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THE C-9 CONFIGURATION OF JERVINE AND RELATED ALKALOIDS[1]

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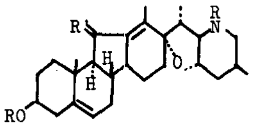
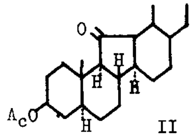
Recently, Mitsuhashi and Shimizu[2] have correlated jervine (I) with hecogenin through 3β-acetoxy-C-nor-D-homo-5α-pregnane-11-one (II). While the configurations of C-3, C-8 and C-14 of I have been established, the configuration of C-9 is still open, since the transformation from I to II involved a reaction under rather severe conditions,[3] which would render C-9 readily epimerizable. On the other hand, veratramine (III) possessing the same C-nor-D-homosteroid skeleton as I, has been shown to have B/C _trans_ configuration (9αH) on the basis of n.m.r. studies[4] or by degradation of hecogenin to the ketone (IV).[5] Although I has been related to III directly,[6] or _via_ triacetyldihydroveratramine-11-one,[7] the possibility still remains of epimerization at C-9 during the reactions. In view of the range in relative stability between _trans_ and _cis_ isomers of hydrindanone derivatives,[8] it is desirable to determine the configuration of C-9 in an unambiguous manner. The present paper will describe evidence that these alkaloids indeed have B/C _trans_ configuration.

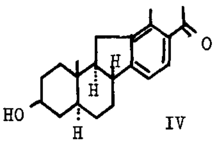
5,6-Dihydroveratramine (V),[9] m.p. 191-193°, was degraded to IV in the same manner as Johnson's fragmentation reaction;[10] V was converted to N-chloro derivative with N-chlorosuccinimide, which gave, when treated with sodium methoxide and subsequent hydrolysis, an aldehyde (VI), i.r. (in Nujol) ν_{max} 2720 and 1723 cm^{-1}; n.m.r. (60 or 100 Mc., in deuterochloroform) a singlet at τ 0.17 (1H, aldehyde proton) and a doublet (J = 6.5 c.p.s.) centered at τ 8.61 (3H, C-21 methyl group). The aldehyde was further degraded, with n-butyl nitrite and sodium n-butoxide, to the oxime, m.p. 228-232°, which was hydrolyzed to a ketone $C_{21}H_{28}O_2$ (Found: C, 80.58; H, 8.89), m.p. 169-171°; i.r. ν_{max} 1667 and 1597 cm^{-1}; u.v. (in ethanol) λ_{max} 258 mμ (ϵ 15,000); n.m.r. three singlets at τ 7.42, 7.56 and 9.05 (each 3H, C-21, C-18 and C-19 methyl groups). This ketone (over-all yield from V, 15%) was identical with the ketone (IV) prepared from hecogenin.[5]



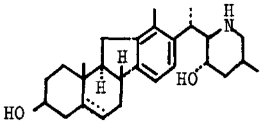
I. R' = O
X R' = H_2
XV R' = ${}^{H}_{OH}$



