The Crystal and Molecular Structures of Two Isostructural N-(Haloacetyl)-L-phenylalanyl-L-phenylalanine Ethyl Esters, C₂₂H₂₅XN₂O₄*

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The crystal and molecular structures of *N*-(bromoacetyl)-L-phenylalanyl-L-phenylalanine ethyl ester and the isostructural chloroacetyl derivative have been determined from three-dimensional X-ray diffractometer data. The bromo derivative crystallizes with two molecules in a monoclinic unit cell of symmetry *P*₂₁ and parameters a=12.951 (9), b=17.617 (26), c=4.951 (3) Å, and $\beta=103.23$ (7)°. The chloro derivative has a unit cell with parameters a=12.844 (3), b=17.677 (4), c=4.931 (1) Å, and $\beta=$ 103.30 (2)°. The structure of the bromo derivative was first solved by the heavy-atom technique and refined by the full-matrix least-squares method to R(F)=0.090 based on 522 observed intensity data. The refinement of the chloro derivative, carried out with starting parameters obtained from the bromo derivative, gave a value of R(F)=0.105 based on 487 data. Because of a disorder problem, the ethoxy terminus was treated as a rigid group in the refinements for both derivatives. The molecular configuration is of the parallel-chain pleated-sheet type. In the chloro derivative, the lengths of the peptide units are 3.79 and 3.81 Å; the end-to-end length of the two units is 6.09 Å; the interchain hydrogen bond lengths are 2.78 and 2.90 Å; the backbone conformation angles are $\varphi_1 = -102^\circ$, $\varphi_2 = -122^\circ$, $\psi_1 = 106^\circ$, $\psi_T^T = -133^\circ$, $\psi_T^2 = 53^\circ$; and the principal side-chain conformation angles are $\chi_1^1 = -175^\circ$ (γ -carbon position II) and $\chi_2^1 = -71^\circ$ (γ -carbon position III).

Introduction

Relatively few three-dimensional structure determinations have been accomplished for peptides, and very few for peptides containing more than one large side chain (Kennard & Watson, 1970). We report here the crystal and molecular structure of *N*-(haloacetyl)-Lphenylalanyl-L-phenylalanine ethyl ester, a substrate of pepsin and a molecule containing two aromatic groups. Although crystalline disorder prevented a very precise determination of individual interatomic distances and bond angles, the molecular conformation has been clearly established and may be of use in comparative and theoretical studies of peptide conformation.

Experimental

Crystal specimens

The chloroacetyl and bromoacetyl dipeptide esters were each prepared in good yield and purity by coupling the haloacetyl halide to L-phenylalanyl-L-phenylalanine ethyl ester hydrobromide and by coupling the haloacetyl-L-phenylalanine to L-phenylalanine ethyl ester hydrochloride. Full details of the syntheses will be given elsewhere (Doherty, 1971). The crystalline products, obtained by evaporation from ethyl acetate– ligroin mixtures, were quite pure, as shown by the following analyses. Calculated for $C_{22}H_{25}ClN_2O_4$ (416·89): C, 63·38; H, 6·04; N, 6·72. Found: C, 63·21; H, 6·22; N, 6·74. Calculated for $C_{22}H_{25}BrN_2O_4$ (461·35): C, 57·27; H, 5·46; N, 6·07. Found: C, 57·40; H, 5·56; N, 6·04. The melting points were 155–157° for the chloro derivative, 168–170° for the bromo derivative. The dipeptide esters synthesized by either method were 95% hydrolyzed in four hours by pepsin, indicating that little if any racemization had occurred in the preparations.

Samples of both derivatives were recrystallized by slow evaporation from ethanol solutions in an attempt to obtain single crystals large enough for X-ray work. Since the needle-shaped crystals were very fragile and difficult to handle, specimens were mounted in thinwalled glass capillaries. The crystal dimensions were $0.39 \times 0.05 \times 0.03$ mm for the chloro derivative and $0.26 \times 0.07 \times 0.05$ mm for the bromo derivative, with the longest dimension (corresponding to the *c* axis) in each case nearly parallel to the capillary axis.

Unit cells and space groups

From the preliminary Weissenberg and precession X-ray photographs with nickel-filtered Cu $K\alpha$ radiation $(\lambda = 1.5418 \text{ Å})$, approximate cell parameters for both compounds were obtained; and space groups for both crystals were found from systematic absences to be $P2_1$ (C_2^2 , No. 4) (see International Tables for X-ray Crystallography, 1965). In each case, the crystal was transferred from the camera to an Oak Ridge automatic computer-controlled diffractometer (Busing, Ellison, Levy, King & Roseberry, 1968). The cell parameters, together with the orientational parameters of the crystal, were refined by the method of least

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squares from angle data of six reflections for the chloro derivative and nine reflections for the bromo derivative. The cell parameters thus determined, together with other crystal data, are tabulated in Table 1.

Table 1. Unit-cell parameters of $C_{22}H_{25}XN_2O_4$, with estimated standard errors

	Chloro derivative	Bromo derivative
а	12·844 (3) Å	12·951 (9) Å
b	17.677 (4)	17.617 (26)
с	4.931 (1)	4.951 (3)
β	103·30 (2)°	103·23 (7)°
Z	2	2
V	1089·5 ų	1099∙6 ų
D_o^*	1·27 (1) g.cm ⁻³	1.39 (1) g.cm ⁻³
Dc	1.27 g.cm ⁻³	1.39 g.cm ⁻³
F(000)	440	476
Space group	P21	P21

* The observed densities of the compounds were obtained by the flotation method.

X-ray intensity data

(a) Chloro derivative. The three-dimensional data were measured with the automatic diffractometer using Cu K α radiation. Reflections with $2\theta \le 60^{\circ}$ were measured by an ω step-scan technique (Levy, 1966; Brown, 1969) in which three scans were run for each reflection: a main scan with the detector set at the computed 2θ , and two background scans with the detector offset lower and higher in 2θ . The detector-slit width and the 2θ offset were adjusted for different ranges of 2θ in a manner similar to that described by Brown (1969).

