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Synthesis of 2,6-Disubstituted Pyridines, Polypyridinyls, and Annulated Pyridines[1]

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1,5-Enediones containing a variety of substituents in the 1,5-positions are formed in good yields by the reaction of methyl ketone enolates, generated with potassium *tert*-butoxide, with α-oxoketene dithioacetals, the latter being prepared from alkyl, cycloalkyl, aryl, or heteryl methyl ketones, NaH, CS_2, and CH_3I. Ring closure of the 1,5-enediones with NH_4OAc gave 2,6-disubstituted 4-(methylthio)pyridines in good to excellent yields. This procedure is particularly suited for the synthesis of 2,6-diheterylpyridines and provides a simple synthesis of terpyridinyl and other oligopyridines. The methylthio groups in the α-oxoketene dithioacetals may be oxidized to the mono- and disulfoxides with *m*-chloroperbenzoic acid, but with excess peracid, in addition to oxidation to the disulfone, epoxidation of the double bond also occurs. The pyridine 4-methylthio substituent may also be oxidized to the sulfoxide and to the sulfone, and the latter may be displaced with cyanide ion to form the corresponding 4-carbonitrile.

Numerous methods for the synthesis of a wide variety of substituted pyridines have been described[2] in the literature, involving principally either modification of a preformed pyridine nucleus or pyridine ring formation from suitably substituted precursors. Most useful in the latter approach have been procedures leading to 1,5-diketone intermediates which, with a variety of nitrogen-containing reagents, undergo ring closure to the pyridine. We now describe a new and versatile synthesis of 1,5-enediones which, as a consequence, makes readily available a wide variety of 2,6-disubstituted pyridines as well as annulated pyridines. As shown below, this procedure is the method of choice for the synthesis of 2,6-diheteryl substituted pyridines and oligopyridines and has the additional advantage of a readily transformable 4-alkylthio substituent.

Preparation of 1,5-Enediones. Studies have shown[3] that 1,5-enediones undergo ring closure to six-membered heterocycles more efficiently than their saturated counterparts and readily form pyridines with a variety of ammonia sources.[4] Methods for their preparation involve reaction of β-chlorovinyl ketones with β-diketones or β-keto esters,[5] HIO_4 oxidation of cyclopentane-1,2-diols,[6] or a reverse process involving ring opening of pyridines or pyrylium salts.[7] None of these reaction sequences provide a general synthesis of this class of compounds.

The dithioacetal functional group, in addition to its well established role as a protecting group,[8] had found many applications as an acyl anion equivalent[9] and has also been utilized as a means of introduction of other functional groups such as α,β-unsaturated ketones,[10] carboxylic acids,[11] α-chlorocarboxylic acids,[12] *S*-methyl thiocarboxylates,[13] aldehydes, and β-keto esters.[14] The corresponding monosulfoxide provides an attractive route to 1,4-dicarbonyl compounds with one carbonyl group being an aldehyde function.[15] Vinyl ketene dithioacetals behave

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(2) For summaries see: Klingsberg, E. "The Chemistry of Heterocyclic Compounds. Pyridine and Its Derivatives"; Interscience: New York, 1960; Vol. I–III. Abramovitch, R. "The Chemistry of Heterocyclic Compounds. Supplement to Pyridine and Its Derivatives"; Wiley-Interscience: New York, 1978.

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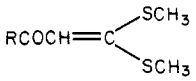
Table I. α-Oxoketene Dithioacetals



R	mp, °C	yield, %	crystal habit[a]	mol formula[b]	m/e of M+·	ν_{CO}, cm^{-1}
C_6H_5	90-92[c]	58	yellow needles[d]	$C_{11}H_{12}OS_2$	224 (42)	1610
4-$CH_3OC_6H_4$	98-99[e]	61	yellow needles[d]	$C_{12}H_{14}O_2S_2$	254 (36)	1595
2-C_5H_4N	110-111	71	yellow prisms	$C_{10}H_{11}NOS_2$	225 (2)	1625
2-C_4H_3O	114-115	44	yellow prisms	$C_9H_{10}O_2S_2$	214 (73)	1610
2-C_4H_3S	95.5-97	68	light brown prisms	$C_9H_{10}OS_3$	230 (31)	1595
6-Br-2-C_5H_3N	172-173	66	yellow needles	$C_{10}H_{10}BrNOS_2$	303 (11), 305 (12)	1620
5-Br-2-C_4H_2S	129-130	73	pale yellow needles	$C_9H_9ClOS_3$	308 (55)	1601
5-Cl-2-C_4H_2S	127-127.5	69	pale yellow needles	$C_9H_9ClOS_3$	264 (38)	1597

[a] All crystallized from ethanol except as noted. [b] All compounds gave satisfactory analytical data (±0.4% for C, H, and N where appropriate). [c] Lit.[14c] mp 93 °C. [d] Crystallized from methanol. [e] Lit.[14b] mp 103 °C.

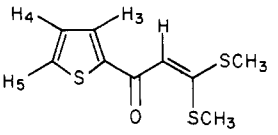
as dienes with reactive dienophiles.[16] The utility[17] of ketene dithioacetals is enhanced by incorporation of an unsaturated group α to the ketene dithioacetal function and such systems have found considerable application in heterocyclic synthesis.[18]

It was anticipated that α-oxoketene dithioacetals would undergo 1,4-addition with ketone enolates and, after elimination of methanethiolate, yield 1,5-enediones. We have now found that this reaction proceeds under mild conditions, providing ready access to a variety of 1,5-enediones in good to excellent yields.

Although α-oxoketene dithioacetals may be prepared by several methods,[19] we have found the most direct and economical synthesis to be the reaction of a methyl ketone (1 equiv; alkyl, cycloalkyl, aryl or heteryl) with sodium hydride (2 equiv) in benzene or toluene, carbon disulfide (1.5 equiv), and methyl iodide (3 equiv).[14b] With these solvents it is essential to have present a small amount (ca. 5% v/v) of a polar solvent such as *N,N*-dimethylacetamide. With the ketene dithioacetal derived from 2-acetylpyridine, Me_2SO was the solvent of choice. A marked increase in yield (71%) occurred compared to that obtained (47%) when toluene was used as the solvent. The α-oxoketene dithioacetals, described in Table I, were all obtained as pale yellow crystalline products with characteristic ν_{CO} = 1595–1625 cm^{-1}. Their mass spectra all showed an M+·, and in most cases the most intense ion corresponded to (RC≡O+]. The NMR spectra were all consistent with the assigned structures and contained two nonequivalent methyl groups between δ 2.6 and 2.4 in the ^{1}H NMR spectra and between 17.5 and 15.0 ppm in the ^{13}C NMR spectra. The nonequivalent methyl groups suggest that, on the NMR time scale, there is very little rotation about the 2–3 bond and also that electron delocalization from the sulfur atoms over the α,β-unsaturated ketone system is insufficient to be detected by the NMR technique.

The actual conformation adopted by the ketene dithioacetals is of interest. Depending on the relationship of the carbonyl group to the double bond and to the other nucleus attached to the carbonyl group, four conformations are possible *Z–Z*, *E–Z*, *Z–E*, and *E–E*. In a series of 2-thienyl methyl ketones the *E* conformation has been shown[20] to predominate on the basis of the slightly positive nature (generally Δ = δ 0.18–0.70) of the chemical shift changes[21] of H_3 and H_4 when the NMR spectra were determined in CCl_4 and then benzene. On application of this procedure to 3,3-bis(methylthio)-1-(2-thienyl)-2-propen-1-one (1), the chemical shifts (Table II) of each proton or methyl group show a positive Δ value, indicating that there are no protons in close proximity to the oxygen atom on the negative side of the reference plane. These data suggest that the *E–E*, *E–Z*, and *Z–E* conformations are unlikely ones, leaving the *Z–Z* conformation as being best suited to accommodate the NMR data. However, CPK models suggest considerable steric interaction in this conformation, and, at best, only partial coplanarity of all functional groups is achieved. Double-resonance experiments on 1 were also carried out. No nuclear Overhauser effect was observed on irradiation of each thienyl proton and methyl group, indicating that a distance of at least 3 Å separates each resonating proton from any other nonequivalent proton.[20] Although it cannot be established with absolute certainty, and CPK models show that the H_3 thienyl proton and the vinyl proton overlap to a small degree, the available data suggest that the α-oxoketene dithioacetals are best represented as having a *Z–E* conformation (see the paragraph at the end of the paper about supplementary material).

Table II. Chemical Shifts of Protons in 3,3-Bis(methylthio)-1-(2-thienyl)-2-propen-1-one (1) Measured in CCl_4, C_6D_6, and $CDCl_3$



proton	δ(CCl_4)	δ(C_6D_6)	Δδ-(CCl_4-C_6D_6)	δ($CDCl_3$)
H_3	7.60 (d)	7.48 (d)	0.12	7.60
H_4	7.06 (dd)	6.73 (dd)	0.33	7.07
H_5	7.48 (d)	7.06 (d)	0.42	7.53
vinyl	6.52 (s)	6.44 (s)	0.08	6.57
SCH_3	2.51 (s)	2.09 (s)	0.42	2.55
	2.43 (s)	1.80 (s)	0.63	2.45

Oxidation of 1 with 1 equiv of *m*-chloroperbenzoic acid gave the monomethyl sulfoxide 2 in 65% yield. Oxidation occurred cleanly at one sulfur atom. Although it is not possible to say with certainty which sulfur atom was ox-

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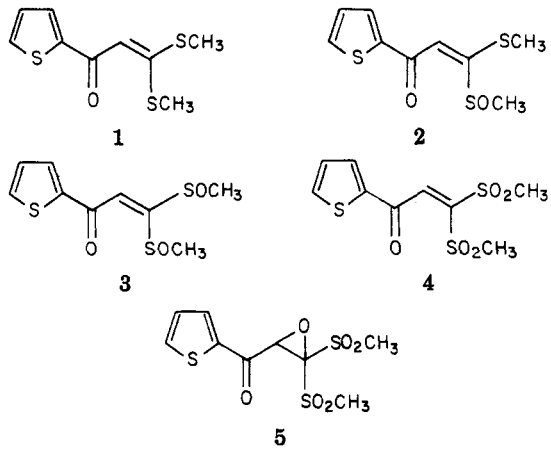
(19) Kelher, C. *Ber.* **1910**, *43*, 1252. Sachel, H. D. *Chem. Ber.* **1962**, *92*, 2166; *Arch Pharm.* **1962**, *295*, 224. Ziegler, F. E.; Chan, C. M. *J. Org. Chem.* **1978**, *43*, 3065. Schuijl, P. J. W.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1966**, *85*, 1263.
(20) Kaper, L.; Deboer, T. J. *Recl. Trav. Chim. Pays-Bas* **1970**, *89*, 825.
(21) Timmons, C. J. *Chem. Commun.* **1965**, 576.

