densed in a 50-mL three-neck round-bottom flask, equipped with a dry ice/acetone condenser. Potassium (390 mg) and a few crystals of $Fe(NO_3)_3 \cdot 9H_2O$ catalyst were added. After stirring for 30 min at reflux temperature 0.58 g of 4-chloro-2-dimethylamino-5-phenylpyrimidine (**1b**) was added at −60 °C. After 4 h the reaction was quenched with ammonium chloride and the ammonia was evaporated. The residue was extracted with ether and the extract was evaporated to dryness. Separation from the by-product 4-amino-2-dimethylamino-5-phenylpyrimidine (yield 0.037 g (7%); mp 119–120 °C. Anal. Calcd for $C_{12}H_{14}N_4$: C, 67.3; H 6.6. Found: C, 67.2; H, 6.8) was performed by column chromatography (silica): yield 0.32 g; oil; picrate mp 143–144 °C. Anal. (picrate) Calcd for $C_{18}H_{17}N_7O_7$: C, 48.8; H, 3.9. Found: C, 48.8; H, 4.0.

Acknowledgment. We are indebted to Dr. C. A. Landheer and Mr. W. P. Combé for mass spectroscopic data, to Mr. W. Ch. Melger for chromatographic advice, and to Mr. H. Jongejan for carrying out the microanalyses.

Registry No.—**5b** picrate, 65942-58-7; 2-dimethylamino-5-phenyl-4-pyrimidone, 65942-56-5; 4,6-dichloro-2-dimethylamino-5-phenylpyrimidine, 61769-99-1; 4-chloro-2-dimethylamino-6-hydrazino-5-phenylpyrimidine, 65942-57-6; *N,N*-dimethylguanidine hydrochloride, 22583-29-5; diethyl phenylmalonate, 83-13-6.

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(10) In order to assign C-4 and C-5 in **3** correctly we acquired ^{13}C-NMR spectral information on the chemical shifts of acetylide anions. It was found by dissolving 3-methoxypropyn ($HC^1{\equiv}C^2C^3H_2OCH_3$) in liquid ammonia containing 2 equiv of potassium amide that in the acetylide anion thus formed the ^{13}C-NMR signals of C-1 and C-2 are shifted downfield 75.7 and 28.2 ppm with respect to the parent compound measured in $CDCl_3$ (74.8 ppm → 150.5 ppm for C-1 and 79.9 ppm → 108.1 ppm for C-2). Distinction between C-1 and C-2 in the acetylide form could be made on the basis of the triplet splitting ($^2J_{C-H}$ = 5.6 Hz) found for C-2 when wide band proton noise decoupling was *not* utilized. A deshielding effect upon anion formation is also found in a number of organolithium compounds, in which the metallated acetylenic carbons are shifted downfield with respect to the parent acetylenes.[11,12] Furthermore we compare the ^{13}C-NMR spectrum of ethoxyethyn (δ_{C-1} 23.2 and δ_{C-2} 89.4)[13] [in this compound the ^{13}C NMR shifts of the acetylenic carbons are strongly subjected to the +M and −I effects due to the neighboring oxygen atom] with that of its anion generated in KNH_2/NH_3. In this medium C-1 and C-2 are found to resonate at δ 72.5 and 116.2, respectively (downfield shifts of 49.3 and 26.8 ppm with respect to the parent compound). These data clearly show that the assignments proposed for C-4 and C-5 in **3** are quite reliable.
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Chemistry of Heterocyclic Compounds. 28. Reactions of Halopyridines with Mercaptide. Synthesis of Multiheteromacrocycles Possessing 2,6-Pyridino Subunits Connected by Carbon–Sulfur Linkages[1]

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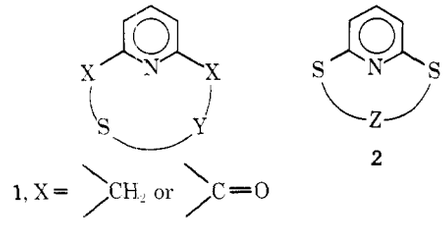
2,6-Dihalopyridines have been successfully incorporated into "crown ethers" (3); however, utilizing similar procedures to prepare the related thio "crown ethers" (e.g., 8) has met with very limited success. The major isolated products from nucleophilic displacement of halide from **7** by mercaptide were derived from numerous competitive reactions of the thiols, such as polymerization, fragmentation, oxidation, and oligomerizations. The desired carbon–sulfur bridged 2,6-pyridino macrocycles were isolated as minor components from these reactions.

Recently, we reported the synthesis of ethereal macrocycles which incorporated the 2,6-pyridino moiety.[2] Although numerous related thioethereal macrocycles have been reported,[3] the vast majority possess a backbone (**1**) in which the sulfur atom is isolated from the pyridine ring by either a methylene[4] or a carbonyl group.[5] Only recently has a second type of macrocyclic system (**2**) been constructed in which the sulfur atoms are directly connected to the 2 and 6 positions of the pyridine nucleus.[6] We herein describe the reactions of 2,6-dihalopyridines with different sulfur nucleophiles as well as the preparation and characterization of carbon–sulfur bridged 2,6-pyridino macrocycles of the latter type (**2**).



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The preparation of macrocyclic polyethers possessing the 2,6-pyridino subunit (e.g., **3**) has been accomplished,[2] and their general catalytic behavior is currently being studied;[7] however, the corresponding thioethers were yet unknown but were desirable for comparison studies. Important differences

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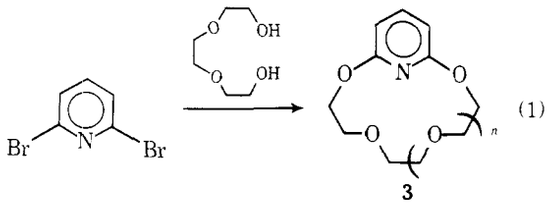
were anticipated in view of the increased nuclear size of sulfur vs. oxygen, a smaller C–S–C vs. C–O–C bond angle, decreased electronegativity of sulfur relative to oxygen, and diminished C–S vs. C–O ionic bond character. General nucleophilic substitution (eq 1) of 2,6-dihalo (pyridine) substituents, as uti-



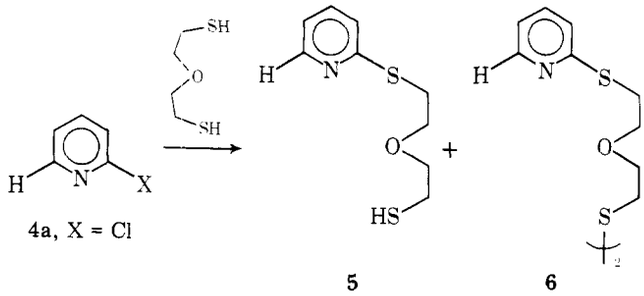
(1)

3

lized in the construction of **3**,[2] should be applicable to the synthesis of the thioether macrocycles.[8] The mercaptides were generated by either treatment of the appropriate bisthiol with diisopropylethylamine, as both base and solvent, or with sodium hydride in anhydrous xylene. As noted previously for glycols,[9] in order to minimize thermal fragmentation or oligomerization of the thioglycols, the reaction temperatures must be maintained below the upper 140 °C limit.

