Crystal Structure of Tolazoline Hydrochloride (Priscoline), an α-Adrenergic Antagonist

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The crystal and molecular structure of tolazoline hydrochloride (priscoline), an α-adrenergic antagonist which is clinically used as a vasodilating drug, has been studied by *X*-ray diffraction methods. The results show that the imidazole group is involved in a protonation process, the positive charge being dispersed over both nitrogen atoms of the imidazole ring, and the molecule adopts a biplanar conformation with an angle of 89.3(2)° between the phenyl and imidazole rings—an orientation which seems to be relevant for their interaction at the receptor site. Critical sites for the interaction of the adrenergic dihydroimidazoles with the α-receptors are discussed.

The 2-substituted dihydroimidazoles have a wide range of pharmacological actions. Structurally, a typical compound in this imidazoli(di)ne series consists of an imidazole ring separated from a substituted phenyl ring by one carbon or nitrogen atom. Several of these drugs are used in clinical therapy for their α-adrenergic activity as either nasal or ocular decongestants, antihypertensive agents, or as peripheral vasodilators. Tolazoline hydrochloride (priscoline) is an α-adrenergic antagonist and is clinically used as a peripheral vasodilator and a smooth muscle relaxant. It produces a moderately effective competitive α-adrenergic blockade that is relatively transient. In addition it has important direct actions on cardiac and smooth muscles.[1] The α-adrenergic receptors appear to pose some structural demands on the molecules interacting with them and thereby producing a bioresponse.[2,3] Studies concerning the structural and conformational aspects of the α-adrenergic agonists and antagonists might give us some insight into the nature and mode of action at the complementary α-receptor site. The crystal-structure analysis of the title compound forms a part of our studies on the structural and conformational discriminating factors, if any, between the α-adrenergic imidazoli(di)ne agonists and antagonists.

Experimental

X-Ray Structure Analysis.—Crystals were obtained from an aqueous solution of the commercially available compound by slow evaporation at room temperature. A plate-shaped crystal was chosen for *X*-ray structure analysis. The crystal density was measured by flotation in a mixture of benzene and bromoform.

Crystal data.—$C_{10}H_{13}N_2^+$ Cl^-, M = 196.67, monoclinic, a = 8.981 1(5), b = 9.657 7(5), c = 12.282 5(8) Å, β = 104.352(5)°, V = 1 032.07 Å^3, refined cell parameters from 87 reflections in the range θ < 45°, D_m = 1.260 g cm^{-3}, Z = 4, D_c = 1.266 g cm^{-3}, $F(000)$ = 416, μ = 29.50 cm^{-1}, space group $P2_1/c$.

A crystal of dimensions 0.75 × 0.50 × 0.40 mm was used for collecting intensity data on a Philips PW1100 four-circle diffractometer with graphite-monochromated Cu-K_α radiation. 1 852 Reflections with h 0–10, k 0–11, l −14 to +14, and $\theta_{max.}$(λ = 1.5418 Å) 65° were measured in the ω/2θ scan mode. Two standard reflections remeasured after every 90 min showed no significant variation. 1 628 Reflections were considered as observed with $I \geqslant 2.0\sigma(I)$ [σ(I) being the e.s.d. based on counting statistics]. Data were corrected for Lorentz and polarization effects but not for absorption.

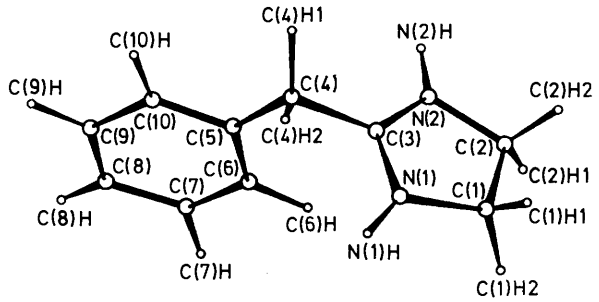


Figure 1. View of the molecular conformation and numbering scheme of tolazoline.

The phase problem was solved by direct methods with MULTAN.[4] An *E*-map generated from the phase set (252 reflections), with the highest combined figure of merit, located a fragment of the molecule; the remaining atoms were found by difference Fourier syntheses. The H-atoms except the ones attached to N(1) and N(2) were located stereochemically. Structure refinement was done by least-squares methods by minimizing $\Sigma w(\Delta F)^2$ [where $w = 1/\sigma^2(F)$] for 13 anisotropically refined non-H atoms and 11 isotropically fixed H-atoms. The amine hydrogen atoms N(1)H and N(2)H were calculated stereochemically when the analysis was complete and were included in the final calculations. Final R 0.098 and R_w 0.085. Highest parameter shift to e.s.d. ratio was 0.23, and S 2.56. Residual electron density was within ±0.65 e Å^{-3} in the final difference Fourier map. Scattering factors were taken from International Tables for *X*-ray Crystallography[5] and the XRAY ARC[6] program system was used for most of the calculations. The structure and the numbering scheme are presented in Figure 1 and the final positional parameters for non-H atoms are given in Table 1. Anisotropic thermal parameters and least-squares planes calculations have been deposited with the Cambridge Crystallographic Data Centre.

