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Structure of the Tripeptide Amide H-L-Pro-L-Leu-L-Pro-NH_2, a Dopamine Receptor Modulating Agent

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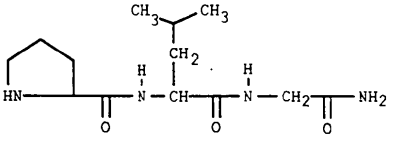
Abstract

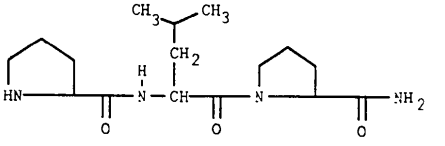
The title compound, L-Prolyl-L-leucyl-L-prolinamide, $C_{16}H_{28}N_4O_3$, is folded at the N-terminal L-Pro residue and semi-extended at the central L-Leu and C-terminal L-Pro residues. The L-Leu side chain is in the common $g^-(t,g^-)$ disposition.

Comment

Several of the hypothalamic release-inhibiting factors have effects on the central nervous system which are independent of their endocrine effects. Among these oligopeptides is H-L-Pro-L-Leu-Gly-NH_2 (1). This tripeptide amide, the hypothalamic factor that inhibits the release of melanocyte-stimulating hormone from the anterior pituitary gland, has been shown to possess a pharmacological profile typical of a dopamine-receptor modulating agent (Johnson, Rajakumar & Mishra, 1986). In an attempt to gain better understanding of the bioactive conformation of (1), we have undertaken the structural analysis of a number of conformationally restricted analogues of this tripeptide (Valle *et al.*, 1988; Valle, Crisma, Toniolo, Yu & Johnson, 1989). In this paper, we describe the structure of H-L-Pro-L-Leu-L-Pro-NH_2 (2), a bioactive analogue of (1), which possesses a



(1)



(2)

chiral cyclic amino acid residue at the C-terminal position (Johnson *et al.*, 1986). The synthesis and characterization of (2) have been reported (Johnson, Smissman & Plotnikoff, 1978).

The backbone conformation of (2) is folded at the N-terminal L-Pro residue [$\psi_1 = -5.9$ (5)°] and semi-extended at the central L-Leu [$\phi_2 = -98.8$ (5)°, $\psi_2 = 129.6$ (6)°] and at the C-terminal L-Pro [$\phi_3 = -72.5$ (5)°, $\psi_T = 154.4$ (6)°] residues (IUPAC–IUB Commission on Biochemical Nomenclature, 1970). The peptide torsion angles are in the usual *trans*-planar conformation [$\omega_1 = 175.4$ (6), $\omega_2 = 178.3$ (6)° (Benedetti, 1982)]. Interestingly, in the crystal state the prototype tripeptide amide (1) is extended at the N terminus, while folded in a type-II β-turn conformation (Venkatachalam, 1968) at the -L-Leu-Gly- sequence (Reed & Johnson, 1973).

The L-Leu side chain of (2) takes the common $g^-(t,g^-)$ conformation (Benedetti, Morelli, Némethy & Scheraga, 1983), with the χ^1, $\chi^{2,1}$ and $\chi^{2,2}$ torsion angles −66.8 (6), 167.4 (7) and −70.4 (6)°, respectively. The pyrrolidine rings of the L-Pro[1] and L-Pro[3] residues have close to C_2 (twist) symmetry, with ring-puckering parameters $q_2 = 0.353$ Å and $\phi_2 =$

97.6° for the former and $q_2 = 0.378$ Å and $\phi_2 = 84.8°$ for the latter (Cremer & Pople, 1975).

In the crystal, the molecules of (2) pack by forming layers parallel to the xy plane. The H atoms of the prolinamide group are linked to peptide carbonyl O atoms of two symmetry-related molecules. The N4···O1($-1-x$, $y-\frac{1}{2}$, $\frac{1}{2}-z$), N4···O2($-x$, $\frac{1}{2}+y$, $\frac{1}{2}-z$) and N1···O3(x, $y-1$, z) distances are 3.19 (2), 2.90 (1) and 3.01 (2) Å, respectively.

