

Structure of the Neuroleptic Drug *N*-[(1-Allyl-2-pyrrolidinyl)methyl]-6-methoxy-1*H*-benzotriazole-5-carboxamide Hydrochloride (Alizapride)

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Abstract. $C_{16}H_{22}N_5O_2^+ \cdot Cl^-$, $M_r = 351.5$, monoclinic, $P2_1/c$, $a = 8.8439$ (7), $b = 16.6827$ (9), $c = 12.2196$ (10) Å, $\beta = 92.510$ (6)°, $V = 1801.2$ (2) Å³, $Z = 4$, $D_m = 1.29$, $D_x = 1.297$ Mg m⁻³, Ni-filtered Cu $K\alpha$ radiation, $\lambda = 1.54178$ Å, $\mu = 2.045$ mm⁻¹, $F(000) = 744$, $T = 293$ K. Final $R = 0.052$ for 2281 unique observed reflections. The benzamide moiety is planar. This planar conformation is stabilized by an intramolecular hydrogen bond which is typical for most *o*-methoxybenzamides. The folded conformation of the pyrrolidine side chain is stabilized by an intramolecular hydrogen bond between H(14) and Cl. Part of the pyrrolidine ring seems to be disordered.

Introduction. Alizapride belongs to the pharmacological class of neuroleptic drugs and acts, like sulphiride, by blocking the dopamine D₂-receptor (Kebabian & Calne, 1979). The present investigation is part of a study examining the structural requirements for the blocking action.

Experimental. Colorless crystals from an ethanol-ether solution, $1.37 \times 0.15 \times 0.15$ mm. Density measured by flotation in *n*-heptane/CCl₄. Weissenberg photograph shows systematically absent reflections $h0l$ with l odd and $0k0$ with k odd. Hilger & Watts computer-controlled diffractometer, cell constants by least-squares refinement of the setting angles of 24 reflections with $15 < \theta < 25^\circ$, ω/θ scan, $[(\sin \theta)/\lambda]_{\max} = 0.5877$ Å⁻¹, $0 \leq h \leq 9$, $-19 \leq k \leq 19$, $-14 \leq l \leq 14$. Intensities were corrected by linear scaling for average decrease (+1.9% was the maximum correction) in intensity of four standard reflections (020, 300, 002, 223) monitored every 50 reflections. From the 6959 reflections measured, 2281 unique were considered observed with $I > 3\sigma(I)$, $R_{\text{int}} = 0.022$. Lorentz and polarization corrections, absorption corrections by the method of North, Phillips & Mathews (1968) based on one reflection (300). Scattering factors for the non-H atoms from Cromer &

Waber (1974), while for H from Stewart, Davidson & Simpson (1965). Anomalous-dispersion corrections were included for all non-H atoms (Ibers & Hamilton, 1964). The structure was solved by MULTAN82 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1982). The E map calculated from the solution with the best figure of merit showed 23 of the 24 non-H atoms. The remaining C(17) was obtained from a subsequent Fourier synthesis. Refined on F by full-matrix least squares, first with isotropic temperature factors and then anisotropically. All but four H atoms were found in a difference synthesis and they were included in the refinement with fixed isotropic temperature factors of their parent atoms. H(12*A*), H(12*B*), H(17*A*) and H(17*B*) were placed on their calculated positions with a riding distance of 0.95 Å and fixed isotropic temperature factors of their parent atoms. Final $R = 0.052$, $wR = 0.058$, with $w = 4F^2/[\sigma^2(F^2) + (0.02F^2)^2]$, $S = 3.2$. Largest parameter shift/e.s.d. = 0.16. Min. and max. residual electron density -0.30 and 0.22 e Å⁻³. The number of reflections per refined variable was $2281/271 = 8.4$. All calculations were performed on a PDP11/73 microcomputer using SDP (Enraf-Nonius, 1982) and PARST (Nardelli, 1983).

Discussion. Atomic coordinates and equivalent isotropic thermal parameters are given in Table 1.† Bond lengths, bond angles and selected torsion angles are given in Table 2. A PLUTO plot (Motherwell & Clegg, 1978) of the molecule, with the adopted numbering scheme, is shown in Fig. 1.

