Preparation and NMR Study of 7,7′-(α,ω-Alkanediyl)bis[theophylline], 1,1′-(α,ω-Alkanediyl)bis[theobromine], and 1,1′-(α,ω-Alkanediyl)bis[3-methyluracil]

Toshio ITAHARA* and Kazuhiko IMAMURA
Institute of Chemistry, College of Liberal Arts, Kagoshima University, Korimoto, Kagoshima 890
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The treatment of theophylline, theobromine, and 3-methyluracil with $X(CH_2)_nX$ (X=Br or I, n=1—12) in *N,N*-dimethylformamide containing sodium hydride gave the corresponding 7,7′-(α,ω-alkanediyl)-bis[theophylline], 1,1′-(α,ω-alkanediyl)bis[theobromine], and 1,1′-(α,ω-alkanediyl)bis[3-methyluracil]. The interaction of the theophylline, theobromine, and 3-methyluracil rings of these compounds was studied based on their ^{1}H NMR spectra, and stacking of the two purine rings of 7,7′-(α,ω-alkanediyl)bis[theophylline] was observed.

Nucleic acid bases containing purines and pyrimidines are stacked one above the other in nucleic acids, and there is a distance of 0.34 nm between each bases. As a model for dinucleotides, an approach towards linking between two nucleic acid bases with the trimethylene group and the reaction of the compounds have been investigated.[1] However, little attention has been paid to a systematic investigation concerning the linking between the purine and pyrimidine bases with polymethylene chains $(CH_2)_n$ (n=1—12). On the other hand, recently much attention has been paid to the synthesis of ionophores and, in this connection, the synthesis of two uracil units linked at the N-3 position with various spacers was reported.[2] These observations led us to attempt linking between purine and pyrimidine bases with polymethylene chains $(CH_2)_n$ (n=1—12). This paper describes an easy preparation of 7,7′-(α,ω-alkanediyl)bis[theophylline] (**2**), 1,1′-(α,ω-alkanediyl)bis[theobromine] (**4**) and 1,1′-(α,ω-alkanediyl)bis[3-methyluracil] (**6**) from theophylline (**1**), theobromine (**3**), and 3-methyluracil (**5**), although some compounds such as **2b**,[3] **2e**,[4] **2h**,[5] **2j**,[5] **4b**,[6,7] **4c**,[6] and **4e**,[4] had already been prepared by several groups of workers. Furthermore, a comparison of protons in the NMR spectra of compounds **2**, **4**, and **6** was studied in connection with the interaction of the purine and pyrimidine bases.

Results and Discussion

The treatment of theophylline (**1**) with $Br(CH_2)_nBr$ (n=1—7, 9—12) or $I(CH_2)_nI$ (n=1, 3—6, 8, 10) in *N,N*-dimethylformamide containing sodium hydride gave 7,7′-(α,ω-alkanediyl)bis[theophylline] (**2**). The reaction of theobromine (**3**) and 3-methyluracil (**5**) with $X(CH_2)_nX$ also gave 1,1′-(α,ω-alkanediyl)bis-[theobromine] (**4**) and 1,1′-(α,ω-alkanediyl)bis[3-methyluracil] (**6**), respectively, whereas a similar treatment of uracil or thymine with $X(CH_2)_nX$ resulted in the formation of pyrimidinophanes (Chart 1).[8] These results are summarized in Table 1. Although cross-linking between theophylline and 3-methyluracil with polymethylene chains was attempted, the yield of the expected product was not good, i.e., the treatment of a mixture of **2** and **5** with $I(CH_2)_6I$ gave the expected compound (**7f**) in 14% yield together with the homo-linking products **2f** (14%) and **6f** (8%).

Figure 1 shows a comparison of the melting points of compounds **2**, **4**, and **6**. Generally, the increasing carbon numbers of polymethylene chains on **2**, **4**, and **6**led to a lowering of their melting points, although a difference between the even carbon number and odd carbon number of the polymethylene chains was observed, i.e., the melting points of the compounds with the odd carbon numbers of polymethylene chains were somewhat lower than that predicted with the even carbon numbers. The melting points of **2c**, **4c**, **6c** (n=3), and **2e** were particularly low.

Circular dichroism (CD) and ^{1}H NMR have frequently been used in order to study the conformations of oligonucleotides. We have studied the interaction between the purine and pyrimidine bases of **2**, **4**, and **6** linked with polymethylene chains on the basis of the chemical shifts on the ^{1}H NMR spectra. Figure 2 shows a comparison of the chemical shifts of H-8 of **2** and **4** and H-6 of **6** on the ^{1}H NMR spectra in $CDCl_3$ at 27 °C. Furthermore, Figs. 3 and 4 show a comparison in D_2O at 27 and 70 °C, respectively. These results provided interesting information regarding the conformation of **2** in D_2O, while they did not shed any light on the conformational analyses of **4** and **6**. Figure 5 shows a comparison of **2** in acetone-d_6 (27 °C), dimethyl-d_6 sulfoxide (DMSO-d_6) (27 °C), and acetic-d_3 acid-d (27 and 70 °C). These results suggest that almost only the chemical shifts of **2** in D_2O (shown in Figs. 3 and 4) are clearly up to a higher field with a decrease in the carbon numbers of the polymethylene chains, except for **2a** (n=1), although the results in DMSO are somewhat similar to those in D_2O. Figures 2, 3, and 5 also show pronounced solvent effects among $CDCl_3$, D_2O, acetone, DMSO, and acetic acid. We further compared the concentration effect of **2c** and caffeine in D_2O (Fig. 6). In spite of the known reports concerning the concentration effects of purines and pyrimidines,[9] the concentration effects were only little observed in the concentration range shown in Fig. 6.

