Yield, 0.3 g. *Anal.* Calcd. for $C_{19}H_{22}O_3$: C, 76.51; H, 7.38. Found: C, 76.23; H, 7.24. Mixed melting point with natural auraptene did not show depression.

Summary

Auraptene, m.p. 68°, previously isolated by Komatsu and Tanaka from orange oil obtained by the expression of fresh peels of *Citrus aurantium Natsudaidai* (Japanese summer orange), corresponded to formula $C_{19}H_{22}O_3$ and was proved to be umbelliferone-7-geranyl ether, instead of heptyl ether, $C_{16}H_{20}O_3$, as considered by Komatsu and Tanaka. We have obtained umbelliferone and geraniol (identified as geranyl diphenyl urethane, m.p. 82~83°) by heating auraptene in acetic acid solution. Synthetic umbelliferone-7-geranyl ether was proved to be identical with auraptene.

(Received March 24, 1953)

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29. **Kyosuke Tsuda, Nobuo Ikekawa, Hiroshi Mishima, Akira Iino, and Tomoo Morishige:** Studies on the Coal Tar Bases. I. Synthesis of Tetramethylpyridine.

(*Pharmaceutical Institute, Medical Faculty, University of Kyushu**)

It has hitherto been reported that all the polymethylpyridines except 3,4,5-trimethylpyridine and pentamethylpyridine exist in the coal tar bases. In many cases, the structures of these pyridines are presumed from that of pyridine-polycarboxylic acids derived by oxidation. However, the determination of the configuration of alkyl radicals of pyridine only by the properties of those polycarboxylic acids has proved inaccurate since the constants of alkylpyridines differ from those given in some references.

During studies on coal tar bases as described in the present paper, it became necessary to synthesize polymethylpyridines, the samples of which could be compared with those isolated from coal tar and an attempt was made to obtain polymethylpyridines.

Only one of the tetramethylpyridines has been synthesized. Oparina[1] obtained a series of methyl homologs of pyridine, by passing a mixture of methyl ethyl ketone, formaldehyde, and ammonia over heated alumina, from which 2,3,5,6,-tetramethylpyridine was isolated. For obtaining a pure sample, we found a better process of synthesis.

2,3,5,6,-Tetramethylpyridine. Recently, Karrer and Mainoni[2] prepared pentamethylpyridine from 3,5-dicarbethoxy-2,4,6,-trimethylpyridine and, by utilizing this principle, 2,3,5,6,-tetramethylpyridine was synthesized. 2,6-Dimethyl-3,5-dicarbethoxypyridine (I)[3], prepared by the Hantzsch cyclization using ammonia, acetoacetic ester, and formaldehyde, was reduced with lithium aluminum hydride to the dicarbinol (II), derived to the dichloride (III) by chlorination, and finally to 2,3,5,6,-tetramethylpyridine (IV) by catalytic reduction.

2,3,5,6-Tetramethylpyridine thereby obtained was a prismatic crystals, m.p. 76°, b.p. 198°, giving a picrate of m.p. 173.5°. These constants coincide with those in the literature. Chloroplatinate, yellow needles, m.p. 179°, mercuric chloride salt, colorless needles, m.p. 170°. This compound (IV) was found to be identical with the tetramethylpyridine, m.p. 76°, which was separated from a fraction of $b.p_{100}$ 130~132°, from coal tar bases

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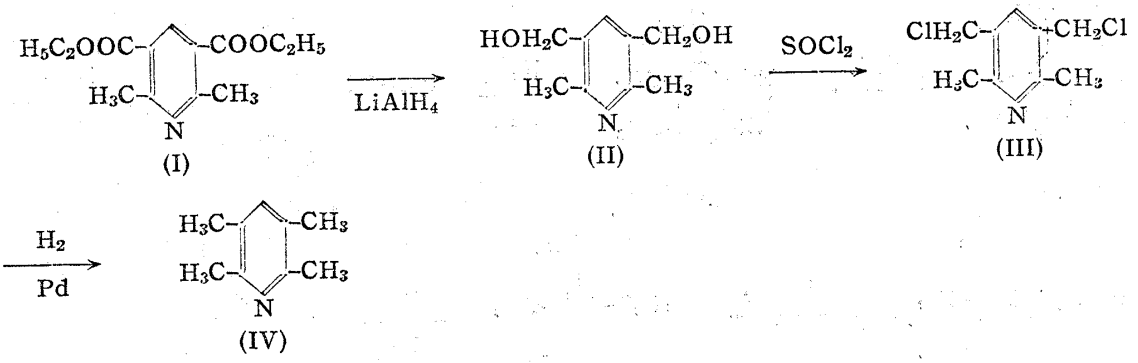
[1] M. P. Oparina: Ber., 64, 569 (1931); C. A., 44, 1108 (1950).

