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Berberis ALKALOIDS.
XXXVII. INVESTIGATION OF THE ALKALOIDS OF *B. oblongata* AND *B. integerrima*. CRYSTAL STRUCTURE OF 8-TRICHLOROMETHYLDIHYDROBERBERINE

I. I. Khamidov,[a] B. Tashkhodzhaev,[a] S. F. Aripova,[a] M. V. Telezhenetskaya,[a] and A. K. Karimov[b]

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Two species of Berberis *have yielded 10 isoquinoline alkaloids. In addition to known bases, two artifacts have been isolated — 8-trichloromethyldihydroberberine (1) and 8-trichloromethyldihydropalmatine. An x-ray structural analysis has been made of (1).*

The alkaloid composition of *Berberis oblongata* growing under natural conditions in Uzbekistan has been investigated previously [1, 2]. In the present paper we give the results of a study of the alkaloid composition of the stems of this plant cultivated in the Karaganda Botanical Garden of the Academy of Sciences, Republic of Kazakhstan.

By the methanol extraction of the stems of *B. oblongata* gathered in the incipient fruit-bearing phase, we isolated 0.40% of total bases, of which 0.11% consisted of berberine. Separation of the mixture on a column of silica gel gave oxyacanthine, berbamine, isocorydine, thalicmidine, and the quaternary bases palmatine, jatrorrhizine, and columbamine in the form of the iodides. All these alkaloids have been isolated previously from *B. oblongata* growing in Uzbekistan. Thus, the qualitative compositions of the wild and the cultivated plants are identical.

A series of isoquinoline alkaloids has been isolated previously from various organs of *B. integerrima* [3]. We have now studied the stems of this plant for the first time.

The stems were extracted successively with chloroform and methanol. The total amount of alkaloids was 0.59%. Separation on a column of silica gel gave glaucine, isocorydine, thalicmidine, oxyacanthine, armepavine, berberine, palmatine, columbamine, jatrorrhizine, and berbamine. This is the first time that the last three bases have been isolated from this species.

In addition to the alkaloids mentioned above, from both *Berberis* species we isolated bases (1), with mp 183-184°C, and (2), with mp 195-197°C. The mass spectrum of (1) contained the peaks of ions with *m/z* 337, 336 (100%, $C_{20}H_{18}NO_4$), 321, 320, 306, 292, and 178; and that of (2) those of ions with *m/z* 353, 352 (30%, $C_{21}H_{22}NO_4$), 336, 323, and 311. UV spectra (ν_{max} 280, 360 nm) and mass-spectrometric fragmentation permitted these bases to be assigned to the dihydroprotoberberine alkaloids [4, 5]; however, their PMR spectra lacked signals characteristic for a C-8 methylene group. The remaining signals corresponded to dihydroberberine and dihydropalmatine. In order to establish the structures of (1) and (2) reliably and to reveal some stereochemical features of alkaloids of the dihydroberberine type, we carried out an x-ray structural analysis (XSA) of a single crystal of compound (1).

The results of the analysis showed that base (1) was 8-trichloromethyldihydroberberine. The spatial structure of the (1) molecule is shown in Fig. 1. Ring *A* has the conformation of a strongly flattened 15β-envelope, while benzene rings *B* and *E* are planar. The six-membered heterocycles *C* and *D* assume unusual forms: ring *D* has the conformation of a C8β-sofa, while ring *C* is present in an intermediate state between a distorted boat (*twist*-boat) and a sofa flattened at C6. To all appearance, these distortions are connected with the presence of the voluminous CCl_3 substituent.

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a) Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan, Tashkent, fax (3712) 40 64 75. *b*) Andizhan State Medical Institute. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 889-893, November-December, 1996. Original article submitted April 15, 1996.

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TABLE 1. Bond Lengths r (Å) and Valence Angles ω (degrees) in the (1) Molecule

