Chemistry of Heterocyclic Compounds. 48. Synthesis of Multiheteromacrocycles Containing the 4,6-Pyrimidino Moiety Connected by Carbon–Oxygen and/or –Sulfur Linkages[1]

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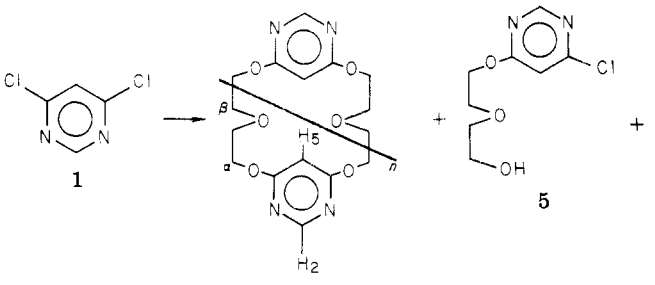
The 4,6-pyrimidino moiety was incorporated into a "crown ether" macrocyclic framework, when 4,6-dichloropyrimidine (1) was treated with the disodium salt of (poly)ethylene glycols. Several 1:1 and 2:1 noncyclic products were isolated and characterized. Ring fragmentation of these pyrimidino macrocycles occurred upon treatment with methyl iodide; 1-methyl-4-methoxy-1,6-dihydro-6-oxopyrimidine (**16**) was isolated, as the major product. The 10-membered, C,S,O-macrocycle **23** was isolated from the reaction of **1** with the disodium salt of bis(2-mercaptoethyl) ether; this macrocycle was the smallest macrocycle prepared by this procedure.

In view of the biological and medicinal interest in substituted pyrimidines[3] as well as the limited examples of pyrimidino inclusion in a macrocyclic framework,[4] we herein describe the synthesis and characterization of multiheteromacrocycles which contain the 4,6-pyrimidino subunit.

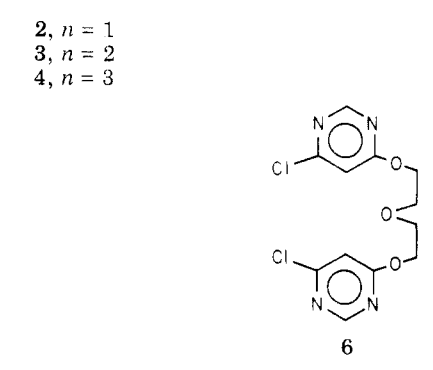
When 4,6-dichloropyrimidine (**1**) is treated with 1 equiv of sodium alkoxide in alcohol at room temperature, 4-chloro-6-alkoxypyrimidine is the predominant product formed.[5] With the use of 2 or more equiv of alkoxide at either room or elevated temperatures, the corresponding disubstituted product is formed in excellent yield. Thus, selective substitution can be realized, if the reaction conditions are controlled.

A. 4,6-Pyrimidino Macrocycles with Carbon–Oxygen Linkages. 1. Diethylene Glycol. The reaction of 4,6-dichloropyrimidine (**1**) with disodium diethylene glycolate, generated from diethylene glycol and 2 equiv of sodium hydride, in refluxing anhydrous xylene gave several macrocyclic (**2**–**4**) and noncyclic (**5**,**6**) products. Under these reaction conditions, numerous other noncyclic oligomeric and fragmentation products[4,6] were detected and in certain cases isolated; however, further characterization of the minor side products was not attempted.[7] At lower (80–110 °C) reaction temperatures, the 1:1 adduct **5** can be isolated as the major product. However, subsequent treatment of **5** with 1 equiv of sodium hydride, followed by prolonged refluxing in xylene, gave the desired 2:2 macrocycle **2** and related larger oligomers **3** and **4**.



1

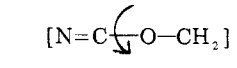
5



2, n = 1
3, n = 2
4, n = 3

6

The cyclic structure of **2**–**4** was confirmed by ^{1}H NMR spectrometry. The 2- and 5-pyrimidine hydrogens of **2**–**4** appear as singlets at δ 8.30–8.36 and 5.67–6.15, respectively, whereas the α-methylenes appear as broadened triplets at δ 4.44–4.51. The H-5 protons for 2:2 macrocycle **2** exhibit an unusual upfield shift ($\Delta\delta$ ~0.5) suggestive of enhanced rigidity within this smaller macrocyclic ring. Such a shift for H-5 is indicative of a long-range anisotropic effect (or shielding effect) caused by the juxtaposition of the adjacent pyrimidine nucleus. Such macrocyclic immobility is associated with a low



dihedral bond angle and attributed to the imidate ester characteristics within the subunits. Figure 1 depicts the layering of the pyrimidino subunits in order to maintain the near-zero imidate dihedral angle, thus subjecting H-5 to the environment of the neighboring pyrimidine ring current. Recent X-ray studies on related macrocycles support this imidate dihedral angle.[8] Except for the H-5 chemical shift for **2**, the NMR chemical shift data and UV and IR data for all these pyrimidine macrocycles were nearly superimposable. Molecular weight determinations (mass spectrometry and/or osmometry) firmly establish the size of the macrocyclic unit; R_f values correspond quite well to macrocyclic size. The 1:1 C,O-macrocycle [i.e., **2** (n = 0)], which possesses a "meta"-bridged 10-membered ring, was not detected. This inability to form a small 10-membered ring via this procedure is consistent with previous observations.[4,7]

