

N-(2-Amino-1,6-dihydro-5-nitroso-6-oxopyrimidin-4-yl)-*L*-isoleucine–water (4/1): interplay of molecular and supramolecular structures

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In the title compound, $2C_{10}H_{15}N_5O_4 \cdot 0.5H_2O$, there are two independent molecules of the pyrimidinylisoleucine in general positions and a water molecule lying on a twofold rotation axis. The bond lengths within the organic moieties demonstrate significant polarization of the electronic structure. Each of the organic molecules participates in 12 intermolecular hydrogen bonds, of O—H...O and N—H...O types, while the water molecule acts as a double donor and as a double acceptor of O—H...O hydrogen bonds. The organic components are linked by the hydrogen bonds into a single three-dimensional framework, reinforced by the water molecules.

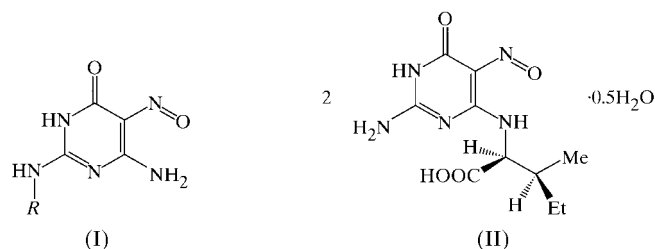
Comment

The molecular and supramolecular structures of the nitroso-pyrimidine derivatives of amino acids, (I), are characterized by several unexpected features (Low *et al.*, 2000). The bond lengths are consistent with a marked polarization of the electronic charge, and there are very short intermolecular O—H...O hydrogen bonds involving the carboxyl group as donor and the nitrosyl O atom as acceptor, with O...O distances around 2.50 Å; where the amidic O acts as a hydrogen-bond acceptor, it does so only weakly. We have now investigated an analogous hydrated derivative (II), formed by *L*-isoleucine [(2*S*,3*S*)-2-amino-3-methylpentanoic acid], in which the amino acid side chain is *ortho* to the *C*-nitroso group, rather than *para* to it as in (I); the molecular and supramolecular structures of (II) exhibit some significant differences compared with those of (I).

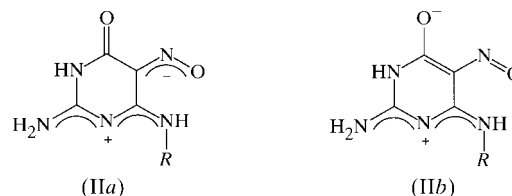
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Compound (II) crystallizes in space group *C*2 with two molecules in the asymmetric unit; in addition, there is a water molecule lying on a twofold rotation axis, so that the overall composition is $4C_{10}H_{15}N_5O_4 \cdot H_2O$. The conformation of the acidic side chains (Table 1 and Fig. 1) and the hydrogen-bonding characteristics (Table 2) of the two independent organic molecules rule out the possibility of any additional symmetry; in particular, only molecule 1 (Fig. 1) forms hydrogen bonds with the water molecule.



- (I) $R = CH_2COOH$
 (b) $R = CH(COOH)CH_2CH_2SCH_3$
 (c) $R = CH(COOH)CH(CH_3)_2$
 (d) $R = CH(COOH)CH_2OH$
 (e) $R = CH(COOH)CH(OH)CH_3$



The intramolecular distances for the two molecules are extremely similar, apart from $Cn4-Cn5$ and $Cn5-Cn6$ ($n = 1, 2$) which are both significantly longer in molecule 1; however, in each of the two individual molecules, these two distances are virtually identical. There are a number of metrical features which indicate the inadequacy of representation (II) for the electronic structure. Firstly, in the sequence of C—N bonds $Nn2-Cn2-Nn3-Cn4-Nn4$ ($n = 1, 2$) it is not possible from the observed distances to assign $Cn2-Nn3$ as a double bond and the remainder as single bonds; indeed, in these sequences the shortest bonds are the exocyclic bonds $Nn2-Cn2$. Secondly, the $Cn4-Cn5$ and $Cn5-Cn6$ bonds cannot plausibly be assigned as double and single bonds, respectively; the $Cn4-Cn5$ distances are, in fact, similar to those for single bonds between two three-connected C atoms (Allen *et al.*, 1987). Finally, the differences between the C—N and N—O distances in the *C*-nitroso fragment are small; in simple neutral compounds where there is no possibility of significant electronic delocalization, these distances normally differ by at least 0.20 Å (Talberg, 1977; Schlemper *et al.*, 1986) and the NO distance rarely exceeds 1.25 Å (Davis *et al.*, 1965; Bauer & Andreassen, 1972; Talberg, 1977; Schlemper *et al.*, 1986). These observations point to the importance of the contributions (IIa) and (IIb) to the electronic structure. By contrast, in compounds of type (I) (Low *et al.*, 2000), forms analogous to (IIa) are important contributors to the electronic structures, whereas forms analogous to (IIb) are not. The importance of (IIb) in the title compound is demonstrated by the hydrogen-

