Acta Cryst. (1986). C**42**, 446–449

Structure of 2-Hydroxy-3-isopropylaminopropyl 3,4-Methylenedioxybenzoate Hydrochloride

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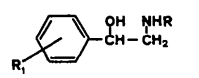
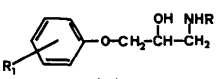
(*Received* 10 *February* 1985; *accepted* 31 *October* 1985)

Abstract. $C_{14}H_{20}NO_5^+.Cl^-$, $M_r = 317{\cdot}8$, triclinic, $P\bar{1}$, $a = 7{\cdot}301$ (1), $b = 7{\cdot}483$ (2), $c = 15{\cdot}241$ (4) Å, $\alpha = 88{\cdot}28$ (3), $\beta = 77{\cdot}28$ (1), $\gamma = 84{\cdot}30$ (1)°, $V = 808{\cdot}2$ Å^3, $Z = 2$, $D_x = 1{\cdot}306$ g cm^{-3}, $\lambda(\text{Cu } K\bar{\alpha}) = 1{\cdot}5418$ Å, $\mu = 21{\cdot}9$ cm^{-1}, $F(000) = 336$, $T = 294$ K, final $R = 0{\cdot}039$, $wR = 0{\cdot}049$ for 2122 reflections. The principal cation–anion interactions involve O—H···Cl$^-$ and N—H···Cl$^-$ hydrogen bonds. The compound, a 1-amino-3-benzoyloxypropanolamine derivative, is a potent β-adrenoreceptor blocker. The structure is compared to those of 2-arylethanolamine derivatives and 3-aryloxypropanolamine derivatives, β-antagonists. It is suggested that the planar $-CH_2-O-C(=O)-$ moiety can mimic an aromatic nucleus in interactions with the β-adrenoreceptor.

Introduction. β-Adrenergic drugs, *i.e.* the agents capable of stimulating or blocking the β-adrenoreceptors, have found widespread therapeutic application in several fields of human pathology. These drugs, with few exceptions, can be divided into two structural classes: derivatives of 2-arylethanolamine (I) and derivatives of 3-aryloxypropanolamine (II). The principal structural difference between these two classes is the CH_2—O group separating the ethanolamine chain and the aromatic portion in (II).



(I)



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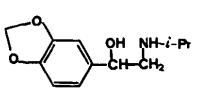

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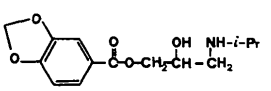

(IV)

The $CH_2NHR_1CH(OH)$ moiety is associated with the drug's affinity for the adrenergic receptors and the stimulating or blocking properties are determined by the nature of the aryl group (Petrongolo, Macchia, Macchia & Martinelli, 1977). To explain the similar pharmacological activity of the two classes of drugs, several hypotheses have been advanced (Ariens, 1967; Dangoumau, Barrans & Cotrait, 1973; Cromer, 1970; Barrett, 1972; Kaiser, Jen, Garvey, Bowen, Colella & Wardell, 1977; Jen & Kaiser, 1977; Ammon, Howe, Erhardt, Balsamo, Macchia, Macchia & Keefe, 1977; Ammon, Balsamo, Macchia, Macchia, Howe & Keefe, 1975; Petrongolo *et al.*, 1977; Macchia, Macchia & Martinelli, 1980; Lövgren, Hedberg & Nilsson, 1980) on the mechanism through which the CH_2—O—Ar portion of the class (II) agents can substitute for the single aromatic moiety (Ar) of the class (I) compounds in the drug–receptor interaction. On the basis of the observation that the insertion of the CH_2—O group modifies the distances between the Ar group and the other active centers of the drug, it had been proposed (Ariens, 1967; Dangoumau *et al.*, 1973) that complementary additional receptor areas could be involved in the drug–receptor interaction. It had also been suggested (Cromer, 1970; Barrett, 1972) that the CH_2—O bridge could keep the aryl group of the class (II) drugs in a position, with regard to the ethanolamine side chain, comparable to that of the Ar group of the class (I) drugs. Later, on the basis of a conformational analysis of protonated aryloxypropanolamines by NMR spectroscopy, Kaiser proposed (Kaiser *et al.*, 1977; Jen & Kaiser, 1977) a rigid bicyclic model, involving a six-membered ring formed by a hydrogen bond between an amino hydrogen atom and the aryloxy oxygen, which allows an almost complete superim-

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position of both the aryl and the amino groups in the two classes of drugs. In this model, however, there is no possibility for OH group overlap. The results of subsequent NMR studies (Zaagsma, 1979) have led to some doubts of the validity of this model.

