Some Substitution Reactions of Thieno[3,2-*f*]quinoline

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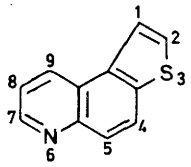
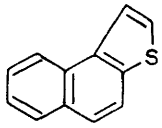
Mononitration, monobromination, and Friedel–Crafts acylation of thieno[3,2-*f*]quinoline occurred in the 2-position; dibromination in concentrated sulphuric acid gave the 1,2-dibromo-derivative. The Hunsdiecker reaction of thieno[3,2-*f*]quinoline-2-carboxylic acid gave a mixture of 1,2,5-tribromothieno[3,2-*f*]quinoline and 5-bromothieno[3,2-*f*]quinoline-2-carboxylic acid in addition to unchanged starting material. Bromination of sodium thieno[3,2-*f*]quinoline-2-carboxylate gave the 5-bromo-acid. *N*-Methylthieno[3,2-*f*]quinolinium hydrogen sulphate was oxidised to *N*-methylthieno[3,2-*f*]quinolin-7-one, which, on treatment with phosphorus pentachloride, gave 7-chlorothieno[3,2-*f*]quinoline. However, the methosulphate reacted with aqueous potassium cyanide to give 6,9-dihydro-*N*-methylthieno[3,2-*f*]quinoline-9-carbonitrile which when oxidised with iodine in pyridine yielded 9-cyano-*N*-methylthieno[3,2-*f*]quinolinium iodide. Demethylation gave thieno[3,2-*f*]quinoline-9-carbonitrile. The Reissert compound derived from thieno[3,2-*f*]quinoline reacted with phosphorus pentachloride to yield thieno[3,2-*f*]quinoline-7-carbonitrile, which on hydrolysis with concentrated hydrochloric acid yielded the 7-carboxylic acid. This was methylated with diazomethane to give methyl thieno[3,2-*f*]quinoline-7-carboxylate. The assignment of these structures has been confirmed whenever possible by conversion of the compounds into known compounds and comparison with authentic samples, or is derived from a study of the relevant ^{1}H n.m.r. spectra.

THE thienoquinoline system is particularly interesting because it results from the fusion of a benzo[*b*]thiophen nucleus, which easily undergoes electrophilic substitution, with a pyridine nucleus which undergoes electrophilic substitution with difficulty, but has characteristic nucleophilic substitution reactions. The synthesis of a number of thienoquinolines by use of the Skraup reaction or the Conrad–Limpach method has been described recently by Royer and his associates.[1] Because 5-nitro-[2] and hence 5-amino-benzo[*b*]thiophen were already available to us, we were particularly interested in thieno[3,2-*f*]quinoline (I). This compound was



(I)



(II)

synthesised by Fries and his co-workers [3] by the Skraup reaction of 5-aminobenzo[*b*]thiophen but the yield was not reported; more recently 7- and 9-methylthieno-[3,2-*f*]quinoline have been reported by Zhiryakov and Abramenko.[4] The reactions of this system have received little attention.

5-Aminobenzo[*b*]thiophen was treated with glycerol and concentrated sulphuric acid in the presence of sodium *m*-nitrobenzenesulphonate as oxidising agent and boric acid as a moderating agent [5] and gave the required thieno[3,2-*f*]quinoline (40%). Similarly 5-amino-3-methylbenzo[*b*]thiophen [6] gave 1-methylthieno[3,2-*f*]quinoline (18%) and a low-melting fraction which, from spectral evidence, appeared to be a mixture of the foregoing compound with its linear isomer, thieno[2,3-*g*]quinoline. Unfortunately, we were unable to separate the components of this mixture. When ethyl 5-aminobenzo[*b*]thiophen-2-carboxylate was treated similarly, partial hydrolysis of the ester group occurred and it was convenient to re-esterify the crude product as part of the work-up. Pure ethyl thieno-[3,2-*f*]quinoline-2-carboxylate (33%) was thus obtained. Hydrolysis with 8% ethanolic potassium hydroxide gave the corresponding acid (95%) which, because of its insolubility and high m.p., was unsatisfactory as a reference compound and was therefore methylated with diazomethane to give methyl thieno[3,2-*f*]quinoline-2-carboxylate (80%). Thieno[3,2-*f*]quinoline-2-carboxylic acid reacted with toluene-*p*-sulphonamide in the presence of phosphorous pentachloride [7] to give thieno-[3,2-*f*]quinoline-2-carbonitrile (55%). The foregoing

[1] J.-P. Lechartier, P. Demerseman, J.-P. Buisson, A. Cheutin, M.-L. Desvoye, and R. Boyer, *Bull. Soc. chim. France*, 1969, 797.
[2] S. Rossi and R. Trave, *Farmaco* (*Pavia*), *Ed. Sci.*, 1960, **15**, 396 (*Chem. Abs.*, 1960, **54**, 24,501).
[3] K. Fries, H. Heering, E. Hemmecke, and G. Siebert, *Annalen*, 1937, **527**, 83.
[4] V. G. Zhiryakov and P. I. Abramenko, *Khim. geterotsikl. Soedinenii*, 1967, (1), 166 (*Chem. Abs.*, 1967, **67**, 6046).
[5] A. O. Fitton and R. K. Smalley, 'Practical Heterocyclic Chemistry,' Academic Press, New York, 1968, p. 82.
[6] N. B. Chapman, K. Clarke, and S. N. Sawhney, *J. Chem. Soc.* (*C*), 1968, 518.
[7] C. S. Miller, *Org. Synth.*, 1949, **29**, 75.

are the authentic reference compounds used later in assignments of structure.

