

## Crystal and Molecular Structure of Clonidine Hydrochloride, 2-(2,6-Dichlorophenylamino)-2-imidazoline Hydrochloride

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The crystal structure of the title compound has been determined by X-ray diffraction methods using 3209 observed reflections collected on a counter diffractometer. The crystals are monoclinic, space group  $C2/c$  with unit cell dimensions  $a=17.957(2)$  Å,  $b=11.950(1)$  Å,  $c=13.664(1)$  Å and  $\beta=128.64(1)^\circ$ . The structure was refined to a conventional  $R$ -factor of 0.040, the standard deviations for bond lengths and angles involving non-hydrogen atoms were 0.002 Å and  $0.1^\circ$ , respectively.

The planes of the phenyl ring and the imidazoline ring form an angle of  $75^\circ$ ; the structure of the molecule may thus to a certain extent be compared to that of phenylethylamines. Bond orders and charge distribution based on CNDO-calculations are discussed, as is the hydrogen bonding in the crystal.

2-(2,6-Dichlorophenylamino)-2-imidazoline (clonidine) is an effective hypotensive drug with action similar to that of methyl-DOPA.<sup>1,2</sup> Several studies seem to indicate that clonidine acts as an agonist on central as well as peripheral  $\alpha$ -adrenergic receptors.<sup>3,4</sup>

At this laboratory we have for some time been studying structures of compounds active in adrenergic systems<sup>5-8</sup> and it was considered to be of interest to compare the structure of clonidine to those of the earlier determinations as well as to the model structure discussed by Wermuth.<sup>9</sup>

### EXPERIMENTAL

A sample of clonidine hydrochloride kindly given to us by Boehringer-Ingelheim Ltd. was supplied as colourless, nearly hexagonal prismatic crystals which could be used for the X-ray experiments without recrystallization. The specimen selected for data collection was 0.30

mm along the prism edge and 0.35 mm along the diagonals of the hexagon. Data were collected on a SYNTEX PI four-circle diffractometer using graphite crystal monochromated MoK $\alpha$  radiation ( $\lambda=0.71069$  Å).

The crystals are monoclinic; systematic absences are  $h+k$  odd for  $(hkl)$  and  $l$  odd for  $(h0l)$  and the space group is thus  $Cc$  or  $C2/c$ . Cell parameters were determined by a least-squares fit to the diffractometer settings for 15 general reflections.

Intensity data were recorded using the  $\theta/2\theta$  scanning mode with a scan speed ( $2\theta$ ) of  $2-8^\circ \text{ min}^{-1}$  depending on the intensity; the scan range was from  $0.8^\circ$  below  $2\theta(\alpha_1)$  to  $0.9^\circ$  above  $2\theta(\alpha_2)$  and background counts were taken for 0.35 times the scan time at each of the scan limits. All unique reflections with  $\sin \theta/\lambda < 0.54 \text{ \AA}^{-1}$  were measured, reflections in the interval  $0.54 \text{ \AA}^{-1} < \sin \theta/\lambda < 0.80 \text{ \AA}^{-1}$  were measured only if a quick scan gave an intensity larger than a preset value. Out of the 4218 reflections recorded, 3209 with  $I > 2\sigma(I)$  were retained for the structure analysis. The standard deviations for the intensities were calculated by  $\sigma(I)=[C_T + (0.02 C_N)^2]^{1/2}$  where  $C_T$  is the total number of counts and  $C_N$  is the scan count minus background count. The usual corrections were made for Lorentz and polarization effects and also for absorption.

Scattering factors used were those of Doyle and Turner for Cl, Cl $^-$ , N and C,<sup>10</sup> and of Stewart, Davidson and Simpson for H.<sup>11</sup> Descriptions of the computer programs used are given in Refs. 12 and 13. The quantity minimized in the least-squares calculations was  $\sum W\Delta F^2$  where  $W$  is the inverse of the variance of the observed structure factors.

### CRYSTAL DATA

2-(2,6-Dichlorophenylamino)-2-imidazoline hydrochloride (clonidine, HCl),  $C_9H_9N_3Cl_2 \cdot HCl$ , monoclinic,  $a=17.957(2)$  Å;  $b=11.950(1)$  Å;

$c = 13.664(1) \text{ \AA}$ ;  $\beta = 128.64(1)^\circ$ ; ( $t = 18 \pm 1^\circ \text{C}$ );  $V = 2290.2 \text{ \AA}^3$ ;  $M = 266.56$ ;  $Z = 8$ ;  $F(000) = 1088$ ;  $D_{\text{calc}} = 1.546 \text{ g cm}^{-3}$ ;  $\mu = 7.67 \text{ cm}^{-1}$ . Absent reflections: ( $hkl$ ) for  $h+k$  odd, ( $h0l$ ) for  $l$  odd. Space group  $C2/c$  (No. 15).

