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(2*S*)-2-Hydroxy-4-methylvaleryl-L-valyl-L-phenylalanyl Methyl Ester

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Abstract. $C_{21}H_{32}N_2O_5$, $M_r = 392{\cdot}50$, orthorhombic, $P2_12_12_1$, $a = 10{\cdot}273\ (2)$, $b = 18{\cdot}862\ (3)$, $c = 24{\cdot}226\ (3)$ Å, $V = 4694{\cdot}2$ Å^3, $Z = 8$, $D_x = 1{\cdot}111$ Mg m^{-3}, $\lambda(\text{Cu } K\alpha) = 1{\cdot}5418$ Å, $\mu = 0{\cdot}652$ mm^{-1}, $F(000) = 1696$, room temperature, $R = 0{\cdot}051$ for 2053 observed reflections. In the region of the central valyl residue, the two peptide molecules in the asymmetric unit have very similar β-pleated sheet-type conformations. The oxygen O1 atoms which replace the classical N terminal participate in four different hydrogen-type interactions between the two independent molecules. The peptide units are *trans* and at least one of them shows significant deviation from planarity (9°).

Introduction. Renin is a proteolitic enzyme which cleaves the Leu-Leu peptide bond in equine (Skeggs, Kanh, Lentz & Shumway, 1957) or the Leu-Val bond in human substrates (Tewksbury, Dart & Travis, 1981). Inhibition of that reaction may have important therapeutic implications in the regulation of blood pressure. Among the number of ways explored in the search for potent inhibitors, one concerns the modification of the normal peptide bond with the object of producing a non-hydrolysable analogue. The natural peptide bond can be replaced by the reduced carbonyl analogue (Szelke, Leckie, Hallett, Jones, Suieras, Atrash & Lever, 1982), the hydroxy methylene analogue (Tree, Brown, Leckie, Lever, Manhem, Morton, Robertson, Szelke & Webb, 1984), the amino alcohol analogue (Dann, Stammers, Harris, Arrowsmith, Davies, Hardy & Morton, 1986), or the oxyacetyl analogue. The title compound is the tripeptide analogue obtained after transesterification of Leu-ψ(CO—O)-Leu-Val-Phe-OMe.

We describe in this report the crystal structure of the title compound (*O*-Leu-Val-Phe-OMe) and compare the conformations and the modes of interaction with those observed for Leu-Leu-Val-Tyr-OMe (Precigoux, Courseille, Geoffre & Leroy, 1987) and phenyloxyacetyl-Leu-Val-Phe-OMe (Geoffre, Leroy & Precigoux, 1986).

Experimental. The title compound *O*-Leu-Val-Phe-OMe was crystallized by slow diffusion of diisopropyl ether into a methanolic solution. Space group and preliminary unit-cell parameters determined from X-ray diffraction photographs. Crystal of dimensions $0{\cdot}1 \times 0{\cdot}2 \times 0{\cdot}4$ mm. Computer-controlled CAD-4 diffractometer, ω–2θ scan to a maximum Bragg angle of 50°, graphite-monochromated Cu $K\alpha$ radiation. 25 reflections in the range $10 \le \theta \le 32°$ used for cell-parameters refinement. Intensities not corrected for absorption. h: 0 to 10; k: 0 to 18; l: 0 to 24. Maximum variation in intensity of standard reflections 3%. 2738 reflections measured, 2053 with $I \ge 2\sigma(I)$ used in refinement. Structure solved by the direct-methods program *MITHRIL* (Gilmore, 1984). The non-H atoms were refined anisotropically and the H atoms, for the tertiary CH and the secondary CH_2 groups, were located geometrically and refined isotropically on F using the block-diagonal least-squares method. Refinement converged at $R = 0{\cdot}051$, $wR = 0{\cdot}053$, $S = 1{\cdot}0786$ (max. $\Delta/\sigma = 0{\cdot}07$). The weighting scheme was $w^{1/2} = 1$ if $|F_o| < p$ and $w^{1/2} = p/F_o$ if $|F_o| \ge p$ with $p = |F_o^2\ (\text{max.})/10|^{1/2}$. Maximum and minimum values in the difference Fourier map were 0·031 and

