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Structure of (3*S*,9*S*)-1,7-Diazatricyclo[7.3.0.0^{3,7}]dodecane-2,8-dithione [*cyclo*(-Prot-Prot-)]

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Abstract. $C_{10}H_{14}N_2S_2$, $M_r = 226{\cdot}36$, orthorhombic, $P2_12_12_1$, $a = 6{\cdot}258$ (1), $b = 8{\cdot}671$ (1), $c = 20{\cdot}255$ (3) Å, $V = 1099{\cdot}2$ (5) Å^3, $Z = 4$, $D_x = 1{\cdot}368$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 4{\cdot}02$ mm^{-1}, $F(000) = 480$, $T = 295$ K, final $R = 0{\cdot}036$ for 1258 unique observed reflections. The 2,5-piperazinedithione ring assumes a boat conformation while the two pyrrolidine rings have an envelope shape. The molecule shows approximate C_2 symmetry with the twofold rotation axis perpendicular to the mean plane of the 2,5-piperazinedithione ring.

Introduction. The geometry of the *Z* thioamide unit and of its environment in peptides is known from X-ray crystallographic data on linear endothiopeptide models (La Cour, Hansen, Clausen & Lawesson, 1983; Jensen, Lawesson, Bardi, Piazzesi & Toniolo, 1985). This paper reports the crystal structure of *cyclo*(-L-thioprolyl-L-thioprolyl-) (I), the thionated analogue of proline-diketopiperazine [*cyclo*(-L-Pro-L-Pro-)] (Benedetti, Goodman, Marsh, Rapoport & Musich, 1975), featuring *E* amide groups.

Lawesson's reagent (Cava & Levinson, 1985) was used to convert *cyclo*(-L-Pro-L-Pro-) into its dithioamide derivative. This method (2 h heating at 363–373 K in dry toluene at a 2:1 amide-to-reagent ratio) was reported (Clausen, Thorsen & Lawesson, 1981; Kajtár, Hollósi, Kajtár & Majer, 1986) to result in protected endothiopeptide derivatives in high yields and without racemization.

A violet-coloured crystal (sample *A*) of the title compound was used first in an attempt to determine its crystal structure. The symmetry class of this compound was found to be monoclinic. No appropriate description for the unique space group could be obtained, however. A set of intensity data (1065 reflections, cell data are 8·340, 5·888, 11·500 Å, $\beta = 102{\cdot}72°$) were measured for sample *A* assuming space group $P2_1/c$ initially, which was subsequently complemented by $P2_1$. Reasonable structural models were obtained in both space groups which did not differ significantly ($R = 0{\cdot}07$ and 0·065, respectively). Both of these models featured statistical disorder. Refinement of the models obtained for alternative space groups *P*2, *P*2/*c*, and *Pc* added to the confusion as to the true space group of this crystal. One could reasonably suppose that an internal twofold molecular symmetry is coinciding with crystallographic ones, still not excluding the possibility of conformational disorder.

All these problems could also be assigned to the existence of co-crystallized enantiomorphous pairs in sample *A*. Thus, it became imperative to clarify the optical purity of these crystals. Circular dichroism, ^{1}H and ^{13}C NMR studies also showed that sample *A* contained *ca* 20% enantiomeric (D, D) but no diastereoisomeric (L, D) form, and this unexpected double-racemization was found to take place during the thionation at elevated temperature (Majer, Hollósi, Kajtár, Kajtár & Radics, 1987). The exclusive formation of the enantiomeric side product is due to the known fact that a diketopiperazine ring cannot be formed from two proline or dehydroproline residues of opposite configuration (Karle, Ottenheym & Witkop, 1974).

