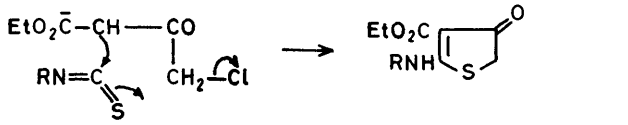
Some Reactions of Ethyl 2-Anilino-4-oxo-4,5-dihydrothiophen-3-carboxylate

By **Alan W. Faull** and **Roy Hull,*** Imperial Chemical Industries Limited, Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire SK10 4TG

Phenyl isothiocyanate reacts with ethyl γ-chloroacetoacetate in the presence of sodium hydride to give ethyl 2-anilino-4-oxo-4,5-dihydrothiophen-3-carboxylate (1b). The compound (1b) shows typical reactions of a keto-methylene compound; the Vilsmeier reagent and phosphorus oxychloride give the chloroformylthiophen (10). A possible sulphine derivative (11) is obtained from (1b) with thionyl chloride. Further exploitation of the chloroformylthiophen (10) yields normal aromatic aldehyde condensation products and with thioglycolic ester the thieno[3,2-*b*]thiophen (25).

RECENTLY we have shown that 2-isothiocyanatovinyl acetate reacted readily with the carbanion of ethyl γ-chloroacetoacetate to give ethyl 2-(2-acetoxyvinylamino)-4-oxo-4,5-dihydrothiophen-3-carboxylate (1a),[1] presumably by the mechanism shown in Scheme 1. The



(1a) R = AcO–CH=CH–
(1b) R = Ph

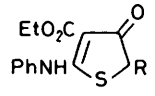
SCHEME 1

reaction may be extended to the simple phenyl isothiocyanate which reacts under like conditions to yield the anilinothiophen (1b). The reaction is complementary to the analogous 2-aminofuran-4(5*H*)-ones obtained from ethyl γ-chloroacetoacetate and isocyanates.[2] The present paper describes some reactions of the readily available intermediate (1b). The n.m.r. spectrum ($CDCl_3$) of (1b) shows the two protons (C-5) as a singlet at δ 3.6 and many of the reactions carried out, for example bromination (2), condensation with benzaldehyde (3) and acetophenone (4), lead tetra-acetate (5), and the coupling reaction with diazotised *p*-chloroaniline (6) are typical of compounds with a reactive methylene group. Hydrolysis and decarboxylation of the ester group took place under alkaline conditions to yield the thiophen (7). The hydrazone (8) was formed with hydrazine. Acetylation with acetyl chloride and pyridine gave the *O*-acetyl derivative (9).

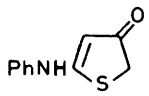
Meth-Cohn and his co-workers [3] have shown that a wide variety of chloroquinolinecarbaldehydes may be obtained by the Vilsmeier formylation of acetanilides. We found that treatment of the thiophen (1b) with the Vilsmeier reagent and $POCl_3$ in tetrachloroethane at room temperature gave the chloroformylthiophen (10) in good yield. This useful intermediate has been developed further.

The reaction of thionyl chloride and active methylene compounds may give rise to a variety of products including sulphinyl chlorides,[4] sulphines,[5] sulphoxides,[5] or Pummerer type rearrangements leading to α-chlorosulphinyl chlorides.[6] The position has been aptly summarised by Oka and Hara.[5]

We found that a facile reaction took place between the thiophen (1b) and thionyl chloride in dimethoxyethane and gave a compound whose elemental analysis established the formula $C_{13}H_{11}NO_4S_2$, and mass-spectral data showed a parent ion at *m/e* 309. We were unable to obtain a satisfactory n.m.r. spectrum because of decomposition of the compound in dimethyl sulphoxide (DMSO). Sheppard and Diekmann,[7] who prepared the fluorenethione *S*-oxide (12), have assigned bands in the i.r. spectrum at 1 120 and 1 019 cm^{-1} to the C=S=O function. We found corresponding bands at 1 085 and 1 010 cm^{-1} which might be attributed to the same radical. We suggest that the compound is the sulphine (11) possibly obtained by the route shown in Scheme 2.



