Tetrahedron Letters No.40, pp. 3907-3911, 1967. Pergamon Press Ltd. Printed in Great Britain.

VERALKAMINE, A NOVEL TYPE OF STEROIDAL ALKALOID WITH A 17ß-METHYL-18-NOR-17-ISOCHOLESTANE CARBON SKELETON *

J. Tomko[a], A. Vassová[a], G. Adam[b], K. Schreiber[b], and E. Höhne[c]

(a) Institute of Chemistry of the Slovak Academy of Sciences, Bratislava, Czechoslovakia, (b) Institute for Research of Cultivated Plants Gatersleben and (c) Institute of Structural Research Berlin-Adlershof of the German Academy of Sciences at Berlin, German Democratic Republic

(Received in UK 26 June 1967)

Some years ago, Tomko et al. (1) isolated a secondary alkaloid, veralkamine, from Veratrum album ssp. lobelianum (Bernh.) Suessenguth. In alteration of a formerly proposed provisional constitution (2) its complete structure has been established by recent chemical and physical reinvestigations including an X-ray structural analysis of veralkamine hydroiodide. According to these studies briefly described in this paper veralkamine was shown to be (22S:25S)-22.26-epimino-17ß-methyl-18-nor-cholesta-5.12-diene-3ß.16ß-diol [(17S:22S:25S)-22.26-epimino-18(13→17)-abeo-cholesta-5.12-diene-3ß.16ß-diol, I].

Elemental analysis and mass spectroscopy indicated that veralkamine (I) has the empirical formula $C_{27}H_{43}NO_2$. Selenium dehydrogenation afforded in addition to 2-ethyl-5-methylpyridine γ-methylcyclopentenophenanthrene (Diels' hydrocarbon) demonstrating the steroidal nature of the alkaloid as well as the absence of a C-nor-D-homo steroidal skeleton characteristical for many other Veratrum bases. The mass spectra (negative and positive

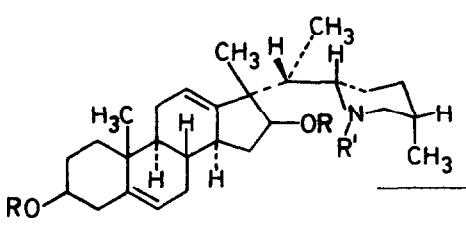
* Alkaloids from Veratrum album ssp. lobelianum (Bernh.) Suessenguth, Part XIV. - Part XIII of this series cf. G. Adam, K. Schreiber, and J. Tomko, Liebig's Ann., in press.

ionization) show peaks at m/e 412 (M^+ - 1) and 315 (M^+ - 98) as well as 413 (M^+) and 98 (M^+ - 315), respectively, fragmentation patterns typical of a 22.26-epiminocholestane side chain resulting by cleavage of the 20.22-bond (3). The NMR spectrum of I is characterized by a singlet at δ = 0.96 (18-H_3 and 19-H_3), two dublets at 0.97 (27-H_3) and 0.81 (21-H_3), as well as three multiplets at 3.41 (3-H), 4.0 (16-H), and 5.25 ppm (6-H and 12-H). The IR spectrum (CCl_4) shows hydroxyl absorption at 3230 (broad) and 3635 cm^{-1}.

