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129. Haruo Saikachi and Takuzo Hisano : Synthetic Studies on Antituberculous Agent. VIII.¹⁾ Reaction between 4-Picoline and Aromatic Primary Amines in the Presence of Sulfur.

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In connection with researches on chemotherapeutic agents for tuberculosis, a considerable number of pyridinecarboxylic acid derivatives have been synthesized and tested by many investigators.²⁾ Of these, only isonicotinoylhydrazine³⁾ and isonicotinoylhydrazine-methanesulfonic acid⁴⁾ are used in the clinical field. Unfortunately, it appears that a specificity existed in these chemical structures and their tuberculostatic activity has not yet been cleared. In connection with this fact, it is very interesting that thioisonicotinoyl amide and hydrazide derivatives were proposed by Freeman and his co-workers.⁵⁾

In the light of their work, the authors attempted to prepare thioisonicotinoyl compounds in order to test them against microorganisms.

In the previous work^{1,6)} of this series, the treatment of 2-picoline with aromatic primary amines and nitro compounds in the presence of sulfur gave many 2-thiopicolin-anilide-type and sometimes benzothiazole-type derivatives. Further, it was shown in previous papers^{1,6)} that chemical reactivity affected the nitro group at *para*-position of some substituted benzene rings.

Consequently, 4-thiopicolinanilide-type derivatives were prepared by treatment of 4-picoline, as a component possessing one active methyl group, in place of 2-picoline. Previously, Emmert, *et al.*⁷⁾ and Porter⁸⁾ carried out the reaction of 4-picoline with aromatic primary amines, but no systematic and quantitative studies had been attempted, except for a few compounds. In using aromatic nitro compounds, it was assumed that two moles of nascent hydrogen sulfide evolved during the reaction will be able, first, to reduce the nitro group to their corresponding amino group, and then effect condensation of 4-dithiopicolinic acid which may be produced during this reaction. It seems that the reaction may depend to some extent upon the difficulty of reduction of aromatic nitro group by nascent hydrogen sulfide gas as one of the rate-determining steps of this overall reaction.

On the basis of such prediction and in order to avoid such experimental complications, the following systematic and simple compounds were used: Aniline (I), *p*-toluidine (II), *p*-anisidine (III), *p*-phenetidine (IV), *p*-propoxyaniline (b.p.₃ 90~95°) (V), *p*-isopropoxyaniline (b.p.₂ 108~112°) (VI), and *p*-butoxyaniline (b.p.₄ 120~125°) (VII).

However, past reports^{7,8)} on the reaction between 4-picoline and aromatic primary amines in the presence of sulfur show that the product and yield of this reaction were not always constant.

Consequently, the effect of the quantity ratio of reactants, the reaction temperature,

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1) Part VII : This Bulletin, **7**, 349(1959).

2) W. Steeken, J.E. Walinsky : Am. Rev. Tuberc., **65**, 4(1952); G. Stüttger : Arzneimittel Forsch., **5**, 703(1955); H. Fox, *et al.* : J. Org. Chem., **21**, 349(1956).

3) J. Havell, *et al.* : J. Am. Pharm. Assoc., **42**, 402(1953).

4) Japan. Pat. 212,376 (Daiichi Seiyaku Co., Ltd. (Japan)); O. Kitamoto, *et al.* : Nihon Kagakuryoho Gakkai Shi, **1**, 36 (1953); Malous : Am. Rev. Tuberc., **65**, 511(1952).

5) H. Freeman, *et al.* : J. Am. Pharm. Assoc., **42**, 457(1953).

6) H. Saikachi, T. Hisano, S. Yoshina : Yakugaku Zasshi, **74**, 1318(1954).

7) B. Emmert, A. Holz : Ber., **87**, 676(1954).

8) H.D. Porter : J. Am. Chem. Soc., **76**, 127(1954).

and duration of reaction upon the yield were examined.

