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Structure of an Anti-Arrhythmic and Hypotensive Agent: 1-[2-Hydroxy-3-(4-phenyl-1-piperazinyl)propyl]pyrrolidin-2-one

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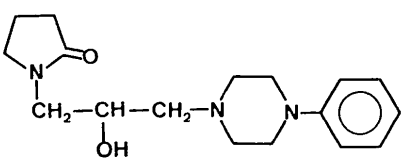
Abstract

$C_{17}H_{25}N_3O_2$, $M_r = 303{\cdot}41$, m.p. 374–376 K, monoclinic, *Cc* (C_s^4), $a = 18{\cdot}141\ (3)$, $b = 6{\cdot}4878\ (4)$, $c = 29{\cdot}528\ (3)$ Å, $\beta = 107{\cdot}2\ (1)°$, $V = 3321\ (2)$ Å^3, $Z = 8$ (two independent molecules), $D_m = 1{\cdot}203\ (3)$, $D_x = 1{\cdot}214\ (1)$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, $\mu = 0{\cdot}610$ mm^{-1}, $F(000) = 1312$, $T = 295$ K, $R = 0{\cdot}0355$ for 3096 unique observed reflections [$|F_o| \geq 3\sigma(F)$]. The conformation of the two independent molecules, (I) and (II), differs significantly about the torsion angles N(1)—C(6)—C(7)—C(8), N(1)—C(6)—C(7)—O(7), C(6)—C(7)—C(8)—N(9) and O(7)—C(7)—C(8)—N(9) [(I): 169·1 (3), −67·4 (4), −61·3 (4), 173·7 (3)°; (II): 57·4 (5), 66·2 (4), 175·3 (3), 54·2 (5)°]. A relatively strong intermolecular hydrogen bond [OH···O distance 2·712 (2) Å] was found between two molecules of type (I) related by *b*. A weaker hydrogen bond, distance 2·826 (4) Å, between the OH groups of molecule (II) (donor) and molecule (I) (acceptor) is approximately directed along *a*. The compound shows anti-arrhythmic and hypotensive activity and is the subject of routine pharmacological tests.

Introduction

2-Pyrrolidinone and its derivatives are well known for the variety of their biological activity. They include widely used drugs which affect the central nervous system through their nootropic, antidepressant or analeptic activity. Some derivatives influence the cardiovascular system, *e.g.* hypotension, improvement of coronary flow or thrombocyte aggregation, have all been observed. The alkyl-, aryl- and *N*-methylamine derivatives of 2-pyrrolidinone have been found to possess analgesic and anti-inflammatory properties (Malawska, Gorczyca, Chojnacka-Wójcik & Tatarczyńska, 1982).

Recently, a new series of *N*-(β-hydroxy-γ-aminopropyl)-2-pyrrolidinones was reported to have an effect on the circulatory system (Malawska, Gorczyca, Cebo & Krupińska, 1988). Hypotensive and anti-arrhythmic properties were detected for a number of these derivatives. The title compound, for which a structural diagram is given below, falls within this class and therefore a structure analysis was undertaken in order to investigate the geometrical features of the molecule, including the shape of its aminoalcohol chain, which seem to be common to both broad groups into which Szekeres & Papp (1971) divided anti-arrhythmics, *i.e.* non-specific drugs such as quinidine and specific drugs, especially β-adrenolytics, such as propranolol.



Experimental

The title compound was obtained in the course of a study of new *N*-aminoalkyl-2-pyrrolidinone derivatives from aminolysis of 1-(β,γ-epoxypropyl)-2-pyrrolidinone and *N*-phenylpiperazine (Malawska, Gorczyca, Filipek, Cros, Liutkus & Serrano, 1990). Crystals suitable for X-ray analysis were obtained from a mixture of tetrahydrofuran and cyclohexane. The crystal structure was successfully solved by direct methods (*SHELXS*86; Sheldrick, 1985) in space group *Cc* (C_s^4). R_{int} and R_{sigma} for merged Friedel pairs were 0·047 and 0·013, respectively. No

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Table 1. *Summary of data collection and structure refinement*

