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3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-3-yl]propionic acid and the corresponding methyl ester

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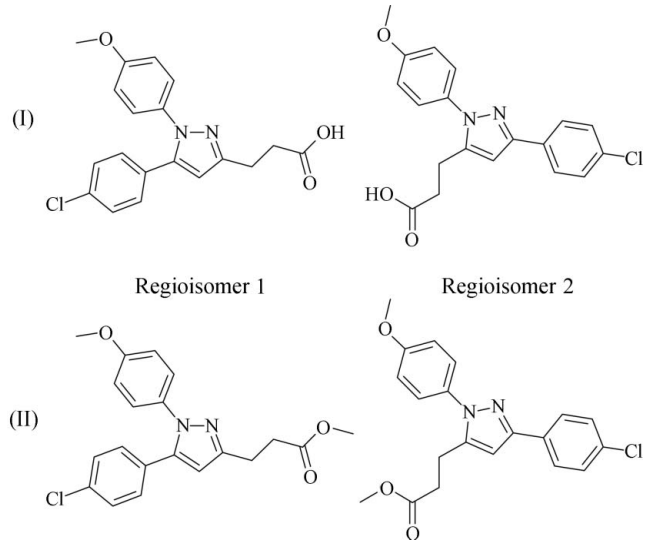
The synthesis of 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-3-yl]propionic acid, $C_{19}H_{17}ClN_2O_3$, (I), and its corresponding methyl ester, methyl 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-3-yl]propionate, $C_{20}H_{19}ClN_2O_3$, (II), is regiospecific. However, correct identification of the regioisomer formed by spectroscopic techniques is not trivial and single-crystal X-ray analysis provided the only means of unambiguous structure determination. Compound (I) crystallizes with $Z' = 2$. The propionic acid groups of the two crystallographically unique molecules form a hydrogen-bonded dimer, as is typical of carboxylic acid groups in the solid state. Conformational differences between the methoxybenzene and pyrazole rings give rise to two unique molecules. The structure of (II) features just one molecule in the asymmetric unit and the crystal packing makes greater use than (I) of weak C—H$\cdots A$ interactions, despite the lack of any functional groups for classical hydrogen bonding.

Comment

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the oldest and most widely accepted way to treat mild to moderate pain. One possible side-effect of NSAIDs is bronchial constriction in patients (Charlier & Michaux, 2003; Young, 1999), and so they are not therapeutically advisable for asthma patients. In addition, prolonged treatment may result in gastric irritation and renal impairment. In order to increase the analgesic efficacy and reduce the side effects, we are investigating the synthesis and properties of a range of bifunctional NSAID precursors containing amino acid groups. In the process of synthesizing a precursor to the NSAID tepoxalin, we found that a mixture of regioisomers were possible, identified as 1 and 2 in the scheme below. Efforts to identify unambiguously the correct regioisomer by NMR spectroscopy, using one-dimensional nuclear Overhauser effect or heteronuclear multiple bond correlation experiments, were not successful, leaving single-crystal X-ray diffraction as the only possible means of unambiguous identification. We report here the structure of the tepoxalin precursor 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-3-yl]propionic acid, (I), and the corresponding methyl ester, (II).



The asymmetric unit of (I) is shown in Fig. 1. The compound crystallizes in the space group $P\overline{1}$ with two crystallographically unique molecules in the asymmetric unit and no solvent of crystallization. The compound is unambiguously regioisomer 1. Discussion is restricted to the molecule containing atoms Cl1 to H19 (hereafter 'molecule *A*'), with relevant results for the molecule containing atoms Cl51 to H69 (hereafter 'molecule *B*') presented in square brackets. The propionic acid groups of the two crystallographically unique molecules form a hydrogen-bonded dimer with a graph-set motif $R_2^2(8)$, as is typical of carboxylic acid groups in the solid state (Bernstein *et al.*, 1995).

