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Structure of a Potent Oxytocin-Receptor Ligand

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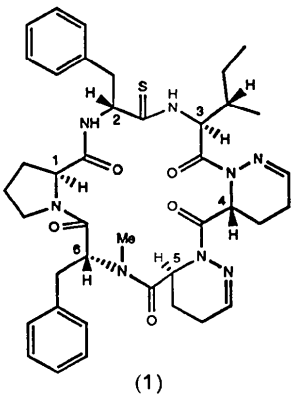
Abstract. *cyclo*[-Pro-D-Phe-ψ(CS—NH)-Ile-D-Thp-Thp-D-MePhe-] [where D-Thp is the residue formed from the cyclic imino acid (*R*)-2,3,4,5-tetrahydropyridazine-3-carboxylic acid], $C_{40}H_{50}N_8O_5S$, M_r = 754·96, monoclinic, $P2_1$, a = 10·413 (7), b = 17·225 (8), c = 11·200 (4) Å, β = 97·77 (4)°, V = 1990 Å^3, Z = 2, D_x = 1·260 Mg m^{-3}, λ(Cu $K\alpha$) = 1·54184 Å, μ = 1·12 mm^{-1}, $F(000)$ = 804, T = 296 K, $R(F)$ = 0·067 for 2343 observed [$I \geq 3\sigma(I)$] reflections. A macrocycle containing six amino acids, all with peptide linkages, adopts a conformation in which the backbone is relatively flat except at Phe-ψ(CS) which is well out of the plane of the rest of the molecule. The presence of an S instead of an O atom in an amide unit may contribute to conformational changes as a result of the larger steric requirements of sulfur. Changing an amide to a thioamide does not result in changes to the bond distances or angles within an amino-acid residue.

Introduction. The compound *cyclo*[-Pro-D-Phe-ψ(CS—NH)-Ile-D-Thp-Thp-D-MePhe-]* (1) has been prepared (Bock, DiPardo, Williams, Pettibone, Clineschmidt, Ball, Veber & Freidinger, 1990) and found to be a highly potent and selective oxytocin-receptor ligand. The crystal structure analysis was undertaken to determine the conformation of the cyclic ring, the relative positioning of the ring substituents and what, if any, steric requirements can be ascribed to the presence of the isoteric group C=S in a modified phenylalanine.



(1)

Experimental. Crystals grown by slow evaporation of an ethanol solution. Crystal 0·15 × 0·07 × 0·24 mm. Enraf–Nonius CAD-4 diffractometer. Lattice parameters determined using 11 reflections with 18 < 2θ < 34°. Lorentz–polarization correction applied; absorption correction using empirical method (absorption surface) (Walker & Stuart, 1983). Maximum and minimum correction coefficients applied to F_o were 1·6394 and 0·6809. Intensity measurements in range 0 < 2θ < 120° (index limits: h, 11; k, 19; l, ±

* The nomenclature used is in accordance with IUPAC–IUB Joint Commission on Biochemical Nomenclature (1984).

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12). Intensity standards: two reflections remeasured every 60 min of X-ray exposure time showed changes in intensity of 2·3 and 4·1%, respectively. No decay correction. Total reflections measured: 3260; unique: 3074; 731 unobserved [$I < 3\sigma(I)$]. R factor for averaging equivalent reflections 0·015. Structure solved by direct methods using *SHELXS*86 (Sheldrick, 1985). Full-matrix least-squares refinement using F magnitudes. Non-methyl H atoms located at calculated positions (C—H 0·95 Å), methyl H atoms fitted to peaks observed in a difference Fourier synthesis using idealized geometry. H-atom thermal parameters fixed at 1·2 times those of the attached atom, positional parameters constrained to 'ride' with those of the parent atom. All non-H atoms refined with isotropic thermal parameters except for 25 with large thermal motion which were allowed to refine anisotropically. For 342 variables refined: $R = 0{\cdot}067$, $wR = 0{\cdot}086$, $S = 2{\cdot}75$. Weights of $1/\sigma^2(F)$ with $\sigma(F)$ defined by Stout & Jensen (1968, equation H.14) with instability factor defined to be 0·04. $(\Delta/\sigma)_{max} = 0{\cdot}05$. Maximum peak height in final difference Fourier map 0·91 (6) e Å^{-3}. Included as a variable was a secondary-extinction coefficient which refined to $1{\cdot}28 \times 10^{-6}$. Neutral-atom atomic scattering factors, f' and f'' anomalous-dispersion values from *International Tables for X-ray Crystallography* (1974, Vol. IV, Table 2.2B). Computer programs used include the Enraf–Nonius (1985) *SDP-Plus* software and *ORTEP*II (Johnson, 1976). All calculations performed on a Sun Microsystems 3-260 computer.

