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2,3-Dihydro-3,3-dimethylspiro-[1*H*-4-oxanthracene-5,2′-oxiran]-10(5*H*)-one

Vitor F. Ferreira,[a] Antonio V. Pinto,[b] Maria C. R. F. Pinto,[b] Milton N. da Silva,[a] Janet M. S. Skakle,[c] Maria C. B. V. de Souza[a] and Solange M. S. V. Wardell[a]*

[a]Departamento de Química Orgânica, Universidade Federal Fluminense, 24020-150 Niterói, RJ, Brazil, [b]Departamento de Química Orgânica, Universidade Federal do Rio de Janeiro, 21941-970 Rio de Janeiro, RJ, Brazil, and [c]Department of Chemistry, University of Aberdeen, Meston Walk, Old Aberdeen, AB24 3UE, Scotland
Correspondence e-mail: s.wardell@abdn.ac.uk

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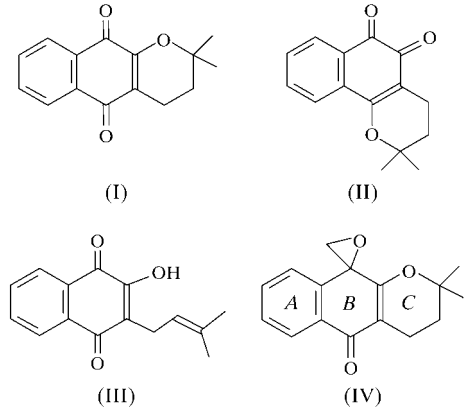
The central six-membered ring in the title compound, $C_{16}H_{16}O_3$, is almost planar (and almost coplanar with the aromatic ring), despite one of its C atoms being formally sp^3 hybridized. The planarity is a consequence of the C atom at the centre of the spirocyclic system also being part of the three-membered epoxide ring. The molecules are linked by π–π and C—H$\cdots\pi$ interactions.

Comment

α-Lapachone, (I), a 1,4-naphthoquinone, and its 1,2-isomer, β-lapachone, (II), are present as minor components of the lapacho tree (*Tabebuia avellanedae* Lorentz ex Griseb; Carvalho *et al.*, 1988). Both have important biological activities. Compound (I), for example, is an irreversible inhibitor of topoisomerase II (Krishnan & Bastow, 2000) and has a number of useful pharmacological properties, including acting as a bacteriocide, fungicide and trypanocide. Compound (II) has been intensively investigated pharmacologically, *e.g.* in cancer chemotherapy (Huang & Pardee, 1999), and in interactions with both topoisomerase I (Li *et al.*, 1993) and topomerase II (Frydman *et al.*, 1997). Lapachol, (III), an open-chain isomer of (I), is also biologically active (dos Santos *et al.*, 2001; Austin, 1974; Pinto *et al.*, 1977). Bioactivation of (III) can lead to DNA scission by NADPH–cytochrome P450 reductase (Kumagai *et al.*, 1997; Molina Portela *et al.*, 1996).

Modification of the redox centre of a naphthoquinone can result in a dramatic change in the biological activity. For example, Pinto *et al.* (1977) demonstrated that transformations of the *o*-quinone moieties of lapachones resulted in significant changes in trypanocidal activity. Despite the known pharmacological activities of (I) and the interest in related molecules, few procedures for the selective modification of the redox centre have been described to date. As part of our studies in this area, we have investigated the reaction of (I) with diazomethane. This reaction regiospecifically produced the title monoepoxide, (IV).



The structure of (IV) is shown in Fig. 1. From the determination of a centrosymmetric space group, both enantiomers of (IV) are present in the crystal, the chiral centre being C12. Ring *B* is only slightly distorted from planarity, as shown by the puckering parameters (Cremer & Pople, 1975) Q = 0.0852 (14) Å and φ = 51.4 (10)°. This is despite the presence of the formally sp^3-hybridized C12 ring atom. As well as being in the six-membered *B* ring, atom C12 is also part of the three-membered epoxide ring. The near 60° constraint of angles within the three-membered ring results in an opening up of the other angles at C12, including that within the six-membered ring, to near trigonal angles. The C11—C12—C13 bond angle of 116.57 (11)° is indeed very similar in value to the other internal bond angles in ring *B*, all of which reflect the sp^2 hybridization of the ring carbon atoms. Aromatic ring *A*, as expected, is planar. The maximum deviation [−0.0981 (14) Å] of atoms from the best plane through rings *A* and *B* is exhibited by atom C12. Ring *C* has a half-chair conformation, with puckering parameters Q = 0.4502 (19) Å and φ = 283.5 (3)°.

