A Versatile New Synthesis of Quinolines and Related Fused Pyridines. Part 9.[1] Synthetic Application of the 2-Chloroquinoline-3-carbaldehydes

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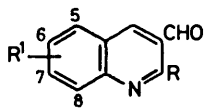
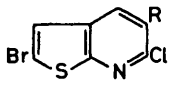
The 2-chloro-groups of the title compounds have been replaced by H, I, OH, SR, Li, CO_2H, CHO, Ph, piperidine, and N_3 (giving a tetrazole). The aldehyde group has also been converted into oxime, hydrazone, and acrylic acid derivatives. From these and related derivatives a variety of fused quinolines have been made including thieno-, pyridazino-, tropono-, pyrano-, thiopyrano-, and furo-quinolines.

In earlier papers in this series[2] we have delineated methods for the synthesis of 2-chloroquinoline-3-carbaldehydes (1a) and its thiophen analogues[3] [*e.g.* (2)] from the corresponding *N*-arylacetamides. The use of higher amides similarly gave quinolines (3).[4] We herein demonstrate the considerable synthetic potential of these fused pyridines, in particular for the preparation of tricyclic derivatives.



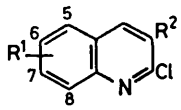
(1)

a; R^2 = Cl
b; R^2 = I
c; R^2 = SBu^t
d; R^2 = CO_2H
e; R^2 = CHO
f; R^2 = Ph



(2)

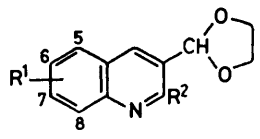
a; R = CHO
b; R = H



(3)

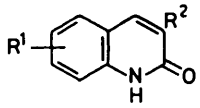
a; R^2 = CH_2CH_2Cl

Functional-group Interconversion of the 2-*Chloro-group.*—(a) *Replacement by hydrogen.* The reduction of the 2-chloro-group in several such quinolines (3) by zinc and acetic acid has been discussed elsewhere.[2] Although this method gave tars with the aldehydes (1), the corresponding ethylene glycol acetal (4) was reduced in reasonable yield (54%) by zinc and ethanolic sodium hydroxide at



(4)

a; R^2 = Cl
b; R^2 = H
c; R^2 = I
d; R^2 = CO_2H
e; R^2 = CHO



(5)

a; R^2 = CHO
b; R^2 = CH=NOH
c; R^2 = $CONH_2$
d; R^2 = CN
e; R^2 = CH_2CH_2Cl

ambient temperature. An alternative route to the 2-H system (4b) is outlined later. Interestingly, 2-chloro-6-bromothieno[2,3-*b*]pyridine (2b) gives the parent thieno-[2,3-*b*]pyridine in 83% yield by this method, constituting a simple approach to the thienopyridine series.[5]

(b) *Replacement by iodine.* The 2-chloroquinoline (1a) was easily converted into the 2-iodo-analogue (1b) by the action of sodium iodide in refluxing acetonitrile in 85—92% yield. Surprisingly the reaction was ineffective in ethanol or sulpholan, and in methyl ethyl ketone[6] gave some further products from attack of the solvent at the aldehyde group.

(c) *Replacement by a hydroxide group.* This hydrolysis is best accomplished by the brief action of hot 4M-hydrochloric acid, when the quinolines (5) are isolated in 87—95% yield. Occasionally this method proved ineffective and hot acetic acid was then used.

(d) *Replacement by* SR. The corresponding thione (5a; S in place of O) was obtained in almost quantitative yield by the action of hot ethanolic sodium hydrosulphide. This thione (5a; R^1 = H) has been shown by Hull to be a versatile intermediate.[7] Our much simpler synthesis gives this valuable intermediate in two steps from acetanilide in 80% yield.

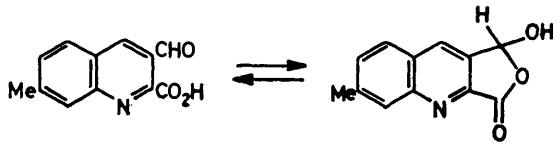
Replacement of the chloro-group by a t-butylthio-group, giving (1c), is readily achieved with a mildly basic solution of t-butylmercaptan (1,1-dimethylethanethiol). We have noted elsewhere the value of *o*-formyl t-butylthio-derivatives in synthesis.[8]

The 2-chloro-6-bromothienopyridine (2b) undergoes selective replacement of the 2-chloro-group with thiophenol giving the 2-phenylthio-derivative in 89% yield.

(e) *Replacement by various functions* (H, CO_2H, CHO) via *the lithio-derivative.* Although the acetal-protected 2-chloro-derivative (4e) was resistant to the action of butyl-lithium,[9] the corresponding iodo-compound (4c) readily underwent halogen–metal exchange at −70 °C. By subsequent action of water, carbon dioxide, or dimethylformamide, the 2-H (4b), 2-acid (4d), and 2-aldehyde (4e) were formed respectively in 96, 87, and 69% yields, being readily transformed into the corresponding free 3-aldehydes (1) by acid treatment. The 3-formyl-2-carboxylic acid (1d; R^1 = 7-Me) was prone to decarboxylation on warming as is known for quinoline-2-carboxylic acids. Although the solid state infrared spectrum showed appropriate OH (3 200br cm^{-1}) and carbonyl absorptions (1 740 and 1 680 cm^{-1}), in solution the n.m.r. spectrum suggested that the hydroxy-lactone tautomer (Scheme 1) was preferred, a feature noted with phthalaldehydic acids.[10]

The lack of reactivity of the 2-chloro-group allowed the selective replacement of the 6-bromo-substituent in

2-chloro-6-bromothienopyridine (2b; R = 6-Br) by the action of butyl-lithium. Hence the 6-H and 6-formyl derivatives were easily made by subsequent action of water (87%) and dimethylformamide (82%) respectively.

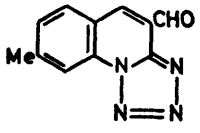


SCHEME 1

(f) *Replacement by a phenyl group.* Prolonged photolysis of 2-iodo-7-methylquinoline-3-carbaldehyde (1b; R^1 = 7-Me) in benzene gave the corresponding 2-phenyl derivative (1f) in moderate yield.

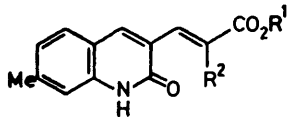
(g) *Replacement by nitrogen nucleophiles.* Although primary amine derivatives tended to react with the quinolines (1a) at the 3-carbaldehyde group (see below) secondary amines reacted effectively at the 2-chloro-position. Thus, 6-bromo-2-chlorothienopyridine (2b) reacted with hot piperidine to give the 6-bromo-2-piperidino-derivative in 84% yield.

Treatment of 2-chloro-7-methylquinoline-3-carbaldehyde with sodium azide in dimethyl sulphoxide solution at 40 °C gave the tetrazoloquinoline (6) in 80% yield.



(6)

Reactions at the 3-Formyl Group.—Hydroxylamine, hydrazine, and *NN*-dimethylhydrazine reacted normally with representative quinolinecarbaldehydes [(1a) and (5a)] and the products showed no tendency to cyclise on prolonged action, presumably owing to the unfavourable *E*-configuration of the oximes and hydrazones formed. Similarly, several condensations of the aldehydes (5a) and (1c) with cyanoacetic acid, ethyl cyanoacetate, malononitrile, and malonic acid proceeded normally giving condensation products such as (7) and (8) in good yield.

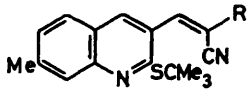


(7)

a; R^1 = H, R^2 = CN

b; R^1 = Et, R^2 = CN

c; R^1 = R^2 = H



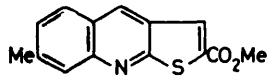
(8)

a; R = CO_2Et

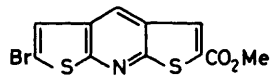
b; R = CN

The use of the acetal protecting group (4) has already been noted. We have also attempted to utilise the *NN*-dimethylhydrazone derivative of (1a) [supposedly readily deprotected with copper(II) acetate,[11] though unsuccessfully in our system] and have also made the dithioacetal analogue of (4) as an acid-stable group.

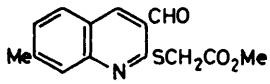
Cyclisations at the Pyridine 2,3-Position.—(a) *Bimolecular condensations.* The failure of bidentate nitrogen nucleophiles to cause heterocyclisation has been noted above. However, sulphur nucleophiles prefer to react first at the 2-chloro-group of 2-chloroquinoline-3-carbaldehydes (1a) and thus both the quinoline (1a; R^1 = 7-Me) and the thienopyridine (2a) reacted efficiently



(9)



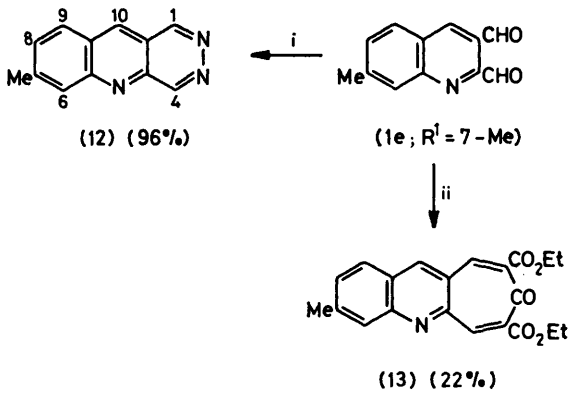
(10)



(11)

with methyl thioglycolate to give the thienoquinoline (9) and dithienopyridine (10) respectively in good yield and in one step. The intermediate (11) may be isolated if a brief reaction time is employed in support of the proposed order of reactivity.