(1) For Paper 47 of the Chemistry of Heterocyclic Compounds: Newkome, G. R.; Roper, J. M. *J. Organomet. Chem.* **1979**, in press.
(2) (a) On leave from Sambalpur University, Sambalpur (Orissa), India, 1975–1977. (b) Undergraduate Researchers.
(3) Chang, C. C. *Prog. Med. Chem.* **1969**, *6*, 67–134. Chang, C. C.; Roth, B. *Ibid.* **1970**, *7*, 285–341. *Ibid.* **1971**, *8*, 61–117.
(4) Newkome, G. R.; Nayak, A.; Otemaa, J.; Van, D. A.; Benton, W. H. *J. Org. Chem.* **1978**, *43*, 3362 and references cited therein.
(5) Isbecque, D.; Promel, R.; Quanaux, R. C.; Martin, R. H. *Helv. Chim. Acta* **1959**, *42*, 1317
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(8) (a) Fronczek, F.; Nayak, A.; Newkome, G. R. *Acta Crystallogr.* **1979**, *1335*, 775. (b) Newkome, G. R.; Majestic, V. K.; Fronczek, F.; Atwood, J. L. *J. Am. Chem. Soc.* **1979**, *101*, 1047. (c) Newkome, G. R.; Nayak, A.; Fronczek, F.; Kawato, T.; Taylor, H. C. R.; Meade, L.; Mattice, W. L. *J. Am. Chem. Soc.*, **1979**, *101*, 4472. (d) Newkome, G. R.; Nayak, A.; Sauer, J. D.; Mattschei, P. K.; Watkins, S. F.; Fronczek, F.; Benton, W. H., *J. Org. Chem.*, **1979**, *44*, in press.

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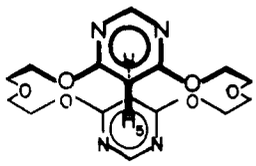
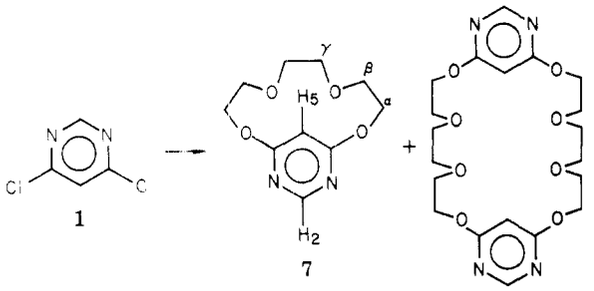


Figure 1. Layering of the pyrimidine subunits in order to maintain the near-zero imidate dihedral angle.

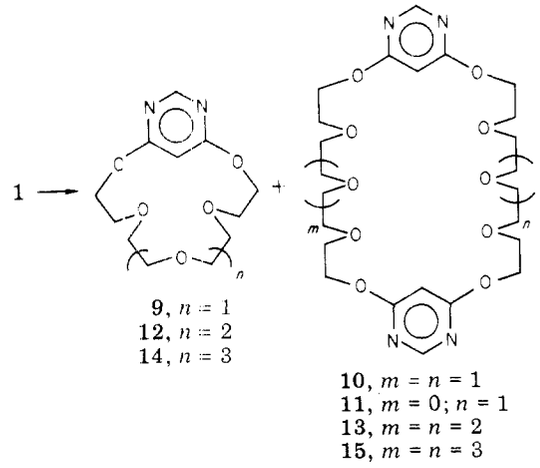
The major noncyclic product was the 2:1 ether, whose structure was supported by two singlets at δ 6.85 and 8.55 for the 5- and 2-pyrimidine hydrogens, respectively. The downfield position of H-5 is characteristic of a 4-oxo-6-chloropyrimidine substitution pattern. The 1:1 intermediate **5** possesses a similar NMR ring pattern as well as an exchangeable hydroxyl proton evidenced by the broad singlet at δ 2.78.

2. Triethylene Glycol. When a xylene solution of **1** was treated with disodium triethylene glycolate under anhydrous conditions at 140 °C, two major macrocyclic products (**7** and **8**) were prepared. The macrocyclic



structure was easily ascertained by the simple NMR pattern: two singlets at δ 8.35–8.37 and 6.10–6.15 for the 2- and 5-pyrimidine ring hydrogens and a spike at δ 3.67 for the γ-methylene hydrogens. Broad triplets of the α- and β-hydrogens were at the expected position. All other spectral and physical data were consistent with the assignments. Along with the expected macrocycles, numerous noncyclic products were isolated but not characterized further, other than by NMR comparisons.

3. Tetra-, Penta-, and Hexaethylene Glycol. The disodium glycolates of tetra-, penta-, and hexaethylene glycols were reacted independently with **1** at 140 °C to give **9**, **12**, and **14**, respectively, in increasing yields with increasing ring size.[9] With tetraethylene glycol, the an-

