temperature for 4 days, 130 mg (21.8%) of **4b** and 390 mg (65.5%) of **3b**.

Treatment of β-Lactone 5 Dimer of TBCK with 2-(Dimethylamino)-5-methyl-1,3-thiazole (1b). A solution of TBCK (4 mmol) in 20 mL of benzene was treated at room temperature with a few drops of Et_3N. After 21 h the IR spectrum of the solution did not show the presence of the ketene absorption at 2130 cm^{-1}. Addition of 284 mg (2 mmol) of **1b** in 20 mL of benzene resulted (TLC) in immediate formation of a mixture of products. The solvent was removed under reduced pressure, and the residue was chromatographed (silica, 9:1 benzene–ethyl ether) to give 362 mg (90%) of 1,3-di-*tert*-butyl-1,3-dicyanoallene (**6**), mp 50–51 °C (lit. mp 50.5–51.5 °C),[15] and 250 mg of unchanged **1b**.

Thermolysis of Thiazolo[4,5-*d*]-2-tetrahydropyranone (3a). Method A. A benzene solution (20 mL) containing 187 mg (0.5 mmol) of **3a** was refluxed for 48 h. The solvent was removed under reduced pressure, and the crude mixture was chromatographed (silica, 2:2:1 benzene–ethyl ether–cyclohexane) to give 145 mg (77.5%) of **4a**, 35 mg (18%) of **3a**, and 8 mg (5%) of **2**.

Method B. A methanol solution (20 mL) containing 200 mg (0.53 mmol) of **3a** was refluxed for 12 h. The usual workup as detailed above gave 15 mg (7%) of **4a** and 120 mg (90%) of **2**.

Thermolysis of Thiazolo[4,5-*d*]-2-tetrahydropyranone (3b). Method A. A benzene solution (20 mL) containing 321 mg (0.82 mmol) of **3b** was refluxed for 29 h. The solvent was removed under reduced pressure, and the residue was chromatographed (silica, 2:2:1 benzene–ethyl ether–cyclohexane) to give 200 mg (62.3%) of **4b**, 75 mg (23%) of unaltered **3b**, and 9.7 mg (8.5%) of **1b**.

Method B. A methanol solution (20 mL) containing 148 mg (0.38 mmol) of **3b** was refluxed for 12 h and then worked up by the usual procedure. Chromatography (silica, 9:1 benzene–ethyl ether) gave 53 mg (33%) of Δ^2-thiazoline **9** and 34 mg (62%) of **1b**. Compound **9** gave the following: mp 105–107 °C (from *n*-hexane); IR (KBr) 2240 (C≡N), 1720 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (s, 9, CMe_3), 1.26 (s, 9, CMe_3), 1.98 (s, 3, CH_3), 3.02 (s, 6, NMe_2), 3.82 (s, 3, OCH_3), 4.0 (s, 1, >CH), 4.85 (s, 1, >CH); mass spectrum *m/e* (relative intensity) 364 ($M^+ - CMe_3$, 13), 349 (15), 266 (50), 181 (11), 180 (13), 142 (100), 88 (15), 57 (24).

Anal. Calcd for $C_{21}H_{23}N_4O_3S$: C, 59.98; H, 7.67; N, 13.32; S, 7.61. Found: C, 60.14; H, 7.54; N, 13.48; S, 7.84.

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Registry No. **1a**, 6142-08-1; **1b**, 52963-36-7; **2**, 72228-68-3; **3a**, 72228-69-4; **3b**, 72228-70-7; **4a**, 72258-09-4; **4b**, 72258-10-7; **5**, 72244-63-4; **6**, 36982-41-9; **9**, 72228-71-8; **10**, 72228-72-9; TBCK, 29342-22-1.

Nicotinic Acid Crown Ethers.[1] Synthesis of Macrocyclic Lactones from 2-Chloronicotinic Acid and Polyethylene Glycols. Template Effect on the Cyclization

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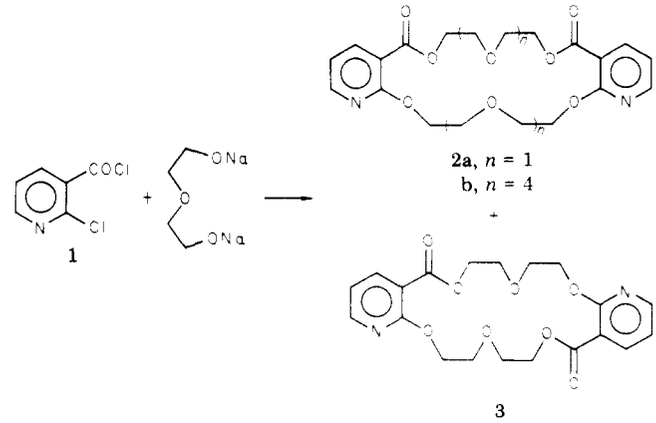
Crown ethers possessing a 2-oxanicotinate moiety were prepared by simple reaction of 2-chloronicotinoyl chloride with disodium di- and pentaethylene glycolates. Transesterification and the template effect on this cyclization were observed; they resulted in the 1:1 lactonic macrocycles as the major product.

