Fraction C gave the 2:2 macrocycle **24**: clear crystalline solid, mp 192–193 °C; 60 mg (3%); R_f 0.07; NMR ($CDCl_3$) δ 3.35 (t, β-CH_2O, J = 5 Hz, 8 H), 3.80 (t, α-CH_2O, J = 5 Hz, 8 H), 7.2 (s, 5-pyrim H, 2 H), 8.41 (s, 2-pyrim H, 2 H); IR (KBr) 2850, 1500, 1490, 1330, 1250, 1070 cm^{-1}; mass spectrum, m/e 428 (M^+).

Anal. Calcd for $C_{16}H_{20}N_4O_2S_4$: C, 44.86; H, 4.67; N, 13.08. Found: C, 44.70; H, 4.72; N, 13.16.

Acknowledgment. We are grateful to the National Institutes of Health and the National Science Foundation for partial support of this work.

Registry No. **1**, 1193-21-1; **2**, 71370-90-6; **3**, 71411-03-5; **4**, 71370-91-7; **5**, 71370-92-8; **6**, 71370-93-9; **7**, 71370-94-0; **8**, 71370-95-1; **9**, 71370-96-2; **10**, 71370-97-3; **11**, 71370-98-4; **12**, 71370-99-5; **13**, 71371-00-1; **14**, 71371-01-2; **15**, 71371-02-3; **16**, 5270-93-9; **19**, 71371-03-4; **20**, 71371-04-5; **21**, 71371-05-6; **22**, 71371-06-7; **23**, 71371-07-8; **24**, 71371-08-9; diethylene glycol, 111-46-6; triethylene glycol, 112-27-6; tetraethylene glycol, 112-60-7; pentaethylene glycol, 4792-15-8; hexaethylene glycol, 2615-15-8; methyl iodide, 74-88-4; ethylene glycol, 107-21-1; bis(2-mercaptoethyl) ether, 2150-02-9.

Molecular Inclusion Compounds.[1] Ketonic and Spiro Heteromacrocycles Possessing 2,6-Pyridino Moieties Connected by a Carbon–Oxygen and/or –Sulfur Bridge

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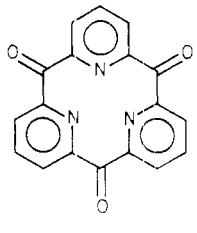
Spiro and ketonic macrocycles with specific cavities were synthesized by application of a heteroaromatic nucleophilic-substitution reaction. Initial ketalization of 2,6-bis(6-bromo-2-picolinoyl)pyridine (**3**) with β-bromoethanol and base was accomplished in 90% yield to give diketal **4**. When β-chloroethanol was used in this ketalization reaction, **3** afforded a new macrocycle, which has been assigned structure **34** on the basis of spectral and analytical data. Macrocycle **11**, prepared by the reaction of **4** and disodium glycolate, was characterized and hydrolyzed to give a series of ring-fragmented ketals (**12**), instead of the expected diketone **13**. All other diketal macrocycles were hydrolyzed to give the corresponding diketones in good yield with no evidence of macrocyclic cleavage. The X-ray structures of **14** and **15** were determined to afford insight into (a) the subtle structural alterations of these macrocycles upon hydrolysis and (b) the rationale for ring cleavage of **12**, rather than simple hydrolysis of the protecting groups. Sulfur-bridged spiro and ketonic macrocycles were also synthesized; however, the cyclization step was plagued by typical sulfur side reactions.

Recently, we reported the synthesis of the novel 1,-3,5-tri[2,6]pyridacyclohexaphane-2,4,6-trione[3] (**1**), which



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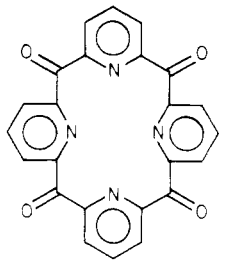

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possesses an unusually crowded 6N-electron-rich cavity. This trione represents the second member in a new macrocyclic system, of which the third member (**2**) would be the first example of a pyridine-containing xantho-porphinogen-type model. During the preliminary studies[4] directed toward syntheses of these ketonic macrocycles, dione **3** was treated with lithium carbonate and β-chloroethanol to give the desired diketal **4** and a new macrocyclic structure A ($C_{23}H_{21}N_3O_6$). A typical acid-catalyzed hydrolysis of A gave a new ketone B ($C_{19}H_{13}N_3O_4$), which was also deemed macrocyclic on the basis of physical and spectral characteristics. Since a new bond to pyridine was formed, independent synthesis of A (tentatively envisioned to be **11**) was conducted via application of a crown ether synthetic procedure. We herein describe (1) the results of our synthetic and structural endeavors to unravel this problem and (2) the construction of a new series of polyfunctionalized macrocycles.

Results

A. Preliminary Results. In our initial procedures directed toward the synthesis of trione **1**, methyl 2,6-pyridinedicarboxylate was added to 2 equiv of 6-lithio-2-bromopyridine[6] at −100 °C to generate (48%) the desired 2,6-bis(6-bromo-2-picolinoyl)pyridine (**3**). Substitutes for the diester, for example, either 2,6-dicyanopyridine or 2,6-dipicolinoyl chloride, did not afford substantial improvement in the yield of **3**. The IR spectrum of **3** showed a carbonyl absorption at 1680 cm^{-1}, characteristic of these dipyridyl ketones. Dione **3**, when subjected to our standard ketalization procedure,[7] that is, β-bromoethanol and lithium carbonate for 5 h, gave (48–65%) the desired diketal **4**, along with variable quantities of monoketal **5**, and unchanged starting material. Prolonged reaction times (36 h) at this ketalization stage resulted in yields of **4** that

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(3) Newkome, G. R.; Sauer, J. D.; Mattschei, P. K.; Nayak, A. *Heterocycles* **1978**, *9*, 1555.
(4) Sauer, J. D. Ph.D. Dissertation, LSU, 1976.
(5) (a) Newkome, G. R.; Danesh-Khoshboo, F.; Nayak, A.; Benton, W. H. *J. Org. Chem.* **1978**, *43*, 2685. (b) Newkome, G. R.; Nayak, A.; McClure, G. L.; Danesh-Khoshboo, F.; Broussard-Simpson, J. *Ibid.* **1977**, *42*, 1500. (c) Newkome, G. R.; McClure, G. L.; Broussard-Simpson, J.; Danesh-Khoshboo, F. *J. Am. Chem. Soc.* **1975**, *97*, 3232.
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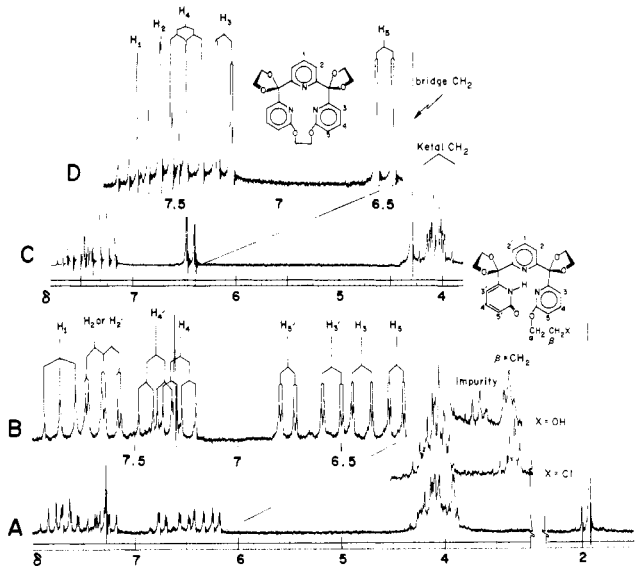
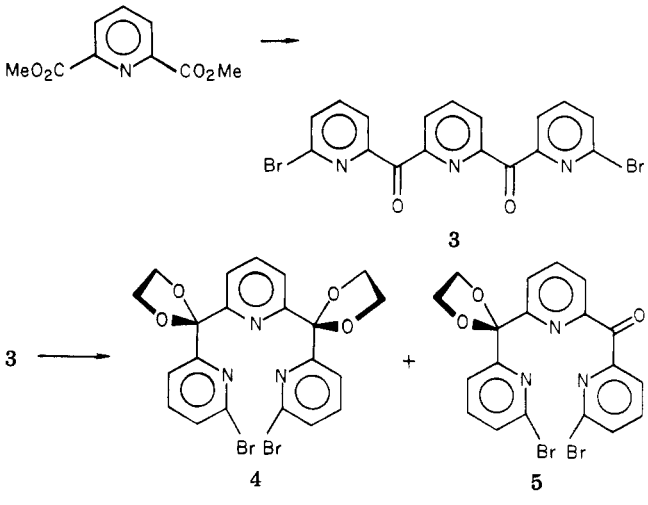
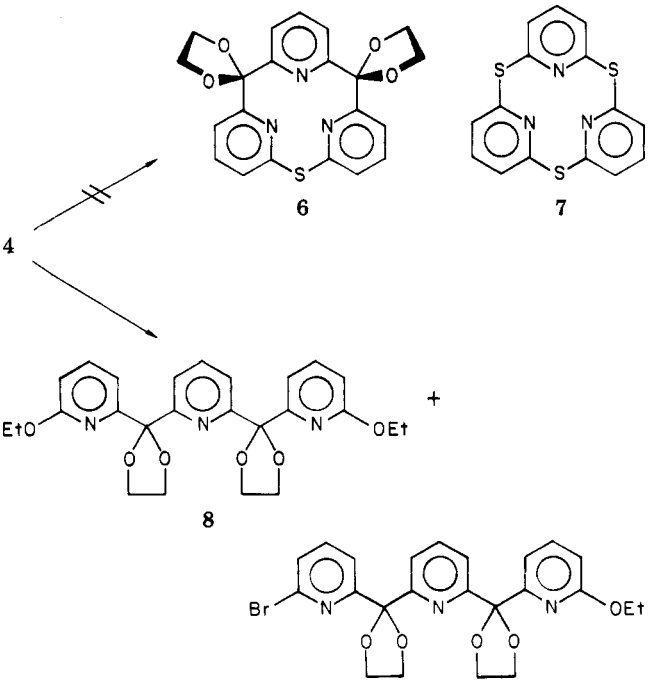


Figure 1. ^{1}H NMR spectra of **11** and **12** in C_6D_6 in $CDCl_3$ (20% (v/v)): (A) **12a** (X = OAc) with overlays of **12b** (X = Cl) and **12c** (X = OH); (B) expanded aromatic region of **12**; (C) diketal **11**; (D) diketal **11** expanded aromatic region.

