Potential Thiophen Chemotherapeutics. Part III. Some 5-Substituted 2-Thienyl Sulphides and Sulphones.*

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A series of alkyl 5-aminomethyl-2-thienyl sulphones has been prepared from 2-phthalimidomethylthiophen *via* the 5-sulphinic acid. The 2 : 5-orientation of the disubstituted derivatives has been proved by two independent routes, the first involving the preparation of 5-aminomethyl-2-thienyl methyl sulphone from (*a*) 2-chloromethylthiophen and (*b*) methyl 2-thienyl sulphone, and the second comprising the preparation of 5-methylsulphonylthiophen-2-aldehyde from (*a*) 2-aminomethylthiophen and (*b*) methyl 2-thienyl sulphide.

A greatly improved method of preparation of methyl 2-thienyl sulphide (60% overall yield from 2-iodothiophen) was developed.

In view of the antibacterial properties of the *p*-alkylsulphonylbenzylamines (Fuller, Tonkin, and Walker, *J.*, 1945, 633; Forrest, Fuller, and Walker, *J.*, 1948, 1501) it was of interest to prepare their thiophen isosteres, and a series of alkyl 5-aminomethyl-2-thienyl sulphones is now reported.

The preparation of 2-phthalimidomethylthiophen from 2-chloromethylthiophen (Cymerman and Faiers, *J.*, 1952, 165) has been improved by the use of dimethylformamide as solvent (Sheehan and Bolhofer, *J. Amer. Chem. Soc.*, 1950, **72**, 2786) to give 94% of pure product. This material could also be obtained in 71% yield by the use of equimolecular proportions of phthalic anhydride and 2-aminomethylthiophen; it has previously been prepared in 19% yield by Hartough, Lukasiewicz, and Murray (*ibid.*, 1948, **70**, 1146) from the same reactants in the ratio 1 : 2.

Reduction of 5-phthalimidomethylthiophen-2-sulphonyl chloride (Cymerman and Faiers, *loc. cit.*) with sodium sulphite gave an excellent yield of the crystalline sulphinic acid which decomposed in acidic solution, or when heated, with loss of sulphur dioxide to form 2-phthalimidomethylthiophen. This reaction does not appear to have been previously noted for sulphinic acids.

Alkylation of sodium 5-phthalimidomethylthiophen-2-sulphinate gave the methyl, ethyl, and pentyl sulphones in good yield. Hydrolysis of the phthalimido-group with hydrochloric acid was extremely slow, but hydrazine hydrate (Ing and Manske, *J.*, 1926, 2348) readily afforded the alkyl 5-aminomethyl-2-thienyl sulphone hydrochlorides. Professor S. D. Rubbo has kindly examined these compounds against a range of organisms, including *Clostridium welchii*, and reports that they are devoid of appreciable activity.

Reduction of 5-acetamidomethylthiophen-2-sulphonyl chloride (Cymerman and Faiers, *loc. cit.*) was effected with sodium sulphite, but the sulphinic acid was not precipitated on acidification, nor could it then be extracted by solvents, owing presumably to the basic properties of the 2-acetamidomethylthiophen group (*idem, loc. cit.*). The aqueous solution, with a catalytic quantity of hydriodic acid, slowly deposited di-(5-acetamidomethyl-2-thienyl) disulphide in 31% yield. Reductions of sulphinic acids to disulphides have been previously noted (cf. Bauer and Cymerman, *J.*, 1950, 109). The disulphide was also prepared from the sulphonyl chloride by direct reduction with hydriodic acid in acetic acid (Bauer and Cymerman, *J.*, 1949, 3434), and the same method gave di-(5-phthalimidomethyl-2-thienyl) disulphide in 93% yield from the corresponding sulphonyl chloride.

In order to provide a rigid proof of the orientation of the sulphone group in the alkyl 5-phthalimidomethyl-2-thienyl sulphones, chloromethylation of methyl 2-thienyl sulphone (Cymerman and Lowe, *J.*, 1949, 1666) was investigated. In the benzene series, chloromethylation of compounds containing electron-attracting groups has been found (Stephen, Short, and Gladding, *J.*, 1920, 510; Matsukawa and Shirakawa, *J. Pharm. Soc. Japan*,

* Part II, *J.*, 1952, 165.