The ring proton resonance in purines is known to be shifted to higher fields as the solute concentration is increased because of stacking effects,[9] whereas the self-

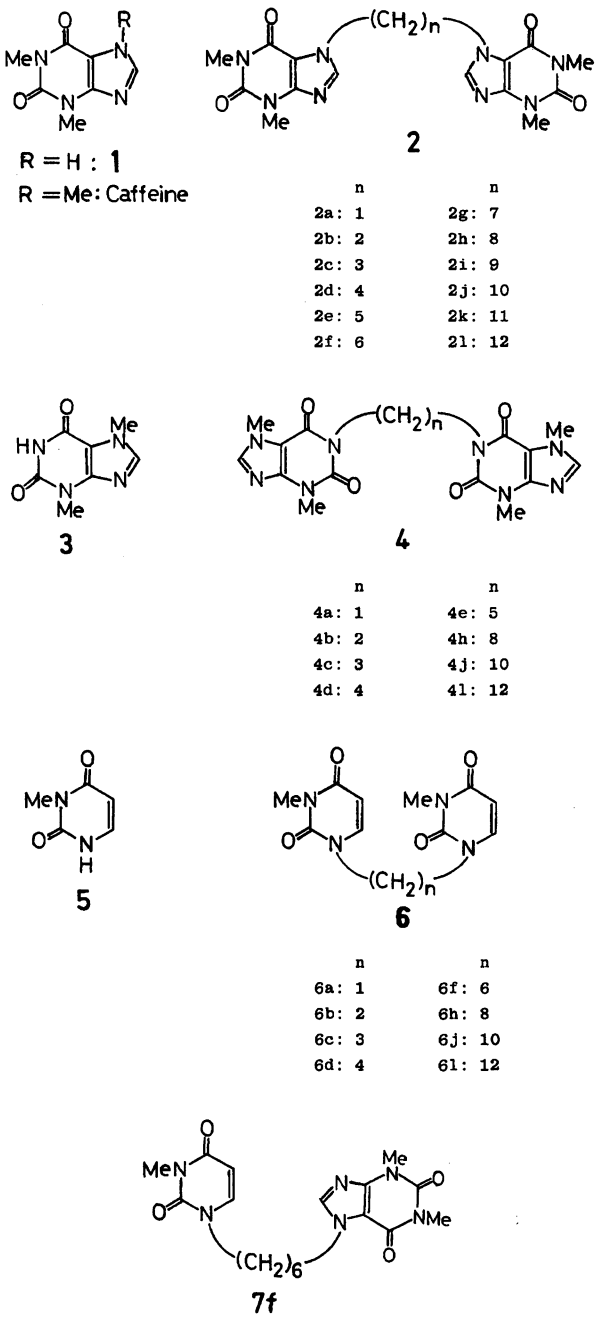


Chart 1.

association of purines was reported to be much greater than that of the pyrimidines.[9,10] The calculated[11] and measured[12] shifts of H-8 of adenine due to the stacking of two adenosine nucleosides were both reported to be ca. 0.2 ppm. Similar results were described in reports dealing with the temperature-dependent chemical shifts of oligonucleotides.[13] On the other hand, there are differences of 0.22 and 0.17 ppm between the chemical shifts of **2c** ($n=3$) and that of **2j** ($n=10$) in D_2O at 27 and 70 °C, respectively, while the differences in the chemical shifts between **4c** ($n=3$) and **4h** ($n=8$) and between **6c** ($n=3$) and **6j** ($n=10$) are 0.02 and 0.01 ppm, respectively. These results suggest a possibility

Table 1. Preparation of 7, 7′- (α,ω- Alkanediyl)-bis[theophylline] (**2**), 1, 1′- (α,ω- Alkanediyl)bis-[theobromine] (**4**), and 1,1′-(α,ω-Alkanediyl)bis[3-methyluracil] (**6**)[a]

Substrate	$X(CH_2)_nX$		Product[b]
	X	n	Isolated Yield/%
1	I	1	**2a**/75
1	Br	1	**2a**/53
1	Br	2	**2b**/26
1	I	3	**2c**/70
1	Br	3	**2c**/66
1	I	4	**2d**/77
1	Br	4	**2d**/66
1	I	5	**2e**/80
1	Br	5	**2e**/68
1	I	6	**2f**/82
1	Br	6	**2f**/71
1	Br	7	**2g**/61
1	I	8	**2h**/73
1	Br	9	**2i**/71
1	I	10	**2j**/80
1	Br	10	**2j**/71
1	Br	11	**2k**/70
1	Br	12	**2l**/77
3	I	1	**4a**/52
3	Br	2	**4b**/25
3	I	3	**4c**/66
3	I	4	**4d**/78
3	I	5	**4e**/80
3	I	8	**4h**/77
3	I	10	**4j**/77
3	Br	12	**4l**/55
5	I	1	**6a**/40
5	Br	2	**6b**/20
5	I	3	**6c**/35
5	I	4	**6d**/43
5	I	6	**6f**/48
5	I	8	**6h**/43
5	I	10	**6j**/56
5	Br	12	**6l**/42

a) Reaction conditions are shown in Experimental part.
b) Yield of recovered substrate was not determined.

of stacking between the two purine rings of **2**, although the stacking effect on **4** and **6** were not confirmed.

The polymethylene chains of compounds **2** may aggregate in D_2O so as to decrease the hydrocarbon–D_2O interfacial area because of the hydrophobic effect.[14] We are therefore thinking of a hypothesis in which the polymethylene chains may be surrounded by the two purine rings (Scheme 1, A), except for compounds **2a** ($n=1$) and **2b** ($n=2$). In order to elucidate this hypothesis, the chemical shifts of the polymethylene chains of **2** are compared with those of **6**, since there is little shielding effects between the two pyrimidine bases of **6**, except for **6b** ($n=2$). The results and those of the chemical shifts of H-8 of **2** and H-6 of **6** are summarized in Table 2. However, since Table 2 does not show any definitive evidence for the hypothesis, compounds **2**, except **2a**

Table 2. Chemical Shifts of 7,7′-(α,ω-Alkanediyl)bis[theophylline] (**2**) and 1,1′-(α,ω-Alkanediyl)-bis[3-methyluracil] (**6**) in D_2O at 27 °C[a)]

R–CH_2–CH_2–$(CH_2)_{n-4}$–CH_2–CH_2–R (R=theophylline and 3-methyluracil)
(α) (β) (γ)

	Chemical Shifts/δ					Chemical Shifts/δ				
n	**2**	H-8	$CH_2(\alpha)$	$CH_2(\beta)$	$(CH_2)_{n-4}(\gamma)$	**6**	H-6	$CH_2(\alpha)$	$CH_2(\beta)$	$(CH_2)_{n-4}(\gamma)$
1	**2a**	8.43	6.82			**6a**	7.91	5.67		
2	**2b**	7.73	4.81			**6b**	7.54	4.17		
3	**2c**	7.77	4.48	2.73		**6c**	7.63	3.92	2.18	
4	**2d**	7.87	4.30	1.83		**6d**	7.61	3.85	1.74	
5	**2e**	7.90	4.29	1.82	1.20					
6	**2f**	7.94	4.28	1.82	ca. 1.2	**6f**	7.61	3.82	1.69	ca. 1.3
7	**2g**	7.96	4.27	1.80	ca. 1.2					
8	**2h**	7.97	4.27	1.80	ca. 1.2	**6h**	7.62	3.81	1.69	ca. 1.3
9	**2i**	7.98	4.27	1.80	ca. 1.2					
10	**2j**	7.99	4.27	1.80	ca. 1.2	**6j**	7.62	3.81	1.69	ca. 1.3

a) Sodium 3-(trimethylsilyl)propionate-2,2,3,3-d_4 as the internal standard.

