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Structure of Bis[{3-[(4-acetyl-2-propoxymethyl)phenoxy]-2-hydroxypropyl}-(isopropyl)ammonium] Fumarate

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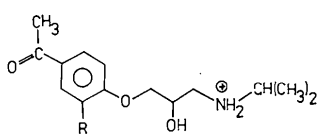
Abstract. $2C_{18}H_{30}NO_4^+.C_4H_2O_4^{2-}$, $M_r = 762{\cdot}9$, triclinic, $P\bar{1}$, $a = 7{\cdot}622\ (6)$, $b = 9{\cdot}921\ (7)$, $c = 14{\cdot}607\ (9)$ Å, $\alpha = 103{\cdot}25\ (5)$, $\beta = 95{\cdot}30\ (6)$, $\gamma = 101{\cdot}30\ (6)°$, $V = 1043\ (1)$ Å^3, $Z = 1$, $D_m = 1{\cdot}21\ (1)$, $D_x = 1{\cdot}214$ Mg m^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, $\mu = 0{\cdot}87$ cm^{-1}, $F(000) = 412$, $T = 293$ K, intensities measured diffractometrically, structure refined by block-diagonal least squares, final $R = 0{\cdot}054$ for 1975 unique observed reflections. The crystal structure consists of centrosymmetric groups of three ions: two monocations and one (fumarate) dianion, the principal interaction between the ions being strong hydrogen bonding of the hydroxy and ammonium groups with the carboxylate group of the fumarate dianion. The arrangement of the aryloxy and 2-hydroxy groups around the conformationally flexible OCH_2—$CH(OH)CH_2$ bond of the oxypropanolamine side chain is antiperiplanar. The results do not reveal any significant intramolecular charge transfer from the donor ethereal oxygen to the acceptor acetyl group; thus, the through conjugation, which was shown previously to cause the lack of β-adrenoceptor blocking activity in the carbamate analogue, appears to be almost completely removed in the present derivative by the electron-releasing effect of the propoxymethyl substituent.

Introduction. The title compound (I) belongs to the phenoxypropanolamine group of β-adrenergic drugs which are used clinically throughout the world to treat a variety of cardiovascular disorders (Frishman, 1980).



(I): R = $CH_2OCH_2CH_2CH_3$
(II): R = $NHCOOCH_2CH_2CH_3$

The crystal and molecular structure of (I) is of threefold interest. Firstly, it extends the available structural data on phenoxypropanolamines, thus allowing more general conclusions to be drawn about the preferred conformation of the flexible oxypropanolamine side chain, which in turn determines the spatial disposition of the pharmacophoric elements. Secondly, the structure determination could help in understanding pharmacological differences between (I) and (II); thus, while (I) exhibits (moderate) β-adrenoceptor blocking activity (Čižmáriková, Borovanský, Kozlovský, Béderová & Dingová, 1985), (II), having a carbamate group instead of the propoxymethyl substituent, has been found to be totally inactive (Csöllei, Račanska, Švec & Kettmann, 1991). The inactivity of (II) was attributed to the positive electrostatic potential generated by the π-deficient phenyl ring as a result of through conjugation between the ethereal oxygen and the acceptor acetyl group (Kettmann, 1991). Therefore, the electronic structure of the π-electron portion of (I) (as can be inferred from the bond-length distribution) was of prime interest here.

The third point of interest in the present structure is the mode of interaction of cation (I) with the fumarate dianion since the carboxylate group of Asp 113 of the receptor is generally believed to act as a counterion for the positively charged amine of both agonists and antagonists (Strader, Sigal, Candelore, Rands, Hill & Dixon, 1988, and references therein). Previous studies on the hydrochloride salts of many adrenergic ligands not containing aromatic hydroxyl(s) (as competing hydrogen-bond donors) have shown that these cations, both in the solid state and in solution, prefer simultaneous hydrogen bonding of the OH and N^+H groups to the common Cl^- anion, thus forming a seven-membered ring (Kettmann & Csöllei, 1989, and references therein; Zaagsma, 1979). Nonetheless, the present structure

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Table 1. *Final atomic coordinates* ($\times 10^4$) *with e.s.d.'s in parentheses and equivalent isotropic thermal parameters* (Å^2)

