110. *The Synthesis of Some Aryl 2-Thienyl Sulphones and the Nitration of Thiophen-2-sulphonyl Chloride.*

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Alternative methods for the synthesis of aryl 2-thienyl sulphones (and sulphides) have been investigated. The Friedel–Crafts method using thiophen-2-sulphonyl chloride appeared to be satisfactory for aryl = phenyl, but interaction of thiophen-2-sulphinic acid with aryl iodides proceeded slowly or not at all. Nitration of thiophen-2-sulphonyl chloride was reinvestigated; the 4-nitro-derivative was obtained pure.

IN attempts to synthesise aryl 2-thienyl sulphones and related compounds structurally similar to 4 : 4′-diaminodiphenyl sulphone and sulphanilamide, we have examined various synthetic methods. We avoided using thiophen itself as a starting material since it is well known that profound decomposition of this compound usually occurs under the action of acids and metal salts. Thiophen-2-sulphonyl chloride (Steinkopf and Höpner, *Annalen*, **1933**, **501**, 174) being readily available, we first investigated its reaction with resorcinol dimethyl ether in presence of zinc chloride (see Burton and Hoggarth, *J.*, **1945**, 14); this resulted in the formation of a small amount of the expected 2 : 4-*dimethoxyphenyl 2-thienyl sulphone.* We assign this constitution since the compound gave the correct analysis and differed from the alternative reaction product, *viz.*, m-*methoxyphenyl thiophen-2-sulphonate.* Since 2-iodothiophen did not react with sodium 2 : 4-dimethoxythiophenoxide we could not verify the constitution.

The Friedel–Crafts reaction between thiophen-2-sulphonyl chloride and benzene proceeded fairly satisfactorily giving a 55% yield of *phenyl 2-thienyl sulphone* (as expected, benzenesulphonyl chloride and thiophen gave tars), which could also be obtained by oxidation of *phenyl 2-thienyl sulphide.* This sulphide was formed in a somewhat impure state by treating 2 : 2′-dithienyl disulphide (Challenger and Miller, private communication) with phenylmagnesium bromide in benzene.

2-Iodothiophen did not react with potassium *p*-acetamidobenzenesulphinate, and use of the more reactive silver salt (Bambas, *J. Amer. Chem. Soc.*, **1945**, **67**, 668) gave only traces of the acetyl derivative of the required p-*aminophenyl 2-thienyl sulphone.* An alternative route to this compound *via* p-*nitrophenyl 2-thienyl sulphone* was no more successful, since we found that 2-thienylthiol and *p*-chloronitrobenzene in an alkaline medium gave very little p-*nitrophenyl 2-thienyl sulphide.*

We then explored the possibility of using thiophen-2-sulphinic acid which is readily prepared in good yield by the sodium sulphite reduction of the 2-sulphonyl chloride. The acid reacted rapidly with *p*-benzoquinone to give 2 : 5-*dihydroxyphenyl 2-thienyl sulphone,* slowly (as the potassium salt) with methyl iodide to form 2-*thienyl methyl sulphone,* but not at all with *p*-chloronitrobenzene.

In view of the well-known reaction between an arylsulphenyl chloride and a reactive molecule (for references see Burton and Davy, *J.*, **1947**, 52), we attempted to prepare thiophen-2-sulphenyl chloride by the action of chlorine on 2 : 2′-dithienyl disulphide in chloroform. The typical colour change from pale yellow to orange was observed, but all attempts to condense the supposed sulphenyl chloride with resorcinol were unsuccessful. Dark tarry products were always obtained, and no crystalline product was obtainable even after acetylation.

The action of fuming nitric acid on thiophen-2-sulphonyl chloride is known (Steinkopf and Höpner, *loc. cit.*) to give a mixture of the 4- and 5-nitro-derivatives in the ratio of about 8 : 3. This ratio was deduced from the relative amounts of the known 3- and 2-nitrothiophen respectively obtained by desulphonation of the mixed sulphonic acids with superheated steam. Fractional distillation of the nitration mixture has now resulted in the separation of the crystalline 4-*nitrothiophen*-2-*sulphonyl chloride* which is concentrated in the higher-boiling fractions. Hydrolysis followed by desulphonation then gave 3-nitrothiophen in at least 64% yield thus establishing the constitution. We consider the alternative structure, namely 3-nitrothiophen-2-sulphonyl chloride (which would similarly give 3-nitrothiophen), as excluded, since formation of this would necessitate substitution of a nitro-group *ortho* to the sulphonyl chloride group. This chloride led to 4-*nitrothiophen*-2-*sulphonamide* which was reduced to the 4-*amino-amide*. 5-Nitrothiophen-2-sulphonyl chloride was not obtained absolutely pure (see experimental section) and although the *nitro-amide* could be prepared satisfactorily attempted reduction of this caused profound decomposition.

