and after 1 h additional THF (10 mL) was added. It was allowed to warm to ambient temperature and stand for 5 h 30 min; it was then poured into ice water. This mixture was neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was crystallized from MeOH–EtOAc to give 1.1 g, mp 285–286 °C, and 0.184 g, mp 275–276 °C (79.1% yield), of **19**. The analytical sample gave the following data: mp 286–288 °C dec; UV (EtOH) λ_{max} 221 (ϵ 33 720), 266 (15 090); IR (Nujol) 1690, 1660 (sh) (C=O), 1620, 1610, 1590, 1575, 1565, 1510 (C=N/C=C) cm^{-1}; NMR [$(CD_3)_2NCDO$] δ 3.94 (s, 3, NCH_3), ~4.9 (broad s, 2, (C-4)H_2); MS *m/e* 324, 296, 282, 253.

Anal. Calcd for $C_{17}H_{13}ClN_4O$: C, 62.87; H, 4.03; Cl, 10.92; N, 17.25. Found: C, 62.23; H, 4.06; Cl, 10.93; N, 17.17.

8-Chloro-1-mercapto-3-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepinium Hydroxide Inner Salt (20). A stirred mixture of **7** (4.48 g, 0.015 mol), triethylamine (4.68 mL, 0.033 mol), and THF (60 mL) was cooled, under N_2, in salt–ice bath and treated, dropwise during 1 h 20 min with a solution of thiophosgene (1.26 mL) in THF (30 mL). The mixture was allowed to warm slowly to ambient temperature, stand for 15 h 40 min, and finally reflux on the steam bath for 1 h 10 min. The cooled mixture was poured into ice water. The solid was collected by filtration, dissolved in $CHCl_3$, washed with brine, and dried (Na_2SO_4). The aqueous filtrate was concentrated in vacuo to remove THF and extracted with $CHCl_3$. The extract was washed with brine and dried (Na_2SO_4). The $CHCl_3$ solutions were combined and concentrated and the residue was chromatographed on silica gel (300 g) with 2% MeOH–98% $CHCl_3$. The product thus obtained was recrystallized from CH_2Cl_2–MeOH to give 1.33 g, mp 261.5–267 °C dec with softening at 253 °C, and 1.94 g, mp 258–267 °C dec with softening at 245 °C. The analytical sample gave the following data: mp 258–262 °C dec with softening at 245 °C; UV (EtOH) λ_{max} 219.5 (ϵ 46 100), 278 (8250), inflections 245 (19 150), 260 (11 250), 310 (4200) nm; IR (Nujol) 1615, 1600, 1565, 1490 (C=N/C=C), 1360, 1350, 1335, 1320, 1310, 1195, 1125, 1000 (=CH, C=S, etc.) cm^{-1}; NMR [$(CD_3)_2SO$] δ 3.95 (s, 3, NCH_3), 4.24, 5.63 (d, d, 2, J_{AB} = 14 Hz, (C-4)H_2); MS *m/e* (relative intensity) 340 (999).

Anal. Calcd for $C_{17}H_{13}ClN_4S$: C, 59.91; H, 3.84; Cl, 10.40; N, 16.44; S, 9.41. Found: C, 59.99; H, 3.99; Cl, 10.67; N, 16.81; S, 9.38.

1-Acetamido-8-chloro-3-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepinium Hydroxide Inner Salt Hydrate (21). Compound **17** (X = Cl) (1.43 g, 0.00396 mol) was added, under N_2, to a stirred, ice-cold mixture of triethylamine (8 mL) and acetic anhydride (4 mL); the resulting mixture was kept in the ice bath for 6 h 25 min, treated with absolute EtOH (10 mL), and allowed to warm slowly to ambient temperature during 15 h. The mixture was concentrated in vacuo and the residue was mixed with dilute $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with brine, dried (K_2CO_3), and concentrated in vacuo. The residue was dissolved in MeOH, decolorized with Darco, and crystallized from MeOH–EtOAc (wet) to give 0.317 g, mp 170–171 °C dec, and 0.264 g, mp 170–171 °C dec, of **21**. The analytical sample gave the following data: mp 169–171 °C dec; UV (EtOH) end absorption, λ_{max} 221 (ϵ 38 200), inflection 272 (11 550) nm; IR (Nujol) 3510, 3370 (H_2O), 1640 (sh), 1620, 1605, 1600, 1580, 1515 (C=O, C=N, C=C) cm^{-1}; NMR ($CDCl_3$) δ 2.10 (s, 3, C(=O)CH_3), 4.02 (s, 3, NCH_3), 4.18, 5.36 (d, d, 2, J_{AB} = 14 Hz, (C-4)H_2); MS *m/e* (relative intensity) 365 (141), 350 (999).

Anal. Calcd for $C_{19}H_{16}ClN_5O$: C, 62.38; H, 4.41; Cl, 9.69; N, 19.14. Found: C, 60.18; H, 4.76; Cl, 9.48; N, 18.44; H_2O, 4.04. Analytical data corrected for water: C, 62.71; H, 4.50; Cl, 9.88; N, 19.22.

