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X-RAY STRUCTURE OF LAGOCHIRSIDINE AND DI-*o*-CYCLOHEXYLIDENELAGOCHILIN

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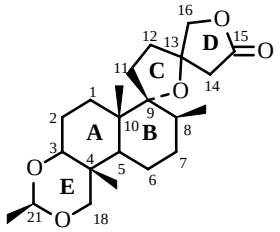
The structures of two diterpenoids from the lagochiline group, lagochirsidine and di-o-cyclohexylidenelagochilin, were determined by x-ray structure analysis.

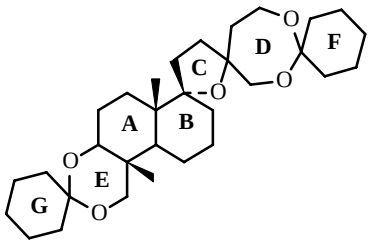
Key words: lagochilin, lagochirsidine, di-*o*-cyclohexylidenelagochilin, crystal structure, x-ray structure analysis.

Diterpenoids isolated from plants of the *Lagochilus* genus are highly physiologically active and can be used as starting materials to prepare highly effective medical preparations [1].

We report the x-ray structures of two diterpenoids of the lagochilin group, lagochirsidine (**1**) and di-*o*-cyclohexylidenelagochilin (**2**), because PMR spectral data using measurements of the nuclear Overhauser effect did not enable an unambiguous determination of the configuration of rings *E* and *D* or the methyls on C21 and C8 [2]. The first compound was isolated from the aerial part of thick-haired lagochilus; the second, via chemical synthesis from starting lagochilin.



1



2

The conformation of the molecules and the atomic numbering are shown in Figs. 1a and -b. We will arbitrarily consider rings *A*, *B*, and *C* to be the part of the molecules from the basic lagochilin skeleton; *D*, the five-membered ring of **1** and the seven-membered ring of **2**; *E*, the six-membered heterocycle *trans*-fused to ring *A* through atoms C3 and C4; *F* and *G*, the cyclohexane rings of **2**. Asymmetry parameters were calculated using the program RING [3] for a more accurate evaluation of the conformation of all rings (Table 1). These characterize the degree of deviation of a given conformation from the ideal one. Like in starting lagochilin [4], the six-membered cyclohexane rings *A* and *B* of these compounds have slightly distorted chair conformations (the values ΔC_S and ΔC_2 for both compounds are insignificant). The conformations of the five-membered *C* rings were refined by analyzing the asymmetry parameters: whereas the conformation in **1** is closer to a half-chair [smaller $\Delta C_2(O1) = 1.0^o$], that in **2** is closer to an envelope [$\Delta C_S(C12) = 4.6^o$]. Atoms C9, C11, C13, and O1 lie in a plane with a maximum least-squares deviation of 0.02 Å. Atom C12 deviates from this plane by 0.45 Å. The five-membered *D* ring (**1**) also has the envelope conformation [$\Delta C_S(C13) = 5.9^o$]. Atoms C14, C15, C16, and O4 lie in a plane with a maximum least-squares deviation of 0.02 Å. The deviation of C13 is 0.54 Å. The seven-membered *D* heterocycle (for **2**) has the half-chair conformation [$\Delta C_2(C21) = 1.2^o$]. Ring *E* is a slightly distorted chair owing to the presence of the heteroatoms. Substituted cyclohexane rings *F* and *G* are almost ideal chairs (extremely low values ΔC_S and ΔC_2). Rings *A*/*B* and *A*/*E* are *trans*-fused. The methyls on C4 and C10 in **1** and **2**, respectively, are axial. The methyl on C8 is equatorial.

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TABLE 1. Asymmetry Parameters for All Rings of **1** and **2**

Compound	Parameters	Ring						
		A	B	C	D	E	F	G
1	ΔC_2	4.2	1.8	1.0	10.1	1.5		
		C3-C4	C7-C8	O1	C15	C20-O3		
	ΔC_S	0.4	0.5	10.4	5.9	1.6		
		C3	C5	C12	C13	C3		
	φ	55.7	58.4	21.0	24.7	60.3		
2	ΔC_2	3.4	1.2	8.9	1.2	9.5	0.7	1.1
		C2-C3	C6-C7	O1	C21	C20-O3	C23-C24	C28-C29
	ΔC_S	2.4	0.4	4.6	32.6	6.3	0.9	0.8
		C3	C6	C12	C14	C3	C21	C29
	φ	57.1	59.0	21.1	70.4	56.2	56.6	55.0

