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CYTOTOXIC GERMACRANOLIDES OF *ELEPHANTOPUS CAROLINIANUS* AND THE STRUCTURE AND STEREOCHEMISTRY OF ISODEOXYELEPHANTOPIN*

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Key Word Index—*Elephantopus carolinianus*; Compositae; cytotoxic and antitumor activity; sesquiterpene lactones; germacranolides; deoxyelephantopin; isodeoxyelephantopin; 11β,13-dihydrodeoxyelephantopin.

Abstract—The whole parts of North Carolina *Elephantopus carolinianus* yielded two cytotoxic sesquiterpene lactones, deoxyelephantopin and isodeoxyelephantopin, as well as 11β,13-dihydrodeoxyelephantopin which is devoid of cytotoxicity. The structures and stereochemistries of isodeoxyelephantopin and 11β,13-dihydrodeoxyelephantopin were determined by spectroscopic analysis, chemical transformations and X-ray analysis.

INTRODUCTION

We reported previously on the isolation of deoxyelephantopin (**1**), an antitumour principle from North Carolina *Elephantopus carolinianus* [1]. Further investigation of the cytotoxic fractions remaining after the removal of **1** has now led to the isolation of isodeoxyelephantopin (**2**), which showed significant cytotoxicity with ED_{50} = 2.5 μg/ml against the *in vitro* growth of KB tissue culture cells, and 11β,13-dihydrodeoxyelephantopin (**3**). Although **2** and **3** were isolated previously from India *Elephantopus scaber* [2] and West Virginia *Elephantopus carolinianus* [3] and Sri Lanka *Elephantopus scaber* [4], respectively, their structures and stereochemistries were not fully defined. This report describes the isolation of **2** and **3** and the elucidation of their structures.

RESULTS AND DISCUSSION

Compound **2**, $C_{19}H_{20}O_6$, mp 160–161° (lit. [2] 150–153°), $[\alpha]_D$ +180.7°, (lit [2] +188.4°), was isolated in 0.023% yield from the active fraction by silica gel chromatography. IR, NMR (Table 1) and mass spectral data for **2** were very similar to those of **1** [1], and indicated the presence of an α-methylene-γ-lactone [IR: 1755 (γ-lactone) and 1635 (C=C) cm^{-1}; ^1H NMR: δ5.66 (1H, *d*, $J_{7,13a}$ = 4.0 Hz, H-13_a) and 6.20 (1H, *d*, $J_{7,13b}$ = 4.0 Hz, H-13_b)] and a methacrylate ester group [IR: 1705 and 1635 cm^{-1}; ^1H NMR: δ5.70 and 6.15 (each 1H, *br s*, H-18), and 1.93 (3H, *dd*, $J_{18,19a}$ = $J_{18,19b}$ = 1.0 Hz, H-19); MS: *m/z* 69 (base peak, $[CH_2{=}CH(Me)CO]^+$) and 258 (strong peak, $[M-C_4H_6O_2]^+$]. Epoxidation of **2** with *m*-chloroperbenzoic acid yielded monoepoxide **4** for which the mass spectrum was very similar to that of elephantopin (**5**) [5, 6].

The co-occurrence of **2** with **1**, coupled with the foregoing evidence in addition to the close correspondence between the ^1H NMR data (Table 1) for **1** and isodeoxyelephantopin [2], as well as for **4** and isoelephantopin [2], led to the assignment of structure **2** to isodeoxyelephantopin. The ^1H NMR (Table 1) downfield shifts of H-5 (δ5.13 in **2** *vs.* 4.77 in **1**) and H-7 (δ3.16 in **2** *vs.* 2.94 in **1**) suggested that the γ-lactone ring oxygen atom at C-2 must be oriented α in **2** rather than β as in **1**, in order that the lactone C=O group in **2** would be in close proximity to both H-5 and H-7 and thereby cause a paramagnetic shift due to its anisotropic effect.