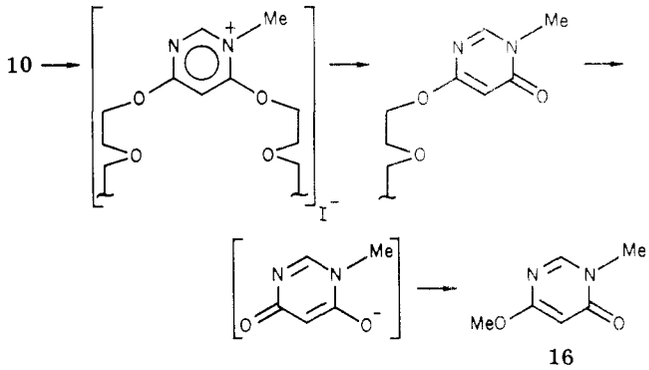


9, n = 1
12, n = 2
14, n = 3

10, $m = n = 1$
11, $m = 0; n = 1$
13, $m = n = 2$
15, $m = n = 3$

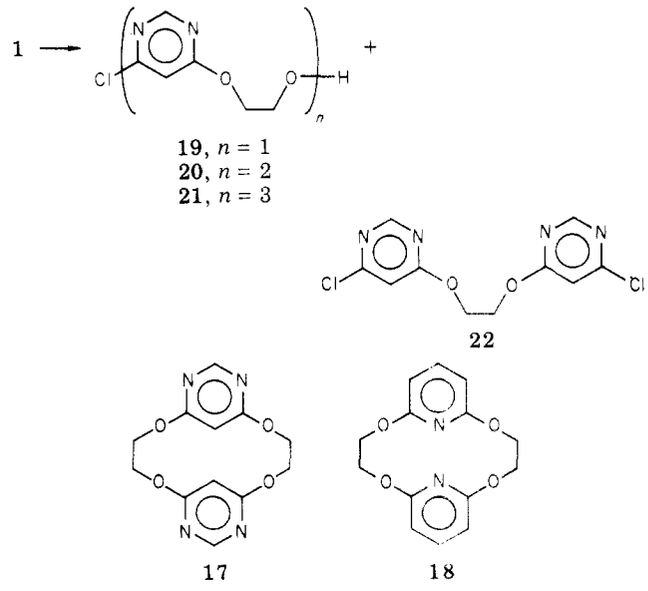
ticipated symmetrical macrocycle **10** was isolated as well as the unsymmetrical 2:2 macrocycle **11**. This type of unsymmetrical macrocycle resulted from slow fragmentation of either the starting polyethylene glycols or the noncyclized intermediate under the reaction conditions.[10] Reduction of the reaction temperature (50 °C) resulted in the formation of noncyclic 1:1 compounds, which have been shown to undergo cyclization under prolonged reaction conditions.

In an attempt to determine the stability of these macrocycles to methyl iodide and the site of initial quaternization, **10** was heated with redistilled methyl iodide in a sealed tube at 35 °C for 8 h. The major product was 1-methyl-4-methoxy-1,6-dihydro-6-oxopyrimidine (**16**), which was isolated and identified by comparison with an authentic sample.[11] Initial mono (one subring) N-quaternization was followed by ring fragmentation via the well-known Hilbert–Johnson reaction.[12] Subsequent nucleophilic attack on the remaining α-methylene group was then terminated by reaction of a second equivalent of methyl iodide. The 1:1 macrocycles (e.g., **9**) reacted with methyl iodide in a similar manner. Brown and Teitei[11] have previously demonstrated the facile isomerization of 4,6-dimethoxypyrimidine with methyl iodide to give **16**,



as the major product, and 1,4-dihydro-6-methoxy-1-methyl-4-oxopyrimidine; thus precedence for this unexpected second fragmentation can be cited.

4. Ethylene Glycol. In an attempt to prepare the smallest 2:2 macrocycle (**17**), disodium ethylene glycolate was treated with **1** under similar conditions. Although



19, n = 1
20, n = 2
21, n = 3

22

17 **18**

(9) Mattice, W. L.; Newkome, G. R. *J. Am. Chem. Soc.*, **1979**, *101*, 4479.

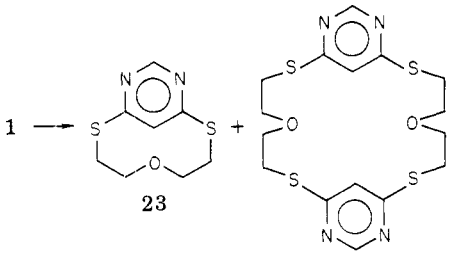
(10) Staude, E.; Patat, F. *Chem. Ether Linkage* **1967**, 46–9. Lubowicz, R. E.; Reich, P. *Chem. Eng. Prog.* **1971**, *67*, 59.

(11) Brown, D. J.; Teitei, T. *Aust. J. Chem.* **1964**, *17*, 567.

(12) Johnson, T. B.; Hilbert, G. *Science* **1929**, *69*, 579. Brown, D. J. "The Pyrimidines"; Interscience: New York, 1962; p 371.

in the pyridine series **18** had been prepared in low yield,[7,13] all attempts to prepare **17** failed via this synthetic procedure. A complex series of open-chained products **19–22** were isolated and characterized.

B. 4,6-Pyrimidino Macrocycles with Carbon–Sulfur–Oxygen Linkages. Bis(2-mercaptoethyl) Ether. The 1:1 C,S,O-macrocycle **23** and the corresponding 2:2 macrocycle **24** were prepared as a high-boiling liquid and a crystalline compound, respectively, from the reaction of **1** with the disodium salt of bis(2-mercaptoethyl) ether. The 4,6 carbon–sulfur bonds in **23** and **24** are



23 **24**

confirmed by the dramatic downfield shift ($\Delta\delta \sim 1$ ppm) for the 5-pyrimidine ring hydrogen in comparison with corresponding carbon–oxygen-bridged macrocycles (e.g., **9**). The chemical shifts of the 2-pyrimidine protons were influenced only slightly by the 4,6-ring functionality. Macrocycle **23** is the smallest ring formed via this procedure. The lesser C–S–C vs. C–O–C bond angle and the increased atomic size of sulfur vs. oxygen afford a rationale for favorable cyclization in the case of **23** vs. the yet unknown 10-membered C–O macrocyclic analogue.

