Crystal structures of two therapeutically active 2-imidazolines: naphazoline nitrate and tymazoline hydrochloride monohydrate

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Naphazoline · HNO_3 (1): $C_{14}H_{15}N_3O_3$, $M_r = 273.3$, crystallizes in the orthorhombic space group *Pbca* ($Z = 8$) with $a = 12.028(1)$, $b = 14.408(2)$ and $c = 15.894(2)$ Å, $V = 2754.4$ Å^3, $D_x = 1.318$ g cm^{-3}, $\mu = 0.70$ mm^{-1}, λ (Cu $K\alpha$) = 1.54178 Å, $F(000) = 1152$. Final $R = 0.092$ and $wR = 0.088$ for 1348 observed reflections collected on a diffractometer. The structure was solved with direct methods, it shows two distinct positions of the naphthyl group with populations about 0.5, which differ by a 180° rotation. As in other arylmethyl-2-imidazolines, the imidazoline ring is approximately perpendicular to the aromatic ring. The molecules are linked by two hydrogen bonds N(3)—H · · · O (nitrate anion) · · · H—N(1) into infinite chains running along the 2_1 axis in the [100] direction. Tymazoline · HCl · H_2O (2): $C_{14}H_{23}ClN_2O_2$, $M_r = 286.8$, crystallizes in the monoclinic space group $P2_1/n$ ($Z = 4$) with $a = 8.136(1)$, $b = 10.015(1)$, $c = 18.601(1)$ Å and $\beta = 97.20(1)°$, $V = 1503.7$ Å^3, $D_x = 1.266$ g cm^{-3}, $\mu = 2.27$ mm^{-1}, λ(Cu $K\alpha$) = 1.54178 Å, $F(000) = 636$. Final $R = 0.115$ and $wR = 0.119$ for 3073 observed reflections collected on a diffractometer. The structure was solved with direct methods. Unlike other aryloxymethyl-2-imidazolines, the molecule is almost planar with an angle of 12.8(2)° between the two rings. Hydrogen bonding networks consist of N(1)—H · · · O (water) · · · Cl$^-$ · · · H—N(3) chains joined by an additional link O(water)—H · · · Cl$^-$ between chains running in opposite directions.

Introduction

Though 2-substituted imidazolines have a wide range of pharmacological actions, their structures are similar. In 1981, Carpy *et al.* (1981) proposed a geometrical model for the interactions of clonidine-type imidazolines with the adrenoreceptor. The authors suggested that the active conformations of imidazolines are those observed in the crystals and that clonidine–adrenoreceptor interactions consist of: (i) electrostatic attractions between a protonated guanidine moiety and a negatively charged site of the α-receptor, (ii) a hydrophobic interaction between the aromatic ring and an electron deficient area of the receptor, (iii) the possible formation of a hydrogen bond with the exocyclic NH group. However, both naphazoline (1) and tymazoline

(2) differ from clonidine in the linkage between aromatic and imidazoline rings and they can not form the hydrogen bond suggested in the Carpy model. Therefore we considered the crystal structures of 1 and 2 to be of interest. The crystal structure of another naphazoline form (hydrochloride) has been published by Podder *et al.* (1983).

Experimental

4,5-Dihydro-2-(1-naphthalenylmethyl)-1H-imidazole nitrate (naphazoline · HNO_3)

Prismatic, colorless crystals were grown by slow evaporation from methanol–water mixture. A crystal of dimensions 0.35 × 0.24 × 0.23 mm was used for unit-cell determination and data collection on a CAD4 dif-

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fractometer. The accurate cell constants were determined from setting angles of 25 reflections with $17 <$ $\theta < 26°$. The data were collected over a range of h(0/15), k(0/18), and l(0/19) to a maximum θ of 75° in an $\omega/2\theta$ scan mode. Three standard reflections were measured every 1 h of exposure; the variation in the intensities of these reflections was less than 4%. Of the 2822 unique reflections that were measured, 1348 had $[F \geqslant 3\sigma\,(F)]$ and were taken as observed. The data were corrected for Lorentz and polarization effects, and an absorption correction according to Walker and Stuart (1983) was applied.

