(cf. Table IV). *Anal.* Calcd. for $C_8H_{10}NCl \cdot C_6H_3O_7N_3$(2-(α-Chloropropyl)pyridine picrate): C, 43.69; H, 3.38; N, 14.56. Found: C, 43.60; H, 3.39; N, 14.18. *Anal.* Calcd. for $C_8H_{10}NCl \cdot C_6H_3O_7N_3$(4-(α-chloropropyl)pyridine picrate). Found: C, 43.46; H, 3.36; N, 14.25.

Reduction of α- or γ-Chloro Compounds—A solution of 0.5 g. of chloro compounds, obtained by the above method, dissolved in 10% HCl was catalytically reduced with Pd-C (30%). After removal of the catalyst, HCl solution was distilled off, the residue was dissolved in a small amount of water, basified with 10% NaOH, and extracted with ether. The ether residue was distilled in an oil bath (cf. Table IV). *Anal.* Calcd. for $C_8H_{11}N \cdot C_6H_3O_7N_3$(2-Propylpyridine picrate): C, 48.00; H, 4.00; N, 16.00. Found: C, 47.93; H, 4.09; N, 16.10. *Anal.* Calcd. for $C_8H_{11}N \cdot C_6H_3O_7N_3$(4-Propylpyridine picrate): C, 48.00; H, 4.00. Found: C, 48.10; H, 4.51.

Summary

Alkyl- or benzylpyridylcarbinols (α or γ) were obtained from alkyl or benzyl (α or γ) picolyl ethers by the application of sodium amide in Decalin, xylene, or benzene. This indicates that the sodium amide forms a carbanion by the polar effect of nitrogen and the carbanion electron attacks the carbon with a low electron density in the rearranging radical, thus the rearrangement takes place. Ethyl, benzyl, *sec*-butyl (α or γ)-picolyl ethers underwent the rearrangement to carbinols, but rearrangement product could not be isolated from ethyl β-picolyl ether, in which the effect of nitrogen is small, and from phenyl (α or γ) picolyl ethers, in which a carbon with a low electron density is not formed. In benzyl picolyl ethers, the carbanion is formed from the carbon directly bonded to the pyridine ring, and benzyl-(α or γ)-pyridylcarbinol is obtained by the rearrangement reaction.

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41. Torizo Takahashi and Kan-ichi Ueda: Sulfur-containing Pyridine Derivatives. XLVIII.* Synthesis of Thiazolo[5,4-*c*]pyridines.

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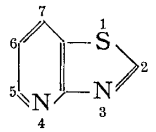
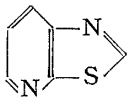
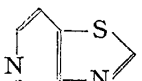
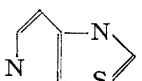
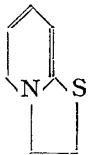
In thiazolopyridine system formed by the fusion of pyridine and thiazole rings, there are following four possible isomers, except for the [3,2-*a*] series.


Thiazolo[4,5-*b*]pyridine


[5,4-*b*]


[4,5-*c*]


[5,4-*c*]


[3,2-*a*]

Previous reports on thiazolopyridines were confined to the [4,5-*b*], [5,4-*b*], and [4,5-*c*] series. The synthesis of thiazolopyridines of these series was demonstrated by earlier workers. The method may be divided broadly into two classes: (1) Application of the procedure used by Kaufmann[1] in the synthesis of aminobenzothiazoles from aniline derivatives to aminopyridines by thiocyanation, and (2) cyclization of *o*-aminopyridinethiols with suitable reagents such as acid anhydride, acid halide, urea, and thiophosgene.

Similar method was adopted by Bernstein *et al.*,[2] who synthesized thiazolo[4,5-

* Part XLVII: This Bulletin, **4**, 133(1956).

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1) H. P. Kaufmann, *et al.*: Arch. Pharm., **266**, 197 (1928).; **273**, 31(1935); Ber., **67**, 944(1934).

