Benzo[*b*]thiophene Derivatives. XIX. The Sulfur Isosteres of Psilocin and Related Isomers (1)

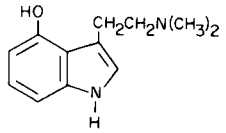
E. Campaigne and R. B. Rogers

Chemistry Laboratories, Indiana University, Bloomington, Indiana 47401

Received December 19, 1972

The sulfur analog of psilocin, 3-(β-dimethylaminoethyl)-4-hydroxybenzo[*b*]thiophene, and some *O*-methylated and *N*-demethylated isomers have been synthesized for pharmacological evaluation. Preliminary tests indicate central nervous system (CNS) activity, but weak pressor activity.

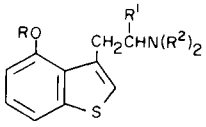
Though the hallucinogenic effects of certain mushrooms, generally of the species *Psilocybe*, have been known for centuries, it has only been recently that the chemistry has been studied to any extent. In 1958, Hofmann, *et al.*, (2) isolated two potent hallucinogenic substances [oral dose, 4-8 mg./man (3)] from the mushroom *Psilocybe mexicana* which they named psilocybin and psilocin. Subsequently, Hofmann's group (3) determined the structure of psilocin to be that of 3-(β-dimethylaminoethyl)-4-hydroxyindole (**1**) and that of psilocybin to be the phosphate ester of **1**.



1

In continuing our studies of the synthesis and pharmacological properties of benzo[*b*]thiophene isosteres of biologically active indole derivatives (4,5), we have now synthesized the sulfur analog of psilocin (SAP), 3-(β-dimethylaminoethyl)-4-hydroxybenzo[*b*]thiophene (**2**), and for comparative purposes, several *O*-methylated and *N*-demethylated derivatives (**3-6**).

Compound **3**, 3-(β-aminoethyl)-4-hydroxybenzo[*b*]thiophene, is a position isomer of the sulfur analog of serotonin (SAS) which has been shown to have substantial CNS activity (6). Thus, it was deemed desirable to test the structure-activity relationship of the 4-hydroxy group. Similarly, it will be of interest to determine the effect of methylating the hydroxyl as well as the β-carbon atom of the side chain. It has been shown that the *O*-methyl derivative of bufotenine is much more active in a conditioned avoidance response test (7) than bufotenine itself. While tryptamine and β-methyltryptamine differ significantly in potency in the CNS, the sulfur analogs of



2 - 6

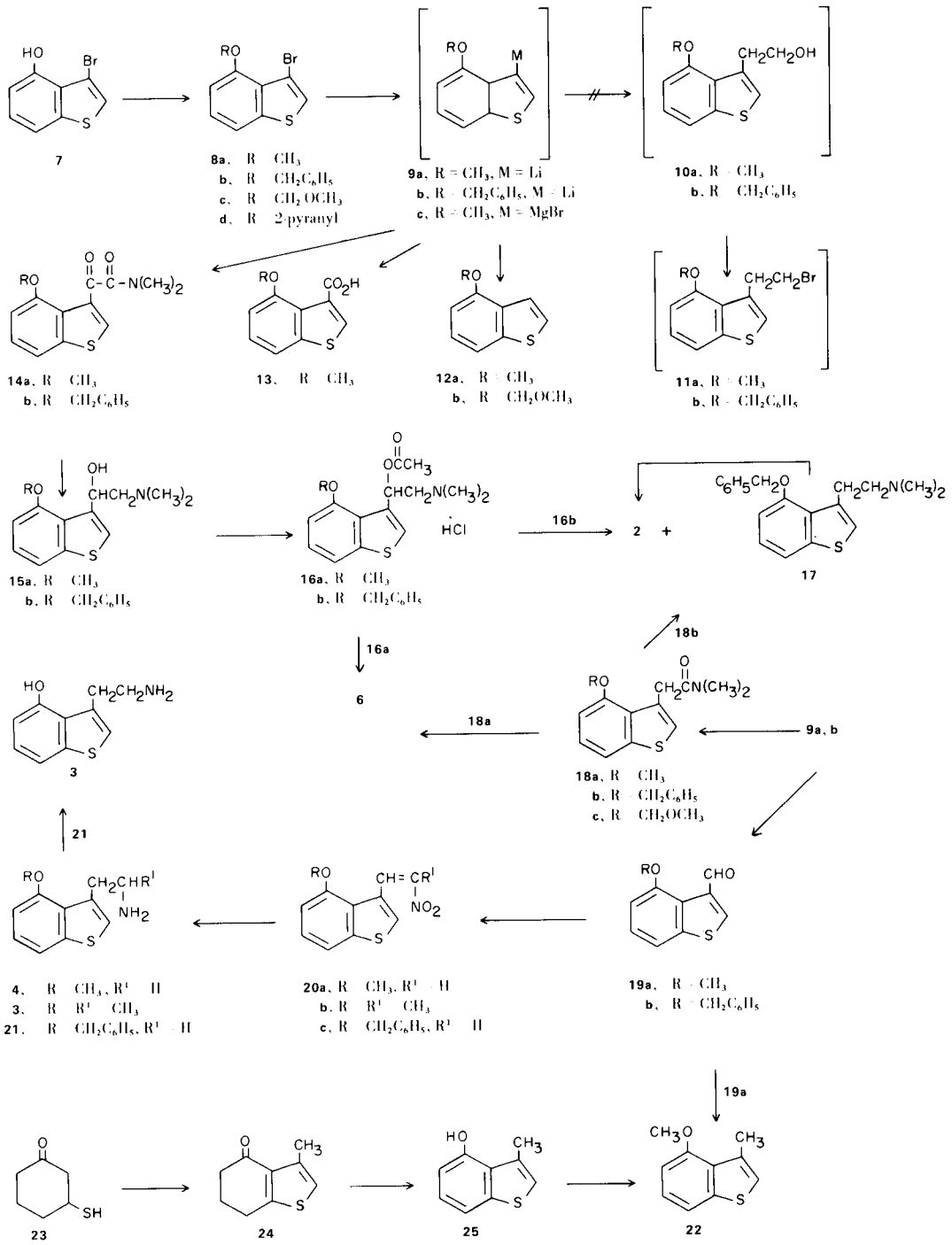
	R	R^1	R^2
2	H	H	CH_3
3	H	H	H
4	CH_3	H	H
5	CH_3	CH_3	H
6	CH_3	H	CH_3

tryptamine and β-methyltryptamine appear to have similar potency (8). To determine if this trend is general, **4** and **5** were prepared.

Our synthesis depended upon the availability of 4-hydroxybenzo[*b*]thiophene (9) which, as has been previously shown (10) can be readily brominated in the 3-position after prior conversion to the benzoate. Hydrolysis of the resulting 3-bromo-4-benzoyloxybenzo[*b*]thiophene gave 3-bromo-4-hydroxybenzo[*b*]thiophene (**7**) (10) in an overall yield of 58%. During subsequent reactions, the 4-hydroxy group was masked as either the methyl (**8a**) or benzyl (**8b**) either by condensation with methyl iodide (11) or benzyl chloride respectively (Scheme I).