## STRUCTURE DETERMINATION

Intensity statistics indicated the presence of centres of symmetry; the space group was thus assumed to be  $C2/c$ . The structure was solved by direct methods using the program assembly MULTAN.<sup>13</sup> Phases were determined for 300 reflections with  $E > 1.56$ ; an  $E$ -map based on the set with the highest absolute figure of merit (1.06) revealed the positions of the three chlorine atoms and a few of the lighter atoms. The remaining non-hydrogen atoms were localized by the use of successive Fourier refinements; the positions of the hydrogen atoms were calculated from stereochemical considerations after a preliminary least-squares refinement. All positional parameters, anisotropic thermal parameters for non-hydrogen atoms, and isotropic thermal parameters for hydrogen atoms were refined by least-squares methods to a conventional  $R$ -factor of 0.04 and a goodness of fit,  $S = (\sum W \Delta^2 / m - n)^{1/2}$ , of 2.02. A repeated least-squares calculation where the weights for reflections with  $\sin \theta / \lambda < 0.55 \text{ \AA}^{-1}$  were multiplied by a factor varying from 0 to 1 as  $\sin \theta / \lambda$  increases from 0 to  $0.55 \text{ \AA}^{-1}$  gave a conventional  $R$ -factor of 0.040,  $R_w = 0.045$ , whereas  $S$  decreased to 1.59.

The final parameters are listed in Table 1. Tables of observed and calculated structure factors are available from the authors.

The anisotropic thermal parameters were analysed in terms of rigid-body motion both for the organic ion as a whole and separately for the dichlorophenylamine part and the aminoimidazoline part. The results indicated that the latter description justified correction of bond lengths for libration effects.

## DISCUSSION

Selected interatomic distances and bond angles are listed in Table 2. Estimated standard deviations calculated from the correlation matrix were about  $0.002 \text{ \AA}$  for distances and  $0.1^\circ$  in angles involving non-hydrogen atoms. Fig. 1 shows the conformation, thermal ellipsoids and bond lengths corrected for libration.

C-H bonds were found in the range  $0.91 - 0.94 \text{ \AA}$  (mean  $0.92 \text{ \AA}$ ) in the phenyl group and  $0.92 - 1.01 \text{ \AA}$  (mean  $0.96 \text{ \AA}$ ) in the imidazoline ring; N-H bonds were found to be  $0.79 - 0.88 \text{ \AA}$  (mean  $0.84 \text{ \AA}$ ).

The dichlorophenyl moiety has a quite normal geometry with the average C-C bond length of  $1.389 \text{ \AA}$  and C-Cl bond length of  $1.734 \text{ \AA}$ . The internal valence angles are slightly exceeding  $120^\circ$  at carbon atoms to which the electro-negative chlorine atoms are attached. The imidazoline part is protonized and the two nitrogen atoms are thus chemically equivalent. It has nearly  $mm$  symmetry, the C7-N2 and

Table 1. Fractional atomic coordinates and thermal parameters with estimated standard deviations. The temperature factor is given by  $\exp(-2\pi^2(U_{11}a^2h^2 + \dots + 2U_{12}a^*b^*hk + \dots))$ .