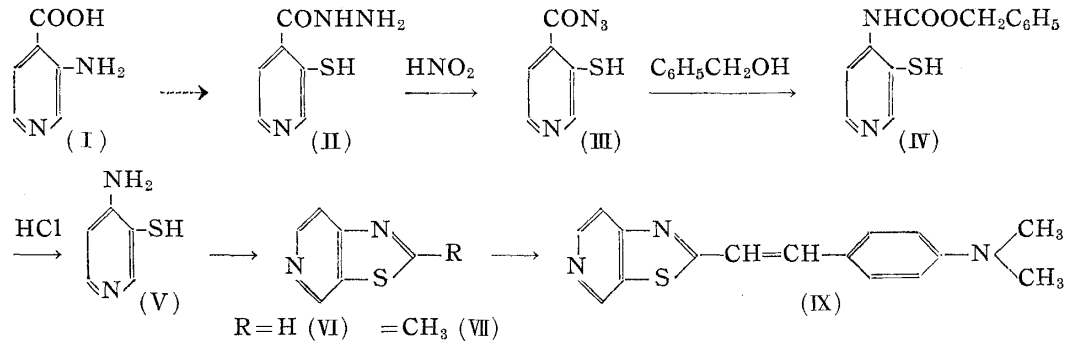
2) J. Bernstein, B. Stearns, E. Shaw, W. A. Lott: J. Am. Chem. Soc., **69**, 1151(1947).

b]pyridines from 6-R-2-aminopyridines (R=NH_2 or $NHCOCH_3$). One of the authors (Takahashi) and Yamamoto[3] also applied this method to 5-aminopyridines possessing a variety of substituents in the 2-position of the pyridine ring, and obtained an interesting result, indicating that when a substituent that shows −E effect large enough to compensate for the +E effect of ring nitrogen is present in the 2-position of the pyridine ring, such compounds are comparatively easily affected by thiocyanogen, yielding thiocyano compounds which can be changed to thiazolopyridines.

For the purpose of extending this method to the other aminopyridines and thereby synthesizing thiazolopyridines fused in the 3,4-position of the pyridine ring, 4-amino-2,6-lutidine,[4] 4-amino-2-bromopyridine,[5] and 3-amino-6-ethoxy-2-methylthiopyridine[6] were taken up as the starting amines, but this attempt ended in failure, only recovering the starting materials. This indicates that even if aminopyridines which possess substituents compensating the effect of the ring nitrogen are selected, Kaufmann's method would not be applicable for the synthesis of the [4,5-*c*] or [5,4-*c*] series.

On the other hand, the second method lends itself advantageously to the synthesis of a variety of 2-substituted thiazolopyridines from *o*-aminopyridinethiols. A number of 2-substituted derivatives of [5,4-*b*] isomer were prepared previously by Takahashi and Yamamoto[7] from *o*-aminopyridinethiols, easily obtainable by ring cleavage of the thiazole moiety of 2-amino derivatives of [5,4-*b*] series by alkaline hydrolysis. Also, the method[8] by simultaneous reduction and cyclization of nitropyridines possessing a mercapto group adjacent to the nitro group was often utilized.

In connection with previous investigations on the antitubercular activity of thiazolopyridines, an attempt to synthesize [5,4-*c*] series was made by the following route.



3-Mercaptoisonicotinic acid hydrazide (II), necessary for the preparation of 4-aminopyridine-3-thiol (V), was prepared by the method of Katz *et al.*[9] from the amino acid (I) by diazotization (Leuckart's method), esterification, and treatment with excess hydrazine hydrate.

Application of Sugasawa[10] and Saito's modification of the Curtius degradation to (II) afforded, via 3-mercaptoisonicotinic acid azide (III), benzyl 3-mercaptopyridyl-

3) T. Takahashi, Y. Yamamoto : J. Pharm. Soc. Japan, **71**, 169, 662(1951).
4) E. Ochiai, M. Fujimoto : This Bulletin, **2**, 131(1954).
5) H. J. den Hertog, C. R. Kolder, W. P. Combé : Rec. trav. chim., **70**, 591(1951).
6) T. Takahashi, K. Ueda : J. Pharm. Soc. Japan, **73**, 442(1952).
7) T. Takahashi, Y. Yamamoto : *Ibid.*, **71**, 920, 1436(1951).
8) S. J. Childress, R. L. McKee : J. Am. Chem. Soc., **73**, 3504(1951); T. Takahashi, K. Ueda, T. Ichimoto : This Bulletin, **2**, 196(1954).
9) L. Katz, W. Schroeder, M. Cohen : J. Org. Chem., **19**, 711(1954).
10) S. Sugasawa, S. Akaboshi, S. Toda, H. Tomisawa : J. Pharm. Soc. Japan, **72**, 192(1952).