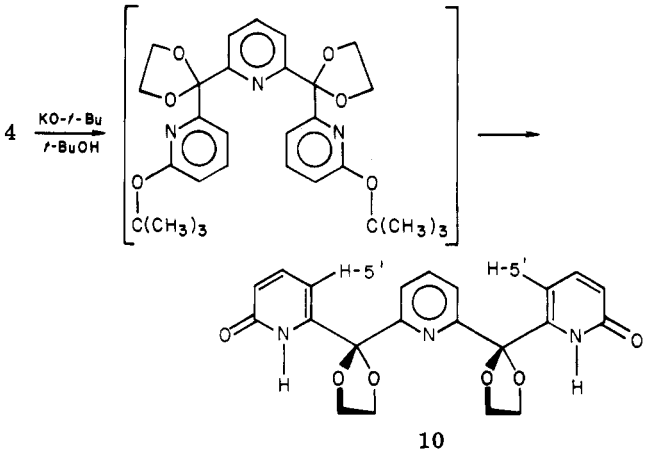
approached 90%. The NMR spectra of these ketals show either a singlet or multiplet at ca. δ 4.0 for the ketal methylene protons. Hydrolysis of **4** regenerated (>80%) **3**; however, extremely rigorous hydrolytic conditions are always necessary to ensure complete ketal to ketone conversion. In view of the tremendous difficulties associated with the ketal workup, the more volatile β-chloroethanol,[8] replacing β-bromoethanol, was used; however, not only were **3**, **4**, and **5** isolated but a fourth component was isolated and tentatively assigned as a macrocyclic diketal A, based on both analytical and limited spectral data.[9]



In-order to evaluate cyclization procedures applied to **4**, we made initial attempts to prepare **6**, especially since macrocycle **7** was known to exist.[10] Diketal **4** was treated with sodium sulfide in refluxing absolute ethanol for 24 h to give predominantly (75%) the ethoxy ketal **8**, as well as (16%) the monoether **9**. The reaction of mercaptide nucleophiles under these conditions has been demonstrated to proceed sluggishly and to generate a multitude of unwanted sulfur-containing byproducts.[5a] No evidence was found for the desired cyclization products, e.g., **6**.



Nucleophilic displacement of halide by oxygen nucleophiles was further demonstrated by treatment of **4** with potassium *tert*-butoxide in anhydrous refluxing *tert*-butyl alcohol for 18 h.[11] Facile nucleophilic substitution occurred followed by a smooth elimination of isobutylene to generate (66%) the bis(pyridinone) **10**. The NMR spectrum of **10** showed an unexpected singlet at δ 4.15 for the ketal methylene hydrogens and a doublet of doublets at δ 6.42 for the H-5 proton; the latter pattern is typical of a 6-substituted pyridinone moiety.[12]



B. Carbon–Oxygen Macrocycles. (1) Ethylene Glycol. The reaction of 2(or 6)-halopyridines with alk-

(8) Under the ketalization conditions,[7] dione **3** will undergo a slow bromide–chloride exchange whenever β-chloroethanol is utilized in this procedure. For subsequent metal–halogen-exchange reactions, this exchange reaction is detrimental, whereas in most nucleophilic-substitution reactions, the particular halide ion is unimportant.

(9) White crystalline solid: 9.6%; R_f 0.20; NMR ($CDCl_3$–1% Me_4Si) δ 4.25 (bd, ketal CH_2O, J = 5 Hz, 8 H), 4.6 (s, bridge CH_2O, 4 H), 7.12–7.80 (m, Pyr-H, 9 H); IR 1350 (CO), 1250 (CO) cm^{-1}. Hydrolysis of ketal A gave ketone B: 85%; mp 122–124 °C (CH_2Cl_2); NMR (100 MHz, $CDCl_3$–1% Me_4Si) δ 4.23 (s, bridge CH_2O, 4 H), 5.93 (ddd, Pyr-H, J = 6.5, 6.5, 1.5 Hz, 2 H), 6.44 (ddd, Pyr-H, J = 9.0, 1.5, 0.7 Hz), 6.93 (Pyr-H, J = 6.5, 2.0, 0.7 Hz, 2 H), 7.12–7.30 (m, 3 H); IR (KBr) 1680 (C=O) cm^{-1}. Analytical data for A and B fit **11** and **13**, respectively.

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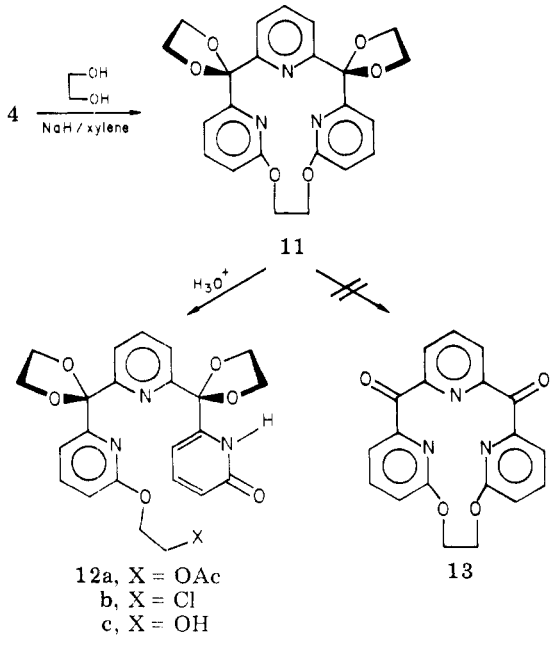
oxide as well as the dianion of (poly)ethylene glycol (5) has been previously demonstrated.[5] When diketal 4 was treated with disodium ethylene glycolate in refluxing anhydrous xylene, the 1:1 spiromacrocycle 11 was isolated in 46% yield. Along with unchanged starting ketal, several noncyclic products were isolated, each in minor (<1%) amounts, and not characterized further. Figure 1 shows the NMR spectrum of macrocycle 11 in 20% (v/v) C_6D_6 in $CDCl_3$. This particular solvent mixture was utilized throughout these studies since, in most cases, the AB_2 pattern for the central pyridine ring was indiscernible in pure $CDCl_3$, whereas with added C_6D_6, the typical nine-line AB_2 pattern could be generated and analyzed[13] (Table I). The upfield shift ($\Delta(\delta) = 1$) for H-5,5′ upon C–Br → C–O conversion, the singlet at δ 4.37 for the bridging methylenes, and the multiplet at δ 4.04 for the ketal hydrogens substantiate the formation of the symmetrical C,O-bridged spiromacrocycle 11. The ^{13}C NMR of 11 (Table II) provided strong support for the postulated symmetrical cyclic structure. Peaks with suitable shifts were found for each of the carbon atoms and could be assigned by application of the usual shift parameters and comparisons with data in the literature for model compounds.[14]



Diketal 11 was subjected to standard hydrolysis conditions, such as refluxing 80% aqueous acetic acid for 24 h, to give (>85%) *a colorless solid, which still possessed the ketal functionality and lacked macrocyclic character.* Treatment of 11 with either refluxing methanolic 5 N hydrochloric acid or Amberlite IR-120 (acid form)[15] in refluxing aqueous methanol gave a similar ring-opened chloride **12b** (80%) or alcohol **12c** (46%), respectively. Numerous modifications of these hydrolytic procedures were attempted; however, only ring-opened products resulted! Figure 1 shows the NMR spectrum of **12**. The unsymmetrical pattern for the central pyridine moiety [δ(H-2) ≠ δ(H-2′)] is indicative of ring fragmentation.

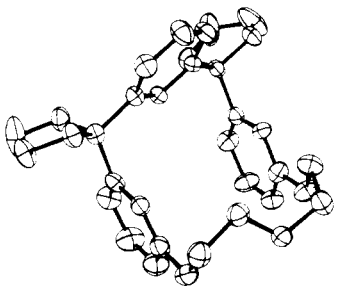


Figure 2. Projection[36] of diketal 14. Hydrogen atoms have been omitted for clarity.

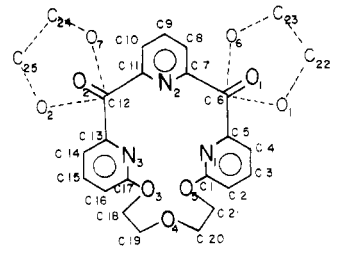


Figure 3. Numbering scheme for X-ray analysis of diketal 14 (with dashed portion) and diketone 15.

Further support for ring cleavage is found in (a) the complex (unsymmetrical) ketal region (ca. δ 4), (b) the typical H-3 and H-5 pattern for one pyridyl ring and H-3′ and H-5′ chemical shift for the pyridinone ring, (c) two distinct H-4 and H-4′ triplets, (d) a singlet at δ 1.92 for a new acetate methyl group in **12a** or broad triplets at ca. δ 3.4 for the β-CH_2 groups in either **12b** or **12c**, and (e) the loss of the singlet at δ 4.30 for the bridge methylenes. There was *no* indication of any cyclic diketonic macrocycle 13 from any of these hydrolytic reactions. Upon prolonged hydrolysis of 11, sufficient to remove the ketal functionality, only complex degradation products were obtained.

(2) Diethylene Glycol. When diketal 4 was treated with the disodium salt of diethylene glycol in refluxing xylene, the desired 1:1 macrocycle 14 was isolated in 51% yield. Thermal fragmentation of (poly)ethylene glycol(s) has been well documented;[16] thus, the isolation of 11 was to be expected.[5b] Both fragmentation and oligomerization reactions are very common for (poly)ethylene glycol(s); however, these side reactions are minimized when the reaction temperatures are maintained at less than 140 °C.[5] The NMR spectrum of 14 (Table I), measured in 20% (v/v) C_6D_6–$CDCl_3$, showed the desired AB_2 pattern for the central pyridine moiety, whereas in pure $CDCl_3$, only a singlet was realized. A slight downfield shift for the ketal hydrogens was attributed to solvation factors. The ^{13}C NMR spectrum was analogous to that of 11; therefore, only minor conformational orientation differences between 11 and 14 were realized in solution.

