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The Structure of 8-Chloro-11-(4-methyl-1-piperazinyl)-5*H*-dibenzo[*b*,*e*][1,4]diazepine Dihydrobromide, Clozapine Dihydrobromide

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Abstract

The X-ray crystal structure of the psychoactive agent clozapine as its dihydrobromide salt [8-chloro-11-(4-methyl-1-piperazinyl)-5-dibenzo[*b*,*e*][1,4]diazepine dihydrobromide] has been determined. Crystals of $C_{18}H_{19}ClN_4.2HBr$ are monoclinic, space group $P2_1/c$, with $a = 10{\cdot}047$ (2), $b = 11{\cdot}775$ (2), $c = 16{\cdot}711$ (5) Å and $\beta = 99{\cdot}94$ (2)°. The structure was solved by direct methods and Fourier techniques and refined by standard least-squares methods to $R = 0{\cdot}044$ for 4498 observed unique intensities. Compared to the free base [Petcher & Weber (1976). *J. Chem. Soc. Perkin Trans.* 2, pp. 1415–1420], the bond lengths and angles associated with the distal N of the piperazine ring become characteristic of a protonated tertiary N, while the bond lengths and angle associated with the imino N of the seven-membered ring increase upon protonation, causing a concomitant increase in the angle formed between the normals to the benzene rings.

Introduction

We present here a conformational study of the neuroleptic (antischizophrenic) drug clozapine dihydrobromide, including a comparison to the free base determined both by the present authors and by Petcher & Weber (1976)† to explore the effects of protonation. It is also of interest to compare these structures to that of the neurotransmitter dopamine to discern the three-dimensional similarities. It has been shown that clozapine, as well as other neuroleptic drugs, is capable of competing with dopamine for dopaminergic receptor sites in the brain (Burt, Enna, Creese & Snyder, 1975; Seeman, Chau-Wong, Tedesco & Wong, 1975). Although the monoprotonated form of clozapine is probably the active species, no suitable crystals have been obtained.

Experimental

A sample of the free base of clozapine was supplied by Sandoz Pharmaceutical Company. Crystals of the dihydrobromide salt were obtained by slow diffusion of the free base from ethyl acetate into acidified ethanol. The crystals were dark-orange rectangular plates and that used in the study had approximate dimensions $0{\cdot}12 \times 0{\cdot}30 \times 0{\cdot}46$ mm. The density was measured by flotation in a mixture of chloroform and dibromomethane ($\rho_m = 1{\cdot}640$, $\rho_c = 1{\cdot}665$ g cm^{-3} for $Z = 4$).

Accurate cell parameters (*Abstract*) were obtained by the least-squares refinement of the angular positions of nine Mo $K\alpha_1$ ($\lambda = 0{\cdot}70926$ Å) reflections (Busing, Ellison, Levy, King & Roseberry, 1968) in the 2θ range of 35° to 45° ($T = 299 \pm 1$ K). Intensity data were measured on an Oak Ridge computer-controlled diffractometer using Nb-filtered Mo $K\bar{\alpha}$ radiation ($\lambda = 0{\cdot}71069$ Å) and the θ–2θ scan technique, where $\sin\theta/\lambda < 0{\cdot}65$ Å^{-1}. Absorption corrections for the 4498 observed unique intensities [$>3\sigma(I)$] were calculated by the method of Busing & Levy (1957); the linear absorption coefficient was taken to be 42·55 cm^{-1}, and the calculated corrections were in the range 0·31 to 0·47.

