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Structures of Two Indolactams

BY TAKATOSHI KAWAI, YASUYUKI ENDO, KOICHI SHUDO AND AKIKO ITAI†

Faculty of Pharmaceutical Sciences, Tokyo University, 7-3-1 *Hongo, Bunkyo-ku, Tokyo* 113, *Japan*

AND KENTARO YAMAGUCHI

School of Pharmaceutical Sciences, Showa University, 1-5-8 *Hatanodai, Shinagawa-ku, Tokyo* 142, *Japan*

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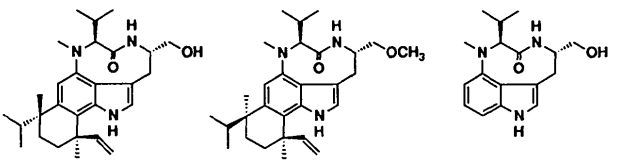
Abstract

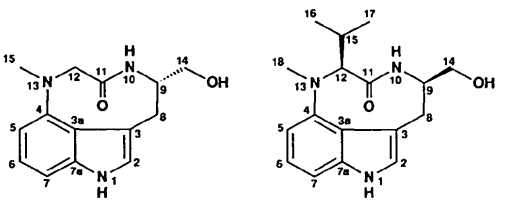
The crystal structures of two indolactam congeners have been solved. $C_{14}H_{17}N_3O_2$, 1,2,4,5,6,8-hexahydro-5-(hydroxymethyl)-1-methyl-3*H*-pyrrolo[4,3,2-*gh*]-1,4-benzodiazonin-3-one (indolactam-G), M_r = 259.31, monoclinic, $P2_1/c$, a = 16.48 (2), b = 6.399 (3), c = 13.88 (1) Å, β = 113.50 (8)°, V = 1342.2 Å^3, Z = 4, D_x = 1.28 Mg m^{-3}, λ(Cu $K\alpha$) = 1.54184 Å, μ = 0.678 mm^{-1}, $F(000)$ = 552, T = 300 K, R = 0.054 for 1938 observed reflections. $C_{17}H_{23}N_3O_2$, (2*R**,5*S**)-1,2,4,5,6,8-hexahydro-5-(hydroxymethyl)-1-methyl-2-(1-methylethyl)-3*H*-pyrrolo[4,3,2-*gh*]-1,4-benzodiazonin-3-one (*epi*-indolactam-V), M_r = 301.39, monoclinic, $P2_1/n$, a = 15.248 (5), b = 17.578 (5), c = 6.010 (1) Å, β = 92.01 (2)°, V = 1609.7 Å^3, Z = 4, D_x = 1.24 Mg m^{-3}, λ(Cu $K\alpha$) = 1.54184 Å, μ = 0.629 mm^{-1}, $F(000)$ = 648, T = 300 K, R = 0.054 for 2449 observed reflections. The conformations of the nine-membered lactam rings in the two indolactams were different from those found in teleocidin and olivoretin crystals. The notable bond angles and torsion angles related to the anilide N atoms in these compounds can be ascribed to the high strain of the rings. The geometries of the four ring conformations are compared.

Introduction

Indolactams have a common nine-membered lactam ring which is the key structure of the potent tumor promoters teleocidins (Fujiki *et al.*, 1981). Two different ring conformations, with twist and sofa forms in the lactam rings, as shown in Fig. 1, have been found in the crystal structures of three teleocidins [dihydroteleocidin B-4 bromoacetate: Harada, Sakabe, Hirata, Tomiie & Nitta, 1966; teleocidin B-2: Hitotsuyanagi, Fujiki *et al.*, 1984; teleocidin B-4 (1): Sakai *et al.*, 1984] and two olivoretins [*O*-methyl derivatives of teleocidins, which have no tumor-promoting activity; olivoretin B (2) and C: Hitotsuyanagi, Yamaguchi *et al.*, 1984]. All the teleocidins have the twist form, whereas the olivoretins have the sofa form. The absolute stereochemistry of teleocidins was determined by comparison with the circular dichroism spectrum of optically active synthesized (−)-indolactam-V (3) (Endo *et al.*, 1984).



