Benzo[*b*]thiophene Derivatives. XXVI. 5-Methoxy-6-chloro-3-β-acetamidoethylbenzo[*b*]thiophene, A Blocked Analog of Melatonin (1)

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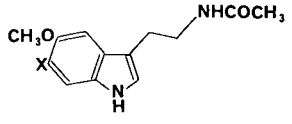
Received July 15, 1982

A potential anti-ovulatory agent, 5-methoxy-6-chloro-3-β-acetamidoethylbenzo[*b*]thiophene, a sulfur analog of melatonin having the 6-position blocked to inhibit oxidative metabolism, has been synthesized from 3-hydroxy-4-chloroacetophenone.

J. Heterocyclic Chem., **20**, 55 (1983).

The synthesis of a variety of melatonin analogs was recently undertaken with the intention of producing compounds of similar physiological properties but greater resistance to metabolism (4). In view of evidence that the major pathway in the metabolism of melatonin was hydroxylation in the 6-position (5), particular emphasis was placed on the synthesis of melatonin derivatives (A) having a substituent blocking the 6-position. The assumption that these compounds would be more slowly metabolized than melatonin was born out by the prolonged serum half-life of 6-chloromelatonin (A, X = Cl), which was found to be



A

27 minutes, following *i.v.* administration, in contrast to 12-15 minutes reported for melatonin. However, the metabolism of A (X = Cl) still appeared to be relatively rapid, and secondary metabolic routes, involving tryptophan pyrrolase and/or *p*-quinoid oxidation are quite facile and are capable of disposing of melatonin in a very short time.

The metabolism of several biologically active benzo[*b*]thiophenes has been investigated (6,7). Studies of the metabolism of 3-β-dimethylaminoethylbenzo[*b*]thiophene, the sulfur analog of dimethyltryptamine, *in vitro* and *in vivo* in rats (6) indicates the major pathways are 6-hydroxylation, *N*-dealkylation, and MAO oxidation. No evidence of sulfoxidation or ring degradation was obtained. Bosin, Bickers and Dinner (7) reported the metabolic fate of tritium labeled 3-benzo[*b*]thienylalanine (the sulfur analog of tryptophan) in the rat. After 48 hours essentially all of the radioactivity could be accounted for by side-chain degraded benzo[*b*]thiophenes. There was a complete absence of the usual tryptophan metabolic pathways of tryptophan pyrrolase and ring 5-hydroxylase oxidation, which are possibly due to the greater propensity of the indole nucleus to electrophilic attack.

The sulfur analog of melatonin, (S-Mel) 5-methoxy-3-β-acetamidoethylbenzo[*b*]thiophene, has been shown to be approximately equal to melatonin itself in the Pencil Fish Melanophore assay (8), and to be approximately 100 times more lipid soluble than melatonin, with half-lives longer than melatonin in plasma and all tissues (9). The metabolic pathways of melatonin and its sulfur analog are different. Apparently 6-hydroxylation is important for both (6), but alternate pathways, involving ring cleavage or *p*-quinoid oxidation are not likely to occur in the sulfur analog. For these reasons, the sulfur analog of melatonin bearing a blocking group at the 6-position should have advantages as a biologically active analog of melatonin.

We report here the synthesis of 5-methoxy-6-chloro-3-β-acetamidoethylbenzo[*b*]thiophene (**14**, Scheme I) a sulfur analog of melatonin having a chloro group in the 6-position. The synthesis of S-Mel has been reported (10), and depended on the synthesis of the sulfur analog of serotonin (11), starting with commercially available *m*-hydroxyacetophenone (**1**). The synthesis of the 6-chloro-analog is outlined in Scheme 1, and depended on the availability of 3-hydroxy-4-chloroacetophenone (**4**) to duplicate the S-Mel synthesis (10,11).

