STRUCTURE OF THE Z,Z-GERMACRANOLIDE
1(10)Z,4Z-HANPHYLLIN

T. T. Edil'baeva, K. M. Turdybekov, N. M. Gafurov,
S. M. Adekenov, and Z. M. Muldakhmetov

The spatial structure of 1(10)Z,4Z-hanphyllin has been established by the x-ray method. A new conformation of the ten-membered ring in Z,Z-germacranolides has been found — the $_{15}D_{5,1}D_{14}$ boat-boat type. The probabilities of the realization of the conformers of this compound and of its C3-epimer have been calculated by the method of molecular mechanics.

Germacranolides, which contain a ten-membered carbocycle, are, in the structural respect, the most interesting class of sesquiterpene γ-lactones. The numerically smallest subgroup among the germacranolides is that of the Z,Z-isomers [1]. For this reason, the stereochemistry of these compounds has scarcely been investigated. In view of the absence of reports on the interconversion of isomeric germacranolides, we decided to obtain new isomers photochemically from known E,E-isomers and, in particular, from hanphyllin (1) [2].

When a solution of (1) was irradiated with the light of a high-pressure mercury lamp, the crystalline substance (2) was obtained:
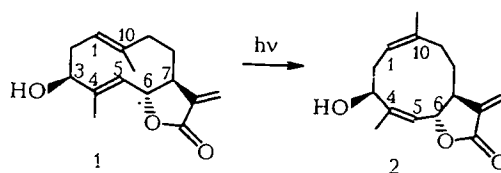
Analysis of PMR results (see the Experimental part) showed that compound (2) was a germacranolide analogous in structure to the initial (1). In order to determine the orientation of the OH group at the C3 atom of the (2) molecule more accurately and also to establish the conformations of the rings, we carried out an x-ray investigation.

The structure of the molecule is shown in Fig. 1. The bond lengths (Table 1) in the two crystallographically independent molecules (2a) and (2b) have the usual values [3]. The valence angles (Table 2) also differ insignificantly from the ideal values for sp^3- and sp^2-hybridized atoms, except for the angles C6C7C11 (101.9 and 100.6°) and C2C3C4 (121.6 and 121.2°).

As can be seen from Fig. 1, in the (2) molecule the conformation along the two double bonds C1=C10 and C4=C5 is *cis* (the torsional angles C2C1C10C9 are 2 and 1° and C3C4C5C6 −1 and −3° in the two crystallographically independent molecules (2a) and (2b), respectively). The ten-membered and lactone rings are linked in the *trans* manner (the torsional angles H6C6C7H7 are −102° (2a) and −97° (2b)). The hydroxy group at C3 has the β-orientation. Thus, compound (2) is a stereoisomer of hanphyllin and is 3β-hydroxy-6β,7αH-germacra-1(10)Z,4Z,11(13)-trien-6,12-olide.

The conformation of the lactone ring in (2) is intermediate between a 6α,7β-half-chair and a 7β-envelope (ΔC_2^{12} = 4.3°; C_5^7 = 5.6° (2a) and C_2^{12} = 7.3°; C_5^7 = 5.4° (2b)) (the torsional angles are given in Table 3). In the ten-membered 1,5-dienic ring the methyl groups at the C4 and C10 atoms have the α-*syn*-orientation, and the pseudotorsional angle C10C1C4C5 in (2a) and (2b) is 8°. Analysis of literature figures on the crystal structures of Z,Z-germacronolides has shown

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TABLE 1. Bond Lengths (Å) in Structure (2)

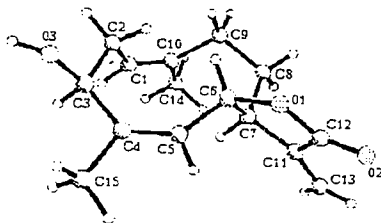| Bond	2 a	2 b	Bond	2 a	2 b
O1–C6	1.451(9)	1.47(1)	C5–C6	1.52(1)	1.52(1)
O1–C12	1.335(9)	1.38(1)	C6–C7	1.54(1)	1.54(1)
O2–C12	1.18(1)	1.22(1)	C7–C8	1.53(1)	1.54(1)
O3–C3	1.44(1)	1.42(1)	C7–C11	1.47(1)	1.50(1)
C1–C2	1.50(1)	1.50(1)	C8–C9	1.52(1)	1.53(1)
C1–C10	1.30(1)	1.35(1)	C9–C10	1.50(1)	1.50(1)
C2–C3	1.52(1)	1.56(1)	C10–C14	1.54(1)	1.48(1)
C3–C4	1.51(1)	1.49(1)	C11–C12	1.52(1)	1.46(2)
C4–C5	1.29(1)	1.34(1)	C11–C13	1.33(1)	1.34(1)
C4–C15	1.51(1)	1.51(1)			

