of NaOEt. A solution of NaOEt was prepared from sodium (2.0 g, 0.087 mol) and absolute ethanol (150 mL). 3,3-Bis(methylthio)-1-(4-methoxyphenyl)-2-propen-1-one (**12**, R = 4-$CH_3OC_6H_4$; 10.0 g, 0.039 mol) and 4-methoxyacetophenone (5.9 g, 0.039 mol) were added. After being stirred under reflux overnight, the orange reaction mixture was cooled and treated with cold HCl solution (200 mL, 4%). It was then extracted with $CHCl_3$, and the $CHCl_3$ extract was washed with saturated $NaHCO_3$ and water and then dried ($MgSO_4$). Evaporation of the $CHCl_3$ left a yellow oil which was distilled under reduced pressure, giving a forerun of 4-methoxyacetophenone which was followed by ethyl (4-methoxybenzoyl)acetate: 3.0 g (34%); bp 145 °C (0.5 mm); IR (film) ν_{CO} 1750, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.96 (d, 2, J = 9.0 Hz, aromatic), 6.97 (d, 2, J = 9.0 Hz, aromatic), 4.23 (q, 2, J = 8.4 Hz, CH_2CH_3), 3.94 (s, 2, CH_2), 3.88 (s, 3, OCH_3), 1.24 (t, 3, J = 8.4 Hz, CH_2CH_3); mass spectrum, m/e (relative intensity) 222 (89, $M^{+\cdot}$).

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.82; H, 6.53.

Trituration of the distillation residue with acetone resulted in the separation of light yellow prisms of **15**: 1.0 g (7%); mp 207-208 °C; IR (Nujol) ν_{CO} 1690, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.96 (d, 2, J = 7.8 Hz, aromatic), 7.88 (d, 2, J = 9.0 Hz, aromatic), 7.02 (d, 2, J = 9.0 Hz, aromatic), 6.96 (d, 2, J = 7.8 Hz, aromatic), 6.61 (s, 1, C_5 H), 4.24 (q, 2, J = 6.6 Hz, CH_2CH_3), 3.89 (s, 6, OCH_3), 1.29 (t, 3, J = 6.6 Hz, CH_2CH_3); mass spectrum, m/e (relative intensity) 380 (59, $M^{+\cdot}$).

Anal. Calcd for $C_{22}H_{20}O_6$: C, 69.46; H, 5.30. Found: C, 69.37; H, 5.32.

5,6-Dihydro-4-(methylthio)-2-phenylbenzo[*h*]quinoline (21). Potassium *tert*-butoxide (8.0 g, 0.072 mol) in freshly distilled THF (100 mL) was treated with acetophenone (4.32 g, 0.036 mol) and 2-[bis(methylthio)methylene]-1-tetralone (**20**; 8.90 g, 0.036 mol). After the mixture was stirred at room temperature overnight, ice-cold HCl (200 mL, 4%) was added, and the bright red precipitate that formed was collected. The crude 1,5-enedione was added to acetic acid (150 mL) and ammonium acetate (30.0 g, 0.38 mol), and, after 2 h of reflux, the reaction mixture was kept at room temperature overnight. Iced water (200 mL) was added and the resulting solid collected. Chromatography on silica gel (toluene–petroleum ether C (1:1) gave a colorless solid that crystallized from ethanol as colorless irregular prisms: 2.0 g (18%); mp 123-124 °C; ^1H NMR ($CDCl_3$) δ 8.64-7.27 (m, 10, aromatic), 2.98 (s, 4, CH_2CH_2), 2.59 (s, 3, SCH_3); mass spectrum, m/e (relative intensity) 303 (100, $M^{+\cdot}$).

Anal. Calcd for $C_{20}H_{17}NS$: C, 79.17; H, 5.65; N, 4.62. Found: C, 79.16; H, 5.65; N, 4.62.

2-(4-Methoxyphenyl)-4-(methylthio)-5,6,7,8-tetrahydroquinoline (22). Potassium *tert*-butoxide (10.2 g, 0.09 mol) was added to a solution of 3,3-bis(methylthio)-1-(4-methoxyphenyl)-2-propen-1-one (**12**, R = 4-$CH_3OC_6H_4$); 10.0 g, 0.039 mol) and cyclohexanone (3.95 g, 0.04 mol) in freshly distilled THF (100 mL). After the reaction mixture was stirred overnight, iced water (200 mL) was added and the orange solid that separated collected. This was added to glacial acetic acid (80 mL) and ammonium acetate (30.0 g, 0.39 mol), and the whole was heated under reflux for 1 h, resulting in a dark-colored solution. After the mixture cooled, iced water (200 mL) was added, the reaction mixture was extracted with CH_2Cl_2, and the extract was dried ($MgSO_4$) and concentrated, resulting in an oil that solidified on standing. Recrystallization from methanol–diethyl ether afforded colorless needles: 1.0 g (11%); mp 105-106 °C; ^1H NMR ($CDCl_3$) δ 7.93 (d, 2, J = 9.0 Hz, aromatic), 7.21 (s, 1, H_3), 7.05 (d, 2, J = 9.0 Hz, aromatic), 3.87 (s, 3, OCH_3), 2.52 (s, 3, SCH_3), 2.97, 2.66, 1.88 (m, 8, cyclohexyl); mass spectrum, m/e (relative intensity) 285 (100, $M^{+\cdot}$).

Anal. Calcd for $C_{17}H_{19}NOS$: C, 71.54; H, 6.71; N, 4.91. Found: C, 71.55; H, 6.72; N, 4.87.

2-Methyl-4-(methylthio)-6-(4-methoxyphenyl)pyridine (16; **R = Me, R^1 = 4-$CH_3OC_6H_4$, R^2 = SCH_3).** A stirred solution of 3,3-bis(methylthio)-1-(4-methoxyphenyl)-2-propen-1-one (10.0 g, 0.042 mol) and acetone (2.4 g, 0.043 mol) in freshly distilled THF (100 mL) was treated with potassium *tert*-butoxide (10.1 g, 0.09 mol), and stirring was continued at room temperature for 8 h. The yellow potassium salt of the enedione was collected and added to glacial acetic acid (80 mL) and ammonium acetate (30.0 g, 0.39 mol). After the reaction mixture was refluxed for 2 h, the orange solution was cooled and iced water (200 mL) added. This was then extracted with CH_2Cl_2, the extracts were dried ($MgSO_4$), and concentration yielded a brown oil (11.3 g). It distilled as a viscous yellow oil [bp 140-165 °C (0.005 mm)] that crystallized from petroleum ether as colorless needles: 7.2 g (70%); mp 69-70 °C; ^1H NMR ($CDCl_3$) δ 7.86 (d, 2, J = 9.0 Hz, aromatic), 7.21 (s, 1, H_5), 6.89 (d, 2, J = 9.0 Hz, aromatic), 6.79 (s, 1, H_3), 3.72 (s, 3, OCH_3), 2.45 (s, 3, SCH_3), 2.36 (s, 3, CH_3); mass spectrum, m/e (relative intensity) 245 (93, $M^{+\cdot}$).

Anal. Calcd for $C_{14}H_{15}NOS$: C, 68.54; H, 6.16; N, 5.71. Found: C, 68.54; H, 6.17; N, 5.70.

Supplementary Material Available: ^1H NMR data for compounds in Tables I and III-VII and ^{13}C NMR data for compounds in Tables V and VII (7 pages). Ordering information is given on any current masthead page.

Macrocyclic Polyether Diesters Containing Di- and Triheteryl Subcyclic Units[1]

Kevin T. Potts* and Michael J. Cipullo

Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12181

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2,6-Bis(2-thienyl)-4-(methylthio)pyridine was readily converted into the corresponding 2,6-bis(5-carboxy-2-thienyl)-4-(methylthio)pyridine by using *n*-butyllithium and CO_2. Formyl, chlorocarbonyl, hydroxymethyl, and chloromethyl groups were also readily introduced into the α-positions of the thiophene nuclei. 2,4-Bis(2-thienyl)-6-(methylthio)pyrimidine also readily gave the corresponding 5',5''-dicarboxylic acid under analogous conditions. These carboxylic acids as well as 2,2'-difuryl- and 2,2'-dithienyl-5,5'-dicarboxylic acids on conversion into their cesium salts in DMF reacted with α,ω-dibromopolyethyl ethers to give a variety of polyether diester macrocycles. Cyclic *O,O'*-ethylenebis(oxyethylene) 2,2'-bifuryl-5,5'-dicarboxylate and cyclic oxybis(ethyleneoxyethylene) 2,2'-bifuryl-5,5'-dicarboxylate formed crystalline 1:1 complexes with potassium thiocyanate.

