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6-[1-(4-Ethoxyphenyl)ethyl]-5-methoxy-1,3-benzodioxole

Paul Ala and Daniel S. C. Yang

Department of Biochemistry, McMaster University, Hamilton, Ontario, Canada L8N 3Z5

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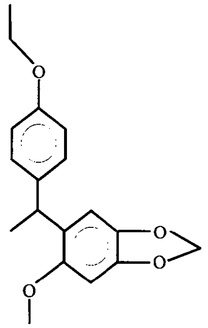
Abstract

The title compound, $C_{18}H_{20}O_4$, is structurally similar to podophyllotoxin. It contains a fused dioxole and phenyl ring system and an unfused phenyl ring which are almost perpendicular to each other. However, this compound lacks the cyclohexyl and lactone rings which are present in podophyllotoxin. In addition, the unfused phenyl ring in podophyllotoxin contains three methoxy groups in the *para* and *meta* positions, whereas the title compound contains only an ethoxy group in the *para* position.

Comment

The title compound, (I), belongs to a series of 6-benzyl-1,3-benzodioxole derivatives that are structurally similar to podophyllotoxin and have podophyllotoxin-like antimitotic activity (Batra, Jurd & Hamel, 1985). These derivatives have been used to study structure–function relationships of podophyllotoxin. For example, tubulin polymerization is inhibited if the 6-benzyl-1,3-benzodioxole derivative contains an intact dioxole ring, a methoxy group at the *para* position of the unfused phenyl ring and a methoxy or ethoxy group at the 5-position of the fused rings (Batra *et al.*, 1985). The title compound contains all these key structural features except that the methoxy group at the *para* position of the unfused phenyl ring is replaced by an ethoxy group, which reduces its potency as an inhibitor of tubulin polymerization by only twofold (Batra *et al.*, 1985).



(I)

The structure determination reveals that the fused dioxole and phenyl rings and the unfused phenyl ring are both planar and almost perpendicular to each other. The relative orientation between these two ring systems is likely to be an important factor that enables the derivative to bind tubulin. The only other report of a crystal structure of a 6-benzyl-1,3-benzodioxole derivative ap-

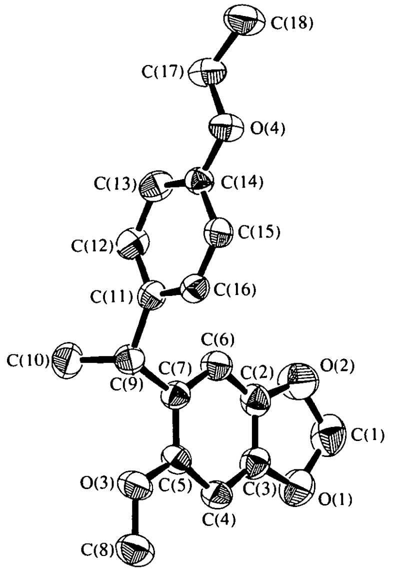


Fig. 1. *ORTEP*II (Johnson, 1976) plot of the molecular structure of the benzyl–benzodioxole derivative (ellipsoids represent 50% probability).

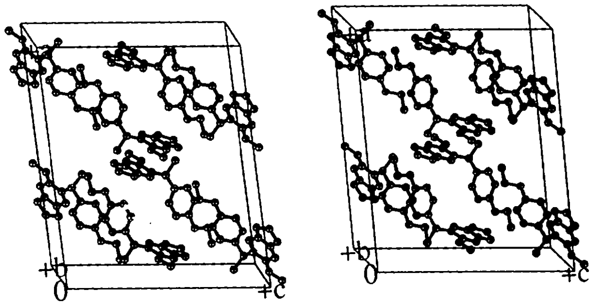


Fig. 2. *PLUTO* (Motherwell & Clegg, 1978) stereoplot of the packing of the benzyl–benzodioxole derivative.

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peared recently (Sicheri, Derry, Gupta & Yang, 1992). A structural analysis of other benzyl–benzodioxole derivatives may help us to better understand the importance of the relative orientations between the two ring systems and identify additional features that make podophyllotoxin a potent mitotic inhibitor.