The metal ion complexation and thermal O→N rearrangements of these macrocycles are in progress. Although the biological testing of these macrocycles is currently in progress, preliminary data indicate that the halopyrimidine intermediates exhibit enhanced fungicidal and sporicidal activity.

Experimental Section

General Comments. All melting points were taken in capillary tubes with a Thomas-Hoover Uni-Melt instrument and are uncorrected. Infrared (IR) spectra were recorded on Beckmann IR-7 spectrophotometers. Unless otherwise noted, ^{1}H NMR spectra were recorded in $CDCl_3$ solution with Me_4Si as internal standard (δ 0) and recorded on either a Varian A-60A or a Bruker WP200 spectrometer. Molecular weights were determined by Mr. D. Patterson on a Hewlett-Packard Model 5985 GC/MS. The recorded R_f values were determined by a standardized thin-layer chromatograph (TLC) procedure: 0.25-mm Brinkman silica gel HF-254 + 366 plates eluting with cyclohexane–ethyl acetate (1:4). For preparative thick-layer chromatography[14] (ThLC) 2-mm Brinkman silica gel PF-254 + 366 plates were used, eluting with the stipulated solvent system. Elemental analyses were performed by Mr. R. Seab in these laboratories.

All reaction solvents were distilled from sodium wire under a nitrogen atmosphere. Sodium hydride (57% oil dispersion) was washed with anhydrous petroleum ether (bp 30–60 °C) and then dried in vacuo prior to the reaction. Ethylene glycol and di-, tri-, and tetraethylene glycol were purchased from Aldrich Chemical Co., whereas penta- and hexaethylene glycols were purchased from Columbia Organic Chemicals, and all reagents were fractionally distilled in vacuo prior to use. Bis(2-mercaptoethyl) ether was purchased from Fairfield Chemical Co. and used directly without further purification.

Reaction of 4,6-Dichloropyrimidine with Diethylene Glycol. General Procedure. Diethylene glycol (1.06 g, 10 mmol) was slowly added to a suspension of oil-free sodium hydride (480 mg, 20 mmol) in anhydrous xylene (300 mL) with stirring under argon. After 20 min, a solution of 4,6-dichloropyrimidine (1.5 g, 10 mmol) in xylene (100 mL) was added, and the mixture was refluxed for 16–18 h. Xylene was removed under reduced pressure, and unreacted sodium hydride was carefully decomposed with water. The mixture was extracted several times with dichloromethane, and the combined organic layer was washed with water, dried over anhydrous magnesium sulfate, and concentrated to afford a residue, which was chromatographed (ThLC), eluting four times with cyclohexane–ethyl acetate (1:1) to give the following components.

Fraction A gave 40 mg (3%) of 4,6-dichloropyrimidine, mp 64–66 °C.

Fraction B, after recrystallization from ethanol, gave 6,6′-dichloro-4,4′-[oxybis(ethyleneoxy)]dipyrimidine (**6**): colorless flakes, mp 125–127 °C; 100 mg (7%); R_f 0.32; NMR δ 3.85 (t, β-CH_2O, J = 5 Hz, 4 H), 4.55 (t, α-CH_2O, J = 5 Hz, 4 H), 6.82 (s, 5-pyrim H, 2 H), 8.55 (s, 2-pyrim H, 2 H); IR (KBr) 2855, 1596, 1446, 1300, 1230, 1140, 1110, 1090 cm^{-1}; mass spectrum, m/e 331 (M^+).

Anal. Calcd for $C_{12}H_{12}N_4O_3Cl_2$: C, 43.50; H, 3.63; N, 16.92. Found: C, 43.41; H, 3.56; N, 16.87.

Fraction C afforded the 2:2 macrocycle **2**: white shining needles (recrystallized from ethanol), mp 149–150 °C; 65 mg (3%); R_f 0.20; NMR δ 3.79 (t, β-CH_2O, J = 5 Hz, 8 H), 4.47 (t, α-CH_2O, J = 5 Hz, 8 H), 5.67 (s, 5-pyrim H, 2 H), 8.3 (s, 2-pyrim H, 2 H); IR (KBr) 2980, 1610, 1553, 1480, 1346, 1275, 1200, 1150, 1062 cm^{-1}; mass spectrum, m/e 364 (M^+).

Anal. Calcd for $C_{16}H_{20}N_4O_6$: C, 52.74; H, 5.49; N, 15.38. Found: C, 52.63; H, 5.56; N, 15.20.

Fraction D yielded the 3:3 macrocycle **3**: recrystallized from alcohol as colorless plates, mp 156–158 °C; 49 mg (3%); R_f 0.13; NMR δ 3.85 (t, β-CH_2O, J = 5 Hz, 12 H), 4.51 (t, α-CH_2O, J = 5 Hz, 12 H), 6.15 (s, 5-pyrim H, 3 H), 8.35 (s, 2-pyrim H, 3 H); IR (KBr) 2950, 1600, 1555, 1476, 1340, 1265, 1180, 1130, 1060 cm^{-1}; mass spectrum, m/e 546 (M^+).

Anal. Calcd for $C_{24}H_{30}N_6O_9$: C, 52.74; H, 5.49; N, 15.38. Found: C, 52.57; H, 5.38; N, 15.25.

The combined base lines from the preparative plates were extracted with ethanol–chloroform (1:1). The residue was chromatographed (ThLC), eluting two times with cyclohexane–ethyl acetate (1:2) to afford the following components.

