Chemistry, University of California, Berkeley.
(24) H. Meerwein, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 1080.
(25) F. P. Doyle, M. D. Mehta, G. S. Sach, R. Ward, and P. S. Sherman, *J. Chem. Soc.*, 578 (1964).
(26) D. St. C. Black, R. F. C. Brown, and A. M. Wade, *Aust. J. Chem.*, **25**, 2155 (1972).
(27) L. A. Carpino, *J. Org. Chem.*, **29**, 2820 (1964).

Chemistry of Heterocyclic Compounds. 29. Synthesis and Reactions of Multihetero Macrocycles Possessing 2,4-Pyrimidino Subunits Connected by Carbon–Oxygen and/or –Sulfur Linkages[1a]

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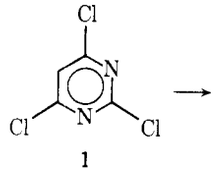
The 2,4-pyrimidino moiety has been incorporated into the "crown-ether" framework. 1:1 macrocycles have been characterized, whereas isomeric 2:2 and 3:3 macrocycles containing the 2,4-pyrimidino unit have been isolated and the isomeric distribution has been ascertained via NMR analysis. The 1:1 macrocycles (**11**, **12**, and **14**) undergo a facile Hilbert–Johnson reaction in the presence of methyl iodide at elevated temperature. Thermolysis of these 1:1 compounds causes a rearrangement to afford the corresponding uracil macrocycles. The CS and CSO 1:1 and 2:2 macrocycles have been prepared by similar procedures using the appropriate mercaptides.

In the course of our studies of multihetero macrocycles[2] which contain 2,6-pyridino,[3] 2,6-pyrazino,[4] 3,6-diazino,[5] and other heterocyclic subunits,[2] we have now investigated the inclusion of the 2,4-pyrimidino moiety. The general area of pyrimidines is so vast that it is beyond total review; however, Brown has made a Herculean effort to summarize the first 150 years of pyrimidine chemistry.[6,7] From a survey of pyrimidine chemistry, the inclusion of the pyrimidino moiety within a "crown-ether" framework has not been considered. The biological and medicinal interest in pyrimidines[8] affords further impetus to prepare this new type of macrocyclic system, the topic of this paper.

In view of the electron deficiency of the 2, 4, and 6 positions of the pyrimidine nucleus, halogen atoms located at these positions are susceptible to substitution by nucleophilic reagents. The general preparation of amines, ethers, and mercaptides, as well as a variety of other functions, at these positions on the pyrimidine ring is via direct displacement of chloride ion with the appropriate nucleophile.[9] Selective substitution can be also realized if the reaction conditions are controlled. For example, 2,4,6-trichloropyrimidine (**1**) reacts with sodium methoxide in methanol at 0 °C to generate **2**,[10] with 2 equiv at room temperature to give **3**,[11] and with 3 equiv at 70–100 °C to give 2,4,6-trimethoxypyrimidine (**4**).[11c,d] Thus,



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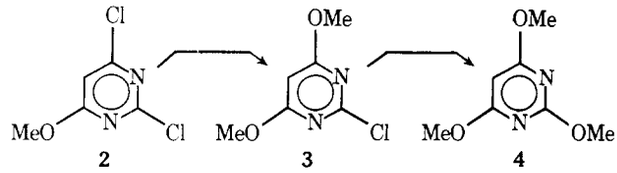
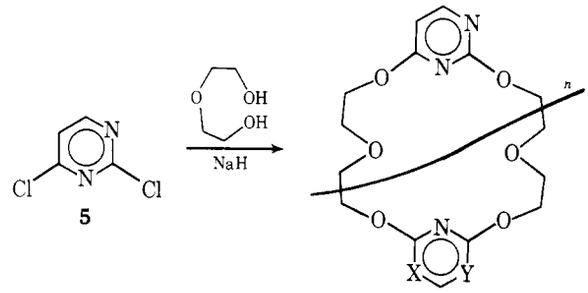


2 **3** **4**

initial 4 substitution of 2,4-dichloropyrimidine (**5**) should be preferred to 2 substitution by alkoxide ion;[12] however, the picture is less simple for polysubstituted pyrimidines.[9]

A. 2,4-Pyrimidino Macrocycles with Carbon–Oxygen Bridges. (1) Diethylene Glycol. Reaction of 2,4-dichloropyrimidine (**5**) with the dianion generated from anhydrous diethylene glycol and 2 equiv of sodium hydride afforded the 2:2 macrocycles **6** as the major cyclic products. When the reaction was conducted at 140 °C (in refluxing xylene), only numerous polymeric open-chain compounds were isolated but not characterized. At lower reaction temperatures (78 °C, refluxing benzene) the 3:3 macrocycle **7** was isolated along with **6**. Approximately equal amounts of the two dimers **6a** (mp 171–173 °C) and **6b** (mp 163–165 °C) were separated by careful thick-layer chromatography. Spectral data afforded little assistance in the structural assignment of these dimers[13] as well as trimer **7**; NMR chemical shift differences ($\Delta\delta$) were <0.1 ppm, and UV and IR data were nearly superimposible. The 1:1 C,O macrocycle **6** (n = 0) was not detected; however,



5

X ≠ Y = CH or N

6a,b, n = 1

7, n = 2

as experienced in our previous studies with this synthetic procedure,[3,5] only when the "meta" bridge possesses sulfur atoms with their diminished bond angles can the ten-membered ring be formed.

The structures of these C,O macrocycles were easily confirmed by molecular weight determination (mass spectrometry and/or osmometry) and ^{1}H NMR spectroscopy. The 5,6-pyrimidine hydrogens appear as doublets (J = 5 Hz) at δ 6.25–6.41 and δ 8.10–8.20, respectively, whereas the α methylenes appear as ill-defined triplets at δ 4.5–4.6.

(2) Triethylene Glycol. When 2,4-dichloropyrimidine (**5**) was treated with the disodium salt of triethylene glycol in refluxing xylene, the desired 1:1 macrocycle **8** was isolated in low yield (2%). The inseparable isomeric 2:2 macrocycles **9**

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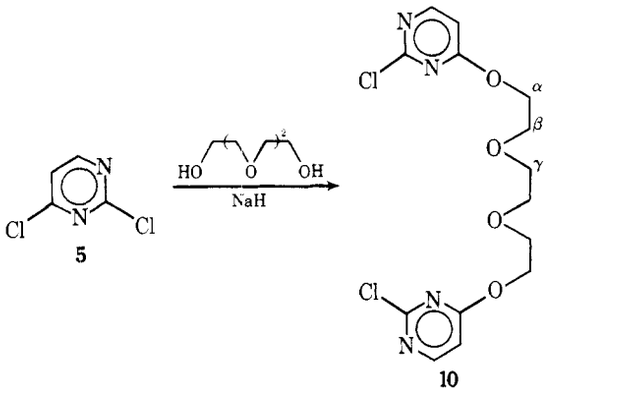
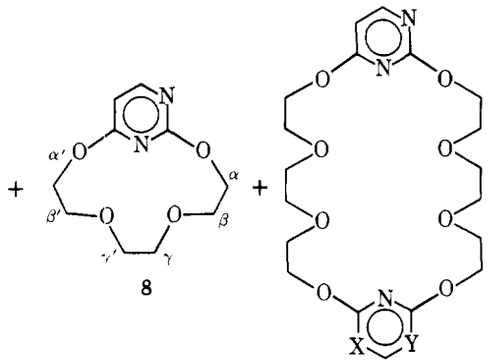
were isolated, and the isomeric ratio was easily ascertained by NMR spectroscopy to be 60:40 since both the pair of singlets for the γ methylenes and the pair of doublets for the 5 and 6 hydrogens can be accurately integrated. The major noncyclic product was the open 2:1 ether **10**, whose structure was supported by the *single* pair of doublets at δ 6.66 and 8.25 for the 5- and 6-pyrimidine hydrogens. This product further confirms the enhanced reactivity of the 4 position of **5** toward alkoxide substitution. The isomers of **10** were detected in minor amounts but were not characterized.

