(14) C. A. Grob, H. R. Kiefer, H. Lutz, and H. Wilkings, *Tetrahedron Lett.*, 2901 (1964).
(15) C. F. Wilcox, Jr., M. Sexton, and M. F. Wilcox, *J. Org. Chem.*, **28**, 1079 (1963).
(16) G. D. Sargent, "Carbonium Ions", Wiley-Interscience, New York, N.Y., 1972, Chapter 24, p 1099.
(17) The relatively large amount of endo acetate **15** formed in acetolysis of *exo-p*-bromobenzenesulfonate **13** suggests that a cationic product forming intermediate does not possess sufficient steric hindrance to preclude approach from the endo face. It is therefore probable that the starting ester **13** is likewise subject, in some measure, to endo-face solvent assistance. Based on simple steric observations, the endo ester **16** should be at least equally, if not more, subject to this type of assistance.
(18) Infrared spectra were determined utilizing a Perkin-Elmer 247 grating infrared spectrometer with sodium chloride optics. Nuclear magnetic resonance spectra were obtained via a Varian Associates A-60A spectrometer; approximately 20% solutions in $CDCl_3$, acetone-d_6, or Me_2SO-d_6 were employed with teramethylsilane as the internal standard. A Perkin-Elmer 881 flame ionization gas chromatograph or a Perkin-Elmer F-11 gas chromatograph employing 20 ft × 0.125 in. columns of 3% OV-210 on Chromosorb W were used in product analyses. Elemental analyses were performed by either the Baron Consulting Co., Orange, Conn., or by Micro-Analysis, Inc., Wilmington, Del.

Synthesis of the Three Isomeric Ortho-Substituted Phenylthienyl Benzoic Acids

Alexander L. Johnson

Contribution No. 2332 from the Central Research and Development Department, E. I. du Pont de Nemours and Company, Experimental Station, Wilmington, Delaware 19898

Received November 25, 1975

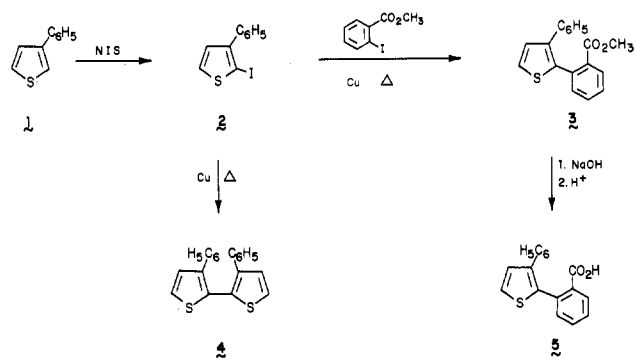
The syntheses of the three isomeric 2-(phenyl-2-thienyl)benzoic acids (**5, 19b, 19d**) are described. 2-(3-Phenyl-2-thienyl)benzoic acid (**5**) was prepared via the Ullmann biaryl synthesis from 2-iodo-3-phenylthiophene (**2**) and methyl 2-iodobenzoate. The 4- and 5-phenyl isomers (**19b, 19d**) were prepared by constructing the benzoic acid moiety by Diels–Alder reaction of butadiene with the acrylate esters (**15b, 15d**), derived from the Knoevenagel reaction of 4- and 5-phenylthiophene-2-carboxaldehydes (**14a, 14b**) with malonic acid. A cyclohexenyl group which is conjugated to the thiophene ring, as in **12a** and **12b**, was dehydrogenated rapidly to a phenyl group with 2,3-dichloro-4,5-dicyanobenzoquinone (DDQ) whereas an unconjugated cyclohexenyl group, as in **17a** and **17b** was difficult to aromatize by this procedure.

Over the past several years, I have been interested in the synthesis of benzoic acid derivatives which have a heterocyclic substituent in the ortho position and the heteroatom γ to the carboxyl group.[1-4] This paper describes the syntheses of the hitherto unknown 2-(3-, 4-, and 5-phenyl-2-thienyl)benzoic acids (**5, 19b, 19d**) shown in Schemes I and II. The literature syntheses[5-7] of the parent compound, 2-(2-thienyl)benzoic acid, and its methyl ester suggest the Ullmann method as being applicable to the phenyl compounds.

The bromination or iodination of 2- and 3-phenylthiophene[8-10] was the starting point for the new compounds. The synthesis and electrophilic substitutions of these thiophenes has been extensively studied by Gronowitz[10-13] and Wynberg[11,14] and their collaborators. 2-Bromo-5-phenyl- and 2-bromo-3-phenylthiophene are readily obtained in high yield by treating 2- and 3-phenylthiophene, respectively, with NBS,[11,14] and they appeared to be good candidates with which to start the synthesis of **5** and **19d.** Bromination of 3-phenylthiophene in acetic acid[11] gives a difficultly separable mixture of 2-bromo-3-phenyl- and 2-bromo-4-phenylthiophene, in which the former predominates. In acetic acid, 2-bromo-3-phenylthiophene equilibrates with its isomer, and undergoes disproportionation to 3-phenylthiophene and 2,5-dibromo-3-phenylthiophene.[11-14] This did not appear to be a promising method of preparing quantities of 2-bromo-4-phenylthiophene to use as starting material for **19b.**

In Scheme I, attempts to condense 2-bromo-3-phenylthiophene with methyl 2-iodobenzoate using copper powder at 200 °C were unsuccessful. 2-Iodo-3-phenylthiophene (**2**), prepared from 3-phenylthiophene and *N*-iodosuccinimide in 80% yield, was successfully used to give a 45% yield of the desired ester **3** as a distillable oil. As expected in a mixed Ullmann reaction,[15,16] bibenzoic acid ester was

