THE JOURNAL OF Organic Chemistry

VOLUME 48, NUMBER 16

AUGUST 12, 1983

Preparation of Macrocyclic Polyether–Thiono Diester and -Thiono Tetraester Ligands Containing either the Pyridine Subcyclic Unit or the Oxalyl Moiety, Their Complexes, and Their Reductive Desulfurization to Crown Ethers

Brian A. Jones, Jerald S. Bradshaw,* Philip R. Brown, James J. Christensen, and Reed M. Izatt

Department of Chemistry and Institute for Thermochemical Studies,† Brigham Young University, Provo, Utah 84602

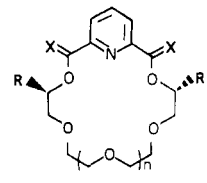
Received January 4, 1983

The preparation of seven new macrocyclic polyether–thiono diesters and one new macrocyclic polyether–thiono tetraester is reported. The new macrocyclic compounds containing a pyridine subcyclic unit formed complexes with metal and alkylammonium salts. Complex formation by some of these ligands was shown by variable-temperature ^1H NMR spectroscopy and by cation transport through a $CHCl_3$ membrane. All of the thiono compounds were reductively desulfurized to form the corresponding crown ethers.

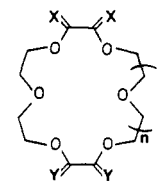
A variety of macrocyclic polyether–diester compounds (the diester crowns) have been prepared via an alkoxide-catalyzed transesterification procedure.[1,2] This method gives higher yields and cleaner products for a majority of systems than the traditional synthetic procedure using diacid chlorides and glycols. Our work on the desulfurization of thiono esters[3] coupled with their known ability to undergo transesterification with alkoxide catalysts[4] prompted us to investigate thiono diesters as macrocycle precursors.

We now report the preparation of new thiono diester (and tetraester in the case of **13**) crowns containing pyridine and oxalate units (**1–5**, **11–13** Chart I). The pyridine-containing crowns are good complexing agents for alkali metal and primary alkylammonium cations.[5–7] Many of the new thiono-substituted pyridino ligands formed stable complexes with a variety of salts. Macrocycle **5** is the dithiono analogue of the chiral dimethyl dioxo compound[8] which exhibited high enantiomeric selectivity when complexed with the enantiomers of chiral amine salts as shown by variable-temperature ^1H NMR spectroscopy, titration calorimetry, and selective crystallization.[9] Not only are these new thiono-substituted crowns interesting for their chemical properties but they also are precursors to the etheral crowns when treated with Raney nickel. Each thiono crown prepared here was subjected to the Raney nickel reductive desulfurization procedure[3,10] to give the series of macrocyclic polyether pyridino crowns **6–10** and crowns **14** and **15**. The pyridino crowns are expected to form thermodynamically stable complexes with bivalent transition-metal ions as well as alkali, alkaline earth, and

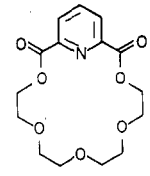
Chart I



1 n=0, R=H, X=S
2 n=1, R=H, X=S
3 n=2, R=H, X=S
4 n=3, R=H, X=S
5 n=1, R=CH_3, X=S
6 n=0, R=H, X=H_2
7 n=1, R=H, X=H_2
8 n=2, R=H, X=H_2
9 n=3, R=H, X=H_2
10 n=1, R=CH_3, X=H_2



11 n=0, X=S, Y=H_2
12 n=1, X=S, Y=H_2
13 n=1, X,Y=S
14 n=0, X,Y=H_2
15 n=1, X,Y=H_2



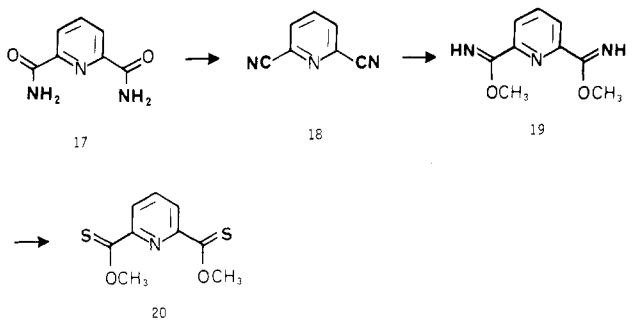
16

† Contribution No. 304 from the Institute for Thermochemical Studies.

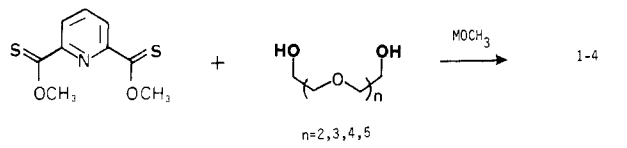
(1) Bradshaw, J. S.; Jones, B. A.; Nielsen, R. B.; Spencer, N. O.; Thompson, P. K. *J. Heterocycl. Chem.*, in press.
(2) Bradshaw, J. S.; Spencer, N. O.; Hansen, G. R.; Izatt, R. M.; Christensen, J. J. *J. Heterocycl. Chem.* **1983**, *20*, 353–357.
(3) Baxter, S. L.; Bradshaw, J. S. *J. Org. Chem.* **1981**, *46*, 831–832.
(4) Scheithauer, S.; Mayer, R. In "Topics in Sulfur Chemistry"; Senning, A., Ed.; Georg Thieme verlag: Stuttgart, 1979; Vol. 4, pp 122–132.
(5) Newcomb, M.; Timko, J. M.; Walba, D. M.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 6392–6398.
(6) Izatt, R. M.; Lamb, J. D.; Asay, R. E.; Maas, G. E.; Bradshaw, J. S.; Christensen, J. J.; Moore, S. S. *J. Am. Chem. Soc.* **1977**, *99*, 6134–6136.

