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8-Chloro-5-(4-methylpiperazin-1-yl)-11*H*-pyrido[2,3-*b*][1,5]benzodiazepine

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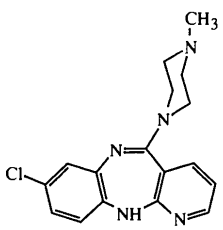
Abstract

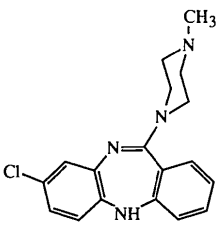
The crystal structure determination of $C_{17}H_{18}ClN_5$ has been undertaken as part of our studies of dopamine receptors. The diazepine ring is in a boat conformation while the piperazine ring is in the normal chair conformation. The dihedral angle between the two aromatic rings that lie on the same side of the diazepine moiety is 126.4 (1)°. There is one N—H···N hydrogen bond [N···N 3.184 (3) Å].

Comment

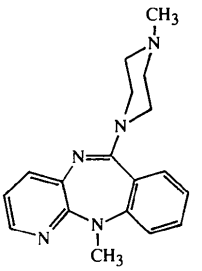
The title compound, (I), was prepared as part of our study of dopamine receptors and related binding sites implicated in schizophrenia diseases (Liégeois, 1992; Liégeois, Bruhwyler *et al.*, 1993; Liégeois, Rogister *et al.*, 1994). (I) is a strict bioisoster of clozapine, (II), the crystal structure of which was determined by Petcher & Weber (1976). Despite a great similarity between the two structures, (I) presented lower affinities for the studied receptors (Liégeois, 1992). In order to find a successor to clozapine, and to better understand the mechanisms of action of antipsychotic drugs, different studies are in development. Among them, some crystallographic structures of related compounds have been determined, such as that of 3-methyl-6-(4-methylpiperazin-1-yl)-11*H*-pyrido[2,3-*b*][1,4]benzodiazepine, (III) (Dupont, Liégeois, Rogister & Delarge, 1995).



(I)



(II)



(III)

In (I), the diazepine ring has a boat conformation where the four C atoms of the outer ring junctions are almost coplanar: the maximum deviation from their mean plane is 0.034 (2) Å [(II) 0.013 (3), (III) 0.017 (1) Å]. The deviation of the 'prow of the boat', N5, is −0.551 (4) Å, and those of N12 and C13 ('the stern') −0.668 (4) and −0.667 (4) Å, respectively. The corresponding deviations in (II) are −0.647 (3), −0.733 (3) and −0.712 (3) Å, respectively, and in (III) −0.582 (2), −0.712 (3) and −0.767 (3) Å, respectively. The distances between the *N*-methylpiperazine atom and the centres of the two aromatic rings are 7.739 (4) and 6.021 (4) Å [7.716 (3) and 5.972 (3) Å in (II), 7.727 (4) and 6.084 (4) Å in (III)]. The dihedral angle between the two aromatic rings [126.4 (1)°] is larger than in (II) [115.0 (1)°] and in (III) [119.4 (1)°]. There is one intermolecular hydrogen bond, N5—H5···N3^{i} [N5···N3^{i} 3.184 (3), H5···N3^{i} 2.19 Å, N5—H5···N3^{i} 165°; symmetry code: (i) $1-x, -1-y, -z$].

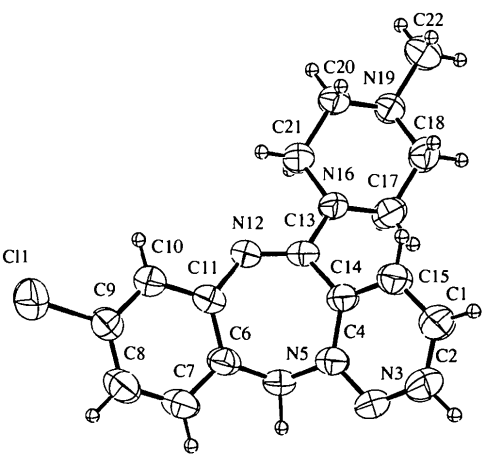


Fig. 1. Molecular structure with atom-labelling scheme. Displacement ellipsoids are shown at the 50% probability level. H atoms are drawn as small circles of arbitrary radii.