Crystal shape and size (mm)	Colourless prisms 0·40 × 0·37 × 0·28
Method of measuring D_m	Flotation in nitrobenzene
Diffractometer	Enraf–Nonius CAD-4 (graphite-monochromated Cu $K\alpha$ radiation)
Lattice-parameter measurement	
θ range (°), number of reflections	$12 \le \theta \le 27$, 25
Intensity measurement	
θ range (°)	$2 \le \theta \le 73$
Indices range	$-22 \le h \le 22$, $-8 \le k \le 0$, $-36 \le l \le 0$
Scan width (°) and mode	$0{\cdot}60 + 0{\cdot}20\tan\theta$, $\omega/2\theta$
Intensity control reflections	$00\bar{8}$, $\bar{2}2\bar{4}$ measured every hour
Changes in intensity (%)	< 2·4
Number of reflections measured	3191
Criterion for observed reflections	$\lvert F_o\rvert \ge 3\sigma(F_o)$
Number of observed unique reflections	3096
Corrections applied	Lorentz, polarization effects
Extinction reflections omitted	$40\bar{4}$, $\bar{2}0\bar{4}$, $11\bar{4}$, $11\bar{5}$
Refinement method	Full-matrix least squares on F_o
Parameters refined	596
Non-H atoms	Positional and anisotropic thermal
H atoms*	Positional and isotropic thermal
Weighting scheme	$w = k[\sigma^2(F_o) + gF_o^2]^{-1}$
k and g converged to	1·000, 0·00173
R, wR, S	0·0355, 0·0528, 1·135
Average, max. Δ/σ	
Non-H atoms	0·03, 0·11
H atoms	0·05, 0·83
Max., min. heights in final difference Fourier map (e Å^{-3})	0·13, −0·10

* Initial positional parameters of H atoms from the difference Fourier map.

Table 2. *Atomic coordinates* ($\times 10^4$) *and equivalent isotropic displacement parameters* (Å$^2 \times 10^4$) *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}
Molecule (I)				
N(1)	3701 (1)	2146 (2)	606 (1)	487 (3)
C(2)	3554 (1)	170 (2)	669 (1)	509 (3)
O(2)	3847 (1)	−806 (2)	1037 (1)	669 (3)
C(3)	2990 (1)	−642 (3)	221 (1)	686 (4)
C(4)	2936 (2)	1090 (4)	−137 (1)	1012 (4)
C(5)	3259 (1)	2969 (3)	145 (1)	619 (4)
C(6)	4206 (1)	3384 (2)	982 (1)	485 (3)
C(7)	3807 (1)	4093 (2)	1341 (1)	436 (3)
O(7)	3205 (1)	5523 (2)	1146 (1)	577 (3)
C(8)	4383 (1)	5025 (2)	1777 (1)	485 (3)
N(9)	4983 (1)	3613 (2)	2037 (1)	448 (3)
C(10)	5548 (1)	4728 (2)	2409 (1)	571 (4)
C(11)	4679 (1)	1938 (3)	2256 (1)	601 (4)
C(12)	6190 (1)	3356 (3)	2687 (1)	587 (4)
C(13)	5312 (1)	527 (3)	2537 (1)	625 (4)
N(14)	5895 (1)	1648 (2)	2897 (1)	489 (3)
C(15)	6426 (1)	514 (3)	3253 (1)	499 (4)
C(16)	7160 (1)	1280 (3)	3484 (1)	623 (4)
C(17)	7651 (1)	233 (4)	3865 (1)	718 (4)
C(18)	7441 (2)	−1601 (4)	4018 (1)	773 (4)
C(19)	6729 (2)	−2413 (4)	3783 (1)	786 (4)
C(20)	6222 (1)	−1386 (3)	3408 (1)	657 (4)
H(O7)	3400 (7)	6651 (8)	1085 (6)	890 (5)
Molecule (II)				
N(21)	349 (1)	3836 (3)	−213 (1)	711 (3)
C(22)	−89 (2)	2148 (4)	−326 (1)	825 (4)
O(22)	−557 (2)	1599 (4)	−132 (1)	1329 (5)
C(33)	116 (2)	1074 (4)	−724 (1)	998 (5)
C(24)	617 (2)	2606 (5)	−889 (1)	986 (4)
C(25)	841 (2)	4215 (4)	−513 (1)	860 (5)
C(26)	329 (1)	5226 (4)	174 (1)	829 (4)
C(27)	990 (1)	4927 (4)	626 (1)	750 (4)
O(27)	1681 (1)	5493 (3)	530 (1)	805 (4)
C(28)	1015 (2)	2736 (4)	807 (1)	794 (4)
N(29)	1679 (1)	2323 (3)	1220 (1)	693 (4)
C(30)	1613 (2)	3378 (3)	1645 (1)	727 (4)
C(31)	1740 (2)	109 (3)	1320 (1)	792 (4)
C(32)	2306 (1)	2943 (3)	2065 (1)	700 (4)
C(33)	2431 (2)	−395 (3)	1728 (1)	739 (4)
N(34)	2428 (1)	735 (2)	2156 (1)	646 (4)
C(35)	2958 (1)	116 (3)	2583 (1)	624 (4)
C(36)	3083 (1)	1275 (4)	2998 (1)	792 (4)
C(37)	3577 (2)	597 (4)	3423 (1)	905 (4)
C(38)	3970 (2)	−1255 (4)	3460 (1)	900 (4)
C(39)	3840 (2)	−2423 (4)	3058 (1)	879 (4)
C(40)	3352 (1)	−1773 (3)	2628 (1)	775 (4)
H(O27)	2085 (7)	5250 (8)	759 (6)	1062 (5)