0022-3263/83/1948-2635$01.50/0

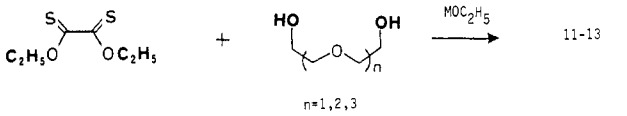
Scheme I



Scheme II



Scheme III



post-transition-metal cations. This expectation, in the case of the bivalent transition-metal ions, is based on the observation[11] that log K for Cu^{2+}–pyridino-18-crown-6 formation in CH_3OH is 4.63. This log K value is the same order of magnitude as those for Na^+ (4.09), K^+ (5.35), Ca^{2+} (5.26), and Ba^{2+} (>5.5).

Results and Discussion

O,O'-Dimethyl 2,6-pyridinedicarbothioate (**20**) was prepared as shown in Scheme I. Dicarbonitrile **18** was sublimed from a mixture of P_2O_5 and diamide **17**. Treatment of **18** with a catalytic amount of $NaOCH_3$ in MeOH gave imino ester **19** which was not purified. Compound **20** was prepared by sulfhydrolysis of **19** in pyridine solution with H_2S. Compound **20** was obtained in 70% overall yield from **18**. *O,O'*-Diethyl dithiooxalate was prepared by the established procedure.[12] The dimethyl ester was not used because of its ready rearrangement to the *S,S'* diester under basic catalysis.[12]

Macrocycles **1–5** and **11–13** were prepared from the appropriate dithiono ester and glycol in benzene by using alkali methoxides as catalysts (see Schemes II and III). The transesterification reaction is an equilibrium process and was forced to completion by azeotropic removal of the product alcohol or by absorbing the alcohol in molecular sieves. Yields ranged from 10% to 71% for the pyridino macrocycles and from 5% to 14% for the thionooxalates. There was a definite template effect in the transesterification reaction to form the macrocycles as the yield of **5** more than doubled when the ring closure was effected in the presence of excess KSCN.

Table I. Dithiono Crown Compounds

compd	yield, %	mp, °C	complex (mp, °C)
1	71	140–141	$NaClO_4$ (232), NaSCN (173–173.5)
2	39	124–125	KSCN (151.5–152.5), $KClO_4$ (205.5 dec), benzylammonium perchlorate (156–156.5)
3	26	124–125	CsSCN (151–151.5)
4	10	51	
5	30 (69)[a]	63.5–64	KSCN (188–188.5)

[a] Ring closure effected in the presence of excess KSCN.

Table II. Cation Flux Values (mol × 10^{-8}, s m^2) Using Compounds **2** and **16**

cation	compd 2	compd 16[a]
Na^+	2.51 ± 0.01	6
K^+	48 ± 21	200
Rb^+	7 ± 2	71
Cs^+	0.9 ± 0.2	4.1
Ca^{2+}	0.4 ± 0.1	2.5
Sr^{2+}	2.3 ± 0.9	35
Ba^{2+}		3.9
blank	>0.7	

[a] Data from ref 16.

Crown ethers **6–10**, **14**, and **15** were prepared in 21–76% yields by treating the dithiono crowns with W-2 Raney nickel.[3] The Raney nickel had to be washed with pyridine at the conclusion of the reaction in order to isolate good yields of the macrocyclic products. Although crowns **8–10** have not been reported previously, **8** and **9** were also prepared in low yields by the reaction of penta- and hexaethylene glycol ditosylates with 2,6-pyridinedimethanol, according to established procedures.[5,13] These products were identical with those prepared by reduction of the thiono esters. Compounds **6**, **7**, **14**, and **15** were identical in all respects with those prepared by others by using a cycloaddition reaction.[5,14,15]

The mass spectra of **1–5** all exhibited similar fragmentation patterns under electron-impact ionization. In addition to peaks for the molecular ions and a series corresponding to cleavage of ethyleneoxy units, all specta exhibited a base peak of 121 mass units. The mass spectra of **8–10** showed strong similarities to those of **6** and **7** described previously in detail.[15] The structures of all new macrocycles were consistent with their IR and NMR spectra, molecular weight determinations, and combustion analyses.

Ligands **1–3** and **5** formed stable crystalline complexes with a variety of salts (Table I). In fact, **2** and **5** could only be purified as the potassium thiocyanate complexes. Ligands **2** and **5** were recovered by converting the thiocyanate complexes to the unstable chloride complexes by ion exchange with Amberlite IRA-400 (chloride form) followed by recrystallization from hexane. It is interesting that the potassium thiocyanate complex of **2** had a molecular weight twice the calculated value. This was not observed for the complex with **5**.

Complexation by these new thiono macrocycles was also shown by their use as cation carriers across H_2O–$CHCl_3$–H_2O liquid membranes.[16] The transport data for

(7) Bradshaw, J. S.; Maas, G. E.; Lamb, J. D.; Izatt, R. M.; Christensen, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 467–474.
(8) Jones, B. A.; Bradshaw, J. S.; Izatt, R. M. *J. Heterocycl. Chem.* **1982**, *19*, 551–556.
(9) Bradshaw, J. S.; Jones, B. A.; Davidson, R. B.; Christensen, J. J.; Lamb, J. D.; Izatt, R. M.; Morin, F. G.; Grant, D. M. *J. Org. Chem.* **1982**, *47*, 3362–3364.
(10) Bradshaw, J. S.; Jones, B. A.; Gebhard, J. S. *J. Org. Chem.* **1983**, *48*, 1127–1129.
(11) Lamb, J. D.; Izatt, R. M.; Swain, C. S.; Christensen, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 475–479.
(12) Hartke, K.; Hoppe, H. *Chem. Ber.* **1974**, *107*, 3121–3129.
(13) Newcomb, M.; Gokel, G. W.; Cram, D. J. *J. Am. Chem. Soc.* **1974**, *96*, 6810–6817.
(14) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017–7034.
(15) Whitney, R. R.; Jaeger, D. A. *Org. Mass. Spectrom.* **1980**, *15*, 343–347.

several alkali and alkaline earth cations are given in Table II for **2** and are compared to values obtained previously[16] for **16**. A correlation has been shown between cation flux and the magnitude of the complex stability constant.[17] The data in Table II indicate that the thionopyridine ligands are somewhat poorer complexing agents than the coresponding dioxopyridine ligands.