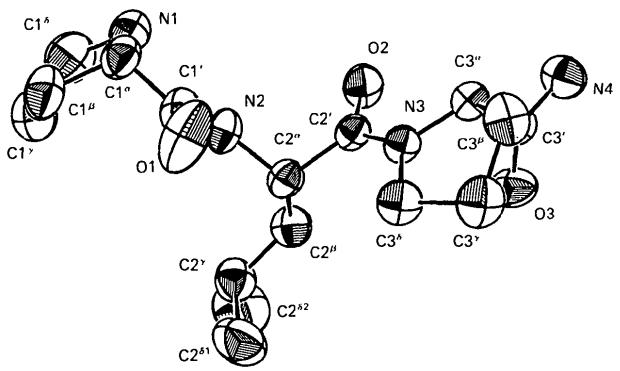


Fig. 1. *ORTEP* (Johnson, 1965) drawing of the H-L-Pro-L-Leu-L-Pro-NH_2 molecule with the numbering of the non-H atoms. Thermal ellipsoids are shown at the 50% probability level.

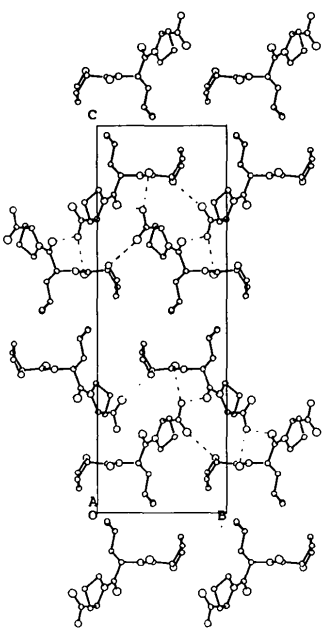


Fig. 2. Mode of packing of the H-L-Pro-L-Leu-L-Pro-NH_2 molecules viewed down the a axis. The intermolecular hydrogen bonds are indicated as dashed lines.

Experimental

Crystal data

$C_{16}H_{28}N_4O_3$
$M_r = 324.43$
Orthorhombic
$P2_12_12_1$
$a = 6.502$ (8) Å
$b = 9.682$ (5) Å
$c = 28.629$ (3) Å
$V = 1802.2$ Å^3
$Z = 4$
$D_x = 1.196$ Mg m^{-3}
Cu $K\alpha$ radiation
$\lambda = 1.5418$ Å
Cell parameters from 25 reflections
$\theta = 15$-$27°$
$\mu = 0.6$ mm^{-1}
$T = 295$ K
Needles
$0.8 \times 0.5 \times 0.4$ mm
Colourless
Crystal source: slow evaporation of an ethyl acetate solution

Data collection

CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: none
2015 measured reflections
1989 independent reflections
1749 observed reflections [$I \geq 3\sigma(I)$]
$R_{int} = 0.05$
$\theta_{max} = 70°$
$h = 0 \rightarrow 7$
$k = 0 \rightarrow 11$
$l = 0 \rightarrow 34$
2 standard reflections
frequency: 60 min
intensity variation: 3%

Refinement

Refinement on F
$R = 0.042$
$wR = 0.043$
$S = 0.672$
1760 reflections
209 parameters
H-atom parameters not refined
$w = 1/\sigma(F_o^2)$
$(\Delta/\sigma)_{max} = 0.009$
$\Delta\rho_{max} = 0.17$ e Å^{-3}
$\Delta\rho_{min} = -0.20$ e Å^{-3}
Atomic scattering factors from Cromer & Waber (1974)

Program used to solve structure: *MULTAN80* (Main *et al.*, 1980). Structure refined by blocked full-matrix least squares with anisotropic displacement parameters for all non-H atoms. Program used to refine structure: least-squares *SDP* (Enraf-Nonius, 1985).

