THE JOURNAL OF Organic Chemistry

VOLUME 46, NUMBER 5

FEBRUARY 27, 1981

Chemistry of Heterocyclic Compounds. 61. Synthesis and Conformational Studies of Macrocycles Possessing 1,8- or 1,5-Naphthyridino Subunits Connected by Carbon–Oxygen Bridges[1a]

George R. Newkome,* Sam J. Garbis,[1b] Veronica K. Majestic, Frank R. Fronczek, and Giacomo Chiari[1c]

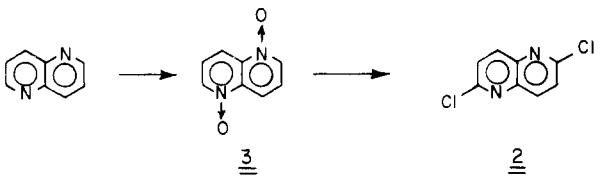
Department of Chemistry, Louisiana State University, Baton Rouge, Lousiana 70803

Received September 15, 1980

Polyethereal macrocycles were prepared from both 2,6-dichloro-1,5-naphthyridine (**2**) and 2,7-dichloro-1,8-naphthyridine (**6**). The "cross-the-face" structures of 1:1 macrocycles **7**, derived from **2**, were confirmed by NMR. The 2,7-(1,8-naphthyridino) macrocyclic structures **9** and **10** were also supported by NMR data which were indicative of diminished *N*-electron density, when compared to the parent 1,8-naphthyridine. Template reactions did not appreciably enhance product yields. The X-ray crystal structure of 1:1 macrocycle **9b** was conducted and showed that the imidate moieties possess a nearly 0° dihedral angle and that the naphthyridine subunit exhibits marginal deviation from planarity.

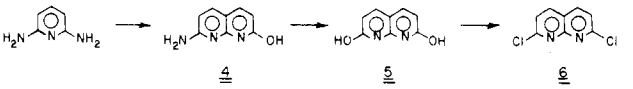
During our recent studies in the synthesis of heteromacrocycles,[2] we have evaluated macroligands containing 2,6-pyridino,[3] 2,4-pyrimidino,[4] 2,6-pyrazino,[5] and 3,6-diazino[6] groups in order to ascertain a better molecular picture of multifunctional cyclic ligands. The successful inclusion of a site-localized complexing region within a macroligand has recently been reported;[3o,7] however, these subunits have been limited generally to a bis(Schiff base) moiety, best represented by 1. In view of the limited

Scheme I

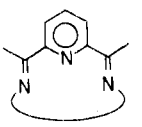


3 2

Scheme II



4 5 6



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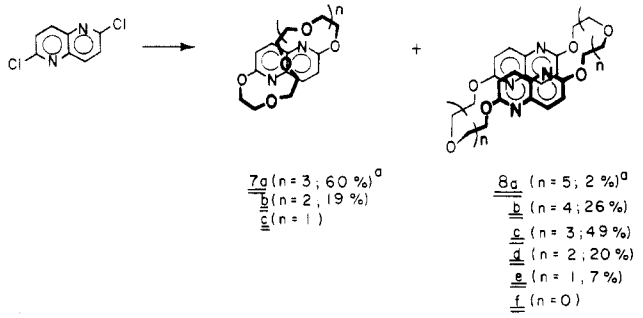
Scheme III



[a] Isolated yields.

examples of naphthyridine complexes,[8] the nonexistence of macrocycles containing a naphthyridino subunit,[2] and the practical application as medicinals,[9] we herein report syntheses, spectral studies, and X-ray data of macrocycles possessing either a 1,8- or 1,5-naphthyridino moiety.

Synthesis of Naphthyridine Starting Materials. A. 2,6-Dichloro-1,5-naphthyridine (2). Hart[10] initially prepared **2** from 1,5-naphthyridine di-*N*-oxide (**3**) upon treatment with phosphorus oxychloride, whereas equally attractive routes have been employed such as the treatment of 1,5-dimethyl-1,5-naphthyridine-2,6(1*H*,5*H*)-dione with a mixture of phosphorus pentachloride and phosphorus oxychloride[11] and the reaction of 2-hydroxy-1,5-naphthyridine 5-oxide[12] under Hart's conditions.[10] In view of the differing physical properties reported for **2**,[11-13] the authenticity of **2** was recently established.[14] Repetition of Hart's procedure (Scheme I) has afforded (36%) **2**, which conforms to the desired physical and spectral data.

B. 2,7-Dichloro-1,8-naphthyridine. Treatment of 2,6-diaminopyridine with malic acid in concentrated sulfuric acid gave (97%) 2-amino-7-hydroxy-1,8-naphthyridine (**4**),[15] which was diazotized with sodium nitrite in concentrated sulfuric acid to give (87%) 2,7-dihydroxy-1,8-naphthyridine (**5**).[16] Upon treatment of **5** with refluxing phosphorus oxychloride and phosphorus pentachloride for 2 h, the desired **6** was isolated in 81% yield (Scheme II). The NMR spectrum of **6** showed an anticipated AB pattern with doublets at δ 7.5 and 8.1 for the H-3,6 and H-4,5 protons, respectively.

2,6-(1,5-Naphthyridino) Macrocycles. Reaction of 2,6-dichloro-1,5-naphthyridine (**2**) with the dianion, generated from anhydrous hexaethylene glycol and 2 equiv of sodium hydride, afforded the desired 1:1 macrocycle **7a** as well as the 2:2 compound **8a**. Scheme III indicates isolated percentages. Numerous open-chain compounds were detected but not characterized further since they were deemed similar to those previously isolated.[3c] Reactions of **2** with hexa- to diethylene glycols were conducted, in which 1:1 macrocycles **7a,b** were isolated only from hexa- and pentaethylene glycols, respectively, whereas 2:2 macrocycles **8a–e** were isolated from the respective reactions. Inspection of the space-filling CPK models of **7c** supports the fact that the 13-membered bridge is too short to span the 2,6-positions of the naphthyridine nucleus only when the restrictive, near-zero, dihedral angle caused by the imidate moiety[17] is imposed. Therefore the bridging distance is not to be considered between the two α-positions (first atoms from the subheterocyclic unit) but rather between the two β-bridge positions.[18] Without this constraint, dictated by the presence of the two imidate groups, the tetraethylene glycol (13-membered) bridge may be constructable, for example, in the 2,6-bridging of the related naphthalene nucleus.

