rac-N-(4-Ethoxyphenyl)-3-hydroxybutanamide

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In the title compound, racemic bucetin [systematic name: N-(4-ethoxyphenyl)-3-hydroxybutanamide], $C_{12}H_{17}NO_3$, the molecule is in an extended conformation as illustrated by the C—O—C—C torsion angle [170.14 (15)°] in the ethoxy group and the subsequent C—N—C—C [−177.24 (16)°], N—C—C—C [170.08 (15)°] and C—C—C—C [171.41 (15)°] torsion angles in the butanamide chain. In the crystal, the O—H group donates an intermolecular O—H⋯O hydrogen bond to the amide carbonyl oxygen atom and also accepts an intermolecular N—H⋯O hydrogen bond from an adjacent N—H group. The former forms 12-membered dimeric rings about inversion centers, and the latter form chains in the [001] direction. The overall hydrogen-bonded network is two-dimensional, with no propagation in the [100] direction.

3D view
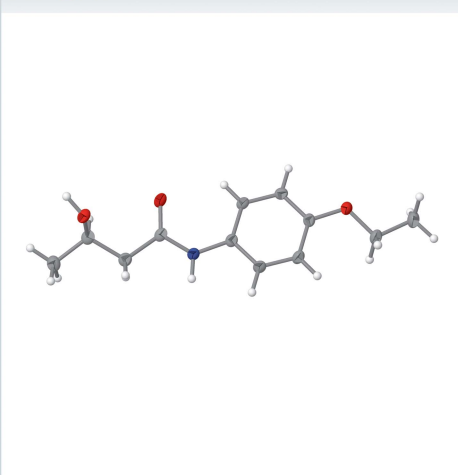
Chemical scheme
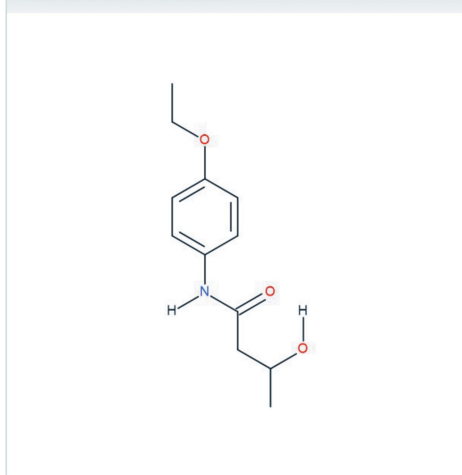
Structure description

N-(4-Ethoxyphenyl)-3-hydrobutanamide, popularly known as bucetin, is an analgesic and antipyric that is similar in structure to phenacetin [N-(4-ethoxyphenyl)acetamide]. Once thought to be a better substitute for phenacetin (Ehrhart et al., 1965; Ehrhart & Ott, 1958), bucetin was introduced into the markets in Germany but was soon withdrawn from use because of renal toxicity and risk of carcinogenesis (Fung et al., 2001; Togei et al., 1987). The renal toxicity of bucetin, renal papillary necrosis, is similar in nature to that induced by phenacetin but is somewhat less pronounced, presumably due to differences in the rates of deacylation by microsomal enzymes leading to the formation of 4-ethoxyaniline (Nohmi et al., 1984). Thus, the renal papillary necrosis by phenacetin and bucetin appears to be a manifestation of the formation of 4-ethoxyaniline and the subsequent inhibitory action(s) of this putative metabolite (or its hydroxylated and/or autooxidation products, N-(4-ethoxyphenyl)hydroxylamine and 1-ethoxy-4-nitroso-

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Table 1
Hydrogen-bond geometry (Å, °).

$D—H\cdots A$	$D—H$	$H\cdots A$	$D\cdots A$	$D—H\cdots A$
$O3—H3O\cdots O2^{i}$	0.89 (2)	1.85 (2)	2.7268 (17)	167 (2)
$N1—H1N\cdots O3^{ii}$	0.88 (2)	1.99 (2)	2.8611 (19)	169.7 (19)
$C2—H2\cdots O2$	0.95	2.32	2.908 (2)	119
$C3—H3A\cdots O1^{iii}$	0.95	2.60	3.482 (2)	154
$C6—H6\cdots O2^{ii}$	0.95	2.65	3.468 (2)	145
$C6—H6\cdots O3^{ii}$	0.95	2.48	3.269 (2)	141
$C8—H8B\cdots O2^{iv}$	0.99	2.58	3.553 (2)	167

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

benzene) on PGE2 synthesis and a possible reduction of COX-2 expression (Camus *et al.*, 1982; Goodin *et al.*, 2002; Kankuri *et al.*, 2003; Wirth *et al.*, 1982).