Variable-temperature ^1H NMR spectral analysis of the complexes of **2**, **7**, and **16** with benzylammonium perchlorate gave the following values for the free energy of activation for dissociation of the complexes: 13.0, 11.6, and 13.4 kcal/mol, respectively.[7,18] The lower value for **7** by this method was suprising. Macrocycle **7**, because of the higher electron density in its pyridine ring, should form stronger complexes with most cations than **16**. The introduction of carbonyl groups in the macrocycle nearly always leads to a decrease in complex stability.[19] In the pyridine system, however, the carbonyls must play another role. As they are conjugated to the aromatic ring, the most stable conformation is a planar one. Since the macrocycle must adopt a planar configuration to complex with cations, the already planar portion of ligands **2** and **16** appears to assist in the acceptance of the cation. CPK models indicate that the most stable conformation of **7**, which lacks carbonyl groups, is one where the pyridine subcyclic unit is tipped out of the plane of the macrocycle cavity. As energy input is required to attain planarity, the resulting complex is weaker.

Titration calorimetry and variable-temperature ^1H NMR studies are in progress on the interaction of **5** and **10** with optically active amine salts. The results of these experiments will be presented at a later date.

Experimental Section

IR spectra were obtained on a Beckman Acculab 2 spectrometer. The proton and carbon-13 (^1H and ^{13}C) NMR spectra were obtained on a JEOL FX-90Q spectrometer. Mass spectrometric analyses (MS) were obtained on a Hewlett-Packard Model 5982A mass spectrometer using electron-impact ionization. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. Molecular weights were obtained by osmometry on a Hitachi Perkin-Elmer Model 115 molecular weight apparatus. Rotations were determined on a Perkin-Elmer 241 polarimeter. Chromatographic separations were performed on a Waters Prep LC/500 A using Prep Pak 500/silica cartridges. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. All unsubstituted glycols were used as purchased from Aldrich. The (2*S*,12*S*)-4,7,10-trioxatridecane-2,12-diol used to prepare **5** was previously prepared.[8]

***O*,*O*′-Dimethyl 2,6-Pyridinedicarbimidate (19).** 2,6-Pyridinedicarbonitrile (**18**; prepared by sublimation of a mixture of the dicarboxamide **17** and P_2O_5 under vacuum; 50.0 g, 0.387 mol) in 700 mL of CH_3OH was stirred while 2.5 g (38.7 mmol) of sodium methoxide was added. After 2 h, 50% methanolic HCl (2.9 g, 39.8 mmol) was added with stirring, and the CH_3OH was removed under vacuum to give a white solid, which decomposes on standing, and thus it was used immediately in the following step: IR (KBr) 665, 760, 835, 952, 1093, 1198, 1217, 1345, 1437, 1457, 1575, 1650, 3280 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.04 (s, 6 H, CH_3), 7.93 (s, 3 H, Ar H).

***O*,*O*′-Dimethyl 2,6-Pyridinedicarbothioate (20).** The imino ester **19** was added to a suspension of 89.4 g (77.4 mmol) of pyridinium chloride in 700 mL of pyridine in a bomb at 0 °C. Hydrogen sulfide was added until a pressure of 10 psig was maintained. The inlet tube was sealed and the bomb was placed in the freezer for 15 h. The excess H_2S was vented, and the orange pyridine solution was poured into 2 L of ice containing 760 mL of 1.2 M hydrochloric acid. The aqueous slurry was extracted with five portions of 400 mL of CH_2Cl_2. The extracts were combined, washed with 200-mL portions of water and a saturated aqueous NaCl solution, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the product chromatographed in 20-g portions on silica gel with 30% $CHCl_3$/hexane as the eluent. The first yellow band to elute was the product. Evaporation of the solvent followed by recrystallization from CH_3OH gave 61.6 g (70% from **18**) of orange crystals: mp 100–100.5 °C; IR (KBr) 735, 830, 990, 1070, 1080, 1225, 1258, 1308, 1445 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.38 (s, 6 H, CH_3), 7.88 (AB d, 1 H, Ar H, J = 8.1 Hz), 8.50 (d, 2 H, Ar H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$; proton decoupled) δ 59.9, 127.4, 137.0, 152.5, 208.9; MS (EI), m/e (relative intensity) 75 (16.8), 94 (6.0), 109 (5.8), 121 (34.0), 138 (18.6), 152 (4.9), 165 (100.0), 197 (84.7), 212 (14.3), 227 (M^+, 81.6). Anal. Calcd for $C_7H_9NO_2S_2$: C, 47.56; H, 3.99, mol wt 227.3. Found: C, 47.36; H, 3.94; mol wt 227.8.