Reflections in the range 60–90° 2θ , selected by rapid screening, were measured by θ –2 θ step scans. Because the reflections were in general very weak, no filter was used, and two reflections (900 and 10,00) significantly affected by $K\beta$ overlap were removed from the data set. The intensity of a reference reflection, measured periodically throughout the data collection (overall decrease 8%), was used to normalize the data for the effects of radiation damage. Lorentz-polarization corrections, and an empirical absorption correction depending only on φ and based on azimuthal scans of three reflections, were applied.

Variances $\sigma^2(F_o^2)$ for use in least-squares weighting were estimated according to the expression:

$\sigma^2(F_o^2) = K^2[G + (t_G/t_B)^2 B]/(Lp)^2,$

in which G is the gross intensity count, B is the background count, t_G/t_B is the ratio of the counting times of gross intensity and background, K is the appropriate scaling constant, and Lp is the Lorentz-polarization factor. Where several measurements were made, the average F_o^2 value and its variance were computed, using as weights the reciprocals of the variances for the individual observations. Finally, the quantity (0.03 F_o^2)² was added to the variance of the average F_o^2 , in order to make allowance for possible instability in the instrument, errors in absorption corrections, deficiencies of the structure model, *etc.* (Peterson & Levy, 1957). After the preliminary processing of the intensity data, 566 independent reflections with intensities greater than zero were obtained, of which 487 had $F_a^2 \ge 3\sigma(F_a^2)$.

(b) Bromo derivative Measurement and initial processing of the data paralleled that for the chloro derivative, except that θ -2 θ step scans with no filter were used for the entire 2 θ range of 0-90°, and that no absorption corrections were applied. Of the 864 independent reflections having intensities greater than zero, 522 had $F_o^2 \ge 3\sigma(F_o^2)$.

Solution and refinement of the structures

The structure of the bromo derivative was solved by conventional heavy-atom methods, with the use of a three-dimensional Patterson function computed with the Blount (1965) program, full-matrix least-squares refinements (Busing, Martin & Levy, 1962), and successive Fourier syntheses. After 29 independent nonhydrogen atoms had been located, the R(F) value, defined as $\sum ||F_o| - |F_c|| / \sum |F_o|$, was 0.12, with the thermal motion of the bromine atom treated anisotropically, and the thermal motion of the other atoms treated isotropically. Refinement of the chloro derivative data, with starting parameters obtained from the bromo derivative, yielded an R(F) value of 0.10 in a similar refinement. Although the structure appeared to be essentially correct, the bond lengths and bond angles involving the ethoxy group [in the bromo derivative, O(26)-C(27) = 1.80 Å; C(27)-C(28) = 1.23 Å; O(26)-C(28) = 1. $C(27)-C(28)=74^{\circ}$ did not conform to a physically meaningful arrangement. For both derivatives, difference Fourier syntheses phased on all atoms except the ethyl carbons revealed two very broad peaks of electron density in the region of the ethyl group. Since refinements with both derivatives yielded essentially the same abnormal arrangement of the ethyl group, we have concluded that these results were not due to error, but that the ethyl group was disordered in a similar



Fig. 1. Two configurations for the ethyl group found by a model-building computer program to be consistent with packing requirements. The atoms in bold outline lie close to the positions obtained by refinement with a single ethoxy group.

manner in both crystals, and that the refined position of each ethyl carbon atom represented the average of two or more sites.

With the aid of a model-building computer program (assuming standard bond distances and angles and varying torsion angles) it was determined that two general configurations for the ethoxy group were consistent with packing restrictions, *i.e.*, implied no interatomic distances 0.2 Å less than the normal van der

Waals distances. The pairs of positions, roughly related by mirror symmetry across the plane of the carboxyl group, are illustrated in Fig. 1.

A number of attempts were made to refine, by the method of least-squares, a randomly disordered model with two alternative configurations for the ethoxy group. With the use of a rigid-group refinement program, kindly supplied by Dr L. F. Dahl of the University of Wisconsin, constraints were applied in several

	Atom		x	У	Z	В	
	Х	Cl	0.4666 (8)	1	0.4949 (25)	 .†	
		Br	0.4655 (4)	$\frac{1}{4}$	0·5062 (10)	†	
	C(1)	Cl	0.374 (3)	0.284 (2)	0·678 (7) ́	6.1 (9)	
		Br	0.371 (3)	0.302(2)	0.676 (7)	6.3 (10)	
	C(2)	Cl	0.273 (2)	0.307 (2)	0.463 (7)	4.8 (7)	
	. ,	Br	0.268 (2)	0.323(2)	0.479 (7)	3.9 (7)	
	O(3)	Cl	0.259(2)	0.308(2)	0.202(5)	5.6 (5)	
		Br	0.256 (2)	0·326 (1)	0·222 (5)	5.1 (5)	
	N(4)	Cl	0.197 (2)	0.323(2)	0.601 (5)	4.5 (6)	
		Br	0.192 (2)	0·339 (1)	0·610 (́5)́	3.7 (6)	
	C(5)	C1	0.086 (2)	0·349 (2)	0.452 (5)	3.6 (6)	
		Br	0.087(2)	0.365 (2)	0.468 (5)	2.8 (6)	
	C(6)	C1	0.002(3)	0.307 (2)	0.565 (6)	5.5 (8)	
		Br	0.004(2)	0.318(2)	0.582 (6)	4.6 (8)	
	C(13)	Cl	0.082(2)	0.434 (2)	0.494 (6)	4.0 (6)	
		Br	0.084(2)	0·448 (2)	0.502 (7)	3.9 (7)	
	O(14)	Cl	0.085 (2)	0.458 (2)	0.736 (5)	6.6 (6)	
	• •	Br	0.084(2)	0.476 (1)	0.748 (5)	4.7 (5)	
	N(15)	Cl	0.084(2)	0.483 (2)	0.293 (5)	4·0 (5)	
		Br	0.081(2)	0.494 (1)	0.295 (4)	2.5 (5)	
	C(16)	C1	0.095 (2)	0.562(2)	0.336 (8)	6.2 (8)	
		Br	0.095 (3)	0.578 (2)	0.320 (7)	5.9 (9)	
	C(17)	Cl	0.190 (3)	0.597 (2)	0.229 (7)	6.5 (9)	
		Br	0.185 (3)	0.608 (2)	0.247 (7)	5.1 (8)	
	C(24)	Cl	-0.011(4)	0.598 (3)	0.130 (10)	9.1 (12)	
		Br	-0·010 (4)	0.613 (3)	0.152 (10)	8.3 (12)	
	O(25)	Cl	-0.008(2)	0.651 (2)	-0.023 (6)	9.5 (8)	
		Br	-0·010 (2)	0.659 (2)	-0.031 (6)	9.0 (8)	
Group‡		xc	Yc	Zc	φ	0	Q
PH(1)8	Cl	-0.214(1)	0.340(1)	0.267(4)	-2.86(2)	2.45(2)	-0.70(2)
(-/3	Br	-0.213(1)	0.354(1)	0.280(4)	-2.89(2)	2.50(2)	-0.66(2)
PH(2)8	ĉi	0.388(2)	0.545(1)	0.619(4)	0.22(2)	-2.51(2)	0.84(2)
	Br	0.381(2)	0.557(1)	0.590(4)	0.19(2)	-2.45(2)	0.81(2)
ETO	ci	-0.200(4)	0.604(3)	0.036(10)	0.92(7)	3.00(4)	-1.99(6)
-	Br	-0.201(3)	0.618(3)	0.046(10)	0.92(7)	3.05 (5)	-2.03(9)
	_	(-)		10 (10)	(.)	= = = = (=)	= = = = (=)