Compound **4** has apparently not been previously reported. It would seem that the direct chlorination of **1** would produce **4** as the major product, in view of the hindering effect of the acetyl group on the activated 2- and 6-positions of the phenol. However, chlorination of **1** with *t*-butyl hypochlorite gave a mixture of chlorinated phenols, which by glc was shown to be mainly 2-chloro-3-hydroxyacetophenone, with some 6-chloro-3-hydroxyacetophenone, some 2,4-dichloro-3-hydroxyacetophenone and a little 4-chloro-3-hydroxyacetophenone, which could not be isolated (12). When the dioxolane **2** was chlorinated with *t*-butyl hypochlorite, the major product was 4'-chloro derivative **3**, which, although contaminated with other isomers, could be isolated and crystallized. Since dioxolane **2** was prepared using technical grade butylene glycol (Aldrich) which is a mixture of stereoisomers, the melting points of **2** and **3** are broad, but the compounds showed only one spot on tlc after crystallization, and analyzed well. The aromatic pmr spectrum of **3** was consistent with

an unsymmetrically substituted benzene. Diololane **3** was stable, and required refluxing in a THF/aqueous hydrochloric acid solution for some time to hydrolyze to **4**. Compound **4**, melting at 106-107°, was characterized as a 4-nitrophenylhydrazone, melting at 231-232°. Final proof of the correct structure of **4** depended on methylation and oxidation to the known 3-methoxy-4-chlorobenzoic acid, melting at 212-214° (13).

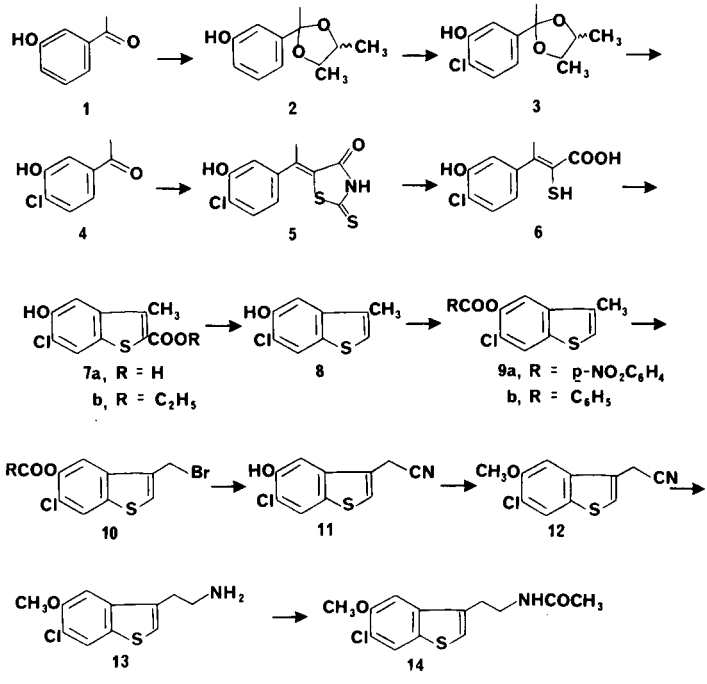
Compound **4** was converted to the rhodanine derivative **5** in good yield, and careful hydrolysis in 5% sodium hydroxide at 65° for 10 minutes produced the mercaptoacid **6**. As has previously been noted, attempts to crystallize these unsaturated mercapto-acids seem to cause decomposition (14), but the corresponding disulfides are stable, analyze well, and may be used in the cyclization step if storage of this intermediate is required.

Compound **6** cyclized well when treated with iodine in ethanol, refluxed for 24 hours (15). This reaction produced 5-hydroxy-6-chloro-3-methylbenzo[*b*]thiophene-2-carboxylic acid (**7a**) along with an appreciable amount of the ester (**7b**). In this preparation, it was always necessary to work up the by-product ester, which could be easily hydrolyzed, to maximize the yields of **7a**.

The decarboxylation of **7a**, using the copper-quinoline method which has been quite successful for decarboxylating benzo[*b*]thiophene-2-carboxylic acids (11,15) proved refractory in this case, producing highly colored products in low yield (30-50%). Recently, decarboxylation of 5-hydroxy-3-methylbenzo[*b*]thiophene-2-carboxylic acid in refluxing 48% hydrobromic acid has been reported (16). These conditions were repeated to treat **7a**, but yields varied from 10% to a maximum of 37% of **8**. We therefore relied on the copper quinoline method, and accepted our losses at this step. The compound readily sublimes, which may account for some loss on work-up.

