Chemistry of Heterocyclic Compounds. 23. Synthesis of Multiheteromacrocycles Possessing 2,6-Pyridino Subunits Connected by Carbon–Oxygen Linkages[1]

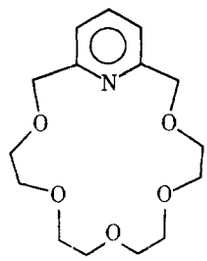
George R. Newkome,* Ashutosh Nayak, Gregory L. McClure, Farah Danesh-Khoshboo, and Janell Broussard-Simpson

Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803

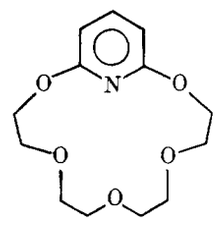
Received October 14, 1976

Treatment of 2-bromopyridine with diethylene glycol dianion afforded the diether **6** and triether **7** as well as traces of 2-(2-pyridyloxy)ethanol (**8**) and 2,2′-(ethylenedioxy)dipyridine (**9**). Similar products were isolated from 2-bromopyridine with ethylene glycol dianion. 2,6-Dibromopyridine (**10a**) with diethylene glycol dianion and excess sodium hydride generated the heteromacrocyclic ethers **11**, **12**, and **13** along with various expected intermediates. 2,6-Dibromopyridine (**10a**) with tri-, tetra-, penta-, and hexaethylene glycol dianions afforded the analogous 2:2 macrocyclic ethers along with the novel 1:1 macrocycles; **10b** with ethylene glycol dianion gave macrocycle **38**, which was subjected to variable temperature NMR analysis. The first (±)-oxamuscopyridine (**26**) was synthesized and characterized.

Synthetic procedures for the construction of macrocycles possessing subheterocyclic units have been known for about a century; however, it has only been within the past few years that these compounds have been shown to possess unique chemical and biochemical properties.[2] Of the 2,6-carbon–oxygen bridged pyridino macrocycles, presently the majority possess bridging oxygen atoms that are isolated from the pyridine nucleus by one[3] (e.g., 1) or more[4] methylene groups.



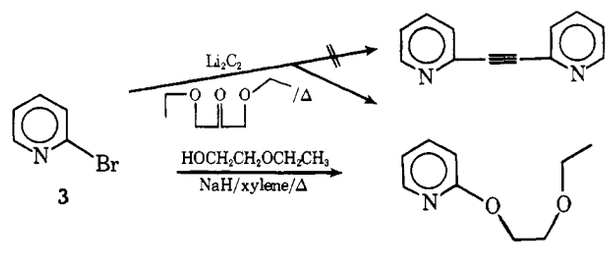
1



2

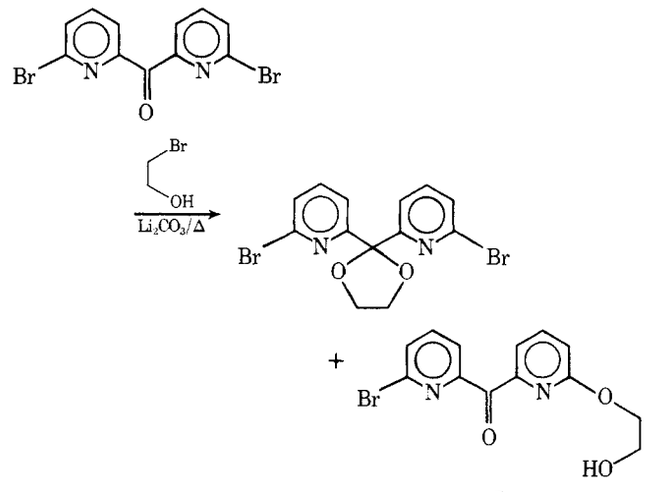
We herein describe the preparation and characterization of a second type of carbon–oxygen bridged 2,6-pyridino macrocycle in which the bridging oxygens are directly attached to the pyridine ring (e.g., **2**).

Preliminary Observations. In our quest for a simple synthesis of di(2-pyridyl)acetylene,[5] we attempted the reaction of 2-bromopyridine (**3**) with lithium carbide in bis(2-ethoxyethyl) ether at elevated temperatures; however, the major isolated product was not the desired acetylene but rather 2-pyridyl 2-ethoxyethyl ether (**4**), which resulted from direct nucleophilic substitution of halide by an alkoxide solvent fragment. In order to establish the structure of **4**, the reaction of 2-bromopyridine with sodium 2-ethoxyethoxide, generated from 2-ethoxyethanol and sodium hydride, in bis(2-ethoxyethyl) ether gave **4** in 50% yield. A similar nucleophilic



3 4

displacement occurred during the base-catalyzed ketalization of bis(6-bromo-2-pyridyl) ketone,[6] in which **5** was isolated as

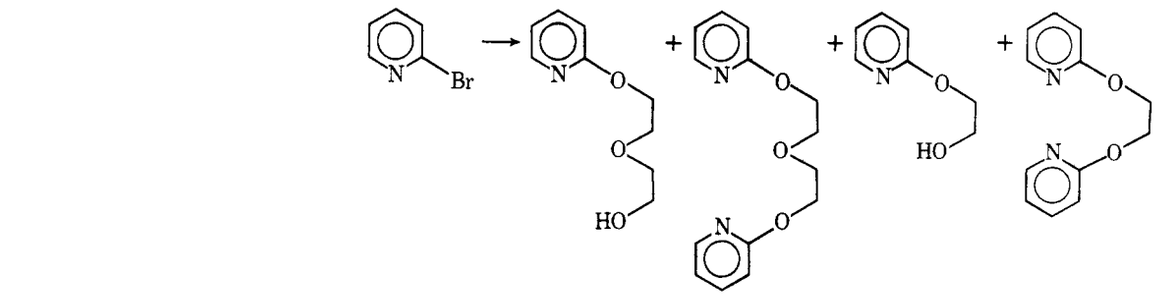


5

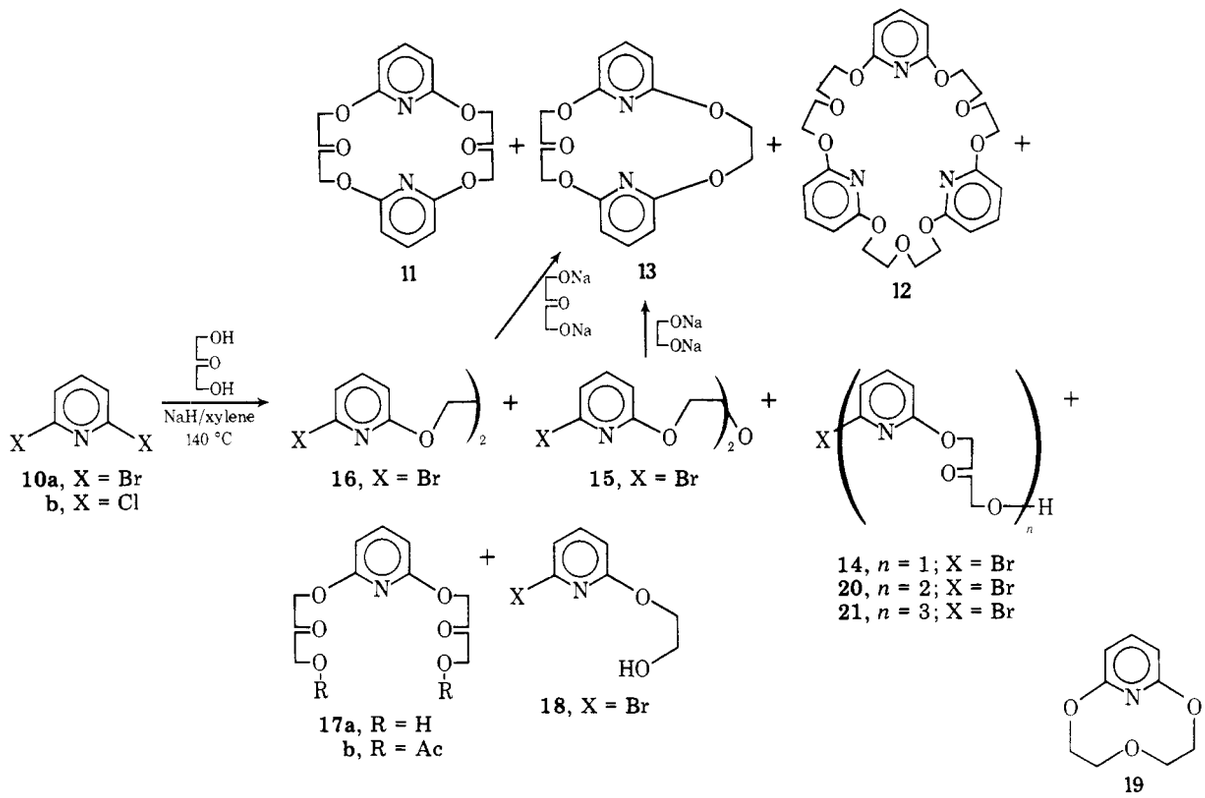
a trace (<5%) side product. Successful application of this substitution procedure has been demonstrated for the conversion of 2-halopyridines into 2-pyridones.[7]

In order to ascertain the generality of this reaction to the construction of macrocycles, 2-bromopyridine was treated with diethylene glycol dianion in bis(2-ethoxyethyl) ether at 160–180 °C affording the expected ethereal products **6** and **7**, along with lesser amounts of fragmentation products **8** and **9**. In order to reduce the formation of fragmentation-derived products, the reaction temperature was reduced; thus, refluxing xylene (bp 140 °C) was selected as the solvent medium to both maintain the desired temperature range and eliminate solvent-derived reactions. Reaction of 2-bromopyridine with ethylene glycol dianion at 140 °C afforded the expected products **8** and **9** as well as traces of both **6** and **7** which arose via oligomerization of ethylene glycol. Although thermal fragmentation and oligomerization of (poly)ethylene glycol(s) are well documented,[8] these side reactions are minimized when the reaction temperatures are maintained within the 135–145 °C range. Further reduction in reaction temperature caused prolonged, unreasonable reaction times.

