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ALKALOIDS OF THE MONGOLIAN FLORA.

III. ALTACONITINE – A NEW ALKALOID FROM Aconitum altaicum

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UDC 547.944/945+548.737

Aconitine, mesaconitine, and a new alkaloid, which has been called altaconitine, have been isolated from the total alkaloids of the epigeal part of Aconitum altaicum. Altaconitine has the structure of 8β-acetoxy-14α-benzoyloxy-2β,3α,13β,-15α-tetrahydroxy-1α,6α,16β-trimethoxy-4β-methoxymethy-N-ethylaconitan, which was established on the basis of a study of IR, PMR, ^{13}C NMR, and mass spectra and by the x-ray structural method.

The isolation of napelline from the epigeal part of Aconitum altaicum Steinb. has been reported previously [1]. Continuing the separation of the total alkaloid, we have obtained aconitine, mesaconitine, and a new alkaloid, which has been called altaconitine (I). Altaconitine has the composition $C_{34}H_{47}NO_{12}$ (M 661.30982, HRMS). Its IR spectrum contained absorption bands of hydroxy, ester, and ether bonds. Its PMR spectrum showed the signals of N-ethyl, acetoxy, and four methoxy groups, of the protons of a monosubstituted benzene ring, and of four methine protons. The spectral characteristics permitted altaconitine to be assigned to the alkaloids of the aconitine type. A comparison of the developed formulas of the two alkaloids showed that altaconitine (I) differed from aconitine (II) by the presence of an additional hydroxy group.

In the PMR spectrum of altaconitine, the signals of the protons of an acetoxy group appeared in an unusually strong field (1.41 ppm), while the signal of the C14β proton appeared at 4.88 ppm in the form of a doublet with a SSCC of 5 Hz, which permitted the acetoxy group to be located at C8, the benzoyl group at C14, and the hydroxy group at C13. By analogy with the spectrum of aconitine, it was possible to assign a one-proton doublet at 4.08 ppm (J = 5 Hz) to the C6β proton geminal to a methoxy group, and a doublet at 4.33 ppm (J = 3 Hz) to the C15β proton at a hydroxy group.

The mass spectrum of altaconitine contained the peaks of the ion $M^+ - 31$, showing the presence of a methoxy group at C1. An unusual feature of the mass spectrum of (I) consisted in the fact that its maximum peak was that of the $M^+ - 59$ ion, instead of the expected $M^+ - 60$ ion observed in the spectrum of aconitine and aconifine (III) [2, 3]. The peak of the $M^+ - 59$ ion arises on the cleavage of the 7–17 bond with the splitting out of an acetoxy radical and the formation of 17–N and 7–8 double bonds. The mass spectrum of altaconitine also lacked the peak of the $M^+ - 49$ ($M^+ - 31 - 18$) ion, which is formed as the result of the successive splitting out of a methoxy radical from C1 and a molecule of water with the participation of the hydroxy group at C3 [2]. The absence of the peak of the $M^+ - 49$ ion showed that altaconitine and aconitine differed by the substitution of ring A.

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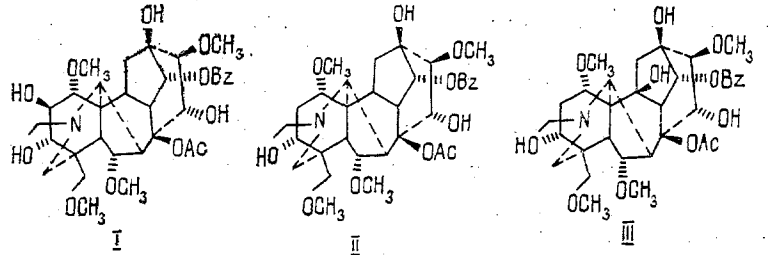
TABLE 1. ^{13}C Chemical Shifts of Altaconitine (I), Aconitine (II) and Aconifine (III)

