Some Reactions of 7-Hydroxy- and 7-Mercapto-3-methylbenzo[*b*]thiophen

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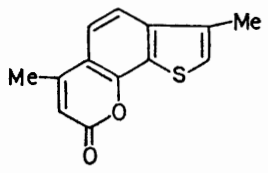
Bromination of 7-hydroxy-3-methylbenzo[*b*]thiophen gave the 4- and the 6-monobromo- and the 4,6-dibromo-derivative. Nitration gave the 6-nitro- and the 4,6-dinitro-derivative, and formylation by the Gattermann reaction gave the 6-formyl derivative. 7-Allyloxy-3-methylbenzo[*b*]thiophen underwent the Claisen rearrangement to give the expected 6-allyl compound, whereas Fries rearrangement of the 7-acetoxy-compound gave 2-acetyl-7-hydroxy-3-methylbenzo[*b*]thiophen. With ethyl acetoacetate in the presence of gaseous hydrogen chloride, 7-hydroxy-3-methylbenzo[*b*]thiophen condensed to give 3,6-dimethylthieno[3,2-*h*][1]benzopyran-8-one. 7-Mercapto-3-methylbenzo[*b*]thiophen and 2-bromopropionic acid in alkaline solution gave 2-(3-methyl-7-benzo[*b*]thienylthio)propionic acid, which was cyclised in hot polyphosphoric acid to give 7,8-dihydro-3-methylthieno[3,2-*h*][1]benzothiopyran-6-one.

We recently described[1] improved preparations of 7-hydroxy- and 7-mercapto-3-methylbenzo[*b*]thiophen. We now report an investigation of some substitution reactions of the 7-hydroxy-compound, two rearrangements of its derivatives, and the preparation of new ring systems from both 7-hydroxy- and 7-mercapto-3-methylbenzo[*b*]thiophen.

Bromination of 7-hydroxy-3-methylbenzo[*b*]thiophen with *N*-bromosuccinimide in carbon tetrachloride yielded the 6-bromo- (40%) and the 4-bromo-compound (20%), with traces of the 4,6-dibromo-compound. Bromine (1 mol. equiv.) in glacial acetic acid gave the 4-bromo- (40%) and the 4,6-dibromo-compound (40%), and unchanged 7-hydroxy-3-methylbenzo[*b*]thiophen (20%). These yields, which are approximate, are based on the heights of the peaks due to the 3-Me group in the n.m.r. spectrum of the mixture. Use of 2 mol. equiv. of bromine gave 4,6-dibromo-7-hydroxy-3-methylbenzo[*b*]thiophen (90%). Nitration of 7-hydroxy-3-methylbenzo[*b*]thiophen with concentrated nitric acid in glacial acetic acid at 20° gave the 6-nitro- (25%) and the 4,6-dinitro- (38%) derivative, together with 3-methylbenzo[*b*]thiophen-4,7-quinone (10%). The isolation of quinones from the nitration of hydroxybenzo[*b*]thiophens has previously been reported by Martin-Smith and Gates.[2] With 2 mol. equiv. of nitric acid only the dinitro-compound and the quinone were obtained. Formylation with anhydrous zinc cyanide and hydrogen chloride in dry ether,[3] gave the 6-formyl derivative (53%) but no 4-isomer.

7-Hydroxy-3-methylbenzo[*b*]thiophen was boiled with allyl bromide and anhydrous potassium carbonate in butanone to give the 7-allyloxy-compound, which gave 6-allyl-7-hydroxy-3-methylbenzo[*b*]thiophen (82%) when heated at 190° in dimethylaniline for 3·5 h.[4] 7-Acetoxy-3-methylbenzo[*b*]thiophen was treated with anhydrous aluminium chloride in dry benzene[5] to give 2-acetyl-7-hydroxy-3-methylbenzo[*b*]thiophen (78%). This result accords with that obtained for the 5-acetoxy-3-methyl compound, which also rearranged to give the 2-acetyl derivative.[6] This structure follows from (*a*) the continued presence in the n.m.r. spectrum of the characteristic peak due to 6-H, (*b*) the absence of the characteristic peak due to 2-H, and (*c*) the shift downfield (0·3—0·4 p.p.m.) of the peak due to the 3-Me group.

When 7-hydroxy-3-methylbenzo[*b*]thiophen was treated with ethyl acetoacetate and dry hydrogen chloride in methanol,[7] 3,6-dimethylthieno[3,2-*h*][1]-benzopyran-8-one (I) (79%) was obtained. 2-Bromopropionic acid reacted with 7-mercapto-3-methylbenzo[*b*]thiophen in aqueous 8% sodium hydroxide to give 2-(3-methyl-7-benzo[*b*]thienylthio)propionic acid (87%). Cyclisation with polyphosphoric acid at 100° gave 7,8-dihydro-3-methylthieno[3,2-*h*][1]benzothiopyran-6-one (II) (36%).