The X-ray crystal structure of 14 was determined since it was the smallest member of this macrocyclic series in which *both* the diketal *and* corresponding diketone are available for X-ray comparison purposes. The numbering scheme is shown in Figure 3. Ketal 14 is shown in Figure 2 to exist in the crystal in such a conformation that the pyridine N-lone-pair electrons *do not* all point inward toward a central cavity. Taking the C → N vector across the center of the pyridine ring to be a good approximation to the direction of the N lone pair, it can be seen that the

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Table I. ^{1}H NMR Spectral Data for the Ketonic and Spiro Heteromacrocycles

compd	solv system[a]	chem Shifts, δ (J, Hz) H-5	H-4	H-3	H-2,2′	H-1	ketal CH_2	bridge CH_2 α	β	γ
					C,O Diketals					
4	A	7.47 (8, 2)	7.30 (8, 8)	7.18 (8, 2)	7.63 s		3.96 m			
11	A	6.48 (8, 1.5)	7.39 (8, 8)	7.26 (8, 1.5)	7.56 (7.5, 1.5)	7.63 (7.5)	4.04 m	4.37 s		
14	A	6.43 (8, 2)	*b*	*b*	7.66 s		4.02 s	4.18 (5, 5)	3.28 (5, 5)	
14	B	6.45 (8, 2)	7.37 (8, 8)	7.23 (8, 2)	7.68 (7.5, 1.5)	7.76 (7.5)	4.10 m	4.21 (5)	3.30 (5)	
17	A	6.50 (8, 1.7)	7.37 (8, 7)	7.24 (7, 1.7)	7.55 (7.5, 1.5)	7.64 (7.5)	4.03 s	4.10 (6, 6)	3.44 (6, 6)	3.42 s
					C,O Diketones					
3	A	7.43 (8, 2)	7.53 (8, 7)	7.99 (7, 2)	8.22 s					
15	A	6.74 (8, 2)	*b*	*b*	8.05 s			4.21 (6, 6)	3.57 (6, 6)	
15	B	6.85 (8, 2)	7.63 (8, 7.5)	7.50 (7.5, 2)	7.85 (7.5, 2)	7.90 (7.5)		4.23 (5)	3.64 (5)	
18	A	6.83 (8, 2)	7.45 (8, 7.5)	7.57 (7.5, 2)	7.85 (7.5, 2)	8.03 (7.5)		4.23 (5, 5)	3.63 (5, 5)	3.5 s
					C,O,S Diketals					
26	A	6.94 (8, 2)	7.29 (8, 8)	7.46 (8, 2)	7.57 (7.5, 1.5)	7.42 (7.5)	4.05 s	3.07 m		
					C,S Diketals					
33	A	6.93 (8, 2)	7.25 (8, 8)	7.37 (8, 2)	7.63 s		4.05 m	3.07 s		
28	A	6.95 (8, 2)	7.32 (8, 8)	7.45 (8, 2)	7.54 (7.5, 1.5)	7.35 (7.5)	4.06 m	3.07 (8, 7)	2.44 (8, 7)	
					C,O,S Diketones					
27	A	7.17 (8, 1.5)	7.47 (8, 8)	7.84 (8, 1.5)	7.74 s			3.21 m	3.04 m	
					C,S Diketones					
34	A	7.17 (8, 1.5)	7.34 (8, 7.5)	7.50 (7.5, 1.5)	7.85 (7.5, 2)	7.93 (7.5)		3.48 s		
30	A	7.17 (8, 1.5)	7.46 (8, 8)	7.77 (8, 1.5)	7.77 s			3.08 (9, 7)	2.45 (9, 7)	

[a] Solvent A: 20% (v/v) C_6D_6 in $CDCl_3$; Me_4Si as an internal standard (100 MHz). Solvent B: $CDCl_3$. [b] Complex pattern.

Table II. ^{13}C NMR Spectral Data for Selected Ketonic and Spiro Heteromacrocycles[a]

	11	14	15	17	18
C-1	135.8	134.0	136.3	134.0	136.7
C-2	119.8	119.5	125.0	119.5	126.0
C-3	159.0	157.5	151.0	157.5	151.0
C-4	108.5	107.0	192.0	107.0	192.1
C-5	157.1	157.5	154.0	157.5	154.2
C-6	113.3	111.5	117.2	111.5	118.4
C-7	138.4	136.5	138.6	136.5	138.7
C-8	110.3	109.0	114.5	109.0	114.5
C-9	162.0	160.0	162.3	160.0	162.7
α	62.5	62.5	67.9	65.2	70.8
β		67.0	64.1	69.2	69.2
γ				70.7	64.7
ketal	65.5	64.5		66.0	

[a] Run at 90 MHz in $CDCl_3$ solution; shifts are in parts per million.

Table III. Selected Torsion Angles (deg) for Diketal 14 and Diketone 15

	14	15
N(2)-C(11)-C(12)-C(13)	−57.1	14.4
N(2)-C(7)-C(6)-C(5)	51.8	3.1
N(3)-C(13)-C(12)-C(11)	−51.3	56.4
N(1)-C(5)-C(6)-C(7)	76.3	−134.1
N(3)-C(17)-O(1)-C(18)	10.1	−0.4
N(1)-C(1)-O(3)-C(21)	−8.6	26.4

N lone pairs on the two pyridine rings substituted by the polyether chain are approximately parallel and separated by about 4.5 Å. The central pyridine ring points its lone pair approximately antiparallel to the other two. The overall conformation of the molecule may usefully be thought of as that of a tennis ball; the large 24-atom ring formed by the carbon backbone of the pyridine rings and the polyether chain trace out a shape similar to the seam of a tennis ball, wrapping around the central cavity. The polyether oxygen atoms all point *outward* from this cavity.

Table III lists selected torsion angles for the diketal **14**. Of particular interest are the torsion angles about the chemically equivalent bonds C(6)–C(7) and C(11)–C(12), as well as the chemically equivalent bonds C(5)–C(6) and C(12)–C(13). Examination of these angles reveals that the main carbon backbone forms a large dihedral angle (averaging ca. 60°) with the plane of the pyridine ring in all four cases. Other important torsion angles given in Table III are those about the chemically equivalent bonds O(1)–C(17) and O(3)–C(1). The two angles are similar, and their absolute values average about 9°. Stated simply, the linkage of the polyether chain to the pyridine ring is approximately in the plane of the ring and cis to the nitrogen atom. This conformation has also been noted in similar structures[18] and appears to be a rigid constraint upon the flexibility of such molecules.

Hydrolysis of **14** with 80% aqueous acetic acid proceeded *smoothly* to give diketone **15** (52%), monoketone **16** (27%), which resulted from partial hydrolysis, and unchanged diketal. Continued hydrolysis of ***16 quantitatively afforded 15***; *no ring-fragmented products were detected*! The NMR spectrum (Table I) of **15** showed (a) a distinct downfield shift for the pyridyl and β-hydrogens, (b) an α-methylene chemical shift (δ 4.23) similar to that of the corresponding diketal, and (c) loss of the multiplet

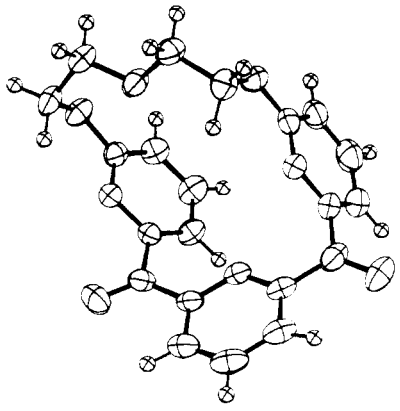


Figure 4. Projection[36] of diketone **15**.

at δ 4.02 for the ketal methylene groups. The ^{13}C NMR spectrum indicated a symmetrical pattern and the presence of the downfield signal at 192.0 ppm for the carbonyl carbon atom, as expected for diketone **15**.

In order to further delineate the precise stereochemistry of **15** and to obtain insight into the structural differences between **14** and **15**, we determined the X-ray crystal structure of **15**.[17] This molecule is also seen (Figure 4) to exist in the crystal in a conformation such that the N lone pairs of the pyridine groups do not point inward toward a central cavity. The N lone pairs of the asymmetrically disubstituted pyridine rings are approximately parallel and separated by about 4.4 Å. The direction of the N lone pair of the central pyridine ring deviates from antiparallelism with the other two by about 60°. The overall conformation of the molecule is suggestive of the shape of a wheelchair, with the "back" of the chair (the central pyridine ring) tilted distinctly away from the interior of the molecule.

Torsion angles of interest (Table III) reveal several notable features of the conformation. It is obvious that most of the distortion from a possible conformation in which all three pyridine rings are coplanar and N lone pairs converge is accomplished via rotation about the bonds C(5)–C(6) and C(12)–C(13), leaving the carbonyl groups closely in the plane of the central pyridine ring, as they are in dipicolinic acid.[19] The torsion angles about O(1)–C(17) and O(3)–C(1) average 13.4° in absolute value, indicating that, as in the diketal **14**, the linkage of the polyether chain to the pyridine ring is essentially cis to the nitrogen atom.

The structure of monoketal **16** was deduced by spectral and analytical data. The IR spectrum of **16** showed a distinct carbonyl absorption at 1675 cm^{-1}, whereas the ^1H NMR spectrum still exhibited a diminished multiplet at δ 4.1 for a ketal moiety. The complex, near-first-order spectrum of **16** further indicated the presence of *both* the ketal and ketone groups by the unsymmetrical nature of the α-CH_2 vs. α'-CH_2, H-5 vs. H-5′, and H-3 vs. H-3′ hydrogens ($\Delta(\delta)$ = −0.39, −0.13, and ca. −0.27, respectively).

(3) Tri-, Tetra-, Penta-, and Hexaethylene Glycols. When diketal **4** was subjected to the sodium salt of these polyethylene glycols in refluxing xylene, the crystalline diketal macrocycles possessing either a tri-, tetra-, penta-, or hexaethylene glycol bridge were prepared in 52, 40, 40, and 38% yields, respectively. In most cases, the polyethylene glycol fragmented products were also isolated and characterized. In general, as the glycol units increased in length, the yield of the corresponding 1:1 macrocycles decreased. This effect has been calculated[20] for related

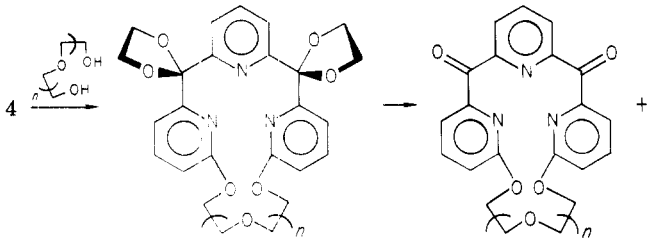
(17) Fronczek, F.; Watkins, S. F.; Nayak, A.; Sauer, J. D.; Newkome, G. R. *Acta Crystallogr.*, submitted for publication.