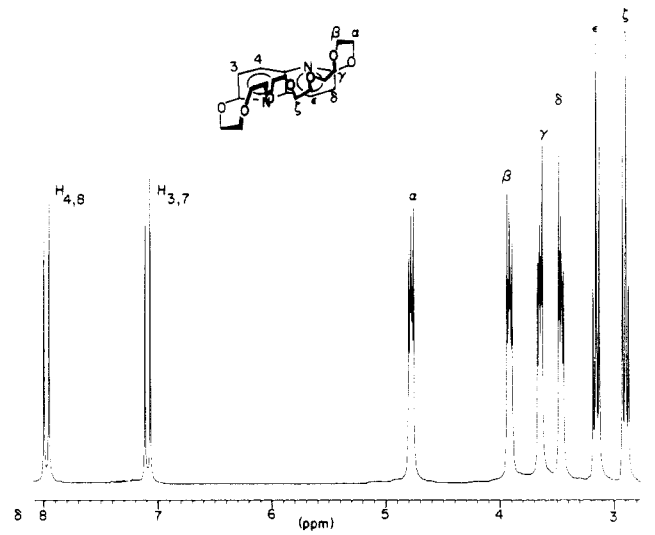


Figure 1. 200-MHz ^{1}H NMR spectrum of **7a** in CD_2Cl_2 at 40 °C.

The structures of these C,O-macrocycles were confirmed by molecular weight determinations (mass spectrometry and/or osmometry) and ^{1}H NMR spectroscopy. The 3-(7),4(8)-naphthyridine hydrogens appear as doublets (J = 9 Hz) at δ 7.0–7.1 and 7.6–8.6, respectively. The bridging methylenes in **7** possess varying degrees of ring anisotropy as the bridge spans the face of the naphthyridine subunit. Figure 1 shows the separation of the different methylenes by ring-current proximity. The corresponding 2:2 macrocycles **8** show considerably less discrimination between the various methylenes, since they are not subjected to the effects of the ring currents. Further evidence for the existence of the bridged conformation in **7** was derived from variable-temperature NMR. At −80 °C, the 2-methylene proton signal coalesced, indicative of a specific conformation imposed by the rigidity of the nonmobile bridging glycol moiety, very similar to that recently demonstrated in the 2,2′-dipyridyl series.[3f,18] The imidate moiety also imposes an additional spanning distance.[3f] The ϵ- and ξ-CH_2 protons exhibit a shielding of 1.4 ppm caused by their direct juxtaposition to the naphthyridine ring current. Recently similar bridging discrimination of the methylene groups caused by the magnetically anisotropic benzene[19] and naphthalene[20] groups has been reported. The β,γ-

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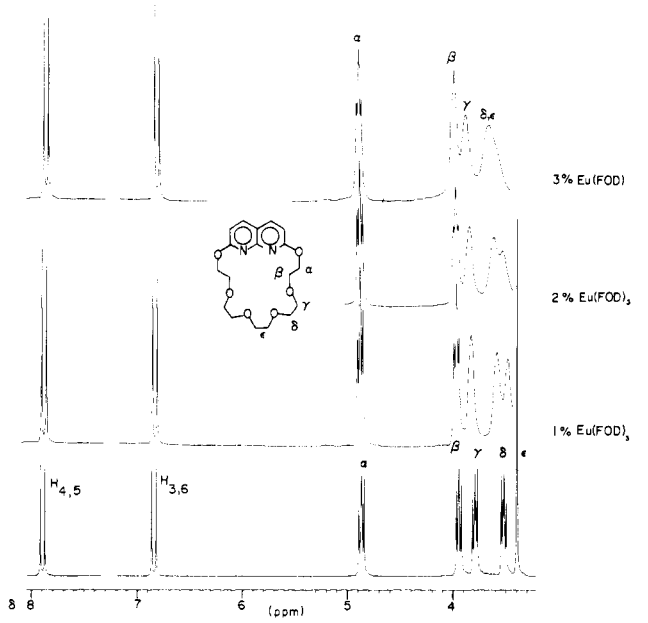


Figure 2. 200-MHz ^1H NMR spectrum of **9b** in CD_2Cl_2 at 40 °C with 0–3% added $Eu(fod)_3$.

methylene protons showed a deshielding of 0.7 ppm at −80 °C, which further indicates that these protons are more nearly coplanar with the aromatic nucleus.

2,7-(1,8-Naphthyridino) Macrocycles. The reaction of **6** with various dianions of polyethylene glycols was conducted in a similar fashion to that described above. Three new 1:1 macrocycles, **9a–c**, were isolated and characterized. (Scheme IV indicates the isolated percentages.) The supportive NMR data of **9a–c** for the macrocyclic structure are the doublets (J = 9 Hz) at δ 6.7–7.0 and 7.7–7.8 for the H-3,6 and H-4,5 protons, respectively (see Figure 2). The bridging methylenes are less clearly separated [δ 4.7 (α), 3.8–3.2 (β–ξ)] due to the lack of proximal ring current. The orthogonal N-electron density is lessened in magnitude due to their inclusion in the imidate moiety. In order to ascertain the site of ion complexation, $Eu(fod)_3$ shift reagent was added to **9b**. From the downfield shift of the spike for the ϵ-methylene protons, the shift reagent is predominantly associated with the central region of the polyethereal bridge and *not* with the naphthyridine nucleus.

Attempts to increase the yields of macrocyclic products were made by templation about a transition-metal cation. Slight increases (ca. 5%) were realized, but these minor increases could not be attributed exclusively to the usage of the metal ion.

Open-chain compounds **11** were also isolated from these reactions. Since the IR spectrum of **6** contained an absorption band at 748 cm^{-1} for the C–Cl vibrational mode, which was not present in the parent 1,8-naphthyridine or macrocyclic derivatives, the presence of the absorption at 750 ± 10 cm^{-1} in these 2:1 compounds supports the presence of the C–Cl bond. Further spectral support was provided by mass and NMR spectroscopic data. The NMR spectrum of **11** shows two close doublet of doublets at δ 6.55 and 6.59–6.65 for the H-3 and H-6 protons, respectively; the unsymmetrical nature of the ring and the complexity of the NMR spectrum further substantiate monooxygen substitution.

There were no 2:2 macrocyclic products, e.g., **10**, isolated when our xylene procedure[3] was used; however, when *N,N*-dimethylformamide (DMF) was utilized, not only the 1:1 macrocycles were isolated but also the desired 2:2

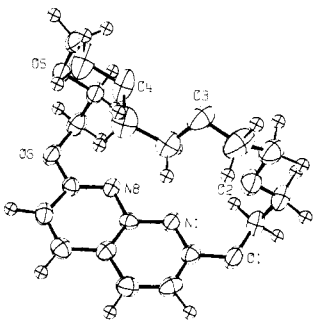


Figure 3. Perspective drawing of macrocycle **9b**. Nonhydrogen atoms are represented by thermal ellipsoids drawn at the 30% probability level, and hydrogen atoms are drawn as spheres of arbitrary radius.

macrocycles were realized. The NMR data for **10d,e** show an anticipated symmetrical pattern for the naphthyridine subunits. Furthermore, the trimer **12** was isolated and characterized from the reaction of **6** with sodium diethylene glycolate.

