Berberis ALKALOIDS.

XV. STRUCTURE OF BARGUSTANINE

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Bargustanine (I), belonging to a new type of isoquinoline alkaloids, has been isolated from the phenolic fraction of the total alkaloids from the roots of Berberis vulgaris L. Its structure has been established by chemical and spectral methods.

Continuing investigations of the alkaloid composition of the roots of B. vulgaris L. [1] gathered in the Bargustan range (Stavropol' krai, Predgornyi region), from the phenolic part of the ether fraction we have isolated a new crystalline base with mp 193-194°C, which has been called bargustanine.

Bargustanine (I) – an optically active base with the composition $C_{29}H_{24}N_2O_7$ – possesses phenolic properties. Its IR spectrum showed absorption bands in the region of (cm^{-1}) 3540 (OH), 1273 (asymmetric stretching vibrations of a C–O–C bond), and 840, 810, 750, and 710 (nonplanar deformation vibrations of aromatic rings). In the mass spectrum we observed the peaks of ions with m/z 522 (0.3%), 381 (100%), 367 (44%), 191 (44%), 191.5 (11%), 192 (16%). The UV spectrum contained absorption maxima at 218 nm (shoulder) and 286 nm ($\log \varepsilon$ 4.85 and 3.98), which are characteristic for benzyltetrahydroisoquinolines [2]. Details of the ^1H and ^{13}C NMR spectra and also of the ^{13}C NMR spectrum obtained in the DEPT regime are given in Tables 1 and 2.

According to its spectral characteristics, (I) is a new type of dimeric isoquinoline alkaloid composed of benzyltetrahydroisoquinoline and simple tetrahydroisoquinoline. The presence of the maximum ion with m/z 381 in the mass spectrum of (I) showed that there were two methoxy groups, two N-methyl groups, and one hydroxy group in rings A, B, A', and B', and an ether bridge [3]. When (I) was methylated with diazomethane, a tri-O-methyl ether (II) was obtained. The mass spectrum of (II) contained the weak peak of the molecular ion with m/z 564 (0.2%) and the maximum peak of an ion with m/z 396. The ^1H NMR spectrum of (II) taken in $CDCl_3$ showed the presence of signals from five methoxy groups at (ppm) 3.81 (6H, s), 3.77 (6H, s), 3.51 (3H, s).

The cleavage with sodium in liquid ammonia of a toluene solution of (II) gave d-laudanosine (III) and corypalline (IV), which were shown to be identical with authentic samples by TLC, melting points, and spectral charactersitics (see Scheme 1). The formation of (IV) on cleavage by sodium in liquid ammonia showed that the ether bridge was present in position 7' of one half, and that one of the methoxy groups occupied position 6'. The formation of (III) showed that, on cleavage, hydrogenolysis of the benzyl hydroxyl had taken place [9, 12], and the substituents in ring B occupied the 6,7 positions and in ring C the 11,12 positions.

TABLE 1. Details of the ^1H NMR Spectrum of Bargustanine (δ scale, Py-d_5, 0 – TMS)

Position of the protons	ppm	Position of the protons	ppm. (J, Hz)
2-N–CH_3	2,51 s	C_{15}–H	4,51 d (5 Hz)
2'-N–CH_3	2,46 s	C_{15}–OH	6,39 d (5 Hz)
6-OCH_3	3,79 s	13-H	7,65 d (8,5 Hz)
6'-OCH_3	3,79 s	14-H	6,85 dd (3,5; 1,5 Hz)
3-CH_2	3,14–3,42 (m)	10-H	6,74 d (1,5 Hz)
4-CH_2	2,74–2,92 (m)	5'-H	6,45 s
3'-CH_2	3,14–3,42 (m)	8'-H	6,67 s
		5-H	6,46 s
4'-CH_2	2,74–2,92 (m)	1'-CH_2	3,54 s

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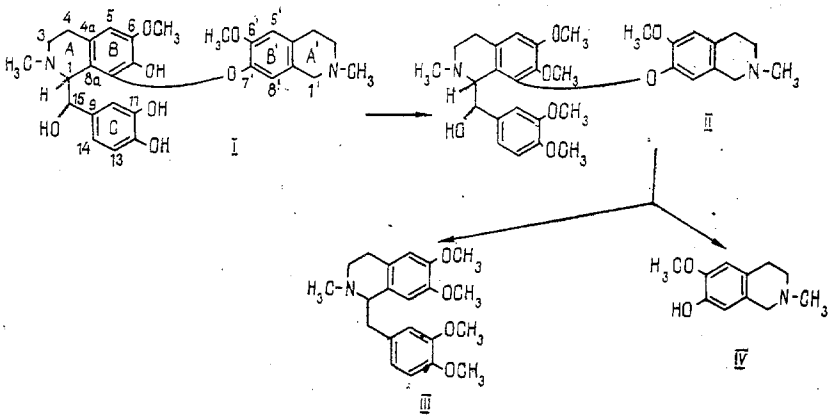
TABLE 2. Chemical Shifts of the ^{13}C Carbon Atoms of Bargustanine in CD_3OD (δ, ppm, 0 – TMS)