Macrocycle Synthesis. A. Diethylene Glycol. The reaction of 2,6-dibromopyridine (**10a**) with diethylene glycol dianion afforded the 2:2 and 3:3 macrocycles (**11** and **12**, respectively) along with numerous noncyclized products. The smallest 1:1 macrocycle, **19**, which would possess a ten-membered ring, was not detected; this was probably due to the difficulty in formation of this strained carbon–oxygen bridge. Similarly, when methyl *m*-benzenedialkanoates were



	6	7	8	9
(a)	14%	21%	7%	8%
(b)	27%	35%	<3%	<3%
(c)	<3%	<7%	28%	32%



subjected to the Dieckmann condensation in order to form oxometacyclophanes, the inability to generate a ten-membered ring and reluctance in the formation of the 12-membered cyclophane were indicative of the nonbonded interactions which either retard or reduce the desired nucleophilic cyclization.[9] It should be noted that 2,6-[*n*]pyridinophanes, where *n* is less than 10, can be synthesized if (a) 2,6-dihalopyridine is subjected to more reactive nucleophiles,[4] (b) different routes were used in ring formation,[10] or (c) the bridge possesses sulfur atoms.[11] A novel, unsymmetrical macrocycle **13** was isolated and then independently synthesized by treatment of **16** with diethylene glycol dianion; the attempted cyclization of **15** with ethylene glycol failed to generate **13.**

Treatment of **10b** with diethylene glycol dianion in refluxing xylene afforded a similar distribution of products. The 1:1 uncyclized intermediate **14** was cyclized under the standard reaction conditions to afford (42%) the 2:2 macrocycle **11** along with traces (<1%) of **12** and **13** as well as their immediate precursors **20** and **21,** respectively. High-dilution techniques[12] were utilized in an attempt to increase the yield of cyclized products; however, no drastic increase in macrocyclic products (**11–13**) was realized.

The structures of these macrocycles were easily confirmed by ^{1}H NMR spectroscopy. Since the macrocycles are generally (or nearly so) symmetrical, the 3,5-pyridyl hydrogens show up as a doublet at δ 6.2–6.3 and the 4-pyridyl hydrogen as a triplet at δ 7.4–7.5, whereas in the noncyclized products, the 3- and 5-pyridyl hydrogens appear as doublet of doublets (J = 8 and ca. 2 Hz) with different ($\Delta^{3,5}$ 0.3 ppm) chemical shifts. The type of macrocyclic bridges can also be easily ascertained by NMR in that with an even number of $-CH_2CH_2O-$ units per bridge, the methylene hydrogens appear as triplets [α: δ 4.4–4.7; β: δ 3.8–3.9; γ–δ: δ 3.6–3.7 (J = 6 Hz)], whereas with an odd number of $-CH_2CH_2O-$ units, the *middle* methylene groups appear as a singlet [α: δ 4.6–4.7; γ: δ 3.6–3.7; ϵ: δ 3.5–3.6].

B. Triethylene Glycol. When 2,6-dibromopyridine was subjected to the disodium salt of triethylene glycol in refluxing

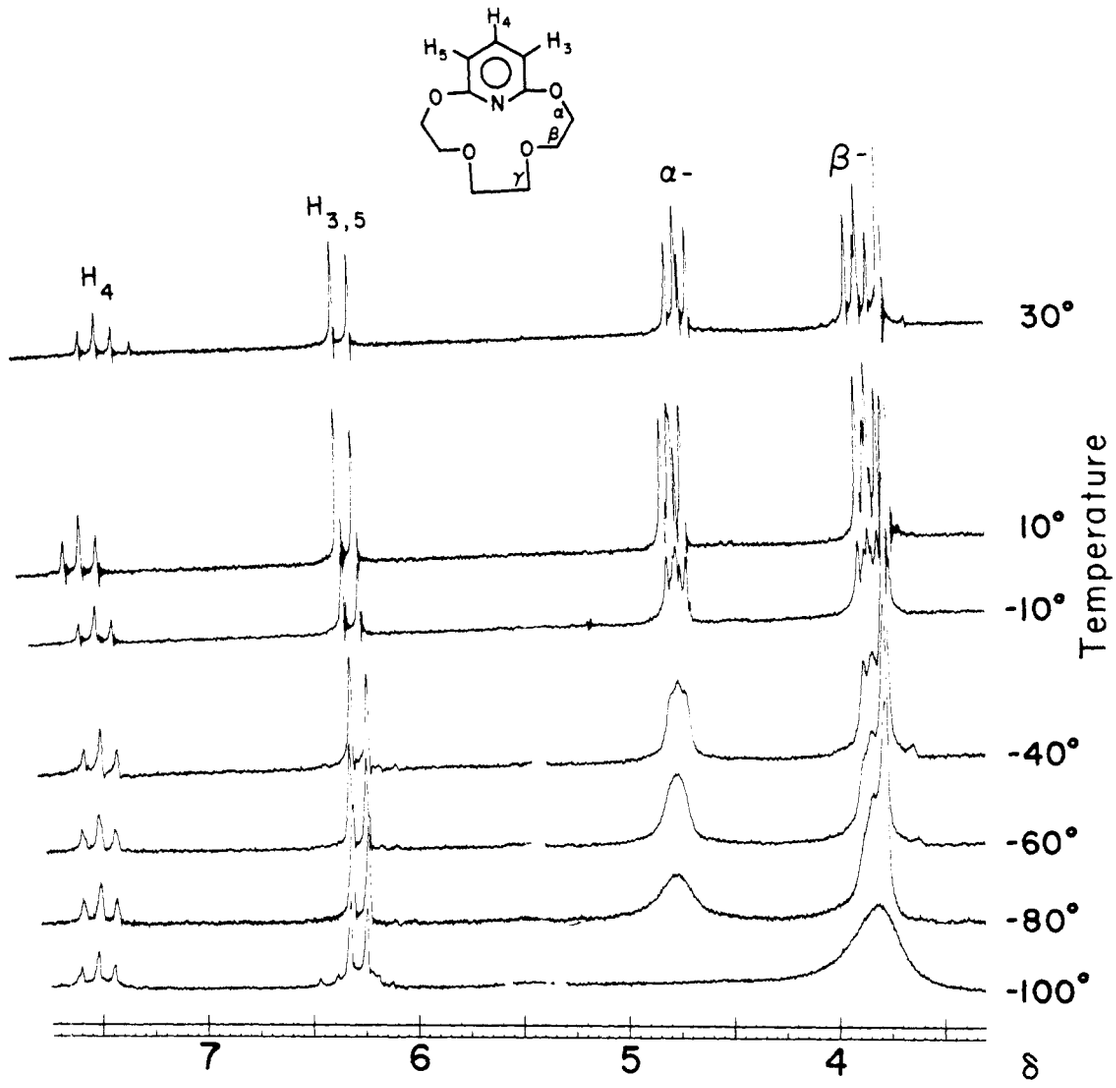
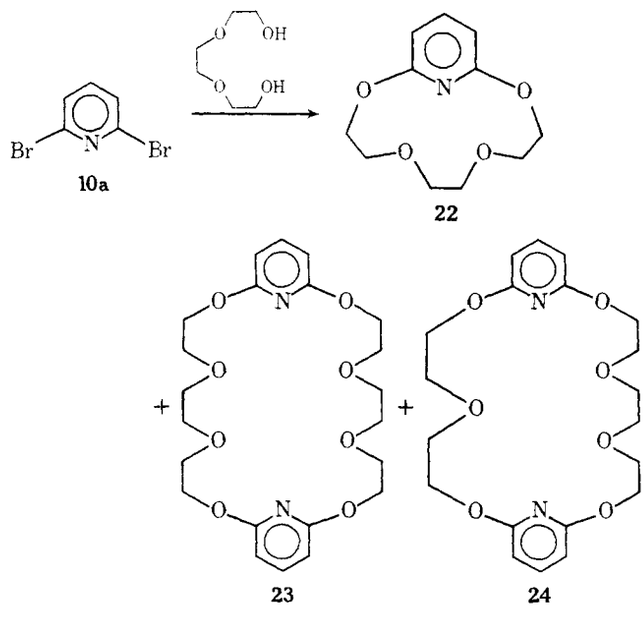


Figure 1. Variable temperature ^1H NMR spectral data for **22** in D_2CCl_2 below 10 °C and $DCCl_3$ at 30 °C.

xylene, only the two expected macrocyclic products **22** and **23** were isolated in low yields. The unsymmetrical macrocycle **24**, analogous to **13**, was not detected. The uncyclized intermediates were also not isolated, although they could be easily obtained, if desired.



The NMR spectrum of **22** is shown in Figure 1. The apparent doublet of doublets at δ 4.68 and 3.84 due to the α- and β-methylenic hydrogens, respectively, remains virtually unchanged over elevated temperatures (<160 °C). These signals each become more complicated at −10 °C, then eventually disappear at ca. −100 °C (in CD_2Cl_2), whereupon the γ hydrogens simply broaden over this lower temperature range. The dynamic change is indicative of a conformational equilibrium of two enantiomeric conformers which are gradually frozen at lower temperatures. The energy barrier ($\Delta G_c^{\ddagger}$) for this conformational equilibrium was estimated to be ca. < 8 kcal/mol at an approximate coalescence temperature of −100 °C. This $\Delta G_c^{\ddagger}$ value for **22** is slightly lower than those of [7](2,6)pyridinophane ($\Delta G_c^{\ddagger}$ 9.0 kcal/mol, T_c −75.5 °C),[10] 2,6-dithia[7](2,6)pyridinophane ($\Delta G_c^{\ddagger}$ < 10.2 kcal/mol, T_c < −60 °C),[13] and [7]metacyclophane ($\Delta G^{\ddagger}$ 11.5 kcal/mol, T_c −27.6 °C).[14] The greater flexibility in **22** can be ascribed to a combination of larger carbon–oxygen bridge, and the removal of numerous methylene–methylene interactions, while these changes will be countered by the four diminished C–O–C bond angles.

