Tetrahedron. Vol. 24, pp. 3461 to 3474 Pergamon Press. 1968 Printed in Great Britain

ESTABLISHMENT OF THE C_9 CONFIGURATION OF JERVINE AND RELATED ALKALOIDS

STRUCTURE OF THE BIRCH REDUCTION PRODUCTS OF "JERVINE-11β-OL" AND 11-DEOXOJERVINE[1]

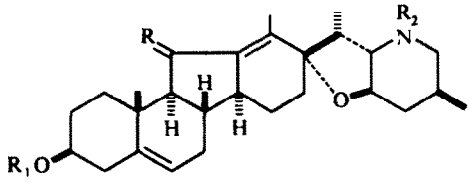
T. MASAMUNE, K. KOBAYASHI, M. TAKASUGI, Y. MORI and A. MURAI
Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo, Japan

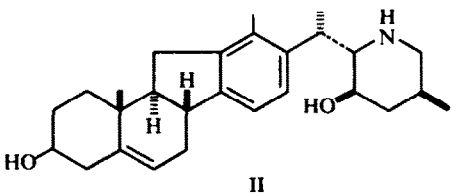
(*Received in Japan* 4 *September* 1967; *accepted for publication* 21 *November* 1967)

Abstract—Reduction of "jervine-11β-ol" (IV), possessing the same C_9 configuration as jervine (I), with lithium in ethylamine gave 22,27-imino-17β(?)-jerva-5,12-diene-3β,23β-diol (V) as a main product. The same treatment for 11-deoxojervine (III) afforded the same compound V, along with 8β,9α-dihydro-11-deoxoisojervine (XV), indicating that both I and III have the same configuration at C_9. Compound V was converted, through reactions causing no migration of the double bond in the D-ring, into the 5α,6-dihydro derivative (IX). The disposition of the double bond at C_{12}–C_{13} has been confirmed by oxidative cleavage of the bond with osmium tetroxide and then with periodic acid. On the other hand, the C_9 configuration of veratramine (II) has been determined by the conversion into a ketone XVII which has been prepared from hecogenin. Treatment of II with lithium in ethylamine in the presence of isopropyl alcohol followed by hydrogenation gave compound IX and a saturated compound X, which were also obtained by hydrogenation of V. This correlation establishes the α-configuration of C_9 hydrogen in I and III.

A FEW years ago Mitsuhashi and Shimizu[2] reported the establishment of C_3, C_8, C_9, C_{10} and C_{14} configurations in jervine (I) by conversion of hecogenin into a degradation product of I. However, the C_9 configuration seemed to be still open, because the degradation involved a reaction under rather severe conditions,[3] which would render C_9 readily epimerizable. On the other hand, veratramine (II) has been shown to have a *trans*-fused B/C linkage (9α-H) on the basis of NMR studies.[4] Although I has been related to II directly[5] or *via* triacetyldihydro-11-oxoveratramine,[6] the possibility still remained of epimerization at C_9 during the reactions. In view of the range in relative stability between *trans* and *cis* isomers of hydrindanone derivatives,[7] it was desirable to determine the configuration of C_9 in an unambiguous manner.

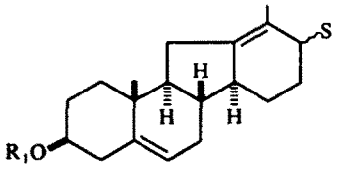
We have recently correlated jervine I and 11-deoxojervine (III) with veratramine II through a series of reactions involving no epimerization at C_9 and established that those alkaloids indeed have B/C *trans*-configuration.[8] The most important, key step in the transformation has been the reductive cleavage of a 17α,23β-oxido linkage by treatment with lithium in ethylamine. Major products in the reductions for "jervine-11β-ol"[9] (IV) and for 11-deoxojervine (III) have been reported to have m.p. 198–199° and 190–192° and formulated tentatively as V and VI, respectively. In a continuing study, these compounds proved to be identical with each other and it became necessary to reexamine the structure. In this paper, we present evidence that the compound has a double bond at C_{12}–C_{13} and also describe the experimental details of the correlation presented as a preliminary communication.[8]

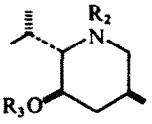


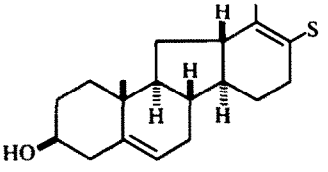


II

I: R = O, $R_1 = R_2 = H$
III: R = H_2, $R_1 = R_2 = H$
IV: R = —OH, —H, $R_1 = R_2 = H$
IVa: R = —OH, —H, $R_1 = R_2 = Ac$







V(=V'): $R_1 = R_2 = R_3 = H$
Va(=V'a): $R_1 = R_2 = R_3 = Ac$

VI: $R_2 = R_3 = H$

Reduction of IV with lithium in ethylamine produced a mixture of two compounds (V), m.p. 193–195°, and (VII), m.p. 222–224°. The latter VII, isolated in 5% yield, was identified as 22,27-iminojerva-5,13(17)-diene-3β,11β,23β-triol by comparison with a sample prepared by reduction of the known compound, 8β,9α-dihydroisojervine[10] (VIII), with LAH. On the other hand, acetylation of V, isolated in 50% yield, gave the triacetyl derivative (Va), m.p. 188–190°, whose NMR spectrum showed in the lower field, beside a broad peak at τ 4·58 due to the C_6 proton, a signal which consisted of three peaks centered at τ 4·88, 5·21 and 5·38 and was attributable to protons at C_{22} and C_{23}.[11] Furthermore, the 19- and 18-Me protons appeared as singlet at τ 9·02* and 8·47. This spectral behavior indicated both the cleavage of the 17α,23β-oxido linkage and removal of the 11β-OH group as well as the presence of a double bond either at C_{12}–C_{13} or at C_{13}–C_{17}. The compound V was further submitted to catalytic hydrogenation over platinum in acetic acid, with the expection that some of the products might be correlated with certain reduction products of II, to produce a multi-component mixture, from which two compounds (IX), m.p. 177–179°, and (X), m.p. 185–187°, were isolated in 24% and 18% yields, respectively, by fractional recrystallizations. The triacetyl derivative (IXa), m.p. 217–219°, of IX showed almost the same NMR spectrum as Va except the absence of the peak due to the C_6 proton and the up-field shift of the 19-Me signal to τ 9·23. This suggests that the remaining one double bond in the D-ring of IX would be located at the same position as the corresponding bond of V. On the other hand, the product X proved to be a saturated compound on the basis of the mass spectrum (M^+, 417) and the NMR spectrum of its N-acetyl derivative (Xa), m.p. 178–180°, (no sharp absorption near τ 8·4).

