Tetrahedron Vol. 39, No. 12, pp. 2001 to 2008, 1983
Printed in Great Britain.

0040-4020/83 $3.00 + .00
Pergamon Press Ltd.

NICOTINIC ACID CROWN ETHERS[1]: SYNTHESIS, COMPLEXATION AND REDUCTION

GEORGE R. NEWKOME* and CHARLES R. MARSTON
Department of Chemistry, Louisiana State University, Baton Rouge, LA 70803-1804, U.S.A.

(*Received in USA* 15 *August* 1982)

Abstract – 2, 6-*Bis* (bromomethyl)nicotinic oxazoline (**15**), prepared from ethyl 2, 6-dimethylnicotinate, was converted into the 1:1-macrocyclic oxazolines **19** and **22** as well as the isomeric macrocyclic dimers **20**. Ethyl 2, 6-*bis*(bromomethyl)nicotinate (**23**), prepared from **6b**, was converted to the corresponding 1:1-dibenzo-18-crown-6 macrocyclic analog **24**. NMR and mass spectral data were used to ascertain the macrocyclic structures. Reaction of **22** with EtMgBr afforded, after oxidation, the 4-substituted pyridino macrocycle **26** in high yield. However, under identical conditions, the non-oxazoline macrocycle **27** was recovered *in toto*.

Mimesis of the stereospecific reduction with nicotinamide adenine dinucleotide (NAD) dehydrogenase has been a major concern of numerous research groups over the past several decades.[2] Metal ion participation in the stereospecific enzyme mediated hydride transfer to a carbonyl substrate *in vivo* is well established.[3] It has also been demonstrated that N-metallodihydropyridines can similarly transfer hydride ion to a suitable electrophilic center;[4] thus, N-metallo-1, 4-dihydropyridines, generated by reduction of pyridine with $LiAlH_4$[4a,b], ZnH_2,[4c,5a,b] MgH_2,[4c,5] or selected organometallic reagents,[2,6] have been used to reduce carbonyl compounds.

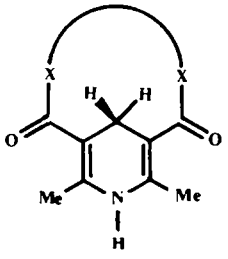
The incorporation of the 1, 4-dihydronicotinic acid subunit within a macrocyclic framework has taken several different pathways. Kellogg *et al.*[7] used two different models (e.g. **1** and **2**) to accomplish this purpose; in each case the symmetrical Hantzsch-type intermediate was invoked.

In order to insure a more representative NAD model, Newkome *et al.*[8] synthesized a series of 2, 6-nicotino crown ethers (**3**) from 2, 6-dichloronicotinic acid[9] *via* nucleophilic substitution. Even though the crown ether portion of **3** should stabilize an included metal ion (e.g. an alkali metal), the imidate moiety inherent in this series and the low ligandophilocity of the N-donor were, in part, detrimental to the generation of N-metallodihydronicotinic acid derivatives. Further, to establish the site of metal ion coordination in **3**, NMR shift reagents were utilized;[8d] in the cases evaluated, the ester, acid, and amide moieties were the preferred coordination site over the ethereal bridge. Only in the parent **3** (R = H) and nitrile **3d**, was metal ion coordination with the bridge realized; in these cases pyridine reduction was demonstrated by isolation of the open-chain polyethylene glycol and substituted imide. In order to circumvent the deleterious imidate moieties, a new series of nicotinic acid macrocycles was prepared and our preliminary studies in this series are described.

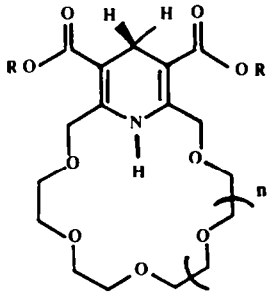
RESULTS AND DISCUSSION

1. *Syntheses of the nicotino macrocycles.* Two general procedures were envisioned to generate macrocycles, such as **4**: firstly a "one-step" self-condensation of **5** or secondly a more traditional approach based on dimethylnicotinic acid **6a**, *via* free radical α-halogenation and subsequent nucleophilic substitution.

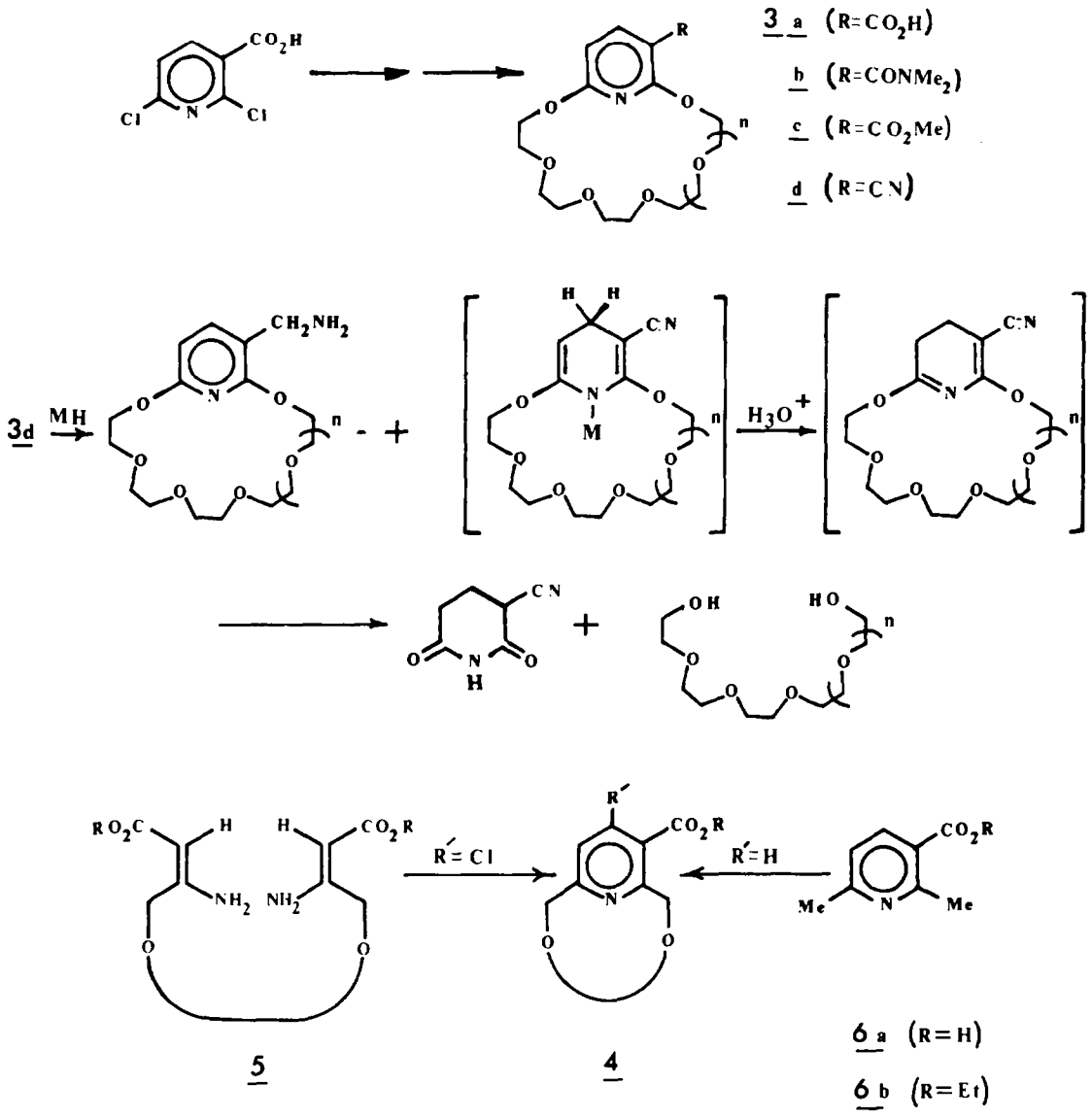
Since ethyl 2, 6-dimethylnicotinate (**6b**) was a convenient starting material for the latter procedure as well as could be used to model the cyclization route, the desired enamine **7**, prepared from ethyl acetoacetate with anhydrous ammonia,[10] was added to $POCl_3$ at 90° from which the chloro derivative **8**[11] was isolated in 73% yield. Dechlorination of **8** under phase-transfer conditions [triethylamine, aqueous formic acid (88%), and Pd (10%) on C][12] at 80° for several days gave **6b** in 95% yield besides a 4, 4′-dimer **9** in 3.5% yield. The use of Pd (10%) on C in ethanol under 3 atm. of hydrogen circumvented dimer formation; **6b**



