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Structure of 1-(N'-Ethoxycarbonylhydrazino)phthalazinium Chloride Monohydrate

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Abstract. $C_{11}H_{13}N_4O_2^+.Cl^-.H_2O$, monoclinic, $P2_1/c$, $a = 5.110$ (1), $b = 15.435$ (3), $c = 17.948$ (5) Å, $\beta = 105.13$ (2)°, $U = 1366$ Å^3, $D_m = 1.397$, $D_x = 1.393$ Mg m^{-3}, $Z = 4$. The structure was solved by the heavy-atom method and refined to $R = 0.086$ for 1784 counter-collected independent reflections. In the title compound (an antihypertensive agent) water molecules and chloride anions bridge the cations *via* hydrogen bonds in a three-dimensional net.

Introduction. The title compound (I) is used (as ethoxy-carbonylhydralazine or Binazin) in the treatment of hypertension because of its hypotensive and antihypertensive properties (Biniecki, Haase, Izdebski, Kesler & Rylski, 1958). This structure analysis was performed to compare its molecular geometry with those of other phthalazine derivatives which act as vasodilators: hydralazine (Stadnicka & Lebioda, 1978) and dihydralazine (Stadnicka & Lebioda, 1979).

(I)
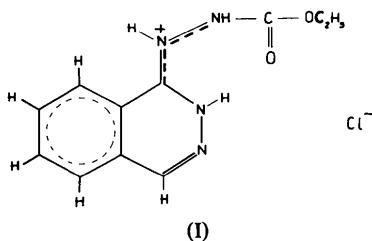
Colourless needle-shaped single crystals of (I) were obtained by recrystallization from aqueous solution. The systematic absences $h0l$ for l odd and $0k0$ for k

odd were found from Weissenberg photographs. A crystal with dimensions $0.12 \times 0.05 \times 0.12$ mm was used to collect intensity data with a CAD-4 (Enraf–Nonius) diffractometer using graphite-monochromated Mo $K\alpha$ radiation. Unit-cell parameters were obtained by least-squares refinement from the setting angles of 15 reflections used in the auto-indexing procedure. All reflections in the range $2° \le \theta \le 23°$ were measured with a $\theta/2\theta$ scan and a $(0.8 + 0.3 \tan \theta)°$ scan range. The intensities were corrected for Lorentz and polarization effects, but not for absorption $[\mu(\text{Mo } K\alpha) = 0.296$ mm$^{-1}]$. The fluctuation in the intensity of a standard reflection was less than 5%. 1879 independent reflections were measured and 1784 of these, with positive intensities, were used in further calculations. The structure of the hydrobromide counterpart, which is isomorphous (Chojnacki, Lebioda & Stadnicka, 1975), was solved by the heavy-atom method but not refined ($R = 0.18$). The parameters of this structure were used as the starting values in the full-matrix least-squares refinement of the hydrochloride. Neutral-atom scattering factors (Cromer & Waber, 1965) for all atoms and anomalous-scattering corrections (Cromer, 1965) for the Cl scattering function were used. A difference map revealed 12 of the 15 H atom positions; those missing were from the ethyl group which undergoes strong thermal motion as shown in Fig. 1. The positional parameters of the H atoms were refined, except for those of the C_2H_5 group which were located from geometrical considerations (C–H = 1.08 Å, and tetrahedral valence angles). The H atoms were given isotropic thermal parameters equivalent to the aniso-

tropic parameters of the atoms to which they were bonded. In the final least-squares cycle, the maximal and average shift to e.s.d. ratios were 0·4 and 0·2 for non-hydrogen atoms and 0·9 and 0·4 for H atoms respectively. No peaks of chemical significance were observed on the final difference map. Discrepancy indices were $R = 0.086$, $R_w = 0.070$ and $R_G = 0.067$

Table 1. *The final atomic coordinates* ($\times 10^4$ *for non-hydrogen atoms*, $\times 10^3$ *for hydrogen atoms*) *with e.s.d.'s in parentheses*

