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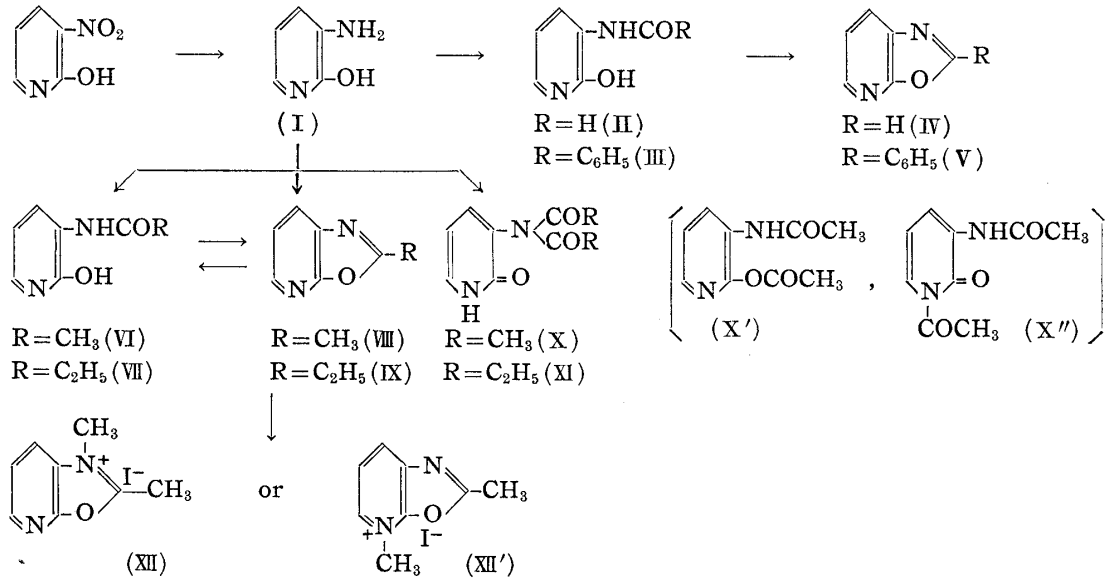
1) This work is a part of series entitled "Syntheses of Heterocyclic Compounds of Nitrogen" by Torizo Takahashi. Part CXIX, Part (5) : This Bulletin **7**, 720(1959).
2) H. Saikachi : Yakugaku Zasshi, **64**, 201(1944).
3) A. Albert, A. Hampton : J. Chem. Soc., **1952**, 4985.

For the diacetate, three possible structures (X, X′, and X″) can be considered. Its infrared spectrum shows split absorption band at 1715 and 1699 cm^{-1} originating from $-N(COCH_3)_2$, $\nu_{C=O}$ at 1658 cm^{-1}, and ν_{N-H} at around 3000 cm^{-1} which originates from the pyridone type, but does not show $\nu_{C=O}$ of $-OCOCH_3$ near 1750 cm^{-1}, ν_{N-H} of open-chain secondary amide in the region of 3270~3370 cm^{-1}, and the amide-II band of -NHCO- near 1530 cm^{-1}.

Judging from above facts, diacetate seems to have the structure of (X). This observation is in contrast to the indistinct absorptions of the diacetate reported in the previous paper[1] of this series.

Similarly, (I) was converted to 2-hydroxy-3-propionamidopyridine (VII) and 3-dipropionylamino-2-pyridone (XI) by heating with propionic anhydride but 2-ethyloxazolo[5,4-*b*]pyridine (IX) could not be isolated. (IX) and (VIII) could be prepared conveniently by the distillation of (VII) and (VI), respectively, with or without phosphorus pentoxide, under a reduced pressure. It is interesting that cyclization could be produced without phosphorus pentoxide in contrast to the case of (II) and (III).

(VIII) obtained in this way was rapidly hydrolyzed to (VI) on being allowed to stand with 5% hydrochloric acid at 15~20°, but no change was found when it was kept standing with 20% sodium hydroxide under the same condition. Treatment of (VIII) with an excess of methyl iodide afforded 2-methyloxazolo[5,4-*b*]pyridine monomethiodide (XII or XII′) which was immediately decomposed to a dark red oily substance on heating with methanol or ethanol.