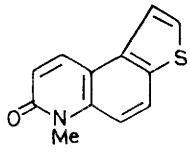
Thieno[3,2-*f*]quinoline in concentrated sulphuric acid reacted with bromine (1 mol. equiv.) to give a monobromo-derivative (57%) contaminated with traces of a dibromo-derivative. In acetic acid only the same monobromo-derivative (65%) was formed, identified as the 2-bromo-compound by treatment with copper(I) cyanide in boiling dimethylformamide to give the known thieno[3,2-*f*]quinoline-2-carbonitrile. When thieno[3,2-*f*]quinoline in concentrated sulphuric acid was treated with bromine (2 mol. equiv.), 1,2-dibromothieno[3,2-*f*]quinoline (81%) was obtained. This is somewhat unexpected, as the 1-position will be hindered both by the adjacent 2-bromine atom and by *peri*-interaction with the neighbouring 9-position. As recently reported,[8] bromination of naphtho[2,1-*b*]thiophen (II) gave first the 2-bromo- and then the 2,5-dibromo-compound, but no bromination occurred in the 1-position. However, the n.m.r. spectrum showed clearly the typical AMX system of the intact pyridine ring and the characteristic AB pattern due to the 4- and 5-proton. Moreover, the 9-proton is deshielded by *ca.* 126 Hz, thus confirming the presence of the bromine at the 1-position. It is inferred that in concentrated sulphuric acid the protonation of the nitrogen deactivates not only the pyridine ring but also the adjacent benzene ring so that substitution is forced into the 1-position. Nitration with sodium nitrate in concentrated sulphuric acid gave the 2-nitro-derivative (80%). Its n.m.r. spectrum showed the typical AMX system of the unsubstituted pyridine ring and an AB quartet with J 9·2 Hz, the characteristic value for $J_{4,5}$. All protons appeared to be deshielded in comparison with those of the unsubstituted thieno[3,2-*f*]quinoline but the effect was negligible on the 9-proton, whereas a nitro-group in the 1-position would have been expected to have a strong deshielding effect on the nearby 9-proton. Acetylation with acetyl chloride and anhydrous aluminium chloride in ethylene dichloride failed, but use of acetic anhydride and aluminium chloride in nitrobenzene at 0° gave the 2-acetyl derivative (29%). Its structure was confirmed by oxidation with sodium hypobromite in dimethyl sulphoxide and methylation of the resulting acid (69%) in dimethyl sulphoxide with ethereal diazomethane to give the known methyl thieno[3,2-*f*]quinoline-2-carboxylate (84%).

Although it has been reported [9] that the Hunsdiecker reaction of 5-nitrobenzo[*b*]thiophen-2-carboxylic acid gives mainly 3-bromo-5-nitrobenzo[*b*]thiophen-2-carboxylic acid and some 2,3-dibromo-5-nitrobenzo[*b*]thiophen, we hoped to use this reaction to prepare 2-bromothieno[3,2-*f*]quinoline from the corresponding 2-carboxylic acid. When silver thieno[3,2-*f*]quinoline-2-carboxylate was treated with bromine in carbon tetrachloride, 1,2,5-tribromothieno[3,2-*f*]quinoline (16%), 5-bromothieno[3,2-*f*]quinoline-2-carboxylic acid (4%), and unchanged thieno[3,2-*f*]quinoline-2-carboxylic acid (40%) were isolated. The assignments of structures to the brominated products rest on n.m.r. evidence, as follows. The n.m.r. spectrum of methyl 5-bromothieno[3,2-*f*]quinoline-2-carboxylate (obtained by the action of diazomethane on the foregoing acid) shows the AMX system of the pyridine ring and two isolated peaks displaying long-range coupling of *ca.* 0·5 Hz. The disappearance of the AB quartet due to the 4-and 5-proton indicates that one of these positions has been brominated. Long-range coupling can occur between the 1- and 4-proton or between the 2- and 5-proton. As the carboxy-group occupies the 2-position the long range coupling must be caused by interaction between the 1- and 4-proton and the bromine must occupy the 5-position. The n.m.r. spectrum of the tribromo-compound shows only a typical AMX system and a singlet. One bromine atom has replaced the carboxy-group in the 2-position, and as the 9-proton is deshielded to the extent of 132 Hz a second bromine atom must have entered the 1-position. In addition either the 4- or 5-position must be substituted and the previous isolation of 5-bromothieno[3,2-*f*]-quinoline-2-carboxylic acid strongly suggests the latter. (Experiments with naphtho[2,1-*b*]thiophen [8] showed the 5-position to be next in reactivity to the 2-position.) Martin-Smith and Reid have reported [10] that the bromination of sodium 5-nitrobenzo[*b*]thiophen-2-carboxylate gave the corresponding 3-bromo-derivative. However, treatment of sodium thieno[3,2-*f*]quinoline-2-carboxylate with bromine (1 mol. equiv.) gave a mixture of unchanged starting material and 5-bromothieno[3,2-*f*]quinoline-carboxylic acid (25%). The mixture of acids was treated with diazomethane and the product was analysed by column chromatography on silica gel. The resulting methyl 5-bromothieno[3,2-*f*]-quinoline-2-carboxylate was identical with that isolated from the Hunsdiecker reaction already described.

There is a considerable similarity between the electrophilic substitution pattern of naphtho[2,1-*b*]thiophen and that of thieno[3,2-*f*]quinoline. The 2-position is the most active; which position is next most active depends on the pH of the reaction medium. The 5-position is next substituted unless strongly acidic conditions prevail, when 1-substitution occurs. However, no electrophilic attack occurs on the nitrogen-containing ring. This was expected and we decided, therefore, to investigate the reactions of the quaternary salts of thieno[3,2-*f*]quinoline. Thieno[3,2-*f*]quinoline with dimethyl sulphate in benzene gave the corresponding methosulphate (75%) which was converted into *N*-methylthieno[3,2-*f*]quinolin-7-one (III) (84%) by oxidation with alkaline potassium ferricyanide.[11] When

[8] K. Clarke, G. Rawson, and R. M. Scrowston, *J. Chem. Soc.* (*C*), 1969, 537.
[9] M. Martin-Smith and M. Gates, *J. Amer. Chem. Soc.*, 1956, **78**, 5351, 6177.
[10] M. Martin-Smith and S. T. Reid, *J. Chem. Soc.*, 1960, 938.
[11] W. H. Perkin, jun. and R. Robinson, *J. Chem. Soc.*, 1913, **103**, 1973.

