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SECOKARACONITINE, A NEW DITERPENOID ALKALOID FROM *Aconitum karacolicum*

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The known diterpenoid alkaloids karacoline, karakanine, songorine, napelline, 12-acetylnapelline, cammaconine, and a new 7,17-secoalkaloid of the lycoctonine type, secokaraconitine, were isolated from tubers of Aconitum karacolicum. *An x-ray structure analysis of the new alkaloid was performed.*

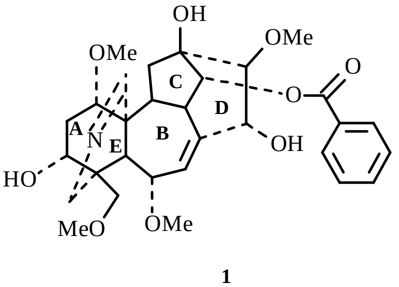
Key words: diterpenoid alkaloids, secokaraconitine, XSA.

We investigated tubers of *Aconitum karacolicum* Rapaics collected during budding in the Turuk river canyon of Issykkul′skaya District of Kyrgyzstan in order to determine the alkaloid content as a function of habitat.

The $CHCl_3$ extract afforded 1.21% total alkaloids from the dried plant material. These were separated to isolate the known diterpene alkaloids karacoline [1], karakanine [2], songorine [3], napelline [4], 12-acetylnapelline [4], cammaconine [5], and a new crystalline base of formula $C_{30}H_{39}NO_9$, called secokaraconitine (**1**). The structure of **1** was proved by an x-ray structure analysis (XSA) because of the small quantity isolated. The crystalline form of the alkaloid is a crystal hydrate in which two base molecules incorporate one water molecule, i.e., the composition of the crystallographically independent unit is $C_{30}H_{39}NO_9 \cdot 0.5H_2O$.

The structure of **1** (Fig. 1) shows that the base is a secojesaconitine [6] 7,17-secoalkaloid.

The substituents in the carbon skeleton at C1, C6, C3, C15, and C14 have the α-orientation whereas those at C13 and C16 have the β-orientation. The hydrocarbon skeleton is a framework consisting of two six-membered (A, D), two five-membered (C, E), and one seven-membered (B) ring. These rings are conformationally more flexible than in the usual lycoctonine skeleton because the C7–C17 bond is lacking. The ring fusions are A/B-*trans* and B/C-*cis*.



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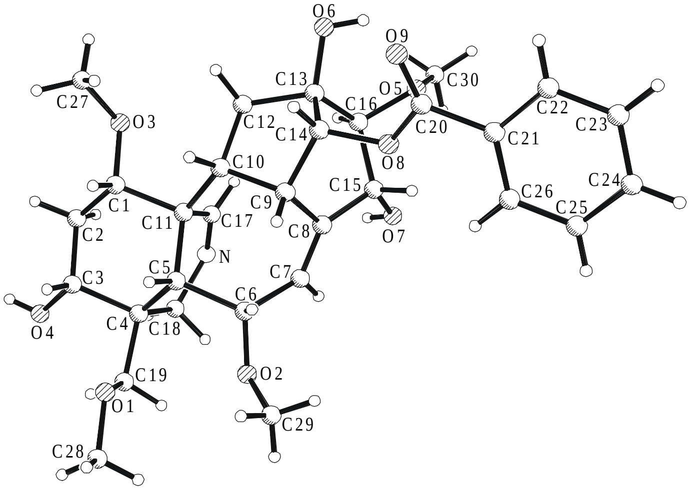

Fig. 1. Structure of secokaraconitine.

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TABLE 1. Bond Lengths (r, Å) and Angles (ω, deg) in **1**