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Table 1. *Final positional* ($\times 10^4$) *and equivalent isotropic thermal parameters for the non-hydrogen atoms; standard deviations are given in parentheses*

$$B_{eq} = \tfrac{4}{3}\sum_i\sum_j B_{ij}\mathbf{a}_i.\mathbf{a}_j.$$

	Molecule I				Molecule II			
	x	y	z	B_{eq}(Å^2)	x	y	z	B_{eq}(Å^2)
O-Leucyl								
O1	11205 (8)	−31 (6)	808 (4)	8·8 (6)	11750 (7)	1210 (4)	1811 (4)	6·7 (5)
C*A*	9974 (11)	−304 (7)	641 (5)	6·5 (8)	12950 (12)	1588 (6)	1830 (6)	6·1 (7)
C′	8924 (10)	119 (7)	913 (7)	5·7 (7)	14003 (11)	1133 (6)	1542 (6)	6·3 (7)
O	7769 (7)	6 (5)	778 (4)	7·1 (5)	15142 (8)	1341 (5)	1542 (5)	9·4 (6)
C*B*	9855 (17)	−1103 (8)	830 (7)	9·8 (11)	13350 (12)	1769 (7)	2424 (6)	7·2 (8)
C*G*	10806 (22)	−1602 (10)	521 (11)	16·9 (18)	12443 (15)	2303 (8)	2714 (7)	9·5 (10)
C*D*1	10100 (33)	−1746 (13)	−37 (11)	22·8 (25)	12269 (20)	2983 (8)	2389 (8)	12·6 (13)
C*D*2	10900 (32)	−2290 (11)	864 (13)	23·2 (25)	13024 (19)	2388 (9)	3320 (6)	11·6 (12)
Valyl								
N	9264 (9)	554 (5)	1306 (4)	6·2 (6)	13631 (9)	543 (5)	1309 (4)	5·7 (5)
C*A*	8345 (11)	953 (6)	1658 (6)	6·2 (7)	14528 (11)	53 (7)	1023 (5)	6·1 (7)
C′	8516 (12)	1731 (6)	1553 (5)	5·9 (7)	14376 (11)	210 (6)	410 (5)	5·8 (7)
O	9604 (8)	2015 (4)	1593 (4)	7·2 (5)	13306 (7)	214 (5)	180 (3)	6·8 (5)
C*B*	8553 (15)	762 (8)	2284 (5)	7·4 (8)	14252 (13)	−726 (7)	1176 (6)	6·8 (8)
C*G*1	8137 (15)	−52 (7)	2343 (6)	8·6 (9)	14612 (18)	−839 (9)	1794 (6)	9·8 (11)
C*G*2	7663 (15)	1223 (8)	2643 (6)	8·8 (10)	15002 (16)	−1207 (7)	804 (7)	8·7 (9)
Phenylalanyl-OMe								
N	7460 (9)	2092 (5)	1446 (4)	6·2 (6)	15452 (9)	316 (5)	117 (4)	5·7 (5)
C*A*	7449 (11)	2846 (7)	1414 (6)	6·5 (7)	15437 (13)	410 (7)	−478 (5)	6·7 (8)
C′	7771 (14)	3165 (7)	1979 (7)	9·0 (10)	15035 (15)	−297 (8)	−760 (6)	8·5 (9)
O	7247 (14)	2998 (6)	2382 (5)	12·6 (9)	15182 (17)	−854 (6)	−558 (5)	14·2 (10)
O1	8550 (12)	3718 (6)	1896 (5)	12·8 (8)	14542 (11)	−186 (6)	−1248 (4)	11·2 (8)
C1	8694 (25)	4084 (16)	2480 (11)	21·5 (23)	14095 (21)	−843 (11)	−1550 (8)	15·0 (16)
C*B*	6097 (13)	3094 (8)	1215 (6)	8·1 (9)	16777 (13)	657 (8)	−702 (6)	7·6 (9)
C*G*	5838 (12)	3861 (7)	1230 (6)	6·9 (8)	17157 (12)	1382 (8)	−513 (5)	7·1 (8)
C*D*1	6401 (14)	4291 (7)	841 (6)	7·3 (8)	16534 (14)	1980 (9)	−728 (6)	8·6 (9)
C*D*2	5082 (15)	4174 (8)	1627 (7)	9·2 (10)	18194 (15)	1454 (8)	−170 (6)	8·7 (9)
C*E*1	6229 (14)	5022 (8)	840 (6)	7·9 (9)	16965 (14)	2635 (8)	−562 (6)	9·0 (10)
C*E*2	4897 (18)	4899 (9)	1650 (7)	11·6 (12)	18619 (17)	2127 (9)	−22 (7)	10·5 (11)
C*Z*	5466 (10)	5314 (8)	1244 (7)	9·5 (10)	17976 (15)	2714 (8)	−208 (6)	9·5 (11)

