Some Derivatives of 2- and 3-Phenylthiophen

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Some 2-(4-substituted phenyl)thiophens and their 3-methyl derivatives have been used to prepare substituted methylamines, ethylamines, and acetic acids with potential biological activity. Similar derivatives from 3-phenylthiophen and its 2-methyl derivative have also been prepared. Electrophilic substitution of 3-methyl-2-phenylthiophen and of 2-methyl-3-phenylthiophen takes place in the vacant α-postion of the thiophen ring.

CONSIDERABLE biological activity has been reported [1] for derivatives of benzo[*b*]thiophen, and since it seemed possible that comparable activity might be shown by similar molecules in which the benzo[*b*]thiophen moiety had been replaced by the phenylthiophen system, we undertook the relevant synthetic work.

All the isomeric methylphenylthiophens have been prepared by Broun and Voronkov [2] by using the high-temperature cyclisation with sulphur of the appropriately substituted butene. However, the yields were low and more efficient methods were sought.

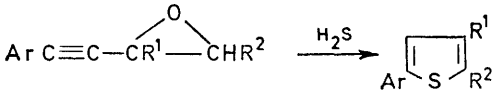
We decided to study first the preparation of 5-phenyl-2-thienyl derivatives. Suitable starting materials for our syntheses were 2-phenylthiophen, 5-phenylthiophen-2-carboxylic acid, 2-methyl-5-phenylthiophen, and the (4-substituted phenyl) derivatives. In addition to the classical syntheses involving the reaction of a 1,4-dicarbonyl system with phosphorus pentasulphide, several more recent routes have been described.[3]

[1] E. Campaigne, E. D. Weinberg, G. Carlson, and E. S. Neiss, *J. Medicin. Chem.*, 1965, **8**, 136; E. Campaigne, T. R. Bosin, D. R. Knepp, and E. S. Neiss, *Adv. Drug. Res.*, 1970, **5**, 1.

[2] A. S. Broun and M. G. Voronkov, *Zhur. obshchei Khim.*, 1947, **17**, 1162 (*Chem. Abs.*, 1948, **42**, 1591); *Doklady Akad. Nauk S.S.S.R.*, 1948, **59**, 1293 (*Chem. Abs.*, 1949, **43**, 2614).

[3] (*a*) S. Gronowitz and N. Gjøs, *Acta Chem. Scand.*, 1967, **21**, 2823; (*b*) N. Gjøs and S. Gronowitz, *ibid.*, 1970, **24**, 99; (*c*) M. Nilsson and C. Uelenius, *ibid.*, 1970, **24**, 2379.

Perveev and Kudryashova [4] treated alkynic epoxides with hydrogen sulphide to give a number of substituted thiophens [reaction (i)]. We therefore treated phenylpropargylaldehyde (phenylpropynal) with dimethylsulphonium methylide to give 1-(phenylethynyl)oxiran



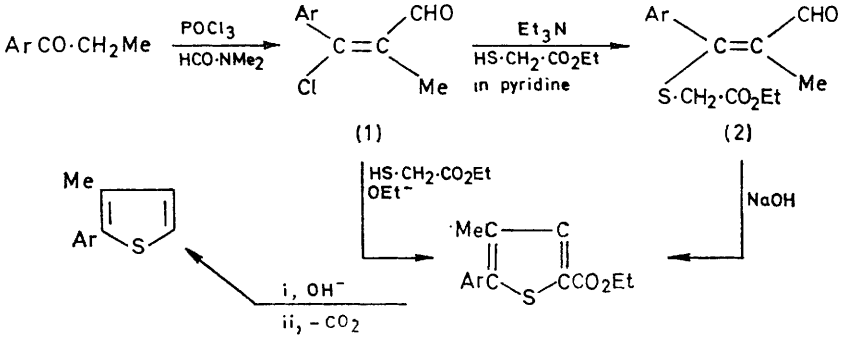
(i)

(19%), which was converted into 2-phenylthiophen (70%) by treatment with hydrogen sulphide in alkaline solution. The low yield of oxiran makes this sequence uneconomical.

Fiesselmann [5] condensed α-bromobenzylideneacetone (4-bromo-4-phenylbut-3-en-2-one) with methyl thioglycolate in the presence of sodium methoxide to give methyl 3-methyl-5-phenylthiophen-2-carboxylate. We found that the analogous condensation of α-bromocinnamaldehyde (3-bromo-3-phenylpropenal) with methyl thioglycolate ultimately gave 5-phenylthiophen-2-carboxylic acid (47%). However, a higher yield (>90%) of this acid was obtained from the oxidative cyclisation of α-mercapto-β-styrylacrylic acid (2-mercapto-5-phenylpenta-2,4-dienoic acid) with chlorine in carbon tetrachloride.[6] Decarboxylation of the thiophencarboxylic acid with copper powder in boiling quinoline by the method of Rinkes [7] gave 2-phenylthiophen (73%).

Neither of these sequences, both involving the initial preparation of the appropriately substituted cinnamaldehyde, seemed suitable for the preparation of a range of (4-substituted phenyl)thiophens and we reverted to the use of the Gomberg reaction. We used a modification of the method described by Buü-Hoi and Noan [8] in which a 4-substituted benzenediazonium acetate was decomposed in the presence of an excess of thiophen to give a low yield of the 2-(4-substituted phenyl)thiophen. Since the starting amines were readily available the following (4-substituted phenyl)thiophens could be obtained: 4-methyl- (18%), 4-chloro- (31%), and 4-bromo- (38%). These 2-arylthiophens were carboxylated either by lithiation followed by reaction with carbon dioxide or by Vilsmeier–Haack formylation followed by oxidation of the product with moist silver(I) oxide.

We also wished to prepare 2-phenyl-3-thienyl and 3-phenyl-2-thienyl derivatives; the condensation of ethyl thioglycolate with 3-chloro-2-methyl-3-phenylpropenal (1) used by Hauptmann [9] and his co-workers to prepare 2-methyl-3-phenylthiophen (Scheme) appeared the most suitable route to our required starting materials. β-Chloroacrylaldehydes of type (1) were readily prepared by the Vilsmeier–Haack formylation of the appropriate aldehyde or ketone under the conditions described by previous workers.[10] However, the reaction mixture was decomposed with cold aqueous 10% sodium acetate. This modification allowed better temperature control thus increasing the yields of the rather unstable chloroacrylaldehydes. Liquid chloroacrylaldehydes were distilled under reduced pressure in an atmosphere of nitrogen. They were characterised as the semicarbazones and were used within a few days as they had a tendency to explode.[11] Solid chloroacrylaldehydes were quite stable. The chloroformylation produced a mixture of *E*- and *Z*-isomers and with solid products the isomers were separated by crystallisation. With liquid products, the isomer ratio was readily obtained from a comparison of the peak heights assigned to the formyl proton in the ^{1}H n.m.r. spectrum of the mixture. The chemical shifts (Table 1) were obtained in this way and no account was taken of possible interactions between the isomers. In general, phenylacetaldehydes and propiophenones gave high yields of the *E*-isomer whereas acetophenones and phenylpropanones gave considerable amounts of the *Z*-isomer. These findings agree with previous results,[11] but the subject seems to have received relatively little attention.



