

Molecular Structure Analysis of Benzamide Neuroleptics and Analogs. VII. 1-Benzyl-4-(2,3-dimethoxyphenylaminocarbonyl)-2,6-ethanopiperidinium Chloride

BY SONIA COLLIN, FRANCOIS DURANT AND GUY EVRARD

Laboratoire de Chimie Moléculaire Structurale, Facultés Universitaires Notre-Dame de la Paix,
Rue de Bruxelles 61, B-5000 Namur, Belgium

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Abstract. $C_{23}H_{29}N_2O_3^+Cl^-$, $M_r = 416.9$, monoclinic, $P2_1/c$, $a = 16.270$ (3), $b = 9.839$ (1), $c = 15.644$ (4) Å, $\beta = 118.15$ (2)°, $V = 2208.1$ (7) Å³, $Z = 4$, $D_x = 1.25$ g cm⁻³, $Mo K\alpha$, $\lambda = 0.71069$ Å, $\mu = 0.61$ cm⁻¹, $F(000) = 888$, $T = 293$ K, $R = 0.04$ for 2576 observed reflections. The dimethoxyphenyl and amide groups are coplanar and held together by means of an intramolecular H bond [O...N 2.691 (4), N—H 1.057 (2), H...O 2.295 (2) Å, O...H—N 100.2 (2)°] as observed in the potent antidopaminergic benzamides. There are no unusual bond distances or angles.

Introduction. This work is part of a general study on the optimal topography of benzamide neuroleptics and analogs. It was interesting to obtain the X-ray structure of the title compound (supplied by the Delalande Research Centre) in which the inversion of the amide group, compared to the benzamides, modifies the pharmacological profile. We would like to know if the main structural features of this compound are similar to those occurring in the very potent benzamide analogues: an intramolecular H bond, and the relative orientation of the phenyl and carbonyl groups with regard to the N lone pair or, in our case, to the N(1)—H(1) direction since our compound is protonated.

Experimental. This compound crystallized from a methanol/ethyl acetate mixture at room temperature. Colourless prismatic crystal $0.28 \times 0.13 \times 0.43$ 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. $4^\circ \leq 2\theta \leq 52^\circ$. 4326 independent reflections measured ($-20 \leq h \leq 20$, $0 \leq k \leq 12$, $0 \leq l \leq 19$), 2576 observed [$I \geq 2.5\sigma(I)$]. Structure solved by direct methods (SHELX76, Sheldrick, 1976). 28 of the 29 non-H atoms found in the best FOM E map; the missing C(28) located on a difference Fourier map. Full-matrix least-squares refinement on F using SHELX76. All H atoms located on difference Fourier map. Anisotropic temperature factors (U_{ij}) for all non-H atoms and isotropic ones for H atoms. $R = 0.04$, $wR = 0.04$, $w = 1.0/[\sigma^2(F) + 0.0001F^2]$,

$(\Delta/\sigma)_{\max} = -0.340$ [U_{22} of C(26)], $S = 0.69$; max. and min. heights in final difference Fourier synthesis 0.59 and -0.23 e Å⁻³. Scattering factors from SHELX76 (Cl⁻ from International Tables for X-ray Crystallography, 1974). Structural analysis by XRAY76 (Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976).

Discussion. Atomic parameters are given in Table 1.* Fig. 1 shows the atom numbering and bond lengths (Å) and angles (°).

* Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and torsion angles have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 42524 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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

$$B_{eq} = \frac{2}{3}\pi^2 \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j$$

	x	y	z	B_{eq} (Å ²)
N(1)	-1023 (1)	2261 (2)	1505 (1)	3.63 (1)
C(2)	-1078 (2)	1170 (2)	799 (2)	4.01 (1)
C(3)	-88 (2)	672 (2)	1127 (2)	4.14 (1)
C(4)	517 (2)	1804 (2)	1040 (2)	3.85 (1)
C(5)	431 (2)	3088 (2)	1560 (2)	4.21 (1)
C(6)	-591 (2)	3429 (2)	1219 (2)	3.91 (1)
C(7)	-1499 (2)	1948 (3)	-169 (2)	4.81 (1)
C(8)	-1175 (2)	3438 (3)	105 (2)	4.63 (1)
C(9)	-1952 (2)	2665 (3)	1435 (2)	4.38 (1)
C(10)	-2472 (2)	1478 (3)	1552 (2)	4.30 (1)
C(11)	-2299 (2)	1063 (3)	2470 (2)	5.38 (1)
C(12)	-2795 (2)	1 (3)	2591 (3)	6.63 (1)
C(13)	-3451 (2)	-673 (3)	1805 (3)	6.77 (1)
C(14)	-3644 (2)	-285 (3)	880 (3)	6.85 (1)
C(15)	-3154 (2)	795 (3)	752 (2)	5.70 (1)
C(16)	1517 (2)	1353 (3)	1450 (2)	4.48 (1)
O(17)	1887 (2)	571 (2)	2138 (1)	6.59 (1)
N(18)	1975 (2)	1890 (2)	991 (2)	4.69 (1)
C(19)	2935 (2)	1790 (3)	1270 (2)	5.06 (1)
C(20)	3304 (2)	2716 (3)	871 (2)	4.38 (1)
C(21)	4245 (2)	2694 (3)	1129 (2)	5.40 (1)
C(22)	4818 (2)	1730 (4)	1769 (3)	7.82 (1)
C(23)	4450 (3)	797 (5)	2148 (3)	9.48 (2)
C(24)	3513 (2)	804 (4)	1911 (3)	7.99 (1)
O(25)	2713 (1)	3689 (2)	248 (1)	4.74 (1)
C(26)	2529 (2)	3571 (3)	-743 (2)	6.01 (1)
O(27)	4540 (1)	3666 (2)	712 (2)	6.73 (1)
C(28)	5462 (3)	3534 (5)	827 (3)	9.32 (2)
Cl(29)	182 (1)	1936 (1)	3720 (1)	4.58 (1)

