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Structure of 3-(2,6-Dichlorobenzylidenehydrazino)-1,2,4-triazol-4-amine: Nebidrazine (FLA-136), $C_9H_8Cl_2N_6$

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Abstract. α_2-Adrenoceptor agonist. Antihypertensive action. $M_r = 270\cdot97$, monoclinic, $P2_1/c$, $a = 5\cdot608$ (1), $b = 8\cdot486$ (1), $c = 23\cdot421$ (5) Å, $\beta = 95\cdot28$ (2)°, $V = 1109\cdot7$ (3) Å^3, $Z = 4$, $D_x = 1\cdot62$ g cm^{-3}, Cu $K\bar{\alpha}$, $\lambda = 1\cdot54178$ Å, $\mu = 51\cdot55$ cm^{-1}, $F(000) = 552$, room temperature, final $R = 0\cdot034$ for 952 reflections. The total charges on the atoms are calculated by means of the CNDO/2 method and some π delocalization in the bridge chain and triazole ring was found. The phenyl and triazole rings are almost coplanar with each other within the limits of error. The structure is compared with an α-adrenoceptor drug model.

Introduction. A series of 3-(benzylidenehydrazino)-1,2,4-triazol-4-amines were synthesized and tested for antihypertensive activity a few years ago (Eriksson & Florvall, 1976). Only the title compound (Fig. 1) shows antihypertensive activity and a strict structure–activity relationship of these compounds has not been clarified (Werner, Florvall & Stjernström, 1977).

A recent pharmacological investigation of the drug showed that it stimulates central α-autoreceptors which appear to be different from peripheral pre- and postsynaptic α-adrenoceptors (Hamilton & Longman, 1982).

The solid-state conformation of nebidrazine free base is analysed and the geometrical parameters are compared with those of dihydroimidazole α-agonists related to clonidine (Carpy, Léger, Leclerc, Decker, Rouot & Wermuth, 1982).

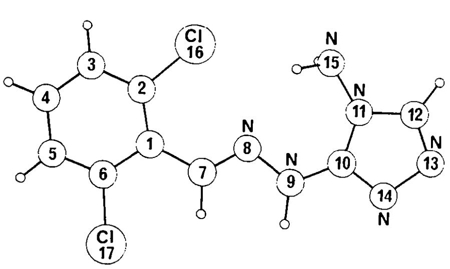

Fig. 1. Perspective view of the molecule showing the numbering of atoms. The lone numbers are for C atoms.

Experimental. Small white prisms (from ethanol), $0\cdot18 \times 0\cdot10 \times 0\cdot10$ mm, Enraf–Nonius CAD-4 diffractometer with graphite monochromator, Cu $K\bar{\alpha}$, 25 reflections ($9 < \theta < 25°$) used to refine orientation matrix, systematic absences: $h0l$ for l odd, $0k0$ for k odd, 1648 ($h, k, \pm l$) independent with $\theta < 60°$, h from 0 to +6, k from 0 to +9, l from −26 to +26, 952 with $I \geq 3\sigma(I)$, Lp correction, absorption ignored; two check reflections ($1\bar{2}0$, $\bar{1}\bar{2}0$) every 5400 s showed no unusual variation (all within $\pm 3\sigma$); direct methods, *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980), anisotropic diagonal-matrix refinement on F using observed reflections and weight w with $w = 1$ if $|F_o| < P$, $P = (F_o^2 \text{ max}/10)^{1/2}$, $w = (P/F_o)^2$ if $|F_o| > P$, H atoms from ΔF synthesis, isotropic, $R = 0\cdot034$, $R_w = 0\cdot041$, $S = 0\cdot554$ (952 reflections, 186 parameters), max. peak $\pm 0\cdot5$ e Å^{-3} in final ΔF map, mean and max. Δ/σ in final cycle: 0·1 and 0·4;* H-atom form factors from Stewart, Davidson & Simpson (1965), all other form factors from *International Tables for X-ray crystallography* (1974), Mini 6 CII computer.

