The mother liquor from the lycoramine perchlorate was made alkaline and the liberated base was recovered with ether. After concentration of ethereal solution to dryness, a small amount of perchloric acid was added to the residue, and a small quantity of the solid material which separated out was filtered off. The mother liquor was treated as before and this procedure was repeated several times until no insoluble material was obtained by the addition of perchloric acid to the free base. Thus 0.05 g. of viscous oil, b.p$_{0.05}$ 190~200°, $[\alpha]_D^{24.5}$: −136.3° (c=0.375 in 90% EtOH), was obtained which could not be induced to crystallize by addition of a few seed crystals of lycoramine or lycoremine. *Anal.* Calcd. for $C_{17}H_{23}O_3N$: C, 70.56; H, 8.01. Found: C, 70.12; H, 8.40.

Summary

A new alkaloid, lycoremine, was isolated from *Lycoris radiata.* This compound can be represented by a formula $C_{17}H_{21}O_3N$ and contains one OCH_3, one N-CH_3, and one alcoholic hydroxyl group. Lycoremine was converted into lycoramine, $C_{17}H_{23}O_3N$, by hydrogenation from which the relationship between the two alkaloids was established.

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34. Kyosuke Tsuda, Nobuo Ikekawa, Rinji Takasaki, and Yasumasa Yamakawa: Studies on the Coal Tar Bases. III[1]. Synthesis of Dimethylpyridines.

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Six possible isomers of lutidine have hitherto been found[2] from coal tar bases. All of these were obtained from coal tar bases of low temperature coking[3]. Ordinarily, 2,6-lutidine is distilled mixed with β- and γ-picoline from a fraction of b.p. 140~145°, and is separated by recrystallization of the hydrochloride or by the fractional distillation in vacuum of its N-oxide[4]. 2,4-, 2,5- and 2,3-Lutidine are distilled from a fraction of b.p. 157~163°, and these three bases are separated by recrystallization of their picrates but the yield of each base is small. It seemed that the best method to obtain 2,4-lutidine from coal tar was by a fractional distillation of its N-oxide[4]. 3,5-Lutidine is distilled from a fraction of b.p. 169~172°, and 3,4-lutidine from a fraction of b.p. 177~180° mixed with a certain amount of trimethylpyridine. In each case the base is separated by the recrystallization of the picrate.

All the lutidines, with the exception of 3,5-lutidine, have already been synthesized. 3,5-Lutidine was prepared in the present experiments, and 2,5-, and 2,3-lutidine by different methods from those given in literatures, which are described in the present paper.

3,5-Lutidine 3,5-Pyridinedicarboxylic acid (I)[5] was obtained by heating 2,3,5,6-pyridinetetracarboxylic acid[6], derived from 3,5-dicarbethoxy-2,6-dimethylpyridine[7], in glacial acetic acid. After esterification of the dicarboxylic acid of pyridine (I), ethyl ester (II) was reduced to the diol (III) with lithium aluminum hydride, and chlorinated to 3,5-dichloromethylpyridine (IV), m.p. 86~87°, with thionyl chloride. The dichloromethyl compound (IV) was converted readily to 3,5-dimethylpyridine (V), b.p. 171°, by reduction. It

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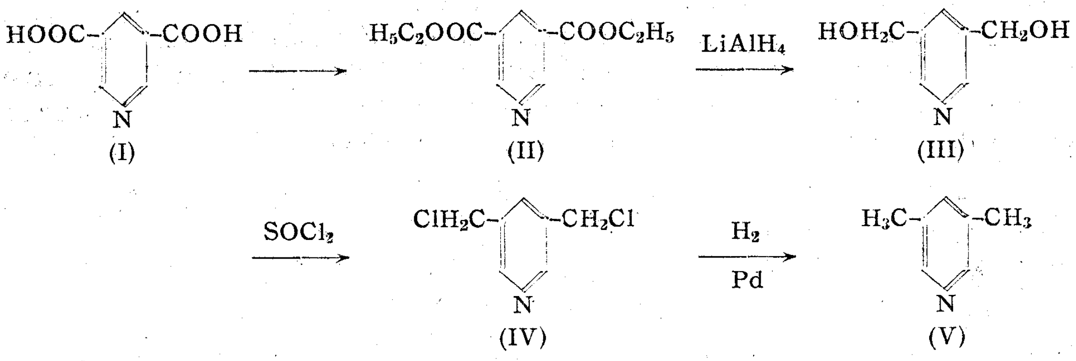
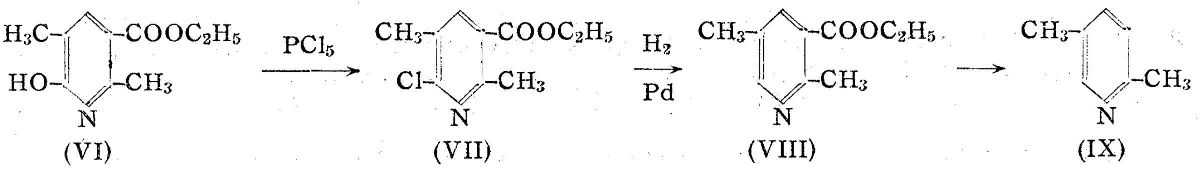
* Hakata, Fukuoka (津田恭介, 池川信夫, 高崎林治, 山川泰正).
1) Part II: This Bulletin, 1, 126 (1953).
2) A. A. Morton: "The Chemistry of Heterocyclic Compounds". p. 206 (1946).
3) This Bulletin, 1, 149 (1953).
4) E. Ochiai, M. Ikehara, T. Kato, N. Ikekawa: J. Pharm. Soc. Japan, 71, 1385 (1951).
5, 6) A. Hartzsch, L. Weiss: Ber., 19, 284 (1886).
7) Org. Syntheses, 14, 30 (1936).

