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5-(2,5-Dimethylphenoxy)-2,2-dimethylpentanoic acid (gemfibrozil)

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Key indicators

Single-crystal X-ray study
T = 296 K
Mean σ(C–C) = 0.004 Å
R factor = 0.058
wR factor = 0.188
Data-to-parameter ratio = 14.6

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

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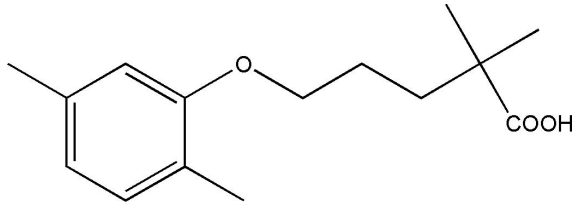
The structure of gemfibrozil, $C_{15}H_{22}O_3$, a hypolipidemic agent, is reported in the context of studies on polymorphism, which is considered to affect the stability and bioavailability of the drug. The structure contains two molecules in the asymmetric unit, which are linked *via* two O—H···O hydrogen bonds [O···O = 2.631 (2) and 2.652 (2) Å].

Comment

5-(2,5-Dimethylphenoxy)-2,2-dimethylpentanoic acid, (I), commonly known as gemfibrozil (CAS No. 25812–30-0), is a fibrate hypolipidemic agent that is clinically effective in reducing serum cholesterol and triglyceride levels. It has also been demonstrated that this drug lowers the incidence of coronary heart disease in humans (Spencer & Barradell, 1996). Gemfibrozil is officially recognized in the *28th US Pharmacopoeia*. The stability and bioavailability of a drug may be affected to some extent by its solid-state properties, for instance specific features of the crystal packing and the possible existence of polymorphs and pseudopolymorphs (the latter being associated with the presence of solvent molecules in the crystal structure). A knowledge of the solid-state structure is also of importance for quality control and regulatory purposes (Datta & Grant, 2004). In view of this, and considering that, to our knowledge, no structure determination of (I) has so far been reported, the crystal structure of the non-solvated title compound was determined and the results are presented here.



(I)

In the asymmetric unit of the monoclinic unit cell, there are two independent molecules (Fig. 1), linked by hydrogen bonds between the carboxylic acid groups and related to each other by a pseudo-twofold axis (details of the hydrogen-bond geometries are listed in Table 2). The geometric parameters for the two molecules agree closely, with the exception of torsion angles involving the carboxylic acid groups; selected values are given in Table 1. In each molecule, the non-H atoms, excluding those which form the carboxylic acid groups and the methyl groups in the α-position, lie approximately in a plane, with 0.118 (2) Å being the largest deviation from the

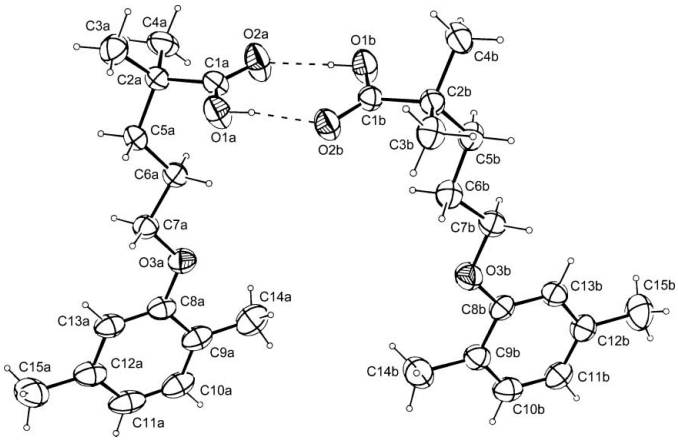


Figure 1
A view of the two independent molecules forming the asymmetric unit of (I). Displacement ellipsoids are at the 30% probability level and H atoms are shown as small spheres of arbitrary radii. Hydrogen-bond interactions are indicated by dashed lines.

plane for atom C2*A* (Nardelli, 1995).

Molecules in the crystal structure are arranged in layers normal to the *b* axis, with hydrogen bonding between adjacent layers. A view of the packing is shown in Fig. 2.

Experimental

Samples of compound (I) were kindly provided by SIMS (SIMS srl, Reggello, Firenze, Italy). Crystals suitable for X-ray analysis were obtained by slow evaporation of water–methanol (1:1) solutions.