The molecule adopts a folded conformation reflected by the *gauche* conformation of the N(8)—C(9)—C(10)—N(14) chain [torsion angle

† Lists of structure factors, anisotropic thermal parameters, H-atom coordinates, distances and angles involving H atoms and details of least-squares planes have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52482 (39 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Table 1. Atomic coordinates and equivalent isotropic temperature factors ($\text{\AA}^2 \times 10^4$) with e.s.d.'s in parentheses

$$U_{eq} = (1/3) \sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j$$

	x	y	z	U_{eq}
Cl	0-15525 (8)	0-36130 (5)	0-93580 (6)	684 (2)
C(1)	0-1928 (3)	0-5083 (2)	0-5639 (2)	546 (8)
C(2)	0-1044 (3)	0-5504 (2)	0-6420 (2)	533 (8)
C(3)	0-0587 (3)	0-6278 (2)	0-6238 (2)	550 (8)
C(4)	0-1009 (3)	0-6643 (2)	0-5283 (2)	533 (8)
C(5)	0-1896 (3)	0-6256 (2)	0-4529 (2)	601 (8)
C(6)	0-2342 (3)	0-5473 (2)	0-4714 (2)	623 (9)
C(7)	0-2431 (3)	0-4220 (2)	0-5741 (2)	621 (9)
N(8)	0-2051 (3)	0-3789 (1)	0-6597 (2)	602 (6)
C(9)	0-2393 (4)	0-2938 (2)	0-6684 (3)	654 (9)
C(10)	0-3988 (4)	0-2739 (2)	0-7040 (3)	646 (9)
C(11)	0-4292 (5)	0-1849 (2)	0-7138 (3)	1045 (13)
C(12)	0-5441 (6)	0-1760 (2)	0-8014 (3)	1130 (13)
C(13)	0-5204 (4)	0-2393 (2)	0-8808 (3)	799 (11)
N(14)	0-4427 (3)	0-3063 (2)	0-8172 (2)	579 (6)
C(15)	0-5335 (4)	0-3817 (2)	0-8152 (3)	704 (10)
C(16)	0-5650 (4)	0-4147 (2)	0-9244 (3)	915 (11)
C(17)	0-6989 (5)	0-4273 (3)	0-9687 (4)	1256 (13)
O(18)	0-0723 (2)	0-5091 (1)	0-7335 (2)	709 (6)
C(19)	-0-0146 (4)	0-5478 (2)	0-8147 (3)	826 (10)
N(20)	0-0786 (3)	0-7378 (1)	0-4852 (2)	645 (8)
N(21)	0-1443 (3)	0-7450 (2)	0-3881 (2)	793 (9)
N(22)	0-2131 (3)	0-6778 (2)	0-3681 (2)	794 (9)
O(23)	0-3156 (3)	0-3922 (1)	0-5007 (2)	899 (8)

Table 2. Bond lengths (\AA), bond angles ($^\circ$) and selected torsion angles ($^\circ$) with e.s.d.'s in parentheses

