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rac-2-Methyl-3,4,5,6-tetrahydro-2*H*-2,6-methano-1,3-benzoxazocin-4-one

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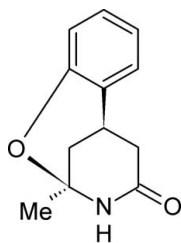
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Key indicators: single-crystal X-ray study; $T = 296$ K; mean $\sigma(\text{C}-\text{C}) = 0.002$ Å; R factor = 0.049; wR factor = 0.145; data-to-parameter ratio = 21.8.

The title compound, $\text{C}_{12}\text{H}_{13}\text{NO}_2$, represents a conformationally restricted 2-pyridone analogue of 1,4-dihydropyridine-type calcium antagonists and was selected for a crystal structure determination in order to explore some aspects of drug-receptor interaction. In the molecule, two stereogenic centres are of opposite chirality, whereas a racemate occurs in the crystal. It was found that the formally aminic N atom of the heterocycle is essentially sp^2 -hybridized with the lone-pair electrons partially delocalized through conjugation with the adjacent carbonyl bond. As a result, the central pyridone ring assumes an unsymmetrical half-chair conformation. The critical 4-phenyl ring is fixed in a pseudo-axial and perpendicular orientation [dihedral angle $85.8(1)^\circ$] with respect to the pyridone ring *via* an oxygen bridge. In the crystal a pair of centrosymmetric $\text{N}-\text{H}\cdots\text{O}$ hydrogen bonds connect molecules of opposite chirality into a dimer. The dimers are packed by hydrophobic van der Waals interactions.

Related literature

For background to 1,4-dihydropyridines (DHPs) as the most potent class of calcium-channel antagonists, see: Goldmann & Stoltefuss (1991); Kettmann *et al.* (1996). For bond-lengths in cyclic amino acids, see: Benedetti *et al.* (1983). For the preparation of the title compound, see: Světlík *et al.* (1990).



Experimental

Crystal data

$\text{C}_{12}\text{H}_{13}\text{NO}_2$
 $M_r = 203.23$
 Triclinic, $P\bar{1}$
 $a = 5.564(1)$ Å
 $b = 9.820(2)$ Å
 $c = 10.596(2)$ Å
 $\alpha = 108.73(1)^\circ$
 $\beta = 95.09(2)^\circ$
 $\gamma = 103.60(1)^\circ$
 $V = 524.37(17)$ Å³
 $Z = 2$
 Mo $K\alpha$ radiation
 $\mu = 0.09$ mm⁻¹
 $T = 296$ K
 $0.30 \times 0.25 \times 0.20$ mm

Data collection

Siemens P4 diffractometer
 3821 measured reflections
 2983 independent reflections
 2242 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.052$
 3 standard reflections every 97 reflections
 intensity decay: none

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.049$
 $wR(F^2) = 0.145$
 $S = 1.03$
 2983 reflections
 137 parameters
 H-atom parameters constrained
 $\Delta\rho_{\text{max}} = 0.26$ e Å⁻³
 $\Delta\rho_{\text{min}} = -0.17$ e Å⁻³

Table 1

Hydrogen-bond geometry (Å, °).

| $D-\text{H}\cdots A$ | $D-\text{H}$ | $\text{H}\cdots A$ | $D\cdots A$ | $D-\text{H}\cdots A$ |
|--|--------------|--------------------|-------------|----------------------|
| $\text{N1}-\text{H1}\cdots\text{O2}^i$ | 0.86 | 2.07 | 2.9274 (15) | 176 |

Symmetry code: (i) $-x + 1, -y + 1, -z + 1$.

Data collection: *XSCANS* (Siemens, 1991); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *PLATON* (Spek, 2009); software used to prepare material for publication: *SHELXL97*.

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: KP2259).