Fig. 1. Structure of the 1(10)Z,4Z-haphyllin molecule.

that the ten-membered dienic ring in the molecules of longicornin A and melrosin A, studied previously, assume a conformation of the $_{15}D_5,^1D^{14}$ chair-chair type [4, 5]. Thus, in the (2) molecule we have observed experimentally a conformation of the ten-membered ring that is new for Z,Z-germacronolides — the $_{15}D_5,_1D_{14}$ boat-boat type [6].

To determine the relative stabilities of these two conformers in the Z,Z-germacranolides, we calculated the two conformers of the (2) molecule and its C3-epimer (3) by the method of molecular mechanics [7].

It was found that the difference in conformational energies (ΔE) for the conformers of the $_{15}D_5,^1D^{14}$ chair-chair type and of the $_{15}D_5,_1D_{14}$ boat-boat type was 0.6 kcal/mole in (2) and 2.0 kcal in (3), while for both (2) and (3) the chair-chair conformer proved to be more favorable than the boat-boat conformer. The probability of the realization of the chair-chair conformer in (2) was 73% and in (3) 97% (without taking the entropy factor into account).

A comparison of the geometries of the conformers of the (3) molecule shows that the conformation of the $_{15}D_5,^1D^{14}$ chair-chair type is more favorable basically because of the equatorial position of the α-oriented C3 hydroxy group. In the $_{15}D_5,_1D_{14}$ boat-boat type of conformation, because of the axial orientation of the C3-OH group steric repulsion arises between the C15-Me group and this hydroxy group. For this reason, the probability of the realization of such a conformer in the (3) molecule is substantially less than in the (2) molecule, which shows a considerable dependence of the conformational equilibrium in the Z,Z-germacranolides on the presence of any substituents in the main skeleton.

EXPERIMENTAL

Preparation of 1(10)Z,4Z-Hanphyllin. A solution of 300 mg (1.2 mmole) of (1) in 50 ml of acetone was irradiuated with the light of a high-pressure mercury lamp in an atmosphere of argon at room temperature for 16 h. After elimination of the solvent, 310 mg of a mixture of substances was obtained. This was chromatographed on a column containing 9 g of silica gel. Elution with hexane—ethyl acetate (2:3) led to the isolation of 45 mg (15%) of crystalline substance (2) with mp 110-112°C.

PMR spectrum (CHCl$_3$, TMS, ppm): 1.70 (s, 3H, 14-3H); 1.72 (d, 3H, 15-3H, J = 1.5 Hz); 4.28 (q, 1H, 6-H, J_1 = 8.0 Hz, J_2 = 7.0 Hz); 5.10 (m, 1H, 3-H); 5.15 (br.dd, 1H, 5-H, J_1 = 8 Hz, J_2 = 1.5 Hz); 5.60 (br.dd, 1H, 1-H, J_1 = 3 Hz, J_2 = 9.5 Hz); 5.52 (d, 1H, J = 2.0 Hz) and 6.21 (d, 1H, J = 2.5 Hz).

X-Ray Structural Investigation of (2). The cell parameters and the intensities of 2810 independent reflections were measured on a Siemens P3/PC automatic four-circle diffractometer with monochromatized Mo-K$_\alpha$ radiation, $\theta/2\theta$ scanning,

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

Angle	2a	2b	Angle	2a	2b
C6–O1–C12	112.6(6)	108.8(7)	C6–C7–C11	101.9(6)	100.6(7)
C2–C1–C10	128.5(7)	128.2(9)	C8–C7–C11	111.8(7)	111.9(7)
C1–C2–C3	115.5(6)	114.1(7)	C7–C8–C9	113.9(7)	114.0(7)
O3–C3–C2	109.3(6)	109.6(7)	C8–C9–C10	114.4(7)	112.0(8)
O3–C3–C4	106.5(7)	103.7(7)	C1–C10–C9	125.7(7)	122.9(9)
C2–C3–C4	121.6(7)	121.2(7)	C1–C10–C14	120.0(8)	119.0(9)
C3–C4–C5	129.5(8)	129.3(7)	C9–C10–C14	114.2(7)	118.1(8)
C3–C4–C15	111.2(7)	113.0(7)	C7–C11–C12	107.9(6)	108.3(8)
C5–C4–C15	119.3(8)	117.7(8)	C7–C11–C13	130.5(8)	127.4(10)
C4–C5–C6	134.6(8)	130.8(7)	C12–C11–C13	121.5(8)	124.3(10)
O1–C6–C5	107.5(6)	108.4(6)	O1–C12–O2	124.6(7)	120.4(9)
O1–C6–C7	104.9(6)	106.7(6)	O1–C12–C11	107.0(6)	109.4(8)
C5–C6–C7	114.6(6)	112.2(7)	O2–C12–C11	128.4(7)	130.1(9)
C6–C7–C8	114.3(6)	110.5(7)			

