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## Structure of 2-[(1-Ethyl-2-imidazolyl)methyl]-2,3-dihydro-1,4-benzodioxin Hydrochloride Monohydrate: RS-21361, C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>·HCl·H<sub>2</sub>O

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**Abstract.**  $\alpha_2$ -Adrenoceptor antagonist.  $M_r = 298.7$ , monoclinic,  $P2_1/c$ ,  $a = 11.964$  (2),  $b = 13.410$  (3),  $c = 9.766$  (1) Å,  $\beta = 96.02$  (1)°,  $V = 1558.2$  (4) Å<sup>3</sup>,  $Z = 4$ ,  $D_x = 1.27$  g cm<sup>-3</sup>, Cu  $K\alpha$ ,  $\lambda = 1.54178$  Å,  $\mu = 22.5$  cm<sup>-1</sup>,  $F(000) = 632$ , room temperature, final  $R = 0.038$  for 1226 reflections. Bond lengths and angles are normal for this type of compound. The molecule adopts a biplanar conformation with an angle of  $\sim 60^\circ$  between the two rings. The crystal is stabilized by hydrogen bonds between Cl and the protonated imidazolyl N atom. Critical sites for antagonism of  $\alpha_2$ -adrenoceptors are discussed.

**Introduction.** Among a series of 2-(2-imidazolylmethyl)-2,3-dihydro-1,4-benzodioxins recently prepared and tested for  $\alpha$ -adrenoceptor antagonist activity, RS-21361 exhibits the most pronounced selectivity for  $\alpha_2$ -adrenoceptors (Michel & Whiting, 1981). Moreover, this drug was found to be the most selective for  $\alpha_2$ -adrenoceptors of a series of benzodioxin antagonists including piperoxan, prosympal and WB-4101. This work is part of a research program developed in our laboratory concerning the conformational discriminating factors between agonists and antagonists,  $\alpha_1/\alpha_2$ -adrenergic (Carpy, Léger, Leclerc, Decker, Rouot & Wermuth, 1982). Fig. 1 shows the molecule of RS-21361.

**Experimental.** Small white blocks (from methanol),  $0.40 \times 0.30 \times 0.30$  mm, Enraf–Nonius CAD-4 diffractometer with graphite monochromator, Cu  $K\alpha$ , 25 reflections ( $8 < \theta < 16^\circ$ ) used to refine orientation matrix, systematic absences:  $h0l$  for  $l$  odd,  $0k0$  for  $k$  odd,  $2765$  ( $\pm h, k, l$ ) independent with  $\theta < 65^\circ$ ,  $h$  from  $-14$  to  $+14$ ,  $k$  from  $0$  to  $+15$ ,  $l$  from  $0$  to  $+11$ , 1226 with  $I \geq 3\sigma(I)$ , Lp correction, absorption ignored; two check reflections ( $3\bar{3}0$ ;  $2\bar{3}0$ ) every 3600 s showed no

unusual variation (all within  $\pm 3\sigma$ ); direct methods, MULTAN80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980), anisotropic diagonal-matrix refinement on  $F$  using observed reflections and weight  $w$  with  $w = 1$  if  $|F_o| < P$ ,  $P = (F_o^2 \max/10)^{1/2}$ ,  $w = (P/F_o)^2$  if  $|F_o| > P$ , water then all hydrogen atoms from  $\Delta F$  synthesis, H isotropic,  $R = 0.038$ ,  $R_w = 0.048$ ,  $S = 0.689$  (1226 reflections, 257 parameters), max. peak  $\pm 0.5$  e Å<sup>-3</sup> in final  $\Delta F$  map, mean and max.  $\Delta/\sigma$  in final cycle: 0.2 and 0.5,\* H-atom form factors from Stewart, Davidson & Simpson (1965), all other form factors from *International Tables for X-ray Crystallography* (1974), Mini 6 CII computer.

\* Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and least-squares-planes' data have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39362 (21 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

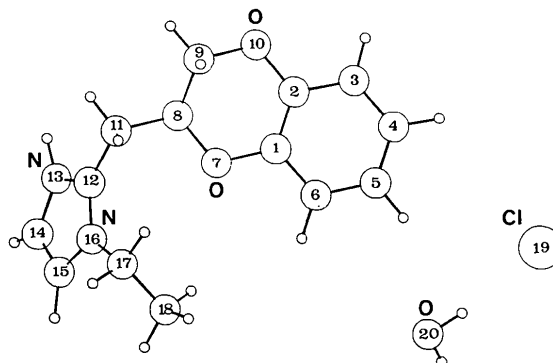


Fig. 1. Perspective view of the molecule showing the numbering of atoms. The lone numbers are for C atoms.