this quinolone was heated under reflux with a mixture of phosphoryl chloride and phosphorus pentachloride unchanged starting material was recovered. Lutz *et al.*[12] have reported similar difficulties with 2-quinolones and have described a satisfactory procedure involving phosphorus pentachloride in *p*-dichlorobenzene in a sealed tube at 240°. The reaction of *N*-methylthieno[3,2-*f*]-quinolin-7-one under these conditions gave the required 7-chlorothieno[3,2-*f*]quinoline (73%). The structure of this compound is based on analogy with similar reactions in the quinoline system, and the n.m.r. spectrum is consistent with the proposed structure. When thieno-[3,2-*f*]quinoline was treated with benzoyl chloride in methylene dichloride in the presence of aqueous potassium cyanide[13] the corresponding Reissert compound (86%) was obtained. Phosphorus pentachloride in hot chloroform converted this Reissert compound into thieno[3,2-*f*]quinoline-7-carbonitrile (79%). Hydrolysis of the Reissert compound with hydrochloric acid gave the 7-carboxylic acid (60%), which was methylated without further purification with diazomethane in dimethyl sulphoxide to give methyl thieno[3,2-*f*]-quinoline-7-carboxylate (77%). When *N*-methyl quinolinium hydrogen sulphate is treated with aqueous potassium cyanide the cyano-group enters the 4-position.[14,15] With *N*-methylthieno[3,2-*f*]quinolinium hydrogen sulphate a similar reaction would yield the 9-cyano-compound, although one might expect some hindrance from the hydrogen atom in the adjacent 1-position. In fact 6,9-dihydro-*N*-methylthieno[3,2-*f*]-



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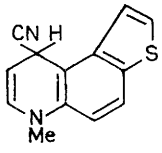

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quinoline-9-carbonitrile (IV) (79%) was obtained and was oxidised with iodine in pyridine[15] at 0° to give 9-cyano-*N*-methylthieno[3,2-*f*]quinolinium iodide (35%) Dry distillation of this methiodide failed to cause the expected demethylation, but when the methiodide was boiled in ethyl benzoate[16] a high yield (83%) of thieno-[3,2-*f*]quinoline-9-carbonitrile was obtained. The m.p. and i.r. spectrum of this compound differed considerably from those described for the 7-cyano-compound and the n.m.r. spectrum showed a deshielding of the 1-proton by *ca.* 90 Hz, thus confirming the location of the cyano-group in the 9-position.

EXPERIMENTAL

^{1}H N.m.r. spectra (100 MHz) were obtained with a JNM-4H-100 spectrometer, for solutions in deuteriochloroform except where otherwise stated, with tetramethylsilane as internal standard. I.r. spectra were determined for potassium chloride discs with a Perkin-Elmer PE457 spectrophotometer.

Thieno[3,2-f]*quinoline*.—Concentrated sulphuric acid (55 ml) was added to a thoroughly stirred intimate mixture of 5-aminobenzo[*b*]thiophen (49·7 g, 0·33 mol), sodium *m*-nitrobenzenesulphonate (37·5 g, 0·17 mol), boric acid (15·5 g), and dry glycerol (74 ml) and the mixture was heated to 170°, and then cooled as necessary. When the vigorous exothermic reaction had subsided, the mixture was maintained at 170° for 1 h, and then was cooled, poured into water, and made alkaline. The alkaline mixture was shaken with chloroform (5 × 100 ml), the combined extracts were washed with water and dried ($MgSO_4$), and the solvent was removed. The black residue dissolved in benzene was passed down an alumina column and the decolourised product was eluted with benzene. Evaporation of the benzene gave a residue, m.p. 88—89° (lit.,[3] 88°), flakes (24·6 g, 40%) [from light petroleum (b.p. 60—80°)] (Found: C, 71·5; H, 3·7; N, 7·7; S, 16·8. Calc. for $C_{11}H_7NS$: C, 71·3; H, 3·8; N, 7·6; S, 17·2%), τ 1·06 (dd, 7-H), 1·39 (dd, 9-H), 1·89 (d, 5-H), 1·99 (d, 4-H), 2·05 (d, 1-H), 2·34 (d, 2-H), and 2·49 (dd, 8-H) ($J_{1,2}$ 5·5, $J_{4,5}$ 8·9, $J_{7,8}$ 4·3, $J_{7,9}$ 1·5, and $J_{8,9}$ 8·5 Hz).

1-*Methylthieno*[3,2-f]*quinoline*.—5-Amino-3-methylbenzo-[*b*]thiophen (8·15 g, 0·05 mol) was treated with glycerol (15 ml) in the presence of sodium *m*-nitrobenzenesulphonate (6·0 g), boric acid (3·0 g) and concentrated sulphuric acid (11·0 ml) as in the previous preparation and the product was worked up similarly. Evaporation gave an oil (3·5 g) which was dissolved in the minimum quantity of chloroform. Neutral alumina (20·0 g) was added and the solvent was evaporated off. The impregnated adsorbent was put on the top of a neutral alumina column (30 × 2 cm) and the adsorbate was eluted with benzene (500 ml). The first fraction (200 ml) gave a low-melting solid and probably still contained more than one component, although further separation of the components proved impossible. The second fraction (300 ml) on evaporation and crystallisation from benzene–light petroleum (b.p. 60—80°) gave *plates*, (1·8 g, 18%), m.p. 78—79° (Found: C, 72·0; H, 4·7; N, 7·2; S, 15·9. $C_{12}H_9NS$ requires C, 72·3; H, 4·55; N, 7·0; S, 16·1%), τ 1·13 (dd, 7-H), 1·19 (dd, 9-H), 2·05 (d, 5-H), 2·11 (d, 4-H), 2·61 (dd, 8-H), 2·80 (d, 2-H), and 7·27 (s, Me) ($J_{4,5}$ 9, $J_{7,8}$ 4·5, $J_{7,9}$ 1·5, and $J_{8,9}$ 9 Hz), $\nu_{max.}$ 1380 cm^{-1} (Ar–Me).

