THE STRUCTURE AND CONFIGURATION OF VERALODINE

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From the chloroform-extracted combined alkaloids of the epigeal part of Veratrum lobelianum collected on May 5, 1968 [1], by separation according to basicity, and also by chromatography on a column of alumina we have isolated a new alkaloid – veralodine (I) – with the composition $C_{27}H_{39}O_3N$. The base is tertiary, and its IR spectrum shows absorption bands at (cm^{-1}) 3470 (OH), 2960–2830, 1465, 1445 ($-CH_3$, ($-CH_2-$), 1690, 1610 (α,β-unsaturated ketone), and 1610, 1257 (lactam carbonyl) (Fig. 1), the fingerprint region being similar to that of the C-nor-D-homosteroid alkaloid cevine lactam [2]. Its UV spectrum [λ_{max} 245 nm (log ε 4.26)] shows the presence of a system of conjugated double bonds in the molecule of the base. In the NMR spectrum there are singlets at 1.25 ppm (3H, 19-CH_3), and 5.63 ppm (olefinic proton), doublets at 0.93 ppm (3H, 21-CH_3; J = 6.0 Hz) and 0.85 ppm (3H, 27-CH_3; J = 6.0 Hz); a one-proton signal split into six lines at 3.50 ppm (H, H–C–OH) and a quadruplet at 4.73 ppm (H, H_e–C–N–CO–; J = 12.0; 2.0 Hz) (Fig. 2) [3]. In the mass spectrum of veralodine, the main peaks are those of ions with m/e 98, 111, 125, 126, 131, 149, 151, 165, 204, 220(100%), 249, 285, 302, 392, $(M-18)^+$, $(M-15)^+$, $(M-1)^+$, 425 (M^+).

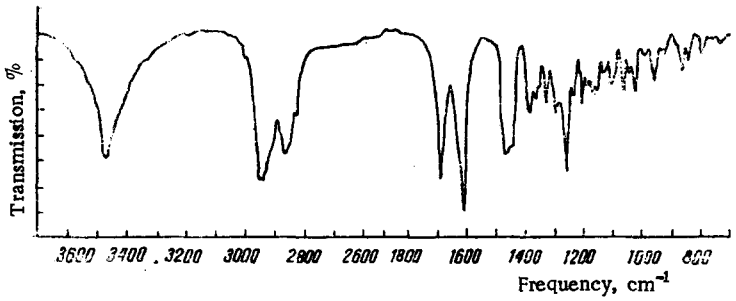

Fig. 1. IR spectrum of veralodine.

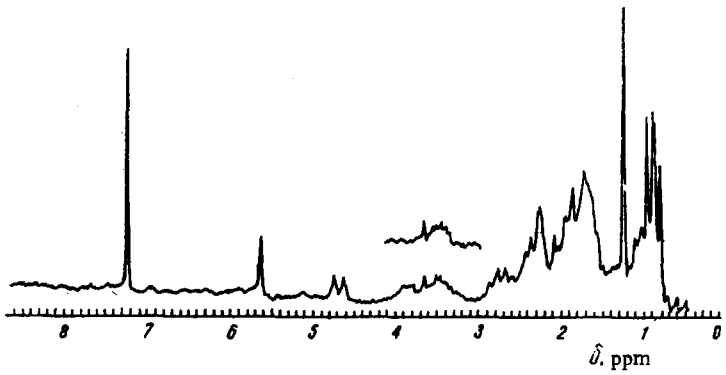

Fig. 2. NMR spectrum of veralodine.

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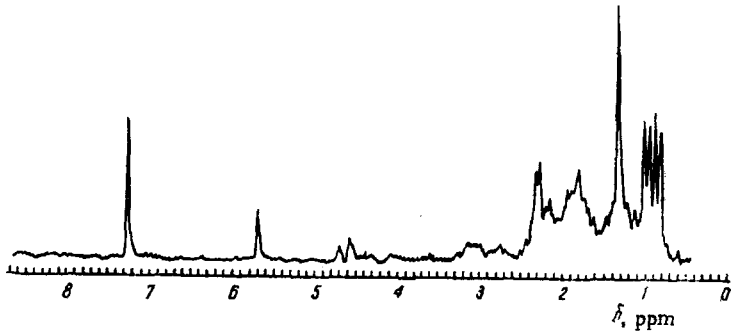


Fig. 3. NMR spectrum of veralodinone.