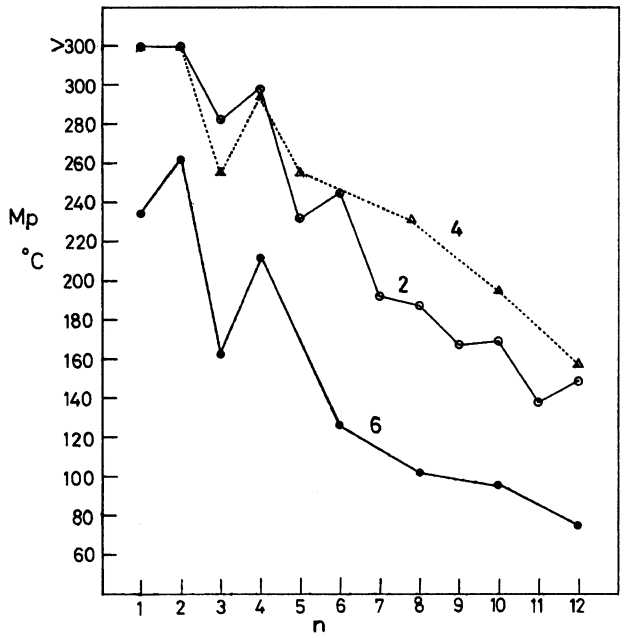


Fig. 1. Relationship between the melting points and carbon numbers (n) of the polymethylene chains of **2**, **4**, and **6**.

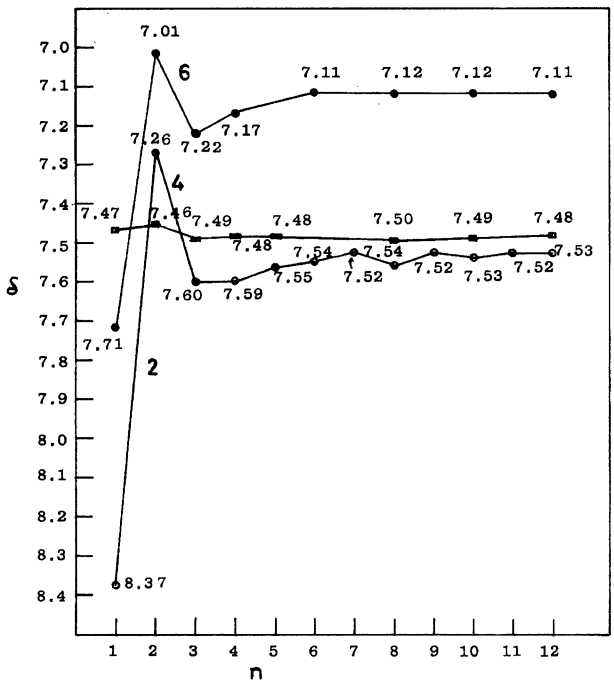


Fig. 2. Relationship between the chemical shifts (H-8 of **2** and **4** and H-6 of **6**) and the carbon numbers (n) of polymethylene chains in $CDCl_3$ at 27 °C; the concentrations of compounds: ca. 10 mg/0.5 ml ($CDCl_3$).

(n=1), may be shown to associate in D_2O through the formation of stacking, as shown in Scheme 1, B.

Although compounds **2** and **4** are structural isomers, no stacking effect on **4** was observed. The difference between **2** and **4** is due to the positions of the purine ring bonded to the polymethylene chains, i.e., in the case of **4**, the indicated protons at 8-position are far from the position of the polymethylene chains. There may be two possible explanations for the difference between **2** and **4**: (1) A partial positive charge at the N_1 position, as can be seen in Scheme 2, C, may result in a repulsion between the two positive charged N_1, and there may be no stacking in the case of **4**. (2) The concentration dependence of the chemical shifts for H-2 of the purine bases and nucleosides was reported to be substantially larger than that for H-8; the results were explained on the basis of a preferred average orientation of the two purine rings in the stacks.[10] Even if there is stacking in the case of **4**, the repulsion between the two positive charged N_1 may result in a deviation from the circumstances of the shielding effect on H-8 of this purines, as shown in Scheme 2, D (for example).

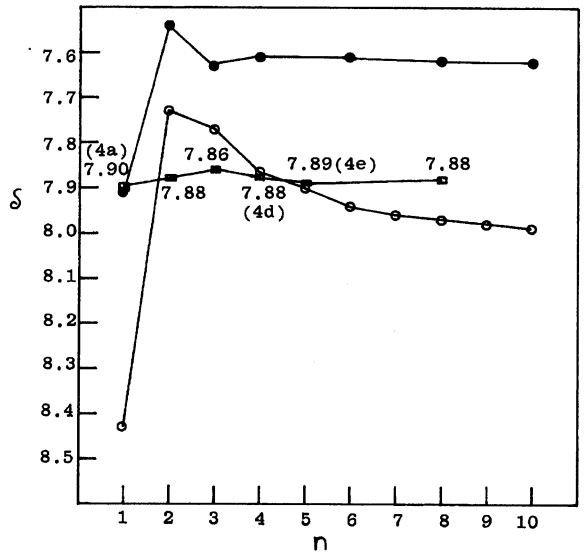


Fig. 3. Relationship between the chemical shifts (H-8 of **2** and **4** and H-6 of **6**) and the carbon numbers (n) of polymethylene chains in D_2O at 27 °C using sodium 3-(trimethylsilyl)propionate-2,2,3,3-d_4 as the internal standard; the concentrations of compounds: <1 mg/0.5 ml (D_2O). The values of chemical shifts of **2** and **6** are summarized in Table 2.