During the course of our studies of pyridine-linked nucleotide [NAD(H)] models, the synthesis and chemistry of numerous 2,6-disubstituted nicotinic acid derivatives were conducted.[3] Evaluation of 2- vs. 6-nucleophilic displacement of halide ions on nicotinic acid derivatives has suggested that the 2-chloro substituent is displaced faster than the related 6-halide.[4] In view of the few examples of pyridine macrocyclic lactones[5] and the limited reported chemistry of these substituted nicotinate derivatives, 2-chloronicotinic acid was transformed into a subheterocyclic unit within a crown ether backbone.

Results and Discussion

2-Chloronicotinic acid was smoothly converted by refluxing in excess thionyl chloride[6] into 2-chloronicotinoyl chloride (**1**). Treatment of **1** with 1 equiv of disodium diethylene glycolate in refluxing xylene (138 °C) for 24 h gave an isomeric mixture of **2a** and **3** in 7.4 and 6.9% isolated yield, respectively. As noted previously in related



macrocycles,[7] the anti isomer (**3**) has generally the higher melting point. Definitive structure proof of both **2a** and **3** is based on lactone fragmentation upon treatment with

(1) Chemistry of Heterocyclic Compounds Series, 54. For the previous paper in this series, see: Newkome, G. R.; Kawato, T. *J. Am. Chem. Soc.* **1979**, *101*, 7088.

(2) (a) On leave from Kyushu University, Fukuoka, Japan (1977–1979). (b) Undergraduate Researcher.

(3) (a) Newkome, G. R.; Kawato, T. *Tetrahedron Lett.* **1978**, 4638. (b) *Ibid.* **1978**, 4643. (c) *J. Org. Chem.* **1979**, *44*, 2693. (d) *Ibid.*, in press. (e) Newkome, G. R.; Nayak, A.; Kawato, T. *Ibid.* **1979**, *44*, 2697. (f) Newkome, G. R.; Kawato, T., submitted for publication in *J. Org. Chem.*

(4) Kawato, T., unpublished results, 1979.

(5) Newkome, G. R.; Sauer, J. D.; Roper, J. M.; Hager, D. C. *Chem. Rev.* **1977**, *77*, 513. Bradshaw, J. S.; Maas, G. E.; Izatt, R. M.; Christensen, J. J. *Ibid.* **1979**, *79*, 37.

(6) Bernstain, J.; Losee, K. A. U.S. Patent 2713049; *Chem. Abstr.* **1956**, *50*, 7148. Meyer, H.; Graf, R. *Chem. Ber.* **1928**, *61B*, 2202.

(7) Newkome, G. R.; Nayak, A.; Otemaa, J.; Van, D. A.; Benton, W. H. *J. Org. Chem.* **1978**, *43*, 3362. Fronczek, F.; Nayak, A.; Newkome, G. R. *Acta Crystallogr., Sect. B* **1979**, 775.

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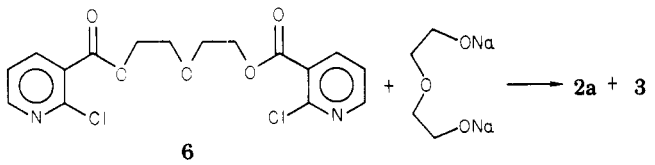
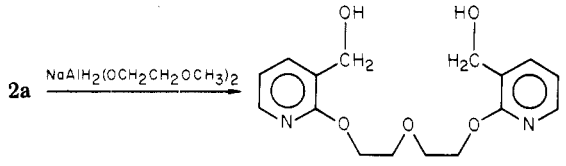
Scheme I



