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6(*S*)-Methyl-3(*S*)-(1-methylethyl)piperazin-2-one

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Key indicators

Single-crystal X-ray study
T = 200 K
Mean σ(C–C) = 0.002 Å
R factor = 0.032
wR factor = 0.073
Data-to-parameter ratio = 12.3

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

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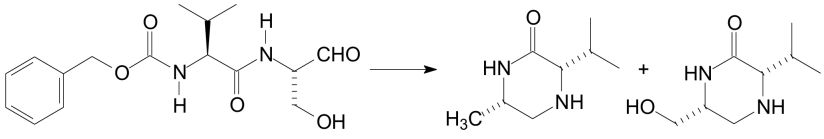
The identity of the title piperazinone, $C_8H_{16}N_2O$, obtained by an unusual deoxygenation reaction, has been confirmed by its crystal structure. We describe the conformation of this template used to mimic conformationally flexible peptides and lipids and compare it to related piperazinones.

Comment

The title chiral 3,6-disubstituted piperazin-2-one, (I), was obtained during the synthesis of a potential head group mimic of the naturally occurring bioactive lipid ceramide. The piperazinone skeleton has been used before as a conformationally restricted analog in the synthesis of peptidomimetics (Kolter *et al.*, 1995; Suarez-Gea *et al.*, 1996; Schanen *et al.*, 1996; Uchida & Achiwa, 1996). More recently, 4-*N*-alkylated piperazin-2-ones have been synthesized by a different route as conformationally rigid analogs of another bioactive lipid, *viz*. diacylglycerol (Endo *et al.*, 1997). Compound (I) has been prepared from the protected, configurationally stable dipeptide aldehyde (III) (Kolter *et al.*, 1992) by hydrogenolysis. During this reaction, a reproducible deoxygenation of the 6-hydroxymethyl residue to a methyl group occurs as an unexpected side reaction in about 20% yield. Similar results have been obtained with a starting material in which the isopropyl group is replaced by a benzyl residue (not shown). The mechanism of this reaction is not clear, but the identity of the deoxygenated compound (I) was confirmed by this crystallographic investigation. Furthermore, the crystal structure gives information on the three-dimensional structure of the piperazinone scaffold and the influence of ring substituents on the ring conformation (Michel *et al.*, 1987).



(III) (I) (II)

The structure of (I), with the atom numbering, is shown in Fig. 1. Selected geometrical parameters are listed in Table 1. The six-membered ring system adopts a distorted half-chair conformation, with atoms N4 and C5 on opposite sides with respect to the C6/N1/C2/C3 plane. In the piperazinone, the substituents at the 3- and 6- positions are in a *cisoid* configuration. The methyl group shows a pseudo-axial orientation [torsion angle C2—N1—C6—C61 is −100.2 (2)°], whereas the isopropyl substituent is pseudo-equatorially orientated [the torsion angle C31—C3—N4—C5 is −174.9 (2)°]. There is one moderate intermolecular hydrogen bond (Steiner, 2002)

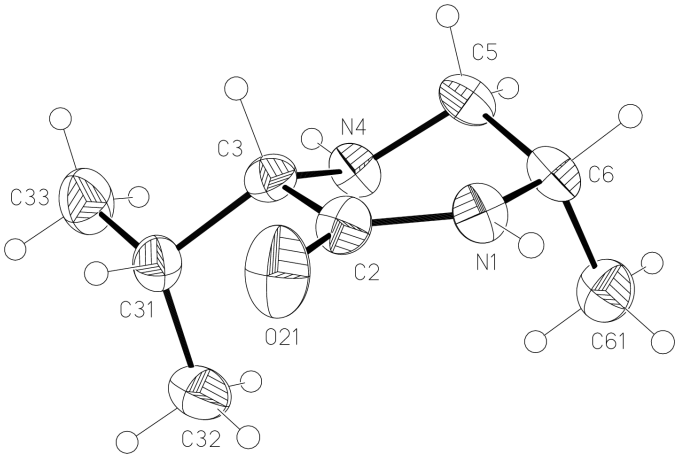


Figure 1
The structure of (I), showing the atom-numbering scheme and displacement ellipsoids at the 50% probability level for the non-H atoms. H atoms are shown as small spheres of arbitrary radii.

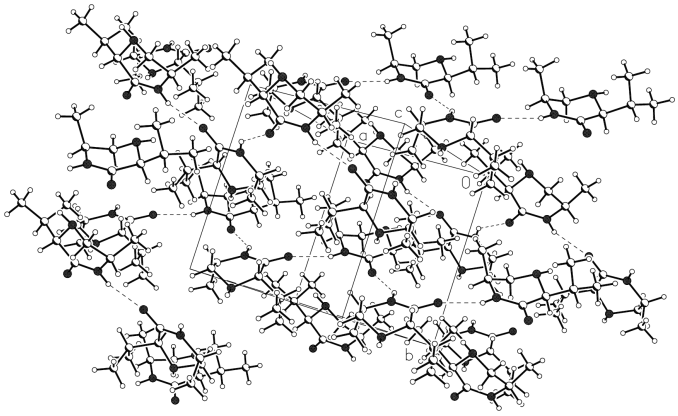


Figure 2
A view of the unit cell, showing the intermolecular hydrogen bonding.