Table 2. Positional, thermal, and group parameters for C₂₂H₂₅XN₂O₄*

* Standard deviations in units of the last significant figures are given in parentheses here and in Table 3.

† For the halogen atoms anisotropic temperature factors of the form: $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$ were used; the resulting thermal coefficients × 10⁴ are as follows:

		β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Х	Cl	86 (7)	191 (12)	805 (60)	58 (9)	20 (17)	-95 (26)
	Br	118 (4)	132 (4)	795 (28)	61 (4)	18 (8)	-109 (11)

‡ x_e , y_c , and z_e are the fractional coordinates of the origins for the rigid phenyl-ring groups, PH(1) and PH(2), and for the ethoxy group, ETO. The rigid-body positional coordinates are defined relative to right-handed orthogonal axes x', y', and z' with origins at the centers of the phenyl rings and at C(27) of the ETO group, and with each group in the x'y' plane. In PH(1), C(10) lies on the +x' axis, and the +y' axis intersects the midpoint of C(8)–C(9). In PH(2), C(21) lies on the +x' axis, and the +y' axis intersects the midpoint of C(22)–C(23). In the ETO group C(28) lies on the +x' axis, and the +z' direction is the vector product of +x' and the vector C(27)→O(26). For each group, the three angular parameters φ , θ , and ϱ (in radians) define the orientation of the rigid-body axial system with respect to an orthogonal set of crystal axes a_0 , b_0 , c_0 , where $a_0 = a$, $b_0 = c_0 \times a_0$, and $c_0 = a \times b$. Three successive rotations bring the crystal axes into parallel coincidence with the rigid-body axes as follows. A positive rotation φ about c_0 brings a_0 to a_1 and b_0 to b_1 ; next, a positive rotation θ about a_1 brings b_1 to b' and c_0 to c_1 ; lastly, a positive rotation ϱ about b' brings a_1 to a' and c_1 to c'.

§ PH(1) and PH(2) are bonded to C(6) and C(17), respectively.

different ways to the bond distances, bond angles, occupancies, and thermal parameters. However, none of these attempts with either the chloro derivative or the bromo derivative data led to convergence. Refinement did converge when the structure was assumed to contain a single ethoxy group, treated as a rigid group O(26)-C(27) = 1.47 Å; C(27)-C(28) = 1.54 Å; O(26)-C(28) = 1. $C(27)-C(28) = 109.5^{\circ}$ of occupancy factor 1.0. The refined positions of the group atoms then corresponded closely to those indicated in bold outline in Fig. 1. In the final refinements, the two phenyl rings were also constrained to possess D_{6h} symmetry in order to improve the ratio of the number of observations to the number of varied parameters. The orthogonal axes for the rigid ethoxy and phenyl groups were as defined in Table 2. The thermal motions of the halogen atoms were treated anisotropically, whereas all other atoms, independent or within groups, received individual isotropic thermal parameters. In the following, numerical results of the refinement for the chloro derivative are followed by those for the bromo derivative in parentheses. Based on the 487(522) reflections for which $F_o^2 \ge 3\sigma(F_o^2)$, R(F)was 0.105 (0.090); $R_w(F)$, defined as $[\sum w ||F_o| - |F_c||^2 / \sum w |F_o|^2]^{1/2}$, was 0.112 (0.111); and the standard deviation of an observation of unit weight, defined as $\left[\sum w|\Delta|F|\right]^{2}/(n-p)$, where *n* is the number of observations and p the number of parameters fitted to the data set, was 3.84 (1.77). The parameter shifts in the final cycle were all less than 20 (20)% of the corresponding standard deviations. Final difference Fourier syntheses

Table 3.	Derived	parameters	of	group	atoms	for
		$C_{22}H_{25}XN_{2}$	\mathbf{D}_2			