Teleocidin B-4 (1) Olivoretin B (2) (−)-Indolactam-V (3)



Indolactam-G (4) *epi*-Indolactam-V (5)

An indolactam congener indolactam-V (3) also shows tumor-promoting activity 10- to 100-fold weaker than that of teleocidins (Fujiki *et al.*, 1984). Indolactam-V (3) crystals suitable for X-ray diffraction have not been produced. The NMR studies, however, have revealed that all the teleocidins, olivoretins and indolactam-V exist in an equilibrium of the twist and sofa forms in solution (Cardellina, Marner & Moore, 1979; Endo, Shudo, Itai, Hasegawa & Sakai, 1986). It was proved that the conformational difference between teleocidins and olivoretins found in crystals was not inherent to the molecular structures but resulted from the crystal-packing forces. These results raised the question as to which is the important conformer for the tumor-promoting activity.

Since then, various indolactam congeners (with various substituents at C12) have been synthesized and their conformations and biological activities examined in order to elucidate the relationship between them (Endo, Shudo & Okamoto, 1982). Among the congeners tested, the NMR signals of the

† Author for correspondence.

dominant conformers of indolactam-G (4) and *epi*-indolactam-V (5) cannot be interpreted in terms of the twist or the sofa form. Molecular-dynamics calculations were performed to search their preferred conformations (Kawai *et al.*, 1992). Although the results of the calculations seemed to support the results of the NMR experiments well, further structural confirmation is necessary for validating new unknown conformations. This paper describes the crystal structure determinations of (±)-indolactam-G (4) and (±)-*epi*-indolactam-V (5), and the comparison of their geometries and conformations with those of teleocidin B-4 (1) and olivoretin B (2).

Experimental

(±)-Indolactam-G (4) and (±)-*epi*-indolactam-V (5) were obtained synthetically (Endo, Shudo & Okamoto, 1982). The former compound was recrystallized from a mixed solution of methanol and acetone and the latter from a mixed solution of methanol and ethyl acetate. Crystal dimensions, details of data collections and structure refinements are given in Table 1.

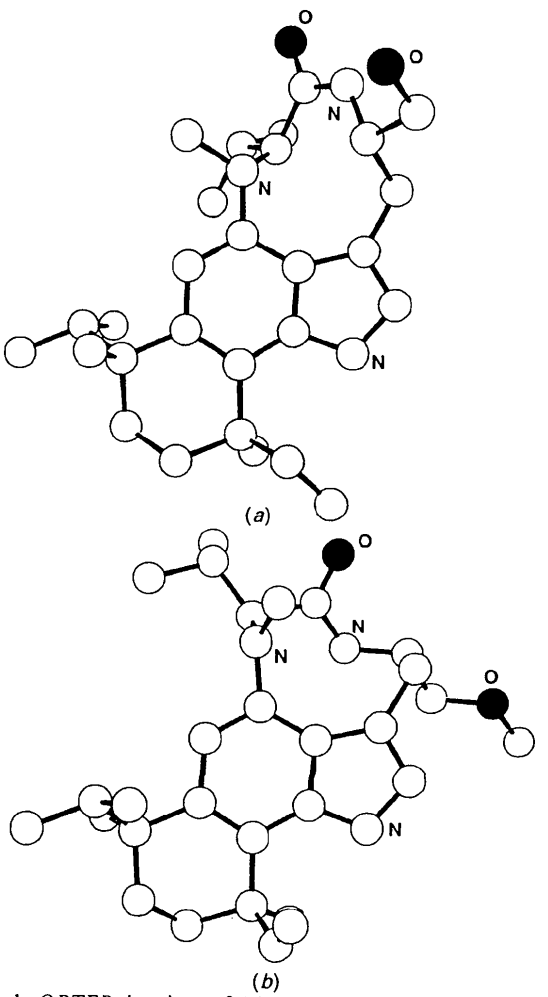


Fig. 1. *ORTEP* drawings of (*a*) teleocidin B-4 (1) in twist form (Sakai *et al.*, 1984) and (*b*) olivoretin B (2) in sofa form (Hitotsuyanagi, Yamaguchi *et al.*, 1984).

