

**STRUCTURE OF 18-DE(HYDROXYMETHYL)-3-O-3';
3-O-18'-DILAGOHIRSIN — A PRODUCT OF THE
DEHYDRATION OF LAGOCHILIN**

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The structure of a dimeric dehydration product of the diterpenoid lagochilin — 18-de(hydroxymethyl)-3-O-3';3-O-18'-dilagohirsin — has been investigated by PMR spectroscopy and x-ray structural analysis. It has been established that the molecule of this compound has an unsymmetrical dimeric linkage of two fragments of the lagohirsin molecule with the participation of the C3 and C4 carbon atoms of one of them. An analysis of the structure of the "dimer" permitted the hypothesis that the condensation of two lagohirsin molecules took place with the elimination of one molecule of water and one molecule of methyl alcohol.

Plants of the *Lagochilus* genus contain diterpenoids of the labdane series. Lagochilin (1), lagohirsin (2), and isomeric acetyl derivatives of lagochilin have been isolated from various species of this genus [1—6]. An effective hemostatic preparation has been created from the diterpene lactone (2) [7]. The level of compound (2) in species of *Lagochilus* is very low (0.1—0.2%), with 1—2% of (1). With the aim of obtaining (2) from (1), we dehydrogenated the latter with Raney nickel and obtained a mixture of compounds: (2) (15—20%), anhydrolagochilin (3) (4—5%), and 3,16,18-trihydroxy-9,13-epoxy-15-methylabdane (4) (10—15%). A deep study of the by-products of the dehydrogenation of lagochilin led to the isolation of another minor dehydro product (5) with mp 256—258°C. Compound (5) did not change on being treated with dilute acids, but with alkalis it underwent hydrolysis. Under the action of acids the hydrolysis product re-formed the initial substance (5). Consequently (5) has a lactone ring. In view of the fact that compound (5) has a higher molecular mass (654) than known derivatives of (1) and differs considerably in its physicochemical constants, we investigated the structure of (5) by PMR spectroscopy and x-ray structural analysis (Tables 1—4).

The PMR spectrum of (5) was taken for solutions in CDCl₃ and pyridine-d₅. The most informative spectrum proved to be that taken in pyridine, from which it clearly followed that the compound is a dimer consisting of two lagohirsin fragments. In actual fact, two pairs of doublets at 2.68 and 2.22 and at 2.57 and 2.22 ppm with the constant J = 17.0 Hz related to geminal pairs of protons adjacent to the carbonyls of lactone rings [6]. Another two pairs of geminal protons of lactone rings formed AB systems of signals at 4.12 and 3.67 ppm and at 3.98, and 3.75 ppm with the constant J = 8.5 Hz. Yet another two doublets were observed in the PMR spectrum at 3.14 and 2.71 ppm with the constant J = 11.6 Hz, forming an AB system characteristic for methylene protons adjacent to the C18 atom [3]. However, the higher value of this constant in comparison with (2) showed that this methylene group participated in the formation of a ring. A broad singlet (ΔW = 7.5 Hz) at 3.33 ppm was, from the value of its chemical shift, characteristic for H₃; however, the width of the signal showed its equatorial orientation, in contrast to (2) itself. In the region of methyl signals, 0.2—0.7 ppm, a large number of peaks of CH₃ groups incapable of interpretation was observed.

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TABLE 1. Bond Lengths d (Å) and Valence Angles ω (degrees) of the (5) Molecule

