Synthesis and Properties of New Macrocyclic Compounds: Utilization of Bond Character of Hypervalent Sulfur in Tetraazathiapentalene Derivatives

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2,3-Bis[(*p*-isothiocyanatomethylphenyl)methyl]-6,7-dihydro-5*H*-2a-thia(2a-S^{IV})-2,3,4a,7a-tetraazacyclopent[*cd*]indene-1,4(2*H*,3*H*)-dithione (**3**), prepared by the reaction of 2,3-dimethyl-6,7-dihydro-5*H*-2a-thia(2a-S^{IV})-2,3,4a,7a-tetraazacyclopent-[*cd*]indene-1,4(2*H*,3*H*)-dithione (**1**) with *p*-xylylene diisothiocyanate, reacted with N,N'-dialkyl substituted diamines to give macrocyclic compounds bearing hypervalent sulfur by a ring closure reaction in good yields. These macrocyclic compounds were converted into ring-expanded macrocyclic compounds with release of the hypervalent sulfur by treating with $NaBH_4$ and CF_3COOH.

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Introduction.

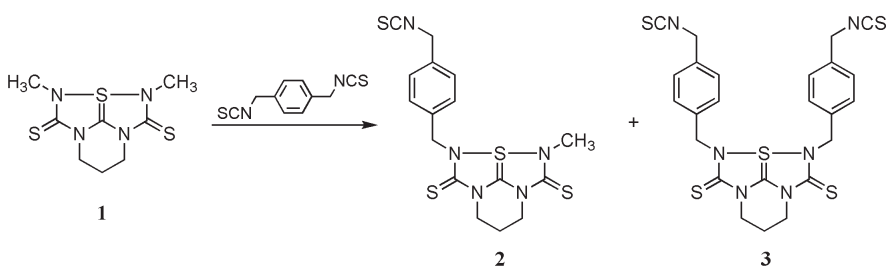
π-Hypervalent heterocyclic systems have attracted considerable attention because of their unusual structure and reactivity [1]. An example of such systems is compounds containing a 10-S-3 sulfurane species, and their chemistry has extensively been studied [2-3]. However, little is reported about the utility of the bond character of the hypervalent sulfur in these π-electron systems in organic synthesis. Previously, we have reported an efficient method for the synthesis of 10-S-3 tetraazathiapentalene derivatives, 2,3-disubstituted 6,7-dihydro-5*H*-2a-thia(2a-S^{IV})-2,3,4a,7a-tetraazacyclopent[*cd*]-indene-1,4(2*H*,3*H*)-dithiones, and have found that they undergo unique reactions that depend on the nature of the hypervalent sulfur [4]. For example, the reaction of the tetraazathiapentalene derivative **1** with an excess of isothiocyanates and isocyanates gave substituted tetraazathiapentalene derivatives bearing thiocarbonyl and carbonyl groups in the compounds [5]. The reaction of **1** with $NaBH_4$ and $LiAlH_4$ gave the ring-opened compound, 1,3-bis(methylthiocarbamoyl)-perhydropyrimidine, in good yield with release of the hypervalent sulfur [6]. Furthermore, treatment of **1** with acids gave the ring-opening product, 1,3-dimethyl perhydropyrimidin-2-one, in high yield with release of the hypervalent sulfur [7]. The alkaline hydrolysis of the tetraazathiapentalene derivative that contains octyl group at the 6 position of **1** gave the ring-opened compound bearing two thiourea groups with elimination of the $C{=}S^{IV}$ moiety [8]. On the basis of these results, we have recently synthesized macrocyclic compounds that contain thiourea groups in the ring and are soluble in organic solvents [8-9]. These macrocyclic compounds have been shown to be useful as anion receptors [10]. We now report a new method for preparing new macrocycles having a π-hypervalent sulfur in the ring and the subsequent conversion of these macrocycles to new compounds that bear various functional groups such as thiourea moiety, amino group, ether chain, and carbonyl groups in the ring *via* various ring-opening reactions [11].

Result and Discussion.

