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Antidiarrhetic loperamide hydrochloride

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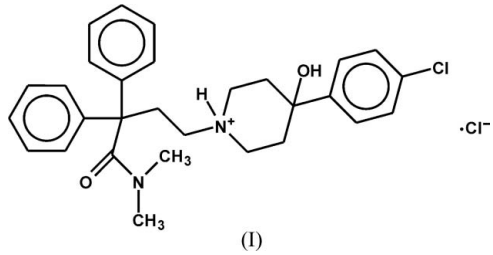
Single crystals of the anhydrous form of the title compound {systematic name: 1-[3-(dimethylcarbamoyl)-3,3-diphenylpropyl]-4-hydroxy-4-(4-chlorophenyl)piperidin-1-ium chloride}, $C_{29}H_{34}ClN_2O_2^+\cdot Cl^-$, were obtained by diffusion of acetone into a solution in 2-propanol. In the structure, N—H···Cl^- and O—H···Cl^- hydrogen bonds connect neighbouring molecules and chloride anions to form chains along the *c*-axis direction. Neighbouring chains along the *b*-axis direction are connected by intermolecular C—H···Cl^- contacts, defining layers parallel to the (100) planes. The layers are connected by weak intermolecular C—H···Cl interactions only, which may account for the plate-like shape of the crystals.

Comment

Loperamide hydrochloride {systematic name: 1-[3-(dimethylcarbamoyl)-3,3-diphenylpropyl]-4-hydroxy-4-(4-chlorophenyl)-piperidin-1-ium chloride}, (I), is the most potent active pharmaceutical ingredient known for the treatment of diarrhoea (Garwin, 1989; O'Neil, 2006). It is sold as an over-the-counter drug with the brand name Imodium™. Various generica are also known. The compound belongs to the group of opioids but does not show opioid-typical side effects such as analgesia, miosis or respiratory depression (Ruppin, 1987; Steinhilber *et al.*, 2005). Its effects are found only within the intestine by means of lowering intestinal activity. Generally, the compound is well tolerated (Baker, 2007; Hanauer, 2008). Crystal structures of polymorphs and pseudopolymorphs of loperamide are known, including loperamide monohydrate (Germain *et al.*, 1977) and loperamide hydrochloride tetrahydrate (Caira *et al.*, 1995). All of the forms, including the title compound, (I), have been characterized by various spectroscopic and thermal analysis techniques (Van Rompay & Carter, 1990). However, the crystal structure of (I) has not yet been reported.

A polymorph screen was performed for (I) in order to search for other polymorphic forms (including solvates), by using various solvents and solvent mixtures. The compound, which has quite high solubility, was recrystallized in order to obtain either suitable single crystals, or at least a powder of improved crystallinity, or other phases. Two different crystallization methods were used: (i) recrystallization from solvents and (ii) diffusion of an antisolvent *via* the gas phase into a solution of (I). The solvents used included *N*-methylpyrrolidone, dimethyl sulfoxide, alcohols, ethers and esters, acetone, chloroform and water. The solvents were not dried before use. Altogether about 200 experiments were carried out. From these experiments, the known tetrahydrate of (I), the monohydrate of loperamide, the anhydrous structure of (I) described here and an amorphous form were found. For all forms, except the amorphous one, crystals were obtained which were characterized using single-crystal structure analysis. No other solid forms were found.



(I)

The molecular structure of (I) is shown in Fig. 1. The central piperidinium ring adopts a chair conformation. The bridging N1—C12 and C7—C1 bonds are in equatorial positions, whereas the hydroxy group is in an axial position with respect to the piperidinium ring. The 4-chlorophenyl ring is almost coplanar with the C7—O1 bond [torsion angle O1—C7—C1—C6 = 18.72 (18)°]. A similar coplanarity is observed in loperamide hydrochloride tetrahydrate (Caira *et al.*, 1995), loper-

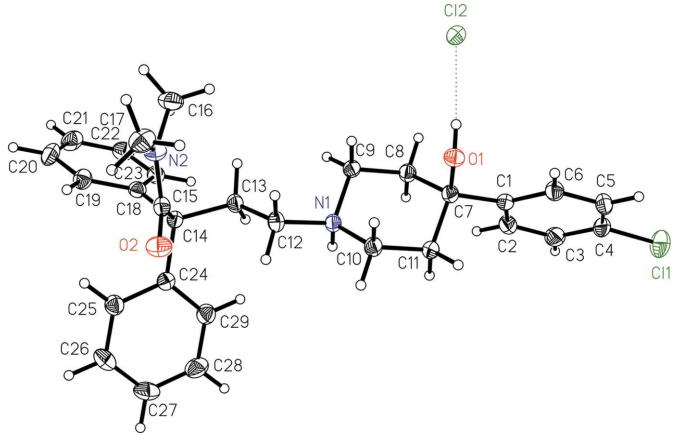


Figure 1
The molecular structure of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level. H atoms are drawn as small spheres of an arbitrary radius. The dashed line represents a hydrogen bond.