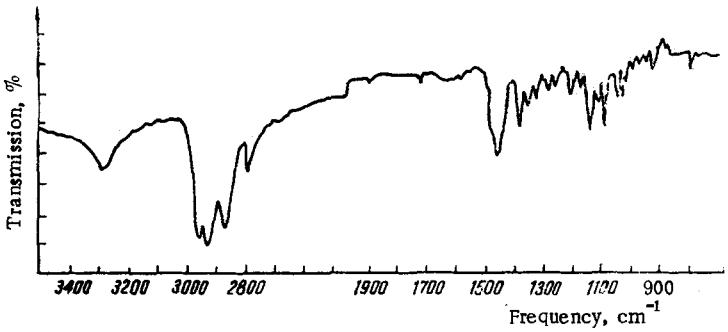


Fig. 4. IR spectrum of deoxotetrahydroveralodine.

The formation of a monoacetyl derivative (II) of the base showed the secondary nature of the hydroxy group. In the IR spectrum of (II) there are absorption bands at 1733 and 1245 cm^{-1} (ester carbonyl) and there is no absorption band of a hydroxy group. The NMR spectrum of acetylveralodine (II) has singlets at 1.24 ppm (3H, 19-CH_3), 1.97 ppm (3H, $OCOCH_3$), and 5.64 ppm (C = CH_2), a multiplet at 4.66 ppm (H, CH–$OCOCH_3$), and doublets at 0.91 ppm (3H, 21-CH_3; J = 6.0 Hz) and 0.85 ppm (3H, 27-CH_3; J = 6.0 Hz), and a quadruplet at 4.74 ppm (H, H_e–C(|)–N(|)–CO–). The saponification of (II) with ethanolic alkali gave the initial base (I).

The oxidation of veralodine with chromium trioxide in acetic acid formed an amorphous unsaturated diketone – veralodinone (III). The IR spectrum of (III) had absorption bands in the following regions (cm^{-1}): 2970–2850, 1470, 1440 (–CH_3–CH_2–), 1709, 1680 (C = O), 1630, 1250 (lactam carbonyl and C = CH). In the NMR spectrum of (III) there were singlets at 1.33 ppm (3H, 19-CH_3), and 5.68 ppm (olefinic proton), doublets at 0.96 ppm (3H, 21-CH_3; J = 6.0 Hz) and 0.84 ppm (3H, 27-CH_3; J = 6.0 Hz), and a quadruplet at 4.65 ppm (H, H_e–C(|)–N(|)–CO–) (Fig. 3). The mass spectrum of (III) contained the peaks of ions with m/e 98, 125, 126, 147, 149, 220, 300, 380 $(M-18)^+$; $(M-15)^+$; $(M-1)^+$; 423^+ M (100%).

The Adams catalytic hydrogenation of (I) in acetic acid gave a mixture of four isomeric tetrahydroveralodines the separation of which on a column of alumina gave a tetrahydroveralodine (IV) with mp 251-253°C and another tetrahydroveralodine (IVa) with mp 302-305°C, M^+ 429. The IR spectrum of (IV) had absorption bands at (cm^{-1}) 3465 (OH), 2940–2863, 1460, 1450 (–CH_3–CH_2–), 1618, 1263 (lactam carbonyl).

The reduction of veralodine with lithium tetrahydroaluminate in a mixture of tetrahydrofuran and absolute ether formed a mixture of products with mp 231-234°C, R_f 0.00, 0.45, and 0.61, the separation of which on a column of alumina yielded dihydroveralodine (V) with mp 234-236°C, R_f 0.45. IR spectrum of (V), cm^{-1}: 3465, 3320 (OH), 2940–2865, 1450 (–CH_3–CH_2–), 1605, 1260 (lactam carbonyl and C = CH). The NMR spectrum of (V) had singlets at 1.11 ppm (3H, 19-CH_3) and 5.24 ppm (olefinic proton), doublets at 0.90 ppm (3H, 21-CH_3; J = 7.0 Hz) and 0.83 ppm (3H, 27-CH_3; J = 7.0 Hz), and a quadruplet at 4.68 ppm

