The Preparation and Properties of Thiophen Analogues of Porphyrins and Related Systems. Part III.†

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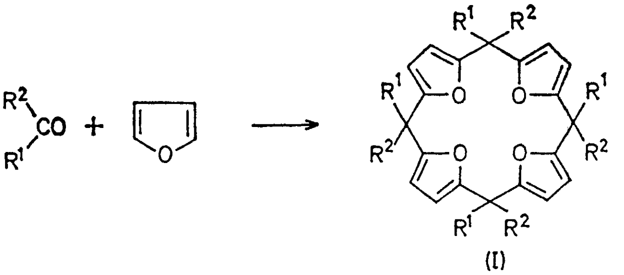
Routes to *meso*-substituted thiophen isosteres [(VIII), (IX), and (X)] of porphyrinogens involving interaction of di-2-thienylmethane derivatives are elaborated. The synthesis of thiophen isosteres [(XIV) and (XV)] of the tetrapyrrole system is described and the attempted cyclisation of some of them is discussed.

The porphyrin ring and related macrocyclic structures play a vital role in living systems. The haemoproteins, cytochromes, catalases and peroxidases and chlorophylls all include such a skeleton. These macrocycles are also of intrinsic chemical interest because of their relationship to the aromatic [18]annulenes and their unique ligand properties.

In 1955, Canadian workers[1] described the acid-catalysed reaction of furan with aliphatic ketones, whereby the furan isosteres (I) of the porphyrinogen system were obtained. The reaction could be carried out stepwise and pyrrole could be substituted for furan. However, the reaction did not proceed with thiophen.[1d] This paper describes our attempts to prepare the first thiophen isosteres of the porphyrin ring system.



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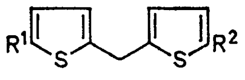
† Part II, M. Ahmed and O. Meth-Cohn, *Tetrahedron Letters*, 1969, 1493.

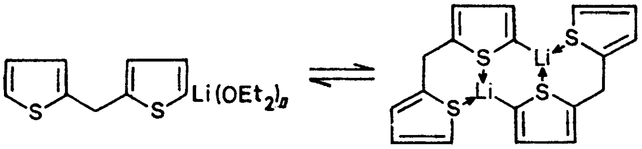
[1] (*a*) R. G. Ackman, W. H. Brown, and G. F. Wright, *J. Org. Chem.*, 1955, **20**, 1147; (*b*) W. H. Brown and H. Sawatsky, *Canad. J. Chem.*, 1956, **34**, 1147; (*c*) R. E. Beals and W. H. Brown, *J. Org. Chem.*, 1956, **21**, 447; (*d*) W. H. Brown and W. N. French, *Canad. J. Chem.*, 1958, **36**, 371, 537.

The majority of porphyrin syntheses involve either the cyclisation of a linear molecule incorporating four pyrrole rings (a tetrapyrrole) or the condensation of systems involving two pyrrole units.[2] Since di-2-thienylmethane (IIa) is readily prepared, we chose this compound as the basic unit in our syntheses. By careful temperature control (—7 to —4°), efficient stirring, and very slow addition of reagents, consistent yields of 65—70% of dithienylmethane (IIa) were obtained by the chloromethylation of thiophen in the presence of zinc chloride.[3] The chemistry of this compound has been thoroughly explored, primarily by Gol'dfarb [3,4] and his group. Thus, electrophilic substitutions occur at the 5- and 5'-positions, whereby mono- and di-bromo-[4b] (bromide–bromate mixture) and acetyl[4a] (acetic anhydride–phosphoric acid) derivatives may be readily prepared. Metallation is accomplished with butyl-lithium in ether at the free thiophen α-positions, although Gol'dfarb was not able to obtain pure disubstituted derivatives by this means.[4b] Thus, use of an excess of butyl-lithium at —5 to 0° followed by treatment with carbon dioxide gave a mixture of the 5-mono- and 5,5'-dicarboxylic acid. We have found that this reaction is critically dependant upon temperature. Thus, above 5° complete dimetallation is readily accomplished, whereas below —10° only one lithium atom is incorporated, regardless of the amount of butyl-lithium present. This suggests that an equilibrium exists in which the metal is solvated either by the solvent (III) or by the thiophen sulphur atoms of another molecule [*e.g.* (IV)], the position of equilibrium being determined primarily by the temperature of the dilute solution employed for metallation. At lower temperatures the solvation site necessary for introduction of a second metal atom is thus no longer available.



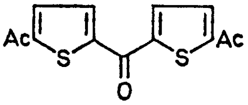
(II)

	R^1	R^2
a;	H	H
b;	Ac	Ac
c;	CHO	CHO
d;	Li	Li
e;	CO_2H	CO_2H
f;	H	CO_2H



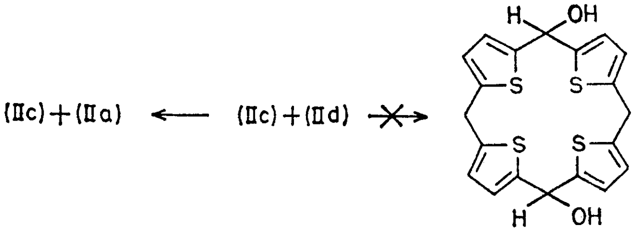
(III) (IV)

Gol'dfarb's work was conducted at the critical intermediate temperatures at which production of mixtures is inevitable. Attempts to lower the equilibrium temperature by use of tetrahydrofuran instead of ether succeeded insofar as dimetallation did occur; however much tar was also produced. Furthermore, the temperature necessary to metallate in a non-solvating solvent (hexane) was also sufficiently high to cause considerable charring. Treatment of the dilithio-compound (IId) with dimethylformamide gave a good yield of the dialdehyde (IIc). The diacyl compounds (IIb and c) bear an acidic methylene group. Thus the diacetyl compound gives a deep turquoise solution of the mesomeric carbanion is aqueous alkali, the colour of which in the presence of oxygen is rapidly discharged, with formation of the triketone. Attempts to convert the diketone (IIb) into the diacid (IIe) with hypochlorite not surprisingly gave the diacetyl ketone (V).[4a]



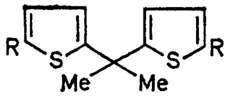
(V)

Our first attempt to synthesise a thiaporphyrinogen * involved the action of the dilithio-compound (IId) on the dithienylmethanedialdehyde (IIc) under high dilution conditions. In accord with the foregoing observations, instead of the hoped for condensation, dimetallation of the acidic methylene group of the dialdehyde occurred, producing the characteristic turquoise colour of the mesomeric anion. Treatment of the reaction mixture with water gave only the parent dithienylmethane and the corresponding dialdehyde (IIc). The interaction of dilithiodithienylmethane (IId) with methyl formate also gave no recognisable product.



