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VERATRENONE, A NEW ALKALOID FROM *VERATRUM* SPECIES

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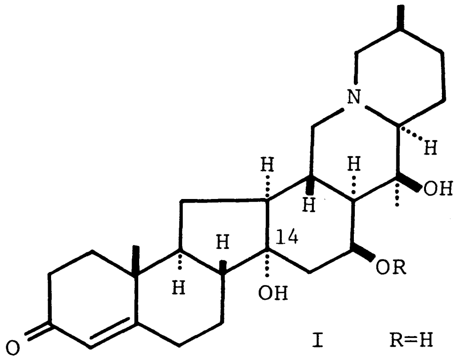
A new alkaloid, designated as veratrenone, was isolated from *Veratrum album L. var. glandiflorum Maxima.* and assigned formula I on the basis of the spectral data and X-ray crystallography. The alkaloid is the first compound, whose structure represents the transition between the *Fritillaria* and ceveratrum alkaloids.

In a continuing study$^{1)}$ on components of *Veratrum* alkaloids, we isolated a new alkaloid, designated as veratrenone. This alkaloid (I) is not highly oxygenated and consists of the cevane skeleton as the *Fritillaria* alkaloids, but possesses a hydroxy group at C_{14} as the ceveratrum alkaloids, highly oxygenated *Veratrum* alkaloids. Hence the structure represents the transition between both the groups.$^{2)}$ The present paper describes the isolation and structure determination of the alkaloid.

The ground, dried roots (3.0 kg) of *V. album L. var. glandiflorum Maxima.* (*V. glandiflorum Loesen. fil.*)$^{3)}$ were basified and extracted with benzene, and the benzene extracts were shaken with 5% aqueous tartaric acid. The acidic solution, on being basified to pH 8.5, separated an amorphous mixture (56 g), which was removed by filtration. The aqueous filtrate was extracted with chloroform repeatedly. The chloroform solution$^{4)}$ was evaporated to leave an amorphous alkaloid mixture (9.0 g), containing rubijervine, 11-deoxojervine, veratramine, veratroylzygadenine, and an apparently new alkaloid. The mixture was separated and purified by trituration with aqueous ethanol (for removal of rubijervine) followed by preparative paper chromatographies$^{5)}$ to give a crude solid (4.0 g), which on recrystallizations from aqueous methanol afforded the new alkaloid (3.5 g) in pure state.

Veratrenone (I), $[\alpha]_D$ +60.5° (EtOH), softened at 160-162°C and melted gradually, but melted at 217-218°C after being dried at 113°C. The alkaloid I was analyzed for $C_{27}H_{41}O_4N$ (Found: C, 73.02; H, 9.39; N, 3.22%, and Calcd: C, 73.10; H, 9.32; N, 3.16%), which was confirmed by the high-resolution mass spectrum6) (Found: m/e 443.3005, and Calcd: m/e 443.3035), and exhibited the following spectra; Mass, m/e 443 and 112 (base peak);7) UV (EtOH), λ_{max} 240 nm (ε 14,000); IR (KBr, after drying), ν_{max} 3490, 3450, 3390, 2830, 2800, 2750,8) 1649, 1603, and 878 cm^{-1}; NMR ($CDCl_3$), δ 1.08 (3H, d J = 7 Hz, 27-C$\underline{H}_3$), 1.18 and 1.22 (total 6H, each s, 19- and 20-C$\underline{H}_3$ or *vice versa*),9) 4.43 [1H, br s W_H = 8 Hz, C$\underline{H}$(OH)], and 5.79 (1H, s, C=C$\underline{H}$CO). Acetylation of I (Ac_2O and Py, steam-bath) gave only monoacetate (II), amorphous; NMR ($CDCl_3$), δ 1.08 (3H, d J = 7 Hz), 1.16 and 1.22 (total 6H, each s), 2.02 (3H, s, OCOC$\underline{H}_3$), 5.63 [1H, br s W_H = 8 Hz, C$\underline{H}$(OAc)], and 5.79 (1H, s), which was reconverted readily into the starting alcohol I only by trituration with aqueous methanol.10) All these facts were explained well by adopting for the alkaloid formula I, except the disposition of a tertiary hydroxy group at C_{14}. The complete structure and stereochemistry of veratrenone was elucidated by the X-ray crystallography of the hydrobromide (III); IR (KBr), ν_{max} 3400, 3200, 1675, 1622, and 758 cm^{-1}, which was prepared by slow evaporation of a methanol solution of III and decomposed gradually from 210°C to 282°C.



