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Syntheses of a Series of Linear Pentaamines with Three and Four Methylene Chain Intervals[1)]

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Ten kinds of linear pentaamines with various combinations of 3 or 4 methylene chain intervals were synthesized. The methods were tentatively classified into two, leading to symmetrical and unsymmetrical pentaamines, all of which were prepared by successive alkylation of secondary amino derivatives of benzylamine with *N*-(3-bromopropyl or 4-bromobutyl)phthalimide in the presence of KF–Celite, coupled with the purification of the phthaloyl compounds by silica gel column chromatography. Protecting benzyl and phthaloyl groups were removed by usual methods. The carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra of the ten pentaamines were recorded in D_2O as fully protonated forms, and a comparative analysis of their spectra allowed the complete assignment of all ^{13}C chemical shifts.

Keywords——polyamine; pentaamine; benzylamine; *N*-(3-bromopropyl)phthalimide; *N*-(4-bromobutyl)phthalimide; alkylation; potassium fluoride–Celite; ^{13}C-NMR spectrum

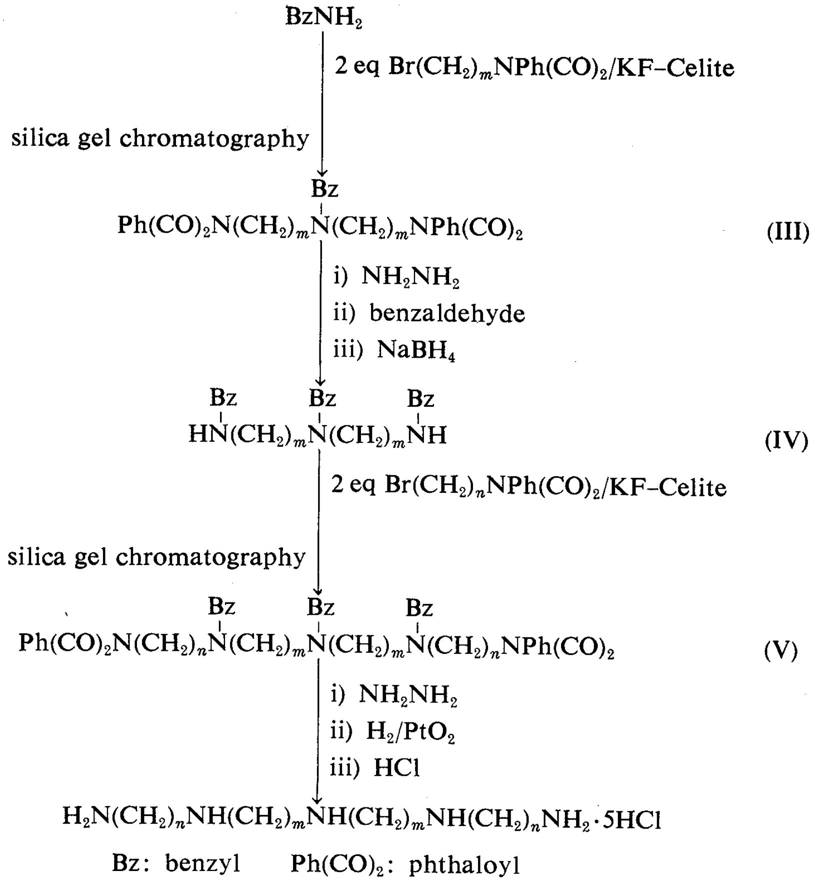
It has been well recognized that naturally occurring di- and polyamines play important roles in the regulation of cell growth, proliferation and differentiation,[2)] although their interactions with cellular components at the molecular level are still unknown. Most of these amines so far found in various living cells are composed of chains of 3 or 4 methylene units linking amine groups, as is observed in diamines, *e.g.* 1,3-propanediamine and putrescine, triamines, *e.g.* *sym*-norspermidine,[3)] spermidine, and *sym*-homospermidine,[4)] and tetraamines, *e.g.* *sym*-norspermine,[3)] spermine, thermospermine,[5)] canavalmine,[6)] and 1,13-diamino-4,9-diazatridecane.[7)] A tetraamine with 4 methylene chain intervals only, 1,14-diamino-5,10-diazatetradecane, has not yet been found in natural sources. Oshima recently discovered two pentaamines, caldopentaamine[8)] and homocaldopentaamine,[9)] in the extreme thermophile *Thermus thermophilus*. It seems likely that other pentaamines will be found in natural sources. In the previous paper,[10)] we reported methods for the synthesis of ^{15}N-enriched putrescine, spermidine and spermine, and we suggested that the methods would be useful for general syntheses of polyamines, offering high yields and wide applicability. The present paper deals with a further application of the methods to syntheses of all ten kinds of pentaamines with 3 and 4 methylene chain intervals, and a complete assignment of their carbon-13 nuclear magnetic resonance (^{13}C-NMR) chemical shifts.