Unequivocal proof of the structure and stereochemistry of **2** was derived from a single-crystal X-ray analysis of dimethylamine adduct (**6**). The crystal structure was solved by direct method [7]. Full-matrix least-squares refinement of atomic positional and thermal parameters converged to R = 0.050 over 1458 reflections. Final non-hydrogen atom positional parameters are given in Table 2. A view of the solid-state conformation is presented in Fig. 1, while bond lengths and angles are recorded in Fig. 2.

With an α-orientation of the oxygen substituent at C-2 in **2**, in contrast to the β-orientation at this centre in elephantopin [5], formation of the corresponding γ-lactone ring incorporating C-15 requires that the latter also lies on the α-face of the *trans,trans*-cyclodeca-1,5-diene ring, i.e. *anti* to the β-oriented C-14 methyl group. This has a profound effect on the comformation of the ten-membered ring [endocyclic torsion angles (deg.): $\omega_{1,2}$ 106, $\omega_{2,3}$ −33, $\omega_{3,4}$ −67, $\omega_{4,5}$ 159, $\omega_{5,6}$ −105, $\omega_{6,7}$ 77, $\omega_{7,8}$ −115, $\omega_{8,9}$ 64, $\omega_{9,10}$ 76, $\omega_{1,10}$ −163] which is consequently quite different from the chair–chair–chair [8] form, with its *syn*-oriented methyl groups or their equivalents, encountered in, for example, eupatolide [9], costunolide [10], alatolide [11], elephantol [12] and eupahyssopin [13]. In accord with the results from other X-ray diffraction studies on germacradienes, torsion angles associated with both of the *trans* double bonds

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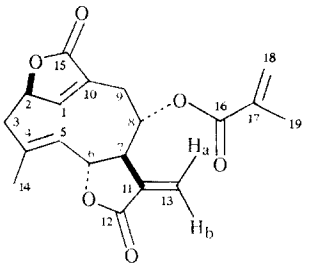

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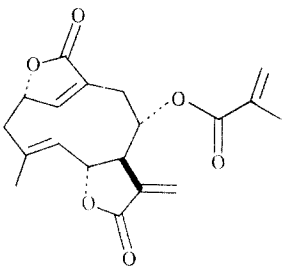

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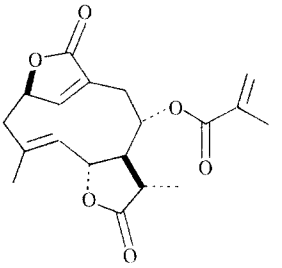

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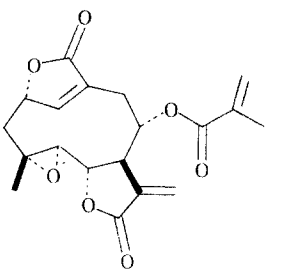

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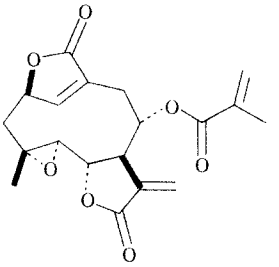

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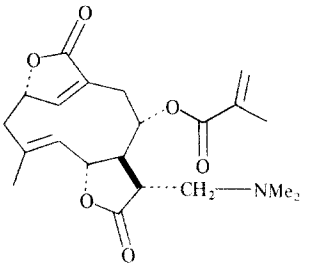

6

depart significantly ($\Delta_{1,10}$ 17°, $\Delta_{4,5}$ 21°) from 180°. That equal contributions to the distortion in the C-1=C-10 bond arise from out-of-plane bending at C-10 and actual twisting about the double bond is reflected in the fact that the C-1, C-10, C-9/C-1, C-10, C-15 dihedral angle (8.8°) is not significantly different from the C-2–C-1–C-10–C-15 torsion angle (8.5°), whereas for the C-4=C-5 bond, the C-14–C-4–C-5–C-6 torsion angle (−12.8°) is slightly larger in magnitude that the C-3, C-4, C-5/C-5, C-4, C-14 dihedral angle (8.4°), indicating that there is a marginally greater contribution from true twisting about this double bond.