1



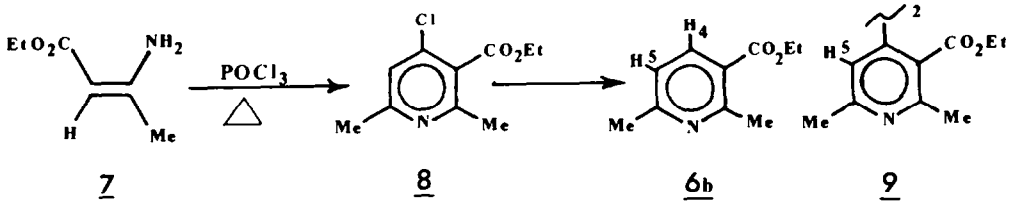
2

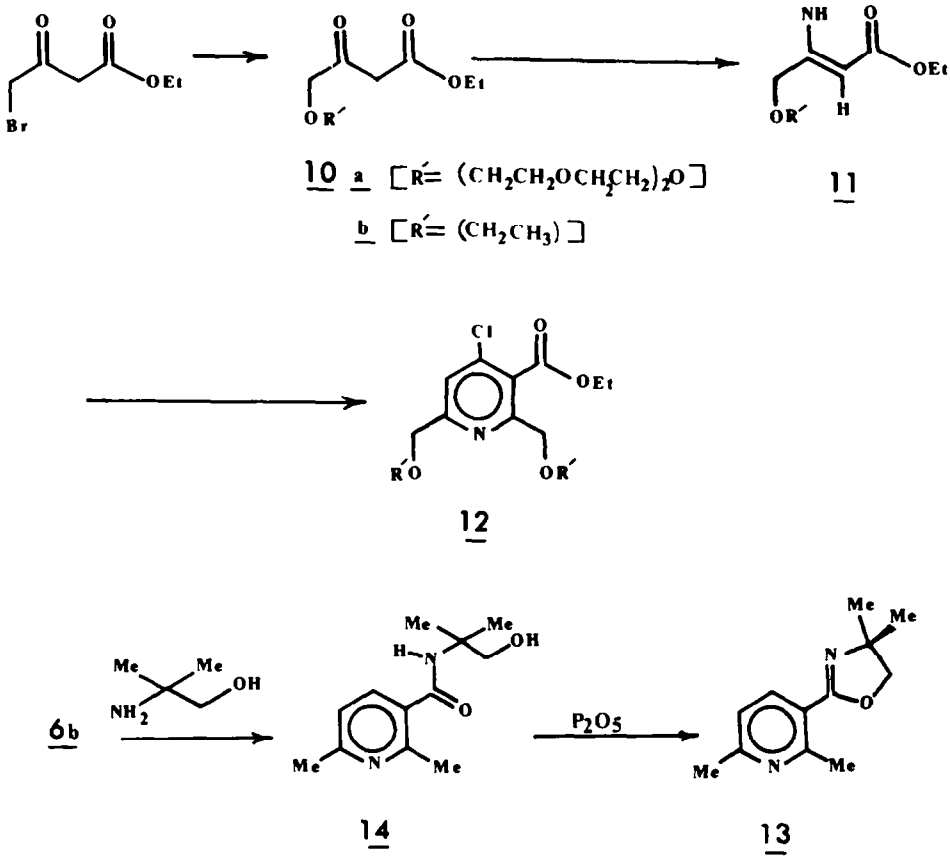


was prepared in 100% yield. The ^{1}H NMR spectrum of **6b** showed doublets at δ8.09 and 7.05 for the 4- and 5-ring hydrogens, respectively. The down-field singlet at δ2.81 for the 2-Me group (vs δ2.56 for the 6-Me substituent) is indicative of the adjacent ethoxycarbonyl moiety. Dimer **9** was generated by a coupling of the stable 4-pyridinyl radical[13] during the hydrodechlorination reaction.

In view of the successful conversion of **7**→**6b**, ether **10a**, prepared from ethyl 4-bromoacetoacetate[14] by the method of Kellogg *et al.*,[7a] was transformed in near quantitative yield to the *bis*-enamine **11a** upon treatment with anhydrous NH_3 under dehydrative conditions. Several attempts were made to cyclize **11a** with $POCl_3$ under diverse conditions, however polymeric residues were created from which the pyridine product (e.g. **4**) was not detected. The simpler ethereal ester **10b** was prepared, transformed to **11b**, but cyclization conditions with $POCl_3$ also failed to generate the desired pyridine nucleus (**12b**).

To circumvent transesterification of the ethoxycarbonyl moiety under nucleophilic conditions,[8g] ester **6b** was treated with 2-amino-2-methylpropan-1-ol and P_2O_5 in anhydrous xylene to give the oxazoline derivative **13** in 50% yield. Without P_2O_5, the intermediate amide **14** was isolated



