Synthesis of Isothiourea Derivatives

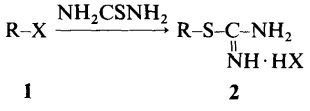
Jiro HORIUCHI,* Kazuo SUZUKI, Eiki SHITARA, Ryuji NIWA, and Tetsuzo KATO

Central Research Institute, MECT Corporation, 1780 Kitano, Tokorozawa, Saitama 359, Japan. *Received September 27, 1988*

The reaction of thioureas (9) with 2-chloromethylpyridine hydrochloride (5), 3-chloromethylpyridine hydrochloride (6), 2-chloromethylquinoline hydrochloride (7), and 5-chloromethyl-4-methylimidazole hydrochloride (8) gave the isothiourea dihydrochlorides (10—13).

Keywords 2-(or 3-)chloromethylpyridine; 2-chloromethylquinoline; 5-chloromethyl-4-methylimidazole; thiourea; isothiourea

Extensive work[1-4] has been done on the reaction of thiourea with alkyl halides to give isothiourea derivatives. For example, thiourea reacts with alkyl halides to give the *S*-alkylisothioureas (**2**)[1-3] (Chart 1). As early as 1879, Bernthsen and Klinger[4] obtained *S*-benzylisothiourea by reacting thiourea with benzyl chloride. However, only a few references[5,6] are available concerning such reactions with heterocyclic compounds. Phillips and Shapiro[5] and Forrest and Walker[6] reported the reaction of 2-halopyridines (**3**) with thiourea to afford 2-(2-pyridyl)isothioureas (**4**) (Chart 2).



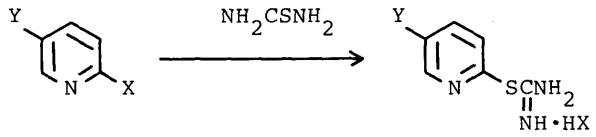
1 **2**

(R = ethyl, dodecyl, hexadecyl, cyclohexyl, *tert*-butyl, *p*-nitrobenzyl, α-naphthylmethyl; X = Br, Cl)

Chart 1

In view of these facts, we have investigated the reaction of thioureas with chloromethyl derivatives such as chloromethylpyridine (**5**, **6**), quinoline (**7**), and imidazole (**8**) derivatives, which were prepared from the corresponding 2-hydroxymethylpyridine, 3-hydroxymethylpyridine, 2-hydroxymethylquinoline, and 5-hydroxymethyl-4-methylimidazole, respectively (Chart 3).

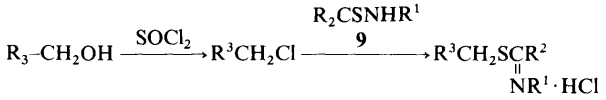
Firstly, by employing the procedure reported by Claus,[1] the reaction of thiourea with 2-chloromethylpyridine hydrochloride (**5**) was carried out. When 2-chloromethylpyr-



3 **4**

(X = Br, Cl; Y = CN, $CONH_2$, NH_2, NO_2)

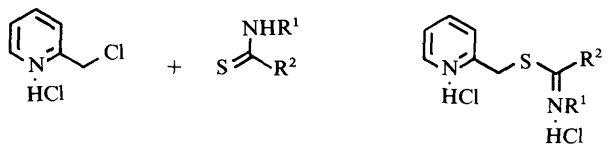
Chart 2



5—8 **10—13**

Chart 3

TABLE I. Reaction of 2-Chloromethylpyridine Hydrochloride (**5**) with Thioureas (**9a—d, f—j**)



5 **9a—d, f—j** **10a—d, f—j**

Compd. No.	Thiourea 9		Compd. No.	Isothiourea 10		
	R^1	R^2		Appearance (Recryst. solvent)	mp (°C)	Yield (%)
9a	H	NH_2	**10a**	Prisms (MeOH–MeCN)	196—200 (lit.[7] 220)	77
9b	H	NHMe	**10b**	Needles (EtOH)	179—184	86
9c	H	$NHCH_2CH=CH_2$	**10c**	Needles (EtOH)	134—136	74
9d	H	NHPh	**10d**	Prisms (MeOH–MeCN)	169—174	92
9f	H	$NHNH_2$	**10f**	Needles (EtOH)	164—166	75
9g	Me	NHMe	**10g**	Needles (EtOH)	185—188	80
9h	Me	$NHNH_2$	**10h**	Prisms (EtOH)	178—180	49
9i	$\backslash CH_2CH_2NH/$		**10i**	Needles (EtOH)	208—209	80
9j	$\backslash N=C(-NH_2)S/$		**10j**	Prisms (EtOH)	175—180	89

