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Structure of Xylometazoline (Otrivin) Hydrochloride, an α-Adrenergic Agonist

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Abstract. 2-(4-*tert*-Butyl-2,6-dimethylbenzyl)-4,5-dihydro-1*H*-imidazole hydrochloride, $C_{16}H_{25}N_2^+.Cl^-$, $M_r = 280{\cdot}84$, monoclinic, $P2_1/c$, $a = 14{\cdot}430\ (4)$, $b = 9{\cdot}545\ (3)$, $c = 12{\cdot}250\ (4)$ Å, $\beta = 104{\cdot}73\ (2)°$, $V = 1631{\cdot}8$ Å^3, $Z = 4$, $D_m = 1{\cdot}15$, $D_x = 1{\cdot}14$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 19{\cdot}72$ cm^{-1}, $F(000) = 608$, $T = 277\ (1)$ K, $R = 0{\cdot}053$ for 1320 observed reflections. The substituted phenyl and imidazole rings in the molecule are planar with a dihedral angle of 95·0° between them. The positive charge is dispersed over both the N atoms of the imidazole ring and they are involved in hydrogen bonds with the Cl^- ions. Critical sites for the interaction of the adrenergic imidazolines with the α-receptors are discussed.

Introduction. An important group of drugs capable of interacting with the adrenergic receptors, other than the well known phenethylamines, are the imidazoli(di)ne derivatives, which are selective for the α-receptors only. In view of the clinical importance of the adrenergic imidazoli(di)nes, the X-ray crystal structure of xylometazoline has been determined in order to compare its conformation with those of a few such drug molecules, and also to gain some idea of the nature of the interaction of these compounds at the α-receptors. Structurally, a typical compound in this imidazoli(di)ne series consists of an imidazole ring separated from a substituted phenyl ring by one C or N atom. Xylometazoline is a sympathomimetic amine and the hydrochloride of the compound is used chiefly as a nasal vasoconstrictor. In this compound, the ethylamine chain (which is flexible in most phenethylamines) forms a part of the imidazole ring.

Experimental. Commercially available compound recrystallized (301 K) from an aqueous solution. D_m by flotation in bromoform/benzene, crystal size 0·30 × 0·20 × 0·08 mm, Syntex $P\bar{1}$ diffractometer, cell dimensions from setting angles of 15 reflections in the range $45° < 2\theta < 67°$; $P2_1/c$ from systematic absences ($0k0$ for k odd and $h0l$ for l odd), ω–2θ-scan mode, graphite-monochromated Cu $K\alpha$, 1414 independent reflections, $2\theta \leq 120°$, hkl: h 0 to 15, k 0 to 10, l −13 to 12, 1320 observed with $I > 2\sigma(I)$; three standard reflections, measured after every 97 reflections, showed no significant intensity variation; no absorption correction. Structure solved by *MULTAN*78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978), 21 H atoms from difference Fourier map and remaining four in calculated positions, non-H atoms refined anisotropically, H atoms (except the ones attached to terminal methyl C atoms) isotropically, least-squares refinement, $\sum w(\Delta F)^2$ minimized, $w = 1/\sigma^2(F)$. $R = 0{\cdot}053$, $wR = 0{\cdot}074$, $S = 2{\cdot}23$, highest parameter shift to e.s.d. ratio 0·24, maximum height in final difference Fourier map 0·3 e Å^{-3}; scattering factors from *International Tables for X-ray Crystallography* (1974); *XRAY ARC* program system (Vickery, Bright & Mallinson, 1971) used for most of the calculations.

