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74. **Kyosuke Tsuda, Yoshinobu Satoh, and Seitaro Saeki:** The Migration of Benzyl Group from Nitrogen to the Carbon in the Methyl Group of α- and γ-Picolines.

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Some time ago, Tsuda and Hayatsu reported[1] on the thermal reaction of N-cholestenylpyridinium (α- and γ-picolinium) tosylate. In the case of N-cholestenyl-γ-picolinium tosylate, 3(β)-cholestenyl-(γ-pyridyl)-methane is formed with comparative ease, showing that the cholestenyl group migrates from nuclear nitrogen to the carbon in the γ-methyl group. The same phenomenon was also witnessed with α-picoline. The existing literatures have shown such transition reactions to take place in alkyl halides of pyridine[2], β-ethylpyridine[3], and γ-picoline[4], in which the alkyl group migrated from the nuclear nitrogen to the nuclear carbon at 2- or 4-position by the simple heating or in a better yield by the use of a copper catalyst in heating. However, migration of the alkyl group from nuclear nitrogen to the methyl carbon, as described above, is a new observation and the authors examined the reaction with benzyl group, in place of the cholestenyl group, to see if such a phenomenon would occur.

In the present series of experiments, pyridine, α-, β-, and γ-picolines, 2,4-lutidine, and 2,6-lutidine were used as the pyridines. The chief reaction products obtained by heating the benzyl chloride salt of these pyridines, with the addition of a copper catalyst, were invariably the monobenzyl compounds formed by the migration of the benzyl group to the 2- or 4-position of pyridine nucleus. However, all of the products were accompanied by a by-product of a dibenzyl compound which, except in the case of pyridine and β-picoline, possessed the benzyl groups in both the nuclear and methyl carbons. Formation of such a dibenzyl compound indicates that this reaction is not only intramolecular but is also intermolecular and therefore it cannot be taken solely as the rearrangement reaction. The only point that is clear from these results is the fact that the benzyl proup migrates from the nuclear nitrogen in pyridines to the nuclear or methyl carbon, either in a single molecule or between two molecules.

Reaction between pyridine and benzyl chloride has been reported comparatively recently[2b], and the structure of the two kinds of monobenzylpyridines thereby formed has been determined by a different synthetic route as 2-benzylpyridine (I) and 4-benzyl-

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1) K. Tsuda, R. Hayatsu: J. Pharm. Soc. Japan, **72**, 1303(1952) (C.A., **47**, 4892(1953)); This Bulletin, **1**, 40(1953).

2a) A. Ladenburg: Ber., **16**, 1410(1883); *ibid.*, 32, 42(1899); A. E. Tschitschibabin: Chem. Zentr., **1916**, II, 146.

2b) Julius V. Braun: Ber., **64**, 1871(1931); La Forge: J. Am. Chem. Soc., **50**, 2484(1928); K. E. Crook: *Ibid.*, **70**, 416(1948); A. J. Nunn, *et al.*: J. Chem. Soc., **1952**, 583.

3) E. Kōnig, *et al.*: Ber., **58**, 195(1925).

4) A. E. Tschitschibabin: Chem. Zentr., **1924**, I, 912.

pyridine (II). A kind of dibenzylpyridine and a minute amount of tribenzylpyridine were isolated in the present experiments and the structure of the former was determined by the following manner.

The oxidation of this dibenzyl compound gives a dibenzoyl compound of m.p. 89∼90°, which is identical with 2,4-dibenzoylpyridine (IIIa) obtained by the oxidation of 2,4-dibenzylpyridine (III) formed by the reaction of (I) or (II) with benzyl chloride. This will indicate that the original dibenzyl compound is 2,4-dibenzylpyridine (III). Reaction of (I) and benzyl chloride also yields 2,6-dibenzylpyridine as well as (III) but the former cannot be obtained by the reaction of pyridine and benzyl chloride. The minute amount of the tribenzyl compound mentioned above was assumed from the formation of tribenzoylpyridine, m.p. 155∼156°, by oxidation and the position of the benzyl group has not been confirmed as yet, although it must be 2,4,6-tribenzylpyridine. The course of these reactions are shown in Fig. 1. The yield of these reactions are about 50% with 20% recovery of pyridine.