Carbon	I	II	III	Carbon	I	II	III
1	83,6	83,4	79,8	17	59 3	60,1	61,2
2	65,2	36,0	33,5	18	71,6	75,6	74,9
3	67,7	70,4	71,6	19	48,6	48,8	47,7
4	43,8	43,2	43,1	$N-CH_2$	43.8	46 9	47,2
5	45,6	46,6	42,8	|	12,0	13,3	13,3
6	82,4	82,3	83,6	CH_3	56,0	55,7	55,4
7	44,9	44,8	44,7	1′	58.4	57,9	58,2
8	91,5	92,0	89,7	6′	60,9	60,7	61,2
9	45,3	44,2	54,0	16′	58,7	58,9	59,1
10	40,5	40,8	78,6	18′	172,2	172.2	172,1
11	52,4	49,8	55.9	C=O	21,2	21,3	21,5
12	38,1	34.0	48,9	|	166,0	165,9	166,1
13	73,8	74,0	77,0	CH_3	129,7	129,8	130,2
14	78,6	78,9	77,3	C=O	129,5	129,6	129,7
15	78,6	78,9	78,7	|	128,5	128,6	128,6
16	90,1	90,1	90,1	C_6H_5	133,2	129,2	133,2



I II III

The complete structure of altaconitine was definitively established by an x-ray structural investigation, which showed that altaconitine has the structure of 8β-acetoxy-14α-benzoyloxy-2β,3α,13β,15α-tetrahydroxy-1α,6α,16β-trimethoxy-4β-methoxymethyl-N-ethylaconitane. Altaconitine (I) is the first alkaloid with a lycoctonine skeleton containing a hydroxy group at C2 and a 2,3-trans-diol system.

The structure (I) found by the x-ray structural method permitted the signals in the ^{13}C NMR spectrum to be assigned in comparison with the spectra of aconitine (II) and aconifine (III) (Table 1).

The spatial structure of the altaconitine molecule in a projection on the plane of the three atoms C1C4C9 is shown in Fig. 1. The molecule of (I) has a rigid bridge structure in which the positions and orientations of the substituents agree completely with those observed in aconitone [3], which confirms the structure proposed on the basis of structural characteristics, while the "additional" hydroxy group at C2 has the β-orientation. The conformations of the rings are as follows: ring A (the C1−C5 and C11 atoms) − chair with deviations of the C1 (0.71 Å) and C4 (−0.73 Å) atoms from the plane of the other four, which are coplanar with an accuracy of ±0.03 Å; the seven-membered ring B (C5−C11) − boat (±0.03 Å) with deviations of the C5 (1.34 Å), C5 (1.50 Å), and C9 (0.50 Å) atoms; the five-membered ring C (C9, C19, and C12−C14) − envelope (±0.04 Å) with a deviation of the C14 atom by 0.71 Å: ring D (C8, C9, and C13−C16) − boat (±0.01 Å) with flattening on the C15 side (0.22 Å) and a deviation of C14 by 0.83 Å; the six-membered heterocycle H (C4, C5, C11, C17, C18, and N) − chair (±0.01 Å) with deviations of the C11 and C18 atoms by −0.91 and 0.97 Å, respectively; the six-membered ring E (C7−C11 and C17) − chair with deviations of the C9 (0.50 Å) and C17 (−0.87 Å) atoms; and the five-membered ring F (C5−C7, and C17) with a conformation close to half-chair with deviations of the C11 and C19 atoms from the plane of the other three on different sides by 0.49 and 0.63 Å, respectively. The benzoyl fragment (C14, C25−C31, O9, O10) is almost planar (±0.07 Å).

The conformations of the rings and the orientation of substituent in the molecule of (I), on the whole, favor the formation of intramolecular-bonds of the O−H...O and O−H...N types as is shown by the O3...O2 distance of 2.66 Å and the O2...N distance of 2.66 Å, and also the O7...O11 and O8...O12 distances of 2.75 and 2.60 Å. Consequently, all the active H atoms participate in intramolecular H-bonds and there are no intermolecular H-bonds in the crystal structure of (I).