Discussion. The atomic coordinates are given in Table 1 and the atoms are labelled in Fig. 1. Intramolecular bond distances and angles are given in Table 2.* Both the phenyl and imidazole rings are planar within experimental limits and the dihedral angle (φ) between these two planes is 95·0°. The geometry of the linking CH_2 group is described by the bond angle C(5)–C(4)–C(3) = 114·9°, and the torsion angles τ_1[C(6)–C(5)–C(4)–C(3)] = 75·7° and τ_2[C(5)–C(4)–C(3)–N(1)] = −142·9° define the relative orientation of the two rings. The C(11)–C(14), C(11)–C(15) and C(11)–C(16) bonds are shorter than expected. This is obviously a consequence of anisotropic refinement of the highly vibrating methyl groups. This has also been found to be the case in some other structures with terminal methyl groups (Kojić-Prodić, Ružić-Toroš & Linek, 1983; Bosch, Voges, Jung & Winter, 1983; Rychlewska, 1985).

In the imidazole ring, on protonation of N(1), the C(3)–N(1) and C(3)–N(2) bond lengths become very similar, 1·309 (4) and 1·304 (4) Å, respectively, and they are shorter than the C(2)–N(2) and C(1)–N(1) bonds. This indicates that the C(3)–N bonds have

* Lists of structure factors, anisotropic thermal parameters, coordinates and isotropic thermal parameters of the H atoms and least-squares planes have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 43085 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Table 1. *Final positional* ($\times 10^4$) *and equivalent isotropic thermal parameters of the non-*H *atoms with e.s.d.'s in parentheses*

$$B_{eq} = \tfrac{4}{3}\sum_i\sum_j \beta_{ij}\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	B_{eq}(Å^2)
Cl	6136 (1)	9718 (1)	3012 (1)	3·95 (2)
N(1)	5360 (2)	1670 (4)	923 (3)	3·80 (8)
N(2)	5597 (2)	3291 (4)	−207 (3)	3·84 (8)
C(1)	4399 (3)	1913 (5)	203 (4)	4·2 (1)
C(2)	4576 (3)	2968 (5)	−645 (4)	4·6 (1)
C(3)	5991 (3)	2495 (4)	650 (3)	2·95 (9)
C(4)	7027 (3)	2491 (4)	1253 (4)	3·7 (1)
C(5)	7498 (2)	3919 (4)	1403 (3)	2·97 (9)
C(6)	7329 (3)	4834 (4)	2219 (3)	3·16 (9)
C(7)	7776 (3)	6148 (5)	2364 (3)	3·43 (9)
C(8)	8404 (2)	6566 (4)	1742 (3)	2·93 (9)
C(9)	8551 (3)	5629 (4)	943 (3)	3·13 (9)
C(10)	8115 (3)	4318 (4)	750 (3)	3·07 (9)
C(11)	8897 (3)	7999 (4)	1898 (4)	3·8 (1)
C(12)	6655 (3)	4452 (5)	2924 (4)	4·5 (1)
C(13)	8337 (3)	3404 (5)	−155 (4)	4·2 (1)
C(14)	8927 (5)	8640 (7)	3024 (6)	9·8 (2)
C(15)	9897 (4)	7939 (6)	1775 (6)	7·1 (2)
C(16)	8342 (5)	8975 (6)	1058 (8)	13·6 (3)

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

N(1)–C(1)	1·461 (5)	C(6)–C(12)	1·500 (5)
N(1)–C(3)	1·309 (4)	C(7)–C(8)	1·383 (4)
N(2)–C(2)	1·467 (5)	C(8)–C(9)	1·382 (4)
N(2)–C(3)	1·304 (4)	C(8)–C(11)	1·531 (4)
C(1)–C(2)	1·514 (5)	C(9)–C(10)	1·393 (4)
C(3)–C(4)	1·490 (5)	C(10)–C(13)	1·508 (4)
C(4)–C(5)	1·513 (4)	C(11)–C(14)	1·499 (6)
C(5)–C(6)	1·395 (4)	C(11)–C(15)	1·490 (5)
C(5)–C(10)	1·393 (4)	C(11)–C(16)	1·466 (6)
C(6)–C(7)	1·400 (4)		

