organic compounds

The hydrochloride salt of L-ecgonine, a congener of cocaine

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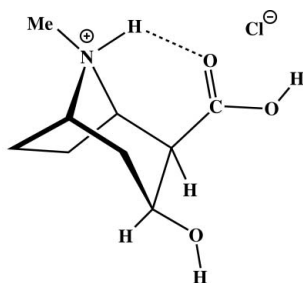Correspondence e-mail: rogerlal@andromeda.rutgers.edu

The title compound, (1R,2R,3S,5S,8S)-3-hydroxy-8-methyl-8-azoniabicyclo[3.2.1]octane-2-carboxylic acid chloride, $C_9H_{16}NO_3^+ \cdot Cl^-$, is both a metabolite and a precursor of the tropane alkaloid L-cocaine. The carboxyl group is not involved in dimerization, but instead donates a hydrogen bond to the chloride counter-ion, which participates in two additional hydrogen bonds. The chloride ion is thus trigonally hydrogen bonded to three L-ecgonine cations. The quaternary N proton is intramolecularly hydrogen bonded to the carboxyl C=O group, an arrangement identical to that reported for both (−)-norcocaine and the tetrachloroaurate(III) salt of L-cocaine. One close intermolecular C—H···O contact exists.

Related literature

For related literature, see: Logan (2001); Wood *et al.* (2007); Zhu *et al.* (1994, 1999).

Experimental

Crystal data

$C_9H_{16}NO_3^+ \cdot Cl^-$	$b = 12.0519$ (8) Å
$M_r = 221.68$	$c = 13.0632$ (8) Å
Orthorhombic, $P2_12_12_1$	$V = 1054.23$ (11) Å^3
$a = 6.6962$ (4) Å	$Z = 4$

Cu $K\alpha$ radiation	$T = 100$ (2) K
$\mu = 3.09$ mm^{-1}	$0.48 \times 0.32 \times 0.09$ mm

Data collection

Bruker APEXII CCD area-detector diffractometer	7772 measured reflections
Absorption correction: numerical (*SADABS*; Sheldrick, 2001) $T_{min} = 0.319$, $T_{max} = 0.768$	1891 independent reflections 1869 reflections with $I > 2\sigma(I)$ $R_{int} = 0.037$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.026$	$\Delta\rho_{max} = 0.28$ e Å^{-3}
$wR(F^2) = 0.064$	$\Delta\rho_{min} = -0.16$ e Å^{-3}
$S = 1.09$	Absolute structure: Flack (1983), 766 Friedel pairs
1891 reflections	Flack parameter: 0.038 (12)
140 parameters	
H atoms treated by a mixture of independent and constrained refinement	

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1A···Cl1	0.84 (2)	2.754 (18)	3.2816 (13)	122.3 (14)
N1—H1A···O1	0.84 (2)	2.066 (19)	2.7608 (17)	140 (2)
O2—H2A···Cl1^i	0.86 (3)	2.12 (3)	2.9585 (12)	165 (2)
O3—H3A···Cl1^{ii}	0.78 (2)	2.37 (2)	3.1332 (12)	169 (2)
C8—H8B···O3^{iii}	0.98	2.45	3.2280 (19)	136

Symmetry codes: (i) $-x+\frac{5}{2}, -y, z-\frac{1}{2}$; (ii) $-x+\frac{3}{2}, -y, z-\frac{1}{2}$; (iii) $-x+2, y+\frac{1}{2}, -z+\frac{3}{2}$.

Data collection: *APEX2* (Bruker, 2006); cell refinement: *APEX2*; data reduction: *SAINT* (Bruker, 2005); program(s) used to solve structure: *SHELXTL* (Sheldrick, 2008); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL* software used to prepare material for publication: *SHELXTL*.

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: RN2039).

