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Structure of Ethyl 2-[(2-Hydroxy-3-isopropylamino)propoxy]carbanilate Hydrochloride

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Abstract. $C_{15}H_{25}N_2O_4^+.Cl^-$, $M_r = 332{\cdot}8$, monoclinic, $C2/c$, $a = 9{\cdot}576$ (1), $b = 11{\cdot}807$ (2), $c = 32{\cdot}080$ (7) Å, $\beta = 97{\cdot}73$ (2)°, $V = 3594{\cdot}1$ Å^3, $Z = 8$, $D_m = 1{\cdot}22$, $D_x = 1{\cdot}230$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, $\mu = 2{\cdot}05$ mm^{-1}, $F(000) = 1424$, $T = 293$ K, $R = 0{\cdot}057$ for 1525 observed reflections. The structure consists of discrete cations connected by hydrogen-bonded chloride anions. The arrangement of the aryloxy and 2-hydroxyl groups around the conformationally flexible OCH_2–$CH(OH)CH_2$ bond of the oxypropanolamine side chain is +synclinal [based on active (−)-*S*-enantiomer]. The orientation of the isopropylamine moiety is −synclinal relative to the 2-hydroxyl, as expected. The carbamate group is planar but somewhat inclined with regard to the adjacent phenyl and acts as an electron-donating substituent.

Introduction. This work is part of a more general study on structural properties of a new series of β-adrenoceptor blocking drugs belonging to the 3-aryloxy-1-(alkylamino)-2-propanol family. Indeed, some of these have been reported as potent β-blocking agents (Csöllei, Borovanský, Beneš, Béderová & Švec, 1982). The title compound (hereafter referred to as BL-223) was studied by X-ray crystallography to examine the conformational properties of the flexible oxypropanolamine side chain, which is common to all β-blockers, and to establish the detailed stereochemistry and electronic structure of a carbamate moiety directly attached to the benzene ring.

Experimental. Colourless crystals obtained from acetone/ether solution, crystal used 0·4 × 0·15 × 0·1 mm; D_m by flotation in bromoform/cyclohexane; systematic absences, hkl for $h+k$ odd and $h0l$ for l odd, from oscillation and Weissenberg photographs; Syntex $P2_1$ diffractometer; accurate unit-cell parameters by least-squares refinement of 15 reflections, $15 < \theta < 45°$; intensity data ($h = 0$ to 10, $k = 0$ to 12, $l = -34$ to 33) by θ–2θ scans, variable rate 4·9 to 29·3° min^{-1} in 2θ, background-to-scan-time ratio = 1·0, scan width 2° plus α_1–α_2 dispersion, Cu $K\alpha$ radiation filtered by graphite monochromator; two standards every 98 reflections: no appreciable changes; 2250 unique reflections, $3 < \theta \leq 55°$, 1525 with $I \geq 1{\cdot}96\sigma(I)$ considered observed and included in the refinement; Lp correction but none for absorption or extinction; structure solved by direct methods using *MULTAN*78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978) and refined by iterated Fourier and block-diagonal least-squares methods, $\Delta\rho$ map showed positions of all H atoms, refinement continued on all positional parameters, anisotropic thermal parameters for non-H atoms and isotropic thermal parameters for H atoms; in final cycle $R = 0{\cdot}057$, $wR = 0{\cdot}062$ for observed reflections only, max. shift/e.s.d. = 0·09, function minimized $\sum w(\Delta F)^2$, where $w = 1$ if $|F_o| < 35$ and $w = 35/|F_o|$ if $|F_o| \geq 35$, max. and min. height in final $\Delta\rho$ synthesis 0·31 and −0·27 e Å^{-3}; scattering factors for neutral atoms from *International Tables for X-ray Crystallography* (1974); all calculations except *MULTAN* performed with local version of the *NRC* system (Ahmed, Hall, Pippy & Huber, 1973).

Discussion. Final atomic coordinates of non-H atoms and equivalent isotropic B's are listed in Table 1,* bond distances and angles in Table 2. The numbering scheme for the BL-223 cation is shown in Fig. 1, which also displays the overall conformation of the molecule and corresponds to the biologically less active (+)-*R*-enantiomer.

