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Tetrahydroberberine, a pharmacologically active naturally occurring alkaloid

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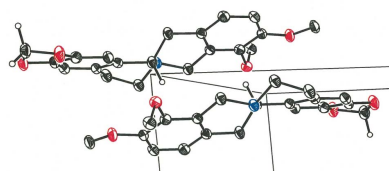
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Tetrahydroberberine (systematic name: 9,10-dimethoxy-5,8,13,13a-tetrahydro-6*H*-benzo[*g*][1,3]benzodioxolo[5,6-*a*]quinolizine), C₂₀H₂₁NO₄, a widely distributed naturally occurring alkaloid, has been crystallized as a racemic mixture about an inversion center. A bent conformation of the molecule is observed, with an angle of 24.72 (5)° between the arene rings at the two ends of the reduced quinolizinium core. The intermolecular hydrogen bonds that play an apparent role in crystal packing are 1,3-benzodioxole —CH₂...OCH₃ and —OCH₃...OCH₃ interactions between neighboring molecules.

1. Introduction

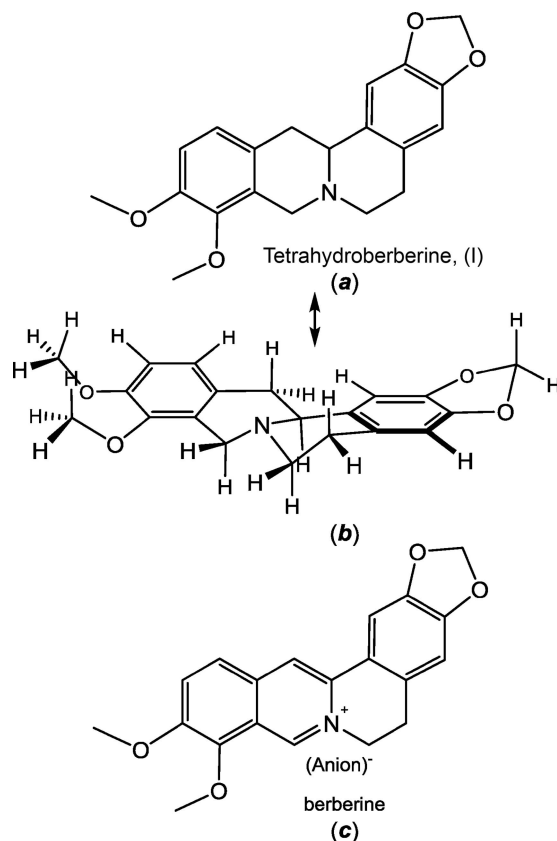
Tetrahydroberberine, also known as canadine and xanthopuccine, is a naturally occurring alkaloid that occurs in widely distributed shrubs, both deciduous and evergreen, of the genus *Berberis*. Berberine (see Scheme 1), the fully oxidized form of the compound, has long been known to exert a broad variety of potentially useful pharmacological and therapeutic properties, ranging from antimalarial (Ho, 2013; Bansal & Silakari, 2014) to anticancer agents (Kaboli *et al.*, 2014; Anwarul Bashar *et al.*, 2014; Ortiz *et al.*, 2014). The understanding of these properties and their application to human medicine continue to be active areas of research. Only more recently has recognition emerged that the fully reduced form of berberine, *i.e.* tetrahydroberberine, has significant pharmacological activity that differs from the parent berberine. For example, in contrast to the cytotoxic effects of berberine, tetrahydroberberine has been reported to show little cytotoxicity toward several lines of cells, but instead to be effective as an antioxidant (Correché *et al.*, 2008). Consequently, it holds promise as an anti-inflammatory agent. Other studies have reported biological effects of tetrahydroberberine and its derivatives as a Ca²⁺ channel blocker (Kubota *et al.*, 1994; Li *et al.*, 1995, 2002; Dai *et al.*, 1996), which enables the induction of vascular muscle relaxation and its use as antihypertension and anti-arrhythmia agents. Tetrahydroberberine has also been observed to block ATP-sensitive K⁺ ion channels that are associated with the pathogenesis of Parkinson's disease (Wu *et al.*, 2010), indicating an important neuroprotective role. Still other research has found an inhibitory effect upon platelet aggregation, suggesting an important role in protecting against thrombosis (Bo *et al.*, 1994).

In earlier work (Pingali *et al.*, 2014), we described the structure of dihydroberberine in the crystalline state and noted that it shows a capacity to engage in CH₂...*X* (*X* = O, N) hydrogen bonding that could have pertinence to the nature of interactions with *in vivo* systems. As noted in that



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report, dihydroberberine and derivatives of it show manifold pharmacological effects that may have use in the treatment of human disease. In a continuing effort to more fully characterize small organic molecules that exert important therapeutic properties, we report the crystal structure of ($\pm$)-tetrahydroberberine, which has heretofore not been described. Earlier works by others have reported the structures of protonated (Sakai *et al.*, 1987) and *N*-methylated (Kamigauchi *et al.*, 2003) forms of tetrahydroberberine and of tetrahydroberberine in a 2:1 complex with (+)-2,3-di-*p*-toluyltartaric acid (Gao *et al.*, 2008).