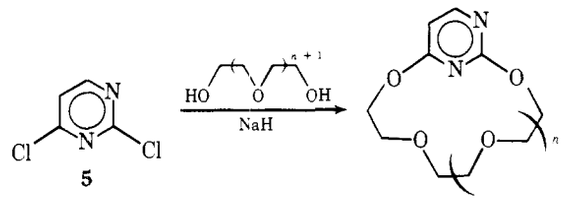


5 **10**



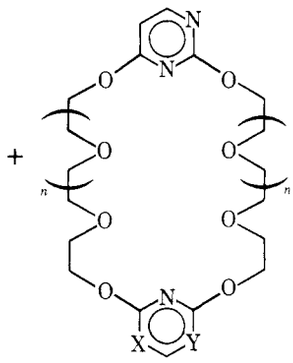
8 **9** (X ≠ Y = CH or N)

(3) Tetra-, Penta-, and Hexaethylene Glycols. The glycolates of tetra-, penta-, and hexaethylene glycols were independently reacted with **5** to afford increasing yields (8, 16, and 18%) of the 1:1 macrocycles **11, 12,** and **14,** respectively.



5

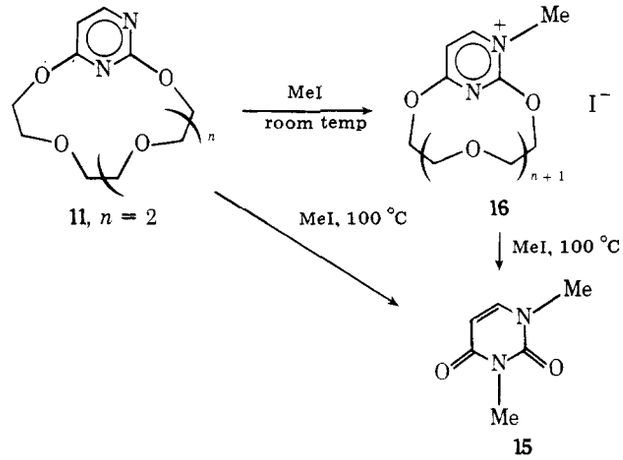
11, n = 2
12, n = 3
14, n = 4



X ≠ Y = CH or N
13, n = 3

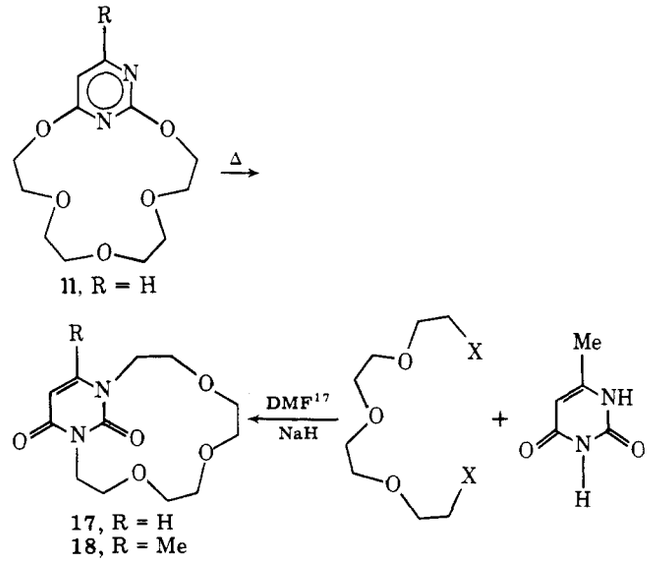
With the pentaethylene glycol, the 2:2 macrocycle **13** was also isolated in an unexpectedly high yield (8%). Fragmentation and oligomerization of these polyethylene glycols are well documented,[14] even when the reaction conditions are regulated at less than 140°C. Reduction of the reaction temperature to 80 °C generally resulted in a slight increase in the 1:1 macrocycle products and almost complete elimination of these side reactions of glycols.

In an attempt to determine the site of possible quaternization of these 1:1 macrocycles, **11,** as well as **12** and **14,** was heated with redistilled methyl iodide in a sealed tube at 100 °C for 6 hours. A single product was isolated in nearly quantitative yield and was shown by NMR spectral data and independent synthesis to be 1,3-dimethyl-2,4-dioxopyrimidine (**15**). In 1929, Johnson and Hilbert[15] first demonstrated that alkoxypyrimidines upon treatment with alkyl iodides undergo an oxygen to nitrogen rearrangement; currently, this specific rearrangement is named for the discoverers.



11, n = 2 **16** **15**

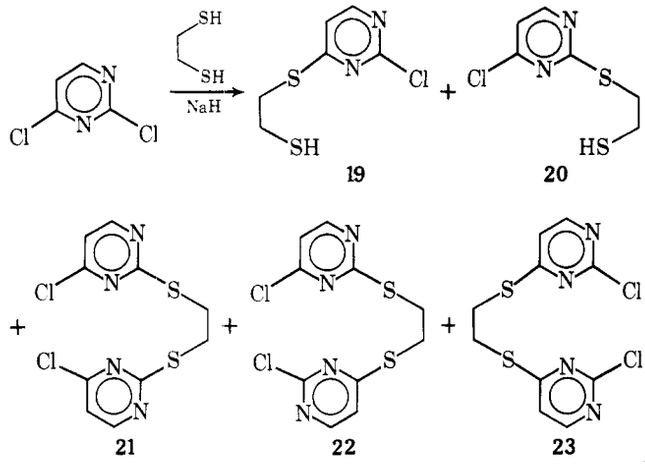
Under very mild conditions, **11** can be successfully monoquaternized with methyl iodide to give **16,** thus indicating that (1) the more readily accessible external nitrogens are initially alkylated and that (2) the Hilbert–Johnson reaction occurs via a stepwise reaction sequence of repetitious alkylation–dealkylation steps. Since the conversion of 2,4-dimethoxypyrimidine to **15** by either thermolysis at 230 °C or in the presence of methyl iodide at elevated temperatures has been demonstrated,[16] the thermolysis of **11** in a sealed tube at 250 °C for 20 h resulted in variable isolated yields of the uracil macrocycle **17,** as characterized by its NMR, IR, and physical properties. Recently, Htay and Meth-Cohn[17] have reported the synthesis of a related crown ether (**18**) which possesses a