Recently, the one-step construction of racemic muscopyridine (**25**) has been accomplished (20%) via cyclocoupling the di-Grignard of 2-methyl-1,10-dibromodecane with 2,6-di-

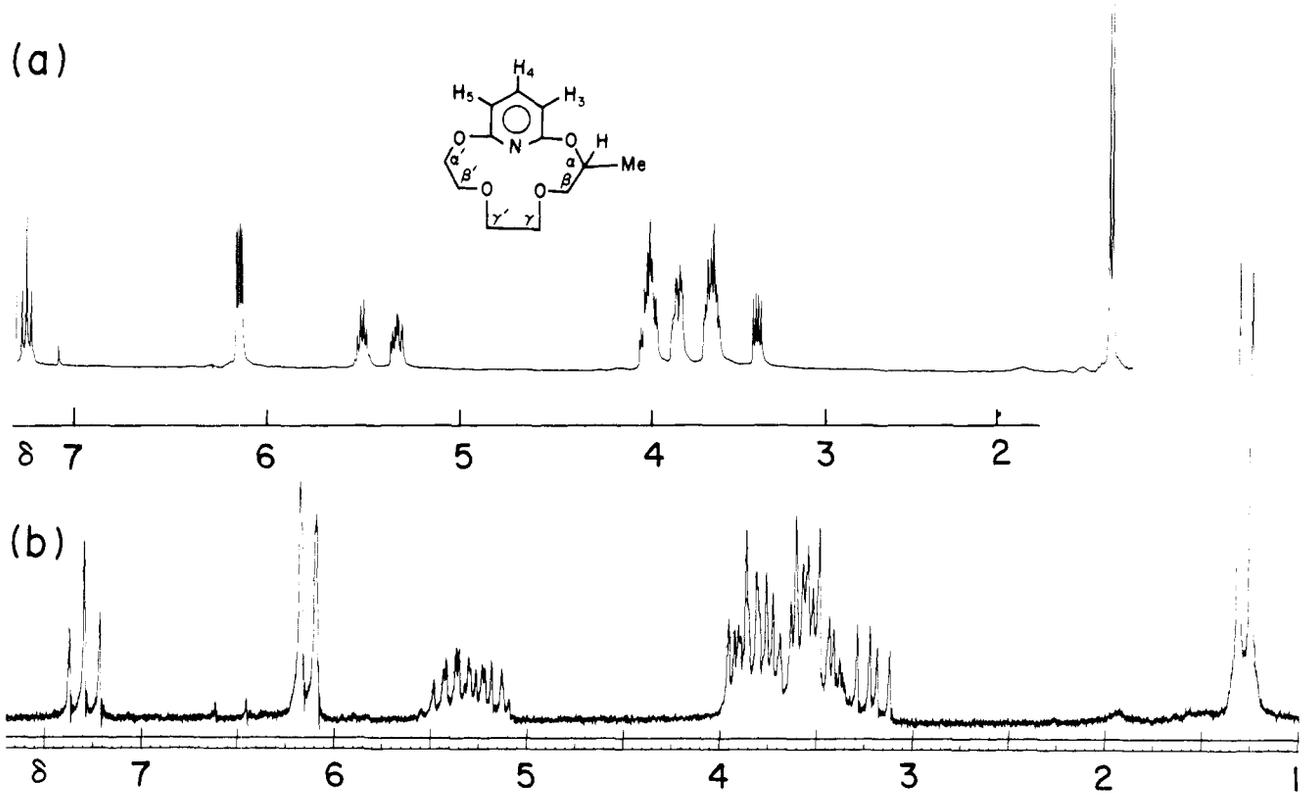
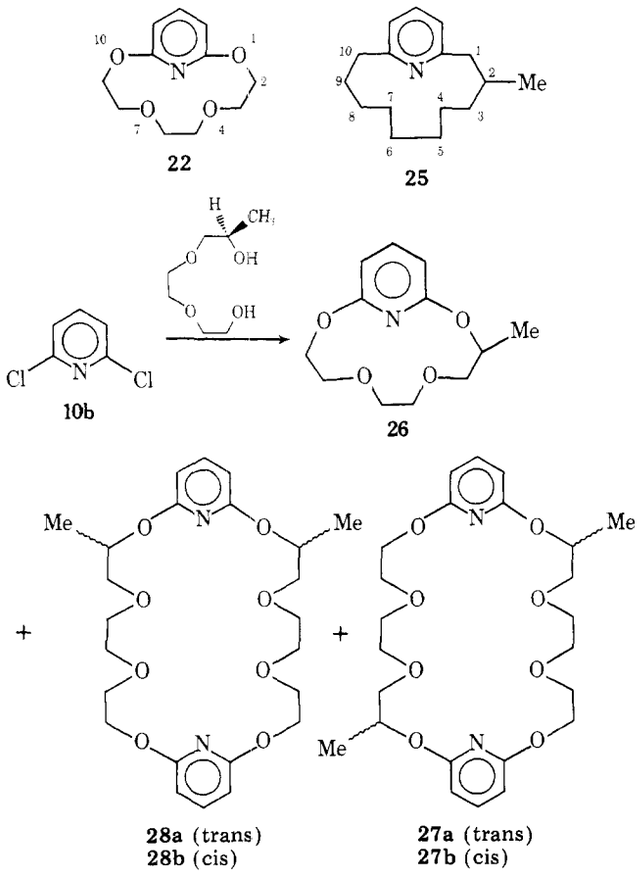


Figure 2. NMR spectra of tetraoxamuscopyridine (**26**) at 360 MHz (a) and 100 MHz (b) in $CDCl_3$.

chloropyridine in the presence of a catalytic amount of a nickel–phosphine complex.[4] Since no oxamuscopyridines have yet been reported, 2,6-dichloropyridine (**10b**) was treated with the disodium salt of 1-methyl-3,6-dioxa-1,8-octanediol, prepared from diethylene glycol and propylene oxide by standard procedures,[15] to afford the desired 1,4,7,10-tetraoxamuscopyridine (**26**) along with three isomeric 2:2 macrocycles. The major dimer has been tentatively assigned to either **27a** or **27b**, on the basis that it would be formed by dimerization of the 1:1 uncyclized intermediate leading to **26**. Other oily dimers, isolated in low yields, were not characterized further.



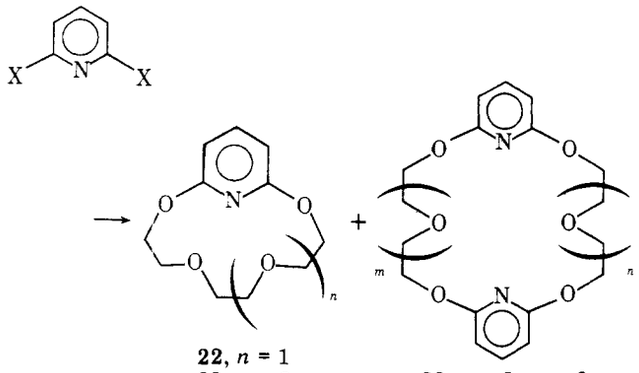
The NMR spectrum of **26** is shown in Figure 2. The increased complexity exhibited in Figure 2 is caused by (a) the diastereotopic nature of the methylene groups as a result of the α-chiral center, and (b) a possible preferred conformation as a result of a pseudoequatorial disposed methyl group. The spectral data remain virtually unchanged at elevated temperatures (~160 °C) and, as expected upon cooling to −100 °C, the attempted coalescence of the unique methylene hydrogens causes a complex broadening of the spectrum. The multiplet at δ 5.50 is assigned to the single α hydrogen and upon its irradiation the pattern at δ 3.35 collapses to a doublet and the complex pattern at δ 4.01 is simplified. The multiplet at δ 5.32 as assigned to one α' hydrogen, whereas, the second α hydrogen is located within the δ 4.01 multiplet. Inspection of molecular models of **26** indicates that one α hydrogen is forced close to the pyridine π cloud in the preferred conformation in which the α-methyl group is free of steric effects. Table I shows the hydrogen assignments for **26** as well as the average values for each methylene position based on both decoupling data and variable temperature NMR studies; the average values for **26** correspond quite well to the chemical shift data for **22**.

C. Tetra-, Penta-, and Hexaethylene Glycols. Commercially available tetraethylene glycol was treated with sodium hydride in anhydrous xylene at room temperature, followed by addition of 2,6-dibromo- (or chloro-) pyridine, and refluxed for 24 h. After standard workup, the major isolated macrocycle was **29** and **22** was realized in a lesser amount. The 2:2 symmetrical macrocycle **31** as well as unsymmetrical **30**

Table I

Bridged hydrogen chemical shifts (δ) of **26**						Av chem shifts for **26**	Chem shifts of **22**
5.50 (1 H)	5.32 (1 H)	4.01 (3 H)	3.76 (2 H)	3.58 (3 H)	3.35 (1 H)		
α-H						5.50	
	α'-Ha	α'-Hb				4.67	4.68
		β-Ha			β-Hb	3.68	
		β'-Ha	β'-Hb			3.88	3.84
			1γ-H	3γ-H		3.6 (3)	3.72

were isolated in 5 and <1% yields, respectively. High-dilution conditions increased the formation of **29** whereas the general percentages of **22, 30,** and **31** remained approximately the same. Alternate bases (KH, CaH_2, LiH) were used in the tetraethylene glycol case but had little or no effect on the product distribution.



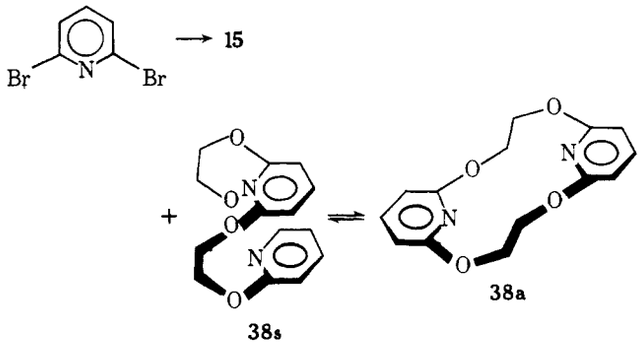
22, n = 1
29, n = 2
32, n = 3
35, n = 4

30, n = 2; m = 3
31, n = m = 3
33, n = 3; m = 4
34, n = m = 4
36, n = 4; m = 5
37, n = m = 5

Pentaethylene glycol was prepared according to the procedure of Perry and Hibbert[16] from 1,8-dichloro-3,6-dioxaoctane and ethylene glycol. 2,6-Dibromopyridine was reacted with the disodium salt of pentaethylene glycol to afford traces of the crystalline **29** and, as the major product, the viscous, colorless, oily 1:1 macrocycle **32.** Although the unsymmetrical 2:2 macrocycle **33** was not detected, the 2:2 symmetrical **34** was isolated as a crystalline solid.