Initial attempts were directed at synthesizing the intermediates **11a, b** which could be converted directly to variously substituted amines. Using dry tetrahydrofuran (THF) **8a** (R = CH_3) could be converted to the Grignard

Scheme I



9c. For a reason not yet clarified, **9c** failed to condense with ethylene oxide though a variety of conditions were tried. The only product which could be isolated after an acid work-up was the reduced product, 4-methoxybenzo-[*b*]thiophene (**12a**). That the Grignard reagent was actually formed was demonstrated by the fact that a THF solution of **9c** reacted with carbon dioxide to form, after acidification, 4-methoxybenzo[*b*]thiophene-3-carboxylic acid (**13**) in good yield.

Compounds **8a**, **b** could be converted to the corresponding 3-lithio derivatives (**9a**, **b**) *via* metal-halogen exchange using *n*-butyllithium in either THF or diethyl

ether at -78°. As was the case for the Grignard reagent **9c** (R = CH_3), the lithio derivative **9a** failed to react with ethylene oxide to give the desired alcohol **10a**. Again, only the reduced product **12** could be detected. As a consequence, this route was abandoned.

The first successful synthesis of SAP (**2**) as well as the *O*-methyl derivative (**6**) is outlined in the Scheme (24). The lithio derivatives, **9a**, **b** could be condensed with *N*,*N*,*N'*,*N'*-tetramethyloxamide to give the respective ketoamides **14a**, **b**. Unlike analogous indole ketoamides which give complete reduction of the side chain (12), reduction of **14a**, **b** with lithium aluminum hydride (LAH) gave the alcohols **15a**, **b** which were subsequently converted to their respective acetate hydrochlorides (**16a**, **b**). The acetate functionality of **16a** (R = CH_3) was smoothly hydrogenated using a palladium on charcoal catalyst to give 3-(β-dimethylaminoethyl)-4-methoxybenzo[*b*]thiophene (**6**). It was anticipated that hydrogenolysis of **16b** (R = $CH_2C_6H_5$) would not only reduce the acetate group but also cleave the benzyl ether yielding the desired SAP (**2**). After hydrogenation, however, it was found that **2** constituted only 15% of the product mixture. The remainder of the product was composed mainly of 3-(β-dimethylaminoethyl)-4-benzyloxybenzo[*b*]thiophene (**17**) plus small amounts of other unidentified products. Attempts to cleave the benzyl group of **17** *via* low-pressure hydrogenation under a variety of conditions proved futile. Apparently, the acetate group of **16b** in some manner facilitates the cleavage of the benzyl group. Failure of the benzyloxy groups in the benzo[*b*]thiophene series to undergo hydrogenolysis has been previously observed (13).

Thus, a different approach was necessary for the successful cleavage of the ether protective group. Recently Feutrill and Mirrington (14) found that aromatic methoxy derivatives were rapidly and efficiently cleaved to the corresponding phenols by sodium ethylmercaptide in boiling dimethylformamide (DMF). Using this technique, it was found that **17** was readily converted to SAP (2) and, presumably benzyl ethyl sulfide.

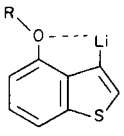
Condensation of lithio derivatives, **9a**, **b** with tetramethyloxamide suffers from the fact that the best yields of the ketoamides (**14a**, **b**) which could be obtained were in the range of 45-55%. Though these ketoamides and their reduction products (**15a**, **b**) are potentially interesting in their own right, a more direct route to SAP was devised. It was found that the lithio derivatives (**9a**, **b**) would condense with bromo-*N*,*N*-dimethylacetamide to give the respective acetamide derivatives, **18a**, **b**. Subsequent reduction with LAH gave the *O*-alkylated derivatives (**6**, **17**) of SAP in about 50% yield.

A route to the unsubstituted amine derivatives (**3**, **4**, **5**) was patterned after the method of Young (15) and used by Campaigne *et al.* (6) in the synthesis of SAS. The lithio derivatives **9a**, **b** were converted to the 4-alkoxybenzo[*b*]-thiophene-3-carboxaldehydes (**19a**, **b**) by condensation with DMF. Reaction of **19a**, **b** with either nitromethane or nitroethane gave the corresponding nitrovinyl derivatives (**20a**, **b**, **c**) which were smoothly reduced with LAH to the desired amines (**4**, **5**, or **21**). The benzyl protective group of **21** was cleaved using sodium ethylmercaptide to give 3-(β-aminoethyl)-4-hydroxybenzo[*b*]thiophene (**3**).

Discussion.

Due to the recent work of Dickinson and Iddon on the rearrangement of 3-lithiobenzo[*b*]thiophene in THF or hexane solution (16), the halogen-metal exchange reactions and subsequent condensations were initially run in diethyl ether. It was found, however, that best results were obtained if the halogen-metal exchange were done in ether, then THF added immediately prior to the addition of a THF solution of the condensation reactant. The improvements in yields upon the addition of the THF is thought to be due to the improved solubilities of the reactants in the THF-ether mixture over that of the corresponding pure ether solutions.

The 4-alkoxy-3-lithiobenzo[*b*]thiophenes are probably somewhat more stable to rearrangement as the *peri* oxygen atom would be expected to exert a stabilizing complexing effect on the lithium atom in the 3-position. Barnes and Nehmsmann (17) found, however, that 1-methoxy-8-lithionaphthalene rearranged on standing to 1-methoxy-2-lithionaphthalene. The absence of a stabilizing effect due to the lithium-oxygen coordination was felt to be caused by destabilizing steric interactions between the two *peri* substituents. Molecular models show that the *peri*-positions (3 and 4) in benzo[*b*]thiophene are less crowded than in naphthalene. Thus, in the present case, the oxygen and metal atoms may be in ideal positions for stabilizing complexation to occur; hence decreased reactivity of both the lithio (**9a**) and Grignard (**9c**) reagents toward ethylene oxide.



That the substituents resulting from the condensation of the 4-alkoxy-3-lithiobenzo[*b*]thiophenes were, in fact, in the 3-position of the benzo[*b*]thiophene ring was shown by unambiguous synthesis (see Scheme I). Wolff-Kishner reduction of 4-methoxybenzo[*b*]thiophene-3-carboxaldehyde (**19a**) gave 4-methoxy-3-methylbenzo[*b*]-thiophene (**22**). This compound was identical in all respects with that synthesized by the method of Napier and Chu (18). Thus, cyclohexen-3-one was condensed with hydrogen sulfide to give 3-mercaptocyclohexanone

(**23**). The acid catalyzed reaction of **23** with pyruvaldehyde gave 3-methyl-4-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene (**24**) (9). Aromatization was accomplished by boiling **24** with a decalin suspension of palladium on charcoal to give 4-hydroxy-3-methylbenzo[*b*]thiophene (**25**). This was converted to the methyl ether by reaction first with sodium hydride in DMF, then with methyl iodide.