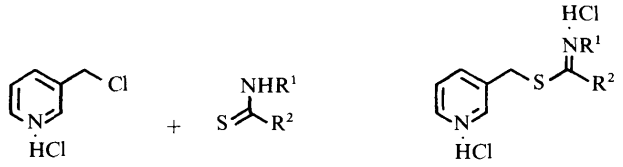
TABLE II. Analytical and Spectral Data for **10a—d, f—j**

Compd. No.	Formula	Analysis (%) Calcd (Found)				IR ν_{max}^{KBr} cm^{-1}
		C	H	Cl	N	
10a	$C_7H_9N_3S \cdot 2HCl$	35.01 (35.07)	4.62 (4.59)	— (—)	17.50 (17.69)	1660, 1640, 1620
10b	$C_8H_{11}N_3S \cdot 2HCl$	37.80 (37.75)	5.15 (5.07)	— (—)	16.53 (16.51)	1660, 1600
10c	$C_{10}H_{13}N_3S \cdot HCl$	49.27 (48.77)	5.79 (5.39)	— (—)	17.24 (17.37)	1600, 1610
10d	$C_{13}H_{13}N_3S \cdot 2HCl$	49.37 (49.49)	4.78 (4.75)	— (—)	13.29 (13.35)	1640, 1620, 1560
10f	$C_7H_{10}N_4S \cdot 2HCl$	32.95 (33.08)	4.74 (4.60)	— (—)	21.96 (21.60)	1650, 1620, 1600
10g	$C_9H_{13}N_3S \cdot 2HCl$	40.30 (40.12)	5.64 (5.62)	26.44 (26.21)	15.67 (15.55)	1620, 1520
10h	$C_8H_{12}N_4S \cdot 2HCl$	35.96 (35.43)	5.24 (5.24)	— (—)	20.80 (21.27)	1650, 1570
10i	$C_9H_{11}N_3S \cdot 2HCl$	40.61 (40.26)	4.92 (4.97)	— (—)	15.79 (15.67)	1570, 1540
10j	$C_8H_8N_4S_2 \cdot HCl$	36.85 (36.67)	3.48 (3.12)	— (—)	21.49 (21.56)	1620, 1460

TABLE III. NMR Spectral Data for **10a—d, f—j**

	^{1}H-NMR (DMSO-d_6) δ	^{13}C-NMR (DMSO-d_6) δ
10a	5.07 (2H, s), 7.74—8.95 (4H, m), 9.00—10.00 (3H, br), 10.97 (2H, br)	32.5 (t), 125.3 (d), 125.8 (d), 143.5 (d), 144.8 (d), 152.3 (s), 169.1 (s)
10b	2.94 (3H, br), 5.00 (2H, s), 7.66—8.44 (4H, m), 9.00—10.00 (2H, br), 10.35 (2H, br)	30.8 (q), 33.4 (t), 125.0 (d), 125.5 (d), 142.7 (d), 145.2 (d), 152.8 (s), 164.8 (s)
10c	4.09 (2H, t), 5.03 (2H, s), 5.30 (2H, s), 5.60—6.00 (1H, m), 7.67—8.85 (4H, m), 9.00—10.50 (1H, br), 10.62 (2H, br)	32.5 (t), 45.6 (t), 117.3 (t), 125.7 (d), 126.2 (d), 131.4 (d), 143.9 (d), 144.4 (d), 151.6 (s), 163.7 (s)
10d	5.14 (2H, s), 7.42 (5H, s), 7.55—8.87 (4H, m), 9.50—10.50 (2H, br), 12.51 (2H, br)	33.5 (t), 125.3 (d), 126.0 (d), 128.1 (d), 129.7 (d), 134.9 (d), 143.6 (d), 144.6 (d), 151.9 (s), 167.2 (s, s)
10f	4.72 (2H, s), 7.84—8.94 (6H, m), 9.70—11.00 (4H, br)	31.1 (t), 125.7 (d), 127.1 (d), 142.0 (s), 145.8 (d), 152.7 (d), 161.7 (s)
10g	2.98 (6H, d), 5.01 (2H, s), 7.62—8.82 (4H, m), 9.40—10.40 (2H, br)	31.1 (q), 33.9 (t), 124.9 (d), 125.7 (d), 142.6 (d), 152.3 (s), 165.2 (s)
10h	2.84 (3H, s), 4.76 (2H, s), 7.13 (5H, br), 7.56—9.00 (4H, m)	30.6 (q), 31.8 (t), 125.5 (d), 126.8 (d), 142.8 (d), 152.2 (s), 163.6 (s)
10i	3.87 (4H, s), 5.04 (2H, s), 6.22 (1H, br), 7.50—9.00 (4H, m), 11.02 (2H, br)	33.5 (t), 45.2 (t), 125.0 (d), 145.8 (d), 152.6 (s), 168.0 (s)
10j	4.85 (2H, s), 7.86—8.93 (4H, m), 10.90—13.70 (3H, br)	34.4 (t), 125.9 (d), 127.2 (d), 141.9 (d), 145.8 (d), 150.9 (s), 152.0 (s), 170.1 (s)

