

Bufotenidinium iodide

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Received 2 February 2021

Accepted 2 February 2021

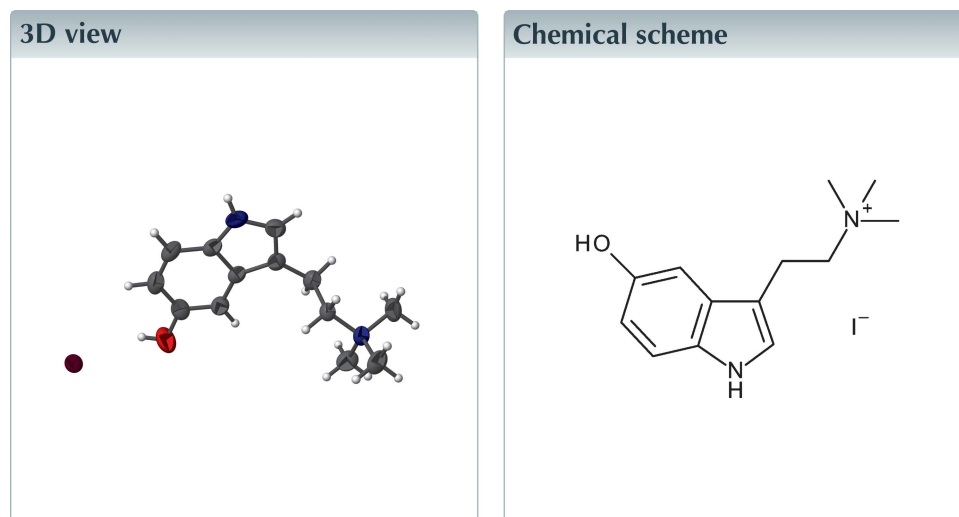
Edited by M. Bolte, Goethe-Universität Frankfurt, Germany

Keywords: crystal structure; natural product; tryptamines; indoles; hydrogen bonding.

CCDC reference: 2060560

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

The title compound, 5-hydroxy-*N,N,N*-trimethyltryptammonium (5-HTQ) iodide {systematic name: [2-(5-hydroxy-1*H*-indol-3-yl)ethyl]trimethylazanium iodide}, C₁₃H₁₉N₂O⁺·I[−], has a single tryptammonium cation and one iodide anion in the asymmetric unit. The ions are held together by N—H···I and O—H···I hydrogen bonds in infinite chains along [100].



Structure description

Bufotenidine, the *N,N,N*-trimethyl analog of serotonin, was first identified in toad secretions in 1934 (Wieland *et al.*, 1934). This is one of many indoalkylamines found in the secretions of the Colorado River toad, including bufotenine (5-hydroxy-*N,N*-dimethyltryptamine), 5-MeO-DMT (5-methoxy-*N,N*-dimethyltryptamine), 5-methoxytryptophol, and bufoviridine. The primary psychedelic in these secretions, 5-MeO-DMT, has been studied individually to treat anxiety and depression (Davis *et al.*, 2019). The inhalation of vaporized dried toad secretions has also been examined in the treatment of depression, anxiety and stress (Uthaug *et al.*, 2019). As this area of research continues, it will be important to understand the difference between pure 5-MeO-DMT and natural toad secretions, to understand the significance of each component, and examine if an entourage effect is present (Bauer, 2020). To this end, we have begun to examine some of the minor components of these secretions, and report the first single-crystal structure of the natural product bufotenidine herein.

