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CRYSTAL AND MOLECULAR STRUCTURE OF 13-DIETHANOLAMINO-DEACETYLLAURENOBIOLIDE. MACROCYCLE CONFORMATION IN LINEAR GERMACROLIDES

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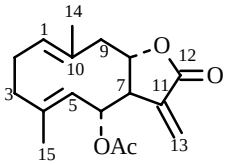
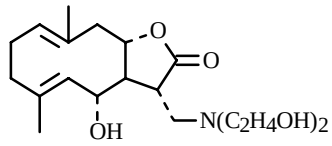
An x-ray structure analysis of the 13-diethanolamino derivative of deacetyllaurenobiolide, a germacrane sesquiterpene lactone, was performed. The germacrane macrocycle has the chairchair conformation with the $^{15}D_{5,1}D^{14}$ configuration. The conformation of the macrocycle in linear germacrolides was analyzed.

Key words: sesquiterpene lactone, germacranolide, 13-diethanolamino-deacetyllaurenobiolide, x-ray structure analysis.

NMR studies [1, 2] of laurenobiolide (**1**) revealed that the germacrane ring exists in solution as four canonical forms (**a**, **b**, **c**, **d**) in a 5:4:3:1 ratio [3]. We analyzed data in the Cambridge Structural Database and found that the existence of one conformer or another in crystals of germacrolides depends on the orientation of the substituents on C6 and C2 [4].



1



2

Therefore, conformer **a** or **b** can exist in crystals of laurenobiolide and its derivatives if the C6 substituent and the endocyclic double bonds remain in the α-orientation. However, the macrocycle in linear 7,8-lactones is considered [5] to be more flexible than that in nonlinear ones because all four conformers are observed in 7,8-lactones. In our opinion, this is due to a fortuitous collection of substances and is not connected with the flexibility of the macrocycle since the barrier height for conformational transitions (one of the criteria of macrocycle flexibility) in both instances is practically identical and lies at the level of thermal vibrations [5, 6]. Data indicating that derivatives of linear germacrolides with the same orientation of the substituent have different macrocycle conformations in the crystal have not been reported.

Thus, it seemed interesting to examine the effect of intramolecular H-bonds formed by the functional groups on the macrocycle conformation in the new 13-diethanolamine derivative of deacetyllaurenobiolide (**2**) prepared by us and to compare it with those observed in other natural derivatives of germacranolides. It should be noted that proton signals in the PMR spectrum of **2** are not broadened and the multiplicity is not changed by conformational exchange at room temperature, which is characteristic of germacranolides with structures related to laurenobiolide [7-11].

Figure 1 shows the molecular structure of **2** from an x-ray structure analysis (XSA). An analysis of the torsion angles shows that the macrocycle in **2** has the chair—chair conformation (**a**) with the $^{15}D_{5,1}D^{14}$ configuration (where the methyls on C4 and C10 are parallel and mutually β-*syn*-oriented whereas the endocyclic double bonds are perpendicular). This corresponds with conformation **a**, which is primarily found for laurenobiolide in solution [1].

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TABLE 1. Torsion Angles (φ, deg) of the Macrocycle in **2**, **3**, and **4**

Angle	φ (**2**)	φ (**3**)	φ (**4**)
C10-C1-C2-C3	-101.5	-101.4	-106.6
C1-C2-C3-C4	46.7	47.0	45.7
C2-C3-C4-C5	-91.9	-90.2	-91.5
C3-C4-C5-C6	169.3	170.5	167.2
C4-C5-C6-C7	-116.2	-119.0	-116.1
C5-C6-C7-C8	65.2	64.9	72.3
C6-C7-C8-C9	-94.9	-90.4	-105.0
C7-C8-C9-C10	96.1	94.0	96.5
C8-C9-C10-C1	-106.3	-108.7	-99.0
C9-C10-C1-C2	157.7	157.6	158.8