Results and Discussion

The structures of ten pentaamines with various combinations of 3 or 4 methylene chain units are shown in Table I. In the present syntheses of these pentaamines, we adopted successive alkylation of secondary amino derivatives of benzylamine with *N*-(3-bromopropyl)phthalimide (I) for the introduction of the 3 methylene unit or *N*-(4-bromobutyl)phthalimide (II) for the 4 methylene unit in the presence of KF–Celite, coupled with purification of the phthaloyl intermediates by a simple silica gel column chromatog-

Table I. Synthetic Pentaamines

Pentaamine	Compd. No.
$H_2N(CH_2)_3NH(CH_2)_3NH(CH_2)_3NH(CH_2)_3NH_2$	**1**
$H_2N(CH_2)_3NH(CH_2)_3NH(CH_2)_3NH(CH_2)_4NH_2$	**2**
$H_2N(CH_2)_3NH(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$	**3**
$H_2N(CH_2)_3NH(CH_2)_3NH(CH_2)_4NH(CH_2)_4NH_2$	**4**
$H_2N(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH(CH_2)_4NH_2$	**5**
$H_2N(CH_2)_3NH(CH_2)_4NH(CH_2)_4NH(CH_2)_3NH_2$	**6**
$H_2N(CH_2)_4NH(CH_2)_3NH(CH_2)_3NH(CH_2)_4NH_2$	**7**
$H_2N(CH_2)_3NH(CH_2)_4NH(CH_2)_4NH(CH_2)_4NH_2$	**8**
$H_2N(CH_2)_4NH(CH_2)_3NH(CH_2)_4NH(CH_2)_4NH_2$	**9**
$H_2N(CH_2)_4NH(CH_2)_4NH(CH_2)_4NH(CH_2)_4NH_2$	**10**



Bz: benzyl Ph(CO)$_2$: phthaloyl

1: $m=3$, $n=3$ **7**: $m=3$, $n=4$

6: $m=4$, $n=3$ **10**: $m=4$, $n=4$

Chart 1. Syntheses of Symmetrical Pentaamines

raphy. The methods can be tentatively classified into two groups, *i.e.*, those used to obtain symmetrical and unsymmetrical pentaamines.