Discussion

The intramolecular bond lengths and angles are normal and are given in Table 2, and a packing diagram of the molecules is shown in Figure 2. The maximum deviation of an atom from

Table 1. Positional parameters with e.s.d.s in parentheses.

	x	*y*	*z*
Cl	0.371 9(2)	0.220 5(2)	0.948 3(2)
N(1)	0.605 6(6)	0.067 6(6)	0.398 7(4)
N(2)	0.682 6(6)	−0.078 4(6)	0.282 3(4)
C(1)	0.764 9(7)	0.033 5(8)	0.458 0(5)
C(2)	0.816 5(8)	−0.072 6(7)	0.382 2(6)
C(3)	0.575 6(7)	0.002 0(7)	0.298 5(5)
C(4)	0.423 8(8)	0.022 7(7)	0.213 8(6)
C(5)	0.302 0(7)	−0.077 4(7)	0.221 7(5)
C(6)	0.317 1(7)	−0.183 8(7)	0.301 7(5)
C(7)	0.198 0(8)	−0.273 9(8)	0.306 6(6)
C(8)	0.052 6(8)	−0.254 5(9)	0.229 9(7)
C(9)	0.036 7(9)	−0.151 8(9)	0.152 1(7)
C(10)	0.155 8(8)	−0.063 8(8)	0.145 9(6)

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

N(1)–C(1)	1.472(8)	C(5)–C(6)	1.405(9)
N(1)–C(3)	1.352(8)	C(6)–C(7)	1.392(10)
N(2)–C(2)	1.491(8)	C(7)–C(8)	1.421(10)
N(2)–C(3)	1.289(8)	C(8)–C(9)	1.360(12)
C(1)–C(2)	1.532(10)	C(9)–C(10)	1.383(11)
C(3)–C(4)	1.509(9)	C(10)–C(5)	1.415(10)
C(4)–C(5)	1.481(9)		
C(1)–N(1)–C(3)	107.2(5)	C(4)–C(5)–C(6)	125.3(6)
C(2)–N(2)–C(3)	109.3(5)	C(4)–C(5)–C(10)	118.5(6)
N(1)–C(1)–C(2)	104.6(5)	C(5)–C(6)–C(7)	123.1(6)
N(2)–C(2)–C(1)	102.8(5)	C(6)–C(5)–C(10)	116.2(6)
N(1)–C(3)–N(2)	115.8(6)	C(6)–C(7)–C(8)	118.6(7)
N(1)–C(3)–C(4)	120.5(6)	C(7)–C(8)–C(9)	118.7(7)
N(2)–C(3)–C(4)	123.7(6)	C(8)–C(9)–C(10)	122.6(6)
C(3)–C(4)–C(5)	115.1(6)	C(9)–C(10)–C(5)	120.7(7)

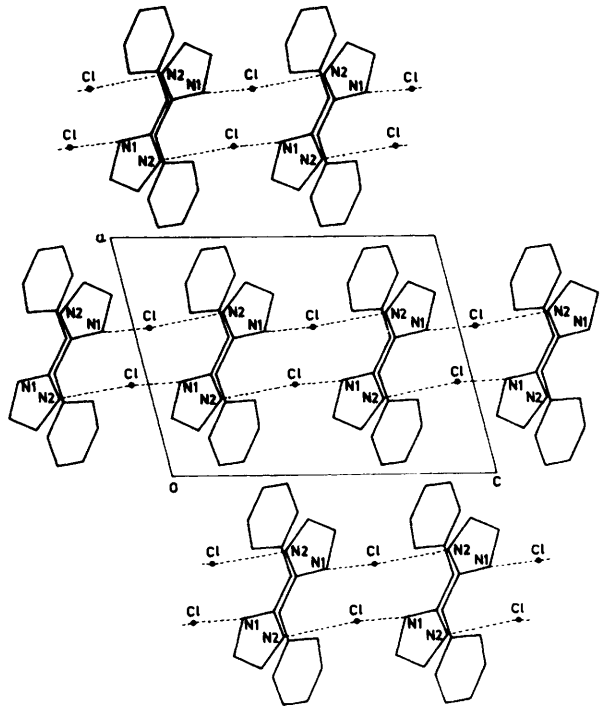
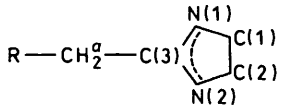
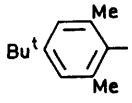
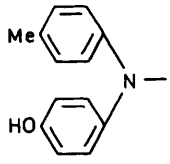


Figure 2. Molecular packing viewed down the *b* axis.

planarity in the phenyl ring is 0.012(7) Å while that for the imidazole ring is 0.035(7) Å, and the dihedral angle (φ) between the two rings is 89.3(2)°. The imidazole part of the molecule is protonated. Both C(3)–N bonds are shorter than the C(1)–N(1)

Table 3. Relevant structural features of some α-adrenergic dihydroimidazoles.



