

LABDANOIDS OF *Marrubium anisodon*

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The first chemical investigation has been made of Marrubium anisodon (fam. Lamiaceae). Two diterpenoids of the labdane type — vulgarol and marrubiin — have been isolated. An x-ray analysis has been performed for the latter and its crystal and molecular structures have been determined.

Two species of hoarhound, *Marrubium* (fam. Lamiaceae Linde), grow in the territory of Central Asia [1]. We have investigated the epigeal part of *Marrubium anisodon* C. Koch (*M. alternides* Rech. fil) [2], which has not been studied previously for its terpenoid content, there being only general information on the presence of individual classes of substances in this plant [1]. In the systematic respect, the plant is close to *M. vulgare* L., grown widely in Uzbekistan; it grows in pastures and in the foothills and low mountain regions rising to a height of 1800-2000 m above sea-level. It is used together with *M. vulgare* in folk medicine [3, 4].

We investigated raw material collected on the south-eastern slopes of the Kurama range (Western Tien-Shan) at a height of 1640 m above sea-level. By column chromatography of an alcoholic extract, two crystalline substances were isolated: (1), C₂₀H₃₆O₂, mp 150-152°C, and (2), C₂₀H₂₈O₄, mp 156-158°C.

The PMR spectrum of substance (1) showed the signals of five methyl groups: three singlets of tertiary methyls at 0.79, 0.82, and 0.89 ppm, the singlet of a methyl at a carbon atom linked to an oxygen function at 1.42 ppm, and that of a vinyl methyl at 1.63 ppm. A doublet (2H) at 4.1 ppm (*J* = 6.0 Hz) and a triplet (1H) at 5.39 ppm (*J* = 6.0, 6.0 Hz) could be assigned to the protons of a >C=CH—CH₂—O— grouping.

The mass spectrum of substance (1) contained as the 100% peak that of an ion with a mass of 151, which is highly characteristic for labdane derivatives [5], while the molecular ion with a mass of 308 had a very low intensity since the ionized molecule readily loses a molecule of water and forms the ion [M—H₂O] = 290 m.u. The mass spectrum of (1) was very close to that of peregrinol [5], but its PMR and physical constants were evidence in favor of vulgarol — a labdane alcohol isolated previously in trace amounts from *M. vulgare* [6].

From its IR spectrum it was possible to assign substance (2) to the furo lactones with a hydroxy group: 740, 790, 875, 1585, 1760, 3135, 3150, 3550 cm⁻¹. The mass spectrum contained the peak of the molecular ion, 332 (35%), the peak of an ion formed by the loss of a molecule of water [M—H₂O] = 314, of low intensity, and other peaks — 67, 81 (100%), 95, 109, 123, 135, 152, 165 — characteristic of fragments of labdane derivatives with a furan ring and a tertiary hydroxy group [7].

The PMR spectrum of (2) (CDCl₃, 100 MHz) contained the following signals: those of three methyl groups at (ppm) 0.80 (s, 3H), 0.91 (d, *J* = 7.5 Hz, 3H), and 1.25 ppm (s, 3H), of a lactone proton at 4.63 ppm (t, *J* = 5.5, 5.5 Hz, 1H), and of the protons of a furan ring at 6.2 (d, *J* = 2.0 Hz, 1H), 7.15 (br.s, H), and 7.31 (t, *J* = 2.5, 2.5 Hz, 1H).

The number and nature of the signals of the protons in the PMR spectrum also formed evidence in favor of the labdane furo lactone marrubiin, which has been isolated previously from *M. vulgare* [6], *M. supinum* [7], and *M. incanum* [8].

Thus, from its physicochemical and spectral parameters, substance (2) must have the structure of marrubiin. The limited amount of the substance did not allow us to perform additional experiments to establish the identity of the stereochemistry of