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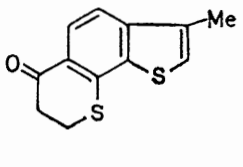

(II)

Structures were assigned to the substitution products of 7-hydroxy-3-methylbenzo[*b*]thiophen on the basis of their n.m.r. spectra. The n.m.r. spectrum of 7-hydroxy-3-methylbenzo[*b*]thiophen shows a multiplet due to 4-H and 5-H which is difficult to resolve. The distinctive signal due to 6-H occurs upfield of that of the other aromatic protons by *ca.* 0·3 p.p.m., whilst that of 2-H is separated from those of the remaining protons by 0·1—0·2 p.p.m. and is seen as a singlet under normal resolution, but as a multiplet when the spectrum is expanded, because of coupling with the 3-Me protons and with 6-H.

Any 2-substituted derivative is characterised by the loss of the typical 2-H peak. If the substituent is a nitro- or an acetyl group, the chemical shifts of the 3-Me

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[2] M. Martin-Smith and M. Gates, *J. Amer. Chem. Soc.*, 1956, **78**, 5351.
[3] R. Adams and I. Levine, *J. Amer. Chem. Soc.*, 1923, **45**, 2373.
[4] D. S. Tarbell, *Org. Reactions*, 1944, **2**, 1.
[5] A. M. Blatt, *Org. Reactions*, 1942, **1**, 342.
[6] P. M. Chakrabarti, N. B. Chapman, and K. Clarke, *J. Chem. Soc.* (*C*), 1969, 1.
[7] S. Sethna and R. Phadke, *Org. Reactions*, 1953, **7**, 1.

protons occur downfield to the extent of 0·3—0·4 p.p.m. A 4-substituted product, however, reveals a typical AB pattern for 5-H and 6-H, and although a nitro-group has little effect on the chemical shifts of the 3-Me protons, a bromo-group will cause a downfield shift (*ca.* 0·25 p.p.m.). This pattern conforms with that observed for 4-substituted derivatives of 5-hydroxybenzo[*b*]thiophen. A 6-substituted product likewise reveals an AB pattern for 4-H and 5-H, and in addition, a large downfield shift of the resonance of the hydroxy-proton, due to intramolecular hydrogen bonding. The characteristic pattern due to 6-H is also missing.

A 4,6-disubstituted derivative has only a singlet peak due to 5-H. As with 4-substituted derivatives, the chemical shifts due to the 3-Me protons may be altered by the presence of suitable 4-substituents.

EXPERIMENTAL

^{1}H N.m.r. spectra (100 MHz) were obtained with a JNM-4H-100 spectrometer, for solutions in deuteriochloroform except where otherwise stated, with tetramethylsilane as internal standard. I.r. spectra were determined for potassium chloride discs with a Perkin-Elmer PE 457 spectrophotometer. Mass spectra were determined with an A.E.I. MS902 spectrometer.

7-Hydroxy- and 7-mercapto-3-methylbenzo[*b*]thiophen were prepared as previously described.

Bromination of 7-Hydroxy-3-methylbenzo[b]*thiophen.*—(*a*) *N*-Bromosuccinimide (0·01 mol) was added during 30 min to a stirred solution of 7-hydroxy-3-methylbenzo[*b*]thiophen (1·64 g, 0·01 mol) in dry carbon tetrachloride (25 ml) kept at 40—45° and illuminated with a tungsten lamp (200 W). After 1 h, the mixture was filtered and the carbon tetrachloride was removed *in vacuo* to give mainly *6-bromo-7-hydroxy-3-methylbenzo*[b]*thiophen* (0·91 g, 40%). Recrystallisation first from aqueous methanol and then from chloroform–light petroleum (b.p. 60—80°) gave prisms, m.p. 66°, *M*, 241·939 (C_9H_7BrOS requires *M*, 241·940); $\nu_{max.}$ (CCl_4) 3525 cm^{-1} (OH); δ 7·44 (d, 5-H), 7·18 (d, 4-H), 7·06 (s, 2-H), 5·75 (s, 7-OH), and 2·38 p.p.m. (s, Me).

