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tert-Butyl (3*S*,6*R*,9*R*)-(5-oxo-3-{[1(*R*)-phenylethyl]carbamoyl}-1,2,3,5,6,7,8,8a-octahydroindolizin-6-yl)carbamate monohydrate at 95 K

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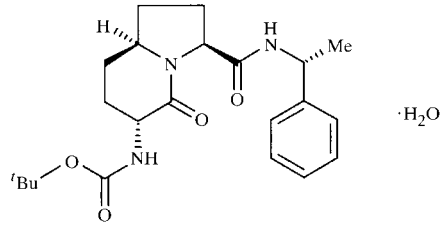
The asymmetric unit of the title compound, $C_{22}H_{31}N_3O_4\cdot H_2O$, incorporates one water molecule, which is hydrogen bonded to the 3-oxo O atom of the indolizidinone system. The two rings of the peptidomimetic molecule are *trans*-fused, with the six-membered ring having a slightly distorted half-chair conformation and the five-membered ring having a perfect envelope conformation. The structure is stabilized by intermolecular O—H···O interactions between the water and adjacent peptide molecules, and by N—H···O interactions between the peptide molecules, which link the molecules into infinite chains.

Comment

Indolizidinone-type 6,5-fused bicyclic lactams are of considerable pharmaceutical interest, as they can act as dipeptide mimics (Kim *et al.*, 1996; Colombo *et al.*, 1998; Angiolini *et al.*, 2000). The synthesis of so-called peptidomimetic molecules has been a very active and productive field of research in drug design (Hanessian *et al.*, 1997). The rationale for the development of peptide analogues is that these molecules have the same biological effects as natural peptides but, at the same time, are metabolically more stable. Of particular interest has been the replacement of reverse-turn dipeptide motifs with constrained molecules that reproduce their conformational features (Kahn, 1993). 6,5- and 7,5-fused 2-oxo-1-azabicyclo[*n*.3.0]alkane amino acids can be regarded as conformationally restricted substitutes for Ala–Pro and Phe–Pro dipeptide units. Their conformations, studied using a combination of computer modelling with ^{1}H NMR and FT–IR spectroscopy (Belvisi *et al.*, 2000), have been shown to meet specific criteria, so they can be used to replace the central (*i*+1 and *i*+2) residues of β-turns.

To validate the conformational information obtained by these methods, the structure determination of the title compound, (I), a synthetic derivative of a 6,5-fused bicyclic lactam whose crystallinity allows an X-ray crystallographic analysis, has been undertaken. A preliminary data collection at room temperature showed that the crystal had very low diffracting power. To increase the percentage of significant data, the temperature of the experiment was reduced to 95 K. The asymmetric unit of (I) comprises one molecule of *tert*-butyl (3*S*,6*R*,9*R*)-(5-oxo-3-{[1(*R*)-phenylethyl]carbamoyl}-1,2,3,5,6,7,8,8a-octahydroindolizin-6-yl)carbamate and one water molecule (Fig. 1), which interact through an intramolecular O—H···O hydrogen bond (see Table 2). The absolute configuration of (I) was based on the known configuration of the starting material (Angiolini *et al.*, 2000).



(I)

The six-membered ring of the indolizidinone system has a quite distorted half-chair conformation, with puckering parameters (Cremer & Pople, 1975) Q = 0.522 (2) Å, θ = 46.2 (3)° and φ = 216.4 (4)° for the atom sequence N2—C5—C6—C7—C8—C9. Atoms C7 and C8 are 0.325 (4) and −0.467 (4) Å, respectively, from the mean plane defined by atoms C9, N2, C5 and C6, and the r.m.s. deviation of these latter four atoms from their plane is 0.024 Å. The amido substituent at C6 (6*R*) is oriented equatorially, in agreement with the orientation reported for another bicyclic lactam (Kim *et al.*, 1996). The same authors also indicate that the six-membered ring of the bicycle adopts a pseudo-chair conformation, while Hua *et al.*