Since Pederson's initial publications[2] dealing with the synthesis and properties of cyclic polyethyl ethers, numerous structural variations have been reported.[3] Much of the interest has focused on the incorporation of other

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functional groups into the macrocycle to observe how the substitution would affect properties such as complexation with metals and to increase selectivity in cation complexation. The oxygen atoms have been replaced by sulfur,[4] nitrogen,[5] phosphorus,[6] and arsenic,[7] and the ethyleneoxy units have been interchanged with heterocycles[8] such as pyridine,[9] furan,[10] thiophene,[11] and pyrimidine.[12] Biaryl subunits have also been incorporated, including binaphthyl[13] and bipyridyl.[14] We now describe the preparation and characterization of several macrocyclic polyether diesters containing triheteryl subunits utilizing our recently described synthesis of 2,6-diheterylpyridines,[15] as well as the synthesis and characterization of analogous systems containing 2,2′-difuryl and 2,2′-dithienyl subcyclic units.

2,6-Bis(2-thienyl)-4-(methylthio)pyridine (1), having a nitrogen atom and two sulfur atoms to act as donor atoms, is a convenient starting point for evaluation of the effect of introducing a subcyclic unit having a rigid three-membered heteryl system into the macrocyclic ring (Scheme I). It is particularly suited for the introduction of substituents in the 2-positions of the thiophene rings. Reaction of an ether solution of 1 (R = H) with approximately 2.2 equiv of *n*-butyllithium (in hexane) in the presence of 2.2 equiv of TMEDA produced excellent yields of the corresponding 5′,5″-dilithium salt 1 (R = Li) as a very light colored, air-sensitive precipitate. This intermediate was converted into 2,6-bis(5-carboxy-2-thienyl)-4-(methylthio)pyridine (1; R = COOH), a high-melting, microcrystalline solid, on reaction with solid CO_2 followed by acidification with HCl and crystallization from dioxane. The isomeric acid 3 was found as a minor byproduct (4%) on scaling up of the reaction and was isolated by precipitation from the dioxane mother liquor with petroleum ether. This indicates that the dilithium intermediate is actually a mixture of 1 (R = Li) and 2, the latter being formed as a result of heteroatom-directed lithiation. A similar heteroatom-directed lithiation of 2-(2-thienyl)pyrimidine has been reported,[16] and by appropriate modification of the solvent, temperature and metalating agent, either the 3′- or 5′-position of the thiophene can be metalated. The 5,5′-dilithio intermediate 1 (R = Li) was also exclusively accessible by lithium–halogen exchange using 2,6-bis(5-bromo-2-thienyl)-4-(methylthio)pyridine (1; R = Br). However, the lower yield of 1 (R = COOH) (39%) on reaction workup with CO_2 and HCl and the extra step required in the preparation of 1 (R = Br) make the former route the method of choice. Reaction of the analogous dichlorodithienylpyridine 1 (R = Cl) with *n*-butyllithium, CO_2, and HCl under similar reaction conditions resulted in the formation of tarry products and an 8% recovery of unreacted 1 (R = Cl).

Other intermediates of interest for macrocycle formation were also accessible from 1 (R = Li). Treatment with *N*-methylformanilide followed by acidification with HCl resulted in the formation of 2,6-bis(5-formyl-2-thienyl)-4-(methylthio)pyridine (1; R = CHO) in good yield. This compound was also accessible in comparable yields in small scale reactions through direct formylation of 1 (R = H) at ca. 110 °C by using *N*-methylformanilide and phosphorous oxychloride in the absence of solvent. A limitation of the latter method is tar formation when the reaction was carried out on a scale larger than 1 g. Reaction of 2,6-bis(5-carboxy-2-thienyl)-4-(methylthio)pyridine (1; R = COOH) with thionyl chloride produced very good yields of the corresponding acid chloride 1 (R = COCl). Analytical and spectral data establishing the structures of these products are described in the Experimental Section.

Other derivatives of 1 containing functional groups α to the thiophene sulfur atoms were also prepared but were sufficiently unstable to prevent satisfactory analytical data from being obtained. Thus the bis(hydroxymethyl) derivative 1 (R = CH_2OH) was obtained (29%) from the dilithium derivative of 1 and formaldehyde. Reduction of the dialdehyde 1 (R = CHO) with LiAlH/THF also gave the same alcohol which slowly decomposed at room temperature, even under vacuum. Spectral data readily established the structure of 1 (R = CH_2OH) (Experimental Section). The corresponding chloromethyl compound 1 (R = CH_2Cl) also could not be obtained analytically pure due to ready hydrolysis and polymerization. It was readily prepared from 1 (R = H) by using 37% formalin, concentrated hydrochloric acid, and HCl gas and had lachrymator properties. Similar instability has been observed with 2,5-bis(chloromethyl)thiophene.[17]

A common route to macrocycles containing heterocyclic subunits has involved displacement of an activated nuclear halogen atom with alkaline metal salts of glycols. However,

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this procedure with 2,6-bis(5-bromo-2-thienyl)-4-(methylthio)pyridine (1; R = Br) was unsuccessful, reaction with the disodium salt of tetraethylene glycol in DMF at 110 °C resulting in a complex mixture of products which could not be purified. However, macrocycles containing 1 as a heterocyclic component were prepared by utilizing the ester functional group to effect macrocycle formation.

2,6-Diheterylpyrimidines have also been synthesized from α-oxoketene dithioacetals and heterocyclic carboxamidines,[18] and this reaction provided a convenient route to 2,4-bis(2-thienyl)-6-(methylthio)pyrmidine (5; R = H). This intermediate provides an opportunity to evaluate the effect of replacing the pyridine ring in the above macrocycles with a pyrimidine ring.

Reaction of an ether solution of 2,4-bis(2-thienyl)-6-(methylthio)pyrmidine (5; R = H) with 2.2 equiv of *n*-butyllithium (in hexane) in the presence of 2.2 equiv of TMEDA produced the corresponding 5′,5″-dilithium salt 5 (R = Li) and hence the 2,4-bis(5-carboxy-2-thienyl)-6-(methylthio)pyrimidine (5; R = COOH). The structure of 5 (R = COOH) was readily confirmed by analytical and spectra data, especially ν_{OH} 2400–3200 cm^{-1} (br) and ν_{CO} 1675 cm^{-1} in its infrared spectrum, an $M^{+}\cdot$ at *m/e* 378 (100%) in the mass spectrum, and the ^{1}H and ^{13}C NMR spectra which were those of an unsymmetrical molecule (Table II).

The acetic acid extract of the crude acid obtained above was diluted with water to precipitate material which was purified by column chromatography (silica, THF–ether) and final crystallization from acetic acid–water. Analytical and spectral data established that this byproduct was 2,4-bis(5-carboxy-2-thienyl)-6-*n*-butylpyrimidine (6, Scheme II) which resulted (in 24% yield) from addition of *n*-butyllithium across the pyrimidine N–C bond followed by elimination of lithium methyl sulfide. The structure of this byproduct was evident from its analytical and spectral data. The infrared spectrum with ν_{OH} 2500–3100 cm^{-1} and ν_{CO} 1675 cm^{-1} showed its carboxylic acid nature, and the ^{1}H NMR spectrum had four thiophene doublets at δ 8.16, 8.03, 7.85, and 7.81 (J = 4.0 Hz), a pyrimidine singlet at δ 7.91, and aliphatic multiplets at δ 2.80 (2 H), 1.77 (2 H), 1.35 (2 H), and 0.97 (3 H). Its ^{13}C NMR spectrum contained a separate resonance for each of the 18 carbon atoms including the aliphatic carbon atoms which appeared at 36.7, 30.0, 21.9 and 13.8 ppm. No displacement of the methylthio group with *n*-butyllithium was observed in the pyridine series and in this present instance may be attributed to an enhanced electron-deficiency at C-4 of the pyrimidine nucleus due to the extra C=N group.