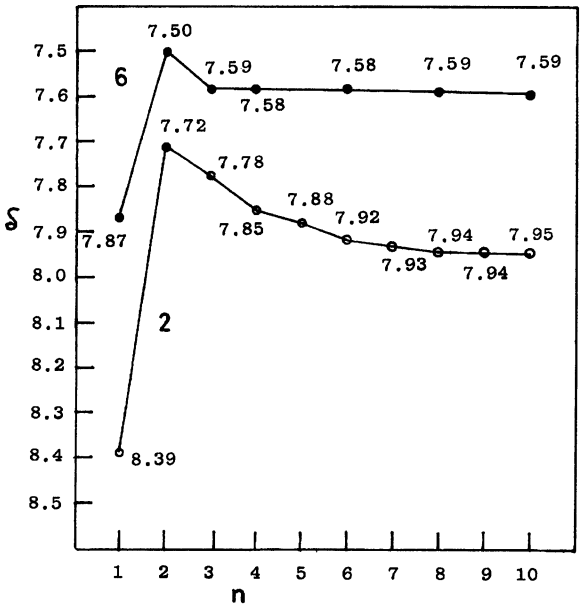


Fig. 4. Relationship between the chemical shifts (H-8 of **2** and H-6 of **6**) and the carbon numbers (n) of polymethylene chains in D_2O at 70 °C using sodium 3-(trimethylsilyl)propionate-2,2,3,3-d_4 as the internal standard; the concentrations of compounds: ca. <1 mg/0.5 ml (D_2O).

Experimental

The melting points were determined on a Yanagimoto micro melting-point apparatus and are uncorrected. The ^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MNz) were obtained with a JEOL GSX400 spectrometer

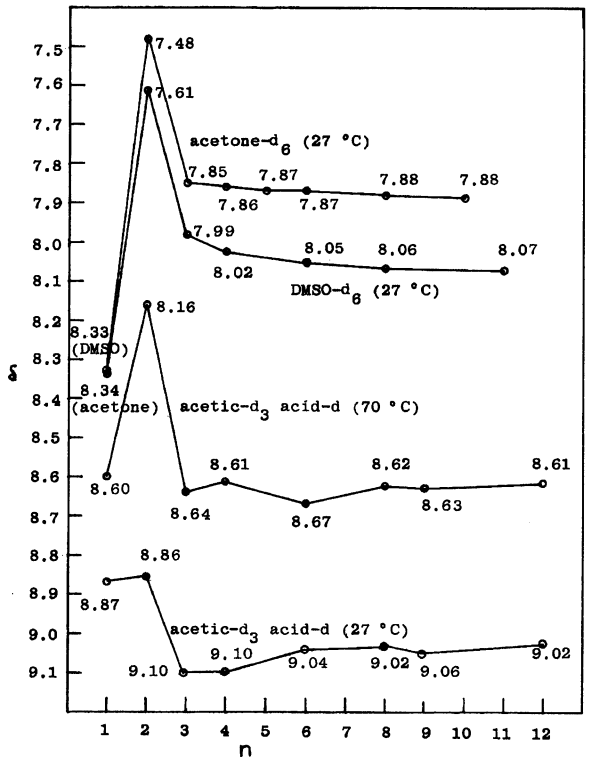


Fig. 5. Relationship between the chemical shifts (H-8 of **2**) in acetone-d_6 (27 °C), dimethyl-d_6 sulfoxide (27 °C), and acetic-d_3 acid-d (27 and 70 °C) and the carbon numbers (n) of polymethylene chains; the concentrations of compounds: 2 mg/0.5 ml (solvent). For reference, the chemical shifts of H-8 of caffeine are as follows; δ=7.80 (acetone-d_6 at 27 °C), δ=7.99 (dimethyl-d_6 sulfoxide at 27 °C), δ=8.38 and 8.23 (acetic-d_3 acid-d, at 27 and 70 °C, respectively).

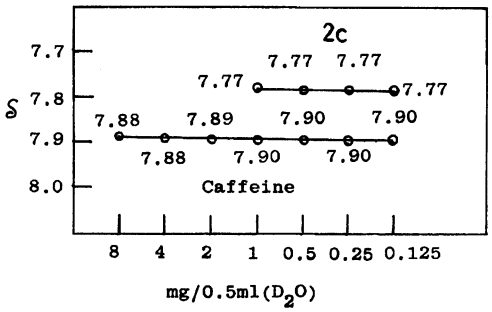
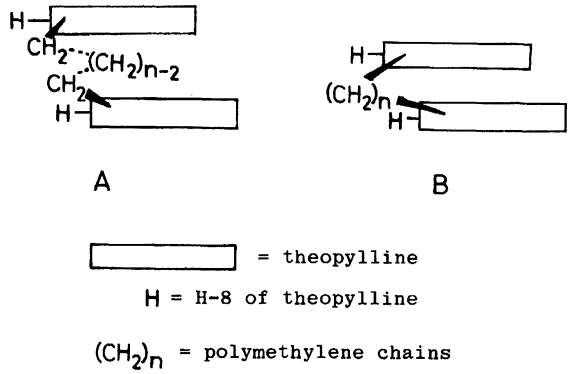


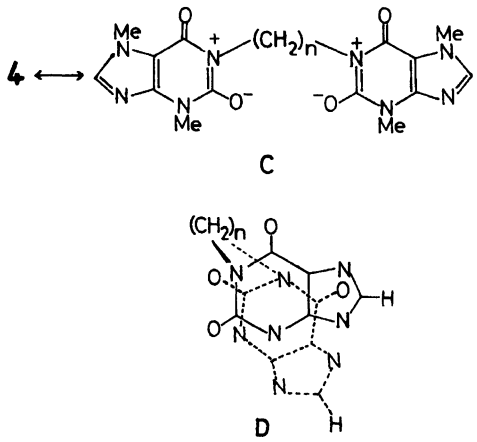
Fig. 6. Relationship between the chemical shifts (H-8 of **2c** and caffeine) in D_2O at 27 °C using sodium 3-(trimethylsilyl)propionate-2,2,3,3-d_4 as the internal standard and the concentrations of **2c** and caffeine.

using tetramethylsilane as an internal standard, except for D_2O. Mass spectra were obtained with a JEOL JMS-D300 spectrometer. The elemental analyses were performed by the Analytical Center of Kyoto University. Theophyline (**1**), theobromine (**3**), $I(CH_2)_nI$, $Br(CH_2)_nBr$, *N*,*N*-dimethylformamide, and sodium hydride were obtained commercially. 3-Methyluracil (**5**) was prepared according to the method described by Brown et al.[15]

7,7′-(α,ω-alkanediyl)bis[theophylline] (2). Into a



Scheme 1.