Bond	r	Angle	ω	Angle	ω
O1-C28	1.414(4)	C28-O1-C19	111.2(2)	C29-O2-C6	112.9(3)
O1-C19	1.420(3)	C27-O3-C1	113.6(2)	C30-O5-C16	115.3(3)
O2-C29	1.402(4)	C20-O8-C14	119.0(2)	C17-N-C18	120.3(3)
O2-C6	1.409(3)	O3-C1-C2	109.8(3)	O3-C1-C11	110.0(3)
O3-C27	1.419(3)	C2-C1-C11	113.1(2)	C1-C2-C3	110.9(3)
O3-C1	1.430(3)	O4-C3-C2	110.5(3)	O4-C3-C4	109.6(3)
O4-C3	1.420(4)	C2-C3-C4	112.3(3)	C18-C4-C5	108.8(3)
O5-C30	1.417(3)	C18-C4-C19	108.2(2)	C5-C4-C19	114.8(3)
O5-C16	1.426(4)	C18-C4-C3	111.8(2)	C5-C4-C3	108.9(3)
O6-C13	1.418(4)	C19-C4-C3	104.2(3)	C4-C5-C11	108.5(2)
O7-C15	1.426(3)	C4-C5-C6	114.8(2)	C11-C5-C6	111.1(3)
O8-C20	1.355(4)	O2-C6-C7	109.1(3)	O2-C6-C5	112.6(3)
O8-C14	1.452(4)	C7-C6-C5	115.0(2)	C8-C7-C6	122.0(3)
O9-C20	1.186(3)	C7-C8-C9	116.4(3)	C7-C8-C15	126.1(3)
N-C17	1.266(3)	C9-C8-C15	117.1(3)	C8-C9-C14	112.3(3)
N-C18	1.471(4)	C8-C9-C10	108.4(2)	C14-C9-C10	101.9(2)
C1-C2	1.491(4)	C9-C10-C12	101.8(3)	C9-C10-C11	117.7(2)
C1-C11	1.557(4)	C12-C10-C11	117.4(2)	C17-C11-C1	107.8(3)
C2-C3	1.507(4)	C17-C11-C5	107.3(2)	C1-C11-C5	107.5(3)
C3-C4	1.566(4)	C17-C11-C10	113.8(3)	C1-C11-C10	104.6(2)
C4-C18	1.527(4)	C5-C11-C10	115.5(2)	C13-C12-C10	107.9(3)
C4-C5	1.534(4)	O6-C13-C14	114.6(3)	O6-C13-C12	107.7(3)
C4-C19	1.550(4)	C14-C13-C12	99.7(3)	O6-C13-C16	111.5(3)
C5-C11	1.561(4)	C14-C13-C16	110.7(3)	C12-C13-C16	112.2(3)
C5-C6	1.594(5)	O8-C14-C9	108.6(3)	O8-C14-C13	114.4(3)
C6-C7	1.501(5)	C9-C14-C13	101.3(3)	O7-C15-C8	113.7(2)
C7-C8	1.318(4)	O7-C15-C16	113.1(3)	C8-C15-C16	112.9(3)
C8-C9	1.501(4)	O5-C16-C15	108.2(3)	O5-C16-C13	108.8(2)
C8-C15	1.510(4)	C15-C16-C13	114.4(3)	N-C17-C11	127.3(3)
C9-C14	1.524(4)	N-C18-C4	117.0(2)	O1-C19-C4	108.7(2)
C9-C10	1.547(4)	O9-C20-O8	125.0(3)	O9-C20-C21	126.0(3)
C10-C12	1.567(4)	O8-C20-C21	108.9(3)	C26-C21-C22	120.1(3)
C10-C11	1.569(4)	C26-C21-C20	121.9(3)	C22-C21-C20	117.9(3)
C11-C17	1.510(4)	C23-C22-C21	118.3(3)	C24-C23-C22	121.2(4)
C12-C13	1.543(4)	C25-C24-C23	120.2(4)	C24-C25-C26	119.7(3)
C13-C14	1.526(4)	C21-C26-C25	120.4(3)		
C13-C16	1.546(4)				
C15-C16	1.530(4)				
C20-C21	1.499(5)				
C21-C26	1.383(4)				
C21-C22	1.394(5)				
C22-C23	1.391(5)				
C23-C24	1.373(5)				
C24-C25	1.373(5)				
C25-C26	1.384(5)				

Six-membered ring A in **1** adopts the ideal chair conformation (deviations of atoms from the plane of four atoms is less than ±0.02 Å). Ring D has the boat conformation (±0.04 Å) but is flattened toward C15 (deviations of C14 and C15 from the plane of the four ring atoms are 0.70 and 0.41 Å, respectively). Ring E has the half-chair (±0.05 Å) conformation with C5 deviating from the other five ring atoms by 0.71 Å. The conformation of seven-membered ring B is close to a boat (±0.08 Å) whereas five-membered ring C adopts a 14α-envelope (±0.02 Å). The plane of the 14-ester (±0.02 Å) is slightly rotated (20.5°) relative to the plane of the benzene ring (±0.03 Å).