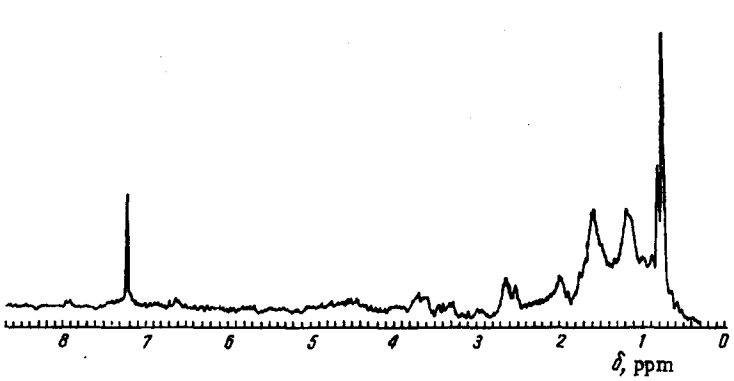


Fig. 5. NMR spectra of deoxotetrahydroveralodine.

(H, $H_e-\underset{|}{\overset{|}{C}}-N-CO-$). The mass spectrum of (V) had the peaks of ions with m/e 98, 125, 126, 151, 220 (100%), 249, 285, 304, 376, 390, 394; $(M-18)^+$; $(M-15)^+$; $(M-1)^+$; 427 (M^+).

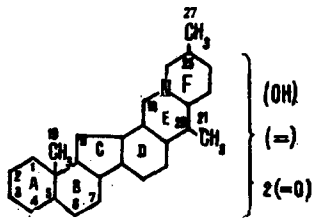
The catalytic hydrogenation of dihydroveralodine (V) formed a mixture of two isomeric tetrahydroveralodines (IV) and (IVa).

Tetrahydroveralodine (IV) is readily acetylated by acetic anhydride in pyridine, giving an amorphous diacetyltetrahydroveralodine (VI) with R_f 0.86.

The reduction of (VI) with lithium tetrahydroaluminate in absolute ether also gave a mixture of products, with R_f 0.05, 0.22, and 0.84, the separation of which on a column of alumina gave deoxotetrahydroveralodine (VII) with mp 172-173°C, R_f 0.84. The IR spectrum had absorption bands at 3285 cm^{-1} (OH) and 2787 cm^{-1} (trans-quinolizidine) [4], and the absorption bands of a lactam carbonyl were absent (Fig. 4).

In the NMR spectrum of (VII) there was a singlet at 0.73 ppm (3H, 19-CH_3), and doublets at 0.75 ppm (3H, 21-CH_3; J = 6.5 Hz) and 0.76 ppm (3H, 27-CH_3; J = 6.5 Hz),while the signal in the form of a quadruplet at 4.73 ppm (H, $H_e-\underset{|}{\overset{|}{C}}-N-CO-$) was absent (Fig. 5). The mass spectrum showed the peaks of ions with m/e 98, 111, 112 (100%), 124, 125, 138, 139, 140, 150, 164, 178, 194, 204, 328, 342, 343, 370, 371, 382, 386 $(M-18)^+$; (M−17); (M−15); $(M-1)^+$; 415 (M^+), which are characteristic of the alkaloids edpetilidine, petilinine, and petilidine [5-7]. In addition, the oxidation of deoxotetrahydroveralodine (VII) with chromium trioxide formed deoxodihydroveralodinone (VIII). UV spectrum: λ_{max} 273 nm (log ε 3.42). Its IR spectrum showed absorption bands at 2960−2860 and 1460 cm^{-1} ($-CH_3$, $-CH_2$), 2770 cm^{-1} (trans-quinolizidine) and 1710 cm^{-1} (carbonyl group); the absorption bands of a hydroxy group were absent. The mass spectrum of (VIII) showed the appearance of fragments with m/e 98, 112 (100%), 124, 125, 138, 139, 149, 165, 204, 328, 368, $(M-15)^+$, $(M-14)^+$, $(M-1)^+$, 411 (M^+), which are characteristic for the C-nor-D-homosteroid alkaloids of the cevine group [5, 8].