−0·18 e Å^{-3}, respectively. Atomic scattering factors were taken from *International Tables for X-ray Crystallography* (Cromer & Waber 1974) for non-H atoms and from Stewart, Davidson & Simpson (1965) for H atoms. The final positional parameters and equivalent isotropic thermal parameters are given in Table 1.*

Discussion. Fig. 1 shows the structural formula along with the atom-labelling scheme proposed by the IUPAC–IUB Commission on Biochemical Nomenclature (1970). The bond lengths, angles and main dihedral angles of the two crystallographically independent molecules are given in Table 2. The overall shapes of the two independent molecules are not very different. At the level of the central valyl residue, they possess a very similar conformation to the extended ones of Leu-Leu-Val-Tyr-OMe and phenyloxyacetyl-Leu-Val-Phe-OMe. A more precise comparison between molecules I and II shows that the main conformational fluctuations are located at the phenyl side chains and at the methyl ester ends. The maximum observed deviations are 10° with respect to the angles (C′—O1—C1) and 16° with respect to the torsion angles (N—C*A*—C′—O1). The angles C*B*—C*G*—C*D*1 for the first residues are quite different. They are associated with one of the highest temperature factors in the structure (B_{eq} = 22·8 Å^2) and there is evidence for some disorder of the C*D*1 atom of molecule I. The

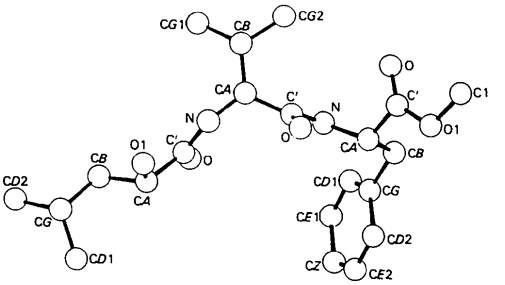

Fig. 1. Perspective view of one of the molecules showing the atom-labelling scheme.

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51109 (20 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

two peptide units of molecule I show significant deviation from planarity ($\chi^1 = 173°$, $\chi^2 = 171°$). Such non-planar conformations have been observed previously (Lalitha, Subramanian & Parthasarathy, 1986).

The conformations of the *O*-leucyl side chains are not far from that occurring most frequently for the natural leucyl residue ($\chi^2 \simeq 180°$ and $-60°$) (Janin, Wodak, Levitt & Maigret, 1978). The conformations of the valyl side chains correspond to the favoured conformations found in small-peptide crystal structures (Benedetti, Morelli, Nemethy & Scheraga, 1983). The phenyl rings are planar, with all C atoms deviating less than 0·01 Å from their mean planes. The conformations of the two aromatic side chains are characterized by dihedral angles χ^2 in the commonly found range near 90°, in agreement with other Phe-containing peptide structures (Cruse, Egert, Viswamitra & Kennard, 1982; Precigoux, Cotrait & Geoffre, 1986), but differ in the values of the χ^1 angles: 172 and $-66°$ for molecules I and II, respectively. The *CG* atom is *trans* with respect to the N atom in molecule I and *gauche* in molecule II.