In order to ascertain the dimensions of these cavities and the actual hindrance to the naphthyridine N electrons, we

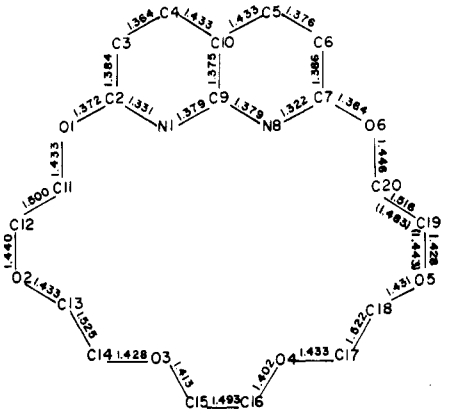


Figure 4. Average interatomic distances and numbering scheme. Standard deviations in individual distances are about 0.008 Å within the naphthyridyl subunit and from 0.008 to 0.012 Å within the polyethereal bridge. Where distances differ by more than 2σ between the two independent molecules, both are given.

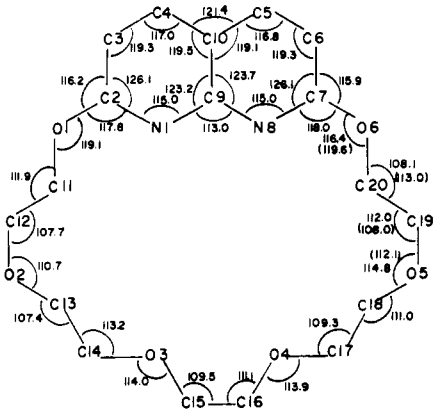
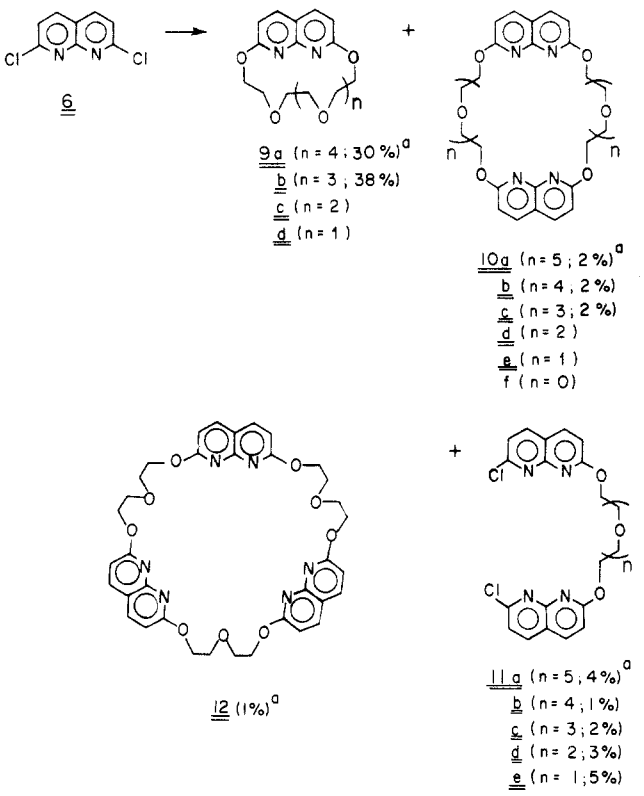


Figure 5. Average bond angles. Standard deviations are about 0.4–0.6°. Both angles are given if they differ by more than 2σ.

determined the X-ray crystal structure of **9b**. Two independent molecules exist in the asymmetric unit of the crystal. One is illustrated in Figure 3; average interatomic distances and average angles are given in Figures 4 and 5, respectively. Two distinct molecules lie in almost identical orientations with respect to the crystal axes and

Scheme IV



[a] Isolated yields.

have very similar conformations. The only substantial differences in conformation exist in the portion of the polyethereal bridge between O4 and O6, which is also the only portion of the molecule in which statistically significant differences in distances and angles exist between the primed and unprimed molecules. The 16-atom bridge is apparently quite flexible and subject to quite subtle packing effects.

Substitution of the polyethereal bridge to the naphthyridyl moiety (the imidate group) is in all cases essentially cis to the nitrogen atom. Torsion angle N1–C2–O1–C11 is 3.8° and N8–C7–O6–C20 is 0.2°. The corresponding values for the primed molecule are 6.7° and –1.8°, respectively. This conformation is universally found in *N*-heterocycles, e.g., pyridine, pyrimidine, substituted by an α-oxygen atom ortho to the N atom.[3e-g,m,o,p,4]

The 1,8-naphthyridyl fragment exhibits marked structural differences from the parent 1,8-naphthyridine,[21] many of which can be understood as consequences of the polyethereal disubstitution. 1,8-Naphthyridine has a clearly nonplanar, twisted structure, in which the two nitrogen atoms lie on opposite sides of the best plane of the molecule. The N–C–N angle in 1,8-naphthyridine is 115.3 (2)°, which is significantly larger than the corresponding angle found in complexed naphthyridines.[22,23] These facts have been rationalized in terms of repulsion between the nitrogen lone-pair electrons. The naphthyridyl fragment of **9b** does not have the twisted structure of the parent molecule but exhibits only marginally significant deviations from planarity. The N1–C9–N8 angle has an average value of 113.0 (5)°. *Both of these geometrical features coupled with the lanthanide shift studies (Figure 2) indicated a reduced electron density for the N lone pairs due to their inclusion in the imidate moiety.* Such reduced *N*-electron density has also been observed in polyethereal, substituted pyridine and bipyridyls.[3f] The twisting of naphthyridine also causes the central bond (e.g., C9–C10) to be lenghthened relative to the two bonds parallel to it.[21] Compound **9b** showed no such lenghthening. In general, the naphthyridyl subunit of **9b** more closely exhibits the pattern of lengths expected from a hybrid of the three naphthalene-like structures[24] than does naphthyridine.

Experimental Section

General Comments. All melting points were taken in capillary tubes with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. IR spectra were measured on a Perkin-Elmer 621 grating spectrophotometer, and the UV spectra were recorded on a Cary 14 spectrophotometer. Unless otherwise noted, NMR spectra were obtained in $CDCl_3$ solutions with Me_4Si as the internal standard (δ 0) and recorded on either a Varian Associates A-60A or Bruker WP 200. Low-temperature (+40 to –80 °C) NMR studies were conducted in CD_2Cl_2, whereas with the high-temperature range (40–100 °C), perchlorobutadiene was used. Mass spectral data were measured on a Hitachi Perkin-Elmer RMS-4 mass spectrometer by Mr. J. Murphy or on a Hewlett-Packard Model 5985 GC/MS spectrometer by Mr. D. Patterson. Elemental analyses were performed by Mr. R. L. Seab in these laboratories.

The recorded R_f values were determined by a standardized thin-layer chromatography (TLC) procedure: 0.25-mm Brinkmann silica gel HF-254+366 plates eluting with the stipulated solvents. For preparative thick layer chromatography (ThLC), 2-mm Brinkmann silica gel P/UV-254-366 or aluminum oxide (Type T) HF-254-366 plates were used. Xylene was distilled from sodium wire under a nitrogen atmosphere, while DMF was purified by specific conditioning to retard cyanide formation.[25] Sodium hydride (57% oil dispersion) was washed with anhydrous petroleum ether (bp 30–60 °C) and then dried in vacuo prior to the reaction. Ethylene glycol and di-, tri-, and tetraethylene glycols were purchased from Aldrich Chemical Co., whereas penta- and hexaethylene glycols[26] were purchased from Columbia Organic Chemicals, Inc.