The phenol **8** was characterized as a *p*-nitrobenzoate (**9a**) and as a benzoate (**9b**). These two compounds were tested as substrates for bromination with *N*-bromosuccinimide, to produce **10a** or **10b**. Bromination of 5-benzoyloxy-3-methylbenzo[*b*]thiophene with NBS, using a 15% excess of NBS produced the 3-bromomethyl derivative in 90% yield (11). However, bromination of **9a** under these conditions produced a mixture of 3-dibromomethyl, 3-bromomethyl, and unreacted **9a**, which could not be readily separated. Reducing the amount of NBS to one equivalent only increased the amount of unreacted **9a** in the product mixture, the ratio of **10a** to dibromomethyl derivative remained about 4/1. The product mixture was readily analyzed by the pmr ratio of $-CH_3$, $-CH_2Br$ and $-CHBr_2$ which are distinct. When the benzoyl ester **9b** was treated with one equivalent of NBS, a mixture containing about 90% of **10b** and 10% of the dibromomethyl product was obtained, which on treatment with sodium cycanide in DMSO, followed by hydrolysis, gave a satisfactory yield of 5-hydroxy-6-chloro-3-cyanomethylbenzo[*b*]thiophene **11**. It appears, from the fact that bromination always gave some dibromomethyl compound, that the 6-chloro group has an activating effect on the methyl group toward bromination with NBS.

SCHEME I



The proposed synthetic steps from **11** to **14** were straightfoward. The phenol **11** was methylated with dimethyl sulfate in acetone, and the resulting nitrile **12** reduced with borane/dimethyl sulfide according to the method of Brown (17), to give the hydrochloride salt of amine **13**, which was acetylated in good yield to **14**. Compound **14** has been submitted to the Contraceptive Development Branch, Center for Population Research, National Institute of Child Health and Human Development, for evaluation as an anti-ovulatory agent.

EXPERIMENTAL

Melting points were determined on a "uni-melt" Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 137-B infrared spectrometer. Nuclear magnetic resonance spectra were obtained with a Varian T 60A spectrometer using tetamethylsilane as an internal standard. Mass spectral analyses were performed on a Varian MAT CH7 at 70 eV ionization potential. Eastman chromatogram sheets (# 13181 Silica gel with fluorescent indicator #6060) were used for thin layer chromatography. Elemental analyses were performed by Midwest Microlab, Indianapolis.

2-(3'-Hydroxyphenyl)-2,4,5-trimethyl-1,3-dioxolane (**2**).

Using the method of Nikles (18), a mixture of 13.6 g (0.1 mole) of **1** (3-hydroxyacetophenone, Aldrich, Tech. grade, recrystallized from hot water after treatment with activated carbon to melting point 94-96°), 12.5 g (0.15 mole) of technical grade 2,3-butanediol (Aldrich, a mixture of

stereoisomers), 0.2 g of anhydrous zinc chloride, 0.2 ml of 85% phosphoric acid and 70 ml of toluene was refluxed till the ketone had disappeared (by tlc). After cooling, 100 ml of ether was added, and the solution washed with aqueous sodium bicarbonate solution (2×). The aqueous layers were washed with ether, and the combined ether layers dried (magnesium sulfate) and concentrated to give 17.8 g (88%) of white crystals, melting at 100-103°; pmr (acetone-d_6): δ 1.1 (d, 3H), 1.2 (d, 3H), 1.53 (s, 3H), 3.3-4.3 (m, 2H), 6.6-7.3 (m, 4H), 8.2 (s, 1H). The compound showed only one spot on tlc. The broad melting point is undoubtedly due to the presence of stereoisomers (19).

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.23; H, 7.69; MW 208. Found: C, 69.13; H, 7.84; M^+ 208.

2-(4'-Chloro-3'-hydroxyphenyl)-2,4,5-trimethyl-1,3-dioxolane (**3**).

