Notes

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Synthesis of New Antimicrobials. III.[1] Synthesis of Chlorine-substituted 4-Thiocyanatoaniline and 2-Amino-6-chlorobenzothiazole Derivatives

Takahiro Yabuuchi, Masakatu Hisaki, and Ryuichi Kimura

Reseach Institute for Production Development[2]

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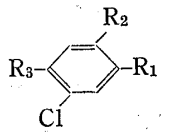
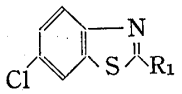
In order to examine their antimicrobial activity, new N-derivatives of chlorine-substituted 4-thiocyanatoanilines (A) and 2-amino-6-chlorobenzothiazole (B) were prepared by the reaction of compound A or B with haloacetyl halides, alkyl chloroformates, phenoxyacetyl chlorides, phenyl isocyanates, or arylaldehydes.

The potent antibacterial activity of thiocyanatoaniline[3] and 2-aminobenzothiazole derivatives[4] prompted us to prepare a number of new N-derivatives of chlorine-substituted 4-thiocyanatoanilines (A) and 2-amino-6-chlorobenzothiazole (B). The general structure of these compounds synthesized is as follows:





R_1=-NHCOR′R″, -NHCOCHSCN (R), -NHCOOR, -NHCOCH$_2$- (R), -N=CH- (R)

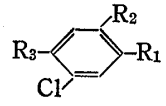
R_2, R_3=H, -SCN, Cl

Chlorine-substituted 2-bromo-4′-thiocyanatoacylanilides (I and II) were prepared by the reaction of chlorine-substituted 4-thiocyanatoanilines with α-bromoacyl bromide. Syntheses of chlorine-substituted α-thiocyanatoacylanilides (III—VII) were carried out by the thiocyanization of chlorine-substituted α-haloacylanilides with ammonium thiocyanate or potassium thiocyanate. In a similar fashion, N-cyclohexyl-α-thiocyanatopropionamide (VIII) was synthesized from α-bromo-N-cyclohexylpropionamide and ammonium thiocyanate. Methyl 3-chloro-4-thiocyanatophenylcarbamate (IX) was prepared by pyridine-catalyzed condensation of 3-chloro-4-thiocyanatoaniline with methyl chloroformate, and also was synthesized from 3-chloro-4-thiocyanatophenyl isocyanate and methanol by the method reported by Nifant'eva, *et al.*[5] Chlorine-substituted 4′-thiocyanatophenoxyacetanilides (X to XVI) were synthesized by the reaction of 3-chloro-4-thiocyanatoaniline or 2,5-dichloro-4-thiocyanatoaniline with phenoxyacetyl chloride or chlorine-substituted phenoxyacetyl chlorides. 1-Phenyl-3-(3-chloro-4-thiocyanatophenyl)ureas (XVII and XVIII) were derived from 3-chloro-4-thiocyanatoaniline and phenyl isocyanate or 4-nitrophenyl isocyanate. N-Benzylidene-3-chloro-4-thiocyanatoanilines (XIX to XXII) were prepared by the condensation of 3-chloro-4-thiocyanatoaniline with arylaldehydes. These reactions are summarized in Chart 1, and data of these new compounds obtained are listed in Table I.

The reaction of trichloroacetyl chloride, alkyl chloroformates, phenyl isocyanates, or *p*-chlorobenzaldehyde with compound (B)[6] afforded N-trichloroacetyl, N-alkoxycarbonyl,

1) Part II: R. Kimura, T. Yabuuchi, and M. Hisaki, *Chem. Pharm. Bull.* (Tokyo), **10**, 1231 (1962).
2) Location: *15-Morimoto-cho, Sakyo-ku, Kyoto.*
3) T. Kaneko, H. Kuroda, and T. Ueda, *Yakugaku Zasshi*, **75**, 303 (1956).
4) E. Grunbert, *N.Y. Trans. Acad. Sci.*, **13**, 29 (1950).
5) L.V. Nifant'eva, K.D. Shvetsova-Shilovskaya, and N.N. Mel'nikov, *Zh. Obshch. Khim.*, **38**, 1641 (1961).
6) H.P. Kaufmann, W. Oehring, and A. Clanberg, *Arch. Pharm.* **266**, 197 (1928).