reasonable solutions were found in space group $C2/c$. Scattering factors for neutral atoms were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV). Experimental data and the details of structure refinement using *SHELX*76 (Sheldrick, 1976) are summarized in Table 1. The final atomic coordinates and thermal parameters are given in Table 2.* Geometrical calculations were carried out with *PARST* (Nardelli, 1983) and the figures drawn with *ORTEP* (Johnson, 1965). No significant difference in R factors was found for a model of the anti-structure (*i.e.* the same space group Cc but with the atomic coordinates changed to $-x$, $-y$, $-z$: $R = 0{\cdot}0358$, $wR = 0{\cdot}0422$ and $R_G = 0{\cdot}0531$).

Discussion

The two symmetrically independent molecules, (I) and (II) (Fig. 1), have bond lengths and angles which are generally the same within the limits of experimental error (Table 3). Each of the molecules has an asymmetric carbon atom, C(7) or C(27), and, because of the space-group symmetry, both R and S configurations are present in the structure. The two molecules differ in conformation, especially with respect to the flexible chain part as can be seen from the selected torsion angles given in Table 4.

The conformation of the pyrrolidine five-membered ring of (I) is intermediate between an envelope and twist form with ring-puckering coordinates $q_2 = 0{\cdot}179$ (6) Å and $\varphi_2 = 115$ (2)°. A pseudo-mirror plane through C(4) and a pseudo-diad axis through C(2) were detected and have symmetry parameters [as defined by Nardelli (1983)] of 0·018 (3) and 0·019 (2), respectively. In (II) the analogous ring has a clear twist conformation: $q_2 = 0{\cdot}136$ (5) Å and $\varphi_2 = -86$ (2)°. A pseudo-diad axis through N(21) is observed with an asymmetry parameter of 0·005 (2). Another difference is that the C—O bond length is slightly longer for (I) because O(2) acts as an acceptor and forms a hydrogen bond. The configuration at the pyrrolidine N atom is planar in both molecules and its lone pair seems to

* Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and bond lengths, and least-squares-planes data have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 53575 (18 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

be involved in N(1)—C(2) or N(21)—C(22) bonding; these bonds are thus shorter than the neighbouring N—C bonds.

The piperazine rings of both molecules have the usual chair conformation with puckering coordinates $q_2 \simeq 0$, $q_3 \simeq \pm QT$ and $\theta_2 \simeq 180°$. The values are 0·026 (4), −0·555 (4), 0·556 (4) Å and 177·3 (4)°, respectively, for (I) and 0·067 (5), −0·551 (5), 0·555 (6) Å and 173·1 (5)° for (II). The asymmetry parameters for the pseudo-mirror planes through the N atoms are 0·004 (2) for (I) and 0·001 (3) for (II). The lone pair of N(14), or N(34), interacts with the π system of the aromatic ring leading to shortening of N(14)—C(15), or N(34)—C(35), and a decrease in the bond angles C(16)—C(15)—C(20), or C(36)—C(35)—C(40). The phenyl ring is planar with atoms deviating from the best least-squares plane by between 0·011 (5) and −0·013 (4) Å for (I) and by between 0·009 (6) and −0·007 (6) Å for (II). The phenyl-ring plane is inclined at a similar angle to the mean piperazine plane for both molecules [(I) 7·0 (1), (II) 9·7 (2)°]. There is a big difference, however, in the angles between the phenyl plane and the mean pyrrolidine plane as well as between the piperazine and pyrrolidine mean planes [(I) 30·7 (2) and 26·3 (2)°, (II) 99·0 (2) and 105·6 (2)°, respectively]. The different conformations of molecule (I) and (II) and possibly the difference between their charge distributions can be seen as a consequence of the different hydrogen-bonding patterns. The hydroxyl group of (I) acts as a donor in a relatively strong hydrogen bond to the pyrrolidine oxygen of the molecule shifted along *b*: O(7)···O(2)(x, $y+1$, z) = 2·712 (2), O(7)—H(O7) = 0·85 (1), H(O7)···O(2) = 1·863 (8) Å, and O(7)—H(O7)···O(2) = 173 (2)°. The O(7) atom is an acceptor of hydrogen from the hydroxyl group of (II), which has the same configuration as (I): O(7)···O(27)(x, y, z) = 2·826 (4), O(7)···H(O27) = 2·02 (1), H(O27)—O(27) = 0·85 (1) Å, O(7)···H(O27)—O(27) = 156 (1)°. There are no other intermolecular contacts which are shorter than the sum of the appropriate van der Waals radii.

