Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

(3a*R*,8b*R*)-(+)-1-Methyl-1,2,3,3a,4,8b-hexahydropyrrolo[2′,3′:3,4]cyclopenta-[1,2-*b*]pyridine-1,5-diium dichloride monohydrate

Thomas Ullrich,[a] Michael Pyerin[a] and Kurt Mereiter[b]*

[a]Institute of Applied Synthetic Chemistry, Vienna University of Technology, Getreidemarkt 9/163, A-1060 Vienna, Austria, and [b]Institute of Chemical Technologies and Analytics, Vienna University of Technology, Getreidemarkt 9/164SC, A-1060 Vienna, Austria

Correspondence e-mail: kurt.mereiter@tuwien.ac.at

Key indicators

Single-crystal X-ray study
T = 295 K
Mean σ(C–C) = 0.004 Å
R factor = 0.051
wR factor = 0.092
Data-to-parameter ratio = 22.5

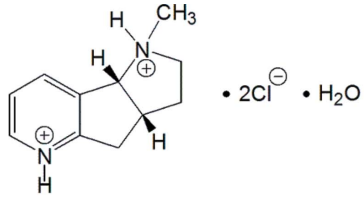
For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Received 11 May 2006
Accepted 12 June 2006

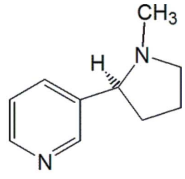
The title compound, $C_{11}H_{16}N_2^{2+}\cdot 2Cl^-\cdot H_2O$, is a novel conformationally constrained tricyclic analogue of nicotine, in which the pyridine and pyrrolidine rings of the latter are bridged by a CH_2 group. As result of this bridge, these two rings are no longer approximately perpendicular as in various salts of nicotine.

Comment

The alkaloid (*S*)-(−)-nicotine, (II), is a mimic of the important neurotransmitter acetylcholine and interacts with a wide range of biological binding sites, including those in acetylcholin-esterases and nicotinic acetylcholine receptors (nAChR) (Schmitt & Bencherif, 2000). Such receptors have been implicated in a number of cognitive and learning processes, making them a promising target for the treatment of neuro-degenerative diseases, such as Alzheimer's or Parkinson's diseases (Meyer *et al.*, 2000; Levin & Simon, 1998). In this context, and in view of the alkaloid epibatidine (Spande *et al.*, 1992), conformationally constrained nicotine analogues became of interest because restrictions in conformation may potentially tune potency and selectivity, while reducing toxi-city in comparison with nicotine (Glassco *et al.*, 1993).



(I)



(II)

The title compound, (I), is such a derivative, having the *N*-methylpyrrolidine and pyridine units of nicotine fixed relative to each other *via* a bridging CH_2 group (Ullrich *et al.*, 2002). As the compound was synthesized in a non-enantioselective route and optically resolved with a chiral auxiliary (Binder & Pyerin, 2005), it was necessary to determine its absolute configuration. The result is shown in Fig. 1. The chiral centre at position 2 of the pyrrolidine ring in the (+)-enantiomer of (I) has a configuration opposite to that of the analogous chiral centre in (II).

Whereas covalent bond lengths are normal (Table 1; Allen *et al.*, 1999), bond angles in the central five-membered ring C1/C2/C6/C7/C11 (e.g. C1—C2—C6 and C1—C11—C7) indicate moderate strain and the expected rigidity of the whole mol-ecule. The central five-membered ring is almost flat and coplanar with the pyridine ring (r.m.s. deviation of both rings

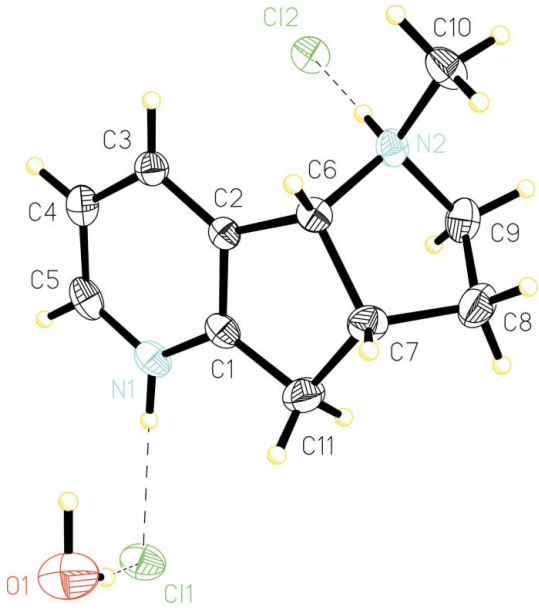


Figure 1
A view of the asymmetric unit of (I), with displacement ellipsoids drawn at the 30% probability level. Dashed lines indicate hydrogen bonds.

