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(3R,6R)-3-Benzyl-8-thia-1,4-diazabicyclo[4.3.0]nonane-2,5-dione, $C_{13}H_{14}N_2O_2S$

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Abstract. $M_r = 262\cdot3$, orthorhombic, $P2_12_12_1$, $Z = 8$, $a = 9\cdot256\,(2)$, $b = 10\cdot154\,(2)$, $c = 27\cdot420\,(8)$ Å, $D_c = 1\cdot352$ Mg m^{-3}. $R_w = 0\cdot039$ for 1546 reflections with $I > 2\cdot5\sigma(I)$, out of 3190 independent measurements. The benzyl group is a (pseudo-)axial substituent on the diketopiperazine ring and is folded above this ring in such a way that the overall distance is equal to the sum of the van der Waals values. The piperazine ring has a boat-like form. The molecules in the crystal occur as dimers formed through two hydrogen bridges. The geometry of the compound, also called *cyclo*|-D-Phe-L-(γS)Pro-|, is compared to *cyclo*(-D-Phe-L-Pro-).

Introduction. The title compound, shown in Fig. 1, contains the 2,5-diketopiperazine moiety (abbreviated DKP) and is a cyclic dipeptide composed of D-phenylalanine and L-γ-thiaproline, known as *trans-cyclo*|-D-Phe-L-(γS)Pro-|. It belongs to a group of compounds which show interesting biological and medical properties. Due to the restrictions brought about by the DKP ring in combination with the rigidity of the cyclic proline residue it is an attractive model compound in
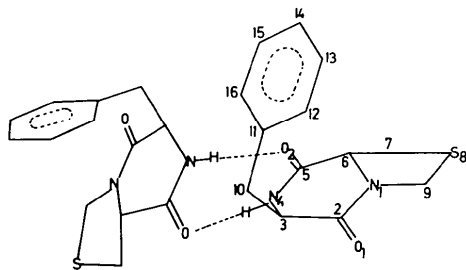
which to study side chain/side chain and side chain /backbone interactions (Ramani, Sasisekharan & Venkatesan, 1977; Anteunis, 1978). NMR spectra in CD₃OD had indicated a strong preference for a rotameric state in which the benzene ring is folded above the DKP ring (Schrooten, 1981). The amount of folded conformers seemed to be coupled to the concentration and to the amount of association through hydrogen bonding resulting in either long polymeric chains or dimers. The X-ray determination is one of a series, the results of which should be useful in the interpretation of NMR spectra and chemical activity.

Experimental. 3190 independent reflections $(0 \le \theta \le 27°)$, room temperature, Enraf–Nonius CAD-4 diffractometer, Zr-filtered Mo radiation; absorption correction omitted because of the small size of the crystal $(0\cdot1 \times 0\cdot2 \times 0\cdot2$ mm) and the low absorption coefficient $(\mu = 0\cdot25$ mm$^{-1})$; structure solved with *MULTAN* (Germain, Main & Woolfson, 1971) and refined by a block-diagonal least-squares procedure; each reflection given a weight based on counting statistics; H atoms kept at their expected sites; their Debye–Waller temperature parameter was fixed at 5 Å², the value of the overall B in the Wilson plot; weighted R value converged to $0\cdot039$. The largest shift in the last cycle was 10% of the corresponding e.s.d.; the highest maximum in the final difference Fourier map was $0\cdot2$ e Å^{-3}. Relevant parameters* are listed in Table 1, the numbering of the atoms is given in Fig. 1.

Fig. 1. Structural formula, conformation and numbering of atoms.

Table 1. *Positional parameters in fractions of cell edges and isotropic temperature factors* ($Å^2$)

The e.s.d.'s given in parentheses refer to the last significant digit. Isotropic temperature factors are calculated from anisotropic temperature parameters assuming equal volume of the 50% probability region. All anisotropic thermal parameters were physically acceptable. B_{iso} was calculated according to Lipson & Cochran (1966): $B_{iso} = 8\pi^2(U_{11}^o\ U_{22}^o\ U_{33}^o)^{1/3}$.

