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VERAMINE, A NOVEL TYPE OF VERATRUM ALKALOID WITH A 17ß-METHYL-18-NOR-17-ISO-SPIROSOLANE SKELETON *

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Recently, we reported the constitution and stereochemistry of the Veratrum base veralkamine, the first member of a new steroidal alkaloid type with 18-nor-17ß-methyl-17-iso-cholestane carbon skeleton (1). The present communication briefly describes the structure elucidation of veramine, a further alkaloid of this group isolated previously (2) from Veratrum album ssp. lobelianum (Bernh.) Suessenguth. By chemical and physical investigations, veramine is regarded as (25S)-17ß-methyl-18-nor-17-iso-16α0.22ßN-spirosola-5.12-dien-3ß-ol [(17S:22S:25S)-22.26-epimino-16α,22-epoxy-18(13→17)-abeo-cholesta-5.12-dien-3ß-ol, I].

Elemental analysis and mass spectroscopy (positive and negative ionization) of the amorphous alkaloid ($[\alpha]_D^{27}$ -93.9°)** indicated the

* Alkaloids from Veratrum album ssp. lobelianum (Bernh.) Suessenguth, Part XVII. - Part XVI of this series see, loc. cit. (1c).

** Melting points are corrected. All optical rotations were taken in chloroform. Satisfactory analytical and/or mass spectral data were secured for all new compounds described in this communication. We are indebted to Prof. C. Djerassi, Stanford, for NMR measurements and electron impact mass spectra, and to Dr. R. Tümmler, Dresden, for molecular mass spectra.

composition $C_{27}H_{41}NO_2$. After selenium dehydrogenation in addition to 2-ethyl-5-methylpyridine γ-methylcyclopentenophenanthrene (Diels' hydrocarbon) was isolated indicating the steroidal nature of the alkaloid. The electron impact mass spectrum of veramine (I) shows the molecular ion at m/e 411 (M^+) and a main fragment at m/e 114, the latter being typical of spirosolane alkaloids with a normal carbon skeleton (3). The NMR spectrum of I is characterized by two singlets at δ = 0.92 and 1.09 (C-19 and C-17a methyl, respectively), two dublets at 0.97 (C-21 methyl) and 0.84 (C-27 methyl), one multiplet at 3.47 (C-3 proton), one dublet at 4.0 (C-16 proton), and one multiplet at 5.3 ppm (C-6 and C-12 protons). The IR spectrum (KBr) shows prominent spiroaminoketal bands at 878, 919, 949, and 975 cm^{-1} (4), weak maxima at 1670 and 3030 cm^{-1} (C=C) as well as hydroxyl absorption at 3420 cm^{-1} (broad).

Acetylation of veramine (I) with acetic anhydride/pyridine at 20° for 16 hrs. afforded the amorphous N,O-diacetate II ($[\alpha]_D^{26}$ -52.8°, IR: 1663 (N-acetyl), 1740 cm^{-1} (O-acetyl)); with acetic anhydride at 20° for 10 min. I yielded amorphous N-acetylveramine III ($[\alpha]_D^{26}$ -50.8°, IR ($CHCl_3$): 1664 (N-acetyl), 3628 cm^{-1} (hydroxyl)). The formation of these N-acetates, as well as the N-nitroso derivative IV (UV: λ_{max} 234 (log ε = 3.7), 360 nm (log ε = 1.75)) proved the secondary amine character of the nitrogen atom. Although veramine (I) is not precipitated with digitonin the observed molecular rotation difference of O-acetylation ($[M]_D$ of II - $[M]_D$ of III = -31°) suggested the 3β position of the hydroxyl group (reported by Fieser (5) for other 3β-hydroxy steroids as being -34°).

Further evidence for the presence of the spiroaminoketal function is given by the following chemical proofs. Acetylation of I by refluxing with acetic anhydride/pyridine for 30 min. yielded under fission of the ring F the $\Delta^{20(22)}$ unsaturated N,O-diacetylpseudoveramine V (m.p. 155-157°, $[\alpha]_D^{23}$ -162.3°, IR: 1522, 1695, 3365, 3462 (sec. amide), 1740 cm^{-1} (O-acetyl)). Such a rearrangement is also typical of other spiroaminoketal alkaloids,

e.g. solasodine and tomatidine, leading to furostene derivatives corresponding to V under similar reaction conditions (6). In analogy to these spirosolanes (7), veramine (I) underwent fission of ring E by lithium aluminium hydride reduction affording the 17ß-methyl-18-nor-epimino-cholestanediol VI (m. p. 208-210°, $[\alpha]_D^{23}$ -96.0°) which can be recyclized (8) to veramine (I) by reaction with N-chloro succinimide and subsequent alkaline treatment of the obtained N-chloro derivative VII. Compound VI was further characterized by its amorphous triacetyl derivative VIII ($[\alpha]_D^{20}$ -36.8°, IR: 1650 (N-acetyl), 1747 cm^{-1} (O-acetyl)) and the N-monoacetate IX (m. p. 195-197°, $[\alpha]_D^{20}$ -99.5°, IR: 1630 (N-acetyl), 3629 cm^{-1} (hydroxyl)) obtained from VIII after alkaline saponification.

