alpha-Phenylpropionic Acid Derivatives. Synthesis and Dethiation of 5-Benzoylbenzo[*b*]thiophene-3-carboxylic Acid

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The total synthesis of the title compound **8** started with *p*-thiocresol which was acylated with oxalyl chloride to give compound **1**. This product underwent a condensation reaction with chloroacetic acid under basic conditions yielding compound **2**. Two different synthetic pathways were used to convert compound **2** into the title compound **8**. The first consisted in decarboxylation of **2** to **3**, which was then converted to the ester **4**, which was brominated and the product **5** was subjected to a Friedel-Craft's reaction with benzene. The resulting benzyl derivative **6** was oxidized to the benzoyl stage *i.e.* compound **7**, which was finally hydrolyzed to **8**. The second pathway was similar to the first one so that the steps of esterification, bromination, Friedel-Craft's alkylation and oxidation started with the dicarboxylic acid **2**. Thus compounds **12-16** were obtained, and the last product was decarboxylated to **8**. The yields in both procedures were similar. Finally, the dethiation of compound **8** with Raney nickel afforded compounds **18**, **19** and **20**.

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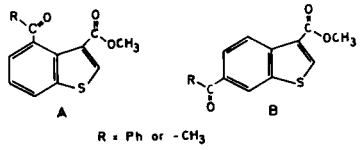
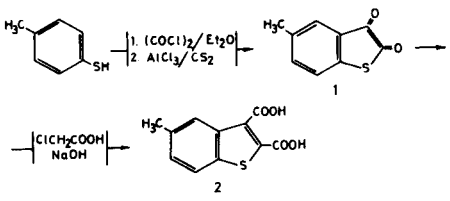
In a previous publication (3) we reported the synthesis of 4(6)-acetyl- and 4(6)-benzoyl-3-carboxymethylbenzo[*b*]-thiophene derivatives **A** and **B** by Friedel-Craft's acylation of the corresponding 3-carboxymethylbenzo[*b*]thiophene.

Formulae A and B



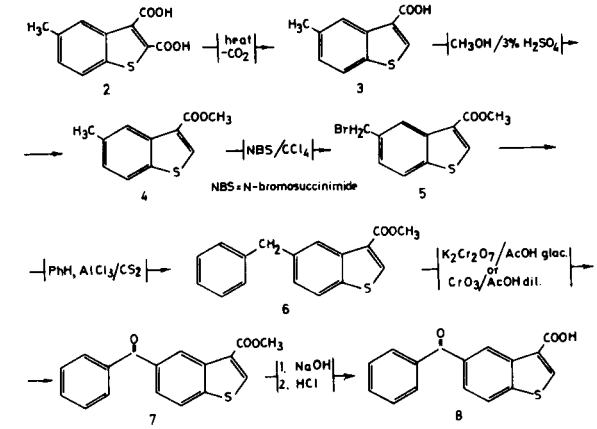
As our attempts to synthesize 5-substituted-benzo[*b*]-thiophene derivatives by the same procedure failed, we decided to develop alternative pathways leading to this kind of compound. None of the necessary starting materials and intermediates, except *p*-thiocresol were commercially available. Therefore we proceeded first to develop a synthetic procedure to obtain compound **2** which can be used to start in a preparation of compound **8**. The steps used in synthesizing **2** are presented in Scheme 1.

Scheme 1



As shown, *p*-thiocresol was acylated with oxalyl chloride, and the resulting product subjected without isolation, to the Friedel-Craft's reaction which gave the 5-methyl-2,3-benzo[*b*]thiophenedione (**4**). This product was condensed with chloroacetic acid under basic conditions (5), which caused a subsequent rearrangement, so that the desired 5-methylbenzo[*b*]thiophene-2,3-dicarboxylic acid **2** was obtained in 68% yield as the final product. This compound was used as a starting material in two synthetic pathways, each leading to the same compound **8**. We have studied the procedural conditions for both pathways and tried to optimize the yields of their final products. The first route in the synthesis of desired compound **8** can be represented with the Scheme 2.

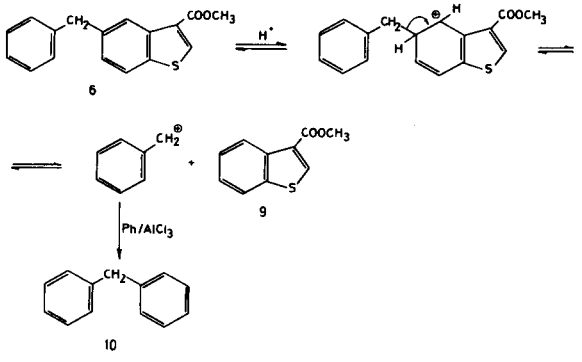
Scheme 2



Decarboxylation of compound **2** was carried out in an atmosphere of dry nitrogen at 270-280°. The molecule lost only one mole of carbon dioxide giving 5-methylbenzo[*b*]-thiophene-3-carboxylic acid **3** in 60% yield, which means that carbon dioxide was eliminated from the C-2 position. As the remaining carboxylic group must be protected from further reactions in the sequences, we converted **3** to its