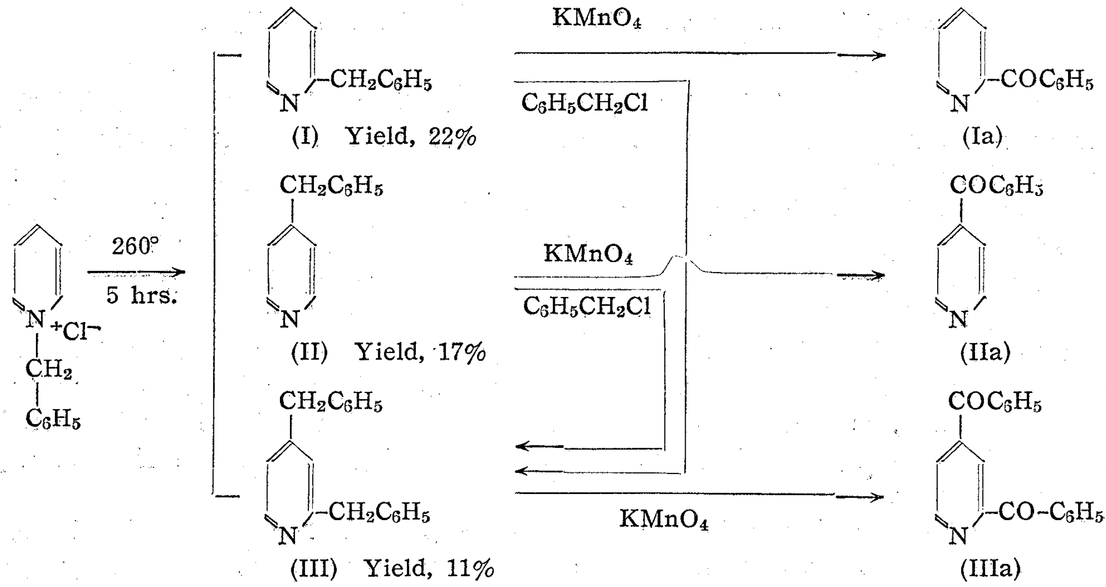
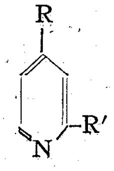


Fig. 1.

TABLE I. Thermal Reaction Product of N-Benzylpyridinium Chloride and the Oxidation Product



Product		Picrate	Other Derivatives
(I) R=H R′=$CH_2C_6H_5$	Oil	m.p. 140∼142°[a]	Meconate[b], m.p. 146∼147°
(Ia) R=H R′=COC_6H_5	Oil	m.p. 127∼128° Calcd. for $C_{18}H_{12}O_8N_4$: N, 13.60 Found: N, 14.02	Oxime[c], m.p. 157∼160°
(II) R=$CH_2C_6H_5$ R′=H	Oil	m.p. 140∼142°[a]	——
(IIa) R=COC_6H_5 R′=H	Plate cryst.[e] m.p. 70∼71°	m.p. 159∼160°[a] Calcd. for $C_{18}H_{12}O_8N_4$: N, 13.60 Found: N, 13.84	Oxime[d], m.p. 179∼181°
(III) R=R′= $CH_2C_6H_5$	Oil	Oil	——
(IIIa) R=R′= COC_6H_5	Plate cryst.[f] m.p. 89∼90°	——	2,4-Dinitrophenylhydrazone, m.p. 241∼243°

a) cf. Footnote 2b).
b) From MeOH. Calcd. for $C_{18}H_{14}O_6N$: C, 60.2; H, 4.47; N, 3.88. Found: C, 59.52; H, 4.19; N, 3.89.
c) From EtOH. Calcd. for $C_{12}H_{10}ON_2$: N, 14.10. Found: N, 14.88.
d) From EtOH+benzene. Calcd. for $C_{12}H_{10}ON_2$: N, 14.10. Found: N, 14.47.
e) From petroleum ether. Calcd. for $C_{12}H_9ON$: N, 7.60. Found: N, 7.82.
f) From benzene+petroleum ether. Calcd. for $C_{19}H_{13}O_2N$: N, 4.87. Found: 5.26.

The same results are obtained whether an equimolar mixture of α-picoline and benzyl chloride is heated with the addition of a copper catalyst, or the salt, m.p. 99∼100°, of these is heated with the copper catalyst.

Fractional distillation of the reaction product gives three fractions of an entity, A, B, and C, whose respective yields are 27, 12, and 3.8%, making a total of 42.8%, with 20% recovery of α-picoline. Oxidation of Fraction A with potassium permanganate gives benzoylpyridine-monocarboxylic acid of m.p. 141∼142° whose heating with copper dust, under a reduced pressure, yields 4-benzoylpyridine (IIa), m.p. 71°. Fraction A is, therefore, 4-benzyl-2-methylpyridine (IV) while the benzoyl-monocarboxylic acid, m.p. 142°, is 4-benzoylpyridine-2-carboxylic acid (IVb). 4-Benzoyl-2-methylpyridine (IVa) is formed as a by-product during the oxidation, which shows that the benzyl group in the pyridine nucleus is oxidized before the methyl group.

Fraction B yields benzoylpyridine-monocarboxylic acid, m.p. 136∼137°, by oxidation, whose decarboxylation gives 2-benzoylpyridine (Ia). This shows that Fraction B is 6-benzyl-2-methylpyridine (V) and the carboxylic acid of m.p. 137° is 6-benzoylpyridine-2-carboxylic acid (Va).

