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Fenofibric acid

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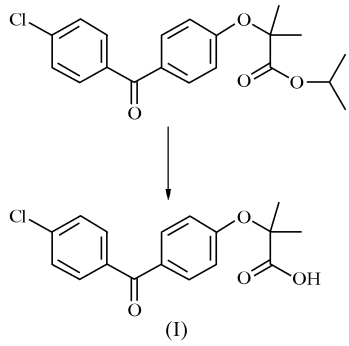
Unlike the related fenofibrate molecule [Henry, Zhang, Gao & Bruckner (2003). *Acta Cryst*. E**59**, o699–o700], fenofibric acid {systematic name: 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoic acid}, $C_{17}H_{15}ClO_4$, contains a carboxylic acid moiety instead of an ester moiety. This polar moiety plays an important role in the formation of a rare acid-to-ketone hydrogen-bond-type packing interaction. The lack of an isopropyl group in fenofibric acid aligns the carboxyl group on the same side as the ketone carbonyl group; this conformation may play an important role in discrimination between the acid and the fenofibrate molecule in molecular recognition.

Comment

Fibrates, such as bezafibrate, clofibric acid and fenofibrate, which are ligands for the nuclear receptor PPARα (peroxisome proliferator-activated receptor α), are used as therapeutic agents in the treatment of hyperlipidemia, heart disease and diabetic complications (Throp, 1962; Miller & Spence, 1998; Forcheron *et al.*, 2002). Fenofibrate (TRICOR) is a lipid-regulating agent available as tablets for oral administration (Adkins & Faulds, 1997; Guay, 1999; Keating & Ormrod, 2002). Fenofibrate treatment also reduces the angiographic progression of coronary-artery disease in type 2 diabetes (Taniguchi *et al.*, 2001). Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to its active metabolite, *viz*. fenofibric acid, (I). Unchanged fenofibrate has been reported to be undetectable in plasma samples following an oral dose (Streel *et al.*, 2000). The mechanism of action of fenofibrate and its metabolites is not fully understood. Fenofibric acid is also an activator of PPARα, which ultimately results in the reduction of triglycerides, total cholesterol and low-density lipoprotein cholesterol (LDL-C), as well as an increase in high-density lipoprotein cholesterol (HDL-C) (Adkins & Faulds, 1997; Guay, 1999; Keating & Ormrod, 2002). Our lead optimization effort indicates that fenofibric acid may have improved potency over bezafibrate. Since fenofibric acid is not commercially available, we have prepared it in our laboratory by alkaline hydrolysis following modified conditions for biochemical studies. In this article, we describe the synthesis, crystallization and structural characterization of fenofibric acid. This is the first crystal structure report of fenofibric acid.



(I)

The C—O bond distances in the carboxyl group of fenofibric acid indicate that it is in the acid form [C15═O3 = 1.2014 (19) Å and C15—O4 = 1.3248 (19) Å; Table 1] rather than the carboxylate form. This observation is further confirmed by the location and refinement of the acidic H atom. The molecules form strong hydrogen-bonded dimers as a result of the presence of the carboxyl OH group (Table 2). The two molecules in the dimer (Fig. 2) are related by an inversion center. The dimer is formed by hydrogen bonding between the carbonyl O atom of the ketone moiety in one fenofibric acid molecule and the carboxyl OH group of the second molecule, rather than by the more usual hydrogen-bonding interaction between two carboxylic acid groups. The crystal packing, viewed down the *a* axis, shows that the dimers form layers that stack in the *b* direction and form a zigzag pattern in the *bc* plane (Fig. 3). By contrast, fenofibrate, which is the isopropyl ester of fenofibric acid, does not have the hydroxy H atom required for the formation of the hydrogen-bonding interaction and so packs in a completely different way (Henry *et al.*, 2003).

