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Molecular Structure Analysis of Benzamide Neuroleptics and Analogs. X. *exo*-2,3-Dimethoxy-*N*-(9-phenylmethyl-9-azabicyclo[3.3.1]non-3-yl)benzamide Hydrochloride

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Abstract. $C_{24}H_{31}N_2O_3^+.Cl^-$, $M_r = 430.9$, monoclinic, $P2_1/c$, $a = 10.518$ (1), $b = 23.624$ (3), $c = 9.268$ (1) Å, $\beta = 93.03$ (2)°, $V = 2299.7$ Å^3, $Z = 4$, $D_x = 1.24$ g cm^{-3}, Mo $K\bar{\alpha}$, $\lambda = 0.71069$ Å, $\mu = 1.53$ cm^{-1}, $F(000) = 920$, $T = 293$ K, $R = 0.03$ for 1400 observed reflections. The dimethoxyphenyl and amide groups are coplanar and held together by means of an intramolecular H bond as usually observed in the active antidopaminergic benzamides. Unexpectedly, the *N*-benzyl side chain is in an axial position with respect to the piperidinyl ring which holds the benzamide group. This piperidinyl moiety adopts a more planar geometry compared with the corresponding part in the tropapride, the well known nortropane benzamide analog.

Introduction. This X-ray structure determination is part of a general study on conformational properties of dopamine antagonists which bind to a subpopulation of DA receptors, the so-called D_2 receptors, in a sodium-dependent manner. Compared with tropapride (Durant, De Beys, Collin & Evrard, 1986), a very potent benzamide analog, the title compound has one more carbon in the piperidine bridge. This results in a slight decrease of activity. Therefore, it seemed to be of interest to analyze the conformation of this analog and in particular to clarify the orientation of the benzyl group at the ternary endocyclic N atom.

Experimental. This compound crystallized from a methanol–ethyl acetate mixture at room temperature. Colourless prismatic crystal 0.40 × 0.10 × 0.10 mm for all X-ray measurements. Enraf–Nonius CAD-4 diffractometer. Lattice parameters from least-squares refinement of 25 medium-angle reflections. No absorption or extinction correction. No intensity variation of standard reflection. $4 \leq 2\theta \leq 46°$. 3180 independent reflections measured $(-11 \leq h \leq 11, 0 \leq k \leq 26, 0 \leq l \leq 10)$, 1400 observed $[I \geq 2.5\sigma(I)]$. Structure solved by direct methods (*SHELX*76, Sheldrick, 1976). All non-H atoms found in the best FOM E map. Full-matrix least-squares refinement on F using *SHELX*76. All H atoms located on difference Fourier map and not refined. Anisotropic temperature factors (U_{ij}) for all non-H atoms and isotropic ones for H atoms (corresponding to the isotropic temperature factors of the carrier atoms incremented by 0.02). $R = 0.03$, $wR = 0.03$, $w = 1.0/[\sigma^2(F) + 0.005F^2]$, $(\Delta/\sigma)_{max} = -0.053$ $[U_{33}$ of C(27)], $S = 0.74$; max. and min. heights in final difference Fourier synthesis 0.18 and -0.14 e Å^{-3}. Scattering factors from *SHELX*76. Structural analysis by *XRAY*76 (Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976).

Discussion. Atomic parameters are given in Table 1.* Fig. 1 shows the atom numbering and bond lengths and angles. Fig. 2 is a stereoview of the unit cell.

The existence of an intramolecular hydrogen bond between N(17) and O(26) $[O(26)\cdots N(17)$ 2.698 (4), $H(17)\cdots O(26)$ 1.882 (2) Å, $N(17)-H(17)\cdots O(26)$ 124.8 (2)°] leads to the formation of a virtual six-membered ring like those occurring in the active

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* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 43533 (8 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

$$C_{24}H_{31}N_2O_3^+.Cl^-$$

nortropane benzamides (see Fig. 2 and Table 2) (Durant, Renard, De Beys & Evrard, 1984). A second hydrogen bond exists between the endocyclic proton-ated N(1) atom and the chloride anion: N(1^i)$\cdots$Cl(30^{ii}) 3·031 (3), H(1^i)$\cdots$Cl(30^{ii}) 1·824 (5) Å, N(1^i)—H(1^i)$\cdots$ Cl(30^{ii}) 168·3 (1)° with (i) x, y, z and (ii) $-x$, $-y$, $-z+2$.

Table 1. *Final atomic coordinates* ($\times 10^4$) *and* B_{eq} *values with e.s.d.'s in parentheses*

$B_{eq} = 8\pi^2 U_{eq}(\text{Å}^2)$ and $U_{eq} = \frac{1}{3}\sum_i\sum_j U_{ij}a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$.