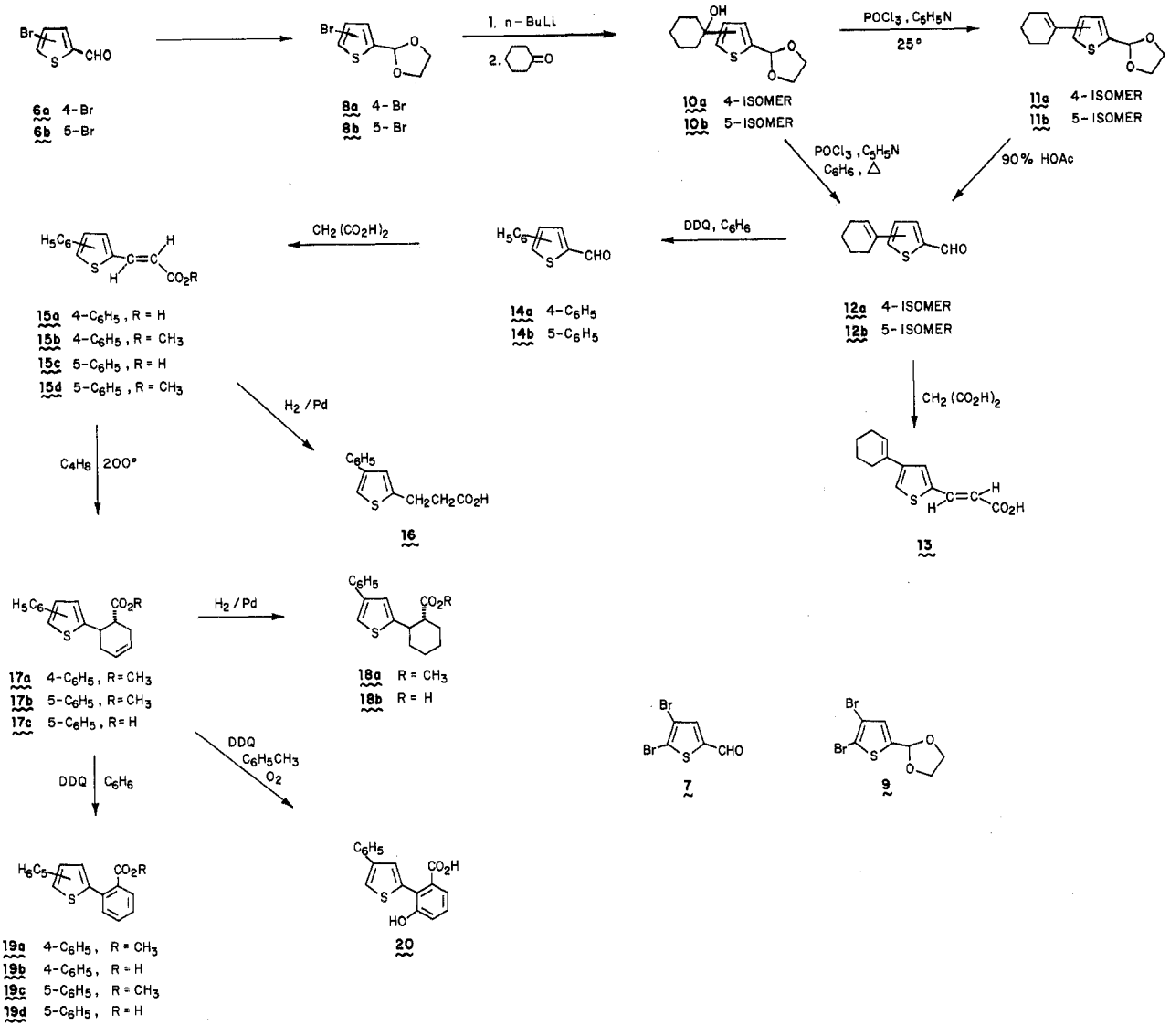
Scheme I



present in the reaction mixture, but 3,3′-diphenyl-2,2′-bithiophene (**4**) was not detected. Structure **4**, a new compound,[17] was prepared separately in 13% yield from **2** by the Ullmann reaction. 2-(3-Phenyl-2-thienyl)benzoic acid (**5**) was obtained in good yield by saponification of ester **3.**

The problems discussed above in preparing sufficient quantities of pure 2-bromo-4-phenylthiophene by the direct bromination of 3-phenylthiophene[11-14] required a different approach to the synthesis of 2-(4-phenyl-2-thienyl)benzoic acid (**19b**). In Scheme II, 4-bromothiophene-2-carboxaldehyde (**6a**), the aluminum chloride catalyzed bromination product of thiophene-2-carboxaldehyde,[18,19] was chosen because it was readily prepared in quantity and had the necessary orientation of functional groups which could be modified to produce **19b** in a sequence of eight steps. The product distribution in this bromination depends upon how well the reaction mixture, which has the consistency of heavy grease, is stirred. In tenth-mole runs good conversion to **6a** was observed, the minor amounts of 4,5-dibromothiophene-2-carboxaldehyde (**7**) being readily

Scheme II



separable by fractional distillation. In 0.5–1.0-mol runs, the inhomogeneity of the reaction mixture gave higher proportions both of unreacted thiophene-2-carboxaldehyde and **7**. A more convenient separation procedure, which also provided the next compound in the sequence, 4-bromothiophene-2-carboxaldehyde ethylene acetal (**8a**), was to separate the ethylene acetals of the aldehyde mixture by fractional distillation. The two aromatic subtituents were then introduced in sequence as shown in Scheme II.

The 4-phenyl substituent was introduced into **8a** by sequential treatment with *n*-BuLi and cyclohexanone, followed by dehydration and deacetalization of the hydroxy acetal (**10a**) to 4-(1-cyclohexenyl)thiophene-2-carboxaldehyde (**12a**), and dehydrogenation of **12a** to 4-phenylthiophene-2-carboxaldehyde (**14a**). I isolated the previously unreported[10] 3-(1-hydroxycyclohexyl)thiophene and 3-(1-hydroxycyclohexyl)thiophene-2-carboxaldehyde ethylene acetal (**10a**), respectively, from 3-bromothiophene and **6a**. They are crystalline solids which are readily dehydrated to the corresponding 3-(1-cyclohexenyl)thiophenes with phosphorus oxychloride and pyridine. Direct conversion of **10a** to **12a** occurs when **10a** is stirred briefly at reflux with a benzene solution of phosphorus oxychloride and benzene. The product thus obtained is difficult to purify, and decomposes on storage within a few days, because of the presence of unknown by-products. A two-step room temperature procedure (**10a** → **11a** → **12a**) with phosphorus oxychloride and pyridine, followed by 90% acetic acid, eliminates this problem. The dehydrogenation of cyclohexene **12a** to **14a** and of 3-(1-cyclohexenyl)thiophene to 3-phenylthiophene is accomplished more rapidly and in higher yield with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) than with chloranil.[10] This dehydrogenation occurs so readily that each portion of DDQ changes color almost as soon as it is added, and the benzene solvent goes from 25 °C to reflux during the course of the addition. 4-Phenylthiophene-2-carboxaldehyde is a known compound which was previously prepared[13] in 60% yield by treating the difficultly accessible 2-bromo-4-phenylthiophene with EtLi and DMF. My synthesis of this intermediate aldehyde is free of isomer ambiguities, may be carried through from **6a** to **14a** without purification of intermediates, and is applicable to the preparation of large quantities of **14a**.

