tion was then evaporated and the residue was heated with 100 cc. of 10% ethanolic $KHCO_3$ solution on a water bath for 30 mins. The reaction mixture was diluted with a little water and concentrated to remove EtOH, and the residue was extracted with ether. The ether solution was washed with water, dried over anhyd. Na_2SO_4, and evaporated, leaving ca. 80 mg. of crystals, m.p. 175~185°. Examination was not made on the crystals. The above-mentioned conc. $KHCO_3$ solution was slightly acidified with dil. HCl, the resulting precipitate was taken up in ether, and the ethereal solution, after successively washing with saturated NaCl solution and water, and drying over anhyd. Na_2SO_4, was evaporated to leave 760 mg. of the crude keto-acid (XXI). The crude product was dissolved in a solution of 1 g. of $KHCO_3$ in 40 cc. of water, and the solution was allowed to stand with 10 cc. of 30% H_2O_2 at room temperature for 17 hrs. The reaction mixture was weakly acidified with dil. H_2SO_4 under cooling with ice-water and the resulting precipitate was extracted with ether. The ether solution was washed with satd. NaCl soln. and water, dried over anhyd. Na_2SO_4, and evaporated.

The residue was dissolved in a small amount of MeOH and methylated with CH_2N_2 solution in ether. The reaction mixture, after addition of glacial AcOH to decompose the excess CH_2N_2, was washed with $NaHCO_3$ solution and water, dried over anhyd. Na_2SO_4, and evaporated. The residue (690 mg.) was then acetylated with 5 cc. each of pyridine and Ac_2O, the reaction mixture was evaporated under a reduced pressure, and the residue was recrystallized from ether-hexane to 310 mg. of needles, m.p. 173°; $[\alpha]_D^{20}$ +9°(c=0.5, $CHCl_3$). *Anal.* Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found : C, 69.11; H, 8.52.

Summary

Several years ago the author isolated rhodeasapogenin, a new steroidal sapogenin, from the leaves of *Rhodea japonica* Roth. and presumed its structure to be 5β,22b-spirostane-2β,3α-diol. In the present work it was found that isorhodeasapogenic acid is identical with tokorogenic acid and that isorhodeasapogenin has a structure of 1β,3b-dihydroxy-5β,25D-spirostane. Further, finding that rhodeasapogenin is degradated to methyl 1β,3β-diacetoxyetiocholanate, the author corrected the previously proposed structure of rhodeasapogenin to 1β,3β-dihydroxy-5β,25L-spirostane. The two reactions of isorhodeasapogenin which appeared unusual could be well explained by assigning the above structure to this compound.

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46. **Nobuo Ikekawa** : Studies on Naphthyridines. I. Synthesis of 1,6-Naphthyridine.

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Synthesis of 1,6-naphthyridines is generally not easy.[1] 1,6-Naphthyridine itself has not been obtained as yet and the syntheses of its alkyl derivatives have only been reported by Kato[2] and by Okuda.[3] The new synthetic process described in this paper is to build up another pyridine ring by utilizing the reactive methyl group in the 2- or 4-position of a pyridine ring and a carboxyl group adjacent to it, and is one of a general method for the synthesis of naphthyridines. In this paper, syntheses of 1,6-naphthyridine and its 7-methyl compound are described.

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[1] C. F. H. Allen : Chem. Revs., **47**, 275(1950).

[2] T. Kato, F. Hamaguchi, T. Oiwa : This Bulletin, **4**, 178(1956).

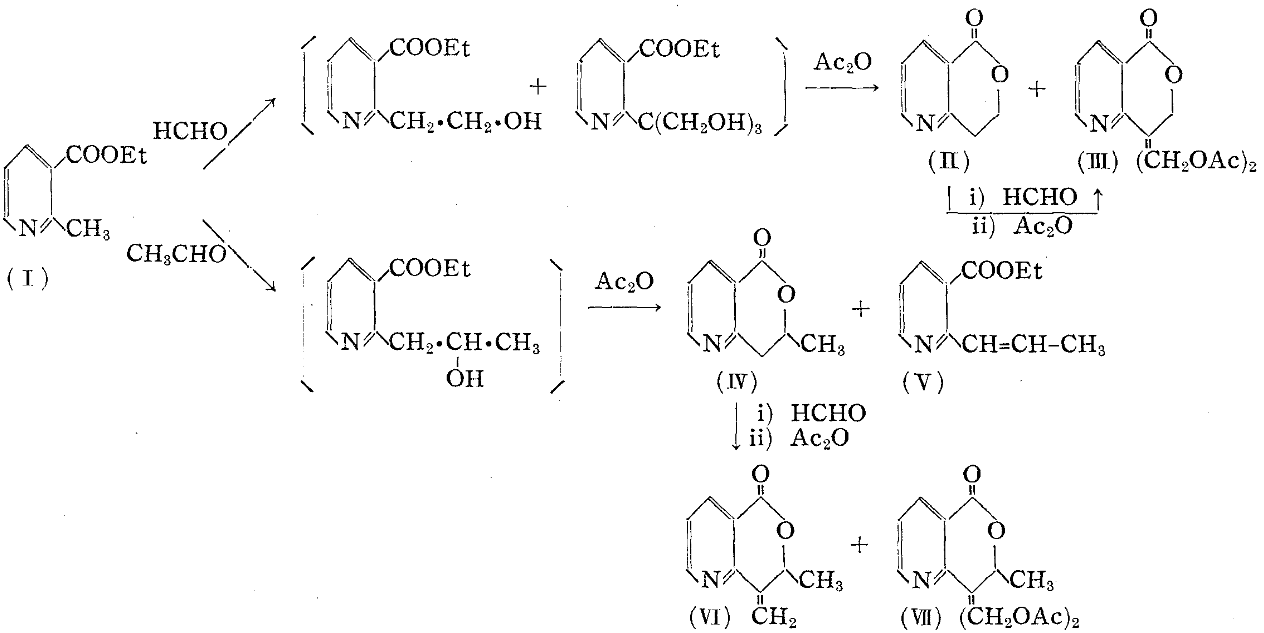
[3] S. Okuda : *Ibid.*, **5**, 460(1957).