Scheme 1

2. Experimental

2.1. Synthesis and crystallization

To a stirred refluxing solution of berberine chloride (3.71 g, 10 mmol) and K_2CO_3 (3.6 g, 26 mmol) in MeOH (125 ml), solid $NaBH_4$ (0.4 g, 10 mmol) was added portionwise. The reaction mixture was allowed to reflux for an additional 20 min, during which time it became a homogeneous solution. Stirring was continued for an additional 4 h at ambient temperature, and the precipitated product was then collected by filtration and recrystallized from absolute EtOH (400 ml) to afford 2.6 g (77%) of material as pale-yellow–brown needles (m.p. 447–449 K).

2.2. Spectroscopic data

MS (m/z) 339; 1H NMR (DMSO- d_6): δ 6.90 (s, 1H), 6.87 (d, 1H, $J = 8.4$ Hz), 6.84 (s, 1H, $J = 8.4$ Hz), 6.65 (s, 1H), 5.93 (d,

Table 1

Experimental details.

Crystal data	
Chemical formula	$C_{20}H_{21}NO_4$
M_r	339.38
Crystal system, space group	Monoclinic, $P2_1/n$
Temperature (K)	150
a, b, c (Å)	10.516 (3), 14.796 (5), 10.620 (3)
β (°)	101.986 (4)
V (Å ³)	1616.3 (9)
Z	4
Radiation type	Mo $K\alpha$
μ (mm ⁻¹)	0.10
Crystal size (mm)	0.39 × 0.17 × 0.03
Data collection	
Diffractometer	Bruker SMART APEX CCD diffractometer
Absorption correction	Multi-scan (SADABS; Sheldrick, 2009)
T_{min}, T_{max}	0.650, 0.997
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	23937, 3306, 2468
R_{int}	0.069
$(\sin \theta/\lambda)_{max}$ (Å ⁻¹)	0.625
Refinement	
$R[F^2 > 2\sigma(F^2)], wR(F^2), S$	0.050, 0.132, 1.09
No. of reflections	3306
No. of parameters	310
H-atom treatment	All H-atom parameters refined
$\Delta\rho_{max}, \Delta\rho_{min}$ (e Å ⁻³)	0.25, -0.28

Computer programs: APEX2 (Bruker, 2010), SAINT (Bruker, 2009), SHELXS97 (Sheldrick, 2008), SHELXL2014 (Sheldrick, 2015) and SHELXTL (Bruker, 2008).

2H, $J = 2.4$ Hz), 4.04 (d, 1H, $J = 16.0$ Hz), 3.76 (s, 3H), 3.71 (s, 3H), 3.35 (d, 1H, $J = 16.0$ Hz), 3.27–3.36 (m, 2H), 3.08 (q, 1H, $J = 3.6$ Hz), 2.85–2.93 (m, 1H), 2.61 (m, 1H), 2.55 (q, 1H, $J = 4.0$ Hz), 2.43 (q, 1H, $J = 3.2$ Hz).

2.3. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 1. H atoms were identified in the later difference maps, and their positions were refined, as were their isotropic displacement parameters. The latter were approximately 1.2–1.5 times those of the C atoms to which they were attached.

3. Results and discussion

The structure of tetrahydroberberine, (I), is presented in part (a) of Scheme 1 and rendered three dimensionally in part (b) such that its nonplanarity is emphasized. The compound may be described as a saturated quinolizine system fused at the 1,2-positions to a 1,3-benzodioxole system and to a dimethoxybenzene fragment at the 7,8-positions. The saturation of bonds within the central quinolizine system induces pseudo-chair-type conformations to its two rings and necessitates chirality at the tertiary N atom and at atom C13A. The H atom bound to C13A has an *anti* disposition relative to the electron lone pair of N7 [see part (b) of Scheme 1, and Fig. 1]. In the displacement ellipsoid plot shown in Fig. 1, atoms N7 and C13A display *R* and *S* configurations, respectively. Because of the

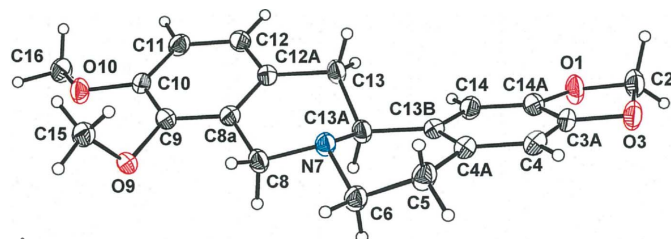


Figure 1

Displacement ellipsoid plot drawn at the 50% probability level, showing the complete atom labeling for tetrahydroberberine.

