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 fingerprint 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.\(^3\) 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.\(^3\)

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 (IIa and b) to the amides and their oxidation with chromic acid afford 1-hydroxynaphthyridines (VII) in approximately 50% yield.

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\(^1\) Yayoi-cho, Hongo, Bunkyo-ku, Tokyo (澀川信夫).
\(^2\) Part I: This Bulletin, 6, 263(1958).
\(^3\) S. Gabriel, J. Coleman: Ber., 35, 1358(1902).
Their ultraviolet spectra are shown in Fig. 1. Treatment of (VII) with phosphoryl chloride, derivation of the chloro compound so obtained to the hydrazino compound, and decomposition with copper sulfate finally afford 2,7-naphthyridine (Xa), m.p. 92~94°, and 3-methyl-2,7-naphthyridine (Xb), m.p. 36~38°.

![Fig. 1. Ultraviolet Spectra (in MeOH)](image)

**Fig. 1.** Ultraviolet Spectra (in MeOH)

---: 1-Hydroxy-2,7-naphthyridine (VIIa)

---: 1-Hydroxy-3-methyl-2,7-naphthyridine (VIIb)

The ultraviolet spectra of these compounds, as indicated in Fig. 2, are very similar to that of quinoline. Discussions on their infrared spectra will be made in a later report.

![Fig. 2. Ultraviolet Spectra (in MeOH)](image)

**Fig. 2.** Ultraviolet Spectra (in MeOH)

---: 2,7-Naphthyridine (Xa)

---: 3-Methyl-2,7-naphthyridine (Xb)

Huff obtained a fluorescent substance by the reaction of nicotinamidemethochloride and acetone, in the presence of potassium hydroxide, and he assumed its structure to
be 1,7-dimethyl-5-hydroxy-1,6-naphthyridine hydrochloride (XII). Birkofer\(^4\) reported that he obtained 5-hydroxy-7-methyl-1,6-naphthyridine\(^4\)(XIII) by sublimation of (XII). Examination of this reaction revealed that the product obtained from it is 1-hydroxy-3-methyl-2,7-naphthyridine (VIIb), described above, and this indicates that acetone reacts in the 4-position of the pyridine ring. Kröhnke\(^5\) has recently reported similar opinion by synthesis of this substance by another route.

\[
\begin{align*}
\text{CONH}_2 & \xrightarrow{\text{KOH}} \text{CH}_3\text{CONH}_2 \\
\text{Cl}^- & \xrightarrow{\text{CH}_3\text{COCH}_3} \\
\text{CH}_3 & \xrightarrow{\text{HCl}} \\
\text{NH} & \xrightarrow{\text{HCl}} \\
\end{align*}
\]

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**Experimental**

4-(1,1-Diacetoxymethyl-2-hydroxyethyl)nicotinic Acid Lactone (II)—A mixture of 4 g. of 4-methylnicotinic acid (I), 2 g. of 35% HCHO, and 10 g. of water was heated in a sealed glass tube for 10 hrs. at 100°. The resulting solution was evaporated under a reduced pressure and 20 cc. of MeOH was added to the residue. The recovered material (3 g.) undissolved in MeOH was removed by filtration. MeOH was evaporated and the residue was refluxed for 3 hrs. with 20 cc. of AcO. After removing AcO, the residue was dissolved in water, made alkaline, and extracted with ether. The ether, after being dried, was distilled off and recrystallized of the residue from MeOH gave (II), m.p. 143°-145°. Yield, 0.45 g. Anal. Calcd. for $C_7H_5NO_3N$: $C$, 57.34; $H$, 5.12; $N$, 4.78. Found: $C$, 57.19; $H$, 5.21; $N$, 5.14.

4-Hydroxyethylnicotinic Acid Lactone (IIa)—A mixture of 5 g. of (I), 1.4 g. of NaOH, 5 g. of 35% HCHO, and 3 cc. of water was heated in a sealed tube for 10 hrs. at 90°-100°. The resulting solution was evaporated under a reduced pressure and the residue was dissolved in 20 cc. of 20% HCl. After 1 hr., the solution was made alkaline and extracted with CHCl₃. The aqueous layer was adjusted to pH 3 and evaporated. Extract of the residue with hot EtOH gave 3.5 g. (70%) of (I). The CHCl₃ layer was dried over anhyd. Na₂SO₄ and the solvent was evaporated. The residue was extracted with ether and the extract gave 0.81 g. (15%) of (IIa), m.p. 68°-70°. Anal. Calcd. for $C_8H_7O_3N$: $C$, 64.43; $H$, 4.70; $N$, 9.37. Found: $C$, 64.50; $H$, 5.09; $N$, 9.61. U. V. $\lambda_{max}^{MeOH}$: 263 m\(_\mu\) (log ε 3.22).