In the solid-state structure of bufotenidine iodide, the 5-hydroxy-*N,N,N*-trimethyltryptammonium cation and the iodide anion are held together in the asymmetric unit *via* O—H···I hydrogen bonds (Fig. 1). The cation possesses a near planar indole group with a mean deviation from planarity of 0.010 Å. The ethylamino group is turned away from the plane with a C1—C8—C9—C10 torsion angle of 92.6 (3)°. The N—H of the indole ring hydrogen bonds with a symmetry generated iodide. The N—H···I and O—H···I

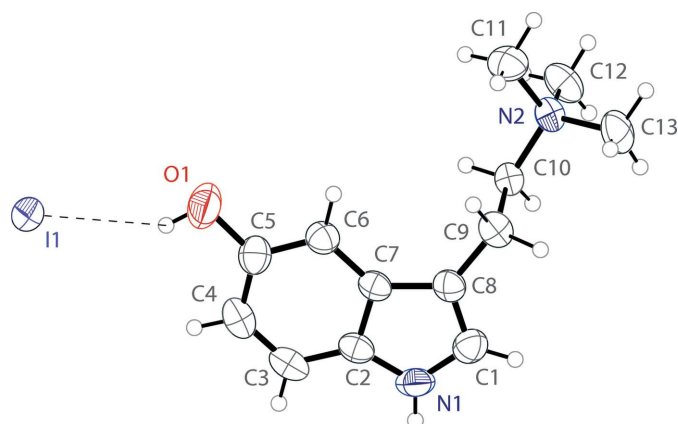


Figure 1
The molecular structure of 5-hydroxy-*N,N,N*-trimethyltryptammonium (5-HTQ) iodide, showing the atom labeling. Displacement ellipsoids are drawn at the 50% probability level. A hydrogen bond is shown as a dashed line.

hydrogen bonds (Table 1) link the ions together in infinite chains along the [100] direction with graph-set notation $C_2^1(9)$ (Etter *et al.*, 1990). The packing of 5-HTQ iodide is shown in Fig. 2.

The structure of the closely related natural product from toad secretions, bufotenine, 5-hydroxy-*N,N*-dimethyltryptamine (BUFTEN; Falkenberg, 1972) has been previously reported. There are only six reported structures of quaternary

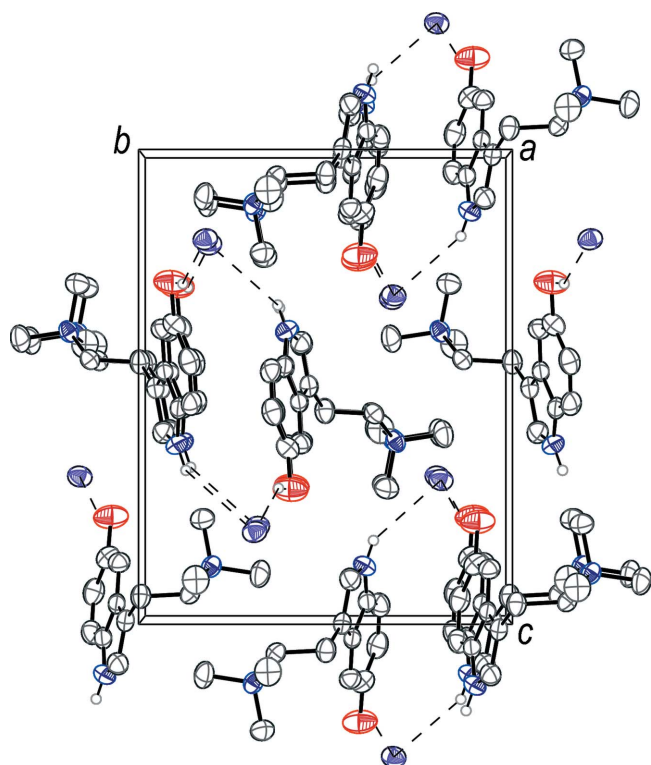


Figure 2
The crystal packing of 5-hydroxy-*N,N,N*-trimethyltryptammonium (5-HTQ) iodide, viewed along the *a* axis. The hydrogen bonds (Table 1) are shown as dashed lines. Displacement ellipsoids are drawn at the 50% probability level. Hydrogen atoms not involved in hydrogen bonds are omitted for clarity.

