

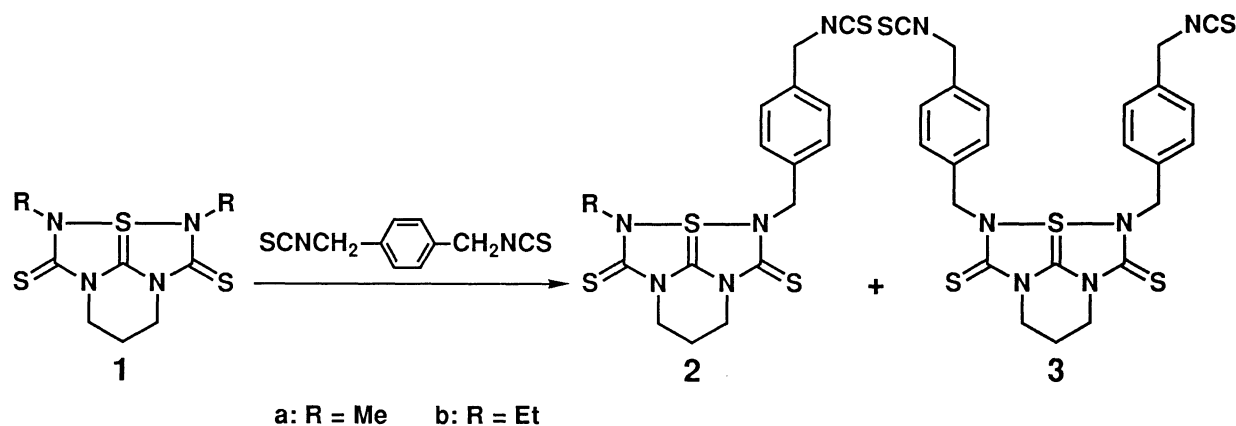
New Synthesis of Macrocyclic Compounds from Tetraazapentalene Derivatives with the Hypervalent Sulfur

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2,3-Bis[(*p*-isothiocyanatomethyl)phenyl)methyl]-6,7-dihydro-5*H*-2*a*-thia(2*a*-*S*^{IV})-2,3,4*a*,7*a*-tetraazacyclopent[*cd*]indene-1,4(2*H*,3*H*)-dithione, prepared from 2,3-dialkyl substituted tetraazapentalene derivatives and *p*-xylylene diisothiocyanate, reacted with *N,N'*-dialkyl substituted diamines to give macrocyclic compounds by ring closure in good yields. These macrocyclic compounds were converted into desulfurized macrocyclic compounds by treatment with NaBH₄ and CF₃COOH.

Cyclic π -electron systems with the hypervalent sulfur have attracted considerable attention because of their unusual structure and reactivity. Many 6*a*-thia(*S*^{IV})pentalene derivatives containing 10 π -electrons in the framework have been synthesized and their physical and chemical properties have been studied.¹⁾ Recently we have synthesized the 10-*S*-3 tetraazapentalene derivatives, 2,3-dimethyl- and 2,3-diethyl-6,7-dihydro-5*H*-2*a*-thia(2*a*-*S*^{IV})-2,3,4*a*,7*a*-tetraazacyclopent[*cd*]indene-1,4(2*H*,3*H*)-dithiones (**1a,b**),²⁾ and reported the unique reactions caused by the nature of the hypervalent sulfur: the isothiocyanate moiety of **1** was replaced by alkyl and aryl isothiocyanates or isocyanates to give other *N*-substituted tetraazapentalene derivatives,³⁾ and the hypervalent sulfur of **1** was eliminated upon treatment with NaBH₄⁴⁾ and CF₃COOH⁵⁾ to give the perhydropyrimidine and perhydropyrimidin-2-one derivatives, respectively. We applied these reactions to the synthesis of macrocyclic compounds and now report the novel method for preparing macrocycles from the tetraazapentalene derivatives with the hypervalent sulfur.



p-Xylylene diisothiocyanate⁶⁾ (881 mg, 4.0 mmol) was added to a stirred solution of **1a,b** (0.40 mmol) in dry benzene (20 cm³) and the mixture was heated at 50 °C for 24 h. After removal of benzene under reduced

pressure, the residue was chromatographed on silica gel with CH_2Cl_2 to give 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**) as a white solid in 46 and 54% yields from **1a,b**, respectively, together with **2a,b** in 33 and 20% yields, respectively. The products were purified by recrystallization from *n*-hexane-chloroform. Their structures were determined by their IR, ^1H NMR,⁷⁾ ^{13}C NMR, and mass spectra, and elemental analyses.