(VI)

In order to eliminate the possibility of metallation at the bridge position, the di-2-thienylpropane (VIIa) was prepared. This was readily converted into the diacetyl derivative (VIIb) by direct acetylation, or into the diformyl derivative (VIIc) by way of the dilithio-compound (VIId). Similar high-dilution action of these acyl compounds with the corresponding dilithio-derivative (VIId) accomplished the required goal. The



(VII)

	R
a;	H
b;	Ac
c;	CHO
d;	Li

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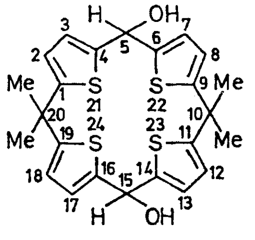
* For the sake of convenience the system (VI) and its analogues are referred to as thiaporphyrinogens and the system (XIV) as tetrathiophen, both by analogy with the relevant pyrrole isosteres.

[2] R. L. N. Harris, A. W. Johnson, and I. T. Kay, *Quart. Rev.*, 1966, **20**, 211.

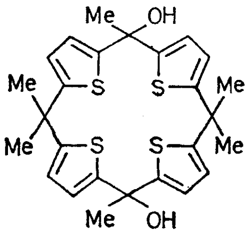
[3] Ya. L. Gol'dfarb and Ya. L. Danyushevsky, *Bull. Acad. Sci., U.S.S.R.*, 1956, 1395.

[4] (*a*) T. L. Cairns, B. C. McCusick, and V. Weinmayr, *J. Amer. Chem. Soc.*, 1951, **73**, 1270; (*b*) Ya. L. Gol'dfarb and M. L. Kirmalova, *J. Gen. Chem.* (*U.S.S.R.*), 1955, **25**, 1321; (*c*) Ya. L. Gol'dfarb and M. L. Kirmalova, *ibid.*, 1956, **26**, 3797.

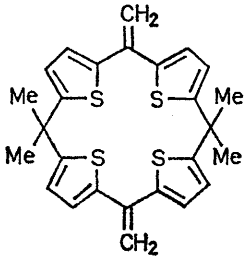
diformyl compound (VIIc) yielded the dihydroxytetramethylthiaporphyrinogen (VIII) (4·2%), m.p. 280° (decomp.), and the diacetyl compound (VIIb) gave the corresponding hexamethyl analogue (IX) (2·5%), m.p. 280° (decomp.), together with some of the diolefin (X) (0·8%), m.p. 250° (decomp.), probably resulting from dehydration of the alcohol (IX) during chromatography. These assignments were verified by the spectral properties of the products (see Experimental section). The i.r. spectra of compounds (VIII) and (IX) show the presence of OH groups and 2,5-disubstituted thiophenes and the absence of carbonyl groups. The n.m.r. spectra are very simple, showing a pair of doublets in the aromatic region and singlet signals for the geminal dimethyl groups, with an extra methyl absorption in the case of (IX). An extra, small allylic coupling of the bridge CH group in (VIII) with one aromatic proton is also observed. The mass spectra are particularly informative.* In each case a strong molecular ion (of correct accurate mass for the proposed structure) is seen and the primary fragmentation paths involve loss of a methyl group. The hexamethyl derivative (IX) also showed thermal loss of both one and two molecules of water, with the relevant fragmentation of both of the resulting products being evident. In a similar way the analogue (VIII) shows a second group of fragments derived from the $M - 2$ ion, which is also probably of thermal origin. The second methyl loss gives in each case a stronger doubly- rather than singly-charged ion, indicating the stability of the dithienyl carbonium ion (XI), in which the charges are insulated from each other. Indeed, the base peak from the diolefin is the corresponding mesomeric doubly-charged ion (XII) which is capable of [18]annulene aromatic stability. Peaks are also evident which result from ring fragmentation.



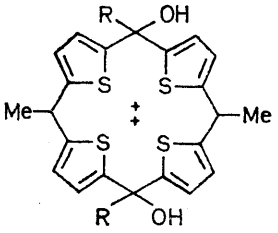
(VIII)



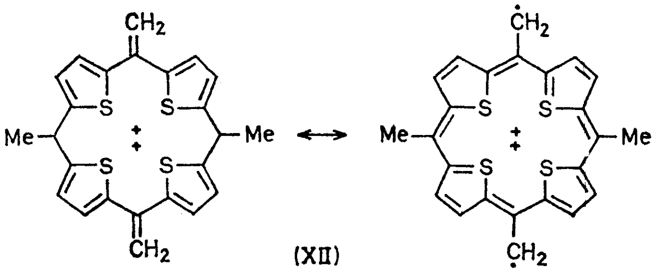
(IX)



(X)

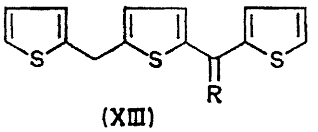


(XI)



(XII)

The success of the foregoing syntheses, albeit in low yield, suggested the possibility of obtaining improved yields by cyclisation of a linear tetrathiophen, since it is evident that the formation of a macrocycle from two segments is less favourable on several grounds than formation from one molecule.[6] Gol'dfarb and Danyushevsky[3] have observed that the action of thenoyl chloride on dithienylmethane in the presence of 1 equiv. of tin(IV) chloride only results in monothenoylation, and that in very low yield (12%). We found that use of only small amounts of tin(IV) chloride gave high yields of the monothenoyl derivative (XIIIa), which was readily reduced to the hydrocarbon (XIIIb) in high yield by the Wolff-Kishner method or by the action of lithium aluminium hydride–aluminium chloride. However, dithenoylation was readily accomplished in essentially quantitative yield by treatment of dithienylmethane with 2-thenoic acid in polyphosphoric acid (PPA) at 50—60° for 2·5 hr., to give bis-[5-(2-thenoyl)-2-thienyl]-methane (XIVa). The same product was obtained when the ketone (XIII) was similarly treated. The structure (in particular the positions of substitution) is fully confirmed by the i.r. and n.m.r. spectra. The carbonyl groups showed a strong absorption at 1590 cm.$^{-1}$ and the 'substitution' region showed a strong signal at 792 cm.$^{-1}$. The 100 MHz n.m.r. spectrum (deuteriochloroform) was first-order, with signals for the protons a, b, and c at low field and d and e at higher field, each showing the



a; R = O
b; R = H_2

(XIII)

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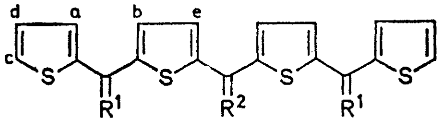
* These spectra have been fully recorded in an earlier report.[5] Tentative fragmentation patterns were outlined, which, in the light of accurate mass measurements, have now been shown to contain errors. For example, the proposed loss of methane is no longer tenable.