C(1)–N(1)–C(3)	111·5 (3)	C(6)–C(5)–C(10)	119·6 (3)
C(2)–N(2)–C(3)	111·3 (3)	C(6)–C(7)–C(8)	122·3 (3)
N(1)–C(1)–C(2)	102·7 (3)	C(7)–C(6)–C(12)	119·3 (3)
N(2)–C(2)–C(1)	102·6 (3)	C(7)–C(8)–C(9)	116·4 (3)
N(1)–C(3)–N(2)	111·5 (3)	C(7)–C(8)–C(11)	122·5 (3)
N(1)–C(3)–C(4)	123·2 (3)	C(8)–C(9)–C(10)	123·9 (3)
N(2)–C(3)–C(4)	125·3 (3)	C(9)–C(8)–C(11)	121·1 (3)
C(3)–C(4)–C(5)	114·9 (3)	C(9)–C(10)–C(13)	118·3 (3)
C(4)–C(5)–C(6)	119·8 (3)	C(8)–C(11)–C(14)	112·5 (3)
C(4)–C(5)–C(10)	120·6 (3)	C(8)–C(11)–C(15)	112·6 (3)
C(5)–C(6)–C(7)	119·5 (3)	C(8)–C(11)–C(16)	109·1 (3)
C(5)–C(6)–C(12)	121·2 (3)	C(14)–C(11)–C(15)	107·8 (4)
C(5)–C(10)–C(9)	118·4 (3)	C(14)–C(11)–C(16)	105·6 (5)
C(5)–C(10)–C(13)	123·4 (3)	C(15)–C(11)–C(16)	108·9 (5)

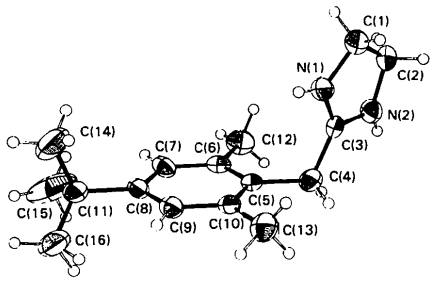

Fig. 1. *ORTEP* (Johnson, 1965) drawing of the xylometazoline cation with anisotropic thermal parameters at the 40% probability level. H atoms are shown as spheres of arbitrary radius.

partial double-bond character, the positive charge being dispersed over both the N atoms of the imidazole ring. Both N(1) and N(2) participate in hydrogen bonding. N(1)–H···Cl(x, $y-1$, z) = 3·134 (3) Å [H···Cl = 2·22 (4) Å] and N(2)–H···Cl(x, $\frac{3}{2}-y$, $z-\frac{1}{2}$) = 3·136 (3) Å [H···Cl = 2·47 (3) Å] and the N–H···Cl angles are 167·8 (3) and 148·2 (3)° respectively. The crystal packing is dominated by hydrogen bonds that form infinite chains of the type N(1)–H···Cl···H–N(2) and the hydrophobic and hydrophilic layers are parallel to the *bc* plane, with translations along **a** (Fig. 2).

In xylometazoline the methyl substitution at the *ortho* positions of the phenyl ring leads to the stabilization of the nearly mutually perpendicular arrangement ($\varphi = 95·0°$) of the two rings. A similar ring conformation has been found in other di-*ortho*-phenyl-substituted compounds like clonidine hydrochloride (Cody & DeTitta, 1979) and clonidine phosphate (Carpy, Hickel & Leger, 1979*a*) where the Cl atoms constrain the two rings in an approximate perpendicular arrangement. But in tolonidine nitrate (Carpy, Hickel & Leger, 1979*b*, 1980), which has only one *ortho* substituent, φ is close to 60°.

