

Fig. 1. The conformation of the *cyclo(L-Phe)*₂ molecule viewed along N(2)–C(P2).

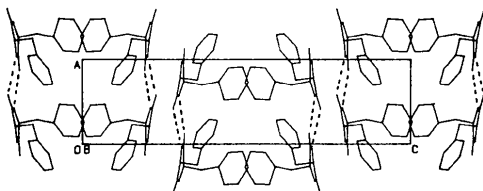


Fig. 2. The crystal structure of *cyclo(L-Phe)*₂ viewed down the *b* axis.

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Structure of *N*-[(3*RS*,5*SR*)-1-Benzyl-5-methyl-3-pyrrolidinyl]-5-chloro-2-methoxy-4-methylaminobenzamide Hydrochloride*

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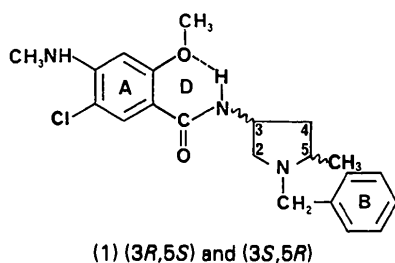
(Received 19 March 1986; accepted 29 May 1986)

Abstract. C₂₁H₂₇ClN₃O₂⁺.Cl⁻, *M*_r = 424.37, monoclinic, *P*2₁/*c*, *a* = 13.820 (3), *b* = 13.002 (3), *c* = 12.714 (3) Å, β = 100.66 (2)°, *V* = 2245.1 (9) Å³, *Z* = 4, *D*_x = 1.256 g cm⁻³, λ(Cu Kα) = 1.54184 Å, μ =

28.6 cm⁻¹, *F*(000) = 896, *T* = 298 K, *R* = 0.062 for 2222 observed reflections with |*F*_o| > 3σ(|*F*_o|). An intramolecular H bond between the amide N and the methoxy O is observed. The distance between the tertiary N and the center of the benzene ring is 7.12 Å, and the deviation of the N from the benzene plane is 0.57 Å.

* New Potent Neuroleptic Drugs of Benzamide Derivatives. VI.

Introduction. The crystal-structure determination of the title compound (1) was undertaken as part of serial studies for finding new potent neuroleptic drugs in benzamide derivatives. The previous papers (Furuya, Iwanami, Takenaka & Sasada, 1982, 1986*a,b*) have reported the crystal structures of the benzamide derivatives having a methyl group at the 2- or 4-position of the pyrrolidine ring. The present compound, which has a methyl group at the 5-position of the ring, exhibits lower neuroleptic activity than compounds with a 2-substituent but higher activity than 4-substituted derivatives (Usuda, 1986).



Experimental. Colorless plates from a methanol-ethyl acetate solution; crystal size, 0.3 × 0.3 × 0.2 mm, Rigaku AFC-5R automated four-circle diffractometer, graphite-monochromated Cu K α radiation ($\lambda = 1.54184$ Å). Accurate cell constants determined using 20 high-angle reflections in range $45 < 2\theta < 55^\circ$. Intensities measured for $3 < 2\theta < 120^\circ$, $-15 \leq h \leq 15$, $0 \leq k \leq 14$, $0 \leq l \leq 14$, θ - 2θ scan mode, scanning rate $4^\circ (2\theta) \text{ min}^{-1}$. Five reference reflections showed no significant intensity deterioration. 3327 independent reflections, 1105 reflections with $|F_o| < 3\sigma(|F_o|)$ considered unobserved. Corrections for Lorentz and polarization factors, but not for absorption and secondary extinction. Standard deviations $\sigma^2(|F_o|) = \sigma_p^2(|F_o|) + q|F_o|^2$, where $\sigma_p(|F_o|)$ evaluated by counting statistics and q (9.80×10^{-4}) derived from variations of monitored reflections (McCandlish, Stout & Andrews, 1975).