CH		CH_2		CH_3		Quaternary carbons	
carbon atom	ppm	carbon atom	ppm	carbon atom	ppm	carbon atom	ppm
C-1	60,51	C-3	45,45	2-N–CH_3	43,53	C-4a	126,17
C-15	67,13	C-3′	40,37	2′-N–CH_3	41,98	C-8a	128,01
C-5	106,30	C-4	28,47	6-OCH_3	56,46	C-6	149,18
C-10	117,89	C-4′	24,56	6′-OCH_3	55,64	C-7	146,94
C-13	124,81	C-1′	51,34			C-8	142,5
C-14	132,03					C-9	136,41
C-5′	112,12					C-11	145,46
C-8′	116,03					C-12	146,6
						C-6′	148,15
						C-7′	147,65
						C-4a′	130,15
						C-8a′	129,10



Scheme 1. Chemical transformations of bargustanine.

The signals of the aromatic protons in the ^1H NMR spectrum of compound (I) at 6.46, 6.45, and 6.67 were assigned to the protons at C-5, C-5', and C-8', respectively. The presence of an aromatic proton at C-5 was also confirmed by the PMR spectrum of (II) in which there was no upfield shift of the signals of the aromatic protons [4-6]. On this basis, in ring B, the ether bridge had to be at C-8.

In the PMR spectrum of bargustanine, none of the signals of methoxy groups in the strong field that are characteristic for the C-7 methoxy group of benzyltetrahydroisoquinolines [4], bisbenzylisoquinolines [5], and secobisbenzylisoquinolines [6] were observed, and, consequently, the OCH_3 group in ring B of compound (I) was at C-6. This was confirmed by the PMR spectrum of compound (II) which showed a signal at 3.51 ppm, which is characteristic for a methoxyl at C-7 [4, 5]. The PMR spectrum of (I) (see Table 1) showed one-proton doublets at 4.50 (J_{gem} = 5 Hz) at 6.53 ppm (J_{gem} = 5 Hz), which showed the presence of a benzyl hydroxyl at C-15. From the nature of the C_{15}–H and C_{15}–OH signals it was possible to judge that the C_1–H and C_{15}–H were present in the trans position and, consequently, C_1–H and C_{15}–OH were in the gauche position.

In the PMR spectrum of (I) there were the signals of another three aromatic protons (see Table 1), which, from their multiplicities, were assigned to protons at C-10, C-13, and C-14. The PMR spectrum of (I) agreed well with the ^{13}C NMR spectrum and also with the spectrum obtained in the DEPT regime (see Table 2): the presence of signals at 60.51, 67.13, and 51.34 ppm, which were assigned to the C-1, C-15, and C-1' atoms, respectively.

The assignments of the signals of the other carbon atoms were made on the basis of a comparison of the spectra of analogous structures and fragments [6-8].

Thus, bargustanine is the first representative of a new type of dimeric isoquinoline alkaloid, and has the structure (I).

EXPERIMENTAL

General Observations. For chromatography we used type KSK silica gel. The individuality of the compounds obtained was checked by TLC in the following solvent systems: 1) chloroform–methanol (9:1, 95:5); and 2) chloroform–methanol–conc. HCl (50:50:0.1).

Temperatures were determined on a Kofler block and a Boëtius stage. IR spectra were recorded on a UR-20 instrument using tablets with KBr. UV spectra were taken on a Hitachi spectrophotometer in ethanol, mass spectra on a MKh 1310 instrument, and ^1H and ^{13}C NMR spectra on Bruker WH-360 MHz and WM-400 and Varian XL-200 instruments.

Isolation of Bargustanine. The phenolic fraction of the ethereal total [1] (2.5 g) was ground with type KSK silica gel (3 g), and the mixture was placed on a column of silica gel at a ratio of material to sorbent of 1:40. On elution by chloroform–methanol (96:4), an individual base (60 mg) was isolated, and, after crystallization from methanol, this had mp 193-194°C, optically active, $[\alpha]_D^{20}$ +114.2°C (c 0.3; CH_3OH).

IR spectrum (ν_{max}^{KBr}, cm^{-1}): 3540, 2940, 2850, 1610, 1275, 1210, 1080, 810, 840, 750, 710.

UV spectrum ($\lambda^{C_2H_5OH}$, nm): 218 (shoulder), 286 (log ε 4.85, 3.98).

Mass spectrum, m/z (%): 522 (M^+, 0.3), 381(100), 368(19), 367(44), 191.5(11), 191(44), 192(16).

