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O-Benzyl-*N*-*tert*-butoxycarbonyl-*N*-methyl-L-tyrosine

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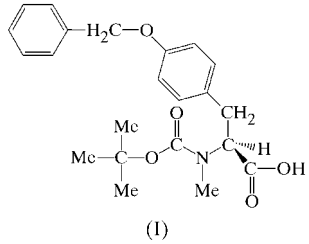
The crystal structure of the title compound, alternatively called 3-[4-(benzyloxy)phenyl]-2-(*N*-*tert*-butoxycarbonyl-*N*-methylamino)propionic acid, $C_{22}H_{27}NO_5$, has been studied in order to examine the role of *N*-methylation as a determinant of peptide conformation. The conformation of the *tert*-butoxycarbonyl group is *trans–trans*. The side chain has a folded conformation and the two phenyl rings are effectively perpendicular to one another. The carboxylate hydroxyl group and the urethane carbonyl group form a strong intermolecular O—H···O hydrogen bond.

Comment

Conformational studies of peptides and pseudopeptides (peptidomimetics) represent an ongoing project in our laboratory aimed at finding new biologically active peptide analogues and new protease inhibitors. *N*-Alkylated amino acids occur in many natural compounds, such as antibiotics or toxins, and are widely used in the synthesis of peptide analogues. As an example, incorporation of *N*-methylglycine (sarcosine) and *N*-methylalanine at position 7 of oxytocin has led to new derivatives with interesting properties (Grzonka *et al.*, 1983; Gazis *et al.*, 1984). The well known and widely



(I)

used immunosuppressant drug cyclosporin A contains seven *N*-methylated amino acid residues (Loosli *et al.*, 1985). The *N*-alkylated peptide bond is more resistant to enzymatic cleavage. The *cis–trans* isomerization of *N*-alkylated peptide

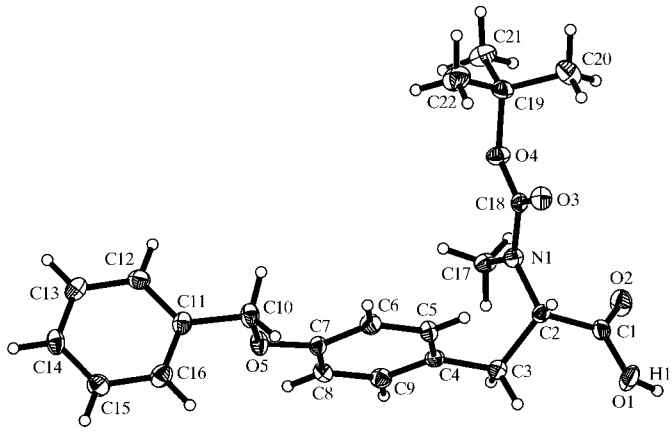


Figure 1
Displacement-ellipsoid view (50% probability level) of the title compound with the atom-numbering scheme.

bonds is shifted towards the *cis* isomer. Finally, incorporation of *N*-alkylamino acid residues into the polypeptide chain decreases the possibility of hydrogen-bond formation, and at the same time, increases the hydrophobicity of such peptide fragments (Spatola, 1983). The present study is a contribution to our understanding of the structural role of *N*-methylation in amino acids and peptide derivatives.

The molecular structure and atom-numbering scheme of the title compound, (I), is shown in Fig. 1. A selection of bond distances and angles is given in Table 1 together with some notable torsion angles. The bond lengths within the *tert*-butoxycarbonyl group are very similar (except for the C19—O4 bond, which is lengthened by nearly 0.02 Å) to the average lengths for this blocking group compiled by Benedetti *et al.* (1980). There is one notable variation from these averages in the bond angles involving the urethane bond. Thus, the C18—O4—C19 angle [123.1 (2)°] is 2° wider than the computed averages for these urethane linkages (Table 1). The conformation of the *tert*-butoxycarbonyl group, characterized by the torsion angles Θ_0 (C19—O4—C18—O3) and ω_0 (O4—C18—N1—C2), is *trans–trans* (Table 1). This is opposite to most of the published X-ray structures of compounds containing the

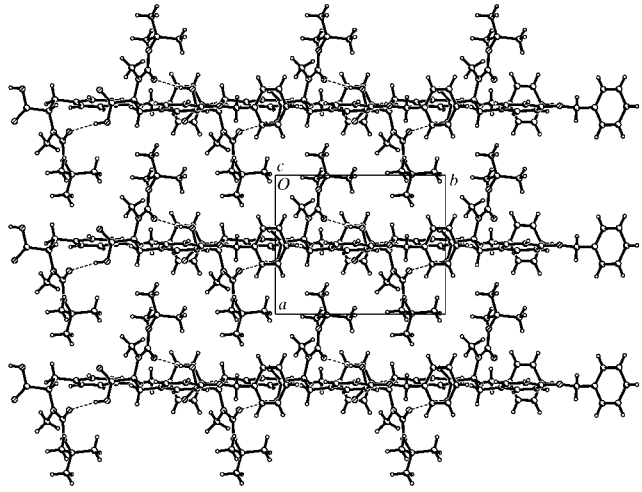


Figure 2
The crystal packing of the title compound viewed along *c*.

