The Configuration of Verarine[1]

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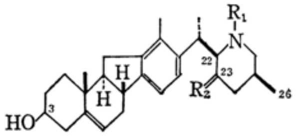
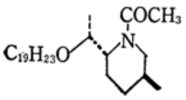
Tomko and Bauer have recently isolated a steroid alkaloid named verarine from *Veratrum album subsp. lobelianum.* From a chemical and spectroscopic investigation of this substance, they have concluded that the alkaloid is 23-desoxyveratramine,[2] but until now no details have been available of its steric configuration. Our present study confirms their structural formula and, in addition, provides the stereochemistry of the compound.

The treatment of veratramine (I) with acetic anhydride (6 mol.) in pyridine at -10°C, followed by chromatography, afforded, in a 44% yield, 3, *N*-diacetylveratramine[3] (II), m. p. 161—163°C; IR,[3] ν_{max} 1027 cm^{-1}. On oxidation with Jones' reagent, II was converted to 23-dehydro-3, *N*-diacetylveratramine (III) in a 73% yield, m. p. 196—198°C; UV,[3] λ_{max} 302 mμ (ε 250); ORD,[3] a strong negative Cotton effect. The treatment of III with sodium methoxide in refluxing methanol and subsequent acetylation led to an isomeric ketone (IV), m. p. 246—248°C; UV, λ_{max} 303 mμ (ε 290); ORD, a weak negative Cotton effect. III and IV were isolated in the ratio of 1 : 10 from an equilibrium mixture in an alkaline solution. As the benzyl part at C-22 and the 26-methyl group in the piperidine ring are *cis*-oriented in III,[4] those groups in IV must have a *trans*-configuration.

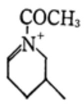
III was treated with ethane-1, 2-dithiol in methanol saturated with hydrogen chloride at 0°C. The product showed two main spots on a thin-layer chromatogram on silica gel. The fraction with the large R_f value yielded 23-ethylene thioketal (V), m. p. 155—156°C, while the product obtained from the fraction with the small R_f value again showed the same two spots. Having available the facile isomerization of the latter, V was isolated in a 73% yield. The treatment of V with Raney nickel in refluxing ethanol resulted in desulfurization, giving *N*-acetyl-23-desoxyveratramine (VI) in a 60% yield, m. p. 195—197°C; $[\alpha]_D$[3] -21°; UV, λ_{max} 267 mμ (ε 930) and 275 (900); IR, ν_{max} 3410, 1610, 1068 and 808 cm^{-1}. On the other hand, the Huang-Minlon reduction of III led to the removal of the 23-oxygen, with a concomitant epimerization at C-22, and gave an isomeric 23-desoxy compound (VII) in a good yield, m. p. 240—242°C; $[\alpha]_D$ -28°; UV, λ_{max} 269 mμ (ε 870) and 278 (810); IR, ν_{max} 3419, 1622, 1060 and 810 cm^{-1}. Both VI and VII showed strong peaks at *m/e* 140 due to a fragment, VIII, in the mass spectra.[5] In view of the process of the Huang-Minlon reaction, it is apparent that VI has the same configuration as III. Through the kindness of Dr. J. Tomko, VI was proved to be identical with *N*-acetylverarine in all respects. Since the configurations of all the asymmetric carbon atoms in I have already been established,[6] the present transformation completes the stereochemistry of verarine.



I $R_1=H$, $R_2=$-H, ···OH
VI $R_1=Ac$, $R_2=H_2$



VII



VIII

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[1] Part V of "*C*-Nor-D-homosteroids and Related Alkaloids"; Part IV: T. Masamune et al., This Bulletin, **38**, 1374 (1965).

[2] J. Tomko and S. Bauer, *Coll. Czech. Chem. Comm.*, **29**, 2570 (1964).

[3] Satisfactory analyses were obtained for all the new compounds described herein. The optical rotations, ORD curves, UV and IR spectra were measured in chloroform, in methanol, in ethanol and in Nujol respectively.

[4] J. Sicher and M. Tichy, *Tetrahedron Letters*, **1956**, 6; R. L. Augustine, *Chem. & Ind (London)*, **1961**, 1448.

[5] H. Budzikiewicz, *Tetrahedron*, **20**, 2267 (1964).

[6] T. Masamune, M. Takasugi and Y. Mori, *Tetrahedron Letters*, **1965**, 489; O. Wintersteiner and M. Moore, *Tetrahedron*, **20**, 1947 (1964), and the references cited therein.