IUCrData

ISSN 2414-3146

N-(4-Hydroxy-2-nitrophenyl)acetamide

James E. Hines III,[a] Curtistine J. Deere,[a] Frank R. Fronczek[b] and Rao M. Uppu[a]*

[a]Department of Environmental Toxicology, College of Agriculture, Southern University and A&M College, Baton Rouge, LA 70813, USA, and [b]Department of Chemistry, Louisiana State University, Baton Rouge, LA 70803, USA. *Correspondence e-mail: rao_uppu@subr.edu

Received 27 January 2022
Accepted 20 February 2022

Edited by W. T. A. Harrison, University of Aberdeen, Scotland

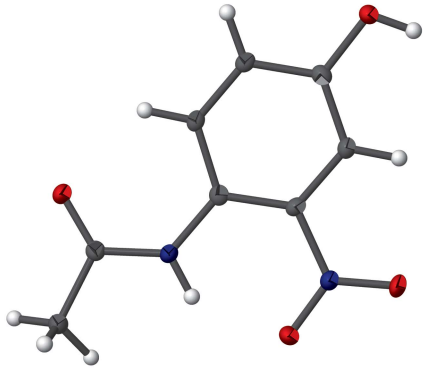
Keywords: crystal structure; hydrogen bonding.

CCDC reference: 2153454

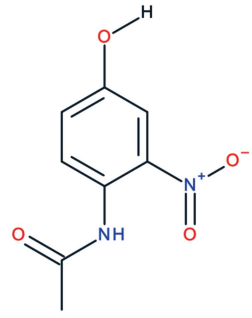
Structural data: full structural data are available from iucrdata.iucr.org

The title compound, $C_8H_8N_2O_4$, differs in its degree of planarity from the 3-nitro isomer and also in its hydrogen-bonding pattern. Its NH group forms an intramolecular hydrogen bond to a nitro oxygen atom, and its OH group forms an intermolecular hydrogen bond to an amide oxygen atom, generating $[10\bar{1}]$ chains in the crystal.

3D view



Chemical scheme



Structure description

The putative free-radical products of the peroxynitrite anion (PN)—CO_2 reaction ($^{\cdot}NO_2$ and $CO_3^{\cdot-}$) have long been thought to constitute an important source of non-CYP450-mediated oxidative biotransformation of *N*-(4-hydroxyphenyl)acetamide (4-HPA; acetaminophen or paracetamol) and other xenobiotics (Babu *et al.*, 2012; Dou *et al.*, 2017; Gernapudi *et al.*, 2009; Rangan *et al.*, 2006; Uppu *et al.*, 2005). In reactions of 4-HPA/PN/CO_2, we find that *N*-(4-hydroxy-3-nitrophenyl)acetamide is one of the major products formed along with *N*,*N*′-(6,6′-dihydroxy[1,1′-biphenyl]-3,3′-diyl)bisacetamide (dimer of 4-HPA) and a metastable *N*-acetyl-1,4-benzoquinone (NBQI; demonstrated through its binding to *N*-acetyl-L-cysteine; Uppu & Martin, 2005; Deere *et al.*, 2022). It was shown that NBQI can react with electrophiles such as the nitrite ion and form yet another nitro product, *N*-(4-hydroxy-2-nitrophenyl)acetamide (Matsuno *et al.*, 1989). Although we did not find evidence for the formation of this 2-nitro isomer in 4-HPA/PN/CO_2 reactions, we believe that this isomer along with other oxidation products of 4-HPA may play a role in the pharmacology and toxicology of 4-HPA (4-HPA overdose, either unintentional or intentional, is the most common cause of hepatic failure in the USA and elsewhere).

Towards a better understanding of this chemistry, we have synthesized *N*-(4-hydroxy-2-nitrophenyl)acetamide and *N*-(4-hydroxy-3-nitrophenyl)acetamide and determined their single-crystal structures. Interestingly, the 2-nitro and 3-nitro isomers have signifi-

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

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1*O*···O4^{i}	0.84 (2)	1.88 (2)	2.7183 (14)	172.0 (18)
N2—H2*N*···O3	0.883 (19)	1.901 (17)	2.6363 (15)	139.6 (15)

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

cantly different degrees of molecular planarity in the solid-state and also differ in their hydrogen bonding patterns.