4-carbamate (IV), the identity of which was confirmed by its analytical values, infrared spectrum (3.14 and 5.78 μ; -NHCOO-), and, as shown later, hydrolysis with hydrochloric acid to 4-aminopyridine-3-thiol (V). The infrared absorption spectrum of (IV) is given in Fig. 1.

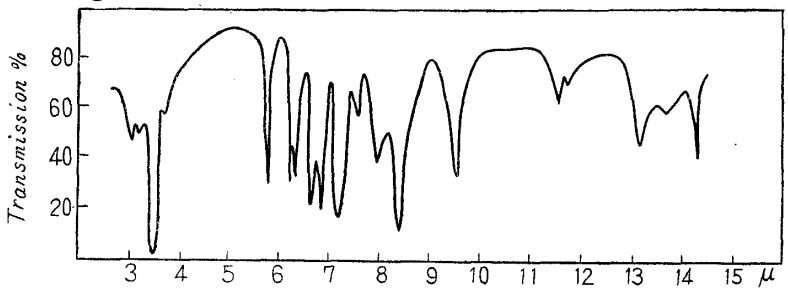
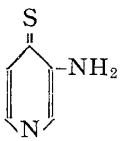


Fig. 1. Benzyl 3-Mercaptopyridyl-4-carbamate (in Nujol)

Hydrolysis of (IV) with hydrochloric acid in acetic acid, followed by neutralization with aqueous ammonia, gave a semisolid product. This product was insoluble in aqueous alkali, but produced a reddish purple color by Grote's reagent, evidently indicating the existence of a mercapto group. Because of the difficulty of crystallization, it was purified as a picrate, which was found by elemental analyses to be 4-aminopyridine-3-thiol picrate.



(VIIIb)

Compared with isomeric 3-aminopyridine-4-thiol (VIIIa),[11] interesting results were obtained. Contrary to 4-aminopyridine-3-thiol (V), (VIII) was soluble in alkali and gave a blue-green coloration, with the Grote's reagent, indicating that it exists in the thioketone (VIIIb) rather than the thiol form. The fact that (V) is insoluble in alkali in spite of possessing a mercapto group, seems to be ascribable to a decreasing acidity of the mercapto group. It would be reasonable to consider that resonance involving the amino group and the pyridine ring is formed at the expense of the resonance involving the thiol group.

The cyclization of (V) with formic acid-acetic anhydride mixture in the presence of zinc dust gave rise to thiazolo[5,4-*c*]pyridine (VI) itself. Similarly, (V) was cyclized with acetic anhydride in the presence of potassium acetate to 2-methylthiazolo-[5,4-*c*]pyridine (VII), along with a small amount of a disulfide.

The condensation of (VII) with *p*-dimethylaminobenzaldehyde was then effected by using hydrochloric acid as a condensing agent, yielding 2-*p*-dimethylaminostyryl-thiazolo[5,4-*c*]pyridine (IX).

This work was supported partly by a Grant in Aid for Fundamental Scientific Research from the Ministry of Education to which the authors are greatly indebted. The authors are also grateful to Dr. H. Kano and Mr. A. Narisada of Shionogi & Co. Ltd. for the infrared determination, and to the members of the Analytical Center of the University of Kyoto for the microanalyses.

Experimental[12]

Curtius Degradation of 3-Mercaptoisonicotinic Acid Hydrazide (II)—A solution of 2.5 g. of 3-mercaptoisonicotinic acid hyrazide in 25 cc. of water containing 30 cc. of conc. HCl was chilled to −2° in an ice-salt bath, and a solution of 1.0 g. of $NaNO_2$ in 3 cc. of water was then added at a moderate rate, while the reaction mixture was stirred rapidly. The azide began to precipitate out toward the end of the addition. Stirring was continued for a further 1 hr. and the mixture was neutralized with $NaHCO_3$ with good cooling. The deposited azide was collected by filtration, washed with cold water, and finally dried in a vacuum desiccator. The azide weighed about 2.5 g.