Syntheses of Symmetrical Pentaamines

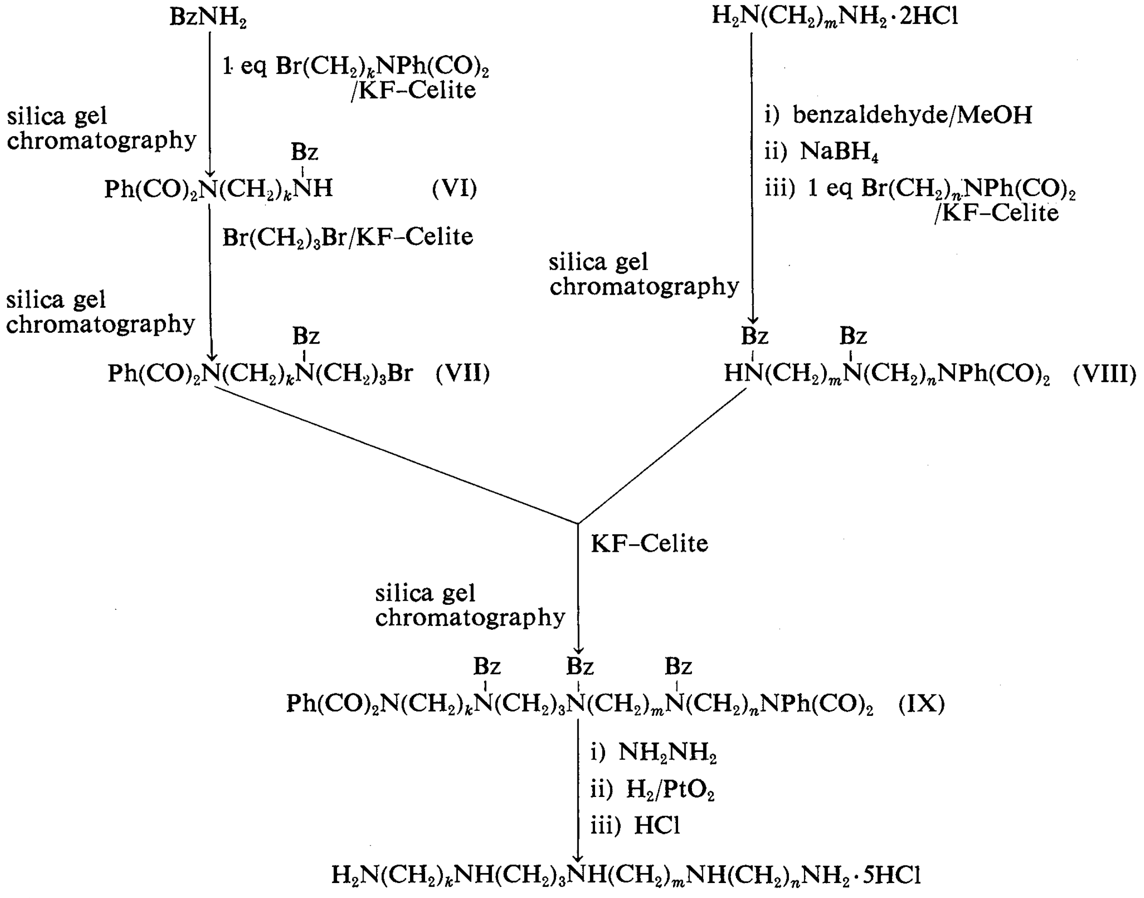
The methods are summarized in Chart 1. Benzylamine was first reacted with 2 eq of I or II in the presence of KF–Celite, and the product, *N*,*N*-bis(phthalimidoalkyl)benzylamine (III), was purified by silica gel chromatography using a solvent system of benzene and acetone. After removal of the phthaloyl groups of III by hydrazine treatment, the *N*,*N*′,*N*″-

tribenzyl derivative (IV) was prepared in high yield by *in situ* reduction of the intermediate Schiff base of the primary amine groups and benzaldehyde with $NaBH_4$. Compound IV was then reacted with 2 eq of I or II in the presence of KF–Celite. The protected pentaamine (V), purified similarly by silica gel chromatography, was first deprotected by hydrazine treatment followed by catalytic reduction to give the pentaamine, which was recrystallized as the pentahydrochloride. By this method, using various combinations of I and II, pure symmetrical pentaamines (**1**, **6**, **7** and **10**) were successfully synthesized in 50—60% yields from III.

Syntheses of Unsymmetrical Pentaamines

A starting spermidine precursor, *N*-(3-phthalimidopropyl)-*N*-(4-phthalimidobutyl)-benzylamine prepared according to the previous method,[10] was used for the syntheses of two unsymmetrical pentaamines (**3** and **9**). The next procedures, removal of phthaloyl groups of the spermidine precursor, preparation of the corresponding *N*,*N*′,*N*″-tribenzyl derivative, alkylation of the tribenzyl derivative with I or II, purification by column chromatography and final deprotection of the pentaamine precursors, were carried out by procedures similar to those described above for the symmetrical pentaamines.