1950, **70**, 535) to give *meta*-substitution accompanied by the formation of substituted methanes. No reaction occurred, however, when methyl 2-thienyl sulphone was treated with aqueous formaldehyde and hydrogen chloride at room temperature. Under anhydrous conditions and in the presence of catalysts, reaction occurred with chloromethyl ether, and the product was subjected to a phthalimide synthesis in dimethylformamide. The phthalimido-compounds were readily separated into a bisphthalimidomethyl-2-thienyl methyl sulphone (m. p. 226°) and an inseparable mixture of monophthalimidomethyl compounds.

Separation of the picrates was achieved after hydrolysis, giving as the major component 5-aminomethyl-2-thienyl methyl sulphone picrate, identical with that from 2-phthalimidomethylthiophen. The small quantity of insoluble higher-melting picrate also obtained was insufficient for identification. The desired orientation was thus provided, the final disubstituted compound having been prepared from mono-derivatives in which each substituent was known to be in the 2-position. The diphthalimido-derivative is tentatively considered to be 4 : 5-bisphthalimidomethyl-2-thienyl methyl sulphone.

The direct aminomethylation of thiophen with *N*-hydroxymethylacetamide has been carried out (Hartough, " Thiophene and its Derivatives," Interscience Publ. Corpn., New York, 1952). Methyl 2-thienyl sulphone and *N*-hydroxymethylphthalimide (Buc, *J. Amer. Chem. Soc.*, 1947, **69**, 254) gave a product similar to the mixture of monophthalimidomethyl compounds obtained before.

An additional approach to the proof of configuration involved the preparation of 5-methylsulphonylthiophen-2-aldehyde by two independent routes. By the Sommelet reaction (Angyal, Morris, Tetaz, and Wilson, *J.*, 1950, 2141) 5-aminomethyl-2-thienyl methyl sulphone gave the desired 5-methylsulphonylthiophen-2-aldehyde. The synthesis of this aldehyde required the preparation of methyl 2-thienyl sulphide, previously obtained in only poor yield by the action of phosphorus trisulphide on dimethyl succinate (Steinkopf and Leonhardt, *Annalen*, 1932, **495**, 166) or sodium succinate (Meyer and Neure, *Ber.*, 1887, **20**, 1756). Successive treatment of a solution of 2-thienylmagnesium iodide with sulphur and methyl iodide afforded pure methyl 2-thienyl sulphide in 60% overall yield from 2-iodothiophen. It was readily oxidised to the known methyl sulphone by hydrogen peroxide in acetic acid.

Attempted chloromethylation of methyl 2-thienyl sulphide with formaldehyde and hydrochloric acid at −5° (Blicke and Burckhalter, *J. Amer. Chem. Soc.*, 1942, **64**, 478), and treatment of the oily product with potassium phthalimide in dimethylformamide, did not give a crystalline product, and none was obtained from the reaction of the sulphide with formaldehyde and ammonium chloride at 35° (Hartough, Meisel, Schick, and Koft, *ibid.*, 1948, **70**, 4013) followed by treatment with phthalic anhydride.

Direct introduction of the phthalimidomethyl group was next attempted. No reaction occurred between the sulphide and *N*-hydroxymethylphthalimide at room temperature in absolute ethanol saturated with dry hydrogen chloride, or at the boiling point in dry dioxan saturated with hydrogen chloride in presence of stannic chloride. Repetition of the experiment by refluxing with potassium hydrogen sulphate gave *N*-ethoxymethylphthalimide. However, the action of iodine in the presence of mercuric oxide on methyl 2-thienyl sulphide afforded a good yield of 5-iodo-2-thienyl methyl sulphide, and oxidation by hydrogen peroxide gave 5-iodo-2-thienyl methyl sulphone. The iodine atom in this substance was readily replaced on reaction with cuprous cyanide in pyridine, leading to 5-cyano-2-thienyl methyl sulphone. Attempted reduction of this nitrile to the aldehyde by means of lithium aluminium hydride at 0° was, however, unsuccessful, but alkaline hydrolysis afforded the carboxylic acid; in view of the low solubility of the acid, it was converted into the methyl ester, from which it was hoped to obtain the alcohol by lithium aluminium hydride, but again this reagent at 0° did not lead to the desired product. In view of the normal reduction of thiophen compounds lacking a sulphone substituent (*e.g.*, Cairns and McKusick, *J. Org. Chem.*, 1950, **15**, 790; Campbell and Kaeding, *J. Amer. Chem. Soc.*, 1951, **73**, 4019) these two failures may be connected with the presence of the sulphone group.

