SPATIAL STRUCTURE OF THE GERMACRANE LACTONES HANPHYLLIN, SALONITENOLIDE, AND SACHOSIN

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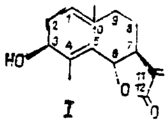
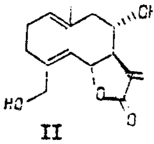
An x-ray structural study has been made of the sesquiterpene lactones hanphyllin, salonitenolide, and sachosin: diffractometer; CuK_α radiation; 997, 950, and 1245 reflections, respectively; direct method; R factors 0.049, 0.099, and 0.081. All three molecules have the chair-chair conformation with configurations of the $_1D^{14}$ and $^{15}D_5$ types.

Continuing a study of the spatial structures of sesquiterpene lactones by the x-ray structural method [1, 2] we have investigated compounds isolated previously – hanphyllin (I) [3] and salonitenolide (II) [4, 5] – and the new germacrane lactone sachosin (III) isolated from Saussurea sachosa. The results of the investigation have permitted the reliable determination of stereochemical aspects of their structure: the linkage of the rings, the conformation of the ten-membered ring, and the orientations of the substituents.



I



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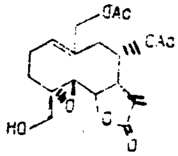

III

Spatial illustrations of the molecules are shown in Figs. 1-3. The lactone rings in the 6, 7 positions in these molecules are trans-linked with the germacrane rings. In compounds (I) and (II) the hydroxy groups at C3 (I) and C8 (II) have the β- and α-orientations, respectively. In compound (III), the OAc group at C8 and the hydroxy methyl group at C4 have the α- and β-orientations respectively.

The values of the torsion angles of the germacrane ring (Table 1) permit compounds (I), (II), and (III) to be assigned to the trans-trans-germacranolides – germacrolides [6].

By projecting the molecules of (I), (II), and (III) onto a plane perpendicular to the mean square plane of the germacrane ring it is possible to see that the endocyclic double C1═C10 and C4═C5 (in compound (III), the 4(5)-epoxy group can be considered as the stereochemical equivalent to a double bond) are twisted, and the substituents in positions C4 and C10 are syn-directed and are β-oriented relative to the plane of the germacrane ring. Consequently, the germacrane rings assume the chair-chair conformation and a configuration of the $_1D^{14}$, $^{15}D_5$ type [7]. This conformation of the ten-membered ring is typical for trans-linked 6,7-germacrolides [8].

Earlier, on the basis of the results of a study of the structures of the germacrane esters chimganidin [9], shiromodiol [10], and 7,8-germacrane lactones a hypothesis was expressed on the predominance of certain conformations out of the four possible ones – chair-chair (A), boat-chair (C), and two types of boat-boat (B, D), i.e., 1(10), 4(5) dienic germacrolides with the α-orientation of the substituent at C6 should have conformation A or B with the β-orientation of the C15 methyl group [2]. In view of the α- and β-orientations of the C6-O1 and C4-C15 bonds, respectively and the A conformation adopted in compounds (I), (II), and (III), and also from an analysis of literature information, this hypothesis can also be extended to 6,7-germacrolides.

