Registry No. **1**, 287-27-4; **4**, 93530-08-6; **5**, 99810-16-9; **7a**, 99809-99-1; **7b**, 99810-00-1; **7c**, 99810-01-2; **7d**, 99810-02-3; **7e**, 99810-03-4; **7f**, 99810-04-5; **7g**, 99810-05-6; **7h**, 99810-06-7; **7i**, 88738-51-6; **8a**, 99810-07-8; **8b**, 99810-08-9; **8c**, 99810-09-0; **8d**, 99810-10-3; **8e**, 99810-11-4; **8f**, 99810-12-5; **8g**, 99810-13-6; **8h**, 99810-14-7; **8i**, 99810-15-8; **9a**, 99810-17-0; **9b**, 87373-80-6; **10a**, 99810-18-1; **10b**, 99810-19-2; **10c**, 87373-82-8; *p*-$MeSC_6H_4CH_2OH$, 3446-90-0; *o*-$O_2NC_6H_4CH_2Br$, 3958-60-9; *p*-$O_2NC_6H_4CH_2Br$, 100-11-8; *o*-$CH_3C_6H_4CH_2Br$, 89-92-9; *p*-$CH_3C_6H_4CH_2Br$, 104-81-4; *p*-$CH_3OC_6H_4CH_2Br$, 2746-25-0; *o*-$BrC_6H_4CH_2Br$, 3433-80-5; *p*-$BrC_6H_4CH_2Br$, 589-15-1; *o*-$NCC_6H_4CH_2Br$, 22115-41-9; $C_6H_5CH_2Br$, 100-39-0; *o*-$O_2NC_6H_4CH_2Cl$, 612-23-7; *p*-$O_2NC_6H_4CH_2Cl$, 100-14-1; *o*-$CH_3OC_6H_4CH_2Cl$, 7035-02-1; *m*-$CH_3OC_6H_4CH_2Cl$, 824-98-6; *p*-$CH_3OC_6H_4CH_2Cl$, 824-94-2; *o*-$ClC_6H_4CH_2Cl$, 611-19-8; *p*-$ClC_6H_4CH_2Cl$, 104-83-6; *m*-$FC_6H_4CH_2Cl$, 456-42-8; *p*-$CH_3SC_6H_4CH_2Cl$, 874-87-3.

Synthesis of Halogenated Terpyridines and Incorporation of the Terpyridine Nucleus into a Polyethereal Macrocycle[1]

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Received September 30, 1985

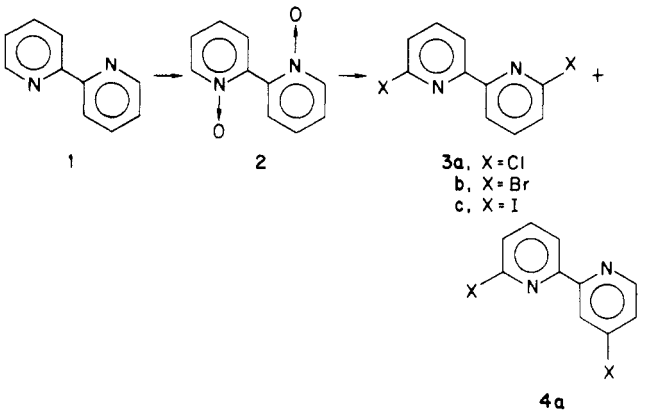
Two synthetic approaches to haloterpyridines are herein described. The first method involved direct halogenation of terpyridine *N*-oxides with $POCl_3$ to generate a mixture of polyhalogenated terpyridines. A more efficient approach to 6,6″-dibromo-2,2′:6′,2″-terpyridine utilized the Kröhnke synthesis to form the terpyridine moiety from appropriately halosubstituted precursors. Direct nucleophilic substitution on terpyridine was found to give low yields of macrocyclic products; however, if 1,5-bis(6-bromo-2-pyridyl)-1,5-dioxopentane was employed, macrocyclization afforded improved yields of the desired terpyridines.

