Reactions of Heterocycles with Thiophosgene. Part V.[1] 7-Chloro-1,2-dihydro-4-methoxy-2-thioxoquinoline-3-carbaldehyde, a Product from 7-Chloro-4-methoxyquinoline

By Roy Hull,* Mrs. Patricia J. van den Broek, and Michael L. Swain, Imperial Chemical Industries Limited, Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire

7-Chloro-4-methoxyquinoline undergoes ring scission on treatment with thiophosgene and barium carbonate. The resulting 4-chloro-2-isothiocyanato-β-methoxycinnamaldehyde (3) undergoes ready ring closure to 7-chloro-1,2-dihydro-4-methoxy-2-thioxo-quinoline-3-carbaldehyde (4). Some reactions of the thioxoquinoline (4) and the corresponding ethylthio- (7) and sulphone (44) derivatives are described which give rise to other heterocyclic systems.

In Part IV [1] the preparation of β,4-dichloro-2-isothiocyanatocinnamaldehyde (1) by the interaction of thiophosgene and alkali with 4,7-dichloroquinoline was described. The same procedure has now been applied to 7-chloro-4-methoxyquinoline.[2]

Ring fission took place, probably *via* the dihydroquinoline (2), to yield the rather unstable isothiocyanate (3). The product (3) could be observed by t.l.c. and was identified by i.r. spectroscopy [$\nu_{max.}$ 2 100 (NCS) and 1 670 cm^{-1} (conj. CHO)]. The stereochemistry is unknown. Attempted isolation by evaporation of the solution in methylene chloride led to violent decomposition. However, the compound in methylene chloride underwent smooth spontaneous ring closure to the alkali-soluble methoxyquinolinecarbaldehyde (4), $\nu_{max.}$ 3 250w (NH) and 1 685 cm^{-1} (CHO), τ −0.5 (s, CHO) and 6.00 (OMe), M^+ 253 (1 × Cl). Attempts to induce attack by an external nucleophile on the isothiocyanato-group of (3) led to complex mixtures which were not further investigated.

Some Reactions of 7-Chloro-1,2-dihydro-4-methoxy-2-thioxoquinoline-3-carbaldehyde (4).—This intermediate, formed in 73% yield, appeared to be most useful for the development of new heterocycles since it has a formyl group conveniently situated between two substituents suitable (the thioxo-group at C-2 could be transformed into alkylthio or alkylsulphonyl) for nucleophilic replacement. This expectation, to a large extent, has been borne out.

Reduction of the formylquinoline (4) (as the sodium salt) with sodium borohydride in methanol gave the corresponding alcohol (5).

Alkylation of the sodium salt of the thioxoquinoline (4) in dimethylformamide (DMF) with methyl iodide, ethyl iodide, or benzyl chloride gave the alkylthio-derivatives [(6)—(8), respectively]. Reaction of the sodium salt of (4) in DMF with an excess of 1,2-dibromoethane gave the cyclised derivative (9). Acidic hydrolysis of the methoxyquinolines (6) and (7) gave the 1,4-dihydro-4-oxoquinolines (10) and (11). An alternative approach to the corresponding 3-carboxylate esters and a 2-thioxo-derivative has been described by Kay [3] and Junek,[4] respectively. During an unsuccessful attempt to alkylate the sodium salt of (4) with cyclohexyl bromide it was found that refluxing the sodium salt of (4) alone in DMF caused a rearrangement to the sodium salt of (10). This reaction may well be an example of intermolecular dealkylation (*cf.* demethylation of aryl methyl ethers by sodium ethanethiolate) [5] rather than intramolecular *O* ⟶ *S*-alkyl migration. Other alkylation reactions with methyl chloroacetate, chloroacetamide, and chloroacetone yielded the thienoquinolines (12)—(14) respectively. The i.r. spectrum of the methoxythienoquinoline ester (12) no longer showed NH (3 250 cm^{-1}) and aldehyde carbonyl (1 685 cm^{-1}) absorptions but exhibited an ester carbonyl band at 1 725 cm^{-1}. The n.m.r. spectrum showed loss of the aldehyde proton and appearance of the 3-proton signal as a singlet at τ 1.63. Two three-proton singlets at τ 5.48 and 5.99 were assigned to 4-OMe and 2-CO_2Me, respectively, by comparison of the chemical shift of 2-CO_2Me with those of 2-CO_2Me in the 4,7-unsubstituted ester (15) [6] (τ 6.05) and the 4-hydrazino-ester (40) (Scheme 3) (τ 6.16).

Reaction of the formylquinoline (4) with hydrazine gave the pyrazoloquinoline (16). The i.r. spectrum showed loss of the aldehyde function and the n.m.r. spectrum showed the loss of the methoxy-group with the 3-proton signal present as a singlet at τ 1.54. The product was not obtained analytically pure but was converted into a pure methoxycarbonylmethylthio-derivative (17) by reaction with methanolic sodium methoxide and methyl chloroacetate. A similar attempt to form an ethylthio-derivative by reaction with ethyl iodide and ethanolic sodium ethoxide was unsuccessful, a deep blue solution being formed. Similar reactions of (4) with acetamidine and guanidine gave the pyrimidoquinolines (18) and (19), respectively. (Some derivatives of this ring system have been investigated by Mamaev and Kim,[7] using alternative synthetic procedures.) Compounds (18) and (19) were difficult to purify, but they were identified conclusively by conversion into the

[1] R. Hull, P. J. van den Broek, and M. L. Swain, *J.C.S. Perkin I*, 1975, 922.
[2] N. D. Heindel and S. A. Fine, *J. Heterocyclic Chem.*, 1969, **6**, 961.
[3] I. T. Kay and P. J. Taylor, *J. Chem. Soc.* (*C*), 1968, 2656.
[4] H. Junek, A. Metallidis, and E. Ziegler, *Org. Prep. and Procedures*, 1970, **2**, 161.
[5] G. I. Feutrill and R. N. Mirrington, *Tetrahedron Letters*, 1970, 1327.
[6] R. Hull, *J.C.S. Perkin I*, 1973, 2911.
[7] V. P. Mamaev and A. M. Kim, *Khim. geterotsikl. Soedinenii*, 1966, 266 (*Chem. Abs.*, 1966, **65**, 710d).

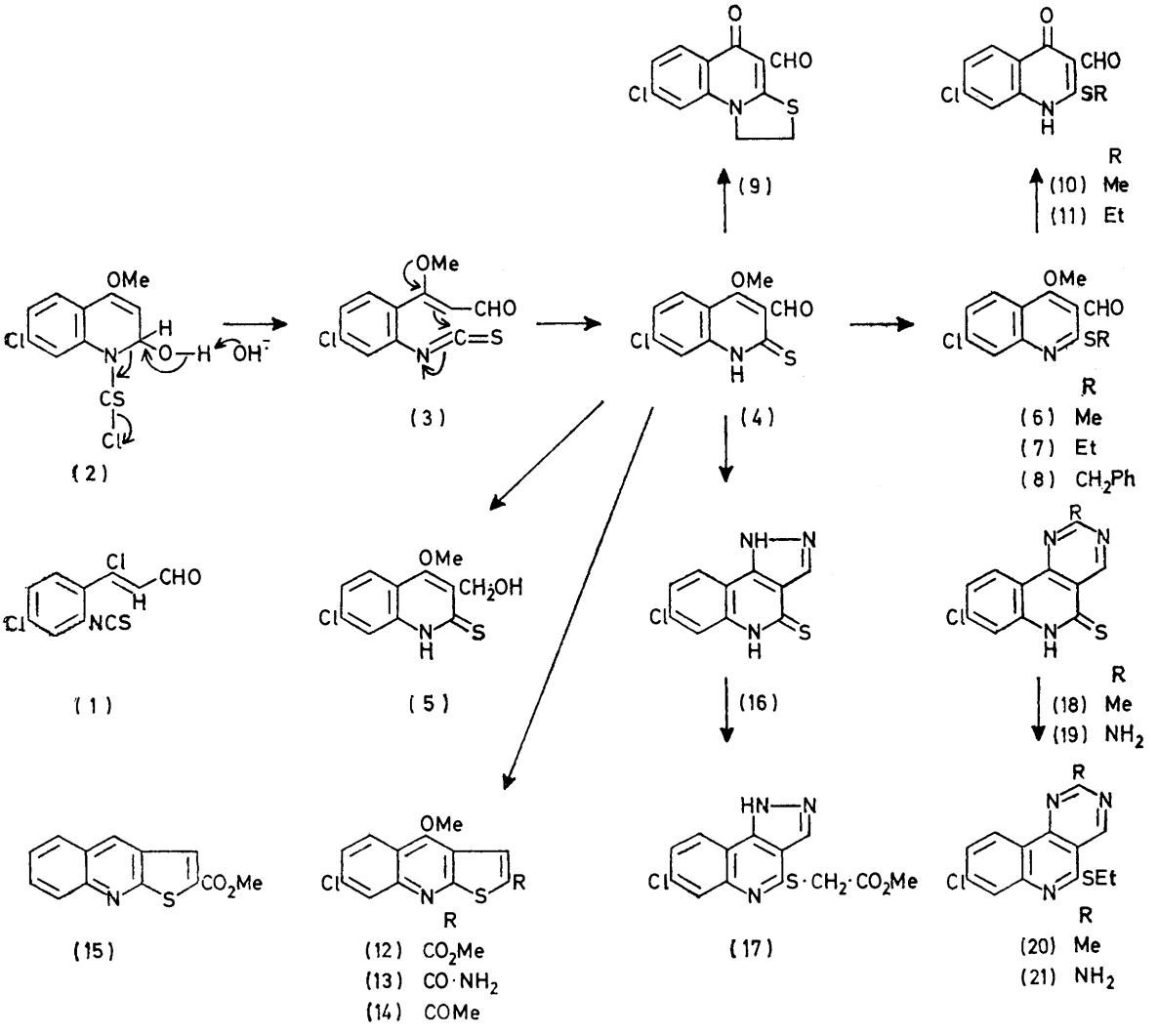
ethylthio-derivatives (20) and (21), respectively. Identical compounds were obtained by reactions of the ethylthio-derivative (7) in like manner with acetamidine and guanidine, respectively.