Hexaethylene glycol, prepared in a similar manner,[16] was converted smoothly to the disodium salt and reacted with 2,6-dibromopyridine. Both 1:1 fragmented products **29** and **32** were isolated in ca. 3% yield. Macrocycle **35** was isolated in an astonishing 48% yield as a colorless, viscous oil. 2:2 macrocycles **34** and **36** were both isolated in 4% yield; however, the 2:2 unsymmetrical **37** was not isolated.

D. Ethylene Glycol. Reaction of 2,6-dibromopyridine with sodium glycolate in xylene or bis(2-ethoxyethyl) ether afforded (16%) macrocycle **38** along with the uncyclized intermediate **18.** A pure sample of **38** was isolated as the fastest moving component from the chromatography (ThLC) of the reaction mixture. Structure **38** was confirmed by NMR which showed a triplet at δ 7.50 for the 4-pyridyl hydrogen, a doublet at δ 6.30 for the 3,5-pyridyl hydrogens, and a broad singlet at δ 4.66 for the bridging methylenes. The variable temperature NMR spectrum (Figure 3) of **38** at 100 MHz exhibits a sharpening of the singlet at δ 4.66 at elevated temperatures, while at 15 °C coalescence of this singlet occurred and at −50 °C two complex multiplets (δ 3.57 and 4.94) were resolved. Similarly, the doublet for the 3,5-pyridyl hydrogens was transformed to two resolved doublets at −50 °C. Based on these data, the syn–anti isomer interconversion (**38s** ⇄ **38a**) was calculated to be $\Delta G_c^{\ddagger}$ = 13.5 ± 0.3 kcal/mol. This value is in accord with related flipping of syn and anti conformers.[17,19]



38s **38a**

Further work is in progress on the application of this procedure to other heterocyclic systems as well as complexation studies of these and related multiheteromacrocycles.

Experimental Section

General Comments. All melting points were taken in capillary tubes with a Thomas-Hoover Uni-Melt and are uncorrected. Infrared and ultraviolet spectra were recorded in Beckman IR-7 and Cary 14 spectrophotometers, respectively. Unless otherwise noted, ^{1}H NMR spectra were in deuteriochloroform solutions with Me_4Si as internal standard (δ 0 ppm) and recorded on either Varian A-60A or HA-100 spectrometers. Molecular weights were determined with a Hewlett-Packard 302 vapor pressure osmometer.

The recorded R_f values were determined by a standardized thin layer chromatography (TLC) procedure: 0.025 mm Brinkmann silica gel HF eluting with cyclohexane–ethyl acetate (4:1). For preparative ThLC 2-mm silica gel PF-254–366 plates were used, eluting with the stipulated solvent. Elemental analyses were performed either by Mr. R. Seab in these laboratories or by Galbraith Laboratories, Knoxville, Tenn.

All reaction solvents were distilled from lithium aluminum hydride under nitrogen. Sodium hydride (57% oil dispersion) was first washed with petroleum ether (bp 30–60 °C), then dried in vacuo prior to the reaction.

Reaction of 2-Bromopyridine with Lithium Carbide in Bis(2-ethoxyethyl) Ether. A mixture of 2-bromopyridine (10 g, 63.5 mmol) and lithium carbide (powdered, 80%, 3 g) in 50 mL of bis(2-ethoxyethyl) ether was refluxed for 24 h under nitrogen. The solvent was removed in vacuo, then the excess and unreacted lithium carbide was carefully decomposed with ice water. The suspension was extracted with ether, dried over anhydrous magnesium sulfate, and concentrated. After removal of unreacted 2-bromopyridine and solvent, the viscous residue was vacuum distilled affording a colorless oil, 4 g, bp 80–100 °C (2 mm), that was identified as 2-pyridyl 2-ethoxyethyl ether (**4**): R_f 0.36; bp 80–85 °C (2 mm); NMR δ 1.12 (t, $-CH_2CH_3$, J = 7 Hz, 3 H), 3.48 (q, CH_2CH_3, J = 7 Hz, 2 H), 3.75 (t, OCH_2CH_2OEt, J = 5 Hz, 2 H), 4.5 (t, Pyr-OCH_2, J = 5 Hz, 2 H), 6.6–6.9 (m, 3,5-Pyr-H, 2 H), 7.3–7.65 (m, 4-Pyr-H, 1 H), 8.05–8.3 (m, 6-Pyr-H, 1 H). Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84, N, 8.38. Found: C, 64.39; H, 7.92; N, 8.41.

2-Pyridyl 2-ethoxyethyl ether (**4**) was independently prepared (50%) by reaction of 2-bromopyridine (10 g, 63.5 mmol), sodium hydride (4.0 g, 30 mmol), and 2-ethoxyethanol (40 mL) utilizing the same reaction and workup procedures.

Reaction of 2-Bromopyridine with Ethylene Glycol. To a suspension of sodium hydride (4.0 g, 80 mmol) in anhydrous xylene (150 mL), ethylene glycol (2.5 g, 40 mmol) was added dropwise under

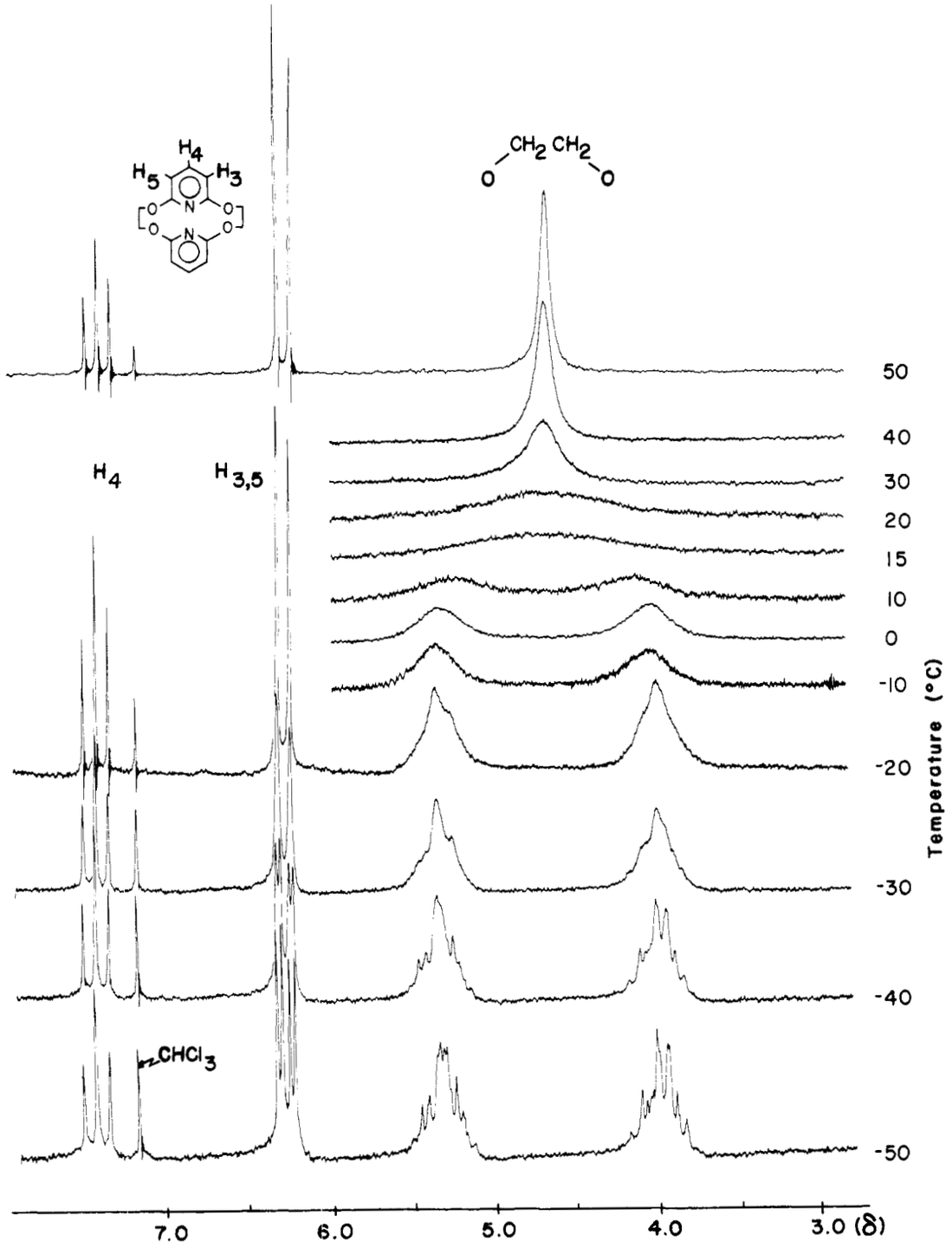


Figure 3. Variable temperature ^1H NMR spectral data for **38** in $DCCl_3$.

nitrogen. The mixture was stirred for 30 min, then 2-bromopyridine (12.6 g, 80 mmol) in 20 mL of xylene was added. After the mixture was refluxed for 24 h, the solvent and unreacted starting materials were removed in vacuo. The residue was carefully treated with crushed ice, extracted with dichloromethane, and concentrated, and an aliquot was subjected to thick layer chromatography eluting three times with cyclohexane–ethyl acetate (10:1). Four major fractions, other than unreacted 2-bromopyridine, were eluted and characterized.

2-(Pyridyloxy)ethanol (**8**): bp 60 °C (0.15 mm); 28%; R_f 0.06; NMR δ 3.90 (m, β-CH_2O, 2 H), 4.40 (m, α-CH_2O, 2 H), 6.79 (m, 3,5-Pyr-H, 1 H), 7.52 (ddd, 4-Pyr-H, J = 8, 8, 2 Hz), 8.07 (bd, 6-Pyr-H, 1 H); IR (neat) 3470 (broad, -OH), 1579, 1572, 1479, 1438, 1291, 1049, 781 cm^{-1}. Anal. Calcd for $C_7H_9NO_2$: C, 60.41; H, 6.52; N, 10.07. Found: C, 60.28; H, 6.42; N, 10.16.

2,2′-(Ethylenedioxy)dipyridine (**9**): mp 66.5–68 °C (petroleum ether, bp 60–80 °C); 32%; R_f 0.31; NMR δ 4.70 (s, $-CH_2-$, 4 H), 6.75 (m, 3,5-Pyr-H, 4 H), 7.45 (ddd, 4-Pyr-H, J = 8, 8, 2 Hz, 2 H), 8.15 (bd, 6-Pyr-H, J = 8 Hz, 2 H); IR (KBr) 1611, 1596, 1573, 1479, 1430, 1298, 1249, 1147, 1058, 990 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.43; H, 5.59; N, 13.11.