On the whole, within the 3σ limits, the bond lengths agree with those generally adopted [4]. The appreciable shortening of the C33−C34 bond (1.38 Å) is apparently due to the thermal

TABLE 2. Bond Lengths (r, Å) and Valence Angles (ω, deg) in the Structure of (I)

Bond	r	Bond	r	Angle	ω	Angle	ω	Angle	ω
C1—C2	1,55	C13—O8	1,39	C11—C1—C2	119	O6—C8—C15	108	C7—C17—N	117
C1—C11	1,53	C14—O9	1,48	O1—C1—C2	107	C10—C9—C8	114	C11—C17—N	109
C1—O1	1,41	C15—C16	1,56	O1—C1—C11	110	C14—C9—C8	114	C7—C17—C11	100
C2—C3	1,51	C15—O11	1,43	C3—C2—C1	111	C10—C9—C14	102	C4—C18—N	108
C2—O2	1,41	C16—O12	1,45	O2—C2—C1	113	C9—C10—C11	117	C4—C19—O4	112
C3—C4	1,57	C17—N	1,48	C3—C2—O2	109	C9—C10—C12	103	C24—C23—O6	109
C4—C5	1,58	C18—N	1,51	C2—C3—C4	116	C11—C10—C12	115	C24—C23—O7	125
C4—C18	1,55	C19—O4	1,43	C2—C3—O3	110	C1—C11—C5	113	O6—C23—O7	126
C4—C19	1,53	C20—O1	1,38	O3—C3—C4	112	C1—C11—C10	106	C26—C25—O9	111
C5—C6	1,63	C21—O4	1,42	C3—C4—C5	108	C1—C11—C17	118	C26—C25—O10	129
C5—C11	1,55	C22—O5	1,36	C3—C4—C18	111	C5—C11—C10	113	O9—C25—O10	120
C6—C7	1,58	C23—C24	1,51	C5—C4—C18	109	C5—C11—C17	100	C25—C26—C27	122
C6—O5	1,40	C23—O6	1,34	C3—C4—C19	108	C10—C11—C17	108	C25—C26—C31	118
C7—C8	1,53	C23—O7	1,20	C5—C4—C19	111	C10—C12—C13	107	C27—C26—C31	120
C7—C17	1,55	C25—C26	1,47	C18—C4—C19	109	C12—C13—C14	102	C26—C27—C28	119
C8—C9	1,55	C25—O10	1,22	C4—C5—C6	110	C12—C13—C16	107	C27—C28—C29	118
C8—C15	1,59	C26—C27	1,37	C4—C5—C11	109	C14—C13—C16	110	C28—C29—C30	123
C8—O6	1,45	C26—C31	1,39	C6—C5—C11	103	C12—C13—O8	111	C29—C30—C31	120
C9—C10	1,56	C27—C28	1,42	C5—C6—C7	103	C14—C13—O8	114	C26—C31—C30	120
C9—C14	1,51	C28—C29	1,38	C5—C6—O5	116	C16—C13—O8	113	C34—C33—N	116
C10—C11	1,58	C29—C30	1,34	C7—C6—O5	113	C13—C14—C9	103	C1—O1—C20	116
C10—C12	1,58	C30—C31	1,38	C6—C7—C8	106	O9—C14—C13	107	C19—O4—C21	122
C11—C17	1,56	C32—O12	1,48	C6—C7—C17	106	O9—C14—C9	113	C6—O5—C22	117
C12—C13	1,56	C34—C33	1,39	C8—C7—C17	115	C16—C15—C8	117	C8—O6—C23	122
C13—C14	1,54	C33—N	1,50	C7—C8—C9	108	O11—C15—C8	113	C14—O9—C25	119
C13—C16	1,55			C7—C8—C15	114	O11—C15—C16	108	C16—O12—C32	113
				C7—C8—O6	109	C13—C16—C15	117	C17—N—C18	116
				C15—C8—C9	113	C13—C16—O12	105	C17—N—C32	111
				O6—C8—C9	105	C15—C16—O12	110	C18—N—C32	110