Table 1. Atomic coordinates for non-hydrogen atoms ( $\times 10^4$ ) and equivalent isotropic thermal parameters
$$B_{eq} = \frac{4}{3} \sum_i \sum_j \beta_{ij} \mathbf{a}_i \cdot \mathbf{a}_j$$

	x	y	z	$B_{eq}(\text{\AA}^2)$
C(1)	-1208 (3)	1234 (3)	4499 (4)	5.0 (2)
C(2)	-1548 (4)	1722 (3)	5622 (4)	5.9 (2)
C(3)	-736 (4)	2162 (4)	6564 (5)	8.4 (3)
C(4)	384 (4)	2096 (4)	6363 (5)	8.5 (3)
C(5)	718 (4)	1588 (3)	5268 (5)	7.2 (2)
C(6)	-81 (3)	1150 (3)	4301 (4)	5.8 (2)
O(7)	-1987 (2)	814 (2)	3500 (3)	5.2 (1)
C(8)	-3114 (3)	1168 (3)	3582 (4)	4.8 (2)
C(9)	-3375 (3)	1124 (3)	5051 (4)	6.3 (2)
O(10)	-2655 (2)	1802 (2)	5865 (3)	7.4 (2)
C(11)	-3899 (3)	475 (3)	2686 (4)	4.9 (2)
C(12)	-3777 (3)	576 (3)	1194 (4)	4.6 (2)
N(13)	-4369 (2)	1230 (2)	360 (3)	5.1 (1)
C(14)	-4072 (4)	1124 (3)	-958 (4)	6.1 (2)
C(15)	-3300 (3)	391 (3)	-932 (4)	5.9 (2)
N(16)	-3126 (2)	59 (2)	430 (3)	5.0 (1)
C(17)	-2343 (3)	-759 (3)	896 (5)	6.2 (2)
C(18)	-1191 (4)	-505 (5)	570 (6)	9.3 (3)
Cl(19)	3992 (1)	2226 (1)	6322 (1)	6.2 (1)
O(20)	3175 (4)	1223 (3)	3387 (4)	11.5 (3)

Table 2. Bond distances ( $\text{\AA}$ ) and angles ( $^\circ$ )

C(1)–C(2)	1.375 (5)	C(8)–C(11)	1.529 (5)
C(1)–C(6)	1.387 (5)	C(9)–O(10)	1.434 (5)
C(1)–O(7)	1.395 (4)	C(11)–C(12)	1.486 (5)
C(2)–C(3)	1.397 (6)	C(12)–N(13)	1.347 (5)
C(2)–O(10)	1.374 (5)	C(12)–N(16)	1.329 (5)
C(3)–C(4)	1.378 (7)	N(13)–C(14)	1.378 (5)
C(4)–C(5)	1.363 (7)	C(14)–C(15)	1.347 (6)
C(5)–C(6)	1.401 (6)	C(15)–N(16)	1.397 (5)
O(7)–C(8)	1.440 (4)	N(16)–C(17)	1.483 (5)
C(8)–C(9)	1.501 (5)	C(17)–C(18)	1.486 (7)
C(2)–C(1)–C(6)	121.6 (4)	C(8)–C(9)–O(10)	109.4 (3)
C(2)–C(1)–O(7)	121.2 (3)	C(2)–O(10)–C(9)	112.8 (3)
C(6)–C(1)–O(7)	117.2 (3)	C(8)–C(11)–C(12)	112.9 (3)
C(1)–C(2)–C(3)	118.9 (4)	C(11)–C(12)–N(13)	123.6 (3)
C(1)–C(2)–O(10)	123.1 (4)	C(11)–C(12)–N(16)	128.8 (3)
C(3)–C(2)–O(10)	118.0 (4)	N(13)–C(12)–N(16)	107.6 (3)
C(2)–C(3)–C(4)	119.9 (4)	C(12)–N(13)–C(14)	109.0 (3)
C(3)–C(4)–C(5)	120.9 (5)	N(13)–C(14)–C(15)	107.6 (3)
C(4)–C(5)–C(6)	120.2 (4)	C(14)–C(15)–N(16)	106.5 (3)
C(5)–C(6)–C(1)	118.5 (4)	C(12)–N(16)–C(15)	109.3 (3)
C(1)–O(7)–C(8)	112.8 (3)	C(12)–N(16)–C(17)	127.1 (3)
O(7)–C(8)–C(9)	109.3 (3)	C(15)–N(16)–C(17)	123.7 (3)
O(7)–C(8)–C(11)	106.8 (3)	N(16)–C(17)–C(18)	109.6 (4)
C(9)–C(8)–C(11)	110.3 (3)		