R
(2) Br_2
(3) =CHPh
(4) =CMePh
(5) 
(6) =N.NHC$_6$H$_4$Cl-*p*



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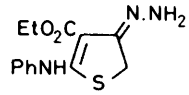

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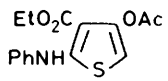

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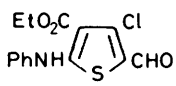
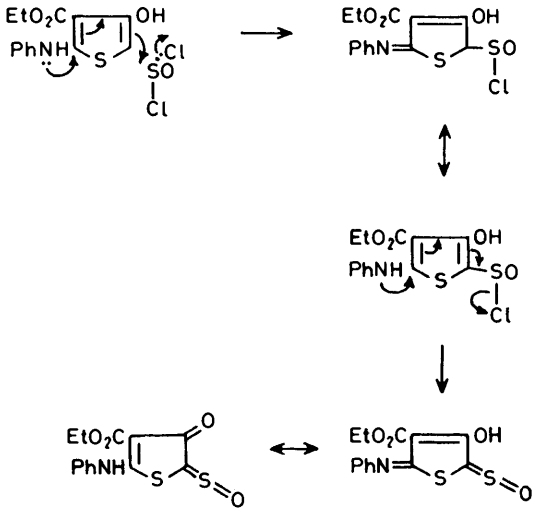


(10)

We next considered the reaction of thionyl chloride with a dihydrothiophen (13) having a carbamate radical at C-2 in order to investigate the generality of the 'sulphine' preparation. The thiophen (13) was easily prepared from ethoxycarbonyl isothiocyanate [8] and ethyl γ-chloroacetoacetate. The subsequent reaction with thionyl chloride gave a compound $C_{20}H_{22}N_2O_{10}S_2$ and whose mass spectrum showed a parent ion at *m/e* 514. There was no characteristic band in the i.r. spectrum in

the region 1 080—1 120 cm^{-1}, but a band at 1 010 cm^{-1} remains unexplained. It would appear that 2 mol of the original thiophen (13) have been oxidatively condensed together to give either the substituted dioxan (14) or the enedicarbonyl derivative (15) either in the *E* or *Z* configuration, possibly formed from a carbene *via* a sulphine intermediate. The reaction of thionyl chloride

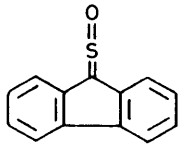


(11)

SCHEME 2

with thiophens of type (1) appears to be a fruitful field for future investigation.

The readily available chloroformylthiophen (10) was used in a further series of reactions. Normal condensations took place with the primary amine (16), the hydrazines (17) and (23), the substituted hydrazines (18) and



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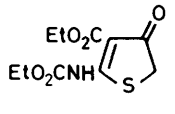

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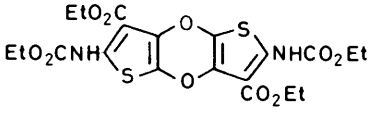

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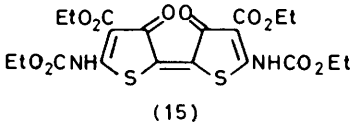
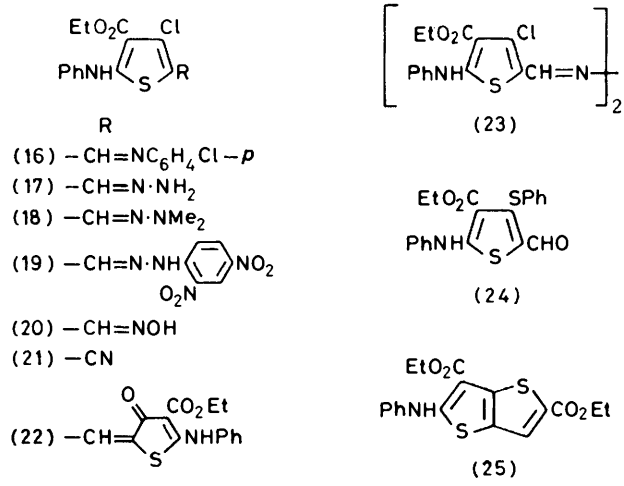


(15)