Chart I



idized, no oxidation of the thiophene sulfur atom was detected. A thiomethyl resonance in the original ketene dithioacetal had shifted from approximately δ 2.5 to 3.0 in the ^{1}H NMR spectrum of the oxidized product and from 17.0 to 43.5 ppm in its ^{13}C NMR spectrum. Other evidence that substantiates this structural assignment included the following: IR ν_{CO} 1610, ν_{SO} 1050 cm^{-1}; mass spectrum, m/e (relative intensity) 246 (3, M$^{+\cdot}$), 199 (4, M$^{+\cdot}$ – SCH_3), 183 (100, M$^{+\cdot}$ – $SOCH_3$), m/e 111 (93, 2-thienoylium ion).

Reaction of 1 with 2 equiv of *m*-chloroperbenzoic acid gave the bis sulfoxide 3,3-bis(methylsulfinyl)-1-(2-thienyl)-2-propen-1-one (**3**) in 44% yield. Infrared absorptions at ν_{CO} 1625 and ν_{SO} 1060, 1032 cm^{-1}, ^{1}H NMR chemical shifts at δ 3.21 and 3.18, and ^{13}C NMR chemical shifts at 42.6 and 41.1 ppm showed that oxidation had occurred at both exocyclic sulfur atoms.

When 5 equiv of *m*-chloroperbenzoic acid was used in the oxidation of 1, a good yield of 3,3-bis(methylsulfonyl)-1-(2-thienyl)-2,3-epoxypropan-1-one (**5**) was obtained. The structure of this product was evident from analytical data and the following spectral characteristics. Infrared absorptions (ν_{CO} 1667, ν_{SO_2} 1150, 1330 cm^{-1}), an M$^{+\cdot}$ at 310 (23%), and an intense 2-thienoylium ion at m/e 111 provided gross structural information. The presence of the epoxide group was evident from the ^{1}H and ^{13}C NMR spectral data. The epoxide proton appeared as a singlet at δ 4.75 while the analogous vinylic proton was at δ 6.57 in 1 and at δ 6.75 and 7.90 in **2** and **3**, respectively. Similarly, a significant upfield shift was observed for the chemical shifts of the epoxide carbon atoms which occurred at 80.5 and 60.7 ppm. Less substantial chemical shifts were observed for the methyl groups, which appeared at δ 3.30 and 3.80 in the ^{1}H NMR spectrum and at 40.0 and 42.5 ppm in the ^{13}C NMR spectrum.

With either 3 or 4 equiv of *m*-chloroperbenzoic acid, 1 gave mixtures of **3**, **5**, and very minor amounts of another product which, on the basis of the NMR spectrum, was most likely the sulfinyl sulfonyl product corresponding to **3**. No evidence was obtained for the presence of the disulfonyl product **4** (Chart I).

The α-oxoketene dithioacetal derived from 2-acetylpyridine, 3,3-bis(methylthio)-1-(2-pyridinyl)-2-propen-1-one (**12**; R = 2-pyridinyl), deserves special mention. It is a useful synthetic starting material that shows striking differences in its preparation from others described here. The workup of the initial black Me_2SO reaction mixture with water and filtration of the precipitated black product was followed by dissolution of the material in $CHCl_3$ and percolation through a small bed of silica. This resulted in the yellow-green product described in Table I. In contrast, the ketene dithioacetal derived from 2-acetyl-6-bromopyridine separated from the crude reaction mixture in a relatively pure state, and no darkening of the reaction mixture was observed. The presence of the 6-bromo substituent was also found to stabilize later products in this series.

The preparation of bis(ketene dithioacetals) was also readily achieved by using the appropriate bis(methyl ketone). 2,6-Diacetylpyridine (**6**) on reaction with the requisite amount of $NaH/CS_2/CH_3I$ gave a product mixture that was solvent dependent. 2,6-Diacetylpyridine (**6**) on reaction with the requisite amount of $NaH/CS_2/CH_2I$ gave a product mixture that was solvent dependent. In toluene, the monoketene dithioacetal **7**, the bis(ketene dithioacetal) **8** (R = H), and unreacted ketone were obtained. Increasing the amount of *N*,*N*-dimethylacetamide used in the reaction improved the yield of **8** (R = H) although polymeric material was obtained. When this reaction was carried out in Me_2SO with NaH as the base, the bis(ketene dithioacetal) was obtained exclusively in 59% yield. Analytical and spectral data showed that both acetyl groups had undergone reaction, the product having m/e 371 (M$^{+\cdot}$) and ν_{CO} 1605 cm^{-1}. The NMR spectrum ($CDCl_3$) showed the characteristic nonequivalent *S*-methyl groups at δ 2.63 and 2.59. In CF_3COOH, however, in addition to the three pyridine protons at δ 8.92–8.60 and two vinylic protons at δ 7.10, the most outstanding feature of the spectrum was the sharp singlet for the *S*-methyl groups at δ 2.83. This equivalence of the methyl groups reflects protonation of the carbonyl oxygen atom with formation of a sulfur-stabilized carbonium ion. Such a carbonium ion intermediate has been postulated in the reduction of ketene dithioacetals to dithioacetals in a CF_3COOH/CH_2Cl_2 solvent system.[23] This ready protonation of the carbonyl oxygen atom in the α-oxoketene dithioacetals is a general characteristic. For example, in 3,3-bis(methylthio)-1-(2-pyridinyl)-2-propen-1-one, the two nonequivalent *S*-methyl groups have chemical shifts of δ 2.60 and 2.54 in $CDCl_3$. In CF_3COOH, a downfield shift occurs, with the *S*-methyl groups now being a singlet at δ 2.81.

The bis product **8** (R = H) was poorly soluble in common organic solvents, restricting its effectiveness as a synthon. The solubility of the bis product, however, was improved markedly by increasing the chain length of the *S*-alkyl groups. With *S*-ethyl substituents, the bis(ketene dithioacetal) **8** (R = CH_3) was soluble in $CHCl_3$ and sparingly soluble in hydrocarbon solvents. Introduction of *S*-*n*-propyl substituents resulted in the corresponding bis(ketene dithioacetal) **8** (R = CH_2CH_3) being very soluble in the majority of organic solvents. Although an alkyl chain of any length may be introduced via the corresponding alkyl halide during the synthesis of the bis(ketene dithioacetal), for practical purposes the *n*-propyl chain is the maximum desirable length. Alkanethiols of longer chain length have sufficiently high boiling points to unnecessarily complicate the reaction workup in those reactions in which an alkanethiol is eliminated.

Monofunctionalization of 2,6-diacetylpyridine (**6**) to give **7** was also possible by careful modification of the reaction conditions. With Me_2SO as the solvent, 1 equiv each of NaH, CS_2, and CH_3I were added to the diketone. Once the initial reaction had subsided, a second equivalent of NaH and CH_3I were added. The reaction mixture was quenched with water, causing **7** to separate in good yield.

2,5-Diacetylthiophene (**9**), prepared in our study by direct lithiation of thiophene[22] with *n*-butyllithium in the

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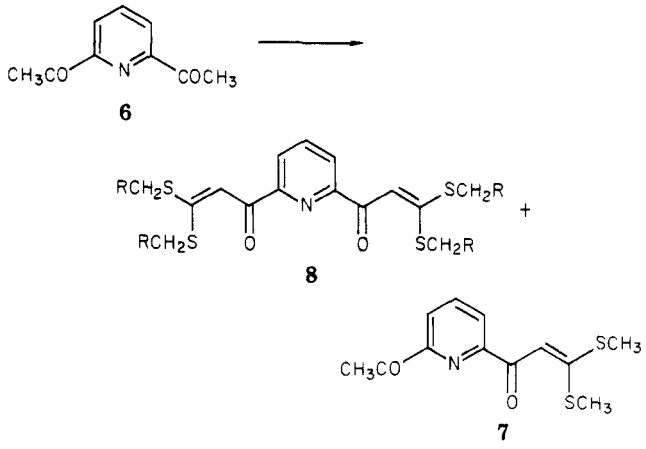
(23) Carey, F. A.; Nuegaard, J. R. *J. Org. Chem.* **1971**, *36*, 2731, ref 14a.

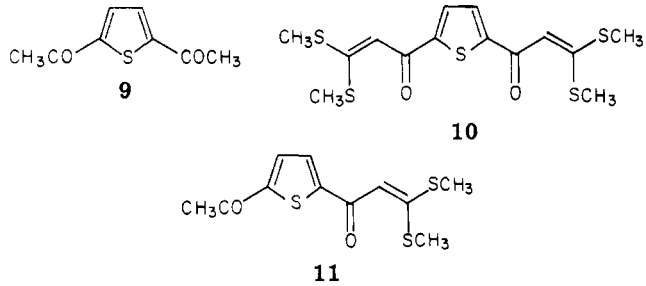


6

8

7

presence of *N,N,N',N'*-tetramethylethylenediamine and subsequent reaction with *N,N*-dimethylacetamide, a procedure preferable to those reported in the literature,[24] was also converted into its bis(ketene dithioacetal). With toluene/*N,N*-dimethylacetamide as the solvent, 2,5-bis-[3,3-bis(methylthio)-1-oxo-2-propen-1-yl]thiophene (**10**)



9

10

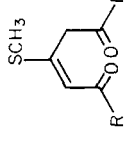
11

was always contaminated by the monoketene dithioacetal **11** (NMR and mass spectral data), and these could not be separated satisfactorily by fractional crystallization or column chromatography. Separation was achieved by using HPLC with a hexane–ethyl acetate (50:50) solvent system. The gross structure of **10** was readily established by analytical and spectral data, especially an intense $M^+\cdot$ at *m/e* 376 (88%) with a compatible fragmentation pattern and a ν_{CO} at 1592 cm^{-1}. The NMR spectrum showed a singlet for H_3 and H_4 of the thiophene nucleus at δ 7.62, a singlet vinyl proton at δ 6.60, and the characteristic nonequivalent thiomethyl singlets at δ 2.56 and 2.51.

Formation of the 1,5-enediones described in Table III occurred readily under mild conditions when the above α-oxoketene dithioacetals **12** in anhydrous THF were treated at room temperature with the potassium enolates of a variety of methyl ketones. The enolates were generated by potassium *tert*-butoxide, and, as 2 equiv of base were used in the reaction, the 1,5-enediones were isolated initially as their air-sensitive potassium salts **13**. After separation and acid treatment the 1,5-enediones **13a** were readily isolated and characterized. Elevated temperatures enhanced the reaction rate, but the 1,5-enediones obtained under these conditions were all highly colored and required laborious purification to obtain pure products. Although the reaction will proceed with only 1 equiv of potassium *tert*-butoxide present, reduced yields of the 1,5-enediones were obtained. In addition to aiding in product isolation, the formation of the potassium enolate of the 1,5-enedione also suppressed any second addition of the ketone enolate

(24) Hartough, H. D.; Kosak, A. I. *J. Am. Chem. Soc.* **1947**, *69*, 1012. Yakubov, A. P.; Gol'dfarb, L.; Belen'kŭ, L. I. *Dokl. Chem. (Engl. Transl.)* **1969**, 147. Tsukerman, S. V.; Nikitchenko, V. M.; Laurushin, V. L.; Thien, L. N. USSR Patent 202 174; *Chem. Abstr.* **1968**, *69*, 35926.

