

THE MOLECULAR STRUCTURE OF 7 α -HYDROXY-3-DESOXY-ZALUZANIN C, A MOLLUSCICIDAL SESQUITERPENE LACTONE

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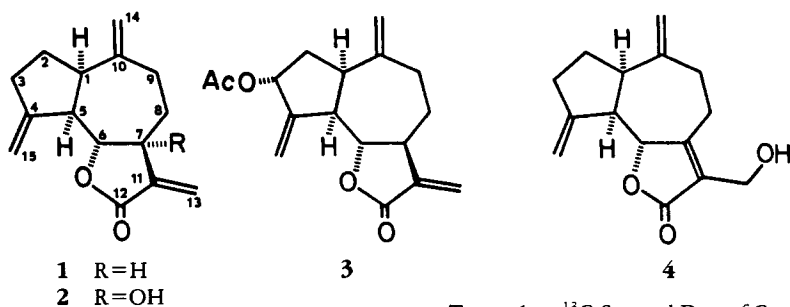
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Chromatographic procedures applied to the crude terpenoid extract (1) of *Podachaenium eminens* (Lagasca) Schultz-Bip. provided three lactonic constituents, which were found to be identical with the sesquiterpene lactones 7 α -hydroxy-3-desoxyzaluzanin C (2) and 11,13-dihydro-7,11-dehydro-13-hydroxy-3-desoxyzaluzanin C (4), previously described by Bohlmann and Le Van (2), and the third constituent was shown to be zaluzanin C acetate (3) (3). The identity of the three lactones was established by comparison of their ¹H-

Two independent molecules (unrelated by symmetry) exist in the crystal, distinguished in Table 2 by atom names with and without primes. Their conformations differ only slightly. One of the two molecules is represented in stereopair in Figure 1. The molecule is seen to be a *cis*-fused guaianolide with an α -methylene- γ -lactone *trans*-fused at C(6)-C(7) and a unique α -OH at C(7). The conformation of the seven-membered ring may be thought of as somewhat distorted from ideal C_s (mirror) symmetry, with the local mirror passing



nmr spectra with the data reported in the literature (2,3). ¹³C-nmr data of compounds 2-4 (Table 1) further confirmed the previous structural assignments.

Because of the dramatic difference in molluscicidal activity between the guaianolide dehydrocostus lactone (1) (4) and its 7 α -hydroxyderivative (2), it was desirable to determine the molecular structure of the highly active 7 α -hydroxy-3-desoxyzaluzanin C¹ by single crystal X-ray diffraction.

¹The molluscicidal activity was tested on *Biomphalaria glabrata* snails in the Lausanne laboratory according to the World Health Organization's recommendations. Lactones 1, 3, and 4 were not active but the 7 α -hydroxyderivative (2) killed the snails at the 1.0 ppm level within 24 h.

TABLE 1. ¹³C-Spectral Data of Compounds 2, 3, and 4 (50 MHz in CDCl₃).

Carbon	2	3	4
C-1	46.14 d	45.04 d	48.63 d
C-2	32.86 t	34.33 t	29.41 t
C-3	36.21 t	83.57 d	30.69 t
C-4	150.38 s	147.56 s	149.02 s
C-5	45.90 d	44.32 d	51.13 d
C-6	87.89 d	74.43 d	81.19 d
C-7	75.71 s	49.99 d	207.22 s
C-8	30.03 t	30.39 t	28.81 t
C-9	34.10 t	36.19 t	30.42 t
C-10	142.74 s	139.36 s	148.83 s
C-11	151.79 s	147.93 s	125.30 s
C-12	169.94 s	170.45 s	165.71 s
C-13	122.75 t	120.00 t	54.75 t
C-14	111.54 t	114.22 t	113.28 t
C-15	108.79 t	114.07 t	112.33 t
C-16	—	169.95 s	—
C-17	—	20.95 q	—

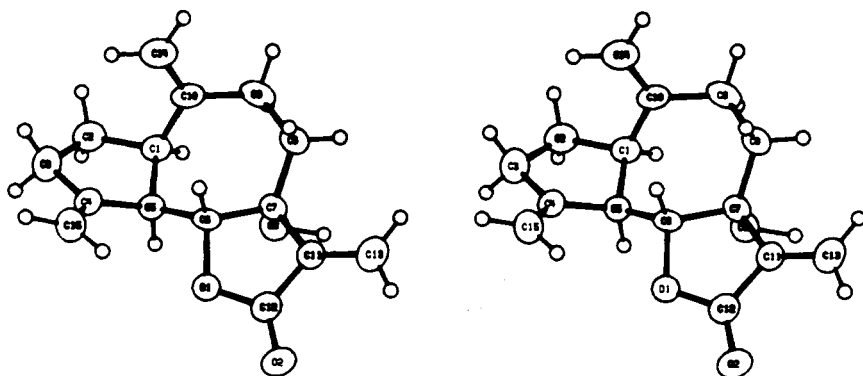
TABLE 2. Coordinates and Equivalent Isotropic Thermal Parameters

