Synthesis of Quinoline Derivatives Using Ketene Dithioacetals

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Methyl 3-(*N*-arylamino)-2-cyano-3-methylthioacrylates **3a-h**, which are readily prepared by the reaction of the ketene dithioacetal, methyl 2-cyano-3,3-bis(methylthio)acrylate (**1**) with arylamines, was heated at reflux in diphenyl ether to give the corresponding 2-methylthio-4-hydroxyquinoline-3-carbonitriles **4a-h** in 14-77% yields. The reaction of **1** with excess aryl amines in diphenyl ether at reflux gave also the corresponding 2-arylamino-4-hydroxyquinoline-3-carbonitriles **6a-d**. The 2-methylthioquinoline-3-carbonitriles **4a-h**, thus obtained, are useful intermediates for the synthesis of various quinoline derivatives.

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Quinolines are important and interesting substances for the synthesis of pharmacologically active compounds and serve as fundamental key structural units in nitrogen-containing heterocyclic chemistry [1]. For this reason, many syntheses of quinoline derivatives have been reported. Among these, the Gould-Jacobson reaction, accompanied by the cyclization of alkyl 3-arylaminoacrylates at elevated temperature, is known as a versatile method for the synthesis of alkyl 4-oxo-1,4-dihydroquinoline-3-carboxylates [2-4]. This method facilitated the synthesis of naldixic acid which was used as a urinary antiseptic drug. Quinolines easily undergo nucleophilic attack and are strongly deactivated for electrophilic attack due to π-electron defficiency. However, the direct introduction of certain substituents into the quinoline nucleus is not easy. Introduction of functional groups concomitant with ring formation might be a valuable and efficient method for preparing substituted quinolines.

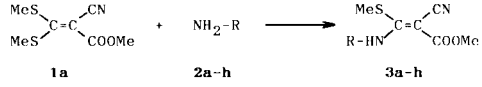
Electrophilic ketene dithioacetals are versatile and useful reagents for the synthesis of heterocyclic compounds [5-10]. The three carbon unit of ketene dithioacetals is imparted into the newly-formed ring when used in the synthesis of 2-pyrone and 2-pyridone derivatives [11,12]. We now report the synthesis of polyfunctionalized quinoline derivatives starting from ketene dithioacetals. Ketene dithioacetals are also versatile reagents for the preparation of methyl 3-arylaminoacrylates which are key intermediates for the synthesis of 4-hydroxyquinoline derivatives.

Ketene dithioacetals readily react with amines under mild conditions to give the corresponding mono-displaced ketene *S,N*-acetals [5-10,13]. Methyl 3-arylamino-2-cyano-3-methylthioacrylates **3a-h** were obtained by the reaction of the ketene dithioacetal, methyl 2-cyano-3,3-bis(methylthio)acrylate (**1a**), with arylamines (**a**; aniline, **b**; *p*-toluidine, **c**; *o*-anisidine, **d**; *m*-anisidine, **e**; *p*-anisidine, **f**; *o*-chloroaniline, **g**; *p*-chloroaniline, **h**; *p*-bromoaniline). This reaction was smoothly carried out at 100° to give the corresponding 3-arylaminoacrylate derivatives **3a-i** in good yields.

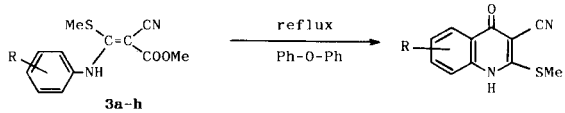
The cyclization of **3** occurred after reflux for 1 hour in diphenyl ether to give the desired poly-functionalized quinoline derivatives **4a-h** in 14-77% yield. The ir spectra of these quinoline derivatives show the carbonyl bands at 1600-1622 cm^{-1}, respectively. These carbonyl absorption bands appear lower than those of the 4-pyridone derivatives due to the participation of the enol tautomer in compounds **4a-h**.

In general, the methylthio groups of heterocyclic compounds react smoothly with amines or active methylene compounds to give the corresponding displacement products. However, the methylthio group of **3** did not react with amines even upon heating at temperatures of 100-150°. Methyl 3,3-dianilino-2-cyanoacrylate (**5a**), prepared by the displacement of **3a** with aniline at 150°, was heated at reflux in diphenyl ether to give 2-anilino-

Scheme 1



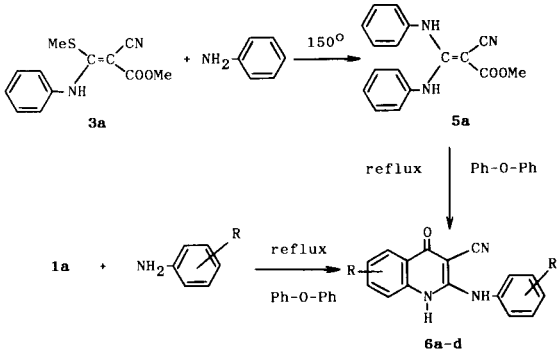
No.	R	mp(°C)	Yield(%)
3a	C_6H_5	81	92
b	C_6H_4-Me(p)	99	87
c	C_6H_4-OMe(o)	103	83
d	C_6H_4-OMe(m)	83	75
e	C_6H_4-OMe(p)	106	77
f	C_6H_4-Cl(o)	137	62
g	C_6H_4-Cl(p)	125	79
h	C_6H_4-Br(p)	144	87



No	R	mp(°C)	Yield(%)
4a	C_6H_5	318	63
b	C_6H_4-Me(6)	331	14
c	C_6H_4-OMe(8)	204	54
d	C_6H_4-OMe(7)	306	35
e	C_6H_4-OMe(6)	303	45
f	C_6H_4-Cl(8)	231	47
g	C_6H_4-Cl(6)	336	65
h	C_6H_4-Br(6)	325	77

quinoline derivatives **6a** in 28% yield. Compound **6a** was also synthesized in 21% yield in step by heating **1a** and aniline in diphenyl ether. Compounds **6b-d** were also directly prepared from **1a** and arylamines (*p*-anisidine, *o*-chloroanilin, *p*-chloroaniline) in 20-32% yield in a manner similar to that described for the preparation of **6a**.

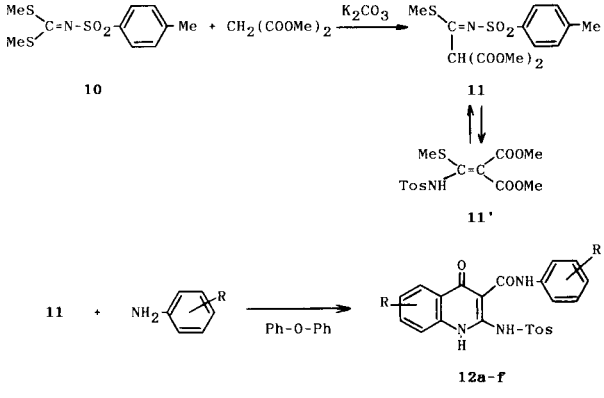
Scheme 2



No.	R	mp(°C)	Yield(%)
6a	H	314	20
b	OMe(6 and 4')	352	23
c	Cl(8 and 2')	302	20
d	Cl(6 and 4')	368	32

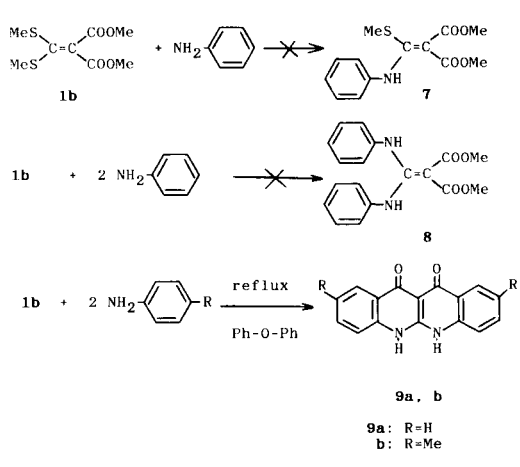
The reaction of dimethyl bis(methylthiomethylidene)-malonate (**1b**) with aniline at reflux temperature in diphenyl ether, however, did not give the desired quinoline derivative, but gave instead the quinolino[2,3-*b*]-quinoline derivative **9a** in 21% yield. Reaction of **1b** with *p*-toluidine gave a similar product **9b**. Mono- or di-displacement products could not be obtained after several attempts under various conditions because of the low activity of **1b** toward nucleophilic reagents. While the introduction of a second nucleophile requires more stringent reaction conditions, the reaction of *N*-acetyl or *N*-tosylketene *S,N*-acetals with amines occurs smoothly under mild conditions to give the corresponding diamine derivatives [14,15]. Therefore, we examined the synthesis of quinoline derivatives derived from *N*-tosylketene *S,N*-acetal **11**. The latter compound was prepared by the displacement of the methylthio group of *N*-bis(methylthio)methylene-*p*-toluenesulfonamide [2,16] with dimethyl malonate in the presence of potassium carbonate and dimethyl sulfoxide. A mixture of **11** and aromatic amines (aniline, *o*-, *m*- and *p*-anisidine, *o*- and *p*-chloroaniline) was heated at reflux in diphenyl ether for 1 hour to give the corresponding -aryl-4-hydroxy-2-(*p*-toluenesulfonyl)aminoquinoline-3-carboxamides **12a-f** in 32-52% yields.

