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The synthesis of the four monoaminodibenzothiophenes and the four monohydroxydibenzothiophenes is described.

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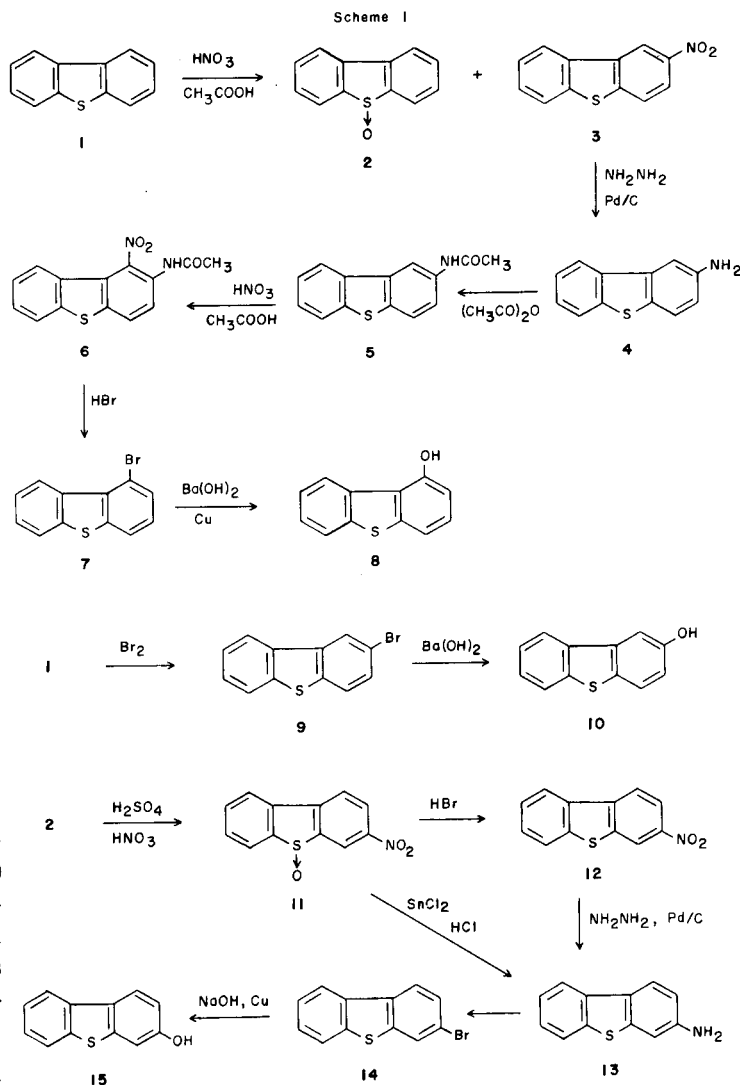
Previous publications from this laboratory [2-25] have reported the syntheses of a number of unsubstituted polycyclic thiophenes and selected monomethyl, dimethyl and monoethyl derivatives in order to positively determine their presence in coal liquids, shale oils and coal-derived products and to make the synthetic compounds available for biological screening.

We now have preliminary evidence [26] that monoamino and monohydroxy polycyclic thiophenes also occur in coal-derived products. Therefore it is necessary to synthesize the suspected oxygen and nitrogen-containing polycyclic thiophenes.

In this paper we report the synthesis of the title compounds. 2-Aminodibenzothiophene (**4**) [27] and 1-hydroxydibenzothiophene (**8**) [28] were prepared from dibenzothiophene in two and six steps respectively. When **1** was allowed to react with concentrated nitric acid and glacial acetic acid, a separable mixture of dibenzothiophene 5-oxide (**2**) [27] (40% yield) and 2-nitrodibenzothiophene (**3**) (40% yield) [27] was obtained. By reduction of **3** with hydrazine and Pd-C, 2-aminodibenzothiophene (**4**) was obtained in 81% yield. Acetylation of **4** (acetic anhydride) gave 2-acetylaminodibenzothiophene (**5**) [29] in 95% yield. The action of fuming nitric acid and glacial acetic acid on **5** gave 2-acetylmino-1-nitrodibenzothiophene (**6**) [29] in 73% yield. When **6** was allowed to react with 48% hydrobromic acid and ethanol, 1-bromodibenzothiophene (**7**) [29] was obtained in 49% yield. The reaction of **7** with copper powder and barium hydroxide produced the required 1-hydroxydibenzothiophene (**8**) in 54% yield. The obvious shorter method of synthesis of **8** from **27** was unsatisfactory in our hands.