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

	x	y	z	B_{eq}
C(1)	2154 (3)	6789 (2)	1955 (2)	3·11
C(2)	2288 (3)	6445 (2)	992 (2)	3·06
C(3)	2383 (3)	7503 (2)	519 (2)	3·39
C(4)	2347 (3)	8874 (2)	984 (2)	3·58
C(5)	2162 (3)	9173 (2)	1935 (2)	3·75
C(6)	2073 (3)	8140 (2)	2428 (2)	3·40
C(7)	2277 (3)	6011 (3)	3383 (2)	3·58
C(8)	2583 (3)	4697 (2)	3663 (1)	3·06
C(9)	4163 (3)	4216 (3)	3268 (2)	3·40
C(10)	5864 (3)	2283 (3)	3258 (2)	3·93
C(11)	6274 (5)	1327 (3)	3875 (2)	6·28
C(12)	7534 (4)	3157 (3)	3063 (2)	6·20
C(13)	2307 (3)	4951 (2)	508 (1)	3·43
C(14)	2615 (3)	3486 (2)	−931 (2)	3·35
C(15)	2851 (4)	3465 (3)	−1936 (2)	3·96
C(16)	2977 (4)	2018 (3)	−2485 (2)	4·88
C(17)	2464 (4)	10016 (3)	489 (2)	4·97
C(18)	2412 (6)	9662 (3)	−563 (2)	7·00
N(1)	4716 (3)	3183 (2)	3754 (1)	3·01
O(1)	2110 (2)	5698 (2)	2370 (1)	3·74
O(2)	2883 (2)	5064 (2)	4667 (1)	3·12
O(3)	2513 (2)	4868 (2)	−448 (1)	3·79
O(4)	2636 (4)	11227 (2)	934 (2)	8·05
C(19)	1217 (3)	1788 (2)	4817 (2)	3·56
C(20)	152 (3)	667 (2)	5187 (2)	3·59
O(5)	1361 (3)	3019 (2)	5289 (1)	5·93
O(6)	1842 (3)	1438 (2)	4080 (1)	5·03

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

C(1)—C(2)	1·387 (3)	C(10)—C(12)	1·483 (4)
C(2)—C(3)	1·378 (3)	C(2)—C(13)	1·492 (3)
C(3)—C(4)	1·381 (4)	C(13)—O(3)	1·405 (3)
C(4)—C(5)	1·379 (4)	O(3)—C(14)	1·411 (3)
C(5)—C(6)	1·375 (4)	C(14)—C(15)	1·493 (4)
C(6)—C(1)	1·376 (3)	C(15)—C(16)	1·502 (4)
C(1)—O(1)	1·353 (3)	C(4)—C(17)	1·471 (4)
O(1)—C(7)	1·430 (3)	C(17)—O(4)	1·204 (4)
C(7)—C(8)	1·506 (4)	C(17)—C(18)	1·491 (4)
C(8)—C(9)	1·496 (4)	C(19)—O(5)	1·235 (3)
C(8)—O(2)	1·413 (3)	C(19)—O(6)	1·222 (3)
C(9)—N(1)	1·476 (3)	C(19)—C(20)	1·480 (4)
N(1)—C(10)	1·489 (3)	C(20)—C(20′)	1·276 (4)
C(10)—C(11)	1·505 (4)		

C(1)—C(2)—C(3)	118·3 (2)	C(11)—C(10)—C(12)	112·0 (3)
C(2)—C(3)—C(4)	121·3 (2)	C(1)—C(2)—C(13)	119·2 (2)
C(3)—C(4)—C(5)	119·0 (2)	C(3)—C(2)—C(13)	122·6 (2)
C(4)—C(5)—C(6)	121·0 (2)	C(2)—C(13)—O(3)	109·0 (2)
C(5)—C(6)—C(1)	119·0 (2)	C(13)—O(3)—C(14)	111·3 (2)
C(6)—C(1)—C(2)	121·4 (2)	O(3)—C(14)—C(15)	109·0 (2)
C(2)—C(1)—O(1)	114·5 (2)	C(14)—C(15)—C(16)	111·3 (2)
C(6)—C(1)—O(1)	124·1 (2)	C(3)—C(4)—C(17)	121·8 (2)
C(1)—O(1)—C(7)	118·0 (2)	C(5)—C(4)—C(17)	119·2 (2)
O(1)—C(7)—C(8)	106·9 (2)	C(4)—C(17)—O(4)	120·0 (3)
C(7)—C(8)—O(2)	106·0 (2)	C(4)—C(17)—C(18)	119·4 (3)
C(7)—C(8)—C(9)	111·8 (2)	O(4)—C(17)—C(18)	120·6 (3)
C(9)—C(8)—O(2)	110·8 (2)	C(20)—C(19)—O(5)	115·4 (2)
C(8)—C(9)—N(1)	110·0 (2)	C(20)—C(19)—O(6)	118·7 (2)
C(9)—N(1)—C(10)	116·1 (2)	O(5)—C(19)—O(6)	125·8 (3)
N(1)—C(10)—C(11)	107·1 (2)	C(19)—C(20)—C(20′)	125·6 (2)
N(1)—C(10)—C(12)	111·6 (2)		

offered an opportunity to mimic more realistically the actual drug–receptor interaction.

