[χ = O(4)–C(13)–C(14)–C(15) = 95·2 (6)°]. Thus, the conformation of the unionized carboxyl of LA2 is different from that usually encountered in α,β-saturated carboxylic acids which prefer a synplanar placement of the 'carbonyl' oxygen ($\chi \simeq 0°$; Leiserowitz, 1976).

Bond lengths and angles within the TMP^+ cation reflect a strain resulting from crowding of the methyl groups on the piperidine ring. Thus, the N(1)–C(25) and N(1)–C(29) bonds are significantly stretched [the respective distances are 1·521 (4) and 1·523 (4) Å] with respect to the normal value of 1·499 Å reported for the N^+–C single bond (Birnbaum, 1967), or to the value of 1·497 Å as observed for the similar bond in the parent, unstrained piperidine hydrochloride (Rérat, 1960). Similarly, the C(25)–N(1)–C(29) bond angle of 120·7 (2)° is considerably wider than the usual value of about 112° and bond angles around C(25) and C(29) show marked deviations from normal tetrahedral angles, varying within 106·4–113·5°; a narrowing of the endocyclic angles at C(25) and C(29) is accompanied by a widening of the angles at C(26) and C(28). Consequently, the chair conformation of the piperidine ring is flattened. The puckering angle on the side of the N is about 48, while that on the side of the C(OH) group is about 60°. The flattening of the ring at N(1) is also illustrated by the asymmetry parameters (Duax & Norton, 1975), ΔC_2[C(25),C(26)] = 12·6 and ΔC_s[N(1)] = 0·4°, indicating loss of rotation symmetry with retention of the orthogonal mirror plane.

The above-mentioned bond-length, valence-angle and ring-torsional distortions have also been observed in the structure of 2,2,6,6-tetramethylpiperidinone hydrochloride (Rees & Weiss, 1971) and result from the need to relieve the very short intramolecular contact H1(C33)···H3(C31) between the axial methyl substituents. In spite of all these adaptions of molecular geometry, this contact of distance 2·07 (4) Å as observed in the structure is still highly repulsive and should actually be even more severe considering that the diffraction experiment gives systematically shortened C–H distances with respect to the internuclear distance of about 1·09 Å. Other unfavourable H···H steric contacts, significantly below the sum of van der Waals radii (2·40 Å) and separated by at least four bonds, are: H2(C32)···H3(C33) 2·15 (5), H1(C33)···H(C27) 2·25 (4) and H3 (C30)···H1 (C26) 2·26 (4) Å.

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Three Conformers in a Crystal of *N*-Ac-L-Leu-L-Tyr-OMe

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Abstract. $C_{18}H_{26}N_2O_5$, three independent molecules with different conformations, $M_r = 350·4$, orthorhombic, $P2_12_12_1$, $a = 16·077$ (10), $b = 28·935$ (18), $c = 12·597$ (6) Å, $V = 5860·0$ Å^3, $Z = 12$, $D_x = 1·191$ g cm^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, $F(000) = 2256$, room temperature, final $R = 4·9\%$ for 4596 data with $|F_o| > 3\sigma$ and 5·4% for all 4977 measured data. The three independent molecules have different conformations for the backbones and the side-chains, although each molecule is relatively flat and has an approximate H shape. The backbone in one of the conformations has φ, ψ angles near those for a β-turn. There is extensive

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intermolecular hydrogen bonding, but there are no intramolecular hydrogen bonds. The 75-atom structure was solved with the aid of the Connection Machine computer, a parallel processor for which the symbolic addition procedure was programmed.

Introduction. Effective inhibitors of chymotrypsin include the synthetic *cyclo*(-L-Leu-L-Tyr-δ-Ava-δ-Ava-), where δ-Ava is δ-aminovaleryl, and the linear Ac-L-Leu-L-Tyr-OMe (Tsetlin, Portnova, Balashova, Ivanov & Ovchinnikov, 1973; Tsetlin, Shepel, Ivanov & Ovchinnikov, 1975). The conformation of *cyclo*-(-L-Leu-L-Tyr-δ-Ava-δ-Ava-) has been reported in two different crystalline polymorphs, one obtained from Me_2SO (Karle, 1976) and the other from acetone (Karle & Flippen-Anderson, 1978). Although the cocrystallized solvent molecules are different in each, and the space groups are different, the conformation of the peptide molecule is nearly identical in both crystals.