Cleavage of the benzyl ether by acid catalyzed hydrolysis was not attempted as there is precedent (13,19) for the stability of benzyl ethers of the benzo[*b*]thiophene series to mild (concentrated hydrochloric acid) acid hydrolysis. Hydrolysis with 48% hydrobromic acid is sufficient to destroy the benzo[*b*]thiophene ring system (13,20). Attempted hydrolysis of compound **18** using anhydrous hydrogen chloride in glacial acetic acid (21) (90°, 3 hours) resulted only in the recovery of starting material. Other alcoholic protective groups which are somewhat more sensitive to hydrolysis were considered. Thus, the methoxymethyl ether (**8c**) was synthesized from 3-bromo-4-hydroxybenzo[*b*]thiophene (**7**) and chloromethylmethyl ether. However, condensation of the 3-lithio derivative of this ether with bromo-*N*,*N*-dimethylacetamide gave only 5-15% yields of the desired amide **18c**. The main compound resulting from this condensation was the dehalogenated product **12b**. Similarly, the pyranyl ether **8d** was synthesized. However, attempts (distillation, chromatography) to purify this oily compound resulted mainly in the hydrolysis of the ether.

It should be noted that the infra-red spectrum of **2** is characteristic of a trialkylammonium phenolate, and does not show free OH or tertiary amine bands. The ir spectrum is very similar to that of SAS (6).

Biological Evaluation.

The pressor effects of **2**, **3**, **4**, **5**, and **6** were compared to a standard indole derivative, 4-methoxydimethytryptamine, and are reported in Table I. The sulfur analog of 4-methoxydimethyltryptamine was only about one-fourth as active as its bioisostere in causing an increase in blood pressure in anesthetized rats (850 μg./kg. *vs* 200 μg./kg.). However, the most potent compound in this test was the isopropylamine derivative **5**, which gave excessive pressor effects at the lowest dose tested.

Preliminary tests on the CNS activity of two of these compounds, **2** and **3**, are shown in Table II, compared to 5-hydroxy-3-(β-aminoethyl)benzo[*b*]thiophene (SAS). The quantitative EEG analyses were performed as previously described (8). Compound **3**, 4-hydroxy-3-(β-aminoethyl)benzo[*b*]thiophene has similar, but weaker, activity than the 5-hydroxy isomer, SAS. Both are sedatives, agonistic to pentobarbital at 1 μg./kg. However, 4-hydroxy-3-(β-dimethylaminoethyl)benzo[*b*]thiophene (**2**) acts as a stimulant at these dosages.

TABLE I

Pressor Effect of the Sulfur Isosteres of Psilocin and Related Isomers (22)

Compound (a)	ED+20 mm Hg. (μg./kg.) (c)
2	1800
3	515
4	(d)
5	<125 (e)
6	850
4-CH_3O-DMT (b)	200

(a) All compounds were administered as hydrochlorides. (b) 4-Methoxydimethyltryptamine. (c) Adult male Sprague-Dawley rats weighing 300-350 g. were anesthetized with Nembutal, 60 mg./kg. and systolic and diastolic blood pressures were recorded directly using a polyethylene cannula inserted into the carotid artery and connected *via* a Statham Model P23AA transducer to a Physiograph PMP-4A. Test drugs were dissolved in a 0.93% saline solution containing 1000 units heparin per ml. and injected *via* a similar cannula into the jugular vein, beginning at a dose of 125 μg./kg. and increasing by doubling until a maximal effect was achieved. Minimum doses to give an increase of 20 mm/Hg were determined from dose-response curves. (d) Does not show dose-response curve. At 1000 μg./kg. a mean elevation of 55 mm Hg was observed, but lower doses had no effect. (e) Lowest dose tested.

TABLE II

Quantitative EEG Analysis of Benzo[*b*]thiophene Isosteres of Psilocin and Serotonin (23)

	% Reversal of Sedation	
Compound (a)	1 μg./kg.	2 μg./kg.
2	59.2	84
3	-27.7 (c)	89
SAS (b)	-100 (d)	

(a) All compounds administered as hydrochlorides. (b) Sulfur analog of Serotonin, 5-hydroxy-3(β-aminoethyl)benzo[*b*]thiophene. (c) Sedative at 1 μg./kg. (d) At 0.01 μg./kg. it is agonistic to pentobarbital.

EXPERIMENTAL

The infrared spectra were obtained on a Perkin-Elmer Model 137-B infracord spectrometer using either potassium bromide mulls or as neat liquids between silver chloride or sodium chloride plates. Nmr spectra were determined on a Varian Associates Model HA-100 spectrometer. Mass spectra were determined either on a Varian MAT CH-7 spectrometer or on an Associated Electrical Industries' MS-9 spectrometer at 70 eV. Melting points were obtained on a Mel-Temp capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Midwest Microlab of Indianapolis, Indiana.

All bromine-lithium exchange reactions were performed using a dry ice-acetone cooling bath and under a static nitrogen atmosphere. The tetrahydrofuran (THF) was dried by refluxing over lithium aluminum hydride and distilled immediately prior to use. Mallinckrodt analytical reagent grade ether was used directly from freshly opened cans. Petroleum ether, unless otherwise stated, refers to that fraction boiling between 65-75°.

3-Bromo-4-hydroxybenzo[*b*]thiophene (**7**).

This compound was prepared by the procedure of Campaigne, Dinner, and Haseman (10) in approximately 58% overall yield starting with 4-hydroxybenzo[*b*]thiophene (9).

3-Bromo-4-methoxybenzo[*b*]thiophene (**8a**).

To a stirred solution of sodium hydride (5.55 g., 56.8% oil dispersion) in dry DMF (400 ml.) cooled to 0° was added 30 g. (0.13 mole) of **7**. After hydrogen evolution ceased (approximately 30 minutes), methyl iodide (30 g., 0.21 mole) was added, the mixture was stirred at 0° for one hour, then at 25° for twelve hours, poured into water (1000 ml.), and extracted with ether. The combined ether layers were back-extracted with 10% sodium hydroxide then with water, dried (magnesium sulfate), filtered, and the solvent evaporated leaving a yellow oil (26 g., 81%), which solidified upon cooling to room temperature. Purification was accomplished by distillation (b.p. 115-120°/0.2 mm) followed by recrystallization from hexane (charcoal) to yield colorless crystals: m.p. 83-85°.

Anal. Calcd. for C_9H_7BrOS: C, 44.46; H, 2.88; S, 13.18; M.W. 242, 244. Found: C, 44.68; H, 3.15; S, 12.82; M.W. m/e 242, 244.

3-Bromo-4-benzyloxybenzo[*b*]thiophene (**8b**).

In a manner identical with the synthesis of **8a**, 7.4 g. (0.032 mole) of **7** was condensed with benzyl chloride (5.05 g., 0.04 mole) to yield, after recrystallization from methanol (charcoal), 6.4 g. (63%) of crystals, m.p. 64-65°; ir: 7.90 μ (C-O-C); nmr (deuteriochloroform) δ 5.08 (s, 2H), 6.70 (d of d, 1H, $J_{5,6}$ = 7.3 Hz, $J_{5,7}$ = 1.2 Hz, H-5), 7.04-7.46 (m, 8H).

Anal. Calcd. for $C_{15}H_{11}BrOS$: C, 56.43; H, 3.45; S, 10.03; M.W. 318, 320. Found: C, 56.51; H, 3.56; S, 10.06; M.W. m/e 318, 320.

3-Lithio-4-methoxybenzo[*b*]thiophene (**9a**).

To a cold (-78°) stirred solution of ether (60 ml.) and *n*-butyllithium (8 ml. of 2.5 *M* hexane solution, 0.02 mole) under a nitrogen atmosphere was slowly added a solution of **8a** (4.88 g., 0.02 mole) in ether (20 ml.). The mixture was stirred for an additional 30 minutes after which the formation of **9a** was assumed to be complete.

