5,6,7,8-Tetrahydroquinolines. Part II.† Preparation and Reactions of Substituted 5,6,7,8-Tetrahydroquinoline-8-carboxylic Esters

By **Roger Crossley, Adrian C. W. Curran,*‡ and David G. Hill,** Institute of Medical Research, Wyeth Laboratories, Huntercombe Lane South, Maidenhead, Berkshire SL6 0PH

A series of substituted 5,6,7,8-tetrahydroquinoline-8-carboxylic esters have been prepared by the reaction of the 8-lithio- and 8-magnesio-derivatives of 5,6,7,8-tetrahydroquinolines with carbon dioxide followed by esterification. The esters were converted into the corresponding amides, nitriles, and thioamides.

We report a general, non-reductive synthesis of 5,6,7,8-tetrahydroquinoline-8-carboxylic acids and esters, -carboxamides, -carbonitriles, and -thiocarboxamides by carboxylation of 5,6,7,8-tetrahydroquinolines (THQs) *via* their 8-halogenomagnesio- and 8-lithio-derivatives.

The 8-bromomagnesio-derivative of 3-methyl-THQ (1e; X = MgBr), prepared by an exchange reaction with ethylmagnesium bromide,[1] reacted with carbon dioxide to give an intermediate isolable bromomagnesium salt of 3-methyl-THQ-8-carboxylic acid, which was esterified to give the ester (1e; X = CO_2Me) in 7% yield. The yield of ester was increased to 58% when the initial Grignard exchange reaction was effected with isopropylmagnesium bromide (Method 1).

Although the Woodward–Kornfeld ethoxycarbonylation [2] of 2-ethylpyridine gave a very low yield of ester [3]

† Part I, A. C. W. Curran, preceding paper.

‡ *Present address:* Reckitt and Colman Ltd., Pharmaceutical Division, Dansom Lane, Hull, HU8 7DS.

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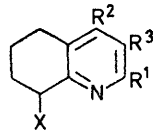
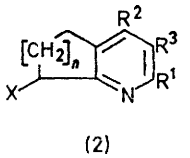
and 2-isobutylpyridine did not react,[4] the THQs (1a—d; X = H) gave moderate yields of the esters (1a—d;



(1)

a; R^1 = Ph, R^2 = R^3 = H
b; R^1 = R^2 = R^3 = H
c; R^1 = Me, R^2 = R^3 = H
d; R^1 = Bu^t, R^2 = R^3 = H
e; R^1 = R^2 = H, R^3 = Me



(2)

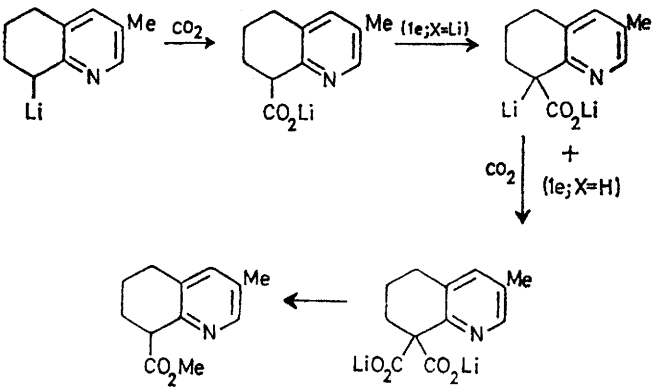
a; R^1R^3 = $[CH_2]_4$, R^2 = H, n = 2
b; R^1 = R^2 = H, R^3 = Me, n = 1
c; R^2 = H, R^1R^3 = $[CH_2]_3$, n = 1
d; R^2 = H, R^1R^3 = $[CH_2]_5$, n = 3

X = CO_2Me) (Table 1). Methoxycarbonylation of 2-methyl-THQ (1c; X = H) by treatment with phenyl-lithium followed by carbon dioxide and then esterification (Method 2) gave an ester which appeared to be pure by g.l.c., but n.m.r. analysis showed the presence of a mixture of the required ester (1c; X = CO_2Me) and methyl 5,6,7,8-tetrahydroquinolin-2-ylacetate. Although 3-methyl-THQ (1e; X = H) and 4-methyl-THQ [5] demonstrate no competitive methoxycarbonylation at the methyl group, the acidity of the 2-methyl group is sufficiently like that of the corresponding group in α-picoline or quinaldine for a lithio-derivative to be formed competitively with reaction at C-8.

Phenyl-lithium is known to react with 2,5-dimethylpyridine to give 2,5-dimethyl-6-phenylpyridine as a significant by-product from ethoxycarbonylation reactions; [2] the analogous side reaction was not observed with the THQs (1b and e; X = H). The use of other organolithium reagents in this work was *originally* contraindicated since methyl-lithium was known to be less successful than phenyl-lithium in the ethoxycarbonylation of α-picoline [6] and it is only recently that 2-picolyl-lithium has been prepared in good yields by using butyl-lithium.[7] However it was found that methoxycarbonylation of 8-lithio-3-methyl-THQ, prepared by using butyl-lithium (Method 3), gave a 42% yield of the ester (1e; X = CO_2Me) and, when the reaction was carried out by inverse addition of the intermediate lithio-derivative to carbon dioxide, the yield was increased to 68%. Addition of a further 0.5 mol. equiv. of butyl-lithium to the pre-esterification mixture from Method 3, followed by treatment with carbon dioxide and esterification, increased the yield from 42 to 58%. These two modifications to Method 3 support the proposal that proton transfer (Scheme) causes low methoxycarbonylation yields.