General Procedure for the Preparation of Macrocyclic Compounds. The dithiono ester and glycol were combined in 700 mL of dry benzene. **Method A**: Molecular sieves (4 Å) were added to the solution, and after the mixture was stirred for 1 h, 0.1 mL of 30% alkali metal methoxide solution in CH_3OH was added. Stirring was continued until TLC (silica gel/$CHCl_3$) showed that all the starting material had reacted. Acetic acid (0.5 mL) was then added and the sieves were filtered and washed with CH_2Cl_2. The filtrate and washings were combined and the solvents removed under reduced pressure. **Method B**: Molecular sieves were placed in a Soxhlet thimble, and the solution was refluxed through the Soxhlet for 1 h. Alkali metal methoxide (0.1 mL of 30% solution in CH_3OH) was added to the flask and refluxing continued until TLC showed that the starting material had reacted. Acetic acid (0.5 mL) was added, and the solvent was removed under reduced pressure. Specific details are given for each compound.

3,6,9,12-Tetraoxa-18-azabicyclo[12.3.1]octadeca-1(18),14,16-triene-2,13-dithione (1). Compound **20** (6.95 g, 30.6 mmol) and 4.65 g (31 mmol) of triethylene glycol were used in method B with $NaOCH_3$ as the catalyst. The product was recrystallized from CH_3OH (700 mL) to give yellow plates: 6.76 g (71%); mp 140–141 °C; IR (KBr) 830, 1085, 1130, 1140, 1220, 1255, 1280, 2860 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.94 (s, 4 H, CH_2), 4.02 (m, 4 H, $CSOCH_2CH_2$), 4.76 (m, 4 H, $CSOCH_2$), 7.85 (AB d, 1 H, Ar H, J = 8.1 Hz), 8.56 (d, 2 H, Ar H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$; proton decoupled) δ 68.4, 70.1, 72.4, 128.3, 137.2, 152.3, 208.2; MS (EI), m/e (relative intensity) 105 (27.9), 121 (100.0), 137 (30.5), 139 (29.4), 165 (40.7), 200 (16.1), 252 (13.7), 267 (18.3), 280 (20.0), 313 (M^+, 6.4). Anal. Calcd for $C_{13}H_{15}NO_4S_2$: C, 49.82; H, 4.82; mol wt 313.4. Found: C, 49.94; H, 4.67; mol wt 312.9.

3,6,9,12,15-Pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dithione (2). Compound **20** (16.95 g, 74.6 mmol) and tetraethylene glycol (14.49 g, 74.6 mmol) were used in method B with $KOCH_3$ as the catalyst. The product was isolated by continuous extraction with hexane followed by recrystallization from CH_3OH to give 15.1 g of crude product, mp 110–120 °C. This material was purified through its KSCN complex as follows: the crude **2** was dissolved in 200 mL of 2-propanol, and 4.5 g of KSCN was added. After the mixture was stirred for 1 h, 100 mL of toluene was added, and the solution was filtered to remove excess salt. The solution was heated, and toluene was added until crystallization began. The mixture was then placed in the freezer. When precipitation was complete, the orange crystals were filtered, washed with toluene, and dried to give the product: 17.9 g (93% from crude **2**); mp 151.5–152.5 °C; IR (KBr) 950, 1065, 1089, 1119, 1239, 2029 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.81 (s, 8 H, OCH_2), 4.00 (m, 4 H, $CSOCH_2CH_2$), 5.09 (m, 4 H, $CSOCH_2$), 7.91 (AB d, 1 H, Ar H, J = 7.2 Hz), 8.60 (d, 2 H, Ar H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$; proton decoupled) δ 68.3, 69.7, 70.4, 73.1, 130.7, 137.7, 153.2, 208.2; calcd for $C_{16}H_{19}O_5S_3K$ mol wt 455, found mol wt 910.

Compound **2** was recovered from its KSCN complex by forming the unstable chloride complex by ion exchange with Amberlite IRA-400 (chloride form) with 2-propanol as the solvent. The solvent was removed under vacuum, and the product was dissolved

(16) Lamb, J. D.; Izatt, R. M.; Garrick, D. G.; Bradshaw, J. S.; Christensen, J. J. *J. Membr. Sci.* **1981**, *9*, 83–107.
(17) Lamb, J. D.; Christensen, J. J.; Oscarson, J. L.; Nielsen, B. L.; Asay, B. W.; Izatt, R. M. *J. Am. Chem. Soc.* **1980**, *102*, 6820–6825.
(18) Baxter, S. L.; Bradshaw, J. S. *J. Heterocycl. Chem.* **1981**, *18*, 233–245.
(19) Lamb, J. D.; Izatt, R. M.; Swain, C. S.; Bradshaw, J. S.; Christensen, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 479–482.

in hexane. The insoluble material was filtered, and the hexane was removed under vacuum. The resulting product was recrystallized from CH_3OH to give orange prisms: 10.3 g (39% overall); mp 124–125 °C; IR (KBr) 857, 945, 1080, 1120, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.78 (s, 8 H, OCH_2), 4.06 (m, 4 H, $CSOCH_2CH_2$) 4.87 (m, 4 H, $CSOCH_2$), 7.85 (m, 1 H, Ar H), 8.57 (d, 2 H, Ar H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$; proton decoupled) δ 68.2, 70.4, 71.3, 73.6, 129.1, 136.8, 152.0, 209.3; MS (EI), m/e (relative intensity) 73 (30.6), 105 (37.0), 117 (46.0), 121 (100.0), 139 (36.5), 166 (24.0), 296 (30.6), 358 (M^+, 1.0). Anal. Calcd for $C_{15}H_{19}NO_5S_2$: C, 50.40; H, 5.36; mol 357.4. Found: C, 50.59; H, 5.40; mol wt 360.2.