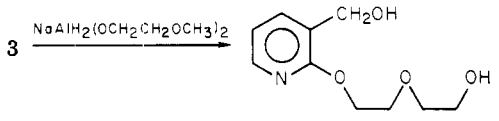
6

temp, °C	time, h	2a, %	3, %
25	48	15	21
80	24	18	17
140	12	9.2	11

"Vitride"; **2a** gave the 2:1 diol **4**, whereas **3** gave the 1:1 diol **5**. Reductive cleavage of the lactone units supports



4

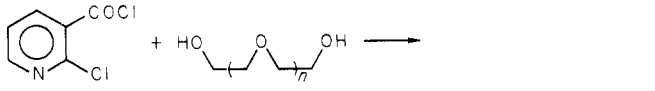


5

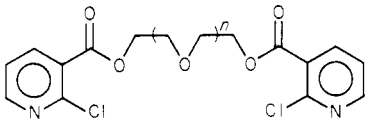
the premise that macrocycle **3** possesses the center of symmetry. Esterification of **1** with diethylene glycol in refluxing benzene gave (96%) the desired 2:1 ester **6**, as a colorless oil. The NMR spectrum of **6** showed a multiplet at δ 8.52 for the 6-pyridyl hydrogen; thus, the 2-chloro substituent was still intact.

Cyclization of **6** when treated with disodium diethylene glycolate gave a mixture of **2a** and **3** even at 25 °C (Scheme I). When the cyclization was conducted at elevated temperatures (140 °C), at thermodynamic equilibrium, an approximately equal ratio of 2:2 macrocycles was realized. Facile transesterification even under mild reaction conditions (25 °C) has been detrimental to the synthesis of a specific 2:2 macrocycle; isolation of an isomeric macrocyclic mixture could thus not be totally circumvented.

Esterification of **1** with pentaethylene glycol gave the desired diester **7** in excellent yields. However, in an at-

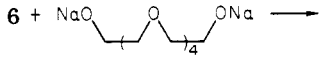


1

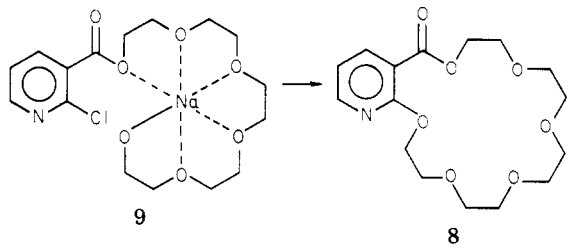


6, n = 1
7, n = 4

tempt to prepare the 2:2 macrocycle **2b** by treatment of **7** with disodium pentaethylene glycolate, the major product was the corresponding 1:1 macrocycle **8**. The NMR spectrum of **8** exhibited an upfield doublet of doublets at δ 8.32 for the 6-pyridyl hydrogen, indicative of 2-oxa substitution; infrared and mass spectral data further substantiated the 1:1 lactone framework. The reaction course proceeds via either transesterification, followed by nucleophilic cyclization, or nucleophilic attack to generate the pyridyl ether, and then transesterification. Treatment of **1** with disodium pentaethylene glycolate afforded **8** in 30% isolated yield. Since the relationship between crown ether cyclization yields and the size of the base cations has been demonstrated,[8] this homo-18-crown-6 (i.e., **8**) should favor potassium vs. sodium cations, if a template reaction is operative. Treatment of **1** (or **6**) with dipotassium



(or 1)



9 8

pentaethylene glycolate gave (48% isolated yield) **8**, indicative of a cyclic conformation (**9**), in which the cation is favorably coordinated to the oxygen chain and thus holding the termini in a desirable juxtaposition for facile cyclization.

Recently, the effect of reaction temperature has been shown to be a very important factor in the maximization of yield in such template reactions.[9] Although a complete temperature profile has not been conducted, the reaction temperature of ca. 60 °C suggested by Kawamura et al.[9a] appears to be a reasonable value based on these studies.

Experimental Section

General Comments. All melting points were taken in capillary tubes with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. NMR spectra were recorded on a Varian Associates A-60A spectrometer in $CDCl_3$ solution with tetramethylsilane as the internal reference (δ = 0 ppm). IR spectra were recorded on a Perkin-Elmer 621 grating infrared spectrophotometer. Recorded R_f values were determined by a standardized thin-layer chromatography (TLC) procedure: 0.25 mm Brinkmann silica gel 60HF-254-366 plates eluting with ethyl acetate–cyclohexane (1:1). For preparative thick-layer chromatography (ThLC), 2-mm silica gel PF-254+366 plates were used, with ethyl acetate–cyclohexane (1:1) as eluant. Elemental analyses were performed by Mr. R. Seab in these laboratories.