Reaction of Ethyl 2-Methylnicotinate and Formaldehyde or Acetaldehyde

On heating ethyl 2-methylnicotinate[4] and 35% formaldehyde solution at 130°, followed by refluxing with acetic anhydride and low-pressure distillation, 2-(2-hydroxyethyl)nicotinic acid lactone (II) and 2-(1,1-diacetoxymethyl-2-hydroxyethyl)nicotinic acid lactone (III) are obtained. In this case, the use of one mole of formaldehyde will afford 14% of (II) and 7.5% of (III) but no product formed by the reaction of two moles of formaldehyde. Further application of formaldehyde to (II) gives (III).

Heating of ethyl 2-methylnicotinate and 80% acetaldehyde at 180° and treatment with acetic anhydride affords 2-(2-hydroxypropyl)nicotinic acid lactone (IV) in 23% yield and ethyl 2-propenylnicotinate (V) in 10% yield. Application of formaldehyde to (IV) gives the vinyl compound (VI) and the diacetoxymethyl compound (VII).

In the reaction of 2-picoline and acetaldehyde,[5] the yield of the condensation product is only 3~5% but in the case of ethyl 2-methylnicotinate, the methyl group is more reactive due to the effect of the ester group in 3-position and the yield will become approximately 50%, allowing for the recovered material. In the case of formaldehyde, three moles of it undergoes facile reaction.



Synthesis of 1,6-Naphthyridine

The lactone compounds (II and IV) are derived to the naphthyridine in two steps. On leaving the lactone with ammonia in methanol, an amide (VIII) is obtained in 75~80% yield and its oxidation with chromium trioxide will effect concurrent dehydrative cyclization and 5-hydroxy-1,6-naphthyridines (IX) are obtained in approximately 50% yield. Their ultraviolet spectra are given in Fig. 1.

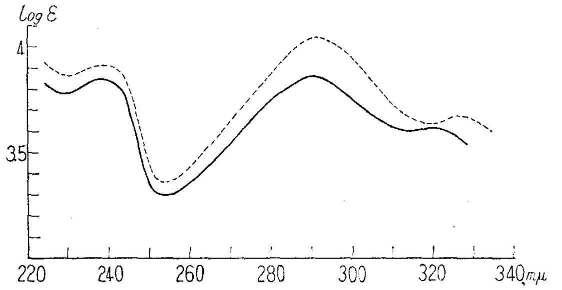


Fig. 1. Ultraviolet Spectra (in MeOH)

—— 5-Hydroxy-1,6-naphthyridine (IXa)

------ 5-Hydroxy-7-methyl-1,6-naphthyridine (IXb)