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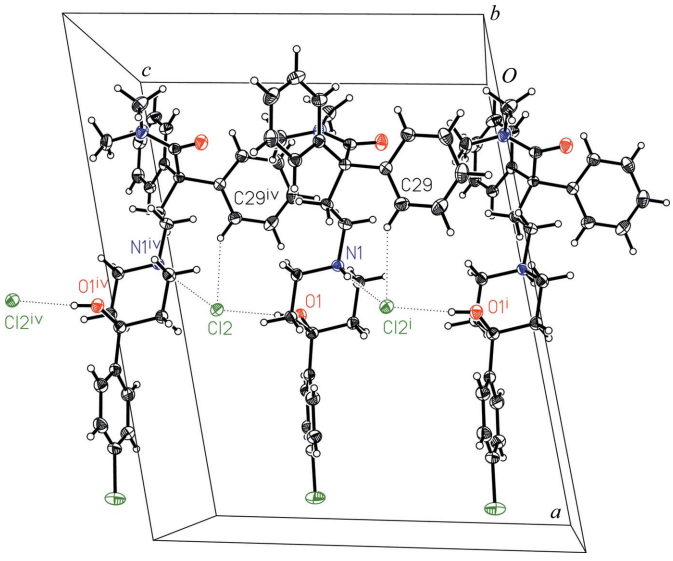

Figure 2
A hydrogen-bonded chain of (I). The hydrogen bonds are shown as dashed lines. Displacement ellipsoids are drawn at the 50% probability level. [Symmetry codes: (i) $x, -y+\frac{1}{2}, z-\frac{1}{2}$; (iv) $x, -y+\frac{1}{2}, z+\frac{1}{2}$.]

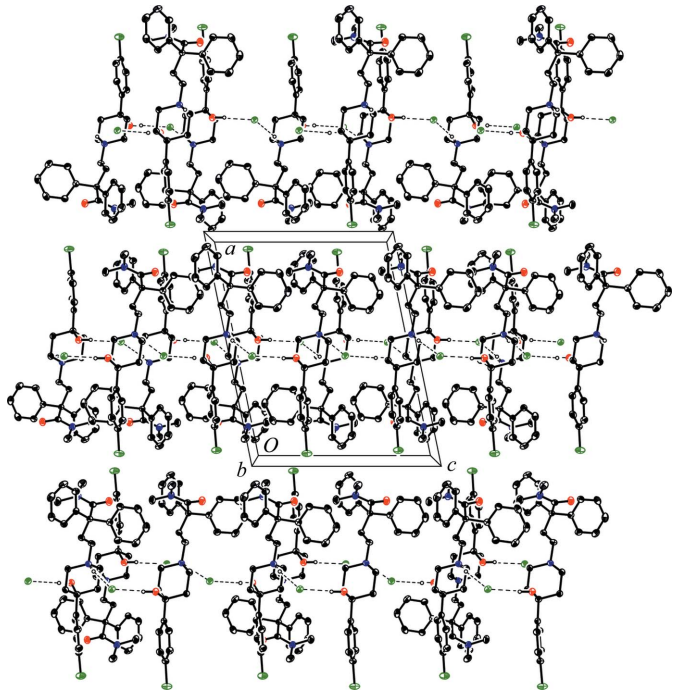

Figure 3
The crystal packing of (I), viewed down [010]. Hydrogen bonds are shown as dashed lines and H atoms on C atoms have been omitted for clarity. Displacement ellipsoids are drawn at the 50% probability level.

amide hydrate (Germain *et al.*, 1977) and loperamide *N*-oxide hydrate (Peeters *et al.*, 1996) (Table 2). The geometry around amide atom N2 is approximately planar, the sum of the three valence angles being 358.5 (1)°. The chloride anion accepts O—H···Cl^- and N^+—H···Cl^- hydrogen bonds (Table 1), and connects two symmetry-related loperamide units. The hydrogen bonding results in chains of molecules related by *c*-glide planes extending along the *c*-axis direction, as shown in Fig. 2. In the graph-set notation of Etter (1990) and extended by Bernstein *et al.* (1995), the hydrogen bonding is described as $C_2^1(8)$. Additionally, the chain exhibits a C—H···Cl^- contact (Table 1, entry 6). Neighbouring chains along the *b*-axis direction are connected by two additional intermolecular C—H···Cl^- contacts (Table 1, entries 3 and 4), defining layers parallel to the (100) planes (Fig. 3). Neighbouring layers along the *a*-axis direction exhibit only weak intermolecular phenyl–chlorophenyl C—H···Cl interactions (Table 1, entry 5), which may explain why the compound crystallizes as thin plates.

Comparing the structure of (I) with the structures of loperamide hydrochloride tetrahydrate (Caira *et al.*, 1995), loperamide hydrate (Germain *et al.*, 1977) and loperamide *N*-oxide hydrate (Peeters *et al.*, 1996) shows the central part of the molecule to have the same conformation in all four structures. The ethane fragment has a *trans* conformation and is also *trans*-positioned with respect to one of the N—C bonds of the piperidinium ring (Table 2). The main difference between the molecules results from the orientation of the dimethylaminocarbonyl and two phenyl groups at C14 with respect to the ethane fragment. The butanoyl C12—C13—C14—C15 torsion angle is 43.81 (15)° in (I), compared to *ca* 70° for the other three structures (Table 2). The angle between the planes of the two phenyl rings at C14 is 74.7 (1)° in (I), which differs by approximately 20° from the values of 57.4 (6), 51.1 (3) and 57.4 (2)° reported for loperamide hydrochloride tetrahydrate, loperamide hydrate and loperamide *N*-oxide hydrate, respectively.