Previous studies from our laboratory and elsewhere have shown that celluar oxidants, such as peroxynitrite/peroxynitrous acid and hypochlorite/hypochlorous acid, can constitute an important pathway for non-enzymatic biotransformation of *N*-(4-hydroxyphenyl)acetamide (Bedner & MacCrehan, 2006; Uppu & Martin, 2004; Whiteman *et al.*, 1996), apocynin (Gernapudi *et al.*, 2009), clozapine (Frimat *et al.*, 1997; Uppu *et al.*, 2005), and certain other xenobiotics (Babu *et al.*, 2012; Ju & Uetrecht, 1998; Rattay & Benndorf, 2021). We believe that the above referenced oxidants may also be involved in the biotransformation of bucetin, leading to the formation of hydroxylated, chlorinated, and nitrated products and thus contribute to the toxicity. To address this and to better understand the mechanisms of toxicity of bucetin and phenacetin and its congeners, we determined the crystal structure of racemic bucetin.

The molecular structure of the title compound, racemic bucetin, is shown in Fig. 1. The molecule is in an extended conformation as illustrated by torsion angle C4—O1—C11—C12 [170.14 (15)°] in the ethoxy group and torsion angles C1—N1—C7—C8 [−177.24 (16)°], N1—C7—C8—C9 [170.08 (15)°] and C7—C8—C9—C10 [171.41 (15)°] in the butanamide chain. In the arbitrarily chosen asymmetric molecule, atom C9 has an *R* configuration, but crystal symmetry generates a racemic mixture.

As shown in Fig. 2, the OH group donates an intermolecular hydrogen bond to the amide carbonyl oxygen atom and accepts an intermolecular hydrogen bond from an adjacent
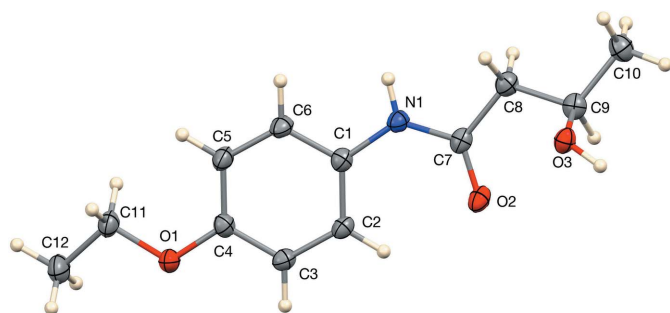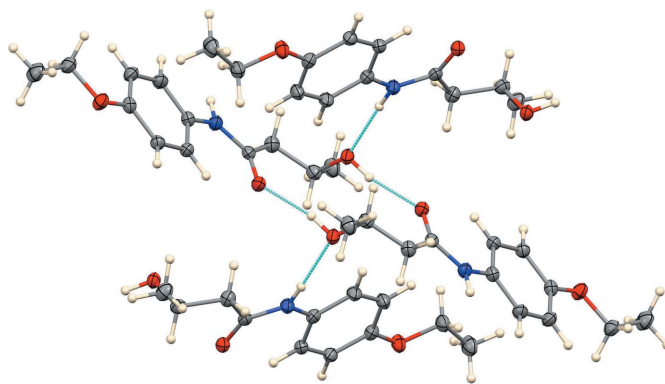

Figure 2
The hydrogen bonding in the packing of *N*-(4-ethoxyphenyl)-3-hydroxybutanamide.

N—H group. The donor–acceptor separations for these hydrogen bonds are 2.7268 (17) Å for O—H$\cdots$O($-x + 1$, $-y + 1$, $-z + 2$) and 2.8611 (19) Å for N—H$\cdots$O(x, $-y + \frac{1}{2}$, $z - \frac{1}{2}$). The former thus forms 12-membered dimeric rings about inversion centers, and the latter form chains in the [001] direction. The overall hydrogen-bonded network is two-dimensional, with no propagation in the [100] direction. The packing in the unit cell is shown in Fig. 3 and includes also C—H$\cdots$O interactions (Table 1).