No 8,8-bis-esters were isolated from Methods 1—3 because of spontaneous decarboxylation of the intermediate bis-acid in acid. Evidence for bis-ester formation was, however, obtained in the reaction of the lithio-derivative (1e; X = Li) with methyl chloroformate, which gave, in addition to the ester (1e; X = CO_2Me) (23%), an unidentified high-boiling ester (20%) which, after hydrolysis and re-esterification, gave the ester (1e; X = CO_2Me). Similar proton transfer mechanisms have been reported in the acylation [8] and ethoxycarbonylation [9] of α-picoline. When the lithium derivative (1e; X = Li) was prepared from naphthyl-lithium [10] and 8-chloro-3-methyl-THQ and further treated *in situ* with methyl chloroformate, the ester (1e; X = CO_2Me) (18%) was isolated with no detectable bis-ester.

The scope and limitations of Methods 1—3 were further investigated by using *sym*-octahydroacridine (2a; X = H),[11] the pyrindine (2b; X = H),[12] the dicyclopenta[*b*,*e*]pyridine (2c; X = H),[11] and the dicyclohepta[*b*,*e*]pyridine (2d; X = H).[11] For these derivatives the reactions of the halogenomagnesio-derivatives



SCHEME

(2; X = MgBr) gave low yields (20%) of the esters (2a—d; X = CO_2Me).

The esters (1a—e; X = CO_2Me) and (2a—d; X = CO_2Me) were converted into crystalline amides as further proof of structure. The conditions for ammonolysis of ethyl 2-pyridylacetate with ammonium hydroxide [13] failed to have any effect on the esters in this study and it was only by pressure reaction with anhydrous ammonia in methanol that the amides (1a—e; X = CO·NH_2) (Table 1) and the amides (2a—d; X = CO·NH_2) (Experimental section) were obtained. The mixture of esters obtained from the THQ (1c; X = H)

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[11] N. S. Gill, K. B. James, F. Lions, and K. T. Potts, *J. Amer. Chem. Soc.*, 1952, **74**, 4923.
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gave an equivalent mixture of amides which were separated by fractional recrystallisation. The sodium methoxide-catalysed formamide exchange reaction [14] was most effective for producing the amide (1e; X = $CO{\cdot}NH_2$). Pressure reaction of the ester (1e; X = CO_2Me) with methylamine gave the corresponding secondary amide (1e; X = CO·NHMe).

An interest in thioamides led to an investigation of their formation by reaction of the amides (1a—e; X = $CO{\cdot}NH_2$) and (2a—d; X = $CO{\cdot}NH_2$) with phosphorus pentasulphide (Method A). However this reaction often gave a proportion of the nitrile (1 or 2; X = CN), which was separated from the thioamide by chromatography. Further reaction of the nitriles with hydrogen sulphide in pyridine–triethylamine (Method C) gave the appropriate thioamides. To prevent nitrile formation, Method A was carried out in the presence of hydrogen sulphide (Method B), giving high yields of thioamide (90%). Physical characteristics of the thioamides (1a—e; X = $CS{\cdot}NH_2$) are summarised in Table 2 and of the thioamides (2a—d; X = $CS{\cdot}NH_2$) in the Experimental section. The secondary thioamide (1e; X = CS·NHMe) was prepared from the secondary amide by Method A, and the tertiary thioamide (1e; X = $CS{\cdot}NMe_2$) was prepared from the corresponding primary thioamide by reaction with dimethylamine.

5,6,7,8-Tetrahydroquinoline-8-carbonitriles could be obtained by Method A, but it was discovered that a high yield (98%) of the nitrile (1e; X = CN) resulted from treatment of the thioamide (1e; X = $CS{\cdot}NH_2$) with hydrogen peroxide at 0 °C. The nitrile (1a; X = CN) was also obtained by dehydration of the amide (1a; X = $CO{\cdot}NH_2$) with hexamethylphosphoric triamide,[15] but the tertiary amide (1a; X = $CO{\cdot}NMe_2$) (20%) was formed in a side reaction.

EXPERIMENTAL

M.p.s were determined with a Mettler FPI instrument, microanalyses with a Perkin-Elmer 240 autoanalyser, and i.r. spectra with a Perkin-Elmer 521 instrument (for Nujol mulls unless otherwise stated); g.l.c. was performed with a Perkin-Elmer F11 instrument. All reactions with organometallic compounds were carried out in anhydrous solvents and under an inert atmosphere. N.m.r. data for new compounds are available as Supplementary Publication No. SUP 21683 (5 pp.).†

The starting materials [(1) and (2)] were prepared from quinolines by the method of Eliel [16] [for (1b; X = H)], from cycloalkanones by the method of Breitmaier [12] [for (1e and 2b; X = H)], or from 1,5-diketones by the method of Gill [11] [for (1a, c, and d, and 2a, c, and d; X = H)].