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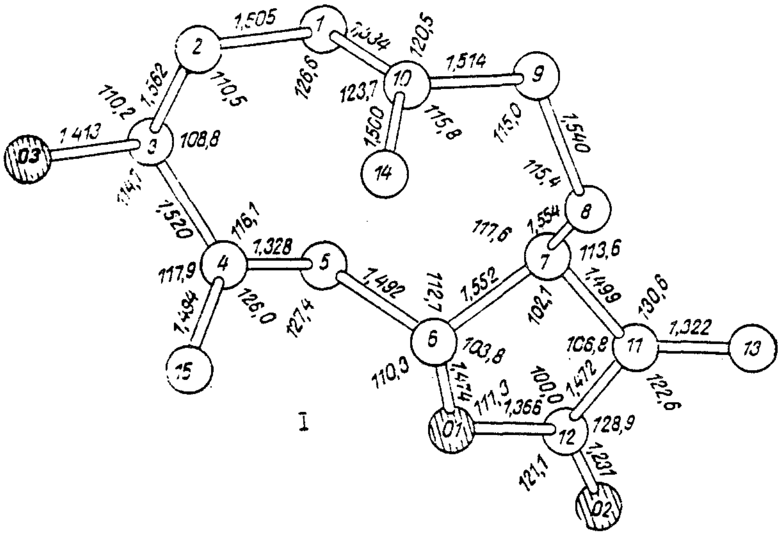
TABLE 1. Intracyclic Torsion Angles (deg) of the Hanphyllin (I), Salonitenolide (II), and Sachosin (III) Molecules

Angle	I	II	III
C1—C2—C3—C4	52,1	52,2	43,6
C2—C3—C4—C5	—87,7	—84,1	—90,8
C3—C4—C5—C6	156,1	150.6	146,0
C4—C5—C6—C7	—130,4	—148.0	—108,3
C5—C6—C7—C8	91.6	91,5	102,0
C6—C7—C8—C9	—86,8	—69,5	—116,9
C7—C8—C9—C10	70,6	67,2	83,4
C8—C9—C10—C1	—109,8	—126.0	—89,9
C9—C10—C1—C2	166.7	168.5	168,8
C10—C1—C2—C3	—102.0	—94,2	—115.0
C6—C7—C11—C12	22,5	19,9	7.5
C7—C11—C12—O1	—12,9	—7,6	2,1
C11—C12—O1—C6	—3,5	—8,5	7,5
C12—O1—C6—C7	17,8	20,3	—1,2
O1—C6—C7—C11	—23,9	—23,1	—4,6



I

Fig. 1. Spatial structure of hanphyllin (I).

A comparison of the torsion angles of the germacrane rings of the (I), (II), and (III) molecules shows a general closeness of the corresponding magnitudes (see Table 1), although the difference in the values of the angles relative to the C5—C6, C7—C8, and C9—C10 bonds reaches 40°. Consequently, the presence of dissimilar substituents in various positions (C3, C8, C14, and C15) and also the inclusion of an epoxy group in place of a double bond in the C4(5) position do not substantially affect the conformation of the germacrane rings of these molecules.

The lactone rings of the molecules of (I) and (II) (Figs. 1 and 2) have the envelope conformation and the corresponding symmetry C_s. It can be seen from Table 1 that the values of the torsion angles of the lactone rings of molecules (I) and (II) are almost the same and their changes are symbatic with those calculated theoretically for unsubstituted cyclopentane [12]. It can be seen from the values of the torsion angles of molecule (III) that the lactone ring in it is highly flattened.

Figure 3 gives the values of the bond lengths and valence angles (the errors of their determination are not greater than 0.016 Å and 0.8°, respectively), which agree with the standard figures [13].

Packing of the Molecules in the Structures of (I), (II), and (III). An analysis of intermolecular contacts shows the formation of H-bonds of the O—H...O type in all three structures investigated. In structures (I) and (III), and hydroxy groups at C3 (I) and C15 (III)