Positional and thermal parameters are listed in Table 1, selected distances and angles are presented in Table 2.* The molecule is depicted in Fig. 1 with the numbering scheme employed.

Table 1. *Positional* ($\times 10^4$) *and thermal* ($\times 10^3$) *parameters, with e.s.d.'s in parentheses*

The equivalent isotropic thermal parameter U is given by $U = \frac{1}{3}\sum_{i=1}^{3} r_i^2$ where r_i are the principal root-mean-square amplitudes of vibration. Those parameters without an e.s.d. were not refined.

	x	y	z	U(Å^2)
S	361 (2)	3617	9153 (2)	70·3 (5)
O1	4011 (5)	3371 (4)	7332 (5)	71 (2)*
O2	6768 (5)	4251 (3)	10549 (5)	73 (2)*
O3	7818 (5)	1630 (3)	12187 (5)	62 (2)*
O4	3893 (5)	2027 (3)	12964 (6)	71 (2)*
O5	4004 (4)	1602 (3)	10411 (5)	63 (2)*
N1	4228 (5)	3926 (4)	9176 (5)	52 (1)
N2	6728 (6)	3125 (4)	9551 (5)	54 (2)
N3	7033 (6)	2834 (4)	12401 (6)	58 (2)*
N4	5535 (5)	1164 (4)	13269 (5)	50 (1)
N5	5846 (6)	392 (4)	13193 (6)	57 (2)
N6	2423 (5)	1140 (4)	11392 (5)	49 (1)
N7	1102 (5)	1193 (4)	11499 (6)	63 (2)*
N8	2551 (6)	2806 (4)	9566 (5)	51 (1)
C1	1964 (7)	3475 (5)	9300 (6)	53 (2)
C2	1854 (7)	2080 (4)	9757 (6)	48 (2)
C3	1379 (7)	1701 (5)	8515 (7)	56 (2)
C4	2483 (9)	1419 (6)	7874 (8)	79 (3)*
C5	398 (8)	1036 (6)	8652 (8)	70 (2)
C6	−320 (10)	793 (7)	7463 (10)	92 (3)
C7	2845 (7)	1587 (4)	10527 (6)	49 (2)
C8	704 (9)	759 (8)	12231 (11)	122 (4)*
C9	1492 (12)	132 (10)	12938 (13)	210 (6)*
C10	2765 (8)	296 (6)	13176 (9)	86 (3)*
C11	3389 (7)	746 (5)	12249 (7)	51 (2)
C12	4300 (7)	1370 (4)	12869 (7)	50 (2)
C13	6946 (7)	161 (5)	13728 (6)	58 (3)*
C14	7959 (8)	667 (5)	14409 (8)	65 (2)
C15	7423 (7)	1425 (5)	14758 (7)	61 (2)
C16	6459 (7)	1772 (4)	13747 (7)	54 (2)
C17	7152 (7)	2070 (5)	12682 (7)	54 (2)
C18	6190 (9)	3369 (5)	12960 (9)	79 (3)*
C19	7881 (7)	3172 (5)	11595 (7)	53 (2)
C20	8817 (7)	3777 (5)	12273 (7)	60 (2)
C21	9563 (7)	3479 (5)	13372 (7)	61 (2)
C22	10477 (8)	2905 (7)	13334 (8)	79 (3)*
C23	11245 (12)	2644 (8)	14358 (11)	117 (5)*
C24	11078 (10)	2938 (6)	15465 (9)	86 (3)
C25	10206 (12)	3494 (8)	15533 (9)	107 (4)*
C26	9425 (10)	3773 (6)	14485 (9)	86 (4)*
C27	7084 (7)	3547 (5)	10517 (7)	57 (2)
C28	7078 (9)	2309 (5)	9363 (8)	71 (3)*
C29	6661 (11)	2187 (6)	8041 (9)	90 (4)*
C30	6648 (10)	2964 (6)	7450 (8)	86 (4)*
C31	6181 (7)	3494 (5)	8401 (6)	60 (2)*
C32	4685 (7)	3589 (5)	8228 (6)	55 (2)
C33	2855 (7)	4155 (5)	9086 (7)	59 (2)
C34	2704 (8)	4864 (5)	9842 (8)	68 (2)
C35	3283 (7)	4782 (5)	11177 (7)	58 (3)*
C36	2745 (8)	4292 (5)	11947 (8)	65 (2)
C37	3215 (9)	4268 (6)	13159 (9)	80 (3)
C38	4203 (9)	4760 (6)	13582 (8)	83 (3)*
C39	4758 (9)	5246 (6)	12863 (9)	78 (3)*
C40	4305 (9)	5243 (5)	11666 (9)	75 (3)*

