Synthesis and Characterization of Macrocyclic Polyaza(2,5)pyridinophanes Possessing Vitamin B_6 Functionality

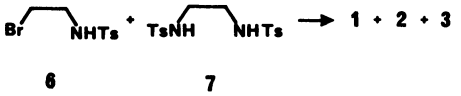
Masaaki IWATA* and Hiroyoshi KUZUHARA
Riken (The Institute of Physical and Chemical Research), Wako, Saitama 351-01
(Received November 14, 1985)

Series of macrocyclic polyaza[*m*](2,5)pyridinophanes (poly=tri, tetra, penta; *m*=9, 12, 15)(**8**—**10**) and polyaza[*m*]paracyclophanes (**11**—**13**) were synthesized in excellent yields by the reaction of dichloropyridoxine derivatives (**4**) and α,α'-dibromo-*p*-xylene (**5**), respectively, with a series of 1,2-ethanediamine derivatives (**1**—**3**). These phanes were characterized on the basis of ^{1}H NMR spectra. The methyl group at C_6 of the pyridoxine moiety (**a**-series) revealed restricted rotation for all bridge sizes (*m*=9—15). In **8**—**10** without the methyl group (**b**-series), *m*=12 was the boundary between restricted and free rotation. In series **11**—**13**, only **11** (*m*=9) showed restricted rotation. Atomic group equivalence was discussed in terms of boundary restricted rotation and an empirical rule for the prediction of the relationship between the bridge size and restricted rotation was proposed.

Along the line of our continuing interest in chemical congeners for coenzyme-B_6, dithia(2,5)pyridinophanes[1] and diaza(2,5)pyridinophanes[2] have been prepared and characterized. Their properties have been compared with those of coemzyme-B_6. These artificial coenzymes feature outstanding stability and efficiency in comparison with natural coenzyme, with excellent stereoselectivity for specific amino acids. By functionalizing the bridge moiety, we have designed new artificial coenzymes with additional sites for complexation in consideration of host-guest complexation.[3] In terms of the previously reported relationship between restricted rotation and the length of the bridge chain[2b] and predictable synthetic feasibility owing to molecular symmetry, we selected 1,2-ethanediamine derivatives (**1**—**3**) as the bridge moiety. In the present report, we would like to describe the details of synthesis and properties of macrocyclic polyaza(2,5)pyridinophanes and -paracyclophanes.

Results and Discussion

Preparation of 1,2-Ethanediamine Derivatives (1—3). It was expected that chain elongation of the 1,2-ethanediamine could be achieved by iterative reaction of *N*-(2-bromoethyl)tosylamide (**6**) with *N,N'*-ditosyl-1,2-ethanediamine (**7**). It was difficult, however, to prepare pure *N,N*-bis[2-(tosylamino)ethyl]tosylamide (**1**), since further alkylation occurred to give the higher homologues, **2** and **3**. Thus, **1**—**3** were obtained by chromatographic separation of the reaction mixture. ^{1}H NMR spectral data of **1**—**3** are summarized in Fig. 1.



6 **7**

Scheme. 1. Synthesis of poly(*N*-tosyl-1,2-ethanediamine) derivatives (**1**—**3**).

Synthesis of Polyaza[*m*](2,5)pyridinophanes (8—10) and Polyaza[*m*]paracyclophanes (11—13) (*m*=9, 12, 15).[4] The synthetic procedure was based on a previously reported method[2] except that the reaction temperature was lowered to room temperature and the sulfonamide was not metallated before the reaction but reacted directly in the presence of excess potassium carbonate. Therefore, 1,2-ethanediamine derivatives (**1**—**3**) reacted independently in DMF with protected dichloropyridoxine hydrochloride (**4**) at room temperature to give polyaza[*m*](2,5)pyridinophanes (**8**—**10**) (*m*=9, 12, 15). Work-up was just the same as in the preceding report.[2b] Likewise, **1**—**3** reacted with α,α'-dibromo-*p*-xylene (**5**) to afford polyaza[*m*]pracyclophanes (**11**—**13**) (*m*=9, 12, 15). The results obtained are summarized in Table 1.

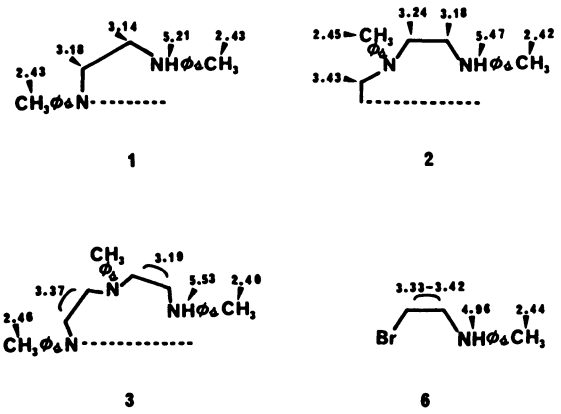
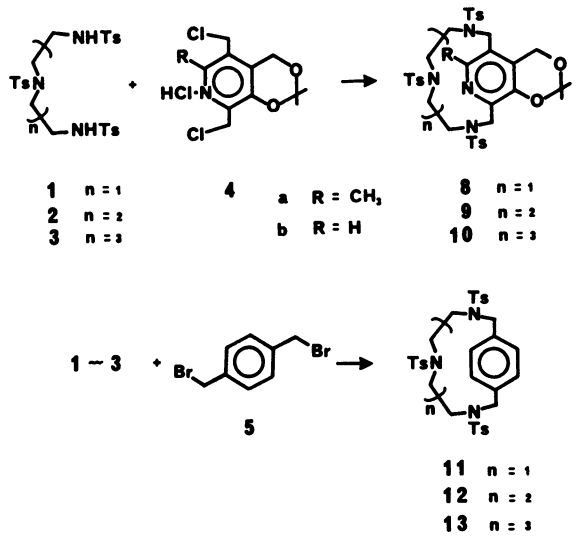