Scheme 2.

solution of theophylline (**1**) (20 mmol) in *N*,*N*-dimethylformamide (200 ml), sodium hydride (20 mmol) and $X(CH_2)_nX$ (X=I of Br; n=1—12) (10 mmol) were added. The mixture was stirred at room temperature at 15 h and then heated at 70 °C for 3 h. The resulting mixture was poured into water to give (**2**) as a solid mass. The spectral data are given below.

7,7′-Methylenebis[theophylline] (2a): Mp >300 °C; ^{1}H NMR ($CDCl_3$) δ=8.37 (s, 2H), 6.73 (s, 2H), 3.57 (s, 6H), 3.42 (s, 6H); ^{13}C NMR ($CDCl_3$) δ=155.51, 151.41, 149.40, 143.06, 105.65, 53.60, 29.94, 28.10; MS *m/z* (rel intensity, %) 372 (M^+, 51), 193 (100). Calcd for $C_{15}H_{16}N_8O_4$: C, 48.00; H, 4.33; N, 30.09%. Found: C, 48.45; H, 4.22; N, 30.01%.

7,7′-Ethylenebis[theophylline] (2b): Mp >300 °C; ^{1}H NMR ($CDCl_3$) δ=7.26 (s, 2H), 4.78 (s, 4H), 3.57 (s, 6H), 3.44 (s, 6H); (DMSO-d_6) δ=7.61 (s, 2H), 4.64 (s, 4H), 3.40 (s, 6H), 3.23 (s, 6H); ^{13}C NMR ($CDCl_3$) δ=155.40, 151.55, 149.61, 141.64, 106.62, 47.15, 29.91, 28.13. Calcd for $C_{16}H_{18}N_8O_4$: C, 49.74; H, 4.70; N, 29.00%. Found: C, 49.53; H, 4.74; N, 28.89%.

7,7′-Trimethylenebis[theophylline] (2c): Mp 283—285 °C; ^{1}H NMR ($CDCl_3$) δ=7.60 (s, 2H), 4.38 (t, 4H, J=7 Hz), 3.58 (s, 6H), 3.40 (s, 6H), 2.57 (quintet, 2H, J=7 Hz); ^{13}C NMR ($CDCl_3$) δ=155.25, 151.62, 149.23, 141.08, 106.93, 44.36, 32.07, 29.81, 28.05. Calcd for $C_{17}H_{20}N_8O_4$: C, 51.00; H, 5.03; N, 27.99%. Found: C, 51.07; H, 5.01; N, 28.28%.

7,7′-Tetramethylenebis[theophylline] (2d): Mp 297—299 °C; ^{1}H NMR ($CDCl_3$) δ=7.59 (s, 2H), 4.34 (broad t, 4H, J=7 Hz), 3.58 (s, 6H), 3.41 (s, 6H), 1.93 (broad, 4H); ^{13}C NMR ($CDCl_3$) δ=155.18, 151.62, 149.10, 141.13, 106.83, 46.26, 29.83, 28.05, 27.63; MS *m/z* (rel intensity, %) 414 (M^+, 7), 372 (19), 193 (41), 180 (100). Calcd for $C_{18}H_{22}N_8O_4$: C, 52.17; H, 5.35; N, 27.04%. Found: C, 51.70; H, 5.26; N, 26.90%.

7,7′-(1,5-Pentanediyl)bis[theophylline] (2e): Mp 230—232 °C (lit,[4] mp 233—234 °C); ^{1}H NMR ($CDCl_3$) δ= 7.55 (s, 2H), 4.28 (t, 4H, J=7 Hz), 3.59 (s, 6H), 3.41 (s, 6H), 1.96 (quintet, 4H, J=7 Hz), 1.38 (quintet, 4H, J=7 Hz); ^{13}C NMR ($CDCl_3$) δ=155.21, 151.71, 149.13, 140.92, 106.98, 46.74, 30.18, 29.79, 28.02, 23.00. Calcd for $C_{19}H_{24}N_8O_4$: C, 53.26; H, 5.65; N, 26.15%. Found: C, 52.97; H, 5.59; N, 26.03%.

7,7′-(1,6-Hexanediyl)bis[theophylline] (2f): Mp 243—245 °C; ^{1}H NMR ($CDCl_3$) δ=7.54 (s, 2H), 4.28 (t, 4H, J=7 Hz), 3.59 (s, 6H), 3.41 (s, 6H), 1.89 (quintet, 4H, J=7 Hz), 1.38 (broad, 4H); ^{13}C NMR ($CDCl_3$) δ=155.13, 151.67, 148.98, 140.82, 106.95, 47.06, 30.70, 29.78, 28.01, 25.76; MS *m/z* (rel intensity, %) 442 (M^+, 20), 194 (22), 180 (100). Calcd for $C_{20}H_{26}N_8O_4$: C, 54.29; H, 5.92; N, 25.32%. Found: C, 54.08; H, 6.05; N, 25.44%.

7,7′-(1,7-Heptanediyl)bis[theophylline] (2g): Mp 192—194 °C; ^{1}H NMR ($CDCl_3$) δ=7.52 (s, 2H), 4.27 (t, 4H, J=7 Hz), 3.59 (s, 6H), 3.41 (s, 6H), 1.87 (quintet, 4H, J=7 Hz), 1.3—1.4 (m, 6H); ^{13}C NMR ($CDCl_3$) δ=155.19, 151.75, 149.05, 140.79, 107.03, 47.17, 30.18, 29.77, 28.45, 28.00, 26.19. Calcd for $C_{21}H_{28}N_8O_4$: C, 55.25; H, 6.18; N, 24.55%. Found: C, 55.08; H, 6.22; N, 24.33%.