The conformational differences that give rise to two unique molecules can be easily appreciated by considering an overlay of the two molecules, formed by fitting together the five atoms of each pyrazole ring (r.m.s. deviation = 0.0062 Å; Fig. 2). From this it is clear that, although there are some small differences between the conformations of the propionic acid and chlorobenzene rings in molecules *A* and *B*, the most striking difference is found in the methoxybenzene group. Although it first seems that the differences are due to methoxy group orientation, we show by careful systematic numbering that it is the angle between the methyoxybenzene and pyrazole rings which gives rise to two different conformations. The methoxy group is essentially coplanar with the benzyl ring to which it is bonded, and a mean plane fitted through all six ring C atoms and the two methoxy atoms has an r.m.s. deviation of 0.0350 Å [0.0288 Å]. This plane is rotated by 53.51 (5)° [37.32 (8)°] from the central pyrazole ring plane. In molecule *A*, the N1—N2—C4—C5 torsion angle is −130.75 (16)°, yet using the same numbering system for *B*, the N51—N52—

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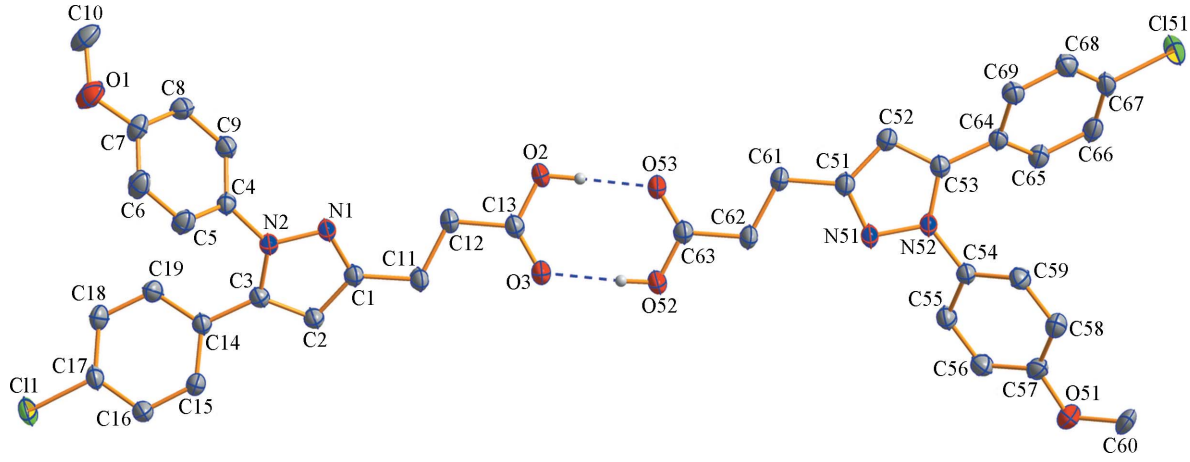

Figure 1
The asymmetric unit of (I), with anisotropic displacement ellipsoids drawn at the 50% probability level.

C54—C55 torsion angle is 36.4 (2)°. The related compound 1-(4-methoxyphenyl)-5-phenylpyrazole (Spivey *et al.*, 2000) also features two molecules in the asymmetric unit. In both cases, the methoxy group is coplanar with the benzyl ring to which it is bonded, but the torsion angle corresponding to the atoms named above is approximately 54.34° for one molecule and −53.12° for the other.

The chlorophenol ring is rotated by 37.07 (8)° [42.10 (6)°] from the pyrazole ring. The propionic acid unit has an extended conformation, and a mean plane fitted through atoms O2, O3, C1, C11, C12 and C13 has an r.m.s. deviation of 0.230 Å [0.0148 Å]. The covalent molecular geometry is unexceptional, as is the crystal packing, which consists principally of van der Waals interactions and some minor C—H···π interactions. In some parts of the structure, there is evidence of favorable $\delta+$ and $\delta-$ alignment (for example, C59—H59···N1). The geometry of these interactions is such that we do not believe that these are formal weak hydrogen bonds but rather they result from simple electrostatic attraction.

Obtained as a reaction side-product in the synthesis of (I) was the corresponding methyl ester, (II). This was isolated by flash chromatography and crystallized separately. The molecular structure of (II) is shown in Fig. 3 and as with molecule (I) matches that of the predicted regioisomer 1; there is only one molecule in the asymmetric unit of this compound. The molecule adopts an extended conformation with the ester group essentially planar (a mean plane fitted through atoms C1, C11, C12, C13, C20, O2 and O3 has an r.m.s. deviation of 0.0406 Å) and that plane is rotated by 31.79 (5)° from the pyrazole ring plane. As with (I), the methoxy group is essentially coplanar with the benzyl ring to which it is bonded, and a mean plane fitted through all six ring C atoms and the two methoxy atoms has an r.m.s. deviation of 0.0323 Å. This plane is rotated by 71.01 (3)° from that of the pyrazole ring. Finally, the chlorobenzene group is rotated by 22.93 (5)° from the plane of the central pyrazole ring. The covalent molecular geometry is unexceptional.

