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Betaxolol Hydrochloride: 1-{4-[2-(Cyclopropylmethoxy)ethyl]phenoxy}-3-isopropylamino-2-propanol Hydrochloride, $C_{18}H_{30}NO_3^+.Cl^-$

BY CLAUDINE PASCARD AND ELISE TRAN HUU DAU

Institut de Chimie des Substances Naturelles, CNRS, 91190 – *Gif-sur-Yvette, France*

AND PHILIPPE MANOURY AND BERNARD MOMPON

Laboratoire d'Etudes et de Recherches SYNTHELABO, 31 *avenue Paul Vaillant Couturier*, 92220 – *Bagneux, France*

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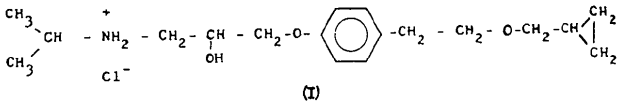
Abstract. $M_r = 343{\cdot}9$, triclinic, $P\bar{1}$, $a = 16{\cdot}646\ (4)$, $b = 8{\cdot}170\ (1)$, $c = 7{\cdot}631\ (1)$ Å, $\alpha = 93{\cdot}01\ (2)$, $\beta = 104{\cdot}29\ (2)$, $\gamma = 100{\cdot}75\ (3)°$, $V = 984{\cdot}25$ Å^3, $Z = 2$, $D_x = 1{\cdot}16$ Mg m^{-3}, $\lambda(\text{Cu } K\alpha) = 1{\cdot}5418$ Å, $\mu = 17{\cdot}29$ mm^{-1}, $F(000) = 372$, $T = 295$ K. The structure, showing a partial disorder, was refined to $R = 14\%$ for 1400 observed reflections. The molecule is fully extended. The most interesting feature is the close contact of the chloride ion to the ammonium and the hydroxy groups of the same molecule, thus forming a seven-membered ring. There are only loose van der Waals contacts between the cyclopropane ends which explain the disorder.

Introduction. Betaxolol (SL 75.212-10) is a new potent cardioselective β-adrenoceptor antagonist (Cadigan, London, Pentecost, Bianchetti, Goméni, Kilborn & Morselli, 1980) which has been found to possess important clinical advantages (full oral absorption, almost total oral bioavailability and long half-life) over the β-adrenoceptor blocking agents presently available in clinical practice (Bianchetti, Blatrix, Goméni, Kilborn, Larribaud, Lucker, Morselli, Thébault & Trocherie, 1980; Balnave, Neill, Russell, Harron, Leahey, Wilson & Shanks, 1981).

To try to rationalize the favorable pharmacokinetic properties of betaxolol on a molecular basis, an X-ray crystallographic structure determination of the molecule (I) was carried out.



(I)

Experimental. Title compound crystallized from methanol/isopropyl ether, crystal dimensions: 0·05 × 0·1 × 0·02 mm; 23 reflections used to refine unit-cell dimensions; Philips PW 1100 four-circle diffractometer, graphite-monochromatized Cu $K\alpha$ radiation, diffraction data collected from $\theta = 3°$ up to $\theta = 60°$, ω–2θ scan technique, followed by two background counts of 10 s at each end of the scan, scan width: 1·5°, speed: 0·03° s^{-1}; three standard reflections (040, 10,0,0, 004), no intensity fluctuation; only 1400 reflections out of 2558 considered observed with $I > 2{\cdot}5\sigma(I)$, this lack of experimental data being due, mainly, to the lack of thickness of the crystals; index range: h −17 to 13, k −8 to 9, l 0 to 8; Lp correction, no absorption correction. Structure solved by Patterson and heavy-atom techniques, assuming $P\bar{1}$ symmetry. All non-H atoms appeared on the Fourier synthesis, and the isotropic refinement (*SHELX*76, Sheldrick, 1976) led to $R = 18\%$. A further refinement with an anisotropic temperature factor for Cl lowered R to 15%. The subsequent difference Fourier synthesis showed that, if the N terminus of the molecule is well stabilized by close contacts with the Cl atom, or on the other hand, if the molecule is disordered from the phenyl ring to the cyclopropane, a ghost fragment appears, including the aromatic ring up to C(19); the cyclopropane ring is even more disordered as it did not show up at the end of this fragment.