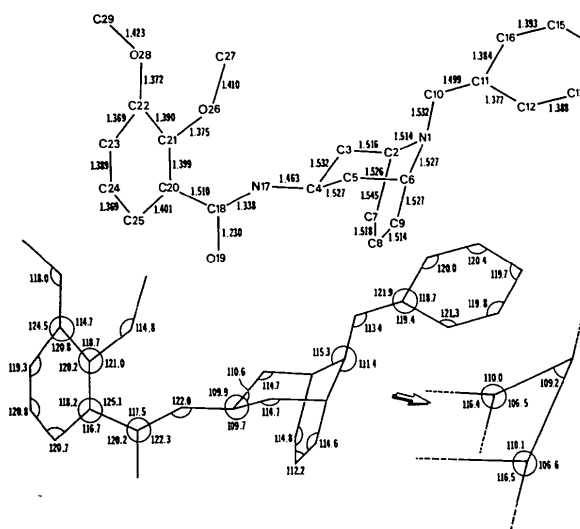|	x	y	z	B_{eq}
N(1)	−1032 (3)	975 (1)	9642 (3)	3·60 (1)
C(2)	−1698 (3)	1506 (2)	9086 (4)	4·16 (1)
C(3)	−900 (3)	2022 (2)	9490 (4)	4·45 (1)
C(4)	462 (3)	2005 (1)	8983 (4)	4·11 (1)
C(5)	1082 (3)	1434 (2)	9339 (4)	3·99 (1)
C(6)	250 (4)	921 (1)	8953 (4)	4·20 (1)
C(7)	−2011 (4)	1411 (2)	7457 (4)	5·24 (1)
C(8)	−880 (4)	1253 (2)	6590 (4)	6·16 (1)
C(9)	−42 (4)	811 (2)	7346 (4)	5·63 (1)
C(10)	−886 (3)	922 (1)	11289 (4)	3·90 (1)
C(11)	−2090 (3)	1043 (1)	12029 (3)	3·61 (1)
C(12)	−2176 (4)	1528 (2)	12843 (4)	5·10 (1)
C(13)	−3265 (4)	1652 (2)	13566 (4)	6·10 (1)
C(14)	−4274 (4)	1286 (2)	13484 (4)	5·68 (1)
C(15)	−4204 (4)	797 (2)	12677 (5)	5·72 (1)
C(16)	−3106 (4)	670 (2)	11965 (4)	4·94 (1)
N(17)	1216 (3)	2459 (1)	9678 (3)	4·27 (1)
C(18)	1444 (3)	2946 (1)	9001 (4)	3·78 (1)
O(19)	999 (2)	3049 (1)	7775 (3)	4·72 (1)
C(20)	2255 (3)	3381 (1)	9812 (4)	3·75 (1)
C(21)	3001 (3)	3277 (2)	11078 (4)	3·83 (1)
C(22)	3671 (3)	3715 (2)	11768 (4)	4·52 (1)
C(23)	3626 (4)	4253 (2)	11213 (5)	5·61 (1)
C(24)	2908 (4)	4357 (2)	9939 (5)	5·94 (1)
C(25)	2238 (4)	3931 (2)	9246 (4)	4·63 (1)
O(26)	3029 (2)	2750 (1)	11711 (3)	5·20 (1)
C(27)	4106 (5)	2421 (2)	11428 (6)	9·39 (2)
O(28)	4346 (3)	3563 (1)	13014 (3)	6·31 (1)
C(29)	4759 (4)	4000 (2)	13988 (5)	7·79 (1)
Cl(30)	−2449 (1)	−99 (1)	8766 (1)	5·82 (1)
H(1)	−1721	577	9284	4·74
H(17)	1583	2393	10842	4·74

Fig. 1. Atom numbering, bond lengths (Å) and valence angles (°). Max. e.s.d.'s: 0·006 Å and 0·4°.

The two twinned piperidine rings of the title compound adopt a chair conformation. The *N*-benzyl group is in an axial position with respect to the ring which holds the benzamide moiety. As reported before for nortropanes (Smith-Verdier, Florencio & Garcia Blanco, 1977), this might be the reason why the N(1), C(2), C(3), C(4), C(5), C(6) part of the molecule is more planar than the corresponding one in the 'tropapride' as shown by the increase of valence angles N(1)—C(2)—C(3), N(1)—C(6)—C(5), C(2)—C(3)—C(4) and C(6)—C(5)—C(4) in the title compound (see Table 3).

