Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Cinnamoyl shikonin[1]

Sanjay Sarkhel,[a] Shefali,[b] Vijayvitthal T. Mathad,[b] Kanwal Raj,[b] Amiya P. Bhaduri,[b] Prakas R. Maulik,[a]* Charlotte K. Broder[c] and Judith A. K. Howard[c]

[a]Molecular and Structural Biology Division, Central Drug Research Institute, Lucknow 226 001, India, [b]Medicinal Chemistry Division, Central Drug Research Institute, Lucknow 226 001, India, and [c]Department of Chemistry, University of Durham, Durham DH1 3LE, England
Correspondence e-mail: maulik_prakas@yahoo.com

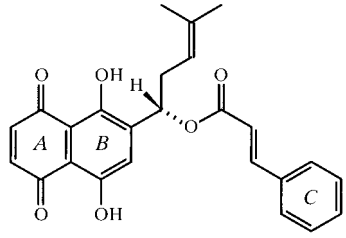
Received 27 March 2001
Accepted 12 July 2001

The title compound, 1-(5,8-dihydro-1,4-dihydroxy-5,8-dioxo-2-naphthyl)-4-methylpent-3-en-1-yl cinnamate, $C_{25}H_{22}O_6$, crystallizes in space group $P2_1$. The phenyl ring of the cinnamate is *anti* to the carbonyl group of the same moiety [C—C—C—C = −175.6 (2)°] and is nearly parallel to the naphthyl ring system. Two six-membered rings formed by intramolecular hydrogen bonds, with O—H···O distances of 2.587 (2) and 2.589 (2) Å, occur on either side of the fused ring system, creating a tetracyclic pyrene-shaped system. The phenyl ring forms an intermolecular stack with the benzoquinone ring, as a result of aromatic π–π interactions.

Comment

Arnebin-1 (β,β-dimethyl acryloyl shikonin), a naturally occurring naphthoquinone from the root of the plant *Arnebia nobilis*, belongs to the alkanin/shikonin family (Shukla *et al.*, 1969). The toxic effects of this compound restricted its further development as a clinically useful therapeutic agent, in spite of its wound healing, anti-inflammatory, antithrombotic, antimicrobial and anticancer activities (Papageorgiou *et al.*, 1999). This necessitated the development of numerous analogues of shikonin with greatly reduced toxicity. One such analogue is the title compound, (I), which shows a growth-inhibitory effect on prostate cancer cells (Gaddipati *et al.*, 2000). This prompted us to undertake the present diffraction study in order to confirm the overall three-dimensional structure of (I).

The conformation of (I) and the atom-numbering scheme are shown in Fig. 1. The molecule contains one napthaquinone ring (*A*/*B* fused ring system), to which a phenyl ring (*C*) is attached *via* an ester bond, and one chiral centre (C11). Although the present study does not establish the absolute configuration of the molecule [Flack (1983) parameter 0.3 (9)], the parent shikonin has the *R* configuration, as determined by the chemical degradation method (Arakawa & Nakazaki, 1961). The phenyl ring *C* is almost parallel to the *A*/*B* ring system; the interplanar angle between the two rings is 1.7 (1)°. Moreover, the phenyl ring at C19 is *anti* to the carbonyl group at C17 [C17—C18—C19—C20 = −175.6 (2)°].



(I)

The molecule of (I) contains two potential hydrogen-bond donors (–OH groups O5—H5 and O8—H8), which are involved in intramolecular hydrogen-bonding interactions with carbonyl groups C4═O4 and C1═O1 (Table 2) through the formation of six-membered rings (Fig. 1). The formation of such rings is preferred to intermolecular hydrogen bonding (Bilton *et al.*, 2000). The strong intramolecular O···O distances observed in (I) are in the same range as those found in the parent naphthazarin C at 60 K (Herbstein *et al.*, 1985).

The hydroxyl H atoms, H5 and H8, were located in a difference Fourier map, in view of the ambiguity with regard to their positions in related naphthazarin systems (Herbstein *et al.*, 1985). A comparison of bond lengths in (I) with those of naphthazarin C (neutron diffraction at 60 K) and other related systems (Herbstein *et al.*, 1985, and references therein) shows that, on average, C═O is *ca* 0.05 Å longer in (I), while C—OH is *ca* 0.03 Å shorter. This suggests that, in close analogy with the crystal structure of naphthazarin C, the hydroxyl H atoms are not completely localized in (I) at 100 K and ordering will be favoured at lower temperatures, since a complete localization is only possible at 0 K.