TABLE IV. Reaction of 3-Chloromethylpyridine Hydrochloride (**6**) with Thioureas (**9a, b, d, f, j**)



6 **9a, b, d, f, j** **11a, b, d, f, j**

Compd. No.	Thiourea **9** R^1	Thiourea **9** R^2	Compd. No.	Isothiourea **11** Appearance (Recryst. solvent)	mp (°C)	Yield (%)
9a	H	NH_2	**11a**	Needles (MeOH–MeCN)	188—191 (lit.[8] 220)	93
9b	H	NHMe	**11b**	Prisms (EtOH)	192—193	83
9d	H	NHPh	**11d**	Prisms (EtOH)	155—157	71
9f	H	$NHNH_2$	**11f**	Prisms (MeOH–MeCN)	147—149	87
9j	$^{\backslash}N=C(-NH_2)S^{/}$		**11j**	Prisms (EtOH)	169—173	60

idine hydrochloride (**5**) was allowed to react with thiourea (**9a**) in methanol or ethanol, 2-(2-pyridylmethyl)isothiourea dihydrochloride (**10a**) was obtained in good yield. Isothioureas (**10b—d, f—h**) were also obtained by the same treatment of thioureas (**9b—d, f—h**) with 2-chloromethylpyridine hydrochloride (**5**) in methanol at room temperature. Similar reaction of **5** with 2-imidazolidinethione (**9i**) and 2-amino-5-mercapto-1,3,4-thiadiazole (**9j**) gave 2-imidazolin-2-yl 2-pyridylmethyl sulfide dihydrochloride (**10i**) and 2-amino-1,3,4-thiadiazol-5-yl 2-pyridylmethyl sulfide dihydrochloride (**10j**) in 80 and 89% yields, respectively. The results are summarized in Table I.

The infrared (IR) spectra showed the absorption band due to the imino group at 1570—1660 cm^{-1}. In the proton nuclear magnetic resonance (^{1}H-NMR) spectra, the signal due to *S*-methylene protons was observed at 4.72—5.14 ppm (2H, s), being shifted to higher field than the chloromethylene protons (5.30 ppm) of 2-chloromethylpyridine. The ^{13}C-nuclear magnetic resonance (^{13}C-NMR) spectra of **10a—d, f—j** also supported the isothiourea

TABLE V. Analytical and Spectral Data for **11a, b, d, f, j**

Compd. No.	Formula	Analysis (%) Calcd (Found) C	H	N	IR ν_{max}^{KBr} cm^{-1}
11a	$C_7H_9N_3S\cdot 2HCl$	35.01 (34.88)	4.62 (4.69)	17.50 (17.41)	1640, 1600, 1530
11b	$C_8H_{11}N_3S\cdot 2HCl$	37.80 (38.01)	5.15 (5.16)	16.53 (16.48)	1640, 1600, 1530
11d	$C_{13}H_{13}N_3S\cdot HCl$	55.80 (55.31)	5.04 (4.56)	15.02 (14.91)	1600, 1580, 1560
11f	$C_7H_{10}N_4S\cdot 2HCl$	32.95 (32.57)	4.74 (4.75)	21.96 (22.08)	1660, 1610, 1550
11j	$C_8H_8N_4S_2\cdot 2HCl$	32.33 (32.38)	3.39 (3.41)	18.85 (18.62)	1620, 1540

structures. Elemental analyses and spectral data for isothioureas (**10a—d, f—j**) are shown in Tables II and III.

Similar reaction of 3-chloromethylpyridine hydrochloride (**6**) with thioureas (**9a, b, d, f, j**) afforded the corresponding isothiourea derivatives (**11**). The above results are summarized in Tables IV—VI.

Similarly, 2-chloromethylquinoline hydrochloride (**7**) reacted with thioureas (**9a—d, f—h**), 2-imidazolidinethione (**9i**), and 2-amino-5-mercapto-1,3,4-thiadiazole (**9j**) to give isothiourea derivatives (**12a—d, f—j**). Lastly, reaction of 5-chloromethyl-4-methylimidazole hydrochloride (**8**) with thioureas (**9a—h**), 2-imidazolinethione (**9i**), and 2-amino-5-mercapto-1,3,4-thiadiazole (**9j**) gave the corresponding isothiourea derivatives (**13a—j**). These results are summalized in Tables VII—XII.

The biological activities of these products were investigated, and compounds **10b** and **12d** were found to have platelet aggregation-inhibitory and inotropic activities.