TABLE I



Compd. No.	R_2	R_3	R_1	mp (°C) ( ): Cryst.[a] solvent	Appearance (colorless)	Formula	Analysis (%) Calcd. (Found) C	H	N
I	H	SCN	$CO\text{-}NHCHC_2H_5$ (Br)	110—111 (75% EtOH)	prisms	$C_{11}H_{10}ON_2BrClS$	39.59 (39.30)	3.02 (3.12)	8.39 (8.50)
II	Cl	SCN	$-NHCOCHCH_3$ (Br)	128—129 (MeOH)	needles	$C_{10}H_7ON_2BrCl_2S$	33.92 (33.91)	1.99 (2.03)	7.91 (7.68)
III	H	H	$-NHCOCH_2SCN$	171 (acetone)	prisms	$C_9H_7ON_2ClS$	47.65 (47.90)	3.11 (3.21)	12.36 (12.20)
IV	H	Cl	$-NHCOCH_2SCN$	170—171 (acetone)	prisms	$C_9H_6ON_2Cl_2S$	41.39 (41.50)	2.32 (2.10)	10.73 (10.90)
V	H	Cl	$-NHCOCHSCN$ (CH_3)	164—165 (EtOH)	prisms	$C_{10}H_5ON_2Cl_2S$	43.65 (43.76)	2.93 (2.90)	10.18 (10.30)
VI	H	SCN	$-NHCOCH_2SCN$	199.5 (acetone)	prisms	$C_{10}H_6ON_3ClS_2$	42.32 (42.10)	2.13 (2.22)	14.81 (14.90)
VII	Cl	H	$-NHCOCHSCN$ (CH_3)	182—183 (benzene)	prisms	$C_{10}H_8ON_2ClS$	43.65 (43.36)	2.31 (2.31)	10.18 (10.09)
VIII		H	$-NHCOCHSCN$ (CH_3)	98—99 (benzene)	prisms	$C_{10}H_{14}ON_2S$	56.57 (56.32)	7.59 (7.66)	13.19 (13.36)
IX	H	SCN	$-NHCOOCH_3$	134—135 (95% EtOH)	prisms	$C_9H_7O_2N_2ClS$	44.54 (44.65)	2.91 (3.06)	11.54 (12.00)
X	H	SCN	$-NHCOCH_2O-C_6H_5$	150—151 (acetone)	needles	$C_{15}H_{11}O_2N_2ClS$	56.52 (56.70)	3.48 (3.52)	8.79 (9.01)
XI	H	SCN	$-NHCOCH_2O-C_6H_4(Cl)$	172.5—173 (THF)	prisms	$C_{15}H_{10}O_2N_2Cl_2S$	51.00 (51.21)	2.85 (3.02)	7.95 (8.09)
XII	H	SCN	$-NHCOCH_2O-C_6H_3(Cl)(Cl)$	169—170 (acetone)	needles	$C_{15}H_9O_2N_2Cl_3S$	46.47 (46.46)	2.34 (2.26)	7.23 (7.33)
XIII	H	SCN	$-NHCOCH_2O-C_6H_2(Cl)_3$	232—233 (THF)	prisms	$C_{15}H_8O_2N_2Cl_4S$	42.68 (42.68)	1.91 (1.99)	6.64 (6.70)
XIV	Cl	SCN	$-NHCOCH_2O-C_6H_5$	148—149 (benzene)	needles	$C_{15}H_{10}O_2N_2Cl_2S$	51.00 (51.33)	2.85 (2.86)	7.95 (7.79)
XV	Cl	SCN	$-NHCOCH_2O-C_6H_4(Cl)$	166—167 (THF)	prisms	$C_{15}H_9O_2N_2Cl_2S$	46.47 (46.45)	2.34 (2.43)	7.23 (7.34)
XVI	Cl	SCN	$-NHCOCH_2O-C_6H_3(Cl)(Cl)$	210—211 (THF)	needles	$C_{15}H_8O_2N_2Cl_4S$	42.68 (42.70)	1.91 (1.92)	6.64 (6.70)
XVII	H	SCN	$-NHCONH-C_6H_5$	187—188 (EtOH)	prisms	$C_{14}H_{15}ON_3ClS$	55.35 (55.30)	3.32 (3.31)	13.83 (13.60)
XVIII	H	SCN	$-NHCONH-C_6H_4(NO_2)$	256—257 (acetone)	light yellow prisms	$C_{14}H_9O_3N_4ClS$	48.21 (48.30)	2.60 (2.70)	16.07 (16.01)
XIX	H	SCN	$-N{=}CH-C_6H_4(Cl)$	135—136 (EtOH)	needles	$C_{14}H_8N_2ClS$	54.74 (59.69)	2.62 (2.62)	9.12 (9.33)
XX	H	SCN	$-N{=}CH-C_6H_4(NO_2)$	147—148 (iso-PrOH)	needles	$C_{14}H_8O_2N_3ClS$	52.92 (53.21)	2.54 (2.53)	13.22 (13.21)
XXI	H	SCN	$-N{=}CH-C_6H_4(NO_2)$	136—137 (benzene)	needles	$C_{14}H_8O_2N_3ClS$	52.92 (52.63)	2.54 (2.62)	13.22 (13.37)
XXII	H	SCN	$-N{=}CH-C_4H_2O(NO_2)$	157—158 (benzene)	needles	$C_{12}H_6O_3N_3ClS$	46.84 (47.03)	1.97 (1.86)	13.66 (13.56)