2-[2-(2-Pyridyloxy)ethoxy]ethanol (**6**): bp 75 °C (0.5 mm, short path); <2%; R_f 0.04; NMR δ 3.50 (bs, -OH; exchanged with D_2O, 1 H), 3.80 (m, β-CH_2O–, 6 H), 4.47 (m, α-CH_2O, 2 H), 6.77 (m, 3,5-Pyr-H, 2 H), 7.54 (ddd, 4-Pyr-H, J = 8, 8, 2 Hz, 1 H), 8.10 (bd, 6-Pyr-H, J = 8 Hz, 1 H); IR (neat) 3440 (broad, -OH), 1599, 1479, 1436, 1291, 1134, 1053, 785 cm^{-1}. Anal. Calcd for $C_9H_{13}NO_3$: C, 58.97; H, 7.15; N, 7.65. Found: C, 58.84; H, 7.20; N, 7.62.

2,2′-[Oxybis(ethyleneoxy)]dipyridine (**7**): mp 38–40 °C [recrystallized from petroleum ether (bp 60–80 °C), sublimed 90 °C (0.5 mm)]; <5%; R_f 0.20; NMR δ 3.90 (t, β-CH_2O, J = 6 Hz, 4 H), 4.50 (t, α-CH_2O, J = 6 Hz, 4 H), 6.80 (m, 3,5-Pyr-H, 4 H), 7.52 (m, 4-Pyr-H, J = 8, 8 Hz, 2 H), 8.13 (bd, 6-Pyr-H, J = 6 Hz, 2 H); IR (KBr) 1599,

1480, 1437, 1280, 1057, 785 cm^{-1}. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.33; H, 6.24; N, 10.84. Found: C, 64.24; H, 6.47; N, 10.75.

Reaction of 2-Bromopyridine with Diethylene Glycol. To a suspension of sodium hydride (2 g, 40 mmol) in bis(2-ethoxyethyl) ether [BEE, 150 mL, bp 84 °C (22 mm)], diethylene glycol (2.12 g, 20 mmol) was slowly added. The mixture was stirred for 30 min, then 2-bromopyridine (3.16 g, 20 mmol) was added. The reaction mixture was maintained at 140–150 °C for 24 h and worked up as previously described. The major products were 2-[2-(2-pyridyloxy)ethoxy]-ethanol [27%, bp 75–77 °C (0.5 mm, short path)], 2,2′-[oxybis(ethyleneoxy)]dipyridine [35%, mp 38–40 °C (sublimed)], and traces (<3%) of both 2-(pyridyloxy)ethanol and 2,2′-(ethylenedioxy)dipyridine.

General Macrocycle Preparation. Reaction of 2,6-Dibromopyridine with Diethylene Glycol. To a suspension of sodium hydride (1 g, 20 mmol) in 50 mL of xylene, diethylene glycol (1.16 g, 10 mmol, bp 240–250 °C) was added slowly under nitrogen. The mixture was stirred for 30 min at room temperature, then 2,6-dibromopyridine (2.37 g, 10 mmol) in 25 mL of xylene was added. After the reaction mixture was heated to 140–150 °C for 24 h, the solvent was removed in vacuo. The residue was dissolved in water, extracted with dichloromethane, and chromatographed (ThLC) on four plates eluting with cyclohexane–ethyl acetate (1:1). Owing to the numerous components, the plates were divided into the fast-moving (R_f 1–0.5) and slow-moving (R_f 0.5–0) components. The fast-moving portion of these plates was combined and rechromatographed (ThLC) developing eight times with cyclohexane–ethyl acetate (10:1) to afford five major fractions.

Fraction A yielded unreacted 2,6-dibromopyridine: 80 mg; R_f 0.50; mp 117–118 °C.

Fraction B afforded 6,6′-dibromo-2,2′-(ethylenedioxy)dipyridine (**16**): 29 mg; mp 150–152 °C (cyclohexane); R_f 0.53; NMR δ 4.62 (s, $-CH_2O-$, 4 H), 6.68 (dd, 3-Pyr-H, J = 8, 2 Hz, 2 H), 7.02 (dd, 5-Pyr-H, J = 8, 2 Hz, 2 H), 7.40 (dd, 4-Pyr-H, J = 8, 8 Hz, 2 H); IR (KBr) 1601, 1586, 1557, 1443, 1288, 1263, 1165 1032, 984, 875, 795 cm^{-1}. Anal. Calcd for $C_{12}H_{10}N_2O_2Br_2$: C, 38.53; H, 2.69; N, 7.49. Found: C, 38.44; H, 2.66; N, 7.36.

Fraction C crystallized from petroleum ether (bp 60–80 °C) yielding macrocycle **13** as colorless needles: 90 mg; mp 94.5–95.5 °C; R_f 0.47; NMR δ 3.81 (dd, β-CH_2O, J = 6, 6 Hz, 4 H), 4.50 (dd, α-CH_2O, J = 6, 6 Hz, 4 H), 4.64 (s, $-OCH_2CH_2O-$, 4 H), 6.38 (2 d, 3- and 5-Pyr-H, J = 8 Hz each, 4 H), 7.48 (t, 4-Pyr-H, J = 8 Hz, 2 H); IR (KBr) 1605, 1590, 1471, 1447, 1302, 1253, 1033, 975 cm^{-1}; UV (EtOH) λ 225.0 nm (ϵ 23 100), 277.5 (14 300). Anal. Calcd for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.09; H, 5.71; N, 8.64.

Fraction D afforded 6,6′-dibromo-2,2′-[oxybis(ethyleneoxy)]dipyridine (**15**), which was recrystallized from petroleum ether (bp 60–80 °C) to give colorless needles: 820 mg; mp 91–92 °C; R_f 0.43; NMR δ 3.87 (dd, β-CH_2O, J = 6, 6 Hz, 4 H), 4.47 (dd, α-CH_2O, J = 6, 6 Hz, 4 H), 6.68 (dd, 3-Pyr-H, J = 8, 2 Hz, 2 H), 7.02 (dd, 5-Pyr-H, J = 8, 2 Hz, 2 H), 7.42 (dd, 4-Pyr-H, J = 8, 8 Hz, 2 H); IR (KBr) 1608, 1590, 1558, 1435, 1302, 1138, 1030, 983, 883, 804, 786 cm^{-1}. Anal. Calcd for $C_{14}H_{14}N_2O_3Br_2$: C, 40.30; H, 3.31; N, 6.54. Found: C, 40.22; H, 3.38; N, 6.70.

Fraction E afforded the 2:2 macrocycle **11** which was recrystallized from petroleum ether (bp 60–80 °C) to give colorless needles: 250 mg (6.5%); mp 111–112 °C; R_f 0.37; NMR δ 3.86 (t, β-CH_2O, J = 5 Hz, 8 H), 4.48 (t, α-CH_2O, J = 5 Hz, 8 H), 6.23 (d, 3,5-Pyr-H, J = 8 Hz, 4 H), 7.45 (t, 4-Pyr-H, J = 8 Hz, 2 H); IR (KBr) 1605, 1578, 1468, 1435, 1297, 1235, 1026, 1073, 1052, 1020, 789 cm^{-1}; UV (EtOH) λ 223.0 nm (ϵ 19 900), 2780 (14 600). Anal. Calcd for $C_{18}H_{22}N_2O_6$: C, 59.66; H, 6.12; N, 7.73; mol wt, 362. Found: C, 59.88; H, 6.27; N, 7.62; mol wt (osmometry), 364 (av).

The slower moving portions from the original plates were combined and rechromatographed (ThLC) developing eight times with cyclohexane–ethyl acetate (4:1) to afford fractions F–H.

Fraction F yielded 2-[2-[2-(6-bromopyridyloxy)]ethoxy]ethanol (**14**) as a colorless oil: 620 mg; bp 80 °C (0.3 mm, short path); R_f 0.07; NMR δ 3.20 (s, –OH, exchanged with D_2O), 3.80 (m, $-CH_2-$, 6 H), 4.45 (dd, PyrOCH_2-, J = 5 Hz, 2 H), 6.70 (dd, 3-Pyr-H, J = 8, 2 Hz, 1 H), 7.02 (dd, 5-Pyr-H, J = 8, 2 Hz, 1 H), 7.42 (dd, 4-Pyr-H, J = 8, 8 Hz, 1 H); IR (neat) 3500 (–OH), 1605, 1590, 1560, 1465, 1440, 1315, 1240, 1135, 1050, 790, 733 cm^{-1}. Anal. Calcd for $C_9H_{12}NO_3Br$: C, 41.24; H, 4.61; N, 5.34. Found: C, 41.27; H, 4.72; N, 5.19.

Fraction G yielded the 3:3 macrocycle **12**, which was recrystallized from petroleum ether (bp 60–80 °C) affording colorless needles: 95 mg (1.6%); mp 120.5–121.5 °C; R_f 0.20; NMR δ 3.83 (t, β-CH_2O, J = 5 Hz, 12 H), 4.42 (t, α-CH_2O, J = 5 Hz, 12 H), 6.28 (d, 3,5-Pyr-H, J = 8 Hz, 6 H), 7.45 (t, 4-Pyr-H, J = 8 Hz, 3 H); IR (KBr) 1613, 1583, 1462, 1444, 1342, 1307, 1247, 1078, 788 cm^{-1}. Anal. Calcd for $C_{27}H_{33}N_3O_9$: C, 59.66; H, 6.12; N, 7.73; mol wt, 543. Found: C, 59.59; H, 6.15; N, 7.51; mol wt (osmometry), 528 (av).

Fraction H afforded 2,2′-[2,2′-(2,6-pyridinediyldioxy)diethoxy]-diethanol (**17a**) as a high-boiling, colorless oil: 60 mg; bp 150 °C (0.3 mm, short path); R_f 0.01; NMR δ 3.80 (m, β-CH_2O, 12 H), 4.38 (t, α-CH_2O, J = 5 Hz, 4 H), 4.62 [bs, –OH (exchanged with D_2O), 2 H], 6.28 (d, 3,5-Pyr-H, J = 8 Hz, 2 H), 7.45 (t, 4-Pyr-H, J = 8 Hz, 1 H); IR (neat) 3400 (broad, –OH), 1605, 1595 1580, 1441, 1242, 1132, 1068 cm^{-1}.