Some Reactions of 7-Chloro-2-ethylthio-4-methoxyquinoline-3-carbaldehyde (7).—Reduction of the quinolinecarbaldehyde (7) with sodium borohydride gave the corresponding alcohol (22). Reaction of (7) with hydroxylamine gave the oxime (23) without replacement of the 4-methoxy-group; this is surprising in view of its very ready displacement by other nucleophiles (see above). In contrast, treatment of the thioxoquinoline (4) with hydroxylamine gave a complex mixture, possibly owing to replacement of the methoxy-group. The oxime (23) gave a mixture of the expected nitrile (24), $\nu_{max.}$ 2 200 cm^{-1} (CN), and the novel isothiazoloquinoline (25), τ 0.65 (1 H, s, 3-H) and 5.39 (3 H, s, OMe), on treatment with acetic anhydride in acetic acid.

The i.r. spectrum of the isothiazoloquinoline (25) showed no functional group absorptions. The mass spectrum showed the molecular ion at *m/e* 250, from which it was deduced that the product was the isothiazoloquinoline rather than an isoxazoloquinoline, a conclusion confirmed by the analytical figures. The alternative formulation of the product as a thiazoloquinoline (26), which might arise by Beckmann rearrangement of the oxime (23) with subsequent ring closure, was rejected on the basis of evidence provided by treatment of the product with sodium methoxide. Scission of the isothiazole ring occurred to give a yellow solution of the anion (27), which upon treatment with ethyl iodide gave the cyanoquinoline (24), identical with the material previously prepared.

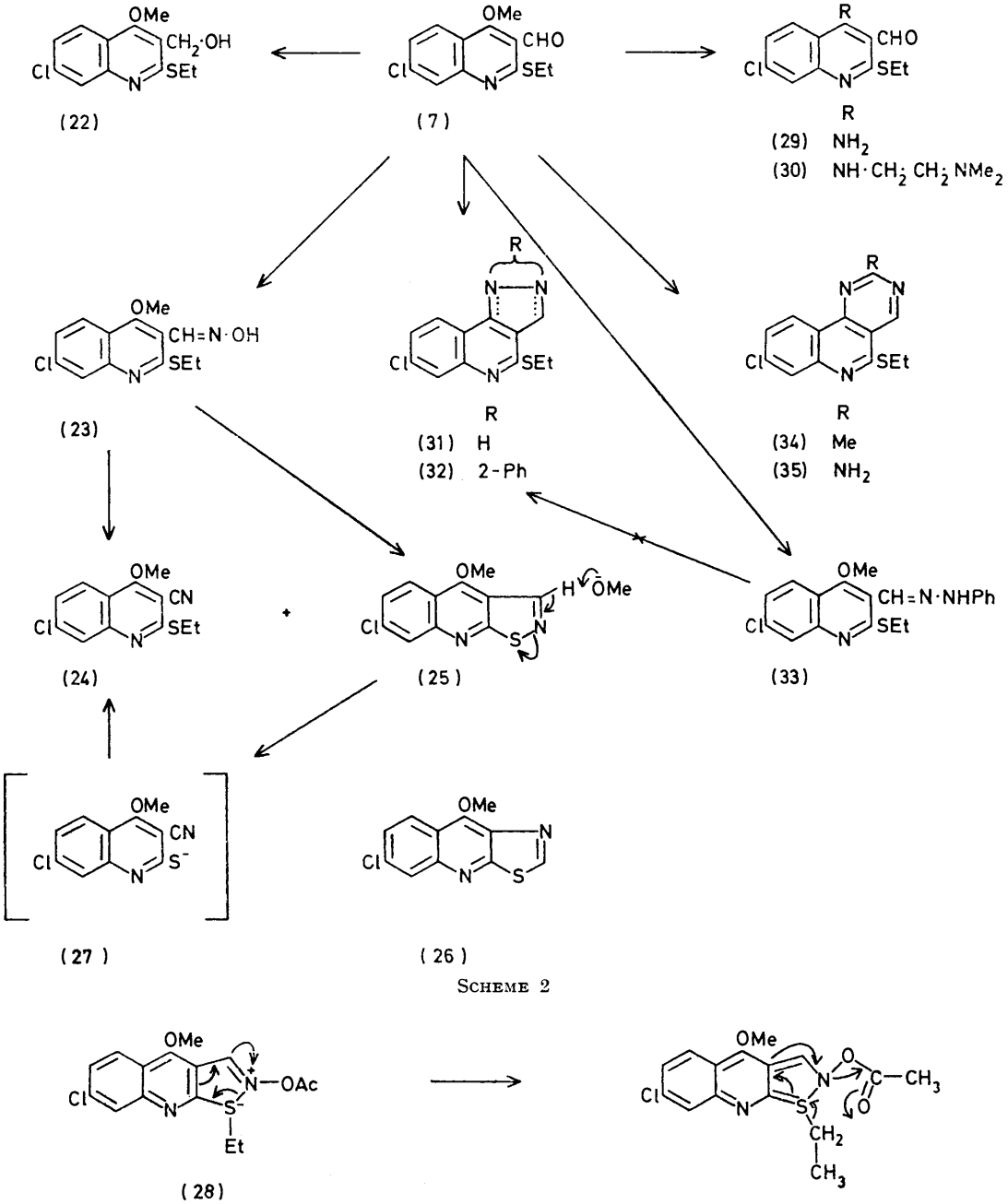
The conversion of the oxime (23) into the isothiazoloquinoline (25) may well take place *via* the oxime acetate dipolar complex (28).

The 4-methoxy-group in (7) was readily displaced by amines. Aqueous ammonia in tetrahydrofuran (THF)



SCHEME 1

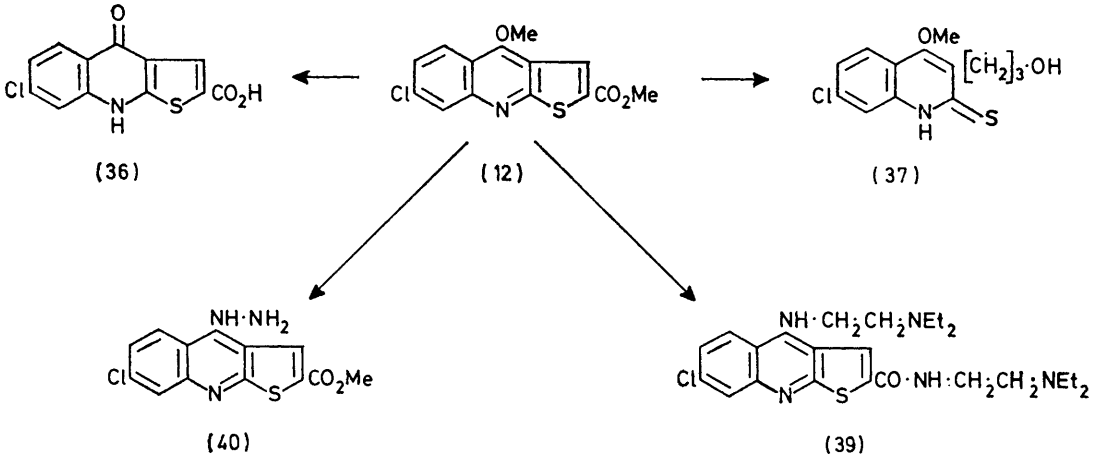
at room temperature gave the aminoquinoline (29), $\nu_{max.}$ 3 400, 3 300, and 3 200 (NH) and 1 640 cm^{-1} (CHO), τ −0.22 (1 H, s, CHO), 6.7 (4 H, brs + q, NH_2 and SCH_2), and 8.67 (3 H, t, Me or SEt); there was no methoxy-signal. The quinoline (30) was prepared similarly from 2-dimethylaminoethylamine. Nucleophilic displacement of the methoxy-group of (7) with ring formation took place with hydrazine to give the pyrazoloquinoline (31). [Examples of 1*H*- (ref. 8) and 2*H*- (ref. 9) pyrazolo[4,3-*c*]quinolines have already been described.] Phenylhydrazine reacted with (7) to give either of two compounds, according to the reaction conditions. Thus addition of an excess of phenylhydrazine in one portion to a refluxing ethanolic solution of the aldehyde (7) gave the pyrazoloquinoline (32) as the major product. The i.r. spectrum showed no NH or carbonyl absorptions. The n.m.r. spectrum showed no aldehyde or methoxy-signals, but a 3-H signal was present as a singlet at τ 1.66 and the ethylthio-group was was retained. The 2 and 1-phenyl derivatives could arise by initial attack by phenylhydrazine on the



