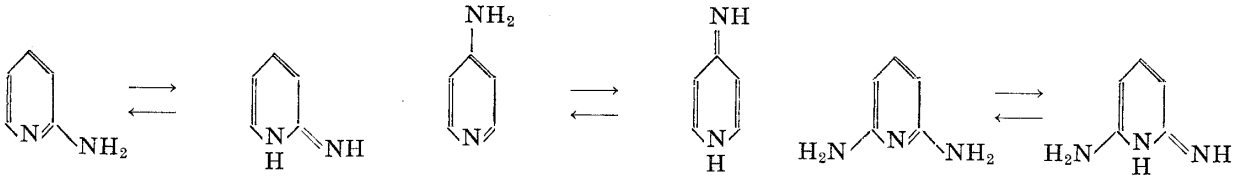
U.D.C. 547.822.7.07

34. Tetsuzo Kato, Fumiko Hamaguchi, and Teruko Oiwa : Synthesis of Methylpyridine Derivatives. X.[1] The Skraup Reaction of 4-Aminomethylpyridine 1-Oxides.

(*Women's Department, Tokyo College of Pharmacy**)

The work described in this paper was attempted in order to prepare 1,6-naphthyridine derivatives by the Skraup reaction. In literature, the synthesis of the naphthyridine ring system, which are built up from aminopyridine by this method, failed except in the case of 3-aminopyridine.[2] In this case, the cyclization takes place in the 2-position of the pyridine ring, giving 1,5-naphthyridine, so that by this method 1,7-isomer, which would result from a ring closure through the 4-position, is not obtained.[3] Even when the 2-position is blocked with methyl group as in 3-amino-2,6-lutidine, regardless of the reactive polarization effect of its methyl groups, cyclization to the 1,7-naphthyridine ring system does not occur.[4]

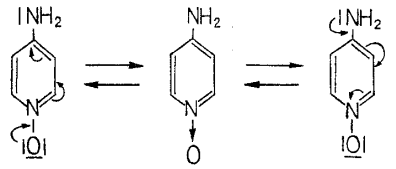
It is known that 2- and 4-aminopyridines exist in tautomeric structures (A and B) and (C and D),[5] so that most attempts to prepare 1,8- or 1,6-naphthyridine from 2- or 4-aminopyridine have been unsuccessful, because the pyridineimino structure (B or D) prefers to react with acroleine.



(A) (B) (C) (D) (E) (F)

2,6-Diaminopyridine exists in tautomeric structures (E and F), both of which react with acroleine and undergo the Skraup reaction to form 2-amino-1,8-naphthyridine in a good yield.[6] Actually, 2-aminopyridine is negative to diazo color test for primary amines but 2,6-diaminopyridine is positive, while 4-aminopyridine is somewhat positive to diazo color test, so that the preparation of 1,6-isomer by this method would be possible.

4-Aminopyridine 1-oxide is clearly positive to diazo color test. Therefore, it is certain that the (G) structure, which takes the benzenoid form by resonance, is more stable than (H), which takes the quinoid form.



(G) (H)

* Uenosakuragi-cho, Taito-ku, Tokyo (加藤鉄三, 浜口文子, 大岩照子).

1) Part IX. T. Kato, F. Hamaguchi : This Bulletin, **4**, 174(1956).
2) Plazzo, Marogna : Chem. Zentr., **84**, I, 171(1913); Bobranski, Sucharda : Ber., **60**, 1081(1927).
3) C. Allen : Chem. Revs., **47**, 276(1950).
4) E. Ochiai, K. Iwai, G. Negoro : J. Pharm. Soc. Japan, **61**, 230(1941).
5) Tschitschibabin : Ber., **60**, 1607(1927).
6) Seide : Ber., **59**, 2468(1926); T. Miyaki : J. Pharm. Soc. Japan, **62**, 31(1942).

Based upon these facts, attempt was made to prepare 1,6-naphthyridine derivatives from 4-amino-methylpyridine 1-oxides by the Skraup reaction.

