Other Tests.—The substances were screened also for their actions on the isolated rabbit heart, following the method of Setnikar, *et al.*,[11] changes in amplitude of contractions, rate of contractions, coronary flow, and resistance to anoxia[12] were recorded. Furthermore the substances were screened for their actions on blood pressure and respiration in rats anesthetized with 1.0 g/kg ip of urethan, on formaldehyde paw edema in rats, on electroshock convulsions in mice, and on $CaCl_2$-induced ventricular fibrillations in rats.

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The Sulfur Analog of Serotonin[1]

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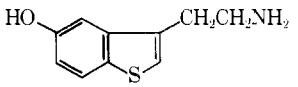
A number of structural analogs of serotonin (5-hydroxytryptamine) have been prepared.[2] Due to isoelectronic and steric relationships, the benzo[*b*]thiophene analog has been of particular interest as a possible agonist or antagonist of serotonin. The synthesis of this compound has proved to be refractory.[3] We wish to report the synthesis of 3-(β-aminoethyl)-5-hydroxybenzo[*b*]thiophene (I), and preliminary pharmacological evaluation.



I

3-Methyl-5-hydroxybenzo[*b*]thiophene,[4] prepared by the cyclization procedure[5] from *m*-hydroxyacetophenone, followed by decarboxylation of the resulting 3-methyl-5-hydroxybenzo[*b*]thiophene-2-carboxylic acid, was converted to its benzoate ester. This ester was subsequently converted to 3-bromomethyl-5-benzoyloxybenzo[*b*]thiophene by the procedure of Chapman, *et al.*,[6] and the corresponding carboxaldehyde was prepared in satisfactory yield *via* the Sommelet reaction,[7] without hydrolysis of the ester linkage. The 5-benzoyloxybenzo[*b*]thiophene-3-carboxaldehyde was then condensed with nitromethane, employing ammonium acetate as catalyst. Two products were isolated, the major product being 5-benzoyloxy-3-(2-nitrovinyl)-benzo[*b*]thiophene, and the minor product being 5-hydroxy-3-(2-nitrovinyl)benzo[*b*]thiophene. 5-Benzoyloxy-3-(2-nitrovinyl)benzo[*b*]thiophene was reduced with lithium aluminum hydride and the reaction was worked-up according to the method of Martin-Smith, *et al.*[2a] Compound I was isolated as the hydrochloride.

The central nervous system effect of I and 5-hydroxytryptophan (II) was studied by amplitude analysis of the cortical electroencephalogram (EEG) of male albino rabbits.[8] It has been demonstrated that animals given intravenous doses of II have significant increases of brain serotonin.[9,10] Administration of 400 μg/kg of I or II resulted in desynchronization of the EEG, indicative of a highly stimulated state; I caused a drop of the mean energy content (MEC) to 32.5% below control levels and II a drop of 41.0%. No peripheral effects were observed in rabbits treated with I. Animals pretreated with pentobarbital (3 mg/kg) showed a very similar polyphasic response to both I and II: at 50 μg/kg both were synergistic to the sedative, maximally stimulated at 200 μg/kg, and again sedative at 500 μg/kg. The barbiturate effect was 50% reversed (RD_{50}) at a dose of 160 μg/kg of I and 140 μg/kg of II.

Further studies on the synthesis and biological activity of benzo[*b*]thiophene analogs of biologically active indole derivatives are currently under investigation.

Experimental Section[11]

5-(α-Methyl-3-hydroxybenzylidene)rhodanine.—Rhodanine (67 g, 0.5 mole) was added to a solution of 4 g of ammonium acetate and 12 ml of glacial acetic acid in 400 ml of dry benzene and boiled for a few minutes. *m*-Hydroxyacetophenone (68 g, 0.5 mole) was added to the hot reaction mixture and the flask was connected to a Dean–Stark trap. The reaction mixture was refluxed vigorously until solid began to separate, cooled to room temperature, and filtered. The yellow precipitate was washed with two 100-ml portions of water and air dried. Recrystallization from dioxane–water gave 100 g (80%) of product which melted at 201–202°. An analytical sample melted sharply at 207°.