Bond	d	d'	Angle	ω	ω'
O1-C13	1.446(14)	1.416(13)	C13-O1-C9	113.8(8)	112.5(8)
O1-C9	1.455(13)	1.471(12)	C15-O3-C16	111.5(14)	108.9(11)
O2-C15	1.21(2)	1.23(2)	C10-C1-C2	112.4(9)	113.0(10)
O3-C15	1.36(2)	1.38(2)	C3-C2-C1	107.9(10)	110.9(10)
O3-C16	1.44(2)	1.45(2)	O4-C3-C2	115.0(9)	105.0(9)
O4-C3	1.409(12)	1.451(12)	O4-C3-C4	106.6(8)	111.9(8)
C1-C10	1.53(2)	1.54(2)	C2-C3-C4	109.7(9)	113.2(10)
C1-C2	1.58(2)	1.52(2)	C19-C4-C3	110.3(10)	110.6(9)
C2-C3	1.52(2)	1.51(2)	C19-C4-C5	111.6(9)	114.6(10)
C3-C4	1.53(2)	1.52(2)	C3-C4-C5	109.0(8)	111.7(9)
C4-C19	1.53(2)	1.57(2)	C6-C5-C4	112.9(9)	113.3(9)
C4-C5	1.57(2)	1.58(2)	C6-C5-C10	111.1(9)	111.7(10)
C5-C6	1.54(2)	1.53(2)	C4-C5-C10	111.9(8)	113.5(8)
C5-C10	1.581(14)	1.60(2)	C7-C6-C5	109.8(11)	109.2(10)
C6-C7	1.52(2)	1.51(2)	C8-C7-C6	116.0(11)	114.0(11)
C7-C8	1.51(2)	1.52(2)	C17-C8-C7	109.9(13)	109.1(11)
C8-C17	1.52(2)	1.57(2)	C17-C8-C9	114.0(11)	116.2(11)
C8-C9	1.56(2)	1.53(2)	C7-C8-C9	110.8(10)	113.7(10)
C9-C11	1.51(2)	1.53(2)	O1-C9-C11	106.3(11)	102.9(9)
C9-C10	1.61(2)	1.595(14)	O1-C9-C8	107.4(9)	106.5(8)
C10-C20	1.56(2)	1.56(2)	C11-C9-C8	112.6(10)	114.8(10)
C11-C12	1.56(3)	1.49(2)	O1-C9-C10	107.8(8)	107.2(8)
C12-C13	1.48(3)	1.53(2)	C11-C9-C10	112.0(10)	113.6(9)
C13-C14	1.52(2)	1.54(2)	C8-C9-C10	110.3(9)	111.0(10)
C13-C16	1.52(2)	1.55(2)	C1-C10-C20	109.7(11)	109.4(9)
C14-C15	1.43(3)	1.45(2)	C1-C10-C5	108.1(9)	107.9(9)
C18'-C4'	1.53(2)		C20-C10-C5	112.2(10)	114.4(9)
O4'-C3	1.443(12)		C1-C10-C9	109.6(9)	112.0(9)
O4-C18'	1.453(12)		C20-C10-C9	110.2(10)	106.4(9)
			C5-C10-C9	106.9(8)	106.8(8)
			C9-C11-C12	103.4(14)	107.5(11)
			C13-C12-C11	108.9(13)	103.0(9)
			O1-C13-C12	104.0(13)	106.4(10)
			O1-C13-C14	111.1(11)	112.3(10)
			C12-C13-C14	115(2)	115.1(11)
			O1-C13-C16	110.2(11)	112.0(9)
			C12-C13-C16	114(2)	110.3(11)
			C14-C13-C16	102.5(13)	100.9(11)
			C15-C14-C13	108(2)	103.1(12)
			O2-C15-O3	115(2)	119(2)
			O2-C15-C14	135(2)	129(2)
			O3-C15-C14	109(2)	111.7(13)
			O3-C16-C13	105.8(14)	104.1(10)
			O4-C18'-C4'	113.0(9)	
			C3-O4'-C3'	115.3(8)	
			C3-O4-C18'	112.3(8)	
			O4-C3-O4'	110.4(8)	
			O4'-C3-C2	108.9(9)	
			O4'-C3-C4	105.9(8)	
			C3'-C4'-C18'	106.4(9)	
			C18'-C4'-C19'	104.7(9)	
			C18'-C4'-C5'	108.1(9)	

A prime denotes the second half of the molecule.