Ethoxycarbonylation of 5,6,7,8-Tetrahydroquinolines.—*Method* 1. The 5,6,7,8-tetrahydroquinoline (0.22 mol) was added dropwise to an ethereal solution of isopropylmagnesium bromide [from isopropyl bromide (0.44 mol)] and the mixture was heated, first at 60 °C to remove the ether and, after the addition of toluene (25 ml), at 130° for 2 h, allowing the toluene to distil off. The cooled mixture was diluted with ether (200 ml) and filtered under nitrogen, and the deep red solution was added dropwise with vigorous stirring to ether (400 ml) through which a stream of carbon dioxide was passed. When the colour had been discharged the solid was filtered off and added to methanol (300 ml) previously saturated at 0 °C with dry hydrogen chloride. After 8 h at room temperature the solvent was removed *in vacuo* and the residual oil diluted with water (100 ml) and washed with ether (2 × 50 ml). The aqueous phase was adjusted to pH 9.0 (Na_2CO_3) and extracted with ether (4 × 50 ml). The combined extracts were dried and evaporated *in vacuo* to give the desired ester.

Method 2. A solution of the 5,6,7,8-tetrahydroquinoline (0.091 mol) in ether (50 ml) was added dropwise over 0.5 h to an ethereal solution of phenyl-lithium [from bromobenzene (0.25 mol)] and, after 1 h at room temperature, the deep-red solution was treated with a stream of carbon dioxide until the colour was discharged. The solvent was removed *in vacuo* and the residual solid was esterified as in Method 1.

Method 3. A solution of the 5,6,7,8-tetrahydroquinoline (0.034 mol) in ether (20 ml) was treated with 9% (w/v) butyl-lithium in hexane (26.5 ml, 0.037 mol). The subsequent reaction with carbon dioxide and the esterification were as described in Method 2.

The esters derived from Methods 1—3 were separated from starting material by distillation or by hydrolysis to the sodium salt which, after purification, was re-esterified as described for (1e; X = CO_2Me).

Methyl 5,6,7,8-tetrahydro-3-methylquinoline-8-carboxylate (1e; X = CO_2Me). The crude ester obtained from 5,6,7,8-tetrahydro-3-methylquinoline (10.2 g) by Method 1 was heated under reflux for 3 h in 10% sodium hydroxide (100 ml). The resulting mixture was cooled and extracted with ether (3 × 100 ml). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* and the residue was distilled at 15 mmHg to give 5,6,7,8-tetrahydro-3-methylquinoline (4.1 g, 40%), b.p. 120°. The aqueous phase was adjusted to pH 7.3 with concentrated hydrochloric acid and the water was removed *in vacuo*. The residual solid was extracted with warm ethanol (2 × 50 ml); the extracts were filtered and evaporated to give *sodium 5,6,7,8-tetrahydro-3-methylquinoline-8-carboxylate hemihydrate* as a white amorphous powder (8.3 g) (Found: C, 60.0; H, 5.6; N, 6.4. $C_{11}H_{12}NaNO_2,0.5H_2O$ requires C, 59.6; H, 5.8; N, 6.4%). A suspension of the sodium salt in methanol (50 ml) at 0 °C was saturated with dry hydrogen chloride and, after 12 h at room temperature, the solvent was removed *in vacuo* and the residue dissolved in water (25 ml). The pH was adjusted to 9.0 (Na_2CO_3) and the mixture extracted with ether (3 × 50 ml) to give, after drying ($MgSO_4$) and evaporation, the ester as a pale yellow oil (6.8 g, 50%), g.l.c. (10% SE30; 200 °C) t_R 3.25 min (98%).

Application of Methods 1—3 gave the following esters (the method used and the yields and b.p.s of these and other esters are recorded in Table 1): *methyl 5,6,7,8-tetrahydro-2-phenylquinoline-8-carboxylate* (1a; X = CO_2Me) (Found: C, 76.8; H, 6.5; N, 5.1. $C_{17}H_{17}N$ requires C, 76.4; H, 6.4; N, 5.2%), $\nu_{max.}$ 1 725 cm^{-1} (CO_2Me); *methyl 5,6,7,8-tetrahydroquinoline-8-carboxylate* (1b; X = CO_2Me)

† For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1975, Index issue.

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hydrochloride (Found: C, 58.2; H, 6.3; N, 6.3. $C_{11}H_{13}NO_2$,HCl requires C, 58.0; H, 6.2; N, 6.2%), $\nu_{max.}$ 2 200—2 500, 2 000, 2 040, and 2 080 (pyridine hydrochloride), and 1 735 cm^{-1} (CO_2Me); 5,6,7,8-*tetrahydro*-3-*methylquinoline*-8-*carboxylate* (1e; X = CO_2Me) *hydrochloride* (Found: C, 59.9; H, 6.7; N, 6.0. $C_{12}H_{15}NO_2$,HCl requires C, 59.6; H, 6.7; N, 5.8%), $\nu_{max.}$ 2 300—2 600, 2 050, and 1 960 (pyridine hydrochloride), and 1 725 cm^{-1} (CO_2Me).