1,5-Naphthyridine Series. 2,6-Dichloro-1,5-naphthyridine (2) was prepared from 1,5-naphthyridine in 35% yield by a previously described procedure;[14] mp 250–251 °C.

Reaction of 2,6-Dichloro-1,5-naphthyridine (2) with Hexaethylene Glycol. General Macrocyclic Preparation. Under a nitrogen atmosphere an oil suspension of sodium hydride (120 mg) was washed with anhydrous hexane (75 mL) and then dried in vacuo. Sodium-dried xylene (100 mL) was added, the mixture was stirred 10 min, and then hexaethylene glycol (370 mg, 1.3 mmol) was added *carefully*. The suspension was stirred for 1 h, and then **2** (250 mg, 1.3 mmol) was added with additional xylene (100 mL). The mixture was refluxed for 24 h under a nitrogen atmosphere. After the mixture cooled, the excess sodium hydride was carefully hydrolyzed with water (75 mL). The water layer was extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated in vacuo to afford a yellow paste, which was chromatographed (ThLC) by eluting with cyclohexane–ethyl acetate (1:1) to give two major fractions.

Fraction A was recrystallized from absolute ethanol to give **7a**: white needlelike crystals; mp 125–125.5 °C; yield 320 mg; NMR δ 2.98 (t, ξ-CH_2, J = 4 Hz, 4 H), 3.15 (t, ϵ-CH_2, J = 4 Hz, 4 H), 3.46 (m, δ-CH_2, 4 H), 3.65 (m, γ-CH_2, 4 H), 3.91 (m, β-CH_2, 4 H), 4.78 (m, α-CH_2, 4 H), 7.09 (d, 3,7-Naph H, J = 9Hz, 2 H),

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(26) Samples of penta- and hexaethylene glycols should be analyzed (high-performance LC) prior to use due to the variability in purity. Professor K. Potts (Rensselaer Polytechnic Institute), personal communication, 1980.

7.98 (d, 4,8-Naph H, J = 9 Hz, 2 H); IR (KBr) 1620, 1340, 1260, 1170 cm^{-1}; UV (EtOH) λ_{max} 344 nm (ϵ 2.0 × 10^4), 336 (1.7 × 10^4), 329 (2.0 × 10^4), 316 (1.3 × 10^4), 241 (1.8 × 10^4); mass spectrum, m/e (assignment, relative intensity) 408 (M^+, 53), 300 ($C_{16}H_{20}N_2O_4$, 30), 256 ($C_{14}H_{16}N_2O_3$, 32), 208 ($C_{10}H_{12}N_2O_3$, 90), 194 ($C_{10}H_{12}N_2O_2$, 80), 160 ($C_8H_4N_2O_2$, *100*).

Anal. Calcd for $C_{20}H_{28}H_2O_7$: C, 58.58; H, 6.86; N, 6.86. Found: C, 58.72; H, 6.88; N, 6.68.

Fraction B was recrystallized from absolute ethanol to afford **8a**: white microcrystals; mp 87–88.5 °C; yield 21 mg; NMR δ 3.68 (m, ξ-, γ-CH_2, 32 H), 3.96 (m, β-CH_2, 8 H), 4.59 (m, α-CH_2, 8 H), 7.03 (d, 3,7-Naph H, J = 9 Hz, 4 H), 7.94 (d, 4,8-Naph H, J = 9 Hz, 4 H); mass spectrum, m/e (relative intensity) 816 (M^+, 14), 704 (11), 680 (20), 560 (37), 404 ($M^+/2$, 64), 300 ($C_{16}H_{20}N_2O_4$, 18), 194 ($C_{10}H_{12}N_2O_2$, 23), 160 ($C_8H_4N_2O_2$, *100*).

Anal. Calcd for $C_{40}H_{56}N_4O_{14}$: C, 58.58; H, 6.86; N, 6.86. Found: C, 58.75; H, 6.88; N, 6.70.

Reaction of 2,6-Dichloro-1,5-naphthyridine with Pentaethylene Glycol. The above general procedure was used except for the substitution of pentaethylene glycol (600 mg, 2.5 mmol), and the following two major macrocyclic fractions were isolated.

Fraction A was recrystallized from absolute ethanol to afford **7b**: colorless needlelike crystals; mp 94–95 °C; yield 100 mg; R_f 0.5; NMR δ 2.65 (s, ϵ-CH_2, 4 H), 3.44 (m, γ-, δ-CH_2, 8 H), 3.83 (m, β-CH_2, 4 H), 4.95 (m, α-CH_2, 4 H), 7.11 (d, 3,7-Naph H, J = 9 Hz, 2 H), 8.03 (d, 4,8-Naph H, J = 9 Hz, 2 H); IR (KBr) 1610, 1520, 1250, 1140 cm^{-1}; UV (EtOH) λ_{max} 345 nm (ϵ 2.3 × 10^4), 337 (2.0 × 10^4), 330 (2.4 × 10^4), 317 (1.4 × 10^4), 242 (2.2 × 10^4); mass spectrum, m/e (relative intensity) 364 (M^+, 6.2), 216 (5.2), 180 ($C_{10}H_8N_2O_3$, 57), 160 ($C_8H_4N_2O_2$, 20), 128 ($C_9H_4N_2$, 4), 44 (C_2H_4O, *100*).

Anal. Calcd for $C_{18}H_{24}N_2O_6$: C, 59.37; H, 6.59; N, 7.69. Found: C, 59.10; H, 6.88; N, 7.52.

Fraction B was recrystallized from absolute ethanol to give **8b**: white microcrystals; mp 101–103 °C; yield 250 mg; R_f 0.13; NMR δ 3.5–4.1 (m, β-, ϵ-CH_2, 32 H), 4.6 (t, α-CH_2, J = 8 Hz, 8 H), 7.0 (d, 3,7-Naph H, J = 9 Hz, 4 H), 7.9 (d, 4,8-Naph H, J = 9 Hz, 2 H); IR (KBr) 1630, 1510, 1280, 1130 cm^{-1}; UV (EtOH) λ_{max} 340 (ϵ 6.5 × 10^4), 332 (5.2 × 10^4), 325 (6.7 × 10^4), 319 (4.7 × 10^4), 312 (3.9 × 10^4), 300 (2 × 10^4); mass spectrum, m/e (relative intensity) 728 (M^+, 32), 568 (24), 408 (27), 364 ($M^+/2$, *100*), 336 (36), 320 (86), 276 (73), 248 (96), 232 (95), 160 (14).

Anal. Calcd for $C_{36}H_{48}N_4O_{12}$: C, 59.39; H, 6.59; N, 7.69. Found: C, 59.67; H, 6.64; N, 7.39.

