UDC 547.821.411.22 : 547.552 : 615.778

67. Haruo Saikachi and Takuzo Hisano : Synthetic Studies on Fungicidal Agent. VII. Reaction of 2-Picoline and Aromatic Primary Amines (or Aromatic Nitro Compounds) in the Presence of Sulfur.

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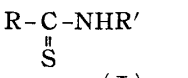
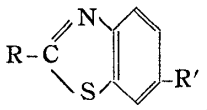
The discovery during these years of antibacterial activity in 2,6-disubstituted benzothiazoles,[1] *p*-acetamidobenzaldehyde thiosemicarbazone,[2] and N-(2-thiazolyl)nicotinamide[3] suggested that some more new fungicidal substances may also be found from the closely related pyridine derivatives possessing thiocarbamoyl (I) or benzothiazolyl group (II).



(I)

R=2-pyridyl
R′=aryl



(II)

R=2-pyridyl
R′=alkyl, aryloxyl

As a first step in this work, it seemed of interest to examine in more detail the products and mechanisms of condensation of 2-picoline with aromatic primary amines (or nitro compounds) in the presence of sulfur at elevated temperature.

It has recently been reported[4] that when a mixture of 2-picoline, aniline, and sulfur is heated at 180~220° for 12 hours, N-phenyl-thiopicolinamide (III) and 2-(2-pyridyl)benzothiazole (IV)[5] are formed in an almost constant ratio.

In a similar experiment in this Laboratory, N,N′-diphenylpicolinamidine, corresponding to N,N′-diphenylisonicotinamidine[6] formed from 4-picoline, was not obtained. Further, under several experimental conditions tried in this Laboratory, the mixture of 2-picoline, aniline, and sulfur, in some cases gave a very small amount of 2-(2-pyridyl)-benzothiazole. However, the use of aniline contaminated with a very small amount of nitrobenzene resulted in the formation of 2-(2-pyridyl)benzothiazole in a moderate yield. Therefore, it may be presumed from the previously reported experimental results[7] that oxidative cyclization of N-pheylthiopicolinamide to 2-(2-pyridyl)benzothiazole might be due to some extent to the presence of nitrobenzene as a moderate oxidizing agent.[8]

Although this over-all reaction mechanism has not been established yet, it seems reasonable to assume that first, free dithiopicolinic acid (V) (not isolated yet but potassium dithiopicolinate[9] and dithioisonicotinate[10] are known) is formed by the reaction of sulfur and the active methyl group, and second, the condensation of dithiopicolinic acid with aniline (or that formed by reduction of nitrobenzene with nascent hydrogen sulfide produced during the reaction of 2-picoline and sulfur). It is still uncertain, however, why

* Katakasu, Fukuoka (西海枝東雄，久野拓造).

1) B. L. Freedlander, F. A. French : Proc. Soc. Biol. Med., **66**, 362(1947).
2) G. Domagk, *et al.* : Naturwiss., **33**, 315(1946).
3) S. Kushnet, *et al.* : J. Org. Chem., **13**, 834(1948).
4) P. E. Miller, *et al.* : *Ibid.*, **22**, 664(1957).
5) B. Emmert, M. Groll : Ber., **86**, 208(1953).
6) B. Emmert, A. Holz : *Ibid.*, **87**, 676(1954).
7) H. Saikachi, T. Hisano, S. Yoshina : Yakugaku Zasshi, **74**, 1318(1954).
8) O. Brünig : Ber., **6**, 25(1873); O. Skraup : Monatsh., **2**, 141(1881).
9) D. L. Hammick, P. Dyson : J. Chem. Soc., **1937**, 781.
10) H. B. Koenig : Ber., **87**, 825(1954).

2-(2-pyridyl)benzothiazole is sometimes formed in spite of using pure aniline. Therefore, further discussions will be made on the reaction mechanism, based on more experimental results obtained in this Loboratory.

For the present, the over-all reaction mechanism is tentatively illustrated in Chart 1.