A. Reactions of 2-Halo- and 2,6-Dihalopyridines with Bis(2-mercaptoethyl) Ether. Reaction of 2-chloropyridine (**4a**) with the bismercaptide generated from bis(2-mercaptoethyl) ether upon treatment with 2 equiv of oil-free sodium hydride in anhydrous xylene gave a low yield of the 1:1 thiol **5** accompanied by its oxidation product, disulfide **6.** Isolation of a considerable amount of unreacted **4a** was unexpected in view of the lengthy reaction time. The overall nucleophilic displacement of chloride to give the corresponding pyridyl sulfides was considerably slower than the reaction of **4a** with the dianion of diethylene glycol.[2] Abramovitch and Newman[10] have specifically studied the action of 2-halopyridines with MeO^- and MeS^- and have concluded that MeS^- has a higher reactivity than MeO^- in either MeOH or HMPA. Thus, in hydrocarbon solvents a reversal of the sensitive balance in nucleophilicities of MeS^- and MeO^- occurs, which is attributed to either solvation of the thioalkoxide ion or the polarizability of the nucleophile and/or leaving group.

Thiol **5** undergoes facile air oxidation to the corresponding disulfide **6.** Total exclusion of air during the reaction was at-

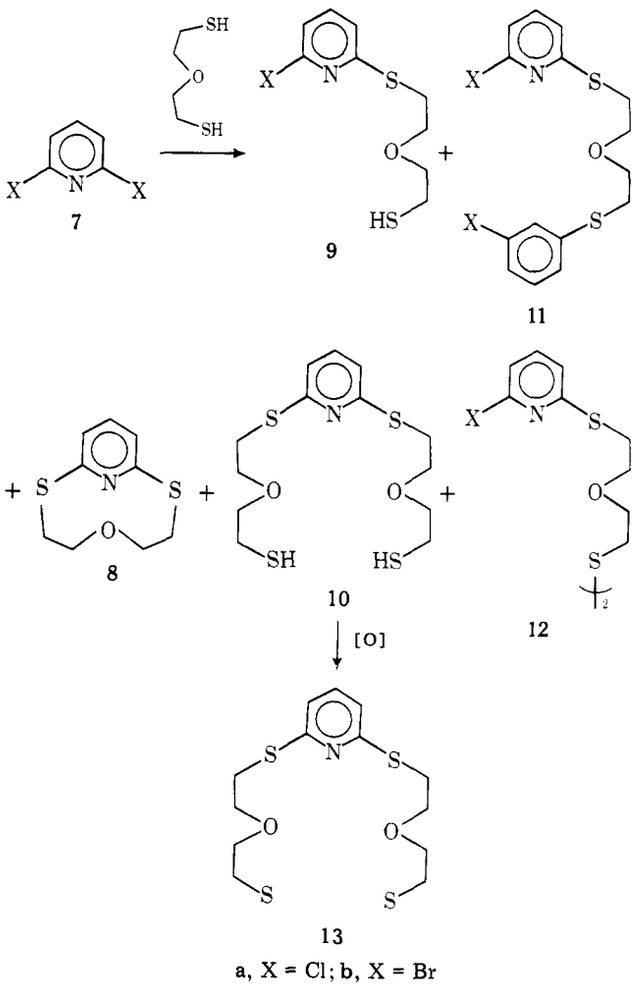


4a, X = Cl

5 6

tempted; however, during the workup procedure air oxidation could not be easily prevented.

The similar reaction of 2,6-dichloropyridine (**7a**) with bis(2-mercaptoethyl) ether dianion afforded the desired 1:1 macrocycle **8** along with numerous noncyclized thiols **9a** and **10,** sulfide **11a,** and disulfide **12a.** Macrocycle **8,** which possesses a ten-membered ring, is the smallest cyclic ring formed via this ring formation procedure. The diminished C–S–C bond angles and increased nuclear size of sulfur in **8** are believed to relieve the strain which is present in the corresponding unknown carbon–oxygen macrocycle (**3,** n = 0). The down-field shift ($\Delta\delta$ = ca. 0.2) experienced by the β protons of **8** is indicative of the rigidly held 2,6-hetero bridge. Vögtle and Weber[4a] have previously synthesized **8** by a reverse procedure in which 2,6-dimercaptopyridine was treated with β,β-dihaloethyl ether.[11]



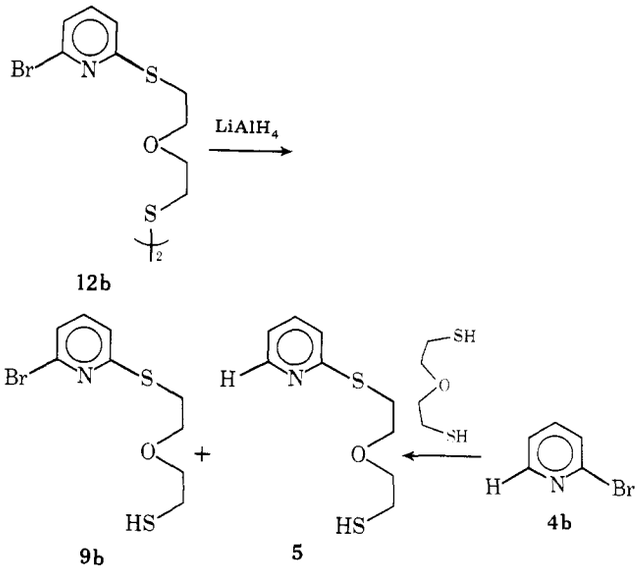
7

8 9 10 11 12

13

a, X = Cl; b, X = Br

In order to evaluate the effect of a leaving group and varied dianion preparations, 2,6-dibromopyridine (**7b**) was refluxed with bis(2-mercaptoethyl) ether in anhydrous diisopropylethylamine under nitrogen for 30 h. Only traces of **8** were detected, whereas **11b** was isolated in 18% yield at the expense of the 1:1 thiol **9b.** Extended reaction times (7 days) did not greatly effect the product distribution; similar percentages of unreacted **7b** were isolated. The dithiols in the reaction appear to be undergoing diverse competitive degeneration, the fate of which has not been determined. The 1:1 thiol **9b** was refluxed in diisopropylethylamine, resulting in cyclization to **8** in low yield and in oxidation to disulfide **12b.** Bisthiol **10**



