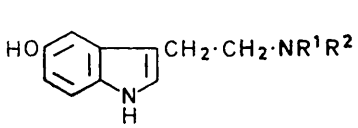
Synthesis of the Sulphur Analogue of Psilocin and Some Related Compounds

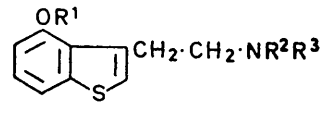
By **N. B. Chapman,* R. M. Scrowston, and T. M. Sutton,** Department of Chemistry, The University, Hull HU6 7RX

Possible routes to *NN*-dimethyl-2-(4-hydroxy-3-benzo[*b*]thienyl)ethylamine, the sulphur analogue of the hallucinogen, psilocin, have been examined, and several new 4-benzyloxy- and 4-methoxy-benzo[*b*]thiophen derivatives have been obtained. In particular, 4-benzyloxy-3-methylbenzo[*b*]thiophen was prepared by a four-stage process from *o*-benzyloxyacetophenone. A successful synthesis of the required amine started from 4-methoxy-3-methylbenzo[*b*]thiophen-2-carboxylic acid, the crucial stage being the conversion of the derived 4-methoxy-3-methylbenzo[*b*]thiophen into 3-bromomethyl-4-methoxybenzo[*b*]thiophen. An attempted synthesis of 4-hydroxy-3-methylbenzo[*b*]thiophen from 3-methylthiophen is described.

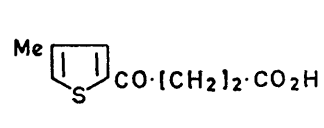
THE isosteric relationship between indole and benzo[*b*]-thiophen has prompted the synthesis of many benzo[*b*]-thiophen analogues of biologically active indole derivatives.[1,2] Because of the outstanding importance in nature of 5-hydroxyindole derivatives, the synthesis of the corresponding 5-hydroxybenzo[*b*]thiophen compounds has aroused the greatest interest: successful syntheses of the sulphur analogues of 5-hydroxytryptamine (1),[2-4] 5-hydroxytryptophan, bufotenine (2), and melatonin (3) [5] have been reported recently. Although these hydroxybenzo[*b*]thiophens have relatively simple structures, the introduction of the side-chain into the 3-position in the presence of either a free or a protected 5-hydroxy-group has met with unforseen difficulties.



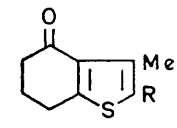
(1) $R^1 = R^2 = H$
(2) $R^1 = R^2 = Me$
(3) $R^1 = H$, $R^2 = Ac$



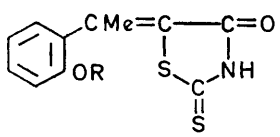
(4) $R^1 = H$, $R^2 = R^3 = Me$
(5) $R^1 = Me$, $R^2 = R^3 = Me$
(6) $R^1 = Me$, $R^2 = Me$, $R^3 = H$
(7) $R^1 = Me$, $R^2 = R^3 = H$



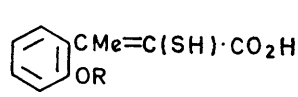
(8)



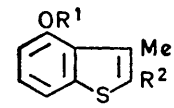
(9) R = Ac
(10) R = H



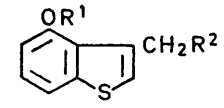
(11) R = CH_2Ph
(12) R = Me



(13) R = CH_2Ph
(14) R = Me



(15) $R^1 = CH_2Ph$, $R^2 = CO_2H$
(16) $R^1 = CH_2Ph$, $R^2 = H$
(17) $R^1 = Me$, $R^2 = CO_2H$
(18) $R^1 = Me$, $R^2 = H$



(19) $R^1 = Me$, $R^2 = CO_2H$
(20) $R^1 = H$, $R^2 = CO_2H$
(21) $R^1 = Me$, $R^2 = CO{\cdot}NMe_2$
(22) $R^1 = H$, $R^2 = CO{\cdot}NMe_2$

Our present work has culminated in the synthesis of the sulphur analogue (4) of psilocin. Psilocin exhibits potent psychotomimetic activity, producing effects similar to those of lysergic acid diethylamide or mescaline.[6] 4-Hydroxybenzo[*b*]thiophen derivatives have received relatively little attention,[7] presumably because of their relative inaccessibility. Campaigne and his co-workers [8] have described independent preliminary experiments on 4-hydroxybenzo[*b*]thiophen, which were directed towards an eventual synthesis of the psilocin isostere (4). Their results confirm our present observation that syntheses of 3-substituted 4-hydroxybenzo-[*b*]thiophens, like those of the corresponding 5-hydroxy-compounds, are by no means straightforward.

