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1-Substituted derivatives of 2-aryl-5-oxopyrrolidine-2-carboxylic acid

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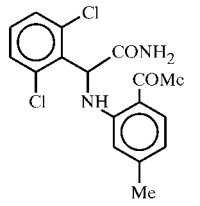
The structures of two potential anti-human immunodeficiency virus type 1 (HIV-1) non-nucleoside reverse transcriptase inhibitors (NNRTI), namely 1-benzyl-5-oxo-2-phenylpyrrolidine-2-carboxamide, $C_{18}H_{18}N_2O_2$, (III), and 2-(4-isopropoxyphenyl)-5-oxo-1-(4-tolyl)pyrrolidine-2-carbonitrile, $C_{21}H_{22}N_2O_2$, (IV), have been investigated by X-ray diffraction, confirming the butterfly-like conformation of both compounds. The pyrrolidine ring is in an envelope conformation in (III) and a half-chair conformation in (IV). Two intermolecular N—H···O hydrogen bonds are present in the crystal structure of (III), with N···O distances of 2.995 (2) and 2.927 (2) Å.

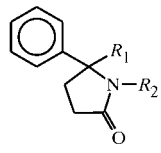
Comment

In the last few years, interest in non-nucleoside reverse transcriptase inhibitors (NNRTIs) has grown, primarily because of their anti-HIV-1 activity. One of the best representatives of this class of compounds is loviride, (I) (Pauvels *et al.*, 1993). The common structural feature of these compounds is their butterfly-like conformation, and the molecular structure consists of a hydrophilic ('body') and two hydrophobic ('wing') moieties. According to the literature, the anti-HIV-1 activity of a compound depends on the conformational rigidity and on the orientation of the wings relative to the body (De Clercq, 1996).

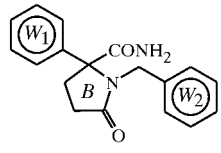
The inclusion of a pyrrolidine ring into the structure of loviride might increase the conformational rigidity. For this reason, a new method for the synthesis of 1,2-substituted derivatives of 5-oxopyrrolidine-2-carboxylic acid, (II), has been developed (Martirosyan *et al.*, 2000). Using this method, 1-benzyl-5-oxo-2-phenylpyrrolidine-2-carboxamide, (III), and 2-(4-isopropoxyphenyl)-5-oxo-1-(4-tolyl)pyrrolidine-2-carbonitrile, (IV), were synthesized as racemic mixtures. Since (III) and (IV) contain structural fragments from loviride, (I), their structures are of interest and are presented here.



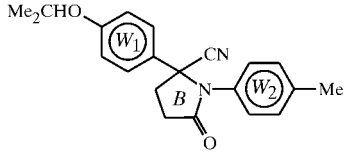
(I)



(II)
R_1 = CN, $CONH_2$ or COOH
R_2 = alkyl or aryl



(III)



(IV)

Views of molecules (III) and (IV), with the atomic numbering schemes, are depicted in Figs. 1 and 2, respectively. In the crystal structure of (III), two neighbouring asymmetric molecules of (III) are related by an inversion centre and are connected into a dimer *via* double hydrogen bonding through the amide groups (Fig. 3). Just one amide H atom (H8*A*) of each molecule takes part in this double hydrogen bonding, leading to the formation of dimers with graph-set $R_2^2(8)$. The dimers are connected into a chain through hydrogen bonding between the other amide H atom (H8*B*) and the O atom (O22) of the carbonyl group of the pyrrolidine ring (Fig. 3). The hydrogen-bond geometry is listed in Table 1. A weaker interaction, C5—H5*A*···O7, is also present; details are also given in Table 1.