II

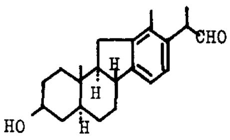


IV



III with Δ^5

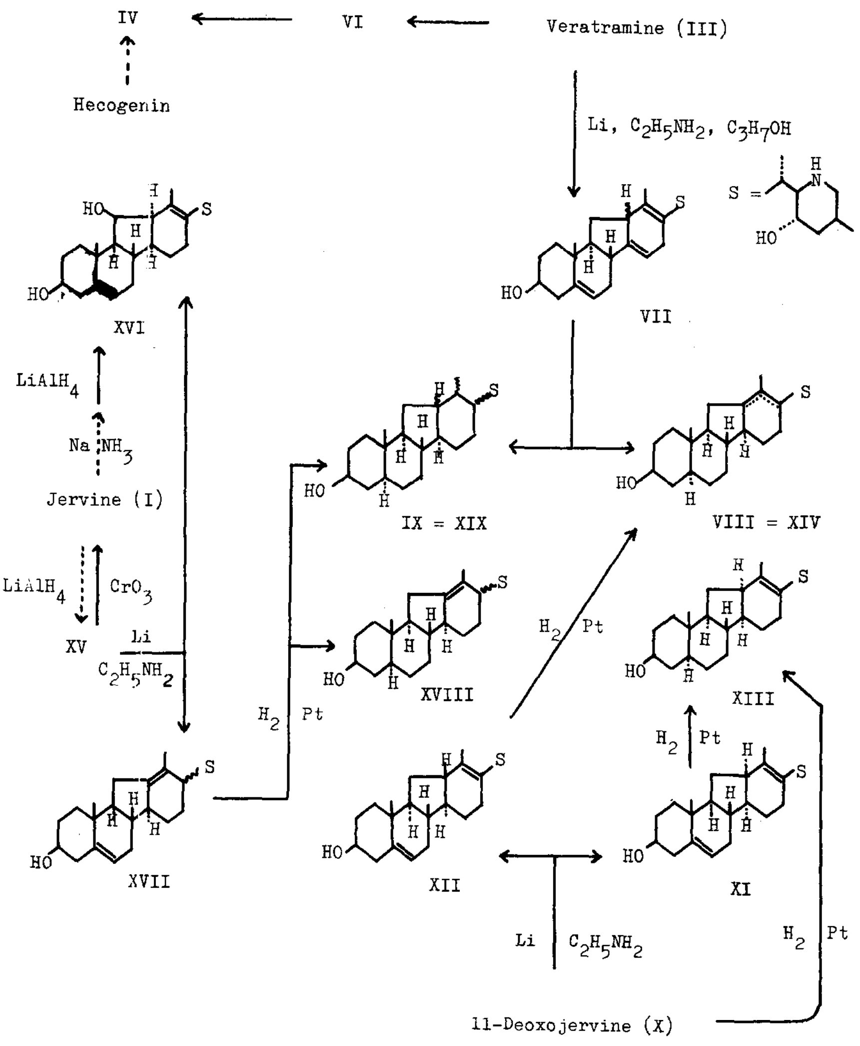
V no Δ^5



VI

The Birch reduction of III with lithium in ethylamine in the presence of isopropanol[11] effectively reduced the D-ring to yield a mixture of dihydro derivatives, from which three crystalline substances were isolated by repeated recrystallizations. The main product $C_{27}H_{41}NO_2$ (Found: C, 78.55; H, 10.20), obtained in 33% yield, had m.p. 182-184° and the spectral data were consistent with the structure (VII); u.v. only end absorption ϵ 16,000 at 210 mμ. The triacetyl derivative (VIIa), m.p. 144-146°, prepared by acetylation with acetic anhydride and pyridine, showed the presence of two olefinic protons (at C-6 and C-15) as a broad peak centered at τ 4.58 and that of a methyl group (C-18) attached to olefinic carbon as a singlet at τ 8.47 in the n.m.r. spectrum. Catalytic hydrogenation of VII over platinum in acetic acid gave two compounds (VIII), m.p. 174-176° and R_f[12] 0.41, and (IX), m.p. 181-183° and R_f 0.58, and their structures will be discussed later.

Treatment of 11-deoxojervine (X)[6] with lithium and ethylamine resulted in cleavage of the ether linkage to yield two isomeric substances (XI) $C_{27}H_{43}NO_2$ (Found: C, 78.10; H, 10.65), m.p. 157-159° and R_f 0.78, i.r. ν_{max} 3300, 1715 (acetone), 1063, 877[13] and 806 cm^{-1}, and (XII) $C_{27}H_{43}NO_2$ (Found: C, 78.55; H, 10.30), m.p. 190-192°, $[\alpha]_D$ (in 95% ethanol) -53.6° and R_f 0.56, i.r. ν_{max} 3400, 1063, 883 and 806 cm^{-1}. Hydrogenation of XI afforded in good yield the 5,6-dihydro derivative (XIII) $C_{27}H_{45}NO_2$ (Found: C, 78.31; H, 10.83; N, 3.33), m.p. 155-157° and $[\alpha]_D$-59.4°, i.r. ν_{max} 3300, 1719 (acetone), 1032 and 878 cm^{-1}, a good yield of which was also produced by direct hydrogenation of X. On acetylation, XIII and XII were converted to the corresponding triacetyl derivatives (XIIIa), m.p. 157-159°, and (XIIa), m.p. 188-190° and $[\alpha]_D$ -10.2°. Their n.m.r. spectra indicated the presence of a C-18 methyl group on the olefinic carbon, and also suggested the configuration of the C/D ring linkage;[14,15] n.m.r. of XIIIa, a broad multiplet which consisted of three peaks centered at τ 4.93, 5.17 and 5.35 (3H, protons at C-3, C-22 and C-23)[16], a singlet at τ 8.34 (3H, C-18 methyl group) and a singlet at τ 9.28 (3H, C-19 methyl group); n.m.r. of XIIa, a broad peak centered at τ 4.61 (1H, proton at C-6), a broad multiplet resulting from protons at C-3, C-22 and C-23, a singlet at τ 8.47 (3H, C-18 methyl group) and a singlet at τ 9.02 (3H, C-19 methyl group). On the other hand, XII was hydrogenated to yield two crystalline substances. The main product (XIV) had m.p.


IV
VI
Veratramine (III)
Hecogenin
Li, $C_2H_5NH_2$, C_3H_7OH
S =
HO
HO
H
N
S
XVI
VII
$LiAlH_4$
Na NH_3
Jervine (I)
IX = XIX
VIII = XIV
$LiAlH_4$
CrO_3
XV
Li
$C_2H_5NH_2$
XVIII
H_2
Pt
XIII
H_2
Pt
H_2
Pt
XVII
XII
XI
Li
$C_2H_5NH_2$
H_2
Pt
11-Deoxojervine (X)

172-174° and R_f 0.43, and was analyzed for $C_{27}H_{45}NO_2$ (Found: C, 78.30; H, 10.80); i.r. ν_{max} 3300, 1041 and 855 cm^{-1}; n.m.r. a singlet at τ 8.35 (3H, C-18 methyl group) and a singlet at τ 9.25 (3H, C-19 methyl group). This compound (XIV) was identical in all respects with the VIII prepared from III.