In a systematic study[2-5] dealing with the conformational effects of polypyridino macrocycles and resulting transition-metal complexes, we required efficient synthetic routes to the starting terminal dihalopolypyridines. Historically, 6,6″-dihalo-2,2′:6′,2″-terpyridines have been prepared, albeit in poor overall yields, via vapor-phase halogenation of the unsubstituted terpyridine.[6] We herein report two improved synthetic routes to haloterpyridines, which may provide viable alternatives to the older procedure as well as give entrance to novel terpyridine macrocycles.

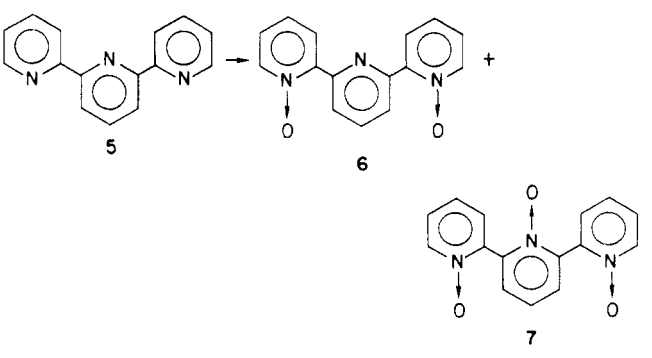
Results and Discussion

The reaction of 2,2′-dipyridine di-*N*-oxide (**2**) with $POCl_3$ has been demonstrated to give a variable product distribution, which was temperature dependent (Scheme I).[7-9] At 45–50 °C, 6,6′-dichloro-2,2′-dipyridine (**3a**) was generated (40%) along with traces of the 4,6-isomer **4a**; whereas, **3a** and **4a** were formed in 35% and 17% yields, respectively, at 75 °C.[7,10] In view of the inertness of **3a** to transmetalation, the more reactive bromide **3b** and iodide **3c** were prepared (>80%) via treatment of **3a** with HBr or HI in glacial AcOH, respectively.[11]

Scheme I



Scheme II



Initially the same general approach found successful for the preparation 2,2′-dipyridine (Scheme I) was applied to terpyridine. Attempts to prepare terpyridine di-*N*-oxide (**6**) via partial oxidation of 2,2′:6′,2″-terpyridine (**5**) with AcO_2H gave an inseparable mixture of *N*-oxides (Scheme

(1) Chemistry of Heterocyclic Compounds Series. Part 119. For the previous part in this series, see: Newkome, G. R.; Taylor, H. C. R.; Fronczek, F. R.; Gupta, V. K. *J. Org. Chem.*, in press.
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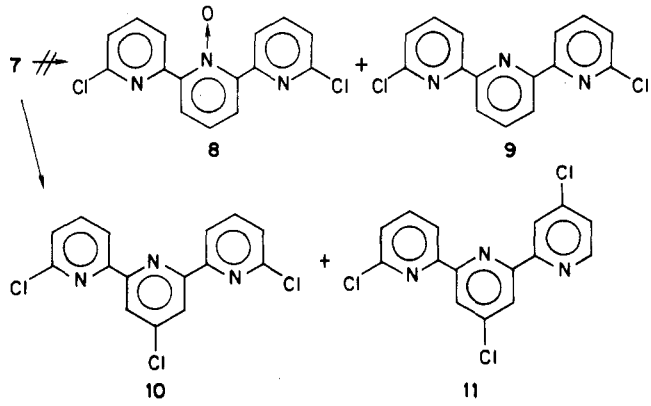
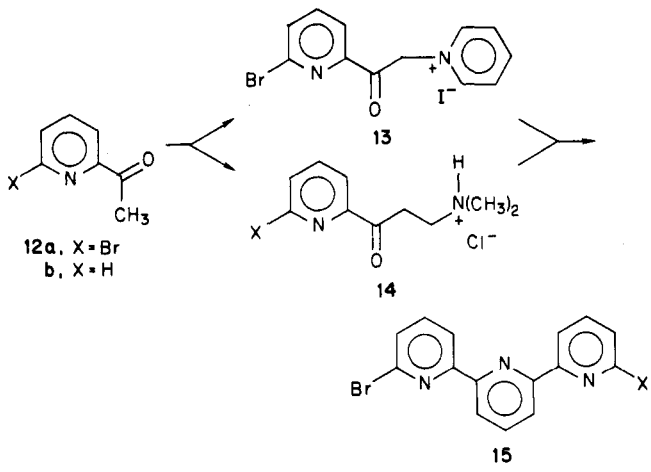
Scheme III