Structure solved by direct methods, *MULTAN78* (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978), and block-diagonal least squares. All H atoms found on a difference map, refined isotropically. $\sum w(|F_o| - |F_c|)^2$ minimized, with $w = 1/\sigma(|F_o|)$. Final $R = 0.062$ ($wR = 0.075$, $S = 1.19$) for 2222 observed reflections; maximum shifts of parameters 0.2σ for C, 0.2σ for N, 0.08σ for O, 0.07σ for Cl and 0.5σ for H atoms. $\Delta\rho_{\text{max}} = 0.30$, $\Delta\rho_{\text{min}} = -0.27 \text{ e } \text{Å}^{-3}$. Atomic scattering factors from *International Tables for X-ray Crystallography* (1974). Computations performed on a Digital VAX-11/785 computer.

Table 1. *Fractional coordinates and isotropic temperature factors*

The B_{eq} values accompanied by $\langle \rangle$ are the isotropic temperature factors calculated from anisotropic thermal parameters using the equation $B_{\text{eq}} = 8\pi^2(U_1 + U_2 + U_3)/3$, where U_1 , U_2 , and U_3 are principal components of the mean square displacement matrix U . Values in $\langle \rangle$ are anisotropy defined by $[\sum(B - 8\pi^2U_i)^2/3]^{1/2}$ and those in $()$ are e.s.d.'s; they refer to last decimal places.

	<i>x</i>	<i>y</i>	<i>z</i>	B_{eq} (Å ²)
Cl(H)	0.99548 (8)	0.13828 (8)	0.11416 (8)	6.71 (186)
Cl	0.42126 (9)	-0.10058 (9)	0.28982 (9)	7.76 (135)
O(1)	0.7444 (2)	0.0413 (2)	0.0863 (2)	6.6 (15)
O(2)	0.6882 (2)	0.1781 (2)	0.3648 (2)	7.5 (16)
N(1)	0.4677 (3)	-0.1837 (3)	0.0894 (3)	7.3 (13)
N(2)	0.7844 (2)	0.1809 (2)	0.2404 (3)	6.8 (25)
N(3)	1.0050 (2)	0.3108 (2)	0.2781 (2)	5.8 (19)
C(1)	0.5295 (3)	-0.1068 (3)	0.1330 (3)	5.8 (13)
C(2)	0.5170 (3)	-0.0602 (3)	0.2283 (3)	5.9 (11)
C(3)	0.5772 (3)	0.0176 (3)	0.2735 (3)	5.9 (12)
C(4)	0.6553 (3)	0.0539 (3)	0.2269 (3)	5.4 (14)
C(5)	0.6674 (2)	0.0069 (3)	0.1310 (3)	5.5 (12)
C(6)	0.6056 (3)	-0.0708 (3)	0.0842 (3)	5.8 (9)
C(7)	0.4744 (3)	-0.2360 (3)	-0.0091 (4)	8.0 (20)
C(8)	0.7524 (3)	0.0118 (3)	-0.0199 (3)	7.0 (5)
C(9)	0.7119 (3)	0.1429 (3)	0.2833 (3)	6.0 (16)
C(10)	0.8354 (3)	0.2751 (3)	0.2835 (3)	7.1 (20)
C(11)	0.9421 (3)	0.2557 (3)	0.3429 (3)	6.6 (11)
C(12)	0.9851 (4)	0.4459 (4)	0.1352 (4)	9.3 (33)
C(13)	0.9459 (3)	0.4001 (3)	0.2259 (3)	6.8 (24)
C(14)	0.8443 (3)	0.3510 (3)	0.1954 (4)	8.2 (36)
C(15)	1.1026 (3)	0.3439 (3)	0.3425 (3)	7.2 (24)
C(16)	1.1694 (3)	0.2533 (3)	0.3809 (3)	6.4 (25)
C(17)	1.1749 (3)	0.2161 (3)	0.4822 (3)	7.8 (14)
C(18)	1.2381 (4)	0.1330 (4)	0.5160 (4)	9.1 (19)
C(19)	1.2931 (3)	0.0908 (4)	0.4484 (4)	9.1 (35)
C(20)	1.2867 (4)	0.1280 (4)	0.3476 (4)	9.2 (24)
C(21)	1.2240 (3)	0.2112 (4)	0.3132 (3)	8.3 (18)

Discussion. Final atomic parameters for non-H atoms are given in Table 1.* The structures of the molecule and of the crystal are shown in Figs. 1 and 2, respectively. The bond lengths and angles are listed in Table 2.

