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1,2,5-Substituted derivatives of 2-phenylpyrrolidine

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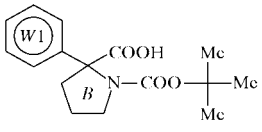
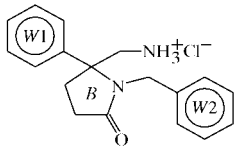
The structures of the potential anti-human-immunodeficiency virus type 1 (HIV-1) non-nucleoside reverse transcriptase inhibitors (NNRTI) 1-*tert*-butoxycarbonyl-2-phenylpyrrolidine-2-carboxylic acid, $C_{16}H_{21}NO_4$, (I), and 2-ammoniomethyl-1-benzyl-5-oxo-2-phenylpyrrolidine chloride, $C_{18}H_{21}N_2O^+\cdot Cl^-$, (II), have been investigated by X-ray diffraction. The investigations confirm a butterfly-like conformation for both compounds. In (I), the pyrrolidine ring has a marked half-chair conformation, while it has a weakly pronounced envelope conformation in (II). Intermolecular hydrogen bonds, *viz*. O—H···O in (I), and N—H···O and N—H···Cl in (II), build infinite chains in both structures. Rotational disorder of the three methyl groups is observed in (I).

Comment

The title compounds (I) and (II), belong to a family of non-nucleoside reverse transcriptase inhibitors (NNRTIs), with potential properties as inhibitors of HIV-1 RT. The characteristic structural feature of these compounds is their butterfly-like conformation, with a hydrophilic 'body' and two hydrophobic 'wing' moieties, as depicted in the scheme below (De Clercq, 1996). Both (I) and (II) were synthesized as racemic mixtures. Views of the molecules of (I) and (II) with



(I)



(II)

their atomic numbering schemes are depicted in Figs. 1 and 2, respectively. Details of the hydrogen-bonding interactions are given in Tables 1 and 2.

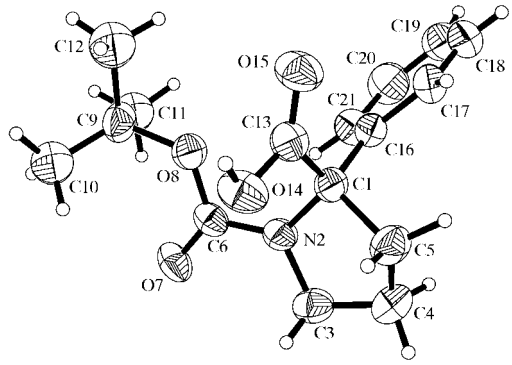


Figure 1
A view of (I), with the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level. The methyl C atoms at C9 are disordered over two orientations; only one of these is shown.

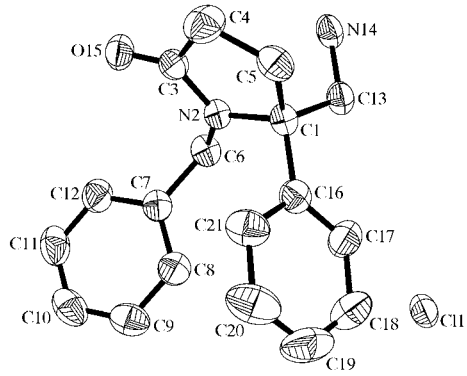


Figure 2
A view of (II), with the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

It has been observed that the anti-HIV-1 activity of compounds with butterfly-like structures depends on the orientational relationship between the wings and the body of the structure. These relationships may be described by the dihedral angles between the aryl groups ('wing' planes *W*1 and *W*2 in the scheme) and the pyrrolidine ring (part of the 'body', plane *B* in the scheme) (Karapetyan *et al.*, 2002; Tamazyan *et al.*, 2002).

In contrast with other compounds in this class, the almost flat 'wing' (*W*2) is replaced by a bulky and non-planar *tert*-butoxycarbonyl group in (I). For this reason, two of the above-described dihedral angles, *W*1/*W*2 and *B*/*W*2, are no longer defined. The *B*/*W*1 dihedral angle is 79.48 (9)°. The pyrrolidine ring has the same half-chair conformation as in 1-(2-chlorobenzoyl)-2-phenylpyrrolidine-2-carboxamide (Tamazyan *et al.*, 2002), but its biological activity is substantially lower.

