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N^{α}-Benzyloxycarbonyl-α-aminoisobutyryl-glycyl-L-isoleucyl-L-leucine Methyl Ester Monohydrate

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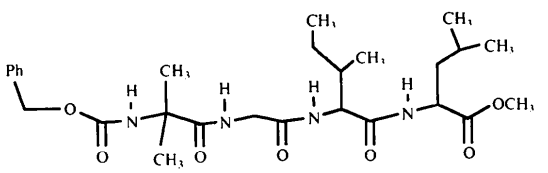
Abstract

(*Z*)-Aib-Gly-L-Ile-L-Leu-OMe.H_2O, $C_{27}H_{42}N_4O_7.H_2O$, is a protected analogue of the C-terminal sequence of the membrane-active peptaibol antibiotic trichogin A IV. The peptide backbone is folded. The urethane carbonyl O atom acts as the acceptor of two intramolecular hydrogen bonds which give rise to a β bend and to an α bend. The geometry of the latter is significantly distorted from that observed in α helices. This structure represents the first observation of an α bend in a protected tetrapeptide sequence.

Comment

Trichogin A IV, a membrane-active, channel-forming lipo-undecapeptide antibiotic of the peptaibol family, has been isolated and characterized recently (Auvin-Guette, Rebuffat, Prigent & Bodo, 1992). In the course of the total chemical synthesis of trichogin A IV undertaken in our laboratory (Formaggio, Pirrone, Monaco, Crisma & Toniolo, 1994), the protected tetrapeptide (*Z*)-Aib-Gly-L-Ile-L-Leu-OMe, (I), an analogue of its C-terminal sequence with L-Leu-OMe replacing the naturally occurring β-aminoalcohol L-leucinol, has been prepared and crystallized as the monohydrate by slow evaporation from ethyl acetate.



(I)

The (*Z*)-urethane and peptide —CONH— bonds are *trans*, but the urethane is markedly nonplanar. The backbone of the peptide molecule is folded. Two intramolecular hydrogen bonds are observed, both involving the urethane carbonyl O atom as the acceptor, the N—H groups of Ile^3 and Leu^4 being the donors. Thus, a β-bend (Venkatachalam, 1968) and an α-bend (Toniolo, 1980) conformation are each formed. The sets of φ and ψ backbone torsion angles (IUPAC-IUB Commission on Biochemical Nomenclature, 1970) of Aib^1 and Gly^2 are close to those of an ideal type I β bend. The backbone conformation of the α bend, encompassing the residues Aib^1, Gly^2 and Ile^3, is significantly distorted from the average values, $\varphi = -62°$, $\psi = -41°$, reported for α helices in peptides (Benedetti *et al.*, 1991) and proteins (Arnott & Wonacott, 1966). Particularly noteworthy is the large value of φ for Ile^3, which compensates for the small value of ψ shown by Gly^2. The α-bend conformational parameters reported here are similar to those adopted by the first three residues of the pentapeptide Boc-Aib-L-Pro-L-Val-Aib-L-Val-OMe (Francis, Iqbal, Balaram & Vijayan, 1982).

The occurrence of an α bend in peptides shorter than seven residues is a rare event and, to our knowledge, it has not been observed previously in a protected tetrapeptide sequence. In particular, for protected tetrapeptides containing the highly helicogenic Aib residue the most common structural motif is produced by the formation of two consecutive β bends (Toniolo *et al.*, 1983). In this case it is noteworthy that the carbonyl O atom of Aib^1, which could have been hydrogen bonded to the Leu^4 N—H group in the case of the onset of a second β bend, is hydrogen bonded to the cocrystallized water molecule.

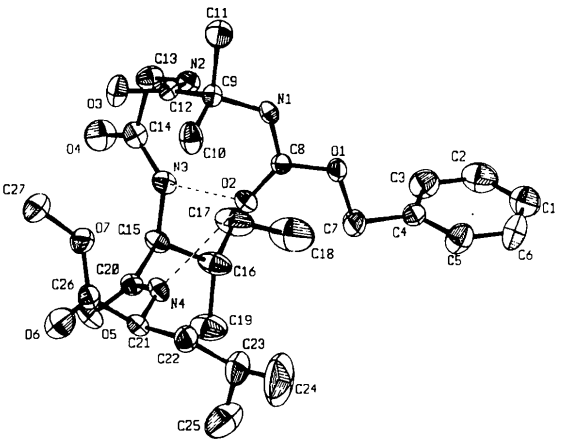


Fig. 1. *ORTEP* (Johnson, 1965) drawing of (*Z*)-Aib-Gly-L-Ile-L-Leu-OMe, showing non-H atoms as 30% probability ellipsoids. Intramolecular hydrogen bonds are indicated as dashed lines.

