950. *The Synthesis of Monohalogeno-2,2′-bithienyls*

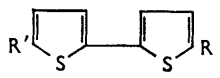
By R. F. Curtis and G. T. Phillips

The synthesis of 5-halogeno-2,2′-bithienyls from 2,2′-bithienyl by direct halogenation is complicated by the production of mixtures which invariably contain the 5,5′-disubstituted derivatives. This was originally pointed out by Steinkopf [1] and later by Uhlenbroek and Bijloo [2] who were unable to prepare 5-chloro-2,2′-bithienyl (I) or the corresponding bromo-analogue (II). These authors cast doubt on the structure of the compound claimed to be (I) by Thöl and Eberhard.[3]

5-Iodo-2,2′-bithienyl (III) was required for the synthesis of several naturally-occurring bithienyl derivatives [4,5] and simple syntheses of compounds (I), (II), and (III) are now reported. 5-Methoxycarbonyl-2,2′-bithienyl [6] (IV) was treated under standard conditions [7] with iodine and mercuric oxide to give the corresponding iodo-derivative (V) in good yield.

[1] W. Steinkopf, " Die Chemie des Thiophens," Steinkopff, Dresden and Leipzig, 1941, p. 143.
[2] J. H. Uhlenbroek and J. D. Bijloo, *Rec. Trav. chim.*, 1960, **79**, 1181.
[3] A. Thöl and O. Eberhard, *Ber.*, 1893, **26**, 2945, 2947.
[4] R. E. Atkinson, R. F. Curtis, and G. T. Phillips, *Tetrahedron Letters*, 1964, **43**, 3159.
[5] R. E. Atkinson, R. F. Curtis, and G. T. Phillips, *Chem. and Ind.*, 1964, 2100.
[6] H. Wynberg and A. Bantjes, *J. Amer. Chem. Soc.*, 1960, **82**, 1447.
[7] W. Minnis, *Org. Synth.*, Coll. Vol. II, 357.

Alkaline hydrolysis gave the corresponding acid (VI) which was decarboxylated using a standard method [8] *via* the mercuriacetate and mercurichloride derivatives. Vapour-phase chromatography showed that the product contained 5-iodo-2,2′-bithienyl (III) (83%) and 2,2′-bithienyl (17%) and these could be separated by fractional distillation. 2,2′-Bithienyl presumably arises by replacement of an iodide radical by a hydrogen radical from the acetic acid used as a solvent, or mercuric acetate. Similar processes catalysed by cuprous acetate have recently been described.[9]



(I; R = Cl, R′ = H)
(II; R = Br, R′ = H)
(III; R = I, R′ = H)
(IV; R = H, R′ = CO_2Me)
(V; R = I, R′ = CO_2Me)
(VI; R = I, R′ = CO_2H)

(VII; R = R′ = I)
(VIII; R = Br, R′ = CO_2Me)
(IX; R = Br, R′ = CO_2H)
(X; R = Cl, R′ = CO_2Me)
(XI; R = Cl, R′ = CO_2H)

The direct iodination of 2,2′-bithienyl was also examined after the pure monoiodo derivative (III) had been prepared, since the physical properties of compound (III) indicated that direct isolation might be possible. Vapour-phase chromatography showed that the product, using one mole of iodine and mercuric oxide, contained 2,2′-bithienyl (23%), 5-iodo-2,2′bithienyl (44%), and 5,5′-di-iodo-2,2′-bithienyl [10] (VII) (33%). The monoiodo-derivative (III) could be separated by fractional distillation.

The much greater similarity between the physical properties, *e.g.*, boiling point, of 2,2′-bithienyl and the 5-chloro- and 5-bromo-derivatives prevented the use of the direct halogenation approach. Both of these compounds were prepared by the indirect method from 5-methoxycarbonyl-2,2′-bithienyl (IV).

An attempt to produce direct interconversions in this series similar to those recently reported for halogenonaphthalenes [11] was unsuccessful. When 5-bromo-2,2′-bithienyl was heated with cuprous iodide in dimethyl sulphoxide, reduction occurred and the product contained principally 2,2′-bithienyl.