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supporting information

The hydrochloride salt of ʟ-ecgonine, a congener of cocaine

Matthew R. Wood, Thomas A. Brettell, Hugh W. Thompson and Roger A. Lalancette

S1. Comment

l-Ecgonine is a naturally occurring alkaloid found in the leaves of the coca plant, *Erythroxylum coca*. This tropane alkaloid is both a metabolite and a precursor of its congener, *l*-cocaine; it is the hydroxy acid obtained by complete acidic, alkaline, or enzymatic hydrolysis of both ester functions in *l*-cocaine. The presence of *l*-ecgonine in postmortem blood specimens demonstrates cocaine use when the provenance of the specimen is unknown, when preservation has been inadequate, or when other cocaine metabolites have been shown to be undetectable (Logan, 2001).

The authors have begun a study of the three-dimensional structures of several cocaine derivatives and report here the structure of the hydrochloride salt (I) of *l*-ecgonine. We have previously reported the absolute configuration of the gold(III) tetrachloride salt of *l*-cocaine (Wood *et al.*, 2007).

Figure 1 shows the asymmetric unit with its numbering. The Cl⁻ counterion in (I) was chosen on the basis of its proximity to the site of the positive charge on N1. This hydrochloride salt does not form carboxyl dimers; rather, the carboxyl donates a hydrogen bond to the chloride ion, which participates in two additional hydrogen bonds (see below), while the quaternized N atom is intramolecularly H bonded through its H atom to the O atom of the acid's C=O group [N1···O1 = 2.7608 (17) Å, N1—H1A···O1 = 140 (2)°]. These values compare closely to those found in the gold(III) tetrachloride salt of *l*-cocaine [N···O = 2.755 (6) Å, N—H···O = 136°] (Wood *et al.*, 2007). In the structure of (-)-norcocaine, Zhu *et al.* (1994) found an arrangement identical to that in (I), with N···O = 2.306 (2) Å and N—H···O = 129°. However, in the structure of *l*-cocaine.HCl, Zhu *et al.* (1999) reported that the protonated N atom is H bonded to the methoxy O atom (not the C=O) [N···O = 2.894 (9) Å, N—H···O = 110.5 (9)°]. The torsion angle C3—C2—C9—O2 in (I) [99.61 (14)°] is similar to those found in the gold(III) tetrachloride salt of *l*-cocaine [89.9 (6)°] and in (-)-norcocaine (114.6°), but is very different from that found in *l*-cocaine.HCl [-138.4 (8)°]. According to potential energy calculations performed by Zhu *et al.* (1999), the energy minimum for the H bond to the carbonyl group in (I) occurs at a torsion angle C3—C2—C9—O2 of 95–110°.

Figure 2 shows the packing of the cell, with extra molecules to illustrate the trigonal H bonding to the Cl⁻ counterion from three different *l*-ecgonine cation units: [N1···Cl1 = 3.2816 (13) Å, N1—H1A···Cl1 = 122.3 (14)°]; [hydroxyl O3B (-*x* + 3/2,-*y*,*z* + 1/2)···Cl1 = 3.1332 (12) Å, O3B—H3A···Cl1 = 169 (2)°]; [acid O2A (-*x* + 5/2,-*y*,*z* + 1/2)···Cl1 = 2.9585 (12) Å, O2A—H2A···Cl1 = 165 (2)°]. The chloride anion lies 0.1975 (8) Å below the plane formed by its three contact atoms (N1, O2A & O3B). One close intermolecular C—H···O contact exists within the 2.6 Å range we survey for non-bonded C—H···O packing interactions (Table 1).

S2. Experimental

l-Ecgonine hydrochloride (I) was dissolved in water to yield a 500 μg ml⁻¹ solution, 200 μl of which was combined with 200 μl of 0.5% gold(III) chloride (HAuCl₄.3H₂O) solution acidified with HCl and allowed to crystallize by slow evaporation. Thin, flat colourless plates of (I), containing no gold, formed, m.p. 519 K.

