Heterocyclic Syntheses from *o*-Halogeno-acids. Part II.[1] Thienopyridinones and Thienopyranones from 3-Bromothiophen-2- and 4-Bromothiophen-3-carboxylic Acids

By **Donald E. Ames** * and **Odartey Ribeiro**, Chemistry Department, Chelsea College, Manresa Road, London SW3 6LX

The sodium salts of 3-bromothiophen-2- and 4-bromothiophen-3-carboxylic acids react with carbanions in the presence of copper or copper(II) acetate to give condensation products by displacement of bromide ion (often with simultaneous deacylation). Thus ethyl acetoacetate gives the mono-ethyl esters of the homophthalic acid analogues, 2- and 4-carboxythiophen-3-acetic acids. Cyclisation reactions of the condensation products provide convenient routes to thienopyranones and thienopyridinones. 4-Phenacylthiophen-3-carboxylic acid is reduced to the 4-phenethyl-acid, which is cyclised by polyphosphoric acid at 100 °C to give 9,10-dihydrobenzo[4,5]-cyclohepta[1,2-*c*]thiophen-4-one. At 160 °C, however, this ketone, or the acid, yields the isomeric 4,5-dihydro-benzo[5,6]cyclohepta[1,2-*b*]thiophen-10-one, apparently by acidic cleavage to form an acylium ion which recyclises by attack on the α-position of the thiophen ring.

HURTLEY [2] showed that *o*-bromobenzoic acid condensed with carbanions in copper-catalysed reactions under basic conditions. The process is of potential value in the synthesis of heterocyclic compounds but it has been little used for this purpose.[1,3] Of the three *ortho*-bromothiophencarboxylic acids, 3-bromothiophen-2-[4] and 4-bromothiophen-3-carboxylic acids [5] are readily available, and we report here condensations of salts of these acids with carbanions and some cyclisation reactions of the products.

4-Bromothiophen-3-carboxylic acid was used for much of this work as 3,4-disubstituted thiophens are relatively inaccessible owing to the reactivity of the 2-position. The carbonyl compound, bromo-acid, and copper or copper(II) acetate were added to ethanolic sodium ethoxide and heated.[2] Diethyl malonate, ethyl phenylsulphonylacetate, and benzoylacetanilide gave simple condensation products but benzoylacetonitrile yielded 4-carboxythiophen-3-acetonitrile (Ia), with loss of the benzoyl group by alcoholysis, and ethyl acetoacetate, benzoylacetone, and *o*-benzyloxybenzoylacetone reacted with accompanying deacetylation. With acetylacetone partial deacetylation occurred to give a mixture of mono- and di-oxo-acids, but deacetylation could be avoided by using a large excess of acetylacetone or by taking potassium t-butoxide in t-butyl alcohol as base and solvent.[6] The resulting 4-(1-acetylacetonyl)thiophen-3-carboxylic acid (Ib) gave isoxazole and pyrazole derivatives and it was efficiently deacetylated by treatment with aqueous ammonia to form 4-acetonylthiophen-3-carboxylic acid (Ic).

Condensation of the oxo-acids obtained by these reactions with ammonium acetate and with amine acetates provided a convenient route to thieno[3,4-*c*]-pyridin-4(5*H*)-ones of type (II; X = NH or N-alkyl). The dioxo-acid (Ib) gave a mixture of 7-acetyl-6-methylthieno[3,4-*c*]pyridin-4(5*H*)-one (IIa) and deacetyl-

[1] The paper by D. E. Ames and W. D. Dodds, *J.C.S. Perkin I*, 1972, 705, is regarded as Part I.

[2] W. R. H. Hurtley, *J. Chem. Soc.*, 1929, 1870; *cf.* K. A. Ciriguttis, E. Ritchie, and W. C. Taylor, *Austral. J. Chem.*, 1974, **27**, 2209.

[3] R. Adams, B. R. Baker, and R. B. Wearn, *J. Amer. Chem. Soc.*, 1940, **62**, 2204, and preceding papers.

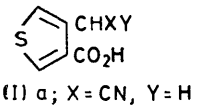
[4] S. Gronowitz, *Arkiv Kemi*, 1954, **7**, 361.

[5] S. O. Lawesson, *Arkiv Kemi*, 1957, **11**, 325.

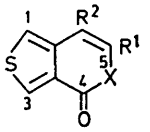
[6] *Cf.* A. Bruggink and A. McKillop, *Angew. Chem. Internat. Edn.*, 1974, **13**, 340.

ation product (IIb). Treatment of 6-phenylthieno[3,4-*c*]-pyridin-4(5*H*)-one with phosphoryl chloride yielded 4-chloro-6-phenylthieno[3,4-*c*]pyridine (III).

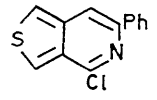
Dehydration of 4-phenacylthiophen-3-carboxylic acid at 250° furnished 6-phenylthieno[3,4-*c*]pyran-4-one (IIc), which has been prepared [7] from 3-iodothiophen-4-carboxylic acid by condensation with the copper(I) derivative of phenylacetylene in dimethylformamide. The 6-methyl- (IId) and 7-acetyl-6-methyl- (IIe) analogues were prepared by dehydration of the oxo-acids with acetic anhydride, but the enol lactone could



(I) a; X = CN, Y = H
b; X = Y = Ac
c; X = Ac, Y = H
d; X = Bz, Y = CO·NHPh



(II) a; R^1 = Me, R^2 = Ac, X = NH
b; R^1 = Me, R^2 = H, X = NH
c; R^1 = Ph, R^2 = H, X = O
d; R^1 = Me, R^2 = H, X = O
e; R^1 = Me, R^2 = Ac, X = O
f; R^1 = NAc_2, R^2 = H, X = O

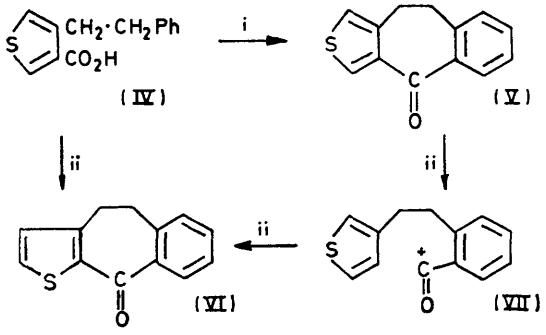


(III)

not be prepared from α-benzoyl-α-(4-carboxy-3-thienyl)-acetanilide (Id) by either process. The 6,7-dihydro-derivative of the pyranone (IIc) was obtained by reduction of 4-phenacylthiophen-3-carboxylic acid to the hydroxy-acid and lactonisation.