Scheme 3



No.	R	mp(°C)	Yield(%)
12a	H	235	48
b	OMe(8 and 2')	204	52
c	OMe(7 and 3')	225	37
d	OMe(6 and 4')	255	40
e	Cl(8 and 2')	255	32
f	Cl(6 and 4')	270	50

Scheme 3'

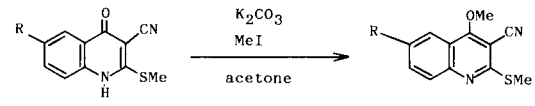


N-Alkyl-4-oxo-4*H*-quinoline-3-carboxylic acids bearing an alkyl group at the 1-position are interesting compounds having pharmacological activity (e.g., nalidixic acid). Therefore, alkylation of the ring nitrogen in quinolines **4** was examined. The methylation of **4a,b,e,g** with methyl iodide in the presence of potassium carbonate in acetone did not give the desired *N*-alkylated products, but gave instead the 4-methoxyquinoline derivatives **13a-d** in good yield.

4-Aminoquinoline derivatives like chloroquinine are expected to exhibit potent pharmacological activity [17]. 4-Chloroquinoline derivatives are the most versatile intermediates for the synthesis of 4-substituted quinolines such as 4-aminoquinolines.

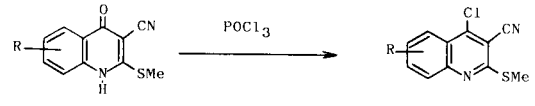
Chlorination of **4a** with phosphorus oxychloride gave 2-methylthio-4-chloroquinoline-3-carbonitrile (**14a**) in 78% yield. Chlorination of **4c-e,g** also occurred smoothly to produce the expected products **14b-e** in 37-89% yields.

Scheme 4



4a,b,e,g 13a-d

No.	R	mp(°C)	Yield(%)
13a	H	115	81
b	Me	112	85
c	OMe	147	81
d	Cl	161	81

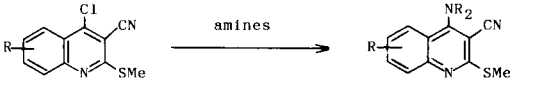


4a,c-e,g 14a-e

No.	R	mp(°C)	Yield(%)
14a	H	130	78
b	OMe(8)	207	37
c	OMe(7)	187	82
d	OMe(6)	198	89
e	Cl(6)	164	85

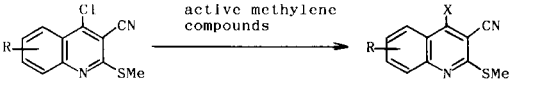
Reaction of **14a-e** with amines (such as *N,N*-diethylethylenediamine, benzylamine, morpholine and piperidine) gave the corresponding 4-aminoquinoline-3-carbonitriles in good yield. The reaction of **14c-e** with active methylene compounds (i.e., ethyl cyanoacetate, methyl cyanoacetate and diethyl malonate) in the presence of potassium carbonate in dimethyl sulfoxide gave the corresponding products **16a-d** which showed that the chloro groups were displaced and the methylthio groups remained intact. Since the methylthio groups were retained in these reaction products, the quinoline derivatives can serve as useful synthetic intermediates, especially for the synthesis of 2,4-disubstituted and fused quinoline derivatives.

Scheme 5



14a,e 15a-f

No.	R	NR_2	mp(°C)	Yield(%)
15a	H	$NHCH_2CH_2NEt_2$	105	52
b	H	$NHCH_2$-C_6H_5	180	77
c	H	morpholino	153	82
d	H	piperidino	144	50
e	Cl(6)	morpholino	180	80
f	Cl(6)	piperidino	160	80



14c-e 16a-d

No.	R	X	mp(°C)	Yield(%)
16a	OMe(6)	CHCN(COOEt)	139	73
b	OMe(6)	CHCN(COOMe)	194	89
c	Cl(6)	CHCN(COOMe)	224	70
d	OMe(7)	$CH(COOEt)_2$	134	77

In conclusion, the ketene dithioacetals shown in this paper are found to be useful reagents for the synthesis of various types of quinoline derivatives.

EXPERIMENTAL

All melting points were determined in capillary tubes and are uncorrected. Infrared (ir) spectra were recorded using potassium bromide pellets on a JASCO IRA-2 spectrometer and ultraviolet (uv) absorption spectra were determined in 95% ethanol on a Hitachi EP-S2 spectrometer. Nuclear magnetic resonance (nmr) spectra were obtained on JNM-PS-100 (100 MHz) and JNM-FX-90Q(90 MHz) spectrometers with tetramethylsilane as an internal standard. Mass spectra (ms) were recorded on a JEOL-01SG mass spectrometer.

Methyl 3-Anilino-2-cyano-3-methylthioacrylate (**3a**).

A mixture of 2.03 g (10 mmoles) of methyl 2-cyano-3,3-bis-(methylthio)acrylate (**1a**) and 0.93 g (10 mmoles) of aniline was heated at 100° for 2 hours. After cooling, the product crystallized out of the reaction mixture and was later recrystallized from methanol to give 2.29 g (9.23 mmoles, 92%) of colorless needles, mp 81° (lit [13], mp 79-81°); ir (potassium bromide): ν max 3055 (NH), 2205 (CN), 1660 (CO) cm^{-1}; uv (ethanol): λ max (log ϵ) 320 (4.34) nm; ^{1}H-nmr (deuteriochloroform): δ 2.25 (3H, s, SMe), 3.82 (3H, s, OMe), 7.22-7.50 (5H, m, phenyl-H), 11.45 (1H, bs, NH).

Methyl 2-Cyano-3-methylthio-3-(*p*-toluidino)acrylate (**3b**).

This compound (2.28 g, 8.70 mmoles) was prepared from **1** (2.03 g, 10 mmoles) and *p*-toluidine (**2b**) (1.61 g, 15 mmoles) in 87% yield in a manner similar to that described for the preparation of **3a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 99°; ir (potassium bromide): ν max cm^{-1} 3160 (NH), 2205 (CN), 1655 (CO); uv (ethanol): λ max nm (log ϵ) 320 (4.35); ^{1}H-nmr (deuteriochloroform): δ 2.27 (3H, s, SMe), 2.37 (3H, s, *p*-Me), 3.81 (3H, s, OMe), 7.17 (4H, s, phenyl-H), 11.40 (1H, bs, NH).

Anal. Calcd. for $C_{13}H_{14}N_2O_2S$: C, 59.50; H, 5.38; N, 10.67; S, 12.22. Found: C, 59.49; H, 5.33; N, 10.61; S, 12.11.

Methyl 3-(*o*-Anisidino)-2-cyano-3-methylthioacrylate (**3c**).

This compound (2.30 g, 8.27 mmoles) was prepared from **1** (2.03 g, 10 mmoles) and *o*-anisidine (**2c**) (1.85 g, 15 mmoles) in 83% yield in a manner similar to that described for the preparation of **3a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 103°; ir (potassium bromide): ν max cm^{-1} 3185 (NH), 2195 (CN), 1655 (CO); uv (ethanol): λ max nm (log ϵ) 322 (4.26); ^{1}H-nmr (deuteriochloroform): δ 2.28 (3H, s, SMe), 3.82 (3H, s, OMe), 3.88 (3H, s, OMe), 6.88-7.06 (2H, m, 3',4'-H), 7.26 (1H, m, 6'-H), 7.44 (1H, nd, J = 5.0 Hz, 5'-H).

Anal. Calcd. for $C_{13}H_{14}N_2O_3S$: C, 56.10; H, 5.07; N, 10.06; S, 11.52. Found: C, 55.96; H, 5.03; N, 10.05; S, 11.61.

Methyl 3-(*m*-Anisidino)-2-cyano-3-methylthioacrylate (**3d**).

