Synthesis of Unsymmetrical Arylthiophenes and Bithienyls *via* Oxidative Cyclization of 1,3-Butadiene-1-thiols [1]

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Received July 13, 1987

Dedicated to Professor Norman H. Cromwell

Oxidative cyclization of 2-mercapto-5-aryl-2,4-pentadienoic acids with iodine produced the respective 5-aryl-2-thenoic acids. The method was also suitable for the synthesis of unsymmetrical substituted 2,2′-bithienyls, and 2,3′-bithienyls. The synthesis of 5-carboxy-2′-bromo-5′-phenyl-2,3′-bithienyl from benzalacetone demonstrated that oxidative cyclization of 1,3-butadiene-1-thiols is a useful procedure for preparing 5′-aryl-2,3′-bithienyls from simple carbonyl compounds. Preferential ring bromination of 2-phenyl-4-methylthiophene with *N*-bromosuccinimide and a radical catalyst was also observed.

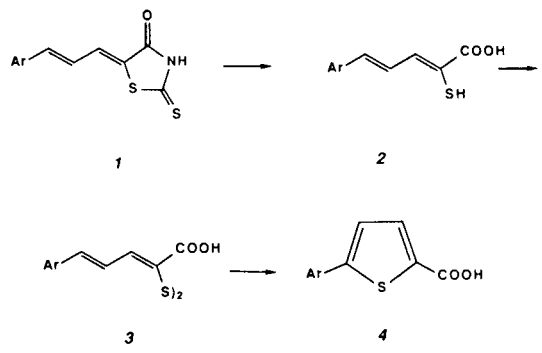
J. Heterocyclic Chem., **25**, 367 (1988).

With the isolation and indentification of α-terthienyl as the active nematocidal principle of *Tagetes erecta L* [2], a systematic study of thiophenes was conducted which revealed that the bithienyl nucleus was requisite for significant nematocidal activity [3]. Intensive investigations concerning the variety of plant species containing naturally occurring thiophene compounds [4] and the potential nemotocidal activity of bithienyls point to the need for a general synthetic route to unsymmetrical bithienyls.

Of the commonly employed routes to bithienyls, the Ullmann biaryl synthesis has been most widely used. Its limitations were noted by observation that, "out of a total of 202 examples of preparations of unsymmetrical biaryls, 74 were obtained in yields of 30% or greater, which may arbitrarily be considered as exceptionally good" [5]. Other methods of preparing polythienyl derivatives are the Hinsberg condensation [6] (requiring a 1,2-dicarbonyl system), coupling Grignard reagents (to produce a symmetrical bithienyl) [7], a Grignard route to unsymmetrical bithienyl derivatives [8], and the low-yielding synthesis of thiophene ring systems by ring-closure of hydrocarbon chains with a sulfur source [7].

Oxidative cyclization of 1,3-butadiene-1-thiols offers a convenient synthetic route to specific unsymmetically substituted thiophenes. The general synthetic utility of this reaction has been reviewed [9], and the mechanism discussed [10]. The original report [11] described the synthesis of a biaryl derivative, 5-phenylthiophene-2-carboxylic acid, *via* the path outlined in Scheme 1. Cinnamylidenerhodanine (**1**, Ar = C_6H_5) was hydrolyzed to 5-phenyl-2-mercapto-2,4-pentadienoic acid (**2**, Ar = C_6H_5), then oxidized to the disulfide (**3**, Ar = C_6H_5) and finally cyclized by exposure to iodine for 24 hours to give **4** (Ar = C_6H_5) in 68% yield from **3**. This sequence (**1** → **4**) could lead to a variety of unsymmetrically substituted 5-arylthiophene-2-carboxylic acids **4**. For example, Dodson [12] prepared 5-carboxy-2,2′-bithienyl (**4c**) and 5-carboxy-2,3′-bithienyl (**4**, Ar = 3-C_4H_3S) by this method.

Scheme 1



Ar = a) p-ClC_6H_4, b) p-$CH_3OC_6H_4$, c) 2-C_4H_3S,
d) 2-Cl-3-C_4H_2S, e) 2,5-diCl-3-C_4HS, f) 2-C_4H_3O

We wish to report here an investigation of the general utility of this synthesis. The intermediates, 2-chloro-3-thenaldehyde, 2,5-dichloro-3-thenaldehyde and 2-bromo-5-phenyl-3-thenaldehyde were prepared from the corresponding *methyl* precursors by the Sommelet reaction on the bromomethyl derivatives [13]. Initial efforts to prepare the required 3-arylacrolein derivatives *via* the Aldol condensation gave relatively low yields, so they were prepared by selective reduction of the appropriate 3-arylacrylic acid chlorides with lithium tri-*t*-butoxyaluminohydride [14]. This sequence involved condensation of the appropriate heterocyclic aldehyde with malonic acid, conversion to the acid chloride, reduction to the unsaturated aldehyde and condensation with rhodanine to give compounds **1**. It was not necessary to use highly purified intermediates at any step, since the rhodanine derivatives are generally high-melting easily crystallized products. No effort was made to

maximize yields in any of the sequences described in the experimental.

The unsaturated aldehydes prepared by this scheme apparently possess *trans* double bonds, as evidenced by infrared and nuclear magnetic resonance spectra. For example, the ir spectrum of 3-(2-chloro-3-thienyl)acrolein had an absorption at 967 cm^{-1}, indicative of a *trans*-substituted double bond. The mmr spectrum exhibited a doublet for one proton at δ 9.68, J = 8 Hz, for the aldehyde proton, a doublet (1H, δ 7.49) with J = 16 Hz for the proton on carbon 3, and a doublet of doublets (1H, δ 6.50) J = 16 Hz and J = 8 Hz for the proton on carbon 2. Spin-spin coupling constants for *trans* ethylene derivatives range from 11 to 18 Hz [15].

