5,6,7,8-Tetrahydroquinolines. Part III.[1] Synthesis of 5,6,7,8-Tetrahydroquinoline-8-thiocarboxamides

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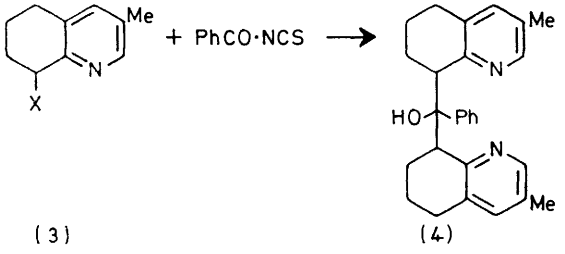
Reactions of the 8-lithio-derivative of 5,6,7,8-tetrahydroquinolines with trimethylsilyl isocyanate and isothiocyanate, followed by mild hydrolysis, provide a convenient one-step synthesis of 5,6,7,8-tetrahydroquinoline-8-carboxamides and thio-carboxamides respectively. The corresponding secondary thioamides were prepared by a similar reaction with appropriately substituted isothiocyanates.

THE preparation of 5,6,7,8-tetrahydro-8-lithio-2-phenylquinoline (1) and its reaction *in situ* with carbon dioxide was the first reported synthesis of a 5,6,7,8-tetrahydroquinoline-8-carboxylic acid (2).[1] This work has now been extended to the direct synthesis of the corresponding amides and thioamides by the reactions of 5,6,7,8-tetrahydro-8-lithioquinolines with isocyanates and isothiocyanates substituted by readily hydrolysable groups (*e.g.* *N*-ethoxycarbonyl, *N*-benzoyl, and *N*-trimethylsilyl). Ethoxycarbonyl isothiocyanate ($EtO_2C{\cdot}NCS$) and benzoyl isothiocyanate ($PhCO{\cdot}NCS$) have been used to prepare primary thioureas by reactions with primary and secondary amines,[2] but little is known of their reactions with anions to give thioamides. 5,6,7,8-Tetrahydro-8-lithio-3-methylquinoline (3; X = Li) did not react with ethoxycarbonyl isothiocyanate, and reacted with benzoyl isothiocyanate to give only the bis(tetrahydroquinolyl)-benzyl alcohol (4).



Apart from a report [3] on the preparation of triphenylsilyl isothiocyanate, which describes its reactions with phenyl-lithium and with phenylmagnesium bromide to give thiobenzamide, the use of silyl isothiocyanates to prepare primary thioamides has been little studied. In contrast, the preparation of primary thioureas by reactions of primary and secondary amines with trimethylsilyl isothiocyanate has been well documented.[4] The reactions of substituted isothiocyanates (R^5NCS) with organolithium compounds [5] and Grignard reagents [6] to give secondary thioamides are not as well known as their reactions with primary and secondary amines to give substituted thioureas.[7]

For the reaction with 5,6,7,8-tetrahydro-8-lithioquinolines, trimethylsilyl isothiocyanate and isocyanate were selected in preference to the triphenylsilyl derivatives because of their ready availability [8] and the greater ease of hydrolysis of the trimethylsilyl group.[3,4] The preparation of the novel 8-lithio-derivatives of 5,6,7,8-tetrahydroquinolines was modelled on a method used for 2-picolyl-lithium [9] [n-butyl-lithium in hexane (Method 1)]. Reaction of the lithium salt (3; X = Li) with trimethylsilyl isocyanate, followed by mild hydrolysis, gave a 34% yield of 5,6,7,8-tetrahydro-3-methylquinoline-8-carboxamide (3; $X = CO{\cdot}NH_2$). The application of trimethylsilyl isothiocyanate to the synthesis of thioamides was first studied with the anion (3; X = Li), and the conditions giving optimum yields of the thioamide (3; $X = CS{\cdot}NH_2$) were then applied to subsequent reactions with anions.