The residue after filtration was triturated with water to remove succinimide and yielded crude *4-bromo-7-hydroxy-3-methylbenzo*[b]*thiophen* (0·45 g, 20%) [prisms from chloroform–light petroleum (b.p. 60—80°)], m.p. 110—110·5° (Found: C, 44·7; H, 2·9. C_9H_7BrOS requires C, 44·7; H, 2·9%); $\nu_{max.}$ 3600 cm^{-1} (OH); δ 7·37 (d, 5-H), 7·10 (s, 2-H), 6·55 (d, 6-H), 5·50br (OH), and 2·70 p.p.m. (s, Me), $J_{5,6}$ 8·0 Hz.

(*b*) A solution of bromine (0·27 ml, 0·005 mol) in glacial acetic acid (8 ml) was added dropwise during 5 min to a stirred solution of 7-hydroxy-3-methylbenzo[*b*]thiophen (0·82 g, 0·005 mol) and anhydrous sodium acetate (0·8 g) in glacial acetic acid (10 ml). After 10 min, the mixture was warmed on a steam-bath for 5 min, cooled, and poured into ice–water. The resulting white solid (0·89 g) was a mixture (t.l.c. and n.m.r.) of the 4-bromo- (*ca.* 40%) and the 4,6-dibromo-compound (*ca.* 40%), and unchanged 7-hydroxy-3-methylbenzo[*b*]thiophen (*ca.* 20%). Steam distillation of the mixture gave *4,6-dibromo-7-hydroxy-3-methylbenzo*[b]*thiophen* (0·155 g, 9%), m.p. 177—178° [from light petroleum (b.p. 60—80°)] (Found: C, 33·8; H, 1·6; Br, 49·2. $C_9H_6Br_2OS$ requires C, 33·75; H, 1·9; Br, 49·5%); δ 7·56 (s, 5-H), 7·07 (s, 2-H), 5·83 (s, 7-OH), and 2·65 p.p.m. (s, 3-Me).

When this experiment was repeated with twice the amount of bromine, dilution with water gave crude 4,6-dibromo-7-hydroxy-3-methylbenzo[*b*]thiophen (1·67 g, 100%).

Nitration of 7-Hydroxy-3-methylbenzo[b]*thiophen.*—Concentrated nitric acid (1·8 g, 0·02 mol) in glacial acetic acid (120 ml) was added to a stirred solution of 7-hydroxy-3-methylbenzo[*b*]thiophen (3·28 g, 0·02 mol) in glacial acetic acid (100 ml) during 2 h at 20—22°. After 1 h, the acetic acid was removed at 25° and 1 mmHg, and the residue was dissolved in chloroform (200 ml) and shaken with aqueous 5% sodium hydrogen carbonate (5 × 100 ml). Acidification of the aqueous layer gave *4,6-dinitro-7-hydroxy-3-methylbenzo*[b]*thiophen* (1·97 g, 38%), contaminated (t.l.c.) with a little of the 6-nitro-compound, yellow needles (chloroform), m.p. 163—164° (Found: C, 42·5; H, 2·6; N, 11·2%; *M*, 254. $C_9H_6N_2O_6S$ requires C, 42·5; H, 2·4; N, 11·0%; *M*, 254); δ 11·63br (7-OH), 8·59 (s, 5-H), 7·68 (s, 2-H), and 2·48 p.p.m. (s, 3-Me).

The chloroform layer was shaken with 0·05M-sodium carbonate (7 × 100 ml) and the filtered aqueous layer was acidified to give *7-hydroxy-3-methyl-6-nitrobenzo*[b]*thiophen* (1·04 g, 25%) contaminated with a little of the 4,6-dinitro-derivative. Crystallisation from aqueous methanol and then from chloroform–light petroleum (b.p. 60—80°) gave pale orange needles (0·7 g, 17%), m.p. 107—107·5° (Found: C, 51·6; H, 3·3; N, 6·6. $C_9H_7NO_3S$ requires C, 51·7; H, 3·4; N, 6·7%); δ 11·47 (s, 7-OH), 8·05 (d, 5-H), 7·45 (s, 2-H), 7·25 (d, 4-H), and 2·44 p.p.m. (s, 3-Me), $J_{4,5}$ 8·75 Hz.

The chloroform layer was washed with aqueous 2% sodium hydroxide (2 × 100 ml) to remove starting material, then with water, and dried ($MgSO_4$). Concentration of the solution gave crude *3-methylbenzo*[b]*thiophen-4,7-quinone* (0·36 g, 10%). It was crystallised from aqueous methanol and then from chloroform–light petroleum (b.p. 60—80°) to give yellow prisms, m.p. 137—138° (decomp.) (Found: *M*, 178. $C_9H_6O_2S$ requires *M*, 178); $\lambda_{max.}$ (EtOH) 227 (ε 11,300), 257 (10,200), and 332 nm (2900); $\nu_{max.}$ 1655 and 1682 (1,4-quinone) cm^{-1}; δ 7·29 (s, 2-H), 6·82 (s, 5-H or 6-H), 6·73 (s, 6-H or 5-H), and 2·50 p.p.m. (s, 3-Me), $J_{5,6}$ 8·74 Hz.