(19), and the hydroxylamine (20) which gave the nitrile (21) with thionyl chloride. Reaction of (10) with the thiophen (1b) gave the condensation product (22). Nucleophilic displacement of the chlorine atom in (10) took place with thiophenol to give the sulphide (24), and, similarly, with ethyl thioglycolate and further cyclisation to the thieno[3,2-*b*]thiophen (25). Litvinov and Gol'dfarb [9] have reviewed the chemistry of thienothiophens. Our method, for the formation of the thieno-[3,2-*b*]thiophen (25) complements earlier work on similar systems using methyl (5-ethyl-3-thienylthio)acetate [10] and a methylchloroformylthiophen.[11]



EXPERIMENTAL

Uncorrected melting points were determined on a Reichert hotstage apparatus. N.m.r. spectra were obtained with Varian HA 100D and EM 390 spectrometers. Mass spectra were measured with A.E.I. MS9 + MS902S or Du Pont 491BR or V.G. 70/70F with Finnigan 1NCOS Data System spectrometers.

Ethyl 2-Anilino-4-oxo-4,5-dihydrothiophen-3-carboxylate (1b).—The sodium salt of ethyl γ-chloroacetoacetate (from 16 g, 97 mmol of ester and 4.7 g, 0.097 mol of NaH; 50%) in 1,2-dimethoxyethane (75 ml) was treated with a solution of phenyl isothiocyanate (13.1 g, 97 mmol) in 1,2-dimethoxyethane (25 ml). After stirring for 5 h the mixture was added to water and extracted with dichloromethane and dried ($MgSO_4$). Evaporation and crystallisation of the resulting solid from ethanol gave the *thiophen* (1b) (13.3 g, 52%) as needles, m.p. 146—148 °C (Found: C, 59.3; H, 5.1; N, 4.8; S, 12.0. $C_{13}H_{13}NO_3S$ requires C, 59.3; H, 4.9; N, 5.3; S, 12.2%); δ($CDCl_3$) 1.35 (3 H, t, *J* 6 Hz, Me), 3.6 (2 H, s, $COCH_2$), 4.35 (2 H, q, *J* 6 Hz, OCH_2), 7.35 (5 H, s, aromatic), and 11.5 (1 H, br, NH); *m/e* 263 (M^+).

Compounds from Ethyl 2-Anilino-4-oxo-4,5-dihydrothiophen-3-carboxylate.—(a) Bromine (0.85 ml, 15.6 mmol) in acetic acid (10 ml) was added dropwise to a solution of the thiophen (1b) (2 g, 7.6 mmol) in acetic acid (50 ml). After 4 h the mixture was added to water and extracted with dichloromethane and dried ($MgSO_4$). Evaporation and recrystallisation of the resulting solid from ethanol gave *ethyl 2-anilino-5,5-dibromo-4-oxo-4,5-dihydrothiophen-3-carboxylate* (2) (2.1 g, 47%) as yellow needles, m.p. 147—151 °C (Found: C, 37.6; H, 2.6; N, 3.3; S, 7.8. $C_{13}H_{11}Br_2NO_3S$ requires C, 37.1; H, 2.6; N, 3.3; S, 7.6%); δ($CDCl_3$) 1.5 (3 H, t, *J* 7 Hz, Me), 4.45 (2 H, q, *J* 7 Hz, OCH_2), 7.2—7.7 (5 H, m, aromatic), and 11.7 (1 H, br, NH); *m/e* 423 (M^+).

(b) A mixture of the thiophen (1b) (1.5 g, 5.7 mmol),

benzaldehyde (0.64 ml, 6.27 mmol) and piperidine (0.56 ml, 5.7 mmol) in ethanol (50 ml) was heated under reflux for 4 h. After cooling, the mixture was shaken with water and chloroform. The organic layer was washed (2N HCl, water) and dried ($MgSO_4$). Evaporation and crystallisation of the resulting solid from ethanol gave *ethyl 2-anilino-5-benzylidene-4-oxo-4,5-dihydrothiophen-3-carboxylate* (3) (1.5 g, 75%) as prisms, m.p. 170—172 °C (Found: C, 68.6; H, 4.9; N, 3.9; S, 9.3. $C_{20}H_{17}NO_3S$ requires C, 68.4; H, 4.8; N, 4.0; S, 9.1%); δ($CDCl_3$) 1.5 (3 H, t, *J* 8 Hz, Me), 4.5 (2 H, q, *J* 8 Hz, CH_2), 7.5 (5 H, s, aromatic), and 11.5 (1 H, br, NH); *m/e* 351 (M^+).

