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A monoamine oxidase B inhibitor: *N*-(2-aminoethyl)-*p*-chlorobenzamide (Ro16-6491) hydrochloride

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Key indicators

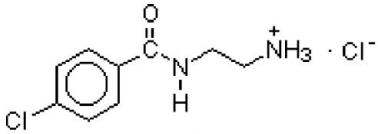
Single-crystal X-ray study
T = 294 K
Mean σ(C–C) = 0.017 Å
R factor = 0.076
wR factor = 0.206
Data-to-parameter ratio = 9.3

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

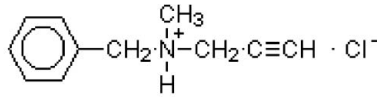
In the title compound, 2-(4-chlorobenzamido)ethanaminium chloride, $C_9H_{12}ClN_2O^+\cdot Cl^-$, both independent cations have linearly extended conformations, with protonation occurring at the terminal N atom. The interplanar angles between the chlorobenzoyl rings and the planar amide groups are 137.6 (3) and 149.3 (5)° for cations *A* and *B*, respectively. The cations are N—H···O hydrogen-bonded in a head-to-head/tail-to-tail fashion, producing distinct hydrophobic and hydrophilic layers running parallel to [110]. The Cl^- anions are hydrogen-bonded to the terminal positively charged $-NH_3^+$ groups. Weak C—H···Cl^- interactions further coordinate the Cl^- anions. Structural comparison with pargyline, an irreversible MAO-B inhibitor, is presented.

Comment

The compound Ro16-6491 was discovered some years ago and characterized as a potent and selective short-acting reversible inhibitor of monoamine oxidase B (MAO-B) (Da Prada *et al.*, 1990). Although some studies suggest that the inhibitor binds to an active site amino acid (Cesura *et al.*, 1996), recent structure determination of an MAO-B inhibitor complex (Binda *et al.*, 2003) has been interpreted as covalent inhibitor binding, with loss of the terminal amino group, to the enzyme flavin cofactor at the same site (Binda *et al.*, 2002) as the irreversible inhibitor pargyline. We present here the structure of Ro16-6491, (I), and a comparison with that of pargyline, (II).



(I)



(II)

The structure of (I), shown in Fig. 1, contains two independent cations and two anions in the asymmetric unit. Bond distances and angles are within normal ranges. The small conformational differences between the two cations are best described in terms of the C6—C5—C8—N10 torsion angles of 42.3 (12) and 31.1 (14)°, and the planes between the chlorobenzoyl rings and amide-group planes (atoms C5/C8/O9/N10), which intersect at angles of 137.6 (3) and 149.3 (5)° for cations *A* and *B*, respectively.

Hydrogen bonds (Table 1) produce a two-dimensional network running parallel to [110] (Fig. 2), giving rise to distinct hydrophobic (chlorobenzoyl rings) and hydrophilic (amidoethanaminium group) layers, and a head-to-head/tail-to-tail packing order. The Cl^- anions are coordinated by H atoms

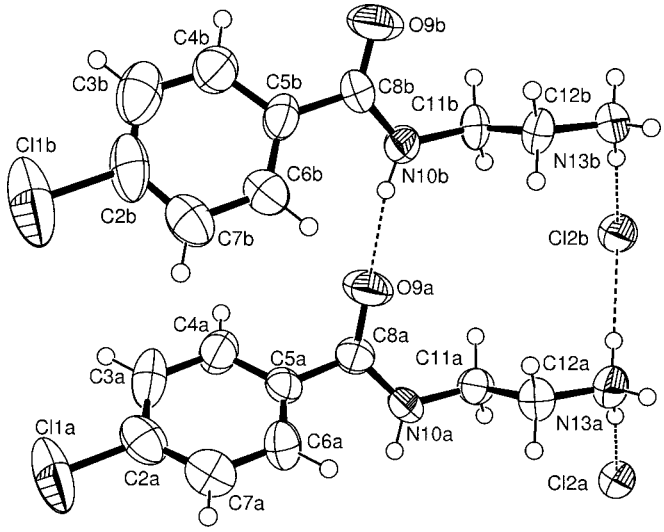


Figure 1
The asymmetric unit of (I), showing 50% probability displacement ellipsoids. H atoms are drawn as small circles of arbitrary radii. Hydrogen bonds are shown as dashed lines.

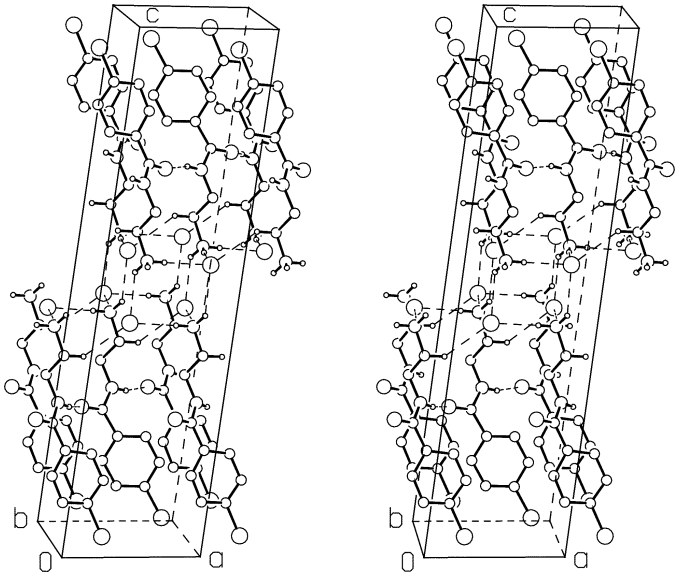


Figure 2
A stereoscopic diagram of the molecular packing and hydrogen-bond scheme (shown as dashed lines between atoms). Atoms are drawn as circles of arbitrary radii. For clarity, only H atoms involved in the hydrogen bonding are shown.

from the hydrogen-bond donors N13 and C12. Van der Waals interactions also contribute to the crystal packing.

