

Polar crystal of vanillylformamide through replacement of the alkene by an isosteric formamide group

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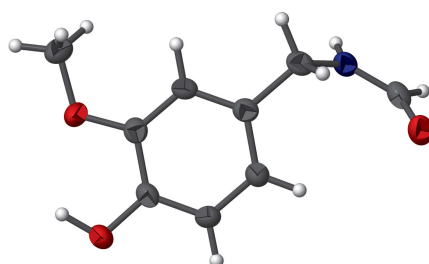
Keywords: polar crystal structure; vanillylamine; eugenol; capsaicin analogs; isosteres.

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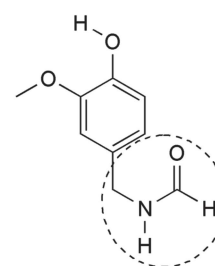
Structural data: full structural data are available from iucrdata.iucr.org

Vanillylformamide [systematic name: *N*-(4-hydroxy-3-methoxybenzyl)formamide], C₉H₁₁NO₃, (**II**), has been synthesized from vanillylamine hydrochloride and studied by single-crystal X-ray diffraction. Compound (**II**) and the well known biologically active eugenol compound (**I**) can be considered to be 'isosteres' of each other, since they share comparable molecular shape and volume. The product (**II**) crystallizes in the space group *P1*. In the crystal, the vanillylformamide molecules are linked mainly by N–H···O, O–H···O and Csp²–H···O hydrogen bonds, forming infinite two-dimensional polar sheets. These two-dimensional layers pack in a parallel fashion, constructing a polar three-dimensional network. Except for van der Waals forces and weak Csp³–H···O hydrogen bonds, there are no significant intermolecular interactions between the layers. A Cambridge Structural Database search revealed that vanillylamide-related crystals are scarce.

3D view



Chemical scheme



Structure description

Eugenol is a natural molecule that exhibits versatile properties useful in various domains. Indeed, there is increasing interest from the scientific and industrial community in eugenol-based polymers (Miao *et al.* 2017; Guzmán *et al.*, 2017; Chen *et al.*, 2017; Modjinou *et al.*, 2016; Wan *et al.*, 2016a,b; Deng *et al.*, 2015). Moreover, this bioactive compound has high potential as a therapeutic agent since it has antiparasitic, antiviral, antibacterial, antifungal, anticancer, antioxidant and anti-inflammatory activities (Raja *et al.*, 2015; Khalil *et al.*, 2017). On the other hand, to the best of our knowledge, no study on the bioisosteres of eugenol has been undertaken. The definition of bioisosterism has been

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

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
$N1-H1\cdots O2^i$	0.88	2.05	2.910 (4)	167
$O3-H3\cdots O1$	0.96 (3)	2.15 (7)	2.672 (4)	113 (5)
$C6-H6\cdots O3^{ii}$	0.95	2.54	3.391 (5)	149
$O3-H3\cdots O2^{iii}$	0.96 (3)	1.90 (4)	2.771 (4)	149 (6)
$C5-H5B\cdots O3^{iv}$	0.99	2.60	3.374 (5)	135
$C5-H5A\cdots O3^v$	0.99	2.70	3.676 (5)	167

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

broadened by Burger (1991) as ‘Compounds or groups that possess near-equal molecular shapes and volumes, approximately the same distribution of electrons, and which exhibit similar physical properties’. Thus, chemical modification of lead compounds represents a rational approach in drug design (Patani *et al.*, 1996). Alkenes and amides are isosteric since they are both planar and possess two sp^2 -hybridized atoms in the main chain (Choudhary *et al.*, 2011). In this context, effort has been focused in our group to determine the crystal structure of the vanillylformamide (**II**), which mimics eugenol (**I**) (Fig. 1) and could have some biological interest. We were also pleased that the title compound crystallized in a polar space group, since several functional properties of advanced materials (piezoelectricity, pyroelectricity, ferroelectricity, second harmonic generation, and electro-optic response) are only allowed or significantly enhanced in polar crystal structures (Centore *et al.*, 2012, 2016; Takahashi *et al.*, 2016).