TABLE 2. Coordinates of the Nonhydrogen Atoms (10^4) and Equivalent Isotropic Temperature Factors ($\text{\AA}^2 \times 10^3$)

Atom	x	y	z	U_{eq}
O1	2645(6)	6901(4)	4912(4)	55(2)
O2	2251(14)	9352(9)	3840(8)	149(6)
O3	3099(13)	8939(7)	4801(8)	116(4)
O4	1285(6)	7062(4)	6935(3)	48(2)
O1'	-2249(6)	6344(4)	8260(3)	49(2)
O2'	-4526(14)	3997(7)	7855(8)	142(5)
O3'	-2769(11)	4260(6)	8429(6)	94(3)
O4'	1668(6)	6247(4)	7899(3)	48(2)
C1	3639(11)	6630(7)	6306(6)	55(3)
C2	3343(10)	6479(8)	7103(6)	58(3)
C3	1960(8)	6407(6)	7177(6)	48(3)
C4	1504(9)	5687(7)	6764(6)	51(3)
C5	1800(9)	5813(6)	5970(6)	46(3)
C6	1300(13)	5143(8)	5502(7)	68(3)
C7	1535(12)	5338(8)	4739(6)	62(3)
C8	2851(12)	5530(7)	4548(6)	63(3)
C9	3373(10)	6193(7)	5032(6)	55(3)
C10	3219(9)	5949(7)	5840(6)	54(3)
C11	4680(12)	6407(11)	4857(8)	83(5)
C12	4551(24)	7212(15)	4470(14)	137(10)
C13	3345(12)	7560(8)	4641(7)	70(3)
C14	2688(22)	7949(11)	4029(9)	106(7)
C15	2579(16)	8777(13)	4172(12)	105(6)
C16	3395(18)	8225(9)	5179(10)	91(5)
C20	3996(15)	5193(11)	6003(9)	83(5)
C17	2940(19)	5717(10)	3774(8)	91(5)
C19	127(11)	5563(8)	6886(6)	61(3)
C18'	1484(11)	7762(6)	7360(6)	49(3)
C1'	35(9)	6429(7)	9068(6)	55(3)
C2'	1408(11)	6608(8)	9077(6)	61(3)
C3'	1834(10)	6909(7)	8374(5)	51(3)
C4'	1140(10)	7639(7)	8130(6)	56(3)
C5'	-300(9)	7518(7)	8174(6)	48(3)
C6'	-1031(11)	8257(7)	7970(8)	61(3)
C7'	-2378(12)	8046(8)	7913(7)	66(3)
C8'	-2905(12)	7657(8)	8564(7)	63(4)
C9'	-2168(10)	6942(7)	8816(5)	53(3)
C10'	-752(9)	7160(7)	8907(5)	51(3)
C11'	-2715(11)	6515(7)	9447(7)	58(3)
C12'	-3486(13)	5855(8)	9177(8)	71(4)
C13'	-2878(10)	5654(7)	8477(6)	59(3)
C14'	-3758(15)	5337(8)	7909(9)	85(5)
C15'	-3773(16)	4495(9)	8041(8)	88(5)
C16'	-2000(12)	4941(8)	8563(8)	75(4)
C20'	-678(13)	7752(8)	9534(6)	61(3)
C17'	-4321(13)	7525(9)	8460(8)	73(4)
C19'	1630(13)	8399(7)	8514(7)	59(3)

TABLE 3. Endocyclic Torsional Angles, (ψ , degrees)

Angle	ψ	ψ'
C10-C1-C2-C3	-61.50	-60.99
C1-C2-C3-C4	63.02	56.85
C2-C3-C4-C5	-62.14	-50.78
C3-C4-C5-C10	57.50	48.08
C4-C5-C10-C1	-54.08	-50.02
C2-C1-C10-C5	55.89	56.38
C10-C5-C6-C7	-57.69	-59.51
C5-C6-C7-C8	53.80	54.61
C6-C7-C8-C9	-52.75	-52.58
C7-C8-C9-C10	54.46	52.62
C8-C9-C10-C5	-58.64	-54.74
O1-C9-C11-C12	-12.95	-21.15
C13-O1-C9-C11	2.64	5.49
C9-O1-C13-C12	9.54	11.68
C11-C12-C13-O1	-17.68	-24.13
C9-C11-C12-C13	19.35	27.80
C16-C13-C14-C15	8.92	30.86
C13-C14-C15-O3	0.12	-19.50
C16-O3-C15-C14	-10.11	-1.64
C15-O3-C16-C13	15.73	22.11
C14-C13-C16-O3	-14.28	-32.26
C18'-O4-C3-O4'	56.13	
C3'-O4'-C3-O4	-55.13	
C3-O4'-C3'-C4'	53.84	
C3-O4-C18'-C4'	-58.55	
O4-C18'-C4'-C3'	53.35	
O4'-C3'-C4'-C18'	-50.10	

A prime indicates the second half of the molecule.

