

Fig. 2. View of the unit cell, *a*-axis projection.

*trans-trans* chair conformation. The two C=N bonds [C(7)–N' and C(7)'–N] are parallel to each other. The C(7)–N' and C(7)'–N distances are 3.60 Å. This shows that the structure can take the conformation shown

in (IV) (*cis-anti-cis*) if two bonds move toward each other. Fig. 1 shows thermal ellipsoid plot of the molecule and Fig. 2 shows the view of the unit cell, *a*-axis projection. The intermolecular contacts are all greater than van der Waal's distances.

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## The Crystal Structure of Phenmetrazine Hydrochloride

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The semi-rigid amphetamine analogue phenmetrazine crystallizes as the hydrochloride in both the orthorhombic and the monoclinic systems. Monoclinic crystals with  $a=6.11$ ,  $b=29.58$ ,  $c=7.19$  Å,  $\beta=112.4^\circ$ , space group *Cc* and four molecules of  $C_{11}H_{15}ON \cdot HCl$  in the unit cell were used for the investigation. The structure was determined from 1098 unique and significant counter-recorded reflexions within  $\sin \theta/\lambda \leq 0.65$  by the heavy-atom procedure and direct methods independently and was refined to an *R* index of 0.055. The conformation of the molecule was found to be almost identical with corresponding parts of amphetamine. The structure contains two strong  $NH \cdots Cl$  hydrogen bonds with  $N \cdots Cl$  distances of 3.09 and 3.07 Å which give rise to infinite layers of phenmetrazine and chloride ions. The layers are held together by van der Waals forces.

#### Introduction

Phenmetrazine (phenmetraline) is a semi-rigid analogue of amphetamine. Having a psychostimulating action like that of amphetamine (although weaker) it

has been widely abused as a stimulating drug. Its main action, however, of decreasing appetite, has earlier made it a commonly used anorexic drug (Anorex, Preludin *etc.*).

The present study forms part of a research project

on biologically active amines related to naturally occurring monoamines. The aim has been to compare the molecular conformation of phenmetrazine with that of related compounds.

### Experimental

Recrystallization of phenmetrazine hydrochloride in a xylene-chloroform solution yielded crystals in the shape of thin plates. Some of these crystals were found to be orthorhombic with the unit-cell dimensions  $a = 11.67$ ,  $b = 19.96$ ,  $c = 10.02$  Å ( $Z = 8$ ) and with the long axis perpendicular to the plates. The majority of the crystals, however, were monoclinic and it was decided to perform the investigation on the latter form because of the larger dimensions of the plates. Preliminary unit-cell dimensions and systematic absences were determined from rotation and Weissenberg diagrams while accurate cell parameters were derived from diffractometer measurements.

#### Crystal data

Phenmetrazine (3-methyl-2-phenylmorpholine)hydrochloride

$C_{11}H_{15}ON \cdot HCl$	F.W. 213.71
$a = 6.112$ (3) Å	$V = 1200.85$ Å <sup>3</sup>
$b = 29.576$ (18)	$D_x (Z = 4) = 1.182$ g cm <sup>-3</sup>
$c = 7.187$ (4)	$\mu (Mo K\alpha) = 2.90$ cm <sup>-1</sup>
$\beta = 112.43$ (8)°	$F(000) = 456$ .

Systematic extinctions:  $hkl$  absent with  $h+k = \text{odd}$ ,  $h0l$  absent with  $l = \text{odd}$ , indicating either of the space groups  $Cc$  or  $C2/c$ . Since the latter requires eight general positions it could be excluded and the structure analysis also confirmed the non-centrosymmetric space group  $Cc$ .