In contrast to normal spirosolanes (9), veramine failed to undergo opening of ring E by catalytic hydrogenation on platinum oxide in glacial acetic acid but uptaking 2 moles of hydrogen yielded the tetrahydro compound X (m. p. 168-170°, $[\alpha]_D^{25}$ -10.0°) for which we assume 13α-configuration resulting from a more favoured α-hydrogenation of the Δ^{12} double bond. Partial reduction of the $\Delta^{5.12}$ diol VI in the presence of platinum oxide in ethanol gave the Δ^{12} derivative XI (m. p. 190-195°, $[\alpha]_D^{25}$ -34.0°). The negative molecular rotation difference ($[M]_D$ of VI - $[M]_D$ of XI = -260°) is in good agreement with the reported (5) increment ($\Delta[M]_D$ = -298°) for a Δ^5 double bond. Acetylation of XI with acetic anhydride/pyridine afforded the amorphous triacetyl derivative XII ($[\alpha]_D^{26}$ -12.5°, IR: 1652 (N-acetyl), 1745 cm^{-1} (O-acetyl)) and, after alkaline saponification, the N-monoacetate XIII ($[\alpha]_D^{25}$ -55.1°, IR: 1630 (N-acetyl), 3405, 3629 cm^{-1} (hydroxyl)). Oxidation of the latter compound with chromium trioxide/pyridine at 20° led to the Δ^{12} N-acetyl-3.16-diketone XIV (double m. p. 129-131° and 176-178°, $[\alpha]_D^{25}$ -32.0°) which was shown to be identical in every respect with (22S:25S)-22.26-acetylepimino-17ß-methyl-18-nor-17-iso-5α-cholest-12-ene-3.16-dione prepared from veralkamine (1a,b).

The unusual 17ß-methyl-18-nor-17-iso-cholestane carbon skeleton, the Δ^{12} position of the second double bond and the stereochemistry at C-25 of veramine (I), and its corresponding derivatives were established from this correlation. Furthermore the 22S-configuration of the reduction products VI - IX and XI - XIV was clarified. As there is no identity between veralkamine which possesses 16ß-hydroxyl group and the diol VI the only structural difference between both compounds must be the configuration at C-16. In agreement with this, veramine (I) has a 16α.17α-construction of the spiroaminoketal side chain.

Thus far only the configuration of I at C-22 remained unestablished. This was revealed by ORD comparison of N-nitrosoveramine (IV) and the corresponding derivatives of tomatidine [(25S)-5α.22ßN-spirosolan-3ß-ol] and solasodine [(25R)-22αN-spirosol-5-en-3ß-ol] the latter both showing oppósite Cotton effects because of the different configuration at C-22 (10). The negative Cotton effect of IV at 352 nm (a = -12.8 in methanol) corresponding to the ORD curve of N-nitrosotomatidine proves the 22S-configuration (= 22ßN) of veramine (I).

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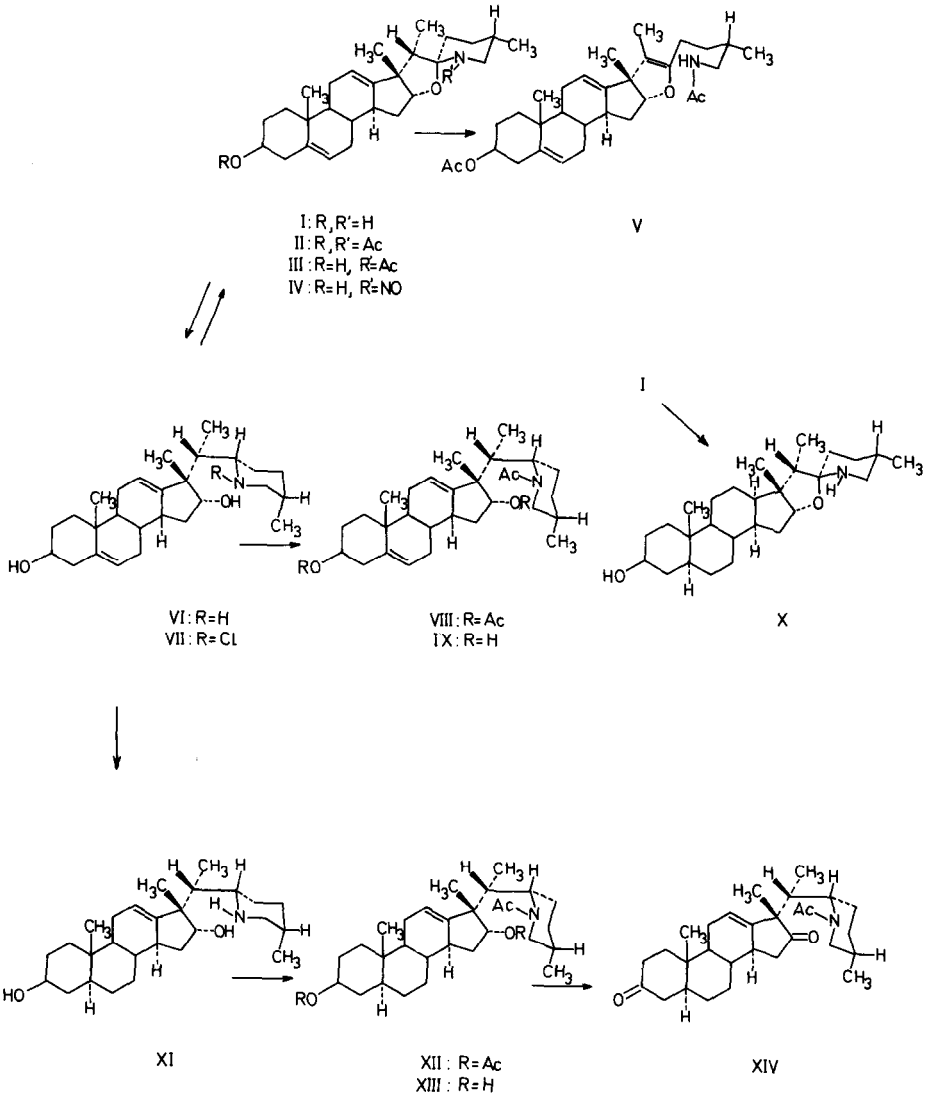

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