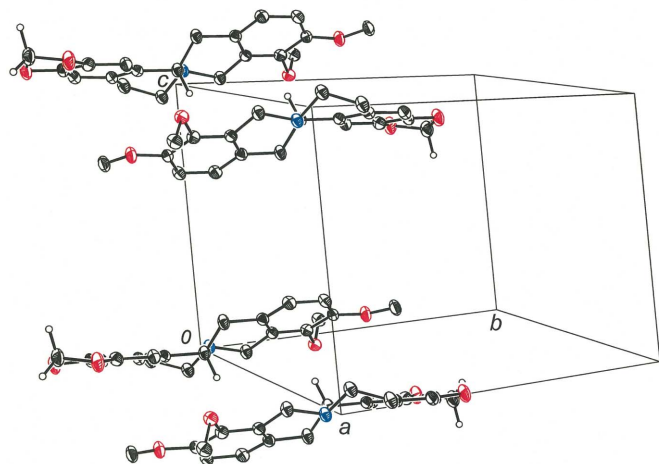


Figure 2

Pairs of tetrahydroberberine enantiomers arranged about the inversion centers at the mid-points of the *a* edges of the unit cell.

centrosymmetry of the space group, the *S* (N7) and *R* (C13A) enantiomer must occur in the cell as well. Pairs of enantiomers are arranged about the inversion centers at the mid-points of the *a* edges of the cell (Fig. 2). The dihedral angle between the C_6 arene groups at the two ends of the molecule is $24.72(5)^\circ$, which is the simplest way to quantify its departure from planarity. The corresponding value in dihydroberberine was observed to be modestly larger at $27.94(5)^\circ$ (Pingali *et al.*, 2014).

Table 2

Hydrogen-bond geometry ($\text{\AA}$, $^\circ$).

<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>
C2—H2B...O10 ⁱ	0.94 (2)	2.58 (2)	3.212 (3)	124.5 (17)
C16—H16A...O9 ⁱⁱ	0.95 (2)	2.53 (2)	3.455 (3)	162.9 (18)

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

A dihedral angle of $31.5(1)^\circ$ between the mean planes of the C_6 arene rings at the ends of the tetrahydroberberine molecule in the 2:1 tetrahydroberberine (+)-2,3-di-*p*-toluyl-tartaric acid complex has been reported (Gao *et al.*, 2008). For a rigid molecule such as tetrahydroberberine, this appreciably larger value is greater than would be plausibly attributed to packing effects or to statistical variance. Our independent assessment of the structure reported by Gao and co-workers finds values of $25(1)$ and $22(1)^\circ$ for the two independent molecules in the unit cell. Rather than being a single optical isomer as reported, the two tetrahydroberberine molecules appear to be enantiomers, and the occurrence of noncentric *P1* as space group appears to be due to the presence of the optically pure (+)-2,3-di-*p*-toluyltartaric acid cocrystallite.

As was found in the crystal structure of dihydroberberine, weak intermolecular hydrogen bonding appears to play a role in governing the packing of molecules in the crystalline state of tetrahydroberberine. A notable difference between the packing arrangements of the two molecules is that tetrahydroberberine molecules are disposed relative to one another in such a way that their tertiary N atoms are unable to engage potential hydrogen-bond donors. Whereas the acetal-type $-\text{CH}_2-$ group of 1,3-benzodioxole of dihydroberberine participates in both $\text{CH}_2\cdots\text{N}$ and $\text{CH}_2\cdots\text{OMe}$ hydrogen bonds with neighboring molecules, only the latter type of hydrogen bond is found in the arrangement of molecules for tetrahydroberberine. As seen in Fig. 3, molecules of tetrahydroberberine related by translation along the *b* axis of the unit cell present the $-\text{CH}_2-$ group of the 1,3-benzodioxole fragment near the methoxy O atom of the next molecule such that it can serve as a hydrogen-bond acceptor (Table 2). Weak

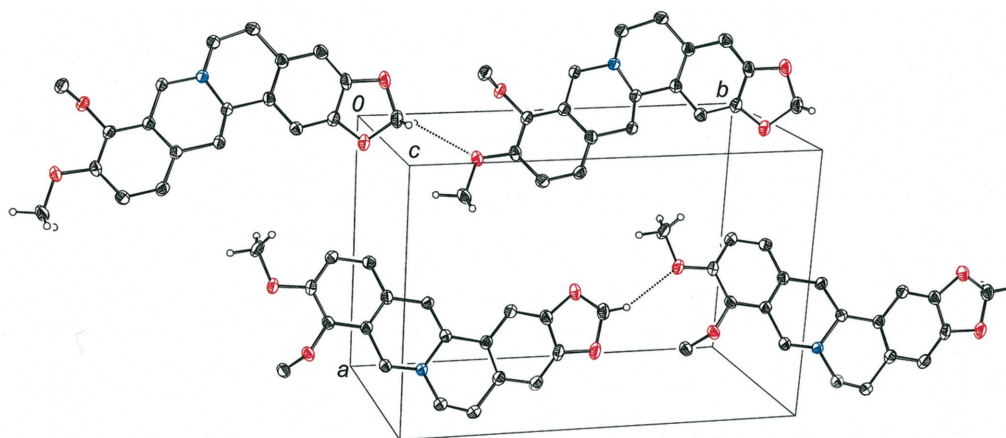


Figure 3

Tetrahydroberberine molecules related by translation along the *b* axis of the unit cell. Dashed lines show the intermolecular $\text{C—H}\cdots\text{OCH}_3$ hydrogen bonds.