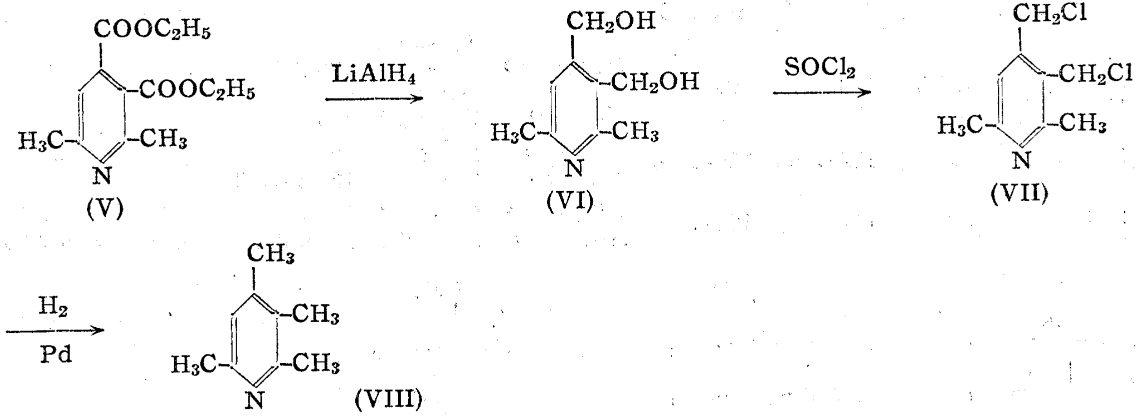
[2] P. Karrer, S. Mainoni: Helv. Chim. Acta, 34, 2151 (1951).

[3] A. Hantzsch: Ann., 215, 1 (1882); Ber., 18, 1744 (1885); F. Erglemann: Ann., 231, 50 (1885); L. Claisen: *Ibid.*, 297, 39 (1897).

by Nisbet and Pryde[4], the mixed melting point showing no depression and the comparison of infrared absorption spectrograms of these compounds[5] confirmed this evidence.



2,3,4,6-Tetramethylpyridine. Jones and Kornfeld[6] prepared 2,6-dimethyl-3,4-dihydroxymethylpyridine (VI) by the reduction of 2,6-dimethyl-3,4-dicarbethoxypyridine (V)[7] with lithium aluminum hydride. 2,3,4,6-Tetramethylpyridine (VIII) was obtained in the present experiments by the catalytic reduction of the dichloride (VII), which was formed by chlorination of (VI). 2,3,4,6-Tetramethylpyridine came as a colorless liquid, b.p. 203~204°, which gave a picrate of yellow needles, m.p. 122°, and was found to be identical with m.p. 122~123° of 2,3,4,6-tetramethylpyridine picrate obtained from the fraction of b.p$_{100}$ 135~135.2° of coal tar bases by Nisbet and Pryde[8]. This compound gave a mercuric chloride salt of colorless needles, m.p. 152~153°, and a chloroplatinate of yellow needles, m.p. 105~106°.



2,3,4,5-Tetramethylpyridine. Guareschi[9] obtained 5-cyano-2,3,4-trimethyl-6-pyridone (IX) from methylacetylacetone, cyanoacetic ester, and ammonia. In the present case, (IX) was derived to 6-chloro-5-cyano-2,3,4-trimethylpyridine (X) by chlorination and led to 5-aminomethyl-2,3,4-trimethylpyridine (XI) by simultaneous dehalogenation and reduction of the nitrile through catalytic hydrogenation with Pd-CaCO$_3$. (XI) was derived to the carbinol (XII) by diazotization. After the chlorination of (XII), 2,3,4,5-tetramethylpyridine was obtained by hydrogenation of (XIII), as colorless liquid, b.p. 218°, giving a picrate of yellow needles, m.p. 166°, chloroplatinate of yellow needles, m.p. 153~155°, and mercuric chloride salt of colorless needles, m.p. 141°. The picrate of 2,3,4,5-tetramethylpyridine (XIV), obtained from the fraction of b.p. 220~230° from coal tar bases by Ahrens[10] melts at 170~172°