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

$U_{eq} = \frac{1}{3}\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
N1	−0.0885 (5)	−0.5856 (3)	0.3582 (1)	0.069 (1)
C1$^\alpha$	−0.3094 (6)	−0.5770 (3)	0.3695 (1)	0.063 (1)
C1$^\beta$	−0.3383 (7)	−0.6560 (4)	0.4152 (1)	0.078 (2)
C1$^\gamma$	−0.1320 (8)	−0.6442 (4)	0.4377 (1)	0.087 (2)
C1$^\delta$	0.0171 (7)	−0.6508 (5)	0.3975 (1)	0.090 (1)
C1′	−0.3814 (6)	−0.4278 (3)	0.3744 (1)	0.062 (1)
O1	−0.5645 (4)	−0.4015 (3)	0.3803 (1)	0.101 (1)
N2	−0.2351 (4)	−0.3318 (2)	0.3722 (1)	0.0531 (8)
C2$^\alpha$	−0.2784 (5)	−0.1838 (3)	0.3729 (1)	0.0475 (9)
C2$^\beta$	−0.1162 (6)	−0.1066 (3)	0.4011 (1)	0.059 (1)
C2$^\gamma$	−0.1122 (6)	−0.1355 (4)	0.4525 (1)	0.066 (1)
C2$^{\delta1}$	0.0886 (8)	−0.0757 (6)	0.4734 (1)	0.111 (2)
C2$^{\delta2}$	−0.2997 (8)	−0.0745 (5)	0.4770 (1)	0.101 (2)
C2′	−0.2748 (5)	−0.1291 (3)	0.3234 (1)	0.0442 (8)
O2	−0.1269 (3)	−0.1528 (2)	0.29760 (8)	0.0601 (6)
N3	−0.4319 (4)	−0.0531 (2)	0.30830 (9)	0.0434 (6)
C3$^\alpha$	−0.4307 (5)	0.0042 (3)	0.2614 (1)	0.0447 (9)
C3$^\beta$	−0.6556 (5)	0.0546 (4)	0.2555 (1)	0.062 (1)
C3$^\gamma$	−0.7160 (5)	0.0975 (4)	0.3047 (1)	0.067 (1)
C3$^\delta$	−0.6128 (5)	−0.0109 (4)	0.3356 (1)	0.059 (1)
C3′	−0.2758 (4)	0.1234 (3)	0.2583 (1)	0.0450 (8)
O3	−0.2331 (4)	0.1909 (2)	0.29281 (8)	0.0660 (8)
N4	−0.2000 (5)	0.1481 (3)	0.2162 (1)	0.065 (1)

Table 2. *Geometric parameters* (Å, °)

N$_1$—C1$^\alpha$	1.474 (6)	C1′—O1	1.229 (5)
N$_1$—C1$^\delta$	1.462 (6)	C1′—N2	1.331 (5)
C1$^\alpha$—C1$^\beta$	1.528 (6)	N2—C2$^\alpha$	1.461 (4)

$C1^{\alpha}$—$C1'$	1.525 (5)	$C2^{\alpha}$—$C2^{\beta}$	1.525 (5)
$C1^{\beta}$—$C1^{\gamma}$	1.493 (7)	$C2^{\alpha}$—$C2'$	1.513 (4)
$C1^{\gamma}$—$C1^{\delta}$	1.507 (7)	$C2^{\beta}$—$C2^{\gamma}$	1.497 (5)
$C2^{\gamma}$—$C2^{\delta 1}$	1.548 (7)	$C3^{\alpha}$—$C3^{\beta}$	1.551 (5)
$C2^{\gamma}$—$C2^{\delta 2}$	1.526 (7)	$C3^{\alpha}$—$C3'$	1.535 (5)
$C2'$—O2	1.234 (4)	$C3^{\beta}$—$C3^{\gamma}$	1.519 (6)
$C2'$—N3	1.330 (4)	$C3^{\gamma}$—$C3^{\delta}$	1.528 (6)
N3—$C3^{\alpha}$	1.453 (4)	$C3'$—N4	1.325 (4)
N3—$C3^{\delta}$	1.470 (4)	$C3'$—O3	1.216 (4)
$C1^{\alpha}$—N_1—$C1^{\delta}$	108.3 (6)	N2—$C2^{\alpha}$—$C2^{\beta}$	110.8 (5)
N_1—$C1^{\alpha}$—$C1^{\beta}$	106.2 (5)	N2—$C2^{\alpha}$—$C2'$	109.1 (4)
N_1—$C1^{\alpha}$—$C1'$	111.9 (5)	$C2^{\beta}$—$C2^{\alpha}$—$C2'$	108.3 (5)
$C1^{\beta}$—$C1^{\alpha}$—$C1'$	110.9 (6)	$C2^{\alpha}$—$C2^{\beta}$—$C2^{\gamma}$	116.2 (5)
$C1^{\alpha}$—$C1^{\beta}$—$C1^{\gamma}$	102.8 (6)	$C2^{\beta}$—$C2^{\gamma}$—$C2^{\delta 1}$	109.0 (6)
$C1^{\beta}$—$C1^{\gamma}$—$C1^{\delta}$	104.2 (7)	$C2^{\beta}$—$C2^{\gamma}$—$C2^{\delta 2}$	111.4 (6)
N_1—$C1^{\delta}$—$C1^{\gamma}$	105.5 (7)	$C2^{\delta 1}$—$C2^{\gamma}$—$C2^{\delta 2}$	110.5 (7)
$C1^{\alpha}$—$C1'$—O1	120.4 (6)	$C2^{\alpha}$—$C2'$—O2	120.5 (5)
$C1^{\alpha}$—$C1'$—N2	115.9 (6)	$C2^{\alpha}$—$C2'$—N3	119.0 (5)
O1—$C1'$—N2	123.7 (6)	O2—$C2'$—N3	120.5 (5)
$C1'$—N2—$C2^{\alpha}$	123.1 (5)	$C2'$—N3—$C3^{\alpha}$	120.5 (5)
$C2'$—N3—$C3^{\delta}$	126.6 (5)	$C3^{\beta}$—$C3^{\gamma}$—$C3^{\delta}$	103.6 (5)
$C3^{\alpha}$—N3—$C3^{\delta}$	112.9 (4)	N3—$C3^{\delta}$—$C3^{\gamma}$	103.6 (5)
N3—$C3^{\alpha}$—$C3^{\beta}$	102.5 (4)	$C3^{\alpha}$—$C3'$—N4	115.7 (5)
N3—$C3^{\alpha}$—$C3'$	110.1 (4)	$C3^{\alpha}$—$C3'$—O3	120.5 (5)
$C3^{\beta}$—$C3^{\alpha}$—$C3'$	112.0 (5)	N4—$C3'$—O3	123.9 (5)
$C3^{\alpha}$—$C3^{\beta}$—$C3^{\gamma}$	103.3 (5)		