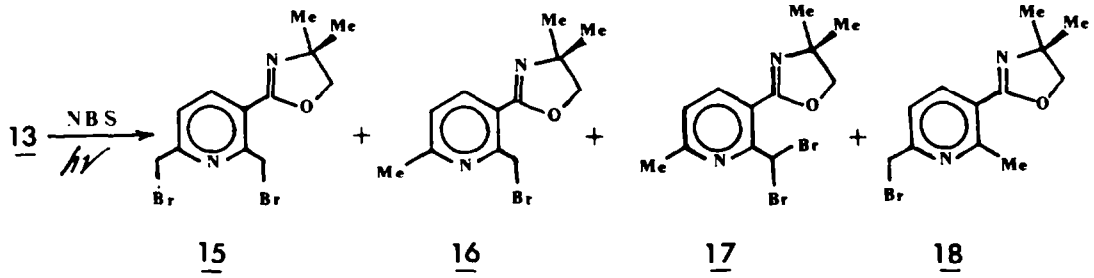


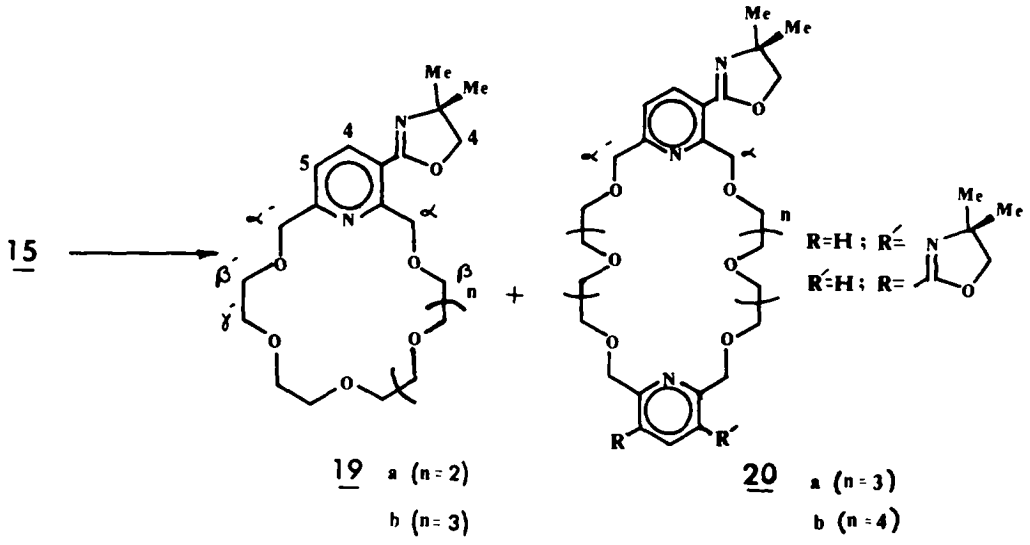
(93%), subsequent treatment with P_2O_5, caused cyclization to **13** in 70% yield; the use of pyridine, as solvent, enhanced (> 80%) oxazoline formation.

Oxazoline **13** was brominated with N-bromosuccinimide (NBS) in CH_2Cl_2 under irradiation with a 125W incandescent light and AIBN, as the initiator, to give four major products, of which the *bis*-bromomethyl derivative **15** was isolated (24%) and characterized (^{1}H NMR) by the two singlets at δ4.48 and 5.08 for the 6- and 2-methylene groups, respectively. Interestingly, **16** was the major (40%) monobrominated product as shown by the downfield singlet at δ5.12 for the 2-CH_2Br moiety as well as singlet at δ2.57 for the 6-methyl group. Bromination of **16** gives predominately **17** as suggested by the growth of the singlet at δ6.63 for the methyne hydrogen. Monobromination at the remote 6-position of **13** afforded **18** in low yield, as shown by the singlet at δ2.87 for the 2-Me group.

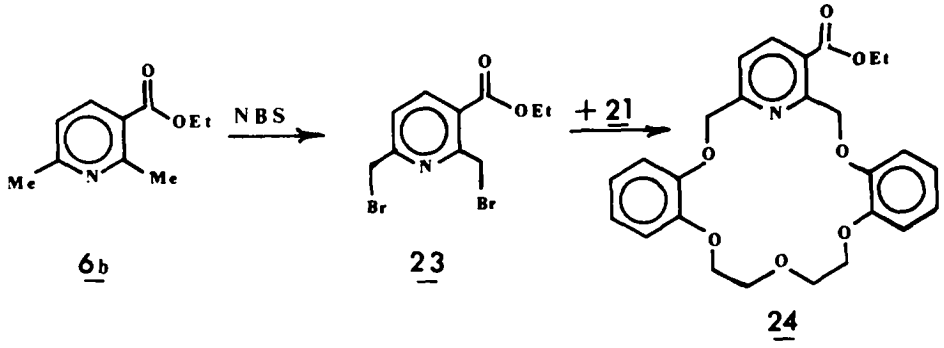
Synthesis of the polyethereal bridge was accomplished by treatment of **15** with sodium polyethyleneglycolate in dimethoxyethane under high-dilution conditions. With pentaethylene glycol, the 1:1-macrocycle **19a** was isolated (45%) and characterized (^{1}H NMR) by the two singlets at δ4.81 and 5.05 for the α'- and α-CH_2O moieties, respectively, as well as the intact oxazoline ring. Isomeric 2:2-macrocycles **20a** were also isolated (48%) but not separated. The hexaethylene glycol macrocycles **19b** (46%) and **20b** (43%) were spectrally characterized; the ^{1}H NMR data were nearly identical to that of **19a** and **20a**, respectively.

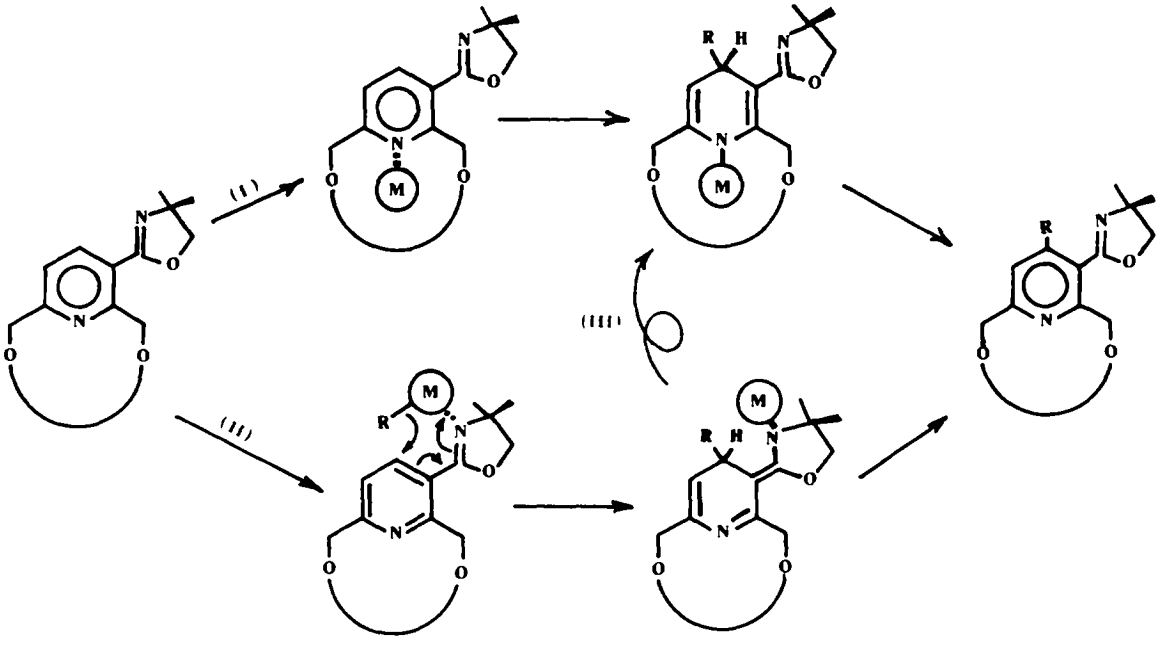
Treatment of diol **21** with **15** in the presence of cesium carbonate, as both base and template ion, gave the dibenzo macrocycle **22** in 46% yield. The use of cesium carbonate has been demonstrated[15] to enhance the cyclization process. The up-field shift ($\Delta\delta$0.5) for both α, α'-methylene hydrogens in **22** is indicative of increased rigidity caused by the fused benzo moieties.





