

Structure of 1-[6-(2-Chlorophenyl)-3-pyridazinyl]piperidin-4-ol, an Anticonvulsant Drug

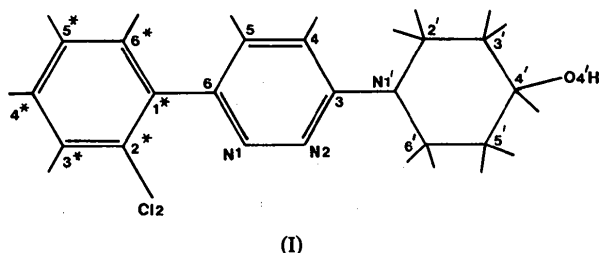
BY JOHN N. LISGARTEN AND REX A. PALMER*

Department of Crystallography, Birkbeck College, University of London, Malet Street, London WC1E 7HX, England

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Abstract. $C_{15}H_{16}ClN_3O$, $M_r = 289.76$, monoclinic, $C2/c$, $a = 50.278$ (3), $b = 6.531$ (7), $c = 8.676$ (6) Å, $\beta = 95.649$ (1)°, $V = 2837.0$ (6) Å³, $Z = 8$, $D_m = 1.36$ (2), $D_x = 1.356$ g cm⁻³, $\lambda(\text{Cu } K\alpha) = 1.54184$ Å, $\mu = 22.60$ cm⁻¹, $F(000) = 1261$, $T = 293$ K, $R = 0.049$ for 2680 observed reflections. The piperidine ring has a slightly distorted chair conformation. Molecules are packed as centrosymmetric dimers, hydrogen-bonded through hydroxyl O atoms while the same atoms generate infinite hydrogen-bonded ribbons through c -glide-related molecules.

Introduction. The title compound (I) is a new, potent and chemically original antiepileptic drug which exhibits a broad spectrum of anticonvulsant activities with few side effects (Biziere, Brochard, Chambon, Hallot & Rodier, 1985). The structure analysis reported here was undertaken as part of a programme of study of convulsant and anticonvulsant compounds being carried out in this Department.



Experimental. Sample provided by Sanofi UK Ltd. Transparent, needle-shaped crystals prepared by slow evaporation from methanol. Specimen $0.02 \times 0.15 \times 0.06$ mm used for data collection, preliminary Weissenberg photographs yielded approximate cell dimensions and showed monoclinic ($2/m$) Laue symmetry. Space group $C2/c$ from systematic absences (hkl , $h+k = 2n+1$; $h0l$, $l = 2n+1$); D_m by flotation (n -hexane/ CCl_4). Enraf–Nonius CAD-4 automated diffractometer,† graphite monochromator, $\text{Cu } K\alpha$ radiation, 25 high-angle reflections ($25 \leq 2\theta \leq 28^\circ$)

* To whom correspondence should be addressed.

† SERC Data Collection Service, Queen Mary College, London.

used to obtain accurate cell dimensions by least-squares fit. ω - 2θ scan, scan width $(0.85 + 0.15 \tan \theta)^\circ$, vertical aperture = 4 mm. 3937 unique reflections with $3 \leq \theta \leq 69^\circ$ measured ($-60 \leq h \leq 60$; $0 \leq k \leq 7$; $0 \leq l \leq 10$), 2680 with $I \geq 3\sigma(I)$; three intensity standards (20,2,0, $\bar{2}4,0,0$ and $\bar{1}7,0,0$) monitored at intervals of 100 measurements showed no significant variations during data collection; intensity data corrected for Lorentz–polarization factors; empirical absorption correction based on φ scans for each of three reflections (North, Phillips & Mathews, 1968) for $\chi \approx 90$ measured at 10° intervals from $\varphi = 0$ to $\varphi = 360^\circ$, normalized transmission factors 0.89 to 0.96. Structure solution by direct methods with *SHELX76* (Sheldrick, 1976). Atomic scattering factors from *SHELX76*; E map gave positions of all non-H atoms. Refinement by full-matrix least squares with anisotropic thermal factors for non-H atoms, isotropic for H atoms which were placed in calculated positions riding on the corresponding C atoms ($C-H = 1.08$ Å) except H(41') which was not identified on the difference map and was positioned geometrically by use of the molecular-graphics package *CHEMX* (Chemical Design Ltd, 1983) on a Melordata Colourgraphics terminal, function minimized was $\sum w(|F_o| - |F_c|)^2$, $w = (\sigma^2 |F_o|^2 + 0.0444 |F_o|^2)^{-1}$, $R = 0.049$, $wR = 0.060$, R (all data) = 0.078, max. (shift/ σ) = 0.47 [for H(41')]. Final difference electron density synthesis showed residual electron density -0.70 to $+0.45$ e Å⁻³. Calculations carried out on Amdahl 470V/8 computer. Geometrical calculations were performed with *XANADU* (Roberts & Sheldrick, 1975) and molecular illustrations were drawn with *PLUTO* (Motherwell & Clegg, 1978).