(c) HCl gas was passed through a solution of the thiophen (1b) (1.6 g, 6.1 mmol) and acetophenone (0.8 ml, 6.7 mmol) in ethanol (70 ml) for 3 h at 60—70 °C. After the usual work-up, chromatographic purification of the product on silica (10% methanol–chloroform as eluant) gave *ethyl 2-anilino-5-methylbenzylidene-4-oxo-4,5-dihydrothiophen-3-carboxylate* (4) (0.35 g, 16%) as an orange solid, m.p. 148—150 °C (Found: C, 68.9; H, 5.3; N, 3.6; S, 8.8. $C_{21}H_{19}NO_3S$ requires C, 69.1; H, 5.2; N, 4.0; S, 8.8%); δ($CDCl_3$) 1.45 (3 H, t, *J* 7 Hz, ester Me), 2.8 (3 H, s, Me), 4.5 (2 H, q, *J* 7 Hz, CH_2), 7.35 (5 H, s, aromatic), 7.45 (5 H, s, aromatic), and 11.4 (1 H, br, NH).

(d) To a solution of the thiophen (1b) (1.2 g, 4.56 mmol) in dichloromethane was added a filtered solution of lead tetra-acetate in dichloromethane until in excess. The mixture was stirred for 72 h, filtered, and the resulting solution treated with ethylene glycol, to destroy any excess of lead tetra-acetate; it was then acidified (2N HCl). The organic layer was washed (H_2O), dried ($MgSO_4$), and evaporated. The crude product crystallised from ethanol to give *ethyl 5-acetoxy-2-anilino-4-oxo-4,5-dihydrothiophen-3-carboxylate* (5) (0.7 g, 48%) as yellow prisms, m.p. 182—186 °C (Found: C, 55.9; H, 4.7; N, 4.1; S, 9.8. $C_{15}H_{15}NO_5S$ requires C, 56.1; H, 4.7; N, 4.4; S, 10.0%); δ($CDCl_3$) 1.4 (3 H, t, *J* 7 Hz, Me), 2.2 (3 H, s, COMe), 4.4 (2 H, q, *J* 7 Hz, CH_2), 5.9 (1 H, s, CH), 7.4 (5 H, br, aromatic), and 11.6 (1 H, br, NH); *m/e* 321 (M^+).

(e) Diazotised *p*-chloroaniline (prepared in the usual manner from 0.3 g, 2.35 mmol of base in dilute hydrochloric acid) was added to an ice-cold solution of the thiophen (1b) (0.6 g, 2.35 mmol) in acetic acid (30 ml) and set aside at room temperature. After 3 d the product was collected and washed with acetic acid. Recrystallisation from acetonitrile gave *ethyl 2-anilino-5-p-chlorophenylhydrazono-4-oxo-4,5-dihydrothiophen-3-carboxylate* (6) (0.35 g, 38%) as yellow needles, m.p. 220—222 °C (Found: C, 56.8; H, 4.2; N, 10.2; S, 7.8. $C_{19}H_{16}ClN_3O_3S$ requires C, 56.8; H, 4.0; N, 10.5; S, 8.0%); δ[$(CD_3)_2SO$] 1.2 (3 H, t, *J* 8 Hz, Me), 4.2 (2 H, q, *J* 8 Hz, CH_2), 7.0—7.6 (10 H, m, aromatic), and 10.25 (1 H, br, NH); *m/e* 401 (M^+).