7,7′-(1,8-Octanediyl)bis[theophylline] (2h): Mp 186—187 °C; ^{1}H NMR ($CDCl_3$) δ=7.54 (s, 2H), 4.27 (t, 4H, J=7 Hz), 3.59 (s, 6H), 3.41 (s, 6H), 1.87 (quintet, 4H, J=7 Hz), 1.3—1.4 (m, 8H); ^{13}C NMR ($CDCl_3$) δ=155.13, 151.71, 148.96, 140.81, 106.98, 47.22, 30.83, 29.78, 28.80, 28.01, 26.24; MS *m/z* (rel intensity, %) 470 (M^+, 35), 364 (54), 194 (35), 180 (100). Calcd for $C_{22}H_{30}N_8O_4$: C, 56.16; H, 6.43; N, 23.81%. Found: C, 55.96; H, 6.51; N, 23.52%.

7,7′-(1,9-Nonanediyl)bis[theophylline] (2i): Mp 170—171 °C; ^{1}H NMR ($CDCl_3$) δ=7.52 (s, 2H), 4.27 (t, 4H, J=7 Hz), 3.59 (s, 6H), 3.41 (s, 6H), 1.86 (quintet, 4H, J=7 Hz), 1.3—1.4 (m, 10H); ^{13}C NMR ($CDCl_3$) δ=155.18, 151.76, 149.03, 140.77, 107.04, 47.28, 30.89, 29.77, 29.23, 28.90, 27.99, 26.34. Calcd for $C_{23}H_{32}N_8O_4$: C, 57.01; H, 6.66; N, 23.13%. Found: C, 57.03; H, 6.71; N, 22.91%.

7,7′-(1,10-Decanediyl)bis[theophylline] (2j): Mp 169—170 °C; ^{1}H NMR ($CDCl_3$) δ=7.53 (s, 2H), 4.28 (t, 4H, J=7 Hz), 3.59 (s, 6H), 3.41 (s, 6H), 1.86 (quintet, 4H, J=7 Hz), 1.25—1.4 (m, 12H); ^{13}C NMR ($CDCl_3$) δ=155.14, 151.73, 148.95, 140.79, 106.99, 47.31, 30.90, 29.77, 29.30, 28.96, 28.00, 26.36. Calcd for $C_{24}H_{34}N_8O_4$: C, 57.82; H, 6.87; N, 22.47%. Found: C, 57.54; H, 6.99; N, 22.39%.

7, 7′- (1, 11- Undecanediyl)bis[theophylline] (2k): Mp 138—139 °C; ^{1}H NMR ($CDCl_3$) δ=7.52 (s, 2H), 4.28 (t, 4H, J=7 Hz), 3.59 (s, 6H), 3.41 (s, 6H), 1.87 (quintet, 4H, J=7 Hz), 1.2—1.35 (m, 14H); ^{13}C NMR ($CDCl_3$) δ=155.18, 151.76, 149.02, 140.79, 107.05, 47.32, 30.91, 29.76, 29.37, 29.35, 29.00, 27.99, 26.40. Calcd for $C_{25}H_{36}N_8O_4$: C, 58.58; H, 7.08; N, 21.86%. Found: C, 58.70; H, 6.97; N, 21.57%.

7, 7′- (1, 12- Dodecanediyl)bis[theophylline] (2l): Mp 152—153 °C; ^{1}H NMR ($CDCl_3$) δ=7.53 (s, 2H), 4.28 (t, 4H, J=7 Hz), 3.59 (s, 6H), 3.41 (s, 6H), 1.86 (quintet, 4H, J=7 Hz), 1.2—1.35 (m, 16H); ^{13}C NMR ($CDCl_3$) δ=155.05,

151.67, 148.89, 140.87, 106.93, 30.86, 29.73, 29.38, 29.37, 28.99, 27.95, 26.35; MS m/z (rel intensity, %) 526 (M^+, 22), 392 (62), 364 (83), 360 (54), 180 (73), 68 (100). Calcd for $C_{26}H_{38}N_8O_4$: C, 59.30; H, 7.27; N, 21.28%. Found: C, 59.17; H, 7.33; N, 21.01%.

1,1′-(α,ω-Alkanediyl)bis[theobromine] (4). Into a solution of theobromine (**3**) (10 mmol) in *N*,*N*-dimethylformamide (200 ml) containing sodium hydride (10 mmol), $X(CH_2)_nX$ (10 mmol) was added. The mixture was heated at 50 °C for 15 h and then at 80 °C for 3 h. The resulting mixture was poured into water to give a solid which triturated with a mixture of chloroform and ether to give (**4**).

1,1′-Methylenebis[theobromine] (4a): Mp >300 °C; ^{1}H NMR ($CDCl_3$) δ=7.47 (s, 2H), 6.32 (s, 2H), 3.99 (s, 6H), 3.54 (s, 6H); ^{13}C NMR ($CDCl_3$) δ=154.83, 151.05, 149.16, 141.63, 107.55, 46.80, 33.73, 29.64. Calcd for $C_{15}H_{16}N_8O_4$: C, 48.00; H, 4.33; N, 30.09%. Found: C, 48.27; H, 4.22; N, 30.34%.

1,1′-Ethylenebis[theobromine] (4b): Mp >300 °C (lit,[6] >300 °C); ^{1}H NMR ($CDCl_3$) δ=7.46 (s, 2H), 4.38 (s, 4H), 3.91 (s, 6H), 3.49 (s, 6H); ^{13}C NMR ($CDCl_3$) δ=155.50, 151.96, 149.06, 141.32, 107.67, 40.06, 33.54, 29.66; MS m/z (rel intensity) 386 (M^+, 49), 206 (100), 180 (49). Calcd for $C_{16}H_{18}N_8O_4$: C, 49.74; H, 4.70; N, 29.00%. Found: C, 49.66; H, 4.54; N, 29.23%.

1,1′-Trimethylenebis[theobromine] (4c): Mp 256—258 °C (lit,[6] mp 257—258 °C; lit,[7] mp 263—265 °C); ^{1}H NMR ($CDCl_3$) δ=7.49 (s, 2H), 4.12 (t, 4H, J=7 Hz), 3.97 (s, 6H), 3.55 (s, 6H), 2.06 (quintet, 2H, J=7 Hz); ^{13}C NMR ($CDCl_3$) δ=155.30, 151.53, 148.90, 141.43, 107.71, 39.43, 33.55, 29.70, 27.12. Calcd for $C_{17}H_{20}N_8O_4$: C, 51.00; H, 5.03; N, 27.99%. Found: C, 51.50; H, 5.13; N, 27.43%.

