PSEUDOGUAIANOLIDES OF Inula aspera.
SPATIAL STRUCTURE OF ERIGEROLIDE

M. K. Makhmudov, B. Tashkhodzhaev,
F. B. Zhonkhozhaeva, and I. D. Sham'yanov

UDC 547.992:547.37+548.737

The sesquiterpene lactones erigerolide and britanin have been isolated from the epigeal part of the plant _Inula aspera_ Poir. The spatial structure of the erigerolide molecule has been determined by the x-ray structural method. Erigerolide and inuchinenolide C isolated from difference plant materials are identical and are crystalline polymorphs.

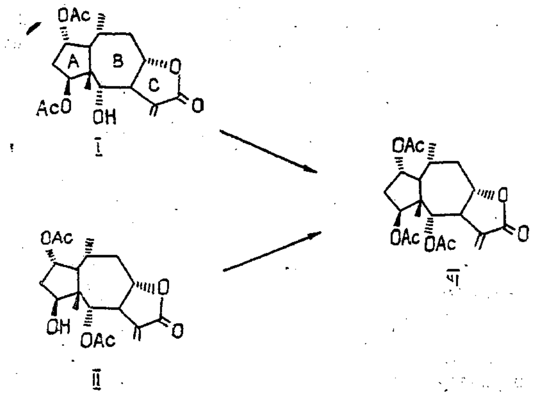
Inula aspera Poir is a plant that is widespread on the territory of Central Asia and Kazakhstan. It is found in valleys and on mountain slopes among semidesert steppe and meadow vegetation in saline locations [1]. According to a preliminary evaluation, this inula species contains sesquiterpene γ-lactones [2].

We used aqueous extraction to isolate the lactones from the epigeal part of the plant gathered in the mass-flowering phase in the Talas valley, Kyrgyzstan Republic [2]. Two crystalline substances were isolated by chromatography from the total extractive materials obtained.

Substance (I) had the composition $C_{19}H_{26}O_7$, M^+ 366, mp 152-153°C, $[\alpha]_D^{20}$ −27° (c 0.0158; $CHCL_3$) and its IR spectrum contained absorption bands at (cm^{-1}) 3540 (OH); 1770 (C=O of a γ-lactone): 1730, 1715 (ester C=O): 1665 (C=C).

Substance (II), $C_{19}H_{26}O_7$, M^+ 366, mp 190-192°C $[\alpha]_D^{20}$ −26° (c 0.5; alcohol); its IR spectrum contained absorption bands at (cm^{-1}) 3535 (OH); 1765 (CO of a γ-lactone); 1730, 1715 (ester C=O); 1668 (C=C).

The nature of the fragmentation of these two lactones under electron impact was the same [(m/z 366 (M^+), 306 ($M^+ - CH_3COOH$), 246 ($M^+ - 2CH_3COOH$)], which is characteristic for structural isomers. According to their IR and PMR spectra, (I) and (II) each contained one hydroxy group. The acetylation with acetic acid in pyridine of the lactones that had been isolated gave one and the same product, with the composition $C_{21}H_{28}O_8$, M^+ 408 (white amorphous powder). The IR spectra of the acetates were identical. The physicochemical properties and spectral characteristics of the substances isolated from _Inula aspera_ corresponded to known pseudoguaianolides − erigerolide (I) and britanin (II) − as was confirmed by mixed melting points with authentic samples of erigerolide and britanin isolated previously from the plant _Erigeron khorassanicus_ Boiss. [3].



Institute of the Chemistry of Plant Substances, Uzbekistan Republic Academy of Sciences, Tashkent. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 232-237, March-April, 1993. Original article submitted June 15, 1992.

0009-3130/93/2402-0191$12.50

TABLE 1. Intracyclic Torsional Angles φ_I and φ_{Ia} of Structures (I) and (Ia) (according to XSI results) and φ_{theor} (degrees) after Optimization by the MM Method

Ring	Angle	φ_I	φ_{Ia}	φ_{theor}
A	C1C2C3C4	−9.1	−8.2	−6,8
	C2C3C4C5	29.2	34,9	31,6
	C3C4C5C1	−37,3	−45.9	−43,6
	C4C5C1C2	31,0	38,8	37,6
	C5C1C2C3	−14,4	−19,5	−20,0
B	C1C5C6C7	35,9	21,1	29.8
	C5C6C7C8	40,3	53,1	41,5
	C6C7C8C9	−89,2	−91,6	−87,5
	C7C8C9C10	69,4	68,1	73,4
	C8C9C10C1	−50,4	−53.9	−54.8
	C9C10C1C5	70,9	77,7	69,8
	C10C1C5C6	−86,2	−81,0	−78.5
C	C7C11C12O1	10,5	10,2	17,5
	C11C12O1C8	8,0	4,8	2,5
	C12O1C8C7	−22,5	−18,1	−20.8
	O1C8C7C11	27,3	22,9	28,3
	C8C7C11C12	−23,1	−20,1	28,1