Oxidation of the Fraction C gives the carboxylic acid (IVb) of m.p. 141∼142° and the corresponding amount of benzoic acid from which C should correspond to 4-benzyl-2-phenethylpyridine (VI) and the fact was confirmed by the synthesis of (VI) by a different

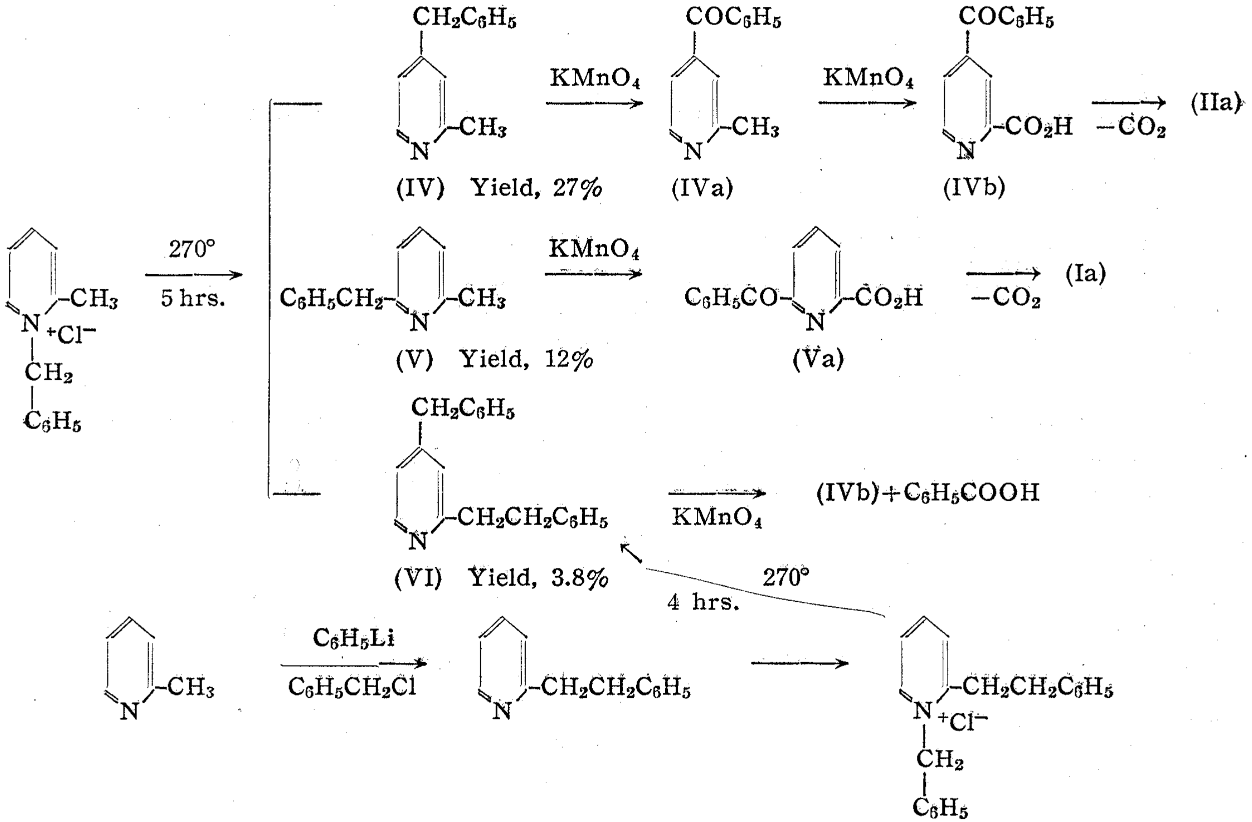
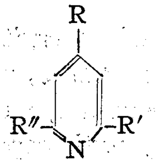


Fig. 2.

route. α-Picolinium lithium[5] obtained from α-picoline and phenyl lithium was reacted with benzyl chloride to form α-phenethylpyridine (VII), which was heated with benzyl chloride at 270° and (VI) was obtained. The mixed fusion of the respective meconates, m.p. 165~167°, confirmed their identity. This reaction route is shown in Fig. 2 and the data of the derivatives of reaction products are shown in Table II.