None of the three possible thiophen analogues of homophthalic acid has been described previously. Alkaline hydrolysis of the ethyl ester obtained from 4-bromothiophen-3-carboxylic acid and ethyl acetoacetate gave 4-carboxythiophen-3-acetic acid, which was converted into the anhydride. 4-Carboxythiophen-3-acetate reacted with ammonia to form 4-carboxythiophen-3-acetamide which, on strong heating yielded the imide. Treatment of the amide-acid with acetyl chloride–dioxan, however, gave 6-diacetylaminothieno[3,4-*c*]-pyran-4-one (IIf), the structure of which was indicated by the close resemblance of its u.v. spectrum to those of other thienopyranones and by the n.m.r. spectrum, which showed the equivalence of the two acetyl groups.

Wolff–Kishner reduction of 4-phenacylthiophen-3-carboxylic acid gave the 4-phenethyl-acid (IV) which, on treatment with polyphosphoric acid at 100 °C, gave 9,10-dihydrobenzo[4,5]cyclohepta[1,2-*c*]thiophen-4-one (V). At 160 °C, however, the reaction yielded the isomeric ketone (VI), which was also obtained by treatment of the first ketone under these conditions. Presumably the ketone rearranges by acidic cleavage to the acylium ion (VII) which then cyclises by attack on the more reactive α-position of the thiophen ring to give the isomer (VI). This sequence, involving the unusual reversal of a Friedel–Crafts acylation, is similar to that reported recently [8] in the conversion of 2-(2-naphthyl)benzoic acid into two isomeric ketones (the products of acylation on the naphthalene 1- and 3-positions).

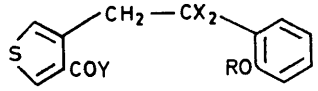


(IV) (V) (VI) (VII)

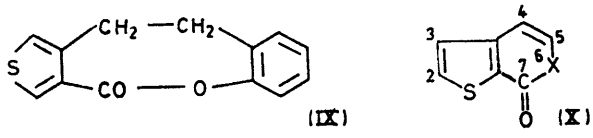
i, polyphosphoric acid (PPA), 100 °C; ii, PPA, 160 °C

Reduction of 4-(*o*-benzyloxyphenacyl)thiophen-3-carboxylic acid (VIIIa) by the Wolff–Kishner method gave a mixture of 4-(*o*-benzyloxyphenethyl)thiophen-3-carboxylic acid (VIIIb) and the hydroxy-acid (VIIIc), formed by alkaline cleavage of the ether. The hydroxy-acid was cyclised to the lactone (IX) by the action of dicyclohexylcarbodi-imide, which also gave the *N*-acylurea (VIIId).

3-Bromothiophen-2-carboxylic acid reacted with carbanions in the same way as the isomeric acid. Trans-



(VIII) a; R = CH_2Ph, X_2 = O, Y = OH
b; R = CH_2Ph, X = H, Y = OH
c; R = X = H, Y = OH
d; R = X = H, Y = NC_6H_{11}·CO.NHC_6H_{11}



(IX) (X)

formations similar to those described above then led to thieno[2,3-*c*]-pyridinones and -pyranones of type (X), to the homophthalic acid analogue, and to other compounds which are described in the Experimental section. When 3-phenacylthiophen-2-carboxylic acid was heated at 220 °C partial decarboxylation occurred to give a mixture of phenyl 3-thienyl ketone and 5-phenyl[2,3-*c*]pyran-7-one, which was more efficiently prepared by the action of acetic anhydride on the oxo-acid.

EXPERIMENTAL

Evaporations were carried out under reduced pressure; petrol refers to light petroleum (b.p. 60—80°). ^{1}H N.m.r. spectra were measured on a Perkin-Elmer R32 spectrometer at 90 MHz. U.v. spectra were recorded on a Perkin-Elmer 402 spectrophotometer with ethanol as solvent.

[7] S. A. Mladenovic and C. E. Castro, *J. Heterocyclic Chem.*, 1968, **5**, 227.
[8] I. Agranat and D. Avniv, *J.C.S. Chem. Comm.*, 1973, 362.

o-*Benzyloxybenzoylacetone*.—Acetone (34.8 g) in ether (35 ml) was added gradually to a suspension of sodamide [from sodium (13.8 g)] in ether (200 ml). Methyl *o*-benzyloxybenzoate [9] (72.6 g) in ether (50 ml) was added slowly and then the mixture was stirred and heated under reflux for 2 h, cooled, and poured into ice–hydrochloric acid. The separated ether layer was washed with 0.5M-sodium carbonate and water and evaporated. The residue in methanol was added to a hot solution of copper(II) acetate [40 g in water (350 ml) which had been filtered hot] and left overnight. The complex was collected, washed with petrol, and shaken with M-sulphuric acid (500 ml) and ether (200 ml). Isolation with ether and crystallisation from benzene gave the *diketone* (21 g), m.p. 57—59° (Found: C, 76.1; H, 6.0. $C_{17}H_{16}O_3$ requires C, 76.1; H, 6.0%). o-*Bromobenzoylacetone* (40%), prepared similarly, was an oil, b.p. 120° at 1.5 mmHg (Found: C, 50.1; H, 3.8. $C_{10}H_9BrO_2$ requires C, 49.8; H, 3.8%).