A solution of **2** (20.8 g, 0.1 mole) in 400 ml of a 9:1 benzene/chloroform mixture was cooled to 0°, and 12.3 g (0.11 mole) of *t*-butyl hypochlorite added dropwise with vigorous stirring. Addition of the hypochlorite required about 1.5-2.0 hours, after which stirring at 0° was continued for 2 hours, then continued while the reaction mixture was allowed to come to room temperature overnight. Solvents were removed on a rotovap, and the residual oil was triturated with petroleum ether, and stored in the cold overnight. The white solid was collected and washed with cold petroleum ether, to give 14.6 g (60%) of **3**, melting at 89-93°. An analytical sample, recrystallized from carbon tetrachloride/petroleum ether, melted at 92.5-95°; pmr (deuteriochloroform): δ 1.14 (d, 3H, CH_3), 1.26 (d, 3H, CH_3), 1.6 (s, 3H, CH_3), 3.73 (m, 2H, CH), 5.82 (s, 1H, OH), 7.01 (dd, 1H, ArH-6'), 7.21 (d, 1H, ArH-2'), 7.25 (d, 1H, ArH-5').

Anal. Calcd. for $C_{12}H_{15}ClO_3$: C, 59.39; H, 6.19; Cl, 14.62. Found: C, 59.33; H, 6.26; Cl, 14.64.

3-Hydroxy-4-chloroacetophenone (**4**).

A solution of 11.5 g (0.047 mole) of **3** in a mixture of 100 ml of THF, 80 ml of water and 20 ml of concentrated hydrochloric acid was refluxed for 2 hours. The solution was then concentrated on a rotovap, extracted three times with ether, and the combined ether extracts washed with water, then saturated sodium bicarbonate solution, and finally with brine. After drying over anhydrous magnesium sulfate, concentration of the ether gave 7.6 g (94%) of 3-hydroxy-4-chloroacetophenone (**4**), melting at 101-104°. Several recrystallizations from toluene gave an analytical sample, mp 106-107°; ir: 3290, 1660 cm^{-1}; pmr (acetone-d_6): δ 2.54 (s, 3H, CH_3), 7.46 (s, 2H, ArH), 7.58 (s, 1H, ArH), 7.5-8.5 (broad, 1H, OH).

Anal. Calcd. for $C_8H_7ClO_2$: C, 56.33; H, 4.14; MW, 170. Found: C, 56.18; H, 4.21; M^+, 170.

3-Hydroxy-4-chloracetophenone 4-Nitrophenylhydrazone.

A small sample of **4** was converted to the 4-nitrophenylhydrazone (20), mp 231-232°.

Anal. Calcd. for $C_{14}H_{12}ClN_3O_3$: C, 55.08; H, 3.93; N, 13.77. Found: C, 54.80; H, 4.07; N, 13.58.

3-Methoxy-4-chlorobenzoic Acid.

Treatment of **4** with methyl sulfate and potassium carbonate in acetone, followed by oxidation with sodium hypochlorite solution, gave 3-methoxy-4-chlorobenzoic acid, mp 212-214° (13).

5-(3'-Hydroxy-4'-chloro-α-methylbenzylidene)rhodanine (**5**).

A mixture of 13.2 g (77.4 mmoles) of **4**, 10.3 g (77.4 mmoles) of rhodanine (Aldrich), 2 g ammonium acetate and 6 ml of acetic acid was refluxed in 12.5 ml of benzene, removing water with a Dean-Stark trap. After 30 hours, the theoretical amount of water had been collected, and the mixture was washed with water, dried (magnesium sulfate) and the benzene removed (rotovap), giving a yellow solid. After several recrystallizations from acetonitrile, 22 g (77%) of **5**, mp 189-190° were obtained; ir (potassium bromide): 1667 cm^{-1}; pmr (acetone-d_6): δ 2.64 (s, 3H, CH_3), 6.3-6.8 (broad, 2H, OH, NH), 6.89 (dd, J = 2 and 8 Hz, 1 H, 5'-ArH), 7.09 (d, J = 2 Hz, 1H, 2'-ArH), 7.40 (d, J = 8 Hz, 1H, 6'-ArH).

Anal. Calcd. for $C_{11}H_8ClNO_2S_2$: C, 46.23; H, 2.82; N, 4.90; S, 22.44; MW, 285. Found: C, 46.73; H, 2.79; N, 4.46; S, 22.17; M^+, 285.

3-(3'-Hydroxy-4'-chlorophenyl)-2-mercapto-2-butenoic Acid (**6**).