The following esters were also prepared by one of the general methods: (i) *methyl* sym-*octahydroacridine*-4-*carboxylate* (2a; X = CO_2Me) in 15% yield from *sym*-octahydroacridine by Method 3, purified *via* the sodium salt of the acid, as described for the ester (1e; X = CO_2Me); g.l.c. (2% OV 17; 200 °C) t_R 2.5 min; (ii) *methyl* 6,7-*dihydro*-3-*methyl*-5H-*pyrindine*-7-*carboxylate* (2b; X = CO_2Me) in 22% yield from 6,7-dihydro-3-methyl-5*H*-pyrindine by Method 1, b.p. 100—105° at 0.4 mmHg, g.l.c. 6.1; N, 6.5. $C_{10}H_{12}ClN$,HCl requires C, 55.1; H, 6.0; N, 6.4%). A solution of the hydrochloride in water (200 ml) was adjusted to pH 9.0 and extracted with ether (3 × 100 ml). The combined extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to give 8-*chloro*-5,6,7,8-*tetrahydro*-3-*methylquinoline* (13.5 g, 75%) as an oil.

Reaction of 5,6,7,8-*Tetrahydro*-8-*lithio*-3-*methylquinoline with Methyl Chloroformate*.—(i) A solution of 5,6,7,8-tetrahydro-3-methylquinoline (14.7 g, 0.1 mol) in ether (100 ml) was treated with a 9% (w/v) solution of butyl-lithium in hexane (86 ml, 0.12 mol) and, after 1 h at room temperature, the deep-red solution was added dropwise to a solution of methyl chloroformate (9.45 g, 0.1 mol) in ether (100 ml). After 1 h at 50 °C the mixture was treated with water (20 ml), acidified with 2N-hydrochloric acid, and washed with ether. The aqueous solution was adjusted to pH 9.0 (Na_2CO_3) and extracted with chloroform (3 × 50 ml). The combined extracts were dried ($MgSO_4$) and

TABLE 1

Esters and amides from carboxylation of 5,6,7,8-tetrahydroquinolines

Amide (1; X = CO·NH_2)	Intermediate ester (1; X = CO_2Me) Method	Yield [a,b] (%)	B.p. (°C) [mmHg]	g.l.c. (10% SE 30) t_R/min [°C]	Yield (%)	M.p. (°C)	Solvent [d]	Analysis Found (%) C	H	N	Formula	Required (%) C	H	N
(1a)	2 [e]	46	75—76 [f]		40	145—147	A	76.4	6.5	11.1	$C_{16}H_{16}N_2O$	76.2	6.4	11.1
(1b)	2	57	92 [0.05]	12 [150]	52	131—132	A	67.7	7.1	16.0	$C_{10}H_{12}N_2O$	68.1	6.9	15.9
(1c)	2	44 [g]	96—98 [0.3]	7 [165]	66 [h]	114—115	B	69.3	7.45	14.5	$C_{11}H_{14}N_2O$	69.45	7.4	14.7
(1d)	2	40	106—108 [0.4]	3.5 [165]	41	131—132	C	72.1	8.7	11.6	$C_{14}H_{20}N_2O$	72.4	8.7	12.0
(1e)	1 [i]	58 [j]	120—121 [0.5]	3.25 [200°]	73 [k]	118—119	C	69.6	7.5	14.8	$C_{11}H_{14}N_2O$	69.45	7.4	14.7

[a] The yield was determined by g.l.c. prior to distillation. [b] The balance was recovered as starting material (1; X = H). [c] Based on conversion from ester. [d] Solvents for recrystallisation: A = $MeCO_2Et$, B = $Pr^i{}_2O$, C = n-C_6H_{14}. [e] The methanol–hydrogen chloride reaction gave only 5,6,7,8-*tetrahydro*-2-*phenylquinoline*-8-*carboxylic acid* (1a; X = CO_2H) *hydrochloride*, m.p. 196—197° (Found: C, 66.6; H, 5.7; N, 4.8. $C_{16}H_{15}NO_2$,HCl requires C, 66.4; H, 5.6; N, 4.8%), which was esterified by refluxing with methanol–hydrogen chloride. [f] M.p. [g] Mixture of the ester (1c; X = CO_2Me) and methyl 5,6,7,8-tetrahydroquinolin-2-ylacetate (2:1 by n.m.r.). [h] The amide (1c; X = CO·NH_2) was separated from 5,6,7,8-tetrahydroquinolin-2-ylacetamide by fractional recrystallisation. [i] Ethylmagnesium bromide gave 7% yield of the ester (1e; X = CO_2Me). [j] Yield by method 2 44%; by method 3 42%, and by method 2 (inverse addition) 65%. [k] Formamide–sodium methoxide gave the amide (1e; X = $CONH_2$) in 88% yield.

(3% SE 30; 200 °C) t_R 1.5 min; (iii) *methyl* 1,2,3,5,6,7-*hexahydrodicyclopenta*[b,e]*pyridine*-3-*carboxylate* (2c; X = CO_2Me) in 18% yield from 1,2,3,5,6,7-hexahydrodicyclopenta[*b,e*]pyridine by Method 1, purified *via* the sodium salt of the acid as described for the ester (1e; X = CO_2Me); g.l.c. (10% SE 30; 220 °C) t_R 3.5 min; (iv) *methyl* 1,2,3,4,5,7,8,9,10,11-*decahydrodicyclohepta*[b,e]*pyridine*-5-*carboxylate* (2d; X = CO_2Me) in 17% yield from 1,2,3,4,5,7,8,9,10,11-decahydrodicyclohepta[*b,e*]pyridine by Method 1, purified *via* the sodium salt of the acid as described for the ester (1e; X = CO_2Me); g.l.c. (10% SE 30; 220 °C) t_R 11 min.