This compound (2.09 g, 7.50 mmoles) was prepared from **1** (2.03 g, 10 mmoles) and *m*-anisidine (**2d**) (1.85 g, 15 mmoles) in 75% yield in a manner similar to that described for the preparation of **3a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 83°; ir (potassium bromide): ν max cm^{-1} 3100 (NH), 2190 (CN), 1650 (CO); uv (ethanol): λ max nm (log ϵ) 320 (4.26); ^{1}H-nmr (deuteriochloroform): δ 2.28 (3H, s, SMe), 3.82 (6H, s, OMe), 6.88-6.90 (3H, m, 2',3',6'-H), 7.25 (1H, nt, J = 3.85 Hz, 5'-H), 11.41 (1H, bs, NH).

Anal. Calcd. for $C_{13}H_{14}N_2O_3S$: C, 56.10; H, 5.07; N, 10.06; S, 11.52. Found: C, 56.11; H, 5.17; N, 10.01; S, 11.61.

Methyl 3-(*p*-Anisidino)-2-cyano-3-methylthioacrylate (**3e**).

This compound (2.14 g, 7.70 mmoles) was prepared from **1** (2.03 g, 10 mmoles) and *p*-anisidine (**2e**) (1.85 g, 15 mmoles) in 77% yield in a manner similar to that described for the preparation of **3a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 106°; ir (potassium bromide): ν max cm^{-1} 3165 (NH), 2200 (CN), 1665 (CO); uv (ethanol): λ max nm (log ϵ) 320 (4.30); ^{1}H-nmr (deuteriochloroform): δ 2.27 (3H, s, SMe), 3.81 (3H, s, OMe), 3.83 (3H, s, OMe), 6.90 (2H, d, J = 9.23 Hz, 2',6'-H), 7.19 (2H, d, J = 9.23 Hz, 3',5'-H), 11.42 (1H, bs, NH).

Anal. Calcd. for $C_{13}H_{14}N_2O_3S$: C, 56.10; H, 5.07; N, 10.06; S, 11.52. Found: C, 56.02; H, 5.09; N, 10.06; S, 11.68.

Methyl 3-(*o*-Chloroanilino)-2-cyano-3-methylthioacrylate (**3f**).

This compound (1.75 g, 6.21 mmoles) was prepared from **1** (2.03 g, 10 mmoles) and *o*-chloroaniline (**2f**) (1.91 g 15 mmoles) in 62% yield in manner similar to that described for the preparation of **3a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 137°; ir (potassium bromide): ν max cm^{-1} 3150 (NH), 2195 (CN), 1655 (CO), uv (ethanol): λ max nm (log ϵ) 318 (4.30); ^{1}H-nmr (deuteriochloroform): δ 2.26 (3H, s, SMe), 3.82 (3H, s, OMe), 7.16-7.59 (4H, m, phenyl-H), 11.44 (1H, bs, NH).

Anal. Calcd. for $C_{12}H_{11}ClN_2O_2S$: C, 50.98; H, 3.92; N, 9.91; S, 11.34. Found: C, 50.71; H, 3.86; N, 9.88; S, 11.76.

Methyl 3-(*p*-Chloroanilino)-2-cyano-3-methylthioacrylate (**3g**).

This compound (1.75 g, 6.21 mmoles) was prepared from **1** (2.03 g, 10 mmoles) and *p*-chloroaniline (**2h**) (1.91 g, 15 mmoles) in 62% yield in a manner similar to that described for the preparation of **3a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 125°; ir (potassium bromide): ν max cm^{-1} 3150 (NH), 2195 (CN), 1658 (CO); uv (ethanol): λ max nm (log ϵ) 322 (4.37); ^{1}H-nmr (deuteriochloroform): δ 2.29 (3H, s, SMe), 3.81 (3H, s, OMe), 7.23 (2H, d, J = 9.0 Hz, 2',6'-H), 7.40 (2H, d, J = 9.0 Hz, 3',5'-H), 11.62 (1H, bs, NH).

Anal. Calcd. for $C_{12}H_{11}ClN_2O_2S$: C, 50.98; H, 3.92; N, 9.91; S, 11.34. Found: C, 50.91; H, 3.89; N, 9.83; S, 11.52.

Methyl 3-(*p*-Bromoanilino)-2-cyano-3-methylthioacrylate (**3h**).

This compound (2.84 g, 8.69 mmoles) was prepared from **1** (2.03 g, 10 mmoles) and *p*-bromoaniline (**2i**) (2.58 g, 15 mmoles) in 87% yield in an manner similar to that described for the preparation of **3a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 144°; ir (potassium bromide): ν max cm^{-1} 3155 (NH), 2205 (CN), 1680 (CO); uv (ethanol): λ max nm (log ϵ) 323 (4.30); ^{1}H-nmr (deuteriochloroform): δ 2.29 (3H, s, SMe), 3.82 (3H, s, OMe), 7.17 (2H, d, J = 9.0 Hz, 2',6'-H), 7.53 (2H, d, J = 9.0 Hz, 3',5'-H), 11.38 (1H, bs, NH).

Anal. Calcd. for $C_{12}H_{11}BrN_2O_2S$: C, 44.05; H, 3.39; N, 9.81; S, 9.80. Found: C, 44.13; H, 3.38; N, 9.57; S, 9.80.

4-Hydroxy-3-methylthioquinoline-3-carbonitrile (**4a**).

A solution of 2.48 g (10 mmoles) of **3a** in 50 ml of diphenyl ether was heated at reflux temperature (235°) for 30 minutes. The precipitate which formed on cooling was collected by filtration, washed thoroughly with ether and methanol, and dried to give 1.36 g (6.29 mmoles, 63%) of tan crystals. An analytical sample was recrystallized from methanol using charcoal to give colorless needles, mp 339°; ir (potassium bromide): ν max cm^{-1} 3170 (NH or OH), 2190 (CN), 1600 (CO); uv (ethanol): λ max nm (log ϵ) 227 (4.30), 264 (4.42), 310 (4.02); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.84 (3H, s, SMe), 7.47 (1H, m, 6-H), 7.71-7.78 (2H, m, 5,7-H), 8.06 (1H, nd, J = 8.2 Hz, 8-H), 11.88 (1H, bs, OH).

Anal. Calcd. for $C_{11}H_8N_2OS$: C, 61.09; H, 3.73; N, 12.90; S, 14.83. Found: C, 60.99; H, 3.61; N, 12.80; S, 14.64.

4-Hydroxy-6-methyl-3-methylthioquinoline-3-carbonitrile (**4b**).

This compound (0.55 g, 2.39 mmoles) was prepared from **3a** (2.62 g, 10 mmoles) in 24% yield in a manner similar to that described for the preparation of **4a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 331°; ir (potassium bromide): ν max cm^{-1} 3400 (broad, NH or OH), 2200 (CN), 1605 (CO); uv (ethanol): λ max nmr (log ϵ) 214 (4.32), 239 (4.37), 270 (4.55), 305 (340); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.41 (3H, s, 6-Me), 2.83 (3H, s, SMe), 7.47 (1H, dd, J = 2.0, 7.7 Hz, 7-H), 7.68 (1H, d, J = 7.7 Hz, 8-H).

Anal. Calcd. for $C_{12}H_{10}N_2OS$: C, 62.59; H, 4.38; N, 12.16; S, 13.92. Found: C, 62.48; H, 4.41; N, 12.16; S, 13.79.

4-Hydroxy-8-methoxy-3-methylthioquinoline-3-carbonitrile (**4c**).

This compound (1.32 g, 5.36 mmoles) was prepared from **3c** (2.78 g, 10 mmoles) in 54% yield in a manner similar to that described for the preparation of **4a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 204°; ir (potassium bromide): ν max cm^{-1} 3360 (broad, NH or OH), 2200 (CN); uv (ethanol): λ max nm (log ϵ) 215 (4.28), 261 (4.49), 303 (4.04); ^{1}H-nmr (deuteriochloroform + trifluoroacetic acid): δ 2.82 (3H, s, SMe), 4.08 (3H, s, OMe), 7.30 (1H, d, J = 7.0 Hz, 7-H), 7.50 (1H, d, J = 7.0 Hz, 6-H9), 7.79 (1H, d, J = 7.0 Hz, 5-H).

Anal. Calcd. for $C_{12}H_{10}N_2O_2S$: C, 58.52; H, 4.09; N, 11.37; S, 13.02. Found: C, 58.54; H, 4.02; N, 11.58; S, 12.91.

4-Hydroxy-7-methoxy-3-methylthioquinoline-3-carbonitrile (**4d**).