X-ray diffraction studies of both class (I) and (II) compounds showed (Ammon *et al.*, 1977) that the C(3)–O(2)–C(4)–C(5) atoms of a class (II) drug define a plane, and the spatial relationship between this plane and the ethanolamine side chain is the same as that observed between the aromatic ring and the ethanolamine side chain in class (I) drugs (see Fig. 1). On the basis of this observation, it was hypothesized (Ammon *et al.*, 1975) that the C(3)–O(2)–C(4)–C(5) portion of class (II) adrenergic β-blocking drugs could in some way 'simulate' a portion of an aromatic ring, thereby substituting for the aryl group that is directly linked to C(2) in the class (I) drug–receptor interaction. This hypothesis was later strengthened (Petrongolo *et al.*, 1977; Macchia *et al.*, 1980; Macchia, Macchia & Martinelli, 1983) through quantum-mechanical studies, which showed that the C(3)–O(2)–C(4)–C(5) portion of class (II) drugs and the aryl moiety of class (I) drugs have comparable 'chemical reactivity'.

The title compound, 2-hydroxy-3-isopropylaminopropyl 3,4-methylenedioxybenzoate hydrochloride (IV), has a class (II) type of structure, but with an aroyl group in place of the aryl moiety. The compound is a potent β-adrenergic blocker, with an activity approximately the same as that for the corresponding class (I) derivative (III) (Tatsuno, Goto, Shigenobu, Kasuya, Obase, Yamada & Kudo, 1977).

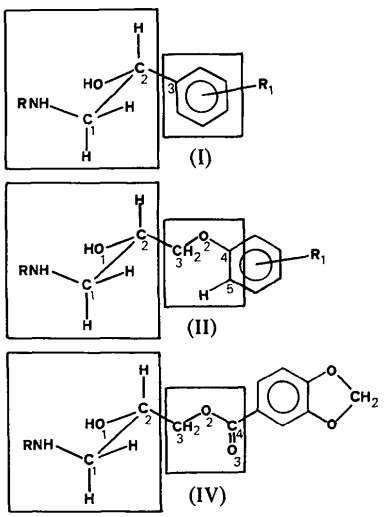

Fig. 1. Perspective views of 2-arylethanolamine derivatives (I), 3-aryloxypropanolamine derivatives (II) and 2-hydroxy-3-isopropylaminopropyl 3,4-methylenedioxybenzoate hydrochloride (IV).

The β-blocking activity of (IV) cannot be explained by use of the Kaiser model, because the introduction of the C=O group between the aryl nucleus and the oxygen of a class (II) drug makes this model ineffective. An X-ray crystallographic study of the hydrochloride of (IV) was undertaken in an attempt to establish a structural basis for its pharmaceutical activity.

Experimental. Pale yellow elongated needles (ethanol–benzene), 0·20 × 0·18 × 0·15 mm, Picker FACS-I diffractometer with graphite monochromator, Cu $K\bar{\alpha}$; 18 reflections ($19 < \theta < 29$) used to refine cell parameters; no systematic absences; reflections measured to $2\theta_{max} = 126°$ with 2θ–θ scans (10 s backgrounds); h from 0 to 8, k from −8 to 8, l from −17 to 17; 4 check reflexions (480, 233, 060, 022) after every 60 reflections, no significant variation in intensity; 2301 unique reflections; 2122 with $I > 3\sigma(I)$; Lp correction, absorption ignored; structure solved with *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980). Full-matrix least-squares minimization of $\sum w(F_o - F_c)^2$, $w = 1/\sigma^2(F)$; Cl, C, N, O parameters refined with anisotropic temperature factors; H atoms from ΔF synthesis, isotropic temperature factors refined; refinement included only those reflections for which $I_c > 3\sigma(I_o)$; av. and max. shift/error 0·04 and 0·35 [U_{13} of C(7)]; final R, wR and S values of 0·039, 0·049 and 2·1; max. and min. in final difference map 0·25 and −0·12 e Å^{-3}. Atom form factors for C, O, N and Cl from Cromer & Mann (1968), for H from Stewart, Davidson & Simpson (1965); UNIVAC 1100/82 computer; *XRAY* system of crystallographic programs (Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976).