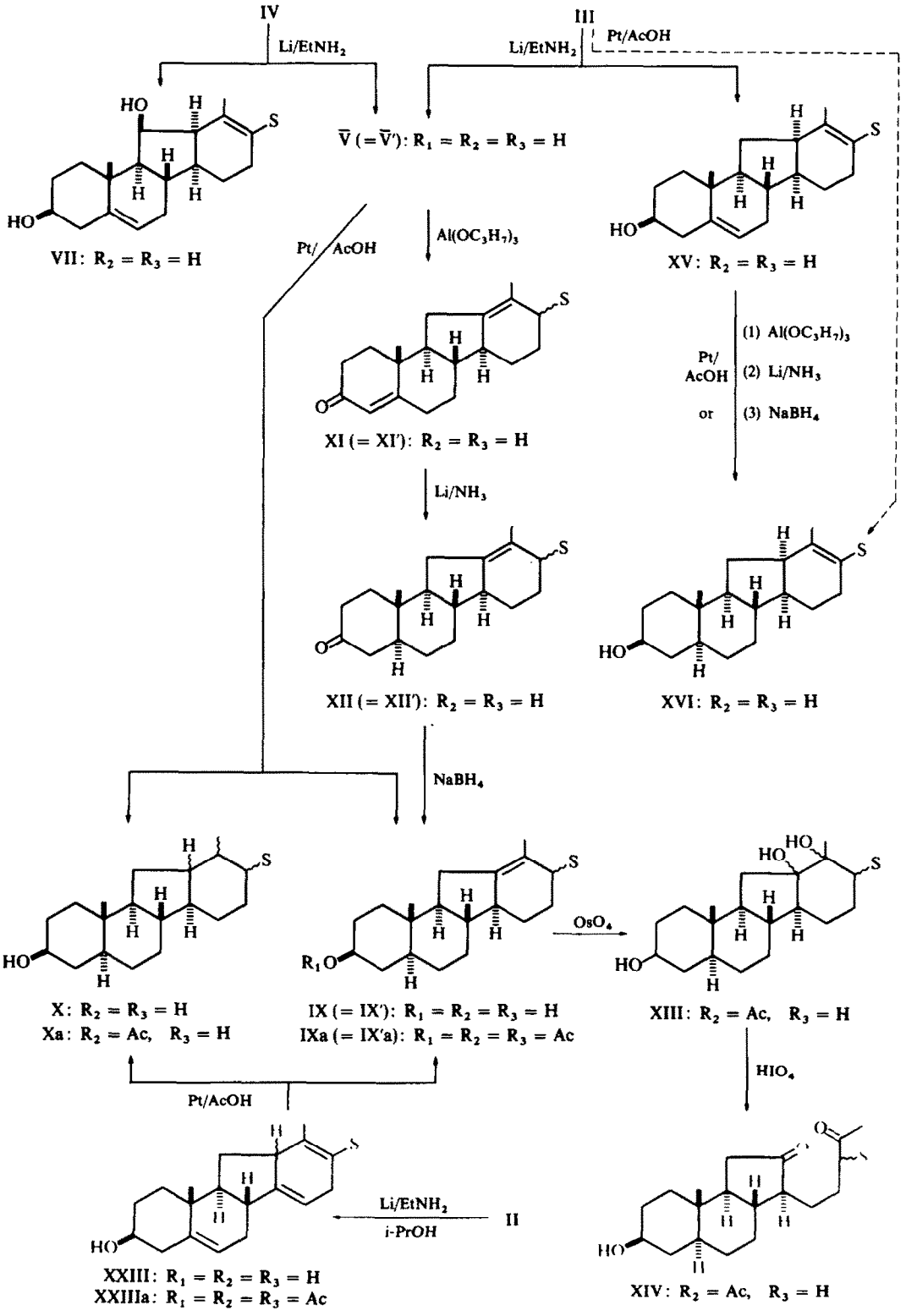
As mentioned above, compound IX is considered to differ from V only by saturation of the double bond at C_5–C_6. However, since there remained the possibility that

* The corresponding peak of diacetyl-11-deoxojervine (IIIa) appears at τ 9·06. T. Masamune, N. Sato, K. Kobayashi, I. Yamazaki and Y. Mori, *Tetrahedron* 23, 1591 (1967).

the relevant double bond in the D-ring might migrate during the hydrogenation under acidic conditions, it became desirable to convert V into IX in an indisputable way. The Oppenauer oxidation of V afforded an α,β-unsaturated ketone XI, m.p. 176–178°, which in turn was reduced with lithium in liquid ammonia to give a 3-ketone XII, m.p. 159–161°. The IR spectra of XI, ν_{max} 1660 and 1616 cm^{-1}, and XII, ν_{max} 1714 cm^{-1}, supported the assigned structures and also the ORD curve (a positive Cotton effect) of XII indicated that the compound had a *trans*-fused A/B ring (5α-H). On reduction with sodium borohydride, the 3-ketone XII was converted into the corresponding alcohol, m.p. 176–178°, which on acetylation gave the triacetyl derivative having m.p. 218–220°. This compound of m.p. 178° proved to be identical with IX by comparison of the R_f values, IR and NMR spectra of both the compound and its triacetyl derivative. Since this transformation of three steps involves no acidic conditions which affect the double bond, the D-ring in V, IX, XI and XII must have the same structure and stereochemistry. In order to confirm the position of this double bond, IXa was oxidized with osmium tetroxide in ether containing a small amount of pyridine at room temperature for 40 days,[12] and afforded, after treatment with sodium sulfite in refluxing aqueous ethanol, a tetraol (XIII), m.p. 249–251°, which showed no absorption near 1700 cm^{-1} except a band at 1626 cm^{-1} due to the N-acetyl group. Further oxidation of XIII with periodic acid in aqueous methanol gave a diketone (XIV), amorphous, in 63% yield, which showed a single spot on TLC and two sharp absorptions at 1734 and 1712 cm^{-1} in the IR spectrum. The former band must be attributed to a ketonic group in a 5-membered ring and, therefore, the double bond in question in V and IX must be located at C_{12}–C_{13}.

Treatment of 11-deoxojervine (III) with lithium and ethylamine resulted in cleavage of the 17α,23β-oxido bond and yielded two isomeric compounds (XV), m.p. 154–155°, and (V'), m.p. 188–190°, in 16% and 42% yields, respectively. Hydrogenation of the former XV afforded in good yield the corresponding 5α,6-dihydro derivative (XVI), m.p. 155–157°. This compound XVI was also obtained by the transformation similar to that of V to IX; the Oppenauer oxidation of XV, the Birch reduction of the resulting α,β-unsaturated ketone and subsequent sodium borohydride reduction to the 3-alcohol XVI, m.p. 151–153°. Since the compound XVI has been prepared by direct hydrogenation of III[13] and its structure has been elucidated,[14] compound XV must be formulated as 8β,9α-dihydro-11-deoxoisojervine.

Compound V' of m.p. 190° in the preceding section will be shown to be identical with V. In the preliminary communication,[8] we assumed that V' was different from V on the basis of a slight difference of their m.ps, the R_f values on the paper chromatogram and their optical rotations, although their IR and NMR spectra were completely superimposable. The most definite reason for the presumption was the different behavior in hydrogenation of both the compounds. In the present reinvestigation, compound V' was converted into the corresponding 5α,6-dihydro derivative (IX') in the same manner as V. All the transformation intermediates, the α,β-unsaturated ketone (XI'), m.p. 175–177°, the 3-ketone (XII'), m.p. 159–161°, and the 3-alcohol (IX'), m.p. 176–178°, as well as V' itself showed the R_f values on various TLC and IR spectra identical with those of the corresponding compounds, XI, XII and IX, and V itself, respectively. This result prompted us to reexamine the hydrogenation in question. When hydrogenated over platinum in acetic acid, compound V' gave a mixture, from which compounds IX and X were isolated by TLC as main


IV
Li/EtNH2
III
Li/EtNH2
Pt/AcOH
V̄ (=V̄'): R1 = R2 = R3 = H
VII: R2 = R3 = H
Pt/AcOH
Al(OC3H7)3
XV: R2 = R3 = H
(1) Al(OC3H7)3
Pt/AcOH
(2) Li/NH3
or
(3) NaBH4
XI (= XI'): R2 = R3 = H
Li/NH3
XII (= XII'): R2 = R3 = H
XVI: R2 = R3 = H
NaBH4
X: R2 = R3 = H
Xa: R2 = Ac, R3 = H
IX (= IX'): R1 = R2 = R3 = H
IXa (= IX'a): R1 = R2 = R3 = Ac
OsO4
XIII: R2 = Ac, R3 = H
HIO4
Pt/AcOH
XXIII: R1 = R2 = R3 = H
XXIIIa: R1 = R2 = R3 = Ac
Li/EtNH2
i-PrOH
II
XIV: R2 = Ac, R3 = H

components. The product in the corresponding reaction in the preliminary note,[15] was then carefully examined by TLC; the main product of m.p. 172–174° has been shown to be a 3:1 mixture of IX and X, and the other crystalline substance to be IX.

The remaining problem concerning the structure of V was the stereochemistry of C_{17}. If the relevant reduction (Li–$EtNH_2$) is a substitution of S_N2 type and proceeds with the inversion of the configuration,* the C_{17} hydrogen must have the β-orientation. This assignment appears to be valid, because the formation of the other reduction products VII and XV, which would have resulted from migration of the C_{12}–C_{13} double bond to C_{13}–C_{17}, is interpretable well if the reduction is a substitution of S_N2' type. However, this is a mere inference deduced from the result, and for want of any experimental evidence supporting this assignment, we prefer to leave the configuration of C_{17} in V undefined.