As reported in Part (5)[1] of this series, (2-hydroxy-3-pyridyl)urea (XIII) was prepared by the application of cyanogen bromide to (I) and 2-aminoxazolo[5,4-*b*]pyridine (XV) was not obtained. Structure of the product (XIII) was determined from its analytical values and ultraviolet absorption spectrum (Fig. 1). In comparison with the spectra of (VI) and (XIII), close similarity in the intensity and the wave lengths of their absorption maxima was observed. Similar facts were observed in the case of previously obtained 2-hydroxy-3-acetamido-5-bromopyridine[1] and (2-hydroxy-5-bromo-3-pyridyl)urea,[1] though their absorption maxima shifted toward longer wave-lengths owing to the bathochromic effect of bromine atom.

Bendix[4] and Kalckhoff[5] first reported the synthesis of 2-aminobenzoxazole by warm-

4) J. Bendix: Ber., **11**, 2264(1878).
5) F. A. Kalckhoff: Ber., **16**, 1828(1883).

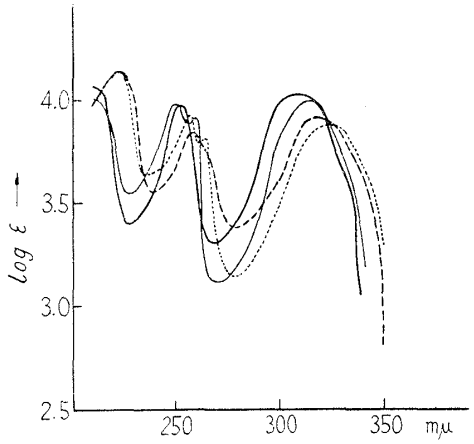
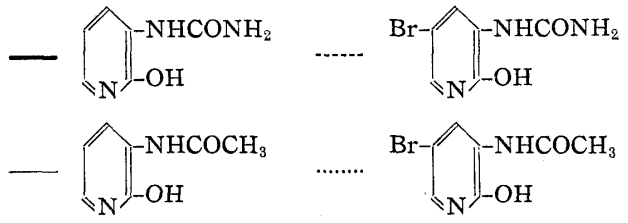
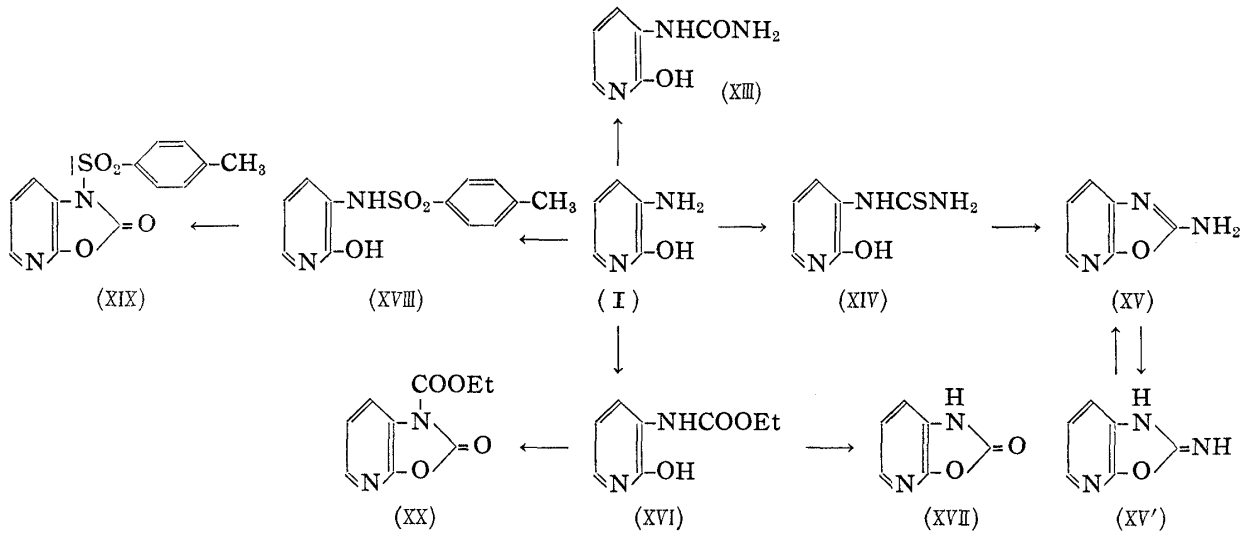


Fig. 1. Ultraviolet Absorption Spectra (in EtOH)





ing *o*-hydroxyphenylthiourea with mercuric oxide in ethanol. By applying this method to (2-hydroxy-3-pyridyl)thiourea (XIV), which was derived from (I) by reaction with potassium thiocyanate, 2-aminoxazolo[5,4-*b*]pyridine (XV) was prepared successfully. Tautomerism can be considered between amino form (XV) and imino form (XV'), but the diazo reaction for aromatic primary amines was positive. This fact indicates that above material reacts as the amino form (XV) and accordingly introduction of various substituents at 2-position of oxazolopyridine is possible via the diazonium salt.

