37. *Potential Thiophen Chemotherapeutics. Part II.* A Thiophen Analogue of "Marfanil" (Maphenide).*

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2-Aminomethylthiophen-5(?)-sulphonamide hydrochloride has been obtained from 2-acetamidomethyl- and from 2-phthalimidomethyl-thiophen.

THE antibacterial properties of *p*-substituted benzenesulphonamides are well known, in particular, that of "Marfanil" (maphenide), *p*-sulphamylbenzylamine (Klarer, *Klin. Wschr.*, 1941, **20**, 1250; Domagk, *ibid.*, 1942, **21**, 448; Jensen and Schmith, *Z. Immunitatsf.*, 1942,

* The communication, "Some 2-Thienyl Alkyl Sulphones" (*J.*, 1949, 1666), is regarded as Part I.

102, 261). It has been shown in numerous instances that replacement of a benzene nucleus by the 2-thienyl group leads to isosteres possessing comparable biological activity, and the preparation of a thiophen analogue of maphenide has now been carried out by two parallel routes.

Acetylation of 2-aminomethylthiophen (Hartough, *J. Amer. Chem. Soc.*, 1948, **70**, 4018) afforded a product which was separated by fractional distillation into crystalline 2-acetamidomethyl- and oily 2-diacetylaminomethyl-thiophen. This recalls the similar behaviour of benzylamine on acetylation (Holmes and Ingold, *J.*, 1925, 1820). Chlorosulphonation of 2-acetamidomethylthiophen afforded what is presumed to be the 5-sulphonyl chloride, which gave the desired 2-acetamidomethylthiophen-5-sulphonamide by reaction with either alcoholic ammonia or, in better yield, dry ammonium carbonate. Acid hydrolysis of this sulphonamide gave a good yield of 2-aminomethylthiophen-5-sulphonamide hydrochloride, m. p. 234—235°. Chlorosulphonation is presumed to have occurred in the 5-position (cf. Cundiff and Estes, *J. Amer. Chem. Soc.*, 1950, **72**, 1424; Steinkopf and Kohler, *Annalen*, 1937, **532**, 264).

Work directed towards a rigid proof of the orientation of the sulphonyl group is in progress.

In the other preparation, reaction of 2-chloromethylthiophen (Blicke and Burckhalter, *J. Amer. Chem. Soc.*, 1942, **64**, 478) with potassium phthalimide by Ing and Manske's method (*J.*, 1926, 2348) gave 2-phthalimidomethylthiophen, previously prepared by Hartough (*J. Amer. Chem. Soc.*, 1948, **70**, 1146) from 2-aminomethylthiophen and phthalic anhydride. Chlorosulphonation of 2-phthalimidomethylthiophen readily afforded the (presumably) 5-sulphonyl chloride in good yield. The halogen atom in this substance possessed remarkably low reactivity towards ammonia but reaction with ammonium carbonate at 180° gave 61% of the sulphonamide. Hydrolysis of this by means of hydrazine hydrate (Ing and Manske, *loc. cit.*) readily afforded the desired salt (m. p. 234—235°), identical with the sample obtained by the previous route. The free base was obtained as a very hygroscopic solid, m. p. 96—97°.

Maphenide hydrochloride has been reported (Heideman and Rutledge, *J. Pharm. Exp. Therap.*, 1948, **93**, 451) to possess an ultra-violet absorption spectrum showing a single maximum at 2650 Å. The ultra-violet absorption spectrum of a 95%-alcoholic solution of the hydrochloride of our thiophen analogue, obtained by using a Beckman quartz spectrophotometer, model DU, showed a single maximum at 2440 Å, $\varepsilon = 10\,950$.

Professor S. D. Rubbo has kindly examined this compound against a range of organisms and reports that it is devoid of appreciable bacteriological activity.

