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1β,10α-DIHYDROXYARGLABIN — A NEW SESQUITERPENE LACTONE FROM *Artemisia glabella*

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The new sesquiterpene lactone 1β,10α-dihydroxydihydroxyarglabin has been isolated from the epigeal part of Artemisia glabella *Kar. et Kir., and its structure has been established on the basis of spectral characteristics, independent synthesis, arglabin, and an x-ray structural investigation.*

Sesquiterpene lactones — arglabin (I), glabellin, argolide, matricarin, and ketopelenolide b have been isolated previously from the flower heads and leaves of *Artemisia glabella* Kar. et Kir.. Continuing an investigation of the lactone from a chloroform extract of the epigeal part of this plant, we isolated from the polar fractions a crystalline substance (II), composition $C_{15}H_{20}O_4$, mp 155-156°C (from diethyl ether–ethanol), M^+ 264.

Acording to its spectral characteristics (IR, PMR, and mass spectrum), substance (II) was a guanolide. The IR and mass spectra permitted us to assume the presence in the molecule (II) of a hydroxy group, and the close values of the chemical shifts and the identical multiplicities of the signals of the protons in the PMR spectra of substances (I) and (II) (Table 1) showed a structure close to that of the arglabin molecule.

To refine the structure of the compound isolated (II) we carried out a reaction opening the epoxide ring in the molecule of (I). The interaction of (I) with HBF_4 was accompanied by the formation of a reaction mixture consisting of three products, the main one of which proved on chromatographic purification to be a colorless crystalline substance (III) with the composition $C_{15}H_{20}O_4$, mp 184-185°C (from ether), $[\alpha]_D^{20}$ + 72.3° (c 0.3; chloroform), yield 42%. The presence in the IR spectrum of (III) of an absorption band characteristic for a hydroxy group (3440 cm^{-1}) and also the mass spectrum with peaks having m/z 246 ($M^+ - H_2O$) and 228 ($M^+ - 2H_2O$) permitted the assumption of the presence of two hydroxy groups in the structure of the derivative (III) that had been obtained. Since, in the PMR spectrum, the signals of the methyl group at C-4 and of the olefinic proton at C-6 had not changed their positions relative to the same signals in the spectrum of (I), the reaction had taken place through the opening of the epoxy group at the C1 and C10 atoms. The downfield shift of the signal of the H6 lactone proton in (III) (4.18 ppm) as compared with

(II) (3.97 ppm) showed the effective descreening action of the OH group at the C10 atom which was apparently present in the β-orientation, just like the lactone proton which correlates with a similar shift of the signal of the H6 atom in compound (I) (see Table 1). Thus, in its physicochemical constants and spectral characteristics, compound (III) was identical with the lactone (II) that had been isolated and was stereoisomeric with respect to it at the C1 and C10 positions.

A minor product of the reaction of arglabin that has been described was a colorless crystalline substance (IV) with the composition ($C_{15}H_{10}O_3$, mp 220-221°C (from ethanol), $[\alpha]_D^{22}$ + 80.6° (c 0.57; chloroform), yield 5%. Its IR spectrum showed the presence of an OH group (3550 cm^{-1}), the carbonyl of a γ-lactone (1770 cm^{-1}), and a conjugated double bond (1680 and 1550 cm^{-1}). The mass spectrum showed an intense peak with m/z 228, corresponding to the loss of water by the molecular ion. The PMR spectrum showed the spectrum of another olefinic proton (br.s, 5.24 ppm). The PMR spectrum of compound (IV), and that of (III) showed a downfield shift of the signal of the lactone proton (tr, 4.32 ppm, with SSCC 10.5 Hz), i.e., it was possible to assume the β-orientation of the OH group at the C10 atom (Table 1). These facts permitted the assumption of the possibility of the splitting out of the hydroxy group at the C1 atom with the formation of a C1=C2 double bond in the five-membered ring.