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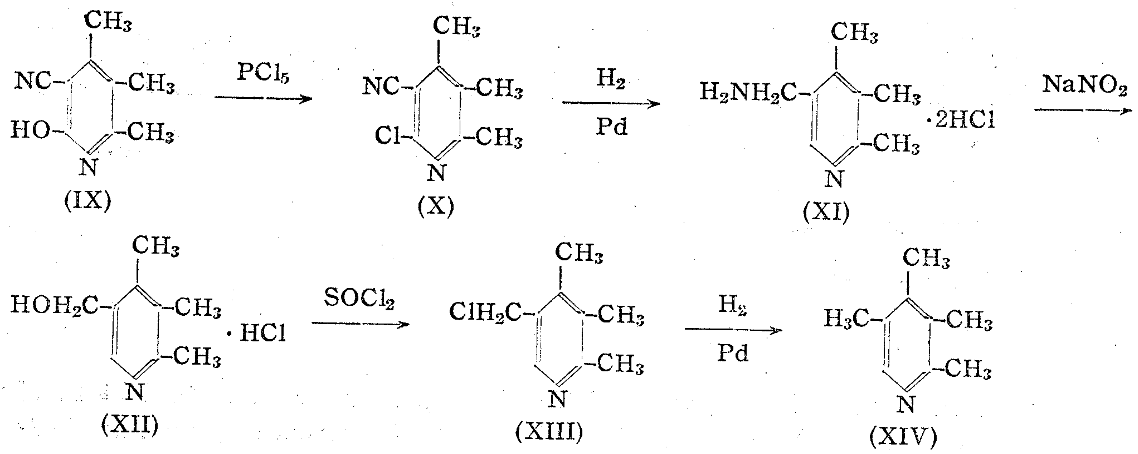
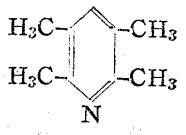
4) H.B. Nisbet and A.M. Pryde: Nature, **167**, 863 (1951). The authors are indebted to Prof. H.B. Nisbet of Heriot-Watt College for the sample of 2,3,5,6,-tetramethylpyridine from coal tar.
5) Cf. This Bulletin, **1**, 146 (1953). 6) R.G. Jones, E.C. Kornfeld: J. Am. Chem. Soc., **73**, 107 (1951).
7) J.N. Collie: Ann., **226**, 294 (1884); O.S. Mumm, H. Hüneke: Ber., **50**, 1568 (1917).
8) H.B. Nisbet, A.M. Pryde: Nature, **168**, 832 (1951).
9) I. Guareschi: Chem. Zentr., **70**, I 289 (1899). 10) F.B. Ahrens: Ber., **28**, 795 (1895).

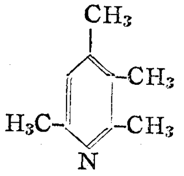
and is not identical with the one obtained by us. According to the synthetic process, the base obtained by us should be a pure product.

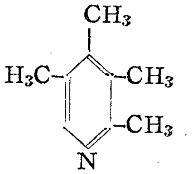


Infrared absorption spectrograms of tetramethylpyridines will be described in the following reports[5]. The physical constants of these bases and those hitherto reported are as follows:

	Present Authors'				Literature				
	b.p.°C	Picrate m.p.°C	$HgCl_2$ salt m.p.°C	Chloroplatinate m.p.°C		b.p.°C	Picrate m.p.°C	$HgCl_2$ salt m.p.°C	Chloroplatinate m.p.°C
I	198 76 (m.p.)	173.5	170	179	Oparina[a]	197∼198 81∼82 (m.p.)	173.5	—	—
					Nisbet[b]	76 (m.p.)	176	—	—
II	203∼204	122	152∼153	105∼106	Eguchi[c]	203.3	107	—	—
					Nisbet[d]	203	122.5∼123	—	—
III	218	166	141	153∼155	Dürkopf[e]	216∼217	—	—	—
					Ahrens[f]	232∼234	170∼172	156	209∼210


(I)


(II)


(III)

a) M. P. Oparina: J. Gen. Chem., 19, 1351(1949); C. A., 44, 1108(1950), from methyl ethyl ketone, formaldehyde, and ammonia.
b) H. B. Nisbet, A. M. Pryde: Nature, 167, 862(1951), from coal tar.
c) T. Eguchi: Bull. Chem. Soc. Japan, 3, 235(1928), from shale tar.
d) H. B. Nisbet, A. M. Pryde: Nature, 168, 832(1951), from coal tar.
e) E. Dürkopf, H. Göttsch: Ber., 23, 685, 1110(1890), from propionaldehyde and propionaldehyde ammonia.
f) F. B. Ahrens: Ber., 28, 795(1895), from coal tar.