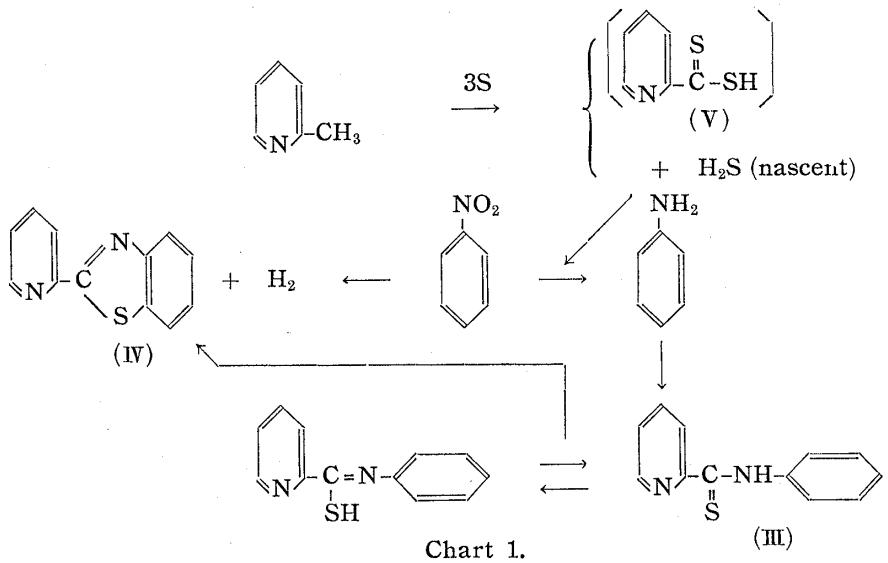


Chart 1.

For the second purpose of this work, namely microbiological screening, preparation of the analogs by the above reaction was attempted and in all, the following eleven compounds possessing amino and/or nitro group were used : *p*-Toluidine (VI), *p*-propoxyaniline (VII), 1-chloro-4-nitrobenzene (VIII), sulfanilic acid (IX), N^1-2-thiazolylsulfanilamide (X), dianisidine (XI), sulfanilamide (XII), homosulfanilamide (XIII), 2-aminopyridine (XIV), 2-aminopyrimidine (XV), and 2-amino-5-nitropyridine (XVI).

Among these compounds, (VIII), (IX), (X), and (XV) did not afford the corresponding thiopicolinamides or 2-(2-pyridyl)benzothiazoles and the unchanged reactants were quantitatively recovered.

Except for 2-aminopyrimidine (XV), these above results suggest that the condensability of 2-picoline with the amino or nitro group is affected by the kind of substituent present in *para*-position.

On the other hand, (VI) produced both N-*p*-tolyl-thiopicolinamide (XVII) and 2-(2-pyridyl)-6-methylbenzothiazole (XVIII), and (VII) formed N-*p*-propoxyphenyl-thiopicolinamide (XIX) and 2-(2-pyridyl)-6-propoxybenzothiazole (XX) (Chart 2).

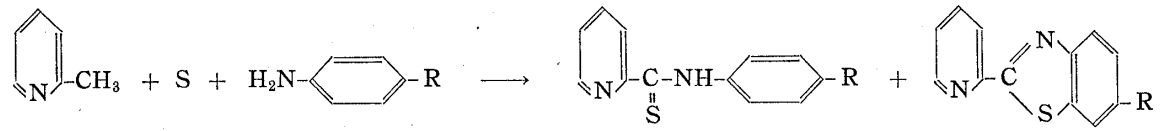


Chart 2.

Similarly (XI), (XII), (XIII), and (XIV) afforded the corresponding N,N'-bis(thiopicolinoyl)-3,3'-dimethoxybenzidine (XXI), N^1,N^4-bis(thiopicolinoyl)sulfanilamide (XXII), 4-thiopicolinamidomethyl N-thiopicolinoylbenzenesulfonamide (XXIII), and 2-thiopicolinamidopyridine (XXIV) (Chart 3).

When (XVI) was used as an amino component in this reaction, (XXV), m.p. 200~201°, and (XXVI), m.p. 131~132°, were isolated both as orange crystals from alkali-soluble substances of the reaction mixture. From the elementary analytical data 2,5-bis(thiopicolinamido)pyridine was assigned for (XXV) and 5-thiopicolinamido-2-aminopyridine for