Discussion. The final atomic coordinates and equivalent isotropic thermal parameters for the non-H atoms are given in Table 1.‡ Bond distances and angles are listed in Table 2. The molecular structure is shown in Fig. 1.

‡ Lists of structure factors, anisotropic thermal parameters and H-atom coordinates have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51337 (15 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. Atomic positional parameters and equivalent isotropic temperature factors for non-H atoms with *e.s.d.*'s in parentheses

$$U_{eq} = (U_{11}U_{22}U_{33})^{1/3}.$$

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{eq} (Å ²)
Cl(2)	0.20833 (2)	0.47430 (14)	0.82282 (12)	0.065
C(1)*	0.1734 (1)	0.7326 (4)	0.6596 (3)	0.041
C(2)*	0.2001 (1)	0.0678 (5)	0.6994 (3)	0.045
C(3)*	0.2214 (1)	0.7910 (5)	0.6518 (4)	0.052
C(4)*	0.2158 (1)	0.9620 (6)	0.5604 (4)	0.063
C(5)*	0.1897 (1)	1.0201 (5)	0.5187 (4)	0.063
C(6)*	0.1687 (1)	0.9049 (5)	0.5683 (4)	0.054
N(1)	0.1317 (1)	0.7363 (4)	0.7646 (3)	0.048
N(2)	0.1098 (1)	0.6498 (3)	0.8156 (3)	0.045
C(3)	0.1068 (1)	0.4477 (4)	0.8128 (4)	0.041
C(4)	0.1259 (1)	0.3173 (5)	0.7556 (4)	0.049
C(5)	0.1481 (1)	0.4068 (5)	0.7086 (4)	0.052
C(6)	0.1505 (1)	0.6211 (5)	0.7128 (3)	0.041
N(1')	0.0831 (1)	0.3742 (4)	0.8599 (4)	0.047
C(2')	0.0810 (1)	0.1670 (5)	0.9239 (5)	0.058
C(3')	0.0528 (1)	0.0885 (5)	0.8900 (5)	0.052
C(4')	0.0326 (1)	0.2329 (4)	0.9490 (4)	0.044
C(5')	0.0359 (1)	0.4452 (5)	0.8853 (4)	0.051
C(6')	0.0643 (1)	0.5178 (5)	0.9193 (5)	0.056
O(4')	0.00589 (4)	0.16229 (37)	0.91021 (29)	0.056

* Atoms in chlorophenyl ring.

The phenyl ring is planar. There are no significant deviations from the average C—C bond length [1.389 (7) Å]. The bond angles C(1)*—C(2)*—C(3)* [122.3 (3)°] and C(2)*—C(1)*—C(6)* [117.2 (3)°] differ significantly (8σ and 9σ) from the average bond angle for the ring of 120.0 (3)°. Distortion of the ring in these regions, probably due to the presence of the Cl attached to C(2)* and the pyridazine group on C(1)*, is in general keeping with the findings of Domenicano, Murray-Rust & Vaciago (1983). The C—Cl bond length [1.732 (3) Å] is typical of *Csp*²—Cl bonds in substructures of the type C(ar)—Cl (Allen, Kennard, Watson, Brammer, Orpen & Taylor, 1987). The Cl atom is slightly out of the plane having a deviation of 0.102 Å. The C(1)*—C(6) [1.476 (4) Å] bond connecting the phenyl and pyridazine groups approximates to a normal biphenyl-link bond length (Allen *et al.*, 1987). The C(3)—N(1') [1.385 (4) Å] bond connecting the pyridazine and piperidine rings is intermediate between the values expected for C—N single and double bonds (Allen *et al.*, 1987).

The pyridazine ring is planar (r.m.s. displacement of the six atoms from the plane is 0.007 Å). The average C—C and C—N bond lengths in this ring, 1.391 (5) and 1.327 (4) Å respectively, are typical of aromatic bonds in planar nitrogenous heterocycles, whereas the N(1)—N(2) [1.349 (4) Å] bond is longer than the normal N(ar)—N(ar) bond in this type of structure (Allen *et al.*, 1987).