An intermolecular H bond is found between the amino N(1) and the carbonyl O(2) in the molecule related by *c* glide, the N(1)...O(2) distance being 2.945 (5) Å. The Cl⁻ anion is H bonded to the protonated N(3), the Cl⁻...N(3) distance being 3.094 (3) Å. The other intermolecular contacts are all larger than the sum of the van der Waals radii.

The bonds C(2)-C(3) [1.368 (5) Å] and C(5)-C(6) [1.384 (5) Å] are short in comparison with the other bonds in the ring [1.393 (5)-1.406 (5) Å], whereas the angles C(2)-C(1)-C(6) [117.7 (3)°] and C(3)-C(4)-C(5) [116.4 (3)°] are appreciably smaller than the other angles [120.6 (3)-122.0 (3)°]. Moreover, the bonds C(1)-N(1) [1.364 (5) Å] and C(4)-C(9)

* Lists of structure factors, anisotropic thermal parameters of non-H atoms, parameters of H atoms, bond lengths and angles involving H atoms, and least-squares planes for the two benzene rings have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 43027 (22 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

[1.502 (5) Å] are rather short for ordinary single bonds. This indicates some contribution from the quinonoidal form. Benzene rings *A* [C(1)–C(6)] and *B* [C(16)–C(21)] are almost planar with maximum atomic deviations of 0.009 and 0.004 Å, respectively.

An intramolecular H bond between the amide N(2) and methoxy O(1) results in a six-membered ring fused with benzene ring *A*. This type of H bond is also observed in the benzamide neuroleptics we studied and in metoclopramide (Cesario, Pascard, Moukhtari & Jung, 1981). The N(2)···O(1) length [2.653 (4) Å] is within the range found for compounds in this series of studies [2.635 (4)–2.716 (9) Å] and metoclopramide [2.683 (6) Å].

The distance between the tertiary amino N atom and the center of benzene ring *A* and the deviation of this N atom from the mean plane of ring *A* are used as the parameters relevant to neuroleptic activity. Comparing

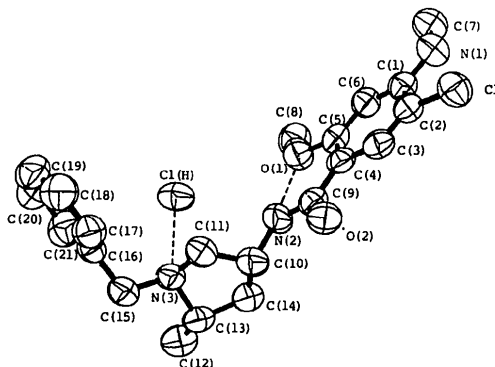


Fig. 1. Molecular structure and atom numbering.

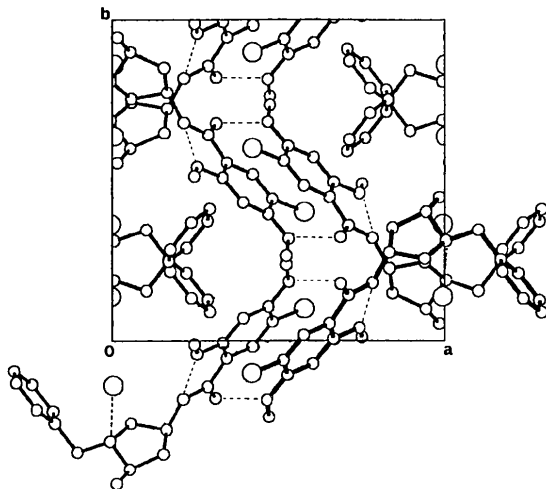


Fig. 2. Projection of the structure on the *ab* plane.