The quinoline-2,3-carbaldehyde (1e; R^1 = 7-Me) is a versatile intermediate for further annulation. Thus, brief interaction with hydrazine hydrate in ethanol at ambient temperature gave the pyridazinoquinoline (12) in 96% yield, while with acetonedicarboxylate, the quinolinotropone (13) was isolated albeit in low yield (Scheme 2). Curiously guanidine carbonate, thiourea, ethyl glycinate, diethyl succinate, hippuric acid, and ethylenediamine did not yield useful products with the dialdehyde (1e) or its monoacetal (4e). However, the acetal (4e) reacted with *o*-phenylenediamine giving a product which we consider to be the benzimidazol-2-ylquinoline (14) (Scheme 3). The dialdehyde (1e) gave only gummy products with *o*-phenylenediamine.

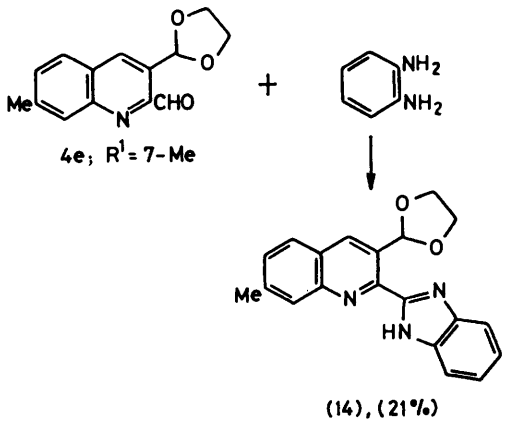


(12) (96%) (1e; R^1 = 7-Me) (13) (22%)

SCHEME 2 *Reagents:* i, $NH_2NH_2 \cdot H_2O$, EtOH, room temp., 30 min; ii, $CO(CH_2CO_2Et)_2$, $C_5H_{11}N$, dioxan, heat, 3 h

(b) *Cyclisations.* Attempts to cyclise the oxime (5b) to an isoxazoloquinoline (16) with polyphosphoric acid (PPA) or acetic anhydride led respectively to the amide and nitrile (5c) and (5d) (Scheme 4), although it is

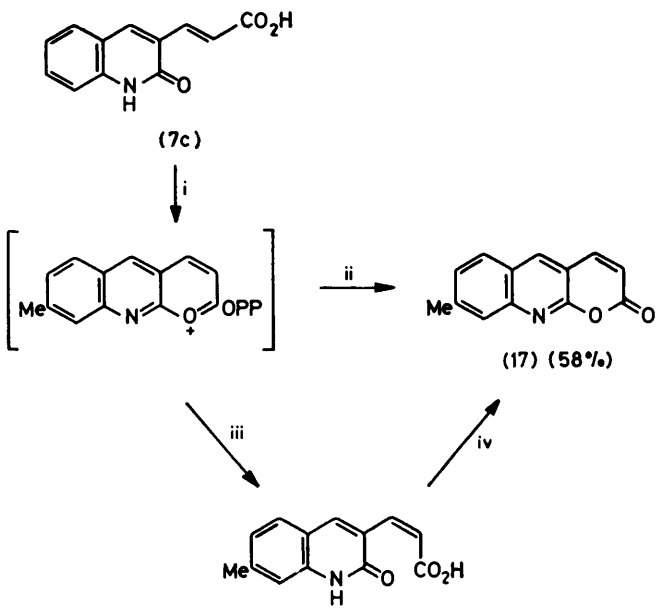
possible that the isoxazole intervened. Similarly, the 2-(t-butylthio)quinoline-3-carbaldehyde oxime (15) was observed to eliminate t-butylmercaptan on heating but the final product was again the nitrile (5d) rather than the



SCHEME 3

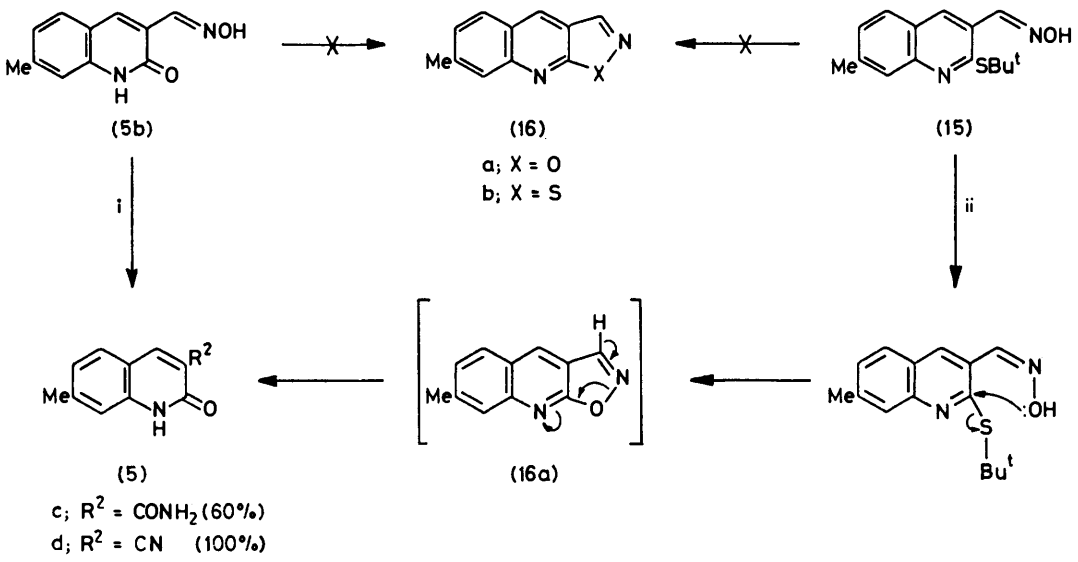
isoxazole (16a). The isothiazole (16b) was also not formed by PPA or hydrochloric acid action despite similar previously reported examples.[12] The unsubstituted isothiazoloquinoline has indeed been prepared by Hull from the 3-formyl-2-thione.[7]

Fusion of a six-membered ring proved more successful. Thus, the quinolonylacrylic acid (7c) was readily converted into a pyranoquinoline (17) with polyphosphoric acid (PPA), the intermediate being selectively converted either into the pyran with cold alkali or into

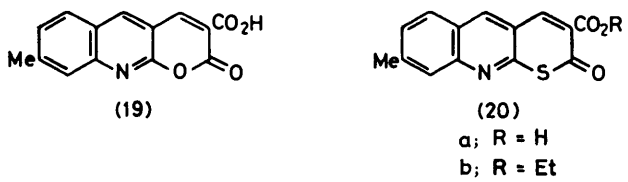


SCHEME 5 *Reagents:* i, PPA, 2 h, 245 °C; ii, aq. NaOH; iii, H_2O, heat; iv, heat

the *cis*-acrylic acid by acidic hydrolysis (Scheme 5). The *cis*-acid spontaneously cyclised on heating to give the same pyranoquinoline.



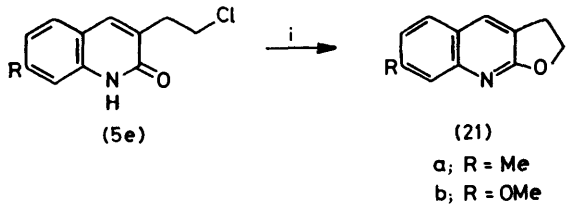
SCHEME 4 *Reagents:* i, PPA or Ac_2O; ii, 21 °C, 50 min



In a similar manner the related cyanoacrylic acid (7a) and its ethyl ester (7b) both gave a pyranoquinoline-3-carboxylic acid (19) in 90% yield on treatment with PPA. Although treatment of the 3-(2-t-butylthio-3-quinolyl)-2-cyanoacrylate (8) with PPA failed to give the thiopyranoquinoline (20), the use of ethanolic hydrochloric acid proved highly successful giving a quantitative conversion into a mixture of the acid (20a) (30%) and ester (20b) (70%). It is probable that the partial hydrolysis occurred during chromatographic purific-

ation. Thus, an analytically pure sample of the ester showed two ' spots ' on t.l.c. on silica the lower of which corresponded to the acid.

Another approach to fused quinolines lay in the use of alternative 3-substituted quinolines prepared earlier.[1] Thus 3-chloroethyl-2-quinolones (5e) are easily transformed into furanoquinolines (21) in high yield (61—79%) (Scheme 6). This system is the parent of a large

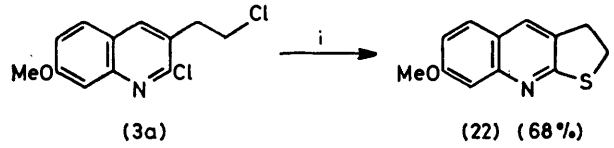


(5e) (21)
a; R = Me
b; R = OMe

SCHEME 6 *Reagents*: i, KOH–MeOH, heat, 2 h

group of furoquinoline alkaloids and this route should offer a ready entry to their synthesis. Interestingly, the same product (21a) was obtained in 90% yield when the quinolone (5e; R = Me) was treated with sodium azide in hot ethanol.

The related thienoquinoline (22) is also easily made by the action of thiourea on the chloroethylquinoline (3a) (Scheme 7).