ATOM	X	Y	Z	U11	U22	U33	U12	U13	U23
CL1	.39246(3)	.04499(3)	.28877(4)	.0394(2)	.0291(2)	.0413(2)	-.0014(1)	.0233(2)	-.0026(1)
CLP	.11145(3)	.09576(4)	.27312(4)	.0348(2)	.0468(2)	.0492(2)	-.0024(2)	.0165(2)	-.0074(2)
CL3	.36934(3)	.39215(5)	.41592(7)	.0743(4)	.0475(3)	.0991(5)	-.0143(2)	.0532(4)	.0041(3)
N1	.19141(12)	.30305(11)	.24426(13)	.0576(8)	.0293(6)	.0376(6)	.0141(6)	.0275(6)	.0061(5)
N2	.18866(12)	.18249(13)	.18596(13)	.0538(8)	.0439(7)	.0320(6)	.0219(6)	.0208(6)	.0064(5)
N3	.09896(12)	.33221(14)	.02918(14)	.0592(9)	.0438(7)	.0424(7)	.0246(7)	.0209(7)	.0163(6)
C1	.25683(11)	.23840(12)	.35331(13)	.0406(7)	.0294(6)	.0302(6)	.0066(5)	.0207(6)	.0013(5)
C2	.22852(10)	.14102(13)	.37769(13)	.0333(6)	.0336(6)	.0318(6)	.0029(5)	.0180(5)	-.0011(5)
C3	.29184(12)	.08789(14)	.48484(16)	.0426(8)	.0390(7)	.0378(7)	.0045(6)	.0232(7)	.0000(6)
C4	.38521(12)	.11311(16)	.57002(15)	.0386(8)	.0540(10)	.0307(7)	.0096(7)	.0164(6)	.0061(7)
C5	.41519(12)	.20938(17)	.54939(16)	.0338(7)	.0539(9)	.0386(8)	-.0015(7)	.0176(6)	.0077(7)
C6	.35144(12)	.27139(14)	.44185(16)	.0443(8)	.0350(7)	.0463(8)	-.0020(6)	.0294(7)	.0045(6)
C7	.16182(11)	.27365(13)	.13132(14)	.0393(7)	.0308(6)	.0308(7)	.0077(5)	.0226(5)	.0074(5)
C8	.13999(17)	.17429(18)	-.02736(17)	.0715(12)	.0546(11)	.0369(8)	.0172(9)	.0292(9)	.0051(7)
C9	.07643(15)	.27859(19)	-.00141(17)	.0548(10)	.0589(11)	.0363(8)	.0153(9)	.0244(8)	.0132(7)

ATOM	X	Y	Z	B	ATOM	X	Y	Z	B
HCl3	.271	.014	.496	4.1	HCl4	.420	.072	.644	4.1
HCl6	.476	.236	.603	4.1	H1C8	.108	.107	-.058	5.9
H2C8	.182	.174	-.049	5.9	H1C9	.089	.323	-.127	5.9
H2C9	.007	.255	-.148	5.9	HN1	.192	.373	-.254	4.7
HN2	.238	.146	.163	4.7	HN3	.472	.386	.027	4.7

Table 2. Distances (Å) and angles (°) in the crystals of clonidine hydrochloride.

Bond	Length	Bond angles	
C1-C2	1.391	C6-C1-C2	117.3
C2-C3	1.382	C1-C2-C3	121.5
C3-C4	1.377	C2-C3-C4	119.8
C4-C5	1.371	C3-C4-C5	120.2
C5-C6	1.385	C4-C5-C6	119.8
C6-C1	1.392	C5-C6-C1	121.4
C1-N1	1.418	C1-C2-C12	120.0
C2-C12	1.733	C3-C2-C12	118.5
C6-C13	1.724	C1-C6-C13	118.9
N1-C7	1.328	C5-C6-C13	119.7
N2-C7	1.322	C2-C1-N1	121.4
N3-C7	1.321	C6-C1-N1	121.3
N2-C8	1.450	C1-N1-C7	123.0
N3-C9	1.447	N1-C7-N3	123.1
C8-C9	1.533	N1-C7-N2	125.2
		C7-N2-C8	110.6
		N2-C8-C9	103.5
		C8-C9-N3	102.6
		C9-N3-C7	111.5
		N2-C7-N3	111.8

Torsional angles  
(positive for a clockwise rotation)

C2-C1-N1-C7	-76.5
C1-N1-C7-N2	0.0
C1-N1-C7-N3	178.1
C6-C1-N1-C7	105.2

Hydrogen bonds

C11-N1( $\frac{1}{2}-x, -\frac{1}{2}+y, \frac{1}{2}-z$ ) (Å)	3.094
C11-HN1 (Å)	2.25
C11-HN1-N1 (°)	161.2
C11-N2( $x, y, z$ ) (Å)	3.193
C11-HN2 (Å)	2.38
C11-HN2-N2 (°)	163.4

C7-N3 bond lengths being 1.337 Å and 1.331 Å, respectively, and the N2-C8 and N3-C9 both close to 1.454 Å. The arrangement of bonds about the bridging atom, N1, is nearly planar with a C1-N1-C7 angle of 123.0°.

In order to determine bond orders and net charges on the atoms CNDO calculations were performed for the free organic ion.<sup>14</sup> The  $\pi$  bond order for the three C7-N bonds is 0.55, for the C1-N1 bond 0.19, and for the N2-C8 and N3-C9 bonds 0.17. The main part of the positive charge is situated on the C7 atom (+0.45) and on the three hydrogen atoms bonded to nitrogen (+0.17).