Sodium hydride (50% oil dispersion) was first washed with dry petroleum ether (bp 30–60 °C) and then dried under nitrogen before use. All the reaction solvents were dried over sodium and distilled before use.

Reaction of 2-Chloronicotinoyl Chloride with Disodium Diethylene Glycolate. General Procedure of Macrocycle Preparation. To a suspension of sodium hydride (300 mg, 12.5 mmol) in xylene (150 mL) was slowly added diethylene glycol (550 mg, 5.2 mmol) under nitrogen. The mixture was stirred at room temperature for 30 min and then **1**[6] (910 mg, 5.2 mmol) in xylene (50 mL) was added dropwise. The mixture was refluxed for 24 h, cooled, and quenched with water. The organic layer was separated and the aqueous layer extracted with dichloromethane. The combined organic fraction was dried over anhydrous sodium sulfate and concentrated in vacuo to give a white crystalline powder, which was chromatographed (ThLC), with ethyl acetate-cyclohexane (1:1) as eluant, to afford the following components.

Fraction A gave the syn-2:2 macrocycle **2a** as colorless needles: mp 112.5–113.0 °C (diethyl ether); 160 mg (7.4%); R_f 0.24; NMR δ 3.90–4.12 (m, β,β'-CH_2, 8 H), 4.46–4.70 (m, α,α'-CH_2, 8 H), 6.98

(8) Vögtle, F.; Neumann, P. *Chem.-Ztg.* **1973**, *97*, 600. Gokel, G. W.; Durst, H. D. *Synthesis* **1976**, 168. Newkome, G. R.; Robinson, J. M. *J. Chem. Soc., Chem. Commun.* **1973**, 831. Dale, J.; Kristiansen, P. O. *Acta Chem. Scand.* **1972**, *26*, 1471. Greene, R. N. *Tetrahedron Lett.* **1972**, 1793. Ring-Lin, K.; Miki, M.; Okahara, J. *J. Chem. Soc., Chem. Commun.* **1978**, 504.

(9) (a) Kauramura, N.; Miki, M.; Ikeda, I.; Okahara, M. *Tetrahedron Lett.* **1979**, 535. (b) Mattice, W. L.; Newkome, G. R. *J. Am. Chem. Soc.* **1979**, *101*, 4477. (c) Newkome, G. R.; Nayak, A.; Fronczek, F.; Kawato, T.; Taylor, H. C. R.; Meade, L.; Mattice, W. *Ibid.* **1979**, *101*, 4472.

(dd, 5-Pyr-H, J = 5.0, 7.3 Hz, 2 H), 8.21 (dd, 4-Pyr-H, J = 2.1, 7.3 Hz, 2 H), 8.32 (dd, 6-Pyr-H, J = 2.1, 5.0 Hz, 2 H); IR (KBr) 1695 (C=O), 1685 (C=O) cm^{-1}; mass spectrum (70 eV) m/e (relative intensity) 417 ($M^+ - 1$, 1.4), 375 ($M^+ - C_2H_3O$, 82.0), 254 ($C_{12}H_{16}NO_5$, 53.0), 236 ($C_{12}H_{14}NO_4$, 17.0), 210 ($C_{10}H_{12}NO_4$, 23.7), 166 ($C_8H_8NO_3$, *100*), 148 ($C_8H_6NO_2$, 28.1), 122 ($C_6H_4NO_2$, 80.5), 121 ($C_6H_3NO_2$, 24.5).

Anal. Calcd for $C_{20}H_{22}N_2O_8$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.25; H, 5.34; N, 6.52.

Fraction B yielded the anti-2:2 macrocycle **3** as colorless crystals: mp 169.5–170.0 °C ($CHCl_3$ + diethyl ether); 150 mg (6.9%); R_f 0.20; NMR δ 3.95–4.10 (m, β,β'-CH_2, 8 H), 4.45–4.70 (m, α,α'-CH_2, 8 H), 6.91 (dd, 5-Pyr-H, J = 4.9, 7.8 Hz, 2 H), 8.16 (dd, 4-Pyr-H, J = 2.1, 7.8 Hz, 2 H), 8.27 (dd, 6-Pyr-H, J = 2.1, 4.9 Hz, 2 H); IR (KBr) 1698 (C=O) cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 418 (M^+, 0.2), 417 ($M^+ - 1$, 0.3), 375 (27.8), 236 (19.6), 210 (31.0), 166 (*100*), 148 (14.3), 122 (83.1), 121 (19.3).