Takahashi and the author reported in Part (3)[6] of this series that not (4-hydroxy-3-pyridyl)urethan but 1-ethoxycarbonyl-3-ethoxycarbamido-4-pyridone was obtained on treatment of 3-amino-4-hydroxypyridine with ethyl chloroformate in sodium hydrogen carbonate solution. On the contrary, it is interesting that in a similar manner (I) was only converted to (2-hydroxy-3-pyridyl)urethan (XVI) in good yield. By distillation of (XVI) under a reduced pressure, oxazolo[5,4-*b*]pyridin-2(1*H*)-one (XVII) was obtained mixed with some amount of the starting material (XVI) which was separated by fractional recrystallization. The 1-position of (XVII) is supposed to be active by the effect of the carbonyl group at 2-position and possibility of the substituted reaction is expected. However, the yield of (XVII) by the above cyclization was only 8% and the preparation of 1-substituted oxazolo[5,4-*b*]pyridin-2(1*H*)-one was attempted through the following procedure. 1-*p*-Toluenesulfonyloxazolo[5,4-*b*]pyridin-2(1*H*)-one (XIX) was obtained in a satisfactory yield by

6) T. Takahashi, A. Koshiro : Yakugaku Zasshi, **79**, 1123 (1959).

application of carbonyl chloride in pyridine to 2-hydroxy-3-*p*-toluenesulfonamidopyridine (XVIII) which was prepared by treatment of (I) with *p*-toluenesulfonyl chloride in sodium hydrogen carbonate solution. Similarly, (XVI) was converted easily to 1-ethoxycarbonyl-oxazolo[5,4-*b*]pyridin-2(1*H*)-one (XX) and thus an efficient synthetic method for 1-substituted oxazolopyridinone was established.

More detailed investigation on oxazolopyridinones and above-mentioned 2-aminoxazolopyridine will be carried out in the near future.

The author is grateful to Prof. T. Takahashi for his kind and unfailing guidance throughout the course of this work. He is indebted to Dr. H. Kano and Mr. A. Narisada of the Research Laboratory, Shionogi & Co. Ltd., for the measurement of infrared spectra, to Mr. S. Matsuo of the Research Laboratory, Nihon Shinyaku Co. Ltd., for measurement of the ultraviolet spectra, and to the members of the analytical center of the University of Kyoto for the microanalyses. The author is also grateful to Messrs. I. Shinohara and H. Koyama for their technical co-operation.

Experimental*2

3-Amino-2-hydroxypyridine (I)—A suspension of 2-hydroxy-3-nitropyridine (10 g.) in MeOH (100 cc.) was hydrogenated over 1.5 g. of 5% Pd-carbon. After the theoretical volume of H_2 (6105 cc. at 20°) was absorbed, the catalyst was filtered off, the filtrate was evaporated *in vacuo*, and the residue was extracted with hot benzene (about 1000 cc.). The benzene solution was concentrated to about 30 cc. and the separated (I) was recrystallized from benzene to cream-colored needles, m.p. 129°, which was in agreement with the m.p. in the literature.[3] Yield, 6.7 g.

3-Formamido-2-hydroxypyridine (II)—(I) (2 g.) was refluxed with 30 cc. of 80% formic acid for 4 hr. After removal of the excess acid, the residue was washed with water, dried, and recrystallized from water to colorless needles, m.p. 223~224°. Yield, 1.5 g. *Anal.* Calcd. for $C_6H_6O_2N_2$: C, 52.17; H, 4.38. Found: C, 52.20; H, 4.60.

