269 (3.73) 277 nm (3.62); $[\alpha]_D$ +13° (*c*, 0.84); n.m.r.: 9.10 (angular methyl, 3H, singlet), 8.41 (C_{21} methyl, 3H, $J_{21,20}$ = 7.0 Hz, doublet), 8.03 (CH_3CO, 3H, singlet), 7.90 (C_{18} methyl, 3H, singlet), 7.80 (C_{26} methyl, 3H, singlet), 5.61 (C_{20}, 1H, $J_{20,21}$ = 7.0 Hz, quartet), 3.22–3.0 (C_{15} or C_{16} and C_{23}, 2H, two overlapping doublets), 2.94 (C_{15} or C_{16}, 1H, J = 8 Hz, doublet), 2.72 (C_{24}, 1H, $J_{24,23}$ = 8.0 and $J_{24,27}$ = 2 Hz, two doublets), 1.7 (C_{27}H, 1H, $J_{27,24}$ = 2 Hz, doublet); mass spectrometry: *m/e* 431, prominent peaks at 416, 402.

Mol. Wt. Calcd. for $C_{29}H_{37}O_2N$: 431.2824. Found (high resolution mass measurement): 431.2809.

Aromatic II

Compound **B** (80 mg) was ground with 10% palladized charcoal (20 mg) until a homogeneous powder was formed. This powder was heated at 200° for 7 min and the solid residue washed several times with chloroform. Thin-layer chromatographic examination of the chloroform extract indicated the major component was a new compound which appeared as a light orange spot when the chromatoplate was sprayed with antimony pentachloride – carbon tetrachloride reagent. This compound was separated from the reaction mixture by preparative layer chromatography (20 × 20 cm, 0.4 mm, 1% methanol in chloroform, developed twice) as a light oil (60 mg) which could not be induced to crystallize. An analytical sample of the compound, which was designated 'aromatic **II**', was obtained as a clear glass after sublimation at 185°/0.01 mm; i.r.: 5.82, 6.26, 6.39 μ; u.v.: λ_{max} 265sh, 269 (3.73), 277 nm (3.62); n.m.r.: 9.10 (angular methyl, 3H, singlet), 8.40 (C_{21} methyl, 3H, $J_{21,20}$ = 7 Hz, doublet), 8.02 (CH_3CO, 3H, singlet), 7.89 (C_{18} methyl, 3H, singlet), 7.80 (C_{26} methyl, 3H, singlet), 5.58 (C_{20}, 1H, $J_{20,21}$ = 7.0 Hz, quartet), 3.14 (C_{23}, 1H, $J_{23,24}$ = 8 Hz, doublet), 3.09 (C_{15} or C_{16}, 1H, J = 8 Hz, doublet), 2.91 (C_{15} or C_{16}, 1H, J = 8 Hz, doublet), 2.75 (C_{24}, 1H, $J_{24,23}$ = 8 and $J_{24,27}$ = 2 Hz, two doublets), 1.73 (C_{27}, 1H, $J_{27,24}$ = 2 Hz, doublet); mass spectrometry: *m/e* 431 (M^+), prominent peaks at *m/e* 416, 402.

Mol. Wt. Calcd. for $C_{29}H_{37}O_2N$: 431.2824. Found (high resolution mass measurement): 431.2809.

N-Acetyl-22,27-iminojerva-12(13),14(15),16-triene-3β-ol (5)

Isomers i–iv

Aromatic compound **II** (50 mg) was dissolved in glacial acetic acid (10 ml) and the solution hydrogenated at 20° and 45 p.s.i. over Adams' catalyst (PtO_2, 20 mg) for 3 h. The mixture was filtered to remove the catalyst which was carefully washed with additional acetic acid (5 ml). The combined filtrates were reduced in volume to 2 ml *in vacuo*, then diluted with water (20 ml) and made basic with ammonia solution. The resultant suspension was extracted with methylene chloride (3 × 10 ml) before drying over anhydrous sodium sulfate. Thin-layer chromatography revealed the presence of four compounds of similar R_f value and color reaction with various spray reagents. These compounds were designated **i–iv** in order of decreasing R_f value, (silica gel G, 5% methanol in chloroform) and were separated by careful preparative layer chromatography (20 × 20 cm, 0.3 mm, 1% methanol in chloroform, plates developed three times). The bands corresponding to the four compounds were delineated by inspection of the developed plates under u.v. light. Extraction of the various bands and removal of the solvent (methanol–chloroform 1:1) gave each of the compounds as a clear oil. None of the compounds could be induced to crystallize.

All four compounds were separately converted via the 3-*O*,*N*-diacetates (**13**) to the *N*-acetyl derivatives **12** (since a sample of *N*-acetyl-5α,6-dihydroverarine was available for comparison) as outlined for one of the isomers below.

Compound **ii** was dissolved in pyridine – acetic anhydride (2 ml, 1:1) and allowed to stand for 12 h at 20°. The solution was then poured into ice water (5 ml) and the resulting suspension extracted with methylene chloride (3 × 3 ml). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate (10 ml) and then with water (2 × 5 ml), before drying over anhydrous sodium sulfate. Removal of the methylene chloride *in vacuo* gave a light oil which crystallized from ether (the diacetates of compounds **i**, **iii**, and **iv** were not obtained crystalline) as needles, m.p. 203–205°; i.r. ($CHCl_3$): 5.80 (OAc), 6.19 (NAc) μ; u.v.: λ_{max} 268 (2.7), 277 nm (2.7).

The diacetate (20 mg) was refluxed with 0.1 *M* potassium hydroxide in methanol (5 ml) for 1 h, the solution cooled, and diluted with water (20 ml). The aqueous suspension was extracted with methylene chloride (3 × 5 ml) and the combined extracts washed with water (2 × 5 ml) prior to drying over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* gave a light oil which was readily crystallized from anhydrous ether. (All four *N*-acetyl derivatives were obtained crystalline via this procedure.)

