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ANOLIDE – A NEW GUAIANOLIDE FROM *Achillea nobilis*

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The new sesquiterpene lactone anolide has been isolated from the epigeal part of Achillea nobilis. *From its spectral characteristics and the results of an x-ray structural investigation, the structure of 3α,4β-dihydroxy-1,5,7α(H),6β(H)-guaia-10(14),11(13)-dien-6,12-olide is proposed for anolide.*

The isolation of the sesquiterpene lactones anobin, estafiatin, and hanphyllin from *Achillea nobiis* L. has been reported previously [1]. In a further investigation of the components of the epigeal part of this plant, we have isolated from the total extractive substances a colorless crystalline compound with the composition $C_{15}H_{20}O_4$ (1), mp 167-169°C (from alcohol).

The IR spectrum of (1) contained absorption bands in the regions of 3550 (OH group), 1740 (γ-lactone carbonyl), and 1670 and 1640 cm^{-1} (C=C). The UV spectrum showed an absorption band with a maximum in the region of 204 nm (ε 18,321), which is characteristic for an exocyclic methylene group conjugated with a γ-carbonyl. In the ^{13}C NMR spectrum obtained under the conditions of complete and incomplete decoupling ("off resonance") from protons, the signals of 15 carbon atoms were detected. Of them, ten had sp^3 hybridization and five had sp^2 hybridization. The PMR spectrum of (1) contained the following signals (δ, ppm): 1.49 (2 H, s) – the protons of a methyl group geminal to a hydroxy group; 2.08 (2H, s) – the protons of hydroxy groups; 3.92 (1H, d, J = 3.5 Hz) – a hemihydroxylic proton; 4.23 (1 H, dd, J_1 = 11.5 and J_2 = 9.5 Hz) – a lactone proton; 4.92 (2H, d, J = 3.5 Hz) – the protons of a methylene group; and 5.47 and 6.17 (1 H each, d, J = 3.5 Hz) – the protons of an exocyclic methylene group conjugated with a γ-lactone carbonyl. The SSCC values of the lactone proton permitted the assumption of the *trans*-linkage of the lactone with the main carbon skeleton.

The acetylation of (1) gave a monoacetyl derivative with the composition $C_{17}H_{22}O_5$ (2), mp 183-185° C. The IR spectrum of (2) contained absorption bands in the regions of 3460 (OH group), 1740 (γ-lactone carbonyl), 1665 and 1640 (C=C), and 1250 cm^{-1}. The NMR spectrum of (2) contained the following signals (δ, ppm): 1.40 (3H, s) – the protons of a methyl group geminal to a hydroxy group; 2.02 (3 H, s) – the protons of an acetyl group; 4.24 (1 H, t, $J_1 = J_2$ = 10 Hz) – a lactone proton; 4.95 (1 H, m) – a hemiacyl proton; and 5.46 and 6.17 (1 H each, d, J = 3.5 Hz) – the protons of an exocyclic methylene group conjugated with a γ-lactone carbonyl. Analysis of the PMR spectrum of the acetyl derivative of (1) showed that (1) contained two hydroxy groups, one of them being secondary and the other tertiary and geminal to one of the methyl groups.

To determine the positions of the hydroxy groups in the molecule of (1) and to establish its relative configuration, we carried out an x-ray structural investigation. The general form of the (1) molecule is shown in Fig. 1. The lengths of the bonds and the valence angles are the usual ones and are close to the corresponding values in the structures of solstitialin (3 [2]), 3-oxograndolide (4) [3], and 8-epideacylcynaropicrin (5) [4]. Rings A and B are *cis*-linked and rings B and C are *trans*-linked (torsional angles H1C1C5H5 = −0.4°and H6C6C7 = −143.0°).

The conformation of the five-membered carbocycle (A is that of a 3-envelope (ΔC_s^3 = 3.0°). Such a conformtion of ring A in guaianolides and pseudoguaianolides is observed extremely rarely and has been detected experimentally only in the structure of a fluoroguaianolide (6) (ΔC_s^3 = 1.0 and 1.0° for the two independent molecules) [5]. This is connected with the fact that in this conformation the torsional angle C1C2C5C4 assumes a value close to 0° (Table 1) and because of the *cis*-

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TABLE 1. Intracyclic Torsional Angles (°) in the Structure (1)