Our first attempts to synthesise the amine (4), like those of Campaigne *et al.*,[8] started from 4-hydroxybenzo[*b*]thiophen, the crystalline 4-methylsulphonyloxy-derivative of which was easily obtained. We had hoped that we could use this to introduce a substituent directly into the 3-position of the benzo[*b*]thiophen system. However, unlike the corresponding 5-methylsulphonyloxy-compound,[3] it was recovered unchanged after several attempted chloromethylation reactions, and gave a complex mixture of products when treated with bromine in acetic acid at room temperature.

We next attempted to prepare 4-hydroxy-3-methylbenzo[*b*]thiophen from the readily available 3-methylthiophen, in the hope that the 3-methyl group of the

[1] E. Campaigne, D. R. Knapp, E. S. Neiss, and T. R. Bosin, *Adv. Drug Res.*, 1970, **5**, 1.
[2] E. Campaigne, E. S. Neiss, and T. Bosin, *Quart. Reports Sulphur Chem.*, 1969, **4**, 229.
[3] M. Martin-Smith, W. E. Sneader, I. Brown, and S. T. Reid, *J. Chem. Soc.* (*C*), 1967, 1899.
[4] E. Campaigne, T. Bosin, and E. S. Neiss, *J. Medicin. Chem.*, 1967, **10**, 270.
[5] E. Campaigne and A. Dinner, *J. Medicin. Chem.*, 1970, **13**, 1205.
[6] M. Gordon, 'Psychopharmacological Agents,' Academic Press, New York, 1964, vol. 1, p. 562.
[7] B. Iddon and R. M. Scrowston, *Adv. Heterocyclic Chem.*, 1970, **11**, 177.
[8] E. Campaigne, A. Dinner, and M. Haseman, *J. Heterocyclic Chem.*, 1971, **8**, 755.

former could be suitably modified if the 4-hydroxy-group were appropriately protected. Friedel–Crafts succinoylation of 3-methylthiophen gave a mixture of β-(4-methyl-2-thenoyl)propionic acid (8) and the corresponding 3-methyl isomer in the ratio of 2 : 1. The components were readily separated by chromatography and were identified spectroscopically. The keto-acid (8) was reduced by the Huang-Minlon procedure, but attempts to cyclise the resulting γ-(4-methyl-2-thienyl)-butyric acid generally gave intractable mixtures. Use of a mixture of polyphosphoric acid and acetic anhydride, which readily cyclises γ-(2-thienyl)butyric acid to 6,7-dihydrobenzo[*b*]thiophen-4(5*H*)-one,[9] gave a clean reaction, but the major product (85%) was 2-acetyl-6,7-dihydro-3-methylbenzo[*b*]thiophen-4(5*H*)-one (9). This was identified spectroscopically (see Experimental section) and by the formation of a crystalline dioxime.

We did not pursue further our attempts to prepare the ketone (10), from which 4-hydroxy-3-methylbenzo[*b*]-thiophen might have been prepared by dehydrogenation. Instead we prepared 4-benzyloxy-3-methylbenzo[*b*]-thiophen (16) from *o*-benzyloxyacetophenone by a modification [10] of the general method of Campaigne and Cline.[11] *o*-Benzyloxyacetophenone condensed with rhodanine (2-thioxothiazolidin-4-one) to give compound (11), which on alkaline hydrolysis gave the mercapto-acrylic acid (13). This was cyclised by treatment with chlorine in carbon tetrachloride to give 4-benzyloxy-3-methylbenzo[*b*]thiophen-2-carboxylic acid (15), decarboxylation of which with copper and quinoline at 200° gave the required product (16). Attempts to brominate 4-benzyloxy-3-methylbenzo[*b*]thiophen (16) in the methyl group with *N*-bromosuccinimide gave a complex mixture of products, probably because of competitive bromination of the benzyl group and the benzenoid ring. Further, the protecting benzyl group of the parent compound (16) was not easily removed: treatment with hydrogen bromide and acetic acid gave mainly polymeric material; catalytic hydrogenolysis gave <10% of the required product, possibly because of catalyst poisoning by the sulphur atom (*cf.* ref. 3).