This compound (0.861 g, 3.5 mmoles) was prepared from **3d** (2.78 g, 10 mmoles) in 35% yield in a manner similar to that described for the preparation of **4a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 306°; ir (potassium bromide): ν max cm^{-1} 3400-3000 (br, NH or OH), 2205 (CN), 1622 (CO); uv (ethanol): λ max nm (log ϵ) 222 (4.51), 247 (4.53), 272 (4.52), 298 (4.13); ^{1}H-nmr (deuteriodimethylsulfoxide): δ 2.86 (3H, s, SMe), 4.03 (3H, s, OMe), 7.23-7.70 (2H, m, 5, 6-H), 7.40 (1H, s, 8-H), 11.00 (1H, bs, OH).

Anal. Calcd. for $C_{12}H_{10}N_2O_2S$: C, 58.52; H, 4.09; N, 11.37; S, 13.02. Found: C, 58.42; H, 4.09; N, 11.34; S, 12.84.

4-Hydroxy-6-methoxy-3-methylthioquinoline-3-carbonitrile (**4e**).

This compound (0.554 g, 2.25 mmoles) was prepared from **3e** (1.39 g, 5.0 mmoles) in 45% yield in a manner similar to that described for the preparation of **4a**. An analytical sample was

recrystallized from methanol to give colorless needles, mp 303°; ir (potassium bromide): ν max cm^{-1} 3450, 3400 (NH or OH), 2205 (CN), 1610 (CO); uv (ethanol): λ max nm (log ε) 222 (4.32), 238 (4.35), 272 (4.53), 3.05 (3.95, sh), 342 (3.67, shoulder); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.84 (3H, s, SMe), 3.89 (3H, s, OMe), 7.50 (1H, dd, J = 2.0, 8.1 Hz, 7-H), 7.55 (1H, s, 5-H), 7.88 (1H, d, J = 8.1 Hz, 8-H), 12.44 (1H, bs, OH).

Anal. Calcd. for $C_{12}H_{10}N_2O_2S$: C, 58.52; H, 4.09; N, 11.37; S, 13.02. Found: C, 58.42; H, 4.09; N, 11.34; S, 12.81.

8-Chloro-4-hydroxy-3-methylthioquinoline-3-carbonitrile (**4f**).

This compound (0.588 g, 2.35 mmoles) was prepared from **3f** (1.41 g, 5.0 mmoles) in 47% yield in a manner similar to that described for the preparation of **4a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 231°; ir (potassium bromide): ν max cm^{-1} 3335 (NH or OH), 2224 (CN), 1614, 1600 (CO); uv (ethanol): λ max nm (log ε) 245 (4.30, shoulder), 269 (4.60), 305 (3.99); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.77 (3H, s, SMe), 7.43 (1H, t, J = 7.9 Hz, 6-H), 7.92 (1H, dd, J = 1.5, 7.9 Hz, 5 or 7-H), 8.13 (1H, dd, J = 1.5, 7.9 Hz, 7 or 5-H), 10.88 (1H, bs, OH).

Anal. Calcd. for $C_{11}H_7ClN_2OS$: C, 52.68; H, 2.81; N, 11.17; S, 12.78. Found: C, 52.65; H, 2.82; N, 11.08; S, 12.77.

6-Chloro-4-hydroxy-3-methylthioquinoline-3-carbonitrile (**4g**).

This compound (0.813 g, 3.25 mmoles) was prepared from **3g** (1.41 g, 5.0 mmoles) in 65% yield in a manner similar to that described for the preparation of **4a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 336°; ir (potassium bromide): ν max cm^{-1} 3420 (NH or OH), 2200 (CN), 1615 (CO); uv (ethanol): λ max nm (log ε) 238 (4.43), 259 (4.63), 310 (4.14); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.84 (3H, s, SMe), 7.78-7.80 (2H, m, 7, 8-H), 7.97 (1H, dd, J = 1.0, 1.5 Hz, 5-H).

Anal. Calcd. for $C_{11}H_7ClN_2OS$: C, 52.70; H, 2.81; N, 11.17; S, 12.79. Found: C, 52.64; H, 3.01; N, 11.21; S, 12.36.

6-Bromo-4-hydroxy-3-methylthioquinoline-3-carbonitrile (**4h**).

This compound (1.14 g, 3.86 mmoles) was prepared from **3h** (1.41 g, 5.0 mmoles) in 65% yield in a manner similar to that described for the preparation of **4a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 325°; ir (potassium bromide): ν max cm^{-1} 3420 (NH or OH), 2050 (CN), 1615 (CO), uv (ethanol): λ max nm (log ε) 218 (4.31), 234 (4.33), 274 (4.59), 310 (3.97); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.87 (3H, s, SMe), 7.76 (1H, d, J = 8.1 Hz, 8-H), 7.94 (1H, d, J = 1.5, 8.1 Hz, 7-H), 8.14 (1H, d, J = 1.5 Hz, 5-H), 12.28 (1H, bs, NH or OH).

Anal. Calcd. for $C_{11}H_7BrN_2OS$: C, 44.76; H, 2.39; N, 9.49; S, 10.86. Found: C, 44.57; H, 2.33; N, 9.46; S, 10.81.

Methyl 3,3-Dianilino-3-cyanoacrylate (**5**).

A mixture of 2.03 g (10 mmoles) of **1** and 3.72 g (40 mmoles) of aniline was heated at 150° for 6 hours. After cooling, 10 ml of acetic acid and 20 ml of methanol were added to the reaction mixture. The crystallized product was collected by filtration and recrystallized from methanol to give colorless crystals, mp 232°. This compound was in accord with an authentic sample of **5** obtained by the reaction of *N,N'*-diphenylcarbondiimide with methyl cyanoacetale [18]; ir (potassium bromide): ν max cm^{-1} 3205, 3010 (NH), 2190 (CN), 1645, 1620 (CO); uv (ethanol): λ max nm (log ε) 305 (4.33); ^{1}H-nmr (deuteriochloroform): δ 3.79 (3H, s, OMe), 6.86-7.22 (11H, m, phenyl-H, NH), 11.20 (1H, bs, NH).

2-Anilino-4-hydroxyquinoline-3-carbonitrile (**6a**).

Method a).

This compound (0.366 g, 1.40 mmoles) was synthesized in 28% yield from **5** (1.47 g, 5.0 mmoles) in a manner similar to that described for the preparation of **4a**. An analytical sample recrystallized from methanol to give colorless needles, mp 314°.

Method b).

A solution of 1.02 g (5 mmoles) of **1** and 1.86 g (20 mmoles) of aniline in 30 ml of diphenyl ether was refluxed for 30 minutes. After cooling, 20 ml of methanol was added to the reaction mixture. The resulting precipitate was collected by filtration and then washed with 10 ml of methanol. This product was recrystallized from methanol to give 0.274 g (1.05 mmoles, 21%) of cololess needles, mp 314°; ir (potassium bromide): ν max cm^{-1} 3270, 3230, 3180, 3100 (NH), 2195 (CN), 1615 (CO); uv (ethanol): λ max nm (log ε) 213 (4.44), 240 (4.39), 269 (4.47); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 7.08-7.56 (8H, m, phenyl-H, 5,6,7-H), 7.96 (1H, d, J = 8.0 Hz, 8-H), 9.52 (1H, s, NH), 11.08 (1H, bs, NH or OH).

Anal. Calcd. for $C_{16}H_{11}N_3O$: C, 71.91; H, 4.12; N, 15.73. Found: C, 72.02; H, 4.06; N, 15.82.

4-Hydroxy-6-methoxy-2-(*p*-methoxyanilino)quinoline-3-carbonitrile (**6b**).

This compound (0.369 g, 1.15 mmoles) was prepared from **1** (1.02 g, 5.0 mmoles) and *p*-anisidine (2.46 g, 20 mmoles) in 23% yield in a manner similar to that described for the preparation of **6a**. An analytical sample was recrystallized from methanol to give yellow needles, mp 352°; ir (potassium bromide): ν max cm^{-1} 3400, 3220 (NH), 2200 (CN), 1620 (CO); uv (ethanol): λ max nm (log ε) 240 (4.52), 267 (4.56); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 3.77 (6H, s, OMe), 6.87-6.55 (7H, m, 2',3',5',5,7,8-H), 9.16 (1H, bs, NH), 10.76 (1H, bs, NH or OH).

Anal. Calcd. for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.11; H, 4.70; N, 13.09.

8-Chloro-2-(*o*-chloroanilino)-4-hydroxyquinoline-3-carbonitrile (**6c**).