bonding behaviour, where the amidic O16 and O26 atoms (Fig. 1) both act as triple acceptors (Table 2).

In each of the two independent molecules of (II), there is an intramolecular N—H···O hydrogen bond. In addition, each molecule acts as a sixfold donor of intermolecular hydrogen bonds and as a sixfold acceptor. Finally, the water molecule acts as a twofold donor and as a twofold acceptor. The resulting hydrogen-bonded supramolecular structure, a three-dimensional framework, is thus of considerable complexity; however, adoption of the substructure approach (Gregson *et al.*, 2000) leads to a rather straightforward description in terms of a single-chain motif and the connections between such chains.

Within the asymmetric unit, atom N21 acts as hydrogen-bond donor to both N15 and O15 in a nearly planar three-centre hydrogen bond; likewise, N22 acts as donor, *via* H22B, to both N15 and O16 in a similar but strictly planar system. In an entirely similar way, N11 at (x, y, z) acts as donor to N25 and O25 at $(\frac{1}{2} + x, \frac{1}{2} + y, 1 + z)$, and N12 at (x, y, z) acts as donor, *via* H12B, to N25 and O26, also at $(\frac{1}{2} + x, \frac{1}{2} + y, 1 + z)$. Hence these four distinct three-centre hydrogen bonds generate, by translation, a complex chain of rings running parallel to the [112] direction (Fig. 2). There are four chains of this type running through each unit cell: two, related to one another by the action of the C-centring operation, are parallel to [112], and a second pair, related to the first pair by the action of the twofold rotation axis, run parallel to $[1\bar{1}2]$.

Each two-molecule aggregate within the chain forms six further hydrogen bonds exterior to its own chain, and these

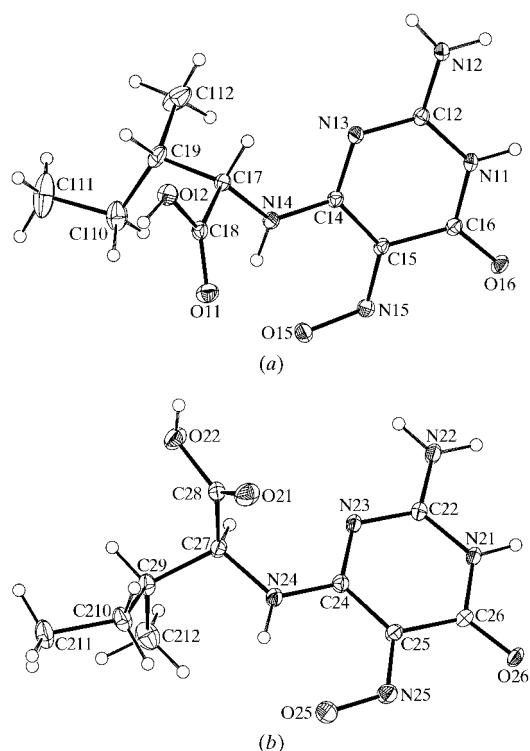


Figure 1

The two independent pyrimidine molecules in (II) showing the atom-labelling scheme of (a) molecule 1 and (b) molecule 2. Displacement ellipsoids are drawn at the 30% probability level.

