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Dihydroelephantopin, C₁₉H₂₂O₇

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Abstract

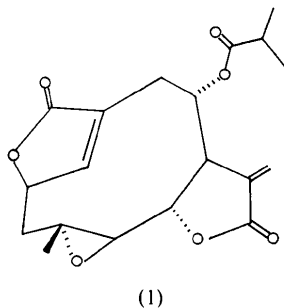
C₁₉H₂₂O₇, $M_r = 362.38$, is orthorhombic, $P2_12_12_1$, with $a = 10.952(4)$, $b = 25.642(19)$, $c = 6.386(2)$ Å, $V = 1793(2)$ Å³, $Z = 4$, $d_c = 1.342$ Mg m⁻³, $\mu = 0.87$ mm⁻¹. Full-matrix least-squares refinement (nonhydrogen atoms anisotropic, H atoms isotropic) based on 1568 reflexions led to a final R of 0.061. Dihydroelephantopin is a germacranolide-type sesquiterpene lactone containing a ten-membered ring which exhibits a chair–chair conformation in the solid state. The C(4)–C(5) double bond of the germacradiene skeleton has been transformed into a *trans* epoxide function. The C(15) methyl group has been oxidized and forms an α,β -unsaturated γ -lactone by closure at C(2) with the C(1)–C(10) double bond remaining undisturbed. The second α,β -unsaturated γ -lactone is *trans*-fused at C(6)–C(7) and exhibits an exocyclic double bond. Dihydroelephantopin exhibits antitumor activity.

Introduction

The genus *Elephantopus* (Compositae) is a member of the tribe Vernonieae, and is composed of approximately 32 species which are distributed throughout the tropical areas of the world (Heywood, Harborne & Turner, 1977). Perhaps a dozen of these species are found in the United States with *Elephantopus*

tomentosus distributed from Eastern Texas through the Southeastern portions of the country. *E. mollis*, *E. spicatus* and *E. scaber* have been used as folk remedies in Latin America, India and China to treat wounds and dysentery and as a cardiac tonic, astringent and febrifuge (Altschul, 1973; Nadkarni, Nadkarni & Chopra, 1976). The chemistry of the genus *Elephantopus* is not well enough established to clarify its phyletic position within the tribe Vernonieae; therefore, a survey of the chemistry of members of the genera composing this tribe has been initiated. The sesquiterpene dilactones elephantopin, elephantin and elephantol were isolated from *E. elatus* (Kupchan, Aynehchi, Cassady, McPhail, Sim, Schnoes & Burlingame, 1966; Kupchan, Aynehchi, Cassady, Schnoes & Burlingame, 1969), while deoxyelephantopin and isodeoxyelephantopin were isolated from *E. scaber* L. (Kurkawa, Nakanishi, Wu, Hsu, Maruyama & Kupchan, 1970; Govindachari, Viswanathan & Fuhrer, 1972). The sesquiterpene lactone molephantin was isolated from *E. mollis* (Lee, Furukawa, Kozuka, Huang, Luhan & McPhail, 1973). All compounds exhibit antitumor properties. *Elephantopus tomentosus* L. (tobacco-weed, devil's grandmother) was collected in Georgia and extracted by the usual procedures to yield dihydroelephantopin, a white crystalline compound which exhibits tumor-inhibiting properties against leukemia tumor cells (type PS) (Rustaiyan, Niknejad, Watson, Zabel, Mabry, Yabuta & Jones, 1978). We would like to report the structure of dihydroelephantopin (1).

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A crystal of dimensions 0.18 × 0.06 × 0.55 mm was used to collect intensity data on a Syntex P2₁ diffractometer system by the $\theta:2\theta$ scanning technique with a variable scan speed, a graphite monochromator and Cu K α radiation ($\lambda = 1.54178 \text{ \AA}$). Room-temperature lattice parameters were refined by a least-squares procedure utilizing 15 reflexions whose angles were measured by a centering routine associated with the Syntex diffractometer. Systematic absences were consistent with space group P2₁2₁2₁. A periodically monitored reflexion showed no significant change in intensity. Of the 1870 reflexions measured ($2\theta < 140^\circ$), 297 had intensities less than $2\sigma(I)$ and were not used in the refinement. Five additional reflexions showed significant secondary extinction and were dropped from the final refinement. Lorentz and polarization corrections were applied, but no absorption corrections were made.