A three-dimensional difference Fourier map, phased from the Br positions obtained from *MULTAN* (Germain, Main & Woolfson, 1971), revealed the remaining 21 non-hydrogen atoms. After several cycles of full-matrix least-squares refinement with anisotropic thermal parameters for the non-hydrogen atoms, all 21 H atoms were located in a three-dimensional difference Fourier map. These H atoms were given isotropic thermal parameters, placed into the refinement along with the non-hydrogen atoms and refined by block-diagonal least squares. The function minimized was $\sum w(|F_o| - |F_c|)^2$ in which the weights w were set according to the equation $w(|F_o|) = 1/[\sigma_c^2(|F_o|) + 0{\cdot}0004|F_o|^2]$, where $\sigma_c^2(|F_o|)$ is the variance from counting statistics. An isotropic extinction correction was applied during refinement (Larson, 1967).

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† Due to the similarities in the two determinations of the free base, the parameters determined by the present authors will be used for comparisons. (See also deposition footnote.)

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Table 1. *Fractional positional parameters* ($\times 10^4$, *for* Br *and* Cl $\times 10^5$) *and equivalent isotropic temperature factors* (Å^2 $\times 10^4$, *for* Br *and* Cl $\times 10^5$) *for the non-hydrogen atoms, with e.s.d.'s in parentheses*

$U_{eq} = \frac{1}{3} \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i . \mathbf{a}_j$.

	x	y	z	U_{eq}
C(1)	3424 (4)	9883 (3)	1298 (2)	352 (19)
C(2)	3091 (5)	10842 (4)	852 (3)	435 (22)
C(3)	1740 (5)	11161 (4)	667 (3)	535 (26)
C(4)	751 (4)	10554 (4)	957 (3)	454 (23)
N(5)	62 (3)	8967 (3)	1721 (2)	392 (18)
C(6)	−812 (4)	9163 (4)	2982 (3)	438 (22)
C(7)	−699 (4)	9003 (4)	3810 (3)	451 (23)
C(8)	472 (4)	8542 (4)	4238 (3)	411 (22)
C(9)	1511 (4)	8211 (3)	3853 (2)	372 (20)
N(10)	2363 (3)	7799 (3)	2630 (2)	347 (16)
C(11)	2876 (4)	8158 (3)	2003 (2)	313 (18)
C(12)	217 (4)	8833 (3)	2575 (3)	355 (19)
C(13)	1370 (4)	8328 (3)	3017 (2)	340 (19)
C(14)	1079 (4)	9577 (3)	1423 (2)	339 (18)
C(15)	2423 (4)	9215 (3)	1576 (2)	310 (18)
N(16)	3891 (3)	7590 (3)	1765 (2)	329 (16)
C(17)	3965 (4)	7439 (4)	892 (2)	385 (20)
C(18)	5393 (4)	7445 (3)	744 (2)	385 (21)
N(19)	6188 (3)	6558 (3)	1254 (2)	362 (17)
C(20)	6155 (4)	6805 (4)	2127 (2)	407 (21)
C(21)	4714 (4)	6772 (3)	2297 (2)	369 (20)
C(22)	7582 (5)	6467 (5)	1086 (3)	557 (28)
Cl	6088 (12)	83317 (12)	52835 (7)	5572 (65)
Br(1)	30034 (4)	95281 (4)	88080 (3)	4468 (18)
Br(2)	53434 (5)	91244 (4)	38451 (3)	5352 (25)

The final measures of goodness of fit are: $R(F) = 0.044$; $R_w(F) = 0.046$; $R(F^2) = 0.042$ and $\sigma = 0.668$ {standard deviation of an observation of unit weight, defined as $[\sum w|\Delta F|^2/(n-p)]^{1/2}$, where n is the number of observations and p is the number of adjusted parameters}. A final difference map showed excursions of density from −0·70 to 0·76 e Å^{-3}, associated with the Br^- ions. The final atomic coordinates of the non-hydrogen atoms are given in Table 1.*

The atomic scattering factors used were from Cromer & Mann (1968), except for H for which the factors of Stewart, Davidson & Simpson (1965) were used. The value of the dispersion correction for Br^- was taken from Cromer (1965). All refinement was performed with the XRAY system (Stewart, Kruger, Ammon, Dickinson & Hall, 1972).