Atom	x	y	z	Beqv	Atom	x	y	z	Beqv
O(1)	0.8973(2)	0.23844(7)	1.0434(6)	4.37(7)	O(1')	1.0801(2)	0.37531(7)	0.5845(6)	4.67(7)
O(2)	0.8085(2)	0.29348(8)	1.0676(7)	5.72(8)	O(2')	1.1069(2)	0.31221(8)	0.4578(7)	5.91(8)
O(3)	0.7978(2)	0.19132(8)	0.6578(5)	4.54(7)	O(3')	0.9301(2)	0.36413(7)	0.9824(6)	4.99(7)
C(1)	0.9528(3)	0.13257(11)	0.8004(9)	4.4(1)	C(1')	0.9448(3)	0.45595(11)	0.9402(8)	4.4(1)
C(2)	1.0511(3)	0.11667(13)	0.7773(11)	6.2(1)	C(2')	0.9875(3)	0.49662(13)	1.0245(12)	6.4(1)
C(3)	1.1094(3)	0.13895(14)	0.9629(13)	7.0(1)	C(3')	1.0720(4)	0.50258(14)	0.8724(14)	8.6(2)
C(4)	1.0502(3)	0.17231(11)	1.0632(9)	4.4(1)	C(4')	1.0916(3)	0.46465(13)	0.7361(10)	4.9(1)
C(5)	0.9664(3)	0.17577(11)	0.9041(9)	3.9(1)	C(5')	1.0277(3)	0.43199(11)	0.8345(8)	3.8(1)
C(6)	0.8843(3)	0.19416(10)	1.0334(8)	3.60(9)	C(6')	0.9997(3)	0.40074(11)	0.6450(9)	3.7(1)
C(7)	0.7893(3)	0.18852(11)	0.9207(8)	3.80(9)	C(7')	0.9246(3)	0.37023(11)	0.7213(8)	3.8(1)
C(8)	0.7438(3)	0.14920(12)	1.0025(10)	4.7(1)	C(8')	0.8303(3)	0.38544(13)	0.6420(9)	4.7(1)
C(9)	0.7895(3)	0.11081(12)	0.9022(10)	5.8(1)	C(9')	0.7991(3)	0.42445(13)	0.7737(11)	5.8(1)
C(10)	0.8902(3)	0.10767(11)	0.9635(9)	4.8(1)	C(10')	0.8649(3)	0.45920(12)	0.7610(9)	4.6(1)
C(11)	0.7435(3)	0.22628(11)	1.0147(9)	4.1(1)	C(11')	0.9557(3)	0.33242(12)	0.5904(8)	4.2(1)
C(12)	0.8159(3)	0.25674(12)	1.0477(9)	4.5(1)	C(12')	1.0537(3)	0.33707(12)	0.5339(8)	4.4(1)
C(13)	0.6559(3)	0.23527(14)	1.0699(11)	6.1(1)	C(13')	0.9101(3)	0.29923(13)	0.5393(10)	5.6(1)
C(14)	0.9181(4)	0.08479(13)	1.1451(12)	6.8(1)	C(14')	0.8525(4)	0.48967(14)	0.6104(12)	6.8(1)
C(15)	1.0694(3)	0.19343(14)	1.2614(10)	5.6(1)	C(15')	1.1507(4)	0.46179(15)	0.5591(13)	7.9(2)

through C(8) and bisecting the C(1)-C(5) bond. The distortion is a twisting of the two fused rings about the C(1)-C(5) bond such that the torsion angles about C(1)-C(10) and C(5)-C(6) bonds become unequal in magnitude by ca. 40°. In both molecules, the cyclopentane ring is nonplanar and exists in the half-chair conformation, with the local twofold axis passing through C(2) and bisecting C(1)-C(5). The average difference in torsion angle magnitudes in comparing this portion of the two independent molecules is 2.1°. The largest difference in conformation between the two molecules occurs in the lactone ring. The molecule with primes in Table 2 has its lactone in the half-chair conformation with the local twofold axis passing through C(12') and bisecting C(6')-

C(7'). The molecule without primes has its lactone in an intermediate form between half-chair with C(12) on the axis and envelope with C(7) at the flap. The largest individual difference between analogues torsion angles of the two molecules is for the exocyclic torsion angle of the lactone, O(2)-C(12)-C(11)-C(13) in which the two differ by 12.7°. Bond distances are normal and show no significant differences between the two molecules. Variation in bond angles is somewhat larger but within accepted limits.