Fenofibric acid utilizes a rare hydrogen-bonding pattern to form intermolecular dimers, rather than the acid-to-acid hydrogen-bonding dimerization that is most common in carboxylic acids. Ketocarboxylic acid-type compounds, such as fenofibric acid, contain only one acidic donor H atom and two possible acceptors, namely the O atoms in the ketone carbonyl and carboxyl moieties of the organic acid. Studies have

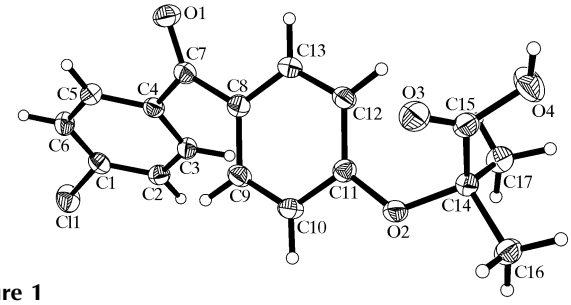


Figure 1
A view of the molecule of (I). Non-H atoms are shown with 50% probability displacement ellipsoids.

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established that ketocarboxylic acids exhibit five hydrogen-bonding modes or patterns (Newman *et al.*, 2002), *viz*. acid-to-acid dimer (Barcon *et al.*, 2002), acid-to-ketone catemer (Barcon *et al.*, 2002), intramolecular or internal (Coté *et al.*, 1996), acid-to-acid catemer (Lalancette *et al.*, 1998), and acid-to-ketone dimer (Newman *et al.*, 2002). Analysis of the structural entries in the Cambridge Structural Database (CSD; Allen, 2002) reveals that acid-to-acid dimerization and acid-to-ketone catemer hydrogen-bonding patterns are the most common (Leiserowitz, 1976; Lalancette *et al.*, 1998), while intramolecular, acid-to-acid catemer and acid-to-ketone dimer hydrogen-bonding patterns are rare (Coté *et al.*, 1996). We have identified six compounds in the CSD that form acid-to-ketone hydrogen-bonding patterns out of 92 compounds in the literature. These six compounds are BOZTUF (Peters *et al.*, 1983), FAZGAO (Nuhrich *et al.*, 1986), JIKDEM (Abell *et al.*, 1991), TEVGIK (Kosela *et al.*, 1995), EFANEE (Newman *et al.*, 2002) and MOZZOQ (Armstrong *et al.*, 2002). Thus, fenofibric acid is the seventh compound to join a very small number of examples in the CSD that form acid-to-ketone hydrogen-bonding dimers.

The intramolecular hydrogen-bonding pattern involving a carbonyl O atom and a carboxyl OH group has been found in only a few organic acids. Formation of the intramolecular hydrogen-bonding pattern requires mostly a seven-membered hydrogen-bonded ring arrangement (Griffe *et al.*, 1972; Sheldrick & Trowitzsch, 1983; Halfpenny, 1990; Abell *et al.*, 1990). The distances between carbonyl atom O1 and the carboxyl O atoms are more than 6.8 Å in fenofibric acid. This distance is too long to allow the formation of intramolecular hydrogen-bonding interactions and may explain why fenofibric acid does not form an intramolecular hydrogen-bonding interaction.

Alignment of the sp^2 ketone moiety (the C4/C7/O1/C8 plane) of fenofibric acid and the corresponding plane in the fenofibrate molecule reveals that the carboxyl moiety is positioned almost on the same side as the ketone carbonyl group in fenofibric acid (Fig. 4). This conformation may facilitate the formation of intermolecular C—O···H—O hydrogen bonding over the carboxyl OH dimer. However, the carboxyl moiety of the fenofibrate molecule is located away from the ketone carbonyl group, at the back of the molecule.