C(1)	C(2)	1-442 (4)	C(9)	C(10)	1-497 (4)				
C(1)	C(6)	1-368 (4)	C(10)	C(11)	1-518 (5)				
C(1)	C(7)	1-511 (4)	C(10)	N(14)	1-519 (4)				
C(2)	C(3)	1-371 (4)	C(11)	C(12)	1-460 (6)				
C(2)	O(18)	1-355 (3)	C(12)	C(13)	1-450 (5)				
C(3)	C(4)	1-382 (4)	C(13)	N(14)	1-507 (5)				
C(4)	C(5)	1-393 (4)	N(14)	C(15)	1-490 (4)				
C(4)	N(20)	1-346 (4)	C(15)	C(16)	1-462 (5)				
C(5)	C(6)	1-383 (4)	C(16)	C(17)	1-309 (6)				
C(5)	N(22)	1-375 (4)	O(18)	C(19)	1-434 (4)				
C(7)	N(8)	1-326 (4)	N(20)	N(21)	1-349 (4)				
C(7)	O(23)	1-229 (4)	N(21)	N(22)	1-303 (4)				
N(8)	C(9)	1-452 (4)							
C(2)	C(1)	C(6)	119-2 (3)	C(7)	N(8)	C(9)	121-8 (2)		
C(2)	C(1)	C(7)	125-2 (2)	N(8)	C(9)	C(10)	115-3 (2)		
C(6)	C(1)	C(7)	115-7 (2)	C(9)	C(10)	C(11)	113-6 (3)		
C(1)	C(2)	C(3)	121-3 (2)	C(9)	C(10)	N(14)	112-6 (2)		
C(1)	C(2)	O(18)	116-0 (2)	C(11)	C(10)	N(14)	103-6 (2)		
C(3)	C(2)	O(18)	122-8 (2)	C(10)	C(11)	C(12)	106-3 (4)		
C(2)	C(3)	C(4)	117-4 (2)	C(11)	C(12)	C(13)	106-8 (3)		
C(3)	C(4)	C(5)	122-5 (3)	C(12)	C(13)	N(14)	106-7 (3)		
C(3)	C(4)	N(20)	133-7 (3)	C(10)	N(14)	C(13)	107-3 (2)		
C(5)	C(4)	N(20)	103-9 (2)	C(10)	N(14)	C(15)	113-5 (2)		
C(4)	C(5)	C(6)	119-7 (3)	C(13)	N(14)	C(15)	113-6 (2)		
C(4)	C(5)	N(22)	108-3 (3)	N(14)	C(15)	C(16)	112-7 (3)		
C(6)	C(5)	N(22)	132-1 (3)	C(15)	C(16)	C(17)	125-5 (4)		
C(1)	C(6)	C(5)	120-1 (3)	C(2)	O(18)	C(19)	118-7 (2)		
C(1)	C(7)	N(8)	119-8 (3)	C(4)	N(20)	N(21)	111-3 (2)		
C(1)	C(7)	O(23)	119-0 (3)	N(20)	N(21)	N(22)	108-0 (2)		
N(8)	C(7)	O(23)	121-1 (3)	C(5)	N(22)	N(21)	108-5 (3)		
C(2)	C(1)	C(7)	O(23)	178-3 (3)	N(14)	C(10)	C(11)	C(12)	-25-1 (4)
C(1)	C(2)	O(18)	C(19)	179-6 (2)	C(10)	C(11)	C(12)	C(13)	31-8 (4)
C(7)	N(8)	C(9)	C(10)	79-1 (3)	C(11)	C(12)	C(13)	N(14)	-25-2 (4)
N(8)	C(9)	C(10)	C(11)	178-8 (3)	C(12)	C(13)	N(14)	C(10)	9-0 (3)
C(9)	C(10)	C(11)	C(12)	-147-7 (3)	C(12)	C(13)	N(14)	C(15)	-117-2 (3)
C(9)	C(10)	N(14)	C(13)	133-0 (2)	C(13)	N(14)	C(15)	C(16)	-61-4 (3)
C(9)	C(10)	N(14)	C(15)	-100-7 (3)	C(10)	N(14)	C(15)	C(16)	175-8 (3)
C(11)	C(10)	N(14)	C(13)	9-8 (3)	N(14)	C(15)	C(16)	C(17)	120-4 (4)
C(11)	C(10)	N(14)	C(15)	136-1 (3)					

61.3 (3) $^\circ$]; the dihedral angle formed by the weighted least-squares planes through the aromatic and pyrrolidine rings is 51.0 (1) $^\circ$.

For this pyrrolidine ring we calculated, using the method of Cremer & Pople (1975), a phase angle $\varphi_2 = 52.2 (6)^\circ$, indicating a twisted conformation, and a puckering amplitude $q_2 = 0.287 (4) \text{\AA}$ for the sequence C(10)—C(11)—C(12)—C(13)—N(14). This amplitude is significantly smaller than the 0.38 \AA of a normal pyrrolidine ring (Pfafferott, Oberhammer, Boggs & Caminati, 1985); the C(11)—C(12) and C(12)—C(13) bond lengths of 1.460 (6) and 1.450 (5) \AA respectively are short, and the thermal parameters of C(11), C(12) and C(13) are unusually large. Therefore, we suspect the pyrrolidine ring to be partially disordered.

The aromatic ring atoms are only slightly displaced from the least-squares plane [max. deviation is 0.008 (3) \AA for C(1) and C(4)]. The dihedral angle between the least-squares planes of the aromatic ring and the triazole ring is 0.4 (1) $^\circ$, with a maximum deviation of 0.018 (3) \AA out of the aromatic plane for N(21). The methyl group of the methoxy moiety has an out-of-plane deviation of only 0.060 (3) \AA , which is in contrast with the 1.166 (7) \AA of eticlopride (Wagner, Stensland, Csöregi & De Paulis, 1985), but in quite good agreement with most of the other *o*-methoxybenzamide, such as sulpiride (Blaton, Peeters, De Ranter, Denisoff & Molle, 1981) and tiapride (Blaton, Peeters, De Ranter, Denisoff & Molle, 1982). The plane through the amide moiety forms a dihedral angle of 3.8 (3) $^\circ$ with the aromatic plane.