The intermediate 3-(1-cyclohexenyl)thiophene-2-carboxaldehyde (**12a**) was characterized as the crystalline 3-[4-(1-cyclohexenyl)-2-thienyl]acrylic acid (**13**) using the Knoevenagel reaction. Similar treatment of **14a** gave 3-(4-phenyl-2-thienyl)acrylic acid (**15a**); both **13** and **15a** had a trans double bond,[20] shown conclusively by the proton NMR coupling constant of 16 Hz for the vinyl protons. Product **15a** was also characterized by catalytic reduction to 3-(4-phenyl-2-thienyl)propionic acid (**16**). The necessary

number of carbon atoms of the benzoic acid moiety was completed by Diels–Alder addition of butadiene to the methyl ester **15b**. The ester was chosen because (1) preliminary experiments with 2-thienylacrylic acid[21] showed that while addition was complete, it was difficult to isolate the free acid in the pure state; (2) dehydrogenation of the resulting cyclohexene with DDQ gives a more tractable product from the ester than from the acid. Reaction of ester **15b** with butadiene at 200 °C for 20 h gave the expected trans adduct[22] (**17a**). This was characterized by catalytic reduction to methyl *trans*-2-(4-phenyl-2-thienyl)cyclohexanecarboxylate (**18a**), and saponification of the latter to its parent acid (**18b**).

In sharp contrast to **12a**, the dehydrogenation of unconjugated methyl *trans*-2-(4-phenyl-2-thienyl)-4-cyclohexenylcarboxylate (**17a**) to the completely aromatic ester **19a** occurred very slowly with DDQ. This method gave more tractable results than attempts to use sulfur or palladium on carbon. The progress of the reaction was monitored by the disappearance of the aliphatic proton signals in the NMR, and required 2 days for completion in refluxing benzene. Saponification of **19a** gave the desired final product 2-(4-phenyl-2-thienyl)benzoic acid (**19b**). An attempt to accelerate the rate of dehydrogenation by using refluxing toluene as the solvent gave a 4% yield of hydroxy acid **20** as the only recognizable product after saponification. This product presumably arises by allylic oxidation of **17a** at the higher reaction temperature.

In considering a synthesis of the third isomer, **19d**, both Schemes I and II appeared to be equally difficult. Scheme II was chosen for the following reasons. (1) The experience in making **19b** encouraged the belief that a parallel sequence would work for **19d**. (2) 5-Bromothiophene-2-carboxaldehyde (**6b**) is commercially available in large amounts. (3) The Ullmann reaction route would require the preparation of 2-phenylthiophene. (4) The literature[17,23] indicates that a mixed Ullmann reaction with 5-phenyl-2-iodothiophene would produce a fairly high proportion of 5,5′-diphenyl-2,2′-bithienyl, the formation of which is less sterically hindered than that of its isomer **4**. Accordingly, Scheme II was also used to prepare **19d**, and pure isolated samples of the intermediate products **8b**, **10b**, **12b**, **14b**, **15c**, **15d**, **17b**, **19c**, and **19d** were obtained in an analogous manner to their 4-phenyl isomers in the **a** series. The same marked difference in reactivity of the conjugated and unconjugated cyclohexenes **12b** and **17b** toward DDQ dehydrogenation was noted as in the **a** series. Completely conjugated **17b** did appear to be more reactive than its cross-conjugated isomer **17a**. The saponification of esters **17b** and **19c** was normal, and good recoveries of parent acids were obtained.

Experimental Section[24]

2-Iodo-3-phenylthiophene (2) was prepared from *N*-iodosuccinimide and 3-phenylthiophene[10–14,25] in 79–81% yield, using the procedure described for the bromo compound.[14] Pure **2** is a liquid: bp 126–130 °C (0.90 mm); ν_{max} 1600, 1480, 955, 860, and 680 cm^{-1}; λ_{max} (C_8H_{18}) 258 nm (ϵ 10 300) and 233 (16 100); ^{1}H NMR δ 7.52–7.12 (m) 6 H (C_6H_5, thiophene), and 6.88 ppm (d, J = 6 Hz) 1 H (thiophene). Anal. Calcd for $C_{10}H_7SI$: C, 41.97; H, 2.47. Found: C, 42.24; H, 2.50.

Methyl 2-(3-Phenyl-2-thienyl)benzoate (3). A preheated mixture (180 °C) of **2** (14.44 g, 50.5 mmol) and methyl 2-iodobenzoate (13.20 g, 50.5 mmol) was treated in small portions with Cu powder (Venus No. 44, fine, 15.90 g, 0.25 g-atom). The temperature rose spontaneously to 230 °C, and it was held at 210 °C for 30 min. The cooled mixture was extracted with C_6H_6 to give a brown oil which was short-path distilled at 150° (0.2 mm) to remove ~1 g of **2**. The residue was chromatographed on 330 g of Woelm activity III neutral Al_2O_3 (50-ml fractions). Fractions 1–8 (hexane) and 9–12 (C_6H_6) gave 2.15 g of **2**; fractions 13–15 (C_6H_6) gave 6.19 g (22.7 mmol, 45%) of product **3**; and fractions 16–20 (C_6H_6) gave 2.54 g of bibenzoic ester and other substances. Pure **3**, sublimed at 110 °C (0.25 mm), had mp 61–65 °C; ν_{max} 1725, 690, and 650 cm^{-1}; λ_{max} (MeOH) 225 nm (ϵ 20 500); ^{1}H NMR δ 7.83–7.08 (m) 6 H (C_6H_4, thiophene), 7.15 (s) 5 H (C_6H_5), and 3.52 ppm (s) 3 H (CO_2CH_3). Anal. Calcd for $C_{18}H_{14}SO_2$: C, 73.46; H, 4.80; *m/e* 294.0714. Found: C, 73.59; H, 4.64; *m/e* 294.0746.

The above product appeared to be free of 3,3′-diphenyl-2,2′-bithienyl (**4**), which was not identified in any of the fractions. 2-Bromo-3-phenylthiophene[14] was unsatisfactory in this Ullmann condensation, and no coupling product was found.

3,3′-Diphenyl-2,2′-bithiophene (4) was prepared by heating **2** (5.0 g, 18.5 mmol) and Cu powder (6.35 g, 0.1 g-atom) at 200 °C for 30 min. Extraction of the cooled residue with C_6H_6 gave a brown oil from which 0.7076 g (2.22 mmol, 13%) of colorless prisms of **4** sublimed at 130 °C (0.1 mm). Pure **4** has mp 107–109°; ν_{max} (KBr) 1600, 865, 685, and 645 cm^{-1}; λ_{max} (C_8H_{18}) 300 nm (ϵ 6650), 251 (21 000), and 232 (22 100); ^{1}H NMR δ 7.70–7.22 (m) 10 H and 7.12 ppm (s) 4 H. Anal. Calcd for $C_{20}H_{14}S_2$: C, 75.46; H, 4.43; *m/e* 318.0536. Found: C, 75.99; H, 4.64; *m/e* 318.0531.

