Potential Thiophen Chemotherapeutics. Part IV. The Thiophen Analogues of* p-*Acetamidobenzaldehyde Thiosemicarbazone and Sulphanilamide.*

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Formylation of 2-acetamidothiophen (whose preparation from methyl 2-thienyl ketoxime is improved) gave 2-acetamido-5-formylthiophen, the structure of which was rigidly proved by an alternative synthesis from 2-formylthiophen.

2-Phthalimidothiophen was converted into 5-phthalimidothiophen-2-sulphonamide. On attempted hydrolysis, both these compounds either resisted hydrolysis or underwent ring fission, but the analogous 4-phthalimidobenzenesulphonamide was hydrolysed normally.

IN view of the tuberculostatic properties of thiosemicarbazones of aromatic and heterocyclic aldehydes, notably *p*-acetamidobenzaldehyde thiosemicarbazone (Behnisch, Mietzsch, and Schmidt, *Angew. Chem.*, 1948, **60**, 113; Hoggarth, Martin, Storey, and Young, *Brit. J. Pharmacol.*, 1949, **4**, 248), it was of interest to prepare the thiophen isostere of this compound.

2-Acetamidothiophen has been obtained by acetylation of the unstable 2-aminothiophen (Steinkopf, *Annalen*, 1914, **403**, 17; Lew and Noller, *J. Amer. Chem. Soc.*, 1950, **72**, 5715), and the Schmidt reaction on methyl 2-thienyl ketone gave a mixture of 2-acetamidothiophen and the isomeric *N*-methyl-2-thenoylamine (Hurd and Moffat, *J. Amer. Chem. Soc.*, 1951, **73**, 613). The Beckmann rearrangement of the more accessible methyl 2-thienyl

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ketoxime with phosphorus pentachloride has been reported by Steinkopf and by Hurd and Moffat (*locc. cit.*) to give very poor yields of amide. Repetition of Steinkopf's procedure gave 5—10% of amide until it was found that 2-acetamidothiophen was readily soluble in the cold at pH 1, but insoluble above pH 2. It was thus not extracted from the acid media resulting from the hydrolysis of phosphorus pentachloride, but by buffering the solution to pH 5—6 before extraction, the yield was readily raised to 55%. Similar solubility has been observed with 2-acetamidomethylthiophen (Cymerman and Faiers, *J.*, 1952, 165) and 5-acetamidomethylthiophen-2-sulphonic acid (Cymerman-Craig and Loder, *J.*, 1954, 237).

Attempts to carry out the Beckmann rearrangement of methyl 2-thienyl ketoxime with agents other than phosphorus pentachloride failed (cf. Hurd and Moffat, *loc. cit.*). Ethereal hydrogen chloride left the oxime unchanged, while hydrogen chloride in acetic anhydride (Beckmann, *Ber.*, 1887, **20**, 2581) gave the stable oxime acetate.

Reaction of 2-acetamidothiophen with *N*-methylformanilide and phosphorus oxychloride (1—3 mols.) at 0—5° by King and Nord's method (*J. Org. Chem.*, 1948, **13**, 635) gave an oil containing 45—69% of the desired 2-acetamido-5-formylthiophen (estimated as the semicarbazone); although its pure derivatives were readily obtained from the oily product, the pure aldehyde was obtained only by carrying out the reaction at 0—5° in dimethylformamide (74% yield) (cf. *Chem. and Ind.*, 1953, 797).

2-Acetamido-5-formylthiophen thiosemicarbazone was tested against *Mycobacterium tuberculosis* H37Rv by Professor S. D. Rubbo who reports it to be active *in vitro* at a concentration of M/512,000 in Youman's medium, in the presence or absence of 10% of serum.

Attempted regeneration of the aldehyde from its semicarbazone (Kon, *J.*, 1930, 1616) failed with both 2% and 10% sulphuric acid at room temperature, while more vigorous conditions gave evidence of hydrolysis of the acetamido-group. Its structure was proved by an alternative synthesis from 2-formylthiophen. The aldehyde diacetate was obtained in 78% yield by a modification, using anhydrous zinc chloride as catalyst, of Patrick and Emerson's method (*J. Amer. Chem. Soc.*, 1952, **74**, 1356), which employed stannous chloride and gave a low yield in our hands. These authors nitrated the aldehyde diacetate, and proved the structure of the 5-nitro-aldehyde diacetate by hydrolysis, oxidation, and conversion into the known methyl 5-nitro-2-thenoate. The nitro-aldehyde diacetate was subjected to reductive acetylation with iron and acetic anhydride in acetic acid, the product (after brief acid hydrolysis) giving crystalline derivatives identical with those of 2-acetamido-5-formylthiophen obtained previously.