It was then decided* to refine in $P1$ symmetry with two molecules in the asymmetric unit. The isotropic refinement led to $R = 18\%$, and introducing the anisotropy for the two Cl^- ions gave a final agreement factor of 13%. The subsequent density map showed that the two molecules had largely different bond values for the N termini, and three atoms of one molecule were completely misplaced.

Comparing the two refinements at this stage, we chose the centrosymmetric space group, our choice being based on better coherent bond lengths and a more comprehensive disorder.

We then resumed the refinement in the following steps:

–Constraints were applied to the cyclopropane ring, the aromatic ring and the interatomic distances of the chain.

* The authors thank the referee for suggesting this possibility.

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Table 1. *Atomic coordinates* ($\times 10^4$) *and isotropic thermal parameters* ($\times 10^4$)

$U_{eq} = \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i . \mathbf{a}_j$.

The atoms of the molecular part which has the smaller occupation factor (30%) are labeled *P*. The mean e.s.d.'s are given in parentheses.

	x	*y*	*z*	U_{eq}/U_{iso}(Å^2)
Cl	−18 (3)	−2117 (4)	3225 (6)	79 (5)
C(3)	1745 (8)	3282 (16)	1782 (24)	72 (23)
C(4)	1040 (10)	2131 (15)	2369 (21)	66 (24)
O(5)	979 (6)	506 (11)	1461 (15)	86 (16)
C(6)	212 (8)	2720 (16)	1879 (20)	66 (21)
N(7)	−446 (6)	1573 (12)	2493 (16)	60 (17)
C(8)	−1319 (9)	1873 (19)	1860 (23)	71 (25)
C(9)	−1379 (10)	3562 (18)	2707 (24)	87 (26)
C(10)	−1909 (10)	429 (19)	2318 (27)	90 (30)
O(2)	1842 (6)	4895 (11)	2730 (15)	89 (16)
C(13)	3519 (9)	8988 (15)	1856 (21)	59 (1)
C(12)	2911 (9)	9180 (15)	2779 (21)	59 (1)
C(11)	2353 (9)	7777 (15)	3051 (21)	59 (1)
C(1)	2402 (9)	8181 (15)	2400 (21)	59 (1)
C(15)	3011 (9)	5989 (15)	1477 (21)	59 (1)
C(14)	3569 (9)	7392 (15)	1205 (21)	59 (1)
C(16)	3972 (18)	10492 (23)	1184 (28)	79 (1)
C(17)	4831 (13)	11076 (18)	2600 (28)	79 (1)
O(18)	5276 (10)	12516 (18)	1970 (20)	79 (1)
C(19)	5507 (13)	13867 (17)	3321 (28)	79 (1)
C(20)	5948 (10)	15408 (20)	2556 (22)	79 (1)
C(21)	6888 (9)	16007 (23)	3121 (32)	79 (1)
C(22)	6335 (13)	17013 (16)	3770 (30)	79 (1)
C(13*P*)	3866 (19)	8805 (36)	2775 (51)	59 (1)
C(12*P*)	3203 (19)	9036 (36)	3516 (51)	59 (1)
C(11*P*)	2533 (19)	7698 (36)	3434 (51)	59 (1)
C(1*P*)	2527 (19)	6128 (36)	2611 (51)	59 (1)
C(15*P*)	3189 (19)	5896 (36)	1870 (51)	59 (1)
C(14*P*)	3859 (19)	7235 (36)	1953 (51)	59 (1)
C(16*P*)	4550 (24)	10263 (47)	2759 (72)	79 (1)
C(17*P*)	4283 (28)	11594 (41)	1501 (64)	79 (1)
O(18*P*)	4972 (23)	12678 (45)	1374 (49)	79 (1)
C(19*P*)	5047 (35)	14301 (46)	2596 (74)	79 (1)

Table 2. *Interatomic distances* (Å) *and bond angles* (°) *between atoms not subjected to constraints during the refinement*