TABLE 2. Intermolecular H-Bonds in **1**

D-H...A	d(D...A), Å	d(D-H), Å	d(H...A), Å	<(DHA), deg
O4-H...O7 (X+1, Y, Z)	2.89	0.77	2.12	174
O6-H...N3 (-X-2, Y+0.5, -Z-0.5	2.79	0.81	2.12	167
O7-H...O6 (-X-2, Y-0.5, -Z-0.5)	2.85	0.76	2.11	140

D - donor, A - acceptor.

TABLE 3. Atomic Coordinates ($\times 10^4$) and Equivalent Thermal Parameters U_{eq} ($Å^2 \times 10^3$) in **1**

Atom	x	y	z	U_{eq}
O1	-5458(3)	-10670(2)	-5239(1)	40(1)
O2	-8210(2)	-11249(2)	-4973(1)	33(1)
O3	-5986(2)	-9241(2)	-2545(1)	31(1)
O4	-3776(3)	-11691(2)	-3904(1)	38(1)
O5	-12141(2)	-9290(2)	-2404(1)	37(1)
O6	-10386(3)	-7796(2)	-2217(1)	32(1)
O7	-11437(3)	-11230(2)	-3198(1)	35(1)
O8	-11447(2)	-8021(2)	-3626(1)	31(1)
O9	-11722(2)	-6294(2)	-3365(1)	37(1)
N	-7332(3)	-11878(2)	-3247(1)	29(1)
C1	-5835(3)	-9583(2)	-3183(1)	29(1)
C2	-4829(3)	-10436(2)	-3218(1)	30(1)
C3	-4674(3)	-10833(2)	-3882(2)	30(1)
C4	-6000(3)	-11190(2)	-4178(1)	25(1)
C5	-6952(3)	-10250(2)	-4158(1)	28(1)
C6	-8301(4)	-10454(2)	-4508(1)	31(1)
C7	-9428(3)	-10702(3)	-4083(1)	28(1)
C8	-9986(3)	-9966(2)	-3732(2)	27(1)
C9	-9358(3)	-8886(2)	-3735(1)	27(1)
C10	-8087(3)	-8948(2)	-3347(1)	27(1)
C11	-7174(3)	-9931(2)	-3456(1)	26(1)
C12	-8599(3)	-8755(2)	-2662(1)	29(1)
C13	-10071(3)	-8527(2)	-2702(2)	28(1)
C14	-10143(3)	-8068(2)	-3365(1)	29(1)
C15	-11091(3)	-10138(2)	-3276(2)	28(1)
C16	-10893(3)	-9555(2)	-2652(2)	30(1)
C17	-7599(3)	-10922(2)	-3110(2)	29(1)
C18	-6597(3)	-12126(2)	-3822(1)	30(1)
C19	-5633(4)	-11574(2)	-4847(1)	34(1)
C20	-12108(4)	-7088(3)	-3603(2)	30(1)
C21	-13382(4)	-7221(2)	-3937(1)	30(1)
C22	-14369(4)	-6493(3)	-3807(2)	38(1)
C23	-15527(4)	-6570(3)	-4143(2)	47(1)
C24	-15704(4)	-7348(3)	-4589(2)	41(1)
C25	-14736(4)	-8074(3)	-4708(2)	38(1)
C26	-13578(4)	-8017(3)	-4377(2)	33(1)
C27	-5429(4)	-8229(3)	-2421(2)	40(1)
C28	-5259(4)	-10972(3)	-5872(2)	52(1)
C29	-8698(4)	-10918(3)	-5557(2)	54(1)
C30	-12598(4)	-9967(3)	-1919(2)	47(1)
Ow	-12543(8)	-10344(5)	-5107(3)	97(4)

Table 1 lists the bond lengths and angles. The bond lengths and the presence of one H atom each at positions C7 and

C17 are consistent with double bonds at N=C17 [1.266(3) Å] and C7=C8 [1.318(4) Å] in the lycoctonine skeleton. Furthermore, the bond angles for N, C7, C8, and C17 are consistent (Table 1) with sp^2-hybridization, which again supports the above hypothesis. The lengths of ordinary Csp^3–Csp^3 bonds vary in the range 1.510-1.570 Å; C–O bonds, 1.402-1.426 Å. Bonds lengths in the aromatic ring cover the range 1.373-1.395 Å. The significant increase of the bond angle for O8 (119.0°) compared with those observed for analogous O atoms O1 (112.2°), O2 (112.9°), O3 (113.6°), and O5 (115.3°) is apparently due to Van-der-Waals repulsion of the benzene ring from the hydrocarbon framework.

