794. *Potential Thiophen Chemotherapeutics. Part V.* Preparation and Proof of Structure of Some Substituted 5-Aminothiophen-2-sulphonamides.†*

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Nitration of methyl 2-thienyl sulphide gave the 5-nitro-compound, converted into methyl 5-phthalimido-2-thienyl sulphone. The unstable 5-*o*-carboxybenzamidothiophen-2-sulphinic acid lost sulphur dioxide and could not be transformed into the methyl sulphone.

Pure 5-nitrothiophen-2-sulphonyl chloride has been obtained by nitration of thiophen-2-sulphonyl chloride (improved preparation) and converted into 5-phthalimidothiophen-2-sulphonamide, which was opened to the phthalamic acid. Analogous reactions led to *N*-(5-sulphonamido-2-thienyl)succinamic acid, also obtained from 5-nitrothiophen-2-sulphonamide. The 2 : 5-orientation has been rigidly established for all these compounds.

In work on the synthesis of 5-aminothiophen-2-sulphonamide, the thiophen isostere of sulphanilamide, some thiophen compounds related to " Succinylsulphathiazole " 2-*p*-β-carboxypropionamidobenzenesulphonamidothiazole) and its phthaloyl analogue have been prepared.

Rigid proof of the 2 : 5-orientation was attempted by the preparation of methyl 5-phthalimido-2-thienyl sulphone independently from 2-nitrothiophen and methyl 2-thienyl sulphide.

Although potassiocarbazole condenses with, *e.g.*, *p*-bromochlorobenzene,[1] the more weakly basic potassiophthalimide did not react with 2-bromo- or 2-iodo-thiophen,[2] or with the activated 5-iodo-2-thienyl methyl sulphone [2] in dimethylformamide, with or without a copper catalyst, and attempted condensation with *o*- or *p*-chloronitrobenzene failed even at 200°.

Methyl 2-thienyl sulphide and acetyl nitrate (cf. Rinkes [3]) gave methyl 5-nitro-2-thienyl sulphide, and thence the sulphone, reduction of which in presence of phthalic anhydride afforded methyl 5-phthalimido-2-thienyl sulphone ; this was converted into *N*-(5-methylsulphonyl-2-thienyl)phthalamic acid by sodium hydrogen carbonate.

2-Phthalimidothiophen was prepared by direct treatment of 2-thienylammonium chlorostannate with sodium acetate, acetic acid, and phthalic anhydride without isolation of the unstable 2-aminothiophen.

Reduction of 5-phthalimidothiophen-2-sulphonyl chloride was accompanied by ring-opening, giving 5-*o*-carboxybenzamidothiophen-2-sulphinic acid. This was exceedingly unstable, losing sulphur dioxide at room temperature (half-life *ca.* 90 min.) to give *N*-2-thienylphthalamic acid, also obtained on drying *in vacuo* at room temperature for 10 min. or on attempted recrystallisation.

Attempted alkylation of the disodium salt of 5-*o*-carboxybenzamidothiophen-2-sulphinic acid with methyl iodide or sulphate [4] was unsuccessful, and treatment of the silver salt with methyl iodide led only to methyl *N*-2-thienylphthalamate. No identifiable product was obtained from 5-*o*-carboxybenzamidothiophen-2-sulphinic acid and diazomethane.

Reduction of 5-phthalimidothiophen-2-sulphonyl chloride with zinc and sulphuric acid [5] gave only 1% of the supposed 5-phthalimidothiophen-2-thiol (m. p. 135°). The alkali-soluble product from reduction [6] of the sulphonyl chloride by lithium aluminium hydride

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[1] Montmollin and Montmollin, *Helv. Chim. Acta*, 1923, **6**, 94.
[2] Cymerman-Craig and Loder, *J.*, 1954, 237.
[3] Rinkes, *Rec. Trav. chim.*, 1932, **51**, 1134.
[4] Baldwin and Robinson, *J.*, 1932, 1445.
[5] Zinke and Jorg, *Ber.*, 1909, **42**, 3362.
[6] Marvel and Caesar, *J. Amer. Chem. Soc.*, 1950, **72**, 1033.

decomposed on reaction with methyl iodide, and treatment of the sulphonyl chloride with hydriodic acid in acetic acid [7] proved abortive, none of the disulphide being isolated.

