

# The Crystal and Molecular Structure of (—)-Phenylephrine

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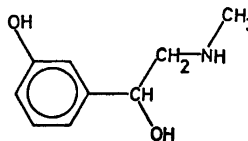
The crystal structure of (—)-phenylephrine has been determined by X-ray methods, using 929 observed reflections collected by counter diffractometer techniques. The crystals are monoclinic; space group  $P2_1$ , with  $a = 7.833(3)$  Å,  $b = 6.572(3)$  Å,  $c = 8.658(4)$  Å, and  $\beta = 99.09(1)^\circ$ . Least-squares refinements yielded a conventional  $R$ -factor of 0.040. Standard deviations in bond lengths are 0.003–0.004 Å and in bond angles  $0.2$ – $0.3^\circ$ . The phenylephrine molecules were found to exist as zwitterions in the crystals, formed by a proton transfer from the phenolic hydroxyl group to the nitrogen atom. The ions are connected by hydrogen bonds to build double molecular layers parallel to (100).

The structure investigation of (—)-phenylephrine forms part of a research project on the free base form of sympathomimetic amines. So far, crystal structure determinations of (—)-adrenaline<sup>1</sup> and (—)-noradrenaline<sup>2</sup> have been reported.

Generally, maximal adrenergic activity of sympathomimetic amines depends on the presence of hydroxyl groups in *p*- and *m*-positions on the benzene ring. The absence of one or both of these groups results in a reduction in adrenergic potency, and especially  $\beta$ -activity is reduced. This is clearly seen in the different pharmacological activity of phenylephrine and adrenaline. Phenylephrine differs chemically from adrenaline only by lacking the *para* hydroxyl group, and is thus in contrast to adrenaline a weak  $\beta$ -adrenergic agonist.

It is assumed that a functional group in *m*-position on the phenyl ring is a requirement for  $\beta$ -adrenergic activity in particular.<sup>3</sup> The nature of this group is critical, but its chemical role in stimulating the receptor is not established. The crystal structures of (—)-

adrenaline<sup>1</sup> and (—)-noradrenaline<sup>2</sup> revealed a zwitterionic state of the amines, formed by a proton transfer from the *meta* hydroxyl group to the nitrogen atom. In view of the central role this *meta* substituent is assumed to play in  $\beta$ -receptor stimulation, it seems of importance to obtain more information about the zwitterionic character of this class of drugs.



## EXPERIMENTAL

Commercially obtained (—)-phenylephrine hydrochloride was dissolved in a 1 M ammonia solution. By slow diffusion of ethanol into the solution, thin needle-formed crystals appeared. The low water solubility of these crystals indicated the formation of the free base form of the compound.

The crystals are monoclinic; systematically absence of reflections  $0k0$  with  $k$  odd determined the space group to be  $P2_1$  since the phenylephrine molecule is optically active. Unit cell parameters were determined from measurements on a manual Picker diffractometer with  $\text{CuK}\alpha$ -radiation. Three-dimensional intensity data were obtained from a crystal of dimensions  $0.48 \times 0.16 \times 0.05$  mm<sup>3</sup> on an automatic Picker diffractometer with crystal monochromated  $\text{MoK}\alpha$ -radiation. Intensities of 1030 reflections with  $2\theta < 60^\circ$  were measured using the  $\omega$ - $2\theta$  scan technique. The scan speed was  $1^\circ \text{ min}^{-1}$ , and scan range  $2^\circ$ . 929 reflections with net intensities larger than  $2.5\sigma(I)$  were considered to be observed and were used in the structure determination. Lorentz and polarization corrections were applied to the intensity data.

Atomic form factors used were those of Doyle and Turner<sup>4</sup> for oxygen, nitrogen, and

carbon atoms, and of Stewart *et al.*<sup>5</sup> for hydrogen atoms.

The computer programs employed during the present study are described in Ref. 6.