Table 1
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—H1A...I1 ⁱ	0.85 (1)	2.89 (2)	3.662 (2)	152 (3)
O1—H1...I1	0.85 (1)	2.72 (3)	3.468 (2)	147 (4)

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

Table 2
Experimental details.

Crystal data	
Chemical formula	$C_{13}H_{19}N_2O^+ \cdot I^-$
M_r	346.20
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Temperature (K)	297
<i>a</i> , <i>b</i> , <i>c</i> (Å)	8.9944 (4), 11.3250 (6), 14.4042 (7)
<i>V</i> (Å ³)	1467.23 (12)
<i>Z</i>	4
Radiation type	Mo $K\alpha$
μ (mm ⁻¹)	2.17
Crystal size (mm)	0.25 × 0.19 × 0.18
Data collection	
Diffractometer	Bruker D8 Venture CMOS
Absorption correction	Multi-scan (SADABS; Bruker, 2018)
T_{min} , T_{max}	0.672, 0.745
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	45268, 2937, 2866
R_{int}	0.023
($\sin \theta/\lambda$) _{max} (Å ⁻¹)	0.625
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, <i>S</i>	0.013, 0.032, 1.08
No. of reflections	2937
No. of parameters	165
No. of restraints	2
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å ⁻³)	0.42, -0.37
Absolute structure	Flack <i>x</i> determined using 1216 quotients $[(I^+) - (I^-)] / [(I^+) + (I^-)]$ (Parsons <i>et al.</i> , 2013)
Absolute structure parameter	-0.021 (4)

Computer programs: APEX3 and SAINT (Bruker, 2018), SHELXT2014 (Sheldrick, 2015b), SHELXL2018 (Sheldrick, 2015a), OLEX2 (Dolomanov *et al.*, 2009) and publCIF (Westrip, 2010).

tryptamines, which are all from the past year. Those are the iodide salts of 4-hydroxy-*N,N,N*-trimethyltryptamine (4-HO-TMT) and 4-acetoxy-*N,N,N*-trimethyltryptamine (4-AcO-TMT) (XUXFAA and XUXDUS; Chadeayne, Pham, Reid *et al.*, 2020), *N,N*-dimethyl-*N-n*-propyltryptamine (DMPT) and *N,N*-dimethyl-*N*-allyltryptamine (DMALT) (CCDC 2017817 and CCDC 2017818; Chadeayne, Pham, Golen & Manke, 2020), 5-methoxy-2-methyl-*N,N,N*-trimethyltryptamine (5-MeO-2-Me-TMT) and its hydrate (CCDC 2058144 and CCDC 2058145; Pham *et al.*, 2021).

Synthesis and crystallization

5-Hydroxy-*N,N,N*-trimethyltryptammonium iodide was prepared according to literature procedure (Adhikari *et al.*, 2015), and crystals suitable for diffraction study were grown from the evaporation of a methanol solution.

Refinement

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

Acknowledgements

Financial statements and conflict of interest: This study was funded by CaaMTech, Inc. ARC reports an ownership interest in CaaMTech, Inc., which owns US and worldwide patent applications, covering new tryptamine compounds, compositions, formulations, novel crystalline forms, and methods of making and using the same.

Funding information

Funding for this research was provided by: National Science Foundation, Directorate for Mathematical and Physical Sciences (grant No. CHE-1429086).