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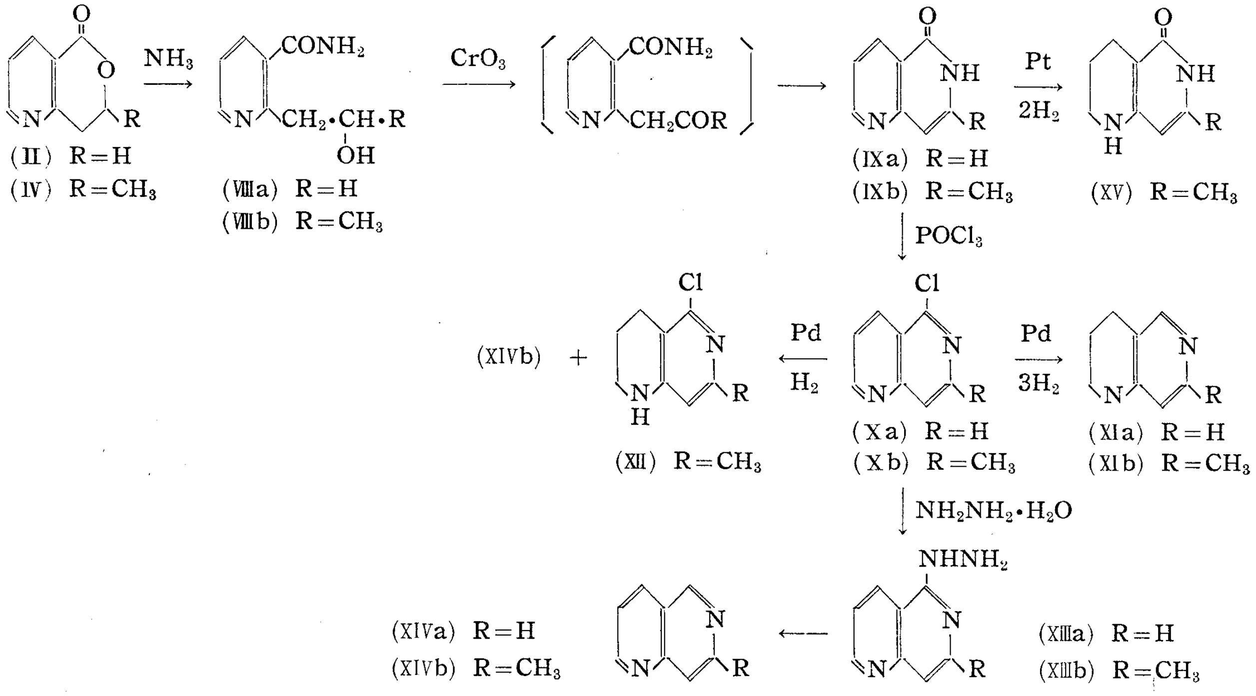
[4] K. Tsuda, Y. Satoh, N. Ikekawa, H. Mishima: J. Org. Chem., **21**, 800(1956).

[5] Ladenburg: Ann., **301**, 140(1898).

The treatment of the 5-hydroxy compound (IX) with phosphoryl chloride and catalytic reduction of the 5-chloro compound (X) thereby obtained with palladium will result in the absorption of three moles of hydrogen to form the 1,2,3,4-tetrahydro compound (XI). The structure of this reduction product cannot be doubted since its ultraviolet absorption varies with pH.[6] If this reduction is stopped with absorption of 1.2 moles of hydrogen, 3% of naphthyridine (XIV) and 10% of 5-chloro-1,2,3,4-tetrahydronaphthyridine (XII) are obtained. This shows that catalytic reduction is not suitable for dechlorination.

This dechlorination is effected with a good result by the method of McFadyen and Stevens,[7] and 5-hydrazinonaphthyridines (XIII) are obtained in a quantitative yield. From (XIII), 1,6-naphthyridine (XIVa), m.p. 25~27°, and 7-methyl-1,6-naphthyridine (XIVb), m.p. 86~87°, are obtained, with 65~70% yield. 1,6-Naphthyridine without any substituent has now been prepared for the first time.

The ultraviolet spectra of (XIVa) and (XIVb)[8] are shown in Fig. 2 and indicate quite specific curves as compared to those of quinoline and 2,7-naphthyridine.[9]



Structure of the Product from Skraup Reaction of 4-Amino-2-picoline 1-Oxide

The structure of the product from the Skraup reaction of 4-amino-2-picoline 1-oxide reported by Kato and others[2] was not established as 5-methyl (XVI) or 7-methyl (XVII) compound. Deoxygenation of the sample of methylnapthyridine N-oxide with phosphorus trichloride afforded a methyl-1,6-naphtyridine as needle crystals of m.p. 74~75°, which showed obvious depression of the melting point on admixture with the 7-methyl compound (XIVb). Therefore, the product obtained from the Skraup reaction must be the 5-methyl compound (XVIII) and this assumption is also supported by its ultraviolet spectrum (Fig. 2) and from infrared spectrum, which will be dealt with in the subsequent paper.

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6) S. Okuda : This Bulletin, **4**, 257(1956).

7) J.S. McFadyen, T.S. Stevens : J. Chem. Soc., **1936**, 584.

8) On introduction of a methyl group into 5-position, the absorption maximum shifts 4.5 mμ to a longer wave-length region, and 9 mμ when introduced into 7-position. In 5,7-dimethyl compound, the shift is the sum of these shifts.

9) N. Ikekawa : This Bulletin, **6**, 269(1958).