a) THF: tetrahydrofuran

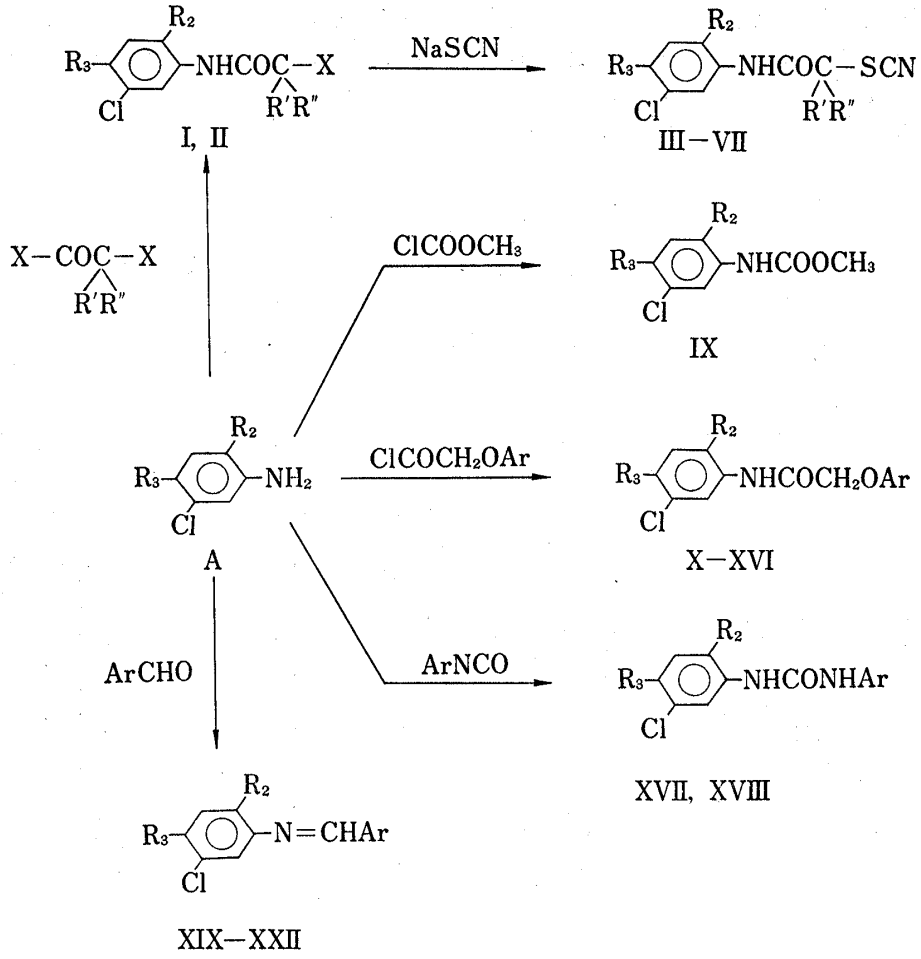


Chart 1

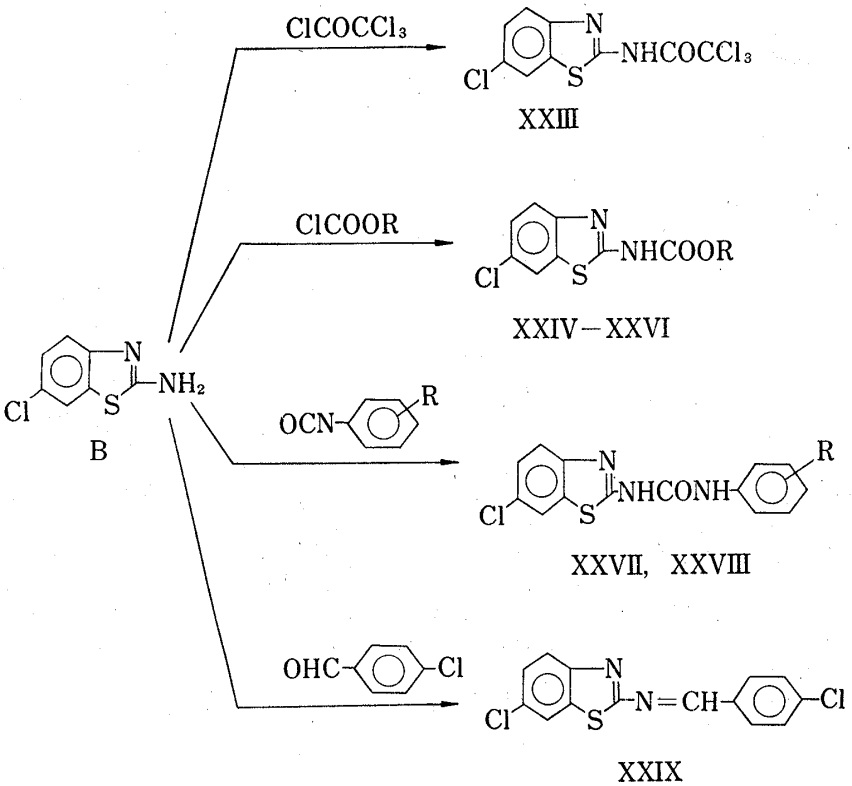
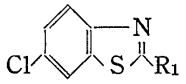
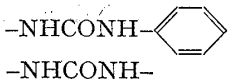
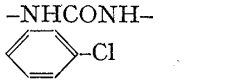
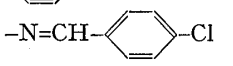


Chart 2

N-phenylcarbamoyl, and N-*p*-chlorobenzylidene derivatives (XXIII to XXIX) of compound (B) respectively, by the same procedure as for N-derivatives of chlorine-substituted 4-thiocyanatoanilines. The general synthetic routes for these compounds are shown in Chart 2, and physical data of new compounds obtained are listed in Table II.

Table II. 