The crystal structure of the linear *N*-Ac-L-Leu-L-Tyr-OMe is reported here. Three peptide molecules have cocrystallized side-by-side in the asymmetric unit of the cell and each molecule has assumed a different conformation. The conformation of the backbone and side-chains of one of the three cocrystallized conformers is quite similar to that found in *cyclo*-(-L-Leu-L-Tyr-δ-Ava-δ-Ava-) (Karle, 1976; Karle & Flippen-Anderson, 1978).

Experimental. The peptide was synthesized according to the procedure outlined by Tsetlin *et al.* (1975). Colorless, well formed needles were grown from isopropyl ether/ethyl acetate solution. Intensity data were measured on a Picker four-circle automated diffractometer 13 years ago with Cu radiation, Ni filter, θ–2θ scan technique, $2\theta_{max} = 126°$, scan of $2{\cdot}0° + 2\theta(\alpha_1) - 2\theta(\alpha_2)$, and a scan speed of $2°\ min^{-1}$. The intensities of three reflections, monitored every hour, remained essentially constant during the experiment. The crystal size was $0{\cdot}15 \times 0{\cdot}15$ mm in cross section and 1·2 mm long. The data were corrected for Lorentz and polarization factors.

Initial attempts at determining the structure by various direct phase determination procedures were not successful. With the advent of the Connection Machine, made by the Thinking Machines Company, the symbolic addition procedure (Karle & Karle, 1966) was programmed in the Lisp language for the model with 16000 parallel processors (Anderson & Flippen-Anderson, 1988). With the assignment of symbolic phases for seven reflections, in addition to origin assignment, the structure was derived quite directly. Coordinates for 84 atoms were refined (on *F*) by a full-matrix least-squares program in the *SHELXTL* system (Sheldrick, 1980). The refinement of anisotropic thermal factors for 75 non-hydrogen atoms and isotropic thermal factors for nine H atoms bonded to N

Table 1. *Atomic coordinates* ($\times 10^4$) *and equivalent isotropic displacement parameters* ($Å^2 \times 10^3$)