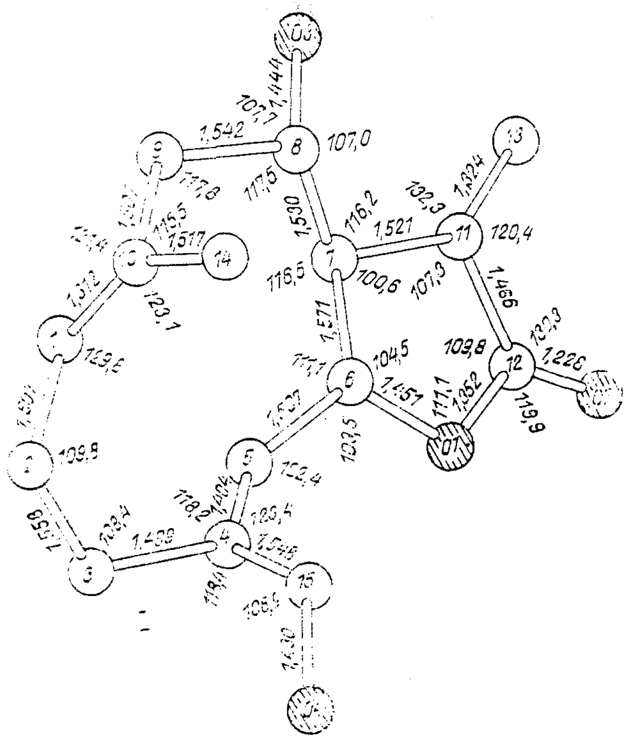


Fig. 2. Spatial structure of salonitenolide (II).

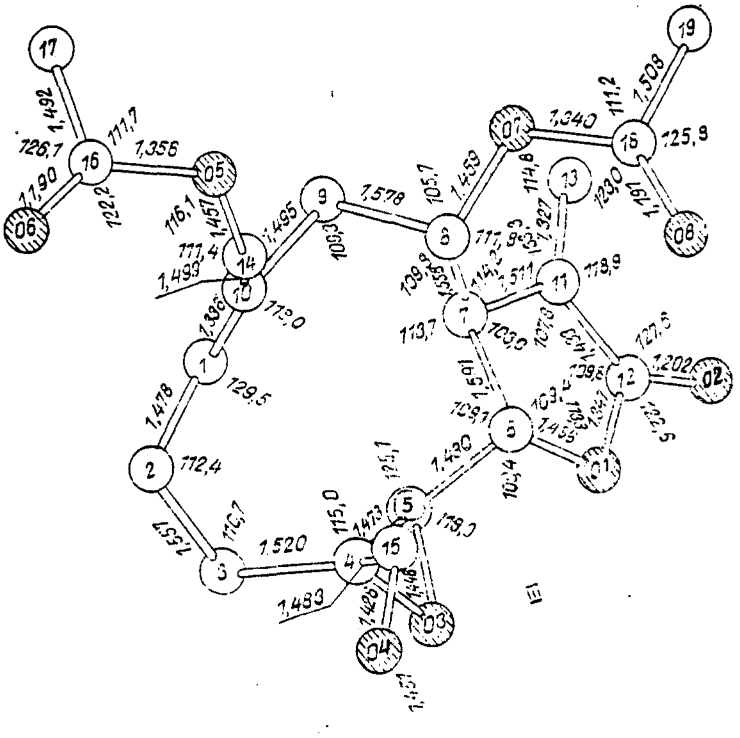


Fig. 3. Spatial structure of sachosin (III):

C1—C10—C14	123,3	C4—C5—O3	59.6
C5—C4—C15	122,1	C4—C15—O4	110,6
C5—C4—O3	59,4	C5—O3—C4	61,0
C3—C4—O3	116,1	C14—C10—C1	111.4
C3—C4—C15	117,2	C14—C10—C9	116,9
C15—C4—O3	108,8		

TABLE 2. Coordinates of the Nonhydrogen Atoms (×10^4) in the Structures of (I), (II), and (III)