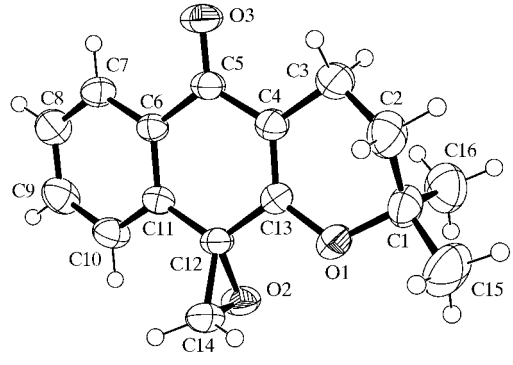


Figure 1
A view of the molecule of (IV), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

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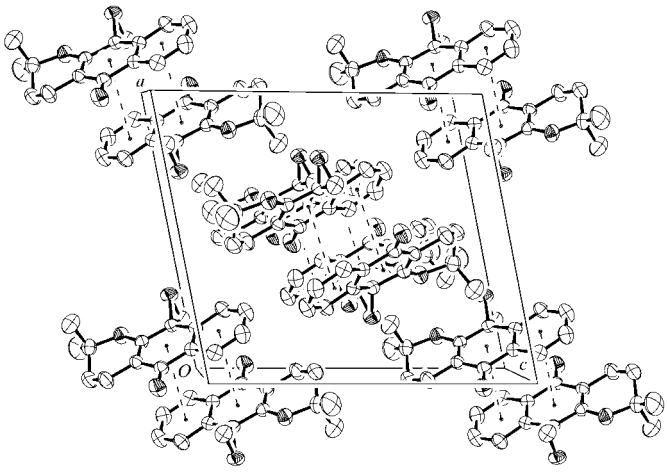

Figure 2
The molecules of (IV) within the unit cell. The π–π interactions between centroids are shown as dashed lines. H atoms have been omitted for clarity.

Intermolecular interactions in (IV) take the form of π–π and C—H$\cdots\pi$ interactions; there are no C—H$\cdots$O hydrogen bonds present. Intermolecular interactions in two polymorphs of compound (III) were reported to include O—H$\cdots$O hydrogen bonding, as well as π–π interactions (Larsen *et al.*, 1992).

Molecules of (IV) at (x, y, z) and ($2-x$, $1-y$, $-z$) form π–π-stacking interactions involving the *A* and *B* rings. The *B* rings in the two molecules are parallel, with an interplanar spacing of 3.54 Å, a distance between the ring centroids of 4.05 Å, and a centroid offset of 1.98 Å. The angle between the planes of ring *A* at (x, y, z) and ring B^{i} is 5.39°, with a distance between the ring centroids of 3.74 Å [symmetry code: (i) $2-x$, $1-y$, $-z$]. The perpendicular distances of the ring centroids, *Cg*(*A*) and *Cg*(*B*), from the symmetry-related centroids, *Cg*(*B*)^{i} and *Cg*(*A*)^{i}, are 3.66 and 3.58 Å, respectively, with the interactions forming dimers centred on (1,$\frac{1}{2}$,0) (see Fig. 2). Rings *A* and A^{i} are necessarily parallel, with an interplanar separation of 3.49 Å. Here, however, the distance between the ring centroids is 4.86 Å, so that the offset of the centroids is too long for interaction, at 3.39 Å.

The C—H$\cdots\pi$ interactions involve methyl H atoms on ring *C* in molecules at (x, y, z) and the centroid of ring *B* of molecules at ($\frac{3}{2}-x$, $\frac{1}{2}+y$, $\frac{1}{2}-z$), with parameters for C15—H15*C*$\cdots$*Cg*(*B*) of H$\cdots$*Cg* 3.32 Å, C—H$\cdots$*Cg* 139° and C$\cdots$*Cg* 4.093 (3) Å, and for C16—H16*A*$\cdots$*Cg*(*B*) of H$\cdots$*Cg* 3.04 Å, C—H$\cdots$*Cg* 146° and C$\cdots$*Cg* 3.879 (2) Å.

As far as we are aware, compound (IV) is the first spiro-oxirane derivative of a *p*-quinone to be reported to date. The regiospecificity of the reaction between diazomethane and (I) clearly shows that the enhanced electrophilic character of the carbonyl C12 atom compared with that of atom C5 far outweighs the greater steric hindrance at the C12—O2 carbonyl group resulting from the neighbouring methyl groups in ring *C*.