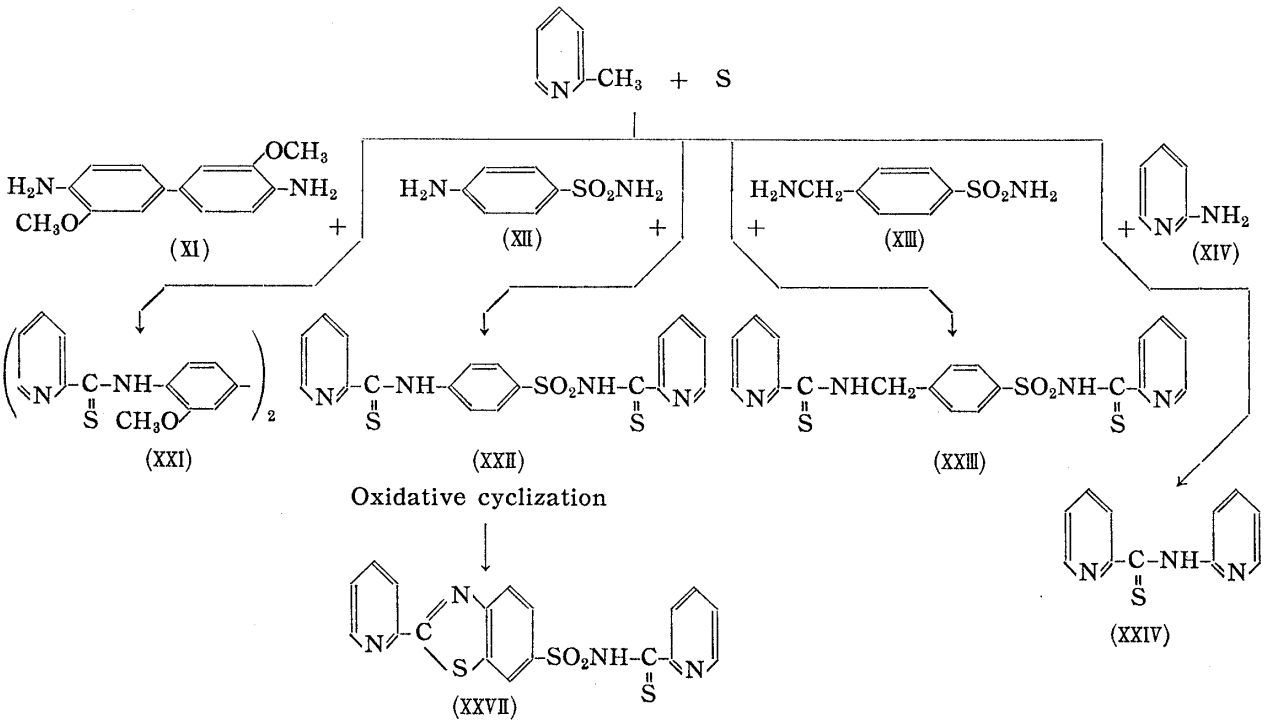


Chart 3.

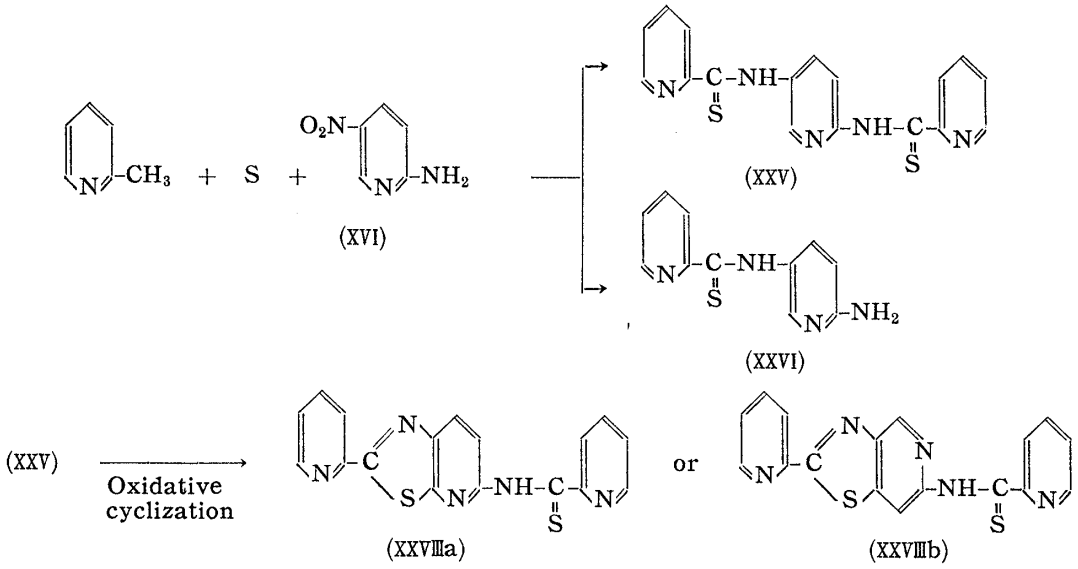


Chart 4.