Synthesis of Tetraazathiapentalene Derivative **3**.

p-Xylylene diisothiocyanate [12-13] was added to a stirred solution of **1**, which was prepared by a one-pot reaction using lithium cyclic thioureide/phenacyl chloride/methyl isothiocyanate reagent system [14], in dry benzene, and the mixture was heated at 50 °C for 24 hours. Work-up of the reaction mixture gave the tetraazathiapentalene derivative **3** as a colorless solid in 46% yield from **1**, together with tetraazathiapentalene derivative **2** in 33% yield. Compounds **2** and **3** were stable in air and highly soluble in organic solvents.

Scheme 1



1 **2** **3**

Scheme 2

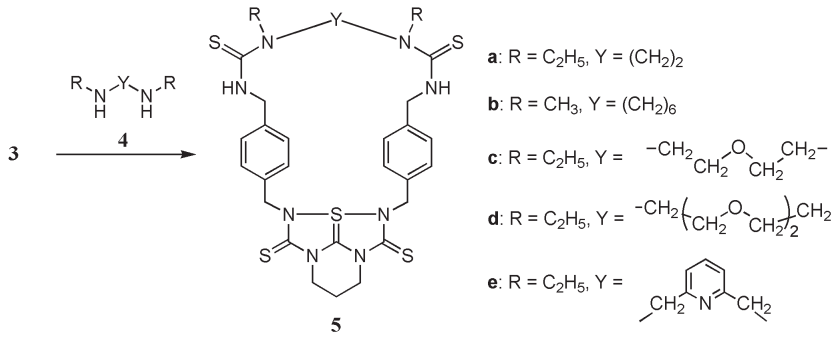


Table 1
Yields, Melting Points and Analytical Data of Macrocyclic Compounds **5a-e**

Compound	Yield %[a]	mp (°C)	Molecular Formula	calcd.(Found)% C	H	N
5a	72	198.5-200[b]	$C_{30}H_{38}N_8S_5$	53.70 (53.85)	5.71 (5.80)	16.70 (16.81)
5b	68	168-170	$C_{32}H_{42}N_8S_5$	54.98 (55.21)	6.06 (6.07)	16.03 (15.89)
5c	85	175-176[b]	$C_{32}H_{42}N_8OS_5$	54.43 (54.13)	5.97 (5.92)	15.47 (15.67)
5d	66	222-224[b]	$C_{34}H_{46}N_8O_2S_5$	53.80 (53.51)	6.11 (6.16)	14.76 (14.46)
5e	69	188-189[b]	$C_{35}H_{41}N_9S_5$	56.19 (56.42)	5.52 (5.39)	16.85 (16.88)

[a] Isolated yields of **5a-e** obtained by the reaction of **3** with **4** ; the yields based on **3**. [b] Decomposed.

Synthesis of Macrocyclic Compounds Bearing Hyperalent Sulfur.

The ring closure reactions of **3** with an equimolar amount of N,N'-dialkyl substituted diamines such as 1,2-bis(ethylamino)ethane (**4a**), 1,6-bis(methylamino)-hexane (**4b**), 1,5-bis(ethylamino)-3-oxapentane (**4c**), 1,8-bis(ethylamino)-3,6-dioxaoctane (**4d**), and 2,6-bis(ethylaminomethyl)pyridine (**4e**) were carried out in DMSO at room temperature for 48 hours (Scheme 2). The 23-29 membered macrocyclic compounds **5a-e** that bear the tetraazathiapentalene ring were obtained in good yields (Table 1) with the recovery of a small amount of **3**.

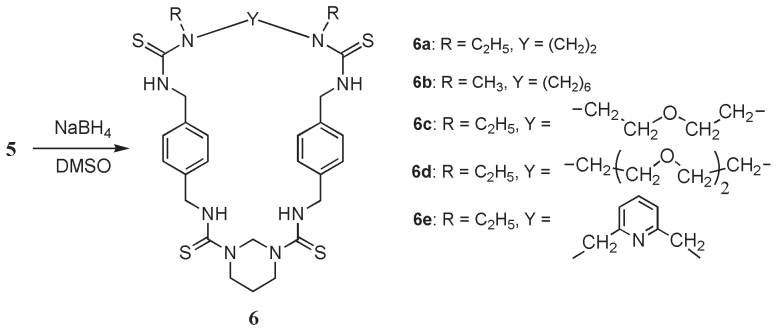
Table 2
Spectral Data of Macrocyclic Compounds **5a-e**