Condensation of 4-Bromothiophen-3-carboxylic Acid with Carbanions.—Benzoylacetonitrile (2.1 g, 14.5 mmol) was added to a cooled solution of sodium ethoxide [from sodium (530 mg, 23 mg atom)] in ethanol (30 ml). The bromo-acid (2 g, 9.7 mmol) and copper (100 mg) were added and the mixture was boiled under reflux for 1.5 h, poured into water (100 ml), and filtered. The solution was acidified with hydrochloric acid and extracted three times with ether; the combined ethereal solutions were extracted with 0.5M-sodium carbonate (2 × 50 ml). The extracts were washed with ether, filtered, and acidified to give *4-carboxythiophen-3-acetonitrile* (1.5 g), m.p. 171—172.5° (from benzene–ethanol) (Found: C, 50.1; H, 3.0; N, 8.3; S, 19.2. $C_7H_5NO_2S$ requires C, 50.3; H, 3.0; N, 8.4; S, 19.2%); τ [$(CD_3)_2SO$] 1.65 (1H, d, *J* 4 Hz, H-5), 2.40 (1H, d, *J* 4 Hz, H-2), and 5.82 (2H, s, CH_2).

The following were prepared similarly (starting material, reflux time, and catalyst are given in parentheses): *ethyl 4-carboxythiophen-3-acetate* (ethyl acetoacetate, 6 h, Cu) (95%), m.p. 159.5—161° (from toluene–petrol) (Found: C, 50.1; H, 4.6; S, 15.1. $C_9H_{10}O_4S$ requires C, 50.5; H, 4.7; S, 14.9%), τ[$CDCl_3$–$(CD_3)_2SO$] 1.90 (1H, d, *J* 3 Hz, H-5), 2.81 (1H, d, *J* 3 Hz, H-2), 5.88 (2H, q, *J* 8 Hz, CH_2·CH_3), 6.10 (2H, s, CH_2·CO_2Et), and 8.77 (3H, t, *J* 8 Hz, CH_2·CH_3); *4-phenacylthiophen-3-carboxylic acid* (benzoylacetone, 4.5 h, Cu) (67%), m.p. 212—214° (from ethanol) (Found: C, 63.6; H, 4.1; S, 13.0. $C_{13}H_{10}O_3S$ requires C, 63.4; H, 4.1; 2, 13.0%), τ[$(CD_3)_2SO$] 1.75 (1H, d, *J* 4 Hz, H-2), 2.0—2.4 (5H, m, ArH), 2.64 (1H, d, *J* 4 Hz, H-5), and 5.38 (2H, s, CH_2); *4-(o-benzyloxyphenacyl)thiophen-3-carboxylic acid* (*o*-benzyloxybenzoylacetone, 5 h, Cu) (75%), m.p. 126—128° (from benzene–petrol) (Found: C, 68.2; H, 4.3; S, 9.4. $C_{20}H_{16}O_4S$ requires C, 68.2; H, 4.6; S, 9.1%), τ[$(CD_3)_2SO$] 1.75 (1H, d, *J* 3 Hz, H-2), 2.3—3.1 (11H, m, ArH + CO_2H), 4.70 (2H, s, OCH_2Ph), and 5.47 (2H, s, CH_2·CO); *ethyl 4-carboxy-α-phenylsulphonylthiophen-3-acetate* [ethyl phenylsulphonylacetate, 16 h, $Cu(OAc)_2$] (52%), m.p. 201—203.5° (from ethanol) (Found: C, 51.0; H, 4.1; S, 18.0. $C_{15}H_{14}O_6S_2$ requires C, 50.9; H, 4.0; S, 18.1%); *α-benzoyl-α-(4-carboxy-3-thienyl)acetanilide* [benzoylacetanilide, 16 h, $Cu(OAc)_2$] (63%), m.p. 190—191°, from aqueous ethanol (Found: C, 65.6; H, 4.1; N, 3.7; S, 8.7. $C_{20}H_{15}NO_4S$ requires C, 65.8; H, 4.1; N, 3.8; S, 8.8%); *diethyl 4-carboxy-3-thienylmalonate* [diethyl malonate, 18 h, $Cu(OAc)_2$] (31%), m.p. 124—125.5° (from benzene–petrol) (Found: C, 50.6; H, 4.9; S, 11.3. $C_{12}H_{14}O_6S$ requires C, 50.4; H, 4.9; S, 11.2%).

4-(1-*Acetylacetonyl*)*thiophen-3-carboxylic Acid*.—Acetylacetone (15.4 g), the bromo-acid (6.37 g), and copper (0.2 g) were added successively to potassium t-butoxide [from potassium (2.4 g)] in t-butyl alcohol (150 ml). After the mixture had been heated under reflux for 6 h, it was evaporated to small volume, poured into water (250 ml), and acidified. The precipitate was collected and crystallised from aqueous ethanol to give the *dioxo-acid* (5.4 g), m.p. 198—199° (Found: C, 53.6; H, 4.5; S, 14.5. $C_{10}H_{10}O_4S$ requires C, 53.1; H, 4.5; S, 14.2%), τ ($CDCl_3$) 0.45br (1H, s, enolic OH), 1.74 (1H, d, *J* 4 Hz, 2-H), 2.83 (1H, d, *J* 4 Hz, 5-H), and 8.13 (6H, s, 2Me). Condensation by similar use of sodium ethoxide in ethanol gave a lower yield (40%).

4-(3,5-*Dimethyloxazol-4-yl*)*thiophen-3-carboxylic Acid*.—The dioxo-acid (0.5 g) and hydroxylamine hydrochloride (0.31 g) in water (10 ml) were treated with 4M-sodium hydroxide (1.1 ml) and boiled under reflux for 2.5 h. Acidification gave the *oxazole* (0.3 g), m.p. 206—208° (from aqueous ethanol) (Found: C, 53.8; H, 4.2; N, 6.3; S, 14.0. $C_{10}H_9O_3NS$ requires C, 53.8; H, 4.1; N, 6.3; S, 14.3%), τ ($CDCl_3$) 1.64 (1H, d, *J* 4 Hz, 5-H), 2.85 (1H, d, *J* 4 Hz, 2-H), 7.73 (3H, s, Me), and 7.89 (3H, s, Me).