Scheme IV



II). However, with a slight excess of oxidant, **5** was transformed to **7**[12] from which it was hoped that either **8** or **9** could be prepared with $POCl_3$ under mild conditions (Scheme III). Unfortunately, the major products isolated were the trihalo derivatives **10** and **11**, as determined by ^1H NMR spectral data; additional products arose from partial halogenation. A report that appeared after the completion of the work described herein outlines the high yield (88%) preparation of **6** via *m*-chloroperbenzoic acid oxidation of **5**.[13]

Ultimately the terpyridines **15** were successfully prepared via the Kröhnke synthesis[14,15] utilizing 2-acetyl-6-bromopyridine **12a**. Treatment of **12a** with pyridine–I_2 afforded (80%) the desired pyridinium salt **13**. Further, the reaction of **12a** with Me_2NH_2Cl and paraformaldehyde in absolute EtOH generated the Mannich base **14a**. Subsequent combination of **13** and **14a** with NH_4OAc in hot MeOH afforded (27%) **15a** (Scheme IV). The 6-bromoterpyridine **15b** was synthesized from **13** and **14b** under identical conditions.[13,14] Due to the complicated ^1H NMR spectrum of **15b**, it was independently prepared via the low-temperature reaction of 6-bromo-2-lithiopyridine with **1**.[16] No dimeric products similar to those previously reported[17] were isolated. An alternate approach utilized the Hantzsch synthesis[18,19] to convert diketone[20] **16** into

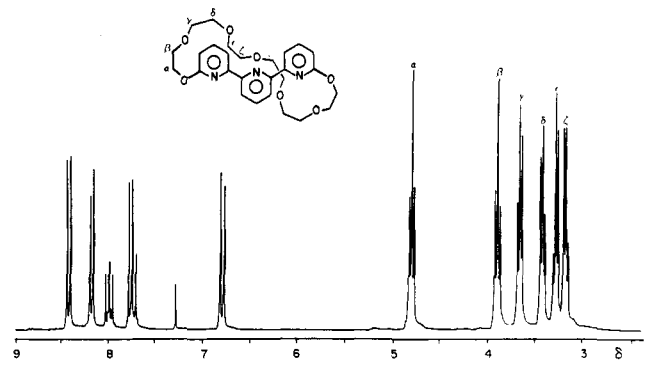
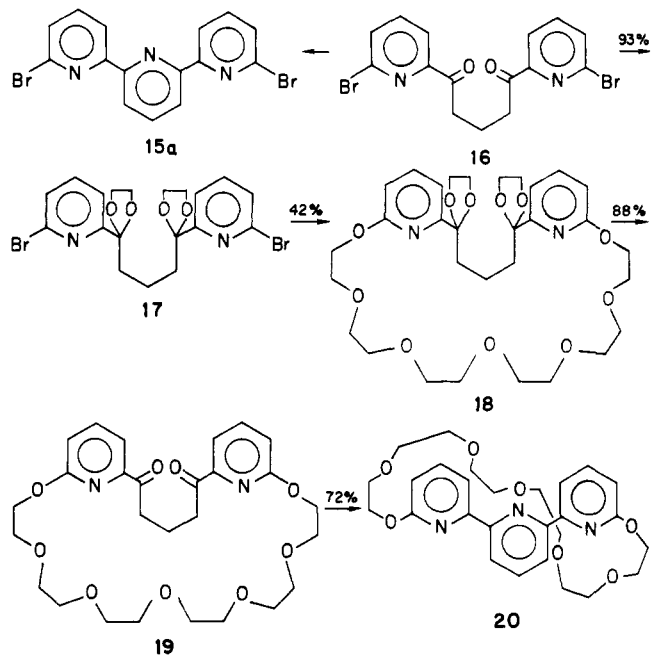


Figure 1. 200-MHz ^1H NMR of macrocycle **20**.

Scheme V



the desired bromide (64%) **15a** (Scheme V).