3-Lithio-4-benzyloxybenzo[*b*]thiophene (**9b**).

In a manner identical with the synthesis of **9a**, compound **8b** was converted to the lithio-derivative **9b**.

4-Methoxybenzo[*b*]thiophene-3-carboxaldehyde (**19a**).

To an ether solution of **9a** (0.01 mole) was slowly added dry THF (20 ml.), then dry DMF (1.09 g., 0.015 mole). The reaction mixture was stirred at -78° for an additional hour, allowed to warm to room temperature and then quenched by pouring into excess 2*N* hydrochloric acid solution. The aqueous mixture was extracted with ether, the combined ether extracts were dried (magnesium sulfate), filtered and the solvent was evaporated to yield an orange solid. Recrystallization of the solid from hexane (charcoal) gave yellow needles (1.0 g., 51%), m.p. 92-96°. Repeated recrystallizations from hexane gave a colorless analytical sample: m.p. 95-96°; ir (potassium bromide): 6.0 μ (C=O); nmr (deuteriochloroform) δ 4.02 (s, 3H), 6.90 (d of d, 1H, $J_{5,6}$ = 7.5 Hz, $J_{5,7}$ = 1.5 Hz, H-5), 7.2-7.5 (m, 2H, H-6,7), 8.28 (s, 1H, H-2), and 10.42 (s, 1H, CHO).

Anal. Calcd. for $C_{10}H_8O_2S$: C, 62.50; H, 4.17; S, 16.67; M.W. 192. Found: C, 62.22; H, 4.35; S, 16.41; M.W. m/e 192.

4-Benzyloxybenzo[*b*]thiophene-3-carboxaldehyde (**19b**).

In a manner identical with the synthesis of **19a**, lithio derivative **9b** was converted to aldehyde **19b**. Recrystallization from cyclohexane (charcoal) gave 7.15 g. (67%) of light yellow crystals, m.p. 101-104°. A colorless analytical sample was obtained by repeated recrystallization from cyclohexane, m.p. 104°; ir (potassium bromide): 6.01 μ (C=O); nmr (deuteriochloroform) δ 5.06 (s, 2H), 6.80 (d, 1H, $J_{5,6}$ = 7.6 Hz), 7.08-7.46 (m, 7H), 8.17 (s, 1H, H-2), 10.51 (s, 1H, CHO).

Anal. Calcd. for $C_{16}H_{12}O_2S$: C, 71.63; H, 4.47; S, 11.94; M.W. 268. Found: C, 71.42; H, 4.39; S, 12.23; M.W. m/e 268.

4-Methoxy-3-(2-nitrovinyl)benzo[*b*]thiophene (**20a**).

A solution of **19a** (0.59 g., 3 mmoles), ammonium acetate (0.35 g.) and nitromethane (15 ml.) was refluxed for one hour, then the solvent evaporated leaving a dark orange-red oil. Chromatography of the oil on silica gel (100 g.) using a 7:3 (v:v) mixture of petroleum ether and chloroform gave 0.22 g. (31%) of a light orange crystalline compound which, after recrystallization from cyclohexane, had m.p. 114-115°; ir (potassium bromide) 6.14 (C=C), 6.65 (NO_2), and 7.50 (NO_2) μ; and nmr (deuteriochloroform) δ 8.78 (d, 1H, J = 13.5 Hz), 7.28-7.66 (m, 4H), 6.79 (d of d, 1H, $J_{5,6}$ = 7 Hz, $J_{5,7}$ = 2 Hz, H-5), 3.96 (s, 3H).

Anal. Calcd. for $C_{11}H_9NO_3S$: C, 56.17; H, 3.83; S, 13.62; N, 5.96; M.W. 235. Found: C, 56.01; H, 3.99; S, 13.35; N, 6.01; M.W. m/e 235.

4-Methoxy-3-(2-nitro-1-propenyl)benzo[*b*]thiophene (**20b**).

A solution of **19a** (0.60 g., 3.13 mmoles), ammonium acetate (0.34 g., 4.38 mmoles), in nitroethane (20 ml.) was heated at reflux for three hours. The solvent was evaporated and the residual oil heated with cyclohexane, and the resulting solution decanted from the insoluble residue. Upon adding hexane and cooling in an ice-bath 0.35 g. (45%) of yellow crystals were obtained, m.p. 98-102°. A second recrystallization from hexane gave m.p. 104-105°; ir (potassium bromide) 6.05 (C=C), 6.65 and 7.65 (NO_2) μ; nmr (deuteriochloroform) δ 2.41 (d, 3H, J = 1 Hz, $C(NO_2)CH_3$), 3.89 (s, 3H), 6.77 (d of d, 1H, $J_{5,6}$ = 7.5 Hz, $J_{5,7}$ = 1.5 Hz, H-5), 7.18-7.46 (m, 3H, H-2, 6, 7) 8.73 (m, 1H).

Anal. Calcd. for $C_{12}H_{11}NO_3S$: C, 57.83; H, 4.42; S, 12.85; M.W. 249. Found: C, 57.67; H, 4.55; S, 12.88; M.W. m/e 249.

4-Benzyloxy-3-(2-nitrovinyl)benzo[*b*]thiophene (**20c**).

A solution of **19b** (6.65 g., 0.024 mole) and ammonium acetate (2.80 g., 0.036 mole) in nitromethane (120 ml.) was heated at reflux for 1 hour then the solvent was evaporated leaving a yellow-orange solid. The solid was triturated with warm absolute ethanol, then filtered, leaving 5.96 g. (79%) of yellow needles, m.p. 157-158°; ir: 6.20 (C=C), 6.75 (NO_2) and 7.60 (NO_2) μ.

Anal. Calcd. for $C_{17}H_{13}NO_3S$: C, 65.59; H, 4.18; S, 10.29; M.W. 311. Found: C, 65.36; H, 4.08; S, 10.38; M.W. m/e 311.

3-β-Aminoethyl-4-methoxybenzo[*b*]thiophene (**4**).

To a solution of LAH (3.0 g., 80 mmoles) in THF (100 ml.) was slowly added a solution of **20a** (1.0 g., 4.2 mmoles) in THF (20 ml.). After the addition was complete, the stirred suspension

was heated at reflux for one hour, cooled in an ice bath, and quenched by adding in succession the following solutions: water (3 ml.), 15% sodium hydroxide (3 ml.), and water (9 ml.). The resulting slurry was filtered, the solid was washed with THF, the filtrate was dried (magnesium sulfate) and the solvent was evaporated leaving a yellow oil (0.52 g., 60%); ir (neat): 3.05 (N-H), 3.25 (aromatic C-H), 3.40, and 3.50 (C-H) μ; nmr (deuteriochloroform) δ 1.49 (broad s, 2H, N-H), 2.8-3.2 (m, 4H), 3.78 (s, 3H, $-CH_3$), 6.62 (d of d, 1H, $J_{5,6}$ = 7.5 Hz, $J_{5,7}$ = 1.0 Hz, H-5), 6.84 (broad s, 1H, H-2), 7.06-7.40 (m, 2H, H-6, 7), M.W. 207.