Fig. 1. ^{1}H NMR spectral data of open chain *p*-tosylamides **1**, **2**, **3**, and **6** (δ, in $CDCl_3$); the structure shown is a half part of the molecule due to its molecular symmetry for **1**, **2**, and **3**.

Although the reaction conditions were not optimized, product yields were unexpectedly excellent. The compounds, **11** and **12**, were incidentally purified by one recrystallization of the reaction mixture after work-up without the necessity of silica-gel chromatography.

Properties. Referred to the present design, it is of special importance to characterize the property with regard to relationship between induced restricted rotation and miximum numbers of nitrogen atoms included on the bridge chain. The presence of restricted rotation has been judged by the simple criteria based on



Scheme 2. Preparation of polyaza[m](2,5)pyridinophanes (**8—10**) and polyaza[m]paracyclophanes (**11—13**) (poly=tri, tetra, penta).

Table 1. Preparation of Polyaza[m](2,5)pyridinophanes and Polyaza[m]paracyclophanes

Compd	Yield[a] %	Mp θ_m/°C	Rotation[b]	Bridge size[c]/m	Included N atom
8a	94	230[d]	R	9	3
9a	70	126—128	R	12	4
10a	47	155—157	R	15	5
8b	95	230—232[d]	R	9	3
9b	98	247—249[d]	B	12	4
10b	68	133—135	F	15	5
11	96	274—275	B	9	3
12	96	282—284	F	12	4
13	72	131—133	F	15	5

a) Isolated yield after purification. b) Represents the presence or the absence of molecular rotation judged from ^{1}H NMR spectral signal (see Table 2). c) Numbers of the disposed atoms on the bridge chain. d) Decomposed.

^{1}H NMR spectral analysis.[1a,g,2b] The methyl protons in the isopropylidene group are informative as well for the judgment of restricted rotation. They appear as two separate sharp singlets if restricted rotation is induced. They become broadening to be one singlet signal if the bridge is in the boundary length. A sharp singlet signal is detected if free rotation is allowed. On the basis of these empirical criteria, rotational properties of the polyaza[m](2,5)pyridinophanes (**8—10**) and polyaza[m]paracyclophanes (**11—13**) are clearly determined. In Figs. 2, 3, and 4, parts of ^{1}H NMR spectra are depicted in the region δ 2.5—5.5. These signals are assignable to the methylene protons attached to the aromatic ring and to the methylene protons in the bridge. In Fig. 2, it is common feature that the methylene protons contiguous to the pyridine ring are split into AB quartet patterns though the methylene protons contiguous to the oxygen atom appear as incidental singlet (spectrum a) at δ 4.78 and signal overlapping

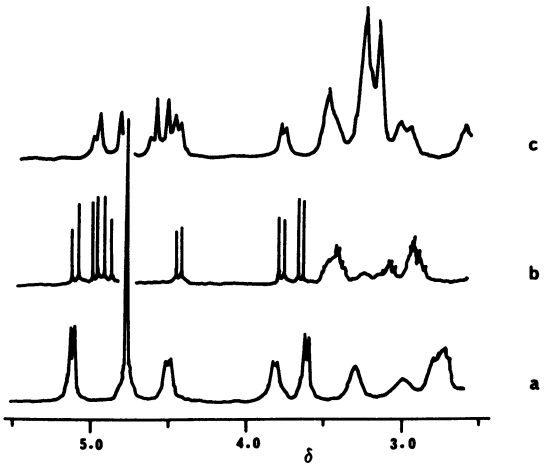


Fig. 2. ^{1}H NMR spectra of methyl-polyaza[m](2,5)-pyridinophanes (a-series) in the region δ=2.5—5.5; **a** for **8a** (m=9), **b** for **9a** (m=12), and **c** for **10a** (m=15) ($CDCl_3$, 18°C).