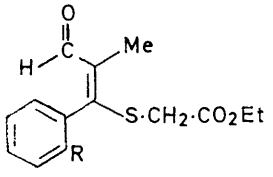
SCHEME

Hauptmann [9] and his co-workers used a two-step pro-

[4] F. Ya. Perveev and N. Y. Kudryashova, *Zhur. obshchei Khim.*, 1953, **23**, 976, 1569 (*Chem. Abs.*, 1954, **48**, 8219, 10,727).
[5] H. Fiesselmann, *Angew. Chem.*, 1960, **72**, 573.
[6] P. M. Chakrabarti, N. B. Chapman, and K. Clarke, *Tetrahedron*, 1969, **25**, 2781.
[7] R. Rinkes, *Rec. Trav. chim.*, 1932, **51**, 1134.
[8] N. P. Buü-Hoi and N. Noan, *Rec. Trav. chim.*, 1950, **69**, 1455.
[9] S. Hauptmann and E.M. Werner, *J. prakt. Chem.*, 1972, **314**, 499; Ng. D. Trieu and S. Hauptmann, *Z. Chem.*, 1973, **13**, 58.
[10] (*a*) Z. Arnold and J. Žemlička, *Coll. Czech. Chem. Comm.*, 1959, **24**, 2385; (*b*) K. Bodendorf and R. Mayer, *Chem. Ber.*, 1965, **98**, 3554.
[11] J. M. G. Gagan, A. G. Lane, and D. Lloyd, *J. Chem. Soc.* (*C*), 1970, **92**, 2484.

cess to prepare thiophencarboxylic esters, first condensing a β-chloroacrylaldehyde with ethyl thioglycolate in the presence of triethylamine in pyridine and then cyclising the resulting substituted thioglycolic ester (2) with aqueous sodium hydroxide. We hoped to simplify the procedure by using sodium ethoxide in a single operation and we were successful with the β-chloroacrylaldehydes obtained from acetophenone, phenylacetaldehyde, phenylpropanone, and propiophenone and its *p*-bromo-derivative. The modification failed with nitro-substituted β-chloroacrylaldehydes and here we reverted to Haupmann's method for the initial condensation with ethyl thioglycolate, but found that aqueous sodium hydroxide was not suitable for the cyclisation. Good yields of thiophen derivatives were obtained by boiling the substituted thioglycolic esters with triethylamine in pyridine, but attempts to carry out the condensation and cyclisation in a single stage gave only poor yields. We were also unable to achieve a satisfactory cyclisation of any (*ortho*-substituted phenyl)thioacetic esters, mild conditions giving unchanged ester and vigorous conditions yielding multi-component tars which probably contained (^{1}H n.m.r. spectrum) a little of the required cyclic product. 3-(*o*-Bromophenyl)-3-chloro-2-methylpropenal (derived from *o*-bromopropiophenone), on treatment with ethyl thioglycolate and sodium ethoxide, gave (*E*)-ethyl (1-*o*-bromophenyl-2-methyl-3-oxoprop-1-enylthio)acetate (3) (50%) with no cyclisation product.

Two observations are relevant in this context. First, the unsaturated esters were isolated mainly in the *E*-form, and before cyclisation can take place isomerisation must occur so that the formyl and the reactive methylene group can interact. It is probable that this isomerisation takes place by the reversible addition of triethylamine to the αβ-unsaturated aldehyde. Any bulky



(3) R = Br
(4) R = H

ortho-substituent would hinder this process. Secondly, from its ^{1}H n.m.r. spectrum, ethyl (2-methyl-3-oxo-1-phenylprop-1-enylthio)acetate (4) exists as an extended conjugated system with the nodal planes of the π-systems of the unsaturated side chain and of the phenyl ring coplanar. The signal for the methylene protons in the mercaptoacetic acid residue occurs as a singlet (*i.e.* equivalent protons). This pattern is adhered to by all *meta*- and *para*-substituted phenyl analogues, and from a study of suitable models it is apparent that such compounds can adopt a planar configuration. However, the methylene group in the mercaptoacetic acid residue of the bromo-substituted derivative (3) produces a doublet of doublets (J 15.8 Hz). It seems likely that the molecule is twisted to accommodate the bulky *o*-bromo-substituent and this is reflected in the non-equivalence of the methylene protons.

Hydrolysis of the substituted thiophen-2-carboxylic esters with hot aqueous ethanolic sodium hydroxide and acidification gave high yields (>90%) of the corresponding acids, which were decarboxylated (>90%) with copper-bronze in hot quinoline under nitrogen. Alternatively, the arylthiophen-2-carboxylic acids were treated with boiling thionyl chloride to give the corresponding acid chlorides, which reacted readily with ammonia, dimethylamine, pyrrolidine, piperidine, and morpholine. The resulting amides were reduced with lithium aluminium hydride in boiling ether to give the corresponding aryl-2-thienylmethylamines, which were isolated as their hydrochlorides. The reduction of 5-(4-bromophenyl)thiophen-2-carboxamides was, however, accompanied by a considerable loss of nuclear bromine unless the calculated quantity of lithium aluminium hydride was used. Indeed, use of a four-fold excess of hydride resulted in complete loss of nuclear bromine.

The primary amines could also be prepared by direct aminomethylation [12] of the arylthiophen with formalin and ammonium chloride at 65 °C. Alternatively, side-chain bromination of arylmethylthiophens with recrystallised *N*-bromosuccinimide in boiling carbon tetrachloride, followed by treatment with the potassium derivative of phthalimide and treatment of the resulting phthalimido-derivative with hydrazine hydrate [13] also gave primary aminomethyl compounds.

The tertiary amines could also be prepared by direct chloromethylation of the arylthiophen, followed by treatment of the product with the secondary amines, dimethylamine, pyrrolidine, piperidine, and morpholine in benzene at room temperature (or similarly from the above bromomethyl compounds in hot carbon tetrachloride). This modification was particularly useful for the 4-bromophenyl derivatives because of the difficulties experienced during the reduction of the corresponding amides.

The chloromethyl derivatives were readily converted into the corresponding cyanomethyl derivatives with sodium cyanide in hot dimethyl sulphoxide.[14] However, under these conditions the bromomethyl compounds gave mixtures of the required cyanomethyl derivative and the corresponding formyl derivative,[15] and better conversions were achieved with aqueous acetone as solvent. Reduction of the cyanomethyl derivatives with lithium aluminium hydride and anhydrous aluminium trichloride [14] in dry ether gave the corresponding phenylthienylethylamines. 2-Cyanomethyl-5-phenylthiophen was treated with hydrogen chloride and ethanol to give the corresponding acetimidate. This readily

[12] H. D. Hartough, S. L. Meisel, E. Koft, and J. W. Schick, *J. Amer. Chem. Soc.*, 1948, **70**, 4013.
[13] H. R. Ing and R. H. F. Manske, *J. Chem. Soc.*, 1926, 2348.
[14] N. B. Chapman, K. Clarke, A. J. Humphries, and S. U.-D. Saraf, *J. Chem. Soc.* (*C*), 1969, 1612.
[15] N. Kornblum, W. J. Jones, and G. J. Anderson, *J. Amer. Chem. Soc.*, 1959, **81**, 4113.

reacted with ethanolic ammonia to produce 5-phenyl-2-thienylacetamidine, isolated as its hydrochloride. Hydrolysis of the cyanomethyl compounds with aqueous ethanolic sodium hydroxide led to the corresponding phenylthienylacetic acid, which could also be obtained by the Arndt–Eistert reaction of the corresponding phenylthiophencarbonyl chloride. The acetic acids were converted into the acyl chlorides and treated with methylamine or dimethylamine in benzene. However, the reaction with dimethylamine gave poor yields and the *NN*-dimethylacetamides were best obtained (>90%) by the reaction of the thienylacetic acid with an excess of dimethylamine in tetrahydrofuran in the presence of titanium tetrachloride.[16] Reduction of these amides with borane in dry tetrahydrofuran[17] gave the corresponding *N*-methyl- and *NN*-dimethyl-ethylamines respectively.