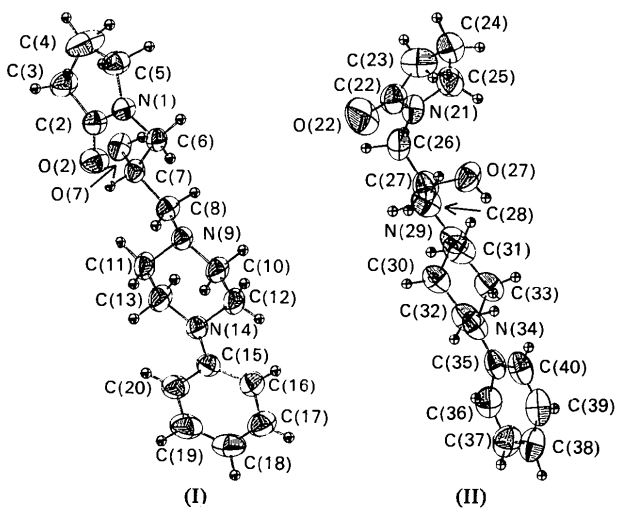

Fig. 1. Conformations of the two independent molecules, (I) and (II), both in the *R* configuration, shown with atom numbering. Thermal-vibration ellipsoids are scaled to enclose 50% probability.