gave a picrate of yellow needles, m.p. 240°, coincidental with the meltng point of 3,5-lutidine picrate obtained from coal tar bases[8], cracked gasoline[9], and shale oil[10].

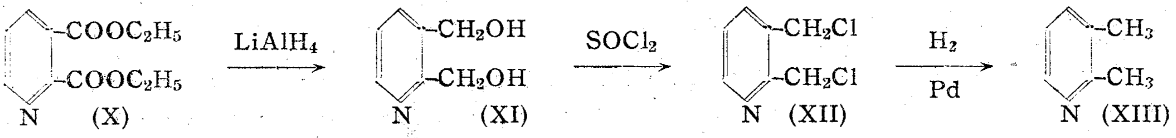


2,5-Lutidine Errera[11] synthesized 2,5-lutidine by the zinc dust distillation of 2,5-dimethyl-6-pyridone, obtained by the decarboxylation of 3-carbethoxy-2,5-dimethyl-6-hydroxypyridine (VI). In the present experiments, (VI) was derived to 3-carbethoxy-6-chloro-2,5-dimethylpyridine (VII) by chlorination, and converted to 2,5-lutidine (IX) by dechlorination[1] and decarboxylation.



The picrate, m.p. 167°, of the base corresponded well with the melting point of that synthesized by Errera, as well as with that of 2,5-lutidine picrate isolated from coal tar bases, etc.[8~10;12~14].

2,3-Lutidine Tracy, *et al.*[15] synthesized 3-carboxy-5,6-dimethyl-2-pyridone from formylmethyl ethyl ketone and cyanoacetamide and derived it to 2,3-lutidine. Wibaut, *et al.*[16] obtained 2,3-lutidine from 3-carbethoxy-2,4-dihydroxy-5,6-dimethylpyridine, yielded by the condensation of β-amino-α-methylcrotonic ester and malonic ester. In the present experiments, diethyl quinolinate (X) was reduced to the diol (XI) with lithium aluminum hydride, and the diol (XI) was derived to 2,3-lutidine (XIII) by chlorination and hydrogenation.



Its picrate, m.p. 187°, was in good agreement with the picrates of the samples reported in the literature described above and with the picrates of the bases isolated from coal tar, etc.[10;12;17;18].

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8) F. B. Ahrens, R. Gorkow: Ber., 37, 2062 (1904).
9) A. C. Bratton, J. R. Bailey: J. Am. Chem. Soc., 59, 175 (1937).
10) T. Eguchi: Bull. Chem. Soc. Japan, 3, 227 (1928).
11) G. Errera: Ber., 34, 3691 (1901).
12) J. T. Hackmann, J. P. Wibaut, H. P. L. Gitsels: C. A., 38, 3117 (1944).
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16) J. P. Wibaut, E. C. Kooyman: C. A., 41, 450 (1947).
17) F. C. Garett, J. A. Smythe: J. Chem. Soc., 83, 763 (1903).
18) F. B. Ahrens: Chem. Zentr., 1906, I, 510.

2,6- and 2,4-Lutidine are isolated readily from coal tar bases and their synthetic method is well-known[19].