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supporting information

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rac*-2-Methyl-3,4,5,6-tetrahydro-2*H*-2,6-methano-1,3-benzoxazocin-4-one*Viktor Kettmann, Jan Světlík and Lucia Veizerová****S1. Comment**

1,4-Dihydropyridines (DHPs) are known as the most potent class of calcium-channel antagonists widely used in clinical medicine. It was reported that the essential pharmacophore, recognizable by the DHP receptor, consists of the NH moiety, (substituted) phenyl ring and two ester groups (Goldmann & Stoltefuss, 1991). Nevertheless, we have previously observed that the rigid compound (I), lacking the ester groups in positions 3 and 5, retains some level of activity (Kettmann *et al.*, 1996). This implies that (I) presents its key pharmacophoric elements, *viz.* the NH and phenyl groups, in an optimal position and orientation for favourable binding to the complementary sites of the receptor. To establish the latter, a single-crystal X-ray analysis of (I) was undertaken.

The bond lengths and angles within the molecule (Fig. 1) are normal. As expected, there is a strong conjugation between N1 and the C2=O2 carbonyl bond, as usually observed for cyclic amino acids (Benedetti *et al.*, 1983).

As mentioned above, the main aim of this work was to determine the three-dimensional disposition of the key pharmacophoric groups, *i.e.* the phenyl and NH moieties (Fig. 1). The conformation of the central heterocycle acts as a scaffold to orient substituents in space. Thus, the pyridone ring adopts an unsymmetrical half-chair conformation in which atoms C6, N1, C2 and C3 are coplanar with r.m.s. deviation of 0.012 (1) Å, and atoms C4 and C5 are displaced from this plane by -0.348 (3) and 0.470 (3) Å, respectively. The phenyl ring at C4 occupies a pseudoaxial position (Fig. 1) and is fixed approximately in a perpendicular orientation with respect to the mean plane of the pyridone ring [dihedral angle 85.8 (1)°]; the ring is rotated on the C4—C7 bond in such a manner that it almost eclipses the C4—C5 bond [dihedral angle C5—C4—C7—C8 23.0 (2)°].

The crystal packing is governed by an intermolecular hydrogen bond *N—H*⋯*O*(carbonyl) (Table 1); as a result, the molecules associate into pairs to form hydrogen-bonded dimers across the centre of symmetry at (1/2,1/2,1/2). The dimers are packed by van der Waals forces only.

S2. Experimental

As described in details earlier (Světlík *et al.*, 1990), the title compound, (I), was prepared by cyclocondensation of 4-(2-hydroxyphenyl)but-3-en-2-one with Meldrum's acid in refluxing ethanol for 4 hours (27% yield; m.p. 530-531 K). Single crystals suitable for an X-ray analysis were obtained by slow crystallization of ethanol solution.

S3. Refinement

H atoms were visible in difference maps and were subsequently treated as riding atoms with distances N—H = 0.86, C—H 0.93 (CH_{arom}), 0.97 (CH₂) or 0.98 (CH) and 0.96 Å (CH₃); U_{iso} of the H atoms were set to 1.2 (1.5 for the methyl H atoms) times U_{eq} of the parent atom.