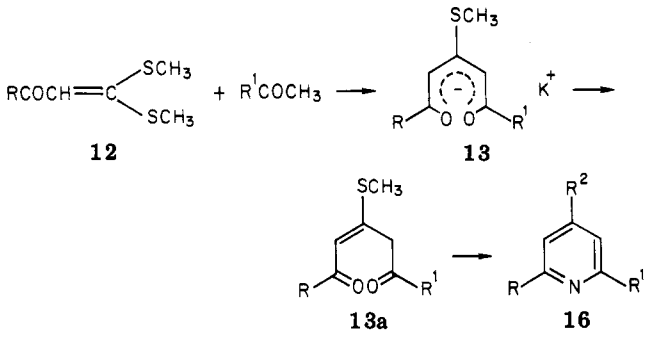
Table III. 1,5-Enediones Derived from α-Oxoketene Dithioacetals



R	R'	mp, °C	yield, %	crystal habit	mol formula[a]	*m/e* of $M^+\cdot$ (rel intens)	ν_{CO}, cm^{-1}
C_6H_5	C_6H_5	106–108	76	pale yellow prisms (benzene/petroleum ether	$C_{18}H_{16}O_2S$	296 (7)	1680, 1630
C_6H_5	2-C_4H_3S	116–118	61	pale yellow needles (benzene/petroleum ether)	$C_{16}H_{14}O_2S_2$	302 (8)	1700, 1680, 1645, 1625
C_6H_5	2-C_5H_4N	124–125	58	colorless needles (cyclohexane)	$C_{17}H_{15}NO_2S$	248 (2)	1680, 1640
2-C_4H_3S	2-C_4H_3S	164–165	70	pale yellow prisms (benzene)	$C_{14}H_{12}O_2S_3$	308 (7)	1670, 1620
2-C_4H_3O	2-C_4H_3S	140–142	47	pale yellow needles (benzene/petroleum ether)	$C_{14}H_{12}O_3S_2$	292 (11)	1690, 1670, 1640, 1620
2-C_5H_4N	2-C_5H_4N	120–122	13	pale yellow prisms (petroleum ether)	$C_{16}H_{14}N_2O_2S$	298 (1)	1700, 1646
2-C_5H_4N	2-C_4H_3S	102–104	60	colorless prisms (benzene/cyclohexane)	$C_{15}H_{13}NO_2S_2$	303 (1)	1700, 1630
3-BrC_6H_4	3-BrC_6H_4	118–119	81	colorless needles (methanol)	$C_{18}H_{14}Br_2O_2S$	454 (3)	1690, 1640
4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	159–161	100	yellow needles (benzene)	$C_{20}H_{20}O_4S$	356 (20)	1655
4-$CH_3OC_6H_4$	CH_3	106–107	42	colorless needles (methanol/ether)	$C_{14}H_{16}O_3S$	264 (18)	1710, 1640
2-C_4H_3S	5-Cl-2-C_4H_2S	134–134.5	75	pale yellow prisms (benzene)	$C_{14}H_{11}ClO_2S_3$	342 (10)	1665, 1623
5-Br-2-C_4H_2S	5-Br-2-C_4H_2S	125–126.5	97	pale yellow prisms (ethanol)	$C_{14}H_{10}Br_2O_2S_3$	464 (7)	1669, 1620

[a] All compounds gave satisfactory analytical data (±0.4% for C, H, and N where appropriate).

Scheme I

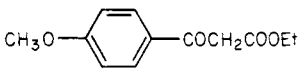


to the α,β-unsaturated ketone system of the 1,5-enedione. Attempts to methylate the potassium salt with methyl iodide proved unsuccessful. In the formation of the 1,5-enedione the potassium ion most likely exerts a template effect, and other bases were not as satisfactory (see below) in effecting the condensation.

The structures of the substituted 1,5-enediones were established from analytical and spectral data (Table III). Infrared carbonyl absorptions occurred between 1615–1625 and 1665–1670 cm^{-1}. All showed an $M^{+\cdot}$ in their mass spectra, and the most intense ion was the $(RC{\equiv}O)^+$ ion, the overall fragmentation pathway being straightforward with ions corresponding to $[M^{+\cdot} - CH_3]$ and $[M^{+\cdot} - SCH_3]$. The NMR spectra of these 1,5-enediones were also relatively simple when the 1,5-substituents were the same. For example, the NMR spectrum of 1,5-bis(2-thienyl)-3-(methylthio)-2-pentene-1,5-dione (**13a**; R = R^1 = 2-thienyl) showed aromatic protons (six) at δ 7.96–7.03, a singlet vinylic proton at δ 6.70, singlet methylene protons at δ 4.60, and a sharp *S*-methyl chemical shift at δ 2.50. However, with dissimiliar 1,5-substituents as in 1-(2-pyridinyl)-5-(2-thienyl)-3-(methylthio)-2-pentene-1,5-dione (**13a**; R = 2-thienyl, R^1 = 2-pyridinyl) two distinct singlets were obtained for the vinylic proton (δ 7.70 and 6.70), methylene protons (δ 4.80 and 4.57), and the methylthio groups (δ 2.56 and 2.51). These data suggest that the product obtained was actually a mixture of the two isomers formed by migration of the allylic double bond. Attempts to separate these isomers by chromatography were unsuccessful. The stereochemistry about the double bond needs also to be considered, but from our data it is not possible to assign either the *E* or *Z* configuration with any degree of certainty. Both *E* and *Z* isomers of 1,5-enediones have been isolated[25] and characterized,[26] and both isomers undergo cyclodehydration to pyrylium salts,[25] although this conversion is slower for the *Z* isomer. Rationalization of the above NMR data for unsymmetrical 1,5-enediones in terms of configurational isomerism about the double bond is not consistent with the magnitude of the chemical shift differences observed (see the paragraph at the end of the paper about supplementary material).

Inspection of the 1,5-enediones in Table III shows that there is usually a choice as to which substituent is introduced via the α-oxoketene dithioacetal component or via the ketone enolate component. Thus 1-(2-pyridinyl)-5-phenyl-3-(methylthio)-2-pentene-1,5-dione (**13a**; R = 2 pyridinyl, R^1 = C_6H_5) when prepared from 3,3-bis(methylthio)-1-(2-pyridinyl)-2-propen-1-one (**12**; R = 2-pyridinyl) and acetophenone was obtained in 58% yield (see Scheme I). However, when it was prepared from 3,3-bis(methylthio)-1-phenyl-2-propen-1-one (**12**; R = C_6H_5) and 2-acetylpyridine, the 1,5-enedione was formed in 50% yield. As the α-oxoketene dithioacetals containing an aromatic group were relatively easy to prepare, we have found their use to be more efficient overall in the preparation of the 1,5-enediones.

As mentioned above, potassium *tert*-butoxide was the most effective base for the formation of the 1,5-enediones. Although NaH may be used, byproduct formation increased markedly. With sodium ethoxide in ethanol, the reaction took a different course. Thus reaction of 3,3-bis(methylthio)-1-(4-methoxyphenyl)-2-propen-1-one (**12**; R = 4-$CH_3OC_6H_4$) with 4-methoxyacetophenone gave the β-keto ester **14** and the α-pyranone **15**. No 1,5-enedione containing an ethoxy substituent in place of the *S*-methyl group was isolated. Formation of **14** can be readily rationalized in terms of an initial displacement of methanethiolate by ethoxide ion to form the α-oxoketene acetal which, under acid workup conditions, gave[14b] the β-keto ester **14**. Condensation of two molecules of the acetal with subsequent ring closure also satisfactorily explains formation of the α-pyrone derivative **15**.



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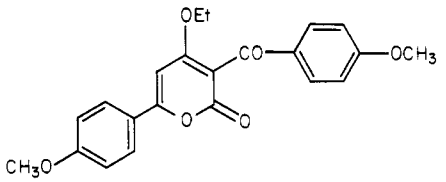


15

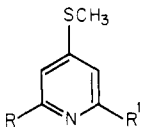
Preparation of 2,6-Diarylpyridines. The 1,5-enediones **13a** are useful synthons for the preparation of 2,6-disubstituted pyridines when treated with ammonia sources. Such 2,6-diarylpyridines have usually been prepared from 1,5-diaryl-1,5-alkanediones and ammonia at high temperatures,[27] by direct arylation of pyridine with an aryllithium,[28] or by the reaction of chalcones with N-substituted pyridinium salts.[4]

The symmetrically and unsymmetrically substituted pyridines described in Table IV were prepared either by reaction of the 1,5-enediones with ammonium acetate in hot glacial acetic acid or by a more direct procedure in which the enedione was not isolated. In the latter, the α-oxoketene dithioacetal **12** and the methyl ketone in the presence of potassium *tert*-butoxide/THF were allowed to react as before. Glacial acetic acid and ammonium acetate were then added, and the reaction mixture was heated under reflux with continuous removal of THF. Quenching the reaction mixture with water usually gave the pyridine in good yield. This was the more convenient procedure and in most instances resulted in the better overall yield.