[5] O. Meth-Cohn, *Quart. Reports Sulphur Chem.*, 1970, **5**, 129.

[6] L. I. Belenkii, *Russ. Chem. Rev.*, 1964, **33**, 551.

expected coupling characteristics (see Experimental section). In addition, the absorption for proton e (a double triplet) also revealed allylic coupling to the methylene group, which was simplified to a doublet upon double irradiation at the methylene absorption frequency.



(XIV)

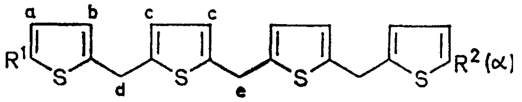
	R^1	R^2
a;	O	H_2
b;	H_2	H,OH
c;	H,OH	H_2
d;	H_2	H_2
e;	O	H,Me
f;	O	Me_2
g;	O	$[CH_2]_4$
h;	O	O

The tetrathiophen system was also synthesised, by the action of methyl formate on the monolithiodithienylmethane (III), yielding the monohydroxy-derivative (XIVb), and by the interaction of thiophen-2-carbaldehyde on the dilithiodithienylmethane (IId), giving the dihydroxy-compound (XIVc). However both of these compounds were unstable and neither reacted with reagents (benzyl chloride, dihydropyran) intended to protect the hydroxy-group. These methods were thus rejected in favour of the polyphosphoric acid-catalysed acylation.

The tetrathiophen diketone (XIVa) proved a versatile intermediate. The Wolff-Kishner reduction was accomplished in high yield to give the parent tetrathiophen (XIVd). The same results were achieved with aluminium chloride–lithium aluminium hydride. The central methylene group was readily substituted with one or two alkyl groups by the action of sodium hydride in tetrahydrofuran, followed by an alkyl halide. By this means the monomethyl (XIVe), dimethyl (XIVf), and tetramethylene (XIVg) derivatives were prepared. The turquoise anion derived by addition of aqueous alkali was readily decolourised by the passage of air through the solution to yield the triketone (XIVh).

The acylation of dithienylmethane (IIa) with 5-bromo-2-thenoic acid in PPA as before gave the corresponding dibromotetrathiophen diketone [*cf.* (XIVa)]. However reduction of the keto-groups with lithium aluminium hydride–aluminium chloride occurred with some loss of bromine, to give a mixture of the mono- and di-bromo-compounds (XVa and b). The Wolff-Kishner procedure gave only tars, presumably as a result of nucleophilic substitution of the activated bromine atoms.

The chemistry of the parent tetrathiophen was next explored. This compound is remarkably inert to electrophilic substitution, which tends to occur at the free α-positions. The conditions which would readily substitute thiophen or dithienylmethane are totally without effect upon the tetrathiophen system. The reason for this phenomenon is at present obscure. It is clearly not only a statistical effect since, for example, the work of Gol'dfarb[7] demonstrates that thiophens bearing a long chain in one α-position are readily acylated at the other α-site. It is possible that either charge-transfer interactions between the terminal and inner rings or solvent–solute interactions occur, as a result of which the molecule is less capable of electrophilic substitution. Thus no bromination occurred with bromide–bromate reagent, and bromine in various solvents (carbon tetrachloride, pyridine, chloroform, acetic acid) was unsatisfactory for preparative purposes; mixtures of unchanged material and the mono- and di-bromo-derivatives (XVa and b) were formed together with much tar. Similar troubles were experienced with the mild reagent of Wynberg and his co-workers[8] (*N*-bromosuccinimide–chloroform–acetic acid). Iodination with iodine and mercury(II) oxide was more successful, although slow, and the pure di-iodo-compound (XVc) was isolated in good yield. The positions of substitution during halogenations were confirmed not only spectroscopically but by conversion of the halides into the acid (XVe) by the action of butyl-lithium followed by carbon dioxide. The same mixture of the mono- and di-carboxylic acids was obtained by metallation of the tetrathiophen with butyl-lithium followed by carbon dioxide treatment. Conditions for complete dimetallation were also sufficiently vigorous to decompose the system extensively. However the mixture of acids was readily separated after conversion into the methyl esters, by chromatography.



(XV)

	R^1	R^2
a;	Br	H
b;	Br	Br
c;	I	I
d;	CO_2H	H
e;	CO_2H	CO_2H
f;	CO_2Me	H
g;	CO_2Me	CO_2Me
h;	Ph	Ph

Acylation experiments proved to be particularly fruitless. Thus the tetrathiophen was unchanged under Vilsmeier–Haack formylation conditions and also on treatment with acetic anhydride–phosphoric acid, acetyl chloride–tin(IV) chloride, or acetic acid–PPA at 50—60°. However with a large excess of acetic acid in PPA at 100° an interesting series of reactions occurred. The final product has suffered the introduction of four acetyl groups with loss of one molecule of water. Spectroscopic evidence pointed to the benzodithiophen structure (XIX). The analysis data were supported by a mass spectral

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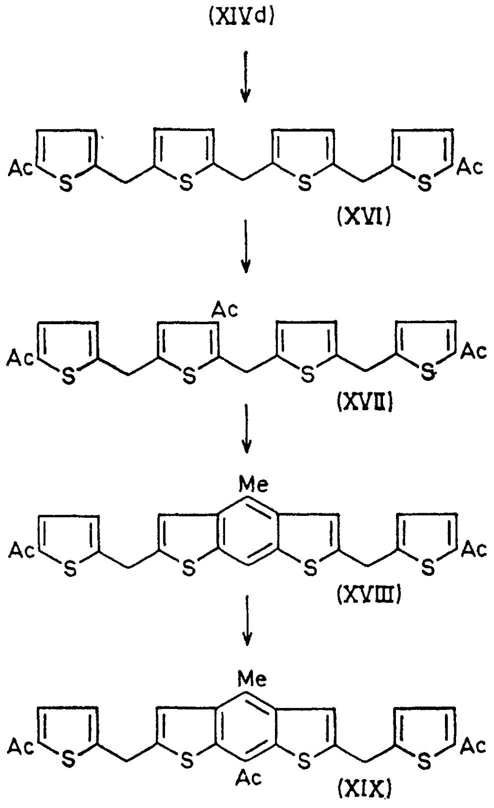
[7] Ya. L. Gol'dfarb, S. Z. Taits, and L. I. Belenkii, *Tetrahedron*, 1963, **19**, 1851.