Fig. 3 is a superimposition of the structures of Ro16-6491, (I), and pargyline, (II) (Hempel *et al.*, 2005), in which the phenyl C atom and adjacent C and N atoms in each cation (C5, C8 and N10 in Ro16-6491) were used in the fitting procedure. Both structures are linearly extended, and rotation of 180° about the C8—N10 bond in Ro16-6491, *i.e.* a *trans* conformation of atoms C11 to O9, would result in a close conformational similarity between the two cations, indicating a possibility of occupying similar positions in enzyme complexes, provided surroundings are favorable for the

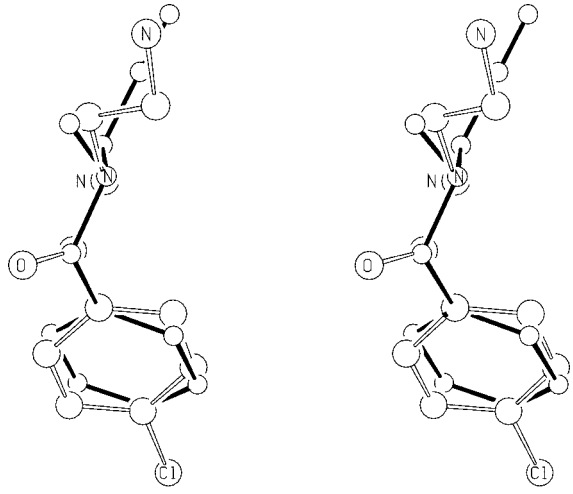


Figure 3
A stereoscopic diagram of the superimposition of the cation of (I) and that of pargyline hydrochloride (shown with filled bonds and small circles).

carboxyl O atom of Ro16-6491. The present structure may be useful for interpretation of future complexes.

Experimental

The title compound was obtained from Hoffmann Le Roche. Experiments to find proper crystallization conditions produced only small crystals of low quality. The crystal used was obtained by slow evaporation from a 3:3:1 methanol–ethanol–butanol solution at 278 K. Efforts to obtain better crystals proved unsuccessful.

Crystal data

$C_9H_{12}ClN_2O^+\cdot Cl^-$
M_r = 235.11
Triclinic, $P\overline{1}$
a = 6.726 (2) Å
b = 6.837 (2) Å
c = 25.267 (5) Å
α = 83.57 (2)°
β = 83.03 (2)°
γ = 88.03 (2)°
V = 1145.8 (5) Å^3
Z = 4
D_x = 1.363 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 32 reflections
θ = 19–37°
μ = 4.87 mm^{-1}
T = 294 (2) K
Prism, colorless
0.29 × 0.17 × 0.15 mm

Data collection

Picker FACS-1 four-circle diffractometer
$\omega/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.423, T_{max} = 0.480
2628 measured reflections
2386 independent reflections
1613 reflections with $I > 2\sigma(I)$
R_{int} = 0.019
θ_{max} = 65.0°
$h = 0 \rightarrow 7$
$k = -8 \rightarrow 8$
$l = -29 \rightarrow 29$
3 standard reflections every 100 reflections
intensity decay: 3.9%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.076
$wR(F^2)$ = 0.206
S = 1.07
2386 reflections
257 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0929P)^2 + 2.1584P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.47 e Å^{-3}
$\Delta\rho_{min}$ = −0.41 e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N10A—H10A···O9B^{i}	0.86	1.95	2.762 (11)	157
N10B—H10B···O9A	0.86	2.02	2.826 (10)	155
N13A—H13A···Cl2A	0.89	2.31	3.198 (7)	174
N13A—H13B···Cl2B^{ii}	0.89	2.52	3.231 (8)	137
N13A—H13C···Cl2B	0.89	2.26	3.143 (8)	172
N13B—H13D···Cl2B	0.89	2.30	3.187 (7)	173
N13B—H13E···Cl2A^{ii}	0.89	2.49	3.206 (7)	138
N13B—H13F···Cl2A^{iii}	0.89	2.27	3.157 (7)	172
C12A—H12B···Cl2B^{iv}	0.97	2.80	3.569 (10)	137
C12B—H12D···Cl2A^{v}	0.97	2.70	3.501 (9)	140

Symmetry codes: (i) $x+1, y+1, z$; (ii) $-x, -y+1, -z+1$; (iii) $x-1, y-1, z$; (iv) $x+1, y, z$; (v) $x, y-1, z$.

All H atoms were visible in a difference map but, due to the paucity of the intensity data, their positions were calculated and refined in a riding-model approximation. The difference map showed clearly that the protonation of the molecule occurs at the terminal atom N13 in both independent cations. One overall isotropic displacement parameter was refined for H atoms in the methylene groups [U_{iso}(H) = 0.060 (7) Å^2] and another for the remaining H atoms [0.077 (7) Å^2]. The range of C—H distances is 0.93–0.97 Å and the range of N—H distances is 0.86–0.89 Å.

Data collection: *Picker Manual* (Picker, 1967); cell refinement: *Picker Manual*; data reduction: *DATRDN* (Stewart, 1976); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP3 for Windows* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97*.

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