The structures of these substituted pyridines are evident from the analytical and spectral data reported in Table IV. High-resolution mass spectral data for 2,6-diphenyl-4-(methylthio)pyridine (**16**; R = R^1 = Ph, R^1 = SCH_3) showed a measured mass of 277.0932 (calcd mass 277.0922). It was also prepared from the corresponding pyrylium salt[29]

(25) Dilthey, W.; Bottles, T. *Ber.* **1919**, *52*, 2042. Basselier, J. J. *Ann. Chim. (Paris)* **1961**, *6*, 1131.
(26) Basselier, J. J. *C. R. Hebd. Seances Acad. Sci.* **1959**, *248*, 700. Rio, G.; Fellion, Y. *Tetrahedron Lett.* **1962**, 1213.
(27) See ref 2 Part I, pp 99–589; Part II, pp 155–298.
(28) Ziegler, K.; Zeiser, H. *Ber.* **1930**, *63*, 1847. Overberger, C. G.; Lombardino, J. G.; Hiskey, R. G. *J. Am. Chem. Soc.* **1957**, *79*, 6430. Bryce, D.; Skinney, A. C. *J. Chem. Soc.* **1963**, 577.
(29) Potts, K. T.; Ralli, P.; Theodoridis, G., to be submitted for publication in *J. Org. Chem.*

Table IV. Some 2,6-Disubstituted 4-(Methylthio)pyridines



R	R′	mp, °C	yield, %	crystal habit	mol formula[a]	m/e of M+.[b]
C_6H_5	C_6H_5	105–107	75	colorless prisms (petroleum ether C)	$C_{18}H_{15}NS$	277
2-C_4H_3S	2-C_4H_3S	115–116	99	pale yellow prisms (cyclohexane)	$C_{14}H_{11}NS_3$	289
2-C_4H_3S	C_6H_5	108–109	83	colorless needles (benzene/petroleum ether)	$C_{16}H_{13}NS_2$	283
2-C_4H_3S	2-C_4H_3O	95–97	74	yellow prisms (petroleum ether C)	$C_{14}H_{11}NOS_2$	273
2-C_5H_4N	2-C_5H_4N	120–121	81	colorless needles (ethanol/water)	$C_{16}H_{13}N_3S$	279
2-C_5H_4N	C_6H_5	80–81	89	colorless prisms (petroleum ether C)	$C_{17}H_{14}N_2S$	278
2-C_5H_4N	2-C_4H_3S	133–134	80	light brown prisms (benzene/petroleum ether)	$C_{15}H_{12}N_2S_2$	284
4-$CH_3OC_6H_4$	C_6H_5	77.5–78.5	81	colorless needles (ethanol)	$C_{19}H_{17}NOS$	307
4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	90.5–91	48	colorless needles (ethanol)	$C_{20}H_{19}NO_2S$	337
4-$CH_3OC_6H_4$	CH_3	69–70	70	colorless prisms (petroleum ether C)	$C_{14}H_{15}NOS$	245

[a] All compounds gave satisfactory analytical data (±0.4% for C, H, and N). [b] All 100% relative intensity.

by reaction with ammonium acetate in refluxing methanol.

By an appropriate choice of α-oxoketene dithioacetal **12** and methyl ketone enolate this procedure leads to bipyridinyl derivatives containing only one 2-substituent. Thus, 4-(methylthio)-6-phenyl-2,2′-bipyridinyl (**16**; R = Ph, R^1 = 2-pyridinyl, R^2 = SCH_3) was readily prepared from 1-(2-pyridinyl)-5-phenyl-3-(methylthio)-2-pentene-1,5-dione (**13a**; R = 2-pyridinyl, R^1 = Ph) and ammonium acetate. Its high-resolution mass spectrum showed a measured mass of 278.0897 (calcd mass 278.0875), and in the NMR spectrum, proton H_3, adjacent to the pyridine ring, occurred at δ 8.23, while H_5 was observed at δ 7.53, both signals being doublets (J = 1.90 Hz). A similar deshielding of the protons in the 3- and 5-positions was also observed in 2-(2-pyridinyl)-4-(methylthio)-6-(2-thienyl)-pyridine (**16**; R = 2-pyridinyl, R^1 = 2-thienyl, R^2 = SCH_3) (measured mass 284.0463, calcd mass 284.0440). Proton H_3, adjacent to the pyridine ring, occurred at δ 8.09 (d, J = 1.90 Hz) and H_5, adjacent to the thiophene ring, appeared at δ 7.36 (d, J = 1.90 Hz). These chemical shifts are readily rationalized in terms of a trans arrangement of the bipyridinyl system.[30,31]

Preparation of 2,6-Diheterylpyridines. The variety of pyridines of this type described in Table IV emphasizes the potential of this synthetic scheme for the synthesis of triheteryl systems containing at least one pyridine nucleus. The preparation of terpyridinyl can be achieved very efficiently by reaction of 3,3-bis(methylthio)-1-(2-pyridinyl)-2-propen-1-one (**12**; R = 2 pyridinyl) with 2-acetylpyridine and potassium *tert*-butoxide in THF followed by the addition of NH_4OAc/glacial acetic acid. The structure of **16** (R = R^1 = 2-pyridinyl; R^2 = SCH_3) was consistent with its spectral data (Table IV) and the NMR spectrum showed appreciable deshielding of the protons at the 3,3′, and 5-positions. H_3 and H_5 appeared as a singlet at δ 8.30 while $H_{3'}$ was a broad doublet at δ 8.60. These data indicate that in the terpyridinyl system the pyridine rings in solution have a trans–trans arrangement of their nitrogen atoms (see the paragraph at the end of the paper about supplementary material).

Reaction of the corresponding 1,5-enedione **13a** (R = R^1 = 2-pyridinyl) with ammonium acetate/boiling glacial acetic acid gave **16** (R = R^1 = 2-pyridinyl; R^2 = SCH_3) in 81% yield. However, the direct procedure is preferable due to the low yield obtained in the preparation of the 1,5-enedione.

Desulfurization of **16** (R = R^1 = 2-pyridinyl; R^2 = SCH_3) with Raney nickel in refluxing ethanol occurred readily, giving 2,2′,6′,2″-terpyridinyl[32] (**16**; R = R^1 = 2-pyridinyl; R^2 = H) in 60% overall yield. Its high-resolution mass spectrum showed a measured mass of 233.0976 (calcd mass 233.0951), verifying the assigned molecular formula. This represents a convenient and simple synthesis of this important terdentate ligand[33] which has been prepared previously in modest yields by a variety of methods.[32,34]

The presence of the 4-thiomethyl group in the pyridines described above imparts desirable solubilities to these compounds when compared to the solubilities of their parent compounds. The thiomethyl group is also attractive for elaboration to other functional groups, providing a convenient method for attachment of terpyridinyl to solid supports. We have found that the thiomethyl group was unreactive to a variety of nitrogen and carbon nucleophiles. Oxidation of the thiomethyl group to the corresponding methyl sulfone was necessary for displacement to occur. Treatment of a methylene chloride solution of **16** (R = R^1

(30) Castellano, S.; Günther, H.; Ebersole, S. *J. Phys. Chem.* **1965**, *69*, 4166. Spotswood, T. M.; Tanzer, C. I. *Aust. J. Chem.* **1967**, *20*, 1227. Goethals, C. A. *Recl. Trav. Chim. Pays-Bas* **1935**, *54*, 299.

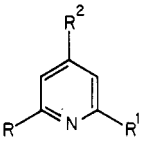
(31) For ^{13}C NMR data relative to this topic see: Marker, A.; Canty, A. J.; Brownlee, R. T. C. *Aust. J. Chem.* **1978**, *31*, 1255.

(32) Burstall, F. H. *J. Chem. Soc.* **1938**, 1662. Morgan, G. T.; Burstall, F. H. *Ibid.* **1937**, 1649.

(33) Derivatives of terpyridinyl have found many applications as ligands. For example, see: Wilkins, C. J.; Doublas, J. E. *Inorg. Chim. Acta* **1969**, *3*, 635. Deggan, E.; Kröhnke, F.; Schnalke, K. E.; Staundinger, H. J.; Weiss, W. *Z. Klin. Chem.* **1965**, *3*, 102. Stam, D.; Staundinger, H. J.; Weiss, W. *Ibid.* **1966**, *3*, 222.

(34) Kauffmann, T.; König, J.; Woltermann, A. *Chem. Ber.* **1976**, *109*, 3864, ref 4.

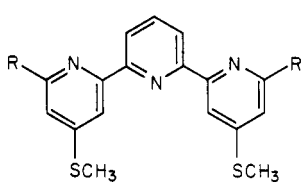
Table V. Some 2,6-Disubstituted Pyridines Derived from 2,6-Disubstituted 4-(Methylthio)pyridines



R, R^1	R^2	recryst solv	yield, %	mp, °C	mol formula[a]	IR, cm^{-1}	m/e of $M^{+\cdot}$ (rel intens)	λ_{max}, nm	log ϵ[b]
2-thienyl	SO_2CH_3	benzene/petroleum ether[c]	88	214-215	$C_{14}H_{11}NO_2S_3$	1315	321 (100)	262, 296, 350	1.28, 4.39, 4.12
2-furyl	SO_2CH_3	MeOH[e]	48	194.5-195	$C_{14}H_{11}NO_4S$	1318,[d] 1142	289 (100)	284, 350	4.50, 4.05
2-pyridyl	SO_2CH_3	EtOH[c]	79	213-215	$C_{16}H_{13}N_3O_2S$	1311,[d] 1143	311 (35)	232, 276, 312	4.29, 4.31, 4.05
2-thienyl	CN	EtOH[e]	62	162-163	$C_{14}H_8N_2S_2$	2240[f]	268 (100)	212, 262, 296, 358	4.23, 4.28, 4.36, 4.08
2-furyl	CN	EtOH[e]	61	134-136	$C_{14}H_8N_2O_2$	2220[f]	236 (100)	214, 284, 360	4.21, 4.52, 4.04
2-pyridyl	CN	EtOH[g]	70	168.5-169	$C_{16}H_{10}N_4$	2220[f]	258 (100)	276, 318	4.35, 4.04

[a] All compounds gave satisfactory analytical data (±0.4% for C, H, and N). [b] Methanol. [c] Colorless needles. [d] ν_{SO_2}. [e] Pale yellow needles. [f] ν_{CN}. [g] Pale yellow microprisms.

Table VI. Some Oligopyridines Derived from α-Oxoketene Dithioacetals



R	mp, °C	yield, %	mol formula[a]	m/e for $M^{+\cdot}$[g]	λ_{max} (log ϵ), nm
C_6H_5	210-212	55[b]	$C_{29}H_{23}N_3S_2$	477	316[c] (4.20), 258 (4.90)[d]
2-C_4H_3S	241-242	33[e]	$C_{25}H_{19}N_3S_4$	489	284 (4.65)[d]
2-C_5H_4N	265-266	53[f]	$C_{27}H_{21}N_5S_2$	479	275 (4.83)[d]

[a] All compounds gave satisfactory analytical data (±0.4% for C, H, and N). [b] Colorless prisms from DMF. [c] Shoulder. [d] CH_2Cl_2. [e] Colorless flakes from DMF–ethanol. [f] Colorless flakes from DMF. [g] The relative intensity was 100% in all cases.

= 2-pyridinyl; $R^2 = SCH_3$) with 2–3 equiv of *m*-chloroperbenzoic acid at room temperature cleanly oxidized the thiomethyl group to the methyl sulfone in 79% yield. Analytical and spectral data were consistent with the assigned structure, with $M^{+\cdot}$ at *m/e* 311 (35%) and ν_{SO_2} at 1311 and 1143 cm^{-1}. Confirmation that oxidation of the SCH_3 group had occurred was immediately clear from the ^1H NMR spectrum. A downfield shift of the methyl protons attached to sulfur to δ 3.23 from 2.63 and shifts of approximately the same magnitude and direction were observed for the protons of the pyridine ring to which the sulfur atom is attached. Similarly, the ^{13}C NMR chemical shift of the methyl group moved from 14 to 44 ppm. No evidence of any *N*-oxide formation was obtained, even when elevated temperatures were used.

