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Weak intermolecular interactions in 11-chloro-2,3,4,5-tetrahydro-1*H*-cyclohepta[*b*]quinoline

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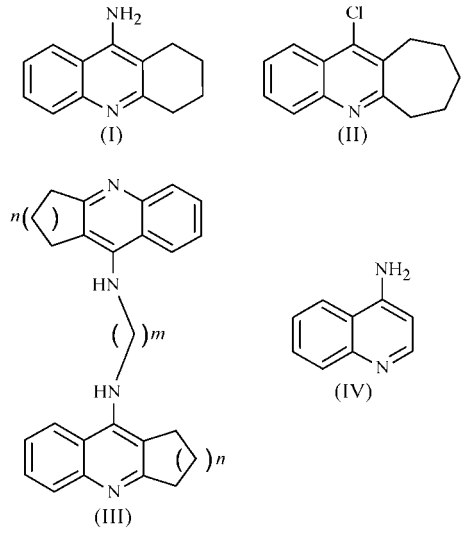
The title compound, $C_{14}H_{14}ClN$, is a chloro analogue of tacrine, an acetylcholinesterase inhibitor. The compound comprises a seven-membered alicyclic ring whose CH donor groups are engaged in extensive intermolecular interactions. The important feature of this crystal structure is that, regardless of the presence of two typical hydrogen-bonding acceptors, *viz*. chlorine and nitrogen, the corresponding C—H···Cl and C—H···N interactions take no significant role in crystal stabilization. The molecules form dimers through π–π interactions with an interplanar distance between interacting pyridine rings of 3.576 (1) Å. Within the dimers, the molecules are additionally interconnected by four C—H···π interactions. The dimers arrange into regular columns *via* further intermolecular C—H···π interactions.

Comment

Tacrine, (I), is the first reversible inhibitor of acetylcholinesterase (AChE, EC 3.1.1.7) to be approved by the US Food and Drug Administration for palliative treatment of Alzheimer's disease. Harel *et al.* (1993) have determined the TcAChE crystal structure (from *Torpedo californica*) complexed with (I) (Protein Data Bank code 1acj). Tacrine forms stacking interactions with Trp 84 and Phe 330 aromatic rings inside the AChE active site gorge. Protonated aromatic N atoms form hydrogen bonds with carbonyl O atoms of His 440 (a part of the AChE catalytic triad), while amino N atoms form hydrogen bonds with conserved water molecules. However, the determined AChE–tacrine crystal structure does not reveal the nature of the influence of the cycloalkyl group on the anticholinesterase activity. Severe hepatotoxicity has reduced the therapeutic use of (I), but the search for tacrine analogs with improved properties is of persistent interest (Munoz-Torrero & Camps, 2006).



In the past decade, approximately 100 homo- and heterodimeric tacrine analogs, (III) (n = 1–3 and m = 6–8), have been synthesized. These compounds are diverse with respect to the linker length, the substituents on the tetrahydroacridine nucleus and the size of the alicyclic ring. 4-Aminopyridine and 4-aminoquinoline, (IV), have very weak anticholinesterase activity, indicating the importance of the cycloalkyl ring for the inhibition potency (Kaul, 1962). The same is true for the homodimeric AChE inhibitors. 4-Aminoquinoline dimers are considerably weaker AChE inhibitors than tacrine homodimers (Han *et al.*, 1999). Furthermore, a decrease in the size of the alicyclic ring to five-membered causes a 100-fold decrease in the AChE inhibition abilities, while their increase to seven-membered produces a negligible decrease (Hu *et al.*, 2002). Different 9-chloro analogs of tacrine serve as synthons for the synthesis of dual homo- and heterodimeric tacrine derivatives. Having this in mind, we report here the molecular structure of the title compound, (II).

Compound (II) (Fig. 1) consists of a 4-chloroquinoline system and a cycloheptyl ring, which is fused to the aromatic moiety. As expected, the quinoline system is highly planar, having an r.m.s. deviation of fitted atoms of 0.016 Å. The Cl

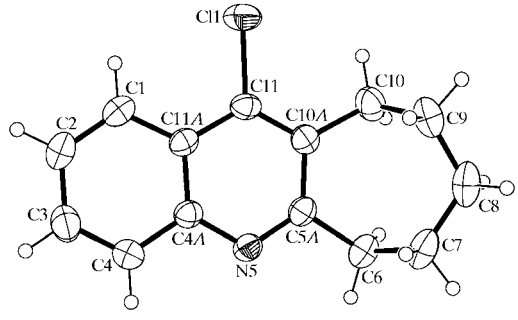


Figure 1
A view of the molecule of (II), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 40% probability level.

