kept at 45~50° for further 1 hr. This was cooled and extracted twice with ether. The extract was dried over Na_2SO_4 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 temparature. 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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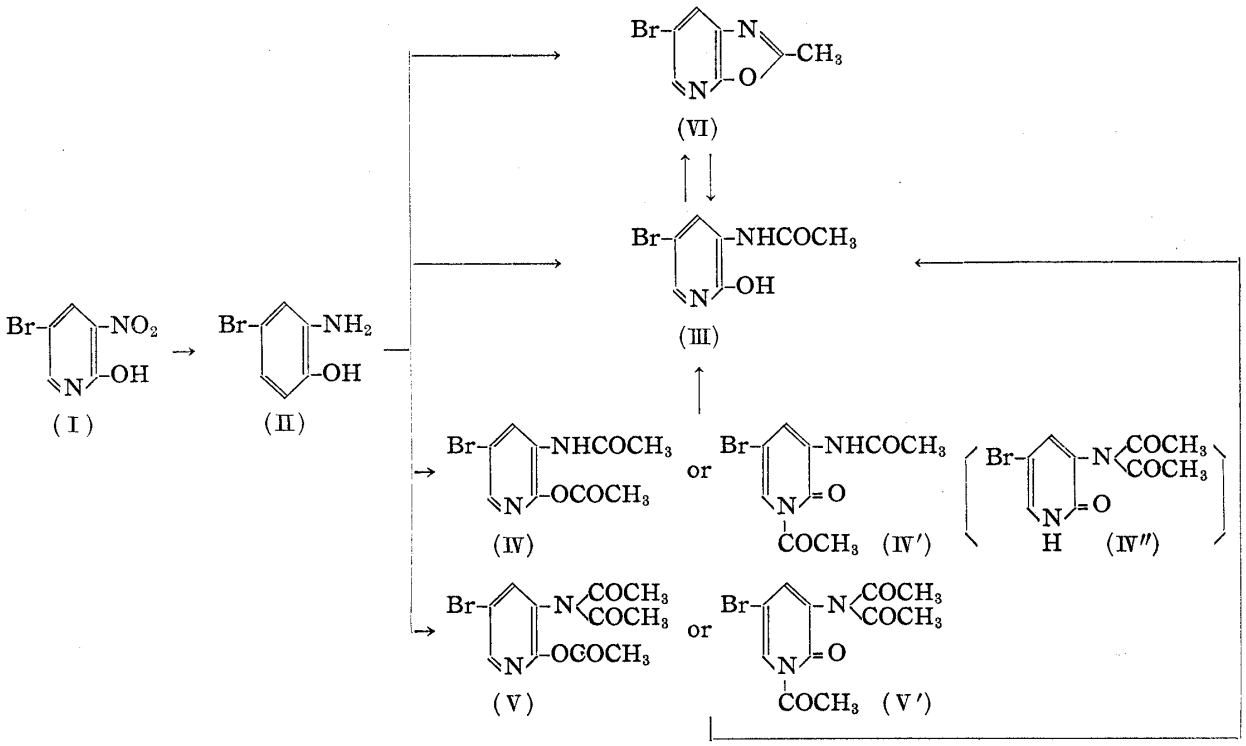
1) Paper presented at the Monthly Meeting of the Pharmaceutical Society of Japan, Osaka, June 21, 1958. Part CXVIII. Part (4) : Yakugaku Zasshi, **79**, 1129(1959).
2) T. Takahashi, H, Saikachi, H. Goto, S. Shimamura : Yakugaku Zasshi, **64**, 81(1944).
3) Y. Yamamoto : *Ibid.*, **72**, 1491(1952).
4) R. E. Lyons, L. T. Smith : Ber., **60**, 173(1927).
5) Y. Yamamoto : Yakugaku Zasshi, **71**, 169(1951).



hydroxypyridine (III). However, the structures of (IV), (IV'), and (IV") may be considered for the diacetate, and (V) and (V') for the triacetate.