SCHEME 2

[8] A. Musierowski, S. Niementowski, and Z. Tomasik, *Roczniki Chem.*, 1928, **8**, 325 (*Chem. Abs.*, 1929, **23**, 1900).
[9] L. Knorr and F. Jodicke, *Chem. Ber.*, 1885, **18**, 2256.

methoxy- or the formyl group, respectively, of (7). Evidence in support of the structure of the 2-phenyl isomer was provided by the failure of the phenylhydrazone (33) (see later) to undergo thermal cyclisation to a 1-phenylpyrazoloquinoline under the prevailing reaction conditions, presumably because of steric hindrance. Dropwise addition of 1 equiv. of phenylhydrazine to a refluxing solution of (7) in ethanol, especially in the presence of acetic acid, gave mainly the phenylhydrazone (33), $\nu_{max.}$ 3 300 cm^{-1} (NH). The n.m.r. spectrum showed a multiplet for the aromatic protons which obscured the CH=N·NH signals, and (CONH), the n.m.r. spectrum of which showed the loss of both methoxy-signals and the presence of two non-equivalent 2-diethylaminoethylamino-groups. Addition of hydrazine to a refluxing solution of (12) in benzene–ethanol gave the hydrazino-derivative (40) in which the ester group remained intact. The i.r. spectrum showed a strong absorption at 1 705 cm^{-1}, characteristic of an aromatic ester rather than a hydrazide. The n.m.r. spectrum showed a methoxy-signal at τ 6.16, the chemical shift of which may be compared with those of the ester methoxy-group (τ 5.99) and 4-methoxy-group (τ 5.48) in the ester (12).



SCHEME 3

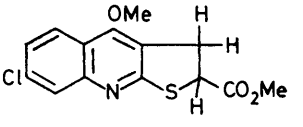
resonances at τ 6.28 (s, OMe), 6.66 (q, S·CH_2·CH_3), and 8.56 (t, S·CH_2·CH_3). The product was unchanged after refluxing in alcohol, alone or in the presence of phenylhydrazine, for 3 days. Slight decomposition occurred on refluxing the compound in *NN*-dimethylacetamide for 24 h.

The quinoline (7) reacted with acetamidine and guanidine to give the pyrimidoquinolines (34) and (35), respectively.

Some Reactions of Methyl 7-Chloro-4-methoxythieno-[2,3-b]*quinoline-2-carboxylate* (12).—Hydrolysis of the ester (12) with 5N-hydrochloric acid gave the thienoquinoline acid (36). Reduction of (12) with lithium aluminium hydride caused fission of the thiophen ring to give the hydroxypropylquinoline (37). This yellow alkali-soluble product gave a n.m.r. spectrum having no signal corresponding to the 3-H of a thienoquinoline, but showing two-proton multiplets at τ 6.48, 7.57, and 8.23 ($[CH_2]_3$). The mass spectrum showed ions at *m/e* 283 (M^+), 252 [$(M - CH_2OH)^+$], 238 [$(M - CH_2·CH_2·OH)^+$], and 224 {$(M - [CH_2]_3·OH)^+$}. In addition, very weak impurity peaks were observed at *m/e* 297 (M^+) and 266 [$(M - MeO)^+$], probably arising from the dihydrothienoquinoline ester (38).

The 4-methoxy-group of (12) underwent ready nucleophilic displacement; for example, 2-diethylaminoethylamine gave the amino-amide (39), $\nu_{max.}$ 1 650 cm^{-1}

Some Reactions of 4-Amino-7-chloro-2-ethylthioquinoline-3-carbaldehyde (29).—Reduction of the aminoquinoline (29) with sodium borohydride gave the alcohol (41). Ready condensation and ring closure took place when acetone or malononitrile reacted with the aminoquinoline (29) in the presence of sodium hydroxide,

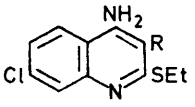


(38)

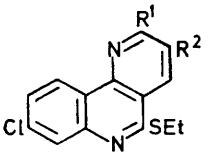
to yield the pyridoquinolines (42) and (43), respectively. The i.r. spectrum of the pyridoquinoline (42) showed no NH or CHO absorption. In confirmation of the tricyclic structure the n.m.r. spectrum showed the 4-H signal as a doublet (J 9 Hz) at τ 1.19 coupled to the 3-H signal (d, J 9 Hz) at τ 2.74. The 2-methyl signal appeared as a singlet at τ 7.24. The i.r. spectrum of (38) showed absorptions at $\nu_{max.}$ 3 350, 3 300, and 3 200 (NH) and 2 230 cm^{-1} (CN).

Preparation and Chemistry of Some Ethyl Sulphones (*Scheme* 4).—The ethylthio-derivatives (7), (31), (32), and (42) underwent oxidation to the corresponding sulphones (44)—(47) with potassium permanganate in

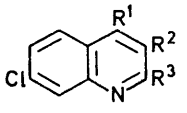
acetone and acetic acid. The pyrimidoquinoline (20) did not yield the sulphone (48) under similar conditions. The sulphones were generally characterised by strong i.r. bands at *ca.* 1 310 and 1 130 cm^{-1} (SO_2), strong peaks in the mass spectra arising from the ions $(M - SO_2C_2H_4)^+$ and $(M - SO_2C_2H_5)^+$, and downfield shifts of the ethyl group resonances in the n.m.r. spectra. The oxidation of the ethylthio-group in (7) in preference to the aldehyde (46) was displaced by morpholine to give (49). Nucleophilic displacement of the ethylsulphonyl group in the pyridoquinoline (47) with 3-dimethylaminopropylamine gave the tricyclic basic side-chain compound (50). Under similar conditions no reaction took place between the corresponding ethylthio-derivatives (32) and (42) and diamines. Treatment of the methoxyquinoline (44) with ammonia in THF gave the amino-derivative (51) in



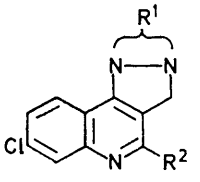
	R
(29)	CHO
(41)	CH_2OH



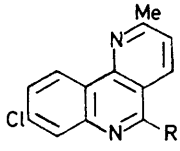
	R^1	R^2
(42)	Me	H
(43)	NH_2	CN



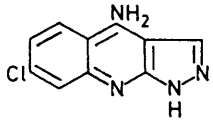
	R^1	R^2	R^3
(7)	OMe	CHO	SEt
(44)	OMe	CHO	SO_2Et
(51)	NH_2	CHO	SO_2Et
(52)	NH_2	CH:N·NH_2	SO_2Et



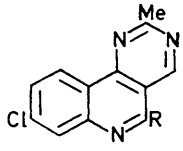
	R^1	R^2
(31)	H	SEt
(32)	2-Ph	SEt
(45)	H	SO_2Et
(46)	2-Ph	SO_2Et
(49)	2-Ph	



	R
(42)	SEt
(47)	SO_2Et
(50)	$NH[CH_2]_3 \cdot NMe_2$



(53)



	R
(20)	SEt
(48)	SO_2Et

SCHEME 4

group is perhaps surprising. The sulphone (44) was obtained in moderate yield after purification by chromatography; $\nu_{max.}$ 1 695 (CHO) and 1 300 and 1 130 cm^{-1} (SO_2), τ −0.95 (1 H, s, CHO), 5.78 (3 H, s, OMe), 6.18 (2 H, q, $SO_2 \cdot CH_2 \cdot CH_3$), and 8.47 (3 H, t, $SO_2 \cdot CH_2 \cdot CH_3$). The molecular ion in the mass spectrum was not observed but the ions $(M - Et)^+$ and $(M - SO_2Et)^+$ gave the correct mass measurement.

The ethylsulphonyl group of the pyrazoloquinoline which the methoxy-group had been replaced in preference to the ethylsulphonyl group; $\nu_{max.}$ 3 400, 3 250, and 3 200 (NH), 1 660 (CHO), and 1 290 and 1 120 cm^{-1} (SO_2), τ −0.79 (1 H, s, CHO), 6.16 (2 H, q, $SO_2 \cdot CH_2 \cdot CH_3$), and 8.52 (3 H, t, $SO_2 \cdot CH_2 \cdot CH_3$). The aminoquinoline (51) formed a hydrazone (52) which did not cyclise to the pyrazoloquinoline (53) on refluxing in ethanol.