The atoms of the six-membered ring are strictly coplanar, as are the atoms of the five-

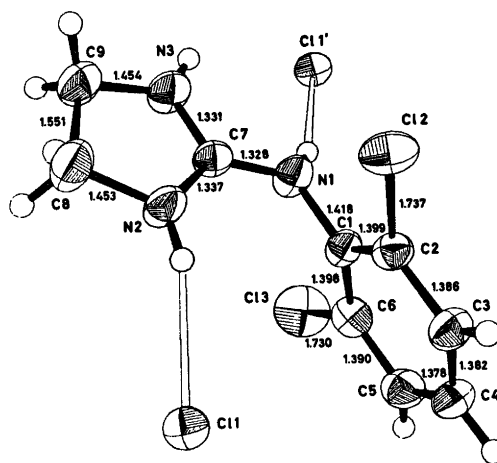


Fig. 1. Perspective view of the molecule showing bond lengths corrected for libration. Hydrogen bonds are indicated. Non-hydrogen atoms are represented by thermal ellipsoids defined by the principal axes of thermal vibration and scaled to include 50% probability.

membered ring. The chlorine atoms are situated 0.01-0.02 Å out of the benzene plane; the N1 atom is situated 0.02 Å out of the benzene plane and 0.05 Å out of the imidazoline ring plane. The angle between the ring planes is 75°.

The structure of the phenyl-N1-C7-N3 part of the molecule is strikingly similar to that of the phenylethylamines previously investigated. The sympathomimetic amines of this kind showing adrenergic activity have without exception been found to crystallize in a conformation with a fully extended side chain. The atoms of the side chain are thus close to a plane which is normally found to be nearly perpendicular to that of the phenyl ring. Wermuth *et al.* propose a structure with the characteristic measures  $D=5.0-5.1$  Å (distance from the phenyl ring centre to the projection of the N3 position on the phenyl ring plane) and  $H=1.28-1.36$  Å (distance from N3 to the phenyl ring plane); this is in accordance with the figures given by Pullmann *et al.*<sup>15</sup> for favourable distances in  $\alpha$ -sympathomimetic amines. The distances for clonidine are slightly overestimated, however, the actual numbers found in the present investigation being  $D=4.89$  Å and  $H=1.02$  Å. Results from previous investigations for 6-hydroxydopamine,<sup>5</sup> 5-hy-

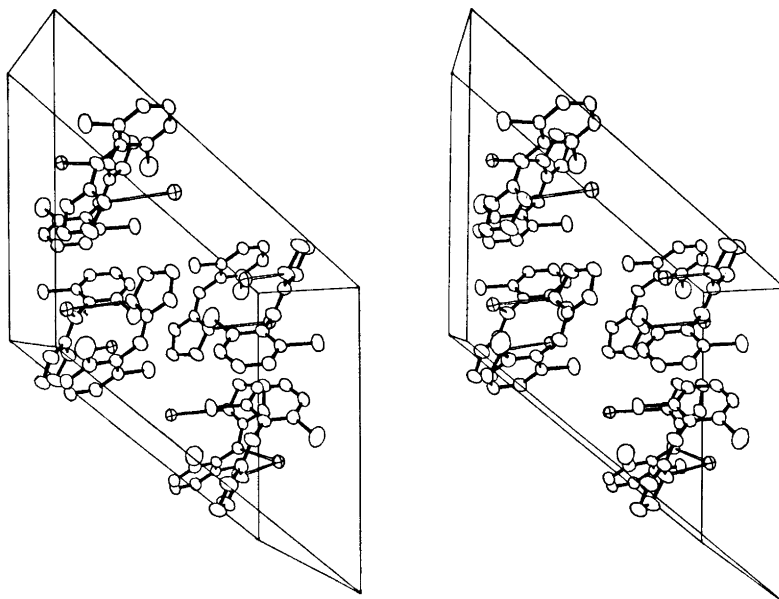


Fig. 2. Stereoscopic view of the crystal structure of clonidine.

droxydopamine,<sup>6</sup> adrenaline,<sup>7</sup> and noradrenaline<sup>8</sup> give  $D$  in the range 4.89–5.00 Å and  $H$  from 1.39 to 1.43 Å.

A stereoscopic drawing of the crystal structure is shown in Fig. 2. There is a strong hydrogen bond between N1 and a chlorine ion (3.094 Å) and a weaker between N2 and another chlorine ion (3.193 Å); N3 is not engaged in hydrogen bonding. Correspondingly, N1–HN1 was found to be the longest of the N–H bonds and N3–HN3 to be the shortest of the three.

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