Experimental. Single crystals by crystallization from ethyl acetate; colourless prism-like crystal: 0·6 × 0·6 × 0·4 mm, D_m by flotation; Weissenberg photographs consistent with Laue symmetry $\bar{1}$; Syntex $P2_1$ diffractometer; unit-cell parameters by least-squares refinement of 15 reflections, $10 < 2\theta < 22°$; intensity data ($h = 0$ to 9, $k = -12$ to 12, $l = -18$ to 18) collected with graphite-monochromated Mo $K\alpha$ radiation, θ–2θ scan mode, variable scan speed, scan width 2° (in 2θ) plus α_1–α_2 dispersion; two standard reflections measured every 100 reflections, these varied by less than 5%; intensities corrected for Lorentz–polarization effects but not for absorption; 4815 unique reflections, $2\theta \leq 55°$ (2084 with $2\theta \leq 45°$), 1975 with $I \geq 2\theta(I)$ considered observed (315 with $2\theta \geq 45°$) and included in the refinement; structure solved by direct methods using *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980) and refined by 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 $R = 0{\cdot}054$, $wR = 0{\cdot}070$ for observed reflections only, $S = 1{\cdot}52$, max. shift/e.s.d. 0·13, function minimized $\sum w(\Delta F)^2$, where $w = 1$ if $|F_o| < 17$ and $w = 17/|F_o|$ if $|F_o| \geq 17$, max. and min. heights in final $\Delta\rho$ synthesis 0·18 and −0·20 e Å^{-3}, scattering factors for neutral atoms from *International Tables for X-ray Crystallography* (1974, Vol. IV); all calculations except *MULTAN* performed with local version of the *NRC Crystallographic Programs for the IBM*360 *System* (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. A stereoview of the asymmetric unit and the numbering scheme is given in Fig. 1.

The data of Table 1 and the cation illustrated in Fig. 1 correspond to the biologically less active R enantiomer. The centre of the fumarate dianion coincides with a crystallographic inversion centre and the cation (I) is in a general position.

Bond distances and angles along the oxypropanolamine side chain are comparable with those reported for a number of similar compounds in which the amino N atom is protonated. However, from the pharmacological point of view the most important structural features of the oxypropanol-

* Lists of structure factors, anisotropic thermal parameters, H-atom parameters, least-squares planes and torsion angles have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 53242 (22 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

amine chain are its conformational properties, since the spatial distribution of the pharmacophoric groups (*i.e.* the amino N atom, 2-hydroxyl group and the aromatic system) depends on the torsion angles at four potentially rotatable bonds; 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). For an active *S* isomer, in the present derivative (I), τ_1 = 10·3 (4), τ_2 = 168·2 (2), τ_3 = −54·8 (3) and τ_4 = −165·1 (2)°. Comparison with other aryloxypropanolamines studied (n = 20, including the present structure) shows that $\tau_1 \sim 0$, $\tau_2 \sim \tau_4 \sim 180°$ are consistently found in the crystals (Ammon, Howe, Erhardt, Balsamo, Macchia, Macchia & Keefe, 1977, and references therein; Leger, Gadret & Carpy, 1980, and references therein; Kettmann & Csöllei, 1989, and references therein; Cotrait, Pastor & Giral, 1986; Kettman, Pavelčík, Majer & Rybár, 1989), indicating a strong preference for these conformations. On the other hand, all three staggered conformers arising from rotation around τ_3 are observed in the solid state (n = 8, 4 and 8 for $\tau_3 \sim -60$, 60 and 180°, respectively), demonstrating the flexibility of the chain at C(7)—C(8). The coplanarity of the O(1)—C(7) bond with the adjacent aromatic system seems to be preferred on electronic grounds due to some degree of conjugation between the ether O(1) atom and the phenyl ring, as evidenced by a shortening of the C(1)—O(1) bond [1·353 (3) Å] relative to a C(sp^2)—O single bond [1·406 (4) Å; Ammon, Mazzochi, Regan & Colicelli, 1979] and by a widening of the C(1)—O(1)—C(7) bond angle [118·0 (2)°] from the normal sp^3 value.

