Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

β-Lapachone

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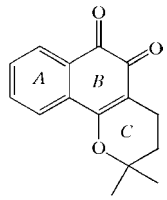
Received 16 March 2006
Accepted 7 June 2006
Online 14 July 2006

The most remarkable aspect of the crystal structure of the title compound (systematic name: 3,4-dihydro-2,2-dimethyl-2*H*-naphtho[1,2-*b*]pyran-5,6-dione), $C_{15}H_{14}O_3$, is that a π-stacking interaction is present between the two naphthalene ring systems of symmetry-related molecules. Apart from these π–π interactions, different molecules are held together by weak C—H···O hydrogen-bonding interactions.

Comment

The title compound, (I), is a naphthoquinone which can be isolated on a small scale from South American trees of the families Bigoniaceae and Verbenaceae (Burnett & Thomson, 1968). It can be produced chemically on a large scale from lapachol, following the procedures developed by Hooker (1892). These consist of cyclization in sulfuric acid by nucleophilic attack on the O atom of the lapachol isoprenyl side chain, followed by further recrystallizations (Hooker *et al.*, 1936). A research group at the Federal University of Pernambuco, Brazil, first noted the activity of (I) against several micro-organisms (Lima *et al.*, 1962; D'Alburquerque, 1968) and tumour cells (Ferreira de Santana *et al.*, 1968; D'Alburquerque *et al.*, 1972). In recent years, compound (I) has become very interesting as a potential agent against several diseases. It has antifungal, antiviral, antipsoriatic and anti-inflammatory activities (Guiraud *et al.*, 1994; Li *et al.*, 1993; Mueller *et al.*, 1999). It is also active against parasites such as *Tripanosoma cruzi*, the etiologic agent of Chagas disease (Pinto *et al.*, 2000). But it is its antineoplastic activity that has generated the greatest expectations of this molecule. *In vitro* and *in vivo* studies have shown that (I) inhibits conventional therapy-resistant tumours, particularly malignant neoplasms with a slow cell cycle, such as prostate, colon and some ovarian and breast cancers (Planchon *et al.*, 1995; Li *et al.*, 2003; Park *et al.*, 2005). 300 research articles and nearly 40 patents have been published on the subject in the last 15 years. Thus, its excellent pharmacological potential suggests that this drug could shortly be included in the therapeutic arsenal.



(I)

In this paper, we report the molecular and crystal structures of (I) (Fig. 1). Some X-ray data from structural derivatives of (I) have previously been reported (De Simone *et al.*, 2002; Reibenspies *et al.*, 1989; Di Chenna *et al.*, 2001). It should be noted that the most similar structure already reported, 3-bromo-β-lapachone (De Simone *et al.*, 2002), presents the benzo and quinone rings lying in the same plane, and the heterocycle is in a distorted half-chair conformation. In the present case, the structure of (I) also has benzo and quinone rings, designated *A* and *B*, respectively. A Cremer & Pople (1975) analysis of the six-membered non-planar ring (ring C) gives ring-puckering parameters φ = 248.4 (3)° and θ = 52.4 (2)°, and a puckering amplitude Q = 0.4497 (19) Å. Thus, the conformation of the ring is between the half-chair (*H*) and envelope (*E*) symmetrical forms.

The main differences between the reported analogues and compound (I) seem to be the strategy of self-assembly through weak intermolecular interactions. In the case of (I), the two planar rings in the molecule at (x, y, z) stack above the symmetry-related rings of the molecule at ($-x+\frac{3}{2}$, $y-\frac{1}{2}$, z), with distances of 3.659 and 3.509 Å between the centroids of rings *A* and *B*, respectively, a perpendicular distance between the rings of 3.432 Å, and centroid offsets of 1.270 and 0.731 Å, respectively. Fig. 2 shows this stacking interaction, which generates stacked molecules running almost parallel to the [010] direction. The supramolecular structure also contains a weak intermolecular C—H···O hydrogen bond between