Molecules of the same chirality in (I) form infinite chains along [010] *via* O14—H14···O7^{i} and O7···H14^{ii}–O14^{ii} hydrogen bonds (Fig. 3; symmetry codes as defined in Fig. 3). The crystal packing of (I) creates two hydrophobic planes parallel to the *ab* and *ac* planes. This packing evidently allows for the detected rotational disorder around the C9—O8 bond for the three methyl groups of the *tert*-butoxycarbonyl moiety.

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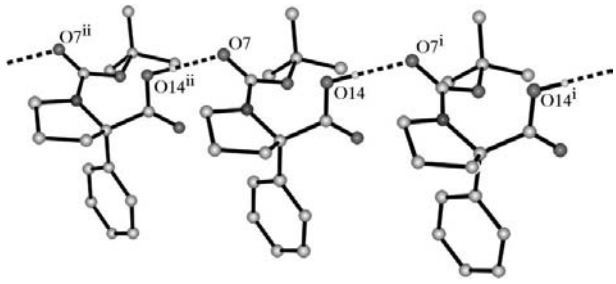

Figure 3
The connection of molecules of (I) into an infinite chain *via* hydrogen bonding [symmetry codes: (i) $x, 1 + y, z$; (ii) $x, y - 1, z$].

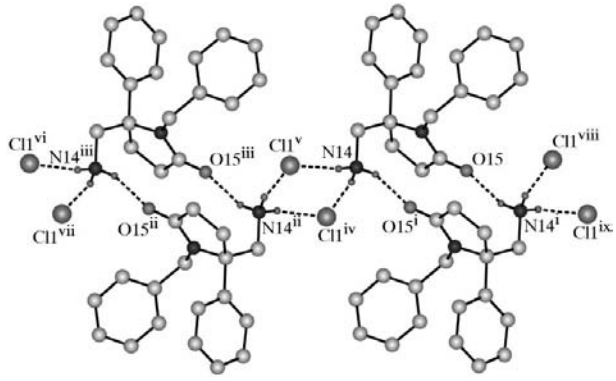

Figure 4
The connection of dimers of molecules of (II) into an infinite chain [symmetry codes: (i) $2 - x, 2 - y, 1 - z$; (ii) $2 - x, 2 - y, -z$; (iii) $x, y, z - 1$; (iv) $x + 1, y, z$; (v) $1 - x, 2 - y, -z$; (vi) $1 - x, 2 - y, -1 - z$; (vii) $x + 1, y, z - 1$; (viii) $1 - x, 2 - y, 1 - z$; (ix) $x + 1, y, z + 1$].

In the crystal structure of (II), two neighbouring molecules related by an inversion centre are connected into dimers *via* double hydrogen bonding, *viz*. N14—H14*A*···O15^{i} and N14^{i}—H14*A*^{i}···O15 (Fig. 4; symmetry codes as defined in Fig. 4). Simultaneously, these dimers are connected into infinite chains *via* hydrogen bonding between two aminium H atoms and two Cl^- ions.

The dihedral angles *W*1/*W*2, *B*/*W*1 and *B*/*W*2 are 55.20 (6), 88.09 (6) and 60.70 (5)°, respectively, in (II). The structure of (II) may be derived from that of 1-benzyl-5-oxo-2-phenylpyrrolidine-2-carboxamide (Karapetyan *et al.*, 2002) by simply replacing the carboxamide group in the body by an aminomethyl group. This replacement does not have a great effect on the conformation of the pyrrolidine ring, as both compounds still retain an envelope conformation. However, the dihedral angles and the hydrogen-bonding properties between neighbouring molecules change drastically. Nonetheless, these changes have only a minor effect on the biological activity of the compound.

Experimental

Both title compounds were synthesized as described by Martirosyan *et al.* (2000). Recrystallization from ethanol afforded colourless crystals suitable for X-ray analysis.