The *N*-acetyl derivatives of compounds **i** and **ii** had R_f values comparable with that of *N*-acetyl-5α,6-dihydroverarine whereas those of the *N*-acetyl derivatives of compounds **iii** and **iv** were slightly smaller. All compounds showed similar color reactions when the chromatoplate was sprayed with various reagents. The *N*-acetyl derivatives were characterized as follows.

*Compound **i**, N-acetate;* prisms, m.p. 249–250° (6 mg); i.r. ($CHCl_3$): 6.20 9.70 μ; u.v.: λ_{max} 268 (2.68), 277 nm (2.66); $[\alpha]_D$ +36° (*c*, 0.605); n.m.r.: 9.07 (angular methyl, 3H, singlet), 8.19 (CH_3CON, 3H, singlet), 7.74 (C_{18} methyl, 3H, singlet), 3.15 (C_{15} or C_{16}, J = 8 Hz, doublet), 2.96 (C_{15} or C_{16}, J = 8 Hz, doublet); mass spectrometry: *m/e* 437 (M^+), prominent peaks at *m/e* 297, 140, 98.

Mol. Wt. Calcd. for $C_{29}H_{43}O_2N$: 437.329. Found (high resolution mass measurement): 437.325.

*Compound **ii**, N-acetate;* prisms, m.p. 263–264° (17 mg); i.r. ($CHCl_3$): 6.19, 9.70 μ; u.v.: λ_{max} 268 (2.65), 277 nm (2.61); $[\alpha]_D$ +26° (*c*, 1.71); mass spectrometry: *m/e* 437 (M^+), prominent peaks at *m/e* 298, 297, 140, 98.

*Compound **iii**, N-acetate;* rosettes, m.p. 270–274° (5 mg); i.r. ($CHCl_3$): 6.20, 9.70 μ; u.v.: λ_{max} 268, 277 nm; mass spectrometry: *m/e* 437 (M^+), prominent peaks at *m/e* 297, 140, 98.

*Compound **iv**, N-acetate;* long needles, m.p. 260–261° (10 mg); i.r. ($CHCl_3$): 6.20, 9.70, 9.80 μ; u.v.: λ_{max} 268, 277 nm; mass spectrometry: *m/e* 437 (M^+), prominent peaks at *m/e* 298, 297, 140, 98.

Isomers v–viii

Aromatic compound **I** (50 mg) was dissolved in glacial acetic acid (10 ml) and the solution shaken with Adams' catalyst (PtO_2, 20 mg) in an atmosphere of hydrogen at 45 p.s.i. and 20° for a period of 3 h. The mixture was filtered to remove the catalyst which was washed with a further 10 ml of glacial acetic acid and the filtrates combined. The volume of the acetic acid was reduced to 2 ml by use of a rotary evaporator before dilution with water (20 ml). The aqueous acid solution was made basic with dilute ammonia and the resulting suspension extracted several times with methylene chloride (3 × 10 ml) prior to drying over anhydrous sodium sulfate. Thin-layer chromatographic investigation of the light oil (45 mg) obtained by removal of the methylene chloride indicated the presence of four compounds, of similar R_f value and color reaction to the spray reagent. These compounds were numbered **v–viii** in order of decreasing R_f value and were separated by careful preparative layer chromatography (silica gel G 20 × 20 cm, 0.3 mm, 1% methanol in chloroform, plates developed three times). The compounds were obtained as colorless oils which could not be crystallized. Conversion of these compounds via the 3-*O*,*N*-diacetates to the *N*-acetyl derivatives was accomplished as outlined above for the 3β-acetoxy-22,27-iminojerva-12(13),14(15),16-triene isomers **i–iv** obtained from aromatic compound **II**. None of the *N*-acetyl derivatives of compounds **v–viii** could be induced to crystallize although compounds **v** and **vi** had R_f values comparable with *N*-acetyl-5,6-dihydroverarine. These compounds were not fully characterized but their spectral properties were in accord with structure **5**.

Compound v, N-acetate: i.r.: 6.19, 9.28 μ; u.v.: λ_{max} 267, 276 nm; mass spectrometry: *m/e* 437 (M^+), prominent peaks at *m/e* 298, 297, 98.

Spectral properties for the *N*-acetyl derivatives of compounds **vi–viii** are virtually the same as for the acetate of ***v*** and no additional data were obtained for any of these compounds.

Hydrogenation of 3-O,N-Diacetylverarine

The 3-*O*,*N*-diacetylverarine utilized in this reaction was prepared from veratramine (1) and had the following physical constants, m.p. 189–190° (lit. (1) m.p. 189–190°); $[\alpha]_D$ −23 ±2° (ethanol).

A solution of 3-*O*,*N*-diacetylverarine (190 mg) in glacial acetic acid (5 ml) was stirred with Adams' catalyst (PtO_2, 60 mg) in an atmosphere of hydrogen at 20°. After 14 h, 9.1 ml of hydrogen had been consumed and the mixture was filtered to remove the catalyst which was washed with a further 10 ml of acetic acid. The combined filtrates were reduced in volume (to 2 ml) *in vacuo* and diluted with water (30 ml) to give a white precipitate which was taken up in ether. The ethereal phase was washed with water (3 × 10 ml) before drying over anhydrous sodium sulfate. Thin-layer chromatographic examination on both silica gel and alumina using a variety of solvents indicated that a single new compound had been formed.