(3a) (22) (68%)

SCHEME 7 *Reagents:* thiourea, EtOH, heat, 1 h

EXPERIMENTAL

The general conditions are as described in Part 5.[2]

The 2-chloroquinolines (1a) and (3) and thienopyridines (2) were prepared as described earlier.[2,3]

Reactions at the 2-Chloro-group.—(a) *Replacement by* H. The method described in Part 8 [1] was employed whereby 6-bromo-2-chlorothieno[2,3-*b*]pyridine (1.0 g) was converted into thieno[2,3-*b*]pyridine (0.45 g, 83%) as a pale yellow oil, b.p. 76 °C at 0.6 mmHg (lit.,[13] 61—62 °C at 0.2 mmHg); δ($CDCl_3$) 7.10 (d, H-5), 7.43 (d, H-6), 7.85 (dd, H-4), and 8.46 (dd, H-2) ($J_{5,6}$ 6, $J_{3,4}$ 8, $J_{2,4}$ 1.5, $J_{2,3}$ 4.5 Hz); δ_C ($CDCl_3$) 161.6 (C-7a), 146.3 (C-2), 132.3 (C-4a), 130.8 (C-4), 126.75 (C-6), 121.4 (C-3), and 119.1 (C-5).

2-Chloro-3-(1,3-dioxolan-2-yl)-7-methylquinoline (4a; R^1 = 7-Me) (0.6 g, 0.0024 mol) (see below for preparation) was added to a stirred suspension of zinc dust (0.40 g) in ethanol (9 ml) and aqueous sodium hydroxide (1 ml; 40% w/v), and the mixture was stirred at ambient temperature for 5 days. Water (50 ml) was added, the mixture was extracted with ether, and the extract was dried and evaporated. The residue was stirred with aqueous hydrochloric acid (20 ml; 2M) and then extracted with ether (1 × 50 ml). From the dried organic phase was obtained 2-chloro-7-methylquinoline-3-carbaldehyde (1a; R^1 = 7-Me) (0.17 g, 35%). The aqueous phase was made alkaline and extracted with chloroform (2 × 50 ml) and the extracts were dried and evaporated giving 3-formyl-7-methylquinoline (1; R^1 = Me, R^2 = H) (0.22 g, 54%) as yellow crystals, m.p. 119—120 °C (from ethanol) (Found: C, 77.1; H, 5.4; N, 8.4. $C_{11}H_9NO$ requires C, 77.2; H, 5.3; N, 8.2%); $\nu_{max.}$ (Nujol) 1 685 (CHO), 1 615, 1 560d, 910, 810, 760, and 710 cm^{-1}; δ($CDCl_3$) 2.59 (s, Me), 7.45 (dd, H-6), 7.84 (d, H-5), 7.93 (s, H-8), 8.51 (d, H-4), and 9.29 (d, H-2 ($J_{2,4}$ 2, $J_{5,6}$ 9 Hz).

(b) *Replacement by* I. To sodium iodide (20.0 g), hydrochloric acid (1.3 ml, 55% w/v aqueous solution), and acetonitrile (200 ml) was added 2-chloro-3-formyl-7-methylquinoline (1a; R^1 = 7-Me) (10.0 g, 0.49 mol) and the mixture was stirred under reflux for 4.5 h. Most of the solvent (*ca.* 150 ml) was removed (and re-used in subsequent preparations), and water (*ca.* 150 ml) and saturated aqueous sodium carbonate were added to render the mixture alkaline. The crude product (13.5 g, 93%) was filtered off, washed well with water, and dried in air, and was pure enough for further use. A sample was recrystallised from ethanol to give *3-formyl-2-iodo-7-methylquinoline* (16; R^1 = 7-Me) as needles, m.p. 180—181 °C (Found: C, 44.4; H, 2.8; N, 4.8. $C_{11}H_8INO$ requires C, 44.5; H, 2.7; N, 4.7%); $\nu_{max.}$ (Nujol) 1 680 (CHO), 1 620, 1 565, 1 175, 1 020, and 810 cm^{-1}; δ($CDCl_3$) 2.57 (s, Me), 7.45 (dd, H-6), 7.83 (d, H-5), 7.87 (s, H-8), 8.45 (s, H-4), and 10.22 (s, CHO) ($J_{5,6}$ 9 Hz); *m/e* 297 (M^+, 100%), 170 (M − I, 85), 142 (85), 115 (40), and 89 (15).

In a similar manner 2-chloroquinoline-3-carbaldehyde (1a; R^1 = H) (10.0 g) gave *2-iodoquinoline-3-carbaldehyde* (12.5 g, 85%), m.p. 150—152 °C (from ethanol) (Found: C, 42.4; H, 2.2; N, 5.1. $C_{10}H_6INO$ requires C, 42.4; H, 2.1; N, 4.95%); $\nu_{max.}$ (Nujol) 1 680 (CHO), 1 610, 1 560, 1 320, 1 175, 1 020, 1 010, and 765 cm^{-1}; δ($CDCl_3$) 7.5—8.3 (m, H-5, -6, -7, and -8), 8.52 (s, H-4), and 10.27 (s, CHO).

(c) *Replacement by* OH.—2-Chloro-3-formyl-7-methylquinoline (1a; R^1 = 7-Me) (10.0 g) in aqueous hydrochloric acid (350 ml; 4M) was refluxed for 1 h and then cooled in ice and filtered, and the solid was washed well with water and dried. The crude product (8.7 g, 96%) was pure enough for further use. A sample was recrystallised from aqueous acetic acid to give 3-formyl-7-methyl-2-quinoline (5a; R^1 = 7-Me) as yellow crystals, m.p. 294—295 °C (decomp.) (Found: C, 70.3; H, 5.0; N, 7.7. $C_{11}H_9NO_2$ requires C, 70.6; H, 4.85; N, 7.5%); $\nu_{max.}$ (Nujol) 1 675 (CO), 1 555 (amide II), 900, 810, 770, and 645 cm^{-1}; $\nu_{max.}$ (hexachlorobutadiene) 3 200—2 500 cm^{-1} (NH); δ(CF_3COOD) 2.77 (s, Me), 7.79 (d, H-6), 7.84 (s, H-8), 8.21 (d, H-5), 9.32 (s, H-4), and 10.48 (s, CHO); *m/e* 187 (M^+, 25%), 159 (M − CO, 100), 141 (7), 131 (37), 130 (63), 103 (18), and 77 ($C_6H_5^+$, 15). In a similar manner was obtained *6-chloro-3-formyl-2-quinolone* (87%), identical (m.p., mixed m.p., i.r. spectrum) with a sample prepared earlier;[2] also *3-(2-chloroethyl)-7-methyl-2-quinolone* (5e; R^1 = 7-Me) (89%) as needles, m.p. 212—214 °C (from ethanol) (Found: C, 65.1; H, 5.5; N, 6.4. $C_{12}H_{12}ClNO$ requires C, 65.0; H, 5.5; N, 6.3%); $\nu_{max.}$ (Nujol) 1 658 (CO) and 1 565 cm^{-1}; δ([$^2H_6$]DMSO) 2.38 (s, Me), 2.95 (t, CH_2Ar), 3.90 (t, CH_2Cl), 7.01 (d, H-6), 7.12 (s, H-8), and 7.52 (d, H-5) ($J_{5,6}$ 8 Hz).

2-Chloro-3-(2-chloroethyl)-7-methoxyquinoline (3a; R^1 = 7-MeO) (10.0 g) in acetic acid (100 ml) was refluxed for 3 h when most of the solvent was removed and the residue poured into ice–water. The precipitate was filtered off, washed with water, and dried in air giving *3-(2-chloroethyl)-7-methoxy-2-quinolone* (5e; R^1 = 7-MeO) (7.6 g, 82%), m.p. 165 °C (from ethyl acetate–light petroleum) (Found: C, 61.0; H, 5.1; N, 5.7. $C_{12}H_{11}Cl_2NO$ requires C, 60.6; H, 5.05; N, 5.9%); $\nu_{max.}$ (Nujol) 1 658 cm^{-1} (CO); δ($CDCl_3$)

3.85 (s, MeO), 6.82 (dd, H-6), 6.85 (d, H-8), 7.42 (d, H-5), and 7.65 (s, H-4) ($J_{5,6}$ 9, $J_{6,8}$ 2 Hz).

(d) *Replacement by* SR. (*i*) 2-Chloro-3-formylquinoline (1a; R^1 = H) (0.96 g, 0.005 mol) was added to a solution of sodium hydrosulphide ($NaSH \cdot xH_2O$) (0.73 g) in ethanol (20 ml). The mixture was warmed at 60 °C for 10 min, cooled, and poured into ice–water (*ca.* 50 ml) and made acidic with acetic acid. The product, 3-formylquinoline-2-thione, was filtered off, washed, dried (0.93 g, 91%), and recrystallised from n-propanol to give a red solid m.p. 286 °C (decomp.) [lit.,[7] 288 °C (decomp.)], identical (i.r. and ^1H n.m.r. spectra) with an authentic sample.[7]

(*ii*) A mixture of potassium carbonate (8.0 g, 0.58 mol), ethanol (50 ml), and t-butyl thiol (2.63 g, 3.3 ml, 0.0292 mol) was stirred and 2-chloro-3-formyl-7-methylquinoline (1a; R^1 = 7-Me) (5.0 g, 0.243 mol) was added and the mixture was refluxed for 2 h. After cooling, water (120 ml) was added and the mixture was allowed to stand overnight. The separated oil was extracted with ether and washed with water, aqueous sodium hydroxide, and then water. It was dried ($MgSO_4$) and evaporated and the residue was eluted through silica with chloroform to give *3-formyl-7-methyl-2-(t-butylthio)quinoline* (1c; R^1 = 7-Me) as a yellow solid (8.0 g). Recrystallisation from light petroleum containing a little toluene gave the pure product as pale yellow needles (5.87 g, 47%), m.p. 120—121 °C (Found: C, 69.3; H, 6.7; N, 5.4. $C_{15}H_{17}NOS$ requires C, 69.5; H, 6.6; N, 5.4%); $\nu_{max.}$ (Nujol) 1 695 (CHO), 1 625, 1 585, 1 495, 1 380 (CMe_3), 1 170, 1 140, 1 060, and 800 cm^{-1}; $\delta(CDCl_3)$ 1.71 (s, CMe_3), 2.56 (s, Me), 7.31 (dd, H-6), 7.74 (d, H-5), 7.79 (s, H-8), 8.42 (s, H-4), and 10.41 (s, CHO).