Experimental

Crystal data

$C_{27}H_{42}N_4O_7.H_2O$
M_r = 552.67
Monoclinic
$P2_1$
a = 14.556 (2) Å
b = 11.759 (2) Å
c = 9.473 (2) Å
β = 104.1 (2)°

Mo $K\alpha$ radiation
λ = 0.71070 Å
Cell parameters from 25 reflections
θ = 7–12°
μ = 0.08049 mm^{-1}
T = 298 K
Prism

V = 1573 (1) Å^3
Z = 2
D_x = 1.1671 Mg m^{-3}
D_m = 1.16 Mg m^{-3}
D_m measured by flotation in benzene-bromobenzene
0.4 × 0.4 × 0.4 mm
Colourless
Crystal source: crystallized by slow evaporation from ethyl acetate

Data collection

Philips PW1100 diffractometer
$\theta/2\theta$ scans
Absorption correction: none
4204 measured reflections
3991 independent reflections
1614 observed reflections [$F > 7\sigma(F)$]
R_{int} = 0.034
θ_{max} = 28.0°
$h = -19 \rightarrow 18$
$k = 0 \rightarrow 15$
$l = 0 \rightarrow 12$
3 standard reflections
frequency: 180 min
intensity variation: 4%

Refinement

Refinement on F
R = 0.045
wR = 0.049
S = 0.892
1614 reflections
515 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F) + 0.003554F^2]$
$(\Delta/\sigma)_{max}$ = 0.332
$\Delta\rho_{max}$ = 0.17 e Å^{-3}
$\Delta\rho_{min}$ = −0.19 e Å^{-3}
Extinction correction: none
Atomic scattering factors from *International Tables for X-ray Crystallography* [1974, Vol. IV, Tables 2.2A, 2.3.1 (C, N, O) and 2.2C (H)]
Absolute configuration: assigned to agree with the known chirality of L-Ile and L-Leu residues

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2)

$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
O1	0.1850 (3)	0.1114	0.4620 (3)	0.055 (1)
O2	0.2243 (2)	0.1995 (4)	0.2733 (3)	0.058 (1)
O3	0.4109 (3)	0.4486 (4)	0.3378 (5)	0.074 (2)
O4	0.5608 (3)	0.1813 (5)	0.1679 (5)	0.088 (2)
O5	0.3178 (3)	0.1891 (4)	−0.1996 (3)	0.064 (1)
O6	0.1533 (3)	0.4761 (5)	−0.2022 (6)	0.091 (2)
O7	0.2700 (3)	0.4258 (3)	−0.0172 (4)	0.062 (1)
N1	0.2611 (3)	0.2749 (4)	0.5008 (4)	0.045 (1)
N2	0.4345 (3)	0.2724 (4)	0.4326 (4)	0.048 (2)
N3	0.4076 (3)	0.1604 (4)	0.1720 (4)	0.050 (2)
N4	0.2306 (3)	0.2099 (4)	−0.0362 (4)	0.050 (1)
C1	0.1052 (5)	−0.2684 (4)	0.6229 (5)	0.095 (4)
C2	0.1951 (5)	−0.2446 (4)	0.6029 (5)	0.098 (4)
C3	0.2086 (5)	−0.1507 (4)	0.5203 (5)	0.079 (3)
C4	0.1322 (5)	−0.0806 (4)	0.4577 (5)	0.061 (2)
C5	0.0424 (5)	−0.1043 (4)	0.4777 (5)	0.078 (3)
C6	0.0288 (5)	−0.1982 (4)	0.5604 (5)	0.107 (4)
C7	0.1471 (6)	0.0180 (6)	0.3659 (7)	0.087 (3)
C8	0.2231 (3)	0.1965 (5)	0.4023 (5)	0.043 (2)
C9	0.2987 (3)	0.3849 (5)	0.4663 (5)	0.045 (2)
C10	0.2241 (4)	0.4530 (6)	0.3617 (7)	0.070 (2)
C11	0.3314 (5)	0.4487 (6)	0.6110 (7)	0.073 (2)
C12	0.3852 (3)	0.3703 (5)	0.4048 (5)	0.044 (2)
C13	0.5171 (3)	0.2512 (5)	0.3755 (6)	0.056 (2)
C14	0.4962 (3)	0.1954 (5)	0.2268 (5)	0.052 (2)
C15	0.3767 (4)	0.1013 (5)	0.0337 (5)	0.050 (2)
C16	0.3360 (5)	−0.0162 (6)	0.0571 (6)	0.071 (3)
C17	0.4140 (7)	−0.0882 (7)	0.1554 (8)	0.100 (3)
C18	0.382 (1)	−0.1992 (9)	0.199 (1)	0.159 (6)
C19	0.2962 (7)	−0.0757 (7)	−0.0904 (8)	0.097 (3)
C20	0.3065 (4)	0.1721 (5)	−0.0760 (5)	0.046 (2)
C21	0.1606 (4)	0.2841 (5)	−0.1239 (5)	0.047 (2)
C22	0.0679 (4)	0.2790 (7)	−0.0768 (6)	0.066 (3)
C23	0.0278 (6)	0.157 (1)	−0.080 (1)	0.126 (5)
C24	−0.0663 (9)	0.173 (2)	−0.036 (2)	0.24 (1)
C25	0.017 (1)	0.098 (1)	−0.217 (2)	0.175 (7)
C26	0.1937 (3)	0.4059 (5)	−0.1196 (5)	0.050 (2)
C27	0.3071 (5)	0.5409 (6)	−0.0015 (8)	0.082 (3)
O1*W*	0.4155 (3)	0.0735 (5)	−0.3976 (5)	0.088 (2)