The successful synthesis of the psilocin analogue (4) started from 4-methoxy-3-methylbenzo[*b*]thiophen, use of which we had avoided earlier, partly because the activating methoxy-group would probably lead to ring substitution rather than side-chain substitution in attempts to form the 3-bromomethyl compound, and partly because of the difficulties often encountered in demethylating certain methoxybenzo[*b*]thiophen derivatives.[5,12] The 2-carboxylic acid (17), which had been obtained previously [10] *via* the intermediates (12) and (14) readily gave 4-methoxy-3-methylbenzo[*b*]thiophen (18) when heated with copper and quinoline. As anticipated, 4-methoxy-3-methylbenzo[*b*]thiophen reacted readily with *N*-bromosuccinimide in carbon tetrachloride under the usual [13] conditions to give ring-substituted products, details of which will be described in a later paper. However, when the solvent and the reactants were carefully purified, and when the reaction time was carefully controlled, the required 3-bromomethyl-4-methoxybenzo[*b*]thiophen could be obtained in >95% yield. This reacted with sodium cyanide in aqueous acetone to give the corresponding 3-cyanomethyl compound, which was hydrolysed with warm (45°) concentrated hydrochloric acid to 4-methoxy-3-benzo[*b*]-thienylacetic acid (19). A minor product (*ca.* 5%) from the cyclisation of ethyl 4-(*m*-methoxyphenylthio)-3-oxobutyrate with polyphosphoric acid had previously [14] been identified as the ethyl ester of the acid (19), but mainly on the basis of i.r. evidence. The acid (19) was converted by the usual procedures into the *NN*-dimethyl-amide (21), and thence into *NN*-dimethyl-2-(4-methoxy-3-benzo[*b*]thienyl)ethylamine (5) by reduction ($LiAlH_4$–$AlCl_3$). Attempts to demethylate the methoxy-amine (5) gave intractable tars. However, the methoxy-amide (21) was more easily demethylated. Treatment of compound (21) with pyridine hydrochloride at *ca.* 200° gave the required hydroxy-amide (22) (30%), together with a hydrolysis product, 4-hydroxy-3-benzo[*b*]thienyl-acetic acid (20) (50%), and 4-hydroxy-3-methylbenzo-[*b*]thiophen (20%), the decarboxylation product of the latter acid. Demethylation of (21) with boron trichloride in methylene chloride [15] proceeded more smoothly and yielded the required product (22) almost quantitatively. Reduction of the hydroxy-amide (22) with diborane then gave the psilocin analogue (4) as an oily product which formed a crystalline hydrochloride and maleate.

Finally we prepared the primary and secondary amines (7) and (6) by reduction ($LiAlH_4$–$AlCl_3$) of the corresponding amides, in the hope that they might show interesting biological activity. The amine (7) could also be obtained by reduction of the corresponding 3-cyanomethyl compound. We had hoped to prepare the hydroxy-amines corresponding to (6) and (7), but demethylation of the methoxy-amines themselves, or of their precursors, failed to give homogeneous products.

EXPERIMENTAL

General experimental directions are as described previously.[16]

4-Methylsulphonyloxybenzo[b]*thiophen.*— Methanesulphonyl chloride (7·5 ml) was added dropwise to a stirred solution of 4-hydroxybenzo[*b*]thiophen (1·5 g) in dry pyridine (50 ml) at 0°, and the mixture was stirred for a further 1·5 h. It was then poured into ice–water and the suspension was stirred for 15 min. The solid was filtered

[9] D. T. Drewry and R. M. Scrowston, *J. Chem. Soc.* (*C*), 1969, 2750.
[10] P. M. Chakrabarti, N. B. Chapman, and K. Clarke, *Tetrahedron*, 1969, **25**, 2781.
[11] E. Campaigne and R. E. Cline, *J. Org. Chem.*, 1956, **21**, 39.
[12] R. M. Scrowston and R. Westwood, unpublished data.
[13] *Cf.* N. B. Chapman, K. Clarke, and B. Iddon, *J. Chem. Soc.*, 1965, 774.
[14] R. D. Schuetz and R. L. Titus, *J. Heterocyclic Chem.*, 1967, **4**, 465.
[15] L. F. Fieser and M. Fieser, ' Reagents for Organic Synthesis,' Wiley, New York, 1967, p. 67.
[16] J. Cooper, D. F. Ewing, R. M. Scrowston, and R. Westwood, *J. Chem. Soc.* (*C*), 1970, 1949.