TABLE 3. Torsional Angles (degrees) in the Rings of Structure (2)

Angle	2a	2b	Angle	2a	2b
C10C1C2C3	−129.0	−128.8	C8C9C10C1	104.1	108.4
C1C2C3C4	75.1	60.2	C9C10C1C2	2.4	0.5
C2C3C4C5	12.6	26.1			
C3C4C5C6	−0.6	−3.0	O1C6C7C11	23.5	24.2
C4C5C6C7	−96.4	−106.0	C12O1C6C7	−18.6	−18.0
C5C6C7C8	145.1	147.2	C6O1C12C11	5.3	3.5
C6C7C8C9	−60.5	−61.5	C7C11C12O1	11.0	12.9
C7C8C9C10	−48.8	−44.4	C6C7C11C12	−21.0	−22.4

TABLE 4. Coordinates of the Atoms ($\times 10^4$; for H, $\times 10^3$) in Structure (2)

Atom	2a			2b		
	x	y	z	x	y	z
O1	1753(7)	8201(4)	352(2)	−227(8)	2903(5)	1945(2)
O2	3174(7)	6795(5)	565(2)	1595(10)	2807(7)	2572(3)
O3	−114(8)	12043(5)	275(2)	2714(9)	3292(5)	375(2)
C1	−2989(10)	10282(7)	956(3)	4633(10)	5095(7)	1316(3)
C2	−2078(10)	10758(6)	532(3)	4351(10)	4143(8)	1009(3)
C3	−536(11)	11347(6)	670(3)	−2859(11)	4223(6)	653(3)
C4	1019(10)	10791(6)	813(3)	−1176(10)	4400(6)	846(3)
C5	1398(10)	9823(6)	767(3)	−547(10)	4164(6)	1289(3)
C6	527(10)	8873(6)	568(3)	−1336(10)	3688(6)	1744(3)
C7	−320(10)	8207(6)	967(3)	−1611(10)	4490(7)	2159(3)
C8	−1916(10)	7705(7)	797(3)	−3160(10)	4229(8)	2456(3)
C9	−3220(10)	8477(6)	642(3)	−4726(11)	4240(9)	2148(3)
C10	−3496(9)	9338(7)	1005(3)	−4808(10)	5165(8)	1811(3)
C11	941(10)	7430(6)	1078(3)	−88(13)	4336(8)	2461(3)
C12	2106(10)	7392(6)	641(3)	549(13)	3305(9)	2358(3)
C13	1103(11)	6793(7)	1462(3)	582(14)	5002(9)	2783(3)
C14	−4401(10)	9005(8)	1481(3)	−5066(13)	6197(8)	2037(4)
C15	2254(12)	11532(8)	1030(4)	−43(13)	4875(7)	465(3)
HO3	−69(10)	1266(6)	27(3)	−348(9)	327(6)	24(3)

$2\theta \leq 50°$. Crystals rhombic, $a = 8.190(2)$, $b = 12.920(3)$, $c = 26.994(5)$ Å, $V = 2856.4(1.8)$ Å^3, $d_{calc} = 1.335$ g/cm^3, $Z = 8$ ($C_{15}H_{18}O_3$), sp.gr. $p2_12_12_1$.

In the calculation we used 1999 reflections with $I \geq 3\sigma$. The structure was interpreted by the direct method and was refined by the full-matrix MLS in the anisotropic approximation for the nonhydrogen atoms. The H-atoms were given geometrically, with the exception of the hydrogens of the hydroxy groups, which were revealed in a difference synthesis and were refined isotropically. The final divergence factors were $R = 0.076$ and $R_w = 0.078$. The coordinates are given in Table 4. All the calculations were performed on an IBM PC/AT computer using the Siemens program package SHELXTL (PC Version).

The calculations by the method of molecular mechanics were done by means of an MMX program adapted for the IBM PC/AT.

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