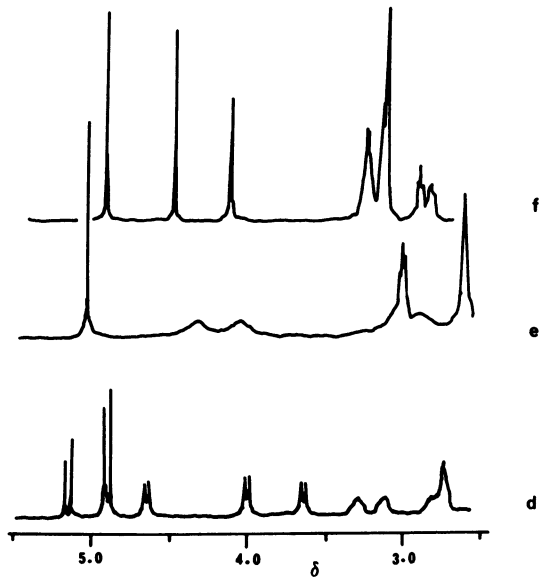


Fig. 3. ^{1}H NMR spectra of polyaza[m](2,5)pyridinophanes (b-series) in the region δ=2.5—5.5; **d** for **8b** (m=9), **e** for **9b** (m=12), and **f** for **10b** (m=15) ($CDCl_3$, 18°C).

is observable (spectrum c). In Fig. 3, three typical patterns of restricted rotation (spectrum d), boundary (spectrum e), and free rotation (spectrum f) are incidentally demonstrated. Since polyaza[m]paracyclophanes (**11—13**) have symmetry element in each case, it would not be chiral in any case. However, restricted rotation resulting in line-broadening are detectable in **11** (spectrum g in Fig. 4).

Relationship between restricted rotation and bridge chain length for all series of (2,5)pyridinophanes so far investigated is summarized in Table 2. This presents information about practical spherical bulk of atomic groups, S, N, and CH_2, and about prediction rule for restricted rotation of unsynthesized congeners. In comparison of dithiapyridinophanes (S-series)[1a,b,g]

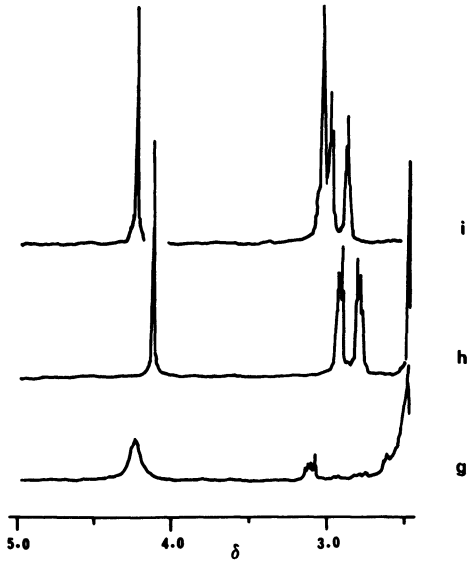


Fig. 4. ^{1}H NMR spectra of polyaza[m]paracyclophanes in the region δ=2.5—5.0; **g** for **11** (m=9), **h** for **12** (m=12), and **i** for **13** (m=15) ($CDCl_3$, 18°C).

with diazapyridinophanes (N-series),[2b] it is found that spherical bulk of two sulfur atoms is correlated nearly to that of two nitrogen atoms plus one methylene group. Equivalence of spherical bulk of one nitrogen atom to that of one methylene group could be seen when diazapyridinophanes (N-series)[2b] and polyazapyridinophanes (N-pAz-series), or methyl-diazapyridinophanes (Me-N-series)[2b] and methyl-polyazapyridinophanes (Me-N-pAz-series) are compared. Furthermore, it is seen that introduction of the methyl group into the pyridine ring at C_6-position provides expansion of the bridge chain required for restricted rotation by three to four methylene units (compare N-series with methyl-diazapyridinophanes (Me-N-series)[2b] or N-pAz-series with Me-N-pAz-series). Therefore, it is predictable that methyl-dithiapyridinophanes (Me-S-series), in which complete set of comparable series of congeners has not been synthesized, would show boundary bridge size at m=14 for restricted rotation. In addition, empirical conclusion drawn from the consideration of spherical bulk of atomic groups is well coincident with theoretical result calculated from covalent radii for individual atoms as has been previously pointed out.[2b]

It is of special significance that methyl-pentaaza[15]-(2,5)pyridinophane (**10a**) still retains restricted rotation since this contains five nitrogen atoms on the bridge probably enough to incorporate a guest in a mechanism of peripheral complexation proposed for catecholamine-macrocyclic polyamine complex.[3b] Since appropriate guests should be a matter of choice, polyaza[m]paracyclophanes (**11**—**13**) would contribute to provide informations about selection of guest molecules and mechanism of complexation.

Table 2. Relationship between Restricted Rotation and Bridge Chain Length in [m](2,5)Pyridinophanes Based on ^{1}H NMR Spectra
(F; free rotation, R; restricted rotation, B; boundary)

$(CH_2)_n$ n	Bridge Size/m	Compound Types[a]					
		S	Me-S	*N*	Me-N	N-pAz	Me-N-pAz
4	8	R					
5	9	R		R	R	R	R
6	10	R		R	R		
7	11	B[b]		R	R		
8	12	F	R	B	R	B	R
9	13		R[b]	F	R		
10	14		B[b]	F	R		
11	15		F[b]		B[b]	F	R
12	16			F	F		

a) S and N stand for pyridinophane with sulfur and nitrogen atoms at juncture point. Prefix Me- represents the presence of the methyl substituent on pyridoxine moiety at C_6-position. Suffix -pAz shows polyaza-containing bridge repeated by the iminoethylene group. See actual structures in Ref. 1a, b, g) for S, in Ref. 2b) for Me-S, N, and Me-N, and in the present report for N-pAz (**8a**—**10a**) and Me-N-pAz (**8b**—**10b**). b) Based on the empirical rule for the prediction of spherical bulk of the atomic group.