Mitsuhashi and Shibata[17] has recently converted hecogenin into 17-acetyletiojerva-12,14,16-trien-3β-ol (XVII). The structure of XVII has been confirmed by identification with an authentic specimen prepared from veratramine II in our laboratory as follows; hydrogenation of II over platinum in acetic acid followed by chromatographic separation on alumina produced 5α,6-dihydroveratramine[18a] (XVIII), m.p. 191–193°, in 41% yield along with 44% yield of the 5β-isomer (XIX). The latter XIX was isolated as a benzene complex, m.p. 80°, and gave the triacetyl, N-acetyl and 23-O,N-diacetyl derivatives (XIXa, XIXb and XIXc) having m.p. 179–180°, 193–194° and 163–165°, respectively. While 3-dehydro-23-O,N-diacetyl derivatives (XX)[18b] and (XXI), m.p. 200–202°, of XVIII and XIX exhibited no distinct difference in the ORD curves, the NMR spectra of the isomers XVIII and XIX and their derivatives proved the hydrogen at C_5 of XIX to be β-oriented; the 19-Me protons of 5β-compounds, XIX, XIXa, XIXb and XIXc, appeared at lower fields, τ 8·89 to 8·92, than those of the respective 5α-compounds,[18] and the difference (0·12–0·16 ppm) was reasonable for change in passing from the *trans*-fused A/B ring to the *cis*-fused.† It is to be noted that almost equal amounts of the 5α- and 5β-isomers XVIII and XIX have been formed by hydrogenation of a double bond at C_5–C_6 in veratramine II. Compound XVIII was degraded to XVII in the same manner as Johnson's fragmentation;‡ XVIII was converted into the N-chloro derivative with N-chlorosuccinimide, which gave, when treated with sodium methoxide and then with acid, an aldehyde (XXII), whose structure was assigned on the spectral data, ν_{max} 2726 and 1723 cm^{-1}, and τ 0·17 (1H, broad singlet, C<u>H</u>O) and 8·61 (3H, doublet J = 6·5 c/s, 21-Me). The aldehyde was further degraded, with n-butyl nitrite and sodium n-butoxide, to an oxime, m.p. 228–232°, which was then hydrolyzed to a ketone, m.p. 172–174°. This ketone was identical with the sample derived from hecogenin in all respects.§ This transformation of II to XVII, coupled with Mitsuhashi's skilful degradation,[17] establishes the B/C *trans*-configuration (9α-H) of veratramine II.

* No definite mechanism appears, to our knowledge, to be reported on the cleavage of a single bond by dissolving metal reductions.[16]

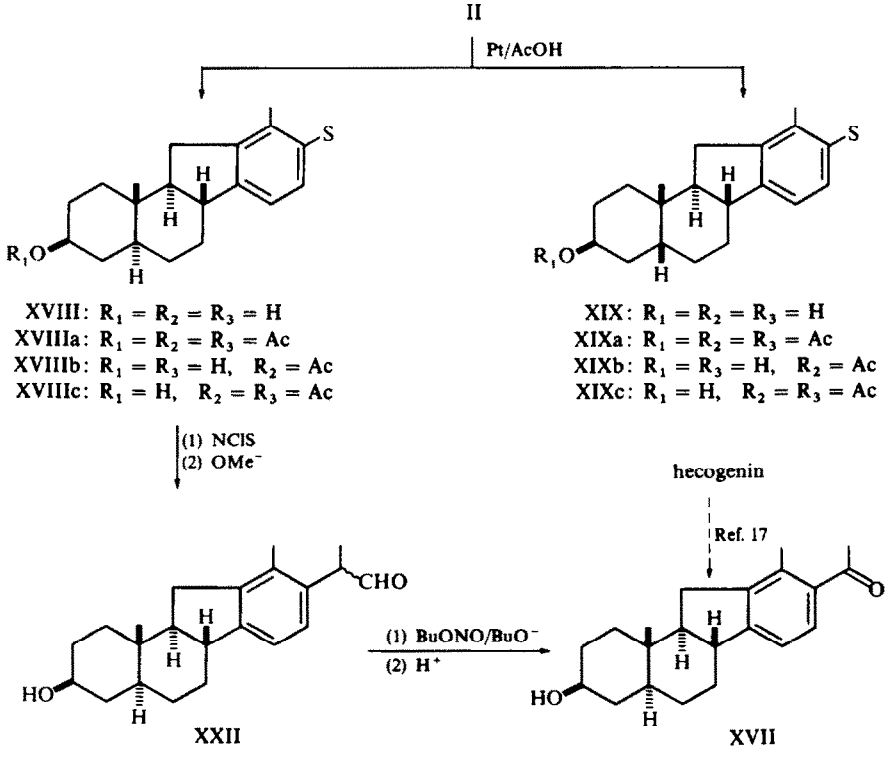
† See footnote on p. 3462.

‡ After we had completed this degradation for XVIII (cf. Ref. 18), we received the report that Johnson *et al.* have also done with the same transformation.[19]

§ The authors wish to express their appreciation to Professor Mitsuhashi for kind donation of a sample of XVII.

The Birch reduction of II with lithium in ethylamine containing isopropyl alcohol[20] effected reduction of the D-ring to yield a mixture of dihydro derivatives. The main product, obtained in 33% yield after repeated recrystallizations, had m.p. 182–184° and was formulated as XXIII. In accordance with this assigned structure, the UV spectrum showed only end absorption, ε 16,000 at 210 mμ, and also the NMR spectra of both XXIII and the triacetyl compound (XXIIIa), m.p. 144–146°, exhibited the presence of two olefinic protons at C_6 and C_{15} as a broad peak centered near τ 4·6 and of a 18-Me group attached to a olefinic carbon as a singlet at τ 8·47. On hydrogenation over platinum in acetic acid, XXIII afforded a mixture showing two spots on TLC. Purification through the chloroform addition compounds followed by repeated recrystallizations led to the isolation of two crystalline substances, m.p. 183–185° and 174–176°, in 19% and 28% yields, respectively. The former of m.p. 185°, which showed a single spot on various TLC, was identified as compound X by rigorous comparison. On the other hand, the latter of m.p. 176°, although it gave the same IR spectrum as the so-called main product XIV[15] in the preliminary communication,[8] was shown to be a 1:1 mixture of IX and X.

A series of transformations including in this paper involve no reactions which affect the C_9 configuration and, moreover, "jervine-11β-ol" (IV) has the same configuration as jervine, since diacetyljervine (Ia) has been regenerated in good yield from "Diacetyljervine-11β-ol"[9] (IVa) by oxidation with chromic anhydride with pyridine. Consequently, jervine, 11-deoxojervine and veratramine have been established to possess the *trans*-fused B/C linkage.



EXPERIMENTAL

All the m.ps are uncorrected. The homogenity of each compound was always checked by TLC on silica gel (Wakogel B-5) using various solvent systems, and the spots were developed with cerric sulphate in dil H_2SO_4 and/or I_2, and the "R_f" denotes that in TLC unless otherwise stated. Purity of some compounds was also examined by paper chromatography (PC).* The optical rotations, UV and IR spectra were measured in 95% EtOH, in 99% EtOH and in Nujol, respectively, unless otherwise stated. The NMR spectra were obtained in $CDCl_3$ at 60 and/or 100 Mc, and the chemical shifts were given in τ-values, using TMS as an internal reference. The abbreviations "s, d, t, b, m and sh" in the NMR and IR spectral data mean "singlet, doublet, triplet, broad, multiplet and shoulder," respectively.

The Birch reduction of "jervine-11β-ol" (IV) *to* 22,27-*imino*-17β(?)-*jerva*-5,12-*diene*-3β,23β-*diol* (V) *and* 22,27-*iminojerva*-5,13(17)-*diene*-3β,11β,23β-*triol* (VII)

To anhydrous $EtNH_2$ (120 ml) containing IV[9] (2·5 g) was added finely divided Li (1·1 g) under stirring and cooling with dry ice–acetone. The mixture became blue when refluxed, and was then stirred at the temp for 2·5 hr. After addition of NH_4Cl, the mixture was warmed to remove the $EtNH_2$, and the residue diluted with water and extracted repeatedly with $CHCl_3$. The $CHCl_3$ soln, after being washed with water and dried with Na_2SO_4, was evaporated to dryness, and the residue crystallized on trituration with acetone. Fractional recrystallizations from acetone gave V (1·35 g), m.p. 190–192°, and an analytical sample had m.p. 193–195°;† $[\alpha]_D$ −61°;‡ R_f (PC) = ·48; IR, ν_{max} 3400, 1064, 885[21] and 806 cm^{-1}; NMR, τ 4·55 (1H, m, H at C_6), 8·42 (3H, s, 18-Me), 9·00 (3H, s, 19-Me), and 9·14 (6H, bd J = 6 c/s, 21- and 26-Me). (Found: C, 78·11; H, 10·23; N, 3·51. $C_{27}H_{43}O_2N$ requires: C, 78·40; H, 10·48; N, 3·39%). The mother liquors were combined, evaporated and again recrystallized to give a mixture (0·13 g) of V and VII and a pure sample (0·17 g) of VII, m.p. 222–224°;§ $[\alpha]_D$ −27°; R_f (PC) = 0·15; IR, ν_{max} 3400, 3300, 1063, 879 and 800 cm^{-1}. (Found: C, 75·23; H, 9·85; N, 3·54. $C_{27}H_{43}O_3N$ requires: C, 75·48; H, 10·09; N, 3·26%).

