Condensed Thiophen Ring Systems. Part XIX.[1] Synthesis of 6,7-Dihydrothieno[3,2-*c*]pyridines and 4,5-Dihydrothieno[2,3-*c*]pyridines by Intramolecular Cyclisation of 2-(2- or 3-Thienyl)ethyl Isothiocyanate †

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Cyclisation of 2-(2-thienyl)ethyl isothiocyanate (8) with methyl fluorosulphate or triethyloxonium tetrafluoroborate gave 1-methylthio- (1) or 1-ethylthio-6,7-dihydrothieno[3,2-*c*]pyridine (2), respectively. Compound (1) was prepared also by cyclisation of the isothiocyanate (8) with polyphosphoric acid and subsequent alkylation of the 6,7-dihydrothieno[3,2-*c*]pyridine-4(5*H*)-thione (6) produced with methyl fluorosulphate. Compounds (5) and (7) were prepared similarly from 2-(3-thienyl)ethyl isothiocyanate (9). The amines (3) and (4) were prepared by reaction of compound (1) or (2) with the appropriate aliphatic amine.

BECAUSE thienopyridines are structurally analogous to quinolines and isoquinolines they are of potential pharmacological interest; consequently their chemistry has received considerable attention in recent years.[2] Our novel synthesis of 3,4-dihydroisoquinolines from 2-arylethyl isothiocyanates[3] prompted us to investigate an analogous synthesis of the dihydrothienopyridines (1)—(7).

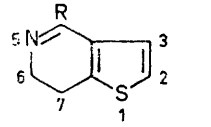
Heating 2-(2-thienyl)ethyl isothiocyanate (8) with methyl fluorosulphate or triethyloxonium tetrafluoroborate followed by work-up in the usual way[3] gave 1-methylthio- (1) or 1-ethylthio-6,7-dihydrothieno[3,2-*c*]-pyridine (2), respectively. We did not isolate the intermediate salts in these cases.[3] Reaction times of 1—4 h did not convert all the starting material but these short times were preferred; longer heating yielded inseparable mixtures of oils. The possibility that intermolecular condensation of the isothiocyanate (8) occurs is greater than in the previously reported cases[3] because of the high susceptibility of the thiophen ring to electrophilic attack. The 1-methylthio-compound (1) was more conveniently prepared by cyclisation of the isothiocyanate (8) with polyphosphoric acid followed by alkylation of the intermediate 6,7-dihydrothieno[3,2-*c*]pyridine-4(5*H*)-thione (6) with methyl fluorosulphate and treatment of the resulting hydrofluorosulphate salt (isolated in this case) with base.

A comparison of the ^{1}H n.m.r. spectra of the 4-alkylthio-compounds (1) and (2) with spectra of their salts shows that the signals for the 7-protons in the salts are shifted to a greater extent downfield than those for the 6-protons. A similar observation was reported[3] for the ^{1}H n.m.r. spectra of 1-alkylthio-3,4-dihydroisoquinolines as compared with their salts. As before, we attribute this effect to extensive delocalisation of the charge on the basic nitrogen atom of the salts, particularly over the aromatic ring.

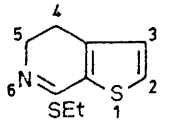
† A few of the compounds reported in this paper have been claimed in a patent [M. W. Gittos, Ger. Offen. 2,318,399/1973 (*Chem. Abs.*, 1974, **80**, 14,857)].

[1] Part XVIII, B. Iddon, M. W. Pickering, H. Suschitzky, and D. S. Taylor, *J.C.S. Perkin I*, 1975, 1686.
[2] S. W. Schneller, *Internat. J. Sulfur Chem.* (*B*), 1972, **7**, 309.
[3] M. W. Gittos, M. R. Robinson, J. P. Verge, R. V. Davies, B. Iddon, and H. Suschitzky, *J.C.S. Perkin I*, 1975, 33.

Cyclisation of 2-(3-thienyl)ethyl isothiocyanate (9) with polyphosphoric acid gave 5,6-dihydrothieno[2,3-*c*]pyridine-7(4*H*)-thione (7), which yielded the 7-ethylthio-compound (5) with triethyloxonium tetrafluoroborate.