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TABLE 1. Details of the PMR Spectra of Arglabin and its Hydroxy Derivatives*

Compound	δ, $CDCl_3$, ppm, multiplicity, SSCC, Hz					
	C_{10}-Me	C_4-Me	H-6	H-3	H-13a	H-13b
I	s 1.35 (3H)	br.s 1.92 (3H)	tr 4.39 (1H; 10)	br.s 5.48 (1H)	d 5.44 (1H; 3.5)	d 6.14 (1H; 3.5)
II	s 1.33 (3H)	s 1.92 (3H)	tr 3.97 (1H; 10)	br.s 5.53 (1H)	d 5.42 (1H; 3)	d 6.10 (1H; 3)
III	s 1.30 (3H)	br.s 1.92 (3H)	dd 4.18 (1H; 11; 10)	br.s 5.43 (1H)	d 5.38 (1H; 3.5)	d 6.14 (1H; 3.5)
IV	s 1.47 (3H)	br.s 1.92 (3H)	tr 4.32 (1H; 10.5)	br.s 5.50 (1H)	d 5.41 (1H; 3.5)	d 6.15 (1H; 3.5)

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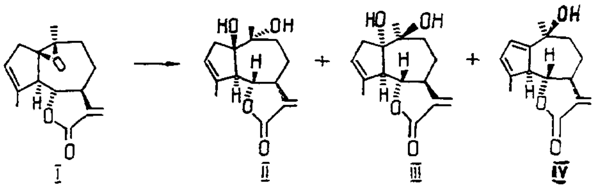
*s) singlet; d) doublet; tr) triplet; br) broadened.

Thus, as a result of the opening of the epoxy group of arglabin three products with the following structures were formed:



In order to refine the orientation of the OH groups at the C1 and C10 atoms in the (II) molecule, and also to establish the conformations of the rings, it was subjected to an x-ray structural investigation.

The structure of the (II) molecule is shown in Fig. 1. The bond lengths (Table 2) and valence angles are the usual ones within the limits of error [3]. We may mention only an appreciable deviation from the ideal tetrahedral value (109.5°) of the valence angles C2C1C5 101.8(4)°, O3C1C10 103.9(4)°, C1C5C4 102.1(4)°, C4C5C6 119.4(4)°, O1C6C7 103.6(4)°, C6C7C11 99.8(4)° and C8C7C11 117.3(5)° as a consequence of the linkage of the rings, and also of the angles C1C2C3 102.1(5)° and C8C9C10 121.0(5)°. A similar increase in the C8C9C10 valence angle to 122.3° has been observed in the seven-membered ring of 3α,10α-dichloro-1β,4β-dihydroxyarglabin (V) [4] and is apparently due to the conformation of this ring.

The conformation of the seven-membered carbocycle (*b*) in (II) — 6,7α,1,5β-twist-chair ($\Delta C_2^9 = 4.4°$) (the torsional angles are given in Table 3) is the same as in the molecule of (V). The hydroxy groups at C1 and C10 have, respectively, the β-equatorial and α-pseudoequatorial orientations relative to ring *B*. The methyl group at the C10 atom is oriented axially in the β-direction. Ring *B* has the trans- type of linkage with the five-membered carbocycle (*A*) and with the γ-lactone ring (*C*); the O3C1C5H5 and H6C6C7H7 torsional angles are, respectively, −161 and 168°. The conformation of ring *A* is that of a 1β-envelope ($\Delta C_S^1 = 2.9°$), and ring *C*, that of a 6β,7α-half- chair ($\Delta C_2^{12} = 3.3°$).

EXPERIMENTAL

The individuality of the substances was checked by TLC on Silufol plates in the following systems: a) petroleum ether–diethyl ether (1:1); b) ether. The revealing agent was concentrated H_2SO_4. Type KSK silica gel was used for column chromatography. The eluents employed were benzene, ether, ethyl acetate, and acetone.