off, washed successively with 10% hydrochloric acid and water, and formed *needles* (2·25 g, 98%), m.p. 68—69° [from light petroleum (b.p. 40—60°)] (Found: C, 47·35; H, 3·5; S, 28·05%; *M*, 228. $C_9H_8O_3S_2$ requires C, 47·35; H, 3·55; S, 28·1%; *M*, 228), δ 3·2 p.p.m. (s, Me).

Starting material was recovered when attempts were made to chloromethylate this material under various conditions.

Friedel–Crafts Succinoylation of 3-Methylthiophen.—Powdered aluminium chloride (58·7 g) was added in portions over 20 min to a stirred, cooled (20°) solution of succinic anhydride (22 g) in methylene chloride (500 ml), and the mixture was stirred for 15 min. 3-Methylthiophen (19·5 g) was added dropwise during 15 min, the mixture was then stirred for 1 h at 35—40°, cooled, and poured into a mixture of ice (300 g) and concentrated hydrochloric acid (300 ml). More methylene chloride (300 ml) was added and the mixture was kept at 45—50° for 10 min. The aqueous layer was separated and shaken (×2) with methylene chloride, and acidic material (24·2 g, 73%) was recovered in the usual way from the combined organic extracts. A portion of this was esterified with ethereal diazomethane. The product contained two methyl esters in the ratio 2 : 1 (g.l.c.).

The mixture of acids (6·0 g) was chromatographed in chloroform on silica gel. Elution with chloroform–ethanol (9 : 1) gave β-(*3-methyl-2-thenoyl*)*propionic acid* (1·95 g, 32% of the mixture), pale yellow platelets, m.p. 109—111° (from water) (Found: C, 54·5; H, 4·95; S, 15·8%; *M*, 198. $C_9H_{10}O_3S$ requires C, 54·55; H, 5·1; S, 16·3%; *M*, 198), $\nu_{max.}$ 1660 (ketone C=O) and 1705 (acid C=O) cm^{-1}, δ 2·58 (s, Me), 2·85 and 3·72 (t, each CH_2, *J* 6·5 Hz), 6·93 (d, 4-H), and 7·40 (d, 5-H) p.p.m. ($J_{4,5}$ 5·5 Hz). Continued elution gave β-(*4-methyl-2-thenoyl*)*propionic acid* (8) (3·9 g, 64% of the mixture) as lustrous plates, m.p. 115—117° (from water) (Found: C, 54·55; H, 5·15; S, 16·3%; *M*, 198), $\nu_{max.}$ 1645 (ketone C=O) and 1690 (acid C=O) cm^{-1}, δ 2·30 (s, Me), 2·65 and 3·38 (t, each CH_2, *J* 6·0 Hz), 7·21 (d, 5-H), and 7·55 (d, 3-H) p.p.m. ($J_{3,5}$ 1·8 Hz).

γ-(*4-Methyl-2-thienyl*)*butyric Acid.*—Hydrazine hydrate (98% w/w; 3·05 g) was added dropwise to a stirred solution of potassium hydroxide (18 g) and the acid (8) (14·5 g) in diethylene glycol (110 ml). The mixture was heated to 200—210° with removal of the distillate, then stirred at this temperature for 3 h. The cooled solution was poured on ice–hydrochloric acid, an excess of sodium chloride was added, and the mixture was shaken with ether in the usual way. The resulting dark brown solid crystallised as *needles* (11·9 g, 94%), m.p. 81—82° [from water (charcoal)] (Found: C, 58·7; H, 6·5; S, 17·35%; *M*, 184. $C_9H_{12}O_2S$ requires C, 58·65; H, 6·55; S, 17·4%; *M*, 184), $\nu_{max.}$ 1715 cm^{-1} (acid C=O), δ 2·2 (s, Me), 7·25 (d, 3-H), and 7·28 (d, 5-H) p.p.m. ($J_{3,5}$ 1·3 Hz).