Adduct **5** (10 g, 35 mmoles) was rapidly stirred into a solution of 10 g of sodium hydroxide in 200 ml of water, maintained at 65°. After 10 minutes, the mixture was cooled in an ice-bath, then poured into 200 ml of cold 6 *N* hydrochloric acid saturated with sodium chloride. The precipitate was collected and dried, to give 6.2 g (73%) of mercaptoacid **6**, mp 130-132°. Further attempts to recrystallize this acid caused decomposition, with lowered melting ponts. However, the initial product is reasonably pure, and can be used directly in the cyclization step with good results. It had the following spectral properties: ir 3510 (OH), 1672 (CO) cm^{-1}; pmr (acetone-d_6): δ 2.29 (s, 3H, CH_3), 6.5-8.5 (broad, 3H, OH, SH, COOH), 6.74 (dd, J = 2 and 8 Hz, 1H, 5'-ArH), 6.90 (d, J = 2 Hz, 1H, 2'-ArH), 7.35 (d, J = 8 Hz, 1H, 6'-ArH).

Anal. Calcd. for $C_{10}H_9ClO_3S$: C, 49.18; H, 3.71; S, 13.10; MW, 244. Found: C, 49.26; H, 3.55; S, 12.52; M^+, 244.

Oxidation of a small sample of **6** with benzoyl peroxide in benzene (14) gave the disulfide of **6**, melting at 203° after recrystallization from ethyl acetate/hexane.

Anal. Calcd. for $C_{20}H_{16}Cl_2O_6S_2$: C, 49.29; H, 3.31; S, 13.14. Found: C, 49.46; H, 3.30; S, 13.19.

6-Chloro-5-hydroxy-3-methylbenzo[b]thiophene-2-carboxylic Acid (**7a**).

A mixture of 10 g (41 mmoles) of crude mercapto-acid **6**, 12 g (47 mmoles) of iodine in 300 ml of 90% ethanol was refluxed for 24 hours. Most of the solvent was removed under reduced pressure, and 20 ml of saturated sodium bisulfite solution, 70 ml of water, and 200 ml of ether added. After thorough mixing, which removed the iodine color, the layers were separated, and the aqueous bisulfite layer acidified with dilute sulfuric acid, and washed once with ether. The combined ether layers were separated, and the aqueous bisulfite layer acidified with dilute sulfuric acid, and washed once with ether. The combined ether layers were washed with water, then saturated sodium bicarbonate solution (twice). Neutralization of the bicarbonate layers with concentrated hydrochloric acid gave a copious white precipitate of **7a** which was dissolved in 175 ml of ethanol, and 175 ml of hot water added. On cooling, 8.7 g (87%) of white acid **7a**, mp 288-290° dec, was obtained. An analytical sample, recrystallized several times from aqueous alcohol, melted at 299-301° dec; ir 3279 (OH), 1647 (CO) cm^{-1}; pmr (acetone-d_6): δ 2.65 (s, 3H, CH_3), 7.43 (s, 1H, ArH), 7.86 (s, 1H, ArH).

Anal. Calcd. for $C_{10}H_7ClO_3S$: C, 49.49; H, 2.91; S, 13.21. Found: C, 49.62; H, 3.04; S, 12.94.

Ethyl 6-Chloro-5-hydroxy-3-methylbenzo[b]thiophene-2-carboxylate (**7b**).

Concentration of the ether layer which had been extracted with bicarbonate in the above preparation gave 1.0 g (9%) of ester **7b**, mp 189-190° after one recrsytallization from aqueous alcohol; ir: 3280 (OH), 1650 (CO) cm^{-1}; pmr (acetone-d_6): δ 1.38 (t, J = 8 Hz, 3H, CH_3), 2.66 (s, 3H, CH_3), 4.37 (q, J = 8 Hz, 2H, CH_2), 7.42 (s, 1H, ArH), 7.92 (s, 1H, ArH).

Anal. Calcd. for $C_{12}H_{11}ClO_3S$: C, 53.24; H, 4.10; S, 11.84; MW, 270. Found: C, 52.98; H, 4.19; S, 11.76; M^+, 270.

The ester was quantitatively converted into the acid **7a** by heating for 30 minutes in 1 *M* sodium hydroxide solution on a steam bath.