In addition, weak hydrogen-bonding interactions of the type C—H···O are also observed (Table 2). The crystal packing (Fig. 2) further shows that the phenyl ring *C* stacks

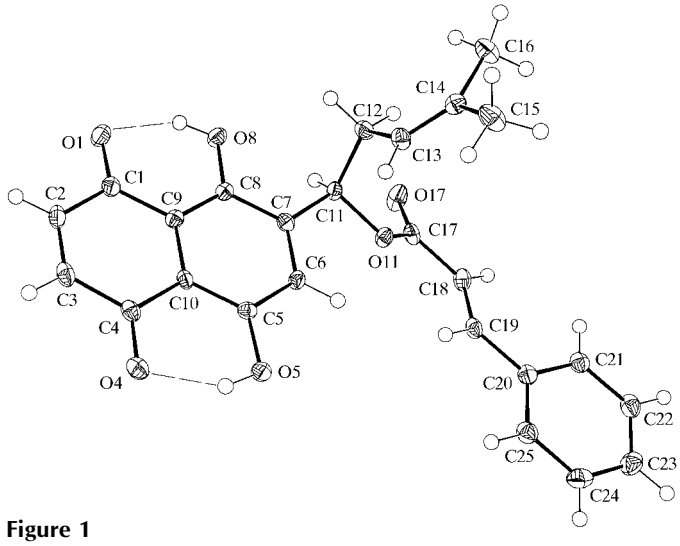


Figure 1
The molecular structure of (I) with the atom-numbering scheme, showing displacement ellipsoids at the 50% probability level. H atoms are drawn as small spheres of arbitrary radii and intramolecular O—H···O bonds are shown by dotted lines.

[1] CDRI Communication No. 6153.

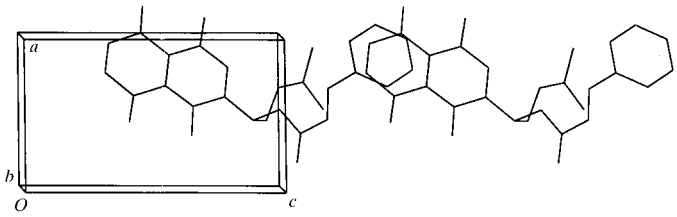


Figure 2
The packing in (I), showing the intermolecular stacking of rings *C* and *A* as a result of aromatic π–π interactions.

with the benzoquinone ring *A*, as a result of aromatic π–π interactions. The average intermolecular stacking distance and the angle between the rings, which overlap substantially in a 'face-to-face' orientation as per the model proposed by Hunter & Sanders (1990), are 3.3 Å and 1.1 (1)°, respectively. Since the benzoquinone ring is electron deficient, it can allow a substantial face-to-face overlap with the relatively neutral phenyl ring without much π–π repulsion.

Experimental

The synthesis of (I) was carried out by hydrolysing β,β-dimethyl acryloyl shikonin with sodium hydroxide, followed by esterification with cinnamic anhydride and 1,3-dicyclohexylcarbodiimide. Crystals of (I) of diffraction quality were grown from a hexane–methylene chloride solution at room temperature.

Crystal data

$C_{25}H_{22}O_6$
M_r = 418.43
Monoclinic, $P2_1$
a = 6.16770 (10) Å
b = 15.7416 (3) Å
c = 10.5141 (2) Å
β = 90.7630 (10)°
V = 1020.72 (3) Å^3
Z = 2
D_x = 1.361 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 510 reflections
θ = 4.1–27.4°
μ = 0.10 mm^{-1}
T = 100 (2) K
Block, red
0.5 × 0.1 × 0.1 mm

Data collection

Bruker SMART CCD area-detector diffractometer
ω scans
Absorption correction: ψ scan (*XPREP*; Sheldrick, 1994)
T_{min} = 0.885, T_{max} = 1.000
7463 measured reflections
4357 independent reflections
4011 reflections with $I > 2\sigma(I)$
R_{int} = 0.028
θ_{max} = 27.5°
$h = -8 \rightarrow 7$
$k = -20 \rightarrow 20$
$l = -13 \rightarrow 11$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.041
$wR(F^2)$ = 0.096
S = 1.09
4357 reflections
290 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0219P)^2 + 0.7688P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.25 e Å^{-3}
$\Delta\rho_{min}$ = −0.25 e Å^{-3}

The hydroxyl H atoms, H5 and H8, were located from the difference Fourier map and refined freely. The remaining H atoms were placed in geometrically idealized positions and allowed to ride on their parent atoms, with C—H = 093–0.98 Å and U_{iso}(H) = 1.2U_{eq}(C). Three reflections [largest deviation $\Delta(F^2)/\sigma > 6.4$] were suppressed during the final cycles of refinement.