The intra- and intermolecular hydrogen bonds which determine the conformation of the molecule are summarized in Table 3. One intramolecular hydrogen bond links H(8) with O(18) and forms a typical additional six-membered pseudo-ring which is fused with the aromatic ring.

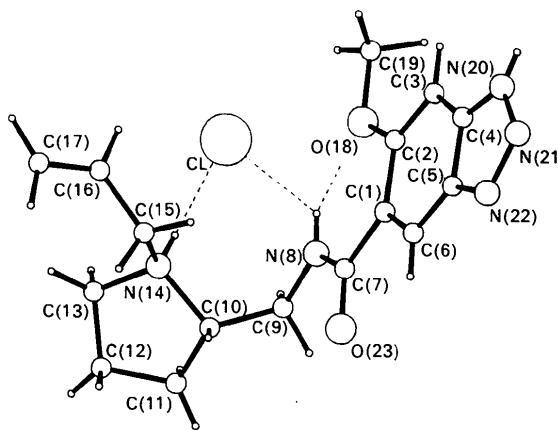


Fig. 1. A PLUTO plot showing the numbering scheme and intramolecular hydrogen bonds (indicated by dashed lines).

Table 3. *Geometry of intra- and intermolecular hydrogen bonds with e.s.d.'s in parentheses*

X—H...Y	H...Y (Å)	X...Y (Å)	X—H...Y (°)
N(8)—H(8)...O(18)	2.02 (2)	2.646 (3)	135 (2)
N(8)—H(8)...Cl	2.85 (2)	3.433 (2)	131 (2)
N(14)—H(14)...Cl	2.33 (2)	3.118 (2)	174 (2)
N(20)—H(20)...Cl'	2.39 (2)	3.103 (2)	169 (2)

Symmetry code: (i) $-x, y + \frac{1}{2}, -z + \frac{1}{2}$.

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2,3,6,7-Tetrahydro-9-methyl-1*H*,5*H*-quinolizino[9,1-*gh*]coumarin

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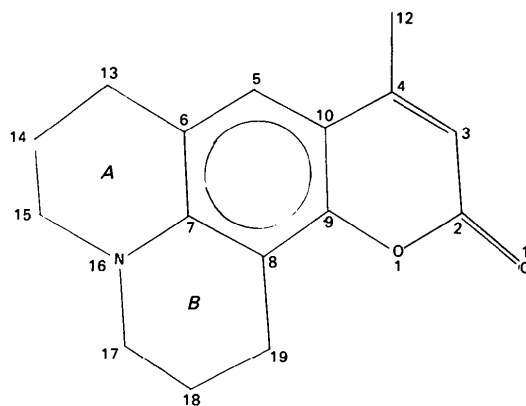
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Abstract. 2,3,6,7-Tetrahydro-9-methyl-1*H*,5*H*,11*H*-pyrano[2,3-*d*]benzo[1,2,3-*ij*]quinolizino-11-one, $C_{16}H_{17}NO_2$, $M_r = 255.32$, monoclinic, $P2_1/a$, $a = 8.253$ (2), $b = 15.660$ (7), $c = 10.112$ (4) Å, $\beta = 95.82$ (3)°, $V = 1300.2$ (6) Å³, $Z = 4$, $D_m = 1.315$, $D_x = 1.304$ g cm⁻³, $\lambda(Mo K\alpha) = 0.71069$ Å, $\mu = 0.80$ cm⁻¹, $F(000) = 544$, $T = 296$ K. The final R value is 0.065 for 1020 observed reflections. The coumarin moiety is planar and the two piperidine rings adopt flattened half-chair conformations with mean absolute torsion angles of 24.6 and 28.8° respectively.

Introduction. Coumarin derivatives having an amino group in the 7-position are very efficient laser dyes in the blue and green region of the spectrum (Drexhage, 1973). The mobility of the amino group reduces the fluorescence efficiency of these dyes in polar solvents (Tuccio, Drexhage & Reynolds, 1973; Reynolds & Drexhage, 1975) but, with a structurally rigid amino group, these derivatives show a high quantum yield of fluorescence in polar solvents. The title compound (I), which is such a derivative, is found to have

excellent laser efficiency at 480 nm (Marling, Hawley, Liston & Grant, 1974; Reynolds & Drexhage, 1975). The structural study of this compound was performed to understand the ground-state conformation of the fused quinolizine ring system.



(I)