In contrast with (III), compound (IV) does not have active H atoms, such as NH_2, and for this reason, no strong hydrogen bonding is observed in the crystal structure, apart from two

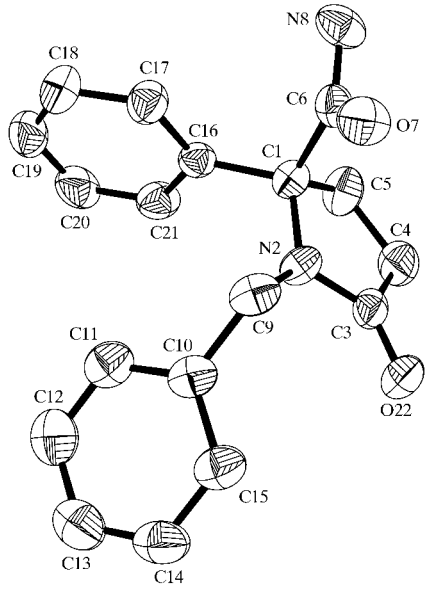


Figure 1
A view of (III) with the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms have been omitted for clarity.

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C—H···N/O interactions involving atoms N7 and O8. Nevertheless, (IV) also crystallizes in a centrosymmetric space group.

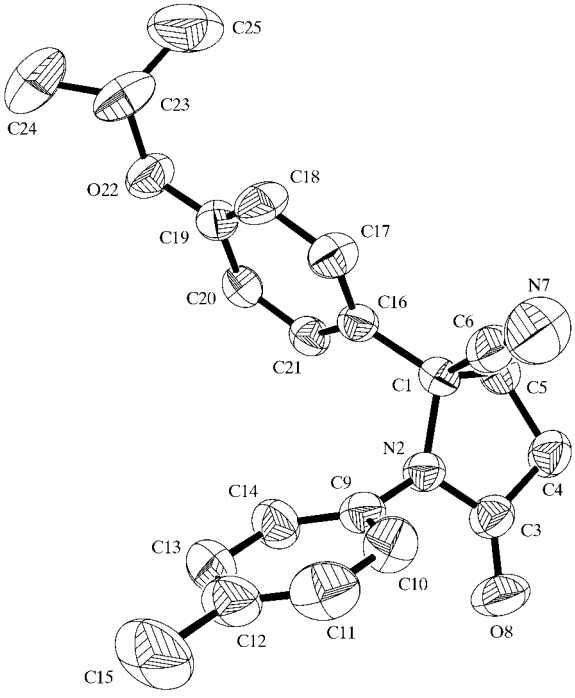

Figure 2
A view of (IV) with the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms have been omitted for clarity.

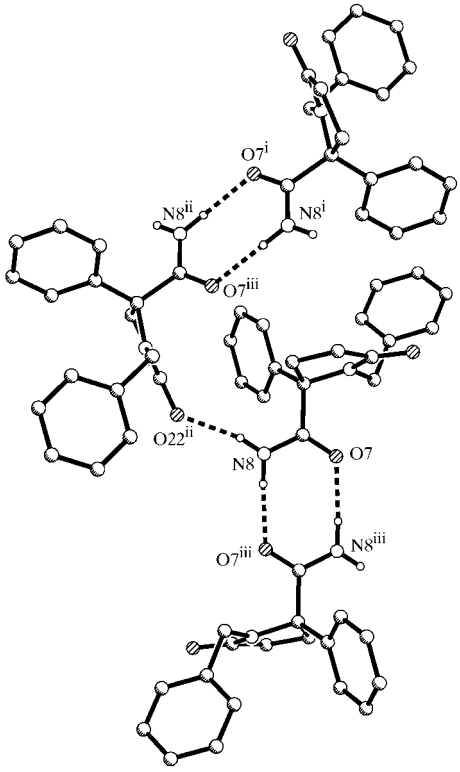

Figure 3
The connection of molecules of (III) into dimers and chains [symmetry codes: (i) $1+x, \frac{1}{2}-y, z-\frac{1}{2}$; (ii) $-x, \frac{1}{2}+y, \frac{3}{2}-z$; (iii) $-1-x, 1-y, 1-z$].