Compound V (80 mg) was heated with Ac_2O (0·8 ml) and pyridine (0·8 ml) on a water bath for 3 hr. After removal of the solvents by azeotropization with benzene, the residue was crystallized from MeOH aq and then recrystallized from the same solvent to yield Va (72 mg), m.p. 188–190°; $[\alpha]_D$ −12·3°; IR, ν_{max} 1736, 1636, 1237, 1022 and 803 cm^{-1}; NMR, a broad peak which consisted of 4 peaks centered at τ 4·88, 5·21, 5·38 and 5·54 (3H, H at C_3, C_{22} and C_{23}),[11] τ 4·58 (1H, b, H at C_6), 8·47 (3H, s, 18-Me), 8·82 and 9·19 (each 3H, d J = 7·5 and 7·0 c/s, 21- and 26-Me or *vice versa*), and 9·02 (3H, s, 19-Me). (Found: C, 73·28; H, 9·38; N, 2·35. $C_{33}H_{49}O_5N$ requires: C, 73·43; H, 9·15; N, 2·60%).

Reduction of 8β,9α-*dihydroisojervine* (VIII) *with lithium aluminium hydride to* VII

To a soln of VIII[10] (255 mg) in THF (15 ml) was added LAH (264 mg), and the whole mixture was stirred at room temp overnight. The mixture was treated with ice-water to decompose the excess LAH and then filtered. The filtrate was evaporated, diluted with water and shaken with $CHCl_3$ repeatedly. The $CHCl_3$ soln left an amorphous substance after drying and removal of the solvent, which crystallized on trituration with acetone. The crystalline mixture (109 mg), m.p. 189–201°, was recrystallized from MeOH–acetone to yield a single compound (36 mg), needles, having m.p. 215–217°, which was identified as VII by the mixture m.p. and by comparison of the R_f values and IR spectra.

The Birch reduction of 11-*deoxojervine* (III) *to* V′ (= V) *and* 22,27-*iminojerva*-5,13(17)-*diene*-3β,23β-*diol* (8β,9α-*dihydro*-11-*deoxoisojervine*, XV)

To a soln of III (3·0 g) in anhyd $EtNH_2$ (100 ml) was added finely divided Li (1·5 g), and the mixture was refluxed under stirring. After stirring for 1 hr, the blue color appeared and the mixture was continuously stirred at the temp for 3·0 hr. After addition of NH_4Cl followed by removal of the $EtNH_2$, the residue was diluted with water and extracted with $CHCl_3$ (ca. 300 ml). The $CHCl_3$ soln, after being washed with water and dried, was concentrated to ca. 50 ml, when $CHCl_3$-addition compounds (0·65 g) crystallized out and were collected by filtration. Recrystallization from MeOH–acetone gave XV (0·48 g), m.p. 154–155°;‖ $[\alpha]_D$ −101°; R_f (PC) = 0·78; IR, ν_{max} 3300, 1715 (acetone), 1063, 877 and 806 cm^{-1}. (Found: C, 78·10; H, 10·65; N, 3·18. $C_{27}H_{43}O_2N$ requires: C, 78·40; H, 10·48; N, 3·39%). The $CHCl_3$ filtrate was evaporated

* Ref. 10, footnote 40.

† Reported m.p., 198–199°.[8]

‡ Reported rotation, −64·9°.[8]

§ Reported m.p., 217–218°.[8]

‖ Reported m.p., 157–159°.[8]

to yield a crystalline substance, which on recrystallization from acetone afforded V' (1·27 g), m.p. 188–190°;* $[\alpha]_D$ −58°;* R_f (PC) = 0·51;* IR, ν_{max} 3400, 1063, 883 and 806 cm^{-1}; NMR, τ 4·55 (1H, m, H at C_6), 8·40 (3H, s?, 18-Me), 9·00 (3H, s, 19-Me), and 9·11 (6H, broad d J = 5·5 c/s, 21- and 26-Me). (Found: C, 78·55; H, 10·30; N, 3·56. $C_{27}H_{43}O_2N$ requires: C, 78·40; H, 10·48; N, 3·39%). This compound V' was identical with compound V in all respects.

Acetylation of V' (48 mg) with Ac_2O (0·5 ml) and pyridine (0·5 ml) afforded V'a (41 mg), which had m.p. 188–190° and $[\alpha]_D$ −10·2° on recrystallization from MeOH aq and showed the same R_f value, IR and NMR spectra as those of Va.

Hydrogenation of V *and* V' *to* 22,27-*imino*-17β(?)-*jerv*-12-*ene*-3β,23β-*diol* (IX) *and* 22,27-*imino*-12ξ,13ξ,17ξ-*jervane*-3β,23β-*diol* (X)

(a) Compound V (913 mg) was hydrogenated in the presence of prereduced Adams' PtO_2 (500 mg) at room temp in AcOH and 104 ml of H_2 (ca. 2·1 moles) was absorbed for 21 hr. After removal of the catalyst and the solvent, the residue was diluted with water, made alkaline with 10% Na_2CO_3 aq and then shaken with $CHCl_3$ (60 ml), when $CHCl_3$-addition compounds (215 mg) remained suspended between the aqueous and $CHCl_3$ layers and were collected by filtration. Recrystallization from MeOH–acetone afforded X (158 mg), m.p. 185–187°;* $[\alpha]_D$ −28·5°; R_f (PC) = 0·59; IR, ν_{max} 3300, 1715 (acetone), 1039 and 878 cm^{-1}; mass spectrum, *m/e* 417. (Found: C, 77·85; H, 11·01; N, 3·24. $C_{27}H_{47}O_2N$ requires: C, 77·64; H, 11·34; N, 3·35%).

The aqueous soln obtained on removal of the afore-mentioned compounds was shaken with $CHCl_3$ (2 × 50 ml), and all the $CHCl_3$ solns were combined, washed with water and dried. The residue (658 mg) obtained after removal of the solvent was crystallized from acetone. Recrystallization from acetone gave, as the 1st crop, a compound (X', 88 mg), m.p. 184–186°, IR, ν_{max} 3510, 3200, 1030 and 883 cm^{-1}, which showed a single spot on TLC and proved to be a saturated compound, a stereoisomer of X, on the basis of the NMR spectrum of its triacetyl derivative described below. (Found: C, 77·38; H, 11·19; N, 3·58. $C_{27}H_{47}O_2N$ requires: C, 77·64; H, 11·34; N, 3·35%).

Further fractional recrystallizations of the mother liquor from acetone and MeOH–acetone afforded an additional amount (28 mg) of X, m.p. 187–188°, a mixture (280 mg) of X and IX, and a pure sample of IX (210 mg), m.p. 177–179°;† R_f (PC) = 0·50; IR, ν_{max} 3400, 3300, 1041 and 885 cm^{-1}; mass spectrum, *m/e* 415. (Found: C, 78·33; H, 10·80; N, 3·21. $C_{27}H_{45}O_2N$ requires: C, 78·02; H, 10·91; N, 3·37%).

Compound X (50 mg) was treated with Ac_2O (0·5 ml) and pyridine (0·5 ml) on a water bath for 3 hr. After removal of the solvents *in vacuo*, the residue was refluxed with KOH (1·0 g) in MeOH (10 ml) for 2 hr under a stream of N_2. After cooling and removal of the solvent, the residue was diluted with water (20 ml) and extracted with $CHCl_3$ (24 ml). The $CHCl_3$ soln left a resinous substance after drying and evaporation, which was crystallized and then recrystallized from EtOAc to yield Xa (33 mg), m.p. 178–180°; IR, ν_{max} 3360, 1645, 1614 and 1043 cm^{-1}; NMR, no absorption near τ 4·5 and 8·4, τ 7·84 (3H, s, N–Ac), 8·73 (s, O<u>H</u>), 9·125 (6H?, d J = 5 c/s), and 9·24 (3H, s, 19-Me). (Found: C, 75·63; H, 10·98; N, 2·88. $C_{29}H_{49}O_3N$ requires: C, 75·77; H, 10·74; N, 3·05%).

Acetylation of X' (50 mg) with Ac_2O (0·5 ml) and pyridine (0·5 ml) gave X'a (45 mg), which had m.p. 157–159° on recrystallization from EtOAc or MeOH; IR, ν_{max} 1733, 1618, 1245 and 1025 cm^{-1}; NMR, no sharp peak near τ 4·5 and 8·4, a broad peak consisting of 3 peaks centered at τ 4·86, 5·33 and 5·58 (3H, H at C_3, C_{22} and C_{23}); τ 9·125 (6H?, d J = 7 c/s), and 9·24 (3H, s, 19-Me). (Found: C, 72·68; H, 10·05; N, 2·44. $C_{33}H_{53}O_5N$ requires: C, 72·89; H, 9·82; N, 2·58%).

