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Structure of an Adrenergic Drug: L-Phenylephrine Hydrochloride, $C_9H_{14}NO_2^+.Cl^-$

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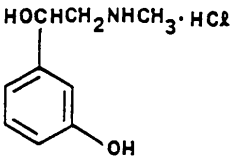
Abstract. $M_r = 203{\cdot}7$, monoclinic, $P2_1$, $a = 14{\cdot}151$ (3), $b = 6{\cdot}790$ (2), $c = 11{\cdot}404$ (3) Å, $\beta = 103{\cdot}08$ (2)°, $V = 1067{\cdot}3$ Å^3, $Z = 4$, $D_x = 1{\cdot}267$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54184 Å, $\mu = 2{\cdot}93$ mm^{-1}, $T = 277 \pm 1$ K. Final $R = 0{\cdot}045$ for 1434 observed reflections. Both the molecules in the asymmetric unit have extended *trans* conformations and the atoms in the two molecules are related by an approximate pseudo glide plane except for the ethanol OH group. The crystal structure is stabilized by a three-dimensional network of hydrogen bonds of types N–H···Cl, O–H···Cl and O–H···O.

Introduction. Phenylephrine (more commonly known as neosynephrine) hydrochloride, 1-(3-hydroxyphenyl)-2-methylaminoethanol hydrochloride, is a sympathomimetic drug and is used mainly as a nasal decongestant. Phenylephrine differs chemically from epinephrine only by lacking an –OH in the *para* position of the benzene ring. It was first studied by Barger & Dale (1910) but was not used clinically until years later when it was found to have greater potency, because of its direct action in receptors. Phenylephrine is a powerful postsynaptic α-receptor stimulant with little effect on the β-receptors of the heart (Weiner, 1980). The structure of L-phenylephrine (free-base form) was reported earlier (Andersen, 1976). It was thought worthwhile to look at the structure of the therapeutically prescribed form, L-phenylephrine hydrochloride, so that one can compare the structural and conformational features with those of the free base L-phenylephrine, synephrine (Dattagupta, Meyer & Mukhopadhyay, 1982), norsynephrine (Paxton & Hamor, 1977), and of other sympathomimetic drugs most of which are found to assume a preferred conformation in the crystalline state (Carlström, Bergin & Falkenberg, 1973). A preliminary account of this structure was reported earlier (Bhaduri & Saha, 1975), and the complete solution of the structure and its refined parameters are presented here.



Experimental. Aqueous solution of title compound (Sigma Chemical Co.) evaporated at 298 K, hy-

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groscopic, transparent, plate-shaped single crystals, pronounced cleavages parallel to (010), displaying sharp extinction under polarized light; crystals cut with a razor blade, coated with silicon grease, sealed in glass capillaries; cell dimensions initially determined from rotation and Weissenberg photographs at room temperature, later more accurately at 277 ± 1 K on a four-circle diffractometer using 15 reflections in range $40 < 2\theta < 70°$; systematic absences $0k0$ for k odd indicated space group $P2_1$ or $P2_1/m$, second possibility incompatible with chiral nature of compound and ruled out by successful refinement with $P2_1$; $h0l$ reflections with h odd were relatively weak but sharp (see below).

Intensity data collected from Weissenberg photographs, room temperature, multiple film equi-inclination techniques, Ni-filtered Cu $K\alpha$ radiation, intensities estimated visually with intensity wedges, 1403 unique reflections out of 2145 possible non-equivalent reflections within effective limiting sphere of Cu $K\alpha$ radiation, data corrected for Lorentz and polarization factors but not for absorption, Cl^- ions located from a Patterson map, structure solved by heavy-atom method; chirality R chosen to agree with published results (Lyle, 1960; Dirkx & De Boer, 1964); full-matrix isotropic and block-diagonal anisotropic least-squares refinement, $R = 0.11$.