Discussion. Atomic coordinates and temperature factors for the C, N, O and Cl atoms are listed in Table 1.* The bond lengths and angles (Table 2) are within normal ranges. The *ORTEP* drawing (Fig. 2) is that of the (*S*) enantiomer, the most pharmacologically active isomer of the class (II) structures. The amino and hydroxyl groups adopt the *gauche* conformation [N–C(1)–C(2)–O(1) = 63·8 (2)°], typical of all class (I) and (II) compounds despite the absence of any well defined intramolecular interactions (*e.g.* hydrogen bonding) capable of holding the substituents in this orientation. The angle compares well with literature values (50–73° in 16 compounds surveyed). A minimum-energy conformation is found for the $(CH_3)_2$-CH–NH_2–CH_2– moiety with one CH_3 *gauche* and one *anti* to the CH_2 [C(13)–C(12)–N–C(1) =

* Lists of structure factors, anisotropic thermal parameters and H-atom coordinates have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 42620 (13 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

63·4 (2); C(14)–C(12)–N–C(1) = 171·9 (2)°]. The methylenedioxybenzoate fragment is planar. The average out-of-plane distances and interplanar angles from least-squares-plane calculations are: plane (1) = C(4)C(5)C(6)C(7)C(8)C(9)C(10)C(11)O(2)O(3)O(4)O(5) = 0·028 (3); plane (2) = C(4)C(5)C(6)C(7)C(8)C(9) = 0·004 (3); plane (3) = C(7)C(8)O(5)C(11)O(4) = 0·006 (3); plane (4) = C(3)O(2)C(4)O(3) = 0·001 (3) Å; (2)/(3) = 0·9 (3)°; (2)/(4) = 5·6 (3)°.

Table 1. *Fractional coordinates and equivalent isotropic temperature factors* (Å²) *with e.s.d.'s in parentheses*

$U_{eq} = (1/3)\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
Cl	1·17075 (7)	0·76770 (7)	0·51678 (4)	0·050 (8)
C(1)	0·6823 (3)	0·7125 (3)	0·5082 (1)	0·040 (4)
C(2)	0·7522 (3)	0·7761 (3)	0·4126 (1)	0·043 (4)
C(3)	0·7162 (3)	0·6478 (3)	0·3469 (1)	0·049 (4)
C(4)	0·7797 (4)	0·6712 (3)	0·1858 (2)	0·047 (4)
C(5)	0·9235 (3)	0·7113 (3)	0·1054 (1)	0·049 (4)
C(6)	0·8717 (4)	0·7189 (3)	0·0218 (2)	0·057 (5)
C(7)	1·0057 (4)	0·7570 (3)	−0·0516 (2)	0·068 (6)
C(8)	1·1849 (4)	0·7885 (4)	−0·0460 (2)	0·079 (5)
C(9)	1·2398 (4)	0·7798 (5)	0·0336 (2)	0·078 (2)
C(10)	1·1045 (4)	0·7403 (4)	0·1104 (2)	0·063 (6)
C(11)	1·1672 (5)	0·8185 (5)	−0·1911 (2)	0·095 (7)
C(12)	0·6633 (3)	0·7935 (3)	0·6709 (1)	0·057 (5)
C(13)	0·7552 (4)	0·6142 (4)	0·6954 (2)	0·073 (6)
C(14)	0·7013 (4)	0·9482 (4)	0·7233 (2)	0·071 (3)
N	0·7293 (4)	0·8349 (2)	0·5729 (1)	0·041 (8)
O(1)	0·6584 (2)	0·9478 (2)	0·3969 (1)	0·047 (7)
O(2)	0·8389 (2)	0·6830 (2)	0·2615 (1)	0·057 (7)
O(3)	0·6243 (3)	0·6321 (4)	0·1856 (1)	0·064 (7)
O(4)	0·9913 (3)	0·7718 (3)	−0·1392 (1)	0·096 (8)
O(5)	1·2886 (3)	0·8253 (3)	−0·1294 (1)	0·107 (7)