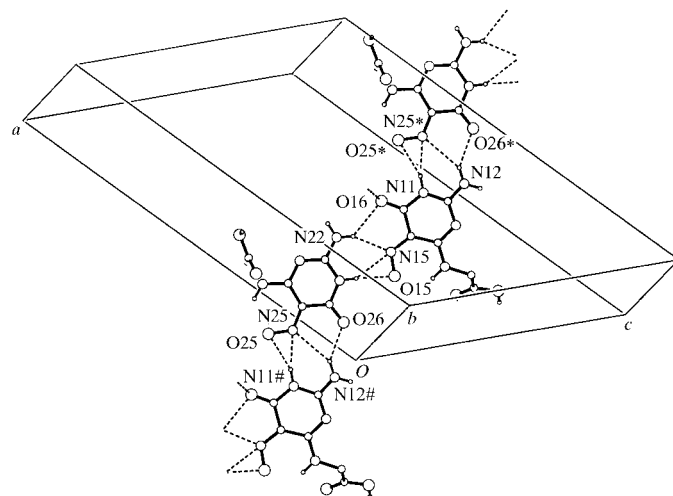


Figure 2

Part of the crystal structure of (II) showing the formation of one of the [112] chains. Atoms marked with an asterisk (*) or hash (#) are at the symmetry positions $(\frac{1}{2} + x, \frac{1}{2} + y, 1 + z)$ and $(-\frac{1}{2} + x, -\frac{1}{2} + y, -1 + z)$, respectively. H atoms bonded to C atoms and some leucyl alkyl C atoms have been omitted for the sake of clarity.

serve to link all of the chains into a single framework, although the behaviour of the two independent organic molecules is quite different. Carboxylic O22 at (x, y, z) acts as hydrogen-bond donor to amidic O26 at $(\frac{1}{2} - x, \frac{1}{2} + y, -z)$, while O22 at $(\frac{1}{2} - x, \frac{1}{2} + y, -z)$ in turn acts as donor to O26 at $(x, 1 + y, z)$, so producing a spiral $C(9)$ chain parallel to the [010] direction, built entirely from type 2 molecules and generated by the 2_1 screw axis along $(\frac{1}{4}, y, 0)$ (Fig. 3). A second spiral motif parallel to [010] involves molecules of types 1 and 2 and is generated by the 2_1 screw axis along $(\frac{1}{4}, y, \frac{1}{2})$. Amino N12 acts as donor, *via* H12A, to O26 at $(\frac{1}{2} - x, \frac{1}{2} + y, 1 - z)$ and N12 at $(\frac{1}{2} - x, \frac{1}{2} + y, 1 - z)$ acts in turn as donor to O26 at $(x, 1 + y, z)$, generating a $C_2^2(11)$ motif (Fig. 4). These two [010] motifs serve not only to link parallel [112] chains into sheets, and likewise the $[1\bar{1}2]$ chains, but are sufficient to link the [112] and $[1\bar{1}2]$ chains into a continuous framework, which can thus be generated without the intervention of the water molecules.

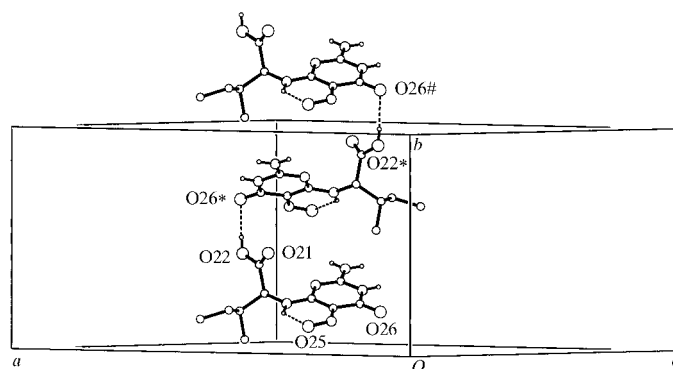


Figure 3

Part of the crystal structure of (II) showing the formation of the $C(9)$ spiral motif linking the [112] and $[1\bar{1}2]$ chains. Atoms marked with an asterisk (*) or hash (#) are at the symmetry positions $(\frac{1}{2} - x, \frac{1}{2} + y, -z)$ and $(x, 1 + y, z)$, respectively. H atoms bonded to C atoms have been omitted for the sake of clarity.