2-Acetyl-6,7-dihydro-3-methylbenzo[b]*thiophen-4*(5H)*-one* (9).—A solution of γ-(4-methyl-2-thienyl)butyric acid (10·5 g) and polyphosphoric acid (1 ml) in acetic anhydride (25 ml) was heated under reflux for 3·5 h, then cooled and poured into ice–water (150 g) and hydrochloric acid (5 ml). A dark oil was extracted with chloroform, and distillation of the oil gave the *product* (10 g, 85%), b.p. 184—186° at 0·2 mmHg; this formed needles, m.p. 127·5—129° [from light petroleum (b.p. 60—80°)] (Found: C, 63·45; H, 5·85; S, 15·35%; *M*, 208. $C_{11}H_{12}O_2S$ requires C, 63·45; H, 5·8; S, 15·4%; *M*, 208), $\nu_{max.}$ 1700 (ring C=O) and 1680 (C=O) cm^{-1}, δ 2·5 (s, Ac) and 2·8 p.p.m. (s, Me).

The *dioxime* crystallised from ethanol as pale yellow needles, m.p. 175—177° (Found: C, 55·45; H, 5·9; N, 11·75; S, 13·6%; *M*, 238. $C_{11}H_{14}N_2O_2S$ requires C, 55·45; H, 5·9; N, 11·75; S, 13·45%; *M*, 238).

5-(*o-Benzyloxy-α-methylbenzylidene*)*rhodanine* (11).—Powdered rhodanine (47·7 g) was added to the suspension formed by adding benzene (360 ml) to a warm, stirred solution of ammonium acetate (7·2 g) in acetic acid (25 ml) and the mixture was stirred under reflux for 5 min. *o*-Benzyloxyacetophenone [17] (81 g) was added, and the mixture was boiled with stirring for 18 h under a Dean–Stark separator. The mixture was then cooled and seeded, kept overnight at 0°, and filtered. The product (11) formed pale yellow *prisms* (92 g, 75%), m.p. 163—165° (from ethanol) (Found: C, 63·4; H, 4·5; N, 4·25; S, 18·75%; *M*, 341. $C_{18}H_{15}NO_2S_2$ requires C, 63·3; H, 4·4; N, 4·1; S, 18·8%; *M*, 341), $\nu_{max.}$ 1690 cm^{-1} (C=O), δ 2·63 (s, Me) and 5·05 p.p.m. (s, O·CH_2Ph).

β-Methyl-β-(o-benzyloxyphenyl)-α-mercaptoacrylic Acid (13).—A mixture of the rhodanine derivative (11) (34·1 g), sodium hydroxide (18·5 g), and water (200 ml) was kept at 100° for 45 min, then cooled and acidified. The resulting solid was collected and gave off-white *needles* (28·2 g, 94%), m.p. 115—117° (from benzene) (Found: C, 68·1; H, 5·35; S, 10·65%; *M*, 300. $C_{17}H_{16}O_3S$ requires C, 68·0; H, 5·35; S, 10·65%; *M*, 300), $\nu_{max.}$ 1675 cm^{-1} (C=O), δ 2·25 (s, Me) and 5·15 p.p.m. (s, O·CH_2Ph).

4-Benzyloxy-3-methylbenzo[b]*thiophen-2-carboxylic Acid* (15).—A solution of chlorine (6·2 g, 0·087 mol) in dry carbon tetrachloride (150 ml) was added with swirling to a cooled (10°) solution of the foregoing acid (13) (25·9 g, 0·087 mol) in carbon tetrachloride (900 ml). The rose colour faded rapidly and hydrogen chloride was evolved. The product was filtered off after 1 h and formed *needles* (17·1 g, 72%), m.p. 201—203° (from benzene) (Found: C, 68·6; H, 4·7; S, 10·75%; *M*, 298. $C_{17}H_{14}O_3S$ requires C, 68·45; H, 4·75; S, 10·75%; *M*, 298), $\nu_{max.}$ 1680 cm^{-1} (C=O), δ [$(CD_3)_2SO$] 2·95 p.p.m. (s, Me).

4-Benzyloxy-3-methylbenzo[b]*thiophen* (16).—A stirred mixture of the acid (15) (38·4 g), copper bronze (11·4 g), and dry quinoline (230 ml) was kept at 190—200° for 1·5 h under nitrogen, then cooled to 100° and filtered (Hyflo). The filtrate was acidified and shaken with ether. Neutral material was isolated in the usual way as a dark oil, which slowly crystallised at room temperature. Recrystallisation (×2) from light petroleum (b.p. 40—60°) afforded off-white *needles* (31 g, 95%), m.p. 43—44° (Found: C, 75·6; H, 5·5; S, 12·6%; *M*, 254. $C_{16}H_{14}OS$ requires C, 75·55; H, 5·55; S, 12·6%; *M*, 254), δ 2·6 (d, Me) and 7·15 (q, 2-H) p.p.m. ($J_{2,3\text{-Me}}$ 0·7 Hz).