Fraction E yielded **5**: viscous brown liquid, bp 206–207 °C (0.1 mm, shortpath); 50 mg (2%); R_f 0.08; NMR δ 2.78 [s, OH (exchanged with D_2O), 1 H], 3.80 (m, β-δ-CH_2O, 6 H), 4.44 (t, α-CH_2O–, J = 5 Hz, 2 H), 6.80 (s, 5-pyrim H, 1 H), 8.56 (s, 2-pyrim H, 1 H); IR (neat) 3430 (OH), 1603, 1585, 1550, 1460, 1310, 1221, 1100, 1040 cm^{-1}.

Anal. Calcd for $C_8H_{11}N_2O_3Cl$: C, 43.94; H, 5.07; N, 12.81. Found: C, 43.80; H, 5.11; N, 13.06.

Fraction F, after recrystallization from ethanol, gave the 4:4 macrocycle **4**: colorless flakes, mp 120–121 °C; 52 mg (3%); NMR δ 3.83 (t, β-CH_2O, J = 5 Hz, 16 H), 4.50 (t, α-CH_2O, J = 5 Hz, 16 H), 6.18 (s, 5-pyrim H, 4 H), 8.35 (s, 2-pyrim H, 4 H); IR (KBr) 2940, 1600, 1530, 1481, 1335, 1250, 1171, 1110, 1062 cm^{-1}; mass spectrum, m/e 728 (M^+).

Anal. Calcd for $C_{32}H_{40}N_8O_{12}$: C, 52.74; H, 5.59; N, 15.38. Found: C, 52.83; H, 5.41; N, 15.33.

Reaction of 4,6-Dichloropyrimidine with Triethylene Glycol. The above general procedure was followed except for the substitution of triethylene glycol (1.5 g, 10 mmol). The crude reaction residue was chromatographed (ThLC), eluting four times with cyclohexane–ethyl acetate (1:3) to afford the following compounds.

Fraction A gave unchanged **1**: 90 mg.

Fraction B, after recrsytallization from ethanol, gave the 1:1 macrocycle **7**: colorless needles, mp 114–115 °C; 96 mg (4%); R_f 0.18; NMR δ 3.67 (s, γ-CH_2O, 4 H), 3.83 (t, β-CH_2O, J = 5 Hz, 4 H), 4.47 (t, α-CH_2O, J = 5 Hz, 4 H), 6.15 (s, 5-pyrim H, 1 H), 8.37 (s, 2-pyrim H, 1 H); UV (EtOH) λ_{max} (ϵ) 240 nm (3200); IR (KBr) 2915, 1600, 1555, 1470, 1430, 1338, 1260, 1185, 1135, 1060 cm^{-1}; mass spectrum, m/e 266 (M^+).

Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.19; N, 12.38. Found: C, 53.12; H, 6.37; N, 12.24.

(13) Dr. T. Kawato, unpublished results, 1978.
(14) "Operating Manual 103-D"; Brinkmann Instruments, Inc.: Waterbury, NY; p 11 590.

Fraction C yielded 2:2 macrocycle **8**: recrystallized from ethanol as colorless needles, mp 71–72 °C; 100 mg (4%); NMR δ 3.67 (s, γ-CH_2O, 8 H), 3.83 (t, β-CH_2O, J = 5 Hz, 8 H), 4.45 (t, α-CH_2O, J = 5 Hz, 8 H), 6.10 (s, 5-pyrim H, 2 H), 8.35 (s, 2-pyrim H, 2 H); IR (KBr) 2940, 1600, 1560, 1476, 1350, 1270, 1180, 1060, 990, 850 cm^{-1}; mass spectrum, m/e 452 (M^+).

Anal. Calcd for $C_{20}H_{28}N_4O_8$: C, 53.09; H, 6.19; N, 12.38. Found: C, 52.82; H, 6.02; N, 12.38.

Reaction of 4,6-Dichloropyrimidine with Tetraethylene Glycol. The general procedure was followed except for the substitution of tetraethylene glycol (1.94 g, 10 mmol). The reaction mixture was chromatographed (ThLC), eluting four times with cyclohexane–ethyl acetate (1:3). The following fractions were isolated and characterized.

Fraction A afforded unchanged 4,6-dichloropyrimidine: 100 mg.

Fraction B gave 1:1 macrocycle **9**: viscous oil, bp 189–193 °C (0.1 mm, shortpath); 160 mg (6%); R_f 0.16; NMR δ 3.45 (brd, γ, δ-CH_2O, 8 H), 3.78 (t, β-CH_2O, J = 5 Hz, 4 H), 4.65 (t, α-CH_2O, J = 5 Hz, 4 H), 6.42 (s, 5-pyrim H, 1 H), 8.42 (s, 2-pyrim H, 1 H); UV (EtOH) λ_{max} (ϵ) 241 nm (2500), 252 (1500); IR (neat) 2890, 1595, 1565, 1480, 1425, 1350, 1290, 1175, 1050 cm^{-1}; mass spectrum, m/e 270 (M^+).

Anal. Calcd for $C_{12}H_{18}N_2O_5$: C, 53.33; H, 6.66; N, 10.37. Found: C, 53.20; H, 6.63; N, 10.60.

Fraction C gave the unsymmetrical macrocycle **11**: recrystallized from ethanol as a colorless solid, mp 65–67 °C; 55 mg (3%); NMR δ 3.62 (brs, γ,δ-CH_2O, 12 H), 3.83 (t, β-CH_2O, J = 5 Hz, 8 H), 4.45 (t, α-CH_2O, J = 5 Hz, 8 H), 6.17 (s, 5-pyrim H, 2 H), 8.37 (s, 2-pyrim H, 2 H); IR (KBr) 2980, 1575, 1530, 1473, 1410, 1365, 1200, 1180, 1030 cm^{-1}; mass spectrum, m/e 496 (M^+).