The direct-methods program MULTAN (Germain, Main & Woolfson, 1971) was used to calculate phases for the 400 $|E|$ values greater than 1.22. The phase set with the largest combined figure of merit was selected, and the E map calculated with these phases revealed the positions of 23 nonhydrogen atoms. Alternate least-squares refinements and difference Fourier calculations were used to locate the three missing side-chain atoms. All hydrogen atoms except those

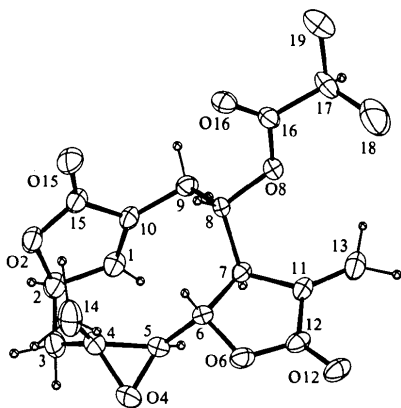


Fig. 1. ORTEP drawing of dihydroelephantopin. Thermal ellipsoids are drawn at the 35% probability level. Hydrogen atoms are represented by spheres of arbitrary size.

associated with the side-chain methyl groups could be located in a difference Fourier calculation. Least-squares refinement was terminated at a final R of 0.061 where $R = \sum |F_o| - |F_c| / \sum |F_o|$. The function minimized in the refinement was $\sum w(|F_o| - |F_c|)^2$, where $w = 1/\sigma(I)$ was determined from counting statistics. H atom thermal parameters were refined isotropically.

A final difference map showed no peak larger than 0.35 e \AA^{-3} . Atomic scattering factors and corrections for the real and imaginary portions of the anomalous

Table 1. Atomic positional parameters ($\times 10^4$; $\times 10^3$ for hydrogen) and U_{eq} or U thermal parameters ($\times 10^2$)

$$U_{eq} = \frac{1}{3} \sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j$$

	x	y	z	U_{eq}/U (\AA^2)
C(1)	7539 (5)	7121 (2)	1107 (7)	54†
C(2)	6342 (6)	7389 (2)	1224 (7)	61
O(2)	6296 (4)	7576 (1)	3367 (6)	64
C(3)	5250 (6)	7023 (2)	0875 (10)	76
C(4)	5297 (5)	6556 (2)	2240 (11)	69
O(4)	4928 (4)	6062 (2)	1329 (10)	90
C(5)	6185 (5)	6147 (2)	1687 (9)	58
C(6)	6860 (4)	5835 (2)	3295 (8)	50
O(6)	6539 (3)	5288 (1)	3009 (6)	59
C(7)	8259 (4)	5875 (1)	3108 (7)	42
C(8)	8819 (4)	6263 (1)	4682 (7)	40
O(8)	9955 (3)	6047 (1)	5466 (5)	53
C(9)	9143 (4)	6791 (2)	3705 (8)	50
C(10)	8045 (4)	7079 (1)	2984 (7)	45
C(11)	8640 (4)	5309 (1)	3207 (6)	46
C(12)	7524 (6)	4986 (2)	3077 (6)	51
O(12)	7445 (4)	4521 (1)	3007 (6)	65
C(13)	9723 (6)	5083 (2)	3275 (11)	71
C(14)	4806 (7)	6615 (3)	4395 (15)	92
C(15)	7255 (5)	7375 (2)	4460 (7)	53
O(15)	7370 (4)	7452 (2)	6304 (6)	75
C(16)	10293 (4)	6164 (2)	7435 (8)	55
O(16)	9695 (3)	6441 (1)	8554 (5)	60
C(17)	11469 (7)	5902 (3)	8010 (16)	96
C(18)	11958 (11)	6111 (5)	10013 (26)	162
C(19)	11395 (11)	5324 (4)	8045 (27)	148
H(1)	791 (5)	698 (2)	-010 (9)	47 (12)
H(2)	640 (8)	769 (3)	038 (14)	102 (22)
H(3a)	445 (6)	720 (2)	123 (10)	69 (16)
H(3b)	498 (9)	696 (4)	-079 (17)	119 (3)
H(5)	676 (14)	611 (6)	086 (3)	186 (50)
H(6a)	666 (6)	594 (3)	457 (13)	73 (18)
H(7)	850 (5)	598 (2)	163 (10)	54 (13)
H(8)	828 (6)	632 (2)	581 (11)	69 (17)
H(9a)	947 (5)	699 (2)	480 (10)	64 (14)
H(9b)	959 (6)	672 (2)	251 (11)	75 (18)
H(13a)	1000 (5)	470 (3)	343 (11)	76 (17)
H(13b)	1050 (7)	526 (3)	365 (11)	82 (18)
H(14a)	463 (10)	623 (5)	513 (19)	139 (30)
H(14b)	376 (10)	666 (4)	449 (17)	142 (33)
H(14c)	549 (14)	691 (6)	557 (25)	193 (49)
H(17)	1217 (4)	600 (1)	692 (6)	29 (9)

† Standard deviations range from 4 to 7 for all U_{eq} values except for C(18) and C(19) where the values are 17 and 15, respectively.

