Reactions of Heterocycles with Thiophosgene. Part II.[1] The Chemistry of 3-Formylquinoline-2(1*H*)-thione

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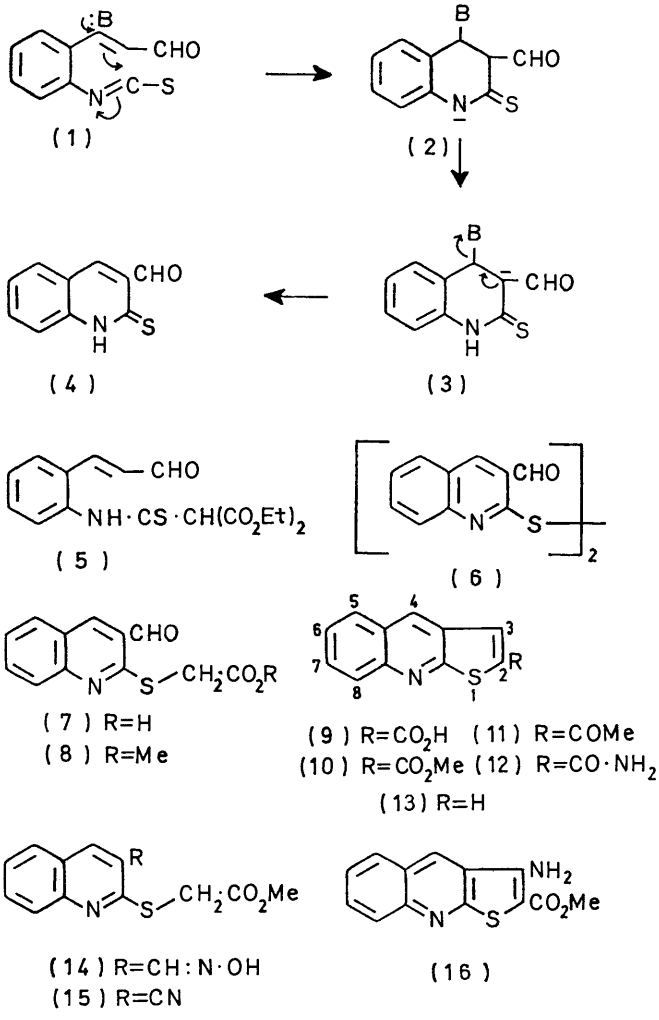
Reaction of *o*-isothiocyanato-*trans*-cinnamaldehyde, a scission product from quinoline and thiophosgene, with diethyl sodiomalonate gives 3-formylquinoline-2(1*H*)-thione. This compound has been used as an intermediate in the synthesis of thieno[2,3-*b*]quinolines, isothiazolo[5,4-*b*]quinoline, and some 2,3-substituted quinolines.

EARLIER studies [1] demonstrated that quinoline undergoes ring fission with thiophosgene and base to give *o*-isothiocyanato-*cis*-cinnamaldehyde, which isomerises in solution to the *trans*-isomer (1). The present paper describes the synthesis of some compounds from this useful intermediate.

The action of a variety of nucleophiles on the isothiocyanate (1) was first examined. Dilute alkali, in aqueous or alcoholic solution, alkoxides or tertiary bases gave the quinolinethione (4). Serendipity played a part in the production of our best yields (92%). An attempt to obtain the thioamide (5) by conventional attack on the isothiocyanate group by malonate ion [2] failed; instead the quinolinethione (4) was obtained. To account for these results we envisage an initial attack of base at the β-carbon atom of the unsaturated aldehyde, resulting in the tetrahydroquinoline (2) (a Michael type condensation) which by charge transfer and elimination of base yields the quinolinethione (4). Oxidation of the thione (4) with iodine solution gave the disulphide (6). The mass spectrum (M^+ **376**) showed initial losses of CHO and SH to give fragments of *m/e* **347** and **343**, respectively (dipyrimidin-2-yl disulphide shows an initial loss of S_2 [3]).