Experimental

The ^{1}H NMR spectra ware recorded in $CDCl_3$ on a JEOL JNM-GX 400 (400 MHz) spectrometer with Me_4Si as the internal standard; chemical shifts (δ) and coupling constants (J) are in parts per million and Herz, respectively. Infrared spectra (IR) were obtained as KBr disks on a Shimadzu IR-27G spectrophotometer. Mass spectra (MS, rel intensity) were obtained on a Hitachi RMU 6-MG spectrometer by using a direct-inlet method, an ionizing potential of 20 eV, and sample and chamber temperatures of 230°C. Merck silica gel 60 (Art. 7734, 0.063—0.20) was used for column chromatography, and Merck precoated silica gel 60 F_{254} plates (Art. 5715, 20×20 cm) were used for thin-layer chromatography (TLC). Two solvent systems were used for column chromatography and TLC unless otherwise mentioned; benzene-acetone 9:1 v/v (solvent A) and chloroform-acetone 93:7 v/v (solvent B). Product spots on TLC were detected either with a UV-lamp or in an iodine vapor bath. *N,N*-Dimethylformamide (DMF) was dried over molecular sieves (Type A), and the supernate was used directly for the reaction. The uncorrected melting points were measured with a micro melting point apparatus (Yanagimoto Seisakusho, Serial No. 2647). *N,N'*-Ditosyl-1,2-ethanediamine (**7**) was prepared from 1,2-ethanediamine according to a method previously reported.[5] 5'-Deoxy-2',5'-dichloro-3,4'-*O*-isopropylidene-6-methylpyridoxine hydrochloride (**4a**)[6] and 5'-deoxy-2',5'-dichloro-3,4'-*O*-isopropylidenepyridoxine (**4b**)[2b] were prepared immediately preceding the coupling reaction to sulfonamides from the corresponding dihydroxypyridoxine derivatives.

***N*-(2-Bromoethyl)-*p*-toluenesulfonamide (6).**[7] To a stirred solution of 2-bromoethylamine hydrobromide (40.0 g, 0.195 mol) in 320 ml of pyridine at 0—5°C, *p*-toluenesulfonyl chloride (48.38 g, 0.245 mol; 1.3 equiv) was added at once. The reaction was monitored by TLC (solvent B) every ten

min. When the absence of HBr-free 2-bromoethylamine was detected by spraying ninhydrin at R_f=0 (3 h), the mixture was poured into 2.6 l of water containing NaCl and stirred for ca. 1 h. The precipitate was collected by filtration and recrystallized from chloroform–cyclohexane to give 49.13 g of **6** (91%) as colorless leaflets: mp 93.5—94.5 °C (lit,[7] mp 88—90 °C); Calcd for $C_9H_{12}O_2NSBr$: C, 38.86; H, 4.35; N, 5.04; S, 11.53; Br, 28.73. Found: C, 38.99; H, 4.36; N, 5.01; S, 11.45; Br, 28.60. The yield of **6** was dependent on reaction temperature and time; at ambient temperature, the reaction mixture included considerable amounts of the corresponding dimer, *N*-(2-bromoethyl)-*N,N'*-ditosyl-1,2-ethanediamine. It was difficult to separate this from **6**, either on TLC or by recrystallization. Thus, the purity marker of **6** was elemental analyses and ^{1}H NMR. ^{1}H NMR data are shown in Fig. 1.

1,2-Ethanediamine Derivatives (1—3). Method A. To a suspended mixture of disodium *N,N'*-ditosyl-1,2-ethanediamine in DMF (55 ml) which was prepared by the reaction of *N,N'*-ditosyl-1,2-ethanediamine (2.0 g) with sodium metal (0.29 g, 2.3 equiv) in ethanol (30 ml) (refluxed for 1.5 h) followed by evaporation of ethanol, *N*-(2-bromoethyl)-*p*-toluenesulfonamide (**6**) (3.02 g, 2 equiv) in 20 ml of DMF was added dropwise at ca. 80 °C and then stirred until **6** disappeared. The reaction mixture was poured into 200 ml of water and the precipitate was collected by filtration. Silica-gel chromatography eluting with benzene–ethyl acetate (4:1 v/v) provided 1.26 g (63%) of the starting *N,N'*-ditosyl-1,2-ethanediamine, 0.47 g (15%) (R_f=0.3) of **1**, and 0.9 g (22%) (R_f=0.4) of **2** were isolated. Recrystallization of **1** from ethanol gave colorless crystals; mp 164—166 °C. Calcd for $C_{25}H_{31}O_6N_3S_3$: C, 53.07; H, 5.52; N, 7.43; S, 17.00. Found: C, 52.87; H, 5.58; N, 7.37; S, 16.96. MS: *m/z* 410 (the highest peak, 1.2%, M^+−155(Ts)) and 184 (100%, CH_2NHTs). IR: 3290(NH), and 1325 and 1150(SO_2) cm^{-1}. ^{1}H NMR spectral data are shown in Fig. 1. Recrystallization of **2** from ethanol gave colorless crystals; mp 193—195 °C. Calcd for $C_{34}H_{42}O_8N_4S_4$: C, 53.52; H, 5.55; N, 7.34; S, 16.81. Found: C, 53.57; H, 5.53; N, 7.20; S, 16.45. IR: 3290(NH), and 1325 and 1155(SO_2) cm^{-1}. ^{1}H NMR spectral data are shown in Fig. 1.

