Intermolecular hydrogen bonding in (2S)-2-(1-oxo-1H-2,3-dihydroisoindol-2-yl)propanoic acid

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The title compound, C_{11}H_{11}NO_{3}, a condensation product of L-alanine and ortho-phthalaldehyde, crystallizes in space group P2_12_12_1. Intermolecular O−H⋯O=C and C−H⋯O hydrogen bonds are present with O⋯O and C⋯O distances of 2.623 (3) and 3.338 (4) Å, respectively.

Comment

The study of biologically active molecules is of primary importance in medicinal chemistry. Processes such as hormone processing, viral replication and cancer cell invasion are critically dependent on protease enzymes which have recently become attractive target molecules in drug design (Testa et al., 1993). Many inhibitors are based on modified amino acids which incorporate the basic structural features determining normal enzyme-substrate interactions. Phthalimidine (isoin-dolin-1-one) derivatives often display biological activity as potential anti-inflammatory agents and antipsychotics (Allin et al., 1996). The majority of structurally determined phthalimidine systems are either N-substituted or have a hydroxy substituent at the 3-position (McNab et al., 1997). The title compound (I), synthesized from L-alanine, is part of an ongoing study of hydrogen-bonding interactions in phthalimidine derivatives (Dalton et al., 1999; Gallagher et al., 2000; Gallagher & Murphy, 1999; Gallagher & Brady, 2000; Brady & Gallagher, 2001).

A view of the molecule of (I) (S configuration) with the atomic numbering scheme is given in Fig. 1 and selected dimensions are in Table 1. The bond lengths and angles in the heterocyclic ring are similar to those reported previously (McNab et al., 1997) and are in agreement with expected values (Orpen et al., 1994). The angle between the five- and six-membered rings of the isoindole system is 1.21 (18)° and the maximum deviation from planarity for an atom in either ring plane is 0.0125 (16) Å for N1, while the carbonyl atom O3 is 0.066 (4) Å from the C_{5}N ring plane. The five-membered ring is oriented at an angle of 71.72 (9)° to the CCO_{2} carboxylic acid plane. Examination of (I) with PLATON (Spek, 1998) revealed no voids in the crystal lattice.
The hydrogen-bonding in (I) is dominated by an O–H⋯O and a C–H⋯O interaction in a two-dimensional network (Table 2). Conventional carboxylic acid O–H⋯O hydrogen bonding between pairs of carboxylic acid groups with graph set $R_{2}(8)$ (Ferguson et al., 1995) is not observed in (I), mainly due to symmetry constraints; instead, the (acid)O⋯C(phenyl) interaction generates a one-dimensional zigzag chain of molecules along the $b$ axis, and these chains are further linked by the C–H⋯O interactions along the $a$ axis.

The crystal structure of (I) contrasts with that of compound (II), $(2R/2S)$-2-(1-oxo-1,3-dihydro-2H-isooindol-2-yl)-3-phenylpropanoic acid (Brady et al., 1998), in which the extra phenyl group facilitates two C–H⋯(arene) interactions. Molecule (I) is similar, however, to a valine derivative, $(2S)$-3-methyl-2-(1-oxo-1H-2,3-dihydroisoindol-2-yl)butanoic acid, in which the five-membered isoindolyl ring carbonyl C is oriented transoid to the H at the chiral centre C2 (Gallagher & Brady, 2000).

The presence of C–H⋯O interactions together with stronger hydrogen bonds, e.g. O–H⋯O, has been commented on previously (Steiner, 1997). Further studies are in progress on interactions in related phthalimidine derivatives for application as medicinal drugs.

**Experimental**

The title compound was prepared by the overnight reaction of L-alanine and o-phthalaldehyde in refluxing CH$_3$CN under N$_2$ (Allin et al., 1996). Filtration of the hot solution and subsequent slow cooling of the filtrate allowed the isolation of needle-like colourless crystals. IR, (ν$_{c}$ cm$^{-1}$), 1730, 1644 (KBr). Melting point 485–487 K (uncorrected).