1,1′-Tetramethylenebis[theobromine] (4d): Mp 295—297 °C; ^{1}H NMR ($CDCl_3$) δ=7.48 (s, 2H), 4.06 (broad t, 4H, J=7 Hz), 3.97 (s, 6H), 3.55 (s, 6H), 1.75 (broad, 4H); ^{13}C NMR ($CDCl_3$) δ=155.34, 151.55, 148.85, 141.36, 107.77, 41.10, 33.53, 29.67, 25.68. Calcd for $C_{18}H_{22}N_8O_4$: C, 52.17; H, 5.35; N, 27.04%. Found: C, 51.90; H, 5.34; N, 27.00%.

1,1′-(1,5-Pentanediyl)bis[theobromine] (4e): Mp 244—246 °C (lit,[4] mp 245—246 °C); ^{1}H NMR ($CDCl_3$) δ=7.48 (s, 2H), 4.02 (t, 4H, J=7.5 Hz), 3.98 (s, 6H), 3.56 (s, 6H), 1.72 (quintet, 4H, J=7.5 Hz), 1.45 (quintet, 2H, J=7.5 Hz); ^{13}C NMR ($CDCl_3$) δ=155.36, 151.54, 148.84, 141.34, 107.77, 41.27, 33.54, 29.67, 27.87, 24.43.

1,1′-(1,8-Octanediyl)bis[theobromine] (4h): Mp 230—232 °C; ^{1}H NMR ($CDCl_3$) δ=7.50 (s, 2H), 3.99 (s, 6H), 3.99 (t, 4H, J=7 Hz), 3.57 (s, 6H), 1.64 (quintet, 4H, J=7 Hz), 1.30—1.40 (m, 8H); ^{13}C NMR ($CDCl_3$) δ=155.34, 151.51, 148.75, 141.31, 107.73, 41.46, 33.57, 29.67, 29.33, 28.08, 26.98. Calcd for $C_{22}H_{30}N_8O_4$: C, 56.16; H, 6.43; N, 23.81%. Found: C, 55.93; H, 6.35; N, 23.77%.

1,1′-(1,10-Decanediyl)bis[theobromine] (4j): Mp 193—194 °C; ^{1}H NMR ($CDCl_3$) δ=7.49 (s, 2H), 3.98 (s, 6H), 3.99 (t, 4H, J=7.5 Hz), 3.57 (s, 6H), 1.65 (quintet, 4H, J=7.5 Hz), 1.25—1.4 (m, 12H); ^{13}C NMR ($CDCl_3$) δ=155.34, 151.51, 148.73, 141.33, 107.72, 41.49, 33.58, 29.67, 29.49, 29.34, 28.10, 26.99; MS m/z (rel intensity, %) 498 (M^+, 68), 364 (77), 180 (81), 68 (100). Calcd for $C_{24}H_{34}N_8O_4$: C, 57.82; H, 6.87; N, 22.48%. Found: C, 57.58; H, 6.87; N, 22.50%.

1, 1′- (1, 12- Dodecanediyl)bis[theobromine] (4l): Mp 158—159 °C; ^{1}H NMR ($CDCl_3$) δ=7.48 (s, 2H), 3.98 (s, 6H), 3.98 (t, 4H, J=7 Hz), 3.57 (s, 6H), 1.63 (quintet, 4H, J=7 Hz), 1.20—1.40 (m, 16H); ^{13}C NMR ($CDCl_3$) δ=155.39, 151.56, 148.81, 141.32, 107.77, 41.53, 33.54, 29.66, 29.58, 29.56, 29.39, 28.13, 27.05. Calcd for $C_{26}H_{38}N_8O_4$: C, 59.30; H, 7.27; N, 21.28%. Found: C, 59.04; H, 7.28; N, 20.98%.

1,1′-(α,ω-Alkanediyl)bis[3-methyluracil] (6). Into a solution of 3-methyluracil (**5**) (5 mmol) in *N*,*N*-dimethylformamide (100 ml), sodium hydride (5 mmol) and $X(CH_2)_nX$ (X=I, n=1, 3, 4, 6, 8, 10; X=Br, n=2, 12) (2.5 mmol) were added. The reaction mixture was stirred at room temperature for 17 h and then heated at 80 °C for 3 h. The mixture was evaporated to give a solid which was chromatographed on silica gel, eluted with ethyl acetate, to give (**6**). The spectral data of **6** are as follows.

1,1′-Methylenebis[3-methyluracil] (6a): Mp 235—237 °C; ^{1}H NMR ($CDCl_3$) δ=7.71 (d, 2H, J=8 Hz), 5.77 (d, 2H, J=8 Hz), 5.52 (s, 2H), 3.31 (s, 6H); ^{13}C NMR ($CDCl_3$) δ=162.51, 152.43, 142.63, 102.01, 61.56, 27.74. MS m/z (rel intensity, %) 264 (M^+, 85), 139 (88), 82 (100). Calcd for $C_{11}H_{12}N_4O_4$: C, 50.00; H, 4.58; N, 21.20%. Found: C, 50.17; H, 4.64; N, 21.22%.

1,1′-Ethylenebis[3-methyluracil] (6b): Mp 260—262 °C; ^{1}H NMR ($CDCl_3$) δ=7.01 (d, 2H, J=7.5 Hz), 5.73 (d, 2H, J=7.5 Hz), 4.04 (s, 4H), 3.34 (s, 6H); ^{13}C NMR ($CDCl_3$) δ=162.81, 151.76, 141.90, 102.31, 48.45, 27.80; MS m/z (rel intensity, %) 278 (M^+, 17), 153 (45), 152 (72), 95 (42), 82 (100). Calcd for $C_{12}H_{14}N_4O_4$: C, 51.79; H, 5.07; N, 20.14%. Found: C, 51.52; H, 5.05; N, 20.16%.