Bond distances and angles along the oxypropanolamine side chain are normal and compare well with those

* Lists of structure amplitudes, anisotropic thermal parameters, H-atom parameters, mean planes and selected torsion angles have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51361 (14 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 atomic coordinates* ($\times 10^4$) *with e.s.d.'s in parentheses and equivalent isotropic thermal parameters* B_{eq}

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

	x	y	z	B_{eq}(Å^2)
N(1)	12876 (2)	−770 (2)	5315 (1)	3·76
N(2)	10207 (3)	−341 (2)	3234 (1)	4·51
C(1)	10956 (3)	1304 (3)	3628 (1)	4·51
C(2)	10161 (3)	844 (3)	3273 (1)	4·25
C(3)	9372 (4)	1557 (3)	2993 (1)	6·05
C(4)	9371 (5)	2694 (3)	3064 (1)	8·40
C(5)	10116 (6)	3153 (3)	3418 (1)	9·22
C(6)	10943 (5)	2463 (3)	3698 (1)	6·67
C(7)	12220 (3)	921 (3)	4303 (1)	4·11
C(8)	12626 (3)	−86 (3)	4577 (1)	3·74
C(9)	12676 (3)	227 (3)	5031 (1)	3·98
C(10)	13040 (3)	−549 (3)	5773 (1)	4·72
C(11)	11767 (4)	67 (4)	5894 (1)	6·60
C(12)	13298 (5)	−1658 (4)	6005 (1)	7·53
C(13)	9250 (4)	−990 (3)	2993 (1)	4·97
C(14)	8570 (4)	−2884 (3)	2842 (1)	6·33
C(15)	8970 (5)	−4046 (3)	3003 (1)	7·33
O(1)	11712 (2)	552 (2)	3892 (1)	4·49
O(2)	13961 (2)	−481 (2)	4479 (1)	5·03
O(3)	8302 (3)	−662 (2)	2741 (1)	7·65
O(4)	9537 (2)	−2082 (2)	3073 (1)	5·37
Cl(1)	9779·8 (8)	2284·0 (7)	4986·2 (3)	4·83

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

C(1)–C(2)	1·392 (5)	C(9)–N(1)	1·486 (4)
C(2)–C(3)	1·381 (5)	N(1)–C(10)	1·478 (4)
C(3)–C(4)	1·361 (5)	C(10)–C(11)	1·514 (5)
C(4)–C(5)	1·368 (6)	C(10)–C(12)	1·509 (6)
C(5)–C(6)	1·381 (6)	C(2)–N(2)	1·406 (4)
C(6)–C(1)	1·387 (5)	N(2)–C(13)	1·355 (4)
C(1)–O(1)	1·364 (4)	C(13)–O(3)	1·194 (5)
O(1)–C(7)	1·413 (4)	C(13)–O(4)	1·337 (4)
C(7)–C(8)	1·499 (5)	O(4)–C(14)	1·457 (5)
C(8)–C(9)	1·497 (5)	C(14)–C(15)	1·498 (5)
C(8)–O(2)	1·434 (4)		

C(1)–C(2)–C(3)	119·1 (3)	C(8)–C(9)–N(1)	112·7 (3)
C(2)–C(3)–C(4)	120·3 (3)	C(9)–N(1)–C(10)	117·3 (2)
C(3)–C(4)–C(5)	121·2 (4)	N(1)–C(10)–C(11)	110·9 (3)
C(4)–C(5)–C(6)	119·7 (4)	N(1)–C(10)–C(12)	109·0 (3)
C(5)–C(6)–C(1)	119·6 (4)	C(11)–C(10)–C(12)	120·0 (3)
C(6)–C(1)–C(2)	120·1 (3)	C(1)–C(2)–N(2)	116·2 (3)
C(6)–C(1)–O(1)	123·9 (3)	C(3)–C(2)–N(2)	124·7 (3)
C(2)–C(1)–O(1)	116·0 (3)	C(2)–N(2)–C(13)	126·0 (3)
C(1)–O(1)–C(7)	117·7 (2)	N(2)–C(13)–O(3)	126·6 (3)
O(1)–C(7)–C(8)	109·5 (2)	N(2)–C(13)–O(4)	109·2 (3)
C(7)–C(8)–C(9)	110·2 (3)	O(3)–C(13)–O(4)	124·1 (3)
C(7)–C(8)–O(2)	107·3 (2)	C(13)–O(4)–C(14)	115·4 (3)
C(9)–C(8)–O(2)	112·4 (3)	O(4)–C(14)–C(15)	107·7 (3)