Originally it was anticipated that **15a** would serve as a convenient starting material for the incorporation of the terpyridine subunit into varied macrocyclic frameworks; however, nucleophilic macrocyclization was found to be sluggish due to the difficulty associated with obtaining the correct series of conformers. In order to circumvent this problem, nucleophilic macrocyclization was conducted on the more flexible polyfunctional intermediate **17** to afford (42%) the bis ketal macrocycle **18**. Following hydrolysis of bis ketal **18**, the Hantzsch synthesis was employed to generate the central pyridine ring of macrocycle **20** in 25% overall yield from **16** (Scheme V), thus irreversibly introducing the molecular rigidity in the last step. Such technology was recently applied to the construction of sexipyridine.[21]

The ^1H NMR of **20** is unique in that all resonances appearing for the ethylene bridge protons have distinctly different chemical shifts and are well resolved. This unusual behavior can be attributed to a molecular conformation in which the polyethereal chain spans the heteroaromatic rings, thus, subjecting each set of ethylene protons to a varying magnitude of the shielded environment.

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The upfield shift observed for the polyethylene bridge protons as well as a partially resolved X-ray structure[22] confirm the preferred anti–anti conformation of **20** (Figure 1). In contrast, the HI adduct of **20** exhibited a collapse of the polyethylene proton resonances[2] and a *down*field shift of the 4′-proton ($\Delta\delta \sim 0.92$) suggesting a syn–syn conformation, which was confirmed via the X-ray data.[22]

We are presently engaged in the synthesis of various macrocycles, which will incorporate the terpyridine nucleus along with another dissimilar bonding locus.

Experimental Section

All melting points were taken in capillary tubes with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. ^{1}H NMR spectra were determined on either an IBM-Bruker NR/80 or Bruker WP-200 spectrometer using $CDCl_3$, as solvent, with Me_4Si, as internal standard. Mass spectral (MS) data (70 eV) were determined by D. A. Patterson on a Hewlett-Packard HP 5985 GC/mass spectrometer and reported as m/e (assignment, relative intensity). Preparative thick-layer chromatography (ThLC) was performed on a 20 × 40 cm glass plates coated with a 2-mm layer of Brinkmann silica gel (PF-254-366). IR spectra were recorded on a Perkin-Elmer 621 grating infrared spectrophotometer. Elemental analyses were performed by R. Seab in these laboratories.

Reaction of 2,2′:6′,2″-Terpyridine *N*,*N*′,*N*″-Trioxide (7) with Phosphorus Oxychloride. A mixture of **7** (1.0 g, 3.6 mmol) and $POCl_3$ (25 mL) was heated at 40 °C with stirring for 1 h. The solution was then poured into ice-cold aqueous NH_4OH (50 mL) and extracted with $CHCl_3$ (3 × 50 mL). The combined organic extract was dried over anhydrous $MgSO_4$ and concentrated in vacuo to afford an off-white solid (350 mg), which was chromatographed (ThLC) by eluting with C_6H_{12}/EtOAc (4:1), yielding two major products:

Fraction A afforded **10**, as colorless needles: 120 mg (10%); mp 199–200 °C (EtOH); R_f 0.5; ^{1}H NMR δ 7.40 (d, 5,5″-py H, J = 8.0 Hz, 2 H), 7.81 (dd, 4,4″-py H, J = 8.0, 8.0 Hz, 2 H), 8.49 (s, 3′-py H, 2 H), 8.50 (d, 3,3″-py H, J = 8.0 Hz, 2 H); IR ($CHCl_3$) 2970, 1560, 1530, 1390, 1050 cm^{-1}; MS, m/e 339 (32), 337 (88), 335 (M^+, 100). Anal. Calcd for $C_{15}H_8Cl_3N_3$: C, 53.57; H, 2.38; N, 12.50. Found: C, 53.73; H, 2.33; N, 12.58.