The saturated γ-lactone ring, *trans*-fused at C-6 and C-7, has an envelope conformation with C-7 displaced by 0.59 Å to the α-side of the least-squares plane through C-6, C-11, C-12, O-22, 0-23. In the α,β-unsaturated γ-lactone ring, the mean endocyclic torsion angle is 7°, and, with C-1 and C-2 displaced by 0.06 and 0.10 Å, respectively, to opposite sides of the C-10, C-15, O-20, O-21 least-squares plane, the ring has a very flattened half-chair form.

Compound **3**, $C_{19}H_{22}O_6$, was isolated in 0.0004% yield as a minor component. Spectral data revealed that it possessed a methacrylate ester side chain [IR: 1710 and 1633 cm^{-1}; ^1H NMR: δ5.68 and 6.17 (each 1H, *br s*, H-18) and 1.99 (3H, *br s*, H-19); MS: *m/z* 69 (base peak)] and two γ-lactone rings, one of which was an α,β-unsaturated lactone [IR: 1742 cm^{-1}; ^1H NMR: δ6.95 (1H, *br s*, H-1) and 5.45 (1H, *dd*, J = 2.0 and 5.0 Hz, H-2)] while the other was a saturated α-methyl γ-lactone [IR: 1770 cm^{-1}; ^1H NMR: presence of signals for a new methyl group at δ1.38 (3H, *d*, $J_{11,13}$ = 6.4 Hz, Me-11) in place of those for the well-defined α-methylene protons of the γ-lactone ring in **1** (Table 1)]. Treatment of **1** with zinc–copper couple [14, 15] gave rise to a product which was identical with **3**. The foregoing data led to the conclusion that **3** is 11,13-dihydrodeoxyelephantopin which had been isolated previously from *Elephantopus scaber* [4]. The configuration of the methyl group at C-11 was deduced as α based upon the large coupling constant (J = 11.4 Hz) between H-7 and H-11.

EXPERIMENTAL

Mps are uncorrected. ^1H NMR spectra were recorded at 250 MHz. MS were determined at 70 eV using a direct inlet system. Silica gel (Merck silica gel 60, 70–230 mesh) was used for CC, and precoated silica gel (Merck silica gel 60 F 254) was used for TLC. Detection of components was made either by spraying