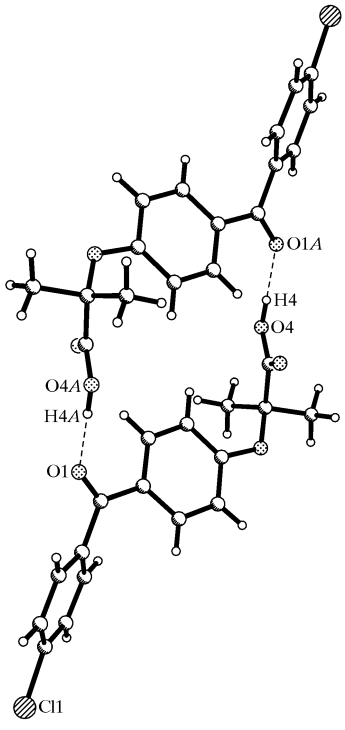

Figure 2
A dimer of fenofibric acid, showing the rare acid-to-ketone hydrogen-bonding pattern. The symmetry operator $(-x, -y, 1-z)$ was used to generate atoms labeled with the suffix *A*.

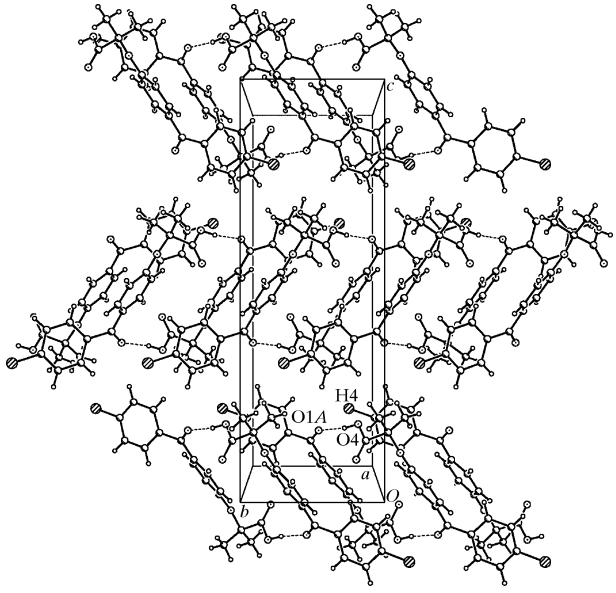

Figure 3
A packing diagram of fenofibric acid, in the orthorhombic space group *Pbca*, viewed along the *a* axis.

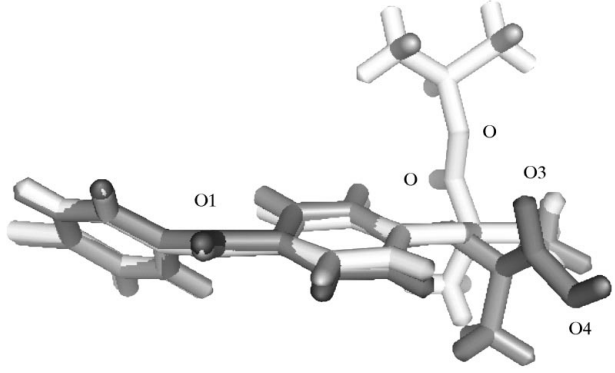

Figure 4
A view down the C4/C7/O1/C8 plane along the C═O double-bond direction of the ketone moiety. Fenofibric acid and fenofibrate are superimposed with black and grey, respectively. Fenofibric acid atom labels O1, O3 and O4 are shown, while the corresponding carboxyl atoms of fenofibrate are denoted by O labels.

This conformation may be due to steric effects and packing interactions, which are caused by the presence of the isopropyl group. This phenomenon may play a significant role in distinguishing fenofibric acid as an activator of PPARα over fenofibrate. In general, if polar groups, such as the carbonyl and carboxyl groups in fenofibrate and fenofibric acid, are involved in the formation of specific interactions with their target molecules, the orientation of these moieties will alter the binding affinities. Alternatively, these O atoms may change the binding orientation with a given target molecule.