The molecular structure of the title compound (**II**) is shown in Fig. 2. All bond lengths and angles are within normal ranges. Although the $O3-H3\cdots O1$ angle [$113(5)^\circ$] is far from linear, we can consider that the phenol and methoxy group are partners in an intramolecular hydrogen bond (Hunt *et al.*, 2005). The *cis/trans* conformational equilibrium of the formamide group is fixed in the solid state in the *trans* conformation, as can be confirmed by the torsion angle $C5-N1-C6-O2$ [$1.3(6)^\circ$].

In the crystal, the vanillylformamide molecules are linked by a series of classical hydrogen bonds ($N1-H1\cdots O2$, $O3-H3\cdots O1$, $O3-H3\cdots O2$; Table 1) and non-conventional $Csp^2-H\cdots O$ hydrogen bonds ($C6-H6\cdots O3$; Table 1), forming infinite two-dimensional polar sheets [Fig. 3(a)]

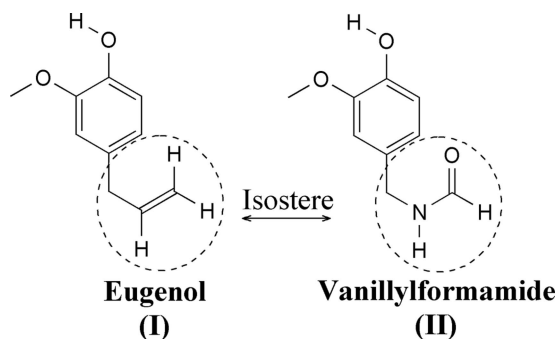


Figure 1
Eugenol (**I**) and the title compound (**II**).

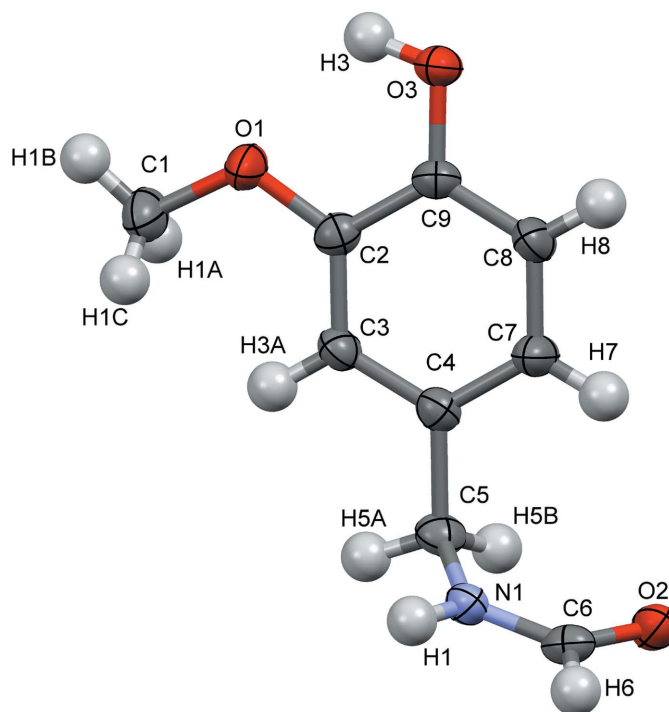


Figure 2
The molecular structure of compound (**II**), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level. H atoms are shown as fixed-size spheres of 0.30 Å.

parallel to $(01\bar{1})$. Moreover, $C6\cdots O1$ close contacts stabilize this architecture. The stacking pattern reveals that each layer is oriented in the same direction [Fig. 3(b)], generating a complete three-dimensional polar network. The main intermolecular contacts between layers [Fig. 2(c)] consist of van der Waals forces ($C1\cdots H7$ and $H1B\cdots H7$) and weak $Csp^3-H\cdots O$ hydrogen bonds ($C5-H5B\cdots O3$ and $C5-H5A\cdots O3$ of neighbouring molecules).