In the area of the substituted phenyl ring, which is of prime interest to this study, calculation of the least-squares planes shows that although the acetyl group is rotated out of the plane of the phenyl ring by only 8·4°, the bond lengths within the acetyl group indicate localized single and double bonds, although the C(4)—C(17) bond distance of 1·471 (4) Å is slightly shorter than normal C(sp^2)—C(sp^2) single bond (1·487 Å; Shmueli, Shanan-Atidi, Horwitz & Shvo, 1973). Within the aromatic ring, inspection of Table 2 reveals that there is no quinonoid distortion of the phenyl-ring bond distances; similarly, the pattern of the endocyclic bond angles is different from that which is usually observed for quinonoid-distorted phenyl rings (Chattopadhyay, Banerjee, Mazumdar & Podder, 1985). All these facts indicate that, although the lone-pair electrons of O(1) are definitely delocalized through the phenyl ring, the π density is not transferred to any appreciable extent to the acetyl group. This appears to be in marked contrast to the carbamate analogue (II), where the through conjugation between the *p*-phenyl substituents of opposite type (and hence a deficiency of π charge on the phenyl group) was clearly indicated and proposed to be responsible for the inactivity of the compound as a β-adrenoceptor antagonist (Kettmann, 1991). Consequently, the pharmacological differences between (I) and (II) appear to be related to the electronic differences, the latter most likely arising from different effects of the substituent *R* (Scheme 1). Indeed, while the carbamate group in this congeneric class of compounds was found to have essentially no effect on the π-electron distribution of the phenyl ring, the propoxymethyl group, probably acting as an electron-releasing substituent, at the position *meta* to the acetyl group, does not favour the aforementioned conjugation. The near coplanarity of the propoxymethyl group (the group adopts a fully extended conformation with torsion angles close to 180°) with the adjacent phenyl ring [torsion angle C(3)—C(2)—C(13)—O(3) = 2·6 (3)°] supports this proposition. Nevertheless, to solve the problem conclusively, a calculation of the molecular electrostatic potential, which is a much better reactivity index than small (though significant) stereochemical differences, is awaited.

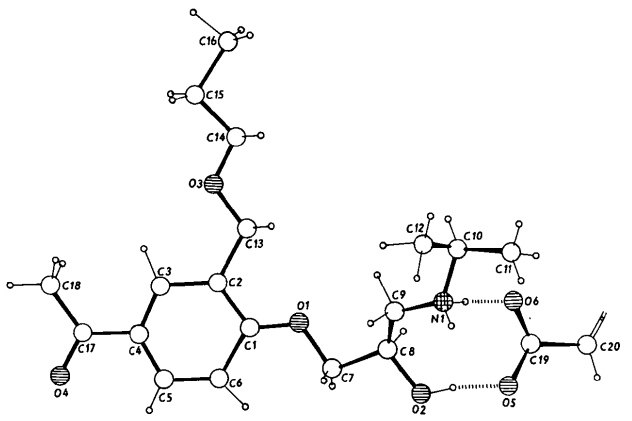

Fig. 1. A perspective view of the asymmetric unit, comprising cation (I) and half of the fumarate dianion, and the numbering of the atoms.

As noted in the introduction, the present structure may serve as a model system to study the mode of interaction of the protonated ethanolamine portion of the β-adrenergic ligands with the anionic site (carboxylate group) of the receptor. Of special interest is whether the ethanolammonium moiety is able to hydrogen bond to both oxygens of the carboxylate anion or whether the interaction is restricted to a single oxygen as is currently assumed in the literature (Strader *et al.*, 1988, and references therein). As can be seen in Fig. 1, the cation (I) associates with the fumarate dianion through strong hydrogen bonding of the N^+H and OH moieties with different O atoms of the carboxylate group, thus leading to the formation of a nine-membered ring. The details of the

geometry of these 'strong' hydrogen bonds are: $N(1)^+$—H···O(6), N(1)—H = 0·93 (3), N(1)···O(6) = 2·666 (3), H···O(6) = 1·74 (3) Å, N(1)—H···O(6) = 173 (2)°; O(2)—H···O(5), O(2)—H = 0·94 (3), O(2)···O(5) = 2·530 (3), H···O(5) = 1·60 (3) Å, O(2)—H···O(5) = 174 (3)°. Thus, such an association leads to the formation of centrosymmetric groups containing two cations of opposite chirality and one dianion. The second N^+—H bond is involved in a 'normal' N(1)—H···O(2) $(1-x, 1-y, 1-z)$ hydrogen bond [N(1)—H = 0·89 (2), N(1)···O(2) = 2·798 (2), H···O(2) = 1·92 (2) Å, N(1)—H···O(2) = 167 (2)°] which connects two adjacent groups related by an inversion centre to form larger groups of six ions. The latter groups are held together by van der Waals forces only. Thus, although the packing is controlled by hydrogen bonding, it totally ignores the hydrogen-acceptor capability of the acetyl O(4) atom.