In another approach, formylation of methyl 2-thienyl sulphide by means of *N*-methyl-

formanilide gave a good yield of the desired 5-methylthiothiophen-2-aldehyde (estimated as solid derivatives) which could, however, not be separated from unchanged *N*-methylformanilide present as contaminant, this having an almost identical boiling point. The use of dimethylformamide in place of *N*-methylformanilide made possible the isolation of the pure aldehyde (m. p. 26°) in 58% yield. [Its thiosemicarbazone is of interest in view of the reported antituberculous activity of its benzene analogue (Behnisch, Mietzsch, and Schmidt, *Angew. Chem.*, 1948, **60**, 113) and is under examination.] Oxidation of the crude diacetate of the aldehyde by hydrogen peroxide readily gave the 5-methylsulphonylthiophen-2-aldehyde obtained by the Sommelet reaction mentioned above. This confirms the 2 : 5-orientation of the disubstituted compounds in this series.

A Cannizzaro reaction of 5-methylthiothiophen-2-aldehyde afforded the corresponding acid, oxidised by hydrogen peroxide to 5-methylsulphonylthiophen-2-carboxylic acid, identical with that obtained from 5-cyano-2-thienyl methyl sulphone.

Experimental

2-Phthalimidomethylthiophen.—(*a*) A vigorously stirred solution of 2-chloromethylthiophen (22·4 g.) in dimethylformamide (100 c.c.) was treated with potassium phthalimide (31·2 g., 10% excess). The mixture was heated to 90° (an exothermic reaction set in at 70°) and kept at this temperature with stirring for 1 hr. Chloroform (150 c.c.) was added to the cooled mixture which was poured into water (350 c.c.), and the aqueous portion twice extracted with chloroform. The combined extracts were washed (sodium hydroxide solution and water) and dried ($CaCl_2$). Removal of solvent gave colourless crystals (38·8 g., 94%) of 2-phthalimidomethylthiophen, m. p. 124—125° (Hartough, Lukasiewicz, and Murray, *loc. cit.*, give m. p. 126—127°).

(*b*) 2-Aminomethylthiophen (19 g.), phthalic anhydride (28·5 g., 1 mol.), and benzene (20 c.c.) were refluxed for 45 min. The solid which separated on cooling crystallised from alcohol, giving needles (28·4 g., 71%) of 2-phthalimidomethylthiophen, m. p. 125·5—126°, undepressed on admixture with the material obtained above.

5-Phthalimidomethylthiophen-2-sulphinic Acid.—5-Phthalimidomethylthiophen-2-sulphonyl chloride (Cymerman and Faiers, *loc. cit.*) (19 g., 0·055 mole) was added slowly to a vigorously stirred solution of sodium sulphite heptahydrate (27·7 g., 0·11 mole) in water (150 c.c.) at 70°, the mixture being kept at pH 8—9 by suitable addition of sodium hydrogen carbonate, and stirring was continued at 70° for a further 2 hr. after the addition. Acidification of the filtered ice-cold solution with sulphuric acid (18N) gave a pale yellow oil which was extracted with ethyl acetate, and the ethyl acetate extracts were shaken with sodium hydrogen carbonate solution. Acidification precipitated the *sulphinic acid*, m. p. 117—118° (decomp.) (from water) (Found : N, 4·55. $C_{13}H_9O_4NS_2$ requires N, 4·55%). It darkened on exposure to light. Its aqueous solution decomposed when kept for several days at room temperature in presence of sulphuric acid, or when heated at 95° for a few hours, giving 2-phthalimidomethylthiophen, m. p. 125° (Found : C, 64·3; H, 3·95; S, 13·35. Calc. for $C_{13}H_9O_2NS$: C, 64·2; H, 3·95; S, 13·2%). A mixed m. p. with authentic material showed no depression.

Alkyl 5-Phthalimidomethyl-2-thienyl Sulphones.—A solution of sodium 5-phthalimidomethylthiophen-2-sulphinate (from 0·01 mole of the sulphonyl chloride) in water (45 c.c.) was brought to pH 7·1—7·5 with hydrochloric acid and refluxed with the alkyl halide (0·02—0·03 mole) and sufficient ethanol to render the hot solution homogeneous. The cold mixture deposited needles of the *sulphone*, and a further crop was obtained by concentration of the filtrate *in vacuo*. One crystallisation from alcohol gave the pure products (Table 1).