Treatment of a dry DMF solution of 2,6-bis(5-carboxy-2-thienyl)-4-(methylthio)pyrimidine (1; R = COOH) with 1 equiv of cesium carbonate[19] followed by removal of the DMF, water, and carbon dioxide under reduced pressure gave the corresponding dicesium salt as a dry, light-colored powder. This material was suspended in dry DMF, and 1 equiv of 1,2-dibromomethane or an α,ω-dibromo poly(ethyl ether) prepared[20] from the corresponding glycol and PBr_3 was added. After being stirred for several days at ca. 60 °C the macrocycles 4 described in Table I were obtained. The crude products, containing the desired macrocycle as well as open chain and polymer-like impurities, were generally isolated by concentration of the reaction mixture under reduced pressure and precipitation of the product with water or by extraction of the residue with chloroform. Purification was generally accomplished by HPLC (silica, Prep 500) with ethyl acetate–hexane and/or recrystallization (Table I). Reaction of 2,4-bis(5-carboxy-5-thienyl)-6-(methylthio)pyrimidine (5; R = COOH) under analogous conditions with 1,2-bis(2-bromoethoxy)ethane, bis[2-(2-bromoethoxy)ethyl] ether, and 1,2-bis[(2-bromoethoxy)ethoxy]ethane produced moderate yields of the macrocycles 7 (n = 1, 2, and 3, respectively; Table II).

Cyclic bis[ethylene[4-(methylthio)-2,6-pyridindiyl]-5,5′-bis[thiophene]-2,2′-dicarboxylate] **4a**, cyclic *O,O′*-ethylenebis(oxyethylene)[4-(methylthio)-2,6-pyridinediyl]-5,5′-bis[thiophene]-2,2′-dicarboxylate (**4b**), cyclic *O,O′*-oxybis(ethyleneoxyethylene)[4-(methylthio)-2,6-pyridinediyl]-5,5′-bis[thiophene]-2,2′-dicarboxylate (**4c**), and cyclic *O,O′*-ethylenebis(oxyethyleneoxyethylene)[4-(methylthio)-2,6-pyridindiyl]-5,5′-bis[thiophene]-2,2′-dicarboxylate (**4d**) were characterized by the analytical and spectral data described in Table I. All compounds lacked a ν_{OH} in their infrared spectra and were characterized by ν_{CO} 1703–1710 cm^{-1}. A feature of their NMR spectra was the downfield shift of the methylene hydrogens α to the ester linkage which occurred as a multiplet between δ 4.40–4.50 compared to δ 3.4 for the corresponding protons of the CH_2Br group in the α,ω-dibromo polyethers. The protons β to the ester linkages generally occurred as multiplets around δ 3.8 in both the starting halo compounds and the derived macrocycles. The mass spectra of these macrocycles were very complex, **4b** and **4c** giving intense molecular ions whereas the $M^{+}\cdot$ of **4a** was appreciably less intense, this being attributed to its high molecular weight and low volatility. Analysis of the high-resolution spectra showed an appreciable number of doubly charged ions.

Similarly the macrocycles 7 were characterized by analytical and spectral data, and the unsymmetrical nature of the products was clearly evident from their ^{1}H NMR spectra. The four individual thiophene protons were readily distinguishable. For example, in **7b** they occurred as doublets (J = 3.9 Hz) at δ 7.86, 7.77, 7.76, and 7.45. The pyrimidine proton was found as a singlet at δ 7.16, and the methylene protons were found at δ 4.52 (m, CO_2CH_2), 3.92 (m, $CO_2CH_2CH_2$), and 3.90 (s). It is interesting to note that the pyrimidine-containing macrocycles have higher melting points and slightly reduced solubility in most organic solvents when compared to the analogous pyridine-containing systems described above. No effort was made to prepare the macrocyclic dimers that one would expect upon treatment of diacid 5 with Cs_2CO_3 followed by reaction with 1,2-dibromoethane or 2-bromoethyl ether due to the anticipated large cavity size and poor solubility of these products. A mixture of syn and anti dimers would result because of the unsymmetrical nature of the diacid, further complicating separation and purification.

In addition to the above oxygen-containing macrocycles, attempts were made to introduce other desirable atoms into the aliphatic chain. Several sulfur-containing glycols were used, e.g., 1,7,13-trioxa-4,10-dithiatridecane,[21] for the preparation of the corresponding dibromide by using PBr_3. This conversion proved quite difficult due in part to the decomposition of β-halo sulfides on vacuum distillation, and only impure products were obtained. No homogeneous products were obtained on reaction of the cesium salt of 1 (R = COOH) with these dibromides.

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Table I. Macrocyclic Polyether Diester Compounds 4 Derived from 2,6-Bis(5-carboxy-2-thienyl)-4-(methylthio)pyridine (1; R = COOH)

compd[a]	m	n	yield, %	mp, °C	size[b]	cavity diameter,[c] Å	formula[d]	IR (ν_{CO}), cm^{-1}	MS, m/e of M^{+} (rel intens)	UV, λ_{max}, nm (log ϵ)[e]	^1H NMR,[f] δ	^{13}C NMR,[f] ppm
4a	2	0	63[g]	289–291 dec	30	6.0	$C_{36}H_{26}N_2O_8S_6$	1710	806 (5)	*h*	7.66 (d, 4, J = 4.0 Hz, thiophene H), 7.50 (d, 4, J = 4.0 Hz, thiophene H), 7.39 (s, 4, pyridine H), 4.46 (s, 8, CH_2), 2.35 (s, 6, CH_3)	
4b	1	2	23[i]	148–150	21	2.8	$C_{22}H_{21}NO_6S_3$	1710	491.0516 (100)	303 (4.66), 346 (4.21)	7.78 (d, 2, J = 4.0 Hz, thiophene H), 7.39 (d, 2, J = 4.0 Hz, thiophene H), 7.22 (s, (s, 2, pyridine H), 4.40 (m, 4, CO_2CH_2), 4.01 (s, 4, CH_2CH_2), 3.87 (m, 4, $CO_2CH_2CH_2$), 2.52 (s, 3, CH_3)	
4c	1	3	58[j]	177–179	24	4.1	$C_{24}H_{25}NO_7S_3$	1703	535.0795 (100)	304 (4.64), 345 (4.26)	7.82 (d, 2, J = 4.2 Hz, thiophene H), 7.43 (d, 2, J = 4.2 Hz, thiophene H), 7.32 (s, 2, pyridine H), 4.45 (m, 4, CO_2CH_2), 3.86 (m, 4, $CO_2CH_2CH_2$), 3.82 (s, 8, CH_2CH_2), 2.55 (s, 3, CH_3)	162.1, 152.4, 151.0, 150.8, 150.7, 134.8, 124.4, 114.0, 71.6, 71.2, 69.5, 65.7, 13.9
4d	1	4	60[k]	167–168.5	27	5.2	$C_{26}H_{29}NO_8S_3$	1708	579 (12)	298 (4.67), 343 (4.29)	7.85 (d, 2, J = 4.2 Hz, thiophene H_4), 7.50 (d, 2, thiophene H_3), 7.35 (s, 2, pyridine H), 4.50 (m, 4, CO_2CH_2), 3.90 (m, 4, $CO_2CH_2CH_2$), 3.86 (s, 12, CH_2CH_2), 2.57 (s, 3, CH_3)	162.1, 152.3, 151.1, 151.0, 150.6, 134.6, 124.5, 114.1, 71.1, 71.0, 69.3, 65.0, 14.0