The ring closure of **3** (61 mg, 0.11 mmol) with equimolar quantity of *N,N'*-dialkyl substituted diamines, such as 1,5-bis(ethylamino)-3-oxapentane (**4a**), 1,8-bis(ethylamino)-3,6-dioxaoctane (**4b**), and 2,6-bis(ethylaminomethyl)pyridine (**4c**), was carried out in DMSO (30 cm^3) at room temperature for 48 h. The macrocyclic compounds (**5a-c**) with the tetraazapentalene ring were obtained in good yields with the recovery of **3** in small amounts. The results are shown in Table 1. The structure of **5a-c** was determined by their IR, ^1H NMR,⁷⁾ and FAB mass spectra,⁸⁾ and elemental analyses.

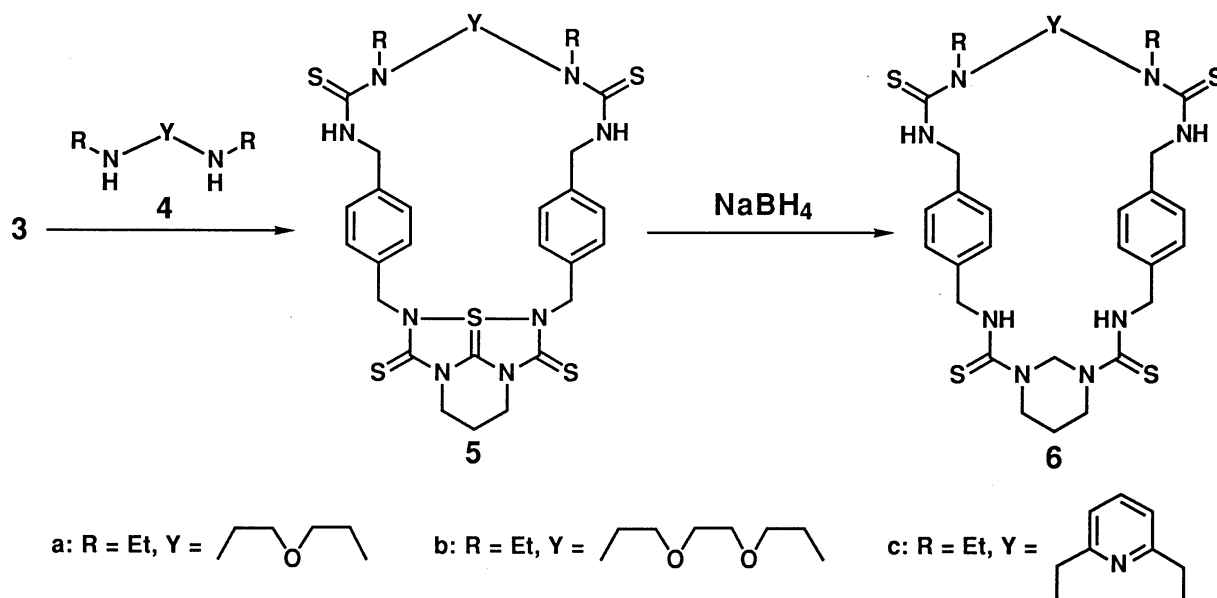


Table 1. The Yields and the Melting Points of the Products **5a-c** and **6a-c**

Diamine	5a-c		6a-c	
	Yield/% ^{a)}	Mp/°C ^{b)}	Yield/% ^{a)}	Mp/°C
4a	85	175-176	66 ^{c)}	140-141
4b	66	223-224	59 ^{d)}	237-238 ^{b)}
4c	69	188-189	40 ^{c)}	213-214 ^{b)}

a) The yields of **5a-c** and **6a-c** were based on **3** and **5a-c**, respectively. b) Decomposed.