Acknowledgments. The authors are indebted to Dr. E. C. Olson and his associates for physical and analytical data and especially to Dr. L. Baczynskyj, Mr. P. A. Meulman, and Mr. T. A. Scahill for helpful discussions regarding mass, infrared, and NMR spectra, respectively. The authors are also indebted to Dr. R. P. Holysz and his associates for the preparation of chemical intermediates, to Mr. J. R. Greene and Mr. L. G. Laurian for technical assistance, and to Mrs. H. Branch for preparing this paper for publication.

Registry No. **1**, 28981-97-7; **3**, 55775-75-2; **4**, 41154-37-4; **5**, 18091-89-9; **6**, 28910-89-6; **7**, 56167-78-3; **8**, 70524-39-9; **9**, 4547-02-8; **10** (X = BF_4), 41506-84-7; **10** (X = Br), 41154-41-0; **11**, 41154-39-6; **13**, 41212-87-7; **14**, 70524-40-2; **15** (X = $C_7H_7SO_3$), 56167-86-3; **15** (X = Cl), 56167-87-4; **16** (X = HSO_4), 67171-61-3; **16** (X = Cl), 56167-84-1; **17** (X = Br), 56167-82-9; **17** (X = Cl), 56167-83-0; **18**, 56167-89-6; **19**, 56167-80-7; **20**, 56167-79-4; **21**, 56167-88-5.

Nicotinic Acid Crown Ethers.[1] Synthesis, Reactions, and Complexation of Nicotinonitrile Macrocycles

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2,6-Dichloronicotinamide (**6**), prepared from the corresponding disubstituted nicotinic acid, was dehydrated with refluxing thionyl chloride to give the nitrile **8**, which was subsequently converted into the 1:1 macrocyclic nicotinonitriles **9**. Isomeric macrocyclic dimers **10** were also isolated from the reaction. NMR and mass spectral data were used to ascertain the macrocyclic structures. Eu(fod)$_3$ shift reagent was employed to demonstrate that the predominant site of europium ion coordination in these nitrile macrocycles is the central bridging ethereal oxygens. Reduction of **9b** with lithium aluminum hydride or Vitride gave fragmentation of the macrocyclic ring nucleus resulting in formation of pentaethylene glycol and reduction products derived from the pyridine nucleus.

The synthesis and reactions of 1,4-dihydropyridines have been demonstrated to be a dynamic area in organic and bioorganic chemistry in view of their potential simplistic mimicking of the pyridine-linked nucleotide's reactions.[3,4] 1-Metallodihydropyridines (**1**), prepared from pyridine upon treatment with various reducing agents such as $LiAlH_4$,[5a,b] ZnH_2,[5c] or organometallic reagents,[3] have been

(1) Part 42 of the series "Chemistry of Heterocyclic Compounds". For Part 41 see: Newkome, G. R.; Majestic, V. K.; Fronczek, F.; Atwood, J. L. *J. Am. Chem. Soc.* **1979**, *101*, 1047.

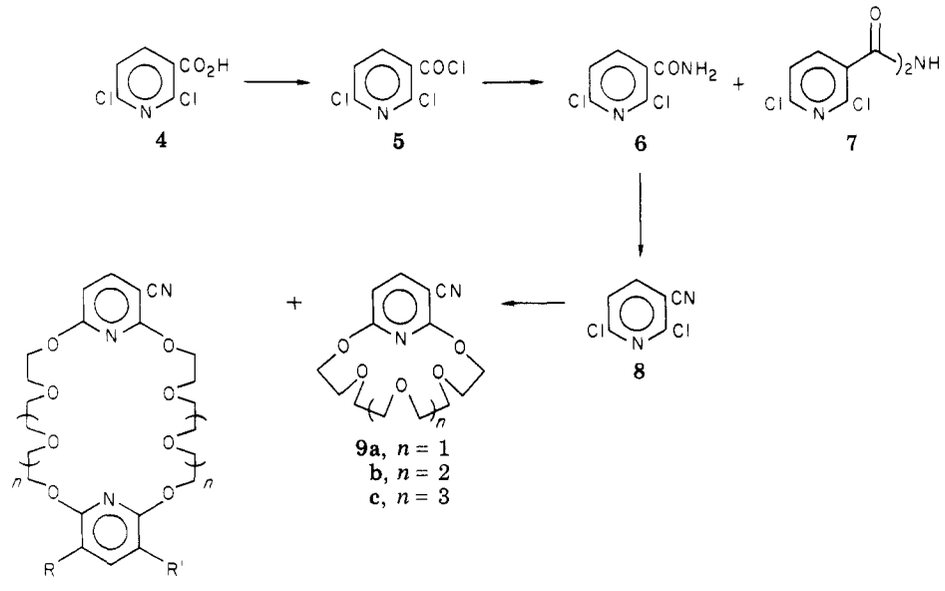
(2) On leave from Kyushu University, Fukuoka, Japan (1977–1979).

(3) For examples see: (a) Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, *72*, 1. (b) Ohno, A.; Ohnishi, Y. *Kagaku No Ryoiki, Zokan* **1976**, *No. 110*, 57.