Removal of the ether *in vacuo* gave an oil which could not be induced to crystallize. A small scale investigation revealed that after selective hydrolysis of the 3-*O*-acetate the product appeared as two components of similar R_f value on a silica gel chromatoplate. Consequently 3-*O*,*N*-diacetyl-5,6-dihydroverarine (170 mg) was refluxed with 0.1 *N* methanolic potassium hydroxide (5 ml) for 1 h, the solution cooled, and then diluted with water (20 ml). The resulting aqueous suspension was extracted with methylene chloride (3 × 10 ml) and the combined extracts washed with water (3 × 10 ml) before drying over anhydrous sodium sulfate. Removal of the solvent *in vacuo* gave a light oil which on trituration with ether gave crystals, m.p. 190–225°. Thin-layer chromatography showed the crystalline product to consist of two compounds which were separated by preparative layer chromatography on silica gel (20 × 20 cm, 0.4 mm, 2% methanol in chloroform). The least polar compound (75 mg) was tentatively assigned the 5β configuration on the basis of its n.m.r. spectrum. Recrystallization from ether gave an analytical sample of *N*-acetyl-5β,6-dihydroverarine (**20**), m.p. 198–199°; i.r. ($CHCl_3$): 6.21 (—NC(=O)—CH) μ; u.v.: λ_{max} 267 (2.74), 276 nm (2.74); n.m.r.; 9.02 (C_{26} methyl, 3H, $J_{26,25}$ = 7 Hz, doublet), 8.94 (angular methyl, 3H, singlet), 8.82 (C_{21} methyl, 3H, $J_{21,20}$ = 8 Hz, doublet) 8.14 (CH_3CON, 3H, singlet), 7.71 (C_{18} methyl, 3H, singlet), 6.45 (C_{20}, 1H, $J_{20,21}$ = 8 and $J_{20,22}$ = 10 Hz, multiplet), 5.97 (*H*—C—OAc, 1H, multiplet), 3.12 (C_{15} or C_{16}, 1H, J = 8 Hz, doublet), 2.96 (C_{15} or C_{16}, J = 8 Hz, doublet); mass spectrometry: *m/e* 437 (M^+), prominent peaks at *m/e* 297, 140, 98.

Anal. Calcd. for $C_{29}H_{43}O_2N$: C, 79.58; H, 9.90; N, 3.20. Found: C, 79.51; H, 10.02; N, 3.25.

The more polar compound was crystallized from ether as prisms, m.p. 249–250°. This compound was tentatively assigned the 5α configuration on the basis of its n.m.r. spectrum and an analytical sample of *N*-acetyl-5α,6-dihydroverarine (**11**) was prepared by sublimation at 220°/0.01 mm, as prisms, m.p. 249–250°; i.r.: 6.22 (N—C(=O)CH_3), 12.23 μ; u.v.: λ_{max} 267 (2.69), 276 nm (2.68); $[\alpha]_D$ +41° (*c*, 0.961); n.m.r.: 9.06, 9.02 (angular and C_{26} methyl, 6H, singlet and doublet), 8.19 (CH_3CON, 3H, singlet), 7.72 (C_{18} methyl, 3H, singlet), 3.13 (C_{15} or C_{16}, 1H, J = 8 Hz, doublet), 2.99 (C_{15} or C_{16}, 1H, J = 8 Hz, doublet); mass spectrometry: *m/e* 437 (M^+), prominent peaks at *m/e* 394, 297, 140.

Anal. Calcd. for $C_{29}H_{43}O_2N$: C, 79.58; H, 9.90. Found: C, 79.32; H, 9.99.

*N-Acetyl-3-keto-5α,6-dihydroverarine (**23**)*

A solution of *N*-acetyl-5α,6-dihydroverarine (**11**; 212 mg) in acetone (75 ml) was treated with Jones' reagent (0.3 ml) and allowed to stand at 20° for 2 min. Isopropanol (2 ml) was added to remove the excess oxidant and the mixture diluted with water (600 ml). The aqueous acetone solution was extracted with methylene chloride (3 × 30 ml) and the combined extracts washed with water (3 × 30 ml) before drying over anhydrous sodium sulfate. Evaporation of the methylene chloride gave a colorless oil (191 mg) which could not be crystallized but appeared homogeneous when examined by thin-layer chromatography. An analytical sample was obtained as a clear glass after sublimation at 185°/0.01 mm; i.r.: 5.89 (saturated carbonyl), 6.14 (N—C(=O)—CH_3) μ; u.v.: λ_{max} 267 (2.73), 276

nm (2.71); $[\alpha]_D$ +66° (*c*, 1.15); o.r.d. $[\phi]_{305}^{peak}$ +1090°, $[\phi]_{270}^{trough}$ +115°, $[\phi]_{230}^{peak}$ +3910°; n.m.r.: 9.03 (C_{26} methyl, 3H, $J_{26,25}$ = 7.0 Hz, doublet), 8.88 (angular methyl, 3H, singlet), 6.45 (C_{20}, 1H, $J_{20,21}$ = 7.5, $J_{20,22}$ = 9.0 Hz, multiplet), 3.13 (C_{15} or C_{16}, 1H, J = 8 Hz, doublet), 2.95 (C_{15} or C_{16}, 1H, J = 8 Hz, doublet); mass spectrometry: *m/e* 435 (M^+), prominent peaks at *m/e* 392, 295, 140, 98.

Mol. Wt. Calcd. for $C_{29}H_{41}O_2N$: 435.313. Found (high resolution mass measurement): 435.312.

*N-Acetyl-Δ⁴-3-keto-5,6-dihydroverarine (**28**)*

A solution of *N*-acetyl-3-keto-5α,6-dihydroverarine (162 mg, 0.372 mmol) in acetic acid (6 ml) containing hydrogen bromide (60 mg, 0.744 mmol) was placed in a dry round-bottom flask. Bromine (130 mg, 0.8 mmol) in acetic acid (5 ml) was added slowly and the mixture stirred at 20° for 20 min and then diluted with water (25 ml). The resulting heavy white precipitate was taken up in methylene chloride and the extract washed with water (3 × 10 ml) prior to drying over anhydrous sodium sulfate. Removal of the solvent *in vacuo* gave a colorless gum (225 mg) which was shown by thin-layer chromatography to consist of one major compound. This crude product was immediately subjected to the conditions of Evans (12) for introduction of the 4,5-double bond as outlined below. Bromine (0.26 ml) was added to acetone (7.5 ml) at 0° and the solution stirred until the color disappeared. Sodium carbonate (0.7 g) was then added and the mixture was stirred for a further 30 min, then filtered directly into hot acetone containing sodium iodide (7.0 g). This solution was refluxed for 15 min during which time a precipitate of sodium bromide was formed.