Table 1. ^{1}H NMR spectral data* of compounds **1–4** and **6**

Compound	H-1	H-2	H-3	H-5	H-6	H-7	H-8	H-9	H-11	H-13a	H-13b	H-14	H-18	H-19	Misc.
1†	7.05 (*s*)	5.46 (*dd*; 2.0, 4.0)	2.69 (*dd*; 2.0, 14.0) 2.85 (*dd*; 4.0, 14.0)	4.77 (*d*; 10.0)	5.15 (*dd*; 10.0, 8.0)	2.94 (*dddd*; 8.0, 4.0, 3.2, 4.0)	4.66 (*ddd*; 4.0, 11.0 2.0)	2.80 (*dd*; 11.0, 12.0) 3.05, (*dd*; 2.0, 12.0)	—	5.64 (*d*; 3.2)	6.23 (*d*; 4.0)	1.87 (*br s*)	5.66 (*br s*) 6.14 (*br s*)	1.93 (*br s*)	—
2†	7.14 (*br s*)	5.37 (*br d*; 5.0)	2.39 (*dd*; 5.0, 14.5) 2.97 (*dd*; 1.0, 14.5)	5.13 (*br d*; 10.5)	5.17 (*dd*; 10.5, 8.0)	3.16 (*dddd*; 8.0, 4.0 4.0, 4.0)	4.54 (*ddd*; 4.0, 4.0, 12.0)	2.74 (*dd*; 4.0, 13.0) 3.06 (*dd*; 12.0, 13.0)	—	5.66 (*dd*; 4.0, 1.0)	6.20 (*dd*; 4.0, 1.0)	1.79 (*d*; 1.0)	5.70 (*br s*) 6.15 (*br s*)	1.93 (*dd*; 1.0, 1.0)	—
3†	6.95 (*br s*)	5.45 (*dd*; 2.0, 5.0)	2.61 (*dd*; 2, 13) 2.85 (*dd*; 5, 13)	4.57 (*br d*; 10.0)	4.86 (*dd*; 10.0, 8.7)	2.11 (*ddd*; 8.7, 5.7, 11.4)	5.17 (*ddd*; 5.7, 11.6, 2.0)	2.72 (*dd*; 11.6, 14.0 2.96 (*dd*; 2.0, 14.0)	2.47 (*d, q*; 11.4, 6.4)	—	—	1.86 (*d*; 1.0)	5.68 (*br s*) 6.17 (*br s*)	1.99 (*br s*)	1.38 (3H, *d*; 6.4, H-13)
4	7.26 (*br s*)	5.37 (*br d*; 5.0)	2.56 (*dd*; 5.0, 15.0) 2.17 (*br d*, 15.0)	2.81 (*d*; 9.4)	4.31 (*dd*; 9.4, 9.4)	3.29 (*dddd*; 9.4, 4.0, 4.0, 4.0)	4.56 (*ddd*; 4.0, 4.0, 11.7)	2.89 (*dd*; 4.0, 12.0) 3.11 (*dd*; 11.7, 12.0)	—	5.74 (*d*; 4.0)	6.27 (*d*; 4.0)	1.50 (*br s*)	5.69 (*br s*) 6.15 (*br s*)	1.93 (*br s*)	—
6	7.09 (*br s*)	5.34 (*br d*; 5.0)	2.35 (*dd*; 5.0, 14.5) 2.90 (*dd*; 1.0, 14.5)	5.11 (*br d*; 10.0)	4.93 (*dd*; 10.0, 10.0)	2.80 (*ddd*; 10.0, 4.0, 11.0)	4.64 (*ddd*; 4.0, 4.0, 12.0)	2.65 (*dd*; 4.0, 11.4) 3.01 (*dd*; 12.0, 11.4)	2.48 (*dt*; 11.0, 5.0)	—	—	1.90 (*d*; 1.0)	5.70 (*br s*) 6.20 (*br s*)	1.98 (*br s*)	2.70 (2H, *d*, 5.0, CH_2N) 2.31 (6H, s, NMe_2)

*Run in $CDCl_3$ at 250 MHz. Values are in ppm (δ). Coupling constants (J) are in Hz and in parentheses.

†All assignments were confirmed by extensive double resonance experiments.

Table 2. Non-hydrogen atom fractional coordinates ($\times 10^4$) for **6**, with standard deviations in parentheses

Atom	x	y	z
C-1	2988 (3)	533 (3)	−2605 (6)
C-2	3745 (3)	380 (3)	−3816 (6)
C-3	4585 (3)	261 (3)	−2693 (6)
C-4	4600 (3)	736 (2)	−954 (6)
C-5	4648 (3)	1485 (2)	−1079 (6)
C-6	4390 (3)	2038 (2)	372 (6)
C-7	3535 (3)	2429 (2)	−76 (6)
C-8	2737 (3)	1931 (2)	309 (5)
C-9	2221 (3)	1730 (2)	−1457 (6)
C-10	2773 (3)	1253 (2)	−2714 (5)
C-11	3639 (3)	3160 (2)	1006 (6)
C-12	4590 (3)	3312 (2)	785 (6)
C-13	3047 (4)	3824 (3)	545 (7)
C-14	4441 (4)	305 (3)	817 (7)
C-15	3291 (3)	1598 (3)	−4227 (5)
C-16	1693 (3)	1900 (2)	2714 (6)
C-17	1154 (3)	2360 (3)	3987 (6)
C-18	483 (4)	2012 (3)	4787 (8)
C-19	1366 (4)	3148 (3)	4276 (8)
O-20	3830 (2)	1066 (2)	−4895 (4)
O-21	3281 (2)	2225 (2)	−4830 (4)
O-22	5009 (2)	2664 (2)	421 (4)
O-23	4966 (2)	3903 (2)	935 (5)
O-24	2171 (2)	2327 (2)	1564 (4)
O-25	1724 (2)	1226 (2)	2729 (5)
N-26	2748 (3)	3829 (2)	−1377 (6)
C-27	3404 (5)	4085 (4)	−2653 (9)
C-28	1979 (5)	4287 (4)	−1562 (10)