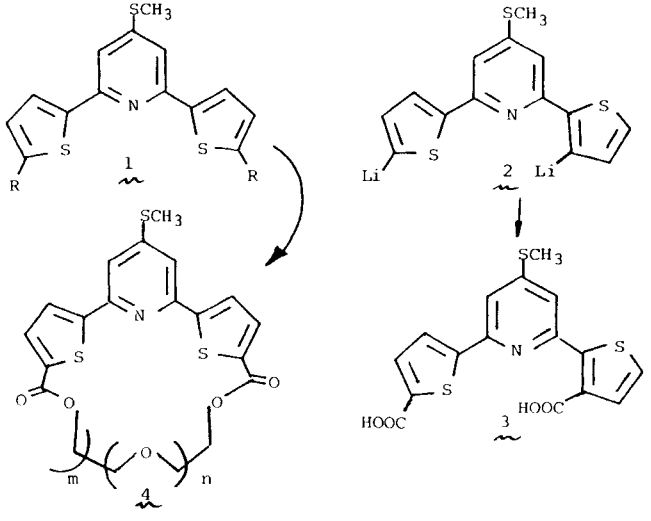
[a] All were recrystallized from acetonitrile except 4a which was obtained from pyridine. [b] Number of atoms comprising the crown ring. [c] Measured by using CPK models. [d] All compounds gave satisfactory analytical data (±0.4% C, H, N). [e] CH_3CN. [f] $CDCl_3$ except for 4a which was taken in TFA. [g] Recrystallization once from Me_2SO and once from pyridine. [h] Insoluble in common UV-transparent solvents. [i] Purified by chromatography (neutral Al_2O_3, CH_3CN). [j] Recrystallized from CH_3CN. [k] From CH_3CN after HPLC (90:10 ethyl acetate/hexane, silica, Prep 500).

Table II. Macrocyclic Polyether Diester Compounds 7 Derived from 2,4-Bis(5-carboxy-2-thienyl)-6-(methylthio)pyrimidine (5; R = COOH)

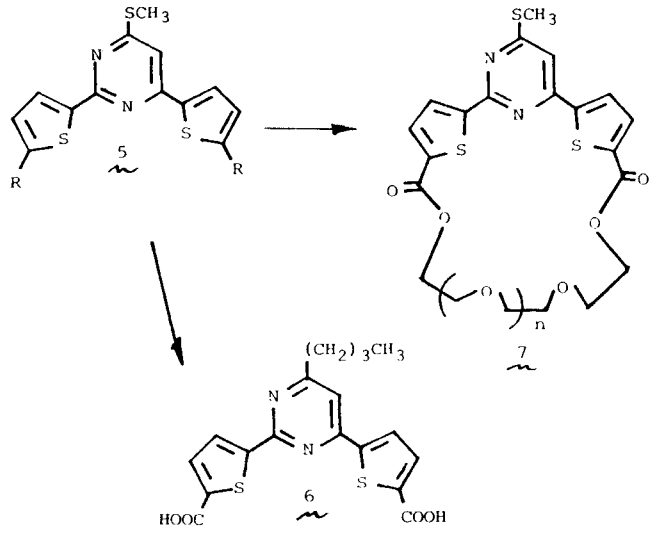
compd[a]	n	yield, %	mp, °C	size[b]	cavity diam,[c] A	formula[d]	IR (ν_{CO}), cm^{-1}	MS, m/e of $M^{+\cdot}$ (rel intens)	UV, λ_{max}, nm (log ϵ)[e]	^{1}H NMR,[f] δ	^{13}C NMR,[f] ppm
7a	1	8	232-234	21	2.8	$C_{21}H_{20}N_2O_6S_3$	1717	492.0482 (100)	292 (4.54), 332 (4.51), 338[g] (4.36), 354[g] (4.15)	7.24-7.87 (m, 5, aryl H), 7.47 (m, 4, CO_2CH_2), 4.03 (s, 4, CH_2CH_2), 3.90 (m, 4, $CO_2CH_2CH_2$), 2.66 (s, 3, CH_3)	
7b	2	28	206-207.5	24	4.1	$C_{23}H_{24}N_2O_7S_3$	1710	536.0743 (100)	296 (4.68), 320 (4.68), 338[g] (4.45), 354[g] (4.25)	7.86 (d, 1, J = 3.9 Hz, thiophene H), 7.77 (d, 1, J = 3.9 Hz, thiophene H), 7.76 (d, 1, J = 3.9 Hz, thiophene H), 7.45 (d, 1, J = 3.9 Hz, thiophene H), 7.16 (s, 1, pyrimidine H), 4.52 (m, 4, CO_2CH_2), 3.92 (m, 4, $CO_2CH_2CH_2$), 3.90 (s, 8, CH_2CH_2), 2.65 (s, 3, CH_3)	171.7, 161.8, 161.6, 159.6, 155.6, 148.8, 148.0, 136.0, 135.8, 134.5, 129.0, 126.2, 110.2, 71.6, 71.1, 69.4, 65.7, 12.5
7c	3	55[h]	151-154	27	5.2	$C_{25}H_{28}N_2O_8S_3$	1717	580.1262 (11)	298 (4.45), 318 (4.45), 337[g] (4.36), 353[g] (4.13)	8.00 (d, 1, J = 4.0 Hz, thiophene, H), 7.85 (d, 1, J = 4.0 Hz, thiophene H), 7.83 (d, 1, J = 4.0 Hz, thiophene H), 7.55 (d, 1, J = 4.0 Hz, thiophene H), 7.29 (s, 1, pyrimidine H), 4.51 (m, 4, CO_2CH_2), 3.91 (m, 4, $CO_2CH_2CH_2$), 3.80 (s, 12, CH_2CH_2), 2.68 (s, 3, CH_3)	171.6, 162.2, 161.8, 159.7, 155.8, 148.8, 148.0, 136.2, 136.1, 134.6, 129.2, 126.4, 110.5, 71.1, 71.0, 69.3, 65.1, 12.5

[a] All were recrystallized from acetonitrile after purification by HPLC (80:20 ethyl acetate–hexane, silica, Prep 500). [b] Numbers of atoms comprising the crown ring. [c] Measured by using CPK models. [d] All compounds gave satisfactory analytical data (±0.4% C, H, N). [e] CH_3CN. [f] $CDCl_3$. [g] Shoulder. [h] Ethyl acetate–hexane composition 85:15.

Scheme I



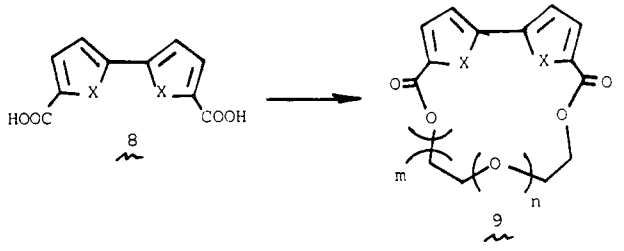
Scheme II



An alternative approach involves the reaction of the appropriate glycol with the bis(chlorocarbonyl) compound by using high-dilution techniques.[22] Simultaneous addition of dry toluene solutions of 1 (R = COCl) and 1,7,13-trioxa-4,10-dithiatridecane to a refluxing toluene solution[23] resulted after 3 days of reflux in a quantitative recovery of 1 (R = COCl). Use of the disodium salt of the glycol and 1 (R = COCl) in DMF solution at 155 °C produced a complex mixture containing mainly unreacted 1 (R = COCl) and its acid. Similar unreactivity of 1 (R = COCl) was found with triethylenetetraamine in hot toluene solution. Insoluble, polymeric-type material only was isolated.

Attempts to use the tricyclic system 1 in macrocycle formation containing a cyclic Schiff base were also unsuccessful. 2,6-Bis(5-formyl-2-thienyl)-4-(methylthio)-pyridine (1; R = CHO) and triethylenetetraamine on attempted reaction in hot methanol gave only insoluble, polymeric type material. Use of lead thiocyanate as a template did not alter appreciably the course of the reaction, no macrocycle being isolated.

Reaction of either 2,2′-bithienyl-5,5′-dicarboxylic acid[24] (8; X = S) or 2,2′-bifuryl-5,5′-dicarboxylic acid[25] (8; X = O) with cesium carbonate in dry DMF produced the corresponding dicesium salt which was reacted further with a series of α,ω-dibromo polyethers, giving the desired macrocycles[9] (Table III) in moderate yields. Thus 8 (X = S) and bis[2-(2-bromoethoxy)ethyl] ether gave cyclic *O,O′*-oxybis(ethyleneoxyethylene) 2,2′-bithienyl-5,5′-dicarboxylate (**9a**; X = S, m = 1, n = 3) in poor yield (5%).



