139. The Crystal and Molecular Structure of Hydroxybenzylpindolol[1])

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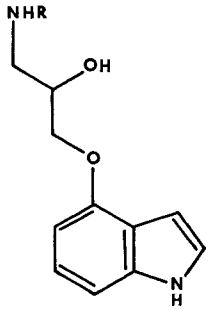
Kristalline und molekulare Struktur von Hydroxybenzylpindolol

Zusammenfassung

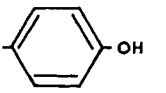
Im Zusammenhang mit einer Studie über die Konformation von adrenergen β-Blockern wurde die kristalline Struktur von Hydroxybenzylpindolol durch Röntgenanalyse bestimmt. Die Kristalle sind triklin, Raumgruppe $P\bar{1}$, $a = 10{,}041(2)$, $b = 11{,}386(2)$, $c = 10{,}131(2)$ Å, $\alpha = 114{,}03(2)$, $\beta = 107{,}82(3)$, $\gamma = 99{,}32(3)°$, mit zwei Molekeln pro Zelle. Die Struktur wurde nach dem «Multisolution»-Prinzip gelöst und bis zu $R = 0{,}050$ verfeinert. Die Molekeln sind im Kristall durch ein Netz von Wasserstoffbrücken miteinander verbunden.

Hydroxybenzylpindolol, **2**, a derivative of pindolol (*Visken*®) [1], **1**, is a specific and highly potent β-adrenergic antagonist [2] with pronounced intrinsic activity [3]. ^{125}I-labelled hydroxybenzylpindolol has proved useful in studying interactions with β-adrenergic receptors in both cell fragments [4–7] and in intact [8] cells.



1 R = $CH(CH_3)_2$

Pindolol

2 R = $C(CH_3)_2-CH_2$ –  – OH

Hydroxybenzylpindolol

Crystal Data. – Hydroxybenzylpindolol, **2**, $C_{21}H_{26}N_2O_3$, $M = 354.45$, colourless prisms grown from a solution of methanol/ether, triclinic, space group $P\bar{1}$, $a = 10.041(2)$, $b = 11.386(2)$, $c = 10.131(2)$ Å, $\alpha = 114.03(3)$, $\beta = 107.82(3)$, $\gamma = 99.32(3)°$, $V = 951$ Å^3, $Z = 2$, $d_{calc} = 1.12$ g cm^{-3}, $d_{exp} = 1.12(2)$ g cm^{-3} (by flotation in chlorocyclohexane/bromocyclohexane), linear absorption coefficient for Cu$K\alpha$, $\mu = 6.1$ cm^{-1}.

Intensity Data. – Intensity profiles of reflexions were measured by the normal-beam equatorial method on a CAD-4F-diffractometer with Cu$K\alpha$ radiation (graphite monochromator, $\bar{\lambda} = 1.542$ Å),

[1]) Trivial name for 1-(1-*p*-hydroxyphenyl-2-methyl-2-propylamino)-3-(4-indoloxy)-2-propanol.

($\omega/2\theta$)-scan mode, scan width $\Delta\omega = 0.7° + 0.3 \operatorname{tg}\theta$, scan time adjusted so as to maintain a constant ratio $\sigma(I)/I = 0.02$ (maximum scan time limited to 120 sec.) The net intensity, I, and statistical variance, $V(I)$, of a reflexion were evaluated from profile analysis using *Diamond's* method [9]. The variance, based on *Poisson* statistics, was increased by an empirical intensity dependent contribution, c^2I^2, (with $c = 0.2$), to obtain an experimental standard deviation $\sigma(I) = \{V(I) + c^2I^2\}^{1/2}$.

Throughout the data collection intensity and orientation checks were made, whereby no measurable deterioration of the crystal was observed. 3324 unique reflections within $\theta \leqslant 65°$ were measured, of which 2057 reflexions were judged to be significant [$I \geqslant 2.5\sigma(I)$]. Data reduction by *Wilson's* method yielded $\bar{B} = 3.2$ Å^2, $\langle |E| \rangle = 0.749$, $\langle |E^2 - 1| \rangle = 1.089$, $\langle |E|^2 \rangle = 1.012$. Intensities were not corrected for absorption (maximal error about 4%).

Structure Solution and Refinement. – The structure was solved by the multi-solution method [10]. The signs of nine reflexions – three of which were fixed to define an origin, six were varied – were expanded to 309 E-values ($E \geqslant 1.3$) by use of about 7700 triple relations. The E-map calculated with the set of phases with the fourth best figure of merit gave the complete structure.