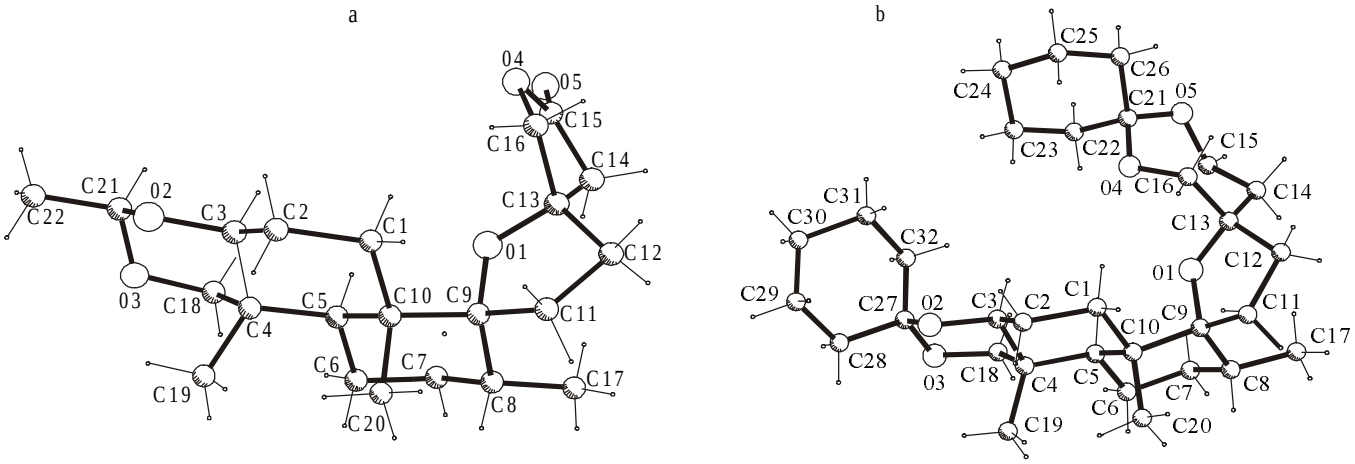

Fig. 1. Molecular structure of lagochirsidine (**1**, a) and di-*o*-cyclohexylidenelagochilin (**2**, b).

The crystal structures of lagochirsidine and di-*o*-cyclohexylidenelagochilin are determined by van-der-Waals interactions.

EXPERIMENTAL

The isolation and physicochemical properties of lagochirsidine have been reported [5].

Di-*o*-cyclohexylidenelagochilin. Lagochilin (1.2 g, 0.0034 mole) was dissolved in cyclohexanone (10 mL) and treated with 2-3 drops of conc. H_2SO_4. The reaction mixture was diluted after 24 h with H_2O:C_2H_5OH (7:3). The reaction products were extracted three times with benzene (30 mL). The benzene extracts were washed with $NaHCO_3$ solution (0.5%) and distilled water until the washings were neutral, dried over anhydrous Na_2SO_4, and filtered. The solvent was removed. The solid was chromatographed on a silica-gel column (150×1.5 cm) using benzene—ether with increasing ether content. Fractions (400 mL) 3-6 yielded after recrystallization from benzene:hexane (1:1) crystals of di-*o*-cyclohexylidenelagochilin, $C_{32}H_{52}O_5$, mp 156-158°C, yield 0.67 g (39%) of theoretical based on lagochilin.

IR spectrum (cm^{-1}): 2810-2990, 1420, 1340, 1250, 1140.

PMR spectrum (Varian XL100-15, HMDS, $CDCl_3$): 0.76 (d, 3H-17), 0.85 (s, 3H-20), 0.97 (s, 3H-19), 1.10-2.06 (protons of the basic skeleton), 3.38-3.90 (m, H-3, 2H-18, 2H-16).