After this work had been completed, Campaigne and Archer (*J. Amer. Chem. Soc.*, 1953, **75**, 989) reported the synthesis of 2-acetamido-5-formylthiophen in 47% yield from 2-acetamidothiophen and dimethylformamide alone at elevated temperatures, and also prepared its thiosemicarbazone (Campaigne, Monroe, Arnwine, and Archer, *ibid.*, p. 988). These authors also claim a proof of structure of the aldehyde by oxidation to the corresponding acid, m. p. 271—272°, but the configuration of this acid has not been definitely settled: it is described by Steinkopf and Muller (*Annalen*, 1926, **448**, 210) as 4-acetamido-2-thenoic acid, and was obtained by these authors from a nitro-2-thenoic acid which gave both 2- and 3-nitrothiophen on decarboxylation and was shown later by Rinkes (*Rec. Trav. chim.*, 1932, **51**, 1134) to consist of 5-nitro-2-thenoic acid accompanied by the 4-nitro-isomer. Since our 2-acetamido-5-formylthiophen was identical with that of Campaigne and Archer (*loc. cit.*), the alternative synthesis from 2-formylthiophen described above also proves that Steinkopf and Muller's acid, m. p. 271—272°, was in fact the 5-isomer.

The preparation of 2-aminothiophen-5-sulphonamide, the thiophen analogue of sulphanilamide, has been attempted by a number of workers. Nitration of thiophen-2-sulphonyl chloride (Burton and Davy, *J.*, 1948, 525) and chlorosulphonation of 2-nitrothiophen (Lew and Noller, *loc. cit.*) gave only 5-aminothiophen-3-sulphonamide; chlorosulphonation of 2-acetamidothiophen (Lew and Noller, and Hurd and Moffat, *locc. cit.*) afforded only a disulphonyl chloride; and attempted conversion of 5-acetamidothiophen-2-sulphonic acid (Hurd and Priestley, *J. Amer. Chem. Soc.*, 1947, **69**, 859) into the sulphonyl chloride proved abortive (cf. Dann and Moller, *Chem. Ber.*, 1947, **80**, 23).

Re-investigation confirmed that chlorosulphonation of 2-acetamidothiophen at temperatures between −5° and 50° gave only sulphonic acids, while the action of sulphuryl chloride, reported to act as both chlorinating and chlorosulphonating agent (Tohl and Eberhard, *Ber.*, 1893, **26**, 2940; Boeseken, *Rec. Trav. chim.*, 1911, **30**, 382), on the same compound gave 2-acetamido-5-chlorothiophen (70%), previously obtained in 9% yield (Hurd and Moffat, *loc. cit.*) by the action of *N*-chloroacetamide on 2-acetamidothiophen.

The use of 2-phthalimidothiophen offered the possibility of reducing disubstitution. Reaction of 2-aminothiophen with phthalic anhydride in benzene gave *N*-2-thienylphthalamic acid; reaction in xylene gave 2-phthalimidothiophen, also obtained (80%) by dehydration of the phthalamic acid. Use of dimethylformamide as solvent did not improve the yield, and attempted reaction of potassium phthalimide in dimethylformamide solution (Sheehan and Bolhofer, *J. Amer. Chem. Soc.*, 1950, **72**, 2786) with 2-bromo- or 2-iodo-thiophen was unsuccessful.

Reduction of nitrobenzene with iron and acetic acid in presence of phthalic anhydride yielded *N*-phenylphthalimide, and similar treatment of 2-nitrothiophen gave 20% (overall) of 2-phthalimidothiophen. Reduction of 2-nitrothiophen with iron and hydrochloric acid and reaction of the amine hydrochloride with phthaloyl chloride in pyridine gave similar results.

Chlorosulphonation of 2-phthalimidothiophen gave 55% of 5-phthalimidothiophen-2-sulphonyl chloride, smoothly converted into the sulphonamide. By analogy with previous work (Cundiff and Estes, *ibid.*, p. 1424; Steinkopf and Kohler, *Annalen*, 1937, **532**, 264; Cymerman-Craig and Loder, *loc. cit.*) chlorosulphonation is presumed to have occurred in the 5-position; an attempted proof of the 2 : 5-orientation is in progress.