This oxidation is a general reaction and occurred equally as readily with 2,6-bis(2-thienyl)-4-(methylthio)pyridine (16; R = R^1 = 2-thienyl, $R^2 = SCH_3$) and 2,6-bis(2-furyl)-4-(methylthio)pyridine (16; R = R^1 = 2-furyl, $R^2 = SCH_3$), giving the products described in Table V. Peracetic acid may also be used as the oxidizing agent and with 16 (R = R^1 = 2-thienyl; $R^2 = SCH_3$) gave the corresponding methyl sulfone in 93% yield. The reaction may also be controlled so that oxidation to the sulfoxide only occurs. Thus when 16 (R = R^1 = 2-thienyl; $R^2 = SCH_3$) was treated with 1 equiv of *m*-chloroperbenzoic acid in CH_2Cl_2, a 65% yield of the methyl sulfoxide was obtained. The spectral data shown in Table V are consistent with monooxidation occurring at the methylthio sulfur atom (see the paragraph at the end of the paper about supplementary material).

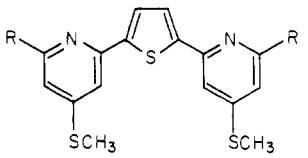
The methylsulfonyl group was readily displaced by cyanide ion on using potassium cyanide in DMF after 11–24 h at 100–110 °C. The corresponding carbonitriles are described in Table V, and their structures were established from their analytical and spectral data. Each IR spectrum showed ν_{CN} 2220–2240 cm^{-1} and the absence of the characteristic ν_{SO_2} absorption, and both ^1H and ^{13}C NMR spectra showed the absence of the SO_2CH_3 group and the latter the presence of the cyano group with a chemical shift between 116.6 and 117.6 ppm.

Nucleophilic displacement reactions with other carbon and nitrogen nucleophiles were unsuccessful. Pyrrolidine, morpholine, sodium amide, sodium azide, sodium thiocyanate, and sodium diethylmalonate in DMF failed to undergo reaction. At elevated temperatures either no reaction occurred or decomposition of the reagents predominated.

Preparation of Polyheteryl Systems. The reactions described above are also suitable for the synthesis of oligopyridines and related systems. Products of this type are described in Tables VI and VII, and the number of products possible results from the versatility of the α-oxoketene dithioacetal approach to pyridine ring formation. The following examples illustrate some of the possible combinations of reactants that yield oligopyridine systems.

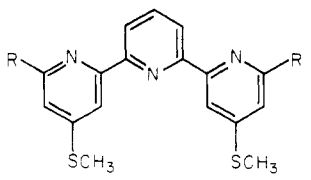
Reaction of 3,3-bis(methylthio)-1-phenyl-2-propen-1-one (12; R = C_6H_5) with 2,6-diacetylpyridine (1 equiv) and 4

Table VII. Some Polyheteryl Systems Derived from α-Oxoketene Dithioacetals



R	mp, °C	yield, %	mol formula[a]	m/e for M+·[g]	λmax (log ε), nm
2-C_4H_3S	196-197[b]	32	$C_{24}H_{18}N_2S_5$	494	376[c] (4.47), 362 (4.54), 288 (4.71)[d]
C_6H_5	166-167[e]	37	$C_{28}H_{22}N_2S_3$	482	368[c] (4.45), 354 (4.54), 254 (4.60), 202 (4.64)[d]
2-C_4H_3O	177-178.5[e]	34	$C_{24}H_{18}N_2O_2S_3$	462	373[c] (4.45), 359 (4.52), 284 (4.75), 226 (4.30)
2-C_5H_4N	223.5-224.5[f]	6	$C_{26}H_{20}N_4S_3$	484	367[c] (4.39), 3.54 (4.47), 282 (4.56), 253 (4.46), 239[c] (4.44)[d]

[a] All compounds gave satisfactory analytical data (±0.4% for C, H, and N). [b] Yellow microprisms from $CDCl_3$. [c] Shoulder. [d] CH_3CN. [e] Yellow prisms from CH_3CN. [f] Cream microprisms from DMF-ethanol. [g] The relative intensity was 100% in all cases.



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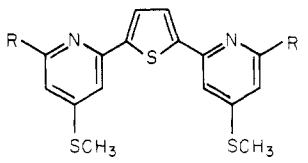

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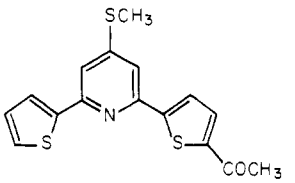


19

equiv of potassium *tert*-butoxide in THF, followed by the addition of ammonium acetate and glacial acetic acid, gave 2,6-bis[2-[4-(methylthio)-6-phenyl]pyridinyl]pyridine (**17**; R = C_6H_5) in 55% yield. Analytical and mass spectral data [M+· *m/e* 477 (100%)] established the molecular formula of this substituted terpyridinyl derivative, and its NMR spectrum indicated that the pyridine rings existed in a trans,trans arrangement (see the paragraph at the end of the paper about supplementary material). Protons at the 3′-position of the pyridine rings appeared as a doublet at δ 8.40 (J = 1.9 Hz), and those at the 5′-position were also observed as a doublet (J = 1.9 Hz) at δ 7.50. The methylthio protons occurred as a singlet at δ 2.67.

A quinquepyridine derivative may also be readily obtained by using this approach and varying the α-oxoketone dithioacetal. Two equivalents of 3,3-bis(methylthio)-1-(2-pyridinyl)-2-propen-1-one (**12**; R = 2-pyridinyl), 1 equiv of 2,6-diacetylpyridine, and 4 equiv of potassium *tert*-butoxide under the standard conditions described above gave the dipotassium salt of the intermediate bis-1,5-diketone. However, the corresponding bis-1,5-diketone could not be isolated in a pure state, black polymeric material being formed on acidification (dilute HCl or AcOH) of the dipotassium salt. Addition of ammonium acetate/hot glacial acetic acid to the potassium salt gave 2,6-bis[4-(methylthio)-6-(2′-pyridinyl)-2-pyridinyl]pyridine (**17**; R = 2-pyridinyl) in 53% yield. Analytical and high-resolution mass spectral data [measured mass 479.1245 (calcd mass 479.1235)] were consistent with this structure, and the NMR spectrum indicated a trans–trans arrangement for this quinquepyridine. Protons at the 3′- and 5′-positions appeared as two doublets at δ 8.45 and 8.30 ($J_{3',5'}$ = 1.9 Hz). These protons were no longer equivalent due to the dissimilar substituents at the 2′- and 6′-positions of the pyridine ring, and the conformation of **17** (R = 2-pyridinyl) is analogous to those observed above for the dipyridinyl and terpyridinyl derivatives.

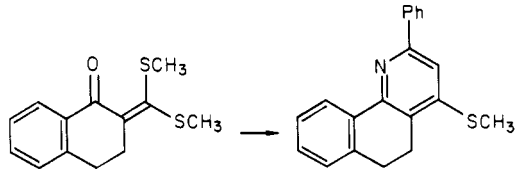
Other quinqueheteryl systems are readily available on using appropriate diacetyl-substituted heterocycles. Thus, reaction of 2,5-diacetylthiophene (**9**) with 3,3-bis(methylthio)-1-(2-thienyl)-2-propen-1-one (**12**; R = 2-thienyl) in the presence of 4 equiv of potassium *tert*-butoxide/THF, followed by ammonium acetate/hot glacial acetic acid treatment, gave 2,5-bis[4-(methylthio)-6-(2′-thienyl)-2-pyridinyl]thiophene (**18**; R = 2-thienyl) in 32% yield. Analytical and spectral data (Table VI) were consistent with this structure, and in this group of quinqueheteryl systems, the M+· was by far the most intense ion in their mass spectra. Ions were always observed resulting from loss of a methyl group [M+· − 15, (2–5%)] and loss of SCH_2 [M+· − 46, (2–13%)].

A byproduct isolated in the synthesis of **18** (R = 2-thienyl) was 2-(5-acetyl-2-thienyl)-4-(methylthio)-6-(2′-thienyl)pyridine (**19**), derived from reaction of **12** (R = 2-thienyl) with only one acetyl group of 2,5-diacetylthiophene (**9**). It was also obtained (9% yield) when equimolar quantities of the α-oxoketene dithioacetal and 2,5-diacetylthiophene were used. The structure of **19** was established from its analytical and spectral data, especially *m/e* 331 (M+·, 100%), ν_{CO} 1655 cm^{-1}, and δ_{COCH_3,SCH_3} 2.60 (6 H). TLC analysis and mass spectrometry showed that similar monoacetyl products were present in very small concentrations in all of the unpurified reaction products described in Table VI.

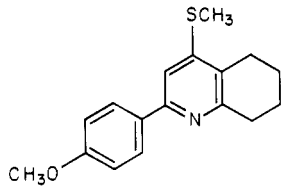
An alternative route to this type of quinqueheteryl system is illustrated by the reaction of 2,5-bis[3,3-bis(methylthio)-1-oxo-2-propenyl]thiophene (**10**) with a methyl ketone enolate and subsequent reaction with ammonium acetate/glacial acetic acid. The yield of **18** (R = C_6H_5) by this route was only 10%.

Preparation of Annulated Pyridines. This pyridine ring synthesis procedure is also an effective way for annulation of pyridine rings. Ketene dithioacetals may be readily prepared from annular ketones such as α-tetralone,[35] and on reaction with methyl ketone enolates and subsequent reaction of the intermediate 1,5-enedione with ammonium acetate/glacial acetic acid, the annulated pyridine was formed in moderate yields.

Reaction of 2-[bis(methylthio)methylene]-1-tetralone (**20**) with the potassium enolate of acetophenone, followed by closure of the intermediate enedione with ammonium acetate/glacial acetic acid, gave the benzo[*e*]dihydro-



20 21



22

quinoline derivative **21**. Its structure was readily apparent from the analytical and spectral data (Experimental Section). Similarly, reaction of **11** (R = 4-$CH_3OC_6H_4$) with the potassium enolate of cyclohexanone gave the 5,6,7,8-tetrahydroquinoline derivative **22** in modest yield.

Use of an aliphatic ketone such as acetone provided a simple route to 2-methylpyridine derivatives. For example, 3,3-bis(methylthio)-1-(methoxyphenyl)-2-propen-1-one (**12**; R = 4-$CH_3OC_6H_4$) with acetone under the above conditions gave 2-methyl-4-(methylthio)-6-(4-methoxyphenyl)pyridine **16** (R = H; R^1 = 4-$CH_3OC_6H_4$; R^2 = SCH_3) in 70% yield.

Experimental Section[35]

Preparation of α-Oxoketene Dithioacetals. The procedures below illustrate the two general methods used.