An alternative approach was evolved from thiophen-2-sulphonyl chloride, prepared by an improved direct method instead of the customary preparation [8,9] *via* sodium thiophen-2-sulphonate. Nitration by a modification of Burton and Davy's method [9] gave the mixed 4- and 5-nitrothiophen-2-sulphonyl chlorides, containing a somewhat higher proportion of the 5-nitro-compound which was obtained pure for the first time. Reduction of this afforded *N*-(5-sulphonamido-2-thienyl)phthalamic acid, identical with the compound obtained by successive treatment of 5-phthalimidothiophen-2-sulphonyl chloride with ammonia and sodium hydrogen carbonate. This synthesis confirms the 2 : 5-orientation of the compounds derived from 2-phthalimidothiophen in this and an earlier paper,[10] and affords rigid proof of the configuration of 5-nitrothiophen-2-sulphonyl chloride, previously shown [8] (in admixture with the 4-nitro-compound) only to give both 2- and 3-nitrothiophen on hydrolysis and desulphonation.

While 5-phthalimidothiophen-2-sulphonyl chloride and aniline gave 5-phthalimidothiophen-2-sulphonanilide, the more strongly basic 2-aminopyridine caused simultaneous ring-opening, affording 2-(5-*o*-carboxybenzamidothiophen-2′-sulphonamido)pyridine.

Reaction of 2-aminothiophen with succinic anhydride gave *N*-2-thienylsuccinamic acid, cyclised to 2-succinimidothiophen and thence converted, *via* 5-succinimidothiophen-2-sulphonyl chloride, into the sulphonamide. Ring-opening gave *N*-(5-sulphonamido-2-thienyl)succinamic acid, also obtained by reduction of 5-nitrothiophen-2-sulphonamide in presence of succinic anhydride. The identity of the two compounds affords proof of the 2 : 5-orientation of the succinimido-compounds of this series. Those sulphonamides soluble in sodium hydrogen carbonate are being examined for antibacterial activity.

Experimental

Methyl 5-Nitro-2-thienyl Sulphide.—A mixture of nitric acid (7 c.c., *d* 1·51, 0·17 mole) and acetic anhydride (20 c.c.) was added dropwise with stirring to methyl 2-thienyl sulphide (17·5 g., 0·14 mole) in acetic anhydride (25 c.c.) at $< -10°$. The mixture was stirred for a further 0·5 hr. at $-10°$, poured on ice, and extracted with ether. Distillation of the washed (sodium carbonate solution) and dried (Na_2SO_4) extracts gave *methyl 5-nitro-2-thienyl sulphide* (9 g., 40%), b. p. 106—112°/0·01 mm., yellowish plates (from hexane), m. p. 81—82° (Found: C, 34·2; H, 2·8. $C_5H_5O_2NS_2$ requires C, 34·25; H, 2·9%).

Methyl 5-Nitro-2-thienyl Sulphone.—Methyl 5-nitro-2-thienyl sulphide (2 g., 0·011 mole), 30% hydrogen peroxide (5·4 c.c., 0·05 mole), and acetic acid (20 c.c.) were heated at 100° for 45 min., poured on ice, neutralised with 2N-sodium hydroxide, and extracted with ether. Working-up gave the *sulphone* (1·2 g., 50%) as fawn needles (from aqueous alcohol), m. p. 93—94° (Found: C, 29·0; H, 2·6. $C_5H_5O_4NS_2$ requires C, 29·0; H, 2·45%).