Experimental

The title compound was obtained in crystalline form from the National Cancer Institute (NSC 353648). This compound has one chiral centre but crystallized in an achiral space group. Therefore, both enantiomers crystallized together.

Crystal data

$C_{18}H_{20}O_4$
$M_r = 300.35$
Monoclinic
$C2/c$
$a = 22.662\ (5)$ Å
$b = 7.671\ (1)$ Å
$c = 18.443\ (1)$ Å
$\beta = 99.60\ (1)^\circ$
$V = 3161.2$ Å^3
$Z = 8$
$D_x = 1.262$ Mg m^{-3}

Cu $K\alpha$ radiation
$\lambda = 1.54178$ Å
Cell parameters from 25 reflections
$\theta = 25.05$–32.7°
$\mu = 0.683$ mm^{-1}
$T = 296$ K
Rectangular
0.14 × 0.06 × 0.04 mm
Transparent

Data collection

Rigaku AFC-6*R* diffractometer
ω–2θ scans
Absorption correction: ψ scan (North, Phillips & Mathews, 1968)
$T_{\min} = 0.87$, $T_{\max} = 1.00$
2644 measured reflections
2567 independent reflections
1416 observed reflections $[I > 3\sigma(I)]$

$R_{\rm int} = 0.043$
$\theta_{\max} = 60.05^\circ$
$h = 0 \rightarrow 25$
$k = 0 \rightarrow 8$
$l = -20 \rightarrow 20$
3 standard reflections monitored every 150 reflections
intensity decay: none

Refinement

Refinement on F
$R = 0.050$
$wR = 0.061$
$S = 1.41$
1416 reflections
200 parameters
H-atom parameters not refined
$w = 1/\sigma^2(F)$
$(\Delta/\sigma)_{\max} = 0.03$

$\Delta\rho_{\max} = 0.14$ e Å^{-3}
$\Delta\rho_{\min} = -0.13$ e Å^{-3}
Extinction correction: *MITHRIL* (Gilmore, 1984)
Extinction coefficient: 0.14012×10^{-5}
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2)

$$B_{\rm eq} = (8\pi^2/3)\Sigma_i\Sigma_jU_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$B_{\rm eq}$
O(1)	0.1101 (1)	0.7891 (4)	0.1109 (2)	5.6 (2)
O(2)	0.1668 (2)	0.8318 (4)	0.0189 (2)	6.3 (2)
O(3)	0.0442 (1)	0.2172 (3)	0.0148 (2)	4.4 (1)
O(4)	0.3273 (1)	0.2573 (3)	−0.2084 (1)	4.2 (1)
C(1)	0.1536 (2)	0.8982 (6)	0.0858 (3)	5.7 (2)
C(2)	0.1394 (2)	0.6703 (5)	0.0108 (2)	3.9 (2)
C(3)	0.1062 (2)	0.6454 (5)	0.0654 (2)	3.8 (2)
C(4)	0.0736 (2)	0.4981 (6)	0.0706 (2)	3.8 (2)
C(5)	0.0748 (2)	0.3724 (5)	0.0156 (2)	3.4 (2)
C(6)	0.1414 (2)	0.5468 (5)	−0.0423 (2)	3.9 (2)
C(7)	0.1080 (2)	0.3943 (5)	−0.0407 (2)	3.4 (2)
C(8)	0.0110 (2)	0.1844 (6)	0.0718 (2)	5.5 (2)
C(9)	0.1066 (2)	0.2547 (5)	−0.0998 (2)	3.6 (2)
C(10)	0.0488 (2)	0.2742 (6)	−0.1563 (2)	5.0 (2)
C(11)	0.1634 (2)	0.2555 (5)	−0.1335 (2)	3.4 (2)
C(12)	0.1674 (2)	0.3262 (6)	−0.2012 (2)	4.1 (2)
C(13)	0.2210 (2)	0.3295 (5)	−0.2288 (2)	3.9 (2)
C(14)	0.2716 (2)	0.2596 (5)	−0.1880 (2)	3.2 (2)
C(15)	0.2687 (2)	0.1851 (5)	−0.1198 (2)	3.6 (2)
C(16)	0.2154 (2)	0.1824 (5)	−0.0940 (2)	3.5 (2)
C(17)	0.3325 (2)	0.3268 (6)	−0.2782 (2)	4.8 (2)
C(18)	0.3970 (2)	0.3162 (7)	−0.2870 (3)	6.1 (2)