3-Benzamido-2-hydroxypyridine (III)—(I) (2 g.) was dissolved in $NaHCO_3$ solution (10.7 g. in 150 cc. of water). To this solution BzOH (7.7 g.) was added dropwise with stirring at 6~10°. After continued stirring, the separated crystals were collected, washed with water, and dried. Recrystallization from EtOH gave colorless needles, m.p. 189°. Yield, 3 g. *Anal.* Calcd. for $C_{12}H_{10}O_2N_2$: C,67.28; H, 4.71. Found: C, 67.37; H, 4.85.

Oxazolo[5,4-*b*]pyridine(IV)—A mixture of (I) (0.7 g.) and P_2O_5 (0.6 g.) was distilled *in vacuo* at 240~260°(bath temp.), at 2 mm. Hg.*3 The distillate solidified immediately. Recrystallization from petr. ether gave colorless needles, m.p. 65°. Yield, 0.2 g. *Anal.* Calcd. for $C_6H_4ON_2$: C, 60.00; H, 3.36. Found: C, 60.07; H, 3.47.

2-Phenyloxazolo[5,4-*b*]pyridine(V)—A mixture of (III) (0.5 g.) and P_2O_5 (0.5 g.) was distilled *in vacuo* as above.*3 The solidified distillate was recrystallized from EtOH to colorless needles, m.p. 60°. Yield, 0.05 g. *Anal.* Calcd. for $C_{12}H_8ON_2$: C, 73.46; H, 4.11. Found: C, 73.22; H, 4.27.

Reaction of (I) with Acetic Anhydride—A mixture of 2 g. of (I) and 15 cc. of Ac_2O was refluxed for 10 hr., the solvent was distilled off *in vacuo*, and the residue was extracted with ether. The ether-insoluble substance was collected, washed with ether, and recrystallized from MeOH to colorless plates. Its elementary analysis was in agreement with 3-acetamido-2-hydroxypyridine*4 (VI), m.p. 215°. Yield, 0.7 g. *Anal.* Calcd. for $C_7H_8O_2N_2$: C, 55.25; H, 5.30. Found: C, 55.03; H, 5.52.

The above ether extract was concentrated to a one-half volume and cooled. Separated product was collected and recrystallized from acetone to colorless plates, m.p. 133~134°. It was confirmed as 3-diacetylamino-2-pyridone (X) from analytical values and infrared spectrum (Fig. 1). Yield, 0.2 g. *Anal.* Calcd. for $C_9H_{10}O_3N_2$: N, 14.43. Found: N, 14.65.

The ether extract was finally evaporated and the residue was extracted with hot petr. benzine (120 cc.). The filtrate was cooled to 0° to 5° for several hours and the precipitated 2-methyloxazolo-[5,4-*b*]pyridine (VII) was recrystallized from petr. benzine to colorless needles, m.p. 75~76°. Yield, 0.2 g. *Anal.* Calcd. for $C_7H_6ON_2$: C, 62.68; H, 4.51; N, 20.89. Found: C, 62.76; H, 4.69; N, 20.69.

The above petr. benzine-insoluble substance was recrystallized from MeOH to colorless plates, m.p. 215°, which showed no depression on mixed fusion with authentic specimen of (VI). Yield, 0.3 g. Total yield of (VI), 1.0 g.

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*2 All m.p.s are uncorrected.

*3 Above cyclization did not proceed by distillation of (II) or (III) without P_2O_5, and the distillate, $b.p_8$ 170~180°, and $b.p_2$ 80°, were identified as (II) and (III), respectively.

*4 Ultraviolet spectral data are given in Table I.

(Ⅷ) was more conveniently prepared as follows : A mixture of (Ⅵ) (2 g.) and P_2O_5 (2 g.) was distilled *in vacuo* at 240~250°(bath temp.), at 3 mm. Hg. The solidified distillate was recrystallized from petr. benzine to colorless needles, m.p. 75°, which showed no depression on admixture with (Ⅷ) obtained as above. Yield, 0.9 g. When (Ⅵ) was distilled without P_2O_5, a similar result was obtained.

Reaction of (I) with Propionic Anhydride—A mixture of (I) (2 g.) and propionic anhydride (15 cc.) was refluxed for 10 hr., the solvent was distilled off *in vacuo*, and the residue was extracted with hot petr. benzine (30 cc.). Insoluble residue was recrystallized from MeOH or acetone to colorless needles, m.p. 166°. Its elementary analysis was in agreement with 2-hydroxy-3-propionamidopyridine (Ⅶ). Yield, 1.8 g. *Anal.* Calcd. for $C_8H_{10}O_2N_2$: C, 57.82; H, 6.07. Found : C, 57.87; H, 6.22.