Many of the compounds obtained were tested for both antibacterial and antifungal activity, and for analgesic activity by using the tail clip test and an anti-writhing test based upon the work of Siegmund *et al.*[18] and of Hendershot and Forsaith.[19] No significant activity was observed at sub-lethal dose levels.

Both 2-methyl-3-phenylthiophen and 3-methyl-2-phenylthiophen were brominated, nitrated, formylated by the Vilsmeier–Haack process, and acetylated with acetyl chloride and tin(IV) chloride. In all cases the vacant α-position was substituted.

EXPERIMENTAL

Tables 3—6 are available as Supplementary Publication No. SUP 21849 (7 pp.).*

The aldehydes and ketones used as starting materials were obtained by published methods. *o*-Nitropropiophenone was obtained by nitrating propiophenone as described by Leonard and Boyd,[20] removing the *m*-isomer, and converting the residue into the oxime. Crystallisation gave *o*-nitropropiophenone oxime, m.p. 112—113 °C (lit.,[21] 143—144 °C), which on hydrolysis gave the required *o*-nitro-ketone. (*N.B. p*-Nitropropiophenone oxime has m.p. 143—144 °C.[22]) 5-Phenylthiophen-2-carboxylic acid (90%) was prepared by cyclisation of α-mercapto-β-styrylacrylic acid with chlorine in carbon tetrachloride [6] and was decarboxylated by heating with copper powder in quinoline [7] to give 2-phenylthiophen (72.4%).

5-Phenylthiophen-2-carboxylic Acid.—α-Bromocinnamaldehyde (10.55 g, 0.05 mol) in methanol (50 ml) was added to a stirred, ice-cold solution of methyl thioglycolate (5.3 g, 0.05 mol) in methanolic 2M-potassium hydroxide (50 ml). The mixture was stirred at room temperature for 1 h, then poured into water and shaken with ether to remove unchanged α-bromocinnamaldehyde (2.4 g, 23%). The aqueous phase was acidified with concentrated hydrochloric acid and shaken with ether to give 5-phenylthiophen-2-carboxylic acid (3.67 g, 47%), m.p. 186—187 °C (lit.,[23] 187—188 °C).

2-Phenylthiophen.—A solution of trimethylsulphonium iodide (20.4 g, 0.1 mol) in dry dimethyl sulphoxide (DMSO) (80 ml) was added over 3 min to a stirred solution of sodium methylsulphinylmethanide (0.1 mol) in dry DMSO (50 ml) and dry tetrahydrofuran (THF) (50 ml) at −30 °C. Phenylpropynal (11 g, 0.085 mol) in dry THF (100 ml) was added dropwise at −30 °C and the mixture was stirred for 15 min, and then for 1 h at room temperature. The mixture produced was diluted with water and shaken with ether. Distillation of the dry ethereal solution gave the (1-phenylethynyl)oxiran (2.3 g, 19%) as an oil, b.p. 78—81 °C at 1.0 mmHg, $\nu_{max.}$ (CS_2) 3 020 and 2 960 (C–H), 2 250 (C≡C), and 1 230 cm^{-1} (C–O), δ(liquid) 2.87 (d, CH_2·O), 3.52 (t, CH·O), and 7.20—7.47 (m, ArH). This product still contained traces of DMSO but was not purified further and was treated as follows. A slow stream of hydrogen sulphide was passed for 22 h through a stirred mixture of the oxiran (1 g, 0.007 mol), barium hydroxide (1 g), and water (15 ml) at room temperature. The mixture was acidified with aqueous 30% acetic acid (15 ml) and the product was extracted into ether. Evaporation of the extract and steam distillation of the residue gave 2-phenylthiophen (0.78 g, 70%) as plates, m.p. 42—43 °C (from ethanol) (lit.,[24] 42 °C).

Gomberg Reaction.—A solution of the 4-substituted aniline (0.4 mol) in water (160 ml) and concentrated hydrochloric acid (90 ml) was diazotised with sodium nitrite (29 g) in water (100 ml), and thiophen (350 g) was added to the stirred solution at 0 °C. Anhydrous sodium acetate (160 g) in water (400 ml) was added slowly, and stirring was continued for 3 h at 0—5 °C, then for 24 h at room temperature. The organic layer was separated and the aqueous layer shaken with ether. Evaporation of the combined organic layers followed by vacuum or steam distillation gave the following 2-(4-substituted phenyl)thiophens: 2-(4-bromophenyl)- (38%), pale yellow plates, m.p. 99—100 °C (from ethanol) (lit.,[24] 100 °C); 2-(4-chlorophenyl)- (31%), plates, m.p. 83—84 °C (from ethanol) (lit.,[24] 83 °C); 2-(*p*-tolyl)-thiophen (18%), plates, m.p. 82—83 °C (from ethanol) (lit.,[20] 77—78 °C).

5-(4-Bromophenyl)thiophen-2-carbaldehyde.—An ice-cold mixture of phosphoryl chloride (4.62 g, 0.03 mol) and dry dimethylformamide (DMF) (10 ml) was added to a stirred solution of 2-(4-bromophenyl)thiophen (4.8 g, 0.02 mol) in dry toluene (50 ml) at 0 °C. The mixture was heated for 3 h on a steam-bath, boiled for 30 min, cooled, and decomposed with sodium acetate (30 g) in water (200 ml). The organic layer was separated, combined with the ethereal extract from the aqueous phase, and distilled under reduced pressure. The *aldehyde* (68%) had m.p. 111—112 °C (from ethanol) (Found: C, 49.6; H, 2.4. $C_{11}H_7BrOS$ requires C, 49.45; H, 2.6%), $\nu_{max.}$ ($CHCl_3$) 2 800 (C–H) and 1 665 cm^{-1} (C=O), δ 7.40 (d, 4-H), 7.56 (s, ArH), 7.75 (d, 3-H), and 9.92 (s, CHO). The *thiosemicarbazone* (93%) had m.p. 211—213 °C (from ethanol) (Found: C, 41.9; H, 2.8. $C_{12}H_9BrN_3S_2$ requires C, 42.4; H, 2.7%).

* For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1975, Index issue.

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[17] H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, 1957, **22**, 1135.
[18] E. Siegmund, R. Cadmus, and G. Lu, *Proc. Soc. Exp. Biol. Med.*, 1957, **95**, 729.
[19] L. C. Hendershot and J. Forsaith, *J. Pharm. Exp. Therap.*, 1959, **125**, 237.
[20] N. J. Leonard and S. N. Boyd, *J. Org. Chem.*, 1946, **11**, 405.
[21] 'Dictionary of Organic Compounds,' Eyre and Spottiswoode, London, 1965, p. 2500.
[22] W. H. Puterbaugh, F. W. Swamer, and C. R. Hauser, *J. Amer. Chem. Soc.*, 1952, **74**, 3438.
[23] E. Campaigne and R. E. Cline, *J. Org. Chem.*, 1956, **21**, 39.
[24] M. Gomberg and W. E. Bachmann, *J. Amer. Chem. Soc.*, 1924, **46**, 2339.