11, R = H

17, R = H
18, R = Me

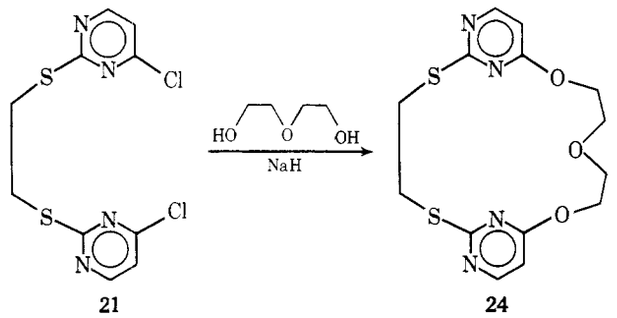
Scheme I



6-methyluracil moiety; their procedure reacted 6-methyluracil with α,ω-dibromoalkanes in dimethylformamide in the presence of sodium hydride, resulting in a 0.2% yield of the 1:1 macrocycle **18** (R = Me). The details of this thermal conversion (**11** → **17**) will be published later.[18]

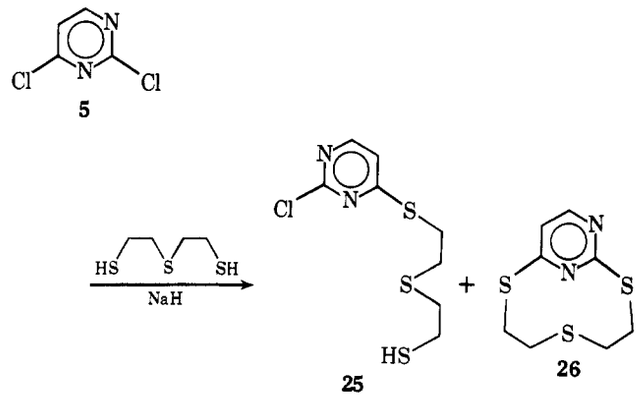
B. 2,4-Pyrimidino Macrocycles with Carbon–Sulfur and Carbon–Sulfur–Oxygen Bridges. (1) Ethanedithiol. The reaction of **5** with the disodium salt of ethanedithiol gave none of the desired macrocyclic products. This lack of C,S macrocyclic products is reminiscent of the results obtained in pyridine-[19] and pyrazine-containing[4] macrocycles. The major isolated products are shown in Scheme I. The two 1:1 noncyclized thiols **19** and **20** were isolated in about equal amounts and were characterized by their NMR spectra. Generally in this carbon–sulfur series, the 2-chloro-4-thio compounds (e.g., **19**) show the 5 hydrogen at ca. δ 7.0 and the 6 hydrogen at ca. δ 8.4, whereas the corresponding 4-chloro-2-thio isomer (**20**) possesses the two doublets at δ 7.15 and 8.25 for the 5 and 6 hydrogens, respectively.[20] Thus, from these spectral interpretations the structural assignments of the 2:1 isomers (**21–23**) were straightforward. As expected, **23** was obtained as the major 2:1 isomer resulting from 4,4′ disubstitution, followed by **22** from 4,2′ substitution, and **21** in lowest yield via 2,2′ substitution.

Cyclization of **21** with diethylene glycolate under the standard conditions afforded the unusual CO–CS bridged macrocycle **24.**

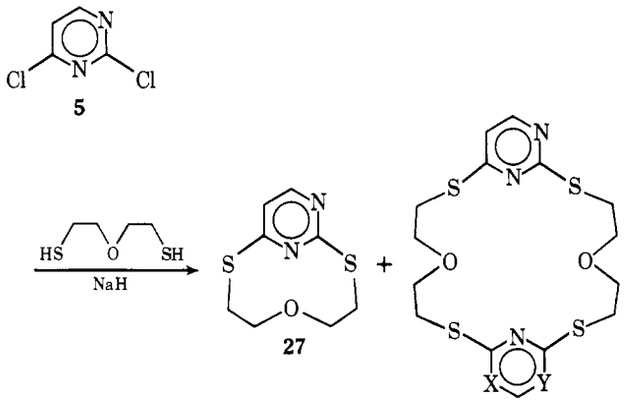


(2) Bis(2-mercaptoethyl) Sulfide. Treatment of **5** with the disodium salt of bis(2-mercaptoethyl) sulfide gave rise to the 1:1 noncyclized thiol **25** along with the desired 1:1 macrocycle **26.** As experienced previously,[3,4,19] the oligomerization of bis(2-mercapto) sulfide in the presence of base was the major reaction pathway; pyrimidines containing polysulfur units were not isolated.

(3) Bis(2-mercaptoethyl) Ether. The 1:1 CSO macrocycle **27** and the corresponding 2:2 macrocycle **28** were isolated as crystalline compounds from the reaction of **5** with bis(2-mercaptoethyl) ether. The spectral data are in accord with the proposed structures. The 2,4 carbon–sulfur bonds of **27** and



28, as well as those of **26,** are confirmed by the downfield shift of the 5 hydrogen from δ 6.4 to 6.9 when compared to the corresponding 2,4 carbon–oxygen bridged macrocycles. The 6 hydrogen is generally less sensitive to the 2,4 substituents.



28 (X ≠ Y = CH or N)

The pharmaceutical aspects of these pyrimidine-containing macrocycles are being conducted, and the results will be published elsewhere. The complexation and general chemistry is currently being investigated.[18]

Experimental Section

General Comments. All melting points were taken in capillary tubes with a Thomas-Hoover uni-melt apparatus and are uncorrected. Infrared (IR) and ultraviolet (UV) spectra were recorded on 621 Perkin–Elmer grating infrared and Cary-14 spectrophotometers, respectively. Unless otherwise noted ^{1}H NMR spectra were taken in deuteriochloroform solutions with Me_4Si as an internal standard (δ = 0 ppm) and recorded either on a Varian A-60A or HA-100 spectrometer. The molecular weights were determined with either a Hitachi Perkin-Elmer RMS-4 mass spectrometer by Mr. J. Murphy or a Hewlett-Packard 302 vapor pressure osmometer. The R_f values were determined by a standardized thin-layer chromatograph (TLC) procedure: 0.25 mm Brinkmann silica gel 60HF-254 + 366 plates eluting with cyclohexane–ethyl acetate (1:2). For preparative chromatography (ThLC), 2 mm Brinkmann 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.

Ethylene glycol and di-, tri-, and tetraethylene glycols were purchased from Aldrich Chemical Co. and were distilled in vacuo prior to use. Penta- and hexaethylene glycols were purchased from Columbia Organic Chemicals. Ethanedithiol, bis(2-mercaptoethyl) ether, and bis(2-mercaptoethyl) sulfide were purchased from Fairfield Chemical Co. and were used directly without further purification.

Although the noncyclized products could in most cases be isolated, in general, complete characterization of the materials was undertaken *only* when they were a major product of the reaction. The cited yield data were based on analytically pure components and were not maximized.