Compared with the tropapride, the slight activity decrease might be explained by the different position of the nitrogen N(1) lone pair. The title compound axial epimer (as observed in the crystal) is probably more stable than the corresponding form of the tropapride. The addition of a methylene group in the nortropane moiety indeed favors the axial epimer to the detriment of the equatorial form which is suggested as the active one at the receptor level (Collin, Durant & Evrard, 1986; Collin, Evrard & Durant, 1986).
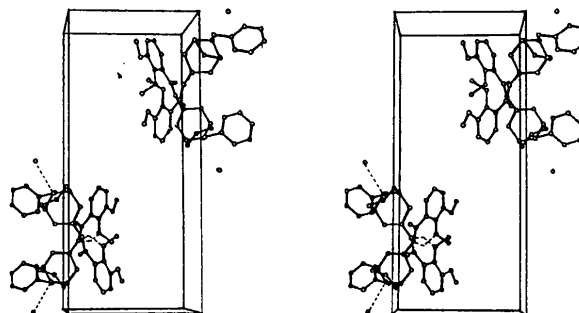
Fig. 2. Stereoview of molecular conformation and crystal packing. Dotted lines represent intra- and intermolecular hydrogen bonds.

Table 2. *Main torsion angles* (°) *with e.s.d.'s in parentheses*

C(2)—N(1)—C(10)—C(11)	47·6 (3)
N(1)—C(10)—C(11)—C(12)	−110·3 (3)
N(17)—C(18)—C(20)—C(21)	14·0 (5)
C(21)—O(26)—H(17)—N(17)	35·1 (3)
C(20)—C(21)—O(26)—H(17)	−16·5 (4)

Table 3. *Main valence angles* (°) *in piperidine moieties of tropapride and the title compound*

	Tropapride		Title compound
N(1)—C(2)—C(3)	107·5 (4)	<	110·0 (3)
N(1)—C(6)—C(5)	107·9 (4)	<	110·1 (2)
C(2)—C(3)—C(4)	110·5 (5)	<	114·7 (3)
C(6)—C(5)—C(4)	109·6 (5)	<	114·7 (3)

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(Pyrazinyl-2 méthyl)-2 Benzonitrile

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Abstract. $C_{12}H_9N_3$, $M_r = 195 \cdot 2$, monoclinic, $P2_1/c$, $a = 5 \cdot 9045$ (8), $b = 6 \cdot 896$ (1), $c = 25 \cdot 197$ (5) Å, $\beta = 98 \cdot 61$ (1)°, $V = 1014 \cdot 4$ Å^3, $Z = 4$, $D_x = 1 \cdot 278$ Mg m^{-3}, λ(Mo $K\alpha$) = $0 \cdot 7107$ Å, $\mu = 0 \cdot 074$ mm^{-1}, $F(000) = 408$, $T = 294$ (1) K, final $R = 0 \cdot 033$ for 984 independent reflections. The bond distances and angles agree with previously published values. The structure can be regarded as constituted of layers of molecules which spread out along the (100) planes. Its cohesion is due to van der Waals interactions.

Introduction. Le composé étudié est issu de l'action de la méthylpyrazine métallée sur l'*o*-chlorobenzonitrile. Les méthodes spectrographiques habituelles (masse, IR, RMN de ^{1}H et de ^{13}C) n'ont pas permis de connaître la position occupée par la fonction nitrile sur le noyau benzénique. Selon les schémas réactionnels envisagés (SNAr ou cinésubstitution), celle-ci peut se situer en position *ortho* ou en position *méta*. L'étude cristallographique a donc eu pour objectif de résoudre ce problème. Elle a eu aussi pour perspective de permettre l'utilisation de ce composé comme réactif dans d'autres synthèses. Des cristaux ont été obtenus par évaporation lente d'une solution dans le toluène.

Partie expérimentale. Cristal parallélépipédique: 0,06 × 0,25 × 0,32 mm. Dimensions de la maille déterminées sur monocristal avec 25 réflexions telles que $4,92 \leq \theta \leq 17,45°$. Diffractomètre Enraf–Nonius CAD-4. $0,039 \leq (\sin\theta)/\lambda \leq 0,572$ Å^{-1}; $0 \leq h \leq 6$, $0 \leq k \leq 7$, $-28 \leq l \leq 28$. Réflexions de contrôle: $0\bar{2}4$, $1\bar{1}8$ et 024. $\sigma(I)/I$ moyen (contrôle): 0,0034. 1588 réflexions indépendantes mesurées. 604 réflexions inobservées $[I \leq 2\sigma(I)]$. Méthodes directes, programme *MULTAN*11/82 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1982). H: coordonnées calculées. Affinement sur F. Facteurs de diffusion des *International Tables for X-ray Crystallography* (1974). Paramètres affinés: x, y, z de tous les atomes et β_{ij} de N et de C. $R = 0,033$, $wR = 0,037$, $w = 1/\sigma^2(F)$, $S = 1,17$, g(coefficient d'extinction secondaire isotrope) = 1,5 (2) × 10^{-6}. $(\Delta/\sigma)_{max} = 0,00$. $|\Delta\rho|_{max} = 0,11$ (3) e Å^{-3}. Programmes de calcul du système *SDP*