EXPERIMENTAL.

Thiophen-2-sulphonyl chloride was prepared in 50% yield by Steinkopf and Höpner's method (*loc. cit.*). It had b. p. 131—132°/20 mm. and m. p. 32°, after crystallisation from ligroin. The colourless plates turned green after being kept for more than about a week.

2 : 4-*Dimethoxyphenyl* 2-*Thienyl Sulphone*.—An intimate mixture of thiophen-2-sulphonyl chloride (9·2 g.), resorcinol dimethyl ether (6·9 g.), and powdered, anhydrous zinc chloride (6·8 g.) was heated at 105° until effervescence ceased. The tarry reaction mixture was heated with concentrated hydrochloric acid (50 c.c.) and water (50 c.c.) and then extracted with benzene. The small amount of residue from the dried ($CaCl_2$) benzene extract solidified on trituration with cold methyl alcohol and crystallised (charcoal) from butyl alcohol, giving the *sulphone* as colourless needles, m. p. 128—129° (Found : C, 50·9; H, 4·3; S, 22·9. $C_{12}H_{12}O_4S_2$ requires C, 50·7; H, 4·2; S, 22·5%).

m-*Methoxyphenyl Thiophen*-2-*sulphonate*.—Thiophen-2-sulphonyl chloride (9·2 g.) and *m*-methoxyphenol (6·2 g.) were dissolved in pyridine (25 c.c.) and the mixture was kept overnight. Filtration from pyridine hydrochloride and extraction with ether gave, after washing with dilute hydrochloric acid and drying ($CaCl_2$), the *ester* (7 g.) which separated from alcohol–ligroin in colourless needles, m. p. 51—53° (Found: C, 48·8; H, 3·8; S, 24·2. $C_{11}H_{10}O_4S_2$ requires C, 48·9; H, 3·7; S, 23·7%).

2 : 4-Dimethoxythiophenol, b. p. 138—140°/15 mm., was obtained in 30% yield by reduction of 2 : 4-dimethoxybenzenesulphonyl chloride with zinc dust and dilute sulphuric acid. The oil gradually deposited crystals of *di*-2 : 4-*dimethoxyphenyl disulphide* which crystallised from alcohol in colourless plates, m. p. 117° (Found : C, 56·9; H, 5·9; S, 18·4; *M*, 338. $C_{16}H_{18}O_4S_2$ requires C, 56·8 ; H, 5·3; S, 18·9%; *M*, 338).

Phenyl 2-*Thienyl Sulphone*.—(*a*) Aluminium chloride (3·5 g.) was added gradually to thiophen-2-sulphonyl chloride (4·6 g.) in benzene (20 c.c.) at room temperature. After 15 minutes the black mixture was added with stirring to warm dilute hydrochloric acid. The benzene layer on evaporation under reduced pressure gave the *sulphone* (3·1 g.) which crystallised from alcohol in colourless flattened needles, m. p. 123° (Found : C, 53·7; H, 3·7; S, 28·7. $C_{10}H_8O_2S_2$ requires C, 53·6; H, 3·6; S, 28·6%).

Attempted preparation from benzenesulphonyl chloride (17·65 g.), thiophen (8·4 g.), and aluminium chloride (15 g.) at 35—40° gave a black tar.

(*b*) A solution of 2 : 2′-dithienyl disulphide (7·1 g.; 0·03 mol.) in benzene (75 c.c.) was added slowly, with cooling and stirring, to ethereal phenylmagnesium bromide (0·1 mol.). The pale brown solution was then boiled on the steam-bath, the ether being allowed to evaporate, and benzene (100 c.c.) added. After boiling for 18 hours the mixture was decomposed with ice and ammonium chloride. Fractionation of the dried benzene layer gave : (i) diphenyl, b. p. 120—140°/20 mm., m. p. and mixed m. p. 70° after crystallisation from alcohol, (ii) a fraction (3·9 g.), b. p. 155—160°/20 mm., which redistilled almost entirely at 155—157°/15 mm. This was impure *phenyl* 2-*thienyl sulphide* (Found : S, 28·5. $C_{10}H_8S_2$ requires S, 33·3%).

