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

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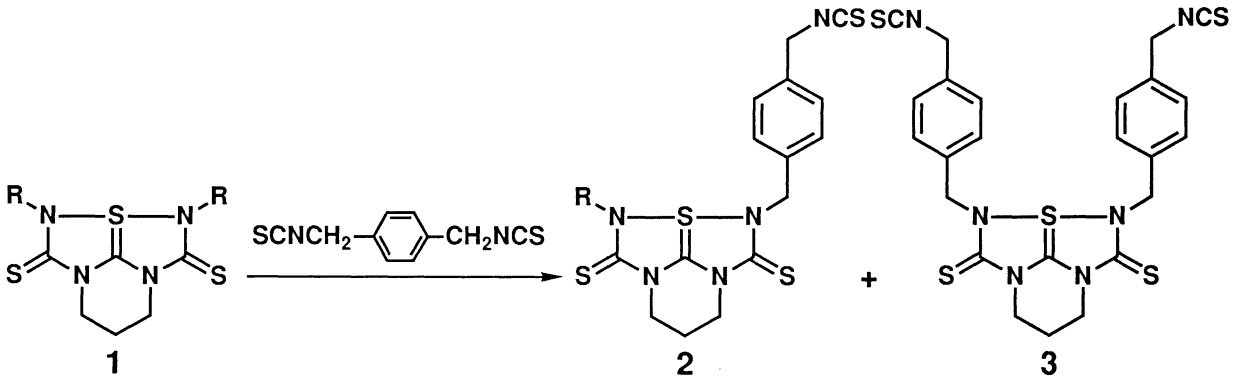
2,3-Bis[(*p*-isothiocyanatomethylphenyl)methyl]-6,7-dihydro-5*H*-2a-thia(2*a*-S^{IV})-2,3,4a,7a-tetraazacyclopent[*cd*]indene-1,4(2*H*,3*H*)-dithione, prepared from 2,3-dialkyl substituted tetraazapentalene derivatives and *p*-xylylene diisothiocyanate, reacted with N,N'-dialkyl substituted diamines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

Cyclic π-electron systems with the hypervalent sulfur have attracted considerable attention because of their unusual structure and reactivity. Many 6a-thia(S^{IV})pentalene derivatives containing 10π-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*-2a-thia(2*a*-S^{IV})-2,3,4a,7a-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 $NaBH_4$[4] and CF_3COOH[5] 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 diisothiocyanate[6] (881 mg, 4.0 mmol) was added to a stirred solution of **1a,b** (0.40 mmol) in dry benzene (20 cm^3) 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(2*a*-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, ^{1}H 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, ^{1}H NMR,[7] and FAB mass spectra,[8] and elemental analyses.

