Acta Cryst. (1998). C**54**, 811–813

Isostructural Metabolites of Two Anti-Parkinson Drugs

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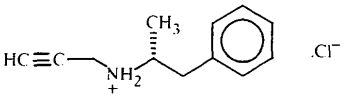
(*Received 9 April 1997; accepted 19 December 1997*)

Abstract

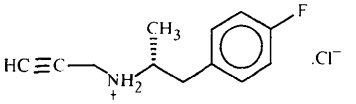
The absolute configurations of desmethylselegiline hydrochloride [(*R*)-(−)-1-benzyl-*N*-(2-propynyl)ethylammonium chloride, $C_{12}H_{16}N^+.Cl^-$], (1), and *p*-fluorodesmethylselegiline hydrochloride [(*R*)-(−)-1-(4-fluorobenzyl)-*N*-(2-propynyl)ethylammonium chloride, $C_{12}H_{15}FN^+.Cl^-$], (2), have been determined. The two compounds are metabolites of the anti-Parkinson agent selegiline and its backup, *p*-fluoroselegiline. The two crystal structures are highly isostructural.

Comment

Selegiline (or Jumex), a selective monoamine oxidase B (MAO-B) inhibitor, has been widely used in the treatment of Parkinson's disease, while *p*-fluoroselegiline is its backup drug (Knoll *et al.*, 1992). When given orally, considerable first-pass metabolism takes place in the liver, one of the main products of which is the desmethylated derivative of the drug (Heinonen *et al.*, 1989). In order to understand the biological significance of the metabolites, compounds (1) and (2) have been synthesized (Plenevaux *et al.*, 1980) and crystallized from acetonitrile. We now report the crystal structures of (1) and (2).



(1)



(2)

In the case of selegiline, the *R* enantiomer has superior pharmacological properties compared with the *S* isomer (Robinson, 1985; Magyar *et al.*, 1967), and it is also known that metabolic processes leave the configuration at C4 unaltered (Schachter *et al.*, 1980). Therefore, it is important to unambiguously determine the absolute configuration of the synthesized compounds. Our structure determinations show that both compounds have an *R* stereochemistry at C4 (Figs. 1 and 2).

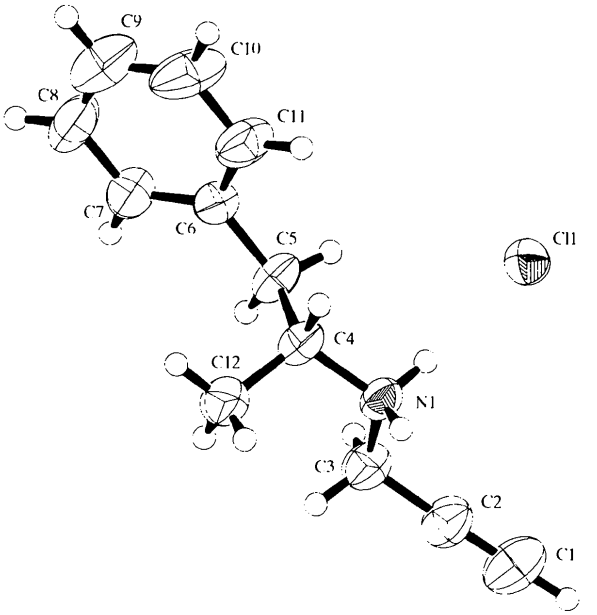


Fig. 1. The molecular structure and atomic numbering for (1) with displacement ellipsoids drawn at the 50% probability level.