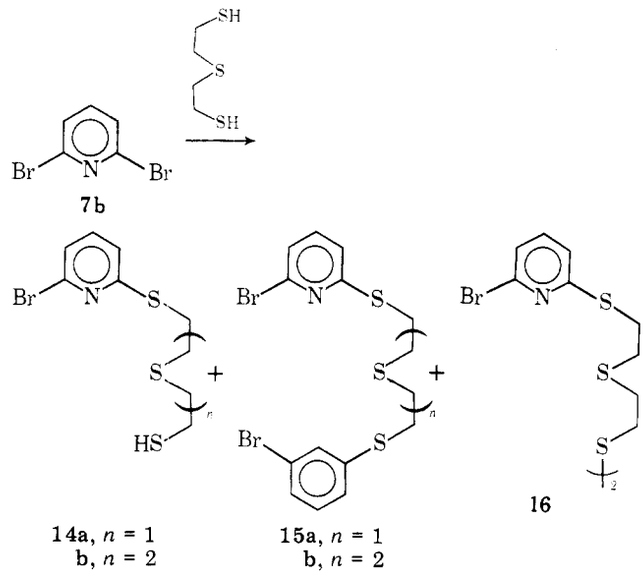
12b

9b 5 4b

was isolated in 2% yield and could be converted into the novel macrocyclic disulfide **13** upon oxidation.

Disulfide **12b** was reduced with lithium aluminum hydride in ether to give **9b** in 20% yield along with the debrominated thiol **5**. Hydrogenolyses of halo substituents from the pyridine nucleus by the action of hydride are known.[12] The other disulfides prepared in this study have similarly been reduced to prove the presence of the S–S bond.

B. Reactions of 2-Halo- and 2,6-Dihalopyridines with Bisthiols. 2,6-Dibromopyridine (**7b**) and bis(2-mercaptoethyl) sulfide in refluxing diisopropylethylamine afforded the expected thiol **14a**, the 2:1 sulfide **15a**, and disulfide **16**, as well as sulfide **15b**, which resulted from initial oligomerization of bis(2-mercaptoethyl) sulfide followed by reaction with 2 equiv of **7b**. Intermediate **14b** was not isolated from the reaction. The percentage of oligomerization products is very similar to that of previous alkoxide studies.[2] Treatment of **7a** with the dianion of bis(2-mercaptoethyl) sulfide (via the sodium hydride procedure) afforded only **17** and **18**. Disulfide **18** was smoothly reduced to **17**, thus confirming its assignment.

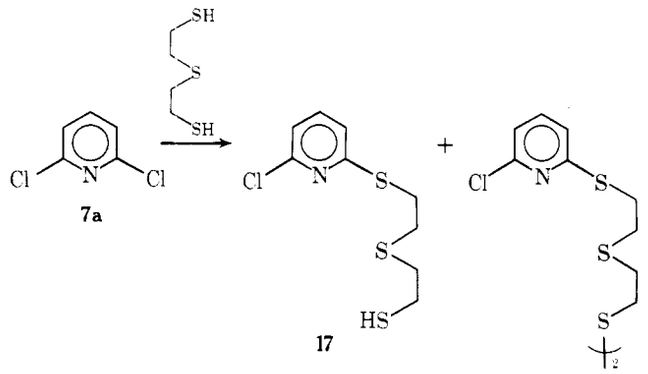


7b

14a, n = 1
b, n = 2

15a, n = 1
b, n = 2

16

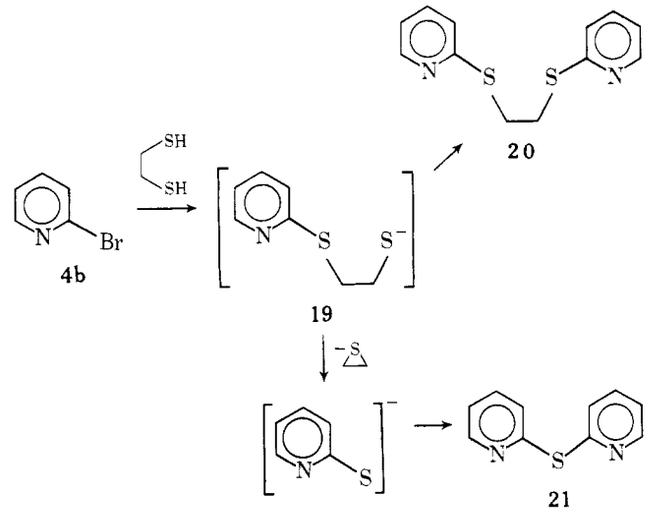


7a

17

The NMR spectra of these polysulfides are ill-defined, and only the α methylenes can be assigned unequivocally. Elemental analyses and mass spectral data help to substantiate the structural assignments of oligomerized products.

2-Bromopyridine (**4b**) was treated with 1,2-ethanedithiol in the tertiary amine to generate initially intermediate **19**, which undergoes conversion to 2,2′-ethylenedithiodipyridine (**20**). Competitively, **19** fragmented ethylene sulfide, under the basic conditions, to give 2-pyridyl mercaptide, which reacted with **4b** to yield (23%) bis(2-pyridyl) sulfide (**21**). Sulfide **21** has been previously prepared from 2-pyridinethiol and **4a**,[13] as well as the action of 2-halopyridines with either sodium sulfide or thiourea.[14] Oligomers of **20** were noted in



4b

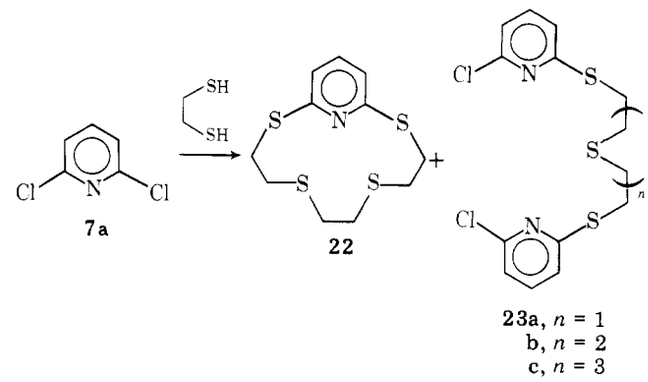
19

20

21

the reaction mixture; however, no attempt was made to isolate or characterize these side products.