Diol **17a** failed repeatedly to afford an acceptable analytical analysis. Therefore, **17a** was converted by the standard pyridine–acetic anhydride procedure to the corresponding diacetate **17b**: bp 140 °C (2 mm, short path); NMR δ 2.03 (s, $COCH_3$, 6 H), 3.75 (dd, β-CH_2O, J = 6 Hz, 8 H), 4.19 (dd, α-CH_2OAc, J = 6 Hz, 4 H), 4.38 (dd, α-CH_2O, J = 6 Hz, 4 H), 6.29 (d, 3,5-Pyr-H, J = 8 Hz, 2 H), 7.45 (t, 4-Pyr-H, J = 8 Hz, 1 H); IR (neat) 1742 (C=O), 1607, 1582, 1442, 1243, 1138, 1058, 793 cm^{-1}. Anal. Calcd for $C_{17}H_{25}NO_8$: C, 54.97; H, 6.79; N, 3.78. Found: C, 54.75; H, 6.91; N, 3.48.

Macrocycle 13. Oil-free sodium hydride (ca. 20 mg) suspended in 25 mL of anhydrous bis(2-ethoxyethyl) ether was stirred under nitrogen and diethylene glycol (30 mg, 0.28 mmol) was slowly added, followed by **16** (100 mg, 0.27 mmol). The mixture was heated at 140 °C for 24 h. After the previously described workup, preparative chromatography (ThLC) of the residue afforded, along with recovered starting material, macrocycle **13** (26 mg, 30%, mp 94–95 °C), which was recrystallized from cyclohexane and shown to be indistinguishable from the previously obtained sample.

Reaction of Excess 2,6-Dibromopyridine with Diethylene Glycol. The above general procedure was followed except that excess 2,6-dibromopyridine (23.7 g, 100 mmol) was used. Along with unreacted starting material, the major fraction isolated was alcohol **14** (25%, mp 91–92 °C). Only traces (<2%) of the desired macrocycles **11**, **12**, and **13** were isolated.

Cyclization of Alcohol 14. Alcohol **14** (3 g, 11 mmol) was dissolved in anhydrous bis(2-ethoxyethyl) ether (300 mL) and sodium hydride (600 mg, 12 mmol) was carefully added. The mixture was heated to 140–150 °C for 24 h and worked up as previously described to afford 42% of **11** (mp 110–112 °C) along with traces (<1%) of **12**, **20**, and **21**. Owing to limited amounts of pure **20** and **21**, the NMR data, which were identical with those of **14**, and osmometric analyses were used to assign their structures.

Reaction of 2,6-Dibromopyridine with Triethylene Glycol. Following the general procedure, except for the substitution of triethylene glycol (1.5 g, 10 mmol), two major macrocyclic ethers were characterized.

1:1 macrocycle **22:** mp 83–84 °C (petroleum ether, bp 60–80 °C); 6%; R_f 0.24; NMR δ 3.72 (s, γ-CH_2O, 4 H), 3.82 (t, β-CH_2O, J = 5 Hz, 4 H), 4.68 (t, α-CH_2O, J = 5 Hz, 4 H), 6.27 (d, 3,5-Pyr-H, J = 8 Hz, 2 H), 7.47 (t, 4-Pyr-H, J = 8 Hz, 1 H); IR ($CHCl_3$) 1602, 1587, 1456, 1303, 1205 cm^{-1}. Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.23; mol wt, 225. Found: C, 58.73; H, 6.65; N, 6.35; mol wt (osmometry), 223 (av).

2:2 macrocycle **23:** mp 117–120 °C (petroleum ether, 60–80 °C); <2%; R_f 0.1; NMR δ 3.70 (s, γ-CH_2O, 6 H), 3.82 (t, β-CH_2O, J = 6 Hz, 8 H), 4.40 (t, α-CH_2O, J = 6 Hz, 8 H), 6.27 (d, 3,5-Pyr-H, J = 8 Hz, 4 H), 7.41 (t, 4-Pyr-H, J = 8 Hz, 2 H). Anal. Calcd for $C_{22}H_{30}N_2O_8$ (450): C, 58.66; H, 6.71; N, 6.23. Found: C, 58.53; H, 6.77; N, 6.31; mol wt (osmometry), 460. Other intermediates were easily detected but were neither isolated nor characterized.

1-Methyl-3,6-dioxa-1,8-octanediol. Diethylene glycol (35 g) was treated with sodium (0.1 g) at 50 °C under nitrogen, then warmed to 100 °C for 2 h. Propylene oxide (20 g) was added dropwise over 10 min followed by maintaining the suspension with stirring at 120 °C for 12 h. After cooling, the solution was neutralized with acetic acid (ca. 2 mL) and then vacuum distilled affording a mixture of diols, bp 160–200 °C (5 mm). Fractional distillation via a spinning band column afforded the pure (>97%) methyltriethylene glycol: bp 106 °C (2 mm); NMR δ 1.08 (d, CHCH_3, J = 6 Hz, 3 H), 3.2–4.0 (m, $CHCH_2$, OH, 13 H).

Reaction of 2,6-Dichloropyridine with Methyltriethylene Glycol. Sodium hydride (2.5 g, 50 mmol) suspended in xylene (300 mL) was treated with methyltriethylene glycol (4.1 g, 25 mmol) over 15 min with stirring under nitrogen, then 2,6-dichloropyridine (3.7 g, 25 mmol) in xylene (50 mL) was added. The mixture was refluxed for 30 h. After cooling, the unreacted sodium hydride was neutralized with water and the aqueous layer separated. The organic layer was dried and concentrated in vacuo affording a viscous residue, part of which was chromatographed (ThLC) eluting four times with cyclohexane–ethyl acetate (4:1). Four major macrocyclic fractions were isolated:

Fraction A gave the 1:1 macrocycle, 1,4,7,10-tetraoxamuscopyridine

(**26**), which crystallized from absolute ethanol as colorless plates: mp 55 °C; 210 mg (ca. 3%); R_f 0.45; NMR (300 MHz) δ 1.41 (d, $CHCH_3$, J = 6 Hz, 3 H), 3.35 (dd, β-CH_2O, J = 8, 6 Hz, 1 H), 3.58 (m, α′- and γ- or γ′-H, 3 H), 3.76 (m, γ- or γ′-H, 2 H), 4.01 (m, β- and β′-H, 3 H), 5.32 (m, α′-H, 1 H), 5.50 (m, α-H, 1 H), 6.14 (d, 3,5-Pyr-H, J = 5 Hz, 2 H), 7.25 (t, 4-Pyr-H, J = 5 Hz, 1 H) (see Figure 1); IR (Nujol) 1625, 1575, 1450, 1375, 1300, 1225, 1015, 790 cm^{-1}. Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.25; H, 7.11; N, 5.85; mol wt, 239. Found: C, 60.08; H, 6.91; N, 5.84; mol wt (MS), 239 (M^+).

Fraction B furnished a 2:2 macrocycle (**27**) which was crystallized from 95% ethanol as colorless plates: mp 111 °C; 900 mg (ca. 15%); R_f 0.38; NMR δ 1.32 (d, $CHCH_3$, J = 6 Hz, 6 H), 3.72 (m, β- and γ-CH_2O, 16 H), 4.35 (t, α-CH_2O, J = ca. 5 Hz, 4 H), 5.30 (m, $CHCH_3$, J = 6, ~5 Hz, 2 H), 6.28 (d, 3,5-Pyr-H, J = 5 Hz, 4 H), 7.42 (t, 4-Pyr-H, J = 5 Hz, 2 H); IR (Nujol) 1600, 1570, 1440, 1240, 790 cm^{-1}. Anal. Calcd for $C_{24}H_{34}N_2O_8$: C, 60.25; H, 7.11; N, 5.85; mol wt, 478. Found: C, 60.02; H, 7.07; N, 5.75; mol wt (MS), 478 (M^+).

Fraction C gave an isomeric 2:2 macrocycle as a thick, viscous oil which failed to crystallize: 75 mg (<1%); R_f 0.29; NMR δ 3.32 (d, $CHCH_3$, J = 5 Hz, 6 H), 3.75 (m, β- and γ-CH_2O–, 16 H), 4.4 (t, α-CH_2O–, J = 5 Hz, 4 H), 5.30 (m, $CHCH_3$, J = 6, ~5 Hz, 2 H), 6.25 (d, 3,5-Pyr-H, J = 5 Hz, 4 H), 7.35 (t, 4-Pyr-H, J = 5 Hz, 2 H); IR (neat) 2850, 1600, 1570, 1300, 1220, 1100, 950, 790, 740 cm^{-1}. Anal. Calcd for $C_{24}H_{34}N_2O_8$: C, 60.25; H, 7.11; N, 5.85; mol wt, 478. Found: C, 60.05; H, 6.84; N, 5.89; mol wt (MS), 478 (M^+).

Fraction D gave an isomeric 2:2 macrocycle as a noncrystallizable oil: 80 mg (<1%); R_f 0.22; NMR and IR are identical with those of fraction C. Anal. Calcd for $C_{24}H_{34}N_2O_8$: C, 60.25; H, 7.11; N, 5.85; mol wt, 478. Found: C, 60.34; H, 7.11; N, 5.82; mol wt (MS), 478 (M^+).

Reaction of 2,6-Dibromopyridine with Tetraethylene Glycol. The general procedure was followed except for the substitution of tetraethylene glycol. After the standard workup procedure a portion of the thick, viscous, brown oil was chromatographed (ThLC) eluting four times with cyclohexane–ethyl acetate (1:1) to afford, along with starting materials, four macrocyclic components.

Fraction A afforded the 1:1 macrocycle **22**, which crystallized from petroleum ether (bp 60–80 °C) as colorless plates (mp 84 °C) and had the same IR and NMR spectral data with the previously isolated sample.

Fraction B afforded the desired 1:1 macrocycle **29**, which crystallized from petroleum ether (bp 60–80 °C) as colorless plates: mp 76–78 °C; 100 mg (ca. 4%); R_f 0.13; NMR δ 3.62 (s, γ,δ-CH_2O, 8 H), 3.92 (t, β-CH_2O, J = 5 Hz, 4 H), 4.62 (t, α-CH_2O, J = 5 Hz, 4 H), 6.28 (d, 3,5-Pyr-H, J = 7 Hz, 2 H), 7.46 (t, 4-Pyr-H, J = 7 Hz, 1 H); IR (Nujol), 1590, 1570, 1440, 1300, 1210, 1120 cm^{-1}. Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.06; N, 5.20; mol wt, 269. Found: C, 58.21; H, 7.15; N, 5.19; mol wt (MS), 269 (M^+).