Discussion. Atomic coordinates and equivalent isotropic thermal parameters for non-hydrogen atoms are given in Table 1; intramolecular bond distances and angles in Table 2.

As in the hydrochloride trihydrate and some derivatives (Werner *et al.*, 1977), the shortest bond in the triazole ring is C(12)—N(13) = 1·293 (6) Å, slightly greater than a pure C=N double bond, *i.e.* 1·265 Å (*Molecular Structures and Dimensions,* 1972). The distance C(7)—N(8) = 1·274 (5) Å can be considered as typical of a pure double bond. The lengths of the four other C—N bonds are intermediate between those of a single (1·470 Å) and a double bond, closer to the latter [the longest being N(11)—C(12) = 1·372 (6) Å]. The

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* Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and least-squares-planes' data have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39361 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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N(8)—N(9) bond [1·374 (5) Å] is in resonance between a single bond (1·46 Å) and a double bond (1·26 Å). The N—N bonds in the triazole ring are close to single bonds.

Table 1. *Atomic coordinates* (×10^4) *and equivalent isotropic thermal parameters for non-hydrogen atoms*

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

	x	y	z	B_{eq}(Å^2)
C(1)	3478 (7)	2043 (5)	3627 (2)	2·8 (2)
C(2)	1672 (8)	1027 (5)	3779 (2)	3·2 (2)
C(3)	−23 (8)	327 (6)	3385 (2)	3·8 (2)
C(4)	73 (8)	636 (6)	2806 (2)	4·0 (2)
C(5)	1818 (8)	1659 (6)	2628 (2)	3·5 (2)
C(6)	3456 (7)	2306 (5)	3038 (2)	2·8 (2)
C(7)	5308 (7)	2834 (6)	4019 (2)	3·1 (2)
N(8)	5364 (6)	2789 (5)	4564 (1)	3·1 (2)
N(9)	7185 (6)	3661 (5)	4841 (1)	3·7 (2)
C(10)	7518 (7)	3684 (6)	5422 (2)	2·9 (2)
N(11)	6129 (6)	3054 (5)	5806 (1)	3·1 (2)
C(12)	7284 (8)	3390 (6)	6334 (2)	3·8 (2)
N(13)	9204 (7)	4202 (5)	6284 (1)	4·1 (2)
N(14)	9401 (6)	4388 (5)	5690 (1)	3·5 (2)
N(15)	3992 (6)	2146 (5)	5736 (2)	4·3 (2)
Cl(16)	1389 (2)	528 (2)	4490·2 (5)	4·5 (1)
Cl(17)	5561 (2)	3573 (2)	2774·3 (4)	3·49 (1)

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

C(1)—C(2)	1·401 (6)	C(7)—N(8)	1·274 (5)
C(1)—C(6)	1·396 (6)	N(8)—N(9)	1·374 (5)
C(1)—C(7)	1·474 (6)	N(9)—C(10)	1·358 (5)
C(2)—C(3)	1·396 (6)	C(10)—N(11)	1·353 (5)
C(2)—Cl(16)	1·739 (4)	C(10)—N(14)	1·320 (5)
C(3)—C(4)	1·386 (7)	N(11)—C(12)	1·372 (6)
C(4)—C(5)	1·399 (6)	N(11)—N(15)	1·421 (5)
C(5)—C(6)	1·383 (6)	C(12)—N(13)	1·293 (6)
C(6)—Cl(17)	1·750 (4)	N(13)—N(14)	1·413 (5)