Table 1. *Alkyl 5-phthalimidomethyl-2-thienyl sulphones.*

Alkyl	Reflux period (hr.)	Yield (%)	M. p.	Formula	Found (%) : C	H	N	S	Required (%) : C	H	N	S
Me	12	75	185—185·5°	$C_{14}H_{11}O_4NS_2$	52·55	3·35	4·55	19·95	52·3	3·45	4·35	19·95
Et	14	72	115—116	$C_{15}H_{13}O_4NS_2$	54·1	3·95	4·2	19·45	53·7	3·9	4·2	19·15
n-C_5H_{11}	28	72	101—101·5	$C_{18}H_{19}O_4NS_2$	57·2	5·0	—	17·35	57·25	5·05	—	17·0

Alkyl 5-Aminomethyl-2-thienyl Sulphone Hydrochlorides.—The 2-phthalimido-sulphone (0·01 mole) was warmed with absolute alcohol (25 c.c.) and hydrazine hydrate (0·01 mole; 100%). Dissolution occurred slowly and after 15—30 min. the intermediate compound was

precipitated. Heating was continued for a further 15—30 min., and finally for 5 min. longer after addition of excess of hydrochloric acid (2 c.c.; 10N). The solution was then evaporated to dryness *in vacuo*. The solid residue was dissolved in sodium hydroxide solution, saturated with potassium carbonate, and continuously extracted with ether. The dried extract on saturation with hydrogen chloride gave the pure *hydrochloride*, crystallising from alcohol in needles (Table 2).

TABLE 2. *Alkyl 5-aminomethyl-2-thienyl sulphone hydrochlorides.*

	Yield			Found (%):			Required (%):		
Alkyl	(%)	M. p.	Formula	C	H	N	C	H	N
Me	85	213—214°	$C_6H_9O_2NS_2,HCl$	31·75	4·35	—	31·65	4·45	—
Et	84	196—197	$C_7H_{11}O_2NS_2,HCl$	—	—	5·9	—	—	5·8
n-C_5H_{11}	85	206—207	$C_{10}H_{17}O_2NS_2,HCl$ [a]	42·8	6·4	4·75	42·3	6·4	4·95

[a] Found: S, 22·7. Required: S, 22·6%.

5-*Aminomethyl-2-thienyl methyl sulphone* crystallised from ether as needles, m. p. 56° (Found: N, 6·8. $C_6H_9O_2NS_2$ requires N, 7·3%). The *picrate* formed yellow prisms (from ethanol), m. p. 183—184° (decomp.) (Found: C, 34·4; H, 2·8; N, 13·75; S, 15·0. $C_6H_9O_2NS_2,C_6H_3O_7N_3$ requires C, 34·3; H, 2·9; N, 13·35; S, 15·25%).

5-*Aminomethyl-2-thienyl ethyl sulphone picrate* (needles from ethanol) had m. p. 172—173° (decomp.) (Found: C, 36·15; H, 3·3; S, 14·7. $C_7H_{11}O_2NS_2,C_6H_3O_7N_3$ requires C, 35·9; H, 3·25; S, 14·75%).

Di-(5-acetamidomethyl-2-thienyl) Disulphide.—A mixture of 5-acetamidomethylthiophen-2-sulphonyl chloride (2·52 g.), acetic acid (30 c.c.), and hydriodic acid (10 c.c.; *d* 1·71) was set aside for 22 hr. at room temperature, then decolorised with sodium thiosulphate solution (10%), and anhydrous sodium carbonate (20 g.) was added. After neutralisation with sodium hydroxide solution (10%), the product was filtered off, washed, and crystallised from ethanol as yellow plates (1·02 g., 55%) of the *disulphide*, m. p. 157—157·5° (Found: C, 45·2; H, 4·35. $C_{14}H_{16}O_2N_2S_4$ requires C, 45·15; H, 4·35%).

Attempted Preparation of 5-Acetamidomethylthiophen-2-sulphinic Acid.—The sulphonyl chloride (3·41 g., 0·014 mole) was added to a stirred solution of sodium sulphite heptahydrate (6·9 g., 0·027 mole) in water (30 c.c.) at 6—8°, and the mixture treated as described above. No residue was obtained from the ethyl acetate extract. The aqueous solution was treated with hydriodic acid (2 drops; 50%) and kept for 4 days. Working-up as described above afforded yellow plates (31%) of the disulphide, m. p. and mixed m. p. 157—157·5°.