The structure was solved by direct methods with some troubles due to naphthalene ring disorder, which caused an increase of the intensities of many systematically absent reflections, especially $h0l$. However, all attempts to solve the structure in all other possible space groups (when neglecting suspected absences) failed. The initial E synthesis in the *Pbca* space group revealed disorder of the naphthalene ring. Alternative orientations were clearly visible but many atoms of the two conformations overlapped and could neither be distinguished nor refined in the free atom model. Eventually, a model with constrained bond lengths in the naphthalene ring and isotropic thermal vibrations converged to an R of 0.185 with population parameters refined to 0.537 and 0.463 for the two separate orientations of the naphthyl group. Aromatic hydrogen atoms were neglected, while imidazoline and methylene hydrogen atoms were determined from a difference Fourier synthesis and refined isotropically in riding positions. In the following anisotropic refinement (full-matrix least-squares on F), the structure was divided into three parts, each refined as one block. The first block consisted of the nitrate anion and imidazoline cation atoms (all having occupancy equal 1.0), while the second and the third blocks comprised 1-naphthylmethyl groups with fixed occupancies of 0.537 and 0.463, respectively. The final $R = 0.092$ and $R_w = 0.088$ for 1348 observed reflections, $w^{-1} = \sigma^2(F)$ and ρ_{max} in the final ΔF synthesis of 0.27 e Å^{-3}.

2-[(Thymyloxy)methyl]-2-imidazoline hydrochloride monohydrate (tymazoline · HCl · H_2O)

Big plate-like crystals were grown from a benzene-chloroform mixture. A crystal of dimensions 0.23 × 0.21 × 0.06 mm was cut off from a big plate and was used for unit-cell determination and data collection on a CAD4 diffractometer. The accurate cell constants were determined from setting angles of 25 reflections with 20 $< \theta < 28°$. 3320 unique reflections were measured in

$\omega/2\theta$ scan mode up to $\theta_{max} = 75°$ over the range of h(0, 10), k(0, 12), and l (−23, 23). Three standards were monitored every 1 h, the variations in their intensity were less than 3%. The data were corrected for Lorentz and polarization effects.

The structure was solved by direct methods and refined by anisotropic full-matrix least-squares on F. H atoms were calculated geometrically and included in the refinement by a riding model with isotropic thermal vibrations. The final R (R_w) was 0.115(0.119) for 3073 observed (2.5σ) reflections, $w^{-1} = \sigma^2\,(F) + 0.0006F^2$. The greatest shift/error ratio was 0.2. The final ΔF synthesis showed $\rho_{max} = 0.85$ e Å^{-3}.

All calculations were performed on a 1512 Amstrad PC microcomputer with SHELXS (Sheldrick, 1986) and SHELX (Sheldrick, 1976) programs.

Table 1. Final atomic coordinates and equivalent isotropic temperature parameters for non-H-atoms for 1

| Atom | $B_{eq} = \frac{8}{3}\pi^2\Sigma_i\Sigma_j U_{ij}a_i^*a_j^*\mathbf{a}_i\mathbf{a}_j$ | | | B_{eq}/B_{iso} |
	x	y	z	(Å^2)
N(10)	0.0528(6)	0.7948(5)	0.4924(4)	7.8(2)
O(11)	0.1507(4)	0.7714(4)	0.4791(3)	9.2(2)
O(12)	0.0348(5)	0.8742(4)	0.5164(4)	10.1(2)
O(13)	−0.0229(4)	0.7395(4)	0.4812(4)	11.1(2)
N(01)	0.1448(4)	0.5755(4)	0.4542(3)	6.7(2)
C(02)	0.2151(5)	0.5187(5)	0.4901(3)	5.0(2)
N(03)	0.2151(4)	0.4348(4)	0.4587(3)	6.3(2)
C(04)	0.1330(6)	0.4267(5)	0.3894(4)	7.3(2)
C(05)	0.0857(6)	0.5260(5)	0.3857(4)	7.8(3)
C(106)	0.2951(9)	0.5387(7)	0.5672(6)	6.4(4)
C(1)	0.2103(10)	0.5810(13)	0.6405(7)	12.0(8)
C(2)	0.1742(13)	0.6719(10)	0.6467(10)	9.2(6)
C(3)	0.1024(13)	0.6907(10)	0.7160(10)	9.3(6)
C(4)	0.0691(12)	0.6248(12)	0.7781(8)	8.5(6)
C(5)	0.0805(10)	0.4627(12)	0.8321(8)	8.2(6)
C(6)	0.1171(12)	0.3749(10)	0.8239(9)	7.5(5)
C(7)	0.1848(13)	0.3428(11)	0.7554(9)	10.4(6)
C(8)	0.2150(10)	0.4097(10)	0.6958(7)	7.1(5)
C(9)	0.1818(9)	0.5079(8)	0.6982(7)	4.8(3)
C(10)	0.1115(10)	0.5305(9)	0.7704(8)	6.1(4)
C(206)	0.2906(9)	0.5593(9)	0.5627(7)	5.3(4)
C(11)	0.2388(11)	0.5024(14)	0.6462(9)	14.7(2)
C(12)	0.2535(17)	0.4097(11)	0.6676(10)	8.4(7)
C(13)	0.2010(13)	0.3759(11)	0.7427(9)	7.0(5)
C(14)	0.1340(14)	0.4347(12)	0.7922(10)	8.6(7)
C(15)	0.0413(14)	0.5873(15)	0.8163(10)	9.9(8)
C(16)	0.0149(15)	0.6763(13)	0.7925(12)	9.4(8)
C(17)	0.0731(14)	0.7181(13)	0.7215(10)	8.2(6)
C(18)	0.1426(12)	0.6625(10)	0.6733(8)	6.1(5)
C(19)	0.1666(11)	0.5650(9)	0.6899(8)	5.4(5)
C(20)	0.1136(10)	0.5294(12)	0.7659(7)	6.3(5)