As mentioned previously, the anti-HIV-1 activity of a compound depends on the orientational relationship between the wings and the body of the butterfly-like structures. 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*). The dihedral angles W_1/W_2, B/W_1 and B/W_2 are 62.62 (8), 79.27 (6) and 68.45 (9)°, respectively, in (III), and 73.85 (13), 87.90 (13) and 73.06 (13)°, respectively, in (IV).

In the structures of (III) and (IV), the conformations of the pyrrolidine rings are markedly different, having an envelope conformation in (III) and a half-chair conformation in (IV). This difference in conformation may play an important role in the orientation of the wings and body.

Experimental

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

Compound (III)

Crystal data

$C_{18}H_{18}N_2O_2$
M_r = 294.34
Monoclinic, $P2_1/c$
a = 11.959 (2) Å
b = 10.303 (2) Å
c = 21.489 (4) Å
β = 145.05 (3)°
V = 1516.7 (12) Å^3
Z = 4
D_x = 1.289 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 14.3–15.9°
μ = 0.09 mm^{-1}
T = 293 (2) K
Prism, colourless
0.25 × 0.15 × 0.10 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
4601 measured reflections
4411 independent reflections
2559 reflections with $I > 2\sigma(I)$
R_{int} = 0.025
θ_{max} = 30°
$h = 0 \rightarrow 16$
$k = 0 \rightarrow 14$
$l = -30 \rightarrow 17$
3 standard reflections
frequency: 60 min
intensity variation: ±1.0%

Refinement

Refinement on F^2
$R(F)$ = 0.048
$wR(F^2)$ = 0.121
S = 1.01
4411 reflections
272 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.0453P)^2 + 0.4186P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.20 e Å^{-3}
$\Delta\rho_{min}$ = −0.16 e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.0150 (17)

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

D—H···A	D—H	H···A	D···A	D—H···A
N8—H8A···O7^{i}	0.89 (2)	2.07 (2)	2.955 (2)	169 (2)
N8—H8B···O22^{ii}	0.86 (2)	2.08 (2)	2.927 (2)	165 (2)
C5—H5A···O7^{ii}	0.96 (3)	2.50 (2)	3.329 (2)	145 (4)

Symmetry codes: (i) $-1-x, 1-y, 1-z$; (ii) $-x, \frac{1}{2}+y, \frac{3}{2}-z$.

Compound (IV)

Crystal data

$C_{21}H_{22}N_2O_2$
M_r = 334.41
Monoclinic, $P2_1/c$
a = 7.5182 (15) Å
b = 25.125 (5) Å
c = 10.612 (2) Å
β = 106.07 (3)°
V = 1926.3 (7) Å^3
Z = 4
D_x = 1.153 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 14.4–18.5°
μ = 0.08 mm^{-1}
T = 293 (2) K
Sphere, colourless
0.17 mm (radius)

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
5212 measured reflections
4621 independent reflections
3067 reflections with $I > 2\sigma(I)$
R_{int} = 0.027
θ_{max} = 28°
$h = -9 \rightarrow 0$
$k = 0 \rightarrow 33$
$l = 0 \rightarrow 13$
3 standard reflections
frequency: 60 min
intensity variation: ±1.0%

Refinement

Refinement on F^2
$R(F)$ = 0.049
$wR(F^2)$ = 0.142
S = 1.05
4621 reflections
282 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0453P)^2 + 0.4186P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.18 e Å^{-3}
$\Delta\rho_{min}$ = −0.20 e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.0064 (12)

Both molecules (III) and (IV) crystallized in the monoclinic system. The space groups, determined from the systematic absences, were both $P2_1/c$. The positional and isotropic displacement parameters of all H atoms were refined independently, apart from the methyl H atoms on C15, C24 and C25 in (IV), which were treated as riding, with C—H = 0.96 Å.

For both compounds, data collection: *CAD*-4 *Software* (Enraf–Nonius, 1988); cell refinement: *SETANG* in *CAD*-4 *Software*; data reduction: local program; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *SHELXL*97.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GG1112). Services for accessing these data are described at the back of the journal.

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