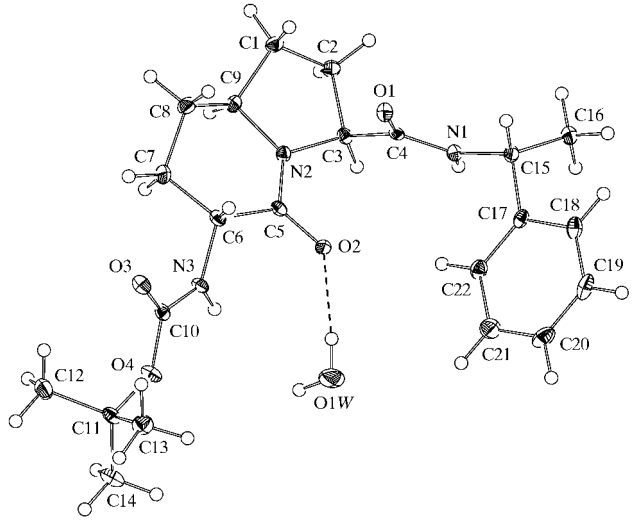


Figure 1
The molecular structure of (I) with the atom-numbering scheme. The intramolecular hydrogen bond is shown as a dashed line and displacement ellipsoids are drawn at the 40% probability level.

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(1995) found that the six-membered lactam ring in a derivative of an octahydroindolizin-5-one could be described as having a distorted envelope conformation. However, we calculated the puckering parameters for the six-membered ring in these two literature structures and found them to be quite similar [Q = 0.479 and 0.531 (6) Å; θ = 40.5 and 55.3 (5)°; φ = 229.2 and 215.6 (8)°, respectively] to those of the title compound, which are close to the ideal values for a half-chair conformation (Cremer & Pople, 1975). Hua *et al.* (1995) state that '*normally, the six-membered lactam ring assumes a distorted chair conformation owing to the tendency of the amide bond to be planar*' and this is in agreement with the perfect chair conformation reported for different indolizidine moieties (Koh *et al.*, 1993; Fleming *et al.*, 1996; Mukhopadhyyay *et al.*, 1998). The five-membered ring adopts an almost perfect envelope conformation for the atom sequence C9—C1—C2—C3—N2; the puckering parameters are q = 0.388 (2) Å and φ = 217.1 (4)° (the nearest ideal value for an envelope amounts to φ = 216°), and atom C1 is 0.596 (4) Å from the mean plane defined by atoms C2, C3, N2 and C9 (the r.m.s. deviation of these four atoms from their plane is 0.002 Å). The same conformation has been found both in indolizidinone (Hua *et al.*, 1995) and indolizidine (Koh *et al.*, 1993; Fleming *et al.*, 1996; Garofano *et al.*, 1998; Mukhopadhyyay, 1998) systems. The two rings are *trans*-fused (Table 1).

The bond distances and angles for the three amide bonds in the title molecule are within the expected range derived from previously reported data (Allen *et al.*, 1987). The value found for the N2—C9 distance is in good agreement with other values reported for this bond in the same environment, which range from 1.469 (2) (Garofano *et al.*, 1998) to 1.479 (3) Å (Koh *et al.*, 1993).

The geometric parameters of the hydrogen bonds are given in Table 2. Intermolecular O—H···O and N—H···O hydrogen bonds link the molecules into extended chains, which run parallel to the *a* axis, as shown in Fig. 2. Within the chain, adjacent peptide molecules are parallel but in a head-to-tail arrangement, as each N—H interacts with the amide O atom at the opposite end of the next molecule. The water molecule also links adjacent peptide molecules within the chain. In addition, one weaker C—H···O interaction is present.

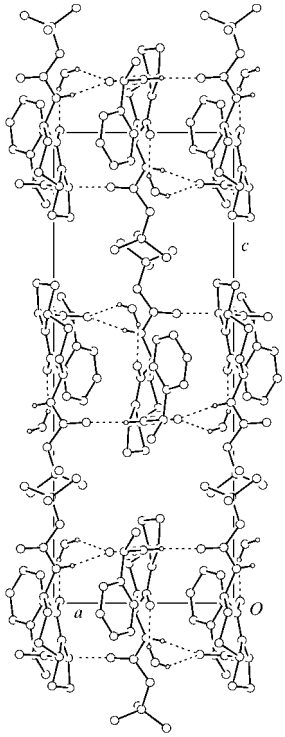

Figure 2
Packing diagram viewed down the *b* axis. Intermolecular O—H···O and N—H···O hydrogen bonds are shown as dashed lines.

