Improved Synthesis of the Sulfur Analog of Serotonin (SAS)

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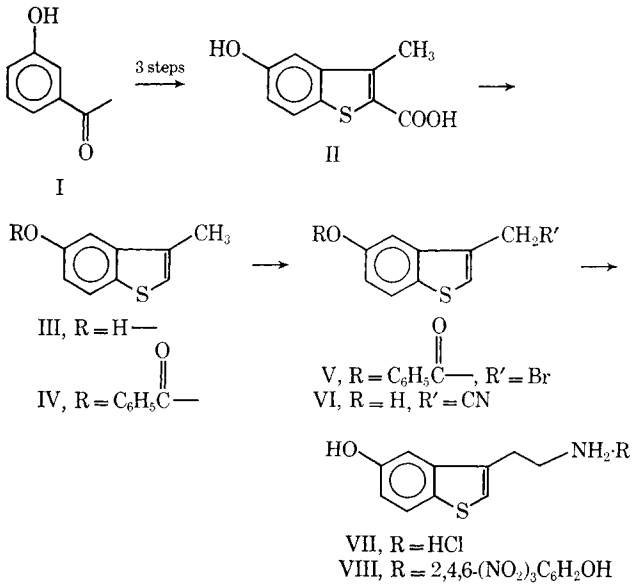
Abstract □ SAS, 3-β-aminoethyl-5-hydroxybenzo(b)thiophene, the sulfur analog of serotonin, has proved refractory to synthesis. The various steps in its preparation have been refined, and its preparation in overall yield of about 20 percent in an eight-step sequence from commercially available *m*-hydroxyacetophenone has been achieved.

Keyphrases □ Serotonin, sulfur analog—synthesis □ 3-β-Aminoethyl-5-hydroxybenzo(b)thiophene—improved synthesis □ NMR spectroscopy—identity, structure □ IR spectrophotometry—identity, structure

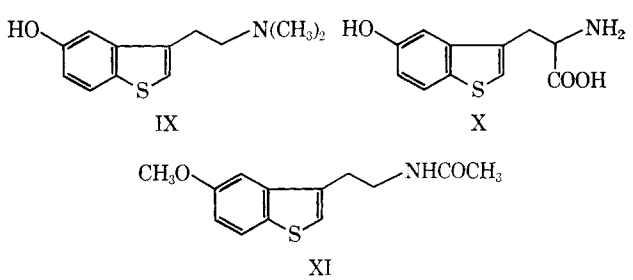
The sulfur analog of serotonin (SAS), VII, which had been first synthesized in this laboratory *via* a nine-step sequence with an overall yield of 0.8% (1), has been shown to possess interesting central nervous system activity (2). Preliminary data also suggest that the pharmacological and toxicological characteristics of SAS may differ from those of 5-hydroxytryptamine (serotonin) (2). In light of these important findings and the fact that the only other reported synthesis of SAS (3) also involves nine steps with a resultant yield[1] comparable to the authors, the original sequence has been improved and modified to eight steps with an overall yield of about 20% (Scheme I).



Scheme I

3-Methyl-5-hydroxybenzo(b)thiophene-2-carboxylic acid (II), prepared from commercially available *m*-hydroxyacetophenone (I) as previously reported (1), was decarboxylated in 96% yield to 3-methyl-5-hydroxybenzo(b)thiophene (III). The improvement over the 57% previously reported (1) is due not to new reaction conditions but rather to a new workup procedure which minimizes the loss of product caused, in this case, by an inefficient extraction procedure. Upon placing the purified product in the decarboxylating solvent (quinoline) and attempting to recover it by the usual extraction procedure employed in this reaction (4), only 57% of the product was obtained! This strongly suggested that the low yield was not due to decomposition of product or incomplete decarboxylation. Removal of solvent quinoline prior to workup improved the yield (see *Experimental* section). The 3-methyl-5-hydroxybenzo(b)thiophene was converted to its benzoate ester (IV) (1) and subsequently brominated to produce 3-bromomethyl-5-benzoyloxybenzo(b)thiophene (V) according to a modified procedure of Chapman *et al.* (5). This modification, using a 15% molar excess of NBS, resulted in an increase in yield from 80% (1) to 90%. The bromomethyl compound was now allowed to react with sodium cyanide in dimethyl sulfoxide to give 5-hydroxy-3-cyanomethylbenzo(b)thiophene (VI) in 87% yield, the conditions being basic enough to hydrolyze the benzoyloxy moiety. It should be noted that as in many other nitrile displacement reactions (6) the type of cyanide (sodium *versus* potassium) and solvent (dimethyl sulfoxide *versus* ethanol, *etc.*) are extremely critical and any variation from optimum conditions may cause a sharp drop in yield. The nitrile was now reduced according to the procedure of Nystrom (7), utilizing the mixed reducing agent $LiAlH_4$–$AlCl_3$, and worked up to yield 3-β-aminoethyl-5-hydroxybenzo(b)-thiophene (SAS) in 63% yield. The compound was isolated as the known picrate (VIII) (3) and hydrochloride (VII) (1).