8-*Chloro*-5,6,7,8-*tetrahydro*-3-*methylquinoline*.— Methanesulphonyl chloride (22.9 g, 0.2 mol) was added to 5,6,7,8-tetrahydro-3-methylquinoline 1-oxide [17] (16 g, 0.1 mol) and the mixture was stirred at 0 °C for 2 h and then at 80 °C for 3 h. The cooled mixture was treated with water (500 ml) and the solution was adjusted to pH 9.0 (Na_2CO_3) and extracted with ether (3 × 100 ml). The combined extracts were dried ($MgSO_4$) and acidified with dry hydrogen chloride in ether to give 8-*chloro*-5,6,7,8-*tetrahydro*-3-*methylquinoline hydrochloride*, m.p. 177° (Found: C, 55.3; H, evaporated *in vacuo* and the residual oil (16 g) was assayed by g.l.c. (3% SE 30; 200 °C): t_R 1.25 (45%), 2.75 (23%), and 6 min (20%). Comparison with authentic methyl 5,6,7,8-tetrahydro-3-methylquinoline-8-carboxylate (t_R 2.75 min) and 5,6,7,8-tetrahydro-3-methylquinoline (t_R 1.25 min) gave the yield of the ester (1e; X = CO_2Me) as 18%. Distillation at 0.25 mmHg gave the ester as a pale yellow oil (3 g), b.p. 120—125°, $\nu_{max.}$ (film) 1 730 cm^{-1} (CO_2Me).

(ii) A solution of 8-chloro-5,6,7,8-tetrahydro-3-methylquinoline (3.43 g, 0.019 mol) and methyl chloroformate (1.49 g, 0.016 mol) in tetrahydrofuran (5 ml) was added over 1 h to a solution of naphthyl-lithium [from naphthalene (5.04 g, 0.039 mol) and lithium (0.354 g, 0.05 g atom)] in tetrahydrofuran (10 ml) at 0 °C. After a further 0.5 h at 0 °C the solvent was removed *in vacuo* and the residue dissolved in 2N-hydrochloric acid (25 ml) and extracted with ether (3 × 20 ml). The aqueous solution was adjusted to pH 9.0 (Na_2CO_3) and extracted with chloroform (3 × 50 ml). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residual oil (3.5 g) was assayed

[17] B. P. 1059702/1967.

by g.l.c. (3% OV1; 150—250 °C at 10 °C min^{-1}): t_R 3.5 (25%), 5 (55%), and 6 min (20%). Comparison with authentic methyl 5,6,7,8-tetrahydro-3-methylquinoline-8-carboxylate (t_R 6 min), 5,6,7,8-tetrahydro-3-methylquinoline (t_R 3.5 min), and 8-chloro-5,6,7,8-tetrahydro-3-methylquinoline (t_R 5 min) gave the yield of the *ester* (1e; X = CO_2Me) as 18%. Distillation at 0.25 mmHg gave the ester as a pale yellow oil (0.5 g), b.p. 120—122°, $\nu_{max.}$ (film) 1 730 cm^{-1} (CO_2Me).

Reaction of the Esters (1a—e; X = CO_2Me) *with Ammonia.*—The ester (4 g) was dissolved in methanol (90 ml) which had been saturated with ammonia at 0 °C, and the solution was heated in a sealed tube at 100 °C for 3 days. The solvent was removed *in vacuo* to give the amides (1a—e; X = $CO{\cdot}NH_2$) (Table 1). The following amides (2a—d; X = $CO{\cdot}NH_2$) were also obtained by reaction of the appropriate ester with ammonia: sym-*octahydroacridine-4-carboxamide* (2a; X = $CO{\cdot}NH_2$) (72%), m.p. 159—160° (needles from di-isopropyl ether) (Found: C, 72.9; H, 8.0; N, 12.0. $C_{14}H_{18}N_2O$ requires C, 73.0; H, 7.9; N, 12.2%); 6,7-*dihydro-3-methyl-5H-pyrindine-7-carboxamide* (2b; X = $CO{\cdot}NH_2$) (75%), m.p. 159—161° (needles from ethyl acetate) (Found: C, 68.0; H, 7.1; N, 15.8. $C_{10}H_{12}N_2O$ requires,C, 68.2; H, 6.9; N, 15.9%); 1,2,3,5,6,7-*hexahydrodicyclopenta*[b,e]*pyridine-3-carboxamide* (2c; X = $CO{\cdot}NH_2$) (20%), m.p. 188—189° (needles from methanol) (Found: C, 71.1; H, 7.2; N, 14.3. $C_{12}H_{14}N_2O$ requires C, 71.3; H, 7.0; N, 13.9%); 1,2,3,4,5,7,8,9,10,11-*decahydrodicycloheptа*[b,e]*pyridine-5-carboxamide* (2d; X = $CO{\cdot}NH_2$) (21%), m.p. 179—180° (needles from methanol) (Found: C, 74.5; H, 8.7; N, 10.7. $C_{16}H_{22}N_2O$ requires C, 74.4; H, 8.6; N, 10.9%).

