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THE SYNTHESIS OF VERATRAMINE*

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Abstract—The transformation of 17-acetyletiojerva-12,14,16-trien-3β-ol (V) into veratramine (I) is described. The starting material (V) was converted by a three-stage process into the two epimeric 20-bromides (XVIII and XIX). Treatment of XVIII or XIX with the pyrrolidine enamine (XXVII) of 1-acetyl-3-(S)-methyl-5-oxopiperidine (XI), prepared from 3-(S)-methylpiperidine (VI) via five steps, produced 3-O,N-diacetyl-23-dehydro-22-epiveratramine (XXII), which was readily isomerized to its 22-epimer (XXI) with the natural veratramine configuration. Reduction of XXI followed by hydrolysis afforded N-acetyl-5α,6-dihydroveratramine (XXb), which was further transformed into I.

THE TITLE alkaloid, veratramine (I), was first isolated along with jervine (II) by Saito[1] and later with 11-deoxojervine (III) in our laboratory[2] from *Veratrum grandifolium* Loes. fil.,[3] and found to possess powerful cardiodecelerator properties.[4,5] Jacobs and his collaborators, who secured it from *V. viride* Aiton, assigned a correct molecular formula $C_{27}H_{39}O_2N$[6] and proposed for the alkaloid formulas with a 19-norsteroid or a hydrochrysen skeleton.[7] These formulas, however, became untenable, and the revised and currently accepted formula I was presented in 1952 by Wintersteiner and his coworkers.[8,9] This structure including a C-nor-D-homosteroid skeleton has been confirmed in subsequent extensive studies on II as well as on interconversions within the alkaloids.[10,11] This interconversion has also established that these alkaloids possess the same configurations at their common asymmetric carbon atoms and, moreover, a series of recent investigations[12] have elucidated the stereochemistry of veratramine as depicted in formula I. Since the structure and configuration have been defined, synthetic approaches[13] to I or verarine[14] (IV, 23-deoxyveratramine) have been published because of their unusual modified skeleton and relative simplicity. Recently we have presented in preliminary from[15] the transformation of 17-acetyletiojerva-12,14,16-trien-3β-ol† (V) into I, and now describe details of these experiments. Compound V has been prepared directly[16] or by degradation[12c,13e] of hecogenin, which had already been derived from totally synthesized isoandrosterone.[17] Hence the present transformation represents, in a formal sense, a total synthesis of veratramine. After publication of our work, the total syntheses of I and IV have also been reported by Johnson,[18] Kutney,[19] and their collaborators, respectively.

The present synthesis involves the preparation of the nitrogen ring of I as the first step. 3-Methylpiperidine (β-pipecoline, *dl*-VI), selected as starting material, was first subjected to optical resolution into the antipode having the same configuration at C_3 as that (S) at C_{25} of I to preclude the stereochemical complexity due to the

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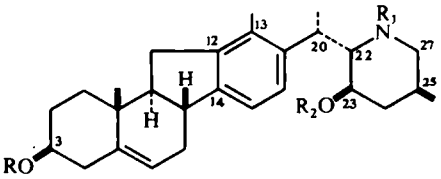
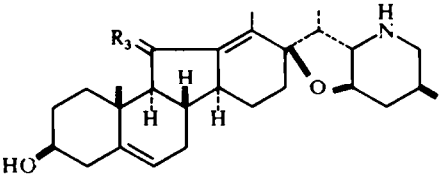
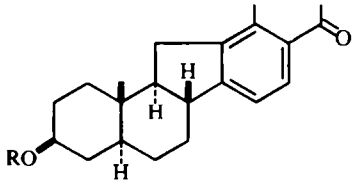
† The structure of this compound has been confirmed by degradation of I into V.[12d,20]



I : R = R_1 = R_2 = H
Ia: R = R_1 = R_2 = Ac
Ib: R = H, R_1 = R_2 = Ac
Ic: R = R_2 = H, R_1 = Ac
IV: R = R_1 = H, OR_2 = H



II : R_3 = O
III: R_3 = H_2



V : R = H
Va: R = Ac

asymmetric carbon: treatment of *dl*-VI with *d*-tartaric acid according to a modification of the Ladenburg procedure[21] afforded two bitartarates, m.ps 173–174° and 74–76°, which on basification regenerated *l*- and d-β-pipecolines, respectively. None of the absolute configurations of these antipodes has been determined but those of the respective N-Me derivatives have been established by Okuda *et al.*[12h] Thus the *d*-pipecoline (VI), $[\alpha]_D$ +0·65° (neat), was methylated with HCOOH and formalin to the N-methylpipecoline (VII), $[\alpha]_D$ −0·92° (neat), which was then converted into the hydrobromide, m.p. 195–196°. By comparison of the ORD curve (plain) in water, $[\alpha]_{589}$ −0·18°, $[\alpha]_{450}$ −0·61° and $[\alpha]_{350}$ −3·66°, with that reported for the corresponding degradation product[12h] from jervine II, *d*-3-methylpiperidine VI proved to possess the desired S-configuration at the carbon atom in question.

Compound VI then had to be transformed into the derivative, whose α-carbon (C_6) could be utilized for linking with C_{20} of the steroid ring. Three substituents, a large steroid part, a OH and a Me group, in the piperidine ring of I have been elucidated to be α-, β- and β-oriented (all equatorial), respectively, in respect to the ring.[12f–12h] Thus we initially planned to prepare a 5β,6β-epoxide with 3β-Me group from VI, with the expectation that, if the oxide ring is cleaved at C_6 by nucleophilic attack of C_{20} of the steroid part, the resulting product would adopt a desirable, all-equatorially substituted conformation.

In order to obtain an olefin available for epoxidation, VI was treated with bleaching powder to give the N-Cl derivative, which underwent dehydrochlorination to yield a mixture of methylpiperideines.[22] Further treatment of the mixture with warm Ac_2O led to formation of a 1:1 mixture of N-acetylmethylpiperideines, separated by column chromatography on silica gel. The more mobile fractions, gave 1-acetyl-3-(S)-methyl-Δ^5-piperidine (VIII), b.p. 88–92° (5 mm) and $[\alpha]_D$ +60·5° (MeOH), in 15%

yield from VI, and the less mobile its Δ^2-isomer (IX), b.p. 99–102° (5 mm) and $[\alpha]_D$ 0·0°, in 14% yield. The former olefin VIII showed absorption maxima at 1670 and 1644 cm^{-1} and at 235 mμ (ε 16,000) due to an α,β-unsaturated acetylamino grouping in the IR and UV spectra as well as a doublet (J = 6 c/s) at τ 8·93 due to the Me group at C_3 in the NMR spectrum. On the other hand, the latter IX likewise included an α-acetylamino olefinic structure as revealed by the IR and UV spectra, ν_{max} 1651 cm^{-1} and λ_{max} 238 mμ (ε 18,600), but lacked a secondary Me group: the NMR spectrum, a singlet at τ 8·31, indicated the presence of a Me group attached to olefinic carbon.

Epoxidation of olefins are well investigated[23] but no example has been reported of oxidation of double bonds adjacent to nitrogen atoms. Oxygen analogs such as enol ethers or enol acetates are readily epoxidized with peracids, although the reaction products are unstable and liable to undergo further degradation.[23c] Likewise, 1-acetyl-Δ^2-piperidine[22] was oxidized with ease, but all attempts to isolate the epoxide failed, giving addition compounds.[24] Oxidation of the olefin VIII with perbenzoic acid in anhydrous ether proceeded at 0° exothermically and gave rise to a crystalline product (X), m.p. 107–109°, (55%) whose IR spectrum, ν_{max} 3300, 1717 and 1634 cm^{-1}, revealed that both hydroxy and benzoyloxy groups had added to the double bond. Compound X was unstable and decomposed gradually at room temperature: pyrolysis at 120–150° under reduced pressure produced 1-acetyl-3-(S)-methyl-5-oxopiperidine (XI) in 50% yield with concomitant elimination of benzoic acid. In accordance with the assigned structure, compound XI exhibited both unconjugated and N-acetyl carbonyl bands at 1727 and 1645 cm^{-1}, respectively. Interestingly, in the NMR spectrum each of the absorptions due to the 3-Me and N-Ac protons appeared as two doublets centered at τ 8·93 and 8·90 and as two singlets at τ 7·88 and 7·85 with equal intensities, respectively. This is explained by assuming the presence of two conformers caused by slow rotation around the bond between the N- and carbonyl-C-atoms. The structure XI was finally confirmed by the synthesis of the racemate *dl*-XI described below, excluding alternate structures such as 1-acetyl-3-methyl-6-oxopiperidine or 1-acetyl-5-formyl-3-methylpyrrolidine.

High pressure catalytic hydrogenation of 5-hydroxy-3-methylpyridine,[7b,25] prepared from β-picoline by a modification of the known procedure,[26] over Raney Ni in dioxane produced the corresponding piperidine (XII), m.p. 94–95·5°, which on acetylation with Ac_2O gave the 3-O,N-diacetyl derivative (XIIa), oil. Compound XIIa, when saponified with alcoholic alkali, was converted into 1-acetyl-5-hydroxy-3-methylpiperidine (XIIb), m.p. 70–73°, which on Jones oxidation[27] afforded a ketone (*dl*-XI). This ketone was identified as the racemate of XI by comparison of the IR and NMR spectra as well as R_f value with those of XI.

The pyrolysis of X would proceed through a cyclic transition state characteristic for the *cis*-type elimination such as thermal decompositions of esters and xanthates.[28] As mentioned, the pyrolysis proceeded at a considerably low temperature compared with those of usual esters and would therefore be facilitated by overlap of the nitrogen lone pair and a partially formed 5,6-double bond in the transition state. This lone pair participation would also operate at the stage of peracid oxidation of VIII, promoting the cleavage of 5,6-oxide ring in an initially formed, epoxy intermediate by benzoate anion. While our attempts to isolate the epoxide failed, compound XI, obtained unexpectedly from VIII, appeared to be an attractive intermediate: it

possessed an oxygen function and an active methylene group at C_5 and C_6, the carbon atoms corresponding to C_{23} and C_{22} of I, respectively.