Table 3. *Bond lengths* (Å) *and bond angles* (°) *with e.s.d.'s in parentheses*

Molecule (I)		Molecule (II)	
N(1)—C(2)	1·334 (2)	N(21)—C(22)	1·336 (3)
N(1)—C(5)	1·462 (4)	N(21)—C(25)	1·452 (5)
N(1)—C(6)	1·455 (3)	N(21)—C(26)	1·465 (4)
C(2)—O(2)	1·234 (3)	C(22)—O(22)	1·209 (5)
C(2)—C(3)	1·509 (3)	C(22)—C(23)	1·504 (5)
C(3)—C(4)	1·526 (4)	C(23)—C(24)	1·521 (5)
C(4)—C(5)	1·495 (3)	C(24)—C(25)	1·491 (4)
C(6)—C(7)	1·520 (4)	C(26)—C(27)	1·521 (3)
C(7)—O(7)	1·419 (2)	C(27)—O(27)	1·413 (3)
C(7)—C(8)	1·525 (3)	C(27)—C(28)	1·515 (4)
C(8)—N(9)	1·456 (3)	C(28)—N(29)	1·464 (4)
N(9)—C(10)	1·455 (3)	N(29)—C(30)	1·465 (4)
N(9)—C(11)	1·454 (3)	N(29)—C(31)	1·464 (3)
C(10)—C(12)	1·503 (3)	C(30)—C(32)	1·509 (4)
C(11)—C(13)	1·511 (3)	C(31)—C(33)	1·496 (4)
C(12)—N(14)	1·447 (3)	C(32)—N(34)	1·462 (2)
C(13)—N(14)	1·454 (3)	C(33)—N(34)	1·462 (4)
N(14)—C(15)	1·406 (3)	N(34)—C(35)	1·400 (3)
C(15)—C(16)	1·396 (3)	C(35)—C(36)	1·398 (4)
C(15)—C(20)	1·402 (3)	C(35)—C(40)	1·405 (3)
C(16)—C(17)	1·389 (3)	C(36)—C(37)	1·381 (4)
C(17)—C(18)	1·366 (4)	C(37)—C(38)	1·385 (4)
C(18)—C(19)	1·378 (5)	C(38)—C(39)	1·369 (4)
C(19)—C(20)	1·384 (4)	C(39)—C(40)	1·382 (4)
C(5)—N(1)—C(6)	123·9 (1)	C(25)—N(21)—C(26)	122·2 (3)
C(2)—N(1)—C(6)	122·1 (2)	C(22)—N(21)—C(26)	123·4 (3)
C(2)—N(1)—C(5)	113·8 (2)	C(22)—N(21)—C(25)	114·4 (3)
N(1)—C(2)—C(3)	109·0 (2)	N(21)—C(22)—C(23)	108·0 (3)
N(1)—C(2)—O(2)	124·3 (2)	N(21)—C(22)—O(22)	124·9 (3)
O(2)—C(2)—C(3)	126·7 (2)	O(22)—C(22)—C(23)	127·1 (3)
C(2)—C(3)—C(4)	103·8 (2)	C(22)—C(23)—C(24)	104·9 (3)
C(3)—C(4)—C(5)	106·3 (2)	C(23)—C(24)—C(25)	106·1 (3)
N(1)—C(5)—C(4)	103·8 (2)	N(21)—C(25)—C(24)	104·7 (3)
N(1)—C(6)—C(7)	112·1 (3)	N(21)—C(26)—C(27)	114·3 (3)
C(6)—C(7)—C(8)	111·1 (3)	C(26)—C(27)—C(28)	111·3 (3)
C(6)—C(7)—O(7)	112·5 (3)	C(26)—C(27)—O(27)	107·9 (3)
O(7)—C(7)—C(8)	109·7 (1)	O(27)—C(27)—C(28)	112·3 (4)
C(7)—C(8)—N(9)	114·6 (1)	C(27)—C(28)—N(29)	113·4 (3)
C(8)—N(9)—C(11)	112·5 (3)	C(28)—N(29)—C(31)	110·0 (3)
C(8)—N(9)—C(10)	109·6 (1)	C(28)—N(29)—C(30)	111·9 (3)
C(10)—N(9)—C(11)	108·1 (2)	C(30)—N(29)—C(31)	107·8 (3)
N(9)—C(10)—C(12)	112·2 (1)	N(29)—C(30)—C(32)	111·0 (3)
N(9)—C(11)—C(13)	111·8 (3)	N(29)—C(31)—C(33)	111·9 (2)
C(10)—C(12)—N(14)	111·3 (3)	C(30)—C(32)—N(34)	112·2 (3)
C(11)—C(13)—N(14)	111·7 (2)	C(31)—C(33)—N(34)	111·8 (3)
C(12)—N(14)—C(13)	110·5 (2)	C(32)—N(34)—C(33)	111·8 (2)
C(13)—N(14)—C(15)	118·4 (2)	C(33)—N(34)—C(35)	117·3 (2)
C(12)—N(14)—C(15)	117·6 (3)	C(32)—N(34)—C(35)	118·2 (2)
N(14)—C(15)—C(20)	121·0 (3)	N(34)—C(35)—C(40)	122·0 (3)
N(14)—C(15)—C(16)	121·6 (2)	N(34)—C(35)—C(36)	121·7 (2)
C(16)—C(15)—C(20)	117·3 (3)	C(36)—C(35)—C(40)	116·1 (3)
C(15)—C(16)—C(17)	120·9 (2)	C(35)—C(36)—C(37)	121·3 (3)
C(16)—C(17)—C(18)	121·3 (4)	C(36)—C(37)—C(38)	121·9 (3)
C(17)—C(18)—C(19)	118·5 (3)	C(37)—C(38)—C(39)	117·3 (3)
C(18)—C(19)—C(20)	121·5 (3)	C(38)—C(39)—C(40)	121·8 (3)
C(15)—C(20)—C(19)	120·5 (3)	C(35)—C(40)—C(39)	121·5 (2)

The packing of the molecules is shown in Fig. 2. As can be seen in the (010) projection, all molecules are oriented in such a way that their longest axis is approximately parallel to [101]. Molecules (I) and (II), having the same configuration and bound by hydrogen bonds, form columns parallel to [010]. Subsequent columns along [100] always contain mol-

Table 4. *Torsion angles* (°) *for molecules* (I) *and* (II), *both in the R conformation, with e.s.d.'s in parentheses*