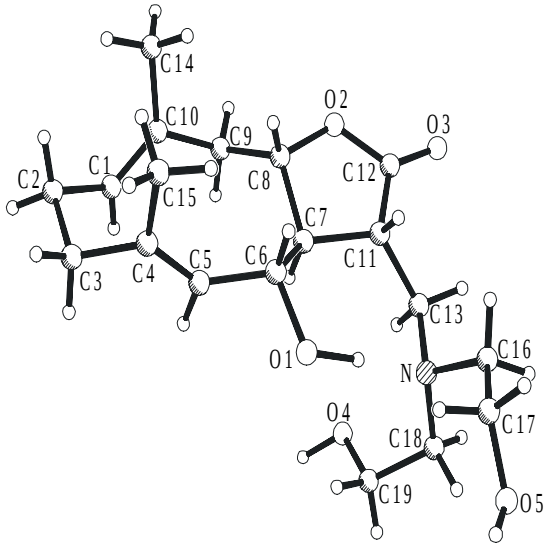
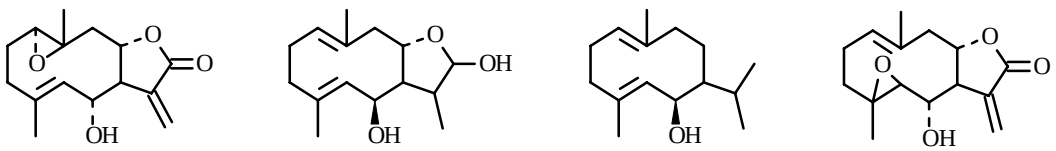


Fig. 1. Structure of **2**.

The positioning of the diethanolamine on C13 and the hydroxyl on C6 in **2** favor formation of an O–H...N intramolecular H-bond with parameters O1...N (2.17 Å), N...H (1.53 Å), and O1–H...N (174°). As a result, the N atom is blocked from forming intermolecular H-bonds. This can be seen in the molecular packing (see below).

The torsion angles (Table 1) of the macrocycle in **2** show no significant differences (up to ±2.5°) except for the C7–C8 angle where two rings are condensed when compared with those in the 13-hydroxymethylene deacetyllaurenobiolide (**3**) natural derivative of laurenobiolide [12]. The difference, which reaches 4.5°, is evidently related to the nature of the C13 substituent and its involvement in forming H-bonds. The macrocycles can be compared by examining another x-ray structure of the 7,8-*trans*-lactone gochnatolide (**4**) (data are averaged from two independent molecules in the unit cell) [13], which differs from **2** and **3** by exo-substituents in the C13 and C14 positions. The torsion angles (Table 1) are also essentially the same.

The macrocycle in another natural derivative 1(10)-epoxydeacetyllaurenobiolide (mucrin) (**5**) [14] has the **b** conformation ($^{15}D_{5,}{}^{1}D_{14}$ type), which is entirely possible. The reason conformation **d** ($_{15}D^{5}$, $_{1}D^{14}$ type) occurs in 6-epideacetyllaurenobiolide [15] and galerol (**6**) [16] is, in our opinion, the *β*-orientation of the C6 OH. According to NMR spectroscopy and molecular mechanics [17], it also occurs in the delactonized natural derivative of 6-epideacetyllaurenobiolide (**7**) and its 4(5)-epoxy analog. Conformations **d** and **c**, respectively, are characteristic of these molecules in solution.