(*iii*) 2-Chloro-6-bromoethieno[2,3-*b*]pyridine (2b) (1.0 g) was added to a solution of thiophenol (0.5 g) in ethanol (10 ml) in which had been dissolved sodium (0.1 g), and the mixture was refluxed for 4 h. The cooled mixture was poured onto ice–water (20 ml) and filtered and the solid was washed with water, aqueous alkali, and water, and dried. Recrystallisation from ethanol gave *6-bromo-2-phenylthiothieno[2,3-b]pyridine* (1.15 g, 89%) as needles, m.p. 245 °C (Found: C, 48.4; H, 2.5; N, 4.4. $C_{13}H_8BrNS_2$ requires C, 48.4; H, 2.6; N, 4.6%); $\delta([^2H_6]DMSO)$: 7.20 (s, H-5), 7.65 (d, H-4), 7.08 (d, H-3), 7.78—6.58 (m, Ph) ($J_{3,4}$ 8.0 Hz).

(e) *Replacement by various functions by way of the lithio-derivative.* (i) *Replacement by* H. 3-(1,3-Dioxolan-2-yl)-2-iodo-7-methylquinoline (4c; R^1 = 7-Me) (0.68 g, 0.002 mol) in dry ether at −70 °C under nitrogen was treated with n-butyl-lithium (1.1 ml, 1.92M-solution in hexane, 0.0021 mol) with stirring. After a few minutes the solution was poured into water (*ca.* 200 ml) and extracted with chloroform (2 × 50 ml), and the extracts were dried ($MgSO_4$) and evaporated. The residue was stirred for 1 h with aqueous hydrochloric acid (20 ml; 2M) and ether (50 ml). From the ether phase was obtained 2-chloro-3-formyl-7-methylquinoline (0.08 g), an impurity in the iodo-compound. The aqueous phase was basified and extracted with chloroform and the chloroform solution was dried and evaporated to give 3-formyl-7-methylquinoline (0.28 g, 97% after correction for chloroquinoline impurity) as pale yellow crystals, m.p. 119—120 °C (from ethanol) identical to the sample reported above.

Similarly, 6-bromo-2-chlorothieno[2,3-*b*]pyridine (2b) (0.62 g, 0.0025 mol) in dry ether (10 ml) gave 2-chlorothieno[2,3-*b*]pyridine (0.37 g, 87%) as needles, m.p. 57—58 °C (from light petroleum) (lit.,[14] 56.5—58.5 °C).

(ii) *Replacement by* CO_2H. 3-(1,3-Dioxolan-2-yl)-2-iodo-7-methylquinoline (4c; R^1 = 7-Me) (0.68 g, 0.002 mol) was metallated as above and the solution poured into crushed solid carbon dioxide. After reaching ambient temperature the solution was treated with water (*ca.* 50 ml) and aqueous hydrochloric acid (10 ml; 2M), and the layers were separated. The organic layer was dried ($MgSO_4$) and evaporated giving 2-chloro-3-formyl-7-methylquinoline (0.08 g). The aqueous layer was subjected to continuous extraction with hot chloroform for 4 h and the extract, after drying and evaporation, gave *3-formyl-7-methylquinoline-2-carboxylic acid* (0.32 g, 87%), m.p. 160 °C (decomp.) (further attempts at purification caused decarboxylation); $\nu_{max.}$ (Nujol) 3 200 (OH), 1 740 (CO_2H), and 1 678 cm^{-1} (CHO); $\delta([^2H_6]DMSO)$ 2.59 (s, Me), 7.66 (dd, H-6), 7.99 (s, H-8), 8.10 (d, H-5), and 8.79 (s, H-4) ($J_{5,6}$ 9 Hz) (a broad resonance at δ 6.5—11 was also evident); *m/e* 215 (M^+, 1%), 214 (3), 186 (M − CHO), 170 (M − CO_2H, 60), 169 (52), 142 (186 − CO_2, 100), 141 (80), 140 (58), 139 (30), and 114 (50) (Found: M^+, 215.0582. $C_{12}H_{19}NO_3$ requires M, 215.0582).

(iii) *Replacement by* CHO.—The iodoquinoline (4c; R^1 = Me) (0.68 g, 0.002 mol) was metallated as above and to the solution was added at −70 °C dimethylformamide (0.5 ml). After reaching ambient temperature, water was added (*ca.* 20 ml) and the layers were separated. The organic phase was dried and evaporated and the residue was stirred with aqueous hydrochloric acid (10 ml; 2M) and ether (20 ml) for 1 h. From the ether phase was obtained 2-chloro-3-formyl-7-methylquinoline (0.08 g). The acidic phase was basified and extracted with chloroform (2 × 100 ml) and the extracts were dried and evaporated to give *2,3-diformyl-7-methylquinoline* (1e; R^1 = 7-Me) (0.32 g, 94%). Recrystallisation from ethyl acetate gave plates, m.p. 162—163 °C (Found: C, 72.4; H, 4.6; N, 7.0. $C_{12}H_9NO_2$ requires C, 72.35; H, 4.55; N, 7.0%); $\nu_{max.}$ (Nujol) 1 705 (CHO), 1 680 (CHO), 1 620 and 1 575 cm^{-1}; $\delta(CDCl_3)$ 2.63 (s, Me), 7.94 (s, H-5), 8.09 (s, H-8), 8.77 (s, H-4), 10.34 (s, 3-CHO), and 10.95 (s, 2-CHO) ($J_{5,6}$ 9 Hz).

Similarly, the iodoquinoline (6.8 g, 0.02 mol) was metallated and treated with dimethylformamide. The resulting solution was treated with water (*ca.* 100 ml) and the organic phase was dried and evaporated. The residual oil slowly solidified and was extracted repeatedly with boiling light petroleum to give, from the extract by evaporation to low bulk, *3-(1,3-dioxolan-2-yl)-2-formyl-7-methylquinoline* (4e; R^1 = 7-Me) (3.35 g, 69%) as needles, m.p. 95—95.6 °C (from light petroleum–toluene) (Found: C, 69.2; H, 5.5; N, 5.8. $C_{14}H_{13}NO_3$ requires C, 69.1; H, 5.4; N, 5.8%); $\nu_{max.}$ (Nujol) 1 705 (CHO), 1 120, 1 065, 920, 880, and 800 cm^{-1}; $\delta(CDCl_3)$ 2.59 (s, Me), 4.12 (s, 2 × CH_2), 6.80 (s, acetal CH), 7.50 (dd, H-6), 7.80 (d, H-5), 8.01 (s, H-8), 8.52 (s, H-4), and 10.29 (s, CHO) ($J_{6,8}$ 2, $J_{5,6}$ 8 Hz). From the residue of the repeated extraction, by acid treatment, was obtained 2,3-diformyl-7-methylquinoline (1.03 g).

6-Bromo-2-chlorothieno[2,3-*b*]pyridine (2b) (0.62 g, 0.0025 mol) was metallated as described above and treated with dimethylformamide (0.5 ml). On reaching ambient temperature, aqueous hydrochloric acid (10 ml; 1M) was added and the phases were vigorously shaken and separated. The ether phase was washed with water, dried ($MgSO_4$), and evaporated. The solid residue obtained was recrystallised from light petroleum (b.p. 80—100 °C) to give *2-chlorothieno[2,3-b]pyridine-6-carbaldehyde* (0.41 g, 82%) as flakes, m.p. 144—145 °C (Found: C, 48.8; H, 2.1; N, 7.0. C_8H_4ClNOS requires C, 48.6; H, 2.0; N, 7.1%); $\nu_{max.}$

(Nujol) 1 680 cm^{-1}; δ($CDCl_3$) 7.49 (d, 5-H), 8.12 (s, H-3), 8.30 (d, H-4), and 10.39 (s, CHO) ($J_{4,5}$ 9 Hz).

(f) *Replacement by* Ph. 3-Formyl-2-iodo-7-methylquinoline (0.5 g, 0.0017 mol) in benzene (150 ml) was photolysed for 60 h at ambient temperature with a medium-pressure 75 W mercury-vapour lamp in an immersion apparatus. The resulting solution was washed with aqueous sodium carbonate (25 ml, saturated), water (25 ml), and aqueous sodium thiosulphate (50 ml; 2% w/v). After drying ($MgSO_4$), the solvent was removed and the residue chromatographed on silica thick-layer plates (200 × 200 × 1 mm), eluting (× 3) with chloroform. The fastest-moving band gave 3-formyl-2-iodo-7-methylquinoline (0.1 g, 20%), followed by *3-formyl-7-methyl-2-phenylquinoline* (1f; R^1 = 7-Me) (0.15 g, 36%) as needles, m.p. 109.5—110.5 °C (from light petroleum–toluene) (Found: C, 82.6; H, 5.2; N, 5.7. $C_{17}H_{13}NO$ requires C, 82.6; H, 5.3; N, 5.7%); $\nu_{max.}$ (Nujol) 1 685 (CHO), 1 620, and 1 580 cm^{-1}; δ($CDCl_3$) 2.58 (s, Me), 7.43 (dd, H-6), 7.45—7.8 (m, Ph), 7.86 (d, H-5), 7.99 (s, H-8), 8.75 (s, H-4), and 10.14 (s, CHO) ($J_{5,6}$ 8 Hz).