TABLE 3. Coordinates ($\times 10^4$) of the Nonhydrogen Atoms of the Altaconitine Molecule

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
C1	2420(9)	1554(7)	0304(6)	C25	—1596(9)	—0273(9)	—2113(7)
C2	3633(10)	1629(8)	0593(7)	C26	—2312(9)	—1003(8)	—2285(7)
C3	4421(9)	1290(7)	—0008(7)	C27	—2870(10)	—1436(8)	—1711(6)
C4	4104(10)	0426(7)	—0393(7)	C28	—3561(11)	—2133(9)	—1909(8)
C5	2938(9)	0528(7)	—0798(7)	C29	—3628(12)	—2357(9)	—2679(9)
C6	2507(9)	—0394(7)	—1098(7)	C30	—3089(12)	—1939(9)	—3250(8)
C7	1728(10)	—0689(6)	—0419(6)	C31	—2427(11)	—1265(11)	—3056(7)
C8	0543(10)	—0630(7)	—0726(7)	C32	—2495(13)	—1087(10)	0848(9)
C9	0367(8)	0289(7)	—1040(6)	C33	2920(13)	—1021(9)	1213(8)
C10	0912(9)	0985(7)	—0526(6)	C34	3269(28)	—0925(13)	1972(11)
C11	2077(9)	0775(7)	—0166(6)	O1	1722(6)	1644(6)	0960(4)
C12	—0029(9)	1187(7)	0089(6)	O2	3802(7)	1190(6)	1295(4)
C13	—1064(10)	0689(8)	—0181(6)	O3	5480(6)	1276(6)	0306(5)
C14	—0814(10)	0563(7)	—1046(7)	O4	4872(7)	0786(6)	—1635(5)
C15	—0377(10)	—0908(6)	—0120(7)	O5	3303(7)	—0993(5)	—1287(5)
C16	—1084(10)	—0183(8)	0249(7)	O6	0428(6)	—1176(5)	—1407(4)
C17	1978(9)	—0095(7)	0269(6)	O7	0540(8)	—2423(5)	—0760(6)
C18	4034(10)	—0304(7)	0209(7)	O8	—2012(6)	1167(5)	—0936(5)
C19	5004(9)	0215(9)	—0993(7)	O9	—1570(6)	—0107(5)	—1336(4)
C20	1655(10)	2455(7)	1270(8)	O10	—1094(8)	0176(6)	—2563(5)
C21	5650(12)	0638(12)	—2236(9)	O11	0072(7)	—1411(5)	0504(4)
C22	3372(17)	—1251(15)	—2046(12)	O12	—2227(7)	—0445(5)	0254(5)
C23	0456(11)	—2031(8)	—1354(9)	N	3012(8)	—0251(6)	0699(5)
C24	0403(14)	—2405(8)	—2151(8)				

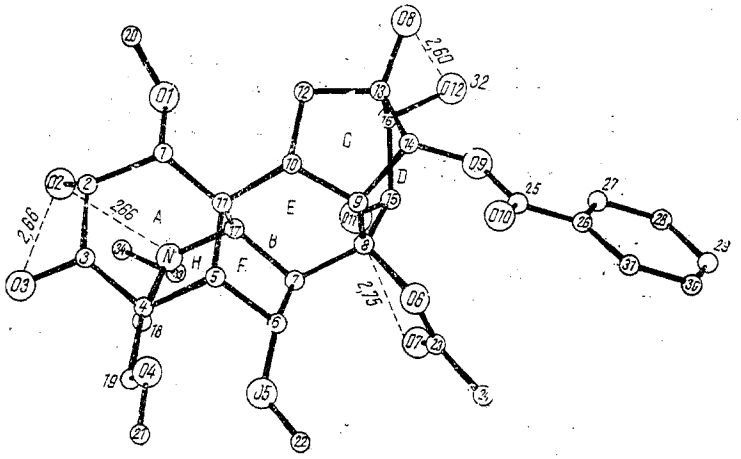


Fig. 1. Spatial structure of altaconitine.