1,1′-Trimethylenebis[3-methyluracil] (6c): Mp 162—163 °C; ^{1}H NMR ($CDCl_3$) δ=7.22 (d, 2H, J=8 Hz), 5.77 (d, 2H, J=8 Hz), 3.82 (t, 4H, J=7 Hz), 3.34 (s, 6H), 2.13 (quintet, 2H, J=7 Hz); ^{13}C NMR ($CDCl_3$) δ=162.93, 151.89, 141.72, 102.15, 47.02, 28.77, 27.83. MS m/z (rel intensity, %) 292 (M^+, 7), 167 (30), 166 (100), 153 (95), 140 (71). Calcd for $C_{12}H_{16}N_4O_4$: C, 53.42; H, 5.52; N, 19.17%. Found: C, 53.37; H, 5.48; N, 19.20%.

1,1′-Tetramethylenebis[3-methyluracil] (6d): Mp 212—213 °C; ^{1}H NMR ($CDCl_3$) δ=7.17 (d, 2H, J=8 Hz), 5.75 (d, 2H, J=8 Hz), 3.81 (broad t, 4H, J=7 Hz), 3.34 (s, 6H), 1.75 (broad quintet, 4H, J=7 Hz); ^{13}C NMR ($CDCl_3$) δ=163.11, 151.73, 141.93, 101.79, 48.95, 27.80, 25.84; MS m/z (rel intensity, %) 306 (M^+, 2), 180 (100). Calcd for $C_{14}H_{18}N_4O_4$: C, 54.89; H, 5.92; N, 18.29%. Found: C, 54.48; H, 5.85; N, 18.35%.

1,1′-(1,6-Hexanediyl)bis[3-methyluracil] (6f): Mp 128—129 °C; ^{1}H NMR ($CDCl_3$) δ=7.11 (d, 2H, J=8 Hz), 5.74 (d, 2H, J=8 Hz), 3.74 (t, 4H, J=7 Hz), 3.34 (s, 6H), 1.71 (broad quintet, 4H, J=7 Hz), 1.39 (broad, 4H); ^{13}C NMR ($CDCl_3$) δ=163.25, 151.64, 141.96, 101.51, 49.68, 28.85, 27.79, 26.00; MS m/z (rel intensity, %) 334 (M^+, 4), 267 (40), 195 (56), 181 (46), 167 (35), 153 (38), 140 (38), 127 (68), 126 (59), 82 (100). Calcd for $C_{16}H_{22}N_4O_4$: C, 57.47; H, 6.63; N, 16.76%. Found: C, 57.45; H, 6.59; N, 16.66%.

1,1′-(1,8-Octanediyl)bis[3-methyluracil] (6h): Mp 101—102 °C; ^{1}H NMR ($CDCl_3$) δ=7.12 (d, 2H, J=8 Hz), 5.73 (d, 2H, J=8 Hz), 3.73 (t, 4H, J=7 Hz), 3.34 (s, 6H), 1.69 (broad quintet, 4H, J=7 Hz), 1.35 (broad, 8H); ^{13}C NMR ($CDCl_3$) δ=163.28, 151.66, 142.03, 101.42, 49.84, 28.97, 28.95, 27.78, 26.34. Calcd for $C_{18}H_{26}N_4O_4$: C, 59.65; H, 7.23; N, 15.46%. Found: C, 59.39; H, 7.40; N, 15.29%.

1,1′-(1,10-Decanediyl)bis[3-methyluracil] (6j): Mp

97—98 °C; ^{1}H NMR ($CDCl_3$) δ=7.12 (d, 2H, J=8 Hz), 5.73 (d, 2H, J=8 Hz), 3.73 (t, 4H, J=7 Hz), 4.34 (s, 6H), 1.69 (broad quintet, 4H, J=7 Hz), 1.2—1.35 (m, 12H); ^{13}C NMR ($CDCl_3$) δ=163.33, 151.64, 142.08, 101.35, 49.94, 29.28, 29.10, 29.02, 27.78, 26.43. Calcd for $C_{20}H_{30}N_4O_4$: C, 61.52; H, 7.74; N, 14.35%. Found: C, 61.89; H, 7.86; N, 14.14%.

1,1′-(1,12-Dodecanediyl)bis[3-methyluracil] (6l): Mp 74—75 °C; ^{1}H NMR ($CDCl_3$) δ=7.11 (d, 2H, J=8 Hz), 5.72 (d, 2H, J=8 Hz), 3.73 (t, 4H, J=7 Hz), 3.34 (s, 6H), 1.68 (quintet, 4H, J=7 Hz), 1.2—1.35 (m, 16H); ^{13}C NMR ($CDCl_3$) δ=163.32, 151.67, 142.06, 101.34, 49.95, 29.43, 29.40, 29.15, 29.05, 27.76, 26.48. Calcd for $C_{22}H_{34}N_4O_4$: C, 63.13; H, 8.19; N, 13.39%. Found: C, 62.97; H, 8.22; N, 13.42%.

7-[6-(3-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)hexyl]theophylline (7f). Into a solution of theophylline (**1**) (10 mmol) and 3-methyluracil (**5**) (10 mmol) in *N*,*N*-dimethylformamide (200 ml), sodium hydride (20 mmol), and 1,6-diiodohexane (10 mmol) were added. The reaction mixture was stirred at room temperature for 15 h and then heated at 70 °C for 3 h. The resulting mixture was evaporated and chromatographed on silica gel to give **2f** (14%), **6f** (8%), and **7f** (14%): Mp 159—160 °C; ^{1}H NMR ($CDCl_3$) δ=7.52 (s, 1H), 7.10 (d, 1H, J=8 Hz), 5.72 (d, 1H, J=8 Hz), 4.28 (t, 2H, J=7 Hz), 3.72 (t, 2H, J=7.5 Hz), 3.59 (s, 3H), 3.41 (s, 3H), 3.33 (s, 3H), 1.85—1.95 (m, 2H), 1.62—1.72 (m, 2H), 1.30—1.40 (m, 6H); ^{13}C NMR ($CDCl_3$) δ=163.20, 155.20, 151.73, 151.68, 149.09, 141.90, 140.79, 107.01, 101.54, 49.65, 47.08, 30.75, 29.77, 28.80, 28.00, 27.77, 25.90, 25.86. Calcd for $C_{18}H_{24}N_6O_4$: C, 55.66; H, 6.23; N, 21.64%. Found: C, 55.38; H, 6.22; N, 21.37%.

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