Attempted hydrolysis of 5-phthalimidothiophen-2-sulphonamide by Ing and Manske's method (*J.*, 1926, 2348), by alcoholic sodium ethoxide and hydrazine (cf. Grassmann and Schulte-Uebbing, *Chem. Ber.*, 1950, **83**, 244), by phenylhydrazine in presence of triethylamine (Schumann and Boissonas, *Helv. Chim. Acta*, 1952, **35**, 2235; Scheiber, *Ber.*, 1913, **46**, 1103), or by hydrazine in dimethylformamide or pyridine at 0°, was unsuccessful. Although phthalhydrazide was always formed in good yield, this was accompanied by the evolution of hydrogen sulphide and no basic product could be isolated. 2-Phthalimidothiophen was also immediately cleaved by Ing and Manske's method with evolution of hydrogen sulphide. Acidic or alkaline hydrolysis of 5-phthalimidothiophen-2-sulphonamide proved equally abortive, and either (saturated alcoholic hydrogen chloride or 20% sodium hydroxide) left the compound unchanged or (concentrated hydrochloric acid at 150°) completely ruptured the molecule with formation of phthalic acid, ammonium chloride, and hydrogen sulphide.

The analogous *p*-phthalimidobenzenesulphonamide, prepared by a modification of Wanag and Veinbergs's method (*Ber.*, 1942, **75**, 1558), is reported (Picard, Reid, Reynolds, and Seymour, *J.*, 1948, 821) to give sulphanilamide on acid, and 4-phthalamidobenzenesulphonamide on alkaline hydrolysis. It was unattacked by hydrazine in 5% sodium hydroxide solution or by phenylhydrazine in triethylamine, but was readily cleaved in the expected manner by hydrazine in amyl alcohol at 140° or in dimethylformamide at 20°.

The case with which the 2-phthalimidothiophen compounds undergo ring-opening is clearly due to the nitrogen atom attached to the ring, and may occur after hydrolysis to the amine, which then decomposes through the tautomeric imino-form (an imino-sulphide) (cf. Hurd and Kreuz, *J. Amer. Chem. Soc.*, 1950, **72**, 5543; 1952, **74**, 2965), since 2-phthalimidomethylthiophen derivatives are hydrolysed normally (Cymerman and Faiers, and Cymerman-Craig and Loder, *locc. cit.*).

Further work directed towards the preparation of 5-aminothiophen-2-sulphonamide is in progress.

Experimental

2-Acetamidothiophen.—Methyl 2-thienyl ketoxime (28 g.) in dry ether (300 c.c.) was treated during 15 min. with phosphorus pentachloride (42 g.), the reaction being moderated by occasional cooling (ice). After 30 min., water (50 c.c.) was added dropwise at such a rate that the internal temperature remained below 20°. Sodium hydroxide solution was added with strong

cooling until the pH was 5—6; ether then extracted the crude product. Chromatography in benzene solution on alumina gave 2-acetamidothiophen (15·4 g., 55%) as plates, m. p. 155—156°. One crystallisation from chloroform–benzene raised the m. p. to 160°. Steinkopf (*loc. cit.*) gives m. p. 161—162°.

2-*Formylthiophen Diacetate*.—2-Formylthiophen (56 g.) was added to acetic anhydride (65 g.), acetic acid (10 c.c.), and anhydrous zinc chloride (1 g.) at <15°. The solid which separated after 8 hr. at room temperature was washed with water and sodium hydrogen carbonate solution, combined with a benzene extract of the neutralised (sodium hydrogen carbonate) mother-liquors, and distilled to give (*a*) 2-formylthiophen (5·5 g.) and (*b*) 2-formylthiophen diacetate (75 g., 78%), b. p. 98—104°/0·3 mm., m. p. 65—67°. Patrick and Emerson (*loc. cit.*) record m. p. 66—68°.