S3. Refinement

All H atoms for (I) were found in electron-density difference maps. The amine, acid and the hydroxyl Hs were all allowed to refine fully. The methyl H atoms were put in ideally staggered positions with C—H distances of 0.98 Å and $U_{iso}(H) =$ $1.5U_{eq}(C)$. The methylene and methine Hs were placed in geometrically idealized positions and constrained to ride on their parent C atoms with C—H distances of 0.99 and 1.00 Å, respectively, and $U_{iso}(H) = 1.2U_{eq}(C)$.
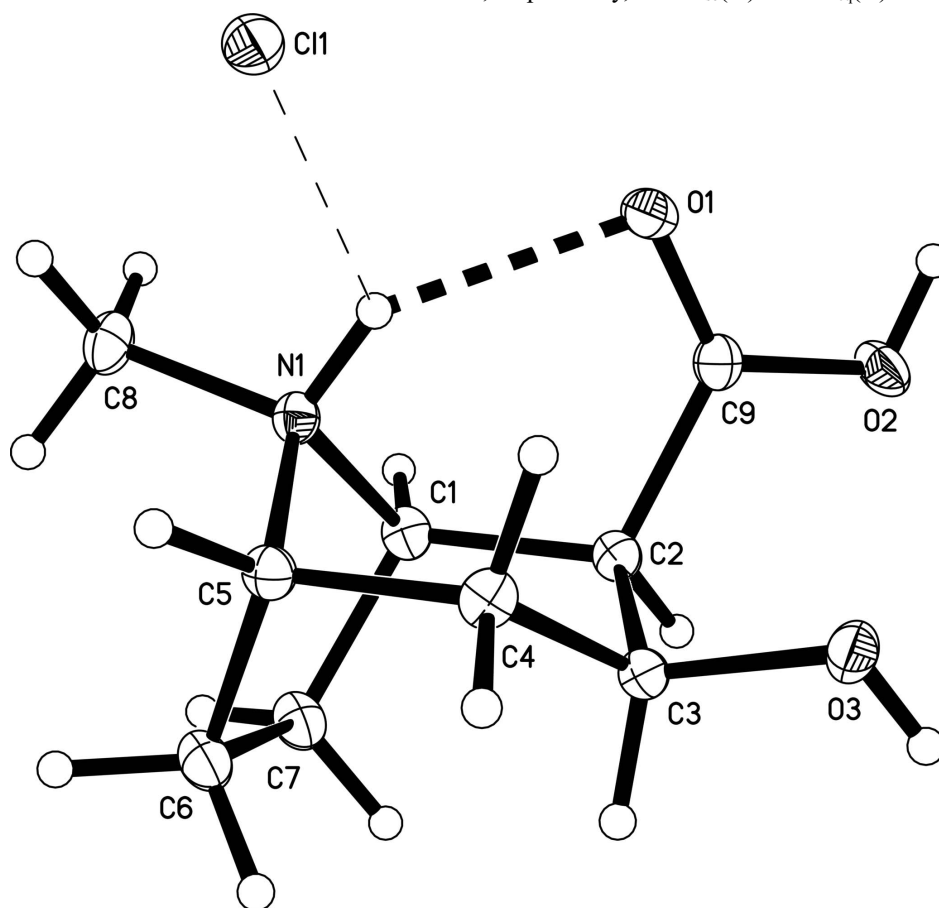