Further evidence of oligomerization was realized when **7a** was treated with the dianion of ethanedithiol generated by method A. The only major macrocycle isolated was **22**, which arose from the dianion of 3,6-dithiaoctane-1,8-dithiol. The oligomerized 2:1 adducts **23** were also isolated, but the desired



7a

22

23a, n = 1
b, n = 2
c, n = 3

product (from ethanedithiol) was not detected. Thus, ethanedithiol, much like ethylene glycol,[2] does not undergo the smooth reactions like the higher members of these glycol series.

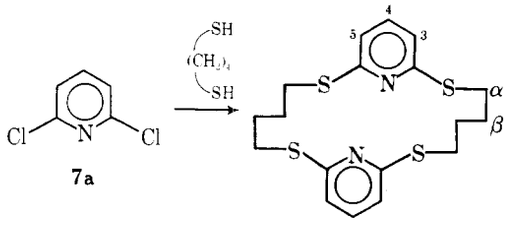
Lastly, in an attempt to evaluate the cyclization of dithiols connected by four methylene groups, **7a** was treated with 1,4-butanedithiol. The desired 2:2 macrocycle **24** was isolated in less than 0.5% yield. The lack of any templating effect was demonstrated in part by this low yield formation of **24** as well as by the isolation of the lower members of the polymeric series [2:1, **25**; 3:2, **26**; 4:3, **27**]. Numerous thiols and bisthiols were detected, but no attempt was made to isolate or characterize these oils. The NMR data for **24–27** have been analyzed and are given in the Experimental Section.

Conclusions

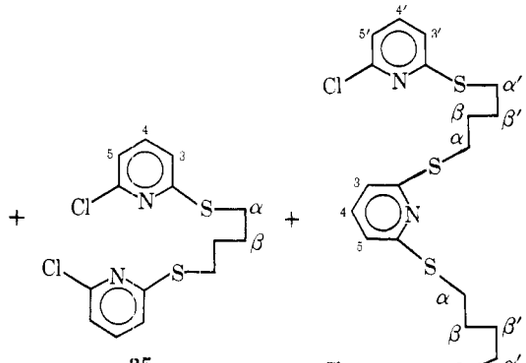
The template effect, which was realized in part during the formation of previous macrocyclic polyoxaethers,[2] was not demonstrated in the studies due to the apparent diminished sulfur to metal ion coordination. This phenomenon has been demonstrated in the synthesis of other simple macrocyclic polythiaethers.[15] The low reactivity of the 2,6 substituents on the pyridine nucleus toward nucleophilic attack as well as the clear decreased nucleophilicity of the mercaptides (vs. alkoxides) under similar reaction conditions further retard the cyclization process in relation to the competitive reactions of the thiols, such as, polymerization, fragmentation, oxidation, and oligomerization.

Table I. Reaction Conditions and Product Distribution

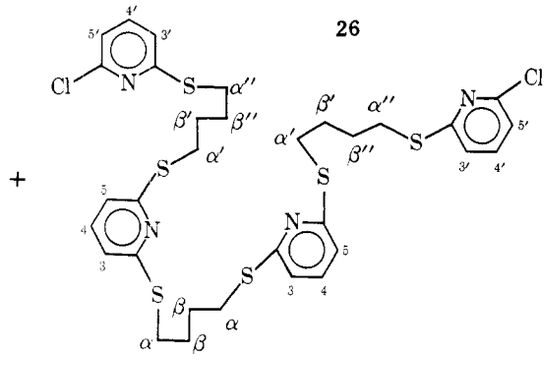
Reagents	Method	Reaction time, h	Products	Starting material
4a + $O(CH_2CH_2SH)_2$	A	72	**5** (9%), **6** (5%)	
7a + $O(CH_2CH_2SH)_2$	A	72	**8** (0.6%), **9a** (24%), **10** (2%), **11a** (6%), **12a** (6%)	**7a** (30%)
7b + $O(CH_2CH_2SH)_2$	B	60	**9b** (17%), **11b** (18%), **12b** (2%)	**7b** (38%)
	B	168	**9b** (13%), **11b** (8%), **12b** (2%)	**7b** (37%)
7b + $S(CH_2CH_2SH)_2$	B	60	**14a** (10%), **15a** (6%), **15b** (1%), **16** (1.2%)	**7b** (66%)
7a + $S(CH_2CH_2SH)_2$	A	72	**17** (6%), **18** (0.5%)	**7a** (85%)
4b + $(CH_2SH)_2$	B	60	**20** (11%), **21** (23%)	**4b** (52%)
7a + $(CH_2SH)_2$	A	72	**22** (1.3%), **23a** (10%), **23b** (4%), **23c** (1%)	**7a** (60%)
7a + $(CH_2CH_2SH)_2$	A	72	**24** (0.1%), **25** (7.5%), **26** (6%), **27** (3%)	**7a** (60%)



7a **24**



25 **26**



27

Experimental Section

General Comments. All melting points were taken in capillary tubes with a Thomas-Hoover Uni-Melt and are uncorrected. Infrared and ultraviolet spectra were recorded with Beckman IR-7 and Cary 14 spectrophotometers, respectively. Unless otherwise noted, ^1H NMR spectra were taken in deuteriochloroform solutions with Me_4Si as an internal standard (δ = 0 ppm) on a Varian HA-100 spectrometer by either Mr. J. Martin or Ms. V. Majestic. Mass spectral data were obtained on a Hitachi Perkin-Elmer RMS-4 mass spectrometer by either Ms. P. Moses or Mr. C. Guzman. Molecular weights were obtained with a Hewlett-Packard 302 vapor pressure osmometer using benzene or chloroform as the solvent and benzil as the reference by Dr. J. D. Sauer. Thermogravimetric analyses (TGA) were performed with a DuPont 950 thermogravimetric analyzer. For preparative thick-layer chromatography (ThLC), 2 mm silica gel (Brinkman PF 254-366) plates (activated at 150 °C for 4 h) were used, eluting with the stipulated solvent system.

All reaction solvents were distilled under an inert atmosphere prior to use. Sodium hydride (57% oil dispersion) was first washed with petroleum ether (bp 30–60 °C) and then dried in vacuo prior to use. The thiols were distilled under argon and stored under anhydrous conditions.

Table I gives the method used, reaction times, and product distributions. All analytical data are tabulated in Table II (furnished as supplementary material); the data for all new compounds are within experimental error (±0.4%).