Acetylation of IX (46 mg) with Ac_2O (0·5 ml) and pyridine (0·5 ml) afforded IXa (41 mg), which had m.p. 201–204° on crystallization from MeOH aq. Recrystallization from the same solvent gave a pure sample of IXa, m.p. 217–219°;‡ IR, ν_{max} 1734, 1638, 1240 and 1021 cm^{-1}; NMR, a broad peak consisting of 4 peaks centered at τ 4·88, 5·25, 5·35 and 5·58 (3H, H at C_3, C_{22} and C_{23}), τ 8·48 (3H, s, 18-Me), 8·80 and 9·20 (each 3H, d J = 6·5 and 6·0 c/s, 21- and 26-Me or *vice versa*), and 9·23 (3H, s, 19-Me). (Found: C, 73·06; H, 9·74; N, 2·33. $C_{33}H_{51}O_5N$ requires: C, 73·16; H, 9·49; N, 2·59%).

(b) Compound V' (250 mg) was hydrogenated over Adams' PtO_2 (150 mg) in AcOH (30 ml) in the same manner as mentioned above, and the reaction was ceased after 24 hr, when 29·4 ml of H_2 (ca. 2·1 moles) had been taken up. After usual work up, the product was completely dissolved in $CHCl_3$ (200 ml), washed

* Reported m.p., rotation and R_f-value (PC), 190–192°, −53·6° and 0·56, respectively.[8]

* Reported m.p., 180–182°.[8]

† Reported m.p., 184–186°.[8]

‡ Reported m.p., 201–204°.[5]

with water and dried. The residue obtained on removal of the $CHCl_3$ was roughly separated into 3 fractions by repeated preparative TLC on silica gel using a 4:1 mixture of ether and benzene. The most mobile fraction (83 mg) gave IX (35 mg), m.p. 175–177°, and the middle (82 mg) X (30 mg), m.p. 183–185° and its stereoisomer (X', 10 mg) m.p. 181–183°, on repeated recrystallizations of the respective fraction from acetone. All these identifications were carried out by the mixture m.p. method and by rigorous comparison of the IR spectra and behaviors on TLC.

The Birch reduction of veratramine (II) *to* 22,27-*imino*-12ξ-*jerva*-5,13(17),14-*triene*-3β,23β-*diol* (XXIII)

To a soln of II (0·60 g) in $EtNH_2$ (70 ml) containing isopropyl alcohol (1·9 ml) was added Li (180 mg), and the mixture was refluxed for 1 hr under stirring. The reaction mixture was worked up as usual and crystallized on trituration with acetone. The product was recrystallized fractionally from acetone, each component being always checked by paper chromatography but not by TLC, because the product was unstable to acidic silica gel, and two compounds were isolated in pure state. One (XXIII, 0·20 g) had m.p. 182–184°; R_f (PC) = 0·41; UV, only end absorption, ε 16,000 at 210 mμ; IR, ν_{max} 3180, 1628, 1067, 1037 and 814 cm^{-1}; NMR, τ 4·62 (2H, b, H at C_6 and C_{15}), 8·47 (3H, s, 18-Me), 9·01 and 9·12 (each 3H, d J = 7·5 and 6·5 c/s, 21- and 26-Me or *vice versa*), and 9·02 (3H, s, 19-Me). (Found: C, 78·55; H, 10·20; N, 3·25. $C_{27}H_{41}O_2N$ requires: C, 78·78; H, 10·04; N, 3·40%). The other compound (54 mg), m.p. 155–157°, had R_f (PC) 0·30, but was not further examined.

Acetylation of XXIII (40 mg) with Ac_2O (0·4 ml) and pyridine (0·4 ml) afforded the triacetyl derivative (XXIIIa, 26 mg), which had m.p. 144–146° on recrystallization from MeOH aq, IR, ν_{max} 1733, 1644, 1630 (sh), 1236, 1035 (sh) and 1025 cm^{-1}; NMR, a broad peak consisting of four peaks centered at τ 4·89, 5·20, 5·39 and 5·55 (3H, H at C_3, C_{22} and C_{23}), τ 4·59 (2H, b, H at C_6 and C_{15}), 8·47 (3H, s, 18-Me), 8·81 and 9·18 (each 3H, d J = 7·5 and 7·0 c/s, 21- and 26-Me or *vice versa*), and 9·02 (3H, s, 19-Me). (Found: C, 73·55; H, 8·99; N, 2·50. $C_{33}H_{47}O_5N$ requires: C, 73·71; H, 8·81; N, 2·61%).

Hydrogenation of XXIII *to* IX *and* X

Compound XXIII (204 mg) was hydrogenated over prereduced Adams' PtO_2 (100 mg) at room temp in AcOH (14 ml) for 19 hr, when 36 ml of H_2 (ca. 3·6 moles) had been consumed. After removal of the catalyst and the solvent, the residue was diluted with water (50 ml), made alkaline with 10% Na_2CO_3 aq and extracted with $CHCl_3$ (80 ml). The $CHCl_3$ soln, after being dried and concentrated to ca. 10 ml, was allowed to stand at room temp, when $CHCl_3$-addition compounds (64 mg) separated out and were collected by filtration. Recrystallization from acetone gave a compound (38 mg), m.p. 183–185°,* which showed a single spot both on TLC and PC (R_f = 0·58) and was identical with X in all respects. The $CHCl_3$ filtrate was evaporated to dryness and crystallized on trituration with acetone. Recrystallization from acetone afforded a crystalline substance (57 mg) having m.p. 174–176°. Although this sample showed one spot on PC (R_f = 0·41), it was found to consist of two compounds, which proved to be IX and X by careful examination of TLC.

The Oppenauer oxidation of V *and* V' *to* 22,27-*imino*-17β(?)-*jerva*-4,12-*dien*-23β-*ol*-3-*one* (XI *and* XI')

(a) To a soln of V (1·0 g) in toluene (200 ml) and dry cyclohexanone (redistilled, 10 ml) was added aluminum isopropoxide (1·0 g). The whole mixture was heated under stirring to distil ca. 70 ml of toluene to dry the system and then refluxed for 6 hr. After being cooled, the mixture was distilled with steam until most of the solvents had been removed, and the residue was extracted repeatedly with $CHCl_3$. The $CHCl_3$ soln after being dried was evaporated to dryness *in vacuo* to leave a yellow resin, which was crystallized from acetone. Recrystallization from acetone afforded XI (0·47 g), m.p. 176–178°; $[\alpha]_D$ +57°; UV, λ_{max} 236 mμ (ε 25,500); IR, ν_{max} 3400, 1660, 1616 and 1015 cm^{-1}; NMR, τ 4·22 (1H, s, H at C_4), 8·44 (3H, s, 18-Me), 8·83 (3H, s, 19-Me), and 9·12 and 9·15 (total 6H, two d J = 6·5 and 7 c/s, 21- and 26-Me or *vice versa*). (Found: C, 78·64; H, 9·90; N, 3·59. $C_{27}H_{41}O_2N$ requires: C, 78·78; H, 10·04; N, 3·40%).

(b) Compound V' (3·7 g) in toluene (300 ml) was treated with dry cyclohexanone (35 ml) in the presence of aluminum isopropoxide (3·7 g) in the same manner as described above, and XI' (1·62 g), m.p. 175–177°, was isolated after recrystallization from acetone. Compound XI' was identical with XI in all respects (m.p. and mixed m.p., optical rotation, TLC and IR).

The Birch reduction of XI *and* XI' *to* 22,27-*imino*-17β(?)-*jerv*-12-*en*-23β-*ol*-3-*one* (XII *and* XII')

(a) To a soln of liquid NH_3 (110 ml) containing Li (109 mg) and cooled with dry ice–acetone was added

* Reported m.p., 181–183°.[8]

XI (0·40 g) in THF (10 ml) under stirring, and the mixture was refluxed for 40 min. NH_4Cl (1 g) was added and the resulting mixture was kept at room temp to remove the NH_3. The residue was diluted with water and shaken with $CHCl_3$ repeatedly. The $CHCl_3$ soln left a resinous substance after drying and removal of the $CHCl_3$, which was crystallized from acetone. Recrystallization from acetone afforded XII (0·16 g), m.p. 159–161°; $[\alpha]_D$ +40°; ORD (dioxan), $[\phi]_{318}^{peak}$ +1890°, $[\phi]_{270}^{trough}$ −1030°; IR, ν_{max} 3250, 1714, 1044 and 1033 cm^{-1}. (Found: C, 78·16; H, 10·28; N, 3·58. $C_{27}H_{43}O_2N$ requires: C, 78·40; H, 10·48; N, 3·39%).