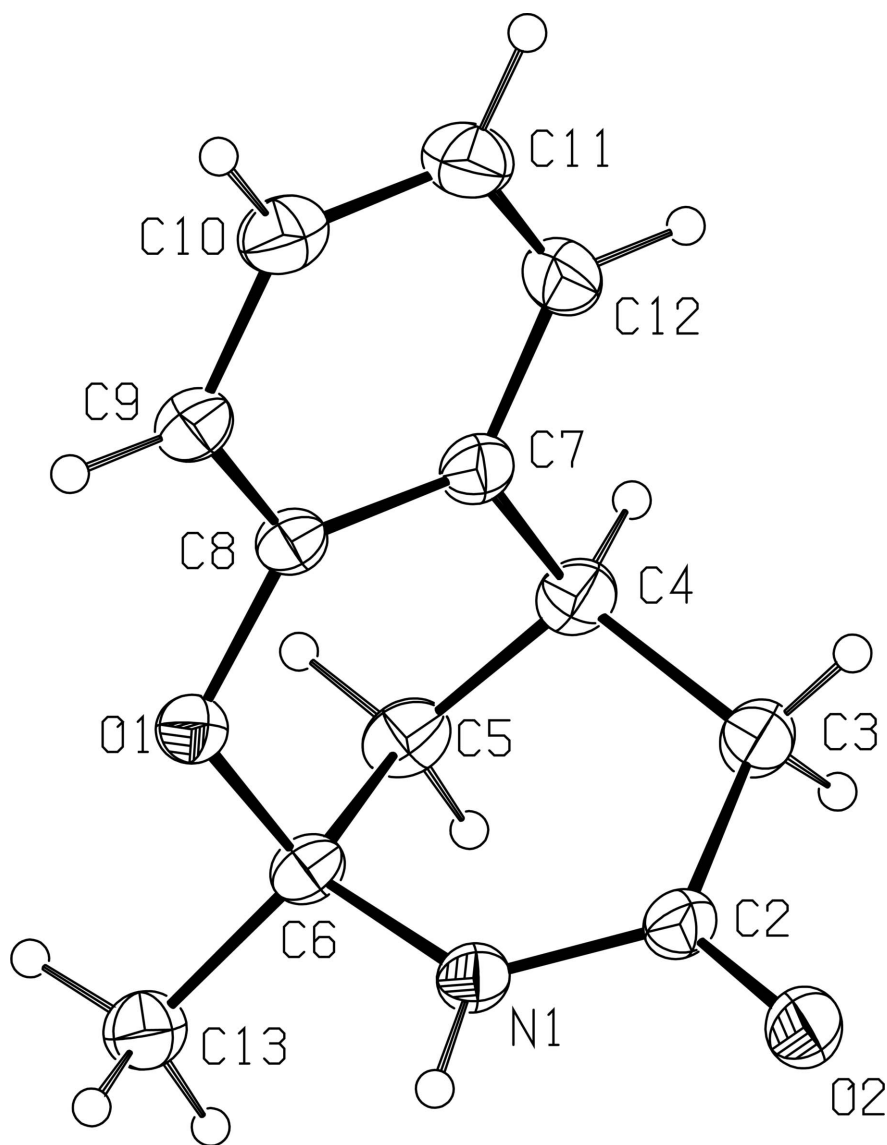


Figure 1

Displacement ellipsoid plot of (I) with the labelling scheme for the non-H atoms, which are drawn as 35% probability level.

***rac*-2-Methyl-3,4,5,6-tetrahydro-2*H*-2,6-methano-1,3-benzoxazocin-4-one**

Crystal data

$C_{12}H_{13}NO_2$

$M_r = 203.23$

Triclinic, $P\bar{1}$

Hall symbol: $-P\ 1$

$a = 5.564\ (1)\ \text{\AA}$

$b = 9.820\ (2)\ \text{\AA}$

$c = 10.596\ (2)\ \text{\AA}$

$\alpha = 108.73\ (1)^\circ$

$\beta = 95.09\ (2)^\circ$

$\gamma = 103.60\ (1)^\circ$

$V = 524.37\ (17)\ \text{\AA}^3$

$Z = 2$

$F(000) = 216$

$D_x = 1.287\ \text{Mg m}^{-3}$

Melting point: 530 K

Mo $K\alpha$ radiation, $\lambda = 0.71073\ \text{\AA}$

Cell parameters from 20 reflections

$\theta = 7\text{--}18^\circ$

$\mu = 0.09 \text{ mm}^{-1}$
 $T = 296 \text{ K}$

Prism, colourless
 $0.30 \times 0.25 \times 0.20 \text{ mm}$

Data collection

Siemens P4
 diffractometer
 Radiation source: fine-focus sealed tube
 Graphite monochromator
 $\omega/2\theta$ scans
 3821 measured reflections
 2983 independent reflections
 2242 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.052$
 $\theta_{\text{max}} = 30.0^\circ$, $\theta_{\text{min}} = 2.1^\circ$
 $h = -1 \rightarrow 7$
 $k = -12 \rightarrow 12$
 $l = -14 \rightarrow 14$
 3 standard reflections every 97 reflections
 intensity decay: none

Refinement

Refinement on F^2
 Least-squares matrix: full
 $R[F^2 > 2\sigma(F^2)] = 0.049$
 $wR(F^2) = 0.145$
 $S = 1.03$
 2983 reflections
 137 parameters
 0 restraints
 Primary atom site location: structure-invariant
 direct methods

Secondary atom site location: difference Fourier
 map
 Hydrogen site location: inferred from
 neighbouring sites
 H-atom parameters constrained
 $w = 1/[\sigma^2(F_o^2) + (0.0608P)^2 + 0.0887P]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\text{max}} = 0.001$
 $\Delta\rho_{\text{max}} = 0.26 \text{ e } \text{\AA}^{-3}$
 $\Delta\rho_{\text{min}} = -0.17 \text{ e } \text{\AA}^{-3}$

