Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

tert-Butyl (6*S*)-4-hydroxy-6-isobutyl-2-oxo-1,2,5,6-tetrahydropyridine-1-carboxylate and *tert*-butyl (4*R*,6*S*)-4-hydroxy-6-isobutyl-2-oxopiperidine-1-carboxylate

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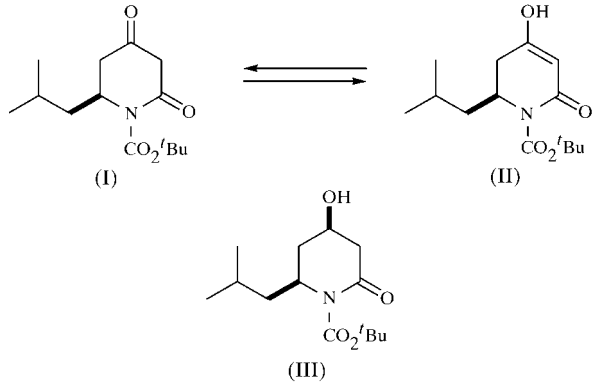
Received 16 July 2003
Accepted 21 October 2003
Online 10 February 2004

X-ray studies reveal that *tert*-butyl (6*S*)-6-isobutyl-2,4-dioxopiperidine-1-carboxylate occurs in the 4-enol form, *viz.* *tert*-butyl (6*S*)-4-hydroxy-6-isobutyl-2-oxo-1,2,5,6-tetrahydropyridine-1-carboxylate, $C_{14}H_{23}NO_4$, when crystals are grown from a mixture of dichloromethane and pentane, and has an axial orientation of the isobutyl side chain at the 6-position of the piperidine ring. Reduction of the keto functionality leads predominantly to the corresponding β-hydroxylated δ-lactam, *tert*-butyl (4*R*,6*S*)-4-hydroxy-6-isobutyl-2-oxopiperidine-1-carboxylate, $C_{14}H_{25}NO_4$, with a *cis* configuration of the 4-hydroxy and 6-isobutyl groups. The two compounds show similar molecular packing driven by strong O—H···O═C hydrogen bonds, leading to infinite chains in the crystal structure.

Comment

The δ-lactam ring system is an important structural subunit in many natural products as well as a useful precursor for the asymmetric synthesis of a variety of biologically relevant compounds, including δ-amino acids (Rodriguez *et al.*, 1990; Casimir *et al.*, 2000), 5-hydroxylysine derivatives (Marin *et al.*, 2002) and substituted piperidines (Varea *et al.*, 1995; Enders & Bartzen, 1997; Hanessian *et al.*, 1997; Laschat & Dickner, 2000). In the course of our studies of the synthesis of enantiopure δ-lactams, monohydroxylated at the β-position, we have investigated the stereoselective reduction of various 6-substituted 2,4-dioxopiperidine-1-carboxylates, including *tert*-butyl (6*S*)-6-isobutyl-2,4-dioxopiperidine-1-carboxylate, (I). The side chain at the 6-position in (I) is believed to adopt a quasi-axial orientation in order to minimize pseudo-allylic $A(1,3)$ strain and should dictate the stereochemical outcome of the reduction reaction. We report here the crystal structures of both the enol form, (II) [*tert*-butyl (6*S*)-4-hydroxy-6-isobutyl-2-oxo-1,2,5,6-tetrahydropyridine-1-carboxylate], of the diketo compound (I) and the β-hydroxylated δ-lactam, (III) [*tert*-butyl (4*R*,6*S*)-4-hydroxy-6-isobutyl-2-oxopiperidine-1-carboxylate], obtained by reduction of the keto functionality in (I).



The keto–enol equilibrium between (I) and (II) is strongly influenced by the solvent. While only the keto form, (I), is observed by NMR spectroscopy in $CDCl_3$, the enol form is populated exclusively in DMSO-d_6. The reduction of (I) by $NaBH_4$ in a mixture of CH_2Cl_2 and 10% acetic acid gave the desired 4-hydroxy derivative in 93% yield, with a preference for the expected *cis* isomer, (III) (diastereomeric ratio 9:1). The ratio of *cis* and *trans* diastereomers was determined by C_{18} RP–HPLC (reversed-phase high-performance liquid chromatography). Isomer (III) was finally isolated in 71% yield and greater than 99% diastereomeric excess after crystallization of the crude mixture.