Experimental

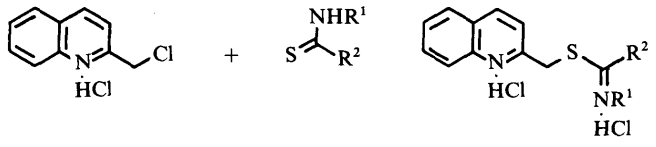
Melting points were determined on a Yanaco model MP apparatus and are uncorrected. IR spectra were taken with a JASCO IR-810 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded by using tetramethylsilane as an internal standard on JEOL JNM FX-60 and JEOL JNM GX-500 spectrometers at 60 and 500 MHz, respectively. Chemical shifts are quoted in parts per million (δ), and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad).

General Procedure for Synthesis of Isothioureas (10a—d, f, j, 11a, b, d, f, j, 12a—c, g, h, j, 13g—j) A solution of a thiourea (**9**) (0.01 mol) in methanol (10 ml) was added to a solution of a chloromethyl compound (**5—8**) (0.01 mol) in methanol (10 ml) with stirring at room temperature.

TABLE VI. NMR Spectral Data for **11a, b, d, f, j**

	^{1}H-NMR (DMSO-d_6) δ	^{13}C-NMR (DMSO-d_6) δ
11a	4.99 (2H, s), 8.00—9.00 (4H, m), 9.80 (4H, br), 12.00—13.00 (1H, br)	30.3 (t), 127.2 (d), 136.6 (s), 141.3 (dd), 145.7 (d), 168.5 (s)
11b	2.86 (3H, d), 4.90 (2H, s), 7.60—9.10 (4H, m), 9.10—10.40 (4H, br)	30.8 (qt), 127.0 (d), 136.4 (s), 141.5 (d), 142.0 (d), 165.5 (s)
11d	5.13 (2H, s), 7.34—7.41 (5H, m), 7.95—9.09 (4H, m), 9.56—11.69 (3H, br)	31.3 (t), 125.1 (d), 127.1 (d), 128.0 (d), 129.6 (d), 134.6 (s), 136.1 (s), 141.3 (d), 145.3 (d), 166.6 (s)
11f	4.62 (2H, s), 7.94—9.00 (6H, m), 9.00—11.00 (4H, br)	30.1 (t), 127.0 (d), 138.0 (s), 140.2 (d), 141.0 (d), 146.1 (d), 162.0 (s)
11j	4.63 (2H, s), 7.98—8.96 (4H, m), 11.15 (4H, br)	33.5 (t), 127.1 (d), 137.9 (s), 140.3 (d), 141.1 (d), 146.3 (d), 151.3 (s), 169.8 (s)

TABLE VII. Reaction of 2-Chloromethylquinoline Hydrochloride (**7**) with Thioureas (**9a—d, f—j**)



7 **9a—d, f—j** **12a—d, f—j**

Compd. No.	Thiourea **9** R^1	Thiourea **9** R^2	Compd. No.	Isothiourea **12** Appearance (Recryst. solvent)	mp (°C)	Yield (%)
9a	H	NH_2	**12a**	Needles (EtOH)	184—185 (lit.[8] 250)	86
9b	H	NHMe	**12b**	Needles (EtOH)	167—172	68
9c	H	$NHCH_2CH=CH_2$	**12c**	Needles (EtOH)	165—171	63
9d	H	NHPh	**12d**	Prisms (EtOH)	156—164	78
9f	H	$NHNH_2$	**12f**	Prisms (EtOH)	154—158	69
9g	Me	NHMe	**12g**	Needles (EtOH)	165—171	69
9h	Me	$NHNH_2$	**12h**	Needles (EtOH)	175—178	57
9i	$\backslash CH_2CH_2NH/$		**12i**	Needles (EtOH)	191—192	67
9j	$\backslash N=C(-NH_2)S/$		**12j**	Prisms (MeOH)	177—182	91