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atom lies 0.067 (1) Å out of the quinoline plane, while atoms C6 and C10 of the fused cycloheptyl ring are coplanar within 0.083 (2) Å. The seven-membered ring adopts a quite regular chair conformation, where the C6—C5*A*—C10*A*—C10 torsion angle and the C6—C7···C9—C10 angle are 2.2 (2) and −1.6 (2)°, respectively. The bond distances within the molecule are in good agreement with those reported for two derivatives that contain an additional benzene ring fused to the cycloheptyl ring, namely 10-chloro-6,7-dihydro-5*H*-benzo-[6,7]cyclohepta[1,2-*b*]quinoline, (V), and 10-methyl-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]-quinoline, (VI) (Ray *et al.*, 1998).

Despite the presence of the typical hydrogen-bonding acceptors nitrogen and chlorine, the crystal structure of (II) lacks the expected intermolecular C—H···N and C—H···Cl hydrogen bonding. On the other hand, the crystal structure is characterized by a number of weak C—H···π interactions (Desiraju & Steiner, 1999), which involve all of the axial H atoms of the cycloheptyl fragment and the quinoline moiety as a π system (Table 1).

The cycloheptyl donors C6 and C10, which are the most coplanar with the quinoline system, are involved in the C—H···π interactions with the shortest perpendicular distances from the H atom to the quinoline plane (Table 1). Two pairs of these interactions connect the centrosymmetrically related molecules into a dimer. The formation of dimers is also favored by π stacking interactions occurring between the pyridine rings of the molecular pair. Owing to inversion symmetry, the stacked pyridine rings have opposite orientations, with a $Cg1\cdots Cg1^{ii}$ distance of 3.837 (1) Å and a slippage of 1.391 Å [$Cg1$ refers to the centroid of the pyridine ring; symmetry code: (ii) $-x+1, -y, -z$]. The pyridine rings are arranged in such a way that atom C10*A* is positioned above the center of the neighboring ring (Fig. 2). The interplanar separation between the rings is 3.576 (1) Å, while the shortest distance found between the atoms, $C5A\cdots C11^{ii}$, is 3.567 (2) Å.

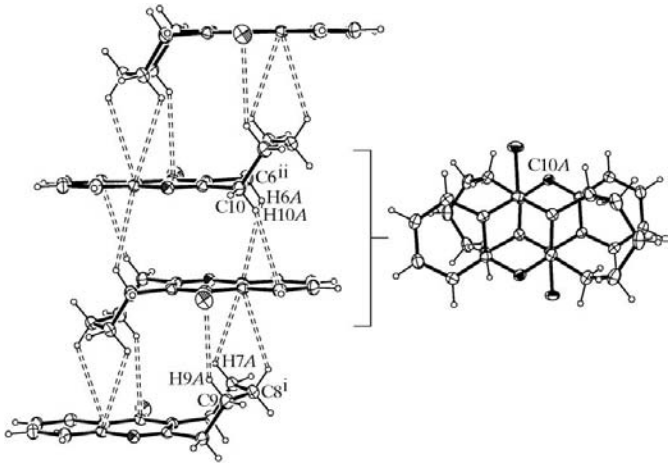

Figure 2
A segment of a column of molecules generated by C—H···π and π–π interactions. [Symmetry codes: (i) $-x+1, -y+1, -z$; (ii) $-x+1, -y, -z$.]

The additional C—H···π interactions (Table 1) formed from each side of the dimer engage the rest of the cycloheptyl CH donors, connecting the dimers into a column extending along the *b* axis (Fig. 2). Although rather weak, the C—H···π interactions between the dimers imply simultaneous engagement of six CH donor groups and their clear directionality toward the two neighboring quinoline systems. The perpendicular distances of all interacting H atoms to quinoline planes are below 3.05 Å. The dimers within a column are strictly parallel; however, the size and chair-like conformation of the cycloheptyl ring increase the separation between the dimers in the *b* direction, preventing the potential π–π stacking between their aromatic parts. In this case, the interplanar distance between the quinoline ring systems is 5.035 (1) Å. The columns of dimers are further related through very weak cyclic C4—H4···N5^{iii} and C9—H9*B*···Cl1^{iv} interactions, forming a two-dimensional structure parallel to the *ab* plane [C4—H4 = 0.93 Å, H4···N5^{iii} = 2.89 Å, C4···N5^{iii} = 3.661 (4) Å and C4—H4···N5^{iii} = 141°; C9—H9*B* = 0.97 Å, H9*B*···Cl1^{iv} = 3.31 Å, C9···Cl1^{iv} = 4.027 (4) Å and C9—H9*B*···Cl1^{iv} = 132°; symmetry codes: (iii) $-x+2, -y+1, -z$; (iv) $-x, -y, -z$; Fig. 3]. These are the shortest intermolecular interactions concerning the N5 and Cl1 acceptors.