TABLE II. Thermal Reaction Product of N-Benzyl-α-picolinium Chloride and the Oxidation Product



	Product		Picrate	Other Derivatives
(IV)	$R=CH_2C_6H_5$ $R'=CH_3$ $R''=H$	Oil	m.p. 140~142°(EtOH) Calcd. for $C_{19}H_{16}O_7N_4$: N, 13.61. Found: N, 13.60	Meconate[a], m.p. 157~159°
(IVa)	$R=COC_6H_5$ $R'=CH_3$ $R''=H$	Oil	m.p. 169~171°(EtOH) Calcd. for $C_{19}H_{14}O_8N_4$: N, 13.07. Found: N, 13.30	——
(IVb)	$R=COC_6H_5$ $R'=COOH$ $R''=H$	Needle cryst.[b] m.p. 141~142°	——	Phenylhydrazone, m.p. 188~189°
(V)	$R=H$ $R'=CH_3$ $R''=CH_2C_6H_5$	Oil	m.p. 114~115°(EtOH) Calcd. for $C_{19}H_{16}O_7N_4$: N, 13.61. Found: N, 13.78	——
(Va)	$R=H$ $R'=COOH$ $R''=COC_6H_5$	Cryst.[c] m.p. 135~137°	——	——
(VI)	$R=CH_2C_6H_5$ $R'=CH_2CH_2C_6H_5$ $R''=H$	Oil	Oil	Meconate[d], m.p. 165~167°

a) From MeOH. Calcd. for $C_{19}H_{17}O_6N \cdot H_2O$: N, 3.76. Found: N, 3.78.
b) From benzene. Calcd. for $C_{13}H_9O_3N$: N, 6.17. Found: N, 6.18.
c) From benzene. Calcd. for $C_{13}H_9O_3N$: N, 6.17. Found: N, 6.52.
d) From EtOH. Calcd. for $C_{26}H_{23}O_6N$: N, 3.15. Found: N, 3.32.

Thermal reaction of the benzyl chloride salt, m.p. 78~82°, of γ-picoline also proceeds in a similar manner as in the case of α-picoline and two kinds of products, A (monobenzyl compound) and B (dibenzyl compound), are obtained by fractional distillation. The yield is 37.5% of A, 2.7% of B, and about 20% recovery of γ-picoline. A and B can be further purified by distillation and recrystallization of their respective picrates. Decarboxylation of the carboxylic acid, m.p. 221~223°, obtained as the oxidation product of A, gives (Ia) from which it can be seen that A is 2-benzyl-4-methylpyridine (VIII) while the carboxylic acid is 2-benzoylpyridine-4-carboxylic acid (VIIIa). Oxidation of B with potassium permanganate gives approximately equal amounts of (VIIIa) and benzoic acid so that B must have the structure of 2-benzyl-4-phenethylpyridine. These reaction routes are shown in Fig. 3 and the data of derivatives in Table III.

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[5] Org. Syntheses, 29, 44(1949).

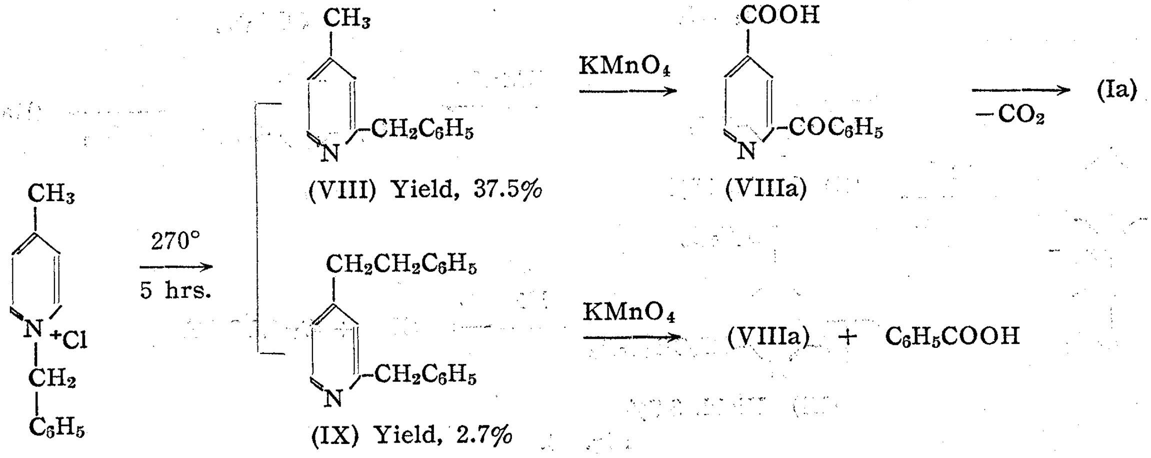
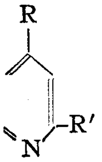


Fig. 3.

Table III. Thermal Reaction Product of N-Benzyl-γ-picolinium Chloride and the Oxidation Product



	Product		Picrate	Other Derivatives
(VIII)	$R=CH_3$ $R'=CH_2C_6H_5$	Oil	m.p. 148~150°(EtOH) Calcd. for $C_{19}H_{16}O_7N_4$: N, 13.61. Found: N, 13.57	—
(VIIIa)	$R=COOH$ $R'=COC_6H_5$	Needle cryst.[a)] m.p. 221~223°	—	Phenylhydrazone[b)], m.p. 215°
(IX)	$R=CH_2CH_2C_6H_5$ $R'=CH_2C_6H_5$	Oil	m.p. 177~178°(EtOH) Calcd. for $C_{26}H_{22}O_7N_4$: N, 11.15. Found: N, 11.48	—

a) From EtOH+ligroine. Calcd. for $C_{13}H_9O_3N$: N, 6.17. Found: N, 6.18.
b) Calcd. for $C_{19}H_{14}O_2N_3$: N, 13.30. Found: N, 13.79.