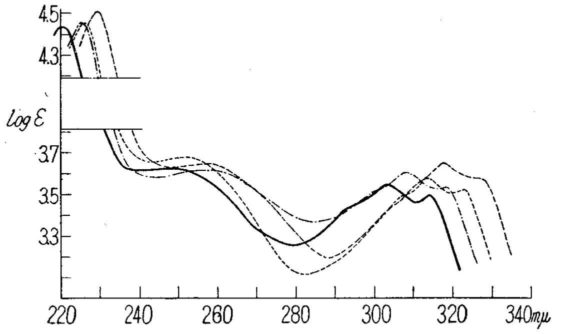


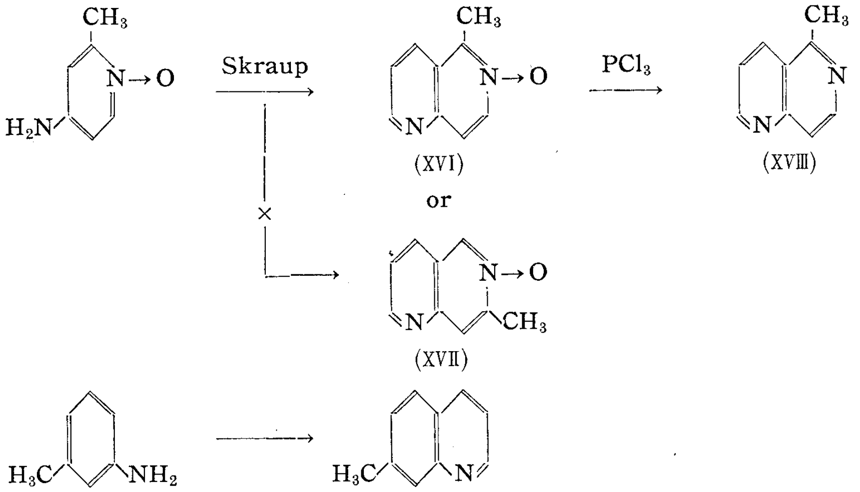
Fig. 2. Ultraviolet Spectra (in MeOH)

——— 1,6-Naphthyridine (XIVa)

-------- 7-Methyl-1,6-naphthyridine (XIVb)

----- 5-Methyl-1,6-naphthyridine (XVIII)

— — — 5,7-Dimethyl-1,6-naphthyridine[3)]



The Skraup reaction of *m*-toluidine results in reaction in the position *para* to the methyl group and 7-methylquinoline is obtained[10)] but the foregoing result has shown that the reaction has unexpectedly occurred in a reverse direction, in the position *ortho* to the methyl group. Since there should exist no difference in the electron density of carbon atoms in the *ortho*- and *para*-positions of the methyl group, it may be assumed that the reactive methyl group takes some part in the formation of a reaction intermediate. Bradford[10)] reported that 5-substituted quinoline is formed in larger amount than the 7-substituted compound in the case of aniline possessing a *meta*-directing group (carboxyl, nitro, etc.) in the *meta*-position. Methylpyridine N-oxide seems to have an effect similar to a *meta*-directing group.

The author expresses his deep gratitude to Prof. K. Tsuda for his kind guidance throughout the course of this work. He is also indebted to Dr. T. Kato and Dr. S. Okuda for the supply of samples, to Mr. E. Ohki for the supply of experimental data, to Mr. H. Shindo of Sankyo Co., Ltd. for the measurement of infrared spectra, and to Mr. Y. Sato and Miss H. Yamanouchi for elemental analyses reported herein.

Experimental

2-(2-Hydroxyethyl)nicotinic Acid Lactone (II)—A mixture of 20 g. of ethyl nicotinate and 14 cc. (2 moles) of 35% HCHO was heated in a sealed glass tube for 15 hrs. at 130°. The resulting solution was evaporated under a reduced pressure and the residue was refluxed for 4 hrs. with 80 cc. of Ac_2O. After removing Ac_2O, the residue was dissolved in water, made alkaline, and extracted with $CHCl_3$. After drying, $CHCl_3$ was distilled off and distillation of the residue gave recovery of 7 g. (35%) of the starting compound, b.p$_3$ 80~90°, and fractions A and B.

Fraction A of b.p$_3$ 110~120° gave 1.4 g. (8%) of (II), m.p. 90~92°, after recrystallization from ether. *Anal.* Calcd. for $C_8H_7O_2N$: C, 64.43; H, 4.70; N, 9.39. Found : C, 64.80; H, 4.98; N, 9.55. Picrate : m.p. 135~138°. *Anal.* Calcd. for $C_{14}H_{10}O_9N_4$: C, 44.44; H, 2.65; N, 14.81. Found : C, 44.70; H, 2.73; N, 14.56. U.V. λ_{max}^{MeOH} : 271.3 mμ (log ε 3.76).

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10) L. Bradford, T. J. Elliot, F. M. Rowe : J. Chem. Soc., **1947**, 437.

Fraction B of b.p$_{0.06}$ 100~110° gave 2.8 g. (11%) of (III), m.p. 98~100°(from benzene-ether). *Anal.* Calcd. for $C_{14}H_{15}O_6N$: C, 57.34; H, 5.12; N, 4.78. Found : C, 57.05; H, 4.72: N, 5.24. U. V. $\lambda_{\max}^{\mathrm{MeOH}}$ 268.3 mμ (log ε 3.51).