**Discussion.** Atomic coordinates and equivalent isotropic thermal parameters are given in Table 1 and bond distances and angles in Table 2. A survey of Table 2 leads to few remarks. Bond distances and angles related to the benzodioxin moiety follow the same criteria as in known structures (*e.g.* Carpy, Colleter & Léger, 1981), C(8) and C(9) being respectively below and above the mean plane containing the eight other atoms. The imidazolyl moiety is protonated on N(13). The four C–N bonds are in resonance between a single bond (1.470  $\text{\AA}$ ) and a double bond (1.265  $\text{\AA}$ ); the two C(12)–N bonds are shorter than C(14)–N(13) and C(15)–N(16). The C(14)–C(15) bond is slightly greater than a pure C=C double bond, 1.347 (6)  $\text{\AA}$  instead of 1.337  $\text{\AA}$ .

The torsion angles defining the position of the two rings are C(9)–C(8)–C(11)–C(12) = 173 (1) and C(8)–C(11)–C(12)–N(16) = 93 (1) $^\circ$ . The angle between the phenyl and the imidazolyl rings is 62 (1) $^\circ$ .

Stereometric criteria for attachment of antagonists to the  $\alpha$ -adrenoceptor, based on similarities in the structures of apoyohimbine and WB-4101 [*N*-[2-(2,6-dimethoxyphenoxy)ethyl]-2,3-dihydro-1,4-benzodioxin-2-ylmethylamine] (Carpy *et al.*, 1981), have recently been proposed (McGrath, 1982). In the yohimbine series, three binding sites may be involved in the binding: the aromatic ring *A*, an amino group and the methoxycarbonyl substituent on ring *E*. These sites can be recognized in long flexible structures such as WB-4101 or labetalol but not in prazosin. The discovery of smaller antagonist structures such as RS-21361 or RX-781094 [2-(4,5-dihydro-2-imidazolyl)-2,3-dihydro-1,4-benzodioxin] leads to the proposal that the critical sites for antagonism of  $\alpha_2$  may be the aromatic ring and the amino groups. We have therefore calculated the positions of the amino groups in RS-21361 with respect to  $\varphi$  [ $\varphi$  is the middle of C(1)–C(2) and represents the focus of the  $\pi$  electrons of the benzodioxin ring]: N(13)– $\varphi$  = 5.53 (1), N(16)– $\varphi$  = 5.14 (1)  $\text{\AA}$ , the distances from N(13) and N(16) to the mean plane of the benzodioxin ring being –2.121 (3) and –0.725 (3)  $\text{\AA}$ , respectively.

The crystalline cohesion is ensured by a hydrogen bond between N(13) and Cl(19) ( $-1 + x, \frac{1}{2} - y, -\frac{1}{2} + z$ ): N(13)···Cl(19) = 3.066 (4), H(113)···Cl(19) = 2.033 (6)  $\text{\AA}$ , N(13)–H(113)···Cl(19) = 163 (5) $^\circ$ . The water molecule is also involved in two hydrogen bonds with Cl(19) ( $x, y, z$ ) and Cl(29) ( $x, \frac{1}{2} - y, -\frac{1}{2} + z$ ) (Fig. 2).

The sample was kindly provided by Syntex Pharmaceuticals Limited, Scotland.

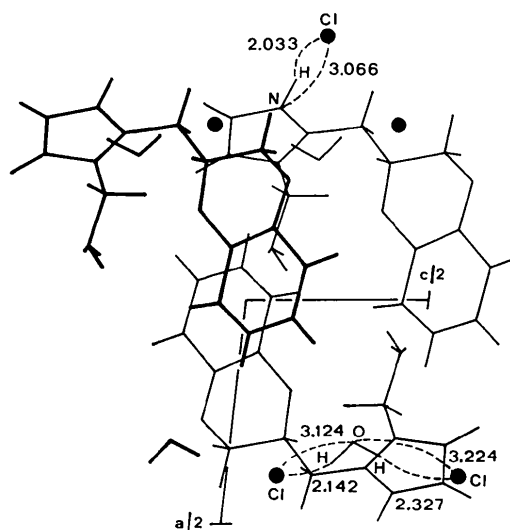


Fig. 2. Packing of the molecules projected on (010) showing the hydrogen bonds (e.s.d.'s 0.004–0.006  $\text{\AA}$ ).