(XXVI). In spite of the presence of a nitro group in the 5-position of pyridine ring, all attempts to isolate the desired thiazolopyridine were unsuccessful (Chart 4).

As can be presumed from Chart 1, 2,5-diaminopyridine, produced by reduction of 2-amino-5-nitropyridine (XVI) with nacsent hydrogen sulfide, may have formed both 2,5-bis(thiopicolinamido)pyridine (XXV) and 5-thiopicolinamido-2-aminopyridine (XXVI). Such a result is similar to the reaction of benzidine and 2-picoline.[11] In addition, the fact[12] that the amino group in the 5-position is generally more active than that in the 2-position of pyridine ring agrees with a greater formation of (XXV) than (XXVI) in this reaction. Further, the formation of (XXIV) and (XXVI), although in poor yield, showed

11) K. V. Martin : J. Am. Chem. Soc., **80**, 273(1958).
12) T. Takahashi, H. Saikachi, T. Tabata : Yakugaku Zasshi, **66**, 26(1941).

that this reaction can utilize protomeric amino group ($\ce{-NH2} \rightleftarrows \ce{=NH}$).

In the hope of preparing corresponding thiazoles from the five thiopicolinamides (XXI, XXII, XXIII, XXIV, and XXV), their oxidation with potassium ferricyanide in alkaline medium was undertaken. According to Mizuno,[13] the ease or difficulty of thiazole-ring formation with oxidizing agent is influenced by substituents in the *para*-position of benzene ring. Consequently, a strong resistance against oxidative ring closure was observed in the present case with N,N′-bis(thiopicolinoyl)-3,3′-dimethoxybenzidine (XXI), 4-thiopicolinamidomethyl N-thiopicolinoylbenzenesulfonamide (XXIII), and 2-thiopicolinamidopyridine (XXIV), while N^1,N^4-bis(thiopicolinoyl)sulfanilamide (XXII) was easily oxidized to form N-thiopicolinoyl-2-(2-pyridyl)benzothiazole-6-sulfonamide (XXVII) under the same conditions. In addition, the difference of molecular weight between (XXII) and (XXVII) is too small to presume ring closure from only elementary analytical data, and ultraviolet spectra of pure (XXII) and (XXVII) were carefully compared.

It is of interest to note that among 12 new compounds described in this paper and 10 compounds in the previous paper,[7] all thiopicolinoyl-type compounds form yellowish orange crystals while benzothiazole-type compounds are all colorless.

In order to compare more strictly the structural difference between the two types, ultraviolet spectra of these thiopicolinoyl- and benzothiazole-type compounds were carefully examined. For this purpose, pure N-phenyl-thiopicolinamide (III), N-*p*-tolyl-thiopicolinamide (XVII), and N-*p*-methoxyphenyl-thiopicolinamide (XXX) were taken as authentic thiopicolinoyl samples, and 2-(2-pyridyl)benzothiazole (IV), 2-(2-pyridyl)-6-methylbenzothiazole (XVIII), and 2-(2-pyridyl)-6-methoxybenzothiazole (XXXI) as the benzothiazole samples. The comparative absorption of the two types is shown in Fig. 1.