Fraction C gave the unsymmetrical ether **30**, which was crystallized from alcohol as a white powder: mp 72 °C; 40 mg (ca. 1%); R_f 0.05; NMR δ 3.65 (bs, γ,δ-CH_2O, 12 H), 3.80 (t, β-CH_2O, J = 5 Hz, 8 H), 4.42 (t, α-CH_2O, J = 5 Hz, 8 H), 6.27 (d, 3,5-Pyr-H, J = 7 Hz, 4 H), 7.4 (t, 4-Pyr-H, J = 7 Hz, 2 H); IR (Nujol) 1610, 1590, 1440, 1300, 1240, 1130 cm^{-1}. Anal. Calcd for $C_{24}H_{34}N_2O_9$: C, 58.30; H, 6.88; N, 5.67; mol wt, 494. Found. C, 58.56; H, 7.08; N, 5.46; mol wt (MS), 494 (M^+).

Fraction D gave the symmetrical 2:2 macrocycle **31** as colorless needles: mp 83–84 °C; 150 mg (5%); R_f 0.03; NMR δ 3.65 (s, γ,δ-CH_2O, 16 H), 3.83 (t, β-CH_2O, J = 6 Hz, 8 H), 4.41 (t, α-CH_2O, J = 6 Hz, 8 H), 6.28 (d, 3,5-Pyr-H, J = 8 Hz, 4 H), 7.42 (t, 4-Pyr-H, J = 8 Hz, 2 H); IR (Nujol) 1600, 1575, 1450, 1325, 1300, 1250, 1100 cm^{-1}. Anal. Calcd for $C_{26}H_{38}N_2O_{10}$: C, 57.99; H, 7.06; N, 5.20; mol wt, 538. Found: C, 58.04; H, 7.12; N, 5.08; mol wt (MS), 538 (M^+).

Reaction of 2,6-Dichloropyridine with Tetraethylene Glycol. High-Dilution Conditions. Sodium hydride suspension (480 mg, 20 mmol) was washed with petroleum ether and dried with a stream of nitrogen, then anhydrous xylene (500 mL) was added. To this refluxing suspension, tetraethylene glycol (1.98 g, 10 mmol) in xylene (500 mL) and 2,6-dichloropyridine (1.5 g, 10 mmol) in xylene (500 mL) were added simultaneously over 24 h via a high-dilution apparatus,[9] then the solution was refluxed for an additional 12 h. The workup procedure mimicked the general procedure. The crude reaction products were chromatographed (ThLC) affording the same macrocyclic products except for product distribution: macrocycle **22** (mp 84 °C, ~1%); 1:1 macrocycle **29** (mp 76–78 °C, 10%); unsymmetrical macrocycle **30** (mp 72 °C, 2%); and symmetrical 2:2 macrocycle **31** (mp 83–84 °C, 3%).

3,6,9,12-Tetraoxa-1,14-tetradecanediol (pentaethylene glycol) was prepared according to the procedure of Perry and Hibbert[16] from 1,8-dichloro-3,6-dioxaoctane and ethylene glycol: bp 185–190 °C (0.15mm) [lit.[20] bp 174–176 °C (0.14 mm)].

Reaction of 2,6-Dibromopyridine with Pentaethylene Glycol. The general procedure for macrocycles was followed except for the substitution of pentaethylene glycol. The product residue was chromatographed (ThLC) eluting two times with cyclohexane–ethyl acetate (1:1); however, since separation was not complete, the faster moving components (R_f > 0.5) were combined and rechromatographed (ThLC) eluting two times with cyclohexane–ethyl acetate (1:1) to give two macrocyclic compounds.

Fraction A crystallized from petroleum ether (bp 60–80 °C) to give macrocycle **29** as colorless plates: mp 76–78 °C; 70 mg (2%); R_f 0.13; spectral data were identical with those of **29** isolated from the previous reaction.

Fraction B gave the desired 1:1 macrocycle **32** as a thick, viscous oil: bp 155–160 °C (0.15 mm); 350 mg (12%); R_f 0.06; NMR δ 3.52 (s, ε-CH_2O, 4 H), ~3.7 (m, δ,γ-CH_2O, 8 H), 3.85 (t, β-CH_2O, J = 6 Hz, 4 H), 4.55 (t, α-CH_2O, J = 6 Hz, 4 H), 6.3 (d, 3,5-Pyr-H, J = 6 Hz, 2 H), 7.45 (t, 4-Pyr-H, J = 6 Hz, 1 H); IR (Nujol) 1600, 1580, 1430, 1300, 1240, 790 cm^{-1}. Anal. Calcd for $C_{15}H_{23}NO_6$: C, 57.50; H, 7.34; N, 4.47; mol wt, 313. Found: C, 56.96; H, 7.43; N, 4.37; mol wt (MS), 313 (M^+).

The slower moving fractions were rechromatographed (ThLC) eluting five times with cyclohexane–ethyl acetate (1:1) to give two compounds.

Fraction C gave an unknown compound as colorless needles from ethanol: mp 189 °C; 5 mg (≪1%); R_f 0.02; insufficient material was available to establish the structure.

Fraction D gave a white powder which upon recrystallization from ethanol yielded colorless needles of the 2:2 macrocycle **34:** mp 91 °C; 200 mg (~8%); R_f 0.01; NMR δ 3.65 (m, ε,δ,γ-CH_2O, 24 H), 3.85 (t, β-CH_2O, J = 5 Hz, 8 H), 4.42 (t, α-CH_2O, J = 5 Hz, 8 H), 6.3 (d, 3,5-Pyr-H, J = 5 Hz, 4 H), 7.40 (t, 4-Pyr-H, J = 5 Hz, 2 H); IR (Nujol) 1600, 1580, 1490 (b), 1250, 785 cm^{-1}. Anal. Calcd for $C_{30}H_{46}N_2O_{12}$: C, 57.50; H, 7.34; N, 4.47, mol wt, 626. Found: C, 57.46; H, 7.50; N, 4.18; mol wt (MS), 626 (M^+).

2,2′-[Oxybis(ethyleneoxyethyleneoxy)]diethanol (hexaethylene glycol) was prepared[16] from 1,5-dichloro-3-oxapentane [bp 179 °C (760 mm)] and diethylene glycol: bp 201–205 °C (0.7 mm) [lit[20] bp 203.0–205.0 (0.3 mm)].

Reaction of 2,6-Dibromopyridine with Hexaethylene Glycol. The general procedure was followed except for the substitution of hexaethylene glycol. The product residue was chromatographed (ThLC) eluting three times with cyclohexane–ethyl acetate (1:1). The following fast-moving fractions were separated.

Fraction A gave a small amount (10 mg) of unreacted dibromopyridine, mp 118 °C.

Fraction B afforded (3%) a crystalline compound which corresponded to the proven macrocycle **29**, mp 76–78 °C, 40 mg.

Fraction C afforded a thick, viscous oil which was shown spectroscopically to be identical with macrocycle **32**, 40 mg (ca. 3%).

Fraction D gave the 1:1 macrocycle **35** as a colorless oil: bp 190–193 °C (0.1 mm); 850 mg (48%); R_f 0.02; NMR δ 3.60 (m, γ,ζ-CH_2O, 16 H), 3.85 (t, β-CH_2O, J = 5 Hz, 4 H), 4.55 (t, α-CH_2O, J = 5 Hz, 4 H), 5.3 (d, 3,5-Pyr-H, J = 7 Hz, 3 H), 7.45 (t, 4-Pyr-H, J = 7 Hz, 1 H); IR (neat) 2900, 1600, 1425, 1300, 1240, 950, 800 cm^{-1}. Anal. Calcd for $C_{17}H_{27}NO_7$: C, 57.14; H, 7.56; N, 3.92; mol wt, 357. Found: C, 56.77; H, 7.53; N, 3.82; mol wt (MS), 357.

The residual baseline was extracted with chloroform–ethanol (1:1). The residue was rechromatographed (ThLC) with cyclohexane and ethyl acetate (1:3) eluting two times. The following fractions were isolated.

Fraction E gave the white, crystalline 2:2 macrocycle **34**, identical in all respects with the above sample, mp 91 °C, 60 mg (4%).

Fraction F, recrystallized from ethanol, afforded a colorless powder of the 2:2 macrocycle **37:** mp 72–74 °C; 75 mg (5%); R_f 0.01; NMR δ 3.67 (m, γ,ζ-CH_2O, 32 H), 3.82 (t, β-CH_2O, J = 5 Hz, 8 H), 4.4 (t, α-CH_2O, J = 5 Hz, 8 H), 6.25 (d, 3,5-Pyr-H, J = 7 Hz, 4 H), 7.41 (t, 4-Pyr-H, J = 7 Hz, 2 H); IR ($CHCl_3$) 2900, 1605, 1595, 1445, 1350, 1310, 1240, 792 cm^{-1}. Anal. Calcd for $C_{34}H_{54}N_2O_{14}$: C, 57.14; H, 7.56; N, 3.92; mol wt, 714. Found: C, 57.20; H, 7.54; N, 3.88; mol wt (MS), 714.

Reaction of 2,6-Dibromopyridine with Ethylene Glycol. To a suspension of sodium hydride (4 g, 80 mmol) in bis(2-ethoxyethyl) ether (250 mL), ethylene glycol (2.5 g, 40 mmol) was added; after 30 min, 2,6-dibromopyridine (4.74 g, 20 mmol) was added. The mixture was heated to 150 °C for 24 h, and worked up as previously described. A portion of the residue was chromatographed (ThLC) eluting six times with cyclohexane–ethyl acetate (10:1). Other than 2,6-dibromopyridine (ca. 30%), the following fractions were characterized.

Macrocycle **38:** mp 215–216 °C; 16%; R_f 0.7; NMR δ 4.66 [bs (38 °C), –CH_2O–, 8 H], 6.30 [d (38 °C), 3,5-Pyr-H, J = 8 Hz, 4 H], 7.50 (t, 4-Pyr-H, J = 8 Hz, 2 H) (see Figure 1); IR (KBr) 1605, 1590, 1470, 1450, 1300, 1250, 1030, 975 cm^{-1}. Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.29; H,

5.14; N, 10.21. Found: C, 61.32; H, 5.10; N, 10.26.