Reaction of 2-Chloropyridine with Bis(2-mercaptoethyl) Ether. Method A. Sodium Hydride. To a suspension of sodium hydride (1.5 g, 63 mmol) in anhydrous xylene (200 mL) were added 2-chloropyridine (3.9 g, 34.4 mmol) and bis(2-mercaptoethyl) ether (2.4 g, 17.4 mmol), and the mixture was refluxed under nitrogen for 3 days. After the mixture was cooled, water was carefully added and the xylene layer separated. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate and concentrated in vacuo (unreacted starting 2-chloropyridine was also removed) to afford a viscous liquid which was chromatographed (ThLC) eluting four times with petroleum ether–acetone (15:1) to give two major fractions.

Fraction A yielded the 1:1 thiol **5:** bp 75–80 °C (0.2 mm, microdistilled); NMR ($CDCl_3$) δ 1.60 (t, SH, J = 8.2 Hz, 1 H), 2.66 (dt, δ-CH_2, J = 8.2, 6.5 Hz, 2 H), 3.40 (t, α-CH_2, J = 6.4 Hz, 2 H), 3.61 (t, γ-CH_2, J = 6.5 Hz, 2 H), 3.72 (t, β-CH_2, J = 6.4 Hz, 2 H), 6.92 (ddd, 5-pyr H, J = 7.3, 5.0, 1.3 Hz, 1 H), 7.14 (ddd, 3-pyr H, J = 8.2, 1.3, 0.9 Hz, 1 H), 7.42 (ddd, 4-pyr H, J = 8.2, 7.3, 2.0 Hz, 1 H), 8.38 (ddd, 6-pyr H, J = 5.0, 2.0, 0.9 Hz, 1 H); IR (neat) 2550 (SH), 1290, 1135 cm^{-1}.

Fraction B afforded disulfide **6:** TGA inflection point, 295 °C; NMR ($CDCl_3$) δ 2.89 (t, δ-CH_2, J = 6.5 Hz, 4 H), 3.39 (t, α-CH_2, J = 6.4 Hz, 4 H), 3.73 (t, γ-CH_2, J = 6.5 Hz, 4 H), 3.75 (t, β-CH_2, J = 6.4 Hz, 4 H), 6.92 (ddd, 5-pyr H, J = 7.3, 5.0, 1.3 Hz, 2 H), 7.15 (ddd, 3-pyr H, J = 8.2, 1.3, 0.9 Hz, 2 H), 7.42 (ddd, 4-pyr H, J = 8.2, 7.3, 2.0 Hz, 2 H), 8.38 (ddd, 6-pyr H, J = 5.0, 2.0, 0.9 Hz, 2 H); IR (neat) 3030, 1590, 1295, 1145 cm^{-1}.

Reaction of 2,6-dichloropyridine with bis(2-mercaptoethyl) ether afforded a residue which was chromatographed (ThLC) eluted four times with hexane–acetone (15:1) to give five major fractions.

Fraction A was recrystallized from hexane to afford the crystalline 1:1 macrocycle **8:** mp 119–121.5 °C (lit. mp 110–112 °C,[10] 92–94 °C[4a]); NMR ($CDCl_3$) δ 3.28 (t, α-CH_2, J = 5.9 Hz, 4 H), 3.95 (t, β-CH_2, J = 5.9 Hz, 4 H), 6.88 (d, 3- or 5-pyr H, J = 8.2 Hz, 1 H), 6.89 (d, 5- or 3-pyr H, J = 7.5 Hz, 1 H), 7.30 (dd, 4-pyr H, J = 8.2, 7.5 Hz, 1 H); MS (70 eV) m/e 213 (M^+, $C_9H_{11}S_2NO$, 49.2%), 168 ($C_7H_6S_2N$, 100%).

Fraction B was microdistilled to give **9a:** bp 110–115 °C (0.7 mm); NMR ($CDCl_3$) δ 1.60 (t, SH, J = 8.1 Hz, 1 H), 2.67 (m, δ-CH_2, J = 8.1, 6.5 Hz, 2 H), 3.37 (t, α-CH_2, J = 6.5 Hz, 2 H), 3.64 (t, γ-CH_2, J = 6.5 Hz, 2 H), 3.73 (t, β-CH_2, J = 6.5 Hz, 2 H), 6.95 (dd, 3- or 5-pyr H, J = 7.9, 0.9 Hz, 1 H), 7.05 (dd, 5- or 3-pyr H, J = 7.9, 0.9 Hz, 1 H), 7.39 (t, 4-pyr H, J = 7.9 Hz, 1 H); IR (neat) 2530 (SH), 1290, 1140 cm^{-1}.

Fraction C afforded **11a:** bp 125–140 °C (0.17 mm, microdistilled); NMR ($CDCl_3$) δ 3.38 (t, α-CH_2, J = 6.5 Hz, 4 H), 3.78 (t, β-CH_2, J = 6.5 Hz, 4 H), 6.92 (dd, 3- or 5-pyr H, J = 7.8, 0.9 Hz, 2 H), 7.04 (dd, 5- or 3-pyr H, J = 7.8, 0.9 Hz, 2 H), 7.36 (t, 4-pyr H, J = 7.8 Hz, 2 H); IR (neat) 2910, 1570, 1290, 1150 cm^{-1}; MS (70 eV) m/e 360 (M^+, 0.96%), 172 ($C_7H_7NS^{35}Cl$, 100%).

Fraction D was rechromatographed (ThLC) eluting three times with hexane–acetone (8:1) to afford **10:** bp 100–110 °C (0.09 mm); NMR ($CDCl_3$) δ 1.58 (t, SH, J = 8.1 Hz, 2 H), 2.67 (m, δ-CH_2, J = 8.1, 6.4 Hz, 4 H), 3.39 (t, α-CH_2, J = 6.4 Hz, 4 H), 3.61 (t, γ-CH_2, J = 6.4 Hz, 4 H), 3.71 (t, β-CH_2, J = 6.4 Hz, 4 H), 6.83 (d, 3- or 5-pyr H, J =

8 Hz, 1 H), 6.84 (d, 5- or 3-pyr H, J = 7.5 Hz, 1 H), 7.22 (dd, 4-pyr H, J = 8, 7.5 Hz, 1 H); IR (neat) 2530 (SH), 1620, 1290, 1130 cm^{-1}.

Fraction E was rechromatographed (ThLC) eluting three times with hexane–acetone (8:1) to afford disulfide **12a:** TGA inflection point, 308 °C; NMR ($CDCl_3$) δ 2.9 (t, δ-CH_2, J = 6.5 Hz, 4 H), 3.37 (t, α-CH_2, J = 6.5 Hz, 4 H), 3.67–3.84 (m, CH_2O, 8 H), 6.94 (dd, 3- or 5-pyr H, J = 7.7, 0.8, Hz, 2 H), 7.05 (dd, 5- or 3-pyr H, J = 7.7, 0.8 Hz, 2 H), 7.37 (t, 4-pyr H, J = 7.7 Hz, 2 H); IR (neat) 2900, 1570, 1290, 1140 cm^{-1}.