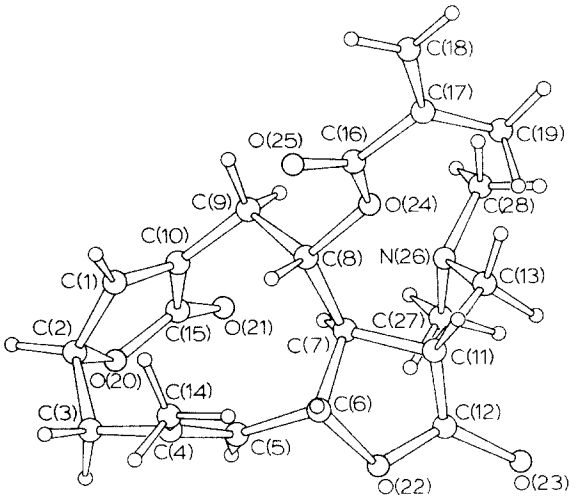

Fig. 1. Structure and solid-state conformation of **6**; small circles denote hydrogen atoms.

with 1% $CeSO_4$ or 10% H_2SO_4 soln, followed by heating or by use of a UV lamp.

Extraction of Elephantopus carolinianus *Willd.* The *E. carolinianus* (Compositae) used was from a collection made in the Fall of 1981 in Chapel Hill, NC. The ground, air-dried whole plant material (1.02 kg) was exhaustively extracted with $CHCl_3$ and worked up in the usual manner [16], affording 5.19 g of a dark brown syrup.

Isolation of isodeoxyelephantopin (**2**). The syrup was column chromatographed on silica gel (4.5 × 30 cm) by elution with hexane–$CHCl_3$ (1:1) and $CHCl_3$. Forty-three fractions of about 100 ml each were collected and examined by TLC. The $CHCl_3$ eluate (fractions 20–21) yielded crystalline residues which were purified by prep. TLC [silica gel, C_6H_6–CH_2Cl_2–Et_2O (1:1:1)] and recrystallization from $CHCl_3$–Et_2O to afford **2** (227 mg) as colourless needles: mp 160–161°; $[\alpha]_D$ + 180.7° ($CHCl_3$; *c* 0.176); IR ν_{max}^{KBr} cm^{-1}: 3070, 1755 (br), 1705, 1635 and 1155; MS *m/z* (rel. int.): 344 $[M]^+$ (0.8), 316 (5.4), 258 (16.3), 162 (15.2), 134 (8.2), and 69 (100). Calc. for $C_{19}H_{20}O_6$: *m/z* 344.1260; found: *m/z* 344.1261.

Deoxyelephantopin (**1**) *and* 11*β*,13*-dihydrodeoxyelephantopin* (**3**). The $CHCl_3$ eluate (fractions 22–26) gave a mixture of deoxyelephantopin (**1**), which was reported previously [1], and a minor compound (**3**). Compound **3** was separated from **1** by repeated prep. TLC (silica gel; EtOAc–C_6H_6, 7:3). Recrystallization from $CHCl_3$–Et_2O (1:4) furnished 4.1 mg of **3** as colourless needles: mp 193–197°; IR ν_{max}^{KBr} cm^{-1}: 3090, 1770, 1742, 1710, 1633 and 1156; MS *m/z* (rel. int.): 346 $[M]^+$ (0.3), 318 (0.2), 260 (34.4), 232 (11.2), 216 (11.0), 214 (15.8), 203 (13.1), 188 (13.1), 175 (10.9), 164 (15.5), 151 (16.7), 121 (15.5), 91 (18.4), 83 (26.1) and 69 (100). Calc. for $C_{19}H_{20}O_6$: *m/z* 346.1417; found: 346.1411.