Earlier, in parallel and independently [3], inuchinenolide C [4] had been isolated from Inula britanica var. Chinensis, with physicochemical characteristics coinciding with those of erigerolide, except for the melting point ($C_{19}H_{26}O_7$, colorless oil $[\alpha]_D^{20}$ −25.9°C (c 1.13; $CHCl_3$)). In these papers, [3] and [4], no determination of the orientation of the methyl groups at C5 and C10 and of the acetate groups at C2 and C4 or of the nature of the linkage rings A and B was reported. The spatial structure of britanin (II) was established in [5] by the use of two-dimensional ^1H NMR spectroscopy. In view of the fact that (I) and (II) form an identical acetate (III), it may be concluded that the orientations of the substituents and the linkages of the rings in the molecules of (I) and (II) are identical.

Later, [6] a sesquiterpene lactone of the pseudoguaiane series was isolated from Inula caspica Blume and it was identified by the x-ray structural method as inuchinenolide C, but with different parameters of the specific rotation and state of aggregation of the molecule (mp 156-158°C (alcohol), $[\alpha]_D^{20}$ +95.5° (c 0.0045; $CHCl_3$)).

In the light of the contradictory literature reports mentioned above, we have made an x-ray structural investigation (XSI) of (I). The spatial structure of the (I) molecule is shown in Fig. 1. The linkages of rings A/B and B/C are trans (the torsional angle H1C1C5C15 is −168.4° and H7C7C8H8 is −163.9°). The acetoxy groups in the C2 and C4 positions, the hydroxy group at C6, and the methyl group at C10 have the α-, and the methyl group in the C5 position the β-. orientation. Consequently, the structrue of (I) is identical with that of inuchinenolide C (Ia) [6].

On the whole, no anomalies are observed in the values of the valence distances and angles (see Fig. 1 and Table 2) in comparison with the standard values [7]. The mean-square errors in the determination of bond lengths do not exceed 0.01 Å.

Ring A has a half-chair conformation with symmetry C_2, as is shown by the asymmetry parameters $\Delta C_2(2)$ = 3.7° and $\Delta C_s(5)$ = 17.3°, the C4 and C5 atoms deviating from the plane of the other three atoms of the ring by 0.232 and −0.370 Å, respectively. The seven-membered ring B has a conformation closer to a twist-chair (ΔC_2(6, 9-10) = 6.1°) than to a chair (ΔC_s(9, 5-6) = 30.7°). The lactone ring (ring C) has a half-chair conformation with symmetry C_2 ($\Delta C_2(12)$ = 1.4°, $\Delta C_s(7)$ = 9.4°).

However, the conformation of the rings in its crystalline polymorph – inuchinenolide C (Ia) – differ slightly: rings A ($\Delta C_2(2)$ = 8.5° and $\Delta C_s(5)$ = 16.3°) and C ($\Delta C_2(12)$ = 4.3° and $\Delta C_s(7)$ = 5.7°) are between envelope and half-chair, the former being close to envelope, while the cycloheptane ring assumes a conformation between chair (ΔC_s(9, 5-6) = 19.8°) and twist-chair (ΔC_2(6, 9-10 = 20.2°).

In structure (I), an intramolecular hydrogen bond is observed between the carbonyl of

TABLE 2. Valence Angles ω (degrees) in Structure (I)

Angle	ω	Angle	ω	Angle	ω	Angle	ω
C5C1C2	105,8(5)	C6C5C1	112,3(5)	C9C8C7	113,4(6)	O2C12C11	127,6(8)
C10C1C2	110,9(5)	C6C5C4	111,5(5)	O1C8C7	103,3(5)	O2C12O1	122,7(7)
C10C1C5	117,0(5)	C15C5C1	113,1(5)	O1C8C9	107,0(5)	O5C18C19	109,7(7)
C3C2C1	108,3(5)	C15C5C4	109,3(6)	C10C9C8	116,1(6)	O6C18C19	125,7(7)
O3C2C1	105,4(5)	C15C5C6	109,7(5)	C9C10C1	114,7(5)	O6C18O5	124,5(6)
O3C2C3	111,1(6)	C7C6C5	115,9(5)	C14C10C1	111,8(6)	O3C16C17	110,6(8)
C4C3C2	105,3(5)	O7C6C5	112,5(5)	C14C10C9	106,3(6)	O4C16C17	126,4(9)
C5C4C3	106,1(5)	O7C6C7	101,6(5)	C12C11C7	105,6(6)	O4C16O3	122,9(6)
O5C4C3	106,2(5)	C8C7C6	117,7(6)	C13C11C7	131,3(6)	C12O1C8	110,9(5)
O5C4C5	113,6(5	C11C7C6	115,4(5)	C13C11C12	123,2(7)	C18O5C4	118,0(5)
C4C5C1	100,84)	C11C7C8	102,7(5)	O1C12C11	109,7(6)	C16 3C2	117,6(5)