In *N*-(4-hydroxy-2-nitrophenyl)acetamide, Fig. 1, the molecule is nearly planar, with an r.m.s. deviation of 0.035 Å for the non-hydrogen atoms. The acetamido group has the largest deviation, with a 5.1 (2)° twist about its central C7—N2 bond. The N—H group forms an intramolecular hydrogen bond (Table 1) to O3 (part of the nitro group) having an N···O distance of 2.6363 (15) Å and N—H···O angle of 139.6 (15)°. The hydroxy group forms an intermolecular hydrogen bond to acetamido atom O4 with O···O = 2.7183 (14) Å and O—H···O = 172.0 (18)°, thereby forming chains propagating in the [10$\bar{1}$] direction (Figs. 2 and 3).

The crystal structure of *N*-(4-hydroxy-3-nitrophenyl)acetamide has been reported (Salahifar *et al.*, 2015; Deere *et al.*, 2019). It is significantly less planar than the title compound, with the acetamido group twisted out of the plane of the phenyl group by 9.0 (2)° and the nitro group twisted out of the phenyl plane by 11.8 (2)°. Its hydrogen-bonding pattern also differs, with the N—H group forming an intermolecular hydrogen bond to the acetamido O atom [N···O = 2.9079 (17) Å; N—H···O = 176.6 (19)°]. Its OH group forms a bifurcated O—H···(O,O) hydrogen bond, with intramolecular component to the adjacent nitro group [O···O = 2.6093 (17) Å] and a longer intermolecular component to a nitro oxygen atom of an adjacent molecule [O···O = 3.1421 (17) Å; Deere *et al.*, 2019].

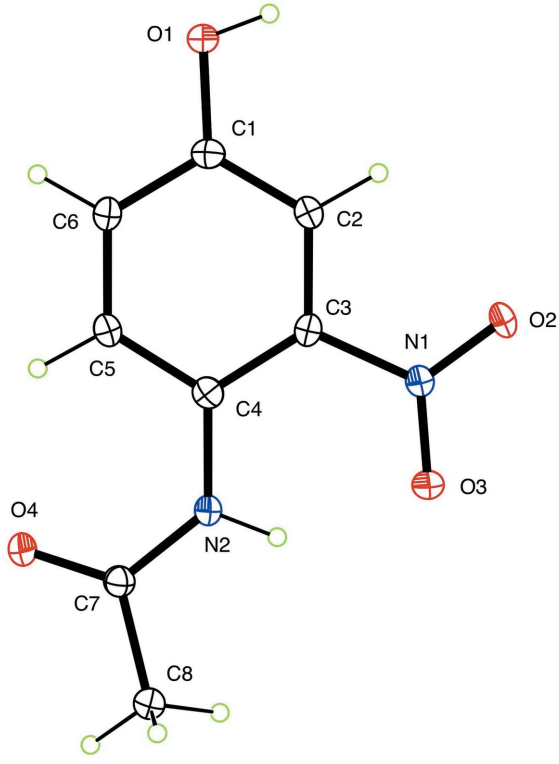


Figure 1
The molecular structure of the title molecule with 50% displacement ellipsoids.

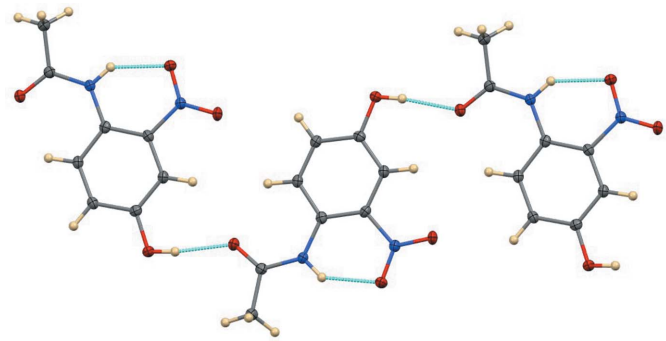


Figure 2
The hydrogen-bonded chain.