Reaction of 2,6-Dibromopyridine with Bis(2-mercaptoethyl) Ether. Method B. Diisopropylamine. A mixture of 2,6-dibromopyridine (4.0 g, 16.9 mmol), bis(2-mercaptoethyl) ether (2.35 g, 17.0 mmol), and diisopropylethylamine (25 mL) was refluxed under nitrogen for 60 h. The solvent was removed in vacuo, affording a residue which was dissolved in dichloromethane and extracted with dilute sodium carbonate solution in order to remove unreacted dithiol (20%). The organic layer was dried over anhydrous magnesium sulfate and concentrated to give a residue which was chromatographed (ThLC) eluting eight times with cyclohexane–ethyl acetate (25:1) to afford three major fractions.

Fraction A afforded thiol **9b** as a pale yellow oil: bp 119–128 °C (0.06 mm, microdistilled); NMR (CCl_4) δ 1.50 (t, SH, J = 8.2 Hz, 1 H), 2.62 (dt, δ-CH_2, J = 8.2, 6.5 Hz, 2 H), 3.32 (t, α-CH_2, J = 6.5 Hz, 2 H), 3.58 (t, γ-CH_2, J = 6.5 Hz, 2 H), 3.67 (t, β-CH_2, J = 6.5 Hz, 2 H), 6.99–7.35 (m, pyr H, 3 H); IR (neat) 2560 (SH), 1570, 1290, 1150, 1120 (br), 1050 cm^{-1}.

Fraction B afforded **11b** as a dark yellow oil: bp 185–200 °C (1.0 mm); NMR (CCl_4) δ 3.32 (t, α-CH_2, J = 6.5 Hz, 4 H), 3.72 (t, β-CH_2, J = 6.5 Hz, 4 H), 6.96–7.32 (m, pyr H, 6 H); IR (neat) 2900, 1570, 1290, 1150, 1080 cm^{-1}.

Fraction C yielded disulfide **12b** as a pale yellow oil: TGA inflection point, 298 °C; NMR (CCl_4) δ 2.83 (t, δ-CH_2, J = 6.5 Hz, 4 H), 3.31 (t, α-CH_2, J = 6.5 Hz, 4 H), 3.64 (t, γ-CH_2, J = 6.5 Hz, 4 H), 3.71 (t, β-CH_2, J = 6.5 Hz, 4 H), 6.94–7.33 (m, pyr H, 6 H); IR (neat) 2880, 1540, 1380, 1250, 1150. 980 cm^{-1}.

Reduction of 2,2-[Dithiobis(ethyleneoxyethylenethio)]-bis[6-bromopyridine] (12b). The disulfide **12b** (50 mg, 0.085 mmol) in anhydrous diethyl ether (7 mL) was added dropwise to a suspension of lithium aluminum hydride (ca. 3 mg, 0.079 mmol) in ether (ca. 10 mL) over a 10-min period. The mixture was refluxed under argon for 20 min; two additional aliquots of lithium aluminum hydride (3 mg each) were added. After the last addition, the mixture was refluxed for 10 min and then stirred overnight at room temperature. The reaction was quenched with water, acidified with dilute (1%) hydrochloric acid, and extracted with diethyl ether. The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated, affording a residue which was chromatographed (ThLC) eluting four times with hexane–acetone (8:1) to give three major fractions. Fraction A yielded the cleaved 1:1 thiol **9a:** 10 mg (20%); identical with the previously isolated material. Fraction B afforded **5:** 10 mg (27%); NMR data were identical with a previously prepared sample. Fraction C afforded unreacted starting disulfide **12b:** 7 mg (14%).

Cyclization of 9b. Preparation of 8. Thiol **9b** (210 mg, 0.71 mmol) in diisopropylethylamine (20 mL) was refluxed under nitrogen for 6 days. The solvent was removed in vacuo, and the residue was chromatographed (ThLC) eluting three times with hexane–acetone (10:1) to give three fractions.

Fraction A afforded the 1:1 macrocycle **8:** 30 mg (20%); mp 117–119 °C (hexane) (lit.[10] mp 110–112 °C). Fraction B yielded unreacted starting material: 60 mg (29%); bp 119–128 °C (0.6 mm, microdistillation). Fraction C afforded the oxidized disulfide **12b:** 65 mg (30%); identical NMR spectrum with a previously prepared sample.

Reaction of 2,6-dibromopyridine with bis(2-mercaptoethyl) sulfide gave a residue which was chromatographed (ThLC) eluting eight times with hexane–acetone (20:1) to afford four major fractions.

Fraction A yielded the 1:1 thiol **14a** as a pale yellow oil: bp 160 °C (2.4 mm, microdistillation); NMR ($CDCl_3$) δ 1.77 (t, SH, J = 8.0 Hz, 1 H), 2.68–2.98 (m, β-CH_2, 6 H), 3.22–3.39 (m, α-CH_2, 2 H), 7.06 (dd, 3- or 5-pyr H, J = 7.5, 1.3 Hz, 1 H), 7.12 (dd, 5- or 3-pyr H, J = 7.5, 1.3 Hz, 1 H), 7.31 (t, 4-pyr H, J = 7.5 Hz, 1 H); IR (neat) 2525 (SH), 1275, 1260, 1140, 780 (br) cm^{-1}.

Fraction B was rechromatographed (ThLC) eluting with hexane–acetone (10:1) to afford pure 2:1 sulfide **15a:** bp 160–170 °C (0.5 mm); NMR ($CDCl_3$) δ 2.87–3.04 (m, β-CH_2, J = 7.2 Hz, 4 H), 3.35–3.51 (m, α-CH_2, J = 7.2 Hz, 4 H), 7.02–7.35 (m, pyr H, 6 H); IR (neat) 2900, 1545, 1375, 1275, 1155, 1070 cm^{-1}.

Fraction C was recrystallized from diethyl ether–acetone to give sulfide **15b:** mp 68–71 °C; NMR ($CDCl_3$) δ 2.77–2.96 (m, β-CH_2, 4 H), 2.97 (s, γ-CH_2, 4 H), 3.26–3.45 (m, α-CH_2, 4 H), 7.07 (dd, 3- or 5-pyr H, J = 7.5, 1.4 Hz, 2 H), 7.12 (dd, 5- or 3-pyr H, J = 7.5, 1.4 Hz, 2 H), 7.30 (t, 4-pyr H, J = 7.5 Hz, 2 H); IR (KBr) 2885, 1565, 1375, 1160 cm^{-1}; MS (70 eV) m/e 524 (M^+, 0.43%), 338, 336 ($C_{11}H_{15}NS_3NBr$, 25%), 218, 216 (C_7H_7NSBr, 100%), 191, 189 (C_5H_4NSBr, 60%).