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

C(1)–C(2)	1·514 (3)	C(7)–C(8)	1·373 (4)
C(1)–N	1·481 (2)	C(7)–O(4)	1·362 (3)
C(2)–C(3)	1·490 (3)	C(8)–C(9)	1·357 (5)
C(2)–O(1)	1·434 (2)	C(8)–O(5)	1·364 (3)
C(3)–O(2)	1·441 (2)	C(9)–C(10)	1·401 (4)
C(4)–C(5)	1·473 (3)	C(11)–O(4)	1·422 (4)
C(4)–O(2)	1·326 (3)	C(11)–O(5)	1·432 (5)
C(4)–O(3)	1·200 (4)	C(12)–C(13)	1·513 (3)
C(5)–C(6)	1·405 (4)	C(12)–C(14)	1·507 (4)
C(5)–C(10)	1·379 (4)	C(12)–N	1·498 (3)
C(6)–C(7)	1·358 (3)		
C(2)–C(1)–N	110·6 (2)	C(8)–C(7)–O(4)	109·0 (2)
C(1)–C(2)–C(3)	111·0 (2)	C(7)–C(8)–C(9)	121·7 (3)
C(1)–C(2)–O(1)	111·0 (1)	C(7)–C(8)–O(5)	110·0 (3)
C(3)–C(2)–O(1)	107·7 (2)	C(9)–C(8)–O(5)	128·3 (3)
C(2)–C(3)–O(2)	107·0 (2)	C(8)–C(9)–C(10)	117·1 (3)
C(5)–C(4)–O(2)	112·8 (2)	C(5)–C(10)–C(9)	121·4 (3)
C(5)–C(4)–O(3)	125·3 (2)	O(4)–C(11)–O(5)	106·2 (2)
O(2)–C(4)–O(3)	121·9 (2)	C(13)–C(12)–N	110·9 (2)
C(4)–C(5)–C(6)	118·0 (2)	C(14)–C(12)–N	107·7 (2)
C(4)–C(5)–C(10)	121·9 (2)	C(13)–C(12)–C(14)	113·4 (2)
C(6)–C(5)–C(10)	120·1 (2)	C(1)–N–C(12)	117·1 (2)
C(5)–C(6)–C(7)	117·2 (3)	C(3)–O(2)–C(4)	120·2 (2)
C(6)–C(7)–C(8)	122·5 (3)	C(7)–O(4)–C(11)	107·9 (3)
C(6)–C(7)–O(4)	128·5 (3)	C(8)–O(5)–C(11)	106·9 (2)

A possible basis for the β-adrenergic activity of (IV), compared to class (I) and (II) compounds, can be found by examining the structural consequences of the introduction of a C=O function between the aromatic ring [C(4)] and oxygen atom [O(2)] in class (II) compounds. We find that the CH_2–O–C(=O)[C(3)–O(2)–C(4)–O(3)] fragment of (IV) is highly planar [plane (4)] and coplanar with the aromatic ring [(2)/(4) = 5·6 (3)°], leading to an extended planar structure. It is important to note that the CH_2–O–C(=O) fragment forms a ring-like structure [C(3)–O(2)–C(4)–O(3) dihedral angle = −0·3 (3)°] rather than an extended conformation with a dihedral angle close to 180°. As can be seen from Fig. 1, there is a clear spatial relationship between the benzene ring of class (I) compounds, the C(3)–O(2)–C(4)–C(5) planar portion of class (II) compounds and the C(3)–O(2)–C(4)=O(3) planar portion of the drug under examination (IV).

As has been said in the *Introduction*, it was hypothesized (Ammon *et al.*, 1975) and then demonstrated (Petrongolo *et al.*, 1977; Macchia *et al.*, 1980; Macchia *et al.*, 1983) that the C(3)–O(2)–C(4)–C(5) planar portion of class (II) compounds could in some way take the place of a portion of the aromatic ring directly linked to the C(2) atom of class (I) compounds in the interaction with the β-adrenergic receptor. On the basis of the above mentioned structural results, it may be possible to suggest that, in the case of drug (IV), the role of the aromatic ring in the drug–receptor interaction could be played by the C(3)–O(2)–C(4)–O(3) planar portion.