Table 1. *Details of data collection and structure refinement*

	Indolactam-G (4)	*epi*-Indolactam-V (5)
Crystal dimensions (mm)	0.33 × 0.23 × 0.03	0.36 × 0.22 × 0.07
θ range (°), number of reflections	$6 \le \theta \le 40$, 24	$5 \le \theta \le 29$, 14
Range h	−19 to 19	−18 to 18
k	0 to 7	0 to 21
l	0 to 16	0 to 7
Maximum θ value (°)	67	67
Standard reflections	$\bar{3}00$ $\bar{3}12$ $00\bar{2}$	141 120 $0\bar{2}1$
Intensity change (%)	+0.5 +0.7 +2.0	−0.4 +2.6 −0.7
Number of unique reflections	2632	2982
Number of observed reflections	1938	2449
Criterion for observed reflections	$I_o \ge 3\sigma(I_o)$	$I_o \ge 3\sigma(I_o)$
Number of parameters	223	268
R, wR, S	0.054, 0.054, 0.93	0.054, 0.057, 0.90
Weighting scheme	$1/\sigma^2(F_o)$	$1/\sigma^2(F_o)$
Max. Δ/σ	0.74	0.13
Max./min. $\Delta\rho$ (e Å^{-3})	0.22/−0.32	0.56/−0.24

Intensity data for both compounds were collected at 300 K on an Enraf–Nonius CAD-4 diffractometer with graphite-monochromated Cu $K\alpha$ radiation (λ = 1.54184 Å), by the ω–2θ scan technique. Intensities of three standard reflections were monitored every 60 min during the data collection.

Both structures were solved by direct methods using *MULTAN*78 (Main *et al.*, 1978). Full-matrix least-squares refinement of the scale factor and positional and anisotropic thermal parameters for non-H atoms was carried out using the Enraf–Nonius *SDP* package (B. A. Frenz and Associates Inc., 1985). All H atoms in both structures were located from difference Fourier maps and positionally refined with fixed isotropic thermal parameters equal to the equivalent thermal parameters (B_{eq}) of their bonded atoms. No absorption corrections were applied. Atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV).

All computations were performed on a VAX 11/750. Other details of the data collection and structure refinement are given in Table 1.

Discussion

The final atomic coordinates and the equivalent thermal parameters for indolactam-G (4) and *epi*-indolactam-V (5) are listed in Table 2.* The molecular structures of both compounds are illustrated by *ORTEP*II (Johnson, 1976) drawings in Figs. 2(*a*) and 2(*b*).

* Lists of structure factors, anisotropic thermal parameters, bond lengths and bond angles have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55989 (32 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: OH0029]

Table 2. *Positional and equivalent isotropic thermal parameters for non-*H *atoms, with e.s.d.'s in parentheses*