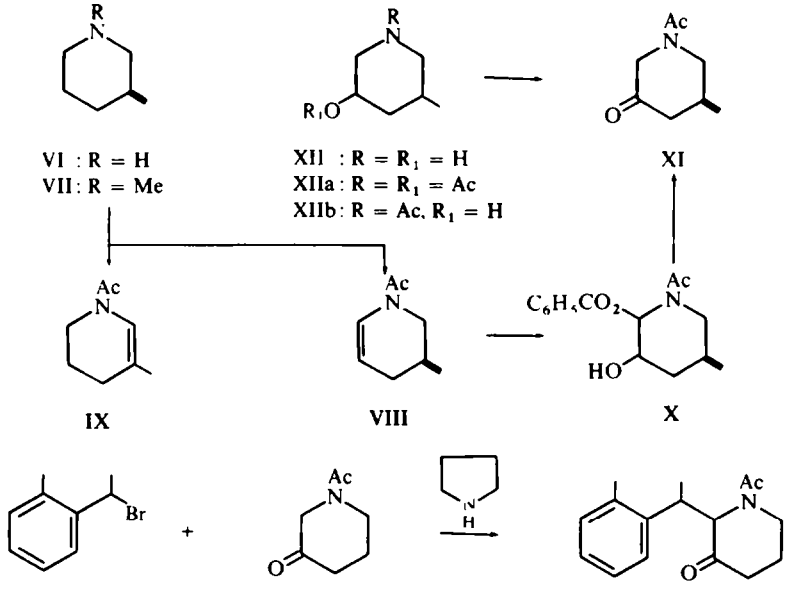


CHART 1 XIII

It was next necessary to develop methods for the construction of the veratramine nucleus starting from both compounds V and XI. With model compounds it was found that 1-(*o*-tolyl)ethyl bromide could condense with 1-acetyl-3-oxopiperidine under the conditions of the Stork reaction[29] to give two diastereoisomeric piperidine derivatives XIII in moderate yields.[24] This fact led to the suggestion that the Stork alkylation reaction might be effective for the present synthesis, although no good result has been reported for *complex* halides. Compound V was first acetylated to the 3-acetate (Va), m.p. 118–119°, which on reduction with $NaBH_4$ gave a mixture of 20-epimeric alcohols. This mixture could be separated by prep. TLC on silica gel, when 20-alcohol XIVa, m.p. 128–129°, and the epimer XVa, m.p. 158–159°, were isolated in 49 and 46% yields from the more and less mobile fractions, respectively. The reduction of Va in *ethanol* alone was always accompanied by hydrolysis of the acetoxy group at C_3, leading to the formation of low yields of the 3-deacetyl 20-alcohols (XIV and XV).

Difficulty was encountered in the bromination of the 20-alcohols. Treatment of XIVa with PBr_3 in Et_2O or C_6H_6 followed by examination of the product by TLC (silica gel) revealed that it consisted mainly of starting alcohol XIVa and its epimer XVa in an almost equal ratio. When the amount of the tribromide was increased, three bands were detected on TLC. The most mobile band gave a crystalline product, possibly a styrene derivative (XVI) on the basis of the mass and UV spectra, *m/e* 338 (M^+) and λ_{max} 255 mμ (ε 13,000). From the least mobile, only the 3-deacetyl derivatives XIV and XV were isolated. The middle band gave a resinous substance, which proved to contain neither Br nor OH by elemental analysis and IR respectively.

The NMR spectrum exhibited a doublet (J = 6·5 c/s) at τ 8·61 and a quartet (J = 6 c/s) at τ 5·36, amounting to 3H and 1H, respectively. If the substance was expected 20-bromide(s), the respective signals would have to be assigned to 21-Me and 20-methine protons. The corresponding protons of 1-(*o*-tolyl)ethyl bromide appear at τ 7·93 and 4·62, while those of 1-(*o*-tolyl)ethyl alcohol at τ 8·71 and 5·09.[24] These chemical shifts as well as those (τ 8·56 and 4·87) of XIVa suggest that the compound be represented by formula XVII. In view of the facts that 1-phenylethyl alcohol gives bis(1-phenylethyl)ether on contact with acid-washed alumina[31] and that *d*-1-phenylethyl bromide racemizes on the solid surface,[32] it would be reasonable that the initially formed bromide reacted immediately with H_2O on silica gel to yield the benzyl alcohol and HBr, which catalyzed the formation of ether XVII. Increase of PBr_3 would result in the increase of HBr concentration on silica gel and promote ether formation. Finally, the expected bromide could be obtained without using prep. TLC: treatment of XIVa with 1·3 equiv of PBr_3 in ether at 0° followed by rapid washing with $NaHCO_3$ and H_2O with cooling afforded a crystalline 20-bromide (XVIII), m.p. 131–133°, (94%). Similarly, the epimeric alcohol XVa was converted into the 20-epimeric bromide (XIX), m.p. 124–126°, (90%). In accordance with the assigned structures, both bromides XVIII and XIX displayed a doublet (J = 7 c/s) at τ 7·89 and a quartet (J = 6 c/s) at τ 4·52 in the NMR spectra.

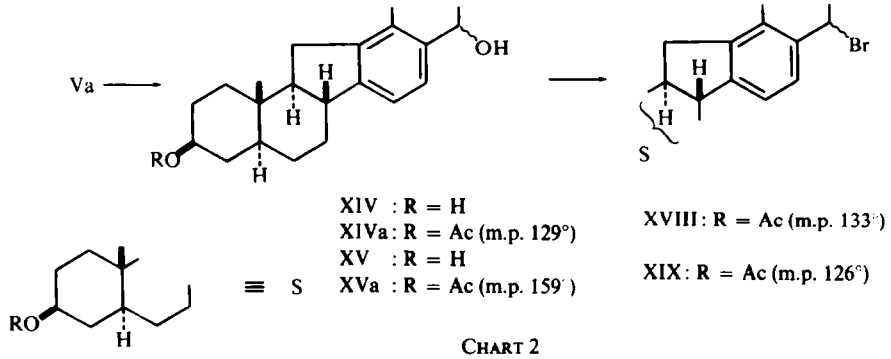
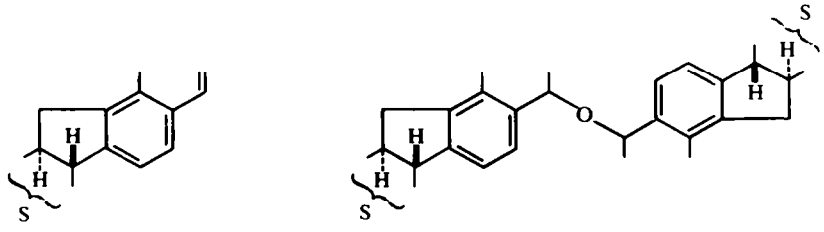


CHART 2

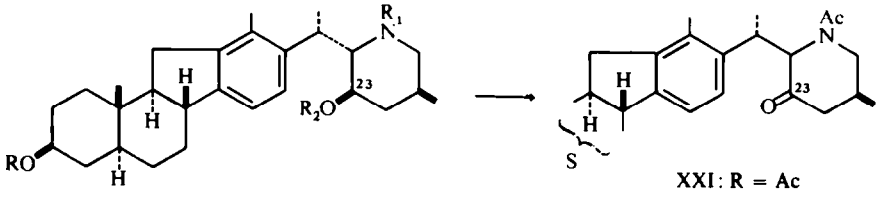
Before proceeding with the condensation of bromide XVIII (or XIX) and oxopiperidine XI, it was deemed efficient to prepare the expected condensation products in advace by derivation from I, because only small amounts of the bromides were available. Acetylation of 5α,6-dihydroveratramine[12d] (XX) with Ac_2O and pyridine under mild conditions gave rise to the 3-O,N-diacetyl derivative (XXa), m.p. 233–



XVI XVII : R = Ac

234°, (50%) after chromatography, which on Jones oxidation[27] formed the corresponding 23-ketone (XXI), m.p. 185–187°, (81%). The 23-ketone XXI on treatment with NaOMe in refluxing MeOH followed by acetylation gave a mixture of 23-ketones, from which the 22-epimeric 23-ketone (XXII), m.p. 222–224°, could be separated in 53% yield by prep. TLC along with a 43% yield of starting ketone XXI. Conversely, when the isomeric ketone XXII was kept under the same conditions, both ketones XXII and XXI were isolated in a ratio of 2:1.

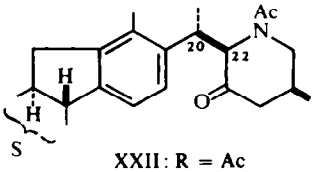
The spectroscopic properties of these ketones deserve some comment. (1) Ketones XXI and XXII showed distinct absorption maxima at 302 mμ (ε 213) and 302 mμ (ε 308), respectively. Similar results had been reported on the corresponding 5,6-dehydro derivatives [302 mμ (ε 250) and 303 mμ (ε 290)],[14b] and N-acetyl-3,23-dehydro-5α,6-dihydroveratramine [304 mμ (ε 230)].[8] Since neither 5-oxopiperidine XI nor the N-acetyl-3-dehydro derivative of XX exhibited such absorption, this anomalous behavior would be explicable as a result of interaction between the 23-ketonic group and the aromatic D-ring. (2) Both ketones XXI and XXII displayed essentially the same mass spectra: while no molecular ion could be detected at *m/e* 493, strong base and two significant peaks appeared at *m/e* 339 ($C_{23}H_{31}O_2$), 279 (339-$C_2H_4O_2$) and 155 ($C_8H_{13}O_2N$), which could probably be attributed to fragments XXIII, XXIV and XXV, respectively. These spectral patterns are noteworthy compared with those of IV and the closely related compounds with 23-methylene substituted by hydroxy, acetoxy or ethylenedithio groups: in these spectra, fragments represented by formula XXVI appeared as very strong, base peaks, but that corresponding to XXIII with only weak intensity.[12d, 14b, 33]



XX : R = R_1 = R_2 = H
XXa : R = R_1 = Ac, R_2 = H
XXb : R = R_2 = H, R_1 = Ac
XXc : R = R_1 = R_2 = Ac
XXd : R = H, R_1 = R_2 = Ac
XXX : 23βH, R = R_2 = H, R_1 = Ac

XXI : R = Ac

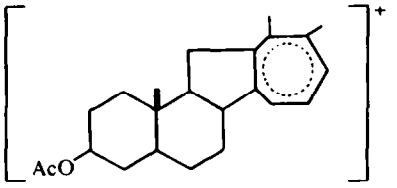
NaOMe



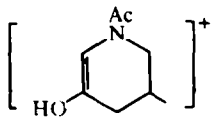
XXII : R = Ac
XXVIII : R = Ac,20βMe

CHART 3

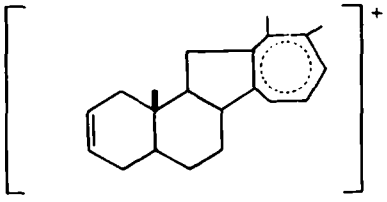
Ketone XI, when refluxed with pyrrolidine in C_6H_6 with continuous removal of H_2O, was converted into the enamine (XXVII), oil, which showed only a carbonyl band due to the N-Ac group at 1638 cm^{-1}. On the analogy of the NMR spectrum of pyrrolidine enamine of 1-acetyl-5-oxopiperidine,[24] the double bond in XXVII would be disposed practically at C_5 and C_6.