Anal. Calcd for $C_{22}H_{32}N_4O_9$: C, 53.22; H, 6.65; N, 11.26. Found: C, 53.17; H, 6.49; N, 11.17.

Fraction D, after recrystallization from ethanol, afforded 2:2 macrocycle **10**: shining colorless plates, mp 94–95 °C; 150 mg (6%); NMR δ 3.63 (s, γ,δ-CH_2O, 16 H), 3.81 (t, β-CH_2O, J = 5 Hz, 8 H), 4.47 (t, α-CH_2O, J = 5 Hz, 8 H), 6.15 (s, 5-pyrim H, 2 H), 8.36 (s, 2-pyrim H, 2 H); IR (KBr) 2840, 1595, 1543, 1475, 1400, 1329, 1250, 1181, 1123, 1050 cm^{-1}; mass spectrum, m/e 540 (M^+).

Anal. Calcd for $C_{24}H_{36}N_4O_{10}$: C, 53.33; H, 6.66; N, 10.37. Found: C, 53.24; H, 6.72; N, 10.23.

Reaction of 4,6-Dichloropyrimidine with Pentaethylene Glycol. The general procedure was followed except for the substitution of pentaethylene glycol (2.38 g, 10 mmol). The crude reaction mixture was chromatographed (ThLC), eluting four times with cyclohexane–ethyl acetate (1:3) to give the following fractions.

Fraction A gave unchanged 4,6-dichloropyrimidine: 80 mg.

Fraction B furnished **12**: viscous light yellow oil, bp 210–215 °C (0.1 mm, shortpath); 200 mg (7%); R_f 0.14; NMR δ 3.41 (s, ϵ-CH_2O, 4 H), 3.62 (m, γ,δ-CH_2O, 8 H), 3.81 (t, β-CH_2O, J = 5 Hz, 4 H), 3.56 (t, α-CH_2O, J = 5 Hz, 4 H), 6.20 (s, 5-pyrim H, 1 H), 8.40 (s, 2-pyrim H, 1 H); UV (EtOH) λ_{max} (ϵ) 241 nm (3000), 252 (1300); IR (neat) 2875, 1590, 1550, 1470, 1340, 1262, 1168, 1048 cm^{-1}; mass spectrum, m/e 314 (M^+).

Anal. Calcd for $C_{14}H_{22}N_2O_6$: C, 53.50; H, 7.00; N, 8.91. Found: C, 53.43; H, 6.94; N, 8.95.

Fraction C gave the 2:2 macrocycle **13**: white crystalline solid, upon recrystallization from ethanol, mp 76–79 °C; 200 mg (7%); R_f 0.06; NMR δ 3.52 (brd, γ-ϵ-CH_2O, 24 H), 3.73 (t, β-CH_2O, J = 5 Hz, 8 H), 4.63 (t, α-CH_2O, J = 5 Hz, 8 H), 6.25 (s, 5-pyrim H, 2 H), 8.37 (s, 2-pyrim H, 2 H); IR (KBr) 2875, 1585, 1550, 1468, 1348, 1254, 1170, 1120, 1045 cm^{-1}; mass spectrum, m/e 628 (M^+).

Anal. Calcd for $C_{28}H_{44}N_4O_6$: C, 53.40; H, 7.00; N, 8.91. Found: C, 53.74; H, 7.26; N, 8.94.

Reaction of 4,6-Dichloropyrimidine with Hexaethylene Glycol. The general procedure was followed except for the substitution of hexaethylene glycol (2.82 g, 10 mmol). The residue was chromatographed (ThLC), eluting five times with cyclohexane–ethyl acetate (1:3) to give the following fractions.

Fraction A gave starting dichloropyrimidine: 100 mg.

Fraction B gave **12**: viscous colorless oil; 30 mg (2%); R_f 0.14.

Fraction C afforded the 1:1 macrocycle **14**: viscous liquid, bp 216–220 °C (0.1 mm, shortpath); 300 mg (9%); R_f 0.16; NMR δ 3.58 (brd, γ-ξ-CH_2O, 16 H), 3.71 (t, β-CH_2O, J = 5 Hz, 4 H), 4.45 (t, α-CH_2O, J = 5 Hz, 4 H), 6.15 (s, 5-pyrim H, 1 H), 8.38 (s, 2-pyrim H, 1 H); UV (EtOH) λ_{max} (ϵ) 240 nm (3300), 251 (1900); IR (neat) 2810, 1575, 1540, 1430, 1325, 1248, 1175, 1050 cm^{-1}; mass spectrum, m/e 358 (M^+).

Anal. Calcd for $C_{16}H_{26}N_2O_7$: C, 53.63; H, 7.26; N, 7.82. Found: C, 53.72; H, 7.45; N, 7.56.

Fraction D gave the 2:2 macrocycle **15**: white solid which after recrystallization from a small amount of ethanol gave pale white microcrystals, mp 69–70 °C; 320 mg (9%); R_f 0.01; NMR δ 3.68 (brd, γ-ξ-CH_2O, 32 H), 3.82 (t, β-CH_2O, J = 5 Hz, 8 H), 4.51 (t, α-CH_2O, J = 5 Hz, 8 H), 6.13 (s, 5-pyrim H, 2 H), 8.38 (s, 2-pyrim H, 2 H); IR (KBr) 2900, 1600, 1541, 1470, 1340, 1265, 1190 cm^{-1}; mass spectrum, m/e 716 (M^+).