Experimental

2-Acetamidomethylthiophen.—A mixture of acetic acid (120 g., 2 mols.), acetic anhydride (25·2 g., 0·2 mol.) and 2-aminomethylthiophen (22·6 g., 0·2 mol.; b. p. 45—52°/0·5 mm.) was refluxed for 2·5 hours. Most of the acetic acid was removed by distillation and the residue poured on ice. The oil which separated was extracted with ether and distillation of the washed (sodium hydrogen carbonate) and dried (Na_2SO_4) extracts afforded a colourless oil (28 g., 90%), b. p. 144—152°/1 mm., which partly solidified to give white crystals (15 g.) separating from ether–light petroleum (b. p. 40—70°) as needles, m. p. 44—45° (Found: N, 8·8; S, 20·35. C_7H_9ONS requires N, 9·0; S, 20·65%), of *2-acetamidomethylthiophen.*

The liquid portion of the distillates from several runs (63 g.) gave, on fractionation, 2 main fractions: (*a*) b. p. 125—130°/1·5 mm. (20·5 g.), n_D^{15} 1·5514, of *2-diacetylaminomethylthiophen* (Found: C, 55·2; H, 6·0; N, 7·25. $C_9H_{11}O_2NS$ requires C, 54·8; H, 5·6; N, 7·1%), sparingly soluble in cold N-hydrochloric acid; and (*b*) b. p. 136—143°/1·5 mm. (31·5 g.), solidifying to crystals, m. p. 44—45°, of the monoacetyl derivative, easily soluble in cold N-hydrochloric acid.

Heating a mixture of the amine (1 mol.) and acetic anhydride (1 mol.) with acetic acid (0·5 or 5 mols.) gave yields of 66 and 80% of the acetyl derivatives respectively.

2-Acetamidomethylthiophen-5-sulphonyl Chloride.—Crystalline 2-acetamidomethylthiophen (15·5 g., 0·1 mol.) was added during 30 minutes to well-stirred chlorosulphonic acid (redistilled; 70 g., 0·6 mol.), at. <5° (ice). The mixture was stirred at 25° for 30 minutes and finally at 50°

for 30 minutes. The oil was poured on ice (200 g.), and the viscous oil which separated was washed well with ice-water. Trituration with dry ether gave a solid (9 g., 37%) which crystallised from benzene in prisms, m. p. 88—89°, of *2-acetamidomethylthiophen-5-sulphonyl chloride* (Found: N, 5·45; S, 25·25. $C_7H_8O_3NS_2Cl$ requires N, 5·5; S, 25·25%).

2-Acetamidomethylthiophen-5-sulphonamide.—(*a*) The above sulphonyl chloride (1·2 g., 0·005 mol.) was added gradually to well-stirred ethanol (100 c.c.) saturated with ammonia (16% w/v) at 0°. The solid dissolved slowly, and the solution was then set aside for 30 minutes. The residue left by evaporation of the solution *in vacuo* was dissolved in sodium hydroxide solution (10%), then filtered, and the filtrate acidified with hydrochloric acid. Concentration of the solution to crystallisation gave plates, m. p. 123—124° (0·2 g., 17%), of *2-acetamidomethylthiophen-5-sulphonamide* (Found: C, 36·5; H, 4·45; N, 11·4; S, 27·6. $C_7H_{10}O_3N_2S_2$ requires C, 35·9; H, 4·3; N, 12·0; S, 27·4%).

(*b*) A well-stirred mixture of the sulphonyl chloride (2·5 g., 0·01 mol.) and dry ammonium carbonate (10 g., 0·1 mol.; "AnalaR") was heated at 120° (oil-bath) for 30 minutes. After the addition of ice-water, the solid was filtered off and recrystallised from alcohol or hot water, giving 1·5 g. (64%) of plates, m. p. 123—124°, undepressed on admixture with the material obtained by method (*a*) (Found: C, 36·15; H, 4·3; N, 12·1; S, 27·5%).

2-Aminomethylthiophen-5-sulphonamide.—(i) A mixture of 2-acetamidomethylthiophen-5-sulphonamide (5 g.) and hydrochloric acid (3N; 50 c.c.) was refluxed for 8 hours and then concentrated *in vacuo* to crystallisation, giving white crystals of *2-aminomethylthiophen-5-sulphonamide hydrochloride* (3·5 g., 73%), crystallising from concentrated hydrochloric acid in plates, m. p. 234—235° (decomp.) (Found: C, 26·65; H, 4·0; S, 27·5. $C_5H_9O_2N_2S_2Cl$ requires C, 26·25; H, 4·0; S, 28·0%). Light absorption: $\lambda_{max.}$ 2440 Å, ε = 10,950, in 95% ethanol.

