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CRYSTAL STRUCTURE OF A DIACETYLDIAZINO ANALOGUE OF THE VALINE RESIDUE

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RÉSUMÉ. — Au cours d'une étude sur les analogues hydrazinés des α -amino acides, nous avons préparé le dérivé (\pm) N^α, N^β -diacétyldiaziné-2 N-méthylisovaléramide (α, β -Ac₂-hVal-NHMe), contenant un analogue hydraziné de la valine (hVal). La détermination de sa structure cristalline par diffraction des rayons X nous a permis de mettre en évidence l'arrangement orthogonal du fragment diacétyl-hydrazine, modèle d'un enchaînement pseudo-peptidique.

ABSTRACT. — As part of a study on diazino-analogues of α -amino acids, we prepared the crystalline derivative (\pm) 2-(N^α, N^β -diacetyldiazino)-N-methyl-isovaleramide (α, β -Ac₂-hVal-NHMe) containing a diazino-analogue of valine (hVal). The resolution of its crystal structure by X-ray diffraction allowed us to determine the orthogonal disposition of the diacetyl-diazino fragment, a pseudo-peptide chain model.

Introduction

In an attempt to enhance biological potency and to discriminate between different biological activities of peptide messengers, it is current practice to introduce surrogates of the amide group in pseudo-peptide analogues^{1,2}. A resistance to biodegradation and a preference for a supposedly bioactive molecular conformation are expected to follow these chemical modifications of the peptide backbone.

The introduction of a diazinoacid residue in an analogue of eleoisin was reported twenty years ago³, but after this seminal work, the study of diazinopeptides has remained very limited, presumably because it is difficult to obtain optically pure diazinoacids and to achieve regioselective coupling of the $N^\beta H_2-N^\alpha H-$ diazino group. Recently, we have developed new protocols for the synthesis of chiral diazinoacids^{4,7}, and found that the reactivity of the $N^\beta H_2-N^\alpha H-$ fragment may depend on various factors: the bulkiness of the side-substituent of the diazinoacids, the nature of the aminoacid to which it is coupled,

and the coupling method⁸. In these reactions, both diazido ($-\text{CO}-N^\beta H-N^\alpha H-$) and N-aminoamide links ($-\text{CO}-N^\alpha(N^\beta H_2)-$) can be obtained.

Very little is known about the three-dimensional structure of diazinopeptides. So far, the crystal structure of the Boc-Pro- $N^\beta H-N^\alpha H-CH_2-CO_2Et$ derivative containing the diazino-analogue of glycine, constitutes the only available set of experimental data for the diazido group ($-\text{CO}-N^\beta H-N^\alpha H-$)⁵.

During our studies on α -diazinoacids, we obtained single crystals of (\pm) 2-(N^α, N^β -diacetyldiazino)-N-methyl-isovaleramide, abbreviated to α, β -Ac₂-hVal-NHMe, containing a diazino-analogue of the valine residue in which both nitrogens had been acetylated. The crystal structure of this compound, which can be considered as a doubly-branched pseudo-peptide model, was solved by X-ray diffraction.

Experimental part

SYNTHESIS

Racemic 2-diazino-3-methylbutyric acid (diazinovaline, hVal) was prepared as follows. To a solution of 2-bromo-3-methylbutyric

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acid (18.1 g, 0.1 mol.) in absolute ethanol (200 mL) was added dropwise 25 mL (0.5 mol) of hydrazine hydrate, and the mixture was refluxed for 2 h. The resulting precipitate (hVal) was collected by suction filtration, washed with methanol, and recrystallized from water; yield 8 g (60%); ¹H-NMR (200.13 MHz, D₂O, δ(HOD) 4.7): 0.90 (d, 6H, (CH₃)₂CH), 2.1 (m, 1H, (CH₃)₂CH), 3.4 (d, 1H, CH); mp 217° C; C₅H₁₂N₂O₂ calcd (%) C 45.44, H 9.15, N 21.20; found C 45.46, H 9.20, N 21.17.

