MOLECULAR AND CRYSTAL STRUCTURE OF THE GERMACRANOLIDES
SALONITENOLIDE AND HANPHYLLIN

K. M. Turdybekov, S. M. Adekenov,
T. V. Timofeeva, S. V. Lindeman,
and Yu. T. Struchkov

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A sesquiterpene lactone of the germacrane type, salonitenolide, has been isolated for the first time from the epigeal part of Centaurea pseudomaculosa Dobrocz (spotted centaurea) and has been identified. The structures of the germacranolides and hanphyllin have been determined by the method of x-ray structural analysis: salonitenolide is 8-hydroxy-6β,8β(H)7α(H)-germacra-1(10),4,11(13)-trien-6,12-olide and hanphyllin is 3-hydroxy-3α,7α(H),6β(H)-germacra-1(10),4,11(13)-trien-6,12-olide. It has been established that the ten-membered rings of salonitenolide and hanphyllin are of the chair-chair type, $_1D^{14}$, $^{15}D_5$. On the basis of the results of CD spectroscopy, the chiral centers in the hanphyllin molecule have been assigned the 3S, 6R, and 7S configurations.

The systematics of sesquiterpene lactones of the germacrane type isolated from plant sources shows that four spatial isomers are characteristic for the germacranolide skeleton due to the geometries of the double bonds at C1—C10 and C4—C5 which can be substituted trans-trans (germacrolide), trans-cis (helioangoloid), cis-trans (melampolide), and cis-cis (cis-cis-germacranolide) [1, 2]. The presence of the above-mentioned double bonds leads to the situation that the ten-membered dienic ring in these compounds assumes only some of the following conformations: chair-chair, boat-boat, chair-boat, and boat-chair [3].

In the present paper we give the results of an x-ray structural investigation of the germacranolides salonitenolide (I) and hanphyllin (II) with the aim of determining the spatial structures and conformations of the hydrocarbon skeletons of their molecules. The conformations of the molecules were calculated by the method of molecular mechanics (MMM).
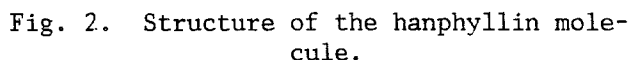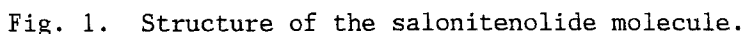
The salonitenolide was isolated from the epigeal part of Centaurea pseudomaculosa Dobrocz [~ false spotted centaurea] and identified by us for the first time. Hanphyllin was isolated from the flower heads and leaves of Achillea nobilis L. by a method described previously [4].

The structures of the molecules of (I) and (II) are shown in Figs. 1 and 2, respectively. The bond lengths and valence angles* are close to the corresponding angles in eupatolide (III) [5], alatolide (IV) [6], tamaulipin-A [7], and costunolide (VI) [8], each likewise containing a 1(10),4-trans-trans-dienic ten-membered carbocycle.

The linkage of the lactone ring with the germacrane skeleton in (I) and (II) is trans (the H6C6C7H7 torsion angles being − 162(2)° and −136(1)°, respectively). The hydroxy group at the C8 atom in (I) has the α-orientation, and that at the C3 atom in (II) the β-orientation. The values of the C2C1C10C9 torsion angles (165(1)° and 166.0(2)° in (I) and (II) and the C3C4C5C6 torsion angles (153(1)° and 154.6(2)° in (I) and (II) at the double endocyclic bonds show that salonitenolide and hanphyllin belong to the $\Delta^{1(10)},^4$-trans, trans-germacranolides. As follows, from Figs. 1 and 2, the values of the C10C1C4C5 pseudotorsion angles (−65(1)° and −74.1(3)° for (I) and (II), respectively), and an analysis of the distances between the C1, C4, C5, and C10 atoms (C1...C4, 2.76 and 2.78 Å; C1...C5, 2.78 and

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*The values of the valence angles can be obtained from the authors.