(1) R = SMe
(2) R = SEt
(3) R = NH·[CH$_2$]$_2$NEt$_2$
(4) R = NH-



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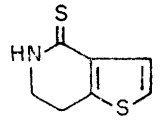
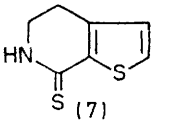
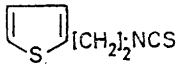


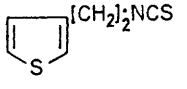
(6)



(7)



(8)



(9)

The amines (3) and (4) were prepared for biological screening by reaction of the alkylthio-compounds (1) and (2), either as free bases or salts, with the appropriate aliphatic amine or its hydrochloride.

Lora-Tamayo *et al.*[4] have reported a synthesis of 1-substituted 6,7-dihydrothieno[3,2-*c*]pyridines from nitrilium salts but the yields were low (0—17%).

EXPERIMENTAL

General comments made previously [3] apply here.

2-(2-Thienyl)ethylamine was prepared from 2-thenyl chloride [5] by the procedure (i). Reactions of the chloride

$$RCH_2Cl \xrightarrow{NaCN} RCH_2CN \xrightarrow[Et_2O]{LiAlH_4} R[CH_2]_2NH_2 \quad (i)$$

with sodium cyanide in dimethyl sulphoxide–tetrahydrofuran gave an 83% yield of the nitrile. The use of dimethyl sulphoxide alone gave a lower yield (60%), and the use of acetone or ethanol according to literature procedures [6] resulted in lower yields and gave 2-thenyl alcohol or ethyl 2-thenyl ether or both as by-products. Reduction of the nitrile in the presence of aluminium chloride [7] gave the amine in 75% yield and was preferable to the literature procedures. This amine rapidly forms a carbonate in air.

2-(3-Thienyl)ethylamine (27% overall yield) was prepared similarly from 3-thenyl bromide.[8]

2-(2-*Thienyl*)*ethyl Isothiocyanate* (8).—A solution of carbon disulphide (7.1 g, 93.4 mmol) in chloroform (15 ml) was added dropwise during 15 min to a stirred mixture of 2-(2-thienyl)-ethylamine (11.2 g, 88.2 mmol), triethylamine (8.9 g, 88.2 mmol), and chloroform (30 ml) at 0 °C, and the resulting mixture was allowed to warm slowly to ambient temperature. It was recooled to 0 °C and ethyl chloroformate (9.5 g, 88.0 mmol) was added dropwise during 15 min. Again, the mixture was allowed to warm slowly to room temperature, and more triethylamine (8.6 ml, 6.22 g, 61.6 mmol) was added. The mixture was stirred for a further 1.5 h at this temperature, heated under reflux for 15 min, and then cooled. Water (200 ml) was added, followed by 2M-sodium hydroxide. Extraction with ether gave 2-(2-thienyl)ethyl isothiocyanate (8) (10.0 g, 68%), b.p. 110° at 1.0 mmHg (lit.,[9] 87—90° at 3.0 mmHg), $\nu_{max.}$ (film) 2 120 and 2 200 cm^{-1} (NCS), τ ($CDCl_3$) 2.80—3.40 (3 H, m, aromatic), 6.42 (2 H, t, J 6.0 Hz, α-H_2), and 6.98 (2 H, t, J 6.0 Hz, β-H_2), *m/e* 169 (M^+); the derived *N-phenyl-N'-2-(2-thienyl)ethylthiourea* had m.p. 109—111° (from ethanol) (Found: C, 59.5; H, 5.2; N, 10.7. $C_{13}H_{14}N_2S_2$ requires C, 59.5; H, 5.4; N, 10.7%).