Atom	I			II			III		
	x	y	z	x	y	z	x	y	z
C1	2253 (3)	2048 (3)	1592 (4)	456 (5)	6569 (5)	324 (0)	−2660 (9)	41 (6)	8057 (3)
C2	2327 (3)	2131 (4)	3059 (4)	28 (5)	7013 (6)	−253 (16)	−2929 (11)	−337 (7)	7426 (3)
C3	3120 (3)	1150 (3)	3520 (3)	539 (6)	7[illegible]58 (6)	462 (13)	−1318 (10)	102 (6)	6996 (3)
C4	4285 (3)	1161 (3)	2[illegible]0[illegible] (3)	700 (5)	7944 (5)	25[illegible]6 (14)	631 (10)	−19 ([illegible])	7292 (3)
C5	4325 (3)	511 (3)	1808 (4)	1369 (4)	7825 (5)	3089 (14)	1[illegible]5[illegible] (10)	957 (5)	7651 (3)
C6	5132 (3)	705 (3)	674 (3)	1283 (5)	7[illegible]5[illegible] ([illegible])	4984 (11)	2146 (10)	900 (6)	8204 (3)
C7	4478 (3)	731 (3)	−[illegible]57 (3)	1841 (4)	6942 ([illegible])	4827 (11)	1151 (10)	1193 (5)	8775 (3)
C8	4081 (3)	1928 (3)	−1187 (4)	1299 (4)	6019 (4)	4345 (13)	519 (10)	141 (6)	9143 (3)
C9	2876 (3)	2149 (3)	−702 (4)	919 (5)	5791 (5)	2336 (13)	−1729 (10)	23 (6)	9124 (3)
C10	2833 (3)	2695 (3)	726 (4)	383 (5)	6972 (4)	1778 (13)	−2300 (9)	−563 (5)	8553 (3)
C11	5320 (3)	114 (3)	−1540 (3)	2287 (4)	7142 (4)	6732 (11)	2296 (9)	2091 (5)	90[illegible]3 (3)
C12	6038 (3)	−605 (3)	−6[illegible]5 (4)	2346 (4)	7914 (4)	7423 (12)	3924 (11)	2393 (5)	8695 (3)
C13	5138 (4)	141 (3)	−2827 (4)	2532 (5)	6739 (5)	7786 (13)	2012 (12)	2680 (6)	9595 (3)
C14	3560 (3)	3726 (3)	1094 (4)	−419 (5)	5761 (5)	3038 (15)	−2221 (12)	−1821 (6)	8557 (3)
C15	5214 (3)	1970 (3)	3382 (3)	51 (5)	7922 (5)	3[illegible]62 (15)	1304 (11)	−1174 (5)	7426 (3)
C16							−5266 (10)	−2422 (6)	8924 (3)
C17							−6293 (12)	−2[illegible]55 (7)	9411 (3)
C18							2863 (9)	52 (6)	9909 (3)
C19							3220 (11)	84 (8)	10582 (3)
O1	5028 (2)	−294 (2)	551 (2)	1885 (3)	8122 (3)	6307 (9)	3867 (7)	1770 (4)	8181 (2)
O2	6737 (2)	−1305 (2)	−1005 (3)	2737 (3)	8362 (3)	8766 (9)	5128 (9)	3095 (5)	8783 (3)
O3	3207 (2)	1253 (2)	4994 (2)	1809 (3)	5342 (3)	4599 (9)	2125 (8)	721 (4)	7070 (2)
O4				−19 (3)	8548 (3)	3685 (10)	1402 (8)	−1824 (4)	6835 (2)
O5							−3377 (7)	−2289 (4)	9013 (2)
O6							−5945 (10)	−2178 (6)	8440 (3)
O7							1016 (7)	241 (4)	9781 (2)
O8							4039 (9)	−117 (5)	9530 (3)

and the carbonyl groups of the lactone ring participate in H-bonds with the distances O3...O2 (−x, 1/2 + y, 1/2 − z) of 2.92 A (I) and O4...O2 (−x, 1/2 + y, 1/2 − z) of 2.83 Å (III); these bonds create continuous chains of molecules along the b axis. In the crystal structure of (II) two groups of intermolecular H-bonds are observed. The hydroxy groups (at the C15 atoms), bound by a 6_1 screw axis participating in O4...O4 H-bonds (x − y, x, 1/6 + z) 2.74 Å, form continuous chains of molecules along the c axis. The second hydroxy group (at C8) and the carbonyl group in the lactone ring of the molecule, by a derived 3_1 screw axis, also form a O3...O2 H-bond (−y, x − y, 1/3 + z), 2.82 Å.