The sulphide (1·07 g.), 30% hydrogen peroxide (0·7 c.c.), and acetic acid (10 c.c.) were mixed and kept at room temperature overnight. The mixture was diluted with water and then extracted with warm ligroin (b. p. 40—60°). The extract was washed with dilute sodium hydrogen carbonate, dried ($CaCl_2$), and evaporated; the residual *phenyl* 2-*thienyl sulphoxide* crystallised from ligroin (b. p. 40—60°) in colourless hair-like needles, m. p. 69—70° (Found : C, 58·0; H, 4·2; S, 30·9. $C_{10}H_8OS_2$ requires C, 57·7; H, 3·8; S, 30·8%).

The sulphide (1·0 g.) and 30% hydrogen peroxide (1·5 c.c.) in acetic acid (15 c.c.) were heated on the steam-bath for 45 minutes. Addition of water to the cold solution precipitated the sulphone, m. p. and mixed m. p. 124°, unaltered by three crystallisations from alcohol (Found : C, 53·3; H, 3·8; S, 28·7%).

p-*Aminophenyl* 2-*Thienyl Sulphone*.—2-Iodothiophen (8·4 g.) and silver *p*-acetamidobenzenesulphinate (12·5 g.) in alcohol (80 c.c.) and water (50 c.c.) were refluxed for 20 hours. After removal of the alcohol by evaporation the residue was extracted twice with ether and the combined ethereal extracts were washed successively with dilute sodium thiosulphate and water. The dried (Na_2SO_4) extract yielded a small amount of *p*-acetamidophenyl 2-thienyl sulphone which crystallised from aqueous alcohol in colourless, minute crystals, m. p. 106° (decomp.). Hydrolysis with 5N-hydrochloric acid at 95° gave, after crystallisation from alcohol, the *sulphone* (0·1 g.) in colourless needles, m. p. 134° (Found : C, 50·5; H, 4·5; N, 6·1; S, 26·7. $C_{10}H_9O_2NS_2$ requires C, 50·2; H, 3·8; N, 6·0; S, 26·8%).

p-*Nitrophenyl* 2-*Thienyl Sulphone*.—2 : 2′-Dithienyl disulphide (2·5 g.) in alcohol (10 c.c.) was treated with glucose (2·5 g.) in water (5 c.c.) followed by sodium hydroxide (2·5 g.) in water (5 c.c.). The mixture soon became hot and gave a clear solution. After being heated on the steam-bath for 5 minutes the dark brown solution was added to *p*-chloronitrobenzene (4·1 g.) in alcohol (10 c.c.). After 30 hours' boiling the alcohol was evaporated and the residue extracted with ether. The residue from the dried (K_2CO_3) extract gradually deposited crystals which separated from alcohol (charcoal) in bright yellow needles (0·1 g.). p-*Nitrophenyl* 2-*thienyl sulphide* had m. p. 62° depressed by admixture with either *p*-chloronitrobenzene or 2 : 2′-dithienyl disulphide (Found : C, 51·3; H, 3·0; N, 5·9; S, 26·6. $C_{10}H_7O_2NS_2$ requires C, 50·6; H, 3·0; N, 5·9; S, 27·0%).

Oxidation of the sulphide with 30% hydrogen peroxide in acetic acid at 100° gave the *sulphone* which crystallised from alcohol in colourless plates, m. p. 139° (Found : N, 5·4; S, 23·5. $C_{10}H_7O_4NS_2$ requires N, 5·2; S, 23·8%).

Thiophen-2-*sulphinic Acid*.—Thiophen-2-sulphonyl chloride (18·25 g.) was shaken mechanically with a solution of crystalline sodium sulphite (62·5 g.) in water (125 c.c.), the mixture being kept slightly alkaline to phenolphthalein by the frequent addition of a few drops of 50% sodium hydroxide solution. After 1¼ hours the mixture was filtered, acidified with cold 60% sulphuric acid, and extracted with two successive portions of ether (100 c.c.). The combined extracts were dried ($CaCl_2$) and evaporated; the pale yellow oil rapidly solidified in a vacuum desiccator to a crystalline mass, m. p. 72—73° (Weitz, *Ber.*, 1884, **17**, 800, gives m. p. 67°). The acid decomposes slowly when kept at room temperature.

2 : 5-*Dihydroxyphenyl* 2-*Thienyl Sulphone*.—*p*-Benzoquinone (0·54 g.) in warm water (15 c.c.) was added to thiophen-2-sulphinic acid (0·75 g.) in water (10 c.c.). Solid was precipitated immediately and the yellow colour of the quinone discharged. The *sulphone* (1·16 g.) crystallised from water containing a little alcohol in colourless plates, m. p. 186° (Found : S, 25·2. $C_{10}H_8O_4S_2$ requires S, 25·0%).