Group	Atom		x	у	Ζ	В
PH(1)	C(7)	Cl	-0.109	0.326	0.412	6.6 (9)
. ,		Br	-0.108	0.342	0.424	6.2 (9)
PH(1)	C(8)	Cl	-0.167	0.384	0.501	8.6 (11)
. ,		Br	-0.166	0.401	0.503	7.0 (10)
PH(1)	C(9)	Cl	-0.273	0.398	0.356	9.7 (12)
		Вг	-0.271	0.414	0.360	9.9 (13)
PH(1)	C(10)	Cl	-0.319	0.355	0.123	8.3 (11)
		Br	-0.318	0.367	0.137	7.2 (10)
PH(1)	C(11)	Cl	-0.261	0.297	0.034	8.0 (10)
		Br	-0.260	0.307	0.028	10.8 (14)
PH(1)	C(12)	Cl	-0.156	0.282	0.179	7.3 (9)
		Br	-0.155	0.295	0.201	7.7 (11)
PH(2)	C(18)	Cl	0.291	0.567	0.445	5·4 (8)
		Br	0.284	0.583	0.429	5.2 (9)
PH(2)	C(19)	Cl	0.336	0.610	0.682	8.5 (11)
		Br	0.333	0.622	0.670	6.1 (9)
PH(2)	C(20)	Cl	0.433	0.587	0.857	8.3 (10)
		Br	0.430	0.596	0.832	9.9 (13)
PH(2)	C(21)	Cl	0.485	0.522	0.794	10.1 (12)
		Br	0.478	0.531	0.751	9.4 (13)
PH(2)	C(22)	Cl	0.440	0.479	0.557	12.5 (17)
		Br	0.428	0.492	0.209	12.9 (19)
PH(2)	C(23)	Cl	0.343	0.502	0.382	11.6 (15)
		Br	0.332	0.518	0.348	7.8 (11)
ETO	O(26)	Cl	-0.098	0.568	0.170	13.9 (12)
		Br	-0.098	0.582	0.164	11.4 (10)
ETO	C(27)	Cl	-0.500	0.604	0.036	13.8 (17)
		Br	-0.501	0.618	0.046	12.2 (16)
ETO	C(28)	Cl	-0.243	0.570	-0.254	19.8 (27)
		Br	-0.250	0.583	-0.240	27.9(41)

were essentially flat except in the immediate vicinity of the ethyl group, where the highest residual was 0.4 (0.6) e.Å⁻³, or about 20% of the average peak height of a carbon atom in these structures. No attempt was made to locate the positions of the 22 hydrogen atoms in either derivative.

The scattering factors used were those of Thomas & Umeda (1957) for the bromine atom, those of Dawson (1960) for the chlorine atom, and those of Berghuis, Haanappel, Potters, Loopstra, MacGillavry & Veenendaal (1955) for carbon, nitrogen, and oxygen. The anomalous scattering corrections of Templeton (1962)



Fig. 2. Molecular configurations with bond distances (Å) for the two derivatives with values for the bromo derivative in parentheses.



Fig.3. Molecular configurations with bond angles (°) for the two derivatives with values for the bromo derivative in parentheses.

for bromine and of Cromer (1965) for chlorine were employed.

The final parameters for nongroup atoms and rigid groups, together with the corresponding standard deviations, are given in Table 2 for both compounds. The derived parameters for the group atoms are given in Table 3. Observed and calculated structure amplitudes ($\times 10$) for the reflections used in the refinements are listed for the chloro derivative and the bromo derivative in Tables 4 and 5, respectively. Bond lengths and angles, calculated with program *ORFFE* (Busing, Martin & Levy, 1964) are illustrated in Figs. 2 and 3. All figures in this paper were prepared with the use of the *ORTEP* program (Johnson, 1965). The calculations were done on the CDC 1604 and IBM 360 computers.

Discussion

Interatomic distances and bond angles: accuracy of the structure determination

For both derivatives the estimated standard deviations (e.s.d.'s) are in the ranges 0.03-0.05 Å for distances and $2-4^{\circ}$ for angles. This relatively poor precision for counter data may be attributed to the small number of intensity data, and to the disorder for which no satisfactory model could be refined. However, the structures for the two derivatives agree closely with each other and, in many details, with previously determined peptide structures. Corresponding distances and angles for the two derivatives involving independently refined (nongroup) atoms agree to within 3 e.s.d.'s

Table 4. Observed and calculated structure amplitudes ($\times 10$) for C₂₂H₂₅ClN₂O₄