Prepared similarly, 5-(4-chlorophenyl)thiophen-2-carbaldehyde (71%) had m.p. 89—90 °C (lit.,[25] 82—83 °C), $\nu_{max.}$ ($CHCl_3$) 2 850 (C–H) and 1 670 cm^{-1} (C=O). The *thiosemicarbazone* (91%) had m.p. 225—226 °C (from ethanol) (Found: C, 48.3; H, 3.3. $C_{12}H_9ClN_3S_2$ requires C, 48.9; H, 3.1%).

the temperature below 40 °C. The resulting mixture was heated on a water-bath for 30 min, cooled, and shaken with ether (3 × 500 ml). The ethereal solution was washed thoroughly and distilled under reduced pressure in an atmosphere of nitrogen to give the appropriate β-chloroacrylaldehyde (see Table 1).

TABLE 1

Some β-chloroacrylaldehydes, $R^1CCl{:}CR^2{\cdot}CHO$

		M.p. or b.p. (°C)			Found (%)			Reqd. (%)		δ					
R^1	R^2	[mmHg]	Time; temp. (°C)	Yield (%)	C	H	Formula	C	H	*Z*-CHO	*E*-CHO	*E*-R^2	*Z*-R^2	*Z*-R^1	*E*-R^1	*Z*/*E*
Ph	H	77—79 [0.15] [a]	18 h; 15—20	50	53.35	4.45	$C_{10}H_{10}ClN_3O$ [e]	53.7	4.5	d, 10.16	d, 9.36	d, 6.63	d, 6.51	m 7.8—7.2		85/15
H	Ph	80—83 [0.2]	24 h; 0—4	54	53.4	4.45	$C_{10}H_{10}ClN_3O$ [f]			s, 10.39	s, 9.48	m, 7.5—6.9		s, 7.17	s, 7.00	9/91
Ph	Me	80—84 [0.2] [b]	4 h; 30—35	92						s, 10.39	s, 9.45	s, 2.07	s, 1.99	m, 7.5—7.3		7/93
Me	Ph	80—86 [0.3] [c]	2 h; 25—30	67						s, 10.40	s, 10.09	m, 7.5—6.9		s, 2.23	2, 268	58/42
o-BrC_6H_4	Me	80—86 [0.15]	5 min; 100—110	85	46.4	3.15	$C_{10}H_8BrClO$	46.3	3.1	s, 10.40	s, 9.30	s, 2.06	s, 1.67	m, 7.7—7.2		5/95
p-BrC_6H_4	Me	58—59	10 min; 110	79	46.2	3.0				s, 10.38	s, 9.48	s, 2.05	s, 1.85	d, 7.58 and d, 7.30		9/91
o-$NO_2{\cdot}C_6H_4$	Me	75—76	5 min; 100—110	69	53.3	3.5	$C_{10}H_8ClNO_3$	53.25	3.6	s, 10.40	s, 9.38	s, 2.08	s, 1.68	m, 8.2—7.3		7/93
m-$NO_2{\cdot}C_6H_4$	Me	83—84 [d]	10 min; 110	58	53.3	3.45				s, 10.40	s, 9.48	s, 2.12	s, 1.90	m, 8.5—7.5		8/92
p-$NO_2{\cdot}C_6H_4$	Me		10 min; 110	80	46.8	3.95	$C_{11}H_{11}ClN_4O_3$ [g]	46.75	3.9	s, 10.40	s, 9.46	s, 2,09	s, 1.85	d, 8.30 and d, 7.26		12/88
o-MeC_6H_4	H	64—67 [0.15]	6 h; 0	63	55.5	5.2	$C_{11}H_{12}ClN_3O$ [h]	55.6	5.1	d, 10.20	d, 9.25	d, 6.54	d, 6.22	s, 2.35	s, 2.32 m, 7.4—7.2	54/46

[a] Lit.[10a] 99—103° at 0.2 mmHg. [b] Lit.[10a] 117° at 1.2 mmHg; lit.,† 82—85 at 0.2 mmHg. [c] Lit.,† 90—96° at 0.2 mmHg. [d] Lit.,[10b] 83—84°. [e] Semicarbazone, m.p. 203—204° (decomp.). [f] Semicarbazone, m.p. 142—143° (decomp.). [g] Semicarbazone, m.p. 224—225°. [h] Semicarbazone, m.p. 201—202° (decomp.).

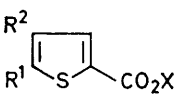
† J. M. F. Gagan, A. G. Lane, and D. Lloyd, *J. Chem. Soc.* (*C*) 1970, 2484.

5-(4-*Bromophenyl*)*thiophen*-2-*carboxylic Acid*.—n-Butyllithium (4.5 g, 0.07 mol) in dry ether (100 ml) was added dropwise to a stirred solution of 2-(4-bromophenyl)thiophen (12 g, 0.05 mol) in dry ether (50 ml) under nitrogen. The mixture was stirred for 15 min and poured onto a slurry of crushed solid carbon dioxide and ether. Water (200 ml) was added, the ethereal layer was removed, and the aqueous layer was acidified with concentrated hydrochloric acid. 5-(4-*Bromophenyl*)*thiophen*-2-*carboxylic acid* (86%) had m.p. 263—264 °C (from aqueous ethanol) (Found: C, 46.9; H, 2.4; S, 11.7. $C_{11}H_7BrO_2S$ requires C, 46.6; H, 2.5; S, 11.3%). Oxidation of 5-(4-bromophenyl)thiophen-2-carbaldehyde with moist silver(I) oxide gave the same acid (81%). The above carboxylation was used to prepare 5-(4-chlorophenyl)thiophen-2-carboxylic acid (81%) as white prisms, m.p. 253—254 °C (from acetic acid) (lit.,[8] 254 °C); and 5-(*p*-tolyl)thiophen-2-carboxylic acid (78%) as white prisms, m.p. 217—218 °C (from chlorobenzene) (lit.,[8] 217 °C).

5-*Arylthiophen*-2-*carbohydrazides* (IIf)—(Vf).—A suspension of the corresponding acid (0.02 mol) in ether (40 ml) was treated with an excess of ethereal diazomethane at 0—5 °C. The solution was kept overnight, then evaporated, and the resulting methyl ester was dissolved in ethanol (50 ml) and treated with hydrazine hydrate (1.5 g of 100%, 0.03 mol). The mixture was boiled for 6 h and cooled, and the crystalline hydrazide was collected and recrystallised from ethanol. Details are given in Table 4.