Oxidation of diacetyljervine-11β-ol (XVa),[17] prepared by reduction of I followed by acetylation, with chromic anhydride in pyridine regenerated a good yield of diacetyljervine (Ia), indicating that jervine-11β-ol (XV) has the same configuration at C-9 as I. The Birch reduction of XV produced a triol and a diol in 5% and 50% yields, respectively. The structure of the triol, m.p. 217-218° and R_f 0.15, was confirmed to be XVI by reduction of 8,9-dihydroisojervine[18] with lithium aluminum hydride. The diol (XVII) $C_{27}H_{43}NO_2$ (Found: C, 78.11; H, 10.23) had m.p. 198-199°, $[\alpha]_D$-64.9° and R_f 0.48; i.r. ν_{max} 3400, 1064, 885 and 806 cm^{-1}. The n.m.r. spectrum of the triacetyl derivative (XVIIa), m.p. 188-190° and $[\alpha]_D$-12.3°, indicated both the cleavage of the ether bond and removal of the 11-hydroxyl group; n.m.r. a broad peak centered at τ 4.58 (1H, proton at C-6), a broad multiplet due to protons at C-3, C-22 and C-23,[16] a singlet at τ 8.47 (3H, C-18 methyl group) and a singlet at τ 9.02 (3H, C-19 methyl group). Further hydrogenation of XVIIled to isolation of two crystalline compounds (XVIII) $C_{27}H_{45}NO_2$ (Found: C, 78.33; H, 10.80), m.p. 184-186° and R_f 0.50, i.r. ν_{max} 3400, 3300, 1041 and 885 cm^{-1}, and (XIX) $C_{27}H_{47}NO_2$ (Found: C, 77.85; H, 11.01), m.p. 180-182° and R_f 0.59, i.r. ν_{max} 3300, 1715 (acetone), 1039 and 878 cm^{-1}. While the triacetyl derivative (XVIIIa), m.p. 201-204°, of XVIII showed the almost same n.m.r. spectrum as XVIIa except the loss of the peak due to the proton at C-6 and the shift of the singnal due to the C-19 methyl group to τ 9.23 and thus the presence of C-18 methyl group on olefinic carbon, the spectrum of the triacetyl derivative (XIXa), amorphous, of XIX exhibited no sharp absorption near τ8.4, suggesting that the C-12-C-13 double bond would be saturated. This compound (XIX) has now been found to be identical with IX prepared from III by the mixed melting method and by comparison of the infrared spectra and the paper chromatogram.

A series of transformations included in this paper involve no reactions which affect the C-9 configuration and, therefore, establish the B/C *trans* configuration of jervine, 11-deoxojervine and veratramine.

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REFERENCES

1) Part III of "C-Nor-D-homosteroids and Related alkaloids"; Part II, reference 6.

2) H. Mitsuhashi and Y. Shimizu, *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) H. Mitsuhashi and K. Shibata, *ibid.*, 2281 (1964).

6) T. Masamune, Y. Mori, M. Takasugi and A. Murai, *ibid.*, 913 (1964).

7) O. Wintersteiner and N. Hosansky, *J. Am. Chem. Soc.*, **74**, 4474 (1952).

8) O. Wintersteiner and M. Moore, *Tetrahedron*, **20**, 1947 (1964) and references cited there; J. Biellmann, P. Crabbé and G. Ourisson, *ibid.*, **3**, 303 (1958); G. Quinkert, *Experientia*, **13**, 381 (1957); H. O. House, V. Paragamian, R. S. Ro and D. J. Wluka, *J. Am. Chem. Soc.*, **82**, 1457 (1960).

9) Ch. Tamm and O. Wintersteiner, *ibid.*, **74**, 3842 (1952); W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, **160**, 555 (1945).

10) R. W. Franck and W. S. Johnson, *Tetrahedron Letters*, 545 (1963).

11) *Cf.* A. W. Burgstahler and L. R. Worden, *J. Am. Chem. Soc.*, **83**, 2587 (1961).

12) Reference 18, footnote 40.

13) Reference 6, footnote 7.

14) Examination of the n.m.r. spectra of a series of "jervane" derivatives has revealed that, when the C/D ring has *cis* configuration, the C-13-C-17 double bond causes the signal of C-19 methyl protons about 0.04 p.p.m. to the higher field. T. Masamune *et al.*, unpublished observations.

15) For the compound XII, another formula, C-17 epimer of XVII, would be possible. The mass spectroscopic studies on most of the compounds included in this paper are in progress.

16) Reference 18, footnote 33a.

17) B. M. Iselin, M. Moore and O. Wintersteiner, *J. Am. Chem. Soc.*, **78**, 403 (1956).

18) T. Masamune, M. Takasugi, M. Gohda, H. Suzuki, S. Kawahara and T. Irie, *J. Org. Chem.*, **29**, 2282 (1964).