Molecule (I)		Molecule (II)	
N(1)—C(2)—C(3)—C(4)	8·8 (4)	N(21)—C(22)—C(23)—C(24)	−11·0 (5)
C(2)—C(3)—C(4)—C(5)	−16·7 (4)	C(22)—C(23)—C(24)—C(25)	14·0 (5)
C(3)—C(4)—C(5)—N(1)	18·1 (4)	C(23)—C(24)—C(25)—N(21)	−11·9 (5)
C(2)—N(1)—C(5)—C(4)	−13·5 (5)	C(22)—N(21)—C(25)—C(24)	5·4 (5)
C(5)—N(1)—C(2)—C(3)	2·9 (5)	C(25)—N(21)—C(22)—C(23)	3·7 (5)
C(5)—N(1)—C(6)—C(7)	96·4 (4)	C(25)—N(21)—C(26)—C(27)	−80·3 (5)
C(2)—N(1)—C(6)—C(7)	−78·1 (5)	C(22)—N(21)—C(26)—C(27)	101·0 (5)
C(6)—N(1)—C(2)—O(2)	−2·9 (7)	C(26)—N(21)—C(22)—O(22)	1·6 (7)
N(1)—C(6)—C(7)—O(7)	−67·4 (4)	N(21)—C(26)—C(27)—O(27)	66·2 (4)
N(1)—C(6)—C(7)—C(8)	169·2 (3)	N(21)—C(26)—C(27)—C(28)	−57·4 (5)
C(6)—C(7)—C(8)—N(9)	−61·3 (4)	C(26)—C(27)—C(28)—N(29)	175·3 (3)
O(7)—C(7)—C(8)—N(9)	173·7 (3)	O(27)—C(27)—C(28)—N(29)	54·2 (5)
C(7)—C(8)—N(9)—C(10)	173·2 (3)	C(27)—C(28)—N(29)—C(30)	70·4 (5)
C(7)—C(8)—N(9)—C(11)	−66·5 (4)	C(27)—C(28)—N(29)—C(31)	−169·8 (4)
C(10)—N(9)—C(11)—C(13)	−57·0 (4)	C(30)—N(29)—C(31)—C(33)	−60·1 (5)
C(11)—N(9)—C(10)—C(12)	57·8 (4)	C(31)—N(29)—C(30)—C(32)	59·3 (4)
N(9)—C(10)—C(12)—N(14)	−57·7 (4)	N(29)—C(30)—C(32)—N(34)	−56·1 (5)
N(9)—C(11)—C(13)—N(14)	56·6 (4)	N(29)—C(31)—C(33)—N(34)	56·6 (5)
C(11)—C(13)—N(14)—C(12)	−54·0 (4)	C(31)—C(33)—N(34)—C(32)	−50·8 (5)
C(10)—C(12)—N(14)—C(13)	54·3 (4)	C(30)—C(32)—N(34)—C(33)	50·9 (5)
C(13)—N(14)—C(15)—C(16)	153·3 (4)	C(33)—N(34)—C(35)—C(36)	170·3 (4)
C(12)—N(14)—C(15)—C(16)	16·3 (6)	C(32)—N(34)—C(35)—C(36)	31·7 (6)
C(13)—N(14)—C(15)—C(20)	−30·3 (6)	C(33)—N(34)—C(35)—C(40)	−14·5 (6)
C(12)—N(14)—C(15)—C(20)	−167·3 (4)	C(32)—N(34)—C(35)—C(40)	−153·1 (4)
C(16)—C(15)—C(20)—C(19)	1·5 (6)	C(36)—C(35)—C(40)—C(39)	−0·7 (6)
C(20)—C(15)—C(16)—C(17)	−2·7 (6)	C(40)—C(35)—C(36)—C(37)	1·1 (6)
C(15)—C(16)—C(17)—C(18)	1·7 (6)	C(35)—C(36)—C(37)—C(38)	−0·1 (7)
C(16)—C(17)—C(18)—C(19)	0·6 (6)	C(36)—C(37)—C(38)—C(39)	−1·2 (7)
C(17)—C(18)—C(19)—C(20)	−1·8 (7)	C(37)—C(38)—C(39)—C(40)	1·6 (7)
C(18)—C(19)—C(20)—C(15)	0·7 (7)	C(38)—C(39)—C(40)—C(35)	−0·6 (7)

ecules of the same configuration, whereas in the [101] direction columns with the molecules of *R* configuration and those with the *S* configuration alternate. Between the columns there is only weak van der Waals interaction.

In order to understand the pharmacological activity of the compound it is illuminating to compare its aminoalcohol chain geometry with that shown by appropriate representatives of the anti-arrhythmics, belonging to class (I), (II) and (III) [according to the modified Vaughan Williams classification (Morganroth, 1985)], for which crystal data are available. At the same time, it is helpful to examine the spatial arrangement of the hydrophobic ring with respect to the positively charged N atom, as was demonstrated by Schwalbe & Scott (1979) from the point of the view of a receptor-pocket model. In our work the distance of this type of nitrogen atom from the π-system plane is introduced after Oleksyn (1987) and similar geometrical parameters are also calculated for the so-called 'helpful' heteroatom at a distance of *ca* 3 Å from the N atom. Results of the comparison are given in Table 5. The most important features concerning the geometry of the chosen anti-arrhythmics appear to be: the separation of the positively charged nitrogen and a 'helpful' heteroatom (*X*), their distance from a π-system plane and the N—C—C—*X* torsion angle. For example, azapropranolol was found to lack β-adrenolitic properties and, as shown in Table 5, its basic nitrogen and the other heteroatom distances from the π plane are far beyond the range observed for active compounds.