First, the following experiment was carried out. The time of reaction was fixed at 10 hours, the molar ratio of 4-picoline, aniline, and sulfur was experimentally fixed at 1:1:3, and the four reactions were carried out at $140^{\circ}\pm 3^{\circ}$, $150^{\circ}\pm 3^{\circ}$, $160^{\circ}\pm 3^{\circ}$, and $170^{\circ}\pm 3^{\circ}$ (Fig. 1).

As can be seen in Fig. 1, the yield of 4-thiopicolinanilide and 2-(4-pyridyl)benzothiazole was subject to the reaction temperature. It was clarified that when the condensation is carried out at the molar ratio of 4-picoline, aniline, and sulfur in 1:1:3 at 160~170° for 10 hours, the over-all yield was the highest.

According to the experiment, it was observed that evolution of hydrogen sulfide markedly decreased after heating for 35~40 hours in comparison with that immediately after start of the reaction (tested by lead acetate paper).

King, *et al.*⁹⁾ previously reported that the condensation was carried out with the maximum yield at a molar ratio of styrene, morpholine, and sulfur at 1:2:2.5.

From the results of various experiments conducted in this laboratory,*² it seems that the ratio of 4-picoline, aniline, and sulfur at 1:1.5:2.5 is good for obtaining the desired

A-type Compounds

Compd. No.	R	Formula	m.p. (°C) ^(a)	Appearance	N (%)		Yield (%) ^b
					Calcd.	Found	
(VIII)	H	C ₁₂ H ₁₀ N ₂ S	180~182 ^c	Orange prisms	13.07	12.98	18.5
(X)	CH ₃	C ₁₃ H ₁₂ N ₂ S	181~183 ^(a)	//	12.27	12.10	16.8
(XII)	OCH ₃	C ₁₃ H ₁₂ ON ₂ S	167~168	//	11.46	11.21	56.7
(XIV)	OC ₂ H ₅	C ₁₄ H ₁₄ ON ₂ S	158.5~160	//	10.84	10.78	50.4
(XVI)	OC ₃ H ₇ (<i>iso</i>)	C ₁₅ H ₁₆ ON ₂ S	150~151	//	10.29	10.38	21.3
(XVIII)	OC ₃ H ₇ (<i>n</i>)	C ₁₅ H ₁₆ ON ₂ S	166~167.5	Orange needles	10.29	10.48	27.9
(XX)	OC ₄ H ₉ (<i>n</i>)	C ₁₆ H ₁₈ ON ₂ S	145~146	Orange prisms	9.78	9.89	29.4

b) The yield is based on 4-picoline.

c) m.p. 181~182° (B. Emmert).⁷⁾

a) m.p. 181° (B. Emmert).⁷⁾

*2 Unpublished work.

9) J. A. King, F. H. McMillan: J. Am. Chem. Soc., **68**, 2335(1946).

condensation products. Hence, in the present work, the reaction conditions adopted were the duration of 40 hours, temperature of 160~165°, and the molar ratio of 1:1.5:2.5 for the said reactants.

According to Emmert's work, condensation of 4-picoline with aniline in the presence of sulfur gave 4-thiopicolinanilide (m.p. 181~182°) and 2-(4-pyridyl)benzothiazole (m.p. 134~135°), and a small amount of N,N'-diphenylisonicotinamidine (m.p. 191~192°) was isolated from the reaction mixture. The present experiment did not give the desired N,N'-diphenylisonicotinamidine, contrary to his work.

The products obtained are shown in Tables I and II.