Bond	r	Angle	ω	Angle	ω
C1–C2	1.363(6)	C2–C1–C14a	117.8(4)	C9–C10–O3	115.2(3)
C1–C14a	1.408(5)	C1–C2–C3	121.4(3)	C11–C10–O3	125.7(4)
C2–C3	1.389(7)	C1–C2–O1	128.9(4)	C10–C11–C12	120.4(4)
C2–O1	1.371(5)	C3–C2–O1	109.6(4)	C11–C12–C12a	121.6(4)
C3–C4	1.363(5)	C2–C3–C4	122.2(4)	C8a–C12a–C12	118.2(3)
C3–O2	1.373(5)	C2–C3–O2	109.9(3)	C8a–C12a–C13	118.9(4)
C4–C4a	1.404(6)	C4–C3–O2	127.9(4)	C12–C12a–C13	122.6(3)
C4a–C5	1.495(5)	C3–C4–C4a	117.4(4)	C12a–C13–C14	119.5(3)
C4a–C14a	1.395(6)	C4–C4a–C5	122.4(4)	N7–C14–C13	120.1(3)
C5–C6	1.504(6)	C4–C4a–C14a	120.8(3)	N7–C14–C14a	116.8(4)
C6–N7	1.467(6)	C5–C4a–C14a	116.8(4)	C13–C14–C14a	122.9(3)
N7–C8	1.441(5)	C4a–C5–C6	109.3(3)	C1–C14a–C4a	120.4(4)
N7–C14	1.388(5)	C5–C6–N7	110.6(4)	C1–C14a–C14	120.8(4)
C8–C8a	1.510(6)	C6–N7–C8	119.4(3)	C4a–C14a–C14	118.8(3)
C8–C16	1.589(5)	C6–N7–C14	119.5(3)	O1–C15–O2	109.2(4)
C8a–C9	1.396(5)	C8–N7–C14	120.6(3)	C8–C16–C11	111.8(3)
C8a–C12a	1.413(5)	N7–C8–C8a	110.0(3)	C8–C16–C12	109.9(3)
C9–C10	1.412(6)	N7–C8–C16	112.0(3)	C11–C16–C12	107.0(2)
C9–O4	1.372(5)	C8a–C8–C16	112.4(3)	C8–C16–C13	112.3(3)
C10–C11	1.392(6)	C8–C8a–C9	120.2(3)	C11–C16–C13	108.4(2)
C10–O3	1.364(5)	C8–C8a–C12a	119.4(3)	C12–C16–C13	107.3(2)
C11–C12	1.382(6)	C9–C8a–C12a	120.2(4)	C2–O1–C15	105.5(3)
C12–C12a	1.399(6)	C8a–C9–C10	120.1(3)	C3–O2–C15	105.2(4)
C12a–C13	1.438(5)	C8a–C9–O4	119.9(4)	C10–O3–C18	117.6(4)
C13–C14	1.375(6)	C10–C9–O4	120.0(3)	C9–O4–C17	112.8(3)
C14–C14a	1.474(5)	C9–C10–C11	119.2(4)		
C15–O1	1.419(7)				
C15–O2	1.424(6)				
C16–C11	1.769(4)				
C16–C12	1.785(5)				
C16–C13	1.761(4)				
C17–O4	1.434(4)				
C18–O3	1.429(7)				

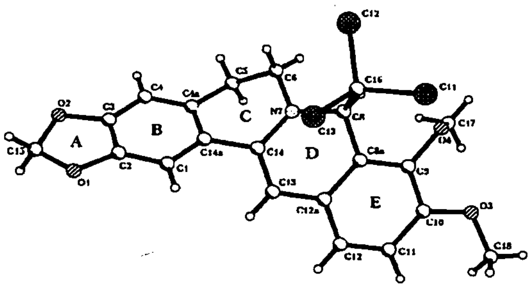

Fig. 1

Bond lengths and valence angles are given in Table 1, the errors in their determination averaging 0.006 Å and 0.3°, respectively. The anomalous lengthening of the ordinary $C_{sp}{}^{3}-C_{sp}{}^{3}$ bond C8-C16 to 1.589 Å can be explained by steric repulsion of the CCl_3 grouping from its closest environment. The lengthening of the C13=C14 double bond in comparison with the standard value [6] shows conjugation of its π-electron system with the unshared electron pair of the N7 atom and the π-electron system of the aromatic ring. In the other sections of the (1) molecule the bond lengths are close to the standard values [6] and to those observed in the related alkaloid intebrine [7].

The absence of the molecular ions from the mass spectra of bases (1) and (2), which complicated the identification of these compounds, can be explained by the existence of steric stress in the section of attachment of the chloroform grouping (see Table 1). As a consequence, the CCl_3 group is readily split out from the molecule, and intense peaks of the $(M - CCl_3)^+$ ions with m/z 336 in (1) and 352 in (2) are formed.

Thus, bases (1) and (2) are 8-trichloromethyldihydroberberine and 8-trichloromethyldihydropalmatine, respectively. They could be formed either during the separation of the mixtures of alkaloids on columns [8] or during the extraction of the raw material and are, therefore, artifacts.