Experimental

The compound was prepared as described by Liégeois (1992), at the Laboratory of Medicinal Chemistry of Liège. Crystals were obtained from *n*-hexane solution at room temperature.

Crystal data

$C_{17}H_{18}ClN_5$
$M_r = 327.81$
Monoclinic
$P2_1/n$
$a = 11.9739\ (12)$ Å
$b = 10.2088\ (11)$ Å
$c = 14.662\ (2)$ Å
$\beta = 113.836\ (7)°$
$V = 1639.4\ (3)$ Å^3
$Z = 4$
$D_x = 1.328$ Mg m^{-3}

Cu $K\alpha$ radiation
$\lambda = 1.5418$ Å
Cell parameters from 35 reflections
$\theta = 24.30–34.46°$
$\mu = 2.109$ mm^{-1}
$T = 293\ (2)$ K
Prism
0.42 × 0.42 × 0.34 mm
Colourless

Data collection

Stoe Siemens AED four-circle diffractometer
ω scans
Absorption correction: ψ scan (*EMPIR*; Stoe & Cie, 1987*b*)
$T_{min} = 0.506$, $T_{max} = 0.564$
2170 measured reflections
2055 independent reflections

1428 observed reflections $[I > 2\sigma(I)]$
$R_{int} = 0.0239$
$\theta_{max} = 55.00°$
$h = -12 \rightarrow 0$
$k = 0 \rightarrow 10$
$l = -14 \rightarrow 15$
2 standard reflections
frequency: 60 min
intensity decay: 5%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.0425$
$wR(F^2) = 0.1313$
$S = 0.965$
2051 reflections
210 parameters
H atoms were restrained (included as riding atoms) except the H(N5) atom which was kept fixed
$w = 1/[\sigma^2(F_o^2) + (0.0684P)^2 + 0.5308P]$ where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.186$ e Å^{-3}
$\Delta\rho_{min} = -0.266$ e Å^{-3}
Extinction correction: *SHELXL*93 (Sheldrick, 1993)
Extinction coefficient: 0.0061 (5)
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
Cl1	0.96610 (9)	0.02019 (9)	0.23743 (7)	0.0870 (4)
C1	0.7752 (3)	−0.7615 (3)	−0.0122 (2)	0.0671 (9)
C2	0.6702 (3)	−0.7370 (3)	0.0020 (2)	0.0690 (9)
N3	0.6237 (2)	−0.6188 (3)	0.0014 (2)	0.0614 (7)
C4	0.6815 (2)	−0.5177 (3)	−0.0176 (2)	0.0514 (7)
N5	0.6368 (2)	−0.3932 (2)	−0.0116 (2)	0.0569 (7)
C6	0.7212 (2)	−0.3013 (3)	0.0513 (2)	0.0511 (7)
C7	0.7030 (3)	−0.2462 (3)	0.1310 (2)	0.0645 (9)
C8	0.7777 (3)	−0.1492 (3)	0.1892 (2)	0.0662 (9)
C9	0.8729 (3)	−0.1059 (3)	0.1678 (2)	0.0573 (8)
C10	0.8950 (3)	−0.1598 (3)	0.0901 (2)	0.0543 (8)
C11	0.8211 (2)	−0.2602 (3)	0.0320 (2)	0.0483 (7)
N12	0.8460 (2)	−0.3013 (2)	−0.0491 (2)	0.0490 (6)
C13	0.8269 (2)	−0.4186 (3)	−0.0835 (2)	0.0461 (7)
C14	0.7809 (2)	−0.5318 (3)	−0.0442 (2)	0.0475 (7)
C15	0.8297 (3)	−0.6560 (3)	−0.0371 (2)	0.0569 (8)
N16	0.8595 (2)	−0.4494 (2)	−0.1612 (2)	0.0508 (6)
C17	0.7896 (3)	−0.5395 (3)	−0.2417 (2)	0.0630 (9)
C18	0.8729 (3)	−0.6026 (3)	−0.2829 (2)	0.0664 (9)
N19	0.9291 (2)	−0.5035 (2)	−0.3215 (2)	0.0545 (6)
C20	0.9983 (3)	−0.4132 (3)	−0.2424 (2)	0.0570 (8)
C21	0.9185 (3)	−0.3481 (3)	−0.1982 (2)	0.0573 (8)
C22	1.0063 (3)	−0.5635 (4)	−0.3656 (3)	0.0813 (11)