Introduction of another C_2H_4O unit into the dibromide by using 1,2-bis[2-(2-bromoethoxy)ethoxy]ethane gave cyclic *O,O′*-ethylenebis(ethyleneoxyethyleneoxy)-2,2′-bithienyl-5,5′-dicarboxylate (**9b**; X = S, m = 1, n = 4) in 18% yield. The structures of these macrocyclic polyether diesters were established by the analytical and spectral data described in Table III.

The NMR spectra of these products are particularly definitive. In **9a** (X = S, m = 1, n = 3) the methylene protons α to the ester group occurred as a triplet at δ 3.80 while those β to the ester group were found at δ 4.42. The remaining aliphatic protons appeared at δ 3.68 and the thiophene protons were doublets at δ 7.96 and 7.17. Molecular models show that **9a** (X = S, m = 1, n = 3) is a strained ring system and the low yield obtained may be rationalized in terms of such strain. This is relieved to a considerable extent in **9b** (X = S, m = 1, n = 4) with an accompanying increase in yield. Reaction of 8 (X = S) with 1,2-dibromomethane or with bis(bromoethyl) ether of 1,2-bis(2-bromoethoxy)ethane would be expected to give a macrocyclic dimer **9** (m = 2) based on CPK models. In all three reactions solid products were obtained which were difficult to purify due to poor solubility characteristics. Although IR spectra indicate that the ester groups were present and the desired molecular ions could be identified in the mass spectra, other physical characteristics suggest that these products were probably complex mixtures of oligomers and macrocycles. Similar results were obtained with the acid 8 (X = O). In these instances the cavities of the macrocycles are relatively large, and cesium may not be acting as an efficient template.

The cesium salt of 8 (X = O) reacted readily with 1,2-bis(2-bromoethoxy)ethane, with bis[2-(2-bromoethoxy)-ethyl] ether, and also with 1,2-bis[2-(2-bromoethoxy)ethoxy]ethane resulting in moderate yields of the crown ethers **9d–f** (X = O; m = 1; n = 2–4, respectively; Table III). Associated with **9d** (X = O, m = 1, n = 2) was a small amount (8%) of the macrocyclic dimer **9c** (X = O, m = 2, n = 3) which was separated by using HPLC (silica, ethyl acetate; Prep 500). However, the macrocyclic dimers **9** (X = O, m = 2, n = 0 and 1), obtained from 8 (X = O) and 1,2-dibromoethane and 1,2-bis(2-bromoethoxy)ethane, respectively, were too insoluble for satisfactory purification.

The structures of these macrocyclic polyether diesters containing a bifuryl system (Table III) were established by analytical and spectral methods. Their NMR spectra were again distinctive. In addition to the furan doublets at approximately δ 7.3 and 6.7 (J = 3.5 Hz), methylene protons α to the ester group occurred at ca. δ 4.5. The β-protons were observed at approximately δ 3.9 and the remaining methylene protons at δ 3.7. The ^{13}C chemical shifts of the ester carbonyl groups were remarkably consistent at 158.3–158.5 ppm.

When the qualitative procedure in which deep-red Meisenheimer complexes of trinitrobenzene were made soluble in nonpolar solvents in the presence of crown ethers[26] was used, none of the macrocycles containing triheteryl subcyclic units formed complexes with alkali, alkaline earth, or ammonium cations. This may be rationalized in terms of several factors such as the rigidity of the molecule, the elliptical shape of the cavity, and the poor donor properties of the thiophene sulfur atoms. Similarly, the diethienyl-containing macrocycles **9a** and **9b** did not complex with similar cations. Similar considerations to those above may be advanced to explain lack of complexation with these systems. However, the difuryl-containing macrocycles **9d** and **9e** showed that cation complexation occurred with potassium, cesium, ammonium, and, to a lesser extent, sodium and lithium cations. No evidence of complexation was seen with **9f**, presumably due to the large cavity present in this macrocycle, and **9d** and **9e** did not complex with Rb^+, Ca^{2+}, or Ba^{2+}.

In confirmation of the strong qualitative test with K^+, macrocycles **9d** and **9e** formed colorless 1:1 potassium thiocyanate complexes from acetone. Analytical and spectral data established the 1:1 nature of these complexes. Their infrared spectra showed ν_{SCN} at 2030 and 2027 cm^{-1} as well as ν_{CO} at 1710 and 1715 cm^{-1}, and their NMR spectra (Experimental Section) were virtually identical with those of the uncomplexed macrocycles except for small downfield shifts (δ 0.02–0.12) in each resonance.

(22) Bradshaw, J. S.; Thompson, M. D. *J. Org. Chem.* **1978**, *43*, 2456. Bradshaw, J. S.; Maas, G. E.; Izatt, R. M.; Lamb, J. D.; Christensen, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 467.

(23) This was accomplished by wrapping the dropping funnel (fitted with a reflux condenser under N_2) with heating tape. The solution was stirred magnetically with a large magnet mounted in a chuck of the stirring motor which was placed in a horizontal position against the dropping funnel.

(24) Wynberg, H.; Bantjes, A. *J. Am. Chem. Soc.* **1960**, *82*, 1447.

(25) Cresp, T. M.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1786.

(26) Htag, M. M.; Cohn, O. M. *Tetrahedron Lett.* **1976**, 469.

Table III. Macrocyclic Polyether Diester Compounds Derived from 2,2′-Bifuryl- and 2,2′-Bithienyl-5,5′-dicarboxylic Acids 8 (X = O, S)

compd[a]	X	m	n	yield, %	mp, °C	formula	IR (ν_{CO}), cm^{-1}	MS, m/e of $M^{\cdot+}$ (rel intens)	UV, λ, nm (log ε)[b]	^1H NMR,[c] δ	^{13}C NMR,[c] ppm
9a	S	1	3	5[d]	148–149.5	$C_{18}H_{20}O_7S_2$	1700	412.0634 (10)	217 (3.96), 345 (4.38)	7.96 (d, 2, J = 3.9 Hz, thiophene H), 7.17 (d, 2, thiophene H), 4.42 (t, 4, CO_2CH_2), 3.80 (t, 4, $CO_2CH_2CH_2$), 3.68 (s, 8, CH_2CH_2)	
9b	S	1	4	18[e]	151–153	$C_{20}H_{24}O_8S_2$	1705	456.0923 (17)	247 (4.04), 346 (4.44)	7.85 (d, 2, J = 4.2 Hz, thiophene H), 7.32 (d, 2, thiophene H), 4.42 (m, 4, $CO_2CH_2CH_2$), 3.90 (m, 4, $CO_2CH_2CH_2$), 3.80 (s, 12, CH_2CH_2)	161.2, 142.6, 134.9, 132.1, 124.8, 71.4, 71.1, 70.3, 69.0, 65.0
9c	O	2	2	8[f]	200–201	$C_{32}H_{32}O_{16}$	1720	672.2 (100)[g]	244 (4.15), 320 (4.79), 337 sh (4.61)	7.30 (d, 4, J = 3.5 Hz, furan H), 6.97 (d, 4, furan H), 4.37 (m, 8, CO_2CH_2), 3.78 (m, 8, $CO_2CH_2CH_2$), 3.67 (s, 8, CH_2CH_2)	
9d	O	1	2	23[f]	246–248	$C_{16}H_{16}O_8$	1710	336.0803 (70)	230 (4.10), 322 (4.44), 337 sh (4.34)	7.30 (d, 2, J = 3.3 Hz, furan H), 6.72 (d, 2, furan H), 4.46 (m, 4, CO_2CH_2), 3.86 (s, 4, CH_2CH_2), 3.81 (m, 4, $CO_2CH_2CH_2$)	158.3, 146.9, 144.2, 119.3, 108.8, 70.6, 68.9, 64.6
9e	O	1	3	36[h]	155–156.5	$C_{18}H_{20}O_9$	1705	380.1094 (11)	227 (3.97), 321 (4.44), 336 sh (4.30)	7.24 (d, 2, J = 3.7 Hz, furan H), 6.66 (d, 2, furan H), 4.52 (m, 4, CO_2CH_2), 3.87 (m, 4, $CO_2CH_2CH_2$), 3.82 (s, 8, CH_2CH_2)	158.5, 147.3, 144.9, 120.4, 110.3, 71.7, 70.5, 69.0, 65.5
9f	O	1	4	19[e]	155–157	$C_{20}H_{24}O_{10}$	1708	424.1359 (18)	230 (4.16), 323 (4.56), 339 sh (4.43)	7.38 (d, 2, J = 3.7 Hz, furan H), 6.80 (d, 2, furan H), 4.52 (m, 4, CO_2CH_2), 3.92 (m, 4, $CO_2CH_2CH_2$), 3.73 (m, 12, CH_2CH_2)	158.4, 147.3, 144.8, 120.1, 110.2, 71.2, 71.0, 69.9, 69.2, 64.8