4-(3,5-*Dimethylpyrazol-4-yl*)*thiophen-3-carboxylic Acid*.—A solution of the dioxo-acid (1 g) and hydrazine hydrate (0.5 ml) in ethanol (10 ml) was boiled under reflux for 1 h and then evaporated. Addition of water (20 ml) and acetic acid (2 ml) and isolation with ether gave the *pyrazole* (0.93 g), m.p. 229—231° (from ethanol) (Found: C, 53.9; H, 4.6; N, 12.8; S, 14.3. $C_{10}H_{10}O_2N_2S$ requires C, 54.1; H, 4.5; N, 12.6; S, 14.4%), τ[$CDCl_3$–$(CD_3)_2SO$] 1.37br (2H, s, NH + CO_2H), 1.82 (1H, d, *J* 4 Hz, 5-H), 2.91 (1H, d, *J* 4 Hz, 2-H), and 7.94 (6H, s, 2Me).

4-*Acetonylthiophen-3-carboxylic Acid*.—The dioxo-acid (3 g) was dissolved in aqueous ammonia (200 ml; *d* 0.88) and left overnight at room temperature. Evaporation to small volume, acidification, filtration, and crystallisation from water gave the *oxo-acid* (2.1 g), m.p. 153—154° (Found: C, 52.4; H, 4.4; S, 17.1. $C_8H_8O_3S$ requires C, 52.2; H, 4.4; S, 17.1%); $\nu_{max.}$ 3 100 (CO_2H), 1 720 (COMe), and 1 675 cm^{-1} (CO_2H); τ[$CDCl_3$–$(CD_3)_2SO$] 1.87 (1H, d, *J* 4 Hz, 2-H), 2.5br (1H, s, CO_2H), 2.91 (1H, d, *J* 4 Hz, 5-H), 6.01 (2H, s, CH_2), and 7.81 (3H, s, Me).

6-*Phenylthieno*[3,4-c]*pyridin*-4(5H)-*one*.—A solution of 4-phenacylthiophen-3-carboxylic acid (1 g) and ammonium acetate (10 g) in acetic acid (15 ml) was boiled under reflux for 16 h and poured into water (75 ml). Filtration and crystallisations from benzene–petrol gave the *pyridone* (0.8 g), m.p. 157—158° (Found: C, 68.7; H, 4.0; N, 6.3; S, 14.3. $C_{13}H_9NOS$ requires C, 68.7; H, 4.0; N, 6.2; S, 14.1%); τ ($CDCl_3$) 0.7br (1H, s, NH), 1.50 (1H, d, *J* 4 Hz, 3-H), 2.2—2.8 (6H, m, ArH), and 3.49 (1H, s, 7-H). The following were prepared similarly: 6-*methylthieno*[3,4-c]-*pyridin*-4(5H)-*one* (70%), m.p. 184—186° (from benzene–petrol) (Found: C, 58.2; H, 4.4; N, 8.6; S, 19.3. C_8H_7NOS requires C, 58.2; H, 4.3; N, 8.5; S, 19.4%), τ[$CDCl_3$–$(CD_3)_2SO$] 1.73 (1H, d, *J* 3 Hz, 3-H), 2.80 (1H, d, *J* 3 Hz, 1-H), 3.82 (1H, s, 7-H), 7.81 (3H, s, Me); 6-(2-*benzyloxyphenyl*)*thieno*[3,4-c]*pyridin*-4(5H)-*one* (63%), m.p. 134.5—136° (from benzene–petrol) (Found: C, 72.2; H, 4.6; N, 4.1; S, 9.7. $C_{20}H_{15}NO_2S$ requires C, 72.1; H, 4.5; N, 4.2; S, 9.6%), τ ($CDCl_3$) 1.05br (1H, s, NH), 1.68 (1H, d, *J* 4 Hz, 3-H), 2.45—3.10 (10H, m, ArH), 3.41 (1H, s,

[9] J. B. Cohen and H. W. Dudley, *J. Chem. Soc.*, 1910, 1732.

7-H), and 4.84 (2H, s, CH_2). When 4-(1-acetylacetonyl)-thiophen-3-carboxylic acid was treated similarly it gave a mixture of *7-acetyl-6-methylthieno*[3,4-c]*pyridin-4(5H)-one* (30%), m.p. 229—231° (from ethanol) (Found: C, 57.8; H, 4.5; N, 6.7; S, 15.5. $C_{10}H_9NO_2S$ requires C, 58.0; H, 4.4; N, 6.8; S, 15.4%), and the 6-methylthienopyridinone (20%).

α-Benzoyl-α-(4-carboxy-3-thienyl)acetanilide was similarly treated with ammonium acetate but ethanol was used as solvent; *6-phenyl-7-phenylcarbamoylthieno*[3,4-c]*pyridin-4(5H)-one* (76%), m.p. 215—216.5° (from aqueous ethanol) was obtained (Found: C, 69.6; H, 4.2; N, 8.2; S, 9.4. $C_{20}H_{14}N_2O_2S$ requires C, 69.4; H, 4.1; N, 8.1; S, 9.2%).

5-Methyl-6-phenylthieno[3,4-c]*pyridin-4(5H)-one.*— 4-Phenacylthiophen-3-carboxylic acid (0.5 g), methylamine (5 ml; 30% in ethanol), and acetic acid (0.5 ml) were boiled under reflux for 6 h and poured into 2M-sodium carbonate. Filtration and crystallisation from petrol gave the *pyridone* (0.2 g), m.p. 91—92° (Found: C, 69.4; H, 4.7; N, 5.7; S, 13.3. $C_{14}H_{11}NOS$ requires C, 69.7; H, 4.6; N, 5.8; S, 13.3%); τ ($CDCl_3$) 1.65 (1H, d, *J* 4 Hz, 3-H), 2.60 (5H, m, ArH), 2.73 (1H, d, *J* 4 Hz, 1-H), 3.67 (1H, s, 7-H), and 6.71 (3H, s, Me).

5,6-Diphenylthieno[3,4-c]*pyridin-4(5H)-one.*— Aniline (230 mg) was added to a suspension of 4-phenacylthiophen-3-carboxylic acid (500 mg) in bis-(2-methoxyethyl) ether (5 ml) and the mixture was boiled under reflux for 24 h and then cooled at 0 °C. Filtration and crystallisations from ethanol gave the *product* (330 mg), m.p. 225—226° (Found: C, 75.1; H, 4.3; N, 4.4; S, 10.8. $C_{19}H_{13}NOS$ requires C, 75.2; H, 4.3; N, 4.6; S, 10.6%).