Figure 1

The asymmetric unit for (I), with its numbering. The Cl⁻ counterion is shown in its relation to the nearest positively charged N [3.281616 (13) Å]. The heavy dashed line indicates the intramolecular hydrogen bond, while the thin dashed line denotes the close contact between the amine H1A and the chloride. Displacement ellipsoids are drawn at the 30% probability level.
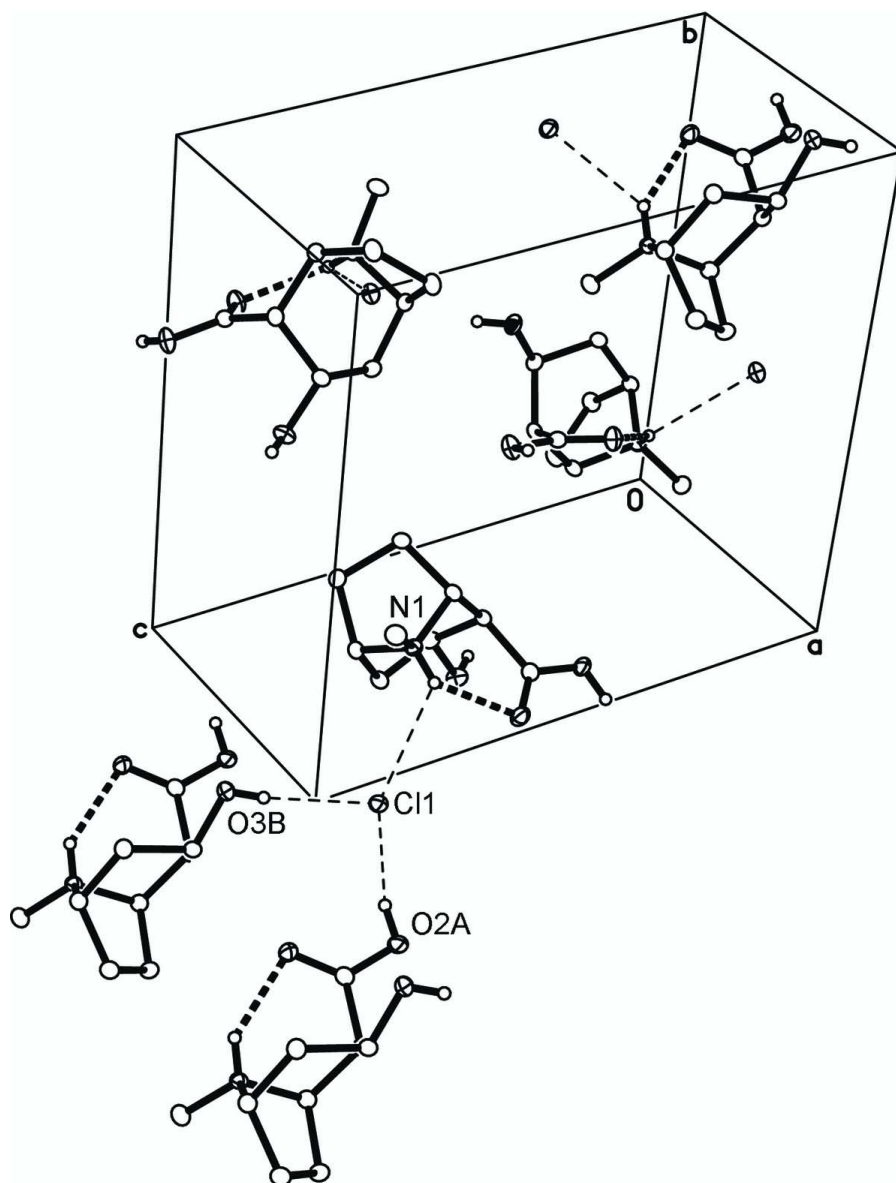
Figure 2

A partial packing diagram with extracellular molecules, showing the hydrogen bonding within each molecule (heavy dashed lines) and the close contacts to the Cl⁻ counterions (thin dashed lines). One Cl⁻ anion is shown with its full trigonal H bonding. For clarity, all C-bound H atoms have been omitted. Displacement ellipsoids are drawn at the 40% probability level.

(1*R*,2*R*,3*S*,5*S*,8*S*)-3-hydroxy-8-methyl-8-azoniabicyclo[3.2.1]octane-2-carboxylic acid chloride

Crystal data

$C_9H_{16}NO_3^+ \cdot Cl^-$	$c = 13.0632$ (8) Å
$M_r = 221.68$	$V = 1054.23$ (11) Å³
Orthorhombic, $P2_12_12_1$	$Z = 4$
Hall symbol: P 2ac 2ab	$F(000) = 472$
$a = 6.6962$ (4) Å	$D_x = 1.397$ Mg m⁻³
$b = 12.0519$ (8) Å	Melting point: 519 K