Method A. Formation of 3,3-Bis(methylthio)-1-(2-thienyl)-2-propen-1-one (12; R = 2-thienyl). An ice-chilled solution of 2-acetylthiophene (94.9 g, 0.78 mol) in dry toluene (1 L) was treated with sodium hydride (64.8 g of a 59% oil suspension, 1.56 mol). Carbon disulfide (89.6 g, 1.17 mol) and methyl iodide (334.0 g, 2.35 mol) were added cautiously to the cold solution, hydrogen being released during this reaction sequence. Dimethylacetamide (50 mL) was added dropwise (with continuous hydrogen evolution) while the mixture was kept below 45 °C. After the mixture was stirred for approximately 24 h at room temperature, a small amount of crushed ice was added to the heterogeneous solution to consume any unreacted NaH. (**Caution**: Unreacted NaH can react violently with H_2O, presenting a fire hazard.) Most of the toluene was removed under reduced pressure, and the residue was partitioned between water and chloroform. The organic layer was washed with water and dried (Na_2SO_4), and the solvent was removed. The oily residue was dissolved in hot ethanol from which yellow prisms separated on cooling: 118.4 g (68%); mp 95.5–97 °C; ^{13}C NMR ($CDCl_3$) 178.0, 165.6, 146.1, 131.7, 129.4, 127.7, 109.2, 17.1, 16.7 ppm (Table I).

Method B. Formation of 3,3-Bis(methylthio)-1-(2-pyridinyl)-2-propen-1-one (12; R = 2-pyridinyl). Dry Me_2SO (300 mL) was treated in small portions with NaH (41.3 g, 50% oil dispersion, 0.86 mol) at such a rate as to prevent frothing. The vigorously stirred solution was treated dropwise with 2-acetylpyridine (50.0 g, 0.41 mol) over 45 min, and carbon disulfide (32.7 g, 0.43 mol) was next added dropwise at such a rate that the reaction proceeded smoothly. This was followed by methyl iodide (122.1 g, 0.80 mol) in a similar fashion, and the dark green mixture was stirred at room temperature for 12–15 h after which the mixture was cautiously quenched with iced water (ca. 500 mL). The dark green solid was collected and washed with water and ice-cold ethanol until the washings were colorless. The dried, dark-colored product was dissolved in a small volume of $CHCl_3$, and this solution was then poured through a short column of TLC-grade silica, complete elution occurring with $CHCl_3$. Removal of the solvent left a green solid which crystallized from methanol as yellow needles: 65.0 g (71%); mp 108–109 °C (Table I).

2-Acetyl-5-bromothiophene. A solution of 2-bromothiophene (81.5 g, 0.5 mol) in acetic anhydride (102.0 g, 1.0 mol) was cooled in an ice bath, and perchloric acid (1.5 mL) was added. After being stirred 3 days at room temperature, the dark reaction mixture was neutralized with NaOH (approximately 375 mL, 4 N). The mixture was extracted twice with chloroform, and the combined extracts were washed three times with 10% potassium bicarbonate and once with water. After drying (Na_2SO_4) and removal of the solvent, the product was distilled [bp 105–110 °C (4 mm); lit.[36] bp 105 °C (0.5 mm)] to give a colorless liquid which solidified on cooling: 92.2 g (90%); mp 92.5–93.5 °C (from ethanol) (lit.[36] mp 94 °C); IR (KBr) ν_{CO} 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41 (d, 1 $J_{3,4}$ = 4.0 Hz, thiophene H_3), 7.08 (d, 1, $J_{3,4}$ = 4.0 Hz, thiophene H_4), 2.48 (s, 3, CH_3); ^{13}C NMR ($CDCl_3$) 189.3, 146.1, 132.5, 131.3, 122.6, 26.1 ppm; mass spectrum, *m/e* (relative intensity) 204 (58, M^+·).

2,5-Diacetylthiophene (9). *n*-Butyllithium (281 mL of a 1.6 M hexane solution, 0.45 mol) was added to a nitrogen-purged, dry ice–acetone-chilled (−10 °C) solution of thiophene (16.8 g, 0.20 mol) and TMEDA (52.3 g, 0.45 mol) in dry ether (350 mL). The ether was removed by distillation and replaced with dry hexane (300 mL). The solution was stirred under reflux (62 °C) for 1 h and cooled to 10 °C, and *N,N*-dimethylacetamide (55.0 g, 0.63 mol) was added, whereupon an exothermic reaction occurred. Stirring was continued under reflux for an additional 0.5 h, and after acidification of the reaction mixture at 0 °C with dilute HCl, the crude product was collected by filtering the cold two-phase solution. Recrystallization from ethyl acetate–petroleum ether gave colorless plates: 3.60 g (11%); mp 170–171 °C (lit.[24] mp 168–169, 172–173 °C); IR (KBr) ν_{CO} 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.78 (s, 2, thiophene H), 2.60 (s, 6, CH_3);^{13}C NMR ($CDCl_3$) 190.8, 149.2, 132.0, 27.1 ppm; mass spectrum, *m/e* (relative intensity) 168 (68, M^+·).

2,5-Bis[3,3-bis(methylthio)-1-oxo-2-propen-1-yl]thiophene (10). 2,5-Diacetylthiophene (**9**; 1.00 g, 0.006 mol) was dissolved in toluene (10 mL), and sodium hydride (1.00 g of a 57% oil suspension, 0.023 mol) was added while the solution was cooled in an ice bath. Carbon disulfide (7.20 g, 90.0 mmol) and methyl iodide (27.0 g, 0.018 mol) were added followed by *N,N*-dimethylacetamide (1.0 mL) which initiated hydrogen evolution. After the mixture was stirred for approximately 24 h at room temperature, a small amount of crushed ice was added to the heterogeneous solution to consume any unreacted NaH. Most of the toluene was removed under reduced pressure, and the residue was partitioned between water and chloroform. The organic layer was washed with water and dried (Na_2SO_4), and the solvent was removed. The oily residue was dissolved in hot ethanol, and the crude product separated from the cooled solution as yellow prisms. Removal of the monoacetyl byproduct was accomplished by using HPLC (silica gel, Prep 500) in which the crude product was dissolved in a minimum of methylene chloride, and the fractions were eluted with an ethyl acetate–hexane (50:50) solution. Crystallization from benzene gave yellow needles: 0.75 g (34%); mp 167–175 °C dec; IR (KBr) ν_{CO} 1592 cm^{-1}; UV (CH_3OH) λ_{max} 290 nm (log ε 4.31), 402 (4.69); ^1H NMR ($CDCl_3$) δ 7.62 (s, 2, thiophene H), 6.60 (s, 2 vinylic), 2.56 (s, 3, SCH_3), 2.51 (s, 3, SCH_3); mass spectrum, *m/e* (relative intensity) 376 (88, M^+·).

Anal. Calcd for $C_{14}H_{16}O_2S_5$: C, 44.65; H, 4.28. Found: C, 44.71; H, 4.32.

(35) Spectral characterizations were carried out on the following instrumentation: infrared spectra, Perkin-Elmer Model 727E or 457 or Nicolet 7000 Series FT infrared spectrophotometers; ultraviolet spectra, Varian-Cary 219 spectrophotometer; ^1H NMR spectra, Varian T-60, Varian EM-390, or Perkin-Elmer R600 spectrometer with Me_4Si as an internal standard; ^{13}C NMR spectra, Varian XL-100 or CFT-20 spectrometer at 25.2 MHz with Me_4Si as an internal standard; mass spectra, Varian Mat No. 311A (high resolution, resolution set to 10 000, 70-eV electron impact), Varian Mat 731 (field desorption), Du Pont 21-104 (low resolution), or Hitachi Perkin-Elmer RMU-6E (low resolution, utilizing the direct insertion probe technique) spectrometers. All melting points were determined in capillaries by using a Thomas-Hoover capillary melting point apparatus or a Mel-Temp apparatus and are uncorrected. Evaporations were carried out under reduced pressure by using a Büchi Rotovap apparatus. Microanalyses were by Galbraith Laboratories, Knoxville, TN, or Atlantic Microlab Inc., Atlanta, GA. Anhydrous solvents were prepared as follows: THF, stirred over LAH then distilled; hexane, stirred over a mixture of benzophenone and sodium then distilled; DMF, stored over 3-Å molecular sieves and decanted; toluene, benzene, and ether, stored over metallic sodium and decanted.

(36) Fenglas, C. *Bull. Soc. Chim. Fr.* **1963**, 2579.

2,6-Bis[3,3-bis(methylthio)-1-oxo-2-propen-1-yl]pyridine (8; R = H). 2,6-Diacetylpyridine (3.0 g, 0.018 mol) was dissolved in Me_2SO (100 mL), and sodium hydride (3.1 g of a 57% oil suspension, 0.074 mol) was added slowly while cooling. Carbon disulfide (4.3 g, 0.054 mol) was then added dropwise, followed by the slow addition of MeI (16.0 g, 0.107 mol) while keeping the temperature of the reaction mixture below 20 °C. The solution was stirred for 2 h at room temperature and ice (80 g) was then added. The dark precipitate was collected, washed with acetone and recrystallized from DMF giving brown prisms: 4.0 g (59%), mp 237–239 °C; IR (KBr) ν_{CO} 1605 cm^{-1}; UV (CH_3OH) λ_{max} 345 nm (log ϵ 4.35), 282 (3.91), 227 (3.97); ^1H NMR ($CDCl_3$) δ 8.92–8.60 (m, 3, aromatic), 7.10 (s, 2, vinylic), 2.83 (s, 12, SCH_3); mass spectrum, m/e (relative intensity) 371 (3, $M^+\cdot$).

Anal. Calcd for $C_{15}H_{17}NO_2S_4$: C, 48.52; H, 4.62; N, 3.77. Found: C, 48.84; H, 4.70; N, 3.81.

3,3-Bis(methylthio)-1-(6-acetyl-2-pyridinyl)-2-propen-1-one (7). 2,6-Diacetylpyridine (10.0 g, 0.06 mol) was added to a mixture of NaH (2.5 g, 0.062 mol, 50% oil dispersion) in Me_2SO (150 mL). After the initial reaction had subsided, carbon disulfide (4.7 g, 0.062 mol) was added dropwise followed by methyl iodide (8.8 g, 0.062 mol). After the ensuing reaction had subsided, another equivalent of NaH (2.5 g) and methyl iodide (8.8 g) were added. After the dark-colored reaction mixture was stirred at room temperature for 5 h, it was quenched with iced water, and the material that separated was collected and washed with water. It crystallized from methanol as brown prisms: 11.5 g (71%); mp 160–162 °C; IR (KBr) ν_{CO} 1705, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.40–7.90 (m, 3, aromatic), 7.70 (s, 1, vinylic), 2.80 (s, 3, CH_3), 2.67 (s, 3, SCH_3), 2.60 (s, 3, SCH_3); mass spectrum, m/e (relative intensity) 267 (5, $M^+\cdot$).

Anal. Calcd for $C_{12}H_{13}NO_2S_2$: C, 53.93; H, 4.90; N, 5.24. Found: C, 53.85; H, 4.93; N, 5.13.