Compound (II) crystallizes in an orthorhombic cell (with $Z' = 2$), whereas the reduced compound (III) crystallizes in a monoclinic cell (with $Z' = 1$). The absolute configuration of atom C6 in each compound was assumed from our knowledge of the stereochemistry of the precursor Boc-βLeu-OH compound (Seebach *et al.*, 1996). Views of the independent

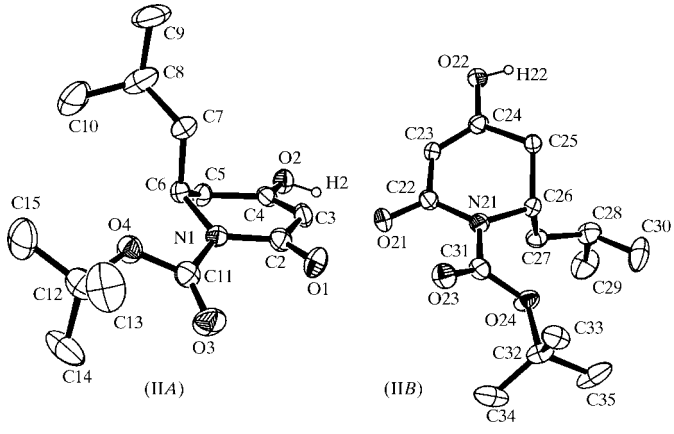


Figure 1
ORTEP-3 (Farrugia, 1997) view of the two independent molecules in the asymmetric unit of (II), with the atom-numbering scheme and displacement ellipsoids shown at the 25% probability level. H atoms, except for those of the hydroxy groups, have been omitted for clarity.

  DOI: 10.1107/S0108270103024053

molecules of (II) and (III), with their atom-numbering schemes, are shown in Figs. 1 and 2, respectively. The bond lengths and angles in (II) and (III) are in agreement with those of related piperidine rings (Allen *et al.*, 1987; Marin *et al.*, 2002; Tomas *et al.*, 1996; Bocelli & Grenier-Loustalot, 1981). Selected geometrical data are given in Tables 1 and 3.

In the crystal structure of (II), the two independent molecules, *viz.* (II*A*) and (II*B*), have similar conformations. The piperidine ring adopts a sofa conformation, with the C atom at the 6-position displaced from the mean plane defined by the five other atoms of the ring by 0.562 (4) and 0.618 (5) Å in (II*A*) and (II*B*), respectively. The sums of the bond angles about atoms N1 (359.9°) in (II*A*) and N21 (359.6°) in (II*B*) indicate a planar geometry for the N atoms of both independent piperidine rings. The dihedral angles around the C11—N1 and N1—C2 bonds in (II*A*) [C31—N21 and N21—C22 in (II*B*); Table 2] show that the amide moiety of the ring and the *tert*-butoxycarbonyl group are nearly coplanar. The observed C4—O2 and C3—C4 bond distances in (II*A*) [C24—O22 and C23—C24 in (II*B*)] indicate that these bonds correspond to single and double bonds, respectively, revealing the presence of an enolic tautomer in the solid state. In addition, the hydroxy group at the 4-position, the only potential strong H-atom donor in (II), is involved in the crystal packing described below. The expected axial orientation of the C6-substituent, caused by minimization of the allylic *A*(1,3) strain, was confirmed in (II*A*) and (II*B*), as can be seen from the C7—C6—C5—C4 [78.9 (4)°] and C27—C26—C25—C24 [74.8 (4)°] torsion angles. This side-chain orientation could induce the very high diastereoselectivity observed in the reduction of (I) to (III).