Chloroformylation.—The Vilsmeier–Haack reagent was prepared by adding phosphoryl chloride (2.5 mol. equiv.) dropwise with stirring, to ice-cold DMF (3 mol. equiv.) during 15 min.[10] The mixture was stirred at room temperature for 30 min, then cooled to 0 °C and the carbonyl compound (1.0 mol. equiv.) was added over 30 min. Solid carbonyl compounds were added as warm solutions in DMF. After a suitable period (see Table 1), the mixture was cooled to 0 °C and decomposed with aqueous 10% sodium acetate (3 600 ml) with stirring and cooling to keep

Substituted Ethyl Thiophen-2-*carboxylates* (I; X = Et).—(*a*) Ethyl thioglycolate (60 g, 0.5 mol) was added to a stirred solution of sodium ethoxide [from sodium (12.7 g, 0.55 g atom) in dry ethanol (300 ml)] under nitrogen at 0 °C. A solution of the appropriate β-chloroacrylaldehyde (0.5 mol) in dry ethanol (100 ml) was then added dropwise during 15 min and stirring was continued at 0 °C for 1 h. The mixture was kept at room temperature for 12 h, poured into water (1.5 l), and shaken with ether (3 × 150 ml). The ethereal solution was washed, dried ($MgSO_4$), and evaporated under reduced pressure. The residual oil



	R^1	R^2
(I)	Ph	H
	Ph	Me
	4-BrC_6H_4	Me
	3-$NO_2{\cdot}C_6H_4$	Me
	4-$NO_2{\cdot}C_6H_4$	Me
	H	Ph
	Me	Ph

was either distilled under reduced pressure or crystallised from an appropriate solvent to give the required substituted ethyl thiophen-2-carboxylate (yields and properties are given in Table 3).

Under such conditions 3-(*o*-bromophenyl)-3-chloro-2-methylpropenal gave only *ethyl* (1-o-*bromophenyl*-2-*methyl*-3-*oxoprop*-1-*enylthio*)*acetate* (48%), as pale yellow prisms, m.p. 64—65 °C (from ethanol) (Found: C, 49.1; H, 4.35%; *M*, 342/344. $C_{14}H_{15}BrO_3S$ requires C, 49.0; H, 4.4%; *M*, 342/344), $\nu_{max.}$ 1 737 (ester C=O) and 1 660 cm^{-1} (CHO), δ 9.05 (s, CHO), 7.75—7.2 (m, ArH), 4.06 (q, CH_2Me), 3.23 (d, C*H*H′), 3.06 (d, CH*H*′), 1.98 (s, Me), and 1.17 (t, CH_2Me) ($J_{HH'}$ 15.8 Hz).

(*b*) Triethylamine (5 ml) was added to an ice-cold, stirred solution of the appropriate β-chloroacrylaldehyde (0.02 mol) and ethyl thioglycolate (2.4 g, 0.02 mol) in dry pyridine (25 ml), and the mixture was stirred at room

[25] D. M. O'Mant, G.P. 1,919,381/1969.

temperature for 1 h and then poured into ice-cold 2M-hydrochloric acid (200 ml) and shaken with ether (2 × 50 ml). The ethereal solution was washed with dilute hydrochloric acid and then with water, dried ($MgSO_4$), and evaporated *in vacuo*. The product (yields and properties in Table 2) was used without further purification, but was characterised as the semicarbazone. A solution of triethylamine (5 ml) and the appropriate ethyl 2-(3-oxoprop-1-enylthio)acetate (0.02 mol) in dry pyridine (25 ml) was boiled under reflux for 2 h, cooled and then poured into ice-cold 2M-hydrochloric acid (200 ml). The product was collected and crystallised (charcoal) to give the required ester (yields and properties in Table 3).

Substituted Thiophen-2-carboxylic Acids (I; X = H).—A mixture of the appropriate ethyl thiophen-2-carboxylate (0.1 mol), ethanol (25 ml), and aqueous 10% sodium hydroxide (90 ml) was boiled under reflux for 2 h, cooled, poured into water (500 ml), and shaken with ether (75 ml). The aqueous layer was acidified with 2M-hydrochloric acid, and the precipitated acid was filtered off, dried, and crystallised (charcoal) from ethanol (see Table 3).

Some Phenylmethylthiophen Derivatives. The substituted thiophen-2-carboxylic acids were decarboxylated in >90% yield by heating with copper-bronze in dry quinoline under nitrogen as described previously.[26] The decarboxylation of both 5-methyl-4-phenylthiophen-2-carboxylic acid and 4-methyl-5-phenylthiophen-2-carboxylic acid gave the expected methylphenylthiophen (*ca.* 95% of the product) contaminated with 2-methylnaphthalene (3—5% of the product), and 1-methylnaphthalene (0.5—1% of the product) derived from the quinoline used in the decarboxylation. In both cases the required product was isolated by spinning-band fractional distillation (Nester/Faust NFT-50 apparatus).

Bromomethyl-phenylthiophen Derivatives.—Dibenzoyl peroxide (0.2 g) was added to a stirred boiling solution of the appropriate methylphenylthiophen (0.05 mol) in dry carbon tetrachloride (100 ml) and the solution was irradiated with a tungsten lamp (200 W). Dry recrystallised *N*-bromosuccinimide (8.9 g, 0.05 mol) was added quickly in portions and the mixture was boiled for 20 min, cooled in ice, and filtered. Removal of the solvent under reduced pressure left the required bromomethyl-phenylthiophen which was used without further purification.

The above procedure was used to prepare the following compounds: 3-bromomethyl-2-phenyl- (98%), straw coloured oil, δ (CCl_4) 7.55—7.25 (m, Ph), 7.19 (d, 5-H), and 7.01 (d, 4-H) ($J_{4,5}$ 5.5 Hz), hexamine salt, m.p. 175—176 °C (decomp.); 2-bromomethyl-3-phenyl- (95%), pale brown oil, δ (CCl_4) 7.5—7.2 (m, Ph), 7.26 (d, 5-H), and 6.93 (d, 4-H) ($J_{4,5}$ 5 Hz), hexamine salt, m.p. 182—183 °C (decomp.); 5-bromo-2-bromomethyl-3-phenyl- (97%), pale yellow oil, δ (CCl_4) 7.5—7.2 (m, Ph), 6.9 (s, 4-H), and 4.55 (s, CH_2); and *5-bromo-3-bromomethyl-2-phenyl-thiophen* (98%), needles, m.p. 78—79 °C [from light petroleum (b.p. 60—80 °C)] (Found: C, 39.8; H, 2.45. $C_{11}H_8Br_2S$ requires C, 39.8; H, 2.45%), δ (CCl_4) 7.5—7.35 (m, Ph), 7.06 (s, 4-H), and 4.32 (s, CH_2).

5-Arylthiophen-2-carboxamides (II)—(VII).—A mixture of the 5-arylthiophen-2-carboxylic acid (0.05 mol) and thionyl chloride (15 ml) was boiled under reflux for 1 h, then distilled under reduced pressure to give the acid chloride. The acid chloride (0.02 mol) in dry benzene (40 ml) was cooled and treated with either the appropriate amine (0.1 mol) in benzene (40 ml) or saturated methanolic ammonia (100 ml). The primary amides were precipitated and could be filtered off and crystallised from ethanol, but with the *N*-substituted amides it was necessary to wash the benzene solution with dilute hydrochloric acid, to evaporate, and to crystallise the residue from carbon tetrachloride. Details of these amides are given in Table 4.

5-Arylthien-2-ylmethylamines (VIII).—(*a*) The amide (0.015 mol) in dry benzene (40 ml) was added to a stirred suspension of lithium aluminium hydride (0.76 g, 0.02 mol) in dry ether (20 ml). The mixture was boiled for 12 h, (24 h for primary amides), cooled, treated with aqueous 10% sodium hydroxide, and filtered. The dried ($MgSO_4$) filtrate was treated with dry hydrogen chloride to give the amine hydrochloride, which was crystallised from ethanol.