(18) Fronczek, F.; Nayak, A.; Newkome, G. R. *Acta Crystallogr., Sect. B* **1979**, *35*, 775. Newkome, G. R.; Majestic, V.; Fronczek, F.; Atwood, J. L. *J. Am. Chem. Soc.* **1979**, *101*, 1047.

(19) Takusagawa, F.; Hirotsu, K.; Shimada, A. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2020.

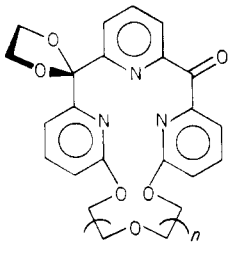
systems, and the theoretical values are closely aligned to actual experimental facts. The NMR spectral data of these diketals are given in Table I and are in accord with the assigned structures. The ^{13}C NMR spectral data (Table II) for **17** are tabulated; the data for **19** were shown to be identical with those of **17** except for the λ and δ carbons (70.7 and 71.2 ppm, respectively). The remaining members in this diketal series possess superimposable ^{13}C NMR data to those of **17**.

Hydrolysis of the diketal functionality in **17**, **19**, **22**, or **24** with 80% aqueous acetic acid or aqueous methanolic hydrochloric acid gave (45–60%) the corresponding *highly* crystalline diketones **18**, **20**, **23**, and **25**. The IR spectra of these diketones showed the anticipated carbonyl absorption at ca. 1680 cm^{-1}. The NMR spectrum further indicated the removal of the ketal group by loss of signal at δ 4.0 and the distinct downfield shift of H-2 and H-3 caused by the anisotropy of the carbonyl groups. ^{13}C NMR spectra of these diketones were nearly identical with that of **15** and **18**. From the hydrolysis of **19**, the crystalline monoketal **21** was also isolated and characterized in a manner similar to that used for **16**.



14, $n = 1$
17, $n = 2$
19, $n = 3$
22, $n = 4$
24, $n = 5$

15, $n = 1$
18, $n = 2$
20, $n = 3$
23, $n = 4$
25, $n = 5$

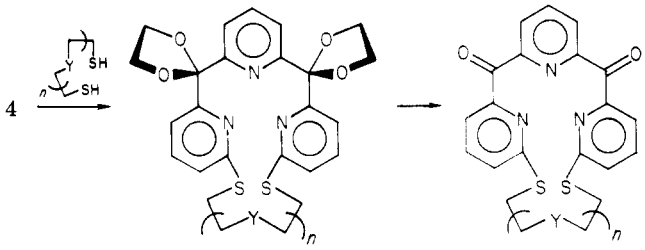


16, $n = 1$
21, $n = 4$

C. Carbon–Sulfur (and –Oxygen) Macrocycles. Recently, pyridine macrocycles constructed by nucleophilic displacement of a 6-halide substituent by sulfur nucleophiles have been reported.[5] In general, the major isolated products from such mercaptide displacements[5a] were derived from numerous competitive reactions of the thiols, such as polymerization, fragmentation, oxidation, and oligomerization.

(1) Bis(2-mercaptoethyl) Ether. Reaction of **4** with the bis(mercaptide), generated from bis(2-mercaptoethyl) ether upon treatment with 2 equiv of oil-free sodium hydride in anhydrous xylene, gave the desired 1:1 macrocycle **26**, which can be isolated as colorless plates in 39% yield. The upfield shift ($\Delta(\delta) \simeq 0.4$) experienced by H-5 coupled with the lesser downfield shift for H-3 is indicative of a 6-Pyr-Br → 6-Pyr-SCH_2 conversion.[5a] The α-methylenic-bridged hydrogens reflect the difference in the oxygen vs. sulfur linkage by a notable upfield shift ($\Delta(\delta) = 1.3$). This shift of the α-hydrogens nearly into the normal β-methylene region gives rise to an indiscernible spectral pattern for the bridging methylene groups.

Hydrolysis of **26** with refluxing aqueous acetic acid gave (71%) the crystalline diketonic macrocycle **27**, whose NMR spectrum exhibited appropriate shifts in comparison with **14**.

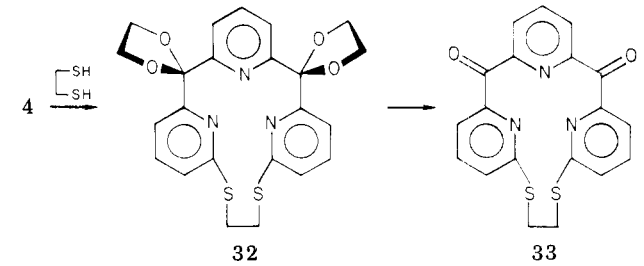


26, Y = O; $n = 1$
28, Y = S; $n = 1$
29, Y = S; $n = 2$

27, Y = O; $n = 1$
30, Y = S; $n = 1$
31, Y = S; $n = 2$

(2) Bis(2-mercaptoethyl) Sulfide. The dibromo ketal **4** was treated with bis(2-mercaptoethyl) sulfide in refluxing diisopropylethylamine to give a complex mixture of cyclic and noncyclic products. However, treatment of **4** with the bis(mercaptide), generated via the standard sodium hydride procedure, gave **28** and its oligomer **29** in 38% and 3% yields, respectively. The NMR spectral data for **28** are given in Table I and are consistent with the assigned macrocyclic structures. Other higher macrocycles, arising from the facile oligomerization of bis(2-mercaptoethyl) sulfide, were isolated in trace amounts but not fully characterized; this, in part, explains the diminished yields of the desired macrocycle (i.e., **28**). The NMR spectra of these polythioethers exhibit an ill-defined methylenic region for the bridges, except for the α-methylene hydrogens, which can be unequivocally assigned. Elemental analyses and mass spectral data support the assignments. Hydrolysis of **28** and **29** gave **30** and **31**, respectively.

(3) Ethanedithiol. Treatment of **4** with the dianion of ethanedithiol gave meager yields (9%) of desired 1:1 macrocycle **32** as pale tan needles. The oligomeric macrocycles, such as **28**, as well as numerous other sulfur-containing compounds were isolated. The increased nuclear size of sulfur vs. oxygen, a smaller C–S–C vs. C–O–C bond angle, decreased electronegativity of sulfur vs. oxygen, and diminished C–S vs. C–O ionic bond character are several of the key factors contributing to the enhanced difficulty (compared to **11**) in ring formation. The singlet at δ 3.07 for the bridging methylene protons and downfield shift of H-5 support the proposed cyclic structure **32**. Mass spectral data further substantiate the 1:1 nature of this macrocycle.



32 **33**

Hydrolysis of ***32*** *with aqueous acetic acid gave (40%) the diketone* ***33***! Repetitive hydrolyses of **32** under widely varied hydrolytic conditions gave *only* ***33*** and unchanged starting diketal; no evidence was found for ring-fragmented products which would be similar to **12**. The NMR spectrum of **33** showed a distinct downfield shift ($\Delta(\delta) = 0.41$) for the α-methylenic hydrogens, indicative of their removal from the proximity of the central pyridine π face

(20) Mattice, W.; Newkome, G. R. *J. Am. Chem. Soc.* **1979**, *101*, 4477.

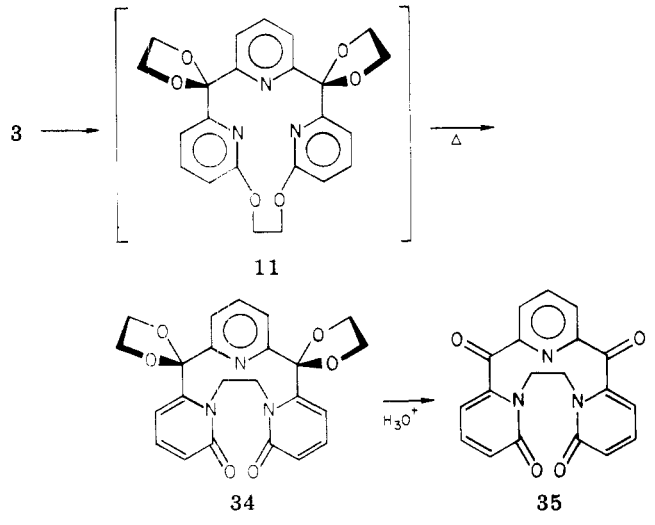
upon hydrolysis. A similar less dramatic shift is noted for the β-hydrogens of ketones **15** ($\Delta(\delta) = 0.3$), **18** ($\Delta(\delta) = 0.2$), and **20** ($\Delta(\delta) = 0.1$), when compared with that for their corresponding diketal.

Discussion

During our quest of macrocyclic systems which possess a directed electron-rich core, a new macrocyclic diketal **A** was synthesized from **3**, when subjected to ketalization conditions, e.g., β-chloroethanol and lithium carbonate under reflux for several hours. A tentative structure (i.e., **11**) was assigned to **A**,[9] since the spectral data reasonably fit this then unknown system and hydrolysis of **A** gave a new diketonic macrocycle **B**,[9] which also exhibited acceptable spectral and exact analytical data (for **13**). These hypotheses fit the available experimental data and initially appeared to be logical assumptions on the basis of these facts.

The structures of **A** and **B** were ascertained by synthesizing **11** by established procedures: treatment of **4** with the dianion of ethylene glycol in xylene at 140 °C. The simplest macrocyclic member of the diketal series (**11**) was spectroscopically different from **A** and subsequent hydrolysis of **11** with 80% aqueous acetic acid gave the ring-opened pyridinone **12a** rather than the anticipated diketone **13**. Numerous hydrolytic modifications were attempted to convert **11** into **13**, but in each case only **12a–c** were isolated and fully characterized. Thus, on the basis of spectral data and chemical reactivity, macrocycle **A** is not **11** and **B** is not **13**, but rather isomers!