Methyl 5-Phthalimido-2-thienyl Sulphone.—A solution of methyl 5-nitro-2-thienyl sulphone (7·5 g., 0·036 mole) and phthalic anhydride (5·4 g., 0·036 mole) in acetic acid (50 c.c.) was treated with water (10 c.c.) and reduced iron powder (10 g., 0·18 mole) for 2 hr. at 50—60°. Stirring was continued for a further 2·5 hr., and the mixture poured into ice-water (300 c.c.) and extracted with chloroform. The extracts were washed with sodium hydrogen carbonate solution and on removal of solvent gave *methyl 5-phthalimido-2-thienyl sulphone* (8·2 g., 72%), crystallising from chloroform–light petroleum (b. p. 60—90°) as plates, m. p. 220° (Found: C, 50·65; H, 3·05; O, 20·4. $C_{13}H_9O_4NS_2$ requires C, 50·8; H, 2·95; O, 20·8%).

N-(5-*Methylsulphonyl-2-thienyl*)*phthalamic Acid.*—Methyl 5-phthalimido-2-thienyl sulphone (2 g.) and saturated sodium hydrogen carbonate solution (20 c.c.) were kept at 100° for 5 min., then filtered and acidified at 0° with 2N-hydrochloric acid, affording the *phthalamic acid* (1·9 g., 90%), crystallising from acetone–light petroleum (b. p. 60—90°) as prisms, m. p. 220° (Found: C, 48·0; H, 3·5. $C_{13}H_{11}O_5NS_2$ requires C, 48·0; H, 3·4%).

5-o-*Carboxybenzamidothiophen-2-sulphinic Acid.*—(*a*) 5-Phthalimidothiophen-2-sulphonyl

[7] Bauer and Cymerman, *J.*, 1949, 3434.
[8] Steinkopf and Höpner, *Annalen*, 1933, **501**, 174.
[9] Burton and Davy, *J.*, 1948, 525.
[10] Cymerman-Craig and Willis, *J.*, 1955, 1071.

chloride (3·7 g., 0·011 mole) was added slowly to a stirred solution of sodium sulphite heptahydrate (5·4 g., 0·022 mole) in water (30 c.c.) at 70°, the pH being kept at 8 by addition of sodium hydrogen carbonate. Stirring at 70° was continued for a further 2 hr., and the filtered solution acidified at 0° with 2N-sulphuric acid. The white precipitate was washed with ice-water and quickly dried on porous tile over phosphoric oxide, giving the *sulphinic acid* (3·1 g., 94%), m. p. 138° (Found : C, 44·95; H, 3·2. $C_{12}H_9O_5NS_2,0{\cdot}5H_2O$ requires C, 45·0; H, 3·15%).

(*b*) 5-Phthalimidothiophen-2-sulphonyl chloride (1·64 g., 0·005 mole), zinc dust (1 g., 0·015 mole), water (4 drops), and 1 : 2-dimethoxyethane (20 c.c.) were refluxed for 2 hr. The cooled solution was filtered, the solid boiled with a solution of sodium carbonate (1 g.) in water (5 c.c.), the whole filtered, and the filtrate acidified at 0° as in (*a*), affording the sulphinic acid (0·65 g., 42%), m. p. and mixed m. p. 138°. Extraction of the residual zinc salts with chloroform gave 2-phthalimidothiophen (0·4 g., 35%), m. p. and mixed m. p. 198°.

(*c*) Attempted recrystallisation of the sulphinic acid from non-hydroxylic solvents, or drying *in vacuo*, gave *N*-2-thienylphthalamic acid, m. p. and mixed m. p. 185° (Found : C, 58·2; H, 3·75. Calc. for $C_{12}H_9O_3NS$: C, 58·3; H, 3·7%).

(*d*) On attempted recrystallisation of the sulphinic acid from hydroxylic solvents, or on storage of it in acid solution, 2-phthalimidothiophen was formed (m. p. and mixed m. p. 198°) (Found : C, 62·9; H, 3·15. Calc. for $C_{12}H_7O_2NS$: C, 62·8; H, 3·1%).