2-*Thienyl Methyl Sulphone*.—A mixture of thiophen-2-sulphinic acid (2·96 g.), potassium hydroxide (1·12 g.), water (20 c.c.), methyl iodide (3 g.), alcohol (10 c.c.), and traces of iodine and copper powder was boiled for 27 hours. After filtration the alcohol was evaporated and the slightly acidic residue made alkaline with sodium carbonate. The *sulphone* solidified; it crystallised from aqueous alcohol in colourless plates (0·73 g.), m. p. 47° (Found : C, 36·6; H, 3·95; S, 39·3. $C_5H_6O_2S_2$ requires C, 37·0; H, 3·7; S, 39·5%).

Nitration of Thiophen-2-*sulphonyl Chloride*.—The chloride (27 g.) was added gradually during 1 hour to well-stirred fuming nitric acid (110 c.c.) at 25—30°. After being stirred for 2 hours at 40° the mixture was added to crushed ice (350 g.), and the oily product extracted with carbon tetrachloride. Evaporation of the dried ($CaCl_2$) extract gave the mixed nitrothiophen-2-sulphonyl chlorides (26 g.). Distillation then gave two fractions, b. p. 130—134°/0·9 mm. and 135—140°/0·9 mm. When kept, the latter fraction solidified almost completely to pale yellow crystals, m. p. 42—44°, which turned orange when exposed to light. Recrystallisation from benzene–ligroin (b. p. 60—80°) gave 4-*nitrothiophen*-2-*sulphonyl chloride* in almost colourless long prisms, m. p. 48°, unchanged by further crystallisation (Found : N, 6·2. $C_4H_2O_4NClS_2$ requires N, 6·15%). A small amount of the same chloride also crystallised from the first fraction and was separated by filtration.

Hydrolysis of this chloride (0·8 g.) by boiling water (4 c.c.) for 1½ hours followed by the addition of water (5 c.c.) and concentrated sulphuric acid (7 c.c.) and distillation in superheated steam gave, at 130—150° (temperature of reaction mixture), 3-nitrothiophen (0·29 g.; 64%), m. p. 74—76°, after crystallisation from alcohol.

4-*Nitrothiophen*-2-*sulphonamide*.—In initial experiments the oily mixture of nitrothiophen-2-sulphonyl chlorides was added slowly to a mixture of acetone (20 c.c.) and aqueous ammonia (*d* 0·88) (20 c.c.) at 5—10°. After filtration from ammonium chloride the acetone solution was evaporated to dryness and the residue crystallised from water. Fractional crystallisation from butyl alcohol gave a dark brown crystalline product, m. p. 156—157°, unchanged by further crystallisation.

The solid chloride (above) (4·8 g.) in acetone (15 c.c.) was added slowly to a cold saturated solution of ammonia in acetone (75 c.c.) and the mixture again saturated with ammonia. Filtration, followed by evaporation of the acetone under reduced pressure, gave an oil which solidified on being stirred with water. The *sulphonamide* (2·4 g.) crystallised from water in pale brown, lustrous plates, m. p. 164°, unchanged by further crystallisation (Found : N, 13·9. $C_4H_4O_4N_2S_2$ requires N, 13·5%).

5-*Nitrothiophen*-2-*sulphonamide*.—The liquid nitrothiophen-2-sulphonyl chloride left after removal of the solid isomer, m. p. 48°, was refractionated and the lower-boiling material, from which no solid separated, was hydrolysed and desulphonated as above. A very small amount of 3-nitrothiophen distilled at 135—145°, but at 150—175° the distillate consisted entirely of 2-nitrothiophen, m. p. 43—44°.

Treatment of the liquid chloride with ammonia in acetone as described above gave the *sulphonamide*, almost colourless plates from water, m. p. 136° (Found : N, 13·2. $C_4H_4O_4N_2S_2$ requires N, 13·5%).

4-*Aminothiophen*-2-*sulphonamide*.—The nitrosulphonamide, m. p. 164°, was reduced with hydrogen in the presence of Raney nickel and absolute alcohol at ordinary temperature and pressure. Evaporation of the alcoholic solution under reduced pressure to a small volume and addition of ligroin (b. p. 60—80°) gave the *amino-sulphonamide* in colourless, flattened needles, m. p. 133° (decomp.), unchanged by recrystallisation from alcohol–ligroin (Found : C, 27·2; H, 3·5; N, 15·7; S, 36·3. $C_4H_6O_2N_2S_2$ requires C, 27·0; H, 3·4; N, 15·7; S, 36·0%).

5-Aminothiophen-2-sulphonamide was obtained similarly as an amorphous solid, m. p. 116—118° (decomp.), which could not be obtained crystalline. A crystalline benzoyl derivative could not be prepared.

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