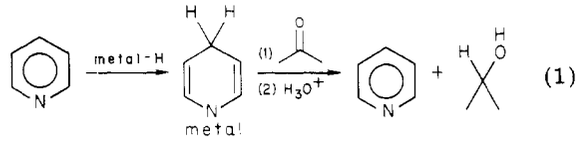
(4) van Bergen, T. J.; Kellogg, R. M. *J. Am. Chem. Soc.* **1977**, *99*, 3882. *J. Chem. Soc., Chem. Commun.* **1976**, 964. Piepers, O.; Kellogg, R. M. *Ibid.* **1978**, 383. Hedstrand, D. M.; Kruizinga, W. H.; Kellogg, R. M. *Tetrahedron Lett.* **1978**, 1255. van der Veen, R. H.; Kellogg, R. M.; Vos, A.; van Bergen, T. J. *J. Chem. Soc., Chem. Commun.* **1978**, 923. Also see: Overman, L. E. *J. Org. Chem.* **1972**, *37*, 4214. Dittmer, D. C.; Blinder, B. B. *Ibid.* **1973**, *38*, 2873.

0022-3263/79/1944-2693$01.00/0

Scheme I

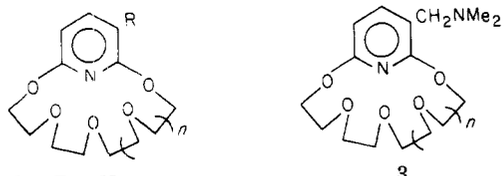


recently shown to be themselves good reducing agents (eq 1). Our initial attempts to reduce simple heteromacro-



(1)

cycles (e.g., **2a**) failed either because of the diminished



reactivity of the pyridine nucleus toward nucleophilic attack or because of the limited, if any, participation of the pyridine nitrogen atom in complexation.[6,7] Subsequently, **2b** was devised[7,8] since the 4-position was assumed to be activated to nucleophilic attack; however, metal ion coordination was shown to occur predominantly with the carbonyl oxygen atom at low metal ion concentration[8] and reduction of **2b** gave **3** rather than products derived from ring attack. Therefore in order to circumvent this unwanted mode of complexation, we consider in this paper the synthesis and chemistry of nicotinonitrile-containing macrocycles, in which the nitrile function does not complex strongly with diverse metal ions as demonstrated by recent lanthanide shift reagent studies.[9]

Results and Discussion

Synthesis of the necessary 2,6-dichloronicotinonitrile (**8**) was accomplished by initial treatment of 2,6-dichloronicotinic acid (**4**)[10] with thionyl chloride to generate the acid chloride **5**. Dropwise addition of triethylamine to a dichloromethane suspension of **5** and ammonium chloride, while the temperature was maintained below −5 °C, afforded (45%) the desired amide **6**[11] along with the corresponding bis(amide) **7**. A near-quantitative separation of **6** and **7** was achieved by simple fractional recrystallization. Subsequent treatment of amide **6** with refluxing thionyl chloride for 30 h gave (91%) the crystalline nitrile **8** (Scheme I).[13]

The reaction of **8** with pentaethylene glycol dianion, generated in situ from pentaethylene glycol and 2 equiv of oil-free sodium hydride, gave the desired macrocycle **9b** in 48% yield, along with the smaller macrocycle **9a**. Thermal fragmentation and oligomerization of polyethylene glycols are well documented,[6,15] thus affording a rationale for the formation of **9a** in trace (<1%) quantities. The larger macrocycle **9c**, prepared from hexaethylene glycol, was also isolated (7%) from this reaction. This percentage of **9c** is too large for oligomerization to be the *only* source of hexaethylene glycol; thus, the pentaethylene glycol reagent was subsequently shown to be contaminated with several percent of the hexa oligomer. Isomeric 2:2 symmetrical macrocycles (**10**) were also isolated in 3% yield; separation of these isomers was not attempted.

(5) (a) Lansbury, P. T.; Paterson, J. O. *J. Am. Chem. Soc.* **1963**, *85*, 2236. (b) Lansbury, P. T.; Macleay, R. E. *Ibid.* **1965**, *87*, 831. (c) de Konig, A. J.; Boersma, J.; van der Kerk, G. J. M. *Tetrahedron Lett.* **1977**, 2547.

(6) (a) Newkome, G. R.; Nayak, A.; McClure, G. L.; Danesh-Khoshboo, F.; Broussard-Simpson, J. *J. Org. Chem.* **1977**, *42*, 1500. (b) Newkome, G. R.; McClure, G. L.; Broussard-Simpson, J.; Danesh-Khoshbpo, F. *J. Am. Chem. Soc.* **1975**, *97*, 3232. (c) Newkome, G. R.; Danesh-Khoshboo, F.; Nayak, A.; Benton, W. H. *J. Org. Chem.* **1978**, *43*, 2685.

(7) Newkome, G. R.; Kawato, T.; Nayak, A. *J. Org. Chem.*, following paper in this issue.

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(9) Beaute, C.; Wolkowski, Z. W.; Thoai, N. *J. Chem. Soc., Chem. Commun.* **1971**, 700. Klarner, F.-G. *Tetrahedron Lett.* **1971**, 3611.

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(11) Amide **6** had been previously prepared[12] by a different procedure; the physical and spectral data were not accessible.

