A Study of Some Thiophene Analogues of Glycolic Acid

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Reaction of phenyl(3-thienyl)glycolic acid (1) with $AlCl_3$ in benzene solution leads to the formation of 4*H*-indeno[1,2-*b*]thiophene-4-carboxylic acid (2) whereas analogous reaction of phenyl(2-thienyl)glycolic acid (4) produces no indenothiophene but only a mixture of 5 and 6. In the case of di-(2-thienyl)glycolic acid (**14b**) and di-(3-thienyl)glycolic acid (**16b**) analogous results are obtained, with the former leading to the formation of **15** and the latter producing **17**. In the case of the (benzo[*b*]thienyl)phenylglycolic analogues of 1 and 4 the acids were unstable to heat so the ethyl esters, ethyl (2-benzo[*b*]thienyl)phenylglycolate (**21**) and ethyl (3-benzo[*b*]thienyl)phenylglycolate (**20**), upon treatment with $AlCl_3$ in benzene led to cyclized products only. The former gave **23** which was saponified and decarboxylated to yield **25** and compared with an authentic sample obtained by synthesis. Ester **20** similarly gave **22** which was similarly converted to the known **24**. A mechanistic explanation of these findings is proposed.

During a study of the chemistry of indenothiophenes, 4*H*-indeno[1,2-*b*]thiophene-4-carboxylic acid (**2**) was prepared in 39% yield by the interaction of phenyl(3-thienyl)glycolic acid (**1**) with aluminum chloride in the presence of benzene.[2] An attempt to obtain the isomeric 8*H*-indeno[2,1-*b*]thiophene-8-carboxylic acid (**3**) by analogous treatment of phenyl(2-thienyl)glycolic acid (**4**) gave no indenothiophene derivative. The product,[2] obtained in 40% yield, appeared to be a mixture of two components. consideration of the elemental and NMR spectral analysis of the mixture suggested the presence of two phenylated derivatives of phenyl(2-thienyl)acetic acid (**5** and **6**) in a ratio of 1:12 as indicated by singlets at δ 5.33 and 5.35 in the NMR spectrum of the mixture (Scheme I).

Attempts to separate the components of the mixture by a variety of methods were unsuccessful. To confirm these assignments we have prepared samples of **5** and **6** and found that a 1:12 mixture of these was identical in all respects with the mixture obtained from *4*.

The synthetic routes to phenyl(5-phenyl-2-thienyl)acetic acid (**5**) and 4′-biphenylyl(2-thienyl)acetic acid (**6**) are shown in Scheme II.

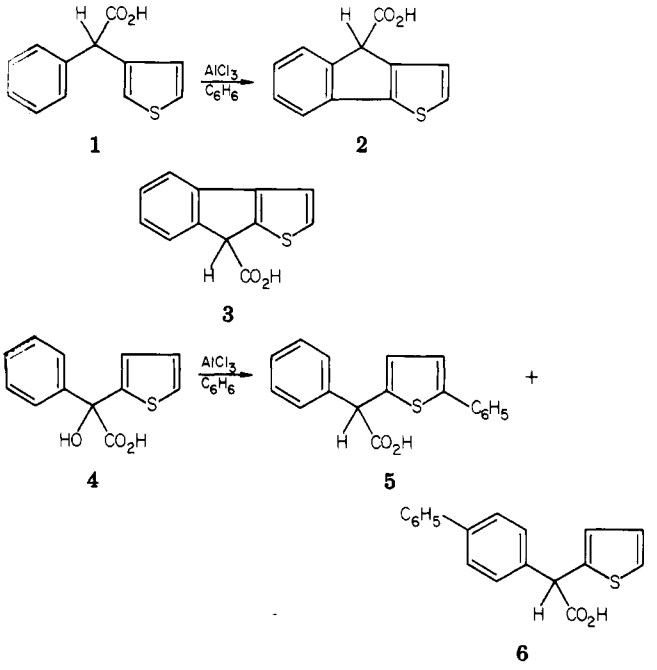
We have now extended the investigation to the analogous dithienylglycolic acids and benzo[*b*]thienylglycolic acids. Treatment of di-(2-thienyl)glycolic acid[5] (**14b**) and di-(3-thienyl)glycolic acids (**16b**) with aluminum chloride in benzene solution afforded the products shown in Scheme III.

Only one product was detected in each case by examination of the crude reaction products by NMR spectroscopy. The structure of **15** was verified by synthesis (Scheme IV).

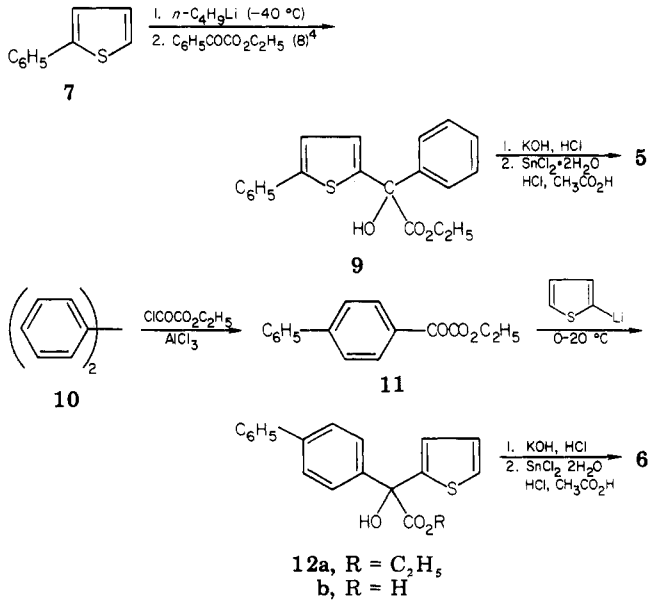
The structure of **17** was verified by decarboxylation to the known 4*H*-cyclopenta[2,1-*b*:3,4-*b*′]dithiophene[6] (**18**) which could be reconverted to the carboxylic acid **17** by lithiation and carbonation.