A crystal measuring  $0.35 \times 0.35 \times 0.25$  mm was trimmed from a large plate by partial solution in water. The crystal was mounted about  $b$  running perpendicular to the surface of the plate. Integrated intensities were recorded using a linear diffractometer (PAILRED) with graphite-monochromated  $Mo K\alpha$  radiation ( $0.7107$  Å) for the layers  $h0l$  to  $h38l$  within  $\sin \theta / \lambda \leq 0.65$ . Of the 1420 independent reflexions observable within a quarter-sphere, 1098 were significantly above background. The net intensities were not corrected for absorption because of the low absorbance of the material. The observed structure amplitudes were brought on an absolute scale by Wilson statistics and normalized structure factors,  $|E_{(hkl)}|$ , were calculated.

#### Determination and refinement of the structure

The structure was determined by the heavy-atom technique and by direct methods independently. In the former case the  $y$  coordinate of the chlorine atom was first found in a Patterson synthesis. With phases from the chlorine atom alone, a three-dimensional

electron density map showed several peaks of which four could be interpreted as probable atomic positions. A second electron density map based on the chlorine atom and these four maxima revealed all the missing non-hydrogen atoms. The automatic phasing program *MULTAN* by Germain, Main & Woolfson (1971) proved equally efficient. The best of the sets with phases calculated for the 322 strongest  $|E|$  values ( $\geq 1.20$ ) gave an  $E$  map showing a strong peak corresponding to the chlorine atom as well as six other maxima consistent with ordinary bond lengths and bond angles. A Fourier map calculated with the phases based on these seven maxima readily gave the positions of all non-hydrogen atoms. The refinement was carried out by a full-matrix least-squares procedure. After two cycles of isotropic refinement of all non-hydrogen atoms and one cycle of anisotropic refinement the conventional  $R$  index ( $R = \sum ||F_o| - |F_c|| / \sum |F_o|$ ) was 8.3%. In a subsequent difference synthesis all hydrogen atoms were located. From a further refinement cycle including the hydrogen atoms, which were given a fixed  $B$ -value of  $4.5$  Å<sup>2</sup>, it became evident that there were substantial discrepancies between the very strongest  $|F_o|$  and  $|F_c|$ . A final cycle of refinement where the eight reflexions with  $|F_o| > 70$  were excluded yielded an  $R$  value of 5.5%. As the crystal used for the measurements was not of the very best quality it was decided that further refinement procedures should be of limited value. Moreover, the intensities probably suffered from a minor systematic error due to a slight misalignment of the detector.

Unit weight was applied to all  $|F_o|$  and the scattering factors were those of *International Tables for X-ray Crystallography* (1962) except for those of the hydrogen atoms which were taken from Stewart, Davidson & Simpson (1965). The computations were performed on an IBM 360/75 using our program system (Bergin, 1971). The final positional and thermal parameters are given in Tables 1 and 2. A list of the observed and calculated structure factors are available by request from the authors.