2-(3-Phenyl-2-thienyl)benzoic Acid (5). A mixture of ester **3** (6.68 g, 22.7 mmol), H_2O (25 ml), MeOH (25 ml), and NaOH (8.0 g, 0.20 mol) was stirred at reflux for 5 h. The brown solid which precipitated after acidification (pH 3, HCl) was recrystallized (75% MeOH, 105 ml): yield 3.66 g (13.0 mmol, 55%); mp 173–175°. The analytical sample formed colorless crystals with mp 176 °C dec; ν_{max} (KBr) 1675 and 1295 cm^{-1}; λ_{max} (MeOH) 225 nm (ϵ 19 300); ^{1}H NMR (Me_2SO-d_6) δ 7.80–7.22 (m) 6 H (C_6H_4, thiophene) and 7.13 ppm (s) 5 H (C_6H_5). Anal. Calcd for $C_{17}H_{12}SO_2$: C, 72.85; H, 4.32. Found: C, 72.94; H, 4.42.

4-Bromothiophene-2-carboxaldehyde (6a) was prepared by the literature procedure[18] from thiophene-2-carboxaldehyde, Br_2, and $AlCl_3$. In large-scale runs, the thick reaction mixture is difficult to stir, and this reduces the yield of **6a**, and increases the proportions of starting aldehyde and 4,5-dibromothiophene-2-aldehyde (**7**). Small proportions of these impurities are readily separated by distillation, but for larger samples conversion of the crude aldehyde mixture to the corresponding acetals is more effective for purification.

4-Bromothiophene-2-carboxaldehyde Ethylene Acetal (8a). A. A mixture of pure **6a** (76.0 g, 0.397 mol), ethylene glycol (62 g, 1.0 mol), C_6H_6 (400 ml), and *p*-TsOH (1.0 g) was stirred at reflux under H_2O separation for 5 h. Distillation at 87–88 °C (0.4 mm) gave 83.5 g (0.355 mol, 90%) of **8a** with ν_{max} 1170, 1080 cm^{-1}; λ_{max} (C_8H_{18}) 247 nm (ϵ 4380) and 229 (5750); ^{1}H NMR δ 7.22 (s) 1 H (H_3), 7.08 (s) 1 H (H_5), 6.03 (s) 1 H (OCHO), and 6.00 ppm (m) 4 H (OCH_2). Anal. Calcd for $C_7H_7BrO_2S$: C, 35.76; H, 3.00. Found: C, 35.64; H, 2.82. Its properties are similar to those of the diethyl acetal described by Goldfarb.[18]

B. The crude bromination mixture (186 g) was similarly converted to a mixture of acetals which was separated on a 16-in. spinning band column to give thiophene-2-carboxaldehyde ethylene acetal (15 g), bp 74 °C (0.2 mm), **8a** (85.4 g), bp 92 °C (0.1 mm), and 4,5-dibromothiophene-2-carboxaldehyde ethylene acetal (**9**) (56.1 g), bp 108 °C (0.2 mm).

C. Aldehyde **6a** was regenerated from **8a** in 78% yield by stirring a mixture of **8a** (19.6 g, 84 mmol), $POCl_3$ (20 ml), C_6H_6 (50 ml), and C_5H_5N (20 ml) at reflux for 30 min, followed by adding the mixture to water, separation, extraction with dilute HCl, and distillation of the residue from the dried C_6H_6 layer at 60° (0.1 mm).

4,5-Dibromothiophene-2-carboxaldehyde ethylene acetal (9) was prepared in 91% yield from solid aldehyde **7** as described above. It is a colorless liquid with λ_{max} (C_8H_{18}) 298 nm (ϵ 234) and 241 (8800); ^{1}H NMR δ 6.86 (s) 1 H (H_3), 5.90 (s) 1 H (OCHO), and 3.95 ppm (s) 4 H (OCH_2). Anal. Calcd for $C_7H_6Br_2O_2S$: C, 26.77; H, 1.92. Found: C, 27.06; H, 1.98.

4-(1-Hydroxycyclohexyl)thiophene-2-carboxaldehyde Ethylene Acetal (10a). A solution of *n*-BuLi in hexane (1.6 M, 45 ml, 72 mmol) was stirred at −70 °C and treated in sequence with a solution of **8a** (15.25 g, 65 mmol) in Et_2O (45 ml) and with cyclohexanone (6.36 g, 65 mmol). The mixture was stirred at 25 °C overnight, decomposed with 10 ml of HOAc, and the volatile materials were removed by vacuum distillation to leave 7.5 g of brown residue which solidified overnight. The impurities were rinsed away with hexane, and the residue recrystallized (C_6H_6–C_6H_{14}) as colorless needles (6.9 g, 27.1 mmol, 42%), mp 76–77 °C. Sublimation at 150 °C (0.1 mm) causes decomposition. The pure tertiary alcohol **10a** has ν_{max} 3560 and 3440 cm^{-1}; λ_{max} (dioxane) 293 nm (ϵ 118) and 232 (7350); ^{1}H NMR δ 7.13 (s), 2 H (H_3, H_5), 6.00 (s) 1 H (OCHO), 4.00 (m) 4 H (OCH_2), 2.12 (s) 1 H (OH), and 1.76 ppm

(m) 10 H (cyclohexyl). Anal. Calcd for $C_{13}H_{18}SO_3$: C, 61.40; H, 7.14. Found: C, 61.59; H, 7.11.

4-(1-Cyclohexenyl)thiophene-2-carboxaldehyde (12a). A. A mixture of **10a** (27.78 g, 0.109 mol), $POCl_3$ (38.4 g, 0.25 mol), C_5H_5N (50 ml), and C_6H_6 (150 ml) was left overnight at 25 °C. The clear solution became warm within 15 min, and deposited a crystalline solid. The mixture was poured onto 250 g of ice and separated, and the C_6H_6 layer was washed with 2 × 250 ml of H_2O, dried, and evaporated to leave 15.8 g (67 mmol, 62%) of crude 4-(1-cyclohexenyl)thiophene-2-carboxaldehyde ethylene acetal (**11a**) identified by ^1H NMR δ 6.25 (m) (vinyl), 6.12 (s) (OCHO), and 4.05 ppm (m) (OCH_2).

B. The crude acetal **11a** was stirred with 90% HOAc (75 ml) for 2 h at 25 °C to effect deacetalization. The mixture was poured into 300 ml of H_2O and extracted with 3 × 75 ml of $CHCl_3$, the extracts were rinsed with 5% $NaHCO_3$, dried, and evaporated, and the residue was distilled at 123 °C (0.1 mm), yield 7.10 g (37 mmol, 34% overall) of **12a.** Pure aldehyde **12a** was a yellow solid with mp 38–39°; ν_{max} 1670 cm^{-1}; λ_{max} (C_8H_{18}) 318 nm (ϵ 6100) and 245 (21 500); ^1H NMR δ 9.88 (s) 1 H (CHO), 7.87 (s) and 7.47 (s) 2 H (H_3, H_5), 6.25 (m) 1 H (vinyl), 2.27 (m) 2 H (allylic), and 1.70 ppm (m) 6 H (CH_2). Anal. Calcd for $C_{11}H_{12}SO$: C, 68.73; H, 6.29. Found: C, 68.75; H, 6.25.