A *picrate* was prepared in the usual way from ethanolic solution, m.p. 220—221°, yellow needles (from acetic acid) (Found: C, 50·6; H, 2·9; N, 13·2; $C_{18}H_{12}N_4O_7S$ requires C, 50·5; H, 2·8; N, 13·1%).

Ethyl Thieno[3,2-f]*quinoline-2-carboxylate*.—Ethyl 5-aminobenzo[*b*]thiophen-2-carboxylate (13·3 g, 0·06 mol) was treated as already described. Dry benzene (200 ml) was added to the cooled mixture and any water present was removed by azeotropic distillation. The excess of benzene was evaporated off, dry ethanol (100 ml) and concentrated sulphuric acid (2 ml) were added, and the

[12] R. E. Lutz, G. Ashburn, J. A. Freck, R. H. Jordan, N. H. Lecke, T. A. Martin, R. J. Rowlett, jun., and J. W. Wilson, jun., *J. Amer. Chem. Soc.*, 1946, **68**, 1285; R. E. Lutz and R. Rowlett, jun., *ibid.*, p. 1288; E. B. Hartshorn and S. L. Baird, jun., *ibid.*, p. 1562.

[13] F. D. Popp, W. Blount, and P. Melvin, *J. Org. Chem.*, 1961, **26**, 4930.

[14] A. Kaufmann and A. Albertini, *Ber.*, 1909, **42**, 3776; A. Kaufmann and R. Widmer, *ibid.*, 1911, **44**, 2058; A. Kaufmann, *ibid.*, 1918, **51**, 116.

[15] A. D. Ainley and H. King, *Proc. Roy. Soc.*, 1938, *B*, **125**, 60.

[16] V. G. Ramsey, W. E. Baldwin, and R. S. Tipson, *J. Amer. Chem. Soc.*, 1947, **69**, 67.

mixture was boiled under reflux for 8 h. Most of the ethanol was then removed and the mixture was poured into water, made alkaline, and shaken with chloroform (5 × 50 ml). The combined chloroform extracts were washed with water, dried ($MgSO_4$), and evaporated. The residue, dissolved in benzene, was passed down an alumina column and the adsorbate was eluted with benzene. Evaporation of the eluate gave a residue (5·1 g, 33%), m.p. 136—137°, *plates* [from benzene–light petroleum (b.p. 60—80°)] (Found: C, 65·3; H, 4·2; N, 5·7; S, 12·2. $C_{14}H_{11}NO_2S$ requires C, 65·35; H, 4·3; N, 5·4; S, 12·45%), τ 1·04 (dd, 7-H), 1·37 (s, 1-H), 1·39 (dd, 9-H), 1·92 (d, 5-H), 1·94 (d, 4-H), and 2·46 (dd, 8-H) ($J_{4,5}$ 8·5, $J_{7,8}$ 4·3, $J_{7,9}$ 1·6, and $J_{8,9}$ 8·3 Hz), $\nu_{max.}$ 1710 cm^{-1} (ester C=O).

Methyl Thieno[3,2-f]*quinoline-2-carboxylate*.—A solution of potassium hydroxide (10·0 g) in ethanol (50 ml) and water (5 ml) was added to ethyl thieno[3,2-*f*]quinoline-2-carboxylate (10·0 g) in ethanol (100 ml) and the mixture was boiled under reflux for 8 h. Water (150 ml) was added and the ethanol was removed under reduced pressure. Acidification of the hot solution with acetic acid gave a grey solid which was washed and dried. The crude acid (8·9 g, 95%), m.p. 328—330° (decomp.), was insoluble in most organic solvents except dimethyl sulphoxide and was not purified further. An excess of diazomethane in ether was added to a cold solution of the crude acid (1·0 g) in dimethyl sulphoxide (20 ml). Water (100 ml) was then added and the ethereal layer was separated. The aqueous layer was shaken with chloroform (3 × 10 ml) and the combined organic layers were washed with water and dried ($MgSO_4$). The solvent was evaporated off and the residue had m.p. 163—164°, *plates* (0·9 g, 80%) [from benzene–light petroleum (b.p. 60—80°)] (Found: C, 63·9; H, 3·8; N, 5·9; S, 12·9. $C_{13}H_9NO_2S$ requires C, 64·2; H, 3·7; N, 5·8; S, 13·2%), τ 1·06 (dd, 7 H), 1·33 (s, 1-H), 1·37 (dd, 9-H), 1·92 (s, 4-H and 5-H), 2·44 (dd, 8-H), and 6·00 (s, CO_2Me) ($J_{7,8}$ 4·3, $J_{7,9}$ 1·5, and $J_{8,9}$ 8·5 Hz), $\nu_{max.}$ 1720 cm^{-1} (ester C=O).

Thieno[3,2-f]*quinoline-2-carbonitrile*.—An intimate mixture of thieno[3,2-*f*]quinoline-2-carboxylic acid (2·29 g, 0·01 mol), toluene-*p*-sulphonamide (1·9 g), and phosphorus pentachloride (4·5 g) was warmed gently. When the vigorous initial reaction had subsided, the mixture was heated at 220° until no more phosphorus halide distilled over. The cooled residue was ground in a mortar with acetone (50 ml) and concentrated ammonia (*d* 0·880; 15 ml). The acetone and excess of ammonia were distilled off and the solid was washed with water and dried. The crude cyanide was dissolved in chloroform and the solution was filtered and evaporated to dryness. The residue was dissolved in benzene and the solution was passed down a column (30 × 2 cm) of silica gel and the adsorbate was eluted with benzene–acetone (4 : 1; 500 ml). Evaporation gave a residue, m.p. 207—208°, *needles* (1·1 g, 55%) (from benzene) (Found: C, 68·4; H, 3·0; N, 13·1; S, 15·4. $C_{12}H_6N_2S$ requires C, 68·55; H, 2·9; N, 13·3; S, 15·3%), τ 0·98br (d, 7-H), 1·43 (dd, 9-H), 1·56 (s, 1-H), 1·84 (d, 5-H), 1·96 (d, 4-H), and 2·40 (dd, 8-H) ($J_{4,5}$ 9·0, $J_{7,8}$ 4·0, $J_{7,9}$ 1·5, and $J_{8,9}$ 8·5 Hz), $\nu_{max.}$ 2210 cm^{-1} (C≡N).