**Crystal data**

$C_{11}H_{11}NO_{3}$

$M_r = 205.21$

Orthorhombic, $P2_{1}2_{1}2_{1}$

$a = 5.1787$ (5) Å

$b = 9.9128$ (18) Å

$c = 18.918$ (5) Å

$V = 971.2$ (3) Å$^3$

$Z = 4$

$D_x = 1.403$ Mg m$^{-3}$

$Mo$ Kα radiation

Cell parameters from 25 reflections

$\theta = 9.0–18.9^\circ$

$\mu = 0.10$ mm$^{-1}$

$T = 294$ (1) K

Plate, colourless

$0.42 \times 0.21 \times 0.04$ mm

**Table 1**

| Selected geometric parameters (Å, °) |  
|-----------------------------------|---|
| O1–C1 | 1.324 (3) |
| O2–C1 | 1.197 (3) |
| O3–C3 | 1.235 (3) |
| N1–C2 | 1.453 (3) |
| N1–C3 | 1.342 (3) |
| N1–C10 | 1.453 (3) |
| C2–N1–C3 | 122.6 (2) |
| C2–N1–C10 | 123.1 (2) |
| C3–N1–C10 | 112.9 (2) |
| O1–C1–O2 | 123.9 (3) |
| O1–C1–C2 | 112.5 (2) |
| O2–C1–C2 | 123.5 (2) |
| N1–C2–C1 | 107.8 (2) |
| C3–N1–C2–C1 | 58.3 (3) |
| O2–C1–C2–N1 | 25.0 (4) |

**Data collection**

Enraf–Nonius CAD-4 diffractometer

$\theta$–2$\theta$ scans

Absorption correction: none

1803 measured reflections

1086 independent reflections

866 reflections with $I/2I$ $(I)$

$R_{int} = 0.024$

$wR(F^2)$ = 0.087

$S = 1.02$

3 standard reflections

frequency: 240 min

intensity decay: 0.5%

**Refinement**

Refinement on $F^2$

$R[F^2 > 2\sigma(F^2)] = 0.039$

$wR(F^2) = 0.087$

$S = 1.02$

1086 reflections

139 parameters

H-atom parameters constrained

$w = 1/[\sigma^2(F^2) + (0.0513P)^2]$ where $P = (F^2 + 2F^2)/3$

$\Delta/\sigma$ max = 0.01 e Å$^{-3}$

$\Delta r_{	ext{max}} = 0.14$ e Å$^{-3}$

Extinction correction: SHELXL97

Extinction coefficient: 0.012 (3)

Figure 1

A view of (I) with the atomic numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

Figure 2

A view of the interactions in the crystal structure.
Table 2
Hydrogen-bonding geometry (Å, °).

<table>
<thead>
<tr>
<th>D—H—A</th>
<th>D—H</th>
<th>H—A</th>
<th>D—A</th>
<th>D—H—A</th>
</tr>
</thead>
<tbody>
<tr>
<td>O1—H1—O3’</td>
<td>0.82</td>
<td>1.80</td>
<td>2.623 (3)</td>
<td>178</td>
</tr>
<tr>
<td>C2—H2—O2’</td>
<td>0.98</td>
<td>2.51</td>
<td>3.338 (4)</td>
<td>142</td>
</tr>
<tr>
<td>C11—H11—O3</td>
<td>0.96</td>
<td>2.58</td>
<td>3.135 (4)</td>
<td>117</td>
</tr>
</tbody>
</table>

Symmetry codes: (i) x, 1/2+y, 1/2-z; (ii) 1-x, y, z.

Compound (I) crystallized in the orthorhombic system, space group $P2_12_12_1$ from the systematic absences. A full Friedel dataset was collected for this structure although the anomalous dispersion terms for O, N and C are small. The absolute configuration was not determined [Flack (1983) parameter = 1 (2)] by our X-ray analysis, but can be inferred from the known absolute configuration of the L-alanine starting material used in the synthesis. Friedel pairs were averaged in the final stages of refinement. H atoms were treated as riding atoms using the SHELXL97 defaults with C—H 0.93 to 0.98 Å, O—H 0.82 Å.

Data collection: CAD4 (Enraf–Nonius, 1992); cell refinement: SET4 and CELDIM (Enraf–Nonius, 1992); data reduction: DATRD2 in NRCVAX96 (Gabe et al., 1989); program(s) used to solve structure: SHELXS97 (Sheldrick, 1997); program(s) used to refine structure: NRCVAX96 and SHELXL97 (Sheldrick, 1997); molecular graphics: NRCVAX96, ORTEPII (Johnson, 1976), PLATON (Spek, 1998); software used to prepare material for publication: NRCVAX96, SHELXL97 and WordPerfect macro PREP8 (Ferguson, 1998).

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References