Experimental

Fenofibric acid was prepared by alkaline hydrolysis of fenofibrate under mild conditions, according to the procedures described below. Fenofibrate (300 mg) was suspended in methanol (10 ml), and a 2 *N* NaOH solution (1 ml) was added to the reaction mixture. Stirring was continued for several hours at room temperature. Thin-layer chromatography (TLC) was used to monitor the progress of the reaction. The reaction mixture contained approximately 10% hydrolyzed material and 90% starting material as the intact ester form. The hydrolysis did not proceed further, even after 15–16 h of stirring, and a major amount of starting material was recovered after work-up. In a second experiment, fenofibrate (300 mg) was suspended in methanol (10 ml), 2 *N* NaOH (2.5 ml) was added, and the resulting suspension was stirred at 343 K for 4 h. The reaction mixture became a clear solution during this period (quantitative conversion as per TLC). The solvent was removed under reduced pressure and water (5 ml) was added to the residue. This solution was acidified to an approximate pH of 2 by adding 2 *N* hydrochloric acid. At a pH of ~2, a thick precipitate formed. The precipitate was extracted in ethyl acetate (25 ml), and the organic layer was washed three times with brine, dried over sodium sulfate and concentrated to a solid residue. The residue was crystallized from ethyl acetate/hexane to obtain fenofibric acid as a white powder (>97% pure, high-performance liquid chromatography) in excellent yield (>85%). To obtain single crystals, fenofibric acid (5.0 mg) was dissolved in high-purity absolute ethanol (225 ml) and heated at 313 K in a water bath. To this solution was added deionized water (25 ml) and the tube was shaken under vortex for 2 min. The clear solution was allowed to cool slowly to room temperature and was left overnight. After several hours, colorless plate-like crystals started to form in the tube; these were preserved by sealing the tube and were stored for structural characterization and future studies.

Crystal data

$C_{17}H_{15}ClO_4$
M_r = 318.74
Orthorhombic, *Pbca*
a = 18.2168 (4) Å
b = 7.5623 (2) Å
c = 22.1355 (5) Å
V = 3049.41 (13) Å^3
Z = 8
D_x = 1.389 Mg m^{-3}
D_m = no Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 8481 reflections
θ = 2.2–28.3°
μ = 0.27 mm^{-1}
T = 160 (2) K
Plate, colorless
0.47 × 0.43 × 0.14 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.885, T_{max} = 0.964
47 753 measured reflections
3497 independent reflections
3081 reflections with $I > 2\sigma(I)$
R_{int} = 0.036
θ_{max} = 27.5°
$h = -23 \rightarrow 23$
$k = -9 \rightarrow 9$
$l = -28 \rightarrow 28$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.042
$wR(F^2)$ = 0.099
S = 1.11
3497 reflections
259 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.0404P)^2 + 1.7773P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.32 e Å^{-3}
$\Delta\rho_{min}$ = −0.29 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

O1—C7	1.2353 (18)	O3—C15	1.2014 (19)
O2—C11	1.3689 (17)	O4—C15	1.3248 (19)
O2—C14	1.4430 (17)		
C11—O2—C14	122.62 (11)	O3—C15—C14	124.35 (14)
O3—C15—O4	124.54 (15)	O4—C15—C14	111.05 (13)
C4—C7—C8—C9	−30.5 (2)	O2—C14—C15—O3	18.6 (2)
C11—O2—C14—C15	68.90 (17)		

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

D—H···A	D—H	H···A	D···A	D—H···A
O4—H4···O1^{i}	0.91 (3)	1.72 (3)	2.6264 (17)	170 (3)

Symmetry code: (i) $-x, -y, 1-z$.

All H atoms were located in difference Fourier maps and were refined freely using isotropic displacement parameters [O—H = 0.91 (3) Å and C—H = 0.936 (18)–0.986 (14) Å].

Data collection: *SMART* (Bruker, 2003); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 2003); program(s) used to solve structure: *SHELXTL* (Sheldrick, 2003); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SQ1185). Services for accessing these data are described at the back of the journal.

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