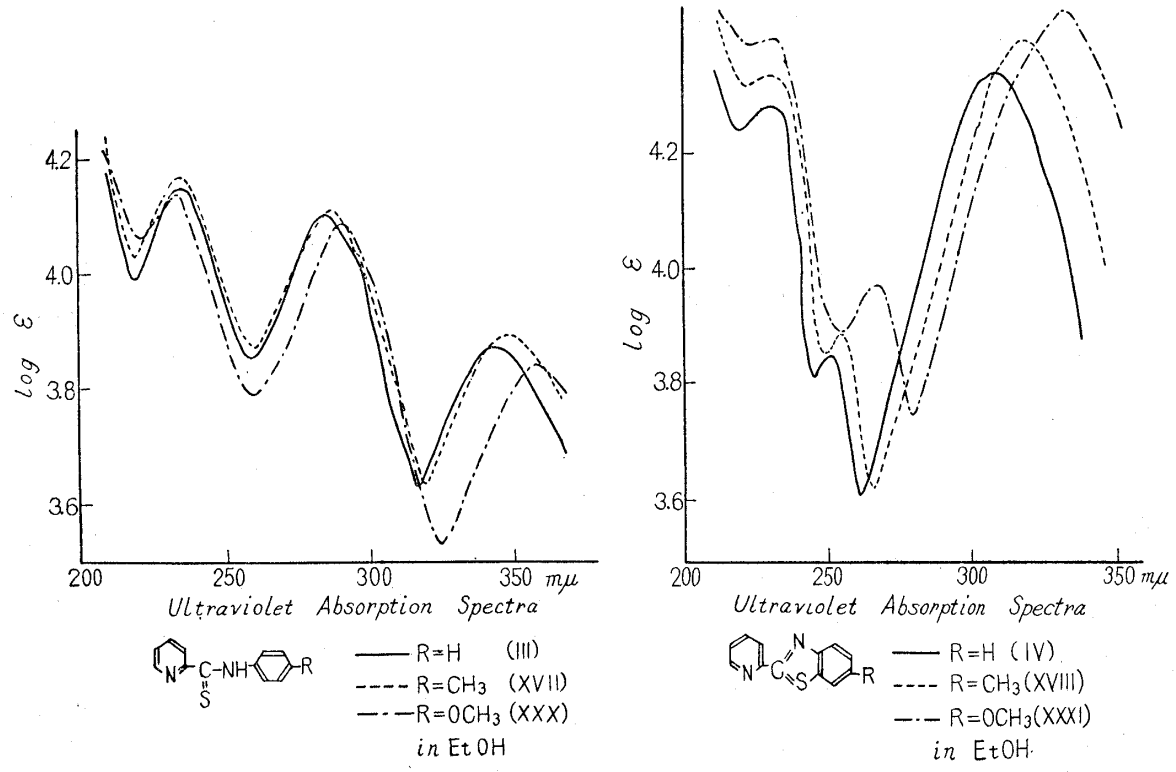


Fig. 1.

13) Y. Mizuno, *et al.*: Yakugaku Zasshi, **72**, 739, 745(1952).

Type A shows three maxima in each curve (Nos. 1, 2, and 3 in numerical order from the right side). From these curves, it can be seen that change of substituents (CH_3 to OCH_3) in the *para*-position of benzene ring causes a bathochromic shift. Type B shows three irregular maxima and especially a strong maximum in No. 1 curve. In this case, the chromophor substituents such as methyl and methoxyl groups produce a bathochromic shift to some extent and a hyperchromic effect. Comparison of the spectra of (XXII) with (XXVII) is given in Fig. 2.

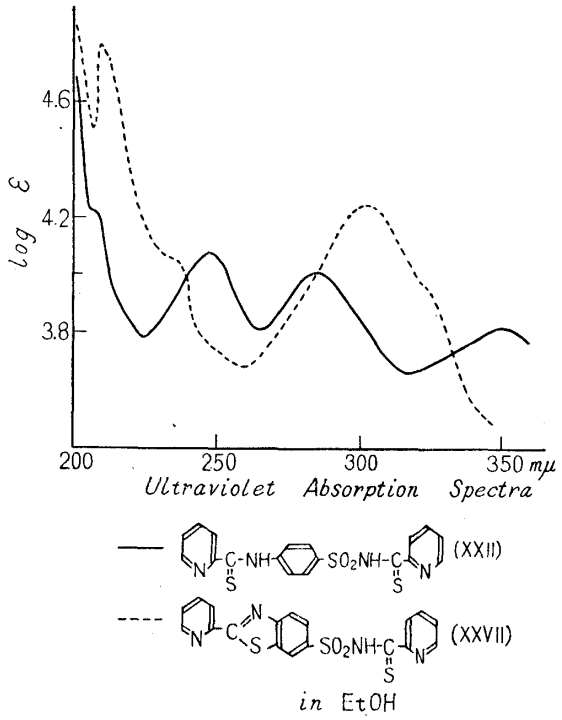


Fig. 2.

The spectrum of (XXII) shows three maxima at 248, 285, and 350 mμ, and this curve is similar to the spectra of type A in Fig. 1. In contrast, there is a maximum at 302 mμ in the spectrum of (XXVII), similar to that of type B in Fig. 1 but shows a small hypsochromic shift.

As can be seen from Chart 4, oxidative cyclization of 2,5-bis(thiopicolinamido)pyridine (XXV) produces either 2-(2-pyridyl)-5-thiopicolinamidothiazolo[5,4-*b*]pyridine (XXVIIIa) or 2-(2-pyridyl)-6-thiopicolinamidothiazolo[4,5-*c*]pyridine (XXVIIIb) in a good yield. In this connection there is not sufficient experimental data to confirm the structure of the oxidation product. However, it seems most reasonable to presume that the one-sided ring-formation between the 5- and 6-positions of pyridine ring may occur preferentially by virtue of electronic correlation (or interaction) between +E effect of one nitrogen atom in the pyridine ring and −E effect of another nitrogen atom in the 5-position.