vibrations of the C34 atom. The considerable variation of the valence angels at the tetrahedral carbons is caused by strain in the bridge fragments of the molecule (Table 2).

EXPERIMENTAL

For chromatography we used type KSK silica gel and alumina (activity grade I).

Mass spectra were taken on a MKh-1310 with a system for direct introduction into the ion source, IR spectra on a UR-20 spectrometer (KBr), PMR spectra on Bruker AM-300 Hz spectrometer ($CDCl_3$; standard – TMS); and ^{13}C NMR spectra on the same instrument at a frequency of 75 MHz using the INEPT technique.

Isolation of the Total Alkaloids. The air-dry epigeal part of Aconitum altaicum gathered in the vegetation period in the Kobdo aimak, Mongolia, (17 kg) was moistened with a 5% solution of sodium carbonate and extracted with chloroform (50 liters). A total of five extractions was made. The combined chloroform extracts were evaporated to a volume of 40 liters, and the alkaloids were exhaustively extracted with 5% sulfuric acid. With cooling, the acid solution was made alkaline with sodium carbonate and was then extracted with chloroform. After distillation and the elimination of the chloroform, a total of 30 mg of alkaloids (0.17% of the weight of the dry plant) was obtained.

Separation of the Total Alkaloids. The total alkaloids (10 g) were chromatographed on a column of alumina (ratio of sorbent to substance 100:1) with gradient elution (hexane, chloroform, methanol). On elution with hexane–chloroform (8:2), with the aid of acetone 0.2 g of aconitine was isolated, while from the chloroform–methanol (40:1) eluates 0.1 g of altaconitine was obtained (acetone). The fractions obtained on elution with hexane–chloroform (1:1) were rechromatographed on a column of silica gel. The benzene–methanol (50:1) eluates yielded 0.2 g of mesaconitine, and the benzene–methanol (10:1) eluates 0.3 g of napelline.

Altaconitine (I). mp 235-247°C (decomp.). IR spectrum (ν_{max}^{KBr}, cm^{-1}): 3500, 3520, 1710, 1730, 1120. PMR spectrum ($CDCl_3$, δ, ppm): 1.34 (3H, t, J = 7 Hz, $N-CH_2-CH_3$), 1.41 (3H, s, 8-$OCOCH_3$), 3.24; 3.31; 3.33; 3.72 (each 3H, s, 4 × OCH_3), 4.11 (1H, d, J = 5 Hz, C6β–H), 4.35 (1H, d, J = 3 Hz, C15β–H), 4.47 (1 H, dd, J_1 = 6 Hz, J_2 = 3 Hz), 4.88 (1H, d, J = 5 Hz, C14β–H), 7.47-8.06 (5H, m, Ar–H). Mass spectrum, m/z (%): M 661(33), 602(100), 646(44), 630(55), 616(22), 614(24), 586(66), 570(33), 554(77), 555(33), 556(22).

X-Ray Structural Investigation of Altaconitine. The cell parameters and the intensities of 1809 reflections ($I > 2\sigma$) were measured on a Syntex $P2_1$ diffractometer (CuK_α radiation, $\theta/2\theta$ scanning): a = 12.148(3), b = 15.718(5), c = 17.196(7) Å, V = 3283.4(1.7) $Å^3$, d_{calc} = 1.325 g/cm^3, space group $P2_12_12_1$, Z = 4. The structure was interpreted by the direct method using the SHELXS-86 program [5]. Refinement was carried out by the full-matrix method of least squares in the isotropic-anisotropic approximation by the SHELX-76 programs [6], R = 0.078, R_w = 0.078. The hydrogen atoms were placed in the calculated positions. The coordinates of the nonhydrogen atoms are given in Table 3.

