STRUCTURE OF SEVEDININE

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The new steroidal alkaloid sevedinine was isolated from the aerial part of Korolkovia severtzovii. *The structure of sevedinine was established as 6β,12α-dihydroxy-5α-cevanin-3-one using spectral data, chemical transformations, and an x-ray structure analysis. The location of the tertiary hydroxyl in ten cevine alkaloids from* Korolkovia severtzovii *was corrected based on the results.*

Key words: steroidal alkaloid, sevedinine, x-ray structure analysis.

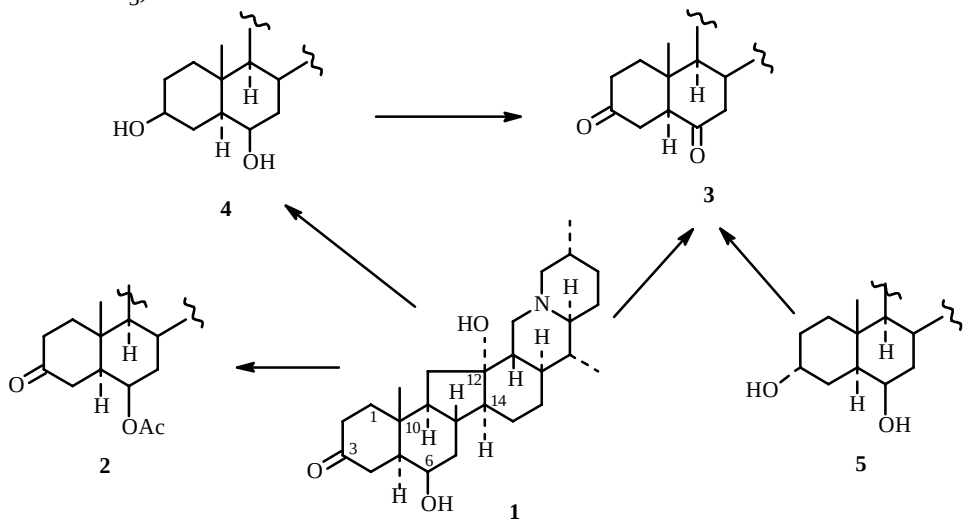
In continuation of research on alkaloids from the aerial part of *Korolkovia severtzovii* Regel., we separated the ether fraction of total alkaloids [1, 2] and isolated the new alkaloid sevedinine (**1**), mp 233-235°C, $C_{27}H_{43}NO_3$.

The IR spectrum of **1** contains absorption bands at 3537 and 1038 (OH), 2760 (*trans*-quinolizidine), and 1710 cm^{-1} (C=O).

The mass-spectral fragmentation of sevedinine is analogous to that of sevedine [3].

The PMR spectrum of **1** exhibits signals at 1.11 (3H, s, 19-CH_3) and 0.80 ppm (6H, d, 21-CH_3 and 27-CH_3).

Acetylation of sevedinine with acetic anhydride in pyridine produced acetylsevedinine (**2**), the IR spectrum of which showed absorption bands at 3480 and 1030 (OH), 2770 (*trans*-quinolizidine), 1737 and 1240 (ester C=O), and 1710 cm^{-1} (C=O). The PMR spectrum of **2** had signals at 1.09 (3H, s, 19-CH_3), 0.80 (6H, d, 21-CH_3 and 27-CH_3), 2.01 (3H, s, $OCOCH_3$), and 4.91 ppm (H, m, HC-$OCOCH_3$).



Oxidation of sevedinine with chromic anhydride in acetic acid formed a ketone, sevedininone, which had physicochemical constants and spectral properties identical to the oxidation product of sevedine, sevedinedione (**3**). Reduction of **1** with $NaBH_4$ produced dihydrosevedinine, identical to sevedine (**4**) [3].