This compound (0.33 g, 1.0 mmoles) was prepared from **1** (1.02 g, 5.0 mmoles) and *o*-chloroaniline (2.55 g, 20 mmoles) in 20% yield in a manner similar to that described for the preparation of **6a**. An analytical sample was recrystallized from methanol to give tan crystals, mp 302°; ir (potassium bromide): ν max cm^{-1} 3260, 3220, 3180 (NH), 2200 (CN), 1625 (CO); uv (ethanol): λ max nm (log ε) 240 (4.32), 288 (4.68); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 7.19-7.60 (5H, m, aromatic-H), 7.80 (1H, d, J = 7.0 Hz, aromatic-H), 7.94 (12H, d, J = 8.0 Hz, aromatic-H), 9.60 (1H, bs, NH), 10.42 (1H, bs, NH).

Anal. Calcd. for $C_{16}H_9Cl_2N_3O$: C, 58.20; H, 2.75; N, 12.73. Found: C, 58.21; H, 2.58; N, 12.69.

6-Chloro-2-(*p*-chloroanilino)-4-hydroxyquinoline-3-carbonitrile (**6d**).

This compound (0.207 g, 0.63 mmoles) was prepared from **1** (1.02 g, 5.0 mmoles) and *p*-chloroaniline (2.54 g, 20 mmoles) in 32% yield in a manner similar to that described for the preparation of **6a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 368°; ir (potassium bromide): ν max cm^{-1} 3370, 3230 (NH), 2195 (CN), 1615 (CO); uv (ethanol): λ max

nm (log ϵ) 218 (4.50), 285 (4.59); ^{1}H-mr (deuteriochloroform): δ 7.40-7.90 (7H, m, 2',3',5',6',5,7,8,-H), 9.76 (1H, s, NH), 11.45 (1H, bs, NH).

Anal. Calcd. for $C_{16}H_9Cl_2N_3O$: C, 58.20; H, 2.75; N, 12.73. Found: C, 58.03; H, 2.74; N, 12.61.

11-Hydroxy-5,12-dihydroquinolino[2,3-*b*]quinolin-12-one (**9a**).

This compound (0.50 g, 2.10 mmoles) was prepared in 21% yield from **1b** (2.38 g, 10 mmoles) and aniline (2.79 g, 30 mmoles) in a manner similar to that described for the preparation of **6a**. This product was recrystallized from a mixture of benzene and methanol to give yellow crystals, mp > 360° (lit [18] mp > 360°).

11-Hydroxy-2,9-dimethyl-5,12-dihydroquinolino[2,3-*b*]quinolin-12-one (**9b**).

This compound (0.522 g, 1.80 mmoles) was prepared from **1b** (2.38 g, 10 mmoles) and *p*-toluidine (**2b**) (3.21 g, 30 mmoles) in 18% yield in a manner similar to that described for the preparation of **6a**. An analytical sample was recrystallized from methanol to give yellow crystals, mp > 360° (lit [18] mp >360°).

Methyl 2-Methoxycarbonyl-3-methylthio-3(*p*-toluenesulfonylamino)acrylate (**11**).

A mixture of 10.7 g (50 mmoles) of *N*-bis(methylthio)methylene-*p*-toluenesulfonamide (**10**), 13.1 g (100 mmoles) of dimethyl malonate, 13.8 g (100 mmoles) of potassium carbonate, and 100 ml of dimethyl sulfoxide was heated with stirring at 70° for 2 hours. After cooling, the reaction mixture was poured into 300 ml of ice-water and acidified with 10% hydrochloric acid. The precipitate that appeared was collected by filtration and recrystallized from methanol to give 16.8 g (46.8 mmoles, 47%) of colorless prisms, mp 84°; ir (potassium bromide): ν max cm^{-1} 3430 (NH), 1775 (CO); uv (ethanol): λ max nm (log ϵ) 230 (4.04), 272 (4.16); ^{1}H-nmr (deuteriochloroform): δ 2.37 (3H, s, SMe), 2.43 (3H, s, *p*-Me), 3.83 (6H, s, OMe), 5.78 (1H, s, -CH-), 7.32 (2H, d, J = 7.2 Hz, 2', 6'-H), 7.85 (2H, d, J = 7.2 Hz, 3',5'-H).

Anal. Calcd. for $C_{14}H_{17}NO_6S$: C, 46.79; H, 4.77; N, 3.90; S, 17.84. Found: C, 46.78; H, 4.75; N, 3.89; S, 17.68.

N-Phenyl-4-Hydroxy-2-(*p*-toluenesulfonyl)aminoquinoline-3-carboxamide (**12a**).

A solution of 3.59 g (10 mmoles) of **11**, 3.72 g (40 mmoles) and aniline in 100 ml of diphenyl ether was refluxed for 1 hour (temperature 250°). The precipitate which formed on cooling was collected on by filtration washed thoroughly with ether and methanol, and dried to give colorless needles, mp 235°. An analytical sample was recrystallized from methanol to give 2.07 g (4.76 mmoles, 48%) of colorless needles, mp 235°; ir (potassium bromide): ν max cm^{-1} 3260 (NH), 1640 (CO); uv (ethanol, only partial solubility): λ max nm 228, 268; λ min 246.

Anal. Calcd. for $C_{23}H_{19}N_3O_4S$: C, 63.73; H, 4.42; N, 9.69; S, 7.40. Found: C, 64.05; H, 4.45; N, 9.61; S, 7.34.

6-Chloro-4-hydroxy-2-(*p*-toluenesulfonyl)amino-*N*-(*p*-chlorophenyl)quinoline-3-carboxamide (**12b**).

This compound (2.51 g, 5.0 mmoles) was prepared from **11** (3.59 g, 10 mmoles) in 50% yield in a manner similar to that described for the preparation of **3a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 270°; ir (potassium bromide): ν max cm^{-1} 3400, 3280 (NH or OH), 1635, 1585 (CO); uv (ethanol, paritial solubility): λ max nm 267, 293; λ min 251, 275.

Anal. Calcd. for $C_{23}H_{17}Cl_2N_3O_4S$: C, 54.99; H, 3.41; N, 8.36; S, 6.38. Found: C, 54.77; H, 3.33; N, 8.23; S, 6.49.

8-Chloro-*N*-(*o*-chlorophenyl)-4-hydroxy-2-(*p*-toluenesulfonyl)aminoquinoline-3-carboxamide (**12c**).

This compound (1.61 g, 3.21 mmoles) was prepared from **11** (3.59 g, 10 mmoles) and *o*-chloroaniline (3.82 g, 30 mmoles) in 32% yield in a manner similar to that described for the preparation of **12a**. An analytical sample was recrystallized from methanol to give tan needles, mp 255°; ir (potassium bromide): ν max cm^{-1} 3400 (NH or OH), 1624, 1580 (CO); uv (ethanol, partial solubility): λ max nm 225, 268, 296; λ min 240, 275.

Anal. Calcd. for $C_{23}H_{17}Cl_2N_3O_4S$: C, 54.99; H, 3.41; N, 8.36; S, 6.38. Found: C, 55.12; H, 3.42; N, 8.29; S, 6.22.

4-Hydroxy-6-methoxy-*N*-(*p*-methoxyphenyl)-2-(*p*-toluenesulfonyl)-aminoquinoline-3-carboxamide (**12d**).

This compound (1.97 g, 3.99 mmoles) was prepared from **11** (3.59 g, 10 mmoles) and *p*-anisidine (3.69 g, 30 mmoles) in 40% yield in a manner similar to that described for the preparation of **12d**. An analytical sample was recrystallized from a mixture of benzene and methanol to give colorless needles, mp 255°; ir (potassium bromide): ν max cm^{-1} 3400 (NH or OH), 1615, 1588 (CO); uv (ethanol, only partial solubility): λ max nm 235, 2 = 8.0 Hz, (phenyl-H), 7.24-7.96 (9H, m, aromatic-H), 12.04 (1H, bs, NH).

Anal. Calcd. for $C_{25}H_{23}N_3O_6S$: C, 60.84; H, 4.70; N, 8.52; S, 6.50. Found: C, 60.89; H, 4.54; N, 8.35; S, 6.61.

4-Hydroxy-8-methoxy-*N*-(*o*-methoxyphenyl)-2-(*p*-toluenesulfonyl)-aminoquinoline-3-carboxamide (**12e**).

This compound (2.54 g, 5.15 mmoles) was prepared from **11** (3.59 g, 10 mmoles) and *o*-anisidine (3.69 g, 30 mmoles) in 52% yield in a manner similar to that described for the preparation of **12a**. An analytical sample was recrystallized from a mixture of benzene and methanol to give colorless needles, mp 204°; ir (potassium bromide): ν max cm^{-1} 3400-3200 (NH or OH), 1630, 1588 (CO); uv (ethanol, partial solubility): λ max nm (log ϵ) 225 (4.50), 245 (4.43, shoulder), 282 (4.61), 320 (4.26, shoulder); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.32 (3H, s, Me), 3.96 (3H, s, OMe), 4.02 (3H, s, OMe), 6.80-8.40 (11H, m, aromatic-H), 12.04 (1H, bs, NH).