$B_{eq} = (4/3)\sum_i\sum_j \beta_{ij}\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	B_{eq} (Å^2)
(*a*) Indolactam-G (4)				
O11	0.1694 (1)	0.4506 (3)	0.3807 (2)	3.45 (5)
O14	0.0553 (1)	1.1359 (3)	0.2855 (1)	3.25 (4)
N1	0.2235 (2)	0.3659 (4)	0.0387 (2)	3.74 (6)
N10	0.1312 (1)	0.7287 (4)	0.2740 (2)	2.34 (4)
N13	0.3315 (1)	0.7720 (4)	0.3452 (2)	2.67 (5)
C2	0.1661 (2)	0.5301 (5)	0.0303 (2)	3.32 (6)
C3	0.2006 (2)	0.6557 (5)	0.1170 (2)	2.69 (5)
C3a	0.2832 (2)	0.5626 (4)	0.1852 (2)	2.64 (5)
C4	0.3478 (2)	0.6066 (5)	0.2852 (2)	2.71 (5)
C5	0.4246 (2)	0.4873 (5)	0.3246 (2)	3.53 (7)
C6	0.4364 (2)	0.3182 (6)	0.2657 (3)	4.22 (7)
C7	0.3725 (2)	0.2631 (5)	0.1706 (2)	4.12 (7)
C7a	0.2953 (2)	0.3836 (5)	0.1311 (2)	3.20 (6)
C8	0.1604 (2)	0.8640 (5)	0.1229 (2)	3.45 (6)
C9	0.1478 (2)	0.9172 (4)	0.2245 (2)	2.53 (5)
C11	0.1903 (2)	0.6187 (4)	0.3496 (2)	2.51 (5)
C12	0.2840 (2)	0.6969 (5)	0.4086 (2)	2.84 (6)
C14	0.0696 (2)	1.0666 (5)	0.1958 (2)	3.02 (6)
C15	0.4101 (2)	0.8866 (6)	0.4132 (3)	4.18 (8)
(*b*) *epi*-Indolactam-V (5)				
O11	0.3829 (1)	0.5258 (1)	0.5901 (4)	4.79 (5)
O14	0.5528 (1)	0.3497 (1)	0.1772 (4)	4.85 (5)
N1	0.1589 (2)	0.2595 (2)	−0.1076 (5)	4.81 (6)
N10	0.4203 (1)	0.4535 (1)	0.3026 (4)	3.30 (5)
N13	0.2193 (1)	0.4303 (1)	0.4785 (4)	3.05 (4)
C2	0.2483 (2)	0.2680 (2)	−0.0792 (6)	4.47 (7)
C3	0.2669 (2)	0.3133 (2)	0.0999 (5)	3.27 (6)
C3a	0.1837 (2)	0.3358 (2)	0.1884 (5)	3.08 (5)
C4	0.1571 (2)	0.3827 (2)	0.3651 (4)	3.15 (5)
C5	0.0694 (2)	0.3806 (2)	0.4209 (6)	4.39 (7)
C6	0.0070 (2)	0.3386 (2)	0.2926 (7)	5.20 (8)
C7	0.0292 (2)	0.2991 (2)	0.1081 (6)	4.86 (7)
C7a	0.1182 (2)	0.2980 (2)	0.0574 (5)	3.85 (6)
C8	0.3585 (2)	0.3262 (2)	0.1953 (5)	3.47 (6)
C9	0.4047 (2)	0.4000 (2)	0.1183 (4)	2.92 (5)
C11	0.3607 (2)	0.4894 (2)	0.4197 (5)	3.26 (6)
C12	0.2645 (2)	0.4861 (2)	0.3370 (4)	2.71 (5)
C14	0.4931 (2)	0.3832 (2)	0.0158 (5)	3.70 (6)
C15	0.2258 (2)	0.5666 (2)	0.3247 (5)	3.37 (6)
C16	0.1306 (2)	0.5647 (2)	0.2351 (6)	4.56 (7)
C17	0.2810 (2)	0.6162 (2)	0.1733 (6)	4.74 (7)
C18	0.1942 (2)	0.4597 (2)	0.6957 (5)	4.11 (7)

Although the amide bonds are *cis* in both molecules, the conformations of the nine-membered lactam rings are quite different to each other. They are also different to the twist and sofa forms. The ring structure found in indolactam-G (4) is named the fold form because the amide moiety folds back to the indole plane. The ring structure found in *epi*-indolactam-V (5) is named the *cis*-sofa form because the molecular shape of the structure resembles that of the sofa form, even though the former has a *cis* amide bond and the latter has a *trans* amide bond.

Tables 3 and 4 show selected torsion angles, bond lengths and bond angles, and other geometric values necessary for discussing the characteristics of the new conformation in comparison with the known conformation found in crystals of teleocidins and olivoretins. Data for teleocidin B-4 (1) ($R = 0.074$) and olivoretin B (2) ($R = 0.086$) are also listed for comparison. The corresponding torsion angles in the four structures deviate greatly from each other, except for two angles related to the indole ring, N13—C4—C3a—C3 and C4—C3a—C3—C8. The deviations show that the four ring structures are quite different conformationally. An abnormally large deviation from the *trans*-planar structure is found in the amide torsion angle of the sofa form (−139.7°), whereas normal deviations from the *cis* planar structures are found in the twist (−3.5°), fold (10.3°) and *cis*-sofa forms (−10.4°).