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted R -factor wR and goodness of fit S are based on F^2 , conventional R -factors R are based on F , with F set to zero for negative F^2 . The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating R -factors(gt) etc. and is not relevant to the choice of reflections for refinement. R -factors based on F^2 are statistically about twice as large as those based on F , and R -factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (\AA^2)

| | <i>x</i> | <i>y</i> | <i>z</i> | $U_{\text{iso}}^*/U_{\text{eq}}$ |
|-----|------------|--------------|--------------|----------------------------------|
| N1 | 0.7300 (2) | 0.47999 (13) | 0.63412 (11) | 0.0368 (3) |
| H1 | 0.6390 | 0.5366 | 0.6239 | 0.044* |
| C2 | 0.7192 (3) | 0.36033 (16) | 0.52401 (13) | 0.0390 (3) |
| C3 | 0.8893 (3) | 0.26336 (19) | 0.53502 (14) | 0.0464 (3) |
| H3A | 1.0279 | 0.2843 | 0.4883 | 0.056* |
| H3B | 0.7957 | 0.1590 | 0.4900 | 0.056* |
| C4 | 0.9955 (3) | 0.28856 (17) | 0.68250 (14) | 0.0431 (3) |
| H4 | 1.1317 | 0.2410 | 0.6836 | 0.052* |
| C5 | 1.0990 (2) | 0.45662 (18) | 0.75980 (15) | 0.0432 (3) |
| H5A | 1.1854 | 0.4750 | 0.8498 | 0.052* |
| H5B | 1.2176 | 0.5015 | 0.7127 | 0.052* |
| C6 | 0.8791 (2) | 0.52435 (15) | 0.76906 (12) | 0.0353 (3) |
| C7 | 0.7943 (3) | 0.22442 (16) | 0.75190 (13) | 0.0391 (3) |
| C8 | 0.6692 (2) | 0.31756 (14) | 0.83327 (12) | 0.0345 (3) |

| | | | | |
|------|--------------|--------------|--------------|------------|
| C9 | 0.4875 (3) | 0.26224 (16) | 0.90078 (14) | 0.0405 (3) |
| H9 | 0.4077 | 0.3257 | 0.9555 | 0.049* |
| C10 | 0.4269 (3) | 0.11180 (18) | 0.88560 (16) | 0.0506 (4) |
| H10 | 0.3057 | 0.0745 | 0.9303 | 0.061* |
| C11 | 0.5454 (4) | 0.01657 (18) | 0.80448 (17) | 0.0570 (4) |
| H11 | 0.5035 | -0.0843 | 0.7942 | 0.068* |
| C12 | 0.7267 (3) | 0.07306 (18) | 0.73887 (16) | 0.0516 (4) |
| H12 | 0.8059 | 0.0088 | 0.6847 | 0.062* |
| C13 | 0.9524 (3) | 0.69372 (17) | 0.83480 (15) | 0.0470 (3) |
| H13A | 1.0388 | 0.7229 | 0.9260 | 0.071* |
| H13B | 0.8040 | 0.7276 | 0.8358 | 0.071* |
| H13C | 1.0608 | 0.7377 | 0.7842 | 0.071* |
| O1 | 0.72022 (17) | 0.46921 (10) | 0.85435 (9) | 0.0372 (2) |
| O2 | 0.5800 (2) | 0.33318 (13) | 0.41568 (10) | 0.0537 (3) |

Atomic displacement parameters (Å²)