Methyl N-2-*Thienylphthalamate*.—The preceding sulphinic acid (1·6 g., 0·005 mole) was dissolved in cold sodium hydrogen carbonate solution and the solution brought to pH 7·5 with dilute nitric acid. Addition of silver nitrate solution gave a white silver salt which was filtered off and refluxed with aqueous methanol (3 : 7) (30 c.c.) and methyl iodide (10 mols.) for 8 hr. Removal of solvent *in vacuo* and addition of water to the residue gave *methyl* N-2-*thienylphthalamate* (0·7 g., 56%) as needles [from chloroform–light petroleum (b. p. 60—90°)], m. p. 154° (Found : O, 18·2; N, 4·75; S, 12·5. $C_{13}H_{11}O_3NS$ requires O, 18·3; N, 5·25; S, 12·25%).

N-2-*Thienylphthalamic Acid*.—A benzene solution of 2-aminothiophen, prepared from 2-thienylammonium chlorostannate (5·6 g., 0·01 mole) by the method of Cymerman-Craig and Willis,[10] was shaken with phthalic anhydride (3 g., 0·02 mole) in acetone (50 c.c.) in an inert atmosphere for 1 hr. Removal of solvent *in vacuo*, extraction of the residue with cold saturated sodium hydrogen carbonate (3 × 30 c.c.), and acidification of the extract with 10N-hydrochloric acid gave the phthalamic acid (2·1 g., 41%), m. p. 185°, identical with the material described by Cymerman-Craig and Willis.[10]

2-*Phthalimidothiophen*.—2-Thienylammonium chlorostannate (10·6 g., 0·02 mole) was added during 15 min. to a stirred solution of sodium acetate (3·28 g., 0·04 mole), phthalic anhydride (5·92 g., 0·04 mole), and acetic acid (100 c.c.) at 60°, and the mixture heated for a further 2 hr., then poured on ice (500 g.) and extracted with chloroform. The extracts afforded yellow needles of 2-phthalimidothiophen (3·8 g., 42%), m. p. 198°, undepressed on admixture with the material of Cymerman-Craig and Willis.[10]

N-(5-*Sulphonamido*-2-*thienyl*)*phthalamic Acid*.—(*a*) 5-Phthalimidothiophen-2-sulphonamide was gently boiled with sodium hydrogen carbonate solution for 5 min., then filtered, and the filtrate acidified at 0° with 2N-hydrochloric acid, giving the *phthalamic acid* as plates, m. p. 261° (Found : C, 44·05; H, 3·45; S, 19·1; O, 24·6. $C_{12}H_{10}O_5N_2S_2$ requires C, 44·15; H, 3·1; S, 19·6; O, 24·5%).

(*b*) When this acid was heated at 200° for 30 min. at 0·01 mm., it re-cyclised to 5-phthalimidothiophen-2-sulphonamide, m. p. 261°, in 80% yield (Found : C, 46·7; H, 2·75. Calc. for $C_{12}H_8O_4N_2S_2$: C, 46·75; H, 2·6%).

5-*Phthalimidothiophen*-2-*sulphonanilide*.—A solution of 5-phthalimidothiophen-2-sulphonyl chloride (0·33 g., 0·001 mole) in acetone (10 c.c.) was treated with aniline (0·19 g., 0·002 mole) and set aside for 48 hr. Addition of ether and extraction of the resulting precipitate with benzene gave the *sulphonanilide* (0·21 g., 62%), crystallising from benzene–light petroleum (b. p. 60—90°) as yellow plates, m. p. 226° (Found : C, 56·2; H, 3·3; S, 16·6. $C_{18}H_{12}O_4N_2S_2$ requires C, 56·25; H, 3·15; S, 16·65%).