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tert-butoxycarbonyl group at a tertiary N atom (*e.g.* proline or sarcosine derivatives), which usually have a *cis*-urethane bond (Benedetti *et al.*, 1980). The deviation from planarity of the urethane bond is in a typical range found for *tert*-butoxycarbonylamino acid and peptide derivatives (Sopková *et al.*, 1996; Banumathi *et al.*, 1999). The backbone conformation is characterized by the torsion angles Φ (C18—N1—C2—C1) and Ψ (O1—C1—C2—N1), and the conformation of the side chain is characterized by χ_1 (N1—C2—C3—C4) and χ_2 (C2—C3—C4—C5) (Table 1). Therefore, the side chain has a folded conformation. The O5—C10 bond is roughly coplanar with the tyrosine ring [C6—C7—O5—C10 = 1.3 (4)°], but is perpendicular to the benzyl ring [O5—C10—C11—C12 = −85.7 (3)°]. With the O5—C10 bond in the *trans* orientation [C7—O5—C10—C11 = −176.9 (2)°], the two phenyl rings are thus perpendicular to one another [interplanar angle = 86.5 (5)°]. The tyrosine and benzyl rings are planar, with χ^2 values of 43.1 and 11.1°, respectively. In the crystal packing, the tyrosine and benzyl moieties form layers, with the *tert*-butoxycarbonyl groups located between them (Fig. 2).

The carboxylate hydroxyl and the urethane carbonyl group form a strong intermolecular O—H···O hydrogen bond [O1···O3^{i} 2.679 (2) Å and O1—H1···O3^{i} 170 (3)°; symmetry code: (i) $-x-1, y-\frac{1}{2}, -z-\frac{1}{2}$] (Fig. 2). A similar hydrogen bond was also reported in the crystal structure of *tert*-butoxycarbonylphenylalanine (Bats *et al.*, 1980).

Experimental

The title compound was synthesized from *O*-benzyl-*tert*-butoxycarbonyl-L-tyrosine and methyl iodide in the presence of KH and crown ether (18-C-6) (Schuman *et al.*, 1983). The tyrosine derivative thus formed is suitable for peptide synthesis both in solution and in the solid phase *via* peptide-chain elongation because it has a protected amino group (Boc) and an unprotected carboxyl group. Single crystals of (I) (m.p. = 400–401 K) were obtained by slow evaporation from an ethyl acetate/petroleum ether solution.

Crystal data

$C_{22}H_{27}NO_5$
M_r = 385.45
Orthorhombic, $P2_12_12_1$
a = 9.346 (2) Å
b = 11.413 (2) Å
c = 19.493 (4) Å
V = 2079.2 (7) Å^3
Z = 4
D_x = 1.231 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 6728 reflections
θ = 3.4–29.6°
μ = 0.09 mm^{-1}
T = 100 (2) K
Prism, colourless
0.35 × 0.30 × 0.25 mm

Table 1
Selected geometric parameters (Å, °).

C1—O2	1.201 (3)	C17—N1	1.459 (3)
C1—O1	1.327 (3)	C18—O3	1.229 (3)
C2—N1	1.462 (3)	C18—O4	1.340 (3)
C7—O5	1.367 (3)	C18—N1	1.356 (3)
C10—O5	1.440 (3)	C19—O4	1.491 (3)
O1—C1—C2—N1	175.9 (2)	C11—C10—O5—C7	−176.9 (2)
N1—C2—C3—C4	−54.3 (3)	O3—C18—O4—C19	4.3 (4)
C2—C3—C4—C5	−48.6 (4)	O4—C18—N1—C2	172.3 (2)
O5—C10—C11—C12	−85.7 (3)	C1—C2—N1—C18	−103.2 (3)
C6—C7—O5—C10	1.3 (4)		

Data collection

Kuma KM-4 CCD diffractometer
ω scans
11 736 measured reflections
3067 independent reflections
2602 reflections with $I > 2\sigma(I)$
R_{int} = 0.044
θ_{max} = 29.6°
$h = -12 \rightarrow 9$
$k = -15 \rightarrow 15$
$l = -26 \rightarrow 25$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.048
$wR(F^2)$ = 0.112
S = 1.34
3067 reflections
257 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0369P)^2 + 0.4413P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.36 e Å^{-3}
$\Delta\rho_{min}$ = −0.34 e Å^{-3}

The position and isotropic displacement parameter of the hydroxyl H atom were refined. All other H atoms were generated geometrically and treated as riding atoms (C—H = 0.93–0.98 Å). The Friedel-equivalent reflections were merged, as attempted refinement of the Flack (1983) parameter was inconclusive [refined value 0.5 (10)]. The absolute configuration was set by reference to the known configuration of L-tyrosine.

Data collection: *KM4CCD Software* (Kuma, 1995–1999); cell refinement: *KM4CCD Software*; data reduction: *KM4CCD Software*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *Stereochemical Workstation Operation Manual* (Siemens, 1989).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD1196). Services for accessing these data are described at the back of the journal.

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