In the case of the 2- and (3-benzo[*b*]thienyl)phenylglycolic acids, the parent acids were unstable to heat, so the esters **20** and **21** which were prepared by te interaction of ethyl phenylglyoxylate with 2- and (3-benzo[*b*]thienyllithium, respectively, were treated with aluminum chloride in benzene with the production of the products

Scheme I



Scheme II



(1) (a) Taken in part from the Ph.D. Dissertation of A.T.J., West Virginia University, 1970. (b) Taken in part from the M.S. Thesis of K.C.M., West Virginia University, 1969. (c) Taken in part from the M.S. Thesis of D.M.O., West Virginia University, 1978. (d) Taken in part from the Ph.D Dissertation of A.W.S., West Virginia University, 1977.

(2) D. W. H. MacDowell and A. T. Jeffries, *J. Org. Chem.*, **36**, 1053 (1971).

(3) A. J. Kosak, R. F. Palchack, W. A. Steele, and C. M. Stelurtz, *J. Am. Chem. Soc.*, **76**, 4450 (1944).

(4) R. Micetich and R. Raap, *Org. Prep. Proc. Int.*, **3**, 167 (1971).

(5) G. P. Nilles and R. D. Schuetz, *Tetrahedron Lett.*, 4313 (1969).

(6) A. Kraak, A. K. Wiersema, P. Jordens, and H. Wynberg, *Tetrahedron*, **24**, 3381 (1968).

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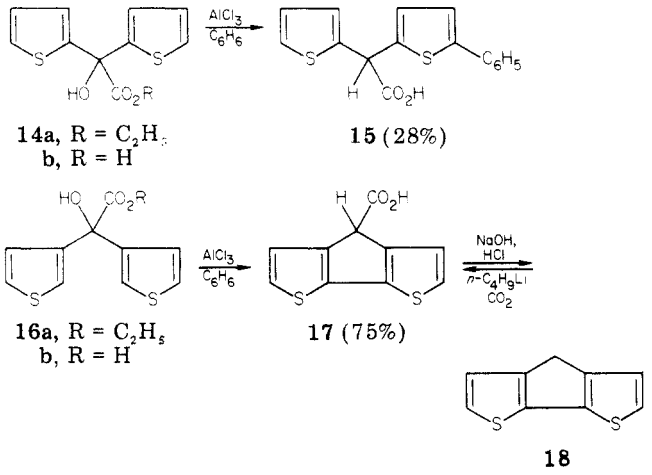
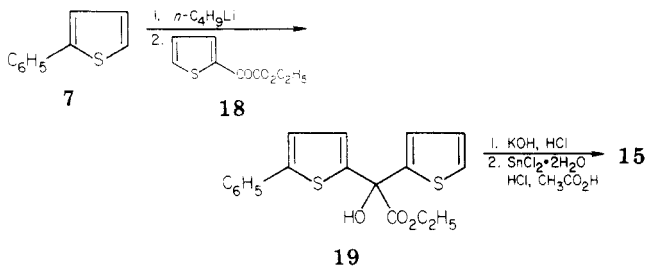
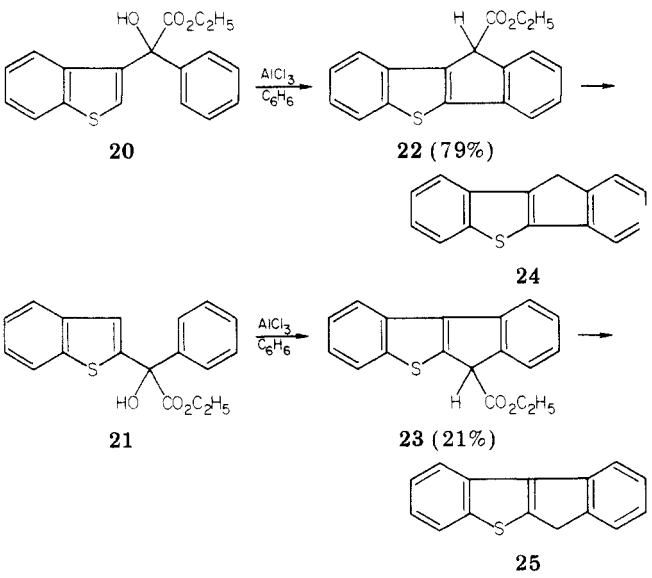
Scheme III