### CRYSTAL DATA

Phenylephrine, C<sub>9</sub>H<sub>13</sub>O<sub>4</sub>N

Space group *P*2<sub>1</sub>, monoclinic

*a* = 7.833(3) Å; *b* = 6.572(3) Å; *c* = 8.658(4) Å;

*β* = 99.09(1)°

*V* = 440.1 Å<sup>3</sup>; *M* = 167.23; *F*(000) = 180; *Z* =

2; *D*<sub>calc</sub> = 1.262 g cm<sup>-3</sup>

### STRUCTURE DETERMINATION

Unit cell dimensions of the phenylephrine crystals correspond closely to those of adrenaline;<sup>1</sup> both compounds crystallize with space group *P*2<sub>1</sub>. Coordinates of nitrogen and carbon atoms from the adrenaline study were therefore selected as trial structure in the calculation of a Fourier map, in which all non-hydrogen atoms could be located. Subsequent least-squares refinement, with anisotropic thermal parameters introduced, yielded an *R*-factor of 0.08. Positional parameters for hydrogen atoms bonded to carbon atoms were calculated. The remaining three hydrogen atoms were located in a difference Fourier map in positions indicating a zwitterionic structure of the molecule. Full-matrix least-squares refinements including positional and isotropic thermal parameters of all hydrogen atoms converged with a conventional *R*-factor of 0.040 and a weighted *R*-factor of 0.029. A final difference Fourier map showed electron density fluctuations in the range ±0.17 e Å<sup>-3</sup>.

An analysis of the molecular thermal motions in terms of a rigid body model indicated that the phenol part of the molecule could be regarded as a rigid unit, as the r.m.s. discrepancy between atomic vibration components calculated from this analysis and those obtained from the structure determination was 0.0028. The bond lengths in the phenol part of the molecule were accordingly corrected for librational effects.

The final parameters for non-hydrogen atoms are listed in Table 1 and for hydrogen atoms in Table 2. Bond lengths and angles are given in Table 3. Thermal ellipsoids drawn at the

Table 1. Fractional atomic coordinates and thermal parameters with estimated standard deviations for non-hydrogen atoms ( $\times 10^4$ ). The temperature factor is given by  $\exp - (B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + B_{12}hk + B_{13}hl + B_{23}kl)$

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> <sub>11</sub>	<i>B</i> <sub>22</sub>	<i>B</i> <sub>33</sub>	<i>B</i> <sub>12</sub>	<i>B</i> <sub>13</sub>	<i>B</i> <sub>23</sub>
O1	95052(26)	31376(46)	83278(19)	1807(45)	1690(53)	624(24)	-495(85)	332(55)	-19(60)
O2	81903(32)	11076(0)	14640(21)	2224(55)	1686(57)	712(27)	909(108)	7(59)	-320(72)
N	81952(34)	52753(51)	5386(25)	1500(54)	1282(60)	588(29)	216(103)	213(66)	55(72)
C1	80430(35)	20701(53)	41821(28)	1119(54)	1150(68)	662(34)	493(109)	278(71)	267(83)
C2	89674(37)	28737(58)	55853(31)	1194(55)	1218(69)	812(37)	-343(116)	622(75)	95(86)
C3	85446(35)	24455(52)	70186(29)	1336(56)	1137(75)	766(36)	227(114)	617(75)	133(84)
C4	71128(39)	12020(68)	70672(31)	1763(66)	1793(83)	853(40)	-330(143)	976(86)	641(110)
C5	61931(43)	3918(63)	57094(39)	1329(65)	2030(93)	1486(51)	-1072(142)	724(94)	90(125)
C6	66600(40)	7958(58)	42642(32)	1297(57)	1718(90)	916(42)	-457(132)	-13(82)	-36(98)
C7	85663(37)	26496(56)	26213(28)	1146(57)	1642(82)	609(33)	433(119)	343(71)	112(85)
C8	75443(45)	45003(60)	19535(32)	1331(64)	1398(72)	776(36)	120(121)	617(82)	64(91)
C9	68903(57)	65157(72)	-4803(43)	2047(88)	2314(109)	1117(48)	982(178)	-200(112)	652(132)

Table 2. Fractional atomic coordinates ( $\times 10^4$ ) and isotropic thermal parameters with estimated standard deviations for hydrogen atoms.