reported for a number of similar compounds in which the amino nitrogen is protonated. From the pharmacological point of view the most important structural features of the oxypropanolamine chain are its conformational properties, as the 3-D distribution of the pharmacophoric groups of the aryloxypropanolamine β-adrenolytics – the alkylamine, 2-hydroxyl and the substituted aromatic system – depend on the torsion angles τ_1 = C(6)–C(1)–O(1)–C(7), τ_2 = C(1)–O(1)–C(7)–C(8), τ_3 = O(1)–C(7)–C(8)–C(9) and τ_4 = C(7)–C(8)–C(9)–N(1). Referring to an active *S*-isomer, in the present derivative, BL-223, $\tau_1 = 16{\cdot}4$ (5), $\tau_2 = 163{\cdot}1$ (3), $\tau_3 = -160{\cdot}1$ (2) and $\tau_4 = 172{\cdot}0$ (2)°. The conformation of the oxypropanolamine chain is thus fully extended and similar to conformations reported in the crystal structures of (–)-propanolol (Gadret, Goursolle, Leger & Colleter, 1975), pindolol (Gadret, Goursolle, Leger & Colleter, 1976) and HYP (Weber & Petcher, 1977). In other derivatives, alternative staggered conformations around C(7)–C(8) are found (Ammon *et al.*, 1977, and references therein; Carpy, Gadret, Leger, Wermuth & Leclerc, 1979; Dubost, Leger, Hickel & Colleter, 1981; Pascard, Huu Dau, Manoury & Mompon, 1984; Leger, Goursolle & Carpy, 1984). This distribution of torsion angles τ_3 indicates that all three staggered conformations are equi-energetic. The particular conformation observed in each crystal structure clearly depends on packing forces. Quantitative evaluation of these effects is, however, difficult though the molecular packing in the present structure is clearly determined by H bonds involving Cl^-; it is possible that in solution three conformers exist in equilibrium. In contrast to τ_3, similar values of τ_1, τ_2, and τ_4 to those observed in BL-223 are uniformly found in the crystal structures of β-blockers (see references cited above), indicating a strong preference for the conformations around C(1)–O(1), O(1)–C(7) and C(8)–C(9). The τ_1 conformation close to 0° seems to be preferred on electronic grounds due to conjugation between the ether O(1) atom and the phenyl ring, a feature well known from the structures of aromatic alkoxy compounds (Domiano, Nardelli, Balsamo, Macchia & Macchia, 1979). This is further

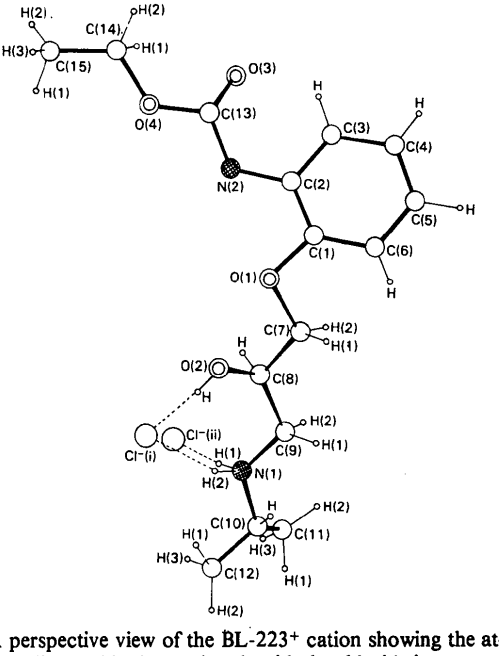
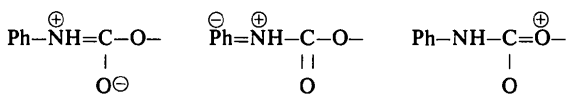


Fig. 1. A perspective view of the BL-223$^+$ cation showing the atom labelling and hydrogen bonds with the chloride ions.