Petr. benzine extract was decolorized with charcoal, cooled, and the separated 3-dipropionylamino-2-pyridone (Ⅺ) was recrystallized from petr. benzine to colorless needles, m.p. 102~103°. Yield, 0.05 g. *Anal.* Calcd. for $C_{11}H_{14}O_3N_2$: C, 59.45; H, 6.35; N, 12.60. Found : C, 59.68; H, 6.51; N, 12.87.

2-Ethyloxazolo[5,4-*b*]pyridine (Ⅸ) could not be obtained by the above method, but it was prepared as follows : (Ⅶ) (2 g.) was distilled *in vacuo* and the distillate was kept standing at 0°. Solidified product was recrystallized from petr. ether to colorless plates, m.p. 25~26°. Yield, 0.2 g. *Anal.* Calcd. for $C_8H_8ON_2$: C, 64.85; H, 5.44. Found : C, 65.06; H, 5.70.

Hydrolysis of (VIII)—A solution of (Ⅷ) (0.2 g.) in 5% HCl (5 cc.) was kept standing at 20° for 2 hr., the separated crystals were collected, and recrystallized from MeOH to colorless plates, m.p. 215°. It showed no depression on mixed fusion with (Ⅵ). Yield, 0.2 g.

2-Methyloxazolo[5,4-*b*]pyridine Monomethiodide (XII or XII')—A mixture of (Ⅷ) (0.2 g.) and MeI (0.5 g.) was heated at 100° in a sealed tube for 6 hr., the solidified reaction mixture was collected, and dried. Recrystallization from acetone gave yellow needles, m.p. 187°(decomp.). Yield, 0.3 g. *Anal.* Calcd. for $C_8H_9ON_2I \cdot H_2O$: C, 32.65; H, 3.74; N, 9.52. Found : C, 32.66; H, 3.91; N, 9.35.

(2-Hydroxy-3-pyridyl)urea (XIII)—To a solution of BrCN (0.5 g.) in 7 cc. of water, (I) (0.4 g.) was added dropwise with stirring at room temp. After continuous stirring for 4 hr., the mixture was refluxed for 30 min. and decolorized with charcoal. On cooling, the separated crystals were recrstallized from water to colorless needles,[*4] m.p. >310°(decomp.). Yield, 0.4 g. *Anal.* Calcd. for $C_6H_7O_2N_3$: C, 47.05; H, 4.61. Found : C, 46.93; H, 4.83.

(2-Hydroxy-3-pyridyl)thiourea(XIV)—To a solution of hydrochloride of (I) (1.5 g.) in water (10 cc.) a solution of KCNS (1.5 g.) in water (5 cc.) was added, the mixture was heated at 100° for 6 hr., and kept standing overnight. Separated crystals were collected and recrystallized from water to pale yellow needles, m.p. 220° (melted crystals solidified once and melted again at 230°). Yield, 1.0 g. *Anal.* Calcd. for $C_6H_7ON_3S$: C, 42.60; H, 4.17; N, 24.85. Found : C, 42.30; H, 4.35; N, 24.79.

2-Aminoxazolo[5,4-*b*]pyridine (XV)—A mixture of (XIV) (1.5 g.) and freshly precipitated HgO (4.2 g.) in water (30 cc.) was refluxed for 12 hr. The reaction mixture was filtered immediately while hot and the filtrate evaporated to dryness *in vacuo*. The residue was recrystallized from MeOH to pale red prisms, m.p. 157°. Yield, 0.5 g. *Anal.* Calcd. for $C_6H_5ON_3$: C, 53.33; H, 3.73; N, 31.10. Found : C, 53.03; H, 4.00; N, 30.81.

(2-Hydroxy-3-pyridyl)urethan (XVI)—To a solution of (I) (2 g.) in $NaHCO_3$ solution (10.7 g. in 15 cc. water), ClCOOEt (6 g.) was added dropwise with stirring at 12~14°, and continuously stirred for 8 hr. at the same temp. Separated crystals were collected, washed with water, and dried. Recrystallization from MeOH gave colorless needles, m.p. 187°. Yield, 2.0 g. *Anal.* Calcd. for $C_8H_{10}O_3N_2$: C, 52.74; H, 5.53; N, 15.38. Found : C, 52.56; H, 5.75; N, 15.18.