The 37.5% yield of the monobenzyl compound in this case is approximately the same as the total yield of 39% of the two kinds of monobenzyl compounds in the case of α-picoline and the 2~3% yield of the dibenzyl compound is also approximately the same. In both α- and γ-picolines, this dibenzyl compound is the one with one benzyl group substituted in the side-chain methyl.

Heating 2,6-lutidine and benzyl chloride at 160° results in the formation of a crystalline salt of m.p. 220°. By heating this salt, without isolating it, with copper dust for 6 hours with the final temperature at 240° and fractional distillation of the reaction product yields 15% of A (monobenzyl compound), 3.7% of B (dibenzyl compound), and 50% recovery of the original lutidine. Purification of both A and B as their picrates and permanganate oxidation of the respective bases give the dicarboxylic acid of m.p. 210°(decomp.) from A, whose decarboxylation yields (IIa). This proves A to be 4-benzyl-2,6-lutidine (X) and the dicarboxylic acid to be 4-benzoylpyridine-2,6-dicarboxylic acid (Xa). Oxidation of B gives the dicarboxylic acid (Xa) and benzoic acid from which it can be seen that B is 4-benzyl-2-methyl-6-phenethylpyridine (XI). The reaction route is shown in Fig. 4 and the data of the derivatives in Table IV.

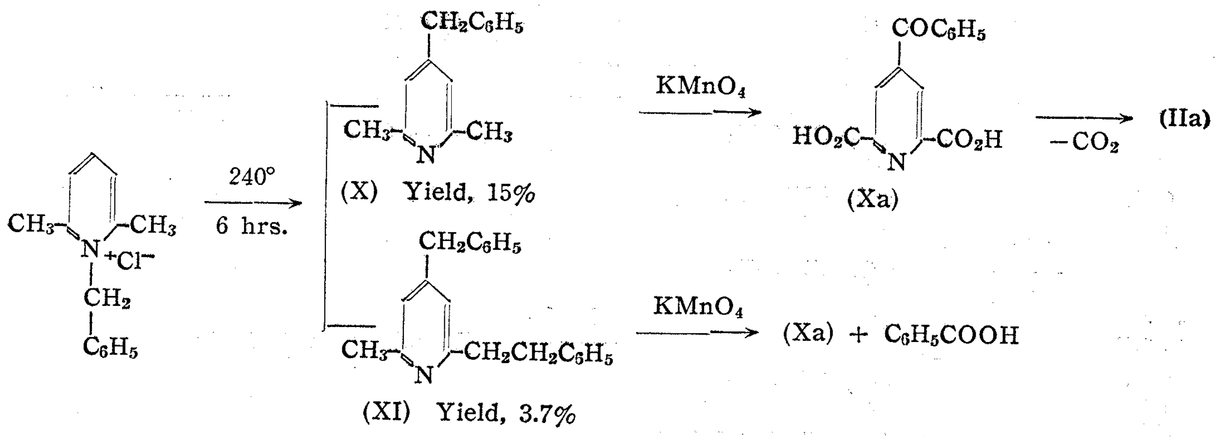
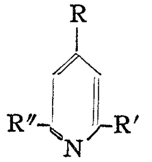


Fig. 4.

TABLE IV. Thermal Reaction Product of N-Benzyl-2,6-lutidinium Chloride and the Oxidation Product



	Product		Picrate
(X)	$R=CH_2C_6H_5$ $R'=R''=CH_3$	Oil	m.p. 140~142°(MeOH) Calcd. for $C_{20}H_{18}O_7N_4$: N, 13.1. Found: N, 13.21.
(Xa)	$R=COC_6H_5$ $R'=R''=COOH$	Needle cryst.[a] m.p. 210°(decomp.)	
(XI)	$R=CH_2C_6H_5$ $R'=CH_2CH_2C_6H_5$ $R''=CH_3$	Oil	m.p. 205°(MeOH) Calcd. for $C_{27}H_{24}O_7N_4$: N, 10.8. Found: N, 10.70.

a) From H_2O. Calcd. for $C_{14}H_9O_5N$: C, 62.0; H, 3.3; N, 5.2. Found: C, 62.20; H, 3.38; N, 5.20.