Anal. Calcd. for $C_{25}H_{23}N_3O_6S$: C, 60.84; H, 4.70; N, 8.52; S, 6.50. Found: C, 60.73; H, 4.67; N, 8.42; S, 6.65.

4-Hydroxy-7-methoxy-*N*-(*m*-methoxyphenyl)-2-(*p*-toluenesulfonyl)-aminoquinoline-3-carboxamide (**12f**).

This compound (1.83 g, 3.70 mmoles) was prepared from **11** (3.59 g, 10 mmoles) and *m*-anisidine (3.69 g, 30 mmoles) in 37% yield in a manner similar to that described for the preparation of **12a**. An analytical sample was recrystallized from a mixture of benzene and methanol to give colorless needles, mp 225°; ir (potassium bromide): ν max cm^{-1} 3250 (NH or OH), 1620, 1585 (CO); uv (ethanol, partial solubility): λ max nm 223, 270; λ min nm 243.

Anal. Calcd. for $C_{25}H_{23}N_3O_6S$: C, 60.84; H, 4.70; N, 8.52; S, 6.50. Found: C, 60.67; H, 4.70; N, 8.20; S, 6.76.

4-Methoxy-2-methylthioquinoline-3-carbonitrile (**13a**).

A mixture of 0.216 g (1.0 mmole) of **4a**, 0.57 g (4.0 mmoles), 0.276 g (2.0 mmoles), and 50 ml of acetone was refluxed for 6 hours. After cooling and removal of potassium carbonate by

filtration, the solvent was evaporated on the rotary evaporator to give a yellow solid. This product was recrystallized from methanol to give 0.186 g (0.81 mmoles, 81%) of colorless needles, mp 113°; ir (potassium bromide): ν max cm^{-1} 2195 (CN), 1545, 1490, 1378, 1290, 1110; uv (ethanol): λ max nm (log ε) 229 (4.58), 264 (4.62), 343 (3.40); ^{1}H-nmr (deuteriochloroform): δ 2.71 (3H, s, SMe), 4.51 (3H, s, OMe), 7.43 (1H, m, 6 or 7-H), 7.81 (1H, m, 7 or 6-H), 7.87 (1H, bd, J = 8.3 Hz, 5-H), 8.08 (1H, bd, J = 8.1 Hz, 8-H).

Anal. Calcd. for $C_{12}H_{10}N_2OS$: C, 62.59; H, 4.38; N, 12.16; S, 13.92. Found: C, 62.97; H, 4.37; N, 12.38; S, 13.52.

4-Methoxy-6-methyl-2-methylthioquinoline-3-carbonitrile (**13b**).

This compound (0.207 g, 0.848 mmole) was prepared from **4b** (0.230 g, 1.0 mmole) in 85% yield in a manner similar to that described for the preparation of **13a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 112°; ir (potassium bromide): ν max cm^{-1} 2190 (CN), 1555, 1455, 1385, 1285, 1115, 897, 830; uv (ethanol): λ max nm (log ε) 234 (4.29), 265 (4.63), 292 (4.02), 3.50 (3.33); ^{1}H-nmr (deuteriochloroform): δ 2.49 (3H, s, 6-Me), 2.69 (3H, s, SMe), 4.48 (3H, s, OMe), 7.53 (1H, dd, J = 1.2, 8.5 Hz, 7-H), 7.77 (1H, d, J = 8.5 Hz, 8-H), 7.85 (1H, J = 1.2 Hz, 5-H).

Anal. Calcd. for $C_{13}H_{12}N_2OS$: C, 63.91; H, 4.95; N, 11.47; S, 13.12. Found: C, 64.00; H, 5.05; N, 11.48; S, 13.02.

4,6-Dimethoxy-2-methylthioquinoline-3-carbonitrile (**13c**).

This compound (0.211 g, 0.811 mmole) was prepared from **4e** (0.230 g, 1.0 mmole) in 81% yield in a manner similar to that described for the preparation of **13a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 147°; ir (potassium bromide): ν max cm^{-1} 2200 (CN), 1555, 1492, 1450, 1386, 1295, 1225, 1100, 1036, 840; uv (ethanol): λ max nm (log ε) 234 (4.29), 265 (4.63), 292 (4.02), 350 (3.33); ^{1}H-nmr (deuteriochloroform): δ 2.68 (3H, s, SMe), 3.91 (3H, s, OMe), 4.49 (3H, s, OMe), 7.39-8.28 (2H, m, 5, 7-H), 7.78 (1H, d, J = 8 Hz, 8-H).

Anal. Calcd. for $C_{13}H_{12}N_2O_2S$: C, 59.98; H, 4.65; N, 10.76; S, 12.32. Found: C, 60.45; H, 4.65; N, 10.88; S, 11.72.

6-Chloro-4-methoxy-2-methylthioquinoline-3-carbonitrile (**13d**).

This compound (0.213 g, 0.81 mmole) was prepared from **4g** (0.250 g, 1.0 mmole) in 85% yield in a manner similar to that described for the preparation of **13a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 161°; ir (potassium bromide): ν max cm^{-1} 2200 (CN), 1565, 1372, 1785, 1028, 946, 825; uv (ethanol, incomplete solubility): λ max nm 235, 266, 360; λ min nm 249, 316; ^{1}H-nmr (deuteriochloroform): δ 2.69 (3H, s, SMe), 4.52 (3H, s, OMe), 7.62 (1H, dd, J = 2.2, 8.3 Hz, 7-H), 7.80 (1H, d, J = 8.3 Hz, 8-H), 8.04 (1H, d, J = 2.2 Hz, 5-H).

Anal. Calcd. for $C_{12}H_9ClN_2OS$: C, 54.44; H, 3.43; N, 10.58; S, 12.11. Found: C, 54.62; H, 3.38; N, 10.53; S, 11.95.

4-Chloro-2-methylthioquinoline-3-carbonitrile (**14a**).

4-Hydroxy-2-methylthioquinoline-3-carbonitrile **4a** (2.16 g, 10 mmoles) was added to 50 ml of phosphorus oxychloride. To this mixture was added 5 ml of dimethylaniline, and the solution was refluxed for 1.5 hours. The excess phosphorus oxychloride was removed under reduced pressure and then poured, with vigorous stirring, onto a mixture of approximately 100 ml of crushed ice and 50 ml of water. After 30 minutes, the aqueous solution was extracted with ether (3 x 50 ml portions). The etheral solution was then washed (2 x 20 ml) with cold water and dried overnight over anhyrous sodium sulfate. Distillation of the etheral solution left 1.83 g, (7.8 mmoles, 78%) of almost colorless product, mp 130°. This crude product was recrystallized from benzene to give a colorless needles, mp 130° (lit [13] mp 130-133°); ir (potassium bromide): ν max cm^{-1} 2200 (CN), 1559, 1442, 1470, 1290; uv (ethanol): λ max nm (log ε) 232 (4.59), 270 (4.60); ^{1}H-nmr (deuteriochloroform): δ 2.70 (3H, s, SMe), 7.50-8.04 (3H, m, 5,6,7-H), 8.16 (1H, d, J = 8.04 Hz, 8-H).

4-Chloro-8-methoxy-2-methylthioquinoline-3-carbonitrile (**14b**).

This compound (0.977 g, 3.70 mmoles) was prepared from **4c** (2.46 g, 10 mmoles) in 37% yield in a manner similar to that described for the preparation of **3a**. An analytical sample was recrystallized from benzene to give colorless needles, mp 207°; ir (potassium bromide): ν max cm^{-1} 2205 (CN), 1600, 1565, 1548, 1400, 1375, 1352, 1300, 1265, 1045, 815, 742; uv (ethanol): λ max nm (log ε) 243 (4.52), 271 (4.63); ^{1}H-nmr (deuteriochloroform): δ 2.76 (3H, s, SMe), 4.06 (3H, s, OMe), 7.22 (1H, dd, J = 1.0, 9.0 Hz, 7-H), 7.54 (1H, dd, J = 8.0, 9.0 Hz, 6-H), 7.76 (1H, dd, J = 1.0, 8.0 Hz, 5-H).

Anal. Calcd. for $C_{12}H_9ClN_2OS$: C, 54.44; H, 3.43; N, 10.58; S, 12.11. Found: C, 54.31; H, 3.32; N, 10.64; S, 12.22.

4-Chloro-7-methoxy-2-methylthioquinoline-3-carbonitrile (**14c**).