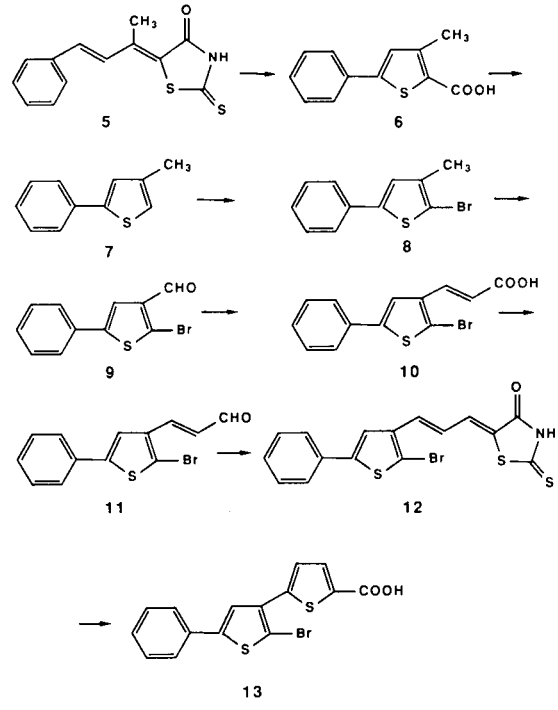
The rhodanine adducts, **1**, of the various 3-arylacroleins **a-f**, were prepared by known methods [16] in high yield. However, 5-(1-methylcinnamylidene)rhodanine (**5**), Scheme 2, synthesized from benzalacetone, exhibited a broad melting range after recrystallization, and thin layer chromatography revealed two components. By column chromatography one pure compound and a second less pure product were isolated. The mixture and the separated compounds had the same infra-red spectra, except for the fingerprint region, and both the mixture and the pure compound gave correct chemical analysis for **5**. We believe that two geometrical isomers of adduct **5**, with alternate steric structures at the ylidene bond, were produced in the reaction, and one pure isomer separated. Although we have not found reports of geometric isomers of rhodanine adducts, Nishio and Ito [17] have isolated geometric isomers of the hydrolysis products of several rhodanine derivatives.

Alkaline hydrolysis of the rhodanine adducts, **1**, gave the 5-aryl-2-mercapto-2,4-pentadienoic acid derivatives, **2**. It was necessary to use mild conditions to prevent further hydrolysis of the mercapto acids *via* the thiones [18]. Yields in this hydrolysis varied from 36% for the *p*-anisyl derivative **2b**, to 96% for the 2-chloro-3-thienyl derivative, **2d**. Although the earlier report [11] indicated that ring-closure occurred *via* the disulfide intermediates, **3**, it was possible to accomplish the reaction directly on **2**, using two equivalents of iodine, which serves both as an oxidizing agent and as a cyclizing reagent. However, we did prepare and isolate the disulfides, **3a** and **3b**, for comparative purposes.

The 5-aryl-2-thenoic acids, **4a-e**, were prepared by ring-closure of the mercapto-acids **2** or the disulfides **3** with iodine. Experimental conditions of 20°-70° for six to seventy-two hours in dioxane or 1,2-dimethoxyethane seemed most desirable, as lower yields were obtained in shorter times at higher temperatures [19]. For example, treatment of the alkaline hydrolysate of **5** (Scheme 2) with iodine in dimethoxyethane at room temperature for 48 hours gave a 35% yield of **6**, but a similar mixture let stand for 10 days at room temperature gave a 53% yield of **6**. We were unable to prepare either the bis-disulfide **3f** or 5-(2-furyl)-2-thenoic acid (**4f**) by iodine oxidation, although the corresponding mercapto acid **2f** was obtained in adequate yield. All attempts to conduct these oxidations led to tars. 5-*p*-Methoxyphenyl-2-thenoic acid (**4b**) was converted to 5-*p*-hydroxyphenyl-2-thenoic acid by ether cleavage with aluminum chloride in good yield.

As an example of an unsymmetrial teraryl compound, we synthesized 5-carboxy-2'-bromo-5'-phenyl-2,3'-bithienyl (**13**, Scheme 2), in which each ring of the bithienyl was synthesized independently. Condensation of benzalacetone with rhodanine gave a mixture of isomers of **5** (see above). This mixture was hydrolyzed and the crude hydrolysate cyclized with iodine to give 5-phenyl-3-methyl-2-thenoic acid (**6**) in satisfactory yield. Compound **6** was readily decarboxylated with copper and quinoline [18] to give 2-phenyl-4-methylthiophene (**7**).

Scheme 2



Bromination of **7** with *N*-bromosuccinimide (NBS), using either benzoyl peroxide or 2,2'-azobisisobutyronitrile as catalyst led to the formation of 2-bromo-3-methyl-5-phenylthiophene (**8**) in fairly high yield. Nuclear bromination under side-chain brominating conditions has been reported previously. Gronowitz [20] reported that bromination of 3-phenylthiophene gave exclusively 2-bromo-3-phenylthiophene with NBS and benzoyl peroxide. We have noted that bromination of 5-hydroxy-3-methylbenzo[**b**]thiophene with NBS led to formation of 4-bromo-5-

hydroxy-3-methylbenzo[*b*]thiophene; however, conversion to the benzoyl or *p*-nitrobenzoyl ester allowed bromination of the methyl side chain [21].

The structural relationship of compounds **6**, **8** and **8** was clearly established by two simple conversions. Carbonation of the Grignard of **8** gave **6** in good yield. Treatment of **8** with lithium aluminum hydride removed the bromine to give **7**. The bromination of **7** with NBS also produced a small amount of 2-bromo-3-bromomethyl-5-phenylthiophene, as shown by isolation of crude hexamethylene tetramine salt, converted to the aldehyde **9** in 2.6%, based on the amount of **7** brominated. Compound **8** was then treated with an equivalent of NBS, and the crude bromomethyl derivative converted directly to the hexamethylene tetramine salt. The crude chloroform-insoluble hexamine salt was collected and hydrolyzed to produce the aldehyde **9** in 30% yield.

Aldehyde **9** was condensed with malonic acid to give the acid 10 in 66% yield, and the crude acid chloride of **10** reduced to produce the aldehyde **11** in 69% yield. The *trans*-nature of the double bond in **11** was clearly established by both infra-red and nuclear magnetic resonance spectra (see experimental). Condensation of **11** with rhodanine gave **12** in excellent yield (89%). Hydrolysis of **12** in dilute alkali produced the mercapto-acid, which was not characterized as it appeared to undergo decomposition easily. The crude mercapto-acid was therefore cyclized with iodine to produce 5-carboxy-2'-bromo-5'-phenyl-2,3'-bithienyl (**13**) in 26% yield from **12**.