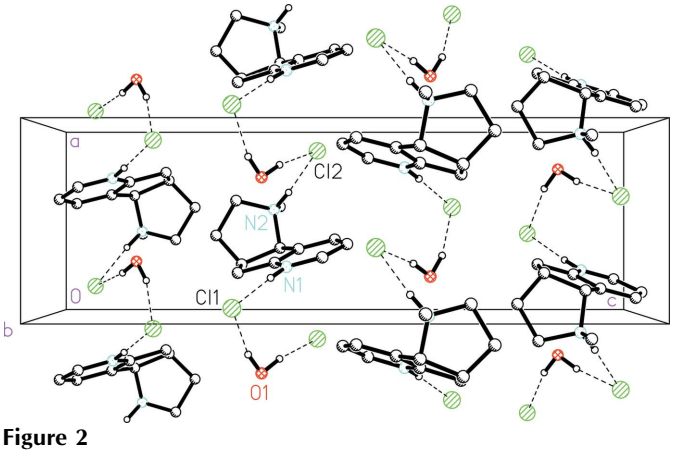


Figure 2
A packing diagram for (I), viewed down the *b* axis, with hydrogen bonds shown as dashed lines. C-bound H atoms have been omitted for clarity.

from a common least-squares plane is 0.023 Å). The pyrrolidine ring has an envelope conformation, with atom C9 deviating by 0.592 (4) Å from the least-squares plane of the other four ring atoms.

Each N atom is protonated and donates a comparatively short hydrogen bond to a neighbouring Cl^- ion (Table 2). The water molecule is hydrogen bonded to Cl^- ions of two adjacent $C_{11}H_{16}N_2^{2+}\cdot 2Cl^-$ units and links them into continuous hydrogen-bonded chains parallel to the *a* axis (Fig. 2).

Compared with typical compounds of nicotine, the molecule of (I) has an atypical shape, as a result of the bridging carbon C11. This can be demonstrated by the torsion angle C1—C2—C6—H6, which is −129° in (I), but in other nicotine compounds is either near 0° [−10° and 38° in nicotinium tetrachlorocuprate(II) (Choi *et al.*, 2002) and 3° in nicotinium iodide (Barlow *et al.*, 1986)] or near 180° (167° in nicotinium salicylate; Kim & Jeffrey, 1971).

Experimental

The synthesis of (I) was recently described by Binder & Pyerin (2005). Crystals for X-ray analysis in the form of thin colourless prisms were obtained by recrystallization from ethanol–H_2O (15:1) by slow evaporation at room temperature. $[\alpha]_D^{20}$ 27.5° (*c* = 0.42, methanol).

Crystal data

$C_{11}H_{16}N_2^{2+}\cdot 2Cl^-\cdot H_2O$
M_r = 265.17
Orthorhombic, $P2_12_12_1$
a = 6.853 (3) Å
b = 8.789 (4) Å
c = 21.537 (9) Å
V = 1297.2 (10) Å^3
Z = 4
D_x = 1.358 Mg m^{-3}
Mo *Kα* radiation
μ = 0.48 mm^{-1}
T = 295 (2) K
Prism, colourless
0.55 × 0.07 × 0.03 mm

Data collection

Bruker SMART CCD area-detector diffractometer
ω scans
Absorption correction: multi-scan (*SADABS*; Bruker, 2003)
T_{min} = 0.92, T_{max} = 0.99
17008 measured reflections
3554 independent reflections
2829 reflections with $I > 2\sigma(I)$
R_{int} = 0.043
θ_{max} = 30.0°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.051
$wR(F^2)$ = 0.092
S = 1.12
3554 reflections
158 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0323P)^2 + 0.2916P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.23 e Å^{-3}
$\Delta\rho_{min}$ = −0.20 e Å^{-3}
Absolute structure: Flack (1983), with 1449 Friedel pairs
Flack parameter: 0.03 (7)

Table 1
Selected geometric parameters (Å, °).