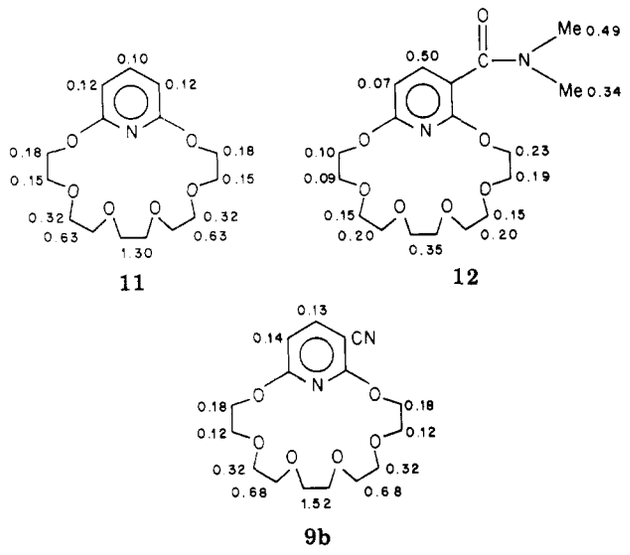
(12) Hoff, R. K.; Gallay, J. J.; Kuehne, M. German Patent 2 624 341; *Chem. Abstr.* **1977**, *86*, 106668.

(13) Nitrile **8** had been cited in patent literature[14] without sufficient physical and spectral data.

(14) Bowden, R. D. British Patent 1 302 287; *Chem. Abstr.* **1973**, *78*, 97503r. Lamm, G. German Patent 2 307 444; *Chem. Abstr.* **1975**, *82*, 32465q.

(15) Staude, E.; Patat, F. In "The Chemistry of the Ether Linkage"; S. Patai, Ed.; Interscience: New York, NY, 1967; pp 46–9. Lubowicz, R. E.; Reich, P. *Chem. Eng. Prog.* **1971**, *67*, 59.

Chart I

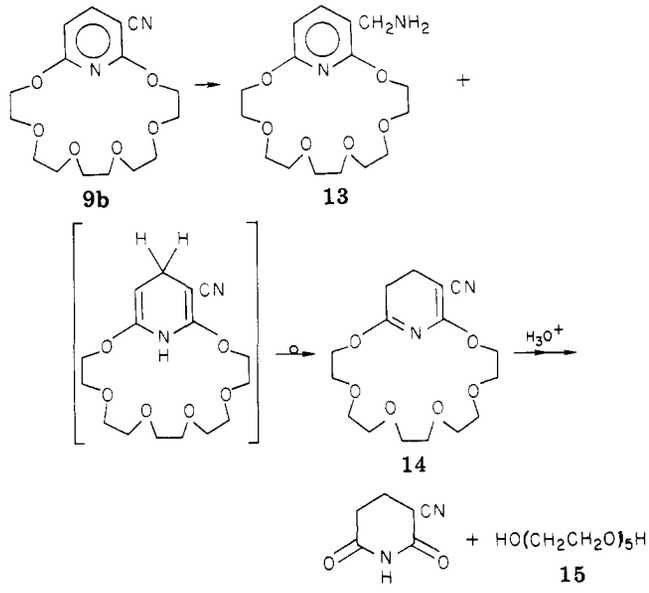


The structures of these C,O-macrocycles **9** were supported by molecular weight determinations (mass spectrometry), ^{1}H NMR spectroscopy, R_f values, and infrared spectroscopy. The NMR spectra exhibited doublets (J = 8 Hz) for the 4,5-pyridine hydrogens at δ 7.73 and 6.40, respectively. The general position for the H-5 doublet has been consistent for all members of this nicotinic acid macrocyclic series,[6,7] whereas the variability in chemical shift for H-4 has reflected the (de)shielding and electronic nature of the 3-substituent. Minor, but discernible, deshielding caused by the 3-cyano group is further shown by the chemical shift differences (ca. $\Delta(\delta)$ 0.1) for the α,α'-methylene groups. Mass spectral fragmentation patterns are very similar to those of simple crown ethers,[16] in which there is a strong molecular ion and a series of major fragments caused by the sequential loss of the neutral ethylene oxide or *p*-dioxane. The dominant peaks at m/e 163 and 162 reflect the terminal C_2H_4O cleavage with and without prior hydrogen transfer; all subsequent major fragments result from cleavage of the pyridine nucleus. The infrared spectra of **9** confirm the presence of the nitrile substituent by the strong spike at 2200 cm^{-1}.

In order to evaluate the possible site(s) of metal ion complexation, we measured the NMR spectrum of **9b** with varying percentages of Eu(fod)$_3$. Chart I shows the shifts induced by 10% Eu(fod)$_3$ for **9b**, **11**, and **12**. The striking similarity between **9b** and **11** indicates that, in both, the predominant site(s) of europium ion coordination is the central bridging ethereal oxygens via the dramatic downfield shift experienced by the singlet for the ϵ-methylene hydrogens, whereas with the corresponding amide **12**, the amide oxygen is the favored site for coordination with the shift reagent.[8] These data further support the observations that nitriles are very weak donors since only small induced shifts are realized.[17]

The prerequisites for 1,4 reduction of the pyridine ring were accomplished by (1) activation of the 4 position toward nucleophilic attack via the presence of the 3-cyano group and (2) complexation of small metal ions predominantly on (or in) the macrocyclic ring. Reduction of pyridine with lithium aluminum hydride was shown in 1952 by Bohlmann[18] to give unstable reduction products, which were later characterized.[5a] Unsubstituted nicotinonitrile was smoothly reduced by action of sodium borohydride,[19] whereas 3,5-dicyanopyridine was reduced with either lithium aluminum hydride[20] or Vitride[20b] to give the 1,4-reduced product with little or no reduction of the nitrile functionality.