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1 9 109	102	54	204	214				2 0	327	221	3.10	0 61	70	5 11	59	76	-6 10	14		-1 2	209	222		200	60	12		21	-11 2	104	100		. 61	/5			21
1 10 81	81	55	127	1 30		r = 1		2 1	228	207	-3 1	0 122	131	5 12	64	66	-6 1	63	68	1	101	143		, ,		2.4						-, ,		70			
1 11 71	95	56	96	89				-2 1	471	44.3	3 1	1 89	98	5 13	63	71	-9			- 3	1 90	151			125	2.		230		,		-3 11		101	1.1	~	~
1 1 2 65	66	59	125	94	00	655	725	2 2	21 9	255	-3 1	2 68	79	-513	62	72	9	99	83		211	234		94		2 :	223	210		1.74	143	- 1	130	8.	12 1	~	60
2 1 88	102	5 10	134	128	0 1	250	276	-2 2	535	569	-31	4 66	80	-60	91	106	9	103	104		317	355				~ .	457	130				7.6			12 ;	60	
2 2 286	321	60	119	109	0 2	711	674	23	100	97		0 114	25	6 1	93	69	-9	101	102					93	/3		24	92	0 2	100	1221			142			
2 3 649	659	6 1	107	52	03	195	215	-2 3	- 75	89	1 7	0 184	166	1.0	225	206					152	183		2 /3	101	1.1	161		0.6	76	81	~ .	81	105	12 :		57
2 4 558	568	62	248	246	04	291	305	2 4	190	212		1 336	343	7.4	241	210			30				1.		84				1 0	111	1.1	2.7	. 176	161	1		
2 7 173	170	63	201	214	0 5	203	211	-2 4	510	458		1 193	176	63				103	80	1:::	1/5				10	1.1									12 1	100	114
2 8 166	162	6 4	89	101	08	114	96	-2 5	194	226		2 218	167	-63	210	183	-9	51	5/		116	150		301	780		81	26		26			3 61	61	12:	87	81
2 9 210	201	65	117	111	0 9	86	65	2 6	126	125	-	2 176	140	• •••	189	219	10							, ,,,	100	;	68					4 1	210	212	- 6		67
2 10 187	200	6 7	76	73	0 11	104	108	-2 6	184	164		3 116	142		100	6/	-10	100	1/4			130			104						108	11		119	1	142	111
2 11 86	81	6 8	199	206	0 12	62				130	1	3 203	254		130	125			40		137	122			148		101	96		28	44		1.60	168	-6 1	100	82
3 0 96	102	6 9	60	64		295	302	1				4 352	310		5/	3/	-10		26		10	8.		111		- 10			14	72	69	1			-	76	60
3 1 551	519	6 12	50	59	-1 0	82	/0	1 4 0		102	1.1	5 202	201	~ .			-10		163			104			~	1 0			-1 -	160	168	. í .		101	- ī í	102	97
3 2 103	134	72	157	163	1	304	313	-2 8		89	17	5 193	159		04												1.10			,		7.7			1	67	80
3 3 382	421	73	214	190	-1 1	734	743	29	110	98	-	6 269	265	~ ~			-10	40	134						108	-/ 0	114		1 0	24	5.	2 3	, <i>1</i>	82	- ' '	•,	
3 4 222	233	74	93	97	1 2	390	401	1-1 9	150	140		/ 1/4	1/3					40	~	1	130			160	201		195	161	-1 9			4	17	184			
3 5 346	339	1)	54	50	-1 2	635	655	-2 10		90	Ľ.	0 /8	60	610						1.1	149		1.1		744		1.68	114	-1 10	96	88	- × 1	101	121	1		
3 6 201	194	1 10	68	64	1 3	162	164	-2 11	- 1	. 82	121		41	1	151	142		152		1.1.1	220	100		788	261	1 ; ;		6.9	-7 0	116	117		. 61	91			
3 7 72	89	7 11	79	80	-1 3	834	780	-2 13		90		4 70	93	-/ !	228	208	1711	140	120	12.1	292	300			26		1.24	110		78	46			80			
3 9 200	215	8 1	256	217	1.1.1	248	218	1				> 5/	82	1 2 2	, 12	102	-·· -	, /0	35		68			186	161	1;;	121	128	;;	57	5	-7 1		135	1		
3 11 104	115 1	K 2	161	1 15		300		1 -3 0				u 160	151		. 8/	102					00								- /						×		

Table 5. Observed and calculated structure amplitudes ($\times 10$) for C₂₂H₂₅BrN₂O₄