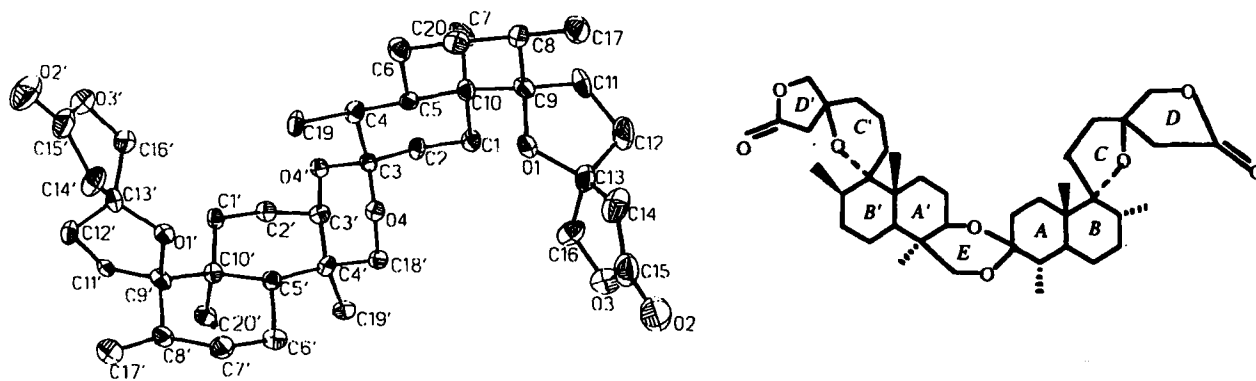


Fig. 1. Conformation of the (5) molecule and numbering of the atoms.

Thus, the two sets of signals of lactone rings witnessed the dimeric nature of the (5) molecule, while the presence of one H_3 signal and of one C18' methylene group shows that the dimeric linkage took place with the participation of the C3 and C4 carbon atoms of one molecule and that the dimer has an unsymmetrical nature. The structure of (5) was shown definitively by x-ray structural analysis.

TABLE 4. Asymmetry Parameters for all the Rings of the (5) Molecule

Ring	A	B	C	D	A'	B'	C'	D'	E
ΔC_s	2.6	2.3	2.7	1.3	4.2	0.2	7.2	2.1	2.8
	C3	C10	C12	C16	C2'	C5'	C12'	C13'	O4
ΔC_2	1.2	0.8	5.9	6.9	0.6	3.7	4.8	6.9	2.4
	C2-C3	C5-C10	O1	C14	C1'-C2'	C5'-C10'	O1'	C15'	C3-O4
$ \phi $	59.1	56.4	13.8	11.2	54.0	55.7	19.8	23.9	54.6

The x-ray structural analysis of (5) confirmed that the molecule has an unsymmetrical dimeric linkage of two fragments of the (2) molecule (Fig. 1). The conformation of the molecule and the numbering of the atoms are given in Fig. 1. Provisionally we may note that rings A, B, C, and D form the first part of the dimer, rings A', B', C', and D' the second part, and ring E the linking part. As also in (1), the six-membered cyclohexane rings A, B, A' and B' have a slightly distorted chair conformation, five-membered rings C, D, C', and D' - half chair [2]. Ring E has conformation of slightly distorted chair. The A/B, A'/B', and A'/E ring linkages are *trans*-. For all the rings, starting from the values of the endocyclic torsional angles (Table 3), we calculated the asymmetry parameters (Table 4) by means of the RING program [9].