Treatment of hVal by thionyl chloride in cold methanol gave an excellent yield of the HCl, hVal-OMe, which was acetylated by two equivalents of acetyl chloride and three equivalents of triethylamine in chloroform. The chloroform was evaporated and the residue taken up with ethyl acetate. After filtration of the triethylammonium chloride, the organic solution was washed by 0.1 M HCl, 5% aqueous NaHCO₃, then water, dried on Na₂SO₄ and evaporated. The crude, oily ester was treated at room temperature by an alcoholic methylamine solution and the resulting methylamide was recrystallized from ethyl acetate. Its purity was checked by thin layer chromatography on silica gel, ¹H-NMR spectroscopy, and its structure was confirmed by the X-ray crystallographic study reported below. ¹H-NMR (200.13 MHz, CDCl₃, TMS) revealed two conformers in slow exchange: A (85%) and B (15%); 0.94 and 1.03 (d, 6H, A+B, (CH₃)₂CH, 1.80 and 2.02 (s, 6H, B, 2 CH₃CO), 2.09 (m, 1H, A+B, (CH₃)₂CH), 2.08 and 2.10 (s, 6H, A, 2 CH₃CO), 2.73 (d, 3H, B, NHCH₃), 2.78 (d, 3H, A, NHCH₃), 4.56 (d, 1H, B, NCH), 4.69 (d, 1H, A, NCH), 6.70 (q, 1H, B, NHCH₃), 6.84 (q, 1H, A, NHCH₃), 8.00 (s, 1H, B, NHN), 8.84 (s, 1H, A, NHN). C₁₀H₁₉N₃O₃ calc (%) C 52.40, H 8.30, N 18.34; found C 52.45, H 8.20, N 18.52.

The conformational equilibrium in chloroform is due to slow *cis-trans* isomerization of the CO-N(NH)-C amide bond. On the basis of a negligible long-range coupling constant (0.1 Hz) between *cis* methyl groups, but of a larger value (0.5 Hz) between *trans* methyl groups for dimethylacetamide¹⁰, resulting in broader signals in the latter case, the minor broader NH singlet at 8.00 ppm was assigned to the *trans* CH₃-CO-N-NH fragment, and the major sharper NH singlet at 8.84 ppm to the *cis* disposition of the same fragment.

X-RAY DIFFRACTION

Single crystals of α,β-Ac₂-hVal-NHMe were obtained by slow cooling and evaporation of an ethyl acetate solution. X-ray data were collected at room temperature in the θ - 2θ scan mode (θ < 70°) on an Enraf Nonius CAD-4 diffractometer equipped with graphite monochromator and Cu-target X-ray tube (λ = 1.5418 Å). Intensity data were corrected for Lorentz and polarization effects, and the absorption was disregarded (μR << 1). Cell dimensions are indicated in Table I, together with other experimental parameters.

Table I. - Crystallographic data.

Formula	C ₁₀ H ₁₉ N ₃ O ₃
Molecular weight	229.28
Space group	Pna2 ₁
Z	4
Cell dimensions	a = 8.301(1) Å b = 15.639(3) Å c = 9.857(2) Å
Calculated density	1.19 g.cm ⁻³
Total reflections	1288
Significant reflections	1026 (I > 1.5 σ(I))
Residual factors	R = 0.041 G.O.F. = 0.96 R _w = 0.045 (w = 2.1788/σ ² (F) + 0.00165 F ²)
Maximum shifts/e.s.d.	0.25 (non hydrogen atoms)
Maximum residual electronic density	0.13 e ⁻ /Å ³

Only reflections with I > 1.5 σ(I) were retained for the resolution of the structure using the computer program MULTAN-80¹¹. E-maps revealed all non-hydrogen atoms, and all hydrogen atoms appeared

on difference maps. Refined parameters¹² were calculated by using anisotropic thermal parameters for non-hydrogen atoms, and isotropic factors for hydrogen atoms. In order to have reliable dimensions for hydrogen bonds, and following Taylor and Kennard's recommendations, the NH hydrogen atoms were replaced at 1.03 Å from N in the direction obtained by refinement¹³. The position of the other hydrogen atoms has not been modified.