References

- Adhikari, B. B., Roshandel, S., Fujii, A. & Schramm, M. P. (2015). *Eur. J. Org. Chem.* **2015**, 2683–2690.
- Bauer, B. E. (2020). *Psychedelic Science Review*. <https://psychedelicreview.com/hamilton-morris-on-5-meo-dmt-the-entourage-effect-and-protecting-toads/>
- Bruker (2018). *APEX3, SAINT, and SADABS*. Bruker AXS Inc., Madison, Wisconsin, USA.
- Chadeayne, A. R., Pham, D. N. K., Golen, J. A. & Manke, D. R. (2020). *Acta Cryst.* **E76**, 1357–1360.
- Chadeayne, A. R., Pham, D. N. K., Reid, B. G., Golen, J. A. & Manke, D. R. (2020). *ACS Omega*, **5**, 16940–16943.
- Davis, A. K., So, S., Lancelotta, R., Barsuglia, J. P. & Griffiths, R. R. (2019). *Am. J. Drug Alcohol Abuse*, **45**, 161–169.
- Dolomanov, O. V., Bourhis, L. J., Gildea, R. J., Howard, J. A. K. & Puschmann, H. (2009). *J. Appl. Cryst.* **42**, 339–341.
- Etter, M. C., MacDonald, J. C. & Bernstein, J. (1990). *Acta Cryst.* **B46**, 256–262.
- Falkenberg, G. (1972). *Acta Cryst.* **B28**, 3219–3228.
- Parsons, S., Flack, H. D. & Wagner, T. (2013). *Acta Cryst.* **B69**, 249–259.
- Pham, D. N. K., Chadeayne, A. R., Golen, J. A. & Manke, D. R. (2021). *Acta Cryst.* **E77**, 190–194.
- Sheldrick, G. M. (2015a). *Acta Cryst.* **A71**, 3–8.
- Sheldrick, G. M. (2015b). *Acta Cryst.* **C71**, 3–8.
- Uthaug, M. V., Lancelotta, R., van Oorsouw, K., Kuypers, K. P. C., Mason, N., Rak, J., Šuláková, A., Jurok, R., Maryška, M., Kuchař, M., Páleníček, T., Riba, J. & Ramaekers, J. G. (2019). *Psychopharmacology*, **236**, 2653–2666.
- Westrip, S. P. (2010). *J. Appl. Cryst.* **43**, 920–925.
- Wieland, H., Konz, W. & Mittasch, H. (1934). *Justus Liebigs Ann. Chem.* **513**, 1–25.

full crystallographic data

IUCrData (2021). 6, x210123 [https://doi.org/10.1107/S2414314621001231]

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[2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]trimethylazanium iodide*Crystal data*

$C_{13}H_{19}N_2O^+ \cdot I^-$	$D_x = 1.567 \text{ Mg m}^{-3}$
$M_r = 346.20$	Mo $K\alpha$ radiation, $\lambda = 0.71073 \text{ \AA}$
Orthorhombic, $P2_12_12_1$	Cell parameters from 9674 reflections
$a = 8.9944 (4) \text{ \AA}$	$\theta = 2.7\text{--}26.4^\circ$
$b = 11.3250 (6) \text{ \AA}$	$\mu = 2.17 \text{ mm}^{-1}$
$c = 14.4042 (7) \text{ \AA}$	$T = 297 \text{ K}$
$V = 1467.23 (12) \text{ \AA}^3$	BLOCK, colourless
$Z = 4$	$0.25 \times 0.19 \times 0.18 \text{ mm}$
$F(000) = 688$	

Data collection

Bruker D8 Venture CMOS diffractometer	2937 independent reflections
φ and ω scans	2866 reflections with $I > 2\sigma(I)$
Absorption correction: multi-scan (SADABS; Bruker, 2018)	$R_{\text{int}} = 0.023$
$T_{\text{min}} = 0.672$, $T_{\text{max}} = 0.745$	$\theta_{\text{max}} = 26.4^\circ$, $\theta_{\text{min}} = 2.9^\circ$
45268 measured reflections	$h = -11 \rightarrow 10$
	$k = -14 \rightarrow 14$
	$l = -18 \rightarrow 18$