An outline of the synthetic method for three pentaamines (**2**, **4** and **5**) is shown in Chart 2;



Bz: benzyl Ph(CO)$_2$: phthaloyl
2: $k=4$, $m=3$, $n=3$
4: $k=3$, $m=4$, $n=4$
5: $k=4$, $m=4$, $n=3$

Chart 2. Syntheses of Unsymmetrical Pentaamines

two intermediate compounds, *N*-(phthalimidoalkyl)-*N*-(3-bromopropyl)benzylamine (VII) and *N*-(phthalimidoalkyl)-*N*-(*N*-benzylaminoalkyl)benzylamine (VIII), were reacted in the presence of KF–Celite to afford the corresponding pentaamine precursor (IX). Compound VII was obtained in 26% yield from chromatographically purified *N*-(phthalimidoalkyl)benzylamine (VI), which was reacted with an excess of 1,3-dibromopropane in the presence of KF–Celite. In this reaction, when 1,4-dibromobutane was used instead of 1,3-dibromopropane, the corresponding homologue of VII could not be obtained, and *N*-benzyl-*N*-(phthalimidoalkyl)pyrrolinium bromide was formed in a quantitative yield. Hence, the low yield of VII may be due partly to the occurrence of similar cyclization. Compound VIII was obtained in 40% yield from the starting diamine after purification of the reaction products of *N*,*N*′-dibenzyl-1,3-diaminopropane or *N*,*N*′-dibenzylputrescine and I or II by silica gel chromatography. Deprotection of IX to the pentaamine was carried out by the same method as described above.

For the synthesis of **8**, the symmetrical *N*,*N*′,*N*″-tribenzyl derivative (IV, $m=4$) was first alkylated with 1 eq of I or II, and the product, a monoalkylated *N*,*N*′,*N*″-tribenzyl derivative, after purification by silica gel chromatography, was alkylated with the other component (II or I) to give the precursor of **8**. The subsequent purification and deprotection procedures were the same as above. By using this method, it was also possible to prepare the pentaamine **2**, when IV ($m=3$) was used.

^{13}C-NMR Data for the Ten Pentaamines

For the identification of the synthesized pentaamines, their ^{13}C-NMR spectra were recorded in D_2O as the fully protonated forms. Although it was difficult to assign all the peaks of a certain pentaamine based on its own spectrum alone, a comparative analysis of ^{13}C chemical shifts and intensities obtained from the spectra of the ten pentaamines made it possible to assign all the shifts consistently, and hence to identify the structures of the compounds. The results are summarized in Table II.

Studies on the ^{13}C chemical shifts for some synthetic and naturally occurring di- and polyamines have been reported,[11] and attempts have been made to find a practical rule for the assignment of peaks of the polyamines through analyses of the spectra of various amines with 2 or 3 methylene chain intervals. The empirical rule was appliciable to caldopentaamine, with acceptable errors between observed and calculated chemical shifts *e.g.* observed (Calcd), 37.39 (37.7), 24.56 (24.9), 45.53 (45.5), 45.42 (45.5), 23.47 (23.8), 45.42 (45.5) (See Table II). Chemical shifts for the other pentaamines with 4 methylene chain intervals, however, could not be calculated according to the rule for compounds with 2 or 3 methylene chain length. The present data, therefore, may be useful in refining and extending the applicability of the rule.

Table II. ^{13}C-NMR Chemical Shifts of Pentaamines

Compd. No.	^+H_3N—$(CH_2)_{3-4}$		NH_2^+	$(CH_2)_{3-4}$	NH_2^+	$(CH_2)_{3-4}$	NH_2^+	$(CH_2)_{3-4}$	NH_3^+
1	37.39	24.56	45.53 45.42	23.47	45.42 45.42	23.47	45.42 45.53	24.56	37.39
2	37.39	24.56	45.55 45.42	23.47	45.42 45.42	23.47	45.25 47.91	23.56 24.73	39.66
3	37.39	24.56	45.55 45.46	23.48	45.28 47.84	23.58 23.58	47.84 45.38	24.56	37.39
4	37.40	24.56	45.53 45.46	23.48	45.28 47.86	23.59 23.59	47.67 47.74	23.59 24.75	39.67
5	37.43	24.58	45.39 47.84	23.59 23.59	47.84 45.31	23.51	45.31 47.91	23.59 24.74	39.66
6	37.43	24.57	45.38 47.85	23.61 23.61	47.68 47.68	23.61 23.61	47.85 45.38	24.57	37.43
7	39.66	24.73 23.57	47.91 45.27	23.48	45.47 45.47	23.48	45.27 47.91	23.57 24.73	39.66
8	37.43	24.57	45.38 47.85	23.62 23.62	47.69 47.69	23.62 23.62	47.69 47.74	23.62 24.76	39.67
9	39.66	24.75 23.57	47.90 45.30	23.50	45.30 47.85	23.57 23.57	47.67 47.74	23.57 24.75	39.66
10	39.67	24.75 23.57	47.73 47.68	23.61 23.61	47.68 47.68	23.61 23.61	47.68 47.73	23.57 24.75	39.67

Counter anion: Cl^-.

