

measure of the deviation of the ring from an ideal cycloheptatriene boat with mirror symmetry, in terms of the endocyclic torsion angles, is 4.3° for (I) and 4.5° for (II). These values are typical of those found in 1,4-benzodiazepin-2-ones (Hamor & Martin, 1983) and also similar to that in brotizolam (3.0°).

The triazolo, phenyl and thieno rings are all planar to within ±0.015 Å. The phenyl ring is steeply inclined to the thieno plane, interplanar angle 88.8 (8)° in (I) and 88.3 (5)° in (II). These angles compare with values of 73–86° in 2'-chloro-substituted 1,4-benzodiazepines and 71.7° in brotizolam. Unlike the situation in the crystal structure of brotizolam, the Cl atom lies on the opposite side of the thieno plane from the bow atom, C(4) [compare Fig. 1 with Fig. 1 in Butcher & Hamor (1985)]. The orientations of the phenyl rings in compounds (I) and (II) thus correspond to that normally found in the crystal structures of 5-phenyl-1,4-benzodiazepines and triazolobenzodiazepines (Hamor & Martin, 1983). The 1-cyclohexyl substituent of compound (II) adopts a normal chair conformational, torsion angles in the range ±54.2 to ±56.8°.

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9-Amino-1,2,3,4-tetrahydroacridine Hydrochloride Monohydrate (THA.HCl)

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Abstract. C₁₃H₁₅N₂⁺.Cl⁻.H₂O, *M_r* = 252.74, monoclinic, *P*2₁/*c*, *a* = 8.776 (2), *b* = 8.514 (1), *c* = 18.046 (4) Å, β = 107.09 (2)°, *V* = 1288.8 (5) Å³, *Z* = 4, *D_x* = 1.302 Mg m⁻³, λ(Cu Kα) = 1.5418 Å, μ = 0.238 mm⁻¹, *F*(000) = 536, *T* = 293 K, final *R* = 0.042 for 2080 observed data. Atoms C2 and C3 of the reduced ring are disordered. The crystal structure has an extensive network of hydrogen bonds in which the water molecule donates its H atoms to two Cl ions and accepts the H atom from the protonated ring N atom. The amino group also donates its H atoms in hydrogen bonding to two Cl ions.

Introduction. The compound 9-amino-1,2,3,4-tetrahydroacridine hydrochloride, THA.HCl (tacrine hydrochloride), a cholinesterase inhibitor, has been of recent interest as a drug for the treatment of

Alzheimer's disease, an affliction that causes a progressively increasing loss of memory and intellectual function (Coyle, Price & DeLong, 1983; Summers, Majovski, Marsh, Tachiki & Kling, 1986). Unfortunately, it causes an elevation in the amount of the enzyme transaminase in the liver, and for the present its use has been discontinued.

We report here the crystal structure of this compound and compare it to the crystal structure of the less-saturated analog 9-aminoacridine hydrochloride (9AA.HCl) (Talacki, Carrell & Glusker, 1974) which is a known mutagen.

Experimental. The compound, THA.HCl, was purchased from Aldrich Chemical Company and used directly. A crystal of dimensions 0.30 × 0.30 × 0.35 mm was used for data collection with a Syntex *PI*

automatic diffractometer. Lattice parameters were determined from 14 reflections in the θ range 26.5 to 33.5°. Data were measured with monochromatized $\text{CuK}\alpha$ radiation to $[(\sin\theta)/\lambda]_{\max} = 0.606 \text{ \AA}^{-1}$ (2θ range = 0–138°); four standard reflections were measured every 96 data collected. The variable θ – 2θ scan was used and, of 2395 reflections scanned, 2080 were considered observed $\{I \geq 2.50\sigma(I)\}$. The ranges of h , k and l were h 0 to 10; k 0 to 10; l –21 to 20. No absorption correction was made ($\mu_{\text{max}} = 0.131$) and no crystal decay was detected.

The structure was determined by Patterson and Fourier methods and all H atoms were located from difference Fourier syntheses. Some disorder was detected in the saturated-ring system and these atoms, C2 and C3, were refined isotropically with an occupancy of 0.5. All other atoms, except for H atoms, which were refined isotropically, were refined by full-matrix least-squares methods applied to F values. The quantity that was minimized was $\sum w(\Delta F)^2$ with 236 parameters refined. The final R value for observed data was 0.042, with a weighted R value of 0.058, $S = 0.67$. Reflections were weighted according to the scheme: $F < 1.3$, $w = 0$; $1.3 < F \leq 10.6$, $w = 0.72$; $10.6 < F \leq 26.3$, $w = 0.72 + 0.054(F - 10.6)$; $F > 26.3$, $w = 1.6 + 0.329(F - 26.3)$. The final $(\Delta/\sigma)_{\max}$ for H atoms was 0.72 and 0.25 for the other atoms. The final difference Fourier map had $\rho_{\max} = 0.28$ and $\rho_{\min} = -0.20 \text{ e \AA}^{-3}$. Atomic scattering factors were obtained from *International Tables for X-ray Crystallography* (1974). Computer programs are from the Computer Program Library of the Molecular Structure Laboratory of the Institute for Cancer Research, Fox Chase Cancer Center. Atomic coordinates are listed in Table 1.* The molecule is illustrated in Fig. 1. A comparison of the molecular geometries of 9AA.HCl and THA.HCl is given in Table 2.