(b) Compound XI′ (0·50 g) in THF (7 ml) was reduced with Li (73 mg) in liquid NH_3 (110 ml) in a manner similar to V, and XII′ (0·17 g), m.p. 159–161°, was isolated after recrystallization from acetone. Compound XII′ was identical with XII in all respects.

Reduction of XII *and* XII′ *with sodium borohydride to* IX *and* IX′

(a) Compound XII (150 mg) was treated with $NaBH_4$ (90 mg) at room temp for 2 hr in abs EtOH under stirring. After decomposition of the excess $NaBH_4$ with acetone, the soln was evaporated to dryness and the residue shaken with water and $CHCl_3$. The $CHCl_3$ soln gave a resinous substance, which was crystallized with acetone, had m.p. 171–174° and amounted to 120 mg. Recrystallization from acetone afforded a pure sample of the 3-alcohol, m.p. 176–178°; $[\alpha]_D$ −7·0°; IR, ν_{max} 3400, 3300, 1042 and 886 cm^{-1}; NMR, τ 8·48 (3H, s, 18-Me), 9·11 (and 9·15?) (total 6H, two(?) d J = 5·5 and 6 c/s, 21- and 26-Me), and 9·25 (3H, s, 19-Me). (Found: C, 77·78, H, 10·71; N, 3·26. $C_{27}H_{45}O_2N$ requires: C, 78·02; H, 10·91; N, 3·37%).

The 3-alcohol (108 mg) was heated with Ac_2O (2·5 ml) and pyridine (2 ml) on a water bath for 2 hr. The soln was worked up as usual and yielded the triacetyl derivative (92 mg), m.p. 218–220° (from MeOH aq); $[\alpha]_D$ +17°; IR, ν_{max} 1735, 1640, 1243 and 1025 cm^{-1}. The alcohol and triacetyl derivatives were completely identical with IX and IXa respectively; in all respects.

(b) Compound XII′ (200 mg) was reduced with $NaBH_4$ (105 mg) in a way similar to XII and worked up as usual. Recrystallization of the product from acetone gave IX′ (153 mg), m.p. 176–178°, which was identical with a sample prepared from XII.

Acetylation of IX′ (1·63 g) with Ac_2O (15 ml) and pyridine (15 ml) was carried out as usual and gave the triacetyl derivative (0·87 g), m.p. 216–218° (from MeOH aq), which was identical with a sample prepared from XII.

Osmium tetroxide oxidation of IXa *to* 22,27-*imino*-17β(?)-*jervane*-3β,12ξ,13ξ,23β-*tetrol* (XIII)

To a soln of IXa (267 mg) in dry ether (23 ml) containing pyridine (0·3 ml) was added OsO_4 (195 mg), and the mixture was allowed to stand at room temp for 40 days. After evaporation of the solvent *in vacuo*, the residue was dissolved in a mixture of EtOH (30 ml) and water (15 ml) containing Na_2SO_3 (800 mg) and then refluxed for 5 hr on a water bath, when black ppts gradually appeared. After removal of the ppt by filtration, the filtrate was evaporated to dryness, diluted with water and extracted with $CHCl_3$ repeatedly. The $CHCl_3$ soln left a resinous substance (196 mg) after drying and evaporation, which was separated by preparative TLC (ether). The main fraction (116 mg) was crystallized from acetone and recrystallized to yield XIII (97 mg), m.p. 249–251°; $[\alpha]_D$ +22°; IR, ν_{max} 3475, 3300, 1626, 1600, 1134, 1114, 1049 and 1024 cm^{-1}. (Found: C, 70·68; H, 9·88; N, 2·95. $C_{29}H_{49}O_5N$ requires: C, 70·84; H, 10·05; N, 2·85%).

Periodic acid oxidation of XIII

To a soln of XIII (52 mg) in MeOH (10 ml) was added $HIO_4 \cdot 2H_2O$ (26 mg) in water (3 ml), and the soln was stirred at room temp. After 26 hr the soln was distilled at room temp *in vacuo*, and the residue was diluted with water and extracted with $CHCl_3$. The $CHCl_3$ soln left a resinous mixture, which was separated into three fractions by repeated TLC (ether: MeOH, 98:2). A fraction obtained from the least mobile and main band amounted to 33 mg (63%) and showed a single spot on careful examination of TLC, although it resisted crystallization. The amorphous compound XIV showed sharp absorption maxima at 1734 and 1712 cm^{-1} besides at 3400, 1627, 1160, 1049 and 1029 cm^{-1} in the IR spectrum in $CHCl_3$. (Found: C, 71·06; H, 9·81; N, 2·68. $C_{29}H_{47}O_5N$ requires: C, 71·13; H, 9·68; N, 2·86%).

Transformation of XV *to* 22,27-*iminojerv*-13(17)-*ene*-3β,23β-*diol* (XVI)

(a) Compound XV (183 mg) was dissolved in MeOH and then evaporated to remove acetone (solvent of crystallization). The residue was hydrogenated over prereduced Adams' PtO_2 (100 mg) at room temp for 21 hr in AcOH (14 ml). After removal of the catalyst and solvent, the residue was diluted with water,

made alkaline and extracted repeatedly with $CHCl_3$ (total 110 ml). On concentration to ca. 10 ml after drying, the chf soln gave $CHCl_3$-addition compounds (120 mg), which were recrystallized from acetone to yield XVI (45 mg), m.p. 153–155°. Further recrystallization raised the m.p. to 155–157°.* This compound was identical with an authentic specimen prepared by hydrogenation of III[13] in all respects.

(b) To a soln of XV (1·5 g) in toluene (200 ml) and dry cyclohexanone (15 ml) was added aluminum isopropoxide (1·5 g). The mixture was heated to distil ca. 70 ml of toluene and then refluxed for 6 hr under stirring. After being cooled, the mixture was distilled with steam for ca. 4·5 hr, and the residue was extracted with $CHCl_3$. The $CHCl_3$ soln left, after drying and evaporation, an amorphous substance (1·25 g), IR, ν_{max} 3400, 1675 and 1045 cm^{-1}, which was used for the next step without further purification. The amorphous α,β-unsaturated ketone (ca. 1·25 g) dissolved in dry THF (30 ml) was reduced with Li (580 mg) in refluxing NH_3 for 50 min under stirring. After addition of NH_4Cl (4 g) and removal of the NH_3, the residue was diluted with water and extracted with chf, and the $CHCl_3$ soln gave a ketone (ca. 0·8 g), IR, ν_{max} 3400, 1714 and 1040 cm^{-1}, which resisted crystallization and was used for the next reduction. The ketone was treated with $NaBH_4$ (0·50 g) at room temp for 2 hr in EtOH (50 ml) under stirring. Acetone was added to the mixture under cooling with ice to decompose the excess $NaBH_4$, and the solvents were removed *in vacuo*. The residue was shaken with water and $CHCl_3$ (120 ml), and the $CHCl_3$ soln, after being dried, was concentrated to ca. 40 ml, when $CHCl_3$-addition compounds (0·50 g) separated out, were collected by filtration, and crystallized on trituration with acetone. Recrystallization from acetone afforded XVI (0·17 g), m.p. 151–153°; $[\alpha]_D$ −61°; IR, ν_{max} 3400, 3240, 1035 and 878 cm^{-1}. This was completely identical with a sample prepared by the afore-mentioned hydrogenation of XV.