Compd. No.	R_1	mp (°C). ( ): Cryst. solvent	Appearance (colorless)	Formula	Analysis (%) Calcd. (Found) C	H	N
XXIII	$-NHCOCCl_3$	207.5—208.5 (acetone)	prisms	$C_9H_4ON_2Cl_4S$	32.75 (32.78)	1.22 (1.46)	8.48 (8.09)
XXIV	$-NHCOOCH_3$	above 300 (THF)	prisms	$C_9H_7O_2N_2ClS$	44.54 (45.08)	2.91 (3.39)	11.54 (11.58)
XXV	$-NHCOOC_2H_5$	above 300 (THF–MeOH)	prisms	$C_{10}H_9O_2N_2ClS$	46.79 (47.26)	3.53 (3.69)	10.91 (11.14)
XXVI	$-NHCOOC_4H_9$ (n)	above 300 (THF–MeOH)	prisms	$C_{12}H_{13}O_2NClS$	50.61 (50.32)	4.60 (4.63)	9.83 (9.97)
XXVII		160 (EtOH)	prisms	$C_{14}H_{10}ON_3ClS$	55.35 (55.45)	3.32 (3.29)	13.83 (13.80)
XXVIII		above 300 (THF–EtOH)	prisms	$C_{14}H_9ON_3Cl_2S$	49.72 (50.52)	2.68 (2.80)	12.42 (15.50)
XXIX		209—210 (benzene)	light yellow prisms	$C_{14}H_8N_2Cl_2S$	54.73 (54.90)	2.62 (2.75)	9.12 (9.30)

Experimental

All melting points are determined in open capillary tubes and are uncorrected.

2-Bromo-3′-chloro-4′-thiocyanatobutyranilide (I)——To a solution of 18.5 g (0.1 mole) of 3-chloro-4-thiocyanatoaniline in 30 ml of dry benzene was slowly added a solution of 25.3 g (0.11 mole) of α-bromobutyryl bromide in 30 ml of dry benzene. After the solution was refluxed for 5 hr, the whole mixture was filtered, and the filtrate obtained was evaporated to dryness under reduced pressure. The residue obtained was recrystallized from 85% MeOH to give 24.4 g (74%) of I as colorless prisms, mp 110—111°.

2-Bromo-2′,5′-dichloro-4′-thiocyanatopropionanilide (II) was prepared in a similar manner to that for I.

3′-Chloro-2-thiocyanatoacetanilide (III)——A mixture of 20.4 g (0.1 mole) of 2,3′-dichloroacetanilide[7] and 19.4 g (0.2 mole) of KSCN in 100 ml of acetone was refluxed for 5 hr, then the reaction mixture was filtered. The filtrate obtained was concentrated to dryness under reduced pressure. After being washed with water, the residue was crystallized from acetone to give 12.6 g (60%) of III as colorless prisms, mp 171°.

Other chlorine-substituted α-thiocyanatoacylanilides (IV to VIII) were prepared in the same way as that for III.

Methyl 3-Chloro-4-thiocyanatophenylcarbamate (IX)——To a solution of 18 g (0.1 mole) of 3-chloro-4-thiocyanatoaniline and 1 g of dry pyridine in 100 ml of dry benzene was added a solution of 10.4 g (0.11 mole) of methyl chloroformate in 100 ml of dry benzene, and the reaction mixture was refluxed for 2 hr. The whole was concentrated under reduced pressure to give a residue, which was recrystallized from 80% EtOH after being washed with H_2O, to give 20 g (83%) of IX as colorless prisms, mp 134—135°.

3′-Chloro-4′-thiocyanatophenoxyacetanilide (X)——To a solution of 18 g (0.1 mole) of 3-chloro-4-thiocyanatoaniline in 100 ml of dry benzene was added a solution of 30.9 g (0.2 mole) of phenoxyacetyl chloride in 100 ml of dry benzene at 5°. The mixture was refluxed for 2 hr and evaporated to dryness to give a residue, which was recrystallized from 95% EtOH after being washed with H_2O to give 26.1 g (82%) of X as colorless prisms, mp 150—151°.

Other chlorine-substituted phenoxyacetanilides (XI to XVI) were prepared in the same way as that for X.

7) A. Kaji, *Nippon Kagaku Zasshi*, **81**, 1776 (1960).