C. Tertiary alcohol **10a** can be converted to **12a** in one step (67% yield) by the hot $POCl_3$–C_5H_5N procedure, but the product so obtained is impure, and decomposes fairly quickly on storage.

***trans*-3-[4-(1-Cyclohexenyl)-2-thienyl]acrylic Acid (13).** A mixture of aldehyde **12a** (4.20 g, 21.9 mmol), malonic acid (2.3 g, 22 mmol), C_5H_5N (20 ml), and piperidine (2 ml) was stirred at reflux for 5 h,[20] then poured into H_2O. The solution was acidifed (HCl, pH 4), cooled, and filtered to give crude acid **13.** Recrystallization (EtOH, 50 ml) gave 3.63 g (15.5 mmol, 71%) of yellow needles of **13** with mp 158–160 °C dec; ν_{max} (KBr) 1675 and 1615 cm^{-1}; λ_{max} (EtOH) 330 nm (ϵ 7600), 287 (15 600), and 252 (18 900); ^1H NMR δ 10.23 (broad) 1 H (CO_2H), 8.00 (d, J = 16 Hz) and 6.32 (d, J = 16 Hz) 2 H (trans CH=CH), 7.52 (d, J = 2 Hz) 1 H (H_3), 7.28 (d, J = 2 Hz) 1 H (H_5), 6.28 (m) 1 H (vinyl), 2.50–2.16 (m) 4 H (allylic), and 1.83–1.58 (m) 4 H (CH_2). Anal. Calcd for $C_{13}H_{14}SO_2$: C, 66.65; H, 6.02. Found: C, 66.45; H, 6.02.

4-Phenylthiophene-2-carboxaldehyde (14a). A mixture of aldehyde **12a** (8.50 g, 44 mmol), C_6H_6 (75 ml), and DDQ (20.4 g, 90 mmol) was stirred at reflux for 1 h, cooled, and filtered. The filtrate was extracted with 5% $NaHCO_3$, dried, and evaporated, and the residue was sublimed at 80 °C (0.1 mm), yield 5.37 g (29 mmol, 65%) of **14a** as a yellow solid with mp 56–57 °C (lit.[13] 67–68 °C); ν_{max} 1690 cm^{-1}; λ_{max} (EtOH) 314 nm (ϵ 2900) and 252 (28 400); ^1H NMR δ 9.88 (s), 1 H (CHO), 7.93 (s) and 7.78 (s) 2 H (H_3, H_5), and 7.45 ppm (s) 5 H (C_6H_5), identical with material prepared by treatment of 2-lithio-4-phenylthiophene with DMF.[13] The steps from **6a** may be done without purification of intermediate products.

***trans*-3-(4-Phenyl-2-thienyl)acrylic Acid (15a).** A mixture of **14a** (1.43 g, 7.60 mmol), malonic acid (0.79 g, 7.60 mmol), C_5H_5N (5 ml), and piperidine (1 ml) was stirred at 120 °C for 5 h, and the product was then isolated as described for **13** above, yield 1.45 g (6.31 mmol, 83%) of yellow solid acid **15a** with mp 190–192 °C dec; ν_{max} (KBr) 1680 cm^{-1}; λ_{max} (CH_3OH) 322 nm (ϵ 9900) and 263 (30 200); ^1H NMR δ 12.33 (broad) 1 H (CO_2H), 7.92–7.35 (m) 8 H (C_6H_5, thiophene, vinyl), and 6.30 ppm (d, J = 16 Hz) 1 H (vinyl). Anal. Calcd for $C_{13}H_{10}SO_2$: C, 67.82; H, 4.38. Found: C, 67.73; H, 4.73.

Methyl *trans*-3-(4-phenyl-2-thienyl)acrylate (15b) was prepared from acid **15a** (10.41 g, 45 mmol) by converting it to its acid chloride with $SOCl_2$ (30 ml) (30 min reflux), and then treating the crude acid chloride with MeOH (75 ml) under reflux for 2 h. Sublimation at 95 °C (0.5 mm) gave 6.87 g (28 mmol, 63%) of yellow solid ester **15b** with mp 85–87 °C; ν_{max} 1720 cm^{-1}; λ_{max} (EtOH) 362 nm (ϵ 10 450) and 265 (24 200); ^1H NMR δ 7.83 (d, J = 16 Hz) 1 H and 6.20 (d, J = 16 Hz) 1 H (trans CH=CH), 7.67–7.20 (m) 7 H (C_6H_5, thiophene), and 3.78 ppm (s), 3 H (OCH_3). Anal. Calcd for $C_{14}H_{12}SO_2$: C, 68.84; H, 4.95. Found: C, 64.45; H, 4.36.

3-(4-Phenyl-2-thienyl)propionic Acid (16). A mixture of **15a** (6.9 g, 30 mmol), 10% Pd/C (0.5 g), and HOAc (200 ml) was hydrogenated in a Parr shaker at 25 °C for 96 h. The catalyst was filtered, and the product was precipitated from the filtrate by dilution with H_2O (300 ml), yield 6.34 g of almost colorless solid. Recrystallization (EtOH, 50 ml) gave 4.89 g (21 mmol, 70%) of acid **16** with mp 159–161 °C; ν_{max} (KBr) 1680 cm^{-1}; λ_{max} (EtOH) 264 nm (ϵ 21 800) and 232 (15 500); ^1H NMR (Me_2SO-d_6) δ 7.98 (m), 7.82–7.53 (m), and 7.47–7.30 (m) 7 H (C_6H_5, thiophene), 3.08 (t, J = 7 Hz), 2 H (CH_2), and 2.63 ppm (t, J = 7 Hz) 2 H (CH_2). Anal. Calcd for $C_{13}H_{12}SO_2$: C, 67.23; H, 5.21. Found: C, 67.47; H, 4.78.

Methyl *trans*-2-(4-Phenyl-2-thienyl)-4-cyclohexenecarboxylate (17a). A mixture of ester **15b** (18.79 g, 77 mmol), butadiene (20 g), and C_6H_6 (35 ml) was held at 200 °C for 20 h in an autoclave. The crude product, isolated by evaporation, was recrystallized (MeOH, 100 ml), yield 19.57 g (66 mmol, 86%). Pure **17a** formed pale yellow prisms with mp 105–106 °C; ν_{max} (KBr) 1720 and 1300 cm^{-1}; λ_{max} (MeOH) 330 nm (ϵ 195), 263 (12 400), and 232 (22 000); ^1H NMR δ 7.57–7.03 (m) 7 H (C_6H_5, thiophene), 5.70 (m) 2 H (vinyl), 3.45 (s) 3 H (OCH_3), and 3.50–2.16 ppm (m) 6 H (cyclohexyl). Anal. Calcd for $C_{18}H_{18}SO_2$: C, 72.46; H, 6.08. Found: C, 72.21; H, 6.39.