2-(3-*Thienyl*)*ethyl isothiocyanate* (9) (75%), prepared similarly from 2-(3-thienyl)ethylamine, had b.p. 107—111° at 0.7 mmHg, $\nu_{max.}$ (film) 2 090 and 2 180 cm^{-1} (NCS), τ ($CDCl_3$) 2.55—3.05 (3 H, m, aromatic), 6.28 (2 H, t, J 6.0 Hz, α-H_2), and 6.99 (2 H, t, J 6.0 Hz, β-H_2) (Found: C, 49.8; H, 3.9; N, 8.6%; M^+, 169. $C_7H_7NS_2$ requires C, 49.7; H, 4.2; N, 8.3%; M, 169).

6,7-*Dihydro-4-methylthiothieno*[3,2-c]*pyridine* (1).—(*a*) A mixture of 2-(2-thienyl)ethyl isothiocyanate (8) (7.5 g, 44.0 mmol), methyl fluorosulphate (5.0 g, 44.0 mmol), and methylene chloride (10 ml) was heated under reflux for 4 h. Water (200 ml) was added to the cooled mixture, which was made alkaline with 2M-sodium hydroxide. The product was extracted with ether; the combined extracts (A) were washed with 2M-hydrochloric acid, and addition of 2M-sodium hydroxide to the acidic washings gave *4-methylthio-6,7-dihydrothieno*[3,2-c]*pyridine* (1) (4.7 g, 58%). This was distilled at 140° and 14 mmHg, initially without decomposition but later with decomposition, and was characterised as its hydrofluorosulphate salt [see (*b*)]. It had $\nu_{max.}$ (film) 1 580 cm^{-1} (C : N), τ ($CDCl_3$) 2.88 (1 H, d, J 5.0 Hz, 2-H), 3.03 (1 H, d, J 5.0 Hz, 3-H), 6.18 (2 H, t, J 7.5 Hz, 6-H_2), 7.20 (2 H, t, J 7.5 Hz, 7-H_2), and 7.58 (3 H, s, Me) (CH_2 triplets showed fine structure), *m/e* 183 (M^+); *hydrochloride*, m.p. 191° (from propanol-2-ol–ethyl methyl ketone), $\nu_{max.}$ (Nujol) 3 440 cm^{-1} (NH^+), τ [$(CD_3)_2SO$] 2.30 (1 H, d, J 5.0 Hz, 2-H), 2.56 (1 H, d, J 5.0 Hz, 3-H), 6.05 (2 H, t, J 7.5 Hz, 6-H_2), 6.71 (2 H, t, J 7.5 Hz, 7-H_2), and 7.04 (3 H, s, Me) (CH_2 triplets showed fine structure). Starting material (2.6 g, 42%) was recovered from the ethereal extracts (A) after the acid wash.

(*b*) (i) 2-(2-Thienyl)ethyl isothiocyanate (8) (20.0 g, 118 mmol) was added dropwise to polyphosphoric acid (200 g) stirred at 150 °C. The mixture was kept at this temperature for a further 1 h, then poured into an excess of water, and the precipitate was filtered off and recrystallised from ethanol to give *6,7-dihydrothieno*[3,2-c]*pyridine-4*(5H)-*thione* (6) (18.8 g, 94%), m.p. 89°, $\nu_{max.}$ (Nujol) 1 225 (C : S) and 3 210 cm^{-1} (NH), τ ($CDCl_3$) 1.38br (1 H, exchangeable, NH), 2.34 (1 H, d, J 5.0 Hz, 2-H), 2.96 (1 H, d, J 5.0 Hz,

[4] M. Lora-Tamayo, R. Madroñero, and M. G. Pérez, *Chem. Ber.*, 1962, **95**, 2188; F. Johnson and R. Madroñero, *Adv. Heterocyclic Chem.*, 1966, **6**, 115.

[5] F. F. Blicke and J. H. Burckhalter, *J. Amer. Chem. Soc.*, 1942, **64**, 477.

[6] F. F. Blicke and F. Leonard, *J. Amer. Chem. Soc.*, 1946, **68**, 1934; F. F. Blicke and M. F. Zienty, *ibid.*, 1941, **63**, 2944; T L. Cairns and B. C. McKusick, *J. Org. Chem.*, 1950, **15**, 790; K. Pettersson, *Acta Chem. Scand.*, 1950, **4**, 395.