Given the current understanding that de-acylation constitutes an important step in the expression of renal toxicity (Kankuri *et al.*, 2003; Nohmi *et al.*, 1984; Taxak *et al.*, 2013), and the fact that the acyl group in bucetin (3-hydroxybutyryl) is much larger in size compared to the acetyl group in phenacetin and its congeners and has a chiral center, the information on the crystal structure of bucetin presented here may help in the development of analgesics with little or no renal toxicity.
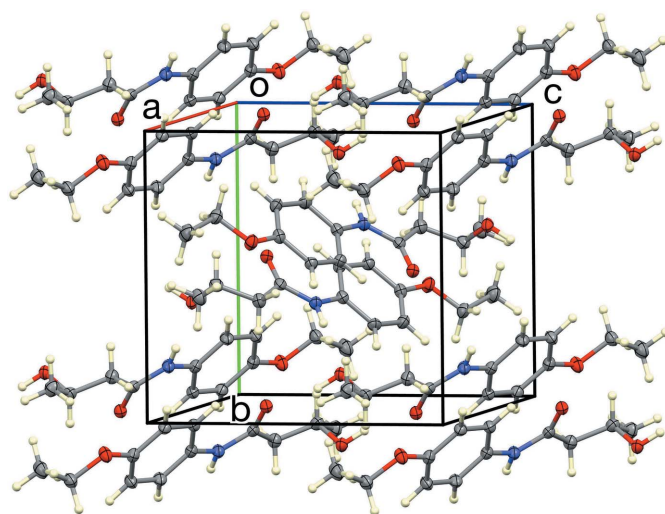

Figure 1
Molecular structure of *N*-(4-ethoxyphenyl)-3-hydroxybutanamide with displacement ellipsoids drawn at the 50% probability level.

Figure 3
Crystal packing of the title compound *N*-(4-ethoxyphenyl)-3-hydroxybutanamide.

Table 2
Experimental details.

Crystal data	
Chemical formula	$C_{12}H_{17}NO_3$
M_r	223.26
Crystal system, space group	Monoclinic, $P2_1/c$
Temperature (K)	100
a, b, c (Å)	12.2343 (4), 9.6404 (3), 9.9098 (3)
β (°)	93.295 (2)
V (Å^3)	1166.86 (6)
Z	4
Radiation type	Cu $K\alpha$
μ (mm^{-1})	0.75
Crystal size (mm)	$0.14 \times 0.14 \times 0.01$
Data collection	
Diffractometer	Bruker Kappa APEXII CCD DUO
Absorption correction	Multi-scan (*SADABS*; Krause *et al.*, 2015)
T_{min}, T_{max}	0.832, 0.993
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	14229, 2139, 1739
R_{int}	0.061
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.603
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.045, 0.116, 1.06
No. of reflections	2139
No. of parameters	153
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.40, −0.23

Computer programs: *APEX2* and *SAINT* (Bruker, 2016), *SHELXT2014/5* (Sheldrick, 2015a), *SHELXL2017/1* (Sheldrick, 2015b), *Mercury* (Macrae *et al.*, 2020), and *publCIF* (Westrip, 2010).

Synthesis and crystallization

The title compound, $C_{12}H_{17}NO_3$ (bucetin; CAS No. 1083–57-4) was obtained from Sigma-Aldrich, St. Louis, MO and was used without further purification. Single crystals of racemic bucetin were prepared by slow cooling of a nearly saturated solution of bucetin in boiling deionized water.

Refinement

Crystal data, data collection and structure refinement details are summarized in Table 2.