Reaction of 2,6-Dichloro-1,5-naphthyridine with Tetraethylene Glycol. The general procedure was followed except for the substitution of tetraethylene glycol (490 mg, 2.5 mmol). After the workup, the xylene layer gave one major macrocycle fraction which was recrystallized from absolute ethanol to afford **8c**: white microcrystals; mp 153–153.5 °C; yield 390 mg; R_f 0.18; NMR δ 3.73 (s, γ-, δ-CH_2, 16 H), 3.92 (m, β-CH_2, 8 H), 4.54 (m, α-CH_2, 8 H), 6.97 (d, 3,7-Naph H, J = 9 Hz, 4 H), 7.80 (d, 4,8-Naph H, J = 9 Hz, 4 H); IR (KBr) 1620, 1550, 1340, 1280, 1150 cm^{-1}; UV (EtOH) λ_{max} 340 (ϵ 4 × 10^4), 325 (4 × 10^4), 317 (2.9 × 10^4), 311 (2.9 × 10^4), 266 (3.5 × 10^4); mass spectrum, m/e (relative intensity) 640 (M^+, 86), 596 (19), 320 ($M^+/2$, 43), 232 ($C_{12}H_{12}N_2O_3$, 15), 204 ($C_{10}H_8N_2O_3$, *100*), 160 ($C_8H_4N_2O_2$, 93), 128 ($C_8H_4N_2$, 24).

Anal. Calcd for $C_{32}H_{40}N_4O_{10}$: C, 60.00; H, 6.24; N, 8.75. Found: C, 59.88; H, 6.47; N, 8.61.

Reaction of 2,6-Dichloro-1,5-naphthyridine with Triethylene Glycols. The general procedure was followed except for the substitution of triethylene glycol (200 mg, 1.5 mmol). After the workup, the organic layer gave one major macrocyclic fraction, which was recrystallized from absolute ethanol to afford **8d** as a white microcrystal: mp 215–216 °C; 140 mg; R_f 0.16; NMR δ 3.74 (s, γ-CH_2, 8 H), 3.88 (m, β-CH_2, 8 H), 4.58 (m, α-CH_2, 8 H), 7.01 (d, 3,7-Naph H, J = 9 Hz, 4 H), 7.91 (d, 4,8-Naph H, J = 9 Hz, 4 H); IR (KBr) 1630, 1560, 1290, 1150 cm^{-1}; mass spectrum, m/e (relative intensity) 276 ($M^+/2$, 43), 232 (3), 204 ($C_{10}H_8N_2O_3$, 78), 160 ($C_8H_4N_2O_2$, *100*), 128 ($C_8H_4N_2$, 30). Anal. Calcd for $C_{28}H_{32}N_4O_8$: C, 60.50; H, 5.80; N, 10.20. Found: C, 60.20; H, 5.64; N, 9.99.

Reaction of 2,6-Dichloro-1,5-naphthyridine with Diethylene Glycol. The general procedure was followed except for the substitution of diethylene glycol (140 mg, 1.3 mmol). After the workup, the organic layer gave one major cyclic fraction, which was recrystallized from absolute ethanol to give **8e** as microcrystals: mp 133–134 °C; 20 mg; R_f 0.14; NMR δ 3.88 (m, β-CH_2, 8 H), 4.60 (m, α-CH_2, 8 H), 7.01 (d, 3,7-Naph H, J = 9 Hz, 4 H), 7.91 (d, 4,8-Naph H, J = 9 Hz, 4 H); IR ($CHCl_3$) 1610, 1430, 1230, 1150 cm^{-1}; mass spectrum, m/e (relative intensity) 232 ($M^+/2$, 64), 188 ($C_{10}H_8N_2O_2$, 86), 160 ($C_8H_4N_2O_2$, *100*), 128 ($C_8H_4N_2$, 36).

Anal. Calcd for $C_{24}H_{24}N_4O_6$: C, 62.10; H, 5.17; N, 12.10. Found: C, 61.98; H, 5.27; N, 11.93.

1,8-Naphthyridine Series. 2,7-Dichloro-1,8-naphthyridine (6). A. 2-Amino-7-hydroxy-1,8-naphthyridine (4). Malic acid (3.0 g, 22 mmol) and 2,6-diaminopyridine (2.2 g, 20 mmol) were ground to an intimate powder and cooled in an ice bath, and then concentrated sulfuric acid (10 mL) was added dropwise. The solution was heated to 110 °C for 2–3 h, poured over ice, and made alkaline with concentrated ammonium hydroxide (pH 8). 2-Amino-7-hydroxy-1,8-naphthyridine was isolated: mp >350 °C (lit.[15] mp >360 °C); yield 3.52 g (97%); NMR (Me_2SO-d_6) δ 6.12 (d, 3-Naph H, J = 9 Hz, 1 H), 6.35 (d, 6-Naph H, J = 9 Hz, 1 H), 6.94 (s, NH_2, 2 H), 7.65 (d, 4,5-Naph H, J = 9 Hz, 2 H).

B. 2,7-Dihydroxy-1,8-naphthyridine (5). 2-Amino-7-hydroxy-1,8-naphthyridine (4.7 g, 29 mmol) was ground to a fine powder and added to concentrated sulfuric acid (40 mL), and then sodium nitrite (2.4 g) was added. The mixture was allowed to stand for 5 min, poured over crushed ice, and allowed to stand for 10 min. Excess sodium nitrite was neutralized with sodium carbonate, and then the solution was acidified with glacial acetic acid (pH 3), giving **5** as a pale green powder: mp 321–323 °C (lit.[16] mp 320–330 °C); yield 4.1 g (87%); NMR (Me_2SO-d_6) δ 3.15 (m, OH, 2 H), 6.25 (d, 3,6-Naph H, J = 9 Hz, 2 H), 7.75 (d, 4,5-Naph H, J = 9 Hz, 2 H).

C. 2,7-Dichloro-1,8-naphthyridine (6). A mixture of 2,7-dihydroxy-1,8-naphthyridine (500 mg, 3.1 mmol), phosphorus pentachloride (1.25 g, 6 mmol), and phosphorus oxychloride (1.12 g, 7 mmol) was refluxed for 2 h, ice was carefully added, and the solution was made alkaline with sodium carbonate. A brown precipitate was collected and recrystallized from acetone to give **6**: a white powder; sublimation point 258 °C (lit.[16] sublimation point 259 °C); yield 500 mg (81%); NMR δ 7.5 (d, 3,5-Naph H, J = 9 Hz, 2 H), 8.1 (d, 4,5-Naph H, J = 9 Hz, 2 H).