Table 2. *Selected geometric parameters* (Å, °)

O(1)—C(1)	1.428 (5)	C(5)—C(7)	1.392 (5)
O(1)—C(3)	1.379 (4)	C(6)—C(7)	1.396 (5)
O(2)—C(1)	1.412 (5)	C(7)—C(9)	1.525 (5)
O(2)—C(2)	1.382 (5)	C(9)—C(10)	1.540 (5)
O(3)—C(5)	1.376 (4)	C(9)—C(11)	1.519 (5)
O(3)—C(8)	1.414 (5)	C(11)—C(12)	1.377 (5)
O(4)—C(14)	1.376 (4)	C(11)—C(16)	1.395 (5)
O(4)—C(17)	1.417 (5)	C(12)—C(13)	1.394 (5)
C(2)—C(3)	1.368 (5)	C(13)—C(14)	1.371 (5)
C(2)—C(6)	1.368 (5)	C(14)—C(15)	1.393 (5)
C(3)—C(4)	1.362 (5)	C(15)—C(16)	1.371 (5)
C(4)—C(5)	1.402 (5)	C(17)—C(18)	1.499 (6)
C(1)—O(1)—C(3)	104.5 (3)	C(5)—C(7)—C(9)	120.0 (4)
C(1)—O(2)—C(2)	105.1 (3)	C(6)—C(7)—C(9)	121.4 (3)
C(5)—O(3)—C(8)	118.3 (3)	C(7)—C(9)—C(10)	109.2 (3)
C(14)—O(4)—C(17)	117.6 (3)	C(7)—C(9)—C(11)	111.8 (3)
O(1)—C(1)—O(2)	109.3 (3)	C(10)—C(9)—C(11)	114.0 (3)
O(2)—C(2)—C(3)	109.8 (4)	C(9)—C(11)—C(12)	124.1 (4)
O(2)—C(2)—C(6)	129.1 (4)	C(9)—C(11)—C(16)	118.9 (3)
C(3)—C(2)—C(6)	121.1 (4)	C(12)—C(11)—C(16)	117.0 (3)
O(1)—C(3)—C(2)	110.4 (4)	C(11)—C(12)—C(13)	122.1 (4)
O(1)—C(3)—C(4)	127.0 (4)	C(12)—C(13)—C(14)	119.5 (3)
C(2)—C(3)—C(4)	122.7 (4)	O(4)—C(14)—C(13)	125.1 (3)
C(3)—C(4)—C(5)	116.4 (3)	O(4)—C(14)—C(15)	115.1 (3)
O(3)—C(5)—C(4)	122.2 (3)	C(13)—C(14)—C(15)	119.8 (3)
O(3)—C(5)—C(7)	115.5 (3)	C(14)—C(15)—C(16)	119.7 (3)
C(4)—C(5)—C(7)	122.3 (4)	C(11)—C(16)—C(15)	121.9 (3)
C(2)—C(6)—C(7)	119.0 (3)	O(4)—C(17)—C(18)	108.1 (4)
C(5)—C(7)—C(6)	118.6 (4)		

Measurements were made on a AFC-6*R* diffractometer with graphite-monochromated radiation and a 12 kW rotating anode generator. The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods using *MITHRIL* (Gilmore, 1984). H atoms were generated using optimum bonding geometry and included in F_c. H-atom displacement parameters and positions were not refined. Non-H atoms were refined anisotropically. Anomalous-dispersion effects were included in F_c (Ibers & Hamilton, 1964). All calculations were performed using *TEXSAN* (Molecular Structure Corporation, 1985).

