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O—H···O, C—H···O and C—H··· π _{arene} Intermolecular Interactions in (2*R*/*S*)-2-(1-Oxo-1,3-dihydroisindol-2-yl)-3-phenylpropanoic Acid

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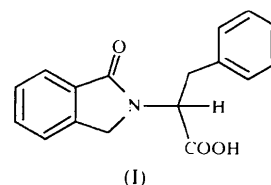
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Abstract

The title compound, C₁₇H₁₅NO₃, forms a hydrogen-bonded network in the solid state consisting of O—H···O=C, C_{arene}—H···O=C and C_{arene}—H··· π _{arene} intermolecular interactions, with shortest O···O, C···O and C···C distances of 2.625 (2), 3.281 (3) and 3.652 (3) Å, respectively. The interplanar angle between the five- and six-membered rings of the isoindole system is 1.07 (14)°, with the carbonyl O atom 0.110 (3) Å from the C₄N ring plane.

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. 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 as a racemic mixture from DL-phenylalanine, is part of an ongoing study of hydrogen-bonding interactions in amino acid derivatives.



A view of molecule (I) (*S* configuration) with the atomic numbering scheme is given in Fig. 1 and selected dimensions are given in Table 1. The bond lengths and angles in the heterocyclic ring are similar to those reported previously (McNab *et al.*, 1997) and in agreement with expected values (Orpen *et al.*, 1994). The angle between the five- and six-membered rings of the isoindole system is 1.07 (14)° and the maximum deviation from planarity for an atom in either ring plane is 0.021 (1) Å for C3, with the carbonyl O3 atom 0.110 (3) Å from the C₄N ring plane. This ring is almost perpendicular to both the carboxylic acid CO₂ plane [84.74 (15)°] and the 3-phenyl ring plane

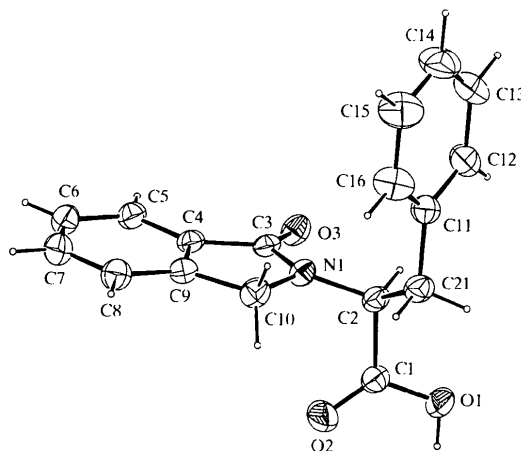


Fig. 1. A view of (I) with the atomic numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

[84.78 (6)°]. Examination of (I) with *PLATON* (Spek, 1997*a*) revealed voids in the crystal lattice of volume 16 Å³, which is too small a volume for a solvent molecule to occupy.

The hydrogen bonding in (I) is dominated by O—H···O=C, C_{arene}—H···O=C and C_{arene}—H···π_{arene} intermolecular interactions (Table 2 and Fig. 2). Conventional carboxylic acid O—H···O hydrogen bonding between pairs of carboxylic acid groups with graph set R₂²(8) (Ferguson *et al.*, 1995) is not observed. Hydrogen-bonded rings with graph set R₂²(9) are formed from the combination of (i) carboxylic acid O1—H1···O3ⁱ interactions with the heterocyclic ring C=O group [O1···O3ⁱ 2.625 (2) Å; symmetry code: (i) $\frac{1}{2} - x, \frac{1}{2} + y, z$] and (ii) phenyl ring C5—H5···O2ⁱⁱ contacts with the carboxylic acid C=O moiety [O2···C5ⁱⁱ 3.281 (3) Å; symmetry code: (ii) $\frac{1}{2} - x, y - \frac{1}{2}, z$]. Association of (I) about inversion centres as *R/S* hydrogen-bonded pairs arises through C—H···π_{arene} interactions [C6···Cg2ⁱⁱⁱ 3.623 (2) Å, with a corresponding shortest C···C distance of 3.652 (3) Å; Cg2 is the ring centroid of the 3-phenyl ring; symmetry code: (iii) $-x, -1 - y, 1 - z$]. The dimers are linked by C—H···π_{arene} interactions [C16···Cg1^{iv} 3.739 (2) Å; Cg1 is the ring centroid of the isoindolinone phenyl ring; symmetry code: (iv) $x - \frac{1}{2}, -\frac{1}{2} - y, 1 - z$].