The infrared spectra of diacetate and triacetate in Nujol were examined in order to decide which structure was suitable. Spectrum of the diacetate showed ν_{N-H} of an open-chain secondary amide at 3330 cm^{-1}, $\nu_{C=O}$ at 1750, 1698, and 1640 cm^{-1}, and did not show ν_{N-H} of a cyclic secondary amide in the region of 3100~3200 cm^{-1}. This denies the structure of (IV"). If the band at 1750 cm^{-1} originates in $-OCOCH_3$ and those at 1698 and 1640 cm^{-1} are from -NHCO-, the diacetate should be (IV), but it is not clear why the absorption band of -NHCO- is split. On the other hand, if the bands at 1750 and 1698 cm^{-1} are considered as the absorption band due to interaction between 2-pyridone and acetyl group, the structure of (IV') would be suitable. The example of such absorption due to interaction has been known in the molecule containing -CO-NH-CO- such as uracil, hydantoin, etc., and these bands appear around 1750 and 1700 cm^{-1}.[6] However, no data have been reported about N-acetylpyridone series and it was impossible to predict the interaction from only a few samples. Therefore, the structure of (IV) includes a little unreasonable assumption and that of (IV') has no data for judgement.

The spectrum of triacetate showed $\nu_{C=O}$ at 1760, 1720, and 1660 cm^{-1}. It was considered that the band at 1760 cm^{-1} originates from $-OCOCH_3$, and those at 1720 and 1660 cm^{-1} from $-N(COCH_3)_2$, but, the band at 1660 cm^{-1} seems to be too low in frequency. On the other hand, in the case of N-acetylpyridone type (V'), the data for judgement are unknown as (IV').

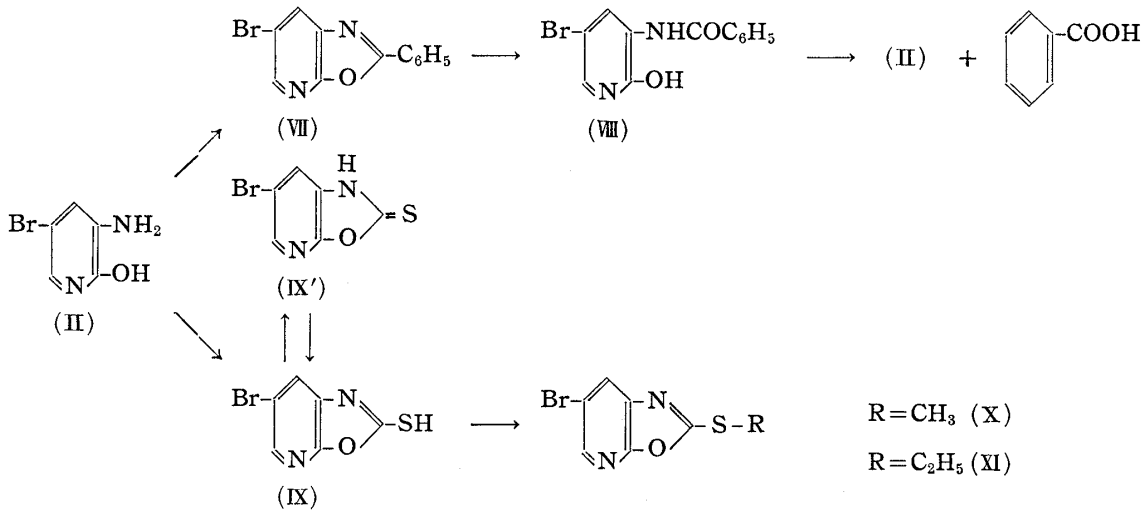
Because some absorption bands could not be assigned, as stated above, structures of the diacetate and triacetate could not be determined.

On heating the above diacetate or triacetate with water for 5~10 minutes, they were rapidly hydrolyzed to (III), and (III) was converted to (VI) satisfactorily by distilling with phosphorus pentoxide under reduced pressure. (VI) thus obtained was very unstable to

6) H.M. Randall, R.G. Fowler, N. Fuson, J.R. Dangl: "Infrared Determination of Organic Structures," 14(1949). D. Van Nostrand Company, U.S.A.

acid and it was hydrolyzed to (III) by leaving with 5% hydrochloric acid at 20~25° for 24 hours. It was more stable to alkali and when allowed to stand with 20% sodium hydroxide at 20~25° for 24 hours, no change could be recognized.

Subsequently, on heating (II) with benzoic anhydride, it was converted to 2-phenyl-6-bromoxazolo[5,4-*b*]pyridine (VII) in good yield. (VII) was very stable to acid and alkali. On leaving (VII) with 20% hydrochloric acid at 20~25° for 34 hours and heating on a boiling water bath for 4 hours, the oxazole ring was opened and (VII) was hydrolyzed to 3-benzamido-5-bromo-2-hydroxypyridine (VIII) which was further decomposed to (II) and benzoic acid.