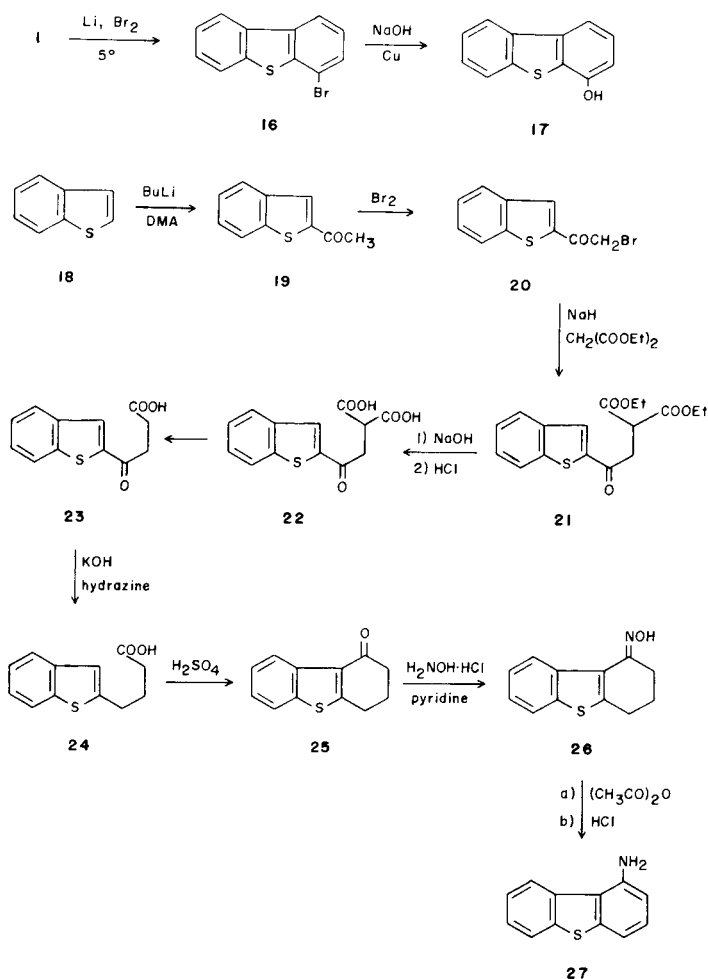
Bromination of dibenzothiophene (**1**) gave 2-bromodibenzothiophene (**9**) [27] in 80% yield which when allowed to react with copper powder and barium hydroxide produced the required 2-hydroxydibenzothiophene (**10**) [30] in 87% yield.

Nitration (fuming nitric acid and concentrated sulfuric acid) of **2** gave 3-nitrodibenzothiophene 5-oxide (**11**) [31]



which when allowed to react with 48% hydrobromic acid and glacial acetic acid produced 3-nitrodibenzothiophene (**12**) [32] in 89% yield. The action of Pd-C and hydrazine on **12** allowed the isolation of the required 3-aminodibenzothiophene (**13**) [31] in 84% yield while the reduction

Scheme 2



of **11** with stannous chloride and concentrated hydrochloric acid produced **13** in 45% yield. When **13** was allowed to react with cuprous bromide, 40% hydrobromic and nitrosylsulfuric acid, 3-bromodibenzothiophene (**14**) [33] was isolated in 23% yield. The reaction of **14** with copper powder and 10% sodium hydroxide solution afforded the required 3-hydroxydibenzothiophene (**15**) [34] in 79% yield. The above transformations are outlined in Scheme 1.

Lithiation of **1** followed by bromine at 5° produced 4-bromodibenzothiophene (**16**) [35] in 34% yield which upon treatment with copper powder and 10% sodium hydroxide afforded the required 4-hydroxydibenzothiophene (**17**) [34] in 72% yield.