Fraction B gave **11**, as colorless needles: 120 mg (10%); mp 191–192 °C (EtOH); R_f 0.45; ^{1}H NMR δ 7.38 (dd, 5-py H, J = 5.0, 2.4 Hz, 1 H), 7.42 (d, 5″-py H, J = 8.0 Hz, 1 H), 7.86 (dd, 4″-py H, J = 8.0, 8.0 Hz, 1 H), 8.50 (s, 3′-py H, 2 H), 8.53 (d, 3″-py H, J = 8.0 Hz, 1 H), 8.55 (d, 3-py H, J = 2.4 Hz, 1 H), 8.60 (d, 6-py H, J = 5.0 Hz, 1 H); IR ($CHCl_3$) 2980, 1560, 1535, 1390, 1370, 1125, 1050 cm^{-1}; MS, m/e 339 (29), 337 (87), 335 (M^+, 100), 300 (96). Anal. Calcd for $C_{15}H_8Cl_3N_3$: C, 53.57; H, 2.38; N, 12.50. Found: C, 53.57; H, 2.46; N, 12.33.

2-(1-Keto-2-*N*-pyridinylethyl)-6-bromopyridine Iodide (13). A solution of 2-acetyl-6-bromopyridine[15] (20 g, 10 mmol), iodine (2.56 g, 10 mmol), and pyridine (1.56 g, 20 mmol) was stirred and slowly heated to 50 °C until the exothermic reaction occurred. After 5 min a black precipitate formed, which was dissolved in hot water (100 mL), filtered, and concentrated in vacuo to afford a yellow solid. Upon recrystallization (EtOH), **13** was obtained as bright yellow crystals: 3.5 g (86%); mp 210 °C dec; ^{1}H NMR δ 4.80 (s, CH_2, 2 H), 7.81 (d, 5′-py H, J = 8.0 Hz, 1 H), 8.00 (dd, 4′-py H, J = 8.0, 8.0 Hz, 1 H), 8.08 (d, 3′-py H, J = 8.0 Hz, 1 H), 8.21 (dd, 3,5-py H, J = 7.5, 5.0 Hz, 2 H), 8.75 (d, 4-py H, J = 7.5 Hz, 1 H), 8.96 (d, 2,6-py H, J = 5.0 Hz, 2 H); IR (KBr) 3025, 1700 (C=O), 1620 (C=C), 1470, 1415, 1330, 1205, 990 cm^{-1}. Anal. Calcd for $C_{12}H_{10}N_2OBrI$: C, 35.56; H, 2.47; N, 6.91. Found: C, 35.60; H, 2.46; N, 6.90.

2-[1-Keto-3-(dimethylammonio)propyl]-6-bromopyridine Chloride (14a). A mixture of 2-acetyl-6-bromopyridine[15] (1.0 g, 5 mmol), Me_2NH_2Cl (400 mg, 5 mmol), paraformaldehyde (450 mg, 5 mmol), and concentrated HCl (50 mg) in EtOH (30 mL) was heated at 60 °C until dissolution was complete. (Continued heating beyond this point resulted in extensive decomposition!) The solution was cooled; the resulting white solid was filtered and washed with small portions of cold EtOH. This salt was used directly in subsequent reactions without further purification due to its hygroscopic nature. Yields normally averaged 50%, based on 10 identical runs.

6,6″-Dibromo-2,2′:6′,2″-terpyridine (15a). Method A. A mixture of **13** (405 mg, 10 mmol), **14a** (294 mg, 10 mmol), and NH_4OAc (2.0 g) in MeOH (10 mL) was refluxed for 1 h. After cooling, the resultant yellow crystals were filtered, dried, and recrystallized ($CHCl_3$) to afford **15a** as white plates: 105 mg (27%); mp 262–263 °C (lit.[6] mp 248 °C); ^{1}H NMR δ 7.51 (dd, 5,5″-py H, J = 8.0, 1.0 Hz, 2 H), 7.68 (dd, 4,4″-py H, J = 8.0, 8.0 Hz, 2 H), 7.95 (dd, 4-py H, J = 8.0, 8.0 Hz, 1 H), 8.47 (d, 3′5′-py H, J = 8.0 Hz, 2 H), 8.54 (dd, 3,3″-py H, J = 8.0, 1.0 Hz, 2 H).