The ready displacement of the 4-methoxy-group by amines in preference to either a 2-ethylthio [in, for

example, (7)] or a 2-ethylsulphonyl group [in, for example, (44)] has been consistently observed throughout this work. The effect is thought to be due to stabilisation of the intermediate (54) by participation of the 3-formyl group when nucleophilic attack occurs at the 4-position. Similar stabilisation by the 3-formyl group without invoking an *ortho*-quinonoid structure is not possible if the nucleophile attacks the 2-position.

EXPERIMENTAL

For general methods see ref. 1.

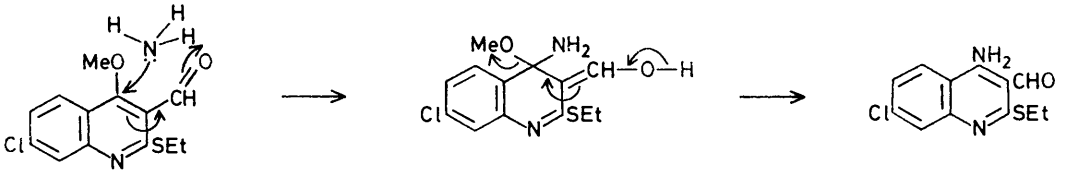
4-Chloro-2-isothiocyanato-β-methoxycinnamaldehyde (3).—Thiophosgene (38.5 ml) in methylene chloride (250 ml) was added dropwise over ½ h to a vigorously stirred suspension of 7-chloro-4-methoxyquinoline (97 g) and barium carbonate (100 g) in methylene chloride (500 ml) and water (500 ml) at 0 °C. The mixture was stirred for 2 h at 0 °C then for 1 h at room temperature and filtered through a pad of Supercel. The methylene chloride layer was separated from the filtrate, washed with water, dried ($MgSO_4$), and filtered to give a solution of the crude cinnamaldehyde, $\nu_{max.}$ (CH_2Cl_2) 2 100br (NCS) and 1 670 cm^{-1} (αβ-unsat. CO).

7-Chloro-1,2-dihydro-4-methoxy-2-thioxoquinoline-3-carbaldehyde (4).—The solution of 4-chloro-2-isothiocyanato-β-methoxycinnamaldehyde in methylene chloride slowly deposited a yellow crystalline solid, which was collected at intervals over several days. Alternatively the methylene chloride was progressively replaced with benzene or toluene and the solution was refluxed. The yellow precipitate formed was collected at intervals, washed with methylene chloride, and dried to give the crude *thioxodihydroquinoline* (92 g, 73%), which crystallised from acetonitrile as yellow needles, darkening at 200°, m.p. 300° (Found: C, 52.4; H, 3.3; N, 5.4. $C_{11}H_8ClNO_2S$ requires C, 52.2; H, 3.2; N, 5.5%), $\nu_{max.}$ (Nujol) 3 200—3 000w,br (NH) and 1 685 cm^{-1} (CHO), τ [$(CD_3)_2SO$] −3.6br (1 H, s, NH), −0.5 (1 H, s, CHO), 2.00 (1 H, d, *J* 9 Hz, 5-H), 2.37 (1 H, d, *J* 3 Hz, 8-H), 2.59 (1 H, dd, *J* 9 and 3 Hz, 6-H), and 6.00 (3 H, s, MeO), *m/e* 253 (1 × Cl) (M^+).

7-Chloro-3-hydroxymethyl-4-methoxyquinoline-2(1H)-thione (5).—The aldehyde (4) (6.3 g) was dissolved in a solution of sodium methoxide [from sodium (0.8 g) and methanol (100 ml)] and the solution was filtered. Sodium borohydride (1.0 g) was added to the stirred filtrate at room temperature. After ½ h the mixture was diluted with water (100 ml) and acidified with dilute hydrochloric acid. The precipitate formed was collected and crystallised from ethanol to give the *alcohol* (5.4 g) as yellow needles, m.p. >360° (Found: C, 52.0; H, 3.9; N, 5.2. $C_{11}H_{10}ClNO_2S$ requires C, 51.7; H, 3.9; N, 5.5%), $\nu_{max.}$ (Nujol) 3 350w,br (OH) and 3 050w,br cm^{-1} (NH), τ [$(CD_3)_2SO$] 2.0—2.8 (3 H, m, 5-, 8-, and 6-H), 5.22 (2 H, s, CH_2O), and 5.96 (3H, s, OMe).

Sodium Salt of the Thione (4).—The thione (4) (5 g) was suspended in DMF (20 ml) and treated with sodium methoxide solution [from sodium (0.5 g) and methanol (5 ml)]. The deep red solution was filtered. The sodium salt was also prepared, less conveniently, by stirring the thione with sodium hydride (1 equiv.; 50% oil dispersion) in DMF until dissolution had occurred.

2-Alkylthio-7-chloro-4-methoxyquinoline-3-carbaldehydes (6)—(8).—The solution of the sodium salt of (4) in DMF was treated with methyl iodide, ethyl iodide, or benzyl chloride (1 equiv.), with cooling if required to prevent loss of volatile reagent. After stirring for 1 h at room temperature the mixture was diluted with water, and the precipitate collected, washed with water, and dried.



(54)

Crystallisation gave the *2-alkylthioquinolines* (6) (67%), needles, m.p. 178—179° (from ethanol) (Found: C, 53.6; H, 3.8; N, 5.0. $C_{12}H_{10}ClNO_2S$ requires C, 53.8; H, 3.7; N, 5.2%), $\nu_{max.}$ (Nujol) 1 680 cm^{-1} (CHO); (7) (84%), cream needles, m.p. 115—116° (from cyclohexane) (Found: C, 55.4; H, 4.5; N, 5.1. $C_{13}H_{12}ClNO_2S$ requires C, 55.4; H, 4.3; N, 5.0%), $\nu_{max.}$ (Nujol) 1 680 cm^{-1} (CHO), τ ($CDCl_3$) −1.03 (1 H, s, CHO), 1.9—2.7 (3 H, m, ArH, 1,2,4-substituted benzene), 5.87 (3 H, s, MeO), 6.73 (2 H, q, *J* 7 Hz, EtS), and 8.60 (3 H, t, *J* 7 Hz, EtS); and (8) (62%), cream needles, m.p. 144—146° (from ethanol) (Found: C, 63.4; H, 4.2; N, 4.1. $C_{18}H_{14}ClNO_2S$ requires C, 62.9; H, 4.1; N, 4.1%), $\nu_{max.}$ (Nujol) 1 675 cm^{-1}.

8-Chloro-5-oxo-1,2-dihydro-5H-thiazolo[3,2-a]quinoline-4-carbaldehyde (9).—The solution of the sodium salt of (4) in DMF was heated with 1,2-dibromoethane (5 equiv.) at 90 °C for 18 h. The mixture was diluted with water and the precipitate collected, washed with water, and dried. Crystallisation of the product (48%) from DMF gave the *thiazoloquinoline* as cream needles, m.p. 323—325° (Found: C, 54.2; H, 3.1; N, 5.4. $C_{12}H_8ClNO_2S$ requires C, 54.2; H, 3.0; N, 5.3%), $\nu_{max.}$ (Nujol) 1 680w, 1 660, 1 625, and 1 600 cm^{-1}, τ ($CDCl_3$) −0.1 (1 H, s, CHO), 1.50 (1 H, d, *J* 9 Hz, 6-H), 2.30 (2 H, m, 7- and 9-H), 4.80 (2 H, t, *J* 8 Hz, CH_2), and 5.97 (2 H, t, *J* 8 Hz, CH_2), *m/e* 265w (1 × Cl) (M^+), 237s (1 × Cl) [$(M - 28)^+$], 209 (1 × Cl) [$(237 - 28)^+$], and 132.5w (M^{2+}).

2-Alkylthio-7-chloro-4-oxo-1,4-dihydroquinoline-3-carbaldehydes (10) *and* (11).—The 2-alkylthio-7-chloro-4-methoxyquinoline-3-carbaldehyde (10 g) was refluxed with 5N-hydrochloric acid (20 ml) in THF (70 ml) for ½ h. The precipitate formed was collected, reprecipitated from aqueous 2N-sodium hydroxide with dilute hydrochloric acid, and dissolved in hot DMF (250 ml). The filtered solution was diluted with hot ethanol and cooled to give the *4-oxo-1,4-dihydroquinoline* (10) (88%), needles, m.p. 266—267° (Found: C, 51.9; H, 3.2; N, 5.8. $C_{11}H_8ClNO_2S$ requires C, 52.1; H, 3.2; N, 5.5%), $\nu_{max.}$ (Nujol) 3 200—

3 000, 1 660, and 1 610 cm^{-1}; or (11) (74%), needles, m.p. 192—193° (Found: C, 54.0; H, 3.6; N, 5.4. $C_{12}H_{10}ClNO_2S$ requires C, 53.8; H, 3.7; N, 5.2%), $\nu_{max.}$ (Nujol) 3 250 and 1 620 cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 1.44 (1 H, d, *J* 9 Hz, 5-H), 1.84 (1 H, d, *J* 2 Hz, 8-H), 2.12 (1 H, dd, *J* 2 and 9 Hz, 6-H), 6.33 (2 H, q, SEt), and 8.35 (3 H, t, SEt).