2-*Acetamido-5-formylthiophen*.—(*a*) Phosphorus oxychloride (14·5 g.) was added dropwise to a stirred solution of 2-acetamidothiophen (10 g.) and *N*-methylformanilide (11·5 g.) in dimethylformamide (25 c.c.) at <10°. The hard yellow cake of aldehyde which was formed after 1 hr. was triturated with benzene, washed with aqueous sodium acetate, and crystallised from ethyl acetate as needles, m. p. 181—182° (8·8 g., 74·5%) (Found: C, 49·75; H, 4·2; N, 8·1; S, 19·1. Calc. for $C_7H_7O_2NS$: C, 49·7; H, 4·2; N, 8·3; S, 19·0%). Campaigne and Archer (*loc. cit.*) give m. p. 183·5—184°. The deep red 2 : 4-*dinitrophenylhydrazone* (from nitrobenzene) had m. p. 307—308° (decomp.) (Found: N, 20·0. $C_{13}H_{11}O_5N_5S$ requires N, 20·0%). The oxime crystallised from water as needles of the *monohydrate*, m. p. 216° (decomp.) (Found: N, 13·95. $C_7H_8O_2N_2S,H_2O$ requires N, 13·85%), becoming anhydrous when at 140° *in vacuo* (Found: C, 46·1; H, 4·4; S, 17·4. Calc. for $C_7H_8O_2N_2S$: C, 45·6, H, 4·4; S, 17·4%); Campaigne and Archer (*loc. cit.*) give m. p. 198—202°. The *semicarbazone* (from aqueous alcohol) had m. p. 260·5—261° (Found: C, 40·7; H, 4·75. $C_8H_{10}O_2N_4S,\frac{1}{2}H_2O$ requires C, 40·85; H, 4·7%), and the thiosemicarbazone (from methanol) had m. p. 237° (Found: C, 39·9; H, 4·65; N, 21·65. Calc. for $C_8H_{10}ON_4S_2,\frac{1}{2}CH_3{\cdot}OH$: C, 39·55; H, 4·7; N, 21·7%); Campaigne, Monroe, Arnwine, and Archer (*loc. cit.*) give m. p. 231—233°.

(*b*) A solution of 2-formyl-5-nitrothiophen diacetate (12·6 g.; Patrick and Emerson, *loc. cit.*) in acetic acid (50 c.c.) containing acetic anhydride (7·5 g.) was reduced at 50—60° by gradual addition of powdered iron (16·4 g.), additional quantities of acetic acid (30 c.c.) and acetic anhydride (2 c.c.) being added when all the iron had been introduced. After 2 hr. at 50—60°, neutralisation of the cooled mixture with sodium hydrogen carbonate precipitated a solid, isolated by extraction into hot ethanol. The product obtained by removal of this solvent was taken up in hot water, and, after brief acid hydrolysis (dilute hydrochloric acid), yielded the 2 : 4-dinitrophenylhydrazone, semicarbazone, and thiosemicarbazone of 2-acetamido-5-formylthiophen identical (m. p. and mixed m. p.) with the derivatives prepared as in (*a*). The yield, based on that of the 2 : 4-dinitrophenylhydrazone, was 32%.

N-2-*Thienylphthalamic Acid*.—2-Thienylammonium chlorostannate (10·8 g.; Steinkopf, *loc. cit.*; Hartough, "Thiophene and its Derivatives," Interscience, New York, 1952) was shaken under nitrogen with sodium hydroxide solution (50 c.c.: 40% w/v) at 40° for 30 sec. The liberated 2-aminothiophen was extracted with benzene (5 × 50 c.c.), the phases were separated by centrifugation at 3000 r.p.m. for 1 min., and the benzene layer (washed with saturated sodium chloride under nitrogen) was immediately run into a suspension of finely powdered phthalic anhydride (6 g.) in benzene (10 c.c.), which was sealed under nitrogen for 45 min. Slow evaporation (30 min.) of the solution left a residue which on extraction with sodium hydrogen carbonate solution and acidification of the extract to pH 1 gave N-2-*thienylphthalamic acid* (0·5—2·0 g., 5—20%) (Found: C, 58·2; H, 3·9. $C_{12}H_9O_3NS$ requires C, 58·3; H, 3·7%). The compound had no true m. p., but cyclised at 160—170° and then had the m. p. of 2-phthalimidothiophen.

2-*Phthalimidothiophen*.—(*a*) *N*-2-Thienylphthalamic acid (0·6 g.) was heated at 170° for 45 min. *in vacuo* (10 mm.) over phosphoric oxide. Crystallisation from ethanol afforded yellow needles of 2-*phthalimidothiophen* (0·45 g., 80%), m. p. 198° (Found: C, 62·6; H, 3·3. $C_{12}H_7O_2NS$ requires C, 62·8; H, 3·1%).

(*b*) 2-Phthalimidothiophen (1 g., 11%) was the sole product obtained when xylene replaced benzene in the preparation of *N*-2-thienylphthalamic acid described above.

(*c*) A solution of 2-nitrothiophen (60 g.) and phthalic anhydride (76 g.) in acetic acid (300 c.c.) and water (80 c.c.) was treated with iron powder (100 g.) during 2 hr., the temperature being kept at 50—60°. After a further 2·5 hr. the cooled mixture was poured into ice-water (1500 c.c.) and brought to pH 3 by addition of hydrochloric acid. The product which separated was chromatographed in benzene solution on alumina, giving 2-phthalimidothiophen (21·6 g., 20%

overall from 2-nitrothiophen), m. p. 198°, identical with material obtained by methods (*a*) and (*b*).