As pointed out earlier, no effort has been made to maximize yields in this sequence, **5** → → **13**. Undoubtedly the use of alternative synthetic methods on some of the low-yield steps, and more careful work, particularly on the last step, **12** → **13**, would improve the overall yield. However, the conversion of **5** to **13** does demonstrate that the cyclization of 1,3-butadiene-1-thiols is a practical method for synthesizing unsymmetrical bithienyl derivatives, and teraryl compounds.

EXPERIMENTAL

Melting points were determined in open capillary tubes in a Mel-Temp heated block apparatus and are corrected. A Perkin-Elmer Model 137 Infracord Spectrophotometer was employed to record all infrared spectra in range 4000 to 667 cm^{-1}. All solids were measured in potassium bromide mulls, and all liquids were measured as liquid films unless otherwise indicated. The nuclear magnetic resonance spectra were obtained with a Varian Associates Model A 60 NMR Spectrometer. All spectra employed tetramethylsilane as internal reference standard. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Indiana.

5-(*p*-Chlorocinnamylidene)rhodanine (**1a**).

A mixture of 21.8 g (0.163 mole) of rhodanine, 40.3 g (0.489 mole) of sodium acetate and 27.2 g (0.163 mole) of *p*-chlorocinnamaldehyde [22] dissolved in 200 ml of glacial acetic acid was refluxed for 0.5 hour, then poured onto 800 g of ice. The orange solid was collected and recrystallized from toluene to give 29.8 g (65%) of **1a**, melting at 249-251°.

Anal. Calcd. for $C_{12}H_8ClNOS_2$: C, 51.15; H, 2.86. Found: C, 51.15; H, 2.76.

5-(*p*-Methoxycinnamylidene)rhodanine (**1b**).

This compound was prepared as previously reported [23] in 82% yield, melting at 235-237° (literature [23] mp 234-236°).

5-[3-(2-Thienyl)acrylidene]rhodanine (**1c**).

Following the procedure of Keskin, Miller and Nord [24], 2-thenaldehyde, prepared by the method of Campaigne and Archer [25] was condensed with acetaldehyde in aqueous alkali, to produce 3-(2-thienyl)-acrolein in low yield, bp 85-88°/1 mm; ir (liquid film): 1675 (C=O) and 1610 cm^{-1} (C=C); nmr (carbon tetrachloride): δ 9.57 (1H, doublet, J = 8 Hz), 7.1 (multiplet, 3H) and 6.13 (2H, dd, J = 8 Hz).

A hot solution of 19.3 g (0.145 mole) of rhodanine and 35.6 g (0.435 mole) of anhydrous sodium acetate in 300 ml of glacial acetic acid was mixed with 19.57 g (0.142 mole) of 3-(2-thienyl)acrolein, and the solution gently refluxed for 0.5 hour. The hot slurry was then poured into 500 ml of ice water to give 32.83 g (90%) of red crystals, melting at 199-208°. Three recrystallizations from toluene gave **1c**, melting at 218-220°; ir (potassium bromide): 1695, 1681, 1575, 987 cm^{-1}.

Anal. Calcd. for $C_{10}H_7NOS_3$: C, 47.40; H, 2.79. Found: C, 47.66; H, 2.90.

3-(2-Chloro-3-thienyl)acrylic Acid.

A solution of 19.05 g (0.130 mole) of 2-chloro-3-thenaldehyde [26], 25.8 g (0.248 mole) of malonic acid and 1.0 ml of piperidine in 100 ml of pyridine was heated for 3 hours at 110°, cooled and poured into 1 l of cold 10% hydrochloric acid. The precipitate was collected, washed with cold water, dried and recrystallized from ethyl acetate to give 20.7 g (84%) of white crystals of 3-(2-chloro-3-thienyl)acrylic acid, melting at 213-215°: ir (potassium bromide): 2940-2440 (acid OH), 1670 (C=O), 1613 (C=C) and 974 cm^{-1} (*trans* CH=CH). (Caution: nasal irritant).

Anal. Calcd. for $C_7H_5ClO_2S$: C, 44.57; H, 2.67. Found: C, 44.78; H, 2.62.

3-(2-Chloro-3-thienyl)acrolein.

A mixture of 25 g (0.132 mole) of 3-(2-chloro-3-thienyl)acrylic acid and 31.4 g (0.264 mole) of redistilled thionyl chloride in 100 ml of dry benzene was refluxed for 2 hours, then distilled to dryness under reduced pressure. After distilling a second added portion of 20 ml of dry benzene from the residue, 250 ml of diglyme (dried and distilled from lithium aluminium hydride) was added to the crude acid chloride, and the solution cooled in a Dry Ice/methanol bath. A solution of 33.4 g (0.132 mole) of lithium tri-*t*-butoxyaluminohydride (Alfa Inorganics, Inc.) was added dropwise with stirring over a period of 1 hour. The solution was warmed to room temperature, 10 ml of saturated sodium sulfate solution added, and the resulting mixture stirred for 2 hours and filtered. The filtrate was concentrated under reduced pressure, and the residue taken up in ether, washed with sodium bicarbonate solution, then brine, and dried (sodium sulfate). Evaporation of the ether gave orange crystals (13.5 g, 59%) of 3-(2-chloro-3-thienyl)acrolein, melting at 78-81°. Twice recrystallized from cyclohexane, it melted at 85-86°; ir: 2710, 1665, 1615 and 967 cm^{-1}; nmr (deuteriochloroform): δ 9.68 (1H, d, J = 8 Hz), 7.49 (1H, d, J = 16 Hz), 7.16 (2H, broad s) and 6.50 (1H, dd, J = 16 Hz and J = 8 Hz).

Anal. Calcd. for C_7H_5ClOS: C, 48.70; H, 2.92; S, 18.57. Found: C, 48.69; H, 2.98; S, 18.36.

5-[3-(2-Chloro-3-thienyl)acrylidenc]rhodanine (**1d**).

A solution of 1.90 g (14.2 mmoles) of rhodanine and 3.52 g (43 mmoles) of anhydrous sodium sulfate in 100 ml of glacial acetic acid was heated and 2.46 g (14.2 mmoles) of 3-(2-chloro-3-thienyl)acrolein rapidly added. The solution was refluxed for 0.5 hour, during which an orange solid separated. The mixture was poured into 200 ml of ice water, and 3.62 g (89%) of **1d** was collected, melting at 225-228°. Two recrystallizations from methanol gave yellow crystals, melting at 234-235.5°; ir: 1695, 1580, 961 cm^{-1}.