The presence of two functional groups on the quinoline nucleus of (4) suggested that a variety of ring systems could be constructed around the 2- and 3-positions. Attention was therefore next turned to the synthesis of thienoquinolines. Only a small amount of work has been published on this tricyclic system. Kuwayama [4] and his co-workers described the preparation of the parent compound (13) as the result of a five-stage process from 3-(2-hydroxyethyl)quinolin-2(1*H*)-one. In our approach we found that the formylquinolinethione (4) in the presence of a slight excess of methyl chloroacetate gave the quinolylthioacetic ester (8), which with sodium methoxide underwent ring closure to the thienoquinoline ester (10). Hydrolysis of the methyl ester (10) gave the acid (9). The ester (10) and acid (9) could also be obtained by one-step reactions from the quinolinethione (4) and methyl chloroacetate or chloroacetic acid, respectively. The ester (10) on reaction with ammonia was converted into the amide (12) in good yield. Treatment of the quinolinethione (4) with chloroacetone in the presence of sodium methoxide gave the methyl ketone (11). The ketone reacted with sodium hypochlorite to give the acid (9), identical with the product obtained before. Decarboxylation of the acid (9) in biphenyl–diphenyl ether yielded the parent thieno[2,3-*b*]quinoline (13), which had the same m.p. as the compound described by



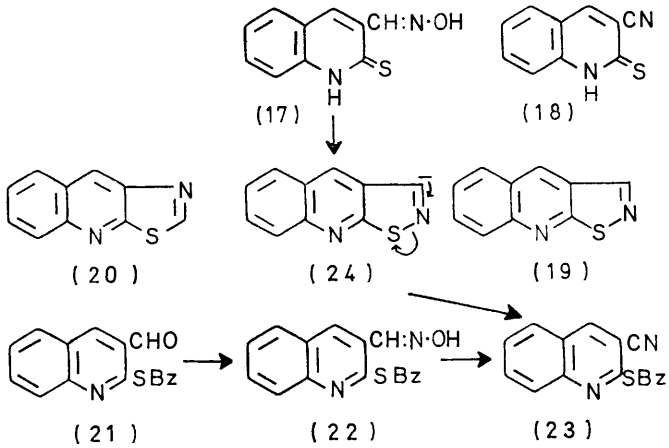
SCHEME 1

Kuwayama and his co-workers.[4] N.m.r. data (100 MHz; $CDCl_3$) are given in the Experimental section. It was thought that the 3-cyano-ester (15) might serve as a useful intermediate to open up functionality at C-3 of the thieno[2,3-*b*]quinoline. This compound (15) was obtained by standard methods from the formylquinoline

[1] R. Hull, *J. Chem. Soc.* (*C*), 1968, 1777 is taken as being Part I of this series.
[2] D. E. Worrall, *J. Amer. Chem. Soc.*, 1928, **50**, 1456.
[3] D. J. Brown and J. A. Hoskins, *J.C.S. Perkin I*, 1972, 522.
[4] Y. Kuwayama, *Yakugaku Zasshi*, 1962, **82**, 1028 (*Chem. Abs.*, 1963, **58**, 5687); G. Kobayashi, Y. Kuwayama, and S. O. Kamura, *ibid.*, 1963, **83**, 234 (*Chem. Abs.*, 1963, **59**, 5144); Y. Kuwayama, *J. Pharm. Soc. Japan*, 1962, **82**, 1028.

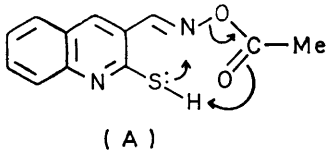
(8) *via* formation of the oxime (14) and dehydration with acetic anhydride. In the presence of methanolic sodium methoxide the cyano-ester (15) cyclised to the amino-ester (16) in a reaction not dissimilar to that observed in the benzothiophen [5] and thienopyrimidine [6] series.

The oxime (17), made by conventional methods from the formylquinoline (4), lost the elements of water on treatment with acetic anhydride to yield a compound $C_{10}H_6N_2S$ (50% yield, not optimised) (Scheme 2). Whereas the aldehyde (4) and the oxime (17) were freely soluble in 5N-sodium hydroxide, this compound was not. The n.m.r. spectrum [τ ($CDCl_3$) 0·95 (1H, s), 1·25 (1H, s), and 1·85—2·7 (4H, m)] showed no proton exchange on