Table 2. *Bond lengths* (Å), *bond angles* (°) *and main dihedral angles* (°); *estimated standard deviations are* 0·01 *to* 0·03 Å, 1 *to* 1·5° *and* 2 *to* 3°, *respectively*

	Molecule I	Molecule II
O-Leucyl		
O1–C*A*	1·43	1·42
C*A*–C′	1·50	1·55
C*A*–C*B*	1·58	1·53
C′–O	1·25	1·23
C′–N	1·31	1·31
C*B*–C*G*	1·55	1·54
C*G*–C*D*1	1·56	1·52
C*G*–C*D*2	1·54	1·59
Valyl		
N–C*A*	1·48	1·48
C*A*–C′	1·50	1·52
C*A*–C*B*	1·57	1·54
C′–O	1·24	1·23
C′–N	1·31	1·33
C*B*–C*G*1	1·60	1·56
C*B*–C*G*2	1·53	1·49
Phenylalanyl-OMe		
N–C*A*	1·43	1·45
C*A*–C′	1·53	1·56
C*A*–C*B*	1·54	1·55
C′–O	1·16	1·17
C′–O1	1·33	1·30
O1–C1	1·58	1·51
C*B*–C*G*	1·47	1·49
C*G*–C*D*1	1·37	1·40
C*G*–C*D*2	1·37	1·36
C*D*1–C*E*1	1·39	1·37
C*D*2–C*E*2	1·38	1·39
C*E*1–C2	1·37	1·35
C*E*2–C*Z*	1·39	1·37
O-Leucyl		
O1–C*A*–C′	109	108
C′–C*A*–C*B*	109	111
C*B*–C*A*–O1	109	112
C*A*–C′–O	119	119
O–C′–N	124	123
N–C′–C*A*	118	118
C*A*–C*B*–C*G*	113	114
C*B*–C*G*–C*D*1	103	113
C*D*1–C*G*–C*D*2	111	116
C*D*2–C*G*–C*B*	107	105
Valyl		
C′–N–C*A*	125	124
N–C*A*–C′	109	106
C′–C*A*–C*B*	112	114
C*B*–C*A*–N	111	112
C*A*–C′–O	121	122
O–C′–N	122	120
N–C′–C*A*	117	118
C*A*–C*B*–C*G*1	106	109
C*G*1–C*B*–C*G*2	110	112
C*G*2–C*B*–C*A*	110	110

Table 2 (*cont.*)

	Molecule I	Molecule II
Phenylalanyl-OMe		
C′–N–C*A*	123	123
N–C*A*–C′	110	110
C′–C*A*–C*B*	111	110
C*B*–C*A*–N	109	112
C*A*–C′–O	123	123
O–C′–O1	128	125
O1–C′–C*A*	108	111
C′–O1–C1	105	115
C*A*–C*B*–C*G*	117	114
C*B*–C*G*–C*D*1	119	120
C*D*1–C*G*–C*D*2	118	120
C*D*2–C*G*–C*B*	123	119
C*G*–C*D*1–C*E*1	112	118
C*G*–C*D*2–C*E*2	122	120
C*D*1–C*E*1–C*Z*	118	122
C*D*2–C*E*2–C*Z*	118	120
C*E*1–C*Z*–C*E*2	121	119
O-Leucyl		
O1–C*A*–C′–N (ψ)	−11	5
C*A*–C′–N–C*A* (ω)	−173	181
Valyl		
C′–N–C*A*–C′ (φ)	−116	−100
N–C*A*–C′–N (ψ)	129	130
C*A*–C′–N–C*A* (ω)	171	175
Phenylalanyl-OMe		
C′–N–C*A*–C′ (φ)	−65	−68
N–C*A*–C′–O1 (ψ)	140	156