For 5-(4-bromophenyl)thiophen-2-carboxamides it was essential that the molar ratio of amide to reducing agent be increased to 2 : 1 and the reaction time reduced to 6 h, to prevent loss of nuclear bromine. Details of products are given in Table 5.

(*b*) A vigorously stirred mixture of 2-phenylthiophen (6.2 g, 0.032 mol), ammonium chloride (3.6 g, 0.067 mol), and aqueous 30% formaldehyde (11 ml, 0.13 mol) was warmed to 65 °C for 30 min. The mixture was stirred at room temperature for 12 h and washed with ether to remove unchanged 2-phenylthiophen (1.2 g). The aqueous layer

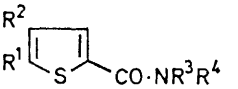
[26] N. B. Chapman, K. Clarke, and S. N. Sawhney, *J. Chem. Soc.* (*C*), 1968, 518.

TABLE 2

Some (*E*)-ethyl 2-(3-oxoprop-1-enylthio)acetates, $EtO_2C{\cdot}CH_2{\cdot}S{\cdot}CR^1{:}CR^2{\cdot}CHO$

				Found (%)			Required (%)		δ					
R^1	R^2	M.p. (°C)	Yield (%)	C	H	Formula	C	H	CHO	R^1	R^2	CH_2	CH_2Me	CH_2Me / J/Hz
Ph	Me								s, 9.16	m, 7.5—7.2	s, 2.04	s, 3.15	q, 4.05	t, 1.17
o-BrC_6H_4	Me	65—65	48	49.1	4.35	$C_{14}H_{15}BrO_3S$	49.0	4.4	s, 9.05	m, 7.8—7.2	s, 1.98	{dd, 3.23 / dd, 3.06	q, 4.06	t, 1.17 $J_{HCH'}$ 15.8
o-$NO_2C_6H_4$ *	Me								s, 9.06	m, 8.2—7.3	s, 2.02	s, 3.61	q, 4.25	t, 1.28
m-$NO_2C_6H_4$	Me	135—137 †	97	49.2	4.9 †	$C_{15}H_{18}N_4O_5S$	49.2	4.95	s, 9.15	m, 8.4—7.6	s, 2.07	s, 3.17	q, 4.08	t, 1.20
p-$NO_2C_6H_4$	Me	174—175 †	98	49.3	5.0 †				s, 9.15	{d, 8.29 / d, 7.54	s, 2.06	s, .317	q, 4.08	t, 1.20 $J_{2',3'}$ 7.5

* Results from crude product. † Semicarbazone.



	R^1	R^2		NR^3R^4
(IIa—f)	Ph	H	a;	NH_2
(IIIa—f)	4-MeC_6H_4	H	e;	NMe_2
(IVa—f)	4-ClC_6H_4	H	c;	Pyrr
(IVa—e)	4-BrC_6H_4	H	d;	Pip
(VIa, b, g)	H	Ph	e;	Morph
(VIIa, b, g)	Me	Ph	f;	$NH{\cdot}NH_2$
			g;	NHMe

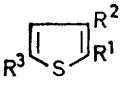
Pyrr = pyrrolidin-1-yl Pip = piperidino Morph = morpholino

was treated with methanol (20 ml) and kept at room temperature for 5 h. The solution was evaporated, the residue was treated with aqueous 40% sodium hydroxide (10 ml) for 2 h, and the product was extracted into ether. The dried ($MgSO_4$) extract was treated with dry hydrogen chloride to precipitate 5-phenyl-2-thienylmethylamine hydrochloride (5.15 g, 73%), m.p. 253—254 °C, identical with that of an authentic sample.

(*c*) A mixture of the appropriate bromomethyl-phenylthiophen (0.05 mol) and the potassium derivative of phthalimide (9.25 g, 0.05 mol) in dry DMF (100 ml) was boiled under reflux for 2.5 h and filtered (charcoal), and sufficient water was added to produce turbidity. The pale brown solid was filtered from the ice-cold mixture and recrystallised from aqueous DMF (charcoal). In this way the following compounds were prepared: *2-phenyl-3-phthalimidomethylthiophen* (11.5 g, 72%), buff platelets, m.p. 81—82 °C (Found: C, 71.1; H, 4.2; N, 4.5%; *M*, 319. $C_{19}H_{13}NO_2S$ requires C, 71.45; H, 4.1; N, 4.4%; *M*, 319), $\nu_{max.}$ 1 705br (C=O) cm^{-1}, δ [$(CD_3)_2SO$] 7.9—7.7 (m, Ph), 7.7—7.4 (m, phthaloyl), 7.49 (d, 5-H), 6.98 (d, 4-H), and 4.82 (s, CH_2) ($J_{4,5}$ 5.5 Hz); *3-phenyl-2-phthalimidomethylthiophen* (11.7 g, 73%), needles, m.p. 111—112 °C (Found: C, 71.6; H, 4.2; N, 4.35%; *M*, 319), $\nu_{max.}$ 1 710br (C=O) cm^{-1}, δ [$(CD_3)_2SO$] 7.95—7.80 (m, Ph), 7.65—7.35 (m, phthaloyl), 7.48 (d, 5-H), 7.09 (d, 4-H), and 5.02 (s, CH_2) ($J_{4,5}$ 5 Hz).

A mixture of the appropriate phthalimidomethylphenylthiophen (9.2 g, 0.03 mol), 100% hydrazine hydrate (1.5 g, 0.03 mol), and ethanol (250 ml) was boiled under reflux for 2.5 h then cooled, and the phthalohydrazide was filtered off. The ethanol was removed from the filtrate under reduced pressure and the semi-solid was suspended in ether; the suspension was filtered and the filtrate dried ($MgSO_4$). Addition of dry ethereal hydrogen chloride precipitated the required amine hydrochloride, which was recrystallised from ethanol–ether. The following compounds were prepared in this way: *2-phenyl-3-thienylmethylamine hydrochloride* (4.6 g, 73%), platelets, m.p. 235—236 °C (Found: C, 58.5; H, 5.3; N, 5.9%; *m/e* 189. $C_{11}H_{12}ClNS$ requires C, 58.5; H, 5.35; N, 6.2%; *M* − HCl, 189); *3-phenyl-2-thienylmethylamine hydrochloride* (4.7 g, 74%), platelets, m.p. 237—238 °C (Found: C, 58.35; H, 5.3; N, 6.3%; *m/e*, 189).

(*d*) A slow stream of hydrogen chloride was passed through a vigorously stirred mixture of aqueous 40% formaldehyde (300 ml), concentrated hydrochloric acid (200 ml), and the 2-arylthiophen (0.1 mol) in chloroform (150 ml) at 60 °C for 2 h. The mixture was poured into water (1.5 l), the organic layer was removed, and the aqueous layer was shaken with more chloroform. The dried combined organic layers were evaporated to give the chloromethyl derivatives, which were crystallised from light petroleum but were not analysed. Obtained in this way, 2-chloromethyl-5-phenyl- (43%) had m.p. 59—61 °C (decomp.), 2-chloromethyl-5-(4-chlorophenyl)- (54%) had m.p. 85—87 °C (decomp.) (lit.,[25] 81.5—83.5 °C), and *2-chloromethyl-5-(4-bromophenyl)-thiophen* (60%) had m.p. 96—97 °C (decomp.) (Found: C, 46.2; H, 2.8; S, 10.9. $C_{11}H_8BrClS$ requires C, 45.9; H, 2.8; S, 11.1%).