Rearrangement of the Sodium Salt of the Thione (4).—The solution of the sodium salt in DMF (prepared from sodium methoxide or sodium hydride) was refluxed for 2 h, cooled, and diluted with water. The solution was filtered (carbon) and the filtrate was acidified with dilute hydrochloric acid. The precipitate formed was collected and crystallised from DMF–ethanol (1 : 1) to give 7-chloro-2-methylthio-4-oxo-1,4-dihydroquinoline-3-carbaldehyde (10) (68%), as needles, m.p. 266—267°, identical (i.r. spectrum and t.l.c.) with the product previously prepared.

Methyl 7-Chloro-4-methoxythieno[2,3-b]*quinoline-2-carboxylate* (12).—A solution of sodium methoxide [from sodium (3.0 g) and methanol (50 ml)] was added to crude 7-chloro-4-methoxy-2-thioxo-1,2-dihydroquinoline-3-carbaldehyde (25 g) suspended in DMF (200 ml). The deep red solution was filtered, and stirred during the addition of methyl chloroacetate (20 ml) in one portion. After the initial exothermic reaction the solution was heated on a steam-bath for 3 h, then cooled and diluted with water (300 ml). The pale pink precipitate (27.3 g, 88%) was collected, washed with water, dried, and crystallised from methyl acetate or benzene to give the *thienoquinoline ester* as fine needles, m.p. 210—211° (Found: C, 55.1; H, 3.1; N, 4.4. $C_{14}H_{10}ClNO_3S$ requires C, 54.6; H, 3.3; N, 4.6%), $\nu_{max.}$ (Nujol) 1 725 cm^{-1} (CO), τ ($CDCl_3$) 1.63 (1 H, s, 3-H), 1.74 (1 H, d, *J* 9 Hz, 5-H), 1.98 (1 H, d, *J* 2 Hz, 8-H), 2.59 (1 H, dd, *J* 9 and 2 Hz, 6-H), 5.48 (3 H, s, 4-OMe), and 5.99 (3 H, s, 2-CO_2Me). Similarly were prepared: from chloroacetone, 2-*acetyl*-7-*chloro*-4-*methoxythieno*[2,3-b]*quinoline* (14) as yellow needles, m.p. 198—199° (decomp.) (from benzene) (Found: C, 57.8; H, 3.6; N, 4.8. $C_{14}H_{10}ClNO_2S$ requires C, 57.6; H, 3.4; N, 4.8%), $\nu_{max.}$ (Nujol) 1 660 cm^{-1} (C=O), τ ($AcNMe_2$) 1.25 (1 H, s, 3-H), 1.69 (1 H, d, *J* 9 Hz, 5-H), 2.08 (1 H, d, *J* 2 Hz, 8-H), 2.45 (1 H, dd, *J* 9 and 2 Hz, 6-H), and 5.32 (3 H, s, OMe) (Ac resonance obscured by solvent); and, from chloroacetamide, 7-*chloro*-4-*methoxythieno*[2,3-b]*quinoline*-3-*carboxamide* (13) as yellow needles, m.p. 360° (darkens *ca.* 280°) (from dimethylformamide) (Found: C, 53.2; H, 3.6; N, 9.0. $C_{13}H_9ClN_2O_2S$ requires C, 53.3; H, 3.1; N, 9.5%), $\nu_{max.}$ (Nujol) 3 300br (NH) and 1 650br cm^{-1} (CO), τ [$(CD_3)_2SO$] 1.46 (1 H, s, 3-H), 1.74 (1 H, d, *J* 9 Hz, 5-H), 2.06 (1 H, d, *J* 2 Hz, 8-H), 2.50 (1 H, dd, *J* 9 and 2 Hz, 6-H), and 5.50 (3 H, s, OMe).

2-*Amino*-8-*chloropyrimido*[5,4-c]*quinoline*-5(6H)-*thione* (19).— 7-Chloro-4-methoxy-2-thioxo-1,2-dihydroquinoline-3-carbaldehyde (2.5 g, 10 mmol) was dissolved in a solution of sodium methoxide [from sodium (0.23 g, 10 mmol) and methanol (60 ml)]. A solution of guanidine [from guanidine hydrochloride (2.9 g, 30 mmol)] and sodium methoxide [from sodium (0.7 g, 30 mmol) in methanol (30 ml)] was added in portions to the refluxing solution during 24 h. Dilution of the solution with water and acidification with acetic acid gave a yellow precipitate, which was purified by reprecipitation from alkaline solution, giving the pyrimidoquinoline as an amorphous yellow powder, m.p. 300°, $\nu_{max.}$ (Nujol) 3 450, 3 300, and 3 100 cm^{-1} (NH), τ [$(CD_3)_2SO$] 0.40 (1 H, s, 4-H), 1.55 (1 H, d, *J* 9 Hz, 10-H), 2.32 (1 H, d, *J* 2 Hz, 7-H), and 2.60 (1 H, dd, *J* 9 and 2 Hz, 9-H), *m/e* 262 (M^+). The product was not obtained analytically pure but upon treatment with methanolic sodium methoxide and ethyl iodide gave 2-amino-8-chloro-5-ethylthiopyrimido[5,4-*c*]quinoline (21), identical with that subsequently prepared [≡ (35)]. Similarly prepared, from acetamidine, was 8-*chloro*-2-*methylpyrimido*[5,4-c]*quinoline*-5(6H)-*thione* (18), as a yellow powder, m.p. 300°, τ [$(CD_3)_2SO$] 0.30 (1 H, s, 4-H), 1.60 (1 H, d, *J* 9 Hz, 10-H), 2.45 (1 H, d, *J* 2 Hz, 7-H), 2.62 (1 H, dd, *J* 9 and 2 Hz, 9-H), and 7.25 (3 H, s, Me), *m/e* 261 (M^+). The product was converted into 8-chloro-5-ethylthio-2-methylpyrimido-[5,4-*c*]quinoline [(20) ≡ (34); see later]. Similarly prepared, from hydrazine, was 7-*chloro*-1H-*pyrazolo*[4,3-c]-*quinoline*-4(5H)-*thione* (16), as a cream powder, m.p. 300°, τ [$(CD_3)_2SO$] 1.54 (1 H, s, 3-H), 1.80 (1 H, d, *J* 9 Hz, 9-H), 2.24 (1 H, d, *J* 2 Hz, 6-H), and 2.62 (1 H, dd, *J* 9 and 2 Hz, 8-H), *m/e* 235 (M^+). This product reacted with methanolic sodium methoxide and methyl chloroacetate to give *methyl* (7-*chloro*-1H-*pyrazolo*[4,3-c]*quinolin*-4-*ylthio*)*acetate* (17) as a white amorphous solid, m.p. 180—181° (Found: C, 51.0; H, 3.3; N, 13.5. $C_{13}H_{10}ClN_3O_2S$ requires C, 50.8; H, 3.3; N, 13.7%), $\nu_{max.}$ (Nujol) 3 300 (NH) and 1 710 cm^{-1} (ester C=O), τ [$(CD_3)_2SO$] 1.67 (2 H, s + d, *J* 9 Hz, 3- and 9-H), 2.16 (1 H, d, *J* 2 Hz, 6-H), 2.39 (1 H, dd, *J* 9 and 2 Hz, 8-H), 5.68 (2 H, s, SCH_2), and 6.25 (3 H, s, CO_2Me), *m/e* 307 (M^+), 276 [$(M - OCH_3)^+$], 275 [$(M - MeOH)^+$], 248 [$(M - CO_2Me)^+$], 203 [$(M - SCH_2{\cdot}CO_2{\cdot}CH_2)^+$], and 202 [$(M - SCH_2{\cdot}CO_2{\cdot}CH_3)^+$].

(7-*Chloro*-2-*ethylthio*-4-*methoxyquinolin*-3-*yl*)*methanol* (22).—7-Chloro-2-ethylthio-4-methoxyquinoline-3-carbaldehyde (5.0 g) was refluxed with sodium borohydride (1.2 g) in ethanol (150 ml) for 2 h. Water was added to incipient crystallisation and the solution cooled. The crystalline product was collected and recrystallised from aqueous ethanol to give the *quinoline alcohol* (4.4 g) as needles, m.p. 90° (Found: C, 55.1; H, 5.1; N, 4.6. $C_{13}H_{14}ClNO_2S$ requires C, 55.0; H, 4.9; N, 4.9%), $\nu_{max.}$ (Nujol) 3 400br cm^{-1} (OH), τ ($CDCl_3$) 2.0—2.9 (3 H, m, ArH, 1,2,4-substituted benzene), 5.20 (2 H, s, CH_2O), 6.02 (3 H, s, OMe), 6.70 (2 H, q, SCH_2), and 8.60 (3 H, t, Me of SEt). Similarly was prepared (4-*amino*-7-*chloro*-2-*ethylthioquinolin*-3-*yl*)-*methanol* (41) (72%) as white needles, m.p. 168—170° (from aqueous ethanol) (Found: C, 53.8; H, 4.9; N, 10.0. $C_{12}H_{13}ClN_2OS$ requires C, 53.6; H, 4.8; N, 10.4%), $\nu_{max.}$ (Nujol) 3 500 (OH), and 3 300 and 3 200 cm^{-1} (NH_2).