#### Description and discussion of the structure

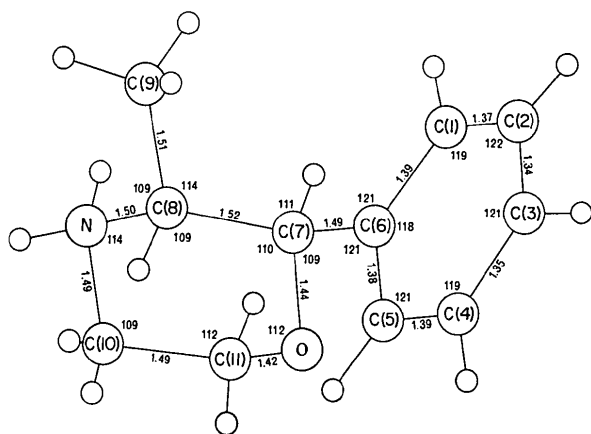
##### *The geometry of the molecule*

The phenmetrazine molecule is shown in Fig. 1, which also gives the numbering of the atoms. As can be seen, the molecule contains two planar parts, a phenyl ring and a maximally extended ethylamine side chain which makes part of a six-membered chair-formed heterocyclic ring. The atoms of the former are coplanar within  $\pm 0.02$  Å whereas the atom C(7) is  $0.05$  Å out of the ring plane. The ethylamine 'side chain' involving the atoms C(6), C(7), C(8) and N is planar within  $\pm 0.03$  Å. The torsion angle  $\tau_1$ , C(1)-C(6)-C(7)-C(8), is  $-105^\circ$ ;  $\tau_2$ , C(6)-C(7)-C(8)-N, is  $-175^\circ$  and  $\tau_3$ , C(6)-C(7)-C(8)-C(9), is  $63^\circ$ . This is a conformation characteristic of most phenethylamines so far investigated where the plane of an extended ethylamine side

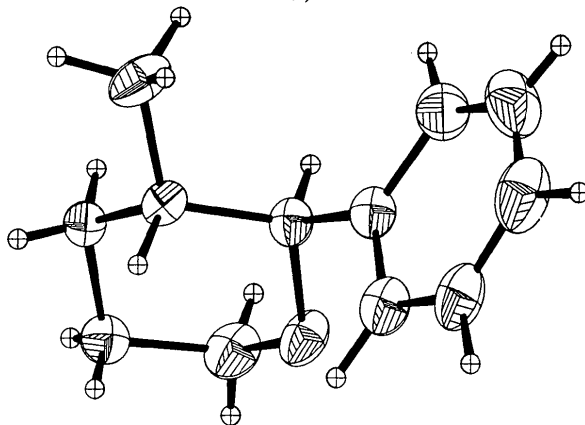
chain is found to be more or less perpendicular to the plane of the aromatic ring (Carlström, Bergin & Falkenberg, 1973). The torsional angles  $\tau_1$ ,  $\tau_2$  and  $\tau_3$  of

Table 1. *Final fractional atomic coordinates and their standard deviations (in parentheses)*

	x	y	z
C(1)	0.7003 (17)	0.43895 (28)	0.4121 (13)
C(2)	0.6385 (26)	0.46602 (33)	0.2449 (18)
C(3)	0.4148 (28)	0.46957 (34)	0.1140 (17)
C(4)	0.2415 (19)	0.44554 (29)	0.1398 (13)
C(5)	0.2984 (16)	0.41686 (28)	0.3051 (11)
C(6)	0.5291 (13)	0.41227 (23)	0.4405 (9)
C(7)	0.5901 (17)	0.38075 (18)	0.6141 (12)
C(8)	0.5952 (12)	0.33187 (21)	0.5490 (8)
C(9)	0.7802 (18)	0.32243 (35)	0.4628 (13)
C(10)	0.4733 (14)	0.30927 (25)	0.8311 (11)
C(11)	0.4753 (18)	0.35830 (29)	0.8800 (12)
N	0.6370 (9)	0.30143 (18)	0.7254 (7)
O	0.4199 (10)	0.38575 (17)	0.7056 (7)
Cl	0.1	0.29908 (5)	0.1
H(1)	0.847 (12)	0.4332 (22)	0.501 (10)
H(2)	0.744 (11)	0.4842 (22)	0.246 (10)
H(3)	0.368 (10)	0.4913 (22)	0.000 (9)
H(4)	0.074 (14)	0.4497 (23)	0.036 (10)
H(5)	0.170 (11)	0.3982 (23)	0.307 (9)
H(7)	0.740 (11)	0.3883 (23)	0.713 (9)
H(8)	0.442 (11)	0.3217 (21)	0.459 (9)
H(9A)	0.819 (11)	0.2904 (23)	0.455 (10)
H(9B)	0.946 (12)	0.3381 (22)	0.580 (10)
H(9C)	0.739 (12)	0.3321 (23)	0.361 (11)
H(10A)	0.336 (11)	0.3054 (22)	0.723 (10)
H(10B)	0.524 (10)	0.2960 (23)	0.937 (10)
H(11A)	0.386 (11)	0.3576 (21)	0.942 (10)
H(11B)	0.617 (12)	0.3663 (22)	0.964 (9)
H(NA)	0.595 (11)	0.2757 (22)	0.695 (9)
H(NB)	0.786 (11)	0.3058 (21)	0.833 (9)