Under the milder reaction conditions and the use of cesium carbonate, competitive transesterification should be minimized. To test this hypothesis, ethyl 2, 6-dimethylnicotinate was brominated with NBS under similar conditions, as described above. The desired *bis*-bromomethyl ester **23** was prepared (25%) and isolated as colorless crystals, which decomposed upon standing. The combination of diol **21** with **23** proceeded smoothly to give (78%) macrocycle **24**. The presence (^{1}H NMR) of singlets at δ5.68 and 5.38 for



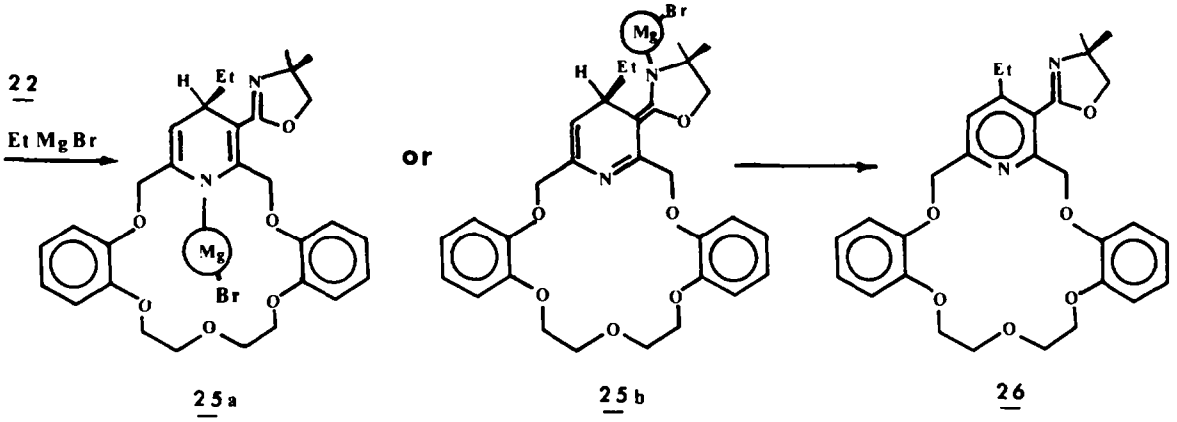


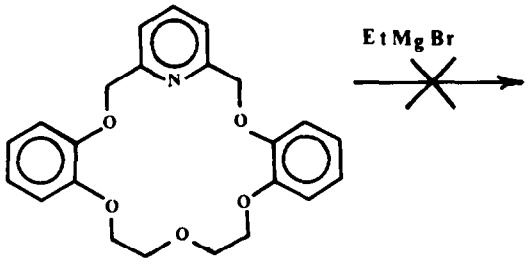
the α, α′-pyridyl methylenes as well as the quartet at δ4.39 for the ethyl ester confirm the macrocyclization process to the near exclusion of transesterification.

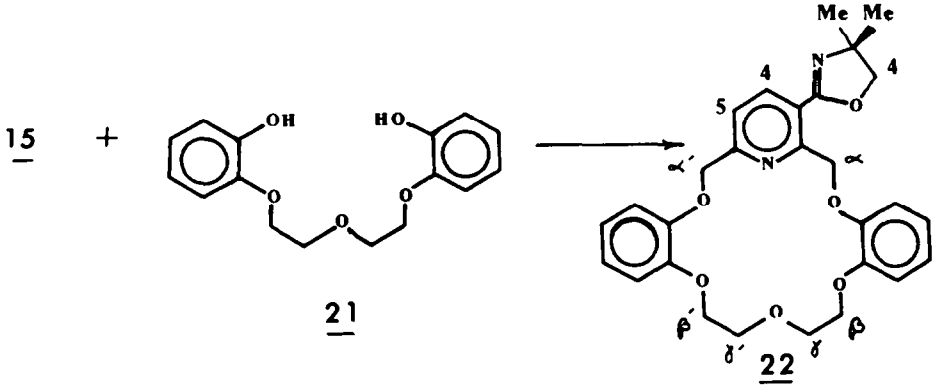
2. *Reactions of the nicotino macrocycles.* These oxazoline macrocycles can be envisioned to undergo reduction of the pyridine subunit by: (i) initial metal ion inclusion, followed by 1, 4-nucleophilic addition; (ii) metal ion coordination, then directed nucleophilic attack; or (iii) a combination of directed metallation-addition, then metal ion rearrangement. Aromatization of the dihydro intermediate(s) (after hydrolysis) is quite facile in the air or under mild oxidative conditions. In the presence of an electrophilic center, hydride transfer via metal ion coordination also leads to aromatization.

In the simple pyridine oxazolines, it has recently been shown that coordination of the organometallic reagent with the oxazoline directs the nucleophile to the 4-position of the pyridine nucleus.[6b-f] Subsequent aromatization gave the 4-substituted products. Asymmetric reduction has also been demonstrated with chiral oxazolines.[6e,f]

In our hands, dibenzooxazoline **22** underwent addition of ethylmagnesium bromide at 0° to give, after hydrolysis, the dihydro intermediate **25** which was readily oxidized to **26** under standard work up conditions or by chloranil oxidation. The ^{1}H NMR spectrum of **26** exhibited a singlet at δ1.40 for the *gem*-dimethyl group and a quartet at δ2.77 for the methylene of the newly incorporated ethyl group. The indicated directivity (route ii) of the oxazoline group is inferred since the unsubstituted dibenzocrown







analog (**27**) of **22** does not undergo 4-substitution under similar reaction conditions. Under more drastic conditions, **19a, 19b** and **22** with excess n-BuLi, gave ring-fragmented products, whereas with one equiv. of n-BuLi, starting materials were obtained.

Under low temperature reductive conditions: $Na_2S_2O_6$, $LiAlH_4$, or $NaBH_4$, macrocycles **19a** and **19b** were recovered *in toto*. However, **22** with $LiAlH_4$ in THF at 25° afforded cleavage of the macrocycle and recovery of an equal ratio of the diol **21** and **13**. Such a fragmentation probably results from hydride attack at the pyridine α-methylene and loss of phenoxide ion. Macrocycle **19a** smoothly complexes KBH_4, as implied by the upfield shift ($\Delta\delta$0.9) of the 4-pyridine-H and the downfield shift of the α-methylene groups. This complex appears to be quite stable under normal conditions but treatment with silver acetate quantitatively regenerates ligand **19a**. Such complexation is comparable to known cavity chemistry of cryptands and crown ethers.[16]

The preliminary chemistry presented herein of these macromolecules with different loci for metal ion coordination suggests that the site(s) or mode(s) of complexation will result through a selective reaction pathway. The non-coplanarity of the oxazoline moiety with the pyridine nucleus caused by the juxtaposition of the bridge connection may diminish an ionic mechanistic course in favor of a radical anion process. Further studies are in progress to afford more insight into the effect and locus preference in transition metal ion complexation.

EXPERIMENTAL

General comments. All m.ps were taken in capillary tubes with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were determined on an IBM-Bruker NR-80 NMR spectrometer using $CDCl_3$ as solvent, except where noted, with tetramethylsilane, as the internal standard. IR spectra were recorded on a Perkin–Elmer 621 grating-IR spectrophotometer. Mass spectral (MS) data (70eV) (assignment, relative intensity) were determined by Mr. D. Patterson on a Hewlett–Packard HP 5985 GC/mass spectrometer. Reported R_f values were ascertained by a standardized TLC procedure: Baker-flex® silica gel IB2-F plates eluting with the stipulated solvent system. For preparative thick-layer chromatography (ThLC), 2-mm silica gel PF-254-366 plates were used. Elemental analyses were performed by Mr. R. Seab in these laboratories.

Ethyl 2, 6-*dimethyl*-4-*chloronicotinate* (**8**) was prepared (69%) via the procedure of Bachmann and Barker,[11] by the reaction of ethyl 3-aminocrotonate[10] and $POCl_3$: b.p. 92–94° (0.5 mm) [lit.[11] b.p. 97–105° (2 mm)]; ^1H NMR δ1.40 (t, CH_2CH_3, J = 7.3Hz, 3H), 2.52 2.53 (2s, py-Me, 6H), 4.44 (q, CH_2CH_3, J = 7.3Hz, 2H), 7.28 (s, 5-pyH, 1H); IR (neat) 1730 (C=O), 855 (C–Cl) cm^{-1}; MS *m/e* 215 [M^+(^{35}Cl), 11], 213 [M^+(^{35}Cl), 39], 168 (M^+–OEt, 100); (Found: C, 56.35; H, 5.83; N, 13.01. Calc for $C_{10}H_{12}ClNO_2$: C, 56.26; H, 5.68; N, 13.12).