Discussion

The conformation of the molecule, including bond angles and distances, is shown in Fig. 1. In both the free base and the dihydrobromide, the central seven-membered heterocycle (ring *C*) is in a boat conformation. The dihedral angle between the planes of the benzene rings (defined as the obtuse angle subtended by the plane normals) is 115° for the free base and 129° for the dihydrobromide.

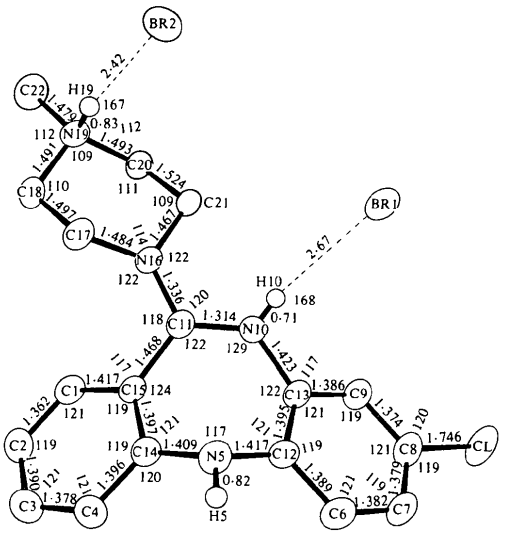


Fig. 1. Bond distances (Å) and bond angles (°) for clozapine dihydrobromide. The non-hydrogen atoms are shown using 45% probability thermal ellipsoids, while the H atoms are of arbitrary size. The average standard deviations in the bond lengths and bond angles are 0·005 Å and 0·3°, respectively.

The major differences, in the bond angles and distances, between the two molecules are associated with the sites of protonation. The bond lengths about N(10) increase slightly in the dihydrobromide. The bond angle C(13)–N(10)–C(11), however, is significantly larger in the dihydrobromide [free base, 121·4 (2); dihydrobromide, 128·6 (3)°], bringing about the increase in dihedral angle between the planes of the benzene rings mentioned earlier. The second site of protonation is the tertiary amine N(19). Upon protonation there is a slight increase in the average bond length [free base, 1·461; dihydrobromide, 1·488 Å], becoming characteristic of a protonated tertiary amine.

The piperazine ring in both compounds is in the normal chair conformation. The piperazinyl C atoms are planar within experimental error. The out-of-plane distances of the N atoms are essentially equal for the free base [N(16), 0·655; N(19), −0·669 Å] whereas for the dihydrobromide they are slightly different [N(16), 0·609; N(19), −0·709 Å]. The methyl group C(22) is equatorially attached to N(19) and the deviation from the piperazinyl C-atom plane is significantly different (free base, −0·625; dihydrobromide, −0·838 Å). The conformation of the piperazine ring with respect to the diazepine ring was analyzed by computing the torsion angle N(10)–C(11) → N(16)–C(21). There is considerably more tilt to the piperazine ring in the

* Positional parameters for all atoms of the free base and the H atoms for the dihydrobromide, anisotropic thermal parameters, and structure factors for both compounds have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36665 (35 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

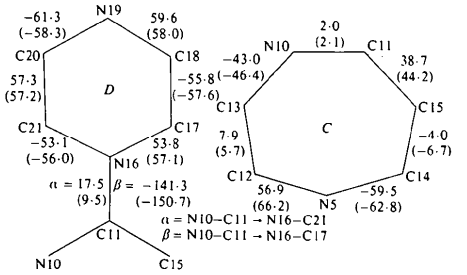


Fig. 2. Torsion angles (°) associated with the piperazine and diazepine rings. Angles for the free base are given in parentheses; angles for the dihydrobromide are for the other enantiomorph to facilitate comparison. The average standard deviation in the torsion angles is 0·5°.