[a] All compounds gave satisfactory analytical data (±0.4% C, H, N). [b] CH_3CN as solvent. [c] $CDCl_3$ as solvent except for 9c where Me_2SO-d_6 was used. [d] Recrystallized from CH_3CN followed by chromatography on silica gel (benzene, eluted with CH_3CN); final recrystallization from benzene. [e] Purified by HPLC (90:10 ethyl acetate–hexane, silica, Prep 500) followed by recrystallization from CH_3CN. [f] Purified by HPLC (ethyl acetate, silica, Prep 500) and recrystallization from CH_3CN. [g] Field-desorption mass spectrometry. [h] Crystallized from CH_3CN or benzene.

Experimental Section[27,28]

2,6-Bis(5-carboxy-2-thienyl)-4-(methylthio)pyridine (1; R = COOH). A solution of 2,6-bis(2-thienyl)-4-(methylthio)pyridine (1; R = H; 1.0 g, 3.5 mmol) and TMEDA (0.81 g, 7 mmol) in dry ether (25 mL) was cooled in an ice bath while *n*-butyllithium (3.0 mL of a 2.5 M hexane solution, 7.5 mmol) was added, and the mixture was stirred mechanically at reflux for 1.5 h, maintaining a dry N_2 atmosphere. The heterogeneous mixture was then cooled to −20 °C, and several pieces of dry ice were added, initially resulting in an exothermic reaction. The temperature soon dropped below −30 °C, and the mixture was allowed to warm to room temperature. The reaction mixture was extracted with water, and the crude product was obtained by acidification of the extract with dilute HCl followed by isolation of the precipitate. Purification was effected by dissolving this solid in a warm THF (50 mL) solution containing approximately 3 mL of 10% aqueous HCl and reprecipitating the acid by the addition of approximately 150 mL of water. After being dried under vacuum, the crude product was recrystallized from dioxane and was ultimately obtained as pale yellow prisims after careful drying: 1.12 g (89%); mp 329–329.5 °C dec; IR (KBr) ν_{OH} 2900, ν_{CO} 1670 cm^{-1}; UV (CH_3OH) λ_{max} 300 nm (log ϵ 4.65), 341 (4.31); ^1H NMR (Me_2SO-d_6), δ 7.91 (d, 2, J = 4.0 Hz, thiophene $H_{4'}$), 7.69 (s, 2, pyridine H), 7.65 (d, 2, J =4.0 Hz, thiophene $H_{3'}$), 2.61 (s, 3, SCH_3); ^{13}C NMR (Me_2SO-d_6) 162.9, 152.9, 150.2, 149.4, 136.1, 133.9, 126.4, 144.4, 13.4 ppm; mass spectrum, m/e (relative intensity) 377 (30, $M^{+\cdot}$).

Anal. Calcd for $C_{16}H_{11}NO_4S_3$: C, 50.94; H, 2.94; N, 3.71. Found: C, 50.68; H, 2.92; N, 3.67.

2-(3-Carboxy-2-thienyl)-6-(5-carboxy-2-thienyl)-4-(methylthio)pyridine (3). The product was isolated from the dioxane mother liquor of 2,6-bis(5-carboxy-2-thienyl)-4-(methylthio)-pyridine (1; R = COOH) by precipitation with petroleum ether. Recrystallization from acetonitrile followed by a second recrystallization from acetic acid gave colorless microprisms: yield ca. 4%; mp 270–272 °C dec; IR (KBr) ν_{OH} 2800–3200, ν_{CO} 1705 cm^{-1}; UV (CH_3OH) λ_{max} 295 nm (log ϵ 4.63), 337 (4.31); ^1H NMR (Me_2SO-d_6) δ 8.00 (d, 1, $J_{3'',4''}$ = 4.2 Hz, thiophene $H_{4''}$), 7.90 (s, 2, pyridine H), 7.80 (d, 1, thiophene $H_{3''}$), 7.75 (d, 1, $J_{4',5'}$ = 4.8 Hz, thiophene $H_{4'}$), 7.50 (d, 1, thiophene $H_{5'}$), 2.68 (s, 3, SCH_3); ^{13}C NMR (Me_2SO-d_6) 164.8, 162.9, 152.0, 150.2, 149.8, 149.4, 146.9, 137.6, 133.9, 131.0, 130.6, 127.8, 126.4, 118.5, 114.4, 13.3 ppm; mass spectrum, m/e (relative intensity 377 (14, $M^{+\cdot}$).

Anal. Calcd for $C_{16}H_{11}NO_4S_3$: C, 50.94; H, 2.94; N, 3.71. Found: C, 50.69; H, 3.01, N, 3.64.

2,6-Bis(5-formyl-2-thienyl)-4-(methylthio)pyridine (1; R = CHO). Method A. Phosphorous oxychloride (1.8 g, 11.3 mmol) was added to a mechanically stirred mixture of 2,6-bis(2-thienyl)-4-(methylthio)pyridine (1; R = H; 0.87 g, 3.0 mmol) and *N*-methylformanilide (1.58 g, 11.7 mmol) and the mixture heated to between 60 and 70 °C. This resulted in a slightly exothermic reaction in which HCl evolved as the mixture became increasingly viscous. (Thin-layer chromatography suggested the reaction was proceeding very slowly or not at all after approximately 4 h at 65–70 °C, possibly due to the high viscosity of the reaction mixture.) The mixture was heated to 90–100 °C for an additional 2.7 h, causing further reaction, additional HCl evolution, and an increase in the reaction viscosity such that stirring was difficult. The nearly completed reaction mixture was dissolved in boiling absolute methanol (15 mL), and, after the mixture was cooled to room temperature and water (1 mL) added, the resultant precipitate was collected. This material was refluxed in methanol (40 mL), cooled to room temperature, and filtered, removing most of the colored impurities from the 0.73 g (70%) of crude product, mp 217–220 °C. Dissolution in hot acetic acid (100 mL) and treatment with charcoal, followed by hot filtration through Celite, cooling, and the addition of water (10–15 mL) gave pale yellow needles: 0.34 g (32%); mp 222.5–224 °C; IR (KBr) ν_{CO} 1657 cm^{-1}; UV (CH_3OH) λ_{max} 315 nm (log ϵ 4.64), 350 (4.40); ^1H NMR (Me_2SO-d_6) δ 10.05 (s, 2, CHO), 8.12 (d, 2, J = 3.8 Hz, thiophene H_4), 8.06 (d, 2, thiophene H_3), 7.92 (s, 2, pyridine H), 2.70 (s, 3, SCH_3); ^{13}C NMR (Me_2SO-d_6) 184.0, 153.1, 151.6, 149.8, 144.1, 137.6, 126.8, 115.3, 13.2 ppm; mass spectrum, m/e (relative intensity) 345 (100, $M^{+\cdot}$).

Anal. Calcd for $C_{16}H_{11}NO_2S_3$: C, 55.63; H, 3.21; N, 4.05. Found: C, 55.79; H, 3.28; N, 4.06.