Bromination of Thieno[3,2-f]*quinoline*.—(*a*) Bromine (1·6 g, 0·01 mol) in glacial acetic acid (10 ml) was added during 30 min to a stirred solution of thieno[3,2-*f*]quinoline (1·85 g, 0·01 mol) in concentrated sulphuric acid (10 ml) at 0°. The mixture was stirred for a further 30 min at room temperature, and then heated on a water-bath for 15 min, cooled, poured into ice–water (200 ml), and basified with 10% sodium hydroxide. The product was extracted with chloroform (3 × 25 ml) and the solution was washed with water, dried ($MgSO_4$), and evaporated. Mass spectrometric analysis of the crude product revealed minor peaks (M^+ 341, 343, and 345) corresponding to a dibromo-derivative, in addition to peaks corresponding to the expected monobromo-compound (M^+ 263 and 265) and starting material (M^+ 185). The material was chromatographed on neutral alumina and the adsorbate was eluted with benzene. Evaporation gave *crystals* (1·5 g, 57%), m.p. 140—141° (from benzene) (Found: C, 50·0; H, 2·4; Br, 29·95; N, 5·3. $C_{11}H_6BrNS$ requires C, 50·0; H, 2·3; Br, 30·25; N, 5·3%), τ 1·07 (dd, 7-H), 1·54 (dd, 9-H), 2·02 (d, 5-H), 2·07 (d, 4-H), 2·11 (s, 1-H), and 2·51 (dd, 8-H) ($J_{4,5}$ 8·5, $J_{7,8}$ 4·3, $J_{7,9}$ 1·8, and $J_{8,9}$ 8·8 Hz).

(*b*) Bromine (1·6 g, 0·01 mol) in glacial acetic acid (20 ml) was added at 8° to a stirred solution of thieno[3,2-*f*]quinoline (1·85 g, 0·01 mol) in glacial acetic acid (20 ml) containing sodium acetate (0·82 g). The reaction was continued as described in (*a*) and yielded the same monobromo-derivative (1·7 g, 65%), uncontaminated with dibromo-derivative.

(*c*) Experiment (*a*) was repeated with 2 molar proportions of bromine; the reaction mixture was kept at room temperature overnight and then was heated for 1 h on a water-bath. The cooled mixture was poured into water and basified. The precipitate gave long needles (2·75 g, 81%), m.p. 160—161° (from benzene). Analysis and the n.m.r. spectrum indicate that this compound was 1,2-*dibromothieno*[3,2-f]*quinoline* (Found: C, 38·5; H, 1·3; Br, 46·9; N, 4·3; S, 9·2. $C_{11}H_5Br_2NS$ requires C, 38·4; H, 1·5; Br, 46·5; N, 4·1; S, 9·3%), τ 0·13 (ddd, 9-H), 1·06 (dd, 7-H), 1·99 (dd, 5-H), 2·11 (d, 4-H), and 2·49 (dd, 8-H) ($J_{4,5}$ 9·0, $J_{5,9}$ 0·6, $J_{7,8}$ 4·5, $J_{7,9}$ 1·8, and $J_{8,9}$ 8·5 Hz).

Identification of the 3-Bromo-derivative.—A mixture of the monobromo-derivative (2·64 g, 0·01 mol) and dry copper(I) cyanide (1·3 g, 0·015 mol) in dry dimethylformamide (50 ml) was stirred and boiled under reflux for 6 h. The cooled mixture was poured into water (500 ml) and the solid produced was filtered off and stirred vigorously for 1 h with a solution of potassium cyanide (5·0 g) in water (50 ml). The product was extracted with chloroform, washed with water, and dried ($MgSO_4$). Evaporation gave unchanged starting material and the required cyanide which were separated by chromatography on neutral alumina, with benzene–acetone (6 : 1; 500 ml) as eluant. The final fractions (300 ml) contained the required cyanide which, after several crystallisations from benzene, gave needles (1·1 g, 50%), m.p. 206—207°, undepressed on admixture with an authentic sample of thieno[3,2-*f*]-quinoline-2-carbonitrile. I.r. and n.m.r. spectra confirmed this structure.

2-*Nitrothieno*[3,2-f]*quinoline*.—Powdered sodium nitrate (0·555 g, 0·0065 mol) was gradually added to a stirred solution of thieno[3,2-*f*]quinoline (0·925 g, 0·005 mol) in concentrated sulphuric acid (20 ml) at 0°. The mixture was stirred at room temperature for 1 h and heated on a water-bath for 30 min to complete the reaction. The mixture was cooled, poured into ice-water (200 ml), and basified with 10% sodium hydroxide. The precipitate was filtered off, washed thoroughly with water, and dried. It gave a light orange *solid* (0·9 g, 80%), m.p. 220—221° (from chloroform–ethanol) (Found: C, 57·5; H, 2·6; N, 12·1; S, 14·2. $C_{11}H_6N_2O_2S$ requires C, 57·4; H, 2·6; N, 12·2; S, 13·9%), τ 0·96 (dd, 7-H), 1·26 (d, 1-H), 1·40 (ddd, 9-H), 1·78 (dd,

5-H), 1·97 (dd, 4-H), and 2·38 (dd, 8-H) ($J_{1,4}$ 0·6, $J_{4,5}$ 9·2, $J_{7,8}$ 4·2, $J_{7,9}$ 1·7, $J_{8,9}$ 8·5, and $J_{5,9}$ 0·5 Hz).