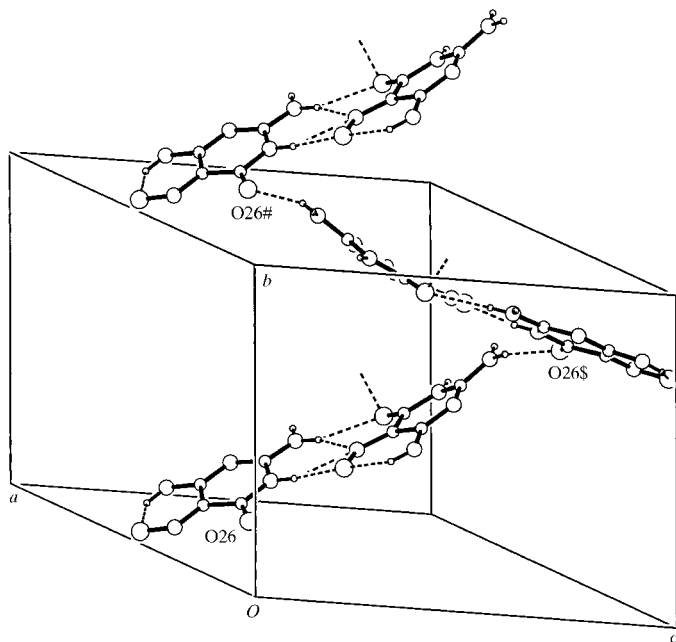


Figure 4
Part of the crystal structure of (II) showing the formation of the $C_2(11)$ spiral motif linking the $[112]$ and $[1\bar{1}2]$ chains. Atoms marked with a hash (#) or dollar sign (\$) are at the symmetry positions $(x, 1 + y, z)$ and $(\frac{1}{2} - x, \frac{1}{2} + y, 1 - z)$, respectively. H atoms bonded to C atoms and some leucyl alkyl C atoms have been omitted for the sake of clarity.

In the event, all four chains are linked by the water molecules: water O1 at (x, y, z) acts as donor to amidic O16 atoms in the molecules at (x, y, z) and $(1 - x, y, 1 - z)$, and as acceptor from carboxylic O12 atoms at $(\frac{1}{2} + x, \frac{1}{2} + y, z)$ and $(\frac{1}{2} - x, \frac{1}{2} + y, 1 - z)$ (Fig. 5). Each of these type 1 molecules lies in a different chain; each water molecule acts as donor to type 1 molecules in one $[112]$ and in one $[1\bar{1}2]$ chain, and each water similarly acts as acceptor from type 1 molecules in one $[112]$ and one $[1\bar{1}2]$ chain.

Of the three $O-H \cdots O$ hydrogen bonds present (Table 2), the two involving the water molecule have much shorter $O \cdots O$ distances than the one not involving water. Four of the intermolecular $N-H \cdots O$ hydrogen bonds form part of three-centre systems; although the ranges of the $N \cdots O$ distances for the two types of $N-H \cdots O$ hydrogen bonds (two-centre and

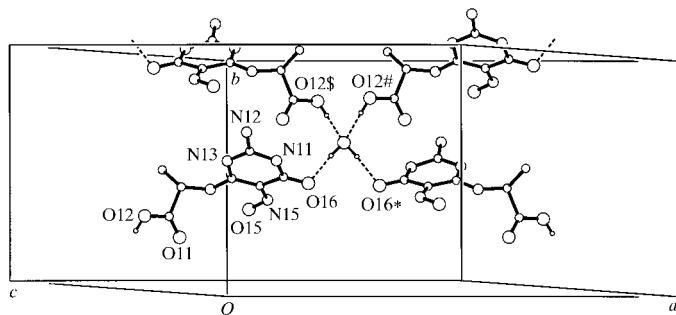


Figure 5
Part of the crystal structure of (II) showing the hydrogen bonds formed by the water molecule. Atoms marked with an asterisk (*), hash (#) or dollar sign (\$) are at the symmetry positions $(1 - x, y, 1 - z)$, $(\frac{1}{2} + x, \frac{1}{2} + y, z)$ and $(\frac{1}{2} - x, \frac{1}{2} + y, 1 - z)$, respectively. H atoms bonded to C atoms and some leucyl alkyl atoms have been omitted for the sake of clarity.