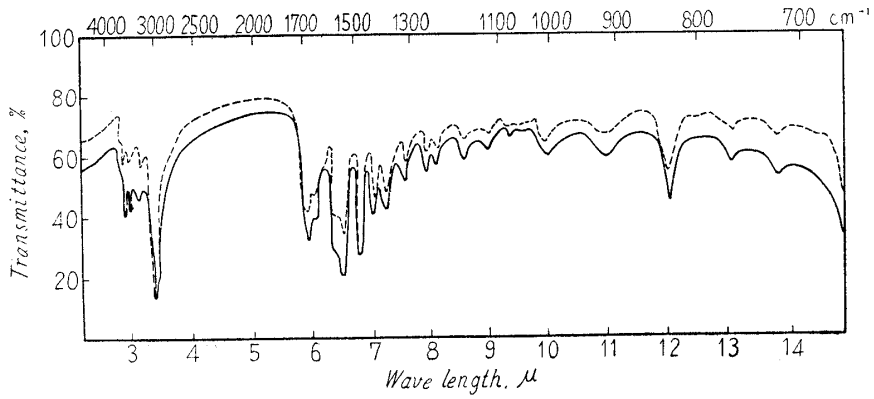
2-Mercapto-6-bromoxazolo[5,4-*b*]pyridine (IX) was prepared in good yield by the reaction of (II) with potassium methylxanthate. The infrared spectrum of (IX) in Nujol showed ν_{N-H} at 3153 cm^{-1}, thioamide-II band at 1524 cm^{-1}, but did not show ν_{S-H} in the region of 2550~2600 cm^{-1}. It was therefore concluded that (IX) existed in a thiolactam form (IX') in the solid state, similarly as 2-mercaptobenzoxazole.[7]

On alkylation with alkyl halides in alkaline medium, (IX) gave the corresponding thioethers (X, XI), the yield of which was not so good.

Cyclization with cyanogen bromide was very convenient in the case of *o*-aminophenol, but application of this method to pyridine derivatives was unsuccessful as reported in Parts (1)[8] and (2)[9] of this series. By the reaction of (II) with cyanogen bromide, a substance was produced to which may be assigned three possible structures from their analytical values, 2-amino-6-bromoxazolo[5,4-*b*]pyridine hydrate (XII), 5-bromo-3-cyanamino-2-hydroxypyridine hydrate (XIII), and (5-bromo-2-hydroxy-3-pyridyl)urea (XIV).

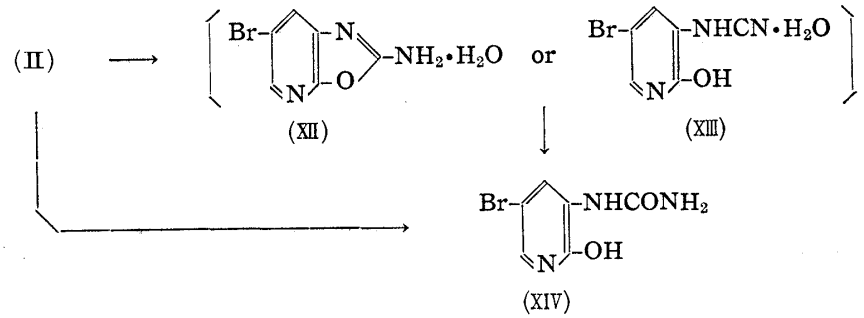
The infrared spectrum of this substance (Fig. 1) did not show $\nu_{C\equiv N}$ in the region of 2000~2300 cm^{-1}, which excludes the structure (XIII). The bands of ν_{N-H} at 3100 cm^{-1} and $\nu_{C=O}$ at 1690 and 1649 cm^{-1} suggested that the substance may be (XIV) and, to confirm this presumption, (XIV) was derived from (II) by the application of potassium cyanate in acetic acid. The melting points of (XIV) and previously obtained substance were above 310° and the change of color began near 270°, and therefore they could not be identified by mixed fusion but as their infrared spectra are identical as shown in Fig. 1, it was concluded that they were the same substance. By this fact it was clearly demonstrated that (XII) or (XIII), which was produced from (II), was hydrolyzed rapidly into (XIV), and the attempt to obtain 2-amino-oxazolopyridine was unsuccessful again.

