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# Cyclo(L-isoleucyl-L-isoleucyl)

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**Key indicators**

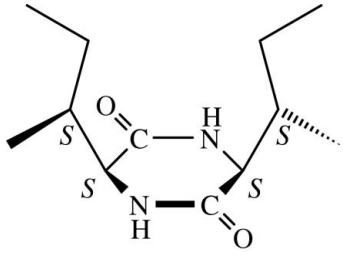
Single-crystal X-ray study
$T$ = 105 K
Mean $\sigma$(C–C) = 0.004 Å
$R$ factor = 0.036
$wR$ factor = 0.106
Data-to-parameter ratio = 11.1

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

The title compound [systematic name: (3*S*,6S)-3,6-bis(*S*-*sec*-butyl)-2,5-piperazine-2,5-dione], $C_{12}H_{22}N_2O_2$, was crystallized from a solution of the corresponding linear peptide L-isoleucyl-L-isoleucine. In the crystal structure, molecules form traditional N—H···O hydrogen-bonded tapes along the *a* axis [*a* = 6.242 (9) Å].

## Comment

Crystals of the title compound, (I), were obtained when carrying out crystallization experiments with the linear dipeptide L-isoleucyl-L-isoleucine (Görbitz, 2004). The use of methanol in some setups yielded poor block-shaped crystals that were identified as the methanol solvate (low-quality structure, not published). Some needles were also obtained, and structure solution after data collection showed that cyclization into the corresponding diketopiperazine *cyclo*-(L-isoleucyl-L-isoleucyl), (I), had taken place. We have previously observed similar cyclization reactions for L-aspartyl-L-alanine (Görbitz, 1987) and L-valyl-L-leucine (unpublished work). The latter of the two is notoriously unstable and can be purchased only as the HCl salt. Curiously enough, aqueous solutions of several other dipeptides with similar chemical compositions are stable almost indefinitely.




(I)

The molecular structure of (I) is shown in Fig. 1. As both residues have the same chirality, side chains are located on the same side of the ring plane. They also have equivalent conformations (Table 1), and in fact only the small difference between the C1—C2—C3—C4 and C7—C8—C9—C10 torsion angles (Table 1) breaks an almost perfect intramolecular twofold symmetry.

There are 122 different structures in the Cambridge Structural Database (CSD; Version 5.27 of November 2005; Allen, 2002) containing a diketopiperazine system, but only 48 entries remain when various 1:1 cocrystallization complexes as well as very large structures (with or without metal ions) are excluded (28 are constructed solely from the 20 common amino acids). Within this group, there is a high propensity for

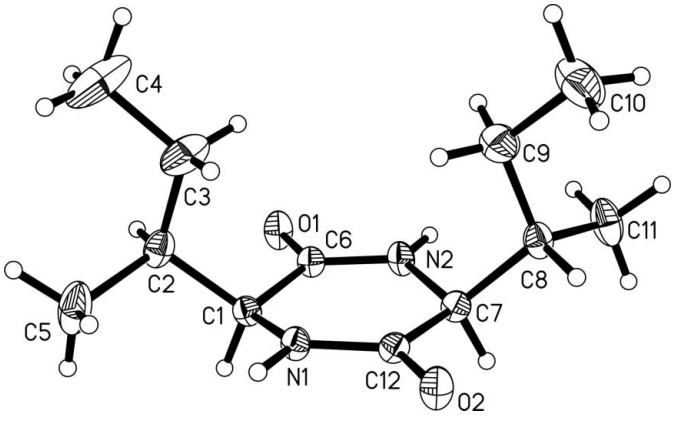



**Figure 1**
The molecular structure of (I). Displacement ellipsoids are shown at the 50% probability level and H atoms are shown as spheres of arbitrary size.