Table 2. *Selected geometric parameters (Å, °)*

Cl1—C9	1.739 (3)	N12—C13	1.284 (3)
C2—N3	1.327 (4)	C13—N16	1.381 (3)
N3—C4	1.333 (3)	C13—C14	1.492 (4)
C4—N5	1.396 (4)	N16—C17	1.463 (3)
C4—C14	1.402 (4)	N16—C21	1.474 (3)
N5—C6	1.414 (4)	C18—N19	1.452 (4)
C6—C11	1.400 (4)	N19—C20	1.451 (3)
C11—N12	1.401 (3)	N19—C22	1.458 (4)
C2—N3—C4	116.9 (2)	N12—C13—N16	118.2 (2)
N3—C4—N5	116.5 (2)	N12—C13—C14	127.2 (2)
N5—C4—C14	120.1 (2)	N16—C13—C14	114.4 (2)
C4—N5—C6	117.0 (2)	C1—C15—C14	120.2 (3)
C7—C6—N5	120.1 (2)	C13—N16—C17	123.2 (2)
C11—C6—N5	120.8 (2)	C13—N16—C21	118.7 (2)
C8—C9—Cl1	120.0 (2)	C17—N16—C21	110.3 (2)
C10—C9—Cl1	119.2 (2)	C20—N19—C18	109.6 (2)
C9—C10—C11	120.7 (3)	C20—N19—C22	111.2 (2)
C10—C11—N12	116.0 (2)	C18—N19—C22	110.9 (2)
C13—N12—C11	123.2 (2)		
N3—C4—N5—C6	126.1 (3)	C11—N12—C13—N16	−177.4 (2)
C14—C4—N5—C6	−54.9 (3)	C11—N12—C13—C14	−2.4 (4)
C4—N5—C6—C7	−120.3 (3)	N5—C4—C14—C13	−10.8 (4)
C4—N5—C6—C11	62.5 (3)	N16—C13—C14—C15	37.0 (4)
Cl1—C9—C10—C11	−179.3 (2)	N12—C13—C14—C4	45.2 (4)
C9—C10—C11—N12	175.6 (2)	N16—C13—C14—C4	−139.6 (3)
C7—C6—C11—N12	−175.8 (3)	N12—C13—N16—C17	−144.2 (3)
N5—C6—C11—N12	1.4 (4)	C14—C13—N16—C17	40.2 (4)
C10—C11—N12—C13	150.2 (3)	C13—N16—C17—C18	−152.5 (3)
C6—C11—N12—C13	−37.3 (4)		

Data collection: *DIF*4 (Stoe & Cie, 1987*a*). Cell refinement: *DIF*4. Data reduction: *REDU*4 (Stoe & Cie, 1987*c*). Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1985). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEP*II (Johnson, 1976). Software used to prepare material for publication: *SHELXL*93.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates, complete geometry and least-squares-planes data have been deposited with the IUCr (Reference: PA1200). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Stoe & Cie (1987*c*). *REDU4. Data Reduction Program*. Version 6.2. Stoe & Cie, Darmstadt, Germany.