* Indicates an atom refined anisotropically.

Discussion. As shown in Fig. 1 the solid-state conformation adopted by the 18-membered ring of the macrocycle is an open ring structure with no β-turns and no 4→1- or 3→1-type hydrogen-bonding interactions. The macrocycle is fairly flat except at the Phe-ψ(CS—NH) residue which is twisted well out of the plane of the rest of the macrocycle [the φ and ψ angles for the proline and Phe-ψ(CS—NH) residues are (−89·9, 50·4°) and (81·7, 2·1°), respectively, and this pair of angles does not comprise one of the standard turn motifs]. This arrangement of the backbone at Phe-ψ(CS—NH) may be stabilized by a weak hydrogen bond of 2·9 Å between O2 of Pro-1 and N1 of Phe-ψ(CS—NH). The side chain of the Phe-ψ(CS—NH) residue is oriented to put the phenyl ring over the macrocycle with a close contact [3·301 (8) Å] between the *N*-methyl group (C18) and the *para* C atom (C38) of the ring. This orientation of this phenyl ring is presumably an artifact of crystal packing forces as there is no evidence in the solution NMR for this ring interacting with the H atoms on C18 (Bock *et al.*, 1990).

With recent publications on the stereochemical and physicological effects of changing amides to thioamides (Spatola, 1983; Sherman & Spatola, 1990) it is of interest to examine what effects, if any, the stereochemical requirements of the modified phenylalanine would have on the conformation of

* Lists of structure factors, anisotropic thermal parameters, H-atom positional and thermal parameters, and references for structures extracted from the CSD have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 53566 (17 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Selected bond lengths* (Å) *and angles* (°), *with e.s.d.'s in parentheses*

S—C1	1·674 (8)	C1—C33	1·532 (13)
O1—C32	1·204 (10)	C2—C3	1·555 (12)
O2—C27	1·259 (11)	C2—C7	1·513 (12)
O3—C17	1·210 (10)	C3—C4	1·515 (13)
O4—C12	1·218 (10)	C3—C5	1·556 (14)
O5—C7	1·231 (9)	C5—C6	1·496 (15)
N1—C32	1·352 (11)	C8—C9	1·51 (2)
N1—C33	1·473 (11)	C9—C10	1·346 (17)
N2—C27	1·315 (11)	C10—C11	1·512 (13)
N2—C28	1·474 (12)	C11—C12	1·536 (12)
N2—C31	1·479 (11)	C13—C14	1·495 (13)
N3—C17	1·355 (11)	C14—C15	1·492 (13)
N3—C18	1·470 (12)	C15—C16	1·530 (12)
N3—C19	1·467 (11)	C16—C17	1·562 (12)
N4—N5	1·374 (10)	C19—C20	1·553 (12)
N4—C12	1·351 (10)	C19—C27	1·513 (13)
N4—C16	1·472 (11)	C20—C21	1·456 (12)
N5—C13	1·282 (11)	C28—C29	1·501 (15)
N6—N7	1·400 (9)	C29—C30	1·493 (17)
N6—C7	1·357 (10)	C30—C31	1·531 (14)
N6—C11	1·461 (11)	C31—C32	1·553 (12)
N7—C8	1·222 (14)	C33—C34	1·507 (14)
N8—C1	1·320 (11)	C34—C35	1·540 (14)
N8—C2	1·477 (11)		