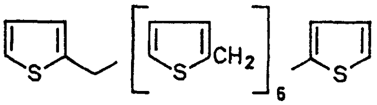
[8] R. M. Kellog, A. P. Schaap, E. T. Harper, and H. Wynberg, *J. Org. Chem.*, 1968, **33**, 2902.

molecular ion at *m/e* 522 and significant fragment ion peaks at 507 ($M - CH_3$) and 479 ($M - CO{\cdot}CH_3$). In the n.m.r. spectrum (deuteriochloroform) three separate singlet methyl absorptions were observed [τ 7·52 (6H), 7·17 (3H), and 7·11 (3H)], the two methylene groups showed as a broadened singlet at τ 5·53, and the aromatic absorptions contained two doublets (τ 3·00 and 2·45, *J* 4·0 Hz), corresponding to the terminal thiophenic protons and a broadened singlet (τ 2·67) for the two benzodithiophen protons. The mode of genesis of this compound is suggested in the Scheme. The initial acetylation at the terminal α-positions (XVI) tends to deactivate inductively the adjacent position on the central thiophen rings, and thus preferentially leads to the third acetyl group entering the position indicated in (XVII). This compound is now capable of a Bradsher-type cyclodehydration to yield the benzodithiophen (XVIII), which may then be finally substituted in the central ring. The occurrence of this type of direct Bradsher reaction has been amply verified by application to several related systems and has been the subject of another paper.[9]



SCHEME

Having several suitable derivatives now available, we next attempted the cyclisation to thiophen analogues of the porphyrinogen and related systems. However, in no case was any evidence for cyclisation observed. Thus, the high dilution treatment of the mono-acid (XVd) with PPA gave only polymer and no evidence for intramolecular acylation. The application of the acyloin synthesis to the preparation of macrocycles containing the thiophen ring has been thoroughly explored by Gol'dfarb and his co-workers.[7] They found that while molten sodium tended to decompose the thiophen, use of a sodium–potassium alloy gave good yields of the required products. The diester (XVg) was completely unaffected by both the alloy and by sodium at temperatures up to 160°. The only reported attempt (to our knowledge) of an acyloin condensation on an aromatic ester was also without success.[10] It would appear that co-ordination of the sulphur atoms with the metallic surface renders the molecule inflexible and thus incapable of the acyloin reaction. Another potential route to corrin analogues lay in the photolysis of the iododerivative (XVc). Iodobenzene is known to form phenyl radicals under photochemical conditions, and in benzene solution this leads to biphenyl.[11] In benzene solution a good yield of the phenylated derivative was indeed formed on photolysis of the iodo-compound (XVc). However photolysis in hexane, which might be expected to give a cyclic product, gave only tar. The possibility of the tetrathiophen showing ligand properties was next considered. Porphyrins are frequently synthesised by use of a metal template around which a tetrapyrrole derivative is complexed to facilitate cyclisation.[2] However the very much weaker ligand properties of a thiophenic sulphur atom are indicated by the total absence of cyclic products from the following reactions. The action of cobalt or copper(II) chloride on the dilithio-compound of the tetrathiophen gave only tar (thienyllithium gives dithienyl under these conditions). The chloromethylation of the tetrathiophen in the presence of zinc chloride gave no cyclic compound but only the octathiophen (XX).



(XX)

It thus appears that substitution of the linear precursor, either at the β- or the bridge positions, is an essential conformational prerequisite for ready cyclisation. This aspect is at present under examination.

EXPERIMENTAL

I.r. spectra were obtained with a Perkin-Elmer 137 spectrometer and n.m.r. spectra either with a Varian A60A or an HA100 instrument, with tetramethylsilane as internal standard. Mass spectra were recorded with an A.E.I. MS 12 instrument and accurate mass measurements were conducted at the Physico-chemical Measurements Unit, Harwell, whom we thank. Commercial butyl-lithium was

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[9] M. Ahmed, J. Ashby, and O. Meth-Cohn, *Chem. Comm.*, 1970, 1094.

[10] I. Ugi, R. Huisgen, and D. Pawallek, *Annalen*, 1961, **641**, 63.

[11] R. K. Sharma and N. Kharasch, *Angew. Chem. Internat. Edn.*, 1968, **7**, 36.

employed as a 20—25% solution in n-hexane (from Pfizer, Sandwich, Kent).

Di-2-thienylmethane (IIa).—The compound was prepared according to the method of Gol'dfarb and Danyushevsky,[3] formaldehyde being added during 1·5—1·75 hr. and the temperature rigorously maintained between −7 and −4°.

5,5'-*Methylenebisthiophen*-2-*carboxylic Acid* (IIe).—To a solution of dithienylmethane (5·4 g., 0·03 mole) in dry ether (60 ml.) at room temperature under nitrogen was added butyl-lithium (0·065 mole); the mixture was stirred for 15 min., then poured on crushed solid carbon dioxide. The precipitated solid was filtered off, washed with ether, dissolved in water, and acidified. The solid (5·6 g., 70%) was collected and recrystallised from aqueous ethanol; m.p. 250° (decomp.) (Found: C, 49·4; H, 2·6; S, 24·2. $C_{11}H_8O_4S_2$ requires C, 49·3; H, 3·0; S, 23·9%), $\nu_{max.}$ (Nujol) 1690 cm.$^{-1}$, τ ($CF_3{\cdot}CO_2D$) −1·47 (CO_2H), 1·96 (4- and 4'-H, d, *J* 3·9 Hz), 2·82 (3- and 3'-H, d, *J* 3·9 Hz), and 5·42 (CH_2).

5,5'-*Methylenebisthiophen*-2-*carbaldehyde* (IIc).—To a mixture of di-2-thienylmethane (6·0 g., 0·033 mole), dry ether (200 ml.), and butyl-lithium (0·074 mole), prepared as before, dimethylformamide (5·8 g., 0·078 mole) in dry ether was added dropwise with stirring at room temperature, and stirring was continued for a further 2 hr. The mixture was washed successively with water, dilute hydrochloric acid, water, and sodium hydrogen carbonate solution, dried and evaporated. The residue (7·0 g., 90%) gave white *prisms* (5·9 g., 75%) from light petroleum (b.p. 80—100°), m.p. 95° (Found: C, 55·55; H, 3·5; S, 27·3. $C_{11}H_8O_2S_2$ requires C, 55·9; H, 3·4; S, 27·1%), $\nu_{max.}$ (Nujol) 1660 cm.$^{-1}$ (CHO), τ ($CDCl_3$) 0·16 (CHO), 2·40 (H-3 and H-3', d, *J* 3·6 Hz), 3·01 (H-4 and H-4', d, *J* 3·6 Hz), and 5·58 (CH_2).