C(1)—C(2)—C(3)	123·9 (4)	C(1)—C(7)—N(8)	124·2 (4)
C(1)—C(2)—Cl(16)	121·7 (3)	C(7)—N(8)—N(9)	113·9 (3)
C(3)—C(2)—Cl(16)	114·4 (3)	N(8)—N(9)—C(10)	120·6 (3)
C(2)—C(3)—C(4)	118·7 (4)	N(9)—C(10)—N(11)	128·8 (4)
C(3)—C(4)—C(5)	120·1 (4)	N(9)—C(10)—N(14)	120·9 (4)
C(4)—C(5)—C(6)	118·5 (4)	N(11)—C(10)—N(14)	110·3 (3)
C(5)—C(6)—C(1)	124·6 (4)	C(10)—N(11)—C(12)	105·3 (3)
C(5)—C(6)—Cl(17)	115·2 (3)	C(10)—N(11)—N(15)	131·9 (3)
C(1)—C(6)—Cl(17)	120·2 (3)	C(12)—N(11)—N(15)	122·7 (3)
C(6)—C(1)—C(2)	114·2 (4)	N(11)—C(12)—N(13)	110·9 (4)
C(6)—C(1)—C(7)	119·0 (4)	C(12)—N(13)—N(14)	106·9 (4)
C(2)—C(1)—C(7)	126·8 (4)	C(10)—N(14)—N(13)	106·6 (3)

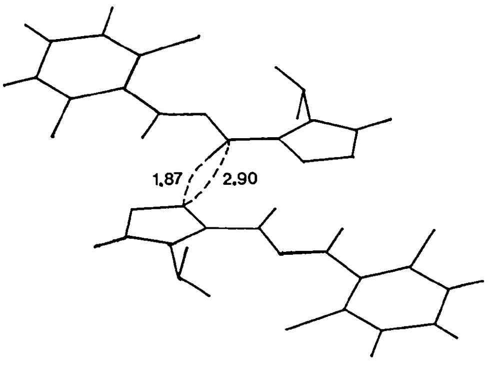

Fig. 2. Two molecules projected on (100) linked by a hydrogen bond (e.s.d. <0·01 Å).

Following these results CNDO calculations (Pople & Segal, 1966) were performed. The bridge chain is almost neutral. Neutral N(8) is surrounded by C(7) (+0·08) and N(9) (−0·09). The charge repartition in the triazole ring is the following: +0·20 on C(10) and C(12), +0·17 on N(14), −0·29 on N(11), −0·25 on N(13) and −0·13 on N(15). The dipole moment is 6·75 D (1 debye ≡ 3·3 × 10^{-30} Cm).

Bond distances and angles and the charge repartition indicate some π delocalization in the bridge chain and in the triazole ring, with a strong tendency for the double bonds to be localized at C(7)—N(8) and C(12)—N(13).

The dichlorophenyl moiety has a quite normal geometry with the average C—C bond length of 1·394 (6) Å and C—Cl bond length of 1·745 (4) Å. The internal valence angles slightly exceed 120° at the carbon atoms to which the electronegative chlorine atoms are attached.

H(107) and H(109) are on the same side of the bridge chain. All torsion angles defining the positions of the two rings in the crystal are close to 180°. The molecule is almost planar; the angle between the phenyl and the triazole rings is 8 (1)°. In contrast, sympathomimetic amines with a fully extended side chain (Pullman, Coubeils, Courrière & Gervois, 1972) and dihydroimidazoles related to clonidine (Carpy *et al.*, 1982) showing an α-adrenergic activity exhibit a biplanar conformation, the two planes being at 60, 75 or 90°. The only characteristic feature common to nebidrazine and the usual model for α-adrenoceptor agonists is $D = 5{\cdot}06$ (5) Å [distance from the phenyl ring centre to N(9) which is hydrogen-bond donor in the salt, together with N(14)]. The H distance [distance of N(9) above the phenyl ring] in nebidrazine is 0·152 (4) Å instead of 1 Å in the model. However, it seems possible that this planar conformation found in the crystals will not persist in solution (Fig. 2).

The sample was kindly provided by Hässle, Astra group, Sweden, for this study.