3,6,9,12,15-Hexaoxa-24-azabicyclo[18.3.1]tetracosa-1(24),20,22-triene-2,19-dithione (3). Compound **20** (9.3 g, 41 mmol) and pentaethylene glycol (9.8 g, 41 mmol) were used in method B with $RbOCH_3$ as the catalyst. The product was isolated by chromatography on silica gel with 30% $CHCl_3$/hexane as the eluent, followed by recrystallization from CH_3OH to give a yellow powder: 4.2 g (26%); mp 124–125 °C; IR (KBr) 833, 868, 960, 1092, 1120, 1223, 1260, 1297, 2880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.64 (s, 4 H, OCH_2), 3.78 (m, 8 H, OCH_2), 4.06 (m, 4 H, $CSOCH_2CH_2$), 4.90 (, 4 H, $CSOCH_2$), 7.85 (m, 1 H, Ar H), 8.49 (d, 2 H, Ar H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$; proton decoupled) δ 68.1, 70.5, 70.7, 71.0, 73.0, 128.3, 136.7, 152.7, 208.9; MS (EI), m/e (relative intensity) 73 (43.8), 121 (100.0), 139 (49.7), 149 (12.9), 166 (43.5), 182 (12.4), 340 (30.3), 368 (9.6), 402 (M^+, 0.6). Anal. Calcd for $C_{17}H_{23}NO_6S_2$: C, 50.86; H, 5.77; mol wt 401.5. Found: C, 50.68; H, 5.56; mol wt 375.

3,6,9,12,15,18,21-Heptaoxa-27-azabicyclo[21.3.1]heptacosa-1(27),23,25-triene-2,22-dithione (4). Compound **20** (10.0 g, 44 mmol) and hexaethylene glycol (12.4 g, 44 mmol) were used in method A with $CsOCH_3$ as the catalyst. The product was purified to ca. 90% purity by chromatography on silica gel with 45% acetone/35% $CHCl_3$/20% hexane as the eluent to give an orange oil, 2.0 g (10%). About 100 mg of the product was purified on a thick-layer silica gel plate with 40% acetone/$CHCl_3$ as the eluent. The product was recrystallized from Et_2O/pentane to give yellow flakes: mp 51 °C; IR (KBr) 850, 1082, 1126, 1222, 1262, 1295, 2865 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.4–3.9 (m, 16 H, OCH_2), 4.06 (m, 4 H, $CSOCH_2CH_2$), 4.90 (m, 4 H, $CSOCH_2$), 7.85 (AB d, 1 H, Ar H, J = 7.6 Hz), 8.48 (d, 2 H, Ar H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$; proton decoupled) δ 68.5, 70.8, 71.3, 73.2, 128.1, 137.0, 153.2, 209.1; MS (EI), m/e (relative intensity) 73 (48.2), 121 (100.0), 139 (51.0), 166 (62.8), 200 (21.8), 226 (20.2), 384 (22.1), 446 (M^+, 4.2). Anal. Calcd for $C_{19}H_{27}NO_7S_2$: C, 51.22; H, 6.11; mol wt 446. Found: C, 50.97; H, 6.28; mol wt 417.

(4*S*,14*S*)-4,14-Dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dithione (5). Compound **20** (12.0 g, 52.8 mmol) and (2*S*,12*S*)-4,7,10-trioxatridecane-2,12-diol (11.7 g, 52.8 mmol) were used in method A with $KOCH_3$ as the catalyst. This compound was purified through its KSCN complex as follows: the crude **5** was taken up in 250 mL of $CHCl_3$ and stirred with KSCN (5.5 g, 57 mmol) for 1 h. The excess salt was filtered, and 400 mL of toluene was added to the filtrate. The solution was concentrated under reduced pressure to a volume of 200 mL. The precipitated complex was collected by filtration, washed with toluene, and dried under vacuum to give 7.8 g of yellow flakes: mp 188–188.5 °C; $[\alpha]^{22}_D$ −529° (*c* 0.50, $CHCl_3$); IR (KBr) 914, 1083, 1120, 1244, 1283, 2060, 2900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54 (d, 6 H, CH_3, J = 6.3 Hz), 3.6–4.3 (m, 12 H, OCH_2), 6.06 (m, 2 H, $OCHCH_3$) 7.96 (AB d, 1 H, Ar H, J = 7.6 Hz), 8.57 (d, 2 H, Ar H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$; proton decoupled) δ 14.8, 68.9, 70.4, 71.6, 79.7, 130.4, 137.3, 152.8, 207.3; calcd for $C_{18}H_{23}N_2O_5S_3K$ mol wt 482.7, found mol wt 450.0.

Compound **5** was recovered from its KSCN complex by forming the unstable chloride complex by ion exchange with Amberlite CG-400 (chloride form) which had been previously washed with 2-propanol and then $CHCl_3$. The solvents were removed under vacuum, and the product was dissolved in hexane. The insoluble salts were removed by filtration, and the product was crystallized from the cooled solution: 6.1 g (30% overall); very long yellow needles; mp 63.5–64 °C; $[\alpha]^{29}_D$ −580° (*c* 1.00, $CHCl_3$); IR (KBr) 849, 932, 1102, 1140, 1263, 1304, 2910, 3350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (d, 6 H, CH_3, J = 6.3 Hz), 3.6–4.1 (m, 12 H, OCH_2), 5.88 (m, 2 H, $OCHCH_3$), 7.82 (m, 1 H, Ar H), 8.41 (d, 2 H, Ar H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$; proton decoupled) δ 15.0, 70.9, 72.0, 73.0, 79.9, 128.4, 136.7, 154.0, 209.5; MS (EI), m/e (relative intensity) 73 (70.4), 105 (84.2), 117 (49.7), 121 (100.0), 139 (27.6), 166 (32.2), 200 (17.2), 324 (53.9), 385 (M^+, 0.4). Anal. Calcd for $C_{17}H_{23}NO_5S_2$: C, 52.97; H, 6.01; mol wt 385.5. Found: C, 52.60; H, 6.04; mol wt 382.