The crystal arrangements in (V) and (VI), and also in 6,9-dichloro-1,2,3,4-tetrahydroacridine (Elsinghorst *et al.*, 2007), which is the cyclohexyl analog of (II), display a similar method of dimer formation. In each of these structures, the centro-

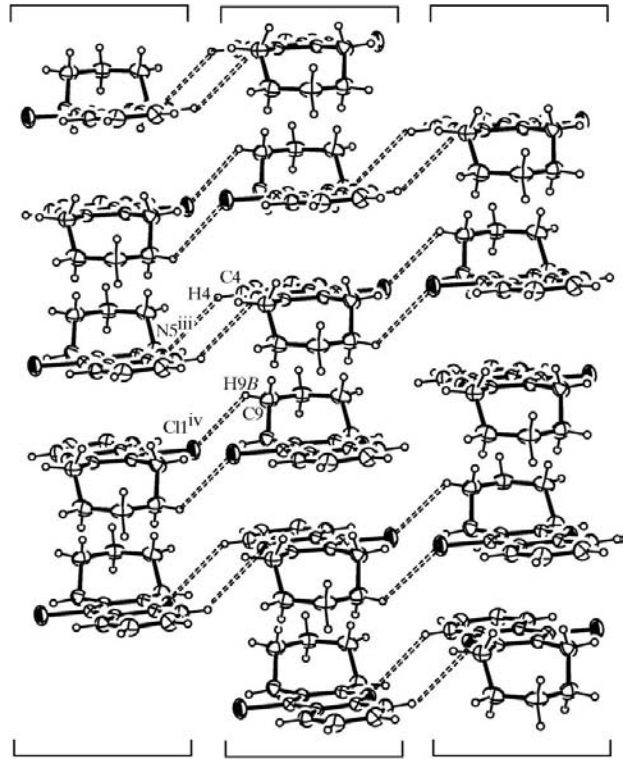

Figure 3
Columns of molecules connected by weak C4—H4···N5^{iii} and C9—H9*B*···Cl1^{iv} interactions, viewed approximately along the *c* axis. The interactions within the columns (presented in Fig. 2) have been omitted for clarity. [Symmetry codes: (iii) $-x+2, -y+1, -z$; (iv) $-x, -y, -z$.]

symmetrically related molecules are associated by weak C—H···π interactions, where the cycloalkyl rings provide the donors and the quinoline cores serve as the acceptors. In addition to C—H···π interactions, the dimers are stabilized by π–π stacking involving only the pyridine fragments of the molecules. The interplanar distances between the parallel quinoline systems in these structures range from 3.55 to 3.70 Å.

In conclusion, weak C—H···π and π–π interactions play a dominant role in the crystal structure of (II) as well as in similar crystal structures.

Table 1
Geometric parameters (Å, °) for C—H···π interactions.

*Cg*1 is the centroid of the pyridine ring, *Cg*2 is the centroid of the benzene ring and H···Perp is the perpendicular distance from the H atom to the quinoline plane.

C—H···*Cg*	H···*Cg*	C···*Cg*	H···Perp	C—H···*Cg*
C8—H8*A*···*Cg*2^{i}	2.92	3.797 (2)	2.88	151
C10—H10*A*···*Cg*2^{ii}	2.97	3.872 (2)	2.89	155
C9—H9*A*···*Cg*1^{i}	3.12	3.907 (3)	2.91	140
C7—H7*A*···*Cg*1^{i}	3.38	4.126 (4)	3.03	135
C6—H6*A*···*Cg*1^{ii}	3.49	3.661 (4)	2.77	141

Symmetry codes: (i) $-x+1, -y+1, z$; (ii) $-x+1, -y, -z$.