The other rational isomeric structure for **A** which is consistent with the facts is **34**. The IR spectrum of **34** indicates the N-bridged pyridinone carbonyl absorption at ca. 1640 cm^{-1}, which is very similar to the heteroaromatic double-bond stretching frequency. The NMR spectrum showed a multiplet at δ 4.25 for the ketal groups and a singlet for the bridging methylene hydrogens at δ 4.6. Hydrolysis of **34** would give diketone **35**, isomeric with **13** and consistent with **B**. The NMR spectral data[9] for **35** showed a singlet at δ 4.23 for the N–CH_2 protons as well as an acceptable pyridinone ring pattern similar to that for bis(pyridinone) **10**. The IR spectrum of **35** (**B**) showed a broad C=O absorption region: 1680 cm^{-1} for the ketonic bridges, 1650 cm^{-1} for the pyridinone carbonyl, and ca. 1630 cm^{-1} for the heteroaromatic double-bond stretch. Molecular weight by osmotic determinations and mass spectral data were in accord. Prolonged hydrolysis of either **34** (or **35**) afforded a complex mixture of products; further structural analyses of these compounds were not conducted.



This N-bridged ketal **34** can be shown to be formed by thermal rearrangement of the O-bridged ketal **11** under prolonged ketalization in which the temperature was not controlled.[21] It has been previously demonstrated that in the liquid state even at 130 °C 2-methoxypyridine rearranges to the more stable *N*-methyl-2-pyridinone ($\Delta G^\circ > -9.3$ kcal/mol).[22] Similarly, we have recently shown that the thermolysis of crown ethers possessing a 2,4-pyrimidino moiety resulted in a *double* O → N rearrangement to generate uracil macrocycles.[23] Currently we are conducting thermolysis reactions on these and related crown ethers possessing various subheterocyclic ring(s) in order to ascertain the limits and utility of these O → N rearrangements in macrocyclic systems.

In order to circumvent the diketal intermediates, we treated **3** directly with ethylene glycolate, via reaction of sodium hydride and ethylene glycol at 140 °C in anhydrous xylene; however, the expected diketonic macrocycle(s) (either **13** or **35**) were not isolated. From the complex reaction mixture, the major products resulted from decarbonylation! In fact, simple di(2-pyridyl) ketones with sodium hydride in xylene at 140 °C undergo smooth decarbonylation to give (>40%) the corresponding bipyridyls.[24] Thus, the diketals were deemed necessary intermediates in this reaction sequence. Further studies are currently in progress to ascertain the limits of this novel mild decarbonylation reaction.

The remaining question to be resolved is: Why do all of the diketals undergo smooth hydrolysis to give the corresponding diketone, except for **11** which undergoes ring fragmentation to give pyridinone **12**, under similar hydrolytic conditions?

Initial protonation of **11** will be directed to the most basic available site(s); thus, the central pyridine nitrogen is of the 2,6-lutidine type ($pK_a \simeq 6.7$)[25] and should be the most favored site for protonation. The remaining two nitrogen atoms are ca. 10^3 less basic[26] and are also hindered from direct approach by an electrophile due to the orientation of the α-methylene group as (1) suggested by MINDO-3 calculations[27] and (2) demonstrated in the crystal structure of **14** as well as related macrocycles.[18,28] From these X-ray data,[17] the N=C–O–CH_2 dihedral angle has been shown to be ca. ±10°. The stereoprojection (Figure 5) of **14** gives a better picture of the inner cavity with the central nitrogen located bottom-center. Protonation at the central nitrogen would be plausible if the cavity is of sufficient size to permit approach of a protonated solvent molecule. Subsequent easy transfer of the proton from nitrogen to the juxtaposed ketal oxygens would accelerate the rate of hydrolysis. Closely related examples of acid hydrolysis in nucleosides enhancing the rate of glycosyl cleavage have been reported.[29] In the larger macrocyclic

(21) Under prolonged ketalization conditions, β-haloethanol in the presence of base decomposes to ethylene oxide and inorganic salts, thus resulting in increased reaction temperatures unless the reaction temperatures are controlled.

(22) Beak, P.; Bonham, J.; Lee, Jr., J. T. *J. Am. Chem. Soc.* **1968**, *90*, 1569. Beak, P.; Bonham, J. *Chem. Commun.* **1966**, 631.

(23) Newkome, G. R.; Nayak, A.; Otemaa, J.; Van, D. A.; Benton, W. H. *J. Org. Chem.* **1978**, *43*, 3362.

(24) Newkome, G. R.; Taylor, H. R. C. *J. Org. Chem.* **1979**, *44*, 1362.

(25) Andon, R. J. L.; Cox, J. D.; Herington, E. F. G. *Trans. Faraday Soc.* **1954**, *50*, 918. Gero, A.; Markham, J. J. *J. Org. Chem.* **1951**, *16*, 1835. Brown, H. G.; Mihm, X. R. *J. Am. Chem. Soc.* **1955**, *77*, 1723.

(26) Albert, A.; Phillips, J. N. *J. Chem. Soc.* **1956**, 1294.

(27) Professor R. D. Gandour (LSU), unpublished results.

(28) Newkome, G. R.; Nayak, A.; Fronczek, F.; Kawato, T.; Taylor, H. C. R.; Meade, L.; Mattice, W. *J. Am. Chem. Soc.* **1979**, *101*, 4472.

(29) Smrt, J.; Sorm, F. *Collect. Czech. Chem. Commun.* **1960**, *25*, 553. Corby, N. S.; Kenner, G. W.; Todd, A. R. *J. Chem. Soc.* **1952**, 3669. Also see: Michelson, A. M. "The Chemistry of Nucleosides and Nucleotides"; Academic Press: New York, 1963; p 26.

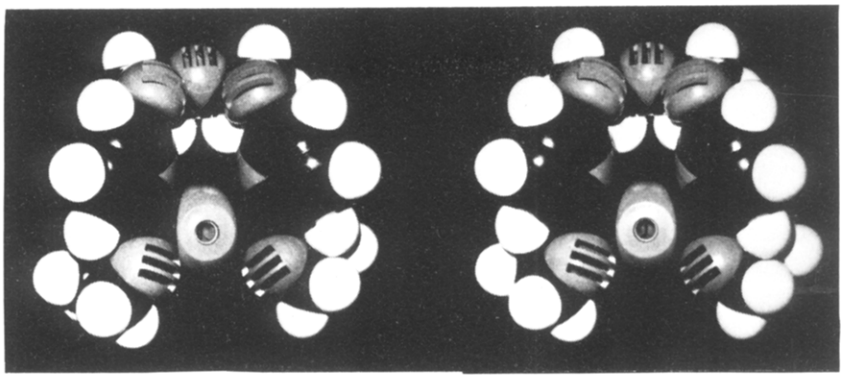


Figure 5. Stereoprojection (CPK models) of diketal **14**.

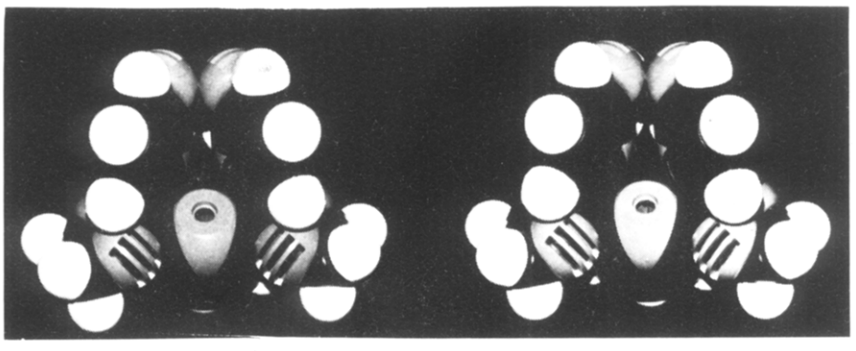


Figure 6. Stereoprojection (CPK models) of diketal **11**.

ketals, the cavity defined by the two pyridine rings and the ketal groups (see Figure 5) will be even larger and more flexible than in the case of **14**; thus protonation and ensuing hydrolysis should be facile. Stereoprojection (Figure 6) of **11** adequately depicts the very narrow and hindered cavity; approach of the solvated proton to the inner pyridine nitrogen should be retarded or prevented. In the sulfur-bridged analogue **32**, hydrolysis was, however, accomplished. The molecular (CPK) model of **32** suggests that, due to the increased size of the sulfur atoms and diminished C–S–C bond angles, the cavity is approximately comparable to that of **14**;[30] thus hydrolysis is the preferred route.

In view of the hindrance to the inner catalytic site in only **11**, deketalization should be retarded in relation to protonation of either the other nitrogen atoms or the very accessible bridge oxygens. Subsequent nucleophilic attack at the α-methylene groups would result in bridge fragmentation and generation of pyridinone **12**.

Lastly, assuming that the crystal structures of **14** and **15** are typical representatives of the ketal and ketone series, comparison of these structures can afford insight into the structural alterations which occur upon hydrolysis. The major structural difference is a tilting of the central pyridine ring away from the center of the molecule resulting a "tennis ball" (in **14**) to "wheelchair" (in **15**) conformational change. The fact that ketone **15** is much less spherical is apparently brought about by the tendency for the carbonyl group(s) to be coplanar with the *central* pyridine ring. This opening of the molecular warping upon hydrolysis is also accompanied by a conformational change in the polyethereal linkage. In the polyethereal chain of **14**, all three of its oxygen atoms are on its exterior, whereas in **15** the central oxygen atom (O(4)) faces *toward* the middle of the molecule. Except for changes ($sp^3 \rightarrow sp^2$) associated with C(6) and C(12) none of the bond distances or angles are dramatically changed.[17]

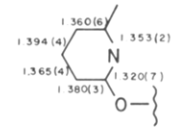


Figure 7. Average bond distances for the asymmetric pyridine rings.

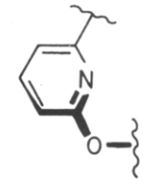


Figure 8. Bonding representation for the asymmetric pyridine rings.

Scrutiny of bond distances within the pyridine rings reveals a trend which is surprising and certainly worth further comment. For the central symmetrically disubstituted pyridine ring of both **14** and **15**, all C–N bonds are equal within experimental error and all C–C bond lengths are likewise equal, as anticipated. However, the asymmetrically disubstituted pyridine rings are shown to possess significant and systematic differences. Choosing any of these four such pyridine rings, the C–N bond, which involves the polyethereal linkage, is *shorter* than the other C–N distance. Discrepancies also exist in the C–C bond lengths, in which the overall pattern is one of alternation of long and short bonds around the pyridine nucleus. This effect is more clearly presented in Figure 7, which illustrates the average distances for the asymmetrically disubstituted subrings. These differences between "long" and "short" bonds are statistically significant and can be better represented by the partial localization of double-bond character as envisioned in Figure 8. Although this effect is presently not well understood, it does emphasize

(30) Preliminary results of the crystal structure determination of **33** confirm this assumption. Details of this structure will appear in a later paper. Professor S. F. Watkins, LSU, 1979.

the imidate ester characteristics in these macrocycles and offers a rationale for the low [N=C–O–CH_2] dihedral bond angle. The literature affords little insight; even though numerous structures of substituted pyridines are known, few are asymmetrically 2,6-disubstituted. The most similar compound for which crystal data are known appears to be 6-chloro-2-hydroxypyridine;[31] however, it does not exhibit partial localization of double bonds.