This work was supported by the Grant from the Ministry of Welfare, for which the authors hereby express gratitude.

Experimental

2,6-Dimethyl-3,5-dihydroxymethylpyridine (II) — A solution of 3 g. of lithium aluminum hydride in 150 cc. of anhydrous ether was stirred and a solution of 15 g. of 2,6-dimethyl-3,5-dicarbethoxypyridine[3] was added during a period of 1 hour. The solution containing a solid, which precipitated instantly with addition of (I), was boiled on a water bath during 1 hour and water was added until the yellow color was decolorized. Hydrolysis was effected by the addition of water, and the precipitate of inorganic salts and the product was filtered. The precipitate was extracted with hot methanol and the evaporation of methanol yielded 2,6-dimethyl-3,5-dihydroxymethylpyridine which was recrystallized readily from water as colorless plates, m.p. 138°. Yield, 4.6 g. (47%). Recovery, 3.1 g. (20%). *Anal.* Calcd. for $C_9H_{13}O_2N$ (2,6-Dimethyl-3,5-dihydroxymethylpyridine): N, 8.4. Found: N, 8.39.

2,6-Dimethyl-3,5-dichloromethylpyridine (III)—Addition of 1.5 g. of 2,6-dimethyl-3,5-dihydroxymethylpyridine, little by little, into 10 g. of freshly distilled thionyl chloride, while chilled in pack ice, resulted in solution of the above alcohol accompanied with generation of heat. The reaction mixture was refluxed on a water bath for 1 hour and the excess thionyl chloride was evaporated in vacuum. A small amount of ice water was added carefully to the yellow residue in the flask, in pack ice, and the mixture was made alkaline by sodium hydroxide. The white precipitate thereby obtained was extracted with ether, the ethereal solution dried over sodium sulfate, and the evaporation of ether yielded 2,6-dimethyl-3,5-dichloromethylpyridine (III) as colorless needles, m.p. 107°, recrystallized from petroleum ether. Yield, 1.6 g. (90%). *Anal.* Calcd. for $C_9H_{11}NCl$ (2,6-Dimethyl-3,5-dichloromethylpyridine): N, 7.60. Found: N, 7.25.

2,3,5,6-Tetramethylpyridine (IV)—A mixture of 1.5 g. of 2,6-dimethyl-3,5-dichloromethylpyridine in 20 cc. of methanol and Pd-$CaCO_3$ (Pd: 5%) was shaken in hydrogen stream and the reaction mixture was worked up as usual. The absorption of hydrogen was 320 cc. (99% of the theoretical amount). The product, b.p. 198°, was recrystallized from petroleum ether as colorless prisms, m.p. 76°. Yield, 0.85 g. (93%). *Anal.* Calcd. for $C_9H_{13}N$ (2,3,5,6-Tetramethylpyridine): C, 80.00; H, 9.63; N, 10.37. Found: C, 79.69; H, 9.39; N, 10.63. Picrate, yellow needles, m.p. 173.5°. *Anal.* Calcd. for $C_9H_{13}N \cdot C_6H_3O_7N_3$ (2,3,5,6-Tetramethylpyridine picrate): C, 49.45; H, 4.39; N, 15.38. Found: C, 49.11; H, 4.33; N, 15.38. Mercuric chloride double salt, colorless needles, m.p. 170°. *Anal.* Calcd. for $C_9H_{13}N \cdot HCl \cdot HgCl_2$: N, 3.16. Found: N, 3.49. Chloroplatinate, yellow needles, m.p. 179°.

2,6-Dimethyl-3,4-dichloromethylpyridine (VII) — 1.1 g. of 2,6-dimethyl-3,4-dihydroxymethylpyridine (VI) was derived to 1 g. of 2,6-dimethyl-3,4-dichloromethylpyridine (VII) by means of 4.5 g. of thionyl chloride by the same process as for (III), as a colorless liquid. Yield, 82%. Picrate, yellow prisms, m.p. 126°. *Anal.* Calcd. for $C_9H_{11}NCl_2 \cdot C_6H_3O_7N_3$ (2,6-Dimethyl-3,4-dichloromethylpyridine picrate): N, 12.99. Found: N, 13.28.