The synthesis of compound **5** was repeated as above only in the presence of excess KSCN. The complex was isolated directly in a 70% yield. The free ligand was obtained in an overall 69% yield.

3,6,9,12-Tetraoxa-18-azabicyclo[12.3.1]octadeca-1(18),14,16-triene (6). Compound 1 (250 mg, 0.80 mmol) was dissolved in 10 mL of dry tetrahydrofuran (THF). The solution was added to a suspension of 12 g of W-2 Raney nickel in 10 mL of THF at −10 °C. The Raney nickel had previously been washed ten times with EtOH and ten times with THF. The mixture was shaken at 0 to −10 °C until the yellow color disappeared (about 1 min). The solution was then filtered, and the nickel was washed with 20-mL portions of 95% EtOH and water. The filtrate and washings were combined and the solvents removed under reduced pressure to give 90 mg (40%) of oil. The ^1H NMR and mass spectra of the oil gave data identical with those for authentic **6**.[14]

3,6,9,12,15-Pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (7). Compound **2** (3.0 g, 8.4 mmol) was dissolved in 200 mL of anhydrous Et_2O and 100 mL of CH_2Cl_2 and was added to 120 g of Raney nickel (treated as above) in 100 mL of anhydrous Et_2O at 0 °C. The mixture was shaken until the orange color disappeared (about 1 min). The suspension was filtered and the solid was washed with 100-mL portions of pyridine, EtOH, and then water. Without the pyridine wash, the yield of product **7** was only 2%. The filtrate and washings were combined, and the solvents were removed under vacuum to give an oil. The product was purified by chromatography on alumina with 1% EtOH/$CHCl_3$ as the eluent and distilled [145 °C (0.1 torr)]: 1.3 g (56%); mp 40 °C. Data from ^1H NMR and mass spectra were identical with those for authentic **7**.[13,15] The ^1H NMR spectrum of **7** complexed with benzylammonium perchlorate showed two peaks of equal intensities separated by 84 Hz, for the hydrogens on the carbon atoms next to the pyridine ring at −60 °C. These peaks coalesced at −30 °C.

3,6,9,12,15,18-Hexaoxa-24-azabicyclo[18.3.1]tetracosa-1(24),20,22-triene (8). Compound **3** (2.00 g, 4.98 mmol) was treated with 80 g of Raney nickel as reported above in 50% $CHCl_3/Et_2O$. The product was filtered and the nickel washed with 30-mL portions of pyridine, EtOH, and water. The filtrate and washings were combined, and the solvents were removed under reduced pressure. The product was chromatographed on alumina with 1.5% EtOH/$CHCl_3$ as the eluent to give an oil: 1.29 g (76%); IR (neat) 1112, 1350, 1452, 1576, 1590, 2860 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.5–3.8 (m, 20 H, OCH_2), 4.69 (s, 4 H, Ar CH_2), 7.28 (d, 2 H, Ar H, J = 8.1 Hz), 7.67 (AB d, 1 H, Ar H, J = 8.1 Hz); MS (EI), m/e (relative intensity) 89 (78.3), 107 (78.0), 122 (100.0), 136 (34.9), 150 (33.0), 164 (46.8), 210 (16.2), 254 (20.4), 341 (M^+, 1.9). Anal Calcd for $C_{17}H_{27}NO_6$: C, 59.81; H, 7.97. Found: C, 59.77; H, 8.11.

This compound was also prepared by the traditional Williamson ether synthesis. Pentaethylene glycol ditosylate (32.7 g, 56 mmol) and 2,6-pyridinedimethanol (8.3 g, 56 mmol) were reacted in 200 mL of THF with NaH as the base.[15] The product was purified by distillation and chromatography (alumina) to give 0.3 g (1.5%) of **8** which was identical with the product described above.

3,6,9,12,15,18,21-Heptaoxa-27-azabicyclo[21.3.1]heptacosa-1(27),23,25-triene (9). Compound **4** (102 mg, 0.229 mmol) in 20 mL of anhydrous ether was treated with 7 g of Raney nickel as above. The mixture was filtered and washed successively with 5-mL portions of pyridine, EtOH, and water. The filtrate and washings were combined, and the solvents were removed under vacuum. The product was dissolved in 20 mL of $CHCl_3$. The solids were filtered, and the $CHCl_3$ was removed under vacuum. The oil was purified by bulb to bulb distillation at 135 °C (0.01 mm): 35.2 mg (40%); IR (film) 1112, 1350, 1452, 1576, 1590, 2860 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.5–3.8 (m, 24 H, OCH_2), 4.68 (s, 4 H, Ar CH_2), 7.40 (d, 2 H, Ar H, J = 8.1 Hz), 7.84 (AB d, 1 H, Ar H, J = 8.1 Hz); MS (EI), m/e (relative intensity) 107 (70.0), 122 (100.0), 136 (33.3), 149 (87.6), 164 (54.2), 210 (21.6), 254 (21.6), 298 (12.6), M^+ unobserved. Anal. Calcd for $C_{19}H_{31}NO_7 \cdot H_2O$: C, 56.56; H, 8.25. Found: C, 56.98; H, 8.53.

This compound was also prepared by the traditional Williamson ether synthesis. Hexaethylene glycol ditosylate (32.6 g, 55 mmol) and 2,6-pyridinedimethanol (7.68 g, 5 mmol) were used.[15] The product was purified by distillation [bp 197 °C (0.02 mm)] and chromatography on alumina to give 1.85 g (8.7%) of **9** which was identical with the product described above.