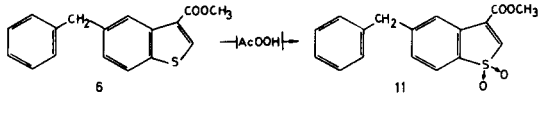
methyl ester **4** by heating with absolute methanol which contained 3% (w/w) of sulfuric acid. The ester remaining after distillation under reduced pressure was obtained in 80% yield. The product was pure enough to be used directly in the next step, which was a bromination of the methyl group in C-5 position carried out with *N*-bromosuccinimide in carbon tetrachloride. After cooling of the reaction mixture the product **5** crystallized in an 86% yield. The bromomethyl derivative **5** underwent Friedel-Craft's phenylation to compound **6**. The yield on **6** was about 70%, and could not be improved by varying the reaction conditions, though an optimum reaction temperature between -15° and -10° had to be maintained. Higher temperatures resulted in very peculiar products, namely 3-carboxymethylbenzo[*b*]thiophene **9** (3) and diphenylmethane (7). These products suggest that a retro Friedel-Craft's reaction takes place at temperatures above -10°, so that compound **6** which is formed first, undergoes decomposition into benzyl cation and 3-carboxymethylbenzo[*b*]thiophene anion. Thus formed products react with benzene giving diphenylmethane **10** in a high yield with proton giving 3-carboxymethylbenzo[*b*]thiophene **9** (Scheme 3).

Scheme 3



Oxidation of the benzyl group in compound **6** was attempted with the following oxidizing agents: peracetic acid (9), potassium permanganate (10), potassium dichromate (11), and chromium trioxide (12). However, the yields in the desired product **7** were very low. In the reaction with peracetic acid the main product was 5-benzyl-3-carboxymethylbenzo[*b*]thiophene 1,1-dioxide **11**.

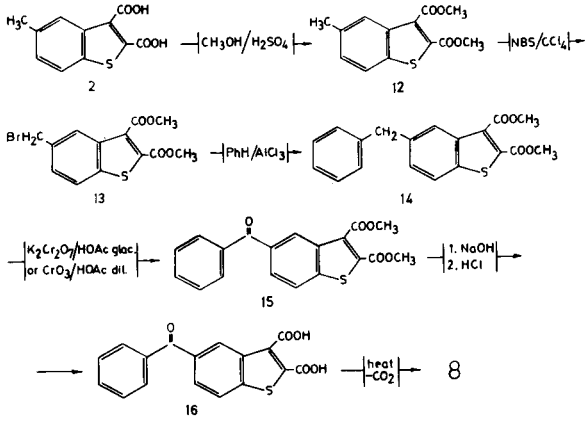
Scheme 4



The oxidation with alkaline potassium permanganate gave 1 to 5% yields, although the starting compound, **6**, completely disappeared from the reaction mixture. Yields as low as that were probably due to very strong adsorption of the product on the manganese dioxide cake resulting from the reduction of potassium permanganate. We were unable to get the substance desorbed so as to increase the yields. In trials with chromium trioxide we could only isolate a very low amount of product although tlc of the reaction mixture indicated complete consumption of the reactant. Satisfactory results, *i.e.* yields of 50-60%, were, however, obtained when the oxidation of **6** was carried out with potassium dichromate in glacial acetic acid.

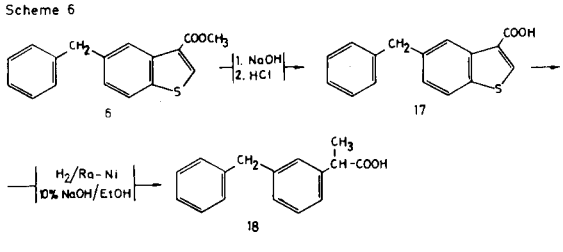
The last step in the procedure, shown in the Scheme 2, was a hydrolysis of compound **7** with methanolic sodium hydroxide. After acidification of the reaction mixture with hydrochloric acid, compound **8** was obtained in 86% yield. The same final product **8** could be obtained from the same starting material by following a different pathway, as shown in Scheme 5.

Scheme 5



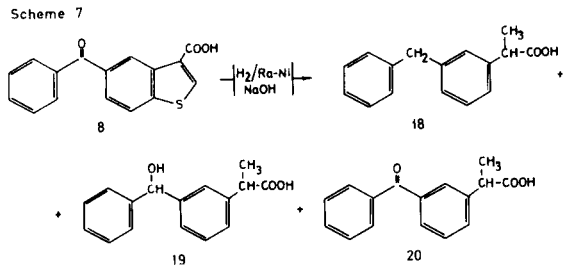
Here the decarboxylation step was preceded by esterification of both carboxyl groups using the same procedure as in the esterification step in the first procedure. The dimethyl ester **12** was obtained in 88% yield and was brominated without isolation with *N*-bromosuccinimide in hot carbon tetrachloride. The 5-bromomethyl dimethyl ester **13** was obtained in 85% yield. Friedel-Craft's alkylation of **13** with benzene gave **14** in 73% yield. Although this reaction was carried out at a comparatively high temperature (70-80°), only small amounts (2-4%) of by-products (diphenylmethane **10** and 2,3-dicarboxymethylbenzo[*b*]thiophene **21** (5)) could be isolated.