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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	1.540(8)	C2-C1-C10	114.3(4)	C1-C2-C3	113.1(4)
C1-C10	1.540(7)	C2-C3-C4	110.0(4)	C3-C4-C5	112.5(4)
C2-C3	1.528(7)	C3-C4-C11	115.4(4)	C5-C4-C11	99.7(4)
C3-C4	1.522(7)	C3-C4-C15	110.1(4)	C5-C4-C15	110.9(4)
C4-C5	1.537(7)	C11-C4-C15	107.8(4)	C4-C5-C6	102.1(4)
C4-C11	1.516(7)	C4-C5-C10	112.7(4)	C6-C5-C10	113.9(4)
C4-C15	1.522(7)	C5-C6-C7	116.3(4)	C5-C6-O1	102.9(4)
C5-C6	1.513(6)	C7-C6-O1	113.3(4)	C6-C7-C8	117.4(4)
C5-C10	1.545(6)	C7-C8-C9	111.6(4)	C7-C8-C13	107.2(4)
C6-C7	1.510(7)	C9-C8-C13	115.1(4)	C8-C9-C10	108.8(4)
C6-O1	1.479(6)	C8-C9-C12	110.8(4)	C10-C9-C12	110.5(4)
C7-C8	1.552(7)	C8-C9-O3	112.1(4)	C10-C9-O3	106.7(4)
C8-C9	1.543(7)	C12-C9-O3	107.9(4)	C1-C10-C5	105.6(4)
C8-C13	1.515(8)	C1-C10-C9	112.6(4)	C5-C10-C9	107.4(4)
C9-C10	1.575(7)	C1-C10-C14	107.4(4)	C5-C10-C14	114.7(4)
C9-C12	1.548(7)	C9-C10-C14	109.2(4)	C4-C11-O1	110.6(4)
C9-O3	1.442(6)	C4-C11-O2	129.5(5)	O1-C11-O2	119.8(4)
C10-C14	1.548(7)	C9-C12-C16	116.6(4)	C12-C16-C17	110.9(5)
C11-O1	1.363(6)	C16-C17-C18	127.5(5)	C16-C17-C19	127.1(6)
C11-O2	1.208(6)	C18-C17-C19	105.4(5)	C17-C18-O4	100.7(6)
C12-C16	1.513(8)	C17-C19-C20	115.1(6)	C19-C20-O4	105.1(6)
C16-C17	1.508(8)	C6-O1-C11	108.7(3)	C18-O4-C20	113.6(6)
C17-C18	1.402(8)				
C17-C19	1.330(9)				
C18-O4	1.44(1)				
C19-C20	1.30(1)				
C20-O4	1.25(1)				

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

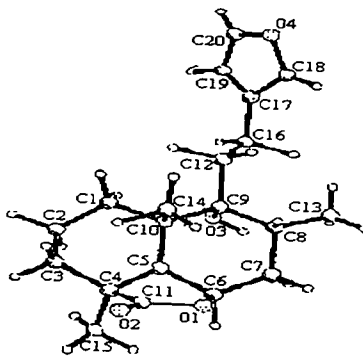
Atom	x	y	z	U
C1	-644(7)	4721(5)	7021(2)	50(2)
C2	388(8)	5839(6)	7309(2)	59(2)
C3	1816(7)	6385(5)	6900(2)	52(2)
C4	999(7)	6898(5)	6325(2)	45(2)
C5	-754(6)	6237(4)	6176(2)	40(1)
C6	-938(7)	6511(5)	5513(2)	47(2)
C7	-2230(7)	5683(5)	5174(2)	51(2)
C8	-2495(7)	4276(5)	5394(2)	51(2)
C9	-2520(6)	4197(5)	6084(2)	44(2)
C10	-758(6)	4785(5)	6333(2)	42(1)
C11	2009(7)	6601(5)	5756(2)	48(2)
C12	-2739(7)	2784(5)	6295(2)	55(2)
C13	-4122(9)	3757(6)	5086(3)	70(2)
C14	814(7)	4012(5)	6079(2)	50(2)
C15	773(7)	8355(5)	6364(2)	56(2)
C16	-4589(8)	2345(5)	6435(3)	64(2)
C17	-4626(7)	925(5)	6583(3)	53(2)
C18	-4211(8)	-108(7)	6204(3)	73(2)
C19	-5080(9)	390(7)	7102(3)	79(3)
C20	-5009(9)	-864(7)	7114(3)	60(2)
O1	885(4)	6389(3)	5291(1)	50(1)
O2	3576(5)	6535(4)	5675(2)	57(1)
O3	-3932(5)	4944(3)	6339(2)	55(1)
O4	-4474(9)	-1187(6)	6605(5)	172(5)

the molecule with greater certainty, and we therefore carried out an x-ray structural investigation, which showed that (2) was identical with marrubiin. Its stereochemistry had been established previously by chemical transformations [9, 10].

