Acta Cryst. (1985). C**41**, 1361–1362

Molecular Structure of Benzamide Neuroleptics. III. *N*-(8-Benzyl-1αH,5αH-nortropan-3α-yl)-2,6-dimethoxybenzamide, $C_{23}H_{28}N_2O_3$

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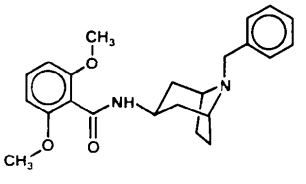
(*Received* 16 *July* 1984; *accepted* 28 *May* 1985)

Abstract. $M_r = 380{\cdot}5$, $P2_1/c$, $a = 10{\cdot}341$ (1), $b = 22{\cdot}478$ (1), $c = 9{\cdot}070$ (1) Å, $\beta = 94{\cdot}66$ (1)°, $V = 2101{\cdot}4$ Å^3, $Z = 4$, $D_x = 1{\cdot}20$ g cm^{-3}, Cu $K\bar{\alpha}$, $\lambda = 1{\cdot}54178$ Å, $\mu = 5{\cdot}36$ cm^{-1}, $F(000) = 812{\cdot}00$, $T = 293$ K, $R = 0{\cdot}036$ for 1916 unique reflections [$I \geq 2{\cdot}5\sigma(I)$]. The dimethoxyphenyl and amide groups of the benzamide moiety are not coplanar owing to steric hindrance between one of the two *ortho* methoxy substituents and the exocyclic carbonyl group. This geometry prevents the formation of an intrabenzamidic H bond as previously reported for active antidopaminergic analogues.

Introduction. The crystal structure determination of the title compound is part of a more general study on a new class of neuroleptics: the 3-benzamido-*N*-benzylnortropanes (Jalfre, Bucher, Dorme, Mocquet & Porsolt, 1983).



Experimental. Suitable crystals at room temperature from an ethanol solution. Colourless parallelepiped crystal: 0·27 × 0·14 × 0·09 mm. Enraf–Nonius CAD-4 diffractometer, graphite monochromator. Lattice parameters from least-squares refinement of 22 reflections ($30 \leq \theta \leq 40°$). No absorption correction. Max. $(\sin\theta)/\lambda = 0{\cdot}62$ Å^{-1} ($-12 \leq h \leq 12$, $0 \leq k \leq 18$, $0 \leq l \leq 11$). No intensity variation of standard reflection. 4258 measured reflections; 1916 observed [$I \geq 2{\cdot}5\sigma(I)$] with $\sigma^2 = S + B + (0{\cdot}03S)^2$, S being scan and B background counts. Direct methods: *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980). Refinement (on F): *SHELX*76 (Sheldrick, 1976). All but one [H(11)] H atoms from difference Fourier synthesis. Full-matrix least-squares anisotropic refinement (H's isotropic). $w = 1/\sigma^2(F)$. Final $R = 0{\cdot}036$ for 1916 observed reflections. Max., min. peaks in final ΔF synthesis: 0·20, −0·17 e Å^{-3}. Max. $\Delta/\sigma = 0{\cdot}76$ [z of O(18)]. Scattering factors from *SHELX*76 (Sheldrick, 1976). Structure analysis using *XRAY*76 (Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976). The final coordinates are given in Table 1 and the bond lengths and angles in Fig. 1.*