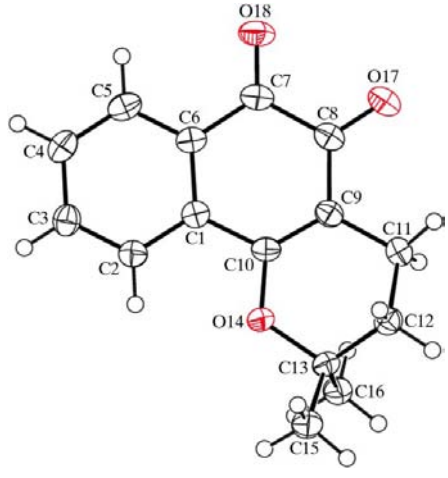


Figure 1
The molecule of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

 DOI: 10.1107/S0108270106021706

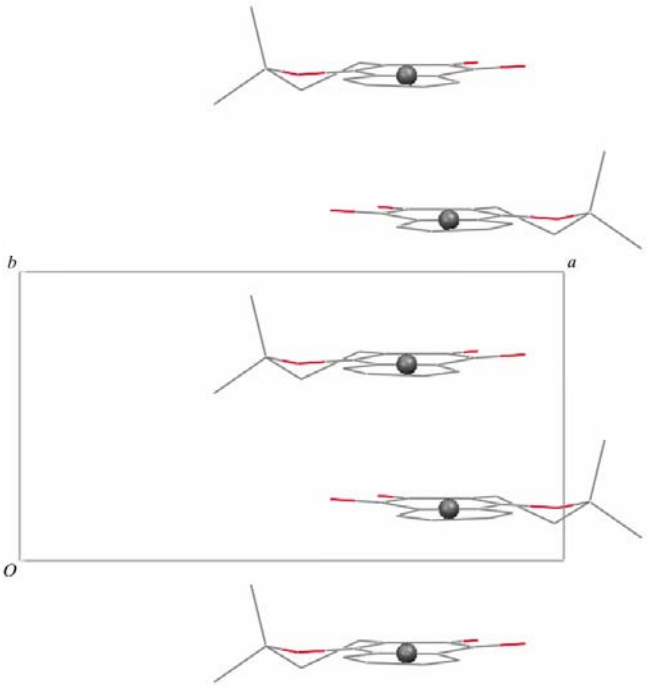


Figure 2
Five adjacent symmetry-related molecules of (I), linked by π-stacking interactions along the *c* axis. Also shown (grey spheres) are the calculated centroids of the planar rings.

atoms O17 and O18 and aromatic and non-aromatic H atoms of symmetry-related molecules. Table 1 presents the geometric parameters of these weak interactions.

As reported previously, the strategy of self-assembly through these weak interactions is of central importance for efficient and specific biological reactions, and for the design of new supramolecules possessing interesting structural and physical or chemical properties. As an example, we have found that by changing the crystal growing conditions of this molecule we can dramatically modify its dissolution rate (Landin *et al.*, 2005). This could be explained according to the different preferred orientations achieved. Further studies will be reported in subsequent publications.

Experimental

Compound (I) was used as supplied, from a batch produced by the Federal University of Pernambuco, Brazil, following the procedure of Hooker *et al.* (1936), and purified by ethanolic recrystallizations. Its ^{1}H and ^{13}C NMR spectra were completely assigned by two-dimensional NMR experiments using two-dimensional ^{1}H-detected heteronuclear one-bond (HMQC) and multiple-bond (HMBC) techniques, as follows: ^{1}H NMR ($CDCl_3$, 750 MHz): δ 1.468 (*s*, 6H, CH_3), 1.854 (*t*, 2H, CH_2), 2.573 (*t*, 2H, CH_2), 7.503 (*t*, 1H, Ar), 7.638 (*t*, 1H, Ar), 7.796–7.822 (*d*, 1H, Ar), 8.049–8.070 (*d*, 1H, Ar); ^{13}C NMR ($CDCl_3$, 750 MHz): δ 16.169 (*s*), 26.768 (*s*), 31.621 (*s*), 79.252 (*s*), 112.729 (*s*) 124.040 (*s*), 128.566 (*s*), 130.16 (*s*), 130.631 (*s*), 132.64 (*s*), 134.736 (*s*), 161.990 (*s*), 178.568 (*s*), 179.854 (*s*). The purity of (I) was confirmed by high-performance liquid chromatography (HPLC) (Waters M600, photodiode array detector) and differential scanning calorimetry (DSC Q100, TA Instruments, Delaware, USA). HPLC results showed a purity of approximately 100%. No impurities or degradation products were detected. DSC thermograms showed a single peak at 430 K, corresponding to the characteristic melting point of the drug (Krishna *et al.*, 2004), with an enthalpy of 109 J g^{-1}.

