

A NEW ALKALOID FROM VERATRUM SPECIES, 11-DEOXOJERVINE¹

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Veratrum species have been extensively investigated² and a large number of alkaloids have been isolated beside jervine, a major alkaloid of the plants. In this paper we wish to report that a new alkaloid has been isolated as a major component from a kind of Veratrum species and the alkaloid is 11-deoxojervine.

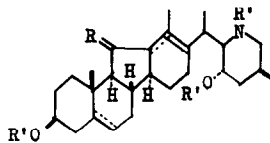
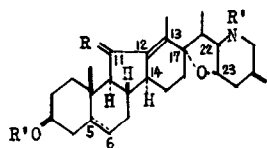
The alkaloid was obtained³ in 0.30 % yield along with veratramine (0.08 %) by purification of the alkaloid fraction obtained by extraction of the alkalinized, ground roots of V. album L. var. glandiflorum Maxim. (V. glandiflorum Loesen, fil.) with benzene, which were collected in May at Tokachi district, Hokkaido, Japan. It is to be noted that jervine was not isolated. The alkaloid (I), m.p. 237-238° (methanol), $[\alpha]_D^{23}$ -44.2° (95 % ethanol), I.R. (in Nujol) ν_{\max} 3270, 1062 and 806 cm^{-1} , U.V. (in ethanol) end absorption, was analyzed for $\text{C}_{27}\text{H}_{41}\text{O}_2\text{N}^4$ (after drying) and the absorption spectra indicated the absence

1. Part II of "C-Nor-D-homosteroids and Related Alkaloids"; Part I, reference 5.
2. For reviews, see, C. R. Narayanan, "Progress in the Chemistry of Organic Natural Products", Springer-Verlag, Wien, 1962, Vol. XX, p. 298; K. J. Morgan and J. A. Bartrop, Quart. Rev., 12, 34 (1958).
3. The isolation was carried out according to the modified Jacobs' procedure and the new alkaloid was found in a fraction in which jervine was supposed to exist. Cf., W. A. Jacobs and L. C. Craig, J. Biol. Chem., 155, 565 (1944); ibid., 160, 555 (1945); A. Stoll, D. Stauffacher and E. Seebeck, Helv. Chim. Acta, 38, 1964 (1955).

of a carbonyl group or a conjugated diene. Acetylation of I with acetic anhydride and pyridine on a steam bath afforded O,N-diacetate (Ia), $C_{31}H_{45}O_4N$, m.p. 163-164° (aqueous methanol, resolidifies and melts at 195-197°, the melting point of the anhydrous form), $[\alpha]_D^{25} +1.1^\circ$. The infrared spectrum (the anhydrous form, ν_{\max} 1733, 1640, 1231, 1037 and 812 cm^{-1}) showed no absorption due to a hydroxyl group in the region of 3 μ and, therefore, the remaining oxygen must be an ether group. An attempted reduction of I with lithium aluminum hydride or with lithium in liquid ammonia led to quantitative recovery of the starting material and ruled out the possibility of an epoxide group. Absorptions near 1050 cm^{-1} in the infrared spectra of I and Ia suggested⁵ the presence of a Δ^5 - β -hydroxyl group, which was supported by the following n.m.r. spectrum. The n.m.r. spectrum (60 Mc., in deuteriochloroform) of Ia resembled closely that of diacetyljervine (IIa), but a new absorption appeared at 8.29 τ instead of that due to 18-methyl group of IIa at 7.81 τ ; that is, it had a broad peak centered at 4.56 τ (1H, olefinic proton at C_6), a broad multiplet centered at 5.40 τ (1H, proton at C_3), two singlets at 7.90 and 7.97 τ (each 3H, N-acetyl and O-acetyl groups), a singlet at 8.29 τ (3H, a methyl group attached to olefinic carbon), two doublets ($J = 7$ c.p.s. and 6 c.p.s.) at 8.99 and 9.06 τ (each 3H, two secondary methyl groups) and a singlet at 9.06 τ (3H, an angular methyl group). All these results strongly suggested that the alkaloid (I) is 11-deoxojervine. In order to confirm the structure, removal of the oxygen on 11-carbon of jervine (II) was attempted.

4. Satisfactory analyses were obtained for the new compounds listed in this report.

5. T. Masamune, M. Takasugi, H. Suzuki, S. Kawahara, M. Gohda and T. Irie, Bull. Chem. Soc. Japan, 35, 1749 (1962); T. Masamune, M. Takasugi, M. Gohda, H. Suzuki, S. Kawahara and T. Irie, J. Org. Chem. in press.



- (I) $R = H_2$, $R' = H$
 (II) $R = O$, $R' = H$
 (III) $R = \begin{array}{c} OH \\ | \\ H \end{array}$, $R' = H$
 (IV) $R = \begin{array}{c} OH \\ | \\ H \end{array}$, $R' = Ac$
- (IV) $R = \begin{array}{c} OH \\ | \\ H \end{array}$, $R' = H$, with Δ^{12} or $\Delta^{13(17)}$
 (IVa) $R = \begin{array}{c} OH \\ | \\ H \end{array}$, $R' = Ac$, with Δ^{12} or $\Delta^{13(17)}$
 (V) $R = H_2$, $R' = H$, with Δ_5^5 and $\Delta_{12}^{13(17)}$
 or with Δ^5 and Δ^{12}