Attempted debenzylation of the product gave the results discussed in the text.

3-Methyl-4-methoxybenzo[b]*thiophen* (18).—3-Methyl-4-methoxybenzo[*b*]thiophen-2-carboxylic acid [10] [m.p. 248—249° (lit.,[10] 247—248°), $\nu_{max.}$ 1695 cm^{-1} (C=O), δ 3·95 (s, OMe) and 3·0 p.p.m. (s, Me)] was decarboxylated by the method already described to give a dark brown oil, distillation of which gave an oil (82%), b.p. 70—72° at 0·2 mmHg, which crystallised rapidly when cooled. It formed *needles*, m.p. 49·5—50° [from light petroleum (b.p. 40—60°)] (Found: C, 67·4; H, 5·6; S, 17·85%; *M*, 178. $C_{10}H_{10}OS$ requires C, 67·4; H, 5·65; S, 18·0%; *M*, 178), δ 3·85 (s, OMe), 6·8 (q, 2-H), and 2·6 (d, Me) p.p.m. ($J_{2,3\text{-Me}}$ 0·8 Hz).

3-Bromomethyl-4-methoxybenzo[b]*thiophen.*—*N*-Bromosuccinimide (2·0 g, 0·011 mol) was recrystallised (×2) from

[17] H. M. Priestley and E. Moness, *J. Org. Chem.*, 1940, **5**, 355.

water and dried *in vacuo*. It was then added during 20 min to a stirred, irradiated (200 W tungsten lamp) solution of 3-methyl-4-methoxybenzo[*b*]thiophen (2·0 g, 0·011 mol) and benzoyl peroxide (25 mg) in boiling carbon tetrachloride (dried and *redistilled*; 60 ml). The mixture was stirred and heated for a further 1·5 h, then cooled and filtered. Removal of the solvent from the filtrate gave an unstable red *oil* (2·8 g, 98%) (Found: *M*, 256. $C_{10}H_9{}^{79}BrOS$ requires *M*, 256), δ 7·05 (s, 2-H), 4·65 (s, CH_2Br), and 3·75 p.p.m. (s, OMe).

4-*Methoxy*-3-*benzo*[b]*thienylacetonitrile*.—A solution of the unpurified bromomethyl compound (3·0 g) in dry acetone (60 ml) was added dropwise to a stirred mixture of sodium cyanide (1·78 g), acetone (30 ml), and water (6 ml). The resulting mixture was boiled with stirring under reflux for 48 h, then cooled and added to water. The precipitate was filtered off, washed with water, and formed *needles* (1·65 g, 75%), m.p. 100—101° [from light petroleum (b.p. 40—60°)] (Found: C, 64·8; H, 4·7; N, 7·2; S, 15·75%; *M*, 203. $C_{11}H_9NOS$ requires C, 65·0; H, 4·45; N, 6·9; S, 15·75%; *M*, 203). $\nu_{max.}$ 2250 cm^{-1} (CN), δ 4·15 p.p.m. (s, CH_2·CN).

4-*Methoxy*-3-*benzo*[b]*thienylacetic Acid* (19).—A stirred mixture of the nitrile just described (2·75 g) and concentrated hydrochloric acid (20 ml) was kept at 45° for 2 h, then water (20 ml) was added and the mixture was stirred at the b.p. for a further 6 h. The mixture was kept overnight at 0° and acidic material was extracted from the resulting precipitate in the usual way. It formed white *needles* (2·45 g, 82%), m.p. 142—143° (from water) (Found: C, 58·9; H, 4·35; S, 14·5%; *M*, 222. $C_{11}H_{10}O_3S$ requires C, 59·2; H, 4·55; S, 14·4%; *M*, 222), $\nu_{max.}$ 1695 cm^{-1} (C=O), δ 4·0 p.p.m. (s, CH_2·CO_2H).