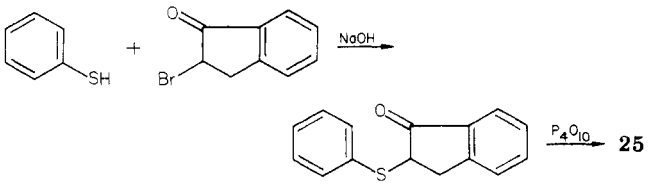
Scheme IV



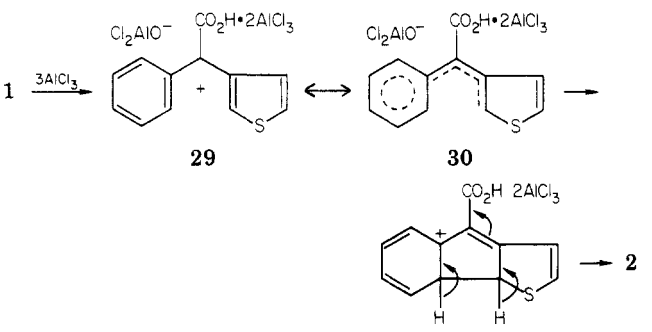
Scheme V



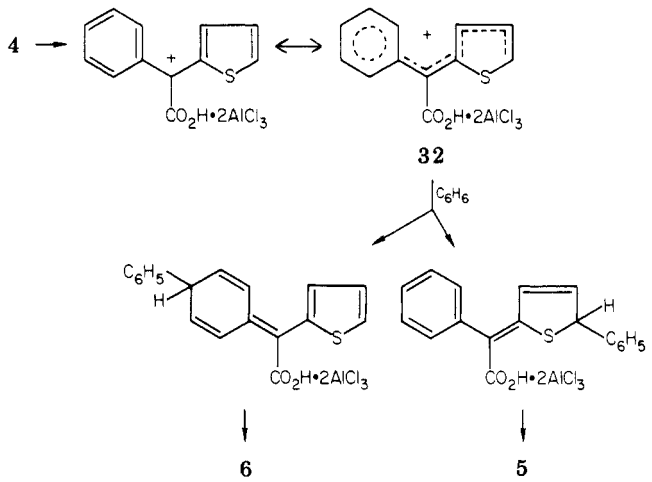
22 and 23 as shown in Scheme V. The structures of 22 and 23 were verified by conversion to the known 10*H*-benz[*b*]indeno[2,1-*d*]thiophene[7] (24) and to 6*H*-benz[*b*]-indeno[1,2-*d*]thiophene (25) which was prepared as shown below.



Scheme VI



Scheme VII



A possible pathway for these transformations is shown in Scheme VI. In the case of 1, the carbocation 29 produced includes resonance contributors such as 30 in which the positive charge is distributed in such a manner as to facilitate electrophilic attack of the phenyl ring at carbon two of the thiophene ring leading to the formation of 2. For the 2-thienyl system 4 the carbocation is shown in Scheme VII. The positive charge is seen to be more extensively delocalized throughout the thiophene ring than in the case of 30. Benzene can add to 32 in typical Friedel–Crafts fashion to form the phenylated products 5 and 6.

The formation of 15 and 17 from 14 and 16 follows the same line of reasoning. Nilles and Schuetz[5] have demonstrated the presence of the carbocation corresponding to 14 or its methyl ester when either of these two compounds is placed in strong acid ($ClSO_3H$–CH_2Cl_2). Quenching of the acid solution of the carbocations afforded no cyclopentadithiophene derivatives, but only products resulting from the reaction of the quenching nucleophile at the carbon α to the acid or ester grouping. Östman and Sjöberg[8] have found that when the methyl ester of **16b** is placed in strong acid ($ClSO_3H$–CH_2Cl_2) the expected carbocation was produced but then cyclization occurred to produce the methyl ester of 17.

For the benzo[*b*]thienyl esters 20 and 21 it is suggested that the presence of the fused benzene ring stabilizes any resulting carbocation in the thiophene portion of the molecule, so promoting cyclization over phenylation.

Experimental Section

General Methods. All melting points are uncorrected. Elemental analyses were carried out by Galbraith Laboratories, Inc.,

(7) T. J. Barton, A. J. Nelson, and J. Clardy, *J. Org. Chem.*, **36**, 3995 (1971).

(8) B. Östman and S. Sjöberg, *Tetrahedron Lett.*, 3137 (1970).

Knoxville, TN. IR spectra were determined on a Beckman IR-8 spectrophotometer, NMR spectra were recorded on a Varian Model T-60 or EM-360 spectrometer, and the mass spectra were obtained on a Nuclide Corp. 12-90G high-resolution mass spectrometer. Reagents were used as received unless otherwise stated.

Phenyl(2-thienyl)glycolic acid (4) was prepared from ethyl phenylglyoxylate[4] and 2-thienyllithium followed by saponification (10% KOH–C_2H_5OH) as white fluffy crystals (benzene–hexane): mp 121–122 °C (lit.[9] mp 122 °C); 17.4 g (40%); IR (KBr) 1710, 3500–3200 cm^{-1}; NMR (acetone-d_6) δ 7.7–7.0 (m, 8), 4.6 (m, 2).

Reaction of Phenyl(2-thienyl)glycolic Acid with Aluminum Chloride in Benzene. To a cooled stirred solution of phenyl(2-thienyl)glycolic acid (2 g, 8.5 mmol) in 75 mL of dry benzene was added in one portion 3.6 g of anhydrous aluminum chloride (30 mmol) and an additional 50 mL of benzene. The purple mixture was stirred under reflux 1 h, then 10 g of ice and 11 mL of HCl were added, and the mixture was evaporated to leave a purple gum. This gum was treated with 40 mL of hot 10% Na_2CO_3 solution and cooled to 5 °C overnight to produce a solid mass of the sodium salt of the acid. The sodium salt was dissolved in hot water, decolorized (Norite), and filtered, then cooled, and acidified to give a pink solid, which was taken up in ether. The ethereal layer was washed, dried ($MgSO_4$), and evaporated to afford pale pink crystals. Recrystallization from benzene/hexane afforded an analytical sample, mp 147–147.5 °C dec with gas evolution. Other runs of this reaction with purified phenyl(2-thienyl)glycolic acid gave comparable yields (42–59%). If the phenyl(2-thienyl)glycolic acid had decomposed at all, yields and purity of the product were greatly decreased: IR (KBr) 1705 (COOH), 3400 cm^{-1} (br, OH); NMR (acetone-d_6) δ 7.4 (m, 12, aromatic), 5.33 and 5.35 (s, total 1 H). Anal. Calcd for $C_{18}H_{14}O_2S$: C, 73.44; H, 4.79; S, 10.89. Found: C, 73.51; H, 4.83; S, 10.89.

Ethyl Phenyl(5-phenyl-2-thienyl)glycolate (9). An ethereal solution of (5-phenyl-2-thienyl)lithium from 2-phenylthiophene (3.2 g, 0.02 mol) in 50 mL of anhydrous ether at 4 °C was added dropwise at 0 °C to a cooled solution of ethyl phenylglyoxylate (3.6 g, 0.022 mol) in 60 mL of dry ether. The reaction mixture was stirred 1 h and then quenched with NH_4Cl and ice. Workup yielded a green oil which solidified under hexane. Recrystallization from hexane afforded white needles (4.8 g, 71%), mp 78–78.5 °C. Further recrystallization from hexane gave an analytical sample, mp 80–80.5 °C; IR (KBr) 3400 (OH), 1720 cm^{-1} (ester C=O); NMR ($CDCl_3$) δ 7.6–7.0 (m, 12), 4.38 (q, 2, CH_2), 4.5 (s, 1, OH), 1.4 (t, 3, CH_3). Anal. Calcd for $C_{20}H_{18}O_3S$: C, 70.98; H, 5.36; S, 9.48. Found: C, 71.21; H, 5.26; S, 9.66.