SCHEME 2

deuteriation. The nitrile structure (18) may be therefore discounted. Of the two structures (19) and (20) open for consideration, that of the thiazoloquinoline (20), which could have arisen from the oxime (17) by a Beckmann transformation, was eliminated by observation of the following reaction sequence. *S*-Benzylation of the thione (4) followed by oxime formation and dehydration (hot acetic anhydride) gave the nitrile (23), which was identical with the compound obtained from the alkaline ring scission of the product $C_{10}H_6N_2S$ followed by *S*-benzylation (Scheme 2). The only possible structure for the compound $C_{10}H_6N_2S$ was therefore that of the novel heterocycle isothiazolo[5,4-*b*]-quinoline (19). The formation of the isothiazole (19) is most readily explained in terms of mechanism (A).



(A)

Other reactions of the thione (4) are under investigation.

EXPERIMENTAL

N.m.r. spectra were obtained on Varian A-60 or HA-100 spectrometers. Mass spectra were determined on an A.E.I. MS9 spectrometer.

Benzene is no longer used in our laboratories. In those experiments where benzene is used as a solvent toluene could most probably be substituted.

3-Formylquinoline-2(1H)-thione (4).—*o*-Isothiocyanato-*trans*-cinnamaldehyde [1] (96·6 g) in dry benzene (450 ml) was added dropwise during 1 h to a suspension of diethyl sodiomalonate [from 50% sodium hydride (24·5 g) and diethyl malonate (87·3 ml)] in dry benzene (2·2 l). After overnight stirring the sodio-derivative (101·3 g) was collected and washed successively with benzene and light petroleum. This was either used as such or was dissolved in water and acidified with acetic acid; the product (18·5 g from 20 g) was collected and washed with water. A sample recrystallised from propan-1-ol gave the *thione* as orange prisms, m.p. 288° (decomp.) (Found: C, 63·8; H, 3·7; N, 7·4. $C_{10}H_7NOS$ requires C, 63·5; H, 3·7; N, 7·4%), τ [$(CD_3)_2SO$] −0·77 (1H, s, CHO), 1·64 (1H, s, 4-H), and 2·3 (4H, m, aromatic H).

Bis-(3-formylquinolin-2-yl) Disulphide (6).—0·1N-Iodine solution (100 ml) was added dropwise to a warm suspension of sodium 3-formylquinoline-2-thiolate (2·11 g) in methanol (80 ml) until a sample of the mixture gave a positive test on starch–iodide paper. Next day the *product* (1·3 g), m.p. 204—207°, was collected. Recrystallisation (yellow plates) from dimethylformamide raised the m.p. to 213·5° (Found: C, 64·0; H, 3·1; N, 7·1%; *M*, 376. $C_{20}H_{12}N_2O_2S_2$ requires C, 63·8; H, 3·2; N, 7·45%; *M*, 376), τ ($CF_3{\cdot}CO_2H$) −0·45 (2H, s, CHO), 0·7 (2H, s, 4-H), and 1·55—1·95 (8H, m, aromatic H).

3-Formyl-2-methoxycarbonylmethylthioquinoline (8).—Methyl chloroacetate (18·9 ml) was added quickly to a stirred solution of sodium 3-formylquinoline-2-thiolate (42·0 g) in dimethylformamide (500 ml) and the mixture was heated under reflux during 15 min. After cooling, the mixture was poured into water (1 l); the product (37·5 g) was collected and washed with water. Recrystallisation from cyclohexane gave the *ester* (21·5 g) as yellow needles, m.p. 109—110° (Found: C, 60·2; H, 4·3; N, 4·9. $C_{13}H_{11}NO_3S$ requires C, 59·75; H, 4·2; N, 5·35%), τ ($CDCl_3$) −0·25 (1H, s, CHO), 1·55 (1H, s, 4-H), 2·0—2·75 (4H, m, aromatic), 5·9 (2H, s, CH_2), and 6·2 (3H, s, CH_3). The 2,4-*dinitrophenylhydrazone* was obtained as orange needles, m.p. 274° (decomp.) (Found: C, 52·3; H, 3·7; N, 15·6. $C_{19}H_{15}N_5O_6S$ requires C, 51·70; H, 3·4; N, 15·85%).