4-(2-Hydroxypropyl)nicotinic Acid Lactone (IIb)—A mixture of 2 g. of (I), 2.3 g. of 80% acetaldehyde, and 5 g. of water was heated for 10 hrs. at 140°-150° and treated by the same method as described for (IIa). 1.3 g. (65%) of (I) was recovered. Distillation under a reduced pressure gave 0.3 g. (12.5%) of (IIb), b.p. 150°-160° (bath temp.). U. V. $\lambda_{max}^{MeOH}$: 263 m\(_\mu\) (log ε 3.20). Picrate: m.p. 140°.

Anal. Calcd. for $C_{11}H_{13}O_3N$: $C$, 45.92; $H$, 3.06; $N$, 14.28. Found: $C$, 45.98; $H$, 3.26; $N$, 13.96.

4-(1-(1-Hydroxyethyl)propionyl)nicotinic Acid Lactone (IV)—The residue from distillation of (IIb)

6) Synthesis of this compound was described in the preceding paper.\(^1\) It is different from the product obtained from nicotinamide by Huff’s method.
8) 4-Methylnicotinic acid\(^9\) was synthesized from 4-methylquinolinic acid, prepared by oxidation of 25 g. of lepidine with KMnO₄ at 40°-50°, which was decarboxylated with dimethylaniline at 160°-180°, to 7 g. of 4-methylnicotinic acid, m.p. 216°(decomp.).
was extracted with ether and from the extract, 0.2 g. of picrate of m.p. 170°, which gave 60 mg. of the base when treated with HCl, was obtained. U. V. $\lambda_{\text{max}}$ (MeOH) = 261.5 m$\mu$ (log $e$ 3.99). I. R. $\nu_{\text{max}}$ cm$^{-1}$: 1722 (lactone); 1656, 835 (trisubstituted double bond).

4-[(2-Hydroxyethyl)nicotinamide (Va)]—A solution of 0.8 g. of (IIIa) in 80 cc. MeOH, cooled in an ice bath, was saturated with NH$_3$ gas and allowed to stand overnight. After removal of MeOH, the residue was recrystallized from MeOH-ether, m.p. 152°~154°. Yield, 0.7 g. (79%)

Anal. Calcd. for C$_{16}$H$_{18}$O$_3$N: C, 57.60; H, 6.02; N, 16.86. Found: C, 57.77; H, 6.17; N, 16.50.

1-Hydroxy-2,7-naphthyridine (Va)—A solution of 0.4 g. (1.2 moles) of CrO$_3$ in 20 cc. of acetic acid was added during a period of 1 hr. to a stirred solution of 0.8 g. of (Va) in 20 cc. AcOH at 40°~50°. After being heated on a steam bath for 3 hrs. majority of the solvent was evaporated in vacuum. The residue was made alkaline and extracted several times with hot CHCl$_3$. Recrystallization of the CHCl$_3$ extract from MeOH gave plates, m.p. 255°~262°. Yield, 0.32 g. (45.5%).

Anal. Calcd. for C$_{16}$H$_{18}$O$_3$N: C, 65.70; H, 4.10; N, 19.20. Found: C, 66.66; H, 4.15; N, 18.81. U. V. $\lambda_{\text{max}}$ (MeOH) = 244.5 m$\mu$ (log $e$ 3.99), 301 m$\mu$ (log $e$ 4.02) (Fig. 1). I. R. $\nu_{\text{max}}$ cm$^{-1}$: 1669 cm$^{-1}$ (pyridone).

1-Hydroxy-3-methyl-2,7-naphthyridine (Vb)—A solution of 300 mg. of (IVb) in 40 cc. MeOH was saturated with NH$_3$ gas and allowed to stand overnight. On removing the solvent, a liquid product (amide) was obtained. A solution of this material in 20 cc. AcOH was oxidized with 100 mg. of CrO$_3$ by the procedure described for (Va). Recrystallization of the product from water gave plates, m.p. 256°~258°. Yield, 120 mg.

Anal. Calcd. for C$_{16}$H$_{18}$O$_3$N: C, 67.50; H, 5.00; N, 17.50. Found: C, 67.23; H, 4.98; N, 17.04. U. V. $\lambda_{\text{max}}$ (MeOH) = 243.9 (37), 305 (4.06) (Fig. 1). I. R. $\nu_{\text{max}}$ cm$^{-1}$: 1679 cm$^{-1}$ (pyridone).