Anal. Calcd. for $C_{10}H_6ClNOS_3$: C, 41.81; H, 2.11; S, 33.48. Found: C, 41.77; H, 1.95; S, 33.43.

3-(2,5-Dichloro-3-thienyl)acrylic Acid.

A solution of 23.6 g (0.13 mole) of 2,5-dichloro-3-thenaldehyde [26] in 100 ml of pyridine and 10 ml of piperidine was treated with 25.7 g (0.247 mole) of malonic acid. The solution was heated on a steam bath for 6 hours, cooled and stirred into 500 ml of 10% hydrochloric acid. The precipitate was collected, dried and recrystallized once from benzene to yield 23.3 g (80%) of white crystals of 3-(2,5-dichloro-3-thienyl)acrylic acid melting at 192-194°; ir: 2860-2500 (acid OH), 1665 (C=O) and 1620 cm^{-1} (C=C).

Anal. Calcd. for $C_7H_4Cl_2O_2S$: C, 37.68; H, 1.81; S, 14.37. Found: C, 37.91; H, 1.95; S, 14.12.

3-(2,5-Dichloro-3-thienyl)acrolein.

Following the procedure described above for 3-(2-chloro-3-thienyl)-acrolein, 4.46 g (0.02 mole) of 3-(2,5-dichloro-3-thienyl)acrylic acid was converted to the acid chloride with excess thionyl chloride, and then reduced with lithium tri-*t*-butoxyaluminohydride to give 1.89 g (46%) of white crystals of 3-(2,5-dichloro-3-thienyl)acrolein, melting at 81-82° after recrystallizing twice from heptane; ir: 1665 (C=O), 1615 (C=C) and 963 cm^{-1} (*trans* CH=CH); nmr (deuteriochloroform): δ 9.66 (1H, d, J = 8 Hz), 7.40 (1H, d, J = 16 Hz), 7.01 (1H, s) and 6.42 (1H, dd, J = 16 Hz and J = 8 Hz).

Anal. Calcd. for $C_7H_4Cl_2OS$: C, 40.58; H, 1.93; S, 15.46. Found: C, 40.48; H, 1.99; S, 15.34.

A 2,4-dinitrophenylhydrazone of this aldehyde was prepared and recrystallized from ethyl acetate to melt at 245-246°.

Anal. Calcd. for $C_{13}H_8Cl_2N_4O_4S$: N, 14.47. Found: N, 14.22.

5-[3-(2,5-Dichloro-3-thienyl)acrylidene]rhodanine (**1e**).

As described for **1d**, 0.80 g (3.86 mmoles) of 3-(2,5-dichloro-3-thienyl)-acrolein was condensed with 0.51 g (3.86 mmoles) of rhodanine, to give 0.53 g (43%) of **1e** melting at 233-234.5°.

Anal. Calcd. for $C_{10}H_5Cl_2NOS_3$: C, 37.27; H, 1.56; S, 29.85. Found: C, 37.19; H, 1.79; S, 29.51.

5-[3-(2-Furyl)acrylidene]rhodanine (**1f**).

Compound **1f** was prepared in 77% yield, following the method of Brown [16], as dark red crystals from toluene melting at 248-249° (literature [16] 251°).

2-Mercapto-5-(*p*-chlorophenyl)-2,4-pentadienoic Acid (**2a**).

A solution of 5.0 g (17.8 mmoles) of **1a** in 50 ml of 5% sodium hydroxide was heated for 0.5 hour at 80° [27]. The red solution was filtered through a charcoal pad, cooled to 1°, and 200 ml of 10% ice-cold hydrochloric acid added. The precipitate of **2a** (3.03 g, 71%) was collected and recrystallized from benzene to melt at 188-189°.

Anal. Calcd. for $C_{11}H_9ClO_2S$: C, 54.89; H, 3.77. Found: C, 54.99; H, 3.91.

2-Mercapto-5-(*p*-methoxyphenyl)-2,4-pentadienoic Acid (**2b**).

Following the procedure for **2a**, above, 2.77 g (10 mmoles) of **1b** was hydrolyzed and worked up to give 0.85 g (36%) of orange crystals from acetone-benzene, melting at 169-170°; ir: 3333-2500 (OH, broad), 1665 (C=O), 1600, 1570, 1550 and 958 cm^{-1}.

Anal. Calcd. for $C_{12}H_{12}O_3S$: C, 60.99; H, 5.08. Found: C, 60.84; H, 5.13.

2-Mercapto-5-(2-thienyl)-2,4-pentadienoic Acid (**2c**).

Following the procedure for **2a**, 2.53 g (10 mmoles) of **1c** was hydrolyzed to give 1.95 g (92%) of yellow solid melting at 151-155°. Two recrystallizations from toluene-cyclohexane gave yellow needles melting at 159-161°; ir: 2700 (OH), 1660 (C=O), 1590 (C=C) and 943 cm^{-1} (*trans* CH=CH).

Anal. Calcd. for $C_9H_8O_2S_2$: C, 50.94; H, 3.77; S, 30.19. Found: C, 51.20; H, 3.78; S, 29.96.

2-Mercapto-5-(2-chloro-3-thienyl)-2,4-pentadienoic Acid (**2d**).

As above, 1.81 g (6.3 mmoles) of **1d** was hydrolyzed in 5% sodium hydroxide on a steam bath for 1 hour (first trace of hydrogen sulfide, see note A). Work up gave 1.50 g (97%) of a yellow solid melting at 148-150°; ir: 2665, 1665, 1605 and 959 cm^{-1}.

Anal. Calcd. for $C_9H_7ClO_2S_2$: C, 43.81; H, 2.84; S, 25.96. Found: C, 44.08; H, 2.89; S, 25.76.

2-Mercapto-5-(2-furyl)-2,4-pentadienoic Acid (**2f**).

As above, 20 g (0.084 mole) of **1f** was hydrolyzed for 0.5 hour. Work up gave 9.19 g (56%) of yellow solid, recrystallized from benzene to melt at 141-142°; ir: 2860-2500 (OH), 1650 (C=O), 1605, 1575 (C=C) and 954 cm^{-1}.

Anal. Calcd. for $C_9H_8O_3S$: C, 55.10; H, 4.08; S, 16.32. Found: C, 55.39; H, 4.05; S, 16.04.