Method B. A solution of 2,6-bis(2-thienyl)-4-(methylthio)-pyridine (1, R = H; 28.9 g, 0.10 mol) and TMEDA (23.24 g, 0.20 mol) in dry ether (600 mL) was cooled in an ice bath while *n*-butyllithium (134 mL of a 1.6 M hexane solution, 0.215 mol) was added. After being stirred under reflux for 1 h, the mixture was cooled to −30 °C, and *N*-methylformanilide (50.0 g, 0.4 mol) was added. The mixture was refluxed for 1 h, acidified with dilute HCl at 0 °C to pH 5–6, and filtered to recover the crude product which was washed with ether and dried. This material was dissolved in a warm mixture of methylene chloride (3.5 L) and acetic acid (approximately 300 mL) and treated with charcoal followed by filtration through Celite. Concentration of the filtrate to a final volume of approximately 140 mL afforded a light-colored crystalline product in three batches: 23.6 g (69%); mp 217–220 °C; identical[28] with that prepared in method A above.

2,6-Bis[5-(chloroformyl)-2-thienyl]-4-(methylthio)pyridine (1; R = COCl). A solution of 2,6-bis(5-carboxy-2-thienyl)-4-(methylthio)pyridine (1, R = COOH; 1.0 g, 2.6 mmol) in thionyl chloride (7 mL) was heated under reflux for 2 h. The thionyl chloride was removed, and the residue, after recrystallization from dry THF (125 mL containing thionyl chloride (2 mL), afforded light-yellow needles. A second recrystallization from dry toluene gave light-yellow microprisms: 0.88 g (80%); mp 245–247 °C; IR (KBr) ν_{CO} 1750, 1720 cm^{-1}; UV (dioxane) λ_{max} 319 nm (log ϵ 4.55), 354 (4.35); ^1H NMR (Me_2SO-d_6) δ 8.01 (d, 2, J = 4.1 Hz, thiophene H_3), 7.97 (s, 2, pyridine H), 7.79 (d, 2, thiophene H_3), 2.67 (s, 3, SCH_3); ^{13}C NMR (Me_2SO-d_6) 162.8, 153.0, 150.2, 149.4, 136.0, 134.0, 126.5, 114.5, 13.4 ppm; mass spectrum, m/e (relative intensity) 413 (35, $M^{+\cdot}$).

Anal. Calcd for $C_{16}H_9Cl_2NO_2S_3$: C, 46.38; H, 2.19; N, 3.38. Found: C, 46.32; H, 2.21; N, 3.37.

2,6-Bis(5-thienyl-2-hydroxymethyl)-4-(methylthio)-pyridine (1; R = CH_2OH). A solution of 2,6-bis(2-thienyl)-4-(methylthio)pyridine (1, R = H; 1.0 g, 3.46 mmol) and TMEDA (0.90 g, 8 mmol) in dry ether (25 mL) was cooled in an ice bath. *n*-Butyllithium (5.0 mL of a 1.6 M hexane solution, 7.5 mmol) was added and the mixture stirred under reflux for 30 min, maintaining a dry N_2 atmosphere. After the mixture was cooled to −40 °C, formaldehyde (2.5 g, 83 mmol) was distilled into the reaction mixture, which was then slowly warmed to reflux. After 1.5 h at reflux, the solution was acidified with dilute HCl and extracted several times with warm $CHCl_3$. This extract was washed with dilute HCl and water and then dried (Na_2SO_4). The solution was concentrated, and a product separated from the cooled residue. Crystallization from toluene, and also from $CHCl_3$, affored yellow microprisms: 0.35 g (29%); mp 144–145 °C; IR (KBr) ν_{OH} 3460–3150 cm^{-1}; UV (CH_3OH) λ_{max} 288 nm (log ϵ 4.53), 334 (4.12); ^1H NMR (Me_2SO-d_6) δ 7.77 (d, 2, J = 3.9 Hz, thiophene H), 7.58 (s, 2, pyridine H), 7.02 (d, 2, J = 3.9 Hz, thiophene H), 5.45 (t, 2, J = 5.8 Hz, OH), 4.69 (d, 4, CH_2), 2.62 (s, 3, SCH_3); mass spectrum, m/e (relative intensity) 349 (100, $M^{+\cdot}$).

Anal. Calcd for $C_{16}H_{15}NO_2S_3$: C, 54.98; H, 4.33; N, 4.00. Found: C, 54.14; H, 4.31; N, 3.75.

2,4-Bis(5-carboxy-2-thienyl)-6-(methylthio)pyrimidine (5; R = COOH). A solution of 2,4-bis(2-thienyl)-6-(methylthio)-pyrimidine (5, R = H; 9.0 g, 31.0 mmol) and TMEDA (8.0 g, 69.0 mmol) in dry ether (240 mL) was cooled in an ice bath while *n*-butyllithium (43.0 mL of a 1.6 M hexane solution, 69.0 mmol) was added, and the mixture was stirred mechanically under reflux for 20 min, maintaining a dry N_2 atmosphere. The heterogeneous mixture was then cooled to −20 °C, and several pieces of dry ice were added, an initial exothermic reaction resulting. The temperature soon dropped below −40 °C, and the mixture was allowed to warm to room temperature. The reaction mixture was extracted

(27) Spectral characterizations were carried out on the following instrumentation: infrared spectra, Nicolet 7000 Series FT and PE Model 337 spectrophotometers; UV spectra, Cary Model 219 spectrophotometer; NMR spectra, Varian T-60 and EM-390 spectrometers (^1H spectra), Varian XL-100 and CFT-20 spectrometers (^{13}C spectra) with Me_4Si as an internal standard; mass spectra, Varian MAT 311A (high resolution), Varian MAT 731 (field desorption), and PE-Hitachi RMU 6E spectrometers. Melting points were determined in capillaries and are uncorrected. Evaporations were carried out under reduced pressure by using a rotatory evaporator, and microanalyses were obtained from Galbraith Laboratories, Inc., Knoxville, TN, or Atlantic Microlab, Inc., Atlanta, GA.

(28) Criteria for identity were superimposable IR spectra, no depression in mixture melting point, and identical R_f values.

with water and the aqueous phase washed with ether. The crude product was obtained by acidification of the extract with concentrated HCl followed by collection of the precipitate which was then extracted with boiling acetic acid. The insoluble product was dissolved in warm DMF (charcoal) and reprecipitated by the addition of water and cooling. It separated as colorless microprisms: 4.76 g (41%); mp 337–340 °C dec; IR (KBr) ν_{OH} 2400–3200, ν_{CO} 1675 cm^{-1}; UV (dioxane) λ_{max} 318 nm (log ϵ 4.65); ^{1}H NMR (Me_2SO-d_6) δ 8.10 (d, 1, J = 4.0 Hz, thiophene H), 7.95 (d, 1, J = 4.0 Hz, thiophene H), 7.85 (s, 1, pyrimidine H), 7.75 (d, 2, two overlapping thiophene H's), 2.68 (s, 3, SCH_3); ^{13}C NMR (Me_2SO-d_6) 171.8, 162.7, 158.7, 155.6, 147.4, 146.6, 138.0, 133.8, 133.6, 129.3, 110.5, 12.3 ppm; mass spectrum, m/e (relative intensity) 378 (100, $M^{+\cdot}$).

Anal. Calcd for $C_{15}H_{10}N_2O_4S_3$: C, 47.61; H, 2.66; N, 4.70. Found: C, 47.72; H, 2.69; N, 7.34.

2,4-Bis(5-carboxy-2-thienyl)-6-*n*-butylpyrimidine (6). The crude product was isolated from the acetic acid extract of 2,4-bis(5-carboxy-2-thienyl)-6-(methylthio)pyrimidine (5; R = COOH) obtained above by precipitation with water after treatment of the acetic acid solution with charcoal. Chromatography (silica) with THF–Et_2O, followed by recrystallization from acetic acid–water, produced colorless microprisms: 2.1 g (24% based on *n*-butyllithium used); mp 299–302 °C dec; IR (KBr) ν_{OH} 2500–3100, ν_{CO} 1675 cm^{-1}; UV (MeOH) λ_{max} 313 nm (log ϵ 4.36); ^{1}H NMR (Me_2SO-d_6) δ 8.16 (1, d, thiophene H, J = 4.0 Hz), 8.03 (1, d, thiophene H, J = 4.0 Hz), 7.91 (1, s, pyrimidine H), 7.85 (1, d, thiophene H), 7.82 (1, d, thiophene H), 2.80 (m, 2, $ArCH_2$), 1.77 (m, 2, $ArCH_2CH_2$), 1.35 (m, 2, CH_2CH_3), 0.97 (t, 3, CH_3); ^{13}C NMR (Me_2SO-d_6) 187.7, 172.4, 162.8, 162.7, 159.4, 157.6, 148.0, 147.0, 137.9, 137.6, 134.0, 133.9, 129.0, 113.0, 36.7, 30.0, 21.9, 13.8 ppm; mass spectrum, m/e (relative intensity) 388 (5, $M^{+\cdot}$).