7) M. St. C. Flett: J. Chem. Soc., **1953**, 347.
8) T. Takahashi, A. Koshiro: Yakugaku Zasshi, **76**, 1388(1956).
9) *Idem.*: *Ibid.*, **79**, 291(1959).



—— (XIV) derived from the reaction of (II) and BrCN
------ (XIV) derived from the reaction of (II) and KNCO

Fig. 1. Infrared Absorption Spectra of (5-Bromo-2-hydroxy-3-pyridyl) urea (XIV) (in Nujol)



The authors are gratefully indebted to Dr. H. Kano and Mr. A. Narisada of the Research Laboratory, Shionogi & Co. Ltd., and to Dr. K. Tsutsui of the Research Laboratory, Dainippon Pharmaceutical Co. Ltd., for measurement of the infrared spectra, and to the members of the Analytical Center of the University of Kyoto for the microanalyses. The authors are also grateful to Miss I. Shinohara for her technical assistance in this work.

Experimental*2

3-Amino-5-bromo-2-hydroxypyridine (II) (cf. Table I)—To a suspended solution of (I) in aq. NaCl, iron powder was added with stirring at 95~97°, and the mixture was heated for 3 hr. The mixture was filtered rapidly. Crystals that separated on cooling were collected and recrystallized from water to colorless needles, which turned dark brown in the air, m.p. 182°(decomp.). *Anal.* Calcd. for $C_5H_5ON_2Br$: C, 31.75; H, 2.65; N, 14.81. Found : C, 32.00; H, 2.87; N, 14.82.

Table I.

Expt. No.	(I) (g.)	Fe (g.)	NaCl (g.)	H_2O (cc.)	Temp. (cc.)	Time (hr.)	Yield of (II) (g.)	Yield of (II) (%)
1	10	10	3	100	95~97	3	3.5	40.7
2	10	10	4.5	150	70~75	3	2.5	29.1
3	10	10	6.5	150	70~75	3	2	23.3
4	10	20	9	150	85~88	2.5	2.5	29.1
5	10	20	4.5	150	95~97	3	3.5	40.7
6	10	20	9	150	95~97	3	3	35.0

Reaction of (II) with Acetic Anhydride—A mixture of (II) (2 g.) and several volumes of Ac_2O was refluxed for 9 hr. After cool, the separated crystals were collected, washed with ether, and dried. The filtrate was evaporated to dryness *in vacuo* and the crystals were recrystallized from AcOH to colorless needles, m.p. 232~233°, which was in agreement with (III) by the elementary ana-

*2 All m.p.s are uncorrected.

lysis. Yield, 0.9 g. *Anal.* Calcd. for $C_7H_7O_2N_2Br$: C, 36.36; H, 3.03; N, 12.12. Found : C, 36.41; H, 3.23; N, 11.94.

The residue obtained by evaporation of the filtrate was extracted with ether to remove a small amount of (III) and then ether was distilled off. Extraction of this residue with hot petr. benzine followed by repetition of cooling and concentration gave three substances.

The substance separated first on cooling was recrystallized from MeOH and it was confirmed as the diacetate (IV or IV') by the elementary analysis. Colorless needles, m.p. 135~137°. Yield, 0.2 g. *Anal.* Calcd. for $C_9H_9O_3N_2Br$: C, 39.56; H, 3.30; N, 10.26. Found : C, 39.64; H, 3.55; N, 9.98.

The substance that separated next at 0° was recrystallized from petr. benzine and it was confirmed as the triacetate (V or V'). Colorless needles, m.p. 102~103°. Yield, 0.5 g. *Anal.* Calcd. for $C_{11}H_{11}O_4N_2Br$: C, 41.90; H, 3.50; O, 20.32; N, 8.88. Found : C, 42.17; H, 3.66; O, 20.22; N, 8.65.

The substance separated finally at −5° was confirmed as (VI) after recrystallization from petr. ether; colorless leaflets, turning pale red slowly in the air, m.p. 121~122°. Yield, 0.1 g. *Anal.* Calcd. for $C_7H_5ON_2Br$: C, 39.44; H, 2.35; N, 13.15. Found : C, 39.41; H, 2.47; N, 12.90.

