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Cilansetron hydrochloride monohydrate, modification A (monoclinic)

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Key indicators

Single-crystal X-ray study
T = 173 K
Mean σ(C–C) = 0.007 Å
Disorder in main residue
R factor = 0.046
wR factor = 0.103
Data-to-parameter ratio = 10.5

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

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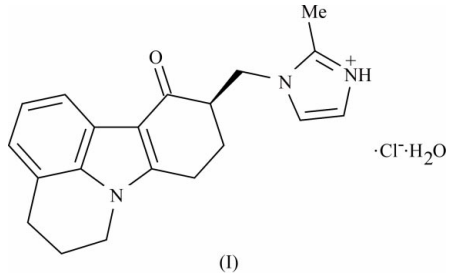
The absolute configuration of the monoclinic form of the title compound, (−)-5,6,9,10-tetrahydro-10-[(2-methyl-1*H*-imidazol-1-yl)methyl]-4*H*-pyrido[3,2,1-*jk*]carbazol-11(8*H*)-one monohydrochloride monohydrate, $C_{20}H_{22}N_3O^+\cdot Cl^-\cdot H_2O$, was established as *R* at the asymmetric carbon adjacent to the carbonyl function. This form [*cf.* the orthorhombic form; Jones *et al.* (2003). *Acta Cryst.* E**59**, o41–o43] involves two independent formula units with different ring conformations of the six-membered N-heterocycle, and somewhat different orientations of the imidazole ring. Each independent formula unit forms a helical hydrogen-bonded chain of alternating water and chloride residues; the cations are hydrogen bonded laterally to the chlorides.

Comment

Serotonin (5-HT) is involved in the regulation of visceral pain *via* 5-HT_3 receptors located in the lower gastrointestinal tract (Camelleri, 2002; Bueno *et al.*, 1997). Cilansetron (CAS 120635–74–7) is a potent and selective 5-HT_3 receptor antagonist (van Wijngaarden *et al.*, 1993; Haeck *et al.*, 1990), which is under development for the treatment of gastrointestinal disorders. During storage at ambient conditions, the hydrochloride salt of cilansetron (CAS 120635–72–5) takes up water and is thereby converted into the monohydrate product (CAS 209859–87–0). Determination of the crystal structure was undertaken to establish the chirality of the stereogenic centre after optical resolution, the hydration state, and the crystal-packing relationship between two different solid-state modifications of cilansetron hydrochloride monohydrate. We report here the crystal structure of modification A (van der Meij & Verbeek, 2002), (I); the following paper (Jones *et al.*, 2003) deals with modification B.



(I)

Compound (I) crystallizes with two independent formula units in the asymmetric unit (Fig. 1); the cations differ in the ring conformation involving the methylene groups C4, C5 and C6, and in the orientation of the imidazole ring. A brief selection of relevant torsion angles is shown in Table 1. A least-squares fit of the cations is shown in Fig. 2. Molecular dimensions may be regarded as normal.

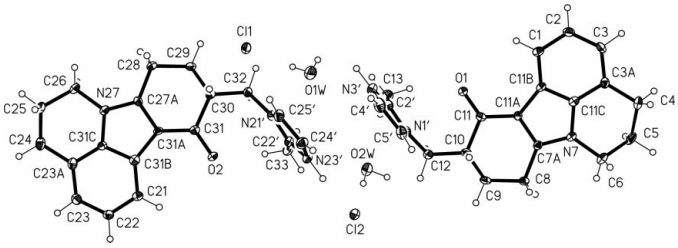


Figure 1
The asymmetric unit of the title compound in the crystal. Ellipsoids are drawn at the 30% probability level.

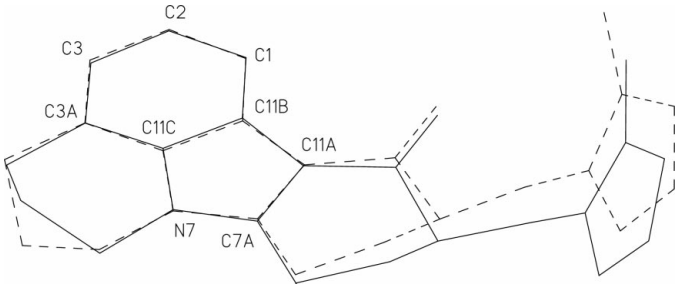


Figure 2
Least-squares fit of both independent cations, calculated using the labelled atoms.