Anal. Calcd for $C_{20}H_{22}N_2O_8$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.12; H, 5.36; N, 6.48.

Reaction of 2-Chloronicotinoyl Chloride with Diethylene Glycol. General Esterification Procedure. A solution of **1** (5.3 g, 30 mmol) and diethylene glycol (1.6 g, 15 mmol) in benzene (50 mL) was refluxed for 6 h. After concentration, the residue was extracted with dichloromethane, washed with diluted aqueous sodium carbonate, dried over anhydrous sodium sulfate, and concentrated in vacuo to give (96%) the desired ester **6** as a viscous colorless oil. The ester was pure enough for further studies without further purification: NMR δ 3.78–3.95 (m, β-CH_2, 4 H), 4.45–4.62 (m, α-CH_2, 4 H), 7.29 (dd, 5-Pyr-H, J = 7.9, 4.7 Hz, 2 H), 8.17 (dd, 4-Pyr-H, J = 7.9, 1.8 Hz, 2 H), 8.52 (dd, 6-Pyr-H, J = 4.7, 1.8 Hz, 2 H); IR (neat) 1730 (C=O), 1715 (C=O) cm^{-1}.

Anal. Calcd for $C_{16}H_{14}N_2O_5Cl_2$: C, 49.89; H, 3.66; N, 7.27. Found: C, 49.40; H, 3.48; N, 6.98.

The reaction of 2-chloronicotinoyl chloride with pentaethylene glycol followed the above general esterification procedure, except for pentaethylene glycol (3.6 g, 15 mmol), to yield (93%) the desired ester **7** as a thick colorless oil. Without further purification, the following spectral data were obtained: NMR δ 3.67 (s, ϵ-CH_2, 4 H), 3.70 (br s, γ,δ-CH_2, 8 H), 3.78–3.95 (m, β-CH_2, 4 H), 4.47–4.63 (m, α-CH_2, 4 H), 7.40 (dd, 5-Pyr-H, J = 4.9, 7.9 Hz, 2 H), 8.24 (dd, 4-Pyr-H, J = 2.0, 7.9 Hz, 2 H), 8.58 (dd, 6-Pyr-H, J = 2.0, 4.9 Hz, 2 H); IR (neat) 1730 (C=O) cm^{-1}.

Reaction of 6 with Disodium Diethylene Glycolate. The above cyclization procedure was conducted with **6** (1.1 g, 2.9 mmol) and disodium diethylene glycolate, generated from sodium hydride (170 mg, 7.1 mmol) and diethylene glycol (310 mg, 2.9 mmol), in benzene (25 or 80 °C, 300 mL) or xylene (140 °C, 300 mL) to yield the isomeric 2:2 macrocycles **2a** and **3**. The reaction times vs. the *isolated* yields are summarized in Scheme I.

Reaction of 2a with "Vitride". General Procedure of Reductive Decyclization of Macrocycles. A solution of **2a** (150 mg, 0.36 mmol) in anhydrous benzene (20 mL) was added dropwise to a benzene solution (10 mL) of sodium bis(2-methoxyethoxy)aluminum hydride (150 mg, 0.69 mmol, 70% benzene solution) at 5 °C with stirring under nitrogen. The reaction mixture was refluxed for 1 h and then cooled in ice. Water (1 mL) was added, and the mixture was stirred vigorously for 1 min. The organic layer was separated, and the residue was extracted with dichloromethane. The combined organic fraction was dried over anhydrous sodium sulfate and concentrated in vacuo to give **4** as a microcrystalline powder, which was recrystallized from dichloromethane: mp 114.5–115.5 °C; 60 mg (52%); R_f 0.10; NMR δ 3.80–3.95 (m, β-CH_2, 4 H), 3.87 (s, OH, 2 H), 4.51–4.66 (m, α-CH_2, 4 H), 4.62 (s, 3-Pyr-CH_2, 4 H), 6.89 (dd, 5-Pyr-H, J = 5.1, 7.2 Hz, 2 H), 7.59 (dd, 4-Pyr-H, J = 1.9, 7.2 Hz, 2 H), 8.10 (dd, 6-Pyr-H, J = 1.9, 5.1 Hz, 2 H); IR (hexachlorobutadiene mull) 3310 (OH), 3240 (sh, OH) cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 320 (M^+, 6.1), 196 ($C_{10}H_{14}NO_3$, 3.8), 152 ($C_8H_{10}NO_2$, *100*), 125 ($C_6H_7NO_2$, 35.2), 124 ($C_6H_6NO_2$, 45.5), 108 (C_6H_6NO, 38.8).

