

2-Hydroxy-3-(3-oxobutyl)naphtha-
lene-1,4-dioneHamid Reza Nasiri,^a M. Gregor Madej,^b C. Roy D.
Lancaster,^b Harald Schwalbe^a and Michael Bolte^{c*}^aInstitute of Organic Chemistry and Chemical Biology, Center for Biomolecular Magnetic Resonance, J. W. Goethe-Universität Frankfurt, Max-von-Laue-Strasse 7, 60438 Frankfurt/Main, Germany, ^bMax Planck Institute of Biophysics, Department of Molecular Membrane Biology, Max-von-Laue-Strasse 3, 60438 Frankfurt/Main, Germany, and ^cInstitut für Anorganische Chemie, J. W. Goethe-Universität Frankfurt, Max-von-Laue-Strasse 7, 60438 Frankfurt/Main, Germany
Correspondence e-mail: bolte@chemie.uni-frankfurt.de

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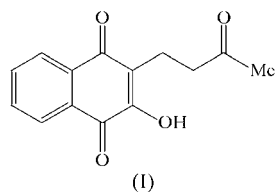
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The title compound, C₁₄H₁₂O₄, forms crystals which appear monoclinic but are actually twinned triclinic. The asymmetric unit consists of two similar molecules, which differ only in the conformation of the 3-oxobutyl side chain. The molecular conformation is characterized by an intramolecular O—H...O hydrogen bond between the hydroxy group and the adjacent carbonyl O atom. The crystal structure is stabilized by O—H...O hydrogen bonds connecting the molecules into zigzag chains running along the *b* axis.

Comment

3-Alkyl-2-hydroxy-1,4-naphthoquinones are well known as antimalarial agents (Fieser & Heymann, 1948; Fieser & Nazer, 1967; Fieser & Schirmer, 1967). In rats, they were found to cause haemolysis and renal damage (Munday *et al.*, 1995). Recently, we have shown that this class of 1,4-naphthoquinones are also able to act as competitive inhibitors, with IC₅₀ values in the μ M range in dihaem-containing membrane protein complexes (Madej, Nasiri, Hilgendorff, Schwalbe & Lancaster, 2006; Madej, Nasiri, Hilgendorff, Schwalbe, Unden & Lancaster, 2006). To possibly improve the binding affinity of



the inhibitors, the alkyl side chain at the 3-position of the 1,4-naphthoquinone system was changed. Here, a Michael-type reaction was used for the introduction of the 3-oxobutyl residue.

The title compound, (I), was originally synthesized by the reaction of 2-hydroxy-1,4-naphthoquinone with methyl vinyl ketone as an α,β -unsaturated ketone in a 2:1 ratio (Rafart *et al.*, 1976). For substituted 2-hydroxy-1,4-naphthoquinone, a higher concentration of the ketone was used (Cassis *et al.*, 1982). In the case of (I), we observed that a slight increase of methyl vinyl ketone results in the formation of the carbon and oxygen bialkylated by-product.

A perspective view of the title compound is shown in Fig. 1. Bond lengths and angles can be regarded as normal (Cambridge Structural Database, Version 5.27 of November 2005, updated August 2006; *MOGUL*, Version 1.1; Allen, 2002). There are two very similar molecules in the asymmetric unit. In each independent molecule, the naphthoquinone ring system is almost planar (the r.m.s. deviations for the non-H atoms are 0.120 and 0.036 Å). The 3-oxobutyl side chain has an all-*trans* conformation and the mean plane through the five

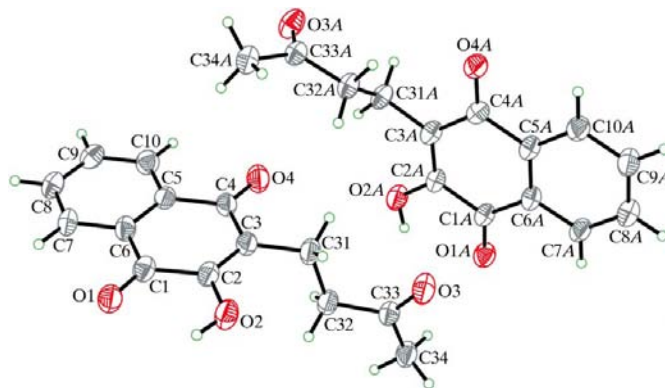


Figure 1

A perspective view of the two molecules in the asymmetric unit of the title compound, showing the atom numbering and displacement ellipsoids at the 50% probability level.