2,2'-Dithiobis[5-(*p*-chlorophenyl)-2,4-pentadienoic Acid] (**3a**).

As above, 10 g (35.6 mmoles) of **1a** was hydrolyzed for 0.5 hour in 10% sodium hydroxide, poured into cold hydrochloric acid, and the yellow acid collected and dried. The crude product was dissolved in 50 ml of pyridine, cooled to 3°, and 4.03 ml (35.6 mmoles) of 30% hydrogen peroxide slowly added with stirring. After standing 5 hours, the solution was poured into 300 ml of 10% hydrohloric acid. The resulting yellow solid was collected, washed and dried to give 2.15 g (25%) of **3a**, melting at 216-217° after two recrystallizations from dioxane-hexane.

Anal. Calcd. for $C_{22}H_{16}Cl_2O_4S_2$: C, 55.11; H, 3.34; S, 13.41. Found: C, 54.84; H, 3.50; S, 13.21.

2,2'-Dithiobis[5-(*p*-methoxyphenyl)-2,4-pentadienoic Acid] (**3b**).

A solution of 2.0 g (8.46 mmoles) of **2b** in 100 ml of dioxane and 50 ml of ethanol was cooled to 5°, and 2.14 g (8.46 mmoles) of iodine in 50 ml of absolute ethanol added dropwise with stirring. The cold solution was then stirred for 2 hours, and poured into 800 ml of ice water containing 5 g of sodium bisulfite. The precipitrate was collected, dried, and recrystallized twice from ethanol to give 0.86 g (43%) of orange crystals melting at 190-192°.

Anal. Calcd. for $C_{24}H_{22}O_6S_2$: C, 61.25; H, 4.71; S, 13.61. Found: C, 61.47; H, 4.87; S, 13.37.

5-*p*-Chlorophenyl-2-thenoic Acid (**4a**).

A suspension of 1.17 g (2.4 mmoles) of **3a** in 200 ml of dioxane and 0.632 g (2.4 mmoles) of iodine was stirred and heated to 80° for 24 hours. The cooled solution was poured into 800 ml of water containing 10 ml of saturated sodium bisulfite solution. The grey precipitate was collected and recrystallized from acetic acid to give 0.93 g (80%) of **4a** as a light yellow powder, melting at 257.5-258.5° (literature [28] 254°).

Anal. Calcd. for $C_{11}H_7ClO_2S$: C, 55.35; H, 2.96; S, 13.44. Found: C, 55.64; H, 3.02; S, 13.22.

5-*p*-Methoxyphenyl-2-thenoic Acid (**4b**).

A solution of 0.86 g (1.8 mmoles) of **3b** in 80 ml of ethanol and 30 ml of dioxane was treated with 0.19 g (1.8 mmoles) of anhydrous sodium carbonate and heated to 70-75° with stirring. A solution of 0.46 g (1.8 mmoles) of iodine in ethanol was added dropwise for a period of 1 hour, and the mixture maintained at 70° for an additional 7 hours. The cooled mixture was then poured into ice water containing 1 g of sodium bisulfite, stirred and acidified with hydrochloric acid. The resulting solid was collected, washed, dried and recrystallized from toluene to give 0.60 g (70%) of **4b** melting at 200-201°; ir: 2940-2500, 1665, 1600, 1535, 1450, 1435 cm^{-1}.

Anal. Calcd. for $C_{12}H_{10}O_3S$: C, 61.52; H, 4.30; S, 13.69. Found: C, 61.72; H, 4.37; S, 13.71.

5-*p*-Hydroxyphenyl-2-thenoic Acid.

Following the procedure of Schapiro and Smith [29], a solution of 2.0 g (8.5 mmoles) of **4b** in 200 ml of dry benzene was treated with 20 g of anhydrous aluminum chloride, and the mixture gently refluxed for 6 hours. The mixture was then cooled and poured over 500 g of ice and 20 ml of concentrated hydrochloric acid. The benzene layer was separated,

washed twice with cold brine, dried, and evaporated to dryness under reduced pressure. The residual white solid was recrystallized once from ethyl acetate/cyclohexane to give 1.19 g (63%) of 5-*p*-hydroxyphenyl-2-thenoic acid melting at 254-255°; ir: 3125 (broad OH), 1665 (C=O), 1600, 1535 cm^{-1}; nmr (hexadeuterioacetone): δ 7.30 (6H, multiplet), 3.68 (1H, broad singlet). This compound gave a positive ferric chloride test.

Anal. Calcd. for $C_{11}H_8O_3S$: C, 59.99; H, 3.66; S, 14.56. Found: C, 59.85; H, 3.82; S, 14.49.

2,2'-Bithienyl-5-carboxylic Acid (**4c**).

A solution of 5.08 g (20 mmoles) of iodine in ethanol was added dropwise to a cold stirred solution of 4.25 g (20 mmoles) of **2c** in 50 ml of ethanol over a 2 hour period. After stirring an additional hour, saturated sodium bisulfite solution was added, and the solution poured into 500 ml of ice water and acidified with hydrochloric acid, giving 3.85 g (91%) of crude disulfide **3c**, melting at 168-170°. Without purification, 1.64 g (3.9 mmoles) of **3c** was dissolved in 50 ml of 1,2-dimethoxyethane and 0.99 g (3.9 mmoles) of iodine dissolved in 50 ml of dimethoxyethane added rapidly. The solution was refluxed for 3 hours, cooled and poured into 500 ml of ice water. After decolorizng the solution with sodium bisulfite, it was acidified with concentrated hydrochloric acid, and the precipitate collected dried, and sublimed at 140°/2 mm to give 1.18 g (72%) of **4c**, melting at 177-179° (literature [30] 176-178°).

Anal. Calcd. for $C_9H_6O_2S_2$: C, 51.41; H, 2.88; S, 30.50. Found: C, 51.85; H, 3.05; S, 30.10.

Methyl 2,2'-Bithienyl-5-carboxylate.

This ester was prepared by refluxing **4c** (0.52 g, 2.5 mmoles) in methanol with a drop of concentrated sulfuric acid, according to the general procedure of Vogel [31]. The solid ester was recrystallized from methanol to yield 0.51 g (92%) of the methyl ester of **4c**, melting at 71-72° (lit [30] 71.5-72°.

2'-Chloro-2,3'-bithienyl-5-carboxylic Acid (**4d**).