Refinement

Refinement on F^2	Hydrogen site location: mixed
Least-squares matrix: full	H atoms treated by a mixture of independent and constrained refinement
$R[F^2 > 2\sigma(F^2)] = 0.013$	$w = 1/[\sigma^2(F_o^2) + (0.0105P)^2 + 0.4198P]$
$wR(F^2) = 0.032$	where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.08$	$(\Delta/\sigma)_{\text{max}} = 0.002$
2937 reflections	$\Delta\rho_{\text{max}} = 0.42 \text{ e \AA}^{-3}$
165 parameters	$\Delta\rho_{\text{min}} = -0.37 \text{ e \AA}^{-3}$
2 restraints	
Primary atom site location: dual	

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. The H atoms bonded to C were positioned geometrically and refined using a riding model with C—H = 0.97 Å and $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$ for CH₂ and C—H = 0.93 Å and $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$ for CH and with C—H = 0.96 Å and $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C})$ for CH₃. The H atoms bonded to O and N were refined isotropically with a distance restraint of 0.86 (1) Å for O—H and N—H.

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

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
I1	1.27678 (2)	0.68783 (2)	0.80214 (2)	0.04918 (6)
O1	0.9362 (3)	0.5938 (3)	0.71675 (17)	0.0750 (7)
N1	0.6590 (3)	0.6055 (2)	0.37895 (16)	0.0498 (5)
N2	0.2789 (2)	0.30817 (18)	0.61774 (13)	0.0391 (4)
C1	0.5215 (3)	0.5666 (2)	0.40501 (19)	0.0485 (6)
H1B	0.441446	0.556178	0.364948	0.058*
C2	0.7484 (3)	0.61161 (18)	0.45606 (16)	0.0406 (6)
C3	0.8962 (3)	0.6469 (2)	0.4660 (2)	0.0497 (7)
H3	0.950871	0.673197	0.415302	0.060*
C4	0.9584 (3)	0.6418 (2)	0.5530 (2)	0.0507 (7)
H4	1.056532	0.665360	0.561501	0.061*
C5	0.8756 (3)	0.6014 (2)	0.6292 (2)	0.0479 (6)
C6	0.7298 (3)	0.5668 (2)	0.62022 (16)	0.0429 (5)
H6	0.676325	0.540356	0.671410	0.052*
C7	0.6637 (3)	0.57222 (19)	0.53238 (16)	0.0364 (5)
C8	0.5182 (3)	0.5451 (2)	0.49817 (17)	0.0391 (5)
C9	0.3882 (3)	0.5012 (2)	0.55239 (19)	0.0447 (6)
H9A	0.296470	0.525310	0.522426	0.054*
H9B	0.389880	0.534545	0.614414	0.054*
C10	0.3953 (3)	0.3676 (2)	0.55785 (17)	0.0358 (5)
H10A	0.386906	0.336400	0.495364	0.043*
H10B	0.492611	0.345643	0.581186	0.043*
C11	0.3074 (4)	0.3325 (3)	0.71866 (17)	0.0547 (7)
H11A	0.406203	0.307458	0.734450	0.082*
H11B	0.236688	0.290083	0.755761	0.082*
H11C	0.297675	0.415645	0.730285	0.082*
C12	0.2907 (3)	0.1772 (2)	0.6019 (2)	0.0566 (6)
H12A	0.388997	0.151050	0.617656	0.085*
H12B	0.271215	0.160013	0.537743	0.085*
H12C	0.219355	0.136997	0.640060	0.085*
C13	0.1260 (3)	0.3483 (3)	0.5916 (2)	0.0599 (8)
H13A	0.113955	0.429832	0.608060	0.090*
H13B	0.053621	0.301558	0.624009	0.090*
H13C	0.112305	0.339099	0.525871	0.090*
H1A	0.686 (4)	0.629 (3)	0.3256 (13)	0.070 (10)*
H1	1.021 (2)	0.625 (3)	0.713 (3)	0.093 (14)*