EXPERIMENTAL

Crystals of (I) and (III) were grown from acetone, and crystals of (II) from a mixture of chloroform and acetone in a ratio of 1:3.

The space groups and parameters of the elementary cells were established by the photographic method and were refined on a Syntex-$P2_1$ (I): diffractometer a = 11.413(2), b = 11.561(1), c = 10.220(2) Å; (III): a = 6.987(3), b = 11.912(4), c = 22.112(3) Å, space group for (I) and (III) $P2_12_12_1$, z = 4; for (II): a = b = 18.570(1), c = 7.035(2) Å; space group $P6_1$, z = 6.

In the calculations we used 997 (I), 950 (II), and 1245 (III) independent nonzero reflections. The structures were interpreted by the direct method using the Rentgen-75 program [14] in the automatic regime and were refined by the method of least squares (MLS) first in the isotropic and then in the anisotropic approximation to R = 0.090 (I), 0.108 (II), and 0.093 (III). Difference series enabled all the hydrogen atoms to be found for the (I), (II), and (III) molecules.

The final values of the divergence factors after four iterations of MLS taking the H atoms into account (without refinement) were 0.049 (I), 0.099 (II), and 0.081 (III). The coordinates of the basis atoms are given in Table 2.

SUMMARY

The spatial structures of three germacrolides − hanphyllin, salonitenolide, and the new sesquiterpene lactone sachosin − have been established by the method of x-ray structural analysis; they have the chair-chair conformation with a configuration ${}_1D^{14}$, ${}^{15}D_5$ type.

LITERATURE CITED

1. M. K. Makhmudov, B. Kh. Abduazimov, B. Tashkhodzhaev, B. T. Ibragimov, and M. R. Yagudaev, Khim. Prir. Soedin., 59 (1988).
2. M. K. Makhmudov, B. Kh. Abduazimov, B. Tashkhodshaev, and B. T. Ibragimov, Khim. Prir. Soedin., 207 (1989).
3. V. A. Tarasov, N. D. Abdullaev, Sh. Z. Kasymov, and G. P. Sidyakin, Khim. Prir. Soedin., 263 (1976).
4. S. Kh. Zakirov, Sh. Z. Kasymov, and G. P. Sidyakin, Khim. Prir. Soedin., 656 (1975).
5. M. Suchy, Z. Samek, V. Herout, and F. Šorm, Coll. Czech. Chem. Commun., 32, 2016 (1976).
6. Z. Samek and J. Havmatha, Coll. Czech. Commun., 43, 2779 (1978).
7. H. O. Fischer, N. H. Fischer, R. W. Franek, and E. J. Oliver, Prog. Chem. Org. Nat. Prod., 89 (1979).
8. M. Calleri, G. Chiari, and P. Viterbo, J. Chem. Soc. Perkin Trans. I, 2027 (1983).
9. M. K. Makhmudov, B. Tashkhodzhaev, A. I. Saidkhodzhaev, M. R. Yagudaev, and V. M. Malikov, Khim. Prir. Soedin., 436 (1986).
10. G. Appendino, M. Calleri, and G. Chiari, J. Chem. Soc. Perkin Trans. II, 205 (1986).
11. K. Tori, J. Horibe, I. Tamura, K. Kyriama, H. Tada, and K. Takeda, Tetrahedron Lett., 5, 387 (1976).
12. A. B. Hendrickson, J. Am. Chem. Soc., 83, 4537 (1961).
13. F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, and R. Taylor, J. Chem. Soc. Perkin Trans. II, 51 (1987).
14. V. I. Andrianov, Z. Sh. Safina, and B. L. Tarnopol'skii, Zh. Strukt. Khim., 15, 911 (1974).