(f) A mixture of the thiophen (1b) (4.5 g, 17 mmol) in ethanol (50 ml) and sodium hydroxide (2.1 g, 52.5 mmol) in water (50 ml) was heated under reflux for 16 h. The reaction mixture was stirred into ice–water and washed free of ester with dichloromethane. The aqueous layer was acidified and again extracted with dichloromethane. The usual work-up procedure and recrystallisation from ethyl acetate gave *2-anilino-4-oxo-4,5-dihydrothiophen* (7) (2.5 g, 76%) as needles, m.p. 185—186 °C (Found: C, 62.6; H, 4.7; N, 7.1; S, 17.3. $C_{10}H_9NOS$ requires C, 62.8; H, 4.7; N, 7.3; S, 16.8); δ($CDCl_3$) 3.7 (2 H, s, $COCH_2$), 5.5 (1 H, s, =CH), 7.1—7.6 (5 H, m, aromatic), and 10.3 (1 H, br, NH); *m/e* 191 (M^+).

(g) Hydrazine hydrate (0.22 ml, 4.4 mmol) was added to a hot solution of the thiophen (1b) (1.1 g, 4.2 mmol) in ethanol (15 ml) and the mixture heated under reflux for 20 h. *Ethyl 2-anilino-4-hydrazonothiophen-3-carboxylate* (8) (0.4 g, 35%) was collected as needles, m.p. 216—218 °C and washed with hot ethanol (Found: C, 56.3; H, 5.1; N, 15.1; S, 11.3. $C_{13}H_{15}N_3O_2S$ requires C, 56.3; H, 5.4; N, 15.2; S, 11.55%); δ(TFA) 1.5 (3 H, t, *J* 8 Hz, Me), 4.3 (2 H, s, SCH_2), 4.5 (2 H, q, *J* 8 Hz, CH_2), and 7.2—7.6 (5 H, m, aromatic), NH protons not observed; *m/e* 277 (M^+).

(h) To a solution of the thiophen (1b) (0.5 g, 1.9 mmol) in 1,2-dimethoxyethane (20 ml) was added acetyl chloride (0.157 g, 1.9 mmol) followed by pyridine (0.16 ml, 1.9 mmol) and the mixture was stirred at the ambient temperature for 1 h. The sequence of adding 1 equiv. of acetyl chloride followed by 1 equiv. of pyridine was repeated at hourly intervals until no starting material remained (*ca.* 4 h). The mixture was poured into dichloromethane–water and the separated organic layer was washed (2N HCl, then water) and dried ($MgSO_4$). Evaporation and crystallisation of the crude product from ethanol gave *ethyl 4-acetoxy-2-anilinothiophen-3-carboxylate* (9) (0.47 g, 81%) as orange needles, m.p. 103—105 °C (Found: C, 58.8; H, 5.0; N, 4.5; S, 10.7. $C_{15}H_{15}NO_4S$ requires C, 59.0; H, 4.9; N, 4.6; S, 10.5%); δ($CDCl_3$) 1.35 (3 H, t, *J* 7 Hz, $MeCH_2$), 2.25 (3 H, s, COMe), 4.3 (2 H, q, *J* 7 Hz, OCH_2), 5.95 (1 H, s, =CH), 7.3 (5 H, m, aromatic), and 11.4 (1 H, br, NH); *m/e* 305 (M^+).

Ethyl 2-Anilino-4-chloro-5-formylthiophen-3-carboxylate (10).—A solution of the thiophen (1b) (43.7 g, 166 mmol) in 1,1,2,2-tetrachloroethane (TCE) (400 ml) was added dropwise with stirring to the Vilsmeier reagent [prepared by adding phosphorus oxychloride (100 ml, 1.1 mol) in TCE (100 ml) to dimethylformamide (36.5 ml, 0.47 mol) in TCE (400 ml) with cooling, stirring for 0.5 h, and the coolant removed]. After stirring for 16 h at room temperature the mixture was added to water, treated with dilute sodium hydroxide until faintly acid, and the organic layer separated and dried ($MgSO_4$). The oil remaining after evaporation crystallised from ethanol to give the *chloroformylthiophen* (10) (37.8 g) as needles, m.p. 117—119 °C. A second crop (2.1 g), obtained by concentrating the liquors gave an overall yield of 78% (Found: C, 54.4; H, 3.8; Cl, 11.3; N, 4.2; S, 10.2. $C_{14}H_{12}ClNO_3S$ requires C, 54.3; H, 3.9; Cl, 11.5; N, 4.5; S, 10.3%); δ($CDCl_3$) 1.4 (3 H, t, *J* 7 Hz, Me), 4.45 (2 H, q, 7 Hz, OCH_2), 7.4 (5 H, m, aromatic), 9.95 (1 H, s, CHO), and 10.7 (1 H, br, NH); *m/e* 309 (M^+).