The crystal structure of (III) reveals the selected (4*R*,6*S*)-diastereomer obtained by reduction of (I). The reduced piperidine ring at the 4-position adopts a chair conformation, with atoms N1 and C4 displaced on opposite sides of the C2/C3/C5/C6 mean plane by −0.221 (5) and 0.659 (1) Å, respectively. The sum of the bond angles about atom N1 (355.9°) reveals a planar geometry for the N atom in (III), although the

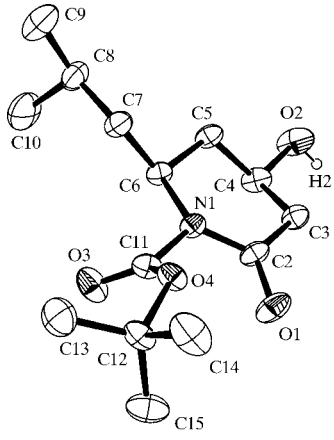


Figure 2
ORTEP-3 (Farrugia, 1997) view of the asymmetric unit of (III), with the atom-numbering scheme and displacement ellipsoids shown at the 25% probability. H atoms, except for those of the hydroxy groups, have been omitted for clarity.

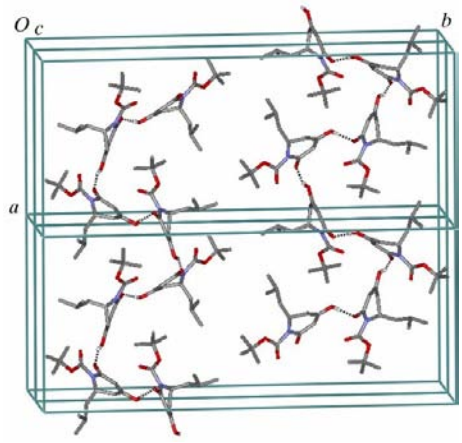


Figure 3
Part of the crystal structure of (II), showing the formation of *C*(7) chains along [100]. Intermolecular hydrogen bonds are marked as dashed lines.

planarity is less pronounced than it is in (II). The dihedral angle around the urethane bond (Table 3) shows that the amide moiety of the ring and the *tert*-butoxycarbonyl group are not coplanar, and that the *tert*-butoxycarbonyl groups in (II) and (III) have very different orientations relative to the ring. The hydroxy and isobutyl groups in the 4- and 6-positions of the piperidine ring assume an equatorial orientation, as can be seen from the C2—C3—C4—O2 [170.1 (3)°] and C4—C5—C6—C7 [166.7 (4)°] torsion angles.

The rules governing the crystal packing of (II) and (III) are similar. First, strong hydrogen bonds, involving the hydroxy group at the 4-position as H-atom donor and the carbonyl group at the 2-position as H-atom acceptor, link the molecules into infinite *C*(6) (Bernstein *et al.*, 1995) chains (Tables 2 and 4). Second, van der Waals interactions between the chains produce bilayers with aliphatic groups on the surfaces, and finally, the bilayers pack together to produce a loosely held three-dimensional structure. In the crystal of (II), the hydrogen-bonded molecules lead to helical columns running along the [100] direction, and planar zigzag chains formed by the screw axes are observed in the crystal structure of (III). The bilayers are parallel to the (010) and (001) planes in the crystals of (II) (Fig. 3) and (III) (Fig. 4), respectively.

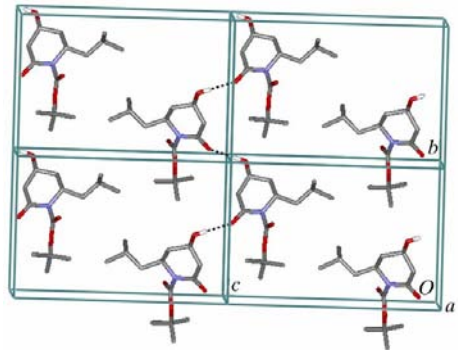


Figure 4
Part of the crystal structure of (III), showing the formation of *C*(6) chains along [010]. Intermolecular hydrogen bonds are marked as dashed lines.