Synthesis and crystallization

The title compound was synthesized by the acetylation of 4-hydroxy-2-nitroaniline using acetic anhydride as described by Naik *et al.* (2004) with some minor modification (Fig. 4). Briefly, 4-hydroxy-2-nitroaniline (3.08 g; 20 mmol) in its hydrochloride form (prepared by addition of a slight molar excess of HCl; 26 mmol) was dissolved in 125 ml of acetonitrile/water (1/4, *v*/*v*). The solution was cooled in an ice bath, followed by addition of acetic anhydride (2.43 ml; 24 mmol). Then, sodium bicarbonate (3.36–5.04 g; 40–60 mmol) was

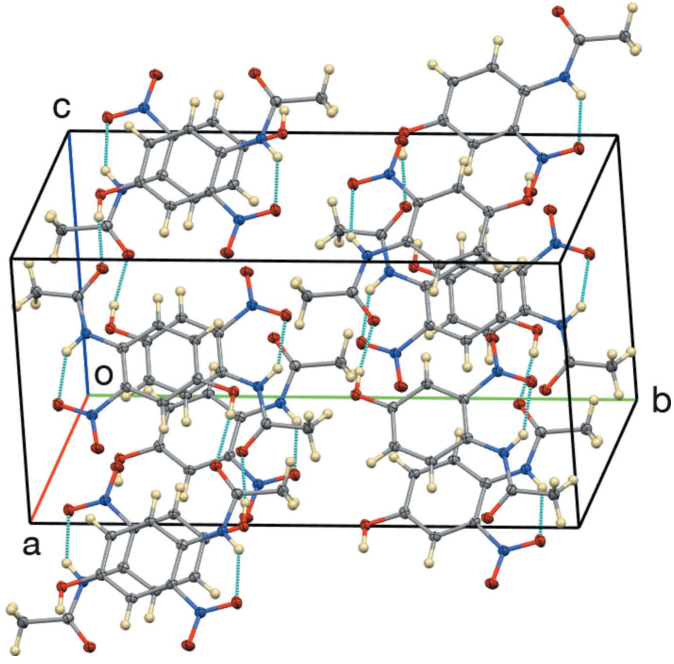


Figure 3
The unit cell of the title compound.

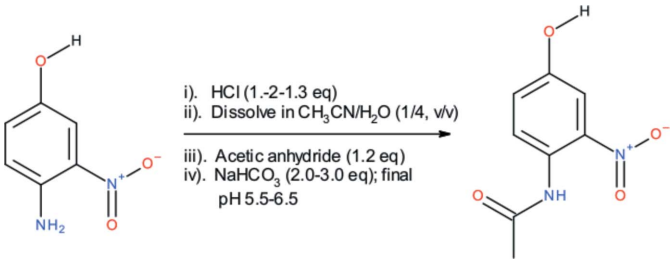


Figure 4
Schematic representation of the synthesis of the title compound.

added to the mixture with the contents being constantly stirred. Care was taken to maintain that the pH of the final reaction mixture was between 5.5 and 6.5. The yellow precipitate of *N*-(4-hydroxy-2-nitrophenyl)acetamide was separated by filtration and purified by recrystallization twice from aqueous solution. Single crystals were grown from methanol solution.

Refinement

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

Funding information

The authors acknowledge the support from the National Institutes of Health (NIH) through the National Institute of General Medical Science (NIGMS) grant No. 5 P2O GM103424–17 and the US Department of Education (US DoE; Title III, HBGI Part B grant No. P031B040030). Its contents are solely the responsibility of authors and do not represent the official views of NIH, NIGMS, or US DoE. The upgrade of the diffractometer was made possible by grant No. LEQSF(2011–12)-ENH-TR-01, administered by the Louisiana Board of Regents.

Table 2
Experimental details.

Crystal data	
Chemical formula	$C_8H_8N_2O_4$
M_r	196.16
Crystal system, space group	Monoclinic, *C*2/*c*
Temperature (K)	90
a, *b*, *c* (Å)	9.6643 (3), 18.5534 (5), 9.3072 (2)
β (°)	95.5075 (14)
V (Å^3)	1661.13 (8)
Z	8
Radiation type	Cu $K\alpha$
μ (mm^{-1})	1.10
Crystal size (mm)	0.21 × 0.07 × 0.02
Data collection	
Diffractometer	Bruker Kappa APEXII DUO CCD
Absorption correction	Multi-scan (*SADABS*; Krause *et al.*, 2015)
T_{min}, T_{max}	0.872, 0.978
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	6856, 1543, 1486
R_{int}	0.028
(sin $\theta/\lambda)_{max}$ (Å^{-1})	0.607
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.035, 0.095, 1.13
No. of reflections	1543
No. of parameters	134
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.29, −0.24

Computer programs: *APEX3* and *SAINT* (Bruker, 2016), *SHELXS97* (Sheldrick, 2008), *SHELXL2014/7* (Sheldrick, 2015), *Mercury* (Macrae *et al.*, 2020); *ORTEP-3* (Farrugia, 2012) and *publCIF* (Westrip, 2010).