	x	*y*	*z*	U_{eq}
Molecule *A*				
C(0)	4370 (3)	11061 (2)	11000 (5)	80 (2)
C′(0)	4403 (3)	10649 (2)	10285 (3)	52 (1)
O(0)	4793 (2)	10294 (1)	10508 (3)	68 (1)
N(1)	3982 (2)	10678 (1)	9373 (3)	49 (1)
Cᵅ(1)	3911 (3)	10283 (1)	8671 (3)	44 (1)
C′(1)	4729 (3)	10160 (1)	8127 (3)	41 (1)
O(1)	4973 (2)	9754 (1)	8080 (2)	51 (1)
N(2)	5144 (2)	10507 (1)	7673 (3)	47 (1)
Cᵅ(2)	5954 (3)	10459 (1)	7176 (3)	44 (1)
C′(2)	6621 (3)	10623 (2)	7936 (4)	51 (2)
O′(2)	6509 (3)	10840 (1)	8731 (3)	80 (1)
O″(3)	7370 (2)	10495 (1)	7604 (3)	77 (1)
C(3)	8072 (4)	10653 (2)	8232 (6)	100 (3)
Cᵝ(1)	3221 (3)	10363 (2)	7853 (4)	55 (2)
Cᵞ(1)	2957 (3)	9930 (2)	7264 (4)	58 (2)
Cᵟ1(1)	2465 (4)	9605 (2)	7977 (5)	88 (2)
Cᵟ2(1)	2462 (4)	10044 (2)	6274 (5)	96 (2)
Cᵝ(2)	6012 (3)	10733 (1)	6131 (3)	48 (1)
Cᵞ(2)	5645 (3)	10500 (1)	5161 (3)	46 (1)
Cᵟ2(2)	5960 (3)	10608 (2)	4161 (3)	58 (2)
Cᵋ2(2)	5656 (3)	10411 (2)	3251 (4)	63 (2)
Cᶻ(2)	5024 (3)	10090 (2)	3311 (4)	60 (2)
Cᵋ1(2)	4706 (3)	9974 (2)	4279 (4)	62 (2)
Cᵟ1(2)	5012 (3)	10173 (2)	5198 (4)	59 (2)
Oᵑ(2)	4706 (3)	9867 (1)	2435 (3)	82 (2)
Molecule *B*				
C(0)	6740 (3)	9753 (2)	10115 (5)	75 (2)
C′(0)	6494 (3)	9253 (1)	10004 (4)	53 (2)
O(0)	6984 (2)	8938 (1)	10195 (4)	82 (1)
N(1)	5726 (2)	9173 (1)	9679 (3)	43 (1)
Cᵅ(1)	5415 (3)	8707 (1)	9475 (3)	43 (1)
C′(1)	5663 (3)	8524 (1)	8390 (3)	43 (1)
O(1)	5672 (2)	8105 (1)	8233 (3)	67 (1)
N(2)	5830 (3)	8828 (1)	7643 (3)	52 (1)
Cᵅ(2)	6187 (3)	8716 (2)	6623 (3)	52 (1)
C′(2)	7099 (3)	8845 (2)	6625 (4)	68 (2)
O′(2)	7383 (3)	9158 (2)	7116 (5)	138 (3)
O″(3)	7542 (2)	8574 (1)	6026 (3)	75 (1)
C(3)	8428 (3)	8660 (2)	5996 (5)	92 (3)
Cᵝ(1)	4471 (3)	8686 (2)	9617 (4)	55 (2)
Cᵞ(1)	4158 (4)	8844 (2)	10688 (4)	79 (2)
Cᵟ2(1)	4604 (6)	8629 (3)	11597 (5)	147 (5)
Cᵟ1(1)	3235 (4)	8753 (2)	10758 (7)	116 (3)
Cᵝ(2)	5748 (3)	8977 (2)	5725 (4)	63 (2)
Cᵞ(2)	4866 (3)	8826 (2)	5486 (3)	52 (1)
Cᵟ2(2)	4680 (3)	8587 (2)	4572 (4)	63 (2)
Cᵋ2(2)	3876 (3)	8458 (2)	4312 (4)	64 (2)
Cᶻ(2)	3231 (3)	8574 (2)	4983 (4)	61 (2)
Cᵋ1(2)	3411 (3)	8796 (2)	5920 (5)	73 (2)
Cᵟ1(2)	4212 (3)	8921 (2)	6160 (4)	67 (2)
Oᵑ(2)	2421 (3)	8464 (2)	4756 (4)	89 (2)
Molecule *C*				
C(0)	2866 (4)	7386 (2)	2295 (6)	104 (3)
C′(0)	2271 (3)	7783 (2)	2225 (4)	60 (2)
O(0)	2300 (2)	8119 (1)	2816 (3)	79 (1)
N(1)	1688 (3)	7762 (1)	1461 (3)	52 (1)
Cᵅ(1)	1050 (3)	8116 (1)	1392 (3)	49 (1)
C′(1)	583 (3)	8169 (1)	2429 (3)	45 (1)
O(1)	382 (2)	8555 (1)	2762 (3)	75 (1)
N(2)	362 (2)	7783 (1)	2933 (3)	43 (1)
Cᵅ(2)	−138 (3)	7788 (1)	3881 (3)	46 (1)
C′(2)	337 (3)	7658 (2)	4884 (4)	59 (2)
O′(2)	72 (3)	7736 (2)	5749 (3)	99 (2)
O″(3)	1046 (2)	7449 (1)	4693 (3)	76 (1)
C(3)	1552 (4)	7345 (3)	5619 (5)	108 (3)
Cᵝ(1)	437 (3)	8023 (2)	496 (4)	69 (2)
Cᵞ(1)	760 (5)	8053 (3)	−613 (4)	94 (3)
Cᵟ1(1)	56 (7)	7931 (4)	−1387 (6)	190 (6)
Cᵟ2(1)	1071 (5)	8530 (3)	−887 (6)	129 (4)
Cᵝ(2)	−910 (3)	7477 (2)	3761 (4)	52 (1)
Cᵞ(2)	−1438 (3)	7616 (1)	2835 (3)	44 (1)
Cᵟ2(2)	−1575 (3)	7320 (2)	1998 (4)	69 (2)
Cᵋ2(2)	−2029 (4)	7452 (2)	1120 (5)	82 (2)
Cᶻ(2)	−2363 (3)	7891 (2)	1064 (4)	60 (2)
Cᵋ1(2)	−2249 (3)	8190 (1)	1885 (4)	54 (1)
Cᵟ1(2)	−1790 (3)	8056 (1)	2764 (4)	53 (1)
Oᵑ(2)	−2809 (3)	8009 (1)	176 (3)	87 (2)