Compound	IR (cm^{-1}) (KBr)	^{1}H NMR (δ, ppm) ($CDCl_3$)	^{13}C NMR (δ, ppm) (solvent)	FAB MS $(M+H)^+$, m/z
5a	3230, 3040, 2920, 1580, 1530, 1480, 1380, 1320, 1245, 1150, 750	1.25(t, 6H, 2x NCH_2CH_3, *J*= 6.9Hz), 2.27(m, 2H, $NCH_2CH_2CH_2N$), 3.62-3.84(m, 8H, 2x $CH_2NCH_2CH_3$), 4.37(t, 4H, $NCH_2CH_2CH_2N$, *J*=5.7Hz), 4.88(s, 8H, 2x $NCH_2C_6H_4CH_2N$), 7.18-7.26(m,10H, 2x CH_2 *NH*, aromatic)	(DMSO-d_6) 12.98, 19.02, 45.08, 47.48, 47.70(x 3), 127.57, 128.08, 136.20, 138.57, 156.84, 169.52, 180.74	671
5b	3320, 2925, 1580, 1530, 1480, 1395, 1320, 1245, 1155, 750	1.48(m, 4H, $NCH_2CH_2CH_2CH_2CH_2CH_2N$), 1.68(m, 4H, $NCH_2CH_2CH_2CH_2CH_2CH_2N$), 2.32(m, 2H, $NCH_2CH_2CH_2CH_2N$), 3.18 (s, 6H, 2x NCH_3), 3.77(t, 4H, $NCH_2CH_2CH_2CH_2CH_2CH_2N$, *J*=7.0Hz), 4.37(t, 4H, $NCH_2CH_2CH_2N$, *J*=5.8Hz), 4.83(s, 4H, 2x NH $CH_2C_6H_4CH_2N$), 4.91(d, 4H, 2x $NHCH_2C_6H_4CH_2N$, *J*= 5.5Hz), 5.81(brs, 2H, 2x $NHCH_2C_6H_4CH_2N$), 7.24-7.39(m, 8H, aromatic)	($CDCl_3$) 19.93, 25.29, 26.30, 38.21, 44.82, 49.36(x2), 53.08, 127.96, 129.33, 135.32, 138.51, 156.54, 169.40,181.83	700
5c	3320, 2930, 1575, 1530, 1470, 1380, 1340, 1240,1155, 935,755	1.20(t, 6H, 2x NCH_2CH_3, *J*=7.0 Hz), 2.31(m, 2H, $NCH_2CH_2CH_2N$), 3.65(m, 12H, 2x $OCH_2CH_2NCH_2CH_3$), 4.36(t, 4H, N $CH_2CH_2CH_2N$, *J*=5.8Hz), 4.73 (s, 4H, 2x $NCH_2C_6H_4$), 4.85(d, 4H, 2x $C_6H_4CH_2NH$, *J*=4.9Hz), 6.45(brs, 2H, 2x $C_6H_4CH_2NH$), 7.16-7.35(m, 8H, aromatic)	($CDCl_3$) 12.73, 20.27, 45.07, 46.73, 49.83, 50.05, 50.47, 70.22, 128.62, 130.26, 135.50, 138.87, 156.92, 169.50, 183.12	715
5d	3300, 2880, 1565, 1520, 1470, 1370, 1330, 1235, 1145, 930, 730	1.25(t, 6H, 2x NCH_2CH_3, *J*=7.0 Hz), 2.32(m, 2H, $NCH_2CH_2CH_2N$), 3.39(s, 4H, OCH_2CH_2O), 3.58- 3.64(m, 8H, 2x NCH_2CH_2O), 3.84(q, 4H, 2x NCH_2CH_3, *J*= 7.1Hz), 4.36(t ,4H, $NCH_2CH_2CH_2N$, *J*=5.8Hz), 4.76(s, 4H, $NCH_2C_6H_4$),4.80(d, 4H, 2x $C_6H_4CH_2NH$, *J*=5.5Hz), 7.14-7.39(m, 10H, 2x $C_6H_4CH_2NH$)	($CDCl_3$) 12.37, 19.95, 44.75, 47.36, 49.44, 50.13, 50.21, 70.32, 70.71, 128.06, 129.57, 135.01, 138.47, 156.68, 169.25, 183.55	760
5e	3300, 3050, 2920, 1580, 1480, 1380, 1340, 1245, 1160, 940, 760	1.24(t, 6H, 2x NCH_2CH_3, *J*=7.0 Hz), 2.30(m, 2H, $NCH_2CH_2CH_2N$), 3.91(q, 4H, 2x NCH_2CH_3, *J*=7.0Hz), 4.29(s, 4H, 2x $NCH_2C_5H_3N$), 4.35(t, 4H, $NCH_2CH_2CH_2N$, *J*=5.8Hz), 4.67(s, 4H, 2x $NCH_2C_6H_4$), 4.85(d, 4H, 2x $C_6H_4CH_2NH$, *J*=4.9Hz), 7.17-7.26(m, 10H, 2x $C_6H_4CH_2NH$), 7.44-7.73(m, 3H, pyridine ring)	($CDCl_3$) 12.51, 19.04, 44.85, 46.31, 48.37, 48.43, 53.83, 121.02, 127.51, 128.71, 135.17, 138.21, 139.03, 156.76, 156.86, 169.40, 182.09	748