Atomic displacement parameters (\AA^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
I1	0.04798 (9)	0.05760 (10)	0.04197 (8)	-0.00650 (8)	-0.00644 (7)	0.00349 (8)
O1	0.0540 (13)	0.118 (2)	0.0527 (13)	-0.0119 (14)	-0.0117 (10)	-0.0055 (13)
N1	0.0669 (15)	0.0466 (12)	0.0357 (11)	-0.0056 (11)	0.0020 (11)	0.0092 (9)
N2	0.0353 (8)	0.0375 (9)	0.0444 (9)	-0.0029 (11)	0.0023 (8)	-0.0056 (8)
C1	0.0556 (15)	0.0419 (13)	0.0480 (14)	0.0001 (12)	-0.0082 (12)	0.0017 (12)

C2	0.0484 (17)	0.0282 (10)	0.0450 (13)	-0.0017 (10)	0.0060 (11)	0.0012 (9)
C3	0.0529 (16)	0.0398 (13)	0.0564 (16)	-0.0067 (12)	0.0170 (14)	0.0026 (12)
C4	0.0401 (14)	0.0433 (13)	0.0688 (18)	-0.0059 (11)	0.0041 (13)	-0.0079 (13)
C5	0.0463 (15)	0.0500 (15)	0.0473 (14)	-0.0004 (12)	-0.0031 (12)	-0.0097 (11)
C6	0.0443 (12)	0.0455 (12)	0.0389 (11)	-0.0029 (12)	0.0044 (11)	-0.0020 (9)
C7	0.0432 (12)	0.0263 (10)	0.0396 (12)	-0.0014 (9)	0.0050 (10)	-0.0021 (9)
C8	0.0441 (13)	0.0288 (11)	0.0442 (13)	-0.0010 (10)	-0.0002 (11)	-0.0021 (10)
C9	0.0402 (13)	0.0375 (13)	0.0564 (16)	0.0024 (11)	0.0048 (12)	-0.0018 (12)
C10	0.0325 (11)	0.0365 (11)	0.0385 (12)	-0.0011 (9)	0.0010 (9)	-0.0048 (9)
C11	0.0672 (19)	0.0554 (16)	0.0414 (13)	-0.0034 (13)	0.0083 (11)	-0.0036 (11)
C12	0.0596 (15)	0.0380 (12)	0.0721 (17)	-0.0109 (14)	0.0107 (14)	-0.0071 (13)
C13	0.0313 (12)	0.069 (2)	0.080 (2)	-0.0019 (12)	0.0037 (14)	0.0006 (16)

Geometric parameters (Å, °)

O1—C5	1.377 (4)	C6—H6	0.9300
O1—H1	0.847 (13)	C6—C7	1.399 (3)
N1—C1	1.366 (4)	C7—C8	1.432 (3)
N1—C2	1.373 (3)	C8—C9	1.492 (4)
N1—H1A	0.849 (13)	C9—H9A	0.9700
N2—C10	1.515 (3)	C9—H9B	0.9700
N2—C11	1.502 (3)	C9—C10	1.516 (3)
N2—C12	1.504 (3)	C10—H10A	0.9700
N2—C13	1.496 (3)	C10—H10B	0.9700
C1—H1B	0.9300	C11—H11A	0.9600
C1—C8	1.364 (4)	C11—H11B	0.9600
C2—C3	1.395 (4)	C11—H11C	0.9600
C2—C7	1.410 (3)	C12—H12A	0.9600
C3—H3	0.9300	C12—H12B	0.9600
C3—C4	1.373 (4)	C12—H12C	0.9600
C4—H4	0.9300	C13—H13A	0.9600
C4—C5	1.403 (4)	C13—H13B	0.9600
C5—C6	1.374 (4)	C13—H13C	0.9600
C5—O1—H1	106 (3)	C1—C8—C9	126.2 (3)
C1—N1—C2	108.9 (2)	C7—C8—C9	127.4 (2)
C1—N1—H1A	128 (2)	C8—C9—H9A	109.9
C2—N1—H1A	123 (2)	C8—C9—H9B	109.9
C11—N2—C10	110.56 (19)	C8—C9—C10	109.0 (2)
C11—N2—C12	108.4 (2)	H9A—C9—H9B	108.3
C12—N2—C10	107.63 (18)	C10—C9—H9A	109.9
C13—N2—C10	110.9 (2)	C10—C9—H9B	109.9
C13—N2—C11	110.2 (2)	N2—C10—C9	116.3 (2)
C13—N2—C12	109.0 (2)	N2—C10—H10A	108.2
N1—C1—H1B	124.8	N2—C10—H10B	108.2
C8—C1—N1	110.3 (2)	C9—C10—H10A	108.2
C8—C1—H1B	124.8	C9—C10—H10B	108.2
N1—C2—C3	131.0 (2)	H10A—C10—H10B	107.4