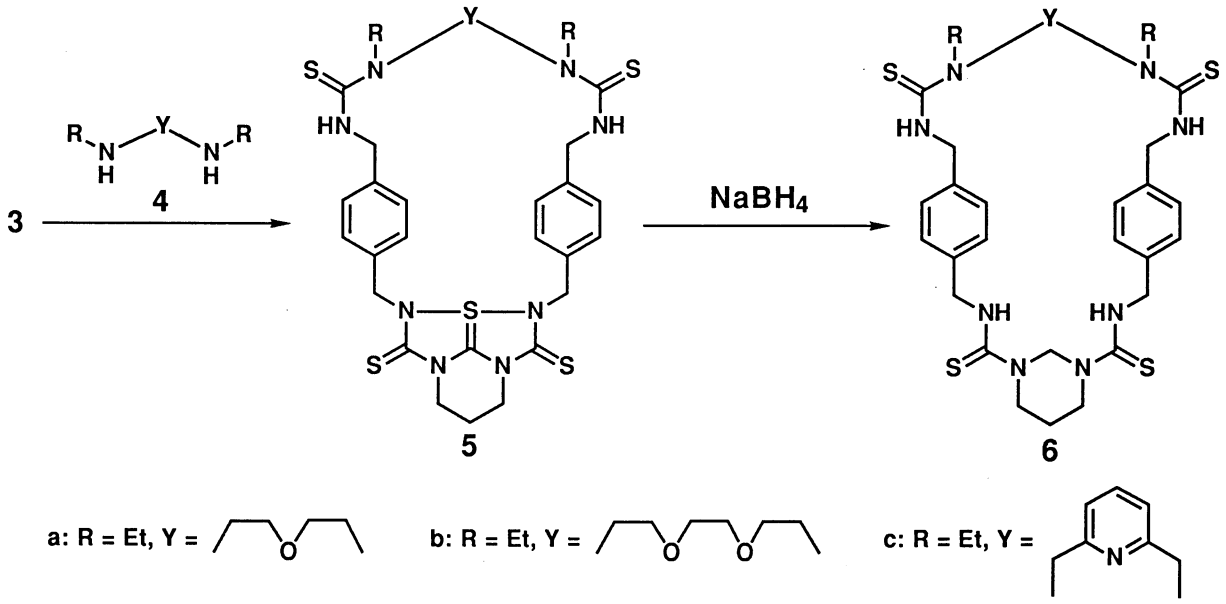


Table 1. The Yields and the Melting Points of the Products **5a-c** and **6a-c**

	5a-c		6a-c	
Diamine	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 CH_2Cl_2/AcOEt (4/1), giving the carbonyl-containing product (**7**; mp 191-192 °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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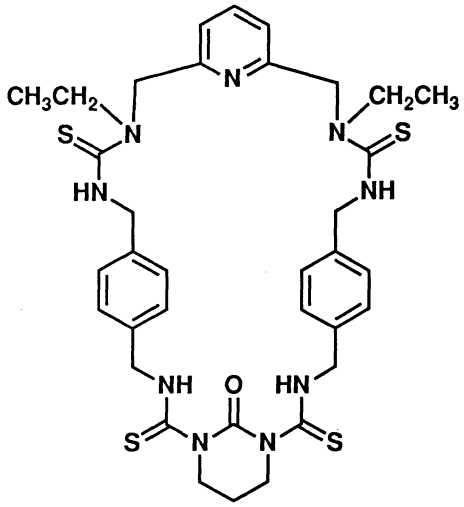

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7) The ^1H NMR spectra were recorded on a JEOL JNM-GX270 spectrometer. **2a**: ^1H NMR($CDCl_3$) δ = 2.36 (quint, 2H, $NCH_2\underline{H_2}CH_2N$, J = 6.0 Hz), 3.18 (s, 3H, $\underline{CH_3}$), 4.40 (t, 2H, $N\underline{CH_2}CH_2CH_2N$, J = 6.1 Hz), 4.43 (t, 2H, $NCH_2CH_2C\underline{H_2}N$, J = 6.1 Hz), 4.69 (s, 2H, $N\underline{CH_2}C_6H_4$), 4.94 (s, 2H, $C_6H_4\underline{CH_2}NCS$), and 7.27 - 7.41 (m, 4H, aromatic); **2b**: ^1H NMR($CDCl_3$) δ = 1.27 (t, 3H, $NCH_2\underline{CH_3}$, J = 7.0 Hz), 2.37 (quint, 2H, $NCH_2\underline{H_2}CH_2N$, J = 5.8 Hz), 3.74 (q, 2H, $N\underline{CH_2}CH_3$, J = 7.3 Hz), 4.40