Data collection: *SMART* (Bruker, 1998); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 1998); program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *NRCVAX* (Gabe *et al.*, 1989), *ORTEP* (Johnson, 1965) and *PLUTO* (Motherwell & Clegg, 1978).

Table 1
Selected torsion angles (°).

C9—C1—C2—C3	−0.3 (3)	C3—C4—C10—C9	−1.3 (3)
C1—C2—C3—C4	−1.7 (3)	C7—C11—O11—C17	148.35 (17)
C2—C3—C4—C10	2.4 (3)	C11—O11—C17—C18	176.89 (18)
C10—C5—C6—C7	−0.9 (3)	O11—C17—C18—C19	12.0 (3)
C5—C6—C7—C8	0.3 (3)	C17—C18—C19—C20	−175.6 (2)
C6—C7—C8—C9	0.3 (3)	C25—C20—C21—C22	−0.8 (3)
C7—C8—C9—C10	−0.2 (3)	C20—C21—C22—C23	0.6 (3)
C2—C1—C9—C10	1.4 (3)	C21—C22—C23—C24	0.3 (4)
C6—C5—C10—C9	1.0 (3)	C22—C23—C24—C25	−0.9 (4)
C8—C9—C10—C5	−0.4 (3)	C21—C20—C25—C24	0.1 (3)
C1—C9—C10—C4	−0.6 (3)	C23—C24—C25—C20	0.7 (4)

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O5—H5···O4	0.87 (3)	1.81 (3)	2.587 (2)	148 (3)
O8—H8···O1	0.88 (4)	1.79 (3)	2.589 (2)	150 (3)
C3—H3···O17^{i}	0.93	2.47	3.356 (3)	160
C11—H11···O5^{ii}	0.98	2.56	3.359 (3)	138
C16—H16*A*···O1^{iii}	0.96	2.72	3.631 (3)	159
C21—H21···O4^{iv}	0.93	2.62	3.538 (3)	170

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

SS thanks CSIR, India, for a Senior Research Fellowship. CKB and JAKH thank the EPSRC for their support. We thank the referee for pointing out the disorder aspects of the hydroxyl H atoms in naphthazarin.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: DE1171). Services for accessing these data are described at the back of the journal.

References

Arakawa, H. & Nakazaki, M. (1961). *Chem. Ind.* (*London*), p. 947.
Bilton, C., Allen, F. H., Shields, G. P. & Howard, J. A. K. (2000). *Acta Cryst.* B**56**, 849–856.
Bruker (1998). *SMART* and *SAINT*. Bruker AXS Inc., Madison, Wisconsin, USA.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Gabe, E. J., Le Page, Y., Charland, J.-P., Lee, F. L. & White, P. S. (1989). *J. Appl. Cryst.* **22**, 384–387.
Gaddipati, P. J., Mani, H., Shefali, Raj, K., Mathad, T. V., Bhaduri, A. P. & Maheshwari, K. R. (2000). *Anticancer Res.* **20**, 2547–2552.
Herbstein, F. H., Kapon, M., Reisner, G. M., Lehman, M. S., Kress, R. B., Wilson, R. B., Shiau, W.-I., Duesler, E. N., Paul, I. C. & Curtin, D. Y. (1985). *Proc. R. Soc. London Ser. A.* **399**, 295–319.
Hunter, C. A. & Sanders, J. K. M. (1990). *J. Am. Chem. Soc.* **112**, 5525–5534.
Johnson, C. K. (1965). *ORTEP*. ORNL-3794. Oak Ridge National Laboratory, Tennessee, USA.
Motherwell, W. D. S. & Clegg, W. (1978). *PLUTO*. University of Cambridge, England.
Papageorgiou, V. P., Assimopoulou, A. N., Couladouros, E. A., Hepworth, D. & Nicolaou, K. C. (1999). *Angew. Chem. Int. Ed.* **38**, 271–300.
Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.
Sheldrick, G. M. (1994). *XPREP* in *SHELXTL*. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Sheldrick, G. M. (1997). *SHELXL*97. University of Göttingen, Germany.
Shukla, Y. N., Tandon, J. S., Bhakuni, D. S. & Dhar, M. M. (1969). *Experientia*, **25**, 357–358.