

154. *2-Thienyl- and 3-Thienyl-thioacetic Acids and their Derivatives.*

By FREDERICK CHALLENGER, SAMUEL A. MILLER, AND GEOFFREY M. GIBSON.

Di-2-thienyl disulphide has been prepared by reduction of 2-thienylsulphonyl chloride with hydriodic acid. Reduction with glucose and alkali followed by treatment with chloroacetic acid gives crude 2-thienylthioacetic acid, characterised as the ester and amide.

The 3-sulphonyl chloride gives a crude disulphide with hydriodic acid; this with sodium amalgam in alcohol gives a crude thiol from which the thioacetic acid, its ester, amide, and anilide have been prepared.

Neither 2- nor 3-thienylthiol could be purified. 3-Methylthiophen-2-sulphonyl chloride and amide are described.

For the purposes of a projected synthesis the preparation of 2-thienylthioacetic acid $\text{C}_4\text{H}_3\cdot\text{S}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ from 2-thienylthiol was attempted. The thiol is a very inaccessible compound

(see Challenger and Miller, *J.*, 1938, 894). Methods for its preparation from 2-thienylsulphonyl chloride (Steinkopf and Hopner, *Annalen*, 1933, 501, 174) or from the corresponding sulphinic acid (Biedermann, *Ber.*, 1886, 19, 1616) were considered.

H. B. Gibson (Thesis, Leeds, 1936) found that thiophen rapidly polymerises in presence of anhydrous stannic or ferric chloride giving amorphous solids which, after removal of occluded inorganic matter, have the approximate composition $(C_4H_4S)_x$. It was therefore deemed inadvisable to employ metals and concentrated hydrochloric acid as reducing agents, preliminary experiments with tin and hydrochloric acid giving much dark solid. Biedermann (*loc. cit.*) obtained only 0.5 g. of 2-thienylthiol by reduction of the sulphonyl chloride (30 g.) with zinc dust and water followed by zinc and hydrochloric acid.

Although aromatic seleninic acids readily yield diselenides with sulphurous acid, this has no action on aqueous benzenesulphinic acid.

Fries and Schurmann (*Ber.*, 1914, 47, 1195) state that arylsulphinic acids but not sulphonyl chlorides yield aryl sulphur bromides or disulphides with hydrobromic acid. We find that benzenesulphonyl chloride gives the disulphide with hydrobromic acid and sodium sulphite. Similar reduction of 2-thienylsulphonyl chloride, however, gave no disulphide but a thiol which decomposed on distillation in steam or under reduced pressure. Fischer (*Ber.*, 1915, 48, 93) reduced sulphonamides to thiols by hydriodic acid and phosphonium iodide in sealed tubes at 70–100°. We find that with benzene- or 2-thienyl-sulphonyl chloride and cold hydriodic acid in glacial acetic acid, ready reduction to the disulphides occurs. This would appear to be a convenient method for the preparation of 2 : 2'-dithienyl disulphide which was first obtained by Meyer and Neure (*Ber.*, 1887, 20, 1756).

2 : 2'-Dithienyl sulphide was obtained by Challenger and Harrison (*J. Inst. Pet. Tech.*, 1935, 21, 153) from 2-thienylmagnesium bromide and sulphur. H. B. Gibson (Thesis, Leeds, 1936) obtained it by using sulphur chloride, S_2Cl_2 , instead of sulphur. Both preparations were characterised as the sulphone.

Claasz (*Ber.*, 1912, 45, 2424) reduced various diaryl disulphides with glucose and alkali and, without isolating the thiol, added sodium chloroacetate, thus obtaining the corresponding thioacetic acids. By this method we have obtained crude 2-thienylthioacetic acid from which the ethyl ester and the *amide* have been prepared. Drs. H. Burton and W. Davy (forthcoming publication from these laboratories) have also employed hydriodic acid followed by glucose-alkali for the reduction of 2-thienylsulphonyl chloride to the thiol (not isolated) and confirm its instability.

3-Thienylsulphonyl chloride gives the 3 : 3'-disulphide with hydriodic acid. This was not purified, but with sodium amalgam in alcohol, followed by chloroacetic acid, it gave 3-thienylthioacetic acid, characterised as the *amide* and *anilide*.

EXPERIMENTAL.