Ethyl 2, 6-*dimethylnicotinate* (**6b**). To a stirred suspension of ethyl 2, 6-dimethyl-4-chloronicotinate (29g, 139 mmol), triethylamine (46.8g, 450 mmol), and Pd–C (10%; 4g), was added formic acid (88%; 21g, 400 mmol) dropwise while maintaining the soln below 85°. The mixture was then refluxed at 95°; the time (*ca* 6 days) was determined by monitoring (TLC) the loss of the starting ester [R_f 0.83 (CH_2Cl_2)]. The cooled mixture was dissolved in CH_2Cl_2, filtered, washed with H_2O, and distilled *in vacuo* to give the desired ester, **6b**, as a colorless oil: 23.2g (95%); b.p. 74–75° (0.5 mm) [lit.[14] b.p. 111–120° (7 mm)]; R_f 0.76 (SiO_2, CH_2Cl_2); ^1H NMR δ 1.39 (t, CH_2CH_3, J = 7.3Hz, 3H), 2.56 (s, 6-pyMe, 3H), 2.81 (s, 2-pyMe, 3H), 4.37 (q, CH_2CH_3, J = 7.3Hz, 2H), 7.05 (d, 5-pyH, J = 7.9Hz, 1H), 8.09 (d, 4-pyH, J = 7.9Hz, 1H); IR (neat) 1715 (C = O) cm^{-1}; MS *m/e* 179 (M^+, 44), 134 (M^+–OEt, 100); (Found: C, 70.32; H, 7.66; N, 13.81. Calc for $C_{10}H_{13}NO_2$: C, 70.59; H, 7.84; N, 13.74).

A second product was isolated from the residue and shown to be the 4, 4′-coupled product **9**, as a white solid: 600mg (3.5%); m.p. 168° ($CHCl_3$–Et_2O); ^1H NMR δ1.33 (t, CH_2CH_3, J = 7.5Hz, 3H), 2.34 (s, 6-pyMe, 3H), 2.49 (s, 2-pyMe, 3H), 4.29 (q, CH_2CH_3 J = 7.5Hz, 2H), 6.33 (bs, 5-pyH, 1H); IR (KBr) 1705 (C–O) cm^{-1}; MS *m/e* 195 (48), 149 (100);(Found: C, 67.64; H, 6.61; N, 7.95. Calc for $C_{20}H_{24}N_2O_4$: C, 67.40; H, 6.79; N, 7.86).

Polyethereal bis-enamine **11a** [~100%; ^1H NMR δ1.20 (t, CH_3, J = 7.2Hz, 6H), 3.6 (m, OCH_2CH_2, 16H), 4.03 (s, $COCH_2O$, J = 7.2Hz, 4H), 4.06 (q, CH_2CH_3, J = 7.2Hz, 2H), 4.44 (s, CH, 2H), 6.5 (bs, NH_2, 2H)] was prepared from the *bis*-ester **10a**[7a] by reaction with anhydrous NH_3 in CH_2Cl_2. Upon evaporation, **11a** was found to be a hygroscopic oil: ~100%; ^1H NMR δ1.28 (t, OCH_2CH_3, J = 7.3Hz, 6H), 3.53 (s, OCH_2CO, 4H), 3.66 (m, OCH_2CH_2, 16H), 4.19 (q, OCH_2CH_3, J = 7.3Hz, 4H), 4.20 (s, $COCH_2$, 4H).

Ethyl 3-*amino*-4-*ethoxybut*-2-*enoate* (**11b**) was similarly prepared from ethyl 4-ethoxy-3-oxobutanoate [^1H NMR δ1.24 (t, OCH_2CH_3, J = 7.0Hz, 3H), 1.28 (t, $CO_2CH_2CH_3$, J = 7.1Hz, 3H), 3.52 (s, $COCH_2CO$, 2H), 3.56 (q, $COCH_2CH_3$, J = 7.0Hz, 2H), 4.10 (s, $OCH_2C{=}O$, 2H), 4.20 (q, $CO_2CH_2CH_3$, J = 7.1Hz, 2H)], which was in turn synthesized from ethyl 4-bromo-3-oxobutanoate[17] by the method of Kellogg *et al.* for the synthesis of the polyethereal *bis*-β-ketoester: *ca* 50% (from bromide); m.p. 109.5°; ^1H NMR (DMSO-d_6) δ1.17 (t, $CO_2CH_2CH_3$, J = 7.0Hz, 3H), 3.48 (q, $COCH_2CH_3$, J = 7.0Hz, 2H), 3.72 (s, $COCH_2$, 2H), 4.00 (q, $CO_2CH_2CH_3$, J = 7.0Hz, 2H), 4.87 (s, CH, 1H). Ester **11b** readily polymerizes upon standing or attempted purification.

2-[3′-(2′, 6′-*Dimethylpyridyl*)]-5, 5-*dimethyloxazoline* (**13**). A stirred mixture of 2-amino-2-methylpropan-1-ol (40g, 449 mmol), ethyl 2, 6-dimethylnicotinate (20g, 112 mmol), and P_2O_5 (15g), and anhyd xylene (100mL) was refluxed under N_2 for 30 hr. The soln was cooled and carefully neutralized with 10% NaOH aq. The organic layer was decanted and the aqueous layer was extracted several times with CH_2Cl_2; then the combined organic extract was dried over $MgSO_4$ and evaporated *in vacuo* to give a black viscous residue, which was distilled to afford **13**, as a colorless oil: 10.5 g (50%); b.p. 104° (0.5 mm); ^1H NMR δ1.38 (s, diMe, 2.54 (s, 6-pyMe, 3H), 2.78 (s, 2-pyMe, 3H), 4.07 (s, 4-CH_2, 2H), 7.00 (d, 5-pyH, J = 8.0Hz, 1H), 7.93 (d, 4-pyH, J = 8.0Hz, 1H); IR (neat) 1635 (C=N), 1585, 1035 cm^{-1}; MS *m/e* 204 (M^+, 100), 189 (M^+–Me, 66), 161 (29), 149 (43), 134 (35), 133 (47); (Found: C, 70.32; H, 7.66; N, 13.81. Calc for $C_{12}H_{16}N_2O$: C, 70.59; H, 7.84; N, 13.74).

The intermediate **14** can also be isolated under non-dehydrative conditions (no P_2O_5): m.p. 154–156°; 21.5 g (93%); ^1H NMR δ 1.41 (s, diMe, 6H), 2.53 (s, 6-pyMe, 3H), 2.62 (s, 2-pyMe, 3H), 3.67 (s, CH_2, 2H), 6.00 (s, OH, 1H), 6.98 (d, 5-pyH, J = 7.8Hz, 1H), 7.53 (d, 4-pyH, J = 7.8Hz, 1H); IR (KBr) 3200 (b, OH), 1660 (C=O), 1555, 1460, 1110, 1065 cm^{-1}; MS *m/e* 222 (M^+, 0.1), 191 (M^+–OCH_3, 9.7), 134 (100), 106 (21); (Found: C, 64.69; H, 7.99; N, 12.69. Calc for : $C_{12}H_{18}N_2O_2$: C, 64.86; H, 8.11; N, 12.61).