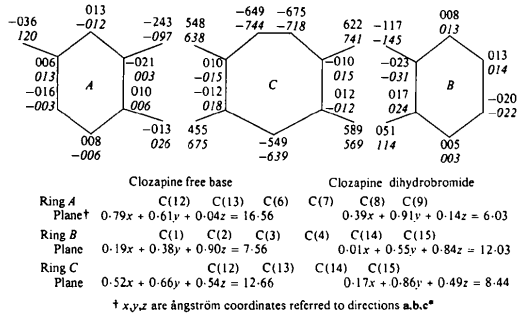


Fig. 3. Least-squares planes through the dibenzodiazepine system. Deviations of atoms from these planes are given in Å × 10^3. Data for the free base are in italics; data for the dihydrobromide are for the other enantiomorph to facilitate comparison. The average standard deviation associated with the displacement of atoms from the least-squares planes is 0·004 Å.

dihydrobromide salt than the free base [N(10)–C(11) → N(16)–C(21): dihydrobromide, 17·5; free base, 9·5°]. Despite the tilt of the piperazine ring, the piperazinyl C-atom plane remains nearly coplanar to ring *A* [angle between planes: free base, 11·3; dihydrobromide, 13·7°]. Fig. 2 illustrates the torsion angles associated with the piperazine ring.

The overall geometry of the dibenzodiazepine ring systems was compared by calculating the least-squares planes through various sets of atoms. Details for these planes and the deviations of the atoms from these planes are shown in Fig. 3. In both structures the aromatic rings are flat within experimental error. The diazepine ring *C* is in a boat conformation with atoms C(12), C(13), C(14) and C(15) coplanar. Atoms N(10) and C(11) form the stern of the boat and are equally displaced from the reference plane for both molecules. This displacement is significantly less in the dihydrobromide indicating a flattening of the ring system. There is a nearly perfect mirror plane bisecting the boat through N(5) and the center of the N(10)–C(11) bond in the free base. This is not the case, however, for the dihydrobromide. This can be seen more clearly by looking at the torsion angles around the ring (Fig. 2).

Table 2. *Hydrogen-bonding distances* (Å) *and angles* (°) *in clozapine dihydrobromide*

Donor–H···Acceptor	*D*–H	H···*A*	*D*···*A*	*D*–H···*A*
N(19)–H(19)···Br(2)	0·83 (4)	2·42 (3)	3·243 (3)	167 (3)
N(10)–H(10)···Br(1)	0·71 (3)	2·67 (3)	3·370 (3)	168 (3)
N(5)–H(5)···Br(1)	0·82 (4)	2·73 (3)	3·351 (3)	166 (3)

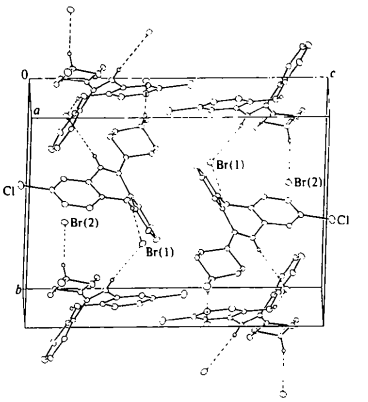
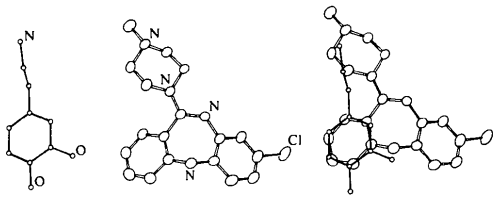


Fig. 4. Molecular packing and hydrogen bonding for clozapine dihydrobromide viewed approximately along **a**. Hydrogen bonding is shown as dashed lines.

There are no intermolecular hydrogen bonds in the free-base structure. For the dihydrobromide structure there are three hydrogen bonds. One hydrogen bond exists between Br(2) and the protonated tertiary nitrogen N(19), while Br(1) is hydrogen bonded to screw-related molecules. Details of the hydrogen bonding are given in Table 2. A packing diagram for the dihydrobromide salt, viewed approximately along **a**, is shown in Fig. 4.