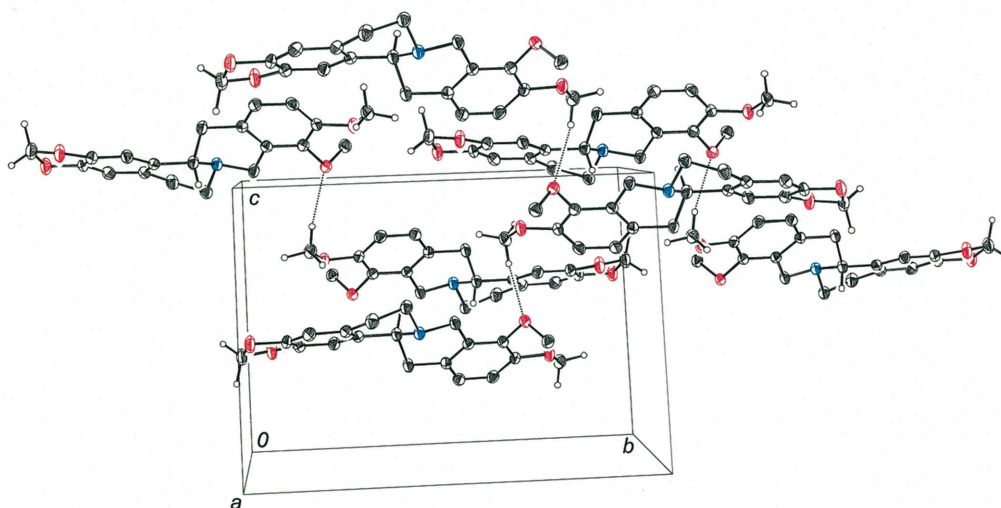


Figure 4

Cell packing diagram for tetrahydroberberine, with intermolecular $\text{OCH}_3 \cdots \text{OCH}_3$ hydrogen bonds shown as dashed lines.

hydrogen bonding may also be operative between a methoxy H atom of one molecule and the methoxy O atom of an adjoining molecule further along in the direction of the *c* axis of the unit cell (Fig. 4 and Table 2). These intermolecular hydrogen bonds are undoubtedly weaker than those involving the acetal-type $-\text{CH}_2-$ hydrogens, as the latter are more activated by the proximity of two electronegative O atoms rather than one.

Much remains to be learned about the physical and chemical underpinnings of the pharmacological activity of tetrahydroberberine. The capacity for tetrahydroberberine to act as both hydrogen-bond donor and acceptor suggest that this property be considered as a key basis for some of its selective activity *in vivo*.

Acknowledgements

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References

- Anwarul Bashar, A. B. M., Hossain, Md. S., Jahan, R., Al-Nahain, A., Mahmudul Haque, A. K. M. & Rahmatullah, M. (2014). *World J. Pharm. Pharm. Sci.* **3**, 1858–1869.