Amides of 4-*Methoxy*-3-*benzo*[b]*thienylacetic Acid*.—The acid (19) (1·7 g) was converted into the acid chloride with thionyl chloride in benzene. A solution of the crude product (2·0 g) in acetone (20 ml) was treated dropwise with an excess of a well cooled solution of dimethylamine in dry benzene. The resulting mixture was stirred for 1 h at 0°, then overnight at room temperature. Water was added, and the benzene layer was separated, dried, and evaporated. 4-*Methoxy*-NN-*dimethyl*-3-*benzo*[b]*thienylacetamide* (21) (1·75 g, 92%) was obtained as needles, m.p. 128—129·5° [from benzene–light petroleum (b.p. 40—60°)] (Found: C, 62·65; H, 6·0; N, 5·4; S, 12·85%; *M*, 249. $C_{13}H_{15}NO_2S$ requires C, 62·6; H, 6·05; N, 5·6; S, 12·85%; *M*, 249), $\nu_{max.}$ 1640 cm^{-1} (C=O), δ 3·95 (s, CH_2·CO), and 3·0 and 2·85 p.p.m. (s, CO·NMe_2).

4-Methoxy-*N*-methyl-3-benzo[*b*]thienylacetamide (85%), $\nu_{max.}$ 1655 cm^{-1} (C=O), M^+ 235, and 4-methoxy-3-benzo[*b*]-thienylacetamide (82%), $\nu_{max.}$ 1660 cm^{-1} (C=O), M^+ 221, were prepared similarly by adding aqueous methylamine or ammonia (*d* 0·88) to the acid chloride. They were difficult to crystallise and were used as white amorphous powders.

NN-*Dimethyl*-2-(4-*methoxy*-3-*benzo*[b]*thienyl*)*ethylamine* (5) *and Related Compounds*.—A suspension of 4-methoxy-*NN*-dimethyl-3-benzo[*b*]thienylacetamide (21) (0·4 g) in dry ether (40 ml) was added dropwise under nitrogen to a stirred suspension of lithium aluminium hydride (0·2 g) and aluminium chloride (0·63 g) in ether (30 ml). The mixture was stirred under reflux for 24 h, then the excess of reducing agent was destroyed and aqueous 10% sodium hydroxide (30 ml) was added. The ethereal layer was separated and the aqueous layer was shaken with ether. The combined ethereal extracts were dried and treated with ethereal hydrogen chloride to precipitate the *amine* (5) *hydrochloride* (0·35 g, 80%), pale yellow needles, m.p. 152—154° (from ethanol) (Found: C, 57·3; H, 6·6; Cl, 13·4; N, 4·9. $C_{13}H_{18}ClNOS$ requires C, 57·45; H, 6·65; Cl, 13·05; N, 5·15%).

Prepared similarly from the appropriate amide were: N-*methyl*-2-(4-*methoxy*-3-*benzo*[b]*thienyl*)*ethylamine* (6) *hydrochloride* (78%), m.p. 210—212° (needles from ethanol) (Found: C, 55·6; H, 6·1; Cl, 13·7; N, 5·2. $C_{12}H_{16}ClNOS$ requires C, 55·9; H, 6·25; Cl, 13·75; N, 5·45%), and 2-(4-*methoxy*-3-*benzo*[b]*thienyl*)*ethylamine* (7) *hydrochloride* (74%), m.p. 249—250° (from ethanol) (Found: C, 53·95; H, 6·1; Cl, 14·95; N, 5·7. $C_{11}H_{14}ClNOS$ requires C, 54·2; H, 5·8; Cl, 14·65; N, 5·75%). The latter compound was also obtained (73%) by similar reduction (heating time reduced to 10 h) of 4-methoxy-3-benzo[*b*]thienylacetonitrile.

Demethylation of 4-*Methoxy*-NN-*dimethyl*-3-*benzo*[b]-*thienylacetamide* (21).—(a) *With pyridine hydrochloride*. A mixture of the amide (21) (2 g) and pyridine hydrochloride (4 g) was kept at 200—210° for 20 min. It was then cooled, treated with water (20 ml) and cold (0°) concentrated hydrochloric acid (5 ml), and shaken with chloroform. 4-*Hydroxy*-3-*benzo*[b]*thienylacetic acid* (20) (0·82 g, 50%), recovered from the combined chloroform extracts with sodium hydrogen carbonate, formed off-white needles, m.p. 184—186° (from water) (charcoal) (Found: C, 57·7; H, 3·85; S, 15·4%; *M*, 208. $C_{10}H_8O_3S$ requires C, 57·65; H, 3·85; S, 15·4%; *M*, 208), $\nu_{max.}$ 1700 cm^{-1} (C=O), δ [$(CD_3)_2SO$] 3·95 p.p.m. (s, CH_2) (no signal due to OMe).