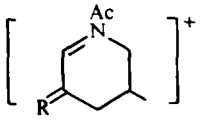
XXIII



XXV



XXIV



XXVI

R = H, OH : H, OAc, SC_2H_4S

20-Bromide XIX was heated with large excess of the enamine XXVII in dioxane at 100° (sealed tube) and treated with H_2O at the temperature. The resinous product was separated into 3 fractions by preparative TLC. The most mobile fraction afforded a resin in about 30% yield, which proved to consist mainly of styrene XVI. The middle fraction, showing a single spot, gave a semi-crystalline material in 24% yield, which had m.p. 133–135° on washing with ether. This compound (XXVIII) indicated essentially the same R_f value on TLC, UV, mass and NMR spectra as 23-ketone XXI, and this spectral data led us to suppose that the expected ketone might be produced. However, the product XXVIII definitely differed from XXI in the m.p., ORD curve [XXVIII (+)-Cotton effect, and XXI (−)-Cotton effect] and finger print of the IR, suggesting that XXVIII would probably be a 21-epimer of XXI or XXII.* The least mobile fraction, showing the same R_f value on TLC as the epimeric 23-ketone XXII, gave also a semi-crystalline material in 23% yield and had m.p. 223–225°, after washing with ether and recrystallizing from ether–acetone, which was undepressed on admixture with XXII, m.p. 222–224°, derived from I. The product was identified as XXII, as the mass, UV, IR and NMR spectra as well as the ORD curve were all superimposable on the respective spectra or curve of XXII.

The epimeric bromide XVIII was treated with the enamine XXVII under the same conditions as described above, and produced almost the same result as XIX. Thus, using the mixture of 20-bromides XVIII and XIX prepared directly from the reduction products of Va, 22-epi-23-ketone XXII could be obtained in pure state from Va (20%). This ketone was further transformed, by the repeated epimerizations, into 23-ketone XXI with the natural configuration at C_{22} (75%).

Here we discuss the above condensations in some detail. The reactions must proceed through an S_N1 mechanism, probably involving a common intermediate,

* The formation of XXI (5%) described in the communication[15] would probably result secondarily from epimerization of XXII.

20-carbonium ion (XXIX), formed in advance by elimination of bromide ion. This carbonium ion would link up with enamine XXVII with continued overlap between the axially oriented π-orbital at C_6 of the latter and the p-orbital at C_{20} of the former, just in the same manner as elaborated by Zimmerman[34] in many examples of re-ketonization of enols. Hence the product would probably be kinetically controlled, explaining why no XXI could be isolated, although XXI exists with XXII in a ratio of *ca.* 1:2 under equilibrating conditions. Moreover, this axial approach would have to result in the formation of a 23-ketone with the steroid part *cis*-oriented to the 25-Me group regarding the piperidine ring, because the Me group would adopt a stable equatorial conformation in XXVII; in fact, the product XXII possessed such configuration. On this premise the alternate product XXVIII would probably be a 21-epimer of XXII rather than that of XXI.

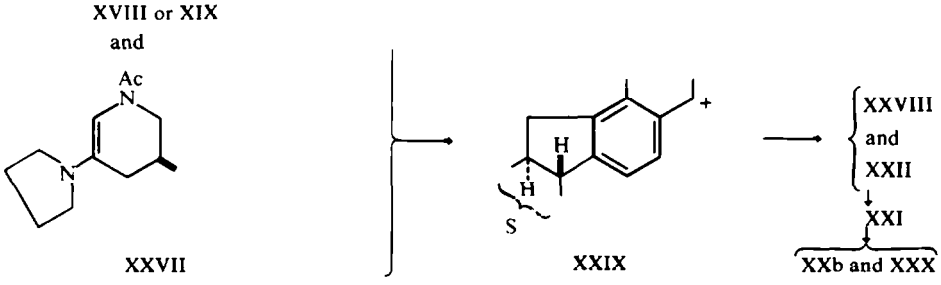


CHART 4

Reduction of the carbonyl group in XXI was conducted under various conditions. Treatment of XXI with $NaBH_4$ in EtOH afforded an alcohol showing a single spot, which, however, on hydrolysis was separated into two fractions. One, (63%), m.p. 202–204°, was identified as N-acetyl-5α,6-dihydro-23-epiveratramine (XXX) on the basis of spectral data and reduction behavior of a closely related ketone.[12g] Another product, (20%) m.p. 219–221°, proved to be N-acetyl-5α,6-dihydroveratramine (XXb) by comparison with an authentic sample.[8] This result could be rationalized by assuming the following. In ketone XXI the steroid part at C_{22} and the Me group at C_{25} are disposed *trans* in respect to the piperidine ring. Moreover, the N-acetyl and 18-Me protons appeared as four sharp signals from τ 8·52 to 7·75 in the NMR spectrum. This suggested that XXI would exist as an equilibrium mixture of two conformers, one with the substituents at C_{22}, C_{25} and the N-Ac group all equatorial, and another with all the groups axial.[35] It would be reasonable to consider the former as a predominant conformer. In view of the UV spectrum as well as the ORD curve [(−)-Cotton effect with large amplitude, a = −183°], the aromatic D-ring and 23-carbonyl group in XXI must be oriented in such close positions that the respective π-electrons can be overlapped [*cf.* the ORD curve of XI, (+)-Cotton effect, a = +34°]. Examination of molecular models reveals that in the former conformation the 21-Me group would obstruct the approach of hydride ion from the α-side and in the latter the N-Ac and 25β-Me groups from the β-side, leading to the formation of XXX and XXb as main products, respectively. Then, the ketone XXI was treated with Li in liquid NH_3 at the dry ice-acetone temperature. In this case the desired alcohol XXb

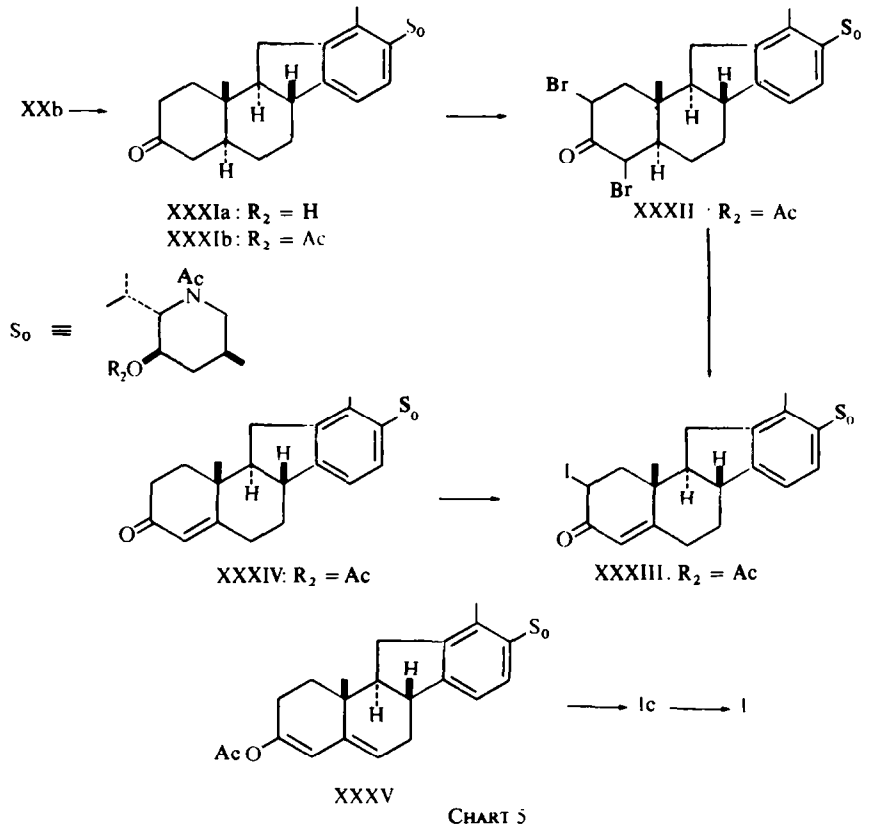
could be isolated in comparable yield (24%)* along with XXX. However, this yield would not be inexplicable, because the Birch reduction of sterically hindered ketones in the absence of alcohol often gives, as major products, alcohols formed by protonation of the intermediate anion radicals from the less hindered side.[37] Thus the reductions were undertaken under the more drastic conditions (in refluxing NH_3) or in the presence of alcohol (MeOH), but all these attempts resulted in the reduction of the D-ring to some extent as well as the epimerization at C_{22}, forming many by-products.

The final step of the synthesis consisted in the introduction of a double bond into C_5–C_6. Selective oxidation of the 3-hydroxy group in XXb to the 3-dehydro derivative[8] (XXXIa) followed by conversion to its 5,6-dehydro derivative seemed to be an ineffective route, because oxidation gives XXXIa only in a low yield with concomitant oxidation of the 23-OH group leading to the 3,23-dehydro derivative.[8] Thus XXb was converted into 3-dehydro-23-O,N-diacetyl-5α,6-dihydroveratramin[7b] (XXXIb) through the triacetyl[8] (XXc) and 23-O,N-diacetyl derivatives[12a] (XXd) of XX by the known process.[12d] It is notable that an attempt to dehydrogenate XXXIb with 2,3-dichloro-5,6-dicyanobenzoquinone proved to be unsuccessful, although the procedure could be applied well to the corresponding jervine derivative.[15] Finally, the formation of the double bond was achieved by the known technique as described below.

3-Ketone XXXIb, when brominated with Br_2 in AcOH containing HBr at room temperature,[38] produced a glassy crude dibromoketone (XXXII) in 86% yield. Further treatment of the crude bromo compound with NaI in refluxing acetone gave a resinous substance, formulated tentatively as 2-iodo-Δ^4-3-ketone (XXXIII) and immediately reduced with chromous chloride[39] under CO_2. The product was separated by prep. TLC to give both an α,β-unsaturated ketone and a saturated ketone. The latter, (26% yield from XXXII), was identified as the starting 3-ketone XXXIb, and the former, isolated in 36% yield in amorphous state, as 23-O,N-diacetyl-Δ^4-veratramin-3-one (XXXIV) by comparison with a sample prepared by acetylation of Δ^4-veratramin-3-one.[8]

Transformation of α,β-unsaturated ketone XXXIV into I proceeded without difficulty. Treatment of XXXIV with isopropenyl acetate in the presence of H_2SO_4[40] afforded the enol acetate (XXXV), m.p. 180–182°, (72%), which exhibited an absorption maximum due to the 3-acetoxy group at 1758 cm^{-1} and two singlet peaks due to the protons at C_4 and C_6, at τ 4·27 and 4·46, respectively, in the IR and NMR spectra. An attempted reduction of XXXV to Δ^5-3-alcohol by its addition to $NaBH_4$ in aqueous EtOH (normal mixing)[41] and subsequent decomposition of excess reagent with AcOH resulted in formation of a complex mixture, from which only a crystalline product, m.p. 165–168°, was isolated (30%) after prep. TLC. This compound, however, differed in the IR spectrum from the expected 3-alcohol, 23-O,N-diacetylveratramine (Ib), m.p. 166–167°, prepared by partial hydrolysis of triacetylveratramine[1,6] (Ia), although it had the same m.p. and R_f value on TLC as Ib. On the other hand, addition of the hydride to XXXV in aqueous EtOH (inverse mixing)[41] followed by treatment of the product according to the Belleau and Gallagner procedure[42] effected the relevant reduction, producing N-acetylveratramine[6] (Ic), (59%). Contrary to the

* The yield "70%" described in the communication[15] should be revised to 17%.