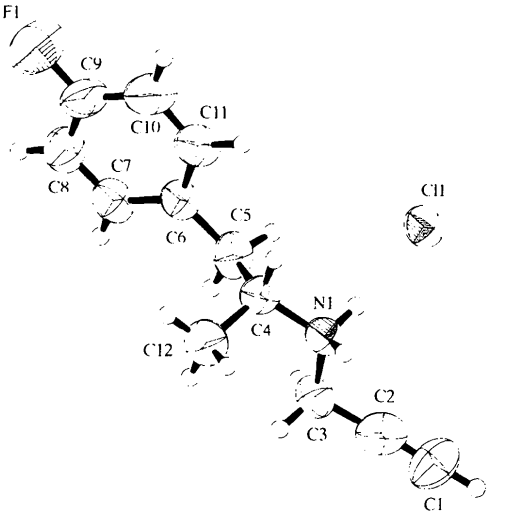


Fig. 2. The molecular structure and atomic numbering for (2) with displacement ellipsoids drawn at the 50% probability level.

Perhaps the most important feature of the two crystal structures is that they are isostructural (Kálmán *et al.*, 1993); in contrast, their methylated parent compounds are not (Simon *et al.*, 1986, 1992). The unit-cell similarity index ($\pi = a_1 + b_1 + c_1/a_2 + b_2 + c_2$) is 0.0033. The unit cell of (1) is 4.5 Å^3 larger than that of (2). In the crystal lattice, chains of hydrogen bonds

between the Cl^- anions and the alkylammonium cations (Fig. 3) form along the 2_1 axes.

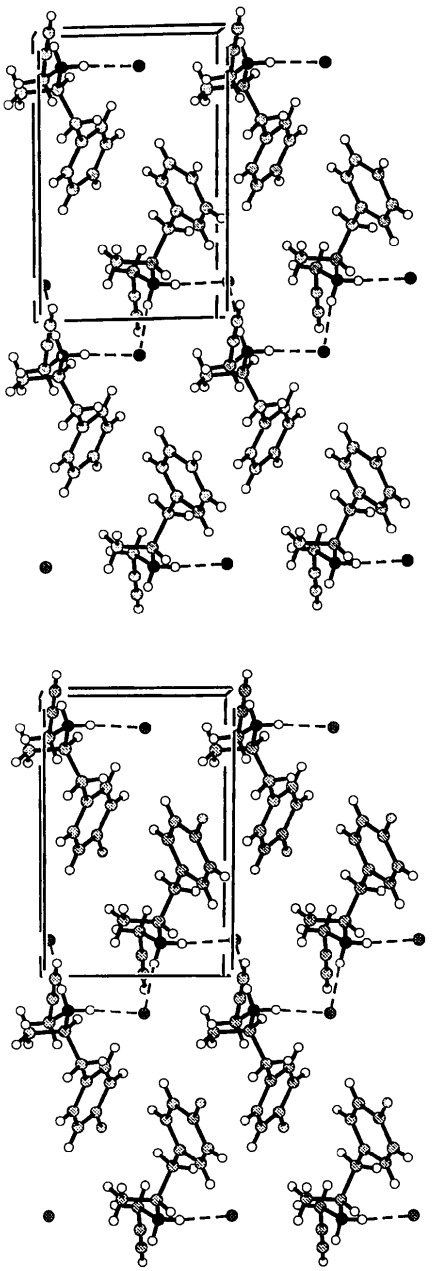


Fig. 3. Packing diagram of (1) (above) and (2) (below). The view is along the *a* axis, with the *b* axis horizontal and the *c* axis vertical.

Compound (1) undergoes polymorphic transformation under increased pressure and temperature (Horváth *et al.*, 1994). The α modification is the stable modification at room temperature, while the β modification can be obtained by recrystallization from acetone. The β form is stable at room temperature when obtained by heating in a KBr pellet. The present single-crystal study of the α modification has also facilitated clarification of the polymorphism by allowing assignment of the peaks due to the α modification in the powder diffractograms of the examined samples.

Experimental

The synthesis details of compounds (1) and (2) have been described previously by Plenevaux *et al.* (1990).