5,5'-*Isopropylidenebisthiophen*-2-*carbaldehyde* (VIIc).—To a solution of di-2-thienylpropane[12] (VIIa) (12·48 g., 0·06 mole) in dry ether (300 ml.) at room temperature, butyl-lithium (0·14 mole) was added under nitrogen. After 15 min. stirring, dimethylformamide (10·22 g., 0·14 mole) in dry ether (30 ml.) was added dropwise, and stirring was continued for 2 hr. The mixture was washed successively with water, dilute hydrochloric acid, water, and sodium hydrogen carbonate solution, dried, and evaporated. The solid *residue* (13·0 g., 82%) was crystallised from light petroleum (b.p. 80—100°); m.p. 72° (Found: C, 59·4; H, 4·4; S, 24·6. $C_{13}H_{12}O_2S_2$ requires C, 59·15; H, 4·6; S, 24·3%), $\nu_{max.}$ (Nujol) 1660 cm.$^{-1}$ (CHO), τ ($CDCl_3$) 8·19 (CMe_2, s), 2·99 (H-3 and H-3', d, *J* 3·8 Hz), 2·37 (H-4 and H-4', d, *J* 3·8 Hz), and 0·12 (CHO, s).

2,2-*Bis*-(5-*acetyl*-2-*thienyl*)*propane and* 2-(5-*Acetyl*-2-*thienyl*)-2-(2-*thienyl*)*propane*.—A mixture of di-2-thienylpropane (50 g., 0·025 mole) and acetic anhydride (6·0 g., 0·6 mole) was heated to 70—75°. The heat was removed and phosphoric acid (85%; 4 drops) was added. After the exothermic reaction had subsided, the mixture was refluxed for 2·5 hr., cooled, poured into water, and extracted with chloroform. The extract was washed with sodium hydrogen carbonate solution, dried, and evaporated. The oily residue (7·0 g.) was chromatographed on silica gel. Elution with benzene–chloroform (3 : 1) gave the *monoacetyl derivative* as an oil (1·5 g., 25%) (Found: C, 62·8; H, 5·3; S, 25·3. $C_{13}H_{14}OS_2$ requires C, 62·4; H, 5·6; S, 25·6%), $\nu_{max.}$ (film) 1640 cm.$^{-1}$ (CO), τ ($CDCl_3$) 8·19 (CMe_2, s), 7·57 (COMe, s), and 2·5—3·2 (aromatic H). Further elution, with benzene–chloroform (1 : 1), gave the *diacetyl derivative* (VIIb) (4·5 g., 64%), m.p. 62° [from light petroleum (b.p. 60—80°)] (Found: C, 62·0; H, 5·8; S, 21·5. $C_{15}H_{16}O_2S_2$ requires C, 61·7; H, 5·5; S, 21·9%), $\nu_{max.}$ (Nujol) 1640 cm.$^{-1}$ (CO), τ ($CDCl_3$) 8·19 (CMe_2, s), 7·55 (COMe, s), 2·90 (H-3 and H-3', d, *J* 3·9 Hz), and 2·50 (H-4 and H-4', d, *J* 3·9 Hz).

Interaction of 2,2-*Bis*-(5-*acylthienyl*)*propanes* (VIIb *and* c) *and* 2,2-*Bis*-(5-*lithiothienyl*)*propane* (VIId).—(*a*) The dithienylpropane (VIIa) (4·57 g., 0·022 mole) in dry ether (500 ml.) and butyl-lithium (0·044 mole) were stirred together at room temperature under nitrogen for 15 min. The resulting solution was transferred under nitrogen to a stirred solution of the diformyldithienylpropane (VIIc) (5·81 g., 0·022 mole) in dry ether (3 l.). A white precipitate formed and stirring was continued for 28 hr. under nitrogen. The mixture was washed with water, dried, and evaporated and the thick, brown oil was chromatographed on alumina. Elution with benzene gave firstly dithienylpropane (1·3 g.), then dithienylpropanedialdehyde (1·8 g.). Further elution, with chloroform–benzene (6 : 4), gave the *tetramethyldihydroxythiaporphyrinogen* (VIII) (0·4 g., 4%), m.p. 280° (decomp.) (from ethyl acetate and light petroleum) (Found: C, 60·8; H, 5·4; S, 27·5. $C_{24}H_{24}O_2S_4$ requires C, 61·1; H, 5·1; S, 27·2%), $\nu_{max.}$ (Nujol) 3180 (OH) and 795 cm.$^{-1}$ (2,5-disubst. thiophen), τ (C_5D_5N) 8·27 (CMe_2, s), *ca.* 5·0 br (OH), 3·52br (H-5 and H-15), 3·24 (H-2, -8, -12, and -18, d, *J* 3·3 Hz), and 2·96 (H-3, -7, -13, and -17, dd, *J* 3·3 and 0·2 Hz), M^+ 472·0623 ($C_{24}H_{24}O_2S_4$ requires 472·0660).

(*b*) The dithienylpropane (VIIa) (2·08 g., 0·01 mole) in dry ether (500 ml.) was treated with butyl-lithium (0·022 mole) at room temperature with stirring. After 15 min., the resulting solution was transferred under nitrogen to a stirred solution of the diacetyldithienylpropane (VIIb) (2·92 g., 0·01 mole) in dry ether (2 l.). A white precipitate slowly separated and stirring was continued for 24 hr. The resultant mixture was worked up as in (*a*) to give a thick brown oil (6·0 g.), which was chromatographed on alumina. Elution with benzene gave firstly dithienylpropane (VIIa) (0·6 g.), then the diacetyldithienylpropane (VIIb) (0·6 g.), and then the *dihydroxyhexamethylthiaporphyrinogen* (IX) (0·12 g., 2·5%), m.p. 280° (decomp.) [from ethyl acetate and light petroleum (b.p. 40—60°)] (Found: C, 62·7; H, 5·5; S, 25·8. $C_{26}H_{28}O_2S_4$ requires C, 62·5; H, 5·6; S, 25·65%), $\nu_{max.}$ (Nujol) 3360, 3315 (OH), 812, and 797 cm.$^{-1}$ (2,5-disubst. thiophen), τ (C_5D_5N) 8·27 (CMe_2, s), 7·79 (CMe, s), 5·4br (OH), 3·27 (H-2, -8, -12, and -18, d, *J* 4·0 Hz), and 2·97 (H-3, -7, -13, and -17, d, *J* 4·0 Hz), τ ($CDCl_3$) 8·24, 7·96, 8·46, 3·29 (d, *J* 4·0), and 3·15 (d, *J* 4·0 Hz).

Further elution, with benzene–chloroform (1 : 1), gave the *tetramethyldimethylenethiaporphyrinogen* (X) (0·05 g., 0·81%), m.p. 250° (decomp.) (Found: C, 67·1; H, 5·3; S, 27·9. $C_{26}H_{24}S_4$ requires C, 67·3; H, 5·2; S, 27·6%).