References

Babu, S., Vellore, N. A., Kasibotla, A. V., Dwayne, H. J., Stubblefield, M. A. & Uppu, R. M. (2012). *Biochem. Biophys. Res. Commun.* **426**, 215–220.
Bruker (2016). *APEX2* and *SAINT*. Bruker AXS Inc., Madison, Wisconsin, USA.
Deere, C. J., Hines, J. E. III, Agu, O. A. & Fronczek, F. R. (2019). *CSD Communication* (CCDC 1910293). CCDC, Cambridge, England. https://doi.org/10.5517/ccdc.csd.cc223tcd.
Deere, C. J., Hines, J. E. III & Uppu, R. M. (2022). Unpublished.
Dou, X., Li, J. Z., Danelisen, I., Trush, M. A., Misra, H. P., Zhu, H., Jia, Z. & Li, Y. R. (2017). *Reactive Oxygen Species* **3**, 127–134.
Farrugia, L. J. (2012). *J. Appl. Cryst.* **45**, 849–854.
Gernapudi, R., Babu, S., Raghavamenon, A. C. & Uppu, R. M. (2009). *FASEB J*, **23** (Suppl. 1), 397. https://faseb.onlinelibrary.wiley.com/doi/10.1096/fasebj.23.1_supplement.LB397
Krause, L., Herbst-Irmer, R., Sheldrick, G. M. & Stalke, D. (2015). *J. Appl. Cryst.* **48**, 3–10.
Macrae, C. F., Sovago, I., Cottrell, S. J., Galek, P. T. A., McCabe, P., Pidcock, E., Platings, M., Shields, G. P., Stevens, J. S., Towler, M. & Wood, P. A. (2020). *J. Appl. Cryst.* **53**, 226–235.
Matsuno, T., Matsukawa, T., Sakuma, Y. & Kunieda, T. (1989). *Chem. Pharm. Bull.* **37**, 1422–1423.
Naik, S., Bhattacharjya, G., Kavala, V. R. & Patel, B. K. (2004). *Arkivoc*, pp. 55–63.
Rangan, V., Perumal, T. E., Sathishkumar, K. & Uppu, R. M. (2006). *Toxicologist* (supplement to *Toxicol. Sci.*) **90**, 242–243. https://www.toxicology.org/pubs/docs/Tox/2006Tox.pdf
Salahifar, E., Nematollahi, D., Bayat, M., Mahyari, A. & Rudbari, H. A. (2015). *Org. Lett.* **17**, 4666–4669.
Sheldrick, G. M. (2008). *Acta Cryst.* A**64**, 112–122.
Sheldrick, G. M. (2015). *Acta Cryst.* C**71**, 3–8.
Uppu, R. M. & Martin, R. J. (2005). *Toxicologist* (supplement to *Toxicol. Sci.*), **319**. https://www.toxicology.org/pubs/docs/Tox/2005Tox.pdf
Uppu, R. M., Sathishkumar, K. & Perumal, T. (2005). Free Radic. Biol. Med. 39 (Suppl. 1) 39, 15. https://www.sciencedirect.com/journal/free-radical-biology-and-medicine/vol/39/suppl/S1
Westrip, S. P. (2010). *J. Appl. Cryst.* **43**, 920–925.

full crystallographic data

IUCrData (2022). **7**, x220201 [https://doi.org/10.1107/S2414314622002012]

N-(4-Hydroxy-2-nitrophenyl)acetamide

James E. Hines III, Curtistine J. Deere, Frank R. Fronczek and Rao M. Uppu

N-(4-Hydroxy-2-nitrophenyl)acetamide

Crystal data

$C_8H_8N_2O_4$
M_r = 196.16
Monoclinic, $C2/c$
a = 9.6643 (3) Å
b = 18.5534 (5) Å
c = 9.3072 (2) Å
β = 95.5075 (14)°
V = 1661.13 (8) Å^3
Z = 8
$F(000)$ = 816
D_x = 1.569 Mg m^{-3}
Cu $K\alpha$ radiation, λ = 1.54184 Å
Cell parameters from 5235 reflections
θ = 4.8–69.3°
μ = 1.10 mm^{-1}
T = 90 K
Lath, yellow
0.21 × 0.07 × 0.02 mm