Experimental

A solution of diazomethane (1.2 equivalents) in diethyl ether was added to solid α-lapachone, (I). After 168 h at 277 K, the reaction mixture was rotary evaporated, subjected to column chromatography on silica gel and recrystallized from acetone. The yield of (IV) was 95% (m.p. 391–393 K). Spectroscopic analysis, ^{1}H NMR (300 MHz, $CDCl_3$, δ, p.p.m.): 1.36 (3H, *s*), 1.37 (3H, *s*), 1.76 (1H, *ddd*, J = 2.4, 6.6 and 7.2 Hz), 1.83 (1H, *ddd*, J = 2.4, 6.6 and 7.5 Hz), 2.39 (1H, *ddd*, J = 2.1, 6.6 and 7.5 Hz), 2.59 (1H, *ddd*, J = 2.1, 6.3 and 7.2 Hz), 3.29 (1H, *d*, J = 6.9 Hz), 3.65 (1H, *d*, J = 6.9 Hz), 7.23 (1H, *dd*, J = 1.5 and 7.5 Hz), 7.46 (1H, *dd*, J = 1.2 and 7.5 Hz), 7.54 (1H, *dd*, J = 1.2 and 7.5 Hz), 8.19 (1H, *dd*, J = 1.5 and 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, δ, p.p.m.): 15.9 (CH_2), 25.7 (CH_3), 31.2 (CH_2), 51.3 (C), 56.8 (CH_2), 77.3 (C), 113.8 (C), 121.9 (CH), 125.7 (CH), 127.8 (CH), 131.4 (CH), 131.9, 136.4 (C), 163.2 (C), 182.9 (C); IR (cm^{-1}): 3063 (C—H, epoxide), 2928–2983 (C—H), 1621 (C=O), 1575, 1149 (C—O); MS (*m*/*z*; low resolution): 200 (100%), 256 (38%), 115 (6%), 223 (5%), 172 (4%); MS (high resolution): M^{+} 256.10107 ($C_{16}H_{16}O_3$).

Crystal data

$C_{16}H_{16}O_3$
M_r = 256.29
Monoclinic, $P2_1/n$
a = 12.2764 (13) Å
b = 7.8543 (9) Å
c = 13.6935 (15) Å
β = 101.666 (2)°
V = 1293.1 (2) Å^3
Z = 4
D_x = 1.316 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 4478 reflections
θ = 3.4–32.3°
μ = 0.09 mm^{-1}
T = 292 (2) K
Block, colourless
0.5 × 0.4 × 0.4 mm

Data collection

Bruker SMART 1000 CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Bruker, 2000)
T_{min} = 0.826, T_{max} = 0.928
12 411 measured reflections
4627 independent reflections
2879 reflections with $I > 2\sigma(I)$
R_{int} = 0.040
θ_{max} = 32.6°
$h = -18 \rightarrow 9$
$k = -11 \rightarrow 11$
$l = -20 \rightarrow 19$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.059
$wR(F^2)$ = 0.187
S = 1.01
4627 reflections
174 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0895P)^2 + 0.2537P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.39 e Å^{-3}
$\Delta\rho_{min}$ = −0.23 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

O1—C1	1.4627 (19)	C4—C5	1.443 (2)
O2—C12	1.4412 (15)	C5—C6	1.4854 (18)
O2—C14	1.416 (2)	C6—C11	1.3817 (17)
O3—C5	1.2255 (16)	C11—C12	1.4721 (19)
C4—C13	1.3430 (18)	C12—C13	1.4818 (18)
C11—C12—C13	116.57 (11)	O2—C12—C13	115.18 (11)
O2—C12—C11	115.47 (11)	C14—O2—C12	61.99 (9)
C14—C12—C11	120.49 (12)	O2—C12—C14	58.17 (9)
C14—C12—C13	117.57 (12)	O2—C14—C12	59.83 (9)

Compound (IV) is monoclinic; space group $P2_1/n$ was uniquely assigned from the systematic absences. All H atoms were treated as riding, with C—H distances of 0.93, 0.97 and 0.96 Å for phenyl, methylene and methyl H atoms, respectively. Conformational and hydrogen-bonding analyses were performed using *PLATON* (Spek, 2002).

Data collection: *SMART* (Bruker, 1998); cell refinement: *SAINT* (Bruker, 2000); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEX* in *OSCAIL* (McArdle, 1994, 2000) and *ORTEP*-3 *for Windows* (Farrugia, 1997); software used to prepare material for publication: *SHELXL*97.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1577). Services for accessing these data are described at the back of the journal.

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