Equivalent isotropic *U* defined as one third of the trace of the orthogonalized U_{ij} tensor.

or O atoms (713 parameters), and the inclusion of 69 H atoms bonded to C atoms riding in idealized positions yielded $R = 0.049$ and $wR = 0.053$ for 4596 data measured $> 3\sigma(F)$ and $R = 0.054$ and $wR = 0.058$ for all 4977 independent reflections within the $2\theta = 126°$ sphere. The weighting function used is $w = 1/[\sigma^2(|F_o|) + g(|F_o|)^2]$ where $g = 0.00025$. The isotropic extinction factor was 0.00134, $S = 1.0$, and the maximum excursions in the final difference map were 0.237 and -0.171 e Å^{-3}.

Coordinates for the non-hydrogen atoms in the molecules are listed in Table 1.* Bond lengths, bond angles and torsion angles are listed in Tables 2, 3 and 4. The labeling for the atoms is shown in Fig. 1 and the

*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 51641 (25 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Bond lengths* (Å) *in the three conformers*

E.s.d.'s for backbone bonds ~0.006 Å; for side-chains ~0.010 Å.

	A	B	C
C(0)–C′(0)	1.496	1.509	1.497
C′(0)–O(0)	1.236	1.228	1.225
C′(0)–N(1)	1.337	1.321	1.345
N(1)–Cᵅ(1)	1.450	1.461	1.452
Cᵅ(1)–C′(1)	1.526	1.521	1.515
C′(1)–O(1)	1.241	1.228	1.234
Cᵅ(1)–Cᵝ(1)	1.532	1.529	1.523
Cᵝ(1)–Cᵞ(1)	1.517	1.509	1.493
Cᵞ(1)–Cᵟ1(1)	1.522	1.510	1.534
Cᵞ(1)–Cᵟ2(1)	1.515	1.488	1.508
C′(1)–N(2)	1.333	1.316	1.335
N(2)–Cᵅ(2)	1.451	1.444	1.439
Cᵅ(2)–C′(2)	1.513	1.514	1.523
C′(2)–O′(2)	1.196	1.190	1.191
Cᵅ(2)–Cᵝ(2)	1.540	1.532	1.540
Cᵝ(2)–Cᵞ(2)	1.516	1.514	1.498
Cᵞ(2)–Cᵟ1(2)	1.388	1.379	1.394
Cᵞ(2)–Cᵟ2(2)	1.394	1.376	1.376
Cᵟ1(2)–Cᵋ1(2)	1.384	1.372	1.387
Cᵟ2(2)–Cᵋ2(2)	1.371	1.384	1.379
Cᵋ1(2)–Cᶻ(2)	1.364	1.376	1.360
Cᵋ2(2)–Cᶻ(2)	1.378	1.379	1.379
Cᶻ(2)–Oᵑ(2)	1.376	1.370	1.372
C′(2)–O″(3)	1.327	1.300	1.312
O″(3)–C(3)	1.452	1.447	1.454

Table 3. *Bond angles* (°) *in the three conformers*

E.s.d.'s ~0.5°.