Discussion. The phenyl and amide groups are not coplanar (65·2°) owing to the steric hindrance between atoms O(18) and O(27). The distance between these two oxygens, 2·985 (3) Å, corresponds to that observed in methicillin, 2·97 Å (Blanpain, Melebeck & Durant, 1977) and is somewhat larger than the sum of van der Waals radii, 2·80 Å (Pauling, 1960). This non-coplanarity prevents the formation of an intramolecular H bond: N(16)–H(16)···O(25), as previously observed in the 2,3,5-trimethoxyphenyl (Durant, Renard & Evrard, 1984) and in the 2-ethoxy-3-methoxyphenyl (Evrard, Renard, De Beys & Durant, 1984) analogues (Table 2 and Fig. 2). It has been reported (Siddall & Garner, 1966) by ^{1}H NMR in 2,6-dimethoxybenzamide that the barrier height of rotation around C(17)–C(19) is $\geq 83{\cdot}7$ kJ mol^{-1} demonstrating unambiguously the rigidity of the benzamide moiety in solution at room temperature. So, as the title compound retains antidopaminergic activity (Delalande Research Centre, 1984), it seems that the neuroleptic power of such molecules is not directly related to the coplanarity of the benzamide moiety and the formation of the intramolecular H bond. This hypothesis is inconsistent with the structure–activity relationships reported for the benzamide neuroleptics (Van de Waterbeemd & Testa, 1983). The *N*-benzyl group is in an axial position contrary to the two other analogues previously reported; however, in solution, the two isomers, axial and equatorial, are in equilibrium as observed by ^{1}H NMR. The crystal packing mainly results from intermolecular H bonds: N(16^{i})–H(16^{i})···O(18^{ii}): 2·998 (4), N(16)–H(16^{i}): 0·953 (3), H(16^{i})···O(18^{ii}): 2·098 (2) Å, ∠N(16)–H(16)···O(18): 156·8 (1)°; where (i) = x, y, z, (ii) = $x, \frac{1}{2}-y, z-\frac{1}{2}$.

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 42246 (11 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

0108-2701/85/091361-02$01.50

We thank Drs Dostert and Langlois (Delalande Research Centre, Rueil-Malmaison, France) for providing the title compound.

Table 1. *Final coordinates* ($\times 10^4$) *and* B_{eq} *values with e.s.d.'s in parentheses for the non-*H *atoms*

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

	x	y	z	B_{eq}(Å^2)
N(01)	5362 (2)	4004 (1)	6202 (3)	4·84 (1)
C(02)	6010 (3)	3435 (1)	6576 (3)	4·83 (1)
C(03)	5206 (3)	2901 (1)	5996 (3)	4·72 (1)
C(04)	3891 (3)	2892 (1)	6638 (3)	4·45 (1)
C(05)	3252 (3)	3506 (1)	6577 (3)	4·98 (1)
C(06)	4246 (3)	3988 (1)	7110 (4)	5·26 (1)
C(07)	6119 (3)	3470 (2)	8263 (3)	6·07 (1)
C(08)	4922 (3)	3827 (2)	8629 (3)	6·13 (1)
C(09)	5091 (3)	4132 (2)	4630 (3)	5·61 (1)
C(10)	6329 (3)	4171 (1)	3871 (3)	5·57 (1)
C(11)	6478 (5)	3863 (2)	2585 (4)	8·00 (1)
C(12)	7603 (6)	3886 (3)	1918 (5)	10·71 (2)
C(13)	8620 (6)	4126 (3)	2482 (6)	10·16 (2)
C(14)	8486 (5)	4536 (2)	3742 (6)	10·09 (2)
C(15)	7348 (4)	4514 (2)	4441 (5)	7·69 (1)
N(16)	3050 (2)	2448 (1)	5886 (3)	4·81 (1)
C(17)	2389 (3)	2041 (1)	6584 (3)	4·17 (1)
O(18)	2493 (2)	1970 (1)	7930 (2)	5·98 (1)
C(19)	1521 (3)	1660 (1)	5562 (3)	4·30 (1)
C(20)	1777 (3)	1056 (1)	5393 (3)	5·08 (1)
C(21)	1033 (4)	718 (2)	4366 (4)	6·82 (1)
C(22)	42 (4)	990 (2)	3517 (4)	8·03 (1)
C(23)	−249 (3)	1576 (2)	3670 (4)	7·15 (1)
C(24)	476 (3)	1914 (1)	4716 (3)	5·32 (1)
O(25)	248 (2)	2494 (1)	5034 (3)	7·19 (1)
C(26)	−659 (6)	2817 (3)	4071 (6)	10·53 (2)
O(27)	2810 (2)	840 (1)	6269 (3)	6·31 (1)
C(28)	3125 (6)	227 (2)	6147 (6)	9·07 (1)

Table 2. *Comparative values of main structural features for the title compound* (I), *2,3,5-trimethoxyphenyl* (II) (*Durant et al.*, 1984) *and 2-ethoxy-3-methoxyphenyl* (III) (*Evrard et al.*, 1984) *analogues*