Lithiation of benzo[*b*]thiophene (**18**) followed by treatment of the 2-lithiobenzo[*b*]thiophene with *N,N*-dimethylacetamide allowed the isolation of 2-acetylbenzo[*b*]thiophene (**19**) [36] in 72% yield. The reaction of **19** with bromine and anhydrous aluminum chloride gave 2-(bromoacetyl)benzo[*b*]thiophene (**20**) [37] in 79% yield. Condensation of **20** with diethyl malonate (sodium hydride) gave ethyl

4-(2'-benzo[*b*]thienyl)-2-ethoxycarbonyl-4-oxobutanoate (**21**) [38] in 76% yield. Hydrolysis of **21** gave 4-(2'-benzo[*b*]thienyl)-2-carboxy-4-oxobutanoic acid (**22**) [38] in 90% yield which was readily decarboxylated to give 4-(2'-benzo[*b*]thienyl)-4-oxobutanoic acid (**23**) [39] in 83% yield. Shorter methods for the synthesis of **23** proved unsatisfactory in our hands. The action of hydrazine and potassium hydroxide on **23** produced 4-(2'-benzo[*b*]thienyl)butanoic acid (**24**) [40] in 45% yield. Cyclization of **24** with concentrated sulfuric acid afforded 1,2,3,4-tetrahydrodibenzothiophen-1-one (**25**) [41] in 71% yield. The reaction of **26** with acetic anhydride produced the 1-acetylaminodibenzothiophene which was not isolated but hydrolyzed in the reaction mixture with concentrated hydrochloric acid to give the required 1-aminodibenzothiophene (**27**) [29] in 54% yield. The above transformations are outlined in Scheme 2.

The amino- and hydroxydibenzothiophenes are being screened for mutagenic activity in the Ames test and these data will be reported elsewhere.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The ¹H nmr spectra were obtained on a Varian EM 360 spectrometer in the solvents indicated with TMS as the internal standard. Mass spectra were obtained on a Hewlett Packard model 5980A mass spectrometer. Elemental analyses were performed by MHW Laboratories, Phoenix, Arizona 85018.

2-Aminodibenzothiophene (**4**).

A solution of hydrazine (10 ml) in 10% ethanol was added to a mixture of 2-nitrodibenzothiophene (**3**) (1 g, 0.043 mole), palladium on carbon (0.3 g, 10%) and ethanol (300 ml) and the mixture was heated to 60° during the addition, then the mixture was refluxed for 30 minutes. After removing the palladium on carbon by filtration, the ethanol was evaporated to give 0.7 g (81%) of colorless prisms which were recrystallized from ethanol, mp 132-133°, lit [27] 133-135°; nmr (deuteriochloroform): δ 3.61 (s, NH₂, 2H), 6.67-6.91 (m, 3-H, 1H, ArH), 7.31-7.68 (m, 4-H, 7-H, 8-H, 3H, ArH), 7.69-8.08 (m, 1-H, 6-H, 9-H, 3H, ArH); ms: *m/e* 200 (M⁺ + 1, 100), 199 (M⁺, 100), 172 (11), 171 (23).

1-Hydroxydibenzothiophene (**8**).

A mixture of 1-bromodibenzothiophene (**7**) (1.5 g, 0.0057 mole), barium hydroxide octahydrate (7.5 g, 0.024 mole), copper powder (1.2 g) and water (20 ml) was heated at 240-260° in a stainless steel autoclave for 24 hours. After removal of copper by filtration the aqueous solution was acidified with dilute hydrochloric acid. The precipitate was collected by filtration and recrystallized from aqueous ethanol to give colorless prisms, 0.7 g (61%), mp 135-136°, lit [34] 134°; nmr (deuteriochloroform): δ 6.46-6.69 (m, 2-H, 1H, ArH), 6.91-7.2 (m, 3-H, 4-H, 7-H, 8-H, 4H, ArH), 7.34-7.74 (m, 6-H, 1H, ArH), 8.24-8.55 (m, 9-H, 1H, ArH), 9.16 (s, 1-OH, 1H); ms: *m/e* 201 (M⁺ + 1, 15), 200 (M⁺, 100), 172 (32), 171 (61).

2-Hydroxydibenzothiophene (**10**).

This compound was synthesized from 2-bromodibenzothiophene (**9**) (1.8 g, 0.0069 mole), barium hydroxide octahydrate (9.5 g, 0.003 mole), copper powder (1.5 g) and water (18 ml) in a manner similar to the preparation of compound **8** and was obtained as colorless needles (1.2 g, 87%), mp 127-128° after recrystallization from aqueous methanol, lit [30] 127°; nmr (deuteriochloroform): δ 4.67 (s, 2-OH, 1H), 6.74-7.02 (m, 3-H, 1H, ArH), 7.5-7.54 (m, 4-H, 7-H, 8-H, 3H, ArH), 7.6 (s, 1-H, 1H, ArH), 7.69-8.19

(m, 6-H, 9-H, 2H, ArH); ms: m/e 201 ($M^+ + 1$, 14), 200 (M^+ , 100), 172 (11), 171 (37).