Experimental

Materials——1,3-Dibromopropane, 1,4-dibromobutane, benzylamine, 100% hydrazine monohydrate, and potassium phthalimide were obtained from Tokyo Kasei, Ltd. (Tokyo). *N*,*N*′-Dimethylformamide (DMF), benzaldehyde, acetonitrile, and magnesium sulfate (anhydrous) were obtained from Wako Pure Chemical Industries, Ltd. (Osaka). Platinic oxide was purchased from Kawaken Fine Chemicals, Ltd. (Tokyo), and potassium fluoride and Celite (535) from Wako. Sodium borohydride was obtained from Metallgesellshaft AG (Germany). All the other organic solvents and reagents used were of analytical grade. *N*-(3-Bromopropyl)phthalimide (I), *N*-(4-bromobutyl)phthalimide (II), and KF–Celite were prepared according to the previous paper.[10]

For column chromatography, silica gel (Wako gel C-300, Wako) was used, and pre-coated silica gel plates (Silica gel 60 F-254, E. Merck) were used for thin-layer chromatography (TLC).

^{13}C-NMR Measurements——NMR samples were prepared as solutions containing 50 mg of pentaamine pentahydrochloride, 0.6 ml of D_2O and 10 μl of dioxane (67.40 ppm downfield from Me_4Si). The NMR spectra were recorded at 24 °C with a JEOL JNM GX-270 NMR spectrometer operating at 67.8 MHz. NMR conditions were: pulse width, 4.5 μs (45 °); spectral width, 6.78 kHz; repetition rate, 1.5 s; data points, 16384; scans, 800.

1,15-Diamino-4,8,12-triazapentadecane (1) Pentahydrochloride[12]——A stirred solution of benzylamine (0.65 ml, 6 mmol), and I (3.48 g, 14.0 mmol) in 24 ml of CH_3CN was refluxed for 14 h in the presence of KF–Celite (2.4 g).[13] The filtrate, after removal of KF–Celite, was evaporated *in vacuo* and the residue was dissolved in benzene (10 ml).[14] The solution was then applied to a silica gel (20 g) column equilibrated with benzene. The column was successively eluted with benzene (100 ml, unreacted I) and benzene–acetone (20 : 1) (100 ml, *N*,*N*-bis(3-phthalimidopropyl)-benzylamine (III, $m=3$)). After removal of the solvent from the latter fraction, practically pure III ($m=3$) was obtained as an oil (1.76 g, 3.7 mmol).

A solution of III ($m=3$) (3.7 mmol) in 34 ml of MeOH containing 2.8 ml of $NH_2NH_2 \cdot H_2O$ was refluxed for 3 h, and evaporated *in vacuo*. The residue was shaken for 30 min with 34 ml of $CHCl_3$ and 34 ml of 4 N NH_4OH, and the ammoniacal phase was again extracted with 34 ml of $CHCl_3$. The combined $CHCl_3$ extract was filtered through a filter paper, and evaporated. The N^4-benzyl-4-aza-1,7-diaminoheptane thus obtained (3.5 mmol), benzaldehyde (0.78 ml, 7.0 mmol), and $MgSO_4$ (1.1 g) were dissolved in 14 ml of MeOH. The solution was then stirred for 1 h at room temperature, and $NaBH_4$ (1.6 g) was carefully added to the solution on ice–NaCl over a period of 1 h, with additional MeOH (10 ml). Stirring was continued for another 1 h. MeOH was then removed *in vacuo*, and the residue was extracted with Et_2O (25 ml × 2) and H_2O (25 ml). The combined Et_2O extract was thoroughly washed with H_2O (25 ml × 2) and Et_2O was removed. The resulting oil (1.49 g), although contaminated with traces of ultraviolet (UV)-absorbing materials, was used as N^1,N^4,N^7-tribenzyl-4-aza-1,7-diaminoheptane (IV, $m=3$) (TLC, *n*-BuOH–AcOH–H_2O (3 : 2 : 2), *Rf* 0.67) for the next reaction (theoretically 1.41 g, 3.5 mmol).