Block-diagonal least squares procedures were used to refine the structure. After initial refinement of atomic positions and isotropic temperature factors, the set of parameters was successively extended to include anisotropic vibrational parameters for the heavier atoms, hydrogen atoms with isotropic temperature factors, and an isotropic extinction correction parameter, G, [11]. Hydrogen positions were taken from difference electron density maps. Special attention was paid to the positions of hydroxyl and amino hydrogen atoms, as these were crucial to the assignment of the donor/acceptor role in the *inter*molecular hydrogen bonds (see below). The weighting scheme proposed by *Dunitz & Seiler* [12] was used in the LS-calculation,

$\omega_h = (1/(\sigma_F^2)) \exp.\{8\pi^2 q/p(q+p) \cdot \sin^2\theta/\lambda^2\}$ with $p = 5$ Å^{-2}, $q = 7$ Å^{-2}, and $\sigma_F = (\sigma_F 2/2F_\sigma)$,

for significant reflexions ($\omega_h = 0$ for insignificant reflexions).

At convergence of all 328 structural parameters the discrepancy factors were $R = 0.050$, $R_\omega =$

Table 1. *Coordinates and e.s.d.'s.* The values for C, N, O have been multiplied by 10^5, those for H by 10^4

N(1)	71804(32)	33341(28)	20562(28)	H(1)	7570(44)	3191(40)	1262(47)
C(2)	61466(41)	24351(32)	21024(35)	H(2)	5515(57)	1531(51)	1105(60)
C(3)	60218(35)	30054(29)	34947(31)	H(3)	5439(48)	2613(43)	3791(50)
C(3A)	70792(29)	43476(25)	44142(29)	H(5)	9134(35)	7352(32)	7637(37)
C(4)	75596(27)	54220(24)	59839(26)	H(6)	10071(40)	7559(36)	5977(42)
C(5)	87108(29)	65809(27)	65110(30)	H(7)	9310(42)	5734(39)	3095(45)
C(6)	93727(33)	67064(32)	55282(37)	H(9X)	7365(38)	7105(35)	8549(41)
C(7)	89327(34)	57049(32)	39928(36)	H(9Y)	8467(62)	6351(56)	9024(65)
C(7A)	77896(30)	45194(27)	34780(30)	H(10)	5436(40)	5703(40)	8650(40)
O(8)	68402(21)	51979(18)	68488(20)	H(11X)	7919(43)	7361(38)	11300(45)
C(9)	73870(30)	62502(26)	84442(31)	H(11Y)	6684(50)	7838(45)	10637(52)
C(10)	64681(27)	59460(22)	92658(28)	H(14X)	5826(47)	8517(42)	15103(50)
O(10)	66698(20)	48148(17)	95098(20)	H(14Y)	4843(54)	7127(48)	13571(56)
C(11)	69608(29)	72093(24)	108528(29)	H(14Z)	6309(43)	7356(40)	14475(46)
N(12)	62611(21)	69849(19)	118419(22)	H(15X)	5384(44)	9771(40)	13513(47)
C(13)	63966(24)	82463(22)	132300(25)	H(15Y)	5746(55)	9284(49)	12080(58)
C(14)	57998(28)	77632(27)	142027(29)	H(15Z)	4431(63)	8274(56)	11914(67)
C(15)	54218(30)	89788(27)	126232(31)	H(16X)	8613(45)	8706(40)	14400(47)
C(16)	80301(25)	91959(23)	142402(26)	H(16Y)	8384(40)	9561(36)	13607(42)
C(17)	82943(23)	103939(22)	157914(25)	H(18)	8655(52)	9419(46)	17140(54)
C(18)	86384(29)	103060(25)	171791(29)	H(19)	9053(47)	11327(43)	19657(50)
C(19)	87757(29)	113644(26)	185775(28)	H(21)	8096(45)	13466(40)	17230(47)
C(20)	85826(26)	125653(24)	186226(27)	H(22)	7928(40)	11732(35)	14969(41)
O(20)	86721(22)	135691(20)	200041(21)	H(O10)	5729(40)	4140(40)	9120(40)
C(21)	83045(28)	126972(24)	172701(29)	H(N12)	6689(50)	6590(50)	12259(40)
C(22)	81525(26)	116192(23)	158742(27)	H(O20)	8180(40)	14089(40)	19769(40)

0.074[2]). The atomic scattering factors used in the structure factor calculations were taken from Vol. III of the 'International Tables of Crystallography' (1962). A complete listing of structure factors and parameters of the final LS-cycle can can be obtained from the authors:

Results. – Coordinates and e.s.d.'s are given in *Table 1*, the numbering of atoms is shown in *Fig. 1*. The mean positional errors around 0.003 Å for C, 0.002 Å for N and O, and 0.05 Å for H. All bond lengths and bond angles are close to 'normal' values (see *e.g.* '*Molecular Structure and Dimensions*', Vol. A1 (1972)). The stereoscopic projection (*Fig. 2*) shows the molecular conformation with the chain from C(4) to C(13) extended and approximately coplanar to the aromatic ring (see also torsion angles in *Fig. 1*).