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Berberis ALKALOIDS.

XVII. INVESTIGATION OF THE ALKALOIDS OF Berberis heteropoda

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The alkaloid composition of young shoots and leaves of Berberis heteropoda Schrenk has been studied. In addition to known alkaloids, two new ones have been isolated – N-methyldihydroberberine and 8-oxoberberrubine, the structures of which were established by chemical transformations and a study of spectral properties. Of known alkaloids, berbamunine, aromoline, glaucine, thalicmidine, isocorydine, and reticuline have been found in this plant for the first time. Pseudopalmitine and laudanosine have been found for the first time in plants of the genus Berberis.

Continuing an investigation of the alkaloid composition of plants of the genus Berberis, we have studied young shoots and leaves of B. heteropoda collected in the fruit-bearing phase in the Dzhungarian Ala-Tau, in the environs of the settlement of Sarybel' (Alma-Ata province) [1]. The ethanolic extraction of the young shoots yielded 2.5% of total alkaloids.

The separation of the ether fraction on a column of silica gel led to the isolation of laudanosine [2], oxyacanthine, berbamunine, and aromoline [3], which were identified by their physicochemical properties, spectral characteristics, and comparison with authentic samples. By separation according to solubility and chromatography on a column of alumina, from the total quaternary alkaloids we isolated berberine, magnoflorine, columbamine, and jatrorrhizine in the form of their chlorides [4]. In addition to those mentioned above, we isolated another two alkaloids: base (I) with mp 212-213°C (chloroform) and base (II) with mp 210-212°C. The UV spectrum of base (I) had absorption bands at $\lambda_{max}^{C_2H_5OH}$ 263, 288, 307 (shoulder), 330, 379 nm ($\log \varepsilon$ 4.14; 4.45; 4.32; 4.10; 3.66), which are characteristic for protoberberine salts [5]. The PMR spectrum of (I), taken in $CDCl_3$, showed signals at (δ scale, ppm) 3.97 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 4.14 (3H, s, OCH_3), 3.25 (2H, t, CH_2), 4.97 (2H, t, CH_2), 6.85 (1H, s), 7.48 (1H, s), 7.90 (2H, s), 8.65 (1H, s), 9.75 (1H, s). According to TLC and its IR spectrum, (I) was different from palmatine chloride [4]. The facts enabled (I) to be identified as pseudopalmatine chloride [5].

The UV spectrum of base (II) had absorption bands at $\lambda_{max}^{C_2H_5OH}$ 241, 350 nm ($\log \varepsilon$ 4.37; 3.92), which are characteristic for dihydroprotoberberines [6]. Its mass spectrum showed the peaks of ions with m/z 351, 337, 337, 336, 321, 320, 308, 307, 292, 278. The PMR spectrum, taken in DMSO-d_6 revealed signals at (δ scale, ppm) 6.05 (2H, s, OCH_2O), 4.05 (3H, s, OCH_3), 4.17 (3H, s, OCH_3), 3.45 (3H, br.s, $\overset{+}{N}CH_3$), 3.22-4.98 (6H, m), 6.49 (1H, s), 6.78(1H, s), 7.44 (2H, s), 7.85 (1H, s). The reduction of (II) with $NaBH_4$ gave (±)-N-methyltetrahydroberberine (III), which, on thermal demethylation at 300°C in vacuum, gave (±)-tetrahydroberberine (IV) [7], identical with an authentic sample (see Scheme 1).

Thus, base (II) was N-methyldihydroberberine, which has been synthesized previously [8].

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