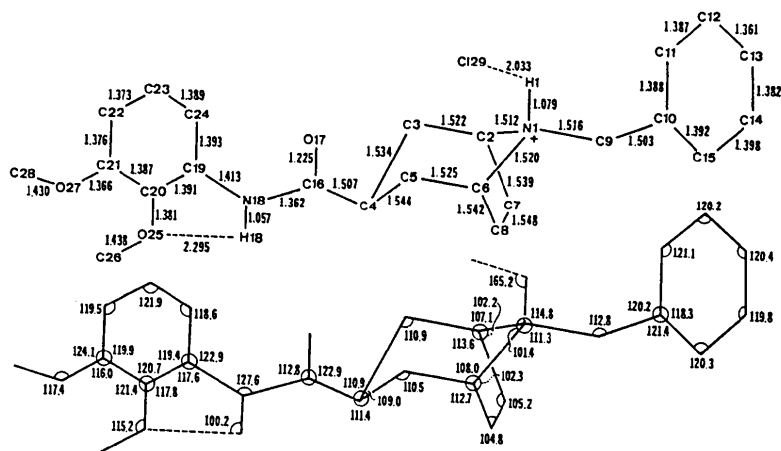


Fig. 1. Atom numbering, bond lengths (Å) and valence angles (°) (max. e.s.d.'s 0.007 Å and 0.4°).

An intramolecular hydrogen bond between N(18) and O(25) [O(25)⋯N(18) 2.691 (4), N(18)⋯H(18) 1.057 (2), H(18)⋯O(25) 2.295 (2) Å, O(25)⋯H(18)—N(18) 100.2 (2)°] leads to a five-membered ring unlike those occurring in the benzamides (six-membered ring) (Durant, Renard, De Beys & Evrard, 1984; Evrard, Renard, De Beys & Durant, 1984; Van de Waterbeemd & Testa, 1983). A second hydrogen bond exists between the endocyclic protonated N(1) atom and the chloride anion: N(1)⋯Cl(29) 3.089 (2), Cl(29)⋯H(1) 2.033 (1), H(1)—N(1) 1.079 (1) Å, N(1)—H(1)⋯Cl(29) 165.2 (1)°. Nevertheless, the crystal packing results mainly from van der Waals interactions.

The *N*-benzyl group is oriented in an equatorial position on the nortropane moiety (Table 2, Fig. 2).

By comparison with a very potent benzamide analogue, tropapride (Jalfre, Bucher, Dorme, Mocquet & Porsolt, 1983), this molecule exhibits the following structural analogies (see also Fig. 3):

- the virtual five- or six-membered ring is formed by the hydrogen bond between the O atom of the *o*-methoxy group and the NH of the amide function resulting in coplanarity between the amide group and the phenyl ring.

- the plane of this virtual ring is nearly parallel with the N(1)—H(1) direction.

- the distance between the centre of the dimethoxyphenyl ring and N(1) is 7.82 Å for the benzamide and 7.98 Å for the anilide (title compound).

However, the substitution of the benzamide by the anilide chain leads to an inversion of the *o*-methoxy orientation by rotation of the phenyl around the N(18)—C(19) bond. This results from the optimum alignment of the anilide to minimize the steric hindrance with the nortropane group. This conformation corresponds to a parallel orientation of the carbonyl group and the N(1)—H(1) direction as opposed to the antiparallel disposition observed in the active benzamide compounds.

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

C(16)—N(18)—C(19)—C(20)	−161.9 (3)
C(4)—C(16)—N(18)—C(19)	172.1 (2)
C(3)—C(4)—C(16)—N(18)	147.1 (2)
C(10)—C(9)—N(1)—C(2)	56.0 (3)
C(11)—C(10)—C(9)—N(1)	86.0 (4)

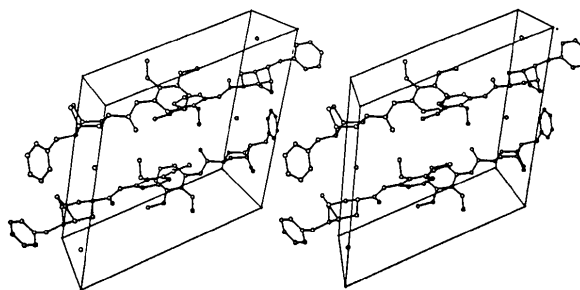


Fig. 2. Stereoview of the molecular conformation and crystal packing.