N1—C1	1.346 (3)	C1—C11	1.474 (4)
N1—C5	1.336 (3)	C2—C6	1.497 (3)
N2—C6	1.523 (3)	C6—C7	1.556 (3)
N2—C9	1.501 (3)	C7—C8	1.520 (4)
N2—C10	1.493 (3)	C8—C9	1.507 (4)
C1—C2	1.370 (3)	C7—C11	1.553 (3)
C1—C2—C6	110.0 (2)	C1—C11—C7	103.8 (2)
C3—C2—C6	129.6 (2)		
C1—C2—C6—C7	−1.9 (2)	C2—C6—C7—C8	124.5 (2)
C1—C2—C6—N2	112.2 (2)	C6—C7—C8—C9	−29.4 (3)

Table 2
Hydrogen-bond geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*N*···Cl1	0.91 (3)	2.09 (3)	3.000 (2)	174 (2)
N2—H2*N*···Cl2	0.95 (3)	2.13 (3)	3.075 (2)	174 (2)
O1—H1*OA*···Cl1	0.99 (4)	2.39 (4)	3.351 (3)	164 (3)
O1—H1*OB*···Cl2^{i}	0.96 (4)	2.31 (4)	3.240 (3)	163 (3)

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

All C-bound H atoms were placed in calculated positions (C—H = 0.93–0.98 Å) and thereafter treated as riding. A torsional parameter was refined for the methyl group. The positions of N- and O-bound H

atoms were refined freely (distances are in Table 2). For all H atoms, $U_{iso}(H) = 1.2U_{eq}(C,N,O)$ or $U_{iso}(H) = 1.5U_{eq}(C_{methyl})$.

Data collection: *SMART* (Bruker, 2003); cell refinement: *SAINT* (Bruker, 2003); data reduction: *SAINT*, *SADABS* and *XPREP* (Bruker, 2003); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 2003); software used to prepare material for publication: *SHELXTL*.

The authors thank Gerhard Denk, René Wissiack, and Heinz A. Krebs for their assistance in the synthesis of key compounds.

References

Allen, F. H., Watson, D. G., Brammer, L., Orpen, A. G. & Taylor, R. (1999). *International Tables for Crystallography*, Vol. C, 2nd ed., pp. 782–803. Dordrecht: Kluwer Academic Publishers.

Barlow, R. B., Howard, J. A. K. & Johnson, O. (1986). *Acta Cryst.* C**42**, 853–856.

Binder, D. & Pyerin, M. (2005). Int. Patent WO 2005 105 800 A1.

Bruker (2003). *SMART* (Version 5.625), *SAINT* (Version 6.36), *SADABS* (Version 2.10) and *SHELXTL* (Version 6.10). Bruker AXS Inc., Madison, Wisconsin, USA.

Choi, S.-N., Lee, Y.-M., Lee, H.-W., Kang, S. K. & Kim, Y.-I. (2002). *Acta Cryst.* E**58**, m583–m585.

Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.

Glassco, W., Suchocki, J., George, C., Martin, B. R. & May, E. L. J. (1993). *J. Med. Chem.* **36**, 3381–3385.

Kim, H. S. & Jeffrey, G. A. (1971). *Acta Cryst.* B**27**, 1123–1131.

Levin, E. D. & Simon, B. B. (1998). *Psychopharmacology*, **138**, 217–230.

Meyer, M. D., Decker, M. W., Rueter, L. E., Anderson, D. J., Dart, M. J., Kim, K. H., Sullivan, J. P. & Williams, M. (2000). *Eur. J. Pharmacol.* **393**, 171–177.

Schmitt, J. D. & Bencherif, M. (2000). *Annu. Rep. Med. Chem.* **35**, 41–45.

Sheldrick, G. M. (1997). *SHELXS97* and *SHELXL97*. University of Göttingen, Germany.

Spande, T. F., Garaffo, H. M., Edwards, M. W., Yeh, H. J., Pannell, L. & Daly, J. W. (1992). *J. Am. Chem. Soc.* **114**, 3475–3478.

Ullrich, T., Krich, S., Binder, D., Mereiter, K., Anderson, D. J., Meyer, M. D. & Pyerin, M. (2002). *J. Med. Chem.* **45**, 4047–4054.