Table 2. *Selected torsion angles* (°)

C3—C4—C7—O1	−82.2 (9)	N3—C15—C20—N4	−54.1 (9)
C5—C4—C7—O1	99.5 (8)	C21—N4—C20—C15	175.8 (6)
C8—O1—C7—C4	164.9 (6)	C20—N4—C21—C26	−77.1 (9)
C7—O1—C8—N1	−176.1 (6)	N4—C21—C26—O7	−12.8 (9)
C9—N1—C8—O1	−172.7 (6)	C27—O7—C26—C21	−178.9 (6)
C8—N1—C9—C12	−65.6 (9)	N3—C15—C16—C17	−62.0 (8)
N1—C9—C12—N2	−21.4 (9)	N3—C15—C16—C19	175.8 (6)
C13—N2—C12—C9	178.9 (6)	C15—C16—C17—C18	174.0 (8)
C12—N2—C13—C14	−89.3 (8)	N4—C21—C22—C23	−56.1 (9)
N2—C13—C14—N3	−7 (1)	C21—C22—C23—C24	−177.5 (9)
C15—N3—C14—C13	−177.4 (6)	C21—C22—C23—C25	−53 (1)
C14—N3—C15—C20	−114.5 (8)		

Table 3. *Geometric parameters for intra- and intermolecular hydrogen bonds* (Å, °)

D	H	*A*	H···*A*	*D*···*A*	*D*—H···*A*
N3	H1N3	O2	2.37 (5)	3.081 (6)	151 (4)
N4	H1N4	O2	2.15 (5)	2.957 (5)	171 (5)
O1*W*	H2*W*	O5	2.02 (8)	2.947 (7)	157 (7)
N1	H1N1	O5^{i}	2.35 (6)	2.935 (6)	141 (6)
N2	H1N2	O1*W*^{i}	2.11 (6)	2.890 (7)	166 (5)
O1*W*	H1*W*	O3^{ii}	2.08 (7)	2.858 (6)	155 (6)

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

Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1985). Program(s) used to refine structure: *SHELX*76 (Sheldrick, 1976). Molecular graphics: *ORTEP* (Johnson, 1965). Software used to prepare material for publication: *PARST* (Nardelli, 1983), locally modified by F. Nicoló.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 71695 (21 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: AD1000]

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Two Cyclic Dipeptide Anticonvulsants: *cyclo*-Glycyl-L-phenylglycine (1) and *cyclo*-L-Alanyl-D-phenylglycine (2)