7-*Chloro*-2-*ethylthio*-3-*hydroxyiminomethyl*-4-*methoxyquinoline* (23).—7-Chloro-2-ethylthio-4-methoxyquinoline-3-carbaldehyde (7.5 g) was refluxed with hydroxylammonium chloride (2.4 g) and fused sodium acetate (2.8 g) in ethanol (200 ml) for 3 h. The mixture was filtered and cooled. The pale pink needles, which separated from the filtrate were collected and recrystallised from ethanol (carbon) to give the *oxime* (5.6 g) as colourless needles, m.p. 153—154° (Found: C, 52.5; H, 4.6; N, 9.5. $C_{13}H_{13}ClN_2O_2S$ requires C, 52.8; H, 4.4; N, 9.5%).

Dehydration of 7-*Chloro*-2-*ethylthio*-3-*hydroxyiminomethyl*-4-*methoxyquinoline* (23).—The oxime (5.6 g) was refluxed with acetic anhydride (5.8 g) in glacial acetic acid (90 ml) for 6 h. The solution was poured into water and neutralised, and the pink precipitate collected and dried. The product was chromatographed on silica (Merck); elution with benzene gave 7-*chloro*-2-*ethylthio*-4-*methoxyquinoline*-3-*carbonitrile* (24) (0.9 g) as needles, m.p. 147—148° (Found: C, 56.2; H, 4.4; N, 9.5. $C_{13}H_{11}ClN_2OS$ requires C, 56.1; H,

3.9; N, 10.0%), $\nu_{max.}$ (Nujol) 2 200w cm^{-1} (CN), τ ($CDCl_3$) 2.04 (1 H, d, *J* 9 Hz, 5-H), 2.22 (1 H, d, *J* 2 Hz, 8-H), 2.68 (1 H, dd, *J* 9 and 2 Hz, 6-H), 5.52 (3 H, s, OMe), 6.71 (2 H, q, *J* 7 Hz, SCH_2), and 8.58 (3 H, t, *J* 7 Hz, $S{\cdot}CH_2{\cdot}CH_3$), *m/e* 278 (1 × Cl) (M^+), 263 [$(M - CH_3)^+$], 250 [$(M - C_2H_4)^+$], 249 [$(M - C_2H_5)^+$], and 245 [$(M - HS)^+$] Elution with ethyl acetate gave *7-cloro-4-methoxyiso-. thiazolo*[5,4-b]*quinoline* (25) (0.7 g) as fine white needles, m.p. 162—163° (Found: C, 53.0; H, 3.1; N, 10.8. $C_{11}H_7ClN_2OS$ requires C, 52.8; H, 2.8; N, 11.2%), τ ($CDCl_3$) 0.65 (1 H, s, 3-H), 1.70 (1 H, d, *J* 9 Hz, 5-H), 2.00 (1 H, d, *J* 2 Hz, 8-H), 2.58 (1 H, dd, *J* 9 and 2 Hz, 6-H), and 5.39 (3 H, s, OMe), *m/e* 250 (1 × Cl) (M^+), 235 [$(M - CH_3)^+$], 207 [$(235 - CO)^+$], 180 [$(207 - HCN)^+$], and 145 [$(180 - Cl)^+$].

Ring Fission of 7-Chloro-4-methoxyisothiazolo[5,4-b]*quinoline* (25).—7-Chloro-4-methoxyisothiazolo[5,4-*b*]quinoline (*ca.* 20 mg) was refluxed with sodium methoxide (1 equiv.) in methanol (5 ml) for 10 min. Ethyl iodide (1 equiv.) was added to the yellow solution, which was then refluxed for 30 min. The then colourless solution was evaporated and the white residue was dissolved in water and ether. The ether layer was separated, dried, and evaporated to yield the slightly impure nitrile (24) as white needles, m.p. 140—144°, $\nu_{max.}$ ($CDCl_3$) 2 200 cm^{-1}, identified by comparison (i.r. spectra and t.l.c.) with the material previously prepared.

4-Amino-7-chloro-2-ethylthioquinoline-3-carbaldehyde (29). —7-Chloro-2-ethylthio-4-methoxyquinoline-3-carbaldehyde (11.0 g) in THF (150 ml) was stirred with aqueous ammonia (*d* 0.88; 10 ml) overnight. Evaporation, and crystallisation of the residue from ethanol gave the *aminoquinoline* (8.4 g) as white needles, m.p. 179—180° (Found: C, 53.7; H, 4.4; N, 10.5. $C_{12}H_{11}ClN_2OS$ requires C, 54.0; H, 4.1; N, 10.5%), $\nu_{max.}$ (Nujol) 3 400, 3 300, and 3 200 (NH), and 1 640 cm^{-1} (C=O), τ ($CDCl_3$) −0.22 (1 H, s, CHO), 1.65 (1 H, d, *J* 9 Hz, 5-H), 2.38 (1 H, d, *J* 2 Hz, 8-H), 2.59 (1 H, dd, *J* 9 and 2 Hz, 6-H), 6.7 (4 H, br,s and q, NH_2 and SCH_2), and 8.67 (3 H, t, Me of EtS), *m/e* 266 (M^+, $C_{12}H_{11}ClN_2OS$), 238 [$(M - CO)^+$], 237 [doublet; $(M - CHO)^+$, $C_{11}H_{10}ClN_2S$ and $(M - C_2H_5)^+$, $C_{10}H_6ClN_2OS$]. Similarly were prepared *7-chloro-4-(2-dimethylaminoethylamino)-2-ethylthioquinoline-3-carbaldehyde* (30) (20%) as cream needles, m.p. 121—123° (from cyclohexane) (Found: C, 56.5; H, 6.2; N, 12.4. $C_{16}H_{20}ClN_3OS$ requires C, 56.9; H, 5.9; N, 12.4%), τ ($CDCl_3$) −1.0br (1 H, s, NH), −0.3 (1 H, s, CHO), 2.0—3.0 (3 H, AMX pattern, 1,2,4-substituted benzene), 6.21 (2 H, 2 overlapping t, *J* 6 Hz, $N{\cdot}CH_2$), 6.77 (2 H, q, *J* 7 Hz, $S{\cdot}CH_2$), 7.42 (2 H, t, *J* 6 Hz, $CH_2{\cdot}N$), 7.70 (6 H, s, NMe_2), and 8.65 (3 H, t, *J* 7 Hz, Me of EtS); and *4-amino-7-chloro-2-ethylsulphonylquinoline-3-carbaldehyde* (51) (63%) as blades or needles, m.p. 222—223° (decomp.) (from ethanol) (Found: C, 48.8; H, 3.9; N, 8.9. $C_{12}H_{11}ClN_2O_3S$ requires C, 48.3; H, 3.7; N, 9.3%), $\nu_{max.}$ (Nujol) 3 400, 3 250, and 3 200 (NH_2), 1 660 (CHO), and 1 290 and 1 120 cm^{-1} (SO_2), τ [$(CD_3)_2SO$] −0.79 (1 H, s, CHO), 1.5—2.5 (3 H, AMX pattern, 1,2,4-substituted benzene), 6.16 (2 H, q, *J* 7 Hz, $SO_2{\cdot}CH_2$), and 8.52 (3 H, t, *J* 7 Hz, Me of $EtSO_2$); the *hydrazone* (52) was obtained as yellow prisms, m.p. 195—196° (decomp.) (from ethanol) (Found: C, 46.3; H, 4.2; N, 18.4. $C_{12}H_{13}ClN_4O_2S$ requires C, 46.1; H, 4.2; N, 17.9%), $\nu_{max.}$ (Nujol) 3 450, 3 300, and 3 150 (NH), and 1 295 and 1 125 cm^{-1} (SO_2), *m/e* 312 (M^+) and 219 [$(M - SO_2Et)^+$].

