

The Structure of the Catecholamines.

V. The Crystal and Molecular Structure of Epinine Hydrobromide

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Epinine (*N*-methyldopamine) hydrobromide crystallizes in the space group $P2_1/a$. The unit cell has the dimensions $a = 13.978$, $b = 14.934$, $c = 5.185$ Å, $\beta = 90.73^\circ$, and contains four formula units. Three-dimensional data for the structure determination were collected on an automatic four-circle diffractometer. The structure was solved with the Patterson method, and refined by a full-matrix least-squares algorithm. The final R was 3.9% for 1815 observed reflexions. The crystal structure is stabilized by a network of hydrogen bonds, where infinite chains of epinine molecules are connected *via* the bromide ions. The epinine molecule has a maximally extended side chain, the plane of which forms an angle of 70° with the catechol plane.

Introduction

There is increasing evidence that *N*-methyldopamine, or epinine, may play an important physiological role. Laduron (1972*a, b*) has found enzymes both in rat brain and bovine adrenal medulla which are capable of *N*-methylating dopamine. He puts forward the idea that epinine rather than noradrenaline is the immediate precursor in the biological synthesis of adrenaline.

Epinine and dopamine have nearly the same pharmacological effects, although epinine has been shown to have a stronger α -adrenergic activity (Palm, Langeneckert & Holtz, 1967). These two substances are the only ones among a large number of phenethylamines studied by Goldberg, Sonnevile & McNay (1968) to produce a non-adrenergic renal vasodilatation. Furthermore, both exhibit a neurogenic vasodilating effect that can be blocked by haloperidol (Willems & Bogaert, 1972).

Experimental

A sample of epinine hydrobromide was kindly supplied by Dr P. Laduron of Janssen Pharmaceutica. The powder was dissolved in distilled water, which was subsequently left to evaporate at room temperature. The crystals obtained were quite large, transparent, but slightly brownish. The one chosen for this study was shaped to a somewhat flattened sphere with a radius of 0.2 mm.

Crystal data

Epinine (*N*-methyldopamine) hydrobromide, $C_9H_{13}O_2N \cdot HBr$; monoclinic, $a = 13.978 \pm 0.001$, $b = 14.934 \pm 0.001$, $c = 5.185 \pm 0.001$ Å; $\beta = 90.73^\circ$; F.W. 248.1; $V = 1082.3$ Å³; $D_x(Z=4) = 1523$ kg m⁻³; $F(000) = 504$.

The systematic absences were: $h00$ when $h = 2n + 1$, and $0k0$ when $k = 2n + 1$, indicating the space group

$P2_1/a$. This space group has four equivalent positions, and it was assumed that the asymmetric unit contained one epinine molecule.

The crystal was mounted on a Philips 1100 automatic four-circle diffractometer. The scan speed was 0.025° s⁻¹ and the scan width 1.8° . Cu $K\alpha$ radiation ($\lambda = 1.5418$ Å) was used. 2003 reflexions from the layers $hk\bar{6}$ through $hk6$ were collected ($\theta \leq 65^\circ$). Three standard reflexions were remeasured after every 90 min. Their intensities did not show any systematic change during the data collection.

After correction for Lorentz and polarization factors it was found that 187 of the 2003 reflexions had an intensity not statistically different from the background intensity. 21 of these had negative intensities, and were immediately discarded from further computations.

Structure determination

The coordinates of the bromine atom were determined by the Patterson method. In the subsequent Fourier synthesis it was quite easy to locate the catechol nucleus of the epinine molecule. After one more Fourier synthesis the positions of the atoms in the chain could also be established.

Refinement procedure

The first cycle of full-matrix least-squares refinement using all reflexions gave an R of 41%. The bromine atoms were then given anisotropic temperature factors, which in a subsequent refinement resulted in an R of 6.7%. In the next cycle the temperature factors of all atoms were changed to anisotropic. Furthermore the remaining 166 unobserved reflexions were excluded from the calculations. Two more cycles of refinement and difference syntheses gave the positions of the 16 hydrogen atoms. These were given an overall isotropic temperature factor of 3.0 Å², which was not refined.