TABLE 2. Coordinates of Nonhydrogen Atoms (10^4) in **1** and **2**

Atom	Lagochirsidine (**1**)			Di-*o*-cyclohexylidenelagochilin (**2**)		
	x/a	y/b	z/c	x/a	y/b	z/c
O1	2427 (5)	4399 (4)	9010 (3)	-183 (4)	2699 (3)	2065 (2)
O2	6305 (6)	116 (4)	8283 (3)	3883 (4)	-1437 (4)	1677 (2)
O3	5262 (6)	-1011 (4)	9070 (3)	2201 (4)	-2719 (4)	2366 (2)
O4	5379 (6)	5993 (4)	9254 (3)	2330 (4)	3167 (3)	2975 (2)
O5	4925 (6)	6373 (4)	10195 (3)	1149 (5)	4142 (4)	4212 (2)
C1	3851 (7)	3036 (5)	8054 (4)	2149 (6)	1563 (5)	962 (3)
C2	4945 (7)	1924 (5)	7879 (4)	3220 (6)	436 (5)	907 (3)
C3	5208 (7)	1114 (5)	8414 (4)	2810 (6)	-448 (5)	1649 (3)
C4	3562 (7)	630 (5)	8661 (4)	1292 (6)	-994 (5)	1509 (3)
C5	2493 (7)	1751 (5)	8831 (4)	211 (6)	197 (5)	1544 (3)
C6	889 (7)	1398 (5)	9149 (4)	-1390 (6)	-148 (5)	1500 (3)
C7	40 (7)	2542 (5)	9392 (4)	-2372 (6)	984 (5)	1703 (3)
C8	-332 (7)	3447 (5)	8895 (4)	-2089 (6)	2044 (5)	1036 (3)
C9	1319 (7)	3846 (5)	8588 (4)	-469 (6)	2391 (5)	1111 (3)
C10	2192 (7)	2685 (5)	8327 (4)	546 (6)	1258 (5)	853 (3)
C11	1013 (7)	4880 (5)	8126 (4)	-157 (6)	3573 (5)	579 (4)
C12	1353 (7)	6084 (5)	8454 (4)	-263 (6)	4605 (5)	1282 (3)
C13	2638 (7)	5694 (5)	8913 (4)	187 (6)	3979 (5)	2184 (4)
C14	2611 (7)	6344 (6)	9510 (4)	-695 (6)	4434 (5)	3029 (3)
C15	4363 (7)	6256 (6)	9712 (4)	-243 (6)	3764 (6)	3898 (3)
C16	4413 (7)	5987 (5)	8725 (4)	1793 (6)	4088 (5)	2349 (4)
C17	-1373 (7)	4551 (5)	9146 (4)	-3211 (7)	3111 (6)	1236 (4)
C18	4095 (7)	-53 (6)	9224 (4)	269 (6)	957 (6)	-170 (4)
C19	2747 (7)	-320 (6)	8240 (4)	1170 (7)	-1730 (6)	639 (4)
C20	1004 (7)	2168 (5)	7832 (4)	1073 (7)	-1757 (6)	2335 (4)
C21	6738 (7)	-543 (5)	8798 (4)	2392 (6)	3462 (5)	3910 (4)
C22	7842 (7)	-1601 (5)	8630 (4)	2579 (7)	2225 (6)	4393 (4)
C23				4047 (7)	1582 (6)	4125 (4)
C24				5330 (6)	2372 (5)	4330 (4)
C25				5120 (6)	3630 (6)	3867 (4)
C26				3670 (7)	4267 (5)	4146 (4)
C27				3650 (7)	-2304 (6)	2377 (4)
C28				4639 (6)	-3409 (6)	2121 (4)
C29				6256 (6)	-3109 (6)	2204 (4)
C30				6609 (6)	-2651 (6)	3145 (4)
C31				5621 (6)	-1507 (6)	3424 (4)
C32				4017 (6)	-1815 (6)	3332 (4)

Mass spectrum (*m/z*): 516 [M], 473, 418, 388, 386, 303, 278, 265, 252, 173, 167, 154, 149, 147, 137, 135, 133, 123.

Single crystals of lagochirsidine and di-*o*-cyclohexylidenelagochilin were grown from acetone containing CH_3CO_2H at room temperature by slow evaporation over 6-7 days.

The crystallographic parameters of the single crystals were determined and refined using 15 reflections on an automated four-circle Syntex $P2_1$ diffractometer. Unit-cell constants for lagochirsidine: a = 8.058(2), b = 10.891(3), c = 22.965(4) Å, V = 2015.5 Å^3, Z = 4, D_{calc} = 1.24 g/cm^3, space group $P2_12_12_1$; for di-*o*-cyclohexylidenelagochilin: a = 9.168(2), b = 10.919(3), c = 14.615(4) Å, γ = 87.92(2)°, V = 1462.1 Å^3, Z = 2, D_{calc} = 1.17 g/cm^3, space group $P2_1$.

Integrated intensities were measured by Θ/2Θ-scanning using graphite-monochromatized Cu Kα-radiation. The structure factors after Lorentz and polarization corrections and elimination of weak reflections with $I < 2\sigma(I)$ consisted of 1694 (**1**) and 2147 (**2**) reflections. The structures were solved by direct methods using the programs SHELXS-86 adapted to an IBM-386 PC [6].

The structures were refined using the programs SHELX-76 [7] loaded on the same PC. The H atoms were located using difference Fourier syntheses. The discrepancy factors after the final stage of refinement of positional and anisotropic thermal parameters were $R = 0.071$ (**1**) and 0.068 (**2**). Coordinates of nonhydrogen atoms are listed in Table 2.

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