2-*Acetylthieno*[3,2-f]*quinoline*.—Acetic anhydride (3·0 g) in dry nitrobenzene (10 ml) was added in 1 ml portions to a stirred, cooled solution of thieno[3,2-*f*]quinoline (3·7 g, 0·02 mol) in nitrobenzene (40 ml) at 0°. Anhydrous aluminium chloride (*ca.* 0·5 g) was added after each portion until the required amount (8·7 g) had been introduced. The mixture was stirred at 0·5° for 30 min then at room temperature for 4 h before being poured into ice–hydrochloric acid, and was then made alkaline with 20% sodium hydroxide solution. The mixture was shaken with chloroform (3 × 50 ml) and the combined extracts were washed with water, dried ($MgSO_4$), and evaporated. The residue was chromatographed on an alumina column (30 × 2 cm) and eluted with benzene–acetone (4 : 1; 500 ml). Each fraction of the eluate (50 ml) was examined by t.l.c. and the last three fractions, which contained only one component, were combined, and evaporated. The residue gave *crystals* (1·3 g, 29%), m.p. 148—149° (from benzene) (Found: C, 68·8; H, 4·1; N, 6·4; S, 14·1. $C_{13}H_9NOS$ requires C, 68·7; H, 4·0; N, 6·2; S, 14·1%), τ 1·03 (dd, 7-H), 1·38 (dd, 9-H), 1·50 (s, 1-H), 1·93 (s, 4-H and 5-H), 2·44 (dd, 8-H), and 7·30 (s, Me) ($J_{7,8}$ 4·5, $J_{7,9}$ 1·5, and $J_{8,9}$ 8·5 Hz), $\nu_{max.}$ 1655 cm^{-1} (conj. C=O). The 2,4-*dinitrophenylhydrazone* formed scarlet needles, m.p. 312—313° (decomp.) (from dimethylformamide) (Found: C, 56·1; H, 3·4; N, 17·0; S, 7·85. $C_{19}H_{13}N_5O_4S$ requires C, 56·0; H, 3·2; N, 17·2; S, 7·9%).

Oxidation of 2-*Acetylthieno*[3,2-f]*quinoline to Thieno*-[3,2-f]*quinoline-2-carboxylic Acid*.—Aqueous sodium hypobromite [from bromine (2·4 g) and sodium hydroxide (1·5 g) in water (10 ml) at 0°] was slowly added to 2-acetylthieno[3,2-*f*]quinoline (1·0 g) in dioxan (50 ml) and the mixture was stirred and heated at 70—80° for 2 h. Dioxan was removed under reduced pressure, the residue was dissolved in hot water (100 ml) and the hot solution was filtered. The cold filtrate was shaken with chloroform and the aqueous layer was acidified with dilute acetic acid. The precipitated acid was filtered off, washed with ice–water, and dried to give a solid (0·7 g, 69%), m.p. 328—330° (decomp.). The crude acid was methylated as described on p. 2337 and gave methyl thieno[3,2-*f*]quinoline-2-carboxylate, m.p. 164—165°, undepressed on admixture with the authentic sample (Found: C, 64·3; H, 3·9; N, 5·7; S, 13·0. Calc. for $C_{13}H_9NO_2S$, C, 64·2; H, 3·7; N, 5·8; S, 13·2%).

Attempted Hunsdiecker Reaction.—Bromine (4·0 g, 0·025 mol) in dry carbon tetrachloride (50 ml) was added dropwise to a stirred suspension of silver thieno[3,2-*f*]quinoline-2-carboxylate (8·4 g, 0·025 mol) in boiling dry carbon tetrachloride (200 ml) during 2 h. The mixture was boiled for a further 4 h, filtered hot and the residue was boiled with chloroform (200 ml) and again filtered. The combined solutions were evaporated and the crude product (2·0 g, 16%) gave *needles*, m.p. 206—207° (from chloroform) (Found: C, 31·2; H, 0·9; Br, 56·6; N, 3·4; S, 7·6. $C_{11}H_4Br_3NS$ requires C, 31·3; H, 0·95; Br, 56·8; N, 3·3; S, 7·6%), τ 0·07 (dd, 9-H), 0·92 (dd, 7-H), 1·70 (s, 4-H), and 2·38 (dd, 8-H) ($J_{7,8}$ 4·5, $J_{7,9}$ 1·5, and $J_{8,9}$ 9·0 Hz). The chloroform-insoluble residue was boiled with aqueous 0·5% sodium hydroxide (200 ml) and filtered hot. The cooled filtrate was acidified with acetic acid and the resulting precipitate was collected, washed with water, dried and treated with ethereal diazomethane as described on p. 2337. T.l.c. indicated that the product contained a mixture of esters; it was chromatographed on a silica gel column, with benzene–acetone (4 : 1) as eluant. The fractions (20 ml) were monitored by t.l.c. (silica gel) and those containing the faster-moving component were combined and evaporated. The residue gave *plates* (0·4 g, 4%), m.p. 216—217° (from benzene) (Found: C, 48·7; H, 2·3; Br, 24·5; N, 4·5. $C_{13}H_8BrNO_2S$ requires C, 48·5; H, 2·5; Br, 24·8; N, 4·35%), τ 0·91 (dd, 7-H), 1·39 (dd, 9-H), 1·40 (d, 1-H), 1·55 (d, 4-H), 2·38 (dd, 8-H), and 6·00 (s, CO_2Me), ($J_{1,4}$ 0·5, $J_{7,8}$ 4·3, $J_{7,9}$ 1·7, and $J_{8,9}$ 8·5 Hz), $\nu_{max.}$ 1710 cm^{-1} (ester C=O). The fractions containing a slower-moving component were combined; they yielded methyl thieno[3,2-*f*]quinoline-2-carboxylate (3·3 g, 40%), m.p. 164—165°, undepressed on admixture with an authentic sample.