This compound (2.16 g, 8.16 mmoles) was prepared from **4d** (2.46 g, 10 mmoles) in 82% yield in a manner similar to that described for the preparation of **3a**. An analytical sample was recrystallized from benzene to give colorless needles, mp 187°; ir (potassium bromide): ν max cm^{-1} 2205 (CN), 1610, 1564, 1470, 1385, 1232, 1140, 1015, 845; uv (ethanol): λ max nm (log ε) 232 (4.57), 247 (4.50), 271 (4.67), 349 (3.96), 364 (3.95); ^{1}H-nmr (deuteriochloroform): δ 2.69 (3H, s, SMe), 3.97 (3H, s, OMe), 7.20 (1H, dd, J = 1.0, 9.0 Hz, 6-H), 7.25 (1H, s, 8-H), 8.03 (1H, d, J = 9.0 Hz, 5-H).

Anal. Calcd. for $C_{12}H_9ClN_2OS$: C, 54.44; H, 3.43; N, 10.58; S, 12.11. Found: C, 54.65; H, 3.37; N, 10.57; S, 12.01.

4-Chloro-6-methoxy-2-methylthioquinolin-3-carbonitrile (**14d**).

This compound (0.977 g, 3.70 mmoles) was prepared from **4e** (2.46 g, 10 mmoles) in 37% yield in a manner similar to that described for the preparation of **3a**. An analytical sample was recrystallized from benzene to give colorless needles, mp 198°; ir (potassium bromide): ν max cm^{-1} 2210 (CN), 1615, 1560, 1482, 1305, 1225, 1063, 824; uv (ethanol): λ max nm (log ε) 241 (4.45), 268 (4.62); ^{1}H-nmr (deuteriochloroform): δ 2.70 (3H, s, SMe), 3.95 (3H, s, OMe), 7.03 (1H, s, 5-H), 7.45 (1H, dd, J = 1.0, 9.0 Hz, 7-H), 7.90 (1H, d, J = 9.0 Hz, 8-H).

Anal. Calcd. for $C_{12}H_9ClN_2OS$: C, 54.44; H, 3.43; N, 10.58; S, 12.11. Found: C, 54.51; H, 3.36; N, 10.64; S, 12.03.

4,6-Dichloro-2-methylthioquinolin-3-carbonitrile (**14e**).

This compound (2.29 g, 8.51 mmoles) was prepared from **4g** (2.46 g, 10 mmoles) in 85% yield in a manner similar to that described for the preparation of **3a**. An analytical sample was recrystallized from benzene to give colorless needles, mp 164°; ir (potassium bromide): ν max cm^{-1} 2205 (CN), 1558, 1295, 1058, 955, 822; uv (ethanol): λ max nm (log ε) 238 (4.63), 271 (4.64); ^{1}H-nmr (deuteriochloroform): δ 2.76 (3H, s, SMe), 7.74 (1H, dd, J = 1.0, 9.0 Hz, 7-H), 7.94 (1H, dd, J = 8.0, 9.0 Hz, 8-H), 7.76 (1H, d, J = 1.0 Hz, 5-H).

Anal. Calcd. for $C_{11}H_6Cl_2N_2OS$: C, 49.08; H, 2.25; N, 10.41; S,

11.91. Found: C, 48.85; H, 2.22; N, 10.30; S, 11.85.

4-(*N*,*N*-Diethylamino)ethylenamino-2-methylthioquinoline-3-carbonitrile (**15a**).

A solution of 0.234 g (1.0 mmole) of **14a** and 0.290 g (2.5 mmoles) of *N*,*N*-diethylethylenediamine in 30 ml of absolute ethanol was refluxed for 5 hours. After removal of the solvent, 50 ml of water was added to the residue. The resulting precipitate was collected by filtration and recrystallized from methanol to give 0.163 g (0.519 mmole) of orange needles, mp 105°; ir (potassium bromide): ν max cm^{-1} 3400 (NH), 2190 (CN); uv (ethanol): λ max nm (log ϵ) 218 (4.37), 258 (4.52), 269 (4.54), 307 (3.99), 343 (3.60), 357 (3.60).

Anal. Calcd. for $C_{17}H_{22}N_4S$: C, 64.93; H, 7.05; N, 17.82; S, 10.20. Found: C, 64.58; H, 7.04; N, 17.73; S, 10.06.

4-Benzylamino-2-methylthioquinoline-3-carbonitrile (**15b**).

This compound (0.189 g, 0.77 mmoles) was prepared from **14a** (0.235 g, 1.0 mmole) in 77% yield in a manner similar to that described for the preparation of **15a**. An analytical sample was recrystallized from methanol to give orange needles, mp 180°; ir (potassium bromide): ν max cm^{-1} 2190 (CN); uv (ethanol): λ max nm (log ϵ) 218 (4.37), 259 (4.53), 270 (4.54), 279 (4.38), 307 (3.92), 342 (351), 358 (3.51); ^{1}H-nmr (deuteriochloroform): δ 2.54 (3H, s, SMe), 5.04 (2H, d, J = 6.0 Hz, N-CH_2-), 7.32 (5H, s, phenyl-H), 7.50 (1H, m, 6 or 7-H), 7.72 (2H, m, 5,6 pr 6,7-H), 8.39 (1H, d, J = 8.0 Hz, 8-H), 8.60 (1H, nt, J = 6.0 Hz, NH).

Anal. Calcd. for $C_{18}H_{15}N_3S$: C, 70.80; H, 4.95; N, 13.78; S, 10.40. Found: C, 70.55; H, 4.98; N, 13.54; S, 10.37.

2-Methylthio-4-morpholinoquinoline-3-carbonitrile (**15c**).

This compound (0.234 g, 0.82 mmole) was prepared from **14a** (0.234 g, 1.0 mmole) and morpholine (0.174 g, 2.0 mmoles) in 82% yield in a manner similar to that described for the preparation of **15a**. An analytical sample was recrystallized from methanol to give orange needles, mp 153°; ir (potassium bromide): ν max cm^{-1} 2190 (CN), 1605, 1560, 1540, 1495; uv (ethanol): λ max nm (log ϵ) 223 (4.43), 269 (4.61), 336 (3.87); ^{1}H-nmr (deuteriochloroform): δ 2.66 (3H, s, SMe), 3.64 (4H, m, N-CH_2-), 3.94 (4H, m, O-CH_2-), 7.37 (1H, m, 6 or 7-H), 7.65 (1H, m, 7 or 6-H), 7.80-7.93 (2H, m, 5, 8-H).

Anal. Calcd. for $C_{15}H_{15}N_3OS$: C, 63.13; H, 5.30; N, 14.72; S, 11.24. Found: C, 62.90; H, 5.34; N, 14.80; S, 11.17.

2-Methylthio-4-piperidinoquinoline-3-carbonitrile (**15d**).

This compound (0.142 g, 0.502 mmole) was prepared from **14a** (0.235 g, 1.0 mole) and piperidine (0.17 g, 2.0 mmoles) in 50% yield in a manner similar to that described for the preparation of **15a**. An analytical sample was recrystallized from methanol to give orange needles, mp 144°; ir (potassium bromide): ν max cm^{-1} 2195 (CN), 1605, 1560, 1535, 1495; uv (ethanol): λ max nm (log ϵ) 225 (4.46), 268 (4.60), 336 (3.89); ^{1}H-nmr (deuteriochloroform): δ 1.79 (6H, m, -CH_2-CH_2-CH_2-), 2.64 (3H, s, SMe), 3.56 (4H, m, -CH_2-N-CH_2-), 7.34 (1H, m, 6 or 7-H), 7.62 (1H, m, 7 or 6-H), 7.74-7.93 (2H, m, 5, 8-H).

Anal. Calcd. for $C_{16}H_{17}N_3S$: C, 67.81; H, 6.05; N, 14.83; S, 11.31. Found: C, 67.46; H, 6.02; N, 14.75; S, 11.41.

6-Chloro-4-morpholino-2-methylthioquinoline-3-carbonitrile (**15e**).

This compound (0.255 g, 0.797 mmole) was prepared from **14e** (0.269 g, 1.0 mmole) and morpholine (0.174 g, 2.0 mmoles) in 80% yield in a manner similar to that described for the preparation of **15a**. An analytical sample was recrystallized from methanol to give orange needles, mp 180°; ir (potassium bromide): ν max cm^{-1} 2200 (CN), 1535, 1425, 1100, 995; uv (ethanol): λ max nm (log ϵ) 229 (4.45), 267 (4.61), 340 (3.80).

Anal. Calcd. for $C_{15}H_{14}ClN_3OS$: C, 56.33; H, 4.41; N, 13.14; S, 10.03. Found: C, 56.06; H, 4.43; N, 13.07; S, 10.04.

6-Chloro-2-methylthio-4-piperidinoquinoline-3-carbonitrile (**15f**).