Crystal data

$C_{15}H_{22}O_3$
$M_r = 250.32$
Monoclinic, $P2_1/n$
$a = 14.861$ (1) Å
$b = 7.364$ (1) Å
$c = 27.948$ (2) Å
$\beta = 93.42$ (1)°
$V = 3053.1$ (5) Å^3
$Z = 8$
$D_x = 1.089$ Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 1644 reflections
$\theta = 5.5$–42.0°
$\mu = 0.60$ mm^{-1}
$T = 296$ (2) K
Rod, colourless
0.70 × 0.18 × 0.10 mm

Data collection

Oxford Diffraction Xcalibur 3 CCD area-detector diffractometer
ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1986)
$T_{min} = 0.698$, $T_{max} = 0.940$
15432 measured reflections
4896 independent reflections
2641 reflections with $I > 2\sigma(I)$
$R_{int} = 0.029$
$\theta_{max} = 63.2°$
$h = -11 \rightarrow 17$
$k = -8 \rightarrow 3$
$l = -29 \rightarrow 32$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.058$
$wR(F^2) = 0.188$
$S = 0.86$
4896 reflections
336 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.1355P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.64$ e Å^{-3}
$\Delta\rho_{min} = -0.24$ e Å^{-3}
Extinction correction: *SHELXL97* (Sheldrick, 1997)
Extinction coefficient: 0.0008 (2)

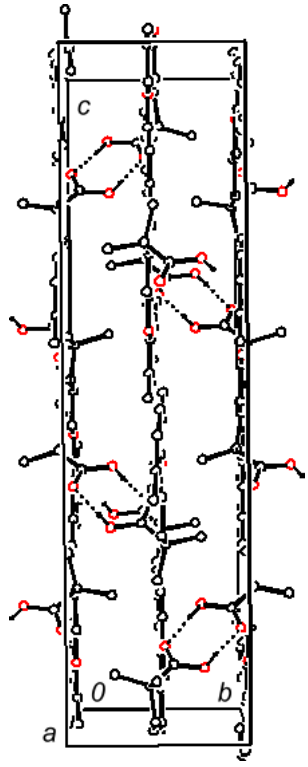


Figure 2
A view of the packing in (I), along a direction approximately normal to the *bc* face. Only the H atoms involved in hydrogen bonding are shown.

Table 1
Selected geometric parameters (Å, °).

O1*A*—C1*A*	1.304 (3)	O1*B*—C1*B*	1.297 (3)
O2*A*—C1*A*	1.224 (2)	O2*B*—C1*B*	1.209 (3)
C1*A*—C2*A*	1.504 (3)	C1*B*—C2*B*	1.505 (3)
C7*A*—O3*A*	1.426 (3)	C7*B*—O3*B*	1.420 (3)
O3*A*—C8*A*	1.362 (3)	O3*B*—C8*B*	1.368 (3)
O2*A*—C1*A*—O1*A*	121.7 (2)	O2*B*—C1*B*—O1*B*	121.3 (2)
C1*A*—C2*A*—C5*A*	109.08 (17)	C1*B*—C2*B*—C5*B*	109.01 (18)
C8*A*—O3*A*—C7*A*	116.96 (19)	C8*B*—O3*B*—C7*B*	117.28 (19)
O2*A*—C1*A*—C2*A*—C5*A*	110.9 (2)	O2*B*—C1*B*—C2*B*—C5*B*	120.3 (3)
O1*A*—C1*A*—C2*A*—C5*A*	−68.4 (2)	O1*B*—C1*B*—C2*B*—C5*B*	−59.6 (3)
C1*A*—C2*A*—C5*A*—C6*A*	−55.4 (3)	C1*B*—C2*B*—C5*B*—C6*B*	−52.5 (3)
C7*A*—O3*A*—C8*A*—C13*A*	−1.6 (3)	C7*B*—O3*B*—C8*B*—C13*B*	−1.6 (3)
C7*A*—O3*A*—C8*A*—C9*A*	178.49 (18)	C7*B*—O3*B*—C8*B*—C9*B*	178.68 (19)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O1*A*—H1*A*···O2*B*	0.82	1.83	2.652 (2)	177
O1*B*—H1*B*···O2*A*	0.82	1.82	2.631 (2)	171

In the final refinement, H atoms were allowed for as riding in geometrically assigned positions [U_{iso}(H) = 1.2U_{eq}(C), or

U_{iso}(H) = 1.5U_{eq}(C,O) for methyl and carboxyl H atoms]. Assigned C---H bond distances were secondary C— = 0.97 Å, methyl C— = 0.96 Å, aromatic C—H = 0.93 Å and carboxylic O—H = 0.82 Å.

Data collection: *CrysAlisCCD* (Oxford Diffraction, 2001); cell refinement: *CrysAlisCCD*; data reduction: *CrysAlisRED* (Oxford Diffraction, 2001); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP3* (Farrugia, 1999); software used to prepare material for publication: *SHELXL97*.

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