(a)



(b)

Fig. 1. (a) Bond distances and angles and (b) a perspective drawing of the phenmetrazine molecule projected onto the *ab* plane. Heavy atoms are represented by thermal ellipsoids of 25% probability (Program *ORTEP* by Johnson, 1965).

phenmetrazine correspond closely to those of amphetamine sulphate where the angles in the four molecules of its asymmetric unit range from:  $\tau_1 = -100$  to  $-114^\circ$ ,  $\tau_2 = -166$  to  $-176^\circ$  and  $\tau_3 = 65$  to  $75^\circ$  (Bergin & Carlström, 1971). The conformation of corresponding parts of the phenmetrazine and amphetamine molecules are thus almost identical.

In phenmetrazine both the  $\alpha$ - and  $\beta$ -carbon atoms are asymmetric. As the space group *Cc* contains glide planes, mirror molecules with torsion angles of opposite signs are also present in the structure. The methyl group on the  $\alpha$ -carbon atom is *anti* to the oxygen atom and the configuration of phenmetrazine is accordingly analogous to that of pseudoephedrine.

Table 2. *Thermal parameters ( $\times 10^4$ ) and standard deviations (in parentheses)*

$\beta_{1i}$  are the coefficients in the expression:  $\exp[-(h^2\beta_{11} + k^2\beta_{22} + l^2\beta_{33} + hk\beta_{12} + hl\beta_{13} + kl\beta_{23})]$ .

	$\beta_{11}$	$\beta_{22}$	$\beta_{33}$	$\beta_{12}$	$\beta_{13}$	$\beta_{23}$
C(1)	568 (35)	17 (1)	375 (24)	-2 (9)	470 (49)	-2 (8)
C(2)	898 (58)	18 (1)	484 (36)	-33 (15)	858 (82)	20 (11)
C(3)	1017 (75)	18 (1)	378 (29)	68 (16)	685 (81)	46 (10)
C(4)	688 (43)	15 (1)	305 (22)	62 (12)	328 (56)	29 (8)
C(5)	538 (34)	15 (1)	277 (18)	23 (9)	327 (43)	4 (7)
C(6)	464 (27)	13 (1)	220 (16)	5 (7)	309 (35)	-1 (6)
C(7)	396 (21)	12 (1)	218 (13)	1 (9)	244 (27)	-4 (7)
C(8)	293 (17)	13 (1)	160 (13)	16 (6)	104 (28)	-7 (4)
C(9)	485 (30)	23 (1)	272 (19)	91 (12)	384 (39)	39 (9)
C(10)	386 (26)	15 (1)	252 (18)	1 (8)	241 (36)	8 (7)
C(11)	604 (39)	19 (1)	272 (19)	34 (11)	523 (46)	9 (8)
N	311 (17)	11 (1)	208 (11)	1 (6)	154 (22)	0 (5)
O	601 (22)	15 (1)	284 (12)	58 (6)	533 (29)	20 (4)
Cl	331 (4)	13 (0)	222 (3)	-18 (2)	74 (5)	7 (2)

Table 3. Intramolecular bond distances (Å) and bond angles (°) with estimated standard deviations in parentheses