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presumption, the hydrolysis of Ic was troublesome. The compound remained intact under the conditions (KOH in refluxing aqueous DMSO) suitable for the complete hydrolysis of N-acetyljervine,[15] while it produced an intractable tarry substance, when heated with alkali in ethylene glycol. However, the same treatment in the solvent containing hydrazine hydrate led to the smooth saponification of Ic and the product, isolated in 97% yield, was identical with natural veratramine in all respects. The conversion of 17-acetyletiojerva-12,14,16-trien-3β-ol into veratramine has now been completed, and the series of these reactions imply, in a formal sense, the first total synthesis of the veratrum alkaloid with the C-nor-D-homosteroid skeleton.

EXPERIMENTAL

All m.ps were measured in open capillaries and uncorrected. Homogeneity was checked by TLC on silica gel (Wakogel B-5) and/or alumina (Merck G) developed with cerric sulfate in dil H_2SO_4 and/or I_2. Column chromatography was carried out on silicic acid (Mallinckrodt, A. R. 100 mesh), acid-washed alumina (Woelm, activity I), and/or alumina (Merck, activity II–III). Optical rotations were measured in 95% EtOH, unless otherwise stated. IR spectra were taken in Nujol on a JASCO Model DS-402G spectrophotometer, and UV spectra and ORD curves in 99% EtOH and MeOH on a JASCO Model ORD/UV-5 spectropolarimeter, respectively, unless otherwise stated. NMR spectra were determined in $CDCl_3$, unless otherwise stated, on a JEOL Model JNM-3H-60, a Varian A-60 and/or a Varian HR-100 spectrometer, TMS being used as an internal reference, and all the chemical shifts are given in τ-values.

Optical resolution of 3-*methylpiperidine* (dl-VI). Although the optical resolution of *dl*-VI was extensively investigated by Ladenburg,[21] no experimental details were described. To a soln of *d*-tartaric acid (113 g)

in a mixture of EtOH (99%, 830 ml) and H_2O (44 ml) was added dropwise *dl*-VI (75·0 g), cooling. The soln kept at room temp. for 48 hr, when crystalline tartarate (94·0 g) m.p. 160–167° and (1·03 g) m.p. 76–78° separated out as 1st and 2nd crops, respectively. Three recrystallizations of the former from EtOH containing a little H_2O gave bitartarate of 3-(R)-methylpiperidine (57·4 g), m.p. 173–174° (lit.[21] 172°). The mother liquors obtained were concentrated to 141 g and, after addition of EtOH (15 ml) and H_2O (3·5 ml), (room temp., 48 hr) gave tartarate (77·0 g) melting at 69–78° and, after another 48 hr, that (2·94 g) melting at 151–154°. The latter crystallized in two forms, needles, m.p. 132–135°, and plates, m.p. 75–77°, from only EtOH and aqueous EtOH, respectively.

Recrystallization of the tartarate (77·0 g) of m.p. 69–78° from 90% EtOH (60 ml) gave the salt (60·9 g), melting at 76–86° (slight turbidity at 96°), which on further recrystallization from 80% EtOH (50 ml) afforded two kinds of crystals, needles and plates. The latter was collected, washed with 80% EtOH, m.p. 76–80° (45·3 g). Two recrystallizations from 80% EtOH produced tartarate of 3-(S)-methylpiperidine (44·1 g), m.p. 74–76°. To the tartarate (40·0 g) of m.p. 76° dissolved in H_2O (30 ml) was added KOH (25 g) in H_2O (25 ml) with cooling, when oil separated and extracted with ether (5 × 20 ml). The ether soln was dried (Na_2SO_4 and KOH), and solvent removed below 65°. The residue was fractionally distilled and a fraction (VI) b.p. 122–124° was collected (13·43 g); [α] (neat) + 0·65°, + 0·72°, + 0·95°, + 1·46°, + 3·48° and + 4·99° at 589, 550, 500, 450, 400 and 350 mμ, respectively, (15°).

1-*Methyl*-3-(S)-*methylpiperidine* (VII) *and its hydrobromide.* Compound VI (1·00 g) was refluxed with HCOOH (85%, 1·50 ml) and formalin (37%, 1·20 ml) for 1·5 hr. The soln was cooled, basified with KOH (5 g in 5 ml of H_2O) and extracted with ether (4 × 15 ml). Dried (Na_2SO_4 and KOH evaporated fractionally distilled to give an oily base (VII, 1·09 g) b.p. 120–124 ; [α] (neat) − 0·92°, − 1·16°, − 1·62°, − 2·74°, − 4·76° and − 9·28° at 589, 550, 500, 450, 400 and 350 mμ, at 15°. Optical rotations have changed from (+) to (−) on N-methylation of VI.

Into a soln of VII (1·00 g) in ether (15 ml) cooled with ice-water was passed dry HBr, (from tetralin and Br_2),[43] when crystalline ppts became suspended in the soln. Gas was further passed until the ether soln became homogeneous. After evaporation, the residue crystallized on addition of a small amount of EtOH and ether, m.p. 194–195° (1·34 g). Recrystallization from EtOH-ether afforded a pure sample of VII·HBr (1·23 g), needles, m.p. 195–196° (lit.[12h] 198–200°), 18° in H_2O; [α] − 0·18°, − 0·21°, − 0·32°, − 0·61°, − 1·69° and − 3·66° at 589, 550, 500, 450, 400 and 350 mμ (*cf.* lit.[15] + 0·012, 0·0° and − 1·7° at 589, 480 and 350 mμ). The [α] values[12h] reported for the corresponding compound obtained by degradation of II is 0·19°, − 0·20°, − 0·26°, − 0·35°, − 1·39° and − 2·44° at 589, 550, 500, 450, 400 and 350 mμ, respectively, at 20°.

1-*Acetyl*-3-(S)-*methyl*-Δ^5-*piperidine* (VIII) *and its* Δ^2-*isomer* (IX). Bleaching powder (100 g) was suspended in H_2O (500 ml) and filtered to remove insoluble material: 1·0 ml of the filtrate was equivalent to 29·8 ml of 0·1 N $Na_2S_2O_3$ aq. To the cooled soln (135 ml, 2 equivs) was added a soln of VI (10·0 g) mixed with ice in AcOH (6·05 ml, 1 equiv) with cooling (− 4 ~ − 1°) during 18 min, when oil separated out. The mixture was shaken with ether (4 × 30 ml), free from peroxide by treatment with $NaHSO_3$ aq and H_2O. The ether soln, after drying over Na_2SO_4 and evaporation below 50° under reduced press, gave an oily residue (14·3 g), which proved to contain 9·43 g (69%) of the NCl derivative by titrating the residue (169·6 mg) in an AcOH soln containing KI with 0·1 N $Na_2S_2O_3$ aq (16·86 ml).

Into a 300 ml three-necked flask equipped with mechanical stirrer, reflux condenser and N_2 inlet tube were added KOH (6·6 g) and 95% EtOH (60 ml), and the mixture heated to boiling. The N_2 tube was replaced by a dropping funnel and crude N-chloropiperidine (14·0 g) added to the soln over 5 min, when vigorous reaction occurred. The mixture was again refluxed (stirring, N_2) for another 10 min and maintained at room temp for 1 hr. After removal of KCl, which separated during the reaction, the filtrate was evaporated below 50° at reduced press. The residue was diluted with H_2O (60 ml) containing the afore-mentioned KCl and extracted repeatedly with peroxide-free ether (100 ml). The ether soln was dried (Na_2SO_4) and evap. to leave an oily residue (13·3 g), which was immediately mixed with Ac_2O.

The Ac_2O soln was heated on a water-bath for 30 min and evaporated below 92° to remove Ac_2O and AcOH under reduced press, leaving an oily substance (14·08 g), neutralised by Na_2CO_3 (anhydrous, 3·5 g) in H_2O (10 ml) and shaken with $CHCl_3$ (3 × 15 ml). The $CHCl_3$ solns were combined, dried and evaporated to give an oily substance, which distilled and separated into 2 fractions: (3·77 g), b.p. 80–88/4 mm, and (2·87 g), b.p. 88–92°/4 mm. Each distillate was further separated by column chromatography on silica gel (200 g, 5 × 23 cm), using $CHCl_3$ as eluent. The more mobile fractions, on removal of solvent followed by distillation, afforded pure VIII (2·13 g), b.p. 88–92°/5 mm; [α] + 60·5°, + 72·3°, + 92·7°, + 126·4°, + 182·0° and + 322·0° at 589, 550, 500, 450, 400 and 350 mμ (MeOH) at 19°; λ_{max} 235 mμ (ε 16,000); ν_{max}^{film} 1670 and

1644 cm^{-1}; NMR (CCl_4), τ 8·93 (3H, d J = 6 c/s, 3-Me), 7·90 (3H, s, NAc), 3·47 (1H, d J = 9 c/s, 6-H) and 5·20 (1H, m, 5-H). A small doublet appeared at τ 2·92 (J = 9 c/s) probably absorption due to proton at C_6 of a conformational isomer. (Found: C, 68·83; H, 9·17; N, 10·34. $C_8H_{13}ON$ requires: C, 69·03; H, 9·41; N, 10·06%).

The less mobile fractions afforded an isomeric olefin (IX, 2·03 g) pure, b.p. 99–102°/5 mm: $[\alpha]_D^{19}$ 0·0°; λ_{max} 238 mμ (ε 18,600); ν_{max}^{film} 1651 cm^{-1}; NMR (CCl_4), τ 8·31 (3H, s, 3-Me), 7·97 (3H, s, NAc) and 3·65 (1H, s, 2-H). Small broad peak at τ 3·07 absorption of C_2 proton of conformational isomer. (Found: C, 68·85; H, 9·28; N, 9·85. $C_8H_{13}ON$ requires: C, 69·03; H, 9·41; N, 10·06%).

1-*Acetyl*-3-(S)-*methyl*-5-*oxopiperidine* (XI). To a soln of VIII (1·50 g) in dry ether (10 ml) was added freshly-prepared perbenzoic acid[44] (93%, 1·50 g) in dry ether (7 ml) and, after 1 hr, additional acid (0·10 g), cooling. Maintained in refrigerator for 2 days, when crystalline hydroxybenzoate (X, 1·32 g), m.p. 107–109°, separated and was collected. The filtrate was oxidized continuously after addition of the acid (0·10 g) overnight, until unreacted VIII disappeared on TLC, and additional X (0·28 g), m.p. 107–109° obtained. The benzoate X, ν_{max} 3300, 1717, 1634, 1268, 937 and 710 cm^{-1}, was sensitive to heat and moisture preventing purification.