C32—N1—C33	120·2 (7)	O4—C12—C11	119·2 (8)
C27—N2—C28	126·6 (8)	N4—C12—C11	118·0 (8)
C27—N2—C31	120·8 (8)	N5—C13—C14	125·5 (9)
C28—N2—C31	111·1 (8)	C13—C14—C15	112·4 (8)
C17—N3—C18	123·5 (8)	C14—C15—C16	112·3 (8)
C17—N3—C19	119·1 (7)	N4—C16—C15	108·8 (7)
C18—N3—C19	117·1 (8)	N4—C16—C17	107·6 (7)
N5—N4—C12	117·1 (7)	C15—C16—C17	111·7 (7)
N5—N4—C16	124·2 (7)	O3—C17—N3	122·8 (9)
C12—N4—C16	118·7 (7)	O3—C17—C16	119·8 (9)
N4—N5—C13	118·4 (8)	N3—C17—C16	117·3 (8)
N7—N6—C7	116·2 (7)	N3—C19—C20	110·8 (7)
N7—N6—C11	124·9 (7)	N3—C19—C27	110·5 (7)
C7—N6—C11	118·2 (7)	C20—C19—C27	110·2 (8)
N6—N7—C8	116·4 (9)	C19—C20—C21	113·9 (8)
C1—N8—C2	123·4 (7)	C20—C21—C22	121·2 (9)
S—C1—N8	125·1 (7)	C20—C21—C26	121·9 (9)
S—C1—C33	119·3 (7)	O2—C27—N2	120·7 (9)
N8—C1—C33	115·5 (7)	O2—C27—C19	120·4 (9)
N8—C2—C3	109·2 (7)	N2—C27—C19	119·0 (9)
N8—C2—C7	104·3 (7)	N2—C28—C29	103·3 (9)
C3—C2—C7	112·6 (7)	C28—C29—C30	107·2 (10)
C2—C3—C4	112·9 (8)	C29—C30—C31	102·2 (9)
C2—C3—C5	110·8 (8)	N2—C31—C30	103·2 (8)
C4—C3—C5	111·1 (9)	N2—C31—C32	114·5 (7)
C3—C5—C6	112·0 (9)	C30—C31—C32	112·5 (9)
O5—C7—N6	120·2 (8)	O1—C32—N1	124·1 (8)
O5—C7—C2	122·1 (8)	O1—C32—C31	122·2 (9)
N6—C7—C2	117·6 (7)	N1—C32—C31	113·6 (8)
N7—C8—C9	125·3 (11)	N1—C33—C1	112·8 (8)
C8—C9—C10	113·8 (14)	N1—C33—C34	110·6 (8)
C9—C10—C11	118·3 (11)	C1—C33—C34	114·9 (8)
N6—C11—C10	111·6 (7)	C33—C34—C35	114·5 (9)
N6—C11—C12	107·5 (7)	C34—C35—C36	121·7 (9)
C10—C11—C12	110·2 (8)	C34—C35—C40	120·8 (10)
O4—C12—N4	122·8 (9)		