	A	B	C
C(0)C′(0)O(0)	122.9	121.7	123.2
C(0)C′(0)N(1)	116.7	116.2	116.9
N(1)C′(0)O(0)	120.4	122.1	119.9
C′(0)N(1)Cᵅ(1)	120.9	122.4	120.2
N(1)Cᵅ(1)C′(1)	112.9	113.0	111.8
N(1)Cᵅ(1)Cᵝ(1)	110.3	110.8	112.2
C′(1)Cᵅ(1)Cᵝ(1)	110.9	110.6	109.6
Cᵅ(1)C′(1)O(1)	120.9	119.5	121.0
Cᵅ(1)C′(1)N(2)	116.7	117.6	117.1
N(2)C′(1)O(1)	122.3	122.9	121.8
C′(1)N(2)Cᵅ(2)	124.2	124.6	122.3
N(2)Cᵅ(2)C′(2)	109.5	109.2	114.0
N(2)Cᵅ(2)Cᵝ(2)	112.0	111.4	111.2
C′(2)Cᵅ(2)Cᵝ(2)	109.7	109.1	110.0
Cᵅ(2)C′(2)O′(2)	125.9	124.0	122.2
Cᵅ(2)C′(2)O″(3)	110.9	112.4	113.3
O′(2)C′(2)O″(3)	123.1	123.6	124.5
C′(2)O″(3)C(3)	116.5	116.7	115.7
Cᵅ(1)Cᵝ(1)Cᵞ(1)	114.0	115.0	117.3
Cᵝ(1)Cᵞ(1)Cᵟ1(1)	111.5	109.0	108.9
Cᵝ(1)Cᵞ(1)Cᵟ2(1)	111.7	113.6	112.4
Cᵟ1(1)Cᵞ(1)Cᵟ2(1)	110.3	110.8	108.0
Cᵅ(2)Cᵝ(2)Cᵞ(2)	115.8	115.8	112.1
Cᵝ(2)Cᵞ(2)Cᵟ1(2)	124.1	122.2	121.7
Cᵝ(2)Cᵞ(2)Cᵟ2(2)	119.1	121.0	121.3
Cᵞ(2)Cᵟ1(2)Cᵋ1(2)	121.0	121.8	121.5
Cᵞ(2)Cᵟ2(2)Cᵋ2(2)	122.1	122.4	121.8
Cᵟ1(2)Cᵋ1(2)Cᶻ(2)	120.9	120.7	120.0
Cᵟ2(2)Cᵋ2(2)Cᶻ(2)	119.9	119.5	120.1
Cᵋ1(2)Cᶻ(2)Cᵋ2(2)	119.3	118.8	119.6
Cᵋ1(2)Cᶻ(2)Oᵑ(2)	117.6	119.2	122.0
Cᵋ2(2)Cᶻ(2)Oᵑ(2)	123.1	122.0	118.3
Cᵟ1(2)Cᵞ(2)Cᵟ2(2)	116.8	116.8	116.9

Table 4. *Torsional angles in N-Ac-Leu-Tyr-OMe*

E.s.d.'s ~0.4°.

		A	B	C	*c*-(Leu-Tyr-δ-Ava-δ-Ava-)*
C′(0)–N(1)	ω'_0	−174	176	175	−174
N(1)–Cᵅ(1)	φ_1	−70	−81	−55	−96
Cᵅ(1)–C′(1)	ψ_1	−48	−25	−44	−5
C′(1)–N(2)	ω_1	176	171	−175	−171
N(2)–Cᵅ(2)	φ_2	−100	−103	−109	−132
Cᵅ(2)–C′(2)	ψ_2	167	148	−17	35
C′(2)–O″(3)	ω'_2	177	−178	176	−171
Cᵅ(1)–Cᵝ(1)	χ^1_1	−166	−56	−66	−74
Cᵝ(1)–Cᵞ(1)	$\chi^2_{1(1)}$	72	173	178	175
	$\chi^2_{2(1)}$	−164	−49	−62	−64
Cᵅ(2)–Cᵝ(2)	χ^1_2	−81	−70	−58	−48
Cᵝ(2)–Cᵞ(2)	$\chi^2_{1(2)}$	26	72	−60	92
	$\chi^2_{2(2)}$	−153	−109	118	−88

*Comparison with *cyclo*(Leu-Tyr-δ-Ava-δ-Ava). The cyclic molecule has a β-turn without a hydrogen bond (Karle, 1976; Karle & Flippen-Anderson, 1978).

