O(4) of molecule (II) $[\mathrm{H(O)_I\cdots O(4)_{II}} = 1{\cdot}87$ Å] and O(3) of molecule (II) to O(4) of another molecule (I) $[\mathrm{H(O)_{II}\cdots O(4)_I} = 1{\cdot}86$ Å], related to the first by the lattice centring. The zigzag chains near $z = \frac{1}{4}$ extend parallel to one *ab* cell diagonal, and near $z = \frac{3}{4}$ they are parallel to the other *ab* diagonal. There are no other intermolecular contacts shorter than the corresponding van der Waals distances.

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Structure of 2-(2-Hydroxy-3-{[2-(1*H*-indol-3-yl)-1,1-dimethylethyl]amino}propoxy)benzonitrile: MJ-13,105-1 (Bucindolol), $C_{22}H_{25}N_3O_2$

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Abstract. $\beta_1 + \beta_2$-adrenoceptor blocking agent. Antihypertensive. $M_r = 363{\cdot}4$, triclinic, $P\bar{1}$, $a = 8{\cdot}801$ (1), $b = 8{\cdot}883$ (2), $c = 13{\cdot}662$ (1) Å, $\alpha = 99{\cdot}79$ (1), $\beta = 92{\cdot}22$ (1), $\gamma = 105{\cdot}43$ (1)°, $V = 1010{\cdot}6$ (4) Å^3, $Z = 2$, $D_x = 1{\cdot}19$ g cm^{-3}, $\lambda(\mathrm{Cu}\ K\bar{\alpha}) = 1{\cdot}54178$ Å, $\mu = 12{\cdot}6$ cm^{-1}, $F(000) = 388$, room temperature. Final $R = 0{\cdot}035$ for 1938 reflections. The conformation is compared with a previous model of aryloxypropanolamine β-blockers and with some pentacyclic alkaloids of the yohimbine series. N—H···O and O—H···N hydrogen bonds contribute to the crystalline cohesion.

Introduction. In the course of determining structure–activity relationships in antihypertensive drugs, bucindolol has attracted our attention. This drug belongs to a series of antihypertensive indole derivatives of phenoxypropanolamines with β-adrenergic receptor antagonism and vasodilating activity (Kreighbaum, Matier, Dennis, Minielli, Deitchman, Perhach & Comer, 1980). In anaesthetized dogs, bucindolol antagonizes β_1 and β_2 adrenoceptors approximately equally and with a potency similar to that of propranolol (Deitchman, Perhach & Snyder, 1980). Part, but not all, of the vasodilator effect of bucindolol is due to α_1-adrenoceptor blockade (Deitchman *et al.*, 1980).

Experimental. White elongated prisms (from ethanol), 0·42 × 0·17 × 0·17 mm, Enraf–Nonius CAD-4 diffractometer with graphite monochromator, Cu $K\bar{\alpha}$, 25 reflections ($5 < \theta < 40°$) used to refine orientation matrix, no systematic absences, 2541 ($\pm h$, $\pm k$, l) independent reflections with $\theta < 55°$, h from −9 to +9, k from −9 to +9, l from 0 to +15, 1938 with $I \geq 3\sigma(I)$, Lp correction, absorption ignored; two check reflections ($1\bar{2}0$, 300) every 3600 s showed no unusual variation (all within $\pm 3\sigma$); direct methods [*MULTAN* (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978)], anisotropic diagonal matrix, refinement on F using observed reflections and weight w with $w = 1$ if $|F_o| < P$, $P = (F_{o\,\max}^2/10)^{1/2}$, $w = (P/F_o)^2$ if $|F_o| > P$, H from ΔF synthesis, isotropic, $R = 0{\cdot}035$, $wR = 0{\cdot}029$, $S = 0{\cdot}612$ (1938 reflections, 344 parameters), maximum peak $\pm 0{\cdot}3$ e Å^{-3} in final ΔF

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map, $(\Delta/\sigma)_{\max} = 0{\cdot}6$, H-atom form factors from Stewart, Davidson & Simpson (1965), all other form factors from *International Tables for X-ray Crystallography* (1974), IRIS 80, CII, computer of the 'Centre Interuniversitaire de Calcul' (Talence).*

Discussion. The atomic coordinates of non-hydrogen atoms listed in Table 1 correspond to the *S* configuration. According to previous results obtained on several aryloxypropanolamines (Dukes & Smith, 1971), the *S* configuration is that of the (–) isomer. Fig. 1 shows the atom numbering.

Interatomic distances and angles listed in Table 2 have the expected values. As in all aryloxypropanolamines previously described (Léger, 1979; Léger, Carpy, Hickel & Laguerre, 1981; Léger, Carpy & Colleter, 1981; Léger, Colleter & Carpy, 1982), one notices a shortening of the bond distances around the ether oxygen suggesting the existence of a potential ring which allows comparison of aryloxypropanolamines with phenylethanolamines having the same pharmacological activity.