|	x	y	z
Cl	10999 (3)	1771 (1)	2266 (1)
O(1)	7538 (9)	4333 (2)	2059 (2)
O(2)	4402 (6)	4071 (2)	2710 (1)
O(3)	663 (8)	4617 (2)	1030 (2)
N(2)	3913 (8)	3726 (2)	358 (2)
N(3)	3330 (9)	4092 (2)	−372 (2)
N(4)	6170 (9)	2789 (3)	1314 (2)
N(5)	4732 (9)	3157 (3)	1796 (2)
C(1)	5730 (10)	3099 (3)	591 (2)
C(4)	4607 (11)	3808 (3)	−852 (3)
C(5)	7856 (11)	2823 (3)	−1225 (3)
C(6)	9687 (12)	2162 (4)	−1041 (3)
C(7)	10261 (11)	1768 (3)	−308 (3)
C(8)	9007 (11)	2057 (3)	243 (3)
C(9)	7160 (10)	2743 (3)	61 (2)
C(10)	6562 (10)	3122 (3)	−678 (2)
C(11)	5768 (11)	3896 (3)	2188 (3)
C(12)	4808 (14)	4934 (3)	3049 (3)
C(13)	4209 (15)	4945 (4)	3783 (3)
H(1)	416 (7)	410 (2)	−139 (2)
H(2)	740 (9)	305 (2)	−176 (2)
H(3)	1069 (9)	194 (3)	−142 (2)
H(4)	1158 (11)	130 (3)	−21 (2)
H(5)	940 (10)	179 (3)	78 (2)
H(6)	349	540	266
H(7)	690	514	312
H(8)	209	474	371
H(9)	550	449	417
H(10)	447	558	404
H(11)	283 (14)	401 (4)	75 (3)
H(12)	779 (10)	235 (3)	160 (2)
H(13)	368 (10)	274 (3)	205 (2)
H(14)	−62 (11)	504 (3)	78 (3)
H(15)	9 (12)	451 (3)	144 (3)
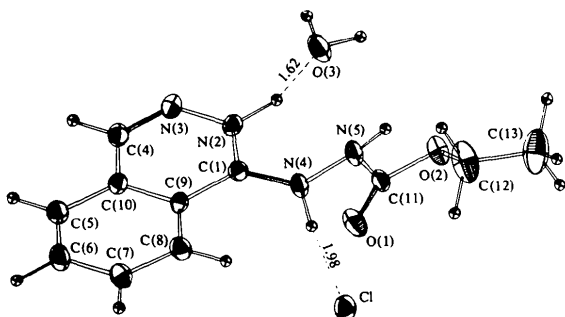
Fig. 1. View of the molecule with thermal ellipsoids drawn at the 30% probability level; H atoms are represented as spheres of arbitrary radius.

where $R = \sum |\Delta F|/\sum |F|$, $R_w = \sum w^{1/2}|\Delta F|/\sum w^{1/2}|F|$ and $R_G = [\sum w\Delta F^2/\sum wF^2]^{1/2}$. The weights used were a combination of those from counting statistics and Cruickshank's (1969) scheme, $w^{-1} = (6·05 + |F_o| + 0·0127F_o^2)[\sigma^2(I) + (0·01I)^2]/(LpI)$. The final positional parameters of the atoms are given in Table 1.* Computations were performed with Sheldrick's (1975) program system adapted to a Honeywell 3200 computer.

Discussion. The configuration of the molecule is illustrated in Fig. 1, where non-hydrogen atoms are represented as ellipsoids corresponding to the thermal parameters (Johnson, 1965). The cation has an additional H atom at N(2) relative to the phthalazine system. The molecular dimensions are shown in Fig. 2. When compared with the structure of hydralazine (Stadnicka & Lebioda, 1978) there are only small differences in the phthalazinium system. Therefore we shall not discuss again the influence of the substituent on the geometry of phthalazine (Huiszoon, van de Waal, van Egmond & Harkema, 1972).

Deviations of the atoms from the best planes through the phthalazine system and the pyridazine ring are small, but statistically significant. The $\chi^2_{n-3} = \sum_n \Delta^2/\sigma^2$ statistics (Hamilton, 1964) were $\chi^2_7 = 84$ for the phthalazine system and $\chi^2_3 = 16$ for the pyridazine ring. The angle between the best planes through the benzene ring and the pyridazine ring is 1·43°. The equations of these planes are $3·4571x + 10·1465y + 2·5812z = 5·2665$ and $3·3817x + 10·4328y + 2·5192z = 5·3070$ respectively.* As in hydrazine, N(4) has sp^2 hy-

* Lists of structure factors, thermal parameters and deviations of the atoms from the best planes have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34052 (13 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.
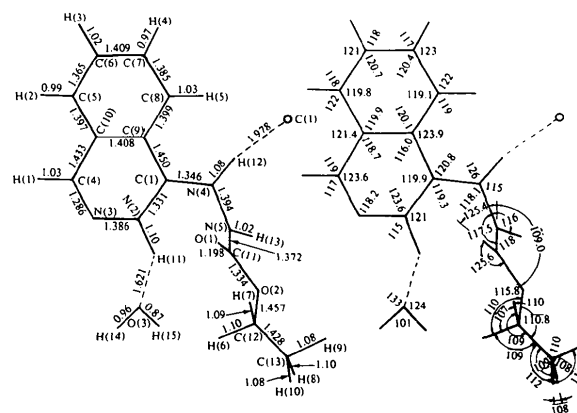

Fig. 2. Bond lengths (Å) and valence angles (°). Estimated standard deviations are 0·006 Å and 0·4° for bonds involving non-hydrogen atoms only, and 0·05 Å and 4·0° for those involving H.