Phenyl(5-phenyl-2-thienyl)acetic Acid (5). Saponification (KOH–C_2H_5OH) of the crude oily hydroxy ester (20 g) afforded a red-brown oil (11.5 g) which was not purified. Treatment of this oil (3.3 g) in 35 mL of glacial acetic aid with stannous cloride dihydrate (4.95 g) and water (1 mL) at 20 °C for 20 min with a stream of HCl gas gave a dark solution which was poured into water and worked up by extraction with ether to afford a red oil. Trituration with hexane afforded a tan solid, which was recrystallized from benzene/hexane to afford off-white needles: 2.1 g; mp 149–152 °C. Further recrystallization from benzene/hexane afforded an analytical sample: mp 154–154.5 °C; mixture melting point with the acid from the Friedel–Crafts reaction 134–141 °C dec; IR (KBr) 3500 (br, OH), 1695 cm^{-1} (C=O); NMR (acetone-d_6) δ 7.8–7.0 (m, 12), 5.33 (s, 1). Anal. Calcd for $C_{18}H_{14}O_2S$: C, 73.44; H, 4.79; S, 10.89. Found: C, 73.61; H, 4.90; S, 11.01.

Addition of a small amount of this acid to the mixed acids from the Friedel–Crafts reaction gave an enhanced NMR signal at δ 5.33, which in the Friedel–Crafts reaction mixture is the smaller of the two peaks.

4′-Biphenylyl(2-thienyl)acetic Acid (6). Ethyl 4-biphenylylglyoxylate (11) was prepared in 45% yield from biphenyl (50.8 g, 0.33 mol) and ethyl oxalyl chloride (100 g) in 200 mL of dry CS_2 with 44 g (0.33 mol) of aluminum chloride, as a yellow liquid, bp 170 °C (1 mm) [lit.[10] bp 205 °C (5 mm)], which solidified upon cooling: yield 26.7 g (45% based on biphenyl used); mp 38 °C (lit.[10] mp 38–39 °C); IR (neat) 1730 (ester C=O), 1670 cm^{-1} (ketone C=O); NMR (CCl_4) δ 8.1–7.3 (m, 9, aromatic), 4.4 (q, 2, CH_2), 1.45 (t, 3, CH_3).

4′-Biphenylyl(2-thienyl)glycolic Acid (12b). Interaction of ethyl 4-biphenylylglyoxate (5.0 g, 0.019 mol) with ethereal 2-thienyllithium (0.02 mol) at 0 °C followed by saponification of the green oily hydroxy ester (KOH–C_2H_5OH) gave a pale yellow solid which was recrystallized from benzene/hexane to give **12b** as small needles: 3.8 g (62%); mp 127–129 °C (lit.[9] mp, 129–130 °C).

Reduction of 4′-biphenylyl(2-thienyl)glycolic acid (12b) was accomplished by using the same procedure as in the reduction of **9** to **5**. From 10.0 g (0.032 mol) of 4-biphenylyl(2-thienyl)glycolic acid 120 mL of glacial acetic acid, 14.4 g (0.064 mol) of stannous chloride dihydrate, and 2 mL of water was obtained yellow crystals which were recrystallized from acetic acid and then from benzene/pentane to give colorless needles: mp 141.5–142.5 °C (lit.[9] mp 137–139 °C); 7.0 g (74%). An analytical sample was recrystallized from benzene: IR (KBr) 3500–2800 (br) (COOH), 1690 (C=O), 710, 650 cm^{-1}; NMR (acetone-d_6) δ 7.0–7.5 (m, 12, aromatic), 5.35 (s, 1). Anal. Calcd for $C_{18}H_{14}O_2S$: C, 73.44; H, 4.79; S, 10.89. Found: C, 73.25; H, 4.82; S, 11.01.

Samples of the synthetic 4′-biphenylyl(2-thienyl)acetic acid and phenyl(5-phenyl-2-thienyl)acetic acid were mixed in a ratio of 12:1. This mixture was identical with the product from the Friedel–Crafts reaction of the phenyl(2-thienyl)glycolic acid with aluminum chloride in benzene in mixture melting point, infrared spectrum, and nuclear magnetic resonance spectrum.

Di-(2-thienyl)glycolic Acid (14b). Ethyl (2,2′-Dithienyl)glycolate (14a). From ethereal 2-thienyllithium (0.05 mol) and ethyl (2-thienyl)glyoxylate[4] (9.2 g, 0.05 mol) at 15 °C, followed by the usual workup, was obtained an oil which was distilled to give 7.13 g (53%) of a pale yellow oil, bp 165 °C (0.3 mm), which solidified on standing at 0 °C to give colorless crystals. Recrystallization from carbon tetrachloride and then pentane afforded an analytical sample: mp 53.5–54.5 °C; IR (KBr) 3450 (OH), 1734 cm^{-1} (C=O); NMR ($CDCl_3$) δ 6.95–7.40 (m, 6, aromatic), 4.95 (s, 1, OH), 4.45 (q, 2, CH_2), 1.40 (5, 3, CH_3). Anal. Calcd for $C_{12}H_{12}O_3S_2$: C, 53.71; H, 4.51; S, 23.90. Found: C, 53.86; H, 4.61; S, 24.01.