M K 10F0 10FC	H K 10F0 10	#c H	K 10F0 1	IOFC	н к	10F0 10F	۲ H	K 10F	0 10FC	* *	10F 0	10FC	н	K 10F0	10FC	в	1050	10FC	н к	1 <i>0</i> F0 1	OFC	H K	IGFO 1	OF C	нк	10F0	IOFC	+ •	10F 0	10FC	нк	10F0 1	1 OF C
	4 0 378	172 8	2 163	152	- 1	855 72	5 -1	1 49	4 148	- 1	189	,,,,	,	s 146	129				2 6	208	234	-4 7	251	224	8 1	149	136	-2 5	110	107	-6 4	104	9
	6 1 166	A A	1 111	121		701 66			+ 100	1::		211		6 333	212			****		148	114	- 8	143	161	-6 1	129	161	2 6	172	172	-6 5	110	116
0 1 161 161						917 70		:		12:			1	ź					123	107			144	170	- 4	102	115	-2 6	178	181	-7 1	188	198
0 4 1111 040				24	1.1	037 70		4 40	409	12 :		- 22	4	4 105					1	111		. 10			-å 1	101	111	2 8	101	108	-7 9	149	110
			2 2 1			15/ 10	<u> </u>	3 19	5 200		300	209	-/				240	205	1						<u>،</u> ه					44	ا م ا	144	141
0 6 492 436	4 4 100 1	/9 0	6 134	127	- 3	1073 89	1.5	3 59	8 490	1 3 3	238	252	1	7 149	167	0 1	199	195	-2 9	120			145					-4 10	104			114	
0 0 430 30/	4 5 102 1	15 0	/ 163	150 [1 4	401 42	1 3	4 13	9 136	1 2 4	1/2	120	-/	/ 100			590	501	2 10	101	20						,				~ ,		
0 12 209 181	4 6 125 1	16 8	8 184	202	-14	645 56	1 -3	4 44	3 388	13 4	174	175	-7	8 103	121	0	3 269	269	-2 10	197	217		2/0	204	-0 9	90							
1 0 162 130	4 7 200 2	19 8	9 105	113	15	267 28		5 43	6 430	1 -5 - 5	681	460	71	1 96	91	0 4	N 143	175	-2 11	156	162		140	155	-9 0	105	113	-3 0		, ,,,,			
1 1 369 369	4 8 124 1	21 9	0 100	91 .	-15	170 15	9 -3	5 18	5 214	5 6	198	209	-71	1 121	126		5 219	214	-2 12	102	112	52	212	219	-91	106	. 72	-3 1	33	134			
1 2 583 598	4 9 121 1	50 9	1 203	208	16	321 36	4 3	6 12	9 134	-5 6	209	211	-0	0 121	130	0 3	7 137	148	2 13	105	103	-5 2	235	248	-93	117	139	31	1,00	136	00		
1 3 427 366	4 10 141 1	53 9	2 130	106 .	-16	290 27	7 -3	6 23	1 247	5 7	98	120	8	1 223	219	0 8	91	108	-2 13	105	105	53	163	188	-9 5	140	159	-3 2	191	173	03	105	112
1 4 822 759	4 11 167 1	61 9	3 203	188	17	146 14	8 3	7 13	8 115	1-5 7	166	158		1 190	187	0.10	207	202	-3 0	336	315	-5 3	184	175	-98	106	79	1-1 1	9/	60		140	124
1 5 340 289	4 12 109 1	10 9	5 97	68 ·	-17	180 21	9 -3	7 41	2 412	58	141	134		2 116	83	0 13	3 117	96	3 1	207	248	-5 4	221	221	-10 4	126	107	3 4	138	153	1 2	117	109
1 6 504 476	5 0 411 4	36 9	6 99	66	1 8	277 28	8 3	8 13	7 119	5 9	164	160	8	3 107	88	1 0	243	219	-3 1	313	288	-55	398	372	-11 0	115	97	-3 4	123	124	-1 2	191	16
1 7 366 364	5 1 616 9	98 9	7 159	155	-18	231 25	8 -3	8 38	2 371	-5 9	98	106	-6	3 151	141	-1 0	102 0	366	32	330	334	56	1 30	136	-11 2	128	138	3 5	125	104	-14	119	103
1 8 354 330	5 2 298 2	70 9	8 113	109	1 9	174 15	1 -3	9 22	7 194	5 10	100	108	8	4 102	93	1 1	126	90	-3 2	150	147	-56	226	232				-3 5	220	205	-20	145	186
1 9 164 153	5 3 166 2	15 10	1 172	196 .	-1 11	105 9	3 3 3	0 13	7 156	-5 10	120	111	a	5 140	132	-1 1	265	243	1 3 3	228	230	-57	254	261	****	L = 3	****	36	148	124	24	109	113
1 10 112 113	5 4 101	01 00	2 114	116	-1 12	116 14	-1	0 17	1 206	1-513	102	117	-0	5 158	190	1 1	2 268	316	-1 1	140	133	-5 12	121	125				-3 6	1 30	132	-2 4	112	118
1 11 125 145	5 5 141 1	58 10	3 118	102	2 0	555 61	1 -1	2 14	6 115	-6 0	81	96	8	7 120	78	-1	2 21 2	219	3 4	200	212	-6 0	200	207	0 0	254	267	-3 7	123	128	30	167	\$73
2 0 261 129	6 6 161 1		4 142	116 .	-2 0	291 10			4 119	1 6 1	217	180	i a	7 214	217	1 1	8 81	95	-1 -	175	138	61	111	129	0 2	268	256	-3 9	148	136	-3 1	114	8
2 1 182 122		12 10	1 101			161 16		1 41	1 1.16	1.4	163	164		8 117	1 2 2		108	109	1 1 4	173	140	-6 1	\$27	332	0 3	96	71	4 0	173	187	-3 6	121	99
2 1 109 177					÷ :	413 69		: 2		12:	,,,,	200		· · · · ·			107		1	184		4 1	176	171		108	104		1 1 9	110	- i i	115	91
2 2 313 373							17			17:									1:::							101	181	4 4 1	109	108	- 1	161	110
2 3 813 /23	3 9 220 2		1 104	· "] .	4.4	435 45			5 475	123								~	1				111	140	1 0	118	168	1	144	114		110	10
2 4 6/2 603	5 10 194 1	<i>"</i>		[`	~ *	609 05		2 90	5 280	1.2.3	350	334					5 90			140				2			1.16		,		123	1.75	
2 5 111 116	6 0 85	78		1	2 3	15/ 16		3 10	A 211		101	120	7	1 122	126		229	196	1	215	207	~ ?	104			110					124		
2 6 221 209	6 2 292 3	00			-23	162 14	s ~	5 36	3 444		232	454		2 100	~~~~	-	264	327		155	190	• •	190		11	110		17 3	219	200			
2 7 200 194	6 3 375 3	73 0	0 975 1	087	2 4	370 39		4 47	7 452	0.5	244	273		3 183	169		192	1/2	-3 8	205	200	- 2	191	190		155	133	127	101	103	2 1	124	144
2 8 309 301	6 5 259 2	72 0	1 312	293 .	2 4	791 70	· ~	4 16	4 147		116		-9	3 181	169	- 1	182	212	-3 11	101	123	~ •	10/		1.1				439			110	121
2 9 187 166	6 6 80	94 0	2 682	730	25	142 14	3 4	5 34	7 307	-6 6	113	136	-9	4 156	143		3 224	166	۱ ۲ ۰	399	366		128		1.7	140	145			37	-6 0	116	
2 10 243 249	6 7 203 1	94 0	3 233	211 -	-25	177 18	1 -4	5 20	9 172	67	169	169	9	5 173	150	-1 6	3 249	249	-+ 0	147	158	-6 9	139	145	-1 4	307	289	- 1	123	137	-6 1	165	174
2 11 115 117	6 8 277 2	98 0	6 531	-98	26	280 27		6 15	0 153	-6 7	140	165	-9	5 138	131	-1 10	5 115	201	* 1	179	154	~6 10	129	146	-1 6	182	136		118	99	~ 3		
3 0 278 302	6 9 130 1	26 0	5 213	218 -	26	149 14	1 -	6 38	5 376	6 8	104	110	9	8 104	80	2 0	373	380		322	337	-6 11	108	79	~1 8	108	118	51	291	260	-7 2	129	10;
3 1 626 571	6 12 111 1	02 0	6 215	211	27	191 194	1 -4	7 32	4 304	6 9	1 27	162	10	1 112	84	~ 0	269	277	4 2	144	145	-70	140	165	-19	106	132	51	156	175			
3 2 262 334	7 1 144 1	54 0 :	7 88	92 -	27	154 16	5 -4	9 11	6 130	-6 9	1 30	136	-10	1 212	223	2 1	158	167	- 2	331	324	, ,	230	214	-1 10	115	117	5 2	147	164			
3 3 477 499	7 2 154 1	72 0	8 239	185	2 B	266 27) 4 I	1 10	7 103	-6 13	102	95	10	2 109	102	-2 1	1 123	106	1 * 3	207	193	-7 1	369	2+3	30	103	137		1 3 2	128			
3 4 374 389	7 3 355 3	33 0	9 125	107 -	-z 8	125 11		1 9	9 100	1 7 0	141	134	10	3 162	108	2	2 389	394		253	261	-7 2	170	172	-2 0	233	243	53	189	175			
3 5 489 491	2 6 108 1	18 0 11	112	1 14	2 9	127 10	5 4 1	2 10	2 138	21	124	135	-10	3 111	100	-2 :	2 525	512	1 4 4	214	224	73	121	126	21	102	84	-5 3	132	. 143			
1 6 157 187	7 6 161 1	64 0 1	96	91 .	2 á	104 10	41	3 11	0 114	-7 1	326	309	-10	4 148	170	-2 1	3 392	342		193	186	-73	201	200	22	1 32	132	-5 5	181	169			
1 7 165 201	7 7 165 1	61 0 1	124	124 .	2 10	171 18	-41	5 10	9 106	1 7 2	112	91	-10	5 154	152	24	206	189	4 5	224	267	75	137	144	-2 2	162	128	3 7	115	- 131			
1 8 130 163	7 10 108 1		576	622 -	2 11	120 13	1 4	0 24	9 263	1 2 3	217	218	-11	0 194	202	-2 /	4 126	125	-4 5	340	308	-75	132	153	-23	199	193	6 1	101	102			
3 0 770 746	2 11 138 1		309	244		651 67		0 48	8 515	-7 3	233	260	-11	2 155	142	2 1	5 109	120	1 - 6	353	358	-78	126	135	2 4	162	180	-6 1	239	, 249 İ			
3 3 229 246	9 1 130 1		1 164	144	11	241 21		1 56	A 100	151	96	80	-11	3 125	119	-	5 195	239	1 4 7	110	114	-7 9	123	131	-2 4	123	134	و احما	148	1 163			
3 10 106 103		, , , ,						• >>	• • • • • •		,.																						