- Bansal, Y. & Silakari, O. (2014). *Eur. J. Med. Chem.* **76**, 31–42.
- Bo, X., Wei, W. & De-Xin, L. (1994). *Acta Pharmacol. Sin.* **15**, 133–135.
- Bruker (2008). *SHELXTL*. Bruker AXS Inc., Madison, Wisconsin, USA.
- Bruker (2009). *SAINT*. Bruker AXS Inc., Madison, Wisconsin, USA.
- Bruker (2010). *APEX2*. Bruker AXS Inc., Madison, Wisconsin, USA.
- Correché, E. R., Andujar, S. A., Kurdalas, R. R., Gómez-Lechón, M. J., Freile, M. L. & Enriz, R. D. (2008). *Bioorg. Med. Chem.* **16**, 3641–1651.
- Dai, D.-Z., Yu, F., Li, H.-T., Tang, Y.-Q., An, L.-F., Huang, W.-L., Peng, S.-X., Hao, X.-M., Zhou, B.-A. & Hu, C.-H. (1996). *Drug Develop. Res.* **39**, 138–146.
- Gao, J.-M., Liu, W.-T., Li, M.-L., Liu, H.-W., Zhang, X.-C. & Li, Z.-X. (2008). *J. Mol. Struct.* **892**, 466–469.
- Ho, J. W. S. (2013). *Anti-Infect. Agents*, **11**, 70–74.
- Kaboli, P. J., Rahmat, A., Ismail, P. & Ling, K.-H. (2014). *Eur. J. Pharmacol.* **740**, 584–595.
- Kamigauchi, M., Yoshida, M., Noda, Y., Nishijo, J., In, Y., Tomoo, K., Ohishi, H. & Ishida, T. (2003). *Bull. Chem. Soc. Jpn*, **76**, 587–593.
- Kubota, K., Morota, T., Yano, S. & Watanabe, K. (1994). Jpn Kokai Tokkyo Koho JP 06072876 A 19940315.
- Li, C., Guo, J. & Liu, T. (2002). *Zhonghua Yixue Zazhi*, **82**, 57–60.
- Li, X. T., Wang, W. L., Wang, J. X. & Yang, S. J. (1995). *Yaoxue Xuebao*, **30**, 567–572.
- Ortiz, L. M. G., Lombardi, P., Tillhon, M. & Scovassi, A. I. (2014). *Molecules*, **19**, 12349–12367.
- Pingali, S., Donahue, J. P. & Payton-Stewart, F. (2014). *Acta Cryst.* **C70**, 388–391.
- Sakai, T., Taira, Z., Kamigauchi, M. & Takao, N. (1987). *Acta Cryst.* **C43**, 98–101.
- Sheldrick, G. M. (2008). *Acta Cryst.* **A64**, 112–122.
- Sheldrick, G. M. (2009). *SADABS*. University of Göttingen, Germany.
- Sheldrick, G. M. (2015). *Acta Cryst.* **C71**, 3–8.
- Wu, C., Yang, K., Liu, Q., Wakui, M., Jin, G.-Z., Zhen, X. & Wu, J. (2010). *Neuropharmacology*, **59**, 567–572.

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Computing details

Data collection: *APEX2* (Bruker, 2010); cell refinement: *SAINT* (Bruker, 2009); data reduction: *SAINT* (Bruker, 2009); program(s) used to solve structure: *SHELXS* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL2014* (Sheldrick, 2015); molecular graphics: *SHELXTL* (Bruker, 2008); software used to prepare material for publication: *SHELXTL* (Bruker, 2008).

9,10-Dimethoxy-5,8,13,13a-tetrahydro-6H-benzo[g][1,3]benzodioxolo[5,6-a]quinolizine

Crystal data

$C_{20}H_{21}NO_4$

$M_r = 339.38$

Monoclinic, $P2_1/n$

$a = 10.516$ (3) Å

$b = 14.796$ (5) Å

$c = 10.620$ (3) Å

$\beta = 101.986$ (4)°

$V = 1616.3$ (9) Å³

$Z = 4$

$F(000) = 720$

$D_x = 1.395$ Mg m⁻³

Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å

Cell parameters from 7019 reflections

$\theta = 2.4$ – 28.8 °

$\mu = 0.10$ mm⁻¹

$T = 150$ K

Needle, pale yellow

$0.39 \times 0.17 \times 0.03$ mm

Data collection

Bruker SMART APEX CCD
diffractometer

Radiation source: fine-focus sealed tube

Graphite monochromator

φ and ω scans

Absorption correction: multi-scan
(SADABS; Sheldrick, 2009)

$T_{\min} = 0.650$, $T_{\max} = 0.997$

23937 measured reflections

3306 independent reflections

2468 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.069$

$\theta_{\max} = 26.4$ °, $\theta_{\min} = 2.4$ °

$h = -13 \rightarrow 13$

$k = -18 \rightarrow 18$

$l = -13 \rightarrow 13$

Refinement

Refinement on F^2

Least-squares matrix: full

$R[F^2 > 2\sigma(F^2)] = 0.050$

$wR(F^2) = 0.132$

$S = 1.09$

3306 reflections

310 parameters

0 restraints

Primary atom site location: structure-invariant
direct methods

Secondary atom site location: difference Fourier
map

Hydrogen site location: difference Fourier map

All H-atom parameters refined

$w = 1/[\sigma^2(F_o^2) + (0.0723P)^2 + 0.074P]$

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

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

$\Delta\rho_{\max} = 0.25$ e Å⁻³

$\Delta\rho_{\min} = -0.28$ e Å⁻³

Special details

Experimental. The diffraction data were obtained from 3 sets of 400 frames, each of width 0.5° in ω , collected at $\varphi = 0.00, 90.00$ and 180.00° and 2 sets of 800 frames, each of width 0.45° in φ , collected at $\omega = -30.00$ and 210.00° . The scan time was 60 sec per frame.