Fraction D was recrystallized from diethyl ether–acetone to afford disulfide **16:** mp 59–62 °C; NMR ($CDCl_3$) δ 2.75–2.95 (m, β-CH_2, J = 7.5 Hz, 4 H), 3.0 (br s, γ, δ-CH_2, 8 H), 3.26–3.45 (m, α-CH_2, J = 7.5 Hz, 4 H), 7.07 (dd, 3- or 5-pyr H, J = 7.6, 1.3 Hz, 2 H), 7.12 (dd, 5- or 3-pyr H, J = 7.6, 1.3 Hz, 2 H), 7.31 (t, 4-pyr H, J = 7.6 Hz, 2 H); IR (KBr) 2900, 1550, 1370, 1210, 1135 cm^{-1}; MS (70 eV) m/e 616 (M^+, 0.25%), 218, 216 (C_7H_7NSBr, 100%), 191, 189 (C_5H_4NSBr, 41%).

Reaction of 2,6-dichloropyridine with bis(2-mercaptoethyl) sulfide according to method A afforded a residue which was chromatographed (ThLC) eluting four times with hexane–acetone (15:1) to give two major fractions other than the unreacted starting material.

Fraction A was rechromatographed (ThLC) eluting once with 10:1 hexane–acetone and then once with 8:1 hexane–acetone to yield the 1:1 thiol **17:** bp 90–100 °C (0.1 mm); NMR ($CDCl_3$) δ 1.75 (m, SH, J = 7.9 Hz, 1 H), 2.67–3.0 (m, β-CH_2, 6 H), 3.26–3.42 (m, α-CH_2, 2 H), 6.95 (dd, 3- or 5-pyr H, J = 7.8, 0.9 Hz, 1 H), 7.03 (dd, 5- or 3-pyr H, J = 7.8, 0.9 Hz, 1 H), 7.39 (t, 4-pyr H, J = 7.8 Hz, 1 H); IR (neat) 2875 (SH), 1565, 1380, 1280, 1160 cm^{-1}.

Fraction B gave disulfide **18:** TGA inflection point, 310 °C; NMR ($CDCl_3$) δ 2.78–2.94 (m, β-CH_2, 4 H), 2.99 (br s, γ, δ-CH_2, 8 H), 3.29–3.45 (m, α-CH_2, 4 H), 6.95 (dd, 3- or 5-pyr H, J = 7.7, 0.8 Hz, 2 H), 7.04 (dd, 5- or 3-pyr H, J = 7.7, 0.8 Hz, 2 H), 7.38 (t, 4-pyr H, J = 7.7 Hz, 2 H); IR (neat) 2820, 1570, 1430, 1290, 1160 cm^{-1}.

Reaction of 2-bromopyridine with 1,2-ethanedithiol afforded a viscous residue which was chromatographed (ThLC) eluting three times with cyclohexane–ethanol (4%) to give two major fractions.

Fraction A was recrystallized three times from dichloromethane–hexane to afford **20:** mp 109–111 °C; NMR ($CDCl_3$) δ 3.5 (s, SCH_2, 4 H), 6.93 (ddd, 5-pyr H, J = 7.2, 5.0, 1.3 Hz, 2 H), 7.22 (ddd, 3-pyr H, J = 8.2, 1.3, 0.9 Hz, 2 H), 7.46 (ddd, 4-pyr H, J = 8.2, 7.2, 2.0 Hz, 2 H), 8.40 (ddd, 6-pyr H, J = 5.0, 2.0, 0.9 Hz, 2 H); IR (KBr) 3350, 1640, 1585, 1460, 1280, 1150 cm^{-1}.

Fraction B was distilled to afford di-2-pyridyl sulfide (**21**): bp 160–170 °C (8 mm) [lit.[12] bp 190 °C (6 mm)]; identical with an authentic sample.

Reaction of 2,6-dichloropyridine and 1,2-ethanedithiol gave a residue which was chromatographed (ThLC) eluting four times with hexane–acetone (10:1) to afford four major fractions.

Fraction A was recrystallized from petroleum ether (bp 30–60 °C) and acetone to afford macrocycle **22:** mp 158.5–160.5 °C; NMR ($CDCl_3$) δ 2.71–2.89 (m, β-CH_2, 4 H), 2.84 (s, γ-CH_2, 4 H), 3.43–3.61 (m, α-CH_2, 4 H), 6.84 (d, 3- or 5-pyr H, J = 8.2 Hz, 1 H), 6.85 (d, 5- or 3-pyr H, J = 7.1 Hz, 1 H), 7.25 (dd, 4-pyr H, J = 8.2, 7.1 Hz, 1 H); IR (KBr) 2870, 1550, 1390, 1280, 1155 cm^{-1}; MS (70 eV) m/e 289 (M^+, 55%), 203 ($C_7H_9NS_3^+$, 75%), 168 ($C_7H_6NS_2^+$, 37%), 143 ($C_5H_5NS_2^+$, 100%).

Fraction B yielded **23a:** bp 160 °C (1.1 mm); NMR ($CDCl_3$) δ 2.88–3.04 (m, β-CH_2, 4 H), 3.37–3.52 (m, α-CH_2, 4 H), 6.92 (dd, 3- or 5-pyr H, J = 7.8, 1.0 Hz, 2 H), 7.03 (dd, 5- or 3-pyr H, J = 7.8, 1.0 Hz, 2 H), 7.37 (t, 4-pyr H, J = 7.8 Hz, 2 H); IR (neat) 3000, 1535, 1375, 1250, 1140 cm^{-1}; MS (70 eV) m/e 376 (M^+, 9.2%), 232 ($C_9H_{11}NS_2{}^{35}Cl^+$, 100%), 172 ($C_7H_7NS^{35}Cl$, 88%), 145 ($C_5H_4NS^{35}Cl^+$, 81%), 112 ($C_5H_3N^{35}Cl^+$, 44%).