Crystal data

$C_{15}H_{14}O_3$
M_r = 242.26
Orthorhombic, *Pbca*
a = 12.8995 (6) Å
b = 6.8681 (3) Å
c = 26.6419 (13) Å
V = 2360.34 (19) Å^3
Z = 8
D_x = 1.363 Mg m^{-3}
D_m = 1.3113(49) Mg m^{-3}
D_m measured by helium–air pycnometer
Cu $K\alpha$ radiation
μ = 0.77 mm^{-1}
T = 120 (2) K
Prism, orange
0.31 × 0.13 × 0.13 mm

Data collection

Nonius KappaCCD 2000 area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2006)
T_{min} = 0.775, T_{max} = 0.905
2300 measured reflections
2300 independent reflections
2001 reflections with $I > 2\sigma(I)$
R_{int} = 0.062
θ_{max} = 69.4°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.061
$wR(F^2)$ = 0.170
S = 1.12
2077 reflections
166 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.1016P)^2 + 0.9714P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.28 e Å^{-3}
$\Delta\rho_{min}$ = −0.30 e Å^{-3}
Extinction correction: *SHELXL97* (Sheldrick, 1997)
Extinction coefficient: 0.0048 (9)

Table 1
Selected geometric parameters (Å, °).

C9—C10	1.365 (2)	O14—C10	1.339 (2)
C9—C11	1.500 (2)	O14—C13	1.483 (2)
C11—C12	1.524 (2)	O17—C8	1.229 (2)
C13—C12	1.516 (2)	O18—C7	1.212 (2)
C9—C11—C12	109.28 (14)	C13—C12—C11	112.47 (14)
C10—O14—C13	119.70 (12)	O14—C13—C12	110.00 (13)

Table 2
Weak hydrogen-bond geometry (Å, °).

D···*A*	*D*···*A*†	*D*—H···*A*‡
C11···O17^{i}	3.507 (2)	142
C12···O17^{iii}	3.340 (2)	143
C12···O17^{iv}	3.539 (2)	165
C16···O18^{i}	3.334 (2)	125
C3···O18^{ii}	3.492 (2)	147

† Distance between donor and acceptor atoms. ‡ Angle between donor, H and acceptor atoms. Symmetry codes: (i) $-x+\frac{3}{2}, y+\frac{1}{2}, z$; (ii) $x-\frac{1}{2}, -y+\frac{1}{2}, -z+1$; (iii) $-x+\frac{3}{2}, y-\frac{1}{2}, z$; (iv) $x-\frac{1}{2}, y, -z+\frac{3}{2}$.

H atoms were positioned geometrically and treated as riding, with C—H = 0.95–0.99 Å with U_{iso}(H) = 1.2U_{eq}(C) or 1.5U_{eq}(methyl C).

Data collection: *COLLECT* (Nonius, 1999); cell refinement: *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *XPREP* (Bruker, 2006); program(s) used to solve structure: *SIR97* (Altomare *et al.*, 1999); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3 for Windows* (Farrugia,

1997) and *MERCURY* (Macrae *et al.*, 2006); software used to prepare material for publication: *WinGX* (Farrugia, 1999) and *PLATON* (Spek, 2003).

Authors thank LAFEPE, Brazil, and Professor Dr Pedro Jose Rolim Neto, Federal University of Pernambuco, Brazil, for their kind gifts of the title compound. This work was supported by the Spanish Government (grant No. SAF2002-03440) and by the Programme Alban, the European Union Programme of High-Level Scholarships for Latin America (scholarship No. E04D043994BR).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GZ3007). Services for accessing these data are described at the back of the journal.

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