3,4-Lutidine was synthesized by Wibaut[16] and his method was utilized. The condensation of the amide of ethyl methylacetoacetate and cyanoacetic ester yielded 5-cyano-3,4-dimethyl-2,6-dihydroxypyridine, and heating it with hydrobromic acid converted it to 3,4-dimethyl-2,6-dihydroxypyridine. This was derived to 3,4-lutidine by chlorination and reduction. Some constants of lutidines synthesized are shown in the following table:

Lutidine	b.p.	Picrate m.p.	$HgCl_2$ Salt m.p.	Chloroplatinate m.p. (decomp.)
2,5-Lutidine	157°	167°	99°	239°
2,3-Lutidine	163°	187°	104°	239°
3,5-Lutidine	171°	240°	157∼159°	273°
3,4-Lutidine	179°	160°	113°	272°

Infrared absorption spectragrams and other physical constants will be described in later reports.

This work was supported by a grant from the Ministry of Welfare for which the authors express their gratitude.

Experimental

3,5-Pyridinedicarboxylic acid (I)—When 25 g. of 3,5-dicarbethoxy-2,6-dimethylpyridine was dissolved in 500 cc. of alcohol containing 50 g. of potassium hydroxide and heated on a water bath for five hours, potassium salt precipitated. The salt was collected by filtration, dissolved in 200 cc. of water, and a solution of 63 g. of potassium permangnate in 1.6 L. of water was dropped in under stirring. After 9 days, the reaction was completely finished. A solution of 55 g. of silver nitrate in 200 cc. of water was added to the solution obtained after the removal of manganese dioxide, and the silver salt thereby obtained was suspended in water and hydrogen sulfide passed into the solution. From the filtrate of this reaction mixture, 2,3,5,6-tetracarboxylic acid of pyridine was obtained on concentration. Yield, 10.5 g. (26%). The mixture of 10.5 g. of 2,3,5,6-pyridinetetracarboxylic acid and 120 cc. of glacial acetic acid was heated at 150° (bath temp.) for 5 hours. By distillation of glacial acetic acid, 3,5-pyridinedicarboxylic acid, m.p. 321°, was obtained. Yield, 6.9 g. (97%).

3,5-Dicarbethoxypyridine (II)—A mixture of 6.9 g. of the dicarboxylic acid, 70 cc. of absolute alcohol, and 40 cc. of conc. sulfuric acid was heated at 110° (bath temp.) for 12 hrs., and alcohol was removed as much as possible. The residue was diluted with 200 cc. of ice-water, neutralized with sodium carbonate, and extracted with ether. Ether residue yielded 3,5-dicarbethoxypyridine as colorless needles (from water), m.p. 46∼47°. Yield, 6.3 g. (68.5%). *Anal.* Calcd. for $C_{11}H_{13}O_4N$ (3,5-Dicarbethoxypyridine): N, 6.3. Found: N, 6.20.

3,5-Dihydroxymethylpyridine (III)—To a solution of 2 g. of lithium aluminum hydride in 100 cc. of ether 3.5 g. of 3,5-dicarbethoxypyridine in 50 cc. of ether was added under stirring during 30 minutes. Yellow precipitate appeared immediately with the addition of the ester solution. The mixture was heated on a water bath for further 1 hour, 10 cc. of water added, and filtered. The filtrate was extracted several times with hot methanol. From methanol extract, an oily product was obtained. Yield, 2 g. (53.3%). Picrate, m.p. 132∼133°. *Anal.* Calcd. for $C_7H_9O_2N \cdot C_6H_3O_7N_3$ (3,5-Dihydroxymethylpyridine picrate): N, 15.22. Found: N, 15.71.

3,5-Dichloromethylpyridine (IV)—To 20 cc. of thionyl chloride cooled well, 1.5 g. of the diol (III) was added little by little and the reaction mixture was heated on a water bath for 1 hour. After the removal of thionyl chloride by low pressure distillation, the residue was treated with chipped ice, made alkaline with sodium carbonate, and extracted with ether. Ether residue was recrystallized from petroleum ether to white plates, m.p. 86∼87°. Yield, 1.2 g. (63.5%). *Anal.* Calcd. for $C_7H_7NCl_2$ (3,5-Dichloromethylpyridine): C, 47.73; H, 3.98; N, 7.96. Found: C, 47.90; H, 4.07; N, 8.07.