Scheme II



Treatment of **9b** with sodium dithionate in water or aqueous methanol or with sodium borohydride in water, methanol, or acetic acid at various temperatures and reaction times gave *only* unchanged starting macrocycle. Reaction of **9b** with ethyl chloroformate[21] in anhydrous tetrahydrofuran failed. With stronger reducing agents, such as lithium aluminum hydride or sodium (methoxyethoxy)aluminum hydride (Vitride), **9b** underwent reduction of the pyridine nucleus to give pentaethylene glycol and *no* single discernible pyridine-based moiety upon hydrolytic workup (Scheme II). Numerous modifications of the latter reductive procedure gave similar results. The nitrile group was apparently resistant to reduction by Vitride, whereas with $LiAlH_4$, the corresponding amine **13** was detected in minor and variable amounts. Even though nitrile **9b** was reduced slowly under these conditions, the pyridine nucleus was quickly reduced, based on the disappearance of the 4,5-pyridine hydrogens (when monitored via NMR) and the high yield of pentaethylene glycol recovered from the reaction. Nitrile **9b** as well as other members of this series are generally impervious to prolonged treatment with either aqueous acid or base **7**.[22] Thus, nitrile **9b** underwent 1,4 (or 1,2) reduction of the pyridine nucleus and then rearranged to **14**.[23] Hydrolysis of the labile imidate ester **14** occurred easily even under hydrolytic workup; it is well-known that such imidate esters are easily solvolyzed in aqueous media.[24]

Studies are currently underway to circumvent this solvolysis reaction.

(16) Jaeger, D. A.; Whitney, R. R. *J. Org. Chem.* **1975**, *40*, 92.
(17) Cockerill, A. F.; Davies, G. L. O.; Harden, R. C.; Rockham, D. M. *Chem. Rev.* **1973**, *73*, 553.
(18) Bohlmann, F.; Bohlmann, M. *Chem. Ber.* **1953**, *86*, 1419.
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(20) (a) Kuthan, J.; Janečková, E. *Collect. Czech. Chem. Commun.* **1964**, *29*, 1654. (b) Kuthan, J.; Procházková, J.; Janečková, E. *Collect. Czech. Chem. Commun.* **1968**, *33*, 3558.
(21) Fowler, F. W. *J. Org. Chem.* **1972**, *37*, 1321.
(22) Macrocycle **9** was subjected to an aqueous sodium hydroxide–methylene chloride slurry for 12 h and quantitatively recovered unchanged.
(23) See: Meyer, H.; Bossert, F.; Horstmann, H. *Justus Liebigs Ann. Chem.* **1976**, 1762.
(24) Roberts, R. M.; DeWolf, R. H. *J. Am. Chem. Soc.* **1954**, *76*, 2411. DeWolf, R. H.; Augustine, F. B. *J. Org. Chem.* **1965**, *30*, 699.

Experimental Section

General Comments. All melting points were taken in capillary tubes with a Thomas-Hoover Uni-Melt melting point apparatus and are uncorrected. The NMR spectra were obtained in deuteriochloroform solution with Me_4Si as the internal standard (δ 0) and were recorded on either a Varian Associates A-60A or HA-100 spectrometer. For the Eu-induced shift studies, a 0.15 M solution of macrocycle and a 0.238 M solution of $Eu(fod)_3$[25] in $DCCl_3$ were used. The chemical shifts were recorded at ambient temperature both before and after addition of $Eu(fod)_3$ solution. Mass spectral (MS) data were obtained on a Hitachi Perkin-Elmer Model RMS-4. Infrared (IR) spectra were recorded on a Beckman IR-7 spectrometer. Recorded R_f values were ascertained by a standardized thin-layer chromatography (TLC) procedure: 0.25-mm Brinkmann silica gel 60HF-254-366 plates eluting with ethyl acetate. For the preparative-thick-layer chromatography (ThLC), 2-mm silica gel PF-254-366 plates were used, eluting with ethyl acetate. 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 prior to use. Pentaethylene glycol was purchased from Columbia Organic Chemicals and used directly without prior distillation; the sample contained ca. 5% of hexaethylene glycol, based on experimental results.

Although the noncyclized products could be isolated, in general, only the major macrocylic products were characterized. The cited yield data were based on analytically pure components and not maximized.

2,6-Dichloronicotinamide (6) and Bis(2,6-dichloronicotinamide) (7). Into an ice-cold mixture of 2,6-dichloronicotinoyl chloride (10.15 g (0.048 mol); bp 117–118 °C (4.5 mm) (lit.[10] bp 72–74 °C (0.01 mm)); mp 28–28.5 °C) and ammonium chloride (2.57 g, 0.048 mol) in dichloromethane (150 mL) was added triethylamine (9.8 g, 0.097 mol) dropwise at a rate to maintain the temperature below −5 °C. The temperature was then allowed to rise to 25 °C and the mixture was stirred for 48 h. After removal of the resultant precipitate by filtration, the filtrate was washed with water and then an aqueous sodium carbonate solution and dried over anhydrous sodium sulfate. After evaporation, the residue was treated with chloroform to give 2,6-dichloronicotinamide (**6**) as a crystalline powder: mp 148–148.5 °C; R_f 0.32; NMR δ ca. 6.6 (bs, NH_2, 2 H), 7.40 (d, 5-pyr-H, J = 8.1 Hz, 1 H), 8.22 (d, 4-pyr-H, J = 8.1 Hz, 1 H); IR (KBr) 1672 (C=O) cm^{-1}.