2-Phthalimidomethylthiophen.—To a solution of 2-chloromethylthiophen (freshly-distilled; b. p. 45—50°/0·5 mm.; 20 g., 0·15 mol.) in xylene (100 c.c.) was added a mixture of dry phthalimide (33 g., 0·22 mol.) and anhydrous potassium carbonate (15·5 g., 0·11 mol.). The reaction mixture was refluxed vigorously for 4 hours, then cooled and washed with water and sodium hydroxide solution (2N). The xylene solution was dried ($CaCl_2$) and the solvent removed *in vacuo*, leaving a residue (20 g., 55%), m. p. 123—124°, which on crystallisation from alcohol or chloroform–light petroleum (b. p. 40—70°) afforded needles, m. p. 127—127·5°, of 2-phthalimidomethylthiophen (Found: C, 63·85; H, 3·75; N, 5·8. Calc. for $C_{13}H_9O_2NS$: C, 64·15; H, 3·7; N, 5·75%) (Hartough, *J. Amer. Chem. Soc.*, 1948, **70**, 1146, gives m. p. 126—127°).

2-Phthalimidomethylthiophen-5-sulphonyl Chloride.—2-Phthalimidomethylthiophen (7·2 g., 0·03 mol.) was added gradually during 20 minutes to well-stirred chlorosulphonic acid (21 g., 0·18 mol.) at <5° (ice). Use of the reaction conditions described above for 2-acetamidomethylthiophen gave 7·5 g. (76%) of *2-phthalimidomethylthiophen-5-sulphonyl chloride*, m. p. 138—147°, crystallising from chloroform–light petroleum (b. p. 40—70°) in prismatic needles, m. p. 147—147·5° (Found: C, 45·2; H, 2·3; N, 4·15; Cl, 10·5. $C_{13}H_8O_4NSCl$ requires C, 45·65; H, 2·35; N, 4·1; Cl, 10·4%). The substance was unchanged after crystallisation from alcohol.

2-Phthalimidomethylthiophen-5-sulphonamide.—An intimate mixture of the sulphonyl chloride (3 g., 0·009 mol.) and ammonium carbonate (19 g., 0·2 mol.) was slowly heated to 180° and kept at this temperature for 30 minutes. The cooled mixture was washed with ice-water and the residue crystallised from ethyl acetate, affording prisms of *2-phthalimidomethylthiophen-5-sulphonamide* (1·7 g., 61%), m. p. 171—173° (Found: N, 8·75. $C_{13}H_{10}O_4N_2S_2$ requires N, 8·7%). The sulphonyl chloride was unchanged after treatment with aqueous ammonia (*d* 0·88), alcoholic ammonia, ammonia in boiling benzene, or ammonium carbonate at 170° for 10 minutes, while reaction at 180° for 10 minutes gave the sulphonamide in 13·5% yield (m. p. 169—173°).

2-Aminomethylthiophen-5-sulphonamide.—(ii) 2-Phthalimidomethylthiophen-5-sulphonamide (0·5 g., 0·0015 mol.) was heated on the steam-bath with absolute alcohol (8 c.c.), and the mixture treated with hydrazine hydrate (0·3 c.c., 50% w/w), giving a clear solution immediately. After a few minutes, the intermediate compound was precipitated. The mixture was heated for 30 minutes and then treated with hydrochloric acid (1 c.c.; 10N) to decompose the intermediate. After 5 minutes, the phthalhydrazide was filtered off and the alcoholic filtrate evaporated *in vacuo*, leaving the hydrochloride (0·17 g., 50%) as white plates, m. p. 234—235° (decomp.), undepressed on admixture with the sample prepared by method (i).

A solution of the hydrochloride in the minimum amount of water was basified to pH 9 with 0·1N-sodium hydroxide, the solution evaporated *in vacuo*, and the residue extracted with

absolute alcohol. Addition of ether to the alcoholic extract gave 2-aminomethylthiophen-5-sulphonamide as a white, extremely hygroscopic, micro-crystalline solid, m. p. 96—97°, for which satisfactory analytical values could not be obtained (Found: N, 11·6. Calc. for $C_5H_8O_2N_2S_2$: N, 14·55%).

The authors acknowledge their indebtedness to Professor S. D. Rubbo for kindly undertaking the bacteriological tests, and to Mrs. E. Bielski for microanalyses.

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