C(1)–C(2)	1.371 (14)	C(7)–C(8)	1.523 (8)
C(2)–C(3)	1.336 (16)	C(8)–C(9)	1.509 (9)
C(3)–C(4)	1.346 (14)	C(8)–N	1.495 (7)
C(4)–C(5)	1.392 (12)	N–C(10)	1.487 (7)
C(5)–C(6)	1.381 (9)	C(10)–C(11)	1.491 (11)
C(6)–C(1)	1.386 (9)	C(11)–O	1.422 (9)
C(6)–C(7)	1.487 (10)	O–C(7)	1.435 (8)
C(2)–C(1)–C(6)	119.4 (8)	C(6)–C(7)–O	109.1 (6)
C(1)–C(2)–C(3)	121.9 (11)	C(8)–C(7)–O	110.0 (6)
C(2)–C(3)–C(4)	120.6 (11)	C(7)–C(8)–C(9)	114.1 (6)
C(3)–C(4)–C(5)	119.1 (9)	C(7)–C(8)–N	109.2 (5)
C(4)–C(5)–C(6)	121.1 (8)	C(9)–C(8)–N	108.9 (6)
C(1)–C(6)–C(5)	117.7 (7)	C(8)–N–C(10)	114.1 (5)
C(1)–C(6)–C(7)	121.3 (7)	N–C(10)–C(11)	109.0 (6)
C(5)–C(6)–C(7)	121.0 (7)	C(10)–C(11)–O	111.7 (7)
C(6)–C(7)–C(8)	111.4 (6)	C(11)–O–C(7)	112.0 (6)

Intramolecular bond lengths and bond angles are given in Table 3 and in Fig. 1. Two distances both involving the carbon atom C(3) in the phenyl ring are much too short and it is obvious that the positional coordinates of C(3) are slightly in error. This part of the molecule also exhibits the largest thermal movements; this is evident from Fig. 1. Otherwise, the bond distances and angles are quite normal. The C–H and N–H distances range between 0.73 and 1.14 Å [both these extremes are found in the methyl group of C(9)] with a mean distance of 0.92 (6) Å. The C–C–H angles of the phenyl ring range from 113 to 127° with a mean value of 120 (4)° and the expected tetrahedral C–C–H or C–N–H angles in the rest of the molecule range from 95 to 120° with a mean value of 107 (4)°.

#### Hydrogen bonds and molecular packing

The arrangement of the molecules in the crystal and the hydrogen bonding system are shown in Fig. 2. There is only one type of hydrogen bond, N···Cl. Each nitrogen atom is bonded through its two hydrogen atoms to two neighbouring chloride ions. The N···Cl distances are quite short, 3.09 and 3.07 Å. Corresponding H···Cl distances are 2.32 and 2.15 Å and the N–H···Cl angles are 160.4 and 165.1° respectively. The structure thus consists of phenmetrazine and chloride ions forming infinite layers perpendicular to the *b* axis. The layers, having a thickness of 15 Å and bounded by the hydrophobic ends of the phenmetrazine ions, are held together by van der Waals forces only. This explains the platy habit of the crystals as

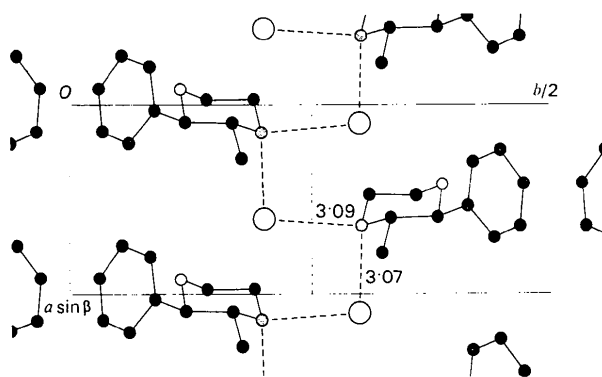


Fig. 2. Projection of half a unit cell of the phenmetrazine structure. The N···Cl hydrogen bonds are indicated by broken lines. Distances in Å. The small filled, shaded and open circles represent carbon, nitrogen and oxygen atoms respectively and the large circles indicate chloride ions. Hydrogen atoms are omitted for clarity. The positive direction of *c* is towards the viewer.

well as the high thermal motion of the phenyl ends of the molecules. The packing is quite loose and there are, apart from the hydrogen bonds, no intermolecular distances involving non-hydrogen atoms less than 3.5 Å and no C···H, O···H or N···H distances less than 3.0 Å, reflecting the comparatively low density of the compound.

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