Cu $K\alpha$ radiation, $\lambda = 1.54178$ Å
Cell parameters from 7772 reflections
$\theta = 5.0–67.9°$
$\mu = 3.09$ mm^{-1}

$T = 100$ K
Plate, colourless
$0.48 \times 0.32 \times 0.09$ mm

Data collection

Bruker SMART CCD APEXII area-detector diffractometer	7772 measured reflections
Radiation source: fine-focus sealed tube	1891 independent reflections
Graphite monochromator	1869 reflections with $I > 2\sigma(I)$
φ and ω scans	$R_{int} = 0.037$
Absorption correction: numerical (*SADABS*; Sheldrick, 2001)	$\theta_{max} = 67.9°$, $\theta_{min} = 5.0°$
$T_{min} = 0.319$, $T_{max} = 0.768$	$h = -8\rightarrow8$
	$k = -14\rightarrow13$
	$l = -15\rightarrow15$

Refinement

Refinement on F^2	Hydrogen site location: inferred from neighbouring sites
Least-squares matrix: full	H atoms treated by a mixture of independent and constrained refinement
$R[F^2 > 2\sigma(F^2)] = 0.026$	
$wR(F^2) = 0.064$	$w = 1/[\sigma^2(F_o^2) + (0.0374P)^2 + 0.1025P]$
$S = 1.09$	where $P = (F_o^2 + 2F_c^2)/3$
1891 reflections	$(\Delta/\sigma)_{max} < 0.001$
140 parameters	$\Delta\rho_{max} = 0.28$ e Å^{-3}
0 restraints	$\Delta\rho_{min} = -0.16$ e Å^{-3}
Primary atom site location: structure-invariant direct methods	Absolute structure: Flack (1983), 766 Friedel pairs
Secondary atom site location: difference Fourier map	Absolute structure parameter: 0.038 (12)

Special details

Experimental. crystal mounted on cryoloop using Paratone-N′

Geometry. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s 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 (Å^2)

	x	y	z	U_{iso}*/U_{eq}
Cl1	1.15082 (5)	0.03004 (3)	0.93490 (2)	0.01911 (12)
O1	1.11678 (16)	0.09863 (10)	0.66307 (8)	0.0223 (3)
N1	0.90975 (18)	0.22175 (10)	0.80625 (10)	0.0151 (3)
H1A	0.993 (3)	0.1724 (15)	0.7911 (13)	0.011 (4)*
C1	0.8277 (2)	0.27231 (12)	0.70884 (11)	0.0166 (3)
H1	0.9205	0.3299	0.6810	0.020*
O2	1.00257 (18)	0.10367 (10)	0.50203 (8)	0.0225 (2)
H2A	1.114 (4)	0.0701 (18)	0.4919 (16)	0.030 (6)*
C2	0.7936 (2)	0.17867 (12)	0.63060 (10)	0.0156 (3)
H2	0.7340	0.2120	0.5675	0.019*

O3	0.65419 (18)	−0.00835 (9)	0.61569 (9)	0.0209 (2)
H3A	0.581 (3)	−0.0049 (18)	0.5697 (17)	0.027 (6)*
C3	0.6447 (2)	0.09137 (11)	0.67333 (11)	0.0167 (3)
H3	0.5062	0.1221	0.6690	0.020*
C4	0.6902 (2)	0.06231 (11)	0.78466 (11)	0.0171 (3)
H4A	0.5763	0.0204	0.8136	0.021*
H4B	0.8093	0.0137	0.7871	0.021*
C5	0.7279 (2)	0.16482 (12)	0.85015 (10)	0.0160 (3)
H5	0.7488	0.1445	0.9236	0.019*
C6	0.5645 (2)	0.25347 (13)	0.83876 (12)	0.0199 (3)
H6A	0.5552	0.2995	0.9013	0.024*
H6B	0.4331	0.2186	0.8258	0.024*
C7	0.6311 (2)	0.32474 (12)	0.74556 (11)	0.0198 (3)
H7A	0.5292	0.3225	0.6907	0.024*
H7B	0.6523	0.4029	0.7662	0.024*
C8	0.9992 (3)	0.30568 (12)	0.87629 (12)	0.0208 (3)
H8A	0.8960	0.3583	0.8980	0.031*
H8B	1.1057	0.3457	0.8404	0.031*
H8C	1.0548	0.2683	0.9365	0.031*
C9	0.9887 (2)	0.12311 (12)	0.60124 (11)	0.0170 (3)