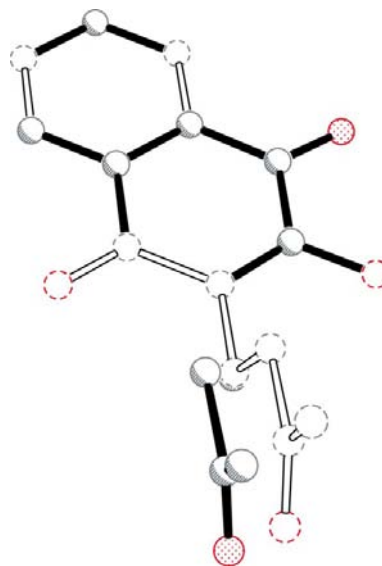


Figure 2

A least-squares fit of the two molecules of (I). Atoms O1 to C34 are shown with open bonds and atoms O1A to C34A with full bonds.

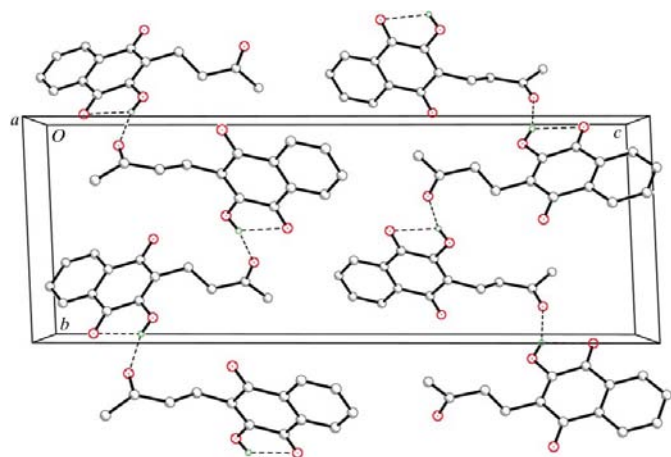


Figure 3

The packing of (I) viewed in the *bc* plane. H atoms not involved in hydrogen bonds have been omitted for clarity. Hydrogen bonds are shown as dashed lines.

non-H atoms is twisted by 86.7 (3) and 71.8 (4)° with respect to the naphthoquinone ring system. This is the only difference between the two molecules in the asymmetric unit (Table 1). A least-squares fit of the ten cyclic C atoms of the two molecules gives an r.m.s. deviation of 0.013 Å (Fig. 2). The crystal packing (Fig. 3) shows that the molecules form hydrogen-bonded zigzag chains running along the *b* axis (Table 2). In addition to the intermolecular hydrogen bonds, an intramolecular O—H...O contact can be observed between the hydroxy group and the adjacent carbonyl O atom (Table 2).

The crystal structure of a related hydroxynaphthoquinone, the natural product lapachone (Larsen *et al.*, 1992), differs from (I) by a methyl group instead of a keto O atom at C33 and by a double bond between atoms C32 and C33 instead of a single bond. Nevertheless, the two molecules show similar geometrical features.

Experimental

The title compound was synthesized according the method described by Rafart *et al.* (1976). Our procedure differed from the original one by using pyridine (absolute) instead of triethylamine in benzene. Single crystals suitable for X-ray diffraction were obtained from a concentrated dichloromethane solution of (I). ¹H NMR (250.13 MHz, CDCl₃): δ 8.0 (*m*, 2H, aromatic), 7.6 (*m*, 2H, aromatic), 7.6 (*s br*, 1H, OH), 2.80 (*m*, 2H, CH₂), 2.65 (*m*, 2H, CH₂), 2.11 (*s*, 3H, CH₃). ¹³C NMR (CDCl₃): δ 208.5, 184.5, 181.0 (C=O), 153.5, 132.7, 129.4, 122.7 (C), 134.8, 132.9, 126.6, 126.1 (CH), 41.6, 29.5 (CH₂), 17.8 (CH₃).