Table 2. *Interatomic distances (Å), valence angles (°) and torsion angles (°) for dihydroelephantopin*

C(1)–C(2)	1.481 (8)	C(8)–C(9)	1.531 (6)
C(1)–C(10)	1.325 (6)	C(9)–C(10)	1.486 (6)
C(2)–C(3)	1.536 (9)	C(10)–C(15)	1.488 (6)
C(2)–O(2)	1.452 (6)	O(2)–C(15)	1.361 (6)
C(3)–C(4)	1.483 (9)	C(15)–O(15)	1.201 (6)
C(4)–C(5)	1.474 (8)	C(11)–C(12)	1.479 (7)
C(4)–O(4)	1.452 (7)	C(11)–C(13)	1.320 (8)
C(4)–C(14)	1.485 (12)	O(6)–C(12)	1.329 (7)
C(5)–O(4)	1.413 (7)	C(12)–O(12)	1.196 (6)
C(5)–C(6)	1.497 (7)	O(8)–C(16)	1.345 (6)
C(6)–C(7)	1.540 (6)	C(16)–O(16)	1.202 (6)
C(6)–O(6)	1.456 (5)	C(16)–C(17)	1.499 (9)
C(7)–C(8)	1.542 (6)	C(17)–C(18)	1.487 (19)
C(7)–C(11)	1.512 (6)	C(17)–C(19)	1.483 (13)
C(8)–O(8)	1.451 (5)		
C(2)C(3)C(10)	111.2 (4)	C(7)C(8)O(8)	108.6 (3)
C(1)C(2)C(3)	113.5 (5)	C(9)C(8)O(8)	106.3 (3)
C(1)C(2)O(2)	103.4 (4)	C(8)C(9)C(10)	112.3 (4)
O(2)C(2)C(3)	108.1 (5)	C(9)C(10)C(1)	131.2 (4)
C(2)C(3)C(4)	112.4 (5)	C(9)C(10)C(15)	121.9 (4)
C(3)C(4)C(5)	117.2 (5)	C(1)C(10)C(15)	106.8 (4)
C(3)C(4)O(4)	117.4 (6)	C(7)C(11)C(12)	107.9 (4)
C(3)C(4)C(14)	116.7 (5)	C(7)C(11)C(13)	132.1 (4)
O(4)C(4)C(5)	57.7 (3)	C(12)C(11)C(13)	119.9 (4)
O(4)C(4)C(14)	111.1 (5)	C(11)C(12)O(12)	110.2 (4)
C(5)C(4)C(14)	122.2 (6)	C(11)C(12)O(12)	128.3 (5)
C(4)C(5)O(4)	60.3 (4)	O(6)C(12)O(12)	121.5 (5)
C(4)O(4)C(5)	61.9 (3)	C(2)O(2)C(15)	109.4 (4)
C(4)C(5)C(6)	122.8 (5)	O(2)C(15)C(10)	108.4 (4)
O(4)C(5)C(6)	120.6 (5)	O(2)C(15)O(15)	121.5 (5)
C(5)C(6)C(7)	113.7 (4)	C(10)C(15)O(15)	130.0 (5)
C(5)C(6)O(6)	108.0 (4)	C(8)O(8)C(16)	118.2 (3)
O(6)C(6)C(7)	107.2 (3)	O(8)C(16)O(16)	122.6 (4)
C(6)C(7)C(8)	112.9 (3)	O(8)C(16)C(17)	111.4 (5)
C(6)C(7)C(11)	101.9 (3)	O(16)C(16)C(17)	126.0 (5)
C(8)C(7)C(11)	118.9 (3)	C(16)C(17)C(18)	111.0 (7)
C(7)C(8)C(9)	113.4 (4)	C(16)C(17)C(19)	113.9 (7)
C(18)C(17)C(19)	111.5 (10)		

dispersion were calculated by the XRAY76 program (Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976). Atomic positional parameters and U_{eq} values are given in Table 1 while interatomic distances and valence angles are presented in Table 2.*