	Molecule (I)				Molecule (II)			
	x	y	z	B_{iso}	x	y	z	B_{iso}
O(1)	0.6911 (5)	0.3080 (5)	0.8337 (2)	4.79	0.5227 (5)	0.5466 (4)	0.5803 (1)	4.84
O(2)	1.0831 (5)	0.5861 (4)	0.9323 (1)	4.72	0.8219 (5)	0.2012 (4)	0.6865 (1)	5.08
N(1)	0.8014 (5)	0.3540 (4)	0.9055 (1)	3.37	0.5761 (5)	0.4589 (4)	0.6533 (1)	3.39
C(2)	0.7709 (7)	0.3780 (5)	0.8577 (2)	4.06	0.6000 (7)	0.4793 (5)	0.6058 (2)	3.85
C(3)	0.8389 (7)	0.4986 (5)	0.8360 (2)	3.88	0.7368 (1)	0.4178 (1)	0.5850 (1)	3.26
N(4)	0.9656 (5)	0.5447 (4)	0.8623 (1)	3.44	0.7869 (5)	0.3086 (4)	0.6141 (1)	4.03
C(5)	0.9833 (1)	0.5288 (1)	0.9102 (1)	3.74	0.7660 (1)	0.2923 (1)	0.6620 (1)	3.89
C(6)	0.8835 (1)	0.4384 (1)	0.9361 (1)	3.12	0.6696 (6)	0.3907 (5)	0.6884 (2)	3.22
C(7)	0.9651 (7)	0.3472 (5)	0.9708 (2)	3.91	0.5670 (7)	0.3236 (5)	0.7231 (2)	3.60
S(8)	0.8387 (2)	0.2180 (2)	0.9846 (1)	4.89	0.4326 (1)	0.4456 (1)	0.7352 (1)	5.18
C(9)	0.7405 (6)	0.2392 (5)	0.9284 (2)	4.59	0.4476 (7)	0.5169 (6)	0.6760 (2)	5.16
C(10)	0.7245 (7)	0.6069 (5)	0.8287 (2)	5.01	0.8550 (7)	0.5223 (5)	0.5788 (2)	4.25
C(11)	0.6569 (7)	0.6460 (5)	0.8770 (2)	4.80	0.8929 (1)	0.5930 (1)	0.6243 (1)	4.51
C(12)	0.7158 (8)	0.7450 (6)	0.9053 (2)	5.81	1.0001 (7)	0.5483 (6)	0.6556 (2)	5.94
C(13)	0.6570 (8)	0.7731 (6)	0.9510 (2)	7.08	1.0274 (1)	0.6099 (1)	0.6995 (1)	6.81
C(14)	0.5392 (8)	0.7055 (7)	0.9672 (2)	7.36	0.9506 (9)	0.7161 (7)	0.7126 (2)	7.13
C(15)	0.4785 (8)	0.6071 (7)	0.9364 (2)	7.72	0.8447 (1)	0.7634 (1)	0.6840 (1)	7.11
C(16)	0.5391 (7)	0.5797 (6)	0.8946 (2)	6.21	0.8173 (7)	0.7021 (5)	0.6382 (2)	5.36

Table 2. *Bond lengths* (Å) *and valence angles* (°) *of the two independent molecules in the title compound* (*columns A and B*) *and of cyclo*(-D-*Phe*-L-*Pro*-) (*column C*)

E.s.d.'s in bond distances are *ca* 0.01 Å, in valence angles *ca* 1°.