The remaining two components (t.l.c.) were separated by preparative t.l.c. [0·5 mm layer of Silica Gel G (Merck); benzene–ethanol (9 : 1)]. The slower running component (R_F 0·23) was 4-*hydroxy*-NN-*dimethyl*-3-*benzo*[b]*thienylacetamide* (22) (0·62 g, 30%); it was sublimed at 190° and 0·1 mmHg, and gave needles, m.p. 190—192° [from benzene–light petroleum (b.p. 60—80°)] (Found: C, 60·95; H, 5·5; N, 5·85; S, 13·6%; *M*, 235. $C_{12}H_{13}NO_2S$ requires C, 61·25; H, 5·55; N, 5·95; S, 13·6%; *M*, 235), $\nu_{max.}$ 1640 cm^{-1} (C=O), δ [$(CD_3)_2SO$] 2·95 and 3·2 (s, NMe_2) and 4·15 p.p.m. (s, CH_2·CO).

The remaining component was 4-*hydroxy*-3-*methylbenzo*-[b]*thiophen* (0·21 g, 20%) (R_F 0·87); it formed white needles, m.p. 84·5—86° [from light petroleum (b.p. 40—60°)] (Found: C, 65·9; H, 4·9; S, 19·5%; *M*, 164. C_9H_8OS requires C, 65·8; H, 4·9; S, 19·5%; *M*, 164), $\nu_{max.}$ *ca.* 3300br cm^{-1} (OH), δ 2·6 (s, Me) and 5·1 p.p.m. (OH). The same product (96%) was obtained when 4-methoxy-3-methylbenzo[*b*]thiophen was treated with pyridine hydrochloride under the foregoing conditions. The resulting dark brown solid was distilled under nitrogen to give material, b.p. 106—108° at 0·1 mmHg, m.p. 85—86°, identical with that just described.

(b) *With boron trichloride*. A solution of the methoxy-amide (21) (0·3 g) in dry methylene chloride (15 ml) was treated at −78° with a solution of boron trichloride (1·2 g) in methylene chloride (7 ml). The resulting wine-red solution was allowed to attain room temperature, then water (10 ml) was added, with cooling and stirring. Extraction with chloroform gave 4-hydroxy-*NN*-dimethyl-3-benzo[*b*]thienylacetamide (22) (98%), m.p. 190—192°, identical with that obtained by method (a).

NN-*Dimethyl*-2-(4-*hydroxy*-3-*benzo*[b]*thienyl*)*ethylamine* (4).—A solution of the hydroxy-amide (22) (0·65 g) in dry tetrahydrofuran (50 ml) was added to a stirred, cooled (0°) solution of diborane [from sodium borohydride (0·72 g) and

boron trifluoride–ether (2·4 g) in bis-(2-methoxyethyl) ether (50 ml)] in tetrahydrofuran (100 ml). The mixture was then stirred under reflux for 2·5 h, cooled, and treated dropwise with a solution of freshly recrystallised maleic acid (0·29 g) in dry ethanol (6 ml). The solvents were removed under reduced pressure to yield the *monohydrogen maleate* (0·62 g, 63%), which formed platelets, m.p. 150—152° (decomp.) (from ethanol) (Found: C, 56·85; H, 5·6; N, 4·15; S, 9·2. $C_{16}H_{19}NO_6S$ requires C, 57·0; H, 5·65; N, 4·15; S, 9·5%).

The *hydrochloride* was obtained when the mixture from the reduction was treated successively with ethanol and dry hydrogen chloride. It formed pale yellow microcrystals, m.p. 354—356° (from ethanol–ether) (Found: C, 55·9; H, 6·25; Cl, 13·75; N, 5·4. $C_{12}H_{16}ClNOS$ requires C, 55·9; H, 6·25; Cl, 13·75; N, 5·45%). Basification of the hydrochloride with aqueous ammonia gave the free base as an *oil* (Found: *M*, 221. $C_{12}H_{15}NOS$ requires *M*, 221).

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