

Facile Synthesis of Pyrimidinophanes

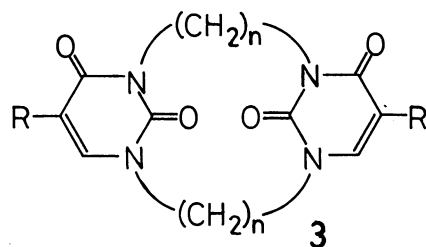
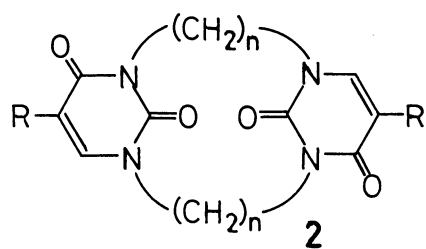
Toshio ITAHARA

Institute of Chemistry, College of Liberal Arts,
Kagoshima University, Korimoto, Kagoshima 890

Treatment of pyrimidine bases with $X(\text{CH}_2)_nX$ ($X = \text{Br}$ or I ; $n = 5-12$) in N,N -dimethylformamide containing sodium hydride afforded three types of pyrimidinophanes.

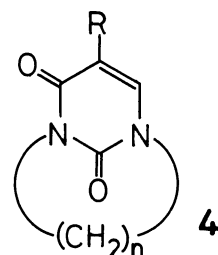
Increasing interest is being shown in macrocyclic compounds in connection with biological active natural products such as petrosins¹⁾ and xestospongins²⁾ and host-guest molecules.³⁾ While macrocyclic oligosaccharides and peptides are well known, little attention has been paid to macrocyclic compounds from nucleic acid related compounds. On the other hand, Sakata et al. studied the macrocyclic compounds containing purines which went by the name of purinophanes and pyrimidinopurinophanes in detail.⁴⁾ However, the preparation of pyrimidinophanes has not been investigated systematically. This paper describes a facile procedure for the preparation of three types of pyrimidinophanes 2, 3, and 4 from pyrimidine bases 1 such as uracil (1a), thymine (1b), and 5-fluorouracil (1c), although the pyrimidinophanes 2a-4 and 3b-3 were prepared from 1-(4-bromobutyl)uracil⁵⁾ and 1,3-bis(thymin-1-yl)propane,⁶⁾ respectively, and compounds similar to 2 were also obtained from 1',2'-secothyridine derivatives.⁷⁾

The experimental procedure is as follows: Into a solution of 1 (10 mmol) in N,N -dimethylformamide (100 ml), sodium hydride (20 mmol) and $X(\text{CH}_2)_nX$ ($X = \text{Br}$ or I , $n = 5-12$) (10 mmol) were added. The resulting mixture was stirred at room temperature for 15 h and then heated at 70 °C for 3 h. The reaction mixture was evaporated to give a residue which was chromatographed on silica gel and eluted with hexane and ethyl acetate. By monitoring at 254 nm the pyrimidinophanes 2, 3, and 4 were obtained.⁸⁾ Although the yields of 2 and 3 were satisfactory in the case of the reaction with $\text{I}(\text{CH}_2)_6\text{I}$, their spectral data did not give evidences to distinguish both structures of 2a-6 and 3a-6. However, in cases of compounds with odd numbers of methylene groups in $X(\text{CH}_2)_nX$ ($n = 5, 7, 9, 11$), the structures of 2 and 3 were confirmed on the basis of the numbers of peaks on ^{13}C -NMR spectra.^{8,9)} The compounds 4 were confirmed by MS spectral data (Table 1).