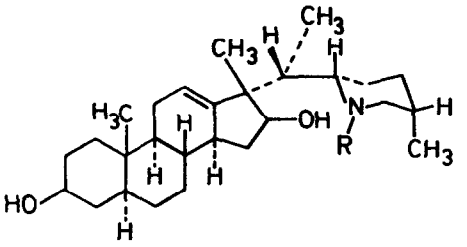
Veralkamine (I) gives a precipitation with digitonin (3β-hydroxy group) and has been further characterized by conversion into the N.O.O-triacetate II (m.p. 152-154°, $[\alpha]_D^{27}$ -8.0°)* and the N-monoacetate III (m.p. 191-193°, $[\alpha]_D^{23}$ -79.1°) obtained by alkaline partial hydrolysis of II. Partial hydrogenation of I with PtO_2 in ethanol gave dihydroveralkamine IV [m.p. 230-233° (dec.), $[\alpha]_D^{26}$ -15.0°, NMR: δ = 0.77 (s, 19-H_3), 0.96 (s, 18-H_3), 5.2 ppm (m, 12-H)]. The observed molecular rotation difference ($[M]_D$ of I - $[M]_D$ of IV = -288°) agrees well with the increment of -298° found for the Δ^5-double bond in other steroids (4). Compound IV has been further characterized by its amorphous triacetyl derivative ($[\alpha]_D^{25}$ +33.0°) which gave after alkaline saponification the crystalline N-monoacetate V (m.p. 179-181°, $[\alpha]_D^{22}$ -14.7°). Complete hydrogenation of I or IV with PtO_2 in glacial acetic acid afforded tetrahydroveralkamine VI [m.p. 219-221°, $[\alpha]_D^{25}$ +6.1°, NMR: δ = 0.74 (s, 19-H_3) and 0.89 ppm (s, 18-H_3)]. Its acetylation and subsequent partial hydrolysis yields the tetrahydro-N-monoacetate VII. Dehydrogenation of V with chromium trioxide led to the unconjugated diketone IX [double m.p. 129-131° and 176-178°, $[\alpha]_D^{25}$ -28.0°, IR: 1650 (N-acetate), 1722 (6-membered ketone), 1748 cm^{-1} (5-membered ketone)] confirming that the second hydroxy group of veralkamine must be located at ring D and the second double bond must have its position in ring C.

---

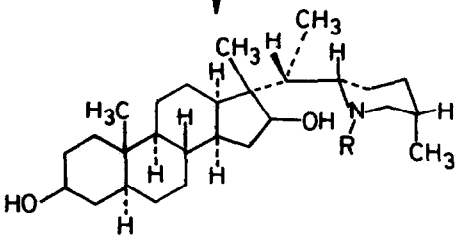
* Melting points are corrected. All optical rotations are taken in chloroform. Satisfactory analytical and/or mass spectral data have been secured for all new compounds described in this communication. We are indebted to Prof. R. Goutarel, Gif-sur-Yvette, for NMR measurements, to Dr. R. Tümmler, Dresden, and Dr. L. Dolejš and Dr. V. Hanuš, Prague, for the mass spectra, to Doz. Dr. G. Snatzke, Bonn, for the CD and to Ing. T. Sticzay, Bratislava, for the ORD measurements.



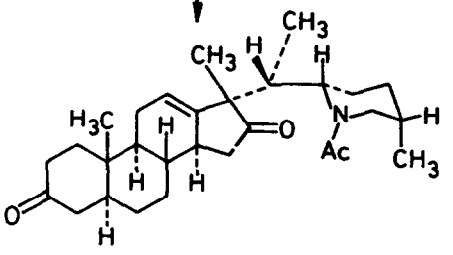
I : R,R' = H
II : R,R' = Ac
III : R = H, R' = Ac