7-Chloro-4-ethylthio-2-phenylpyrazolo[4,3-c]*quinoline* (32). —Phenylhydrazine (7.0 g) in ethanol (50 ml) was added in one portion to a refluxing solution of 7-chloro-2-ethylthio-4-methoxyquinoline-3-carbaldehyde (7.0 g) in ethanol (200 ml). After 2 h the pale yellow needles which had separated were collected and crystallised from ethanol (carbon) to give the *pyrazoloquinoline* (6 g) as white needles, m.p. 158—159° (Found: C, 63.4; H, 4.1; N, 12.4. $C_{18}H_{14}ClN_3S$ requires C, 63.6; H, 4.1; N, 12.4%), $\lambda_{max.}$ (MeOH) 239, 281, 291, 328, and 342 nm (log ε 4.38, 4.65, 4.54, 4.22, and 4.01), τ ($CDCl_3$) 1.66 (2 H, s + d, *J* 9 Hz, 3- and 9-H), 2.0—2.8 (7 H, m, 6- and 8-H, Ph), 6.58 (2 H, q, *J* 7 Hz, SCH_2), and 8.54 (3 H, t, *J* 7 Hz, Me of SEt). Similarly prepared, from hydrazine hydrate, was *7-chloro-4-ethylthio-1H-pyrazolo*[4,3-c]*quinoline* (31) (91%) as cream prisms or needles, m.p. 238—239° (from ethanol) (Found: C, 54.6; H, 4.1; N, 16.1. $C_{12}H_{10}ClN_3S$ requires C, 54.8; H, 3.8; N, 16.1%), τ [$(CD_3)_2SO$] 1.70 (2 H, s + d, *J* 9 Hz, 3- and 9-H), 2.10 (1 H, d, *J* 2 Hz, 6-H), 2.42 (1 H, dd, *J* 9 and 2 Hz, 8-H), 6.61 (2 H, q, SCH_2), and 8.58 (3 H, t, Me), *m/e* 263 (1 × Cl) (M^+), $\lambda_{max.}$ (MeOH) 243, 256, 295, 318, and 333 nm (log ε 4.52, 4.64, 4.10, 3.69, and 3.54).

7-Chloro-2-ethylthio-4-methoxy-3-phenylhydrazonomethylquinoline (33).—Phenylhydrazine (4.4 g, 1 equiv.) in ethanol (50 ml) was added dropwise to a refluxing solution of 7-chloro-2-ethylthio-4-methoxyquinoline-3-carbaldehyde (11.2 g) in ethanol (200 ml) and acetic acid (5 ml). After 2 h the solution was concentrated and cooled. The yellow prisms which separated were collected and crystallised from ethanol giving the *phenylhydrazone* (3.4 g) as yellow needles, m.p. 131—133° (Found: C, 61.3; H, 5.0; N, 11.4. $C_{19}H_{18}ClN_3OS$ requires C, 61.4; H, 4.8; N, 11.3%), $\nu_{max.}$ ($CDCl_3$) 3 300w cm^{-1} (NH), τ ($CDCl_3$) 1.9—3.3 (10 H, m, ArH and $CH{=}N{\cdot}NH$), 6.28 (3 H, s, OMe), 6.66 (2 H, q, SCH_2), and 8.56 (3 H, t, Me of EtS). The product was unchanged after refluxing in ethanol, alone or in the presence of phenylhydrazine, for 3 days. Slight decomposition occurred (t.l.c.) when the product was refluxed in *NN*-dimethylacetamide for 24 h.

8-Chloro-5-ethylthio-2-methylpyrimido[5,4-c]*quinoline* (34). —7-Chloro-2-ethylthio-4-methoxyquinoline-3-carbaldehyde (5.6 g) in hot ethanol (100 ml) was treated with a solution of acetamidine [from acetamidine hydrochloride (7.5 g) and sodium (2.0 g) in ethanol (50 ml)] and then left to cool overnight. The crystals formed were collected and recrystallised from ethanol to give the *pyrimidoquinoline* (3.4 g) as needles, m.p. 149—150° (Found: C, 57.7; H, 4.1; N, 14.5. $C_{14}H_{12}ClN_3S$ requires C, 58.0; H, 4.1; N, 14.5%), τ ($CF_3{\cdot}CO_2H$) −0.27 (1 H, s, 4-H), 0.74 (1 H, d, *J* 9 Hz, 10-H), 1.58 (1 H, d, *J* 2 Hz, 7-H), 1.90 (1 H, dd, *J* 9 and 2 Hz, 9-H), 6.10 (2 H, q, *J* 7 Hz, SCH_2), 6.70 (3 H, s, 2-Me), and 8.28 (3 H, t, *J* 7 Hz, $SCH_2{\cdot}CH_3$), *m/e* 289 (1 × Cl) (M^+), 274 [$(M - CH_3)^+$], 261 [$(M - C_2H_4)^+$], and 256 [$(M - CH_3CN)^+$]. Similarly prepared, from guanidine, was *2-amino-8-chloro-5-ethylthiopyrimido*[5,4-c]*quinoline* (35) (4.8 g) as plates, m.p. 262—263° (from dimethylformamide) (Found: C, 53.4; H, 4.0; N, 19.6. $C_{13}H_{11}ClN_4S$ requires C, 53.5; H, 3.8; N, 19.2%), $\nu_{max.}$ (Nujol) 3 450 and 3 300 cm^{-1} (NH), τ ($CF_3{\cdot}CO_2H$) 0.10 (1 H, s, 4-H), 1.14 (1 H, d, *J* 9 Hz, 10-H), 1.84 (1 H, d, *J* 2 Hz, 7-H), 2.11 (1 H, dd, *J* 9 and 2 Hz, 9-H), 6.22 (2 H, q, SCH_2), and 8.35 (3 H, t, $SCH_2{\cdot}CH_3$), *m/e* 290 (1 × Cl) (M^+).

7-Chloro-4-oxo-4,9-dihydrothieno[2,3-b]*quinoline-2-carboxylic Acid* (36).—The ester (12) (1.0 g) was refluxed with 5N-hydrochloric acid (20 ml) for 16 h. The mixture was filtered and the residue washed with water.

Crystallisation from aqueous dimethylformamide gave the *thienoquinolone acid* as an amorphous powder, m.p. >360°, soluble in an excess of aqueous 2N-sodium hydroxide (Found: C, 51.3; H, 2.3; N, 4.9. $C_{12}H_6ClNO_3S$ requires C, 51.5; H, 2.1; N, 5.0%), $\nu_{max.}$ (Nujol) 3 100—2 880br (acidic OH) and 1 715—1 680br cm^{-1} (acid CO).

7-Chloro-3-(3-hydroxypropyl)-4-methoxyquinoline-2(1H)-thione (37).—The ester (12) (5.0 g) in dioxan (90 ml) was treated with lithium aluminium hydride (2.0 g) under nitrogen and refluxed for 3 h. The mixture was cooled and acetone (20 ml) added to decompose the excess of hydride. The mixture was shaken with dilute aqueous sodium hydroxide (200 ml) and filtered. The filtrate was extracted with chloroform, and the aqueous layer was separated and acidified with dilute hydrochloric acid. The yellow precipitate formed was extracted into chloroform. The extract was dried and concentrated to a yellow solid which was crystallised from benzene giving the *quinolinethione* (1.7 g) as fine yellow needles, m.p. 185—186° (Found: C, 55.4; H, 4.9; N, 4.6. $C_{13}H_{14}ClNO_2S$ requires C, 55.0; H, 4.9; N, 4.9%), $\nu_{max.}$ (Nujol) 3 200br cm^{-1} (NH,OH), τ [$(CD_3)_2SO$] 2.13 (1 H, d, *J* 9 Hz, 5-H), 2.28 (1 H, d, *J* 2 Hz, 8-H), 2.57 (1 H, dd, *J* 9 and 2 Hz, 6-H), 6.03 (3 H, s, MeO), 6.48 (2 H, t, CH_2), 7.57 (2 H, m, CH_2), and 8.23 (2 H, m, CH_2), *m/e* 284 [$(M + 1)^+$], 283 (M^+), 252 [$(M - CH_2OH)^+$], 250 [$(M - HS)^+$], 238 [$(M - CH_2{\cdot}CH_2{\cdot}OH)^+$], and 224 [$(M - CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}OH)^+$].

7-Chloro-4-(2-diethylaminoethylamino)-N(2)-(2-diethylaminoethyl)thieno[2,3-b]*quinoline-2-carboxamide* (39).—The ester (12) (5.0 g) in 2-diethylaminoethylamine (15 ml) was refluxed on an oil-bath at 140 °C for 22 h, then poured into water (100 ml). The precipitate was collected, dried, and crystallised from benzene–cyclohexane (1 : 5) to give the *substituted thienoquinoline* (4.9 g, 63%) as pale yellow needles, m.p. 174—175° (Found: C, 60.7; H, 7.4; N, 14.4. $C_{24}H_{34}ClN_5OS$ requires C, 60.6; H, 7.2; N, 14.7%), $\nu_{max.}$ (Nujol) 3 480 and 3 340 (NH), and 1 650 cm^{-1} (amide CO), τ ($CDCl_3$) 1.84 (1 H, s, 3-H), 2.0—2.8 (3 H, m, ArH, 1,2,4-substituted benzene), 6.4 (4 H, m, methylene H), 7.3 (12 H, m, methylene H), and 8.9 (12 H, 2t, Me), *m/e* 476 (1 × Cl) [$(M + 1)^+$], 389 (1 × Cl) [$(M - CH_2{\cdot}NEt_2)^+$], 376 (1 × Cl) [$(M - CH_2CH_2NEt_2)^+$], and 86vs [$(CH_2{=}NEt_2)^+$].