3-Methyl-5-hydroxy-6-chlorobenzo[b]thiophene (**8**).

A mixture of 4.0 g of **7a**, 3.6 g of copper powder and 45 ml of freshly distilled quinoline was heated for one hour at 180° bath temperature. Most of the quinoline was then distilled at reduced pressure. The residue was washed with 35 ml of 8 *N* hydrochloric acid, 150 ml of THF and 250 ml of ether, and all washings combined. The aqueous layer was saturated with sodium chloride, shaken, and the aqueous layer discarded. The organic layer was washed with brine, and concentrated on a rotary evaporator to give a brown oily residue, which was extracted several times with petroleum ether to give a light brown crystalline solid, recrystallized as white needles from water, followed by sublimation to give 1.6 g (49%) of fine white needles of **8**, mp 81-82°. This experiment was repeated several times, giving from 1.0 to 1.7 g (30 to 50%) of **8**; pmr (deuteriochloroform): δ 2.33 (d, J = 1.0 Hz, 3H, CH_3), 5.05 (br, 1H, OH),

7.00 (d, J = 1.0 Hz, 1H, H-2), 7.25 (s, 1H), 7.60 (s, 1H).

Anal. Calcd. for C_9H_7ClOS: C, 54.41; H, 3.53; S, 16.12; Cl, 17.86. Found: C, 54.64; H, 3.55; S, 15.98; Cl, 17.65.

5-*p*-Nitrobenzoyloxy-6-chloro-3-methylbenzo[*b*]thiophene (**9a**, R = *p*-$O_2NC_6H_4$).

Compound **8** (4.4 g, 22 mmoles) was refluxed with 4.13 g (22.3 mmoles) of *p*-nitrobenzoyl chloride in 125 ml of pyridine for two hours. The cooled mixture was poured into 200 ml of ice-water, and the grey precipitate collected, washed with 5% bicarbonate solution, then water, and dried. The sample of **9a** (R = *p*-$NO_2C_6H_4$) weighed 5.3 g (68%) and melted at 167-170°. After recrystallizing from benzene-hexane, the analytical sample had mp 176°; ir: 1736 cm^{-1} (CO); pmr (hexadeuteriobenzene): δ 7.90 (d, J = 8 Hz, 2H), 7.70 (d, J = 8 Hz, 2H), 7.41 (s, 1H), 7.34 (s, 1H), 6.54 (q, J = 1.2 Hz, 1H (H-2)), 1.86 (d, J = 1.2 Hz, 3H (CH_3)).

Anal. Calcd. for $C_{16}H_{10}ClO_4NS$: C, 55.26; H, 2.90; N, 4.03; S, 9.22; MW, 347. Found: C, 55.57; H, 3.02; N, 4.03; S, 9.36; M^+, 347.

5-Benzoyloxy-6-chloro-3-methylbenzo[*b*]thiophene (**9b**, R = C_6H_5).

A solution of 23 g (0.12 moles) of phenol **8** in 125 ml of dry pyridine containing 32 g (0.23 mole) of benzoyl chloride was refluxed for three hours, then cooled and the reaction mixture poured into cold water. The water layer was decanted, and the pasty residue taken up in ether, and washed several times with aqueous bicarbonate solution, then water, and dried. The ether was evaporated, and the residue twice recrystallized from hexane, to give 19 g (54%) of white crystals melting at 65-67°; ir: 1725 cm^{-1}; pmr (deuteriochloroform): δ = 2.3 (d, J = 1.0 Hz, 3H, CH_3), 7.1 (d, J = 1.0 Hz, 1H, H-2), 7.50-8.50 (m, 7H).

Anal. Calcd. for $C_{16}H_{11}ClO_2S$: C, 63.57; H, 3.64; S, 10.59; Cl, 11.75. Found: C, 63.49; H, 3.72; S, 10.64; Cl, 11.78.

Bromination of **9a**.