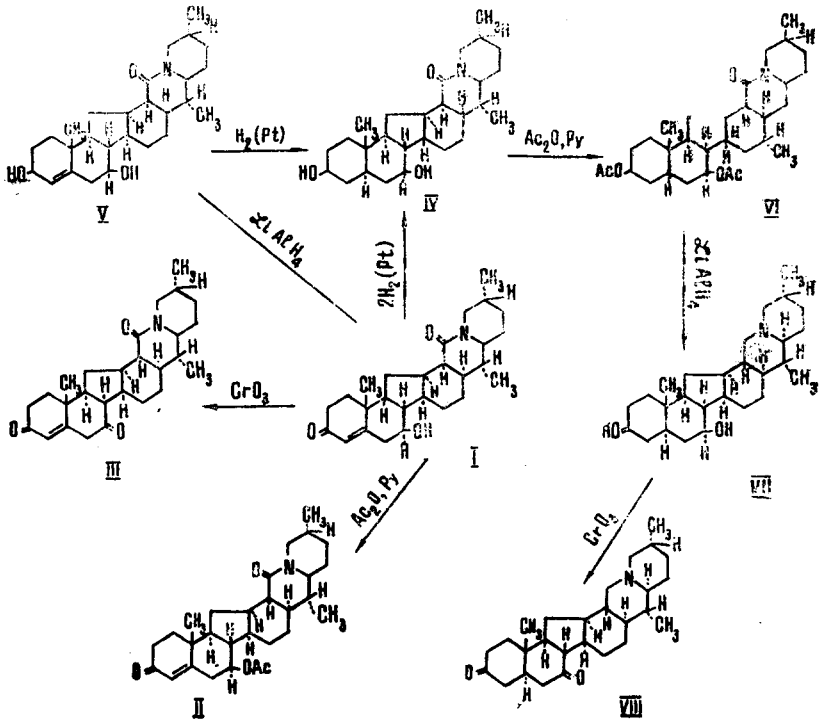
On the basis of what has been said above, veralodine has the heterocyclic skeleton of cevanine [9].



The lactam carbonyl may be present in ring E or ring F. In the NMR spectrum of veralodine and its conversion products the methyl protons from the 21-CH_3 group resonate in a weaker field than those from the 27-CH_3 group. This shows that the lactam carbonyl is probably present in ring E at C−18. The presence in the mass spectra of (I-VIII) of a peak of an ion with m/e 98, which comprises a piperidine ring, also confirms the position of the lactam carbonyl at C−18.

The downfield shift of the resonance signal of the 19-CH_3 group in the NMR spectrum of dihydroveralodine (V) by 14 Hz as compared with the 19-CH_3 signal of veralodine (I) confirms the presence of a carbonyl group in rings A, B, or C. The IR spectrum of veralodine lacks the absorption band of the carbonyl of a five-membered ring, and, therefore, position 11 in ring C is excluded for the carbonyl group.

The resonance of the signal from the 19-CH_3 group in (I) in a field weaker by 52 Hz relative to the center of the corresponding signal in (VII) shows that the α,β-unsaturated ketone group is located in ring A, i.e., that the carbonyl is present at position 3 and the double bond between carbon atoms 4 and 5 [10].



The new carbonyl group in veralodinone (III) may be located in rings A, B, C, D, E, or F. Rings D, E, and F are excluded because of the lower anisotropic influence of the carbonyl group on the chemical shifts on the 21- and 27-CH_3 groups than on the 19-CH_3 group. A carbonyl group in ring C is also excluded because of the absence from the IR spectrum of veralodinone (III) of the absorption band of a carbonyl group in a five-membered ring. Positions 2 and 6 for the carbonyl group are excluded on the basis of the comparative downfield shift of the 19-CH_3 signal on passing from veralodine (I) to veralodinone (III). The difference (8 Hz) in the chemical shifts of the 19-CH_3 group in veralodine (I) and veralodinone (III) excluded a position at C_1 of ring A for the carbonyl group, and only position 7 remains for it [10]. Consequently, in veralodine the hydroxy group is located at C_7.