[7] N. B. Chapman, K. Clarke, A. J. Humphries, and S. U.-D. Saraf, *J. Chem. Soc.* (*C*), 1969, 1612.

[8] E. Campaigne and W. C. McCarthy, *J. Amer. Chem. Soc.*, 1954, **76**, 4466.

[9] K. Antoš, L. Drobnica, P. Nemec, P. Kristián, and L. Fišera, Czech. P. 146, 668/1972 (*Chem. Abs.*, 1973, **78**, 147784).

3-H), 6.22—6.60 (2 H, m, 6-H_2), and 6.82—7.15 (2 H, m, 7-H_2), *m/e* 169 (M^+).

(ii) A mixture of the thione (7.0 g, 41.0 mmol), methyl fluorosulphate (4.9 g, 43.0 mmol), and methylene chloride (50 ml) was heated under reflux for 3 h. Removal of the solvent and the excess of reagent by distillation under reduced pressure gave 4-*methylthio*-6,7-*dihydrothieno*[3,2-c]-*pyridine* (1) *hydrofluorosulphate* (10.0 g, 85%), m.p. 215° (from propan-2-ol), $\nu_{max.}$ (Nujol) 1 585 (C : N^+) and 2 300—3 450br cm^{-1} (NH^+), τ [$(CD_3)_2SO$] 2.30 (1 H, d, *J* 5.0 Hz, 2-H), 2.54 (1 H, d, *J* 5.0 Hz, 3-H), 3.30br (1 H, exchangeable, NH^+), 6.05 (2 H, t, *J* 7.5 Hz, 6-H_2), 6.72 (2 H, t, *J* 7.5 Hz, 7-H_2), and 7.19 (3 H, s, Me) (CH_2 triplets showed fine structure) (Found: C, 34.1; H, 3.9; N, 4.8. $C_8H_{10}FNO_3S_3$ requires C, 33.9; H, 3.6; N, 4.9%).

A mixture of the thione (6) (16.9 g, 100 mmol) and methyl fluorosulphate (11.4 g, 100 mmol) in chloroform (250 ml) was heated under reflux for 3 h, then poured into water (250 ml). The resulting mixture was made alkaline with 2M-sodium hydroxide, and the organic layer was separated. The aqueous layer was extracted with chloroform and the organic layer and extracts were combined and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave 4-methylthio-6,7-dihydrothieno[3,2-*c*]pyridine (1) (13.1 g, 72%), identical (i.r. and n.m.r. spectra) with the sample prepared as described in (*a*).

4-*Ethylthio*-6,7-*dihydrothieno*[3,2-c]*pyridine* (2).—A mixture of 2-(2-thienyl)ethyl isothiocyanate (8) (22.0 g, 130 mmol), triethyloxonium tetrafluoroborate (25.0 g, 132 mmol), and methylene chloride (25 ml) was heated under reflux for 1 h. Work-up as described in the preceding experiment gave 4-*ethylthio*-6,7-*dihydrothieno*[3,2-c]*pyridine* (2) (12.0 g, 46%), b.p. 110—120° at 5.0 mmHg (decomposed in the later stages of the distillation), $\nu_{max.}$ (film) 1 580 cm^{-1} (C : N), τ ($CDCl_3$) 2.83 (1 H, d, *J* 5.0 Hz, 2-H), 2.97 (1 H, d, *J* 5.0 Hz, 3-H), 6.14 (2 H, t, *J* 7.0 Hz, 6-H_2), 7.00 (2 H, q, *J* 7.5 Hz, CH_2), 7.20 (2 H, t, *J* 7.0 Hz, 7-H_2), and 8.68 (3 H, t, *J* 7.5 Hz, Me) (CH_2 triplets showed fine structure), *m/e* 197 (M^+); *hydrochloride*, m.p. 110—112° (from chloroform–light petroleum) (Found: C, 42.9; H, 5.3; N, 5.6. $C_9H_{12}ClNS_2,H_2O$ requires C, 42.9; H, 5.6; N, 5.6%).