Experimental

All chemicals used were of analytical grade. To a mixture of anthranilic acid (2.4 g, 17.5 mmol) and cycloheptanone (2.1 ml, 17.5 mmol) in an ice bath was carefully added phosphorous oxychloride ($POCl_3$, 17.5 ml). The mixture was refluxed for 2 h and then cooled to room temperature. Surplus $POCl_3$ was removed under reduced pressure, and the resulting slurry was subsequently poured into an ice and solid K_2CO_3 mixture with vigorous stirring. The separated solid was taken up in ethyl acetate; the solution was evaporated and the crude residue was recrystallized from acetone to afford 3.20 g (39.42%) of (II) as yellow crystals. The single crystals that were submitted for single-crystal X-ray analysis were obtained after recrystallization from acetone (m.p. 367–369 K). Analysis found for $C_{14}H_{14}ClN$: C 72.06, H 6.17, N 6.04%; calculated: C 72.57, H 6.09, N 6.04%. ^{1}H NMR: δ 1.67–1.95 (*m*, 6H); 3.17, 3.20, 3.22, 3.25 (*m*, 4H); 7.50, 7.53, 7.56 (triplet-like peaks, 1H); 7.62, 7.65, 7.69 (triplet-like peaks, 1H); 7.96, 8.00 (doublet-like peaks, 1H); 8.13, 8.17 (doublet-like peaks, 1H). ^{13}C NMR: δ 26.78, 27.367, 30.26, 31.74, 40.148, 76.38, 77.00, 77.64, 124.45, 125.40, 126.62, 128.80, 129.07, 133.84, 139.63, 146.42, 164.76.

Crystal data

$C_{14}H_{14}ClN$
M_r = 231.71
Triclinic, $P\overline{1}$
a = 8.213 (2) Å
b = 8.727 (2) Å
c = 9.042 (3) Å
α = 90.50 (2)°
β = 95.32 (3)°
γ = 113.86 (3)°
V = 589.4 (3) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.29 mm^{-1}
T = 293 (2) K
0.56 × 0.44 × 0.42 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
2548 measured reflections
2309 independent reflections
2003 reflections with $I > 2\sigma(I)$
R_{int} = 0.011
3 standard reflections
frequency: 60 min
intensity decay: none

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.037
$wR(F^2)$ = 0.107
S = 1.07
2309 reflections
145 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.18 e Å^{-3}
$\Delta\rho_{min}$ = −0.20 e Å^{-3}

All H atoms were found in a difference Fourier map, but they were placed at geometrically calculated positions and refined using a riding model. C—H distances were fixed at 0.97 and 0.93 Å for Csp^3 and Csp^2 atoms, respectively. The U_{iso} values of all H atoms were set at 1.2U_{eq} of the parent atom.

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989); cell refinement: *CAD-4 Software*; data reduction: *XCAD4* (Harms & Wocadlo, 1995); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3* (Farrugia, 1997); software used to prepare material for publication: *WinGX* (Farrugia, 1999) and *PLATON* (Spek, 2003).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3246). Services for accessing these data are described at the back of the journal.

References

Desiraju, G. R. & Steiner, T. (1999). *The Weak Hydrogen Bond in Structural Chemistry and Biology*. New York: Oxford University Press Inc.
Elsinghorst, P. W., Nieger, M. & Gütschow, M. (2007). *Acta Cryst.* E**63**, o1818–o1820.
Enraf–Nonius (1989). *CAD-4 Software*. Version 5.0. Enraf–Nonius, Delft, The Netherlands.
Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
Farrugia, L. J. (1999). *J. Appl. Cryst.* **32**, 837–838.
Han, Z. F., Li, C. P. L., Chow, E., Wang, H., Pang, Y. P. & Carlier, P. R. (1999). *Bioorg. Med. Chem.* **7**, 2569–2575.
Harel, M., Schalk, I., Ehret-Sabatier, L., Bouet, F., Goeldner, M., Hirth, C., Axelsen, P. H., Silman, I. & Sussman, J. L. (1993). *Proc. Natl Acad. Sci. USA*, **90**, 9031–9035.
Harms, K. & Wocadlo, S. (1995). *XCAD4*. University of Marburg, Germany.
Hu, K. M., Wu, J. L., Hsiao, J. & Yen, M. H. (2002). *J. Med. Chem.* **45**, 2277–2282.
Kaul, P. N. (1962). *J. Pharm. Pharmacol.* **14**, 243–248.
Munoz-Torrero, D. & Camps, P. (2006). *Curr. Med. Chem.* **13**, 399–422.
Ray, J. K., Mahato, T. K., Chinnakali, K., Razak, I. A. & Fun, H.-K. (1998). *Acta Cryst.* C**54**, 641–643.
Sheldrick, G. M. (2008). *Acta Cryst.* A**64**, 112–122.
Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.