a: R = H, **b**: R = CH₃, **c**: R = F

	n	R
<u>3b-3</u>	3	CH ₃
<u>2a-4</u>	4	H
<u>2a-5</u> ; <u>3a-5</u>	5	H
<u>2b-5</u> ; <u>3b-5</u>	5	CH ₃
<u>2c-5</u> ; <u>3c-5</u>	5	F
<u>2a-6</u> ; <u>3a-6</u>	6	H
<u>2b-6</u> ; <u>3b-6</u>	6	CH ₃
<u>2a-7</u> ; <u>3a-7</u>	7	H
<u>2b-7</u> ; <u>3b-7</u>	7	CH ₃
<u>2c-7</u> ; <u>3c-7</u>	7	F
<u>2a-9</u> ; <u>3a-9</u>	9	H
<u>2b-9</u> ; <u>3b-9</u>	9	CH ₃
<u>2c-9</u> ; <u>3c-9</u>	9	F
<u>2a-11</u> ; <u>3a-11</u>	11	H



	n	R
<u>4a-9</u>	9	H
<u>4b-9</u>	9	CH ₃
<u>4c-9</u>	9	F
<u>4a-10</u>	10	H
<u>4c-10</u>	10	F
<u>4a-11</u>	11	H
<u>4a-12</u>	12	H
<u>4b-12</u>	12	CH ₃

Table 1. Preparation of Pyrimidinophanes from Pyrimidine Bases

<u>1</u>	<u>X(CH₂)_nX</u>	<u>Product (MS, M⁺/ m/z, rel intensity):^{a)}</u>	<u>Isolated yield/%^{b)}</u>
	n X		
<u>1a</u>	5 I	<u>2a-5</u> (360, 100%): 10; <u>3a-5</u> (360, 100%): 7	
<u>1b</u>	5 I	<u>2b-5</u> (388, 100%): 14; <u>3b-5</u> (388, 100%): 8	
<u>1c</u>	5 I	<u>2c-5</u> (396, 100%): 14; <u>3c-5</u> (396, 100%): 8	
<u>1a</u>	6 I	<u>2a-6</u> + <u>3a-6</u> : 30	
<u>1b</u>	6 I	<u>2b-6</u> + <u>3b-6</u> : 35	
<u>1a</u>	7 Br	<u>2a-7</u> (416, 100%): 12; <u>3a-7</u> (416, 100%): 11	
<u>1b</u>	7 Br	<u>2b-7</u> (444, 100%): 15; <u>3b-7</u> (444, 100%): 15	
<u>1c</u>	7 Br	<u>2c-7</u> (452, 62%): 14; <u>3c-7</u> (452, 45%): 14	
<u>1a</u>	9 Br	<u>2a-9</u> (472, 100%): 10; <u>3a-9</u> (472, 53%): 8; <u>4a-9</u> (236, 100%): 2	
<u>1b</u>	9 Br	<u>2b-9</u> (500, 100%): 8; <u>3b-9</u> (500, 100%): 8; <u>4b-9</u> (250, 100%): 4	
<u>1c</u>	9 Br	<u>2c-9</u> (508, 19%): 7; <u>3c-9</u> (508, 60%): 8; <u>4c-9</u> (254, 100%): 4	
<u>1a</u>	10 I	<u>2a-10</u> and <u>3a-10</u> ; ^{c)} <u>4a-10</u> (250, 100%): 10	
<u>1c</u>	10 I	<u>2c-10</u> and <u>3c-10</u> ; ^{c)} <u>4c-10</u> (268, 100%): 11	
<u>1a</u>	11 Br	<u>2a-11</u> (528, 100%): 3; <u>3a-11</u> (528, 100%): 4; <u>4a-11</u> (264, 100%): 14	
<u>1a</u>	12 Br	<u>2a-12</u> and <u>3a-12</u> ; ^{c)} <u>4a-12</u> (278, 100%): 15	
<u>1b</u>	12 Br	<u>2b-12</u> and <u>3b-12</u> ; ^{c)} <u>4b-12</u> (292, 100%): 15	

a) FAB-MS, m/z; 2c-9 (509, 100%), 3c-9 (509, 100%), 4b-12 (293, 100%).

b) Yield was based on pyrimidine base used and yield of the recovered substrate was not determined. c) Isolation of 2 and 3 was not attempted.