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.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($\text{\AA}^2$)

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
O1	0.01598 (13)	0.06160 (9)	0.36706 (14)	0.0336 (4)
O3	0.22930 (14)	0.01051 (9)	0.41434 (14)	0.0354 (4)
O9	0.17222 (12)	0.72123 (8)	0.45030 (11)	0.0239 (3)
O10	-0.04453 (12)	0.79326 (8)	0.30532 (13)	0.0280 (3)
N7	0.25961 (14)	0.44323 (10)	0.43049 (14)	0.0221 (4)
C2	0.0985 (2)	-0.01444 (14)	0.3572 (2)	0.0343 (5)
H2A	0.0936 (18)	-0.0300 (14)	0.259 (2)	0.031 (5)*
H2B	0.073 (2)	-0.0622 (16)	0.405 (2)	0.042 (6)*
C3A	0.22800 (19)	0.10373 (12)	0.41602 (18)	0.0268 (4)
C4	0.33017 (19)	0.16167 (13)	0.44905 (18)	0.0272 (4)
H4	0.425 (2)	0.1429 (13)	0.4669 (19)	0.035 (6)*
C4A	0.30206 (18)	0.25497 (13)	0.45153 (17)	0.0238 (4)
C5	0.41270 (19)	0.32064 (14)	0.4927 (2)	0.0287 (5)
H5A	0.461 (2)	0.3298 (15)	0.426 (2)	0.039 (6)*
H5B	0.479 (2)	0.2963 (13)	0.563 (2)	0.033 (6)*
C6	0.36381 (18)	0.40983 (13)	0.5335 (2)	0.0262 (4)
H6A	0.4355 (16)	0.4541 (12)	0.5470 (17)	0.017 (5)*
H6B	0.3344 (18)	0.4026 (13)	0.617 (2)	0.026 (5)*
C8	0.22941 (18)	0.53680 (12)	0.4588 (2)	0.0242 (4)
H8A	0.3083 (19)	0.5739 (15)	0.452 (2)	0.036 (6)*
H8B	0.2145 (17)	0.5424 (13)	0.5490 (19)	0.024 (5)*
C8A	0.10988 (16)	0.57312 (12)	0.37059 (17)	0.0212 (4)
C9	0.08419 (17)	0.66546 (12)	0.37020 (17)	0.0219 (4)
C10	-0.02979 (18)	0.70131 (12)	0.29698 (17)	0.0226 (4)
C11	-0.11958 (18)	0.64397 (13)	0.22179 (18)	0.0255 (4)
H11	-0.2030 (19)	0.6661 (13)	0.1691 (19)	0.028 (5)*
C12	-0.09305 (18)	0.55190 (13)	0.22067 (18)	0.0251 (4)
H12	-0.1505 (19)	0.5118 (13)	0.1677 (19)	0.029 (5)*
C12A	0.01994 (17)	0.51544 (12)	0.29443 (17)	0.0223 (4)
C13	0.04806 (19)	0.41507 (12)	0.29529 (19)	0.0254 (4)
H13A	0.0904 (17)	0.3990 (13)	0.216 (2)	0.028 (5)*
H13B	-0.0306 (19)	0.3836 (13)	0.2815 (19)	0.029 (5)*
C13A	0.14229 (17)	0.38655 (12)	0.41905 (18)	0.0225 (4)
H13C	0.1002 (19)	0.3994 (14)	0.499 (2)	0.039 (6)*
C13B	0.17429 (17)	0.28614 (12)	0.41996 (17)	0.0215 (4)
C14	0.07047 (18)	0.22417 (12)	0.38865 (18)	0.0244 (4)