Hydrogenation of II *to* 5α,6- *and* 5β,6-*dihydroveratramine* (XVIII *and* XIX)

Veratramine (II, 7·00 g) was hydrogenated in the presence of prereduced Adams' PtO_2 (1·40 g) at room temp in AcOH (90 ml), and 430 ml of H_2 (ca. 1·1 mole) was absorbed after 32·5 hr. After removal of the catalyst and the solvent, the residue was diluted with water (25 ml) and made alkaline with conc NH_4OH to yield crystalline ppts, which were collected by filtration and recrystallized from EtOH aq. The 1st crop (3·64 g), m.p. 175–180°, was again recrystallized from EtOH to give XVIII[18a] (1·90 g), leaflets, m.p. 191–193°. The filtrate obtained on collection of the crystalline ppts was evaporated and dissolved in AcOH aq, and to the acidic soln was added $(NH_4)_2SO_4$, when insoluble sulphates precipitated. The whole mixture was shaken with $CHCl_3$ to remove resinous material. The insoluble sulphates were then collected by filtration and shaken with 6N NH_4OH and $CHCl_3$, and the $CHCl_3$ soln left amorphous bases on drying and evaporation. On the other hand, the mother liquor obtained on the recrystallization was evaporated, combined with the aforementioned amorphous bases and chromatographed on alumina (Merck, standard, 3·5 × 25 cm) using the following solvents successively; benzene (500 ml), benzene–ether (19 : 1, 600 ml), (9 : 1, 500 ml), (4 : 1, 4700 ml), (3 : 2, 2300 ml), ether (2700 ml), and ether–MeOH (19 : 1, 1200 ml). Fractions eluted with benzene–ether (4 : 1) and with the 1st 200 ml of benzene–ether (3 : 2) were combined and evaporated to yield XIX (3·16 g), rods, which contained benzene as solvent of crystallization and melted near 80° (dec); $[\alpha]_D$ +37°; IR, ν_{max} 3384, 1034 and 674 (benzene) cm^{-1}; NMR, τ 7·67 (3H, s, 18-Me), 8·59 (3H, d J = 7 c/s, 21-Me), 8·90 (3H, s, 19-Me), and 9·17 (3H, d J = 6 c/s, 26-Me). (Found: C, 80·91; H, 9·55; N, 2·71. $C_{27}H_{41}O_2N \cdot C_6H_6$ requires: C, 80·93; H, 9·67; N, 2·86%). Fractions with ether and with ether–MeOH (19 : 1) were combined, evaporated and recrystallized from benzene to give a practically pure sample of XVIII (1·15 g), m.p. 183–185°. Cf. XVIII, NMR,[22] τ 7·68 (3H, s, 18-Me), 8·59 (3H, d J = 7 c/s, 21-Me), 9·06 (3H, s, 19-Me), and 9·17 (3H, d J = 6 c/s, 26-Me).

Compound XIX (2·00 g) was heated to reflux in Ac_2O (20 ml) for 1·5 hr. After removal of the solvent *in vacuo*, the residue was dissolved in $CHCl_3$ washed with 5% Na_2CO_3 aq and water, and dried. The $CHCl_3$ soln left, on removal of the solvent, a crystalline substance, which on recrystallization from ether gave XIXa (1·92 g), platelets, m.p. 177–178°. An analytical sample had m.p. 179–180°; $[\alpha]_D$ +123°; IR, ν_{max} 1731, 1642, 1254, 1246, 1229 and 1027 cm^{-1}; NMR, τ 8·91 (3H, s, 19-Me). (Found: C, 73·85; H, 8·69; N, 2·50. $C_{33}H_{47}O_5N$ requires: C, 73·71; H, 8·81; N, 2·61%). Cf. XVIIIa,[18c] NMR, τ 9·03 (3H, s, 19-Me).

Compound XIXa (80 mg) was refluxed in 10% methanolic KOH (5 ml) for 3 hr, and the soln was then concentrated *in vacuo* to 1 ml and diluted with water (15 ml). The resulting ppt was collected by filtration and crystallized from EtOH aq to afford the N-acetyl derivative (XIXb, 56 mg) of XIX, m.p. 191–193°. Recrystallization from the same solvent gave an analytical sample, m.p. 193–194°; $[\alpha]_D$ +102° IR, ν_{max} 3420, 1611 (sh), 1593 and 1033 cm^{-1}; NMR, τ 8·92 (3H, s, 19-Me). (Found: C, 76·74; H, 9·60; N, 3·07. $C_{29}H_{43}O_3N$ requires: C, 76·78; H, 9·55; N, 3·09%). Cf. XVIIIb,[18c] NMR, τ 9·05 (3H, s, 19-Me).

* lit.,[8] m.p. 156–157°.

23-O,N-*Diacetyl*-5α,6- *and* 5β,6-*dihydroveratramine* (XVIIIc) *and* XIXc)

(a) Compound XVIIIa[18c] (903 mg) was refluxed in MeOH (90 ml) containing conc HCl (1·8 ml) for 1·5 hr. The mixture was evaporated *in vacuo* and diluted with water to yield a white ppt (845 mg), which was collected by filtration, dried and purified by chromatography on acid-washed alumina (Woelm, grade I, 25 g) using the following solvents successively; benzene, benzene–ether (9:1, 4:1, 3:1 and 2:1), and ether–MeOH (9:1). Fractions eluted with benzene–ether were all combined and evaporated to give a crystalline substance (776 mg), which on recrystallization from EtOH aq afforded XVIIIc (580 mg), m.p. 214–215°; $[\alpha]_D$ +123°; IR, ν_{max} 3350, 1735, 1242, 1044, 1030 and 821 cm^{-1}; NMR, τ 9·05 (3H, s, 19-Me). (Found: C, 75·02; H, 9·31; N, 2·58. $C_{31}H_{45}O_4N$ requires: C, 75·11; H, 9·15; N, 2·83%).

(b) Compound XIXa (1·50 g) was hydrolysed in refluxing MeOH (150 ml) containing conc HCl (3 ml) for 1·5 hr. The reaction mixture was worked up and chromatographed in a way similar to XVIIIa. Fractions eluted with benzene–ether (3:1, 2:1 and 1:1) afforded a crystalline substance (1·30 g), which on recrystallization from EtOH gave XIXc (0·60 g), m.p. 163–165°; $[\alpha]_D$ +139°; IR, ν_{max} 3368, 1735, 1633, 1612, 1248 and 1034 cm^{-1}; NMR, τ 8·89 (3H, s, 19-Me). (Found: C, 74·88; H, 9·08; N, 2·85. $C_{31}H_{45}O_4N$ requires: C, 75·11; H, 9·15; N, 2·83%).

3-*Dehydro*-23-O,N-*diacetyl*-5α,6- *and* 5β,6-*dihydroveratramine* (XX and XXI) *from* XVIIIc *and* XIXc

(a) To a soln of XVIIIc (201 mg) in acetone (10 ml) was added the Jones reagent[23] (0·2 ml) at ice-bath temp, and the mixture was allowed to stand at the temp for 1 hr under stirring. After addition of EtOH (2 ml) and removal of the solvent *in vacuo*, the residue was diluted with water (5 ml) and extracted with three portions of 5 ml of $CHCl_3$. The combined extracts were washed successively with water (2 ml), 5% $NaHCO_3$ aq (2 ml) and water (2 ml), dried and left an amorphous residue (206 mg) after removal of the $CHCl_3$. A part (155 mg) of the residue was submitted to purification by TLC, and afforded a homogenous resin (XX, 102 mg), IR, $\nu_{max}^{CHCl_3}$ 1723, 1704 and 1624 cm^{-1}, which, however, resisted crystallization. The compound XX gave the same R_f value and IR spectrum as those of an authentic specimen[18b] prepared by acetylation of XXa.[18b] Cf. XXa, NMR, τ 7·70 (3H, s, 18-Me), 8·61 (3H, d J = 6·5 c/s, 21-Me), 8·88 (3H, s, 19-Me), and 9·175 (3H, d J = 5 c/s, 26-Me).

(b) Oxidation of XIXc (401 mg) in acetone (20 ml) with Jones' reagent (0·4 ml) was carried out and worked up in the same manner as XVIIIc. The product crystallized on trituration with acetone, had m.p. 197–200°, and amounted to 368 mg. Recrystallization from acetone gave an analytical sample of XXI, needles, m.p. 200–202°; $[\alpha]_D$ +144°; IR, ν_{max} 1727, 1722, 1633, 1253 and 1026 cm^{-1}; NMR, τ 8·84 (3H, s, 19-Me). (Found: C, 75·40; H, 8·77; N, 3·02. $C_{31}H_{43}O_4N$ requires: C, 75·42; H, 8·78; N, 2·84%).

Degradation of XVIII *to* 17-*acetyletiojerva*-12,14,16-*trien*-3β-*ol* (XVII)

To a soln of XVIII (1·00 g) in CH_2Cl_2 (125 ml) was added finely powdered N-chlorosuccinimide (0·50 g), and the mixture was stirred at room temp for 1 hr. After being washed with 3 portions of 20 ml of water and then dried, the mixture was evaporated *in vacuo* to leave the crystalline, N-chloro derivative (ca. 1·4 g), which was dried in a desicator. To the chloroamine dissolved in MeOH (25 ml) and cooled in an ice-bath was added a soln of methanolic NaOMe, prepared from Na (0·5 g) and MeOH (30 ml), in a stream of N_2 and under stirring, and the soln was continuously stirred at ice-bath temp for 1 hr. After evaporation of the solvent below 30° *in vacuo*, the residue was vigorously stirred in N HCl (100 ml) at room temp for 22 hr, and the resulting powdered ppt was collected by filtration and dried. An aldehyde mixture (XXI, 765 mg) thus obtained, IR, ν_{max} 3516, 3280, 2726, 1723, 1075, 1038 and 815 cm^{-1}, NMR, τ 0·17 (1H, bs, CHO), 7·72 (3H, s, 18-Me), 8·61 (3H, d J = 6·5 c/s, 21-Me), and 9·05 (3H, s, 19-Me), melted at 82–100° with decomposition and was used for the next reaction without further purification.