Di-(2-thienyl)glycolic acid (14b) was prepared from **14a** (14.4 g) by saponification (KOH–C_2H_5OH) to give **14b** as white crystals (6.3 g, 49%), mp 93–94 °C dec (benzene–pentane) (lit.[9] mp 93–94 °C). This acid darkened readily upon exposure to air and was used immediately.

Reaction of Di-(2-thienyl)glycolic Acid with Aluminum Chloride in Benzene. To a solution of **14b** (1.0 g, 4.17 mmol) in 25 mL of dry benzene cooled to a slush was added, in one portion, freshly sublimed aluminum chloride (1.67 g, 12.5 mmol) and 10 mL of benzene. the cooling bath was removed and the reaction mixture was refluxed with stirring for 1 h, allowed to cool to room temperature, and then hydrolyzed with HCl and ice. Extraction with benzene, followed by washing and drying, gave a gummy purple residue which was then dissolved in 35 mL of hot 10% Na_2CO_3, decolorized (Norite), filtered, and acidified to give a dark red solid. The solid was taken up in ether, dried ($MgSO_4$), and evaporated to give a dark red oil. The oil was taken up in hot 15% v/v benzene/hexane, decolorized (Norite), and cooled to afford pink needles (0.35 g, 28%), mp 80–90 °C. Recrystallization from cyclohexane afforded an analytical sample: mp 98–100 °C; IR (KBr) 3400–2800 (br, OH), 1685 cm^{-1} (C=O); NMR (acetone-d_6) δ 6.95–7.70 (m, 10, aromatic), 5.40 (s, 1, CH). Anal. Calcd for $C_{18}H_{12}O_2S_2$: C, 63.97; H, 4.03; S, 21.35. Found: C, 64.06; H. 3.99; S, 21.14.

Ethyl (5-Phenyl-2-thienyl)(2-thienyl)glycolate (19). From 5-phenyl-2-thienyllithium (20 mmol) and ethereal ethyl (2-thienyl)glyoxylate (3.6 g, 20 mmol) at −40 °C followed by the usual workup was obtained a green oil which was chromatographed (Al_2O_3, $CHCl_3$) to give a pale green oil which upon cooling crystallized to yellow needles (5.2 g, 76%), mp 65–66.5 °C. Recrystallization from hexane afforded an analytical sample: mp 67.5–68 °C; IR (KBr) 3475 (OH), 1720 (C=O), 745, 675 cm^{-1}; NMR (CCl_4) δ 6.95–7.65 (m, 10, aromatic), 4.75 (s, 1), 4.40 (t, 2, CH_2), 142 (t, 3, CH_3). Anal. Calcd for $C_{18}H_{16}O_3S_2$: C, 62.76; H, 4.68; S, 18.62. Found: C, 62.94; H, 4.70; S, 18.70.

(5-Phenyl-2-thienyl)(2-thienyl)acetic Acid (15). Saponification of **19** (8.5 g, 25 mmol) (KOH–C_2H_5OH) followed by stannous chloride reduction of the unpurified hydroxy acid gave (5-phenyl-2-thienyl)(2-thienyl)acetic acid (**15**) as an oil. Re-

(9) F. F. Blicke and M. U. Tsao, *J. Am. Chem. Soc.*, **66**, 1645 (1944).
(10) F. F. Blicke and N. Grier, *J. Am. Chem. Soc.*, **65**, 1725 (1943).

crystallization from benzene/hexane (1:1) and then from ethanol/water, afforded off-white needles, mp 98–100 °C (3.2 g, 43%). This was shown to be identical by mixture melting point and mixture NMR with the sample from the Friedel–Crafts reaction of (2,2′-dithienyl)glycolic acid with aluminum chloride in benzene.

Di-(3-thienyl)glycolic Acid (16b). (a) Ethyl (3-Thienyl)-glyoxylate. A solution of 3-thienyllithium (from 32.6 g of 3-bromothiophene) was stirred at −70 °C for 0.5 h and then added to a stirred solution of magnesium bromide[11] generated from magnesium (9.0 g) and ethylene bromide (50 g) in 150 mL of 10:1 v/v ether/benzene. The mixture was stirred 1 h, cooled to −70 °C, and then added dropwise to a solution of ethyl oxalate (68 g, 0.47 mol) in 200 mL of ether. The resulting thick white suspension was allowed to warm to −20 °C; hydrolyzed with 2 M HCl, poured on ice, and extracted with ether. Evaporation afforded a yellow liquid which was further fractionated under vacuum to give a pale yellow liquid: bp 96 °C (0.3 mm); yield 26.4 g (72%); IR (neat) 1726 ($CO_2C_2H_5$), 1668 cm^{-1} (C=O); NMR (CCl_4) δ 8.42–7.32 (m, 3, aromatic), 4.38 (q, 2, CH_2), 1.44 (t, 3, CH_3).

(b) Ethyl (3,3′-Dithienyl)glycolate (16a) and (3,3′-Dithienyl)glycolic Acid (16b). An ether solution of 3-thienylmagnesium bromide (25 mL, 0.05 mol) was added dropwise to a cooled (−70 °C) solution of ethyl (3-thienyl)glyoxylate (9.2 g, 0.05 mol) in 200 mL of ether. The resulting pale yellow suspension, as it warmed, turned to a bright orange solution which allowed to warm to 9 °C. Hydrolysis and workup afforded a pale yellow oil which failed to give any crystals upon trituration with pentane and cooling. The infrared and NMR spectra indicated the presence of hydroxy ester, **16a**, so the oily product (18.7 g) was converted directly to the desired hydroxy acid; NMR (CCl_4) δ 7.0–7.4 (m, 6, aromatic), 4.0–4.35 (s, overlapping q, H, 3, CH_2), 1.05 (t, 3, CH_3).