In the ^{1}H-NMR spectra of **5a-e** (Table 2), all the compounds showed a singlet at 4.67-4.88 ppm due to benzyl protons attached to the 2,3-positions in the tetraazathiapentalene ring, indicating that these compounds are symmetrical molecules. They are also soluble in polar solvents and stable in air. The reaction of **3** with primary diamines gave complex mixtures.

In the ^{1}H-NMR spectra of **6a-e** (Table 4), a characteristic peak due to the N-CH_2-N protons was observed as a singlet at around 5.6 ppm, indicating that the molecules possess the ring-expanded structures as represented in Scheme 3 with release of the hypervalent sulfur.

Scheme 3



Ring Expansion of **5** by use of Sodium Borohydride.

Previously, we found that **1** is converted into the ring-opened compound, 1,3-bis(methylthiocarbamoyl)-perhydropyrimidine, by reductive elimination of the hypervalent sulfur with $NaBH_4$ [6].

We applied this reaction to the ring-opening reaction of the macrocyclic compounds **5a-e**. Sodium borohydride was added in large excess (ten equiv.) to solutions of **5a-e** in DMSO or 2-propanol at room temperature. The solutions changed immediately from colorless to emerald green. After complete fading of the color, the mixtures were stirred for 48 hours. Usual work-up of the reaction mixtures gave the stable ring expanded 27-33 membered macrocyclic compounds **6a-e** with release of the hypervalent sulfur in fair to good yields (Table 3).

Table 3
Yields, Melting Points and Analytical Data of Macrocyclic Compounds **6a-e**

Compound	Yield [a] %	mp (°C)	Molecular Formula	calcd. (Found) % C	H	N
6a	42[b]	174-175.5[d]	$C_{30}H_{42}N_8S_4$	56.22 (56.10)	6.29 (6.00)	17.48 (17.62)
6b	75[b]	202-203[d]	$C_{32}H_{46}N_8S_4$	57.28 (57.52)	6.91 (6.95)	16.70 (16.45)
6c	66[b]	140-141	$C_{32}H_{46}N_8OS_4$	55.94 (56.13)	6.75 (6.75)	16.31 (16.03)
6d	59[c]	236-238[d]	$C_{34}H_{50}N_8O_2S_4$	55.86 (55.64)	6.89 (6.80)	15.33 (15.12)
6e	40[b]	213-214[d]	$C_{35}H_{45}N_9S_4$	57.75 (58.00)	5.98 (6.20)	16.68 (17.00)