References

AMMON, H. L., HOWE, D. B., ERHARDT, W. D., BALSAMO, A., MACCHIA, B., MACCHIA, F. & KEEFE, W. E. (1977). *Acta Cryst.* B33, 21–29.

AMMON, H. L., MAZZOCHI, P. H., REGAN, M. C. & COLICELLI, E. (1979). *Acta Cryst.* B35, 1722–1724.

CHATTOPADHYAY, D., BANERJEE, T., MAZUMDAR, S. K. & PODDER, G. (1985). *Acta Cryst.* C41, 287–290.

ČIŽMÁRIKOVÁ, R., BOROVANSKÝ, A., KOZLOVSKÝ, J., BÉDEROVÁ, E. & DINGOVÁ, A. (1985). *Collect. Czech. Chem. Commun.* **50**, 2289–2298.

COTRAIT, M., PASTOR, G. & GIRAL, L. (1986). *Acta Cryst.* C42, 1868–1871.

CSÖLLEI, J., RAČANSKÁ, E., ŠVEC, P. & KETTMANN, V. (1991). *Eur. J. Med. Chem.* Submitted.

FRISHMAN, W. (1980). *Am. Heart J.* **99**, 665–674.

KETTMANN, V. (1991). *Eur. J. Med. Chem.* Submitted.

KETTMANN, V. & CSÖLLEI, J. (1989). *Acta Cryst.* C45, 279–282.

KETTMANN, V., PAVELČÍK, F., MAJER, J. & RYBÁR, A. (1989). *Acta Cryst.* C45, 282–285.

LEGER, J. M., GADRET, M. & CARPY, A. (1980). *Mol. Pharmacol.* **17**, 339 343.

MAIN, P., FISKE, S. J., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERCQ, J.-P. & WOOLFSON, M. M. (1980). *MULTAN*80. *A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univs. of York, England, and Louvain, Belgium.

*NRC Crystallographic Programs for the IBM*360 *System* (1973). Accession Nos. 133–147. *J. Appl. Cryst.* **6**, 309–346.

SHMUELI, U., SHANAN-ATIDI, H., HORWITZ, H. & SHVO, Y. (1973). *J. Chem. Soc. Perkin Trans.* 2, pp. 657–662.

STRADER, C. D., SIGAL, I. S., CANDELORE, M. R., RANDS, E., HILL, W. S. & DIXON, R. A. F. (1988). *J. Biol. Chem.* **263**, 10267–10271.

ZAAGSMA, J. (1979). *J. Med. Chem.* **22**, 441–445.

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Lattice Inclusion Compounds of Gossypol. Structure of the 2:3 Gossypol–Benzaldehyde Coordinatoclathrate

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Abstract. $C_{30}H_{30}O_8 \cdot 1{\cdot}5C_7H_6O$, $M_r = 677{\cdot}66$, triclinic, $P\bar{1}$, $a = 10{\cdot}959$ (2), $b = 14{\cdot}116$ (2), $c = 11{\cdot}418$ (2) Å, $\alpha = 73{\cdot}62$ (1), $\beta = 92{\cdot}27$ (1), $\gamma = 91{\cdot}71$ (1)°, $V = 1693{\cdot}0$ (5) Å^3, $Z = 2$, $D_x = 1{\cdot}33$ g cm^{-3}, λ(Cu $K\alpha$) = 1·54184 Å, μ(Cu $K\alpha$) = 7·35 cm^{-1}, $F(000) = 716$, $T = 293$ K, $R = 0{\cdot}054$ for 2499 observed reflections. The structure of the first gossypol lattice inclusion compound with host:guest molecular ratio of 2:3 is presented. The host molecules form centrosymmetric dimers, typical for gossypol, *via* a pair of O(5)—H···O(3) hydrogen bonds. The guest molecules are enclosed in two different types of centrosymmetric cages. In cage *T*1 the guest molecule is statistically disordered and can adopt four different orientations in which it is hydrogen bonded to the O(8)—H hydroxyl of gossypol. Cage *T*2 accommodates two benzaldehyde molecules related by a symmetry center. These guest molecules are hydrogen bonded to the gossypol O(1)—H hydroxyl groups.

Introduction. Gossypol [1,1′,6,6′,7,7′-hexahydroxy-5,5′-diisopropyl-3,3′-dimethyl(2,2′-binaphthalene)-8,8′-dicarboxaldehyde], a physiologically active diesquiterpene localized mainly in cotton seed kernels, shows remarkable inclusion ability towards a number of chemically different guest substrates.

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