Compound X (0·50 g) heated at 3 mm in a sublimation apparatus for 30 min. to 155°, the pyrolysis products (0·39 g) remained adhesive to the cold finger. The products (1·07 g from 1·40 g of X), were dissolved in ether (40 ml), neutralized by addition of powdered anhydrous Na_2CO_3 (*ca.* 6 g) under vigorous stirring, filtered, dried and evaporated. The residue (486 mg) was distilled under reduced press. to yield XI (383 mg), b.p. 100–110° (bath-temp)/2 mm; ORD (dioxane), $[\phi]_{322}^{peak}$ 1770°, $[\phi]_{311}^{peak}$ 1690°, $[\phi]_{276}^{trough}$ − 1630°, a = + 34·0° (the amplitude in MeOH decreased gradually, probably owing to the formation of methyl-hemiketal and/or dimethylketal); ν_{max}^{film} 1727, 1645, 1223 and 1034 cm^{-1}; NMR spectrum showed two doublets with nearly equal intensities due to the Me protons at C_3 at τ 8·93 (J = 6 c/s) and 8·90 (J = 6 c/s), and two singlets due to the N-Ac group at τ 7·88 and 7·85. (Found: C, 61·63; H, 8·22; N, 8·98. $C_8H_{13}O_2N$ requires: C, 61·91; H, 8·44; N, 9·03%).

5-*Hydroxy*-3-*methylpiperidine* (XII) *and its* 3-O,N-*diacetyl and* N-*acetyl derivatives* (XIIa *and* XIIb). To a soln of 5-hydroxy-3-methylpyridine[7, 25] (15·0 g), m.p. 134–136°, in dioxane (150 ml) placed in an autoclave (300 ml) was added W-4 Raney nickel (*ca.* 15 g), previously rinsed with dioxane. H_2 (128 atm.) was applied and autoclave heated to 170° and shaken for 7 hr, 9·9 l of H_2 being absorbed. The mixture cooled overnight and catalyst filtered. The filtrate was evaporated to leave an oily residue, which crystallized from acetone to afford XII (4·45 g), m.p. 93–95°. An analytical sample, from acetone, m.p. 94–95·5°; ν_{max} 3285, 3090, 1043 and 905 cm^{-1}, and $\nu_{max}^{CHCl_3}$ 3580, 3320, 3170, 1103, 1021 and 895 cm^{-1}; NMR, τ 9·11 (3H, d J = 6 c/s, 3-Me). (Found: C, 62·70; H, 11·36; N, 12·14. $C_6H_{13}ON$ requires: C, 62·57; H, 11·38; N, 12·16%).

Compound XII (1·02 g) was dissolved in Ac_2O (5 ml) and heated under reflux for 1 hr. MeOH (5 ml) was added and the mixture further refluxed for 1 hr. After concentration under reduced press anhydrous Na_2CO_3 (3 g) and H_2O (10 ml) were added to the residue and the mixture was extracted with $CHCl_3$ repeatedly (35 ml). The combined soln was dried and evaporated to an oil (2·08 g), distilled to give XIIa colorless oil (1·60 g), b.p. 155–160° (bath temp)/3 mm; ν_{max}^{film} 1740, 1651, 1236, 1089 and 1044 cm^{-1}; NMR, τ 9·03 (3H, d J = 5·5 c/s, 3-Me), 8·00 and 7·98 (each 3H, s, OAc and NAc). (Found: C, 60·33; H, 8·61; N, 7·13. $C_{10}H_{17}O_3N$ requires: C, 60·28; H, 8·60; N, 7·03%).

A soln of diacetate XIIa (1·01 g) in 5% KOH in MeOH (10 ml) was heated under reflux for 1 hr. After removal of most of the solvent, 6N HCl was added and the neutralized mixture extracted with $CHCl_3$ (3 × 10 ml). The combined soln was dried and evaporated to a colorless oil (XIIb, 0·91 g), distillation (bath temp 173–176°/4 mm) gave an oil (713 mg). On standing it crystallized m.p. 70–73°; ν_{max} 3370, 1618, 1250, 1100 and 1037 cm^{-1}; NMR, τ 9·02 (3H, d J = 6 c/s, 3-Me) and 7·87 (3H, s, NAc). (Found: C, 61·05; H, 9·35; N, 8·91. $C_8H_{15}O_2N$ requires: C, 61·12; H, 9·62; N, 8·91%).

Racemic 1-*acetyl*-3-*methyl*-5-*oxopiperidine* (*dl*-XI). To a soln of XIIb (503 mg) in acetone (10 ml), distilled over $KMnO_4$, was added Jones reagent (1·0 ml) cooling with ice-water bath. The mixture was allowed to stand, 0°, for 1·5 hr, and EtOH (2 ml) added. The reaction mixture was concentrated under reduced press and, after addition of saturated brine (4 ml), extracted with $CHCl_3$ (3 × 10 ml). The $CHCl_3$ soln was dried over anhydrous Na_2SO_4 containing a small amount of Na_2CO_3. Evaporation gave an oil, purified by distillation under reduced press (295 mg), IR NMR and R_f identical with XI.

17-*Acetyletiojerva*-12,14,16-*trien*-3β-*ol* 3-*acetate* (Va). A soln of V (1·20 g) in Ac_2O (12 ml) and Py (12 ml) maintained at room temp for 1 hr, and then heated (steam bath) for 0·5 hr. The soln was poured into ice-water, stirred for 40 min and extracted with ether (total 150 ml). The ether soln was washed with 2N HCl, 5% Na_2CO_3 aq and H_2O, dried and evaporated under reduced press to afford an amorphous residue (1·36 g), trituration with EtOH gave crystals of Va (1·01 g), m.p. 112–115°. Two recrystallizations from

EtOH, m.p. 118–119° (lit.[15] 114–115°); $[\alpha]_D$ + 31° ($CHCl_3$); λ_{max} 258 mμ (ε 16,700); ν_{max} 1731, 1682, 1600, 1253 and 1033 cm^{-1}; NMR; τ 9·02 (3H, s, 19-Me), 7·93 (3H, s, OAc), 7·56 (3H, s, 18-Me), 7·42 (3H, s, 21-Me), and 3·02 and 2·48 (each 1H, d J = 8 c/s, aromatic H). (Found: C, 78·01; H, 8·48. $C_{23}H_{30}O_3$ requires: C, 77·93; H, 8·53%).

Sodium borohydride reduction of Va. (a) To acetate Va (199 mg) dissolved in a 1:4 mixture (10 ml) of EtOAc and EtOH was added $NaBH_4$ (105 mg) in the same solvent mixture (20 ml), and maintained at room temp for 5 hr. Excess reagent was decomposed by dropwise addition of AcOH, and most of the solvent then removed. The residue was taken up in ether, washed with 5% Na_2CO_3 aq (5 ml) and H_2O, dried and evaporated to yield an amorphous residue (210 mg), which was subjected to prep. TLC (silica gel) (21 plates, 20 × 20 cm, developed twice with $CHCl_3$). The separated bands were extracted with MeOH-ether (1:19). The more mobile gave 20-alcohol (XIVa, 98 mg), m.p. 119–122°, and the less mobile an epimeric 20-alcohol (XVa, 92 mg), m.p. 147–151°. The former, XIVa from EtOH aq m.p. 128–129° (lit.[15] 122–124°): $[\alpha]_D$ 0·0°, ν_{max} 3380, 1721, 1258 and 1031 cm^{-1}: NMR, τ 9·06 (3H, s, 19-Me), 8·56 (3H, d J = 6·5 c/s, 21-Me), 7·98 (3H, s, OAc), 7·77 (3H, s, 18-Me), 4·87 (1H, q J = 7 c/s, 20-H), and 3·00 and 2·65 (each 1H, d J = 9 c/s, aromatic H). (Found: C, 77·33; H, 8·98. $C_{23}H_{32}O_3$ requires: C, 77·49; H, 9·05%). The latter alcohol XVa from EtOH aq. m.p. 158–159° (lit.[15] 156–158°); $[\alpha]_D$ + 55°; ν_{max} 3560, 1732, 1236 and 1026 cm^{-1}; NMR, τ 9·06 (3H, s, 19-Me), 8·56 (3H, d J = 6·5 c/s, 21-Me), 8·00 (3H, s, OAc), 7·80 (3H, s, 18-Me), 4·88 (1H, q J = 7 c/s, 20-H), and 3·03 and 2·70 (each 1H, d J = 8·5 c/s, aromatic H). (Found: C, 77·48; H, 8·83. $C_{23}H_{32}O_3$ requires: C, 77·49; H, 9·05%).

(b) To a soln of Va (50 mg) in EtOH (2·5 ml) was added $NaBH_4$ (25 mg) in EtOH (2 ml), and maintained at room temp for 2·5 hr. Excess reagent decomposed with acetone (0·5 ml) and most of the solvent removed. The residue was taken into $CHCl_3$, washed with water, dried and evaporated to yield four products (55 mg), separated by prep. TLC ($CHCl_3$) to give XIVa (14 mg), XVa (13 mg) and a mixture of the respective 3-deacetyl derivatives (XIV and XV).

Bromination of the 20-*alcohols* XIVa *and* XVa. (a) To a stirred soln of XIVa (50 mg) in C_6H_6 (2·5 ml) was added PBr_3 (0·5 ml), and stirred for 6·5 hr. The mixture was developed on 5 silica gel plates (20 × 20 cm, $CHCl_3$). The most mobile band gave crystalline styrene (XVI, 3·3 mg); mass *m/e* 338 (M^+); λ_{max} 255 mμ (ε 13,000). The middle band afforded a colorless, resinous ether (XVII, 41 mg), ν_{max} 1735, 1240, 1113 and 1028 cm^{-1} no absorption near 3000 cm^{-1}; NMR, τ 9·06 (s, 19-Me), 8·61 (d J = 6·5 c/s, 21-Me), 7·98 (s, OAc), 7·85 (s, 18-Me), 5·36 (q J = 6 c/s, 20-H overlapped with 3-H), 3·04 and 2·76 (each d J = 8 c/s, aromatic H). From the least mobile band a mixture (7 mg) of 3, 20-glycols XIV and XV was recovered. When a mixture of 20-alcohols XIVa and XVa was used instead of a pure sample of XIVa, a similar result was obtained.

(b) A soln (0·4 ml), prepared by adding PBr_3 (0·1 ml) freshly distilled to anhydrous ether (1 ml), was added dropwise at 0° to a stirred soln of XIVa (103 mg) in anhydrous ether (6 ml). After 16 hr at 0°, the soln was poured into stirred 5% $NaHCO_3$ aq (5 ml) and kept for 15 min at 0°. The ether layer was separated and the aqueous layer was extracted with ether (3 × 2 ml). The combined ether soln was washed with water (1 ml), dried and evaporated under reduced press to afford the 20-bromide (XVIII, 114 mg), m.p. 131–133°; ν_{max} 1726 cm^{-1}, no absorption near 3000 cm^{-1}.