Trimethylsilyl isothiocyanate, assayed by n.m.r. to ensure the absence of hexamethyldisiloxane and trimethylsilanol, was treated with the anion (3; X = Li) and, after mild hydrolysis, gave a 40% yield of 5,6,7,8-tetrahydro-3-methylquinoline-8-thiocarboxamide (3; $X = CS{\cdot}NH_2$), which was purified by trituration with n-hexane to remove starting material and the nitrile (3; X = CN). The yield was marginally improved by using a solution of the anion (3; X = Li) in benzene, but no reaction took place in ether. This contrasts with normal organometallic reactions which proceed more rapidly in ethereal solvents than in hydrocarbons.[10]

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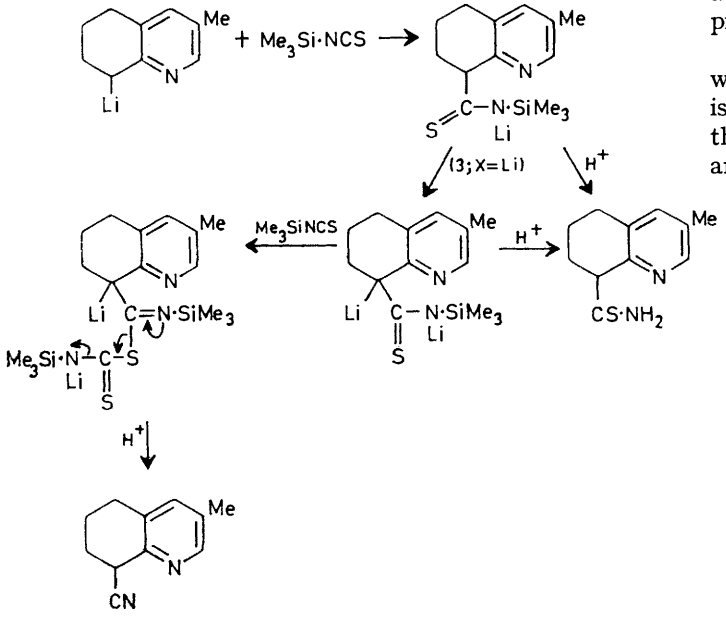
Although inverse addition had no effect on the yield, and very low yields were obtained at temperatures below −20 °C, an apparent optimum yield of 50% suggests the possibility of proton transfer (Scheme).

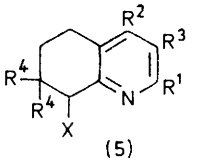


SCHEME

The 50% yield was achieved only when the anion (3; X = Li) was prepared by using lithium di-isopropylamide [11] (Method 2). Under these conditions the isolation of *NN*-di-isopropylthiourea (25%) indicated incomplete anion formation. The ratio of trimethylsilyl isothiocyanate to anion (3; X = Li) had a marked effect on the yield: higher ratios favoured the formation of the nitrile (3; X = CN), suggesting the involvement of a second molecule of isothiocyanate (Scheme).

To determine the scope and limitations of the reactions, the anions of the substituted tetrahydroquinolines (5a—h; X = H) and (6; X = H) and the anions of α-picoline and the 4-azadibenzo[*a*,*d*]cycloheptene (7; X = H) were treated with trimethylsilyl isothiocyanate. Table 1 summarises the yields and the properties of the resultant thioamides. The reaction was successful with all the substituted 5,6,7,8-tetrahydroquinolines, but the yield was highest where no other position was available for competitive anion formation. Although the 5,6,7,8-tetrahydroquinoline (5e; X = H) can form an additional anion at the C-2 methylene group, the product can confidently be assigned the structure (5e; X = CS·NH_2) since 2-picolyl-lithium did not react with trimethylsilyl isothiocyanate and compound (5d; X = H) gave the thioamide (5d; X = CS·NH_2). The anion (7; X = Li) did not form a thioamide with trimethylsilyl isothiocyanate; this probably reflects the steric constraints imposed by this system. It is not possible at this stage to explain the specificity of these reactions for the carbocycle but the strength and stability of the anion appear to be important factors, since the tetrahydroacridine (6; X = H) gave the highest yields of both primary and secondary thioamides.

For the synthesis of secondary thioamides the anions were formed by Method 1 and treated with the substituted isothiocyanates (R^5NCS) in ether. Table 2 summarises the yields and physical properties of the resultant thioamides.