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
Cl1	0.02045 (18)	0.02077 (18)	0.01611 (18)	0.00468 (14)	−0.00101 (13)	0.00132 (12)
O1	0.0185 (6)	0.0301 (6)	0.0183 (5)	0.0077 (5)	−0.0008 (4)	−0.0025 (4)
N1	0.0164 (6)	0.0132 (6)	0.0157 (6)	0.0007 (5)	0.0003 (5)	−0.0015 (5)
C1	0.0207 (7)	0.0145 (6)	0.0146 (7)	0.0008 (6)	0.0011 (6)	0.0021 (5)
O2	0.0237 (6)	0.0285 (6)	0.0153 (5)	0.0099 (5)	0.0032 (4)	−0.0007 (4)
C2	0.0178 (7)	0.0161 (7)	0.0130 (6)	0.0019 (6)	−0.0001 (6)	0.0018 (6)
O3	0.0223 (5)	0.0192 (5)	0.0212 (5)	0.0010 (4)	−0.0055 (5)	−0.0052 (4)
C3	0.0155 (6)	0.0160 (7)	0.0186 (7)	0.0013 (6)	−0.0009 (6)	−0.0031 (5)
C4	0.0190 (7)	0.0152 (7)	0.0171 (7)	−0.0021 (5)	−0.0001 (6)	0.0019 (5)
C5	0.0170 (7)	0.0168 (7)	0.0143 (6)	−0.0007 (6)	0.0015 (6)	0.0014 (5)
C6	0.0213 (8)	0.0215 (8)	0.0168 (7)	0.0036 (6)	0.0025 (6)	−0.0001 (6)
C7	0.0243 (8)	0.0182 (7)	0.0169 (7)	0.0065 (6)	0.0005 (6)	0.0022 (6)
C8	0.0258 (8)	0.0170 (7)	0.0198 (7)	−0.0018 (6)	−0.0034 (7)	−0.0034 (6)
C9	0.0196 (7)	0.0148 (6)	0.0165 (7)	−0.0013 (6)	0.0008 (6)	−0.0003 (5)

Geometric parameters (Å, º)

O1—C9	1.214 (2)	C3—C4	1.5266 (19)
N1—C8	1.4897 (19)	C3—H3	1.0000
N1—C5	1.5106 (18)	C4—C5	1.524 (2)
N1—C1	1.5141 (19)	C4—H4A	0.9900
N1—H1A	0.84 (2)	C4—H4B	0.9900
C1—C7	1.537 (2)	C5—C6	1.536 (2)
C1—C2	1.5397 (19)	C5—H5	1.0000