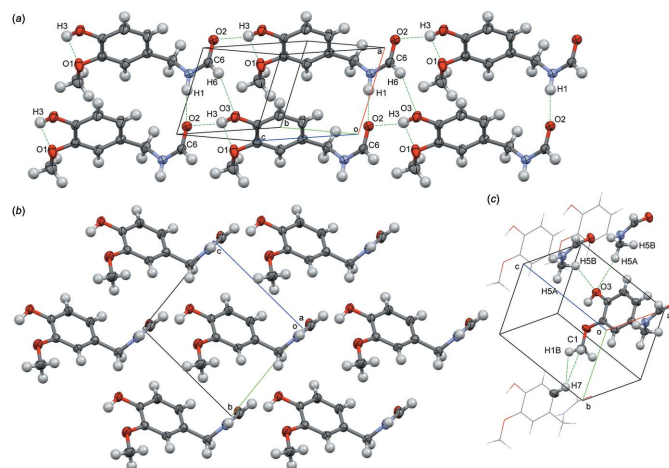


Figure 3
(a) Main hydrogen bonds and dipole-dipole interactions inside the polar sheets of vanillylformamide (**II**). (b) Stacking of the polar sheets along the a axis. (c) Weak interactions between the polar sheets.

Table 2
Experimental details.

Crystal data	
Chemical formula	C ₉ H ₁₁ NO ₃
<i>M_r</i>	181.19
Crystal system, space group	Triclinic, <i>P</i> 1
Temperature (K)	173
<i>a</i> , <i>b</i> , <i>c</i> (Å)	4.8011 (2), 6.5522 (3), 7.5052 (3)
α , β , γ (°)	93.618 (2), 107.044 (2), 95.658 (2)
<i>V</i> (Å ³)	223.58 (2)
<i>Z</i>	1
Radiation type	Cu <i>K</i> α
μ (mm ⁻¹)	0.85
Crystal size (mm)	0.32 × 0.16 × 0.12
Data collection	
Diffractometer	Bruker APEXII
Absorption correction	Multi-scan (<i>SADABS</i> ; Bruker, 2012)
<i>T_{min}</i> , <i>T_{max}</i>	0.574, 0.753
No. of measured, independent and observed [<i>I</i> > 2 σ (<i>I</i>)] reflections	2726, 1206, 1139
<i>R_{int}</i>	0.051
(<i>sin</i> θ / λ) _{max} (Å ⁻¹)	0.609
Refinement	
<i>R</i> [<i>F</i> ² > 2 σ (<i>F</i> ²)], <i>wR</i> (<i>F</i> ²), <i>S</i>	0.052, 0.154, 1.12
No. of reflections	1206
No. of parameters	123
No. of restraints	4
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{\max}$, $\Delta\rho_{\min}$ (e Å ⁻³)	0.25, -0.23

Computer programs: *APEX2* (Bruker, 2012), *SAINT* (Bruker, 2012), *SORTAV* (Blessing, 1995), *SHELXS* (Sheldrick, 2008), *SHELXL2016/6* (Sheldrick, 2015), *ORTEP* for Windows (Farrugia, 2012) and *Mercury* (Macrae *et al.*, 2008), *WinGX* (Farrugia, 2012) and *publCIF* (Westrip, 2010).

A search of the Cambridge Structural Database (CSD, Version 5.38, update May 2017; Groom *et al.*, 2016) indicated that 11 vanillylamide derivatives have been reported [FABVAF and FABVEJ (Oliver *et al.*, 1985); FABVAF01 (David *et al.*, 1998); FOSXOB (Winkler *et al.*, 2009); FOWTUH (Xia *et al.*, 2009); FOWTUH01 and KUTMAO01 (Wang *et al.*, 2010); KUTMAO (Huang *et al.*, 2010); QUZKOM (Xia *et al.*, 2010); SOFTEN (Zhang *et al.*, 2008); SOFTEN01 (Zhang & Cai, 2008)]. However, there was no structural report on vanillylamide analogues containing small amide units (such as a formamide) that could be considered as true isosteres of eugenol.

Synthesis and crystallization

Vanillylformamide (**II**) was already characterized in the literature through NMR spectroscopy (Baldessari *et al.*, 1987). However, this molecule has no known crystal structure.