(g) *Replacement by nitrogen nucleophiles.* (i) *Replacement by piperidino.* 2-Chloro-6-bromothieno[2,3-*b*]pyridine (2b) (1.0 g) in piperidine (5 ml) was heated under reflux for 12 h and then poured into water. The resulting precipitate was filtered off, washed with water, and recrystallised from aqueous ethanol to give *2-bromo-6-piperidinothieno*[2,3-b]*pyridine* (1.0 g, 84%) as brilliant yellow needles, m.p. 60 °C (Found: C, 49.25; H, 4.05; N, 8.9. $C_{12}H_{13}N_2S$ requires C, 48.5; H, 4.4; N, 9.4%) δ($CDCl_3$) 1.85 (m, $[CH_2]_3$), 3.74br (t, 2 × CH_2), 6.83 (d, H-5), 7.23 (s, H-3), and 7.84 (d, H-4) ($J_{4,6}$ 8 Hz).

(ii) *Replacement by azide.* To 2-chloro-3-formyl-7-methylquinoline (1a; R^1 = 7-Me) (4.0 g) in dimethyl sulphoxide (200 ml) and acetic acid (4 ml) was added sodium azide (2.0 g) in water (10 ml) and the mixture was stirred at 40 °C for 3 h. After a further 5 days at ambient temperature, a white crystalline precipitate formed which was filtered off, washed with water, and dried in air (3.30 g, 80%). Recrystallisation from acetone gave *4-formyl-8-methyltetrazolo*[1,5-a]*quinoline* (6) as glistening needles, m.p. 256—258 °C (decomp.) (Found: C, 62.2; H, 4.0; N, 26.4. $C_{11}H_8N_4O$ requires C, 62.3; H, 3.8; N, 26.4%); $\nu_{max.}$ (Nujol) 1 700 cm^{-1} (CO); δ([$^2H_6$]DMSO at 70 °C) 2.60 (s, Me), 7.65 (dd, H-6), 8.25 (d, H-5), 8.42 (s, H-8), and 8.81 (s, H-4); *m/e* 212 (M^+) and 184 ($M - N_2$).

Reactions at the 3-Formyl Group.—(a) *Conversion into ethylene glycol acetals* (4). A solution of 2-chloro-3-formyl-7-methylquinoline (1a; R^1 = 7-Me) (4.0 g, 0.0195 mol) in benzene (100 ml) containing ethylene glycol (3.57 g, 3.2 ml, 0.0575 mol) and a crystal of toluene-*p*-sulphonic acid was heated under reflux for 5 h using a Dean–Stark water separator. The cooled solution was treated with saturated aqueous sodium carbonate (50 ml), dried, and evaporated giving *2-chloro-3-(1,3-dioxolan-2-yl)-7-methylquinoline* (4a; R = 7-Me) (4.75 g, 98%) as a pale yellow solid pure enough for further use. Recrystallisation from light petroleum (b.p. 100—120 °C)–toluene gave a sample as pale yellow needles, m.p. 75—76 °C (Found: C, 62.6; H, 4.8; N, 5.6. $C_{13}H_{12}ClNO_2$ requires C, 62.5; H, 4.8; N, 5.6%); $\nu_{max.}$ (Nujol) 1 620, 1 600, 1 330, 1 100, 1 030, and 920 cm^{-1}; δ($CDCl_3$) 2.54 (s, Me), 4.14 (s) and 4.15 (s) (2 × CH_2), 6.21 (s, acetal CH), 7.36 (dd, H-6), 7.73 (d, H-5), 7.80 (s, H-8), and 8.33 (s, H-4) ($J_{5,6}$ 9 Hz).

Similarly, from 2-iodo-3-formyl-7-methylquinoline (1b; R^1 = 7-Me) (13.5 g, 0.0455 mol) was obtained 3-(1,3-dioxolan-2-yl)-2-iodo-7-methylquinoline (4c; R^1 = 7-Me) (13.5 g, 87%) which was recrystallised from light petroleum (b.p. 100—120 °C)–toluene as pale yellow crystals, m.p. 109—110 °C (Found: C, 45.8; H, 3.6; N, 4.0. $C_{13}H_{12}INO_2$ requires C, 45.8; H, 3.55; N, 4.1%); $\nu_{max.}$ (Nujol) 1 625, 1 585, 1 315, 1 080, and 1 010 cm^{-1}; δ($CDCl_3$) 2.53 (s, Me), 4.15 (s) and 4.17 (s) (2 × CH_2), 6.02 (s, acetal CH), 7.37 (dd, H-6), 7.71 (d, H-5), 7.82 (s, H-8), and 8.12 (s, H-4) ($J_{5,6}$ 9 Hz).

(b) *Conversion into oximes* (1) *and* (5b). Hydroxylamine hydrochloride (2.0 g, 0.029 mol) in water (5 ml) was rendered just alkaline with aqueous sodium hydroxide solution (4M). 3-Formyl-7-methyl-2-quinolone (5a; R^1 = 7-Me) (1.87 g, 0.01 mol) in ethanol (70 ml) was added and the solution was heated under reflux for 1 h. The cooled mixture was poured into ice–water (*ca.* 100 ml) and made acid with aqueous hydrochloric acid (4M). The product was filtered off, washed with water, and dried in air giving *3-hydroxyiminomethyl-7-methyl-2-quinolone* (5b; R^1 = 7-Me) (1.96 g, 97%) pure enough for further use. A sample, recrystallised from aqueous ethanol had m.p. 268 °C (decomp.) (Found: C, 65.4; H, 5.0; N, 13.9. $C_{11}H_{10}N_2O_2$ requires C, 65.3; H, 5.0; N, 13.85%); $\nu_{max.}$ (Nujol) 3 250 (OH), 1 645 (CO), 1 615, and 970 (d) cm^{-1}; δ([$^2H_6$]DMSO) 2.39 (s, Me), 7.04 (d, H-6), 7.12 (s, H-8), 7.65 (d, H-5), and 8.22 (s, H-4 and CH=N) ($J_{5,6}$ 8 Hz); *m/e* 202 (M^+, 96%), 185 (M — OH, 100), 184 ($M - H_2O$, 33), 172 (M — NO, 38), 167 (46), 156 (20), 144 (17), and 130 (10).

Similarly, from 3-formyl-7-methyl-2-t-butylthioquinoline (1c; R^1 = 7-Me) (2.0 g, 0.0077 mol) and hydroxylamine at room temperature (45 min) was obtained *7-methyl-2-t-butylthioquinoline-3-carbaldehyde oxime* [oxime of (1c; R^1 = 7-Me)] (2.01 g, 95%) pure enough for further use. Recrystallisation of a sample from aqueous ethanol gave needles, m.p. 206—207 °C (decomp.); $\nu_{max.}$ (Nujol) 3 150, 3 060 (OH), 1 625, 1 580, 1 150d, 980, 940, and 890 cm^{-1}; δ([$^2H_6$]DMSO) 1.69 (s, CMe_3), 2.50 (s, Me), 7.35 (dd, H-6), 7.70 (s, H-8), 7.85 (d, H-5), 8.36 (s, H-4), 8.38 (s, CH=N), and 11.62br (OH) ($J_{5,6}$ 9 Hz); *m/e* 274 (M^+, 5%), 256 ($M - H_2O$, 5), 217 ($M - C_4H_9$, 8), 201 ($M - C_4H_9O$, 67), 200 (100), 167 (58), and 140 (30) (Found: M^+, 274.1128. $C_{15}H_{18}N_2OS$ requires M, 274.1139).

(c) *Conversion into hydrazones.* (*i*) To 2-chloro-3-formyl-7-methylquinoline (1.0 g, 0.0049 mol) in ethanol (75 ml) was added with stirring hydrazine hydrate (0.3 g, 0.006 mol) and the mixture was refluxed for 30 min. On cooling to 0 °C, a pale yellow crystalline mass was filtered off, washed with cold ethanol and water, and dried (0.75 g). A further portion (0.18 g) of product was obtained by concentration of the reaction filtrate (total crude yield 0.93 g, 84%). Recrystallisation of this material from ethanol gave *2-chloro-3-formyl-7-methylquinoline hydrazone* as yellow crystals which decomposed without melting at 206 °C (Found: C, 60.3; H, 4.8; N, 19.5. $C_{11}H_{10}ClN_3$ requires C, 60.15; H, 4.6; N, 19.1%); $\nu_{max.}$ (Nujol) 3 350 and 3 180 cm^{-1} (NH_2); δ([$^2H_6$]DMSO) 2.52 (s, Me), 6.98br (NH_2), 7.37 (dd, H-6), 7.65 (s, H-8), 7.78 (d, H-5), 8.10 (s, CH=N), and 8.54 (s, H-4).

(*ii*) To a solution of the same aldehyde (2.0 g, 0.0097 mol) in ethanol (20 ml) was added *NN*-dimethylhydrazine (1.0 g, 0.017 mol) and the mixture was stirred and refluxed for 1 h. Addition of water gave a yellow precipitate which was filtered off, washed with water, dried, and recrystallised from ethanol (2.1 g, 88%) as yellow crystals, m.p. 114—115 °C (Found: C, 63.1; H, 5.7; N, 16.85. $C_{13}H_{14}ClN_3$ requires C, 63.0; H, 5.7; N, 17.0%); δ($CDCl_3$) 2.51 (s, Me), 3.07 (s,

NMe_2), 7.30 (dd, H-6), 7.46 (s, H-8), 7.66 (d, H-5), 7.72 (s, CH=N), and 8.53 (s, H-4).