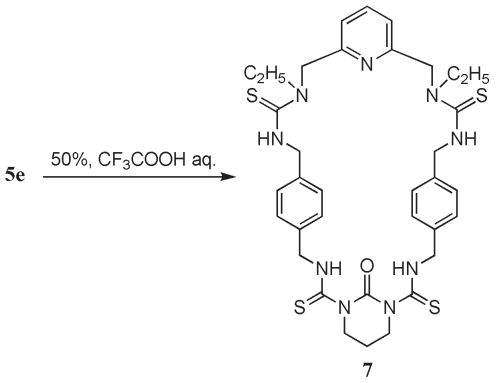
[a] Isolated yields of 6a-e obtained by the reaction of **5a-e** with sodium borohydride; the yields based on **5a-e**. [b] The reactions were carried out in DMSO for 48 hours. [c] The reaction was carried out in 2-propanol for 24 hours. [d] Decomposed.

Ring Opening Reaction of **5e** in Acidic Conditions.

Previously, we found that treatment of 10-S-3 tetraazathiapentalene derivatives under acidic conditions affords the ring-opening products, 1,3-disubstituted perhydropyrimidin-2-ones, in high yields with release of the hypervalent sulfur [7]. For example, **1** undergoes a ring-opening reaction by treating with 10% hydrochloric acid to give 1,3-bis(methylthiocarbamoyl)perhydropyrimidin-2-one with release of the hypervalent sulfur [7]. We applied this reaction to the ring opening reaction of the macrocyclic compound **5e** (Scheme 4).

The ring-opening reaction of **5e** with 10% hydrochloric acid under similar conditions did not proceed successfully. However, when a solution of **5e** in 50% aqueous trifluo-

Scheme 4



Furthermore, in the ^{1}H- NMR spectrum, a new broad NH peak appeared at 10.72 ppm. These results suggest that a hydrogen bond between NH and CO groups is forming.

Conclusions.

In this investigation, we successfully synthesized the reactive hypervalent sulfur compound **3** that bears the *p*-xylyleneisothiocyanate function at the 2,3-positions of the tetraazathiapentalene derivative. Compound **3** was converted into the new macrocyclic compounds **5a-e** by the reaction with substituted diamines containing various spacers. The macrocycles **5a-e** were further converted into ring-expanded macrocyclic compounds. Treatment of **5a-e** with sodium borohydride afforded the new ring-opened macrocyclic compounds **6a-e** that bear the thiourea function and various spacers such as alkyl chain, ether chain, and pyridine ring. Hydrolysis of **5e** with trifluoloacetic acid promoted the ring-opening reaction to give the macrocyclic compound **7** that bears the 1,3-disubstituted perhydropyrimidin-2-one ring in the molecule. The macrocyclic