Method B. A mixture of **16** (1.0 g, 2.4 mmol) and NH_4OAc (5 g) in MeOH (50 mL) was refluxed for 24 h. The solution was neutralized with aqueous Na_2CO_3, followed by the addition of water (50 mL) and extraction with $CHCl_3$ (3 × 50 mL). The combined organic extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a yellow solid, which was recrystallized from $CHCl_3$, affording **15a**, as colorless needles: 600 mg (64%); mp 262–263 °C.

6-Bromo-2,2′:6′,2″-terpyridine (15b). Method A. A mixture of **13** (405 mg, 10 mmol), **14b** (215 mg, 10 mmol), and NH_4OAc (2 g) in MeOH (10 mL) was refluxed for 3 h. After cooling, water (10 mL) was added, and the resulting white precipitate was filtered and dried. Following recrystallization (EtOH), **15b** was isolated as colorless needles: 100 mg (32%); mp 152–153 °C (lit.[6] mp 153 °C); ^{1}H NMR δ 7.33 (ddd, 5-py H, J = 8.0, 6.5, 1.0 Hz, 1 H), 7.51 (d, 5″-py H, J = 8.0 Hz, 1 H), 7.71 (dd, 4″-py H, J = 8.0, 8.0 Hz, 1 H), 7.85 (ddd, 4-py H, J = 8.0, 8.0, 1.0 Hz, 1 H), 7.96 (dd, 4′-py H, J = 8.0, 8.0 Hz, 1 H), 8.45 (dd, 3-py H, J = 8.0, 1.0 Hz, 1 H), 8.47 (d, 3″-py H, J = 8.0 Hz, 1 H), 8.58 (d, 3′,5′-py H, J = 8.0 Hz, 2 H), 8.71 (dd, 6-py H, J = 6.5, 1.0 Hz, 1 H).

Method B. To a solution of 2,6-dibromopyridine (5.9 g, 25 mmol) in anhydrous Et_2O (100 mL) cooled to −60 °C was added *n*-BuLi (25 mmol) in hexane over 30 min. 2,2′-Dipyridine (3.9 g, 25 mmol) in Et_2O (50 mL) was slowly added and the mixture stirred for an additional 6 h at −40 °C. Following the addition of MeOH–H_2O (1:1; 10 mL), the solution was concentrated in vacuo, and dilute $KMnO_4$ (acetone–H_2O) was added until the slurry became purple. The mixture was then extracted with $CHCl_3$ (3 × 50 mL), concentrated in vacuo, and crystallized (EtOH) to give (35%) pure **15b**, as colorless needles: mp 152–153 °C.

1,5-Bis(6-bromo-2-pyridyl)-1,5-dioxopentane (16) was prepared according to the procedure described by Bloomfield et al.[20] via the reaction of 6-bromo-2-lithiopyridine with *N*,*N*,*N*′,*N*′-tetramethylglutaramide.

1,5-Bis(6-bromo-2-pyridyl)-1,5-bis(1,3-dioxolan-2-yl)pentane (17). A mixture of **16** (8.0 g, 19.4 mmol), ethylene glycol (10 mL), concentrated H_2SO_4 (100 mg), and dry toluene (50 mL) was refluxed for 8 h or until no additional water separated in the Dean–Stark trap. A dilute aqueous Na_2CO_3 solution (0.1 M, 20 mL) was then carefully added and the organic layer separated and concentrated in vacuo to give a white solid, which was recrystallized from EtOH/$CHCl_3$ (2:1) to afford **17**, as brilliant white needles: 9.0 g (93%); mp 182–183 °C; ^{1}H NMR δ 1.36 (m, CH_2, 2 H), 2.03 (dd, CH_2, J = 7.0, 7.0 Hz, 4 H), 3.93 (m, ketal CH_2, 8 H), 7.45 (m, py H, 6 H); IR (KBr) 2900, 1580, 1560, 1400, 1200, 1130, 1050, 800 cm^{-1}; MS, m/e 344 (29, M^+ − 155), 342 (25, M^+ − 157), 230 (97), 228 (100), 99 (70). Anal. Calcd for $C_{19}H_{20}N_2O_4Br_2$: C, 45.60; H, 4.00; N, 5.60. Found: C, 45.71; H, 4.16; N, 5.72.