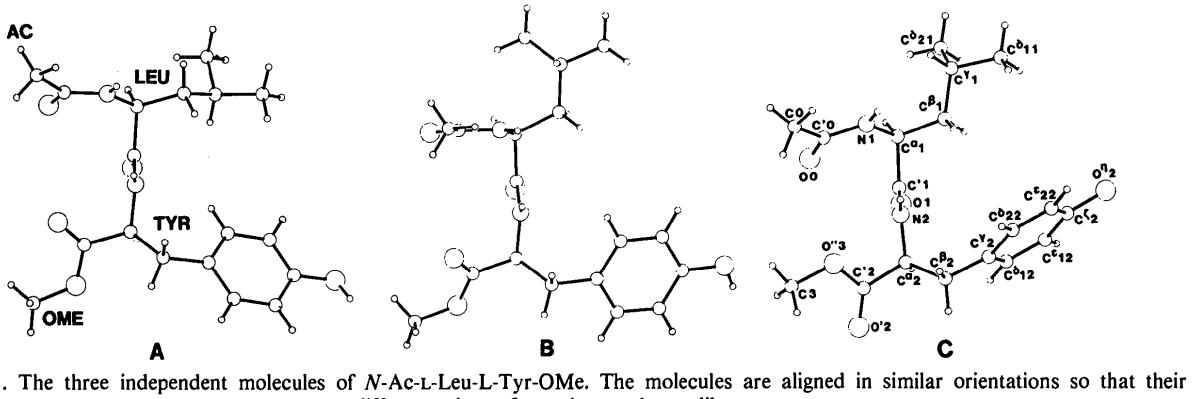

Fig. 1. The three independent molecules of *N*-Ac-L-Leu-L-Tyr-OMe. The molecules are aligned in similar orientations so that their differences in conformation can be readily seen.

three independent molecules are designated as *A*, *B*, and *C*. There were no solvent molecules cocrystallized with the peptide.

Discussion. The three conformers are relatively flat and each has an approximate H shape (Fig. 1). The backbone in each makes a reverse turn; however, only conformer *C* has appropriate φ, ψ angles for both $C^{\alpha}(1)$ and $C^{\alpha}(2)$ that correspond to a β-turn (type I) where values typically observed for φ_1, ψ_1 and φ_2, ψ_2 are near -65, -20 and -95, $+10°$, respectively. Torsional angles φ_2, ψ_2 for conformers *A* and *B* fall far away from the β-turn region of a φ, ψ map (Fig. 2).

The side-chains in the Leu and Tyr residues are extended from the backbone and are very approximately parallel to each other. A similar parallel arrangement for the side-chains has been found in the dipeptide *cyclo*(-L-Leu-L-Tyr-) (Suguna, Ramakumar & Kopple, 1984). However, there are significant differences in the χ^1 and χ^2 torsional angles in the three conformers. For example, Leu in conformer *A* has the $t(tg^-)$ conformation, whereas in conformers *B* and *C*, the Leu side-chain has the $g(tg)$ conformation. Of the three conformers, only conformer *C* is similar in backbone as well as side-chain conformation to *cyclo*(-Leu-Tyr-δ-Ava-δ-Ava-). A comparison of their torsional angles in Table 4 shows a close resemblance. Neither the linear peptide nor the cyclic analog has any intramolecular hydrogen bonds.

Bond lengths and bond angles are very similar in the three conformers (Tables 2 and 3). The C′(2)—O(2) bonds, 1·192 Å average value, are 0·04 Å shorter than the C′(0)—O(0) and C′(1)—O(1) bonds, 1·230 and 1·234 Å average values. The O(2) atoms do not participate in any hydrogen bond, whereas the O(0) atoms are acceptors for one hydrogen bond each, and the O(1) atoms are acceptors for more than one each.