(1). Examination of the Cambridge Structural Database (CSD) (Allen, Kennard & Taylor, 1983) shows entries for 27 cyclic hexapeptides containing no metal ions or other charged species. Unfortunately none of the cyclic hexapeptides in the CSD contain a thioamide group but extending the search revealed a few (seven) structures of acyclic thioamide-containing species and these structures were included with the cyclic hexapeptide molecules extracted from the database. The relevant geometrical parameters for the thioamide compounds, (1) and the mean values for the parameters of the cyclic hexapeptides are presented in Table 3. The C—S bond in (1) is 1·674 (5) Å, which is at the long end of the range of values (1·63–1·67 Å) that has been observed in other thioamides. The Phe-ψ(CS—NH)-Ile peptide bond (C1—N8) is 1·320 (6) Å which compares closely to the 1·34 (2) Å found as the mean value in 222 observations of the cyclic hexapeptides drawn from the CSD. As is shown by the values in Table 3, there is no apparent correlation between C—S bond length and C—N (peptide) bond length nor is the angle at the sp^2 C significantly changed between a standard amide and a sulfur-containing species. The two torsion angles involving the backbone at the thioamide are ω and ψ and they have values of $-177{\cdot}6$ and 2·1°, respectively. These values indicate that the Phe-ψ(CS—NH)-Ile peptide linkage is flat (ω) and that the Phe-ψ(CS—NH) residue has adopted a conformation (ψ) which staggers the substituents on C33 relative to the C=S bond. Very similar values are observed in the structures found in the CSD, although the range of ψ is quite broad in these compounds (approximately 35° either side of two clustering points of 0 and 150°). These observations, as summarized in Table 3, support the conclusion that the presence of a thioamide instead of an amide makes essentially no difference to the bonding parameters of an amino-acid residue (except, of course, the C=*X* double-bond length).

In addition to the actual bond lengths and angles of the thioamide-containing residue it is possible that the presence of the S atom may restrict the torsion angles available to the backbone atoms in order to prevent steric crowding of the S atom. Interestingly, in the 27 cyclic hexapeptides found in the CSD, the 18-membered macrocycle is relatively flat except when the presence of several proline residues serves to restrict the molecule conformationally. Thus the unique molecular conformation of (1) in which the plane formed by atoms C31—C32—N1—C33—C1—N8—C2 is nearly perpendicular to the plane of

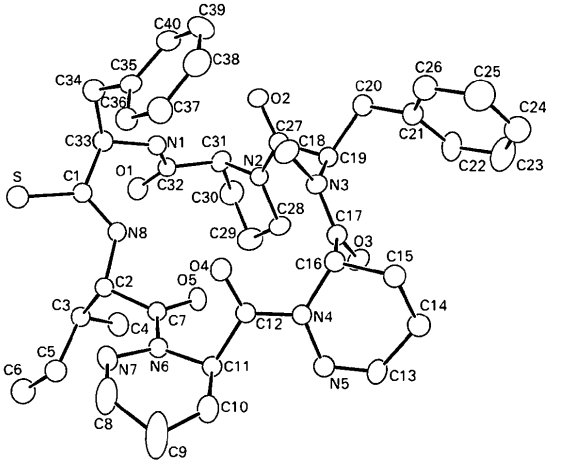
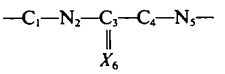


Fig. 1. Perspective view of the molecule with 20% probability ellipsoids. The H atoms have been omitted for clarity.

Table 3. *Selected geometrical parameters of peptide fragments*



	Distances (Å)			Angles (°)		
	$C_3{=}X_6$	$N_2{-}C_3$	$C_3{-}C_4$	$N_2{-}C_3{-}C_4$	ψ^a	ω^a
X = S species						
(1)[b]	1·674	1·320	1·532	115·5	2·1	−177·6
CEVNUM10[c]	1·630	1·330	1·519	115·6	−26·2	−176·4
CEVNUM10	1·639	1·344	1·507	115·6	28·2	179·3
DIDYEU	1·663	1·321	1·532	116·5	−26·2	179·4
DIDYIY	1·663	1·312	1·520	116·8	−28·9	−175·5
FEVBEN	1·655	1·302	1·537	115·0	6·8	−179·1
FEVBEN	1·649	1·330	1·511	113·0	−168·5	−178·4
FUSMIP	1·664	1·320	1·511	113·2	154·2	169·0
IMTYBA	1·671	1·332	1·549	119·5	43·2	−178·6
TCEITZ	1·665	1·339	1·553	119·4	36·2	−177·3
X = O species						
Means[d]	1·231 (20)	1·339 (20)	1·524 (20)	116·9 (23)	*e*	*e*