A stirred suspension of IV ($m=3$) (0.52 g, 1.3 mmol), I (0.72 g, 2.7 mmol), and KF–Celite (1.0 g) in 7 ml of CH_3CN was refluxed for 14 h. The reaction mixture was treated as described above, and the resulting N^4,N^8,N^{12}-tribenzyl-N^1,N^{15}-bis(phthaloyl)-4,8,12-triazapentadecane (V, $m=3$, $n=3$) was purified by silica gel chromatography in the same manner as described above, *i.e.*, on a silica gel (10 g) column with stepwise elution using benzene (100 ml, I), followed by benzene–acetone (20 : 1) (250 ml, V, $m=3$, $n=3$). The yield of V ($m=3$, $n=3$) thus obtained was 0.64 g (0.95 mmol).

A solution of V ($m=3$, $n=3$) (0.95 mmol) and 0.7 ml of $NH_2NH_2 \cdot H_2O$ in 9 ml of MeOH was refluxed for 3 h, then the MeOH was removed, and the residue was extracted with equal volumes (9 ml) of $CHCl_3$ and 4 N NH_4OH. The resulting 1,15-diamino-N^4,N^8,N^{12}-tribenzyl-4,8,12-triazapentadecane (0.79 mmol) was hydrogenolyzed in 10 ml of AcOH at 60 °C in the presence of PtO_2 (79 mg). The mixture was stirred until hydrogen absorption ceased, then filtered through a Teflon Millipore membrane. The filtrate was treated with 0.7 ml of conc. HCl, then evaporated to dryness, and the residue was recrystallized from aqueous EtOH. Pure **1** pentahydrochloride (0.30 g, 0.71 mmol) was obtained in a yield of 75% from V ($m=3$, $n=3$). *Anal.* Calcd for $C_{12}H_{36}Cl_5N_5$: C, 33.70; H, 8.48; N, 16.37. Found: C, 33.45; H, 8.76; N, 16.14.

1,17-Diamino-4,9,14-triazaheptadecane (6) Pentahydrochloride——A symmetrical pentaamine **6** was prepared in the same manner as described for **1**, except for the use of II at the first alkylation step of benzylamine. The yield at each step was similar to that described for **1**. Crystalline **6** pentahydrochloride (1.8 mmol) was obtained from 3.6 mmol of III ($m=4$). *Anal.* Calcd for $C_{14}H_{40}Cl_5N_5$: C, 36.89; H, 8.85; N, 15.37. Found: C, 36.97; H, 9.20; N, 15.26.

1,17-Diamino-5,9,13-triazaheptadecane (7) Pentahydrochloride——A symmetrical pentaamine **7** was prepared in the same manner as described for **1**, except for the use of II at the second alkylation step of IV ($m=3$). Starting with IV ($m=3$) (0.80 g, 2.0 mmol), 1.3 mmol of recrystallized **7** pentahydrochloride was obtained. *Anal.* Calcd for $C_{14}H_{40}Cl_5N_5$: C, 36.89; H, 8.85; N, 15.37. Found: C, 37.20; H, 9.18; N, 15.22.

1,19-Diamino-5,10,15-triazanonadecane (10) Pentahydrochloride——A symmetrical pentaamine **10** was prepared in the same manner as described for **1**, except for the use of II at the two alkylation steps of benzylamine and IV ($m=4$). Starting with IV ($m=4$) (1.50 g, 3.5 mmol), 2.1 mmol of recrystallized **10** pentahydrochloride was obtained. *Anal.* Calcd for $C_{16}H_{44}Cl_5N_5$: C, 39.72; H, 9.17; N, 14.47. Found: C, 39.37; H, 9.47; N, 14.24.

1,16-Diamino-4,8,13-triazahexadecane (3) Pentahydrochloride——An unsymmetrical pentaamine **3** was prepared in the same manner as described for **1**, except for the use of N^4-benzylspermidine prepared according to the reported methods[10,15] instead of the symmetrical III. N^4-Benzylspermidine (0.51 g, 2.2 mmol) was similarly reacted with benzaldehyde followed by *in situ* reduction with $NaBH_4$ to obtain *N,N′,N″*-tribenzylspermidine (0.91 g, 2.2 mmol), which was then alkylated with I, and subjected to the usual purification and deprotection procedures as described above. The yield of recrystallized **3** pentahydrochloride was 1.3 mmol. *Anal.* Calcd for $C_{13}H_{38}Cl_5N_5$: C, 35.35; H, 8.67; N, 15.85. Found: C, 35.17; H, 8.95; N, 15.71.