Compound (1)

Crystal data

$C_{12}H_{16}N^+.Cl^-$
M_r = 209.71
Monoclinic
$P2_1$
a = 7.5540 (8) Å
b = 7.3473 (6) Å
c = 11.8146 (11) Å
β = 107.148 (8)°
V = 626.58 (10) Å^3
Z = 2
D_x = 1.112 Mg m^{-3}
D_m not measured
Cu $K\alpha$ radiation
λ = 1.54178 Å
Cell parameters from 20 reflections
θ = 24.20–34.04°
μ = 2.395 mm^{-1}
T = 296 (2) K
Plate
0.25 × 0.15 × 0.10 mm
Transparent

Data collection

Rigaku AFC-6*S* diffractometer
$\omega/2\theta$ scans
Absorption correction: none
1416 measured reflections
1323 independent reflections
1145 reflections with $I > 2\sigma(I)$
R_{int} = 0.078
θ_{max} = 75.10°
$h = -9 \rightarrow 9$
$k = -9 \rightarrow 9$
$l = -14 \rightarrow 14$
3 standard reflections every 150 reflections
intensity decay: −1.63%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.077
$wR(F^2)$ = 0.256
S = 1.156
1320 reflections
132 parameters
Only H-atom U's refined
$w = 1/[\sigma^2(F_o^2) + (0.1388P)^2 + 0.508P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.014
$\Delta\rho_{max}$ = 0.423 e Å^{-3}
$\Delta\rho_{min}$ = −0.925 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute structure: Flack (1983)
Flack parameter = 0.06 (6)

Table 1. *Selected geometric parameters (Å, °) for (1)*

N1—C3	1.488 (10)	C1—C2	1.184 (11)
N1—C4	1.518 (8)	C2—C3	1.462 (9)
C3—N1—C4	116.8 (6)	C1—C2—C3	178.1 (15)
C4—N1—C3—C2	−173.7 (8)	N1—C4—C5—C6	−163.6 (6)
C3—N1—C4—C5	−67.7 (9)	C4—C5—C6—C7	−118.5 (8)
C12—C4—C5—C6	71.4 (9)		

Table 2. *Hydrogen-bonding geometry (Å, °) for (1)*

D—H···*A*	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*A*···Cl1	2.206 (6)	3.104 (6)	175.47 (14)
N1'—H1*B*'···Cl1	2.225 (5)	3.103 (5)	164.74 (15)

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

Compound (2)

Crystal data

$C_{12}H_{15}FN^+.Cl^-$
M_r = 227.70
Monoclinic
$P2_1$
a = 7.481 (2) Å
b = 7.447 (2) Å
c = 11.8743 (9) Å
β = 107.480 (9)°
V = 631.0 (2) Å^3
Z = 2
D_x = 1.198 Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
λ = 1.54178 Å
Cell parameters from 25 reflections
θ = 55.33–82.06°
μ = 2.535 mm^{-1}
T = 296 (2) K
Plate
0.50 × 0.20 × 0.15 mm
Transparent

Data collection

Rigaku AFC-6*S* diffractometer
$\omega/2\theta$ scans
Absorption correction: none
1415 measured reflections
1332 independent reflections
1050 reflections with $I > 2\sigma(I)$

R_{int} = 0.030
θ_{max} = 75.18°
$h = -8 \rightarrow 9$
$k = -8 \rightarrow 9$
$l = -14 \rightarrow 14$
3 standard reflections
every 150 reflections
intensity decay: −4.07%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.060
$wR(F^2)$ = 0.184
S = 1.108
1332 reflections
142 parameters
Only H-atom U's refined
$w = 1/[\sigma^2(F_o^2) + (0.0831P)^2 + 0.5865P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.002

$\Delta\rho_{max}$ = 0.398 e Å^{-3}
$\Delta\rho_{min}$ = −0.363 e Å^{-3}
Extinction correction: *SHELXL*93
Extinction coefficient: 0.027 (4)
Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute structure: Flack (1983)
Flack parameter = 0.08 (5)