The reaction of (I) with 1 mole of HCHO under the same conditions gave the starting nicotinate, (II), and (III) in respective yields of 40%, 14%, and 7.5%. When 5 moles of HCHO was used (III) was obtained in 60~70% yield.

2-(2-Hydroxypropyl)nicotinic Acid Lactone (IV) and Ethyl 2-Propenylnicotinate (V)—A mixture of 60 g. of (I) and 65 g. of 70% AcH was heated at 180° in a sealed tube for 17 hrs. The resulting solution was treated in the same manner as for (II). Recovered (I), 21 g.(35%).

Fraction A of b.p$_3$ 130~135° gave 14 g.(23%) of (IV), m.p. 83~84°(from ether). *Anal.* Calcd. for $C_9H_9O_2N$: C, 66.30; H, 5.51; N, 8.60. Found : C, 66.44; H, 5.19; N, 8.48. U. V. $\lambda_{\max}^{\mathrm{MeOH}}$: 271 mμ (log ε 3.63). I. R. $\nu_{\max}^{\mathrm{Nujol}}$: 1736, 1715 cm^{-1}(-CO-O-). Picrate : m.p. 173~174°. *Anal.* Calcd. for $C_{15}H_{12}O_9N$: C, 45.92; H, 3.06; N, 14.28. Found : C, 45.82; H, 2.68; N, 14.59.

Fraction B of b.p$_3$ 135~140° was a thick liquid, which was dissolved in dil. HCl, washed with ether, made alkaline, and extracted with ether. Drying of the ether extract over Na_2SO_4, removal of the ether, and distillation of the residue gave 6 g.(10%) of (V), b.p$_3$ 140~145°. *Anal.* Calcd. for $C_{11}H_{13}O_2N$: C, 69.11; H, 6.80; N, 7.32. Found : C, 69.33; H, 6.39; N, 6.96. U. V. $\lambda_{\max}^{\mathrm{MeOH}}$: 263 mμ (log ε 4.32). I. R. $\nu_{\max}^{\mathrm{liq.}}$: 1715 cm^{-1}(-COOEt); 1650, 966 cm^{-1}(-CH=CH-; *trans*). (V) showed normal olefinic reactions towards bromine water and aqueous $KMnO_4$.

2-(1-Methylene-2-hydroxypropyl)nicotinic Acid Lactone (VI) and 2-(1,1-Diacetoxymethyl-2-hydroxypropyl)nicotinic Acid Lactone (VII)—A mixture of 15 g. of (IV) and 16 g.(2 moles) of 35% HCHO was heated for 15 hrs. at 130°. The reaction mixture was treated in the same manner as for (II) and distillation of the residue under reduced pressure gave recovery, 1 g., fractions A and B.

Fraction A : Light violet, thick liquid (VI), b.p$_{0.02}$ 105~110°; yield, 6.8 g.(42%). *Anal.* Calcd. for $C_{10}H_9O_2N$: C, 68.60; H, 5.14; N, 8.00. Found : C, 68.31; H, 5.23; N, 7.88.

The precipitation of formal dimedone by introducing ozonolysis product of (VI) into a dimedone reagent solution proved the presence of vinyl group in the compound (VI). U. V. $\lambda_{\max}^{\mathrm{MeOH}}$: 255~260 mμ (log ε 3.80). I. R. $\nu_{\max}^{\mathrm{liq.}}$: 1730, 1724 cm^{-1}(-CO-O-); 1660, 940 cm^{-1}(>C=CH$_2$).

Fraction B : Light yellow thick liquid, b.p$_{0.01}$ 140~150°; 1.5 g. Redistillation of this fraction gave 1.2 g. of liquid (VII). *Anal.* Calcd. for $C_{15}H_{17}O_6N$: C, 58.63; H, 5.53; N, 4.32. Found : C, 58.78; H, 5.81; N, 4.56. U. V. $\lambda_{\max}^{\mathrm{MeOH}}$: 262 mμ (log ε 3.63). I. R. $\nu_{\max}^{\mathrm{Nujol}}$: 1730 cm^{-1}(-CO-O-).

2-(1,1-Diacetoxymethyl-2-hydroxyethyl)nicotinic Acid Lactone (III)—A mixture of 5.4 g. of (II) and 11 g. of 35% HCHO was heated for 17 hrs. The reaction mixture was treated in the same manner as for (II) and the residue was distilled under reduced pressure. Recovery of (II), 0.4 g. The fraction of b.p$_{0.1}$ 130~140°(1.3 g.) was recrystallized from benzene-ether and gave plates, m.p. 98~100°, which did not depress the m.p. of a sample of (III) described above.

2-(2-Hydroxypropyl)nicotinamide (VIIIb)—A solution of 7 g. of (IV) in 500 cc. MeOH, cooled in ice water, was saturated with NH_3 gas, and allowed to stand overnight. After removing the solvent, the residue was recrystallized from MeOH-ether, and gave crystals of (VIIIb), m.p. 157°. Yield, 5.5 g. (71%). *Anal.* Calcd. for $C_9H_{12}O_2N_2$: C, 60.00; H, 6.60; N, 15.54. Found : C, 60.25; H, 7.03; N, 15.24.