C1—H1	1.0000	C6—C7	1.555 (2)
O2—C9	1.3202 (18)	C6—H6A	0.9900
O2—H2A	0.86 (3)	C6—H6B	0.9900
C2—C9	1.518 (2)	C7—H7A	0.9900
C2—C3	1.553 (2)	C7—H7B	0.9900
C2—H2	1.0000	C8—H8A	0.9800
O3—C3	1.4196 (17)	C8—H8B	0.9800
O3—H3A	0.78 (2)	C8—H8C	0.9800
C8—N1—C5	113.55 (12)	C3—C4—H4B	109.1
C8—N1—C1	112.88 (11)	H4A—C4—H4B	107.8
C5—N1—C1	102.09 (11)	N1—C5—C4	106.79 (11)
C8—N1—H1A	110.9 (12)	N1—C5—C6	102.78 (12)
C5—N1—H1A	107.8 (12)	C4—C5—C6	113.04 (12)
C1—N1—H1A	109.2 (11)	N1—C5—H5	111.3
N1—C1—C7	102.35 (11)	C4—C5—H5	111.3
N1—C1—C2	108.47 (11)	C6—C5—H5	111.3
C7—C1—C2	112.42 (12)	C5—C6—C7	104.81 (12)
N1—C1—H1	111.1	C5—C6—H6A	110.8
C7—C1—H1	111.1	C7—C6—H6A	110.8
C2—C1—H1	111.1	C5—C6—H6B	110.8
C9—O2—H2A	107.2 (14)	C7—C6—H6B	110.8
C9—C2—C1	111.31 (12)	H6A—C6—H6B	108.9
C9—C2—C3	110.15 (11)	C1—C7—C6	105.24 (12)
C1—C2—C3	110.69 (11)	C1—C7—H7A	110.7
C9—C2—H2	108.2	C6—C7—H7A	110.7
C1—C2—H2	108.2	C1—C7—H7B	110.7
C3—C2—H2	108.2	C6—C7—H7B	110.7
C3—O3—H3A	109.7 (16)	H7A—C7—H7B	108.8
O3—C3—C4	107.59 (11)	N1—C8—H8A	109.5
O3—C3—C2	110.75 (11)	N1—C8—H8B	109.5
C4—C3—C2	111.71 (12)	H8A—C8—H8B	109.5
O3—C3—H3	108.9	N1—C8—H8C	109.5
C4—C3—H3	108.9	H8A—C8—H8C	109.5
C2—C3—H3	108.9	H8B—C8—H8C	109.5
C5—C4—C3	112.45 (11)	O1—C9—O2	124.07 (15)
C5—C4—H4A	109.1	O1—C9—C2	123.17 (13)
C3—C4—H4A	109.1	O2—C9—C2	112.76 (13)
C5—C4—H4B	109.1		
C8—N1—C1—C7	−76.54 (14)	C1—N1—C5—C4	73.48 (13)
C5—N1—C1—C7	45.72 (13)	C8—N1—C5—C6	76.10 (14)
C8—N1—C1—C2	164.47 (12)	C1—N1—C5—C6	−45.70 (13)
C5—N1—C1—C2	−73.27 (13)	C3—C4—C5—N1	−62.00 (15)
N1—C1—C2—C9	−63.62 (15)	C3—C4—C5—C6	50.30 (16)
C7—C1—C2—C9	−176.06 (12)	N1—C5—C6—C7	27.58 (14)
N1—C1—C2—C3	59.24 (15)	C4—C5—C6—C7	−87.15 (14)
C7—C1—C2—C3	−53.20 (15)	N1—C1—C7—C6	−27.97 (14)

C9—C2—C3—O3	−40.45 (15)	C2—C1—C7—C6	88.20 (14)
C1—C2—C3—O3	−163.98 (12)	C5—C6—C7—C1	0.32 (16)
C9—C2—C3—C4	79.46 (14)	C1—C2—C9—O1	43.35 (19)
C1—C2—C3—C4	−44.07 (15)	C3—C2—C9—O1	−79.82 (17)
O3—C3—C4—C5	167.87 (12)	C1—C2—C9—O2	−137.22 (13)
C2—C3—C4—C5	46.12 (16)	C3—C2—C9—O2	99.61 (14)
C8—N1—C5—C4	−164.71 (12)		

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*A*···Cl1	0.84 (2)	2.754 (18)	3.2816 (13)	122.3 (14)
N1—H1*A*···O1	0.84 (2)	2.066 (19)	2.7608 (17)	140 (2)
O2—H2*A*···Cl1[i]	0.86 (3)	2.12 (3)	2.9585 (12)	165 (2)
O3—H3*A*···Cl1[ii]	0.78 (2)	2.37 (2)	3.1332 (12)	169 (2)
C8—H8*B*···O3[iii]	0.98	2.45	3.2280 (19)	136

Symmetry codes: (i) −*x*+5/2, −*y*, *z*−1/2; (ii) −*x*+3/2, −*y*, *z*−1/2; (iii) −*x*+2, *y*+1/2, −*z*+3/2.