Of interest is the relationship of neuroleptic drugs to known neurotransmitters. It has been shown that clozapine, along with other neuroleptics, is capable of competing with dopamine for its receptor sites in synaptosomal preparations (Seeman, Chau-Wong, Tedesco & Wong, 1975; Burt, Enna, Creese & Snyder, 1975). One parameter which may be of importance to neuroleptic activity is the relationship of the protonated tertiary amine group to the aromatic ring system (Horn & Snyder, 1971). In an effort to discern the similarities between the title compound and the neurotransmitter dopamine (Fig. 5*a*), the phenyl moiety and primary amine of dopamine.HCl (Bergin & Carlström, 1968) were fit onto the aromatic ring *B* and the tertiary amine N(19) of the drug molecule (Fig. 5*b*) using the program *BMFIT* (Nyburg, 1974). During the fitting process, the centroids of each aromatic ring were matched exactly and the other atoms were allowed to shift until the best fit was obtained; the weight of the N atom was taken to be six times that of a single C atom. The resulting distance between N atoms is 0·99 and 0·92 Å for the free base and dihydrobromide, respec-



(*a*) (*b*) (*c*)

Fig. 5. (*a*) Dopamine, (*b*) clozapine dihydrobromide and (*c*) overlap of dopamine onto clozapine.

tively. These values are similar to the 0·96 Å found for the structural isomer of clozapine, HF-2046 (Petcher & Weber, 1976) and the 1·18 and 1·21 Å found in loxapine succinate hydrate (Fillers & Hawkinson, in preparation) and loxapine free base (Cosulich & Lovell, 1977). Fig. 5(*c*) is an illustration showing the overlap of dopamine onto clozapine dihydrobromide.

A second possibility of overlap exists between dopamine and a portion of the clozapine molecule consisting of ring *A*, the heteroatom bridge and N(16). Derivatives of clozapine featuring the 1,5-benzodiazepine portion of this molecule have been prepared and evaluated for neuroleptic activity (Ellefson, Woo, Miller & Kehr, 1978; Kukla, 1977). It was found, however, that the 1,5-benzodiazepine portion of clozapine was not responsible for neuroleptic activity.

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Structures de Dérivés de l'Amino-2 Thiazoline, Tautomérie et Courte Distance Intramoléculaire S···O: (Cyclohexanecarbonyl)amino-2 Δ-2-Thiazoline-1,3, Benzoylimino-2 Thiazolidine-1,3 et (*p*-Nitrobenzoyl)imino-2 Thiazolidine-1,3

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Abstract

The crystal structures of three aminothiazoline derivatives, of pharmacological interest, have been determined by X-ray diffraction and compared to previous results: 2-(cyclohexanecarbonyl)amino-Δ^2-1,3-thiazoline (I) (anti-inflammatory drug), 2-benzoylimino-1,3-thiazolidine (II), and 2-(*p*-nitrobenzoyl)imino-1,3-thiazolidine (III). They crystallize with the following space groups and lattice parameters: (I) $C_{10}H_{16}N_2OS$, $M_r = 212{\cdot}32$, $P2_1/c$, $a = 9{\cdot}260\ (4)$, $b = 11{\cdot}303\ (5)$, $c = 13{\cdot}316\ (5)$ Å, $\beta = 128{\cdot}15\ (5)°$, $Z = 4$, $d_x = 1{\cdot}28$ Mg m^{-3}; (II) $C_{10}H_{10}N_2OS$, $M_r = 206{\cdot}30$, $P2_1$, $a = 10{\cdot}858\ (6)$, $b = 7{\cdot}236\ (4)$, $c = 6{\cdot}207\ (4)$ Å, $\beta =$

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