Isoelephantopin from epoxidation of isodeoxyelephantopin (**2**). A soln of **2** (21 mg) in $CHCl_3$ (0.6 ml) was treated with a soln of *m*-chloroperbenzoic acid (75 mg) in $CHCl_3$ (1 ml), and the mixture was allowed to stand at room temp. overnight. The soln was then washed with 10% Na_2SO_3, 5% $NaHCO_3$ and H_2O, dried and evaporated *in vacuo* to give a colourless gum purification of which by prep. TLC [silica gel, EtOAc–C_6H_6 (7:3) first, followed by Et_2O as eluting solvents] yielded 10 mg of **4**; MS *m/z* (rel. int.): 360 (0.2), 274 (8.5), 232 (2.1), 216 (3.5), 204 (21.5), 188 (5.4), 176 (9.9), 160 (3.7), 91 (8.6) and 69 (100).

Isodeoxyelephantopin α-dimethylamine adduct (**6**). A soln of **2** (28 mg) in MeOH (1.5 ml) was added dropwise to 40 mg of Me_2NH in MeOH at 0°. The resulting product was recrystallized from $CHCl_3$–Et_2O (1:3) to furnish the amine adduct (**6**) as colourless needles: mp 206–207°; $[\alpha]_D$ + 143.6° ($CHCl_3$; *c* 0.093); IR ν_{max}^{KBr} cm^{-1}: 2815, 2765, 1765, 1745, 1705, 1630 and 1320; MS *m/z* (rel. int.): 389 $[M]^+$ (14.1), 374 (0.1), 316 (1.3), 258 (4.1), 69 (80.7) and 58 (100). Calc. for $C_{21}H_{27}NO_6$: *m/z* 389.1839; found: 389.1842.

11*β*,13*-Dihydrodeoxyelephantopin* (**3**) *from reduction of deoxyelephantopin* (**1**) *with zinc–copper couple.* A mixture of **1** (21 mg), Zn–Cu couple (800 mg) and EtOH (10 ml) was heated under refulx with stirring for 8 days. The reaction product (11 mg) was purified by prep. TLC (silica gel, EtOAc–C_6H_6, 7:3), followed by recrystallization from $CHCl_3$–Et_2O to give a compound (4.4 mg, colourless needles) which was identified by direct comparison (superimposable TLC and IR, NMR, and mass spectra, as well as mmp determination) with an authentic sample of 11*β*,13-dihydrodeoxyelephantopin (**3**), isolated from this plant.

X-Ray analysis of isodeoxyelephantopin α-dimethylamine adduct (**6**). Compound **6**, $C_{21}H_{27}NO_6$, M_r 389.45, crystallizes in the orthorhombic system, space group $P2_12_12_1$ (D_2^4), with *a* = 15.528 (4) Å, *b* = 17.712 (3) Å, *c* = 7.226 (1) Å, *V* = 1987.4 Å^3, *Z* = 4, D_{calc} = 1.302 g cm^{-3}, μ(Cu-*K*α radiation, λ = 1.5418 Å) = 7.5 cm^{-1}.

A crystal of dimensions 0.08 × 0.08 × 0.80 mm was oriented on the end of a thin glass fiber to rotate with its long dimension parallel to the fibre axis. Oscillation, Weissenberg and precession photographs yielded preliminary unit-cell parameters and space group information. One octant of intensity data was recorded on