Anal. Calcd for $C_{11}H_9NO_4S_2$: S, 25.52. Found: S, 25.64.

β-Methyl-β-(3-hydroxyphenyl)-α-mercaptoacrylic Acid.—5-(α-Methyl-3-hydroxybenzylidine)rhodanine (50 g, 0.20 mole) was added to a stirred solution of 1 l. of 10% NaOH at 60°. The amber solution was heated to 80° and stirred for 1 hr prior to saturation with NaCl and filtration through a Norit pad. The solution was cooled to 10° and slowly poured into 400 ml of 6 *N* HCl which was saturated with NaCl and cooled to 10°. The yellow solid was collected and dried to yield 39 g (75%) of product which melted 128–129° after recrystallization from propanol: λ_{max}^{KBr} 3.00 (intermolecular H bonded OH), 3.4 (OH of acid), 3.95 (very weak) (SH), 5.95 (C=O), 6.25 (aryl conjugated C=C), 12.63, 14.2, and 14.45 μ (1,3-disubstituted benzene).

Anal. Calcd for $C_{10}H_{10}O_3S$: S, 15.25. Found: S, 15.11.

3-Methyl-5-hydroxybenzo[*b*]thiophene-2-carboxylic Acid.—β-Methyl-β-(3-hydroxyphenyl)-α-mercaptoacrylic acid (20 g, 0.095 mole) and 30 g of I_2 were allowed to gently reflux for 15 hr in 500 ml of dry dioxane. The solution was reduced to half its volume under reduced pressure and poured into 2 l. of cold

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water containing 60 ml of saturated $NaHSO_3$ solution. The entire dilution was extracted with four 250-ml portions of ether and the combined ether extracts in turn were extracted with two 150-ml portions of 10% $NaHCO_3$. The dark alkaline solution was boiled with Norit, filtered, cooled, and acidified with 6 *N* HCl. The tan precipitate was collected and dried to yield 17.5 g (88%) of product which melted at 241–243°. After two recrystallizations from 95% ethanol, white crystals were obtained and melted at 254–255° dec; λ_{max}^{KBr} 3.0 (OH), 3.4–4.1 (OH of CO_2H), 6.05 μ (C=O).

Anal. Calcd for $C_{10}H_8O_3S$: C, 57.68; H, 3.90; S, 15.39. Found: C, 57.41; H, 3.96; S, 15.11.

3-Methyl-5-hydroxybenzo[*b*]thiophene.—3-Methyl-5-hydroxybenzo[*b*]thiophene-2-carboxylic acid (4 g, 0.019 mole) was slowly heated during 1 hr to 210° in 40 ml of redistilled quinoline containing 2 g of Cu powder. The temperature was maintained at 210° for a further hour and then the reaction mixture was cooled, diluted with 150 ml of ether, and filtered. The etheral solution was extracted with 6 *N* HCl until acidic to congo red paper. The ether layer was then extracted with 20% NaOH, decolorized with Norit, and acidified with 6 *N* HCl. The acidic solution was extracted with three 75-ml portions of ether and dried (Na_2SO_4), and the ether was removed to yield a brown oil. The oil was dissolved in boiling cyclohexane and upon cooling gave 1.8 g (57%) of product. Analytical material was obtained after three recrystallizations from cyclohexane, mp 93–94°;[4] λ_{max}^{KBr} 2.96 (OH), 3.25 (=CH), 3.41 (CH_3), 8.22, 8.59, 7.20 μ (phenolic OH). The ultraviolet spectrum indicated $\lambda_{max}^{95\% \text{ ethanol}}$ in mμ (ϵ): 238 (21,800), 265 (5270), 270 sh (4660), 308 (3060), and 317 (2880); nmr ($CDCl_3$), δ 2.22 (3 H, doublet), 5.72 (1 H, singlet), 6.7–7.2 (3 H, multiplet), 7.5–7.67 (1 H, doublet).