Reaction of 17 with Disodium Hexaethylene Glycolate. To a solution of disodium hexaethylene glycolate (2.2 mmol) in anhydrous toluene (100 mL) was added **17** (1.0 g, 2.2 mmol) and

(22) The crystal structures of **20** and the corresponding HI adduct have been partially resolved (Fronczek, F. R. LSU, 1983). Although the pyridine rings in both molecules are well defined, extreme thermal disorder in the polyethylene bridge precludes further refinement: $C_{27}H_{33}N_3O_2$ is triclinic ($P\bar{1}$) with a = 6.504 (1) Å, b = 7.594 (1) Å, c = 28.876 (3) Å; α = 82.38 (1)°, β = 88.11 (1)°, γ = 68.93 (1)°; Z = 2; d_c = 1.299 g cm^{-3}, R = 0.110 for 1363 observed data of 3893 unique data with 1° < θ < 60°; μ(Cu Kα) = 7.82 cm^{-1}; $[C_{27}H_{34}N_3O_7]^+I_3^-$ is monoclinic ($P2_1/n$) with a = 8.257 (3) Å, b = 17.810 (4) Å, c = 21.950 (8) Å; β = 91.60 (3)°; Z = 4; d_c = 1.839 g cm^{-3}, R = 0.068 for 1133 observed data of 2987 unique data with 2° < θ < 20°; μ(Mo Kα) = 29.19 cm^{-1}. In both structures the polyethereal chain exhibits extremely high thermal parameters and probable disorder, which limits the resolution of the diffraction pattern and prevents refinement to a *precise* structure. The data are qualitative and support the assigned structures.

the mixture heated to 70 °C for 24 h. After the mixture was cooled, water (100 mL) was added and the organic layer separated and dried over anhydrous Na_2SO_4. After concentration in vacuo, the resulting oil was dissolved in Et_2O and passed through a short alumina column to afford **18**, as a viscous oil: 450 mg (42%); ^1H NMR δ 1.38 (m, CH_2, 2 H), 2.04 (dd, CCH_2, J = 7.0, 7.0 Hz, 4 H), 3.65 (s, ϵ,ζ-OCH_2, 8 H), 3.69 (s, γ,δ-OCH_2, 8 H), 3.85 (m, ketal CH_2, 8 H), 4.00 (t, β-OCH_2, J = 7.0 Hz, 4 H), 4.47 (t, α-OCH_2, J = 7.0 Hz, 4 H), 6.66 (d, 5-py H, J = 7.7 Hz, 2 H), 7.03 (d, 3-py H, J = 7.7 Hz, 2 H), 7.50 (dd, 4-py H, J = 7.7, 7.7 Hz, 2 H); IR ($CHCl_3$) 2900, 1560, 1520, 1400, 1180, 1090, 980 cm^{-1}; MS, m/e 620 (0.5, M^+), 99 (100). Anal. Calcd for $C_{31}H_{44}N_2O_{11}$: C, 60.00; H, 7.10; N, 4.52. Found: C, 59.96; H, 7.38; N, 4.40.

Hydrolysis of Bis Ketal 18. A solution of **18** (100 mg, 0.16 mmol) and HCl (4 N, 25 mL) was warmed to 40 °C for 4 h. The solution was then neutralized with solid Na_2CO_3 and extracted with $CHCl_3$ (3 × 30 mL). The combined organic extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford bis ketone **19**, as white microcrystals: 75 mg (88%); mp 99–100 °C (EtOH); ^1H NMR δ 2.08 (m, CH_2, 2 H), 3.20 (dd, $COCH_2$, J = 7.0, 7.0 Hz, 4 H), 3.58 (s, ϵ,ζ-OCH_2, 8 H), 3.65 (m, γ,δ-OCH_2, 8 H), 3.83 (t, β-OCH_2, J = 6.5 Hz, 4 H), 4.46 (t, α-OCH_2, J = 6.5 Hz, 4 H), 6.88 (dd, 5-py H, J = 7.7, 1.0 Hz, 2 H), 7.65 (m, 3,4-py H, 4 H); IR ($CHCl_3$) 2960, 1700 (C=O), 1560, 1390, 1190, 1150, 1090, 970 cm^{-1}; MS, m/e 532 (25, M^+), 313 (43), 176 (100). Anal. Calcd for $C_{27}H_{36}N_2O_9$: C, 60.90; H, 6.77; N, 5.26. Found: C, 60.52; H, 6.91; N, 5.43.