A portion (6 ml) of the supernatant of this hot solution was added to a round bottom-flask containing 2,4-dibromo ketone (220 mg) and the solution refluxed for 2½ h. During this time more sodium bromide precipitated, indicative of the exchange of the 2-bromine for an iodine atom. Oxalic acid (220 mg) was added as a fine powder and the solution refluxed for a further hour before cooling. The reaction mixture was diluted with ethyl acetate (20 ml) and filtered. This filtrate was washed with water (2 × 10 ml), saturated aqueous sodium hydrogen carbonate (2 × 10 ml), and water (2 × 10 ml). The ethyl acetate was decolorized by adding zinc dust (600 mg) and acetic acid (0.2 ml) and then shaking. When the solution had attained a light yellow color the zinc dust was removed by filtration and the ethyl acetate filtrate washed with water (2 × 10 ml), sodium hydrogen carbonate solution (2 × 10 ml), and water (2 × 10 ml) before drying over anhydrous sodium sulfate.

Removal of the ethyl acetate *in vacuo* gave a light yellow gum (158 mg) which was examined by thin-layer chromatography. The spot on the chromatoplate corresponding to the major product exhibited an intense fluorescence under u.v. light and appeared purple when the plate was sprayed with antimony pentachloride – carbon tetrachloride reagent. Preparative layer chromatography on silica gel (20 × 60 cm, 0.4 mm, developed twice with 1% methanol in chloroform) gave this compound as a light gum (110 mg, 50% yield) which was not crystallized. An analytical sample was prepared by sublimation at 180°/0.01 mm which gave a light yellow glass; i.r.: 6.03 (α,β-unsaturated carbonyl), 6.14 (N—Ac) μ; $[\alpha]_D$ +74° (*c*, 1.26); n.m.r.: 9.02 (C_{26} methyl, 3H, $J_{26,25}$ = 7 Hz, doublet), 8.72 (angular methyl, 3H, singlet), 8.18 (CH_3C—N, 3H, singlet), 6.45 (C_{20}, 1H, $J_{20,21}$ = 7.5, $J_{20,22}$ = 10 Hz, multiplet), 4.22 (C_4, 1H, singlet), 3.10 (C_{15} or C_{16}, 1H, J = 8Hz, doublet), 2.94 (C_{15} or C_{16}, 1H, J = 8Hz, doublet); mass spectrometry: *m/e* 433 (M^+), prominent peaks at *m/e* 390, 293, 140, 98.

Mol. Wt. Calcd. for $C_{29}H_{39}O_2N$: 433.2980. Found (high resolution mass measurement): 433.2974.

*N-Acetylverarine (**30**)*

A solution of *N*-acetyl-Δ⁴-3-keto-5,6-dihydroverarine (100 mg) in isopropenyl acetate (3 ml) containing 0.5% sulfuric acid was refluxed for 1 h. Anhydrous sodium acetate (60 mg) was then added and most of the isopropenyl acetate removed by use of a rotary evaporator. The residue was diluted with methylene chloride (10 ml) and then filtered. Thin-layer chromatography of the filtrate indicated the complete absence of (**23**) and the formation of a less polar compound. Evaporation of the methylene chloride gave an oil (100 mg) the i.r. spectrum of which exhibited a carbonyl band at 5.75 μ indicative of an enol acetate.

This oil was dissolved in a mixture of methanol (10 ml) and ether (3 ml) and heated to reflux. During the refluxing a methanolic solution of sodium borohydride (150 mg in 5 ml) was added slowly over a period of 15 min. The solution was refluxed for a further 1 h and then concentrated hydrochloric acid (1 ml) was added and the refluxing continued with stirring for 30 min. During this final period vigorous stirring was necessary to overcome severe bumping.

The reaction mixture was cooled and then diluted with ether (50 ml). The ethereal solution was washed with water and then dried over anhydrous sodium sulfate. Removal of the solvent gave a light oil (70 mg) which was shown to contain a compound of identical R_f value to that of *N*-acetylverarine. Separation by preparative layer chromatography (20 × 20 cm, 0.3 mm, 2% methanol in chloroform) and extraction of the band corresponding to this product yielded an oil (30 mg). This compound was shown to be identical with *N*-acetylverarine by thin-layer chromatography and superimposable i.r. and n.m.r. spectra; i.r. ($CHCl_3$): 6.19 (NC(=O)—CH_3) μ; u.v.: λ_{max} 268 (2.76) 277 nm (2.65); n.m.r.: 9.03 (C_{26} methyl, 3H, $J_{26,25}$ = 7 Hz, doublet), 8.87 (angular methyl, 3H, singlet), 8.18 (CH_3CON, 3H, singlet), 4.56 (C_6 1H, multiplet), 3.12 (C_{15} or C_{16}, 1H, J = 8 Hz, doublet,), 2.94 (C_{15} or C_{16}, 1H, J = 8 Hz, doublet); mass spectrometry: *m/e* 435 (M^+), prominent peaks at *m/e* 295, 140, 98.