Results of microbiological screening of these compounds will be reported elsewhere.

Authors' thanks are due to Mr. Y. Hirosawa, Mitsubishi Chemical Industries, Ltd., and Mr. T. Nakamura, Sumitomo Chemical Industries, Ltd., for contribution of many intermediates for this work. This work was supported by Grant-in-Aid for Scientific Research from the Ministry of Education, which is gratefully acknowledged.

Experimental

Condensation of 2-Picoline with Aromatic Primary Amines (or Aromatic Nitro Compounds) in the Presence of Sulfur : Method A—General Procedure (Compounds (VI) to (IX) in Table I) : A mixture of 9.3 g.(0.10 mole) of 2-picoline (b.p. 126~128°), 9.6 g.(0.30 mole) of S, and 0.10 mole of aromat-

Table I. Condensation of 2-Picoline with Amines in the Presence of Sulfur

	Reactants	Prep. Proc.	Product	Yield[a] (%)	m.p. (°C)	Recrystn. solvent	Appearance	Formula	N (%) Calcd.	N (%) Found
(VI)	*p*-Toluidine	A	N-*p*-Tolyl-thiopicolinamide (XVII)	14.0	101.5～102.5	MeOH	Orange prisms	$C_{13}H_{12}N_2S$	12.28	12.35
			2-(2-Pyridyl)-6-methyl-benzothiazole (XVIII)	2.0	164～165	MeOH	Colorless needles	$C_{18}H_{10}N_2S$	12.38	12.48
(VII)	*p*-Propoxyaniline	A	N-*p*-Propoxyphenyl-thiopicolinamide (XIX)	7.0	89.5～90.5	MeOH	Orange prisms	$C_{15}H_{16}ON_2S$	10.36	10.51
			2-(2-Pyridyl)-6-propoxy-benzothiazole (XX)	0.1	127～128	MeOH	Colorless prisms	$C_{15}H_{14}N_2S$	10.37	10.26
(VIII)	1-Chloro-4-nitrobenzene	A	Resinous matters							
(IX)	Sulfanilic acid	A	Unchanged[b]							
(XI)	Dianisidine	B	N,N′-Bis(thiopicolinoyl)-3,3′-dimethoxybenzidine	22.1	228～230	MeOH	Yellow needles	$C_{26}H_{22}ON_4S_2$	11.5	11.31
(XV)	2-Aminopyrimidine	B	Unchanged[b]							
(XIII)	*p*-(Aminomethyl)benzene-sulfonamide	B	4-Thiopicolinamidomethyl-N-thiopicolinoylbenzene-sulfonamide (XXIII)	18.6	185～187	MeOH	Yellow prisms	$C_{19}H_{15}O_2N_4S_3$	13.07	13.00
(X)	N^1-2-Thiazolylsulfanil-amide	B	Resinous							
(XII)	*p*-Aminobenzenesulfon-amide	B	N^1,N^4-Bis(thiopicolinoyl)-sulfanilamide (XXII)	69.3	251～252.2	EtOH	Yellow crystals	$C_{18}H_{14}O_2N_4S_3$	13.52	13.72
(XIV)	2-Aminopyridine	B	2-Thiopicolinamido-pyridine (XXIV)	10.8	81～82.5	MeOH	Yellow needles	$C_{11}H_9N_3S$[c]	19.52	18.97
(XVI)	2-Amino-5-nitropyridine		5-Thiopicolinamido-2-aminopyridine (XXVI)*	15.6	200～201	EtOH	Golden orange needles	$C_{17}H_{13}N_5S_2$	19.93	19.45
			2,5-Bis(thiopicolinamido)-pyridine (XXV)	0.5	131～133	EtOH	Yellow orange crystals	$C_{11}H_{10}N_4S$	24.33	24.21

a) Yield of pure product and calculated on the basis of amino compounds.
b) Almost quantitatively recovered.
c) Calcd.: C, 61.37; H, 4.21. Found: C, 61.35; H, 4.21.
* See Experimental section.

ic amine (or aromatic nitro compounds) (VI, VII, VIII, and IX) was refluxed for 10 hrs. at 160~165°. The unchanged 2-picoline and amine were completely removed by vacuum distillation in an oil bath. An orange oily residue was extracted with hot 3*N* NaOH solution (5×100 cc.), the combined extracts were carefully acidified with dil. HCl, and the yellowish orange crystalline mass that deposited was collected by filtration. Three recrystallizations from MeOH gave, except for 1-chloro-4-nitrobenzene and sulfanilic acid, thiopicolinoyl compound in about 10% yield. In the above procedure, alkali-insoluble residue was recrystallized three times from MeOH and then a very small amount of benzothiazolyl derivative was isolated from the residue, except for 1-chloro-4-nitrobenzene and sulfanilic acid (see Table I).