2,6-Bis[3,3-bis(*n*-propylthio)-1-oxo-2-propen-1-yl]pyridine (8; R = CH_3). 2,6-Diacetylpyridine (10.0 g, 0.062 mol) was dissolved in dry Me_2SO (200 mL), the solution was cooled to 20 °C, and NaH (13.0 g of a 50% oil suspension, 0.271 mol) was added slowly to the cooled reaction mixture. Carbon disulfide (9.5 g, 0.125 mol) was then added dropwise followed by the slow addition of 1-bromopropane (30.75 g, 0.25 mol), keeping the reaction temperature below 20 °C. The solution was stirred for 12 h at room temperature. Iced water (500 mL) was added, and the dark precipitate was collected and washed with ethanol. Crystallization from methanol gave light yellow needles: 22.0 g (73%); mp 108–109 °C; IR (KBr) ν_{CO} 1610 cm^{-1}; UV (CH_3CN) λ_{max} 345 nm (log ϵ 4.36), 282 (4.02), 231 (4.0); NMR ($CDCl_3$) δ 8.34–7.86 (m, 3, aromatic), 7.66 (s, 2, vinylic), 3.13 (t, 8, SCH_2), 1.86 (m, 8, CH_2), 1.13 (t, 12, CH_3); mass spectrum, m/e (relative intensity) 483 (1.5, $M^+\cdot$).

Anal. Calcd for $C_{23}H_{33}NO_2S_4$: C, 57.13; H, 6.88; N, 2.90. Found: C, 57.01; H, 6.86; N, 2.72.

2-(Methylsulfinyl)-3-(methylthio)-1-(2-thienyl)-2-propen-1-one (2). A solution of 3,3-bis(methylthio)-1-(2-thienyl)-2-propen-1-one (1; 1.0 g, 0.044 mol) in methylene chloride (14 mL) was cooled in an ice bath, and *m*-chloroperbenzoic acid (1.0 g of 85% MCPBA, 0.05 mol) was added. The solution temperature was allowed to reach room temperature, and the reaction mixture was stirred for 4 h, diluted with chloroform, washed twice with 10% $NaHCO_3$ and once with H_2O, dried (Na_2SO_4), and concentrated. The residue crystallized as yellow prisms from ethanol/petroleum ether (bp 40–60 °C). Further purification was achieved by chromatography on silica gel with benzene to remove any unreacted starting material, followed by product elution with chloroform: 0.70 g (65%); mp 125–128 °C; IR(KBr) ν_{CO} 1610, ν_{SO} 1050 cm^{-1}; UV (CH_3OH) λ_{max} 282 nm (log ϵ 3.90) 338 (4.36); ^1H NMR ($CDCl_3$) δ 7.82 (q, 1, $J_{3',4'}$ = 3.0 Hz, $J_{3',5'}$ = 1.2 Hz, thiophene $H_{3'}$), 7.75 (q, 1, $J_{4',5'}$ = 8.8 Hz, thiophene $H_{5'}$), 7.25 (q, 1, thiophene $H_{4'}$), 6.75 (s, 1, vinylic), 3.00 (s, 3, $SOCH_3$), 2.52 (s, 3, SCH_3); ^{13}C NMR ($CDCl_3$) 180.0, 178.0, 144.1, 134.6, 132.3, 128.6, 114.0, 43.9, 15.7 ppm; mass spectrum, m/e (relative intensity) 246 (3, $M^+\cdot$).

Anal. Calcd for $C_9H_{10}O_2S_3$: C, 43.88; H, 4.09. Found: C, 43.93; H, 4.22.

3,3-Bis(methylsulfinyl)-1-(2-thienyl)-2-propen-1-one (3). A solution of 3,3-bis(methylthio)-1-(2-thienyl)-2-propen-1-one (1; 1.00 g, 0.044 mol) in methylene chloride (14 mL) was cooled in an ice bath and *m*-chloroperbenzoic acid (2.0 g of 85% MCPBA, 0.098 mol) was added, an exothermic reaction occurring. After several minutes the solution was allowed to reach room temperature and then stirred for 2 h. The mixture was diluted with chloroform, washed twice with 10% $NaHCO_3$ and water, and then dried over Na_2SO_4. The residue obtained by removal of the solvent was dissolved in benzene and adsorbed onto a silica gel column and the benzene effluent discarded. The product was eluted with chloroform, recrystallized from ethanol, and, after drying at room temperature under vacuum, afforded yellow prisms: 0.50 g (44%); mp 158 °C dec; IR (KBr) ν_{CO} 1625, ν_{SO} 1060, 1032 cm^{-1}; UV (CH_3OH) λ_{max} 322 nm (log ϵ 4.15); ^1H NMR ($CDCl_3$) δ 8.02 (dd, 1, thiophene $H_{3'}$), 7.90 (s, 1, vinylic), 7.82 (dd, 1, thiophene $H_{5'}$), 7.28 (dd, 1, $J_{3',4'}$ = 3.6 Hz, $J_{4',5'}$ = 4.8 Hz, thiophene $H_{4'}$), 3.21 (s, 3, CH_3), 3.18 (s, 3, CH_3); ^{13}C NMR ($CDCl_3$) 178.7, 175.1, 143.8, 137.2, 134.8, 129.1, 125.8, 42.6, 41.1 ppm; mass spectrum, m/e (relative intensity) 262 (5, $M^+\cdot$).

Anal. Calcd for $C_9H_{10}O_3S_3$: C, 41.20; H, 3.84. Found: C, 41.27; H, 3.92.

3,3-Bis(methylsulfonyl)-1-(2-thienyl)-2,3-epoxypropen-1-one (5). A solution of 3,3-bis(methylthio)-1-(2-thienyl)-2-propen-1-one (1; 12.0 g, 0.052 mol) in methylene chloride (200 mL) was cooled in an ice bath, and *m*-chloroperbenzoic acid (60.0 g of 85% MCPBA, 0.29 mol) was added. The solution was then allowed to warm to room temperature and stirred for 4.5 h. After the mixture was diluted with chloroform, washed with 10% $NaHCO_3$ solution (5 × 100 mL) and once with water, and dried with Na_2SO_4, the chloroform was removed in vacuo. Recrystallization of the residue from ethanol gave colorless needles, mp 139–140 °C dec. An analytical sample was obtained after an additional recrystallization from chloroform: 9.03 g (56%); mp 147–147.5 °C dec; IR (KBr) ν_{CO} 1667, ν_{SO_2} 1150, 1330 cm^{-1}; UV (CH_3OH) λ_{max} 269 nm (log ϵ 4.03), 295 (3.98); ^1H NMR ($CDCl_3$) δ 8.07 (dd, 1 $J_{3',5'}$ = 1.1 Hz, $J_{3',4'}$ = 3.9 Hz, thiophene $H_{3'}$), 7.84 (dd, 1, $J_{4',5'}$ = 5.1 Hz, thiophene $H_{5'}$), 7.21 (dd, 1, thiophene $H_{4'}$), 4.74 (s, 1, epoxide H), 3.38 (s, 3, CH_3), 3.30 (s, 3, CH_3); ^{13}C NMR ($CDCl_3$) 180.8, 140.3, 136.9, 135.8, 128.9, 80.5, 60.7, 42.5, 40.0 ppm; mass spectrum, m/e (relative intensity) 310 (23, $M^+\cdot$).

Anal. Calcd for $C_9H_{10}O_6S_3$: C, 34.83; H, 3.25. Found: C, 34.92; H, 2.99.

Preparation of 1,5-Disubstituted 1,5-Enediones 13a. The general procedure used is illustrated by the following preparations.

(A) 1,5-Bis(2-pyridinyl)-3-(methylthio)-2-pentene-1,5-dione (13a; R = R^1 = 2-pyridinyl). 3,3-Bis(methylthio)-1-(2-pyridinyl)-2-propen-1-one (12, R = 2-pyridinyl; 3.0 g, 0.013 mol) was added to a solution of 2-acetylpyridine (1.62 g, 0.013 mol) and potassium *tert*-butoxide (3.0 g, 0.027 mol) in dry THF (60 mL). The reaction mixture was stirred at room temperature for 3 h, and the precipitate was collected and added to glacial acetic acid (20 mL). Ice (50 g) was added, and the resultant dark precipitate was collected and recrystallized from petroleum ether (bp 80–100 °C) from which it separated as pale yellow prisms: 0.50 g (13%); mp 120–122 °C (Table III).

(B) 1,5-Bis(2-thienyl)-3-(methylthio)-2-pentene-1,5-dione (13a; R = R^1 = 2-thienyl). 3,3-Bis(methylthio)-1-(2-thienyl)-2-propen-1-one (12, R = 2-thienyl; 18.40 g, 0.08 mol) was added to an ice-cooled solution of 2-acetylthiophene (10.10 g, 0.08 mol) and potassium *tert*-butoxide (17.92 g, 0.16 mol) in dry THF (460 mL). The solution was stirred overnight at room temperature, and the maroon precipitate was collected and added to an ice-cold HCl solution (700 mL, 4% acid). The precipitate was collected and recrystallized from benzene from which it separated as pale yellow prisms: 19.7 g (80%); mp 161–162.5 °C (Table III).

Preparation of 2,6-Diaryl-4-(methylthio)pyridines 16. The following illustrate the general procedure used.

2,6-Diphenyl-4-(methylthio)pyridine (16; R = R^1 = C_6H_5, R^2 = SCH_3). Method A. 1,5-Diphenyl-3-(methylthio)-2-pentene-1,5-dione (13a, R = R^1 = C_6H_5; 0.25 g, 0.001 mol) was added to a solution of methanol (40 mL) and ammonium acetate (0.70 g, 0.009 mol). The solution was refluxed for 3 h, the solvent removed under reduced pressure, and the residue recrystallized from petroleum ether (bp 80–100 °C), from which it separated as colorless prisms: 0.18 g (75%); mp 105–107 °C (Table IV).

Method B. 3,3-Bis(methylthio)-1-phenyl-2-propen-1-one (12, R = C_6H_5; 2.0 g, 0.009 mol) was added to a solution of acetophenone (1.07 g, 0.009 mol) and potassium *tert*-butoxide (2.0 g, 0.018 mol) in dry THF (60 mL). The solution was stirred ov-

ernight at room temperature. Next, glacial acetic acid (60 mL) and ammonium acetate (7.0 g, 0.09 mol) was added to the above solution which was then refluxed for 2 h with constant removal of THF. The solution was then cooled to 20 °C, diluted with ice (30 g), and allowed to stand for 1 h. Water (60 mL) was added, and the precipitate was collected and recrystallized from petroleum ether (bp 80–100 °C), giving colorless prisms: 2.0 g (81%); mp 105–107 °C.

Preparation of 2,6-Diheteryl-4-(methylthio)pyridines 16. The following preparations illustrate the general procedures used.