Nitration with 2 mol. equiv. of concentrated nitric acid gave mainly 4,6-dinitro-7-hydroxy-3-methylbenzo[*b*]thiophen (>80%) and a little of the foregoing quinone.

7-Hydroxy-3-methylbenzo[b]*thiophen-6-carbaldehyde.*—Dry hydrogen chloride was passed into a mixture of 7-hydroxy-3-methylbenzo[*b*]thiophen (3·28 g, 0·02 mol) and anhydrous zinc cyanide (13 g) in dry ether (15 ml) for 2·5 h at 0°, then for 2·5 h at room temperature. 2M-Hydrochloric acid (40 ml) was added and the mixture was stirred overnight. The acid was neutralised with aqueous sodium hydrogen carbonate, the aqueous layer was removed, and the ether was evaporated. The residue was agitated ultrasonically with a saturated solution of sodium hydrogen carbonate (5 × 50 ml). Acidification of the solution gave the *aldehyde* (2·04 g, 53%), yellow needles (ethanol), m.p. 171—172° (decomp.) (Found: C, 62·7; H, 4·2. $C_{10}H_8O_2S$ requires C, 62·5; H, 4·2%); $\nu_{max.}$ 1640 cm^{-1} (C=O); δ [$(CD_3)_2SO$] 11·45br (OH), 10·5 (s, CHO), 7·91 (d, 5-H), 7·58 (s, 2-H), 6·92 (d, 4-H), and 2·67 p.p.m. (3-Me), $J_{4,5}$ 8·1 Hz.

7-Allyloxy-3-methylbenzo[b]*thiophen.*—A mixture of 7-hydroxy-3-methylbenzo[*b*]thiophen (3·28 g, 0·02 mol), allyl bromide (1·9 ml, 0·022 mol), and anhydrous potassium carbonate (12 g) in butanone (100 ml) was heated under

reflux for 2 h and filtered. The butanone was removed and the residue gave *prisms* (2·6 g, 63%), m.p. 42—43° [light petroleum (b.p. 40—60°) (Found: C, 70·2; H, 5·9. $C_{12}H_{12}OS$ requires C, 70·5; H, 5·9%); δ 7·25 (m, 4-H and 5-H), 7·00 (s, 2-H), 6·70 (dd, 6-H), and 2·40 p.p.m. (s, 3-Me).

6-*Allyl*-7-*hydroxy*-3-*methylbenzo*[b]*thiophen* (with T. M. Sutton).—7-Allyloxy-3-methylbenzo[*b*]thiophen (1·0 g, 0·0049 mol) and freshly distilled dimethylaniline (50 ml) were heated under reflux for 3·5 h. The cooled solution was poured into dilute hydrochloric acid and ice and the product was extracted into benzene (3 × 50 ml). Phenolic material was extracted with Claisen alkali [2 × 15 ml; from potassium hydroxide (35 g) in water (25 ml) diluted to 100 ml with methanol]. The alkaline layer was separated, acidified with 6M-hydrochloric acid, and shaken with benzene (3 × 50 ml). The benzene layer was washed with water (2 × 20 ml), dried ($MgSO_4$), and evaporated to give an orange oil (0·95 g, 95%), which crystallised slowly. Decolourisation (silica column) followed by crystallisation from light petroleum (b.p. 40—60°) gave colourless *needles* (0·82 g, 82%), m.p. 59—60° (Found: C, 70·4; H, 5·9%; *M*, 204. $C_{12}H_{12}OS$ requires C, 70·5; H, 5·9%; *M*, 204); $\nu_{max.}$ 3540—3300br (OH) cm^{-1}; δ 8·3—8·05 (m, 4-H and 5-H), 6·95 (s, 2-H), 5·5 (s, OH), and 2·40 p.p.m. (3-Me).

7-*Acetoxy*-3-*methylbenzo*[b]*thiophen*.—Acetyl chloride (0·87 g) was added to a stirred solution of 7-hydroxy-3-methylbenzo[*b*]thiophen (1·1 g) in pyridine (40 ml). After 4 h, the mixture was poured into ice–water and the product washed thoroughly with water and dried. The *acetoxy-compound* (1·3 g, 94%) had m.p. 45° [from chloroform–light petroleum (b.p. 40—60°)] (Found: C, 63·8; H, 4·9; S, 15·5. $C_{11}H_{10}O_2S$ requires C, 64·05; H, 4·9; S, 15·5%); $\nu_{max.}$ 1762 cm^{-1} (C=O).