It can be seen that in the case of molecule (II), which is involved in only one hydrogen bond, a typical synclinal conformation of the N—C—C—O chain is observed and is accompanied by an N···O distance of 2·896 (4) Å, whereas the hydrogen bonds formed by molecule (I) in the crystal structure are connected with its antiperiplanar conformation. Such a conformation is also present in the lidocaine structure, Table 5(*g*), as a result of stretching caused by a bifurcated, combined intra- and intermolecular, hydrogen bond.

The presence of a hydrophobic phenyl ring was found to be essential for the pharmacological activity of the studied compound since replacement of the aryl ring by an alkyl group (methyl-, 2-hydroxyethyl-, benzyl-) gave inactive compounds (Malawska, Gorczyca, Cebo & Krupińska, 1988). If the phenyl ring is assumed to interact as a hydrophobic moiety with a receptor pocket and the piperazine N(9), or N(29) atom, can be considered as a basic nitrogen then the 'helpful' heteroatom should be the other piperazine nitrogen, N(14) or N(34). It is worth noticing that the geometry of the N—C—C—N fragment complies with the synclinal conformation of the β-aminoethanol chain and in addition the hydroxyl group outside this system is free to form a hydrogen bond by acting as a donor. For propranolol and quinidine the oxygen of the hydroxyl group plays the

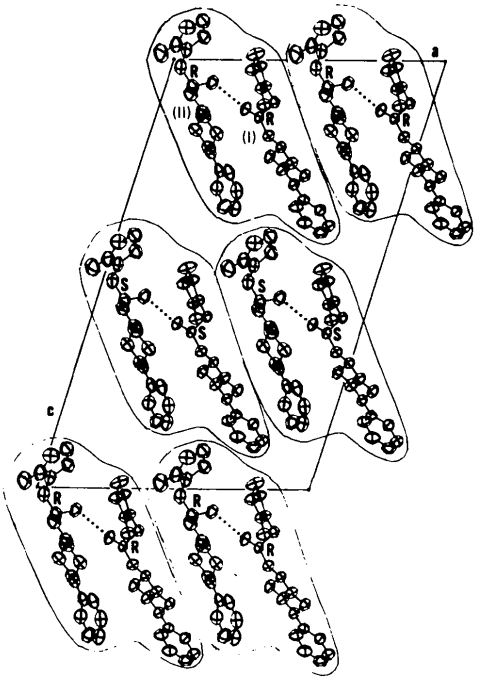

Fig. 2. Packing of the molecules shown in (010) projection. The H bonds between molecules (I) and (II) are marked by dotted lines. H bonds between molecules (I), related by *b*, are not shown for the sake of clarity.

Table 5. *Comparison of some geometrical parameters for chosen anti-arrhythmics, in various environments, from the point of view of a receptor-pocket model and β-aminoethanol chain conformation*

Reference	n_N	d_N (Å)	N···π (Å)	X	X···π (Å)	N···X (Å)	N—C—C—X (°)
Class (I*a*)							
Quinidine	3			OH			
(*a*)		6·39	1·74		−0·35	3·12	74·8
(*b*) (*A*)		6·46	2·03		−0·03	2·93	61·1
(*B*)		6·27	1·43		−0·47	3·17	80·8
(*c*)		6·46	−1·71		0·36	3·09	75·9
Procainamide				NH			
(*d*)		6·21	1·28		0·38	3·74	173·4
Class (I*b*)							
Lidocaine	4			=O			
(*e*)		7·47	−1·89		−2·02	2·68	13·0
(*f*)		7·49	−1·25		2·10	2·97	−49·8
(*g*) (*A*)		6·81	0·51		−2·13	3·59	177·0
(*B*)		6·78	0·53		−2·16	3·57	178·8
(*h*)		7·49	1·67		2·09	2·85	−31·8
	4			NH			
(*e*)		7·47	−1·89		0·04	3·66	−168·0
(*f*)		7·49	−1·25		0·04	3·56	131·4
(*g*) (*A*)		6·81	0·51		0·05	2·69	5·2*
(*B*)		6·78	0·53		0·04	2·66	−1·8*
(*h*)		7·49	1·67		0·04	3·63	−149·7
Class (II)							
Propranolol	5			OH			
(*i*)		8·21	1·67		0·40	2·84	50·4
(*j*)		8·76	0·01		1·42	3·07	−77·7
(*k*)		8·22	−1·11		0·42	2·92	65·8
Pindolol	5			OH			
(*l*)		8·77	−0·70		−1·80	2·82	60·7
Oxprenolol	5			OH			
(*m*)		8·17	−1·30		−0·76	2·78	55·3
Alprenolol	5			OH			
(*n*)		8·17	0·69		−0·39	2·95	−50·0
Class (III)							
Sotalol	3			OH (disordered)			
(*o*)		7·89	0·02		0·82	2·92	25·4
					0·99	2·87	−59·4
Inactive							
Azapropranolol	5			OH			
(*p*)		7·52	−3·14		−2·42	2·88	53·0
	5			NH			
					0·02	3·05	−71·9
This work	4						
Phenyl side				>N—			
(I)		7·08	−0·25		0·12	2·89	−57·7
(II)		7·08	0·49		−0·07	2·89	56·6
Pyrrolidine side				OH			
(I)		6·17	0·31		−2·19	3·72	173·7
(II)		5·66	3·64		1·76	2·90	54·2