*Verarine (**31**)*

A solution of *N*-acetylverarine (20 mg) in ethylene glycol (5 ml) containing 10% potassium hydroxide was refluxed for 12 h. The reaction mixture was cooled, diluted with water (20 ml), and extracted with methylene chloride (3 × 5 ml). Examination of the extract by thin-layer chromatography indicated the presence of *N*-acetylverarine and a more polar compound which had the same R_f value and color reaction to the spray reagent, as an authentic sample of verarine. The more polar compound was separated by preparative layer chromatography (20 × 20 cm, 0.3 mm, 5% methanol in chloroform) as a light oil

(8 mg) which crystallized from ether. This compound was shown to be identical with verarine by thin-layer chromatography, i.r., and n.m.r. comparison; i.r. ($CHCl_3$): 9.57 μ; u.v.: λ_{max} 267 (2.74) 276 nm (2.73); n.m.r.: 9.15 (C_{26} methyl, 3H, $J_{26,25}$ = 6 Hz, doublet), 8.88 (angular methyl, 3H, singlet), 7.73 (C_{18} methyl, 3H, singlet), 4.55 (C_6, 1H, broad doublet), 3.02 (C_{15} and C_{16}H, 2H, singlet); mass spectrometry: *m/e* 393 (M^+), prominent peaks at *m/e* 392, 376, 295, 284, 256, 98.

Mol. Wt. Calcd. for $C_{27}H_{39}ON$: 392.2953. Found (high resolution mass measurement): 392.2922.

*3-Methylbut-3-enal Diethyl Acetal (**40**)*

This compound was prepared according to the procedure of Cornforth and Firth (23) with small modifications as indicated. The additional data obtained in our investigations in this and the next few experiments are also provided. 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 h) 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 (**40**, 19 g), b.p. 60–61°/20 mm (lit. (25) b.p. 60°/19 mm). The compound was found to be pure by v.p.c. examination using a FFAP column; i.r. (film): 6.25 μ; n.m.r. 8.85 (2 × CH_3—CH_2, 6H, triplet), 8.25 (C_2—CH_3, 3H, singlet), 7.7 (C_3—CH_2, 2H, doublet, J = 6.0 Hz), 6.5 (CH_2's of —O—CH_2—CH_3, 4H, multiplet), 5.4 (C_4H, 1H, triplet), 5.2 (CH_2=C<, 2H, singlet).

*3,4-Epoxy-3-methylbutanal Diethyl Acetal (**41**)*

A solution of 3-methylbut-3-enal diethyl acetal (**40**, 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 (**41**) as a colorless oil (4.1 g), b.p. 82–86°/18 mm (lit. (22) b.p. 83–84°/17 mm). The compound was found to be homogeneous by v.p.c. examination; i.r. (film): 10.0, 10.5, 12.5 μ (epoxide); n.m.r.: 8.85 (2 × CH_3—CH_2—O—, 6H, triplet), 8.7 (C_3—CH_3, 3H, singlet), 8.2 (C_2—CH_2, 2H, doublet, J = 7.0 Hz), 7.5 (O; CH_2—C—, 2H, AB quartet, $J_{A,B}$ = 5.5 Hz), 6.5 (CH_2's of —O—CH_2—CH_3, 4H multiplet), 5.4 (C_1H, 1H, triplet).

*3-Methylfuran (**42**)*

A mixture of 3,4-epoxy-3-methylbutanal diethyl acetal (**41**, 5.0 g) and 0.1 *N* sulfuric acid (500 ml) were heated under a fractionating column for 3 h, 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. (22) b.p. 65–65.5°); i.r. (chloroform): 6.67, 8.33, 11.2 μ; n.m.r.: 8.0 (C_3—CH_3, 3H, singlet), 3.85 (C_4H, 1H, singlet), 2.87 (C_2H, 1H, broad singlet), 2.75 (C_5H, 1H, broad singlet).

Propionylation of 3-Methylfuran

3-Methylfuran (1 g) and propionic anhydride (1.6 g) were mixed and to the mixture 2 drops of orthophosphoric acid (85%) were added. The mixture was stirred vigorously and the heat generated was removed by cooling. Gradually the reaction mixture acquired a dark red color. It was then heated to 60–65° and maintained at this temperature for 2 h. The reaction mixture was then cooled and stirred with water (2 ml) for 1 h. The dark organic layer was separated and again stirred with saturated sodium carbonate solution (5 ml) for 24 h. It was then washed thoroughly with water, extracted with ether (2 × 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 colorless fragrant liquid (0.5 g) was collected, b.p. 125–130°/25 mm. The i.r. spectrum (film) of the product showed a double carbonyl absorption (~5.88 μ). 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 min, respectively. These were separated by v.p.c. using a FFAP column (172°). The major component was characterized as 2-propionyl-3-methylfuran (**43**), b.p. 77–80°/5 mm; i.r. (film): 5.99, 6.65, 11.3 (furan) μ; u.v.: λ_{max} 278, 230 nm; n.m.r.: 8.85 (CH_3—CH_2—, 3H, triplet), 7.65 (C_3—CH_3, 3H, singlet), 7.2 (—CO—CH_2—CH_3, 2H, quartet), 3.65 (C_4H, 1H, doublet, $J_{4,5}$ = 2.5 Hz), 2.65 (C_5H, doublet, $J_{4,5}$ = 2.5 Hz); mass spectrometry: *m/e* 138 (M^+), prominent peak at *m/e* 109.

Anal. Calcd. for $C_8H_{10}O_2$: C, 69.56; H, 7.24. Found: C, 69.71; H, 7.27.

The second component was characterized as 2-propionyl-4-methylfuran (**44**), b.p. 78–82°/5 mm; i.r. (film): 5.97, 6.65, 11.3 μ; u.v.: λ_{max} 280, 230 nm; n.m.r.: 8.85 (CH_3—CH_2—, 3H, triplet), 7.9 (C_4CH_3, 3H, singlet), 7.2 (—CO—CH_2—CH_3, 2H, quartet), 3.05 (C_3H, 1H, singlet), 2.75 (C_5H, 1H, broad singlet); mass spectrometry: *m/e* 138 (M^+), prominent peak at *m/e* 109.

Anal. Calcd. for $C_8H_{10}O_2$: C, 69.56; H, 7.24. Found: C, 69.68; H, 7.26.

*Methyl 5,5-Dimethoxy-3-methyl-2,3-epoxypentanoate (**45**)*

This compound was prepared according to the procedure of Burness (25).