1-Phenyl-3-(3-chloro-4-thiocyanatophenyl)urea (XVII)——To a solution of 18 g (0.1 mole) of 3-chloro-4-thiocyanatoaniline in 200 ml of dry benzene was added a solution of 14 g (0.12 mole) of phenyl isocyanate in 200 ml of dry benzene, and the mixture was refluxed for 1 hr. After benzene was evaporated under reduced pressure, the residue was recrystallized from EtOH to give 23 g (76%) of XVII as colorless prisms, mp 187—188°. 1-(4-Nitrophenyl)-3-(3-chloro-4-thiocyanatophenyl)urea (XVIII) was prepared in the same way as that for XVII.

N-(4-Chlorobenzylidene)-3-chloro-4-thiocyanatoaniline (XIX)——To a solution of 18 g (0.1 mole) of 3-chloro-4-thiocyanatoaniline in 200 ml of dry benzene was added a solution of 17 g (0.13 mole) of 4-chlorobenzaldehyde in 200 ml of dry benzene at 5°, the mixture was evaporated to dryness under reduced pressure and the residue was recrystallized from EtOH to give 21 g (70%) of XIX as colorless needles, mp 135—136°.

Other N-benzylidene-3-chloro-4-thiocyanatoanilines (XX to XXII) were prepared in the same way as that for XIX.

2-Trichloroacetamido-6-chlorobenzothiazole (XXIII)——This compound was prepared from compound (B) and trichloroacetyl chloride by the same procedure as that for I.

Alkyl N-[2-(6-Chlorobenzothiazoyl)]carbamate (XXIV to XXVI)——These compounds were prepared from compound (B) and alkyl chloroformates in the same way as that for IX.

2-(3-Arylureido)-6-chlorobenzothiazoles (XXVII and XXVIII)——These compounds were prepared from compound (B) and phenyl isocyanates in the same way as that for XVII.

N-(4-Chlorobenzylidene)-2-amino-6-chlorobenzothiazole (XXIX)——This compound was prepared from compound (B) and 4-chlorobenzaldehyde by the same method as that for XIX.

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Synthesis of New Antimicrobials. IV.[1] Synthesis of Alkylenebis-(thiourea) Derivatives and Their Related Compounds

Takahiro Yabuuchi, Masakatu Hisaki, Masahiro Matuda, and Ryuichi Kimura

Research Institute for Production Development[2]

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In order to examine the antimicrobial activity, alkylenebis(thiourea) derivatives and their related compounds were synthesized. 3,3′-Substituted 1,1′-alkylene-bis-(thiourea) derivatives were prepared from alkylenebis(isothiocyanates) and amines. Also 3,3′-alkylene-bis[2-thio-2,4(1H, 3H)-quinazolinediones] were prepared by the reaction of alkylenebis(isothiocyanates) and anthranilic acid, or alkylene diamines and ethyl *o*-isothiocyanatobenzoate respectively.

Antibacterial and anticandida's activities of thiocyanatobenzene derivatives have been of great interest and the present authors reported the synthesis of thiocyanatoaniline derivatives in previous papers.[1,3] In 1953, Kerk, *et al.*[4] reported the potent antimicrobial activities of isothiocyanates. In general, the potent antimicrobial activity has been found in many compounds which have a thiocyanate or thiourea group. Some of them have been

1) Part III: T. Yabuuchi, M. Hisaki, and R. Kimura, *Chem. Pharm. Bull.* (Tokyo), **23**, 659 (1975).
2) Location: *15-Morimoto-cho, Shimogamo, Sakyo-ku, Kyoto.*
3) R. Kimura, T. Yabuuchi, M. Hisaki, H. Sugimoto, A. Ohyama, and K. Mochida, *Chem. Pharm. Bull.* (Tokyo), **10**, 1226 (1962).
4) G.T.M. van der Kerk, H.C. van Os, G. de Vries, and A.K. Sijpestein, *Mededel. Landbouwhogeschool Opzoekingssta. Staat Gent.*, **18**, 402 (1953).