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c-5-Hydroxy-*r*-2,*c*-4-bis(isopropoxycarbonyl)-*t*-5-methyl-*t*-3-phenylcyclohexanone

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Key indicators

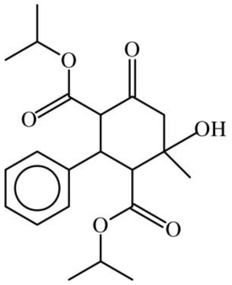
Single-crystal X-ray study
T = 273 K
Mean σ(C–C) = 0.002 Å
R factor = 0.037
wR factor = 0.104
Data-to-parameter ratio = 14.5

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

In the title compound, $C_{21}H_{28}O_6$, the cyclohexanone ring exhibits a chair conformation. The isopropoxy carbonyl groups are oriented in different directions with respect to the cyclohexanone ring. In the crystal structure, weak intermolecular C—H···O hydrogen bonds link the molecules into two-dimensional sheets parallel to the *bc* plane.

Comment

Pharmaceutical preparations such as aminomethylphenylcyclohexanone derivatives used in the treatment of pain, inflammatory reactions, allergic reactions, depression, drug abuse, alcohol abuse, gastritis, cardiovascular disease, respiratory tract disease, coughing, mental illness, epilepsy, urinary incontinence, itching and diarrhoea has been the subject of patents (Puetz *et al.*, 2003). Cyclohexanone derivatives penetrate into the stratum corneum and alter the skin permeability of indomethacin by fluidizing or modifying the hard hydrophobic barrier of the corneum (Danyi *et al.*, 1989). In view of these important applications, an X-ray crystal structure determination of the title compound, (I), has been undertaken.



(I)

In (I) (Fig. 1), the cyclohexanone ring adopts a chair conformation. A similar conformation was observed in related structures (Mootz & Berking, 1969; Groth, 1972; Bocelli, 1981; Spek *et al.*, 1990; Ravikumar & Mehdi, 1993). The mean value [55.4 (6)°] of the endocyclic torsion angles of the cyclohexanone ring in (I) shows that it is slightly more puckered than the idealized cyclohexanone ring [54.1 (3)°, MM2 calculation; Allinger, 1977). The values of the puckering parameters (Cremer & Pople, 1975) of the cyclohexanone ring [Q = 0.567 (2) Å, θ = 177.34 (14)° and φ = 62 (3)°] compare well with the values reported by Ravikumar & Mehdi (1993).

A comparison of the conformation of (I) with those in the related compounds 4-ethoxycarbonyl-3-hydroxy-3-phenylcyclohexanone, (II) (Hernández-Ortega *et al.*, 2001), 4-ethoxycarbonyl-3-ethoxypropanoyl-3-phenylcyclohexanone,

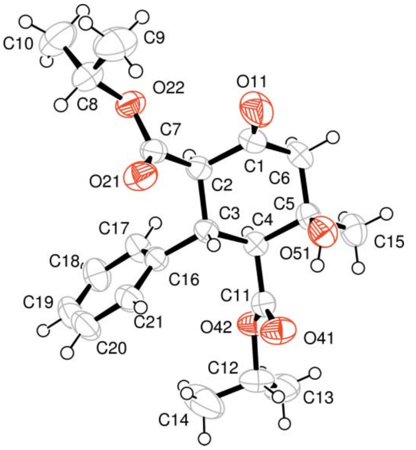


Figure 1
A view of (I), with the atom-numbering scheme and displacement ellipsoids drawn at the 50% probability level.

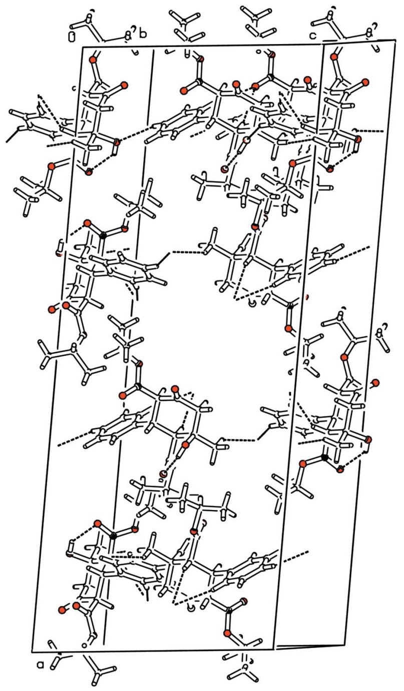


Figure 2
A packing diagram of (I), showing the intermolecular C—H$\cdots$O hydrogen bonds as dashed lines.