	A	B	C		A	B	C
N(1)–C(2)	1.36	1.34	1.331	C(7)–S(8)	1.80	1.79	1.529*
C(2)–O(1)	1.22	1.21	1.222	S(8)–C(9)	1.80	1.78	1.524*
C(2)–C(3)	1.50	1.52	1.518	C(9)–N(1)	1.44	1.46	1.468
C(3)–N(4)	1.45	1.44	1.454	C(13)–C(11)	1.52	1.48	1.503
C(3)–C(10)	1.54	1.53	1.541	C(11)–C(12)	1.38	1.39	1.382
N(4)–C(5)	1.33	1.34	1.330	C(12)–C(13)	1.39	1.38	1.392
C(5)–O(2)	1.25	1.26	1.235	C(13)–C(14)	1.36	1.34	1.396
C(5)–C(6)	1.48	1.52	1.508	C(14)–C(15)	1.42	1.34	1.364
C(6)–N(1)	1.42	1.47	1.457	C(15)–C(16)	1.30	1.42	1.369
C(6)–C(7)	1.53	1.51	1.525	C(16)–C(11)	1.37	1.36	1.395
O(1)–C(2)–C(3)	121	121	119.7	C(6)–N(1)–C(9)	116	113	110.8
N(1)–C(2)–O(1)	123	123	123.1	C(2)–N(1)–C(9)	119	119	122.0
N(1)–C(2)–C(3)	116	116	117.2	C(6)–C(7)–S(8)	105	104	102.9*
C(2)–C(3)–C(10)	110	111	110.0	C(7)–S(8)–C(9)	94	93	105.1*
C(2)–C(3)–N(4)	114	112	113.2	S(8)–C(9)–N(1)	106	107	104.6*
N(4)–C(3)–C(10)	113	111	112.4	C(3)–C(10)–C(11)	111	114	113.4
C(3)–N(4)–C(5)	123	126	127.0	C(10)–C(11)–C(12)	121	122	122.0
N(4)–C(5)–O(2)	121	124	123.8	C(10)–C(11)–C(16)	121	120	119.6
N(4)–C(5)–C(6)	118	118	117.3	C(12)–C(11)–C(16)	118	117	118.4
C(6)–C(5)–O(2)	121	118	118.9	C(11)–C(12)–C(13)	120	122	120.6
C(5)–C(6)–N(1)	115	110	113.8	C(12)–C(13)–C(14)	120	120	120.6
C(5)–C(6)–C(7)	111	112	114.8	C(13)–C(14)–C(15)	118	121	120.0
N(1)–C(6)–C(7)	105	105	102.0	C(14)–C(15)–C(16)	120	119	120.1
C(6)–N(1)–C(2)	125	128	126.8	C(15)–C(16)–C(11)	123	121	120.2

* S(8) replaced by C.

Discussion. Bond distances and valence angles are given in Table 2, torsion angles in Table 3. A comparison with *cyclo*(-D-phenylalanyl-L-prolyl-) (Ramani, Venkatesan, Marsh & Hu Kung, 1976) shows that both molecules are very similar.

The thiazolidine ring is close to a half-chair (pseudo C_2) form with a (pseudo-)twofold axis passing through C(9) and the center of C(6)–C(7). In contrast to the conclusion of Ramani *et al.* (1976) the observed torsion angles (Table 3) show the pyrrolidine ring of *cyclo*-(-D-Phe-L-Pro-) to have an almost identical conformation.

The DKP ring has a rather shallow boat-like conformation with atoms C(3) and C(6) outside the main plane. From the Cremer & Pople (1975) puckering coordinates (Table 3) it can be inferred that the conformation is between the true boat $^{3,6}B$ and the twist form $^3T_1$, using the notation proposed by Boeyens (1978). A parameter of interest to NMR spectroscopists is the angle between the C(3)C(2)N(1)C(6) and C(3)N(4)C(5)C(6) planes. We find 23 and 26 (2)° for the two molecules of *cyclo*[-D-Phe-L-(γS)Pro-] and 18 (1)° for *cyclo*(-D-Phe-L-Pro-). Similar values (20–22°) were observed for *cyclo*[-D-Phe-L-(γS)Pip-] (Van Poucke & Lenstra, 1982*a*) and for *cyclo*(-D-Phe-L-Pip-) (Van Poucke & Lenstra, 1982*b*).

Ramani *et al.* (1976) observed a difference in length of the two C=O bonds in *cyclo*(-D-Phe-L-Pro-), which was tentatively attributed to the effects of hydrogen bonding (see also Ramani & Venkatesan, 1973). A similar difference can be noted in the title compound. However, we are of the opinion that the effect, if real, has nothing to do with hydrogen bonding. No significant difference is observed in the dimeric *cyclo*-[-D-Phe-L-(γS)Pip-], whereas *cyclo*(-D-Phe-L-Pip-), in which N(4) is methylated rendering dimerization through hydrogen bonding impossible, shows an analogous difference in C=O lengths. The N(4)H$\cdots$O(2)(2 − *x*, $\frac{1}{2}$ + *y*, $\frac{3}{2}$ − *z*) hydrogen bridges in both crystallographically independent molecules in the title compound are 2.86 (1) Å.