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Fig. 1. Structure of the salonitenolide molecule.

Fig. 2. Structure of the hanphyllin molecule.

2.80 Å; C4...C10, 3.14 and 3.15 Å; C5...C10, 2.94 and 2.98 Å, according to MMM results, for (I) and (II), respectively), the germacrane ring assumes a chair-chair conformation of the $_1D^{14}$, $^{15}D_5$ type [3]. The intracyclic torsion angles obtained from the x-ray structural experiment and calculated by MMM for the free molecule are in good agreement (Table 1). A comparison of the corresponding torsion angles in (I) and (II) shows that their divergence does not exceed 10°, with the exception of the C4C5C6C7 angles and C6C7C8C9 ($\Delta = 15°$ and 17°, respectively). This divergence is apparently largely due to the influence of crystal packing. Thus, in the MMM calculation for the free molecules of (I) and (II) the difference between the corresponding angles decreases to 4°. The conformation of the lactone ring in (I) is twist: the C6 and C7 atoms depart from the plane of the O1, C11, and C12 atoms by 0.20 and 0.23 Å in the β- and α-directions, respectively. The conformation of the lactone ring in (II) is envelope. The O1, C6, C11, C12 atoms are coplanar to within ±0.02 Å while the C7 atom departs from their plane by 0.40 Å in the α-direction. The O2 atom is in fact in the main plane of the envelope.

In the CD spectrum of the molecule of (II) a negative Cotton effect (CE) was observed for the n → π* transition of the C=C—C=O chromophoric group with an absorption maximum in the 258 nm region. On the basis of a correlation between the nature of the linkage of the rings, the chirality of the C=C—C=O chromophoric group (C13C11C12O2 torsion angle −13.3(4)° and the sign of the CE [9-11], the chiral centers in the (II) molecule were assigned the 3S, 6R, 7S configurations, agreeing with the relative configurations of these centers according to the x-ray structural results.

In the crystal, the molecules of (I) are linked by O3—H...O3 (x − y, x, 1/6 + z) hydrogen bonds (distances: O...O, 2.74 Å; H...O, 1.79 Å; O—H...O angle 154.5(5)°) and O4—H...O2 (1−y), x − y, 2/3 + z) hydrogen bonds (distances O...O, 2.82 Å; H...O, 1.74 Å; O—H...O angle 153.8°) and form helical chains along 6_5 and 3_2 axes, respectively. The molecules of (II) in the crystal are linked by O3—H...O2 (1.5 −x, −y, −0.5 + z) hydrogen bonds (distances: O...O), 2.92 Å; H...O, 2.06 Å; O—H...O angle, 171.6°) and form helical chains along axes of the 2_1 type type (1/4, 0, z).

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TABLE 1. Intracyclic Torsion Angles φ (degrees)

Angle	Molecule I		Molecule II	
	experiment	calculation	experiment	calculation
C10C1C2C3	−98 (1)	−98,1	−99,7 (3)	−97,5
C1C2C3C4	55 (1)	49,4	52,1 (2)	48,1
C2C3C4C5	−83 (1)	−82,7	−86,8 (2)	−82,5
C3C4C5C6	153 (1)	162,9	154 6 (2)	163,0
C4C5C6C7	−145 (1)	−142,5	−130,2 (2)	−131,4
C5C6C7C8	89 (1)	85,6	91,5 (2)	87,5
C6C7C8C9	−70 (1)	−75,9	−86,2 (2)	−80,7
C7C8C9C10	63 (1)	68,1	63,7 (2)	68,0
C8C9C10C1	−120 (1)	−117,3	−110,6 (2)	−114,6
C9C10C1C2	165 (1)	170,0	166,0 (2)	170,8
O1C6C7C11	−26 (1)	−23,2	−24,1 (2)	−23,0
C7C8O1C12	22 (1)	19,1	18,0 (2)	19,1
C8O1C12C11	−8 (1)	−5,6	−3,4 (2)	−5,8
O1C12C11C7	−9 (1)	−10,7	−13,1 (2)	−10,4
C12C11C7C6	22 (1)	20,3	22,9 (2)	20,0