Lists of structure factors and H-atom coordinates have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 71453 (10 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: VJ1000]

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2-[(5-Phenyl-2,3-dihydro-6*H*-1,3,4-thiadiazin-2-ylidene)amino]-3-pyridinol

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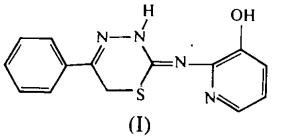
Abstract

The molecules of $C_{14}H_{12}N_4OS$ are dimerized through N—$H_{endo}\cdots N_{exo}$ hydrogen bonds [N···N 2.971 (3) Å] and linked in chains along the *a* axis by a short O—$H\cdots N_{py}$ hydrogen bond [O···N 2.681 (2) Å]. The thiadiazine ring is in a screw-boat conformation.

Comment

Treatment of functionalized 2-(2-oxopropyl-2-oxo-2-phenylethylthio)oxazole[4,5-*b*]pyridines with N-containing nucleophiles leads to the formation of substituted thiadiazines (Tosheva & Kalcheva, 1993). Some of these compounds have shown pronounced bacteriostatic activity and low toxicity (Kalcheva & Tosheva, 1990). The synthetic route for analogous 2*H*-imidazo[2,1-*b*]thiadiazines was given by Sasaki, Ito & Shimizu (1982).



(I)

Ring puckering parameters for the thiadiazine ring $^6S_1$ (Boeyens, 1978) are q_2 = 0.576, q_3 = −0.231 Å, φ = 146.75°; Q = 0.620 (2) Å, θ = 111.8 (2)° (Cremer & Pople, 1975; Evans & Boeyens, 1989). The large φ value indicates that the direction of the ring distortion is towards an inverted screw-boat conformation. The S—C1 1.751 (2) and S—C2 1.815 (2) Å bond lengths correspond to the typical S—C_{sp^2} and S—C_{sp^3} single bonds [1.751 (17), 1.819 (19) Å; Allen, Kennard, Watson, Brammer, Orpen & Taylor, 1987]. The endocyclic C1—N2 distance [1.363 (3) Å] is longer than the exocyclic C1—N1 distance [1.294 (3) Å]. The C1—N1 and the endocyclic N3—C3 [1.286 (3) Å] bonds have values close to that of a double N=C_{sp^2} bond [1.329 (14) Å, Allen *et al.*, 1987]. The N2—N3 bond [1.382 (3) Å] is slightly longer than the average single N(1)—N(2) bond [1.366 (19) Å, Allen