O(2)–C(1)	1·35 (1)	C(11)–C(11*P*)	0·35
O(2)–C(3)	1·43 (2)	C(12)–C(12*P*)	0·67
C(4)–C(3)	1·53 (2)	C(13)–C(13*P*)	0·85
C(4)–O(5)	1·44 (2)	C(14)–C(14*P*)	0·71
C(4)–C(6)	1·51 (2)	C(15)–C(15*P*)	0·40
N(7)–C(6)	1·49 (2)	C(16)–C(16*P*)	1·38
N(7)–C(8)	1·48 (2)	C(17)–C(17*P*)	1·19
C(8)–C(9)	1·53 (2)	O(18)–O(18*P*)	0·74
C(8)–C(10)	1·50 (2)	C(19)–C(19*P*)	0·98

O(2)–C(3)–C(4)	105·6 (1·4)	C(6)–N(7)–C(8)	115·1 (1·1)
C(3)–C(4)–O(5)	104·6 (1·3)	N(7)–C(8)–C(9)	110·6 (1·1)
C(3)–C(4)–C(6)	112·2 (1·2)	C(9)–C(8)–C(10)	112·9 (1·3)
O(5)–C(4)–C(6)	112·3 (1·0)	C(1)–O(2)–C(3)	118·2 (1·1)

–The temperature factors of the disordered atoms were given fixed values, increasing from C(1) to C(19).

–The H atoms of the N–isopropyl end appearing on the difference syntheses were introduced in the refinement but not refined.

$-\sum w(\Delta F)^2$ minimized, unit weights.

With all these constraints, the *R* factor did not fall further than 14%; final Δ/σ: 0·3; residual electron density on final difference map: 0·5 e Å^{-3}; atomic scattering factors are those used in *SHELX*.

Discussion. Atomic coordinates and isotropic thermal parameters are listed in Table 1,* bond lengths and valency angles in Table 2.

Fig. 1 shows the molecule in its two observed conformations; the molecule is fully extended with its head N terminus fixed through hydrogen bonds to the chloride ion. The aromatic ring rotates around C(3)–O(2).

Fig. 2 shows the packing of the molecules. The hydrogen bonding is clearly seen linking the heads of different molecules. There are only loose van der Waals contacts between the cyclopropane ends which explain the disorder.

The most interesting feature is the close contact of the Cl^- ion to the NH_2 and OH groups of the same molecule: Cl···O(5): 3·04 (2), Cl···N(7): 3·27 (2) Å, with Cl···H(7*B*): 2·39 (13) Å.

* Lists of structure factors, anisotropic thermal parameters, H-atom parameters, constraints applied to interatomic distances during the refinement, and torsion angles have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39347 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

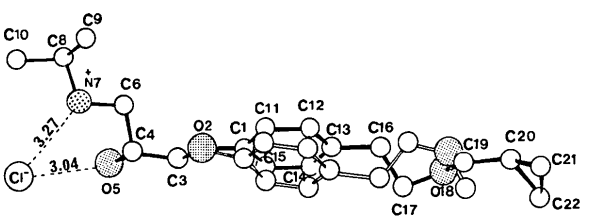

Fig. 1. The molecule with its partial 'ghost'. Distances are in Å.

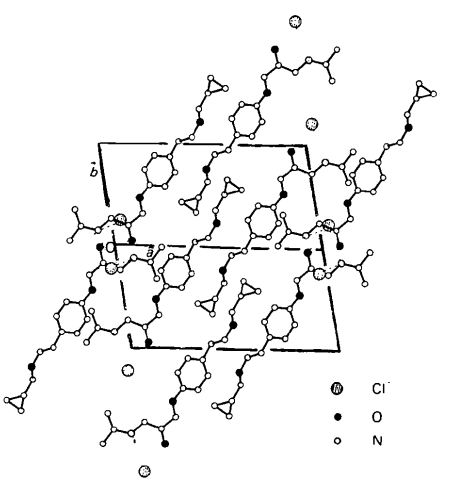

Fig. 2. Packing projected on (*xOy*) with hydrogen bonds shown as dotted lines.