Scheme 6



Oxidation of the methylene group of **14** was carried out either with chromium trioxide in diluted acetic acid, or

Scheme 7



with potassium dichromate in glacial acetic acid. The yield in the first procedure was only 18% and the product could be isolated only by column chromatography. A better yield (65%) and a simpler isolation of the product was achieved by the second procedure. Hydrolysis of the product, ester **15**, was performed in the same way as that of compound **7** to obtain compound **16** in 88% yield, whose decarboxylation resulted in elimination of carbon dioxide from C-2 yielding **8** (51%). Blicke, *et al.* (13) described the dethiation of benzo[*b*]thiophene-3-carboxylic acid with Raney nickel which gave 93.4% yield of α-phenylpropionic acid. Using an analogous procedure, 5-benzylbenzo[*b*]thiophene-3-carboxylic acid **17**, obtained in 85% yield by hydrolysis of **6**, was dethiated with Raney nickel in a mixture of 5% aqueous sodium hydroxide and ethanol. A high yield of over 90% in α-(3-benzylphenyl)propionic acid **18** was obtained. When the same reaction was attempted with compound **8** a mixture of compounds **18, 19** and **20** was obtained. Obviously the catalyst was too active and the reduction was carried beyond the desired stage, *i.e.* further reduction attacked the benzophenone carbonyl group. There are data in the literature (14) that heating of Raney nickel in boiling acetone under reflux can deactivate the catalyst and the use of Raney nickel treated in this manner may be expected to dethiate without reducing the carbonyl group. We found this to be true, as Raney nickel treated for a few hours with refluxing acetone yielded only two compounds **19** and **20**, when used to dethiate **8**. However, the main product was compound **19** (60% yield). The dethiation proceeds with the best yield when carried out in 5% aqueous sodium hydroxide solution and ethanol (1.5:1). Attempted dethiation in an acetone medium left the starting compound unchanged. Likewise our attempts to find conditions under which only dethiation of compound **8** would take place leaving the carbonyl group unattacked, remained unsuccessful. The yields of the compound **18** were always low, and mixtures of compounds **18, 19** and **20** were invariably obtained.

EXPERIMENTAL

The melting points were determined with Boetzius Mikroheiztisch apparatus and are uncorrected. The ir spectra were recorded with Perkin-Elmer 4720 and Pye-Unicam SP 200 instruments using samples in potassium bromide pellets or as a film. The nmr spectra were recorded with Varian T-60 and Perkin-Elmer 12 instruments using TMS as the internal standard. Thin layer chromatograms were prepared on Merck Fertigplatten F_{254}, and the silica gel used in column chromatography was a product of Merck, Darmstadt (particle size 0.05-0.2 mm).

5-Methylbenzo[*b*]thiophene-2,3-dione (**1**).

4-Methylthiophenole (31 g, 0.25 mole) was dissolved in dry diethyl ether (200 ml) and oxalyl chloride (48 g, 0.38 mole) in diethyl ether (200 ml) was added dropwise. The reaction mixture was refluxed on a water-bath for 30 minutes. Ether was evaporated and residue was stored over potassium hydroxide pellets in a vacuum desicator connected with a pump to remove excess oxalyl chloride. This procedure left a yellow oil, which was not purified, but was immediately dissolved in carbon disulphide (400 ml). The solution was cooled to 0°, and aluminum chloride (40 g) was added. This reaction mixture was allowed to warm up to room temperature, then heated to reflux and maintained in this condition for 30 minutes. The solid was allowed to settle and the carbon disulphide was decanted. Ice-cold water (100 ml) was carefully added with cooling and decomposition was allowed to be completed. The resulting orange crystalline product was filtered with suction, yield 30 g (68%), mp 142-143°, lit (4) mp 143-144°; ir: 1702, 1600, 1570, 1475, 1282, 1230, 1150, 920, 800, 680 cm^{-1}; nmr (acetone-d_6): δ ppm 2.35-2.48 (s, 3H), 7.20-7.30 (s, 1H), 7.38-7.50 (d, 2H).

5-Methylbenzo[*b*]thiophene-2,3-dicarboxylic Acid (**2**).