I R=H
II R=Ac
III HBr salt

The crystals were orthorhombic, with four molecules in a unit cell with the dimensions of a = 15.615(4), b = 26.905(5), and c = 6.118(3) Å. The space group was $P2_12_12$. Intensities of reflections with 2Θ values up to 140° were measured on a Rigaku automatic four-circle diffractometer using Cu Kα radiation monochromatized with a LiF crystal, and were corrected for the usual Lorentz and polarization factors. Out of the structure factor magnitudes thus obtained, 2708 above 3 σ(F) were selected for the structural study. The structure was solved by the heavy-atom method on the basis of the bromide position derived from a sharpened Patterson function.11) After several cycles of the least-squares method were carried out using the atomic scattering factors of carbon for all the light atoms, the assignment of a nitrogen and four oxygen atoms was made by taking account of the isotropic temperature factors as well as the interatomic distances. The structure thus obtained was refined by the block-diagonal-matrix least-squares method, anisotropic thermal motions being assumed for all the non-hydrogen atoms. At the stage of the R factor of 7.8%, the absolute configuration was determined by using the anomalous dispersion effect of bromine for Cu Kα radiation. The observed and calculated Bijvoet inequalities for twenty pairs of reflections having the largest $||F_c(hkl)|-|F_c(\overline{hkl})||/\sigma(F_o)$ values were in good agreement with each other, thus establishing the full structure of III including the absolute configuration as shown in Fig. 1. After the 42 hydrogen atoms were located in a difference Fourier map, further least-squares refinement was repeated including these hydrogen atoms and the anomalous dispersion effect of the bromide ion. The R value reached 6.2%. The final fractional coordinates of the non-hydrogen atoms are given in Table 1.

Table 1. The final atomic coordinates

	x/a	y/b	z/c		x/a	y/b	z/c
Br	0.0864	0.2062	0.0335	C(12)	0.2904	0.2569	0.5746
O(1)	0.1317	0.5246	0.2868	C(13)	0.2811	0.2113	0.4250
O(2)	0.3907	0.3177	0.7171	C(14)	0.3720	0.2880	0.5258
O(3)	0.4172	0.2281	0.0972	C(15)	0.4509	0.2567	0.4698
O(4)	0.3115	0.1502	0.0392	C(16)	0.4365	0.2127	0.3171
N	0.1932	0.1348	0.3753	C(17)	0.3625	0.1800	0.3971
C(1)	0.1247	0.3950	0.4143	C(18)	0.2105	0.1792	0.5175
C(2)	0.0836	0.4404	0.3059	C(19)	0.1719	0.3452	0.0837
C(3)	0.1483	0.4811	0.2716	C(20)	0.3441	0.1345	0.2472
C(4)	0.2344	0.4640	0.2127	C(21)	0.4242	0.1029	0.2148
C(5)	0.2598	0.4162	0.2123	C(22)	0.2722	0.1027	0.3491
C(6)	0.3487	0.4023	0.1358	C(23)	0.2494	0.0568	0.2146
C(7)	0.3968	0.3687	0.2942	C(24)	0.1751	0.0278	0.3125
C(8)	0.3403	0.3242	0.3500	C(25)	0.0960	0.0597	0.3401
C(9)	0.2547	0.3416	0.4463	C(26)	0.1184	0.1067	0.4685
C(10)	0.2016	0.3739	0.2900	C(27)	0.0544	0.0713	0.1242
C(11)	0.2138	0.2935	0.5350				

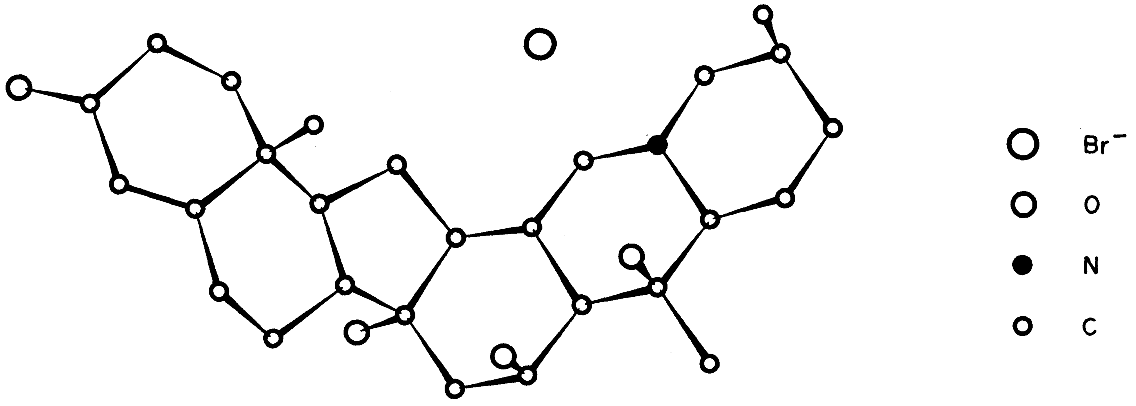


Fig. 1 The molecular structure of veratrenone hydrobromide

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11) All calculations were performed on a Facom 230-60 computer.

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