4-Amino-2,6-lutidine 1-oxide (I) submitted to the Skraup reaction, under conditions somewhat milder than those used ordinarily, to yield pale yellow needles, m.p. 126~130°, in a poor yield. From the results of elementary analyses, molecular weight determination, and ultraviolet spectrum, 5,7-dimethyl-1,6-naphthyridine 6-oxide (II) was attributed to this compound. The picrate came as yellow needles melting at 194~196° with reddish coloration. Concentration of the hydrochloric acid solution of (II) resulted in reddish coloration and no crystalline salt was obtained. It seems, therefore, that (II) is comparatively unstable in acidic medium and the yield was poor. Use of phosphoric acid in place of sulfuric acid failed to raise the yield. The conditions of this reaction are shown in Table I.

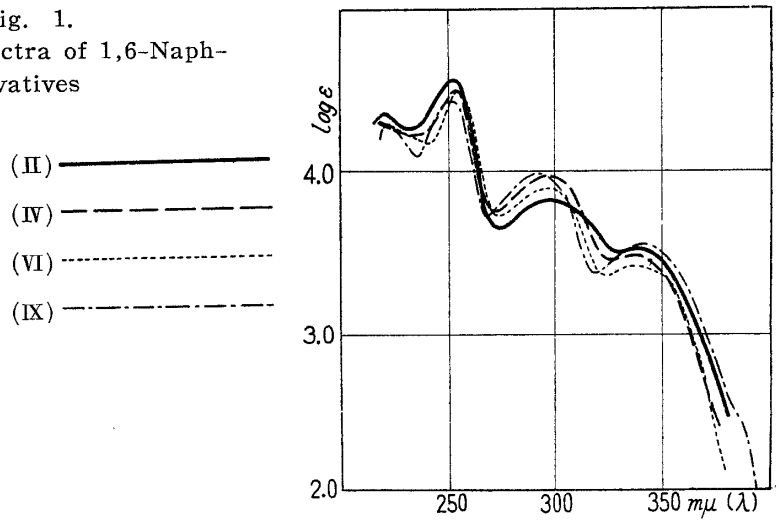
Table I.

	4-NH_2-lut. N→O (I) (g.)	Glycerol (g.)	As_2O_5 (g.)	H_2SO_4 (g.)	H_3PO_4 (g.)	Temp. (°C)	Time (hrs.)	Yield (%)
(1)	0.6	1.6	0.7	1.2	0	150~170	4	low
(2)	1.38	3.68	1.36	1.36	0	155	3	9
(3)	1.3	2.8	1.4	2.0	0	145	2	4
(4)	6.9	18.4	6.9	13.8	0	150~155	3	5
(5)	1.38	3.7	1.4	0	4.6 (85%)	195	5	—
(6)	1.38	3.7	1.4	0	3.9 (100%)	200	6	1.7

4-Amino-3-picoline 1-oxide (III) and 4-aminopyridine 1-oxide (VIII) were treated in the same way as above, and the resulting products proved respectively to be 8-methyl-1,6-naphthyridine 6-oxide (IV) and 1,6-naphthyridine 6-oxide (IX). With 4-amino-2-picoline 1-oxide (V), the cyclization should take place at the 3- or 5-position to form two isomers (VI or VII), but only one compound of m.p. 153~156° was obtained. Bradford *et al.*[7] reported the identity and the relative proportion of the isomeric quinolines formed from *meta*-substituted anilines in the Skraup reaction, and only 7-methylquinoline was prepared from *m*-methylaniline. Based upon this result, the compound of m.p. 153~156° would, perhaps, be the 7-methyl derivative (VI).

Ultraviolet absorption spectra of these 1,6-naphthyridine derivatives are given in Table 2 and Fig. 1. Fig. 2 shows ultraviolet absorption spectra of the starting 4-aminomethylpyridine 1-oxides.

Fig. 1.
Ultraviolet Spectra of 1,6-Naphthyridine Derivatives



7) Bradford, Elliot, Rowe : J. Chem. Soc., **1947**, 437.

