

Oxidation of *o*-Dihydroxybenzo[*b*]thiophene Methyl Ethers (1).

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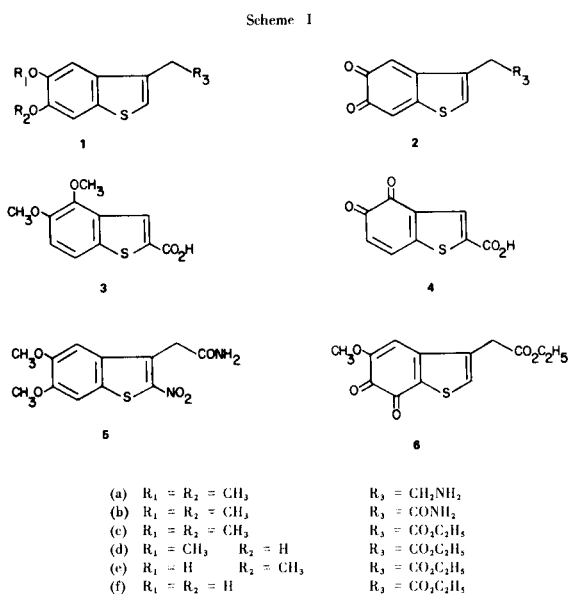
The attempted oxidative demethylation of a series of *o*-dihydroxybenzo[*b*]thiophene methyl ethers with cerium (IV), argentic oxide, periodate and thallate usually led to intractable mixtures. However, in one case, use of ceric ammonium nitrate resulted in nitration of the benzo[*b*]thiophene ring. In another example, treatment with aqueous periodate or thallate resulted in oxidative hydroxylation of benzo[*b*]thiophene.

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As part of our studies on the chemistry of benzo[*b*]thiophenes, we desired a method for the oxidative demethylation of dihydroxybenzo[*b*]thiophene methyl ethers such as **1a-c** and **3** (Scheme 1). The resultant quinones (**2** and **4**) were of interest from a structural viewpoint, since few quinone derivatives of benzo[*b*]thiophene have been reported, and as model compounds related to certain biologically active hydroxyindole derivatives (2). The pharmacological effects of isosteric substitution of nitrogen by sulfur in biologically active indoles have recently been reviewed (3). Also, this oxidative demethylation synthetic step was expected to serve as an entry to the preparation of other useful benzo[*b*]thiophene derivatives.

Jacob, *et al.*, (4), have achieved considerable success with the use of ceric ammonium nitrate as a reagent for the oxidative conversion of a variety of *para*-hydroquinone dimethyl ethers into the corresponding quinones. However, these workers found that side reactions dominated with the use of cerium (IV) and *ortho*-hydroquinone dimethyl ether substrates. Treatment of the dimethoxybenzo[*b*]thiophene derivative **1b** with ceric ammonium nitrate afforded a complex mixture from which was isolated the 2-nitro derivative **5** (21%). The identical compound **5** was obtained upon treating **1b** with nitric acid in acetic acid. The nitrating potential of ceric ammonium nitrate has been noted by other workers (5). The structural assignment of **5** is based upon nmr spectroscopic evidence. It is known that for 3-substituted benzo[*b*]thiophenes such as **1**, the ring 2H proton is broadened due to coupling with the side chain methylene protons (6). The nmr aromatic region of **5** contains two sharp singlets. The downfield shift of the methylene protons in **5** relative to **1b** can be attributed to electron withdrawal of the nitro group in the 2-position. The formation of isomer **5** was not unexpected in view of reported study (7) of electrophilic substitutions of 5,6-dimethoxybenzo[*b*]thiophene, which afforded principally the 2-substituted product upon reaction with a variety of electrophiles.

In order to circumvent the possibility of nitration at the 2-position of benzo[*b*]thiophene, the dimethoxy



derivative **3**, which is blocked at the 2-position by the carboxyl group, was treated with ceric ammonium nitrate. An intractable mixture resulted. The relative insolubility and lack of clean chromatographic separations of the mixture indicated that polymerization had occurred.

Snyder and Rapoport (8) obtained excellent yields of quinones from the oxidative demethylation of several unsubstituted and substituted hydroquinone and naphthoquinone ethers with argentic oxide. After the application of this procedure to substrate **3** we were unable to isolate identifiable products. Other workers have encountered difficulties in obtaining the desired quinone by this method (9).