Data collection

Bruker Kappa APEXII DUO CCD diffractometer
Radiation source: IμS microfocus
QUAZAR multilayer optics monochromator
φ and ω scans
Absorption correction: multi-scan (SADABS; Krause *et al.*, 2015)
T_{min} = 0.872, T_{max} = 0.978
6856 measured reflections
1543 independent reflections
1486 reflections with $I > 2\sigma(I)$
R_{int} = 0.028
θ_{max} = 69.3°, θ_{min} = 4.8°
h = −11→7
k = −22→20
l = −11→10

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.035
$wR(F^2)$ = 0.095
S = 1.13
1543 reflections
134 parameters
0 restraints
Hydrogen site location: mixed
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0487P)^2 + 1.5639P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.29 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. 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 and 0.98 Å for methyl. The 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 OH and methyl).

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

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	0.49965 (11)	0.11112 (5)	0.49610 (11)	0.0180 (2)
H1O	0.435 (2)	0.1126 (10)	0.551 (2)	0.027*
O2	0.36347 (11)	0.35035 (5)	0.64809 (11)	0.0240 (3)
O3	0.47807 (11)	0.43019 (5)	0.53985 (12)	0.0239 (3)
O4	0.79942 (10)	0.37109 (5)	0.17917 (10)	0.0208 (3)
N1	0.44852 (12)	0.36642 (6)	0.56392 (12)	0.0163 (3)
N2	0.65588 (12)	0.39184 (6)	0.35604 (12)	0.0149 (3)
H2N	0.6134 (17)	0.4246 (10)	0.4050 (18)	0.018*
C1	0.53400 (14)	0.18008 (7)	0.46502 (14)	0.0143 (3)
C2	0.47727 (13)	0.23927 (7)	0.52723 (13)	0.0146 (3)
H2	0.4113	0.2327	0.5955	0.018*
C3	0.51647 (13)	0.30877 (7)	0.49012 (13)	0.0138 (3)
C4	0.61410 (13)	0.32179 (7)	0.39015 (13)	0.0137 (3)
C5	0.66952 (13)	0.26010 (7)	0.32904 (13)	0.0140 (3)
H5	0.7356	0.2659	0.2606	0.017*
C6	0.63082 (13)	0.19119 (7)	0.36548 (13)	0.0143 (3)
H6	0.6708	0.1509	0.3220	0.017*
C7	0.74622 (13)	0.41291 (7)	0.25993 (14)	0.0152 (3)
C8	0.77664 (15)	0.49227 (7)	0.26014 (16)	0.0211 (3)
H8A	0.8474	0.5036	0.3395	0.032*
H8B	0.6914	0.5192	0.2729	0.032*
H8C	0.8109	0.5058	0.1681	0.032*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0214 (5)	0.0120 (5)	0.0220 (5)	−0.0007 (4)	0.0096 (4)	0.0002 (4)
O2	0.0279 (6)	0.0189 (5)	0.0287 (6)	0.0003 (4)	0.0202 (4)	0.0005 (4)
O3	0.0298 (6)	0.0121 (5)	0.0327 (6)	−0.0014 (4)	0.0180 (5)	−0.0002 (4)
O4	0.0256 (5)	0.0158 (5)	0.0234 (5)	0.0000 (4)	0.0141 (4)	−0.0013 (4)
N1	0.0175 (6)	0.0143 (6)	0.0182 (6)	0.0003 (4)	0.0073 (4)	−0.0003 (4)
N2	0.0148 (6)	0.0129 (5)	0.0179 (6)	0.0009 (4)	0.0061 (4)	−0.0006 (4)
C1	0.0142 (6)	0.0132 (6)	0.0155 (6)	−0.0010 (5)	0.0005 (5)	0.0010 (5)
C2	0.0143 (6)	0.0159 (7)	0.0143 (6)	−0.0002 (5)	0.0041 (5)	0.0001 (5)
C3	0.0140 (6)	0.0141 (7)	0.0136 (6)	0.0017 (5)	0.0026 (5)	−0.0019 (5)
C4	0.0124 (6)	0.0153 (6)	0.0133 (6)	−0.0002 (5)	0.0004 (5)	0.0004 (5)
C5	0.0122 (6)	0.0165 (7)	0.0138 (6)	0.0003 (5)	0.0031 (5)	−0.0003 (5)
C6	0.0134 (6)	0.0152 (6)	0.0145 (6)	0.0016 (5)	0.0025 (5)	−0.0013 (5)
C7	0.0142 (6)	0.0143 (6)	0.0173 (6)	0.0006 (5)	0.0028 (5)	0.0010 (5)
C8	0.0245 (7)	0.0142 (7)	0.0266 (7)	−0.0006 (5)	0.0125 (6)	−0.0002 (5)