Catalytic hydrogenation of "jervine-11 β -ol"⁶ (III) in the presence of platinum in acetic acid gave a crystalline compound (IV), $C_{27}H_{45}O_3N$, m.p. 124-127° (methanol-acetone, resolidifies and melts at 189-191°), I.R.⁷ ν_{max} 3200, 1040 and 875 cm^{-1} , U.V. end absorption. Acetylation of IV under the same conditions as that of III to the corresponding diacetate (IIIa) yielded 0,0,N-triacetate (IVa), m.p. 184-186° (hexane), I.R. 3460, 1741, 1638, 1238 and 1025 cm^{-1} , U.V. end absorption, n.m.r. spectrum a broad multiplet which consisted of three peaks centered at 4.97, 5.20 and 5.36 τ (3H, protons on C₃, C₂₂ and C₂₃) and was characteristic for all acetylated jervine derivatives formed by cleavage of the ether linkage⁵, a broad peak centered at 5.92 τ (1H, proton on C₁₁), two singlets at 7.95 and 8.00 τ (3H and 6H, N-acetyl and two O-acetyl groups), a singlet at 8.30 τ (3H, 18-methyl group), a doublet ($J = 6$ c.p.s.) at 8.87 τ (6H, 21- and 26-methyl groups) and a singlet at 9.05 τ (3H, 19-methyl group). The spectra of IV and IVa indicated the presence of 11 β -hydroxyl and 23-acetoxyl groups.

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

7. The absorption maxima at 878 ± 5 cm^{-1} with medium intensity were observed for most of isojervine derivatives but not for their acetates or jervine derivatives.

Hence, the hydrogenation effected only cleavage of the ether linkage and saturation of the 5,6-double bond of III and involved no removal of the 11-hydroxyl group. The Birch reduction⁸ of III in the presence of methanol afforded a compound (V), $C_{27}H_{43}O_2N$, m.p. 148-150° (acetone), I.R. ν_{max} 3340, 1715 (acetone), 1062 and 877 cm^{-1} , in a low yield and most of the starting material was recovered unchanged. The molecular formula and infrared spectrum suggested splitting of both the 11-oxygen and ether linkage but a small amount of the product did not permit further examination. Finally, in view of the facile dehydration of isojervinol under acidic conditions⁵, III was treated with hydrochloric acid in refluxing methanol, and veratramine was obtained in 35 % yield. Jervine had been correlated with veratramine through triacetyl-dihydro-11-ketoveratramine⁹, and the present result completes the direct conversion of jervine to veratramine.

The carbonyl group of jervine (II) is hindered¹⁰ and formed no oxime even under severe conditions¹¹. The Clemmensen reduction of 12,13-dihydro-jervine gave rise to no crystalline substance beside the starting compound. However, the Wolff-Kishner reduction of II according to the procedure by Barton¹² resulted in formation of two crystalline compounds (VI), $C_{27}H_{41}O_2N$, m.p. 211-213° (acetone or methanol), $[\alpha]_D^{23} +3.5^\circ$, I.R. ν_{max} 3420, 1615, 1058, 878 and 815 cm^{-1} , U.V., λ_{max} 245 m μ (ϵ 25,500), and (VII), $C_{27}H_{41}O_2N$, m.p. 236-238° (methanol-acetone). The diene (VI) was converted to the corresponding O,O,N-triacetate (VIa), $C_{33}H_{47}O_5N$, m.p. 116-118° (methanol-ethanol),

8. Cf., D. M. Bailey, D. P. G. Hamon and W. S. Johnson, Tetrahedron Letters, 555 (1963).

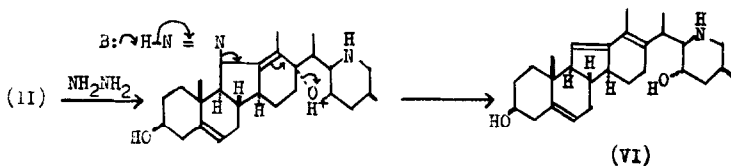
9. O. Wintersteiner and N. Hosansky, J. Am. Chem. Soc., **74**, 4474 (1952).

10. L. F. Fieser and M. Fieser, "Steroids", Reinhold Publishing Corporation, New York, N.Y., 1959, p. 871.

11. Cf., N. L. Hosansky and O. Wintersteiner, J. Am. Chem. Soc., **78**, 3126 (1956).

12. D. H. R. Barton, D. A. J. Ives and B. R. Thomas, J. Chem. Soc., 2056 (1955).

$(\alpha)_D^{23} +46^\circ$, I.R. 1733, 1637, 1615, 1242, 1022 and 811 cm^{-1} , U.V. $\lambda_{\text{max}} 243\text{ m}\mu$ ($\epsilon 23,800$). The n.m.r. spectrum of VIa had a broad peak centered at 4.53τ (2H, protons on C_6 and C_{11}), a broad multiplet which consisted of three peaks centered at 4.93 , 5.25 and 5.36τ (3H, protons on C_3 , C_{22} and C_{23}), a singlet at 7.98τ (9H, N-acetyl and two O-acetyl groups), a singlet at 8.29τ (3H, 18-methyl group), a doublet ($J = 6\text{ c.p.s.}$) at 8.86τ (6H, 21- and 26-methyl groups) and a singlet at 8.99τ (3H, 19-methyl group). These facts indicated that the formula VI would be the most favorable structure for the compound of m.p. 213° , as the reaction is considered to proceed through the following sequence.



On the other hand, the compound (VII) was shown to be identical in all respects with the compound I obtained from natural sources by the mixture melting method and by comparison of the infrared spectra, and thus, the new alkaloid is 11-deoxojervine.

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