Anal. Calcd for $C_{32}H_{52}N_4O_{14}$: C, 53.63; H, 7.26; N, 7.82. Found: C, 53.52; H, 7.43; N, 7.63.

Reaction of 10 with Methyl Iodide. The 2:2 macrocycle **10** (50 mg) was dissolved in methyl iodide (1.1 g) in a sealed thick-walled tube. The mixture was heated at 35 °C for 8 h. After the mixture was cooled, the excess methyl iodide was vented. The reaction mixture was dissolved in water and extracted with dichloromethane. The crude organic extract was concentrated to give a residue, which was chromatographed (ThLC), eluting with acetone–chloroform (3:1) to give 1-methyl-4-methoxy-1,6-dihydro-6-oxopyrimidine (**16**): white crystals; 20 mg (30%); NMR δ 3.02 (s, OMe, 3 H), 3.13 (s, 1-NMe, 3 H), 5.50 (s, 5-pyrim H, 1 H), 8.05 (s, 2-pyrim H, 1 H). Physical and spectral data are similar to those previously reported.[11]

Reaction of 4,6-Dichloropyrimidine with Ethylene Glycol. The above general procedure was followed except for the substitution of redistilled ethylene glycol (620 mg, 10 mmol). The viscous residue was chromatographed (ThLC), eluting four times with cyclohexane–ethyl acetate (1:3) to afford the following fractions.

Fraction A gave **22**: crystalline solid from ethanol; mp 133–134 °C; 70 mg (3%); R_f 0.52; NMR δ 4.74 (s, CH_2O, 4 H), 6.88 (s, 5-pyrim H, 2 H), 8.55 (s, 2-pyrim H, 2 H); IR (KBr) 1550, 1450, 1360, 1030 cm^{-1}; mass spectrum, m/e 286 (M^+).

Anal. Calcd for $C_{10}H_8N_4O_2Cl_2$: C, 41.83; H, 2.80; N, 19.52. Found: C, 42.02; H, 2.79; N, 19.60.

Fraction B afforded the 1:1 adduct **19**: viscous oil, bp 90 °C (0.3 mm, shortpath); 50 mg (3%); R_f 0.23; NMR δ 3.65 [s, OH, 1 H (exchanged with D_2O)], 3.99 (m, β-CH_2O, 2 H), 4.55 (m, α-CH_2O, 2 H), 6.83 (s, 5-pyrim H, 1 H), 8.55 (s, 2-pyrim H, 2 H); IR (neat) 3370, 1500, 1401, 1300, 1000 cm^{-1}; mass spectrum, m/e 174 (M^+).

Anal. Calcd for $C_6H_7N_2O_2Cl$: C, 41.28; H, 4.04; N, 16.05. Found: C, 41.30; H, 4.00; N, 16.25.

Fraction C gave the crystalline **20**: mp 108–109 °C; 60 mg (2%); R_f 0.14; NMR δ 3.92 (m, β'-CH_2O, 2 H), 4.45 (m, α'-CH_2O, 2 H), 4.80 (s, α,β-CH_2O, 4 H), 6.1 (s, 5′-pyrim H, 1 H), 7.78 (s, 5-pyrim H, 1 H), 8.45, 8.52 (2 s, 2,2′-pyrim H, 1 H each); IR (KBr) 3350, 1570, 1460, 1190 cm^{-1}; mass spectrum, m/e 312 (M^+).

Anal. Calcd for $C_{12}H_{13}N_4O_4Cl$: C, 41.81; H, 3.80; N, 16.25. Found: C, 41.96; H, 3.71; N, 16.25.

Fraction D afforded **21**: white crystalline solid upon recrystallization from ethanol, mp 110–112 °C; 40 mg (1%); R_f 0.09; NMR δ 3.95 (brm, β''-CH_2O, 2 H), 4.45 (brm, α''-CH_2O, 2 H), 4.68 (m, α,α',β,β'-CH_2O, 8 H), 6.10 (brs, 5′,5″-pyrim H, 2 H), 6.79 (brs, 5-pyrim H, 1 H), 8.38 (brs, 2′,2″-pyrim H, 2 H), 8.51 (brs, 2-pyrim H, 1 H); IR (KBr) 3400, 1590, 1450, 1150 cm^{-1}; mass spectrum, m/e 450 (M^+).

Anal. Calcd for $C_{18}H_{19}N_6O_6Cl$: C, 47.95; H, 4.25; N, 18.64. Found: C, 47.86; H, 4.21; N, 18.68.

Reaction of 4,6-Dichloropyrimidine with Bis(2-mercaptoethyl) Ether. The general procedure was followed except for the substitution of bis(2-mercaptoethyl) ether (1.38 g, 10 mmol). After standard workup procedures, the residue was chromatographed (ThLC), eluting three times with cyclohexane–ethyl acetate (4:1) to afford the following fractions.

Fraction A gave unchanged 4,6-dichloropyrimidine: 75 mg.

Fraction B afforded the desired 1:1 macrocycle **23**: viscous yellow oil, bp 110 °C (1.3 mm, shortpath); 20 mg (1%); R_f 0.12; NMR ($CDCl_3$) δ 3.40 (brt, β-CH_2O, 4 H), 3.70 (brt, α-CH_2O, 4 H), 7.05 (s, 5-pyrim H, 1 H), 8.40 (s, 2-pyrim H, 1 H); mass spectrum, m/e 214 (M^+).

Anal. Calcd for $C_8H_{10}N_2O_2S_2$: C, 44.86; H, 4.67; N, 13.08. Found: C, 44.95; H, 4.81; N, 12.81.