6,6′-Dibromo-2,2′-(ethylenedioxy)dipyridine (16): mp 150–152 °C; 4%; identical with a known sample.

2-[2-(6-Bromopyridyloxy)]ethanol (18): traces (<1%); NMR ($CDCl_3$) δ 3.90 (m, β-CH_2O, 2 H), 4.40 (m, α-CH_2O, 2 H), 6.68 (dd, 3-Pyr-H, J = 8,2 Hz, 1 H), 7.01 (dd, 5-Pyr-H, J = 8, 2 Hz, 1 H), 7.41 (t, 4-Pyr-H, J = 8 Hz, 1 H).

Acknowledgments. The authors gratefully acknowledge partial support of this work by the Public Health Service grant from the National Institutes of Health, National Science Foundation, and Merck Sharp & Dohme Co. as well as Professor Norman S. Bhacca and Ms. Veronica Majestic for the 360-MHz and 100-MHz NMR spectra.

Registry No.—3, 109-04-6; 4, 61463-64-7; 6, 56446-62-9; 7, 56446-63-0; 8, 56446-64-1; 9, 56446-65-2; 10a, 626-05-1; 10b, 2402-78-0; 11, 56467-84-6; 12, 56446-66-3; 13, 56446-67-4; 14, 56446-68-5; 15, 56446-69-6; 16, 56446-70-9; 17a, 61463-65-8; 17b, 61463-66-9; 18, 61463-67-0; 22, 56446-71-0; 23, 61463-68-1; 26, 61463-69-2; 27, 61463-70-5; 28, 61463-71-6; 29, 56446-73-2; 30, 61463-72-7; 31, 61463-73-8; 32, 61463-74-9; 34, 61463-75-0; 35, 61463-76-1; 37, 61463-77-2; 38, 56446-41-4; bis(2-ethoxymethyl) ether, 112-36-7; 2-ethoxyethanol, 110-80-5; ethylene glycol, 107-21-1; diethylene glycol, 111-46-6; triethylene glycol, 112-27-6; 1-methyl-3,6-dioxa-1,8-octanediol, 61463-78-3; propylene oxide, 75-56-9; tetraethylene glycol, 112-60-7; pentaethylene glycol, 4792-15-8; hexaethylene glycol, 2615-15-8.

References and Notes

(1) (a) Preliminary communication, part 20 in this series: G. R. Newkome, G. L. McClure, J. Broussard-Simpson, and F. Danesh-Khoshboo, *J. Am. Chem. Soc.*, **97**, 3232 (1975). (b) Presented in part at the Fifth International Congress of Heterocyclic Chemistry, Ljubljana, Yugoslavia, July 1975.
(2) Synthetic aspects of this area have been reviewed: G. R. Newkome, J. D. Sauer, J. M. Roper, and D. C. Hager, *Chem. Rev.*, in press.
(3) (a) G. R. Newkome and J. M. Robinson, *J. Chem. Soc., Chem. Commun.*, 831 (1973); (b) M. Newcomb, G. W. Gokel, and D. J. Cram, *J. Am. Chem. Soc.*, **96**, 6810 (1974); (c) J. M. Timko, R. C. Helgeson, M. Newcomb, G. W. Gokel, and D. J. Cram, *ibid.*, **96**, 7097 (1974); (d) G. W. Gokel, J. M. Timko, and D. J. Cram, *J. Chem. Soc., Chem. Commun.*, 444 (1975); (e) J.-M. Girodeau, J.-M. Lehn, and J.-P. Sauvage, *Angew. Chem., Int. Ed. Engl.*, **14**, 764 (1975).
(4) (a) K. Tamao, S.-I. Kodama, T. Nakatsuka, Y. Kiso, and M. Kumada, *J. Am. Chem. Soc.*, **97**, 4405 (1975); (b) K. Tamao, S. Kodama, I. Nakajima, T. Nokatsuka, A. Minato, and M. Kumada, *Hukusokan Kagaku Toronkai Koen Yoshishu, 8th*, 174 (1975).
(5) (a) G. R. Newkome and D. Koppersmith, *J. Org. Chem.*, **38**, 4461 (1973); (b) G. R. Newkome, N. B. Islam, and J. M. Robinson, *ibid.*, **40**, 3514 (1975).
(6) G. R. Newkome, J. D. Sauer, and G. L. McClure, *Tetrahedron Lett.*, 1599 (1973).
(7) G. R. Newkome, J. Broussard-Simpson, S. K. Staires, and J. D. Sauer, *Synthesis*, 691 (1974).
(8) E. Staude and F. Patat in "The Chemistry of the Ether Linkage", S. Patai, Ed., Interscience, New York, N.Y., 1967, pp 46–49; R. E. Lubowicz and P. Reich, *Chem. Eng. Prog.*, **67**, 59 (1971).
(9) C. W. Schimelpfenig, *J. Org. Chem.*, **40**, 1493 (1975).
(10) (a) H. Nozaki, S. Fujita, and T. Mori, *Bull. Chem. Soc. Jpn.*, **42**, 1163 (1969); (b) S. Fujita and H. Nozaki, *ibid.*, *44*, 2827 (1971); (c) S. Fujita, K. Imamura, and H. Nozaki, *ibid.*, **45**, 1881 (1972); (d) *ibid.*, **46**, 1579 (1973).
(11) (a) F. Vögtle and E. Weber, *Angew. Chem., Int. Ed. Engl.*, **13**, 149 (1974); (b) F. Vögtle, E. Weber, W. Wehner, R. Nätscher, and J. Grütze, *Chem. Ztg.*, **98**, 562 (1974); (c) E. Weber and F. Vögtle, *Chem. Ber.*, **109**, 1803 (1976); (d) E. Weber and F. Vögtle, *Justus Liebigs Ann. Chem.*, 891 (1976).
(12) F. Vögtle, *Chem. Ind.* (London), 346 (1972).
(13) F. Vögtle, *Tetrahedron*, **25**, 3231 (1969).
(14) S. Fujita, S. Hirano, and H. Nozaki, *Tetrahedron Lett.*, 403 (1972).
(15) D. G. Parsons, *J. Chem. Soc., Perkin Trans. 1*, 245 (1975).
(16) S. Z. Perry and H. Hibbert, *Can. J. Res. Sect. B*, **14**, 77 (1936).
(17) T. Sato, S. Akabori, M. Kainosho, and K. Hata, *Bull. Chem. Soc. Jpn.*, **39**, 856 (1966); J. R. Fletcher and I. O. Sutherland, *Chem. Commun.*, 1504 (1969); I. Gault, B. J. Price, and I. O. Sutherland, *ibid.*, 540, (1967); J. F. Haley, Jr., and P. M. Keehn, *Tetrahedron Lett.*, 4017, 4021 (1973); S. M. Rosenfeld and P. M. Keehn, *J. Chem. Soc., Chem. Commun.*, 119 (1974).
(18) F. Vögtle, *Tetrahedron Lett.*, 3623 (1968); F. Vögtle, *Justus Liebigs Ann. Chem.*, **728**, 17 (1969); F. Vögtle and L. Schunder, *Chem. Ber.*, **102**, 2677 (1969); F. Vögtle and P. Neumann, *Tetrahedron*, **26**, 5299 (1970); V. Boekelheide and P. H. Anderson, *J. Org. Chem.*, **38**, 3928 (1973).
(19) R. H. Mitchell, *Tetrahedron Lett.*, 1363 (1975); R. H. Mitchell, *Can. J. Chem.*, **54**, 238 (1976).
(20) A. F. Gallaugher and H. Hibbert, *J. Am. Chem. Soc.*, **58**, 813 (1936).

Heterocyclic Amines. 7.[1] Preparation and Reactions of 2- and 3-Thienyl Isothiocyanates

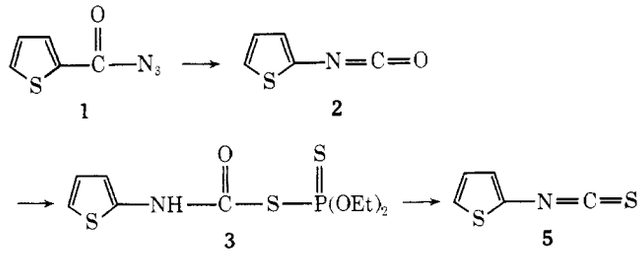
Walter C. McCarthy* and Lanny E. Foss

School of Pharmacy, BG-20, University of Washington, Seattle, Washington 98195

Received September 28, 1976

Both 2- and 3-thienyl isothiocyanates have been prepared by thermal rearrangement of the corresponding *S*-(*N*-thienylcarbamoyl)-*O,O′*-diethyl dithiophosphates. These isothiocyanates have been reacted with a variety of amines, alcohols, and mercaptans to synthesize the 2- and 3-thienyl thioureas, thioncarbamates, and dithiocarbamates.

Isothiocyanates of thiophene have not been previously reported. The classical procedures for the synthesis of aromatic-type isothiocyanates[2] require the corresponding primary amines, which are difficultly accessible in the thiophene series, and require conditions which decompose the unstable aminothiophenes.[1,3,4] Thienyl isocyanates are readily available by Curtius rearrangement of thenoyl azides,[5,6] but the "thio-Curtius" rearrangement does not take place. Attempted preparation of thioacyl azides yields the cyclized thiatriazoles, which thermally decompose to nitriles[7] and sulfur, although small amounts of isothiocyanates have been detected by ultraviolet photolysis[8] of thiatriazoles. Ottmann and Hooks[9] prepared isothiocyanates by thermal decomposition of the reaction product obtained from isocyanates and *O,O′*-diethyl hydrogen dithiophosphate. We have found that by modifying their conditions, it is possible to apply this reaction in the thiophene series to prepare both 2- and 3-thienyl isothiocyanates.



Thenoyl azide (1) was thermally rearranged in boiling carbon tetrachloride to thienyl isocyanate (2). This was reacted with *O,O′*-diethyl hydrogen dithiophosphate, and upon cooling, *S*-(*N*-thienylcarbamoyl)-*O,O′*-diethyl dithiophosphate (3) crystallized. This was thermally rearranged to the thienyl isothiocyanate (5).

Because the thienyl isothiocyanates are labile in acid, it was found necessary to minimize their contact with the