Experimental. Optically pure *cyclo*(-L-thioprolyl-L-thioprolyl-) (I) was obtained by 4–6 h thionation in dry toluene at room temperature (<303 K). The solvent was distilled off at reduced pressure and the solid residue was dissolved in a small volume of dimethylformamide below 313 K. On addition of a few drops of water, blue crystals began to separate. The optical purity was checked by CD spectroscopy (Majer *et al.*, 1987). After the third crystallization, no further increase of the magnitude of the CD bands could be observed. (This was sample *B*.) M.p. 522–523 K, analysis calculated for C 53·06, H 6·23, N 12·38, S 28·33%, found C 53·28, H 6·25, N 12·40, S 27·66%. A crystal of size 0·20 × 0·27 × 0·30 mm was mounted on a CAD-4 diffractometer equipped with graphite monochromator using Cu $K\alpha$ ($\lambda = 1{\cdot}54184$ Å). Lattice

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Table 1. *Fractional coordinates and B_{eq} or B_{iso} (Å^2) for all atoms, with e.s.d.'s in parentheses*

$B_{eq} = \frac{4}{3}$trace (**B.G**), where **G** is the direct metric tensor.

	x	y	z	B_{eq}/B_{iso}
S(1)	0·7903 (1)	0·99472 (8)	0·51317 (2)	5·25 (2)
S(2)	0·2106 (1)	1·29141 (8)	0·72429 (3)	5·15 (2)
N(1)	0·6936 (2)	1·2107 (2)	0·60010 (8)	3·50 (6)
C(2)	0·6713 (3)	1·0671 (2)	0·57951 (9)	3·34 (6)
C(3)	0·5329 (3)	0·9679 (2)	0·62255 (9)	3·43 (7)
C(4)	0·4002 (5)	0·8438 (2)	0·5884 (1)	5·1 (1)
C(5)	0·2249 (5)	0·8090 (3)	0·6377 (1)	5·8 (1)
C(6)	0·1729 (3)	0·9641 (3)	0·6675 (1)	4·74 (9)
N(7)	0·3685 (2)	1·0553 (2)	0·65838 (8)	3·43 (5)
C(8)	0·3929 (3)	1·1986 (2)	0·67940 (9)	3·30 (6)
C(9)	0·6046 (3)	1·2709 (2)	0·66257 (8)	3·28 (6)
C(10)	0·6001 (4)	1·4446 (2)	0·6496 (1)	4·42 (8)
C(11)	0·8001 (4)	1·4712 (2)	0·6085 (1)	5·2 (1)
C(12)	0·8190 (4)	1·3279 (3)	0·5657 (1)	4·9 (1)
H(3)	0·640 (3)	0·921 (2)	0·648 (1)	4·9 (6)
H(4*a*)	0·481 (4)	0·758 (3)	0·581 (1)	6·1 (7)
H(4*b*)	0·345 (4)	0·875 (3)	0·546 (1)	4·7 (6)
H(5*a*)	0·273 (5)	0·743 (3)	0·670 (1)	6·8 (8)
H(5*b*)	0·089 (7)	0·764 (3)	0·615 (1)	8·5 (8)
H(6*a*)	0·141 (4)	0·955 (3)	0·714 (1)	5·9 (7)
H(6*b*)	0·051 (5)	1·019 (4)	0·643 (1)	6·5 (7)
H(9)	0·702 (4)	1·243 (2)	0·698 (1)	4·2 (5)
H(10*a*)	0·467 (4)	1·470 (3)	0·625 (1)	5·7 (6)
H(10*b*)	0·605 (4)	1·495 (3)	0·686 (1)	4·8 (6)
H(11*a*)	0·917 (6)	1·479 (3)	0·637 (1)	5·9 (6)
H(11*b*)	0·788 (5)	1·570 (3)	0·583 (1)	6·0 (7)
H(12*a*)	0·962 (5)	1·303 (3)	0·561 (1)	6·8 (8)
H(12*b*)	0·775 (5)	1·344 (3)	0·520 (1)	6·5 (7)

Table 2. *Bond lengths* (Å) *and angles* (°)