Table 2. Bond lengths (Å) and angles (°) with *e.s.d.*'s in parentheses

Cl–C(2)	1.738 (4)	O(1)–C(5)	1.372 (4)	O(1)–C(8)	1.427 (5)
O(2)–C(9)	1.232 (5)	N(1)–C(1)	1.364 (5)	N(1)–C(7)	1.443 (6)
N(2)–C(9)	1.322 (5)	N(2)–C(10)	1.468 (5)	N(3)–C(11)	1.487 (5)
N(3)–C(13)	1.501 (5)	N(3)–C(15)	1.505 (5)	C(1)–C(2)	1.393 (5)
C(1)–C(6)	1.397 (5)	C(2)–C(3)	1.368 (5)	C(3)–C(4)	1.406 (5)
C(4)–C(5)	1.401 (5)	C(4)–C(9)	1.502 (5)	C(5)–C(6)	1.384 (5)
C(10)–C(11)	1.549 (6)	C(10)–C(14)	1.514 (6)	C(12)–C(13)	1.486 (6)
C(13)–C(14)	1.526 (6)	C(15)–C(16)	1.521 (6)	C(16)–C(17)	1.365 (6)
C(16)–C(21)	1.360 (6)	C(17)–C(18)	1.407 (7)	C(18)–C(19)	1.363 (7)
C(19)–C(20)	1.356 (7)	C(20)–C(21)	1.404 (7)		
C(5)–O(1)–C(8)	120.5 (3)	C(1)–N(1)–C(7)	124.2 (3)		
C(9)–N(2)–C(10)	120.4 (3)	C(11)–N(3)–C(13)	107.0 (3)		
C(11)–N(3)–C(15)	113.1 (3)	C(13)–N(3)–C(15)	112.2 (3)		
N(1)–C(1)–C(2)	120.2 (3)	N(1)–C(1)–C(6)	122.1 (3)		
C(2)–C(1)–C(6)	117.7 (3)	Cl–C(2)–C(1)	119.1 (3)		
Cl–C(2)–C(3)	119.2 (3)	C(1)–C(2)–C(3)	121.6 (3)		
C(2)–C(3)–C(4)	121.7 (3)	C(3)–C(4)–C(5)	116.4 (3)		
C(3)–C(4)–C(9)	115.5 (3)	C(5)–C(4)–C(9)	128.0 (3)		
O(1)–C(5)–C(4)	116.4 (3)	O(1)–C(5)–C(6)	121.6 (3)		
C(4)–C(5)–C(6)	122.0 (3)	C(1)–C(6)–C(5)	120.6 (3)		
O(2)–C(9)–N(2)	123.2 (3)	O(2)–C(9)–C(4)	119.4 (3)		
N(2)–C(9)–C(4)	117.3 (3)	N(2)–C(10)–C(11)	113.2 (3)		
N(2)–C(10)–C(14)	111.5 (3)	C(11)–C(10)–C(14)	105.5 (3)		
N(3)–C(11)–C(10)	104.6 (3)	N(3)–C(11)–C(12)	114.0 (3)		
N(3)–C(11)–C(14)	100.8 (3)	C(12)–C(11)–C(14)	114.9 (3)		
C(10)–C(11)–C(14)	106.4 (3)	N(3)–C(15)–C(16)	112.5 (3)		
C(15)–C(16)–C(17)	120.1 (4)	C(15)–C(16)–C(21)	119.0 (4)		
C(17)–C(16)–C(21)	120.9 (4)	C(16)–C(17)–C(18)	118.9 (4)		
C(17)–C(18)–C(19)	120.2 (5)	C(18)–C(19)–C(20)	120.4 (5)		
C(19)–C(20)–C(21)	119.8 (5)	C(16)–C(21)–C(20)	119.7 (4)		

these values of the present compound with those of the hydrochloride having a methyl group at the 2- or 4-position of the pyrrolidine ring, the distance (7.12 Å) is longer than that of the 4-position (6.91 Å) (Furuya *et al.*, 1986a), but shorter than that of the 2-position (7.25–7.5 Å) (Furuya *et al.*, 1986b). On the other hand, the deviation of N in the present molecule, 0.57 Å, is close to that of the 2-position (0.0–0.7 Å), but smaller than that of the 4-position (1.75 Å). The ordering of these geometrical parameters seems to correspond to the potency order, 2-CH₃ > 5-CH₃ > 4-CH₃.

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