Table 4
Spectral data of macrocyclic compounds **6a-e**

Compound	IR (cm^{-1}) (KBr)	^{1}H NMR (δ, ppm) (Solvent)	FAB MS $(M+H)^+$, m/z
6a	3210, 3030, 2920, 1530, 1380, 1340, 1260, 1170, 1140, 960	(DMSO) 1.12(t, 6H, 2x NCH_2CH_3, *J*= 7.0Hz), 1.84(m, 2H, NCH_2CH_2 CH_2N), 3.74(brs, 12H, NCH_2CH_2 CH_2N, 2x $CH_2NCH_2CH_3$), 4.70(brs, 8H, 2x $CH_2C_6H_4CH_2$), 5.87(s, 2H, NCH_2N), 7.15-7.26(m, 8H, aromatic), 8.38(brs, 4H, 4x N*H*)	643
6b	3250, 3030, 2920, 1530, 1380, 1340, 1250, 1140, 960	($CDCl_3$) 1.37(m, 4H, $NCH_2CH_2CH_2$ $CH_2CH_2CH_2N$), 1.61(m, 4H, NCH_2 $CH_2CH_2CH_2CH_2$ CH_2N), 1.79(m, 2H, $NCH_2CH_2CH_2N$), 3.16(s, 6H, 2x NCH_3), 3.70(t, 4H, $NCH_2CH_2CH_2$ $CH_2CH_2CH_2N$, *J*=7.3Hz), 3.99(t, 4H, $NCH_2CH_2CH_2N$, *J*=5.5Hz), 4.84(m, 8H, 2x $CH_2C_6H_4CH_2$), 5.65(s, 2H, NCH_2N), 5.71(t, 2H, 2x N*H*, *J*=4.3Hz), 7.23-7.65(m, 10H, 2x N*H*, aromatic)	671
6c	3270, 3030, 2910, 1530, 1380, 1330, 1280, 1130, 960	($CDCl_3$) 1.05(t, 6H, 2x NCH_2 CH_3, *J*=6.7Hz), 1.80(m, 2H, NCH_2CH_2 CH_2N), 3.28(brs, 4H, 2x OCH_2CH_2 N), 3.64(brs, 8H, 2x $OCH_2CH_2NCH_2CH_3$), 4.02(brs, 4H, $NCH_2CH_2CH_2N$), 4.70(d, 4H, 2x $NHCH_2C_6H_4$, *J*=4.3 Hz), 4.75(d, 4H, 2x $C_6H_4CH_2NH$, *J*=4.9Hz), 5.55(s, 2H, NCH_2N), 6.13 (brs, 2H, 2x $NHCH_2C_6H_4$), 7.17-7.27(m, 10H, 2x C_6H_4NH, aromatic)	687
6d	3420, 3200, 2920, 1530, 1380, 1330, 1260, 1130, 955	($CDCl_3$) 1.20(t, 6H, 2x NCH_2CH_3, J= 7.0Hz), 1.75(m, 2H, $NCH_2CH_2CH_2N$), 3.14(s, 4H, OCH_2CH_2O), 3.46-3.56(m, 8H, 2x NCH_2CH_2O), 3.78(q, 4H, 2x NCH_2CH_3, *J*=6.9Hz), 4.00(brs, 4H, $NCH_2CH_2CH_2$ N), 4.70(d, 4H, 2x NH $CH_2C_6H_4$, *J*=4.3Hz), 4.74(d, 4H, 2x $C_6H_4CH_2NH$, *J*=4.9Hz), 5.50(s, 2H, NCH_2N), 7.00 (brs, 2H, 2x $NHCH_2$ C_6H_4), 7.16-7.27(m, 8H, aromatic), 7.57(brs, 2H, 2x $C_6H_4CH_2NH$)	731
6e	3300, 3010, 2920, 1530, 1380, 1320, 1270, 1250, 1140, 950	(DMSO-d_6) 1.08(t, 6H, 2x NCH_2 CH_3,*J*=7.0Hz), 1.78(m, 2H, NCH_2 CH_2CH_2N), 3.69(q, 4H, 2x NCH_2 CH_3, *J*= 6.7Hz), 3.89(brs, 4H, NCH_2 CH_2CH_2N), 4.69(s, 4H, 2x NCH_2 C_5H_3N), 4.75(brs, 4H, 2x $NHCH_2$ C_6H_4), 4.81(brs, 4H, 2x $C_6H_4CH_2$ NH), 5.71(s, 2H, NCH_2N), 7.00-7.72 (m, 11H, aromatic), 8.37-8.42(brs, 4H, 2x $NHCH_2C_6H_4CH_2NH$)	720

roacetic acid was stirred at 50 °C for 24 hours, the carbonyl-containing product **7** was obtained in 30% yield along with 50% recovery of **5e**. Reactions of **5c-d** with aqueous trifluoroacetic acid under similar conditions gave complex mixtures. In the IR spectrum of **7**, a carbonyl absorption due to the N-CO-N moiety was observed at 1650 cm^{-1}.

compounds synthesized in this paper are expected to have a potential utility in the field of complexation and host-guest chemistry. The reported methodology provides a useful tool for the synthesis of macrocyclic compounds.