Method B: This procedure was good except for N^1-2-thiazolylsulfanilamide and 2-aminopyrimidine, but was unsuccessful for isolation of new thiazole cyclization products from the reaction mixtures. A mixture of 9.3 g.(0.25 mole) of 2-picoline, 8.0 g.(0.25 mole) of sulfur, and 0.15 mole of aromatic amine was refluxed at 160~170° for 20 hr. The darkish brown reaction mixture was submitted to steam distillation to remove unchanged 2-picoline and the residue was extracted with 3*N* NaOH solution (3×100 cc.). The combined extracts were slightly acidified with dil. HCl and extracted again with AcOEt. The organic layer was dried over fused Na_2SO_4, filtered, and the solvent was distilled off to leave a darkish brown residue. Three recrystallizations from MeOH (or EtOH) gave the desired thiopicolinoyl compound listed in Table I. On the other hand, this procedure resulted in quantitative recovery of unchanged 2-aminopyrimidine. The mixed melting point of crystals with authentic specimen did not show any depression.

The reaction mixture was completely resinified in the case of N^1-2-thiazolylsulfanilamide and the desired product was not isolated.

N-Thiopicolinyl 2-(2-Pyridyl)benzothiazole-6-sulfonamide (XXVII)—To a stirred solution of 44 g. of powdered $K_3Fe(CN)_6$ in 70 cc. of water, a suspension of 2.0 g. of (XXII) and 7.2 g. of NaOH in 100 cc. of water was added dropwise at 40~50° during 50 min. The mixture was then treated for additional 2 hr., 30 g. of K_2CO_3 was added, and extracted with Et_2O. The Et_2O layer was dried over fused Na_2SO_4, filtered, the solvent was distilled off, and 1.5 g. of crude crystalline mass was obtained. Several recrystallizations from EtOH gave 1.2 g. of colorless plates, m.p. 258~260°(yield, 60%). *Anal.* Calcd. for $C_{18}H_{12}O_2N_4S_3$: C, 52.41; H, 2.93; N, 13.58. Found: C, 51.72; H, 3.05; N, 13.88.

5-Thiopicolinamido-2-aminopyridine (XXVI) and 2,5-Bis(thiopicolinamido)pyridine (XXV)—A mixture of 9.3 g.(0.10 mole) of 2-picoline, 8.0 g.(0.25 mole) of S, and 11.1 g.(0.08 mole) of 2-amino-5-nitropyridine was heated in an oil bath at 160~165° for 20 hr. There was a vigorous evolution of H_2S gas in the course of this reaction. After removal of unchanged 2-picoline by steam distillation, the residue was extracted with hot 3*N* KOH solution (5×100 cc.). The combined extract was cooled to room temperature until yellowish orange needles deposited. The crude crystals were collected, washed with water, and three recrystallizations from EtOH gave 2.4 g.(15.6%) of golden orange needles, m.p. 200~201°. *Anal.* Calcd. for $C_{17}H_{13}N_5S_2$: N, 19.93. Found: N, 19.45.

The alkaline mother liquor was acidified with dil. HCl and AcOH to Congo Red and extracted with AcOEt. The organic fraction was dried over fused Na_2SO_4, filtered, and after removal of the solvent, the residue became gradually crystalline. The crystalline mass was collected and three recrystallizations from EtOH gave 0.1 g.(0.5%) of yellow orange crystals, m.p. 131~132°. *Anal.* Calcd. for $C_{11}H_{10}N_4S$: N, 24.33. Found: N, 24.21.

2-(2-Pyridyl)-5-thiopicolinamidothiazolo[5,4-*b*]pyridine (XXVIIIa)—To a stirred solution of 13.0 g. of NaOH and 0.5 g. of 2,5-bis(thiopicolinamido)pyridine (XXV) in 50 cc. of water, a solution of 1.8 g. of $K_3Fe(CN)_6$ in 30 cc. of water was added dropwise at 45° during 50 min. and cooled gradually to room temperature. After additional 2 hr. the reaction mixture was extracted with Et_2O, the organic layer was dried over fused Na_2SO_4, and the solvent was distilled off. The crude crystals were collected by suction and recrystallized from EtOH to 0.5 g.(100%) of colorless plates, m.p. 256~257°. *Anal.* Calcd. for $C_{17}H_{11}N_5S_2$: N, 20.04. Found: N, 19.82.