1-Chloro-2,7-naphthyridine (Vlla)—A mixture of 220 mg. of (Va) and 10 cc. of POCl$_3$ was heated for 15 hrs. in a sealed glass tube at 130°. After removing POCl$_3$ in vacuum, ice-water was added to the residue, the solution was made alkaline with Na$_2$CO$_3$, and extracted with CHCl$_3$. Drying of the CHCl$_3$ and removal of the solvent gave white needles, m.p. 117°~118°, after recrystallization from ether. Yield, 200 mg. (80%).

Anal. Calcd. for C$_{16}$H$_{18}$N$_2$Cl: C, 58.40; H, 3.04; N, 17.02. Found: C, 58.82; H, 3.22; N, 16.73. U. V. $\lambda_{\text{max}}$ (MeOH) = 282.6 (3.74), 295.3 (3.69), 308 (3.57).

1-Chloro-3-methyl-2,7-naphthyridine (Vllb)—A mixture of 220 mg. (Vlb) (2.2 g.) was treated by the same manner described for (Vlla) to give 2.2 g. (90%) of (Vlb), m.p. 105°~106° (white needles).

Anal. Calcd. for C$_{16}$H$_{18}$N$_2$Cl: C, 60.50; H, 3.92; N, 15.39. U. V. $\lambda_{\text{max}}$ (MeOH) = 284 (3.81), 310 (3.65) (shoulder).

2,7-Naphthyridine (Xa)—To a solution of 200 mg. of (Va) in 1 cc. of EtOH, 0.8 cc. of hydrazine hydrate (80%) was added. After the mixture was heated on a steam bath for 10 mins. and allowed to cool, 8-hydrazino-2,7-naphthyridine (Xa) precipitated. The solution of the precipitate in a mixture of 6 cc. water and 3 cc. AcOH was added to 20 cc. of 10% CuSO$_4$ heated on a steam bath. After 10 mins., the resulting solution was made alkaline and extracted with ether, which was dried, ether evaporated, and white needles, m.p. 92°~94°, were obtained. Yield, 120 mg. (76%).

Anal. Calcd. for C$_{16}$H$_{18}$N$_2$: C, 73.84; H, 4.61; N, 21.53. Found: C, 73.83; H, 4.65; N, 21.59. Picrate: m.p. 240°.

Anal. Calcd. for C$_{16}$H$_{18}$N$_4$: C, 46.80; H, 2.51; N, 18.90. Found: C, 46.73; H, 2.58; N, 19.20. U. V. $\lambda_{\text{max}}$ (MeOH) = 274.5 (3.61), 291.8 (3.49), 297.7 (3.43), 305 (3.42) (Fig. 2).

1-Hydrazino-3-methyl-2,7-naphthyridine (Xb)—A mixture of 0.8 cc. of hydrazine hydrate (80%), 0.5 g. of (Vlb), and 3 cc. of EtOH was heated for 10 mins. on a steam bath. After cooling, 0.45 g. of needles precipitated. Sublimation in vacuum gave white needles, m.p. 208°~211°.

Anal. Calcd. for C$_{18}$H$_{18}$N$_5$: C, 62.00; H, 5.74; N, 32.19. Found: C, 61.83; H, 5.75; N, 32.18.

6-Methyl-2,7-naphthyridine (Xb)—By the same procedure described for (Xa), 2.2 g. of (Vlb) yielded 1.05 g. (59%) of (Xb), m.p. 36°~38°.

Picrate, m.p. 220°~221°.

Anal. Calcd. for C$_{16}$H$_{18}$N$_2$: C, 48.26; H, 2.95; N, 18.78. Found: C, 48.04; H, 3.02; N, 18.57. U. V. $\lambda_{\text{max}}$ (MeOH) = 277.8 (3.69), 306 (3.52) (shoulder) (Fig. 2).

1-Hydroxy-3-methyl-2,7-naphthyridine (Vllc) from Nicotinamide Methochloride—From 23 g. of nicotinamide methochloride, 8 g. of 2,6-dimethyl-8-hydroxy-2,7-naphthyridine hydrochloride (Xl) was obtained by the procedure described in Huff's report. Sublimation of 1.5 g. of (Xl) in vacuum gave light yellow needles, which contained halogen. Recrystallization from water gave white needles, m.p. 256°~258° (yield, 0.6 g.), which did not depress the m.p. of the above-described sample of 1-hydroxy-3-methyl-2,7-naphthyridine (Vlb).

Summary

Reaction of 4-methylnicotinic acid with formaldehyde or acetaldehyde gave a lactone, which was led to the amide, and this was oxidized to 1-hydroxy-2,7-naphthyridine. 2,7-Naphthyridine and 3-methyl-2,7-naphthyridine were synthesized from 1-hydroxy derivatives via 1-chloro and 1-hydrazino compounds.

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