The second hydrogen H(7*A*) of the NH_2 group links another Cl^- ion situated at $-x, -y, 1-z$: Cl···N(7): 3·15 (2) Å with Cl···H(7*A*): 2·08 (15) Å.

N(7) is also at a short distance from O(5) of the molecule situated at $-x, -y, -z$: 3·22 (3) Å with H(7*B*)···O(5): 2·58 (20) Å.

Although H(O5) was not observed, its position is clearly directed towards Cl^-. The anion is then in interaction simultaneously with the hydroxy and the ammonium groups, thus forming a seven-membered ring. Such an interaction was proposed to explain NMR and IR spectra of the hydrohalide salt of toliprolol in solution (Zaagsma, 1979).

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Structure du Chlorhydrate de l'[Hydroxy-1-(*R,S*) Isopropylamino-2 Ethyl]-6 Dihydro-2,3 Benzoxazole-1,3 One-2, $C_{12}H_{16}N_2O_3.HCl$

PAR G. MAIRESSE, J. C. BOIVIN ET D. J. THOMAS

Equipe de Cristallochimie et Physicochimie du Solide, ERA-CNRS 1004, *Ecole Nationale Supérieure de Chimie de Lille, BP* 108, 59652 *Villeneuve d'Ascq CEDEX, France*

ET J. P. BONTE, D. LESIEUR ET C. LESPAGNOL

Institut de Chimie Pharmaceutique, 3 *rue du Professeur Laguesse,* 59045 *Lille CEDEX, France*

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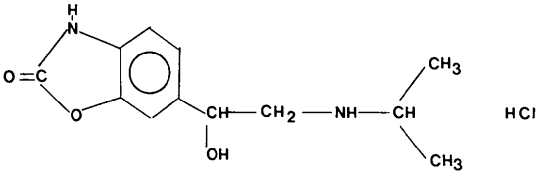
Abstract. $M_r = 272{\cdot}5$, monoclinic, $P2_1/c$, $a = 9{\cdot}562$ (1), $b = 7{\cdot}475$ (1), $c = 18{\cdot}843$ (2) Å, $\beta = 94{\cdot}8$ (1)°, $V = 1342{\cdot}1$ Å^3, $Z = 4$, $D_x = 1{\cdot}35$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}7107$ Å, $\mu = 29$ cm^{-1}, $F(000) = 576$, $T = 298$ K, $R_w = 0{\cdot}062$ for 1588 independent reflexions. The molecule is extended in two perpendicular planes. Hydrogen bonds occur between Cl and three different molecules. The location of active sites is given. The distances between these sites agree well with the values previously reported for various phenyl-(amino)ethanols which exhibit a similar therapeutic behaviour.

Introduction. La synthèse de cette nouvelle molécule a été effectuée dans le cadre d'un travail de préparation de composés capables de se fixer sur les récepteurs adrénergiques (Lesieur, Lespagnol, Vaccher, Bonte, Debaert, Busch & Combarieu, 1980). Des études pharmacologiques ont mis en évidence d'intenses propriétés α et β bloquantes (Lamar, Beauchard, Dureng, Baissat, Michelin & Piris, 1982) et ce produit fait l'objet d'études cliniques pour ses propriétés antihypertensives.



La détermination de sa structure cristalline permet de comparer ses caractéristiques stériques à celles des agonistes et antagonistes adrénergiques utilisés en thérapeutique.

Partie expérimentale. Monocristaux en forme de parallélépipède (0,4 × 0,4 × 0,2 mm) obtenus par évaporation d'une solution alcoolique, diffractomètre Philips quatre cercles PW1100, radiation Mo $K\alpha$, monochromateur au graphite, paramètres de maille déterminés par affinement par moindres carrés à partir de 25 valeurs de θ relevées lors de la mesure des intensités, 4207 réflexions mesurées pour $2 \le \theta \le 30°$ et $-13 \le h \le 13$, $0 \le k \le 10$, $0 \le l \le 26$, 3 réflexions de contrôle ($01\bar{2}$, $\bar{1}20$ et $40\bar{2}$) testées toutes les deux heures, $\Delta I/I < 0{,}01$, absorption ignorée; méthodes

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