Notes: (*a*) The ψ and ω torsion angles are defined as $N_2{-}C_3{-}C_4{-}N_5$ and $C_1{-}N_2{-}C_3{-}C_4$ respectively. (*b*) This work. (*c*) CEVNUM10 (Hansen, Clausen & La Cour, 1987). DIDYEU and DIDYIY: (Jensen, Lawesson, Bardi, Piazzesi, & Toniolo 1985). FEVBEN (Hansen, Clausen & La Cour, 1987). FUSMIP (Bardi, Piazzesi, Toniolo, Jensen, Andersen & Senning, 1988). IMTYBA (Schaumann, Kausch, Klaska, Klaska & Jarchow, 1977). TCEITZ (Schmid, Heimgartner, Schmid & Oberhansli, 1976). (*d*) Mean values for parameters of 222 residues in 27 cyclic hexapeptides. Standard deviations of the samples are given in parentheses. (*e*) Mean values of torsion angles are meaningless but a histogram of the distribution shows a strong preference for ψ to be 0 ± 40 or $\pm(150\pm30)°$ while ω prefers to be near 0 or 180°.

Table 4. *(φ and ψ) angles (°) for -Pro-Phe-X-peptide fragments*

	ψ-Pro	ψ-Phe	ψ-X	φ-Pro	φ-Phe	φ-X
CYBGPP[a]	133·79	−8·65	−161·82	−56·34	100·32	165·34
CYBGPP	130·64	−19·07	−163·79	−71·55	112·21	178·42
CYCAPP	122·48	9·01	171·74	−60·45	78·72	−156·63
DUYTIA	−25·31	−5·99	143·38	−63·78	−116·00	−166·59
DUYTIA	−130·50	18·22	177·73	61·14	−91·35	−130·47
GAJDUQ	−121·90	2·91	175·70	60·69	−84·43	−126·99
GAJFAY	−117·98	−3·29	170·56	61·95	−82·80	−118·18
GAJFAY	−120·52	9·54	−174·84	57·94	−95·34	−131·12
(1)[b]	50·45	2·11	142·70	−89·92	81·67	−156·6

Notes: (*a*) CYBGPP (Brown & Yang 1979). CYCAPP (Brown & Teller, 1976). DUYTIA (Kessler, Klein, Wagner, Bats, Ziegler & Frimmer, 1986). GAJDUQ and GAJFAY (Kessler, Bats, Griesinger, Koll, Will & Wagner, 1988). (*b*) This work.

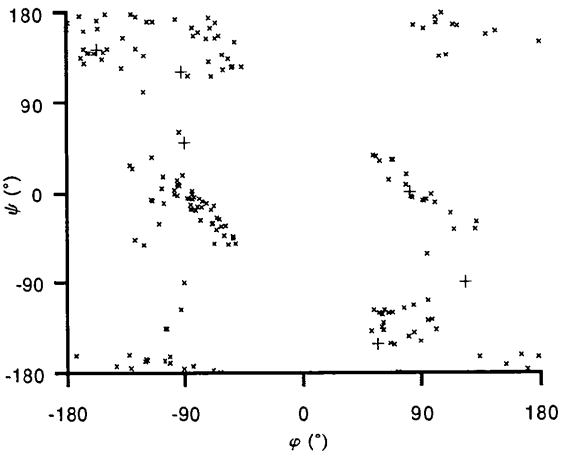


Fig. 2. A Ramachandran plot of the φ and ψ angles for all residues of 27 cyclic hexapeptides selected from the CSD (×) and the residues in (1) (+).