| | U^{11} | U^{22} | U^{33} | U^{12} | U^{13} | U^{23} |
|-----|-------------|------------|------------|------------|-------------|------------|
| N1 | 0.0382 (6) | 0.0428 (6) | 0.0337 (5) | 0.0192 (5) | 0.0020 (4) | 0.0147 (4) |
| C2 | 0.0442 (7) | 0.0449 (7) | 0.0338 (6) | 0.0194 (6) | 0.0061 (5) | 0.0170 (5) |
| C3 | 0.0549 (8) | 0.0582 (9) | 0.0383 (7) | 0.0329 (7) | 0.0129 (6) | 0.0197 (6) |
| C4 | 0.0413 (7) | 0.0589 (9) | 0.0421 (7) | 0.0304 (6) | 0.0100 (5) | 0.0228 (6) |
| C5 | 0.0308 (6) | 0.0599 (9) | 0.0457 (7) | 0.0161 (6) | 0.0043 (5) | 0.0257 (6) |
| C6 | 0.0323 (6) | 0.0418 (7) | 0.0331 (6) | 0.0104 (5) | 0.0020 (5) | 0.0160 (5) |
| C7 | 0.0433 (7) | 0.0459 (7) | 0.0332 (6) | 0.0208 (6) | 0.0016 (5) | 0.0158 (5) |
| C8 | 0.0362 (6) | 0.0375 (6) | 0.0311 (6) | 0.0132 (5) | -0.0004 (5) | 0.0135 (5) |
| C9 | 0.0405 (7) | 0.0459 (7) | 0.0373 (6) | 0.0129 (6) | 0.0038 (5) | 0.0178 (5) |
| C10 | 0.0515 (8) | 0.0509 (9) | 0.0499 (8) | 0.0075 (7) | 0.0049 (6) | 0.0245 (7) |
| C11 | 0.0732 (11) | 0.0395 (8) | 0.0568 (9) | 0.0123 (7) | 0.0033 (8) | 0.0199 (7) |
| C12 | 0.0673 (10) | 0.0449 (8) | 0.0459 (8) | 0.0275 (7) | 0.0051 (7) | 0.0135 (6) |
| C13 | 0.0503 (8) | 0.0423 (7) | 0.0434 (7) | 0.0061 (6) | 0.0000 (6) | 0.0154 (6) |
| O1 | 0.0421 (5) | 0.0377 (5) | 0.0367 (5) | 0.0154 (4) | 0.0102 (4) | 0.0156 (4) |
| O2 | 0.0705 (7) | 0.0545 (6) | 0.0361 (5) | 0.0309 (5) | -0.0060 (5) | 0.0104 (4) |

Geometric parameters (Å, °)

| | | | |
|--------|-------------|---------|-------------|
| N1—C2 | 1.3489 (17) | C6—C13 | 1.518 (2) |
| N1—C6 | 1.4634 (16) | C7—C12 | 1.402 (2) |
| N1—H1 | 0.8600 | C7—C8 | 1.4011 (18) |
| C2—O2 | 1.2399 (16) | C8—O1 | 1.3873 (16) |
| C2—C3 | 1.5137 (19) | C8—C9 | 1.3959 (19) |
| C3—C4 | 1.5399 (19) | C9—C10 | 1.388 (2) |
| C3—H3A | 0.9700 | C9—H9 | 0.9300 |
| C3—H3B | 0.9700 | C10—C11 | 1.386 (2) |
| C4—C7 | 1.518 (2) | C10—H10 | 0.9300 |
| C4—C5 | 1.526 (2) | C11—C12 | 1.385 (3) |
| C4—H4 | 0.9800 | C11—H11 | 0.9300 |
| C5—C6 | 1.5203 (18) | C12—H12 | 0.9300 |