Anal. Calcd for $C_{18}H_{16}N_2O_4S_2$: C, 55.65; H, 4.15; N, 7.21. Found: C, 55.7; H, 4.18; N, 7.18.

General Procedure for the Synthesis of Macrocycles 4, 7, and 9. A solution of the diacid (3.0 mmol) and Cs_2CO_3 (3.0 mmol) in DMF (50 mL) was evaporated to dryness on a rotary evaporator by using a steam bath. Dry DMF (250 mL) was added to the resulting dry powder followed by the α,ω-dibromo polyether, and the mixture was well stirred for 2–7 days at 60–70 °C. The DMF was removed by distillation under reduced pressure (except for **4a**) and the residue extracted with chloroform. The chloroform solution was dried (Na_2SO_4) and concentrated, and the product was purified by column chromatography (silica, EtAc) or HPLC (silica, EtAc–hexane, Prep 500).

Recrystallization from dry acetonitrile generally gave the products (Tables I and II) as colorless prisms. Compound **4a** was obtained by concentration of the reaction mixture followed by precipitation of the crude product by adding 3 volumes of water. This macrocycle was purified by crystallization from dry Me_2SO followed by a second recrystallization from pyridine.

Potassium Thiocyanate Complex (1:1) of Cyclic *O,O'*-Ethylenebis(oxyethylene) 2,2'-Bifuryl-5,5'-dicarboxylate (9d). An acetone (5 mL) solution containing cyclic *O,O'*-ethylenebis(oxyethylene) 2,2'-bifuryl-5,5'-dicarboxylate (**9d**; 160 mg, 0.476 mmol) and potassium thiocyanate (46.3 mg, 0.476 mmol) was heated under reflux for 4 h an then cooled to room temperature. The product precipitated as colorless microneedles: 180 mg (87%); mp 251–253 °C dec; IR (KBr) ν_{SCN} 2030, ν_{CO} 1710 cm^{-1}; UV (MeOH) λ_{max} 222 nm (log ϵ 4.24), 323 (4.50), 336 sh (4.40); ^{1}H NMR (Me_2SO-d_6) δ 7.49 (d, 2, J = 3.6 Hz, furan H_4), 7.17 (d, 2, furan H_3), 4.32 (m, 4, CO_2CH_2), 3.70 (m, 4, $CO_2CH_2CH_2$), 3.66 (s, 4, CH_2CH_2).

Anal. Calcd for $C_{17}H_{16}NO_8SK$: C, 47.10; H, 3.72; N, 3.23. Found: C, 47.18; H, 3.75; N, 3.22.

Potassium Thiocyanate Complex (1:1) of Cyclic *O,O'*-Oxybis(ethyleneoxyethylene) 2,2'-Bifuryl-5,5'-dicarboxylate (9e). An acetone (2 mL) solution containing cyclic *O,O'*-oxybis(ethyleneoxyethylene) 2,2'-bifuryl-5,5'-dicarboxylate (**9e**; 100 mg, 0.263 mmol) and potassium thiocyanate (26.0 mg, 0.267 mmol) was stirred for 30 min, with the formation of a precipitate. After the mixture was cooled in an ice bath, the product was collected as colorless prisms: 95 mg (75%); mp 210–211 °C dec; IR (KBr) ν_{SCN} 2027, ν_{CO} 1715 cm^{-1}; UV (MeOH) λ_{max} 224 nm (log ϵ 4.20), 324 (4.52), 338 sh (4.37); ^{1}H NMR ($CDCl_3$) δ 7.36 (2, d, furan H_4, J = 3.7 Hz), 6.73 (2, d, furan H_3), 4.62 (4, m, CO_2CH_2), 3.90 (4, m, $CO_2CH_2CH_2$), 3.84 (s, 8, OCH_2CH_2O).

Anal. Calcd for $C_{19}H_{20}NO_9SK$: C, 47.79; H, 4.22; N, 2.93. Found: C, 47.70; H, 4.27; N, 2.92.

Registry No. **1** (R = Li), 82093-90-1; **1** (R = Br), 82093-91-2; **1** (R = Cl), 82093-92-3; **1** (R = CO_2H), 82093-93-4; **1** (R = H), 78570-43-1; **1** (R = CHO), 82093-94-5; **1** (R = COCl), 82093-95-6; **1** (R = CH_2OH), 82093-96-7; **2**, 82093-97-8; **3**, 82093-98-9; **4a**, 82093-99-0; **4b**, 82094-00-6; **4c**, 82094-01-7; **4d**, 82094-02-8; **5** (R = CO_2H), 82094-03-9; **5** (R = H), 82094-04-0; **5** (R = Li), 82094-05-1; **6**, 82094-06-2; **7a**, 82094-07-3; **7b**, 82094-08-4; **7c**, 82094-09-5; **8** (X = O), 50738-83-5; **8** (X = O) dicesium salt, 82094-10-8; **8** (X = S), 3515-34-2; **8** (X = S) dicesium salt, 82094-11-9; **9a**, 82094-12-0; **9b**, 82094-13-1; **9c**, 82094-14-2; **9d**, 82094-15-3; **9d**·KSCN, 82094-61-9; **9e**, 82094-16-4; **9e**·KSCN, 82094-63-1; **9f**, 82094-17-5; 1,2-bis(2-bromoethoxy)ethane, 31255-10-4; bis[2-(2-bromoethoxy)ethyl] ether, 31255-26-2; 1,2-bis[(2-bromoethoxy)ethoxy]ethane, 57602-02-5.

Reaction of Chloral Hydrate with Cyanoguanidine

Kurt H. Pilgram,* Richard D. Skiles, Edward J. Silveira, Laird H. Gale, and Glenn E. Pollard

Biological Sciences Research Center, Shell Development Company, Modesto, California 95352

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Reaction of chloral hydrate with cyanoguanidine (molar ratio 2:1) proceeded smoothly in refluxing carbon tetrachloride to give a 3:1 reaction product, $C_8H_7Cl_9N_4O_3$ (**6**). With 15% hydrochloric acid, **6** formed the hydrochloride. Monodehydration of **6** with thionyl chloride in refluxing carbon tetrachloride gave (2*S*,4*S*,6*R*)-2,6,7,9-tetrahydro-2,4,6-tris(trichloromethyl)-8*H*-[1,3,5]triazino[1,2-*c*][1,3,5]oxadiazin-8-one (**7**). A brief analysis of the spectral and single-crystal X-ray crystallographic data is presented.

On mechanistic grounds, reaction of chloral hydrate with cyanoguanidine (dicyandiamide) may give rise to a variety of acyclic and cyclic 3:1 addition–condensation products, depending on whether (a) more than two of the nitrogens participate in the initial addition reaction, (b) hydration of the cyano (C≡N) group takes place, (c) ring closure of the initial acyclic 1:1, 2:1, or 3:1 reaction product results in the formation of six-membered rings, and (d) further addition of one or more chloral units to these ring structures in one or more of their tautomeric forms occurs.

A recent paper[1] describes the synthesis from chloral hydrate and cyanoguanidine (molar ratio 2.17:1) of 3,6-dihydro-4-[(1-hydroxy-2,2,2-trichloroethyl)amino]-6-imino-2-(trichloromethyl)-2*H*-1,3,5-oxadiazine (**2**). The cy-

(1) Dovlatyan, V. V.; Papoyan, T. Z.; Tarkhanyan, G. K. *Chem. Heterocycl. Comp. (Engl. Transl.)* **1975**, *11*, 415; *Chem. Abstr.* **1975**, *83*, 97226 (1975).

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