EXPERIMENTAL

All the solvents used in this study were purified by usual procedures. Column chromatography was performed on silica gel (Merck, 70-230 mesh). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a JEOL JNM-GX (270 MHz) using TMS as an internal standard. IR spectra were obtained with a PERKIN ELMER 1600 FT IR spectrometer. Mass spectra were obtained using a JEOL-DX303HF spectrometer with FAB ionization. Melting points were determined on a Yanagimoto MP-S3 melting point apparatus and were uncorrected. Elemental analyses were recorded on a Yanagimoto MT-3 CHN recorder. Purifications of products were conducted by column chromatography on silica gel (Wakogel C-300) or by preparative tlc on silica gel (Merck Kieselgel 60 GF 254).

Materials.

2,3-Dimethyl-6,7-dihydro-5*H*-2a-thia(2a-S^{IV})-2,3,4a,7a-tetraazacyclopent[*cd*]indene-1,4 (2*H*,3*H*)-dithione (**1**) [14], *p*-xylylenediisothiocyanate [11-12], 1,5-bis(ethylamino)-3-oxapentane (**4c**) [15], 1,8-bis(ethylamino)-3,6-dioxaoctane (**4d**) [16], and 2,6-bis(ethylaminomethyl)pyridine (**4e**) [17] were prepared according to the procedures described in the literature.

Reaction of **1** with *p*-Xylylenediisothiocyanate.

p-Xylylene diisothiocyanate (881 mg, 4.0 mmol) was added to a stirred solution of **1** (104 mg, 0.40 mmol) in dry benzene (20 mL) and the mixture was heated at 50 °C for 24 hours. After removal of benzene under reduced pressure, the residue was chromatographed on silica gel with chloroform to give 2,3-bis[(*p*-isothiocyanatomethylphenyl)methyl]-6,7-dihydro-5*H*-2a-thia(2a-S^{IV})-2,3,4a,7a-tetra-azacyclopent[*cd*]indene-1,4(2*H*,3*H*)-dithione (**3**) (101 mg, 46%) and 2-methyl-3-[(*p*-isothiocyanatomethylphenyl)methyl]-6,7-dihydro-5*H*-2a-thia(2a-S^{IV})-2,3,4a,7a-tetraazacyclopent[*cd*]indene-1,4(2*H*,3*H*)-dithione (**2**) (54 mg, 33%) as colorless solids together with the recovery of a small amount of **1**. Recrystallization of **2** and **3** from chloroform/*n*-hexane gave the analytically pure compounds.

2-Methyl-3-[(*p*-isothiocyanatomethyphenyl)methyl]-6,7-dihydro-5*H*-2a-thia(2a-S^{IV})-2,3,4a,7a-tetraazacyclopent[*cd*]indene-1,4 (2*H*,3*H*)-dithione (**2**).

Compound **2** had a mp 247-248 °C (decomp.); ir (KBr): 2180, 2100, 1580, 1540, 1490, 1400, 1360, 1315, 1245, 1190, 1150, 1050, 955, 940, and 740 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 2.36 (m, 2H, $NCH_2CH_2CH_2N$), 3.18 (s, 3H, CH_3), 4.40 (t, 2H, $NCH_2CH_2CH_2N$, J= 6.1 Hz), 4.43 (t, 2H, $NCH_2CH_2CH_2N$, J=6.1Hz), 4.69 (s, 2H, $NCH_2C_6H_4$), 4.94 (s, 2H,$C_6H_4CH_2NCS$), 7.27-7.41 (m, 4H, aromatic); ^{13}C nmr ($CDCl_3$): δ 20.02, 31.18, 44.95, 48.38, 48.45, 127.18, 128.98, 133.67, 137.09, 156.27, 169.71, 170.20.

Anal. Calcd. for $C_{16}H_{17}N_5S_4$: C, 47.15; H, 4.20; N, 17.18. Found: C, 46.92; H, 3.98; N, 16.90.

2,3-Bis[(*p*-isothiocyanatomethylphenyl)methyl]-6,7-dihydro-5*H*-2a-thia(2a-S^{IV})-2,3,4a,7a-tetraazacyclopent[*cd*]indene-1,4(2*H*,3*H*)-dithione (**3**).