Compound **1** (25 g, 0.14 mole) was dissolved in 10% sodium carbonate (15 ml). To this solution chloroacetic acid (14.3 g, 0.151 mole) dissolved in 10% sodium carbonate solution (75 ml) was added portionwise. The resulting mixture was heated 30 minutes at 80°, then filtered, and under further cooling solid sodium hydroxide (*ca.* 150 g) was added so that the reaction mixture was finally 40% in sodium hydroxide. This mixture was stirred for 1.5 hours on a water bath, then diluted with water and acidified to *p*H 1 with concentrated hydrochloric acid with efficient cooling. The crystals precipitated were collected on a suction filter, washed several times with water and dried in air. Twenty-two g (66%) of product **2** was obtained, mp 251-252°; ir: 1680, 1340, 1270, 1240, 1100, 1042, 800, 750, 680 cm^{-1}; nmr (DMSO-d_6): δ ppm 2.33-2.65 (s, 3H), 7.23-8.01 (m, 3H), 10.30-10.70 (s, 2H).

Anal. Calcd. for $C_{11}H_8O_4S$ (236.19): C, 55.94; H, 3.41; S, 13.55. Found: C, 56.00; H, 3.58; S, 13.82.

5-Methylbenzo[*b*]thiophene-3-carboxylic Acid (**3**).

Compound **2** (10 g, 0.423 mole) was placed into a three necked 100 ml round bottom flask fitted with a reflux condenser, stirrer and nitrogen line. The flask was immersed into a Wood's metal bath heated to 290° and was kept at this temperature, under a steady nitrogen flow for 20 minutes. After cooling the resinous material was suspended in acetone (25 ml), filtered and the residue on the filter was extracted with additional acetone (25 ml). The dark brown filtrate was evaporated *in vacuo*, the residue dissolved in aqueous 10% sodium hydroxide solution (40 ml) and the insoluble material was removed by filtration. The aqueous solution was washed with 3 × 30 ml of ether and the ether layers were discarded. The washed solution was then acidified to *p*H 1 with concentrated hydrochloric acid, whereupon white crystals precipitated. The crystalline product was collected on a suction filter, washed with water then dried in air. The yield was 5.52 g (68%) with mp 200-201°. An analytical sample was obtained in the form of colourless crystals by recrystallization from aqueous methanol, mp 211-212°; ir: 3000-2500, 1650, 1500, 1422, 1340, 1265, 1240, 1160, 910, 860, 785, 760, 740, 710 cm^{-1}; nmr (DMSO-d_6): δ 2.40-2.65 (s, 3H), 7.10-7.35 (m, 1H), 7.80-8.00 (d, 1H), 8.28-8.45 (s, 1H), 8.55-8.65 (s, 1H) ppm.

Anal. Calcd. for $C_{10}H_8O_2S$ (192.19): C, 62.48; H, 4.19. Found: C, 62.56; H, 4.40.

5-Methyl-3-carboxymethylbenzo[*b*]thiophene (**4**).

Compound **3** (19.8 g, 0.103 mole) was suspended in absolute methanol

(200 ml) containing 3% of sulfuric acid and stirred under reflux for 6 hours. The hot reaction mixture was poured onto crushed ice (400 g) and extracted with 4 × 100 ml of methylene chloride or diethyl ether. The organic solvent layers were united, washed with 100 ml of water, dried over sodium sulfate and the solvent removed *in vacuo*. The oily residue was distilled under reduced pressure to yield 17.3 g (81.6%) of pure **4**, bp 141-143° at 1.5 mm Hg; ir: 3400, 3100, 2950, 1720, 1600, 1542, 1500, 1440, 1340, 1300, 1260, 1225, 1182, 1130, 1062, 1035, 1000, 939, 860, 800, 760, 710, cm^{-1}; nmr (deuteriochloroform): δ 2.50-2.58 (s, 3H), 3.92-3.99 (s, 3H), 7.25-7.46 (d, 1H), 7.90-8.08 (d, 1H), 8.31-8.40 (s, 1H), 8.65-8.70 (s, 1H) ppm.

Anal. Calcd. for $C_{11}H_{10}O_2S$ (206.21): C, 64.07; H, 4.88. Found: C, 64.25; H, 5.00.

5-Bromomethyl-3-carboxymethylbenzo[*b*]thiophene (**5**).

Compound **4** (17.3 g, 83.9 mmoles) was dissolved in carbon tetrachloride (75 ml) and a catalytic amount of dibenzoyl peroxide (0.1 g) was added and followed with *N*-bromosuccinimide (15.1 g, 84.4 mmoles). The reaction mixture was stirred and refluxed for 7 hours, filtered while hot and the succinimide formed was removed by filtration. The solid on the filter was washed with hot carbon tetrachloride (50 ml) and the washings added to the filtrate. This liquid was allowed to cool to room temperature, during which **5** crystallized and precipitated. The yield was 15.4 g of product with mp 128-129°. The mother liquor was concentrated under reduced pressure to obtain a second crop of crystals. Total yield was 20.5 g (86%) with the same mp 128-129°. Recrystallization from carbon tetrachloride yielded an analytical sample, mp 130-131°; ir: 3150, 2950, 1700, 1500, 1445, 1440, 1340, 1260, 1230, 1210, 1182, 1130 cm^{-1}; nmr (deuteriochloroform): δ 3.90-4.00 (s, 3H), 4.57-4.67 (s, 2H), 7.25-7.50 (m, 1H), 7.70-7.90 (d, 1H), 8.30-8.40 (s, 1H), 8.51-8.65 (d, 1H) ppm.