In the crystal, the conformers are arranged in infinite rods in the sequence *ABCA′B′C′ABC*..., Fig. 3. The primed molecules are related to the unprimed by the symmetry operation $-x$, $\frac{1}{2}+y$, $\frac{1}{2}-z$. In Fig. 3, each C′(1)—O(1) bond extends to the right and is the acceptor for two hydrogen bonds from atoms N(1)H and N(2)H of the molecule to the right. Each of the conformers is rotated roughly 60° with respect to the conformer at the left, so that the six peptide molecules along the *b* axis make a complete revolution in one cell length, 28·93 Å. The peptide molecules projected down the *b* axis look like a pin-wheel.

Additional hydrogen bonds are made between adjacent rods of peptide molecules. Every rod is surrounded by six others. The six peptides in a rod in one cell length participate in 12 hydrogen bonds of the type $O^{\eta}(2)H\cdots O(0)$, two hydrogen bonds to each of the six surrounding rods. These hydrogen bonds are between the OH of the Tyr side-chain and the C=O of the acetyl end group. The three-dimensional network of hydrogen bonds contributes to a rigid structure.

The hydrogen-bond lengths are shown in Table 5. The three $O^{\eta}(2)\cdots O(0)$ hydrogen bonds are the shortest with O···O bond lengths of 2·65–2·73 Å. The pairs of N(1)H and N(2)H bonds to the O(1) carbonyl atoms are considerably longer, 2·85–3·06 Å for the N···O distances, and even 3·18 Å for $N(1)A\cdots O(1)C$, if the pairing motif is accepted for all three conformers. There is no other possibility for hydrogen bonding for N(1)*A*.

The existence of three distinct conformers in the crystal cell of *N*-Ac-Leu-Tyr-OMe illustrates the ease with which the conformation of a small peptide can vary. The lack of intramolecular hydrogen bonds

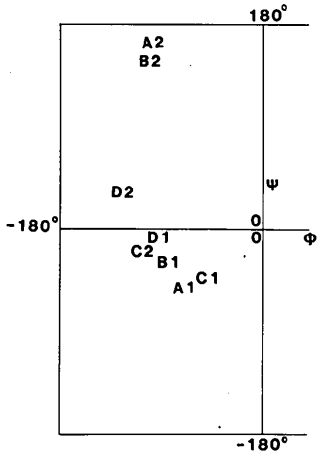

Fig. 2. The backbone conformations are compared for the Leu[1] and Tyr[2] residues on a φ, ψ map for conformers *A*, *B* and *C*. The points denoted by *D*1 and *D*2 represent the φ, ψ values for the Leu-Tyr fragment of *cyclo*(-Leu-Tyr-δ-Ava-δ-Ava-) (Karle, 1976; Karle & Flippen-Anderson, 1978). Only conformer *C* is similar to the same fragment in the cyclic peptide *D*.

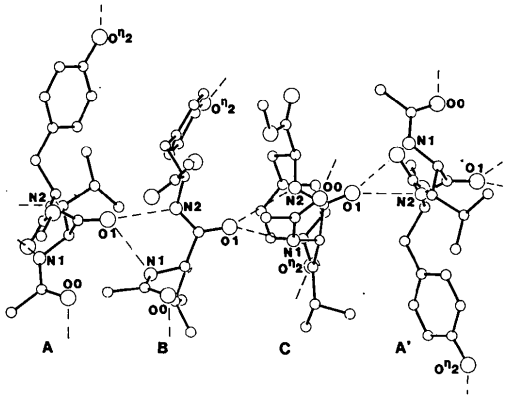

Fig. 3. The stacking of conformers *A*, *B* and *C* along the *b* axis (←**b**, ↓**c**) into continuous rods. Molecules *A′* (and *B′* and *C′*, not shown) are related to *A*, *B* and *C* by a twofold screw operation. Each conformer is rotated by ~60° with respect to the adjacent one, so that the $O^{\eta}(2)$ atoms of the Tyr residues form one helical turn in one length of the *b* axis. Dashed lines indicate hydrogen bonds.