Bromination of oxazoline **13**. A stirred soln of **13** (6g, 34 mmol) and NBS (17g, 98 mmol) in CH_2Cl_2 (400 mL) was irradiated with an 150 W light for 24 hr. The mixture was neutralized, then washed with 10% Na_2CO_3 aq. (300 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a residue, which was chromatographed (column; SiO_2) eluting with CH_2Cl_2 to afford two main fractions:

Fraction A gave the desired symmetrical dibromide **15**, as a colorless oil, which decomposes on standing to a glassy

polymer: 2.94 g (24%); R_f 0.23 (CH_2Cl_2); ^{1}H NMR δ 1.35 (*s*, *di*Me, 6H), 4.06 (s, 4-CH_2, 2H), 4.48 (s, 6-pyCH_2, 2H), 5.08 (s, 2-pyCH_2, 2H), 7.37 (d, 5-pyH, J = 7.8Hz, 1H), 8.09 (d, 4-pyH, J = 7.8Hz, 1H); IR (KBr) 1715 (C=N), 1640, 1035 cm^{-1}; MS *m/e* 364 [M$^+$(^{81}Br), 55], 362 (M$^+$, 100), 360 [M$^+$(^{79}Br), 58]; (Found: C, 39.51; H, 3.72; N, 7.59. Calc for $C_{12}H_{14}N_2OBr_2$: C, 39.78; H, 3.90; N, 7.73).

Fraction B gave the monobromide **16**, as a crystalline solid: 3.82 g (40%); mp 69°; R_f 0.10 (CH_2Cl_2); ^{1}H NMR δ 1.41 (s, diMe, 6H), 2.57 (s, 6-pyMe, 3H), 4.11 (s, 4-CH_2, 2H), 5.12 (s, 2-pyCH_2, 2H), 7.12 (d, 5-pyH, J = 8.2Hz, 1H) 8.02 (d, 4-pyH, J = 8.2Hz, 1H); IR (Neat) 1700 (C=N), 1625, 1290, 1030 cm^{-1}; MS *m/e* 284 [M$^+$(^{81}Br), 63], 282 [M$^+$(^{79}Br), 71], 173 (81), 131 (100); (Found: C, 50.73; H, 5.26; N, 9.75. Calc for: $C_{12}H_{15}N_2OBr$: C, 50.87; H, 5.35; N, 9.89).

A fraction (R_f 0.3) gave a mixture of the monobromide **18** [~ 5%(^{1}H NMR) δ 2.87 (s, 3H)] and the geminal dibromide **17** [~ 7%(^{1}H NMR δ 6.63 (s, 1H)]; further purification was not conducted.

General procedure for macrocycle preparation

Reaction of **15** *with pentaethylene glycol.* To a stirred suspension of NaH (oil-free; 150 mg, 6.0 mmol) in dry DME (450 mL) at 60°, pentaethylene glycol (710 mg, 3 mmol) was added, followed in 30 min by **15** (985 mg, 2.72 mmol). The mixture was maintained for 2 hr, then cooled and carefully neutralized with (15%) NH_4Cl aq (10 mL). The organic layer was separated and was made basic with 10% Na_2CO_3 aq (20 mL) and extracted with CH_2Cl_2. The combined organic extract was concentrated *in vacuo* then chromatographed (ThLC, Al_2O_3) eluting with 5% *i*-prOH–CH_2Cl_2 to give the desired macrocycle **19a**, as a pale yellow oil: 560 mg (45%); R_f 0.28; ^{1}H NMR δ 1.37 (s, diMe, 6H), ~ 3.7 (m, β-β'-ξ-CH_2, 20H), 4.08 (s, 4-CH_2, 2H), 4.81 (s, α'-CH_2, 2H), 5.05 (s, α-CH_2, 2H), 7.39 (d, 5-pyH, J = 7.8Hz, 1H), 8.10 (d, 4-pyH, J = 7.8Hz, 1H); IR (neat) 1634 (C=N), 1581, 1425, 1340, 1290, 1100 cm^{-1}; MS *m/e* 438 (M$^+$, 11), 409 (31), 363 (22), 204 (100); (Found: C, 60.11; H, 8.03; N, 6.25. Calc for $C_{22}H_{34}N_2O_7$: C, 60.24; H, 7.83; N, 6.39).

A second fraction afforded isomeric 2:2-macrocycles **20a**, as an oil: 587 mg (48%); R_f 0.18; ^{1}H NMR δ 1.39 (s, diMe, 12H), ~ 3.7 (m, β-β'-ξ-CH_2, 40H), 4.10 (s, 4-CH_2, 4H), 4.73 (s, α'-CH_2, 4H), 4.97 (s, α-CH_2, 4H), 7.49 (d, 5-pyH, J = 7.8Hz, 2H), 8.10 (d, 4-pyH, J = 7.8Hz, 2H); IR (neat) identical to the 1:1-macrocycle; MS *m/e* 455 (13), 409 (20), 351 (35), 233 (73), 204 (100); (Found: C, 60.31; H, 7.80; N, 6.36. Calc for $C_{44}H_{68}N_2O_{14}$: C, 60.24; H, 7.83; N, 6.39).

Reaction of **15** *with hexaethylene glycol*

Macrocycles **19b** *and* **20b**. A mixture of **15** (1.43g, 3.95 mmol), hexaethylene glycol (1.17g, 4.06 mmol), and NaH(oil-free; 373mg, 8.7 mmol) afforded, after standard workup, the 1:1-macrocycle **19b**, as an oil: 879 mg (46%); R_f 0.30, (5% *i*-prOH-CH_2Cl_2); ^{1}H NMR δ 1.38 (s, diMe, 6H), 3.67 (m, β-β'-η-CH_2, 24H), 4.08 (s, 4-CH_2, 2H), 4.77 (s, α'-CH_2, 2H), 5.03 (s, α-CH_2, 2H), 7.42 (d, 5-pyH, J = 7.8Hz, 1H), 8.10 (d, 4-pyH, J = 7.8Hz, 1H); IR (neat) 1690 (C=N), 1585, 1455, 1342, 1102 cm^{-1}; MS *m/e* 482 (M$^+$, 11), 395 (36), 233 (74), 219 (100), 204 (84); (Found: C, 59.75; H, 8.11; N, 5.73. Calc for $C_{24}H_{38}N_2O_8$: C, 59.75; H, 7.95; N, 5.80).

The 2:2-macrocycle **20b** was also isolated: oil; 823 mg (43%); R_f 0.20; ^{1}H NMR δ 1.39 (s, diMe, 12H), ~ 3.7 (m, β-β-η-CH_2, 48H), 4.10 (s, 4-CH_2, 4H), 4.73 (s, α'-CH_2, 4H), 4.98 (s, α-CH_2, 4H), 7.50 (d, 5-pyH, J = 7.8Hz, 2H), 8.02 (d, 4-pyH, J = 7.8Hz, 2H); IR (neat) identical to 1:1; MS *m/e* 499 (13), 219 (68), 204 (48), 89 (53), 45 (100); (Found: C, 59.78; H, 7.90; N, 5.78. Calc for $C_{48}H_{76}N_4O_{16}$: C, 59.75; H, 7.95; N, 5.80).

Reaction of oxazoline **15** *with the dibenzotetraethylene glycol.* A stirred mixture of dibromide **15** (500 mg, 1.38 mmol), benzoether **21** (400 mg, 1.38 mmol), and Cs_2CO_3 (992 mg, 2.76 mmol) in anhydrous DMF (200 mL) was heated at 60° for 14 hr. The solution was cooled then concentrated *in vacuo* to give a white solid, which was in part dissolved in CH_2Cl_2. After filtration, the macrocycle, precipitated by trituration with MeOH, was recrystallized from EtOH-H_2O to give the desired 1:1-**22**, as a white powder: m.p. 149–150°; 310 mg (47%); ^{1}H NMR δ 1.38 (s, diMe, 6H), 3.83 (m, γ, γ'-CH_2, 4H), 4.08 (s, 4-CH_2, 2H), 4.14 (t, β'-CH_2, J = 5.8Hz, 2H), 4.28 (t, β-CH_2, J = 5.8Hz, 2H); 5.31 (s, α'-CH_2, 2H), 5.63 (s, α-CH_2, 2H), 6.9 (m, phH, 8H), 7.58 (d, 5-pyH, J = 7.8Hz, 1H), 8.19 (d, 4-pyH, J = 7.8Hz, 1H); IR (KBr) 1645 (C=N), 1600, 1500, 1255, 1210, 1130 cm^{-1}; MS *m/e* 490 (M$^+$, 28), 202 (100), 201 (77); (Found: C, 68.60; H, 6.22; N, 5.74. Calc for $C_{28}H_{30}N_2O_6$: C, 68.54; H, 6.12; N, 5.71).