(d) *Condensation with active methylenes.* (i) *Malonic acid.* A mixture of 3-formyl-7-methyl-2-quinolone (5a; R^1 = 7-Me) (1.54 g, 0.0082 mol), malonic acid (1.71 g, 0.0164 mol), pyridine (7 ml), ethanol (10 ml), and piperidine (10 drops) was heated at 100 °C with stirring for 2 h, cooled, and diluted with water. The precipitate was filtered off, washed with water, and dried in air giving (E)-3-(*7-methyl-2-oxo-1,2-dihydro-3-quinolyl*)*acrylic acid* (7c) (1.55 g, 82%) as a fawn solid pure enough for further use. Recrystallisation of a sample from aqueous ethanol gave a pale yellow solid, m.p. 280 °C (decomp.) (Found: C, 68.3; H, 4.95; N, 6.2. $C_{13}H_{11}NO_3$ requires C, 68.1; H, 4.8; N, 6.1%); $\nu_{max.}$ (Nujol) 3 000br (NH and OH), 1 690 (CO), and 1 280 cm^{-1}; δ([$^2H_6$]-DMSO) 2.40 (s, Me), 7.01 (d, C*H*CO_2H), 7.05 (d, H-6), 7.10 (s, H-8), 7.55 (d, H-5), 7.63 (d, ArC*H*), 8.30 (s, H-4), and 11.90 (b, NH and OH) ($J_{5',6'}$ 8, $J_{2,3}$ 18 Hz); *m/e* 229 (M^+, 15%), 212 (M − OH, 1), 184 (M − CO_2H, 100), 156 (6), and 154 (6).

(ii) *Cyanoacetic acid.* Cyanoacetic acid (1.66 g, 0.02 mol) was made just alkaline (to Methyl Orange) using aqueous sodium hydroxide (4 M). Further alkali was added (1 ml), followed by water (25 ml) and 3-formyl-7-methyl-2-quinolone (5a; R^1 = Me) (1.87 g, 0.01 mol). The mixture was heated at 80 °C for 30 min, cooled, and poured into water (*ca.* 50 ml) and the mixture was acidified with aqueous hydrochloric acid (4M). The precipitate was filtered off, washed with water and dried in air to give (E)-2-*cyano*-3-(*7-methyl-2-oxo-1,2-dihydro-3-quinolyl*)*acrylic acid* (7a) (2.54 g, 98%) as a pale yellow solid pure enough for further use. Recrystallisation of a sample from acetic acid gave bright yellow crystals, m.p. 261.5—262.5 °C (decomp.) (Found: C, 66.0; H, 4.05; N, 11.25. $C_{14}H_{10}N_2O_3$ requires C, 66.1; H, 4.0; N, 11.0%); $\nu_{max.}$ (Nujol) 3 000 (OH), 2 225 (CN), 1 710 (CO), 1 680 (CO), 1 660 (C=C), 1 550, 1 380, and 1 285 (d) cm^{-1}; δ([$^2H_6$]DMSO) δ 2.41 (s, Me), 7.10 (d, H-6), 7.14 (s, H-8), 7.66 (d, H-5), 8.49 (s, ArC*H*), 8.80 (s, H-4), and 12.18br (OH and NH) ($J_{5,6}$ 8 Hz); *m/e* 254 (M^+, 22%), 210 (M^+ − CO_2, 45), 209 (M^+ − CO_2H, 100), 191 (3), 184 (7), 183)7), and 181 (6).

(iii) *Ethyl cyanoacetate.* A mixture of 3-formyl-7-methyl-2-quinolone (5a; R^1 = Me) (1.87 g, 0.01 mol), ethyl cyanoacetate (1.14 g, 0.010 mol), and ethanol (15 ml) was stirred and sodium ethoxide solution (0.6 ml, 20% w/v) was added. After 30 min, the thick solution was poured into water (100 ml), and the precipitate was filtered off, washed with water, and dried in air to give *ethyl* (E)-2-*cyano*-3-(*7-methyl-2-oxo-1,2-dihydro-3-quinolyl*)*acrylate* (7b) (2.60 g, 92%), pure enough for further use. Recrystallisation of a sample from ethanol gave bright yellow crystals, m.p. 242 °C (decomp.) (Found: C, 68.0; H, 4.95; N, 10.1. $C_{16}H_{14}N_2O_3$ requires C, 68.1; H, 5.0; N, 9.9%); $\nu_{max.}$ (Nujol) 2 225 (CN), 1 725 (CO), 1 660 (C=C), 1 280, and 1 150 cm^{-1}; δ([$^2H_6$]DMSO) 1.32 (t, C*H*$_3$CH$_2$), 2.40 (s, 7-Me), 4.34 (q, CH_2), 7.05 (d, H-6), 7.10 (s, H-8), 7.61 (d, H-5), 8.52 (s, ArC*H*), 8.79 (s, H-4), and 12.18br (NH).

Similarly from 3-formyl-7-methyl-2-t-butylthioquinoline (1c; R^1 = 7-Me) and ethyl cyanoacetate was obtained *ethyl* 2-*cyano*-3-(*7-methyl-2-t-butylthio-3-quinolyl*)*acrylate* (8a) (91%) as a yellow solid pure enough for further use. Recrystallisation of a sample from light petroleum gave yellow needles, m.p. 97—98 °C (Found: C, 68.0; H, 6.5; N, 7.7. $C_{20}H_{22}N_2O_2S$ requires C, 67.8; H, 6.3; N, 7.9%); $\nu_{max.}$ (Nujol) 2 215 (CN), 1 725 (CO), 1 580, 1 260 (d), 1 190 cm^{-1}; δ($CDCl_3$) 1.40 (t, C*H*$_3$CH$_2$), 1.72 (s, Me_3C), 2.53 (s, Me), 4.42 (q, CH_2), 7.28 (dd, H-6), 7.67 (d, H-5), 7.72 (s, H-8), 8.62 (s, H-4), and 8.69 (s, ArC*H*); *m/e* 354 (M^+, 18%), 298 (M^+ — isobutene, 58), 271 (52), 253 (20), 226 (92), 225 (100), 210 (26), and 198 (14).

(iv) *Malononitrile.* 3-Formyl-7-methyl-2-t-butylthioquinoline (1c; R^1 = 7-Me) (2.4 g) was treated with malononitrile (0.64 g) as in the above method using ethyl cyanoacetate to give 2-*cyano*-3-(*7-methyl-2-t-butylthio-3-quinolyl*)-*acrylonitrile* (8b) (1.83 g, 64%) as a yellow solid pure enough for further use. Recrystallisation of a sample from ethanol gave yellow crystals, m.p. 160 °C (Found: C, 70.3; H, 5.7; N, 13.6. $C_{18}H_{17}N_3S$ requires C, 70.3; H, 5.6; N, 13.7%); $\nu_{max.}$ (Nujol) 2 225 (CN) and 1 620 cm^{-1}.

(e) *Conversion into the dithian* (3; R^1 = 7-Me, R^2 = 1,3-*dithian-2-yl*). To 2-chloro-3-formyl-7-methylquinoline (1.0 g, 0.0049 mol) and ethane-1,2-dithiol (0.46 g, 0.0049 mol) in dry benzene (20 ml) was added boron trifluoride–ether (0.5 ml). A white precipitate formed and the reaction mixture was refluxed for 10 min. On cooling a dark oil separated. The upper benzene layer was decanted and evaporated to give a pale yellow solid, and the dark oil was triturated with cold methanol to give further quantities of the solid. The two crops of solid were combined and recrystallised from methanol to give 2-*chloro*-3-(*1,3-dithian-2-yl*)-*7-methylquinoline* (1.07 g, 75%), m.p. 126—127 °C (Found: C, 55.2; H, 4.1; N, 4.9. $C_{13}H_{12}ClNS_2$ requires C, 55.4; H, 4.3; N, 5.0%); δ($CDCl_3$) 2.53 (s, Me), 3.40 (s, 3 × CH_2), 6.10 (s, CHS_2), 7.36 (dd, H-6), 7.73 (d, H-5), 7.78 (s, H-8), and 8.55 (s, H-4).

Cyclisations. (a) *With thienopyridines* (2a). To 6-bromo-2-chlorothieno[2,3-*b*]pyridine-3-carbaldehyde (2a) (2.8 g, 0.01 mol) in dimethylformamide (10 ml) was added methyl thioglycolate (1.2 g) and anhydrous potassium carbonate (2.0 g). The mixture was stirred for 12 h at ambient temperature and then poured into water. The precipitate was filtered off and washed with water, dried, and recrystallised from aqueous dimethylformamide to give 2-*bromo*-6-*methoxycarbonylditheno*[2,3-b:3′,2′-e]*pyridine* (10) (2.1 g, 64%) as platelets, m.p. 221—222 °C (Found: C, 40.6; H, 1.8; N, 4.7. $C_{11}H_6BrNO_2S_2$ requires C, 40.5; H, 1.85; N, 4.29%); $\nu_{max.}$ (Nujol) 1 700 cm^{-1} (CO); δ($CDCl_3$) 3.95 (s, Me), 7.33 (s, H-3), 8.00 (s, H-4), and 8.31 (s, H-5).

(b) *With 2-chloroquinoline-3-carbaldehydes.* (*i*) *Thieno*-[2,3-b]*quinoline formation.* When 2-chloro-3-formyl-7-methylquinoline (2.05 g), methyl thioglycolate (1.2 g), and sodium carbonate (1.06 g, anhydrous) in ethanol (10 ml) were refluxed for 6 h and then poured onto ice a yellow precipitate was deposited (1.9 g, 76%). Recrystallisation from ethyl acetate and light petroleum gave 2-*methoxycarbonyl-7-methylthieno*[2,3-b]*quinoline* (9) as crystals, m.p. 158—160 °C (Found: C, 65.6; H, 4.3; N, 5.5. $C_{14}H_{11}NO_2S$ requires C, 65.4; H, 4.3; N, 5.45%); δ($CDCl_3$) 2.62 (s, Me), 4.00 (s, CO_2Me), and 7.22—8.51 (m).