2-(2-Hydroxyethyl)nicotinamide (VIIIa)—Treatment of 5 g. of (II) by the same method as for (VIIIb) gave 4.2 g.(75%) of (VIIIa), m.p. 146~147°. *Anal.* Calcd. for $C_8H_{10}O_2N_2$: C, 57.83; H, 6.02; N, 16.86. Found : C, 57.79; H, 5.66; N, 16.57.

5-Hydroxy-7-methyl-1,6-naphthyridine (IXb)—A solution of 3.2 g.(1.2 moles) of CrO_3 in a mixture of 5 cc. water and 80 cc. AcOH, was added during a period of 2 hrs. into a stirred solution of 7 g. (1 mole) of (VIIIb) in 180 cc. AcOH at 40~50°. After 3 hrs., the reaction mixture was concentrated to 50 cc. and made alkaline with NH_3. White needles of (IXb) precipitated (2.9 g.). Extraction of the aqueous layer with $CHCl_3$ gave 0.2 g. of (IXb), m.p. 245°(from MeOH). Total yield, 50%. *Anal.* Calcd. for $C_9H_8ON_2$: C, 67.50; H, 5.00; N, 17.50. Found : C, 67.70; H, 4.86; N, 17.64. U. V. $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 240 (3.91), 291 (4.04), 330 (3.67) (Fig. 1). I. R. $\nu_{\max}^{\mathrm{Nujol}}$: 1678 cm^{-1}(pyridone).

5-Hydroxy-1,6-naphthyridine (IXa)—By the same manner described for (IXb), oxidation of 1.65 g. of (VIIIa) with CrO_3(1.2 mole) gave 0.7 g. of (IXa). Yield, 48% of m.p. 241~242°(from MeOH). *Anal.* Calcd. for $C_8H_6ON_2$: C, 65.70; H, 4.10; N, 19.20. Found : C, 65.63; H, 4.10; N, 19.27. U. V. $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε) : 239.5 (3.84), 289.5 (3.85), 320 (3.64) (Fig. 1). I. R. $\nu_{\max}^{\mathrm{Nujol}}$: 1665 cm^{-1}(pyridone).

5-Hydroxy-7-methyl-1,2,3,4-tetrahydro-1,6-naphthyridine (XV)—Hydrogenation of 50 mg. of (IXb) in 10 cc. EtOH over 50 mg. of PtO_2 catalyst resulted in absorption of 14.5 cc.(2.1 moles) of H_2 in 1 hr. Removal of catalyst and solvent, and recrystallization of the residue gave (XV), m.p. 258~262°(from petr. benzine). *Anal.* Calcd. for $C_9H_{12}ON_2$: C, 65.90; H, 7.30; N, 17.07. Found : C, 65.54; H, 7.48;

N, 16.64. U.V. $\lambda_{\max}^{\mathrm{MeOH}}$ mμ(log ε): 227(4.39), 280(3.92).

5-Chloro-7-methyl-1,6-naphthyridine (Xb)—A mixture of 1 g. of (IXb) and 20 cc. of $POCl_3$ was heated in a sealed tube for 20 hrs. at 130°. After removal of $POCl_3$, ice-water was added to the residue, the solution was made alkaline with Na_2CO_3, and extracted with $CHCl_3$. Drying of the $CHCl_3$ extract and removal of the solvent gave white needles, m.p. 112~113°, after recrystallization from ether. Yield, 0.19 g.(82%). *Anal.* Calcd. for $C_9H_7N_2Cl$: C, 60.50; H, 3.92; N, 15.70. Found: C, 60.34; H, 4.06; N, 15.80. U.V. $\lambda_{\max}^{\mathrm{MeOH}}$ mμ(log ε): 230.7(4.52), 258(3.68), 317.5(3.71), 329(3.63)(shoulder).

5-Chloro-1,6-naphthyridine (Xa)—(IXa)(1.2 g.) was treated by the same manner described for (Xb) to give 1.24 g. of (Xa), m.p. 104~105°. Yield, 91%. *Anal.* Calcd. for $C_8H_5N_2Cl$: C, 58.40; H, 3.04; N, 17.02. Found: C, 58.40; H, 3.13; N, 17.26. U.V. $\lambda_{\max}^{\mathrm{MeOH}}$ mμ(log ε): 226.6(4.47), 257(3.64), 308.6 (3.69), 320(3.63).