2,3,4,6-Tetramethylpyridine (VIII)—By catalytic reduction using Pd-$CaCO_3$ (Pd: 5%) as a catalyst, 0.5 g. of 2,3,4,6-tetramethylpyridine was obtained from 1 g. of 2,6-dimethyl-3,4-dichloromethylpyridine. Absorption of hydrogen: 224 cc. Yield, 76%, of liquid, b.p. 203∼204°. Picrate, yellow needles from methanol, m.p. 122°. *Anal.* Calcd. for $C_9H_{13}N \cdot C_6H_3O_7N_3$ (2,3,4,6-Tetramethylpyridine picrate): C, 49.45; H, 4.39; N, 15.38. Found: C, 49.45; H, 3.95; N, 15.28. Mercuric chloride salt, colorless needles, m.p. 152∼153°. *Anal.* Calcd. for $C_9H_{13}N \cdot HCl \cdot HgCl_2$: N, 3.16. Found: N, 3.19. Chloroplantinate, yellow needles, m.p. 105∼106°.

6-Chloro-5-cyano-2,3,4-trimethylpyridine (X)—After a mixture of 10 g. of 5-cyano-6-hydroxy-2,3,4-trimethylpyridine[9] (IX) and 14 g. of phosphorus pentachloride was heated at 120° in an oil bath until evolution of hydrogen chloride ceased, it was refluxed mildly at 175∼180° for 2.5 hours, and then phosphoryl chloride was distilled in vacuum. The residue was poured into ice-water, the solution was made alkaline by sodium hydroxide, and extracted with ether. The ether after being dried, was distilled off. Colorless needles from ether, m.p. 99°. Yield, 9 g. (81%). *Anal.* Calcd. for $C_9H_9N_2Cl$ (6-Chloro-5-cyano-2,3,4-trimethylpyridine): C, 59.83; H, 4.98; N, 15.50. Found: C, 59.55; H, 5.08; N, 15.35.

5-Aminomethyl-2,3,4-trimethylpyridine dihydrochloride (XI)—A mixture of 3.5 g. of 6-chloro-5-cyano-2,3,4-trimethylpyridine (X) in 50 cc. of methanol and 1 g. of Pd-$CaCO_3$ (Pd: 30%) was shaken in hydrogen stream. Absorption of hydrogen was 1365 cc. at 17° (theoretical volume: 1301 cc.). during about 20 hours. After the filtration of the catalyst, methanol was distilled, and the residue melted at ca. 260°. The product recrystallized from absolute alcohol to crystals of m.p. 265°. Yield, 2.7 g. (62.8%). *Anal.* Calcd. for $C_9H_{16}N_2Cl_2$ (5-Aminomethyl-2,3,4-trimethylpyridine dihydrochloride): C, 48.43; H, 7.17. Found: C, 47.96; H, 7.14.

5-Hydroxymethyl-2,3,4-trimethylpyridine hydrochloride (XII)—120 cc. of 10% hydrochloric acid was added to 2.7 g. of the amine described above and the mixture was heated on a water bath. Under vigorous stirring, 4.8 g. of $NaNO_2$ dissolved in 10 cc. of water was added dropwise. The reaction mixture was kept at 90∼95° for 1 hour. The residue, dried in vacuum, was extracted with alcohol three times. By distillation of alcohol, 1.9 g. of a solid substance was obtained which was recrystallized to white prisms, m.p. 225°. Yield, 83.7%. *Anal.* Calcd. for $C_9H_{14}NOCl$ (5-Hydroxymethyl-2,3,4-trimethylpyridine hydrochloride): N, 7.46. Found: N, 7.36.

5-Chloromethyl-2,3,4-trimethylpyridine (XIII) — This chlorination was effected by the same procedure as for (III) or (VII). 1.9 g. of (XII) was derived to 1.2 g. of (XIII) as colorless needles, m.p. 66°. Yield, 70%. *Anal.* Calcd. for $C_9H_{12}NCl \cdot H_2O$ (5-Chloromethyl-2,3,4-trimethylpyridine hydrate): N, 7.45. Found: N, 7.35.

2,3,4,5-Tetramethylpyridine (XIV)—3.5 g. of the chloromethyl compound (XIII) in 150 cc. of methanol was reduced in hydrogen stream with 1 g. of Pd-$CaCO_3$ (Pd: 5%) as a catalyst. The absorption of hydrogen, 480 cc. (theoretical volume: 497 cc.). The product was a colorless liquid, b.p. 218°. Yield, 2.5 g. (83%). Picrate, yellow needles, m.p. 166°. *Anal.* Calcd. for $C_9H_{13}N \cdot C_6H_3O_7N_3$ (2,3,4,5-Tetramethylpyridine picrate): C, 49.45; H, 4.39; N, 15.38. Found: C, 49.75; H, 4.74; N, 15.72. Mercuric chloride salt, colorless needles, m.p. 141°. *Anal.* Calcd. for $C_9H_{13}N \cdot HCl \cdot HgCl_2$: N, 3.16. Found: N, 3.01. Chloroplatinate, yellow needles, m.p. 153~154°.