Di-(5-phthalimidomethyl-2-thienyl) Disulphide.—A solution of 5-phthalimidomethylthiophen-2-sulphonyl chloride (3·43 g., 0·01 mole) in glacial acetic acid (40 c.c.) was treated with hydriodic acid (10 c.c.; *d* 1·76) and set aside for 3 days. Working-up as described above gave the *disulphide* (2·57 g., 93%) as colourless crystals (from ethanol), m. p. 166—167° (Found: C, 57·05; H, 3·0; N, 5·45; S, 23·05. $C_{26}H_{16}O_4N_2S_4$ requires C, 56·9; H, 2·95; N, 5·1; S, 23·35%).

Chloromethylation of Methyl 2-Thienyl Sulphone.—(*a*) A solution of methyl 2-thienyl sulphone (4·83 g., 0·03 mole) in glacial acetic acid (5 c.c.) was treated at 0° with stannic chloride (1·14 c.c., 0·01 mole) and chloromethyl methyl ether (3·78 c.c., 0·05 mole), and the temperature slowly raised to 95° during 2 hr. After further heating at 100° for 8 hr., the cooled solution was poured into ice-water (25 c.c.) and the oil extracted with ether. Removal of solvent from the washed (sodium hydrogen carbonate solution and water) and dried (Na_2SO_4) extract gave a dark oil (6 g.) giving a positive halogen test with boiling aqueous silver nitrate.

A solution of the oil (6 g.) and potassium phthalimide (5·6 g.) in dimethylformamide (18 c.c.) was heated at 90° with stirring for 1 hr. After addition of chloroform (30 c.c.) the cooled mixture was poured into water (100 c.c.) and extracted with chloroform. Distillation of the washed (sodium hydroxide solution and water) and dried (Na_2SO_4) extracts left a viscous oil which was extracted with boiling ether and ethanol. Evaporation of the combined extracts gave a mixture (*M*) of the monophthalimidomethyl compounds, m. p. 160—174°, which could not be separated by crystallisation.

Extraction of the alcohol- and ether-insoluble residue with boiling acetone gave a *bisphthalimidomethyl-2-thienyl methyl sulphone* as needles (0·7 g.), m. p. 226—226·5° (Found: C, 57·15; H, 3·35; N, 6.05; S, 13·5. $C_{23}H_{16}O_6N_2S_2$ requires C, 57·5; H, 3·35; N, 5·85; S, 13·35%).

The mixture (*M*) (1·38 g.) was heated on a water-bath with alcohol (10 c.c.) and hydrazine hydrate (0·4 c.c.; 100%). Dissolution occurred, and after 15 min. the intermediate compound

was precipitated. After a further 2 hours' heating, the complex was worked up as before and the amine converted into the picrate (0·6 g.), m. p. 160—173°, separated by crystallisation from ethanol into (1) yellow prisms, m. p. 183—184° (decomp.) undepressed on admixture with the picrate of 5-aminomethyl-2-thienyl methyl sulphone described above, and (2) a picrate, m. p. 194—196° (decomp.), insoluble in ethanol, obtained in insufficient quantity for further characterisation.

(*b*) A finely-powdered mixture of methyl 2-thienyl sulphone (0·25 g.) and *N*-hydroxymethylphthalimide (0·28 g.) was added to concentrated sulphuric acid (4 c.c.) at 0° and set aside for 6 days at room temperature. The solution was poured on ice, filtered, and washed with sodium hydroxide solution and water. The dried residue (0·31 g.) had m. p. 165—173°, unaltered on crystallisation from alcohol, and showed similar properties to the mixture (*M*).

5-Methylsulphonylthiophen-2-aldehyde.—(*a*) A mixture of 5-aminomethyl-2-thienyl methyl sulphone hydrochloride (5·5 g.), hexamine (4·2 g.), formaldehyde (1·8 c.c.; 40% aqueous solution), and acetic acid (40 c.c., 50%) was refluxed for 2 hr. The pH was adjusted to 1 with hydrochloric acid, and after dilution with water (200 c.c.) the filtered solution was exhaustively extracted with ether. Evaporation *in vacuo* of the dried (Na_2CO_3 and Na_2SO_4) ethereal extracts gave the aldehyde (0·67 g., 15%) as a water-soluble solid, m. p. >100°. The 2 : 4-*dinitrophenylhydrazone* crystallised from 2-ethoxyethanol as orange-brown needles, m. p. 276—277° (Found : C, 39·4; H, 3·1; N, 15·1. $C_{12}H_{10}O_6N_4S_2$ requires C, 38·9; H, 2·7; N, 15·15%).