Method B. (a) A mixture of *N,N'*-ditosyl-1,2-ethanediamine (7.00 g), *N*-(2-bromoethyl)-*p*-toluenesulfonamide (5.813 g, 1.1 equiv) and 7.88 g (3 equiv) of anhydrous potassium carbonate in 250 ml of DMF was stirred at room temperature for 16 h. The reaction mixture was poured into 2.5 l of water and the precipitate was collected by filtration. Chromatography on silica gel eluting with chloroform–acetone (15:1 to 12:1 to 10:1 to 85:15 v/v) gave **1**, **2**, and **3** in the ratio 5:4:1. Recrystallization of **3** from chloroform–metahnol gave colorless crystals; mp 166—167 °C. Calcd for $C_{43}H_{53}O_{10}N_5S_5$: C, 53.78; H, 5.56; N, 7.29; S, 16.70. Found: C, 53.64; H, 5.53; N, 7.29; S, 16.58. IR: 3280(NH), and 1340 and 1155(SO_2) cm^{-1}. ^{1}H NMR spectral data are shown in Fig. 1.

(b) A mixture of **1** (2.03 g), *N*-(2-bromoethyl)-*p*-toluenesulfonamide (1.098 g, 1.1 equiv) and 0.99 g (2 equiv) of anhydrous potassium carbonate in 50 ml of DMF was stirred at room temperature for 53 h. After work-up as before, the residue was chromatographed on silica gel eluting with chloroform–acetone (10:1 to 9:1 v/v) to give recovered **1** (0.5 g), **2** (1.7 g), and **3** (0.4 g).

General Preparation Method of Polyaza(2,5)pyridinophanes and Polyazaparacyclophanes. To a stirred mixture of *N*-tosylated 1,2-ethanediamine derivatives (**1—3**) and excess anhydrous potassium carbonate (14 equiv mol to **1—3**) in DMF (1.5 g of **1—3**/150 ml of DMF) at room temperature, dichloropyridoxine (**4a,b**) (1 equiv) dissolved in DMF (0.5 g of **4a,b**/15 ml of DMF) was added dropwise (1 h). The stirring was continued for 12 h. The reaction mixture was poured into water containing NaCl. The resulting precipitate was collected by filtration followed by purification with silica-gel chromatography, unless otherwise noted. The product yield and mp are listed in Table 1. Line shapes of their ^{1}H NMR spectra are depicted comparatively in Figs. 2, 3, and 4 at δ 2.5=5.5. IR spectra of **8a—10a, 8b—10b,** and **11—13** are commonly characterized by bands at ca. 1600, 1340, and 1155(SO_2), and ca. 1380($C(CH_3)_2$) cm^{-1}. Specifically reported IR data are limited to the bands in the region 900—500 cm^{-1}.

N^2,N^5,N^8-Tritosyl-14-hydroxy-15-hydroxymethyl-14,15'-*O*-isopropylidene-11-methyl-2,5,8-triaza[9](2,5)pyridinophane (8a). Starting from **1** (1.186 g) and **4a** prepared from the corresponding dihydroxy-6-methylpyridoxine derivative (0.52 g, 1.04 equiv) in the presence of anhydrous potassium carbonate (4.056 g, 14 equiv) in 50 ml of DMF, 1.51 g (94%) of **8a** was obtained. Recrystallization from ethanol gave colorless crystals; Calcd for $C_{37}H_{44}O_8N_4S_3$: C, 57.53; H, 6.10; N, 6.95; S, 11.94. Found: C, 57.33; H, 5.96; N, 6.74; S, 12.13. R_f=0.73 (chloroform–acetone 85:15 v/v). IR: 812, 745, 656, 582, 570, 560, and 545 cm^{-1}. ^{1}H NMR: 1.50 and 1.58 (3H each, s, $C(C\underline{H}_3)_2$), 1.87 (1H, m, H-C-$\underline{H}$), 2.27 (3H, m, $C\underline{H}_2$), 2.73 (2H, m, $C\underline{H}_2$), 3.0 (1H, m, $C\underline{H}_2$), 3.31 (1H, m, $C\underline{H}_2$), 3.62 and 5.13 (1H each, AB-q, J=11.47, py-$C_{(5')}\underline{H}_2$-N), 3.84 and 4.50 (1H each, AB-q, J=12.16, py-$C_{(2')}\underline{H}_2$-N), 4.78 (2H, s, py-$C_{(4')}\underline{H}_2$-O), 2.44, 2.64, 2.47, and 2.49 (3H each, s, Ar-$C\underline{H}_3$), 7.31 (4H, m, aromatic protons) and 7.37, 7.63, 7.67, and 7.70 (2H each, d, J=8.05, aromatic protons). MS *m/z* 613 (31%, M^+−155(Ts); the highest peak).