Bromination of Sodium Thieno[3,2-f]*quinoline-2-carboxylate*.—Bromine (1·6 g, 0·1 mol) in water (100 ml) was added to a stirred solution of thieno[3,2-*f*]quinoline-2-carboxylic acid (2·29 g, 0·01 mol) in 0·2% sodium hydroxide solution (200 ml) during 30 min. After a further 1 h, the solid product (2·0 g) was collected, washed with water, dried, and methylated with ethereal diazomethane. T.l.c. showed two components, and so the mixture was chromatographed on silica gel, with benzene–acetone (4 : 1; 300 ml) as eluant. Each fraction (20 ml) was monitored by t.l.c. and those containing the faster-moving component were combined and evaporated to give methyl 5-bromothieno-[3,2-*f*]quinoline-2-carboxylate (0·5 g, 25%), m.p. 215—216°, undepressed on admixture with a sample from the previous experiment, $\nu_{max.}$ 1710 cm^{-1} (ester C=O). Those fractions containing the slower-moving component were combined and yielded methyl thieno[3,2-*f*]quinoline-2-carboxylate (1·4 g, 60%), m.p. 164—165°, undepressed on admixture with an authentic sample, $\nu_{max.}$ 1720 cm^{-1} (ester C=O).

N-*Methylthieno*[3,2-f]*quinolinium Hydrogen Sulphate*.—Dimethyl sulphate (6·0 g; excess) was added to a shaken solution of thieno[3,2-*f*]quinoline (7·4 g, 0·04 mol) in benzene (200 ml) and the mixture was refluxed for 1 h. The precipitated methosulphate was filtered off, washed thoroughly with benzene, and dried; it gave dull yellow *crystals* (9·4 g, 75%), m.p. 267—268° (from methanol) (Found: C, 49·8; H, 4·0; N, 4·7; S, 20·9. $C_{13}H_{13}NO_4S_2$ requires C, 50·1; H, 4·2; N, 4·5; S, 20·6%).

N-*Methylthieno*[3,2-f]*quinolin-7-one*.—Potassium ferricyanide (10 g) in water (50 ml) was mixed with thieno-[3,2-*f*]quinoline methosulphate (3·11 g, 0·01 mol) in water (200 ml) and ether (100 ml) was added. The mixture was stirred and 10% potassium hydroxide solution was added dropwise until the solution was alkaline. After 15 min the ether layer was separated and the aqueous layer with its suspended solid material was shaken with chloroform. The combined ether and chloroform layers were washed with water, dried, and evaporated. The residue gave the required *quinolone* (1·8 g, 84%), m.p. 217—218° (from benzene) (Found: C, 66·7; H, 4·5; N, 6·7; S, 14·7. $C_{12}H_9NOS$ requires C, 66·95; H, 4·2; N, 6·5; S, 14·9%), τ 1·85 (d, 9-H), 2·02 (d, 5-H), 2·33 (d, 1-H), 2·36 (d, 2-H), 2·64 (d, 4-H), and 3·20 (d, 8-H) ($J_{1,2}$ 5·5, $J_{4,5}$ 9·2, and $J_{8,9}$ 9·3 Hz), $\nu_{max.}$ 1650 cm^{-1} (amide C=O).

7-*Chlorothieno*[3,2-f]*quinoline*.— *N*-methylthieno[3,2-*f*]-quinolin-7-one (1·08 g, 0·005 mol), *p*-dichlorobenzene (2·0 g) and phosphorus pentachloride (2·0 g) were heated in a Carius tube at 230—240° for 6 h. The tube was cooled and the solid product was finely ground, triturated

with ethereal hydrogen chloride, and filtered off. The solid hydrochloride was suspended in water, and the suspension was made alkaline with 5% sodium hydroxide solution and shaken with chloroform. The chloroform layer was washed thoroughly with water and dried ($MgSO_4$). Evaporation gave *crystals* (0·8 g, 73%), m.p. 128—129° [from light petroleum (b.p. 60—80°)] (Found: C, 60·3; H, 2·5; Cl, 16·3; N, 6·2; S, 14·3. $C_{11}H_6ClNS$ requires C, 60·1; H, 2·75; Cl, 16·1; N, 6·4; S, 14·6%), τ 1·47 (d, 9-H), 1·89 (d, 5-H), 2·10 (dd, 4-H), 2·11 (dd, 1-H), 2·32 (d, 2-H), and 2·52 (d, 8-H) ($J_{1,2}$ 5·5, $J_{1,4}$ 0·7, $J_{4,5}$ 8·7, and $J_{8,9}$ 8·5 Hz).

Reissert Compound from Thieno[3,2-f]*quinoline. 6-Benzoyl-6,7-dihydrothieno*[3,2-f]*quinoline-7-carbonitrile.*—Thieno[3,2-*f*]quinoline (3·7 g, 0·02 mol) in methylene chloride (100 ml) was added to a stirred solution of potassium cyanide (3·9 g, 0·06 mol) in water (10 ml). Benzoyl chloride (5·6 g, 0·04 mol) in methylene chloride (20 ml) was then added dropwise during 2 h and stirring was continued for 8 h. The mixture was filtered and the residue was washed with water and then with methylene chloride. The solid (2·5 g) had m.p. 196—197° (from chloroform).

The combined methylene chloride solutions were washed with water, dried ($MgSO_4$) and the solvent was removed. Crystallisation of this residue from chloroform gave a further quantity (2·9 g) of the pure *product*, m.p. 195—196° [total yield 5·4 g (86%)] (Found: C, 71·8; H, 4·0; N, 8·7; S, 10·1. $C_{19}H_{12}N_2OS$ requires C, 72·1; H, 3·8; N, 8·85; S, 10·1%), τ 2·07 (d, 2-H), 2·18 (d, 1-H), 2·34 (d, 5-H), 2·37 (d, 9-H), 3·30 (d, 4-H), and 3·27—3·7 (m, 7-H and 8-H) ($J_{1,2}$ 5·5, $J_{4,5}$ 8·5, $J_{8,9}$ 6·5, and $J_{7,9}$ 1·5 Hz), $\nu_{max.}$ 2230w (C≡N) and 1660 cm^{-1} (amide C=O).