TABLE VIII. Analytical and Spectral Data for **12a—d, f—j**

Compd. No.	Formula	Analysis (%) Calcd (Found) C	H	Cl	N	IR ν_{max}^{KBr} cm^{-1}
12a	$C_{11}H_{11}N_3S\cdot 2HCl$	45.52	4.52	—	14.48	1650, 1600
		(45.71	4.54	—	14.48)	
12b	$C_{12}H_{13}N_3S\cdot 2HCl$	47.37	4.97	—	13.81	1650, 1615
		(47.37	4.80	—	14.17)	
12c	$C_{14}H_{15}N_3S\cdot 2HCl$	50.91	5.18	21.47	12.72	1660, 1640, 1540
		(50.64	5.12	21.31	12.61)	
12d	$C_{17}H_{15}N_3S\cdot 2HCl$	55.74	4.68	—	11.47	1640, 1600
		(55.88	4.71	—	11.54)	
12f	$C_{11}H_{12}N_4S\cdot 2HCl$	43.28	4.62	—	18.36	1640, 1600
		(43.46	4.69	—	18.51)	
12g	$C_{13}H_{15}N_3S\cdot 2HCl$	49.06	5.38	22.80	13.20	1610
		(49.07	5.40	22.12	13.30)	
12h	$C_{12}H_{14}N_4S\cdot 2HCl$	45.14	5.05	—	17.55	1650
		(45.21	4.87	—	17.10)	
12i	$C_{13}H_{13}N_3S\cdot 2HCl$	49.37	4.78	22.42	13.29	1635, 1600, 1560
		(49.55	4.76	22.15	13.45)	
12j	$C_{12}H_{10}N_4S_2\cdot 2HCl$	41.50	3.48	20.42	16.13	1630, 1600, 1560
		(41.20	3.52	20.22	15.97)	

The mixture was stirred at room temperature for 5—10 min. The solvent was evaporated off under reduced pressure, and the crystalline residue was purified by recrystallization from the appropriate solvent to give the product (**10—13**). The results are summarized in Tables I—XII.

1,3-Dimethyl-2-(2-pyridylmethyl)isothiourea Dihydrochloride (10g) A solution of 1,3-dimethylthiourea (**9g**) (1.91 g, 0.018 mol) in methanol (10 ml) was added to a solution of 2-chloromethylpyridine hydrochloride (**5**) (3.00 g, 0.018 mol) in methanol (10 ml) with stirring at room temperature. The mixture was stirred at room temperature for 1 h. The solvent was

TABLE IX. NMR Spectral Data for **12a—d, f—j**

	^{1}H-NMR (DMSO-d_6) δ	^{13}C-NMR (DMSO-d_6) δ
12a	5.00 (2H, s), 6.10 (2H, br), 7.76—8.76 (6H, m), 9.12—10.17 (3H, br)	34.8 (t), 121.6 (d), 125.5 (d), 127.2 (d), 127.9 (d), 128.3 (s), 131.8 (d), 140.6 (d), 143.9 (s), 155.4 (s), 169.8 (s)
12b	2.97 (3H, d), 5.04 (2H, s), 7.53—8.76 (6H, m), 9.01—10.61 (4H, br)	30.9 (q), 34.7 (t), 121.9 (d), 124.1 (s), 127.2 (s, d), 128.4 (d, d), 132.4 (d), 141.9 (d), 155.2 (s), 165.0 (s)
12c	4.11 (2H, br), 4.86—5.44 (4H, m), 5.34—6.30 (1H, m), 7.46—8.98 (6H, m), 9.30—10.95 (3H, br)	35.3 (t), 46.1 (t), 118.3 (t), 122.3 (d), 125.7 (d), 127.7 (s), 128.6 (s), 128.9 (d), 131.5 (d), 132.5 (d), 141.6 (d), 143.9 (s), 156.1 (s), 165.8 (s)
12d	5.31 (2H, s), 7.44 (5H, s), 7.37—9.01 (6H, m), 9.99 (4H, br)	35.1 (t), 122.0 (d), 124.6 (d), 125.3 (d, s), 127.2 (d), 128.1 (d), 128.5 (d), 129.7 (d), 132.3 (d), 135.1 (s), 141.6 (d), 142.7 (s), 155.1 (s), 167.4 (s)
12f	4.94 (2H, s), 7.56—9.10 (8H, m), 9.10—10.68 (4H, br)	32.1 (t), 120.9 (d), 122.7 (d), 127.1 (s), 128.8 (d, d), 134.0 (s), 138.0 (d), 145.2 (d), 156.2 (s), 161.8 (s)
12g	3.03 (6H, d), 5.22 (2H, s), 7.52—9.03 (6H, m), 9.62—10.84 (3H, br)	31.1 (q), 35.2 (t), 121.9 (d), 124.9 (d), 127.2 (s), 128.0 (d), 128.4 (d), 132.2 (d), 141.3 (d), 143.1 (s), 155.0 (s), 165.6 (s)
12h	2.90 (3H, s), 4.98 (2H, s), 6.24 (5H, br), 7.47—9.22 (6H, m)	30.1 (q), 33.9 (t), 122.2 (d), 123.6 (d), 127.2 (s), 128.5 (d, d), 132.8 (d), 141.0 (s), 142.7 (d), 155.8 (s), 165.0 (s)
12i	3.90 (4H, s), 5.16 (2H, s), 5.76 (2H, br), 7.41—8.90 (6H, m), 10.93 (1H, br)	35.1 (t), 45.2 (t), 121.6 (d), 125.4 (d), 128.4 (d), 131.9 (d), 140.7 (d), 143.6 (s), 154.8 (s), 168.3 (s)
12j	5.01 (2H, s), 7.46—9.20 (6H, m), 9.48 (4H, br)	36.1 (t), 122.3 (d, d), 127.2 (s), 128.8 (d, d), 133.5 (d), 139.7 (s), 144.0 (d), 150.6 (s), 155.9 (s), 170.4 (s)

evaporated off under reduced pressure, and the crystalline residue was recrystallized from ethanol to give 3.93 g (80%) of the product (**10g**).