Compound	R	Ligand type	Bond lengths C(3)–N(1) C(3)–N(2) /Å	Dihedral angle φ/°	Torsion angles/° τ_1	τ_2	Ref.
Tolazoline HCl	Ph	Antagonist	1.352(8) 1.289(8)	89.3	179.4	−91.0	Present paper
Naphazoline HCl	1-Naphthyl	Agonist	1.310(5) 1.309(4)	94	176.3	−93.6	8
Xylometazoline HCl		Agonist	1.309(4) 1.304(4)	95	75.7	−142.9	7
Clonidine HCl		Agonist	1.323(3) 1.318(3)	74.5	76.0	178.0	9
Phentolamine HCl		Antagonist	1.316(5) 1.294(5)	88[b]			10

[a] NH Instead of CH_2 in clonidine. [b] φ Is the angle between the *p*-hydroxyphenyl and imidazole rings.

[1.472(8) Å] and C(2)–N(2) [1.491(8) Å] bonds and their values are intermediate between that of a double bond (1.265 Å) and that of a single bond (1.470 Å). However, the difference between the two C(3)–N bonds in this structure is 0.063(11) Å. This result indicates a delocalization of the double bond on the imidazole group and a delocalization of the positive charge on both nitrogen atoms of the imidazole ring.

Some interesting structural similarities have been observed between tolazoline and a few other structurally related α-adrenergic agents containing an imidazole ring. They are listed in Table 3, where xylometazoline,[7] naphazoline,[8] and tolazoline are sympathomimetic agents while clonidine[9] and phentolamine[10] are antihypertensive agents. It is seen that in these compounds (a) both C(3)–N bonds of the imidazole ring have partial double-bond character and they are similar in length, but shorter than the other two C–N bonds, *viz.* C(1)–N(1) and C(2)–N(2) and (b) the dihedral angle between the phenyl and imidazole rings is close to 90°.

Certain conformational features of adrenergic drug molecules seem to be important for their interaction at receptor sites. For the sympathomimetic imidazoles these are the torsion angles τ_1 [C(10)–C(5)–C(4)–C(3)] and τ_2 [C(5)–C(4)–C(3)–N(1)] and φ, the dihedral angle between the phenyl and imidazole rings (or the plane of the flexible ethylamine side chain for the phenethylamines). In tolazoline and naphazoline the torsion angle $\tau_1 \sim 180°$ and $\tau_2 \sim 90°$. These values are in complete contrast with those usually found in the sympathomimetic amines where $\tau_1 \sim 90°$ and $\tau_2 \sim 180°$.[11] So for the α-adrenergic imidazoli(di)nes, it may be possible that a dihedral angle (φ) of 90° between the phenyl and imidazole rings, irrespective of the values of the torsion angles τ_1 and τ_2 and a dispersed charge arrangement within the imidazole ring might be the important factors that influence their interaction with α-adrenergic receptors.

Another significant difference has been observed between the crystal structures of the α-adrenergic imidazoli(di)ne agonists and antagonists listed in Table 3. In the agonists, the C(3)–N bonds in the imidazole ring are very similar in length, while in the antagonists they are different (the difference is more than three times the standard deviation). This implies that in the agonists the positive charge is more or less evenly distributed in the N–C–N region of the imidazole ring, while in the antagonists there is a gradation of the positive charge distribution from one nitrogen atom to the other nitrogen atom in the same region of the imidazole ring. This difference in charge distribution may be one of the factors which influence their mode of interaction at the α-adrenergic receptor.

In tolazoline hydrochloride both N atoms of the imidazole ring participate in hydrogen bonding and each Cl atom is involved in two intermolecular hydrogen bonds of the form N(1)–H · · · Cl · · · H–N(2) that link the molecules in continuous chains in alternate columns of hydrophobic and hydrophilic regions (Figure 2): N(1)–N(1)H · · · Cl $(x, -y + \frac{1}{2}, z - \frac{1}{2})$ 3.099(6) Å, [N(1)H · · · Cl 2.148 Å]; and N(2)–N(2)H · · · Cl $(-x + 1, -y, -z + 1)$, 3.076(6) Å, [N(2)H · · · Cl 2.105 Å], and the N–H · · · Cl angles are 164.0 and 166.6°, respectively.

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