The atomic coordinates and the equivalent thermal parameters are listed in Table II. Atomic indexing is specified in Figure 1.

Table II. - Fractional atomic coordinates and equivalent thermal parameters with estimated deviation.

Atoms	X	Y	Z	B(Å ²)
O1	0.3494(3)	0.3414(2)	0.3382(4)	5.30(7)
O2	-0.0638(3)	0.2932(1)	0.6016(4)	4.38(6)
O3	0.1275(4)	0.4703(2)	0.768	5.19(6)
N1	0.1447(3)	0.3957(2)	0.4607(4)	3.20(5)
N2	-0.0206(3)	0.4101(2)	0.4717(4)	3.36(6)
N3	0.2725(4)	0.3496(2)	0.7466(5)	4.08(7)
C1	0.0836(6)	0.3178(3)	0.2520(6)	5.02(9)
C2	0.2027(4)	0.3516(2)	0.3528(5)	3.73(7)
C3	-0.1165(4)	0.3538(2)	0.5381(5)	3.39(7)
C4	-0.2921(4)	0.3721(3)	0.5246(5)	4.88(9)
C5	0.2524(4)	0.4434(2)	0.5522(5)	3.21(6)
C6	0.2100(4)	0.4225(2)	0.6988(5)	3.31(7)
C7	0.2309(7)	0.3183(4)	0.8797(6)	6.1(1)
C8	0.2539(5)	0.5388(2)	0.5236(5)	4.52(9)
C9	0.2827(7)	0.5559(3)	0.3725(6)	5.7(1)
C10	0.3807(7)	0.5822(3)	0.6090(7)	7.0(1)
H(N2)*	-0.070	0.460	0.417	
H(N3)*	0.329	0.316	0.670	

* The hydrogen atom was replaced at 1.03 Å from N in the direction found by refinement (ref. 13).

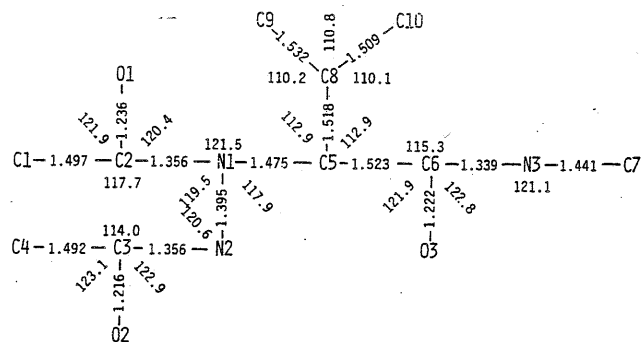


Figure 1. - Bond lengths (Å) and bond angles (°) for α,β-Ac₂-hVal-NHMe. The standard deviations are 0.006 Å and 0.4°. Atomic indexing is specified.

Results

The small residual factors (Table I) and equivalent thermal parameters (Table II) are characteristic of an accurate structure determination. However, some of the terminal methyl groups are, as usual, a little more agitated than the other non-hydrogen atoms.

The bond lengths and bond angles indicated in Figure 1 are quite comparable to those of other unconstrained diacetylhydrazines¹⁴⁻¹⁸. Moreover, the dimensions of the main backbone are compatible with the standard values for peptides¹⁹.

Table III. — Torsion angles with standard deviations (°).