To a solution of 80 cc. of benzene containing 3.0 g. of benzyl alcohol was added the above

11) T. Takahashi, K. Ueda, T. Ichimoto: This Bulletin, **3**, 356(1955).
12) All melting points are uncorrected.

azide, and the mixture was refluxed for 30 mins. The solvent was evaporated, leaving benzyl 3-mercaptopyridyl-4-carbamate (IV), which was recrystallized from benzene to colorless needles, m.p. 147°. Yield, 1.7 g. *Anal.* Calcd. for $C_{13}H_{12}O_2N_2S$: C, 60.00; H, 4.61. Found : C, 60.10; H, 4.68.

4-Aminopyridine-3-thiol (V)—To the acid mixture (40 cc. of 20% HCl and 40 cc. of glacial AcOH) was added 1.7 g. of (IV) and the mixture was boiled for 2 hrs. The reaction mixture was then distilled nearly to dryness under a reduced pressure. The resulting residue was dissolved in water, the solution was decolorized with charcoal, and filtered. The clear filtrate was neutralized with aq. NH_3, thus depositing a semisolid material. This was freed from the solvent by decantation and dissolved in EtOH. After treatment with charcoal, EtOH solution was filtered. Evaporation of the solvent left a semisolid material (ca. 0.8 g.). The picrate (from EtOH), yellow needles, m.p. 228°(decomp.). *Anal.* Calcd. for $C_{11}H_9O_7N_6S$: C, 37.19; H, 2.53. Found : C, 37.36; H, 2.40. The free base in aq. acetone produced a reddish purple color with the Grote's reagent.

Thiazolo[5,4-*c*]pyridine (VI)—The hydrolysis of 1.5 g. of (IV) with the acid mixture was carried out as above. After the solvent was removed under a reduced pressure, the residue was dissolved in 20 cc. of 95% formic acid and 0.3 g. of Zn dust was added. After completion of the reaction, 4 cc. of Ac_2O was added, the mixture was refluxed for 30 mins., and then evaporated *in vacuo* to dryness. The residue was rendered alkaline with aq. NaOH and extracted with ether. The ether extract was dried over anhyd. Na_2SO_4. Removal of the solvent yielded 0.14 g. of (VI). Recrystallization from petr. ether gave colorless pillars, m.p. 105~106°. *Anal.* Calcd. for $C_6H_4N_2S$: C, 52.93; H, 2.94. Found : C, 53.03; H, 3.22.

2-Methylthiazolo[5,4-*c*]pyridine (VII)—A mixture of 0.8 g. of (V) and 0.5 g. of AcONa in 10 cc. of Ac_2O was refluxed for 7.5 hrs., cooled, and then filtered. The filtrate was evaporated to dryness under a reduced pressure, the residue was rendered alkaline with aq. NH_3, and extracted with ether. After being dried over anhyd. Na_2SO_4, the ether solution was evaporated, leaving two substances, which were fractionated by a mixture of petr. ether and ether. 4,4'-Diacetaminopyridyl 3,3'-disulfide insoluble in the above solvent mixture first separated, which after recrystallization from AcOEt formed colorless needles, m.p. 209°. Yield, 50 mg. *Anal.* Calcd. for $C_{14}H_{14}O_2N_4S_2$: C, 50.29; H, 4.19; N, 16.76. Found : C, 50.46; H, 4.01; N, 16.74.

Recrystallization of the soluble material from petr. ether afforded 0.2 g. of colorless crystals (VII), m.p. 94~95°. *Anal.* Calcd. for $C_7H_6N_2S$: C, 55.95; H, 4.07. Found : C, 56.24; H, 4.20.

2-*p*-Dimethylaminostyrylthiazolo[5,4-*c*]pyridine (IX)—A mixture of 0.4 g. of (VII), 0.4 g. of *p*-dimethylaminobenzaldehyde, and a few drops of conc. HCl was heated in an oil bath (100~110°) for 15 hrs. After cooling, the content was washed with aq. Na_2CO_3 and then with hot alcohol. Recrystallization of the residue from AcOEt yielded 0.4 g. of reddish yellow plates (IX), m.p. 219~220°. *Anal.* Calcd. for $C_{16}H_{15}N_3S$: N, 14.94. Found : N, 14.87.

Summary

The synthesis of thiazolo[5,4-*c*]pyridines was accomplished by the Curtius degradation of 3-mercaptoisonicotinic acid hydrazide and cyclization of the resulting 4-aminopyridine-3-thiol with formic acid or acetic anhydride.

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