A stirred mixture of 1.0 g (2.9 mmoles) of ester **9a**, 0.63 g (3.54 mmoles) of NBS, and 10 mg of benzoyl peroxide in 100 ml of carbon tetrachloride was irradiated overnight with a 200 watt incandescent lamp, which caused gentle reflux. After removal of solvent, the residue was taken up in a 4/1 ether-THF mixture and washed with brine, water, dried (magnesium sulfate) and concentrated to give 0.86 g of light brown solid, mp 160-165°. The composition of this crude product was determined by integration of nmr peaks (acetone-d_6): δ 7.56 (-C*H*Br_2) 18 mole %; 4.96 (-C*H*$_2$Br) 74 mole %; 2.45 (-CH_3) 8 mole %.

Several repetitions of this bromination, using benzene as solvent, and only 0.95 equivalent of NBS, gave a product having 24 mole % of **9a**, 62 mole % **10a**, and 14 mole % of the dibromomethyl compound. Attempts at recrystallization from acetonitrile or acetone-water removed unreacted **9a**, but did not separate the brominated products.

Bromination of **9b**.

A three-neck flask, equipped with condenser and stirrer, and containing a solution of 3.02 g (10 mmole) of **9b** in 50 ml of dry carbon tetrachloride and 100 mg of benzoyl peroxide was brought to gentle reflux by irradiation with two 220 watt lamps. Then 1.78 g (10 mmoles) of NBS was added portion-wise over a period of 30 minutes. The mixture was stirred and refluxed another 10 hours. On cooling, the precipitated succinimide (700 mg, 70%) was filtered, and the solution concentrated under reduced pressure The residue was recrystallized from cyclohexane to give 2.8 g (90%) of yellow crystals melting at 127-130°. The pmr integration gave a ratio of 114 at δ 4.8 to 6 at the quartet δ 7.9, equivalent to 10% of dibrominated product.

The following spectrum can be assigned to **10b**; pmr (acetone-d_6): δ 4.83 (s, 2H, CH_2Br), 7.60 (s, 1H, H-2), 7.80 (broad s, 2H, H-4, H-7), 8.0-8.4 (m, 5H, Ar).

5-hydroxy-6-chloro-3-cyanomethylbenzo[*b*]thiophene (**11**).

The crude monobromide obtained by bromination of 1.52 g (4.37 mmoles) of **9b** was dissolved in 50 ml of dry DMSO and added dropwise to a stirred solution of 2.0 g (40 mmoles) of sodium cyanide in 125 ml of DMSO at 18-20°. The mixture was stirred overnight and poured into 200 ml of warm 2% sodium hydroxide solution. After 30 minutes, the mixture was acidified with concentrated hydrochloric acid, then adjusted to *p*H 7.2-7.4 by addition of solid sodium bicarbonate in portions. The mixture was extracted with ether/THF (3 × 125 ml), washed with brine, dried (magnesium sulfate) and concentrated. The dark residue was sublimed at 190-200° (bath temperature) at 2 mm, to give 0.48 g (49%, based on **9b**) of yellow **11**, mp 219.5-220° after recrystallization from acetonitrile/water, then acetone/water; ir: 3300 (OH), 2275 (CN) cm^{-1}: pmr (acetone-d_6): δ 8.0 (br, s, 1H, OH), 7.94 (s, 1H, ArH), 7.62 (t, J = 1.5 Hz, 1H, H-2), 7.40 (s, 1H, ArH), 4.10 (d, J = 1.5 Hz, 2H, -C*H*$_2$CN).

Anal. Calcd. for $C_{10}H_6ClNOS$: C, 53.70; H, 2.70; N, 6.26; MW, 223. Found: C, 53.55; H, 2.78; N, 6.31; M^+, 223.

5-Methoxy-6-chloro-3-cyanomethylbenzo[*b*]thiophene (**12**).

A solution of 7.0 g (31.4 mmoles) of **11** in 200 ml of acetone was treated with 5.0 g (36 mmoles) of anhydrous potassium carbonate and 4.5 g (3.4 ml, 36.5 mmoles) of dimethyl sulfate. After gentle reflux overnight (18 hours), the precipitate was removed, washed with acetone, and the combined acetone solutions concentrated on a rotary evaporator. The residue was dissolved in ether (200 ml), washed with 20 ml of 10% sodium hydroxide solution, water, and dried (magnesium sulfate). The solution was evaporated to dryness, and the residual solid recrystallized from ethanol to give 6.0 g (81%) of **12**, white crystals melting at 155-156°; ir: 2275 cm^{-1} (CN); pmr (acetone-d_6): δ 8.03 (s, 1H, ArH), 7.72 (m, 1H, H-2), 7.57 (s, 1H, ArH), 4.38 (m, 2H, C*H*$_2$CN), 4.02 (s, 3H, OC*H*$_3$).