Fraction C gave the 2:2 macrocycle **24**: clear crystalline solid, mp 192–193 °C; 60 mg (3%); R_f 0.07; NMR ($CDCl_3$) δ 3.35 (t, β-CH_2O, J = 5 Hz, 8 H), 3.80 (t, α-CH_2O, J = 5 Hz, 8 H), 7.2 (s, 5-pyrim H, 2 H), 8.41 (s, 2-pyrim H, 2 H); IR (KBr) 2850, 1500, 1490, 1330, 1250, 1070 cm^{-1}; mass spectrum, m/e 428 (M^+).

Anal. Calcd for $C_{16}H_{20}N_4O_2S_4$: C, 44.86; H, 4.67; N, 13.08. Found: C, 44.70; H, 4.72; N, 13.16.

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Registry No. **1**, 1193-21-1; **2**, 71370-90-6; **3**, 71411-03-5; **4**, 71370-91-7; **5**, 71370-92-8; **6**, 71370-93-9; **7**, 71370-94-0; **8**, 71370-95-1; **9**, 71370-96-2; **10**, 71370-97-3; **11**, 71370-98-4; **12**, 71370-99-5; **13**, 71371-00-1; **14**, 71371-01-2; **15**, 71371-02-3; **16**, 5270-93-9; **19**, 71371-03-4; **20**, 71371-04-5; **21**, 71371-05-6; **22**, 71371-06-7; **23**, 71371-07-8; **24**, 71371-08-9; diethylene glycol, 111-46-6; triethylene glycol, 112-27-6; tetraethylene glycol, 112-60-7; pentaethylene glycol, 4792-15-8; hexaethylene glycol, 2615-15-8; methyl iodide, 74-88-4; ethylene glycol, 107-21-1; bis(2-mercaptoethyl) ether, 2150-02-9.

Molecular Inclusion Compounds.[1] Ketonic and Spiro Heteromacrocycles Possessing 2,6-Pyridino Moieties Connected by a Carbon–Oxygen and/or –Sulfur Bridge

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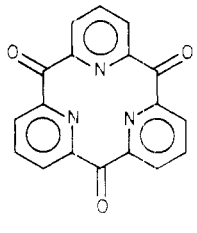
Spiro and ketonic macrocycles with specific cavities were synthesized by application of a heteroaromatic nucleophilic-substitution reaction. Initial ketalization of 2,6-bis(6-bromo-2-picolinoyl)pyridine (**3**) with β-bromoethanol and base was accomplished in 90% yield to give diketal **4**. When β-chloroethanol was used in this ketalization reaction, **3** afforded a new macrocycle, which has been assigned structure **34** on the basis of spectral and analytical data. Macrocycle **11**, prepared by the reaction of **4** and disodium glycolate, was characterized and hydrolyzed to give a series of ring-fragmented ketals (**12**), instead of the expected diketone **13**. All other diketal macrocycles were hydrolyzed to give the corresponding diketones in good yield with no evidence of macrocyclic cleavage. The X-ray structures of **14** and **15** were determined to afford insight into (a) the subtle structural alterations of these macrocycles upon hydrolysis and (b) the rationale for ring cleavage of **12**, rather than simple hydrolysis of the protecting groups. Sulfur-bridged spiro and ketonic macrocycles were also synthesized; however, the cyclization step was plagued by typical sulfur side reactions.

Recently, we reported the synthesis of the novel 1,-3,5-tri[2,6]pyridacyclohexaphane-2,4,6-trione[3] (**1**), which



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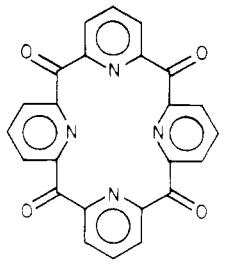

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possesses an unusually crowded 6N-electron-rich cavity. This trione represents the second member in a new macrocyclic system, of which the third member (**2**) would be the first example of a pyridine-containing xantho-porphinogen-type model. During the preliminary studies[4] directed toward syntheses of these ketonic macrocycles, dione **3** was treated with lithium carbonate and β-chloroethanol to give the desired diketal **4** and a new macrocyclic structure A ($C_{23}H_{21}N_3O_6$). A typical acid-catalyzed hydrolysis of A gave a new ketone B ($C_{19}H_{13}N_3O_4$), which was also deemed macrocyclic on the basis of physical and spectral characteristics. Since a new bond to pyridine was formed, independent synthesis of A (tentatively envisioned to be **11**) was conducted via application of a crown ether synthetic procedure. We herein describe (1) the results of our synthetic and structural endeavors to unravel this problem and (2) the construction of a new series of polyfunctionalized macrocycles.

Results

A. Preliminary Results. In our initial procedures directed toward the synthesis of trione **1**, methyl 2,6-pyridinedicarboxylate was added to 2 equiv of 6-lithio-2-bromopyridine[6] at −100 °C to generate (48%) the desired 2,6-bis(6-bromo-2-picolinoyl)pyridine (**3**). Substitutes for the diester, for example, either 2,6-dicyanopyridine or 2,6-dipicolinoyl chloride, did not afford substantial improvement in the yield of **3**. The IR spectrum of **3** showed a carbonyl absorption at 1680 cm^{-1}, characteristic of these dipyridyl ketones. Dione **3**, when subjected to our standard ketalization procedure,[7] that is, β-bromoethanol and lithium carbonate for 5 h, gave (48–65%) the desired diketal **4**, along with variable quantities of monoketal **5**, and unchanged starting material. Prolonged reaction times (36 h) at this ketalization stage resulted in yields of **4** that

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