Heating of 2,4-lutidine and benzyl chloride at 180° results in the formation of an ammonium salt, m.p. 212°, which when heated with copper dust for 4 hours with the final temperature at 240° yields by fractional distillation of the reaction product a monobenzyl compound A and a dibenzyl compound B. Yield is 36% of A, 5% of B, and 27% re-

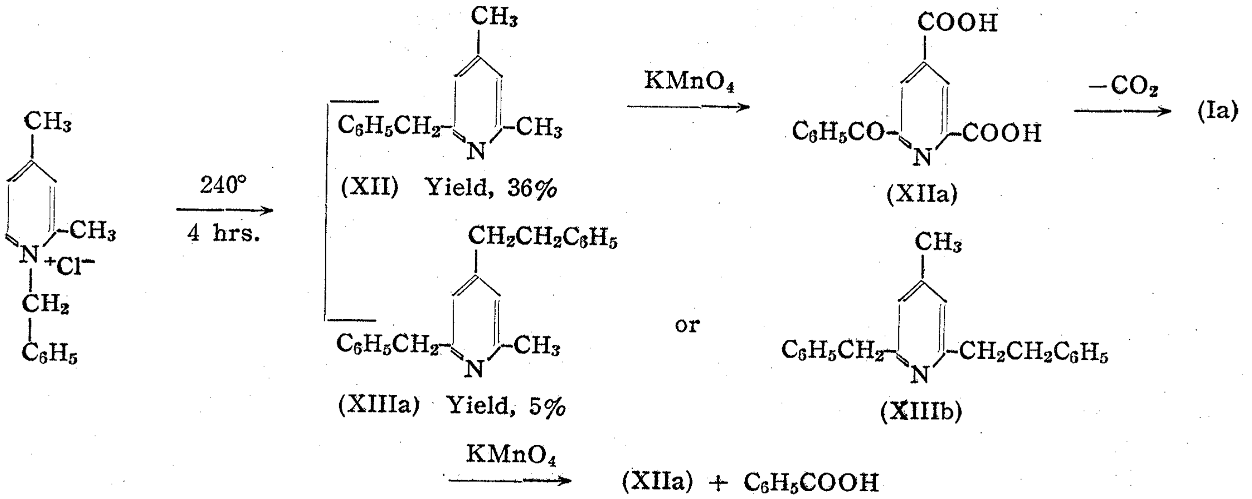
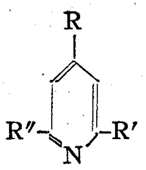


Fig. 5.

covery of the original lutidine. A and B are respectively purified as a picrate and a picrolonate. Permanganate oxidation of A yields the dicarboxylic acid of m.p. 203° whose decarboxylation gives (Ia), proving A to be 6-benzyl-2,4-lutidine (XII) and the dicarboxylic acid as 6-benzoylpyridine-2,4-dicarboxylic acid (XIIa). B gives by oxidation (XIIa) and benzoic acid that it should be either 6-benzyl-2-methyl-4-phenethylpyridine (XIIIa) or 6-benzyl-4-methyl-2-phenethylpyridine (XIIIb). This reaction route is shown in Fig. 5 and the data of the derivatives in Table V.

TABLE V. Thermal Reaction Product of N-Benzyl-2,4-lutidinium Chloride and the Oxidation Product



	Product		Derivatives
(XII)	$R=R'=CH_3$ $R''=CH_2C_6H_5$	Oil	Picrate: Yellow needles from MeOH, m.p. 150~152°. Calcd. for $C_{20}H_{18}O_7N_4$: N, 13.1. Found: N, 12.97
(XIIa)	$R=R'=COOH$ $R''=COC_6H_5$	Needle cryst. (1%HCl·H_2O), m.p. 203°. Calcd. for $C_{14}H_9O_5N$: N, 5.2. Found: N, 5.39.	
(XIIIa)	$R=CH_2CH_2C_6H_5$ $R'=CH_3$ $R''=CH_2C_6H_5$ or	Oil	Picrolonate: Yellow needles from EtOH, m.p. 248~250°. Calcd. for $C_{31}H_{29}O_5N_5$: C, 6.75; H, 5.26; N, 12.6. Found: C, 67.32; H, 5.04; N, 12.72
(XIIIb)	$R=CH_3$ $R'=CH_2CH_2C_6H_5$ $R''=CH_2C_6H_5$		

Heating of β-picoline and benzyl chloride at 180° results in the formation of an ammonium salt, m.p. 220°, which when heated, without isolation of the salt, with copper dust for five hours with the final temperature of 240°, with subsequent fractional distillation of the product yields low and high fractions. The lower fraction is a mixture of three isomeric monobenzyl compounds, A, B, and C, in respective yield of 18.5, 5.5, and 0.2%, which can be separated by the recrystallization of their picrates. The higher boiling fraction is an entity, the dibenzyl compound D, obtained in an yield of 6.8%. The recovery of β-picoline is 33%.

The monobenzyl compound A, that is formed in the largest amount, gives a carboxylic acid of m.p. 226° by oxidation with potassium permanganate, and decarboxylation of the acid yields (IIa) from which it can be seen that A is 4-benzyl-3-methylpyridine (XIV) and the carboxylic acid, 4-benzoylpyridine-3-carboxylic acid (XIVa).