Discussion

Fig. 1 shows an *ORTEP* drawing (Johnson, 1965) of dihydroelephantopin. It has been assumed that the absolute configuration at C(6) is the same for all germacranolides (Neidle & Rogers, 1972), and the 6*S* configuration [*i.e.* H(6) is β] was confirmed for glaucolide-D (Taylor, Watson, Betkouski, Padolina & Mabry, 1976). The ten-membered ring is in the chair–chair conformation (torsion-angle sequence + – + – + – + – + –) which is found for most *trans*, *trans*-germacranolides. Table 3 compares the ten-membered-ring torsion angles for a number of germacranolides with those for dihydroelephantopin. Group *A* contains compounds with 1–10 and 4–5 double bonds and an exocyclic α,β -unsaturated γ -lactone *trans*-fused at 6–7. In parthenolide the 4–5 double bond is replaced by a *trans*-epoxide. Group *B* molecules contain a 1–10 double bond and a 4–5 epoxide, but the α,β -unsaturated γ -lactone contains an endocyclic double bond which leads to sp^2 hybridization at C(7). Dihydroglaucolide-C contains an ad-

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36310 (16 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 3. *Torsion angles (°) for the germacranolide ring system*

	ω^{10-1}	ω^{1-2}	ω^{2-3}	ω^{3-4}	ω^{4-5}
Group <i>A</i>	167 (2)*	–100 (1)	52 (2)	–87 (2)	153 (4)
Parthenolide	168 (1)*	–107 (2)	52 (1)	–88 (2)	147 (1)
Group <i>B</i>	163 (10)*	–109 (0)	49 (1)	–89 (1)	155 (0)
Glaucolide-C	152	–110	49	–89	156
Elephantol	163	–104	42	–77	156
Dihydroelephantopin	171.4†	–108.0	51.5	–74.5	144.0
	ω^{5-6}	ω^{6-7}	ω^{7-8}	ω^{8-9}	ω^{9-10}
Group <i>A</i>	–133 (1)	93 (5)	–80 (2)	65 (5)	–112 (2)
Parthenolide	–124 (3)	96 (0)	–89 (2)	75 (1)	–109 (2)
Group <i>B</i>	–110 (1)	77 (1)	–97 (1)	88 (0)	–105 (1)
Glaucolide-C	–106	74	–103	97	–95
Elephantol	–108	82	–119	83	–89
Dihydroelephantopin	–122.1	99.7	–101.4	65.4	–97.6

References: Group *A*: costunolide (Bovill, Cox, Cradwick, Guy, Sim & White, 1976), eupatolide (McPhail & Onan, 1975), tamaulipin-A (Witt & Watkins, 1978), ovatifolin (Gopalakrishna, Watson, Hoeneisen & Silva, 1977), eupahyssopin (Lee, Kimura, Okamoto, Cowherd, McPhail & Onan, 1976). Parthenolide (Quick & Rogers, 1976). Group *B*: glaucolide-D and -E (Taylor, Watson, Betkouski, Padolina & Mabry, 1976; Gopalakrishna, Adams, Watson, Betkouski & Mabry, 1977). Glaucolide-C (Zabel, Watson, Mabry & Padolina, 1980). Elephantol (McPhail & Sim, 1972).

* Average deviation.

† Standard deviation 0.4–0.7°.

ditional epoxide function at 1–10. Elephantol is similar to dihydroelephantopin except the 6–7 *trans*-fused γ -lactone has been fused at 7–8. The torsion angles around the ten-membered ring are rather insensitive to variations in substitution and to packing interactions. The methyl groups lie *syn* on the β -face of the molecule with the double bonds or epoxide functions lying in a crossed orientation. Introduction of an epoxide function at 1–10 reduces the torsion angle by more than 10°; however, the formation of a γ -lactone in elephantol and dihydroelephantopin does not produce any large changes. Torsion angles ω^{1-2} , ω^{2-3} , ω^{3-4} , ω^{4-5} are remarkably constant although C(4)–C(5) can be either a double bond or part of an epoxide ring. The large variations in ω^{5-6} , ω^{6-7} and ω^{7-8} are associated with shifting the γ -lactone from 6–7 to 7–8 fusion or moving the double bond of the α,β -unsaturated γ -lactone to the endocyclic position. The introduction of the sp^2 hybridization at C(7) leads to a torsion-angle change of more than 20°.

The two five-membered rings in dihydroelephantopin are flattened envelopes with C(6) and C(2) being the flaps. The C(13)C(11)C(12)O(12) and O(15)C(15)C(10)C(1) torsion angles are -0.5° and -178.4° , respectively.

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