Reaction of 2,7-Dichloro-1,8-naphthyridine (6) with Hexaethylene Glycol. General 1,8-Macrocyclic Procedure. Sodium-dried xylene (600 mL) was added to the oil-free sodium hydride, the mixture was stirred for 10 min, and then hexaethylene glycol (1.5 g, 5.2 mmol) was added. After 30 min, **6** (1.0 g, 5.2 mmol) was added in additional xylene (150 mL). The resultant mixture was refluxed for 24 h and cooled to 25 °C, and the excess sodium hydride was hydrolyzed with water (150 7L). The aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined halocarbon extract was dried over anhydrous magnesium sulfate and concentrated in vacuo to afford a yellow oil, which was chromatographed (ThLC) by eluting twice with an ethyl acetate–cyclohexane (4:1) mixture to afford **11a**: white microcrystals; mp 98–100 °C [benzene–cyclohexane (1:1)]; yield 35 mg; R_f 0.19; NMR δ 3.6–4.0 (m, β-, ξ-CH_2, 18 H), 4.5 (t, α-CH_2, J = 5 Hz, 4 H), 6.55 (d, 3-Naph H, J = 10 Hz, 2 H), 6.6 (d, 6-Naph H, J = 8 Hz, 2 H), 7.6 (d, 4-Naph H, J = 10 Hz, 2 H), 7.7 (d, 5-Naph H, J = 8 Hz, 2 H); IR (KBr) 3500, 1540, 1350, 1120 cm^{-1}.

Anal. Calcd for $C_{28}H_{32}N_4O_7Cl_2$: C, 55.35; H, 5.27; N, 9.23. Found: C, 55.04; H, 5.35; N, 9.50.

After the workup, the water layer gave a brown oil, which was chromatographed (ThLC) by eluting twice with ethyl acetate–cyclohexane (4:1) to give **9a**: colorless crystals; mp 73.5–75 °C; yield 306 mg; R_f 0.35; NMR δ 3.49 (s, ξ-, γ-CH_2, 8 H), 3.79 (m, γ-, δ-CH_2, 8 H), 3.95 (t, β-CH_2, J = 5 Hz, 4 H), 4.84 (t, α-CH_2, J = 5 Hz, 4 H), 6.84 (d, 3,6-Naph H, J = 9 Hz, 2 H), 7.91 (d, 4,5-Naph H, J = 9 Hz, 2 H); IR ($CHCl_3$) 1640, 1530, 1220, 1050 cm^{-1}; UV (EtOH) λ_{max} 326 nm (ϵ 2.5 × 10^4), 318 (1.8 × 10^4), 313 (1.8 × 10^4), 299 (1.3 × 10^4), 251 (5 × 10^4); mass spectrum, m/e 404 (M^+, 39), 364 (31), 320 (26), 276 (21), 232 (35), 204 ($C_{10}H_8N_2O_3$, 96), 160 ($C_8H_4N_2O_2$, *100*). Anal. Calcd for $C_{20}H_{28}N_2O_7$: C, 58.62; H, 6.86; N, 6.86. Found: C, 58.73; H, 6.99; N, 6.73.

Reaction of 2,7-Dichloro-1,8-naphthyridine with Pentaethylene Glycol. The general 1,8-naphthyridine procedure was followed except for the substitution of pentaethylene glycol (1.2 g, 5.2 mmol). After the workup, the xylene layer gave a yellow oil, which was chromatographed (ThLC) by eluting once with ethyl

acetate–cyclohexane (5:1) to give **9b**: white microcrystals; mp 77–78 °C [diethyl ether–hexane (3:1)]; yield 360 mg; R_f 0.45; NMR δ 3.39 (s, ϵ-CH_2, 4 H), 3.52 (m, δ-CH_2, 4 H), 3.79 (m, γ-CH_2, 4 H), 3.94 (t, β-CH_2, J = 5 Hz, 4 H), 4.87 (t, α-CH_2, J = 5 Hz, 4 H), 6.86 (d, 3,6-Naph H, J = 9 Hz, 2 H), 7.89 (d, 4,5-Naph H, J = 9 Hz, 2 H); IR ($CHCl_3$) 1630, 1520, 1350, 1250, 1050 cm^{-1}; UV (EtOH) λ_{max} 325 (ϵ 1.5 × 10^4), 319 (1.1 × 10^4), 311 (7.3 × 10^3), 294 (7.3 × 10^3), 254 (7.3 × 10^3); mass spectrum, m/e (relative intensity) 364 (M^+, 28), 320 (38), 276 (17), 232 (33), 188 (96), 160 ($C_8H_4N_2O_2$, *100*).

Anal. Calcd for $C_{18}H_{24}N_2O_6$: C, 59.37; H, 6.59; H, 7.69. Found: C, 59.62; H, 6.81; N, 7.64.

The water layer gave a yellow oil, which was chromatographed (ThLC) by eluting twice with ethyl acetate to give **11b**: white needles; mp 101–103 °C [benzene–cyclohexane (1:1)]; yield 22 mg; R_f 0.16; NMR δ 3.5–4.0 (m, β-, ϵ-CH_2, 16 H), 4.6 (t, α-CH_2, J = 4 Hz, 4 H), 6.57 (d, 3-Naph H, J = 9.5 Hz, 2 H), 6.62 (d, 6-Naph H, J = 8 Hz, 2 H), 7.60 (d, 4-Naph H, J = 9.5 Hz, 2 H), 7.69 (d, 5-Naph H, J = 8 Hz, 2 H); IR (KBr) 1640, 1340, 1230, 1110 cm^{-1}; UV (EtOH) λ_{max} 341 nm (ϵ 1.1 × 10^4), 328 (1.5 × 10^4), 315 (9.8 × 10^3), 307 (6.2 × 10^3), 299 (4.1 × 10^3).

Anal. Calcd for $C_{26}H_{28}N_4O_6Cl_2$: C, 55.42; H, 4.97; N, 9.95. Found: C, 55.22; H, 4.88; N, 9.83.

Reaction of 2,7-Dichloro-1,8-naphthyridine with Tetraethylene Glycol. The general 1,8-naphthyridine procedure was followed except for the substitution of tetraethylene glycol (1.0 g, 5.1 mmol). The xylene layer afforded an oil, which was chromatographed (ThLC) by eluting twice with ethyl acetate to give **10c**: mp 65–67 °C [diethyl ether–hexane (3:1)]; yield 37 mg; R_f 0.51; NMR (Me_2SO-d_6) δ 3.46 (t, δ-CH_2, J = 5 Hz, 4 H), 3.84 (t, γ-CH_2, J = 5 Hz, 4 H), 4.03 (t, β-CH_2, J = 5 Hz, 4 H), 4.98 (t, α-CH_2, J = 5 Hz, 4 H), 7.10 (d, 3,6-Naph H, J = 9 Hz, 2 H), 7.89 (d, 4,5-Naph H, J = 9 Hz, 2 H); IR ($CHCl_3$) 1620, 1490, 1240, 1060 cm^{-1}; UV (EtOH) λ_{max} 325 nm (ϵ 1.3 × 10^4), 319 (1.1 × 10^4), 312 (1.0 × 10^4), 297 (6.6 × 10^4), 250 (6.6 × 10^3); mass spectrum, m/e (relative intensity) 320 (M^+, 49), 276 (32), 232 (40), 204 ($C_{10}H_8N_2O_3$, 95), 160 ($C_8H_4N_2O_2$, *100*).