The crude aldehyde (3·04 g), combined with that obtained in another run, was dissolved in benzene (25 ml), and the soln was evaporated to dryness *in vacuo* to remove a trace of water. The residue was then dissolved in n-butanol (30 ml) containing n-butyl nitrite (3 ml) and cooled in an ice-bath, while a soln of NaOBu which had been prepared from Na (0·72 g) and n-butanol (30 ml) was added under a stream of N_2. The whole mixture was allowed to stand at ice-bath temp for 4 hr. After addition of dry ice, the mixture was treated with ether (50 ml) and water (40 ml), and the organic layer was concentrated *in vacuo*, diluted with water (30 ml) and extracted with $CHCl_3$ (70 ml). The aqueous layers were combined and again extracted with $CHCl_3$ (20 ml). All the $CHCl_3$ solns were combined, washed with water, dried and evaporated *in vacuo*, yielding a semi-crystalline substance, which was crystallized from EtOH to give an oxime (810 mg), m.p. 228–232°; $[\alpha]_D$ +50°; IR, ν_{max} 3245, 1660, 1082, 1044, 1013 and 821 cm^{-1}. (Found: C, 76·84; H, 8·70; N, 4·21. $C_{21}H_{29}O_2N$ requires: C, 77·02; H, 8·93; N, 4·28%). The mother liquor was evaporated and

then dissolved in ether, and the ether soln was repeatedly shaken with Claisen's alkali (total 80 ml) to extract the oxime. The fraction obtained via Claisen's alkali extraction amounted to 2·0 g, from which an additional amount (590 mg) of the crystalline oxime, m.p. 202–209°, was obtained on trituration with EtOH.

To a suspended mixture of the oxime (2·00 g) in EtOH (160 ml) was added 2N HCl (160 ml) under stirring, and the stirred mixture was heated at 50° under an atmosphere of N_2 for 30 hr. The mixture was concentrated *in vacuo* and extracted with ether repeatedly (total 250 ml), and the combined organic solns were washed with Claisen's alkali and water, and then dried. After removal of the solvent, the residue crystallized on trituration with EtOH, and was recrystallized from EtOH to give XVII (1·29 g), m.p. 169–171°. Recrystallization gave an analytical sample, m.p. 172–174°; $[\alpha]_D$ +43°; UV, λ_{max} 258 mμ (ε 15,000); IR, ν_{max} 3473, 1667, 1597, 1268, 1040 and 818 cm^{-1}; NMR, τ 7·42 (3H, s, 21-Me), 7·56 (3H, s, 18-Me), and 9·05 (3H, s, 19-Me). (Found: C, 80·58; H, 8·89. $C_{21}H_{28}O_2$ requires: C, 80·73; H, 9·03%). From the Claisen's alkali extracts there was obtained the crude oxime, m.p. 208–220°.

Oxidation of "diacetyljervine-11β-ol" (IVa) *to diacetyljervine* (Ia)

To a soln of IVa (75 mg) in acetone (10 ml, distilled over $KMnO_4$) was added the Jones reagent (3 drops) under ice-cooling, and the mixture was stirred for 10 min at the temp. After addition of EtOH and removal of the solvent *in vacuo*, the residue was extracted with $CHCl_3$, and the chf soln left a resinous substance (84 mg) after being washed and dried, which was separated by TLC. A fraction extracted from the most mobile and main band gave a resin (52 mg) on evaporation of the solvent, which was crystallized from EtOH and recrystallized from the same solvent to yield Ia (40 mg), m.p. 176–178°. This compound was identical with a sample[24] prepared from I.

Transformation of IV *to* II *by treatment with hydrochloric acid*[5]

Compound IV (200 mg) was treated with conc HCl (7 ml) in refluxing MeOH (50 ml) for 2 hr. After being cooled, the mixture was diluted with water (60 ml), made alkaline to pH 9·2 with 10% Na_2CO_3 aq and allowed to stand overnight, when ppts separated out and were collected by filtration. The ppts (193 mg) showed 3 spots on PC and were crystallized from acetone. Fractional recrystallizations from acetone gave II (70 mg), m.p. 200–202°.

Acknowledgement—The authors wish to express their thanks to Professor S. Okuda, the University of Tokyo, and to Dr. I. Iwai, Sankyo Co. Ltd., for generously providing them with crude jervine. They are also indebted to Mr. S. Shimokawa, Hokkaido University, for the measurement of the NMR spectra.

REFERENCES

[1] Part X of *C-Nor-D-homosteroids and Related Alkaloids*; Part IX, Ref. 14.
[2] H. Mitsuhashi and Y. Shimizu, *Tetrahedron Letters* 777 (1961); *Tetrahedron* **19**, 1027 (1963).
[3] J. Fried and A. Klingsberg, *J. Am. Chem. Soc.* **75**, 4929 (1953); S. M. Kupchan and S. D. Levine, *Ibid.* **86**, 701 (1964).
[4] D. M. Bailey, D. P. G. Hamon and W. S. Johnson, *Tetrahedron Letters* 555 (1963).
[5] T. Masamune, Y. Mori, M. Takasugi and A. Murai, *Tetrahedron Letters* 913 (1964). See also Experimental.
[6] O. Wintersteiner and N. Hosansky, *J. Am. Chem. Soc.* **74**, 4474 (1952).
[7] O. Wintersteiner and M. Moore, *Tetrahedron* **20**, 1947 (1964) and refs cited therein; J. Biellmann, P. Crabbe and G. Ourisson, *Ibid.* 3, 303 (1958); G. Quinkert, *Experientia* **13**, 381 (1957); H. O. House, V. Paragamian, R. S. Rao and D. J. Wluka, *J. Am. Chem. Soc.* **82**, 1457 (1960).
[8] T. Masamune, M. Takasugi and Y. Mori, *Tetrahedron Letters* 489 (1965).
[9] B. M. Iselin, M. Moore and O. Wintersteiner, *J. Am. Chem. Soc.* **78**, 403 (1956).
[10] T. Masamune, M. Takasugi, M. Gohda, H. Suzuki, S. Kawahara, and T. Irie, *J. Org. Chem.* **29**, 2282 (1964).
[11] Ref. 10, footnote 33a.
[12] Cf. [a] J. M. Coxon, M. P. Hartshorn and D. N. Kirk, *Tetrahedron Letters* 119 (1965).
[b] H. Mitsuhashi and K. Shibata, *Tetrahedron* **21**, 1215 (1965).
[13] T. Masamune, K. Orito and A. Murai, *Bull. Chem. Soc. Japan* **39**, 2503 (1966).
[14] T. Masamune, M. Takasugi, A. Murai and K. Kobayashi, *J. Am. Chem. Soc.* **89**, 4521 (1967).
[15] Ref. 8, p. 491, the last line.

[16] Cf. H. O. House, *Modern Synthetic Reactions* p. 50, Benjamin, New York (1965). Investigation on the stereochemistry of the reduction using simpler compounds is now in progress.
[17] H. Mitsuhashi and K. Shibata, *Tetrahedron Letters* 2281 (1964). Also see, W. F. Johns and I. Laos, *J. Org. Chem.* **30**, 4220 (1965).
[18] [a] K. Saito, *Bull. Chem. Soc. Japan* **15**, 22 (1940); W. A. Jacobs and L. C. Craig, *J. Biol. Chem.* **160**, 555 (1945).
[b] W. A. Jacobs and Y. Sato, *Ibid.* **191**, 71 (1951).
[c] Ch. Tamm and O. Wintersteiner, *J. Am. Chem. Soc.* **74**, 3842 (1952).
[19] R. W. Franck, G. P. Rizzi and W. S. Johnson, *Steroids* **4**, 463 (1964).
[20] Cf. A. W. Burgstahler and L. R. Worden, *J. Am. Chem. Soc.* **83**, 2587 (1961).
[21] Ref. 5, footnote 7.
[22] Cf. J. W. Scott, L. J. Durham, H. A. P. deJongh, U. Burckhardt, and W. S. Johnson, *Tetrahedron Letters* 2381 (1967).
[23] A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *J. Chem. Soc.* 2548 (1953).
[24] K. Saito, H. Suginome and M. Takoaka, *Bull. Chem. Soc. Japan* **11**, 172 (1936).