S(1)–C(2)	1·659 (2)	C(4)–C(5)	1·514 (5)
S(2)–C(8)	1·666 (2)	C(5)–C(6)	1·510 (4)
N(1)–C(2)	1·321 (3)	C(6)–N(7)	1·470 (3)
N(1)–C(9)	1·478 (3)	N(7)–C(8)	1·322 (3)
N(1)–C(12)	1·461 (3)	C(8)–C(9)	1·505 (3)
C(2)–C(3)	1·500 (3)	C(9)–C(10)	1·529 (3)
C(3)–C(4)	1·525 (4)	C(10)–C(11)	1·520 (4)
C(3)–N(7)	1·469 (3)	C(11)–C(12)	1·520 (4)
C(2)–N(1)–C(9)	124·3 (3)	C(3)–N(7)–C(6)	111·6 (3)
C(2)–N(1)–C(12)	124·2 (3)	C(3)–N(7)–C(8)	124·3 (3)
C(9)–N(1)–C(12)	111·4 (3)	C(6)–N(7)–C(8)	124·1 (3)
S(1)–C(2)–N(1)	124·4 (3)	S(2)–C(8)–N(7)	123·4 (3)
S(1)–C(2)–C(3)	120·9 (3)	S(2)–C(8)–C(9)	121·7 (3)
N(1)–C(2)–C(3)	114·7 (3)	N(7)–C(8)–C(9)	114·8 (3)
C(2)–C(3)–C(4)	117·1 (3)	N(1)–C(9)–C(8)	112·2 (3)
C(2)–C(3)–N(7)	113·3 (3)	N(1)–C(9)–C(10)	102·0 (3)
C(4)–C(3)–N(7)	102·0 (3)	C(8)–C(9)–C(10)	115·7 (3)
C(3)–C(4)–C(5)	103·7 (4)	C(9)–C(10)–C(11)	103·2 (3)
C(4)–C(5)–C(6)	104·0 (4)	C(10)–C(11)–C(12)	104·6 (4)
C(5)–C(6)–N(7)	104·5 (4)	N(1)–C(12)–C(11)	104·8 (4)

parameters were obtained by least-squares fit for 25 reflections in the range $35 \le \theta \le 40°$. One octant ($0 \le h \le 7$, $0 \le k \le 11$, $0 \le l \le 25$) of independent reflections was measured by the use of an ω–2θ scan [scan range: $0·17 \le (\sin\theta)/\lambda \le 0·75$ Å^{-1}], 1258 taken as observed with $I \ge 2\sigma(I)$, 186 unobserved reflections. Three standard reflections (514, 3,1,12 and 1,12,14) were measured every hour, but no intensity variation was detected. Structure solved by direct methods (*MULTAN*82; Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1982) using 172 $E \ge 1·47$. Full-matrix least squares, $\sum w(\Delta F^2)$ minimized, 127 parameters refined. At the end of isotropic refinement an empirical absorption correction was performed (Walker & Stuart, 1983); the relative transmission coefficients ranged from 0·691 to 1·275 (mean value 0·982). Positions of H atoms were generated from assumed geometries and they were treated isotropically in two least-squares cycles before the final refinement of the heavy atoms was performed. Final $R = 0·036$, $wR = 0·056$, $R_{tot} = 0·037$, $S = 1·35$, $w = 4F_o^2/\sigma^2(F_o^2)$, $(\Delta/\sigma)_{max} = 0·05$. The highest peak in the final $\Delta\rho$ map was 0·15 (5) e Å^{-3}. Scattering factors were taken from *International Tables for X-ray Crystallography* (1974). Programs applied: Enraf–Nonius *SDP-Plus* (Frenz, 1983), *PLUTO* (Motherwell & Clegg, 1978) and local programs, PDP 11/34 minicomputer (128 Kw).

Discussion. The atomic coordinates are listed in Table 1.* The bond distances and bond angles are given in Table 2. They agree within experimental error with the corresponding values found in *cyclo*(-L-Pro-L-Pro-) (Benedetti *et al.*, 1975), *cyclo*(-L-Pro-L-Leu-) (Karle, 1972) and *cyclo*(-L-Pro-Gly-) (Von Dreele, 1975). As in the structure of *cyclo*(-L-Pro-L-Pro-) the molecule (Fig. 1) also exhibits approximate C_2 symmetry with the twofold axis perpendicular to the mean plane of the 2,5-piperazinedithione ring. As shown by the torsion angles ω in Table 3, the 2,5-piperazinedithione ring assumes a boat conformation. The two thioamide groups are nearly planar, with the largest deviation being 0·021 Å, and make a dihedral angle of 150·5 (1)°. Like the oxygen-containing models, both pyrrolidine rings have an envelope shape with N_i, C_i^α, C_i^γ and C_i^δ in a plane (within ±0·016 Å) and C_i^β on the flap ($\Delta = 0·57$ and 0·56 Å, respectively; *cf.* Table 3).