High yields of *o*-quinones have been reported to form from *o*-hydroxymethoxyaromatics and *o*-dihydroxyaromatics upon oxidation with periodate (10) or thallate (11). The treatment of heterocycles **1d-f** with periodate or thallate under a variety of conditions invariably led to intractable mixtures. However, a low yield of the quinone **6** was isolated from a two phase mixture of aqueous periodate or thallate and an ethereal solution of the *o*-hydroxymethoxy derivative **1d**.

In conclusion, the dihydroxybenzo[*b*]thiophene derivatives which were studied were found to be extremely susceptible to cerium (IV), argentic oxide, periodate and thallate. These heterocycles contain a highly activated aromatic system, a sulfur group, and a side chain benzylic methylene group, all of which are expected to be effected by oxidizing agents. Even if the desired selective oxidative demethylation reaction had occurred, it is uncertain if the resultant quinones would be stable under the conditions of the reaction.

EXPERIMENTAL

Melting points were determined on a "Mel-Temp" capillary tube apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. Nmr spectra were obtained with a Varian T60A spectrometer, using tetramethylsilane 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 (No. 6060)] were used for thin layer chromatography. Elemental analysis were performed by Midwest Microlab., Ltd.

The preparations of compounds **1b**, **1c**, **1e**, and **1f** have been reported elsewhere (12).

Ethyl 5-Methoxy-6-hydroxy-3-benzo[*b*]thienylacetate (**1d**).

Compound **1d** was prepared from 3-hydroxy-4-methoxythiophenol and ethyl 4-chloroacetoacetate (Aldrich) by the previously described method (12). A crude sample of **1d** was purified by recrystallization, first from petroleum ether (b.p. 60-90°) containing decolorizing charcoal, and then from pentane/benzene. It formed colorless plates, m.p. 68-69°; ir (liquid melt): 1725 (C=O), 3400 (broad, OH) cm^{-1} ; nmr (liquid melt): δ 1.23 (t, 3H, ester CH_3), 3.77 (s, 2H, ArCH_2), 3.90 (s, 3H, ArOCH_3), 4.17 (q, 2H, ester CH_2), 5.90 (s, 1H, OH, exchanges with deuterium oxide), 7.20 (m, 3H, ArH) ppm; ms: *m/e* 266 (base, M^+), 193 ($\text{M}^+ - \text{CO}_2 \text{Et}$).

Anal. Calcd. for $\text{C}_{13}\text{H}_{14}\text{O}_4\text{S}$: C, 58.63; H, 5.30. Found: C, 58.77; H, 5.19.

4,5-Dimethoxybenzo[*b*]thiophene-2-carboxylic Acid (**3**).

A crude sample of the acid **3** (7) was washed with hot nitromethane and taken up in hot tetrahydrofuran containing decolorizing charcoal. The solution was filtered and evaporated *in vacuo*. Crystallization of the residue from ethanol afforded pale yellow needles, m.p. 234-236° [lit. (7) 240-241°].

5,6-Dimethoxy-2-nitro-3-benzo[*b*]thienylacetamide (**5**).

A.

An aqueous solution (50 ml.) of ceric ammonium nitrate (14.2 g., 26 mmoles) was added dropwise to a stirred solution of 5,6-dimethoxy-3-benzo[*b*]thienylacetamide (**1b**, 12) (3.0 g., 12 mmoles) in acetic acid (100 ml.). The mixture was stirred for one hour, diluted with water (500 ml.) and extracted with chloroform (6 x 50 ml.). The combined organic extracts were dried (sodium sulfate) and the solvent was evaporated under vacuum. The remaining brown solid was crystallized from DMF, affording an orange yellow solid (0.73 g., 21%), m.p. 231° dec. A sample was recrystallized from acetic acid and washed with chilled ethanol, yielding an analytical sample of **5** as a bright yellow powder, m.p. 234° dec.; ir (potassium bromide): ν 1675 (C=O), 3265 (NH_2)

cm^{-1} ; nmr (trifluoroacetic acid): δ 4.08 (s, 6H, OCH_3), 4.53 (s, 2H, CH_2), 7.33 (s, 1H, ArH), 7.47 (s, 1H, ArH) ppm; ms: *m/e* 296 (M^+), 250 (base, $\text{M}^+ - \text{NO}_2$).

Anal. Calcd. for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_5\text{S}$: C, 48.64; H, 4.08; S, 10.82. Found: C, 48.70; H, 4.11; S, 11.27.

B.