Method A. Reaction of 2,4-Dichloropyrimidine with Diethylene Glycol. General Procedure. To a suspension of oil-free sodium hydride (480 mg, 20 mmol) in anhydrous xylene (200 mL) was added diethylene glycol (1.06 g, 10 mmol) slowly with stirring under

nitrogen. After 15 minutes, a solution fo 2,4-dichloropyrimidine (1.49 g, 10 mmol) in xylene (50 mL) was added and the reaction mixture was refluxed for 30 h. After cooling, the xylene was removed in vacuo, and the residue was carefully neutralized with water. From this aqueous suspension organic components were extracted with dichloromethane and dried over anhydrous sodium sulfate, and then the solvent was removed, affording a gummy residue which was chromatographed (ThLC) eluting four times with cyclohexane–ethyl acetate (1:1) to give the following components.

Fraction A gave unreacted 2,4-dichloropyrimidine: 20 mg (1%); mp 58–60 °C; R_f 0.75.

Fraction B was recrystallized from ethanol to give colorless shining needles corresponding to the 2:2 macrocycle **6a:**[13] 105 mg (6%); mp 171–173 °C; R_f 0.07; NMR δ 3.85 (m, β,β'-CH_2O, 8 H), 4.52 (m, α,α'-CH_2O, 8 H), 6.25 (d, 5,5′-pyrim H, J = 5 Hz, 2 H), 8.1 (d, 6,6′-pyrim H, J = 5 Hz, 2 H); IR (KBr) 2950, 1575, 1420, 1350, 1300, 1135, 1090, 980, 830 cm^{-1}; UV (ethanol) λ_{max} (ϵ) 218 nm (1.1×10^4), 260 (9.0×10^3).

Anal. Calcd for $C_{16}H_{20}N_4O_6$: C, 52.74; H, 4.59; N, 15.38; mol wt, 364. Found: C, 52.46; H, 5.48; N, 15.12; mol wt (MS), m/e 364 (M^+).

Fraction C gave the isomeric 2:2 macrocycle **6b** as colorless plates: 90 mg (5%); mp 163–165 °C; R_f 0.06; NMR δ 3.92 (m, β,β'-CH_2O, 8 H), 4.62 (m, α,α'-CH_2O, 8 H), 6.35 (d, 5,5′-pyrim H, J = 5 Hz, 2 H), 8.13 (d, 6,6′-pyrim H, J = 5 Hz, 2 H); IR (KBr) 2970, 1595, 1575, 1480, 1440, 1420, 1350, 1300, 1135, 1110, 990, 825 cm^{-1}.

Anal. Calcd for $C_{16}H_{20}N_4O_6$: C, 52.74; H, 5.49; N, 15.38; mol wt, 364. Found: C, 52.61; H, 5.59; N, 15.17; mol wt (MS), m/e 364 (M^+).

Method B. Reaction of 2,4-Dichloropyrimidine with Diethylene Glycol in Benzene. To a suspension of sodium hydride (480 mg, 20 mmol) in anhydrous benzene (200 mL) were added diethylene glycol (1.06 g, 10 mmol) and 2,4-dichloropyrimidine (1.49 g, 10 mmol) sequentially, followed by refluxing for 24 h. The workup procedure mimicked the general procedure. The reaction products were chromatographed (ThLC) as above to afford the following components.

Fraction A gave unreacted 2,4-dichloropyrimidine: 10 mg (<1%); mp 58–60 °C.

Fraction B gave a small amount (7 mg) of an oil which could not be characterized.

Fraction C afforded the 2:2 macrocycle **6a:**[13] 200 mg (11%); mp 171–173 °C.

Fraction D gave the 2:2 macrocycle **6b:** 120 mg (7%); mp 163–165 °C.

Fraction E gave a thick brown oil corresponding to the 3:3 macrocycle **7:** 135 mg (8%); bp 151–156 °C (0.1 mm; short path); R_f 0.02; NMR δ 3.91 (t, β-CH_2O, J = 5 Hz, 12 H), 4.58 (t, α-CH_2O, J = 5 Hz, 12 H), 6.40 (d, 5-pyrim H, J = 5 Hz, 3 H), 8.17 (d, 6-pyrim H, J = 5 Hz, 3 H); IR (neat) 2950, 2800, 1590, 1460, 1430, 1350, 1290, 1140, 1100, 1050, 990, 820 cm^{-1}.

Anal. Calcd for $C_{24}H_{30}N_6O_9$: C, 52.74; H, 5.49; N, 15.38; mol wt, 546. Found: 52.56; H, 5.37; N, 15.23; mol wt (MS), m/e 546 (M^+).

Reaction of 2,4-Dichloropyrimidine with Triethylene Glycol. The above general procedure was followed except for the substitution of triethylene glycol (1.5 g, 10 mmol). After the standard workup procedure, the residue was chromatographed (ThLC) eluting four times with cyclohexane–ethylene acetate (1:1) to afford the following major fractions.

Fraction A yielded unreacted 2,4-dichloropyrimidine: 30 mg (2%); mp 59–60 °C.

Fraction B, after recrystallization from ethanol, gave 2,2′-dichloro-4,4′-[oxytris(ethylenoxy)]dipyrimidine (**10**) as colorless needles: 65 mg (3%); mp 110–111 °C; R_f 0.12; NMR δ 3.65 (s, γ-CH_2O, 4 H), 3.87 (m, β-CH_2O, 4 H), 4.55 (m, α-CH_2O, 4 H), 6.66 (d, 5,5′-pyrim H, J = 5 Hz, 2 H), 8.25 (d, 6,6′-pyrim H, J = 5 Hz, 2 H); IR (KBr) 2930, 1590, 1410, 1346, 1275, 1109, 1080, 940, 810, 750 cm^{-1}.

Anal. Calcd for $C_{14}H_{16}N_4O_4Cl_2$: C, 44.80; H, 4.27; N, 14.93; mol wt, 375. Found: C, 44.65; H, 4.29; N, 14.88; mol wt (MS), m/e 375 (M^+).

Fraction C afforded the 1:1 macrocycle **8,** which was recrystallized from ethanol as shining white plates: 60 mg (2%); mp 118–121 °C; R_f 0.06; NMR δ 3.67 (s, γ,γ'-CH_2O, 4 H), 3.86 (m, β,β'-CH_2O, 4 h), 4.75 (m, α,α'-CH_2O, 4 H), 6.31 (d, 5-pyrim H, J = 5 Hz, 1 H), 8.2 (d, 6-pyrim H, J = 5 Hz, 1 H); IR (KBr) 2960, 1600, 1580, 1455, 1418, 1325, 1280, 1235, 1117, 1080, 1030, 920, 810 cm^{-1}; UV (ethanol) λ_{max} (ϵ) 230 nm (8.7×10^5), 270 (6.1×10^4).

Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.19; N, 12.38; mol wt, 226. Found: C, 52.89; H, 6.26; N, 12.16; mol wt (MS), m/e 226 (M^+).

Fraction D, after recrystallization from ethanol, gave colorless shining plates corresponding to the isomeric 2:2 macrocycles **9:** 110 mg (5%); mp 131–133 °C; R_f 0.05; NMR δ 3.66 (s, γ-CH_2O, 40% A isomer), 3.68 (s, γ-CH_2O, 60% B isomer), 3.95 (m, β-CH_2O, 8 H), 4.5 (m, α-CH_2O, 8 H), 6.35 (d, 5-pyrim H, J = 5 Hz, 40% A isomer), 6.37 (d, 5-pyrim H, J = 5 Hz, 60% B isomer), 8.15 (d, 6-pyrim H, J = 5 Hz, 60% B isomer), 8.17 (d, 6-pyrim H, J = 5 Hz, 40% A isomer); IR (KBr) 2900, 1580, 1415, 1330, 1270, 1115, 1065, 935, 810 cm^{-1}.