A solution of 3.4 g (13.8 mmoles) of **2d** in 50 ml of dioxane was cooled to 10°, and 1.74 g (6.9 mmoles) of iodine was added. After 1 hour, another 1.74 g (6.9 mmoles) of iodine was added, and the solution heated to 70° and stirred for 4 hours. After cooling, the dark solution was poured into 500 ml of cold water, containing 30 ml of saturated sodium bisulfite solution. The yellow solid was collected and recrystallized twice from toluene to give 1.74 g (52%) of white solid melting at 238-239°; ir: 2940-2500, 1685 and 1510 cm^{-1}.

Anal. Calcd. for $C_9H_5ClO_2S_2$: C, 44.17; H, 2.06; S, 26.21. Found: C, 44.13; H, 2.06; S, 25.96.

2',5'-Dichloro-2,3'-bithienyl-5-carboxylic Acid (**4e**).

A mixture of 3.22 g (10 mmoles) of **1e** was in 50 ml of 5% sodium hydroxide as heated on a steam bath for 2 hours, filtered, cooled and acidified. The yellow solid was collected and dried to yield 2.58 g (92%) of crude **2e**, melting at 135-141°. This crude product (2.15 g, 7.7 mmoles) was dissolved in 50 ml of dioxane and 0.96 g (3.8 mmoles) of iodine in 50 ml of dioxane was added. After stirring for 2 hours, another 0.96 g of iodine was added, and the solution stirred and maintained at 50° for 6 hours. After cooling, the dark solution was poured into 500 ml of water containing 10 ml of saturated sodium bisulfite. The yellow precipitate was collected, dried and sublimed at 195°/4 mm to give 0.74 g (34%) of white microcrystalline **4e**, melting at 238-240°; ir: 2940-2565, 1690 and 1660 cm^{-1}.

Anal. Calcd. for $C_9H_4Cl_2O_2S_2$: C, 38.72; H, 1.44; S, 22.97. Found: C, 38.91; H, 1.56; S, 22.80.

5-(1-Methylcinnamylidene)rhodanine (**5**).

In a 2 l, 3-necked round-bottom flask equipped with mechanical stirrer, Dean-Stark trap and condenser were placed 146 g (1.0 mole) of benzalacetone (Aldrich), 120 ml of glacial acetic acid, 4.0 g of anhydrous ammonium acetate, 133 g (1 mole) of rhodanine and 1 l of dry benzene. The mixture was stirred and refluxed until approximately 18 ml of water had collected in the trap (4 hours). Upon cooling, the orange precipitate was collected, washed with 500 ml of water, then 400 ml of cold ethanol, and dried to give 133.2 g (51%) of crude **5**, melting at 193-218°. An aliquot sample was recrystallized from ethanol to give orange crystals melting at 199-224° (lit [32] 192-194°).

Chromatography of the crude product on silica gel G with benzene revealed two overlapping spots. Separation of 1 g of crude product on a column of 100 g of silica gel eluted with benzene gave two reasonably sharp melting fractions. Fraction A (0.12 g, Rf = 0.4) consisted of red crystals melting at 209-211°; ir: 3200 (NH), 3030 (CH=CH), 1670 (C=O) m 1590, 1520 (aromatic), 961 (*trans* CH=CH), 917, 755, 741 cm^{-1} (aromatic).

Anal. Calcd. for $C_{13}H_{11}NOS_2$: C, 59.74; H, 4.24; S, 24.54. Found: C, 59.68; H, 4.03; S, 24.65.

Fraction E (0.08 g, Rf = 0.3) consisted of orange needles melting at 234-236°; ir: 3200, 3025, 1672, 1588, 1520, 958, 916, 752, 740 cm^{-1}.

Anal. Calcd. for $C_{13}H_{11}NOS_2$: C, 59.74; H, 4.24; S, 24.54. Found: C, 59.69; H, 4.41; S, 24.25.

3-Methyl-5-phenyl-2-thenoic Acid (**6**).

A. The crude rhodanine derivative **5** (130.5 g, 0.50 mole) was added to 600 ml of 10% sodium hydroxide solution at 75°, and the mixture stirred for 1 hour, then poured slowly into 800 ml of cold 10% hydrochloric acid with vigorous stirring. The crude yellow solid was collected and air-dried to give 104 g (94%) of material melting from 102-112°. This product was dissolved in 200 ml of 1,2-dimethoxyethane, cooled to 5°, and 128 g (0.50 mole) of iodine dissolved in 300 ml of dimethoxyethane was added slowly. The solution was stirred for 2 days at room temperature and then poured into 2 l of ice water containing 50 g of sodium bisulfite. After decanting the aqueous supernatant, the orange residue was taken up on 1 l of hot 10% sodium hydroxide, filtered through a steam-heated Buchner funnel and cooled, giving white crystals of the sodium salt of **6**. This product was collected, washed with water, and stirred in dilute hydrochloric acid. Twice recrystallized from benzene, **6** was obtained as a cream-colored powder (38 g, 35%) melting at 191-192°; ir: 2940-2500 (OH), 1655 (C=O), 1540 (thiophene), 1450 (CH_3-C), 1300 (COOH), 763, 758 and 686 cm^{-1} (substituted aromatic); nmr (hexadeuterioacetone): δ 7.5 (6H, m) and 2.52 (3H, s).

Anal. Calcd. for $C_{12}H_{10}O_2S$: C, 66.03; H, 4.62; S, 14.69. Found: C, 65.91; H, 4.79; S, 14.49.

B. A solution of 42.4 g (0.20 mole) of crude mercapto acid obtained from the hydrolysis of crude **5**, as described above, was dissolved in 100 ml of dimethoxyethane and the solution cooled to 5°. A solution of 50.6 g (0.20 mole) of iodine dissolved in cold dimethoxyethane was added slowly with stirring. The black solution was allowed to stand at room temperature for 10 days, then poured into 2 l of water containing 40 g of sodium bisulfite. The resulting yellow solid was collected and dissolved in 1 l of hot 1% sodium hydroxide solution. The hot solution was treated with Norite and filtered through a steam-heated Buchner funnel. Upon concentration of the clear solution to 750 ml and cooling, the sodium salt precipitated. It was collected, suspended in 200 ml of water and acidified with 50 ml of concentrated hydrochloric acid. The cream-colored solid was collected, dried, and recrystallized from benzene to give 22.8 g (53%) of **6**, melting at 190-192°.