Differential thermal analysis (DTA) and thermal gravimetry (TG) experiments were carried out to determine both the temperature at which the tetrahydrate of (I) transforms to the anhydrate and the temperature of decomposition of the anhydrate. The tetrahydrate releases water continuously between 313 and 393 K to form the anhydrate, which is stable up to the decomposition point of 483 K.

In the literature, a second anhydrate form of (I) has been described by Van Rompay & Carter (1990). We tried to obtain this phase by using the described procedure and by varying the experimental conditions. However, none of our experiments led to the formation of this second anhydrate, as shown by X-ray powder diffraction.

Experimental

Loperamide hydrochloride was purchased from TCI Europe (lot No. LO154, >98% purity). The solvents were of analytical grade and were not dried before use. Crystals of (I) were grown by gas diffusion. A suspension of (I) (50 mg) in 2-propanol (2 ml) was heated in a beaker to 323 K and subsequently cooled to room temperature. The beaker was placed in a larger beaker and acetone (4 ml) was added to the larger beaker. The larger beaker was sealed and kept for two weeks at room temperature; after this time colourless plates of (I) were obtained. The DTA–TG measurements were performed on a TGA 92 (SETARAM) device. About 10–20 mg of the sample were placed in corundum crucibles and heated from room temperature to 548 K at a rate of 3 K min^{-1} under a nitrogen atmosphere.

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1A···Cl2^{i}	0.95 (2)	2.15 (2)	3.0802 (12)	165 (2)
O1—H1B···Cl2	0.87 (2)	2.22 (2)	3.0962 (11)	176 (2)
C13—H13A···Cl2^{ii}	0.99	2.78	3.613 (2)	142
C23—H23A···Cl2^{ii}	0.95	2.83	3.771 (2)	173
C25—H25A···Cl1^{iii}	0.95	2.90	3.755 (2)	151
C29—H29A···Cl2^{i}	0.95	2.74	3.578 (2)	148

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

Crystal data

$C_{29}H_{34}ClN_2O_2^+\cdot Cl^-$
M_r = 513.48
Monoclinic, $P2_1/c$
a = 16.6542 (16) Å
b = 12.2529 (12) Å
c = 13.1410 (12) Å
β = 101.577 (9)°
V = 2627.0 (4) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.28 mm^{-1}
T = 169 K
0.60 × 0.60 × 0.07 mm

Data collection

Siemens SMART 1K CCD diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2000)
T_{min} = 0.887, T_{max} = 0.981
30967 measured reflections
6600 independent reflections
4941 reflections with $I > 2\sigma(I)$
R_{int} = 0.045

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.040
$wR(F^2)$ = 0.094
S = 1.06
6600 reflections
326 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.37 e Å^{-3}
$\Delta\rho_{min}$ = −0.42 e Å^{-3}

H atoms on N and O atoms were taken from a difference Fourier synthesis and refined freely with isotropic displacement parameters. H atoms on C atoms were positioned geometrically and treated as riding, with C—H = 0.95 (aromatic), 0.98 (methyl) or 0.99 Å (methylene), and with U_{iso}(H) = 1.5U_{eq}(C) for methyl groups or 1.2U_{eq}(C) otherwise. During refinement, the methyl groups were allowed to rotate about their C—N bonds.

Data collection: *SMART* (Siemens, 1995); cell refinement: *SMART*; data reduction: *SAINT* (Siemens, 1995); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *SHELXTL* (Sheldrick, 2008); software used to prepare material for publication: *SHELXL97*.

Table 2
Selected torsion angles (°) in (I) with corresponding torsion angles in a number of related compounds.

Torsion 1 = O1—C7—C1—C6, torsion 2 = C10—N1—C12—C13, torsion 3 = N1—C12—C13—C14 and torsion 4 = C12—C13—C14—C15. The atom-numbering scheme is as in Fig. 1.

	Torsion 1	Torsion 2	Torsion 3	Torsion 4
(I)	18.7 (2)	−175.3 (1)	160.5 (1)	43.8 (2)
Loperamide hydrochloride tetrahydrate[a]	3 (1)	−173 (1)	169 (1)	74 (1)
Loperamide hydrate[b]	−13.1 (5)	−168.6 (4)	174.2 (4)	−72.9 (4)
Loperamide *N*-oxide hydrate[c]	14.8 (3)	−170.8 (2)	−156.1 (2)	−70.8 (3)

References: (*a*) Caira *et al.* (1995); (*b*) Germain *et al.* (1977); (*c*) Peeters *et al.* (1996).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: BI3035). Services for accessing these data are described at the back of the journal.

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