Compound **3** had a mp 244-246 °C (decomp.); ir (KBr): 2180, 2100, 1580, 1530, 1480, 1420, 1330, 1310, 1240, 1145, 915, 805, 740, and 715 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 2.36 (m, 2H, $NCH_2CH_2CH_2N$), 4.40 (t, 4H, $NCH_2CH_2CH_2N$, J = 6.0 Hz), 4.71 (s, 4H, 2x NCH_2), 4.88 (s, 4H, 2x CH_2NCS), 7.27-7.36 (m, 8H, aromatic); ^{13}C nmr ($CDCl_3$) δ 19.98, 44.97, 48.47, 48.73, 127.20, 127.51, 129.32, 133.89, 136.84, 156.59, 170.00.

Anal. Calcd. for $C_{24}H_{22}N_6S_5$: C, 51.96; H, 4.00; N, 5.15. Found: C, 51.80; H, 3.79; N, 14.85.

Ring Closure Reactions of **3** with Substituted Diamines **4**.

Typical Procedure.

To a solution of **3** (60 mg, 0.108 mmol) in DMSO (30 mL) was added an equimolar amount of 2,6-bis(ethylaminomethyl)pyridine (**4e**) (20.9 mg, 0.108 mmol). The reaction mixture was stirred at room temperature for 48 hours, poured into water, and the solution was extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with dichloromethane/ethylacetate (4/1) to give the macrocylic compound **5e** (55.7 mg, 69%). Recrystallization from chloroform/*n*-hexane gave an analytically pure compound.

Reduction of Macrocylic Compounds **5** with Sodium Borohydride.

A typical Procedure.

Ten equivalents of sodium borohydride (36 mg, 0.94 mmol) was added to a stirred solution of **5c** (67.2 mg, 0.094 mmol) in dry DMSO (30 mL), and the mixture was stirred at room temperature for 48 hours. The reaction mixture was poured into water, and the solution was extracted with chloroform. The extract was washed with water, dried over sodium sulfate and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with dichloromethane/ethylacetate (4/1) to give the ring-opened macrocylic compound **6c** (42.5 mg, 66%). Recrystallization from *n*-hexane/chloroform afforded an analytically pure compound.

Ring-opening Reaction of Macrocylic Compound **5e** under Acidic Conditions.

Compound **5e** (55 mg, 0.074 mmol) was stirred in 50% trifluoroacetic acid (20 mL) at 50 °C for 24 hours. After cooling to room temperature, the reaction mixture was poured into water and neutralized with a saturated aqueous solution of sodium carbonate. The mixture was extracted several times with chloroform. The chloroform layers were combined, washed with water, dried over sodium sulfate, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with dichloromethane/ethylacetate (4/1) to give **7** (16.3 mg, 30%). Recrystallization from chloroform/*n*-hexane gave an analytically pure compound; mp 191-192 °C (decomp.); IR (KBr): 3250, 2930, 1650, 1535, 1405, 1335, 1280, 1190, 1100, 1060, 960, 860, and 750 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.19 (t, 6H, 2x NCH_2CH_3, J = 7.0 Hz), 2.11 (m, 2H, $NCH_2CH_2CH_2N$), 3.82 (q, 4H, 2x NCH_2CH_3, J = 7.1 Hz), 4.37 (t, 4H, $NCH_2CH_2CH_2N$, J = 6.1 Hz), 4.72 (s, 4H, 2x $NCH_2C_5H_3N$), 4.81 (d, 4H, 2x $C_6H_4CH_2NH$, J = 4.9 Hz), 4.89 (d, 4H, 2x $NHCH_2C_6H_4$, J = 3.1 Hz), 7.05-7.78 (m, 13H, aromatic, 2x $C_6H_4CH_2NH$), 10.72 (brs, 2H, 2x $C_6H_4CH_2NHCSNCO$); ^{13}C NMR ($CDCl_3$): δ 12.44, 22.67, 47.07, 49.12, 49.50, 51.28, 55.00, 121.70, 128.27, 128.35, 135.53, 138.36, 138.79, 156.49, 157.36, 183.16, 183.42.

Anal. Calcd. for $C_{35}H_{43}N_9OS_4$: C, 57.27; H, 5.90; N, 17.17. Found: C, 57.54; H, 5.98; N, 17.36.

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