Diffractometer data collected, 277 ± 1 K, Syntex $P\bar{1}$ diffractometer, Cu $K\alpha$ radiation, graphite monochromator, crystal dimensions $0.25 \times 0.20 \times 0.25$ mm; 1511 independent reflections with non-negative h and k measured in range $2\theta \leq 120°$, ω–2θ scan technique, 1434 considered observed with $I > 2\sigma(I)$, intensities of three standard reflections measured after every 97 reflections showed no significant change in intensity, refinement with this data set yielded $R = 0.074$; all H atoms except H(O2) B located from a difference Fourier map, full-matrix least-squares refinement with anisotropic temperature factors for non-H atoms and isotropic temperature factors for H atoms gave $R = 0.054$, function minimized $\sum w(|F_o| - \frac{1}{k}|F_c|)^2$ with $w = 1/\sigma^2(F_o)$, scattering factors from *International Tables for X-ray Crystallography* (1974) including corrections (f' and f'') for anomalous dispersion for non-H atoms, final calculations performed on a PDP 11/40 computer using Enraf–Nonius structure determination package (Frenz, 1978); extinction correction (Stout & Jensen, 1968) applied in final cycles refined to a coefficient $= 1.4 \times 10^{-5}$ mm^{-1}; final $R = 0.045$, $R_w = 0.056$, $S = 1.7$; refinement stopped when non-H parameter shifts less than their standard deviations, maximum shift/error for non-H atoms $= 0.71$, for H atoms only three parameters had shift-to-error ratio above 1 with maximum shift/error $= 1.8$, for all atoms average shift/error $= 0.21$, difference Fourier map featureless, highest difference peak of 0.21 e Å^{-3} had no chemical significance, $F(000) = 432$.

Table 1. *Final positional and isotropic thermal parameters with e.s.d.'s in parentheses*

$B_{eq} = (B_{11}.B_{22}.B_{33})^{1/3}$.