Methyl Thieno[2,3-b]quinoline-2-carboxylate (10).—(*a*) Methanolic sodium methoxide [sodium (0·012 g) in methanol (2 ml)] was added to a stirred suspension of 3-formyl-2-methoxycarbonylmethylthioquinoline (0·13 g) in methanol (6 ml). Next day the solid was collected, suspended in water, and neutralised with hydrochloric acid. The *product* (0·08 g) was collected. Recrystallisation from cyclohexane gave needles, m.p. 154—155° (Found: C, 64·1; H, 3·8; N, 5·6. $C_{13}H_9NO_2S$ requires, C, 64·2; H, 3·7; N, 5·75%), τ ($CDCl_3$) 1·38 (1H, s, 3-H), 1·65—2·8 (5H, m, aromatic), and 6·05 (3H, s, Me).

(*b*) Methyl chloroacetate (1·08 g) was added with shaking to a solution of 3-formylquinoline-2(1*H*)-thione (1·89 g) in methanolic sodium methoxide [sodium (0·23 g) in methanol (50 ml)]. After 0·25 h the product (1·55 g), identical with the above, was collected and washed with methanol.

Thieno[2,3-b]quinoline-2-carboxylic Acid (9).—(*a*) The ester (10) (0·1 g) in methanol (1·0 ml) and N-sodium

[5] C. E. Dalgleish and F. G. Mann, *J. Chem. Soc.*, 1945, 893.
[6] A. A. Santilli, D. H. Kim, and S. V. Wanser, *J. Heterocyclic Chem.*, 1971, **8**, 445.

hydroxide (5·0 ml) was heated under reflux during 1·5 h. The cool mixture was acidified with 5N-hydrochloric acid and the *acid* (0·08 g) was collected and washed with water. A solution of a sample in sodium hydrogen carbonate solution was filtered and acidified with acetic acid. The resulting acid, washed with water and ethanol, had m.p. 328—330° (decomp.) (Found: C, 60·2; H, 3·4; N, 5·6. $C_{12}H_7NO_2S,0·5H_2O$ requires C, 60·5; H, 3·4; N, 5·9%).

(*b*) A solution of chloroacetic acid (4·8 g) in N-sodium hydroxide (50 ml) was added to the thione (4) (9·4 g) in ethanol (80 ml) and N-sodium hydroxide (50 ml); the mixture was heated under reflux for 15 h, then acidified (to pH 5) with 5N-hydrochloric acid. The acid (9) (6·5 g), identical with that from (*a*), was collected and washed with water.

Thieno[2,3-b]*quinoline-2-carboxamide* (12).—The ester (10) (0·9 g) was heated with methanolic ammonia (20 ml; saturated at 0°) in a Carius tube at 100° for 6 h. The solid was collected, combined with the residue obtained by evaporating the filtrate, and recrystallised from methanol, giving the *amide* as hair-like needles (0·6 g), m.p. 267—267·5° (Found: C, 62·7; H, 3·8; N, 12·0. $C_{12}H_8N_2OS$ requires C, 63·1; H, 3·5; N, 12·3%).

2-Acetylthieno[2,3-b]*quinoline* (11).—Freshly distilled chloroacetone (0·925 g) was added with stirring to a solution of the thione (4) (1·89 g) in methanolic sodium methoxide [sodium (0·23 g) in methanol (70 ml)]. After 0·25 h the *ketone* (1·3 g) was collected. It formed yellow plates, m.p. 195° (from benzene) (Found: C, 68·2; H, 3·7; N, 5·8. $C_{13}H_9NOS$ requires C, 68·7; H, 3·95; N, 6·15%), τ [$CDCl_3$–$(CD_3)_2SO$] 1·35 (1H, s, H-3), 1·65—2·5 (5H, m, aromatic), and 6·3 (3H, s, CH_3).