Discussion. The disorder in the saturated ring system of THA.HCl has affected the precision of this structure determination. In the saturated ring there is disorder of C2 and C3 such that C2a and C3b lie on one side of the plane of the ring system and C2b and C3a lie on the other side of this plane. These represent alternate arrangements of the buckled ring system C1–C2a–C3a–C4 and C1–C2b–C3b–C4. This type of disorder would be expected for a molecule that is tightly bound in one area, where there is hydrogen bonding or ring stacking, but loosely packed in the disordered area. The molecule, as expected, forms three hydrogen bonds. The 9-amino group forms hydrogen bonds to

* Lists of anisotropic thermal parameters and structure factors and a figure of the hydrogen-bonding scheme have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51002 (16 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. Atomic coordinates and $B_{\text{eq}}/B_{\text{iso}}$ with e.s.d.'s in parentheses for THA.HCl.H₂O

	x	y	z	$B_{\text{eq}}/B_{\text{iso}}^*$ (Å ²)
C1	1.08958 (5)	0.41984 (5)	0.70444 (2)	4.11 (2)
Ow	0.0919 (2)	0.2629 (2)	0.35641 (7)	5.30 (7)
N1	0.3637 (2)	0.2271 (2)	0.47825 (7)	3.17 (5)
N2	0.7761 (2)	0.1816 (2)	0.65657 (8)	4.20 (7)
C1	0.4935 (2)	0.0465 (2)	0.6767 (1)	3.93 (7)
C4	0.2012 (2)	0.0880 (2)	0.5444 (1)	4.21 (8)
C5	0.4904 (2)	0.3827 (2)	0.40238 (9)	3.67 (7)
C6	0.6249 (2)	0.4536 (2)	0.3952 (1)	4.20 (7)
C7	0.7698 (2)	0.4405 (2)	0.4543 (1)	4.19 (7)
C8	0.7780 (2)	0.3584 (2)	0.5200 (1)	3.67 (7)
C9	0.6413 (2)	0.1965 (2)	0.59833 (9)	3.02 (6)
C10	0.6417 (2)	0.2840 (2)	0.53008 (8)	2.97 (6)
C11	0.4976 (2)	0.2967 (2)	0.47013 (8)	3.03 (6)
C12	0.3602 (2)	0.1485 (2)	0.54230 (9)	3.11 (6)
C13	0.4983 (2)	0.1294 (2)	0.60350 (9)	3.09 (6)
C2b	0.3338 (4)	0.0362 (4)	0.6884 (2)	3.98 (6)
C3b	0.2159 (4)	–0.0224 (5)	0.6126 (2)	4.22 (7)
C2a	0.3309 (5)	–0.0397 (5)	0.6690 (2)	4.21 (7)
C3a	0.1892 (4)	0.0550 (5)	0.6222 (2)	4.13 (7)
H10w	0.032 (3)	0.357 (3)	0.340 (1)	6.4 (6)
H20w	0.105 (4)	0.223 (4)	0.314 (2)	11 (1)
HN1	0.286 (2)	0.236 (2)	0.444 (1)	4.1 (4)
H1N2	0.770 (2)	0.119 (3)	0.694 (1)	5.5 (5)
H2N2	0.872 (3)	0.243 (3)	0.657 (1)	6.1 (6)
H1C1	0.553 (2)	–0.049 (3)	0.682 (1)	5.5 (5)
H2C1	0.551 (3)	0.114 (4)	0.721 (2)	8.0 (7)
H1C2b	0.324 (4)	–0.038 (4)	0.731 (2)	2.6 (7)
H2C2b	0.303 (3)	0.126 (4)	0.704 (2)	2.3 (6)
H1C2a	0.346 (5)	–0.128 (6)	0.643 (3)	6 (1)
H2C2a	0.386 (8)	–0.076 (9)	0.728 (5)	11 (2)
H1C3b	0.259 (5)	–0.108 (5)	0.606 (2)	2.9 (7)
H2C3b	0.107 (8)	–0.075 (8)	0.621 (4)	12 (2)
H1C3a	0.085 (4)	–0.003 (5)	0.620 (2)	2.7 (7)
H2C3a	0.210 (6)	0.154 (7)	0.650 (3)	7 (1)
H1C4	0.158 (3)	0.006 (4)	0.498 (2)	8.6 (8)
H2C4	0.148 (4)	0.163 (4)	0.536 (2)	11.1 (9)
HC5	0.387 (2)	0.387 (2)	0.364 (1)	4.0 (4)
HC6	0.618 (2)	0.508 (3)	0.350 (1)	5.1 (5)
HC7	0.863 (2)	0.495 (2)	0.448 (1)	4.7 (5)
HC8	0.867 (2)	0.351 (2)	0.559 (1)	4.5 (4)

* For non-H atoms, $B_{\text{eq}} = \frac{1}{3}(\text{trace orthogonalized } B_{ij} \text{ matrix})$.