Experimental Section

General Comments. All melting points were taken in capillary tubes with a Thomas-Hoover Uni-Melt and are uncorrected. Infrared (IR) spectra were recorded on a Beckman IR-7 spectrophotometer. Ultraviolet (UV) spectra were recorded in absolute ethanol on a Cary 14 spectrophotometer. Unless otherwise noted, ^{1}H NMR spectra were recorded in $CDCl_3$ solution with Me_4Si as an internal standard (δ 0), using a Varian HA-100 spectrometer. Molecular weights were determined either with a Hewlett-Packard 302 vapor pressure osmometer or on a Hitachi Perkin-Elmer RMS-4 mass spectrometer by J. Murphy. ^{13}C NMR of the compounds were recorded on either Thompson Packard XLFT-100 or Perkin-Elmer Model R-26 spectrometers.

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; elution with cyclohexane–ethyl acetate (1:1). For preparative thick-layer chromatography (ThLC) 2-mm Brinkmann silica gel PF-254 + 366 plates were used, eluting with the stipulated solvent system. Elemental analyses were performed by R. Seab in these laboratories.

All reaction solvents were distilled from sodium under nitrogen. Sodium hydride (57% oil dispersion) was initially 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 glycol were purchased from Aldrich Chemical Co., whereas penta- and hexaethylene glycol were obtained from Columbia Organic Chemicals. All glycol reagents were distilled in vacuo prior to use. Ethanedithiol, bis(2-mercaptoethyl) ether, and bis(2-mercaptoethyl) sulfide were purchased from Fairfield Chemical Co. and used directly without further purification.

2,6-Bis(6-bromo-2-picolinoyl)pyridine (3). Method A. To a solution of 2-bromo-6-lithiopyridine[6,32] [prepared from 2,6-dibromopyridine (24.0 g, 0.1 mol) and *n*-butyllithium (0.1 mol) in anhydrous diethyl ether (500 mL) at −90 °C] was added methyl 2,6-pyridinedicarboxylate [10 g, 0.05 mol, mp 121–122.5 °C (lit.[33] mp 124–125 °C)] with vigorous stirring, and the temperature was maintained at −90 °C for 1 h. The solution was warmed slowly to −40 °C and held there for 1 h. The mixture was treated with methanolic hydrochloric acid [methanol (50 mL), concentrated HCl (10 mL), water (50 mL)]; the ethereal solvent was removed in vacuo and the acidic aqueous solution was refluxed for 6 h, cooled and then neutralized with sodium carbonate, and extracted with dichloromethane (10 × 50 mL). The combined organic extract was dried over anhydrous magnesium sulfate and concentrated in vacuo to afford a brown, pasty mass, which was triturated with several 20-mL portions of boiling diethyl ether. The residue was recrystallized from benzene to afford the crystalline diketone **3**: mp 142–143 °C; 11 g (48%); R_f 0.76; ^{1}H NMR δ 7.38–8.38 (m, Pyr-H); IR (KBr) 1685 (C=O), 1575, 1320, 1170, 1090 cm^{-1}; mol wt (MS) *m/e* 465 (M^+). Anal. for $C_{17}H_9N_3O_2Br_2$: C, H, N.

Method B. The reaction was conducted in an analogous manner to method A, except for the substitution of 2,6-dicyanopyridine [mp 125–127 °C (lit.[34] mp 126–127 °C)] for the dimethyl ester. The workup procedure was as above except for the hydrolysis of the diimine intermediate. Diketone **3** was isolated in 42% yield: mp 142–144 °C.

Method C. The reaction was conducted in a manner similar to method A, except that when 2,6-dipicolinoyl chloride [mp 54–56 °C (lit.[35] mp 56–58 °C)] was added, cooling was much more difficult to maintain; therefore, the dichloride addition rate was conducted over several hours. The overall yield (35%) of **3** was erratic and difficult to repeat: mp 142–143 °C.

2,6-Bis(6-bromo-2-picolinoyl)pyridine Diketal (4) and Monoketal (5). A stirred mixture of diketone **3** (2.0 g, 4.4 mmol), 2-bromoethanol (30 mL), and anhydrous lithium carbonate (15.0 g, 200 mmol) was refluxed under nitrogen for 5 h. The warm reaction mixture was poured into water (600 mL), and the pH was adjusted to 7.2 by addition of 10% aqueous sodium carbonate solution. The mixture was stirred overnight at 25 °C. The precipitate was filtered, washed with cold water, dried, and recrystallized from hot ethanol to afford the desired diketal **4** as colorless needles: mp 189–190 °C; 1.2 g (48%); R_f 0.60; ^{1}H NMR (100 MHz, 20% C_6D_6 in $CDCl_3$), Table I; IR (KBr) 2900, 1602, 1560, 1460, 1270, 1230, 1160, 1130 (ketal) cm^{-1}; mol wt (MS) *m/e* 535 (M^+). Anal. for $C_{21}H_{17}N_3O_4Br_2$: C, H, N.

The mother liquors of several runs were combined to afford, along with unreacted diketone **3** and diketal **4**, the monoketal **5**, which was recrystallized from ethanol: mp 152–153 °C; R_f 0.42; ^{1}H NMR δ 4.12 (bs, OCH_2CH_2O, 4 H), 7.25–7.8 (m, Pyr-H, 6 H), 7.98 (bs, 1,2,2′-Pyr-H, 3 H); IR ($CHCl_3$) 2950, 2865, 1683 (C=O), 1420, 1391, 1159, 1126 cm^{-1}. Anal. for $C_{19}H_{13}N_3O_3Br_2$: C, H, N.

2,6-Bis[2-(6-ethoxy-2-pyridyl)-1,3-dioxolan-2-yl]pyridine (8). Attempted Preparation of 6. To a solution of diketal **4** (535 mg, 1 mmol) in hot ethanol (50 mL) was added a slight excess of a saturated aqueous solution of sodium sulfide. The mixture turned pale green with liberation of heat. The stirred solution was refluxed for 24 h and then cooled and concentrated in vacuo to afford a residue which was dissolved in chloroform and filtered through a short silica gel column. The chloroform eluent was evaporated and the solid residue was chromatographed (ThLC), eluting two times with cyclohexane–ethyl acetate (1:1) to give the following fractions:

Fraction A afforded **8** as a thick viscous liquid: bp 178–180 °C (1.0 mm, short path); 300 mg (75%); R_f 0.46; NMR δ 1.18 (t, $OCH_2\mathbf{CH_3}$, J = 7 Hz, 6 H), 4.08 (s, OCH_2CH_2O, 8 H), 4.16 (q, $\mathbf{OCH_2}CH_3$, J = 7 Hz, 4 H), 6.60 (dd, 5,5′-Pyr-H, J = 9, 2 Hz, 2 H), 7.15 (dd, 3,3′-Pyr-H, J = 9, 2 Hz, 2 H), 7.45 (t, 4,4′-Pyr-H, J = 9 Hz, 2 H), 7.63 (s, 1,2,2′-Pyr-H, 3 H); IR (neat) 2980, 1580, 1430, 1250 (ether), 1150 (ether) cm^{-1}. Anal. for $C_{25}H_{27}N_3O_6$: C, H, N.

Fraction B gave the monoether **9** as pale yellow crystals: mp 46–48 °C; 80 mg (16%); R_f 0.42; NMR δ 1.20 (t, $OCH_2\mathbf{CH_3}$), J = 7 Hz, 3 H), 4.02 (s, OCH_2CH_2O, 8 H), 4.15 (q, $\mathbf{OCH_2}CH_3$, J = 7 Hz, 2 H), 6.5 (dd, 5-Pyr-H, J = 9, 2 Hz, 1 H), 7.10 (dd, 5′-Pyr-H, J = 9, 2 Hz, 1 H), 7.4 (m, 3,4,3′, 4′-Pyr-H, 4 H), 7.6 (m, 1,2,2′-Pyr-H, 3 H); IR (KBr) 2950, 1580, 1420, 1250 (ether), 1130 (ether) cm^{-1}. Anal. for $C_{23}H_{22}N_3O_5Br$: C, H, N.

Reaction of Diketal 4 with Potassium *tert*-Butoxide. Bis(pyridinone) 10. A mixture of **4** (1.07 g, 2 mmol) and potassium *tert*-butoxide (2.5 g) in anhydrous *tert*-butyl alcohol (30 mL) was refluxed for 18 h under nitrogen.[7] The solvent was removed in vacuo, and the residue dissolved in ice–water and then extracted with methylene chloride to remove unreacted diketal (100 mg). The aqueous layer was neutralized with 5 N HCl to pH 6.8–7.4 and extracted with chloroform. After concentration, the residue was recrystallized from ethanol to give the bis(pyridinone) **10** as colorless needles: mp >300 °C; 520 mg (66%); R_f 0.20; NMR δ 4.15 (s, OCH_2CH_2O, 8 H), 6.42 (dd, 5,5′-Pyr-H, J = 8, 2 Hz, 2 H), 7.35 (m, 3,4,3′,4′-Pyr-H, 4 H), 7.65 (m, 1,-2,2′-Pyr-H, 3 H); IR (KBr) 3440 (b, NH), 2950, 1650 (C=O), 1600, 1450, 1200, 1150 cm^{-1}; mol wt (MS) *m/e* 409 (M^+). Anal. for $C_{21}H_{19}N_3O_6$: C, H, N.

Carbon–Oxygen Macrocycles. Reaction of Diketal 4 with Ethylene Glycol. General Procedure for Macrocycle Formation. To a stirred suspension of oil-free sodium hydride (120 mg, 5 mmol) in dry xylene (200 mL) ethylene glycol (155 mg, 2.5 mmol) was slowly added under nitrogen. After 10 min, diketal

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11 (1.34 mg, 2.5 mmol) was added quickly via a solids addition funnel, and the mixture was refluxed for 48 h. After the mixture had cooled, unreacted sodium hydride was carefully neutralized with ice–water, and the xylene layer was separated. The aqueous layer was extracted with methylene chloride. The combined organic fraction was dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed (ThLC), eluting eight times with cyclohexane–ethyl acetate (1:1) to give the following fractions:

Fraction A gave unreacted dibromo diketal (150 mg): mp 189–190 °C.