Anal. Calcd for $C_{20}H_{28}N_4O_8$: C, 53.09; H, 6.19; N, 12.38; mol wt, 452. Found: C, 52.80; H, 6.38; N, 12.14; mol wt (MS), m/e 452 (M^+).

Reaction of 2,4-Dichloropyrimidine with Tetraethylene Glycol. The general procedure was followed except for the substitution of tetraethylene glycol (1.94 g, 10 mmol). The various components were separated (ThLC), eluting two times with cyclohexane–ethyl acetate (1:2). The following major fractions were separated and characterized.

Fraction A afforded unreacted dichloropyrimidine: 50 mg (3%); mp 59–60 °C.

Fraction B initially afforded a thick viscous liquid, which solidified on standing. Recrystallization from 95% ethanol gave **11** as colorless needles: 200 mg (8%); mp 65–67 °C; R_f 0.05; NMR δ 3.55 (m, $\gamma,\gamma',\delta,\delta'$-$CH_2O$, 8 H), 3.92 (m, β,β'-CH_2O, 4 H), 4.70 (t, α- or α'-CH_2O, 2 H), 4.72 (t, α- or α'-CH_2O, 2 H), 6.35 (d, 5-pyrim H, J = 5 Hz, 1 H), 8.20 (d, 6-pyrim H, J = 5 Hz, 1 H); IR (KBr) 2890, 1570, 1456, 1442, 1403, 1345, 1325, 1260, 1130, 1032, 975, 810 cm^{-1}; UV (ethanol) λ_{max} (ϵ) 230 nm (9.0×10^4), 276 (8.0×10^4).

Anal. Calcd for $C_{12}H_{18}N_2O_5$: C, 53.33; H, 6.66; N, 10.37; mol wt, 270. Found: C, 53.16; H, 6.49; N, 10.21; mol wt (osmometry), 277 (av).

Reaction of 11 with Methyl Iodide. A mixture of **11** (314 mg, 1 mmol) and methyl iodide (600 mg) was heated in a sealed tube on a water bath for 6 h.[21] After cooling, excess methyl iodide was removed, affording a yellow residue which was crystallized from ethanol to give a pale yellow solid. Recrystallization from ethanol with decolorization afforded the crystalline 1,3-dimethyl-2,4-dioxopyrimidine (**15**): mp 123–124 °C (lit.[22] mp 120–121 °C); NMR ($CDCl_3$) δ 3.35 (s, N_1-CH_3, 3 H), 3.45 (s, N_3-CH_3, 3 H), 5.75 (d, 5-pyrim H, J = 8 Hz, 1 H), 7.17 (d, 6-pyrim H, J = 8 Hz, 1 H).

Thermolysis of 11. Preparation of Macrocycle 17. Macrocycle **11** (156 mg) was heated in a sealed tube at 250 °C under nitrogen for 24 h. After cooling, the shiny needles which sublimed to the end of the tube were collected. Resublimation afforded an analytical sample of the uracil macrocycle **17:** 42 mg (28%); mp 128–129 °C; IR (KBr) 2910, 1680, 1660 (C=O), 1570, 1420, 985, 715 cm^{-1}.

Anal. Calcd for $C_{12}H_{18}N_2O_5$: C, 53.33; H, 6.66; N, 10.37. Found: C, 53.58; H, 6.58; N, 10.22.

Reaction of 2,4-Dichloropyrimidine with Pentaethylene Glycol. The general procedure was followed except for the substitution of pentaethylene glycol (2.38 g, 10 mmol). After workup, the gummy residue was chromatographed (ThLC) eluting with cyclohexane–ethyl acetate (1:3) to afford the following fractions.

Fraction A gave a small amount of starting material: 30 mg (2%); mp 58–60 °C.

Fraction B was isolated as a colorless viscous liquid, corresponding to the 1:1 macrocycle **12:** 500 mg (16%); bp 178–182 °C (1.0 mm; short path); R_f 0.04; NMR δ 3.55 (bs, ϵ-CH_2O, 4 H), 3.65 (bs, γ,δ-CH_2O, 8 H), 3.86 (m, β,β'-CH_2O, 4 H), 4.65 (2 t, α,α'-CH_2O, 4 H), 6.41 (d, 5-pyrim H, J = 5 Hz, 1 H), 8.20 (d, 6-pyrim H, J = 5 Hz, 1 H); IR (neat) 2900, 1570, 1450, 1410, 1335, 1275, 1100, 1040, 980, 930, 810 cm^{-1}; UV (ethanol) λ_{max} (ϵ) 242 nm (6×10^4), 282 (1.4×10^5).

Anal. Calcd for $C_{14}H_{22}N_2O_6$: C, 53.50; H, 7.00; N, 8.91; mol wt, 314. Found: C, 53.24; H, 7.21; N, 8.70; mol wt (MS), m/e 314 (M^+).

Fraction C was isolated as an oil, which was shown to be the 2:2 macrocycle **13:** 260 mg (8%); bp 200–203 °C (1.0 mm; short path); R_f 0.02; NMR δ 3.64 (bs, ϵ-CH_2O, 8 H), 3.69 (bs, γ,δ-CH_2O, 16 H), 3.80 (m, β-CH_2O, 8 H), 4.68 (2 t, α-CH_2O, J = 5 Hz, 8 H), 6.41 (d, 5-pyrim H, J = 5 Hz, 2 H), 8.20 (d, 6-pyrim H, J = 5 Hz, 1 H); IR (neat) 2950, 1590, 1480, 1410, 1350, 1265, 1110, 1000, 950, 910, 800, 840 cm^{-1}.

Anal. Calcd for $C_{28}H_{44}N_4O_{12}$: C, 53.50; H, 7.00; N, 8.91; mol wt, 628. Found: C, 53.26; H, 7.11; H, 8.73; mol wt (osmometry), 634 (av).

Reaction of 2,4-Dichloropyrimidine with Hexaethylene Glycol. The general procedure was followed except for the substitution of hexaethylene glycol (2.82 g, 10 mmol). The reaction residue was chromatographed (ThLC), eluting three times with cyclohexane–ethyl acetate (1:3). The following fractions were isolated and characterized.

Fraction A gave (2%) unreacted 2,4-dichloropyrimidine, mp 58–60 °C.

Fraction B afforded the 1:1 macrocycle **12** as colorless needles: 45 mg (2%); mp 65–67 °C.

Fraction C yielded a colorless liquid which corresponded to the 1:1 macrocycle **14:** 620 mg (18%); bp 165–169 °C (0.5 mm; short path); R_f 0.03; NMR δ 3.71 (bs, γ-ξ-CH_2O, 16 H), 3.84 (m, β-CH_2O, 4 H), 4.59 (2 t, α-CH_2O, J = 5 Hz, 4 H), 6.38 (d, 5-pyrim H, J = 5 Hz, 1 H), 8.19 (d, 6-pyrim H, J = 5 Hz, 1 H); IR (neat) 2890, 1580, 1460, 1410, 1345,

1285, 1110, 1080, 985, 940, 810 cm^{-1}; UV (ethanol) λ_{max} (ϵ) 236 nm (1.9 $\times 10^5$), 280 (4×10^4).