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- 8) Products were characterized by elemental analyses and ^1H -NMR, ^{13}C -NMR, and mass spectral data; typical spectral data are as follows. 2a-5: Mp 203-205 °C; ^1H -NMR (CDCl_3) δ 7.05 (d, 2H, J=8 Hz), 5.68 (d, 2H, J=8 Hz), 4.06 (t, 4H, J=5.5 Hz), 3.8 (br, 4H), 1.6-1.8 (m, 8H), 1.1-1.25 (m, 4H); ($\text{DMSO}-d_6$, 80 °C) δ 7.53 (d, 2H, J=8 Hz), 5.56 (d, 2H, J=8 Hz), 3.86 (t, 4H, J=6 Hz), 3.77 (t, 4H, J=5.5 Hz), 1.6-1.7 (m, 4H), 1.5-1.6 (m, 4H), 1.05-1.15 (m, 4H), 0.95-1.05 (m, 4H); (D_2O) δ 7.56 (d, 2H, J=8 Hz), 5.82 (d, 2H, J=8 Hz), 4.01 (t, 4H, J=5.5 Hz), 3.9 (br, 4H), 1.6-1.75 (m, 8H), 0.95-1.1 (m, 4H); ^{13}C -NMR (CDCl_3) δ 163.24, 152.00, 142.10, 101.61, 48.33, 40.74, 29.53, 27.65, 23.10. 3a-5: Mp 263-266 °C; ^1H -NMR (CDCl_3) δ 7.05 (d, 2H, J=8 Hz), 5.69 (d, 2H, J=8 Hz), 4.04 (t, 4H, J=5.5 Hz), 3.85 (br, 4H), 1.6-1.8 (m, 8H), 1.25-1.35 (m, 2H), 1.15-1.25 (m, 2H); (D_2O) δ 7.57 (d, 2H, J=8 Hz), 5.83 (d, 2H, J=8 Hz), 4.00 (t, 4H, J=5.5 Hz), 3.9 (br, 4H), 1.6-1.8 (m, 8H), 1.1-1.2 (m, 2H), 1.0-1.1 (m, 2H); ^{13}C -NMR (CDCl_3) δ 162.99, 152.29, 141.54, 102.09, 48.18, 41.22, 29.67, 28.23, 24.13, 23.16. 4b-12: Mp 78-79 °C; ^1H -NMR (CDCl_3) δ 6.94 (s, 1H), 4.09 (t, 2H, J=6 Hz), 3.8 (br, 2H), 1.95 (s, 3H), 1.6-1.8 (m, 4H), 1.1-1.4 (m, 16H); ^{13}C -NMR (CDCl_3) δ 164.03, 152.10, 138.33, 109.65, 48.62, 40.96, 28.40, 27.46, 27.15, 27.10, 26.83, 26.72, 26.18, 26.15, 24.80, 24.44, 13.15.