4-Chloro-6-phenylthieno[3,4-c]*pyridine.*—A mixture of 6-phenylthieno[3,4-*c*]pyridin-4(5*H*)-one (0.5 g) and phosphoryl chloride (10 ml) was boiled under reflux for 16 h, evaporated, and poured into 0.5M-sodium carbonate (25 ml). Isolation with ether and chromatography on silica in benzene–petrol (1 : 9) gave the *chloro-compound* (0.3 g), m.p. 75.5—77° (Found: C, 63.6; H, 3.5; N, 5.6; S, 13.1. $C_{13}H_8ClNS$ requires C, 63.5; H, 3.3; N, 5.7; S, 13.0%).

6-Phenylthieno[3,4-c]*pyran-4-one.*— 4-Phenacylthiophen-3-carboxylic acid (1.0 g) was heated at 250 °C for 20 min. The mixture was cooled, dissolved in ether, and washed with 0.5M-sodium carbonate (10 ml). Evaporation and crystallisations from benzene–petrol gave the pyranone, m.p. 104—106° (lit.,[7] 110—111°) (Found: C, 68.8; H, 3.6; S, 14.3. Calc. for $C_{13}H_8O_2S$: C, 68.4; H, 3.5; S, 14.0%); $\nu_{max.}$ 1 732 cm^{-1} (CO); $\lambda_{max.}$ 257 and 304 nm (ε 23 700 and 20 600); τ ($CDCl_3$) 1.60 (1H, d, *J* 4 Hz, 3-H), 2.10—2.80 (6H, m, ArH and 1-H), and 3.12 (1H, s, 7-H).

7-Acetyl-6-methylthieno[3,4-c]*pyran-4-one.*— 4-(1-Acetylacetonyl)thiophen-3-carboxylic acid (0.5 g) and acetic anhydride (25 ml) were heated under reflux (bath at 150 °C) for 4 h and the mixture was then evaporated. Crystallisations from benzene–petrol gave the *pyranone* (0.42 g), m.p. 147—149° (Found: C, 58.0; H, 3.9; S, 15.3. $C_{10}H_8O_3S$ requires C, 57.7; H, 3.9; S, 15.4%); $\lambda_{max.}$ 222, 229, 238infl, and 308 nm (ε 19 800, 19 300, 16 800, and 3 900); $\nu_{max.}$ 1 735 (ring C:O) and 1 680 cm^{-1} (MeC:O); τ ($CDCl_3$) 1.60 (1H, d, *J* 4 Hz, 3-H), 2.48 (1H, d, *J* 4 Hz, 1-H), 7.42 (3H, s, Me), and 7.58 (3H, s, Me).

4-Acetonylthiophen-3-carboxylic acid similarly gave *6-methylthieno*[3,4-c]*pyran-4-one*, m.p. 94—96.5° (Found: C, 57.7; H, 3.7; S, 18.9. $C_8H_6O_2S$ requires C, 57.9; H, 3.6; S, 19.3%); $\lambda_{max.}$ 232, 239, 262infl, and 321 nm (ε 26 300, 21 300, 4 300, and 2 700); $\nu_{max.}$ 1 735 cm^{-1} (C:O); τ ($CDCl_3$) 1.65 (1H, d, *J* 4 Hz, 3-H), 2.87 (1H, d, *J* 4 Hz, 1-H), 3.80 (1H, s, 7-H), and 7.82 (3H, s, Me).

4-(2-Hydroxy-2-phenylethyl)thiophen-3-carboxylic Acid.— 4-Phenacylthiophen-3-carboxylic acid (0.5 g) was added to a solution of sodium borohydride (0.23 g) and sodium hydroxide (0.4 g) in water (10 ml) at 0 °C. The solution was left at room temperature for 48 h and acidified with 2M-hydrochloric acid. Filtration and crystallisation from aqueous ethanol gave the *hydroxy-acid* (370 mg), m.p. 169—171° (Found: C, 63.1; H, 4.9; S, 12.8. $C_{13}H_{12}O_3S$ requires C, 62.9; H, 4.9; S, 12.9%); τ [$(CD_3)_2SO$] 1.90 (1H, d, *J* 4 Hz, 2-H), 2.55—2.85 (5H, m, Ph), 2.97 (1H, d, *J* 4 Hz, 5-H), 5.12 [1H, dd, C*H*(OH)], and 6.60—6.88 (2H, m, CH_2).

6,7-Dihydro-6-phenylthieno[3,4-c]*pyran-4-one.*—A reaction mixture obtained as in the previous experiment was acidified with acetic acid (20 ml) and boiled under reflux for 6 h. Evaporation, addition of water, and isolation with ether gave the *lactone*, m.p. 83—85° (from benzene–petrol) (Found: C, 68.0; H, 4.5; S, 14.1. $C_{13}H_{10}O_2S$ requires C, 67.9; H, 4.4; S, 13.9%); $\lambda_{max.}$ 248 nm (ε 9 700); $\nu_{max.}$ 1 730 cm^{-1} (C:O); τ ($CDCl_3$) 1.77 (1H, d, *J* 4 Hz, 3-H), 2.64 (5H, s, ArH), 2.87—3.00 (1H, m, 1-H), 4.54 (1H, t, *J* 7 Hz, CH), and 6.80 (2H, d, *J* 7 Hz, CH_2).

4-Carboxythiophen-3-acetic Acid.—Ethyl 4-carboxythiophen-3-acetate (7.1 g) was added to a solution of potassium hydroxide (7.5 g) in water (30 ml) at 0 °C and the solution was left at room temperature for 60 h. Acidification, filtration, and crystallisation from water gave the *diacid* (5.6 g), m.p. 210—213° (Found: C, 45.1; H, 3.3; S, 17.2. $C_7H_6O_4S$ requires C, 45.2; H, 3.3; S, 17.2%).

The acid (1 g) in dioxan (100 ml) was treated with acetyl chloride (15 ml) and the solution was boiled under reflux for 2 h, and then evaporated. Crystallisation from benzene gave the *anhydride* (850 mg), m.p. 157—158° (Found: C, 50.1; H, 2.4; S, 18.9. $C_7H_4O_3S$ requires C, 50.0; H, 2.4; S, 18.9%); $\nu_{max.}$ 1 750 and 1 780 cm^{-1} (CO·O·CO); τ (CD_3CN) 1.58 (1H, d, *J* 4 Hz, 3-H), 2.68 (1H, m, 1-H), and 5.94 (2H, d, *J* 2 Hz, CH_2).