three-centre) overlap, the average value in the three-centre bonds, 3.088 (3) Å, is somewhat larger than that in the two-centre bonds, 2.908 (3) Å. The only $N-H \cdots N$ hydrogen bonds present are all part of three-centre systems; the average value of the $N \cdots N$ distance in these systems, 3.081 (4) Å, is very similar to the corresponding $N \cdots O$ average. In the intermolecular two-centre hydrogen bonds, the $D-H \cdots A$ angles range from 152 to 175°, with a mean value of 166° (Table 2). While none of the $D \cdots A$ distances is particularly short, the co-operative effect of the multiplicity of hydrogen bonds, particularly within the $[112]$ and $[1\bar{1}2]$ chains, produces a coherent and stable supramolecular arrangement. However, none of the hydrogen bonds in (II) approaches the very short $O-H \cdots O$ hydrogen bonds in the series (I). All potential hydrogen-bond donors participate in the supramolecular structure, with the exception of N14–H14 and N24–H24, which both form intramolecular hydrogen bonds. It is notable that none of the O atoms in the carboxylic acid groups acts as a hydrogen-bond acceptor. It may be presumed that atoms N13 and N23 do not act as hydrogen-bond acceptors for steric reasons.

Experimental

To a suspension of 2-amino-4,6-dimethoxy-5-nitrosopyrimidine (92 mg, 0.5 mmol) in CH_3CN (5 ml) was added a solution of L-isoleucine (79 mg, 0.6 mmol) in aqueous 1 mol dm^{-3} Na_2CO_3 solution (0.6 ml). Water (4.4 ml) was added and the final mixture was stirred for 8 h at room temperature. The mixture was evaporated to dryness and the residue was suspended in 5 ml of water and acidified with concentrated HCl to pH 2–3. Slow evaporation at 277 K gave single crystals of (II) suitable for X-ray diffraction (97 mg, 72%; m.p. 463 K). IR (KBr), ν (cm^{-1}): 3369–3181 (NH/OH), 2971 (C–H), 1736 (C=O), 1757, 1708 (C=O), 1656 (*d*, NH_2), 1577, 1539 (C=N, C=C, N=O), 1309 (C–N), 1202 (C–O). 1H NMR (DMSO- d_6) δ (p.p.m., TMS) 12.87 (*d*, 8.44 Hz, NH), 10.94 (*br, s*, NH), 8.29 (*br, s*, 1H, NH_2), 7.01 (*br, s*, 1H, NH_2), 4.70 (*dd*, 8.46 Hz, 4.51 Hz, CH), 1.98–1.85 (*m*, CH), 1.51–1.37 (*m*, 1H, CH_2), 1.27–1.13 (*m*, CH_2), 0.91 (*d*, 7.31 Hz, CH_3CH), 0.85 (*q*, 7.31 Hz, CH_3CH_2); ^{13}C NMR (DMSO- d_6) δ (p.p.m., TMS): 171.5, 161.1, 156.3, 151.9, 140.5, 56.6, 36.7, 24.7, 15.5, 11.4. Analysis, found: C 43.9, H 5.8, N 25.4%; $C_{10}H_{15}N_5O_4 \cdot 0.25H_2O$: requires C 43.9, H 5.7, N 25.6%.

Crystal data

$2C_{10}H_{15}N_5O_4 \cdot 0.5H_2O$
 $M_r = 547.55$
Monoclinic, $C2$
 $a = 21.4179$ (6) Å
 $b = 11.1466$ (2) Å
 $c = 14.9649$ (3) Å
 $\beta = 133.4280$ (6)°
 $V = 2594.61$ (10) Å³
 $Z = 4$

$D_x = 1.400$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3819 reflections
 $\theta = 3.46$ – 30.49 °
 $\mu = 0.111$ mm^{-1}
 $T = 150$ (2) K
Plate, red
 $0.36 \times 0.30 \times 0.05$ mm

Data collection

KappaCCD diffractometer
 φ scans, and ω scans with κ offsets
Absorption correction: multi-scan (DENZO-SMN; Otwinowski & Minor, 1997)
 $T_{min} = 0.961$, $T_{max} = 0.995$
21713 measured reflections
3819 independent reflections

3119 reflections with $I > 2\sigma(I)$
 $R_{int} = 0.061$
 $\theta_{max} = 29.9$ °
 $h = -30 \rightarrow 28$
 $k = -15 \rightarrow 15$
 $l = -20 \rightarrow 20$
Intensity decay: negligible

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.042$
 $wR(F^2) = 0.098$
 $S = 1.04$
 3819 reflections
 354 parameters

H-atom parameters constrained
 $w = 1/[\sigma^2(F_o^2) + (0.0624P)^2]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\max} = 0.001$
 $\Delta\rho_{\max} = 0.24 \text{ e } \text{Å}^{-3}$
 $\Delta\rho_{\min} = -0.34 \text{ e } \text{Å}^{-3}$

Table 1

Selected geometric parameters (Å, °).