For analysis, the substances were dried in a vacuum pistol with P_2O_5 over alcohol for 6-8 h. The elementary analyses of the compounds corresponded to the calculated figures. Specific optical rotations were measured on a Polamat polarimeter in a tube 0.5 dm long having a volume of 1 ml.

IR spectra were taken on a UR-20 spectrophotometer (in chloroform) and in tablets with KBr); PMR on a Bruker WP-200SY spectrometer (200 MHz, $CDCl_3$, 0 — TMS); and mass spectra on Finnigan MS-9200 instrument (direct insertion. 70°, 90°, and 120°).

TABLE 2. Bond Lengths (Å) in the Structure of (II)

O1—C6 1.476(6)	C4—C15 1.489(9)
O1—C12 1.337(7)	C5—C6 1.512(7)
O2—C12 1.203(8)	C6—C7 1.532(7)
O3—C1 1.434(6)	C7—C8 1.522(8)
O4—C10 1.446(6)	C7—C11 1.506(8)
C1—C2 1.550(8)	C8—C9 1.526(8)
C1—C5 1.561(7)	C9—C10 1.547(8)
C1—C10 1.549(7)	C10—C14 1.531(9)
C2—C3 1.500(10)	C11—C12 1.484(8)
C3—C4 1.299(8)	C11—C13 1.300(10)
C4—C5 1.530(7)	

TABLE 3. Intracyclic Torsional Angles (degrees) in the Structure of (II)

C5C1C2C3 29.9	C7C8C9C10 32.6
C1C2C3C4 -18.2	C8C9C10C1 38.1
C2C3C4C5 -2.5	C9C10C1C5 -81.2
C3C4C5C1 22.1	
C4C5C1C2 -31.3	C11C7C6O1 -34.0
	C7C6O1C12 28.2
C10C1C5C6 72.9	C6O1C12C11 -9.3
C1C5C6C7 -61.9	O1C12C11C7 -13.8
C5C6C7C8 80,5	C12C11C7C6 29.2
C6C7C8C9 -83.7	

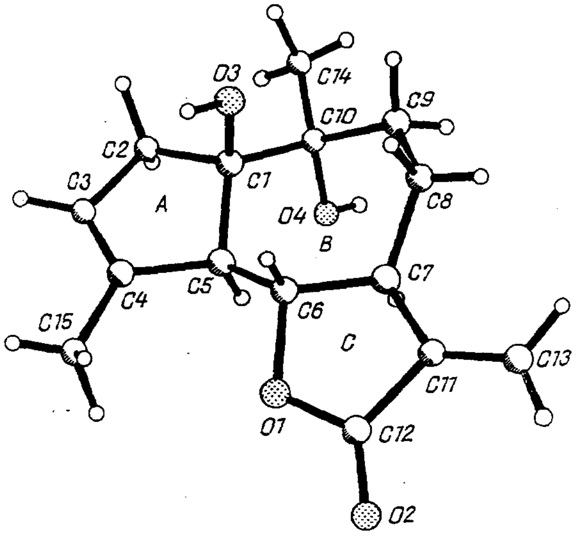


Fig. 1. Structure of the 1β, 10α-dihydroxyarglabin molecule.

Isolation of the Lactones. The epigeal part of *A. glabella* gathered in the flowering phase in the valley of the river Taldy, Karaganda province, (20 kg) was exhaustively extracted with chloroform. The chloroform was evaporated under vacuum, and the residue (1.930 kg) was treated three times with a mixture of ethanol and water in a ratio of 2:1 at 70°C. The ballast substances that precipitated were separated off by decantation, and the filtrate (aqueous alcoholic layer) was treated three

TABLE 4. Coordinates of the Atoms ($\times 10^4$ for $H^3 \times 10^3$) in the Structure of (II)