Anal. Calcd. for $C_{11}H_9BrO_2S$ (285.11): C, 46.33; H, 3.18. Found: C, 46.17; H, 3.36.

5-Benzyl-3-carboxymethylbenzo[*b*]thiophene (**6**).

A mixture of dry benzene (38.5 ml), carbon disulfide (38.5 ml) and aluminum chloride (14.8 g, 0.108 mole) was poured into a three-necked 250 ml round bottom flask equipped with a thermometer, stirrer and reflux condenser. The mixture was cooled to -15° and compound **5** (15.4 g, 0.054 mole) was added in small batches during 10 minutes. The mixture was stirred for 2 hours at -10 to -15°, then poured on crushed ice (300 g). The resulting suspension was extracted with 4 × 100 ml of ether, the ethereal extracts united, dried over magnesium sulfate and the solvent evaporated under reduced pressure. The oil which remained (14.5 g) was chromatographed over silica gel (430 g) in a glass column using a mixture of petroleum ether-diisopropyl ether (5:1). Yield of the pure product obtained after removal of the eluent was 10.62 g (69.7%), mp 73-75°; ir: 1705, 1670, 1555, 1510, 1458, 1358, 1270, 1230, 1190, 1180, 1130, 1065, 1030, 950, 900, 890, 858, 825, 790, 770, 730, 720, 690 cm^{-1}; nmr (deuteriochloroform): δ 3.90-4.00 (s, 3H), 4.10-4.25 (s, 2H), 7.30-7.45 (s, 6H), 7.73-7.97 (d, 1H), 8.40-8.48 (s, 1H), 8.60-8.73 (s, 1H) ppm.

Anal. Calcd. for $C_{17}H_{14}O_2S$ (282.30): C, 72.33; H, 5.00; S, 11.34. Found: C, 72.11; H, 5.20; S, 11.50.

Stirring at room temperature under otherwise unchanged conditions gave two products. One of these was diphenylmethane **10**, yield 7.62 g, and the other 3-carboxymethylbenzo[*b*]thiophene (**9**) 8.30 g. These compounds were characterized by comparing ir, ^{1}H-nmr spectra and the mp or bp with those of authentic samples (7,3).

5-Benzylbenzo[*b*]thiophene-3-carboxylic Acid (**17**).

This compound was obtained in 85% yield starting with **6** and following the same procedure as was used to obtain **8**. Pure compound was obtained after recrystallization from aqueous methanol with mp 189-190°; ir: 3450, 3100, 3000, 2900, 1670, 1600, 1510, 1480, 1355, 1280, 1250, 1060, 920, 860, 785 cm^{-1}; nmr (deuterioacetone-d_6): δ 4.10-4.30 (s, 2H), 7.30-7.50 (s, 6H), 7.85-7.90 (s, 2H), 8.20-8.40 (s, 1H), 9.30-9.60 (s, 1H).

Anal. Calcd. for $C_{16}H_{12}O_2S$ (268.33): C, 71.62; H, 4.51; S, 11.95. Found: C, 71.38; H, 4.69; S, 11.67.

5-Benzoyl-3-carboxymethylbenzo[*b*]thiophene (**7**).

Procedure A.

A mixture of compound **6** (3.428 g, 12.1 mmoles) and potassium dichromate (17.8 g, 60.5 mmoles) in glacial acetic acid (120 ml) was stirred in an oil bath at 100-105° during 16 hours, then was allowed to cool and was poured into 500 ml of cold water. The aqueous phase was extracted with 4 × 150 ml of ether. The united ethereal extracts were washed with 100 ml of water, dried over sodium sulfate, and the ether was removed *in vacuo*. To remove the residual acetic acid, the oil remaining after evaporation of ether was overlayered with 10 ml of benzene and evaporated, repeating this azeotropic procedure twice more. Finally 2.808 g of oil remained, which was dissolved by heating in a mixture of diisopropyl ether-petroleum ether. Colourless crystals separated on cooling, yield 2.02 g (56%) of **7**, mp 86-88°.

Procedure B.