(c) Bromination of the 20-alcohol XVa was carried out as above: from XVa (102 mg) there was obtained the 20-epimeric bromide (XIX, 108 mg), m.p. 124–126°; ν_{max} 1732 cm^{-1}, no absorption near 3000 cm^{-1}; NMR, τ 9·03 (3H, s, 19-Me), 7·89 (3H, d J = 7 c/s, 21-Me), 7·66 (3H, s, OAc), 4·52 (1H q J = 6 c/s, 20-H), and 3·00 and 2·62 (each 1H, d J = 8 c/s, aromatic H

3-O,N-*Diacetyl*-5α,6-*dihydroveratramine* (XXa). To a soln of 5α,6-dihydroveratramine XX (1·00 g) in Py (10 ml) was added Ac_2O (737 mg) in Py (10 ml), and maintained for 24 hr at room temp, when an additional amount of Ac_2O (254 mg) in Py (2 ml) was added. The whole was diluted with EtOH (1 ml) after 55 min and concentrated under reduced press. The residue was dissolved in $CHCl_3$ (20 ml), washed with 2N HCl (5 ml) and H_2O, dried and evaporated to yield amorphous material. On standing the ether soln crystals deposited (XXa, 122 mg). The non-crystalline material in the mother liquor was chromatographed on a column of acid-washed alumina (20 g) and eluted with C_6H_6 and C_6H_6-ether. Fractions eluted with ether-C_6H_6 (1:9) gave crude triacetyldihydroveratramine (XXc, 217 mg). Fractions eluted with ether-C_6H_6 (1:9, 1:4, 2:3) (548 mg), crystallized on trituration with EtOH aq to afford XXa (405 mg), m.p. 221–223°, recrystallization (EtOH) m.p. 233–234°; $[\alpha]_D^{21}$ + 81°; ν_{max} 3360, 1725, 1608, 1253, 1245 and 1027 cm^{-1}; NMR, τ 9·05 (3H, s, 19-Me), 8·10 (3H, s, accompanied with a small peak at τ 8·16, NAc), 7·99 (3H, s, OAc), 7·75 (3H, s, accompanied with a small peak at τ 7·82, 18-Me), 3·16 and 2·95 (each 1H, d J = 8 c/s, aromatic H). (Found: C, 75·07; H, 9·04; N, 2·87. $C_{31}H_{45}O_4N$ requires: C, 75·11; H, 9·15; N, 2·83%). From fractions

eluted with ether there was obtained N-acetyldihydroveratramine (XXb, 319 mg). From the remaining fractions (359 mg), rechromatographed gave additional XXa (48 mg).

3-O,N-*Diacetyl-23-dehydro-5α,6-dihydroveratramine* (XXI). To a soln of XXa (206 mg) in acetone (16 ml) was added Jones reagent (0·2 ml) at 0°, and maintained at 0° for 1 hr. Excess reagent was reduced with EtOH and most solvent removed. The residue was diluted with H_2O (20 ml), extracted repeatedly with ether (80 ml) and the ether soln was washed with 5% Na_2CO_3 aq (6 ml) and water, dried and evaporated to yield a resin (191 mg), m.p. 135–140° from EtOH aq, resolidified m.p. 183–185°. (167 mg). Recrystallization from EtOH aq (drying at 110° *in vacuo*), gave (XXI) m.p. 185–187°: $[\alpha]_D^{21}$ −17° ($CHCl_3$): Mass *m/e* 339 (XXIII), 279 (XXIV) and 155 (XXV); λ_{max} 268 mμ (ε 680), 277 (585), and 302 (210); ν_{max} 1722, 1641, 1249, 1234 and 1029 cm^{-1}; NMR, τ 9·04 (3H, s, 19-Me), 7·98 (3H, s, OAc), and 8·52, 8·10, 7·80, 7·75 (each s, NAc and 18-Me); ORD, $[\phi]_{327}^{trough}$ − 6810°, $[\phi]_{282}^{peak}$ + 11,510°, a = − 183°. (Found: C, 75·28; H, 8·70; N, 2·95. $C_{31}H_{43}O_4N$ requires: C, 75·42; H, 8·78; N, 2·84%).

3-O,N-*Diacetyl-23-dehydro-5α,6-dihydro-22-epiveratramine* (XXII). A soln of XXI (301 mg) in 1N NaOMe in MeOH (60 ml) was refluxed under N_2 for 2 hr and concentrated. H_2O (100 ml) was added to residue and resulting ppt. collected, washed with H_2O and dried. The ppt. (278 mg) was dissolved in Ac_2O (3 ml) and Py (6 ml) and heated on a steam bath for 0·5 hr. The soln was evaporated, residue was taken up in $CHCl_3$ (20 ml). This soln was washed with 5% Na_2CO_3 aq and H_2O, dried and evaporated to give resin, separated by TLC (ether). The more mobile band gave starting material (XXI, 130 mg). The less mobile band afforded an isomeric ketone (XXII, 163 mg), plates, m.p. 220–222°, from acetone m.p. 222–224° $[\alpha]_D^{21}$ +44° ($CHCl_3$). Mass, *m/e* 339 (XXIII), 279 (XXIV) and 155 (XXV); λ_{max} 268 mμ (ε 980), 277 (890) and 302 (310): ν_{max} 1728 (sh), 1717, 1652, 1249 and 1026 cm^{-1}; NMR τ 9·04 (3H, s, 19-Me), 7·97 (3H, s, OAc) and 7·85, 7·80, 7·78 (each s, 18-Me and NAc); ORD, [α] +55°, +75°, +140°, +213°, +456°, +447°, +517°, +448°, +460° and +426°, at 589, 500, 400, 350, 328, 324, 316, 310, 306 and 300 mμ. (Found: C, 75·50; H, 8·84; N, 2·55. $C_{31}H_{43}O_4N$ requires: C, 75·42; H, 8·78; N, 2·84%). XXII was dissolved in $CHCl_3$-ether and two crystals types were obtained (plates and needles). Needles, m.p. 229–231°; ν_{max} 1727, 1716 (sh), 1662, 1246 and 1034 cm^{-1} (lit.[15], m.p. 222–224°, and plates, m.p. 229–231°).

A soln of the epimeric ketone XXII (20 mg) in 1N NaOMe in MeOH (5 ml) was refluxed under N_2 for 2 hr and concentrated. Water (10 ml) was added and the resulting ppt filtered, washed with H_2O and dried. 17·3 mg was acetylated with Ac_2O (0·2 ml) and Py (0·4 ml), giving 20·7 mg amorphous mixture, prep. TLC gave 5·6 mg of XXI and 10·8 mg of XXII. Identification by TLC and IR.

Reaction of enamine (XXVII) *of* XI *with bromides* XVIII *and* XIX. A soln of XI (100 mg) and pyrrolidine (1 ml) in anhydrous thiophene-free C_6H_6 (20 ml) refluxed for 3·5 hr with stirring and N_2 with continuous removal of H_2O, C_6H_6 and excess of pyrrolidine were removed below 50°. Resulting crude enamine (XXVII, 141 mg), ν_{max}^{film} 1638 cm^{-1} and no absorption near 1700 cm^{-1}, was used for the next reaction without further purification.

The enamine XXVII (141 mg) and bromide XIX (118 mg) were dissolved in dry dioxane (0·5 ml), freshly distilled over LAH, and heated at *ca.* 100° for 40 hr (sealed tube). The tube was opened, again sealed after addition of H_2O (0·4 ml) and heated at *ca.* 100° for 3 hr to decompose the enamines. After cooling, the reaction mixture was concentrated and mixed with $CHCl_3$ (3 ml), washed with 2N HCl (3 × 1 ml), 5% $NaHCO_3$ aq (1 ml) and H_2O (1 ml), dried over Na_2SO_4 and evaporated to leave an oily residue (136 mg). The residue was separated into 5 bands (R_f 0·90, 0·74, 0·56, 0·20 and base line) (prep. TLC, silica gel, EtOAc). Detection by I_2 and elution with MeOH-ether (9:1).

Fractions (R_f 0·20 and base line) gave resins (3 and 11 mg, respectively), which were not further characterized. The most mobile band afforded a resin (32 mg), styrene XVI (main) and 3,20-glycols XIV and XV (minor) by TLC (solvent, $CHCl_3$). Fraction (R_f 0·74) gave semi-crystalline substance (26 mg), similar R_f value, mass and NMR as compound XXI; NMR, τ 9·06? (d *J* = 5 c/s, sec Me), 9·04 (3H, s, 19-Me), 8·80 (d *J* = 6·5 c/s, sec Me), 7·95 (3H, s, OAc), 8·53, 8·08, 7·80 and 7·75 (each sharp s, 18-Me and NAc), and 5·36 (1H, br W_H = 23 c/s, 3-H). Rechromatography gave crystals, m.p. 129–134°, which on being washed with ether and dried (110° at 1 mm, 12 hr), afforded XXVIII (18 mg), m.p. 133–135°; Mass *m/e* 339 (XXIII), 279 (XXIV) and 155 (XXV), no detectable M^+ at 493; λ_{max} 268 mμ (ε 1200), 277 (1050) and 304 (380); ν_{max} 1726, 1710 (sh), 1647, 1628 (sh), 1231 and 1030 cm^{-1}; ORD, $[\phi]_{328}^{peak}$ + 7400°, $[\phi]_{284}^{trough}$ − 4200°, *a* = + 116°. An oily substance (7 mg) obtained on rechromatography showed the same Mass spectrum as XXVIII.

Fraction (R_f 0·56) gave semi-crystalline substance (26 mg), similar R_f and NMR as XXII; NMR, τ 9·04 (3H, s, 19-Me), 9·00? (d *J* = 5 c/s, sec Me), 8·71 (d *J* = 6·5 c/s, sec Me), 7·97 (3H, s, OAc), 7·87, 7·82 and 7·79 (each sharp s, 18-Me and NAc), and 5·36 (1H, br W_H = 21 c/s, 3-H). The substance gave crystals (16 mg), m.p. 211–215°, after ether wash, identified as XXII (m. m.p., TLC, Mass, UV and IR and ORD curves),

m.p. 223–225° on recrystallization from ether-acetone; Mass *m/e* 339 (XXIII), 279 (XXIV) and 155 (XXV), no detectable M^+ at 493; λ_{max} 268 mμ (ε 1050), 277 (900) and 302 (300); ν_{max} 1727, 1716, 1652, 1246 and 1027 cm^{-1}; [α] + 38·8°, + 49·2°, + 62·2°, + 77·8°, + 112·6°, + 168·5°, + 374°, + 376°, + 435°, + 368°, + 369° and + 331° at 589, 550, 500, 450, 400, 350, 326, 322, 314, 305, 303 and 298 mμ. An oily substance obtained on washing with ether showed the same Mass spectrum as compound XXII.