(VIII)

R^1	R^2	R^3	R^1	R^2	R^3	R^1	R^2	R^3
Ph	CH_2Morph	H	Ph	Me	CH_2·NH_2	CH_2Morph	Ph	Br
Ph	CH_2Pip	H	Ph	Me	CH_2·NHMe	CH_2Pip	Ph	Br
Ph	CH_2Pyrr	H	Ph	Me	CH_2·NMe_2	CH_2Pyrr	Ph	Br
Ph	CH_2Morph	Br	CH_2Morph	Ph	H	Me	Ph	CH_2·NH_2
Ph	CH_2Pip	Br	CH_2Pip	Ph	H	Me	Ph	CH_2·NHMe
Ph	CH_2Pyrr	Br	CH_2Pyrr	Ph	H	Me	Ph	CH_2NMe_2
Ph	H	CH_2·NH_2	4-MeC_6H_4	H	CH_2Pyrr	4-ClC_6H_4	H	CH_2Morph
Ph	H	CH_2·NMe_2	4-MeC_6H_4	H	CH_2Pip	4-BrC_6H_4	H	CH_2·NH_2
Ph	H	CH_2Pyrr	4-MeC_6H_4	H	CH_2Morph	4-BrC_6H_4	H	CH_2NMe_2
Ph	H	CH_2Pip	4-ClC_6H_4	H	CH_2·NH_2	4-BrC_6H_4	H	CH_2Pyrr
Ph	H	CH_2Morph	4-ClC_6H_4	H	CH_2·NMe_2	4-BrC_6H_4	H	CH_2Pip
4-MeC_6H_4	H	CH_2NH_2	4-ClC_6H_4	H	CH_2Pyrr	4-BrC_6H_4	H	CH_2Morph
4-MeC_6H_4	H	CH_2NMe_2	4-ClC_6H_4	H	CH_2Pip			

(IX)

R^1	R^2	R^3	R^1	R^2	R^3	R^1	R^2	R^3
Ph	H	CH_2·CN	Ph	CH_2·CN	H	CH_2·CN	Ph	H
Ph	H	CH_2·CO_2H	Ph	CH_2·CO_2H	H	CH_2·CO_2H	Ph	H
Ph	H	CH_2·CH_2·NH_2	Ph	CH_2·CONHMe	H	CH_2·CONHMe	Ph	H
4-ClC_6H_4	H	CH_2·CN	Ph	CH_2·$CONMe_2$	H	CH_2·$CONMe_2$	Ph	H
4-ClC_6H_4	H	CH_2·CO_2H	Ph	CH_2·CH_2·NH_2	H	CH_2·CH_2·NH_2	Ph	H
4-BrC_6H_4	H	CH_2·CN	Ph	CH_2·CH_2·NHMe	H	CH_2·CH_2·NHMe	Ph	H
4-BrC_6H_4	H	CH_2·CO_2H	Ph	CH_2·CH_2·NMe_2	H	CH_2·CH_2·NMe_2	Ph	H

The chloromethyl derivative (0.01 mol) in dry benzene (40 ml) was added dropwise to a stirred solution of the appropriate amine (0.1 mol) in benzene (20 ml). After 3 days at room temperature, the mixture was made alkaline with aqueous sodium hydroxide and the organic layer was separated. The aqueous layer was shaken with benzene and the combined organic layers were evaporated. The residue was triturated with light petroleum (b.p. 60—80°), dissolved in dry benzene and treated with dry hydrogen chloride. The resulting amine hydrochloride was crystallised from ethanol. Alternatively the bromomethyl derivative was treated with the secondary amine in boiling carbon tetrachloride for 2 h. Details of products are given in Table 5.

(*Phenylthienyl*)*acetonitriles* (IX).—The 5-aryl-2-chloromethylthiophen (0.06 mol) dissolved in the minimum of dry DMSO was added slowly to a stirred suspension of sodium cyanide (4.9 g, 0.1 mol) in dry DMSO (10 ml) at 70 °C. The mixture was kept at 70 °C for 2 h, then poured into

water, and the product was extracted with chloroform. Distillation under reduced pressure gave the required cyanomethyl derivative. Alternatively, the appropriate bromomethyl-phenylthiophen was boiled under reflux with sodium cyanide in 93% aqueous acetone for 24 h (see Table 6).

(Phenylthienyl)acetic Acids (IX).—The above nitriles, on being boiled for 20 h with 4% potassium hydroxide in 50% aqueous ethanol, followed by acidification, gave the required acids (see Table 6).

Arndt–Eistert Reaction.—5-Phenylthenoyl chloride (5 g, 0.022 mol) in dry ether (100 ml) was added dropwise over 1 h to a stirred solution of diazomethane (2.8 g, 0.067 mol) in dry ether at 0 °C. The mixture was kept overnight and then evaporated to give *diazomethyl 5-phenyl-2-thienyl ketone* (5.1 g, 98%), m.p. 123—124 °C (decomp.) (from ether) (Found: C, 63.6; H, 3.5; N, 11.9. $C_{12}H_8N_2OS$ requires C, 63.2; H, 3.5; N, 12.3%). $\nu_{max.}$ ($CHCl_3$) 2 140 (N≡N) and 1 605 cm^{-1} (C=O).

(i) A mixture of the diazo-ketone (2.2 g, 0.01 mol), dry ethanol (40 ml), and platinum(IV) oxide (0.1 g) was refluxed for 6 h, with the addition of further platinum oxide (0.2 g) every hour. The mixture was boiled for a further 20 h, filtered, and evaporated to give ethyl 5-phenyl-2-thienylacetate, $\nu_{max.}$ ($CHCl_3$) 2 910 (C–H), 1 630 (C=O), and 1 240 cm^{-1} (C–O).

The crude ester was boiled with a mixture of ethanol (40 ml) and aqueous 20% sodium hydroxide (40 ml) for 1 h. The ethanol was evaporated and the residual solution was diluted with water, washed with ether, and acidified with concentrated hydrochloric acid. Extraction into ether gave 5-phenyl-2-thienylacetic acid (1.37 g, 63%), m.p. 228—230 °C (from carbon tetrachloride).

(ii) Freshly prepared silver(I) oxide (0.2 g) was boiled in dry methanol (15 ml) for 30 min until a silver mirror began to form. The diazo-ketone (2 g, 0.009 mol) in dry methanol (40 ml) was added and the mixture boiled for 6 h, with addition of further silver oxide (0.1 g) at hourly intervals. The mixture was boiled for a further 20 h and filtered while hot, and the filtrate was heated with aqueous 20% sodium hydroxide (40 ml) for 1 h. The 5-phenyl-2-thienylacetic acid (1.1 g, 54%) was isolated as in (i), and had m.p. 228—230 °C.

(Phenylthienyl)ethylamines (IX).—(*a*) Reduction of the above nitriles with lithium aluminium hydride and anhydrous aluminium trichloride in boiling ether [14] gave the corresponding (phenylthienyl)ethylamines (Table 6).