Table 2. *Distances* (Å) *and angles* (°) *in the hydrogen-bonding system and contacts of the chloride ion less than* 3·15 Å

D—H···A	Acceptor position	D···A	H···A	∠DHA
N(2)—H(11)···O(3)	(x,y,z)	2·674 (5)	1·62 (6)	158 (5)
O(3)—H(15)···O(1)	$(-1 + x, y, z)$	2·774 (5)	1·94 (5)	159 (5)
O(3)—H(14)···N(3)	$(-1 - x, -y, -z)$	2·876 (5)	1·92 (5)	173 (5)
N(4)—H(12)···Cl⁻	(x,y,z)	3·046 (4)	1·98 (4)	167 (3)
N(5)—H(13)···Cl⁻	$(1 + x, y, z)$	3·125 (4)	2·13 (5)	165 (3)
C(4)—H(1)···Cl⁻	$(-1 + x, \frac{1}{2} - y, \frac{1}{2} + z)$	3·515 (6)	2·86 (5)	122 (4)
C(8)—H(5)···Cl⁻	(x,y,z)	3·533 (6)	2·57 (5)	156 (3)
C(5)—H(2)···Cl⁻	$(x, \frac{1}{2} - y, \frac{1}{2} + z)$	3·547 (6)	2·86 (5)	127 (4)
C(6)—H(3)···Cl⁻	$(x, \frac{1}{2} - y, \frac{1}{2} + z)$	3·669 (6)	3·11 (6)	116 (5)
C(12)—H(7)···Cl⁻	$(2 - x, -\frac{1}{2} + y, \frac{1}{2} - z)$	3·685 (6)	2·89 (–)	130 (–)
C(12)—H(6)···Cl⁻	$(1 - x, -\frac{1}{2} + y, \frac{1}{2} - z)$	4·036 (6)	3·15 (–)	138 (–)
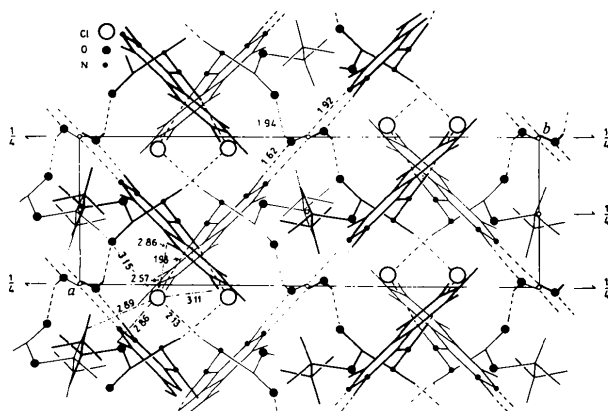
Fig. 3. Packing in the structure viewed along c. Hydrogen bonds are drawn with broken lines. For one chloride anion, other contacts are marked with dashed-dotted lines.

The packing in the structure is shown in Fig. 3. The cations are bridged to form an infinite net with hydrogen bonding through water molecules and chloride ions. The distances and angles in the system of hydrogen bonds are given in Table 2. The water molecule donates both its protons forming hydrogen bonds with O(1) and N(3), and is an acceptor in the N(2)—H(11)···O(3) hydrogen bond. H(11) is approximately in the plane of the H₂O molecule. The Cl⁻ ion is the acceptor in two strong hydrogen bonds with N(4) and N(5); its other contacts with methine H atoms at distances less than 3·15 Å are also given in Table 2.

bridization (as can be inferred from its nearly planar bonds), but there is an elongation of C(1)—N(4) from 1·311 (9) to 1·346 (5) Å and a shortening of N(4)—N(5) from 1·436 (8) to 1·394 (5) Å; this is probably significant, and can be attributed to the electron-withdrawing effect of the ethoxycarbonyl substituent. A deficiency of electrons at N(5) causes delocalization of the π electrons of N(4) along the N(4)—N(5) bond, and hence its shortening. The apparent shortening of bond lengths in the ethyl group is probably due to the strong thermal vibrations of C(12) and C(13).

The therapeutic index for ethoxycarbonyl-hydralazine is four times higher than that for hydralazine (Biniecki, 1976). It may be worth checking the therapeutic activity of a derivative in which a substituent at N(5) is more electron withdrawing than the ethoxycarbonyl group. The rationale behind this is that such a substitution would change the hydrogen-bonding properties in the hydrazine, which are probably crucial for the activity.

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