In acetylveralodine (II) the appearance of the signal of the proton at the acetyl group in a strong field (multiplet, 4.66 ppm) shows its α-axial position and the β-equatorial position of the acetyl group in (II) [11-13]. A confirmation of this is the fact that in the mass spectrum of veralodine the peak of the $(M-18)^+$ ion is less intense than the peak of the molecular ion [14].

The chemical shifts of the 19-CH_3 protons in deoxotetrahydroveralodine (VII) show that rings A and B have the trans linkage. The values of the signals from the secondary methyl protons show that the A/B rings are connected with the trans-quinolizidine part of the molecule in (VII) in the same way as in the alkaloids imperialine, petilinine, and petilidine [5-7], and the 21-CH_3 and 27-CH_3 groups have the α orientation.

On the basis of the facts given above, veralodine (I) has the most probable structure and configuration of 7β-hydroxy-27α-methylcevanin-4-ene-3,18-dione.

EXPERIMENTAL

Thin-layer chromatography (TLC) was performed on KSK silica gel (100 nm) with the following solvent systems: 1) butyl acetate–ethanol–chloroform (3 : 2 : 20); 2) benzene–ethanol (9 : 1); and 3) benzene–ethanol (9 : 2.5). The chromogenic agent was Dragendorff's solution. Column chromatography was performed with alumina (activity grade II). The UV spectra were taken on a Hitachi spectrophotometer, the IR spectra on a UR-10 double-ream spectrophotometer (molded tablets with KBr), the NMR spectra on a JNM-4H-100 MHz instrument (in deuterochloroform) with hexamethyldisiloxane as internal standard using the δ scale, and the mass spectra on an MKh-1303 mass spectrometer.

Veralodine (I). The chloroform-soluble fraction of the total alkaloids from the epigeal part of Veratrum lobelianum (233 g) was dissolved in one liter of chloroform and, by extraction with 8-ml portions of 10% sulfuric acid, it was separated into 14 fractions of different basicities. The weak-acid 14th fraction was neutralized with ammonia. After the chloroform had been distilled off, 100 g of combined alkaloids were dissolved in benzene and passed through a column of alumina, being eluted with benzene, chloroform, chloroform–methanol (98 : 2), and chloroform–methanol (10 : 2). On standing, the concentrated benzene eluate deposited a precipitate which was filtered off, and the filtrate was chromatographed on a column of alumina. Elution was performed with benzene, chloroform, and chloroform–methanol (9 : 1). The benzene fraction was evaporated, and the residue was treated with acetone to give 4.7 g of veralodine with mp 254-257°C (from acetone), $[\alpha]_D$ + 96.4° (c 0.892; chloroform), R_f 0.62 in system 1.

Found %: C 75.8; H 9.51; N 3.31. $C_{27}H_{39}O_3N$. Calculated %: C 76.2; H 9.17; N 3.06. M^+ 425 (mass spectrometrically).

Acetylveralodine (II). A mixture of 0.1 g of veralodine, 1.5 ml of pyridine, and 1 ml of acetic anhydride was kept at room temperature for 35 h. After the pyridine had been eliminated, the residue was dissolved in 5% sulfuric acid, and the solution was made alkaline with ammonia and extracted with chloroform, and the latter was distilled off. The acetyl derivative so obtained melted at 249-250°C (from acetone), $[\alpha]_D$ + 76.4° (c 0.102; chloroform), R_f 0.063 in system 3; composition $C_{29}H_{41}O_4N$, M^+ 467 (mass spectrometry).

Veralodinone (III). A solution of 0.09 g of veralodine in 1.5 ml of acetic acid was mixed with 0.048 g of chromium trioxide in 1.5 ml of acetic acid and one drop of water. The mixture was kept at room temperature for 68 h, and then the solvent was evaporated off in vacuum and the dry residue was dissolved in water. The acid solution was made alkaline with ammonia and extracted with chloroform. The chloroform was distilled off, and the residue (0.06 g) was redissolved in chloroform and chromatographed from alumina. The chloroform eluates after concentration yielded amorphous veralodinone with R_f 0.68 in system 2, $[\alpha]_D$ + 155.63° (c 0.408; chloroform). Composition $C_{27}H_{37}O_3N$, M^+ 423 (mass spectrometrically).