N^2,N^5,N^8,N^{11}-Tetratosyl-17-hydroxy-18-hydroxymethyl-17,18'-*O*-isopropylidene-14-methyl-2,5,8,11-tetraaza[12](2,5)-pyridinophane (9a). Starting from **2** (2.326 g) and **4a** prepared from the corresponding dihydroxy-6-methylpyridoxine derivative (0.765 g, 1.04 equiv) in the presence of anhydrous potassium carbonate (5.90 g, 14 equiv) in 200 ml of DMF, 2.065 g (70.1%) of **9a** was isolated. Recrystallization from ethanol gave colorless crystals; Calcd for $C_{46}H_{55}O_{10}N_5S_4$: C, 57.18; H, 5.74; N, 7.25; S, 13.28. Found: C, 56.92; H, 5.70; N, 7.17; S, 13.32. R_f=0.50 (solvent A). IR: 810, 760, 734, 650, 572, 565, and 545 cm^{-1}. ^{1}H NMR: 1.45 and 1.53 (3H each, s, $C(C\underline{H}_3)_2$), 2.33 (3H, s, py-$C\underline{H}_3$), 2.46, 2.45, and 2.48 (3H, 6H, 3H each, s, $SO_2C_6H_4$-$C\underline{H}_3$), 2.05 (1H, m, $C\underline{H}_2$), 2.25 (1H, m, $C\underline{H}_2$), 2.35 (1H, m, $C\underline{H}_2$), 2.50 (1H, m, $C\underline{H}_2$), 2.93 (3H, m, $C\underline{H}_2$), 3.07 (2H, m, $C\underline{H}_2$), 3.40 (3H, m, $C\underline{H}_2$), 3.65 and 4.97 (1H each, AB-q, J=12.33, py-$C_{(2')}\underline{H}$-N), 3.77 and 4.43 (1H each, AB-q, J=13.31, py-$C_{(5')}\underline{H}_2$-N), 4.89 and 5.09 (1H each, AB-q, J=17.34, py-$C_{(4')}\underline{H}_2$-O), 7.33 (4H, m, aromatic protons), and 7.35, 7.42, 7.67, 7.71, 7.77, and 7.80 (2H each, d, J=8.30, aromatic protons). MS *m/z* 606 (0.1%, M^+−155(Ts)-205; the highest peak).

N^2,N^5,N^8,N^{11},N^{14}-Pentatosyl-20-hydroxy-21-hydroxymethyl-20,21'-*O*-isopropylidene-17-methyl-2,5,8,11,14-pentaaza[15](2,5)pyridinophane (10a). Starting from **3** (2.80 g) and **4a** prepared from the corresponding dihydroxy-6-methylpyridoxine derivative (0.698 g, 1.04 equiv) in the presence of anhydrous potassium carbonate (5.64 g, 14 equiv) in 200 ml of DMF, 1.58 g (46.6%) of **10a** was isolated. Recrystallization from benzene–ethanol gave colorless crystals. Calcd for

$C_{55}H_{66}O_{12}N_6S_5$: C, 56.78; H, 5.72; N, 7.22; S, 13.78. Found: C, 56.91; H, 5.72; N, 7.15; S, 13.66. R_f=0.63 (chloroform–acetone 95:5 v/v). IR: 810, 740, 712, 690, 655, 572, and 546 cm^{-1}. ^{1}H NMR: 1.25 and 14.9 (3H each, b-s, C(CH_3)$_2$), 2.06 (3H, s, py-CH_3), 2.36, 2.38, 2.44, 2.45, and 2.50 (3H each, s, $SO_2C_6H_4$-CH_3), 2.00, 2.40, 2.60, 3.00, and 3.46 (1H, 1H, 1H, 2H, 3H each, m, N-CH_2CH_2-N), 3.14 and 3.23 (8H total, m, N-CH_2CH_2-N), 3.76 and 4.44 (1H each, AB-q, J=12.45, py-$C_{(5')}H_2$-N), 4.49 and 4.59 (1H each, AB-q, J=14.16, py-$C_{(2')}H_2$-N), 4.79 and 4.96 (1H each, AB-q, J=15.75, py-$C_{(4')}H_2$-O), MS m/z 578 (0.1%; the highest peak).

N^2,N^5,N^8-Tritosyl-14-hydroxy-15-hydroxymethyl-14,15′-*O*-isopropylidene-2,5,8-triaza[9](2,5)pyridinophane (8b). Starting from **1** (0.89 g) and **4b** prepared from the corresponding dihydroxypyridoxine derivative (0.48 g, 1.35 equiv) in the presence of anhydrous potassium carbonate (4.1 g, 14 equiv) in 150 ml of DMF, 1.125 g (95%) of **8b** was obtained. Recrystallization from acetone–ethanol gave colorless crystals. Calcd for $C_{36}H_{42}O_8N_4S_3$: C, 57.27; H, 5.61; N, 7.42; S, 12.74. Found: C, 57.37; H, 5.61; N, 7.32; S, 12.75. R_f=0.55 (solvent B). IR: 810, 765, 755, 740, 655, 585, 575, and 545 cm^{-1}. ^{1}H NMR: 1.54 and 1.56 (3H each, s, C(CH_3)$_2$), 1.75, 2.34, 2.40, 2.80, 3.12, and 3.30 (1H each, m, N-CH_2CH_2-N), 2.72 (2H, m, N-CH_2CH_2-N), 2.45 and 2.47 (6H and 3H, s, $SO_2C_6H_4$-CH_3), 3.64 and 4.64 (1H each, AB-q, J=12.45, py-$C_{(5')}H_2$-N), 4.00 and 4.89 (1H each, AB-q, J=11.23, py-$C_{(2')}H_2$-N), 4.90 and 5.14 (1H each, AB-q, J=16.84, py-$C_{(4')}H_2$-O), and 8.00 (1H, s, py-H).