Methylation of Bargustanine (I). An excess of an ethereal solution of diazomethane was added to a solution of 60 mg of (I) in 10 ml of absolute methanol. The mixture was left for three days and then the solvent was driven off and the residue was chromatographed on a column of silica gel. Elution with chloroform–methanol (98:2) gave 52 mg of (II).

Mass spectrum, m/z (%): 564(0.2 M^+), 396(100), 381(37), 206(41), 198.5(12), 192(18).

PMR (200 MHz, $CDCl_3$): 3.81 (6H, s, $2OCH_3$), 3.77 (6H, s, $2OCH_3$), 3.51 (3H, s, OCH_3), 2.49 (3H, s, $N-CH_3$), 2.54 (3H, s, $N-CH_3$), 3.48 (2H, s, CH_2), 2.79-2.84 (4H, m, $2CH_2$), 3.18-3.45 (4H, m, $2CH_2$), 6.71, 6.48, 6.46 (1H, s, 3H), 6.76 (1H, d, J = 1.5 Hz), 6.85 (1H, d, J = 8.5 Hz), 7.63 (1H, d, J = 8.5 Hz).

Cleavage of (II) with Sodium in Liquid Ammonia. A two-necked flask fitted with a stirrer and dropping funnel was charged with 200 ml of dry liquid ammonia and, with stirring, 0.4 g of metallic sodium was dissolved in it. Then a solution of 50 mg of (II) in 20 ml of absolute toluene was added dropwise through the dropping funnel over 45 min.

The mixture was stirred for another 2 h and was left overnight. After evaporation of the ammonia, the residue was diluted with 10 ml of water, and the nonphenolic products of cleavage were extracted with ether; then the alkaline solution was saturated with NH_4Cl, and the phenolic products were extracted with ether.

Isolation of d-Laudanosine (III). The nonphenolic cleavage products (23 mg) were chromatographed on a column of silica gel (5 g), and elution with chloroform yielded a base in the form of an oil which crystallized on standing (10 mg), mp 88-89°C, giving a methiodide with mp 218-219°C; mass spectrum, $[\alpha]_D^{20}$ +49.3°C (c 0.1; $CHCl_3$). The base obtained proved to be identical with an authentic sample of d-laudanosine [10] according to TLC and spectral characteristic and the absence of a depression of the melting point of a mixed sample.

Isolation of Corypalline (IV). The phenolic cleavage products (14 mg) were chromatographed on a column of silica gel (3 g) with elution by chloroform–methanol (96:4); this yielded 8 mg of (IV), mp 167-168°C, which proved to be identical with an authentic sample of corypalline according to TLC, melting point, and spectral characteristics [11]. Mass spectrum, m/z (%): 193 (M^+), 192, 178, 150(100). PMR (CD_3OD): 2.36 (3H, s, $N-CH_3$), 3.49 (2H, s, CH_2), 3.75 (3H, s, OCH_3), 6.59 (1H, s, 5-H), 6.40 (1H, s, 8-H).

LITERATURE CITED

1. M. M. Yusunov, A. Karimov, and K. L. Lutfullin, Khim. Prir. Soedin., 128 (1990).
2. M. Shamma, The Isoquinoline Alkaloids, Academic Press, New York (1972), p. 83.
3. J. Baldas, I. R. C. Bick, T. Ibuka, R. S. Kapil, and Q. N. Porter, J. Chem. Soc. Perkin Trans I., 592 (1972).
4. M. Tomita, T. Shingu, K. Fujitani, and H. Furakawa, Chem. Pharm. Bull., 13, 921 (1965).
5. H. Guinaudeau, A. Freyer, and M. Shamma, Nat. Prod. Reports, 477 (1986); J. E. Leet, A. J. Freyer, R. D. Minard, and M. Shamma, J. Chem. Soc., Perkin I, 1565 (1985).
6. T. A. Broadbent and E. G. Pail, Heterocycles, 20, 863 (1983).

7. M. Shamma and J. L. Moniot, Isoquinoline Alkaloids. Plenum Press, New York (1972), p. 51.
8. M. Shamma and D. M. Hindenlang, Carbon-13 NMR Shift Assignments of Amines and Alkaloids, New York, Plenum Press (1979), p. 117.
9. R. Bartozewicz, W. Mecznikowska-Toljarczik, and B. Opszondek, Methods of Reducing Organic Compounds [Russian translation from Polish], Moscow (1960), p. 93.
10. G. Boit, Ergebnisse der Alkaloid Chemie bis 1960. Academic Verlag, Berlin (1961), p. 219.
11. T. Kametani, The Chemistry of the Isoquinoline Alkaloids, Hirokawa Publishing Company Inc., Tokyo (1969), p. 25.
12. K. W. Bentley and A. W. Murray, J. Chem. Soc., 2501 (1963).

ALKALOIDS OF THE MONGOLIAN FLORA.

III. ALTACONITINE – A NEW ALKALOID FROM Aconitum altaicum

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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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