Oxazolo[5,4-*b*]pyridin-2(1*H*)-one (XVII)—(XVI) (1 g.) was distilled under a reduced pressure and the distillate ($b.p_2$ 80~90°) solidified at once. This product was separated into two components by fractional recrystallization from acetone. The crystals separated first were confirmed to be (XVII) by its analytical values; colorless needles, m.p. 247°. Yield, 0.1 g. *Anal.* Calcd. for $C_6H_4O_2N_2$: C, 52.94; H, 2.96; N, 20.58. Found : C, 52.79; H, 3.11; N, 20.80.

The other component was identified as urethan (XVI) by a mixed fusion. Yield, 0.4 g.

2-Hydroxy-3-*p*-toluenesulfonamidopyridine (XVIII)—To a solution of (I) (2 g.) in $NaHCO_3$ solution (10.7 g. in 150 cc. water), *p*-toluenesulfonyl chloride (9.5 g.) was added dropwise with stirring at 10~15°. After continuous stirring for 2 hr., the reaction mixture was kept standing overnight at room temp., separated crystals were collected, washed with water, and dried. Recrystallization from MeOH gave colorless needles, m.p. 211~212°. Yield, 2.0 g. *Anal.* Calcd. for $C_{12}H_{12}O_3N_2S$: C, 54.54; H, 4.58; N, 20.09. Found : C, 54.69; H, 4.65; N, 19.18.

1-*p*-Toluenesulfonyloxazolo[5,4-*b*]pyridin-2(1*H*)-one (XIX)—To a solution of (XVIII) (1.5 g.) in 30 cc. of pyridine, 15% solution of $COCl_2$ in benzene (20 cc.) was added with stirring at 5° and continuously stirred for 4 hr. Precipitated pyridine hydrochloride was filtered off and the filtrate was evaporated to dryness *in vacuo*. The residue was recrystallized from benzene to colorless needles, m.p. 161~162°. Yield, 1.3 g. *Anal.* Calcd. for $C_{13}H_{10}O_4N_2S$: C, 53.80; H, 3.47; N, 9.65. Found; C,54.00; H, 3.67; N, 9.85.

1-Ethoxycarbonyloxazolo[5,4-*b*]pyridin-2(1*H*)-one (XX)—To a solution of (XVI) (1 g.) in 25 cc. of pyridine, 15% solution of $COCl_2$ in benzene (6 cc.) was added with stirring at 0° to 5° and the reaction mixture was treated in a similar manner as above. The residue was recrystallized from benzene to colorless needles, m.p. 118~120°. Yield, 0.7 g. *Anal.* Calcd. for $C_9H_8O_4N_2$: C, 51.92; H, 3.87; N, 13.46. Found : C, 51.84; H, 4.00; N, 13.61.

Table I. Ultraviolet Absorption Spectra (in 95% EtOH)

	Maxima	
	mμ	log ε
3-Acetamido-2-hydroxypyridine (VI)	210	4.02
	249	3.98
	258	3.91
	312	4.00
(2-Hydroxy-3-pyridyl)urea (XIII)	210	4.06
	250	3.97
	306~308	4.00
3-Acetamido-5-bromo-2-hydroxypyridine	223	4.16
	254	3.88
	263	3.82
	321	3.88
(5-Bromo-2-hydroxy-3-pyridyl)urea	225	4.13
	257	3.84
	315	3.94

Summary

1) 2-Alkyl(or aryl)oxazolo[5,4-*b*]pyridines were prepared by distillation of 3-acylamino-2-hydroxypyridine which was obtained by acylation of 3-amino-2-hydroxypyridine (I).

2) 2-Aminoxazolo[5,4-*b*]pyridine, which could not be obtained by the reaction of (I) with cyanogen bromide, was successfully prepared by heating (2-hydroxy-3-pyridyl)thiourea with mercuric oxide in water.

3) Oxazolo[5,4-*b*]pyridin-2(1*H*)-one was prepared by distillation of (2-hydroxy-3-pyridyl)urethan and also the synthesis of 1-substituted oxazolo[5,4-*b*]pyridin-2(1*H*)-ones was established by treatment of 2-hydroxy-3-(substituted)aminopyridines with carbonyl chloride.

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