Atoms	Angle*	Value	Atoms	Angle*	Value
C1-C2-N1-C5	ω_1	-169.6(3)	N2-N1-C5-C8		-66.9(4)
C1-C2-N1-N2		-1.9(5)	N1-C5-C6-N3	ψ	81.7(3)
O1-C2-N1-C5		9.2(5)	N1-C5-C6-O3		-99.9(4)
O1-C2-N1-N2		176.8(3)	C8-C5-C6-N3		-151.6(3)
C2-N1-N2-C3		90.4(5)	C8-C5-C6-O3		26.7(5)
C5-N1-N2-C3		-101.6(4)	C5-C6-N3-C7	ω_2	-174.6(4)
N1-N2-C3-C4	ω_3	-172.1(4)	O3-C6-N3-C7		7.0(6)
N1-N2-C3-O2		7.2(6)	N1-C5-C8-C9	χ_1	-50.4(5)
C2-N1-C5-C6	Φ	-132.5(3)	N1-C5-C8-C10	χ_2	-173.2(4)
C2-N1-C5-C8		100.9(4)	C6-C5-C8-C9		-175.1(3)
N2-N1-C5-C6		59.7(4)	C6-C5-C8-C10		62.1(5)

* IUPAC-IUB nomenclature (ref. 20).

Table IV. — Least-squares planes with atomic distances^a.

Plane I	$A = 0.0570$	$B = 0.8528$	$C = 0.5191$	$D = 2.9860$		
Atoms	C1	C2	O1	N1	N2*	C5*
Distances	0.002(4)	-0.006(4)	0.002(3)	0.002(3)	0.060(3)	0.222(4)
Plane II	$A = -0.0404$	$B = 0.5679$	$C = -0.8221$	$D = -7.4591$		
Atoms	C3	C4	O2	N2	N1*	H(N ²)*
Distances	-0.004(5)	0.001(4)	0.001(4)	0.001(4)	0.163(4)	0.024(3)
Plane III	$A = -0.8186$	$B = -0.04882$	$C = -0.3027$	$D = -6.7455$		
Atoms	C5	C6	O3	N3	C7*	H(N3)*
Distances	-0.002(3)	0.008(3)	-0.003(3)	-0.003(3)	0.121(6)	0.099(3)

Dihedral angles between planes (°)

I/II: 93.4(2) I/III: 107.8(2) II/III: 56.0(2)

^a The equation of the plane is of the form $Ax + By + Cz - D = 0$

* Atoms not considered for the average plane.

Stereoviews of the molecular conformation are represented in Figure 2 and the torsional angles are given in Table III, which also specifies the usual angles for peptides according to IUPAC convention²⁰. All three amide groups are in a *trans* and nearly planar conformation, but a pyramidalization of the nitrogens is noted, especially for the N1 nitrogen (Table IV) with a distance of 0.087(3) Å from the plane defined by the C2, N1 and C5 atoms. It is noteworthy that the conformation of the C2-N1 amide bond in the crystal corresponds to the major conformer A identified by ¹H-NMR in solution.

The conformation of the peptide backbone characterized by the Φ and Ψ angles (Table III) can be classed as a

β -structure following Ramachandran's map²¹, and the isopropyl side-chain assumes a very common orientation for valine residues with a *trans* disposition of the C5H-C8H fragment^{21,22}.

The diacetylhydrazine fragment is composed of two nearly perpendicular amide planes (Table IV). Although a planar disposition was found for both N,N'-diformyl and N,N'-diacetylhydrazine^{14,16}, this perpendicular disposition is not unique^{17,18}. It is probably due to the presence of a bulky substituent bonded to N1, which would cause severe steric hindrance in a planar conformation.

No intramolecular contact is found in the α,β -Ac₂-hVal-NHMe molecule, but each molecule is bonded

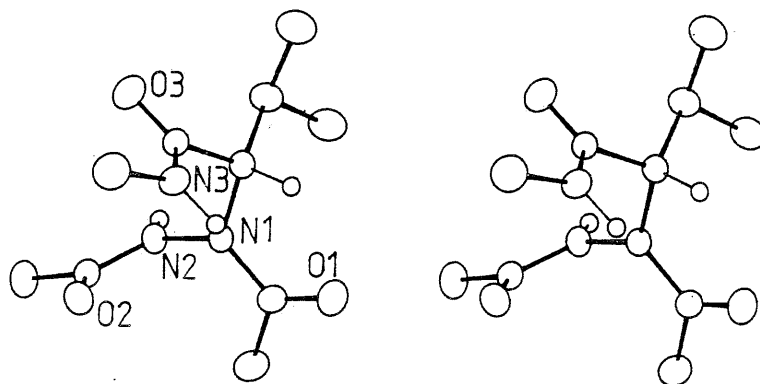


Figure 2. — Stereoviews of the molecular conformation of α,β -Ac₂-hVal-NHMe.

