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

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

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Key indicators

Single-crystal X-ray study

$T = 294\text{ K}$

Mean $\sigma(\text{C}-\text{C}) = 0.004\text{ \AA}$

R factor = 0.039

wR factor = 0.087

Data-to-parameter ratio = 7.8

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

The title compound, $\text{C}_{11}\text{H}_{11}\text{NO}_3$, a condensation product of L-alanine and *ortho*-phthalaldehyde, crystallizes in space group $P2_12_12_1$. Intermolecular $\text{O}-\text{H}\cdots\text{O}=\text{C}$ and $\text{C}-\text{H}\cdots\text{O}$ hydrogen bonds are present with $\text{O}\cdots\text{O}$ and $\text{C}\cdots\text{O}$ distances of 2.623 (3) and 3.338 (4) \AA , respectively.

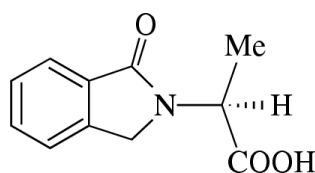
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Comment

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 (isoindolin-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).



(I)

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 $1.21(18)^\circ$ and the maximum deviation from planarity for an atom in either ring plane is 0.0125 (16) \AA for N1, while the carbonyl atom O3 is 0.066 (4) \AA from the C_4N ring plane. The five-membered ring is oriented at an angle of $71.72(9)^\circ$ to the CCO_2 carboxylic acid plane. Examination of (I) with *PLATON* (Spek, 1998) revealed no voids in the crystal lattice.

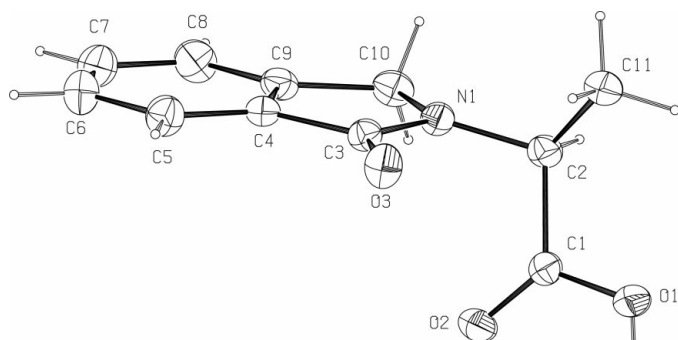


Figure 1
A view of (I) with the atomic numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

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 $R^2_2(8)$ (Ferguson *et al.*, 1995) is not observed in (I), mainly due to symmetry constraints; instead, the (acid)O—H...O=C(phth) interaction generates a one-dimensional zigzag chain of molecules along the *b* axis, and these chains are further linked by the C—H...O=C(acid) interactions along the *a* axis.

The crystal structure of (I) contrasts with that of compound (II), (2*R*/2*S*)-2-(1-oxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-phenylpropanoic acid (Brady *et al.*, 1998), in which the extra phenyl group facilitates two C—H... π (arene) interactions. Molecule (I) is similar, however, to a valine derivative, (2*S*)-3-methyl-2-(1-oxo-1*H*-2,3-dihydroisoindol-2-yl)butanoic acid, in which the five-membered isoindolyl ring carbonyl C=O 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 CH₃CN under N₂ (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, ($\nu_{\text{C=O}}$ cm⁻¹), 1730, 1644 (KBr). Melting point 485–487 K (uncorrected).

Crystal data

C ₁₁ H ₁₁ NO ₃	Mo K α radiation
$M_r = 205.21$	Cell parameters from 25 reflections
Orthorhombic, $P2_12_12_1$	$\theta = 9.0\text{--}18.9^\circ$
$a = 5.1787$ (5) Å	$\mu = 0.10$ mm ⁻¹
$b = 9.9128$ (18) Å	$T = 294$ (1) K
$c = 18.918$ (5) Å	Plate, colourless
$V = 971.2$ (3) Å ³	$0.42 \times 0.21 \times 0.04$ mm
$Z = 4$	
$D_x = 1.403$ Mg m ⁻³	