Crystal data

C ₁₄ H ₁₂ O ₄	$V = 1122.8 (3) \text{ \AA}^3$
$M_r = 244.24$	$Z = 4$
Triclinic, $P\bar{1}$	$D_x = 1.445 \text{ Mg m}^{-3}$
$a = 4.7858 (7) \text{ \AA}$	Mo $K\alpha$ radiation
$b = 9.2295 (15) \text{ \AA}$	$\mu = 0.11 \text{ mm}^{-1}$
$c = 25.447 (3) \text{ \AA}$	$T = 173 (2) \text{ K}$
$\alpha = 87.469 (12)^\circ$	Needle, light brown
$\beta = 89.288 (11)^\circ$	$0.33 \times 0.09 \times 0.09 \text{ mm}$
$\gamma = 89.931 (12)^\circ$	

Data collection

Stoe IPDS-II two-circle
diffractometer
 ω scans
9193 measured reflections

4166 independent reflections
3038 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.082$
 $\theta_{\text{max}} = 25.7^\circ$

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.087$
 $wR(F^2) = 0.282$
 $S = 1.11$
4166 reflections
333 parameters
H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.164P)^2 + 0.9504P]$
where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\text{max}} < 0.001$
 $\Delta\rho_{\text{max}} = 0.37 \text{ e \AA}^{-3}$
 $\Delta\rho_{\text{min}} = -0.35 \text{ e \AA}^{-3}$
Extinction correction: *SHELXL97*
Extinction coefficient: 0.053 (13)

Table 1

Selected torsion angles (°).

C2—C3—C31—C32	80.8 (6)	C2A—C3A—C31A—C32A	118.0 (5)
C3—C31—C32—C33	179.2 (5)	C3A—C31A—C32A—C33A	175.6 (5)
C31—C32—C33—C34	−169.6 (5)	C31A—C32A—C33A—C34A	156.0 (5)

Table 2

Hydrogen-bond geometry (Å, °).

<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>
O2—H2...O3A ⁱ	0.84	2.18	2.916 (6)	147
O2A—H2A...O3 ⁱⁱ	0.84	2.13	2.871 (5)	148
O2—H2...O1	0.84	2.21	2.670 (5)	114
O2A—H2A...O1A	0.84	2.21	2.665 (4)	114

Symmetry codes: (i) $x + 1, y + 1, z$; (ii) $x - 1, y, z$.

The frames collected during data collection did not show split reflections, but only 63% of the reflections used for cell determination could be indexed. For the remaining 37%, no cell could be found at all. This is a warning sign for twinning. Nevertheless, the reflections were integrated the usual way. The cell parameters of (I) ostensibly indicate a monoclinic cell, since two angles are almost rectangular. The R_{int} value for the monoclinic crystal system is 0.17 (compared with 0.082 for the triclinic crystal system). However, there are no systematic extinctions and the structure cannot be solved in any of the monoclinic space groups. Thus, the structure was solved in the triclinic space group $P\bar{1}$. After having encountered severe problems during structure solution, anisotropic refinement remained stalled at $R1 = 0.14$. It was therefore assumed that the crystal was twinned and a test for twinning using the program *PLATON* (Spek, 2003) yielded three twin matrices, *viz.* (a) $(\bar{1}00/010/0.132, \bar{0}.243, 1)$, (b) $(\bar{1}00/010/0, 0.25, \bar{1})$ and (c) $(100/010/00\bar{1})$. Twin laws (a) and (b) do not correspond to any obvious crystallographic symmetry operation. Twin law (c) is a twofold rotation operation which is usually not present in the triclinic crystal system, but which is possible in the present case because two cell angles are almost 90°. On the basis of these twin laws, *PLATON* was used to generate a file containing the original data and the additional reflections. For refinement, the data were read in *via* HKLF5 and three additional variables were introduced (using the BASF command) describing the fractional contributions of the twin components. Applying these twin laws provided the ultimate success ($R1$ dropped below 0.1). All H atoms could now be located by difference Fourier synthesis. They were refined with fixed individual displacement parameters [$U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C}, \text{O})$ or $1.5U_{\text{eq}}(\text{methyl C})$] using a riding model, with O—H distances of 0.84 Å, and C—H distances of 0.95 (aromatic), 0.98 (methyl) or 0.99 Å (methylene). The hydroxy and methyl groups were allowed to

rotate but not to tip. The twin ratios of the minor components refined to 0.101 (3) for twin law (*a*), 0.120 (4) for (*b*) and 0.027 (2) for (*c*). Although the contribution of the domain (*c*) might be rather small, neglecting it leads to significantly worse figures of merit (*wR*2 = 0.299 and *R*1 = 0.097).

Data collection: *X-AREA* (Stoe & Cie, 2001); cell refinement: *X-AREA*; data reduction: *X-AREA*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *XP* in *SHELXTL-Plus* (Sheldrick, 1991); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3066). Services for accessing these data are described at the back of the journal.

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