7-Methyl-1,2,3,4-tetrahydro-1,6-naphthyridine (XIb)—Hydrogenation of 0.55 g.(Xb) in MeOH over 0.2 g. of 5% Pd-$CaCO_3$ catalyst resulted in absorption of 220 cc. of H_2 (3 moles). After removal of catalyst and solvent, the residue made alkaline was extracted with $CHCl_3$. The extract gave white needles, m.p. 144~146°(from benzene). *Anal.* Calcd. for $C_9H_{12}N_2$: C, 72.97; H, 8.11; N, 18.92. Found: C, 72.51; H, 7.68; N, 18.48. U.V. $\lambda_{\max}^{\mathrm{MeOH}}$ mμ(log ε): 220.5(4.09), 279.5(4.15); $\lambda_{\max}^{0.1N\ \mathrm{NaOH}}$ mμ(log ε): 259.2 (4.17); $\lambda_{\max}^{0.1N\ H_2SO_4}$ mμ(log ε): 221(4.24), 279.5(4.33).

1,2,3,4-Tetrahydro-1,6-naphthyridine (XIa)—Hydrogenation of 0.38 g. of (Xa) in MeOH over 0.2 g. of 5% Pd-$CaCO_3$ resulted in absorption of 164 cc. of H_2 (3 moles). Recrystallization from benzene gave 0.29 g. of (XIa), m.p. 155~158°. *Anal.* Calcd. for $C_8H_{10}N_2$: C, 71.64; H, 7.46; N, 20.90. Found: C, 71.74; H, 7.46; N, 20.99. U.V. $\lambda_{\max}^{\mathrm{MeOH}}$: 278.5 mμ(log ε 4.12); $\lambda_{\max}^{0.1N\ \mathrm{NaOH}}$: 259.5 mμ(log ε 4.08); $\lambda_{\max}^{0.1N\ H_2SO_4}$: 280.8 mμ(log ε 4.20).

5-Chloro-7-methyl-1,2,3,4-tetrahydro-1,6-naphthyridine (XII)—1.30 g. of (Xb) was hydrogenated over 0.2 g. of 5% Pd-$CaCO_3$ until absorption of 212 cc. (1.2 moles) of H_2. The product was chromatographed on alumina column with ether and eluted in the following order: 0.48 g.(39%) of (Xb), 20 mg.(3%) of (XIVb), and 120 mg.(10%) of (XII). (XII), m.p. 166~167°. *Anal.* Calcd. for $C_9H_{11}N_2Cl$: C, 59.20; H, 6.30; N, 15.38. Found: C, 59.34; H, 6.31; N, 14.92. U.V. $\lambda_{\max}^{\mathrm{MeOH}}$: 261.3 mμ(log ε 4.12); $\lambda_{\max}^{0.1N\ \mathrm{NaOH}}$: 260.1 mμ(log ε 4.16); $\lambda_{\max}^{0.1N\ H_2SO_4}$: 228.5 mμ(log ε 4.23), 282.8 mμ(log ε 4.29).

5-Hydrazino-7-methyl-1,6-naphthyridine (XIIIb)—To a stirred solution of 0.4 g. of (Xb) in 3 cc. EtOH, 1 cc. of NH_2NH_2-H_2O(80%) was added and heated on steam bath for 10 mins., and on cooling, white needles, m.p. 195°, precipitated; yield, 0.4 g. *Anal.* Calcd. for $C_{10}H_{10}N_4$: C, 62.00; H, 5.74; N, 32.19. Found: C, 61.90; H, 5.78; N, 32.03.

7-Methyl-1,6-naphthyridine (XIVb)—To a stirred solution of 0.4 g. of (XIIIb) in a mixture of 3 cc. water and 1 cc. AcOH, 10 cc. of 10% $CuSO_4$ solution was added, and the resulting solution was heated for 10 mins., during which time N_2 gas evolved. The solution was made alkaline with NaOH and extracted with ether. The ether was dried and evaporation of solvent gave white plates, m.p. 78~84°, in a yield of 0.21 g.(65%), m.p. 86~87°(from petr. ether). *Anal.* Calcd. for $C_9H_8N_2$: C, 75.00; H, 5.55; N, 19.40. Found: C, 74.89; H, 5.79; N, 19.21. U.V. $\lambda_{\max}^{\mathrm{MeOH}}$ mμ(log ε): 226(4.45), 252(3.68), 312.8(3.57), 323(3.51)(Fig. 2). Picrate: m.p. 180~181°. *Anal.* Calcd. for $C_{15}H_{11}O_7N_5$: C, 48.26; H, 2.95; N, 18.78. Found: C, 48.67; H, 3.08; N, 18.97.

5-Hydrazino-1,6-naphthyridine (XIIIa)—80% Hydrazine hydrate (0.5 cc.) was reacted with 0.16 g. of (Xa) in 1 cc. EtOH by the procedure described for (XIIIb) and light yellow needles, m.p. 210°(decomp.), were obtained in 0.15 g. yield. *Anal.* Calcd. for $C_8H_8N_4$: C, 60.00; H, 5.00; N, 34.57. Found: C, 59.63; H, 5.06; N, 35.00.