In *Figure 3*, a schematic representation of the *inter*molecular hydrogen bonds with distances and angles is given. The secondary amino group, N(12) functions only as acceptor in a hydrogen bond, but has no donor role. The packing diagram (*Fig. 4*) shows part of the intermolecular network of hydrogen bonds (the H-bond O(20) ... H–N(1) is not visible in this projection).

Discussion. – A knowledge of the preferred conformation of the side chain of β-blocking agents of the pindolol type would be very valuable in elucidating structure-activity relationships. One way of obtaining this information is to determine the solid-state conformation of some β-blockers by X-ray analysis and to draw inferences about the conformation in solution. Up to now the crystal structures of propanolol [13], of pindolol [14] and of the present compound have been investigated. In all three crystal structures the side chain is in an extended conformation approximately

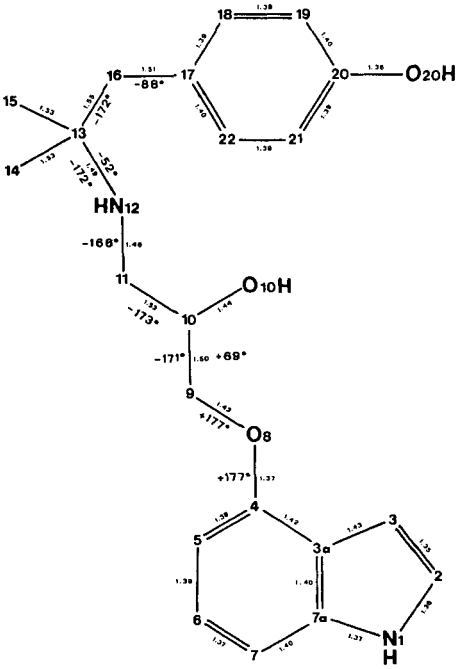


Fig. 1. *Numbering of atoms.* Bonds lengths (average e.s.d. 0.01 Å) and some relevant torsion angles (average e.s.d. 1°) are indicated

[2]) $R = \sum_h ||F_o| - k|G|\,||F_c||\,/\sum_h F_o$ $\qquad R_w = \sum_h \omega_h (F_o - k|G|\,|F_c|)^2 / \sum_h \omega_h F_o^2$