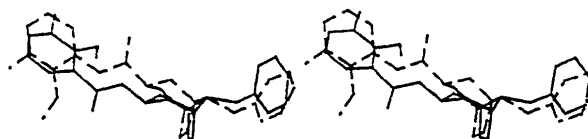


Fig. 3. Stereoscopic view of a rigid fitting between tropapride (full line) and the title compound (dotted line) obtained by superposition of the N lone pairs [N(1)—H(1) directions] and the phenyl rings of the anilide and benzamide groups.

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A Ternary Complex of 1,3-Xylyl-18-crown-5,* *tert*-Butylammonium Perchlorate and Dichloromethane

BY J. VAN EERDEN AND S. HARKEMA

Chemical Physics Laboratory, Twente University of Technology, PO Box 217, 7500 AE Enschede, The Netherlands

AND E. J. R. SUDHÖLTER

Organic Chemistry Laboratory, Twente University of Technology, PO Box 217, 7500 AE Enschede, The Netherlands

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Abstract. $C_{16}H_{24}O_5 \cdot C_4H_{12}N^+ \cdot ClO_4^- \cdot CH_2Cl_2$, $M_r = 554.91$, monoclinic, $P2_1$, $a = 11.582$ (1), $b = 12.396$ (2), $c = 9.281$ (1) Å, $\beta = 91.59$ (1)°, $V = 1332.0$ (5) Å³, $Z = 2$, $D_x = 1.383$ g cm⁻³, $\mu(Mo K\alpha) = 4.0$ cm⁻¹, $F(000) = 588$, $T = 187$ K, final $R = 3.4\%$ for 2154 observed reflections. The crown-*tert*-butylammonium cation complex is of the 'nesting' type: the aryl group of the crown ether and the cation are on the same face of the crown. The $-NH_3^+$ group is hydrogen-bonded to three next-nearest-neighbour O atoms of the macrocycle, which has approximate D_{3d} symmetry. On the opposite face of the ring one Cl of dichloromethane forms a close contact with the $-NH_3^+$ group [Cl...N⁺ 3.554 (3) Å] through the cavity of the ring and also with the intra-annular CH of the aryl group [C...Cl 3.827 (4) Å].

Introduction. As part of a study of the complexing properties of crown ethers (Reinhoudt, de Boer, Uiterwijk & Harkema, 1985, and references therein), the complex of 1,3-xylyl-18-crown-5 with *tert*-butylammonium perchlorate was prepared in dichloromethane solution. Upon standing the solution at room temperature, a crystalline complex was obtained and a structure determination was undertaken.

* IUPAC name: 5,6,8,9,11,12,14,15,16,17-decahydro-4,7,10,13,16-pentaaxabenzol[ab]cyclooctadecene.

Experimental. 1,3-Xylyl-18-crown-5 and *tert*-butylammonium perchlorate were prepared according to literature procedures (Reinhoudt, Gray, Smit & Veenstra, 1976; Kyba, Helgeson, Madan, Gokel, Tarnowski, Moore & Cram, 1977, respectively). Slow evaporation of the solvent from 0.08 *M* 1,3-xylyl-18-crown-5 and 0.16 *M* *tert*-butylammonium perchlorate in dichloromethane solution yielded the crystalline material. D_m not determined.

Intensities measured at 187 K on a Philips PW 1100 diffractometer (Mo *K* α radiation, graphite monochromator). Lattice parameters determined by least squares from 25 reflections ($4.5^\circ < \theta < 8^\circ$). Total of 2606 reflections up to $\theta = 25^\circ$ ($-13 \leq h \leq 13$, $0 \leq k \leq 14$, $0 \leq l \leq 11$) measured in the $\theta/2\theta$ scan mode (scan speed 0.05° s⁻¹, scan width 1.8°); 2154 reflections considered observed [$I > 3\sigma(I)$]. The intensity variation of 3 standard reflections, measured every hour, was less than 3%. No absorption correction. Structure solved with *MULTAN* (Germain, Main & Woolfson, 1971) and refined with a local block-diagonal version of *ORFLS* (Busing, Martin & Levy, 1962). Weights for each reflection in the refinement (on F) calculated from $w = |\sigma(F_o) + 0.01|F_o|^{-2}$, $\sigma(F_o)$ being the e.s.d., based on counting statistics, of the observed structure factor. Scattering factors taken from *International Tables for X-ray Crystallography* (1974) for the non-H atoms and from Stewart, Davidson &