3,5-Dimethylpyridine (V)—One g. of 3,5-dichloromethylpyridine dissolved in 50 cc. of methanol was shaken in hydrogen stream with 0.2 g. of Pd-$CaCO_3$ (5%), and 252 cc. of hydrogen was absorbed during 15 minutes. After filtration and evaporation of methanol, the residue was made alkaline with potassium hydroxide solution and extracted with ether. From ethereal solution, colorless liquid, b.p. 171°, was obtained. Yield, 0.55 g. (91%). Picrate: Yellow needles, m.p. 240°. *Anal.* Calcd. for $C_7H_9N \cdot C_6H_3O_7N_3$ (3,5-Dimethylpyridine picrate): C, 46.41; H, 3.57; N, 16.69. Found:

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19) 2,6-Lutidine: Org. Syntheses, 14, 30 (1936).
2,4-Lutidine: E. Knoevenagel, W. Cremer: Ber., 35, 2390 (1902).

C, 46.62; H, 3.21; N, 16.89. Mercuric chloride salt, colorless needles, m.p. 157~159°. *Anal.* Calcd. for $C_7H_9N\cdot HCl\cdot 2HgCl_2$: N, 2.02. Found: N, 2.14. Chloroplatinate, yellow prisms, m.p. 273° (decomp.).

2,5-Dimethylpyridine (IX)—A solution of 3.5 g. of 3-carbethoxy-2,5-dimethylpyridine (VIII)[1] dissolved in 10% potassium hydroxide solution was heated on a water bath for 1 hour, and the potassium salt thereby obtained was distilled with equal quantity of soda lime. The light yellow liquid obtained was dried over potassium hydroxide, and boiled at 157°. Yield, 1.4 g. (66%). Chloroaurate, yellow needles, m.p. 155°. Picrate, yellow needles (methanol), m.p. 165~166°. *Anal.* Calcd. for $C_7H_9N\cdot C_6H_3O_7N_3$ (2,5-Lutidine picrate): C, 46.41; H, 3.57; N, 16.69. Found: C, 46.13; H, 3.81; N, 16.32. Mercuric chloride salt, colorless needles, m.p. 99°. *Anal.* Calcd. for $C_7H_9N\cdot HCl\cdot 2HgCl_2$: N, 2.02. Found: 2.16. Chloroplatinate, m.p. 239° (decomp.).

2,3-Dihydroxymethylpyridine (XI)—To 1.8 g. of lithium aluminum hydride in 100 cc. of ether, 5 g. of diethyl quinolinate (X) dissolved in 50 cc. of ether was added under stirring. Red precipitate appeared instantly. The reaction mixture was refluxed on a water bath for 1 hour. Excess of lithium aluminum hydride was decomposed by the addition of a small quantity of water, and hydrolyzed. The precipitate was extracted several times with hot methanol. From the methanol extract, 2.5 g. of crude diol compound was obtained, but due to its hygroscopic nature, it was hard to purify, and could not be isolated in a crystalline form.

2,3-Dichloromethylpyridine (XII)—To 15 g. of thionyl chloride packed in ice 2.5 g. of the diol compound was added gradually. After refluxing the mixture on a water bath for an hour, the residue obtained by the evaporation of thionyl chloride in vacuum was treated with ice-water, sodium carbonate, and extracted with ether as usual. From ethereal residue, 2.6 g. of colorless liquid was obtained. Yield, 83%. Picrate, yellow plates, m.p. 143~144°. *Anal.* Calcd. for $C_7H_7NCl_2\cdot C_6H_3O_7N_3$: N, 13.82. Found: N, 13.59.

2,3-Dimethylpyridine (XIII)—With 0.3 g. of Pd-$CaCO_3$ (5%) as a catalyst, 2 g. of the dichloromethyl compound dissolved in 50 cc. of methanol was reduced and worked up as usual. Absorption of hydrogen, 250 cc. at 16° (theoretical amount: 254 cc.). Yield, 1.1 g. (91%). Picrate, yellow needles, m.p. 187°. *Anal.* Calcd. for $C_7H_9N\cdot C_6H_3O_7N_3$(2,3-Dimethylpyridine picrate): C, 46.41; H, 3.57; N, 16.7. Found: C, 46.86; H, 4.04; N, 16.45. Mercuric chloride salt, colorless needles, m.p. 104°. *Anal.* Calcd. for $C_7H_9N\cdot HCl\cdot 2HgCl_2$: N, 2.02. Found: N, 2.15. Chloroplatinate, yellow prisms, m.p. 239° (decomp.).

Summary

3,5-Lutidine was synthesized for the first time. 2,5- and 2,3-Lutidine were synthesized by a method different from that reported in literatures. The synthesis of these compounds gave favorable samples to be compared with the lutidines from coal tar bases.

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