| | | | |
|--------------|--------------|----------------|--------------|
| C5—H5A | 0.9700 | C13—H13A | 0.9600 |
| C5—H5B | 0.9700 | C13—H13B | 0.9600 |
| C6—O1 | 1.4568 (16) | C13—H13C | 0.9600 |
| C2—N1—C6 | 127.38 (11) | N1—C6—C5 | 109.98 (11) |
| C2—N1—H1 | 116.3 | C13—C6—C5 | 114.61 (12) |
| C6—N1—H1 | 116.3 | C12—C7—C8 | 117.50 (14) |
| O2—C2—N1 | 121.03 (12) | C12—C7—C4 | 122.47 (13) |
| O2—C2—C3 | 120.90 (12) | C8—C7—C4 | 120.03 (12) |
| N1—C2—C3 | 118.03 (12) | O1—C8—C9 | 115.93 (11) |
| C2—C3—C4 | 113.10 (11) | O1—C8—C7 | 122.84 (12) |
| C2—C3—H3A | 109.0 | C9—C8—C7 | 121.22 (13) |
| C4—C3—H3A | 109.0 | C10—C9—C8 | 119.44 (14) |
| C2—C3—H3B | 109.0 | C10—C9—H9 | 120.3 |
| C4—C3—H3B | 109.0 | C8—C9—H9 | 120.3 |
| H3A—C3—H3B | 107.8 | C11—C10—C9 | 120.64 (15) |
| C7—C4—C5 | 108.71 (11) | C11—C10—H10 | 119.7 |
| C7—C4—C3 | 111.56 (12) | C9—C10—H10 | 119.7 |
| C5—C4—C3 | 108.61 (12) | C12—C11—C10 | 119.36 (15) |
| C7—C4—H4 | 109.3 | C12—C11—H11 | 120.3 |
| C5—C4—H4 | 109.3 | C10—C11—H11 | 120.3 |
| C3—C4—H4 | 109.3 | C11—C12—C7 | 121.84 (15) |
| C6—C5—C4 | 107.95 (11) | C11—C12—H12 | 119.1 |
| C6—C5—H5A | 110.1 | C7—C12—H12 | 119.1 |
| C4—C5—H5A | 110.1 | C6—C13—H13A | 109.5 |
| C6—C5—H5B | 110.1 | C6—C13—H13B | 109.5 |
| C4—C5—H5B | 110.1 | H13A—C13—H13B | 109.5 |
| H5A—C5—H5B | 108.4 | C6—C13—H13C | 109.5 |
| O1—C6—N1 | 108.80 (10) | H13A—C13—H13C | 109.5 |
| O1—C6—C13 | 105.03 (11) | H13B—C13—H13C | 109.5 |
| N1—C6—C13 | 109.14 (11) | C8—O1—C6 | 116.70 (10) |
| O1—C6—C5 | 109.04 (10) | | |
| C6—N1—C2—O2 | 178.31 (13) | C3—C4—C7—C8 | -96.72 (15) |
| C6—N1—C2—C3 | -3.9 (2) | C12—C7—C8—O1 | 179.75 (11) |
| O2—C2—C3—C4 | -165.37 (14) | C4—C7—C8—O1 | 0.11 (18) |
| N1—C2—C3—C4 | 16.9 (2) | C12—C7—C8—C9 | 1.13 (19) |
| C2—C3—C4—C7 | 71.70 (16) | C4—C7—C8—C9 | -178.51 (11) |
| C2—C3—C4—C5 | -48.10 (17) | O1—C8—C9—C10 | -179.60 (11) |
| C7—C4—C5—C6 | -54.82 (14) | C7—C8—C9—C10 | -0.89 (19) |
| C3—C4—C5—C6 | 66.74 (14) | C8—C9—C10—C11 | 0.1 (2) |
| C2—N1—C6—O1 | -97.04 (15) | C9—C10—C11—C12 | 0.4 (2) |
| C2—N1—C6—C13 | 148.87 (14) | C10—C11—C12—C7 | -0.1 (2) |
| C2—N1—C6—C5 | 22.34 (18) | C8—C7—C12—C11 | -0.6 (2) |
| C4—C5—C6—O1 | 66.77 (13) | C4—C7—C12—C11 | 178.99 (13) |
| C4—C5—C6—N1 | -52.46 (14) | C9—C8—O1—C6 | -170.69 (10) |
| C4—C5—C6—C13 | -175.85 (11) | C7—C8—O1—C6 | 10.63 (16) |
| C5—C4—C7—C12 | -156.59 (12) | N1—C6—O1—C8 | 76.17 (13) |

| | | | |
|--------------|------------|--------------|--------------|
| C3—C4—C7—C12 | 83.67 (16) | C13—C6—O1—C8 | -167.08 (10) |
| C5—C4—C7—C8 | 23.03 (16) | C5—C6—O1—C8 | -43.79 (14) |

Hydrogen-bond geometry (Å, °)

| <i>D</i> —H··· <i>A</i> | <i>D</i> —H | H··· <i>A</i> | <i>D</i> ··· <i>A</i> | <i>D</i> —H··· <i>A</i> |
|-------------------------|-------------|---------------|-----------------------|-------------------------|
| N1—H1···O2 ⁱ | 0.86 | 2.07 | 2.9274 (15) | 176 |

Symmetry code: (i) $-x+1, -y+1, -z+1$.