N11—C12	1.370 (2)	N21—C22	1.369 (3)
C12—N13	1.330 (2)	C22—N23	1.332 (3)
N13—C14	1.337 (3)	N23—C24	1.337 (3)
C14—C15	1.455 (3)	C24—C25	1.435 (3)
C15—C16	1.449 (3)	C25—C26	1.437 (3)
C16—N11	1.364 (3)	C26—N21	1.364 (3)
C12—N12	1.313 (3)	C22—N22	1.311 (3)
C14—N14	1.323 (2)	C24—N24	1.333 (3)
C15—N15	1.330 (3)	C25—N25	1.344 (3)
N15—O15	1.281 (2)	N25—O25	1.279 (2)
C16—O16	1.234 (2)	C26—O26	1.246 (2)
C14—N14—C17—C18	−123.6 (2)	C24—N24—C27—C28	−81.1 (2)
C14—N14—C17—C19	116.0 (2)	C24—N24—C27—C29	154.46 (19)
N14—C17—C18—O12	166.79 (15)	N24—C27—C28—O22	167.91 (17)
N14—C17—C19—C110	57.9 (2)	N24—C27—C29—C210	64.8 (2)
C17—C19—C110—C111	165.4 (2)	C27—C29—C210—C211	161.0 (2)

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 O16	0.95	1.77	2.709 (2)	170
N11—H11 \cdots O25 ⁱ	0.88	2.36	3.147 (3)	149
N11—H11 \cdots N25 ⁱ	0.88	2.19	3.007 (3)	155
O12—H12 \cdots O1 ⁱⁱⁱ	0.84	1.80	2.619 (2)	166
N12—H12A \cdots O26 ⁱⁱⁱ	0.88	2.04	2.851 (3)	152
N12—H12B \cdots O26 ⁱ	0.88	2.20	2.911 (3)	138
N12—H12B \cdots N25 ⁱ	0.88	2.51	3.279 (4)	146
N14—H14 \cdots O15	0.88	2.00	2.672 (3)	133
N21—H21 \cdots O15	0.88	2.01	2.886 (3)	172
N21—H21 \cdots N15	0.88	2.29	3.071 (2)	148
O22—H22 \cdots O26 ^{iv}	0.84	1.97	2.811 (2)	175
N22—H22A \cdots O16 ^v	0.88	2.10	2.965 (3)	165
N22—H22B \cdots O16	0.88	2.37	3.041 (3)	133
N22—H22B \cdots N15	0.88	2.15	2.967 (4)	154
N24—H24 \cdots O25	0.88	1.99	2.647 (3)	130

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

Compound (II) crystallized in the monoclinic system. The systematic absences permitted $C2$, Cm and $C2/m$ as possible space groups; of these, Cm and $C2/m$ were ruled out by the chiral nature of

the organic moieties, and $C2$ was subsequently confirmed by the successful structure solution and refinement. All H atoms were located in difference maps and were treated as riding, with C—H distances of 0.98 Å (CH_3), 0.99 Å (CH_2) or 1.00 Å (CH), an N—H distance of 0.88 Å, and an O—H distance of 0.84 Å or 0.95 Å. In the absence of significant anomalous scattering, the refined Flack parameter of -0.5 (8) (Flack, 1983) was inconclusive (Flack & Bernardinelli, 2000); hence the Friedel equivalents were merged and the absolute configuration was set by reference to the known configuration (2*S*,3*S*) of L-isoleucine. Examination of the structure with *PLATON* (Spek, 2000) showed that there were no solvent-accessible voids in the crystal lattice.

Data collection: *KappaCCD Server Software* (Nonius, 1997); cell refinement: *DENZO-SMN* (Otwinowski & Minor, 1997); data reduction: *DENZO-SMN*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2000); software used to prepare material for publication: *SHELXL97* and *PRPKAPPA* (Ferguson, 1999).

X-ray data were collected at the EPSRC X-ray Crystallographic Service, University of Southampton, using an Enraf-Nonius KappaCCD diffractometer. The authors thank the staff for all their help and advice.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GG1043). Services for accessing these data are described at the back of the journal.

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