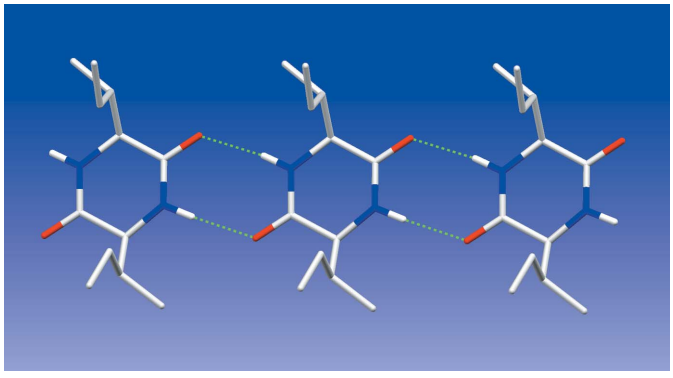


**Figure 2**
Part of a hydrogen-bonded (dashed lines) tape of (I) propagating along the *a* axis.

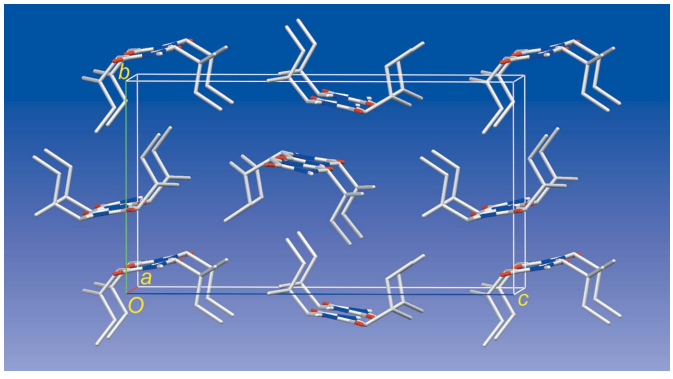



**Figure 3**
Molecular packing and unit cell of (I), viewed along the *a* axis.

formation of hydrogen-bonded tapes (40 structures), as observed also for (I) (Fig. 2 and Table 2). Such tapes are very robust structural motifs that persist even in structures with numerous hydrogen-bond donors and acceptors in addition to those found in the diketopiperazine ring, either in functional groups in the side chains or through inclusion of solvent water molecules. One would then tend to think that the reasonably simple crystal packing arrangement of (I), depicted in Fig. 3, could be found in several other related structures, but previous observations are in fact limited to *cyclo*-(α-aminobutyryl-L-isoleucyl) (Suguna *et al.*, 1982), which is also the only other diketopiperazine structure with an isoleucyl residue.

## Experimental

L-Isoleucyl-L-isoleucine was obtained from Bachem. Upon slow diffusion of methanol into an aqueous solution (50 µl) of this linear dipeptide some thin needles of the title compound were formed.

*Crystal data*

$C_{12}H_{22}N_2O_2$
$M_r$ = 226.32
Orthorhombic, $P2_12_12_1$
$a$ = 6.242 (9) Å
$b$ = 10.814 (15) Å
$c$ = 19.79 (3) Å
$V$ = 1336 (3) Å$^3$
$Z$ = 4
$D_x$ = 1.125 Mg m$^{-3}$
Mo $K\alpha$ radiation
$\mu$ = 0.08 mm$^{-1}$
$T$ = 105 (2) K
Needle, colourless
1.30 × 0.10 × 0.08 mm

*Data collection*

Siemens SMART CCD diffractometer
$\omega$ scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
$T_{min}$ = 0.766, $T_{max}$ = 0.994
7470 measured reflections
1739 independent reflections
1557 reflections with $I > 2\sigma(I)$
$R_{int}$ = 0.040
$\theta_{max}$ = 28.2°

*Refinement*

Refinement on $F^2$
$R[F^2 > 2\sigma(F^2)]$ = 0.036
$wR(F^2)$ = 0.106
$S$ = 1.09
1739 reflections
156 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0514P)^2 + 0.2942P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.006
$\Delta\rho_{max}$ = 0.30 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.19 e Å$^{-3}$

**Table 1**
Selected torsion angles (°).

| | | | |
|---|---|---|---|
| C12—N1—C1—C6 | −13.7 (2) | C6—N2—C7—C12 | −14.3 (2) |
| N1—C1—C6—N2 | 7.1 (2) | N2—C7—C12—N1 | 7.7 (2) |
| C1—C6—N2—C7 | 6.6 (3) | C7—C12—N1—C1 | 6.0 (3) |
| N1—C1—C2—C3 | 59.4 (2) | N2—C7—C8—C9 | 59.4 (2) |
| N1—C1—C2—C5 | −67.0 (2) | N2—C7—C8—C11 | −66.7 (2) |
| C1—C2—C3—C4 | 175.8 (2) | C7—C8—C9—C10 | 162.49 (19) |

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

| $D$—H···$A$ | $D$—H | H···$A$ | $D$···$A$ | $D$—H···$A$ |
|---|---|---|---|---|
| N1—H1···O1$^{i}$ | 0.89 (2) | 2.00 (2) | 2.885 (4) | 172 (2) |
| N2—H2···O2$^{ii}$ | 0.91 (2) | 1.98 (2) | 2.886 (4) | 175 (2) |
| C5—H53···O1$^{i}$ | 0.98 | 2.46 | 3.336 (4) | 148 |
| C7—H71···O1$^{iii}$ | 1.00 | 2.61 | 3.511 (4) | 149 |
| C11—H113···O2$^{ii}$ | 0.98 | 2.50 | 3.389 (4) | 150 |

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

Positional parameters were refined for H atoms in the two peptide bonds. Other H atoms were positioned with idealized geometry and fixed C—H distances in the range 0.98-1.00 Å. $U_{iso}$(H) values were set at 1.2$U_{eq}$ of the carrier atom or 1.5$U_{eq}$ for methyl groups. In the absence of significant anomalous scattering effects, 1171 Friedel pairs

were merged. The absolute configuration was known for the purchased material.

Data collection: *SMART* (Bruker, 1998); cell refinement: *SAINT-Plus* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXTL* (Bruker, 2000); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

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## References

Allen, F. H. (2002). *Acta Cryst.* B**58**, 380–388.
Bruker (1998). *SMART*. Version 5.054. Bruker AXS Inc., Madison, Wisconsin, USA.
Bruker (2000). *SHELXTL* Version 6.10. Bruker AXS Inc., Madison, Wisconsin, USA.
Bruker (2001). *SAINT-Plus*. Version 6.22. Bruker AXS Inc., Madison, Wisconsin, USA.
Görbitz, C. H. (1987). *Acta Chem. Scand. Ser. B*, **41**, 83–86.
Görbitz, C. H. (2004). *Acta Cryst.* B**60**, 569–577.
Sheldrick, G. M. (1996). *SADABS*. University of Göttingen, Germany.
Suguna, K., Ramakumar, S., Shamada, N., Prasad, B. V. V. & Balaram, P. (1982). *Biopolymers*, **21**, 1847–1855.