2,6-Bis(2-pyridinyl)-4-(methylthio)pyridine (16; R = R¹ = 2-pyridinyl, R² = SCH₃). Method A. 1,5-Bis(2-pyridinyl)-3-(methylthio)-2-pentene-1,5-dione (**13a**, R = R¹ = 2-pyridinyl; 0.80 g, 0.003 mol) was added to a solution of glacial acetic acid (40 mL) containing ammonium acetate (2.0 g, 0.026 mol). The solution was refluxed for 2 h, allowed to cool to room temperature, and diluted with ice (20 g). The precipitate was collected and recrystallized from benzene–petroleum ether (bp 80–100 °C) from which it separated as colorless needles: 0.6 g (81%); mp 120–121 °C (Table IV); ^{13}C NMR ($CDCl_3$) 155.9, 154.8, 152.3, 149.0, 136.7, 123.8, 121.3, 116.9, 14.0 ppm.

Method B. 3,3-Bis(methylthio)-1-(2-pyridinyl)-2-propen-1-one (**12**, R = 2-pyridinyl; 3.0 g, 0.013 mol) was added to a solution of 2-acetylpyridine (1.62 g, 0.013 mol) and potassium *tert*-butoxide (3.0 g, 0.027 mol) in dry THF (80 mL). The solution was stirred for 3 h at room temperature. Glacial acetic acid (80 mL) and ammonium acetate (10.0 g, 0.13 mol) were added to the above solution which was then refluxed for 2 h with continuous removal of THF. The solution was cooled to 15 °C, diluted with ice (80 g), and allowed to stand for 3 h. Water (80 mL) was then added, and the precipitate was collected and recrystallized from petroleum ether (bp 80–100 °C) from which it separated as colorless needles: 2.0 g (55%); mp 120–121 °C.

2,2′:6′,2″-Terpyridinyl (16; R = R¹ = 2-pyridinyl, R² = H). 2,6-Bis(2-pyridinyl)-4-(methylthio)pyridine (**16**, R = R¹ = 2-pyridinyl, R² = SCH_3; 11.16 g, 0.04 mol) and Raney nickel (30 g, 0.51 mol) in absolute ethanol (250 mL) were heated under reflux for 6 h. The hot ethanolic solution was then filtered and the Raney nickel residue washed twice with hot ethanol. The combined solutions were then evaporated under reduced pressure, and the residue was recrystallized from petroleum ether (bp 80–100 °C) from which it separated as cream-colored prisms: 5.40 g (60%); mp 84–85 °C (lit.[32] mp 85–86 °C); NMR ($CDCl_3$) δ 8.75–7.13 (m, aromatic); mass spectrum, *m/e* (relative intensity) 233.2735 (100, $M^{+\cdot}$).

2,6-Bis(2-pyridinyl)-4-(methylsulfonyl)pyridine (16; R = R¹ = 2-pyridinyl, R² = SO_2CH_3). A solution of 2,6-bis(2-pyridinyl)-4-(methylthio)pyridine (**16**, R = R¹ = 2-pyridinyl, R² = SCH_3; 1.00 g, 0.004 mol) in methylene chloride (10 mL) was cooled in an ice bath, and *m*-chloroperbenzoic acid (1.60 g of 85% MCPBA, 0.008 mol) was added, whereupon heat was evolved. After being stirred at room temperature for 4 h, the heterogeneous mixture was diluted with chloroform, washed twice with 10% $NaHCO_3$ and once with water, and then dried (Na_2SO_4). After removal of the solvent, the residue was recrystallized from ethanol from which colorless needles separated: 0.88 g (79%); mp 213–215 °C (Table V).

2,6-Bis(2-thienyl)-4-(methylsulfonyl)pyridine (16; R = R¹ = 2-thienyl, R² = SO_2CH_3). A solution of 2,6-bis(2-thienyl)-4-(methylthio)pyridine (**16**, R = R¹ = 2-thienyl, R² = SCH_3; 5.78 g, 0.02 mol) in methylene chloride (60 mL) was cooled in an ice bath and *m*-chloroperbenzoic acid (8.12 g of 85% MCPBA, 0.04 mol) was added, whereupon heat was evolved. After being stirred at room temperature for 2 days, the heterogeneous mixture was diluted with chloroform, washed twice with 10% $NaHCO_3$ and once with H_2O, and then dried (Na_2SO_4). After treatment with decolorizing charcoal the solvent was removed, and the residue was recrystallized from benzene–petroleum ether, from which colorless needles separated: 5.63 g (88%); mp 214–215 °C (Table V).

2,6-Bis(2-thienyl)-4-pyridyl Methyl Sulfoxide (16; R = R¹ = 2-thienyl, R² = $SOCH_3$). A solution of 2,6-bis(2-thienyl)-4-(methylthio)pyridine (**16**, R = R¹ = 2-thienyl, R² = SCH_3; 1.00 g, 0.003 mol) in methylene chloride (14 mL) was cooled in an ice bath, and *m*-chloroperbenzoic acid (0.70 g of 85% MCPBA, 0.003 mol) was added. The solution was allowed to warm to room temperature over the next hour, diluted with chloroform, washed twice with 10% $NaHCO_3$ and once with H_2O, and dried (Na_2SO_4). Removal of the solvent followed by recrystallization of the residue from benzene gave colorless rectangular plates: 0.69 g (65%); mp 162–163 °C; IR(KBr) ν_{SO} 1063 cm^{-1}; UV (CH_3OH) λ_{max} 260 nm (log ε 4.30), 294 (4.38), 340 (4.11); ^{1}H NMR ($CDCl_3$) δ 7.74 (d, 2, $J_{3',4'}$ = 3.6 Hz, thiophene $H_{3'}$), 7.66 (s, 2, pyridine H), 7.48 (d, 2, $J_{4',5'}$ = 5.0 Hz, thiophene $H_{5'}$), 7.15 (dd, 2, thiophene $H_{4'}$) 2.82 (s, 3, $SOCH_3$); ^{13}C NMR ($CDCl_3$) 157.7, 153.2, 143.6, 129.0, 128.2, 126.0, 110.1 43.5 ppm; mass spectrum, *m/e* (relative intensity) 305 (90, $M^{+\cdot}$).

Anal. Calcd for $C_{14}H_{11}NOS_3$: C, 55.05; H, 3.63; N, 4.59. Found: C, 55.22; H, 3.60; N, 4.61.

2,6-Bis(2-pyridinyl)pyridine-4-carbonitrile (16; R = R¹ = 2-pyridinyl, R² = CN). A mixture of 2,6-bis(2-pyridinyl)-4-(methylsulfonyl)pyridine (**16**, R = R¹ = 2-pyridinyl, R² = SO_2CH_3; 1.0 g, 0.003 mol) and potassium cyanide (0.7 g, 0.011 mol) in dry DMF was heated to 110 °C for 14 h and then cooled to room temperature. The solution was diluted with water and extracted twice with chloroform. After the combined extracts were washed with water and dried (Na_2SO_4), the solvent was removed. The residue was recrystallized from ethanol, separating as pale yellow microprisms: 0.58 g (70%); mp 168.5–169 °C (Table V).

2,6-Bis[2-[4-(methylthio)-6-phenyl]pyridinyl]pyridine (17; R = C_6H_5). 3,3-Bis(methylthio)-1-phenyl-2-propen-1-one (**12**, R = C_6H_5; 3.0 g, 0.013 mol) was added to a solution of 2,6-diacetylpyridine (1.10 g, 0.007 mol) and potassium *tert*-butoxide (3.0 g, 0.027 mol) in dry THF (100 mL). The mixture was then stirred overnight at room temperature. Glacial acetic acid (80 mL) and ammonium acetate (9.80 g, 0.13 mol) were added to the above solution which was then refluxed for 2 h with constant removal of THF. The solution was cooled to 20 °C, diluted with ice (60 g), and allowed to stand for 3 h. Water (40 mL) was added and the precipitate collected. Recrystallization from DMF afforded colorless prisms: 1.60 g (55%); mp 210–212 °C (Table VI).

2,6-Bis[4-(methylthio)-6-(2-pyridinyl)-2-pyridinyl]pyridine (17; R = 2-pyridinyl). 3,3-Bis(methylthio)-1-(2-pyridinyl)-2-propen-1-one (**12**, R = 2-pyridinyl; 3.0 g, 0.013 mol) was added to a solution of 2,6-diacetylpyridine (1.09 g, 0.007 mol) and potassium *tert*-butoxide (3.0 g, 0.027 mol) in dry THF (100 mL). The solution was stirred overnight at room temperature. Glacial acetic acid (80 mL) and ammonium acetate (9.80 g, 0.13 mol) were added, and the mixture was refluxed for 2 h with continuous removal of THF. The solution was then cooled to 20 °C and diluted with ice (60 g), and after 3 h, water (40 mL) was added and the precipitate collected. Recrystallization from DMF afforded colorless flakes: 1.50 g (53%); mp 265–266 °C (Table VI).

2,5-Bis[4-(methylthio)-6-(2-thienyl)-2-pyridinyl]thiophene (18; R = 2-thienyl). Potassium *tert*-butoxide (2.24 g, 0.020 mol) was added to an ice-cold solution of 2,5-diacetylthiophene (**9**; 0.84 g, 0.005 mol) in dry THF (60 mL) followed by 3,3-bis(methylthio)-1-(2-thienyl)-2-propen-1-one (**1**; 2.30 g, 0.01 mol). After stirring for 6 days at room temperature, the reaction solution was acidified with glacial acetic acid (60 mL) with ice-bath cooling, and ammonium acetate (2.0 g, 0.03 mol) was then added. The THF was removed by distillation and the solution heated at reflux for 1 day. The crude product separated after cooling and addition of water (50 mL) and was purified by column chromatography (silica gel, benzene), followed by recrystallization from chloroform, giving yellow microprisms: 0.80 g (32%); mp 196–197 °C (Table VII).

2-(5-Acetyl-2-thienyl)-4-(methylthio)-6-(2-thienyl)pyridine (19). After elution of the 2,5-bis[4-(methylthio)-6-(2-thienyl)-2-pyridinyl]thiophene (**18**; R = 2-thienyl) above from the silica gel column with benzene, the title compound was eluted with methylene chloride. The solvent was removed, and the product was recrystallized from carbon tetrachloride, separating as cream-colored microprisms: 0.15 g (9%); mp 134–135 °C; IR(KBr) ν_{CO} 1655 cm^{-1}; UV (CH_3OH) λ_{max} 294 nm (log ε 4.99), 3.47 (4.67); ^{1}H NMR ($CDCl_3$) δ 7.10–7.70 (m, 7, aromatic), 2.60 (s, 3, SCH_3), 2.60 (s, 3, $COCH_3$); mass spectrum, *m/e* (relative intensity) 331 (100, $M^{+\cdot}$).

Anal. Calcd for $C_{16}H_{13}NOS_3$: C, 57.97; H, 3.95; N, 4.23. Found: C, 57.97; H, 3.98; N, 4.19.

Reaction of 3,3-Bis(methylthio)-1-(4-methoxyphenyl)-2-propen-1-one and 4-Methoxyacetophenone in the Presence

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]

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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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