Compound (I)

Crystal data

$C_{16}H_{21}NO_4$
$M_r = 291.34$
Monoclinic, *Cc*
$a = 19.309$ (4) Å
$b = 6.4210$ (13) Å
$c = 13.735$ (3) Å
$\beta = 113.20$ (3)°
$V = 1565.2$ (7) Å^3
$Z = 4$
$D_x = 1.236$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
$\theta = 10.0$–17.2°
$\mu = 0.09$ mm^{-1}
$T = 293$ (2) K
Prism, colourless
0.30 × 0.24 × 0.18 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
$\theta/2\theta$ scans
8331 measured reflections
2273 independent reflections
1635 reflections with $I > 2\sigma(I)$
$R_{int} = 0.036$
$\theta_{max} = 30.0°$
$h = -26 \rightarrow 26$
$k = -8 \rightarrow 9$
$l = -19 \rightarrow 19$
3 standard reflections
frequency: 60 min
intensity variation: <1.0%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.041$
$wR(F^2) = 0.098$
$S = 1.04$
2273 reflections
220 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0494P)^2 + 0.13P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.13$ e Å^{-3}
$\Delta\rho_{min} = -0.12$ e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.0054 (8)

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

D—H···A	D—H	H···A	D···A	D—H···A
O14—H14···O7^{i}	0.82	1.85	2.668 (2)	175

Symmetry code: (i) $x, 1 + y, z$.

Compound (II)

Crystal data

$C_{18}H_{21}N_2O^+\cdot Cl^-$
$M_r = 316.82$
Triclinic, $P\overline{1}$
$a = 8.8302$ (18) Å
$b = 10.077$ (2) Å
$c = 10.094$ (2) Å
$\alpha = 99.74$ (3)°
$\beta = 92.53$ (3)°
$\gamma = 111.39$ (3)°
$V = 818.7$ (4) Å^3
$Z = 2$
$D_x = 1.285$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
$\theta = 12.5$–17.8°
$\mu = 0.24$ mm^{-1}
$T = 293$ (2) K
Sphere, colourless
0.23 mm (radius)

Data collection

Enraf–Nonius CAD-4 diffractometer
$\theta/2\theta$ scans
9597 measured reflections
4767 independent reflections
3895 reflections with $I > 2\sigma(I)$
$R_{int} = 0.017$
$\theta_{max} = 30.0°$
$h = -12 \rightarrow 12$
$k = -14 \rightarrow 14$
$l = -14 \rightarrow 14$
3 standard reflections
frequency: 60 min
intensity variation: <1.0%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.056P)^2 + 0.1106P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.037$	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2) = 0.107$	$\Delta\rho_{max} = 0.26$ e Å^{-3}
$S = 1.03$	$\Delta\rho_{min} = -0.16$ e Å^{-3}
4767 reflections	
283 parameters	
All H-atom parameters refined	

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

D—H···A	D—H	H···A	D···A	D—H···A
N14—H14A···O15^{i}	0.87 (2)	2.01 (2)	2.839 (2)	159 (1)
N14—H14B···Cl1^{ii}	0.88 (2)	2.21 (2)	3.077 (1)	167 (1)
N14—H14C···Cl1^{iii}	0.90 (2)	2.21 (2)	3.093 (1)	167 (1)

Symmetry codes: (i) $2-x, 2-y, 1-z$; (ii) $1-x, 2-y, -z$; (iii) $1+x, y, z$.

Data sets were collected corresponding to a full sphere of reciprocal space. In (I), the three methyl groups (atoms C10, C11 and C12) shows rotational disorder. H atoms in (I) were refined at idealized positions (C—H = 0.93–0.97 Å and O—H = 0.82 Å), with isotropic displacement parameters of 1.5 (CH_3 and OH) and 1.2 (CH and CH_2) times U_{eq} of the parent atom. In (II), the positional and isotropic displacement parameters of all the H atoms were refined independently.

For both compounds, data collection: *CAD*-4 *Manual* (Enraf–Nonius, 1988); cell refinement: *CAD*-4 *Manual*; data reduction: *HELENA* (Spek, 1997); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL-NT* (Bruker, 2000); software used to prepare material for publication: *SHELXTL-NT*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: TR1074). Services for accessing these data are described at the back of the journal.

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