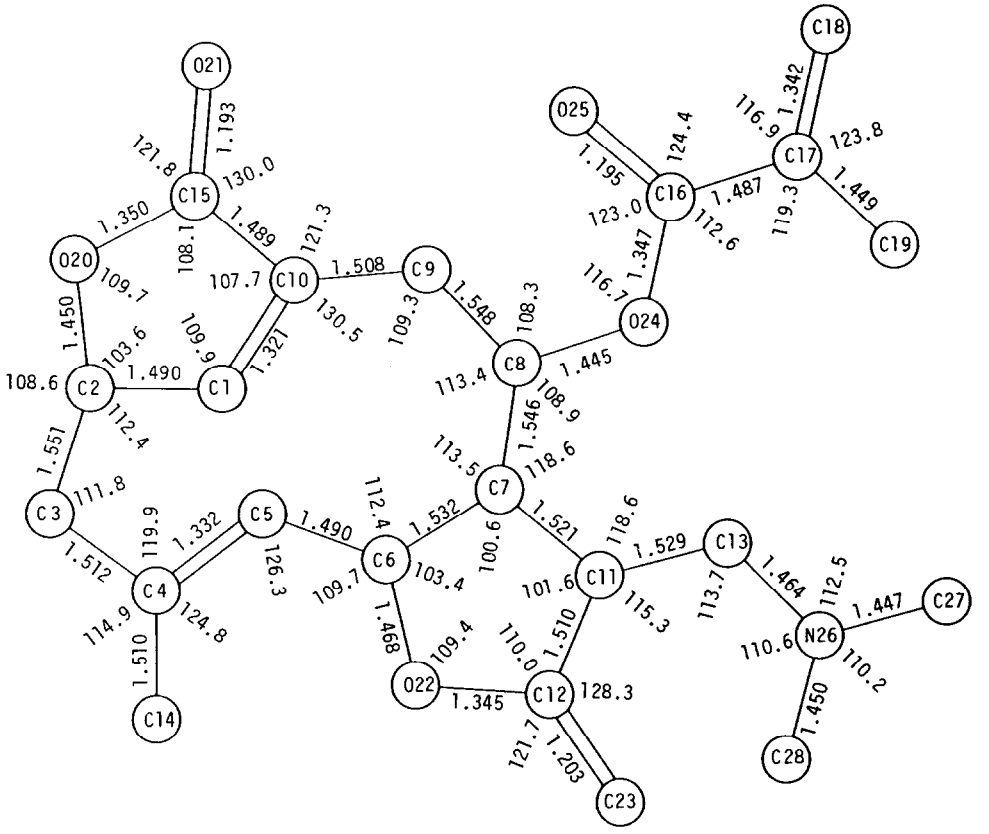

Fig. 2. Bond lengths (±0.005–0.008 Å) and bond angles (±0.03–0.05°) in **6**.

an Enraf-Nonius CAD-4 diffractometer (Cu-$K\alpha$ radiation, incident-beam graphite monochromator; ω-2θ sacans, θ_{max} = 67°). From a total of 2046 independent measurements, those 1458 reflections with $I > 3.0\sigma(I)$ were retained for the structure analysis and corrected for the usual Lorentz and polarization effects. Refined unit-cell parameters were derived by least-squares treatment of the diffractometer setting angles for 25 high order reflections (33° < θ < 49°) widely separated in reciprocal space.

The crystal structure was solved by direct methods [7]. Non-hydrogen atom coordinates, obtained initially from an *E*-map, and anisotropic thermal parameters were adjusted by full-matrix least-squares calculations to $R = 0.078$ at which point a difference Fourier synthesis yielded positions for all hydrogen atoms. Continuation of the refinement of non-hydrogen atom positional and anisotropic thermal parameters, with hydrogen atoms included at their calculated positions, led to convergence at $R = 0.050$ ($R_w = 0.062$). Final non-hydrogen atom positional parameters are in Table 2. Anisotropic temp. factor parameters, hydrogen atom positional and isotropic thermal parameters, and a list of observed and calculated structure amplitudes have been deposited with the Cambridge Crystallographic Data Centre.

Neutral atom scattering factors used in the structure-factor calculations were taken from ref. [17]. In the least-squares iterations, $\sum w\Delta^2(\Delta = \|F_o| - |F_c\|)$ was minimized with weights, w, assigned according to the scheme: $\sqrt{w} = 1$ for $|F_o| < 14.0$, and $\sqrt{w} = 14.0/|F_o|$ for $|F_o| > 14.0$ to ensure no systematic dependence of $\langle w\Delta^2 \rangle$ when analysed in ranges of $|F_o|$.

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