The water layer gave a yellow oil which was chromatographed (ThLC) by eluting twice with ethyl acetate to give **11c**: mp 34–35 °C [benzene–cyclohexane (1:1)]; yield 40 mg; R_f 0.19; NMR δ 3.6–4.1 (m, β-, δ-CH_2, 12 H), 4.5 (t, α-CH_2, J = 4 Hz, 4 H), 6.55 (d, 3-Naph H, J = 9.5 Hz, 2 H), 6.63 (d, 6-Naph H, J = 8 Hz, 2 H), 7.62 (d, 4-Naph H, J = 9.5 Hz, 2 H), 7.74 (d, 5-Naph H, J = 8 Hz, 2 H); IR (KBr) 1640, 1350, 1220 1110 cm^{-1}; UV (EtOH) λ_{max} 345 (ϵ 1.7 × 10^4), 330 (2.3 × 10^4), 315 (1.5 × 10^4), 307 (8 × 10^3), 300 (4 × 10^3).

Anal. Calcd for $C_{26}H_{24}N_4O_5Cl_2$: C, 57.46; H, 4.42; N, 10.31. Found: C, 57.18; H, 4.41; N, 10.39.

Reaction of 2,7-Dichloro-1,8-naphthyridine with Triethylene Glycol. Method A. The general 1,8-procedure was followed except for the substitution of triethylene glycol (1.0 g, 6.2 mmol). The xylene layer gave *no* macrocyclic products. The aqueous layer gave a yellow oil which was chromatographed (ThLC) by eluting twice with ethyl acetate to give **11d**: mp 93–94 °C [benzene–cyclohexane (1:1)]; yield 71 mg; R_f 0.17; NMR δ 3.6–4.0 (m, β-, γ-CH_2, 8 H), 4.6 (t, α-CH_2, J = 4 Hz, 4 H), 6.55 (d, 3-Naph H, J = 10 Hz, 2 H), 6.59 (d, 6-Naph H, J = 8 Hz, 2 H), 7.65 (d, 4-Naph H, J = 10 Hz, 2 H), 7.70 (d, 5-Naph H, J = 8 Hz, 2 H); IR (KBr) 1630, 1450, 1220, 1120, 1040 cm^{-1}; UV (EtOH) λ_{max} 342 nm (ϵ 1.5 × 10^4), 329 (1.9 × 10^4), 316 (1 × 10^4), 306 (6 × 10^3), 299 (2.6 × 10^3); mass spectrum, m/e (relative intensity) 479 (M^+ + 4, 5), 477 (M^+ + 2, 30), 475 (M^+, 46), 312 ($C_{14}H_{16}N_2O_4Cl$, 57), 268 ($C_{13}H_{13}N_2O_3Cl$, 30), 224 ($C_{10}H_8N_2O_2Cl$, 36), 180 ($C_8H_4N_2OCl$, *100*).

Anal. Calcd for $C_{22}H_{20}N_4O_4Cl_2$: C, 55.60; H, 4.23; N, 11.80. Found; C, 55.49; H, 4.55; N, 11.70.

Method B. To a stirred suspension of NaH (960 mg, 20 mmol) in dry DMF (10 mL) was slowly added triethylene glycol (1.5 g, 10 mmol) in DMF (25 mL). The mixture was stirred at room temperature for 1 h, and **6** (2 g, 10 mmol) in DMF (100 mL) was slowly added. The reaction was heated at 80 °C for 72 h and was cooled, and water (50 mL) was cautiously added. The solvent was removed in vacuo, and the resulting solid was washed with methylene chloride (3 × 100 mL) and filtered. The filtrate was dried over magnesium sulfate, filtered, and concentrated in vacuo to give an oil, which was chromatographed (ThLC) on alumina by eluting once with chloroform to give **10d**: white solid; mp 219–220 °C (ethanol); yield 67 mg; R_f 0.36; NMR δ 3.74 (s, γ-CH_2, 8 H), 3.89 (m, β-CH_2, 8 H), 4.70 (m, α-CH_2, 8 H), 6.77 (d, 3,6-Naph H, J = 9 Hz, 4 H), 7.78 (d, 4,5-Naph H, J = 9 Hz, 4 H); IR (neat), 1600, 1495, 1430, 1320, 1250, 1105, 1050, 940, 845, 800 cm^{-1}; mass spectrum, m/e (relative intensity) 552 (M^+, 1.4), 275 (30), 231 (18.9), 189 ($C_8H_6N_2O_2$, *100*), 162 (97.6), 145 (36.9).

Anal. Calcd for $C_{28}H_{32}N_4O_8 \cdot H_2O$: C, 58.94; H, 5.61; N, 9.82. Found: C, 59.12; H, 5.81; N, 9.89.

Reaction of 2,7-Dichloro-1,8-naphthyridine with Diethylene Glycol. Method A. The general 1,8-naphthyridine procedure was followed except for the substitution of diethylene glycol (270 mg, 2.5 mmol). The water layer gave an oil, which was chromatographed (ThLC) by eluting three times with ethyl acetate to afford **11e**: white microcrystals; mp 87–88 °C; yield 54 mg; R_f = 0.16; NMR δ 3.8–4.1 (m, β-CH_2, 4 H), 4.5 (m, α-CH_2, 4 H), 6.55 (d, 3-Naph H, J = 10 Hz, 2 H), 6.60 (d, 6-Naph H, J = 8 Hz, 2 H), 7.63 (d, 4-Naph H, J = 10 Hz, 2 H), 7.71 (d, 5-Naph H, J = 8 Hz, 2 H); IR (KBr) 1630, 1325, 1220, 1130 cm^{-1}; UV (EtOH) λ_{max} 344 (ϵ 1.4 × 10^4), 328 (2 × 10^4), 314 (1.2 × 10^4), 305 (6.5 × 10^3), 298 (3 × 10^3); mass spectrum, m/e (relative intensity) 435 (M^+ + 4, 65), 433 (M^+ + 2, 40), 431 (M^+, 62), 268 (29), 224, 180 ($C_8H_4N_2OCl$, 85), 164 ($C_8H_4N_2Cl$, *100*).

Anal. Calcd for $C_{20}H_{16}N_4O_3Cl_2$: C, 55.68; H, 3.71; N, 12.99. Found: C, 55.45; H, 3.91; N, 12.69.

Method B. The general 1,8-naphthyridine procedure as above was followed except for the substitution of diethylene glycol (1.06 g, 10 mmol). The resulting oil was chromatographed (ThLC alumina) by eluting twice with chloroform to give two macrocycles.

Fraction A afforded **10e**: colorless needles; mp 254–255 °C [chloroform–2-propanol]; yield 78 mg; R_f 0.46 (chloroform, alumina); NMR δ 4.04 (m, β-CH_2, 8 H), 4.82 (m, α-CH_2, 8 H), 6.58 (d, 3,6-Naph H, J = 8.5 Hz, 4 H), 7.67 (d, 4,5-Naph H, J = 8.5 Hz, 4 H); IR (neat) 1630, 1510, 1330, 1270, 1130, 800 cm^{-1}; mass spectrum, m/e (relative intensity) 464 (M^+, 4.5), 259 (22), 231 (51), 189 ($C_8H_6N_2O_2$, *100*), 162 (50), 145 (36.5).