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## Structure du (Méthyl-1 Nitro-4 Imidazolyl-5)thio-3 1H-Triazole-1,2,4, C<sub>6</sub>H<sub>6</sub>N<sub>6</sub>O<sub>2</sub>S

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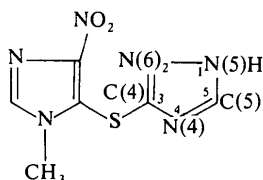
(Reçu le 5 janvier 1984, accepté le 27 mars 1984)

**Abstract.**  $M_r = 226.22$ , monoclinic,  $P2_1/a$ ,  $a = 10.291$  (4),  $b = 14.485$  (5),  $c = 7.263$  (3) Å,  $\beta = 120.38$  (5)°,  $V = 934.03$  Å<sup>3</sup>,  $Z = 4$ ,  $D_x = 1.608$  g cm<sup>-3</sup>, Mo  $K\alpha$ ,  $\lambda = 0.7107$  Å,  $\mu = 3.215$  cm<sup>-1</sup>,  $F(000) = 464$ , 290 K,  $R = 0.071$  for 1659 observed reflexions. Both the intermolecular hydrogen bond NH...N between the imidazole and triazole rings and the difference-Fourier synthesis indicate that in crystals the 1H-1,2,4-triazole tautomer formula is more probable than the 2H one. The aromatic rings are planar. The S and methyl C are slightly out of the imidazole plane with the nitro group rotated by  $\sim 10^\circ$  from this plane.

**Introduction.** Dans le cadre d'un programme réalisé en collaboration avec le National Cancer Institute (NCI: Bethesda, USA), la synthèse d'une série d'imidazolyl-thioéthers a été réalisée.

L'objet du présent travail est l'analyse cristallographique d'une de ces substances sélectionnée par le NCI pour ses propriétés antileucémiques, le (méthyl-1 nitro-4 imidazolyl-5)thio-3 1H-triazole-1,2,4.

**Partie expérimentale.** Composé synthétisé au Laboratoire de Chimie pharmaceutique de l'Université de Liège (n° code JJC 323). Cristal:  $0,3 \times 0,2 \times 0,4$  mm, obtenu par évaporation d'une solution d'acétone (50% en volume) et d'eau (50%); paramètres de la maille déterminés avec 11 réflexions ( $8,4 \leq \theta \leq 17,3^\circ$ ). 3072 réflexions mesurées avec un diffractomètre Hilger-Watts ( $2\theta \leq 50^\circ$ ), balayage  $\omega$ , Mo  $K\alpha$  filtrée;  $0 \leq h \leq 13$ ,  $0 \leq k \leq 20$ ,  $-9 \leq l \leq 8$ ; intensités non corrigées de l'absorption. 2449 réflexions indépendantes,  $R_{int} = 3,7$ ; variations des deux réflexions:  $1883 \leq F_o(201) \leq 1907$ ,  $2333 \leq F_o(220) \leq 2399$ . Structure déterminée par MULTAN80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980). La solution ayant le meilleur critère de confiance a montré tous les atomes non hydrogène, excepté C(6) (Fig. 1). Celui-ci a été obtenu ensuite par Fourier-différence ainsi que tous les atomes d'hydrogène, sauf celui lié à C(5). Affinement basé sur  $F$  (matrice entière des équations normales) avec SHELX76 (Sheldrick, 1976); facteurs de température anisotropes affinés pour tous les atomes non hydrogène; H placés suivant une géométrie standard.  $R = 0,071^*$  pour 1659 réflexions



\* Les listes des facteurs de structure, des paramètres thermiques et des coordonnées des atomes d'hydrogène, les angles de torsion, les plans moyens et les contacts intermoléculaires ont été déposés à la British Library Lending Division (Supplementary Publication No. SUP 39367; 12 pp.). Des copies peuvent être obtenues en s'adressant à The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, Angleterre.