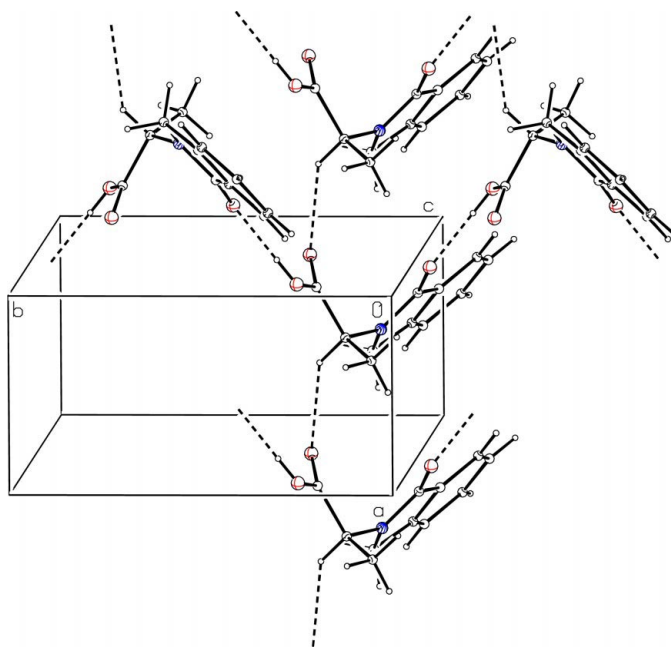


Figure 2
A view of the interactions in the crystal structure.

Data collection

Enraf–Nonius CAD-4 diffractometer	$\theta_{\text{max}} = 25.4^\circ$
ω - 2θ scans	$h = -6 \rightarrow 6$
Absorption correction: none	$k = -11 \rightarrow 11$
1803 measured reflections	$l = -22 \rightarrow 22$
1086 independent reflections	3 standard reflections
866 reflections with $I > 2\sigma(I)$	frequency: 240 min
$R_{\text{int}} = 0.024$	intensity decay: 0.5%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0513P)^2]$
$R[F^2 > 2\sigma(F^2)] = 0.039$	where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.087$	$(\Delta/\sigma)_{\text{max}} < 0.001$
$S = 1.02$	$\Delta\rho_{\text{max}} = 0.15$ e Å ⁻³
1086 reflections	$\Delta\rho_{\text{min}} = -0.14$ e Å ⁻³
139 parameters	Extinction correction: <i>SHELXL97</i>
H-atom parameters constrained	Extinction coefficient: 0.012 (3)

Table 1

Selected geometric parameters (Å, °).

O1—C1	1.324 (3)	C1—C2	1.528 (4)
O2—C1	1.197 (3)	C2—C11	1.512 (4)
O3—C3	1.235 (3)	C3—C4	1.479 (4)
N1—C2	1.453 (3)	C4—C9	1.385 (4)
N1—C3	1.342 (3)	C9—C10	1.493 (4)
N1—C10	1.455 (3)		
C2—N1—C3	122.6 (2)	N1—C2—C11	113.1 (2)
C2—N1—C10	123.1 (2)	C1—C2—C11	115.2 (2)
C3—N1—C10	112.9 (2)	O3—C3—N1	124.7 (2)
O1—C1—O2	123.9 (3)	O3—C3—C4	128.0 (2)
O1—C1—C2	112.5 (2)	N1—C3—C4	107.3 (2)
O2—C1—C2	123.5 (2)	C3—C4—C5	130.0 (3)
N1—C2—C1	107.8 (2)	C8—C9—C10	130.9 (3)
C3—N1—C2—C1	58.3 (3)	O2—C1—C2—C11	152.4 (3)
O2—C1—C2—N1	25.0 (4)	C2—N1—C3—O3	9.6 (4)

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

$D-H \cdots A$	$D-H$	$H \cdots A$	$D \cdots A$	$D-H \cdots A$
$O1-H1 \cdots O3^i$	0.82	1.80	2.623 (3)	178
$C2-H2 \cdots O2^{ii}$	0.98	2.51	3.338 (4)	142
$C11-H11C \cdots O3$	0.96	2.58	3.135 (4)	117

Symmetry codes: (i) $-x, \frac{1}{2} + y, \frac{3}{2} - z$; (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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