Anal. Calcd for $C_6H_4N_2OCl_2$: C, 37.73; H, 2.11; N, 14.67. Found: C, 37.70; H, 2.02; N, 14.60.

From the above filtrate, additional **6** (4.10 g, 45% overall) was separated by fractional recrystallization with either chloroform or ethanol, as well as the bis(amide) **7**: mp 182–183 °C dec; 1.69 g (19%); R_f 0.56; NMR δ 7.42 (d, 5-pyr-H, J = 8.0 Hz, 1 H), 7.98 (d, 4-pyr-H, J = 8.0 Hz, 1 H), ca. 9.4 (bs, NH, 1 H); IR (KBr) 1740 (C=O), 1663 (C=O) cm^{-1}.

Anal. Calcd for $C_{12}H_5N_3O_2Cl_2$: C, 39.49; H, 1.38; N, 11.51. Found: C, 39.53; H, 1.35; N, 11.35.

2,6-Dichloronicotinonitrile (8). A suspension of amide **6** (3.35 g, 17.5 mmol) in thionyl chloride (30 mL) was refluxed for 30 h. After removal of excess solvent, the residue was extracted with chloroform, washed with water, and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded a pale yellow powder; 2.77 g (91%). Recrystallization from benzene–cyclohexane afforded colorless crystals: mp 117–119 °C; NMR δ 7.42 (d, 5-pyr-H, J = 8.1 Hz, 1 H), 7.95 (d, 4-pyr-H, J = 8.1 Hz, 1 H); IR (KBr) 2240 (C≡N) cm^{-1}.

Anal. Calcd for $C_6H_2N_2Cl_2$: C, 41.66; H, 1.17; N, 16.19. Found: C, 41.27; H, 1.10; N, 15.82.

Reaction of 2,6-Dichloronicotinonitrile with Pentaethylene Glycol. Pentaethylene glycol (2.69 g, 11.3 mmol) was slowly added under nitrogen to a suspension of sodium hydride (1.1 g, 22.9 mmol) in xylene (300 mL). The mixture was stirred at 25 °C for 30 min, **8** (1.95 g, 11.3 mmol) in xylene (100 mL) was added, and the mixture was refluxed for 24 h. After the solution had cooled, water was carefully added. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated in vacuo to give a viscous residue, which was chromatographed (ThLC), eluting with ethyl acetate, to afford four major fractions.

Fraction A afforded the 1:1 macrocycle **9a** as white crystals: mp 91–92 °C (diethyl ether–hexane); 20 mg (0.6%); R_f 0.32; NMR δ 3.4–3.7 (m, γ- and δ-CH_2, 8 H), 3.88 (t, 6-β-CH_2, J = 5.2 Hz, 2 H), 3.97 (t, 2-β-CH_2, J = 5.2 Hz, 2 H), 4.67 (t, 6-α-CH_2, J = 5.2 Hz, 2 H), 4.78 (t, 2-α-CH_2, J = 5.2 Hz, 2 H), 6.39 (d, 5-pyr-H, J = 8.4 Hz, 1 H), 7.73 (d, 4-pyr-H, J = 8.4 Hz, 1 H); IR (KBr) 2225 (C≡N), 1275 (CO), 1110 (CO), 1030 (CO) cm^{-1}; MS (70 eV) m/e (assignment, relative intensity) 294 ($C_{14}H_{18}N_2O_5$, 85), 250 ($C_{12}H_{14}N_2O_4$, 18), 224 ($C_{10}H_{12}N_2O_4$, 84), 207 ($C_{10}H_{11}N_2O_3$, 21), 206 ($C_{10}H_{10}N_2O_3$, 30), 192 ($C_9H_8N_2O_3$, 26), 180 ($C_8H_8N_2O_3$, 27), 176 ($C_9H_8N_2O_2$, 22), 175 ($C_9H_7N_2O_2$, 33), 164 ($C_8H_8N_2O_2$, 59), 163 ($C_8H_7N_2O_2$, 93), *162* ($C_8H_6N_2O_2$, 100), 161 ($C_8H_5N_2O_2$, 52), 150 (32), 148 (29), 137 (26), 136 (52), 134 (39), 120 (77), 118 (59).

Anal. Calcd for $C_{14}H_{18}N_2O_5$: C, 57.14; H, 6.16; N, 9.52. Found: C, 56.76; H, 6.21; N, 9.28.