	x	y	z	B_{eq}/B_{iso}(Å^2)
Cl(1)*A*	0·14018 (5)	0·25	0·11304 (7)	3·95
Cl(1)*B*	−0·36575 (5)	0·1189 (2)	0·09707 (7)	4·0
O(1)*A*	0·0608 (2)	0·4217 (5)	0·6880 (2)	4·5
O(2)*A*	0·0305 (2)	0·2508 (5)	−0·1925 (2)	4·8
O(1)*B*	−0·4349 (2)	−0·0396 (5)	−0·6812 (2)	4·3
O(2)*B*	−0·5296 (2)	0·0476 (5)	0·2736 (2)	4·6
N(1)*A*	0·0739 (2)	0·5953 (5)	−0·0751 (2)	3·4
N(1)*B*	−0·4264 (2)	−0·2113 (5)	−0·0955 (2)	3·5
C(1)*A*	0·0998 (2)	0·3556 (6)	−0·5737 (3)	3·2
C(2)*A*	0·0537 (2)	0·4096 (6)	−0·4845 (3)	3·0
C(3)*A*	0·0896 (2)	0·3451 (6)	0·3675 (3)	3·2
C(4)*A*	0·1721 (3)	0·2291 (7)	−0·3414 (3)	3·7
C(5)*A*	0·2173 (3)	0·1755 (6)	0·4319 (3)	3·8
C(6)*A*	0·1808 (3)	0·2392 (6)	−0·5487 (3)	3·6
C(7)*A*	0·0418 (2)	0·4097 (7)	−0·2683 (3)	3·7
C(8)*A*	0·1052 (2)	0·5589 (7)	−0·1904 (3)	3·7
C(9)*A*	0·1274 (3)	0·7581 (7)	−0·0056 (3)	4·8
C(1)*B*	−0·3914 (2)	0·0435 (6)	0·5733 (3)	3·6
C(2)*B*	−0·4312 (2)	0·0060 (6)	−0·4743 (3)	3·5
C(3)*B*	−0·3876 (2)	0·0835 (6)	0·3630 (3)	3·3
C(4)*B*	−0·3042 (3)	0·1948 (7)	−0·3492 (3)	4·1
C(5)*B*	−0·2655 (3)	0·2319 (7)	−0·4479 (3)	4·2
C(6)*B*	−0·3075 (2)	0·1569 (6)	−0·5587 (3)	3·9
C(7)*B*	−0·4276 (2)	0·0383 (7)	−0·2525 (3)	3·6
C(8)*B*	−0·3979 (2)	−0·1667 (6)	−0·2097 (3)	3·5
C(9)*B*	−0·3812 (3)	−0·3936 (8)	−0·0348 (4)	5·0
H(2)*A*	0·008 (3)	0·489 (6)	−0·507 (4)	2·8 (7)
H(4)*A*	0·195 (2)	0·177 (7)	−0·263 (3)	4·2 (8)
H(5)*A*	0·278 (2)	0·103 (8)	0·411 (3)	5·1 (9)
H(6)*A*	0·215 (2)	0·200 (9)	−0·605 (3)	5·8 (10)
H(O1)*A*	0·103 (2)	0·379 (12)	0·265 (3)	9·4 (13)
H(7)*A*	−0·034 (2)	0·467 (6)	−0·308 (2)	3·0 (8)
H(O2)*A*	0·029 (3)	0·690 (11)	0·261 (4)	6·9 (12)
H(8)*A*	0·101 (2)	0·683 (8)	−0·235 (3)	4·3 (9)
H(8′)*A*	0·175 (2)	0·512 (7)	−0·164 (3)	3·8 (8)
H(N1)*A*	0·101 (2)	0·481 (9)	−0·033 (3)	7·8 (12)
H(N1′)*A*	0·008 (2)	0·606 (7)	−0·087 (2)	3·4 (9)
H(9)*A*	0·104 (2)	0·770 (7)	0·056 (3)	3·3 (8)
H(9′)*A*	0·203 (2)	0·733 (8)	0·010 (3)	5·4 (9)
H(9″)*A*	0·119 (2)	0·883 (11)	−0·051 (3)	8·2 (11)
H(2)*B*	−0·488 (3)	−0·062 (8)	−0·488 (4)	4·1 (8)
H(4)*B*	−0·270 (2)	0·255 (8)	−0·260 (3)	5·6 (10)
H(5)*B*	−0·204 (2)	0·305 (7)	−0·432 (3)	4·5 (8)
H(6)*B*	−0·283 (3)	0·192 (11)	−0·629 (3)	8·3 (11)
H(O1)*B*	0·581 (2)	−0·001 (10)	0·265 (3)	6·3 (11)
H(7)*B*	0·396 (2)	0·628 (7)	0·186 (2)	3·0 (8)
H(8)*B*	0·324 (2)	0·331 (7)	0·194 (3)	4·0 (8)
H(8′)*B*	0·423 (2)	0·243 (7)	0·265 (3)	3·9 (9)
H(N1′)*B*	0·493 (2)	0·267 (7)	0·121 (3)	4·9 (9)
H(N1)*B*	0·413 (2)	0·392 (9)	0·040 (3)	3·8 (9)
H(9)	0·675 (2)	0·623 (7)	0·979 (3)	3·0 (8)
H(9′)*B*	0·606 (2)	0·585 (9)	0·039 (3)	7·7 (11)
H(9″)*B*	0·403 (2)	0·003 (8)	0·104 (3)	5·9 (10)

Discussion. The atomic parameters are given in Table 1.*

The intramolecular bond distances and angles are listed in Table 2. The numbering scheme is indicated in Fig. 1. The bond lengths and angles do not show any remarkable deviation from the average model of sympathomimetic amines (Hebert, 1979). Compared to the free-base form of L-phenylephrine (Andersen, 1976) the only significant difference is in the C—O bond length

* Lists of anisotropic thermal parameters, hydrogen-bond parameters, least-squares planes, observed and calculated structure factors and an alternative stereoview of the molecular packing have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38213 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Bond lengths* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

Average C–H = 0·973, N–H = 0·932 and O–H = 0·923 Å.