Funding information

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full crystallographic data

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N-(4-Ethoxyphenyl)-3-hydroxybutanamide

Crystal data

$C_{12}H_{17}NO_3$	$F(000) = 480$
$M_r = 223.26$	$D_x = 1.271$ Mg m^{-3}
Monoclinic, $P2_1/c$	Cu $K\alpha$ radiation, $\lambda = 1.54184$ Å
$a = 12.2343$ (4) Å	Cell parameters from 3666 reflections
$b = 9.6404$ (3) Å	$\theta = 3.6$–68.5°
$c = 9.9098$ (3) Å	$\mu = 0.75$ mm^{-1}
$\beta = 93.295$ (2)°	$T = 100$ K
$V = 1166.86$ (6) Å^3	Plate, colourless
$Z = 4$	$0.14 \times 0.14 \times 0.01$ mm

Data collection

Bruker Kappa APEXII CCD DUO diffractometer	14229 measured reflections
Radiation source: IμS microfocus	2139 independent reflections
QUAZAR multilayer optics monochromator	1739 reflections with $I > 2\sigma(I)$
φ and ω scans	$R_{int} = 0.061$
Absorption correction: multi-scan (SADABS; Krause *et al.*, 2015)	$\theta_{max} = 68.5°$, $\theta_{min} = 3.6°$
	$h = -14 \rightarrow 14$
	$k = -11 \rightarrow 11$
$T_{min} = 0.832$, $T_{max} = 0.993$	$l = -11 \rightarrow 11$

Refinement

Refinement on F^2	Hydrogen site location: mixed
Least-squares matrix: full	H atoms treated by a mixture of independent and constrained refinement
$R[F^2 > 2\sigma(F^2)] = 0.045$	
$wR(F^2) = 0.116$	$w = 1/[\sigma^2(F_o^2) + (0.0542P)^2 + 0.4983P]$
$S = 1.06$	where $P = (F_o^2 + 2F_c^2)/3$
2139 reflections	$(\Delta/\sigma)_{max} < 0.001$
153 parameters	$\Delta\rho_{max} = 0.40$ e Å^{-3}
0 restraints	$\Delta\rho_{min} = -0.23$ e Å^{-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. All H atoms were located in difference maps and those on C were thereafter treated as riding in geometrically idealized positions with C—H distances 0.95 Å for phenyl, 0.98 Å for methyl, 0.99 Å for CH$_2$, and 1.00 Å for methine. Coordinates of the N—H and O—H hydrogen atoms were refined. U_{iso}(H) values were assigned as 1.2U_{eq} for the attached atom (1.5 for methyl and OH).

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	0.93903 (10)	0.38529 (13)	0.33811 (12)	0.0251 (3)
O2	0.56520 (10)	0.51646 (12)	0.76720 (12)	0.0250 (3)
O3	0.43094 (10)	0.37235 (13)	0.97956 (12)	0.0225 (3)
H3O	0.4299 (17)	0.421 (2)	1.056 (2)	0.034*
N1	0.54676 (12)	0.35963 (15)	0.59755 (15)	0.0214 (3)
H1N	0.5043 (17)	0.295 (2)	0.559 (2)	0.026*
C1	0.64870 (14)	0.36976 (17)	0.53789 (17)	0.0203 (4)
C2	0.73038 (14)	0.46664 (17)	0.57328 (17)	0.0204 (4)
H2	0.720136	0.531692	0.643445	0.024*
C3	0.82674 (14)	0.46737 (17)	0.50532 (17)	0.0214 (4)
H3A	0.882226	0.533130	0.529774	0.026*
C4	0.84298 (14)	0.37343 (18)	0.40232 (17)	0.0211 (4)
C5	0.76284 (15)	0.27562 (18)	0.36878 (18)	0.0247 (4)
H5	0.773553	0.209619	0.299592	0.030*
C6	0.66716 (15)	0.27482 (18)	0.43681 (18)	0.0236 (4)
H6	0.612697	0.207359	0.413541	0.028*
C7	0.51039 (14)	0.42701 (17)	0.70506 (17)	0.0204 (4)
C8	0.39683 (15)	0.38164 (18)	0.74180 (18)	0.0238 (4)
H8A	0.342927	0.412240	0.669554	0.029*
H8B	0.394699	0.279044	0.744956	0.029*
C9	0.36269 (15)	0.43784 (18)	0.87556 (18)	0.0237 (4)
H9	0.375158	0.540341	0.878649	0.028*
C10	0.24341 (15)	0.4077 (2)	0.8973 (2)	0.0291 (4)
H10A	0.231907	0.307161	0.899454	0.044*
H10B	0.197425	0.448185	0.823174	0.044*
H10C	0.223748	0.448333	0.983239	0.044*
C11	0.95150 (15)	0.29641 (19)	0.22356 (19)	0.0267 (4)
H11A	0.886016	0.302629	0.160352	0.032*
H11B	0.960301	0.198852	0.253434	0.032*
C12	1.05153 (16)	0.3435 (2)	0.1548 (2)	0.0336 (5)
H12A	1.042081	0.440295	0.126142	0.050*
H12B	1.061736	0.285085	0.075633	0.050*
H12C	1.115910	0.335942	0.217943	0.050*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0241 (7)	0.0297 (7)	0.0221 (7)	−0.0038 (5)	0.0063 (5)	−0.0055 (5)
O2	0.0345 (7)	0.0209 (7)	0.0204 (6)	−0.0026 (5)	0.0082 (5)	−0.0018 (5)
O3	0.0279 (7)	0.0242 (7)	0.0153 (6)	0.0032 (5)	0.0013 (5)	0.0005 (5)
N1	0.0241 (8)	0.0217 (8)	0.0186 (8)	−0.0041 (6)	0.0036 (6)	−0.0017 (6)
C1	0.0244 (9)	0.0196 (9)	0.0171 (9)	−0.0003 (6)	0.0026 (7)	0.0022 (6)
C2	0.0266 (9)	0.0177 (8)	0.0168 (8)	−0.0010 (7)	0.0020 (7)	−0.0006 (6)
C3	0.0250 (9)	0.0204 (9)	0.0188 (9)	−0.0035 (7)	0.0004 (7)	0.0002 (6)
C4	0.0217 (9)	0.0241 (9)	0.0177 (9)	0.0000 (7)	0.0029 (7)	0.0025 (7)