The conformation of the oxypropanolamine chain is defined by the following torsion angles (± 1°):

$\tau_1 = \mathrm{C(2)-C(1)-O(12)-C(13)}$ –6
$\tau_2 = \mathrm{C(1)-O(12)-C(13)-C(14)}$ 178
$\tau_3 = \mathrm{O(12)-C(13)-C(14)-C(16)}$ 63
$\tau_4 = \mathrm{C(13)-C(14)-C(16)-N(17)}$ 182

These four values indicate that (–)-bucindolol is in the *A* conformation as defined by Léger, Gadret & Carpy (1980).

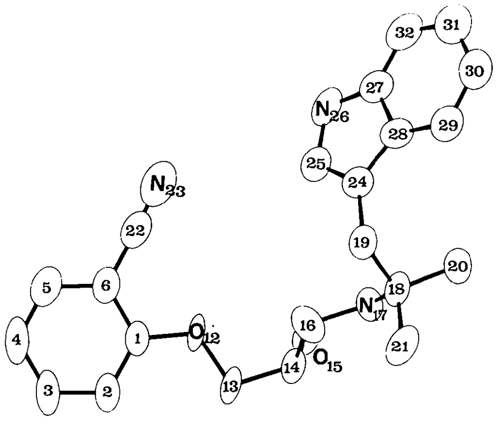

Fig. 1. Perspective view of the molecule showing the numbering of atoms.

Table 1. *Atomic coordinates* $(\times 10^4)$ *and* B_{eq} *values*

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

	x	y	z	$B_{\rm eq}$(Å^2)
C(1)	1389 (2)	2852 (3)	6784 (2)	3·9 (1)
C(2)	1541 (3)	1834 (3)	5927 (2)	4·6 (1)
C(3)	1690 (3)	2384 (3)	5035 (2)	5·5 (1)
C(4)	1712 (4)	3907 (4)	4986 (2)	6·3 (1)
C(5)	1537 (3)	4923 (3)	5829 (2)	5·7 (1)
C(6)	1355 (3)	4396 (3)	6732 (2)	4·2 (1)
O(12)	1261 (2)	2461 (2)	7700 (1)	4·5 (1)
C(13)	1436 (3)	948 (3)	7834 (2)	4·4 (1)
C(14)	1191 (3)	822 (3)	8908 (2)	4·0 (1)
O(15)	–336 (2)	957 (2)	9124 (1)	4·1 (1)
C(16)	2434 (3)	2082 (3)	9609 (2)	5·2 (1)
N(17)	2163 (2)	1981 (2)	10662 (1)	4·1 (1)
C(18)	3604 (3)	2547 (3)	11380 (2)	3·9 (1)
C(19)	4560 (2)	4263 (3)	11350 (2)	4·0 (1)
C(20)	2989 (3)	2435 (3)	12402 (2)	5·0 (1)
C(21)	4665 (3)	1447 (3)	11151 (2)	5·6 (1)
C(22)	1120 (3)	5439 (3)	7598 (2)	5·0 (1)
N(23)	927 (3)	6310 (3)	8269 (2)	7·4 (1)
C(24)	3729 (2)	5526 (2)	11635 (2)	3·8 (1)
C(25)	2778 (3)	6040 (3)	11032 (2)	4·5 (1)
N(26)	2211 (2)	7188 (2)	11571 (2)	5·1 (1)
C(27)	2789 (3)	7435 (3)	12550 (2)	4·5 (1)
C(28)	3750 (2)	6412 (2)	12617 (2)	3·9 (1)
C(29)	4494 (3)	6452 (3)	13548 (2)	4·6 (1)
C(30)	4259 (3)	7478 (3)	14369 (2)	5·5 (1)
C(31)	3289 (3)	8477 (3)	14276 (2)	6·0 (1)
C(32)	2543 (3)	8467 (3)	13377 (2)	5·4 (1)

Table 2. *Bond distances* (Å) *and angles* (°)