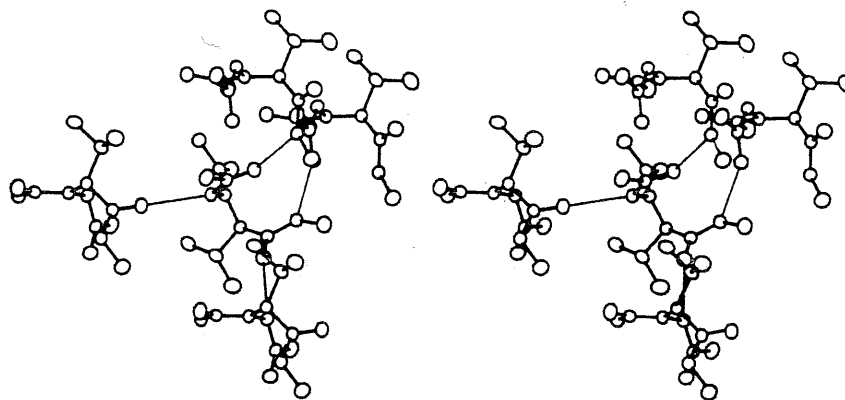


Figure 3. — Stereoviews of the molecular packing in the crystal of α,β -Ac₂-hVal-NHMe.

to four neighbours (Fig. 3) through the two intermolecular N2...O3 and N3...O2 hydrogen bonds (Table V). The O1 oxygen is free of any intermolecular interaction and its nearest neighbours are indicated in Table VI. However, we note a very short intramolecular O1...H(C5) distance of 2.14(4)Å, which is inferior to the van der Waals contact.

Table V. — Intermolecular hydrogen bonds.

N-H...O ^a	N...O(Å)	H...O(Å)	H(N)-N...O(°)
N2-H...O3 ¹	2.884(4)	1.89(4)	12(3)
N3-H...O2 ¹¹	2.979(5)	2.04(4)	20(3)

* Symmetry code: *i*, -*x*, 1-*y*, -1/2+*z*; *ii*, 1/2+*x*, 1/2-*y*, *z*

Table VI. — Nearest intermolecular neighbours of the O1 oxygen atom.

Atom	Symmetry	Distance (Å)
C1	1/2 + <i>x</i> , 1/2 - <i>y</i> , <i>z</i>	3.271(5)
C10	1 - <i>x</i> , 1 - <i>y</i> , -1/2 + <i>z</i>	3.398(7)
O2	1/2 + <i>x</i> , 1/2 - <i>y</i> , <i>z</i>	3.420(5)
C4	1 + <i>x</i> , <i>y</i> , <i>z</i>	3.530(5)

Conclusion

We have solved the crystal structure of (\pm) 2-(N ^{α} ,N ^{β} -diacetylhydrazino)-N-methyl-isovaleramide containing a hydrazino analogue of the valine residue. The bond lengths and bond angles are quite in keeping with the standard values for peptides. The three amide groups are *trans* planar and the pending N ^{α} -acetamido group is practically perpendicular to the N-terminal amide group. There is no intramolecular hydrogen bond and the molecules are bonded by two intermolecular N-H...O=C hydrogen bonds.

The orthogonal arrangement of the N ^{α} ,N ^{β} -diacetylhydrazino fragment, and the *cis-trans* isomerism of the CO-N ^{α} amide bond are to be considered for the design of pseudopeptide analogues containing N ^{α} ,N ^{β} -branched hydrazino acid residues. Hydrazino acids are effectively possible sites for branching or cyclization of analogues of bioactive peptides.

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