(4*S*,14*S*)-4,14-Dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (10). Compound **5** (2.00 g, 5.19 mmol) in 250 mL of anhydrous Et_2O was shaken 1 min at 0 °C with 80 g of Raney nickel as reported above. The solution was filtered and the nickel washed successively with 50-mL portions of pyridine, EtOH, and water. The filtrate and washings were combined, the solvents were removed under vacuum, and the residue was dissolved in 50 mL of $CHCl_3$. The undissolved solid was filtered and the product isolated by distillation [bp 141 °C (0.02 mm)]: 0.95 g (56%); $[\alpha]^{22}_D$ +40.7° (*c* 1.00, $CHCl_3$); IR (film) 1115, 1332, 1370, 1451, 1575, 1589, 2865 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (d, 6 H, CH_3, J = 5.8 Hz), 3.3–4.0 (m, 14 H, OCH_2), 4.80 (s, 4 H, Ar CH_2), 7.22 (d, 2 H, Ar H, J = 8.1 Hz), 7.62 (AB d, 1 H, Ar H, J = 8.1 Hz); MS (EI), *m/e* (relative intensity) 78 (30.6), 107 (48.2), 122 (50.7), 136 (29.7), 150 (14.8), 164 (100.0), 224 (17.5), 268 (13.3), 325 (M^+, 2.3). Anal. Calcd for $C_{17}H_{27}NO_5$: C, 62.75; H, 8.36. Found: C, 62.62; H, 8.59.

General Procedure for the Preparation of Complexes of the Macrocyclic Ligands. The macrocycle (40 mg) in 8 mL of $CHCl_3$ was stirred for 1 h with excess salt. The solution was filtered, 10 mL of toluene was added to the filtrate, and the solution was slowly concentrated until crystals appeared. The solution was then placed in the freezer until precipitation was complete. The crystalline complex was filtered and washed with 5 mL of toluene. Recrystallization from $CHCl_3$/toluene gave the pure complex. Specific details are presented with each compound.

Sodium Perchlorate Complex of 1. Compound **1** and anhydrous $NaClO_4$ were used to give yellow crystals: 41.2 mg (74%); mp 232 °C dec; IR (KBr) 1080, 1135, 1255, 1277 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.06 (s, 4 H, CH_2), 4.23 (m, 4 H, $CSOCH_2CH_2$), 5.06 (m, 4 H, $CSOCH_2$), 8.41 (m, 1 H, Ar H), 9.04 (d, 2 H, Ar H, J = 8.5 Hz).

Sodium Thiocyanate Complex of 1. Compound **1** and anhydrous $NaClO_4$ were used to give yellow crystals: 40 mg (80%); mp 173–173.5 °C; IR (KBr) 828, 862, 935, 1080, 1125, 1240, 1260, 2985 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.94 (s, 4 H, CH_2), 4.08 (m, 4 H, $CSOCH_2CH_2$), 4.90 (m, 4 H, $CSOCH_2$), 8.00 (AB d, 1 H, Ar H, J = 8.2 Hz) 8.66 (d, 2 H, Ar H, J = 8.2 Hz).

Potassium Perchlorate Complex of 2. Compound **2** and anhydrous $KClO_4$ were used to give yellow crystals: 11 mg (20%); mp 205.5 °C dec; IR (KBr) 625, 955, 1090, 1118, 1125, 1245, 2880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.78 (s, 8 H, CH_2), 4.05 (m, 4 H, $CSOCH_2CH_2$), 4.92 (m, 4 H, $CSOCH_2$), 7.86 (AB d, 1 H, Ar H, J = 7.6 Hz), 8.59 (d, 2 H, Ar H, J = 7.6 Hz).

Benzylammonium Perchlorate Complex of 2. Compound **2** and a stoichiometric amount of benzylammonium perchlorate were used to give yellow crystals: 57 mg (90%); mp 156–156.5 °C; IR (KBr) 620, 702, 760, 1090, 1285, 2920, 3090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.6–4.1 (m, 14 H, $PhCH_2$, CH_2), 4.81 (m, 4 H, $CSOCH_2$), 7.1–7.4 (m, 5 H, PhH), 7.99 (AB d, 1 H, Pyr H, J = 7.3 Hz), 8.45 (br s, 3 H, NH_3), 8.55 (d, 2 H, Pyr H, J = 7.3 Hz). When the temperature was lowered to −50 °C, the peak at δ 4.92 separated into two peaks of equal intensity separated by 243 Hz. These peaks coalesced at 10 °C.

Cesium Thiocyanate Complex of 3. Compound **3** and CsSCN were used to give yellow crystals: 40 mg (68%); mp 151–151.5 °C; IR (KBr) 960, 1090, 1105, 1118, 1208, 1220, 1255, 1270, 1290, 1439, 2040, 2910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.81 (s, 4 H, CH_2), 3.88 (s, 8 H, CH_2), 4.16 (m, 4 H, $CSOCH_2CH_2$), 5.30 (m, 4 H, $CSOCH_2$), 8.21 (AB d, 1 H, Ar H, J = 8.1 Hz), 8.99 (d, 2 H, Ar H, J = 8.1 Hz).