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
O1	7914(3)	-441(3)	-620(2)	HO3	638(4)	57(4)	133(2)
O2	9428(4)	-660(3)	-1236(3)	HO4	554(5)	280(5)	-85(3)
O3	6292(3)	1163(3)	1166(2).	H2a	427(5)	89(4)	108(3)
O4	5649(3)	2251(3)	-649(2)	H2b	422(4)	88(4)	24(3)
C1	5772(4)	1139(4)	443(3)	H3	431(5)	-96(5)	70(3)
C2	4647(5)	685(6)	551(3)	H5	608(3)	47(4)	-62(2)
C3	4834(5)	-481(5)	476(3)	H6	772(5)	16(5)	39(3)
C4	5722(5)	-712(4)	148(3)	H7	758(4)	166(4)	-81(3)
C5	6284(4)	303(4)	-94(2)	H8a	845(4)	271(4)	17(3)
C6	7475(4)	343(4)	-86(3)	H8b	819(4)	186(4)	81(3)
C7	7945(4)	1389(4)	-362(3)	H9a	694(5)	348(5)	0(4)
C8	7935(4)	2239(4)	249(3)	H9b	692(4)	305(4)	88(3)
C9	6898(5)	2842(5)	322(4)	H13a	996(6)	220(6)	-49(4)
C10	5830(4)	2296(4)	162(3)	H13b	1052(5)	116(5)	-87(4)
C11	9005(5)	1009(4)	-634(3)	H14a	498(4)	287(5)	111(3)
C12	8845(5)	-100(5)	-878(3)	H14b	432(4)	273(3)	36(2)
C13	9918(6)	1479(6)	-658(5)	H14c	505(5)	372(5)	48(3)
C14	4971(5)	2968(6)	534(4)	H15a	680(5)	-192(5)	19(4)
C15	6148(7)	-1781(5)	-22(5)	H15b	571(5)	-226(5)	21(3)
				H15c	634(6)	-191(6)	-54(4)

times with chloroform. The chloroform extracts were evaporated, and the residue (0.885 kg) was chromatographed on a column of type KSK silica gel at a ratio of the total material to support of 120.

When the column was eluted with benzene, colorless acicular crystals were isolated, and these, after three recrystallizations from hexane, yielded a colorless crystalline substance with the composition $C_{15}H_{18}O_3$, mp 100-102°C, $[\alpha]_D^{20}$ + 45° (c 0.3; chloroform), identified by its physical constants and spectral characteristics (IR, PMR, and mass spectra) as the guanolide arglabin [1].

From the benzene–ether (9:1) fraction we isolated a crystalline mass, after the recrystallization of which from ether–ethanol we obtained a colorless crystalline substance with the composition $C_{15}H_{20}O_3$, mp 133-135°C, $[\alpha]_D^{23}$ + 203.8° (c 0.52; chloroform). Argolide was identified from its IR, PMR, and mass spectra [2].

From fractions 96-100 (benzene–ether (1:1)) we isolated colorless crystals and, after the recrystallization of these from ether–ethanol, we obtained a colorless crystalline substance with the composition $C_{15}H_{22}O_3$, mp 170.5-172°C, $[\alpha]_D^{22}$ + 45.0° (c 0.43; chloroform). A comparison of its physicochemical constants and spectral characteristics with those given in the literature [5] identified this substance as ketopelenolide b.

Fractions 101-125 yielded glassy crystals which, after two recrystallizations from ether–ethanol, gave a colorless crystalline substance (II) with mp 155-156°C. IR spectrum (cm^{-1}): 3600 (OH), 1760 (carbonyl of a γ-lactone), 1670 (C=C) 1150, 1130 (epoxy group). Mass spectrum (m/z; intensity, %): M^+ 264(2.60), 246(19.86), 231(50.67), 213(56.16), 203(93.15), 185(23.28), 175(15.75), 167(7.53), 147(19.18), 131(19.18), 121(34.24), 109(29.45), 95(30.13), 79(21.23), 67(21.23), 53(24.65), 43(100).