(*b*) A solution of 5-methylthiothiophen-2-aldehyde (1 g.) in acetic anhydride (5 c.c.) was treated with concentrated sulphuric acid (1 drop). After 15 min. the dark blue solution was poured into sodium hydrogen carbonate solution, and the oil was separated, dissolved in acetic acid, and heated at 100° with hydrogen peroxide (1·3 c.c.; 30%) for 45 min. The cold neutralised solution gave a 2 : 4-dinitrophenylhydrazone as orange-brown needles (from 2-ethoxyethanol), m. p. 276—277°, undepressed on admixture with those described in (*a*).

Methyl 2-Thienyl Sulphide.—The cooled (ice) and stirred Grignard solution from 2-iodothiophen (70 g.) and magnesium (8 g.) in ether (600 c.c.) was treated with finely powdered sulphur (10·8 g.; freshly sublimed *in vacuo*) in small amounts. After refluxing for 45 min. a clear yellow solution was obtained. To the cooled solution methyl iodide (22·6 c.c.) was added dropwise with stirring, and the mixture left overnight in nitrogen. After 10 hours' refluxing, the ice-cold reaction mixture was decomposed with ammonium chloride solution and extracted with ether. Distillation of the washed (0·5N-potassium hydroxide and water) and dried (Na_2SO_4) extracts afforded methyl 2-thienyl sulphide as a colourless evil-smelling liquid (26·1 g., 60%), b. p. 80—82°/22 mm., 182°/764 mm. (Steinkopf and Leonhardt, *Annalen*, 1932, **495**, 166, give b. p. 181·5—183·5°).

Methyl 2-Thienyl Sulphone.—A mixture of methyl 2-thienyl sulphide (0·65 g.), hydrogen peroxide (1·35 c.c.; 30%), and acetic acid (10 c.c.) was heated on a water-bath for 45 min., cooled, poured on ice, and neutralised with sodium hydroxide solution. Ether-extraction of the filtered solution gave a residue which crystallised from aqueous alcohol in plates (0·51 g., 63%), m. p. 46·5—47° alone and on admixture with an authentic specimen (Cymerman and Lowe, *loc. cit.*).

A mixture of methyl 2-thienyl sulphide and *N*-hydroxymethylphthalimide in absolute alcohol was refluxed with potassium hydrogen sulphate for 3 hr. Evaporation to dryness left an oil, which was taken up in chloroform, and the extract was washed (sodium hydroxide solution and water) and distilled. The residue crystallised from light petroleum (b. p. 40—60°) as needles, m. p. 81—83°, of *N*-ethoxymethylphthalimide, undepressed on admixture with an authentic specimen prepared from ethanol and *N*-bromomethylphthalimide (Sachs, *Ber.*, 1898, **31**, 1230).

5-Iodo-2-thienyl Methyl Sulphide.—A solution of methyl 2-thienyl sulphide (2·73 g.) in benzene (8 c.c.) was treated at 0—5° alternately with small amounts of yellow mercuric oxide (3·75 g.) and iodine (5·45 g.) during 15 min. with vigorous stirring, and then for 15 min. at room temperature. The mixture was filtered and the solid washed with ether. Distillation left the product as a heavy oil (5·74 g.) which was not further purified.

5-Iodo-2-thienyl Methyl Sulphone.—The preceding sulphide (23·26 g.) in acetic acid (180 c.c.) was heated with hydrogen peroxide (24·5 c.c.; 30%) on a water-bath for 45 min. Dilution with ice-water gave colourless needles (16·52 g., 63%) of the *sulphone*, m. p. 84—84·5° (from aqueous methanol) (Found : C, 21·05; H, 1·85; S, 22·1. $C_5H_5O_2S_2I$ requires C, 20·85; H, 1·75; S, 22·25%).