Oxidation of the monobenzyl compound B gives a carboxylic acid of m.p. 167° whose decarboxylation yields (Ia), showing B to be 6-benzyl-3-methylpyridine (XV), while the carboxylic acid is 6-benzoylpyridine-3-carboxylic acid (XVa).

The monobenzyl compound C was assumed to be 2-benzyl-3-methylpyridine (XVI) because of the difficulty of deriving it to an oxidation product due to the small amount available and the assumption was proved correct by the synthesis of (XVI) by the method of Sperber, *et al.*[6] 2-Bromo-3-methylpyridine (XVIII) was derived to the 2-lithium compound (XIX), reacted with benzaldehyde, and the carbinol (XX) thereby formed was reduced with zinc after chlorination to (XVI). The picrate of the monobenzyl compound C and that of 2-benzyl-3-methylpyridine thus prepared were identical, melting at 133°.

The structure of the dibenzyl compound D was determined in the following way. Both (XIV) and (XV) give identical dibenzyl compound when each is heated with benzyl chloride at 250°, and the picrolonate, m.p. 197°, of this dibenzyl compound is identical with the picrolonate of D. This proves that D is 4,6-dibenzyl-3-methylpyridine (XVII).

Foregoing results show that in β-picoline, contrary to the case of α- and γ-picolines, the dibenzyl group does not enter the side-chain methyl and have further provided the evidence of the difference in the activity of 3-position and 2- and 4-positions in the pyridine nucleus.

The reaction routes for β-picoline are shown in Fig. 6 and the data of the derivatives in Table VI.

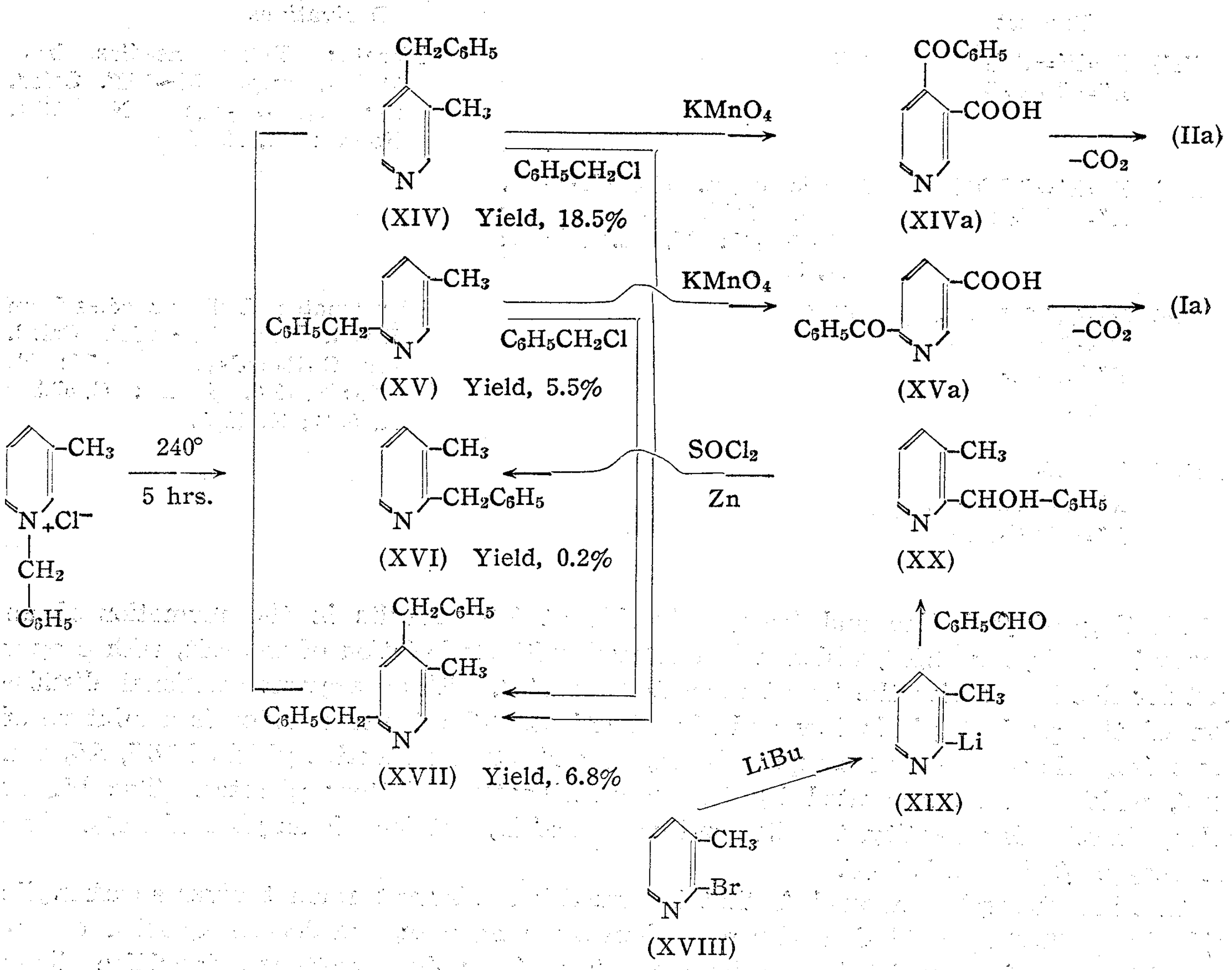


Fig. 6.