With regard to bond lengths (Table 3*b*), no significant differences are found among the four compounds. However, with regard to bond angles (Table 3*c*), there are some rather large differences reflecting the ring strain. The deviations (Δ) in the two bond angles related to the amide bond, C9—N10—C11 and N10—C11—C12, and a bond angle related to

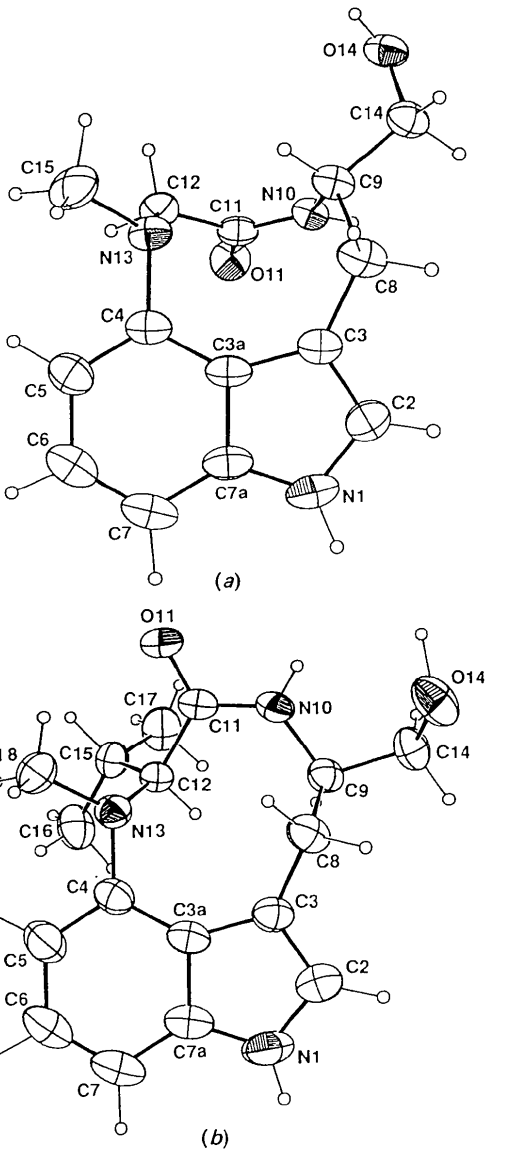


Fig. 2. *ORTEP* drawings of (*a*) indolactam-G (4) in fold form and (*b*) *epi*-indolactam-V (5) in *cis*-sofa form with 50% probability thermal ellipsoids.

Table 3. *Torsion angles* (°), *bond lengths* (Å) *and bond angles* (°) *along the nine-membered lactam ring for indolactam-G* (4), *epi-indolactam-V* (5), *teleocidin B*-4 (1) *and olivoretin B* (2)

E.s.d.'s are given in parentheses for (4) and (5). Coordinates for (1) and (2) were taken from the literature. Δ denotes the differences between maximum and minimum angle values

	Indolactam-G (4)	*epi*-Indolactam-V (5)	Teleocidin B-4 (1)	Olivoretin B (2)	Δ
(*a*) Torsion angles \					
Ring conformation	Fold	*cis*-Sofa	Twist	Sofa	—
C3a—C3—C8—C9	−55.8 (4)	−91.6 (4)	39.2	−77.1	—
C3—C8—C9—N10	−31.1 (4)	114.4 (3)	−122.5	59.2	—
C8—C9—N10—C11	95.1 (3)	−64.7 (3)	64.2	68.1	—
C9—N10—C11—C12	10.3 (4)	−10.4 (4)	−3.5	−139.7	—
(amide)	(*cis*)	(*cis*)	(*cis*)	(*trans*)	—
N10—C11—C12—N13	−49.7 (4)	103.0 (3)	62.3	80.8	—
C11—C12—N13—C4	−65.7 (3)	−140.4 (2)	−143.2	−92.5	—
C12—N13—C4—C3a	88.2 (3)	58.3 (3)	51.9	90.4	—
N13—C4—C3a—C3	6.0 (5)	10.6 (5)	7.3	−0.6	—
C4—C3a—C3—C8	12.2 (6)	9.6 (5)	0.2	−7.9	—
(*b*) Bond lengths					
C3—C8	1.505 (4)	1.509 (4)	1.50	1.50	—
C8—C9	1.544 (4)	1.555 (4)	1.55	1.55	—
C9—N10	1.467 (4)	1.466 (4)	1.46	1.48	—
N10—C11	1.315 (3)	1.328 (4)	1.35	1.34	—
C11—C12	1.517 (3)	1.533 (4)	1.53	1.53	—
C12—N13	1.472 (5)	1.483 (3)	1.47	1.48	—
N13—C4	1.436 (4)	1.421 (3)	1.43	1.43	—
C4—C3a	1.400 (3)	1.415 (4)	1.41	1.41	—
C3a—C3	1.441 (3)	1.447 (4)	1.47	1.45	—
(*c*) Bond angles					
C3a—C3—C8	130.7 (2)	129.2 (2)	131.5	131.4	2.3
C3—C8—C9	117.9 (2)	115.8 (2)	112.6	111.7	6.2
C8—C9—N10	111.5 (2)	111.9 (2)	113.0	108.0	5.0
C9—N10—C11	126.6 (2)	127.5 (2)	126.2	118.2	9.3
N10—C11—C12	121.7 (2)	118.4 (2)	117.6	115.3	6.4
C11—C12—N13	117.1 (2)	107.3 (3)	106.5	104.2	12.9
C12—N13—C4	111.8 (2)	115.5 (3)	117.4	118.4	6.6
N13—C4—C3a	118.7 (2)	120.0 (2)	120.3	125.5	6.8
C4—C3a—C3	135.5 (3)	135.4 (2)	136.2	137.1	1.7