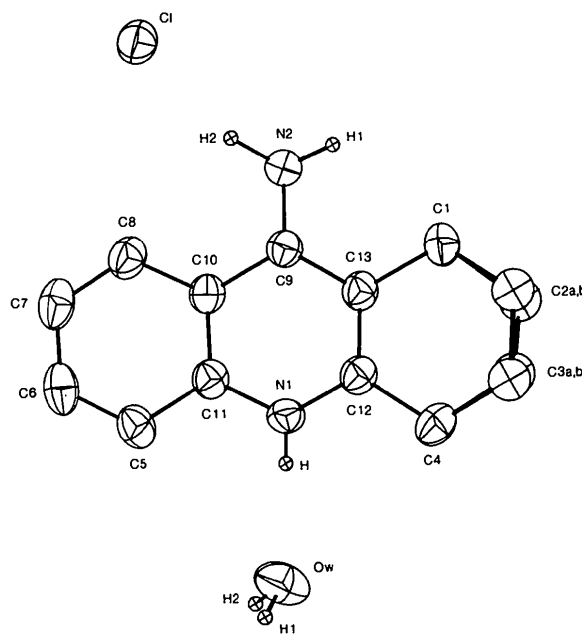


Fig. 1. Thermal-ellipsoid (50% probability) depiction of THA.HCl.H₂O showing numbering scheme.

Table 2. Comparison of bond distances (Å) and angles (°) in THA.HCl and 9AA.HCl

The numbering of atoms in 9AA.HCl has been adapted to that of THA.HCl.H₂O.

THA.HCl		9AA.HCl		THA.HCl		9AA.HCl	
C(1)–C(13)	1.509 (2)	1.418	C(2)–C(1)–C(13)	—	120.9	—	—
C(5)–C(6)	1.366 (2)	1.357	C(2a)–C(1)–C(13)	113.5 (2)	—	—	—
C(6)–C(7)	1.403 (2)	1.408	C(1)–C(2b)–C(3b)	108.0 (2)	—	—	—
C(8)–C(10)	1.411 (2)	1.416	C(2)–C(3)–C(4)	—	120.6	—	—
C(9)–C(11)	1.441 (2)	1.439	C(2a)–C(3a)–C(4)	111.0 (2)	—	—	—
C(10)–C(11)	1.406 (2)	1.409	C(3a)–C(4)–C(12)	114.8 (2)	—	—	—
N(1)–C(12)	1.344 (2)	1.364	C(6)–C(5)–C(11)	119.5 (1)	120.1	—	—
C(1)–C(2)	—	1.362	C(5)–C(6)–C(7)	120.5 (1)	120.7	—	—
C(1)–C(2a)	1.573 (3)	—	C(7)–C(8)–C(10)	120.9 (1)	120.7	—	—
C(2b)–C(3b)	1.536 (5)	—	C(8)–C(10)–C(11)	118.1 (1)	118.5	—	—
C(3)–C(4)	—	1.364	C(10)–C(9)–C(13)	119.6 (1)	118.8	—	—
C(4)–C(12)	1.499 (2)	1.410	C(13)–C(9)–N(2)	120.7 (1)	120.8	—	—
C(5)–C(11)	1.410 (2)	1.412	C(5)–C(11)–C(10)	120.5 (1)	119.8	—	—
C(7)–C(8)	1.361 (3)	1.363	C(4)–C(12)–N(1)	116.7 (1)	119.0	—	—
C(9)–N(2)	1.337 (2)	1.321	N(1)–C(12)–C(13)	120.5 (1)	120.3	—	—
C(9)–C(13)	1.406 (2)	1.434	C(1)–C(13)–C(12)	120.5 (1)	118.0	—	—
N(1)–C(11)	1.362 (2)	1.357	C(2b)–C(1)–C(13)	115.1 (2)	—	—	—
C(12)–C(13)	1.389 (2)	1.410	C(1)–C(2)–C(3)	—	120.5	—	—
C(1)–C(2b)	1.480 (3)	—	C(1)–C(2a)–C(3a)	112.1 (3)	—	—	—
C(2)–C(3)	—	1.403	C(2b)–C(3b)–C(4)	113.2 (3)	—	—	—
C(2a)–C(3a)	1.514 (5)	—	C(3)–C(4)–C(12)	—	119.8	—	—
C(3a)–C(4)	1.466 (4)	—	C(3b)–C(4)–C(12)	112.0 (2)	—	—	—
C(3b)–C(4)	1.524 (4)	—	C(11)–N(1)–C(12)	123.2 (1)	122.7	—	—
			C(6)–C(7)–C(8)	120.5 (1)	120.2	—	—
			C(8)–C(10)–C(9)	123.9 (1)	123.0	—	—
			C(9)–C(10)–C(11)	118.0 (1)	118.8	—	—
			C(10)–C(9)–N(2)	119.8 (1)	120.3	—	—
			C(5)–C(11)–N(1)	119.9 (1)	120.0	—	—
			C(10)–C(11)–N(1)	119.6 (1)	120.5	—	—
			C(4)–C(12)–C(13)	122.8 (1)	120.3	—	—
			C(1)–C(13)–C(9)	120.2 (1)	123.2	—	—
			C(9)–C(13)–C(12)	119.2 (1)	118.9	—	—