(t, 2H, $NC\underline{H}_2CH_2CH_2N$, J = 6.1 Hz), 4.43 (t, 2H, $NCH_2CH_2C\underline{H}_2N$, J = 6.1 Hz), 4.69 (s, 2H, $NC\underline{H}_2C_6H_4$), 4.94 (s, 2H, $C_6H_4C\underline{H}_2NCS$), and 7.26 - 7.43 (m, 4H, aromatic); **3**: ^{1}H NMR($CDCl_3$) δ = 2.36 (quint, 2H, $NCH_2C\underline{H}_2CH_2N$, J = 5.8 Hz), 4.40 (t, 4H, $NC\underline{H}_2CH_2C\underline{H}_2N$, J = 6.0 Hz), 4.71 (s, 4H, 2 × $NC\underline{H}_2C_6H_4$), 4.88 (s, 4H, 2 × $C_6H_4C\underline{H}_2NCS$), and 7.27 - 7.36 (m, 8H, aromatic); **5a**: ^{1}H NMR($CDCl_3$) δ = 1.20 (t, 6H, 2 × $NCH_2C\underline{H}_3$, J = 7.0 Hz), 2.31 (quint, 2H, $NCH_2C\underline{H}_2CH_2N$, J = 5.5 Hz), 3.61 - 3.68 (m, 12H, $CH_3C\underline{H}_2NC\underline{H}_2C\underline{H}_2OC\underline{H}_2C\underline{H}_2NC\underline{H}_2CH_3$), 4.36 (t, 4H, $NC\underline{H}_2CH_2C\underline{H}_2N$, J = 5.8 Hz), 4.73 (s, 4H, 2 × $NC\underline{H}_2C_6H_4$), 4.85 (d, 4H, 2 × $C_6H_4C\underline{H}_2NH$, J = 4.9 Hz), 6.45 (brm, 2H, 2 × $C_6H_4CH_2N\underline{H}$), and 7.16 - 7.35 (m, 8H, aromatic); **5b**: ^{1}H NMR($CDCl_3$) δ = 1.25 (t, 6H, 2 × $NCH_2C\underline{H}_3$, J = 7.0 Hz), 2.27 - 2.37 (m, 2H, $NCH_2C\underline{H}_2CH_2N$), 3.39 (s, 4H, $OC\underline{H}_2C\underline{H}_2O$), 3.58 - 3.64 (m, 8H, 2 × $NC\underline{H}_2C\underline{H}_2O$), 3.84 (q, 4H, 2 × $NC\underline{H}_2CH_3$, J = 7.1 Hz), 4.36 (t, 4H, $NC\underline{H}_2CH_2C\underline{H}_2N$, J = 5.8 Hz), 4.76 (s, 4H, 2 × $NC\underline{H}_2C_6H_4$), 4.80 (d, 4H, 2 × $C_6H_4C\underline{H}_2NH$, J = 5.5 Hz), and 7.14 - 7.39 (m, 10H, 2 × $C_6\underline{H}_4CH_2N\underline{H}$); **5c**: ^{1}H NMR($CDCl_3$) δ = 1.24 (t, 6H, 2 × $NCH_2C\underline{H}_3$, J = 7.0 Hz), 2.26 - 2.36 (m, 2H, $NCH_2C\underline{H}_2CH_2N$), 3.91 (q, 4H, 2 × $NC\underline{H}_2CH_3$, J = 7.1 Hz), 4.29 (s, 4H, 2 × $NC\underline{H}_2C_5H_3N$), 4.35 (t, 4H, $NC\underline{H}_2CH_2C\underline{H}_2N$, J = 5.8 Hz), 4.67 (s, 4H, 2 × $NC\underline{H}_2C_6H_4$), 4.85 (d, 4H, 2 × $C_6H_4C\underline{H}_2NH$, J = 4.9 Hz), 7.17 - 7.26 (m, 10H, 2 × $C_6\underline{H}_4CH_2N\underline{H}$), and 7.44 - 7.73 (m, 3H, pyridine ring); **6a**: ^{1}H NMR($CDCl_3$) δ = 1.05 (t, 6H, 2 × $NCH_2C\underline{H}_3$, J = 6.7 Hz), 1.76 - 1.85 (m, 2H, $NCH_2C\underline{H}_2CH_2N$), 3.18 - 3.42 (m, 4H, 2 × $OC\underline{H}_2CH_2N$), 3.55 - 3.68 (m, 8H, 2 × $OCH_2C\underline{H}_2NC\underline{H}_2CH_3$), 3.96 - 4.08 (m, 4H, $NC\underline{H}_2CH_2C\underline{H}_2N$), 