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

Atom	x	y	z	Atom	x	y	z
C1	—1281(7)	—277(5)	—1028(3)	C14	—1855(13)	—1789(8)	—2086(5)
C2	—1227(7)	539(5)	—1764(4)	C15	—3343(7)	562(7)	—181(5)
C3	—1250(10)	1719(6)	—1428(4)	C16	145(7)	434(6)	—2998(4)
C4	—1073(7)	1596(5)	—494(3)	C17	1498(19)	—13(15)	—3343(1)
C5	—1734(6)	438(5)	—263(3)	C18	—1366(7)	2909(5)	626(4)
C6	—1109(7)	—22(5)	562(4)	C19	—2122(10)	3961(7)	846(6)
C7	—1090(7)	—1281(5)	627(4)	O1	—2149(6)	—3027(4)	746(3)
C8	—2244(8)	—1986(5)	279(4)	O2	—1355(9)	—3583(5)	1991(4)
C9	—2075(9)	—2281(6)	—622(5)	O3	105(5)	303(4)	—2182(2)
C10	—2207(7)	—1312(6)	—1236(4)	O4	—787(5)	69(5)	—3381(3)
C11	—831(7)	—1732(5)	1490(4)	O5	—1810(5)	2545(4)	—123(3)
C12	—1446(10)	—2870(6)	1470(5)	O6	—475(6)	2466(4)	1029(3)
C13	—309(9)	—1286(7)	2154(4)	O7	334(5)	309(5)	686(3)

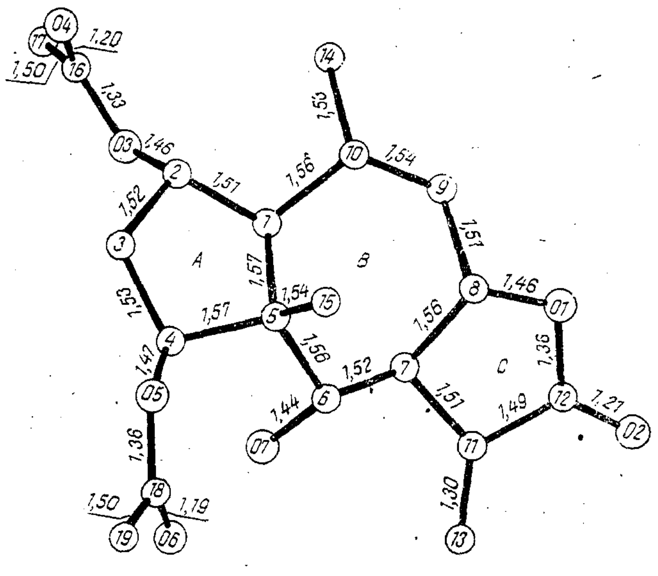


Fig. 1. Spatial structure of erigerolide.

the acetyl group at C4 and the hydroxy group at C6: the O6···O7 distance is 2.76 Å, and O6···H(O7) 2.29 Å, while the O6···H–O7 angle is 134°. In structure (Ia), the hydroxy group at C6 participates in an intermolecular H-bond with an acetyl group. This difference is also shown in the packing; in the crystal structure of (I) there are no intermolecular H-bonds because of the blocking of the OH group by the intramolecular H-bond.

In order to determine their spatial structure in the free state, the geometries of the isolated (I) and (Ia) molecules were calculated by the method of molecular mechanics (MM) [9] with complete optimization, using as the initial parameters those of XSI for erigerolide and inuchinenolide C (hydrogen bonds were not taken into account). It is natural that the optimization of (I) and (Ia) by the MM method brought the geometries of the two molecules to a single one, and the calculated torsional angles φ_{theor} differed by not more than 2.7° (see Table 1). According to the calculation, ring A has a conformation intermediate between envelope ($\Delta C_s(5) = 9.8°$) and half-chair ($\Delta C_2 = 10.2°$), the cycloheptane ring B is closer to a twist-chair conformation ($\Delta C_2(6,\ 9\text{-}10) = 8.8°$ than to a chair ($\Delta C_s(9,\ 5\text{-}6) = 26.0°$), and the conformation of ring C approximates to a 7α-envelope ($\Delta C_s(7) = 3.0°$ and $\Delta C_2(12) = 11.8°$).