TABLE II.
B-type Compounds

Compd. No.	R	Formula	m.p. (°C) ^{a)}	Appearance	N(%)		Yield (%) ^{a)}
					Calcd.	Found	
(IX)	H	C ₁₂ H ₈ N ₂ S	132~134 ^{b)}	Colorless plates	13.20	13.41	30.8
(XI)	CH ₃	C ₁₃ H ₁₀ N ₂ S	167~169 ^{c)}	Colorless needles	12.38	12.47	28.8 ^{e)}
(XIII)	OCH ₃	C ₁₃ H ₁₀ ON ₂ S	158~159	Colorless plates	11.56	11.41	1.5 ^{e)}
(XV)	OC ₂ H ₅	C ₁₄ H ₁₂ ON ₂ S	129~131	Colorless needles	10.93	10.92	6.3
(XVII)	OC ₃ H ₇ (<i>iso</i>)	C ₁₅ H ₁₄ ON ₂ S	111~112	Colorless plates	10.36	10.37	3.7
(XIX)	OC ₃ H ₇ (<i>n</i>)	C ₁₅ H ₁₄ ON ₂ S	109~110	Colorless needles	10.36	10.20	5.2
(XXI)	OC ₄ H ₉ (<i>n</i>)	C ₁₆ H ₁₆ ON ₂ S	98~100	Colorless plates	9.85	9.71	6.4

^{a)} All melting points are uncorrected. All products were recrystallized from MeOH with activated charcoal.

^{b)} m.p. 134~135° (Emmert),⁷⁾ m.p. 131.5~133 (H. D. Porter).⁸⁾

^{c)} m.p. 157~158° (Emmert).⁷⁾

^{d)} The yield was based on 4-picoline.

^{e)} (XI) and (XIII) were respectively identified with oxidation products of (X) and (XII).

In the previous paper,¹⁾ it was reported that a remarkable difference in UV absorption spectra between 2-thiopicolinanilide-type and 2-(2-pyridyl)benzothiazole-type compounds were observed. In the present work, the absorption bands in UV spectra of pure 4-thiopicolinanilide-type and 2-(4-pyridyl)benzothiazole-type compounds were also compared.

It is of interest that the appearance of all 4-thiopicolinanilide-type compounds are yellowish orange without exception, while benzothiazole-type compounds are colorless and the latter show violet fluorescence in alcohol solution.

Although the change of appearance is natural in view of chemical structure, UV spectra of these compounds were observed in order to confirm the above phenomena.

For this purpose, pure 4-thiopicolinanilide (VIII), 4-thiopicolino-*p*-anisidide (XII), 4-thiopicolino-*p*-phenetide (XIV), and 4-thiopicolino-*p*-propoxyanilide (XVIII) obtained were used as samples and for the sake of comparison, 2-(4-pyridyl)benzothiazole (IX), 2-(4-pyridyl)-6-methylbenzothiazole (XI), 2-(4-pyridyl)-6-methoxybenzothiazole (XIII), 2-(4-pyridyl)-6-ethoxybenzothiazole (XV), and 2-(4-pyridyl)-6-propoxybenzothiazole (XIX) were also used as sample of benzothiazoles (Fig. 2).

As can be seen in Fig. 2, type (A) compounds show two maxima in each curve (Nos. I and II in numerical order from right side). From the curves, it can be seen that change of substituents (H to alkoxyl group) at the *para*-position of benzene ring leads to a bathochromic shift, the same as in Doub's work.¹⁰⁾

Type (B) compounds show three irregular maxima. In this case, the chromophoric substituents such as methyl and alkoxyl groups produce to some extent a bathochromic shift.

10) L. Doub, *et al.*: J. Am. Chem. Soc., **69**, 2714(1947).

Fig. 2. Ultraviolet Absorption Spectra of 4-Thiopicolinanilides and 2-(4-Pyridyl)benzothiazoles ($10^{-5}M$ in EtOH).

Results of biological screening of the substances prepared above will be published elsewhere.

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Experimental

Condensation of 4-Picoline with Aromatic Primary Amines in the Presence of Sulfur—The following general procedure was used for the condensation of seven aromatic amines listed in Table I.