(except for the carbon-halogen bond lengths). In a comparison of both derivatives of the main-chain distances and angles with the corresponding weightedaverage values calculated by Marsh & Donohue (1967), the root-mean-square (r.m.s.) difference for bond distances is 0.03 Å, and the maximum difference is 0.07 Å; the r.m.s. difference for bond angles is 4°, and the maximum difference is 7.5° . At positions where rigid groups are attached to independent atoms, the interatomic distances and bond angles are not significantly different (considering the low precision) from normal values. The parameters of interest at the ester linkage are close to published values for three other esters, as shown in Table 6. Thus, it appears certain that the molecular conformations are essentially correct as determined, except for some uncertainty in the region of the disordered ethyl group.

The C(1)-Cl distance of 1.75 Å and C(1)-Br distance of 1.87 Å are roughly in agreement with the average values of 1.77 and 1.94 Å, respectively, given in *Tables* of Interatomic Distances and Configuration in Molecules and Ions (1965).

Molecular structure and packing

A stereoscopic view of the molecule is shown in Fig. 4. Fig. 5 shows the hydrogen bonding of molecules separated by c translations, and Fig. 6 shows the pack-

ing in a stereoscopic view down the c axis. The structure is of the parallel-chain pleated-sheet (PCPS)* type (Pauling & Corey, 1951), as has also been found for the tripeptide Gly-L-Phe-Gly (GPG)* (Marsh & Glusker, 1961). The molecule may be considered to contain two complete peptide units (as does a tripeptide), where we use the term 'peptide unit' to denote a group C^{α} , CO, NH, C^{α}, and where the atom C(1) takes the place of an *a*-carbon atom. As expected (Marsh & Donohue, 1967), both peptide units have trans configuration and are planar within experimental error [maximum out-of-plane deviation 0.05 (0.08) Å, calculated by means of the Smith (1962) program]. Parallel chains related by c-axis translations are connected by $NH \cdots O$ hydrogen bonds to form a sheet with a single pleat. The NH···O distances of 2.90 (2.86) Å and 2.78 (2.74) Å are in rough accord with the value of 2.87 Å for the PCPS, and with the value of 2.90 Å suggested by Marsh & Donohue (1967) as normal for the bonds. The distance between adjacent chains within the sheet is the c-axis period, 4.93 (4.95) Å,

Table 6. Comparison of molecular parameters at ester linkages in several structures



Fig. 4. Stereoscopic view of the molecule.

^{*} Abbreviations used in the text are PCPS: parallel-chain pleated sheet (Pauling & Corey, 1951, 1953); GPG: glycylphenylalanyl-glycine (Marsh & Glusker, 1961); and TPPNBE HBr: threonyl-phenylalanine-*p*-nitrobenzyl ester hydrobromide (Mallikarjunan, Rao & Venkatesan, 1969).

which is close to the values 4.85 Å for the PCPS and 4.90 Å for GPG.

Whereas the peptide chain in GPG is extended in comparison with the PCPS structure, here the chain is considerably contracted (Table 7) with respect to the PCPS model. The pleat angle, or dihedral angle between the peptide-unit planes, is smaller here by 11.5 $(11.8)^{\circ}$ than in the PCPS, and accordingly, the C(1)-C(16) distance, corresponding to the repeat distance along chains in the PCPS, is shortened by 0.41 (0.44) Å. For all three structures in Table 7, the lengths of the peptide units are close to 3.78 Å, the length of a peptide unit of average dimensions given by Marsh & Donohue (1967). In each case of Table 7, the repeat distance or its equivalent is approximately equal to $2 \times (peptide)$ unit length) $\times \sin(\frac{1}{2}$ pleat angle), a relation which holds exactly if the plane of the three successive α carbon atoms is perpendicular to the planes of the two peptide units.

The two side chains of the molecule lie on opposite sides of the pleated sheet, and are very roughly related by a pseudocenter of symmetry midway between the α -carbon atoms of the second peptide unit, so that the molecule is compact and in the form of the letter H (see Figs. 4 & 6). The phenyl rings are nearly parallel with dihedral angle 11.1 (10.8)°. The carboxy group, comprised of C(16), C(24), O(25), and O(26), is nearly planar with a maximum out-of-plane deviation of 0.03 (0.07) Å.