Experimental

The title compound was synthesized according to a previously reported procedure (Angiolini *et al.*, 2000), followed by protective group manipulation. Suitable single crystals were obtained by recrystallization from diethyl ether.

Crystal data

$C_{22}H_{31}N_3O_4\cdot H_2O$
M_r = 419.51
Orthorhombic, $P2_12_12_1$
a = 8.520 (2) Å
b = 12.095 (2) Å
c = 22.323 (5) Å
V = 2300.4 (8) Å^3
Z = 4
D_x = 1.211 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 4199 reflections
θ = 2.4–20.6°
μ = 0.09 mm^{-1}
T = 95 (2) K
Prism, colourless
0.55 × 0.10 × 0.06 mm

Table 1
Selected geometric parameters (Å, °).

N1—C4	1.334 (3)	N2—C9	1.477 (3)
N1—C15	1.458 (3)	N3—C10	1.337 (3)
N2—C5	1.339 (3)	N3—C6	1.453 (3)
N2—C3	1.462 (3)		
C4—N1—C15	124.1 (2)	C10—N3—C6	121.5 (2)
C5—N2—C3	119.8 (2)	O2—C5—N2	121.5 (2)
C5—N2—C9	127.5 (2)	O2—C5—C6	121.5 (2)
C3—N2—C9	112.5 (5)	N2—C5—C6	117.0 (2)
C15—N1—C4—O1	2.5 (4)	C5—C6—C7—C8	−47.7 (3)
C9—N2—C5—O2	178.1 (2)	C5—N2—C9—C8	23.9 (3)
C9—N2—C5—C6	−5.7 (4)	C3—N2—C9—C1	−23.9 (3)
N2—C5—C6—C7	17.5 (3)	C6—N3—C10—O3	−2.8 (4)

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

D—H···A	D—H	H···A	D···A	D—H···A
O1W—H1W···O2	0.82 (4)	2.06 (4)	2.838 (2)	158 (3)
O1W—H2W···O1^{i}	0.86 (5)	2.19 (5)	2.972 (3)	151 (4)
N3—H3···O1^{i}	0.88	1.98	2.847 (2)	167
N1—H1···O3^{i}	0.88	1.93	2.807 (2)	173
C15—H15···O4^{ii}	1.00	2.50	3.502 (3)	175

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

Data collection

Bruker SMART CCD area-detector diffractometer	$R_{int} = 0.047$
	$\theta_{max} = 27.5^\circ$
ω scans	$h = -11 \rightarrow 11$
23 342 measured reflections	$k = -15 \rightarrow 15$
2992 independent reflections	$l = -29 \rightarrow 29$
2933 reflections with $I > 2\sigma(I)$	

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0371P)^2 + 1.2606P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.048$	
$wR(F^2) = 0.109$	
$S = 1.15$	$(\Delta/\sigma)_{max} = 0.001$
2992 reflections	$\Delta\rho_{max} = 0.34$ e Å^{-3}
293 parameters	$\Delta\rho_{min} = -0.22$ e Å^{-3}
H atoms treated by a mixture of independent and constrained refinement	

Due to the absence of any significant anomalous scatterers in the title compound, the absolute configuration could not be determined and Friedel opposites were merged before the final refinement. The absolute configuration of the model was assigned to match the configuration of the chiral centres known from the synthesis. Atoms H1*W* and H2*W* were located from difference Fourier maps and were refined isotropically. All remaining H atoms were treated as riding atoms (C—H = 0.95–1.00 Å), with $U_{iso}(H) = 1.2U_{eq}$(parent atom).

Data collection: *SMART* (Siemens, 1996); cell refinement: *SAINT* (Siemens, 1996); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*III (Burnett & Johnson, 1996); software used to prepare material for publication: *SHELXL*97.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: LN1142). Services for accessing these data are described at the back of the journal.

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