Reduction of Sulphonyl Chlorides.—Benzenesulphonyl chloride (2 c.c.), sodium sulphite (3 g.), and hydrogen bromide in glacial acetic acid (40% ; 8 c.c.) were boiled for a few minutes, diluted with water (10 c.c.), and cooled to below 0°. The deposited solid after crystallisation from alcohol had the m. p., 60–61°, and the properties of diphenyl disulphide.

The acid chloride (2 c.c.), glacial acetic acid (50 c.c.), and hydriodic acid (*d* 1.95; 15 c.c.) were mixed and left overnight at room temperature. The mixture, when diluted with water, treated with sodium thiosulphate to remove iodine, neutralised with sodium carbonate, and extracted with ether, yielded diphenyl disulphide (m. p. 60–61°).

2-Thienylsulphonyl chloride (6 g.), glacial acetic acid (150 c.c.), and hydriodic acid (*d* 1.95; 40 g.) were mixed, and the temperature soon rose to about 40°. In later experiments using larger quantities the mixture was cooled immediately after addition of the hydriodic acid and left overnight below 0°. The mixture was then poured into a solution of sodium thiosulphate (40 g.) in water (250 c.c.). After standing for 2 hours, yellow crystals were deposited, m. p. 53.5–54.5° and 55.5–56° after two crystallisations from aqueous alcohol. These were halogen-free, gave the indophenin reaction, and evolved the odour of a thiol on warming with zinc dust and dilute sulphuric acid. Later experiments gave a 60–70% yield. 2 : 2'-Dithienyl disulphide melts at 56° (Meyer, *loc. cit.*) (Found : C, 41.6; H, 3.0; S, 54.8. Calc. for $C_8H_6S_4$: C, 41.7; H, 2.6; S, 55.6%).

Reduction of Di-2-thienyl Disulphide and Condensation of the Product with Sodium Chloroacetate.—The disulphide (2.5 g.) in alcohol (10 c.c.) was treated with glucose (2.5 g.) in water (5 c.c.) and sodium hydroxide (2.5 g.) in water (5 c.c.). The mixture, at first turbid, became hot, brown, and clear and was warmed for a few minutes at 100°. Acidification of a portion gave an odour of a thiol. (Attempts in later experiments to isolate this thiol failed, decomposition occurring during distillation.) Chloroacetic acid (2.5 g.) and sodium carbonate (1.5 g.) in water (10 c.c.) were then added, and the mixture warmed for 30 mins. No solid separated (sodium phenylthioacetate readily separates under similar conditions). The acidified solution was then extracted with ether, yielding an oil which did not solidify, although by analogy with phenylthioacetic acid (m. p. 61–62°) 2-thienylthioacetic acid should have an approximately similar m. p.

Ethyl 2-thienylthioacetate was prepared by refluxing the crude acid obtained as above with alcohol and a little sulphuric acid or by the Fischer-Speier method. It distilled at 138–140°/20 mm. Two further distillations gave an oil, b. p. 138°/20 mm. (Found: C, 48.1; H, 4.9; S, 31.4. $C_8H_{10}O_2S_2$ requires C, 47.5; H, 4.9; S, 31.7%).

2-Thienylthioacetamide. The ester (3 g.) and concentrated aqueous ammonia (15 c.c.) were shaken mechanically overnight. The resulting solid, and a further quantity obtained on cooling the filtrate, melted at 92–93° (2.5 g.), and at 95–96° on recrystallisation from water. Two further crystallisations failed to alter the m. p. of this *amide* (Found: C, 41.3; H, 4.0; N, 7.8; S, 37.2. $C_6H_7ONS_2$ requires C, 41.6; H, 4.0; N, 8.1; S, 37.0%).

Sulphonation of 3-Methylthiophen.—Methylsuccinic acid (Lapworth and Higginbotham, *J.*, 1922, 121, 49) was distilled with phosphorus trisulphide, and the resulting 3-methylthiophen sulphonated with chlorosulphonic acid by Steinkopf and Hopner's method (*Annalen*, 1933, 501, 174) for thiophen. The reaction mixture was poured on ice and extracted with carbon tetrachloride. Fractionation of the dried extract gave 3-methylthienyl-?-sulphonyl chloride as a pale yellow oil, b. p. 98–99°/0.5 mm. (Found: C, 30.3; H, 2.5; S, 32.4. $C_5H_5O_2S_2Cl$ requires C, 30.5; H, 2.5; S, 32.6%). The sulphonyl chloride (5 g.), alcohol (5 c.c.), and concentrated ammonia (15 c.c.) were left to stand. The resulting *sulphonamide* was recrystallised four times from water and melted at 146° (Found: C, 33.9; H, 4.0; N, 8.5; S, 36.2; $C_5H_5O_2S_2N$ requires C, 33.9; H, 4.0; N, 7.9; S, 36.2%).