	Molecule *A*	Molecule *B*
O(1)–C(1)	1·371 (4)	1·367 (4)
O(2)–C(7)	1·414 (5)	1·410 (5)
N(1)–C(8)	1·499 (4)	1·479 (5)
N(1)–C(9)	1·467 (5)	1·491 (6)
C(1)–C(2)	1·376 (5)	1·395 (5)
C(1)–C(6)	1·368 (5)	1·394 (5)
C(2)–C(3)	1·387 (5)	1·384 (5)
C(3)–C(4)	1·384 (5)	1·380 (5)
C(3)–C(7)	1·508 (5)	1·525 (5)
C(4)–C(5)	1·380 (5)	1·383 (6)
C(5)–C(6)	1·385 (5)	1·367 (6)
C(7)–C(8)	1·504 (5)	1·503 (6)
O(1)–C(1)–C(2)	117·3 (3)	118·1 (3)
O(1)–C(1)–C(6)	121·7 (3)	122·3 (3)
O(2)–C(7)–C(3)	111·6 (3)	114·0 (3)
O(2)–C(7)–C(8)	106·7 (3)	107·3 (3)
N(1)–C(8)–C(7)	112·0 (3)	111·3 (3)
C(1)–C(2)–C(3)	119·7 (3)	119·7 (3)
C(1)–C(6)–C(5)	119·6 (3)	119·8 (4)
C(2)–C(3)–C(4)	119·6 (3)	120·4 (3)
C(2)–C(3)–C(7)	120·1 (3)	120·6 (3)
C(2)–C(1)–C(6)	120·9 (3)	119·6 (3)
C(3)–C(4)–C(5)	120·0 (3)	119·5 (3)
C(3)–C(7)–C(8)	109·3 (3)	109·0 (3)
C(4)–C(5)–C(6)	120·1 (4)	121·1 (4)
C(4)–C(3)–C(7)	120·2 (3)	118·9 (3)
C(8)–N(1)–C(9)	112·2 (3)	113·9 (4)

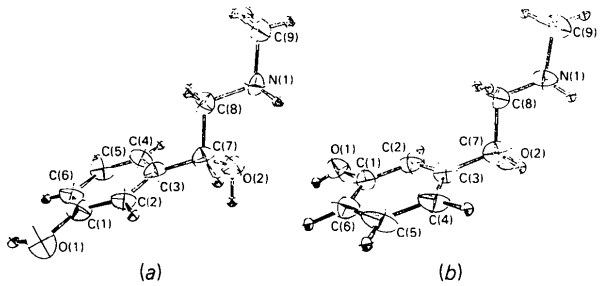

Fig. 1. A perspective view of (*a*) molecule *A* and (*b*) molecule *B* with atom-numbering scheme (*ORTEP*; Johnson, 1965). Thermal ellipsoids of the non-H atoms are scaled to the 50% probability level.

Table 3. *Selected torsion angles* (°)

Average e.s.d. is *ca* 0·5°.

	Molecule *A*	Molecule *B*	Free base (Andersen, 1976)
C(2)–C(3)–C(7)–C(8)	−106·3	76·7	−92·0
C(2)–C(3)–C(7)–O(2)	135·8	−43·1	150·7
C(3)–C(7)–C(8)–N(1)	−167·1	174·3	172·2
C(9)–N(1)–C(8)–C(7)	−172·8	−167·6	158·2
O(2)–C(7)–C(8)–N(1)	−46·2	−61·8	−65·7

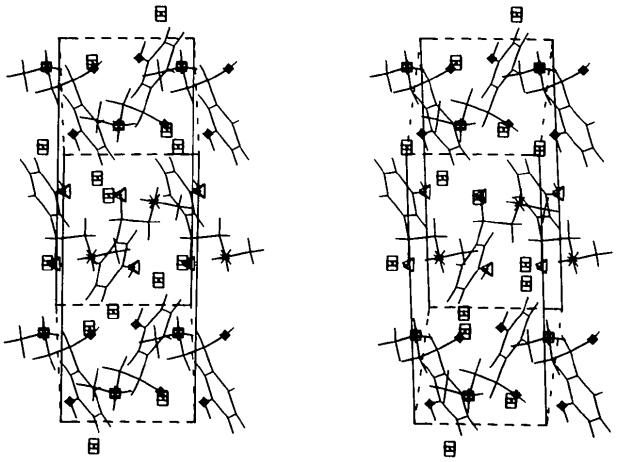

Fig. 2. A stereoview of the crystal packing. Axes *a*,*b* and *c* of the unit cell are distinguished by solid, long-dashed and short-dashed lines respectively. For each molecule the O and N atoms are distinguished by different marks. In molecule *B* the O atoms are marked by tetrahedra and the N atoms by stars. Chloride ions are marked by cubes. Drawings were made by the program *PACK* (Swanson, Rosenfield & Meyer, 1982).