N1—C2—C7	107.4 (2)	N2—C11—H11A	109.5
C3—C2—C7	121.7 (2)	N2—C11—H11B	109.5
C2—C3—H3	121.0	N2—C11—H11C	109.5
C4—C3—C2	118.1 (3)	H11A—C11—H11B	109.5
C4—C3—H3	121.0	H11A—C11—H11C	109.5
C3—C4—H4	119.7	H11B—C11—H11C	109.5
C3—C4—C5	120.7 (3)	N2—C12—H12A	109.5
C5—C4—H4	119.7	N2—C12—H12B	109.5
O1—C5—C4	121.7 (3)	N2—C12—H12C	109.5
C6—C5—O1	116.5 (3)	H12A—C12—H12B	109.5
C6—C5—C4	121.8 (3)	H12A—C12—H12C	109.5
C5—C6—H6	120.7	H12B—C12—H12C	109.5
C5—C6—C7	118.5 (2)	N2—C13—H13A	109.5
C7—C6—H6	120.7	N2—C13—H13B	109.5
C2—C7—C8	107.1 (2)	N2—C13—H13C	109.5
C6—C7—C2	119.3 (2)	H13A—C13—H13B	109.5
C6—C7—C8	133.6 (2)	H13A—C13—H13C	109.5
C1—C8—C7	106.3 (2)	H13B—C13—H13C	109.5
O1—C5—C6—C7	-179.6 (2)	C3—C2—C7—C8	179.1 (2)
N1—C1—C8—C7	-0.1 (3)	C3—C4—C5—O1	179.0 (3)
N1—C1—C8—C9	-179.7 (2)	C3—C4—C5—C6	-0.7 (4)
N1—C2—C3—C4	-178.8 (3)	C4—C5—C6—C7	0.1 (4)
N1—C2—C7—C6	178.5 (2)	C5—C6—C7—C2	0.6 (3)
N1—C2—C7—C8	-1.5 (3)	C5—C6—C7—C8	-179.4 (3)
C1—N1—C2—C3	-179.3 (3)	C6—C7—C8—C1	-179.0 (3)
C1—N1—C2—C7	1.5 (3)	C6—C7—C8—C9	0.6 (4)
C1—C8—C9—C10	92.6 (3)	C7—C2—C3—C4	0.4 (4)
C2—N1—C1—C8	-0.8 (3)	C7—C8—C9—C10	-86.9 (3)
C2—C3—C4—C5	0.4 (4)	C8—C9—C10—N2	174.8 (2)
C2—C7—C8—C1	1.0 (3)	C11—N2—C10—C9	-70.4 (3)
C2—C7—C8—C9	-179.4 (2)	C12—N2—C10—C9	171.4 (2)
C3—C2—C7—C6	-0.9 (3)	C13—N2—C10—C9	52.2 (3)

Hydrogen-bond geometry (\AA , $^\circ$)

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
N1—H1A \cdots I1 ⁱ	0.85 (1)	2.89 (2)	3.662 (2)	152 (3)
O1—H1 \cdots I1	0.85 (1)	2.72 (3)	3.468 (2)	147 (4)

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