Summary

The condensation of 2-picoline with various aromatic primary amines (or nitro compounds) in the presence of sulfur was carried out at elevated temperature. This reaction was tentatively divided into three types: The first type is a simple thiopicolinoyl; the second, a mixed type, yielding thiopicolinoyl and thiazolyl cyclization products; and the last, unchanged (or resinous). It is noteworthy that protomeric amino group, such as that of N^1-position of sulfanilamide and 2-position of pyridine, was active to some extent for this reaction. Oxidative cyclization of five thiopicolinoyl intermediates

(XXI, XXIII, and XXIV) from dianisidine, sulfanilamide, homosulfanilamide, 2-aminopyridine, and 5-nitro-2-aminopyridine with potassium ferricyanide was unsuccessful, but not for (XXII) and (XXV).

The chemical structure of these cyclization products was discussed on the basis of their ultraviolet spectral observation and electronic theory. Microbiological activity of these compounds will be reported elsewhere.

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68. Takeo Ishiguro et Hiroyuki Mogi : Sur la pression de la vapeur d'eau de dissociation des hydrates du diphenylhydantoïnate de calcium.

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Les sels métalliques du diphenylhydantoïne forment généralement des hydrates. Tamayo, *et al.*[1] ont écrit que le sel de nickel du diphenylhydantoïne forme un hexahydrate, et Hiyama, *et al.*[2] ont déduit que le sel de sodium du diphenylhydantoïne forme des mono-, tétra-, et hepta-hydrates. En outre Ishiguro, Kozatani, et Fujita[3] déterminèrent les températures de transition des hydrates : hydrate à 11 H_2O hydrate à 8 H_2O, hydrate à 8 H_2O hydrate à 7 H_2O, et hydrate à 7 H_2O hydrate à 4 H_2O avec la courbe de viscosité-température de la solution saturée et avec celle de solubilité du diphenylhydantoïnate de sodium. Ils[4] déterminèrent aussi l'existence des hydrates à 1, 4, 7, 8, et 11 H_2O à la lumière du résultat de la mesure de la pression de la vapeur d'eau des hydrates du diphenylhydantoïnate de sodium avec le tensimètre différentiel. Cependant sur l'hydrate du sel de calcium aucun compte rendu n'a encore été fait.

Nous avons remarqué que dans le diphenylhydantoïnate de calcium (que nous appellerons en abrégé DHC) venant de se recristalliser en partant d'une solution aqueuse et contenant environ 25% d'eau, si on le laisse longtemps dans l'air atmosphérique, la proportion d'eau diminue vers 15% à 20%. De plus, quand on le laisse dans l'air atmosphérique, après avoir desséché à 100° pendant quelques heures sous la pression ordinaire, nous avons remarqué que le DHC absorbe de l'eau graduellement et qu'il finit par contenir de 15% à 20% d'eau.

Nous avons pensé que ce phénomène vient de la formation d'hydrates, et nous avons mesuré la pression de la vapeur d'eau du DHC pour différentes compositions d'eau à 25.0°. Nous avons établi un diagramme representant la pression de la vapeur d'eau de dissociation-composition, et nous avons déterminé le nombre des mols de l'eau de cristallisation par rapport à un mol de DHC; ensuite nous avons mesuré la pression de la vapeur d'eau de dissociation sur chaque système des hydrates à des températures comprises entre 25.0° et 55.0°. Nous avons ainsi obtenu les courbes de la pression de la vapeur d'eau de dissociation et nous en avons dérivé les formules empiriques (Tableau I) avec lesquelles nous avons examiné la stabilité des hydrates.

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* Yoshida-konoe-cho, Sakyo-ku, Kyoto (石黒武雄, 茂木宏之).

1) M. L. Tamayo, J. G. Marques : Anales fis. y quim. (Madrid), **43**, 1011(1947) (C. A. **42**, 2893(1948)).
2) M. Hiyama, S. Kori, K. Shibata : Yakuzai Buchokai Nempo, **11**, 103(1952).
3) T. Ishiguro, J. Kozatani, T. Fujita : Yakugaku Zasshi, **77**, 775(1957).
4) T. Ishiguro, J. Kozatani, K. Shibata : *Ibid.*, **78**, 391(1958).