(VI) was prepared more conveniently as follows : A mixture of (III) (1 g.) and P_2O_5 (1 g.) was distilled under reduced pressure. The distillate ($b.p_{1.5}$ 95~110°) immediately solidified and was recrystallization from petr. ether to colorless leaflets, m.p. 121~122°. Yield, 0.5 g. It showed no depression when admixed with (VI) obtained above.

Hydrolyses of Diacetate and Triacetate—i) A mixture of 0.2 g. of the diacetate and 5 cc. of water was refluxed for 5 min., then decolorized with charcoal, and on cooling, colorless needles, m.p. 233°, were obtained. Yield, 0.1 g. On mixed fusion with (III), it showed no depression.

ii) 0.2 g. of the triacetate was hydrolysed as above. Colorless needles, m.p. 232~233°, which showed no depression of m.p. by admixture with (III).

Hydrolysis of 2-Methyl-6-bromoxazolo[5,4-*b*]pyridine (VI)—A solution of 0.2 g. of (VI) dissolved in 7 cc. of 5% HCl, was kept standing at 20~25° for 12 hr. Separated crystals were collected, washed with water, and dried. Recrystallization from water gave colorless needles, m.p. 232~233°. It showed no depression on mixed fusion with (III). Yield, 0.1 g.

2-Phenyl-6-bromoxazolo[5,4-*b*]pyridine (VII)—A mixture of (II) (2 g.) and Bz_2O (7 g.) was heated at 300~340° for 20 min., cooled, and the reaction mixture was washed with ether and then EtOH to remove Bz_2O and BzOH. The residue was recrystallized from MeOH to colorless needles, m.p. 159~160°. Yield, 1.5 g. *Anal.* Calcd. for $C_{12}H_7ON_2Br$: C, 52.36; H, 2.56; N, 10.18. Found : C, 52.55; H, 2.76; N, 10.30.

Hydrolysis of (VII)—A mixture of (VII) and 15 cc. of 20% HCl was kept standing at 20~25° for 34 hr., but no change was noticed. Then it was heated on a boiling water bath for 4 hr., cooled, and separated product was collected. The product was recrystallized repeatedly from MeOH to colorless needles, m.p. 252~253°. Yield, 0.2 g. It was confirmed as (VIII) by the elementary analysis. *Anal.* Calcd. for $C_{12}H_9O_2N_2Br$: C, 49.15; H, 3.07. Found : C, 49.32; H, 3.29.

BzOH was obtained from the mother liquor by evaporation of MeOH and sublimation of the residue at 100° under reduced pressure. Yield, 0.5 g.

Acid filtrate was neutralized with NaOH solution and allowed to stand at room temp. Brown needles (II) that separated were recrystallized from water; m.p. 182°(decomp.). Yield, 0.05 g. *Anal.* Calcd. for $C_5H_5ON_2Br$: N, 14.81. Found : N, 14.80.

2-Mercapto-6-bromoxazolo[5,4-*b*]pyridine (IX)-A solution of potassium methylxanthate was prepared by dissolving 2 g. of KOH in 5 cc. of water and 30 cc. of MeOH, and subsequent addition of CS_2 (2.3 g.) while shaking. To this solution 5 g. of (II) was added and the mixture was refluxed for 36 hr. The solution was decolorized with charcoal, filtered, and neutralized with AcOH. Precipitated crystalline powder was recrystallized from pyridine to colorless needles, which turned brown slowly in the air; m.p. 275°(decomp.). Yield, 5 g. *Anal.* Calcd. for $C_6H_3ON_2BrS$: C, 33.49; H, 1.40; N, 12.12. Found : C, 33.20; H, 1.66; N, 12.36.

2-Methylthio-6-bromoxazolo[5,4-*b*]pyridine (X)—1 g. of (VIII) was dissolved in a solution of 0.3 g. KOH in a small amount of water, 10 cc. of EtOH and 1.5 g. of MeI were added, and the mixture was heated under reflux for 10 min. On cooling, separated crystals were washed with water and recrystallized from water to colorless needles, m.p. 95~96°. Yield, 0.3 g. *Anal.* Calcd. for $C_7H_5ON_2BrS$: C, 34.27; H, 2.04. Found : C, 33.99; H, 2.21.