Fig. 2.
Ultraviolet Spectra of 4-Aminomethylpyridine 1-Oxides

(I) ——— $\lambda_{max}^{Et\,OH}$ 275 mμ (log ε 4.32)
(II) — — — $\lambda_{max}^{Et\,OH}$ 282 mμ (log ε 4.23)
(V) ---------- $\lambda_{max}^{Et\,OH}$ 278 mμ (log ε 4.25)
(VIII) —·—·— $\lambda_{max}^{Et\,OH}$ 283 mμ (log ε 4.33)

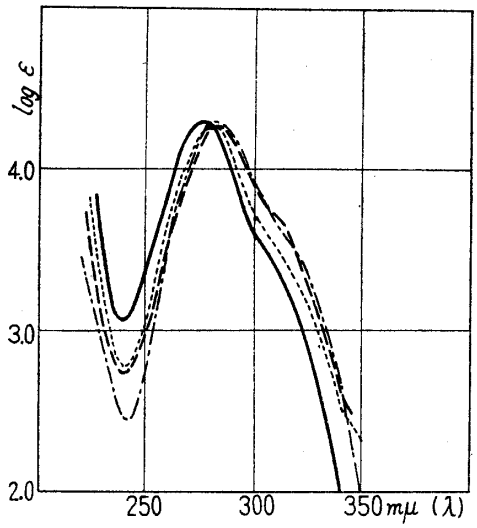
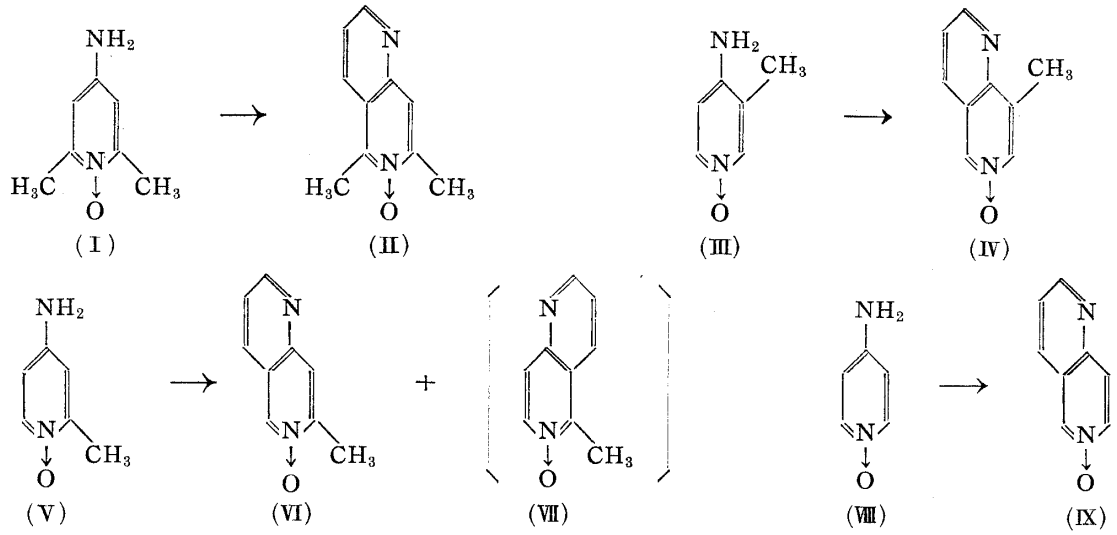


TABLE II.

	1,6-Naphthyridine 6-oxide	m.p. (°C)	Picrate, m.p. (°C)	Ultraviolet absorption λ_{max}^{EtOH} (mμ)	log ε
(II)	5,7-Dimethyl-	127~132	194~196	223, 254, 299, 340	4.31, 4.55, 3.76, 3.49
(IV)	8-Methyl-	187~188.5	170~172	—, 254, 295, 335	—, 4.45, 3.94, 3.46
(VI)	7-Methyl-	158~159	216~219(decomp.)	—, 254, 295, 336	—, 4.48, 3.86, 3.40
(IX)	——	151	185~186	222, 252, 294, 340	4.24, 4.40, 3.97, 3.52



The authors are deeply grateful to Prof. Ochiai of the University of Tokyo for his helpful advices and suggestions during the course of this work. Their thanks are also due to Prof. Murayama, President of this College, and Prof. Terasaka, Dean of this Department, for their encouragements, and to the members of the analysis room of this college and those of Kowa Chemical Laboratories for the microanalytical data and for taking ultraviolet spectra.