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i>
HC2	9885(35)	3727(39)	5482(26)	2.3(6)
HC4	6779(34)	891(49)	8027(31)	3.5(6)
HC5	5319(38)	-484(49)	5746(27)	2.9(7)
HC6	5957(35)	203(45)	3356(30)	3.4(7)
HC7	9935(36)	2960(53)	2722(28)	3.5(6)
H1C8	7596(33)	5716(50)	2720(28)	3.1(6)
H2C8	6291(35)	4078(42)	1676(29)	2.2(6)
HO2	8977(43)	258(53)	1710(36)	4.1(9)
H1N	9282(39)	6114(62)	885(33)	5.4(8)
H2N	8481(38)	4211(48)	-91(32)	3.5(7)
H1C9	7425(44)	6934(57)	-1437(42)	7.1(10)
H2C9	6546(41)	7516(60)	102(38)	4.9(9)
H3C9	5880(49)	5643(70)	-810(38)	7.6(12)

Table 3. Bond lengths (Å) and angles (°) with estimated standard deviations in parantheses.

Bond length	Corrected	Bond angle	
C1-C2	1.382(4)	C2-C1-C6	119.9(3)
C2-C3	1.404(3)	C1-C2-C3	122.1(3)
C3-C4	1.393(4)	C2-C3-C4	116.9(3)
C4-C5	1.385(4)	C3-C4-C5	120.9(3)
C5-C6	1.383(4)	C4-C5-C6	121.2(3)
C1-C6	1.380(4)	C5-C6-C1	119.0(3)
C1-C7	1.521(3)	O1-C3-C4	121.5(2)
C3-O1	1.338(3)	O1-C3-C2	121.7(3)
C7-O2	1.423(3)	C2-C1-C7	118.6(3)
C7-C8	1.519(4)	C6-C1-C7	121.4(2)
C8-N	1.489(3)	C1-C7-O2	113.1(2)
N-C9	1.484(4)	O2-C7-C8	105.3(2)
C2-HC2	0.92(3)	C1-C7-C8	109.8(2)
C4-HC4	0.93(3)	C7-C8-N	111.0(2)
C5-HC5	0.90(3)	C8-N-C9	112.5(3)
C6-HC6	0.97(3)		
C7-HC7	1.08(3)		
C8-H1C8	1.04(3)		
C8-H2C8	1.01(3)		
C9-H1C9	1.02(3)		
C9-H2C9	0.90(3)		
C9-H3C9	0.98(3)		
N-H1N	1.02(3)		
N-H2N	0.94(3)		
O2-HO2	0.83(3)		

50 % probability level are illustrated in Fig. 1, which also presents the numbering of the atoms and bond lengths (corrected).

The structure factor list may be obtained from this institute upon request.

## DISCUSSION

The present study demonstrates a zwitterionic structure of the phenylephrine molecule corresponding to that observed for adrenaline<sup>1</sup> and noradrenaline.<sup>2</sup> The zwitterionic character

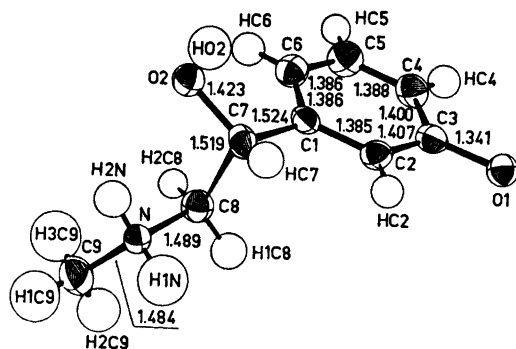


Fig. 1. Bond lengths and ellipsoids of thermal motion. (The drawing was prepared using the computer program ORTEP<sup>15</sup>).

of these molecules is produced by a proton transfer from a *meta* phenolic hydroxyl group to the nitrogen atom. This indicates a stronger acidic character of the *meta* hydroxyl group compared with the protonated amino group, and also a stronger acidity of the *meta* hydroxyl relative to the *para* hydroxyl. Even though the phenolic dissociation constant is reported to be less for monophenolic phenylethylamines than for catecholamines,<sup>7</sup> there is also observed a deprotonation of the *meta* hydroxyl group in the phenylephrine molecule. The bond lengths associated with the zwitterionic character of phenylephrine, C–N<sup>+</sup> (1.489 and 1.484 Å), N<sup>+</sup>–H (0.94 and 1.02 Å), and C–O<sup>–</sup> (1.341 Å), are within the accuracies of the measurements identical to those of the free bases formerly investigated.<sup>1,2</sup> The remaining bond lengths of the molecule are in agreement with corresponding values found in both the free bases and salts<sup>8–11</sup> of sympathomimetic amines.