Saponification of the hydroxy ester with 10% ethanolic KOH followed by the usual workup gave upon evaporation a yellow solid. Repeated recrystallization from benzene/hexane afforded colorless needles: mp 113–114 °C dec; 9.4 g (78%); IR (KBr) 3400 (OH), 3200–2700 (br, COOH), cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.05–7.40 (m, 6, aromatic), 6.0 (br s, 2, OH, CO_2H). Anal. Calcd for $C_{10}H_8O_3S_2$ C, 49.98; H, 3.35; S, 26.69. Found: C, 50.08; H, 3.33; S, 26.70.

Reaction of (3,3′-Dithienyl)glycolic Acid (16b) with Aluminum Chloride in Benzene. To a solution of 1.0 g (4.2 mmol) of **16b** in 35 mL of dry benzene cooled to 4 °C was added in one portion 1.67 g (12.7 mmol) of anhydrous aluminum chloride. The deep purple solution was refluxed 1 h, during which time the purple color disappeared and the reaction mixture turned light yellow. Hydrolysis followed by extraction of organic extracts with Na_2CO_3 and acidification gave a brown solid precipitate (0.8 g) which was extracted (Soxhlet) with carbon tetrachloride to give light tan needles. Recrystallization from 1:2 $CHCl_3/CCl_4$ followed by decolorization afforded white needles of 4*H*-4-carboxycyclopenta[2,1-*b*:3,4-*b*′]thiophene (**17**, 0.7 g, 75%), mp 179–180 °C. An analytical sample was obtained from benzene/hexane: mp 179.5–180 °C (loss of CO_2); IR (KBr) 3.50–2450 (br, OH), 1700 cm^{-1} (COOH); NMR (acetone-d_6) δ 7.20 (dd, 4, aromatic), 4.70 (s, 1, CH). Anal. Calcd for $C_{10}H_6O_2S_2$: C, 54.03; H, 2.72; S, 28.85. Found: C, 53.98; H, 2.71; S, 28.59.

Decarboxylation of 4*H*-4-Carboxycyclopenta[2,1-*b*:3,4-*b*′]dithiophene. 4*H*-Cyclopenta[2,1-*b*:3,4-*b*′]dithiophene (18). A mixture of 4*H*-4-carboxycyclopenta[2,1-*b*:3,4-*b*′]dithiophene (0.6 g, 2.7 mmol), 25 mL of distilled quinoline, and 0.5 g of copper powder was heated with stirring at reflux for 4 h and then poured onto a mixture of ice and HCl. The mixture was extracted with ether and the ether extracts were washed with HCl and Na_2CO_3, then dried ($MgSO_4$), and evaporated to afford a pale yellow oil which upon trituration with ethanol and cooling afforded colorless crystals of 18: 0.38 g (79%); mp 73.5–74.5 °C (lit.[6] mp 74–75 °C); NMR (CCl_4) δ 7.0 (dd, 4, aromatic), 3.40 (s, 2, CH_2). Anal. Calcd for $C_9H_6S_2$: C, 60.63; H, 3.39; S, 35.97. Found: C, 60.60; H, 3.53; S, 35.75.

4*H*-4-Carboxycyclopenta[1,2-*b*:3,4-*b*′]dithiophene (16). To a solution of 4*H*-cyclopenta[1,2-*b*:3,4-*b*′]dithiophene (18; 0.5 g, 2.8 mmol) in 20 mL of anhydrous ether was added ethereal *n*-butyllithium (2.2 mL, 1.27 M, 2.81 mmol). The reaction mixture was stirred at 0 °C for 1 h, then poured onto dry ice (~50 g) in ether, allowed to warm to room temperature, acidified with HCl, extracted with ether, washed, and dried ($MgSO_4$). Evaporation afforded off-white needles (mp 174–176 °C) which were recrystallized from benzene/hexane to afford **17** (0.45 g, 72%), mp 178–179 °C. A mixture melting point with authentic **17** gave no depression of melting point.

Ethyl (3-Benzo[*b*]thienyl)phenylglycolate (20). From ethyl phenylglyoxylate (8.9 g, 0.05 mol) at −70 °C and 3-benzo[*b*]-thienyllithium[12] (0.05 mol) at −70 °C, **20** was obtained as an off-white oily solid, mp 70–75 °C. Recrystallization from hexane afforded ethyl (3-benzo[*b*]thienyl)phenylglycolate (11.5 g, 74%) as white needles, mp 78–79 °C. Recrystallization from hexane yielded an analytical sample: mp 79.5–81 °C; IR (KBr) 3520 (OH), 1713 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.10–7.78 (m, 10, aromatic), 4.03–4.32 (q, s, 3, CH_2 and OH), 1.02–1.27 (t, 3, CH_3). Anal. Calcd for $C_{18}H_{16}O_3S$: C, 69.20; H, 5.16; S, 10.27. Found: C, 69.16; H, 5.26; S, 10.32.

Reaction of Ethyl (3-Benzo[*b*]thienyl)phenylglycolate with $AlCl_3$ in Benzene. Treatment of ethyl (3-benzo[*b*]thienyl)phenylglycolate (1 g, 3.2 mmol) in 45 mL of anhydrous benzene at 0 °C with a 3 molar excess of $AlCl_3$ (1.28 g, 9.6 mmol) gave a red-brown solution which was warmed slowly to 50 °C and stirred at that temperature for 2 h. Workup gave a red-brown oil which solidified to an oily solid, 0.74 g, which when washed with cold ether gave a yellow crystalline solid (0.4 g, 43%), mp 89–91 °C. Two recrystallizations from heptane gave an analytical sample as pale yellow crystals, mp 92.5–93.5 °C. The analysis and spectra agree with the formulation of the product as ethyl 10*H*-benz-[*b*]inden[2,1-*d*]thiophene-10-carboxylate (**22**): IR (KBr) 1730 (s), 745 (s), 715 cm^{-1} (m); NMR ($CDCl_3$) δ 7.9–7.1 (m, 8, aromatic), 4.88 (s, 1, CH), 4.16 (q, 2, CH_2)$_9$ 1.22 (t, 3, CH_3). Anal. Calcd for $C_{18}H_{14}O_2S$: C, 73.44; H, 4.79; S, 10.89. Found: C, 73.59; H, 4.75; S, 10.75.