Dihydroveralodine (V). A suspension of 0.423 g of lithium tetrahydroaluminate in 40 ml of absolute ether was added over 1 h to a solution of 0.335 g of veralodine in 20 ml of undried tetrahydrofuran. After the evolution of gas had ceased, the reaction mixture was heated on the water bath for 5 h. With cooling, 4-5 ml of water was added to the reaction mixture, and it was extracted with chloroform. The chloroform was distilled off, giving a mixture of crystals with mp 231-234°C from acetone with R_f 0.00, 0.45, and 0.61 in system 2. The mixture of crystals with mp 231-234°C was dissolved in chloroform and chromatographed on alumina (20 g) with elution by means of chloroform, 15-ml fractions being collected. The 4th-9th fractions on treatment with acetone yielded dihydroveralodine with mp 234-236°C (from acetone), R_f 0.45 (system 2), composition $C_{27}H_{41}O_3N$, M^+ 427 (mass spectrometrically).

Tetrahydroveralodine (IV and IVa). Dihydroveralodine (V) with mp 234-236°C (0.128 g) was hydrogenated by Adams' method in glacial acetic acid in the presence of 0.089 g of PtO_2. The acetic acid solution, after separation from the platinum black, was diluted with water, made alkaline with ammonia, and extracted with chloroform. On chromatography in system 3, the residue proved to be a mixture, giving two spots with R_f 0.50 and 0.70. The mixture was passed through a column of alumina (20 g) and eluted with chloroform (10-ml portions). The first five fractions yielded 0.047 g of tetrahydroveralodine (IV) with mp 251-253°C (from acetone), $[\alpha]_D$ + 14.5° (c 0.396; chloroform), R_f 0.70 in system 3. The 12th to 18th fractions yielded tetrahydroveralodine (IVa) with mp 302-305°C [ethanol–acetone (1 : 3)] with R_f 0.50 in system 3. Composition $C_{27}H_{43}O_3N$, M^+ 429 (mass spectrometrically).

Diacetyltetrahydroveralodine (VI). Tetrahydroveralodine (IV) (0.043 g) was acetylated with acetic anhydride (1 ml) in pyridine (1 ml) as for the acetylation of veralodine. This gave an amorphous diacetyltetrahydroveralodine with R_f 0.86 (in system 1).

Deoxotetrahydroveralodine (VII). A suspension of 0.13 g of lithium tetrahydroaluminate in 20 ml of absolute ether was added over 30 min to a solution of 0.045 g of diacetyltetrahydroveralodine (VI) in 20 ml of absolute ether. After the evolution of gas had ceased, the reaction mixture was heated in the water bath for 5 h. Then it was cooled, 3 ml of water was added, and it was extracted with ether. The residue from the ethereal extract was dissolved in chloroform and passed through alumina. On elution with chloroform, the first 50 ml of eluate yielded deoxotetrahydroveralodine with mp 172-173°C (from acetone), $[\alpha]_D$ + 37.14° (c 0.28; chloroform), R_f 0.83 in system 2. Composition $C_{27}H_{45}O_2N$, M^+ 415 (mass spectrometrically).

Deoxodihydroveralodinone (VIII). Deoxotetrahydroveralodine (0.018 g) was oxidized with chromium trioxide (0.02 g) in acetic acid (1 ml) as for the oxidation of veralodine.

The yield of deoxodihydroveralodinone was 0.01 g, mp 166-168°C (from acetone), R_f 0.72 in system 2. UV spectrum: λ_{max} 273 nm (log ε 3.42). Composition $C_{27}H_{41}O_2N$. M^+ 411 (mass spectrometrically).

SUMMARY

From the epigeal part of Veratrum lobelianum the new alkaloid veralodine has been isolated, and its most probable structure and configuration have been determined as 7β-hydroxy-27α-methylcevanin-4-ene-3,18-dione.

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