Table 3. *Selected geometric parameters (Å, °) for (2)*

F1—C9	1.359 (9)	C1—C2	1.157 (10)
N1—C3	1.493 (9)	C2—C3	1.457 (9)
N1—C4	1.514 (9)		
C3—N1—C4	116.8 (5)	C1—C2—C3	178.5 (12)
C4—N1—C3—C2	−175.8 (7)	C12—C4—C5—C6	68.9 (8)
C3—N1—C4—C5	−68.0 (8)	C4—C5—C6—C7	−122.3 (7)
N1—C4—C5—C6	−165.7 (6)		

Table 4. *Hydrogen-bonding geometry (Å, °) for (2)*

D—H···A	H···A	D···A	D—H···A
N1—H1A···Cl1	2.221 (6)	3.117 (6)	174.11 (13)
N1^i—H1B^i···Cl1	2.212 (5)	3.101 (5)	169.06 (15)

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

For both (1) and (2), H atoms were refined isotropically and allowed to ride on their parent atoms.

For both compounds, data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1988); cell refinement: *MSC/AFC Diffractometer Control Software*; data reduction: *TEXSAN PROCESS* (Molecular Structure Corporation, 1992); program(s) used to solve structures: *SHELXS*86 (Sheldrick, 1990); program(s) used to refine structures: *SHELXL*93 (Sheldrick, 1993); software used to prepare material for publication: *TEXSAN FINISH*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SX1040). Services for accessing these data are described at the back of the journal.

References

Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Heinonen, E. H., Myllylä, V., Soteniemi, K., Lamintausta, R., Salonen, J. S., Antill, M., Savijärvi, M., Kotila, M. & Rinne, U. K. (1989). *Acta Neurol. Scand.* **126**, 93–99.
Horváth, G., Pusztay, L., Simon, K., Szilagyi, J. & Anton, I. (1994). *Proceedings of the 37th Hungarian Itinerary Congress of Spectral Analysis, 10th Hungarian Molecular Spectroscopic Congress*, p. 349.
Kálmán, A., Párkányi, L. & Argay, Gy. (1993). *Acta Cryst.* B**49**, 1039–1049.
Knoll, J., Knoll, B., Török, Z., Timár, J. & Yasar, S. (1992). *Arch. Int. Pharmacodyn. Ther.* **316**, 5–29.
Magyar, K., Vizi, E. Sz., Ecsery, Z. & Knoll, J. (1967). *Acta Physiol. Acad. Sci. Hung.* **32**, 377–387.
Molecular Structure Corporation (1988). *MSC/AFC Diffractometer Control Software*. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.
Molecular Structure Corporation (1992). *TEXSAN. Single Crystal Structure Analysis Software*. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.
Plenevaux, A., Dewey, S. L., Fowler, J. S., Guillaume, M. & Wolf, A. P. (1980). *J. Med. Chem.* **33**, 2015–2019.
Robinson, B. J. (1985). *Biochem. Pharmacol.* **34**, 4105–4108.
Schachter, M., Marsden, C. D., Parkes, J. D., Jenner, P. & Testa, B. (1980). *J. Neurol. Neurosurg. Psychiatr.* **43**, 1016–1021.
Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.
Sheldrick, G. M. (1993). *SHELXL*93. *Program for the Refinement of Crystal Structures*. University of Göttingen, Germany.
Simon, K., Böcskei, Zs. & Török, Z. (1992). *Acta Pharm. Hung.* **62**, 225–230.
Simon, K., Podányi, B., Ecsery, Z. & Tóth, G. (1986). *J. Chem. Soc. Perkin Trans.* 2, pp. 111–115.

Acta Cryst. (1998). C**54**, 813–816

Hexakis(*p*-anisidinium) *cyclo*-Hexaphosphate Tétrahydrate

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(*Reçu le 19 décembre 1996, accepté le 8 septembre 1997*)

Abstract

The title compound, $6C_7H_{10}O^+.P_6O_{18}^{6-}.4H_2O$, contains $P_6O_{18}^{6-}$ anions connected by hydrogen bonds to water molecules and disordered *p*-anisidinium cations, forming a three-dimensional network.