EXPERIMENTAL

The individuality of the compounds isolated was checked by TLC on Silufol plates in the following systems: a) ether—ethyl acetate (4:1); b) ether. The revealing agent was a saturated solution of $KMnO_4$ in H_2SO_4 IR spectra (tablets with KBr) were recorded on UR-20 spectrophotometer; UV spectra on a Specord UV-vis; PMR spectra on a Bruker HX 90E ($CDCl_3$, 0—TMS, δ-scale); mass spectra on a Finnigan MS-9200; and CD spectra on a Jasco-20 instrument (in methanol). The results of elementary analyses of the compounds corresponded to the calculated figures.

Isolation of Salonitenolide. The ethyl acetate fractions obtained previously [12] on the separation of a chloroform extract from the epigeal part of Centaurea pseudomaculosa on a column of type KSK silca gel yielded by the method of flash chromatography on type LL 100/160 silica gel in the ether—ethyl acetate (1:1) system a crystalline mass, after the recrystallization of which from acetone a colorless crystalline substance was obtained with the compositon $C_{15}H_{24}O_4$, mp 137-139°C, $[\alpha]_D^{20}$ + 199.4° (c 0.04; methanol).

From its physicochemical constants, IR, PMR, and mass spectra, and a comparison of them with the literature [13] this substance was identified as the germacranolide salonitenolide.

X-Ray Structural Experiment. The parameters of the cell and the intensities of the reflections of compound (I) were measured on a Syntex P2$_1$ automatic diffractometer (λ MoKα, graphite monochromator, θ/2θ- scanning $2\theta \leqslant 52°$) . The crystals were hexagonal, a = 18.555(3), c = 7.015(1) Å, V = 2091.6 Å^3, M = 264, d_{calc} = 1.259 g/cm^3, z = 6 ($C_{15}H_{20}O_4$), sp. gr. P6$_5$.

In the calculations we made use of 1413 reflections with I ≥ 2σ. The structure was interpreted by the direct method and was refined by block-diagonal MLS in the anisotropic approximation for the nonhydrogen atoms. The positions of the H atoms were calculated (apart from the H(O3) and H(O4) atoms, which were revealed in a difference synthesis). The coordinates of the H atom were not refined, and their contribution to F_{calc} was allowed for with B_{iso} = 4.0 Å^2. All the calculations were performed on an Eclipse S/200 computer by means of the SHELXTL program [14]. The final divergence factors were R = 0.082 and R_w = 0.082. The coordinates of the nonhydrogen atoms are given in Table 2.

Isolation of Hanphyllin. Hanphyllin — a colorless crystalline substance with the composition $C_{15}H_{20}O_3$, mp 189°C with decomposition (alcohol) $[\alpha]_D^{20}$ + 58.6° (c 0.39 chloroform) — was isolated from the flower heads and leaves of Archillea nobilis by a method described previously [4] and was identified from its IR, PMR and mass spectra and also by comparison with an authentic sample.

X-Ray Structural Experiment. The parameters of the cell and the intensities of the reflections of compound (II) were measured on a SAD-4 automatic diffractometer (λ MoKα, graphite monochromator, θ/ω-scanning (ω:θ = 1.2:1), (2θ ⩽ 56). The crystals were rhombic, a = 10.201(2), b = 11.403(2), c = 11.553(4) Å, V = 1343.8 Å^3; M = 248, d_{calc} = 1.227 g/cm^3, z = 4 ($C_{15}H_{20}O_3$). sp. gr. P2$_1$2$_1$2$_1$.