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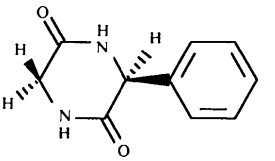
Abstract

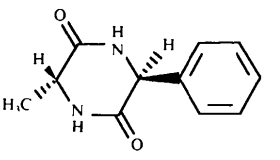
In the title compounds, $C_{10}H_{10}N_2O_2.0.25H_2O$ (1) and $C_{11}H_{12}N_2O_2$ (2), the phenyl rings are almost perpendicular to the mean planes of the diketopiperazine rings, which assume flattened twist-boat conformations. The methyl group of the alanyl residue in (2) lies in a quasi-axial position. In both structures, hydrogen bonds connect molecules into infinite layers. In compound (1), there are two molecules per asymmetric unit and each forms an independent layer. Water molecules bind the neighboring layers of only one type into pairs. There is no interaction between symmetrically independent molecules.

Comment

Both compounds are part of a series of cyclic dipeptides designed to act at an Na channel receptor site for anticonvulsants (Weaver, Edgecombe, Smith & Anderson, 1992). The cyclic alanyl derivative, compound (2), has significant pharmacological activity (ED_{50} = 50 mg kg^{-1} in mice) in the maximal electroshock (MES) test; compound (1) is pharmacologically inactive (Weaver *et al.*, 1992). The conformations and intermolecular interactions of the two compounds were determined as part of our study of Na channel anticonvulsants (Codding, Lee & Richardson, 1984; Codding *et al.*, 1990; Duke & Codding, 1992).



(1)



(2)

The molecular conformations are shown in Figs. 1 and 2; the diketopiperazine ring of each molecule assumes the conformation of a distorted flattened twist boat. The crystal structure of (1) contains two independent molecules per asymmetric unit (the water molecule lies in the special position with the O atom on the twofold axis). In molecule *A* of compound (1), the diketopiperazine ring is almost planar [maximum deviation from the least-squares plane is 0.028 (2) Å], while for molecule *B* of compound (1) and compound (2), the folding is more significant [maximum deviations of 0.081 (2) and 0.056 (2) Å, respectively].

As has been observed for other cyclic dipeptides (Filhol & Timmins, 1976; Benedetti, Marsh & Goodman, 1976), the strain imposed by closing two *cis* peptide bonds to form a ring introduces nonplanarity into the peptide bond [see the ω torsion angles in Table 3; torsion-angle nomenclature is given according to the IUPAC-IUB Commission on Biochemical Nomenclature (1970)]. The methyl group of the alanyl residue in (2) is in a quasi-axial position [C5—N4—C3—C31 −112.3 (4), N1—C2—C3—C31 116.4 (3)°]. In compound (2), the stereochemistry of the phenyl substituents of the phenylglycine residue places the phenyl substituent on the opposite side of the diketopiperazine ring to the methyl group of the alanyl residue [improper torsion angle C1′—C6···C3—C31 of 179.2 (2)°, see Fig. 2]. The phenyl rings are

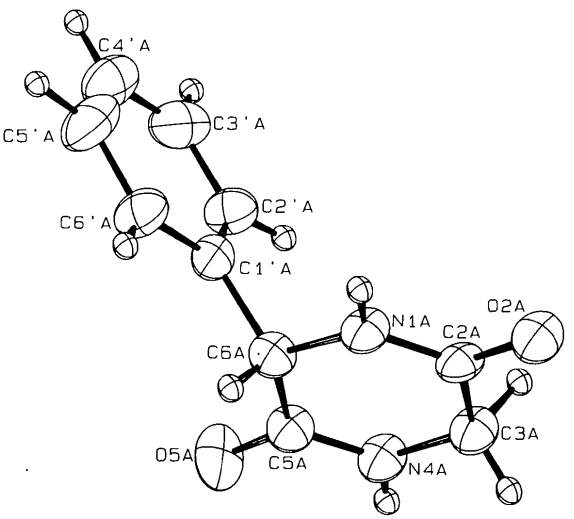


Fig. 1. A thermal-ellipsoid representation of molecule *A* of compound (1). The ellipsoids are drawn at the 50% probability level; the H atoms are drawn as spheres of arbitrary size.

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