4-Carboxythiophen-3-acetamide.—Ethyl 4-carboxythiophen-3-acetate (1 g) was dissolved in aqueous ammonia (100 ml; *d* 0.88) and a slow stream of ammonia was passed through the solution for 24 h. After evaporation to 20 ml, the solution was acidified and filtered to give the *amide* (0.8 g), m.p. 193—194° (from ethanol) (Found: C, 45.5; H, 3.8; N, 7.5; S, 17.5. $C_7H_7NO_3S$ requires C, 45.4; H, 3.8; N, 7.6; S, 17.4%). Similarly the ester (1 g) in aqueous methylamine (90 ml; 30%) left for 24 h gave *4-carboxythiophen-3-N-methylacetamide* (0.64 g), m.p. 162—164° (from water) (Found: C, 48.2; H, 4.5; N, 6.9; S, 16.2. $C_8H_9NO_3S$ requires C, 48.2; H, 4.6; N, 7.0; S, 16.1%).

Thieno[3,4-c]*pyridine-4,6(5H,7H)-dione.*— 4-Carboxythiophen-3-acetamide (400 mg) was heated at 220° and 2 mmHg for 5 min. The sublimate was crystallised from ethanol to give the *imide* (120 mg), m.p. 206—208° (Found: C, 50.2; H, 3.1; N, 8.3; S, 19.2. $C_7H_5NO_2S$ requires C, 50.3; H, 3.0; N, 8.4; S, 19.5%).

4-Carboxythiophen-3-*N*-methylacetamide (1 g), acetyl chloride (20 ml), and dioxan (120 ml) were heated under reflux for 16 h and the mixture was then evaporated. Chromatography on silica in benzene–ether (4 : 1) gave *5-methylthieno*[3,4-c]*pyridine-4,6(5H,7H)-dione* (0.6 g), m.p.

147—148° (from benzene–petrol) (Found: C, 53.3; H, 4.0; N, 7.8; S, 17.9. $C_8H_7NO_2S$ requires C, 53.0; H, 3.9; N, 7.7; S, 17.7%); τ ($CDCl_3$) 1.65 (1H, d, *J* 4 Hz, 3-H), 2.85 (1H, m, 1-H), 6.02 (2H, s, CH_2), and 6.69 (3H, s, Me). When 4-carboxythiophen-3-acetamide was treated similarly, *6-diacetylaminothieno*[3,4-c]*pyran-4-one* (0.3 g) was obtained, m.p. 143.5—145° (from ethanol) (Found: C, 52.8; H, 3.7; N, 5.4; S, 13.0. $C_{11}H_9NO_4S$ requires C, 52.6; H, 3.6; N, 5.6; S, 12.7%); $\nu_{max.}$ 1 730 and 1 660 cm^{-1} (NAc_2); $\lambda_{max.}$ 234, 240infl, 265infl, and 309 nm (ε 29 000, 23 800, 5 100, and 2 900); τ ($CDCl_3$) 1.52 (1H, d, *J* 4 Hz, 3-H), 2.55 (1H, d, *J* 4 Hz, 1-H), 3.47 (1H, s, 7-H), and 7.57 (6H, s, 2Me).

4-Phenethylthiophen-3-carboxylic Acid.—4-Phenacylthiophen-3-carboxylic acid (6.26 g), hydrazine hydrate (5 ml), potassium hydroxide (5 g), and bis-(2-hydroxyethyl) ether (25 ml) were heated under reflux (bath at 160 °C) for 1 h; the mixture was distilled and then refluxed (internal temperature 190—195 °C) for 4 h. Acidification, filtration, and crystallisation from toluene–light petroleum (b.p. 100—120°) gave the *acid* (5.2 g), m.p. 146—147° (Found: C, 67.0; H, 5.2; S, 13.9. $C_{13}H_{12}O_2S$ requires C, 67.2; H, 5.2; S, 13.8%); τ ($CDCl_3$) 0.5br (1H, s, CO_2H), 1.88 (1H, d, *J* 4 Hz, 2-H), 2.8 (5H, s, Ph), 3.11 (1H, d, *J* 4 Hz, 5-H), and 6.94 (4H, m, $CH_2{\cdot}CH_2$).

9,10-Dihydrobenzo[4,5]*cyclohepta*[1,2-*c*]*thiophen-4-one.*—The acid (IV) (1 g) and polyphosphoric acid (50 g) were stirred and heated at 100 °C for 2 h and poured onto ice. After repeated extractions with ether, the extracts were washed with 0.5M-sodium carbonate and water. Evaporation and chromatography on silica in benzene–petrol gave the *ketone* (0.4 g), m.p. 56—58° (from petrol) (Found: C, 72.8; H, 4.6; S, 15.0. $C_{13}H_{10}OS$ requires C, 72.9; H, 4.7; S, 14.9%); $\nu_{max.}$ 1 635 cm^{-1} (C:O); $\lambda_{max.}$ 277 nm (ε 15 400); τ ($CDCl_3$) 1.58 (1H, d, *J* 4 Hz, 3-H), 2.00 (1H, m, 5-H), 2.50—2.87 (3H, m, 6-, and 7-, and 8-H), 3.02 (1H, d, *J* 4 Hz, 1-H), and 6.91 (4H, s, $CH_2{\cdot}CH_2$). Acidification of the washings gave the starting material (120 mg).

When the acid (0.5 g) and polyphosphoric acid (35 g) were heated at 160 °C for 3 h and worked up similarly, thick-layer chromatography on silica, in ether–petrol–acetic acid (20 : 79 : 1), gave 4,5-dihydrobenzo[5,6]cyclohepta[1,2-*b*]-thiophen-10-one (VI) (300 mg), m.p. 56—57.5° (Found: C, 73.0; H, 4.9; S, 14.7%); $\nu_{max.}$ 1 620 cm^{-1} (C:O); $\lambda_{max.}$ 297 nm (ε 12 500); τ ($CDCl_3$) 2.00 (1H, m, 9-H), 2.45 (1H, d, *J* 5 Hz, 2-H), 2.50—2.87 (3H, m, 6-, 7-, and 8-H), 3.07 (1H, d, *J* 5 Hz, 3-H), and 6.91 (4H, s, $CH_2{\cdot}CH_2$) [lit.,[10] m.p. 56—57.5°, for ketone prepared from 3-phenethylthiophen-2-carboxylic acid and from *o*-(3-thienylethyl)benzoic acid].