Methyl *trans*-2-(4-Phenyl-2-thienyl)cyclohexanecarboxylate (18a). A mixture of ester **17a** (4.46 g, 15.0 mmol), MeOH (100 ml), and 5% Pd/C (1.0 g) was hydrogenated in a Parr shaker at 25 °C for 15 h. The catalyst was filtered, and the filtrate evaporated to give a residue which was recrystallized (MeOH, 10 ml), yield 3.66 g (12.2 mmol, 82%) of ester **18a** with mp 58–59 °C; ν_{max} 1720 cm^{-1}; λ_{max} (MeOH) 262 nm (ϵ 12 600) and 232 (23 000); ^1H NMR δ 7.60–7.03 (m) 7 H (C_6H_5, thiophene), 3.45 (s) 3 H (OCH_3), and 3.17–1.17 ppm (m) 10 H (cyclohexyl). Anal. Calcd for $C_{18}H_{20}SO_2$: C, 71.98; H, 6.71. Found: C, 71.81; H, 6.86.

***trans*-2-(4-Phenyl-2-thienyl)cyclohexanecarboxylic Acid (18b).** A mixture of ester **18a** (3.34 g, 11.1 mmol) and 20% NaOH (20 ml) was stirred at reflux for 4 h, then it was cooled, acidified (HCl), and filtered. The precipitate of **18b** was filtered and sublimed at 160 °C (0.1 mm) as a glassy solid with indefinite melting point: ν_{max} 1700 cm^{-1}; λ_{max} (MeOH) 263 nm (ϵ 12 600) and 233 (21 200); ^1H NMR δ 9.87 (broad) 1 H (CO_2H), 7.55–7.00 (m) 7 H (aromatic), 3.17–2.33 (m) 2 H and 2.17–1.17 (m) 8 H (cyclohexyl). Anal. Calcd for $C_{17}H_{18}SO_2$: C, 71.31; H, 6.34. Found: C, 71.05; H, 6.41.

2-(4-Phenyl-2-thienyl)benzoic Acid (19b). A. A mixture of ester **17a** (2.81 g, 9.45 mmol), C_6H_6 (50 ml), and DDQ (4.55 g, 20 mmol) was stirred at reflux for 44 h. Isolation of the product as described for **14a** gave 1.87 g (6.35 mmol, 67%) of methyl 2-(4-phenyl-2-thienyl)benzoate (**19a**) as a brown syrup, characterized by ^1H NMR, δ 7.95–7.33 (m) 11 H (aromatic) and 3.75 ppm (s) 3 H (OCH_3).

B. Crude ester **19a** (1.87 g) was stirred at reflux with 20% NaOH (10 ml) for 3 h. The mixture was cooled and acidified (HCl) and crude **19b** (0.75 g, 29% from **17a**) was extracted ($CHCl_3$). Recrystallization (EtOH, 3 ml) gave yellow needles of **19b** with mp 130–132 °C; ν_{max} (KBr) 1680 cm^{-1}; λ_{max} (MeOH) 257 nm (ϵ 30 000); ^1H NMR δ 9.26 (broad) 1 H (CO_2H), 8.07 (m) 1 H (H_5), and 7.72–7.38 (m) 10 H (aromatic). Anal. Calcd for $C_{17}H_{12}SO_2$: C, 72.85; H, 4.32; *m/e* 280.0577. Found: C, 72.31; H, 4.42; *m/e* 280.0564.

3-Hydroxy-2-(4-phenyl-2-thienyl)benzoic Acid (20). When 12.0 g (40.3 mmol) of **17a** was stirred with refluxing toluene (100 ml) and DDQ (18.4 g, 81.0 mmol) the only recognizable product obtained by the usual isolation procedure was 1.69 g of syrupy ester which was saponified with 20% NaOH (10 ml). The resulting tan solid was recrystallized (40% MeOH), yield 0.4772 g (1.71 mmol, 4% overall) of colorless, crystalline **20** with mp 181–185 °C dec; ν_{max} (KBr) 1685, 1600, and 1575 cm^{-1}; λ_{max} (MeOH) 253 nm (ϵ 29 600); ^1H NMR (Me_2SO-d_6) δ 7.78–7.57 (m) 5 H, 7.43–7.23 (m) 4 H, and 6.88 ppm (m) 2 H (aromatic). Anal. Calcd for $C_{17}H_{12}SO_3$: C, 68.91; H, 4.08; *m/e* 296.0506. Found: C, 68.69; H, 3.99; *m/e* 296.0499. Silylation showed two OH groups, *m/e* 440 corresponding to $C_{23}H_{28}SO_3Si_2$.

5-Bromothiophene-2-carboxaldehyde Ethylene Acetal (8b). 5-Bromothiophene-2-carboxaldehyde (**6b,** 100.5 g, 0.525 mol) (Aldrich) was converted to its ethylene acetal (**8b**) in 95% yield by the procedure described for **8a.** Acetal **8b** is a colorless liquid with bp 68–72 °C (0.025 mm); λ_{max} (C_8H_{18}) 289 nm (ϵ 392) and 242 (9900); ^1H NMR δ 6.82 (s) 2 H (H_3, H_4), 5.92 (s) 1 H (OCHO), and 3.95 ppm (m) 4 H (OCH_2). Anal. Calcd for $C_7H_7BrO_2S$: C, 35.76; H, 3.00. Found: C, 35.66; H, 2.83.

5-(1-Hydroxycyclohexyl)thiophene-2-carboxaldehyde Ethylene Acetal (10b). The *n*-BuLi–cyclohexanone method described for **10a** using 89.25 g (0.38 mol) of **8b** gave, on allowing the crude product to stand overnight at 25 °C, 46.4 g of crystalline **10b** and 26.9 g of oily supernatant material, total yield 73.3 g (0.284 mol, 75%). Recrystallization of 5 g of the solid fraction (1:2 C_6H_6–C_6H_{14}, 31 ml) gave 3.41 g of colorless plates of **10b** with mp 43–44 °C; ν_{max} 3580 and 3400 cm^{-1}; λ_{max} (THF) 291 nm (ϵ 12 300) and 266 (11 400); ^1H NMR δ 6.97 (d, J = 4 Hz) and 6.80 (d, J = 4 Hz) 2 H (H_3, H_4), 5.98 (s) 1 H (OCHO), 4.00 (m) 4 H (OCH_2), 2.63 (s) 1 H (OH), and 2.00–1.33 ppm (m) 10 H (cyclohexyl). Anal. Calcd for $C_{13}H_{18}O_3S$: C, 61.40; H, 7.14. Found: C, 61.52; H, 7.18.