Thieno[3,2-f]*quinoline-7-carbonitrile.*—Phosphorus pentachloride (1·35 g) was added in small portions to a stirred solution of the Reissert compound (2·1 g, 0·0066 mol) in dry chloroform (100 ml). The mixture was stirred and boiled under reflux for 3 h and was then allowed to cool to room temperature. It was made alkaline with sodium carbonate solution and was sitrred for a further 1 h. The chloroform layer was separated, washed thoroughly with water, and dried ($MgSO_4$). The solvent was evaporated and the residue, dissolved in benzene, was chromatographed on a column of silica gel and eluted with acetone–benzene (1 : 4). Evaporation gave *crystals* (1·0 g, 79%), m.p. 197—198° (from benzene) (mixed m.p. with the Reissert compound 174—178°) (Found: C, 68·8; H, 2·9; N, 13·5; S, 15·0. $C_{12}H_6N_2S$ requires C, 68·55; H, 2·9; N, 13·3; S, 15·25%), τ 1·29 (dd, 9-H), 1·80 (dd, 5-H), 1·99 (dd, 4-H), 2·02 (dd, 1-H), 2·19 (d, 8-H), and 2·24 (d, 2-H) ($J_{1,2}$ 5·5, $J_{1,4}$ 0·6, $J_{4,5}$ 9·2, and $J_{8,9}$ 8·5 Hz), $\nu_{max.}$ 2230 cm^{-1} (C≡N).

Thieno[3,2-f]*quinoline-7-carboxylic Acid.*—The Reissert compound (2·1 g, 0·0066 mol) was added to concentrated hydrochloric acid (50 ml) and the mixture was boiled under reflux for 8 h. The solution was shaken with benzene and the benzene solution was evaporated to give benzaldehyde (2,4-dinitrophenylhydrazone, m.p. 237°). The aqueous layer was neutralised with 10% sodium hydroxide solution and was then acidified with dilute acetic acid. The precipitate (0·9 g, 60%) was filtered off, washed with water, and dried. The crude product turned brown at 284—286° and melted with charring at 365—367°.

Methyl Thieno[3,2-f]*quinoline-7-carboxylate.*—Thieno[3,2-*f*]quinoline-7-carboxylic acid (0·8 g) was esterified by ethereal diazomethane in dimethyl sulphoxide by the procedure described on p. 2337. The product gave *crystals* (0·7 g, 77%), m.p. 130—131° (from benzene) (Found: C, 64·3; H, 3·8; N, 5·6; S, 13·2. $C_{13}H_9NO_2S$ requires C, 64·2; H, 3·7; N, 5·8; S, 13·2), τ 1·25 (d, 9-H), 1·78 (d, 8-H), 1·83 (s, 4-H and 5-H), 2·01 (d, 1-H), 2·30 (d, 2-H), and 5·92 (s, CO_2Me) ($J_{1,2}$ 5·5 and $J_{8,9}$ 8·7 Hz), $\nu_{max.}$ 1720 cm^{-1} (ester C=O).

6,9-*Dihydro*-N-*methylthieno*[3,2-f]*quinoline-9-carbonitrile.*—The methosulphate of thieno[3,2-*f*]quinoline (3·1 g, 0·01 mole) in water (25 ml) was treated with potassium cyanide (5·0 g) in water (10 ml). The mixture was stirred for 2 h and the sticky solid which separated was extracted into chloroform; the solution was washed with water and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude dihydrothieno[3,2-*f*]quinoline (2·0 g, 79%). Such compounds are notoriously unstable and hence no attempt was made to crystallise the product but it was used immediately in the next stage, $\nu_{max.}$ 2220 cm^{-1} (C≡N).

9-*Cyano*-N-*methylthieno*[3,2-f]*quinolinium Iodide.*—Iodine (0·5 g) in cold dry ethanol (25 ml) was added to an ice-cold, stirred solution of 6,9-dihydro-*N*-methylthieno[3,2-*f*]-quinoline-9-carbonitrile (2·0 g) in dry pyridine (25 ml). The solution was stirred at 0° for a further 1 h and the mixture was kept overnight in a refrigerator. The solid was filtered off and dissolved in hot water and the hot solution was filtered; the filtrate was cooled in ice and the precipitate was filtered off, and dried. It gave bright red *needles* (1·1 g, 35%), m.p. 238—239° (decomp.) (from water) (Found: C, 44·0; H, 2·8; I, 36·3; N, 7·8. $C_{13}H_9N_2IS$ requires C, 44·3; H, 2·6; I, 36·0; N, 7·95%), τ 0·24 (d, 7-H), 0·90 (d, 5-H), 1·07 (d, 8-H), 1·10 (d, 1-H), 1·45 (d, 2-H), and 1·47 (d, 4-H) ($J_{1,2}$ 5·2, $J_{4,5}$ 9·2, and $J_{7,8}$ 6·0 Hz), $\nu_{max.}$ 2230 cm^{-1} (C≡N).

Thieno[3,2-f]*quinoline-9-carbonitrile.*—9-Cyanothieno[3,2-*f*]quinoline methiodide (0·9 g), suspended in ethyl benzoate (5 ml), was boiled under reflux for 3 h. The cooled mixture was added to ethereal hydrogen chloride and the precipitate was filtered off, dissolved in water (50 ml), and made alkaline with 10% sodium hydroxide solution. The product was extracted with chloroform, and the extract was washed with water and dried ($MgSO_4$). Evaporation afforded *crystals* (0·5 g, 83%), m.p. 185—186° (from benzene) (Found: C, 68·3; H, 3·0; N, 13·6; S, 15·0. $C_{12}H_6N_2S$ requires C, 68·55; H, 2·9; N, 13·3; S, 15·25%), τ 0·97br (d, 7-H), 1·15 (d, 1-H), 1·78 (d, 5-H), 1·95 (d, 4-H), 2·18 (d, 8-H), and 2·20 (d, 2-H) ($J_{1,2}$ 5·5, $J_{1,4}$ 0·7, $J_{4,5}$ 9·2, and $J_{7,8}$ 4·0 Hz), $\nu_{max.}$ 2230 cm^{-1} (C≡N).

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