A mixture of 9.3 g. (0.10 mole) of 4-picoline, 8.0 g. (0.25 mole) of S, and 0.15 mole of aromatic amine (I, II, III, IV, V, VI, and VII) was heated in an oil bath at $160^{\circ} \pm 3^{\circ}$ for about 40 hr. when H_2S evolved vigorously. After end of this reaction, the brown reaction mixture was submitted to vacuum distillation in an oil bath to completely remove unchanged 4-picoline and amines. After removal of excess 4-picoline, the brown oily residue was extracted with hot 3N NaOH solution (5×100 cc.). An appropriate amount of dil. HCl was first added to the above obtained alkaline layer and then AcOH to Congo Red, when yellow precipitate formed. The crude yellow crystals were collected and recrystallized three times from MeOH. The alkali-insoluble residue was recrystallized from MeOH.

Oxidation of 4-Thiopicolino-*p*-toluidide with Potassium Ferricyanide—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 (XI) and 7.2 g. of NaOH in 100 cc. of water was added dropwise at $40 \sim 50^{\circ}$ during 0.5 hr. The mixture was maintained for 2 hr. under the same conditions, 30 g. of K_2CO_3 was added to the reaction mixture, and the mixture was

kept at 45~50° for further 1 hr. This was cooled and extracted twice with ether. The extract was dried over Na₂SO₄ and filtered. Removal of ether gave a crude crystalline mass. Several recrystallizations from MeOH gave crystalline substances.

Summary

Condensation of 4-picoline with various aromatic primary amines was carried out in the presence of sulfur at elevated temperature. This reaction proceeded favorably under the condition of duration of 40 hours, the temperature of 160~165°, and the molar ratio of 1:1.5:2.5 of 4-picoline, aniline, and sulfur.

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130. Torizo Takahashi and Akira Koshiro : Syntheses of Heterocyclic Compounds of Nitrogen. CXIX. Syntheses of Oxazolopyridines and Related Compounds. (5).¹⁾

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Previous attempts to prepare 2-methyl-6-bromoxazolo[5,4-*b*]pyridine (VI) by heating 3-amino-5-bromo-2-hydroxypyridine (II) or its hydrochloride with acetic anhydride by Takahashi and his co-workers^{2,3)} ended fruitless and only monoacetate was obtained. However, the authors succeeded in the syntheses of 2-substituted 6-bromoxazolo[5,4-*b*]pyridine by treatment of (II) with acetic anhydride, benzoic anhydride, or potassium methylxanthate, and the results in this research are herein described.

5-Bromo-2-hydroxy-3-nitropyridine (I), which was prepared in accordance with the method reported in Part (4)¹⁾ of this series, was hydrogenated to (II) in methanol using palladium-charcoal as a catalyst, but the product was rapidly decomposed into black resin while evaporating methanol and the yield of (II) was unsatisfactory. While searching for a better method, it was found that Lyons, *et al.*⁴⁾ had reduced *o*-nitrophenol with iron in sodium chloride solution to *o*-aminophenol quantitatively.

According to this method, (II) could be obtained very easily and in a pure state. In spite of variation in temperature and amounts of iron powder and sodium chloride, the yield of (II) could not be increased more than 40.7% as shown in Table I. (II) was also obtained by reducing (I) with tin and hydrochloric acid,⁵⁾ but the above method was far more convenient.

Subsequently, by heating (II) with acetic anhydride, four substances were isolated. According to analytical values, these substances are monoacetate, diacetate, triacetate, and oxazolopyridine (VI). As the diazo reaction for aromatic primary amines of the monoacetate was negative, it was clear that this monoacetate is 3-acetamido-5-bromo-2-

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1) Paper presented at the Monthly Meeting of the Pharmaceutical Society of Japan, Osaka, June 21, 1958. Part CXVIII. Part (4) : Yakugaku Zasshi, **79**, 1129(1959).

2) T. Takahashi, H. Saikachi, H. Goto, S. Shimamura : Yakugaku Zasshi, **64**, 81(1944).

3) Y. Yamamoto : *Ibid.*, **72**, 1491(1952).

4) R.E. Lyons, L.T. Smith : *Ber.*, **60**, 173(1927).

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