Table 3. *Some torsion angles and Cremer–Pople ring-puckering parameters*

Columns A and B refer to the two crystallographically independent molecules in the title compound, column C refers to cyclo(-D-Phe-L-Pro-).

(a) Torsion angles (°). E.s.d.'s are about 2°. The sign convention of IUPAC (1974) is used. Values marked with an asterisk are where S(8) is replaced by C.

	DKP ring				1,3-Thiazolidine ring		
	A	B	C		A	B	C
N(1)–C(2)–C(3)–N(4)	21	23	16·6	N(1)–C(6)–C(7)–S(8)	−38	−44	−37·9*
C(2)–C(3)–N(4)–C(5)	−30	−28	−19·0	C(6)–C(7)–S(8)–C(9)	26	32	31·9*
C(3)–N(4)–C(5)–C(6)	12	5	2·8	C(7)–S(8)–C(9)–N(1)	−6	−11	−13·5*
N(4)–C(5)–C(6)–N(1)	15	20	14·9	S(8)–C(9)–N(1)–C(6)	−18	−14	−11·3*
C(5)–C(6)–N(1)–C(2)	−23	−25	−17·1	C(9)–N(1)–C(6)–C(7)	37	38	31·2
C(6)–N(1)–C(2)–C(3)	4	4	0·7				

(b) Ring-puckering parameters with e.s.d.'s calculated according to Norrestam (1981). The sequences N(1), C(2), C(3), N(4), C(5), C(6) and N(1), C(6), C(7), S(8), C(9) are used.

q_2 (Å)	0·30 (1)	0·33 (1)	0·23 (1)	q_2 (Å)	0·37 (1)	0·42 (1)	0·37 (1)
q_3 (Å)	0·03 (1)	0·01 (1)	0·01 (1)				
Q (Å)	0·30 (1)	0·33 (1)	0·23 (1)	Q (Å)	0·37 (1)	0·42 (1)	0·37 (1)
φ_2 (°)	133 (3)	124 (2)	121 (2)	φ_2 (°)	232 (2)	237 (2)	237 (2)
θ_2 (°)	83 (3)	88 (2)	88 (2)				

A pyramidal configuration around the peptide N atom in a number of dipeptides has been observed (Sletten, 1970; Pattabhi, Venkatesan & Hall, 1973, 1974; Van Poucke & Lenstra, 1982a,b). In the title compound, however, atom N(1) is insignificantly (ca 0·03 Å) outside the C(2)C(6)C(9) plane. Nor do we observe in the surrounding valence and torsion angles (e.g. Fig. 2a) signs of an appreciable deviation from sp^2-character.

The most prominent feature connected with the side chain/backbone interaction is the way the benzene ring is folded over the DKP ring (Fig. 1); it is characteristic for cyclic dipeptides containing tyrosyl or phenylalanyl residues. If the aromatic nucleus were to sit perfectly symmetrically over the DKP ring then, in the Newman projection around C(3)–C(10), the line C(10)–C(11) should bisect the projected angle C(2)–C(3)–N(4). Torsion angles C(11)–C(10)–C(3)–N(4), i.e. χ^1_{Phe} in the IUPAC–IUB (1970) notation, of about 63° should occur. Furthermore, in the Newman projection around C(10)–C(11) the torsion angles C(phenyl)–C(10)–C(11)–C(3), i.e. χ^2, should be 90°. Inspection of Fig. 2 shows that the aromatic ring is turned slightly over towards N(1)–C(2), but that the planes of the benzene and DKP rings are as parallel as the structure permits. The same conclusion follows from Fig. 3, which shows the distances of the center of the benzene ring to the atoms of the DKP ring. Fig. 3 also reveals that the folding is at a maximum, since all distances are close to the sum of the van der Waals radii of a benzene ring (1·85 Å) and a methylene group (2·0 Å). Comparison of the results of cyclo[-D-Phe-L-(γS)Pro-], the title compound, with those of cyclo(-D-Phe-L-Pro-) by Ramani et al. (1976) and with those of cyclo[-D-Phe-L-(γS)Pip-] and cyclo(-D-Phe-L-Pip-) by