The distance (D_N) of the N atom from the centre of the phenyl ring and its height (H_N) above the phenyl ring are thought to be of considerable significance for the adrenergic agents (Dattagupta, Meyer & Mukhopadhyay, 1982; Dattagupta, Pattanayek & Saha, 1981; Pullman, Coubeils, Courriere & Gervois, 1972). For most of these compounds the values have been found to be around 5·1–5·2 Å and 1·2–1·4 Å respectively. We have calculated the values of D_N and H_N for both the N atoms of the imidazole ring in xylometazoline: D_N of N(1) = 4·96, D_N of N(2) = 3·99 Å and H_N of N(1) = 1·32, H_N of N(2) = 2·43 Å. The values of D_N and H_N related to N(1) are in good agreement with those found in clonidine (Cody & DeTitta; 1979; Carpy, Hickel & Leger, 1979*a*).

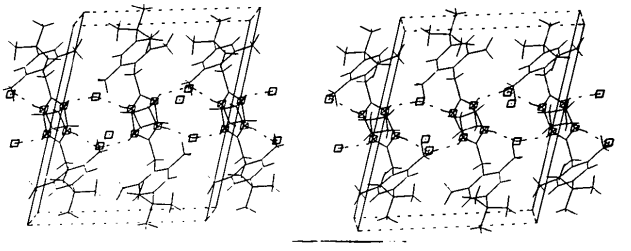

Fig. 2. Stereoview of the packing in the unit cell, viewed approximately down **b**. Unit-cell edges are indicated by a solid line for **a**, long-dashed lines for **b**, and short-dashed lines for **c**. N atoms are designated by tetrahedral marks and the Cl atoms by cubic marks. Hydrogen bonding is denoted by dashed lines between atoms. Drawings were made by the program *PACK* (Swanson, Rosenfield & Meyer, 1982).

When considered as a class, the imidazolines have higher affinities for the α-adrenergic receptor than the phenethylamines (Ruffolo, Dillard, Yaden & Waddell, 1979). One of the reasons for this observation may be that the dispersed-charge arrangement within the imidazole moiety helps it to achieve a better interaction with the α-receptors, which may not be possible in the phenethylamines since the positive charge is concentrated at the N atom in the protonated forms of these molecules.

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Structure of 2,2′-Anhydro-1-β-D-arabinofuranosyl-6-methyluracil Hemihydrate*

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Abstract. $C_{10}H_{12}N_2O_5.\frac{1}{2}H_2O$, $M_r = 249{\cdot}2$ (240·2 for $C_{10}H_{12}N_2O_5$), monoclinic, space group $P2_1$, $a = 9{\cdot}595$ (1), $b = 16{\cdot}196$ (2), $c = 7{\cdot}341$ (2) Å, $\beta = 109{\cdot}39$ (2)°, $V = 1076{\cdot}1$ (4) Å^3, $Z = 4$, D_m not measured, $D_x = 1{\cdot}538$ Mg m^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, $\mu = 0{\cdot}14$ mm^{-1}, $T = 294$ K, $F(000) = 524$. Final $R = 0{\cdot}037$ for 2428 unique X-ray diffractometer data. The two independent molecules of the asymmetric unit have different conformations for sugar rings and side chains; C(4′)-*endo*-C(3′)-*exo*, g^+ (molecule *A*) and C(4′)-*exo*-O(4′)-*endo*, *t* (*B*). There are short intramolecular O(5′)···base contacts in molecule *A*. All hydroxyl and water hydrogen atoms participate in six hydrogen bonds with O(4*A*) (bifurcated), O(4*B*), O(water), O(3′*B*) and N(3*B*) atoms as their acceptors.

Introduction. *O*-Cyclonucleosides can be used as intermediates in nucleoside syntheses owing to easy breaking of their anhydro linkage. The best known example is cycloara C, which can be converted into therapeutically active ara C in physiological conditions (Hoshi, Kanzawa & Kuretani, 1972; Loo, Ho, Bodey & Freireich, 1975). Cycloara C, unlike its acyclic form,

* IUPAC name: 2,3,3a,9a-tetrahydro-3-hydroxy-2-hydroxymethyl-8-methyl-6*H*-furo[2′,3′:4,5]oxazolo[3,2-*a*]pyrimidin-6-one.

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