The oil was dissolved in anhydrous ether, and the ether solution saturated with dry hydrogen chloride. The precipitate was filtered and recrystallized from methanol-ethyl acetate (charcoal) to give 0.43 g. of **4** hydrochloride, m.p. 270-273° dec.; ir (potassium bromide): 3.3-3.55 (broad, C-H, N-H).

Anal. Calcd. for $C_{11}H_{14}ClNOS$: C, 54.21; H, 5.75; S, 13.14; Cl, 14.58. Found: C, 54.23; H, 5.60; S, 13.14; Cl, 14.70.

3-(2-Amino-1-propyl)-4-methoxybenzo[*b*]thiophene (**5**).

To a solution of LAH (7.2 g., 0.19 mole) in dry THF (200 ml.), was slowly added **20b** (7.2 g., 0.029 mole) in THF (50 ml.). The mixture was heated at reflux for 4 hours then cooled in an ice bath and quenched by slowly adding in sequence, water (7.2 ml.), 15% sodium hydroxide (7.2 ml.), and water (21.6 ml.). The solution was filtered and the salts washed with THF. The organic phase was dried (magnesium sulfate) and the solvent was evaporated leaving a brown oil. Bulb to bulb distillation (0.08 mm with bath temperature 160°) gave 5.2 g. (81%) of a light yellow oil; ir (neat, silver chloride) 3.0 (broad, $-NH_2$) μ; nmr (deuteriochloroform) δ 1.11 (d, 3H, J = 5.6 Hz), 1.31 (broad, 2H, exchangeable with deuterium oxide, $-NH_2$), 2.62-2.90 (m, 1H), 3.04-3.38 (m, 2H), 3.82 (s, 3H), 6.65 (broad d, 1H, $J_{5,6}$ = 7.8 Hz, H-5), 6.89 (s, 1H, H-2), 7.08-7.48 (m, 2H, H-6, 7), M.W. m/e 221.

The oil was dissolved in dry ether and the solution saturated with hydrogen chloride. The precipitate was collected and recrystallized from methanol-ethyl acetate to yield a crystalline product, m.p. 205.5-207°.

Anal. Calcd. for $C_{12}H_{16}ClNOS$: C, 55.87; H, 6.21; Cl, 13.79; N, 5.44; S, 12.41. Found: C, 56.04; H, 6.11; Cl, 13.92; N, 5.38; S, 12.27.

3-β-Aminoethyl-4-benzyloxybenzo[*b*]thiophene (**21**).

In a manner similar to the synthesis of **4**, **20c** (5.96 g., 19.2 mmoles) was reduced with LAH (6 g., 158 mmoles) to yield 3.91 g. (72%) of a yellow oil; ir (sodium chloride): 3.0-3.10 (broad, N-H) μ; nmr (deuteriochloroform) δ 0.52 (broad s, 2H, NH_2), 2.4-2.85 (m, 4H, $-CH_2CH_2-$), 4.71 (s, 2H), 6.41 (d of d, 1H, $J_{5,6}$ = 7.6 Hz, $J_{5,7}$ = 1 Hz, H-5), 6.54 (s, 1H, H-2), 6.75-7.20 (m, 7H); M.W.: Calcd. 283.1031; M.W. m/e 283.1025. A portion of the oil was dissolved in dry ether, and dry hydrogen chloride added. The precipitate was collected and recrystallized three times from methanol-ethyl acetate (charcoal) to yield a crystalline product, m.p. 212-214.5° dec.

Anal. Calcd. for $C_{17}H_{17}NOS{\cdot}HCl$: C, 63.85; H, 5.63; S, 10.02. Found: C, 63.71; H, 5.62; S, 10.13.

3-β-Aminoethyl-4-hydroxybenzo[*b*]thiophene (**3**).

To a cooled (0°), stirred solution of sodium hydride (1.25 g., 51.8 mmoles) in DMF (90 ml.) was slowly dropped a solution of ethyl mercaptan (2.15 g., 34.6 mmoles) in DMF (20 ml.). The solution was stirred at 0° until hydrogen evolution ceased (approximately 1 hour) and then allowed to warm to 25°. To this mixture a solution of crude **21** (3.91 g., 13.8 mmoles) in DMF (20 ml.) was rapidly added and the mixture heated at reflux for 1 hour. The resulting mixture was evaporated to dryness *in vacuo*, and the residue taken up in 30% potassium hydroxide (50 ml.). The aqueous solution was extracted with ether and then the *p*H was adjusted to approximately 8 with concentrated hydrochloric acid. The resulting aqueous mixture was extracted with ether, and combined ether extracts were dried (magnesium sulfate) filtered and the solvent evaporated leaving a glassy semi-solid. This residue was taken up in ether and the ether solution filtered from the insoluble material. Dry hydrochloric acid was added to the ether solution, the precipitate was filtered and recrystallized three times from the methanol-ethyl acetate (charcoal) to give 1.15 g. (36%) of crystals, which decomposed without melting.

Anal. Calcd. for $C_{10}H_{11}NOS{\cdot}HCl$: C, 52.34; H, 5.23; N, 6.11; S, 13.96. Found: C, 52.46; H, 5.33; N, 6.01; S, 14.15.

3-(4-Methoxybenzo[*b*]thienyl)-α-ketodimethylacetamide (**14a**).

To an ether solution of **9a** (0.02 mole) was rapidly added a solution of tetramethyloxamide (5.75 g., 0.04 mole) in THF (30 ml.). The solution was stirred at -78° for 16 hours, then slowly allowed to warm to room temperature, and quenched by pouring into excess, cold, 2*N* hydrochloric acid solution. The organic layer was separated, and the aqueous phase extracted with ether and then with chloroform. The combined organic phases were dried (magnesium sulfate), filtered, and the solvent was evaporated leaving a yellow-white solid. The solid was recrystallized from a benzene:hexane solution (charcoal) to yield 3.0 g. (54%) of a colorless crystalline solid, m.p. 153-155°; ir (potassium bromide) 6.10 (broad) (C=O) μ; nmr (deuteriochloroform): δ 3.05 (s, 3H, N-CH_3), 3.14 (s, 3H, N-CH_3), 3.82 (s, 3H, OCH_3), 3.77 (d of d, 1H, $J_{5,6}$ = 8 Hz, $J_{5,7}$ = 1.3 Hz, H-5), 7.17-7.48 (m, 2H, H-6, 7), 8.17 (s, 1H, H-2).

Anal. Calcd. for $C_{13}H_{13}NO_3S$: C, 59.31; H, 4.94; S, 12.17; M.W., 263. Found: C, 59.17; H, 5.01; S, 12.25; M.W. m/e 263.

3-(4-Benzyloxybenzo[*b*]thienyl)-α-ketodimethylacetamide (**14b**).

In a manner identical with the synthesis of **14a**, **9b** (38 mmoles) was converted to 7.15 g. (56%) of **14b**, m.p. 150-151.5°; ir (potassium bromide) 5.98, 6.08 (C=O) μ; nmr (deuteriochloroform): δ 2.84 (broad s, 6H), 5.17 (s, 2H), 6.73 (broad d, 1H, $J_{5,6}$ = 8 Hz, H-5), 7.06-7.48 (m, 7H), 8.18 (s, 1H, H-2).

Anal. Calcd. for $C_{19}H_{17}NO_3S$: C, 67.26; H, 5.01; S, 9.44. Found: C, 67.31; H, 5.14; S, 9.40; M.W. m/e 339.