Experimental

For the preparation of (II), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (4.44 g, 23.14 mmol), 4-dimethylaminopyridine (2.83 g, 23.14 mmol) and Meldrum's acid (2.22 g, 15.43 mmol) were added to a solution of Boc-βLeu-OH (Seebach *et al.*, 1996) (3.57 g, 15.43 mmol) in dichloromethane at 273 K. The mixture was allowed to reach room temperature, was stirred for 3 h and then extracted with 1 *N* $KHSO_4$. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in AcOEt to afford a ~0.1 *M* solution, which was then refluxed for 5 h. After being allowed to cool to room temperature, the mixture was extracted with 1 *N* $KHSO_4$ and brine. Drying over Na_2SO_4 and evaporation of the filtrate afforded crude (II), which was recrystallized from dichloromethane/pentane to give pure (II) (2.69 g, 68%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.94 (*m*, 1H), 4.40–4.34 (*m*, 1H), 3.32 (*bs*, 1H), 2.85 (*m*, 1H), 2.18–2.07 (*m*, 1H), 1.56–1.34 (*m*, 3H), 1.43 (*s*, 9H), 0.89 (*d*, J = 6.6 Hz, 3H), 0.87 (*d*, J = 6.8 Hz, 3H). Single crystals suitable for X-ray analysis were grown from a mixture of dichloromethane and pentane. For the preparation of (III), sodium borohydride (42 mg, 1.11 mmol) was added to a stirred solution of (I) (100 mg, 0.37 mmol) in a mixture of dichloromethane and acetic acid (10%, *v*/*v*) at room temperature. After 72 h, the mixture was quenched with water, and the dichloromethane was evaporated under reduced pressure. Ethyl acetate was added and the organic phase was extracted with water and brine. The organic layer was dried over Na_2SO_4, filtered and evaporated to afford a residue, which was purified by flash chromatography (ethyl acetate/hexane 6:4) to give a 9:1 mixture (94 mg, 93%) of (III) and the corresponding 4*S*,6*S* diastereomer. Single crystals of (III) suitable for X-ray analysis were grown from a mixture of dichloromethane and pentane (m.p. 367–368 K). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.18–4.09 (*m*, 2H), 2.82 (*ddd*, J = 16.6, 5.7, 1.8 Hz, 1H), 2.59 (*m*, 1H), 2.48 (*dd*, J = 16.6, 8.7 Hz, 1H), 2.30–2.21 (*m*, 1H), 1.71–1.57 (*m*, 3H), 1.51 (*s*, 9H), 0.92 (*d*, J = 4.2 Hz, 3H), 0.90 (*d*, J = 4.2 Hz, 3H).

Compound (II)

Crystal data

$C_{14}H_{23}NO_4$
M_r = 269.33
Orthorhombic, $P2_12_12$
a = 14.6670 (3) Å
b = 34.0857 (8) Å
c = 6.3334 (1) Å
V = 3166.29 (11) Å^3
Z = 8
D_x = 1.13 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3128 reflections
θ = 3.3–25.4°
μ = 0.08 mm^{-1}
T = 293 (2) K
Prism, colorless
0.1 × 0.1 × 0.1 mm

Data collection

Nonius KappaCCD diffractometer
φ and ω scans
14 369 measured reflections
3294 independent reflections
2116 reflections with $I > 2\sigma(I)$
R_{int} = 0.047
θ_{max} = 25.4°
$h = -17 \rightarrow 17$
$k = -40 \rightarrow 40$
$l = -7 \rightarrow 7$

Refinement

Refinement on F^2
$R(F)$ = 0.047
$wR(F^2)$ = 0.135
S = 1.02
3294 reflections
344 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0772P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.14 e Å^{-3}
$\Delta\rho_{min}$ = −0.16 e Å^{-3}