5-(1-Cyclohexenyl)thiophene-2-carboxaldehyde (12b). The two-step procedure described for **12a** gave (0.29-mol scale) with **10b** and **11b** a 33–45% yield of **12b,** bp 127–130 °C (0.2 mm). Aldehyde **12b** is a pale yellow solid which darkens on storage, with mp 57–59 °C; ν_{max} (KBr) 1640 cm^{-1}; λ_{max} (CH_3CN) 331 nm (ϵ 16 350) and 226 (7360); ^{1}H NMR δ 9.78 (s), 1 H (CHO), 7.60 (d, J = 4 Hz) and 7.00 (d, J = 4 Hz) 2 H (H_3, H_4), 6.40 (m) 1 H (vinyl), 2.33 (m) 4 H (allylic), and 1.68 ppm (m) 4 H (CH_2). Anal. Calcd for $C_{11}H_{12}OS$: C, 68.73; H, 6.29. Found: C, 68.73; H, 6.17.

5-Phenylthiophene-2-carboxaldehyde (14b). The DDQ procedure described for **14a** gave with **12b** (0.17-mol scale) and 3-h reflux time a 66–71% yield of pale yellow crystalline **14b,** purified by sublimation at 105 °C (0.25 mm). Pure **14b** has mp 80–81 °C; ν_{max} (KBr) 1640 cm^{-1}; λ_{max} (C_8H_{18}) 320 nm (ϵ 16 400) and 228 (8750); ^{1}H NMR δ 9.87 (s) 1 H (CHO), 7.72 (d, J = 4 Hz) and 7.40 (d, J = 4 Hz) 2 H (H_3, H_4), 7.62 (m) and 7.45–7.25 ppm (m) 5 H (C_6H_5). Anal. Calcd for $C_{11}H_8SO$: C, 70.21; H, 4.29. Found: C, 70.28; H, 4.69.

***trans*-3-(5-Phenyl-2-thienyl)acrylic Acid (15c).** The Knoevenagel procedure described for **15a** gave, with **14b** (58.5-mmol scale), after recrystallization (EtOH, 150 ml), 12.28 g (53.3 mmol, 91%) of **15c,** mp 173–175 °C dec. The analytical sample was a pale yellow crystalline solid with mp 183–189 °C dec; ν_{max} (KBr) 1660 cm^{-1}; λ_{max} (EtOH) 346 nm (ϵ 27 600) and 243 (10 000); ^{1}H NMR (Me_2SO-d_6) δ 7.80 (d, J = 16 Hz) and 6.23 (d, J = 16 Hz) 2 H (trans CH=CH), 7.83–7.33 (m) 7 H (aromatic), and 6.50 ppm (broad) 1 H (CO_2H). Anal. Calcd for $C_{13}H_{10}SO_2$: C, 67.82; H, 4.38. Found: C, 67.73; H, 4.65.

Methyl *trans*-3-(5-Phenyl-2-thienyl)acrylate (15d). Esterification of acid **15c** (27.0 g, 0.117 mol) in DMF with CH_3I and Na_2CO_3 (Newman procedure[26]) gave 29.65 g of crude ester **15d** upon dilution of the cooled reaction mixture with H_2O. Recrystallization (MeOH, 300 ml) gave 18.84 g (77 mmol, 65%) of pure **15d,** a yellow, crystalline solid with mp 137–138 °C; ν_{max} (KBr) 1710, 1620, 1295, and 1280 cm^{-1}; λ_{max} (MeOH) 351 nm (ϵ 29 800) and 245 (9800); ^{1}H NMR δ 7.74 (d, J = 16 Hz) and 6.19 (d, J = 16 Hz) 2 H (trans CH=CH), 7.58–7.17 (m) 7 H (aromatic), and 3.75 ppm (s) 3 H (OCH_3). Anal. Calcd for $C_{14}H_{12}SO_2$: C, 68.84; H, 4.95. Found: C, 68.75; H, 4.95.

Methyl *trans*-2-(5-Phenyl-2-thienyl)-4-cyclohexenecarboxylate (17b). A mixture of **15d** (18.8 g, 77 mmol), C_6H_6 (50 ml), and butadiene (25 g) was held at 200 °C for 20 h. The crude product was chromatographed on 450 g of Woelm activity III Al_2O_3 (50-ml fractions), to give butadiene oligomers (fractions 1–8, C_6H_{14}; fractions 9, 10, C_6H_6) and **17b** (12.13 g, 40.7 mmol, 53%) (fractions 11–22, C_6H_6). The analytical sample, purified by sublimation at 100 °C (0.1 mm), had mp 57–58 °C; ν_{max} 1720 cm^{-1}; λ_{max} (MeOH) 347 nm (ϵ 238) and 290 (17 500); ^{1}H NMR δ 7.72–7.27 (m) 5 H (C_6H_5), 7.14 (d, J = 4 Hz) and 6.84 (d, J = 4 Hz) 2 H (H_3, H_4), 5.78 (m) 2 H (vinyl), 3.53 (s) 3 H (OCH_3), and 3.67–2.33 ppm (m) 6 H (cyclohexyl). Anal. Calcd for $C_{18}H_{18}SO_2$: C, 72.46; H, 6.08. Found: C, 72.42; H, 5.95.

***trans*-2-(5-Phenyl-2-thienyl)-4-cyclohexenecarboxylic Acid (17c).** Saponification of 4.0 g (13.4 mmol) of **17b** in 15% aqueous methanolic NaOH gave, after $CHCl_3$ extraction, 2.99 g (10 mmol, 75%) of acid **17c,** mp 104–106 °C. The analytical sample after sublimation at 170 °C (0.1 mm) had ν_{max} 1700 cm^{-1}; λ_{max} (MeOH) 345 nm (ϵ 217) and 292 (16 800); ^{1}H NMR δ 11.03 (s) 1 H (CO_2H), 7.65–7.25 (m) (C_6H_5), 7.09 (d, J = 4 Hz) and 6.84 (d, J = 4 Hz) 2 H (H_3, H_4), 5.77 (m) 2 H (vinyl), and 3.33–1.83 ppm (m) 6 H (cyclohexyl). Anal. Calcd for $C_{17}H_{16}SO_2$: C, 71.82; H, 5.07. Found: C, 71.61; H, 5.30.

Methyl 2-(5-Phenyl-2-thienyl)benzoate (19c). Ester **17b** (7.28 g, 24.4 mmol) was dehydrogenated by the DDQ procedure (24-h reflux). The crude product was filtered through 110 g of Woelm activity III Al_2O_3 to give 4.62 g (15.7 mmol, 65%) of **19c** which was short-path distilled at 135 °C (0.25 mm) as a syrupy liquid with ν_{max} 1710 and 1280 cm^{-1}; λ_{max} (MeOH) 313 nm (ϵ 16 200); ^{1}H NMR δ 7.82–7.27 (m) 6 H (C_6H_5, thiophene), 7.04 (d, J = 4 Hz) 1 H (thiophene), and 3.75 ppm (s) 3 H (OCH_3). Anal. Calcd for $C_{18}H_{14}SO_2$: C, 73.46; H, 4.80. Found: C, 73.34; H, 4.97.