2-(5′-o-*Carboxybenzamidothiophen*-2′-*sulphonamido*)*pyridine*.—A solution of 5-phthalimidothiophen-2-sulphonyl chloride (0·33 g., 1 mol.) and 2-aminopyridine (0·2 g., 2 mols.) in acetone (10 c.c.) was kept for 48 hr. and worked up by addition of ether and extraction of the precipitate into benzene, affording the *phthalamic acid* as colourless needles (0·1 g., 24%), m. p. 231° (Found : C, 50·4; H, 3·45. $C_{17}H_{13}O_5N_3S_2$ requires C, 50·5; H, 3·25%).

Thiophen-2-*sulphonyl Chloride*.—Thiophen (75 g., 0·9 mole) was added during 1 hr. to stirred chlorosulphonic acid (300 g., 1·7 moles) at −15°, at such a rate that the temperature did not rise above −5°. After addition of an equal volume of chloroform, the mixture was

poured on ice, and the chloroform layer separated and washed with ice-water. Distillation gave thiophen-2-sulphonyl chloride, b. p. 94—98°/1·5 mm., as a colourless oil (117 g., 72%). Treatment of a sample with ammonia in chloroform gave thiophen-2-sulphonamide, m. p. and mixed m. p. 142°, in quantitative yield. Burton and Davy [9] report a 50% yield of this sulphonyl chloride by Steinkopf and Hopner's method.[8]

5-Nitrothiophen-2-sulphonyl Chloride.—Thiophen-2-sulphonyl chloride (40 g., 0·23 mole) was added during 1 hr. to well-stirred fuming nitric acid (250 g., 165 c.c., 4 moles, *d* 1·51) at 0—5°. After a further 2 hours' stirring at 25—30°, the mixture was cooled, diluted with an equal volume of chloroform and poured on ice (500 g.). Distillation of the dried ($CaCl_2$) chloroform extracts gave 3 fractions: (i) b. p. 96—100°/0·001 mm. (4·7 g.), n_D^{22} 1·6020, (ii) b. p. 100—103°/0·001 mm. (7·3 g.), n_D^{22} 1·6020, (iii) b. p. 103—108°/0·001 mm. (26 g.), n_D^{22} 1·6033. Fractions (i) and (ii) were pure *5-nitrothiophen-2-sulphonyl chloride* (Found: C, 21·1; H, 0·95. $C_4H_2O_4NS_2Cl$ requires C, 21·1; H, 0·9%) and gave a sulphonamide, m. p. 138°. Fraction (iii) was a mixture of 5- and 4-nitrothiophen-2-sulphonyl chlorides, and gave a sulphonamide, m. p. 155°, unchanged on recrystallisation. Burton and Davy [9] report m. p. 156—157° for the mixed sulphonamide. The total yield of mixed sulphonyl chlorides was 38 g. (76%).

5-Nitrothiophen-2-sulphonamide.—The following method was found preferable to that described by Burton and Davy: Dry ammonia was passed into a solution of 5-nitrothiophen-2-sulphonyl chloride in chloroform for 5 min., the chloroform was washed with water and evaporated *in vacuo*, and the residue crystallised from water as fawn plates, m. p. 138° (Found: C, 23·05; H, 2·15. Calc. for $C_4H_4O_4N_2S_2$: C, 23·1; H, 1·95%). Burton and Davy [9] give m. p. 136°.

N-(5-Sulphonamido-2-thienyl)phthalamic Acid from 5-Nitrothiophen-2-sulphonamide.—Preparation from 5-nitrothiophen-2-sulphonamide (1 g., 0·005 mole), phthalic anhydride (0·71 g., 0·005 mole), acetic acid (10 c.c.), and reduced iron powder (1·25 g., 0·02 mole) by the method described for methyl 5-phthalimido-2-thienyl sulphone, and treatment of the product with sodium hydrogen carbonate solution gave, on acidification of the filtrate, *N*-(5-sulphonamido-2-thienyl)phthalamic acid (0·49 g., 31%), crystallising from acetone–light petroleum (b. p. 60—90°) as plates, m. p. 261° (Found: C, 44·15; H, 3·4. Calc. for $C_{12}H_{10}O_5N_2S_2$: C, 44·15; H, 3·1%). A mixed m. p. with the product from 5-phthalimidothiophen-2-sulphonamide was undepressed.