Concentration of the combined ethereal extracts [(A) as in the preceding experiment] recovered from the acid wash gave starting material (11.9 g, 54% recovery).

7-*Ethylthio*-4,5-*dihydrothieno*[2,3-c]*pyridine* (5).—(*a*) Prepared (40%) in a manner similar to that described in the preceding experiment, this *product* had b.p. 160—165° at 1.0 mmHg, $\nu_{max.}$ (film) 1 570 cm^{-1} (C : N), τ (CCl_4) 2.83 (1 H, d, *J* 5.0 Hz, 2-H), 3.24 (1 H, d, *J* 5.0 Hz, 3-H), 6.27 (2 H, t, *J* 7.5 Hz, 5-H_2), 6.95 (2 H, q, *J* 7.0 Hz, CH_2), 7.36 (2 H, t, *J* 7.5 Hz, 4-H_2), and 8.69 (3 H, t, *J* 7.0 Hz, Me) (CH_2 triplets showed fine structure) (Found: C, 54.5; H, 5.5; N, 7.0%; M^+, 197.0349. $C_9H_{11}NS_2$ requires C, 54.8; H, 5.6; N, 7.1%; *M*, 197.0333).

(*b*) (i) 5,6-Dihydrothieno[2,3-*c*]pyridine-7(4*H*)-thione (7) (84%) was prepared from the isothiocyanate (9) as described for the preparation of its isomer (6). It had m.p. 102—104° (from aqueous acetone), $\nu_{max.}$ (Nujol) 1 230 (C : S) and 3 200 cm^{-1} (NH), τ ($CDCl_3$) 1.54br (1 H, s, exchangeable, NH), 2.40 (1 H, d, *J* 5.0 Hz, 2-H), 2.99 (1 H, d, *J* 5.0 Hz, 3-H), 6.18—6.51 (2 H, m, 5-H_2), and 6.88—7.23 (2 H, m, 4-H_2).

(ii) A mixture of the thione (0.7 g, 4.1 mmol), triethyloxonium tetrafluoroborate (0.79 g, 4.1 mmol), and methylene chloride (25 ml) was heated under reflux for 1 h. Water (50 ml) was added to the cooled mixture which was made alkaline with 2M-sodium hydroxide. Extraction with ether gave 7-ethylthio-4,5-dihydrothieno[2,3-*c*]pyridine (5) (0.55 g, 68%), identical (b.p. and i.r. and n.m.r. spectra) with the sample prepared as described in (*a*).

4-(2-*Diethylaminoethylamino*)-6,7-*dihydrothieno*[3,2-c]-*pyridine* (3) *Dihydrochloride*.—(*a*) A stirred mixture of 4-methylthio-6,7-dihydrothieno[3,2-*c*]pyridine (1) hydrochloride (3.0 g, 13.7 mmol), *NN*-diethylethylenediamine (1.9 g, 16.4 mmol), and dimethylformamide (50 ml) was heated at 100 °C for 4 h, then cooled and poured into water (500 ml). The resulting mixture was made alkaline with 2M-sodium hydroxide, and extraction with ether followed by saturation of the dried extracts with dry hydrogen chloride gave 4-(2-*diethylaminoethylamino*)-6,7-*dihydrothieno*-[3,2-c]*pyridine* (3) *dihydrochloride* (68%), m.p. 250° (from propan-2-ol), $\nu_{max.}$ (Nujol) 1 640 (C : N) and 2 400—3 400br cm^{-1} (NH and NH^+), τ [$(CD_3)_2SO$] 1.95 (1 H, d, *J* 5.0 Hz, 2-H), 2.36 (1 H, d, *J* 5.0 Hz, 3-H), 6.05 (2 H, t, showing fine structure, *J* 7.5 Hz, 6-H_2), 6.25—7.15 (13 H, m, 5 × CH_2, plus 3 exchangeable protons), and 8.73 (6 H, t, *J* 7.0 Hz, 2 × Me), τ (D_2O) 2.45 (2 H, s, 2- and 3-H), 6.00—6.95 (12 H, m, 6 × CH_2), and 8.60 (6 H, t, *J* 7.0 Hz, 2 × Me) (Found: C, 47.6; H, 7.0; 13.1. $C_{13}H_{21}N_3S,2HCl$ requires C, 48.1; H, 7.1; N, 13.0%).