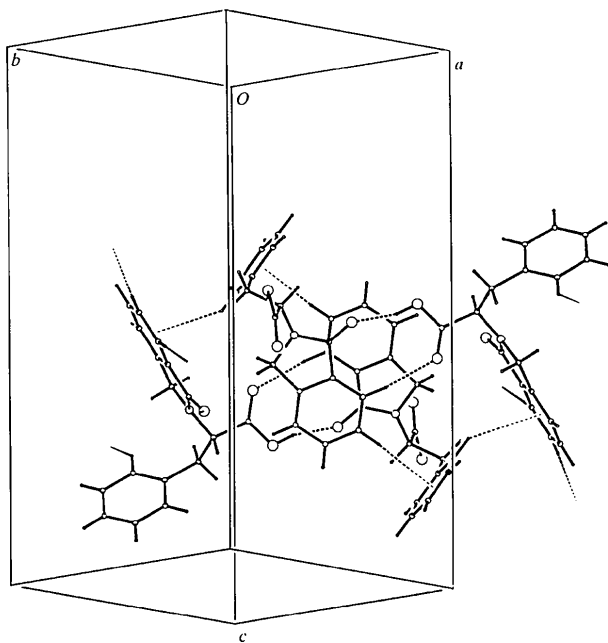


Fig. 2. A view of the hydrogen-bonding interactions in the crystal structure of (I).

The presence of C—H···O and C—H···π_{arene} interactions with stronger hydrogen bonds, *e.g.* O—H···O, has been commented on previously (Steiner, 1997). The formation of one-dimensional molecular zippers in calixarenes has been attributed to result from the in-

tramolecular O—H···O hydrogen bonds pairing off to define the calixarene molecular cavity with cooperative intermolecular C—H···π_{arene} interactions determining the polymeric self-inclusion process (Böhmer *et al.*, 1994; Gallagher *et al.*, 1994). Further studies are in progress on interactions in related amino acid derivatives.

Experimental

The title compound was prepared by the overnight reaction of DL-phenylalanine 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 large colourless crystals [m.p. 469–470 K (uncorrected)].

Crystal data

C₁₇H₁₅NO₃
M_r = 281.30
 Orthorhombic
Pbca
a = 11.4712 (8) Å
b = 12.3457 (8) Å
c = 20.582 (2) Å
V = 2914.9 (4) Å³
Z = 8
D_v = 1.282 Mg m⁻³
D_m not measured

Mo *K*α radiation
λ = 0.7107 Å
 Cell parameters from 25 reflections
θ = 9.55–19.33°
μ = 0.088 mm⁻¹
T = 294 (1) K
 Block
 0.43 × 0.38 × 0.15 mm
 Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
 ω -2*θ* scans
 Absorption correction: none
 5641 measured reflections
 2558 independent reflections
 1620 reflections with *I* > 2σ(*I*)

R_{int} = 0.013
θ_{max} = 25°
h = 0 → 13
k = 0 → 14
l = -24 → 24
 3 standard reflections
 frequency: 120 min
 intensity decay: none

Refinement

Refinement on *F*²
R[*F*² > 2σ(*F*²)] = 0.041
wR(*F*²) = 0.098
S = 1.013
 2558 reflections
 191 parameters
 H atoms riding
w = 1/[σ²(*F_o*²) + (0.0436*P*)² + 0.3708*P*]
 where *P* = (*F_o*² + 2*F_c*²)/3

(Δ/*σ*)_{max} = 0.001
Δ*ρ*_{max} = 0.138 e Å⁻³
Δ*ρ*_{min} = -0.128 e Å⁻³
 Extinction correction: *SHELXL97*
 Extinction coefficient: 0.0040 (6)
 Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. Selected geometric parameters (Å, °)