(III) (Brunner & Maas, 1995), (4-cyano-4-*tert*-butoxycarbonyl-3,5-diphenylcyclohexanone, (IV) (Rowland *et al.*, 1998), and 5-hydroxy-5-methyl-2,4-bis(methylcarbonyl)-3-(3-nitrophenyl)-cyclohexanone, (V) (Ravikumar & Mehdi, 1993), shows the following features. In (I), the two isopropoxycarbonyl groups at C2 and C4 are substituted in β-equatorial positions (Table 1). The phenyl ring (ring *A*) attached to C3 in (I), (II), (IV) and (V) adopts an α equatorial orientation, while in (III) it is in a β axial position. In (I) and (V), the methyl and hydroxy groups at C5 are oriented in equatorial and β axial positions, respectively. The mean planes through C1, C3, C4 and C6 and ring *A* make a dihedral angle of 73.76 (5)°. This value is smaller than those reported for (II) [86.09 (8)°], (III) (81.4°) and (V) (77°). The dihedral angles between ring *A* and the carboxy groups C7/O21/O22 and C11/O41/O42 are 82.84 (10) and 54.30 (15)°, respectively. The latter value is comparable to that reported for (II) (54.9°), (IV) (58.3°) and (V) (53.6°). These two carbonyl groups in (I) are twisted in different directions with C5—C4—C11—O41 and C1—C2—C7—O21 torsion angles of 55.50 (16) and −90.69 (16)°, respectively, facilitating the formation of an intramolecular O—H$\cdots$O hydrogen bond (Table 2). The corresponding torsion angles in (V) are 49.2 (5) and −79.7 (4)°, respectively.

In the crystal structure, weak intermolecular C—H$\cdots$O hydrogen bonds (Desiraju, 1997; Bernstein *et al.*, 1995; Table 2) link the molecules into two-dimensional sheets parallel to the *bc* plane (Fig. 2)

Experimental

A mixture of isopropyl acetoacetate (100 mmol), benzaldehyde (50 mmol) and methylamine (50 mmol) in ethanol (50 ml) was heated to boiling. The reaction mixture was allowed to stand overnight. The separated solid was filtered off and purified by recrystallization from ethanol (yield 80%, m.p. 463 K).

Crystal data

$C_{21}H_{28}O_6$
$M_r = 376.43$
Monoclinic, $C2/c$
$a = 35.775$ (6) Å
$b = 5.7948$ (10) Å
$c = 20.174$ (3) Å
$\beta = 99.893$ (3)°
$V = 4120.1$ (12) Å^3
$Z = 8$
$D_x = 1.214$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 8602 reflections
$\theta = 2.2$–27.9°
$\mu = 0.09$ mm^{-1}
$T = 273$ (2) K
Block, colourless
0.19 × 0.11 × 0.09 mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
ω scans
18792 measured reflections
3617 independent reflections
3175 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.019$
$\theta_{\rm max} = 25.0°$
$h = -42 \rightarrow 42$
$k = -6 \rightarrow 6$
$l = -23 \rightarrow 23$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.037$
$wR(F^2) = 0.104$
$S = 1.05$
3617 reflections
250 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0482P)^2 + 2.014P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\rm max} < 0.001$
$\Delta\rho_{\rm max} = 0.20$ e Å^{-3}
$\Delta\rho_{\rm min} = -0.14$ e Å^{-3}

Table 1
Selected torsion angles (°).

C6—C1—C2—C7	178.36 (11)	C16—C3—C4—C5	179.96 (10)
C1—C2—C3—C16	−176.05 (11)	C11—C4—C5—C6	−177.33 (11)
C7—C2—C3—C4	−172.92 (10)	O51—C5—C6—C1	−61.73 (14)
C2—C3—C4—C11	176.00 (10)	C15—C5—C6—C1	179.52 (12)

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

D—H$\cdots$$A$	D—H	H$\cdots$$A$	$D$$\cdots$$A$	D—H$\cdots$$A$
C4—H4$\cdots$O21^{i}	0.98	2.60	3.4678 (16)	148
C17—H17$\cdots$O21^{i}	0.93	2.57	3.4759 (18)	166
C15—H152$\cdots$O51^{i}	0.96	2.59	3.404 (2)	143
C19—H19$\cdots$O51^{ii}	0.93	2.55	3.4005 (18)	152
O51—H51$\cdots$O41	0.82	2.08	2.7724 (14)	142

Symmetry codes: (i) $x, y+1, z$; (ii) $x, -y+1, z-\frac{1}{2}$.

The methyl H atoms were constrained to an ideal geometry (C—H = 0.96 Å), with $U_{\rm iso}$(H) values of $1.5U_{\rm eq}$(C), but were allowed to rotate freely about the C—C bond. The hydroxy H atom was positioned geometrically, with O—H = 0.82 Å and $U_{\rm iso}$(H) = $1.5U_{\rm eq}$(O). All other H atoms were positioned geometrically in idealized positions (C—H = 0.93–0.98 Å) and refined as riding with $U_{\rm iso}$(H) = $1.2U_{\rm eq}$(parent atom).

Data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *WinGX* (Version 1.64.05; Farrugia, 1999); software used to prepare material for publication: *SHELXL97*.

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