The placement of the hydroxyl on C13 and the methoxyl on C16 favor the formation of an intramolecular H-bond of the O–H...O type with the parameters O5...O6 2.63 Å, O6–H...O5 2.17 Å, and O–H...O 116°.

The crystal packing of **1** indicates that the molecules form intermolecular H-bonds of the O–H...O and O–H...N types. Table 2 lists the geometric parameters of these interactions. The waters of solvation participate in the packing with a multiplicity of 0.5, are situated in voids at Van-der-Waals distances, and do not form intermolecular interactions.

EXPERIMENTAL

Melting points were determined on a Kofler block.

Silica gel (KSK) and deactivated alumina were used for column chromatography. TLC was performed on silica-gel (L 5/40 µm, Czech Rep.) and alumina plates containing 13% gypsum. Solvent systems $CHCl_3$—CH_3OH (100:1 and 50:1) and benzene—methanol (10:1 and 4:1) were used. Alkaloids were visualized with iodine vapor.

Preparation and Separation of Total Alkaloids. Air-dried ground tubers (270 g) were extracted with $CHCl_3$ in a Soxhlet apparatus. The $CHCl_3$ extract was shaken with H_2SO_4 solution (5%) until the alkaloids were completely extracted. The acidic solution was filtered, washed with $CHCl_3$ (3×), cooled, and made basic with Na_2CO_3. The alkaloids were exhaustively extracted with $CHCl_3$. Removal of solvent afforded washed (0.09 g) and basic (3.16 g) $CHCl_3$ total alkaloids.

The basic $CHCl_3$ alkaloids were treated with acetone to separate karacoline (0.72 g). Part of the mother liquor (1.2 g) after removal of acetone was chromatographed over a column of deactivated alumina (60 g) with elution by $CHCl_3$ with gradual addition of CH_3OH. Elution by $CHCl_3$—CH_3OH (100:1) isolated karacoline (0.07 g) and karakanine (0.02 g). Eluates of $CHCl_3$—CH_3OH (50:1) gave 12-acetylnapelline (0.09 g) and cammaconine (0.025 g); of (25:1), songorine (0.29 g) and napelline (0.17 g).

Mother liquors remaining after separation of karacoline and karakanine were combined (0.2 g) and chromatographed over a column of silica gel (4 g). Elution by benzene—methanol (100:1) isolated karacoline (0.03 g); by (50:1) and acetone, secokaraconitine (0.011 g).

Secokaraconitine (1), $C_{30}H_{39}NO_9\cdot 0.5H_2O$, mp 230-232°C (acetone).

X-ray Structure Analysis. Crystals of **1** were grown from an acetone solution. A transparent single crystal shaped like a thin plate of approximate dimensions 0.3×0.2×0.07 mm^3 at 110 K was selected for the analysis. Crystals of **1** are orthorhombic, $a = 10.278(5)$, $b = 12.559(4)$, $c = 21.268(11)$ Å, $V = 2745(2)$ Å^3, $d_{calc} = 1.371$ g/cm^3, absorption coefficient $\mu = 0.102$ mm^{-1}, space group $P2_12_12_1$, $Z = 4$. Intensities of 6001 independent reflections ($R_{int} = 0.065$) were measured on an automated Bruker SMART 1K CCD diffractometer (Mo Kα-radiation, $\lambda = 0.71093$ Å, graphite monochromator, ω-scanning, $2\Theta_{max} = 54.2°$). Absorption corrections were applied semi-empirically using the SADABS program [2]. The maximal and minimal transmission coefficients were 1.000 and 0.677.

The structure was solved by direct methods using the program set SHELXTL PLUS 5.0 [3]. Nonhydrogen atoms were refined by anisotropic full-matrix least-squares methods (over F^2). Positions of H atoms were found in a difference Fourier synthesis and refined with fixed isotropic thermal parameters $U_{iso} = nU_{eq}$, where n = 1.5 for methyls and 1.2 for others and U_{eq} is the equivalent isotropic parameter of the corresponding C, N, or O atom. The final agreement factors were $R_1(F) = 0.0465$ ($wR_2 = 0.0801$) for reflections with $I > 2\sigma(I)$; $R_1 = 0.1092$ ($wR_2 = 0.0925$) and GOF = 0.97 over all 6001 independent reflections included in the final refinement cycle. Table 3 lists coordinates of nonhydrogen atoms from the last least-squares refinement cycle.

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