Compound (**II**): To a solution of 4-nitrophenylformate (575 mg, 3.44 mmol) in ethyl acetate (10 ml) at room temperature was added potassium carbonate (715 mg, 5.17 mmol) and vanillylamine hydrochloride (717 mg, 3.78 mmol) under an argon atmosphere. After 1 h of stirring at room temperature, a catalytic amount of water (30 μ l) was added, the resulting mixture was stirred for an additional 3 h.

The reaction was followed by TLC (30/70 acetone/DCM). The reaction mixture was poured in HCl 0.1M (15 ml) and then extracted twice with ethyl acetate (2 × 15 ml). Hexane (50 ml) was added to the combined organic layers and the resulting organic phase was then filtrated directly through a silica gel pad, eluting with 100 ml of acetone/DCM (5:95) and 100 ml of acetone/DCM (30:70), to yield compound (**II**) as a yellowish white crystalline powder (485 mg, 78%). Single crystals suitable for X-ray diffraction were prepared by slow evaporation of an ether/acetone/hexane (70:5:25) solution of (**II**) at room temperature.

R_f = 0.37 (acetone/DCM 30:70); ¹H NMR (400 MHz, CDCl₃, p.p.m.): 8.20 (*s*, 1H), 6.86–6.71 (*m*, 3H), 6.03 (*m*, 1H), 5.86 (*s*, 1H), 4.37 (*d*, *J* = 5.84 Hz, 2H), 3.85 (*s*, 3H).

Refinement

Crystal data, data collection and structure refinement details are summarized in Table 2. The absolute structure could not be determined reliably from the collected diffraction data.

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full crystallographic data

IUCrData (2018). 3, x181630 [https://doi.org/10.1107/S2414314618016309]

Polar crystal of vanillylformamide through replacement of the alkene by an isosteric formamide group

Pierre Baillargeon, Tarik Rahem, Carl Amigo, Daniel Fortin and Yves L. Dory

(II)

Crystal data

$C_9H_{11}NO_3$

$M_r = 181.19$

Triclinic, *P*1

Hall symbol: P 1

$a = 4.8011$ (2) Å

$b = 6.5522$ (3) Å

$c = 7.5052$ (3) Å

$\alpha = 93.618$ (2)°

$\beta = 107.044$ (2)°

$\gamma = 95.658$ (2)°

$V = 223.58$ (2) Å³

$Z = 1$

$F(000) = 96$

$D_x = 1.346$ Mg m⁻³

Cu $K\alpha$ radiation, $\lambda = 1.54178$ Å

Cell parameters from 2759 reflections

$\theta = 6.2\text{--}70.7^\circ$

$\mu = 0.85$ mm⁻¹

$T = 173$ K

Prism, colorless

$0.32 \times 0.16 \times 0.12$ mm

Data collection

Bruker APEXII

diffractometer

Radiation source: sealed x-ray tube

Graphite monochromator

φ or ω oscillation scans

Absorption correction: multi-scan

(SADABS; Bruker, 2012)