Opening of the Epoxide Ring of Arglabin. A solution of 0.55 g of arglabin in 15 ml of acetonitrile was heated to the boil, and a drop of HBF_4 was added. It was then boiled for 1.5 h. TLC revealed three spots, with R_{f1} 0.75; R_{f2} 0.55; R_{f3} 0.4 (ether). The reaction mixture was treated in a separatory funnel with ether and with a saturated solution of sodium chloride and soda. The ethereal extract was dried over magnesium sulfate and evaporated. The residue (0.35 g) was chromatographed on a column of silica gel.

When the column was eluted with petroleum ether–ether (3:1, 2:1), a crystalline mass was isolated, and its recrystallization from ether gave a colorless crystalline substance (III) with the composition $C_{15}H_{20}O_4$, mp 184-185°C, $[\alpha]_D^{21}$ (c 0.3; chloroform). IR spectrum (cm^{-1}): 3440 (OH), 1770 (carbonyl of a γ-lactone), 1680 (C=C). Mass spectrum (m/z; intensity, %): M+ 264 (5.32), 246 (44.1; M^+-H_2O), 228 (10.8; M^+-2H_2O), 213 (14.28), 203 (26.8), 175 (14.28), 157 (8.6), 149 (10.0), 121 (22.1), 96 (73.8), 81 (20.4), 53 (18.5), 43 (100).

Crystals deposited from fractions 29-37, and after their recrystallization from chloroform–ether a colorless crystalline substance (II) was obtained with the composition $C_{15}H_{20}O_4$, mp 149-151°C, $[\alpha]_D^{25}$ + 106.6° (c 0.3; chloroform). IR spectrum (cm^{-1}) 3460 (OH), 1770 (carbonyl of a γ-lactone), 1670 (C=C). Mass spectrum (m/z; intensity, %: M^+ 264(4.28), 246(44.28; M^+-H_2O), 228 (12.85; M^+-2H_2O), 218(5.71), 213(14.28), 203(25.71), 188(19=8.57), 175(14.28), 167(11.42), 157(8.57), 149(10), 138(35.7), 131(12.85), 109(72.85), 96(72.85), 91(12.85), 81(21.42), 67(18.57), 43(100).

When the column was eluted with petroleum ether–ether (1:3), a colorless crystalline substance (IV) was isolated, and after its recrystallization from ethanol it had the composition $C_{15}H_{18}O_3$, mp 220-221°C, $[\alpha]_D^{22}$ + 80.6° (*c* 0.5; chloroform.) IR spectrum (cm^{-1}): 3350 (OH), 1770 (carbonyl of a γ-lactone), 1680 and 1550 (conjugated C=C bonds). Mass spectrum (m/z; intensity, %): 228 (M^+-H_2O; 100), 213 (39.72), 200 (4.10), 185 (4.79), 157 (4.10), 122 (5.47), 70 (10.95), 43 (20.0).

X-Ray Structural Investigation of Compound (II). The cell parameters and the intensities of 1872 reflections were measured on a Siemens P3/PC automatic four-circle diffractometer (λ MoK_α, graphite monochromator, $\theta/2\theta$ scanning, $2\theta \leq 60°$). The crystals were tetragonal a = 12.681(2), c = 17, 585(4) A, V = 2827.8 A^3, M = 264.3, d_{out} = 1.242 g/cm³, Z = 8 ($C_{15}H_{20}O_4$), $P4_12_12$.

In the calculations we used 1480 independent reflections with $I \geq 3\sigma$. The structure was interpreted by the direct method and was refined by full-matrix MLS in the anisotropic approximation for nonhydrogen atoms. All the H atoms were revealed in a difference synthesis and were refined isotropically. The final discrepancy factors were R = 0.065 and R_w = 0.059. The coordinates of the atoms are given in Table 4.

All the calculations were conducted on an IBM PC/AT computer using the Siemens SHELXTL program packet (PC Version).

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