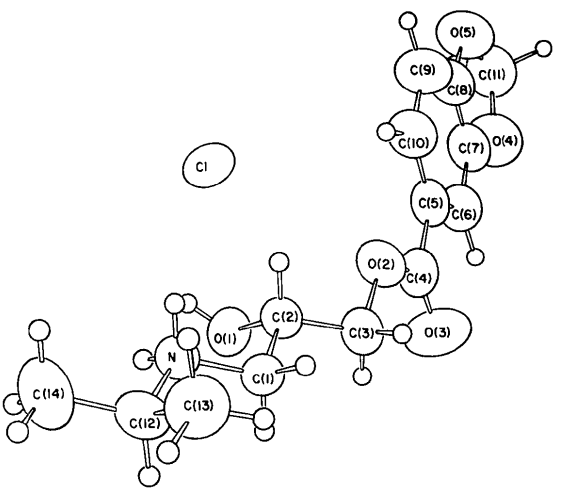

Fig. 2. An *ORTEP* (Johnson, 1971) drawing of (IV) with the C,N,O atoms depicted as 50% probability boundary ellipses. H atoms are shown as 0·1 Å radius circles.

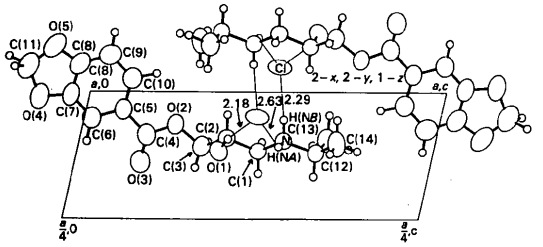

Fig. 3. Packing view down *b*; cation–chloride contact distances (Å).

A previous survey (Ammon *et al.*, 1975), which showed a clear relationship between the Ar–CH(OH) (I) and Ar–O–CH_2–CH(OH) (II) moieties, found that the angle between the aromatic ring and the C(3)–C(2)–C(1)–N plane in class (I) drugs and the angle between the C(3)–O(2)–C(4)–C(5) and C(3)–C(2)–C(1)–N planes in class (II) drugs both fell in the *narrow* range of 56·6–87·0° for nine adrenergic drugs (adrenaline tartrate was the exception at 2·8°). We have made a more recent survey of sixteen class (II) compounds and found a range of 6·3–87·8° for the angle between the C(3)–O(2)–C(4)–C(5) and C(3)–C(2)–C(1)–N planes. In (IV), the corresponding angle, between C(3)–O(2)–C(4)–O(3) and C(3)–C(2)–C(1)–N, is 44·1 (3)°.

A packing diagram is given in Fig. 3. The molecules are elongated approximately parallel to [001]. The only intermolecular contact less than van der Waals distances between the organic cations is N–O(1) (at $1-x, 2-y, 1-z$) of 3·070 (2) Å. The principal cation···chloride interactions involve strong O–H···Cl^- (at $2-x, 2-y, 1-z$) and N–H···Cl^- (at x, y, z) contacts of 2·18 (3) and 2·29 (2) Å respectively, and a weaker N–H···Cl^- (at $2-x, 2-y, 1-z$) contact of 2·63 (2) Å. These distances change to 2·08 (3) and 2·14 (2) Å respectively for 'corrected' O–H and N–H hydrogen-atom positions (O–H = 0·97, N–H = 1·03 Å).

This work was supported in part through the facilities of the University of Maryland Computer Science Center and through a grant from the Progetto finalizzato del CNR Chimica Fine e Secondaria.

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Acta Cryst. (1986). C**42**, 449–451

Nonsteroidal Antiinflammatory Drugs. II. Structure of (2-Ethoxy-5-indanyl)acetic Acid

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(*Received* 12 *September* 1985; *accepted* 12 *November* 1985)

Abstract. $C_{13}H_{16}O_3$, $M_r = 220·3$, triclinic, $P\bar{1}$, $a = 10·950$ (3), $b = 11·699$ (3), $c = 4·721$ (1) Å, $\alpha = 83·39$ (2), $\beta = 104·14$ (3), $\gamma = 88·53$ (3)°, $V = 581·6$ (3) Å^3, $Z = 2$, $D_x = 1·26$ g cm^{-3}, graphite-monochromated Cu $K\alpha$, $\lambda = 1·5418$ Å, $\mu = 7·3$ cm^{-1}, $F(000) = 236$, $T = 298$ K, final $R = 0·095$ for 1032

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