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

C3—C4	1.330 (5)	C23—C24	1.322 (5)
O2—C4	1.338 (4)	O22—C24	1.333 (4)
C4—C3—C2—N1	−6.6 (5)	C24—C23—C22—N21	−13.5 (5)
C2—C3—C4—C5	4.5 (5)	C22—C23—C24—C25	5.9 (5)
C3—C4—C5—C6	22.2 (5)	C23—C24—C25—C26	26.7 (5)
N1—C6—C5—C4	−43.7 (4)	N21—C26—C25—C24	−48.9 (4)
C2—N1—C6—C5	44.2 (4)	C22—N21—C26—C25	45.0 (4)
C6—N1—C2—C3	−19.9 (5)	C26—N21—C22—C23	−14.5 (4)
C11—N1—C2—C3	162.8 (3)	C31—N21—C22—C23	172.7 (3)
C2—N1—C11—O4	160.0 (3)	C22—N21—C31—O24	152.5 (3)
C7—C6—C5—C4	78.9 (4)	C27—C26—C25—C24	74.8 (4)

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

D—H···A	D—H	H···A	D···A	D—H···A
O2—H2···O21	0.82	1.81	2.620 (4)	172
O22—H22···O1^{i}	0.82	1.80	2.576 (4)	158

Symmetry code: (i) $x - \frac{1}{2}, \frac{3}{2} - y, 2 - z$.

Compound (III)

Crystal data

$C_{14}H_{25}NO_4$
M_r = 271.35
Monoclinic, $P2_1$
a = 5.563 (2) Å
b = 9.891 (3) Å
c = 14.800 (3) Å
β = 95.02 (2)°
V = 811.2 (4) Å^3
Z = 2
D_x = 1.111 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 5.4–25.9°
μ = 0.66 mm^{-1}
T = 293 (2) K
Prism, colorless
0.3 × 0.1 × 0.1 mm

Data collection

Nonius MACH3 diffractometer
Non-profiled $\omega/2\theta$ scans
2974 measured reflections
1630 independent reflections
1160 reflections with $I > 2\sigma(I)$
R_{int} = 0.081
θ_{max} = 70.0°
$h = 0 \rightarrow 6$
$k = -12 \rightarrow 10$
$l = -18 \rightarrow 17$
2 standard reflections
frequency: 60 min
intensity decay: 3%

Refinement

Refinement on F^2
$R(F)$ = 0.048
$wR(F^2)$ = 0.155
S = 1.16
1630 reflections
172 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0494P)^2 + 0.2013P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.006
$\Delta\rho_{max}$ = 0.20 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}

Table 3
Selected torsion angles (°) for (III).

C4—C3—C2—N1	−30.2 (6)	C6—N1—C2—C3	17.0 (6)
C5—C4—C3—C2	51.5 (5)	C11—N1—C2—C3	172.9 (4)
C6—C5—C4—C3	−60.5 (5)	O4—C11—N1—C2	65.8 (5)
N1—C6—C5—C4	45.9 (5)	O2—C4—C3—C2	170.1 (3)
C2—N1—C6—C5	−24.7 (5)	C7—C6—C5—C4	166.7 (4)

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

D—H···A	D—H	H···A	D···A	D—H···A
O2—H2···O1^{ii}	0.82	1.94	2.755 (5)	175

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

The absolute configurations of (II) and (III) could not be determined from the diffraction experiments, because of the lack of any significant anomalous dispersion effects, but were, in any case, known from the method of synthesis. Bijvoet pairs were merged prior to refinement. All H atoms were placed in calculated positions and treated using a riding model, with C—H distances of 0.93–0.97 Å and an O—H distance of 0.82 Å. The H-atom U_{iso} parameters were fixed at $1.2U_{eq}$(C) for methine, methylene and aromatic CH groups, at $1.3U_{eq}$(O) for the OH group, and at $1.5U_{eq}$(C) for methyl H atoms.

For compound (II), data collection: *COLLECT* (Nonius, 1998); cell refinement: *COLLECT*; data reduction: *HKL* (Otwinowski & Minor, 1997). For compound (III), data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989); cell refinement: *CAD*-4 *Software*; data reduction: *XCAD*4 (Harms & Wocadlo, 1995). For both compounds, program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 *for Windows* (Farrugia, 1997) and *WebLab ViewerPro* (MSI, 1999); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

The authors would like to thank the Service Commun de Diffraction X sur Monocristaux (Université Henri Poincaré, Nancy I) for providing access to crystallographic experimental facilities.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SX1124). Services for accessing these data are described at the back of the journal.

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