2-Dimethylamino-1-(4-methoxy-3-benzo[*b*]thienyl)ethanol (**15a**) Hydrochloride.

To a stirred solution of LAH (1.2 g., 32 mmoles) in dry THF (75 ml.) was slowly added a solution of **14a** (1.5 g., 5.4 mmoles) in THF (50 ml.). The solution was heated at reflux for 16 hours, cooled in an ice-bath, then quenched by adding in sequence water (1.2 ml.), 15% sodium hydroxide (1.2 ml.), and water (3.6 ml.). The mixture was filtered, and the salts were boiled with THF and filtered. The combined filtrates were dried (magnesium sulfate), filtered and the solvent was evaporated to give 1.22 g. (90%) of a brown oil; ir (neat): 2.90 (broad, -OH) μ; nmr (deuteriochloroform): δ 2.29 (s, 6H), 2.43-2.76 (m, 2H), 3.78 (s, 3H), 4.21 (broad s, 1H, exchangeable with deuterium oxide), 5.41 (m, 1H), 6.63 (d of d, 1H, $J_{5,6}$ = 7.0 Hz, $J_{5,7}$ = 1.2 Hz, H-5), 7.06-7.45 (m, 3H, H-2, 6, 7), M.W. m/e 251.

The oil was taken up in dry ether, the solution saturated with hydrogen chloride, the precipitate collected and recrystallized from methanol-ethyl acetate (charcoal) to give 1.3 g. (80%) of colorless

needles, m.p. 221-223° dec.

Anal. Calcd. for $C_{13}H_{18}ClNO_2S$: C, 54.26; H, 6.26; N, 4.87; Cl, 12.38. Found: C, 54.32; H, 6.23; N, 4.83; Cl, 12.13.

1-(4-Benzyloxy-3-benzo[*b*]thienyl)-2-dimethylaminoethanol (**15b**).

In a manner identical with the synthesis of **15a**, compound **14b** (5.09 g., 15 mmoles) was reduced to **15b** (an oil, 4.5 g., 92%); ir (neat, silver chloride), 2.90 (O-H) μ, (no carbonyl band); nmr (deuteriochloroform): δ 1.96 (s, 6H), 2.20-2.36 (m, 1H), 2.52-2.68 (m, 1H), 4.24 (broad s, 1H), 5.06 (s, 2H), 5.26-5.42 (m, 1H), 6.73 (d of d, 1H, $J_{5,6}$ = 7.8 Hz, $J_{5,7}$ = 1.2 Hz, H-5), 7.04-7.50 (m, 8H); M.W. m/e 327.

Compound **15b** was taken up in dry ether, and the solution saturated with hydrogen chloride. The precipitate was filtered and recrystallized from methanol-ethyl acetate (charcoal) to yield the crystalline hydrochloride of **15b**, m.p. 183-184°.

Anal. Calcd. for $C_{19}H_{22}ClNO_2S$: C, 62.70; H, 6.05; S, 8.80. Found: C, 62.53; H, 6.28; S, 8.88.

1-Acetoxy-1-(4-methoxy-3-benzo[*b*]thienyl)-2-dimethylaminoethane (**16a**) Hydrochloride.

To a solution of acetyl chloride (0.27 g., 3.5 mmoles) in dry THF (30 ml.) heated to reflux was slowly added a solution of **15a** (0.80 g., 3.2 mmoles) in dry THF. Stirring and heating was continued for an additional 3 hours during which time the hydrochloride salt precipitated. After allowing the mixture to cool to room temperature, the precipitate was filtered to give 0.92 g. (87%) of essentially pure **16a**, m.p. 189-190°; ir (potassium bromide) 3.85 and 4.05 (broad, $-N(CH_3)_2\cdot HCl$), 5.75 (C=O) μ.

Anal. Calcd. for $C_{15}H_{20}ClNO_3S$: C, 54.63; H, 6.07; S, 9.71. Found: C, 54.45; H, 5.99; S, 9.85.

1-Acetoxy-1-(4-benzyloxy-3-benzo[*b*]thienyl)-2-dimethylaminoethane (**16b**) Hydrochloride.

In a manner identical with the synthesis of **16a**, compound **15b** (4.0 g., 0.012 mole) was converted to 3.70 g. (76%) of the acetate **16b**, m.p. 177-180° dec.; ir (potassium bromide) 5.75 (C=O) μ.

3-(*N,N*-Dimethylacetamido)-4-methoxybenzo[*b*]thiophene (**18a**).

To an ether solution of **9a** (0.02 mole) was added a solution of *N,N*-dimethylbromoacetamide (3.32 g., 0.02 mole) in THF (15 ml.). The solution was stirred at -78° for 4 hours then allowed to warm to room temperature. The reaction was quenched by pouring the mixture into excess 2*N* hydrochloric acid. The aqueous solution was extracted first with ether, then with chloroform. The combined extracts were dried (magnesium sulfate), and the solvent was evaporated to yield a gummy solid. Trituration of this solid with benzene followed by filtration gave a 2.0 g. (40%) of **18a**. Chromatography of the benzene filtrate on silica gel using a 7:3 petroleum ether:acetone mixture gave first 1.1 g. (34%) of 4-methoxybenzo[*b*]thiophene (identified by comparison with an authentic sample) followed by 0.5 g. (10%) of **21a** (total yield 50%), which after recrystallization from acetone had, m.p. 141-143°; ir (potassium bromide) 6.1 (C=O) μ; nmr (deuteriochloroform) δ 2.96 (s, 3H, N-CH_3), 2.98 (s, 3H, NCH_3) 3.79 (s, 3H), 4.05 (s, 2H), 6.65 (d of d, 1H, $J_{5,6}$ = 7.8 Hz, $J_{5,7}$ = 1.5 Hz, H-5), 6.95-7.41 (m, 3H).

Anal. Calcd. for $C_{13}H_{15}NO_2S$: C, 62.65; H, 6.02; S, 12.85; M.W. 249. Found: C, 62.42; H, 5.85; S, 12.81; M.W. m/e 249.

4-Benzyloxy-3-(*N,N*-Dimethylacetamido)benzo[*b*]thiophene (**18b**).

In a manner identical with the synthesis of **18a**, **9b** (0.02 mole) was condensed with *N,N*-dimethylbromoacetamide. After quenching the reaction, the mixture was stirred for 30 minutes. The resulting precipitate was filtered to yield 4.06 g. (63%) of **18b**. The organic layer of the filtrate was separated and the aqueous phase extracted with chloroform. The combined organic phases were dried (magnesium sulfate), filtered, and the solvent was evaporated leaving an orange-red oil. The oil was chromatographed on silica gel (140 g.) using a 7:3 (v/v) mixture of petroleum ether:acetone. Eluting first was a compound assigned the structure of 4-benzyloxybenzo[*b*]thiophene (0.95 g., 20%) on the basis of its mass spectrum (m/e 240). The second product to elute was 0.50 g. of the desired amide, **18b** (total yield 4.56 g., 70%). After recrystallization from carbon tetrachloride, this compound had m.p. 147-149°; ir (potassium bromide) 6.08 (C=O) μ; nmr (deuteriochloroform) δ 2.57 (s, 3H, -NCH_3), 2.78 (s, 3H, NCH_3), 3.92 (s, 2H), 5.00 (s, 2H, CH_2-O), 6.74 (broad, d, 1H, $J_{5,6}$ = 7.6 Hz, H-5), 6.97 (broad s, 1H, H-2), 7.05-7.60 (m, 7H).