C. A solution of 1.26 g (5.0 mmoles) of compound **8** in 50 ml of anhydrous ether was added to 0.12 g (5.0 mmoles) of magnesium turnings in 50 ml of anhydrous ether. Reaction was initiated by first adding only 10 ml of the halide solution, then warming and crushing the magnesium. As soon as bubbling indicated the reaction had begun, the remainder of the halide solution was added at such a rate as to maintain gentle reflux. After 3 hours dry carbon dioxide was swept through the ether solution to saturation. After evaporating the ether, the resulting solid was stirred with 50 ml of 10% hydrochloric acid, and the product collected, washed with water, dried and recrystallized from benzene to give 0.13 g (12%) of white crystals of **6**, melting at 191-192°.

2-Phenyl-4-methylthiophene (**7**).

A. A mixture of 10 g (46 mmoles) of **6** and 5.0 g of copper powder in 100 ml of freshly distilled (from barium oxide) quinoline was heated at 200° and stirred for 2 hours. Vigorous bubbling was observed during the first hour. The cooled mixture was poured into 500 g of ice containing 150 ml of concentrated hydrochloric acid, stirred until the ice melted, then extracted with two 100 ml portions of ether. The combined ether fractions were washed with 100 ml of 6 *N* hydrochloric acid, 100 ml of water, 100 ml of 10% sodium carbonate solution, then water, and dried (sodium sulfate). Evaporation of the ether left a brown oil, distilled at reduced pressure to give 5.84 g (75%) of a colorless oil, bp 110-120°/5 mm; n_D^{20} = 1.6296; ir: 3050, 2925, 1595, 1540, 1490, 757, 687 cm^{-1}; nmr (carbon tetrachloride): δ 7.6-7.0 (5H, m), 6.87 (1H, d, J = 2 Hz), 6.57 (1H, m) and 2.05 (3H, d, J = 2 Hz). Perveev [33] reported **7**, bp 123-124°/5 mm; n_D^{20} = 1.6299.

B. A suspension of 0.76 g (20 mmoles) of lithium aluminum hydride in *25 ml of anhydrous ether was placed in a 100 ml three-necked flask* equipped with dropping funnel, drying tube and stirrer. The system was flushed with nitrogen, and 2.53 g (10 mmoles) of 8 in 50 ml of ether was added dropwise during 0.5 hour. The mixture was refluxed 14 hours, cooled, and excess lithium aluminum hydrided destroyed by adding saturated sodium sulfate solution. The ether layer was separated, washed with water, dried (sodium sulfate), and evaporated to give 1.49 g (85%) of pale yellow oil, bp 115-120°/5 mm. The ir spectrum was superimposable upon that of **7**.

2-Bromo-3-methyl-5-phenylthiophene (**8**).

A. To a solution of 5.1 g (29 mmoles) of **7** in 50 ml of dry carbon tetrachloride was added 5.34 g (30 mmoles) of *N*-bromosuccinimide and 0.5 g of benzoyl peroxide. The mixture was irradiated with a 200 watt lamp and refluxed for 1 hour, then cooled and filtered to remove succinimide. Evaporation of the filtrate under reduced pressure left a crude brown solid with an irritating odor. It was taken up in 50 ml of chloroform and reflux with 4.2 g (30 mmoles) of hexamethylene tetramine for 1 hour. Chloroform was removed under reduced pressure, and the oily brown residue triturated with 2 x 100 ml of ether. (See preparation of **9** for disposal of this residue of hexamine salt.) The combined ether extracts were washed with water, dried (anhydrous sodium sulfate) and evaporated, and the residue recrystallized from methanol to give 4.54 g (64%) of white plates of **8**, melting at 62-63°; ir: 1600, 1560, 1493, 1445, 834, 753, 684 cm^{-1}; nmr (deuteriochloroform): δ 7.35 (5H, m), 6.92 (1H, s) and 2.17 (3H, s).

Anal. Calcd. for $C_{11}H_9Br$: C, 52.19; H, 3.58. Found: C, 52.08; H, 3.54.

B. In a second experiment, 5.22 g (30 mmoles) of **7** in 50 ml of carbon tetrachloride was treated with 5.34 g (30 mmoles) of *N*-bromosuccinimide which had been freshly recrystallized from acetic acid and dried *in vacuo*. The system was swept with nitrogen and 50 mg of 2,2'-azobisisobutyronitrile added as catalyst to the solution, cooled to 10°. The mixture was refluxed for 1 hour, cooled, filtered, and the solvent evaporated under reduced pressure. The residue was recrystallized from methanol to give 5.96 g (76%) of **8**, melting at 60-62°. The ir spectrum was superimposable on that **8** prepared above.

2-Bromo-5-phenyl-3-thenaldehyde (**9**).

A. A mixture of 7.59 g (30 mmoles) of **8**, 5.34 g (30 mmoles) of *N*-bromosuccinimide and 0.06 g of benzoyl peroxide in 100 ml of dry carbon tetrachloride was placed in a 300 ml 3-necked flask, stirred and irradiated with a 200 watt lamp. The mixture was refluxed for 1 hour, cooled, filtered, and 4.20 g (30 mmoles) of hexamethylene tetramine added to the filtrate, which was returned to the reaction flask and approximately 75 ml of carbon tetrachloride removed by distillation. Then 100 ml of dry chloroform was added, and the mixture refluxed for an additional hour. The reaction mixture was concentrated to dryness under reduced pressure, and the residue washed twice with ether. Concentration of the ether washes recovered 0.38 g (5%) of **8**.

200 ml of water, and extracted twice with ether. The combined ether extracts were washed with water, dilute sodium bicarbonate, water and dried (anhydrous sodium sulfate). Evaporation of the solvent gave a solid which, recrystallized from ethanol, gave 2.32 g (30%) of white needles of **9**, melting at 84-85°; ir: 1680, 1515, 1450, 1026, 843, 749 and 678 cm^{-1}; nmr (deuteriochloroform): δ 7.40 (6H, m), 9.93 (1H, s).

Anal. Calcd. for $C_{11}H_7BrOS$: C, 49.25; H, 2.61; S, 11.94. Found: C, 49.24; H, 2.70; S, 12.25.

The oxime of this aldehyde, recrystallized from cyclohexane as a white fluffy powder, melting at 141-142°.