The epimeric bromide XVIII (121 mg) was treated with the enamine XXVII, prepared from XI (108 mg), (same conditions as XIX) and gave practically the same result: the product worked up as above and resulting tarry residue (172 mg) separated roughly into 3 fractions (R_f 0·90, 0·74 and 0·56) 43, 3 and 31 mg, respectively. The most mobile fraction was reexamined by TLC, using $CHCl_3$ as solvent, and proved to consist of styrene XVI and 20-alcohols XIV and XV as major and minor components, respectively. Fraction with R_f 0·74 exhibited almost the same NMR spectrum as XXI and XXVIII, and afforded semi-crystalline substance (24 mg) after rechromatography (EtOAc), ether wash and drying, m.p. 133–135°, same Mass and IR spectra and ORD as XXVIII (13 mg). Oily substance (13 mg) obtained on treatment with ether showed the same Mass spectrum. The most mobile semi-crystalline showed the same NMR spectrum as XXII, ether wash gave XXII (15 mg), m.p. 212–216°. An oily substance (15 mg) obtained from the ether washings showed the same Mass spectrum.

Reduction of 3-O,N-*diacetyl*-23-*dehydro*-5α,6-*dihydroveratramine* (XXI). (a) To a mixture of liq NH_3 (*ca.* 70 ml) and THF (40 ml) containing Li (397 mg) was added XXI (101 mg) in THF (2 ml), and mix stirred under cooling with dry ice-acetone. An additional amount (108 mg) of Li added after 10 min, and the whole further stirred for 50 min. After addition of NH_4Cl the mixture was evaporated at room temp to remove NH_3. The soln separated by decantation, and evaporated to leave an oil. The decantation residues, on evaporation of THF, were mixed with H_2O, and the mixture extracted with $CHCl_3$ repeatedly. The $CHCl_3$ soln was washed with saturated NaCl aq, dried and evaporated to leave an oil (116 mg) (4 fractions by prep. TLC, 4:1 $CHCl_3$:acetone). Each band checked with I_2 and eluted with MeOH. The most mobile (16 mg) and least mobile (22 mg) appeared to contain starting material and a mixture of compounds with reduced aromatic D rings as main components, respectively, not further characterized. The main fraction (50 mg) crystallized on trituration with dil EtOH and recrystallized (dil EtOH) to give N-acetyl-5α,6-dihydro-23-epiveratramine (XXX, 33 mg), m.p. 202–204°; $[\alpha]_D^{23}$ + 104° ($CHCl_3$); ν_{max} 3475, 3375, 3295, 3190, 1610, 1277, 1102, 1080 and 1045 cm^{-1}; NMR, τ 9·07 (3H, s, 19-Me), 9·05 and 8·65 (each 3H, d J = 7·7 and 6·9 c/s, 26- and 21-Me or *vice versa*), 8·20 (3H, s, NAc), 7·75 (3H, s, 18-Me), and 3·14 (2H, s, aromatic H). (Found: C, 76·58; H, 9·76; N, 3·30. $C_{29}H_{43}O_3N$ requires: C, 76·78; H, 9·55; N, 3·09%). The minor fraction (22 mg) crystallized on trituration with dil EtOH (recrystallized dil EtOH) to give N-acetyl-5α,6-dihydroveratramine (XXb, 15 mg), m.p. 219–221° (lit.[8] 220–223°); $[\alpha]_D$ +78·8° ($CHCl_3$) (lit.[8] +81°); ν_{max} 3480, 3275, 3170, 1607, 1273, 1080 and 1044 cm^{-1}; NMR, τ 9·07 (3H, s, 19-Me), 8·76? (d J = 6 c/s, 26- and 21-Me). This sample was identical with an authentic sample from veratramine in all respects (TLC, IR, NMR).

(b) A soln of XXI (110 mg) in EtOH (10 ml) was treated with $NaBH_4$ (31 mg) at room temp for 2 hr with stirring. The soln was treated with AcOH (0·2 ml) cooling to decompose excess reagent, evaporated, basified with 5% $NaHCO_3$ aq, and extracted with $CHCl_3$ repeatedly. The $CHCl_3$ soln was washed, dried and evap. to leave an oil (117 mg) (one spot, TLC). The residue was dissolved in MeOH (11 ml) containing 5% KOH and refluxed for 2 hr under N_2. After solvent removal, the residue was mixed with H_2O and $CHCl_3$ extracted repeatedly. The $CHCl_3$ soln was water washed, dried and evap. to give an oil (117 mg), 2 fractions by prep. TLC as above. The more mobile fraction (88 mg) gave XXX (63·5 mg) on crystallization from dil EtOH, m.p. 199–201·5°, identical with Birch reduction product of XXI. The less mobile fraction (25·5 mg) likewise crystallized and, on recrystallization from dil EtOH, gave XXb (19 mg), m.p. 215–217°, identical with Birch reduction product.

Conversion of 23-O,N-*diacetyl*-3-*dehydro*-5α,6-*dihydroveratramine* (XXXIb) *into the* 4,5-*dehydro derivative* (XXXIV). To 3-ketone XXXIb[7b] (100 mg) dissolved in AcOH (1 ml) was added at room temp a 1·13N HBr soln in AcOH (0·3 ml) and then a Br_2 soln (1 mol) in AcOH (0·45 ml). The soln kept at room temp for 3 hr, diluted with H_2O (2 ml) and extracted with CH_2Cl_2 (3 × 10 ml). The CH_2Cl_2 soln was washed with 5% $NaHCO_3$ aq (10 ml) and H_2O (10 ml), dried and evaporated to give crude glassy dibromoketone (XXXII, 114 mg); ν_{max} 1725 and 1633 cm^{-1}, used without purification for the next reaction.

A part (51 mg) of XXXII dissolved in acetone (2·2 ml) containing NaI (203 mg) was refluxed under N_2 for 2·5 hr, and mixed with 0·1N $Na_2S_2O_3$ aq (2 ml) and H_2O (5 ml). The whole mixture was shaken with CH_2Cl_2 (2 × 10 ml). The CH_2Cl_2 soln was dried and evaporated to leave a resin (XXXIII, 46·4 mg), which dissolved in acetone (1·5 ml) and treated with a $CrCl_2$ soln[39] (1·0 ml) under CO_2. After 30 min the soln was diluted with H_2O (10 ml) and extracted with CH_2Cl_2 (2 × 10 ml). The CH_2Cl_2 soln was washed with

H_2O (5 ml), dried and evaaorated to yield a resin (39·3 mg) (separated by prep. TLC, ether). Each of two major bands was extracted with ether. The more mobile afforded an amorphous substance (10·3 mg), identical with 3-ketone XXXIb. The less mobile fraction afforded an amorphous substance (13·9 mg); λ_{sh} 227 mμ (ε 32.000); NMR, τ 8·73 (d J = 5·5 c/s, 26- and/or 21-Me?), 8·22, 8·11, 7·94, 7·91, 7·68 (each s, 18Me, NAc and OAc), and 4·18 (1H, s, 4-H). Identified as 23-O,N-diacetyl-Δ^4-veratramin-3-one (XXXIV) by comparison of UV, IR and NMR spectra and by TLC with authentic sample prepared by acetylation of Δ^4-3-ketoveratramine.[8]

Conversion of 23-O,N-*diacetyl-*Δ^4*-veratramin-3-one* (XXXIV) *into the enol acetate* (XXXV). A soln of XXXIV (400 mg) in isopropenyl acetate (4 ml) containing conc H_2SO_4 (33 mg) was refluxed for 1 hr, and 1·68 g of liquid removed under reduced press. After addition of isopropenyl acetate (1 ml) the soln was again refluxed for 1 hr. Anhydrous NaOAc (220 mg) was added and the mixture concentrated. The residue was extracted with $CHCl_3$ (10 ml) and the $CHCl_3$ soln washed with 5% Na_2CO_3 aq and H_2O, then dried. Evaporation of the solvent left an amorphous residue (452 mg), trituration with ether gave XXXV (139 mg), m.p. 164–172°. The filtrate was developed on silica gel eluted with ether to give XXXV (174 mg), m.p. 155–170°. Two recrystallizations from ether gave XXXV, m.p. 180–182°; $[\alpha]_D$ +1°; λ_{max} 222 mμ (ε 28.000); ν_{max} 1758, 1737 and 1630 cm^{-1}; NMR, τ 8·83 (3H, s, 19-Me), 8·71 (d J = 7 c/s, 26- and/or 21-Me?), 8·20, 8·09, 7·93, 7·90, 7·81, 7·73, 7·68 (each s, 18-Me, NAc and OAc), 4·46 (1H, br s, 6-H) and 4·27 (1H, s, 4-H). (Found: C, 74·18; H, 8·15; N, 2·50. $C_{33}H_{43}O_5N$ requires: C, 74·26; H, 8·12; N, 2·62%).

Reduction of enol acetate XXXV. (a) Compound XXXV (102 mg) dissolved in 95% EtOH (20 ml) and cooled (0°) was added to a soln of $NaBH_4$ (0·20 g) in 70% EtOH aq (5 ml). Kept at 0° for 2 hr and room temp for 2 hr. Excess of hydride was decomposed by AcOH and most of solvent removed. The residue was diluted with H_2O and extracted with $CHCl_3$ (2 × 15 ml). The $CHCl_3$ soln was washed with 5% Na_2CO_3 aq and H_2O, dried and evaporated. The residue (102 mg), after prep TLC gave crystals (31 mg), m.p. 165–168°; ν_{max} 3320, 1733, 1610, 1240 and 1027 cm^{-1}. The spectrum differed from Ib, described later, but same R_f.

(b) A soln of $NaBH_4$ (200 mg) in 70% EtOH aq (5 ml) was added to a stirred soln of enol acetate XXXV (100 mg) in EtOH (40 ml) at 0°. The soln was kept at 0° for 2 hr and then refluxed for 5 min. After addition of 5% NaOH aq (5 ml) the mixture was concentrated, and 2N HCl (10 ml) added. The whole was extracted with $CHCl_3$ (3 × 10 ml). The soln was washed with H_2O (10 ml), dried and evaporated to give an amorphous residue (108 mg), which was dissolved in EtOH (5 ml) containing a drop of conc HCl and refluxed for 2 hr. Evaporation of solvent gave a semi-crystalline residue (92 mg), separated on silica gel, (4:1 $CHCl_3$: acetone). Two major bands were treated as usual and afforded resinous (25 mg) and crystalline materials (68 mg). The latter (smaller R_f) was recrystallized from EtOH aq to give N-acetylveratramine (Ic, 50 mg), m.p. 174–177°, identical with the authentic sample.[1,6]

23-O,N-*Diacetylveratramine* (Ib). A soln of triacetylveratramine[1,6] (Ia, 2·00 g) in MeOH (200 ml) containing conc HCl (4 ml) was refluxed for 1 hr. The soln was concentrated and diluted with H_2O to give ppts, collected, washed with H_2O, dried, and crystallized from MeOH. Recrystallization (MeOH) gave Ib (1·24 g), fine needles, m.p. 164–166°. Recrystallization (MeOH), m.p. 166–167°; $[\alpha]_D$ +36°; ν_{max} 3320, 1735, 1609, 1240 and 1030 cm^{-1}; NMR, τ 8·83 (3H, s, 19-Me), 8·72 (d J = 6·5 c/s, 26- and/or 21-Me?), 8·21, 8·10, 7·96, 7·94, 7·90, 7·84, 7·68 (each s, 18-Me, NAc and OAc), and 4·52 (1H, br, 6-H). (Found: C, 75·18; H, 8·88; N, 2·85. $C_{31}H_{43}O_4N$ requires: C, 75·42; H, 8·78; N, 2·84%).