(*b*) The above (phenylthienyl)acetic acids were converted into the corresponding acid chlorides and treated with aqueous methylamine to give *N*-methylacetamides (Table 6). The *NN*-dimethylacetamides (Table 6) were prepared by treating the acids with anhydrous dimethylamine in THF in the presence of titanium tetrachloride at −70 °C.[16] These amides were then reduced to the corresponding *N*-methyl- and *NN*-dimethyl-(phenylthienyl)ethylamines (Table 6) by using diborane in THF.[17]

5-Phenyl-2-thienylacetamidine.—A solution of 2-cyanomethyl-5-phenylthiophen (4 g, 0.02 mol) and dry ethanol (1.0 g, 0.021 mol) in dry benzene (20 ml) and dry ether (20 ml) was saturated at 0 °C with dry hydrogen chloride, and kept for 24 h at 0 °C. The crystalline ethyl 5-phenyl-2-thienylacetimidate hydrochloride (3.93 g, 70%) was collected and dried *in vacuo*. The imino-ether (1.4 g, 0.005 mol) was added in portions to a stirred, cooled, saturated solution of ammonia in dry ethanol (50 ml) and the mixture was kept at 0 °C for 12 h. Addition of dry ether precipitated *5-phenyl-2-thienylacetamidine hydrochloride* (1.15 g, 91%) as cream needles, m.p. 230—232 °C (decomp.) (from ethanol) (Found: C, 56.8; H, 5.2; N, 11.1. $C_{12}H_{13}ClN_2S$ requires C, 57.0; H, 5.2; N, 11.1%), $\nu_{max.}$ (Nujol) 1 690 cm^{-1} (C=N).

Monosubstitution Reactions of 3-Methyl-2-phenylthiophen and 2-Methyl-3-phenylthiophen.—(a) *Bromination.* A solution of bromine (6.4 g, 0.04 mol) in dry carbon tetrachloride (50 ml) was added dropwise during 4 h to a stirred solution of the appropriate methylphenylthiophen (70 g, 0.04 mol) in dry carbon tetrachloride (100 ml) at room temperature. After 2 h the mixture was washed with water, with saturated aqueous sodium hydrogen carbonate, and again with water, dried ($CaCl_2$), and evaporated under reduced pressure. The residual oil was distilled under reduced pressure and gave the following bromo-derivatives: *5-bromo-3-methyl-2-phenylthiophen* (9.7 g, 95%), as a straw-coloured oil, b.p. 96—102 °C at 0.1 mmHg (Found: C, 52.4; H, 3.6%; *M*, 252/254. $C_{11}H_9BrS$ requires C, 52.2; H, 3.6%; *M*, 252/254), δ 7.4—7.2 (m, Ph), 6.80 (s, 4-H), and 2.23 (s, Me); *5-bromo-2-methyl-3-phenylthiophen* (9.5 g, 93%), as a pale yellow oil, b.p. 94—100 °C at 0.1 mmHg (Found: C, 52.1; H, 3.55%; *M*, 252/254), δ 7.35—7.15 (m, Ph), 6.91 (s, 4-H), and 2.34 (s, Me).

(b) *Nitration.* A solution of the appropriate methylphenylthiophen (1.74 g, 0.01 mol) in acetic anhydride (10 ml) was added dropwise during 1 h to a stirred suspension of copper(II) nitrate trihydrate (2.42 g, 0.01 mol) in acetic anhydride (15 ml) at 0 °C. The mixture was stirred at room temperature for 2 h, the copper salts were filtered off and washed with acetic anhydride (2 × 10 ml), and the combined filtrate and washings were poured onto ice (200 g) and kept at room temperature for 24 h. The mixture was shaken with chloroform (3 × 50 ml) and the chloroform solution was washed with water, twice with aqueous sodium hydrogen carbonate, and again with water, dried ($MgSO_4$), and evaporated under reduced pressure. The residual orange oil was boiled with light petroleum (b.p. 60—80 °C) (500 ml) for 6 h, the mixture was cooled, and the solvent was decanted off. This procedure was repeated with light petroleum (b.p. 60—80 °C) (150 ml), the combined light petroleum solutions were evaporated, and the product was crystallised (charcoal) from ethanol. The following nitro-compounds were thus prepared: *3-methyl-5-nitro-2-phenylthiophen* (1.85 g, 84%), as yellow needles, m.p. 73—74 °C (Found: C, 60.4; H, 4.1%; *M*, 219. $C_{11}H_9NO_2S$ requires C, 60.25; H, 4.15%; *M*, 219), $\nu_{max.}$ 1 500 and 1 330 cm^{-1} (NO_2), δ 7.77 (s, 4-H), 7.55—7.35 (m, Ph), and 2.32 (s, Me); *2-methyl-5-nitro-3-phenylthiophen* (1.95 g, 89%), as yellow needles, m.p. 100—101 °C (Found: C, 60.0; H, 4.1%; *M*, 219), $\nu_{max.}$ 1 510 and 1 335 cm^{-1} (NO_2), δ 7.83 (s, 4-H), 7.45—7.25 (m, Ph), and 2.50 (s, Me).

(c) *Formylation.* Phosphoryl chloride (1.15 g, 0.007 5 mol) was added dropwise to a stirred solution of the appropriate methylphenylthiophen (0.87 g, 0.005 mol) in dry DMF (5 ml) and stirring was continued at 100—110 °C for 3 h. The mixture was cooled, aqueous 10% sodium acetate (80 ml) was added, and the mixture was shaken with ether (2 × 25 ml). The ethereal solution was washed with water, with aqueous sodium hydrogen carbonate, and again with water, dried ($MgSO_4$), and evaporated under reduced pressure. The above procedure was used to prepare *4-methyl-5-phenylthiophen-2-carbaldehyde* (0.7 g, 69%), which was chromatographed (silica gel in chloroform) to

give a brown oil (Found: C, 71.1; H, 4.9%; *M*, 202. $C_{12}H_{10}OS$ requires C, 71.3; H, 5.3%; *M*, 202), $\nu_{max.}$ 1 665 cm^{-1} (C=O), δ 9.82 (s, CHO), 7.70 (s, 4-H), 7.45—7.25 (m, Ph), and 2.54 (s, Me).

(d) *Acetylation.* Tin(IV) chloride (1.5 g, 0.005 8 mol) was added dropwise to a stirred solution of the appropriate methylphenylthiophen (0.87 g, 0.005 mol) and acetyl chloride (0.4 g, 0.005 mol) in dry benzene (10 ml) at 0 °C. Stirring was continued at room temperature for 2 h and then dilute hydrochloric acid (10 ml) was added cautiously. The organic solution was separated and the aqueous solution was shaken with benzene (15 ml). The combined benzene fractions were washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was crystallised (charcoal) from light petroleum (b.p. 60—80 °C) and gave the following acetyl derivatives: *5-acetyl-3-methyl-2-phenylthiophen* (0.7 g, 65%), as prisms, m.p. 68—69 °C (Found: C, 72.3; H, 5.6%; *M*, 216. $C_{13}H_{12}OS$ requires C, 72.2; H, 5.6%; *M*, 216), $\nu_{max.}$ 1 650 cm^{-1} (C=O), δ 7.52 (s, 4-H), 7.5—7.3 (m, Ph), 2.52 (s, Ac), and 2.31 (s, Me); *5-acetyl-2-methyl-3-phenylthiophen* (0.8 g, 74%), as pale yellow prisms, m.p. 56—57 °C (Found: C, 72.35; H, 5.55%; *M*, 216), $\nu_{max.}$ 1 660 cm^{-1} (C=O), δ (C_6D_6) 7.29 (s, 4-H), 7.25—7.05 (m, Ph), 2.09 (s, Ac), and 2.02 (s, Me).

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