In the calculations 1154 independent reflections with I ≥ 5σ were used. The structure was interpreted by the direct method and was refined by full-matrix MLS in the anisotropic approximation for the nonhydrogen atoms. The H atoms were revealed in a difference synthesis

TABLE 2. Coordinate of the Nonhydrogen Atoms ($\times 10^4$)

Atom	Molecule I			Atom	Molecule II		
	x	y	z		x	y	z
O1	3763 (4)	1897 (4)	3314 (12)	O1	9442 (1)	931 (1)	300 (1)
O2	4394 (4)	2735 (4)	1359 (13)	O2	11006 (2)	1729 (2)	1388 (1)
O3	1337 (4)	−5 (5)	6480 (16)	O3	4999 (1)	−1801 (2)	−1243 (1)
O4	6150 (4)	1812 (5)	5546 (15)	C1	8404 (2)	−2759 (2)	−2055 (2)
C1	3903 (6)	474 (6)	9885 (0)	C2	6948 (2)	−2670 (2)	−2131 (2)
C2	2982 (8)	37 (8)	10390 (20)	C3	6391 (2)	−1882 (2)	−1163 (2)
C3	2600 (8)	554 (8)	9666 (20)	C4	7100 (2)	−712 (2)	−1160 (2)
C4	2777 (6)	705 (6)	7544 (17)	C5	8191 (2)	−671 (2)	−545 (2)
C5	3487 (6)	1313 (6)	7018 (17)	C6	9331 (2)	130 (2)	−711 (2)
C6	3932 (6)	1356 (6)	5177 (17)	C7	10655 (2)	−521 (2)	−739 (2)
C7	4881 (6)	1824 (5)	5217 (17)	C8	11178 (2)	−920 (2)	−1920 (2)
C8	5245 (6)	1303 (6)	5768 (19)	C9	10704 (2)	−2120 (2)	−2351 (2)
C9	5155 (7)	941 (8)	7804 (19)	C10	9275 (2)	−2159 (2)	−2636 (2)
C10	4246 (6)	307 (6)	8393 (18)	C11	11536 (2)	330 (2)	−115 (2)
C11	5135 (6)	2290 (6)	3412 (16)	C12	10699 (2)	1074 (2)	609 (2)
C12	4418 (6)	2342 (6)	2693 (17)	C13	12819 (2)	451 (3)	−144 (2)
C13	5814 (6)	2543 (8)	2354 (20)	C14	8924 (2)	−1436 (2)	−3714 (2)
C14	3782 (7)	−456 (7)	7148 (21)	C15	6614 (2)	215 (2)	−1964 (2)
C15	2113 (6)	27 (6)	6206 (20)				

and were included in the refinement in the isotropic approximation. The final divergence factors were R = 0.029 and R_w = 0.039. All the calculations were made on a PDP-11/23 PLUS computer by means of SDP—PLUS programs [15]. The coordinates of the nonhydrogen atoms are given in Table 2.

Conformational calculations were made by the MM2 program [16] on a EC-1061 computer with the set of parameters contained in the given version of the program.

SUMMARY

1. The germacranolide salonitenolide has been isolated from the epigeal part of the _Centaurea pseudomaculosa_ Dobrocz. and identified for the first time.

2. The spatial structure of the sesquiterpenes salonitenolide and hanphyllin have been determined by x-ray structural analysis: salonitenolide is 8-hydroxy-6β,8β(H), 7α(H)-germacra-1(10), 4(5),11(13)-trien-6,12-olide, and hanphyllin is 3-hydroxy-3α,7α(H),6β(H)-germacra-1(10),4(5),11(13)-trien-6,12-olide. The configuration of the ten-membered ring in salonitenolide and hanphyllin is of the chair-chair $_1D^{14}$, $^{15}D_5$ type.

3. On the basis of the results of CD spectroscopy, the chiral centers in the hanphyllin molecule have been assigned the 3S, 6R, and 7S configurations.

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