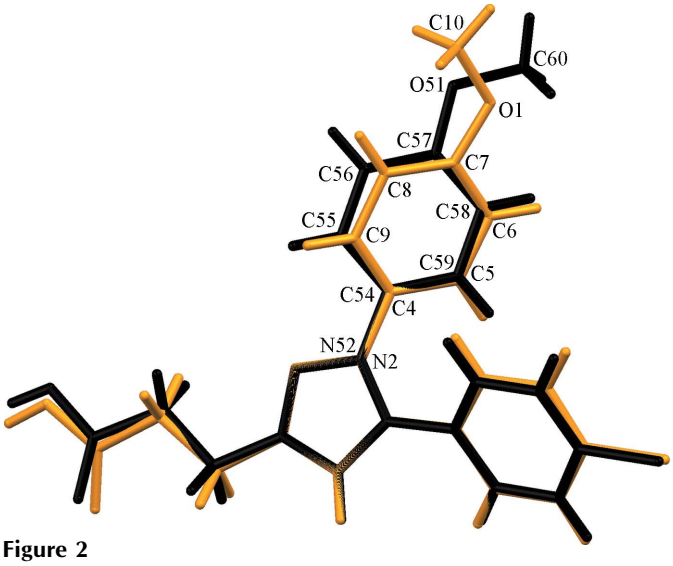

Figure 2
An overlay plot of molecule *A* (gray; orange in the electronic version of the paper) with molecule *B* (black).

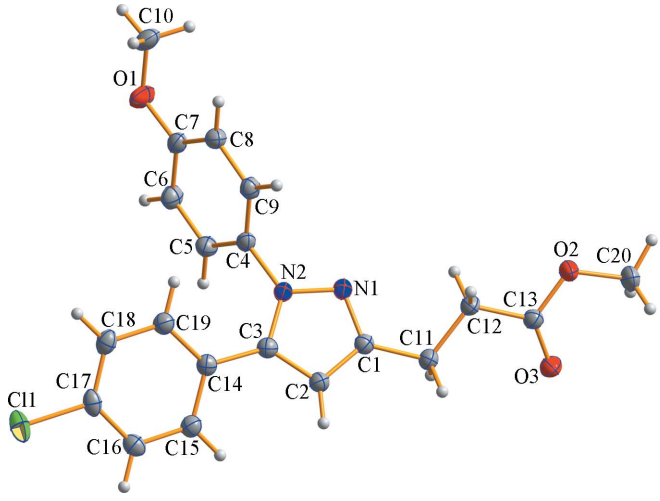

Figure 3
The asymmetric unit of (II), with anisotropic displacement ellipsoids drawn at the 50% probability level.

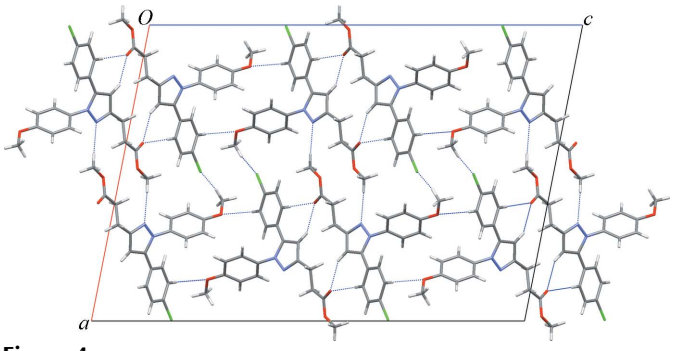

Figure 4
A *b*-axis packing plot of (II). Weak hydrogen bonding is illustrated by dashed lines (blue in the electronic version of the paper).

The crystal packing of (II) is more complex than that of (I), despite the lack of any functional groups for classical hydrogen bonding. A *b*-axis projection of (II) (Fig. 4) shows that the ester carbonyl atom O3 is not involved in the O—H···O hydrogen bond found in (I) and is available to form weak C—H···O hydrogen bonds to atoms H2 and H15, generating an $R_2^1(7)$ motif. Furthermore, one of the methyl H atoms (H20*B*) of the ester function is also able to participate in a weak C—H···N hydrogen bond, as opposed to a purely favorable electrostatic interation by virtue of the way the atoms are oriented, with the pyrazole ring of an adjacent group. Overall, the crystal packing can be most easily described as rippled stacked sheets, as can be seen if a projection is viewed along the *ab* diagonal.