Saponification of Ethyl 10*H*-Benz[*b*]indeno[2,1-*d*]-thiophene-10-carboxylate (22). Unpurified ethyl 10*H*-benz-[*b*]indeno[2,1-*d*]thiophene-10-carboxylate (0.65 g, 2.2 mmol) was treated with 40 mL of 10% ethanolic KOH under reflux for 12 h. Evaporation of the ethanol left a black solid (0.5 g, mp 170–190 °C) which was essentially insoluble in hot water, ether, and acetone. Sublimation at 162–168 °C (0.05 mm) yielded a bright yellow solid which was recrystallized twice from 95% ethanol to yield very pale green platelets of 10*H*-benz[*b*]indeno[2,1-*d*]-thiophene (**24**): 0.17 g (35%); mp 206.5–207.5 °C (lit.[7] mp 201–202 °C); by mass spectrometry 222; IR (KBr) 1450 (vw), 1420 (vw), 1250 (w), 740 (s), 730 (w), 710 cm^{-1} (m); NMR ($CDCl_3$) δ 7.0–7.1 (m, 8, aromatic), 3.8 (s, 2, CH_2). Anal. Calcd for $C_{15}H_{10}S$ (mol wt 222): C, 81.04; H, 4.53; S, 14.43. Found: C, 81.16; H, 4.41; S, 14.46.

Ethyl (2-Benzo[*b*]thienyl)phenylglycolate (21). Reaction of 2-benzo[*b*]thienyllithium[13] (0.05 mol) at 40 °C with ethyl phenylglyoxylate (13.35 g, 0.076 mol) in 100 mL of ether as for **20** gave, followed chromatography over silica gel 60 (70–230-mesh ASTM, partical size 0.063–0.200 mm) and elution with 1:1 (v/v) benzene–hexane containing 1.5% (v) glacial acetic acid, first 1-(2-benzo[*b*]thienyl)-2-phenylethanedione (0.45 g): mp 140–142 °C [analytical sample as pale yellow platelets (hexane) (mp 141–142 °C)]; IR (KBr) 3080 (w), 1680 (s), 1660 cm^{-1} (s); NMR ($CDCl_3$) δ 6.4–8.2 (m). Anal. Calcd for $C_{16}H_{10}O_2S$: C, 72.16; H, 3.78; S, 12.04. Found: C, 72.18; H, 3.65; S, 11.89.

Other runs of this preparation using equimolar amounts of keto ester and a lower temperature (−70 °C) resulted in considerably more diketone impurity.

The glycolic ester was eluted from the column immediately following the diketone as colorless fractions as a white crystalline solid (8.12 g, 52%, mp 84–86 °C). Recrystallization from hexane afforded an analytical sample of ethyl (2-benzo[*b*]thienyl)-phenylglycolate: mp 85–86 °C; IR (KBr) 3480 (OH), 1730 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.2–7.8 (m, 10, aromatic), 4.67 (s, 1, OH), 4.32 (q, 2, CH_2), 1.23 (t, 3, CH_3). Anal. Calcd for $C_{18}H_{16}O_3S$: C, 69.20; H, 5.16; S, 10.27. Found: C, 69.40; H, 5.33; S, 10.06.

(11) K. Nyberg, B. Östman and G. Wallenberg, *Acta Chem. Scand.*, **24**, 1590 (1970).

(12) R. P. Dickinson and B. Iddon, *J. Chem. Soc. C*, 2735 (1968).

(13) A. N. Chow, N. M. Hall, J. R. E. Hoover, M. M. Dolan, and R. J. Ferlauto, *J. Med. Chem.*, **9**, 553 (1966).

The (2-benzo[b]thienyl)phenylglycolic ester **21** was also obtained in 39% yield along with 8% of the dione by using 2-benzo[b]thienylmagnesium bromide instead of the lithium derivative.

Reaction of Ethyl (2-Benzo[b]thienyl)phenylglycolate with $AlCl_3$ in Benzene. Treatment of ethyl (2-benzo[b]thienyl)phenylglycolate (0.5 g, 1.6 mmol) in 45 mL of dry benzene at 0 °C with 3 molar excess of sublimed $AlCl_3$ (0.64 g, 4.8 mmol) followed by reflux overnight gave upon the usual workup a red-brown oil (0.40 g) which was sublimed (110 °C, 0.04 mm) to yield 0.1 g (21%) of bright yellow crystals, which were recrystallized twice from cyclohexane to given an analytical sample of ethyl 6H-benz[b]indeno[1,2-d]thiophene-6-carboxylate (**23**) as white needles: mp 94-95 °C; IR (KBr) 1728 (s), 1220 (m), 1028 (m), 763 (s), 630 cm^{-1} (w); NMR ($CDCl_3$) δ 8.10-7.00 (m, 8, aromatic), 4.81 (s, 1, CH), 4.18 (q, 2, CH_2), 1.26 (t, 3, CH_3). Anal. Calcd for $C_{18}H_{14}O_2S$: C, 73.44; H, 4.79; S, 10.89. Found: C, 73.33; H, 4.70, S, 10.95.

Reaction of Ethyl (2-Benzo[b]thienyl)phenylglycolate with $AlCl_3$ in Carbon Disulfide. Reaction of the glycolate ester **21** with $AlCl_3$ in carbon disulfide using the same as solvent but without any benzene gave a 67% yield of closed ester **23** which was chromatographed over silica gel 60 and eluted with 1:1 benzene-hexane to yield 0.63 g of yellow-orange solid (mp 89-92 °C). Yellow fluffy solid (0.40 g, mp 93.5-95 °C) was obtained on recrystallization from heptane and was shown to be identical with an authentic sample of ethyl 6H-benz[b]indeno[1,2-d]-thiophene-6-carboxylate described above by comparison of their NMR and IR spectra.