3-Aminodibenzothiophene (13).

This compound was synthesized from 3-nitrodibenzothiophene (12) (1 g, 0.043 mole), palladium on carbon (0.6 g, 10%) and ethanol (300 ml) in a manner similar to the preparation of compound 4 and was obtained as white prisms, (0.7 g, 84%), mp 121-122° after recrystallization from aqueous ethanol, lit [31] 121-122°; nmr (deuteriochloroform): δ 3.63 (bs, NH_2 , 2H), 6.57-6.9 (m, 4-H, 1H, ArH), 7.02 (s, 4-H, 1H, ArH), 7.13-7.42 (m, 7-H, 8-H, 2H, ArH), 7.63-8.57 (m, 1-H, 6-H, 9-H, 3H, ArH); ms: m/e 200 ($M^+ + 1$, 15), 199 (M^+ , 100), 184 (21), 171 (19).

3-Hydroxydibenzothiophene (15).

This compound was synthesized from 3-bromodibenzothiophene (14) (2 g, 0.0076 mole), sodium hydroxide (2.4 g, 0.06 mole) copper powder (1.6 g) and water (20 ml) in a manner similar to the preparation of compound 8. It was obtained as colorless prisms after recrystallization from hexane (0.12 g, 19%), mp 154-155°, lit [34] 156°; nmr (deuteriochloroform + acetone- d_6): δ 6.23 (s, 3-OH, 1H), 6.85-7.13 (m, 2-H, 1H, ArH), 7.23-7.56 (m, 3-H, 4-H, 7-H, 8-H, 4H, ArH), 7.66-7.8 (m, 6-H, 1H, ArH), 7.87-8.13 (m, 9-H, 1H, ArH); ms: m/e 201 ($M^+ + 1$, 14), 200 (M^+ , 100), 171 (26).

4-Hydroxydibenzothiophene (17).

This compound was synthesized from 4-bromodibenzothiophene (16) (2 g, 0.0076 mole), sodium hydroxide (2.4 g, 0.06 mole) copper powder (1.6 g) and water (20 ml) in a manner similar to the preparation of compound 8. It was obtained as colorless prisms, (1.1 g, 72%) after crystallization from aqueous ethanol, mp 157-159°, lit [34] 157-159°; nmr (acetone- d_6): δ 6.34-6.56 (m, 3-H, 1H, ArH), 6.66-7.11 (m, 2-H, 7-H, 8-H, 3H, ArH), 7.18-7.53 (m, 1-H, 6-H, 2H, ArH), 7.6-7.84 (m, 9-H, 1H, ArH), 8.82 (bs, 4-OH, 1H); ms: m/e 201 ($M^+ + 1$, 15), 200 (M^+ , 100), 172 (22), 171 (52).

Ethyl 4-(2'-Benzo[b]thienyl)-2-ethoxycarbonyl-4-oxobutanoate (21).

Into a mixture of sodium hydride (1.9 g, 0.04 mole) and anhydrous tetrahydrofuran (200 ml), dimethyl malonate (6.4 g, 0.04 mole) was added dropwise with stirring under nitrogen in an ice bath. When the addition was complete, a clear pale yellow solution resulted. To the solution was added slowly with stirring a solution of 2-bromoacetylbenzo[b]thiophene (10 g, 0.039 mole) in anhydrous tetrahydrofuran (100 ml). When the addition was complete, the ice bath was removed and the mixture was stirred for 2 hours at room temperature. The reaction mixture was poured into ice water (300 ml) and extracted with chloroform (200 ml). The chloroform layer was washed with water then dried over sodium sulfate. After removal of chloroform, the oily residue was used in the next reaction without further purification; nmr (deuteriochloroform): δ 1.26 (t, J = 6 Hz, CH_3), 3.63 (d, J = 7 Hz, 2H, CH_2CH), 4.3 (m, 1H, $CHCH_2$), 7.21-7.61 (m, 5-H, 6-H, 2H, ArH), 7.66-7.92 (m, 4-H, 7-H, 2H, ArH), 7.99 (s, 3-H, 1H, ArH).