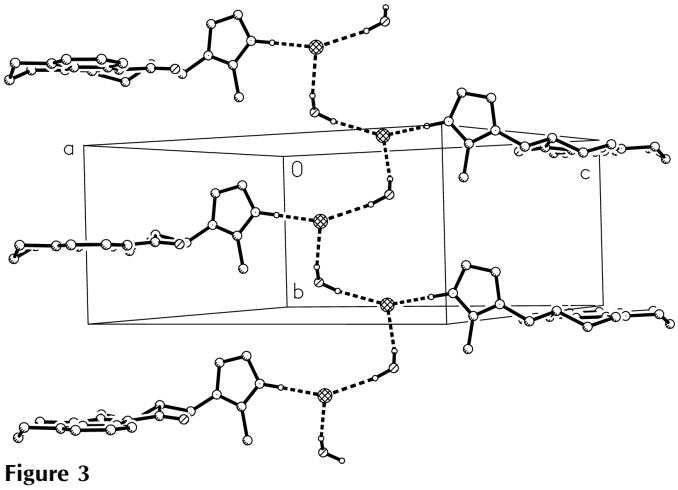


Figure 3
The helical hydrogen-bonding chain of the title compound; this chain corresponds to formula unit 1. Hydrogen bonds are indicated by dashed lines. H atoms not involved in hydrogen bonding have been omitted.

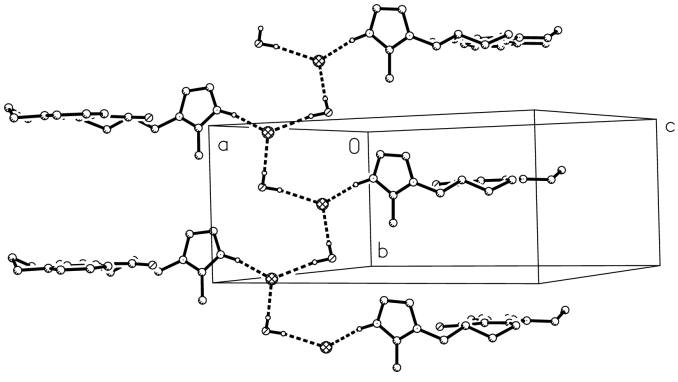


Figure 4
The corresponding chain for formula unit 2, from the same view direction.

The *R* absolute configuration at the asymmetric centre C10 (C30 in the second molecule) was established by the Flack (1983) parameter (see *Experimental*).

The major structural interest, especially in view of the presence of a second crystalline form (Jones *et al.*, 2003), centred on the crystal packing. An analysis of the classical hydrogen bonds (Table 2) reveals that each independent formula unit forms its own helical chains of residues [$\cdots$Cl$\cdots$H—O—H$\cdots$], with overall directions parallel to the *b* axis; the cations are attached laterally to these helices by contacts N—H$\cdots$Cl (Figs. 3 and 4). The helix corresponding to formula unit 1 lies in the region $x \simeq 0.5$, $z \simeq 0.5$, whereas that of formula unit 2 lies at $x \simeq 0.5$, $z \simeq 0$.

Inspection of the non-classical (weak) hydrogen bonds of the form C—H$\cdots$Cl and C—H$\cdots$O$_{water}$ (Table 2) reveals four such interactions that are especially short (H$\cdots$Cl < 2.7 Å and H$\cdots$O < 2.5 Å). Three of these four interactions link the formula units 1 and 2. They presumably play a role subordinate to that of the classical hydrogen bonds and are therefore not included in Figs. 3 and 4.

Experimental

A single crystal was selected by IR microscopy from a mixture of modifications A and B crystallized from 0.1 *M* HCl.