Bromination of ethyl 2, 6-*dimethylnicotinate.* A stirred benzene solution (100 mL) of ethyl 2, 6-dimethylnicotinate (3.85 g, 21.5 mmol) was warmed to 70°, then NBS (9.5 g, 53 mmol) and AIBN (50 mg) were added in small increments. The mixture was refluxed with illumination for 16 hr. The resultant soln was cooled, washed with 10% Na_2CO_3 aq dried over $MgSO_4$, and concentrated *in vacuo* to give a red oil, which was dissolved in a minimum volume of ether and allowed to stand at − 10° for several hr until the desired *bis*-**23** precipitated, as colorless crystals: 1.76 g (25%); m.p. 51–52° (ether); ^{1}H NMR δ 1.43 (t, CH_2CH_3, J = 7.3Hz, 3H), 4.44 (q, CH_2CH_3, J = 7.3Hz, 2H), 4.55 (s, α'-CH_2Br, 2H), 5.00 (s, α-CH_2Br, 2H), 7.49 (d, 5-pyH, J = 8.5Hz, 1H), 8.28 (d, 4-pyH, J = 8.5Hz, 1H); IR (KBr) 1720 (C=O), 1115 cm^{-1}; MS *m/e* 258 (93) 256 (M$^+$–^{79}Br, 100); (Found: C, 35.93; H, 3.53; N, 3.98. Calc for $C_{10}H_{11}Br_2NO_2$: C, 35.63; H, 3.29; N, 4.16).

Reaction of **23** *with dibenzotetraethylene glycol.* The reaction of **23** (624 mg, 2.0 mmol), **21** (540 mg, 2.0 mmol), and Cs_2CO_3 (1.24 g, 4.0 mmol) in anhyd DMF (300 mL) was conducted and worked up as described for **22** to give **24**, as colorless needles: 689 mg (76%); m.p. 124–125° (EtOH–H_2O); ^{1}H NMR δ 1.40 (t, CH_2CH_3, J = 7.3Hz, 3H), 3.85 (m, CH_2, 4H), 4.15 (t, γ-CH_2, J = 5.2Hz, 2H), 4.31 (t, β-CH_2, J = 4.7Hz, 2H), 4.39 (q, CH_2CH_3 J = 7.3Hz, 2H), 5.38 (s, α'-CH_2, 2H), 5.60 (s, α-CH_2, 2H), 7.0 (m, phH, 8H), 7.65 (d, 5-pyH, J = 8.2Hz, 1H), 8.32 (d, 4-pyH, J = 8.2Hz, 1H); IR (KBr) 1705 (C=O), 1585, 1495, 1245, 1200, 740 cm^{-1}; MS *m/e* 465 (M$^+$, 64), 121 (100); (Found: C, 66.97; H, 6.08; N, 2.86. Calc for $C_{26}H_{27}O_7N$: C, 67.07; H, 5.86; N, 3.01).

Reactions of **22** *with ethylmagnesium bromide.* To a stirred soln of **22** (20 mg, 0.04 mmol) in anhyd diethylether (5 mL) at − 70°, EtMgBr (400 L, 3M in ether, 1.2 mmol) was slowly added under a N-atmosphere. After 1 hr, the mixture was warmed to 25° and poured into a sat NH_4Cl aq. The ether was removed *in vacuo* and the residual aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined extract was dried and concentrated *in vacuo* to give a mixture, of **25** and **26** (*ca* 1:1) [^{1}H NMR δ 5.16 (α-CH_2) and 4.57 (α'-CH_2)], which was oxidized with chloranil (20 mg) in toluene (10 mL) for 2 hr at 25°. The toluene solution was extracted with aqueous (10%) NaOH, then dried over $MgSO_4$ and concentrate *in vacuo*. The residue was chromatographed (ThLC) eluting with CH_2Cl_2–MeOH (5%) to give **26**, as solid: m.p. 42–44°; R_f 0.45; 15 mg (85%); ^{1}H NMR 1.26 (t, CH_2CH_3, J = 7.4Hz, 3H), 1.40 (s, diMe, 6H), 2.77 (q, CH_2CH_3, J = 7.4Hz, 2H), 3.6 (m, β', γ'-CH_2, 4H), 4.10 (s, 4-CH_2, 2H), 4.1 (m, β, γ'-CH_2, 4H), 6.9 (m, phH, 8H), 7.40 (s, 5-pyH, 1H); MS *m/e* 518 (M$^+$, 2.1), 149 (100).

General procedure for reaction of n-butyllithium with macrocycles **19a, 20a and 22.** To a stirring 0.01 molar THF soln of the macrocycle (0.05 mmol) at −70°, n-BuLi (0.25 mmol) was added. In each case the mixture became dark brown and upon standard work up as above the starting macrocycle and macrocyclic products were not detected.

Reaction of macrocycles **27**, **19a**, *and* **20a** *with ethylmagnesium bromide.* The macrocycle (0.04 mmol) in diethylether was stirred at − 70°, then EtMgBr (0.4 mL, 3M ether,

1.2 mmol) was added and stirred an additional 1 hr after which it was allowed to warm to 25°. The reaction was worked up as described above; with **27**, only unchanged starting **27** was (100%) recovered. Either **19a** or **20b** (0.23 mmol) in THF (5 mL) treated similarly with excess EtMgBr gave a yellowish ppt. After standard work up each reaction also gave unchanged (100%) starting macrocycle.

Reaction of **19a** *with potassium borohydride.* An anhyd EtOH (15 mL) soln of **19a** (40 mg, 0.9 mmol) and KBH_4 (100 mg, 1.9 mmol) was refluxed for 12 hr under N_2. The soln was evaporated *in vacuo* to give a residue which was extracted with $CHCl_3$ to give, after concentration, a solid that was nearly identical to the starting material [^{1}H NMR δ1.38 (s, diMe, 6H), 3.7 (m, OCH_2, 2H), 4.08 (s, 4-CH_2, 2H), 4.82 (s, α'-CH_2, 2H), 5.12 (s, α-CH_2, 2H), 7.30 (d, 4-pyH, J = 7.9Hz, 1H), 8.12 (d, 5-pyH, J = 7.9Hz, 1H)]. Treatment of the complex in acetonitrile with silver acetate (25 mg) gave an immediate gray suspension. Filtration, evaporation, and dissolution of the residue in CH_2Cl_2 afforded a soln which was washed with water, dried, and concentrated to give (100%) **19a**.

Reaction of **22** *with* $LiAlH_4$. Macrocycle **22** (40 mg, 0.08 mmol) in THF (5 mL) was added to a stirring THF suspension of $LiAlH_4$ (38 mg, 1 mmol) then stirred at 25° for 6 hr. Upon standard work up, starting macrocycle (~85%), oxazoline **13** (~15%), and glycol **21** (~15%) were isolated.

Acknowledgments—We acknowledge partial financial support from the National Institutes of Health and the National Science Foundation for funds to purchase our NMR instrumentation.