1,18-Diamino-5,9,14-triazaoctadecane (9) Pentahydrochloride——An unsymmetrical pentaamine **9** was prepared in the same manner as described for **3**, except for the use of II in the alkylation of *N,N′,N″*-tribenzylspermidine. Starting with *N,N′,N″*-tribenzylspermidine (0.83 g, 2.0 mmol), 1.1 mmol of recrystallized **9** pentahydrochloride was obtained. *Anal.* Calcd for $C_{15}H_{42}Cl_5N_5$: C, 38.35; H, 9.01; N, 14.91. Found: C, 38.34; H, 9.30; N, 14.71.

1,16-Diamino-4,8,12-triazahexadecane (2) Pentahydrochloride[12]——Synthesis of *N*-(4-phthalimidobutyl)-*N*-(3-bromopropyl)benzylamine (VII, $k=4$): A stirred solution of benzylamine (1.31 ml, 12 mmol), and II (3.6 g, 13 mmol) in 48 ml of CH_3CN was refluxed for 2 h in the presence of KF–Celite (4.8 g). From the resulting mixture, *N*-(4-phthalimidobutyl)benzylamine (VI, $k=4$) was purified by silica gel chromatography in the same manner as described above, *i.e.*, on silica gel (40 g) with stepwise elution using benzene (200 ml, II), benzene–acetone (10 : 1) (150 ml, III, $m=4$), and benzene–acetone (10 : 2) (300 ml, VI, $k=4$). The yield of VI ($k=4$) thus obtained was 2.05 g (6.7 mmol). A part (1.07 g, 3.5 mmol) of this was dissolved in 13 ml of CH_3CN, then refluxed for 3 h in the presence of an excess of 1,3-dibromopropane (3.50 g, 17 mmol) and KF–Celite (1.4 g). After removal of KF–Celite by filtration and most of the unreacted 1,3-dibromopropane by evaporation *in vacuo*, the residual oil was chromatographed on silica gel (15 g) with stepwise elution using benzene (200 ml, 1,3-dibromopropane) and benzene–acetone (50 : 1) (50 ml, VII, $k=4$). Practically pure VII ($k=4$) (0.38 g, 0.89 mmol) was obtained as a single band on TLC (benzene–acetone (5 : 1), *Rf* 0.88).

Synthesis of *N,N′*-dibenzyl-*N*-(3-phthalimidopropyl)-1,3-diaminopropane (VIII, $m=3$, $n=3$): *N,N′*-Dibenzyl-1,3-diaminopropane (1.52 g, 5.9 mmol) prepared in the usual way and I (1.60 g, 5.9 mmol) were dissolved in 24 ml of CH_3CN and the solution was refluxed for 3 h in the presence of KF–Celite (2.4 g). After removal of KF–Celite and CH_3CN, the residue was chromatographed on a silica gel (20 g) column with stepwise elution using benzene (100 ml, I), benzene–acetone (20 : 1) (100 ml, a diphthalimide product), and benzene–acetone (10 : 1) (200 ml, VIII, $m=3$, $n=3$). Practically pure VIII ($m=3$, $n=3$) (1.05 g, 2.4 mmol) was obtained as a single band on TLC (benzene–acetone (5 : 1), *Rf* 0.20).