References: (*a*) quinidine.C_2H_5OH (Doherty, Benson, Maienthal & Stewart, 1978); (*b*) (quinidine)$_2$.H_2SO_4.2H_2O (Karle & Karle, 1981); (*c*) quinidine (Kashino & Haisa, 1983); (*d*) procainamide.HCl (Peeters, Blaton, De Ranter, Denisoff & Molle, 1980); (*e*) lidocaine.$HAsF_6$ (Hanson, 1972); (*f*) lidocaine.HCl.H_2O (Hanson & Röhrl, 1972); (*g*) lidocaine (Hanson & Banner, 1974); (*h*) lidocaine.$(NO_2Ph)_2PO_4H$ (Yoo, Abola, Wood, Sax & Pletcher, 1975); (*i*) propranolol.HCl (Barrans, Cotrait & Dangoumau, 1973); (*j*) D-propranolol.HCl (Gadret, Goursolle, Leger & Colleter, 1975); (*k*) propranolol (Ammon, Howe, Erhardt, Balsamo, Macchia, Macchia & Keefe, 1977); (*l*) pindolol (Gadret, Goursolle, Leger & Colleter, 1976); (*m*) oxprenolol.HCl (Leger, Gadret & Carpy, 1977); (*n*) alprenolol.HCl (Barrans, Cotrait & Dangoumau, 1973); (*o*) sotalol.HCl (Gadret, Goursolle, Leger, Colleter & Carpy, 1976); (*p*) azapropranolol (Laguerre, Leger, Merlet, Colleter & Dubost, 1982).

* NH acts as donor in the bifurcated intra- and intermolecular H bonds.

part of the 'helpful' heteroatom, being situated between the positively charged nitrogen and the hydrophobic ring. In the case of our compound the pyrrolidine ring would have to act as the hydrophobic moiety to follow this pattern. However the distance of O(7) and N(29) from the mean pyrrolidine plane, for molecules (I) and (II), respectively, as well as the N(9)···O(7) separation and N(9)—C(8)—C(7)—O(7) torsion angle for molecule (I) do not fall within the range of the expected values and so this model seems to be less plausible.

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Rotation Barriers in Crystals from Diffraction Studies: 2,2′,4,4′,6,6′-Hexa-*tert*-butylazobenzene

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Abstract

X-ray crystal studies yield similar anisotropic displacement parameters (ADPs) for the two chemically equivalent *para tert*-butyl groups in 2,2′,4,4′.6.6′-hexa-*tert*-butylazobenzene ($C_{36}H_{58}N_2$) at 100 K. As the temperature rises, however, the ADPs increase more rapidly for one *para* group than for the other. Both *para* substituents have consistently larger libration amplitudes than those in the more crowded *ortho* positions. We have analyzed the ADPs with an internal-motion model which gives libration amplitudes for the *tert*-butyl groups at 100, 115, 128, 173, 200, 223 and 295 K. The results are consistent with rotational barriers for the six different groups of about 7 to more than 50 kJ mol^{-1}; at higher temperatures one of the *para* groups is best described by a twofold-disorder model. The low apparent barrier for this group and the disappearance of the disorder on cooling both suggest that the disorder is dynamic. Potential-energy calculations are employed to propose models for the hindering potential and for further disorder at room temperature. These calculations support the relative magnitudes of the barriers and the degree of disorder inferred from the X-ray diffraction data.

Introduction

For some time we have been studying internal motion in molecules in crystals, especially torsional oscillations, and have attempted to estimate barriers to such motion (Trueblood & Dunitz, 1983; Maverick & Dunitz, 1987). Molecules that contain chemically equivalent but crystallographically inequivalent groups that undergo internal motion are useful in testing the validity of such estimates. Studies over a range of temperatures can help to distinguish static disorder from motion of parts or all of

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