The sulfur analog of serotonin can now be conveniently synthesized for further biological testing and some closely related hitherto unsynthesized benzo(b)-thiophene analogs of biologically active indole derivatives such as the bufotenine analog (IX), the 5-hydroxytryptophan analog (X), and the melatonin analog (XI) will be synthesized from the readily available intermediates in this sequence.



[1] The complete overall yield can not be calculated since the yield of the last step, a curious Raney nickel reduction of 5-hydroxy-3-cyanomethylbenzo[b]thiophene, is not given. Up to this point the yield based on *m*-hydroxybenzaldehyde is reported at 2.6% (3).

EXPERIMENTAL[2]

3-Methyl-5-hydroxybenzo(b)thiophene (III)—3-Methyl-5-hydroxybenzo(b)thiophene-2-carboxylic acid (26 g., 0.125 mole), obtained as previously described in 53% overall yield (1) from *m*-hydroxyacetophenone[3] was slowly heated during a 30-min. period to 200° with 190 ml. of freshly distilled quinoline and 17.4 g. of copper powder in a 500-ml. round-bottom flask with magnetic stirrer and reflux condenser. The temperature was maintained at 200° for 30 min. and then the reaction mixture was cooled and most of the quinoline removed at reduced pressure (170 ml., 0.6 mm. Hg 65°). The tarry residue was now diluted with 150 ml. of 8 *N* HCl and filtered. The solid copper was repeatedly washed with ether and the acid fraction was extracted with five 60-ml. portions of ether. The ether extracts were pooled and extracted with four 50-ml. portions of 20% NaOH. The combined basic extracts were decolorized twice with decolorizing carbon[4] and acidified with 8 *N* HCl to give a light brown precipitate, 19.58 g. (96%). One recrystallization from cyclohexane with decolorizing carbon gave white plates of III, m.p. 93–94°. The IR spectrum in KBr was identical to that of the known compound (1).

3-Methyl-5-benzoyloxybenzo(b)thiophene (IV)—This compound was obtained in 85% yield by refluxing III with benzoyl chloride in pyridine as described in *Reference 1*.

3-Bromomethyl-5-benzoyloxybenzo(b)thiophene (V)—A 90% yield of V was obtained by refluxing 0.1 mole of IV with 0.115 mole of NBS and 1.0 g. of benzoyl peroxide as described in *Reference 1*.

3-Cyanomethyl-5-hydroxybenzo(b)thiophene (VI)—Sodium cyanide (powdered and dried at 120° for 2 hr. under vacuum), 4.90 g. (0.10 mole), was placed in 100 ml. of freshly opened dimethylsulfoxide (DMSO) and cooled to 18° in a three-necked 500-ml. round-bottomed flask equipped with a reflux condenser, dropping funnel, and magnetic stirrer. Then 17.40 g. (0.05 mole) of 3-bromomethyl-5-benzoyloxybenzo(b)thiophene (V) in 125 ml. of dry DMSO was added from the dropping funnel over a 15-min. period and the solution was allowed to stir for 1 hr. at 18°. The solution was allowed to stand 14 hr. at room temp., then poured into 500 ml. of an ice-cooled saturated NaCl solution and extracted with eight 100-ml. portions of ether. The combined ether fractions were washed with two 150-ml. portions of 10% $NaHCO_3$ solution and dried over anhydrous Na_2SO_4. The ether was now evaporated and a red solid was obtained, 8.19 g. (87%). Recrystallization from ethyl acetate–cyclohexane mixture and/or sublimation at 160° and 0.2 mm. Hg afforded white needles, m.p. 169–170.5°.[5]