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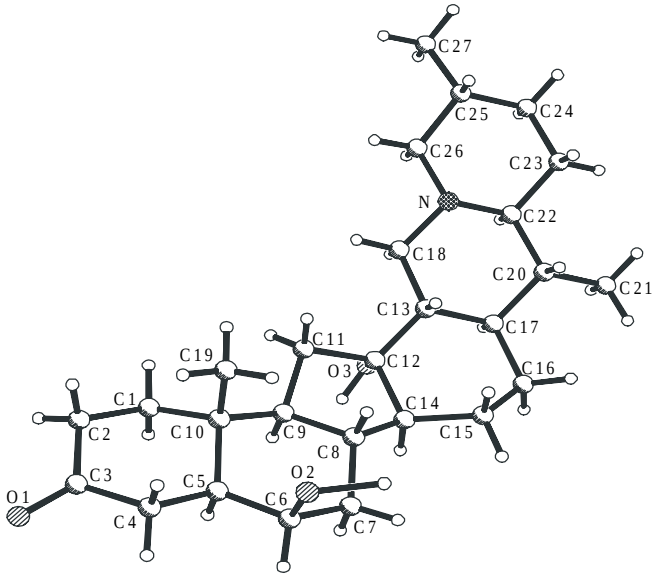

Fig. 1. Molecular structure of sevedinine.

Thus, the data indicate that **1** differs from sevedine by one additional carbonyl that replaces one hydroxyl. The facts that sevedininone is identical to sevedinedione and dihydrosevedinine is identical to sevedine indicate that sevedinine has the heterocyclic cevanine skeleton. Theoretically, the carbonyl and secondary hydroxyl could be located on C3 or C6. Their positions were determined by considering that the multiplet for the geminal proton at 4.97 ppm in the PMR spectrum of diacetylsevedine belongs to C6-αH whereas the geminal proton in the PMR spectrum of acetylsevedinine resonates at 4.91 ppm. This indicates that the hydroxyl is located on C6 and has the β-orientation whereas the carbonyl lies at the C3 position. Therefore, the carbonyl in sevedine is located on C3. The A/B, B/C, C/D, D/E, and E/F ring fusions and orientations of C21 and C27 methyls are the same as in sevedine. The location of the tertiary hydroxyl in sevedine, like in other cevine alkaloids, is defined based on the structure of korseveriline (**5**) [4], for which, according to PMR spectroscopy, the position of the hydroxyl, of the two possible, is probably C14 [3-7].

However, our X-ray structure analysis (XSA) of sevedinine indicates that the position of the tertiary hydroxyl that was previously determined (C14) is incorrect. According to the XSA, the tertiary hydroxyl in sevedinine is in the C12 position. Therefore, the structure and configuration of **1** is 6β,12α-dihydro-5α-hydroxycevanin-3-one.

Figure 1 shows the molecular structure according to the XSA. Figure 1 and an analysis of the torsion angles show that the six-membered rings A, B, E, and F have practically ideal chair conformations (four atoms of the ring lie in the plane within ±0.015 Å). Five-membered ring C has the 9α-envelope conformation (±0.041 Å). Ring D in **1** adopts the boat conformation (±0.046 Å). The A/B, B/C, D/E, and E/F fusions are *trans*; C/D, *cis*. The oxygen-containing groups are situated as follows: the carbonyl is located on C3; secondary hydroxyl, β-axial C6; tertiary hydroxyl, α-axial C12. The methyls are β-axial C10 and α-equatorial C20 and C25.

The Csp^3–Csp^3 bond lengths vary in the range 1.51-1.56 Å; Csp^3–N, Csp^3–O, and C=O heterobonds, 1.47, 1.43, and 1.20 Å, respectively. This agrees within experimental uncertainty with the normal values [8]. Anomalous bond angles were not observed.

Packing effects and intermolecular contacts in **1** indicate the presence of O...H–O H-bonds that form a three-dimensional framework. The geometric parameters of the intermolecular H-bonds are as follows: O1...O3, 2.87 Å; O1...H–O3, 1.97 Å; O3–H...O1, 160.4° (-x, 0.5+y, 0.5-z); O2...O3, 2.84 Å; O2–H...O3, 1.90 Å; O2–H...O3, 164.3° (0.5+x, 0.5-y, 1-z).

In conclusion, it should be noted that the XSA enables the structures of ten natural analogs of sevedinine, representatives of the cevine group from *Korolkovia severtzovii*, to be re-examined because the structures were derived from each other based on chemical transformations of the hydroxy substituents in the C3 and C6 positions. The tertiary hydroxyl at C12α remained the same.

Thus, the tertiary hydroxyl is located on C12 and has the α-axial orientation in korseveriline [4], korseveramine [5], sevedine [3], its N-oxide [9], mono- [10] and diacetyl derivatives [11], korseverilinone [12], severine [13], its N-oxide [14], and sevedamine [15].