Table 1. Final positional and thermal parameters for non-hydrogen atoms

E.s.d.'s in parentheses are in units of the last digit. The temperature expression is of the form:

$$\exp[-(h^2\beta_{11} + k^2\beta_{22} + l^2\beta_{33} + hk\beta_{12} + hl\beta_{13} + kl\beta_{23}) \times 10^{-4}]$$

	<i>x</i>	<i>y</i>	<i>z</i>	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
C(1)	0.4974 (4)	0.1255 (4)	0.4251 (11)	44 (3)	32 (3)	395 (26)	5 (5)	-34 (14)	-93 (13)
C(2)	0.5746 (4)	0.1432 (4)	0.5906 (11)	34 (3)	34 (3)	438 (26)	21 (4)	-46 (14)	-55 (13)
C(3)	0.5685 (3)	0.2128 (3)	0.7594 (10)	26 (2)	27 (2)	316 (20)	1 (4)	-42 (11)	29 (11)
C(4)	0.4875 (3)	0.2669 (3)	0.7652 (9)	29 (2)	23 (2)	247 (18)	-5 (4)	-9 (11)	8 (10)
C(5)	0.4117 (3)	0.2483 (3)	0.5974 (9)	27 (2)	26 (2)	288 (19)	1 (4)	-16 (11)	22 (11)
C(6)	0.4161 (3)	0.1771 (3)	0.4255 (9)	32 (2)	27 (2)	233 (18)	-12 (3)	-23 (11)	24 (10)
C(7)	0.3318 (4)	0.1585 (4)	0.2499 (10)	35 (3)	41 (3)	224 (19)	-12 (4)	-32 (12)	-4 (12)
C(8)	0.2479 (4)	0.1241 (4)	0.3996 (9)	34 (3)	35 (2)	204 (18)	-11 (4)	-34 (12)	28 (11)
C(9)	0.0847 (4)	0.0591 (4)	0.3710 (11)	36 (3)	39 (3)	317 (22)	-12 (5)	21 (13)	33 (13)
N	0.1648 (3)	0.1010 (3)	0.2299 (7)	30 (2)	26 (2)	206 (15)	-8 (3)	-14 (9)	3 (8)
O(1)	0.6425 (3)	0.2377 (2)	0.9252 (8)	35 (2)	28 (2)	470 (18)	14 (3)	-128 (10)	-36 (9)
O(2)	0.4890 (3)	0.3371 (3)	0.9329 (8)	29 (2)	38 (2)	431 (18)	16 (3)	-58 (10)	-99 (9)
Br	0.2835 (0)	0.4222 (0)	0.1010 (1)	41 (0)	29 (0)	333 (2)	-10 (0)	-7 (1)	-8 (1)

Absorption [$\mu(\text{Cu } K\alpha) = 54.8 \text{ cm}^{-1}$] from the approximately spherical crystal, radius 0.2 mm, was corrected (*International Tables for X-ray Crystallography*, 1959) by grouping in 5° shells, within which F_c values were multiplied by the square root of the corresponding absorption factor. All the F_c values were then multiplied by a scale factor to give approximately the same total as before. After this, three cycles of refinement were performed. It was found that this simple attempt to correct for absorption gave higher estimated standard deviations in all parameter values as well as a considerably higher R . This finding is somewhat surprising, but may be explained by the fact that the crystal was not perfectly spherical.