4-Methyl-3-(2-pyridylmethyl)isothiosemicarbazide Dihydrochloride (10h) A solution of 4-methylthiosemicarbazide (**9h**) (1.89 g, 0.018 mol) in methanol (15 ml) was added to 2-chloromethylpyridine hydrochloride (**5**) (3.00 g, 0.018 mol) in methanol (15 ml) with stirring at room temperature. The mixture was stirred at room temperature for 4 h. The solvent was evaporated off under reduced pressure, and the crystalline residue was recrystallized from ethanol to give 2.41 g (49%) of the product (**10h**).

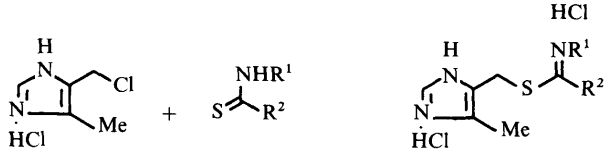
2-Imidazolin-2-yl 2-Pyridylmethyl Sulfide Dihydrochloride (10i) A solution of 2-imidazolidinethione (**9i**) (1.84 g, 0.018 mol) in methanol (10 ml) was added to a solution of 2-chloromethylpyridine hydrochloride (**5**) (3.00 g, 0.018 mol) in methanol (10 ml) with stirring at room temperature. The mixture was refluxed for 30 min. The solvent was evaporated off under reduced pressure, and the crystalline residue was recrystallized from ethanol to give 3.89 g (80%) of the product (**10i**).

1-Phenyl-2-(2-quinolylmethyl)isothiourea Dihydrochloride (12d) A solution of 1-phenyl-2-thiourea (**9d**) (3.80 g, 0.025 mol) in acetone (20 ml) and methanol (5 ml) was added to a solution of 2-chloromethylquinoline hydrochloride (**7**) (5.35 g, 0.025 mol) in acetone (20 ml) and methanol (5 ml) with stirring at room temperature. The mixture was stirred for 5 min at room temperature. The solvent was evaporated off under reduced pressure, and the crystalline residue was recrystallized from ethanol to give 7.16 g (78%) of the product (**12d**).

3-(2-Quinolylmethyl)isothiosemicarbazide Dihydrochloride (12f) A solution of thiosemicarbazide (**9f**) (3.64 g, 0.04 mol) in ethanol (20 ml) was added to a solution of 2-chloromethylquinoline hydrochloride (**7**) (8.56 g, 0.04 mol) in ethanol (20 ml) with stirring at room temperature. The mixture was refluxed for 3 h. The solvent was evaporated off under reduced pressure, and the crystalline residue was recrystallized from ethanol to give 8.42 g (69%) of the product (**12f**).

2-Imidazolin-2-yl 2-Quinolylmethyl Sulfide Dihydrochloride (12i) Ac-

TABLE X. Reaction of 5-Chloromethyl-4-methylimidazole Hydrochloride (**8**) with Thioureas (**9a—j**)



8 **9a—j** **13a—j**

Compd. No.	Thiourea 9		Compd. No.	Isothiourea 13		
	R^1	R^2		Appearance (Recryst. solvent)	mp (°C)	Yield (%)
9a	H	NH_2	**13a**	Prisms (MeOH)	200—202 (lit.[9] 191—192)	90
9b	H	NHMe	**13b**	Prisms (EtOH–MeCN)	201—205	95
9c	H	$NHCH_2CH=CH_2$	**13c**	Prisms (MeOH–MeCN)	100—104	76
9d	H	NHPh	**13d**	Prisms (EtOH)	175—179	98
9e	H	NHC(–NH)–NH_2	**13e**	Prisms (EtOH)	190—195	35
9f	H	$NHNH_2$	**13f**	Prisms (MeOH)	160—165	56
9g	Me	NHMe	**13g**	Prisms (MeOH–AcOEt)	188—191 (lit.[9] 180—182)	90
9h	Me	$NHNH_2$	**13h**	Prisms (EtOH)	170—175	64
9i	$\backslash CH_2CH_2NH/$		**13i**	Prisms (H_2O–MeOH)	223—228	72
9j	$\backslash NH=C(-NH_2)S/$		**13j**	Prisms (EtOH)	180—185	37