C(1)–C(2)	1·387 (4)	C(18)–C(20)	1·525 (4)
C(1)–C(6)	1·394 (4)	C(18)–C(21)	1·525 (4)
C(1)–O(12)	1·356 (3)	C(19)–C(24)	1·501 (4)
C(2)–C(3)	1·386 (4)	C(22)–N(23)	1·144 (4)
C(3)–C(4)	1·361 (5)	C(24)–C(25)	1·366 (4)
C(4)–C(5)	1·378 (5)	C(24)–C(28)	1·433 (4)
C(5)–C(6)	1·393 (4)	C(25)–N(26)	1·369 (4)
C(6)–C(22)	1·431 (4)	N(26)–C(27)	1·373 (4)
O(12)–C(13)	1·433 (3)	C(27)–C(28)	1·407 (4)
C(13)–C(14)	1·510 (4)	C(27)–C(32)	1·391 (4)
C(14)–O(15)	1·419 (3)	C(28)–C(29)	1·399 (4)
C(14)–C(16)	1·506 (4)	C(29)–C(30)	1·379 (4)
C(16)–N(17)	1·481 (4)	C(30)–C(31)	1·402 (4)
N(17)–C(18)	1·491 (3)	C(31)–C(32)	1·367 (4)
C(18)–C(19)	1·542 (4)		
C(2)–C(1)–C(6)	119·7 (2)	C(19)–C(18)–C(20)	110·7 (2)
C(2)–C(1)–O(12)	124·7 (2)	C(19)–C(18)–C(21)	109·0 (2)
C(6)–C(1)–O(12)	115·6 (2)	C(20)–C(18)–C(21)	109·9 (2)
C(1)–C(2)–C(3)	119·2 (3)	C(18)–C(19)–C(24)	116·1 (2)
C(2)–C(3)–C(4)	121·4 (3)	C(6)–C(22)–N(23)	177·6 (3)
C(3)–C(4)–C(5)	119·9 (3)	C(19)–C(24)–C(25)	127·9 (2)
C(4)–C(5)–C(6)	120·0 (3)	C(19)–C(24)–C(28)	126·1 (2)
C(1)–C(6)–C(5)	119·7 (3)	C(25)–C(24)–C(28)	105·9 (2)
C(1)–C(6)–C(22)	120·5 (2)	C(24)–C(25)–N(26)	110·6 (2)
C(5)–C(6)–C(22)	119·8 (3)	C(25)–N(26)–C(27)	108·6 (2)
C(1)–O(12)–C(13)	119·0 (2)	N(26)–C(27)–C(28)	107·6 (2)
O(12)–C(13)–C(14)	107·3 (2)	N(26)–C(27)–C(32)	130·1 (3)
C(13)–C(14)–O(15)	110·0 (2)	C(28)–C(27)–C(32)	122·3 (3)
C(13)–C(14)–C(16)	111·3 (2)	C(24)–C(28)–C(27)	107·3 (2)
O(15)–C(14)–C(16)	109·8 (2)	C(24)–C(28)–C(29)	134·2 (2)
C(14)–C(16)–N(17)	111·1 (2)	C(27)–C(28)–C(29)	118·6 (2)
C(16)–N(17)–C(18)	115·7 (2)	C(28)–C(29)–C(30)	119·3 (3)
N(17)–C(18)–C(19)	112·6 (2)	C(29)–C(30)–C(31)	120·7 (3)
N(17)–C(18)–C(20)	105·0 (2)	C(30)–C(31)–C(32)	121·5 (3)
N(17)–C(18)–C(21)	109·5 (2)	C(27)–C(32)–C(31)	117·7 (3)
N(17)–C(18)–C(20)	105·0 (2)		
N(17)–C(18)–C(21)	109·5 (2)		

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* Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and least-squares planes have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39120 (20 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

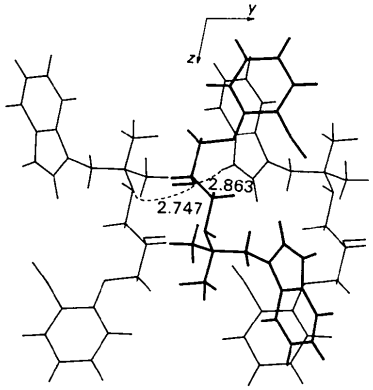

Fig. 2. Packing of the molecules projected along [100]. (Distances in Å.)

The centres which have most frequently been implicated in the interaction between β blockers and their adrenoceptors are the nitrogen which is first protonated in the salts, *i.e.* N(17), the alcoholic OH and the benzyl ring. Therefore, we have calculated the following distances: D_1, the distance between π [middle of C(1)—C(2)] and O(15); D_2, the distance between π and N(17); D_3, the distance between O(15) and N(17); D_4, the distance between O(15) and the plane of the benzyl ring; and D_5, the distance between N(17) and the plane of the benzyl ring [$D_1 = 4{\cdot}434$ (4), $D_2 = 5{\cdot}986$ (4), $D_3 = 2{\cdot}830$ (4), $D_4 = -1{\cdot}073$ (2), $D_5 = 1{\cdot}242$ (2) Å]. On the other hand, one may regard nitrogen N(17) and the indole nucleus as being responsible for binding on the α_1 adrenoceptor (remember that pentacyclic alkaloids of the yohimbine series which are α-adrenoceptor antagonists present such a nucleus). Therefore we have calculated the distance N(17)—φ(centre of the benzyl ring of the indole system) = 5·622 (5) Å, which is in good agreement with that found for yohimbine (Ambady & Kartha, 1973) or raubasine (Dubost, Léger, Goursolle, Colleter & Carpy, 1984).

The crystalline cohesion (Fig. 2) is strengthened by the hydrogen bonds O(15)···N(26)($\bar{x}$,1−y,2−z) = 2·863 (3) Å, N(26)—H(260) = 0·97 (3) Å, O(15)···H(260) = 1·90 (3) Å, O···H—N = 172 (2)° and O(15)···N(17)($\bar{x}$,$\bar{y}$,2−z) = 2·747 (3) Å, O(15)—H(150) = 1·07 (3) Å, N(17)···H(150) = 1·68 (3) Å, O—H···N = 173 (2)°.

Bucindolol is manufactured by Mead Johnson Pharmaceuticals, Evansville, Indiana (USA). The sample was kindly provided by Laboratoires Allard, Marne-la-Vallée (France).

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