*Methyl 3-Methyl-2-furoate (**46**)*

This compound was prepared according to the procedure of Burness (25); i.r. (chloroform): 5.80 μ; u.v.: λ_{max} 252 nm; n.m.r.: 7.65 (C_3—CH_3, 3H, singlet), 6.2 ($COOCH_3$, 3H, singlet), 3.68 (C_4H, 1H, doublet, J = 2.0 Hz), 2.6 (C_5H, 1H, doublet, J = 2.0 Hz).

*Methyl 3-Methyl-5-propionyl-2-furoate (**47**)*

Methyl 3-methyl-2-furoate (25.6 g, 0.2 mol) was dissolved in propionic anhydride (75 ml) and orthophosphoric 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 h. 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 sulfate. The solvent was distilled off under reduced pressure. The unreacted starting materials were removed by distillation *in vacuo* and the semisolid residue was distilled 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%), colorless shining needles, m.p. 113–114°; i.r. (chloroform): 5.73, 5.88 μ; u.v.: λ_{max} 280, 285sh, 212 nm; n.m.r.: 8.8 (—CH_2—CH_3, 3H, triplet), 7.65 (C_3CH_3, 3H, singlet), 7.2 (—CO—CH_2—, 2H, quartet), 6.1 (—$COOCH_3$, 3H, singlet), 3.0 (C_5H, 1H, singlet); mass spectrometry: *m/e* 196 (M^+), prominent peaks at *m/e* 167, 138, 123, 109.

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.22; H, 6.12. Found: C, 61.01; H, 5.97.

*3-Methyl-5-propionyl-2-furoic Acid (**48**)*

A solution of methyl 3-methyl-5-propionyl-2-furoate (**47**, 9.8 g) in aqueous sodium hydroxide (10%, 100 ml) was heated under reflux for 1.5 h. 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°; i.r. (chloroform): 5.67, 5.88 μ; u.v.: λ_{max} 282, 212 nm; n.m.r.: 8.8 (CH_3—CH_2—, 3H, triplet), 7.6 (C_3CH_3, 3H, singlet), 7.0 (—CH_2—CO—, 2H, quartet), 2.85 (C_4H, 1H, singlet), −0.2 (—COOH, 1H, singlet); mass spectrometry: *m/e* 182 (M^+), prominent peak at *m/e* 137.

Anal. Calcd. for $C_9H_{10}O_4$: C, 59.33; H, 5.49. Found: C, 59.21; H, 5.50.

*2-Propionyl-4-methylfuran (**44**)*

A mixture of 3-methyl-5-propionyl-2-furoic acid (9.1 g, 0.05 mol), anhydrous quinoline (20 ml), and powdered copper (2.0 g) was heated 200–210° under a nitrogen atmosphere for 3 h. 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 × 50 ml), water (100 ml), and finally with sodium bicarbonate solution until neutral to litmus. It was then dried over sodium sulfate 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 colorless 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 **44** obtained by the propionylation of 3-methylfuran.

*2-Ethyl-3-hydroxy-5-methylpyridine (**49**)*

2-Propionyl-4-methylfuran (**44**; 1.0 g) and aqueous ammonia (11 *N*, 25 ml), were heated in a sealed tube for 20 h (18). 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 semisolid residue distilled at 150°/0.3–5 mm. A small quantity of pale yellow liquid which collected in the receiver soon solidified into shining prisms (202 mg), m.p. 140–144°. Crystallization from chloroform provided an analytical sample as colorless shining prisms, m.p. 145–147°; i.r. (chloroform): 3.11, 6.29 μ; u.v.: λ_{max} (log ε): 287 (3.95), 225sh nm; n.m.r.: 8.75 (CH_3—CH_2—, 3H, triplet), 7.8 (C_5CH_3, 3H, singlet), 7.1 (—CH_2—CH_3, 2H, quartet), 2.9 (C_4H, 1H, singlet), 2.1 (C_6H, 1H, singlet), 1.0 (C_3OH, 1H, multiplet); mass spectrometry: *m/e* 137 (M^+), prominent peaks at *m/e* 136, 121, 94, 93.

Anal. Calcd. for $C_8H_{11}NO$: C, 70.07; H, 8.02. Found: C, 70.11; H, 8.10.

*2-Ethyl-3-O-benzyl-5-methylpyridine (**50**)*

2-Ethyl-5-methyl-3-hydroxypyridine (274 mg, 0.002 mol) was dissolved in aqueous sodium hydroxide (5%, 10 ml) and benzyl chloride (240 mg, 0.002 mol) was added to it. The mixture was heated at 100° for 2.5 h. 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 × 10 ml). The chloroform extract was washed with water until neutral to litmus and dried over sodium sulfate. The residual oil obtained after the removal of the solvent was distilled *in vacuo*. A colorless 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; i.r. (film): 6.27, 7.87, 9.52 μ; u.v.: λ_{max} 285, 225sh nm; n.m.r.: 8.8 (CH_3—CH_2—, 3H, triplet), 7.75 (C_5CH_3, 3H, singlet), 7.2 (—CH_2—CH_3, 2H, quartet), 5.0 (—O—CH_2—C_6H_5, 2H, singlet), 3.15 (C_4H, 1H, singlet), 2.65 (C_6H_5—CH_2—O—, 5H, singlet), 2.1 (C_6H, 1H, singlet).

*2-Ethyl-3-methoxy-5-methylpyridine (**51**)*

A solution of 2-ethyl-3-hydroxy-5-methylpyridine (2.74 g, 0.02 mol) in methanol (40 ml) containing 10% water was chilled in an ice-salt bath. To this was added a solution of diazomethane (4.2 g, 0.1 mol) 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 made alkaline with sodium hydroxide pellets and again extracted with ether (3 × 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 colorless 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-3-hydroxy-5-methylpyridine (**49**).