Crystal data

$C_{20}H_{22}N_3O^+\cdot Cl^-\cdot H_2O$
$M_r = 373.87$
Monoclinic, $P2_1$
$a = 15.403$ (3) Å
$b = 7.3835$ (14) Å
$c = 16.281$ (3) Å
$\beta = 92.438$ (12)°
$V = 1849.9$ (6) Å^3
$Z = 4$
$D_x = 1.342$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 62 reflections
$\theta = 4$–12.5°
$\mu = 0.23$ mm^{-1}
$T = 173$ (2) K
Lath, colourless
0.7 × 0.3 × 0.1 mm

Data collection

Siemens *P*4 diffractometer
ω scans
5792 measured reflections
5297 independent reflections
3621 reflections with $I > 2\sigma(I)$
$R_{int} = 0.041$
$\theta_{max} = 25.0°$
$h = -18 \rightarrow 18$
$k = -8 \rightarrow 5$
$l = -19 \rightarrow 14$
3 standard reflections every 247 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.046$
$wR(F^2) = 0.103$
$S = 0.90$
5297 reflections
505 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0468P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.26$ e Å^{-3}
$\Delta\rho_{min} = -0.26$ e Å^{-3}
Absolute structure: Flack (1983), 1772 Friedel pairs
Flack parameter = −0.07 (8)

Table 1
Selected torsion angles (°).

C3*A*—C4—C5—C6	−48.4 (8)	C23*A*—C24—C25—C26	47.5 (7)
C4—C5—C6—N7	46.9 (8)	C24—C25—C26—N27	−47.9 (7)
C11*A*—C7*A*—C8—C9	14.4 (7)	C31*A*—C27*A*—C28—C29	21.0 (8)

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

D—H···A	D—H	H···A	D···A	D—H···A
N3′—H3′···Cl1^{i}	1.02 (3)	2.07 (3)	3.093 (4)	178 (3)
N23′—H23′···Cl2	1.03 (3)	2.12 (3)	3.138 (4)	169 (5)
O2*W*—H2*A*···Cl2^{ii}	0.90 (3)	2.33 (3)	3.227 (4)	171 (5)
O2*W*—H2*B*···Cl2	0.91 (3)	2.31 (3)	3.208 (4)	172 (5)
O1*W*—H1*A*···Cl1^{i}	0.92 (3)	2.31 (3)	3.205 (5)	166 (5)
O1*W*—H1*B*···Cl1	0.91 (3)	2.27 (3)	3.165 (4)	170 (4)
C23—H23···Cl1^{iii}	0.95	2.83	3.742 (5)	162
C30—H30···Cl1^{iv}	1.00	2.88	3.791 (5)	152
C3—H3···Cl2^{v}	0.95	2.91	3.834 (5)	165
C5′—H5′···Cl2^{vi}	0.95	2.69	3.616 (5)	165
C2—H2···O2^{v}	0.95	2.64	3.512 (6)	153
C25—H25*B*···O2^{iii}	0.99	2.64	3.465 (7)	141
C13—H13*B*···O2*W*	0.98	2.48	3.431 (6)	164
C24′—H24′···O2*W*^{iv}	0.95	2.48	3.381 (6)	158
C13—H13*A*···O1*W*	0.98	2.61	3.369 (6)	135
C33—H33*B*···O1*W*	0.98	2.49	3.398 (6)	153

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

H atoms bonded to oxygen or nitrogen were refined freely but with chemically equivalent bond lengths restrained to be equal. Methyl H atoms were identified in difference syntheses, idealized and refined as rigid groups allowed to rotate but not tip. Other H atoms were included using a riding model. Fixed C—H bond lengths: methyl = 0.98, methylene = 0.99, methine = 1.00 and sp^2C—H = 0.95 Å. In both cations, atom C5 (C25 in molecule 2) is disordered over two positions. The major components have occupation factors 0.781 (14) and 0.838 (12). The minor positions were refined isotropically. Appropriate similarity restraints were employed. The structure is pseudo-symmetric; reflections *h*0*l* with *l* odd are systematically weak, indicating symmetry corresponding approximately to space group $P2_1/c$.

Data collection: *XSCANS* (Fait, 1991); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *XP* (Siemens, 1994); software used to prepare material for publication: *SHELXL*97.

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