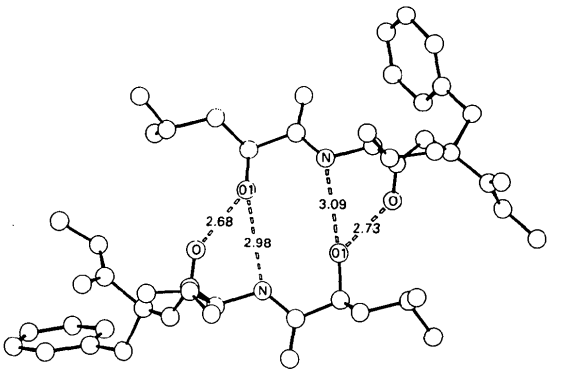

Fig. 2. Perspective view and hydrogen bonds (broken lines) formed by the main chains of molecules I and II.

Table 3. *Hydrogen-bond-like interactions* (Å) *with e.s.d.'s* ≃0·03 Å

O1(*O*-Leu; mol. I)···N(Val; mol. II)(*x,y,z*)	2·98
O1(*O*-Leu; mol. I)···O(Val; mol. II)(*x,y,z*)	2·68
N(Val; mol. I)···O1(*O*-Leu; mol. II)(*x,y,z*)	3·09
O(Val; mol. I)···O1(*O*-Leu; mol. II)(*x,y,z*)	2·73
O(*O*-Leu; mol. II)···N(Phe; mol. I)(1+*x,y,z*)	2·78
N(Phe; mol. II)···O(*O*-Leu; mol. I)(1+*x,y,z*)	2·93

The arrangement of the molecules in the crystal resembles the well known antiparallel β-sheet structure. In the present case, however, the hydrogen-bonding pattern is very different. As seen in Fig. 2, at the level of the *O*-Leu and Val residues, the two classic NH···O hydrogen bonds are replaced by four hydrogen-bond-type interactions. The hydroxyl O1 atoms of both molecules I and II participate in two hydrogen interactions (Table 3). The first is of NH···O1 type (2·98 and 3·09 Å) and the second is of O1H···O type (2·68 and 2·73 Å).

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Structure of 1-Mesitylsulfonyl-4-nitroimidazole

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Abstract. $C_{12}H_{13}N_3O_4S$, $M_r = 295{\cdot}31$, triclinic, $P\bar{1}$, $a = 15{\cdot}841\ (6)$, $b = 10{\cdot}774\ (5)$, $c = 4{\cdot}782\ (1)$ Å, $\alpha = 99{\cdot}26\ (3)$, $\beta = 79{\cdot}43\ (3)$, $\gamma = 59{\cdot}62\ (3)°$, $V = 660{\cdot}4\ (5)$ Å^3, $Z = 2$, $D_x = 1{\cdot}485$ Mg m^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, μ(Mo $K\alpha$) = 0·2634 mm^{-1}, $F(000) = 308$, room temperature, final $R = 0{\cdot}034$ for 2174 unique observed reflections. The molecule, except for the nitro group, has a geometry which is nearly symmetrical with respect to the plane through the atoms C(3)–S(1)–N(13); the dihedral angle between the least-squares planes of the benzene and imidazole rings is 100·8°. The benzene ring and the sulfonyl group are strained as a result of steric hindrance.

Introduction. The present study is part of a series of structural studies on compounds available for the synthesis of oligodeoxyribonucleotides by the phosphotriester approach (Itakura, Katagiri, Bahl, Wightman & Narang, 1973). We report here the structure of the title compound (MSNI) which is a condensing reagent for this approach. Although arylsulfonates of imidazoles, triazoles and tetrazoles are used for such condensing reagents, an X-ray structure analysis has only been reported for 1-(mesitylsulfonyl)-3-nitro-1,2,4-triazole (MSNT) (Kuroda, Sanderson, Neidle & Reese, 1982). We are interested in elucidating the geometry around the sulfonyl group of MSNI.

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