A solution of **1b** (303 mg., 1.2 mmoles) in glacial acetic acid (10 ml.) was added dropwise to a chilled solution of 70% nitric acid (0.3 g.) in acetic acid (5 ml.) and acetic anhydride (10 ml.). An orange yellow solid soon precipitated from solution. It was washed with chilled acetic acid and ethanol, affording a bright yellow solid (190 mg., 53%), m.p. 233° dec. A mixture with **5** gave a mixture m.p. 234° dec.

Reaction of 4,5-Dimethoxybenzo[*b*]thiophene-2-carboxylic Acid (**3**).

A. With Ceric Ammonium Nitrate.

An aqueous solution (50 ml.) of ceric ammonium nitrate (10 g., 18 mmoles) was added dropwise to a stirred solution of 4,5-dimethoxybenzo[*b*]thiophene-2-carboxylic acid (2.0 g., 8.4 mmoles) in acetonitrile (100 ml.). The mixture was stirred for one hour, diluted with water (500 ml.) and extracted with chloroform (4 x 50 ml.). The chloroform extracts were washed with brine (150 ml.), dried (sodium sulfate) and the solvent was evaporated under reduced pressure. The residue was taken up in hot tetrahydrofuran containing decolorizing charcoal and filtered. The filtrate was evaporated, affording a tarry residue. This was taken up in acetonitrile, filtered, and the filtrate evaporated. The residue was triturated over benzene, yielding a brown powder (0.44 g.) whose tlc indicated that it contained at least five compounds.

Similarly, an intractable mixture was formed when this reaction was repeated using sulfolane as the solvent rather than acetonitrile.

B. With argentic Oxide.

A solution of **3** (705 mg., 3 mmoles) in dioxane (20 ml.) was added to a stirred slurry of argentic oxide (Alfa Div., Ventron Corp.) (1.6 g., 13 mmoles) in dioxane (20 ml.). No obvious reaction had occurred. Dropwise addition of 3*M* perchloric acid (4.5 ml.) to the mixture gave an instantaneous color change. The mixture was diluted with water and extracted with chloroform. The chloroform extracts yielded in intractable sticky red oil.

Ethyl 5-Methoxy-6,7-dioxo-6,7-dihydro-3-benzo[*b*]thienylacetate (**6**).

A.

A solution of ethyl 6-hydroxy-5-methoxy-3-benzo[*b*]thienylacetate (**1d**) (0.50 g., 1.9 mmoles) in ether (50 ml.) was added to an aqueous solution (100 ml.) of paraperiodic acid (1.0 g., 4.4 mmoles) and the mixture was stirred for 20 hours. The ethereal layer was dried (sodium sulfate) and evaporated to a small volume, yielding red crystals (141 mg., 27%). A sample was recrystallized from ethanol, affording an analytical sample of the quinone **6** as bright red needles, m.p. 131-133°; ir (potassium bromide): ν 1740, 1690, 1655, 1640 (C=O) cm^{-1} ; nmr (deuteriochloroform): δ 1.28 (t, 3H, ester CH_3), 3.57 (s, 2H, ArCH_2), 3.88 (s, 3H, OCH_3), 4.20 (q, 2H, ester CH_2), 6.42 (s, 1H, ArH), 6.50 (s, 1H, ArH) ppm; ms: *m/e* 280 (M^+), 252 ($\text{M}^+ - \text{CO}$), 224 ($\text{M}^+ - \text{C}_2\text{O}_2$), 207 (base, $\text{M}^+ - \text{CO}_2\text{C}_2\text{H}_5$), 179 ($\text{M}^+ - \text{CO}_2\text{C}_2\text{H}_5 - \text{CO}$), 151 ($\text{M}^+ - \text{CO}_2\text{C}_2\text{H}_5 - \text{C}_2\text{O}_2$).

Anal. Calcd. for C₁₃H₁₂O₅S: C, 55.70; H, 4.32; S, 11.44.
Found: C, 55.47; H, 4.20; S, 11.42.

B.

A solution of ethyl 6-hydroxy-5-methoxy-3-benzo[*b*]thienylacetate (0.50 g., 1.9 mmoles) in ether (50 ml.) was added to a stirred slurry of thallic oxide (1.5 g., 3.3 mmoles) in 1.5*M* perchloric acid (100 ml.). Tlc indicated that after 1.5 hours all the starting material had reacted. The ether layer was separated and the aqueous layer was extracted with ether (2 x 50 ml.). The combined ethereal extracts were washed with water (3 x 5 ml.), dried (sodium sulfate) and the solution was evaporated to a small volume. Bright red crystals (44 mg., 8%) deposited which had an identical nmr spectrum and tlc properties to that of the quinone **6**, above.

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