1,4,7,10,13-Pentaoxacyclopentadecane-2,3-dithione (11). *O,O'*-Diethyl dithiooxalate (6.53 g, 34 mmol), prepared by the method of Hartke and Hoppe,[12] and 6.0 g (34 mmol) of tetraethylene glycol were used in method A with NaOEt as the catalyst and with 5-Å molecular sieves. The product was isolated by chromatography on silica gel with CCl_4/CH_2Cl_2 as the eluent. The product was recrystallized from acetone/hexane to give 0.46 g (4.9%) of yellow needles: mp 108.5 °C; IR (KBr) 1060, 1118, 1135, 1150, 1275, 2900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.70 (s, 4 H, OCH_2), 3.89 (m, 4 H, $CSOCH_2CH_2$), 4.71 (m, 4 H, $CSOCH_2$); ^{13}C NMR ($CDCl_3$; proton decoupled) δ 67.8, 69.9, 70.7, 72.3, 203.8. Anal. Calcd for $C_{10}H_{16}O_5S_2$: C, 42.84; H, 5.75; mol wt 280. Found: C, 42.86; H, 5.79; mol wt 270.

1,4,7,10,13,16-Hexaoxacyclooctadecane-2,3-dithione (12). *O,O'*-Diethyl dithiooxalate (5.50 g, 31 mmol) and pentaethylene glycol (7.34 g, 31 mmol) were used in method B with $NaOCH_3$ as the catalyst and with 5-Å molecular sieves. The product was isolated by extraction with hot hexane followed by recrystallization from $CHCl_3$/heptane to give orange plates: 1.42 g (14.2%); mp 136–137 °C; IR (KBr) 1062, 1100, 1126, 1260, 2890 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.66 (s, 4 H, OCH_2), 3.68 (s, 8 H, OCH_2), 3.90 (m, 4 H, $CSOCH_2CH_2$), 4.74 (m, 4 H, $CSOCH_2$); ^{13}C NMR ($CDCl_3$; proton decoupled) δ 68.0, 70.4, 70.6, 70.9, 72.6, 205.4. Anal. Calcd for $C_{12}H_{20}O_6S_2$: C, 44.43; H, 6.21; mol wt 324. Found: C, 44.20; H, 6.14; mol wt 310.

1,4,7,10,13,16-Hexaoxacyclooctadecane-2,3,11,12-tetrathione (13). *O,O'*-Diethyl dithiooxalate (10.0 g, 56 mmol) and diethylene glycol (5.95 g, 56 mmol) were used in method B with NaOEt as the catalyst and with 5-Å molecular sieves. The product was isolated by cooling the benzene to 25 °C and collected by filtration. The yellow needles were recrystallized from $CHCl_3$/heptane: 1.0 g (9.6%); mp 169.5–170 °C; IR (KBr) 1050, 1078, 1092, 1131, 1272 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.91 (m, 8 H, $CSOCH_2CH_2$), 4.72 (m, 8 H, $CSOCH_2$). Anal. Calcd for $C_{12}H_{16}O_6S_4$: C, 42.84; H, 5.75; mol wt 280. Found: C, 42.86; H, 5.79; mol wt 269.

1,4,7,10,13-Pentaoxacyclopentadecane (15-Crown-5, 14). Compound **11** (100 mg, 0.36 mmol) was dissolved in 10 mL of 50% CH_2Cl_2 in Et_2O and shaken 1 min at 0 °C with 6 g of Raney nickel (treated as above) in 10 mL of Et_2O. The nickel was filtered and washed successively with 10-mL portions of pyridine, EtOH, and water. The filtrate and washings were combined, and the solvents were removed under reduced pressure. The residue was dissolved in $CHCl_3$. The product (52%) was proved by comparison with an authentic sample by vapor-phase chromatography (VPC).

1,4,7,10,13,16-Hexaoxacyclooctadecane (18-Crown-6, 15). Compound **12** (100 mg, 0.308 mmol) and 6 g of Raney nickel (treated as above) were used as in the preparation of **14** to give **15** in a 45% yield. Compound **13** (100 mg, 0.260 mmol) and 12 g of Raney nickel were used in the preparation of **14** to give **15** in a 21% yield. The products were verified by VPC analysis.

Acknowledgment. Financial support by the National Science Foundation (Grant No. CPE-8119634) is gratefully acknowledged.

Registry No. **1**, 86309-67-3; **1** $NaClO_4$ complex, 86309-58-2; **1** NaSCN complex, 86309-59-3; **2**, 86309-68-4; **2** KSCN complex, 86309-61-7; **2** $KClO_4$ complex, 86309-62-8; **2** $PhCH_2NH_3ClO_4$ complex, 86309-69-5; **3**, 86309-70-8; **3** CsSCN complex, 86309-64-0; **4**, 86309-71-9; **5**, 86309-72-0; **5** KSCN complex, 86309-66-2; **6**, 77877-86-2; **7**, 53914-89-9; **8**, 86309-73-1; **9**, 86309-74-2; **10**, 86309-75-3; **11**, 86309-76-4; **12**, 86309-77-5; **13**, 86309-78-6; **14**, 33100-27-5; **15**, 17455-13-9; **18**, 2893-33-6; **19**, 55309-58-5; **20**, 84877-69-0; Na^+, 17341-25-2; K^+, 24203-36-9; Rb^+, 22537-38-8; Cs^+, 18459-37-5; Ca^{2+}, 14127-61-8; Sr^{2+}, 22537-39-9; Ba^{2+}, 22541-12-4; triethylene glycol, 112-27-6; tetraethylene glycol, 112-60-7; pentaethylene glycol, 4792-15-8; hexaethylene glycol, 2615-15-8; (2*S*,12*S*)-4,7,10-trioxatridecane-2,12-diol, 76946-26-4; pentaethylene glycol ditosylate, 41024-91-3; 2,6-pyridinedimethanol, 1195-59-1; hexaethylene glycol ditosylate, 42749-27-9; *O,O'*-diethyl dithiooxalate, 54129-84-9; diethylene glycol, 111-46-6.