N-2-Thienylsuccinamic Acid.—A benzene solution of 2-aminothiophen, prepared from 2-thienylammonium chlorostannate (5·6 g., 0·01 mole), was added to succinic anhydride (2·1 g., 0·02 mole) in benzene (50 c.c.) in an inert atmosphere. The mixture was shaken for 4 hr., and the solid filtered off and crystallised from acetone–light petroleum (b. p. 60—90°), giving plates, m. p. 167·5°, of the *acid* (2·5 g., 61%) (Found: C, 47·9; H, 4·7; S, 15·85. $C_8H_9O_3NS$ requires C, 48·2; H, 4·6; S, 16·1%).

2-Succinimidothiophen.—After the preceding acid (2 g.) had been heated at 175° for 2 min., the residue was extracted with benzene and purified by passage through a column of alumina, *2-succinimidothiophen* (1·1 g., 61%) being obtained as needles, m. p. 150—150·5° (decomp.) (Found: C, 53·4; H, 4·15; O, 17·3. $C_8H_7O_2NS$ requires C, 53·05; H, 3·9; O, 17·6%).

5-Succinimidothiophen-2-sulphonyl Chloride.—Reaction of 2-succinimidothiophen (5·7 g., 0·03 mole) and chlorosulphonic acid (18·3 g., 1·05 mole) at −5° by the method used for the preparation of the phthalimido-analogue by Cymerman-Craig and Willis,[10] gave *5-succinimidothiophen-2-sulphonyl chloride* (2·65 g., 30%) as needles (from chloroform), m. p. 138—140° (Found: C, 34·55; H, 2·6; N, 4·8; S, 23·0. $C_8H_6O_4NS_2Cl$ requires C, 34·35; H, 2·2; N, 5·0; S, 22·95%).

5-Succinimidothiophen-2-sulphonamide.—Treatment of the foregoing sulphonyl chloride (0·7 g.) in chloroform (30 c.c.) with dry ammonia, followed by purification of the product by dissolution in cold N-sodium hydroxide and precipitation at 0° with 2N-hydrochloric acid, gave the *sulphonamide* (0·6 g., 90%) as needles, m. p. 218° (Found: C, 36·0; H, 3·6. $C_8H_8O_4N_2S_2$ requires C, 36·0; H, 3·1%).

N-(5-Sulphonamido-2-thienyl)succinamic Acid.—(*a*) A solution of 5-succinimidothiophen-2-sulphonamide (0·32 g.) in N-sodium hydroxide (4·5 c.c.) was set aside at room temperature for 24 hr. The solution was acidified with 2N-hydrochloric acid, giving the *acid* (0·24 g., 69%) as prisms, m. p. 216—218° (decomp.) (Found: C, 34·25; H, 4·0; O, 28·5; N, 9·7; S, 23·25. $C_8H_{10}O_5N_2S_2$ requires C, 34·5; H, 3·65; O, 28·7; N, 10·0; S, 23·05%).

(*b*) Preparation from 5-nitrothiophen-2-sulphonamide (1 g.) and succinic anhydride (0·5 g., 1 mol.) by reduction with iron powder in acetic acid, as described above for the analogous phthalamic acid, gave the acid as plates, m. p. 216° (decomp.) (0·5 g., 30%) (Found: C, 34·85;

H, 3·8%). When the acid (0·4 g.) was heated for 5 min. at 200°/1 mm., it cyclised to give 5-succinimidothiophen-2-sulphonamide (0·3 g., 60%), crystallising from acetone–light petroleum (b. p. 60—90°) as needles, m. p. 218°, undepressed on admixture with the substance obtained from 5-succinimidothiophen-2-sulphonyl chloride.

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