(*ii*) When the same reaction was refluxed for 1 h and then poured into water a cream precipitate formed. Crystallisation from ethyl acetate–light petroleum gave *methyl* S-(*3-formyl-7-methyl-2-quinolyl*)*thioglycolate* (11) (1.84 g, 67%) as fine crystals, m.p. 110—112 °C (Found: C, 61.4; H, 4.8; N, 5.4. $C_{14}H_{13}NO_3S$ requires C, 61.1; H, 4.8; N, 5.1%); $\nu_{max.}$ (Nujol) 1 700 cm^{-1} (CO); δ($CDCl_3$) 2.63 (s, Me), 3.80 (s, CO_2Me), 4.14 (s, CH_2), 7.30—7.82 (m, ArH), and 10.29 (s, (CHO).

(c) *With 2,3-diformyl-7-methylquinoline* (1c). (*i*) The title compound (0.3 g, 0.0015 mol) in ethanol (10 ml) was treated

with hydrazine hydrate (0.1 g, 0.002 mol) at ambient temperature with stirring for 30 min and then poured into water. Extraction with chloroform (3 × 50 ml), gave, after drying with magnesium sulphate and evaporation, a solid (0.28 g, 96%) which was recrystallised from ethanol as pale yellow needles, m.p. 208—209 °C, of *7-methylpyridazino*[4,5-b]-*quinoline* (12) (Found: C, 74.1; H, 4.7; N, 21.8. $C_{12}H_9N_3$ requires C, 73.8; H, 4.65; N, 21.5%); $\nu_{max.}$ (Nujol) 3 040, 1 630, 1 600, 1 285, 1 260, 1 160, and 790 cm^{-1}; δ($CDCl_3$) 2.68 (s, Me), 7.58 (dd, H-8), 8.04 (d, H-9), 8.10 (s, H-6), 8.84 (s, H-10), 9.61 (d, H-1), and 9.81 (s, H-4) ($J_{8,9}$ 9, $J_{1,4}$ 1.7 Hz). Double irradiation at δ 8.84 (H-10) sharpened the broad singlet for H-4 at δ 9.81 (revealing it as a doublet) but left the signal at δ 9.61 (H-1) unaffected.

(*ii*) To the diformylquinoline (1e; R^1 = 7-Me) (0.4 g, 0.002 mol) and diethyl 3-oxoglutarate (0.43 g, 0.0021 mol) in dioxan (10 ml, distilled from sodium) was added piperidine (2 drops) and the mixture was refluxed for 3 h. Evaporation of the solvent gave an oil which was chromatographed on alumina. Elution with toluene gave an aliphatic polymer, while toluene–chloroform (3 : 1 v/v) gave a brown solid (0.16 g, 22%) which was recrystallised from toluene–light petroleum to give 7,9-*bisethoxycarbonyl*-3-*methylcyclohepta*-[b]*quinolin*-8-*one* (13) as off-white needles, m.p. 162—164 °C (Found: C, 69.1; H, 5.3; N, 3.75. $C_{21}H_{19}NO_5$ requires C, 69.0; H, 5.2; N, 3.8%); $\nu_{max.}$ (Nujol) 1 705, 1 675 (CO), 1 605, 1 275, and 1 240 cm^{-1}; δ($CDCl_3$) 1.40 (t, CH_3CH_2), 2.60 (s, Me), 4.41 (q, CH_3CH_2O), 7.51 (dd, H-2), 7.84 (d, H-1), 7.95 (s, H-4), 8.16 (s, H-10), 8.38 (s, H-6), and 8.48 (s, H-11) ($J_{1,2}$ 8 Hz). Repeating the reaction with twice as much diethyl 3-oxoglutarate, with prolonged heating (6 h), or in a different solvent (acetonitrile) did not improve the yield.

(d) *With* 3-(1,3-*dioxolan*-2-*yl*)-2-*formyl*-7-*methylquinoline* (4e; R^1 = 7-Me). A mixture of the title quinoline (0.5 g, 0.0021 mol), *o*-phenylenediamine (0.25 g, 0.0023 mol), and benzene (20 ml) was refluxed for 3 h and then the solvent was removed to give a red oil. Ethanol (10 ml) and aqueous hydrochloric acid (2 ml; 2M) were added and the solution was stirred for 1 h at room temperature. The solution was made alkaline and extracted with chloroform (3 × 50 ml), and the extract was dried ($MgSO_4$) and evaporated. The residue was chromatographed on alumina with toluene–chloroform (3 : 1 v/v) as eluant to give a red solid (0.21 g) which was further purified by preparative t.l.c. on silica with elution with chloroform (×2). The main band was scraped off, extracted with dichloromethane (2 × 50 ml) to give 2-(*benzimidazol*-2-*yl*)-3-(1,3-*dioxolanyl*-2-*yl*)-7-*methyl*-*quinoline* (14) (0.14 g, 21%) as an off-white oil that solidified on standing. It was recrystallised from toluene as white needles, m.p. 162—164 °C (Found: C, 72.5; H, 5.2; N, 12.8. $C_{20}H_{17}N_3O_2$ requires C, 72.5; H, 5.2; N, 12.7%); $\nu_{max.}$ (Nujol) 1 615, 1 590, 1 395, and 740 cm^{-1}; δ($CDCl_3$) 2.55 (s, Me), 4.21 (s, 2 × CH_2), 7.2—7.45 (m, 4 H), 7.68 (s, OCHO), 7.76 (d, H-5), 7.88 (m, H-6 and -8), 8.60 (s, H-4), and 10.90br (NH) ($J_{5,6}$ 9 Hz); *m/e* 331 (M^+, 6%), 330 (2), 286 (M − EtO, 10), 285 (M − CH_2O_2, 6), 271 (M − $C_2H_4O_2$, 8), 270 (M − EtO_2, 6), and 259 (100).

(e) *With* 3-*formyl*-2-*quinolone oximes* (5b). (*i*) Treatment of 3-hydroxyiminomethyl-7-methyl-2-quinolone (5b; R^1 = 7-Me) (0.15 g, 0.000 74 mol) with polyphosphoric acid (20 g) at 150 °C with stirring for 30 min, followed by dilution with water, gave a solution which on making alkaline with aqueous sodium hydroxide (4M) gave a precipitate. The product was filtered off, washed, dried, and recrystallised from ethanol to give 3-aminido-7-methyl-2-quinolone as a pale fawn solid (0.09 g, 60%), m.p. 282—284 °C (satisfactory elemental analysis not obtained); $\nu_{max.}$ (Nujol): 3 350, 3 175 (NH_2), 1 670 (CO), and 1 220 cm^{-1}; δ([$^2H_6$]-DMSO) 2.43 (s, Me), 7.14 (d, H-6), 7.21 (s, H-8), 7.80 (d, H-5), 8.80 (s, H-4), and 12.25br (NH_2) ($J_{5,6}$ 8 Hz); *m/e* 202 (M^+, 100%), 186 (M − NH_2, 55), 185 (M − OH, 15), 159 (M − CONH, 40), 157 (25), 130 (25), 103 (20), and 77 ($C_6H_5^+$, 15).

(*ii*) The same oxime (0.40 g, 0.002 mol) in acetic anhydride (8 ml) was refluxed for 2 h. The mixture was then cooled, poured into water, and made alkaline with aqueous sodium hydroxide (4M). After 1 h the precipitate was filtered off, washed with water, and dried to give 3-*cyano*-7-*methyl*-2-*quinolone* (5d) as an off-white solid (0.37 g, 100%) which crystallised as white crystals from aqueous ethanol, m.p. 330—335 °C (decomp.) (Found: C, 71.5; H, 4.3; N, 15.3. $C_{11}H_8N_2O$ requires C, 71.7; H, 4.4; N, 15.2%); $\nu_{max.}$ (Nujol) 2 225 (CN), 1 660 (CO), 1 560, and 880 cm^{-1}; $\nu_{max.}$ (hexachlorobutadiene) 2 930 cm^{-1} (NH); δ([$^2H_6$]DMSO) 2.41 (s, Me), 7.12 (d, H-6), 7.15 (s, H-8), 7.65 (d, H-5), 8.69 (s, H-4), and 12.30br (NH) ($J_{5,6}$ 9 Hz); *m/e* 184 (M^+, 100%), 183 (M − H, 9), 156 (M − CO, 41), 155 (M − CHO, 26), 129 (9), 128 (9), 102 (9), and 101 (9).

(f) *With* 7-*methyl*-2-*t*-*butylthioquinoline*-3-*carbaldehyde oxime* (15).—When the title oxime (0.1 g, 0.004 mol) was heated at 210 °C for 50 min under vacuum, the residual solid (0.06 g, 82%) was identical to 3-cyano-7-methyl-2-quinolone (5d) prepared above.

(g) *With* (E)-3-(7-*methyl*-2-*oxo*-1,2-*dihydro*-3-*quinolyl*)-*acrylic acid*. (*i*) The title acid (0.8 g, 0.0035 mol) was stirred in polyphosphoric acid (100 g) for 2 h at 245 °C. After cooling and dilution with ice–water (100 ml), the clear solution was made alkaline with aqueous sodium hydroxide (4M), allowed to stand, and then filtered. The residue was washed with water and dried to give a brown solid (0.76 g) which was sublimed at 200 °C and 0.01 mmHg to give 8-*methylpyrano*[2,3-b]*quinolin*-2-*one* (0.43 g, 58%), m.p. 274 °C (decomp.) (Found: C, 74.0; H, 4.4; N, 6.75. $C_{13}H_9NO_2$ requires C, 73.9; H, 4.3; N, 6.6%); $\nu_{max.}$ (Nujol) 1 720 (CO), 1 620, 1 185, and 1 135 cm^{-1}; δ($CDCl_3$–[$^2H_6$]-DMSO) 2.52 (s, Me), 6.38 (d, H-3), 7.31 (dd, H-7), 7.69 (s, H-9), 7.75 (d, H-6), 7.80 (d, H-7), and 8.31 (s, H-5) ($J_{3,4}$ 12, $J_{6,7}$ 10, $J_{7,9}$ 2 Hz); *m/e* 211 (M^+, 100%), 183 (M − CO, 33), 182 (21), 154 (14).