The saturated piperidine ring has a distorted chair conformation (Table 2c), $\Delta C_s^{N(1)} = 0.45^\circ$ (Duax & Norton, 1975). The average C—C bond length and

Table 2. Molecular geometry; *e.s.d.*'s are in parentheses

(a) Bond lengths (Å)				
C(4')—O(4')	1.428 (4)	C(4)—C(5)	1.355 (5)	
C(4')—C(5')	1.509 (4)	C(5)—C(6)	1.406 (6)	
C(4')—C(3')	1.513 (5)	C(6)—C(1)*	1.476 (4)	
C(5')—C(6')	1.504 (5)	C(6)—N(1)	1.323 (4)	
C(6')—N(1')	1.462 (4)	C(1)*—C(6)*	1.384 (4)	
C(2')—C(3')	1.509 (5)	C(1)*—C(2)*	1.400 (4)	
C(2')—N(1')	1.471 (4)	C(6)*—C(5)*	1.400 (5)	
C(3)—N(1')	1.385 (4)	C(5)*—C(4)*	1.379 (6)	
C(3)—C(4)	1.412 (4)	C(4)*—C(3)*	1.383 (5)	
C(3)—N(2)	1.330 (4)	C(3)*—C(2)*	1.394 (5)	
N(2)—N(1)	1.349 (4)	C(2)*—Cl(2)	1.732 (3)	
(b) Valence angles (°)				
C(5')—C(4')—C(3')	110.3 (3)	C(6)—C(1)*—C(6)*	118.9 (3)	
C(5')—C(4')—O(4')	110.3 (2)	C(6)—C(1)*—C(2)*	123.8 (3)	
O(4')—C(4')—C(3')	111.5 (2)	C(6)*—C(1)*—C(2)*	117.2 (3)	
C(4')—C(5')—C(6')	110.8 (3)	C(1)*—C(6)*—C(5)*	121.3 (3)	
C(5')—C(6')—N(1')	111.2 (3)	C(6)*—C(5)*—C(4)*	119.9 (3)	
C(3')—C(2')—N(1')	109.8 (3)	C(5)*—C(4)*—C(3)*	120.5 (3)	
C(4')—C(3')—C(2')	111.8 (3)	C(4)*—C(3)*—C(2)*	118.7 (3)	
N(1')—C(3')—N(2)	116.0 (3)	C(1)*—C(2)*—C(3)*	122.3 (3)	
N(1')—C(3)—C(4)	122.1 (3)	C(1)*—C(2)*—Cl(2)	120.9 (2)	
N(2)—C(3)—C(4)	121.7 (3)	C(3)*—C(2)*—Cl(2)	116.6 (2)	
C(3)—C(4)—C(5)	117.0 (3)	C(6')—N(1')—C(2')	112.7 (3)	
C(4)—C(5)—C(6)	119.6 (3)	C(6')—N(1')—C(3)	119.1 (2)	
N(1)—C(6)—C(5)	120.8 (3)	C(2')—N(1')—C(3)	121.7 (3)	
N(1)—C(6)—C(1)*	115.7 (3)	C(3)—N(2)—N(1)	120.3 (3)	
N(2)—N(1)—C(6)	120.5 (3)	C(1)*—C(6)—C(5)	123.5 (3)	
(c) Selected torsion angles (°)				
N(1)—C(6)—C(1)*—C(6)*	43.5 (5)	C(5')—C(4')—C(3')—C(2')	-55.0 (6)	
C(5)—C(6)—C(1)*—C(6)*	-134.9 (6)	C(3')—C(4')—C(5')—C(6')	54.4 (6)	
C(2')—N(1')—C(3)—C(4)	-29.1 (6)	C(4')—C(5')—C(6')—N(1')	-55.0 (6)	
C(2')—N(1')—C(3)—N(2)	154.7 (5)	C(2')—N(1')—C(6')—C(5')	57.1 (6)	
C(5')—C(4')—O(4')—H(4')	-164.1 (6)	C(6')—N(1')—C(2')—C(3')	-56.7 (6)	
C(4')—C(3')—C(2')—N(1')	55.3 (6)			
(d) Hydrogen-bond geometry				
	D—H	D...A	H...A	D—H...A
	(Å)	(Å)	(Å)	(°)
O(4')—H(41')...O(4')	0.735	2.731 (5)	2.61	92
O(4')—H(41')...O(4'')	0.735	2.784 (5)	2.38	116

(c) Selected torsion angles (°)

N(1)—C(6)—C(1)*—C(6)*	43.5 (5)	C(5')—C(4')—C(3')—C(2')	-55.0 (6)
C(5)—C(6)—C(1)*—C(6)*	-134.9 (6)	C(3')—C(4')—C(5')—C(6')	54.4 (6)
C(2')—N(1')—C(3)—C(4)	-29.1 (6)	C(4')—C(5')—C(6')—N(1')	-55.0 (6)
C(2')—N(1')—C(3)—N(2)	154.7 (5)	C(2')—N(1')—C(6')—C(5')	57.1 (6)
C(5')—C(4')—O(4')—H(4')	-164.1 (6)	C(6')—N(1')—C(2')—C(3')	-56.7 (6)
C(4')—C(3')—C(2')—N(1')	55.3 (6)		

(d) Hydrogen-bond geometry

	D—H	D...A	H...A	D—H...A
	(Å)	(Å)	(Å)	(°)
O(4')—H(41')...O(4')	0.735	2.731 (5)	2.61	92
O(4')—H(41')...O(4'')	0.735	2.784 (5)	2.38	116

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

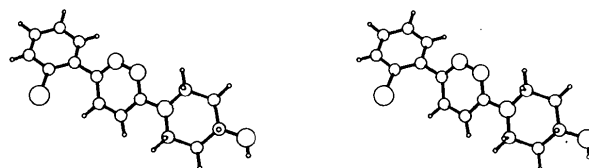


Fig. 1. Stereoview of the molecule looking down *c*.