Thus in the last refinement no absorption correction was applied. During this cycle no parameter changed more than $\frac{1}{3}$ of its estimated standard deviation. The final R was 3.9% for 1815 observed reflexions. The positional and thermal parameters for all atoms are given in Tables 1 and 2.*

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31690 (12 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 2. Final coordinates for hydrogen atoms (temperature factors = 3.0 \AA^2)

	<i>x</i>	<i>y</i>	<i>z</i>
H(1)	0.501 (4)	0.082 (4)	0.366 (10)
H(2)	0.634 (4)	0.119 (3)	0.563 (10)
H(5)	0.352 (4)	0.294 (3)	0.584 (9)
H(7)A	0.309 (4)	0.229 (3)	0.164 (9)
H(7)B	0.343 (4)	0.127 (4)	0.125 (10)
H(8)A	0.220 (4)	0.163 (4)	0.526 (10)
H(8)B	0.263 (4)	0.081 (4)	0.520 (10)
H(N)A	0.141 (4)	0.164 (4)	0.156 (9)
H(N)B	0.177 (4)	0.052 (4)	0.119 (10)
H(9)A	0.059 (4)	0.102 (4)	0.484 (10)
H(9)B	0.042 (4)	0.025 (3)	0.238 (10)
H(9)C	0.114 (4)	0.006 (4)	0.435 (9)
H(O1)	0.671 (4)	0.200 (4)	0.982 (10)
H(O2)	0.445 (4)	0.352 (4)	0.935 (10)

The scattering factors for C, O and Br⁻ were taken from *International Tables for X-ray Crystallography* (1962) whereas that for N⁺ was interpolated from the figures given for B⁺ and O⁺. The values for H were those suggested by Stewart, Davidson & Simpson (1965). All structure factors were given unit weight. The computations were performed on an IBM 360/75 computer using a local program system by Bergin (1971a). The stereoscopic drawing was made using *ORTEP* (Johnson, 1965).

Description and discussion of the structure

The numbering scheme used below is shown in Fig. 1.

The individual values for intramolecular distances and angles (Tables 3 and 4) show no remarkable deviations from what would be expected. The aromatic C-C bonds have an average length of 1.384 Å. The C(6)-C(7) bond is 0.03 Å shorter than the pure carbon-carbon single bond, which can probably be explained by resonance from the nearby phenyl ring. In addition, it is interesting to note that the C(7)-C(8) bond is somewhat shorter than the normal single-bond length. This shortening has also been found in the studies by Bergin (1971b), Andersen, Mostad & Rømming (1972) and Carlström (1973) and may be connected with the pres-

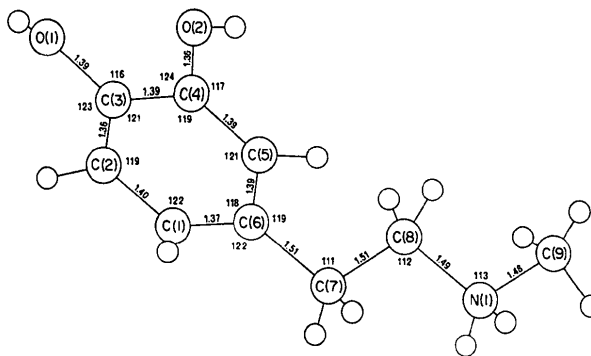


Fig. 1. The epinine molecule. Distances (Å) and angles (°) for bonds connecting non-hydrogen atoms.

ence of the charged nitrogen atom. The average C–N distance is 1.487, and the average C–O distance 1.375 Å. The mean standard deviation for all these bonds is 0.007 Å.

Table 3. *Intramolecular distances* (Å)

E.s.d.'s are in units of the last digit.

C(1)–C(2)	1.396 (8)	C(5)–C(6)	1.390 (7)
C(2)–C(3)	1.362 (7)	C(6)–C(1)	1.374 (7)
C(3)–C(4)	1.391 (6)	C(6)–C(7)	1.505 (7)
C(3)–O(1)	1.387 (6)	C(7)–C(8)	1.505 (7)
C(4)–C(5)	1.391 (6)	C(8)–N	1.489 (6)
C(4)–O(2)	1.362 (6)	N—C(9)	1.484 (7)

Table 4. *Angles between intramolecular bonds* (°)

E.s.d.'s are in units of the last digit.