(*d*) A suspension of 2-nitrothiophen (2·58 g.) in 10N-hydrochloric acid (50 c.c.) at 50° was treated with iron powder (6 g.). Reduction was complete in 30 min.; then the cooled and filtered solution was treated at 0° with phthaloyl chloride (4·1 g.) and excess of pyridine. The red colour was discharged in 15 min. and replaced by a precipitate of 2-phthalimidothiophen (0·9 g., 20%), isolated by dilution with water, extraction with benzene, and chromatography on alumina.

5-Phthalimidothiophen-2-sulphonyl Chloride.—2-Phthalimidothiophen (2·29 g.) was added during 25 min. to redistilled chlorosulphonic acid (9·4 g.) at −5°, and the mixture kept at this temperature for a further 30 min. External cooling was removed and, after a further 45 min. at 25°, dry chloroform (10 c.c.) was added and the whole poured into ice (100 g.), from which the product was extracted with chloroform. Removal of solvent from the washed (water) and dried (Na_2SO_4) extracts gave *5-phthalimidothiophen-2-sulphonyl chloride* (1·8 g., 55%), crystallising from chloroform–light petroleum (b. p. 60—90°) in pale yellowish plates, m. p. 176·5° (decomp.) (Found: C, 43·7; H, 2·1. $C_{12}H_6O_4NS_2Cl$ requires C, 44·0; H, 1·9%).

5-Phthalimidothiophen-2-sulphonamide.—The foregoing sulphonyl chloride (0·7 g.) in chloroform (30 c.c.) was treated with dry ammonia. Separation of the sulphonamide commenced almost immediately and was complete in 45 min. The residual *amide* obtained on removal of solvent was triturated with water, and crystallised from nitrobenzene or pyridine as yellow plates, m. p. 261° (decomp.) (0·52 g., 79%) (Found: N, 9·1. $C_{12}H_8O_4N_2S_2$ requires N, 9·1%).

The same product was obtained in 51% overall yield from 2-phthalimidothiophen when isolation of the pure sulphonyl chloride was omitted.

2-Acetamido-5-chlorothiophen.—Treatment of 2-acetamidothiophen (2 g.) in tetrachloroethane (120 c.c.) at 5° with sulphuryl chloride (2·4 g.) in tetrachloroethane (20 c.c.) gave crystals after 15 min. The reaction was completed by 2 hours' stirring at room temperature. The residue obtained on removal of the solvent *in vacuo* crystallised from chloroform–light petroleum (b. p. 60—90°) and, after chromatography on alumina in benzene, gave needles, m. p. 179°, of 2-acetamido-5-chlorothiophen (1·75 g., 70%) (Found: C, 41·5; H, 3·4; N, 7·7; O, 9·2; S, 18·4. Calc. for C_6H_6ONSCl: C, 41·0; H, 3·4; N, 8·0; O, 9·1; S, 18·3%). Hurd and Moffat (*loc. cit.*) give m. p. 177·5—178°.

4-Phthalimidobenzenesulphonamide.—Sulphanilamide (17·2 g.) and phthalic anhydride (25 g.) were heated under reflux for 5 hr. in acetic acid (250 c.c.). Evaporation *in vacuo* and dilution with water gave 4-*o*-carboxybenzoylaminobenzenesulphonamide in almost quantitative yield, readily cyclised by boiling with nitrobenzene (200 c.c.) for 3 hr. 4-Phthalimidobenzenesulphonamide separated as a white micro-crystalline solid, m. p. 322—323° (28·6 g., 95% overall yield). Wanag and Veinbergs (*loc. cit.*) give m. p. 320—322°.

Hydrolysis. The foregoing sulphonamide (3·02 g.) in amyl alcohol (20 c.c.) was heated with 100% hydrazine hydrate (1·03 g., 2 mols.) under reflux for 2·5 hr. The intermediate was decomposed with alcoholic hydrogen chloride to yield phthalhydrazide (1·3 g., 80%). The solution was shown to contain sulphanilamide and was not further investigated.

N-Phenylphthalimide.—Nitrobenzene (10 g.) and phthalic anhydride (12·5 g.) in aqueous acetic acid (60 c.c., 75%) at 60° were treated with iron powder (20 g.), the temperature being 60—70° throughout. After 2 hr., dilution of the cooled mixture to 500 c.c., extraction of the precipitated solid with chloroform, and evaporation gave *N*-phenylphthalimide (2·1 g., 12%) as needles, m. p. 204—205° undepressed on admixture with an authentic specimen.

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