Thenoylation of Di-2-thienylmethane.—(a) *With thenoyl chloride and tin*(IV) *chloride*. To a solution of di-2-thienylmethane (12·6 g., 0·07 mole) and 2-thenoyl chloride (10·3 g., 0·07 mole) in benzene (150 ml.) at 0°, tin(IV) chloride (1·82 g., 0·007 mole) was added dropwise with stirring. After 30 min. stirring at room temperature and 30 min. at 40—50°, the mixture was treated with water and the benzene layer was washed with sodium carbonate solution and dried. Evaporation gave 2-(2-thenoyl)-5-(2-thenyl)thiophen (XIIIa) as a brown solid which crystallised from ethanol as white needles, m.p. 104° (lit.,[3] 104·5—105·5°) (15·6 g., 77%).

Attempts to introduce a second thenoyl group by use of an excess of thenoyl chloride, longer reaction times, higher temperatures, or more catalyst were without success.

[12] M. Sy, M. Maillet, and P. David, *Bull. Soc. chim. France*, **1967**, 2609.

(b) *With* 2-*thenoic acid and PPA*. A mixture of dithienylmethane (6·3 g., 0·035 mole) and 2-thenoic acid (10·0 g., 0·07 mole) in polyphosphoric acid (300 g.) was stirred for 2·5 hr. at 50°. The dark brown solution was poured into ice–water (600 ml.), when the crystalline product, *bis*-[5-(2-*thenoyl*)-2-*thienyl*]*methane* (XIVa) separated. It was filtered off, washed with sodium carbonate solution and then water, and dried (yield 14·2 g., 98%). Recrystallisation (from ethanol gave needles, m.p. 123° (Found: C, 57·2, H, 2·9; S, 31·7. $C_{19}H_{12}O_2S_4$ requires C, 57·0; H, 3·0; S, 32·0%), $\nu_{max.}$ (Nujol) 1590 cm.$^{-1}$ (CO), τ ($CDCl_3$) 2·13 (H_a, q, J_{ad} 3·8, J_{ac} 1·2 Hz), 2·25 (H_b, d, J_{be} 3·8 Hz), 2·37 (H_c, q, J_{cd} 5·0, J_{ac} 1·2 Hz), 2·85 (H_d, q, J_{ad} 3·8, J_{cd} 5·0 Hz), 3·00 (H_e, dt, J_{be} 3·8, J_{e,CH_2} 0·8 Hz), and 5·58 (CH_2, t, J_{e,CH_2} 0·8 Hz).

The same product was obtained in similar yield by the action of 2-thenoic acid and PPA on 2-(2-thenoyl)-5-(2-thenyl)thiophen under the same conditions.

(c) *With* 2-*bromo*-5-*thenoic acid and PPA*. A mixture of dithienylmethane (4·5 g., 0·025 mole) and 2-bromo-5-thenoic acid (10·35 g., 0·05 mole) in PPA (600 g.) was treated similarly to give a gum (8·8 g.). Chromatography on alumina yielded (elution with ether) a solid, which gave *bis*-[5-(5-*bromo*-2-*thenoyl*)-2-*thienyl*]*methane* (1·75 g., 12%) as white plates, m.p. 145° (from ethanol) (Found: C, 40·65; H, 1·8; Br, 27·5; S, 22·3. $C_{19}H_{10}Br_2O_2S_4$ requires C, 40·9; H, 1·8; Br, 28·5; S, 22·9%), $\nu_{max.}$ (Nujol) 1600 cm.$^{-1}$ (CO), τ ($CDCl_3$) 2·21—3·01 (aromatic H, complex) and 5·56br (CH_2, s).

Reduction of the Tetrathiophen Diketones.—(a) *With hydrazine hydrate and potassium hydroxide*. To the diketone (XIVa) (8·0 g., 0·02 mole) in ethylene glycol (250 ml.) was added hydrazine hydrate (10·0 g., 0·2 mole) with stirring. The resulting light green solution was heated to 165° during 45 min., and stirring at this temperature was continued for 1·5 hr. The temperature was lowered, and water and excess of hydrazine hydrate were removed under a slight vacuum. Potassium hydroxide pellets (16·8 g., 0·3 mole) were added to the brown solution at 60° and the temperature was again raised to 165° and maintained there for 2·5 hr. The yellow solution was cooled and poured into water to give the *tetrathiophen* (XIVd) as a crystalline solid. After filtration, washing and drying (yield 7·1 g., 95%) the product gave white plates, m.p. 78° (from ethanol) (lit.,[13] 78·5—79·5°) (Found: C, 60·9; H, 4·5; S, 34·6. $C_{19}H_{16}S_4$ requires C, 61·2; H, 4·3; S, 34·4%).

A similar reduction of the dibromo-ketone gave only polymeric material.

(b) *With lithium aluminium hydride and aluminium chloride*. To a solution of the diketone (4·0 g., 0·01 mole) in dry 1,2-dimethoxyethane (50 ml.) was added anhydrous aluminium chloride (2·0 g., 0·015 mole). The resulting solution was added slowly to lithium aluminium hydride (1·2 g., 0·032 mole) suspended in dry 1,2-dimethoxyethane (50 ml.) and the resulting solution was heated under reflux for 1 hr. The cooled solution was treated with methyl formate (5 ml.) and then 20% aqueous sulphuric acid. The organic phase was extracted with ether, washed successively with water, sodium carbonate solution, and then water, dried, and evaporated to give the *tetrathiophen* (XIVd) (3·43 g., 92%) as a cream solid, m.p. 75—77°.

In a similar manner the dibromo-ketone (1·0 g.) gave a mixture (0·5 g.) of the tetrathiophen (XIVa) and its *monobromo*- (XVa) and *dibromo*- (XVb) *derivatives*, as indicated by its mass spectrum.

Bis-{5-[*hydroxy*-(2-*thienyl*)*methyl*]-2-*thienyl*}*methane* (XIVc).—To a solution of di-2-thienylmethane (12·6 g., 0·07 mole) in dry ether (450 ml.) at room temperature (22°) was added butyl-lithium (0·15 mole) with stirring during 15 min. Thiophen-2-carbaldehyde (18·0 g., 0·16 mole) in dry ether (60 ml.) was then added dropwise; a white precipitate formed and stirring was continued for 1 hr. The mixture was poured into water (200 ml.) and the organic phase was dried and evaporated. The brown residue was triturated with ether–light petroleum (1 : 1) and the solid was crystallised from carbon tetrachloride to give white *needles*, m.p. 104—106° (13·3 g., 53%) (Found: C, 56·4; H, 3·8; S, 32·2. $C_{19}H_{16}O_2S_4$ requires C, 56·4; H, 3·9; S, 31·7%).