C—C—C bond angle are 1.509 (5) Å and 111.0 (3)° respectively. These compare well with equivalent values for 1-(1-phenylcyclohexyl)piperidine (Argos, Barr & Webber, 1970) of 1.512 (10) Å and 111.1 (3)° respectively. The average C—N bond length and C—N—C bond angle, 1.467 (4) Å and 112.7 (3)°, do not compare well with their counterparts [1.508 (8) Å and 111.1 (4)°] in 1-(1-phenylcyclohexyl)piperidine. The C—N bond length is, however, in agreement with the average C—N(piperidine) of 1.473 (13) Å cited by Allen *et al.* (1987). There is no asymmetry in C—N

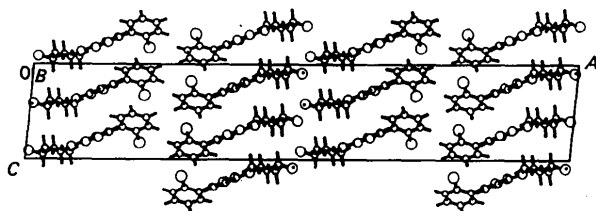


Fig. 2. Crystal packing viewed down *b*.

bond lengths in either structure. The C—O bond of the attached hydroxyl group is normal at 1.428 (4) Å.

The dihedral angle between the planes defining the phenyl and pyridazine rings is 45.55°. The relative orientation of the three ring moieties with respect to one another, and of the hydroxyl group with respect to the piperidine ring, are described by the torsion angles given in Table 2(c).

The packing arrangement of the molecule is shown in Fig. 2. This comprises molecules arranged as dimers across the centre of symmetry in a head-to-head fashion, hydrogen-bonded through the hydroxyl O atoms, while the same atoms generate infinite hydro-

gen-bonded ribbons through *c*-glide-related molecules (Table 2d).

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Structure of (–)-1-Phenylethylammonium Hydrogen (+)-Tartrate

BY E. MOLINS AND C. MIRAVITLLES

*Institut de Ciència de Materials de Barcelona (CSIC), c/ Martí i Franqués,
s/n Apartado de Correos 30102, 08028 Barcelona, Spain*

AND F. LÓPEZ-CALAHORRA, J. CASTELLS AND J. RAVENTÓS

*Departamento de Química Orgánica, División de Ciencias Experimentales y Matemáticas,
Universidad de Barcelona, c/ Martí i Franqués 1–11, 08028 Barcelona, Spain*

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Abstract. $C_8H_{12}N^+ \cdot C_4H_5O_6^-$, $M_r = 271.27$, monoclinic, $P2_1$, $a = 6.352$ (2), $b = 14.195$ (5), $c = 7.507$ (2) Å, $\beta = 107.08$ (2)°, $V = 647.0$ (8) Å³, $Z = 2$, $D_x = 1.39$ g cm⁻³, $\lambda(\text{Mo } K\alpha) = 0.71069$ Å, $\mu(\text{Mo } K\alpha) = 1.05$ cm⁻¹, $F(000) = 288$, $T = 294$ K, $R = 0.037$ for 941 observed reflections [$F > 2\sigma(F)$]. This (+)-tartrate structure is very similar to its *meso*-tartrate analogue. O(6) occupies an unusual antiperiplanar position relative to the carboxyl group. A strong hydrogen-bond network stabilizes the crystal packing.

Introduction. Preferential crystallization of diastereomeric salts is a classical procedure for the resolution of racemic bases and acids. (+)-Tartaric acid is, probably, the most popular acid employed in the resolution of

amines. An investigation directed to exploiting its recognition abilities in solid-phase ('polymer supported') methodology is in progress. Within this context, it was considered that a detailed study of a pair of diastereomeric salts would afford information on the most convenient way in which tartaric acid should be anchored to the polymeric frame. In order to study the (+)-tartrate configuration in a chiral environment, we have undertaken the X-ray structural resolution of (+)-tartrate with the (–)-1-phenylethylammonium cation. A study of (–)-1-phenylethylammonium hydrogen *meso*-tartrate has been published (Kroon, Duisenberg & Peerdeman, 1984). Attempts to crystallize (+)-1-phenylethylammonium (+)-tartrate have been unsuccessful so far.