Coupling of VII and VIII: A mixture of VII ($k=4$) (0.38 g, 0.89 mmol) and VIII ($m=3$, $n=3$) (0.41 g, 0.93 mmol) in 5 ml of CH_3CN was refluxed for 2 h in the presence of KF–Celite (0.4 g). After removal of KF–Celite and CH_3CN, the residue was similarly chromatographed to obtain pure N^4,N^8,N^{12}-tribenzyl-N^1,N^{16}-bis(phthaloyl)-4,8,12-triazahexadecane (IX, $k=4$, $m=3$, $n=3$). The conditions were: silica gel (10 g) column with stepwise elution using benzene–acetone (50 : 1) (50 ml, VII, $k=4$) and benzene–acetone (10 : 1) (100 ml, IX, $k=4$, $m=3$, $n=3$). The yield of IX ($k=4$, $m=3$, $n=3$) thus obtained was almost quantitative (0.70 g, 0.89 mmol). The subsequent deprotection procedures were the same as described above. The yield of recrystallized **2** pentahydrochloride was 0.26 g (0.59 mmol). *Anal.* Calcd for $C_{13}H_{38}Cl_5N_5$: C, 35.35; H, 8.67; N, 15.85. Found: C, 35.27; H, 8.95; N, 15.70.

1,17-Diamino-4,8,13-triazaheptadecane (4) Pentahydrochloride——*N*-(3-Phthalimidopropyl)-*N*-(3-bromopropyl)benzylamine (VII, $k=3$) was prepared in the same manner as described for **2**, except for the use of I in the monoalkylation of benzylamine. *N,N′*-Dibenzyl-*N*-(4-phthalimidobutyl)-1,4-diaminobutane (VIII, $m=4$, $n=4$) was prepared in the same manner as described for **2**, except for the use of *N,N′*-dibenzylputrescine and II. Coupling of VII ($k=3$) (0.31 g, 0.75 mmol) and VIII ($m=4$, $n=4$) (0.39 g, 0.83 mmol) was similarly carried out to yield **4** pentahydrochloride after recrystallization (0.46 mmol). *Anal.* Calcd for $C_{14}H_{40}Cl_5N_5$: C, 36.89; H, 8.85; N, 15.37. Found: C, 36.98; H, 9.08; N, 15.14.

1,17-Diamino-4,9,13-triazaheptadecane (5) Pentahydrochloride——This unsymmetrical pentaamine was prepared in the same manner as described for **2**, except for the use of putrescine instead of 1,3-diaminopropane to prepare *N,N′*-dibenzyl-*N*-(3-phthalimidopropyl)-1,4-diaminobutane (VIII, $m=4$, $n=3$). The alkylation of VIII ($m=4$, $n=3$) (0.35 g, 0.77 mmol) with VII ($k=4$) (0.3 g, 0.70 mmol) yielded 0.38 mmol of **5** pentahydrochloride after recrystallization. *Anal.* Calcd for $C_{14}H_{40}Cl_5N_5$: C, 36.89; H, 8.85; N, 15.37. Found: C, 36.82; H, 9.13; N, 15.15.

1,18-Diamino-4,9,14-triazaoctadecane (8) Pentahydrochloride——Equivalent amounts of IV ($m=4$) (1.53 g, 3.6 mmol) and II (1.02 g, 3.6 mmol) dissolved in 14 ml of CH_3CN were refluxed for 3 h in the presence of KF–Celite (1.5 g). The reaction mixture, after removal of KF–Celite and CH_3CN, was chromatographed in the same manner as described above, *i.e.*, silica gel (20 g) column with stepwise elution using benzene (100 ml, II), benzene–acetone (10 : 1) (200 ml, V, $m=4$, $n=4$), and benzene–acetone (5 : 1) (300 ml). 1-Amino-N^1,N^5,N^9-tribenzyl-N^9-(4-phthalimidobutyl)-5-azanonane (1.6 mmol) was recovered as a single band on TLC with a solvent system of *n*-BuOH–AcOH–H_2O (3 : 2 : 2) (*Rf* 0.71). The compound (1.6 mmol) was further alkylated with I (0.47 g, 1.2 mmol) in the presence of KF–Celite (0.6 g), and 6 ml of CH_3CN. After similar purification by silica gel (10 g) chromatography, N^4,N^9,N^{14}-tribenzyl-N^1,N^{18}-bis(phthaloyl)-4,9,14-triazaoctadecane (a homologue of V) was obtained in the benzene–acetone (10 : 1) eluate (1.2 mmol). Deprotection of the compound in the usual way yielded 0.71 mmol of recrystallized **8** pentahydrochloride. *Anal.* Calcd for $C_{15}H_{42}Cl_5N_5$: C, 38.35; H, 9.01; N, 14.91. Found: C, 38.18; H, 9.20; N, 14.81.

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References and Notes

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