Anal. Calcd for C_9H_8OS: S, 19.45. Found: S, 19.41.

The picric acid charge-transfer complex was prepared in the usual manner,[12] as tiny orange needles which melted at 150–151° after recrystallization from ethanol.

Anal. Calcd for $C_{15}H_{11}N_3O_8S$: N, 10.68; S, 8.14. Found: N, 10.90; S, 8.46.

3-Methyl-5-benzoyloxybenzo[*b*]thiophene.—A solution of 2.76 g (0.017 mole) of 3-methyl-5-hydroxybenzo[*b*]thiophene, 20 ml of dry pyridine, and 2.36 g (0.017 mole) of benzoyl chloride was heated to gentle reflux for 3 hr. The reaction mixture was cooled to room temperature and poured into 125 ml of ice water. The solid which separated was collected and washed with 5% $NaHCO_3$ prior to recrystallization from ethanol to yield 3.85 g (85%) of white needles: mp 67–68.5°; λ_{max}^{KBr} 3.28 (=CH), 3.45 (CH_3), 5.79 (C=O), 6.27 μ (C=C aromatic); nmr ($CDCl_3$), δ 2.33 (3 H, doublet), 7.0–8.5 (9 H, multiplet).

Anal. Calcd for $C_{16}H_{12}O_2S$: C, 71.62; H, 4.51; S, 11.95. Found: C, 71.87; H, 4.88; S, 11.82.

3-Bromomethyl-5-benzoyloxybenzo[*b*]thiophene.—A solution containing 0.5 g (1.87×10^{-3} mole) of 3-methyl-5-benzoyloxybenzo[*b*]thiophene and 0.019 g of benzoyl peroxide dissolved in 20 ml of reagent CCl_4 was heated to a gentle reflux whereupon 0.33 g (1.87×10^{-3} mole) of recrystallized N-bromosuccinimide was added and two 200-w lights focused on the reaction flask. The reaction was allowed to reflux for 2 hr, allowed to cool to room temperature, and filtered to remove succinimide. The CCl_4 was removed under a stream of N_2 to yield a yellow solid. The crude product was recrystallized from cyclohexane to give 0.51 g (80%) of white plates: mp 115–116°; λ_{max}^{KBr} 3.28 (=CH), 5.79 (C=O), 6.26 μ (C=C aromatic); nmr ($CDCl_3$), δ 4.62 (2 H, singlet), 7.0–8.4 (9 H, multiplet).

Anal. Calcd for $C_{16}H_{11}BrO_2S$: C, 55.34; H, 3.19; Br, 23.02. Found: C, 55.03; H, 3.25; Br, 23.59.

5-Benzoyloxybenzo[*b*]thiophene-3-carboxaldehyde.—A solution of 2.87 g (8.27×10^{-3} mole) of 3-bromomethyl-5-benzoyloxybenzo[*b*]thiophene and 1.18 g (8.40×10^{-3} mole) of hexamethylenetetramine in 25 ml of $CHCl_3$ was refluxed for 6 hr, after which time it was cooled to room temperature and the $CHCl_3$ was removed under reduced pressure leaving a light tan crude hexamine salt. This salt was treated with 30 ml of 50% aqueous acetic acid and the resulting solution was heated to reflux for 3 hr. At the completion of the heating period, 40 ml of water and 7 ml of concentrated HCl was added and the mixture refluxed for an additional 5 min. The reaction mixture was allowed to stand overnight, then diluted with 200 ml of water and extracted with three 75-ml portions of ethyl acetate. The combined extracts were dried (Na_2SO_4), and the solvent was removed to yield a tan solid. Recrystallization from ethanol gave 0.94 g (40%) of white needles: mp 96–97°; λ_{max}^{KBr} 3.26 (=CH), 3.59 (CH), 5.79 and 6.0 (C=O), 6.25 μ (C=C).