Methyl 7-Chloro-4-hydrazinothieno[2,3-b]*quinoline-2-carboxylate* (40).—The ester (12) (5.0 g) was refluxed with hydrazine hydrate (10 ml; 100%) in benzene (250 ml) and ethanol (100 ml) for ½ h. The square yellow flakes deposited were filtered from the hot mixture, washed with ethanol, and dried to give the *hydrazinoquinoline ester* (4.4 g), m.p. 259—260° (decomp.) (Found: C, 50.5; H, 3.3; N, 13.9. $C_{13}H_{10}ClN_3O_2S$ requires C, 50.7; H, 3.3; N, 13.7%), $\nu_{max.}$ (Nujol) 3 200w,br (NH) and 1 705 cm^{-1} (CO), τ [$(CD_3)_2SO$] 0.74 (1 H, s, 3-H), 1.67 (1 H, d, *J* 8 Hz, 5-H), 2.32 (1 H, d, *J* 2 Hz, 8-H), 2.71 (1 H, dd, *J* 8 and 2 Hz, 6-H), and 6.16 (3 H, s, CO_2Me), *m/e* 307 (1 × Cl) (M^+).

8-Chloro-5-ethylthio-2-methylpyrido[3,2-c]*quinoline* (42).—Aqueous 5N-sodium hydroxide (2 ml) was added to 4-amino-7-chloro-2-ethylthioquinoline-3-carbaldehyde (2.0 g) in ethanol (50 ml) and acetone (20 ml). The crystals which were slowly deposited were collected and recrystallised from ethanol to give the *pyridoquinoline* as needles, m.p. 125—126° (Found: C, 62.1; H, 4.6; N, 9.5. $C_{15}H_{13}ClN_2S$ requires C, 62.4; H, 4.5; N, 9.7%), τ ($CDCl_3$) 1.19 (1 H, d, *J* 9 Hz, 4-H), 1.75 (1 H, d, *J* 9 Hz, 10-H), 2.14 (1 H, d, *J* 2 Hz, 7-H), 2.58 (1 H, dd, *J* 9 and 2 Hz, 9-H), 2.74 (1 H, d, *J* 9 Hz, 3-H), 6.58 (2 H, q, *J* 7 Hz, SCH_2), 7.24 (3 H, s, 2-Me), and 8.53 (3 H, t, *J* 7 Hz, Me of EtS).

2-Amino-8-chloro-5-ethylthiopyrido[3,2-c]*quinoline-3-carbonitrile* (43).—Aqueous 5N-sodium hydroxide (0.5 ml) was added to 4-amino-7-chloro-2-ethylthioquinoline-3-carbonitrile (2.6 g) and malononitrile (2.8 g) in tetrahydrofuran (40 ml). After 12 h the solvent was evaporated off and the residue diluted with water. The precipitate formed was crystallised from ethanol to give the *pyridoquinoline* (1.7 g) as needles, m.p. 249—250° (Found: C, 57.3; H, 3.6; N, 17.5. $C_{15}H_{11}ClN_4S$ requires C, 57.2; H, 3.5; N, 17.8%), $\nu_{max.}$ (Nujol) 3 350, 3 300, and 3 200 (NH_2), and 2 230 cm^{-1} (CN).

7-Chloro-4-ethylsulphonyl-2-phenyl-2H-pyrazolo[4,3-c]*quinoline* (46).—Potassium permanganate (3.0 g) was added in portions over 1 h to a solution of 7-chloro-4-ethylthio-2-phenyl-2*H*-pyrazolo[4,3-*c*]quinoline (4.0 g) in acetone (180 ml) and acetic acid (20 ml) at 0 °C. After stirring for 3 h at room temperature the solution was decolourised with aqueous sodium sulphite and the acetone evaporated off. The precipitate formed on diluting the residue with water was collected and crystallised from ethanol to give the *sulphone* (3.8 g, 87%) as needles, m.p. 183—185° (Found: C, 57.8; H, 3.8; N, 11.8. $C_{18}H_{14}ClN_3O_2S$ requires C, 58.1; H, 3.8; N, 11.3%), $\nu_{max.}$ (Nujol) 1 310 and 1 140 cm^{-1} (SO_2), *m/e* 371 (1 × Cl) (M^+), 357 [$(M - O)^+$], 307 [$(M - SO_2)^+$], 306 [$(307 - H)^+$], 279vs [$(M - SO_2C_2H_4)^+$], and 278vs [$(M - SO_2C_2H_5)^+$]. Similarly prepared were *7-chloro-4-ethylsulphonyl-1H-pyrazolo*[4,3-c]*quinoline* (45) (75%), as cream prisms, darkening at *ca.* 190°, m.p. >360° (Found: C, 48.9; H, 3.7; N, 14.0. $C_{12}H_{10}ClN_3O_2S$ requires C, 48.7; H, 3.4; N, 14.2%), $\nu_{max.}$ (Nujol) 3 150 (NH) and 1 310 and 1 130 cm^{-1}; *8-chloro-5-ethylsulphonyl-2-methylpyrido*[3,2-c]*quinoline* (47) (85%), as needles, m.p. 167—168° (from ethanol) (Found: C, 56.3; H, 4.3; N, 8.6. $C_{15}H_{13}ClN_2O_2S$ requires C, 56.2; H, 4.1; N, 8.7%), $\nu_{max.}$ (Nujol) 1 310 and 1 130 cm^{-1}, *m/e* 320 (1 × Cl) (M^+), 228vs [$(M - SO_2C_2H_4)^+$], and 227vs [$(M - SO_2C_2H_5)^+$]; and *7-chloro-2-ethylsulphonyl-4-methoxyquinoline-3-carbaldehyde* (44) (47%), which was purified by chromatography on silica (eluant ethyl acetate) and crystallised from cyclohexane as needles, m.p. 94—95° (Found: C, 49.4; H, 3.6; N, 4.3. $C_{13}H_{12}ClNO_4S$ requires C, 49.8; H, 3.8; N, 4.5%), $\nu_{max.}$ (Nujol) 1 695 (CHO), and 1 300 and 1 130 cm^{-1} (SO_2), τ ($CDCl_3$) −0.95 (1 H, s, CHO), 1.5—2.4 (3 H, AMX pattern, 1,2,4-substituted benzene), 5.78 (3 H, s, OMe), 6.18 (2 H, q, SO_2CH_2), and 8.47 (3 H, t, Me of SO_2Et), *m/e* (M^+ not observed) 284 [$(M - Et)^+$] and 220 [$(M - SO_2Et)^+$]. 8-Chloro-5-ethylthio-2-methylpyrimido[5,4-*c*]quinoline (34) was not oxidised under similar conditions.

7-Chloro-4-morpholino-2-phenyl-2H-pyrazolo[4,3-c]*quinoline* (49).—7-Chloro-4-ethylsulphonyl-2-phenyl-2*H*-pyrazolo-[4,3-*c*]quinoline (2.0 g) was refluxed with morpholine (2.0 ml) in benzene (10 ml) for 4 h. The solvent was evaporated off and the residue was dissolved in chloroform and washed with dilute aqueous sodium hydroxide. The chloroform solution was separated, dried, and evaporated. The yellow residue was crystallised from ethanol–toluene (5 : 1) to give the *morpholinopyrazoloquinoline* (0.9 g) as needles, m.p. 242—243° (Found: C, 65.5; H, 4.7; N, 15.5. $C_{20}H_{17}ClN_4O$ requires C, 65.8; H, 4.7; N, 15.4%), τ [$(CD_3)_2SO$] 0.40 (1 H, s, 3-H), 1.3—2.7 (8 H, m, 6-, 8-, and 9-H and Ph), and 6.06br (8 H, s, morpholino-protons), *m/e* 364 (1 × Cl) (M^+), 279 [$(M - C_4H_7NO)^+$], and 278

[(M − C_4H_8NO)$^+$]. Similarly prepared was 8-*chloro*-5-(3-*dimethylaminopropylamino*)-2-*methylpyrido*[3,2-c]*quinoline* (50) (43%), which was purified by chromatography on silica (eluant 1 : 1 ethyl acetate–ethanol) and isolated as a dihydrochloride, m.p. 290—291° (decomp.). The free base formed prisms, m.p. 114—117° (from cyclohexane) (Found: C, 66.1; H, 6.6; N, 17.3. $C_{18}H_{21}ClN_4$ requires C, 65.8; H, 6.4; N, 17.0%), $\nu_{max.}$ (Nujol) 3 300 cm^{-1} (NH), τ ($CDCl_3$) 1.22 (1 H, d, J 9 Hz, 4-H), 2.16 (1 H, d, J 9 Hz, 10-H), 2.34 (1 H, d, J 2 Hz, 7-H), 2.6—2.9 (2 H, d, J 9 Hz, and dd, J 9 and 2 Hz, 3- and 9-H), 6.23 (2 H, m, N·CH_2), 7.26 (3 H, s, 2-Me), 7.42 (2 H, m, CH_2·N), 7.67 (6 H, s, NMe_2), and 8.10 (2 H, m, CH_2).

We are indebted to Mr. P. J. Taylor and Mr. D. Greatbanks for obtaining and discussing the i.r. and n.m.r. spectra and to Dr. P. N. Edwards for discussions.

[5/1043 *Received*, 2*nd June*, 1975]