The spatial structure of the diterpene lactone marrubiin is shown in Fig. 1. The (2) molecule is a tricyclic system with an ethylfuran moiety in which the six-membered rings *A* and *B* are linked in the $14\alpha,5H\beta$ -*trans* manner. The lactone ring is attached axially in the C4,C6 positions. The other substituents are present in the ethylfuran moiety α -equatorially, and the methyl groups at C4 and C8 β -equatorially.

An analysis of the intracyclic torsional angles showed that ring *A* is present in the *twist*-boat conformation with C_2 symmetry passing through the centers of the C2-C3 and C5-C10 bonds (the asymmetry parameter $\Delta C_2 = 5.1^\circ$). The other six-membered ring, *B*, has a *twist*-chair form, also with C_2 symmetry, passing through the centers of the C6-C7 and C9-C10 bonds ($\Delta C_2 = 0.7^\circ$). These states of rings *A* and *B* are connected with the attachment of the lactone ring at the C4 and C6 positions.

The lactone ring adopts the conformation of an ideal (0.001 Å) 5 α -envelope. The other five-membered ring — the furan ring — has a planar (0.01 Å) structure.



An analysis of the geometry of the (2) molecule showed that, on the whole, the bond lengths agreed with the standard values [11]. An anomaly observed in the bond lengths of the furan ring can be ascribed to thermal vibrations (see Table 2) of a fragment remote from the "center" of the molecule, because of which the errors of determination in this section are increased (see Table 1). The valence angles indicate substantial steric stresses in the molecule. They are shown in an increase in the angles at the C8 and C12 atoms (to 116.6°), which is due to the repulsion of the ethylfuran fragment from rings *A* and *B*, on the one hand, and to the mutual repulsion of the *syn*-equatorial substituents at C8 and C9, on the other. An increase in the C5C10C14 angle (114.7°) is connected with the *syn*-axial position of the lactone and methyl (C14H₃) groups.

Packing of the (2) Molecules. An analysis of intermolecular contacts revealed the presence of an H-bond of the O—H...O type. The O2 carbonyl oxygen of the lactone ring of the initial molecule approaches the hydroxy group O3H (2.92 Å) transformed by a 2₁ screw axis. Thanks to these H-bonds, infinite chains are formed along the crystallographic *a* axis.

EXPERIMENTAL

The conditions for recording the spectra and the instruments have been described in [12].

The epigeal part of hoarhound (1 kg) gathered in the flowering period in the basin of the R. Chadaksai, Namangan province, Republic of Uzbekistan, was comminuted, dried, and extracted with ethanol. The concentrated ethanolic extract was treated successively with hexane, benzene, and ethyl acetate.

The benzene extract was concentrated and was chromatographed twice on columns of silica gel (Chemapol) and alumina (neutral), using chloroform as eluent. In this way we isolated vulgarol (15 mg), C₂₀H₃₆O₂ — colorless crystals with mp 150–152°C, optically inactive — and marrubiin (20 mg), C₂₀H₂₈O₄ — colorless crystals with mp 156–158°C, [α]_D +30° (*c* 1, chloroform).

X-Ray Structural Analysis. Crystals grown from aqueous alcohol were first treated by the photo method. The parameters of the unit cell and the space group were determined and refined on a Syntex-P2₁ diffractometer: *a* = 7.615(2); *b* = 10.363(2); *c* = 22.325(4) Å, *d*_{calc} = 1.253 g/cm³; space group P2₁2₁2₁; *Z* = 4.

A three-dimensional set of intensities was obtained on the same diffractometer: $\theta/2\theta$ method of scanning, using CuK α radiation (graphite monochromator), $\sin \theta/\lambda < 0.29$, rate of scanning 10 deg/min, number of independent and nonzero reflections with *I* > 2 σ (*I*) 1258.

The structure was determined by the direct method using the SHELXS-86 program [13] (PS DOS version), where it was possible to find a model of the molecule in the automatic regime. The structure 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 bound to carbon atoms were calculated geometrically, and those in OH groups were found from a difference electron density synthesis and were refined isotropically. The final value of the divergence factor was: *R* = 0.051 (*R*_w = 0.060). The coordinates of the nonhydrogen atoms from the last stage of the MLS are given in Table 2.

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