Compound **6** (3.428 g, 12.1 mmoles) was dissolved with heating in acetic acid (14 ml) and the solution was allowed to cool to room temperature. Thereupon a solution of chromium trioxide (5 g) in acetic acid (15 ml) was added dropwise over a period of 15 minutes. Finally 2.5 ml of water was added. The resulting mixture was heated 4 hours at 90°, then cooled and was diluted with 300 ml of water. The dilute aqueous phase was extracted with 4 × 150 ml of ether, the united ethereal extracts were washed with 100 ml of water, dried over sodium sulfate and was evaporated *in vacuo*. Acetic acid was removed from the residue by azeotropic evaporation with benzene (10-ml portions) repeated three times. Only 0.2 g of brown oil remained, which was dissolved in a mixture of diisopropyl ether-petroleum ether, from which pale yellow crystals separated. The yield was 0.15 g (4.2%), mp 86-89°. The ir and nmr spectra were identical with those of the product obtained using either procedure A or B. An analytical sample was prepared by recrystallization from the same solvent mixture which increased the mp to 91-92°; ir: 1720, 1650, 1595, 1504, 1443, 1345, 1320, 1284, 1245, 1215, 1225, 1065, 960, 905, 860, 795, 760, 730, 705, 690, 670 cm^{-1}; nmr (DMSO-d_6): δ 3.90 (s, 3H), 7.65-8.05 (m, 6H), 8.2-8.5 (m, 1H), 8.8-9.0 (m, 2H).

Anal. Calcd. for $C_{17}H_{12}O_3S$ (296.29): C, 68.90; H, 4.08; S, 10.82. Found: C, 69.02; H, 4.23; S, 10.57.

5-Benzylbenzo[*b*]thiophene-3-carboxylic Acid 1,1-Dioxide (**11**).

Compound **6** (0.5 g, 18.7 mmoles) was dissolved in acetic acid (6 ml) and 40% peracetic acid (4 ml) was added. The mixture was heated and stirred at 50° for 6 hours. The crystals precipitated while the mixture cooled to room temperature, were collected on a suction funnel and washed with petroleum ether, yield 0.31 g (55%) of product, mp 220-222°; ir: 3100, 1710, 1580, 1450, 1320, 1250, 1180, 1107, 1020, 910, 812, 800, 760, 715, 700, 662 cm^{-1}; nmr (deuterioacetone-d_6): δ 4.15-4.30 (s, 2H), 7.32-7.50 (s, 6H), 7.85-7.90 (s, 2H), 8.25-8.40 (s, 1H), 9.30-9.60 (s, 1H).

Anal. Calcd. for $C_{16}H_{12}O_4S$ (300.26): C, 64.00; H, 4.03; S, 10.66. Found: C, 63.75; H, 4.21; S, 10.61.

5-Methyl-2,3-dicarboxymethylbenzo[*b*]thiophene (**12**).

Compound **2** (20 g, 84.7 mmoles) was stirred 6 hours in refluxing 3% sulfuric acid in absolute methanol (400 ml). The mixture was cooled to room temperature and poured onto 400 g of crushed ice. The precipitated crystals were collected on a suction funnel and washed with water. The united aqueous filtrate and washings were extracted with 2 × 50 ml of ether. The ethereal extracts were dried over sodium sulfate and the solvent was removed *in vacuo*. The remaining oil was crystallized from petroleum ether, yield 19.7 g (88%), mp 80-82°; ir: 3500, 2950, 1740, 1710, 1570, 1542, 1467, 1445, 1364, 1300, 1263, 1230, 1200, 1175, 1110, 1068, 1010, 743, 890, 835, 818, 770, 700 cm^{-1}; nmr (deuteriochloroform): δ 2.43-2.53 (s, 3H), 3.92-4.00 (s, 3H), 4.02-4.12 (s, 3H), 7.21-7.90 (m, 3H), ppm.

Anal. Calcd. for $C_{13}H_{12}O_4S$ (264.24): C, 59.08; H, 4.58. Found: C, 59.18; H, 4.70.

5-Bromomethyl-2,3-dicarboxymethylbenzo[*b*]thiophene (**13**).

Compound **12** (19 g, 71.9 mmoles) was dissolved with warming in carbon tetrachloride (80 ml), a catalytic amount of dibenzoyl peroxide (0.1 g) and *N*-bromosuccinimide (12.95 g, 72.3 mmoles) was added with stirring. The stirring under reflux was continued for the next 8 hours and the hot mixture was filtered to remove crystals of succinimide which were washed with 50 ml of hot carbon tetrachloride. While cooling, the filtrate plus washings, 18.3 g of crystalline product, separated and the mother liquor on partial evaporation gave more crystals (2.7 g). Total yield was 85%, mp 122-123°. An analytical sample was prepared by recrystallization from carbon tetrachloride, mp 124-125°; ir: 1718, 1540, 1564, 1418, 1438, 1338, 1282, 1250, 1238, 1098, 1060, 1010, 895, 818, 824, 764, 675 cm^{-1}; (deuteriochloroform): δ 3.93-4.00 (s, 3H), 4.02-4.09 (s, 3H), 4.61-4.68 (s, 2H), 7.45-8.00 (m, 3H) ppm.

Anal. Calcd. for $C_{13}H_{11}BrO_4S$ (343.15): C, 47.72; H, 3.39. Found: C, 47.82; H, 3.50.

5-Benzyl-2,3-dicarboxymethylbenzo[*b*]thiophene (**14**).