C1C2C3C4	45.8	C8C9C10C1	—86.1
C2C3C4C5	—43.9	C9C10C1C5	66.1
C3C4C5C1	22.5	C10C1C5C6	3.2
C4C5C1C2	2.0	C6O1C12C11	—4.7
C5C1C2C3	—29.3	O1C12C11C7	—16.1
C1C5C6C7	—70.7	C12C11C7C6	28.5
C5C6C7C8	87.7	C11C7C6O1	—30.0
C6C7C8C9	—61.2	C7C6O1C12	22.9
C7C8C9C10	62.3		

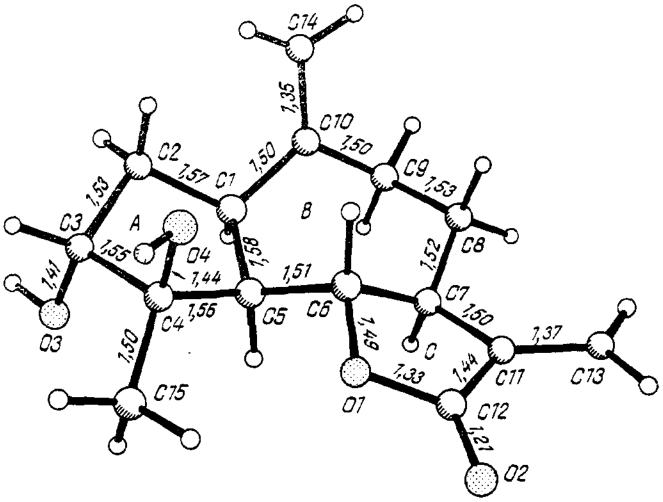

Fig. 1. General view of the anolide molecule with indications of the bond lengths (Å, the arrows do not exceed 0.01 Å).

linkage of rings A and B the latter must assume a chair conformation that is more unfavorable than a *twist*-chair conformation [6]. Usually, in the case of the *cis*-linkage of rings A and B, the conformation of ring B is connected with the departure from the main plane of the C1 and C5 atoms, as in the structures of centaurepensin (7) [7] – a 1α-envelope (ΔC_s^1 = 3.5°), (3) – a 5α-envelope (ΔC_s^5 = 2.4°), eregoyazin (8) [8] – a 1α,5β-half-chair (ΔC_2^3 = 2.8°), and (4) – a 1β,5α-half-chair (ΔC_2^3 = 4.9°). Departure of the C4 atom from the main plane, as in the chlororepdiolide molecule (9) [9] – a 4α-envelope (ΔC_s^4 = 5.0°) is found more rarely.

The conformation of the seven-membered ring of B in the (1) molecule is close to an ideal 1,5α,8β-chair (ΔC_s^8 = 2.9°) (the torsional angles are given in Table 1). The same conformation (ΔC_s^8 = 4.1°) is observed only in the structure of (6) according to the Cambridge structural data bank (1992 version). The corresponding torsional angles in the rings of these molecules differ by an average of 4.2%. The stabilization in the seven-membered ring of the (6) molecule of the chair conformation, more unfavorable than the *twist*-chair conformation, is due, in the opinion of the author, to hydrogen bonds in the crystal [5]. It is possible that this takes place by the same principle in the structure of (1).

The conformation of the lactone ring C is a highly distorted 7α-envelope (ΔC_s^7 = 4.9° and ΔC_2^{12} = 9.0°).

Thus, compound (1) is a new sesquiterpene lactone, which we have called anolide, and has the structure of 3α,4β-dihydroxy-1,5,7α(H),6β(H)-guaia-10(14),11(13)-dien-6,12-olide.

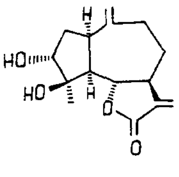

TABLE 2. Coordinates of the Atoms (× 10^4) in the Structure of (1)

Atom.	*x*	*y*	*z*	Atom.	*x*	*y*	*z*
O1	3767(4)	1998(3)	3355(2)	C7	3135(4)	3514(4)	4543(2)
O2	3755(4)	3206(3)	2069(2)	C8	3581(4)	4210(4)	5448(3)
O3	1821(4)	—1471(3)	5418(3)	C9	3179(5)	3468(4)	6350(3)
O4	5094(4)	—0196(3)	4431(2)	C10	3869(4)	2159(4)	6447(3)
C1	3119(4)	1049(4)	5970(3)	C11	3558(4)	4151(4)	3631(3)
C2	3786(5)	—0315(4)	6207(3)	C12	3693(4)	3146(4)	2929(3)
C3	3286(4)	—1184(4)	5389(3)	C13	3839(4)	5436(4)	3457(3)
C4	3579(4)	—0311(4)	4515(2)	C14	5044(4)	2059(4)	6985(3)
C5	3024(4)	1049(3)	4847(2)	C15	2911(5)	—0814(4)	3619(3)
C6	3805(4)	2180(3)	4402(2)				

EXPERIMENTAL

The individuality of the substances was checked by thin-layer chromatography (TLC) on Silufol plates in the benzene–ethanol (9:1) system, with 0.5% $KMnO_4$ in 0.5% H_2SO_4 as the revealing agent. The substances for analysis were dried in a vacuum pistol with P_2O_5 (alcohol) for 6 h).