REFERENCES

[1]Chemistry of Heterocyclic Compounds Series, Part 85. For previous paper in this series: G. R. Newkome and V. K. Gupta, *Inorg. Chim. Acta* **65**, 165 (1982).

[2]Review: U. Eisner and J. Kuthan, *Chem. Rev.* **72**, 1 (1972); J. B. Jones and J. F. Beck, *Tech. Chem.* (N.Y.) **10**, 107 (1976).

[3a] H. Eklund and C. I. Bränden, *J. Biol. Chem.* **245**, 3458 (1979); [b]M. F. Dunn and J. S. Hutchinson, *Biochemistry* **12**, 4882 (1973); [c]J. D. Shore and D. Santiago, *J. Biol. Chem.* **250**, 2008 (1975); [d]G. Boccalon, G. Grillo, V. Baroncelli, P. Renzi and A. Parretta, *J. Mol. Catal.* **4**, 307 (1978); [e]A. S. Mildvan, *The Enzymes* (Edited by P. D. Boyer, Vol. 2, p. 446. Academic Press, New York (1970). [f]R. H. Abeles, R. F. Hutton and F. H. Westheimer, *J. Am. Chem. Soc.* **79**, 712 (1957); [g]A. S. Mildvan and H. Weiner, *Biochemistry* **8**, 552 (1969); *J. Biol. Chem.* **244**, 2465 (1969); [h]M. Hughes and R. H. Prince, *Bioorg. Chem.* **6**, 137 (1977); [i]Zn-ion participation in model systems: Y. Murakami, Y. Aoyama and J.-i. Kikuchi, *J. Chem. Soc. Perkin I*, 2809 1981 and Refs. 5–15 therein.

[4a]P. T. Lansbury and J. O. Peterson, *J. Am. Chem. Soc.* **85**, 2236 (1963); [b]P. T. Lansbury and R. E. Macleay, *Ibid.* **87**, 831 (1965); [c]A. J. de Konig, P. H. M. Budzelaar, B. G. K. van Aarssen, J. Boersma and G. J. M. van der Kerk, *J. Organometal. Chem.* **217**, Cl (1981); **186**, 173 (1980); **199**, 153 (1980).

[5a]A. J. de Konig, J. Boersma and G. J. M. van der Kerk, *Tetrahedron Letters* 2547 (1977); [b]*J. Organometal. Chem.* **186**, 159 (1980).

[6a]A. Ohno and Y. Ohnishi, *Kajaku No Ryoiki, Zohan*, 110 (1976); [b]A. I. Meyers and R. A. Gabel, *J. Org. Chem.* **47**, 2634 (1982) and refs therein; [c]C. S. Giam and A. E. Hauck, *J. Chem. Soc.* Chem. Commun., 615 (1978); [d]D. M. Stout and A. I. Meyers, *Chem. Rev.* **82**, 223 (1982); [e]A. I. Meyers and N. R. Natale, *Heterocycles* **18**, 13 (1982); [f]A. I. Meyers, N. R. Natale, D. G. Wettlaufer, S. Rafii and J. Clardy, *Tetrahedron Letters*, 5123 (1981); [g]A. E. Hauck and C. S. Giam, *J. Chem. Soc.* Perkin I, 2070 (1980).

[7a]R. M. Kellogg, T. J. van Bergen, H. van Doren, D. Hedstrand, J. Kooi, W. H. Kruizinga and C. B. Troostwijk, *J. Org. Chem.* **45**, 2854 (1980); [b]R. M. Kellogg and O. Piepers, *J. Chem. Soc.* Chem. Commun., 402 (1982); [c]P. Jouin, C. B. Troostwijk and R. M. Kellogg, *J. Am. Chem. Soc.* **103**, 2091 (1981); [d]J. G. de Vries and R. M. Kellogg, *Ibid.* **101**, 2759 (1978); [e]T. J. van Bergen, D. M. Hedstrand, W. H. Kruizinga and R. M. Kellogg, *J. Org. Chem.* **44**, 4953 (1979), [f]R. H. van der Veen, R. M. Kellogg, A. Vos and T. J. van Bergen, *J. Chem. Soc.* Chem. Commun., 923 (1978); [g]T. J. van Bergen and R. M. Kellogg, *J. Am. Chem. Soc.* **99**, 3882 (1977).

[8a]G. R. Newkome, G. L. McClure, J. Broussard-Simpson, and F. Danesh-Khoshboo, *J. Am. Chem. Soc.* **97**, 3224 (1975); [b]G. R. Newkome, A. Nayak, G. L. McClure, F. Danesh-Khoshboo and J. Broussard-Simpson, *J. Org. Chem.* **42**, 1500 (1977); [c]G. R. Newkome, F. Danesh-Khoshboo, A. Nayak and W. H. Benton, *Ibid.* **43**, 2685 (1978); [d]G. R. Newkome and T. Kawato, *Tetrahedron Lett.* 4643 (1978); [e]*J. Org. Chem.* **44**, 2693 (1979); [f]*Ibid.* **44**, 2697 (1979); [g]G. R. Newkome, T. Kawato and W. H. Benton, *Ibid.* **45**, 626 (1980); [h]G. R. Newkome, D. K. Kohli and T. Kawato *Ibid.* **45**, 4508 (1980); [i]G. R. Newkome, T. Kawato and W. H. Benton, *Ibid.* **45**, 5433 (1980); [j]G. R. Newkome and H. -W. Lee, *Ibid.* **47** (1982).

[9]F. Mutterer and C. D. Weis, *Helv. Chim. Acta* **59**, 222 (1976). We thank Dr. Weis for a generous sample. Attempted preparation by treatment of nicotinic acid with PCl_5 was unsuccessful; however, 2, 6-dihydroxynicotinic acid was readily prepared and can be transformed to 2, 6-dichloronicotinic acid by treatment with $PCl_5/POCl_3$ [A. Behrmann and A. W. Hofmann, *Ber. Dtsch. Chem. bis Ber.* **17**, 2694 (1884)].

[10]S. A. Glickman and A. C. Cope, *J. Am. Chem. Soc.* **67**, 1017 (1945).

[11]G. B. Bachmann and R. S. Barker, *J. Org. Chem.* **14**, 97 (1948).

[12]Followed the procedure of: N. A. Cortese and R. F. Heck, *J. Org. Chem.* **42**, 3491 (1977). Also see: K. Tsuda, N. Ikekawa, A. Iino, M. Furukawa and T. Hattori, *Pharm. Bull. Japan* **1**, 126 (1973) [*Chem. Abstr.* **49**, 3190b (1955)].

[13]E. M. Kosower, *Free Radicals in Biology* (Edited by W. A. Pryor), Vol. II, Chap. 1. Academic Press, New York (1976).

[14]See: A. Burger and G. E. Ullyot, *J. Org. Chem.* **12**, 342 (1947).

[15]W. H. Kruizinga and R. M. Kellogg, *J. Am. Chem. Soc.* **103**, 5183 (1981).

[16]A. Loupy and J. Seyden-Penne, *Tetrahedron* **36**, 1937 (1980).

[17]D. N. Reinhoudt, F. de Jong and H. P. M. Tomassen, *Tetrahedron Lett.*, 2067 (1979); B. J. van Keulen and R. M. Kellogg, *J. Chem. Soc.*, Chem. Commun. 285 (1978); J. Bater and R. M. Kellogg, *Ibid.* 466 (1980); F. Vögtle and B. Klieser, *Ibid.* 294 (1982); W. H. Kruizinga and R. M. Kellogg, *J. Am. Chem. Soc.* **103**, 5183 (1981).