Hydrolysis of N-*acetylveratramine* (Ic) *to veratramine* (I). A mixture of Ic (200 mg), KOH (1·0 g), 80% hydrazine hydrate (0·5 ml) and ethylene glycol (20 ml) was refluxed under N_2 for 15 hr. The cooled mixture was diluted with H_2O (100 ml) and extracted with $CHCl_3$ (3 × 20 ml). The $CHCl_3$ soln was washed with H_2O, dried and evaporated to afford I (183 mg), m.p. 198–200°, identical with natural veratramine.

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REFERENCES

[1] K. Saito, *Bull. Chem. Soc. Japan* **15**, 22 (1940)

[2] [a] T. Masamune, Y. Mori, M. Takasugi and A. Murai, *Tetrahedron Letters* 913 (1964);
[b] T. Masamune, Y. Mori, M. Takasugi, A. Murai, S. Ohuchi, N. Sato and N. Katsui, *Bull. Chem. Soc. Japan* **38**, 1374 (1965)

[3] [a] H. G. Boit, *Ergebnisse der Alkaloid-Chemie bis* 1960 p. 758. Akademie-Verlag, Berlin (1961);

[b] C. R. Narayanan, *Progress in the chemistry of Organic Natural Products* (Edited by L. Zechmeister) Vol. XX, p. 298. Springer-Verlag, Wien (1962)
[4] O. Krayer, *J. Pharmacol. Expetl. Therap.* **96**, 422 (1949); **97**, 427 (1950)
[5] K. Kimishima and T. Kanno, *Yonago Igaku Zasshi* **8**, 429 (1947)
[6] W. A. Jacobs and L. C. Craig, *J. Biol. Chem.* **160**, 555 (1945)
[7] [a] W. A. Jacobs and Y. Sato, *Ibid.* **181**, 55 (1949);
[b] W. A. Jacobs and Y. Sato, *Ibid.* **191**, 71 (1951)
[8] Ch. Tamm and O. Wintersteinei, *J. Am. Chem. Soc.* **74**, 3842 (1952)
[9] O. Wintersteiner and N. L. Hosansky, *Ibid.* **74**, 4474 (1952)
[10] J. Fried, O. Wintersteiner, M. Moore, B. M. Iselin and A. Klingsberg, *Ibid.* **73**, 2970 (1951)
[11] [a] T. Masamune, *Kagaku to Kogyo* (Chemistry and Ch mical Industry) **19**, 500 (1966);
[b] S. M. Kupchan and A. W. By, *The Alkaloids* (Edited by R. H. Manske) Vol. X, p. 193. Academic Press, New York (1967);
[c] K. S. Brown, Jr., *Chemistry of the Alkaloids* (Edited by S. W. Pelletier) p. 631. Reinhold Book Corporation, New York (1970)
[12] [a] H. Mitsuhashi and Y. Shimizu, *Tetrahedron* **19**, 1027 (1963);
[b] D. H. Bailey, D. P. G. Hamon and W. S. Johnson, *Tetrahedron Letters* 555 (1963);
[c] H. Mitsuhashi and K. Shibata, *Ibid.* 2281 (1964); *Chem. Pharm. Bull.* **15**, 814 (1968);
[d] T. Masamune, M. Takasugi and Y. Mori, *Tetrahedron Letters* 489 (1969); T. Masamune, K. Kobayashi, M. Takasugi, Y. Mori and A. Murai, *Tetrahedron* **24**, 3461 (1968);
[e] G. N. Reeke, Jr., R. L. Vincent and W. N. Lipscomb, *J. Am. Chem. Soc.* **90**, 1663 (1968); S. M. Kupchan and M. I. Suffness, *Ibid.* **90**, 2730 (1968);
[f] J. Sicher and M. Tichy, *Tetrahedron Letters* 6 (1959);
[g] J. W. Scott, L. J. Durham, H. A. P. deJongh, U. Burckhardt and W. S. Johnson, *Ibid.* 2381 (1967); R. L. Augustine, *Chem. & Ind.* (London) 1448 (1961);
[h] S. Okuda, H. Kataoka and K. Tsuda, *Ibid.* 512 (1961)
[13] [a] R. A. Barnes and M. Sedlak, *J. Org. Chem.* **27**, 4562 (1962);
[b] P. W. Schiess, D. M. Bailey and W. S. Johnson, *Tetrahedron Letters* 549 (1963);
[c] J. P. Kutney, A. By, T. Inada and S. Y. Leong, *Ibid.* 2911 (1965);
[d] J. Fried and N. A. Abraham, *Ibid.* 3505 (1965); J. Fried, M. J. Green and G. V. Nair, *J. Am. Chem. Soc.* **92**, 4136 (1970); M. J. Green, N. A. Abraham, E. B. Fleischer, J. Case and J. Fried, *Chem. Comm.* 234 (1970);
[e] W. F. Johns, *J. Org. Chem.* **35**, 3524 (1970); W. F. Johns and I. Laos, *Ibid.* **30**, 4220 (1965);
[f] Ref. 12c, and previous paper;
[g] J. W. Huffman, D. M. Alabran and A. C. Ruggles, *J. Org. Chem.* **33**, 1060 (1968);
[h] A. Chatterjee and S. Bonerjee, *Tetrahedron* **26**, 2599 (1970)
[14] [a] J. Tomko and S. Bauer, *Coll. Czech. Chem. Comm.* **29**, 2570 (1964);
[b] T. Masamune, I. Yamazaki and M. Takasugi, *Bull. Chem. Soc. Japan* **39**, 1090 (1966)
[15] T. Masamune, M. Takasugi, A. Murai and K. Kobayashi, *J. Am. Chem. Soc.* **89**, 4521 (1967)
[16] W. S. Johnson, J. M. Cox, D. W. Graham and H. W. Whitlock, Jr., *Ibid.* **89**, 4524 (1967); W. S. Johnson, N. Cohen, E. R. Habicht, Jr., D. P. G. Hamon, G. P. Rizzi and D. J. Faulkner, *Tetrahedron Letters* 2829 (1968)
[17] Y. Mazur, N. Danieli and F. Sondheimer, *J. Am. Chem. Soc.* **82**, 5889 (1960)
[18] W. S. Johnson, H. A. P. deJongh, C. E. Coverdale, J. W. Scott and U. Burckhart, *Ibid.* 4523 (1967)
[19] J. P. Kutney, J. Cable, W. A. F. Gladstone, H. W. Hanssen, E. J. Torupka and W. D. C. Warnock, *Ibid.* **90**, 5332 (1968)
[20] R. W. Franck and W. S. Johnson, *Tetrahedron Letters* 545 (1963); R. W. Franck, G. P. Rizzi and W. S. Johnson, *Steroids* **4**, 463 (1964)
[21] A. Ladenburg, *Ber. Dtsch. Chem. Ges.* **27**, 75 (1894); A. Ladenburg and O. Bobertag, *Ibid.* **36**, 1649 (1903); A. Ladenburg, *Ann.* **364**, 227 (1909)
[22] Cf. C. Schöpf, A. Komzak, F. Braun and E. Jacobi, *Ibid.* **559**, 1 (1948)
[23] [a] D. Swern, *Organic Reactions* **7**, 378 (1953);
[b] T. Sakan, *Zikken Kagaku Koza* (Edited by Chemical Society of Japan) Vol. XVII, p. 280. Maruzen Co. Ltd., Tokyo (1957);
[c] H. O. House, *Modern Synthetic Reactions* p. 105. W. A. Benjamin, Inc., New York (1965)
[24] T. Masamune, H. Hayashi and M. Takasugi, unpublished observations

[25] E. Matsuura, *Nippon Kagaku Zasshi* (*J. Chem. Soc. Japan, Pure Chem. Sect.*) **74**, 363 (1953)
[26] S. M. McElvain and M. A. Goese, *J. Am. Chem. Soc.* **65**, 2233 (1943)
[27] A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *J. Chem. Soc.* 2548 (1953)
[28] J. March, *Advanced Organic Chemistry* p. 747. McGraw-Hill Book Co., New York (1968)
[29] G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz and R. Torrell, *J. Am. Chem. Soc.* **85**, 207 (1963); J. Szmuszkovicz, *Advances in Organic Chemistry* Vol. IV, p. 1. Interscience Publishers, New York (1963)
[30] W. W. Zorbach, *J. Am. Chem. Soc.* **75**, 6344 (1953)
[31] C. Wang, *J. Org. Chem.* **28**, 2914 (1963)
[32] C. L. Arcus and G. V. Boyd, *J. Chem. Soc.* 1580 (1951)
[33] H. Budzikiewicz, *Tetrahedron* **20**, 2267 (1964)
[34] H. E. Zimmerman and A. Mais, *J. Am. Chem. Soc.* **81**, 4305 (1959)
[35] H. Paulsen and K. Todt, *Angew. Chem.* **78**, 943 (1966)
[36] A. Moscowitz, K. Mislow, M. A. W. Glass and C. Djerassi, *J. Am. Chem. Soc.* **84**, 1945 (1962)
[37] H. O. House, *Modern Synthetic Reactions* p. 55. W. A. Benjamin, Inc., New York (1965)
[38] 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)
[39] G. Rosenkranz, O. Mancera, J. Gatica and C. Djerassi, *J. Am. Chem. Soc.* **72**, 4077 (1950)
[40] W. G. Dauben and J. F. Eastham, *Ibid.* **73**, 3260 (1951)
[41] W. G. Dauben and J. F. Eastham, *Ibid.* **73**, 4463 (1951)
[42] B. Belleau and T. F. Gallagher, *Ibid.* **73**, 4458 (1951)
[43] D. R. Duncan, *Inorganic Syntheses* (Edited by H. S. Booth) Vol. 1, p. 151. McGraw-Hill Book Comp. Inc., New York (1939)
[44] G. Braun, *Organic Syntheses* (Edited by A. H. Blatt) Coll. Vol. I, p. 431. John Wiley & Sons, Inc., New York (1948)