Geometric parameters (Å, º)

O1—C1	1.3599 (16)	C2—C3	1.3966 (18)
O1—H1O	0.84 (2)	C2—H2	0.9500

O2—N1	1.2255 (15)	C3—C4	1.4081 (18)
O3—N1	1.2424 (15)	C4—C5	1.4067 (18)
O4—C7	1.2270 (17)	C5—C6	1.3835 (18)
N1—C3	1.4608 (17)	C5—H5	0.9500
N2—C7	1.3657 (18)	C6—H6	0.9500
N2—C4	1.4063 (17)	C7—C8	1.5014 (18)
N2—H2N	0.883 (19)	C8—H8A	0.9800
C1—C2	1.3795 (18)	C8—H8B	0.9800
C1—C6	1.3938 (19)	C8—H8C	0.9800
C1—O1—H1O	108.0 (12)	N2—C4—C3	122.20 (12)
O2—N1—O3	121.80 (11)	C5—C4—C3	115.65 (12)
O2—N1—C3	118.79 (11)	C6—C5—C4	122.03 (12)
O3—N1—C3	119.41 (11)	C6—C5—H5	119.0
C7—N2—C4	128.89 (12)	C4—C5—H5	119.0
C7—N2—H2N	119.9 (11)	C5—C6—C1	120.94 (12)
C4—N2—H2N	111.2 (11)	C5—C6—H6	119.5
O1—C1—C2	123.01 (12)	C1—C6—H6	119.5
O1—C1—C6	118.27 (12)	O4—C7—N2	123.52 (12)
C2—C1—C6	118.72 (12)	O4—C7—C8	121.83 (12)
C1—C2—C3	120.20 (12)	N2—C7—C8	114.66 (11)
C1—C2—H2	119.9	C7—C8—H8A	109.5
C3—C2—H2	119.9	C7—C8—H8B	109.5
C2—C3—C4	122.46 (12)	H8A—C8—H8B	109.5
C2—C3—N1	114.51 (11)	C7—C8—H8C	109.5
C4—C3—N1	123.02 (12)	H8A—C8—H8C	109.5
N2—C4—C5	122.14 (12)	H8B—C8—H8C	109.5
O1—C1—C2—C3	−179.68 (11)	N1—C3—C4—N2	1.39 (19)
C6—C1—C2—C3	0.19 (19)	C2—C3—C4—C5	0.31 (18)
C1—C2—C3—C4	−0.29 (19)	N1—C3—C4—C5	180.00 (11)
C1—C2—C3—N1	180.00 (11)	N2—C4—C5—C6	178.36 (11)
O2—N1—C3—C2	−1.17 (17)	C3—C4—C5—C6	−0.25 (18)
O3—N1—C3—C2	178.91 (11)	C4—C5—C6—C1	0.18 (19)
O2—N1—C3—C4	179.12 (12)	O1—C1—C6—C5	179.74 (11)
O3—N1—C3—C4	−0.79 (19)	C2—C1—C6—C5	−0.13 (19)
C7—N2—C4—C5	3.1 (2)	C4—N2—C7—O4	5.1 (2)
C7—N2—C4—C3	−178.38 (12)	C4—N2—C7—C8	−174.86 (12)
C2—C3—C4—N2	−178.30 (11)		

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O1—H1*O*···O4^{i}	0.84 (2)	1.88 (2)	2.7183 (14)	172.0 (18)
N2—H2*N*···O3	0.883 (19)	1.901 (17)	2.6363 (15)	139.6 (15)

Symmetry code: (i) $x-1/2, -y+1/2, z+1/2$.