1,6-Naphthyridine (XIVa)—By the same manner described for (XIVb), 0.15 g. of (XIIIa) yielded 0.09 g.(71%) of (XIVa), m.p. 25~27°. U.V. $\lambda_{\max}^{\mathrm{MeOH}}$ mμ(log ε): 220.5(4.43), 248.5(3.62), 303.5(3.54), 314(3.49) (Fig. 2). Picrate, m.p. 219~220°. *Anal.* Calcd. for $C_{14}H_9O_7N_5$: C, 46.80; H, 2.51; N, 19.50. Found: C, 46.91; H, 2.85; N, 19.11.

5-Methyl-1,6-naphthyridine (XVIII)—A solution of 0.3 g. of PCl_3 was added with ice cooling during a period of 20 mins. to a $CHCl_3$ solution of 0.2 g. of methyl-1,6-naphthyridine 1-oxide which was obtained by the Skraup reaction of 4-amino-2-picoline 1-oxide. After 1 hr., the reaction solution was added to ice water, made alkaline, and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by alumina chromatograhy with ether. Yield, 0.13 g. of m.p. 71~73°. Recrystallization from petr. ether gave white needles, m.p. 74~75°, which depressed the m.p. of a sample of 7-methyl-1,6-naphthyridine (XIVb). Therefore, the compound obtained by this Skraup reaction must be the 5-methyl derivative. *Anal.* Calcd. for $C_9H_8N_2$: C, 75.00; H, 5.55; N, 19.40. Found: C, 75.07; H, 5.62; N, 19.13. Picrate, m.p. 200~201°. *Anal.* Calcd. for $C_{15}H_{11}O_7N_5$: C, 48.30; H, 2.95; N, 18.78. Found: C, 48.04; H, 3.16; N, 18.35. U.V. $\lambda_{\max}^{\mathrm{MeOH}}$ mμ(log ε): 225.8(4.46), 256(3.62), 307.8(3.60), 318.5(3.53) (Fig. 2).

During the purification of 5-methyl derivative, 7-methyl derivative might have been discarded and therefore, the following test was undertaken. The reaction mixture[2] was extracted with $CHCl_3$, the solvent removed, and the residue was extracted with hot benzene. The crude product obtained showed m.p. 90~140°. Deoxidation of the material with PCl_3 gave a base of m.p. 40~70° after distillation in vacuum. Infrared spectrum of this sample did not show the characteristic band of 7-methyl-1,6-naphthyridine in the finger-print region. Accordingly, it was found that this Skraup reaction products did not contain the 7-methyl derivative.

Summary

A new synthetic process is described for building up the pyridine ring by the utilization of an active methyl group and a carboxyl adjacent to it in the pyridine ring. The reaction of ethyl 2-methylnicotinate and formaldehyde (or acetaldehyde) gave a lactone which was led to an amide, and its oxidation gave 5-hydroxy-1,6-naphthyridine. 1,6-Naphthyridine and 7-methyl-1,6-naphthyridine were synthesized from their 5-hydroxy derivatives via the chloro and hydrazino compounds.

Methyl-1,6-naphthyridine N-oxide obtained by the Skraup reaction of 4-amino-2-picoline 1-oxide was established as the 5-methyl derivative.

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47. **Nobuo Ikekawa**: Studies on Naphthyridines. II.[1] Synthesis of 2,7-Naphthyridine.

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Synthesis of 2,7-naphthyridines has not been reported with the exception of 1,4-dihydroxy derivative by Gabriel.[2] An attempt was made to synthesize 2,7-naphthyridine from 4-methylnicotinic acid by the route similar to that for 1,6-naphthyridines described in the preceding paper.[1]

Koenigs[3] had already reported on the reaction of 4-methylnicotinic acid and formaldehyde or acetaldehyde, but this reaction was taken up in order to obtain intermediates for synthesis.

Reaction of 4-methylnicotinic acid and formaldehyde at 100° gives only (II) formed by the reaction of 3 moles of formaldehyde and not the product obtained by reaction of one mole of the aldehyde. From this fact, it is seen that the methyl group in this compound is more reactive than that in 2-methylnicotinic acid. However, reaction of the sodium salt results in a product (IIIa) formed with one mole of formaldehyde, in 15% yield.

The same reaction of acetaldehyde affords 4-(2-hydroxypropyl)nicotinic acid lactone (IIIb) in 12.5% yield and a substance which forms a picrate of m.p. 170°. The structure of the latter (IV) had been assumed as (V) by Koenigs but since the infrared spectrum of its base exhibits an absorption for a trisubstituted double bond (1656 and 835 cm^{-1}) and the intensity of its ultraviolet spectrum is abnormally stronger than that of (IIIa), it seems more likely to have a structure (IV) in which the double bonds are conjugated with the pyridine ring.

Derivation of the foregoing lactones (IIIa and b) to the amides and their oxidation with chromic acid afford 1-hydroxynaphthyridines (VII) in approximately 50% yield.

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[1] Part I: This Bulletin, **6**, 263(1958).

[2] S. Gabriel, J. Coleman: Ber., **35**, 1358(1902).

[3] W. Koenigs: *Ibid.*, **34**, 4336(1901).