TABLE XI. Analytical and Spectral Data for **13a—j**

Compd. No.	Formula	Analysis (%) Calcd (Found)			IR ν_{max}^{KBr} cm^{-1}
		C	H	N	
13a	$C_6H_{10}N_4S \cdot 2HCl$	29.64 (29.64	4.97 4.15	23.04 23.04)	1630, 1440
13b	$C_7H_{12}N_4S \cdot 2HCl$	32.69 (32.64	5.48 5.28	21.79 21.90)	1640, 1600
13c	$C_9H_{14}N_4S \cdot 2HCl$	38.17 (38.26	5.69 5.95	19.78 19.67)	1660, 1640, 1600
13d	$C_{12}H_{14}N_4S \cdot 2HCl$	45.14 (45.08	5.05 5.07	17.55 17.65)	1640, 1560
13e	$C_7H_{12}N_6S \cdot 2HCl$	29.48 (29.79	4.95 4.82	29.47 29.27)	1640, 1510
13f	$C_6H_{11}N_5S \cdot 2HCl$	27.91 (27.62	5.08 5.16	27.13 26.98)	1650, 1610
13g	$C_8H_{14}N_4S \cdot 2HCl$	35.43 (35.28	5.95 5.97	20.66 20.25)	1640
13h	$C_7H_{13}N_5S \cdot 2HCl$	30.89 (30.88	5.55 5.37	25.73 25.65)	1660, 1640, 1600
13i	$C_8H_{12}N_4S \cdot 2HCl$	35.69 (35.64	5.24 5.30	20.82 20.68)	1560, 1540
13j	$C_7H_9N_5S_2 \cdot 2HCl$	28.00 (28.45	3.69 3.65	23.33 23.11)	1620, 1560

TABLE XII. NMR Spectral Data for **13a—j**

	^{1}H-NMR (DMSO-d_6) δ	^{13}C-NMR (DMSO-d_6) δ
13a	2.36 (3H, s), 4.84 (2H, s), 9.10 (1H, s), 9.63 (6H, br)	8.8 (q), 24.0 (t), 122.4 (s), 127.6 (s), 133.3 (d), 168.7 (s)
13b	2.35 (3H, s), 2.93 (3H, d), 4.85 (2H, s), 9.08 (1H, s), 9.10—10.60 (3H, br), 11.5—15.50 (2H, br)	8.6 (q), 24.6 (t), 30.7 (q), 122.9 (s), 127.3 (s), 133.1 (d), 164.3 (s)
13c	2.35 (3H, s), 3.70—4.60 (2H, br), 4.04 (2H, s), 4.86 (2H, s), 5.26 (2H, s), 5.30—5.90 (1H, m), 9.08 (1H, s), 9.00—11.00 (3H, br)	9.4 (q), 26.6 (t), 47.6 (t), 118.9 (t), 124.2 (s), 129.8 (s), 131.4 (d), 134.9 (d), 166.3 (s)
13d	2.31 (3H, s), 2.82—4.82 (4H, br), 4.96 (2H, s), 7.43 (5H, m), 9.05 (1H, s), 9.00—11.00 (1H, br)	8.7 (q), 25.1 (t), 102.4 (s), 124.9 (d), 127.7 (s), 129.7 (d), 133.3 (d), 135.0 (s), 166.5 (s)
13e	2.29 (3H, s), 4.32 (2H, s), 9.07 (1H, s), 8.23 (6H, br), 10.90—14.00 (2H, br)	8.7 (q), 23.3 (t), 124.8 (s), 126.3 (s), 132.4 (d), 162.3 (s), 162.8 (s)
13f	2.32 (3H, s), 4.44 (2H, s), 9.02 (1H, s), 8.20 (7H, br)	[a] 10.9 (q), 27.9 (t), 124.9 (s), 131.0 (s), 135.7 (d), 185.2 (s)
13g	2.35 (3H, s), 3.01 (6H, s), 4.90 (2H, s), 9.07 (1H, s), 9.30—10.80 (2H, br), 12.00—15.00 (2H, br)	8.6 (q), 25.2 (t), 31.1 (q), 122.4 (s), 127.7 (s), 133.2 (d), 164.6 (s)
13h	2.34 (3H, s), 2.84 (3H, s), 4.54 (2H, s), 8.50 (6H, br), 9.07 (1H, s)	8.6 (q), 24.0 (t), 30.1 (q), 122.9 (s), 127.2 (s), 132.7 (d), 163.5 (s)
13i	[a] 2.40 (3H, s), 4.01 (4H, s), 4.63 (2H, s), 8.66 (1H, s)	[a] 11.0 (q), 27.2 (t), 48.0 (t), 123.8 (s), 131.4 (s), 135.7 (d), 170.8 (s)
13j	2.26 (3H, s), 4.49 (2H, s), 9.06 (1H, s), 9.64 (3H, br), 12.00—17.00 (2H, br)	7.4 (q), 25.0 (t), 122.2 (s), 125.8 (s), 131.5 (d), 150.3 (s), 168.5 (s)