5,6,7,8-*Tetrahydro-3-methylquinoline-8-carboxamide* (1e; X = $CO{\cdot}NH_2$).—A mixture of methyl 5,6,7,8-tetrahydro-3-methylquinoline-8-carboxylate (25 g, 0.13 mol), formamide (11.6 g, 0.26 mol), and sodium methoxide [from sodium (2.99 g, 0.13 mol)] was heated at 120 °C for 1 h and for a further 3 h at 100 °C and 15 mmHg. The cooled mixture was diluted with water (25 ml), acidified with concentrated hydrochloric acid, and extracted with ether (3 × 25 ml). The aqueous solution was adjusted to pH 9.0 (Na_2CO_3) and extracted with chloroform (2 × 50 ml), and the combined extracts were dried ($MgSO_4$) and evaporated to give 5,6,7,8-*tetrahydro-3-methylquinoline-8-carboxamide* (18.6 g, 88%), m.p. 110—111° (cubes from ethyl acetate) (Found: C, 69.6; H, 7.4; N, 14.4. $C_{11}H_{14}N_2O$ requires C, 69.5; H, 7.4; N, 14.7%); $\nu_{max.}$ 3 395, 3 280, 3 185, 1 680, 1 605, 1 595, 1 560, 900, and 575 cm^{-1}. When the amide (1e; X = $CO{\cdot}NH_2$) was obtained from the ammonia reaction (Table 2) it was isolated from hexane in a different crystalline form: $\nu_{max.}$ 3 395, 3 195, 1 650, 1 620, 1 605, 1 595, 1 560, 1 235, 875, and 620 cm^{-1}.

5,6,7,8-*Tetrahydro-3-methylquinoline-8-(N-methyl)carboxamide* (1e; X = $CO{\cdot}NHMe$).—Methyl 5,6,7,8-tetrahydro-3-methylquinoline-8-carboxylate (5 g) was dissolved in a 33% (w/v) solution of methylamine in ethanol (50 ml) and the solution was heated in a sealed tube at 150 °C for 24 h. The solvent was removed *in vacuo* and the residual solid was dissolved in ethanol (10 ml) and acidified with dry hydrogen chloride in ether to give 5,6,7,8-*tetrahydro-3-methylquinoline-8-(N-methyl)carboxamide hydrochloride* (4.2 g, 84%), m.p. 185—186° (needles from ethanol–ether) (Found: C, 59.8; H, 7.1; N, 11.3. $C_{12}H_{16}N_2O$,HCl requires C, 59.9; H, 7.1; N, 11.6%); $\nu_{max.}$ 3 240 (NH), 2 400—2 600, and 2 060 (pyridine hydrochloride), and 1 660 cm^{-1} ($CONH_2$).

5,6,7,8-*Tetrahydro-2-phenylquinoline-8-(NN-dimethyl)carboxamide* (1a; X = $CO{\cdot}NMe_2$).—A solution of 5,6,7,8-tetrahydro-2-phenylquinoline-8-carboxamide (6 g) in hexamethylphosphoric triamide (24 ml) was heated at 220 °C for 2 h, poured onto water (50 ml), and extracted with chloroform (3 × 100 ml); the combined extracts were washed with water (3 × 100 ml), dried ($MgSO_4$), and evaporated *in vacuo*. The residual oil was chromatographed on silica gel and eluted with chloroform to give 5,6,7,8-*tetrahydro-2-phenylquinoline-8-carbonitrile* (1a; X = CN) (2.5 g, 47%), m.p. 100—101° (needles from ether) (Found: C, 82.0; H, 6.2; N, 11.7. $C_{16}N_{14}N_2$ requires C, 82.0; H, 6.0; N, 11.9%); $\nu_{max.}$ 2 240 cm^{-1} (CN). Further elution with chloroform gave 5,6,7,8-*tetrahydro-2-phenylquinoline-8-(NN-dimethyl)carboxamide* (1.1 g, 20%), m.p. 140° (needles from ether) (Found: C, 77.2; H, 7.2; N, 10.2. $C_{18}H_{20}N_2O$ requires C, 77.1; H, 7.2; N, 9.9%); $\nu_{max.}$ 1 620 $(CONMe)_2$ and 725 and 760 cm^{-1} (aromatic H).

Formation of Thioamides (1a—e *and* 2a—d; X = $CS{\cdot}NH_2$).—*Method* A. A solution of the 5,6,7,8-tetrahydroquinoline-8-carboxamide (8 g) in pyridine (20 ml) was treated with phosphorus pentasulphide (5.2 g) and the mixture was heated under reflux for 0.5 h. The solvent was removed *in vacuo* and the residual oil was made basic with 4N-sodium hydroxide (20 ml) and extracted with chloroform (3 × 100 ml). The combined extracts were washed with water (3 × 50 ml), dried ($MgSO_4$), and evaporated *in vacuo* to give a mixture of the thioamide (1a—e and 2a—d; X = $CS{\cdot}NH_2$) and the nitrile (1a—e and 2a—d; X = CN).