Ethyl 2-Anilino-4-oxo-5-thioxo-4,5-dihydrothiophen-3-carboxylate S^2-*Oxide* (11).—Thionyl chloride (0.6 ml, 8 mmol) was added dropwise with stirring to a warm solution of the thiophen (1b) (1.8 g, 6.8 mmol) in 1,2-dimethoxyethane (35 ml). After stirring for a further 2 h the *thiophen* S^2-*oxide* (11) (1.9 g, 92%) was collected as yellow needles, m.p. >300 °C, the colour darkens *ca.* 190 °C, and washed with 1,2-dimethoxyethane (Found: C, 50.7; H, 3.6; N, 4.3; S, 20.4. $C_{13}H_{11}NO_4S_2$ requires C, 50.5; H, 3.55; N, 4.5; S, 20.7%); *m/e* 309 (M^+), 263 (M^+ — EtOH), and 217 (M^+ — PhNH).

Ethyl 3-Ethoxycarbonyl-4-oxo-4,5-dihydrothiophen-2-carbamate (13).—Prepared in a similar manner to the dihydrothiophen (1b) from ethoxycarbonyl isothiocyanate [8] in 64% yield as yellow needles, m.p. 157—160 °C (Found: C, 46.4; H, 5.1; N, 5.2. $C_{10}H_{13}NO_5S$ requires C, 46.3; H, 5.0; N, 5.4%); δ($CDCl_3$) 1.4 (6 H, t, *J* 8 Hz, Me), 3.65

(2 H, s, SCH_2), 4.4 (4 H, q, *J* 8 Hz, CH_2Me), 11.7 (1 H, b, NH); *m/e* 259 (M^+).

Diethyl 3,7-Bis(ethoxycarbonyl)dithieno[2,3-b:2′,3′-e][1,4]-*dioxin-2,6-dicarbamate* (14) *or Diethyl 3,3′-Bis(ethoxycarbonyl)-4,4′-dioxo-*$\Delta^{5,5'}$*-bi-2-thiazolinylidene-2,2′-dicarbamate* (15).—This compound, prepared from the thiophen (13) and thionyl chloride, in a similar manner to the sulphine (12) was obtained in 63% yield as yellow needles, m.p. >310 °C (Found: C, 47.0; H, 4.3; N, 5.2; S, 12.6. $C_{20}H_{22}N_2O_{10}S_2$ requires C, 46.7; H, 4.3; H, 5.4; S, 12.45%); δ(CF_3CO_2H) 1.4 (6 H, t, Me), 4.5 (4 H, q, CH_2); *m/e* 514 (M^+).

Compounds from Ethyl 2-Anilino-4-chloro-5-formylthiophen-3-carboxylate (10).—(a) *p*-Chloroaniline (0.25 g, 1.9 mmol) and the chlorothiophen (10) (0.6 g, 1.9 mmol) in toluene (50 ml) containing a few mg of toluene-*p*-sulphonic acid were heated under Dean–Stark conditions for 4 h. The solid obtained after evaporation was crystallised from ethanol to give *ethyl 2-anilino-4-chloro-5-(p-chlorophenyliminomethyl)thiophen-3-carboxylate* (16) (0.15 g, 37%) as yellow needles, m.p. 137—139 °C (Found: C, 56.7; H, 3.8; N, 6.0; S, 7.6. $C_{20}H_{16}Cl_2N_2O_2S$ requires C, 57.3; H, 3.8; N, 6.7; S, 7.6%); δ($CDCl_3$) 1.45 (3 H, t, *J* 7 Hz, Me), 4.45 (2 H, q, *J* 7 Hz, CH_2), 7.0—7.5 (9 H, m, aromatic), 8.6 (1 H, s, CH), and 10.7 (1 H, br, NH).