C5	0.0302 (10)	0.0227 (9)	0.0219 (9)	−0.0027 (7)	0.0070 (7)	−0.0054 (7)
C6	0.0282 (9)	0.0209 (9)	0.0222 (9)	−0.0070 (7)	0.0050 (7)	−0.0032 (7)
C7	0.0280 (9)	0.0167 (8)	0.0168 (8)	0.0024 (7)	0.0024 (7)	0.0025 (7)
C8	0.0261 (10)	0.0247 (9)	0.0208 (9)	−0.0002 (7)	0.0016 (7)	0.0012 (7)
C9	0.0272 (10)	0.0220 (9)	0.0220 (9)	0.0025 (7)	0.0024 (7)	0.0029 (7)
C10	0.0267 (10)	0.0327 (10)	0.0283 (10)	0.0003 (8)	0.0053 (8)	0.0033 (8)
C11	0.0304 (10)	0.0260 (10)	0.0245 (10)	0.0005 (7)	0.0082 (8)	−0.0048 (7)
C12	0.0330 (11)	0.0381 (11)	0.0312 (11)	−0.0024 (8)	0.0135 (9)	−0.0070 (8)

Geometric parameters (Å, º)

O1—C4	1.373 (2)	C6—H6	0.9500
O1—C11	1.437 (2)	C7—C8	1.521 (2)
O2—C7	1.235 (2)	C8—C9	1.513 (2)
O3—C9	1.435 (2)	C8—H8A	0.9900
O3—H3O	0.89 (2)	C8—H8B	0.9900
N1—C7	1.345 (2)	C9—C10	1.515 (3)
N1—C1	1.414 (2)	C9—H9	1.0000
N1—H1N	0.88 (2)	C10—H10A	0.9800
C1—C6	1.385 (2)	C10—H10B	0.9800
C1—C2	1.398 (2)	C10—H10C	0.9800
C2—C3	1.391 (2)	C11—C12	1.505 (3)
C2—H2	0.9500	C11—H11A	0.9900
C3—C4	1.387 (2)	C11—H11B	0.9900
C3—H3A	0.9500	C12—H12A	0.9800
C4—C5	1.387 (3)	C12—H12B	0.9800
C5—C6	1.384 (2)	C12—H12C	0.9800
C5—H5	0.9500		
C4—O1—C11	116.67 (13)	C7—C8—H8A	108.7
C9—O3—H3O	110.2 (14)	C9—C8—H8B	108.7
C7—N1—C1	129.62 (15)	C7—C8—H8B	108.7
C7—N1—H1N	118.0 (14)	H8A—C8—H8B	107.6
C1—N1—H1N	112.2 (14)	O3—C9—C8	107.05 (14)
C6—C1—C2	118.62 (16)	O3—C9—C10	109.82 (15)
C6—C1—N1	116.18 (15)	C8—C9—C10	111.86 (15)
C2—C1—N1	125.20 (16)	O3—C9—H9	109.4
C3—C2—C1	119.71 (16)	C8—C9—H9	109.4
C3—C2—H2	120.1	C10—C9—H9	109.4
C1—C2—H2	120.1	C9—C10—H10A	109.5
C4—C3—C2	120.94 (16)	C9—C10—H10B	109.5