The methyl ether was characterized as follows; i.r. (film): 6.26, 6.41, 7.91, 9.52 μ; u.v.: λ_{max} (log ε): 283 (3.86), 2.25sh nm; n.m.r.: 8.8 (CH_3—CH_2—, 3H, triplet),

7.7 (C_5CH_3, 3H, singlet), 7.25 (—CH_2—CH_3, 2H, quartet), 6.25 (—OCH_3, 3H, singlet), 3.2 (C_4H, 1H, singlet), 2.15 (C_6H, 1H, singlet).

Anal. Calcd. for $C_9H_{13}NO$: C, 71.52; H, 8.60. Found: C, 71.47; H, 8.64.

23-Methoxy-22,27-iminojerva-12(13),22,24,27-tetraene-3β-17-diol(s) (53)

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 h. A deep red color slowly developed in the solution. It was then cooled and 3β-acetoxy-5α-etiojerv-12(13)-en-17-one (**1**) was added as a fine powder until the color 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 before drying over sodium sulfate. 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, activity III) eluting with 50% ligroin in benzene removed the unreacted pyridine (**51**). Continued elution with benzene removed the unreacted enone (**1**). 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, **53**; i.r. (chloroform): 3.05, 6.27 μ; u.v.: λ_{max} (log ε) 283.5 nm (3.86); n.m.r.: 9.22 ($C_{19}CH_3$, 3H, singlet), 8.84, 8.81 ($C_{21}CH_3$, 3H, two overlapping doublets $J_{20,21}$ = 7.0 Hz), 6.24, 6.21 (—OCH_3, 3H, two singlets), 3.10 (C_{24}H, 1H, singlet), 2.04 (C_{27}H, 1H, singlet); mass spectrometry: *m/e* 421 (M^+), prominent peaks at *m/e* 406 and 288.

Acetylation of 23-Methoxy-22,27-iminojerva-12(13),22,24,27-tetraene-3β,17-diols (53)

A mixture of acetic anhydride and pyridine (1:1, 5 ml) was added to the condensation product (**53**; 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 × 20 ml). The combined ether extracts were washed with saturated sodium bicarbonate solution and several times with water before drying over sodium sulfate. The solvent was distilled off *in vacuo* when a pale yellow semisolid residue (330 mg) was obtained. Thin-layer chromatographic 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, while the second component appeared as a canary yellow spot. This mixture of acetates was separated by column chromatography on alumina (30 g, activity III). Elution with benzene afforded the less polar compound (designated as compound **F**) in essentially pure state (125 mg). Further elution with 5% chloroform afforded the second component (designated as compound **E**, 191 mg).

An analytical sample of **E** was prepared by crystallization from 5% chloroform in ether whereupon colorless shining prisms were obtained, m.p. 181–182°; i.r.: 3.05, 5.84, 6.25, 6.39 μ; u.v.: λ_{max} (log ε) 284 nm (3.86); n.m.r.: 9.22 ($C_{19}CH_3$, 3H, singlet), 8.82 ($C_{21}CH_3$, 3H, doublet, $J_{20,21}$ = 7.0 Hz), 8.79 ($C_{18}CH_3$, 3H, singlet), 8.0 ($OCOCH_3$, 3H, singlet), 7.7 ($C_{26}CH_3$, 3H, singlet), 6.22 (OCH_3, 3H, singlet), 3.90 (C_{17}OH, 1H, broad multiplet, disappears on D_2O addition), 3.08 (C_{24}H, 1H, singlet), 2.0 (C_{27}H, 1H, singlet); mass spectrometry: *m/e* 463 (*M* − 18), prominent peaks at *m/e* 448, 330, 288, 255, 146.

Anal. Calcd. for $C_{30}H_{41}NO_3$: C, 74.84: H, 8.94. Found: C, 74.65; H, 8.97.

Compound **F**, 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 colorless glassy solid was obtained; i.r.: 5.83, 6.27, 6.39 μ; u.v.: λ_{max} (log ε) 283.5 nm (4.03); n.m.r.: 9.08 ($C_{19}CH_3$, 3H, singlet), 8.45 ($C_{21}CH_3$, 3H, doublet, $J_{20,21}$ = 7.0 Hz), 8.0 ($OCOCH_3$, 3H, singlet), 7.7 ($C_{18}CH_3$ and $C_{26}CH_3$, 6H, singlet), 6.3 ($C_{23}OCH_3$, 3H, singlet), 3.05 (C_{15}H and C_{16}H, 2H, AB quartet, $J_{15,16}$ = 7.0 Hz), 3.16 (C_{24}H, 1H, singlet), 2.0 (C_{27}H, 1H, singlet); mass spectrometry: *m/e* 461 (*M* − 20), prominent peaks at *m/e* 461, 446, 432, 298, 150.

Anal. Calcd. for $C_{30}H_{39}NO_3$ (mol. wt. 461.293): C, 78.09; H, 8.45. Found (high resolution mass measurement, 461.291): C, 77.78; H, 8.47.

3β-Acetoxy-23-methoxy-22,27-iminojerv-12(13),14(15),16(17),22,24,27-hexaene: Compound G (57)

Compound **E** (**54**; 150 g) was thoroughly ground with 10% palladized charcoal (37 mg) until a homogeneous powder was obtained. This powder was heated at 200° under nitrogen for 7 min 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 layer plates (20 × 20 cm, 0.4 mm, chloroform). One of these three components was shown to be 2-ethyl-3-methoxy-5-methylpyridine (**51**) 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 (**1**) by its u.v. spectrum and mixture 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 **G** was obtained as a clear glass after distillation at 170°/0.1 mm; i.r.: 5.84, 6.27, 6.39 μ; u.v.: λ_{max} (log ε) 283.5 nm (4.04); n.m.r.: 9.07 ($C_{19}CH_3$, 3H, singlet), 8.4 ($C_{21}CH_3$, doublet, $J_{20,21}$ = 7.0 Hz), 8.0 ($OCOCH_3$, 3H, singlet), 7.74 ($C_{18}CH_3$ and $C_{26}CH_3$, 6H, singlet), 6.3 (OCH_3, 3H, singlet), 3.1 (C_{15}H and C_{16}H, AB quartet, $J_{15,16}$ = 8.0 Hz), 3.18 (C_{24}H, 1H, singlet), 2.02 (C_{27}H, 1H, singlet); mass spectrometry: *m/e* 461 (M^+), prominent peaks at *m/e* 461, 446, 432, 298, 150.