Both phenyl rings of the molecule stack along the **c** direction. The closest $C \cdots C$ contacts are 3.49 (3.64) Å and 3.42 (3.39) Å, for the rings in residues 1 and 2, respectively. (Residues are numbered sequentially from the haloacetyl-terminal to the carboxyl-terminal end of the chain.)

The atoms of a molecule lie not far from a plane roughly perpendicular to c. The closest contacts between the two vertical columns of molecules in Fig. 6 involve halogen atoms, phenyl rings, and methyl groups. The smallest interatomic distances between neighboring molecules fall within normal van der Waals limits.

Conformation of the molecule

The peptide-chain conformation may be described according to the recommendations of the *IUPAC-IUB Commission on Biological Nomenclature* (1970). In these definitions, the torsion angle about bond B-C in A Da system of four atoms B-C is considered positive (negative) if in a view along B-C the front bond A-B must be rotated clockwise (counterclockwise) in

Table 7. Comparison of peptide-chain parameters with parameters of related structures



Fig. 5. Hydrogen-bonding of parallel chains. The c axis is horizontal and to the left. The direction of view is almost down the a^* axis. For clarity, the main-chain bonds are indicated by solid lines.

order to eclipse the rear bond C-D. The pertinent torsion angles are illustrated in Fig. 7.

The backbone chain conformation around the α carbon C(5) is given by the torsion angles $\varphi_1 = -102$ $(-100)^\circ, \psi_1 = 106 (110)^\circ$. These values can be compared with those for the PCPS $(-126, 132^\circ)$ and for the phenylalanyl residue in GPG $(-119, 113^\circ)$. The pair of values lies within an allowed region of the $\varphi - \psi$ diagram of Ramachandran and co-workers as redrawn with the conventions of the *IUPAC-IUB Commission* (1970, Fig. 6). The torsion angle φ_2 , $-122 (-118)^\circ$, is close to the value for the PCPS structure. However, the torsion angles ψ_T^1 and ψ_T^2 at the carboxyl terminus have the uncommon values of $-133 (-126)^\circ$ and 53 (40)°; ψ_T^2 is usually approximately 0°, or in a minority of cases somewhat negative (down to -56°); and $\psi_T^1 \simeq \psi_T^2 + 180^\circ$ (Lakshminarayanan, Sasisekharan & Ramachandran, 1967, Table 2). The same reference lists only two cases with large positive ψ_T^2 : aspartic acid-HCl, $\psi_T^2 = 42.3^\circ$ (Dawson, private communica-



Fig. 6. Stereoscopic view down the c axis through the center of the unit cell. For clarity, only one row of the molecules approximately perpendicular to the viewing direction is shown. The origin is in the lower-left rear corner, and the b axis is vertical. Only the halogen atom of the basic molecule is labeled.



Fig. 7. Conformation angles for the two derivatives with values for the bromo derivative in parentheses: (a) φ_1 ; (b) φ_2 ; (c) ψ_1 ; (d) $\psi_1^{T}_T$ to O(25) and $\psi_2^{T}_T$ to O(26); (e) ω_1 ; (f) χ_1^{1} ; (g) χ_2^{1} ; (h) $\chi^{2,1}_1$ to C(12) and $\chi^{2,2}_1$ to C(8); (i) $\chi^{2,1}_2$ to C(19) and $\chi^{2,2}_2$ to C(23); (j) $\theta_T^{C}_T$. According to the recommendations of the *IUB-IUPAC Commission* (1970, section 2.3.2), *i.e.* that the smallest positive or negative value of the principal torsion angle be assigned the highest priority and the lowest number, the $\chi^{2,1}_1$ and $\chi^{2,2}_1$ values for the bromo derivative should be reversed so that $\chi^{2,1}_1 = -89^\circ$ and $\chi^{2,2}_1 = 97^\circ$. However, to be compatible with the equivalent values for the chloro derivative, the present values for the bromo derivative are given instead.

tion to Lakshminarayanan *et al.*, 1967); and glycylasparagine, $\psi_T^2 = 63 \cdot 3^\circ$ (Pasternak, Katz & Corey, 1954). In the latter structure the two terminal carboxyl oxygen atoms are involved in four hydrogen bonds in all, but here there are no hydrogen bonds involving O(25) or O(26). Packing may, however, explain the unusual conformation here: a rotation of the carboxyl group about the C(16)-C(24) bond to make $\psi_T^2 \sim 0^\circ$, with atoms 1 through 23 kept stationary in the unit cell, would bring O(25) too close to one of the hydrogen atoms attached to C(6) in the neighboring molecule at $-x, \frac{1}{2} + y, 1 - z$ (see Fig. 6). The estimated $O \cdots H$ interatomic contact, assuming a normal tetrahedral configuration of hydrogen atoms about C(6), would then be less than 2 Å.

Conformational angles for the two side chains are shown in Fig. 7(f) through (i). The three general positions for a C^y atom have been labeled by Ramachandran & Lakshminarayanan (1966) as I, II, and III for χ values of 60, 180, and -60° , respectively. In this structure the C^y atom of the first residue, C(7), is within 5 (3)° of position II; and that of the second residue, C(18), is within 11 (4)° of position III. Position III has not previously been observed for a phenylalanyl residue in a small peptide. Position II has been found previously for the phenylalanyl residues in GPG and TPPNBE HBr, and position I in L-phenylalanine-HCl (Gurskaya, 1964).

Views down the $C^{\beta}-C^{\gamma}$ bonds of the two side chains [Fig. 7(h) and (i)] show that in both cases the planes of the phenyl rings are roughly perpendicular to the $C^{\alpha}-C^{\beta}-C^{\gamma}$ planes, so that all these χ angles approximate 90°; the perpendicular arrangement results in minimum interaction between α - and δ -carbon atoms, and not surprisingly has been found previously for several phenylalanyl residues (Lakshminarayanan *et al.*, 1967, Table 3).

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