Anal. Calcd. for $C_{11}H_8BrNOS$: N, 4.95. Found: N, 5.22.

B. The ether-insoluble brown solid recovered as by-product in the preparation of **8** was refluxed in 100 ml of 50% acetic acid for 2 hours, then 50 ml of concentrated hydrochloric acid added, and refluxing continued for 15 minutes. The cooled solution was poured into 500 ml of water and extracted with two portions of ether, and the combined ether layers washed *with dilute sodium bicarbonate solution, then water, and dried* (sodium sulfate). Evaporation of the ether left a solid which recrystallized from ethanol to give 0.2 g (2.6%) of **9**, melting at 80-82°. The ir spectrum was superimposable on that of **9**, above.

equipped with dropping funnel, drying tube and stirrer. The system was flushed with nitrogen, and 2.53 g (10 mmoles) of 8 in 50 ml of ether was added dropwise during 0.5 hour. The mixture was refluxed 14 hours, cooled, and excess lithium aluminum hydrided destroyed by adding saturated sodium sulfate solution. The ether layer was separated, washed with water, dried (sodium sulfate), and evaporated to give 1.49 g (85%) of pale yellow oil, bp 115-120°/5 mm. The ir spectrum was superimposable upon that of **7**.

(sodium sulfate). Evaporation of the ether left a solid which recrystallized from ethanol to give 0.2 g (2.6%) of **9**, melting at 80-82°. The ir spectrum was superimposable on that of **9**, above.

3-(2-Bromo-5-phenyl-3-thienyl)acrylic Acid (**10**).

A mixture of 2.66 g (10 mmoles) of **9**, 3.12 g (30 mmoles) of malonic acid, 50 ml of pyridine and 4 ml of piperidine was refluxed for 4 hours. The cooled solution was poured into 400 ml of cold 10% hydrochloric acid, and the resulting precipitate collected, washed and dried. Twice recrystallized from benzene, **10** was obtained as pale yellow needles (2.03 g, 66%) melting at 203-204°; ir: 3030-2500 (OH), 1690 (C=O), 1616 (C=C) and 971 cm^{-1} (*trans* CH=CH); nmr (hexadeuterioacetone): δ 7.48-7.40 (6H, m), 7.02 (1H, d, J = 14 Hz), 6.62 (1H, d, J = 14 Hz).

Anal. Calcd. for $C_{13}H_9BrO_2S$: C, 50.50; H, 2.93. Found: C, 50.42; H, 2.90.

3-(2-Bromo-5-phenyl-3-thienyl)acrolein (**11**).

A solution of 1.55 g (5 mmoles) of **10** in 10 ml of thionyl chloride was refluxed for 12 hours, the excess thionyl chloride removed by distillation, 25 ml of dry benzene added and removed by distillation at reduced pressure, leaving a yellow solid. This was dissolved in 50 ml of tetrahydrofuran (freshly distilled over lithium aluminum hydride). The flask was swept with nitrogen and cooled in a dry-ice methanol bath. To the cold, stirred solution was added dropwise 1.27 g (5 mmoles) of lithium tri-*t*-butoxyaluminohydride (Alfa Inorgaincs Inc.) dissolved in 50 ml of tetrahydrofuran. After addition was complete, the solution was stirred for 12 hours and allowed to warm to room temperature, then 10 ml of saturated sodium sulfate solution added, with stirring. The resulting suspension was filtered, and the filtrate concentrated under reduced pressure. The oily residue was taken up in 200 ml of ether, washed with dilute sodium bicarbonate solution, then water, and dried (sodium sulfate). Evaporation of the ether and recrystallizing the product from ethanol gave 1.02 g (69%) of **11** as salmon pink needles melting at 127-127.5°; ir: 1680 (C=O), 1625 (C=C) and 970 cm^{-1} (*trans* CH=CH); nmr (deuteriochloroform): δ 9.61 (H, d, J = 7.5 Hz), 7.50-7.40 (6H, m), 7.34 (1H, d, J = 15 Hz), and 6.49 (1H, dd, J = 15 Hz and J = 7.5 Hz).

Anal. Calcd. for $C_{13}H_9BrOS$: C, 53.06; H, 3.06; S, 10.88. Found: C, 52.99; H, 3.10; S, 10.75.

5-[3-(2-Bromo-5-phenyl-3-thienyl)acrylidenerhodanine (**12**).

A mixture of 0.45 g (3.4 mmoles) of rhodanine, 0.5 g of ammonium acetate, 2 ml of glacial acetic acid and 1.0 g (3.4 mmoles) of **11** in 100 ml of benzene was refluxed for 2 hours, forming a bright orange precipitate. The cooled mixture was filtered and the precipitate washed with dilute alcohol, dried and recrystallized from dioxane to give 1.22 g (89%) of orange needles of **12** melting at 271-272° dec; ir: 3030, 1675, 1575, and 961 cm^{-1}.

5-Carboxy-2'-bromo-5'-phenyl-2,3'-bithienyl (**13**).

A mixture of 1.0 g (2.5 mmoles) of **12** in 50 ml of 10% sodium hydroxide and 10 ml of ethanol was refluxed for 1 hour, poured into 100 ml of cold 10% hydrochloric acid, and the resulting yellow solid collected and dried. The product darkened on standing. It was dissolved in 20 ml of 1,2-dimethoxyethane, cooled to 3° in ice, and 0.63 g (2.5 mmoles) of iodine dissolved in 30 ml of dimethoxyethane added dropwise with stirring. Stirring was continued for 72 hours at room temperature, and then poured into 200 ml of 10% sodium bisulfite solution, stirred and extracted with two x 50 ml of ethyl acetate, and the combined organic layers washed with water and dried (sodium sulfate). Evaporation of the solvent left a brown residue. This was taken up in 200 ml of hot 2% sodium hydroxide solution, and 1.0 g of potassium permanganate added. After stirring for 2 hours, the solution was decolorized with dilute sodium bisulfite, and acidified with dilute hydrochloric acid. The yellow precipitate was collected, dried, and recrystallized twice from benzene to give 0.24 g (26%) of fine yellow needles of **13**, melting at 229-231°; ir: 3030-2500, 1690, 1665, 1603, 1535, 1465 cm^{-1}.

Anal. Calcd. for $C_{15}H_9BrO_2S_2$: C, 49.32; H, 2.48; S, 17.56. Found: C, 49.36; H, 2.65; S, 17.30.

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