This compound (0.254 g, 0.801 mmole) was prepared from **14e** (0.269 g, 1.0 mmole) and piperidine (0.170 g, 2.0 mmoles) in 80% yield in a manner similar to that described for the preparation of **15a**. An analytical sample was recrystallized from methanol to give orange needles, mp 160°; ir (potassium bromide): ν max cm^{-1} 2200 (CN), 1530, 1430, 1108, 987; uv (ethanol): λ max nm (log ϵ) 229 (4.48), 263 (4.60), 344 (3.86).

Anal. Calcd. for $C_{16}H_{16}ClN_3OS$: C, 60.46; H, 5.07; N, 13.22; S, 10.04. Found: C, 60.31; H, 5.07; N, 13.10. S, 10.04.

Methyl α-Cyano-α-(3-cyano-6-methoxy-2-methylthioquinolin-4-yl)-acetate (**16a**).

A mixture of 0.265 g (1.0 mmole) of **14d**, 0.396 g (4.0 mmoles) of methyl cyanoacetate, 0.276 g (2.0 mmoles) and 20 ml of dimethyl sulfoxide was stirred at room temperature for 5 hours. the reaction mixture was poured into 100 ml of ice-water and acidified with 10% hydrochloric acid. The precipitate that appeared was collected by filtration and recrystallized from methanol to give 0.239 g (0.73 mmoles, 73%) of yellow needles, mp 139°; ir (potassium bromide): ν max cm^{-1} 2195 (CN), 1750 (CO); uv (ethanol): λ max nm (log ϵ) 233 (4.54), 263 (4.55), 420 (3.83); ^{1}H-nmr (deuteriochloroform): δ 2.74 (3H, s, SMe), 3.82 (3H, s, OMe), 3.95 (3H, s, OMe), 5.60 (1H, s, -CH-), 7.31 (1H, d, J = 2.8 Hz, 5-H), 7.48 (1H, dd, J = 2.8, 9.0 Hz, 7-H), 7.95 (1H, d, J = 9.0 Hz, 8-H).

Anal. Calcd. for $C_{16}H_{13}N_3O_3S$: C, 58.70; H, 4.00; N, 12.84; S, 9.79. Found: C, 58.54; H, 3.97; N, 12.96; S, 9.64.

Methyl α-Cyano-α-(3-cyano-7-methoxy-2-methylthioquinolin-4-yl)-acetate (**16b**).

This compound (0.291 g, 0.890 mmole) was prepared from **14c** (0.264 g, 1.0 mmole) and methyl cyanoacetate (0.276 g, 2.0 mmoles) in 89% yield in a manner similar to that described for the preparation of **16**. An analytical sample was recrystallized from methanol to give a yellow powder, mp 194°; ir (potassium bromide): ν max cm^{-1} 2205 (CN), 1754 (CO); uv (ethanol): λ max nm (log ϵ) 234 (4.56), 266 (4.59), 300 (4.07), 340 (3.78), 357 (3.85), 412 (3.92); ^{1}H-nmr (deuteriochloroform): δ 2.75 (3H, s, SMe), 3.83 (3H, s, OMe), 3.99 (3H, s, OMe), 5.53 (1H, s, -CH-), 7.23 (1H, dd, J = 2.6, 8.6 Hz, 6-H), 7.35 (1H, d, J = 2.6 Hz, 8-H), 7.96 (1H, d, J = 8.6 Hz, 5-H).

Anal. Calcd. for $C_{16}H_{13}N_3O_3S$: C, 58.70; H, 4.00; N, 12.84; S, 9.79. Found: C, 58.70; H, 3.85; N, 12.69; S, 9.81.

Methyl α-Cyano-α-(6-chloro-3-cyano-2-methylthioquinolin-4-yl)-acetate (**16c**).

This compound (0.232 g, 0.701 mmole) was prepared from **14e** (0.269 g, 1.0 mole) and methyl cyanoacetate (0.276 g, 2.0 mmoles) in 89% yield in a manner similar to that described for the preparation of **16**. An analytical sample was recrystallized from methanol to give tan prisims, mp 224°; ir (potassium bromide): ν max cm^{-1} 2200 (CN), 1760 (CO); uv (ethanol): λ max nm (log ϵ) 230 (4.61), 266 (4.55), 322 (3.73), 340 (3.50), 434 (3.87); ^{1}H-nmr

(deuteriochloroform): δ 2.75 (3H, s, SMe), 3.89 (3H, s, OMe), 5.57 (1H, s, -CH-), 7.76 (1H, dd, J = 2.0, 9.0 Hz, 6-H), 8.00 (1H, d, J = 9.0 Hz, 8-H), 8.01 (1H, d, J = 2.0 Hz, 5-H).

Anal. Calcd. for $C_{15}H_{10}ClN_3O_2S$: C, 58.70; H, 4.00; N, 12.84; S, 9.79. Found: C, 58.61; H, 3.95; N, 12.89; S, 9.83.

Ethyl α-ethoxycarbonyl-α-(3-cyano-7-methoxy-2-methylthioquinolin-4-yl)acetate (**16d**).

This compound (0.338 g, 0.871 mmole) was prepared from **14d** (0.265 g, 1.0 mmole) and diethyl malonate (0.320 g, 2.0 mmoles) in 77% yield in a manner similar to that described for the preparation of **16a**. An analytical sample was recrystallized from methanol to give a yellow powder, mp 184°; ir (potassium bromide): ν max cm^{-1} 2224 (CN), 1753, 1737 (CO); uv (ethanol): λ max nm (log ε) 235 (4.45), 249 (4.45), 271 (4.63), 354 (3.84), 368 (3.88); ^{1}H-nmr (deuteriochloroform): δ 1.23 (6H, t, J = 7.0 Hz, O-CH_2-CH_3), 2.73 (3H, s, SMe), 3.97 (3H, s, OMe), 5.46 (1H, s, -CH-), 7.12 (1H, dd, J = 2.6, 9.2 Hz, 6-H), 7.30 (1H, d, J = 2.6, 8-H), 7.89 (1H, d, J = 9.2 Hz, 5-H).

Anal. Calcd. for $C_{19}H_{20}N_2O_5S$: C, 58.75; H, 5.19; N, 7.21; S, 8.25. Found: C, 58.70; H, 5.18; N, 7.19; S, 8.33.

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REFERENCES AND NOTES

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[1] Comprehensive Heterocyclic Chemistry; Vol **2**, A. R. Katritzky and C. W. Rees, eds, Pergamon Press, Oxford, 1984.

[2] R. G. Gould and W. A. Jacobs, *J. Am. Chem. Soc.*, **61**, 2890 (1939).

[3] R. H. Reitsema, *Chem. Rev.*, **43**, 53 (1948).

[4] I. T. Kay and P. J. Taylor, *J. Chem. Soc.(C)*, 2656 (1968).

[5] Y. Tominaga and Y. Matsuda, *Yuki Gousei Kagaku Kyoukaishi (J. Org. Synth. Japan)*, **43**, 669 (1985).

[6] Y. Tominaga and Y. Matsuda, *J. Heterocyclic Chem.*, **22**, 937 (1985).

[7] R. K. Dieter, *Tetrahedron*, **42**, 3029 (1986).

[8] Y. Tominaga, Y. Shiroshita, and A. Hosomi, *Heterocycles*, **27**, 2251 (1988).

[9] Y. Tominaga, S. Kohra, H. Honkawa, and A. Hosomi, *Heterocycles*, **29**, 1409 (1989).

[10] Y. Tominaga, *Yuki Gousei Kagaku Kyoukaishi (J. Org. Synth. Japan)*, **47**, 413 (1989).

[11] Y. Tominaga, M. Kawabe, and A. Hosomi, *J. Heterocyclic Chem.*, **24**, 1325 (1987).

[12] Y. Tominaga, A. Ushirogouchi and Y. Matsuda, *J. Heterocyclic Chem.*, **24**, 1557 (1987).

[13] R. Gompper and W. Topfl, *Chem. Ber.*, **95**, 2871 (1962).

[14] S. Kohra, Y. Tominaga, and A. Hosomi, *J. Heterocyclic Chem.*, **25**, 959 (1988).

[15] Y. Tominaga, M. Hara, H. Honkawa, and A. Hosomi, *J. Heterocyclic Chem.*, **27**, 0000 (1990).

[16] K. Kuwayama and S. Kataoka, *Yakugaku Zasshi*, **85**, 391 (1965).

[17] A. R. Surrey and H. F. Hammer, *J. Am. Chem. Soc.*, **68**, 113 (1946).

[18] R. Gompper and R. Kunz, *Chem. Ber.*, **98**, 1391 (1965).