within the crystal. This hydrogen bond, between N1—H and O21, shows a nearly linear geometry [deviation from the ideal angle: 40.3 (13)°; Table 2]. The structure of a closely related piperazin-2-one has been published before (Michel *et al.*, 1987), in which the *p*-hydroxybenzyl substituent at the 3- and the ethyl carboxylate residue at the 6-position are also arranged in a *cisoid* configuration. We compared bond lengths and angles within the ring of (I) with those in the published structure. The deviations in bond lengths range from 0.002 to 0.027 Å and for the angles from 0.0 to 3.2°. Therefore, although the authors proposed the contribution of a dipole–dipole interaction between these substituents, the ring conformation is very similar to (I). The structure of an additional piperazin-2-one with a *trans*-relationship between a 3-isopropyl and a 6-hydroxymethyl substituent has been described before (Kolter *et al.*, 1996). Here, the ring also adopts a half-chair conformation, showing stronger distortion compared to (I) [deviation from the ideal C6/N1/C2/C3 dihedral angle is 1.7° greater than that of compound (I)]. Also, the hydrogen bond between the NH group and the intermolecular piperazinone oxo group shows a similar geometry. The absolute configuration of (I) could not be determined reliably [Flack (1983) parameter x = 0.2 (3)]. Therefore, (I) was assigned to agree with the chirality as established by synthesis. In the past, conformationally flexible bioactive molecules, such as lipids and peptides, have been mimicked by heterocycles of this type. The data on the conformation of 3,6-disubstituted piperazin-2-ones in the solid state should be helpful in the design of further lipid and peptide mimics based on this skeleton.

Experimental

Glassware was flame-dried under an argon atmosphere and allowed to cool. Dipeptide aldehyde (III) (Kolter *et al.*, 1992) (321.4 mg, 1 mmol) was dissolved in methanol (10 ml). After addition of a catalytic amount of palladium on charcoal (5%), the mixture was stirred under a hydrogen atmosphere for 18 h. The catalyst was filtered off and washed twice with methanol (10 ml). After evaporation of the solvent, the residue was purified by column chromatography on silicia gel (chloroform/methanol 10:1) as eluant, giving colorless crystals (yield: 32.5 mg, 20.8%) suitable for X-ray analysis. TLC: 20:1 dichloromethane–methanol, R_F: 0.29; α_D: −121.5° (c = 0.38; $CHCl_3$); m.p.: 385 K; ^{1}H NMR (400 MHz, d_6-DMSO): δ 0.81 [*d*, J = 6.8 Hz, 3H; $CH(CH_3)_2$], 0.92 [*d*, J = 6.8 Hz, 3H; $CH(CH_3)_2$], 1.09 (*d*, J = 6.4 Hz, 3H; CH_3), 2.23 [*dqq*, J = 3.4 Hz, J = 6.8 Hz, J = 6.8 Hz, 1H; $CH(CH_3)_2$], 2.62 (*ddd*, J = 0.8 Hz, J = 3.4 Hz, J = 12.4 Hz, 1H; H-5), 2.82 (*dd*, J = 4.0 Hz, J = 12.4 Hz, 1H; H-5), 2.98 (*d*, J = 3.4 Hz, 1H; H-3), 3.30 (*m*, 1H; H-6), 3.36 (*m*, *br*, 1H; NH), 7.62 (*m*, *br*, 1H; CONH); EI–HRMS: calculated: M^+, m/z = 156.1260, found: m/z = 156.1262.

Crystal data

$C_8H_{16}N_2O$
M_r = 156.23
Orthorhombic, $P2_12_12_1$
a = 8.471 (2) Å
b = 9.282 (1) Å
c = 11.271 (1) Å
V = 886.2 (2) Å^3
Z = 4
D_x = 1.171 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 40–46°
μ = 0.62 mm^{-1}
T = 200 (2) K
Block, colourless
0.30 × 0.23 × 0.20 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
ω scans
Absorption correction: none
3164 measured reflections
1315 independent reflections
1289 reflections with $I > 2\sigma(I)$
R_{int} = 0.073
θ_{max} = 60.0°
$h = -9 \rightarrow 9$
$k = -10 \rightarrow 1$
$l = -12 \rightarrow 12$
3 standard reflections
frequency: 60 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.032
$wR(F^2)$ = 0.073
S = 1.12
1315 reflections
107 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0246P)^2 + 0.0864P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.15 e Å^{-3}
$\Delta\rho_{min}$ = −0.15 e Å^{-3}
Extinction correction: *SHELXL97*
Extinction coefficient: 0.053 (2)

Table 1
Selected geometric parameters (Å, °).

N1—C2	1.3324 (17)	C3—N4	1.4561 (17)
N1—C6	1.4639 (18)	N4—C5	1.4568 (18)
C2—C3	1.5241 (19)	C5—C6	1.501 (2)
C2—N1—C6	126.34 (12)	C3—N4—C5	111.70 (10)
N1—C2—C3	118.03 (12)	N4—C5—C6	108.53 (12)
N4—C3—C2	111.27 (11)	N1—C6—C5	108.60 (12)
C6—N1—C2—C3	−7.8 (2)	C2—N1—C6—C61	−100.24 (17)
C31—C3—N4—C5	−174.87 (13)	N4—C5—C6—C61	70.19 (15)
C2—N1—C6—C5	24.42 (18)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O21^{i}	0.90 (1)	2.13 (2)	2.876 (2)	139.7 (13)

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

Friedel pairs (526) were not merged. The positions of the amide H atom and amine H atom were determined from a difference Fourier map and the coordinates were refined freely, with isotropic displacement parameters constrained to $U_{iso}(H) = 1.2U_{eq}(N)$. All remaining H atoms were treated as riding, with C—H = 0.98–1.00 Å, and $U_{iso}(H) = 1.2U_{eq}(CH, CH_2)$ and $1.5U_{eq}(CH_3)$.

Data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989); cell refinement: *CAD*-4 *Software*; data reduction: *XCAD*4 (Sheldrick, 1992); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL-NT* (Sheldrick, 2001); software used to prepare material for publication: *SHELXL*97.

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