* Lists of structure factors, anisotropic thermal parameters and torsion angles have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44259 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

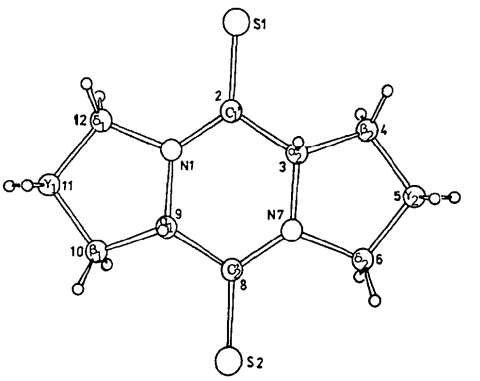

Fig. 1. Perspective view of the molecule with atomic labelling. The bare numbers are for carbon unless indicated otherwise. H atoms are shown but not labelled.

Table 3. *Torsion angles (°) of proline-containing diketopiperazines*

IUPAC designation	Atoms involved	*cyclo*-(-L-Prot-L-Prot-)*	*cyclo*-(-L-Pro-L-Pro-)	*cyclo*-(-L-Pro-L-Leu-)†	*cyclo*-(-L-Pro-Gly-)†
φ	$C_i'C_i^{\alpha}N_iC_{i+1}'$	−34·8 −32·4	−38 −37	−41·5	−44·0
ψ	$N_{i+1}C_i'C_i^{\alpha}N_i$	30·6 28·4	37 36	33·7	38·5
ω	$C_{i+1}^{\alpha}N_{i+1}C_i'C_i^{\alpha}$	1·3 4·1	0·7 −0·7	6·3	0·4
χ_1	$N_iC_i^{\alpha}C_i^{\beta}C_i^{\gamma}$	−35·8 −35·0	−34 −31	−31·5	−32·7
χ_2	$C_i^{\alpha}C_i^{\beta}C_i^{\gamma}C_i^{\delta}$	35·6 37·3	36 35	36·0	35·6
χ_3	$C_i^{\beta}C_i^{\gamma}C_i^{\delta}N_i$	−21·1 −24·5	−23 −24	−25·1	−24·0
χ_4	$C_i^{\gamma}C_i^{\delta}N_iC_i^{\alpha}$	−2·0 2·3	1 5	4·5	3·2
d_1		0·57 0·56	0·55 0·52	0·52	0·55
d_2		150·5	142	143	—

d_1 = the normal distance (Å) of the β-carbon atoms from the best plane formed by the remaining four atoms of the pyrrolidine ring.
d_2 = dihedral angle (°) between the two nearly planar amide groups.

* E.s.d.'s 0·3° for torsion angles.
† Torsion angles of the proline residues.

Close similarity of the critical C—C′ and C—N bond lengths in *cyclo*(-Prot-Prot-) and in the proline-diketopiperazines does not explain the enhanced tendency towards racemization in the course of thionation.

The similarity of the geometry between *cyclo*-(-Prot-Prot-) and related *Z* endothiopeptides (La Cour *et al.*, 1983; Jensen *et al.*, 1985) indicates no major difference in the conformation of the respective amide groups. This suggests that the thioamide unit can serve as a special 'label' in both spectroscopic and biological studies.

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The Structure of 3′-Deoxyformycin Hydrochloride

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Abstract. $C_{10}H_{14}N_5O_3^+.Cl^-$, $M_r = 287{\cdot}71$, orthorhombic, $P2_12_12_1$, $a = 5{\cdot}047\ (1)$, $b = 13{\cdot}850\ (2)$, $c = 18{\cdot}321\ (3)$ Å, $V = 1280{\cdot}7$ Å^3, $Z = 4$, $D_x = 1{\cdot}492$ Mg m^{-3}, $\lambda(\text{Cu } K\alpha) = 1{\cdot}54184$ Å, $\mu = 2{\cdot}8071$ mm^{-1}, $F(000) = 600$, $T = 298$ K, final $R = 0{\cdot}039$ for 1333 observed reflections. Formycin hydrochloride

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