$T_{\min} = 0.574$, $T_{\max} = 0.753$

2726 measured reflections

1206 independent reflections

1139 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.051$

$\theta_{\max} = 69.8^\circ$, $\theta_{\min} = 6.2^\circ$

$h = -5 \rightarrow 5$

$k = -7 \rightarrow 7$

$l = -9 \rightarrow 8$

Refinement

Refinement on F^2

Least-squares matrix: full

$R[F^2 > 2\sigma(F^2)] = 0.052$

$wR(F^2) = 0.154$

$S = 1.12$

1206 reflections

123 parameters

4 restraints

0 constraints

Hydrogen site location: mixed

H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0912P)^2 + 0.0525P]$

where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{\max} < 0.001$

$\Delta\rho_{\max} = 0.25$ e Å⁻³

$\Delta\rho_{\min} = -0.23$ 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. Hydrogen atoms bound to carbon atoms were positioned with idealized geometry and refined isotropically using a riding model, with $U_{\text{iso}}(\text{H}) = 1.2 U_{\text{eq}}(\text{C})$ and $\text{C—H} = 0.95 \text{ \AA}$ for aromatic, $U_{\text{iso}}(\text{H}) = 1.2 U_{\text{eq}}(\text{C})$ and $\text{C—H} = 0.99 \text{ \AA}$ for methylene and $U_{\text{iso}}(\text{H}) = 1.5 U_{\text{eq}}(\text{C})$ and $\text{C—H} = 0.98 \text{ \AA}$ for methyl groups. The N-bound H atom was placed in idealized position with $\text{N—H} = 0.88 \text{ \AA}$ and refined in riding mode with $U_{\text{iso}}(\text{H}) = 1.2 U_{\text{eq}}(\text{N})$. The hydroxyl H atom was refined independently in isotropic mode, with an O—H distance restraint of $0.96 (2) \text{ \AA}$.

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

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
O1	0.7872 (8)	0.7526 (5)	0.5754 (4)	0.0436 (9)
O2	1.0943 (7)	−0.0646 (5)	−0.0270 (5)	0.0376 (8)
O3	1.2189 (6)	0.5811 (5)	0.8054 (4)	0.0346 (8)
N1	0.6936 (8)	0.0863 (6)	−0.0091 (5)	0.0313 (8)
H1	0.506646	0.0619	−0.016887	0.038*
C1	0.5812 (13)	0.8622 (8)	0.4558 (8)	0.0457 (12)
H1A	0.673811	0.934512	0.373509	0.069*
H1B	0.513623	0.962513	0.531259	0.069*
H1C	0.413277	0.765528	0.379819	0.069*
C2	0.8948 (9)	0.6005 (6)	0.4953 (6)	0.0300 (10)
C3	0.8016 (9)	0.5279 (6)	0.3069 (6)	0.0313 (9)
H3A	0.648153	0.586589	0.222842	0.038*
C4	0.9284 (9)	0.3719 (6)	0.2397 (6)	0.0296 (9)
C5	0.8312 (9)	0.2985 (7)	0.0327 (6)	0.0330 (10)
H5A	0.690774	0.388824	−0.035372	0.04*
H5B	1.004057	0.312362	−0.014027	0.04*
C6	0.8314 (9)	−0.0728 (6)	−0.0364 (6)	0.0318 (9)
H6	0.718873	−0.204814	−0.065598	0.038*
C7	1.1468 (11)	0.2848 (7)	0.3628 (6)	0.0387 (11)
H7	1.235762	0.177733	0.317846	0.046*
C8	1.2385 (10)	0.3531 (6)	0.5538 (6)	0.0382 (11)
H8	1.385838	0.289743	0.638179	0.046*
C9	1.1167 (9)	0.5113 (6)	0.6200 (5)	0.0295 (10)
H3	1.144 (16)	0.711 (7)	0.817 (10)	0.061 (18)*

Atomic displacement parameters (\AA^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.054 (2)	0.0452 (19)	0.0316 (18)	0.0282 (16)	0.0062 (14)	−0.0004 (14)
O2	0.0287 (17)	0.0393 (17)	0.0418 (19)	0.0016 (12)	0.0094 (13)	−0.0082 (14)
O3	0.0383 (17)	0.0347 (16)	0.0260 (15)	0.0064 (12)	0.0027 (12)	−0.0021 (12)
N1	0.0234 (16)	0.0360 (18)	0.0309 (19)	0.0017 (13)	0.0047 (14)	−0.0041 (14)
C1	0.054 (3)	0.047 (3)	0.038 (3)	0.024 (2)	0.011 (2)	0.009 (2)
C2	0.033 (2)	0.027 (2)	0.030 (2)	0.0017 (17)	0.0105 (19)	0.0021 (17)
C3	0.032 (2)	0.032 (2)	0.026 (2)	0.0069 (17)	0.0025 (17)	0.0053 (16)
C4	0.028 (2)	0.030 (2)	0.029 (2)	0.0017 (16)	0.0052 (17)	0.0032 (17)
C5	0.038 (2)	0.035 (2)	0.024 (2)	0.0041 (17)	0.0066 (18)	0.0056 (16)
C6	0.035 (2)	0.033 (2)	0.025 (2)	−0.0045 (17)	0.0096 (17)	−0.0031 (16)
C7	0.047 (3)	0.037 (2)	0.028 (2)	0.015 (2)	0.0018 (19)	−0.0023 (18)