Anal. Calcd for $C_{16}H_{26}N_2O_7$: C, 53.63; H, 7.26; N, 7.82; mol wt, 358. Found: C, 53.41; H, 7.16; N, 7.68; mol wt (osmometry), 364 (av).

Reaction of 2,4-Dichloropyrimidine with Ethanedithiol. The general procedure was followed except for the substitution of ethanedithiol (940 mg, 10 mmol). After workup, the residue was chromatographed (ThLC) eluting three times with cyclohexane–ethyl acetate (4:1) to afford the following fractions.

Fraction A gave 2-(2′-chloro-4′-pyrimidylthio)ethanethiol (**19**) as a pale tan liquid: 105 mg (5%); bp 145–150 °C (0.5 mm; short path); R_f 0.58; NMR δ 1.71 [t, –SH (slow exchange with D_2O), 1 H], 2.95 (m, β-CH_2S–, 2 H), 3.4 (m, α-CH_2S–, 2 H), 7.00 (d, 5-pyrim H, J = 5 Hz, 1 H), 8.38 (d, 6-pyrim H, J = 5 Hz, 1 H); IR (neat) 3100, 2940, 2520, 1536, 1400, 1330, 1310, 1200, 1180, 1160, 810, 740 cm^{-1}.

Anal. Calcd for $C_6H_7N_2S_2Cl$: C, 34.86; H, 3.38; N, 13.55; mol wt, 206.5. Found: C, 34.63; H, 3.25; N, 13.42; mol wt (osmometry), 210 (av).

Fraction B gave 2-(4′-chloro-2′-pyrimidylthio)ethanethiol (**20**) as a viscous liquid: 120 mg (6%); bp 156–158 °C (0.5 mm; short path); R_f 0.56; NMR δ 1.75 [t, –SH (slow exchange with D_2O), 1 H], 3.0 (m, β-CH_2S–, 2 H), 3.5 (m, α-CH_2S–, 2 H), 7.15 (d, 5-pyrim H, J = 5 Hz, 1 H), 8.25 (d, 6-pyrim H, J = 5 Hz, 1 H); IR (neat) 3100, 2940, 2540, 1530, 1500, 1400, 1320, 1270, 1180, 975, 810, 740 cm^{-1}.

Anal. Calcd for $C_6H_7N_2S_2Cl$: C, 34.86; H, 3.38; N, 13.55; mol wt, 206.5. Found: C, 34.79; H, 3.25; N, 13.49; mol wt (osmometry), 212 (av).

Fraction C, after recrystallization from ethanol, afforded colorless flakes corresponding to **23:** 160 mg (5%); mp 140–142 °C; R_f 0.54; NMR δ 3.55 (s, –S–CH_2CH_2–S–, 4 H), 7.05 (d, 5-pyrim H, J = 5 Hz, 2 H), 8.40 (d, 6-pyrim H, J = 5 Hz, 2 H); IR (KBr) 2950, 1540, 1510, 1405, 1320, 1226, 1200, 1140, 1090, 800, 740 cm^{-1}.

Anal. Calcd for $C_{10}H_8N_4S_2Cl_2$: C, 37.61; H, 2.50; N, 17.56; mol wt, 319. Found: C, 37.41; H, 2.58; N, 17.31; mol wt (osmometry), 330 (av).

Fraction D, after recrystallization from ethanol, gave pale crystals corresponding to **22:** 150 mg (5%); mp 135–136 °C; R_f 0.50; NMR δ 3.6 (m, –S–CH_2CH_2–S–, 4 H), 7.04 (d, 5-pyrim H, J = 5 Hz, 1 H), 7.18 (d, 5′-pyrim H, J = 5 Hz, 1 H), 8.2 (d, 6-pyrim H, J = 5 Hz, 1 H), 8.40 (d, 6′-pyrim H, J = 5 Hz, 1 H); IR (KBr) 2900, 1530, 1500, 1400, 1325, 1280, 1200, 1175, 970, 810, 750 cm^{-1}.

Anal. Calcd for $C_{10}H_8N_4S_2Cl_2$: C, 37.61; H, 2.50; N, 17.56; mol wt, 319. Found: C, 37.76; H, 2.61; N, 17.28; mol wt (osmometry), 326 (av).

Fraction E, after recrystallization from ethanol, gave a colorless solid corresponding to **21:** 100 mg (3%); mp 127–128 °C; R_f 0.44; NMR δ 3.57 (s, –SCH_2CH_2S–, 4 H), 7.18 (d, 5-pyrim H, J = 5 Hz, 2 H), 8.25 (d, 6-pyrim H, J = 5 Hz, 2 H); IR (KBr) 2950, 1555, 1510, 1413, 1330, 1315, 1185, 1175, 1160, 975, 815, 750 cm^{-1}.

Anal. Calcd for $C_{10}H_8N_4S_2Cl_2$: C, 37.61; H, 2.50; N, 17.56; mol wt, 319. Found: C, 37.52; H, 2.39; N, 17.40; mol wt (MS), *m/e* 319 (M^+).

Reaction of 21 with Diethylene Glycol. Macrocycle 24. Oil-free sodium hydride (24 mg, 1 mmol) suspended in anhydrous xylene (150 mL) was stirred, and diethylene glycol (53 mg, 0.5 mmol) was slowly added followed by **21** (100 mg, 0.32 mmol). The mixture was refluxed under nitrogen for 24 h. After workup, the oily residue was chromatographed (ThLC) eluting with cyclohexane–ethyl acetate (1:1) to give, along with unreacted starting material (20 mg), macrocycle **24,** which was recrystallized from ethanol as colorless needles: 62 mg (55%); mp 169–172 °C; R_f 0.13; NMR δ 3.71 (s, SCH_2CH_2S, 4 H), 3.86 (m, β-CH_2O, 4 H), 4.56 (m, α-CH_2O, 4 H), 6.30 (2 d, 5,5′-pyrim H, J = 6 Hz, 2 H), 8.10 (2 d, 6,6′-pyrim H, J = 6 Hz, 2 H); IR (KBr) 2900, 1560, 1542, 1412, 1338, 1287, 1220, 1100, 1080, 740 cm^{-1}; UV (ethanol) λ_{max} (ϵ) 210 nm (6.3×10^3), 260 (6×10^4), 305 (1.6×10^4).

Anal. Calcd for $C_{14}H_{16}N_4O_3S_2$: C, 44.73; H, 4.55; N, 15.91; mol wt, 352. Found: C, 44.62; H, 4.39; N, 15.86; mol wt (MS), *m/e* 352 (M^+).

Reaction of 2,4-Dichloropyrimidine with Bis(2-mercaptoethyl) Sulfide. The general procedure was followed except for the substitution of bis(2-mercaptoethyl) sulfide (1.54 g, 10 mmol). After workup, the residue was chromatographed (ThLC), eluting two times with cyclohexane–ethyl acetate (4:1). Although most of the materials were found to be polymeric, the following two components were characterized.