Fraction C was rechromatographed (ThLC) with hexane–acetone (15:1), affording **23b:** TGA point of inflection, 343 °C; NMR ($CDCl_3$) δ 2.79–2.94 (m β-CH_2, 4 H), 2.96 (s, γ-CH_2, 4 H), 3.29–3.45 (m, α-CH_2, 4 H), 6.92 (dd, 3- or 5-pyr H, J = 7.8, 1.0 Hz, 2 H), 7.01 (dd, 5- or 3-pyr H, J = 7.8, 1.0 Hz, 2 H), 7.35 (t, 4-pyr H, J = 7.8 Hz, 2 H); IR (neat) 2890, 1550, 1370, 1250, 1150 cm^{-1}; MS (70 eV) m/e 436 (M^+, 1.2%), 292 ($C_{11}H_{15}NS_3{}^{35}Cl^+$, 32%), 172 ($C_7H_7NS^{35}Cl^+$, 100%), 145 ($C_5H_4NS^{35}Cl^+$, 62%).

Fraction D was recrystallized from hexane and acetone to afford **23c:** mp 48–50 °C; NMR ($CDCl_3$) δ 2.77–2.93 (m, β-CH_2S, 4 H), 2.89 (br s, γ, δ-CH_2, 8 H), 3.27–3.44 (m, α-CH_2, 4 H), 6.94 (dd, 3- or 5-pyr H, J = 7.8, 0.9 Hz, 2 H), 7.02 (dd, 5- or 3-pyr H, J = 7.8, 0.9 Hz, 2 H), 7.37 (t, 4-pyr H, J = 7.8 Hz, 2 H); IR (KBr) 2905, 1540, 1380, 1210, 1150 cm^{-1}; MS (70 eV) m/e 496 (M^+, 1%), 352 ($C_{13}H_{19}NS_4{}^{35}Cl^+$, 48%), 204 ($C_7H_7NS_2{}^{35}Cl^+$, 28%), 172 ($C_7H_7NS^{35}Cl^+$, 100%), 145 ($C_5H_4NS^{35}Cl^+$, 85%).

Reaction of 2,6-dichloropyridine and 1,4-butanedithiol afforded a residue which was chromatographed (ThLC) eluting three times with hexane–acetone (10:1) to give three major fractions.

Fraction A was recrystallized from hexane–acetone to give the 2:2 macrocycle **24:** R_f 0.41 [hexane–acetone (10:1)]; MS (70 eV) m/e 394 (M^+, 4%), 198 ($C_9H_{12}NS_2^+$, 100%), 170 ($C_7H_8NS_2^+$, 32%), 168

($C_7H_6NS_2^+$, 41%), 164 ($C_9H_{10}NS^+$, 25%), 143 ($C_5H_5NS_2^+$, 50%), 110 ($C_5H_4NS^+$, 77%). Due to the limited quantity of sample, further spectral studies were not conducted.

The mother liquor from fraction A was concentrated to afford the 2:1 compound **25:** mp 56–58 °C; NMR δ 1.77–1.95 (m, β-CH_2, 4 H), 3.12–3.30 (m, α-CH_2, 4 H), 6.91 (dd, 3- or 5-pyr H, J = 7.9, 1.0 Hz, 2 H), 7.01 (dd, 5- or 3-pyr H, J = 7.9, 1.0 Hz, 2 H), 7.34 (t, 4-pyr H, J = 7.9 Hz, 2 H); IR (KBr) 2990, 1540, 1245, 1130 cm^{-1}.

Fraction B was recrystallized from diethyl ether and hexane to afford the 3:2 open-chain compound **26:** mp 55–56 °C; NMR ($CDCl_3$) δ 1.77–1.96 (m, all β-CH_2, 8 H), 3.10–3.29 (m, all α-CH_2, 8 H), 6.80 (d, 3- or 5-pyr H, J = 8.2 Hz, 2 H), 6.92 (dd, 3′- or 5′-pyr H, J = 7.7, 0.9 Hz, 2 H), 7.01 (dd, 5′- or 3′-pyr H, J = 7.7, 0.9 Hz, 2 H), 7.2 (t, 4-pyr H, J = 8.2 Hz, 1 H), 7.35 (t, 4′-pyr H, J = 7.7 Hz, 2 H); IR (KBr) 2915, 1535, 1395, 1125 cm^{-1}.

Fraction C was recrystallized from hexane and acetone to afford the 4:3 compound **27:** mp 80.5–82 °C; NMR ($CDCl_3$) δ 1.77–1.94 (m, all β-CH_2, 12 H), 3.10–3.27 (m, all α-CH_2, 12 H), 6.79 (d, 3- or 5-pyr H, J = 8.2 Hz, 2 H), 6.80 (d, 5- or 3-pyr H, J = 8.0 Hz, 2 H), 6.92 (dd, 3′- or 5′-pyr H, J = 7.8, 0.9 Hz, 2 H), 7.01 (dd, 3′- or 5′-pyr H, J = 7.8, 0.9 Hz, 2 H), 7.20 (dd, 4-pyr H, J = 8.2, 8.0 Hz, 2 H), 7.34 (t, 4′-pyr H, J = 7.8 Hz, 2 H); IR (KBr) 2920, 1560, 1380, 1130 cm^{-1}.

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Supplementary Material Available: All analytical data for the new compounds in Table II (2 pages). Ordering information is given on any current masthead page.

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A Convenient Synthesis of Tertiary Alkyl *N*-Phenylcarbamates from Tertiary Alcohols and Phenyl Isocyanate with a Lithium Alkoxide Catalyst[1]

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Although the direct addition of tertiary alcohols to isocyanates usually gives no reaction at low temperatures and produces olefins on being heated, the use of catalysts, such as lithium alkoxides and dibutyltin diacetate, makes possible the synthesis of tertiary alkyl *N*-phenylcarbamates in good yields. Thus the addition of *tert*-amyl alcohol to phenyl isocyanate in the presence of lithium *tert*-amyloxide gave *tert*-amyl *N*-phenylcarbamate in an 81% yield. For comparison the same reaction in the presence of dibutyltin diacetate gave a 60% yield of the carbamate and the uncatalyzed reaction gave a 15% yield. The addition of *tert*-butyl alcohol to phenyl isocyanate in the presence of lithium *tert*-butoxide gave an 82% yield of *tert*-butyl *N*-phenylcarbamate. By the same technique the *N*-phenylcarbamates of 1,1-diphenylethanol, 2-phenyl-2-propanol and 3-ethyl-3-pentanol were prepared in 74, 77, and 39% yields, respectively.

In a program to evaluate various tertiary alkyl oxycarbonyl groups as blocking groups for amines a convenient synthesis of tertiary alkyl *N*-phenylcarbamates was desired. However, a search of the literature indicated that there were no good general methods described for the synthesis of tertiary alkyl derivatives. Since a number of very active catalysts have been

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