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Absolute Configuration of (*R*)-1-Phenylethylammonium (*S*)-2-(6-Methoxy-2-naphthyl)propionate

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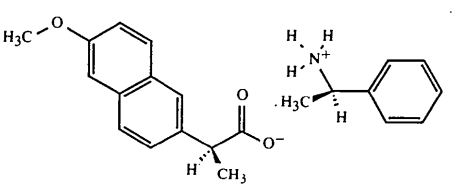
Abstract

The title salt, $C_8H_{12}N^+.C_{14}H_{13}O_3^-$, results from the reaction of known (*R*)-1-phenylethylamine with naproxen, an inhibitor of the cyclo-oxygenase responsible for the biosynthesis of prostaglandins. Naproxen exhibits anti-inflammatory, analgesic and antipyretic activity in man. The crystal structure determination confirms the absolute *S* geometry of the chiral C atom of naproxen previously reported. There are three intermolecular hydrogen bonds between the NH_3^+ and COO^- groups.

Comment

Naproxen, (*S*)-2-(6-methoxy-2-naphthyl)propionic acid, is a non-steroidal anti-inflammatory agent (Goodman & Gilman, 1980) and an optically pure carboxylic acid advantageously used in the resolution of racemic mixtures of aliphatic amines. Moreover, the determination of the crystal structure of the ammonium salt obtained from the reaction of the resolved amine with naproxen allows the identification of the absolute geometry of the chiral C atom in the pure enantiomeric amine. We report here the structure of the title salt, (I).



(I)

The distances and angles in the naproxen ion in the title compound are similar to those found in naproxen itself, $C_{14}H_{14}O_3$, (II) (Ravikumar, Rajan, Pattabhi & Gabe, 1985). The methoxy group is nearly coplanar with the naphthalene moiety in both crystal structures. However, the orientations of the naphthalene moiety with respect to the —CH(CH_3)—COOH group are quite different, as shown by the torsion angles C9—C8—C13—C15 [152.5 (3) in (I), −70.5 (8)° in (II)] and C9—C8—C13—C14 [−82.2 (4) in (I), 48.9 (9)° in (II)]. The torsion angles around the C13—C15 bond differ to a lesser extent [C8—C13—C15—O17 −83.4 (3) in (I), −90.3 (8)° in (II); C14—C13—C15—O17 151.8 (3) in (I), 149.4 (7)° in (II)]. The determination of the structure of the title salt confirms the absolute *S* configuration of the chiral atom C13 of naproxen reported by Riegel, Maddox & Harrison (1974). The crystal packing is characterized by three N—H···O intermolecular hydrogen bonds, detailed in Table 3.

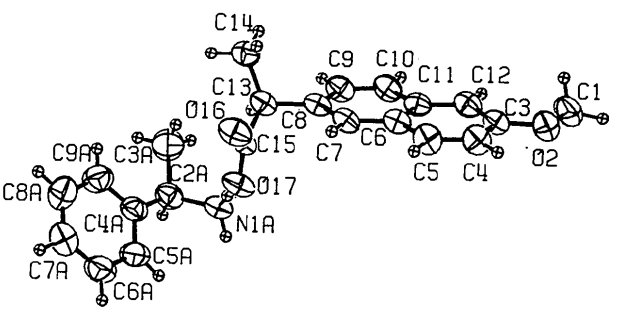


Fig. 1. The molecular structure of the title salt with the atom-labelling scheme. Displacement ellipsoids are shown at the 50% probability level for non-H atoms; H atoms are drawn as small circles of arbitrary radii.

Experimental

(*R*)-(+)-1-Phenylethylamine and naproxen were obtained from Aldrich Chemie (Belgium). The salt was prepared at the Laboratory of Medicinal Chemistry of Liège.

Crystal data

$C_8H_{12}N^+.C_{14}H_{13}O_3^-$
M_r = 351.43
Cu $K\alpha$ radiation
λ = 1.5418 Å