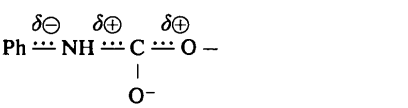
supported by a shortening of the C(1)–O(1) bond [1·364 (4) Å] from a value of 1·406 (4) Å reported for a C(sp^2)–O single bond (Ammon, Mazzochi, Regan & Colicelli, 1979) and by a widening of the C(1)–O(1)–C(7) valence angle [117·7 (2)°] from its normal tetrahedral value, both suggesting an essential sp^2 character for the O(1). A dissymmetry in the exocyclic bond angles at C(1) is caused by close contacts between the methylene H atoms and that of the aromatic ring [H(C6)].

Within the carbamate moiety there are differences from standard values in bond lengths due to conjugation. The observed C(2)–N(2) bond length of 1·406 (4) Å is significantly shorter than a value of 1·451 (2) Å found in 1-phenyl-1,2-dihydro-2-quinoline for a pure C(sp^2)–N(sp^2) single bond (Baenziger & Wawzonek, 1984). Similarly, the N(2)–C(13) and C(13)–O(4) bond distances of 1·355 (4) and 1·337 (5) Å indicate partial double-bond character and the fact that the sum of the valence angles at N(2) is close to 360° [356 (2)°] coupled with the near coplanarity of the C(14) with the carbamate group [the torsion angle O(3)–C(13)–O(4)–C(14) = −2·2 (5)°] indicate that the state of hybridization of the N(2) and O(4) atoms is sp^2. Thus the structure of this molecular fragment cannot be expressed in a satisfactory way by a single canonical formula; instead, forms (1)–(3) should contribute to the electronic state of the arylcarbamate portion of the molecule:



(1) (2) (3)

Form (1) would justify the shortening of the N(2)–C(13) bond as occurs in amides. Form (2) is consistent with the shortening of the N(2)–C(2) bond distance, while form (3) accounts for the considerable difference in the lengths of the C(sp^2)–O and O–C(sp^3) bonds, C(13)–O(4) [1·337 (4) Å] and O(4)–C(14) [1·457 (5) Å], a feature observed systematically in carbamates, esters and lactones. So the model of the arylcarbamate grouping characterized by the π-electron densities could be



which suggests a more extensive π-electron delocalization than in esters and amides.

The importance of the canonical forms (1)–(3) may be estimated by comparing the bond lengths in BL-223 with those found for other carbamates, esters and amides. The –O–C(=O) distances [1·457 (5) and 1·337 (4) Å] observed in the title compound are equal within the limits of accuracy to the average values of 1·447 and 1·340 Å for the corresponding bonds in the carboxylic ester groups in various compounds (Varghese, Srinivasan, Padmanbhan & Ramadas, 1986). On the other hand, for an amide group the N–C distances, due to varying NH···O=C hydrogen-bonding interactions, cover a relatively wide range of 1·30–1·36 Å with an average value of the order of 1·32–1·33 Å which is significantly shorter than the N(2)–C(13) bond distance [1·355 (4) Å] in BL-223. From the above arguments, keeping in mind the bond orders [as estimated from the bond-length–bond-order curve proposed by Burke-Laing & Laing (1976)], it may be concluded that form (2) arises at the expense of (1) and that the contribution of forms (2) and (3) should be approximately equal and half that of (1), *i.e.* 50, 25 and 25% for (1), (2) and (3) respectively. [Estimation of the bond order of the formal double bond C(13)=O(3) from C=O bond length and hence the significance of (2) must be undertaken with caution – because the partial charges on C and O atoms will cause an additional shortening of this bond by electrostatic attraction.]