Table 2. The final coordinates and equivalent isotropic thermal parameters for **2**

$$B_{eq} = \tfrac{8}{3}\pi^2 \cdot \Sigma_i \cdot \Sigma_j \cdot U_{ij} \cdot a^*_i \cdot a^*_j \cdot \mathbf{a}_i \cdot \mathbf{a}_j$$

Atom	x	y	z	B_{eq} (Å^2)
Cl(1)	0.1669(2)	0.3884(2)	0.1211(1)	4.47(5)
O(1)	−0.0161(7)	−0.3474(5)	0.0495(3)	4.78(15)
N(01)	0.1253(6)	−0.1231(5)	0.1176(2)	2.79(11)
C(02)	0.1509(6)	0.0023(5)	0.1030(3)	2.34(12)
N(03)	0.1230(6)	0.0850(5)	0.1552(2)	2.97(12)
C(04)	0.0637(9)	0.0099(6)	0.2150(3)	3.45(16)
C(05)	0.0734(8)	−0.1367(6)	0.1905(3)	3.25(15)
C(06)	0.2116(7)	0.0506(5)	0.0348(3)	2.53(12)
O(07)	0.2037(5)	−0.0603(4)	−0.0132(2)	2.80(10)
C(08)	0.2888(6)	−0.0473(5)	−0.0733(3)	2.20(12)
C(09)	0.3357(6)	−0.1677(5)	−0.1035(3)	2.34(11)
C(10)	0.4176(7)	−0.1546(6)	−0.1650(3)	2.95(14)
C(11)	0.4517(8)	−0.0311(6)	−0.1939(3)	3.16(15)
C(12)	0.4046(7)	0.0849(6)	−0.1629(3)	2.80(13)
C(13)	0.3231(7)	0.0758(6)	−0.1010(3)	2.61(13)
C(14)	0.4415(10)	0.2210(7)	−0.1930(3)	4.02(18)
C(15)	0.2979(7)	−0.3010(5)	−0.0713(3)	2.64(13)
C(16)	0.4129(9)	−0.3238(6)	−0.0002(3)	3.67(16)
C(17)	0.3160(10)	−0.4206(7)	−0.1213(4)	4.02(17)

Fig. 2. General view of **2** and atomic labeling scheme (Johnson, 1976). Thermal ellipsoids are plotted at 50% probability level.