Table 3. Comparison of hydrogen bonding

D–H...A	D...A (Å)	H–D (Å)	H...A (Å)	∠A...H–D (°)
THA.HCl.H ₂ O				
N(2)–H(1)...Cl ⁱⁱ	3.303 (2)	0.88 (2)	2.53 (2)	147 (1)
N(2)–H(2)...Cl	3.321 (3)	0.99 (2)	2.38 (2)	158 (2)
N(1)–H...Ow	2.745 (2)	0.78 (2)	1.96 (2)	178 (2)
Ow–H(1)...Cl ⁱ	3.164 (2)	0.96 (2)	2.21 (2)	175 (2)
Ow–H(2)...Cl ⁱⁱⁱ	3.148 (2)	0.87 (3)	2.30 (4)	166 (2)
Symmetry code: (i) 1–x, 1–y, 1–z; (ii) 2–x, –½+y, ½–z; (iii) –1+x, ½–y, –½+z				
9AA.HCl.H ₂ O				
N(2)–H(1)...Cl ⁱ	3.230 (2)	0.83 (3)	2.45 (3)	159 (1)
N(2)–H(2)...Cl ⁱⁱ	3.233 (2)	0.74 (2)	2.55 (3)	154 (3)
N(1)–H...Ow ^{iv}	2.790 (2)	0.77 (3)	2.03 (3)	170 (3)
Ow–H(1)...Cl	3.180 (1)	0.80 (2)	2.39 (2)	174 (4)
Ow–H(2)...Cl ^{iii*}	3.180 (1)	0.61 (2)	2.87 (3)	115 (4)
Symmetry code: (i) x, y, z–1; (ii) –x, –y, –z; (iii) –x, 1–y, 1–z; (iv) 1+x, y, z				

* Not a hydrogen bond.

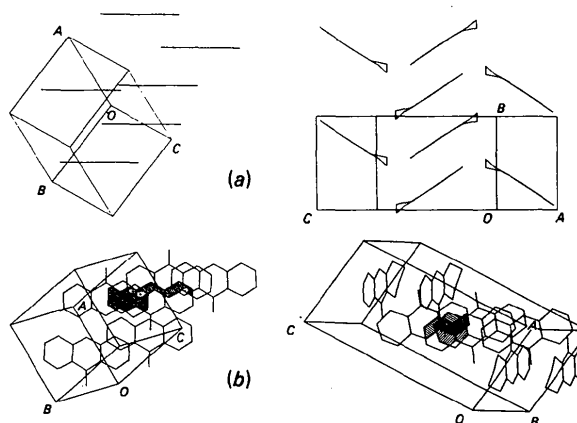


Fig. 2. Comparison of (a) molecular packing and (b) stacking of rings approximately 3.5 Å apart in the hydrates of 9AA.HCl (left) THA.HCl (right) showing the overlap of the ring system.

two Cl ions and the ring N–H group forms a hydrogen bond to the water molecule whose H atoms form hydrogen bonds to two other Cl ions. The hydrogen-bond scheme is listed and compared with that for 9AA.HCl in Table 3 and illustrated in Fig. 3 (deposited). From this comparison, it is evident that the hydrogen-bonding network is the same in both crystal structures.

A comparison with the crystal packing of 9-amino-acridine, a known mutagen, was made. In 9AA.HCl.H₂O crystals the ring systems stack in parallel planes while THA.HCl.H₂O exhibits a herringbone like packing. This is shown in Fig. 2.

Related literature. Davis & Mohs (1986), Editorial (1987), Gormally, Natarajan, Wyn-Jones, Attwood, Gibson & Hall (1984) and Summers, Kaufman, Altman & Fischer (1980).

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