(b) A hot solution of the chlorothiophen (10) (0.5 g, 1.6 mmol) in ethanol (15 ml) was added dropwise to hydrazine hydrate (0.2 ml, 4 mmol) in ethanol (5 ml) and the mixture refluxed for 5 h. Evaporation of the cooled, filtered liquors gave *ethyl 2-anilino-4-chloro-5-hydrazonothiophen-3-carboxylate* (17) (0.45 g, 73%) as needles, m.p. 114—116 °C (Found: C, 52.1; H, 4.4; N, 12.5; S, 9.7. $C_{14}H_{14}ClN_3O_2S$ requires C, 51.9; H, 4.3; N, 13.0; S, 9.9%); δ($CDCl_3$) 1.4 (3 H, t, *J* 8 Hz, Me), 4.35 (2 H, q, *J* 8 Hz, CH_2), 5.2—6.3 (2 H, br, $N.NH_2$), 6.9—7.6 (5 H, m, aromatic), 7.95 (1 H, s, CH), and 10.35 (1 H, br, NH); *m/e* 323 (M^+) and 287 (M^+ − HCl).

(c) Hydrazine hydrate (0.2 ml, 4 mmol) was added to a hot solution of the chlorothiophen (10) (0.5 g, 1.6 mmol) in ethanol and the whole heated under reflux during 16 h. *Diethyl 2,2′-dianilino-4,4′-dichloro-5,5′-azinomethylbi(thiophenyl-3,3′-dicarboxylate*) (23) (0.18 g, 31%) was obtained as orange needles, m.p. 268—270 °C (Found: C, 54.8; H, 3.9; N, 9.3; S, 10.5. $C_{28}H_{24}Cl_2N_4O_4S_2$ requires C, 54.6; H, 3.9; N, 9.1; S, 10.4%); *m/e* 614 (M^+). The compound was unstable in trifluoroacetic acid, preventing an n.m.r. determination.

(d) *NN*-Dimethylhydrazine (0.25 ml, 1.8 mmol) was added to a solution of the chlorothiophen (10) (0.5 g, 1.6 mmol) in ethanol (15 ml) and the mixture heated under reflux for 16 h. *Ethyl 2-anilino-4-chloro-5-dimethylhydrazonothiophen-3-carboxylate* (18) (0.5 g, 75%) was obtained as yellow needles, m.p. 151—153 °C (Found: C, 54.3; H, 5.2; N, 11.9; S, 9.1. $C_{15}H_{18}ClN_3O_2S$ requires C, 54.6; H, 5.1; N, 11.95; S, 9.1%); *m/e* 351 (M^+), 305 (M^+ − EtOH). In a similar manner were prepared, using concentrated hydrochloric acid as a catalyst, *ethyl 2-anilino-4-chloro-5-(2,4-dinitrophenyl)hydrazonothiophen-3-carboxylate* (19) (54%) as red needles (from dimethylformamide), m.p. 217—219 °C (Found: C, 48.9; H, 3.9; N, 14.4; S, 5.8. $C_{20}H_{16}ClN_5O_6S\cdot\frac{1}{2}Me_2NCHO$ requires C, 49.1; H, 3.6; N, 14.6; S, 6.1%); *m/e* 489 (M^+), and *ethyl 2-anilino-4-chloro-5-hydroxyiminothiophen-3-carboxylate* (20) (40%) as pale purple needles, m.p. 184—186 °C (Found: C, 51.0; H, 4.1; N, 8.5; S, 9.8. $C_{14}H_{13}ClN_2O_3S\cdot\frac{1}{4}H_2O$ requires C, 51.1; H, 4.1; N, 8.5; S, 9.7%); δ[$(CD_3)_2SO$] 1.35 (3 H, t, *J* 7 Hz, Me), 4.35 (2 H, q, *J* 7 Hz, CH_2), 7.4 (5 H, s, aromatic), 7.75 (1 H, s, CH), 9.5—12.1 (2 H, vbr, NH + OH); *m/e* 324 (M^+) and 306 ($M^+ - H_2O$).