2-Ethylthio-6-bromoxazolo[5,4-*b*]pyridine (XI)—This was prepared by the method described above using EtI instead of MeI. The solution was evaporated to dryness *in vacuo* and the residue was extracted with benzene. Removal of benzene *in vacuo* left an oily residue which solidified soon. Recrystallization from MeOH gave colorless needles, m.p. 90~91°. Yield, 0.5 g. *Anal.* Calcd. for $C_8H_7ON_2BrS$: C, 37.08; H, 2.70; N, 10.80. Found : C, 37.29; H, 2.93; N, 10.57.

(5-Bromo-2-hydroxy-3-pyridyl)urea (XII)—i) To a solution of 0.3 g. of BrCN in 10 cc. of water 0.5 g. of (II) was added dropwise with stirring at room temp. and continuously stirred thereafter for 3 hr. The mixture was finally heated under reflux for 1 hr., then decolorized with charcoal,

cooled, the separated product was collected, and recrystallized from water to colorless needles, m.p. over 310°(decomp.). Yield, 0.5 g. *Anal.* Calcd. for $C_6H_6O_2N_3Br$: C, 31.01; H, 2.70; N, 17.87. Found: C, 31.11; H, 2.81; N, 18.09.

ii) 0.7 g. of (II) was dissolved in a solution of AcOH (11 cc.) and water (6 cc.). To this solution 0.4 g. of KNCO in 6 cc. of water was added slowly with stirring at 35~40°. After 10 min., brown crystals appeared and stirring was continued for 3 hr. The mixture was allowed to stand overnight at room temp., the crystals that separated were collected, and washed with water to remove acidity. Recrystallization from water gave colorless needles, m.p. over 310°(decomp.). Yield, 0.5 g. *Anal.* Calcd. for $C_6H_6O_2N_3Br$: C, 31.01; H, 2.70; N, 17.87. Found : C, 31.06; H, 2.73; N, 17.81.

Summary

3-Amino-5-bromo-2-hydroxypyridine (II) was successfully converted to 2-substituted 6-bromoxazolo[5,4-*b*]pyridines by treatment with acetic anhydride, benzoic anhydride, or potassium methylxanthate and some of their properties were examined. An attempt to obtain 2-amino-6-bromoxazolo[5,4-*b*]pyridine by the application of cyanogen bromide to (II) ended fruitless and only (5-bromo-2-hydroxy-3-pyridyl)urea was obtained.

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131. Akira Koshiro : Syntheses of Heterocyclic Compounds of Nitrogen. CXX. Syntheses of Oxazolopyridines and Related Compounds. (6).[1]

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The syntheses of oxazolo[5,4-*b*]pyridine series have been left unexamined since Saikachi[2] previously prepared 2-methyloxazolo[5,4-*b*]pyridine (VIII). In order to enlarge this series, the author attempted the following investigation and succeeded in the syntheses of 2-substituted oxazolo[5,4-*b*]pyridines.

Recently, Albert, *et al.*[3] prepared 3-amino-2-hydroxypyridine (I), which was necessary as a starting material in the present experiments, by the catalytic hydrogenation of the corresponding nitro compound in ethanol using palladium-charcoal, but almost the same result was obtained using methanol as a solvent.

Treatment of (I) with 80% formic acid or benzoyl chloride gave 3-formamido-2-hydroxypyridine (II) or 3-benzamido-2-hydroxypyridine (III), which was converted to oxazolo[5,4-*b*]pyridine (IV) or 2-phenyloxazolo[5,4-*b*]pyridine (V), respectively, by the distillation with phosphorus pentoxide under a reduced pressure. Yield of (V) was very disappointing because of the decomposition at distillation, contrary to the satisfactory yield of (IV). Both above-mentioned cyclizations did not proceed without phosphorus pentoxide.

Previously, Saikachi[2] obtained only 2-methyloxazolo[5,4-*b*]pyridine (VIII) on heating 3-amino-2-hydroxypyridine hydrochloride with acetic anhydride. In the present case however three products were isolated by heating (I) with acetic anhydride for 10 hours and they were confirmed as the monoacetate (VI), diacetate, and oxazolopyridine (VIII) from their analytical values. However, the triacetate obtained previously[1] could not be recognized.

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1) This work is a part of series entitled "Syntheses of Heterocyclic Compounds of Nitrogen" by Torizo Takahashi. Part CXIX, Part (5) : This Bulletin **7**, 720(1959).
2) H. Saikachi : Yakugaku Zasshi, **64**, 201(1944).
3) A. Albert, A. Hampton : J. Chem. Soc., **1952**, 4985.