N^2,N^5,N^8,N^{11}-Tetratosyl-17-hydroxy-18-hydroxymethyl-17,18′-*O*-isopropylidene-2,5,8,11-tetraaza[12](2,5)pyridinophane (9b). Starting from **2** (1.526 g) and **4b** prepared from the corresponding dihydroxypyridoxine derivative (0.600 g, 1.33 equiv) in the presence of anhydrous potassium carbonate (3.87 g, 14 equiv) in 150 ml of DMF, 1.86 g (98%) of **9b** was isolated. Recrystallization from chloroform–ethanol gave colorless crystals. Calcd for $C_{45}H_{53}O_{10}N_5S_4$: C, 56.76; H, 5.61; N, 7.36; S, 13.47. Found: C, 56.66; H, 5.56; N, 7.33; S, 13.42. R_f=0.65 (solvent B). IR: 815, 740, 657, 573, and 549 cm^{-1}. ^{1}H NMR: 1.52 (6H, s, C(CH_3)$_2$), 2.45 and 2.47 (four 3H, s, $SO_2C_6H_4$-CH_3), 2.62 (5H, b-s, N-CH_2CH_2-N), 2.90 (2H, b-m, N-CH_2CH_2-N), 3.01 (5H, m, N-CH_2CH_2-N), 4.07 (2H, b-s, py-$C_{(5')}H_2$-N), 4.33 (2H, b-s, py-$C_{(2')}H_2$-N), 5.04 (2H, s, py-$C_{(4')}H_2$-O), and 7.82 (1H, s, py-H).

N^2,N^5,N^8,N^{11},N^{14}-Pentatosyl-20-hydroxy-21-hydroxymethyl-20,21′-*O*-isopropylidene-2,5,8,11,14-pentaaza[15](2,5)pyridinophane (10b). Starting from **3** (0.500 g) and **4b** prepared from the corresponding dihydroxypyridoxine derivative (0.152 g, 1.3 equiv) in the presence of anhydrous potassium carbonate (1.00 g, 14 equiv) in 50 ml of DMF, 0.408 g (68%) of **10b** was isolated. Recrystallization from chloroform–ethanol gave colorless crystals. Calcd for $C_{54}H_{64}O_{12}N_6S_5$: C, 56.42; H, 5.61; N, 7.31; S, 13.95. Found: C, 56.36; H, 5.57; N, 7.20; S, 13.88. R_f=0.70 (solvent B). IR: 813, 739, 715, 696, 657, 571, and 547 cm^{-1}. ^{1}H NMR: 1.46 (6H, s, C(CH_3)$_2$), 2.40, 2.41, 2.44, and 2.48 (3H, 3H, 6H, 3H, respectively, s, $SO_2C_6H_4$-CH_3), 2.83, and 2.90 (2H, each, b-t, CH_2-N^8-CH_2), 3.12 and 3.16 (8H, m, N^2-CH_2CH_2-N^5 and N^{11}-CH_2CH_2-N^{15}), 3.25 (4H, m, N^5-CH_2 and CH_2-N^{11}), and 7.78 (1H, s, py-H).

N^2,N^5,N^8-Tritosyl-2,5,8-triaza[9]paracyclophane (11). By the reaction of **1** (1.130 g) with **5** (0.549 g, 1.04 equiv) in the presence of anhydrous potassium carbonate (1.93 g, 7 equiv) in 80 ml of DMF, 1.274 g (96%) of **11** was isolated through direct recrystallization of the reaction mixture from chloroform–ethanol as colorless crystals. Calcd for $C_{33}H_{37}O_6N_3S_3$: C, 59.34; H, 5.59; N, 6.29; S, 14.40. Found: C, 59.24; H, 5.51; N, 6.17; S, 14.36. R_f=0.85 (solvent A). IR: 815, 785, 759, 742, 729, 653, 580, 560, and 545 cm^{-1}. ^{1}H NMR: 2.50, 2.60, and 3.10 (6H, 1H, and 1H, respectively, m, N-CH_2CH_2-N), 2.45 and 2.46 (3H and 6H, s, $SO_2C_6H_4$-CH_3), 4.24 (4H, b-s, CH_2-C_6H_4-CH_2), 7.34 and 7.67 (4H each, d, J=7.81, N^2- and N^8-aromatic protons), 7.29 and 7.65 (2H each, d, J=7.81, N^5-aromatic protons), and 7.40 (4H, s, C-C_6H_4-C). MS m/z 513 (19%, M^+−155(Ts); the highest peak) and 133 (base peak).