Compound **13** (15 g, 43.7 mmoles) was dissolved in dry benzene (150 ml). The solution was cooled to 0° and aluminum chloride (11.8 g, 87 mmoles) was added in small portions. The mixture was allowed to reach room temperature, then heated at 70-75° for 2-3 hours. Three hundred g of crushed ice was added and the resulting mixture was extracted with 4 × 150 ml of benzene. The united benzene extracts were dried over sodium sulfate and evaporated *in vacuo*. The residual oil was purified by column chromatography (250 g of silica gel, eluent: petroleum ether-ether 3:2). The yield was 10.7 g (72%) of product, mp 77-79°. From this reaction mixture, two more products were isolated, namely 2,3-dicarboxymethylbenzo[*b*]thiophene (**21**) (0.22 g) and diphenylmethane (**10**) (0.14 g). These compounds were identified by comparing mp's and ^{1}H-nmr spectra with those of authentic samples. The melting point of 2,3-dicarboxymethylbenzo[*b*]thiophene was 88-90°, lit (5) mp 91°. The pure compound **14** was obtained by recrystallization from petroleum ether; ir: 3425, 2950, 1720, 1665, 1625, 1490, 1460, 1438, 1420, 1340, 1335, 1305, 1290, 1240, 1200, 1120, 1070, 980, 950 cm^{-1}; nmr (deuteriochloroform): δ 3.93-4.00 (s, 3H), 4.01-4.09 (s, 3H), 4.10-4.18 (s, 2H), 7.21-7.32 (s, 5H), 7.38-7.45 (d, 1H), 7.69-7.78 (s, 1H), 7.80-7.89 (d, 1H) ppm.

Anal. Calcd. for $C_{19}H_{16}O_4S$ (340.34): C, 67.04; H, 4.74. Found: C, 67.08; H, 5.00.

Oxidation of Compound **14** to Compound **15**.

Procedure A.

Compound **14** (11 g, 32.4 mmoles) and potassium dichromate (51 g, 173.3 mmoles) were dissolved in glacial acetic acid (120 ml). The solution was stirred and heated at 105-110° during 16 hours. After cooling, the reaction mixture was poured into 500 ml of cold water, and the aqueous phase was extracted with 4 × 300 ml of ether. The united ethereal extracts were washed with 200 ml of water, dried over sodium sulfate and the solvent removed *in vacuo*. Excess acetic acid was removed by azeotropic evaporation with 50-ml portions of benzene. Finally 8.2 g of brown oil was obtained. On addition of diisopropyl ether-petroleum ether, the product crystallizes in the form of white crystals, 7.5 g (65.4%), mp 140-142°.

Procedure B.

Compound **14** (2 g, 5.88 mmoles) was dissolved in acetic acid (4 ml). A solution of chromium trioxide (2.5 g, 25 mmoles) in water (0.5 ml) and acetic acid (3 ml) was added dropwise over a period of 15 minutes. The mixture was heated at 90° for 3-5 hours, cooled, and poured into 150 ml of cold water. The precipitate was filtered with suction, washed with water and purified over a column of silica gel (75 g) using petroleum ether-ether 3:2 as the eluent. The yield was 0.372 g (18%), mp 140-142°. The compounds obtained by both procedures gave identical ir and nmr spectra and gave no depression in a mixed melting point determination; ir: 3500, 1725, 1650, 1600, 1550, 1430, 1355, 1325, 1287, 1249, 1213, 1155, 1137, 1110, 1053, 1030, 909, 878, 838, 815, 733 cm^{-1}; nmr (deuteriochloroform): δ 3.86-4.10 (s, 6H), 7.20-7.96 (m, 7H), 8.34-8.40 (s, 1H) ppm.

Anal. Calcd. for $C_{19}H_{14}O_5S$ (354.32): C, 64.40; H, 3.98; S, 9.05. Found: C, 64.22; H, 4.20; S, 9.15.

5-Benzoylbenzo[*b*]thiophene-2,3-dicarboxylic Acid (**16**).

Compound **15** (2.0 g, 5.6 mmoles) was dissolved in methanol (20 ml) and 24% sodium hydroxide solution (25 ml) was added. The mixture was heated at 100-120° for 60-90 minutes. The solution was then cooled, filtered and acidified to *p*H 1 with concentrated hydrochloric acid. The product, 1.6 g (88%) was obtained with mp 269-271°. Purification was achieved by recrystallization from diluted ethanol; ir: 3500, 1710, 1650, 1600, 1510, 1360, 1325, 1280, 1250, 950, 890, 770, 720, 682 cm^{-1}; nmr (DMSO-d_6): δ 7.15-7.85 (m, 6H), 8.05-8.25 (d, 1H), 8.90-9.00 (s, 1H) ppm.

Anal. Calcd. for $C_{17}H_{10}O_5S$ (326.27): C, 62.58; H, 3.08. Found: C, 62.87; H, 3.24.

5-Benzoylbenzo[*b*]thiophene-3-carboxylic Acid (**8**).

Procedure A.