(*ii*) The same acrylic acid (0.7 g, 0.003 mol) was heated with PPA as in the above experiment for 30 min at 245 °C, cooled to 70 °C, and diluted to 500 ml with water, and the solution was refluxed for 1 h. After cooling, the products were allowed to stand. The precipitate was filtered off, washed, and dried to give (Z)-3-(7-*methyl*-2-*oxo*-1,2-*dihydroquinolin*-3-*yl*)*acrylic acid* (18) as a pale brown solid (0.63 g, 90%), m.p. 229—230 °C (decomp.) then 266—268 °C (from aqueous ethanol) (Found: C, 68.3; H, 4.9; N, 6.3. $C_{13}H_{11}NO_3$ requires C, 68.1; H, 4.8; N, 6.1%); $\nu_{max.}$ (Nujol) 3 000 (OH), 1 690 (CO), 1 260 (d), and 1 220 cm^{-1}; δ([$^2H_6$]-DMSO) 2.40 (s, Me), 4.20br (NH and OH), 6.07 (d, H_α), 7.05 (d, H-6), 7.06 (d, H_β), 7.10 (s, H-8), 7.55 (d, H-5), and 8.30 (s, H-4) ($J_{5,6}$ 8, $J_{\alpha,\beta}$ 14 Hz); *m/e* 229 (M^+, 18%), 211 (M − H_2O, 20), 184 (M − CO_2H, 100), and 154 (10).

(h) *With* 2-*cyano*-3-(7-*methyl*-2-*oxo*-1,2-*dihydroquinolin*-3-*yl*)*acrylic acid*. (*i*) The title acid (0.75 g, 0.003 mol) was heated with stirring for 1 h at 150 °C in PPA (100 g). After cooling and dilution with water (500 ml) the mixture was allowed to stand and then filtered. The residue was washed

and dried to give 8-*methyl*-2-*oxo*-2H-*pyrano*[2,3-b]*quinoline*-3-*carboxylic acid* (19) as a grey solid (0.68 g, 90%) (attempts at recrystallisation caused decarboxylation); $\nu_{max.}$ (Nujol) 3 520 and 3 420 (OH), 1 740 (CO), 1 680, 1 280, 1 290 (d), 1 190, 805, and 740 cm^{-1}; δ([$^2H_6$]DMSO) 2.40 (s, Me), 7.05 (d, H-7), 7.12 (s, H-9), 7.54 (d, H-6), 7.74 (s, H-4), 8.10 (s, H-5), and 12.00br (NH) ($J_{6,7}$ 8 Hz); *m/e* 255 (M^+, 100%), 211 ($M - CO_2$, 78), 183 (40), 182 (28), 154 (28), and 127 (11) (Found: M^+, 255.054 34. $C_{14}H_9NO_4$ requires *M*, 255.0531).

(*ii*) The ethyl ester (7b) of the title acrylic acid (1.0 g, 0.0035 mol) was similarly heated in PPA for 1½ h at 195 °C. The solution was diluted with water (200 ml) and worked up as above to give the same product (0.84 g, 93%).

(i) *With ethyl* 2-*cyano*-3-(7-*methyl*-2-*t*-*butylthio*-3-*quinolyl*)-*acrylate* (8). The title ester (0.60 g, 0.0017 mol) was heated in ethanol (30 ml) containing concentrated aqueous hydrochloric acid (30 ml) for 1 h under reflux. After cooling, the mixture was poured into ice–water (50 ml) and the precipitate was filtered off. The solid was chromatographed on silica with chloroform as eluant to give 3-*ethoxycarbonyl*-8-*methyl*(*thiopyrano*[2,3-b]*quinolin*-2-*one*) (0.36 g, 70%) which was recrystallised from toluene to afford yellow needles, m.p. 192.5—193.5 °C (Found: C, 64.1; H, 4.4; N, 4.6. $C_{16}H_{13}NO_3S$ requires C, 64.2; H, 4.4; N, 4.7%); $\nu_{max.}$ (Nujol) 1 725 (CO), 1 640 (C=C), 1 595, 1 550, and 1 235 cm^{-1}; δ($CDCl_3$–[$^2H_6$]DMSO): 1.41 (t, CH_3CH_2), 2.60 (s, Me), 4.41 (q, CH_2), 7.45 (dd, H-7), 7.80 (s, H-9), 7.87 (d, H-6), 8.50 (s, H-4), and 8.59 (s, H-5) ($J_{6,7}$ 8, $J_{7,9}$ 2 Hz); *m/e* 299 (M^+, 35%), 271 ($M - C_2H_4$, 100), 254 (M – OEt, 15), 243 (80), 226 (15), 227 (38), 199 (35), 198 (35), 154 (50), and 127 (15). Further elution gave 8-*methoxy*-2-*oxo*-2H-*thiopyrano*[2,3-b]-*quinoline*-3-*carboxylic acid* (0.14 g, 30%) which recrystallised from toluene to give yellow needles, m.p. 220—227 °C; $\nu_{max.}$ (Nujol) 1 730 (CO), 1 585, 1 545, 1 380—1 340, and 1 180 cm^{-1}; δ($CDCl_3$) 2.68 (s, Me), 7.53 (d, H-7), 7.88 (s, H-9), 7.93 (d, H-6), 8.70 (s) and 9.15 (s) (H-4 and -5), and 12.20br (OH); *m/e* 271 (M^+ 76%) 243 (M – CO, 100), 227 ($M - CO_2$, 41), 227 (17), 119 (45), 198 (35), and 154 (31) (Found: M^+, 271.0302. $C_{14}H_9NO_3S$ requires *M*, 271.0302).

(j) *With* 3-(2-*chloroethyl*)-2-*quinolones* (5e). 3-(2-Chloroethyl)-7-methyl-2-quinolone (0.50 g, 0.002 mol) was heated with potassium hydroxide (5 g) in methanol (50 ml) under reflux for 2 h. The cooled solution was poured onto water (200 ml), filtered, washed well, and dried to give 7-*methyl*-2,3-*dihydrofuro*[2,3-b]*quinoline* (21; R = 7-Me) as a solid (0.33 g, 79%) which was recrystallised from ethanol as plates, m.p. 139—140 °C (Found: C, 77.9; H, 6.0; N, 7.6. $C_{12}H_{11}NO$ requires C, 77.8; H, 6.0; N, 7.6%); $\nu_{max.}$ (Nujol) 1 640, 1 620, 1 585, 1 235, and 910 cm^{-1}; δ($CDCl_3$) 2.47 (s, Me), 3.30 (t, 3-CH_2), 4.63 (t, 2-CH_2), 7.14 (dd, H-6), 7.51 (d, H-5), 7.60 (s, H-8), and 7.73 (s, H-4) ($J_{5,6}$ 8 Hz). Irradiation at δ 3.30 (H-3) decoupled the signal δ 4.63 and sharpened the resonance at δ 7.73.

Similarly 3-(2-chloroethyl)-7-methoxy-2-quinolone (5e; R = OMe) gave 7-*methoxy*-2,3-*dihydrofuro*[2,3-b]*quinoline* (21; R = 7-Me) (61%) as white crystals from ethyl acetate and light petroleum, m.p. 130 °C (Found: C, 71.6; H, 5.5; N, 7.1.1 $C_{12}H_{11}NO_2$ requires C, 71.6; H, 5.5; N, 7.0%); $\nu_{max.}$ (Nujol) 1 620 and 1 580 cm^{-1}; δ($CDCl_3$) 3.15 (t, CH_2-CH_2O), 3.85 (s, MeO), 4.52 (t, CH_2O), 6.92 (dd, H-6), 7.15 (d, H-8), 7.40 (d, H-5), and 7.55 (s, H-4) ($J_{CH_2-CH_2}$ 8, $J_{5,6}$ 9, $J_{6,8}$ 2 Hz).

A solution of 3-(2-chloroethyl)-7-methylquinolone (1.0 g, 0.0045 mol) and sodium azide (0.44 g, 0.0068 mol) in ethanol (50 ml) and water (10 ml) was refluxed for 2 h, and then evaporated to low volume. The crystalline precipitate was filtered off, washed with water, and dried to give 7-methyl-2,3-dihydrofuro[2,3-*b*]quinoline (21) (0.76 g, 90%), identical to the sample reported above.

(k) *With* 2-*chloro*-3-(2-*chloroethyl*)*quinolines* (3a). A solution of 2-chloro-3-(2-chloroethyl)-7-methoxyquinoline (1.0 g) and thiourea (1 g) in ethanol (50 ml) was heated under reflux for 1 h and then poured into ice–water. The crystalline mass was filtered off, washed with water, dried, and recrystallised from aqueous ethanol to give 7-*methoxy*-2,3-*dihydrothieno*[2,3-b]*quinoline* (22) (0.6 g, 68%), m.p. 105—106 °C (Found: C, 66.5; H, 5.2; N, 6.3. $C_{12}H_{11}$-NOS requires C, 66.7; H, 5.1; N, 6.5%); δ($CDCl_3$) 3.22 (m, CH_2CH_2), 3.85 (s, MeO), 7.15 (d, H-8), 7.35 (d, H-5), and 7.42 (s, H-4) ($J_{5,6}$ 9, $J_{6,8}$ 2 Hz).

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