Saponification of Ethyl 6H-Benz[b]indeno[1,2-d]-thiophene-6-carboxylate (23). Recrystallized ethyl 6H-benz-[b]indeno[1,2-d]thiophene-6-carboxylate (0.40 g, 1.36 mmol) was saponified to give a dark red-brown solid (0.11 g, mp 80-85 °C) which was sublimed at 108 °C (0.1 mm) to give a yellow solid (60 mg, 20%, mp 106-108 °C). Recrystallization from pentane afforded an analytical sample of 6H-benz[b]indeno[1,2-d]thiophene as pale yellow platelets: mp 109.5-110.5 °C; IR (KBr) 1470 (m), 1420 (m), 1380 (m), 1290 (w), 1225 (w), 1170 (m), 760 (s), 720 (s), 710 (s), 620 cm^{-1} (m); NMR (CCl_4) δ 7.9-6.79 (m, 8, aromatic), 3.59 (s, 2, CH_2). Anal. Calcd for $C_{15}H_{10}S$: C, 81.04; H, 4.53; S, 14.43. Found: C, 81.08; H, 4.57; S, 14.60.

A mixture melting point of this product with synthetic 6H-benz[b]indeno[1,2-d]thiophene showed no depression and the NMR and IR spectra were identical.

6H-Benzo[b]indeno[1,2-d]thiophene (25). Reaction of sodium thiophenoxide from thiophenol (11.0 g, 0.10 mol) in aqueous THF solution with 2-bromo-1-indanone[14] (21.0 g, 0.1 mol) at 20 °C with vigorous stirring for 1 h gave upon extraction with ether a yellow oil which was crystallized from hexane to afford 16.7 g (69%) of 2-(thiophenoxy)-1-indanone, mp 77-67 °C. Anal. Calcd for $C_{15}H_{12}OS$: C, 74.96; H, 5.04; S, 13.34. Found: C, 75.16; H, 5.13; S, 13.42.

To a mixture of 30 g of 85% H_3PO_4 and 30 g of P_4O_{10} at 70 °C was added 2-(thiophenoxy)-1-indanone (6.0 g, 0.025 mol) with stirring. The mixture was maintained at 100 °C for 15 min and poured into ice and water followed by extraction with ether. The residue obtained from the ether extraction was an oil (3.86 g) which was dissolved in benzene and chromatographed over alumina with pentane as eluant to give 1.12 g of a waxy solid (mp 80-85 °C). Two recrystallizations from pentane gave 0.7 g (13%) of 6H-benzo[b]indeno[1,3-d]thiophene (**25**): mp 111-112 °C; NMR (CCl_4) 7.8-6.8 (m, 8, aromatic), 3.58 (s, 2, CH_2). Anal. Calcd for $C_{15}H_{10}S$: C, 81.04; H, 4.53; S, 14.43. Found: C, 80.92; H, 4.43; S, 14.25.

(14) H. O. House, V. Paraganian, R. S. Ro, and D. J. Wlunka, *J. Am. Chem. Soc.*, **82**, 1452 (1960).

Isomeric Phenols of Benzo[e]pyrene

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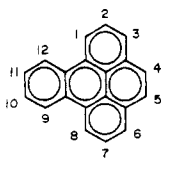
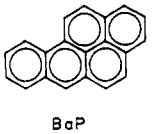
Convenient syntheses of the complete set of isomeric phenols of benzo[e]pyrene, 1-, 2-, 3-, 4-, 9-, and 10-hydroxybenzo[e]pyrene, are described. The structural assignments are supported by high-resolution 270-MHz proton NMR spectra in which the chemical shifts and coupling constants of the aromatic protons are fully assigned. Ultraviolet absorption and fluorescence spectral data for the isomeric benzo[e]pyrene phenols are also presented.

Benzo[e]pyrene (BeP) is a widespread environmental pollutant present in the atmosphere, soil, automobile exhaust, cigarette smoke, and foods.[1] In contrast to the isomeric benzo[a]pyrene which is a potent carcinogen, BeP is only a weak tumor initiator.[2]



BeP



BaP

In connection with biological studies designed to probe the nature of this striking difference in biological activity,[3,4] we required authentic samples of the isomeric phenols of BeP as standards for identification of the metabolites of this hydrocarbon. Since only one of the six isomeric phenols of BeP (4-HO-BeP) appears to have been syn-

(1) International Agency for Research on Cancer. "Monograph on the Evaluation of Carcinogenic Risk of the Chemical to Man: Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds"; World Health Organization: Geneva, Switzerland, 1973; Vol. 3.

(2) Scribner, J. D. *J. Natl. Cancer Inst.* **1973**, *50*, 1717.

(3) Recent studies have implicated a diol epoxide metabolite, *trans*-7,8-dihydroxy-*anti*-9,10-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene (*anti*-BPDE), as the principal active form of benzo[a]pyrene.[4] Significant levels of carcinogenic activity are also exhibited by certain other metabolites of benzo[a]pyrene, notably the 4,5-oxide and 2-, 9-, 11-, and 12-HO-BaP's.[5]

(4) Reviews: (a) Gelboin, H. V., Ts'o, P. O. P. Eds.; "Polycyclic Hydrocarbons and Cancer"; Academic Press: New York, 1978; (b) Harvey, R. G. In "Safe Handling of Chemical Carcinogens, Mutagens, and Teratogens"; Walters, D. B., Ed.; Ann Arbor Science Publishers, Inc.: Ann Arbor, MI, 1980; (c) Harvey, R. G. *Acc. Chem. Res.*, in press.

(5) Slaga, T. J.; Bracken, W. M.; Dresner, S.; Levin, W.; Yagi, H.; Jerina, D. M.; Conney, A. H. *Cancer Res.* **1978**, *38*, 678. Flesher, J. W.; Harvey, R. G.; Sydnor, K. L. *Int. J. Cancer* **1976**, *18*, 351.

0022-3263/81/1946-2889$01.25/0