Anal. Calcd for $C_{24}H_{24}N_4O_6 \cdot H_2O$: C, 59.75; H, 4.97; N, 11.62. Found: C, 59.85; H, 4.99; N, 11.56. Fraction B afford **12**: colorless microcrystals; mp 230–230.5 °C; yield 36 mg; R_f 0.37 (chloroform, alumina); NMR δ 3.97 (m, β-CH_2, 12 H), 4.69 (m, α-CH_2, 12 H), 6.78 (d, 3,6-Naph H, J = 9 Hz, 6 H), 7.79 (d, 2,5-Naph H, J = 9 Hz, 6 H); IR (neat) 1610, 1510, 1340, 1270, 1135, 1025, 850, 805 cm^{-1}.

Anal. Calcd for $C_{36}H_{36}N_6O_9$: C, 62.07; H, 5.17; N, 12.07. Found: C, 61.77; H, 5.40; N, 11.99.

X-ray Experiment. Prismatic, colorless crystals of **9b** were grown from a mixture of diethyl ether–petroleum ether (bp 30–45 °C). A crystal of dimensions 0.33 × 0.45 × 0.52 mm was used for data collection on an Enraf-Nonius CAD 4 diffractometer equipped with a graphite-monochromatized Mo X-ray tube (λ = 0.710 69 Å for Mo Kα).

Crystal Data: $C_{18}H_{24}N_2O_6$ (**9b**); mol wt 364.4; triclinic space group $P\bar{1}$, a = 8.969 (3) Å, b = 10.325 (3) Å, c = 20.107 (5) Å, α = 86.02 (2)°, β = 89.01 (2)°, γ = 79.15 (2)°, Z = 4, d_{calcd} = 1.327 g cm^{-3}, μ (Mo Kα) = 0.93 cm^{-1}. Intensity data were collected by the ω–2θ scan technique. Scan speeds varied from 0.60 deg min^{-1} to 20.0 deg min^{-1} in order to measure all reflections with approximately equal precision. A maximum of 120 s was spent on the measurement of any reflection, and reflections judged to be insignificantly intense in a rapid prescan were flagged as "unobserved" and were not scanned slowly. No significant decrease in the intensities of periodically measured reflections was noted. All reflections within one hemisphere having 1° ≤ 2θ ≤ 20° were measured, yielding 3732 data. Averaging equivalent reflections led to 2374 "observed" data, which were used in further calculations. Background, Lorentz, and polarization corrections were applied to these data, but absorption corrections were deemed insignificant.

Structure Solution and Refinement. The structure of **9b** was solved routinely by use of MULTAN78[27] and completed by Fourier methods using the program SHELX.[28] The model was

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refined by least-square techniques by treating C, N, and O atoms anisotropically and fixing H atoms in calculated positions. Aromatic hydrogen atoms were refined with a common isotropic temperature factor, and methylene hydrogen atoms were treated similarly. Convergence was achieved with $R = 0.055$. Coordinates of nonhydrogen atoms, anisotropic thermal parameters, and hydrogen atoms parameters are given in the supplementary material.

Acknowledgment is made to the National Institutes of Health, to the A. P. Sloan Foundation, to the SREB (travel grant) for partial support of this research, and to Professor J. L. Atwood (University of Alabama) for his assistance in obtaining the X-ray data.

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Supplementary Material Available: Coordinates for the nonhydrogen atoms in **9b** (Table I), anisotropic thermal parameters (Table II), and hydrogen atom parameters (Table III) for the X-ray structure of **9b** (3 pages). Ordering information is given on any current masthead page.

Acid-Mediated Rearrangement of Acylpyrroles[1]

John R. Carson* and Nancy M. Davis

Department of Chemistry, McNeil Pharmaceutical, Spring House, Pennsylvania 19477

Received September 18, 1980

N-Alkyl-2-acylpyrroles are converted by strong anhydrous acid to 1-alkyl-3-acylpyrroles. An equilibrium mixture of 2- and 3-acylpyrrole is produced by treatment of a 2- or 3-acyl NH pyrrole with acid. Pyrrolecarboxaldehydes similarly afford isomeric mixtures. A cross-ring migration, **7** → **8**, is observed when the adjacent position is blocked. The mechanism of acid-mediated rearrangement of acylpyrroles is discussed.

Reversibility of Friedel–Crafts acylation and acid-mediated rearrangement of aromatic ketones have been topics of recent attention.[2] While reversal of aromatic acylation is not common, examples have been found in which it is clearly involved.[2-7]

Several factors promote reversible acylation. For example, systems in which the carbonyl group is tilted out of the plane of the aromatic ring by a bulky neighboring substituent are prone to reversal of acylation.[3,4] Acyl derivatives of aromatic systems which are highly reactive toward electrophilic substitution are also susceptible to reversibility. Acyl derivatives of polycyclic aromatics undergo rearrangement under acidic conditions.[5] Acyl derivatives of π excessive nitrogen heterocycles have also been observed to undergo acid-mediated rearrangement. Palmer and co-workers studied the polyphosphoric acid (PPA) mediated cyclization of some 3-(2-pyrrolyl)propionic acids,[6] and they found products arising from both acyl and alkyl migration. Chastrette observed that 2-acetylindoles, on treatment with PPA, were converted to 3-acetylindoles.[7] We report our findings on the acid-mediated rearrangement of acylpyrroles.

Results and Discussion

Synthetic Methods. Treatment of 2-acyl-1-alkylpyrroles (**1**) with excess anhydrous strong acids at 70–120 °C afforded the corresponding 3-acyl-1-alkylpyrroles (**2**) as the sole monomeric neutral products. Reagents which have been successfully employed include PPA, trifluoroacetic acid (TFA), methanesulfonic acid (MsOH), toluenesulfonic acid (TsOH), trifluoromethanesulfonic acid (TfOH) and "metaphosphoric acid" $[(HPO_3)_n]$. Polymeric materials are the principal byproduct of the reaction. Highest yields are obtained by using TFA (Table I).

Ketones of type **1** where R is an electron-withdrawing group, e.g., trifluoromethyl or carboethoxy, did not rearrange under ordinary conditions and suffer decomposition under forcing conditions. 5-(4-Chlorobenzoyl)furan-2-acetonitrile did not undergo acyl rearrangement in PPA.[8] Reagents which have not proven effective include acetic acid, concentrated sulfuric acid (presumably because of oxidation of the substrate), and hydrogen chloride in organic solvents. Lewis acids including $AlCl_3$ and BF_3 did not bring about the rearrangement.

Structural assignments of the β-acylpyrroles (**2**) are based on the lack of a 3.8–4.0-Hz coupling constant in the ^1H NMR spectra which is characteristic of 3,4-proton substitution[9] and a 30–70-nm hypsochromic shift relative to the α isomer (**1**) in the UV.[10]

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