Discussion

The final atomic coordinates and equivalent isotropic temperature parameters for structures **1** and **2** are given in Tables 1 and 2, respectively. The numbering of atoms and views of **1** and **2** molecules are shown in Figs. 1 and 2, while selected bond lengths and angles are listed in Table 3.
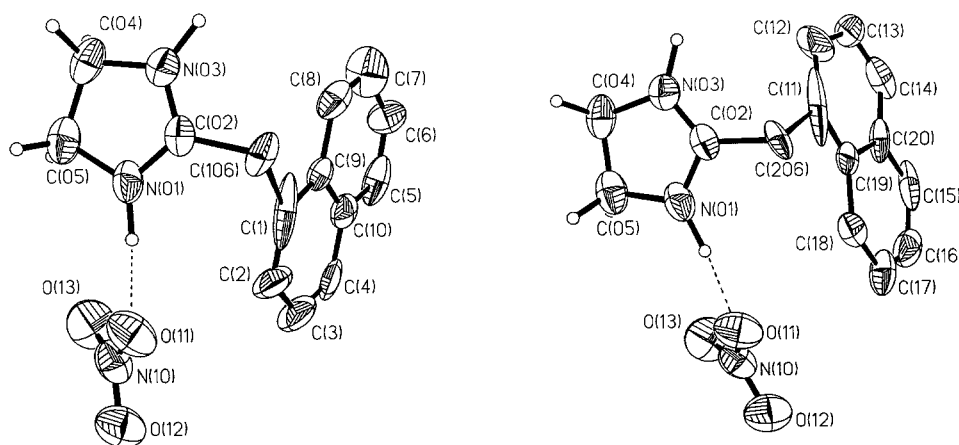
Though a detailed analysis of the present structures and their comparison with other imidazolines showing activity at α-receptors is hindered because of low accuracy, it is still possible to evaluate the main geometrical features important for interactions with the receptor according to the Carpy model (Carpy *et al.*, 1981). Protonation of the imidazoline rings in **1** and **2** results in equivalency of N(01) and N(03) atoms and forces a linear hydrogen bonding pattern of the type N(01)—H $\cdots$ X$^-$ $\cdots$ H—N(03). In **1**, only atom O(11) of a nitrate anion participates in two hydrogen bonds (Table 4).

Fig. 1. General view of **1** and atomic labeling scheme (Johnson, 1976). The molecules with the two differently oriented naphthyl fragments are drawn separately with methylene H atoms omitted for clarity. Thermal ellipsoids are plotted at 30% probability level.
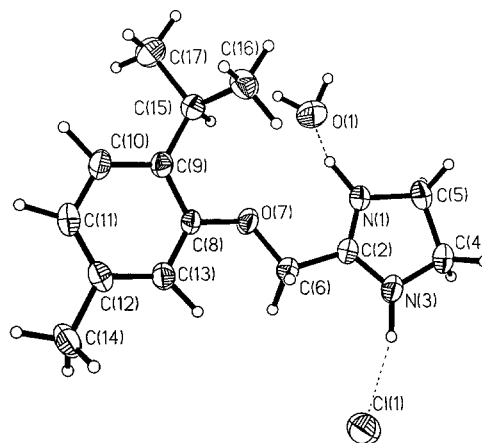
Table 3. Selected bond lengths and angles, and torsional angles

	1	2
Bond lengths (Å)		
N(01)—C(02)	1.308(8)	1.307(7)
C(02)—N(03)	1.308(9)	1.317(7)
N(03)—C(04)	1.484(8)	1.473(8)
C(04)—C(05)	1.541(10)	1.542(8)
C(05)—N(01)	1.483(8)	1.476(7)
Bond angles (°)		
C(05)—N(01)—C(02)	109.2(5)	110.5(5)
N(01)—C(02)—N(03)	114.3(5)	113.8(5)
C(02)—N(03)—C(04)	110.8(5)	109.8(5)
N(03)—C(04)—C(05)	101.6(5)	103.3(5)
C(04)—C(05)—N(01)	104.0(5)	102.4(5)
Torsional angles (°)	X=C(1), C(11)	X=O(07)
N(01)—C(02)—C(06)—X	52.6(10)	10.7(7)
	111.9(9)	
N(03)—C(02)—C(06)—X	−125.2(8)	−171.3(5)
	−70.0(11)	
C(02)—C(06)—C(1)—C(2)	−82.5(15)	
C(02)—C(06)—C(11)—C(19)	−101.3(11)	
C(02)—C(06)—C(1)—C(9)	98.7(10)	
C(02)—C(06)—C(11)—C(12)	73.8(18)	
C(02)—C(06)—O(07)—C(08)		−165.8(4)
C(06)—O(07)—C(08)—C(13)		−24.4(7)

Table 4. Hydrogen bondings[a]