Anal. Calcd. for $C_{30}H_{39}O_3$ (mol. wt. 461.293): C,

78.09; H, 8.45. Found (high resolution mass measurement, 461.293): C, 77.80; H, 8.46.

5α,6-Dihydroveratramine (56)

A solution of compound **F** (45 mg) in 95% ethanol (10 ml) containing 2% 12 *N* hydrochloric acid was stirred with Adams' catalyst (PtO_2, 20 mg) at 20° for 18 h. 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 in volume to 2 ml *in vacuo*. It was diluted with water and extracted with chloroform (3 × 10 ml) before drying over sodium sulfate. 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, while the third compound had an 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 thick-layer chromatography on neutral alumina (20 × 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 an R_f value corresponding to that of 5α,6-dihydroveratramine, was obtained crystalline from 5% methanol in chloroform as colorless fluffy crystals (8 mg), m.p. 198°. This material was characterized as 5α,6-dihydroveratramine; undepressed m.p. (197–198°) and identical i.r., n.m.r., and mass spectra with an authentic sample.

The two less polar components obtained (17 and 13 mg, respectively) were found to be very unstable and hence no detailed investigation of these were 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) while the 23-methoxyl group was intact (signal at 6.3).

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1. T. MASAMUNE, I. YAMAZAKI, and M. TAKASUGI. Bull. Chem. Soc. Jap. **39**, 1090 (1966).
2. S. M. KUPCHAN and M. E. SUFFNESS. J. Am. Chem. Soc. **90**, 2730 (1968).
3. Y. MAZUR, N. DANIELI, and F. SONDHEIMER. J. Am. Chem. Soc. **82**, 5889, (1960).
4. W. A. JACOBS and L. C. CRAIG. J. Biol. Chem. **124**, 659 (1938).
5. R. L. AUGUSTINE. Catalytic hydrogenation – techniques and applications in organic synthesis. Marcel Dekker Inc., New York. 1965. p. 104.
6. J. TOMKO and S. BAUER. Coll. Czech. Chem. Commun. **29**, 2570 (1964).
7. K. SAITO. Bull. Chem. Soc. Jap. **15**, 22 (1940).
8. T. MASAMUNE, N. SATO, K. KOBAYASHI, I. YAMAZAKI, and Y. MORI. Tetrahedron, **23**, 1591 (1967).
9. N. S. BHACCA and D. H. WILLIAMS. Application of NMR spectroscopy in organic chemistry. Holden-Day, San Francisco. 1964. p. 14.
10. T. MASAMUNE, K. KOBAYASHI, M. TAKASUGI, Y. MORI, and A. MURAI. Tetrahedron, **24**, 3461 (1968).
11. H. BUDZIKIEWICZ. Tetrahedron, **20**, 2267 (1964).
12. R. M. EVANS, J. C. HAMLET, J. S. HUNT, P. G. JONES, A. G. LONG, J. F. OUGHTON, L. STEPHENSON, T. WALKER, and B. M. WILSON. J. Chem. Soc. 4356 (1956).
13. W. S. JOHNSON, H. A. P. DE JONGH, C. E. COVERDALE, J. W. SCOTT, and U. BURCKHARDT. J. Am. Chem. Soc. **89**, 4523 (1967).
14. T. MASAMUNE, M. TAKASUGI, A. MURAI, and K. KOBAYASHI. J. Am. Chem. Soc. **89**, 4521 (1967).
15. S. M. KUPCHAN and M. I. SUFFNESS. J. Am. Chem. Soc. **90**, 2730 (1968).
16. B. M. ISELIN, M. MOORE, and O. WINTERSTEINER. J. Am. Chem. Soc. **78**, 403 (1956).
17. T. MASAMUNE, Y. MORI, M. TAKASUGI, A. MURAI, S. OUCHI, N. SATO, and N. KATSUI. Bull. Chem. Soc. Jap. **38**, 1374 (1965).
18. W. GRUBER. Can. J. Chem. **31**, 564 (1953).
19. A. P. DUNLOP and F. N. PETERS. The furans. Reinhold, New York. 1953.
20. P. BOSSHARD and C. H. EUGSTER. *In* Advances in heterocyclic chemistry. Vol. 7. *Edited by* A. R. Katritzky and A. J. Boulton. Academic Press, New York. 1966. p. 377.
21. L. A. PAQUETTE. Principles of modern heterocyclic chemistry. W. A. Benjamin, New York. 1968. p. 124.
22. J. W. CORNFORTH. J. Chem. Soc. 1310 (1958).
23. J. W. CORNFORTH and M. FIRTH. J. Chem. Soc. 1098 (1958).
24. J. P. KUTNEY, H. W. HANSSEN, and G. V. NAIR. Tetrahedron, **27**, 3323 (1971).
25. D. M. BURNESS. *In* Organic syntheses. Vol. 39. *Edited by* M. Tishler. John Wiley and Sons, Inc., New York. 1959. p. 49.
26. J. P. KUTNEY, A. BY, J. CABLE, W. A. F. GLADSTONE, T. INABA, S. Y. LEONG, P. ROLLER, E. J. TORUPKA, and W. D. G. WARNOCK. Can. J. Chem. This issue.
27. J. P. KUTNEY, J. CABLE, W. A. F. GLADSTONE, H. W. HANSSEN, E. J. TORUPKA, and W. D. C. WARNOCK. J. Am. Chem. Soc. **90**, 5333 (1968); Chem. Rep. 4, 265 (1970).