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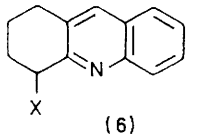
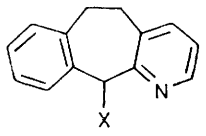


(6)

a; R^1=R^2=R^3=R^4=H
b; R^1=R^2=H, R^3=R^4=Me
c; R^1=R^3=R^4=H, R^2=Me
d; R^1=Et, R^2=R^3=R^4=H
e; R^2=R^3=R^4=H, R^1=Bu^n
f; R^2=R^3=Me, R^1=R^4=H
g; R^1=R^2=Me, R^3=R^4=H
h; R^1=Me, R^2=Ph, R^3=R^4=H



(7)

EXPERIMENTAL

M.p.s were determined with a Mettler FPI instrument, microanalyses with a Perkin-Elmer 240 instrument, i.r. spectra with a Perkin-Elmer 521 instrument, and n.m.r. spectra (100 MHz) with a Varian HA100 spectrometer. 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.

Starting Materials.—Reduction of the appropriately substituted quinoline hydrochloride by the method of Eliel [12] gave the following 5,6,7,8-tetrahydroquinolines (the yield, given in parentheses, was assessed by g.l.c. prior to distillation): 5,6,7,8-tetrahydro-3-methylquinoline (3; X = H) (95%), b.p. 120° at 14 mmHg (lit.,[13] b.p. 46—47° at 0.05 mmHg); 5,6,7,8-tetrahydroquinoline (5a; X = H) (65%), b.p. 120° at 14 mmHg (lit.,[14] b.p. 125° at 14 mmHg); 5,6,7,8-tetrahydro-4-methylquinoline (5c; X = H) (96%), b.p. 122—124° at 15 mmHg (lit.,[15] b.p. 125° at 15 mmHg), 2-*ethyl*-5,6,7,8-*tetrahydroquinoline* (5d; X = H) (95%), b.p. 122—124° at 15 mmHg (Found: C, 81.8; H, 9.7; N, 9.0. $C_{11}H_{15}N$ requires C, 81.9; H, 9.4; N, 8.7%); 2-*butyl*-5,6,7,8-*tetrahydroquinoline* (5e; X = H) (85%), b.p. 65—66° at 0.07 mmHg (Found: C, 82.7; H, 10.2; N, 7.3. $C_{13}H_{19}N$ requires C, 82.5; H, 10.1; N, 7.4%); 5,6,7,8-*tetrahydro*-3,4-*dimethylquinoline* (5f; X = H) (95%), b.p. 144—146 °C at 15 mmHg (Found: C, 82.1; H, 9.75; N, 9.1. $C_{11}H_{15}N$ requires C, 81.9; H, 9.4; N, 8.7%); 5,6,7,8-tetrahydro-2,4-dimethylquinoline (5g; X = H) (95%), b.p. 64—66° at 0.35 mmHg (lit.,[16] b.p. 250°); 5,6,7,8-*tetrahydro*-2-*methyl*-4-*phenylquinoline* (5h; X = H) (90%), m.p. 77—78° (needles

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from ether) (Found: C, 86.0; H, 7.9; N, 6.15. $C_{16}H_{17}N$ requires C, 86.05; H, 7.7; N, 6.3%).

The following starting materials were prepared by literature procedures: 5,6,7,8-tetrahydro-3,7,7-trimethylquinoline (5b; X = H), b.p. 59—60° at 0.2 mmHg (lit.,[17] b.p. 59—60° at 0.2 mmHg); 1,2,3,4-tetrahydroacridine (6; X = H), m.p. 55—57° [needles from petroleum (b.p.60—80 °C)] (lit.,[18] m.p. 57—59°); 5,6-Dihydro-11*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridine (7; X = H), b.p. 115° at 0.3 mmHg (lit.,[19] b.p. 139—146 °C at 1.2 mmHg); *hydrochloride* isolated as needles, m.p. 185—187° (Found: C, 72.5; H, 6.1; N, 5.9. $C_{14}H_{13}N$ requires C, 72.6; H, 6.1; N, 6.0%).

5,6,7,8-*Tetrahydro*-8-*lithio*-3-*methylquinoline* (3; X = Li). —*Method* 1 (*n-butyl-lithium*). A stirred solution of 5,6,7,8-tetrahydro-3-methylquinoline (7.3 g, 0.05 mol) in n-hexane (or ether or benzene) (50 ml) was cooled to 0 °C and treated dropwise with 9% (w/v) n-butyl-lithium in hexane (43 ml, 0.06 mol). After 1 h at 0 °C the anion was immediately treated with the isothiocyanates and isocyanates described below.