Rotations were measured on a SM-2 polarimeter in a tube 10 cm long with a volume of 10 ml. Melting points were determined on a Boetius instrument. IR spectra (tablets with KBr) were taken on a UR-20 spectrophotometer; UV spectra on a Specord UV-Vis instrument; PMR spectra on a Bruker WP200SY instrument (200 MHz, $CDCl_3$, 0 – TMS); and ^{13}C NMR spectra on a Bruker HX-90 pulsed spectrometer (22.63 MHz, $CDCl_3$, 0 – TMS).

Isolation of Anolide. Flowerheads and leaves of *Achillea nobilis* gathered in the flowering phase in the environs of Karaganda (15 kg) were steeped with hot water (80-85°C) for 1 h, followed by treatment of the aqueous extract with chloroform. After evaporation of the chloroform, the syrupy residue obtained (161 g) was chromatographed on a column of KSK silica gel at a ratio of total material to support of 1:22. Elution of the column with ether led to the isolation of 1.5836 g of a colorless crystalline substance with the composition $C_{15}H_{20}O_4$ mp 167-169°C (alcohol), $[\alpha]_D^{20}$ +52.9° (*c* 0.017; ethanol), R_f 0.33. Yield 0.01%, calculated on the air-dry raw material. IR spectrum: 3550, 2985, 2950, 2900, 1740, 1670, 1640, 1455, 1420, 1380, 1325, 1260, 1165, 1125, 1065, 995, 970 cm^{-1}. PMR spectrum: 1.49 (3H, s), 2.08 (2H, s), 3.92 (1H, d, J = 3.3 Hz), 4.23 (1H, d.d, J_1 = 11.5 Hz, J_2 = 9.5 Hz, 4.92 (2H, d, J = 3.5 Hz), 5.47 and 6.17 (1H each, d, J = 3.5 Hz). ^{13}C NMR spectrum (multiplicity from "off-resonance"): 170, s; 148.1, s, 138.9, s; 120.1, tr; 112.6, tr; 82.9, s; 80.3, d; 52.2, d; 48.1, d; 44.1, d; 37.6, tr, 35.9, tr; 31.2, tr; 24.2, q.

Acetylation of Anolide. Acetic anhydride (1 ml) was added to 0.104 g of anolide in 2 ml of pyridine. The mixture was heated in the water bath at 60°C for 2 h. After cooling, it was diluted with a 15-fold amount of water, and was treated with chloroform (3 × 50 ml). The chloroform extract was washed with 3% HCl solution and with water until the wash-waters had a neutral reaction, and was concentrated. An oily product was obtained which crystallized on being washed with ether. Recrystallization from alcohol gave a substance with the composition $C_{17}H_{22}O_5$, mp 183-185°C. IR spectrum: 3460, 2990, 2950, 2870, 1740, 1665, 1640, 1450, 1410, 1380, 1330, 1300, 1265, 1205, 1155, 1135, 1125, 1085, 1040, 1000, 975, 930. PMR spectrum: 1.40 (3H, s), 2.02 (3H, s); 4.24 (1H, tr, J_1 = J_2 = 10 z); 4.95 (3H, s); 5.45 and 6.17 (1H and d, J = 3.5 Hz).

X-Ray Structural Experiment. The cell parameters and the intensities of 1623 reflections were measured on a Syntex $P2_1$ automatic four-circle diffractometer (λMoK_α graphite monochromator, $\theta/2\theta$ scanning, $2\theta < 50°$). The crystals were rhombic, a = 9.437(5), b = 10.281(6), c = 14.073(7) Å, V = 1365 $Å^3$, M = 264.4, d_{calc} = 1.31 g/cm^3, Z = 4 ($C_{15}H_{20}O_4$), sp.gr. $P2_12_12_1$.

In the calculations we used 1403 independent reflections with $I > 2\sigma$. 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 positions of the H atoms were calculated and were not refined. The final discrepancy factor were R = 0.079 and R_w = 0.082. The coordinates of the atoms are given in Table 2. All the calculations were conducted on a IBM PC/AT computer by means of the Siemens SHELXTL group of programs (PC Version).

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