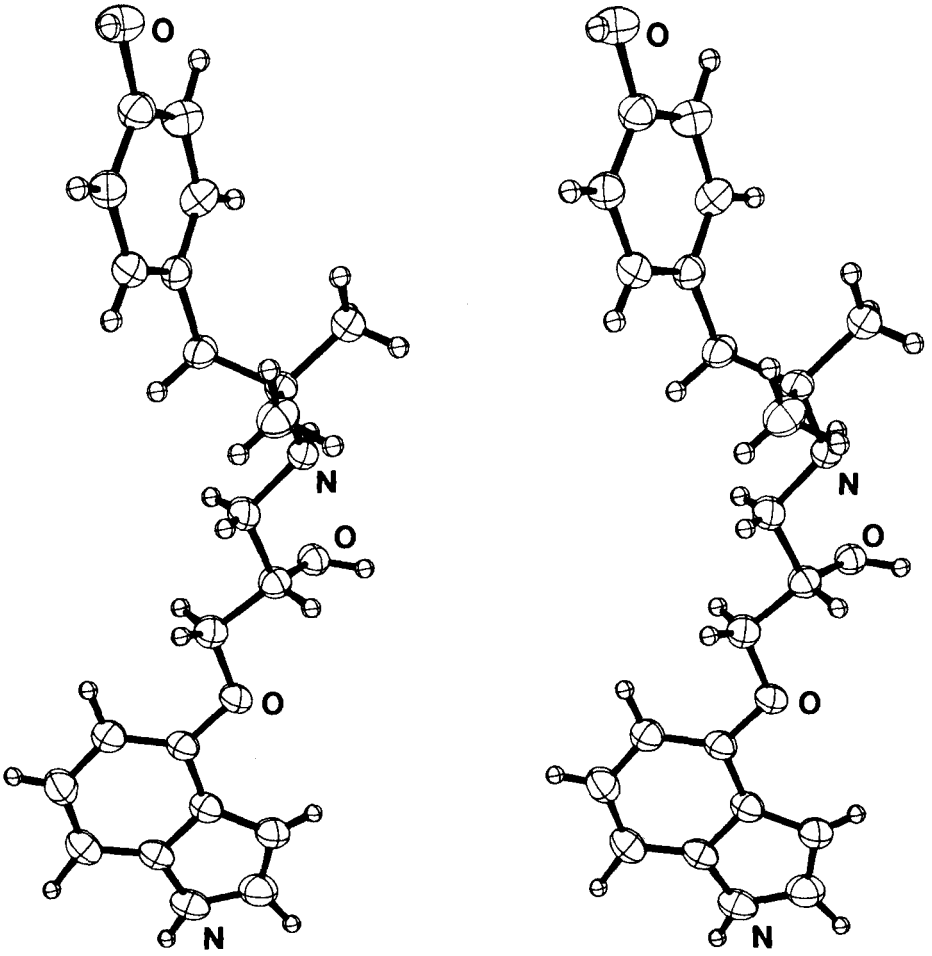


Fig. 2. *Stereoscopic view of the molecule.* The C, N and O atoms are drawn with 50% probability ellipsoids of thermal motion, while H-atoms are uniformly represented by spheres with radius corresponding to $B = 1$ Å^2

coplanar with the aromatic system (see *Figs. 1* and *2*). This threefold observation of the same conformation in the solid state is a strong argument for postulating the extended conformation as the preferred conformation of the β-blocker side chain. However, in all three crystal structures both the amino- and hydroxyl groups of the side chain are engaged in *inter*molecular hydrogen bonds, *i.e.* strong packing forces are involved. As far as *intra*molecular forces are concerned, the ether oxygen, O(8) should stabilize the position of C(9) in the aromatic plane, because of interaction of the oxygen lone pair electrons with the aromatic π-electrons. Steric hindrance between C(9) and the C(3) hydrogen should lead to C(9) being *cis* to C(5) rather than *trans*. The antiperiplanar conformation of the remainder of the side chain is certainly energetically favoured; we cannot, however, exclude *synclinal* partial conformations around C(9)–C(10) and/or C(10)–C(11), which might result in other, more favoured chain conformations in solution.

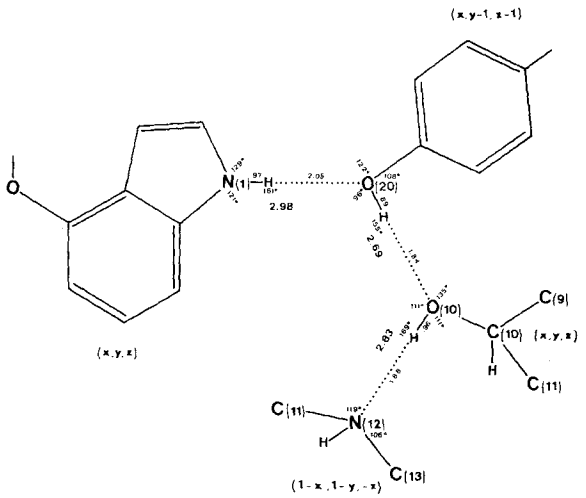


Fig. 3. *Schematic drawing of the network of hydrogen bonds in the crystal.* Distances and angles involving hydrogen atoms have e.s.d.'s of about 0.05 Å, and 4°, resp.

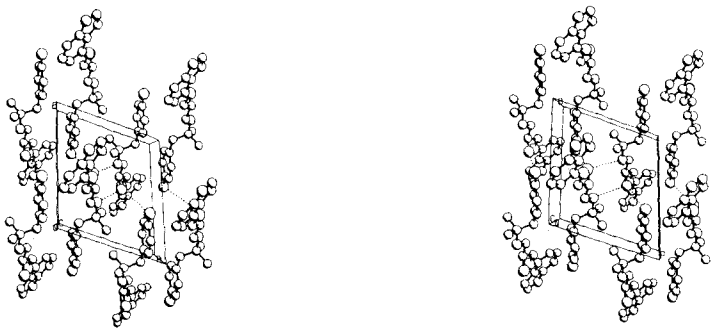


Fig. 4. *Stereoscopic packing diagram viewed along* c. The dashed lines indicate hydrogen bonds (the hydrogen bond O(20)...H – N(1) is not visible in this projection).

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