The appearance of form (2) as a result of *N*-phenyl substitution of the carbamate function may be seen in changes in the N–C(=O) bond distance in 'open' and 'closed' carbamates. The unsubstituted analogues of the former are represented by, for example, carbamoylcholine salts for which the N–C(=O) distances were reported by Jensen (1975) to fall inside the range typical for amides (1·32–1·33 Å). *N*-Phenyl substitution (as in the present derivative) causes a significant lengthening of this bond [1·355 (4) Å] as a result of the contribution of form (2). A similar effect, to an even larger extent [1·301 (8) *vs* 1·354 (4)–1·360 (10) Å], was discussed by Durant, Bufkens, Lefevre, Evrard & Michel (1985) for a series of (unsubstituted and *N*-phenyl-substituted) oxazolidinone derivatives which contain the carbamate function within a ring. Moreover, even among various *N*-arylcarbamates an inverse correlation between N–C(aryl) and N–C(=O) bond distances is clearly discernible from a survey of the literature (*e.g.* Calleri *et al.*, 1977; Spinat, Brouty, Whuler & Sichère, 1985; Meester, Maldar, Hosmane & Chu, 1986), indicating again the competitive relationship between resonance forms (1) and (2).

Due to steric repulsion between O(3) and H(C3), [distance 2·20 (3) Å] and the possibility of electrostatic repulsion between the negatively charged phenyl group and the O(3) atom, the carbamate group is, in spite of extensive conjugation, inclined at an angle of 16·7 (5)° to the phenyl ring plane.

The molecular packing is determined by hydrogen bonding. The chloride ion forms a system of three hydrogen bonds: N(1)–H(1)···Cl$^-$ ($2-x$, $-y$, $1-z$) [N(1)···Cl$^-$ = 3·153 (3), N(1)–H(1) = 0·93 (3), H(1)···Cl = 2·23 (3) Å, N(1)–H(1)···Cl$^-$ = 171 (3)°], N(1)–H(2)···Cl$^-$ ($x+\frac{1}{2}$, $y-\frac{1}{2}$, z) [N(1)···Cl$^-$ =

3·200 (3), N(1)—H(2) = 0·89 (3), H(2)···Cl^- = 2·35 (3) Å, N(1)—H(2)···Cl^- = 160 (3)°] and O(2)—H···Cl^- ($x+\frac{1}{2}$, $y-\frac{1}{2}$, z) [O(2)···Cl^- = 3·143 (3), O(2)—H = 0·81 (3), H···Cl^- = 2·39 (3) Å, O(2)—H···Cl^- = 156 (3)°]. The molecules are thus connected through chloride ions to form sheets perpendicular to the *c* axis. The sheets are held together by van der Waals and dipolar forces acting mainly between the carbamate groups.

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Structure and Absolute Configuration of (−)-3-(*o*-Cyclohexylphenoxy)-1-(isopropylamino)-2-propanol Hydrochloride

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Abstract. $C_{18}H_{30}NO_2^+.Cl^-$, $M_r = 328·0$, orthorhombic, $P2_12_12_1$, $a = 7·224$ (2), $b = 13·961$ (6), $c = 19·424$ (7) Å, $V = 1959·0$ Å^3, $Z = 4$, $D_m = 1·10$, $D_x = 1·11$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, $\mu = 0·55$ mm^{-1}, $F(000) = 712$, $T = 293$ K, final $R = 0·044$ for 927 unique observed reflections. The crystal structure consists of infinite chains along the *a* axis, the molecules within the chains being connected *via* chloride ions by H-bond interactions. Adjacent chains are held together by van der Waals forces. The cyclohexane ring assumes a normal chair conformation with the aromatic ring attached equatorially. The isopropylamino group is oriented −synclinal relative to the 2-hydroxyl group, and the oxymethylene O—CH_2 fragment is approximately coplanar with the aromatic system. A large amount of flexibility in the oxypropanolamine chain of β-blocking drugs arises from rotation about the OCH_2—$CH(OH)CH_2$ bond, and the active (*S*)-enantiomer of the present compound adopts a −synclinal conformation in the crystal.

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