Method 2 (*lithium di-isopropylamide*). A stirred solution of di-isopropylamine (11.1 g, 0.11 mol) in benzene (50 ml) at 0 °C was treated dropwise with 9% (w/v) butyl-lithium in hexane (79 ml, 0.11 mol). After 1 h at 0 °C, 5,6,7,8-tetrahydro-3-methylquinoline (14.7 g, 0.1 mol) was added dropwise and then after 1 h at 0 °C the anion was immediately treated with the isothiocyanates described below.

Trimethylsilyl Isothiocyanate.—A vigorously stirred saturated aqueous solution of ammonium thiocyanate (50 ml) was cooled to 0 °C and treated in portions with trimethylsilyl chloride (pre-cooled to 0 °C) (27.1 g, 0.25 mol) and the mixture was stirred at 0 °C for a further 15 min. The suspension was filtered and the organic layer dried ($MgSO_4$) and distilled under nitrogen at 50 mmHg to give the isothiocyanate as an oil (20.1 g, 61%), b.p. 69—70° (lit.,[8] b.p. 53° at 28 mmHg), showing no absorption at δ 0.15 ($OSiMe_3$).

Reactions of Anions with Isothiocyanates and Isocyanates. —(a) *With ethoxycarbonyl isothiocyanate.*[20] An ethereal solution of 5,6,7,8-tetrahydro-8-lithio-3-methylquinoline (0.05 mol) prepared by Method 1 was treated dropwise with ethoxycarbonyl isothiocyanate (6.55 g, 0.05 mol) in ether (10 ml). After 18 h at 0 °C and acidification with 2N-HCl the aqueous phase was adjusted to pH 10.0 (Na_2CO_3) and extracted with ethyl acetate (3 × 100 ml). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give unchanged 5,6,7,8-tetrahydro-3-methylquinoline (6.8 g).

(b) *With benzoyl isothiocyanate.*[21] An ethereal solution of 5,6,7,8-tetrahydro-8-lithio-3-methylquinoline (0.05 mol) prepared by Method 1 was cooled to 0 °C and added to benzoyl isothiocyanate (9.8 g, 0.06 mol) in ether (50 mol) at 0 °C. After 1 h at 0 °C the mixture was diluted with water (50 ml) and acidified with 2N-HCl and the aqueous phase was adjusted to pH 10.0 (Na_2CO_3) and extracted with chloroform (3 × 50 ml). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give αα-*bis*-(5,6,7,8-*tetrahydro*-3-*methyl*-8-*quinolyl*)*benzyl alcohol* (4 g, 20%) as needles (from ethanol), m.p. 139—140° (Found: C, 81.1; H, 7.7; N, 6.9. $C_{27}H_{30}N_2O$ requires C, 81.4; H, 7.6; N, 7.0%).

(c) *With trimethylsilyl isocyanate.*[22] A solution of 5,6,7,8-tetrahydro-8-lithio-3-methylquinoline (0.05 mol) in hexane prepared by Method 1 was cooled to 0 °C and added dropwise to trimethylsilyl isocyanate (19.5 g, 0.17 mol) in hexane (50 ml) at −20 °C. After 0.5 h at −20 °C the mixture was warmed to room temperature and diluted with water (20 ml), and the pH was adjusted to 2 with 2N-HCl. The aqueous phase was adjusted to pH 9.0 (Na_2CO_3) and extracted with chloroform (3 × 50 ml) and the combined extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residual oil was triturated with n-hexane to give 5,6,7,8-tetrahydro-3-methylquinoline-8-carboxamide [1] (3.1 g, 34%), m.p. 104° (needles from ethyl acetate) (Found: C, 69.1; H, 7.4; N, 14.7. Calc. for $C_{11}H_{14}N_2O$: C, 69.5; H, 7.4; N, 14.7%). The hexane solution was distilled at 15 mmHg to give 5,6,7,8-tetrahydro-3-methylquinoline (4.5 g), b.p. 120°.