Anal. Calcd. for $C_{19}H_{19}NO_2S$: C, 70.15; H, 5.84; S, 9.86. M.W. 325. Found: C, 69.94; H, 6.04; S, 9.99; M.W. m/e 325.

3-(β-Dimethylaminoethyl)-4-methoxybenzo[*b*]thiophene (**6**) Hydrochloride.

A.

A solution of **16a** (1.6 g., 4.4 mmoles) and 10% Pd/C (1 g.) in an ethanol (20 ml.)-water (4 ml.) solution was hydrogenated for 1 hour (initial pressure was 42 psi). An additional gram of Pd/C was added, and the hydrogenation repeated (42 psi, 1 hour). The mixture was filtered, solvent was evaporated, and the resulting solid recrystallized from methanol-ethyl acetate to yield 0.83 g. (70%) of the desired hydrochloride, m.p. 202-205° dec.; ir (potassium bromide) no hydroxy or carbonyl bands.

Anal. Calcd. for $C_{13}H_{18}ClNOS$: C, 57.46; H, 6.62; N, 5.15; S, 11.78; Cl, 13.08. Found: C, 57.26; H, 6.71; N, 5.28; S, 11.73; Cl, 12.86.

The hydrochloride was dissolved in water, then made basic with sodium carbonate. The aqueous solution was extracted with ether, the ether phases were dried (magnesium sulfate), filtered and the solvent was evaporated leaving a pale yellow oil; ir (neat, silver chloride) 3.25 (aromatic C-H), 3.40 (C-H), 3.55, 3.60 (amino C-H) μ; nmr (deuteriochloroform) δ 2.30 (s, 6H), 2.40-2.68 (m, 2H), 3.10-3.29 (m, 2H), 3.84 (s, 3H, OCH_3), 6.65 (d of d, 1H, $J_{5,6}$ = 7.5 Hz, $J_{5,7}$ = 1.6 Hz, H-5), 6.92 (broad s, 1H, H-2), 6.96-7.46 (m, 2H, H-6, 7), M.W. m/e 235.

B.

To a stirred solution of LAH (0.76 g., 0.02 mole) in dry THF (50 ml.) was slowly added a solution of **18a** (2.49 g., 0.01 mole) in THF (20 ml.). The mixture was heated at reflux for 12 hours, then cooled in an ice bath and quenched by adding in sequence water (0.76 ml.), 15% sodium hydroxide (0.76 ml.) and water (2.28 ml.). The mixture was filtered and the salts were washed with THF. The combined filtrates were dried (magnesium sulfate) filtered, and the solvent was evaporated to yield 2.1 g. (90%) of a pale yellow oil which was identical in all aspects with the compound obtained as in A above.

4-Benzyloxy-3-(β-dimethylaminoethyl)benzo[*b*]thiophene (**17**) Hydrochloride.

Reduction of **19b** (2.75 g., 74 mmoles) with LAH in a manner identical with method B above gave a brown oil (6.5 g., 90%); nmr (deuteriochloroform) δ 2.07 (s, 6H, -$N(CH_3)_2$), 2.24-2.44 (m, 2H), 3.05-3.17 (m, 2H), 5.07 (s, 2H, -CH_2-O), 6.66 (broad d, 1H, $J_{5,6}$ = 7.8 Hz, H-5), 6.89 (broad s, 1H, H-2), 7.0-7.50 (m, 7H); M.W. m/e 311.

The oil was dissolved in ether and dry hydrogen chloride added. The ether was decanted and the solid recrystallized from 2-propanol-ether (charcoal) to yield a light brown solid. An analytical sample was obtained by recrystallization from a small amount of DMF, m.p. 157-158°.

Anal. Calcd. for $C_{19}H_{21}NOS \cdot HCl$: C, 65.61; H, 6.33; S, 9.21. Found: C, 65.32; H, 6.28; S, 9.35.

3-(β-Dimethylaminoethyl)-4-hydroxybenzo[*b*]thiophene (**2**).

A.

A solution of **16b** (3.45 g., 8.5 mmoles) and 10% Pd/C (3.5 g.) in an ethanol (45 ml.)-water (5 ml.) solution was hydrogenated (initial pressure 42 psi) for 20 hours. The reaction mixture was filtered, and the solvent evaporated to give a white solid. Thin layer chromatography (silica gel, methanol) showed a mixture of several products. The solid was taken up in water, made basic with sodium carbonate extracted with ether, the ether extracts dried (magnesium sulfate), filtered, and the solvent was evaporated to give a viscous yellow oil. The oil was triturated with 15 ml. of ether upon which a colorless solid precipitated. Collection of the solid and recrystallization from acetone gave 0.30 g. (16%) of **2**, m.p. 143.5-145°; ir (potassium bromide) 4.0 (broad), 5.20-5.95 (broad), no N-H or O-H; nmr (d-6 acetone): δ 2.27 (s, 6H), 2.62-2.82 (m, 2H), 3.08-3.32 (m, 2H), 6.73 (d of d, 1H, $J_{5,6}$ = 7 Hz, $J_{5,7}$ = 1.7 Hz, H-5), 7.0-7.38 (m, 3H).

Anal. Calcd. for $C_{12}H_{15}NOS$: C, 65.16; H, 6.79; S, 14.48; M.W. 221. Found: C, 65.43; H, 6.84; S, 14.60; M.W. m/e 221.

B.

To a cooled (0°), stirred solution of sodium hydride (0.54 g. of a 57% dispersion, 12.5 mmoles) in DMF (50 ml.) was slowly added ethyl mercaptan (0.78 g., 12.5 mmoles). The mixture was stirred for 90 minutes then **17** (1.55 g., 5 mmoles) in DMF (10 ml.) was added. The mixture was then heated at reflux for 1 hour, then the solvent evaporated *in vacuo*. The residue was taken up in 30% potassium hydroxide (40 ml.) and extracted with ether. The *p*H of the aqueous phase was adjusted to approximately 8 with concentrated hydrochloric acid and the cloudy solution extracted with ether. These last ether extractions were combined, dried (magnesium sulfate), filtered, and the solvent was evaporated leaving 0.40 g. (36%) of an off-white solid which was identical in all respects with the product obtained in A above. An additional 0.40 g. of **2** (total yield 72%) could be obtained by working up the ether extracts from the original strongly-basic aqueous solution. When these ether extracts were dried (magnesium sulfate), filtered, and the solvent evaporated, a dark oil which slowly solidified was recrystallized three times from acetone (charcoal) to yield pure **2**.

4-Hydroxy-3-methylbenzo[*b*]thiophene (**25**).

A mixture of 3-methyl-4-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene (**24**) (9) (5 g., 0.03 mole), 5% Pd/C (2.5 g.) and decalin (50 ml.) was refluxed for 1 hour, then the mixture was filtered, and additional Pd/C (2.5 g.) added. The mixture was heated at reflux for an additional 20 hours. The cooled solution was filtered, then extracted with 20% potassium hydroxide. The combined aqueous phases were acidified with concentrated hydrochloric acid, extracted with ether, the combined organic layers were dried (magnesium sulfate), filtered, and the solvent removed to yield, after recrystallization from hexane, 4-hydroxy-3-methylbenzo[*b*]thiophene (1.3 g., 26.4%), m.p. 99-101° [lit.(18b)m.p. 100-101°.