N^2,N^5,N^8,N^{11}-Tetratosyl-2,5,8,11-tetraaza[12]paracyclophane (12). By the reaction of **2** (1.50 g) with **5** (0.54 g, 1.04 equiv) in the presence of anhydrous potassium carbonate (1.90 g, 7 equiv) in 80 ml of DMF, 1.627 g (96%) of **12** was obtained by direct recrystallization of the reaction mixture from chloroform–ethanol as colorless crystals. Calcd for $C_{42}H_{48}O_8N_4S_4$: C, 58.31; H, 5.59; N, 6.49; S, 14.83. Found: C, 58.12; H, 5.52; N, 6.41; S, 14.80. R_f=0.50 (solvent B). IR: 810, 746, 732, 656, 571, 564, and 546 cm^{-1}. ^{1}H NMR: 2.45 (6H, s, N^5- and N^8-$SO_2C_6H_4$-CH_3), 2.47 (6H, s, N^2- and N^{11}-$SO_2C_6H_4$-CH_3), 2.50 (4H, s, N^5-CH_2CH_2-N^8) 2.83 and 2.94 (4H each, A_2B_2-m, N^2-CH_2CH_2-N^5) 4.14 (4H, s, CH_2-C_6H_4-CH_2), 7.33 (4H, s, C-C_6H_4-C), 7.32 and 7.68 (4H each, d, J=8.30, N^5- and N^8-aromatic protons), and 7.37 and 7.78 (4H each, d, J=8.30, N^2- and N^{11}-aromatic protons).

N^2,N^5,N^8,N^{11},N^{14}-Pentatosyl-2,5,8,11,14-pentaaza[15]paracyclophane (13). By the reaction of **3** (0.400 g) with **5** (0.132 g, 1.2 equiv) in the presence of anhydrous potassium carbonate (0.400 g, 7 equiv) in 40 ml of DMF, 0.318 g (72%) of **13** was isolated by chromatography. Recrystallization from acetone–ethanol gave colorless crystals; Calcd for $C_{51}H_{59}O_{10}N_5S_5$: C, 57.66; H, 5.60; N, 6.60; S, 15.09. Found: C, 57.42; H, 5.55; N, 6.45; S, 15.05. R_f=0.8 (solvent B) and 0.4 (benzene–ethyl acetate 9:1 v/v). IR: 813, 740, 715, 695, 657, 568, 546, and 540 cm^{-1}. ^{1}H NMR: 2.44 (3H, s, N^8-$SO_2C_6H_4$-CH_3), 2.45 (6H, s, N^5- and N^{11}-$SO_2C_6H_4$-CH_3), 2.47 (6H, s, N^2- and N^{14}-$SO_2C_6H_4$-CH_3), 2.91 and 3.02 (two 2H each, t, J=6.59, N^5-CH_2CH_2-N^8 and N^8-CH_2CH_2-N^{11}), 3.07 (two 4H, b-s, N^2-CH_2CH_2-N^5 and N^{11}-CH_2CH_2-N^{14}), 4.26 (4H, s, CH_2-C_6H_4-CH_2), 7.32 and 7.59 (2H each, d, J=8.30, N^8-aromatic protons), 7.34 and 7.71 (four 2h each, d, J=8.30, N^5- and N^{11}-aromatic protons), 7.35 and 7.75 (four 2H each, d, J=8.30, N^2- and N^{14}-aromatic protons), and 7.19 (4H, s, C-C_6H_4-C).

We are indebted to Dr. Haruo Homma and his staff in Riken for performing elemental analyses and to Dr. Jun Uzawa and Mrs. Tamiko Chijimatsu in Riken for measurement of ^{1}H NMR spectra.

References

1) a) M. Iwata, H. Kuzuhara, and S. Emoto, *Chem. Lett.*, **1976**, 983; b) H. Kuzuhara, M. Iwata, and S. Emoto, *J. Am. Chem. Soc.*, **99**, 4173 (1977); c) H. Kuzuhara, T. Komatsu, and S. Emoto, *Tetrahedron Lett.*, **1978**, 3563; d) M. Iwata and H. Kuzuhara, *Chem. Lett.*, **1981**, 5; e) Y. Tachibana, M. Ando, and H. Kuzuhara, *Chem. Lett.*, **1982**, 1765 and 1769; f) M. Ando, Y. Tachibana, and H. Kuzuhara, *Bull. Chem. Soc. Jpn.*, **55**, 829 (1982), **56**, 2263 and 3652 (1983); **57**, 237 (1984); g) M. Iwata and H. Kuzuhara, *Bull. Chem. Soc. Jpn.*, **58**, 2502 (1985).

2) a) M. Iwata and H. Kuzuhara, *Chem. Lett.*, **1981**, 1749; b) M. Iwata and H. Kuzuhara, *J. Org. Chem.*, **48**, 1282 (1983).

3) a) I. Tabushi, Y. Kimura, and K. Yamakura, *J. Am. Chem. Soc.*, **103**, 6486 (1981); b) E. Kimura, A. Watanabe, and M. Kodama, *ibid.*, **105**, 2063 (1983); c) H. Tsukube, *J. Chem. Soc., Chem. Commun.*, **1983**, 970.

4) See for phane-nomenclature, F. Voegtle and P. Neumann, *Tetrahedron*, **26**, 5847 (1970).

5) M. Iwata and H. Kuzuhara, *Bull. Chem. Soc. Jpn.*, **55**, 2153 (1982).

6) M. Iwata and H. Kuzuhara, *Bull. Chem. Soc. Jpn.*, **55**, 2295 (1982).

7) D. H. Peacock and U. C. Dutta, *J. Chem. Soc.*, **1934**, 1303.