of the *meta*-hydroxy group. This is because the free-base molecules were found to exist as zwitterions in the crystals, formed by a proton transfer from the phenolic hydroxyl group to the N atom. The distance of the amino N atom from the center of the benzene ring is 5·08 Å for both molecules in the asymmetric unit. This distance seems to be fairly constant in similar biologically active amines (Hebert, 1979; Post & Kennard, 1974; Giesecke, 1973), and appears to be a significant requirement for sympathomimetic activity. The perpendicular distance of this N atom from the plane of the benzene ring is 1·6 and 1·5 Å respectively for the two molecules.

The three-dimensional conformation of the molecules can be described by the torsion angles in Table 3. For comparison, the corresponding torsion angles of the free-base phenylephrine molecule are also included in the table showing the free base to be more similar to molecule *A* of the present structure. The position of O(2), which essentially distinguishes molecule *A* from *B*, is *trans* to the *meta* phenyl oxygen in molecule *A*. The *trans* conformation is rather common in crystal structures of similar sympathomimetic drugs. On the other hand, the *meta* hydroxy group and O(2) are on the same side of the side chain in molecule *B*. This is relatively rare but such a situation has been observed in methoxamine (Gabrielsen & Sorensen, 1974) and in adrenaline (Bergin, 1971).

Molecules and their packing within the unit cell are shown in Fig. 2. A striking feature of the crystal structure is that the atoms of the two molecules in the asymmetric unit are related by an approximate pseudo '*a*' glide perpendicular to the *b* axis (approximately at $y = 0·2$), the significant deviation being the O(2) atom. This is also reflected in the intensity distribution where *h*0*l* reflections are relatively weak for *h* odd.

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Structure of 2,3-Dihydro-1*H*-imidazo[1,2-*b*]pyrazole (IMPY), an Inhibitor of DNA Synthesis, $C_5H_7N_3$

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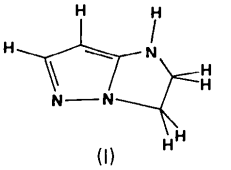
Abstract. $M_r = 109{\cdot}13$, orthorhombic, $P2_12_12_1$, $a = 7{\cdot}098$ (1), $b = 7{\cdot}225$ (1), $c = 10{\cdot}980$ (3) Å, $V = 563{\cdot}09$ Å^3, $Z = 4$, $D_m = 1{\cdot}29$, $D_x = 1{\cdot}29$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, $\mu = 0{\cdot}70$ mm^{-1}. Final $R = 0{\cdot}059$ for 425 significant reflections measured at 298 K. The pyrazole portion is planar, while the dihydroimidazole group has a shallow half-chair conformation with C(4) deviating by 0·136 (4) Å out of the plane of this ring.

Introduction. The title compound (NSC 51143: IMPY, I) is a potent and selective inhibitor of DNA synthesis (Ennis, Möller, Wang & Selawry, 1971), and is currently being evaluated for clinically useful anti-tumour activity (Vogel, Denefrio, Padgett & Silverman, 1980). Evidence has been obtained demonstrating that IMPY acts by inhibiting the ribonucleotide-reductase enzyme system (Cory & Fleischer, 1980), possibly by binding to a non-haem iron site. As a first step in the establishment of structure–activity relationships for IMPY and its congeners, its molecular structure has been established. This is the first reported X-ray study of an imidazo-[1,2-*b*]pyrazole system.



(I)

Experimental. Large prismatic crystals of IMPY obtained from aqueous solution, D_m determined by flotation, crystal *ca* 0·60 × 0·40 × 0·15 mm sealed in glass capillary tube so as to avoid the excessive decomposition noted at an earlier stage, preliminary X-ray photographs showed orthorhombic symmetry, systematic absences $h00$: $h = 2n + 1$; $0k0$: $k = 2n + 1$;

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