5-Cyano-2-thienyl Methyl Sulphone.—A mixture of 5-iodo-2-thienyl methyl sulphone (16·5 g.) and cuprous cyanide (5·7 g.) was refluxed in dry pyridine (80 c.c.) for 2·5 hr. After removal

of pyridine *in vacuo*, the residue was extracted with boiling benzene, and the cold benzene filtered from tar. Distillation of the benzene left a residue which was extracted with boiling ethanol (in which the cuprous salts were insoluble), the ethanol solution was evaporated, and the residue dissolved in chloroform and chromatographed on alumina, to give colourless plates (6·34 g., 59%) of the *nitrile*, m. p. 137—137·5° (from alcohol) (Found: N, 7·6. $C_6H_5O_2NS_2$ requires N, 7·5%).

5-*Methylsulphonylthiophen*-2-*carboxylic Acid*.—(*a*) The foregoing nitrile (2 g.) was refluxed for 3 hr. in sodium hydroxide solution (40 c.c.; 10%), dissolving completely. The solution was acidified and the precipitate purified through sodium hydrogen carbonate solution to give the *acid* (1·84 g., 80%), as plates (from water), m. p. 201—202° (Found: C, 35·45; H, 2·75. $C_6H_6O_4S_2$ requires C, 35·9; H, 2·9%). An ethereal suspension of the acid with diazomethane gave the *methyl ester* (97%), crystallising from methanol as prisms, m. p. 118° (Found: C, 38·5; H, 3·3. $C_7H_8O_4S_2$ requires C, 38·2; H, 3·65%).

(*b*) A solution of 5-methylthiothiophen-2-carboxylic acid (0·1 g.) in acetic acid (1 c.c.) was treated with hydrogen peroxide (0·2 c.c.; 30%) at 100° for 45 min. On cooling, the product formed prisms of the sulphone-acid (0·09 g., 76%), m. p. 201—202°, undepressed on admixture with the sample prepared as in (*a*) above.

5-*Methylthiothiophen*-2-*aldehyde*.—A vigorously stirred solution of methyl 2-thienyl sulphide (4·89 g.) in dimethylformamide (15 c.c.) was treated dropwise with phosphorus oxychloride (3·9 c.c.) at 0—5° during 15 min. The solution was then stirred for 1 hr., during which the temperature rose slightly above room temperature. Next morning, the mixture was poured into ice-cold saturated sodium acetate solution (250 c.c.) with vigorous stirring, and extracted with ether. The ethereal extracts were washed with hydrochloric acid (N), sodium hydrogen carbonate solution and water, dried, and distilled, affording (after a small forerun of recovered sulphide) a single fraction, b. p. 86°/0·3 mm. (3·46 g., 58%), which solidified and crystallised from light petroleum (b. p. 40—60°) as needles of the *aldehyde*, m. p. 26° (Found: C, 45·8; H, 3·7. $C_6H_6OS_2$ requires C, 45·55; H, 3·8%).

The *oxime* crystallised as cream-coloured needles (from aqueous methanol), m. p. 80·5° (Found: C, 41·75; H, 4·25. $C_6H_7ONS_2$ requires C, 41·6; H, 4·1%). The *semicarbazone* (yellow plates from ethanol) had m. p. 186° (Found: C, 39·45; H, 4·1. $C_7H_9ON_3S_2$ requires C, 39·05; H, 4·2%). The *thiosemicarbazone* formed yellow needles (from methanol), m. p. 144—145° (Found: C, 36·55; H, 3·7; S, 41·4. $C_7H_9N_3S_3$ requires C, 36·35; H, 3·9; S, 41·6%), and the 2 : 4-*dinitrophenylhydrazone* dark red plates (from toluene), m. p. 215—216° (Found: N, 16·1; S, 18·6. $C_{12}H_{10}O_4N_4S_2$ requires N, 16·5; S, 18·95%).

5-*Methylthiothiophen*-2-*carboxylic Acid*.—A solution of 5-methylthiothiophen-2-aldehyde (1·15 g.) in methanolic potassium hydroxide (11 c.c.; 25%) was left overnight. The yellow solution was heated for 1 hr. at 100° and then diluted with water to dissolve the salts. Non-acidic material was removed with ether, and the aqueous solution concentrated to remove methanol, acidified, and filtered. The *acid* (0·39 g., 62%; purified through sodium hydrogen carbonate), crystallised from methanol in needles, m. p. 106° (Found: C, 41·8; H, 3·55. $C_6H_6O_2S_2$ requires C, 41·35; H, 3·45%).

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