The compound (2·0 g.) was unchanged after treatment with benzyl chloride (1·2 g.) and sodium iodide (1·65 g.) in acetone (25 ml.) under reflux for 12 hr.

Bis-[5-(2-*thenyl*)-2-*thienyl*]*methanol* (XIVb).—To a stirred solution of di-2-thienylmethane (9·9 g., 0·055 mole) in dry ether (400 ml.) at −30° was added butyl-lithium (0·055 mole). After 30 min., methyl formate (1·65 g., 0·275 mole) in dry ether (15 ml.) was added dropwise during 20 min. The temperature was raised to 22° and the solution was stirred for 3 hr. It was then poured into water. The ether layer was washed successively with water, hydrochloric acid (0·5N), water, and sodium hydrogen carbonate solution, dried, and evaporated. The remaining oil was chromatographed on basic alumina; elution with ether–light petroleum (1 : 1) gave the *alcohol* (XIVb) (5·0 g., 46%) as a viscous oil (Found: C, 58·5; H, 4·5; S, 33·9. $C_{19}H_{16}OS_4$ requires C, 58·7; H, 4·2; S, 33·1%), $\nu_{max.}$ (film) 3340 cm.$^{-1}$ (OH), τ ($CDCl_3$) 2·90—3·42 (aromatic H), 4·13 ($CH{\cdot}OH$), 5·83 (CH_2), and 7·25 (OH).

Reactions of the Diketone (XIVa).—(a) *Oxidation*. (i) *With manganese dioxide*. The diketone (1 g.) in benzene (100 ml.) was boiled with active manganese dioxide (10 g.) for 20 hr. The hot solution was filtered and the residue was washed with further portions of hot benzene. From the cooled extracts a crystalline mass (0·7 g.) was isolated. Recrystallisation from benzene (charcoal) gave the *triketone* (XIVh) as prisms, m.p. 258—260° (Found: C, 54·7; H, 2·4; S, 30·8. $C_{19}H_{10}O_3S_4$ requires C, 55·0; H, 2·4; S, 30·9%), $\nu_{max.}$ (Nujol) 1600 cm.$^{-1}$ (CO).

(ii) *Action of alkali and air*. To the diketone (XIVa) (1 g.) in 1,2-dimethoxyethane (60 ml.) was added ethanolic potassium hydroxide solution. A deep turquoise solution was formed. Air was passed through the solution; the colour faded and the triketone (XIVh) (1·0 g., 96%) precipitated as a white solid, identical (i.r. spectrum, m.p., mixed m.p.) with the foregoing sample.

(b) *Alkylation*. (i) *With methyl iodide*. The diketone (XIVa) (2·0 g., 0·005 mole) in dry 1,2-dimethoxyethane (80 ml.) was treated with sodium hydride (0·12 g., 0·005 mole). To the resulting turquoise solution methyl iodide (2·0 g.) in 1,2-dimethoxyethane (12 ml.) was added dropwise. After 2 hr. boiling the solution became brown, and was poured into water. The precipitated solid was thoroughly extracted with chloroform and the extract was dried and evaporated to give 1,1-*bis*-[5-(2-*thenoyl*)-2-*thienyl*]*ethane* (XIVe) (1·6 g., 77%). Recrystallisation from isopropyl alcohol gave prisms, m.p. 177° (Found: C, 58·05; H, 3·3; S, 30·7. $C_{20}H_{14}O_2S_4$ requires C, 58·0; H, 3·4; S, 30·9%),

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[13] P. A. Konstantinov, L. V. Semerenko, K. M. Suvarova, E. N. Bondar, and Ya. L. Gol'dfarb, *Khim. geterotsikl. Soedinenii*, 1968, 230.

$\nu_{max.}$ (Nujol) 1605 cm.$^{-1}$ (CO), τ ($CDCl_3$) 2·1—3·1 (aromatic H), 5·30 (C*H*Me, q, *J* 7·0 Hz), and 8·12 (CH_3, d, *J* 7·0 Hz).

By a similar procedure, the diketone (1·5 g., 0·00375 mole) and sodium hydride (0·18 g., 0·0075 mole) in 1,2-dimethoxyethane, on treatment with methyl iodide (4 g.) gave 2,2-*bis*-[5-(2-*thenoyl*)-2-*thienyl*]*propane* (1·09 g., 68%) as prisms (from isopropyl alcohol), m.p. 151° (Found: C, 58·6; H, 3·5; S, 30·0. $C_{21}H_{16}O_2S_4$ requires C, 58·9; H, 3·8; S, 29·8%), $\nu_{max.}$ (Nujol) 1600 cm.$^{-1}$ (CO), τ ($CDCl_3$) 2·0—3·1 (aromatic H) and 8·07 (Me, s).

(ii) *With* 1,4-*dibromobutane*. To a solution of the diketone (1·5 g., 0·00375 mole) in dry tetrahydrofuran (100 ml.) was added sodium hydride (0·18 g., 0·0075 mole). To the turquoise solution was added 1,4-dibromobutane (0·89 g., 0·00415 mole) in tetrahydrofuran (15 ml.), and the mixture was boiled for 60 hr. The solvent was removed and the red residue was extracted with chloroform. The extract was washed with water, decolourised with charcoal, dried, and evaporated to give a crystalline product (1·3 g., 76%). Recrystallisation from propan-2-ol gave 1,1-*bis*-[5-(2-*thenoyl*)-2-*thienyl*]*cyclopentane*, m.p. 155° (Found: C, 60·6; H, 4·2; S, 28·25. $C_{23}H_{18}O_2S_4$ requires C, 60·8; H, 4·0; S, 28·2%), τ ($CDCl_3$) 2·12 (H_a, q, J_{ad} 3·8, J_{ac} 1·2 Hz), 2·24 (H_b, d, J_{be} 3·8 Hz), 2·31 (H_c, q, J_{cd} 5·0, J_{ac} 1·2 Hz), 2·82 (H_d, q, J_{ad} 3·8, J_{dc} 5·0 Hz), 2·99 (H_e, d, J_{cb} 3·8 Hz), 7·49br (2 × CH_2, t), and 8·12br ($CH_2{\cdot}CH_2$, quintet).