X···Y (Å)	H···Y (Å)	X—H···Y (°)	X	Y [symm. operation]
Naphazoline·HNO₃ (1)				
2.851(8)	1.81	161	N(01)	O(11) [x, y, z]
2.873(8)	1.83	160	N(03)	O(11) [1/2 − x, y − 1/2, z]
Tymazoline·HCl·H₂O (2)				
2.758(7)	1.95	129	N(01)	O(1) [x, y, z]
3.134(5)	2.08	164	N(03)	Cl(1) [x, y, z]
3.240(5)	2.43	145	O(1)	Cl(1) [x, y − 1, z]
3.281(6)	2.40	146	O(1)	Cl(1) [−x, −y, −z]

[a]esd's for H · · · Y and X—H · · · Y were omitted due to refinement model for H atoms.

There results a lengthening of the O(11)—N(10) bond to 1.243(9) Å as compared with 1.225(9) and 1.223(9) Å for O(12)—N(10) and O(13)—N(10) bonds, respectively. Hydrogen bonds join molecules into chains running along the 2₁ axis in [100] direction. The same hydrogen bonding pattern is observed in naphazoline hydrochloride (Podder *et al.*, 1983) and a similar arrangement is present in structure 2 *i.e.* N(01)—H · · · O(water) · · · Cl⁻ · · · H—N(03). Due to the presence of water molecules, additional hydrogen bonds O(water)—H · · · Cl⁻ are formed between pairs of

chains running in opposite directions ([010] and [01̄0]) and related by a center of symmetry.

The molecular shape of 1 is determined by the approximately perpendicular orientation of the aromatic system to the imidazole ring. The angle between least-squares planes through the two rings is 73.7(3) and 74.5(3)° in 1 (there are two separate positions occupied by the naphthalene ring), 89.3(1)° in tolazoline hydrochloride (Główka and Król, 1990) and 85.9° in naphazoline hydrochloride (Podder *et al.*, 1983). The distances of the protonated N imidazoline atoms from

Table 5. Separations (in Å) of N atoms of imidazole ring from an adjacent aromatic ring plane (H) and from its center (D), and the angle between the two rings least-squares planes (α in °)

Compound	R^a	D_{N1}^b	D_{N3}	H_{N1}	H_{N3}	α
Arylmethyl-2-imidazolines						
Naphazoline · HNO₃ (1)	0.088	4.5^c	4.6	2.3	2.0	74
		4.4	4.7	2.3	2.1	74
Naphazoline · HCl^d	0.040	4.4	4.5	1.2	−0.9	86
Xylometazoline · HCl^e	0.053	4.0	5.0	2.4	1.3	85
Tolazoline · HCl^f	0.063	4.6	4.6	1.2	−1.0	89
Aryloxymethyl-2-imidazolines						
Tymazoline · HCl · H₂O (2)	0.115	5.4	6.1	0.6	1.0	13
Lofexidine^g	0.072	4.3	5.1	3.3	2.1	59
Lofexidine · HCl^h	0.047	5.1	5.8	0.8	−1.2	88
RX-781094^i	0.057	4.2	5.3	2.6	2.1	87

^{a} Crystallographic agreement factor.
^{b} N(1) is the atom closer to the center of aromatic system.
^{c} The values refer to the center of naphthalene ring.
^{d} Podder *et al.* (1983).
^{e} Ghose and Dattagupta (1986).
^{f} Główka and Król (1990).
^{g} Carpy *et al.* (1980b).
^{h} Carpy *et al.* (1980a).
^{i} Cattier-Humblet and Carpy (1985).

the aromatic rings planes and from the rings centers are shown in Table 5. The values are similar to those observed in other tolazoline-type α-receptor agents, except that both N atoms in **1** are more than 2.0 Å distant from an aromatic ring plane.

The situation is different in **2** due to a methyleneoxy link between the two planar systems instead of the methylene in **1**. The angle between least-squares rings planes is only 12.8(2)° and the imidazoline—C—O—aryl torsional angle of −165.8(4)° maintains an approximately planar general shape of the molecule (Fig. 2), which is an exception among 2-imidazolines showing activity at α-adrenoreceptors. The distances of N(01) and N(03) atoms from the center of the benzene ring are 5.365(4) and 6.090(4) Å, respectively. The values are slightly greater the those observed in similar compounds (Table 5).

Acknowledgments

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