Experimental.—Melting points were determined on a Kofler hot-stage apparatus and are corrected. Ultraviolet absorption spectra were measured in ethanol on a Unicam S.P. 800 recording spectrophotometer and infrared absorption spectra for potassium bromide discs on a Perkin-Elmer 137 or 237 instrument. N.m.r. spectra were determined in carbon disulphide using tetramethylsilane as internal standard with a Perkin-Elmer 40 Mc./sec. spectrometer. Peak positions are recorded on the τ scale. Vapour-phase chromatography was carried out on a Perkin-Elmer fraktometer 116E, using silicone oil D.C. 200 as substrate and nitrogen as carrier gas at 212°. Thin-layer chromatographic methods have already been described;[12] "system A" refers to alumina G (Merck) and "system B," silica gel G (Merck), both developed with light petroleum (b. p. 40—60°). Colours were produced with isatin–sulphuric acid.[12]

5-Iodo-5′-methoxycarbonyl-2,2′-bithienyl (V). Iodine (10 g.) and yellow mercuric oxide (8·6 g.) were slowly, and alternately, added to a stirred solution of 5-methoxycarbonyl-2,2′-bithienyl (IV)[6] (9 g.) in dry benzene (100 ml.) at 0° over 2 hr. The buff-coloured precipitate was collected and washed with saturated aqueous potassium iodide solution (200 ml.), and the residual solid redissolved in the initial benzene filtrate. This solution was shaken with aqueous sodium thiosulphate (10%; 3 × 100 ml.), dried, and distilled. The residue was crystallised from acetone to give *5-iodo-5′-methoxycarbonyl-2,2′-bithienyl* (V), (12·3 g.), plates, m. p. 161—162°, $\lambda_{max.}$ 251, 344 mμ (log ε 3·83, 4·36) (Found: C, 34·2; H, 2·3; I, 36·9; S, 18·9. $C_{10}H_7IO_2S_2$ requires C, 34·3; H, 2·0; I, 36·2; S, 18·3%), $\nu_{max.}$ 1725 ($-CO_2Me$), and 790 cm.$^{-1}$ (5,5′-disubstituted bithienyl). N.m.r. spectrum: τ = 2·8 (4, multiplet, bithienyl protons), 6·1 (3, singlet, $-CO_2CH_3$).

5-Carboxy-5′-iodo-2,2′-bithienyl (VI). The preceding ester was heated under reflux with 0·7N-potassium hydroxide in acetone–water (1 : 2·5) for 5 hr. Working up gave *5-carboxy-5′-iodo-2,2′-bithienyl* (VI), plates (from aqueous methanol), m. p. 256—258°, $\lambda_{max.}$ 249, 339 mμ

[8] W. Steinkopf and W. Köhler, *Annalen*, 1937, **532**, 281.
[9] R. G. R. Bacon and H. A. O. Hill, *J.*, 1964, 1112.
[10] W. Steinkopf and W. Köhler, *Annalen*, 1936, **522**, 17.
[11] R. G. R. Bacon and H. A. O. Hill, *J.*, 1964, 1108.
[12] R. F. Curtis and G. T. Phillips, *J. Chromatog.*, 1962, **9**, 366.

(log ε 3·77, 4·33) (Found: C, 32·1; H, 1·75; I, 38·4; S, 19·5. $C_9H_5IO_2S_2$ requires C, 32·15; H, 1·5; I, 37·75; S, 19·1%), $\nu_{max.}$ 1700 (−CO_2H), and 790 cm.$^{-1}$ (5,5′-disubstituted bithienyl).

5-Iodo-2,2′-bithienyl (III). (*a*) *Indirect method.* The acid (VI) (7 g.) and mercuric acetate (16 g.) in glacial acetic acid (760 ml.) were heated under reflux for 4 hr. Acetic acid was then removed under reduced pressure to give a residue containing the corresponding *mercuriacetate*. Aqueous sodium chloride (20%; 600 ml.) was added, the solution heated under reflux for 1 hr., and then hydrochloric acid (*d* 1·18; 25 ml.) added, followed by heating for a further 30 min. The solution was worked up by extraction with ether in the usual way and after evaporation of the ether the residual oil was purified by chromatography on alumina. Elution with n-pentane–ether (9 : 1) gave a low-melting solid (2·9 g.) which was shown by vapour-phase chromatography to be a mixture of 2,2′-bithienyl (17%, retention time 11 min.) and 5-iodo-2,2′-bithienyl (83%, retention time 45 min.). Fractional distillation gave *5-iodo-2,2′-bithienyl* (III), b. p. 75°/0·007 mm. (bath temp.), $\lambda_{max.}$ 248, 314 mμ (log ε 3·73, 4·20) (Found: C, 33·2; H, 1·8; I, 43·15; S, 21·3. $C_8H_5IS_2$ requires C, 32·9; H, 1·7; I, 43·4; S, 22·0%), $\nu_{max.}$ (film) 840 (5′-unsubstituted bithienyl), 800 (2,5-disubstituted thiophen), and 694 cm.$^{-1}$ (5′-unsubstituted bithienyl), R_F 0·70 (system A, dark blue spray colour), 0·67 (system B).