Table 5. *Hydrogen bonds in cell of N-Ac-Leu-Tyr-OMe*

No H bonds for O(2)*A*, O(2)*B* or O(2)*C*.

Donor	Acceptor	Length	H···O*	Symm. equiv. of acceptor
N(1)*A*	O(1)*C*	3·176†	2·79†	$\frac{1}{2}-x, 2-y, \frac{1}{2}+z$
N(1)*B*	O(1)*A*	2·888	2·22	x, y, z
N(1)*C*	O(1)*B*	3·017	2·63†	$-\frac{1}{2}+x, \frac{3}{2}-y, 1-z$
	O″(2)*C*	3·143	2·47	$\frac{1}{2}+x, \frac{3}{2}-y, -z$
N(2)*A*	O(1)*C*	2·847	2·19	$\frac{1}{2}-x, 2-y, \frac{1}{2}+z$
N(2)*B*	O(1)*A*	3·062	2·41	x, y, z
N(2)*C*	O(1)*B*	2·999	2·17	$-\frac{1}{2}+x, \frac{3}{2}-y, 1-z$
O″(2)*A*	O(0)*A*	2·728	1·83	$x, y, -1+z$
O″(2)*B*	O(0)*C*	2·647	1·85	x, y, z
O″(2)*C*	O(0)*B*	2·709	1·95	$-1+x, y, -1+z$

* The amide and hydroxyl hydrogen atom positions were refined by least squares; H···O e.s.d.'s ~0·05 Å.

† Long values for hydrogen bonds; angles N(1)*A*–H···O(1)*C* and N(1)C–H···O(1)*B* are 113 and 114°, respectively.

provides the peptide with flexibility to adjust to its environment in order to make a maximum number of intermolecular hydrogen bonds for efficient packing. Larger peptides, stabilized by intramolecular attractions, are rarely observed to have more than one conformation in a crystal, except for small changes.

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Structures of Colchicine Analogues. I. Allocolchicine

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Abstract. Methyl 5-acetylamino-6,7-dihydro-9,10,11-trimethoxy-5*H*-dibenzo[*a*,*c*]cycloheptene-3-carboxylate, $C_{22}H_{25}NO_6$, $M_r = 399{\cdot}4$, monoclinic, $P2_1$, $a = 7{\cdot}968\ (1)$, $b = 9{\cdot}482\ (1)$, $c = 15{\cdot}063\ (2)$ Å, $\beta = 112{\cdot}95\ (1)°$, $V = 1047{\cdot}9\ (2)$ Å^3, $Z = 2$, D_m(flotation) $= 1{\cdot}27\ (1)$, $D_x = 1{\cdot}266$ Mg m^{-3}, λ(Cu $K\alpha$) $= 1{\cdot}5418$ Å, $\mu = 0{\cdot}68$ mm^{-1}, $F(000) = 424$, $T = 288\ (1)$ K. Final $R = 0{\cdot}050$ for 1765 observed data. The seven-membered ring has the expected boat conformation, and the angle between the normals to the phenyl rings is 48·7 (4)°. The relative orientations of the three adjacent methoxy groups and the acetamido substituent are similar to those observed in crystals of colchicine. Intermolecular hydrogen bonds between the N and O atoms of the acetamido groups link the molecules into infinite spirals along the *b* axis.

Introduction. The tricyclic alkaloid colchicine, (I), exerts a potent antimitotic activity in eukaryotic cells by inhibition of the cytoskeletal tubulin–microtubule equilibrium (Dustin, 1984). The pivotal nature of this equilibrium is a major target for drug design in anticancer agents. While too toxic for clinical use, colchicine (I) plays an essential role in defining the structure–activity relationships of drug action at the 'colchicine binding site' on tubulin. This site is occupied not only by colchicinoids but by a structurally diverse range of compounds such as podophyllotoxin (Kelleher, 1977) and benzimidazole derivatives (Lacey & Watson, 1985).

The complexity of such diverse structural compatibility at the 'colchicine binding site' has led to extensive studies of the solid-state conformations of

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