(e) A mixture of the oxime (20) (4.4 g) and thionyl chloride (6 ml) in 1,2-dimethoxyethane was allowed to stand for 1 h, then poured into ice–water and extracted with chloroform. After drying ($MgSO_4$) and evaporation the residue was crystallised from ethanol to give *ethyl 2-anilino-4-chloro-5-cyanothiophen-3-carboxylate* (21) (3.2 g, 77%) as brown needles, m.p. 122—124 °C (Found: C, 54.8; H, 3.6; N, 9.0; S, 10.5. $C_{14}H_{11}ClN_2O_2S$ requires C, 54.8; H, 3.6; N, 9.1; S, 10.4%); δ($CDCl_3$) 1.4 (3 H, t, *J* 8 Hz, Me), 4.4 (2 H, q, *J* 8 Hz, CH_2), 7.1—7.6 (5 H, m, aromatic), and 10.4 (1 H, br, NH); *m/e* 306 (M^+).

Ethyl 2-Anilino-5-(5-anilino-4-ethoxycarbonyl-3-oxo-2,3-dihydro-2-thienylidenemethyl)-4-chlorothiophen-3-carboxylate (22).—Condensation of the chlorothiophen (10) with the thiophen (1b) using piperidine as catalyst gave the *thienylidenemethylthiophen* (22) (20%) as reddish yellow needles (from ethanol), m.p. 222—225 °C (Found: C, 58.9; H, 4.1; N, 5.1; S, 11.8. $C_{27}H_{23}ClN_2O_5S_2$ requires C, 58.4; H, 4.2; N, 5.1; S, 11.5%); δ($CDCl_3$) 1.4 (6 H, t, *J* 7 Hz, Me), 4.4 (4 H, q, *J* 7 Hz, CH_2), 7.0—7.5 (10 H, m, aromatic), 8.15 (1 H, s, CH), 10.5 (1 H, br, NH), and 11.6 (1 H, br, NH).

Ethyl 2-Anilino-5-formyl-4-(phenylthio)thiophen-3-carboxylate (24).—To a solution of the chlorothiophen (0.7 g, 2.26 mmol) in 1,2-dimethoxyethane (30 ml) was added potassium carbonate (1 g) followed by thiophenol (0.25 ml, 2.5 mmol) and the mixture was refluxed for 18 h. The mixture was poured into ice–water and extracted with dichloromethane. The organic layer was washed (2N KOH, water), dried ($MgSO_4$), evaporated, and the crude product crystallised from ethanol to give the *thioether* (24) (0.45 g, 52%) as needles, m.p. 108—112 °C (Found: C, 62.6; H, 4.5; N, 3.6; S, 16.2. $C_{20}H_{17}NO_3S_2$ requires C, 62.7; H, 4.4; N, 3.65; S, 16.7%) δ($CDCl_3$) 1.05 (3 H, t, *J* 7 Hz, Me), 4.1 (2 H, q, *J* 7 Hz, CH_2), 6.7—7.5 (10 H, m, aromatic), 10.0 (1 H, s, CHO), and 10.7 (1 H, b, NH).

Diethyl (2-Anilinothieno[3,2-b]*thiophen)-3,5-dicarboxylate* (25).—A solution of sodium ethoxide [from sodium (0.17 g, 7.4 mmol) and ethanol (5 ml)] was added to a solution of ethyl thioglycolate (0.84 g, 7 mmol) in ethanol (20 ml), followed by a solution of the chlorothiophen (10) (2.2 g, 7 mmol) in 1,2-dimethoxyethane (25 ml), and the whole heated under reflux during 18 h and evaporated. Dry column chromatography on Merck deactivated Kieselgel 0.05—0.2 mm with chloroform as development solvent gave, as the main product, *the thienothiophen* (25) (2.0 g), m.p. 125—127 °C, which was raised to 133—134 °C as needles (from cyclohexane) (Found: C, 57.9; H, 4.5; N, 3.6. $C_{18}H_{17}NO_4S_2$ requires C, 57.6; H, 4.5; N, 3.7%); δ($CDCl_3$) 1.4 (3 H, t, *J* 7.3 Hz, ester Me), 1.5 (3 H, t, *J* 7.3 Hz, ester Me), 4.4 (2 H, q, *J* 7.3 Hz, ester CH_2), 4.5 (2 H, q, *J* 7.3 Hz, ester CH_2), 7.3—7.5 (5 H, m, aromatic), and 7.82 (1 H, s, thiophen aromatic); *m/e* 375 (M^+).

[0/1133 *Received*, 18*th July*, 1980]

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