Anal. Calcd for $C_{16}H_{10}O_3S$: C, 68.06; H, 3.57; S, 11.36. Found: C, 67.87; H, 3.55; S, 11.06.

The semicarbazone was prepared by the usual procedure[12] as white plates, mp 224–225°, following recrystallization from ethanol.

Anal. Calcd for $C_{17}H_{13}N_3O_3S$: C, 60.16; H, 3.86; N, 12.38. Found: C, 59.99; H, 3.82; N, 12.59.

5-Benzoyloxy-3-(2-nitrovinyl)benzo[*b*]thiophene.—A solution of 0.3 g (1.1×10^{-3} mole) of 5-benzoyloxybenzo[*b*]thiophene-3-carboxaldehyde and 0.12 g of ammonium acetate in 6 ml of nitromethane was brought to a gentle reflux and maintained for 1 hr, after which time the excess nitromethane was removed under a stream of N_2 to leave a yellow solid. The crude solid was dissolved in boiling benzene, filtered, and upon cooling gave 0.275 g (80%) of yellow needles: mp 179–180°; λ_{max}^{KBr} 3.27 (=CH), 5.79 (C=O), 6.14 (C=C olefin), 6.64 and 7.5 μ (NO_2).

Anal. Calcd for $C_{17}H_{11}NO_4S$: C, 62.76; H, 3.41; N, 4.31. Found: C, 63.20; H, 3.60; N, 4.23.

5-Hydroxy-3-(2-nitrovinyl)benzo[*b*]thiophene.—This benzene-insoluble material can be isolated from the condensation reaction between nitromethane and 5-benzoyloxybenzo[*b*]thiophene-3-carboxaldehyde, and composes 5% of the crude reaction mixture. Recrystallization from chloroform gave gold needles: mp 227–228° dec; λ_{max}^{KBr} 3.0 (OH), 3.28 (=CH), 6.18 (C=C olefin), 6.70 and 7.6 μ (NO_2).

Anal. Calcd for $C_{10}H_7NO_3S$: C, 54.29; H, 3.19; N, 6.33. Found: C, 54.41; H, 3.32; N, 6.48.

3-(β-Aminoethyl)-5-hydroxybenzo[*b*]thiophene Hydrochloride.—Lithium aluminum hydride (4.0 g, 0.105 mole) was added to 100 ml of dry tetrahydrofuran (THF), followed by the dropwise addition of 2.25 g (6.9×10^{-3} mole) of 5-benzoyloxy-3-(2-nitrovinyl)benzo[*b*]thiophene which was dissolved in 50 ml of dry THF. The reaction mixture was gently refluxed for 6 hr before the excess $LiAlH_4$ was decomposed by the careful addition of water, 200 ml of 2 *N* NaOH was added, and the entire reaction mixture was filtered. The THF was removed by distillation, and the basic solution was saturated with CO_2 (pH 8.3) and extracted continuously with ether for 48 hr. Dry HCl was passed into the ether solution, yielding a yellow oil which solidified under vacuum. Recrystallization from methanol–ethyl acetate gave 0.19 g (12%) of white plates: mp 195–196.5°; λ_{max}^{KBr} 3.00 (OH), 3.23–3.40 (NH_3^+), and strong absorptions at 6.84, 6.96, 7.25, 8.03, and 8.19 μ. The ultraviolet spectrum indicated $\lambda_{max}^{95\% \text{ ethanol}}$ in mμ (ϵ): 237 (18,630), 264 (5520), 270 sh (4820), 309 (3310), and 316 (3200).

Anal. Calcd for $C_{10}H_{12}ClNOS$: C, 52.28; H, 5.27; N, 6.09. Found: C, 52.38; H, 5.45; N, 6.10.

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Some *p*-Hydroxyphenoxyacetic Acid Derivatives

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The antithyroid activity of α-methyl-β-(3,5-diiodo-4-hydroxyphenyl)propionic acid[3] and of esters of 3,5-

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