4-(2-Hydroxy-2-phenylethyl)thiophen-3-carboxylic Acid.—4-(*o*-Benzyloxyphenacyl)thiophen-3-carboxylic acid (1 g) was reduced by treatment with hydrazine and potassium hydroxide as above. The products were separated by chromatography on a column of silica in benzene–petrol. The first product eluted was *4-(2-benzyloxy-2-phenylethyl)-thiophen-3-carboxylic acid* (0.3 g), m.p. 130—131° (from benzene–petrol) (Found: C, 71.0; H, 5.4; S, 9.1. $C_{20}H_{18}O_3S$ requires C, 71.0; H, 5.4; S, 9.5%); τ ($CDCl_3$) —0.15br (1H, s, CO_2H), 1.81 (1H, d, *J* 4 Hz, 2-H), 2.5—3.2 (10H, m, ArH), 4.95 (2H, s, CH_2Ph), and 6.6—7.2 (4H, m, $CH_2{\cdot}CH_2$). Further elution gave *4-(2-hydroxy-2-phenylethyl)thiophen-3-carboxylic acid* (0.35 g), m.p. 159—160.5° (from benzene) (Found: C, 63.2; H, 5.0; S, 13.1. $C_{13}H_{12}O_3S$ requires C, 62.9; H, 4.9; S, 12.9%); τ [$CDCl_3$–$(CD_3)_2SO$] 1.88 (1H, d, *J* 4 Hz, 2-H), 2.9—3.3 (5H, m, ArH), 4.8—5.4br (2H, CO_2H + OH), and 6.7—7.3 (4H, m, CH_2). When the reaction mixture was heated at 240 °C for 6 h, only the hydroxy-acid (59%) was obtained.

10,11-Dihydrobenzo[g]*thieno*[3,4-c]*oxocin-4-one.*—To the foregoing hydroxy-acid (0.8 g) in ethyl acetate (60 ml) was added dicyclohexylcarbodi-imide (0.67 g) and the mixture was stirred at room temperature for 16 h and filtered, the solid being washed with ethyl acetate. The combined filtrates were washed with 0.5M-sodium carbonate and evaporated, and the residue was chromatographed on a column of silica with benzene–petrol and then benzene–ether as solvent. The first product eluted was *10,11-dihydrobenzo*[g]*thieno*[3,4-c]*oxacin-4-one* (0.27 g), m.p. 94—95° (from benzene–petrol) (Found: C, 67.8; H, 4.5; S, 14.0. $C_{13}H_{10}O_2S$ requires C, 67.8; H, 4.4; S, 13.9%); $\nu_{max.}$ 1 740 cm^{-1} (C:O); τ ($CDCl_3$) 2.41 (1H, d, *J* 4 Hz, 3-H), 2.89 (4H, s, ArH), 3.22 (1H, d, *J* 4 Hz, 1-H), and 6.86 (4H, s, $CH_2{\cdot}CH_2$). Further elution gave *NN'-dicyclohexyl-N-4-(2-hydroxy-2-phenylethyl)-3-thenoylurea* (0.4 g), m.p. 146—147° (from benzene–petrol) (Found: C, 68.9; H, 7.6; N, 6.0; S, 6.8. $C_{26}H_{34}N_2O_3S$ requires C, 68.7; H, 7.5; N, 6.2; S, 7.0%); $\nu_{max.}$ 1 690 and 1 640 cm^{-1}.

Condensation Reactions of 3-Bromothiophen-2-carboxylic Acid. The following were prepared in the same manner as the 3,4-isomers but the volume of solvent was increased by half and the reaction time doubled, as the bromo-acid and its sodium salt were relatively insoluble: *ethyl 2-carboxythiophen-3-acetate* (from ethyl acetoacetate; 89%), m.p. 144—145.5° (from benzene–petrol) (Found: C, 50.6; H. 4.5. $C_9H_{10}O_4S$ requires C, 50.5; H, 4.7%); $\nu_{max.}$ 1 735, (CO_2Et) and 1 660 cm^{-1} (CO_2H); τ ($CDCl_3$) 2.55 (1H, d, *J* 5 Hz, 5-H), 2.95 (1H, d, *J* 5 Hz, 4-H), 5,85 (2H, q, CH_2Me), 5.93 (2H, s, $CH_2{\cdot}CO_2Et$), and 8.76 (3H, t, CH_3); *2-carboxythiophen-3-acetonitrile* (benzoylacetonitrile; 79%), m.p. 135—136° (from benzene–petrol) (Found: C, 50.2; H, 3.0; N, 8.4; S, 19.0. $C_7H_5NO_2S$ requires C, 50.3; H, 3.0; N, 8.4; S, 19.2%); $\nu_{max.}$ 2 260 cm^{-1} (C:N); τ ($CDCl_3$) 1.88br (1H, s, CO_2H), 2.33 (1H, d, *J* 6 Hz, 5-H), 2.71 (1H, d, *J* 6 Hz, 4-H), and 5.83 (2H, s, CH_2); *3-(1-acetylacetonyl)-thiophen-2-carboxylic acid* (acetylacetone; 85%), m.p. 187—189° (from aqueous ethanol) (Found: C, 53.0; H, 4.4; S, 14.5. $C_{10}H_{10}O_4S$ requires C, 53.1; H, 4.5; S, 14.1%); τ ($CDCl_3$) 2.37 (1H, d, *J* 6 Hz, 5-H), 3.05 (1H, d, *J* 6 Hz, 4-H), 4.08br (1H, s, enolic OH), and 8.04 (6H, s, 2Me); *3-phenacylthiophen-2-carboxylic acid* (benzoylacetone; 42%), m.p. 199—201° (Found: C, 63.2; H, 4.1; S, 13.1. $C_{13}H_{10}O_3S$ requires C, 63.3; H, 4.1; S, 13.0%).