Summary

2,3,4,5-, 2,3,4,6-, and 2,3,5,6-Tetramethylpyridines were synthesised for the purpose of comparing these compounds with polymethylpyridines found in coal tar bases.

(Received March 27, 1953)

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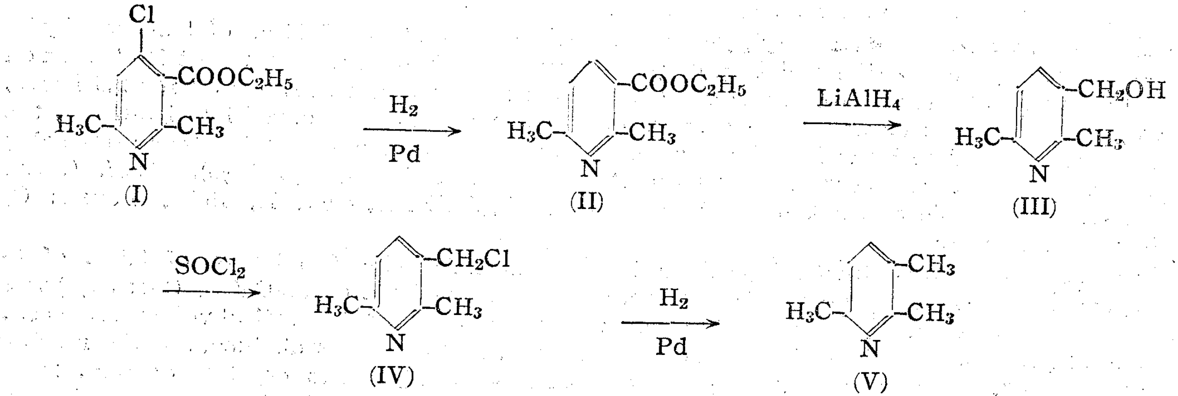
30. Kyousuke Tsuda, Nobuo Ikekawa, Akira Iino, Minoru Furukawa, and Tetsuyasu Hattori: Studies on Coal Tar Bases. II[1]. Synthesis of Trimethylpyridines (1).

(*Pharmaceutical Institute, Medical Faculty, University of Kyushu**)

Having the same object as for the previous report[2], four trimethylpyridines were prepared with the exception of 2,4,6- and 3,4,5-trimethylpyridine. There are some references to the synthesis of 2,4,6-[3], 2,3,4-[4~6], and 2,3,6-trimethylpyridine[4], but the others have not been synthesized as yet.

2,3,6-Trimethylpyridine—3-Carbethoxy-2,6-dimethylpyridine (II), prepared by catalytic reduction of 3-carbethoxy-4-chloro-2,6-dimethylpyridine (I)[7], was reduced by lithium aluminum hydride to 3-hydroxymethyl compound (III), and derived to 2,3,6-trimethylpyridine (V) by chlorination and catalytic reduction, as a liquid of b.p. 173°. Picrate, yellow needles, m.p. 144.5~145.5°; mercuric chloride salt, m.p. 105~106°; chloroplatinate, m.p. 136~137°.



2,3,5-Trimethylpyridine—Errera[8] synthesized 2,5-dimethylpyridine via 3-carbethoxy-2,5-dimethyl-6-hydroxypyridine (VI)**. By the chlorination and catalytic reduction of (VI),

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[1,2] This Bulletin, **1**, 122 (1953).

[3] A. Hantzsch: Ann., **215**, 1 (1882); Ber., **18**, 1744 (1885).

[4] M. P. Oparina: Ber., **64**, 569 (1931).

[5] I. Guareschi: Chem. Zentr., **70**, I, 289 (1899).

[6] R. L. Frank, R. P. Seven: J. Am. Chem. Soc., **71**, 2629 (1949).

[7] A. Michaelis: Ann., **366**, 324 (1909).

[8] G. Errera: Ber., **34**, 111, 3691 (1901).

** This compound was obtained by cyclization of cyanopropionic amide and ethoxymethyleneacetoacetic ester, with conc. hydrochloric acid, in 22% yield.