A comparison of the torsional angles and asymmetry parameters (ΔC) of the two crystalline states of the molecules with those calculated theoretically by the MM method shows that the crystal field (packing factor) and the presence (or absence) of H-bonds leads to small changes in the conformation of the pseudoguaiane skeleton.

The reason for the opposite signs of the specific rotation of lactone (Ia) from Inula capsica Blume [6], identified as inuchinenolide C ($[\alpha]_D^{20}$ +95.5° (c 0.0045; $CHCl_3$)) and erigerolide from Inula aspera Poir ($[\alpha]_D^{20}$ −27° (c 0.0158; $CHCl_3$) and also inuchinenolide C from Inula britanica var. Chinensis [4] ($[\alpha]_D^{20}$ −25.9° (c 1.13; $CHCl_3$) remains open, since it was not considered correct to draw a conclusion about enantiomerism without a direct comparison.

EXPERIMENTAL

^1H NMR spectra were taken on a Tesla BS-567A 100 MHz instrument in C_5D_5N (δ. 0 – TMS), mass spectra on an MKh-1310 spectrometer, and IR spectra on a UR-20 spectrophotometer in KBr tablets.

Isolation of the Lactones. The air-dry leaves, small stems, and flower heads (2 kg) of Inula aspera, gathered in the flowering phase at the beginning of August, were extracted with hot water (80°C). The aqueous extract was treated three times with chloroform and was then evaporated. The total substances obtained (15.4 g) were chromatographed on a column of type KSK silica gel (in a ratio of material to support of 1:20). Elution was conducted successively with benzene, benzene–ethyl acetate (19:1, 9:1, and 1:1), and ethyl acetate. Fractions with a volume of 0.25 liter were collected.

When the column was eluted with benzene—ethyl acetate (9:1), fractions 42-48 yielded 0.152 g of erigerolide (I). IR spectrum: ν_{max}^{KBr} (cm^{-1}): 3960, 1770, 1730, 1715, 1665, 1270-1250. Mass-spectrum (m/z): 366 (M$^+$, $C_{19}H_{26}O_7$), 306, 246, 228.

On continued elution, benzene—ethyl acetate fractions (54-60) yielded 0.21 g of britanin (II). IR spectrum, ν_{max}^{KBr} (cm^{-1}): 3540, 1769, 1730, 1715, 1668, 1270-1235. Mass-spectrum (m/z): 366 (M$^+$, $C_{19}H_{26}O_7$), 306, 246, 228.

Acetylation of (I) and (II). Erigerolide (I) and britanin (II) were each (0.1 g) dissolved in 2 ml of pyridine, and 1.5 ml of acetic anhydride was added. The mixtures were left for a day at room temperature and were then diluted with water, and the products were extracted with chloroform. By chromatographic purification on silica gel with elution by benzene—ethyl acetate (14:1) the two reaction mixtures gave an identical substance (amorphous powder) with the composition $C_{21}H_{28}O_8$ (M$^+$ 408). IR spectrum. ν_{max}^{KBr} (cm^{-1}): 1770, 1745, 1735, 1668, 1260-1235. Mass-spectrum (m/z): 408 (M$^+$), 366, 348, 306, 288, 264, 246, 228.

X-Ray Structural Investigation. Colorless crystals of (I) of tabular form were grown from ethyl acetate. The space group, unit cell parameters, and the intensities of the reflections from a crystal were measured on a Syntex-P2$_1$ automatic four-circle diffractometer at room temperature using CuK$_\alpha$ radiation: a = 9.480 (3), b = 12.011 (3), c = 16.214 (9) Å, d_{calc} = 1.318 g/cm^3.

The intensities of 1675 reflections with $\theta < 58°$ were measured on the above-mentioned diffractometer ($\theta/2\theta$ scanning). In the primary treatment of the group, weak reflections with $I < 2\sigma(I)$ were discarded. The calculations made use of 1664 reflections with $|F| > 4\sigma(|F|)$. The structure was determined by the direct method using the SHELXS-86 program [10]

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and was refined in the full-matrix isotropic-anisotropic approximation by the SHELX-76 program [11] (both programs in the PC MSDOS versions). The H atoms, the initial positions of which were calculated, were refined isotropically. The final discrepancy factor R = 0.050 (R_w = 0.051). The coordinates of the nonhydrogen atoms are given in Table 3.

The conformational calculations were performed on an IBM PC AT personal computer by the PCMODEL and MMX-86 programs [12] using the potential parameters included in this version of the programs.

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