Fraction B yielded the desired 1:1 macrocycle **9b** as a viscous oil: bp 220 °C (0.25 mm); 1.84 g (48%); R_f 0.24; NMR δ 3.55 (s, ϵ-CH_2, 4 H), 3.65 (m, γ- and δ-CH_2, 8 H), 4.39 (t, β-CH_2, J = 5.2 Hz, 4 H), 4.63 (t, 6-α-CH_2, J = 5.2 Hz, 2 H), 4.71 (t, 2-α-CH_2, J = 5.2 Hz, 2 H), 6.40 (d, 5-pyr-H, J = 8.3 Hz, 1 H), 7.72 (d, 4-pyr-H, J = 8.3 Hz, 1 H); IR (neat) 2222 (C≡N), 1275 (CO), 1130 (CO), 1040 (CO) cm^{-1}; MS (70 eV) m/e (assignment or see above, relative intensity) 338 ($C_{16}H_{22}N_2O_6$, 70), 294 (19), 250 (19), 249 ($C_{12}H_{13}N_2O_4$, 23), 224 (68), 207 ($C_{10}H_{11}N_2O_3$, 23), 206 (28), 192 (18), 180 (9), 176 (12), 175 (11), 164 (9), 163 (78), *162* (100), 161 (9), 150 (7), 148 (5), 137 (5), 136 (11), 134 (11), 133 (11), 120 (50), 118 (40).

Anal. Calcd for $C_{16}H_{22}N_2O_6$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.62; H, 6.58; N, 8.20.

Fraction C afforded the 1:1 hexaethylene glycol macrocycle **9c** as a viscous liquid: bp 245 °C (0.20 mm); 310 mg (7.2%); R_f 0.11; NMR δ 3.55–3.75 (m, γ–ξ-CH_2, 16 H), 3.87 (t, β-CH_2, J = 5.2 Hz, 4 H), 4.58 (t, 6-α-CH_2, J = 5.2 Hz, 2 H), 4.67 (t, 2-α-CH_2, J = 5.2 Hz, 2 H), 6.40 (d, 5-pyr-H, J = 8.2 Hz, 1 H), 7.72 (d, 4-pyr-H, J =8.2 Hz, 1 H); IR (neat) 2222 (C≡N), 1270 (CO), 1120 (CO), 1040 (CO) cm^{-1}; MS (70 eV) m/e (assignment or see above, relative intensity) 382 ($C_{18}H_{26}N_2O_7$, 77), 338 (35), 294 (45), 250 (43), 249 (33), 224 (47), 206 (24), 192 (10), 180 (14), 176 (14), 175 (14), 164 (16), *163* (100), 162 (65), 161 (11), 150 (5), 148 (5), 136 (10), 120 (21), 118 (13).

Anal. Calcd for $C_{18}H_{26}N_2O_7$: C, 56.53; H, 6.85; N, 7.33. Found: C, 56.27; H, 7.05; N, 7.07.

Fraction D gave the 2:2 pentamacrocycle **10**, which was recrystallized from diethyl ether to afford white crystals: mp 104–112 °C; 120 mg (3.2%); R_f 0.04; NMR δ 3.65 (s, ϵ-CH_2, 8 H), 3.70 (s, γ- and δ-CH_2, 16 H), 3.84 (t, 6-β-CH_2, J = 5.2 Hz, 4 H), 3.89 (t, 2-β-CH_2, J = 5.2 Hz, 4 H), 4.48 (t, 6-α-CH_2, J = 5.2 Hz, 4 H), 4.57 (t, 2-α-CH_2, J = 5.2 Hz, 4 H), 6.41 (d, 5-pyr-H, J = 8.3 Hz, 2 H), 7.74 (d, 4-pyr-H, J = 8.3 Hz, 2 H); IR (KBr) 2222 (C≡N), 1275 (CO), 1110 (CO), 1045 (CO) cm^{-1}; MS (70 eV) m/e (assignment or see above, relative intensity) 676 ($C_{32}H_{44}N_4O_{12}$, 0.5) 632 ($C_{30}H_{40}N_4O_{11}$, 0.7), 588 ($C_{28}H_{36}N_4O_{10}$, 1.0), 544 ($C_{26}H_{32}N_4O_9$, 0.5), 500 ($C_{24}H_{28}N_4O_8$, 0.5), 456 ($C_{22}H_{24}N_4O_7$, 0.7), 426 ($C_{20}H_{30}N_4O_6$, 0.8), 382 ($C_{18}H_{26}N_2O_6$, 2), 338 ($C_{16}H_{22}N_2O_6$, 41), 294 ($C_{14}H_{18}N_2O_5$, 9.5), 250 ($C_{12}H_{14}N_2O_4$, 21), 249 ($C_{12}H_{13}N_2O_4$, 16), 225 (18), 224 (35), 207 (16), 206 (21), 192 (19), 180 (19), 176 (14), 175 (16), 164 (24), *163* (100), 162 (93), 161 (20), 136 (11), 134 (6), 133 (25), 118 (12).

Anal. Calcd for $C_{32}H_{44}N_4O_{12}$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.51; H, 6.59; N, 8.14.

Reduction of 9b with Sodium Bis(methoxyethoxy)aluminum Hydride. To a stirred solution of **9b** (270 mg, 0.8 mmol) in dry benzene (25 mL) was added dropwise a solution of Vitride (0.3 mL, 70% in benzene, 1.1 mmol) in dry benzene (25 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred for 30 min and then refluxed for 10 min. After the mixture had cooled, water (5 mL) was added, followed by vigorous agitation. The organic layer was separated and the aqueous layer extracted with chloroform. The combined organic fractions were dried over anhydrous sodium sulfate and concentrated in vacuo to give a red oil (210 mg), which was chromatographed (ThLC), eluting with ethyl acetate, to give, along with unchanged starting macrocycle **9b** (30 mg) and pentaethylene glycol (ca. 70%), **15**,

(25) Purchased from Kary Laboratories.