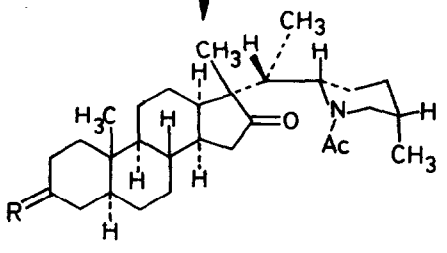
IV : R = H
V : R = Ac



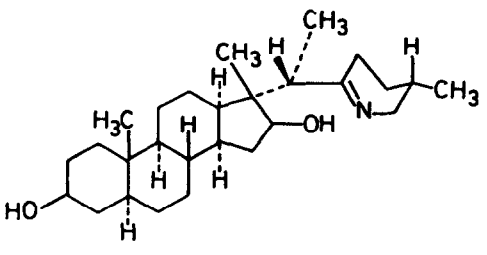
VI : R = H
VII : R = Ac
VIII : R = Cl



IX



X : R = O
XI : R = β-OH, α-H



XII

Veralkamine (I) as well as its hydrogenated derivatives IV and VI possess a strong hydrogen bond indicated by an IR absorption near 3200 cm^{-1} which together with model considerations, exclude the 15-position of the second hydroxy group. Chromic acid oxidation of VII afforded the saturated 3.16-dioxo derivative X [m.p. 209-211°, $[\alpha]_D^{25}$ +57.3°, IR: 1622 (N-acetate), 1712 (3-ketone), 1724 cm^{-1} (16-ketone)] which, by partial hydrogenation in the presence of PtO_2-methanol gave the 16-monoketone XI [m.p. 273-274°, $[\alpha]_D^{19}$ +42.6°, IR: 1621 (N-acetate), 1732 (16-ketone), 3335 cm^{-1} (hydroxyl), ORD: positive Cotton effect at 300 nm (a = +17.4 in dioxane)]. According to the octant rule and model considerations the positive Cotton effect of the 16-carbonyl in XI verified the cis-fusion of ring C and D and therefore the α-position of the hydrogen at C-13 which is in accord with the more favoured α-hydrogenation of the Δ^{12}-double bond from the more unhindered rear side of I. N-Chlorination of VI with N-chlorosuccinimide led to the N-chloro derivative VIII [m.p. 170° (dec.), $[\alpha]_D^{19}$ -56.1°]. The negative molecular rotation difference between VIII and VI (ΔM_D -279°) established the S-configuration at C-22 (5). Alkaline catalyzed HCl-elimination in VIII afforded the cyclic azomethine XII which does not cyclize to the corresponding spiroaminoketal demonstrating a trans-position of the 16-hydroxy group and the heterocyclic side chain moiety at C-17. The weak negative Cotton effect at 240 nm (a = -31.8 in dioxane) of the azomethine XII proves the 25S-configuration (6) of veralkamine and its derivatives.

The unusual 17ß-methyl-18-nor-17-isocholestane carbon skeleton of veralkamine has been established by X-ray analysis of veralkamine hydroiodide confirming the afore-mentioned chemical and spectroscopic evidence. I-Hydroiodide [m.p. 264° (dec.)] crystallizes in the space group $P2_1$ with 2 molecules of $C_{27}H_{44}INO_2$ in a unit cell of dimensions a = 15.50, b = 9.24, and c = 10.36 Å, ß = 108°. Initial phase determination was based on the iodine atom and on the absolute configuration of the known part of the molecule. Fourier and least-squares methods were employed for the refinement of the atomic parameters. All the carbon, nitrogen, and oxygen atoms were

located on successive three-dimensional electron-density distributions which established the structure of veralkamine as shown in formula I; the final value of the discrepancy R (hkl) was 13 %.

Veralkamine represents the first naturally occurring steroid with a 18-nor-17ß-methyl skeleton. The structures of some other steroid alkaloids of this novel type will be reported in forthcoming communications.

References

(1) J. Tomko, I. Bendík, Š. Bauer, and I. Mokrý, Pharm. Zentralhalle 99, 313 (1960).

(2) J. Tomko and I. Bendík, Collection Czechoslov. Chem. Commun. 27, 1404 (1962).

(3) cf. M. von Ardenne, K. Steinfelder, R. Tümmler, G. Adam, and K. Schreiber, unpublished results; H. Budzikiewicz, Tetrahedron 20, 2267 (1964).

(4) cf. L.F. Fieser and M. Fieser, Steroide, Verlag Chemie, Weinheim/ Bergstraße 1961, p. 193.

(5) cf. K. Schreiber and G. Adam, Experientia 17, 13 (1961); Liebig's Ann. 666, 155 (1963).

(6) cf. H. Ripperger, K. Schreiber, and G. Snatzke, Tetrahedron 21, 1027 (1965); G. Adam, K. Schreiber, J. Tomko, and A. Vassová, Tetrahedron 23, 167 (1967).