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and torsion angles have been deposited with the IUCr (Reference: BK1028). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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2,6,6-Trimethyl-2-oxo-1,3-dioxa-6-azonia-2-phosphocyclooctane Iodide

G. Kumaravel and Richard D. Gandour*

Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061-0212, USA

Frank R. Fronczek

Department of Chemistry, Louisiana State University, Baton Rouge, LA 70803-1804, USA

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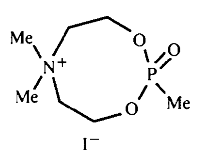
Abstract

The eight-membered ring in the title compound, $C_7H_{17}NO_3P^+.I^-$, has a boat-chair conformation, with the local mirror plane passing through the cyclic O atom and methylene C atom adjacent to the N atom. The P=O bond is pseudo-axial and the P—CH$_3$ bond is pseudo-equatorial. The P—N distance is 3.821 (2) Å.

Comment

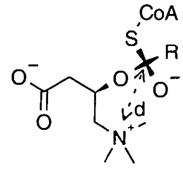
We are interested in the design and synthesis of conformationally restricted reaction-intermediate-analogue inhibitors of carnitine acyltransferases (Gandour *et al.*, 1992). Our inhibitor design suggests that an eight-membered ring would be an excellent match for the putative tetrahedral intermediate in the reactions catalyzed by carnitine acyltransferases. We have produced the title compound, (I), in order to perform the conformational analysis of the eight-membered phosphorus-containing ring.



(I)

Eight-membered phosphorus heterocycles with heteroatoms located in positions 1, 2, 3 and 6 provide interesting models for studying transannular interactions. For example, 2-methyl-2-oxo-6-phenyl-1,3-dioxa-6-aza-2-phosphacynan (Kalinin, Andrianov & Struchkov, 1975) exists in the solid state in the chair-chair or crown conformation and a close contact between the P and N atoms [3.22 Å] indicates a transannular P···N interaction. Another compound, 2-thio-2,6-dimethyl-1,3-dioxa-6-aza-2-phosphacynan (Dutasta, 1980), also exists in the solid state in the crown conformation (Dutasta, Robert & Wiesenfeld, 1980) with a transannular P···N distance shorter than the sum of the van der Waals radii (Piccinni-Leonardi *et al.*, 1986).

Unlike the neutral phosphorus compounds mentioned above, the title compound exists in the solid state in a boat-chair conformation, with the local mirror plane passing through the cyclic O atom and methylene C atom adjacent to the N atom. The P=O bond is pseudo-axial and the P—CH$_3$ bond is pseudo-equatorial.



(II)

In this conformation, the P···N distance [3.821 (2) Å] mimics the distance (d = 3.84 Å) between the tetrahedral C atom and the quaternary N atom of the proposed (Gandour *et al.*, 1992) intermediate, (II), which was calculated by *PCMODEL* (Gajewski & Gilbert, 1992), in the acyl transfer to carnitine. In addition, the N—

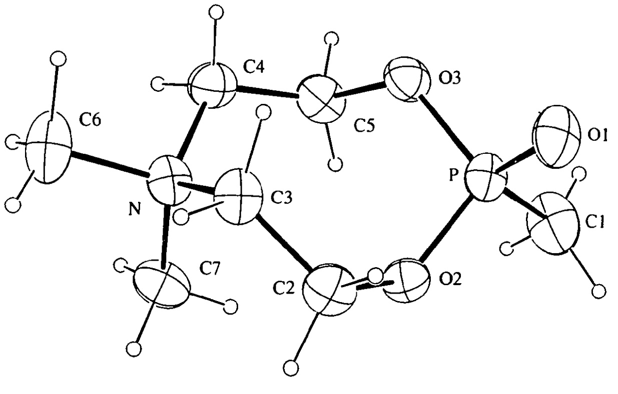


Fig. 1. Plot (*ORTEP*; Johnson, 1965) of the heterocyclic cation. Displacement ellipsoids are drawn at the 40% probability level, with H atoms shown as spheres of arbitrary radii.