the other 11 backbone atoms seems to imply that the presence of a thioamide has changed the conformational energetics. A sulfur atom is considerably larger than an O atom; the C—S bond is about 0·43 Å longer than the corresponding C—O bond and the van der Waals radius of an S atom is about the same amount larger than that of an O atom. Thus it would be expected that an S atom will impose a geometry which allows it to be in a larger pocket than that needed by an O atom while still (as shown by the observed bond distances and angles) maintaining normal peptide geometry. Indeed, in (1) the sulfur atom of the thioamide is pointing out and away from the ring of the macrocycle whereas the O atoms are pointing above, below or into the plane of the macrocycle and the closest non-bonded distances from S to atoms at least three bonds away range from 3·10 to 3·57 Å. In contrast, similar non-bonded distances involving the O atoms of the molecule range from 2·65 to 2·92 Å. If a plot of φ and ψ torsion angles is constructed for each residue of the molecules selected from the CSD and for (1) (Fig. 2) then it is seen that the φ and ψ values for (1) all fall in areas also populated by the cyclic hexapepties (with the possible exception of 123, −89° for residue 5, MePhe, which is slightly displaced from the two nearby clusters). However, if the individual φ and ψ angles are examined for all -Pro-Phe-X sequences (Table 4) then we see that the ψ angle for Pro is unusual at 50·45°. Indeed, if this analysis is extended to all prolines in peptides available from the CSD it is seen that the most probable proline ψ angle is either $\simeq +140$ or $\simeq -20°$ with any angle between 10 and 100° being very rare (three examples in 194 observations). Thus it is possible that the presence of the thioamide forces the proline residue to adopt an unusual geometry thereby resulting in the observed bent geometry of the macrocycle. In order to make a more detailed structural comparison attempts are underway to try and crystallize the molecule in which the thioamide is replaced by a regular amide, but to date these efforts have been unsuccessful.

The two 2,3,4,5-tetrahydropyridazine moieties have their six-membered rings in envelope (C_s) conformations although the atom which is out of the plane is different for the two rings (C9 of Thp-4 and C15 of Thp-5). The proline residue also has its ring in a C_s conformation and in this case C30 is 0·53 Å out of the plane of the other four atoms of the ring.

All six peptide linkages are *trans* and essentially planar (ω angles deviate from planarity by from 0·9

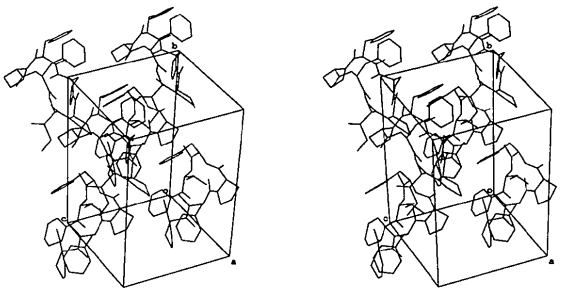


Fig. 3. Stereoview of the molecular packing around a unit cell. The view selected shows more than the contents of a single unit cell.

to 12·9°) with no unusual bond lengths or angles. The χ_1 angles for Ile and the two Phe residues have values indicating standard staggered conformations for the side-chain substituents.

A packing diagram is shown in Fig. 3. There are no intermolecular distances shorter than 3·35 Å and thus no hydrogen bonding between molecules. While this lack of hydrogen bonding is unusual it is not unique and because only N1 and N8 have suitable protons and these are both pointing into the macrocycle it is not that surprising that there are no intermolecular hydrogen bonds. As is evident from the packing diagram there are no apparent stacking interactions of unsaturated systems either and thus it is presumed that only weak van der Waals interactions are present in the crystal structure.

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Conformation of 1-*p*-Fluorophenyl-3,5-bis(iodomethyl)piperidine

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Abstract. $C_{13}H_{16}FI_2N$, $M_r = 459{\cdot}14$, monoclinic, $P2_1/n$, $a = 16{\cdot}771$ (3), $b = 8{\cdot}522$ (2), $c = 10{\cdot}782$ (2) Å, $\beta = 103.18$ (2)°, $V = 1500$ (1) Å^3, $Z = 4$, $D_x = 2{\cdot}02$ Mg m^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, $\mu = 4{\cdot}2$ mm^{-1}, $F(000) = 864$, $T = 293$ K, $R = 0{\cdot}048$ for 2377 independent observed reflections. The piperidine ring adopts a chair conformation with the three substituent groups in equatorial positions. The N—C(aryl) bond is inclined at 42·6 (7)° to the C(2)—N(1)—C(6) plane of the piperidine. The torsion angles in the piperidine ring are 53·4–60·2 (6)°, with the largest angles adjacent to N(1) and the smallest adjacent to C(4).

Introduction. Lone pairs of electrons strongly influence the conformational properties of heterocyclic

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