Anal. Calcd for $C_{16}H_{20}N_2O_5$: C, 59.99; H, 6.29; N, 8.74. Found: C, 59.88; H, 6.16; N, 8.75.

Reduction of 3 with "Vitride" followed the above procedure except for the substitution of the macrocycle **3**. After chromatographic workup (ThLC), alcohol **5** was isolated as a thick colorless oil. Futher purification was not undertaken, but the structure was confirmed by spectral data: 50 mg (65%); R_f 0.07; NMR δ 3.44 (s, OH, 2 H), 3.66–3.73 (m, γ,δ-CH_2, 4 H), 3.75–3.94 (m, β-CH_2, 2 H), 4.51–4.68 (m, α-CH_2, 2 H), 4.66 (s, 3-Pyr-CH_2, 2 H), 6.91 (dd, 5-Pyr-H, J = 7.2, 5.1 Hz, 1 H), 7.62 (dd, 4-Pyr-H, J = 7.2, 2.0 Hz, 1 H), 8.11 (dd, 6-Pyr-H, J = 5.1, 2.0 Hz, 1 H); IR (neat) 3380 (br, OH); mass spectrum (70 eV), m/e (relative intensity) 213 (M^+, 3.4), 198 ($C_{10}H_{16}NO_3$, 6.8), 152 (16.9), 125 (*100*), 124 (58.2), 108 (42.1).

Reaction of 7 with Disodium Pentaethylene Glycolate. The above macrocycle procedure was conducted with the ester **7** (1 g, 2.0 mmol) and disodium pentaethylene glycolate, generated from sodium hydride (130 mg, 5.4 mmol) and pentaethylene glycol (500 mg, 2.1 mmol), in benzene (150 mL) for 48 h. After chromatography (ThLC), the 1:1 macrocycle **8** was isolated as a viscous, colorless oil: 390 mg (28%); R_f 0.11; NMR δ 3.68 (s, ϵ-CH_2, 4 H), 3.76 (br s, γ,δ-CH_2, 8 H), 3.82–4.03 (m, β,β'-CH_2, 4 H), 4.44–4.70 (m, α,α'-CH_2, 4 H), 6.97 (dd, 5-Pyr-H, J = 5.0, 7.8 Hz, 1 H), 8.22 (dd, 4-Pyr-H, J = 1.9, 7.8 Hz, 1 H), 8.32 (dd, 6-Pyr-H, J = 1.9, 5.0 Hz, 1 H); IR (neat) 1725 (sh, C=O), 1705 (C=O); mass spectrum (70 eV), m/e (relative intensity) 342 ($M^+ + 1$, 0.9), 340 ($M^+ - 1$, 0.3), 298 ($M^+ - C_2H_3O$, 3.3), 254 ($C_{12}H_{16}NO_5$, 5.8), 210 ($C_{10}H_{12}NO_4$, 10.4), 166 ($C_8H_8NO_3$, 83.1), 122 ($C_6H_4NO_2$, *100*), 121 ($C_6H_3NO_2$, 51.9).

Anal. Calcd for $C_6H_{23}NO_{7.1}/_3H_2O$: C, 55.32; H, 6.87; N, 4.03. Found: C, 55.52; H, 7.08; N, 3.71.

The reaction of 7 with potassium pentaethylene glycolate was conducted in the above procedure except for the utilization of potassium hydride (24.7% in oil, 900 mg, 5.5 mmol) to give **8**: yield 670 mg (48%).

Reaction of 1 with Disodium Pentaethylene Glycolate. The macrocycle procedure was conducted on **1** (1 g, 5.7 mmol) [sodium hydride (350 mg, 14.6 mmol), pentaethylene glycol (1.3 g, 5.7 mmol)] to afford the 1:1 macrocycle **8** predominantly. After chromatographic workup, **8** was isolated and identified by the comparison of the authentic sample prepared above; 600 mg (31%).

Acknowledgment. We are grateful to the National Institutes of Health and the National Science Foundation for partial support of this work.

Registry No. **1**, 49609-84-9; **2a**, 72269-07-9; **3**, 72269-08-0; **4**, 72269-09-1; **5**, 72269-10-4; **6**, 72269-11-5; **7**, 72269-11-5; **8**, 72269-12-6; disodium diethylene glycol, 69102-38-1; disodium pentaethylene glycol, 70290-40-3; dipotassium pentaethylene glycol, 57624-62-1; diethylene glycol, 111-46-6; pentaethylene glycol, 4792-15-8.