Reaction of Bis Ketone 19 with Ammonium Acetate. A mixture of **19** (100 mg, 0.19 mmol) and NH_4OAc (1.0 g) in MeOH (5 mL) was stirred and refluxed for 3 h. After cooling, the mixture was neutralized with solid Na_2CO_3, water (50 mL) was added, and the solution was extracted with $CHCl_3$ (3 × 30 mL). The combined organic extract was dried over anhydrous Na_2CO_3, filtered, and concentrated in vacuo to give **20**, as colorless needles: 70 mg (72%); mp 127–128 °C; ^1H NMR (see Figure 1); IR ($CHCl_3$) 2950, 1580, 1540, 1395, 1230, 1130, 1050, 980 cm^{-1}; MS, m/e 511 (9, M^+), 292 (38), 266 (44), 265 (100). Anal. Calcd for $C_{27}H_{33}N_3O_7$: C, 63.41; H, 6.46; N, 8.22. Found: C, 63.18; H, 6.55; N, 7.99.

Acknowledgment. We thank the National Science Foundation and the Louisiana State University Center for Energy Studies for partial support of this work.

Studies on 6-Halo- and 6,6-Dihalopenicillins: The Rearrangement of Methyl 6,6-Dibromopenicillanate to 1,4-Thiazepine

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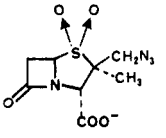
Received August 13, 1985

Methyl 6α-bromo- and 6β-bromopenicillanates underwent reductive dehalogenation with zinc and glacial acetic acid in acetonitrile or with zinc and ammonium acetate in tetrahydrofuran. Similarly methyl 6,6-dibromopenicillanate was reduced cleanly by zinc and ammonium acetate in THF to the corresponding 6,6-dihydropenicillanates; but with zinc and glacial acetic acid (or dilute hydrochloric acid) in acetonitrile or ethyl acetate, (3*S*)-6-bromo-2,3,4,7-tetrahydro-2,2-dimethyl-7-oxo-1,4-thiazepine-3-carboxylate was obtained as the major rearrangement product. However, oxidation of the sulfide to the sulfoxide (α or β) or sulfone stabilized the ring system to this rearrangement, the products being the 6,6-dihydropenicillanate 1-oxides or the sulfones. The 6,6-diiodopenicillanates, on the other hand, underwent extensive decomposition. These dissolving metal reductions have been used as a convenient route to either the 6,6-dihydropenicillanate 1α-oxides or the 6,6-dihydropenicillanate 1β-oxides, depending on the reaction sequence employed.

Recent reports have described many β-lactamase inhibitors such as clavulanic acid,[1] 6β-bromopenicillanic acid,[2] sulbactam[3] and its 6α-chloro analogue,[4] 6-(methoxymethylene)penicillanic acid,[5] and 2β-azidomethyl-substituted 6,6-dihydropenicillanate 1,1-dioxide (**1**)[6] and its triazolyl derivative **2** (YTR-830).[7]



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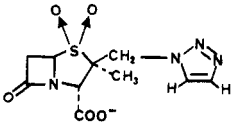

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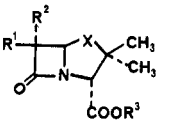
A part of our studies in this area was directed toward developing a high-yield, economical process for the preparation of 6,6-dihydropenicillanate 1β-oxide (**3**, $R^1 = R^2 = H$; X = SO), a useful intermediate for the synthesis of **1**. The key step in our approach was the efficient removal of the 6β-amido (or amino) group of the penicillin. Procedures useful for this purpose have generally relied on the catalytic hydrogenation of 6α-bromo-[8] or 6,6-dibromopenicillins,[3c,9] prepared from 6-aminopenicillanic acid while



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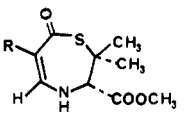

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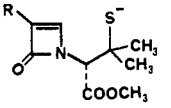

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