TABLE 1. Crystallographic Data, Experimental Conditions, and Refinement Parameters for the Structure of **1**

Empirical formula	$C_{27}H_{43}NO_3$
Molecular weight	429.62
Exposure temperature, K	293
Space group	$P2_12_12_1$, Z = 4
a, Å	12.936 (3)
b, Å	13.210 (3)
c, Å	14.121 (3)
V, Å^3	2413.1 (9)
ρ, g/cm^3	1.183
Abs. coeff., m (Mo) mm^{-1}	0.075
Crystal size, mm	0.75×0.40×0.30
Angle range θ, deg	from 1.54 to 24.99
Total number of reflections	2402
Number of reflections [I > 2σ (I)]	1430
R-factor [I > 2σ (I)]	R1 = 0.0927, wR2 = 0.1219
R-factor (over all reflections)	R1 = 0.1749, wR2 = 0.1523

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument (KBr disks); PMR spectra, on a JNM-4H-100/100 MHz instrument (in $CDCl_3$) with HMDS as an internal standard (δ-scale).

Isolation of Sevedinine (1). The parent severine N-oxide (2.01 g) [13] was dissolved in $CHCl_3$ and chromatographed over a column of Al_2O_3 with elution by $CHCl_3$ and $CHCl_3$:CH_3OH (10:0.5). The $CHCl_3$ eluate afforded sevedinine (0.19 g), mp 233-235°C (acetone), $[\alpha]_D$ -13.6° (*c* 0.4, $CHCl_3$), $C_{27}H_{43}NO_3$. Mass spectrum (*m*/*z*): 429 $[M]^+$, 414, 412, 411, 400, 396, 358, 178, 162, 139, 138, 125, 124, 112, 111 (100%), 98.

Acetylation of 1. A mixture of **1** (0.04 g), pyridine (1 mL), and acetic anhydride (2 mL) was held for 3 d at room temperature and evaporated in vacuum. The solid was dissolved in H_2SO_4 (5%). The acidic solution was made basic with NH_4OH and extracted with $CHCl_3$. The solvent was distilled to afford acetylsevedinine (0.038 g), mp 182-184°C (acetone).

Mass spectrum (*m*/*z*): 471 $[M]^+$, 456, 454, 453, 452, 444, 438, 429, 416, 415, 412, 411, 410, 401, 400, 176, 164, 150, 149, 139, 138, 125, 124, 112, 111 (100%), 98.

Oxidation of 1. A solution of **1** (0.35 g) in acetic acid (2 mL) was treated with chromic anhydride (0.20 g) dissolved in acetic acid (4 mL, 80%). The mixture was heated for 30 min on a water bath and evaporated in vacuum. The solid was dissolved in water, made basic with NH_4OH, and extracted with $CHCl_3$. The oxidation product was chromatographed over a column of Al_2O_3 with elution by $CHCl_3$ to afford sevedininone (0.2 g), mp 215-217°C (benzene), $[M]^+$ 427.

Reduction of 1. A solution of **1** (0.09 g) in CH_3OH (10 mL) was reduced by $NaBH_4$ (0.4 g) for 30 min at room temperature. Solvent was distilled. The solid was dissolved in water and extracted with $CHCl_3$. Treatment of the dry solid with acetone produced dihydrosevedinine (0.07 g), mp 212-214°C, $[M]^+$ 431.

X-ray Structure Analysis. Single crystals of **1** grown from an ethanol solution were transparent prisms. Unit-cell constants and intensities of reflections were determined on a four-circle STOE Stadi-4 diffractometer (θ/2θ-scanning) using Mo Kα-radiation (graphite monochromator). Absorption corrections were not applied. Table 1 gives the principal crystallographic data and conditions for the XSA.

The structure was solved by direct methods using the SHELXS-97 programs and refined by full-matrix isotropic—anisotropic least-squares methods (LS). Nonhydrogen atoms were determined anisotropically by full-matrix LS (over F^2). Positions of H atoms were found geometrically and refined isotropically with fixed positions using $U_{iso} = nU_{eq}$, where n = 1.5 for methyls and 1.2 for others and U_{eq} is the equivalent isotropic thermal parameter of the corresponding C atom. Hydroxyl H atoms were found in a difference electron-density synthesis. The relatively high R-factor for the sevedinine structure is due to the quality of the selected crystal for the x-ray experiment, i.e., high-quality crystals were not available.

Results of the XSA were deposited as a CIF file in the Cambridge Crystallographic Database (registry No. CCDC 236406).

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