3-Acetonylthiophen-2-carboxylic Acid.—Action of aqueous ammonia on the acetylacetonyl-acid gave this *acid* (90%), m.p. 127—129° (from benzene–petrol) (Found: C, 52.2; H, 4.5; S, 17.5. $C_8H_8O_3S$ requires C, 52.2; H, 4.4; S, 17.4%); $\nu_{max.}$ 1 720 (Me·C:O) and 1 665 cm^{-1} (CO_2H); τ ($CDCl_3$) 2.45 (1H, d, *J* 5 Hz, 5-H), 3.00 (1H, d, *J* 5 Hz, 4-H), 5.83 (2H, s, CH_2), and 7.78 (3H, s, CH_3).

5-Phenylthieno[2,3-c]*pyridin-7*(6H)*-one.*—Prepared in the same way as the isomer, this *pyridinone* (40%) had m.p. 195—197.5° (from ethanol) (Found: C, 68.9; H, 3.9; N, 6.0; S, 14.1. $C_{13}H_9NOS$ requires C, 68.7; H, 4.0; N, 6.2; S, 14.1%); τ[$CDCl_3$–$(CD_3)_2SO$] 2.17 (1H, d, *J* 5 Hz, 2-H), 2.20—2.35 (2H, m, ArH), 2.45—2.60 (4H, m, ArH + NH), 2.68 (1H, d, *J* 5 Hz, 3-H), and 3.09 (1H, s, 4-H).

[10] J. M. Bastian, A. Ebnoether, E. Jucker, E. Rissi, and A. Stoll, *Helv. Chim. Acta*, 1971, **54**, 277.

5-Phenylthieno[2,3-c]*pyran-7-one*.— 3-Phenacylthiophen-2-carboxylic acid (0.5 g) and acetic anhydride (25 ml) were boiled under reflux for 5 h; evaporation and crystallisations from benzene–petrol gave the *pyranone* (80%), m.p. 121—123° (Found: C, 68.6; H, 3.5; S, 14.0. $C_{13}H_8O_2S$ requires C, 68.4; H, 3.5; S, 14.0%); $\nu_{max.}$ 1 727 and 1 710 cm^{-1}; τ ($CDCl_3$) 2.05—2.7 (6H, m, ArH), 2.79 (1H, d, *J* 5 Hz, 3-H), and 2.91 (1H, s, 4-H).

3-Phenacylthiophen-2-carboxylic acid was heated at 220 °C for 20 min and the product was dissolved in ether and washed with 0.5M-sodium carbonate. Evaporation and chromatography on silica in benzene–petrol yielded first *phenyl 3-thienyl ketone* (3-phenacylthiophen) (47%), m.p. 73—74.5° (from petrol) (Found: C, 71.1; H, 4.9; S, 15.6. $C_{12}H_{10}OS$ requires C, 71.3; H, 5.0; S, 15.8%); $\nu_{max.}$ 1 680 cm^{-1}; τ ($CDCl_3$) 3.05—1.90 (8H, m, ArH) and 5.70 (2H, s, CH_2). Further elution yielded the pyranone (25%), m.p. 121—123°.

The following compounds were also prepared by the action of acetic anhydride on the oxo-acids: *4-acetyl-5-methylthieno*[2,3-c]*pyran-7-one*, m.p. 112—113.5° (from benzene–petrol) (Found: C, 57.5; H, 3.9; S, 15.3. $C_{10}H_8O_3S$ requires C, 57.7; H, 3.9; S, 15.4%); $\lambda_{max.}$ 262 and 306 nm (ε 10 200 and 7 400); $\nu_{max.}$ 1 720 and 1 680 cm^{-1} (C:O of ring and Ac); τ ($CDCl_3$) 2.2 (1H, d, *J* 6 Hz, 2-H), 2.7 (1H, d, *J* 6 Hz, 3-H), and 7.45 (3H, s, Me); *5-methylthieno*[2,3-c]*pyran-7-one*, m.p. 113—114° (from petrol) (Found: C, 57.7; H, 3.7; S, 19.4. $C_8H_6O_2S$ requires C, 57.8; H, 3.6; S, 19.3%); $\nu_{max.}$ 1 710 cm^{-1}; $\lambda_{max.}$ 231, 237, 282, and 314 nm (ε 12 700, 11 800, 4 400, and 6 900); τ ($CDCl_3$) 2.1 (1H, d, *J* 5 Hz, 2-H), 2.79 (1H, d, *J* 5 Hz, 3-H), 3.51 (1H, s, 4-H), and 7.7 (3H, s, Me).

2-Carboxythiophen-3-acetic Acid.—Alkaline hydrolysis of the ethyl ester gave this *diacid* (83%), m.p. 189—191° (Found: C, 45.2; H, 3.3; S, 17.3. $C_7H_6O_4S$ requires C, 45.2; H, 3.3; S, 17.2%); $\nu_{max.}$ 1 700 and 1 665 cm^{-1}.

3-Phenylsulphonylmethylthiophen-2-carboxylic Acid.—Condensation of 3-bromothiophen-2-carboxylic acid with ethyl phenylsulphonylacetate by the general procedure occurred with partial alcoholysis of the ethoxycarbonyl group. The crude product (0.5 g) was hydrolysed with sodium hydroxide (0.3 g) in water (10 ml) by boiling under reflux for 1 h, cooling, and acidifying. Filtration and crystallisation from aqueous ethanol gave the *sulphone-acid* (34%), m.p. 215—216° (Found: C, 50.8; H, 3.4; S, 22.8. $C_{12}H_{10}O_4S_2$ requires C, 51.1; H, 3.6; S, 22.7%); τ [$(CD_3)_2SO$] 2.21 (1H, d, *J* 6 Hz, 5-H), 2.4 (5H, m, ArH), 2.95 (1H, d, *J* 6 Hz, 4-H), and 4.85 (2H, s, CH_2).

We thank the Governors of this College for a Research Studentship (to O. R.) and Mr A. W. Ellis for discussions of the n.m.r. spectra.

[5/144 *Received*, 22*nd January*, 1975]