H14	−0.023 (2)	0.2423 (14)	0.3727 (19)	0.033 (6)*
C14A	0.10102 (18)	0.13438 (12)	0.38828 (18)	0.0257 (4)
C15	0.2498 (2)	0.77260 (14)	0.3804 (2)	0.0272 (5)
H15A	0.3058 (19)	0.7324 (14)	0.3347 (19)	0.030 (5)*
H15B	0.313 (2)	0.8061 (16)	0.440 (2)	0.049 (7)*
H15C	0.1959 (18)	0.8084 (13)	0.3141 (19)	0.024 (5)*
C16	−0.1724 (2)	0.82776 (15)	0.2625 (2)	0.0320 (5)
H16A	−0.199 (2)	0.8207 (15)	0.172 (2)	0.040 (6)*
H16B	−0.234 (2)	0.7982 (15)	0.311 (2)	0.046 (7)*
H16C	−0.167 (2)	0.8946 (16)	0.283 (2)	0.038 (6)*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0357 (8)	0.0156 (7)	0.0466 (9)	−0.0020 (6)	0.0016 (7)	−0.0014 (6)
O3	0.0438 (9)	0.0155 (7)	0.0424 (9)	0.0039 (6)	−0.0016 (7)	0.0015 (6)
O9	0.0281 (7)	0.0195 (7)	0.0224 (7)	−0.0054 (5)	0.0010 (5)	−0.0020 (5)
O10	0.0313 (7)	0.0163 (7)	0.0340 (8)	0.0037 (5)	0.0010 (6)	0.0012 (6)
N7	0.0207 (8)	0.0176 (8)	0.0252 (8)	0.0000 (6)	−0.0014 (6)	0.0002 (6)
C2	0.0428 (12)	0.0173 (10)	0.0401 (13)	0.0012 (9)	0.0021 (10)	−0.0018 (9)
C3A	0.0382 (11)	0.0154 (9)	0.0249 (10)	0.0035 (8)	0.0019 (8)	0.0020 (8)
C4	0.0284 (10)	0.0256 (10)	0.0258 (10)	0.0050 (8)	0.0015 (8)	0.0037 (9)
C4A	0.0271 (10)	0.0212 (10)	0.0221 (10)	0.0029 (8)	0.0027 (8)	0.0020 (8)
C5	0.0239 (10)	0.0251 (11)	0.0341 (12)	0.0017 (8)	−0.0012 (9)	0.0039 (9)
C6	0.0247 (10)	0.0220 (10)	0.0288 (11)	−0.0003 (8)	−0.0014 (8)	0.0018 (8)
C8	0.0248 (10)	0.0174 (9)	0.0276 (11)	−0.0018 (8)	−0.0012 (8)	−0.0024 (8)
C8A	0.0224 (9)	0.0201 (9)	0.0202 (9)	−0.0003 (7)	0.0025 (7)	0.0008 (8)
C9	0.0235 (9)	0.0198 (9)	0.0214 (9)	−0.0039 (7)	0.0022 (7)	−0.0010 (8)
C10	0.0290 (10)	0.0171 (9)	0.0219 (9)	0.0023 (7)	0.0057 (8)	0.0023 (7)
C11	0.0252 (10)	0.0242 (10)	0.0251 (10)	0.0015 (8)	0.0004 (8)	0.0046 (8)
C12	0.0256 (10)	0.0231 (10)	0.0237 (10)	−0.0029 (8)	−0.0015 (8)	−0.0010 (8)
C12A	0.0253 (9)	0.0189 (9)	0.0216 (9)	−0.0003 (7)	0.0025 (7)	0.0001 (8)
C13	0.0254 (10)	0.0167 (9)	0.0296 (11)	0.0004 (8)	−0.0047 (8)	−0.0020 (8)
C13A	0.0220 (9)	0.0173 (9)	0.0268 (10)	−0.0012 (7)	0.0016 (8)	−0.0011 (8)
C13B	0.0253 (9)	0.0195 (9)	0.0186 (9)	0.0014 (7)	0.0019 (7)	0.0004 (7)
C14	0.0251 (10)	0.0204 (10)	0.0264 (10)	0.0015 (8)	0.0022 (8)	0.0017 (8)
C14A	0.0306 (10)	0.0206 (10)	0.0243 (10)	−0.0039 (8)	0.0019 (8)	−0.0006 (8)
C15	0.0289 (11)	0.0236 (11)	0.0270 (11)	−0.0054 (9)	0.0014 (9)	0.0016 (9)
C16	0.0360 (12)	0.0234 (11)	0.0323 (12)	0.0096 (9)	−0.0031 (9)	0.0030 (9)

Geometric parameters (Å, °)

O1—C14A	1.388 (2)	C8—H8A	1.01 (2)
O1—C2	1.438 (2)	C8—H8B	1.005 (19)
O3—C3A	1.379 (2)	C8A—C9	1.393 (3)
O3—C2	1.431 (3)	C8A—C12A	1.400 (2)
O9—C9	1.391 (2)	C9—C10	1.391 (2)
O9—C15	1.430 (2)	C10—C11	1.391 (3)

