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Form I of desloratadine, a tricyclic antihistamine

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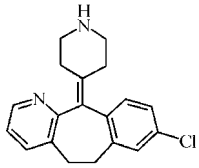
The title compound [systematic name: 8-chloro-11-(piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[4,5]cyclohepta[2,1-*b*]pyridine], $C_{19}H_{19}ClN_2$, was crystallized from ethyl acetate. The interesting feature of the reported structure is that it does not contain any strong hydrogen bonds, although the molecule contains a secondary NH group, which is a good hydrogen-bond donor.

Comment

Desloratadine, (I), is a tricyclic antihistamine and is used to treat allergies. It is sold under brand names such as Clarinex and Aerius. It has a long-lasting effect and does not cause drowsiness because it does not readily enter the central nervous system. Desloratadine is an active metabolite of loratadine, which is also on the market. It is 10–20 times more potent as an antihistamine than loratadine. The solid-state chemistry of active pharmaceutical ingredients (API) is of both academic and applied interest and is concerned with the identification and characterization of different solid forms of APIs and their use in formulations.



(I)

The molecular geometry and atom numbering for desloratadine, (I), are given in Fig. 1, and the packing arrangement is shown in Fig. 2. The only hydrogen bond present in the structure is a C—H···N interaction between benzene atom H11 and pyridine atom N1. This interaction gives rise to an infinite zigzag chain, with piperidine rings alternating and pointing outwards on either side of the chain. Two such adjacent chains pack by placing their piperidine fragments into the space between two fragments of the adjacent chain and *vice versa*, as shown in Fig. 2. This is basically a close-packed arrangement.

The most interesting feature of the crystal structure of (I) is that the piperidine NH group is not hydrogen bonded in a conventional sense (N—H···N), although there are two N-atom acceptors in the molecule. A search of the Cambridge Structural Database (CSD, Version 5.27 of November 2005; Allen, 2002) was carried out for entries which contain only N—H as a hydrogen-bond donor and where this N—H is not hydrogen bonded to any acceptor. The constraints used in this search were as follows: $R < 0.05$, no errors, not polymeric, no ions, only organics. 543 hits were obtained. However, analysis showed that, in almost all these cases, the NH group is sterically hindered. It is therefore surprising that in the case of desloratadine, which has a sterically unhindered NH group, no hydrogen bonds are formed. The reason for this may lie in the awkward shape of the molecule. This reasoning was supported with a computational study using *POLYMORPH PREDICTOR* (Accelrys, 2003). The polymorph prediction was carried out with the DREIDING2.21 force field in five space groups, *viz*. $P2_1$, $C2/c$, $P\overline{1}$, $P2_1/c$ and $P2_12_12_1$. Except in $C2/c$, the most stable structure predicted was very similar to

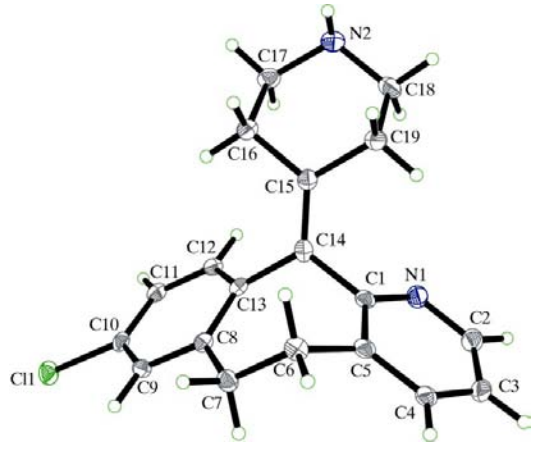


Figure 1
A view of the molecular structure of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