Thieno[2,3-b]*quinoline* (13).—The acid (9) (1·0 g) was heated under reflux in biphenyl–diphenyl ether (1 : 3; 25 ml) during 2·5 h. The mixture was cooled and filtered and the filtrate was extracted thrice with 5N-sulphuric acid; the acidic extract was then extracted with ether and was basified, and the solid (0·2 g) was collected. Sublimation from a bath at 80° (0·4 mmHg) gave the product as needles, m.p. 104—106° (lit.,[4] 105—106°) (Found: C, 71·1; H, 4·2; N, 7·4. Calc. for $C_{11}H_7NS$: C, 71·45; H, 3·8; N, 7·55%), τ ($CDCl_3$) 1·55 (1H, s, 4-H), 1·9 (1H, d, $J_{8,7}$ 8 Hz, 8-H), 2·11 (1H, dd, $J_{5,6}$ 8, $J_{5,7}$ 1·5 Hz, 5-H), 2·21—2·42 (1H, td, $J_{7,8}$ 8, $J_{7,6}$ 6·5, $J_{7,8}$ 1·5 Hz, 7-H), 2·47—2·62 (1H, td, $J_{6,7}$ 6·5, $J_{6,5}$ 8, $J_{6,8}$ 1·5 Hz, 6-H), 2·72 (1H, d, $J_{3,2}$ 6 Hz, 3-H), and 2·5 (1H, d, $J_{2,3}$ 6 Hz, 2-H).

3-Hydroxyiminomethyl-2-methoxycarbonylmethylthioquinoline (14).—Methanolic hydroxylamine [prepared by adding triethylamine (7·575 g) in methanol (10 ml) to hydroxylamine hydrochloride (5·22 g) in water (4 ml)] was added to a warm solution of 3-formyl-2-methoxycarbonylmethylthioquinoline (19·5 g) in methanol (300 ml) and the mixture was heated under reflux during 1 h. The excess of reagent was removed under reduced pressure and the residue (19·8 g; m.p. 144—146°) was stirred with water and collected. Recrystallisation from methanol gave the *oxime* as yellow prismatic needles (15·7 g), m.p. 150—151° (Found: C, 56·5; H, 4·6; N, 10·1. $C_{13}H_{12}N_2O_3S$ requires C, 56·5; H, 4·35; N, 10·15%).

2-Methoxycarbonylmethylthioquinoline-3-carbonitrile (15).—The oxime (14) (0·2 g), acetic anhydride (0·074 g), and acetic acid (10 ml) were heated under reflux during 1 h. The mixture was added to ice–water and neutralised with sodium hydrogen carbonate. The solid (0·15 g) was collected. Recrystallisation from cyclohexane gave the *nitrile* as cream needles, m.p. 138—139° (Found: C, 60·2; H, 4·2; N, 10·4. $C_{13}H_{10}N_2O_2S$ requires C, 60·5; H, 3·9; N, 10·85%), τ ($CDCl_3$) 1·7 (1H, s, 4-H), 2·1—2·65 (4H, m, aromatic H), 5·85 (2H, s, CH_2), and 6·2 (3H, s, Me).

Methyl 3-Aminothieno[2,3-b]*quinoline-2-carboxylate* (16).—Methanolic sodium methoxide [sodium (0·16 g) in methanol (4 ml)] was added to a warm solution of the nitrile (15) (1·6 g) in methanol (50 ml) and the mixture was heated under reflux during 2 h. The *product* (1·2 g), m.p. 262° (decomp.), was collected when cool. Recrystallisation from methanol gave the amino-ester as orange needles, m.p. 263° (decomp.) (Found: C, 60·2; H, 3·8; N, 10·7. $C_{13}H_{10}N_2O_2S$ requires C, 60·5; H, 3·9; N, 10·85%), $\nu_{max.}$ (Nujol) 1680 (ester CO) and 3250 and 3400 cm^{-1} (NH stretch), τ [$CDCl_3$–$(CD_3)_2SO$] 1·0 (1H, s, 4-H), 1·8—2·7 (4H, m, aromatic H), 2·7—3·05br (2H, s, NH_2), and 6·075 (3H, s, CH_3).

3-Hydroxyiminomethylquinoline-2(1H)*-thione* (17).—Sodium acetate (3·24 g) was added to a stirred suspension of hydroxylamine hydrochloride (2·75 g) and the thione (4) (5·0 g) in dimethylformamide (100 mg); the mixture was warmed to 50° during 2 h, then added to water (600 ml), and the *product* (4·6 g), m.p. 197—198°, was collected and washed with water. Recrystallisation of a sample from aqueous ethanol gave the oxime as yellow needles, m.p. 205° (Found: C, 58·4; H, 4·4; N, 13·9. $C_{10}H_8N_2OS$ requires C, 58·8; H, 3·9; N, 13·7%).