O10—C10	1.374 (2)	C11—C12	1.391 (3)
O10—C16	1.422 (2)	C11—H11	0.99 (2)
N7—C6	1.464 (2)	C12—C12A	1.389 (3)
N7—C8	1.466 (2)	C12—H12	0.94 (2)
N7—C13A	1.476 (2)	C12A—C13	1.514 (2)
C2—H2A	1.06 (2)	C13—C13A	1.532 (3)
C2—H2B	0.94 (2)	C13—H13A	1.06 (2)
C3A—C4	1.362 (3)	C13—H13B	0.93 (2)
C3A—C14A	1.383 (3)	C13A—C13B	1.523 (2)
C4—C4A	1.413 (3)	C13A—H13C	1.05 (2)
C4—H4	1.01 (2)	C13B—C14	1.411 (3)
C4A—C13B	1.394 (3)	C14—C14A	1.367 (3)
C4A—C5	1.509 (3)	C14—H14	1.00 (2)
C5—C6	1.512 (3)	C15—H15A	1.03 (2)
C5—H5A	0.96 (2)	C15—H15B	0.96 (2)
C5—H5B	0.98 (2)	C15—H15C	0.97 (2)
C6—H6A	0.987 (18)	C16—H16A	0.95 (2)
C6—H6B	1.00 (2)	C16—H16B	1.01 (2)
C8—C8A	1.503 (2)	C16—H16C	1.01 (2)
C14A—O1—C2	103.91 (15)	O10—C10—C9	115.91 (16)
C3A—O3—C2	104.61 (14)	O10—C10—C11	124.64 (16)
C9—O9—C15	112.13 (14)	C9—C10—C11	119.45 (17)
C10—O10—C16	116.53 (15)	C12—C11—C10	119.25 (17)
C6—N7—C8	109.01 (14)	C12—C11—H11	118.2 (12)
C6—N7—C13A	110.66 (14)	C10—C11—H11	122.5 (12)
C8—N7—C13A	109.92 (14)	C12A—C12—C11	121.67 (17)
O3—C2—O1	107.99 (16)	C12A—C12—H12	117.3 (12)
O3—C2—H2A	108.7 (11)	C11—C12—H12	121.0 (12)
O1—C2—H2A	109.6 (11)	C12—C12A—C8A	119.03 (17)
O3—C2—H2B	108.7 (13)	C12—C12A—C13	121.83 (16)
O1—C2—H2B	107.9 (14)	C8A—C12A—C13	119.14 (16)
H2A—C2—H2B	113.9 (18)	C12A—C13—C13A	111.48 (15)
C4—C3A—O3	128.55 (17)	C12A—C13—H13A	109.2 (11)
C4—C3A—C14A	121.57 (17)	C13A—C13—H13A	108.5 (10)
O3—C3A—C14A	109.69 (16)	C12A—C13—H13B	108.8 (12)
C3A—C4—C4A	117.56 (17)	C13A—C13—H13B	113.0 (12)
C3A—C4—H4	124.6 (11)	H13A—C13—H13B	105.6 (16)
C4A—C4—H4	117.8 (11)	N7—C13A—C13B	111.97 (15)
C13B—C4A—C4	120.90 (17)	N7—C13A—C13	107.14 (15)
C13B—C4A—C5	120.22 (17)	C13B—C13A—C13	112.15 (15)
C4—C4A—C5	118.86 (16)	N7—C13A—H13C	108.4 (11)
C4A—C5—C6	110.94 (16)	C13B—C13A—H13C	107.5 (12)
C4A—C5—H5A	111.9 (13)	C13—C13A—H13C	109.6 (11)
C6—C5—H5A	110.6 (13)	C4A—C13B—C14	120.10 (17)
C4A—C5—H5B	111.7 (12)	C4A—C13B—C13A	121.66 (16)
C6—C5—H5B	109.3 (12)	C14—C13B—C13A	118.23 (16)
H5A—C5—H5B	102.0 (17)	C14A—C14—C13B	117.47 (17)

N7—C6—C5	109.04 (16)	C14A—C14—H14	119.0 (12)
N7—C6—H6A	108.4 (10)	C13B—C14—H14	123.4 (12)
C5—C6—H6A	109.0 (10)	C14—C14A—C3A	122.36 (17)
N7—C6—H6B	112.1 (11)	C14—C14A—O1	127.64 (17)
C5—C6—H6B	110.2 (11)	C3A—C14A—O1	109.95 (16)
H6A—C6—H6B	108.1 (15)	O9—C15—H15A	112.4 (11)
N7—C8—C8A	113.50 (15)	O9—C15—H15B	108.8 (14)
N7—C8—H8A	106.5 (12)	H15A—C15—H15B	103.1 (17)
C8A—C8—H8A	110.9 (12)	O9—C15—H15C	111.0 (11)
N7—C8—H8B	110.9 (11)	H15A—C15—H15C	106.3 (16)
C8A—C8—H8B	106.8 (10)	H15B—C15—H15C	114.9 (18)
H8A—C8—H8B	108.2 (16)	O10—C16—H16A	110.4 (13)
C9—C8A—C12A	119.28 (16)	O10—C16—H16B	110.4 (13)
C9—C8A—C8	119.31 (15)	H16A—C16—H16B	112.3 (19)
C12A—C8A—C8	121.31 (16)	O10—C16—H16C	105.8 (12)
O9—C9—C10	120.16 (16)	H16A—C16—H16C	108.3 (19)
O9—C9—C8A	118.43 (15)	H16B—C16—H16C	109.3 (18)
C10—C9—C8A	121.32 (16)		

Hydrogen-bond geometry (Å, °)

<i>D</i> —H $\cdots$ <i>A</i>	<i>D</i> —H	H $\cdots$ <i>A</i>	<i>D</i> $\cdots$ <i>A</i>	<i>D</i> —H $\cdots$ <i>A</i>
C2—H2B $\cdots$ O10 ⁱ	0.94 (2)	2.58 (2)	3.212 (3)	124.5 (17)
C16—H16A $\cdots$ O9 ⁱⁱ	0.95 (2)	2.53 (2)	3.455 (3)	162.9 (18)

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