Method B. A solution of the 5,6,7,8-tetrahydroquinoline-8-carboxamide (8 g) in pyridine (20 ml) was treated with hydrogen sulphide for 1 h at room temperature and, after the addition of phosphorus pentasulphide (5.2 g), the mixture was heated under reflux for a further 1 h while a slow stream of hydrogen sulphide was maintained. Work up as in Method A gave the thioamide uncontaminated by nitrile.

Method C. A solution of the 5,6,7,8-tetrahydroquinoline-8-carbonitrile (2 g) in pyridine (5 ml) and triethylamine (1.3 ml) was treated with a slow stream of hydrogen sulphide for 3 h. After 18 h at room temperature the solvent was removed *in vacuo* to give the thioamide.

Preparative and analytical data for the *thioamides* (1a—e; X = $CS{\cdot}NH_2$) are recorded in Table 2 and the thioamides (2a—d; X = $CS{\cdot}NH_2$) are described below.

sym-*Octahydroacridine-4-thiocarboxamide* (2a; X = $CS{\cdot}NH_2$). Method B gave the thioamide (4a; X = $CS{\cdot}NH_2$) (14%), m.p. 104—106° (needles from di-isopropyl ether) (Found: C, 68.7; H, 7.5; N, 11.0. $C_{14}H_{18}N_2S$ requires C, 68.3; H, 7.4; N, 11.4%).

6,7-*Dihydro-3-methyl-5H-pyrindine-7-thiocarboxamide* (2b; X = $CS{\cdot}NH_2$). Method B with a reflux time of 5 h and extraction with ether gave the thioamide (4b; X = $CS{\cdot}NH_2$) (73%), m.p. 64—66 °C (needles from di-isopropyl ether); *hydrochloride*, m.p. 198—202° (decomp.) (Found: C, 46.7; H, 5.95; N, 10.9. $C_{10}H_{12}N_2S$,HCl,1.5H_2O requires C, 46.95; H, 6.3; N, 10.95%).

1,2,3,5,6,7-*Hexahydrodicyclopenta*[b,e]*pyridine-3-thiocarboxamide* (2c; X = $CS{\cdot}NH_2$). Method B gave the thioamide (4c; X = $CS{\cdot}NH_2$) (40%), which was dissolved in methanol and acidified with dry hydrogen chloride in ether to give the *hydrochloride*, m.p. 298—299° (needles from methanol–ether) (Found: C, 56.4; H, 6.1; N, 10.8. $C_{12}H_{13}N_2S$ requires C, 56.1; H, 5.9; N, 11.0%).

1,2,3,4,5,7,8,9,10,11-*Decahydrodicyclohepta*[b,e]*pyridine*-5-*thiocarboxamide* (2d; X = CS·NH_2). Method B gave the thioamide (4d; X = CS·NH_2) (50%), which was dissolved in propan-2-ol and acidified with dry hydrogen chloride in ether to give the *hydrochloride hemihydrate*, m.p. 80—85° (needles from propan-2-ol) (Found: C, 60.2; H, 7.5; N, 8.3. $C_{16}H_{21}N_2S$,HCl,0.5H_2O requires C, 60.1; H, 7.6; N, 8.7%).

5,6,7,8-*Tetrahydro*-3-*methylquinoline*-8-*thiocarboxamide* (1e; X = CS·NH_2).—A mixture of 5,6,7,8-tetrahydro-3-methylquinoline-8-carbonitrile (1.7 g, 0.01 mol) and thioacetamide (1.5 g, 0.02 mol) in dimethylformamide (50 ml) was saturated with dry hydrogen chloride, heated at 100 °C for 4 h, poured onto water (200 ml), and extracted with ethyl acetate (2 × 200 ml). The pH was adjusted to 9.0 (Na_2CO_3) and the mixture was extracted with methylene chloride (2 × 200 ml); the combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give 5,6,7,8-*tetrahydro*-3-*methylquinoline*-8-*thiocarboxamide* (1.3 g, 63%), m.p. 149—150° (needles from benzene). The thioamide (1 g) was dissolved in boiling propan-2-ol (25 ml); the solution was filtered and allowed to cool to 40 °C. Addition of dry hydrogen chloride in ether gave the *hydrochloride* (0.95 g), m.p. 219° (needles) (Found: C, 54.3; H, 6.2; N, 11.4. $C_{11}H_{14}N_2S$,HCl requires C, 54.4; H, 6.2; N, 11.5%); $\nu_{max.}$ 3 300, 3 230, 3 060, 2 540, 1 650s, 1 605, and 1 555 cm^{-1}. A second crystalline form of the thioamide (1e; X = CS·NH_2) hydrochloride was obtained by acidifying a solution of the thioamide (0.5 g) in methanol (1 ml) with dry hydrogen chloride in ether. The solution was heated to boiling and ethyl acetate was added to turbidity. Refrigeration gave the *thioamide hydrochloride* (0.4 g), m.p. 244° (needles) (Found: C, 54.1; H, 6.2; N, 11.3. $C_{11}H_{14}N_2S$,HCl requires C, 54.4; H, 6.2; N, 11.5%); $\nu_{max.}$ 3 260, 3 220, 3 050, 2 630, 1 655—1 630 (3 sharp bands), and 1 555 cm^{-1}.