Van Poucke et al. (1982a,b) shows surprisingly little variation in the 3-benzyl-DKP moieties. Apparently the geometry of this part is, at least in the solid state, not very sensitive to trans fusion to a five- or six-membered ring, to the introduction of a γ-S atom, or to the existence of dimers.
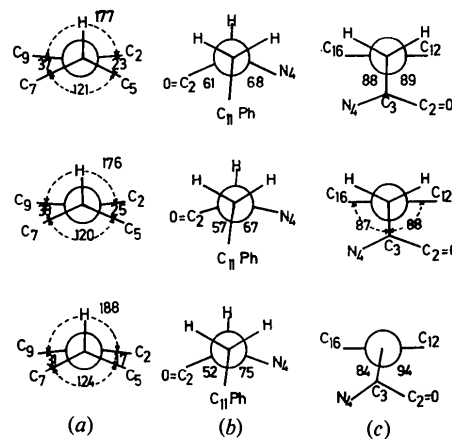

Fig. 2. Newman projections around (a) C(6)–N(1); (b) C(10)–C(3) and (c) C(10)–C(11) for the first molecule of the title compound (top line), the second molecule (middle line) and for cyclo(-D-Phe-L-Pro-) (last line).

	cyclo[-D-Phe-L-(γS)Pro-]		cyclo(-D-Phe-L-Pro-)
	mol I	mol II	
a	5·43	5·49	5·33
b	3·60	3·60	4·00
c	3·88	3·96	4·31
d	4·00	4·03	4·18
e	3·71	3·75	3·77
f	3·85	3·89	3·81
g	3·80	3·80	3·89

Fig. 3. Distances (Å) from the center of the aromatic nucleus to some atoms in the molecule.

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4-Methyl-N-8-quinolylbenzenesulphonamide, C16H14N2O2S. The Active Component of LIX 34

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Abstract. $M_r = 298.35$, triclinic, space group $P\bar{1}$, $a = 6.675$ (2), $b = 15.340$ (3), $c = 16.065$ (4) Å, $\alpha = 116.07$ (2), $\beta = 96.81$ (2), $\gamma = 97.92$ (2)°, $V = 1433.5$ (6) Å^3, $Z = 4$, $D_x = 1.38$ Mg m^{-3}, $F(000) = 624$, Mo $K\alpha$ radiation, $\lambda = 0.71069$ Å, $\mu = 0.23$ mm^{-1}. Final $R = 0.061$ for 1277 observed reflections $[I \geq 2.5\sigma(I)]$. The two molecules of the asymmetric unit are almost identical. The S atom has a distorted tetrahedral coordination.

Introduction. One of the most recent commercial chelating agents is LIX 34, a quinolylsulphonamide which has been used in industrial solvent-extraction processes to recover copper(II) (Kordosky, 1976).

4-Methyl-N-8-quinolylbenzenesulphonamide, with a similar structure to the active component in LIX 34, has been synthesized (Cox & Castresana, 1982). In this paper its crystalline structure is described.

Experimental. Colourless prismatic crystals grown from acetone; data collected from a crystal of approximately $0.4 \times 0.1 \times 0.1$ mm; cell parameters determined by least squares from the setting angles of 15 reflections; 3043 independent reflections measured with graphite-monochromated Mo $K\alpha$ radiation using ω scans up to $2\theta = 42°$; one standard reflection measured every fifty reflections showed only random deviation from its mean intensity; Lorentz and polarization but not absorption corrections were applied; 1277 reflections $[I \geq 2.5\sigma(I)]$ considered as observed and included in the refinement; direct methods with *MULTAN* 80 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1980); an E map showed clearly all the non-H atoms of the molecule; refinement with *SHELX* 76 (Sheldrick, 1976) with anisotropic thermal parameters for the non-H atoms; H positions determined by a difference Fourier synthesis introduced into the refinement with an overall isotropic temperature factor. The final R and R_w were 0.061 and 0.048 respectively $[w = 1/\sigma^2(F)]$.

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