C8	0.040 (3)	0.036 (3)	0.032 (3)	0.014 (2)	-0.002 (2)	0.0008 (19)
C9	0.031 (2)	0.029 (2)	0.025 (2)	-0.0005 (17)	0.0059 (18)	-0.0017 (17)

Geometric parameters (Å, °)

O1—C2	1.352 (6)	C2—C9	1.400 (6)
O1—C1	1.415 (6)	C3—C4	1.382 (6)
O2—C6	1.239 (5)	C3—H3A	0.95
O3—C9	1.364 (5)	C4—C7	1.376 (6)
O3—H3	0.96 (3)	C4—C5	1.516 (6)
N1—C6	1.325 (6)	C5—H5A	0.99
N1—C5	1.453 (6)	C5—H5B	0.99
N1—H1	0.88	C6—H6	0.95
C1—H1A	0.98	C7—C8	1.400 (6)
C1—H1B	0.98	C7—H7	0.95
C1—H1C	0.98	C8—C9	1.374 (6)
C2—C3	1.389 (6)	C8—H8	0.95
C2—O1—C1	117.7 (3)	C3—C4—C5	120.6 (4)
C9—O3—H3	106 (4)	N1—C5—C4	113.5 (3)
C6—N1—C5	124.2 (3)	N1—C5—H5A	108.9
C6—N1—H1	117.9	C4—C5—H5A	108.9
C5—N1—H1	117.9	N1—C5—H5B	108.9
O1—C1—H1A	109.5	C4—C5—H5B	108.9
O1—C1—H1B	109.5	H5A—C5—H5B	107.7
H1A—C1—H1B	109.5	O2—C6—N1	125.7 (4)
O1—C1—H1C	109.5	O2—C6—H6	117.1
H1A—C1—H1C	109.5	N1—C6—H6	117.1
H1B—C1—H1C	109.5	C4—C7—C8	120.4 (4)
O1—C2—C3	125.9 (4)	C4—C7—H7	119.8
O1—C2—C9	114.6 (4)	C8—C7—H7	119.8
C3—C2—C9	119.5 (4)	C9—C8—C7	120.4 (4)
C4—C3—C2	121.1 (4)	C9—C8—H8	119.8
C4—C3—H3A	119.5	C7—C8—H8	119.8
C2—C3—H3A	119.5	O3—C9—C8	119.3 (4)
C7—C4—C3	119.2 (4)	O3—C9—C2	121.3 (4)
C7—C4—C5	120.3 (4)	C8—C9—C2	119.4 (4)
C1—O1—C2—C3	-6.5 (6)	C3—C4—C7—C8	0.2 (7)
C1—O1—C2—C9	174.5 (4)	C5—C4—C7—C8	179.6 (4)
O1—C2—C3—C4	179.7 (4)	C4—C7—C8—C9	-1.6 (7)
C9—C2—C3—C4	-1.3 (6)	C7—C8—C9—O3	-177.1 (4)
C2—C3—C4—C7	1.2 (6)	C7—C8—C9—C2	1.5 (7)
C2—C3—C4—C5	-178.1 (3)	O1—C2—C9—O3	-2.3 (5)
C6—N1—C5—C4	-97.8 (5)	C3—C2—C9—O3	178.5 (4)
C7—C4—C5—N1	65.2 (5)	O1—C2—C9—C8	179.0 (4)
C3—C4—C5—N1	-115.5 (4)	C3—C2—C9—C8	-0.1 (6)
C5—N1—C6—O2	1.3 (6)		

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	0.88	2.05	2.910 (4)	167
O3—H3...O1	0.96 (3)	2.15 (7)	2.672 (4)	113 (5)
C6—H6...O3 ⁱⁱ	0.95	2.54	3.391 (5)	149
O3—H3...O2 ⁱⁱⁱ	0.96 (3)	1.90 (4)	2.771 (4)	149 (6)
C5—H5B...O3 ^{iv}	0.99	2.60	3.374 (5)	135
C5—H5A...O3 ^v	0.99	2.70	3.676 (5)	167

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