Table 4. *Bond angles* (°) *around the anilide* N *atom* (N13) *and their summations in indolactam-G* (4), *epi-indolactam-V* (5), *teleocidin B*-4 (1) *and olivoretin B* (2)

	Indolactam-G (4)	*epi*-Indolactam-V (5)	Teleocidin B-4 (1)	Olivoretin B (2)
C4—N13—C12	111.8 (2)	115.5 (3)	117.4	118.4
C4—N13—C15/C18	115.0 (2)	116.4 (2)	118.4	118.0
C12—N13—C15/C18	108.9 (2)	114.7 (2)	116.3	120.0
Sum of three angles	335.7	346.6	352.1	356.4

the anilide N atom, C11—C12—N13, are especially large. The most remarkable deformations seem to be imposed on the amide bond and the anilide N atom. The bond angles around the anilide N atom (N13) and their summations are listed in Table 4 in order to compare the hybridization character of the N atom in the four compounds. The summation in the fold form (335.7°) shows strong sp^3 character, whereas that in the sofa form (356.4°) shows sp^2 character, and those in the *cis*-sofa form (346.6°) and the twist form (352.1°) show intermediate character between sp^3 and sp^2. In all compounds, there is no conjugation between the indole ring and the anilide N atom, because the C12—N13—C4—C3a torsion angles deviate greatly from zero (51.9–90.4°).

In the crystal structure of indolactam-G (4), three pairs of intermolecular hydrogen bonds are formed between N1—H1···O11(x, $-y+1.5$, $z-0.5$), N10—H10···O14($-x$, $y-0.5$, $-z+1.5$) and O11···H14—O14(x, $y-1$, z). In the crystal structure of *epi*-indolactam-V (5), three pairs of intermolecular hydrogen bonds are also formed between N1—H1···O14($x-0.5$, $-y+0.5$, $z-0.5$), N10—H10···O11($-x+1$, $-y+1$, $-z+1$) and O14—H14···O11($-x+1$, $-y+1$, $-z+1$), and they form a three-dimensional network to stabilize the structure, as shown in Fig. 3(*b*).

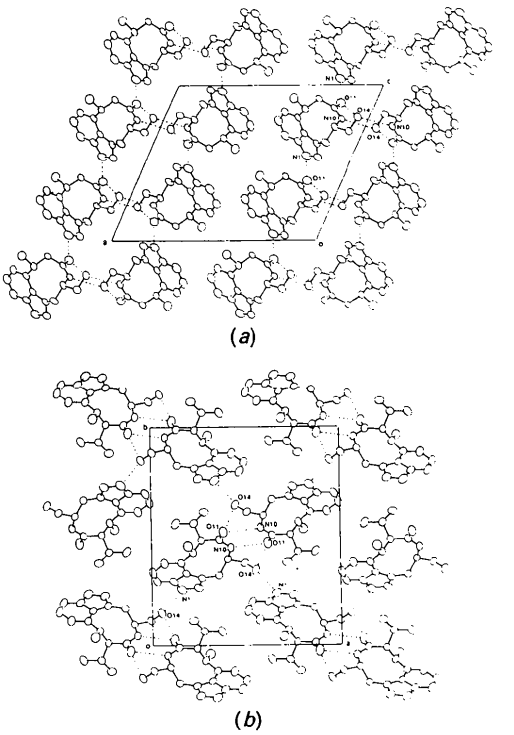


Fig. 3. Hydrogen-bonding networks. (*a*) Indolactam-G (4); viewed along the *b* axis. (*b*) *epi*-Indolactam-V (5); viewed along the *c* axis.