4-Methoxy-3-methylbenzo[*b*]thiophene (**22**).

A.

Methylation of **25** (0.70 g., 4.2 mmoles) was accomplished in a manner identical to the synthesis of **8**. The crude product was recrystallized from a 7:3 (v:v) mixture of methanol:water to give (0.50 g., 66%) of **22**; m.p. 56-57°; nmr (deuteriochloroform) δ 2.56 (d, 3H, J = 1.4 Hz), 3.79 (s, 3H, OCH_3), 6.60 (d of d, 1H, $J_{5,6}$ = 7.5 Hz, $J_{5,7}$ = 1 Hz, H-5), 6.76 (m, 1H, H-2), 7.03-7.37 (m, 2H, H-6, 7).

Anal. Calcd. for $C_{10}H_{10}OS$: C, 67.41; H, 5.62; S, 17.98; M.W. 178. Found: C, 67.70; H, 5.77; S, 18.18; M.W. m/e 178.

B.

A mixture of aldehyde **19a** (1.0 g., 5.2 mmoles) and 95% hydrazine (1.2 ml.) in diethylene glycol (20 ml.) was heated at 160° for 10 minutes, cooled to 60° and finely ground potassium hydroxide (1.0 g.) added. The mixture was then heated at 170° for 1.5 hours, poured onto 200 g. of crushed ice and the resulting suspension extracted with ether. The combined ether extracts were dried (magnesium sulfate) and the solvent was evaporated leaving a yellow oil which solidified on standing. Recrystallization from a 7:3 (v:v) methanol:water mixture gave 0.46 g. of **22** which was identical in all respects with the compound as synthesized in part A above.

4-Methoxybenzo[*b*]thiophene-3-carboxylic Acid (**13**).

A.

A mixture of magnesium (0.099 g., 4.14 mmoles), bromide **8a** (1.0 g., 4.12 mmoles), 1,2-dibromoethane (50 μ liters), and THF (10 ml.) were stirred under a static atmosphere of nitrogen. After 1 hour, additional THF (20 ml.) was added and the mixture stirred an additional 4 hours. After this period, the mixture was poured onto solid carbon dioxide, allowed to warm to room temperature, then quenched with 2*N* hydrochloric acid. The aqueous solution was extracted with chloroform, the combined chloroform extracts were dried (magnesium sulfate), filtered, and the solvent evaporated leaving a pink solid (0.56 g., 65%). Recrystallization from a 7:3 (v:v) mixture of petroleum ether:acetone (charcoal) gave a light pink material, m.p. 129.5-130.5°; ir (potassium bromide) 3.55-3.95 (broad), 5.82 (C=O) μ; nmr (deuteriochloroform) δ 4.10 (s, 3H, OCH_3), 6.92 (broad d, 1H, $J_{5,6}$ = 7.8 Hz, H-5), 7.20-7.60 (m, 2H, H-6, 7), 8.56 (broad s, 1H, H-2), O-H proton was not detected.

Anal. Calcd. for $C_{10}H_8O_3S$: C, 57.68; H, 3.85; S, 15.38; M.W. 208.0191. Found: C, 57.88; H, 4.12; S, 15.19; M.W. m/e 208.0138.

B.

Dry THF (15 ml.) was added to an ethereal solution of **9a** (2.5 mmoles), then the reaction mixture was poured onto solid carbon dioxide. After the mixture had warmed to room temperature, it was quenched with 2*N* hydrochloric acid and extracted with chloroform. The combined chloroform extracts were dried (magnesium sulfate), filtered, and the solvent was evaporated leaving 0.53 g. (100%) of a light pink solid which was identical in all respects to product obtained as in A above.

REFERENCES

(1) Contribution No. 2164 supported by Public Health Service Grant GM-10366-09. This paper was presented in part before the 164th National American Chemical Society Meeting, New York,

August 28, 1972. For Part XVIII of this series, see T. R. Bosin, R. P. Maickel, A. Dinner, A. Snell, and E. Campaigne, *J. Heterocyclic Chem.*, **9**, 1265 (1972).

(2) A. Hofman, R. Heim, A. Brack, and H. Kobel, *Experientia*, 14, 107 (1958).

(3) A. Hofmann, R. Heim, A. Brack, H. Kobel, A. J. Frey, H. Ott, and F. Troxler, *Helv. Chim. Acta*, **42**, 1557 (1959).

(4) E. Campaigne and A. Dinner, *J. Med. Chem.*, **13**, 1205 (1970).

(5) T. R. Bosin, E. Campaigne, A. Dinner, and R. Maickel, *The Pharmacologist*, 13, 282 (1971).

(6) E. Campaigne, T. Bosin, and E. S. Neiss, *J. Med. Chem.*, 10, 270 (1967).

(7) P. K. Gessner, and H. I. Page, *Am. J. Physiol.*, **203**, 167 (1962).

(8) E. Campaigne, E. S. Neiss, C. C. Pfeiffer, and R. A. Beck, *J. Med. Chem.*, **11**, 1049 (1968).

(9) We wish to thank Dr. R. P. Napier of Mobil Chemical Corporation for very generous samples of this compound.

(10) E. Campaigne, A. Dinner, and M. Haseman, *J. Heterocyclic Chem.*, **8**, 755 (1971).

(11) E. Campaigne and S. Hurt, unpublished results.

(12) M. E. Speeter and W. C. Anthony, *J. Am. Chem. Soc.*, 76, 6208 (1954).

(13) S. T. Reid, Ph.D. Thesis, The University of Glasgow, 1960, p. 62.

(14) G. I. Feutrill and R. N. Mirrington, *Tetrahedron Letters*, 1327 (1970).

(15) E. H. P. Young, *J. Chem. Soc.*, 3493 (1958).

(16) R. P. Dickinson and B. Iddon, *J. Chem. Soc. (C)*, 3447 (1971).

(17) R. A. Barnes and L. J. Nehmsmann, *J. Org. Chem.*, **27**, 1939 (1962).

(18) R. P. Napier and Chin-Chiun Chu, *Int. J. Sulfur Chem.* (A), 62 (1971). (b) R. P. Napier, Mobil Chem. Co. Personal Communication, April 30, 1971.

(19) Reference 13, p. 69.

(20) William E. Kreighbaum, Ph.D. Thesis, Indiana University, 1960, p. 82.

(21) W. Baker and N. C. Brown, *J. Chem. Soc.*, 2303 (1948).

(22) We are indebted to Jane Hixon of the Department of Pharmacology, Indiana University, Bloomington, for these results.

(23) We are indebted to Dr. R. A. Beck of the New Jersey Neutropsychiatric Institute, Princeton, New Jersey, for these results.

(24) Since this manuscript was accepted, N. B. Chapman, R. M. Scrowston and T. M. Sutton, *J. Chem. Soc. Perkin Trans.*, 3011 (1972), have reported the preparation of some of the same compounds. Discrepancies in the physical characteristics of the common compounds are being investigated.