	(I)	(II)	(III)
Main torsion angles (°) with e.s.d.'s			
C(17)–N(16)–C(4)–C(3)	130·5 (3)	129·5 (9)	116·6 (3)
C(17)–N(16)–C(4)–C(5)	−104·8 (3)	−108·7 (9)	−120·0 (3)
C(4)–N(16)–C(17)–O(18)	−5·5 (4)	1 (1)	−0·5 (5)
C(4)–N(16)–C(17)–C(19)	176·1 (2)	−177·3 (9)	−179·8 (3)
O(18)–C(17)–C(19)–C(20)	−65·8 (4)	172·2 (9)	179·4 (3)
O(18)–C(17)–C(19)–C(24)	116·9 (3)	−10 (1)	−2·4 (5)
N(16)–C(17)–C(19)–C(20)	112·6 (3)	−9 (1)	−1·2 (5)
N(16)–C(17)–C(19)–C(24)	−64·6 (4)	168·3 (9)	176·9 (3)
C(10)–C(9)–N(1)–C(2)	−62·2 (4)	53·5 (8)	50·7 (4)
C(10)–C(9)–N(1)–C(6)	176·4 (2)	169·5 (6)	167·0 (3)
N(1)–C(9)–C(10)–C(11)	130·5 (3)	68·3 (9)	−110·5 (5)
N(1)–C(9)–C(10)–C(15)	−49·3 (4)	−113·5 (7)	69·2 (5)
Dihedral angles (°)			
Plane *a*: N(1),C(2),C(3),C(4),C(5),C(6)			
Plane *b*: N(16),C(17),O(18)			
Plane *c*: C(10),C(11),C(12),C(13),C(14),C(15)			
Plane *d*: C(19),C(20),C(21),C(22),C(23),C(24)			
a–*c*	46·6 (5)	80·6 (10)	81·3 (4)
a–*d*	53·1 (6)	85·3 (10)	87·5 (4)
b–*d*	65·2 (4)	11·0 (9)	3·0 (3)
c–*d*	69·7 (6)	63·4 (11)	65·6 (6)

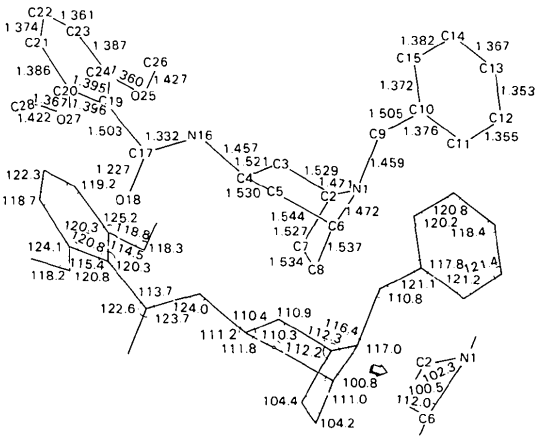


Fig. 1. Atom numbering, bond lengths (Å) and angles (°). Maximum e.s.d.'s are 0·009 Å and 0·7°.

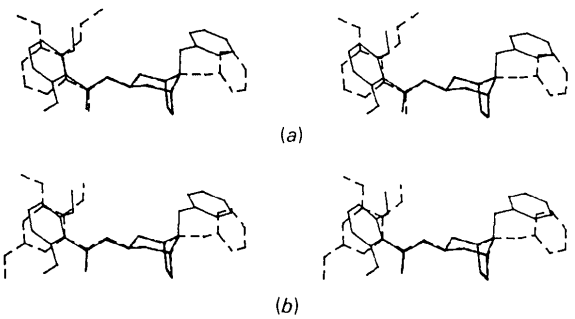


Fig. 2. Stereoscopic views of pairs of molecules after a fitting of the piperidine ring N(1),C(2),C(3),C(4),C(5),C(6). (*a*) Title compound and 2,3,5-trimethoxyphenyl analogue (dashed lines). (*b*) Title compound and 2-ethoxy-3-methoxyphenyl analogue (dashed lines).

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