(d) *With trimethylsilyl isothiocyanate.* (i) A solution of 5,6,7,8-tetrahydro-8-lithio-3-methylquinoline (0.05 mol) in hexane, prepared by Method 1, was cooled to 0 °C and treated dropwise with trimethylsilyl isothiocyanate (13.1 g, 0.1 mol) in hexane (50 ml). After 0.5 h at 0 °C and 0.5 h at room temperature the mixture was diluted with water (50 ml) and the pH adjusted to 2.0 with conc. HCl. The aqueous layer was separated, adjusted to pH 10.0 (Na_2CO_3), and

TABLE 1
Primary thioamides

Compound (X = CS·NH$_2$)	Method [a,b]	Yield [c] (%)	M.p.[d] (°C)	Analysis (%) Found C	H	N	Formula	Required C	H	N
(3), HCl	2 [e]	43 [f,g]	244—245	54.4	6.3	11.2	$C_{11}H_{14}N_2S$,HCl	54.4	6.2	11.5
(5a), HCl	2	20	263—264	52.6	6.0	12.2	$C_{10}H_{12}N_2S$,HCl	52.5	5.7	12.3
(5b), HCl	1	15	162—163	53.3	7.35	9.5	$C_{13}H_{18}N_2S$,HCl,1.25H_2O	53.3	7.4	9.55
(5c), HCl	2	19	212—213	54.9	6.4	11.5	$C_{11}H_{14}N_2S$,HCl	54.4	6.2	11.5
(5d)	2	20	73—75	65.25	7.6	12.75	$C_{12}H_{16}N_2S$	65.4	7.3	12.7
(5e)	2	15	54—56	68.0	8.4	11.2	$C_{14}H_{20}N_2S$	67.8	8.1	11.3
(5f)	2	5	163—165	65.1	7.8	12.2	$C_{12}H_{16}N_2S$	65.4	7.3	12.7
(5g)	1	0.1	83—84	65.8	7.3	12.6	$C_{12}H_{16}N_2S$	65.4	7.3	12.7
(5h)	2	5	174—175	72.0	6.7	9.4	$C_{17}H_{18}N_2S$	72.3	6.4	9.9
(6)	1	70	238—239	58.5	5.9	9.5	$C_{14}H_{14}N_2S$,HCl,0.5H_2O	58.4	5.6	9.9

[a] Method 1 in n-hexane; method 2 in benzene. [b] 1.1 : 1 Molar ratio of anion to trimethylsilyl isothiocyanate. [c] Balance was recovered as starting material. [d] All thioamides were isolated as pale yellow needles (from propan-2-ol). [e] Method 1 gave (3; X = CS·NH$_2$) in 40% yield. [f] 6% 5,6,7,8-Tetrahydro-3-methylquinoline-8-carbonitrile was also isolated. [g] 25% *NN*-Di-isopropylthiourea was also isolated.

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TABLE 2

Secondary thioamides [a]

Compound (X = CS·NHR[5])	R[5]	Yield [b] (%)	M.p.[c] (°C)	Analysis (%) Found C	Found H	Found N	Formula	Required C	Required H	Required N
(3)	Me	27	159—160	65.1	7.3	12.6	$C_{12}H_{16}N_2S$	65.4	7.3	12.7
(3)	Ph	15	139—140	72.0	6.5	9.7	$C_{17}H_{18}N_2S$	72.3	6.4	9.9
(3), HCl	Bu[n]	78	195—197	60.3	7.8	9.5	$C_{15}H_{23}N_2S,HCl$	60.3	7.4	9.4
(3), HCl	$PhCH_2$	36	230—233 [e]	65.1	6.5	8.7	$C_{18}H_{20}N_2S,HCl$	65.1	6.3	8.4
(3), HCl	$Ph[CH_2]_3$	18	238—239	67.0	7.2	7.8	$C_{20}H_{24}N_2S,HCl$	66.6	7.0	7.8
(5a), HCl	Me	46 [d]	250—253	54.5	6.5	11.5	$C_{11}H_{14}N_2S,HCl$	54.4	6.2	11.5
(6), HCl	Me	75	265—267	61.8	6.1	9.5	$C_{15}H_{16}N_2S,HCl$	61.5	5.8	9.6

[a] All lithium salts (X = Li) were prepared by Method 1 in ether. [b] Balance was recovered as starting material. [c] Pale yellow needles from propan-2-ol. [d] 5,6,7,8-*Tetrahydroquinoline*-8,8-*bis*-(N-*methyl*)*thiocarboxamide hydrochloride* (20%) was also isolated; m.p. 217—219 °C (needles from propan-2-ol) (Found: C, 48.7; H, 6.1; N, 12.5. $C_{13}H_{17}N_3S_2,HCl,0.25H_2O$ requires C, 48.7; H, 5.8; N, 13.1%). [e] Needles from ethanol.