Compound **7** (1.0 g, 3.4 mmoles) was dissolved in methanol (10 ml) and 24% sodium hydroxide solution (20 ml) was added. The solution was heated 90 minutes at reflux temperature, cooled, filtered, and acidified to *p*H 1 with the concentrated hydrochloric acid. The precipitate which formed was filtered with suction, washed with water and dried. The yield was 0.82 g (86%), mp 226-228°. The product was recrystallized from a mixture of ethanol-diisopropyl ether-petroleum ether.

Procedure B.

Into a three necked 50 ml round bottom flask fitted with a reflux condenser and a nitrogen inlet, compound **16** (5 g, 15.3 mmoles) was placed and the flask with reaction mixture was heated in a Wood's metal bath at 285-290° for 20 minutes under a steady flow of nitrogen. The dark brown mass was cooled, suspended in acetone (25 ml), filtered and the filtrate evaporated. The residue was dissolved in 10% sodium hydroxide solution (30 ml) and filtered to remove insoluble material. The aqueous solution was acidified to *p*H 1 with concentrated hydrochloric acid. The crystals thereby precipitated were collected on a filter and washed with water. The yield was 2.3 g (50.9%), mp 225-228°. The products obtained in procedure A and B were identical in characteristics; ir: 1680, 1655, 1587, 1505, 1440, 1280, 1250, 1065, 960, 920, 865, 835, 805, 730, 715, 700, 665 cm^{-1}; nmr (DMSO-d_6): δ 7.55-8.06 (m, 6H), 8.2-8.5 (m, 1H), 8.85 (s, 1H), 8.95-9.10 (m, 1H) ppm.

Anal. Calcd. for $C_{16}H_{10}O_3S$ (282.26): C, 68.07; H, 3.57; S, 11.36. Found: C, 68.30; H, 3.82; S, 11.17.

2-(3′-Benzylphenyl)propionic Acid (**18**).

Raney nickel (4 g) was suspended in 5% sodium hydroxide solution (25 ml) and ethanol (10 ml). To this suspension compound **17** (0.2 g, 7 mmoles) was added. The mixture was stirred at 70-80° during 3-4 hours, cooled, filtered, and the solid on the filter washed with 10 ml of 5% sodium hydroxide solution. The filtrate and washings were evaporated to 20 ml under reduced pressure and the concentrate acidified to *p*H 1 with concentrated hydrochloric acid. An oily product separated and was taken up into 3 × 15 ml of ether. The united ethereal extracts were washed with water (2 × 15 ml), dried over sodium sulfate and evaporated *in vacuo*. The resulting oil crystallized on standing at room temperature. The yield was 1.56 g (93%), mp 58-59°. Recrystallization from *n*-heptane gave the pure substance, mp 60-61°; ir: 1710, 1605, 1495, 1455, 1415, 1240, 1215, 1175, 935, 775, 750, 700 cm^{-1}; nmr (deuteriochloroform): δ 1.44 (d, 3H), 3.67 (d, 1H), 3.96 (s, 2H), 7.00-7.35 (m, 9H), 11.65 (s, 1H) ppm.

2-(3′-(α-Hydroxybenzyl))propionic Acid (**19**).

Raney nickel (20 g) was suspended in acetone (150 ml) and the mixture was maintained 2 hours at reflux temperature while continuously stirring. The mixture was allowed to cool to room temperature, whereupon

5% sodium hydroxide solution (150 ml) was added. The acetone was evaporated *in vacuo* and compound **8** (1.0 g, 3.5 mmoles) dissolved in ethanol (100 ml) was added. The suspension was stirred 1 hour at reflux temperature, cooled, the catalyst filtered off and washed with a solution of 5% sodium hydroxide solution and water. Filtrate plus washings were acidified to *p*H 2 with concentrated hydrochloric acid followed by extraction of the aqueous phase with 3 × 20 ml of ether. The united ethereal extracts were washed with water (20 ml) dried over sodium sulfate and the ether evaporated *in vacuo*. An oil resulted and was crystallized from diisopropyl ether-petroleum ether (1:1), yield 510 mg (56.9%), mp 117-118°. An analytical sample was obtained by recrystallization from the same solvent mixture, mp 120-121°; ir: 3400, 1705, 1595, 1450, 1380, 1320, 1235, 1150, 1115, 900, 835, 795, 760, 705, 660 cm^{-1}; nmr (DMSO-d_6): δ 1.34 (d, 3H), 3.4-3.9 (q, 1H), 5.72 (s, 1H), 7.10-7.60 (m, 9H) ppm.

Anal. Calcd. for $C_{16}H_{16}O_3$ (256.30): C, 74.98; H, 6.29. Found: C, 75.09; H, 6.53.

The mother liquor deposited **20** (after crystallization of compound **19**) when the solvent was evaported and **20** was purified over silica gel (50 g) using a mixture of petroleum ether-ether (2:3) as the eluant. Compound **20** was obtained, yield 260 mg (29%), which on crystallization from isopropyl ether melted at 91-92°, lit (15) mp 93-95°. The ir and nmr spectra were identical with those of an authentic sample.

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