TABLE 2. Coordinates ($\times 10^4$) and Temperature Parameters ($\times 10^3 \cdot \text{Å}^2$) of the Nonhydrogen Atoms of the (1) Molecule

Atom	x	y	z	U_{eq}
C1	-5381(4)	1919(4)	3405(4)	36(2)
C2	-6122(5)	2186(4)	4408(4)	37(2)
C3	-6140(4)	3412(4)	4541(4)	37(2)
C4	-5419(5)	4409(4)	3686(4)	38(2)
C4a	-4655(5)	4158(4)	2641(4)	35(1)
C5	-3782(5)	5158(4)	1662(4)	46(2)
C6	-2279(5)	4500(4)	1375(4)	45(2)
N7	-2538(3)	3412(3)	935(3)	31(1)
C8	-1382(4)	2983(3)	159(3)	30(1)
C8a	-2130(4)	2477(3)	-756(3)	29(1)
C9	-1507(4)	2666(4)	-1981(3)	32(1)
C10	-2161(5)	2131(4)	-2809(4)	37(2)
C11	-3505(4)	1517(4)	-2431(4)	37(2)
C12	-4178(4)	1416(3)	-1253(4)	34(1)
C12a	-3519(4)	1889(3)	-393(3)	30(1)
C13	-4271(4)	1913(3)	781(3)	30(1)
C14	-3801(4)	2710(3)	1394(3)	29(1)
C14a	-4638(4)	2932(3)	2497(3)	29(1)
C15	-7496(5)	2156(5)	6151(5)	57(2)
C16	-101(4)	1939(4)	1012(4)	35(1)
C17	-480(5)	4573(4)	-3317(4)	52(2)
C18	-1877(6)	1610(6)	-4737(5)	64(2)
O1	-6869(4)	1361(3)	5433(3)	61(1)
O2	-6925(4)	3413(3)	5641(3)	56(1)
O3	-1389(3)	2281(3)	-3939(3)	48(1)
O4	-201(3)	3299(3)	-2349(2)	40(1)
Cl1	1205(1)	1292(1)	65(1)	61(1)
Cl2	992(1)	2706(1)	1823(1)	62(1)
Cl3	-895(1)	617(1)	2194(1)	59(1)

It must be mentioned that differences of opinion exist on the naming of these artifacts. Some authors call them berberine–chloroform, and palmatine–chloroform [8]. Since the chloroform residues are attached to dihydroberberine and dihydropalmatine skeletons, we consider names reflecting the chemical nature of these compounds to be more correct; such names have been used by other authors previously [9] and by ourselves in the present paper.

EXPERIMENTAL

For general observations, see [10].

Isolation and Separation of the Alkaloids. A. The extraction of 0.8 kg of *B. oblongata* stems and the isolation of the alkaloids were carried out as in [11]. This led to 1.22 g of ether fraction, 1.10 of chloroform fraction, and 0.88 g of berberine in the form of the chloride.

B. Comminuted stems of *B. integerrima* (3 kg) were extracted by the procedure of [12].

In each case, the artifacts (1) and (2), respectively, were isolated from the chloroform fraction by column chromatography with elution by benzene or chloroform.

X-Ray Structural Analysis. Crystals grown from aqueous alcoholic solution were first selected by the photo method. Unit cell parameters and the space group were determined and refined on a Syntex-$P2_1$ diffractometer: $a = 8.757(3)$, $b = 10.873(3)$, $c = 11.083(5)$ Å, $\alpha = 69.87°$, $\beta = 87.40°$, $\gamma = 83.85°$, $d_{calc} = 1.352$ g/cm^3, space group P1, $Z = 2$.

A three-dimensional set of intensities was obtained on the same diffractometer; $\theta/2\theta$ method of scanning, using CuK_α radiation (graphite monochromator), $\sin\theta/\lambda < 0.29$, number of independent and nonzero reflections with $I > 2\sigma$ (1) 2356.

The structure was determined by the direct method using the SHELX-86 program [13] (PC DOS version), where it was possible to find a model of the molecule in the automatic regime, and was refined by the method of least squares (MLS) successively in the isotropic–anisotropic approximation by the SHELX-76 program [14]. The coordinates of the H atoms attached to carbon atoms were calculated geometrically and those in OH groups [sic] from a difference electron density synthesis and were refined isotropically. The final value of the discrepancy factor was R = 0.066 (R_w = 0.071). The coordinates of the nonhydrogen atoms from the last stage of MLS are given in Table 2.

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