In (1) and, correspondingly, in (2) the methyl group at the C4 atom is in the axial position, and the hydroxymethyl group in the equatorial position [2, 8, 9]. As can be seen from Fig. 1, an unsymmetrical linkage is observed at the C3, C3', and C4' atoms. The C4 atom of ring A does not participate in the linkage but it loses the hydroxymethyl group, and the C19H₃ group at the C4 atom changes from the axial to the equatorial position. The methyl group C19H₃ at the C4' atom is present in the axial position relative to ring A' and corresponds to the conformation of the (1) molecule in the pre-reaction state. Thus, in the first half of the molecule the methyl groups at the C10 and C4 atoms are present in the *trans*- position, whereupon the steric hindrance arising in consequence of the *cis*- position of the methyl groups at C10 and C4 that is characteristic for ring A in the (1) molecule [2] is eliminated. However, it is retained in the second half of the molecule.

The analysis of the structure of the (5) molecule permits the assumption that the condensation of two molecules of (2) took place with the elimination of one molecule of water and one molecule of methyl alcohol, to form 18-de(hydroxymethyl)-3-O-3';3-O-18'-dilagohirsin (5).

The bond lengths and valence angles (Table 1) vary within fairly wide limits, which is, to all appearances, characteristic for tri- and tetrasubstituted carbon atoms and may be due to steric factors.

The crystal structure of (5) is due solely to the van der Waals interaction of the molecules. No special features of packing are observed and all the intermolecular contacts are normal from the point of view of intermolecular radii [10].

EXPERIMENTAL

PMR spectra were taken on a Varian XL-100-15 spectrometer with a working frequency of 100 Hz. Hexamethyldisiloxane (HMDS) was used as an internal standard.

Chromatograms were revealed with a 10% solution of sulfuric acid in alcohol. The catalyst was Raney nickel activated by a standard method [11].

The compositions of mixtures of substances and the individuality of compounds were monitored in a fixed layer of type L5/40 silica gel with 13% of gypsum in the solvent systems: 1) diethyl ether—acetone (15:1); and 2) chloroform—acetone (4:1).

Crystals suitable for x-ray structural analysis were grown from solution in acetone with slow evaporation for 3 days. The crystallographic parameters of a single crystal were determined and were refined for 15 reflections on a Syntex P2₁ four-circle diffractometer: $a = 10.886(2)\text{\AA}$, $b = 16.915(3)\text{\AA}$, $c = 19.135(4)\text{\AA}$, $V = 3523.5(12)\text{\AA}^3$, $Z = 4$, $\rho = 1.24\text{ g/cm}^3$, sp. gr. P2₁2₁2₁.

Integral intensities were measured by the $\theta/2\theta$ -scanning method using CuK $_{\alpha}$ radiation monochromatized from a graphite

crystal at room temperature. After Lorentz and polarization factors had been taken into account and weak reflections with $I < 2\sigma(I)$ had been discarded, the working group consisted of 2764 reflections. The structure was interpreted by the direct method with the aid of the SHELXS-86 packet of programs [12] and was refined by the SHELXL-93 full-matrix method of least squares [13]. All the hydrogen atoms of the molecule were localized with the help of difference Fourier syntheses. After the final stage of refinement of the position and anisotropic temperature parameters, the discrepancy factors amounted to $R_1 = 0.0847$ and $R_2 = 0.1239$ (for all reflections). The corresponding atomic coordinates are given in Table 2.

Dehydrogenation of (1). A solution of 5 g of (1) in 500 ml of toluene was treated with 15 g of activated Raney nickel. The reaction mixture was boiled for 3 h, the course of the reaction being monitored by TLC. After the end of the reaction the catalyst was filtered off. The resulting solution was extracted with 5% caustic soda solution and the extract was acidified with 20% sulfuric acid. The acidified solution was extracted with diethyl ether, and the ethereal extract was washed with 0.5% sodium hydrogen carbonate solution and then with distilled water. After the ether had been distilled off, the residue (3.8 g) was chromatographed on a column of LS100/160 μ m silica gel in a ratio of the total material and the sorbent of 1:50. Elution was performed with benzene, 500-ml fractions being collected. The first six fractions contained no substance. After elution with benzene—diethyl ether (100:1), the last fractions yielded compound (5) with R_f 0.72 (system 1), which was recrystallized from methanol, m.p. 256—258°C. Yield 0.2g.

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