4-(2'-Benzo[b]thienyl)-2-carboxy-4-oxobutanoic Acid (22).

The crude product above was added to a potassium hydroxide solution (10%, 100 ml) and the resulting solution was stirred at room temperature for 14 hours. The reaction mixture was filtered to remove insoluble material. The filtrate was acidified with hydrochloric acid solution (10%) and the precipitate was collected by filtration to give 10 g of product (90% yield). The analytical sample was recrystallized from ethanol giving white prisms, mp 177-178°; nmr (deuteriochloroform + trifluoroacetic acid): δ 3.93 (t, J = 5 Hz, 3H, CH_2CH), 7.33-7.73 (m, 5-H, 6-H, 2H, ArH), 7.8-8.07 (m, 4-H, 7-H, 2H, ArH), 8.19 (s, 3-H, 1H, ArH); ms: m/e 234 (17), 161 (100), 133 (16), 89 (25).

Anal. Calcd. for $C_{13}H_{10}O_5S$: C, 56.11; H, 3.62; S, 11.52. Found: C, 56.31; H, 3.80; S, 11.36.

4-(2'-Benzo[b]thienyl)-4-oxobutanoic Acid (23).

The crude dicarboxylic acid 22 (10 g) was decarboxylated by heating in diethylene glycol (100 ml) until the evolution of carbon dioxide had ceas-

ed (about 1 hour). This solution was then added to a mixture of ice and water to which had been added a few drops of hydrochloric acid solution (10%). The keto-acid was extracted with chloroform. The solution was dried over sodium sulfate and evaporated to give a brown solid. The product was recrystallized from benzene to give white prisms, mp 175-176°, lit [39] mp 175.5; nmr (deuteriochloroform): δ 3.63 (s, CH_2 , 2H), 3.72 (s, CH_2 , 2H), 7.19-7.53 (m, 5-H, 6-H, 2H, ArH), 7.69-7.93 (m, 4-H, 7-H, 2H, ArH), 7.96 (s, 3-H, 1H, ArH).

4-(2'-Benzo[b]thienyl)butanoic Acid (24).

This compound was prepared from 23 as described by Mitra and Tilak [40], yield 45%, mp 88°, lit [40].

Anal. Calcd. for $C_{12}H_{12}O_2S$: C, 65.43; H, 5.49; S, 14.56. Found: C, 65.41; H, 5.45; S, 14.69.

1,2,3,4-Tetrahydrodibenzothiophen-1-one (25).

This compound was prepared from 24 as described by Cagniant and Kirsch [41] and was obtained in 71% yield, mp 114°, lit [41].

Anal. Calcd. for $C_{12}H_{10}OS$: C, 71.26; H, 4.98; S, 15.85. Found: C, 71.27; H, 4.99; S, 15.91.

1,2,3,4-Tetrahydrodibenzothiophen-1-one Oxime (26).

The oxime was prepared from 25 as described by Cagniant and Cagniant [39] and was obtained in 80% yield, mp 118° [39].

1-Aminodibenzothiophene (27).

A mixture of 1,2,3,4-tetrahydrodibenzothiophen-1-one oxime (26), acetic anhydride (30 ml) and glacial acetic acid (30 ml) was refluxed for 4 hours. After cooling, the mixture was poured into water (1000 ml). The brown solid which appeared was collected by decantation. A solution of the acetylamine in concentrated hydrochloric acid (20 ml) and ethanol (200 ml) was refluxed for 10 hours. After evaporation of the solvent, the residue was dissolved in hot water (500 ml) and filtered. Ammonium hydroxide was added to the aqueous filtrate and the mixture was extracted with benzene. After removal of the benzene, the residue was recrystallized from aqueous ethanol to give 1.5 g (54%), mp 95-96°, lit mp 96° [29]; nmr (deuteriochloroform): δ 4.19 (bs, NH_2 , 2H), 6.54 (s, 2-H, 1H, ArH), 6.98-7.6 (m, 3-H, 4-H, 7-H, 8-H, 4H, ArH), 7.67-7.88 (m, 6-H, 1H, ArH), 7.99-8.31 (m, 9-H, 1H, ArH); ms: m/e 200 ($M^+ + 1$, 28), 199 (M^+ , 100), 172 (18), 171 (27).

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