(*b*) *Direct method.* Iodine (15·4 g.) and yellow mercuric oxide (13·1 g.) were added slowly, and alternately, to a stirred solution of 2,2′-bithienyl (10 g.) in dry benzene at 0° over 2 hr. After working up as described for the preparation of the ester (V), the product was a green oil, (18 g.). Trituration with n-pentane gave *5,5′-di-iodo-2,2′-bithienyl* (VII), (6·0 g.), as plates from light petroleum (b. p. 60—80°), m. p. 164° (lit.,[10] 164°), $\lambda_{max.}$ 246, 324 mμ (log ε 3·83, 4·30), $\nu_{max.}$ 800 cm.$^{-1}$ (2,5-disubstituted thiophen).

The residue from the trituration was distilled to give 2,2′-bithienyl (2·64 g.), b. p. 100—104°/3·5 mm., and 5-iodo-2,2′-bithienyl (8·14 g.), b. p. 150°/3·5 mm., with retention times on vapour-phase chromatography identical with those of authentic material.

5-Bromo-5′-methoxycarbonyl-2,2′-bithienyl (VIII). Bromine (2·14 g.) in chloroform (15 ml.) was added to a stirred solution of 5-methoxycarbonyl-2,2′-bithienyl [6] (IV) (3·1 g.) in chloroform (125 ml.) at 35° over 35 min. After a further 35 min. the solution was cooled to 10° when a colourless solid separated. This was collected, washed with chloroform, and dried to give 5-bromo-5′-carboxy-2,2′-bithienyl (1·5 g.), m. p. 260—262°, identical with material described below. The combined filtrate and washings were shaken with aqueous sodium hydrogen carbonate (2%) and distilled, and the residue crystallised from light petroleum (b. p. 60—80°) to give the *bromo-ester* (VIII), plates, (2·7 g.), m. p. 125—126°, $\lambda_{max.}$ 245, 339 mμ (log ε 3·77, 4·35) (Found: C, 39·9; H, 2·5; Br, 26·45; S, 21·3. $C_{10}H_7BrO_2S_2$ requires C, 39·6; H, 2·3; Br, 26·4; S, 21·15%), $\nu_{max.}$ 1725 (−CO_2Me) and 795 cm.$^{-1}$ (2,5-disubstituted thiophen).

5-Bromo-5′-carboxy-2,2′-bithienyl (IX). The preceding ester (3 g.) in methanol (150 ml.) was added to 2·5N-sodium hydroxide (50 ml.) and kept at 35° for 8 hr. Working up in the usual way gave *5-bromo-5′-carboxy-2,2′-bithienyl* (IX) (2·8 g.), microcrystalline powder, m. p. 261—262°, $\lambda_{max.}$ 239, 335 mμ (log ε 3·74, 4·25) (Found: C, 37·6; H, 1·95; Br, 27·9; S, 21·9. $C_9H_5BrO_2S_2$ requires C, 37·4; H, 1·75; Br, 27·6; S, 22·2%), $\nu_{max.}$ 1700 (−CO_2H) and 790 cm.$^{-1}$ (2,5-disubstituted thiophen).

5-Bromo-2,2′-bithienyl (II). Mercuric acetate (8·7 g.) and the preceding acid (IX) (3·1 g.) in glacial acetic acid (600 ml.) were heated under reflux for 3 hr. Acetic acid was removed under reduced pressure and aqueous sodium chloride (20%; 720 ml.) added. After being boiled for 1 hr. the solution was cooled, hydrochloric acid (*d* 1·18; 25 ml.) added and the product worked up by extraction with ether. The residue, after distillation of the ether, was dissolved in light petroleum (b. p. 40—60°) containing a minimal amount of benzene (a small amount of solid separated); the solution was chromatographed on alumina (Woelm, neutral, I). Elution with n-pentane–ether (95 : 5) gave *5-bromo-2,2′-bithienyl* (1·85 g.), b. p. 50°/0·006 mm. (bath temp.), m. p. 30—33°, $\lambda_{max.}$ 249, 311 mμ (log ε 3·73, 4·13) (Found: C, 39·7; H, 2·4; Br, 31·8; S, 25·2. $C_8H_5BrS_2$ requires C, 39·2; H, 2·1; Br, 32·6; S, 26·2%), $\nu_{max.}$ 840 (5′-unsubstituted bithienyl), 790 (2,5-disubstituted thiophen), and 694 cm.$^{-1}$ (5′-unsubstituted bithienyl), retention time 28 min., R_F 0·73 (system A, dark blue spray colour), 0·74 (system B).