5,6,7,8-*Tetrahydro*-3-*methylquinoline*-8-(N-*methyl*)*thiocarboxamide* (1e; X = CS·NHMe).—A solution of 5,6,7,8-tetrahydro-3-methylquinoline-8-(*N*-methyl)carboxamide (1.2 g) in pyridine (9 ml) was treated with phosphorus pentasulphide (1.2 g) as described in Method A to give 5,6,7,8-*tetrahydro*-3-*methylquinoline*-8-(N-*methyl*)*thiocarboxamide* (0.9 g, 65%), m.p. 159—160° (needles from benzene) (Found: C, 65.1; H 7.3; N 12.6. $C_{12}H_{16}N_2S$ requires C, 65.4; H, 7.3; N, 12.2%); $\nu_{max.}$ 3 150—3 250 cm^{-1} (NH).

5,6,7,8-*Tetrahydro*-3-*methylquinoline*-8-(NN-*dimethyl*)*thiocarboxamide* (1e; X = CS·NMe_2).—A solution of 5,6,7,8-tetrahydro-3-methylquinoline-8-thiocarboxamide (1 g) in ethanol (100 ml) was treated with hydrogen sulphide for 2 h and then with a 33% (w/v) solution of dimethylamine in ethanol (50 ml). The mixture was heated in a sealed tube at 120 °C for 3 days and the volatile materials were removed *in vacuo* to give 5,6,7,8-*tetrahydro*-3-*methylquinoline*-8-(NN-*dimethyl*)*thiocarboxamide* (0.5 g, 44%), m.p. 135—136° (needles from ethyl acetate) (Found: C, 66.5; H, 7.8; N, 11.8. $C_{13}H_{18}N_2S$ requires C, 66.6; H, 7.7; N, 11.95%).

5,6,7,8-*Tetrahydro*-3-*methylquinoline*-8-*carbonitrile* (1e; X = CN).—A solution of 5,6,7,8-tetrahydro-3-methylquinoline-8-thiocarboxamide (2.06 g, 0.01 mol) in pyridine (7 ml) at 0 °C was treated dropwise with hydrogen peroxide (100 vols.; 1.44 ml, 0.012 mol). After 3 h at room temperature the volatile materials were removed *in vacuo* and the residual oil was dissolved in chloroform (20 ml); the solution was washed with water (3 × 10 ml), dried ($MgSO_4$), and evaporated *in vacuo* to give the *nitrile* (1e; X = CN) (1.5 g, 90%), b.p. 145° at 0.05 mmHg, g.l.c. (10% SE30; 180 °C) t_R 7 min (Found: C, 76.3; H, 7.1; N, 15.9. $C_{11}H_{12}N_2$ requires C, 76.5; H, 7.0; N, 16.2%); $\nu_{max.}$ (film) 2 240 cm^{-1} (CN). A sample (1 g) in ether (5 ml) was acidified with a solution of dry hydrogen chloride in ether to give the *hydrochloride* (0.95 g), m.p. 189—190° (from ethanol–ether) (Found: C, 63.1; H, 6.3; N, 13.3. $C_{11}H_{12}N_2$,HCl requires C, 63.3; H, 6.3; N, 13.4%).

TABLE 2

5,6,7,8-Tetrahydroquinoline-8-thiocarboxamides

Thioamide (1; X = CS·NH_2)	Method	Yield (%)	M.p. (°C)	Solvent	Analysis: Found (%) C	H	N	Formula	Required (%) C	H	N
(1a)	A	14 [a]	154—155	Et_2O	71.8	6.1	10.2	$C_{16}H_{16}N_2S$	71.6	6.0	10.4
(1a),HCl	C	40	211—212	MeOH-Et_2O	63.4	5.7	8.9	$C_{16}H_{16}N_2S$,HCl	63.0	5.6	9.1
(1b),HCl	B [b]	72	160—162	MeOH	59.8	6.2	14.0	$C_{10}H_{12}N_2S$,HCl, 0.25 H_2O	59.6	6.4	13.9
(1c)	B	28	98—99	$MeCO_2Et$	64.3	6.9	13.5	$C_{11}H_{14}N_2S$	64.0	6.8	13.6
(1d)	B [c]	15	126—127	n-C_6H_{14}	68.2	8.25	11.1	$C_{14}H_{20}N_2S$	67.7	8.1	11.2
(1e)	B	87	149—150	PhH	63.7	6.85	13.4	$C_{11}H_{14}N_2S$	64.0	6.8	13.6

[a] 5,6,7,8-*Tetrahydro*-2-*phenylquinoline*-8-*carbonitrile* (1a; X = CN) (16%), m.p. 100°, was also isolated. [b] Method A gave 5,6,7,8-*tetrahydroquinoline*-8-*carbonitrile* (1b; X = CN) *hydrochloride* (44%), m.p. 185° (needles from EtOH–Et_2O) (Found: C, 60.8; H, 5.7; N, 14.0. $C_{10}H_{10}N_2$,HCl, 0.25 H_2O requires C, 60.5; H, 5.8; N, 14.1%). [c] Method A gave 5,6,7,8-*tetrahydro*-3-*methylquinoline*-8-*carbonitrile* (1e; X = CN) *hydrochloride* (48%), m.p. 189—190° (needles from EtOH–Et_2O).

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