Fraction A gave a thick brown liquid which solidified on standing, corresponding to **25:** 85 mg (4%); mp 51–54 °C; R_f 0.61; NMR δ 1.45 [t, –SH (exchanged slowly with D_2O), 1 H], 3.2 (m, –$SCH_2CH_2SCH_2CH_2S$–, 8 H), 6.90 (d, 5-pyrim H, J = 5 Hz, 1 H), 8.15 (d, 6-pyrim H, J = 5 Hz, 1 H); IR (neat) 2920, 2350, 1535, 1510, 1400, 1325, 1195, 1155, 950, 810 cm^{-1}.

Anal. Calcd for $C_8H_{11}N_2S_3Cl$: C, 36.02; H, 4.12; N, 10.50; mol wt, 266.5. Found: C, 36.17; H, 4.31; N, 10.46; mol wt (osmometry), 242 (av).

Fraction B, after recrystallization from ethanol, gave colorless crystals corresponding to **26:** 145 mg (6%); mp 173–175 °C; R_f 0.57; NMR δ 3.0 (bm, β-CH_2S–, 4 H), 3.5 (bm, α-CH_2S–, 4 H), 6.81 (d, 5-pyrim H, J = 5 Hz, 1 H), 8.15 (d, 6-pyrim H, J = 5 Hz, 1 H); IR (KBr) 2920, 1532, 1508, 1406, 1310, 1150, 1180, 1020, 810, 753 cm^{-1}.

Anal. Calcd for $C_8H_{10}N_2S_3$: C, 41.73; H, 4.34; N, 12.17; mol wt, 230. Found: C, 41.69; H, 4.30; N, 12.08; mol wt (osmometry), 238 (av).

Reaction of 2,4-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 workup, the oily residue was chromatographed (ThLC) eluting three times with cyclohexane–ethyl acetate (4:1) to afford the following fractions.

Fraction A gave a small amount of (<20 mg) unreacted 2,4-dichloropyrimidine, mp 59–60 °C.

Fraction B afforded the 1:1 macrocycle **27** as colorless needles (from ethanol): 125 mg (6%); mp 123–125 °C; R_f 0.50; NMR δ 3.41 (m, β,β'-CH_2O, 4 H), 3.86 (m, α,α'-CH_2S, 4-H), 6.95 (d, 5-pyrim H, J = 5 Hz, 1 H), 8.19 (d, 6-pyrim H, J = 5 Hz, 1 H); IR (KBr) 2910, 2880, 1540, 1500, 1430, 1320, 1210, 1155, 1100, 980, 850, 810, 750, 700 cm^{-1}; UV (ethanol) λ_{max} (ϵ) 210 nm (5.4×10^3), 255 (6.2×10^4), 300 (1.3×10^4).

Anal. Calcd for $C_8H_{10}N_2S_2O$: C, 44.85; H, 4.67; N, 13.08; mol wt, 214. Found: C, 44.61; H, 4.44; N, 13.11; mol wt (osmometry), 222 (av).

Fraction C was recrystallized from ethanol to give the 2:2 macrocycle **28** as light flakes: 175 mg (8%); mp 159–160 °C; R_f 0.42; NMR δ 3.41 (m, β-CH_2O, 8 H), 3.73 (m, α-CH_2S, 8 H), 6.86 (d, 5-pyrim H, J = 5 Hz, 2 H), 8.10 (d, 6-pyrim H, J = 5 Hz, 2 H); IR (KBr) 2905, 2880, 1538, 1510, 1400, 1321, 1200, 1155, 1100, 990, 820, 750 cm^{-1}; UV (ethanol) λ_{max} (ϵ) 208 nm (9.8×10^3), 254 (4.1×10^4), 303 (1.4×10^4).

Anal. Calcd for $C_{16}H_{20}N_4S_4O_2$: C, 44.85; H, 4.67; N, 13.08; mol wt, 428. Found: C, 44.80; H, 4.78; N, 12.97; mol wt (osmometry), 421 (av).

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Registry No.—**5,** 3934-20-1; **6** (X = N, Y = CH), 66562-25-2; **6** (X = CH, Y = N), 66562-26-3; **7** (X = N, Y = CH), 66562-27-4; **7** (X = CH, Y = N), 66562-28-5; **8,** 66562-29-6; **9** (X = N, Y = CH), 66562-30-9; **9** (X = CH, Y = N), 66562-31-0; **10,** 66562-32-1; **11,** 66562-33-2; **12,** 66562-34-3; **13** (X = N, Y = CH), 66562-35-4; **13** (X = CH, Y = N), 66562-36-5; **14,** 66562-37-6; **15,** 874-14-6; **17,** 66562-38-7; **19,** 66562-39-8; **20,** 66562-40-1; **21,** 66562-41-2; **22,** 66562-42-3; **23,** 66562-43-4; **24,** 66562-44-5; **25,** 66562-45-6; **26,** 66562-46-7; **27,** 66562-47-8; **28** (X = N, Y = CH), 66562-48-9; **28** (X = CH, Y = N), 66562-49-0; 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; ethanedithiol, 540-63-6; bis(2-mercaptoethyl) sulfide, 3570-55-6; bis(2-mercaptoethyl) ether, 2150-02-9.

References and Notes

(1) (a) For Paper 27 of the Chemistry of Heterocyclic Compounds: G. R. Newkome and D. C. Hager, *J. Org. Chem.*, **43,** 947 (1978). (b) Undergraduate researcher.
(2) G. R. Newkome, J. D. Sauer, J. M. Roper, and D. C. Hager, *Chem. Rev.*, **77,** 513 (1977).
(3) (a) G. R. Newkome and J. M. Robinson, *J. Chem. Soc., Chem. Commun.*, 831 (1973); (b) G. R. Newkome, G. L. McClure, J. Broussard-Simpson, and F. Danesh-Khoshboo, *J. Am. Chem. Soc.*, **97,** 3232 (1975); (c) G. R. Newkome, A. Nayak, G. L. McClure, F. Danesh-Khoshboo, and J. Broussard-Simpson, *J. Org. Chem.*, **42,** 1500 (1977).
(4) G. R. Newkome and A. Nayak, *J. Org. Chem.*, **43,** 409 (1978).
(5) G. R. Newkome and A. Nayak, to be submitted.
(6) D. J. Brown, "The Pyrimidines", A. Weissberger, Ed., Interscience, New York, N.Y., 1962.
(7) D. J. Brown, "The Pyrimidines", Supplement 1, A. Weissberger and E. C. Taylor, Ed., Wiley-Interscience, New York, N.Y., 1970.
(8) (a) C. C. Chang, *Prog. Med. Chem.*, **6,** 67–134 (1969); (b) C. C. Chang and B. Roth, *ibid.*, **7,** 285–341 (1970); (c) *ibid.*, **8,** 61–117 (1971).
(9) Reference 6, pp 183–210, and ref 7, pp 126–156.
(10) W. J. Hale and H. C. Brill, *J. Am. Chem. Soc.*, **34,** 295 (1912).
(11) (a) T. B. Johnson and I. A. Hahn, *Chem. Rev.*, **13,** 193 (1933); (b) H. Rupe and E. Knup, *Helv. Chim. Acta*, **10,** 299 (1927); (c) E. von Meyer, *J. Prakt. Chem.*, **30,** 115 (1884); (d) M. P. V. Boarland and J. F. W. McOmie, *J. Chem. Soc.*, 1218 (1951).
(12) E. Profft and H. Raddatz, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, **295,** 649