a) In D_2O (reference DSS)

cording to the procedure described above, a solution of 2-imidazolidinethione (**9i**) (1.02 g, 0.01 mol) in methanol (7.5 ml) was added to a solution of 2-chloromethylquinoline hydrochloride (**7**) (2.14 g, 0.01 mol) in methanol (7.5 ml) with stirring at room temperature. The mixture was stirred for 1 h at room temperature. The solvent was evaporated off under reduced pressure, and the crystalline residue was recrystallized from ethanol to give 2.13 g (67%) of the product (**12i**).

2-(4-Methyl-5-imidazolylmethyl)isothiourea Dihydrochloride (13a) Following the same procedure described above, thiourea (**9a**) (15.24 g, 0.20 mol) was added to 5-chloromethyl-4-methylimidazole hydrochloride (**8**), (33.40 g, 0.20 mol) in methanol (350 ml). The mixture was stirred at room temperature for 3 h. The solvent was evaporated off under reduced pressure, and the crystalline residue was recrystallized from methanol to give 43.84 g (90%) of the product (**13a**).

1-Methyl-2-(4-methyl-5-imidazolylmethyl)isothiourea Dihydrochloride (13b) A solution of 5-chloromethyl-4-methylimidazole hydrochloride (**8**) (8.35 g, 0.05 mol) in methanol (20 ml) was added to a solution of *N*-methylthiourea (**9b**) (4.55 g, 0.05 mol) in methanol (20 ml) and 10% aqueous hydrochloride (3 ml) with stirring at room temperature. The mixture was stirred for 5 min at room temperature. The solvent was evaporated off under reduced pressure, and the crystalline residue was recrystallized from ethanol–acetonitrile to give 12.28 g (95%) of the product (**13b**).

1-Allyl-2-(4-methyl-5-imidazolylmethyl)isothiourea Dihydrochloride (13c) According to the procedure described above, **8** (8.35 g, 0.05 mol) was allowed to react with 1-allyl-2-thiourea (**9c**) (5.80 g, 0.05 mol). Work-up as above gave **13c** (11.07 g, 76%).

1-Phenyl-2-(4-methyl-5-imidazolylmethyl)isothiourea Dihydrochloride (13d) Employing the same procedure as given for **13b**, **8** (8.35 g, 0.05 mol) was allowed to react with 1-phenyl-2-thiourea (**9d**) (7.60 g, 0.05 mol). Work-up as above gave **13d** (15.76 g, 98%).

1-Amidino-2-(4-methyl-5-imidazolylmethyl)isothiourea Dihydrochloride (13e) Employing the procedure given for **13b**, **8** (8.35 g, 0.05 mol) was allowed to react with 1-amidinothiourea (**9e**) (5.90 g, 0.05 mol). Work-up as above gave **13e** (5.02 g, 35%).

3-(4-Methyl-5-imidazolylmethyl)isothiosemicarbazide Dihydrochloride (13f) Employing the procedure given for **13b**, **8** (8.35 g, 0.05 mol) was allowed to react with thiosemicarbazide (**9f**) 4.56 g 0.05 mol). Work-up as above gave **13f** (7.18 g, 56%).

References and Notes

1) A. Claus, *Ann.*, **179**, 145 (1875).
2) E. Brand, *Org. Synth.*, **22**, 59 (1942).
3) J. M. Sprague and J. B. Johnson, *J. Am. Chem. Soc.*, **59**, 1837 (1937).
4) A. Bernthsen and H. Klinger, *Ber.*, **12**, 574 (1879).
5) M. A. Phillips and H. Shapiro, *J. Chem. Soc.*, **1942**, 584.
6) H. S. Forrest and J. Walker, *J. Chem. Soc.*, **1948**, 1939.
7) A. Jean-Claude, B. Jean, F. Daniel, and J. Claude (Rhone-Poulenc Industries, Paris) Ger. Patent 3012142 A1 (1980) [*Chem. Abstr.*, **94**, 103177*h* (1981)].
8) A. Jean-Claude, B. Jean, F. Daniel, and J. Claude (Rhone-Poulenc Industries, S.A.) European Patent 46417 A1 (1982); Japan Kokai Patent 57-42687 (1982) [*Chem. Abstr.*, **97**, 6313*d* (1982)].
9) J. R. Bartels-Keith, R. A. Boggs, A. J. Puttick, and N. M. Sofen (Polaroid Co.) European Patent 0129033 A2 (1984); Japan Kokai Patent 59-225168 (1984).