C(6)–C(1)–C(2)	121.7 (5)	C(4)–C(5)–C(6)	120.9 (4)
C(1)–C(2)–C(3)	119.1 (5)	C(5)–C(6)–C(1)	118.3 (5)
C(2)–C(3)–C(4)	120.9 (5)	C(5)–C(6)–C(7)	119.2 (4)
C(2)–C(3)–O(1)	123.4 (5)	C(1)–C(6)–C(7)	122.5 (5)
O(1)–C(3)–C(4)	115.6 (4)	C(6)–C(7)–C(8)	111.1 (4)
C(3)–C(4)–C(5)	119.0 (4)	C(7)–C(8)–N	112.4 (4)
C(3)–C(4)–O(2)	117.1 (4)	C(8)–N—C(9)	113.2 (4)
O(2)–C(4)–C(5)	123.9 (4)		

Angles between bonds connecting non-hydrogen atoms differ nowhere by more than 4° from the standard values. The two oxygen atoms are responsible for the largest deviations, which are probably due to hydrogen bonding. Even so, it is interesting to note that the C(2)–C(3)–O(1) angle is a few degrees larger than 120°, as has been found in all the catecholamines studied earlier in this department (Bergin, 1971*b*; Carlström, 1973; Giesecke, 1973). The mean standard deviation of the angles is 0.4°.

The lengths of the C–H and N–H bonds range from 0.73 to 1.18 Å, and the O–H bonds from 0.65 to 0.75 Å (mean standard deviation 0.05 Å). The angles involving hydrogen atoms have a maximum difference of 10° from the expected values.

The planarity of the phenyl ring and the side chain is demonstrated in Table 5. The atoms of the ring all lie within 0.01 Å of the best plane, and the exocyclic atoms are also quite close to it; the angle between this plane and the C(3)–O(1) bond is only 2°. The deviations of the individual atoms in the chain from their best plane are greater, but the chain may still be regarded as almost planar.

Table 5. *Deviations in Å from best planes through the catechol ring and the ethylamine side chain*

Asterisks mark atoms included in calculations of planes.

Equations for the planes

$$\begin{aligned} \text{Ring: } & 0.41X + 0.60Y - 0.68Z = 2.45 \\ \text{Chain: } & -0.36X + 0.92Y + 0.16Z = 0.75 \end{aligned}$$

Ring		Chain	
C(1)*	0.003	C(6)*	-0.025
C(2)*	-0.006	C(7)*	-0.013
C(3)*	0.005	C(8)*	0.063
C(4)*	-0.001	N(1)*	0.013
C(5)*	-0.002	C(9)*	-0.038
C(6)*	0.001	C(3)	-0.004
C(7)	0.021	O(1)	0.114
O(1)	-0.049		
O(2)	-0.044		

An inspection of the stereoscopic pair in Fig. 2 immediately shows two of the main features of the epinine molecule: the ethylamine chain is almost maximally extended, and a plane through this chain is nearly perpendicular to the aromatic ring. In fact, the torsion angle τ_1 [C(1)–C(6)–C(7)–C(8)] is 110°, and τ_2 [C(6)–C(7)–C(8)–N] is -177°. These two values agree well with most biologically active phenethylamines studied, and give further weight to the theory that an extended chain should be a prerequisite for biological activity. The height of the nitrogen atom over the catechol ring is 1.42 Å for epinine, which is 0.2 Å less than that for dopamine, while its distance from the centre of the ring is 5.13 Å – almost exactly the same as for dopamine and apomorphine (Giesecke, 1973). This distance may possibly have something to do with the availability of the charged nitrogen atom at the receptor site.