IR (KBr) 3.0 μ (OH); 4.4 μ (CN); no carbonyl absorption; NMR (acetone-d_6): 3.3 δ (1H, broad s, -O*H*); 4.0 δ (2H, d, J = 1 cps., -CH_2CN); 6.9–7.8 δ (4H, m, aromatic protons). The multiplet of aromatic protons could be interpreted as 7.72 δ (H_7, d, J_{76} = 8 cps.); 7.54 δ (H_2,t,J_{2,CH_2CN} = 1 cps.); 7.27 δ (H_4, d, J_{46} = 2 cps.); 7.05 δ (H_6, d of d, J_{67} = 8 cps., J_{64} = 2 cps.). These chemical shifts and coupling constants are consistent with the NMR parameters of other 5-substituted benzo(b)thiophenes (8).

Anal.—Calcd. for $C_{10}H_7NO_2$: C, 63.49; H, 3.70; S, 16.93. Found: C, 63.21; H, 3.79; S, 16.92.

3-β-Aminoethyl-5-hydroxybenzo(b)thiophene Hydrochloride (VII)—A 500-ml., three-necked round-bottom flask was equipped with a reflux condenser, dropping funnel, and magnetic stirrer. A solution of 48 mmoles of $LiAlH_4$ in 60 ml. of sodium-dried ether was placed in the three-necked flask. Through the dropping funnel a solution of 48 mmoles of $AlCl_3$ in 100 ml. of dry ether was added quickly to the solution. Five minutes after the last addition of halide, a solution of 0.45 g. (2.4 mmoles) of 3-cyanomethyl-5-hydroxybenzo(b)thiophene (VI) in 125 ml. of dry ether was added dropwise to the well-stirred mixture. The addition took 25 min. and the mixture was allowed to stir overnight. Water was added dropwise to decompose the excess reducing agent and then 100 ml. of 6 *N* H_2SO_4 and 100 ml. of H_2O were added. The mixture was transferred to a separator and, after separating the ether layer, extracted with four 100-ml. portions of ether. The aqueous layer was cooled in an ice bath and KOH pellets were added to make the pH of the solution 8. The basic mixture was diluted with 100 ml. of water and extracted with two 100-ml. portions of ether. The pH was successively made 9, 10, and 11 and each time the solution was extracted with two 100-ml. portions of ether. The basic extracts were combined, dried over Na_2SO_4, and saturated with dry HCl to yield 0.34 g. (63%) of a light yellow oil which solidified under vacuum. One recrystallization from methanol–ethyl acetate mixture afforded white plates of VII, m.p. 193–195°, whose IR spectrum was identical to that of the known compound (1). When the ether extracts from the acid fraction were worked up in a similar manner to those of the basic extracts no material was obtained.

The picric acid charge transfer complex (VIII) was prepared by placing 0.1 g. of VII in 5 ml. of anhydrous methanol containing a few drops of NH_4OH and then adding 5 ml. of a saturated solution of picric acid in anhydrous methanol. The solution was boiled and then cooled, whereupon orange needles were collected. The melting point (191–193°) agreed with that reported by Martin-Smith *et al.* (3).

Anal.—Calcd. for $C_{16}H_{14}N_4O_8S$: C, 45.50; H, 3.33; S, 7.58. Found: C, 45.71; H, 3.66; S, 7.84.

[2] Melting ranges were determined with a Mel-Temp apparatus and are corrected. Elemental analyses were obtained from Midwest Microlab, Inc., Indianapolis, Ind. NMR spectra were determined on a Varian HA-100 spectrometer.

[3] Kindly furnished by Dr. H. L. Hansen of the Hilton-Davis Chemical Co., Cincinnati, Ohio.

[4] Norit, American Norit Co., Inc., Jacksonville, Fla.

[5] This compound has been reported by M. Martin-Smith *et al.* (3) who erroneously listed the melting point as 128–130°.

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