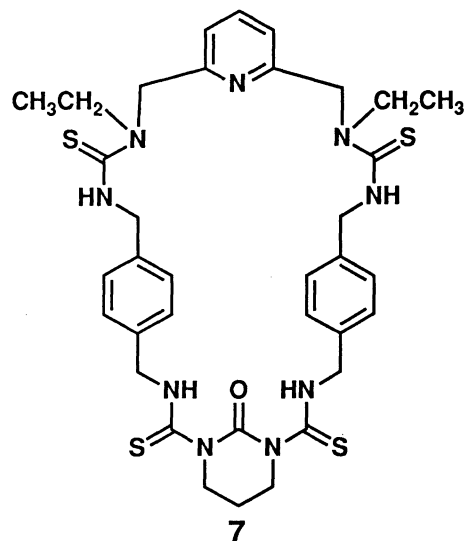
c) DMSO, r.t., 48 h. d) 2-Propanol, r.t., 24 h.

The desulfurization of **5a-c** with NaBH_4 and CF_3COOH was carried out as follows. NaBH_4 was added in large excess (ten equiv.) to a solution of **5a-c** (0.09 mmol) in DMSO or 2-propanol (30 cm^3) at room temperature. The solution changed immediately from colorless to emerald green. After complete fading of the

color, the mixture was stirred for 48 h. Usual work-up of the reaction mixture gave desulfurized macrocyclic compounds (**6a-c**). The results are shown in Table 1. In the case of **5c**, the desulfurization was achieved by treatment with CF_3COOH : a solution of **5c** (52 mg, 0.07 mmol) in 50% aqueous CF_3COOH (15 cm^3) was stirred at 50°C for 24 h and cooled to room temperature. The mixture was poured onto water, neutralized with Na_2CO_3 , and extracted several times with CHCl_3 . The CHCl_3 layer was washed with water, dried over Na_2SO_4 , and concentrated under reduced pressure. The residue was subjected to preparative TLC on silica gel with $\text{CH}_2\text{Cl}_2/\text{AcOEt}$ (4/1), giving the carbonyl-containing product (**7**; mp $191\text{--}192^\circ\text{C}$ (decomp)) in 30% yield with the recovery of **5c** in 50% yield. However, the reactions of **5a,b** with aqueous CF_3COOH under similar conditions gave a complicated mixture. The IR, ^1H NMR,⁷⁾ ^{13}C NMR, and FAB mass spectral data,⁸⁾ and elemental analyses of **6a-c** and **7** supported their structures.

As described above, it became apparent that the novel macrocyclic compounds, **5a-c**, **6a-c**, and **7**, could be prepared from the tetraazapentalene derivatives **1a,b** by utilizing their reactivity. This methodology can be applied to the synthesis of various macrocyclic compounds. Further studies are now in progress.

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- 7) The ^1H NMR spectra were recorded on a JEOL JNM-GX270 spectrometer. **2a**: ^1H NMR(CDCl_3) δ = 2.36 (quint, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$, J = 6.0 Hz), 3.18 (s, 3H, CH_3), 4.40 (t, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$, J = 6.1 Hz), 4.43 (t, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$, J = 6.1 Hz), 4.69 (s, 2H, $\text{NCH}_2\text{C}_6\text{H}_4$), 4.94 (s, 2H, $\text{C}_6\text{H}_4\text{CH}_2\text{NCS}$), and 7.27 - 7.41 (m, 4H, aromatic); **2b**: ^1H NMR(CDCl_3) δ = 1.27 (t, 3H, NCH_2CH_3 , J = 7.0 Hz), 2.37 (quint, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$, J = 5.8 Hz), 3.74 (q, 2H, NCH_2CH_3 , J = 7.3 Hz), 4.40