Hydrogen bonds and molecular packing

The contents of one unit cell of the epinine crystal are shown in Fig. 3. Numerical values for the hydrogen bonds are given in Table 6. The tail of each epinine molecule is connected, *via* the hydrogen bond N(1)–H(N)A...O(1), to the head of the nearest molecule in the next cell, thereby forming infinite chains which are parallel to the *x* axis and perpendicular to the *y* axis, and form an acute angle with the *z* axis. There are two sets of such chains, one going stairwise upwards in the *z* direction with increasing *x* values, the other going downwards with increasing *x* values. Within each set all chains are parallel to each other. If the crystal is

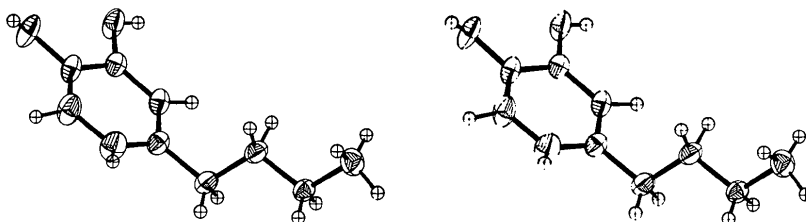


Fig. 2. Stereoscopic drawing of the epinine molecule (ORTEP: Johnson, 1965).

Table 6. *Hydrogen-bonded interactions*

The columns labelled x' , y' , z' give the symmetry code of the acceptor atom Y' . Reference molecule in x , y , z .

X	H	Y'	x'	y'	z'	$X \cdots Y'$	$H \cdots Y'$	$X-H \cdots Y'$
N	H(N)A	O(1)	$x - \frac{1}{2}$	$\frac{1}{2} - y$	$z - 1$	2.90 Å	1.90 Å	155°
O(1)	H(O1)	Br	$\frac{1}{2} + x$	$\frac{1}{2} - y$	$1 + z$	3.22	2.47	170
NO	H(N)B	Br	$\frac{1}{2} - x$	$y - \frac{1}{2}$	$-z$	3.26	2.32	171
O(2)	H(O2)	Br	x	y	$1 + z$	3.27	2.65	161

viewed from the y direction the chains seem to form a net with bromide ions at the nodes. In fact, each bromide ion serves *via* hydrogen bonds as a bridge between two neighbouring, crossing chains, and also between two parallel chains.

All hydrogen atoms belonging to non-carbon atoms form hydrogen bonds. In directing the atom H(O1) towards the bromide ion, the O(1)–H(O1)···Br bond makes possible the formation of the short, 2.90 Å, N–H(N)A···O(1) bond. The three hydrogen bonds with the bromide ion as acceptor all have a length about 3.25 Å and are thus fairly strong. In all these three bonds the hydrogen atoms are very close to the straight line between the donor and the acceptor.

There are two more intermolecular distances which are short, *viz.* those from N to O(2)', 3.03 Å, and C(9) to O(2)', 3.05 Å, but in both these cases the narrow donor–hydrogen–acceptor angles prevent the formation of hydrogen bonds.

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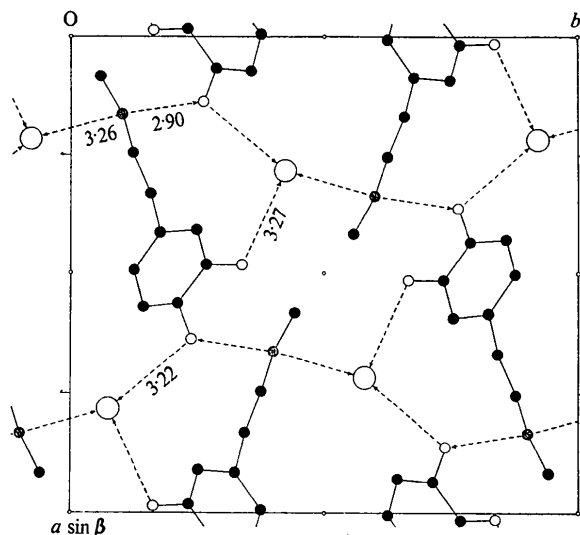


Fig. 3. Molecular packing and hydrogen bonds. In the unit cell shown the c axis is directed towards the viewer. Carbon, nitrogen and oxygen atoms are represented by filled, shaded and unfilled circles respectively. The bromide ions are shown as larger unfilled circles. Dotted lines represent hydrogen bonds (in Å) with arrow-heads towards the acceptor atoms.

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