5 **6** **7** **8**

TABLE 2. Bond Lengths (r, Å) and Angles (W, deg) in **1**

Bond	R	Angle	W	Angle	W
N-C13	1.459 (5)	C13-N-C18	110.3 (4)	O2-C8-C7	105.1 (4)
N-C18	1.469 (6)	C13-N-C16	110.3 (3)	C9-C8-C7	119.6 (4)
N-C16	1.468 (6)	C18-N-C16	111.2 (4)	C10-C9-C8	111.6 (4)
O1-C6	1.423 (6)	C12-O2-C8	112.0 (4)	C1-C10-C14	124.4 (5)
O2-C12	1.348 (6)	C10-C1-C2	127.3 (6)	C1-C10-C9	120.9 (5)
O2-C8	1.452 (6)	C1-C2-C3	107.6 (4)	C14-C10-C9	114.7 (5)
O3-C12	1.206 (6)	C4-C3-C2	111.6 (5)	C12-C11-C13	110.2 (4)
O4-C19	1.396 (6)	C5-C4-C3	119.1 (6)	C12-C11-C7	105.2 (4)
O5-C17	1.404 (7)	C5-C4-C15	123.9 (6)	C13-C11-C7	118.2 (3)
C1-C10	1.322 (8)	C3-C4-C15	116.5 (5)	O3-C12-O2	120.8 (5)
C1-C2	1.485 (8)	C4-C5-C6	130.7 (5)	O3-C12-C11	129.6 (5)
C2-C3	1.535 (9)	O1-C6-C5	107.4 (4)	O2-C12-C11	109.6 (4)
C3-C4	1.504 (8)	O1-C6-C7	110.2 (4)	N-C13-C11	113.7 (4)
C4-C5	1.326 (7)	C5-C6-C7	113.6 (4)	N-C16-C17	115.4 (4)
C4-C15	1.505 (9)	C11-C7-C6	114.0 (4)	O5-C17-C16	112.0 (5)
C5-C6	1.466 (6)	C11-C7-C8	102.2 (3)	N-C18-C19	113.7 (4)
C6-C7	1.543 (7)	C6-C7-C8	114.1 (4)	O4-C19-C18	112.1 (5)
C7-C11	1.526 (6)	O2-C8-C9	106.0 (4)	O4-C13-C11	
C7-C8	1.549 (6)				
C8-C9	1.545 (7)				
C9-C10	1.499 (8)				
C10-C14	1.488 (8)				
C11-C12	1.493 (6)				
C11-C13	1.531 (6)				
C16-C17	1.512 (7)				
C18-C19	1.522 (7)				

However, the configuration of the epoxy addition (instead of the double bond) determines mainly the macrocycle conformation and is beyond the scopy of our hypothesis. Such substitution limits considerably the flexibility, up to making certain conformers unattainable [18]. For example, the macrocycle in 4(5)-epoxydeacetyllaurenobiolide (spiciformin) (**8**) and its acetate [19] adopts conformation **c** ($_{15}D^{5},^{1}D_{14}$ type).

Thus, conformational analysis of the germacrane ring using deacetyllaurenobiolide derivatives as examples showed that the macrocycle in 7(8)-lactones, like in 6(7)-lactones, is stable. Changing the nature of the intramolecular H-bonds in the macrocycle does not change the conformation.

The Csp^3–Csp^3 bond lengths in the carbon skeleton of germacranolides are close on average to the normal value 1.540 Å. The endocyclic double bonds C1=C10 and C4=C5 in **2** average 1.329 Å and are within experimental uncertainty of the standard value [20]. The same is observed for the bond types (Table 2). The N atom in **2** has tetrahedral hybridization (sp^3) as indicated by the bond angles (C13–N–C18 110.3°, C13–N–C16 110.3°, C18–N–C16 111.2°) and the participation of its unshared electron pair in the formation of an intramolecular H-bond.

The packing and intermolecular contacts in **2** showed O–H...O H-bonds. The hydroxyl (O4H) approaches the unshared pairs of O1, which are not involved in intramolecular interactions. This is consistent with the intermolecular distance (2.69 Å) between O1 and O4 (0.5 + x, 0.5 - y, -z).

Therefore, H of the other hydroxyl (O5H) interacts with the unshared pair of O4 [O4...O5 (x - 1, y, z) 2.84 Å]. These H-bonds, which are repeated by a 2_1 screw translation along the *a* axis, form an infinite chain.