4.70 (d, 4H, 2 × $NHC\underline{H}_2C_6H_4$, J = 4.3 Hz), 4.75 (d, 4H, 2 × $C_6H_4C\underline{H}_2NH$, J = 4.9 Hz), 5.55 (s, 2H, $NC\underline{H}_2N$), 6.13 (brm, 2H, 2 × $N\underline{H}CH_2C_6H_4$), and 7.17 - 7.27 (m, 10H, aromatic and 2 × $C_6H_4CH_2N\underline{H}$); **6b**: ^{1}H NMR($CDCl_3$) δ = 1.20 (t, 6H, 2 × $NCH_2C\underline{H}_3$, J = 7.0 Hz), 1.70 - 1.80 (m, 2H, $NCH_2C\underline{H}_2CH_2N$), 3.14 (s, 4H, $OC\underline{H}_2C\underline{H}_2O$), 3.46 - 3.56 (m, 8H, 2 × $NC\underline{H}_2C\underline{H}_2O$), 3.78 (q, 4H, 2 × $NC\underline{H}_2CH_3$, J = 6.9 Hz), 3.93 - 4.05 (m, 4H, $NC\underline{H}_2CH_2C\underline{H}_2N$), 4.70 (d, 4H, 2 × $NHC\underline{H}_2C_6H_4$, J = 4.3 Hz), 4.74 (d, 4H, 2 × $C_6H_4C\underline{H}_2NH$, J = 4.9 Hz), 5.50 (s, 2H, $NC\underline{H}_2N$), 7.00 (brm, 2H, 2 × $N\underline{H}CH_2C_6H_4$), and 7.16 - 7.27 (m, 8H, aromatic), and 7.57 (brm, 2H, 2 × $C_6H_4CH_2N\underline{H}$); **6c**: ^{1}H NMR(DMSO-d_6) δ = 1.08 (t, 6H, 2 × $NCH_2C\underline{H}_3$, J = 7.0 Hz), 1.71 - 1.83 (m, 2H, $NCH_2C\underline{H}_2CH_2N$), 3.69 (q, 4H, 2 × $NC\underline{H}_2CH_3$, J = 6.7 Hz), 3.80 - 3.95 (m, 4H, $NC\underline{H}_2CH_2C\underline{H}_2N$), 4.69 (s, 4H, 2 × $NC\underline{H}_2C_5H_3N$), 4.75 (d, 4H, 2 × $NHC\underline{H}_2C_6H_4$, J = 4.9 Hz), 4.79 - 4.83 (m, 4H, 2 × $C_6H_4C\underline{H}_2NH$), 5.71 (s, 2H, $NC\underline{H}_2N$), 7.00 - 7.72 (m, 11H, aromatic), and 8.37 - 8.42 (brm, 4H, 2 × $N\underline{H}CH_2C_6H_4CH_2N\underline{H}$); **7**: ^{1}H NMR($CDCl_3$) δ = 1.19 (t, 6H, 2 × $NCH_2C\underline{H}_3$, J = 7.0 Hz), 2.11 (quint, 2H, $NCH_2C\underline{H}_2CH_2N$, J = 6.1 Hz), 3.82 (q, 4H, 2 × $NC\underline{H}_2CH_3$, J = 7.1 Hz), 4.37 (t, 4H, $NC\underline{H}_2CH_2C\underline{H}_2N$, J = 6.1 Hz), 4.72 (s, 4H, 2 × $NC\underline{H}_2C_5H_3N$), 4.81 (d, 4H, 2 × $C_6H_4C\underline{H}_2NH$, J = 4.9 Hz), 4.89 (d, 4H, 2 × $NHC\underline{H}_2C_6H_4$, J = 3.1 Hz); 7.05 - 7.78 (m, 13H, aromatic and 2 × $C_6H_4CH_2N\underline{H}$), and 10.72 (brm, 2H, 2 × $C_6H_4CH_2N\underline{H}CSNCO$).

8) **5a**: FAB-MS m/z 715 $(M+H)^+$; **5b**: FAB-MS m/z 759 $(M+H)^+$; **5c**: FAB-MS m/z 748 $(M+H)^+$; **6a**: FAB-MS m/z 687 $(M+H)^+$; **6b**: FAB-MS m/z 731 $(M+H)^+$; **6c**: FAB-MS m/z 720 $(M+H)^+$; **7**: FAB-MS m/z 734 $(M+H)^+$. All FAB mass spectra were measured by using *m*-nitrobenzylalcohol (NBA) as a matrix.

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