Fraction B afforded the desired (1:1) macrocycle **11**, which was recrystallized from ethanol as colorless needles: mp 209–211 °C; 510 mg (46%); R_f 0.11; ^{1}H NMR (100 MHz, 20% C_6D_6 in $CDCl_3$), Figure 1; ^{13}C NMR ($CDCl_3$), Table II; IR (KBr) 2850, 1600, 1475, 1320, 1230, 1140, 1080 cm^{-1}; UV λ_{max} (ϵ) 220 (16 760), 275 (13 249); mol wt (MS) m/e 435 (M^+). Anal. for $C_{23}H_{21}N_3O_6$: C, H, N.

Hydrolysis of Macrocycle 11. Method A. General Hydrolysis Procedure—80% Acetic Acid. Diketal **11** (218 mg, 0.5 mmol) in 80% acetic acid (15 mL) was refluxed under nitrogen for 24 h. After the mixture was cooled, water (20 mL) and a 20% sodium bicarbonate solution to neutralize the acid were added. The mixture was extracted with dichloromethane, and the organic extract was dried over anhydrous sodium sulfate and concentrated to give a residue, which was recrystallized from 95% ethanol affording **12a** as a colorless solid: mp 162–165 °C; 210 mg (85%); ^{1}H NMR (100 MHz, $CDCl_3$), Figure 1; IR (KBr) 2900, 2850, 1740 (ester), 1660 (amide), 1620, 1585, 1260, 1140 cm^{-1}; mol wt (MS) m/e 495 (M^+). Anal. for $C_{25}H_{25}N_3O_8$: C, H, N.

Method B. Diketal **11** (218 mg, 0.5 mmol) in 5 N HCl (20 mL) and methanol (10 mL) was refluxed for 24 h. The workup procedure was as described above, except that the pale yellow residue was recrystallized from chloroform to give chloride **12b** as a colorless solid: mp 185 °C; 160 mg (80%); ^{1}H NMR (100 MHz, $CDCl_3$), Figure 1; IR (KBr) 2950, 1640 (amide), 1590, 1435, 1300, 1190, 1045 cm^{-1}. Anal. for $C_{23}H_{22}N_3O_6Cl$: C, H, N.

Method C. To a solution of **11** (220 mg, 0.5 mmol) in aqueous methanol (50 mL) was added Amberlite IR-120 (acid form). The mixture was refluxed with stirring for 24 h. After removal of the resin by filtration, the workup procedure was as previously described. The yellow residue was recrystallized from chloroform to give **12c** as a colorless solid: mp 196–198 °C; 100 mg (46%); ^{1}H NMR (100 MHz, $CDCl_3$), Figure 1; IR (KBr) 3320 (br, NH, OH), 2950, 1650 (C=O), 1595, 1430, 1410, 1320, 1250, 1200, 1050 cm^{-1}. Anal. for $C_{23}H_{23}N_3O_7$: C, H, N.

Reaction of Diketal 4 with Diethylene Glycol. C,O-Macrocycle 14. The above general macrocycle procedure was followed (2.5-mmol scale), except for the substitution of diethylene glycol (250 mg, 2.5 mmol). The crude reaction mixture was chromatographed (ThLC), eluting three times with cyclohexane–ethyl acetate (1:2) to afford the following fractions:

Fraction A afforded unreacted dibromo diketal: mp 189–190 °C; 50 mg.

Fraction B was recrystallized from ethanol to afford macrocycle **11** as colorless needles: mp 209–211 °C; 40 mg (1%).

Fraction C gave macrocycle **14**, which was recrystallized from ethanol as colorless needles: mp 161–163 °C; 600 mg (51%); R_f 0.07; ^{1}H NMR (100 MHz; 20% C_6D_6 in $CDCl_3$), Table I; ^{13}C NMR ($CDCl_3$), Table II; IR (KBr) 2900, 1600, 1575, 1240, 1210, 1130, 1110 cm^{-1}; UV λ_{max} (ϵ) 225 (9800), 275 (9400); mol wt (MS) m/e 479 (M^+). Anal. for $C_{25}H_{25}N_3O_7$: C, H, N.

Hydrolysis of 14. C,O-Macrocycles 15 and 16. Diketal macrocycle **14** (240 mg, 0.5 mmol) was hydrolyzed according to the general hydrolysis procedure. The residue was chromatographed (ThLC), eluting with cyclohexane–ethyl acetate (1:1) to afford the following fractions:

Fraction A afforded **15**, which was recrystallized from ethanol as yellow microcrystals: mp 119–121 °C; 100 mg (52%); R_f 0.21; ^{1}H NMR (100 MHz, $CDCl_3$ and 20% C_6D_6 in $CDCl_3$), Table I; ^{13}C NMR ($CDCl_3$), Table II; IR (KBr) 2950, 1680 (C=O), 1590, 1450, 1325, 1275, 1240, 1100, 1025 cm^{-1}; UV λ_{max} (ϵ) 218 (25 200), 251 (9300), 300 (9690); mol wt (MS) m/e 391 (M^+). Anal. for $C_{21}H_{17}N_3O_5$: C, H, N.

Fraction B afforded the monoketal macrocycle **16**, which was recrystallized from ethanol to give colorless needles: mp 142–144 °C; 60 mg (27%); R_f 0.17; ^{1}H NMR δ 3.28 (m, β-CH_2O, 2 H), 3.45 (m, β'-CH_2O, 2 H), 3.88 (m, α-CH_2O, 2 H), 4.1 (m, ketal-CH_2, 4 H), 4.27 (m, α'-CH_2O, 2 H), 6.65 (dd, 5-Pyr-H, J = 8, 2 Hz, 1 H), 6.78 (dd, 5′-Pyr-H, J = 8, 4 Hz, 1 H), 7.38 (dd, 3-Pyr-H, J = 8, 2 Hz, 1 H), 7.50 (dd, 4-Pyr-H, J = 8, 8 Hz, 1 H), 7.65 (m, 2,3′,4-Pyr-H, 3 H), 7.83 (dd, 1-Pyr-H, J = 8, 8 Hz, 1 H), 8.0 (dd, 2′-Pyr-H, J = 8, 2 Hz, 1 H); IR (KBr) 2975, 1675 (C=O), 1590, 1320, 1250, 1230, 1140, 1120 cm^{-1}; UV λ_{max} (ϵ) 215 (24 600), 265 (8160), 300 (8275); mol wt (MS) m/e 435 (M^+). Anal. for $C_{23}H_{21}N_3O_6$: C, H, N.

Reaction of Diketal 4 with Triethylene Glycol. C,O-Macrocycle 17. The general macrocycle procedure was followed (2.5-mmol scale), except for the substitution of triethylene glycol (380 mg, 2.5 mmol). After the standard workup, the residue was chromatographed (ThLC), eluting three times with cyclohexane–ethyl acetate (1:2) to give the following fractions:

Fraction A gave unreacted dibromo diketal: mp 189–190 °C.

Fraction B afforded 40 mg of a crystalline compound, which corresponded physically and spectrally to **14**: mp 161–163 °C.

Fraction C after recrystallization from ethanol afforded **17** as colorless plates: mp 132–135 °C; 710 mg (52%); R_f 0.05; ^{1}H NMR (100 MHz, 20% C_6D_6 in $CDCl_3$), Table I; ^{13}C NMR ($CDCl_3$), Table II; IR (KBr) 2875, 1575, 1550, 1220, 1135, 1110, 1050 cm^{-1}; UV λ_{max} (ϵ) 220 (18 420), 275 (15 320); mol wt (MS) m/e 523 (M^+). Anal. for $C_{27}H_{29}N_3O_8$: C, H, N.

Hydrolysis of 17. C,O-Macrocycle 18. The crystalline macrocycle **17** (262 mg, 0.5 mmol) in 80% acetic acid (20 mL) was hydrolyzed according to the general hydrolysis procedure A. The residue was chromatographed (ThLC), eluting two times with cyclohexane–ethyl acetate (1:1). The fastest moving component was isolated and recrystallized from ethanol to give white needles corresponding to macrocycle **18**: mp 145–146 °C; 110 mg (50%); R_f 0.09; ^{1}H NMR (100 MHz, 20% C_6D_6 in $CDCl_3$), Table I; ^{13}C NMR ($CDCl_3$), Table II; IR (KBr) 2950, 1680 (C=O), 1590, 1340, 1250, 1125, 1080, 1040 cm^{-1}; UV λ_{max} (ϵ) 216 (25 720), 250 (8800), 312 (9370); mol wt (MS) m/e 435 (M^+). Anal. for $C_{23}H_{21}N_3O_6$: C, H, N.

Descriptions of the reactions of 4 with tetra-, penta-, and hexaethylene glycols and all spectral and analytical data for **19** (mp 128–131 °C), **20** (mp 118–120 °C), **21** (mp 125–127 °C), **22** (mp 93–95 °C), **23** (mp 76–77 °C), **24** (mp 85–87 °C), and **25** (mp 62–63 °C) are available as supplementary material.

Carbon–Oxygen–Sulfur Macrocycles. Reaction of Diketal 4 with Bis(2-mercaptoethyl) Ether. C,O,S-Macrocycle 26. A mixture of dibromo diketal **4** (1.34 mg, 2.5 mmol), bis(mercaptoethyl) ether (400 mg, 2.5 mmol), and sodium hydride (120 mg, 5 mmol) in xylene (500 mL) was refluxed for 36 h. After the standard workup described above under the general macrocycle procedure, the residue was chromatographed (ThLC), eluting four times with cyclohexane–ethyl acetate (2:1) to afford the following major fractions:

Fraction A gave unreacted starting diketal (50 mg): mp 189–190 °C.

Fraction B was recrystallized from a mixture of benzene–ethanol (1:1) to give **26** as colorless prismatic plates: mp 196–197 °C; 500 mg (39%); R_f 0.18; ^{1}H NMR (100 MHz, 20% C_6D_6 in $CDCl_3$), Table I; IR (KBr) 2900, 1575, 1425, 1380, 1220, 1145 cm^{-1}; UV λ_{max} (ϵ) 215 (93 400), 260 (169 340), 306 (65 920); mol wt (MS) m/e 511 (M^+). Anal. for $C_{25}H_{25}N_3O_5S_2$: C, H, N.