TABLE 3. Crystallographic Data, Experimental Conditions, and Refinement Parameters for the Structure of **2**

Empirical formula	$C_{19}H_{30}O_5N$
Molecular weight	353.45
Temperature, K	293
Space group	$P2_12_12_1$, Z = 4
a, Å	7.330 (4)
b, Å	12.020 (2)
c, Å	22.160 (4)
V, Å	1952.4 (7)
ρ, g/cm^3	1.201
Abs. coeff., μ (Mo) mm^{-1}	0.086
Crystal dimen., mm	0.5 × 0.3 × 0.2
Angle range θ, deg	1.84-24.96
Total number of reflections	1759
Number of reflections [I > 2 σ(I)]	1227
R-factor [I > 2 σ(I)]	R_1 = 0.0496, wR_2 = 0.1327
R-factor (whole data set)	R_1 = 0.0810, wR_2 = 0.1499
S	1.064
Difference electron-density peaks	0.266, -0.164 e. Å^{-3}

EXPERIMENTAL

The course of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using benzene:alcohol (2:1) and hexane:ethylacetate:diethanolamine (3:1:1). The developer was vanillin (1%) in conc. H_2SO_4.

PMR spectra were recorded on a Tesla BS-567A MHz spectrometer in C_5D_5N (0 = TMDS); mass spectra, in an MX-1310 spectrometer; IR spectra, on a UR-20 spectrometer (KBr disks).

Preparation of 6-Hydroxy-7*α*,11*α*,6*β*,8*β*(H)-4(5),1(10)-dien-13-diethanolaminogermacr-8,19-olide (2). Deacetyllaurenobiolide (0.0012 mol) was dissolved in ethanol. Diethanolamine (0.0018 mol) was added over 30 min to the resulting saturated solution. The reaction mixture was stirred for 2 h. The final product was obtained as crystals after 24 h. Yield 90%, $C_{19}H_{30}O_5N$, R_f 0.5 (benzene:alcohol, 4:1), mp 129-131°C, M^+ 353.

IR spectrum (ν, cm^{-1}): 3404 (OH), 3206 (water of crystallization), 1764 (γ-lactone C=O), 1673 (C=C conjugated to γ-lactone), 1489, 1447.

PMR spectrum (100 MHz, Py-d_5, ppm, J/Hz): 5.5 (H, d, J = 9, H-5), 4.28 (H, t, H-1), 4.5 (H, t, H-6), 4.19 (H, t, H-8), 2.75-3.2 (2H, m, N–CH_2), 1.50 (6H, s, H-14, 15).

Mass spectrum (*m*/*z*, I_{rel}, %): 353 $[M]^+$, $C_{19}H_{31}O_5N$ (0.75), 354 $[M + 1]^+$ (1.2), 355 $[M + 2]^+$, (1.5), 335 $[M - 18]^+$ (3), 325 $[M - 28]^+$ (4.5), 324 $[M - 29]^+$ (24.2), 323 $[M - 30]^+$ (100), 304 $[M - 49]^+$ (26), 249 $[M - 104]^+$ (9), 248 $[M - 105]^+$ (48), 233 (30), 230 (65), 215 (42), 32 (48), 31 (36), 30 (57), 29 (67), 28 (74).

X-Ray Structure Analysis. Single crystals of **2** that were grown from ethanol were transparent elongated prisms. The unit-cell constants and intensities of reflections were determined on a Nonius CAD-4 four-circle diffractometer (θ/2θ-scanning) using Mo Kα-radiation (graphite monochromator). Data for **2** were processed using SAINT [21]. Absorption corrections were applied using SADABS [22].

Table 3 gives the principal crystallographic parameters and conditions for the XSA.

The structure was solved by direct methods using the SHELXS-86 programs and refined by full-matrix isotropic and anisotropic least-squares methods. Calculations for the structure refinement used the SHELXL-93 programs. Coordinates of hydroxyl H atoms were determined experimentally from a difference electron-density synthesis. Coordinates of the other H atoms were fixed geometrically and refined isotropically.

The data from the XSA were deposited as a CIF file in the Cambridge Structural Database (CCDC 249724).

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