- 9) ^{13}C -NMR data (CDCl_3) are as follows. 2b-5; δ 163.99, 152.08, 138.11, 109.66, 47.77, 41.21, 29.89, 27.97, 23.29, 13.06. 2c-5; δ 157.32 (d, $J=25$ Hz), 150.63, 140.10 (d, $J=234$ Hz), 129.97 (d, $J=32$ Hz), 48.28, 41.83, 29.61, 27.70, 23.29. 2a-7; δ 163.07, 151.97, 141.69, 101.86, 48.58, 41.15, 29.69, 29.63, 27.64, 26.58, 25.97. 2b-7; δ 163.75, 151.98, 137.82, 109.93, 48.10, 41.42, 29.87, 29.27, 27.76, 26.68, 25.99, 13.02. 2c-7; δ 157.18 (d, $J=25$ Hz), 150.43, 140.15 (d, $J=234$ Hz), 125.98 (d, $J=32$ Hz), 48.62, 42.02, 29.61, 29.48, 27.54, 26.57, 25.87. 2a-9; δ 163.16, 151.79, 141.95, 101.73, 49.20, 41.17, 29.41, 29.32, 29.15, 29.10, 27.47, 26.65, 26.12. 2b-9; δ 163.82, 151.79, 138.09, 109.81, 48.80, 41.39, 29.49, 29.42, 29.26, 29.16, 27.58, 26.74, 26.16, 13.06. 2c-9; δ 157.24 (d, $J=25$ Hz), 150.24, 140.12 (d, $J=234$ Hz), 126.21 (d, $J=32$ Hz), 49.22, 42.00, 29.36, 29.29, 29.13, 29.03, 27.37, 26.62, 26.02. 2a-11; δ 163.18, 151.62, 141.99, 101.67, 49.47, 41.22, 29.45, 29.32, 29.26, 29.22, 29.13, 29.08, 27.47, 26.76, 26.25. 3b-5; δ 163.70, 152.24, 137.85, 109.92, 47.92, 41.39, 29.75, 28.32, 23.14, 23.26, 13.03. 3c-5; δ 157.11 (d, $J=25$ Hz), 150.80, 140.24 (d, $J=234$ Hz), 125.77 (d, $J=32$ Hz), 48.46, 42.13, 29.56, 28.11, 24.07, 23.24. 3a-7; δ 162.99, 152.01, 141.68, 101.90, 48.73, 41.22, 30.04, 29.53, 29.49, 27.85, 26.61, 26.13. 3b-7; δ 163.69, 152.03, 137.77, 110.00, 48.35, 41.48, 30.23, 29.69, 29.67, 27.97, 26.68, 26.22, 13.02. 3c-7; δ 157.13 (d, $J=25$ Hz), 150.48, 140.21 (d, $J=234$ Hz), 125.49 (d, $J=32$ Hz), 48.93, 42.14, 29.97, 29.44, 29.39, 27.75, 26.53, 26.11. 3a-9; δ 163.12, 151.81, 141.84, 101.79, 49.26, 41.22, 29.58, 29.24, 29.21, 29.14, 29.11, 27.54, 26.65, 26.19. 3b-9; δ 163.80, 151.81, 138.04, 109.85, 48.87, 41.42, 29.65, 29.33, 29.25, 29.24, 29.18, 27.63, 26.72, 26.25, 13.06. 3c-9; δ 157.21 (d, $J=25$ Hz), 150.26, 140.15 (d, $J=234$ Hz), 126.11 (d, $J=32$ Hz), 49.35, 42.04, 29.52, 29.20, 29.18, 29.15, 28.99, 27.43, 26.58, 26.13. 3a-11; δ 163.16, 151.64, 141.96, 101.69, 49.52, 41.22, 29.55, 29.38, 29.37, 29.31, 29.22, 29.12, 29.06, 27.48, 26.74, 26.28. 4a-9; δ 163.30, 152.39, 142.44, 101.70, 49.26, 40.63, 25.48, 25.47, 25.1, 24.78, 23.54, 23.44, 23.27. 4b-9; δ 163.92, 152.43, 138.56, 109.79, 48.67, 40.76, 25.71, 25.48, 25.35, 24.81, 23.62, 23.52, 23.43, 13.07. 4c-9; δ 157.30 (d, $J=25$ Hz), 150.86, 140.14 (d, $J=234$ Hz), 126.70 (d, $J=32$ Hz), 49.29, 41.57, 25.59, 25.53, 25.23, 24.67, 23.48, 23.47, 23.29. 4a-10; δ 163.23, 152.67, 141.96, 102.07, 49.13, 41.61, 26.84, 26.69, 26.31, 26.26, 26.12, 25.32, 24.96, 24.90. 4c-10; δ 157.33 (d), 151.07, 140.24 (d), 126.19 (d), 49.10, 42.47, 26.74, 26.70, 26.24, 26.16, 26.15, 25.33, 24.84, 24.78. 4a-11; δ 163.69, 151.24, 143.10, 100.85, 50.59, 40.29, 26.48, 26.17, 25.89, 25.79, 25.43, 24.46, 24.01, 22.67, 22.61. 4a-12; δ 163.39, 152.09, 142.21, 101.59, 49.11, 40.82, 28.23, 27.49, 27.12, 27.00, 26.71, 26.66, 26.15, 26.08, 24.78, 24.36.

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