- (t, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$, $J = 6.1$ Hz), 4.43 (t, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$, $J = 6.1$ Hz), 4.69 (s, 2H, $\text{NCH}_2\text{C}_6\text{H}_4$), 4.94 (s, 2H, $\text{C}_6\text{H}_4\text{CH}_2\text{NCS}$), and 7.26 - 7.43 (m, 4H, aromatic); **3**: ^1H NMR(CDCl_3) $\delta = 2.36$ (quint, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$, $J = 5.8$ Hz), 4.40 (t, 4H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$, $J = 6.0$ Hz), 4.71 (s, 4H, $2 \times \text{NCH}_2\text{C}_6\text{H}_4$), 4.88 (s, 4H, $2 \times \text{C}_6\text{H}_4\text{CH}_2\text{NCS}$), and 7.27 - 7.36 (m, 8H, aromatic); **5a**: ^1H NMR(CDCl_3) $\delta = 1.20$ (t, 6H, $2 \times \text{NCH}_2\text{CH}_3$, $J = 7.0$ Hz), 2.31 (quint, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$, $J = 5.5$ Hz), 3.61 - 3.68 (m, 12H, $\text{CH}_3\text{CH}_2\text{NCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{NCH}_2\text{CH}_3$), 4.36 (t, 4H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$, $J = 5.8$ Hz), 4.73 (s, 4H, $2 \times \text{NCH}_2\text{C}_6\text{H}_4$), 4.85 (d, 4H, $2 \times \text{C}_6\text{H}_4\text{CH}_2\text{NH}$, $J = 4.9$ Hz), 6.45 (brm, 2H, $2 \times \text{C}_6\text{H}_4\text{CH}_2\text{NH}$), and 7.16 - 7.35 (m, 8H, aromatic); **5b**: ^1H NMR(CDCl_3) $\delta = 1.25$ (t, 6H, $2 \times \text{NCH}_2\text{CH}_3$, $J = 7.0$ Hz), 2.27 - 2.37 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$), 3.39 (s, 4H, $\text{OCH}_2\text{CH}_2\text{O}$), 3.58 - 3.64 (m, 8H, $2 \times \text{NCH}_2\text{CH}_2\text{O}$), 3.84 (q, 4H, $2 \times \text{NCH}_2\text{CH}_3$, $J = 7.1$ Hz), 4.36 (t, 4H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$, $J = 5.8$ Hz), 4.76 (s, 4H, $2 \times \text{NCH}_2\text{C}_6\text{H}_4$), 4.80 (d, 4H, $2 \times \text{C}_6\text{H}_4\text{CH}_2\text{NH}$, $J = 5.5$ Hz), and 7.14 - 7.39 (m, 10H, $2 \times \text{C}_6\text{H}_4\text{CH}_2\text{NH}$); **5c**: ^1H NMR(CDCl_3) $\delta = 1.24$ (t, 6H, $2 \times \text{NCH}_2\text{CH}_3$, $J = 7.0$ Hz), 2.26 - 2.36 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$), 3.91 (q, 4H, $2 \times \text{NCH}_2\text{CH}_3$, $J = 7.1$ Hz), 4.29 (s, 4H, $2 \times \text{NCH}_2\text{C}_5\text{H}_3\text{N}$), 4.35 (t, 4H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$, $J = 5.8$ Hz), 4.67 (s, 4H, $2 \times \text{NCH}_2\text{C}_6\text{H}_4$), 4.85 (d, 4H, $2 \times \text{C}_6\text{H}_4\text{CH}_2\text{NH}$, $J = 4.9$ Hz), 7.17 - 7.26 (m, 10H, $2 \times \text{C}_6\text{H}_4\text{CH}_2\text{NH}$), and 7.44 - 7.73 (m, 3H, pyridine ring); **6a**: ^1H NMR(CDCl_3) $\delta = 1.05$ (t, 6H, $2 \times \text{NCH}_2\text{CH}_3$, $J = 6.7$ Hz), 1.76 - 1.85 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$), 3.18 - 3.42 (m, 4H, $2 \times \text{OCH}_2\text{CH}_2\text{N}$), 3.55 - 3.68 (m, 8H, $2 \times \text{OCH}_2\text{CH}_2\text{NCH}_2\text{CH}_3$), 3.96 - 4.08 (m, 4H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$), 4.70 (d, 4H, $2 \times \text{NHCH}_2\text{C}_6\text{H}_4$, $J = 4.3$ Hz), 4.75 (d, 4H, $2 \times \text{C}_6\text{H}_4\text{CH}_2\text{NH}$, $J = 4.9$ Hz), 5.55 (s, 2H, NCH_2N), 6.13 (brm, 2H, $2 \times \text{NHCH}_2\text{C}_6\text{H}_4$), and 7.17 - 7.27 (m, 10H, aromatic and $2 \times \text{C}_6\text{H}_4\text{CH}_2\text{NH}$); **6b**: ^1H NMR(CDCl_3) $\delta = 1.20$ (t, 6H, $2 \times \text{NCH}_2\text{CH}_3$, $J = 7.0$ Hz), 1.70 - 1.80 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$), 3.14 (s, 4H, $\text{OCH}_2\text{CH}_2\text{O}$), 3.46 - 3.56 (m, 8H, $2 \times \text{NCH}_2\text{CH}_2\text{O}$), 3.78 (q, 4H, $2 \times \text{NCH}_2\text{CH}_3$, $J = 6.9$ Hz), 3.93 - 4.05 (m, 4H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$), 4.70 (d, 4H, $2 \times \text{NHCH}_2\text{C}_6\text{H}_4$, $J = 4.3$ Hz), 4.74 (d, 4H, $2 \times \text{C}_6\text{H}_4\text{CH}_2\text{NH}$, $J = 4.9$ Hz), 5.50 (s, 2H, NCH_2N), 7.00 (brm, 2H, $2 \times \text{NHCH}_2\text{C}_6\text{H}_4$), and 7.16 - 7.27 (m, 8H, aromatic), and 7.57 (brm, 2H, $2 \times \text{C}_6\text{H}_4\text{CH}_2\text{NH}$); **6c**: ^1H NMR($\text{DMSO}-d_6$) $\delta = 1.08$ (t, 6H, $2 \times \text{NCH}_2\text{CH}_3$, $J = 7.0$ Hz), 1.71 - 1.83 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$), 3.69 (q, 4H, $2 \times \text{NCH}_2\text{CH}_3$, $J = 6.7$ Hz), 3.80 - 3.95 (m, 4H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$), 4.69 (s, 4H, $2 \times \text{NCH}_2\text{C}_5\text{H}_3\text{N}$), 4.75 (d, 4H, $2 \times \text{NHCH}_2\text{C}_6\text{H}_4$, $J = 4.9$ Hz), 4.79 - 4.83 (m, 4H, $2 \times \text{C}_6\text{H}_4\text{CH}_2\text{NH}$), 5.71 (s, 2H, NCH_2N), 7.00 - 7.72 (m, 11H, aromatic), and 8.37 - 8.42 (brm, 4H, $2 \times \text{NHCH}_2\text{C}_6\text{H}_4\text{CH}_2\text{NH}$); **7**: ^1H NMR(CDCl_3) $\delta = 1.19$ (t, 6H, $2 \times \text{NCH}_2\text{CH}_3$, $J = 7.0$ Hz), 2.11 (quint, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$, $J = 6.1$ Hz), 3.82 (q, 4H, $2 \times \text{NCH}_2\text{CH}_3$, $J = 7.1$ Hz), 4.37 (t, 4H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$, $J = 6.1$ Hz), 4.72 (s, 4H, $2 \times \text{NCH}_2\text{C}_5\text{H}_3\text{N}$), 4.81 (d, 4H, $2 \times \text{C}_6\text{H}_4\text{CH}_2\text{NH}$, $J = 4.9$ Hz), 4.89 (d, 4H, $2 \times \text{NHCH}_2\text{C}_6\text{H}_4$, $J = 3.1$ Hz), 7.05 - 7.78 (m, 13H, aromatic and $2 \times \text{C}_6\text{H}_4\text{CH}_2\text{NH}$), and 10.72 (brm, 2H, $2 \times \text{C}_6\text{H}_4\text{CH}_2\text{NHCSNCO}$).
- 8) **5a**: FAB-MS m/z 715 ($\text{M}+\text{H}$) $^+$; **5b**: FAB-MS m/z 759 ($\text{M}+\text{H}$) $^+$; **5c**: FAB-MS m/z 748 ($\text{M}+\text{H}$) $^+$; **6a**: FAB-MS m/z 687 ($\text{M}+\text{H}$) $^+$; **6b**: FAB-MS m/z 731 ($\text{M}+\text{H}$) $^+$; **6c**: FAB-MS m/z 720 ($\text{M}+\text{H}$) $^+$; **7**: FAB-MS m/z 734 ($\text{M}+\text{H}$) $^+$. All FAB mass spectra were measured by using *m*-nitrobenzylalcohol (NBA) as a matrix.

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