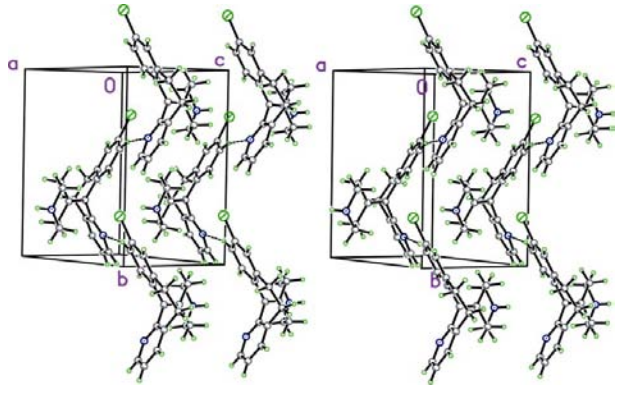


Figure 2
A stereoview of the packing arrangement of (I), showing two close-packed desloratadine zigzag chains.

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the experimental structure, in that no N—H···N hydrogen bond is present. Crystal structure prediction in the experimental space group ($P2_1$) gave the most stable structure, which was identical to the experimental structure. This is a good validation of the force field.

Desiraju (2002) has discussed a similar issue in the article entitled 'Bond free' with respect to the literature example of the oxalic acid–phthalocyanine complex (Liu *et al.*, 2002) and also alloxan (Coombes *et al.*, 1997; Beyer *et al.*, 2001). He concluded that crystal structures are determined by an interplay of both space filling and hydrogen bonding, such that the free energy is a minimum, and that the very occasional appearance of a crystal structure where sterically unhindered X—H groups do not form strong X—H···A interactions is a statistical issue, brought about by the fact that a very large number of crystal structures of small organic molecules are being determined today.

To date, two polymorphs of desloratadine have been reported in a patent application (Toth *et al.*, 2004), but no crystal structure data are available. A comparison of the powder X-ray spectrum given in the patent and that simulated from the single-crystal data of the present study showed that the single crystal obtained by us corresponds to form I of desloratadine. We feel it is possible to realise experimentally the hydrogen-bonded structure obtained computationally in the $C2/c$ space group because it is only 8.4 kJ mol^{-1} per molecule less stable than the experimental $P2_1$ structure reported here.

Experimental

Commercially available desloratadine (100 mg) was dissolved in ethyl acetate (10 ml). The solution was filtered and the filtrate was allowed to crystallize by slow evaporation over a period of 2 d. Plate-like crystals of (I) were obtained from the solution and used for single-crystal X-ray diffraction studies.

Crystal data

$C_{19}H_{19}ClN_2$
M_r = 310.81
Monoclinic, $P2_1$
a = 6.9336 (12) Å
b = 11.998 (2) Å
c = 9.4691 (16) Å
β = 107.365 (2)°
V = 751.8 (2) Å^3
Z = 2
D_x = 1.373 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.25 mm^{-1}
T = 100 (2) K
Plate, colourless
0.47 × 0.24 × 0.11 mm

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

D—H···A	D—H	H···A	D···A	D—H···A
C11—H11···N1^{i}	0.940 (18)	2.485 (18)	3.357 (3)	154.4 (18)

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

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
4424 measured reflections
2661 independent reflections
2550 reflections with $I > 2\sigma(I)$
R_{int} = 0.023
θ_{max} = 26.0°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.032
$wR(F^2)$ = 0.075
S = 1.05
2661 reflections
208 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.035P)^2 + 0.1332P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.21 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}
Absolute structure: Flack (1983), with 1106 Friedel pairs
Flack parameter: 0.04 (5)

Atoms H1 and H11 of NH and CH groups, respectively, were located in difference Fourier maps and refined isotropically. All other H atoms were generated with idealized geometry and included in the refinement using a riding model, with C—H = 0.93 Å and U_{iso}(H) = 1.2U_{eq}(C) for aromatic H atoms, and C—H = 0.97 Å and U_{iso}(H) = 1.2U_{eq}(C) for methylene H atoms. The Flack (1983) parameter was determined using a BASF/TWIN type of refinement and 1106 Friedel pairs were used for the analysis.

Data collection: *SMART* (Bruker, 1999); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 1999); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 1997); software used to prepare material for publication: *SHELXTL*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3005). Services for accessing these data are described at the back of the journal.

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