Hydrolysis of 26. C,O,S-Macrocycle 27. The general hydrolysis procedure was used; **26** (250 mg, 0.5 mmol) was refluxed in acetic acid for 24 h and after the standard workup the residue was chromatographed (ThLC), eluting with cyclohexane–ethyl acetate (1:1) to afford diketonic macrocycle **27**, which was recrystallized from ethanol to give light colorless flakes: mp 198–200 °C; 150 mg (71%); R_f 0.25; ^{1}H NMR (100 MHz, 20% C_6D_6 in $CDCl_3$), Table I; IR (KBr) 3200, 2950, 1690 (C=O), 1550, 1220, 1180, 1140, 1120, 1025 cm^{-1}; UV λ_{max} (ϵ) 235 (29 560), 275 (14 670), 362 (5040); mol wt (MS) m/e 423 (M^+). Anal. for $C_{21}H_{17}N_3O_3S_2$: C, H, N.

Carbon–Sulfur Macrocycles. Reaction of Diketal 4 with Bis(2-mercaptoethyl) Sulfide. C,S-Macrocycle 28. The general macrocycle procedure (2.5-mmol scale) was followed, except for the substitution of bis(2-mercaptoethyl) sulfide (380 mg, 2.5 mmol). After the standard workup, the residue was chromatographed (ThLC), eluting two times with cyclo-

hexane–ethyl acetate (1:2) to afford the following components:

Fraction A gave a pale brown solid, which was recrystallized from boiling ethanol to furnish the macrocycle **29** as brown needles: mp 146–147 °C; 65 mg (3%); R_f 0.27; ^{1}H NMR δ 2.55 (s, γ-CH_2O, 4 H), 2.65 (m, β-CH_2O, 4 H), 3.17 (m, α-CH_2O, 4 H), 4.08 (s, OCH_2CH_2O, 8 H), 7.0 (dd, 5,5′-Pyr-H, J = 7, 2 Hz, 2 H), 7.35 (m, Pyr-H, 7 H); IR (KBr) 2975, 1580, 1530, 1380, 1250, 1200, 1130, 1100 cm^{-1}; mol wt (MS) m/e 587 (M^+). Anal. for $C_{27}H_{29}N_3S_4O_4$: C, H, N.

Fraction B was recrystallized from boiling ethanol to give macrocycle **28** as shiny crystalline plates: mp 183–186 °C; 500 mg (38%); R_f 0.11; ^{1}H NMR (100 MHz, 20% C_6D_6 in $CDCl_3$), Table I; IR (KBr) 2850, 1570, 1430, 1305, 1265, 1210, 1150 cm^{-1}; UV λ_{max} (ϵ) 215 (64 950), 260 (106 100), 306 (40 460); mol wt (MS) m/e 527 (M^+). Anal. for $C_{25}H_{25}N_3S_3O_4$: C, H, N.

Hydrolysis of Macrocycle 28. C,S-Macrocycle 30. A solution of **28** (265 mg, 0.5 mmol) in 80% acetic acid (20 mL) was hydrolyzed according to the above general procedure A. The residue was chromatographed (ThLC), eluting with cyclohexane–ethyl acetate (1:1) to give **30**. Recrystallization from ethanol afforded pale brown needles: mp 158–160 °C; 90 mg (40%); R_f 0.3; ^{1}H NMR (100 MHz, 20% C_6D_6 in $CDCl_3$), Table I; IR (KBr) 3100, 1680 (C=O), 1575, 1240, 1150, 1000 cm^{-1}; UV λ_{max} (ϵ) 237 (29 290), 275 (15 260), 362 (4520); mol wt (MS) 439 (M^+). Anal. for $C_{21}H_{17}N_3S_3O_2$: C, H, N.

Hydrolysis of Macrocycle 29. C,S-Macrocycle 31. Hydrolysis of **29** (298 mg, 0.5 mmol) was carried out as described in procedure A. The residue was chromatographed (ThLC), eluting with cyclohexane–ethyl acetate (1:1) to afford the diketonic macrocycle **31**: mp 129–130 °C; 100 mg (40%); R_f 0.4; ^{1}H NMR δ 2.62 (s, γ-CH_2O, 4 H), 2.80 (m, β-CH_2O, 4 H), 3.20 (m, α-C_2O, 4 H), 7.20 (dd, 5,5′-Pyr-H, J = 7, 2 Hz, 2 H), 7.50 (t, 4,4′-Pyr-H, J = 7 Hz, 2 H), 7.75 (dd, 3,3′-Pyr-H, J = 7, 2 Hz, 2 H), 8.10 (m, 1,2,2′-Pyr-H, 3 H); IR (KBr) 2930, 1685 (C=O), 1580, 1310, 1240, 1160, 1150, 1020 cm^{-1}; mol wt (MS) m/e 499 (M^+). Anal. for $C_{23}H_{21}N_3S_4O_2$: C, H, N.

Reaction of Diketal 4 with Ethanedithiol. C,S-Macrocycle 32. The general macrocycle procedure (2.5-mmol scale) was followed, except for the substitution of ethanedithiol (230 mg, 2.5 mmol). After the standard workup procedure, the residue was chromatographed (ThLC), eluting three times with cyclohexane–ethyl acetate (1:1) to afford the following fractions:

Fraction A gave 15 mg of a crystalline compound: mp 151–152 °C. Insufficient material was available to establish the structure.

Fraction B gave 60 mg (2%) of shining crystalline plates corresponding to **28**: mp 183–186 °C; R_f 0.11.

Fraction C gave a small amount of starting diketal **4**: mp 189–190 °C.

Fraction D was recrystallized from ethanol to give **32** as pale brown needles: mp 236–237 °C; 100 mg (9%); R_f 0.08; ^{1}H NMR (100 MHz, 20% C_6D_6 in $CDCl_3$), Table I; IR (KBr) 2900, 1575, 1560, 1215, 1155, 1110 cm^{-1}; UV λ_{max} (ϵ) 223 (47 740), 261 (112 880), 305 (131 820); mol wt (MS) m/e 467 (M^+). Anal. for $C_{23}H_{21}N_3S_2O_4$: C, H, N.

Hydrolysis of 32. C,S-Macrocycle 33. Macrocycle **32** (233 mg, 0.5 mmol) in 80% acetic acid was hydrolyzed by the standard procedure A. The residue was chromatographed (ThLC), eluting with cyclohexane–ethyl acetate (1:1) to give the diketonic macrocycle **33**, which was recrystallized from ethanol to furnish pale brownish crystalline plates: mp 199–201 °C; 70 mg (40%); R_f 0.12; ^{1}H NMR (100 MHz, 20% C_6D_6 in $CDCl_3$), Table I; IR (KBr) 2960, 1675 (C=O), 1560, 1330, 1310, 1275, 1155 cm^{-1}; UV λ_{max} (ϵ) 235 (102 670), 277 (52 470), 360 (4330); mol wt (MS) m/e 379 (M^+). Anal. for $C_{19}H_{13}N_3S_2O_2$: C, H, N.

Acknowledgment. We thank the National Institutes of Health (Grant GM-20985), the National Science Foundation, and Merck Sharp and Dohme Co. for partial financial support. Supplementary support for J.D.S. from the Dr. Charles E. Coates Memorial Fund of the LSU Foundation is gratefully acknowledged. We are indebted to Professor R. H. Holm (Stanford University) and W. W. Paudler (University of Alabama) for their assistance in acquiring the ^{13}C NMR data and to Professor I. Bernal (University of Houston) for allowing S.F.W. and F.F. to have access to his X-ray instrumentation.

Registry No. **3**, 68871-28-3; **4**, 68871-29-4; **5**, 68871-30-7; **8**, 71435-64-8; **9**, 71435-65-9; **10**, 71435-66-0; **11**, 68871-31-8; **12a**, 68871-32-9; **12b**, 71435-67-1; **12c**, 71435-68-2; **13**, 71435-69-3; **14**, 71435-70-6; **15**, 71435-71-7; **16**, 71435-72-8; **17**, 71435-73-9; **18**, 71435-74-0; **19**, 71435-75-1; **20**, 71435-76-2; **21**, 71435-77-3; **22**, 71435-78-4; **23**, 71435-79-5; **24**, 71435-80-8; **25**, 71435-81-9; **26**, 71435-82-0; **27**, 71435-83-1; **28**, 71435-84-2; **29**, 71435-85-3; **30**, 71435-86-4; **31**, 71435-87-5; **32**, 71435-88-6; **33**, 71435-89-7; 2-bromo-6-lithiopyridine, 37709-60-7; dimethyl 2,6-pyridinedicarboxylate, 5453-67-8; 2,6-dicyanopyridine, 2893-33-6; 2,6-dipicolinoyl dichloride, 3739-94-4; 2-bromoethanol, 540-51-2; ethylene glycol, 107-21-1; acetic acid, 64-19-7; diethylene glycol, 111-46-6; triethylene glycol, 112-27-6; tetraethylene glycol, 112-60-7; pentaethylene glycol, 4792-15-8; hexaethylene glycol, 2615-15-8; bis(2-mercaptoethyl) ether, 2150-02-9; bis(2-mercaptoethyl) sulfide, 3570-55-6; ethanedithiol, 540-63-6.

Supplementary Material Available: Experimental data for **19–25**, analytical data for all new compounds (Table A1) (7 pages). Ordering information is given on any current masthead page.

A New Synthesis of Pyrrolo[3,2-*d*]pyrimidines ("9-Deazapurines") via 3-Amino-2-carboalkoxypyrroles[1]

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Received May 29, 1979

Several 3-amino-2-carboalkoxypyrroles have been obtained by the base-catalyzed cyclization of *N*-(2-cyanovinyl)glycine esters. These substituted pyrroles are readily converted in two steps to 5*H*-pyrrole[3,2-*d*]pyrimidines ("9-deazapurines").

As part of an ongoing program directed toward the synthesis of new C-nucleosides of potential biomedical interest, we have recently described a new synthesis of 5*H*-pyrrolo[3,2-*d*]pyrimidines (9-deazapurines) by the hydrogenolytic ring contraction of various pyrimido-[5,4-*c*]pyridazines.[2] As an extension of these studies, we wish to report here an alternate synthetic route to the 9-deazapurine system.

(1) This investigation was supported by funds from the National Cancer Institute, Department of Health, Education and Welfare (Grants CA-08748, 18856 and 24634).

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0022-3263/79/1944-3826$01.00/0