Experimental

5,7-Dimethyl-1,6-naphthyridine 6-Oxide (II)—To a mixture of 1.38 g. (0.01 mole) of 4-amino-2,6-lutidine 1-oxide (I), 1.38 g. (0.006 mole) of As_2O_5, and 3.68 g. (0.04 mole) of glycerol, there was added dropwise with shaking 2.75 g. (0.03 mole) of conc. H_2SO_4. The mixture was then heated in an oil bath for 3 hrs. at 155°. The reddish brown mixture was cooled and 50 cc. of ice water was added. The mixture was made alkaline with Na_2CO_3, and extracted with ca. 200 cc. of $CHCl_3$. To the brown $CHCl_3$ solution were added Na_2SO_4 and Norit and, after allowing it to stand, the drying agent and decolorizing carbon were removed by filtration. The $CHCl_3$ filtrate was concentrated by evaporation and a crystalline residue was obtained. This was extracted with benzene and the benzene solution was treated again with the drying agent and carbon.

The crystalline residue from the benzene extract was purified several times with benzene or acetone giving white needles, m.p. 127~132°. Yield, 0.15 g. (9%). It was soluble in water, MeOH, acetone, benzene, and $CHCl_3$, but insoluble in ether, giving negative diazo color test. *Anal.* Calcd. for $C_{10}H_{10}ON_2$ (II): C, 68.95; H, 5.79; N, 16.08; mol. wt., 178. Found: C, 68.05; H, 6.26; N, 15.73; mol. wt. (Rast), 166. Picrate: Yellow needles (from MeOH), m.p. 194~196° (with reddish coloration). *Anal.* Calcd. for $C_{10}H_{10}ON_2 \cdot C_6H_3O_7N_3$ ((II) picrate): C, 47.65; H, 3.25; N, 17.37. Found: C, 47.12; H, 3.80; N, 17.49.

8-Methyl-1,6-naphthyridine 6-Oxide (IV)—A mixture of 3 g. (0.024 mole) of 4-amino-3-picoline 1-oxide (III), 6.6 g. (0.072 mole) of glycerol, 2.7 g. (0.012 mole) of As_2O_5, and 4.4 g. (0.048 mole) of conc. H_2SO_4 was heated in an oil bath at 150~160° for 3 hrs. The mixture was treated in the same way as above and 0.4 g. of yellow needles of m.p. 70° (ca.) was obtained from the benzene extract. Slightly hygroscopic white needles, m.p. 187~188.5°, were obtained by recrystallization from acetone. Yield, 0.2 g. (5%). *Anal.* Calcd. for $C_9H_8ON_2$ (IV): C, 67.48; H, 5.03; N, 17.49. Found: C, 67.52; H, 5.05; 17.46.

Its picrate was recrystallized from EtOH to yellow needles, m.p. 170~172°. *Anal.* Calcd. for $C_9H_8ON_2 \cdot C_6H_3O_7N_3$ ((IV) picrate): C, 46.28; H, 2.85; N, 17.99. Found: C, 46.41; H, 2.52; N, 17.62.

4-Amino-2-picoline 1-Oxide (V)—This was prepared according to the method of Kato and Hamaguchi.[1] A suspension of 15.4 g. of 4-nitro-2-picoline 1-oxide in 200 cc. of water was reduced with 7.5 g. of 50% Pd-C in H_2, by which 6.90 L. of H_2 (theoretical amount, 6.95 L.) was absorbed at 9°. The time required was 2 hrs. After removing the catalyst by filtration, the filtrate was concentrated under a reduced pressure. To the reddish residue was added acetone and 12 g. of white crystals of m.p. ca. 120° separated. The crude crystals were recrystallized from EtOH and acetone, treating with activated carbon, to hygroscopic white needles, m.p. 122~128°. Yield, 11.4 g. (92%). This was soluble in water, MeOH, and EtOH, but insoluble in ether, acetone, and $CHCl_3$, giving positive diazo color test for primary amines. Its picrate, m.p. 180°, and the hydrochloride, m.p. 192°, were identified with those obtained by Ochiai and Suzuki.[8]