Due to the dramatic difference in molluscicidal activity between 7 α -hydroxy-3-desoxyzaluzanin C (2) and the corresponding compound lacking the 7 α -OH substituent (1), it would be of extreme interest to compare the struc-

FIGURE 1. Stereoscopic representation of 7 α -hydroxy-3-desoxyzaluzanin C.

tures of these two compounds and note the changes brought about by the hydroxyl group. Unfortunately, the crystal structure of **1** is not yet available. The most closely related compound for which the crystal structure has been determined is solstitialin (**5**), which has no 7 α -OH but is the 11 α ,13 glycol of zaluzanin C. The molecular structures of 7 α -hydroxy-3-desoxyzaluzanin C and solstitialin, as determined by X-ray diffraction, are nearly identical. The only bond distances that differ by more than 2 σ are those involving C(3), where substitution differs, and C(11), where hybridization differs. Bonds C(2)-C(3) and C(3)-C(4) are on the order of 0.03 \AA longer in solstitialin, due to the 3 β -OH substitution. Bond angles also exhibit excellent agreement except in the same regions. The overall conformations of the molecules also show excellent agreement, despite the differences in substitution at C(3), C(7), and C(11). Comparison of the seventeen endocyclic torsion angles of solstitialin with those of the average of the two independent molecules of **2** reveals a mean difference in magnitude of only 4.1 $^\circ$. The largest individual difference, 11.1 $^\circ$, is in the lactone ring, about the C(12)-O bond. While the lactone rings of the two independent molecules of **2** have slightly different conformations, see above, that of solstitialin has a third, best described as an envelope with C(7) at the flap.

Each molecule in the structure of **2** is involved in two intermolecular hydrogen bonds, one as a donor through the hydroxyl group and one as an acceptor through the lactone carbonyl oxygen atom. The hydrogen bond O(3)-H . . . O(2') has a separation of 2.861(4) \AA between oxygen atoms, and hydrogen bond O(3')-H . . . O(2) has a separation 2.969(4) \AA . Thus, the structure contains hydrogen bonded spirals of alternating primed and unprimed molecules, propagated by the 2 $_1$ axis at $x, \frac{1}{4}, \frac{1}{2}$.

EXPERIMENTAL

P. eminens was collected on 1 August 1978, in the state of Morelos, Mexico (Urbatsch No. 3346; voucher deposited at LSU). The air-dried plant material (504 g) was extracted and worked up as previously described (1), providing 2.83 g of syrup. This crude terpenoid extract was chromatographed on a silica gel column with CHCl $_3$ -Me $_2$ CO mixtures of increasing polarity providing 65 fractions of 25 ml each. Fractions 19-25 yielded 280 mg of **2**, C $_{15}$ H $_{18}$ O $_3$, MW 246.2, mp 132-133 $^\circ$ [lit. (2) 128 $^\circ$]; cd (c 1.35 $\times 10^{-4}$, MeOH): $[\theta]_{265} = +2.0 \times 10^2$ $[\theta]_{233} = 2.11 \times 10^2$. Fractions 29-35 provided 63 mg of zaluzanin C acetate (**3**) (3) and fractions 38-43 gave 45 mg of **4** (2), C $_{15}$ H $_{18}$ O $_3$, gum, cd (c 1.14 $\times 10^{-4}$, MeOH): $[\theta]_{231} = -1.03 \times 10^3$; ir ν max (film) 3445 (br, OH), 3010 (C=CH $_2$), 1740 (γ -lactone); ms 70 eV m/z (rel. int.) 246 (4.4, M $^+$), 228 (43.6, M $^+$ -H $_2$ O), 218 (14.7, M $^+$ -CO).

X-RAY DATA.—The crystal size was 0.20 \times 0.20 \times 0.60 mm. The space group was determined to be orthorhombic P2 $_1$ 2 $_1$ 2 $_1$ by systematic absences h00 with h odd, Ok0 with k odd, 00l with l odd. Cell dimensions were determined from the setting angles of 25 reflections have $2\theta > 20^\circ$. Crystal data are: C $_{15}$ H $_{18}$ O $_3$, MW=246.3, $a = 14.611(2)$, $b = 33.024(6)$, $c = 5.420(1)\text{\AA}$, $V = 2615$ (1) \AA^3 , $Z = 8$, $d_c = 1.251\text{gcm}^{-3}$, $\lambda = 0.71073\text{\AA}$, $\mu(\text{MoK}\alpha) = 0.80\text{cm}^{-1}$, $T = 298^\circ\text{K}$. Data collection was performed on an Enraf-Nonius CAD4 diffractometer equipped with MoK α radiation and a graphite monochromator, by $\omega - 2\theta$ scans designed to yield $I \approx 50\sigma(I)$. Scan rates varied 0.26-4.0 deg. min $^{-1}$. Data having $1^\circ < \theta < 25^\circ$ in octant +h,+k,+l were measured and corrected for background, Lorentz, and polarization effects; crystal decay and absorption were negligible.

The structure was solved using MULTAN(6), and refined by full-matrix least squares based upon F, using data for which $I > 1\sigma(I)$, weights $\omega = \sigma^{-2}(F_o)$, and the scattering factors of Cromer and Waber (7) with the Enraf-Nonius SDP programs (8). Nonhydrogen atoms were anisotropic, H atoms were located by ΔF , and included as fixed contributions in calculated positions (C-H 1.00 \AA , B=7.0 \AA^2) where possible. Final R=0.046, Rw=0.045, GOF=1.144 for 325 variables and 1536 observations (of 2133 unique data). The maximum shift was 0.07 σ in the final cycle, and the largest residual electron density was 0.16e \AA^{-3} .

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