C4—C3—H3A	119.5	H10A—C10—H10B	109.5
C2—C3—H3A	119.5	C9—C10—H10C	109.5
O1—C4—C5	123.90 (16)	H10A—C10—H10C	109.5
O1—C4—C3	116.69 (15)	H10B—C10—H10C	109.5
C5—C4—C3	119.40 (16)	O1—C11—C12	107.67 (15)
C6—C5—C4	119.55 (16)	O1—C11—H11A	110.2
C6—C5—H5	120.2	C12—C11—H11A	110.2

C4—C5—H5	120.2	O1—C11—H11B	110.2
C5—C6—C1	121.75 (16)	C12—C11—H11B	110.2
C5—C6—H6	119.1	H11A—C11—H11B	108.5
C1—C6—H6	119.1	C11—C12—H12A	109.5
O2—C7—N1	122.49 (16)	C11—C12—H12B	109.5
O2—C7—C8	123.98 (15)	H12A—C12—H12B	109.5
N1—C7—C8	113.52 (15)	C11—C12—H12C	109.5
C9—C8—C7	114.13 (15)	H12A—C12—H12C	109.5
C9—C8—H8A	108.7	H12B—C12—H12C	109.5
C7—N1—C1—C6	172.74 (17)	C4—C5—C6—C1	0.2 (3)
C7—N1—C1—C2	−7.1 (3)	C2—C1—C6—C5	−1.4 (3)
C6—C1—C2—C3	1.1 (2)	N1—C1—C6—C5	178.76 (16)
N1—C1—C2—C3	−178.98 (16)	C1—N1—C7—O2	2.5 (3)
C1—C2—C3—C4	0.2 (3)	C1—N1—C7—C8	−177.24 (16)
C11—O1—C4—C5	4.6 (2)	O2—C7—C8—C9	−9.6 (2)
C11—O1—C4—C3	−174.53 (15)	N1—C7—C8—C9	170.08 (15)
C2—C3—C4—O1	177.82 (15)	C7—C8—C9—O3	−68.25 (18)
C2—C3—C4—C5	−1.4 (3)	C7—C8—C9—C10	171.41 (15)
O1—C4—C5—C6	−177.96 (16)	C4—O1—C11—C12	170.14 (15)
C3—C4—C5—C6	1.2 (3)		

Hydrogen-bond geometry (Å, °)

D—H⋯A	D—H	H⋯A	D⋯A	D—H⋯A
O3—H3O⋯O2^i	0.89 (2)	1.85 (2)	2.7268 (17)	167 (2)
N1—H1N⋯O3^{ii}	0.88 (2)	1.99 (2)	2.8611 (19)	169.7 (19)
C2—H2⋯O2	0.95	2.32	2.908 (2)	119
C3—H3A⋯O1^{iii}	0.95	2.60	3.482 (2)	154
C6—H6⋯O2^{ii}	0.95	2.65	3.468 (2)	145
C6—H6⋯O3^{ii}	0.95	2.48	3.269 (2)	141
C8—H8B⋯O2^{iv}	0.99	2.58	3.553 (2)	167

Symmetry codes: (i) $-x+1, -y+1, -z+2$; (ii) $x, -y+1/2, z-1/2$; (iii) $-x+2, -y+1, -z+1$; (iv) $-x+1, y-1/2, -z+3/2$.