7,(5?)-Methyl-1,6-naphthyridine 1-Oxide (VI) (VII?)—A mixture of 12.4 g. (0.1 mole) of 4-amino-2-picoline 1-oxide (V), 36.8 g. of glycerol, 13.8 g. of As_2O_5, and 27.4 g. of conc. H_2SO_4, was treated in the same manner as for (II). One g. of pale orange needles, m.p. 140~150°, was obtained, and recrystallized from benzene to white needles of m.p. 158~159°. Yield, 0.85 g. (5%). The solubility of this compound was similar to (II) and (IV). *Anal.* Calcd. for $C_9H_8ON_2$ (VI or VII): C, 67.48; H, 5.03; N, 17.49. Found: C, 67.43; H, 5.32; N, 17.18. Picrate, yellow needles (from EtOH), m.p. 216~219°(decomp.). *Anal.* Calcd. for $C_9H_8ON_2 \cdot C_6H_3O_7N_3$ ((VI) picrate): C, 46.28; H, 2.85; N, 17.99. Found: C, 46.01; H, 3.06; N, 17.72.

4-Aminopyridine 1-Oxide (VIII)—This was prepared in the same way as described above in (V). A suspension of 4.2 g. (0.03 mole) of 4-nitropyridine 1-oxide in 200 cc. of water was reduced in H_2 in the presence of 1.4 g. of 50% Pd-C, and 2120 cc. of H_2 were absorbed at 16°. The time required was 4 hrs. After removing the catalyst by filtration, the filtrate was treated in the same way as above, and 3 g. of white hygroscopic crystals of m.p. ca. 100° were obtained. This was recrystallized from EtOH and acetone to white needles which, after drying *in vacuo* at 80° for 3 hrs., melted at 229°. *Anal.* Calcd. for $C_5H_6ON_2$ (VIII): N, 25.45. Found: N, 24.69. Yield, 2.9 g. (88%). Its picrate melted at 201.5~202°, and was identified with that obtained by Ochiai and Katada.[9]

1,6-Naphthyridine 6-Oxide (IX)—A mixture of 1.1 g. of (VIII), 1.4 g. of As_2O_5, 3.9 g. of glycerol, and 3.1 g. of conc. H_2SO_4 was heated in an oil bath at 143~145° for 3 hrs., and this mixture was treated in the same way as above. The $CHCl_3$ residue was purified several times from benzene or acetone, with activated carbon, forming pale yellowish needles of m.p. 151°. In a long time yellow coloration appeared. Yield, 0.09 g. (6%).

The picrate was recrystallized from EtOH to yellow needles, m.p. 185~186°. *Anal.* Calcd. for $C_8H_6ON_2 \cdot C_6H_3O_7N_3$ ((V) picrate): C, 44.80; H, 2.40; N, 18.67. Found: C, 45.14; H, 2.34; N, 18.28.

Summary

The Skraup reaction of 4-aminomethylpyridine 1-oxides, which were easily prepared from the 4-nitro 1-oxides, afforded 1,6-naphthyridine derivatives; 5,7-dimethyl-1,6-naphthyridine 6-oxide (II) from 4-amino-2,6-lutidine 1-oxide (I), 8-methyl-1,6-naphthyridine 6-oxide (IV) from 4-amino-3-picoline 1-oxide (III), 7(5?)-methyl-1,6-naphthyridine 6-oxide (VI,VII?) from 4-amino-2-picoline 1-oxide (V), and 1,6-naphthyridine 6-oxide (IX) from 4-aminopyridine 1-oxide (VIII), but the yield of these compounds was all poor.

(Received February 14, 1956)

8) E. Ochiai, I. Suzuki: J. Pharm. Soc. Japan, **67**, 158(1947).
9) E. Ochiai, M. Katada: *Ibid.*, **63**, 186(1943).