Isothiazolo[5,4-b]*quinoline* (19).—The oxime (17) (8·0 g) was dissolved in hot acetic acid (320 ml), then cooled to about 40°. Acetic anhydride (5·8 ml) was added and the mixture was heated under reflux during 1 h. When cool it was added to ice–water (500 ml) and neutralised with 5N-sodium hydroxide. The solid obtained by filtration was washed with water and was dissolved in hot 5N-hydrochloric acid. The solution was filtered, and the filtrates neutralised with 5N-sodium hydroxide. The product (5·9 g) was collected. Recrystallisation from ethyl acetate gave the *isothiazoloquinoline* as creamy brown plates (3·7 g, 50%), m.p. 169—170° (Found: C, 64·6; H, 3·6; N, 14·8. $C_{10}H_6N_2S$ requires C, 64·5; H, 3·2; N, 15·05%). The *picrate* was obtained as yellow prismatic needles, m.p. 173—174° (Found: C, 46·7; H, 2·3; N, 16·5. $C_{10}H_6N_2S,C_6H_3N_3O_7$ requires C, 46·3; H, 2·2; N, 16·9%).

2-Benzylthioquinoline-3-carbaldehyde (21).—Benzyl chloride (0·84 ml) was added to a warm solution of sodium 3-formylquinoline-2-thiolate (2·1 g) in methanol (20 ml) and the mixture was heated under reflux during 18 h. After cooling, the product (1·8 g) was collected. Recrystallisation from ethanol gave the *benzylthioquinoline* as pale yellow prisms, m.p. 104° (Found: C, 72·7; H, 4·7; N, 4·8. $C_{17}H_{13}NOS$ requires C, 73·1; H, 4·65; N, 5·0%), τ ($CDCl_3$) −0·1 (1H, s, CHO), 1·85 (1H, s, 4-H), 2·0—2·85 (9H, m, aromatic H), and 5·45 (2H, s, CH_2).

2-Benzylthio-3-hydroxyiminomethylquinoline (22).—Solutions of hydroxylamine hydrochloride (0·695 g) and sodium acetate (0·82 g) in warm water (5 ml) and ethanol (5 ml) and the aldehyde (21) (0·93 g) in ethanol (20 ml) were mixed and heated under reflux during 4 h. After cooling, the product was collected. Recrystallisation from methanol gave the *oxime* as yellow needles (0·55 g), m.p. 169·5° (Found: C, 69·0; H, 5·0; N, 9·4. $C_{17}H_{14}N_2OS$ requires C, 69·45; H, 4·75; N, 9·5%).

2-Benzylthioquinoline-3-carbonitrile (23).—(*a*) A mixture of the oxime (22) (0·294 g), acetic acid (30 ml), and acetic anhydride (0·187 ml), was heated under reflux for 2·5 h.

More acetic anhydride (0·094 ml) was added and the reflux was continued for a further 1·5 h. The mixture was added to water (500 ml) and neutralised with sodium hydrogen carbonate, and the product was extracted with ether. The extracts were washed with sodium hydrogen carbonate solution and water, dried ($MgSO_4$), and evaporated. Recrystallisation of the residue from methanol gave the *nitrile* as fine yellow needles, m.p. 130—131° (Found: C, 73·9; H, 4·6; N, 10·3. $C_{17}H_{12}N_2S$ requires C, 73·9; H, 4·35; N, 10·15%).

(*b*) Ethanolic sodium ethoxide [sodium (0·075 g) in ethanol (6 ml)] was added to a warm solution of isothiazolo-[5,4-*b*]quinoline (0·6 g) in ethanol (20 ml) and the mixture was heated under reflux during 10 min. Benzyl chloride (0·42 g) in ethanol (10 ml) was then added to the cooled mixture (40°), and the reflux was continued for a further 30 min. The mixture was then evaporated to dryness under reduced pressure. The residue was treated with water and extracted with ether, and the extract was washed with water, dried ($MgSO_4$), and evaporated. The residue (0·8 g) was identical (i.r. spectrum, t.l.c., m.p.) with the product from (*a*).

I thank Mr. D. Greatbanks for obtaining and discussing the n.m.r. spectra.

[3/1570 *Received*, 25*th July*, 1973]