The benzene ring is planar, the deviations of the ring carbon atoms from a least-squares plane defined by these atoms being in the

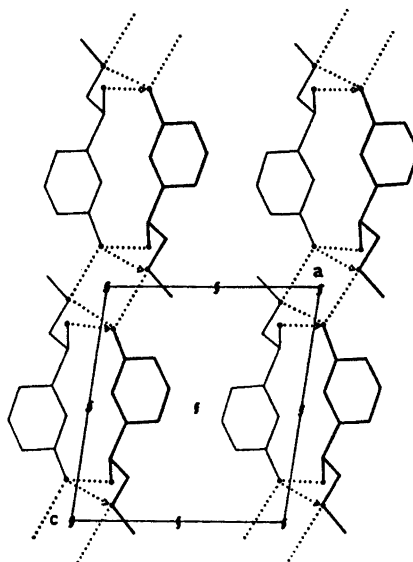


Fig. 2. The structure as viewed down the *b*-axis.

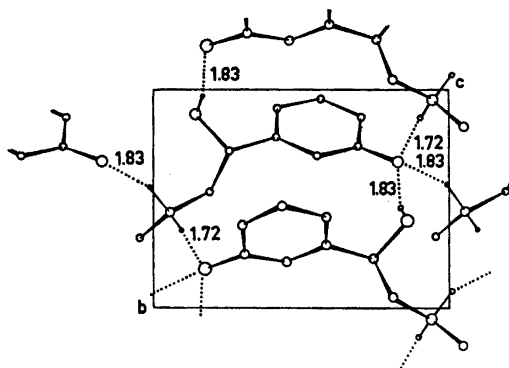


Fig. 3. The structure as viewed down the *a*-axis with hydrogen bonds (Å) indicated.

Table 4. Hydrogen bonded interactions X–H...Y.

X	Y	X...Y(Å)	H...Y(Å)	X–H...Y(°)
N	O1( <i>x</i> , <i>y</i> , <i>z</i> –1)	2.705	1.83	153.7
N	O1(– <i>x</i> +2, <i>y</i> +½, – <i>z</i> +1)	2.681	1.72	157.3
O2	O1(– <i>x</i> +2, <i>y</i> –½, – <i>z</i> +1)	2.645	1.83	163.4

range 0.005–0.012 Å. The exocyclic atoms O1 and C7 are situated 0.090 and –0.056 Å, respectively, out of the ring plane. The external C–C–O<sup>–</sup> angles are identical, in contrast to the situation in the zwitterionic form of the related catechol derivatives.<sup>1,2</sup> For the latter compounds an increase of the C2–C3–O<sup>–</sup> angle is observed, indicative of an attraction between the rather close phenolic hydrogen atom and the charged oxygen atom.

The conformation of the phenylephrine molecule is in conformity with that usually found for this class of compounds in the crystals.<sup>1,2,11</sup> The ethylamine side chain is fully extended and approximately perpendicular to the ring system; the dihedral angle C1–C7–C8–N is 172.2° and C6–C1–C7–C8 is 87.0°. The hydroxyl group of the side chain is situated in a *trans* position relative to the oxygen atom on the benzene ring. The dihedral angle C6–C1–C7–O2 is –30.3°. The valence angles in the side chain are close to the expected tetrahedral value.

The crystal structure is characterized by chains of zwitterions, which are connected through hydrogen bonds to build double molecular layers parallel to (100). The only interactions between these layers are van der Waals contacts between benzene rings of magnitude 3.8 Å. This molecular arrangement, which is illustrated in Fig. 2, corresponds closely to that observed for adrenaline<sup>1</sup> and noradrenaline<sup>2</sup> in the crystals. The charged oxygen atom in all of the free bases mentioned is engaged in three fairly short intermolecular hydrogen bonds, which are arranged in infinite spirals about screw axes. Hydrogen bond distances and angles are given in Table 4 and also indicated in Fig. 3. The intramolecular contact between the nitrogen atom and hydroxyl oxygen atom of the side chain is 2.853 Å. This interaction is not representing a hydrogen bond, as all of the amino and hydroxyl hydrogen atoms are engaged in intermolecular hydrogen bonds, and furthermore their positions are not favourable for the formation of such a bond. This conclusion has also been reached in several other crystal structure determinations of sympathomimetic amines,<sup>1,2,8,9</sup> in which a short intramolecular contact between the amino and hydroxyl groups has been observed.

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