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Conformational Studies on [16]aneS$_4$. Structures of α- and β-[16]aneS$_4$ ([16]aneS$_4$ = 1,5,9,13-Tetrathiacyclohexadecane)

BY ALEXANDER J. BLAKE,* ROBERT O. GOULD, MALCOLM A. HALCROW AND MARTIN SCHRÖDER

Department of Chemistry, The University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ, Scotland

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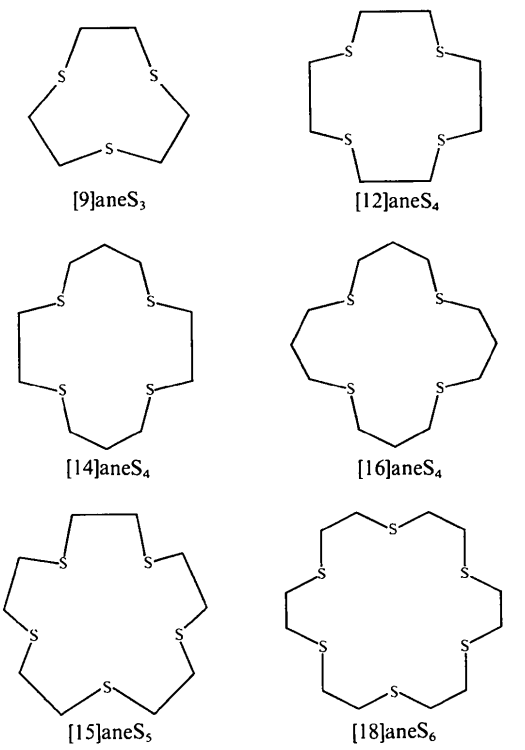
Abstract

Three morphologies – acicular (α), lamellar (β) and columnar (γ) – are observed for crystals of [16]aneS$_4$ (1,5,9,13-tetrathiacyclohexadecane). The absolute structures of the α and β forms have been determined: the molecular structures are essentially the same but the two forms differ in their crystal packing. α-[16]aneS$_4$ crystallizes in the orthorhombic space group $Pbc2_1$ while β-[16]aneS$_4$ crystallizes in the monoclinic space group $P2_1$. The conformation of the molecules is unusual: whereas the other tetrathia macrocycles [12]aneS$_4$ and [14]aneS$_4$ have exclusively *exo* S atoms, in [16]aneS$_4$ only two lie in *exo* positions and this structural feature is related to the chemical properties of the macrocycle. Molecular mechanics calculations have been carried out on selected conformers of [16]aneS$_4$ and the results compared with the observed crystal structures and with the hydrocarbon analogue, $C_{16}H_{32}$. γ-[16]aneS$_4$ appears to crystallize in the orthorhombic space group *Fdd*2 but it suffers from twinning and no structural information could be obtained.

Introduction

Although the trithia macrocycle 1,4,7-trithiacyclononane ([9]aneS$_3$) adopts an *endo* conformation in which the three S donors are preorganized for facial coordination to metal ion centres (solid-state structure: Glass, Wilson & Setzer, 1980; gas-phase structure: Blom, Rankin, Robertson, Schröder & Taylor, 1991), structure determinations on larger ring tetra- and pentathia analogues have revealed exclusively *exo* conformations. Thus the structures of [12]aneS$_4$ (1,4,7,10-tetrathiacyclododecane: Robinson & Sangokoya, 1988; Cooper, Foxman, Hartman, Storey & Wolf, 1987), [14]aneS$_4$ (1,4,8,11-tetrathiacyclotetradecane: DeSimone & Glick, 1976) and [15]aneS$_5$ (1,4,7,10,13-pentathiacyclopentadecane: Cooper,



* Author for correspondence.