5-Chloro-5′-methoxycarbonyl-2,2′-bithienyl (X). Sulphuryl chloride (1·2 g.) in chloroform (8 ml.) was added to a stirred solution of 5-methoxycarbonyl-2,2′-bithienyl (IV) (2 g.) in chloroform (25 ml.) at 20° during 30 min. The solution was set aside overnight, washed with saturated sodium hydrogen carbonate solution, dried, and the chloroform removed by distillation. The residue was crystallised from n-pentane to give *5-chloro-5′-methoxycarbonyl-2,2′-bithienyl* (X)

(1·5 g.), needles, m. p. 95°, $\lambda_{max.}$ 245, 339 mμ (log ε 3·89, 4·27) (Found: C, 46·4; H, 3·1; Cl, 14·4; S, 24·5. $C_{10}H_7ClO_2S_2$ requires C, 46·4; H, 2·7; Cl, 13·7; S, 24·8%), $\nu_{max.}$ 1725 (−CO_2Me), 785 cm.$^{-1}$ (2,5-disubstituted thiophen).

5-Carboxy-5′-chloro-2,2′-bithienyl (XI). The preceding ester (1 g.) in methanol (50 ml.) was added to 2·5N-sodium hydroxide (17 ml.) and kept at 40° for 12 hr. Methanol was removed, neutral material taken into ether, and the aqueous layer acidified to give *5-carboxy-5′-chloro-2,2′-bithienyl* (XI) (900 mg.), plates (from aqueous ethanol), m. p. 270—271°, $\lambda_{max.}$ 244, 337 mμ (log ε 3·14, 4·30) (Found: C, 44·0; H, 2·2; Cl, 14·3; S, 25·7. $C_9H_5ClO_2S_2$ requires C, 44·2; H, 2·1; Cl, 14·5; S, 26·2%), $\nu_{max.}$ 1700 (−CO_2H) and 790 cm.$^{-1}$ (2,5-disubstituted thiophen).

5-Chloro-2,2′-bithienyl (I). The acid (XI) (0·8 g.) was decarboxylated exactly as described for the bromo-analogue (IX). Chromatography of the crude product over alumina (Woelm, neutral, I), and elution with n-pentane–ether (95 : 5) gave *5-chloro-2,2′-bithienyl* (I) (375 mg.), b. p. 55°(bath)/0·05 mm., $\lambda_{max.}$ 247, 311 mμ (log ε 3·77, 4·14) (Found: C, 47·6; H, 2·7; Cl, 17·3; S, 31·4. $C_8H_5ClS_2$ requires C, 47·9; H, 2·5; Cl, 17·7; S, 32·0%), $\nu_{max.}$ 840 (5′-unsubstituted bithienyl), 790 (2,5-disubstituted thiophen), and 694 cm.$^{-1}$ (5′-unsubstituted bithienyl), retention time 20 min., R_F 0·74 (system A, blue-green spray colour), 0·79 (system B).

Attempted preparation of 5-iodo-2,2′-bithienyl. 5-Bromo-2,2′-bithienyl (1·2 g.) and cuprous iodide [13] (1·2 g.) in dimethyl sulphoxide (50 ml.) were heated under reflux for 2·5 hr. The solution was worked up in the usual way and the crude product passed through a short column of alumina in n-pentane. The yellow oil obtained was examined by vapour-phase chromatography and found to contain 2,2′-bithienyl (86%), 5-bromo-2,2′-bithienyl (4%), and 5-iodo-2,2′-bithienyl (10%), by comparison with authentic samples.

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Department of Chemistry, University College of Swansea,
Singleton Park, Swansea. [*Received, March 1st*, 1965.]

[13] G. B. Kauffman and R. P. Pinnell, *Inorg. Synth.*, 1960, **6**, 3.