2-*Acetyl*-7-*hydroxy*-3-*methylbenzo*[b]*thiophen*.—A mixture of anhydrous aluminium chloride (0·7 g) and 7-acetoxy-3-methylbenzo[*b*]thiophen (0·5 g) in dry benzene (12 ml) was heated under reflux for 3 h and was then kept at room temperature overnight. An excess of 2M-hydrochloric acid was added and the product was extracted with ether (3 × 15 ml). The ethereal solution was shaken with aqueous 5% sodium hydroxide (3 × 30 ml), and acidification with 6M-hydrochloric acid gave 2-*acetyl*-7-*hydroxy*-3-*methylbenzo*[b]*thiophen* (0·39 g, 78%), m.p. 229—230° (decomp.) (from ethanol) (Found: C, 64·4; H, 5·1. $C_{11}H_{10}O_2S$ requires C, 64·05; H, 4·9%); $\nu_{max.}$ 1640 cm^{-1} (C=O); δ 10·52 (s, OH), 7·84 (m, 5-H), 7·46 (m, 4-H), 6·93 (m, 6-H), and 2·70 and 2·60 p.p.m. (s, COMe and 3-Me).

3,6-*Dimethylthieno*[3,2-h][1]*benzopyran*-8-*one* (I).—A cooled solution of 7-hydroxy-3-methylbenzo[*b*]thiophen (1·0 g) and ethyl acetoacetate (1·6 ml) in dry methanol (12 ml) was saturated with dry hydrogen chloride (5 min). The flask was sealed and was kept in a refrigerator for 6 h; further hydrogen chloride was then passed in (0·5 min). After a further 1 h in the refrigerator, the *product* was collected (1·1 g, 79%); m.p. 206—207° (needles from methanol) (Found: C, 67·8; H, 4·4; S, 13·8. $C_{13}H_{10}O_2S$ requires C, 67·8; H, 4·4; S, 13·9%); $\lambda_{max.}$ (EtOH) 209·5 (ε 32,600), 228 (16,100), 234 (14,400), 265·5 (21,700), 296 (9250), 305 (9400), 354·5 (7900), and 370 nm (6100); $\nu_{max.}$ 1717 (C=O) and 1598 cm^{-1} (C=C, conj.); δ 7·56 (s, 4-H, 5-H), 7·3 (s, 2-H), 6·3 (s, 7-H), and 7·45 and 7·5 p.p.m. (3-Me and 6-Me).

2-(3-*Methyl*-7-*benzo*[b]*thienylthio*)*propionic Acid*.—A solution of 2-bromopropionic acid (1·53 g, 0·01 mol) in ice-cold aqueous 8% sodium hydroxide (5 ml) was added dropwise to a stirred solution of 7-mercapto-3-methylbenzo[*b*]thiophen (1·81 g, 0·01 mol) in aqueous 2% sodium hydroxide (20 ml). The mixture was heated on a steam-bath for 1·5 h and filtered. Acidification gave the *acid* (2·2 g, 87%), m.p. 96—97°, [from benzene–light petroleum (b.p. 60—80°)] (Found: C, 57·1; H, 4·8. $C_{12}H_{12}O_2S_2$ requires C, 57·1; H, 4·8%).

7,8-*Dihydro*-3-*methylthieno*[3,2-h][1]*benzothiopyran*-6-*one* (II).—A mixture of 2-(3-methyl-7-benzo[*b*]thienylthio)propionic acid (1·47 g, 0·0058 mol) and polyphosphoric acid (15 g) was stirred at 100° for 2 h, and poured into water. The precipitate was collected, stirred with aqueous 5% sodium hydrogen carbonate for 0·5 h, and again filtered off. The residue was boiled with ethanol and the ethanolic solution was evaporated to give the *thiopyranone* (0·492 g, 36%), m.p. 116—117° [pale yellow prisms, from acetone–light petroleum (b.p. 40—60°)] (Found: C, 61·6; H, 4·3. $C_{12}H_{10}OS_2$ requires C, 61·5; H, 4·3%); $\nu_{max.}$ 1655 cm^{-1} (C=O); δ 8·14 (d, 5-H), 7·51 (d, 4-H), 7·28 (s, 2-H), 3·5—3·3 and 3·15—2·95 (7-H_2 and 8-H_2), and 240 p.p.m. (s, 3-Me), $J_{4,5}$ 8·5 Hz.

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