Experimental

The title compounds were synthesized in a two-step procedure. 6-(4-Chlorophenyl)-4,6-dioxohexanoic acid was synthesized by a modification of the method described by Murray *et al.* (1991), using NaHMDS in place of LiHMDS. Next, a mixture of 6-(4-chlorophenyl)-4,6-dioxohexanoic acid (1.27 g, 5 mmol), 4-methoxyphenylhydrazine hydrochloride (873 mg, 5 mmol) and Et_3N (506 mg, 5 mmol) in MeOH (40 ml) was stirred at room temperature for 6 h. The mixture was then concentrated *in vacuo* to a residue, which was partitioned between Et_2O (40 ml) and 5% aqueous HCl (37.5 ml). The ether layer was separated, washed with 5% aqueous HCl (2 × 10 ml) and brine (10 ml), dried over Na_2SO_4, filtered, and concentrated to a residue. The crude residue was flash chromatographed on silica gel using hexane–EtOAc–AcOH (6:2:1) as eluant and separated into the two products (I) and (II). Compound (I) was crystallized by slow evaporation of a diethyl ether solution (yield 70%), while compound (II) was crystallized by slow evaporation of a deuterated methanol solution (yield 30%).

Compound (I)

Crystal data

$C_{19}H_{17}ClN_2O_3$
M_r = 356.80
Triclinic, $P\overline{1}$
a = 9.131 (2) Å
b = 13.759 (3) Å
c = 14.264 (3) Å
α = 103.733 (3)°
β = 96.928 (3)°
γ = 98.459 (3)°
V = 1699.2 (6) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.25 mm^{-1}
T = 150 K
0.32 × 0.21 × 0.11 mm

Data collection

Bruker APEXII CCD diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.916, T_{max} = 0.974
19183 measured reflections
8218 independent reflections
6174 reflections with $I > 2\sigma(I)$
R_{int} = 0.025

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.043
$wR(F^2)$ = 0.115
S = 1.07
8218 reflections
461 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.52 e Å^{-3}
$\Delta\rho_{min}$ = −0.32 e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °) for (I).

D—H···A	D—H	H···A	D···A	D—H···A
O2—H2O···O53	0.90 (3)	1.78 (3)	2.6815 (18)	178 (3)
O52—H52O···O3	0.84 (3)	1.84 (3)	2.6790 (18)	177 (3)

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

D—H···A	D—H	H···A	D···A	D—H···A
C2—H2···O3^{i}	0.95	2.50	3.3651 (15)	152
C15—H15···O3^{i}	0.95	2.41	3.3317 (15)	165
C18—H18···O1^{ii}	0.95	2.60	3.4625 (16)	152
C20—H20*B*···N1^{iii}	0.98	2.61	3.5750 (18)	169
C10—H10*C*···Cl1^{iv}	0.98	2.92	3.7554 (15)	143

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

Compound (II)

Crystal data

$C_{20}H_{19}ClN_2O_3$
M_r = 370.82
Monoclinic, $C2/c$
a = 22.174 (5) Å
b = 5.1352 (11) Å
c = 31.884 (7) Å
β = 101.126 (2)°
V = 3562.4 (13) Å^3
Z = 8
Mo $K\alpha$ radiation
μ = 0.24 mm^{-1}
T = 150 K
0.27 × 0.15 × 0.09 mm

Data collection

Bruker APEXII CCD diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.919, T_{max} = 0.979
18813 measured reflections
4351 independent reflections
3788 reflections with $I > 2\sigma(I)$
R_{int} = 0.022

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.034
$wR(F^2)$ = 0.087
S = 1.02
4351 reflections
237 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.28 e Å^{-3}
$\Delta\rho_{min}$ = −0.24 e Å^{-3}

All H atoms were located from a difference map and constrained to ride on the parent atom, except that the positions and atomic displacement parameters of the hydroxy H atoms in (I) were freely refined. H atoms were supplied with U_{iso}(H) values of 1.2U_{eq}(C) [or 1.5U_{eq}(C) for methyl H atoms] and fixed C—H distances of 0.95 Å for aryl, 0.98 Å for methyl and 0.99 Å for methylene H atoms.

For both compounds, data collection: *APEX2* (Bruker, 2007); cell refinement: *SAINT* (Bruker, 2007); data reduction: *SAINT*; program(s) used to solve structure: *SHELXTL* (Sheldrick, 2008); program(s) used to refine structure: *SHELXTL*; molecular graphics: *DIAMOND* (Brandenburg & Putz, 1999) and *Mercury* (Macrae *et al.*, 2008); software used to prepare material for publication: *SHELXTL*, *publCIF* (Westrip, 2009) and local programs.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3306). Services for accessing these data are described at the back of the journal.

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