which was identical with a known sample (NMR δ 3.68 (s, CH_2CH_2O, 20 H), ~3.3 (bs, 2 H). Two minor slow moving fractions were shown to possess a cyano stretching frequency. **Fraction A**: NMR δ 4.3 (bm, CH_2), 3.68 (s, CH_2), ~2.5 (bs, OH or NH), 2.48 (s, CH_2); IR 2200 (C≡N), 1710 (b, C=O), 1640 (b, C=O), 1590 (C=C). **Fraction B**: NMR δ ~4.6 (bs, CH_2), ~3.7 (bm, CH_2), 3.68 (s, CH_2), ~2.0 (bs, OH or NH); IR 2200 (C≡N), 1730 (b, C=O), 1640 (b, C=O), 1585 (C=C). Attempted purification was unsuccessful and due to the limited amount and apparent instability of material further analysis was not considered.

Reduction of 9b with Lithium Aluminum Hydride. To a stirred solution of **9b** (150 mg, 0.44 mmol) in dry tetrahydrofuran (30 mL) was added lithium aluminum hydride (20 mg, 0.53 mmol) at 25 °C under nitrogen. The reaction conditions and workup were similar to those of the above reaction. A trace of 3-(aminomethyl)pyridine macrocycle **13** (7.6 mg, 5%) was identified (NMR δ ~3.0 (b, CH_2, 2 H), 3.56 (s, ϵ-CH_2, 4 H), 3.68 (b, γ- and δ-CH_2, 8 H), 3.90 (t, β-CH_2, J = 5 Hz, 4 H), 4.55 (t, 6-α-CH_2, J = 5 Hz, 2 H), 4.64 (t, 2-α-CH_2, J = 5 Hz, 2 H), 6.32 (d, 5-pyr-H, J = 8 Hz, 1 H), 7.45 (d, 4-pyr-H, J = 8 Hz, 1 H)) and compared with related macrocyclic nicotinamides.[7]

The major product was suggested to be nitrile **14**, isolated as an unstable oil: NMR δ ~4.3 (bm, CH_2), 3.68 (s, OCH_2), 2.9 (m, CH_2), 2.3 (m, CH_2), 1.7 (m, CH_2); IR 2190 (C≡N), 1595 (C=C), 1535 (C=C, C=N), 1460 (CH_2), 1300 (CO), 1100 (b, CO) cm^{-1}. Under hydrolytic conditions, nitrile **14** underwent decomposition to afford pentaethylene glycol along with other products similar to those of the above reaction.

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Registry No. **6**, 62068-78-4; **7**, 70445-62-4; **8**, 40381-90-6; **9a**, 70445-63-5; **9b**, 70445-64-6; **9c**, 70445-65-7; **10a**, 70445-66-8; **10b**, 70445-67-9; **13**, 70445-68-0; **14**, 70445-69-1; **15**, 4792-15-8; 2,6-dichloronicotinoyl chloride, 58584-83-1.

Nicotinic Acid Crown Ethers.[1] Synthesis and Reactions of 2,6-Disubstituted *N,N*-Dimethylnicotinamides

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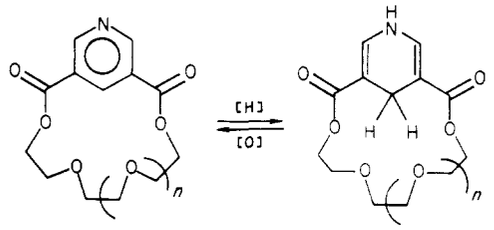
N,N-Dimethyl-2,6-dichloronicotinamide (**3**), prepared from the corresponding disubstituted nicotinic acid, was converted into macrocyclic nicotinamides **10**. Amide **3** was also subjected to sodium ethoxide in hot xylene to afford initially *N,N*-dimethyl-2-ethoxy-6-chloronicotinamide, which was proven by NMR spectral data and chemical degradation. Reduction of **10** with "Vitride" afforded exclusively the corresponding amine **11** in high yield. Enhanced protonation and metal ion coordination to the amide oxygen have been shown by NMR. Without the carboxamide function, $Eu(fod)_3$ complexed predominantly with the central ethereal oxygens as suggested by the dramatic chemical shift of the ϵ-methylene groups. Crown ether fragmentation has been demonstrated to give open-chain pyridones, e.g., **16**, when **15** was treated with either *tert*-butyllithium or, to a lesser extent, reducing agents under rigorous conditions.

Since the initial discovery of coenzyme β-nicotinamide adenine dinucleotide (NAD) in 1904 by Harden and Young,[3] substantial effort has been conducted on the mechanistic and stereochemical aspects of hydrogen transfer.[4] Mimesis of the stereospecific reduction with NAD dehydrogenases has been a direction of numerous organic research efforts.[5] Recently, even the inclusion of a Hantzsch 1,4-dihydropyridine fragment into a crown ether (**1**) was completed and this moiety was shown to mimic reactions of NAD(H).[6] We herein report our initial



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studies on the synthesis and chemistry of simple 2,6-disubstituted *N,N*-dimethylnicotinamides as well as the related 2,6-nicotinamide crown ethers in an attempt to more closely model NAD.

Results and Discussion

The pivotal starting material for the construction of our pyridine-linked nucleotide models was *N,N*-dimethyl-2,6-dichloronicotinamide (**3**), which was prepared by

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