3-Thienylthioacetic Acid.—3-Thienylsulphonyl chloride was prepared by Langer's method (*Ber.*, 1884, 17, 1566), which consists in the sulphonation of 2:5-dibromothiophen and removal of the bromine from the 3-sulphonyl derivative with sodium amalgam. (The sodium salt of the dibromo-acid gives a *d*-bornylamine salt which forms short, colourless needles from hot water, m. p. 266–267°. A quinine salt is also readily formed.)

Later it was found unnecessary to isolate the dibromosulphonic acid, and the sulphonation mixture, after dilution with ice and extraction with ether, was neutralised and reduced at once with sodium amalgam.

The dibromothiophen was prepared from thiophen and bromine (2 mols.) in glacial acetic acid, an extension of Krause and Renwanz's method for the monobromo-derivative (*Ber.*, 1929, 62, 1710).

The sulphonyl chloride (3 g.) in glacial acetic acid (75 c.c.) was treated with cold 65% hydriodic acid (10.5 c.c.) and left for 2 hours. It was then poured into water, the iodine removed with sodium thiosulphate, and the crude disulphide extracted with carbon tetrachloride. After removal of solvent at 40° under diminished pressure, the residue, which could not be solidified and decomposed on attempted distillation, was reduced in alcoholic solution in a stream of carbon dioxide by finely divided 5% sodium amalgam, the mixture being stirred and cooled in water. When reduction was complete the mixture was poured into water, acidified, and extracted with ether. The extract was then shaken with successive small quantities of 2N-sodium hydroxide, and the alkaline layer heated with chloroacetic acid (3 g.) for 1½ hours at 100°. The cooled mixture was acidified, extracted with ether, and the ether washed twice with water to remove chloroacetic and glycolic acids, and shaken with sodium hydrogen carbonate. Acidification and extraction with ether gave a pale yellow odourless oil (1.4 g., yield 50% calculated on the sulphonic chloride) which solidified on cooling, m. p. 47.5–49.5°. On crystallisation from ether-ligroin or by partial evaporation of its aqueous solution over sulphuric acid in a vacuum, 3-thienylthioacetic acid formed short, colourless needles, m. p. 50.5–51°, which gave a deep red indophenin reaction (Found: C, 41.5; H, 3.4; S, 37.1. $C_6H_6O_2S_2$ requires C, 41.3; H, 3.5; S, 36.8%).

The crude acid (2 g.) was refluxed for 3 hours with 2–3% alcoholic hydrogen chloride (8 c.c.). The resulting ester, b. p. 140–142°/9 mm., was readily hydrolysed by 2N-sodium hydroxide.

3-Thienylthioacetamide. The ethyl ester (0.5 c.c.) was shaken for a few hours with concentrated ammonia (8 c.c.). The resulting solid crystallised from hot water in rectangular, iridescent plates, m. p. 115.5–116° (Found: C, 42.0; H, 4.0; S, 37.7. $C_6H_7ONS_2$ requires C, 41.6; H, 4.1; S, 37.0%). The *amide* is readily hydrolysed and affords a convenient source of the pure acid.

3-Thienylthioacetanilide was obtained in poor yield by gently warming 3-thienylthioacetic acid with thionyl chloride for a few minutes, diluting the mixture with dry ether, and adding aniline. The ether was then washed with water, dilute hydrochloric acid, and sodium carbonate, dried, and evaporated, leaving a residue which, when crystallised from hot aqueous alcohol, melted at 118–118.5° (Found: C, 57.45; H, 4.40; S, 25.9. $C_{12}H_{11}ONS_2$ requires C, 57.8; H, 4.45; S, 25.75%).

The authors thank the Institute of Petroleum and Imperial Chemical Industries for grants, and the Department of Scientific and Industrial Research for a maintenance grant to G. M. G.

THE UNIVERSITY, LEEDS.

[Received, June 9th, 1947.]