Anal. Calcd. for $C_{11}H_8ClNOS$: C, 55.58; H, 3.39; N, 5.89; MW, 237. Found: C, 55.38; H, 3.34; N, 5.61; M^+, 237.

5-Methoxy-6-chloro-3-aminoethylbenzo[*b*]thiophene Hydrochloride (**13**).

Following the Brown procedure (17), all glassware was dried in an oven (120°) overnight and assembled under nitrogen, THF was dried with sodium and benzophenone. A 2-neck 50 ml flask containing a magnetic stirrer was equipped with a dropping funnel with septumn cap and a 12" Vigreux column with still head. A measuring cyclinder was fitted to the receiver, and the outlet connected through a mineral oil bubbler to a nitrogen source. After flushing with nitrogen the column was kept warm, using a heating tape, to allow dimethyl sulfide to distill.

A solution of 1.83 g (7.7 mmoles) of **12** in 15 ml of dry THF was heated to reflux, and 0.85 ml (8.47 mmoles) of the borane/dimethyl sulfide reagent (Aldrich) was added dropwise. Stirring was continued for 45 minutes until 0.7 ml of dimethyl sulfide was collected. The flask was then cooled to room temperature, and 8.2 ml (8.2 mmoles) of 1.0 *M* methanolic hydrogen chloride added dropwise. When addition was complete, the flask was gain heated to reflux, and a 1:1 azeotrope of methyl borate and methanol distilled. Then 5 ml of methanol was added and the solution reduced to dryness under reduced pressure. The solid was taken up in methanol and ether added to induce crystallization. The white crystals of **13** hyrochloride (1.5 g, 70%) were collected and used in the next step. A recrystallized sample melted at 243-245°: ir (potassium bromide): 3000, 1596, 1500 cm^{-1}; pmr (deuterium oxide): δ 3.0-3.4 (m, 4H, CH_2), 3.74 (s, 3H, CH_3), 6.8 (s, 1H, H-4), 7.29 (s, 1H, H-2), 7.53 (s, 1H, H-7).

Anal. Calcd. for $C_{11}H_{14}Cl_2NOS$: C, 47.50; H, 4.68; N, 5.04; S, 11.52; Cl, 25.51. Found: C, 47.54; H, 4.61; N, 4.85; S, 11.41; Cl, 25.37.

5-Methoxy-6-chloro-3-(2'-acetamidoethyl)benzo[*b*]thiophene (**14**).

A solution of 0.56 g (2.0 mmoles) of **13** hydrochloride in 20 ml of hot water was filtered, cooled, and 0.612 g (6.0 mmoles) of acetic anhydride added. Then 0.49 g (6.0 mmoles) of sodium acetate in 3.0 ml of water was added with vigorous stirring. The solution was stirred for 30 minutes and cooled in an ice bath. The white precipitate was collected, washed with cold water, and dried to give 0.5 g (87%) of **14**, melting at 141-143°. The analytical sample, recrystallized from aqueous ethanol, melted from 143.5-145°; ir (potassium bromide): 3240, 1640 cm^{-1}; pmr (deuteriochloroform): δ 1.93 (s, 3H, CH_3), 3.01 (t, 2H, CH_2), 3.57 (q, 2H, CH_2), 3.98 (s, 3H, CH_3), 5.76 (br, 1H, NH), 7.14 (s, 1H, H-4), 7.33 (s, 1H, H-2), 7.82 (s, 1H, H-7).

Anal. Calcd. for $C_{13}H_{14}ClNO_2S$: C, 55.04; H, 4.94; N, 4.94; S, 11.29; Cl,

12.51; MW, 283.1. Found: C, 55.34; H, 5.03; N, 5.17; S, 11.26; Cl, 12.72; M^+, 283.

Acknowledgement.

We are indebted to the National Institute of Child Health and Human Development, National Institutes of Health, for the support of this research, under Contract N01-HD-0-2818 with Indiana University.

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