Reactions of the Tetrathiophen (XIVd).—(a) *Iodination*. To a stirred solution of the tetrathiophen (0·93 g., 0·0025 mole) in dry benzene (25 ml.) were added iodine (1·42 g., 0·0055 mole) and yellow mercury(II) oxide (1·82 g., 0·0084 mole) in small portions at room temperature. Stirring was continued until the iodine had disappeared (5 hr.), after which the solution was filtered. The filtrate was washed with sodium thiosulphate solution then water, dried, and evaporated to give *bis*-[5-(5-*iodo*-2-*thenyl*)-2-*thienyl*]*methane* (XVc) (1·15 g., 74%). Recrystallisation from ethanol gave plates, m.p. 98° (Found: C, 36·8; H, 2·3; S, 20·9. $C_{19}H_{14}I_2S_4$ requires C, 36·5; H, 2·5; S, 20·5%), τ ($CDCl_3$) 2·94 (H_a, d, J_{ab} 3·7 Hz), 3·33 (H_c, s), 3·49 (H_b, dt, J_{ba} 3·7, J_{b,CH_2} 0·7 Hz), 5·84 (H_d × 2), and 5·88 (H_e × 2).

(b) *Metallation reactions*. (i) To a stirred solution of the tetrathiophen (11·1 g., 0·03 mole) in dry ether (1 l.) at −8° under nitrogen was added butyl-lithium (0·09 mole) slowly. After stirring for 20 min., during which time the temperature was allowed to reach 1°, the mixture was poured rapidly on crushed solid carbon dioxide and ether. The voluminous precipitate was filtered off, washed with ether dissolved in water, and acidified with ice-cold hydrochloric acid (0·1N). The precipitated mixture of acids was filtered off, washed with water and light petroleum, and dissolved in bis-2-methoxyethyl ether. An excess of ethereal diazomethane was added and the mixture was then poured into water and extracted with ether. The extract was dried and evaporated and the residue (18·0 g.) was chromatographed on silica gel. Elution with benzene–petroleum (b.p. 40—60°) (25 : 75) afforded the *monocarboxylic ester* (XVf) (2·0 g., 15%), m.p. 89° (Found: C, 58·1; H, 4·1; S, 30·0. $C_{21}H_{18}O_2S_4$ requires C, 58·5; H, 4·2; S, 29·8%), $\nu_{max.}$ (Nujol) 1700 cm.$^{-1}$ (CO), τ ($CDCl_3$) 2·34 (H_a, d, *J* 3·8 Hz), 2·82 (α-H, q, $J_{\alpha a'}$ 1·5 Hz), 3·0—3·2 (H_b, $H_{a'}$, $H_{b'}$, complex), 3·33 (H_c, s), 5·75 (H_d, s), 5·82 (H_e, s), and 6·18 (CO_2Me). Elution with benzene–chloroform (75 : 25) gave the *diester* (XVg) (4·2 g., 29%), m.p. 106° (Found: C, 56·4; H, 4·0; S, 26·6. $C_{23}H_{20}O_4S_4$ requires C, 56·6; H, 4·1; S, 26·2%), $\nu_{max.}$ (Nujol) 1700 cm.$^{-1}$ (CO), τ ($CDCl_3$) 2·48 (H_a, d, J_{ab} 3·8 Hz), 3·25 (H_b, d, J_{ab} 3·8 Hz), 3·42 (H_c, s), 5·87 (H_d, s), 5·91 (H_e, s), and 6·27 (CO_2Me, s).

(ii) The di-iodotetrathiophen (XVc) (1·2 g., 0·002 mole) was treated with butyl-lithium (0·0045 mole) as in (i). Treatment with carbon dioxide and diazomethane then yielded, after similar work-up, the diester (XVg) (0·4 g., 42·5%).

(c) *Acylation*. The tetrathiophen (1·8 g., 0·005 mole) and acetic acid (10 ml.) in PPA (200 g.) were heated for 2 hr. at 100°. The mixture was added to water and thoroughly extracted with chloroform. The extract was dried and evaporated and the residue was chromatographed on alumina. Elution with benzene gave firstly the unchanged tetrathiophen (0·3 g.), followed by the *benzodithiophen* (XIX) (0·56 g., 22%), m.p. 218—220° (Found: C, 62·1; H, 4·1; S, 24·7. $C_{27}H_{22}O_3S_4$ requires C, 62·0; H, 4·2; S, 24·55%); see Discussion section for spectral data.

Attempted Cyclisation of the Tetrathiophens (XV).—(a) *Photolysis*. A solution of the di-iodo-compound (XVc) (1·0 g.) in benzene (150 ml.) was added dropwise during 3 hr. to stirred benzene (600 ml.) under nitrogen, with u.v. irradiation (quartz filter). The stirring and irradiation were continued for a further 2 hr., with the formation of iodine. The solution was washed with sodium thiosulphate solution, sodium hydrogen carbonate solution, and water, dried, and evaporated. The solid residue (0·7 g.) was chromatographed on silica gel. Elution with light petroleum (40—60°)–benzene (75 : 25) gave first the starting material then the *diphenyltetrathiophen* (XVh) (0·18 g., 21·5%), which formed plates, m.p. 137° [from light petroleum (b.p. 100—120°)] (Found: C, 71·0; H, 4·5; S, 24·7. $C_{31}H_{24}S_4$ requires C, 70·9; H, 4·6; S, 24·4%), $\nu_{max.}$ (Nujol) 685 and 750 (Ph), and 805 cm.$^{-1}$ (2,5-disubst. thiophen), τ ($CDCl_3$) 2·5—3·3 (aromatic H, complex), 5·78 (H_d), and 5·82 (H_e).

A similar photolysis, in which n-hexane was used in place of benzene, gave only tar and starting material.

(b) *Chloromethylation*. The tetrathiophen (2·0 g.) and zinc chloride (1·0 g.) were dissolved in a stirred mixture of acetic acid (900 ml.) and hydrochloric acid (100 ml.) at 44°, and formaldehyde (40%; 0·4 ml.) in acetic acid (25 ml.) was added dropwise during 2 hr. After a further 2 hr., the mixture was poured into water and extracted with chloroform; the extract was washed with sodium hydrogen carbonate solution, dried, and evaporated. The residue (1·7 g.) was chromatographed on silica. Elution with benzene afforded the starting material; elution with chloroform gave the *octathiophen* (XX) (0·63 g., 15%), m.p. 102°, as white needles (from carbon tetrachloride) (Found: C, 61·8; H, 4·2; S, 33·7. $C_{39}H_{32}S_8$ requires C, 61·9; H, 4·3; S, 33·8%), τ ($CDCl_3$) 2·75—3·34 (aromatic H), 5·72 [2 × CH_2 (terminal)], and 5·82 (5 × CH_2).

(c) *PPA Treatment of the Monocarboxylic Acid* (XVd). The crude acid (XVd) (1·2 g.) [obtained by hydrolysis of the ester (XVf) with boiling hydrochloric acid (20%) for 4 hr.] was heated in PPA (500 g.) at 100° for 2 hr. and the mixture was then poured into water. The solid which separated (1·1 g.), evidently a polymer, was insoluble in all common organic solvents.

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