(*b*) A stirred mixture of 4-ethylthio-6,7-dihydrothieno-[3,2-*c*]pyridine (2) (4.9 g, 25.0 mmol), *N*,*N*-diethylethylenediamine hydrochloride (3.4 g, 22.3 mmol), and dimethylformamide (50 ml) was heated at 100 °C for 2 h (a strong smell of ethanethiol was detected). The resulting solution was stirred overnight at ambient temperature, then an excess of dry ether was added. After 2 h the dihydrochloride (1.8 g, 22%) of compound (3) separated. It was identical (m.p. and i.r. spectrum) with the sample prepared as described in (*a*).

4-*Cyclopropylamino*-6,7-*dihydrothieno*[3,2-c]*pyridine* (4).—Cyclopropylamine (1.5 g, 26.0 mmol) was added to a stirred solution of 4-methylthio-6,7-dihydrothieno[3,2-*c*]pyridine (1) hydrofluorosulphate (7.5 g, 26.5 mmol) in dry dimethylformamide (100 ml) and the mixture was heated at 100 °C for 6 h. Then it was kept at ambient temperature for 24 h. An excess of ether was added to precipitate 4-*cyclopropylamino*-6,7-*dihydrothieno*[3,2-c]*pyridine* (4) *hydrofluorosulphate* (6.0 g, 75%), m.p. 203° (from ethanol–light petroleum), $\nu_{max.}$ (Nujol) 1 640 (C : N) and 2 300—3 300 cm^{-1} (NH and NH^+), τ [$(CD_3)_2SO$] 0.55br (1 H, exchangeable, NH^+), 2.38 (2 H, s, 2- and 3-H), 5.30br (1 H, exchangeable, NH), 6.30 (2 H, t, *J* 7.5 Hz,6-H_2), 6.85 (2 H, t, *J* 7.5 Hz,7-H_2), 7.28 (1 H, m, CH), and 8.90—9.30 (4 H, m, 2 × cyclopropane CH_2) (CH_2 triplets showed fine structure), *m/e* 292 (M^+) and 192 (M^+ of free base) (Found: C, 41.3; H, 4.8; N, 9.5. $C_{10}H_{13}FN_2O_3S_2$ requires C, 41.1; H, 4.5; N, 9.6%). The free base (4) was obtained in almost quantitative yield by treatment of an aqueous solution of the salt with 2M-sodium hydroxide and extraction with chloroform. It had m.p. 115°, $\nu_{max.}$ (Nujol) 1 620 (C : N) and 3 200 (NH), τ ($CDCl_3$) 2.65 (1 H, d, *J* 5.0 Hz, 2-H), 2.98 (1 H, d, *J* 5.0 Hz, 3-H), 5.35br (1 H, exchangeable, NH), 6.42 (2 H, t, *J* 7.0 Hz, 6-H_2), 7.06 (2 H, t, *J* 7.0 Hz, 7-H_2), 7.45 (1 H, m, CH), and 9.10—9.60 (4 H, m, 2 × cylcopropane CH_2) (6- and 7-H_2 triplets showed fine structure as before).

(*b*) Reaction of 4-ethylthio-6,7-dihydrothieno[3,2-*c*]pyridine (1) (20 mmol) with cyclopropylamine hydrochloride (20 mmol) in dry dimethylformamide (40 ml) for 2 h at 100 °C and addition of ether to the cooled mixture precipitated 4-cyclopropylamino-6,7-dihydrothieno[3,2-*c*]pyridine

(4) hydrochloride (25%), m.p. 140–155° (from propan-2-ol–light petroleum). This product was unstable; conversion into the free base (4) in the usual way gave a product identical (m.p. and i.r. and n.m.r. spectra) with that prepared as described in (*a*).

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