extracted with chloroform (3 × 50 ml), and the combined extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residual oil was triturated with n-hexane to give 5,6,7,8-tetrahydro-3-methylquinoline-8-thiocarboxamide [1] (4.1 g, 40%), m.p. 153° (pale yellow needles from benzene) (Found: C, 64.6; H, 7.0; N, 13.9. Calc. for $C_{11}H_{14}N_2S$: C, 64.1; H, 6.8; N, 13.6%). The hexane solution was distilled at 15 mmHg to give 5,6,7,8-tetrahydro-3-methylquinoline (4.1 g, 55%), b.p. 120°.

(ii) A solution of 5,6,7,8-tetrahydro-8-lithio-3-methylquinoline (0.1 mol) in benzene, prepared by Method 2, was cooled to 0 °C and treated with trimethylsilyl isothiocyanate (14.7 ml, 0.11 mol) over 2 min. After 0.5 h at 0 °C and 1 h at room temperature, water (25 ml) was added and the pH was adjusted to 2.0 with 2N-HCl. The mixture was extracted with ethyl acetate (3 × 25 ml) and the combined extracts were dried ($MgSO_4$) and evaporated to give NN-*diisopropylthiourea* (5.1 g, 25%), m.p. 130°(needles from benzene) (Found: C, 52.5; H, 10.4; N, 17.5. $C_7H_{16}N_2S$ requires C, 52.5; H, 10.1; N, 17.5%). The acidic solution was adjusted to pH 10.0 (Na_2CO_3) and extracted with chloroform (3 × 50 ml), and the combined extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residual oil was triturated with n-hexane to give 5,6,7,8-tetrahydro-3-methylquinoline-8-thiocarboxamide (8.9 g, 43%), m.p. 153° (pale yellow needles from propan-2-ol). The hexane solution was distilled at 15 mmHg to give 5,6,7,8-tetrahydro-3-methylquinoline (7.17 g, 48%), b.p. 120°, and at 5 × 10^{-2} mmHg to give 5,6,7,8-tetrahydro-3-methylquinoline-8-carbonitrile [1] (1 g, 6%) as a pale yellow oil, b.p. 115—120 °C (Found: C, 76.3; H, 7.1; N, 16.0. Calc for $C_{11}H_{12}N_2$: C, 76.5; H, 7.0; N, 16.2%).

(iii) *Effect of change in molar ratio.* With hexane as solvent as in (i) the following results were obtained [expressed as Ratio of (3; X = H) to Me_3SiNCS, % yield of thioamide (3; X = $CSNH_2$), % yield of nitrile (3; X = CN) by g.l.c. (1% QF1; 150 °C)]: 1 : 4, 5, 35; 1 : 2, 40, 10; 1 : 1.5, 39, <5; 1 : 1.2, 36, <5; 1 : 1.1, 40, <5, 1 : 08, 34, 0; 1 : 0.5 35, 0. The balance of material was recovered as (3 : X = H).

(e) *With methyl isothiocyanate.* An ethereal solution of 5,6,7,8-tetrahydro-8-lithio-3-methylquinoline (0.05 mol), prepared by Method 1, was cooled to 0 °C and treated dropwise with methyl isothiocyanate (3.8 g 0.5 mol) in ether (10 ml); after 4 h at room temperature the mixture was diluted with 2N-HCl (15 ml) and the aqueous layer was adjusted to pH 10.0 (Na_2CO_3) and extracted with chloroform (3 × 20 ml). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residual oil was triturated with n-hexane to give 5,6,7,8-tetrahydro-3-methylquinoline-8-(*N*-methyl)thiocarboxamide [1] (3 g, 27%), m.p. 159—160° (needles from propan-2-ol) (Found: C, 65.1; H, 7.3; N, 12.6 Calc. for $C_{12}H_{16}N_2S$: C, 65.4; H, 7.3; N, 12.7%). The hexane solution was distilled at 15 mmHg to give 5,6,7,8-tetrahydro-3-methylquinoline (4 g), b.p. 120°.

By this general method the secondary thioamides summarised in Table 2 were obtained.

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