O1—C1	1.314 (2)	C1—C2	1.519 (2)
O2—C1	1.194 (2)	C2—C21	1.531 (3)
O3—C3	1.239 (2)	C3—C4	1.469 (2)
N1—C2	1.452 (2)	C9—C10	1.491 (3)
N1—C3	1.354 (2)	C11—C21	1.511 (3)
N1—C10	1.458 (2)		
C2—N1—C3	121.55 (14)	C1—C2—C21	112.07 (14)
C2—N1—C10	123.06 (14)	O3—C3—N1	123.78 (16)
C3—N1—C10	112.94 (14)	O3—C3—C4	129.44 (16)

O1—C1—O2	124.00 (18)	N1—C3—C4	106.75 (16)
O1—C1—C2	112.05 (16)	C3—C4—C5	129.84 (18)
O2—C1—C2	123.95 (18)	C8—C9—C10	129.88 (18)
N1—C2—C1	109.24 (15)	N1—C10—C9	102.20 (14)
N1—C2—C21	112.79 (15)		

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

Cg1 is the ring centroid of the isoindolinone phenyl ring and Cg2 is the ring centroid of the 3-phenyl ring.

D—H...A	D—H	H...A	D...A	D—H...A
O1—H1...O3 ⁱ	0.87	1.78	2.625 (2)	163
C5—H5...O2 ⁱⁱ	0.93	2.36	3.281 (3)	171
C6—H6...Cg2 ⁱⁱⁱ	0.93	2.69	3.623 (2)	176
C16—H16...Cg1 ^{iv}	0.93	2.97	3.739 (2)	141

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

H atoms were allowed for as riding atoms with C—H distances in the range 0.93–0.98 Å; the coordinates of the carboxylic acid H atom were located in a difference Fourier map in the latter stages of refinement and included in the structure-factor calculations with O—H 0.87 Å and C—O—H 110°.

Data collection: *CAD-4-PC Software* (Enraf–Nonius, 1992). Cell refinement: *SET4* and *CELDIM* in *CAD-4-PC Software*. Data reduction: *DATRD2* in *NRCVAX96* (Gabe *et al.*, 1989). Program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997a). Program(s) used to refine structure: *NRCVAX96* and *SHELXL97* (Sheldrick, 1997b). Molecular graphics: *NRCVAX96*, *ORTEPII* (Johnson, 1976) and *PLUTON* (Spek, 1997b). Software used to prepare material for publication: *NRCVAX96*, *SHELXL97* and *WordPerfect* macro *PRP-CIF97* (Ferguson, 1997).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: CF1250). Services for accessing these data are described at the back of the journal.

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6-(4-Chlorophenyl)-3-methyl-2,4a-diphenyl-5,6-dihydro-1H,4aH-1,3-oxazino[2,3-d][1,5]-benzothiazepin-1-one

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Abstract

The title compound, C₃₁H₂₄ClNO₂S, has a *cis*-ring-fusion tricyclic structure, which is formed from a benzene ring, a seven-membered heterocyclic thiazepine ring and a 1,3-oxazinone ring. The 1,5-thiazepine ring has a slightly distorted boat-like conformation, whereas the 1,3-oxazinone ring adopts a half-chair conformation.

Comment

Benzothiazepines, especially those with a fused heterocyclic ring, are potential pharmaceutical agents (Corral *et al.*, 1985; Bock *et al.*, 1989; Xu & Jin, 1994). 5,6-Dihydro-1H,4aH-1,3-oxazino[2,3-d][1,5]benzothiazepin-1-one derivatives with potential anxiolytic and hypnotic activities (Sternbach, 1979; Xu & Jin, 1992) were synthesized by the Diels–Alder reaction of 2,4-diaryl-2,3-dihydro-1,5-benzothiazepine derivatives and α -diazo- β -diketone (Capuano & Gartner, 1981; Capuano & Wamprecht, 1986). When an asymmetric α -diazo- β -diketone, such as 2-diazo-1-phenyl-1,3-butanedione, is