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Structure of 2-[(1-Ethyl-2-imidazolyl)methyl]-2,3-dihydro-1,4-benzodioxin Hydrochloride Monohydrate: RS-21361, $C_{14}H_{16}N_2O_2.HCl.H_2O$

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Abstract. α_2-Adrenoceptor antagonist. $M_r = 298\cdot7$, monoclinic, $P2_1/c$, $a = 11\cdot964\,(2)$, $b = 13\cdot410\,(3)$, $c = 9\cdot766\,(1)$ Å, $\beta = 96\cdot02\,(1)°$, $V = 1558\cdot2\,(4)$ Å^3, $Z = 4$, $D_x = 1\cdot27$ g cm^{-3}, Cu $K\bar{\alpha}$, $\lambda = 1\cdot54178$ Å, $\mu = 22\cdot5$ cm^{-1}, $F(000) = 632$, room temperature, final $R = 0\cdot038$ for 1226 reflections. Bond lengths and angles are normal for this type of compound. The molecule adopts a biplanar conformation with an angle of ~ 60° between the two rings. The crystal is stabilized by hydrogen bonds between Cl and the protonated imidazolyl N atom. Critical sites for antagonism of α_2-adrenoceptors are discussed.

Introduction. Among a series of 2-(2-imidazolylmethyl)-2,3-dihydro-1,4-benzodioxins recently prepared and tested for α-adrenoceptor antagonist activity, RS-21361 exhibits the most pronounced selectivity for α_2-adrenoceptors (Michel & Whiting, 1981). Moreover, this drug was found to be the most selective for α_2-adrenoceptors of a series of benzodioxin antagonists including piperoxan, prosympal and WB-4101. This work is part of a research program developed in our laboratory concerning the conformational discriminating factors between agonists and antagonists, α_1/α_2-adrenergic (Carpy, Léger, Leclerc, Decker, Rouot & Wermuth, 1982). Fig. 1 shows the molecule of RS-21361.

Experimental. Small white blocks (from methanol), 0·40 × 0·30 × 0·30 mm, Enraf–Nonius CAD-4 diffractometer with graphite monochromator, Cu $K\bar{\alpha}$, 25 reflections ($8 < \theta < 16°$) used to refine orientation matrix, systematic absences: $h0l$ for l odd, $0k0$ for k odd, 2765 ($\pm h, k, l$) independent with $\theta < 65°$, h from -14 to $+14$, k from 0 to $+15$, l from 0 to $+11$, 1226 with $I \geq 3\sigma(I)$, Lp correction, absorption ignored; two check reflections ($3\bar{3}0$; $2\bar{3}0$) every 3600 s showed no unusual variation (all within $\pm 3\sigma$); direct methods, *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980), anisotropic diagonal-matrix refinement on F using observed reflections and weight w with $w = 1$ if $|F_o| < P$, $P = (F_o^2 \max/10)^{1/2}$, $w = (P/F_o)^2$ if $|F_o| > P$, water then all hydrogen atoms from ΔF synthesis, H isotropic, $R = 0\cdot038$, $R_w = 0\cdot048$, $S = 0\cdot689$ (1226 reflections, 257 parameters), max. peak $\pm 0\cdot5$ e Å^{-3} in final ΔF map, mean and max. Δ/σ in final cycle: 0·2 and 0·5,* H-atom form factors from Stewart, Davidson & Simpson (1965), all other form factors from *International Tables for X-ray Crystallography* (1974), Mini 6 CII computer.

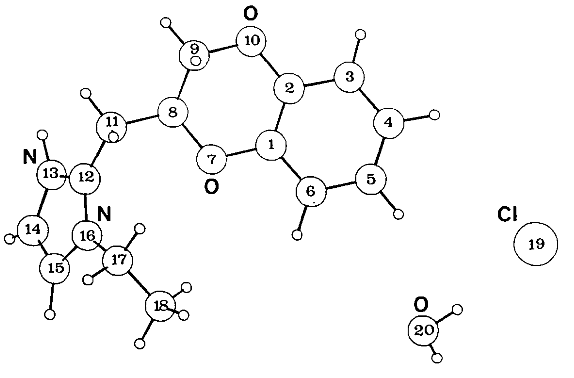

Fig. 1. Perspective view of the molecule showing the numbering of atoms. The lone numbers are for C atoms.

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* Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and least-squares-planes' data have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39362 (21 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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