2-(5-Phenyl-2-thienyl)benzoic Acid (19d) was prepared by saponifying 4.10 g (14.0 mmol) of ester **19c** with 15% aqueous methanolic NaOH. $CHCl_3$ extraction gave 3.55 g (12.7 mmol, 91%) of crude acid, which was recrystallized (MeOH, 20 ml), recovery 2.43 g of yellow crystals with mp 138–189 °C; ν_{max} ($CHCl_3$) 1680 cm^{-1}; λ_{max} (MeOH) 315 nm (ϵ 21 000); ^{1}H NMR δ 11.32 (s) 1 H (CO_2H) and 7.90–7.08 ppm (m) 11 H (aromatic). Anal. Calcd for $C_{17}H_{12}SO_2$: C, 72.85; H, 4.32. Found: C, 72.68; H, 4.37.

Registry No.—**1,** 2404-87-7; **2,** 58267-81-5; **3,** 58267-82-6; **4,** 58267-83-7; **5,** 58267-84-8; **6a,** 18791-75-8; **6b,** 4701-17-1; **7,** 38071-22-6; **8a,** 58267-85-9; **8b,** 52157-62-7; **9,** 58267-86-0; **10a,** 58267-87-1; **10b,** 58267-88-2; **11a,** 58267-89-3; **12a,** 58267-90-6; **12b,** 58267-91-7; **13,** 58267-92-8; **14a,** 26170-87-6; **14b,** 9163-21-4; **15a,** 58267-93-9; **15b,** 58267-94-0; **15c,** 58267-95-1, **15d,** 58267-96-2; **16,** 58267-97-3; **17a,** 58267-98-4; **17b,** 58267-99-5; **17c,** 58268-00-1; **18a,** 58268-01-2; **18b,** 58268-02-3; **19a,** 58268-03-4; **19b,** 58268-04-5; **19c,** 58268-05-6; **19d,** 58268-06-7; **20,** 58268-07-8; *N*-iodosuccinimide, 516-12-1; methyl 2-iodobenzoate, 610-97-9; thiophene-2-carboxaldehyde ethylene acetal, 58268-08-9; malonic acid, 141-82-2.

References and Notes

(1) E. W. Bousquet, M. D. Moran, J. Harmon, A. L. Johnson, and J. C. Summers, *J. Org. Chem.*, **40,** 2208 (1975).
(2) A. L. Johnson and P. B. Sweetser, *J. Org. Chem.*, **41,** 110 (1976)
(3) A. L. Johnson, U.S. Patent 3,849,436 (Nov. 19, 1974).
(4) E. M. Beyer, Jr., A. L. Johnson, and P. B. Sweetser, *Plant Physiol.*, in press.
(5) A. W. Chow, N. M. Hall, J. R. E. Hoover, M. M. Dolan, and R. J. Ferlauto, *J. Med. Chem.*, **9,** 551 (1966).
(6) Y. Poirier and N. Lozac'h, *Bull. Soc. Chim. Fr.*, 1062 (1966).
(7) L. Benati and M. Tiecco, *Boll. Sci. Fac. Chim. Ind. Bologna, Suppl.*, **24,** 225 (1966); *Chem. Abstr.*, **67,** 90193a (1967).
(8) M. Nilsson, *Tetrahedron Lett.*, 679 (1966).
(9) H. Wynberg, R. M. Kellogg, H. van Driel, and G. E. Beekhuis, *J. Am. Chem. Soc.*, **88,** 5047 (1966).
(10) S. Gronowitz and N. Gjøs, *Acta Chem. Scand.*, **21,** 2823 (1967).
(11) S. Gronowitz, N. Gjøs, R. M. Kellogg, and H. Wynberg, *J. Org. Chem.*, **32,** 463 (1967).
(12) N. Gjøs and S. Gronowitz, *Acta Chem. Scand.*, **21,** 2893 (1967).
(13) N. Gjøs and S. Gronowitz, *Acta Chem. Scand.*, **24,** 99 (1970).
(14) R. M. Kellogg, A. P. Schaap, E. T. Harper, and H. Wynberg, *J. Org. Chem.*, **33,** 2902 (1968).
(15) W. E. Bachmann and R. A. Hoffman, *Org. React.*, **2,** 243 (1944).
(16) M. Goshaev, O. S. Ostroshchenko, and A. S. Sadikov, *Usp. Khim.*, **41,** 2198 (1972).
(17) Chemical Abstracts Formula Index (1920–1973) lists only the isomeric 5,5'-diphenyl-2,2'-bithiophene, e.g., *Chem. Abstr.*, **31,** 3046 (1937); **35,** 3631 (1941); **49,** 13213 (1955); **55,** 7383 (1961); **58,** 10705 (1963); **59,** 13917 (1963).
(18) Ya. L. Goldfarb, Yu. B. Volkenshtein, and B. V. Lopatin, *Zh. Obshch. Khim.*, **34,** 969 (1964).
(19) Ya. L. Goldfarb, Yu. B. Volkenshtein, and L. I. Belenskii, *Angew. Chem., Int. Ed. Engl.*, **7,** 519 (1968).
(20) G. Jones, *Org. React.*, **15,** 204 (1967).
(21) W. J. King and F. F. Nord, *J. Org. Chem.*, **14,** 409 (1949).
(22) H. L. Holmes, *Org. React.*, **4,** 62 (1948).
(23) J. H. Uhlenbroek and J. D. Bijloo, *Recl. Trav. Chim. Pays-Bas*, **79,** 1181 (1960).
(24) Melting points are uncorrected, and were determined in a Mel-Temp capillary apparatus; ir spectra were determined in $CHCl_3$ on a Perkin-Elmer 621 instrument; uv spectra were determined on a Cary Model 14 instrument; NMR spectra were determined in $CDCl_3$ vs. internal Me_4Si on a Varian Associates A-60 instrument; mass spectra were determined by direct injection into a consolidated CEC-110 instrument.
(25) The initial adduct of 3-lithiothiophene and cyclohexanone, 1-(3-thienyl)cyclohexanol, was not reported in the original literature;[10–14] it may be obtained as a crystalline solid by allowing the crude product to stand at 25 °C for a few days and filtering the mixture. It has mp 33–35°; ν_{max} 3580 cm^{-1}; λ_{max} (EtOH) 234 nm (ϵ 5730); ^{1}H NMR δ 7.22 (m) 3 H (thiophene), 1.87 (broad) 1 H (OH), and 1.67 ppm (m) 10 H (cyclohexyl). Anal. Calcd for $C_{10}H_{14}OS$: C, 65.91; H, 7.74. Found: C, 66.03; H, 6.89. This product is readily dehydrated to 3-(1-cyclohexenyl)thiophene by 30-min reflux in a mixture of $POCl_3$, C_6H_6, and C_5H_5N.
(26) M. S. Newman and K. Naiki, *J. Org. Chem.*, **27,** 863 (1962).