(1962).
(13) X-ray data are currently being collected by Dr. F. Fronczek, Louisiana State University.[23]
(14) E. Staude and F. Patat, *Chem. Ether Linkage*, 46–49 (1967); R. E. Lubowicz and P. Reich, *Chem. Eng. Prog.*, **67**, 59 (1971).
(15) T. B. Johnson and G. E. Hilbert, *Science*, **69**, 579 (1929).
(16) T. B. Johnson and G. E. Hilbert, *J. Am. Chem. Soc.*, **52**, 2001 (1930).
(17) M. M. Htay and O. Meth-Cohn, *Tetrahedron Lett.*, 79, 469 (1976).
(18) G. R. Newkome, A. Nayak, and W. H. Benton, *J. Org. Chem.*, to be submitted.
(19) G. R. Newkome, F. Danesh-Khoshboo, A. Nayak, and W. H. Benton, *J. Org. Chem.* **43**, 2685 (1978).
(20) Appropriate chlorothioalkylpyrimidine models were used to further substantiate these spectral assignments.
(21) Methiodide **16** can be isolated (10%) with difficulty only when the reaction is conducted at 0 °C, mp >200 °C dec. Prolonged treatment of **16** with excess methyl iodide affords variable mixtures of insoluble intermediate compounds prior to the generation of **15**.
(22) D. Davidson and O. Baudisch, *J. Am. Chem. Soc.*, **48**, 2379 (1926).
(23) **Note added in proof:**[24] The isomer melting at 171–173 °C has been shown to possess a center of symmetry; therefore, **6a** has the configuration X = N, Y =CH and **6b** has the Y = N, X = CH orientation.
(24) F. Fronczek, A. Nayak, G. R. Newkome, and J. L. Atwood, *Acta Crystallogr.*, submitted for publication.

Studies on Pyrazines. 5.[1] Peracetic and Peroxysulfuric Acid N-Oxidation of Phenyl- and Chlorophenylpyrazines

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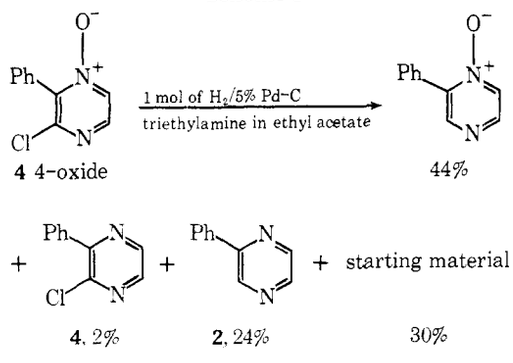
Peracetic and peroxysulfuric acid oxidations of 2-phenyl- (**2**) and 2-chloro-3-, -5-, and -6-phenylpyrazine (**4, 5,** and **6,** respectively) were carried out. On peracetic acid oxidation, **2, 4,** and **6** gave the corresponding 4-oxides and **5** gave a mixture of the 1- and 4-oxides. On the other hand, peroxysulfuric acid oxidation of **4** and **5** afforded the corresponding 1-oxides, but **2** gave a small amount of the 4-oxide and **6** was not oxidized. Structures of these *N*-oxides were determined by NMR spectra and dipole moment measurement. The mechanism of these oxidations is discussed.

N-oxidation of a pyrazine with usual percarboxylic acid reagents takes place on the most basic and least sterically hindered nitrogen.[2–5] The peracetic acid oxidation of a pyrazine bearing an electron-withdrawing substitutent such as halogens occurs in such a manner, e.g., 2-chloropyrazine (**3**) affords exclusively its 4-oxide.[5,6] However, a direct synthesis of 2-chloropyrazine 1-oxides, with the opposite orientation from that in the peracetic acid oxidation of chlorinated pyrazines, was recently reported by Mixan and Pew[7] by treatment of chloropyrazine with peroxysulfuric acid generated in situ from potassium persulfate and concentrated sulfuric acid. On applying these oxidation methods to 2-methyl- (**1**), 2-phenyl- (**2**), 2-chloropyrazine (**3**), and 2-chloro-3-, -5-, and -6-phenylpyrazine (**4, 5,** and **6,** respectively), we have found some interesting observations on the orientation of N-oxidations.

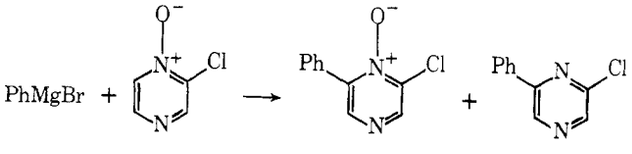
Results

As shown in Table I, methylpyrazine (**1**) was converted to the corresponding 1- and 4-oxides in the relative ratio of about 3:2[8] on treatment with peracetic acid by the procedure of the literature,[9,10] whereas the peroxysulfuric acid oxidation gave no *N*-oxide. The peracetic acid oxidation of phenylpyrazine (**2**) provided only the 4-oxide in the same manner as oxidation of 2-phenylquinoxaline with percarboxylic acids.[11,12] The peroxysulfuric acid oxidation of **2** gave a small amount (2.5%) of the 4-oxide, and the expected 1-oxide was not detected. The preparation of this 1-oxide was eventually achieved by catalytic hydrogenation of 2-chloro-3-phenylpyrazine (**4**) 4-oxide in the presence of 5% palladium on carbon and triethylamine together with other reduced products **2** and **4** as shown in Scheme I. When 10% palladium on carbon was used as the catalyst in this hydrogenation, the reaction proceeded so that it had to be controlled. Other catalysts, 5% palladium on $BaSO_4$ or Raney nickel, were also unappropriate for increasing the proportion of the desired product.

Scheme I



The peracetic acid oxidation of 2-chloro-3-phenylpyrazine (**4**) gave the 4-oxide, and the persulfate oxidation provided the 1-oxide. Thus orientation of N-oxidation of **4** is governed by an effect of the chloro substituent in the same way as that of 2-chloropyrazine (**3**), indicating no effect of the phenyl group. In contrast, oxidation of 2-chloro-5-phenylpyrazine (**5**) with peracetic acid provided equal amounts (by NMR) of the 1- and 4-oxides, and the persulfate oxidation gave only the 1-oxide. Since the 4-nitrogen atom of 2-chloro-6-phenylpyrazine (**6**) is the least sterically hindered among three chlorophenylpyrazines **4, 5,** and **6,** peracetic acid oxidation of **6** provided, as expected, the 4-oxide in excellent yield. However, the persulfate oxidation of **6** afforded no *N*-oxide because the 1-nitrogen is sterically hindered by two substituents. The 1-oxide of **6** was prepared in minor component (2%) by treatment of 2-chloropyrazine 1-oxide with phenylmagesium bromide.



Determination of the position of the N–O group in these *N*-oxides was conveniently accomplished by comparison of

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