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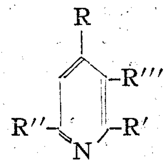
[6] N. Sperber, D. Papa, E. Schwerk, M. Sherlock: J. Am. Chem. Soc., 73, 3856(1951).

TABLE VI. Thermal Reaction Product of N-Benzyl-β-picolinium Chloride and the Oxidation Product



	Product		Derivative
(XIV)	$R=CH_2C_6H_5$ $R'=R''=H$ $R'''=CH_3$	Oil	Picrate: Yellow needles (MeOH), m.p. 156°. Calcd. for $C_{19}H_{16}O_7N_4$: N, 13.6. Found: N, 13.91.
(XIVa)	$R=COC_6H_5$ $R'=R''=H$ $R'''=COOH$	Needle cryst. (Et_2O), m.p. 226°. Calcd. for $C_{13}H_9O_3N$: N, 6.17. Found: N, 6.20	
(XV)	$R=R'=H$ $R''=CH_2C_6H_5$ $R'''=CH_3$	Oil	Picrate: Yellow needles (AcOEt), m.p. 125°. Calcd. for $C_{19}H_{16}O_7N_4$: N, 13.6. Found: N, 13.75.
(XVa)	$R=R'=H$ $R''=COC_6H_5$ $R'''=COOH$	Needle cryst. (H_2O), m.p. 167°. Calcd. for $C_{13}H_9O_3N$: N, 6.17. Found: N, 6.05.	
(XVI)	$R=R''=H$ $R'=CH_2C_6H_5$ $R'''=CH_3$	Oil	Picrate: Yellow prisms (AcOEt), m.p. 130~133°. Calcd. for $C_{19}H_{16}O_7N_4$: N, 13.6. Found: N, 13.49.
(XVII)	$R=R''=CH_2C_6H_5$ $R'=H$ $R'''=CH_3$	Oil	Picrolonate: Yellow needles (MeOH), m.p. 195~197°. Calcd. for $C_{30}H_{27}O_5N_5$: N, 13.0. Found: N, 13.31.

Experimental

Purification of β-Picoline—In accordance with the method of Ochiai and Ikehara[7], 100 g. of Yawata No. 4 Picoline (mfd. by Yawata Steel Works, Yawata) was dissolved in 320 cc. of glacial acetic acid, 143 cc. of 35% H_2O_2 added in small portions, and the mixture was heated at 80~90° for 12 hours. The whole was condensed to 200 cc. by low-pressure distillation of glacial acetic acid and made Na_2CO_3-alkaline. This was extracted with $CHCl_3$, dried with Na_2SO_4, and $CHCl_3$ removed by distillation. The residue crystallized on standing overnight, yielding 60 g. of γ-picoline 1-oxide as crystals. The filtrate obtained after the removal of these crystals was distilled under a reduced pressure and 20 g. of a fraction of b.p$_6$ 122~127° was obtained, giving a picrate, m.p. 135°, of β-picoline 1-oxide. A solution of 20 g. of β-picoline 1-oxide dissolved in 200 cc. of $CHCl_3$ was chilled to 0° to 5° and 60 g. of PCl_3 was dropped in during 4 hours. After allowing the mixture to stand for 3 hours, it was poured into ice water, alkalized with Na_2CO_3, and extracted with $CHCl_3$. The chloroform residue was distilled to give a fraction of b.p. 140~144° which formed a picrate, m.p. 149°, of β-picoline. To 16 g. of this β-picoline warmed to 80°, 18 g. of anhydrous oxalic acid was added and the oxalate crystals thereby formed was dissolved in 20 cc. of EtOH, and allowed to stand overnight. The crystals that separated out were recrystallized from EtOH to m.p. 119°. These crystals were dissolved in water, alkalized with 30% NaOH, and the oil that separated out was taken up in ether. Ethereal residue was distilled to give a fraction of b.p. 142~144°, providing 12 g. of the most pure β-picoline which was used for the experiments.

Purification of 2,4-Lutidine—In accordance with the method of Ochiai, *et al.*[8], 50 g. of Yawata Industrial 2,4-Lutidine (v.s.) was dissolved in 160 cc. of glacial acetic acid, 70 cc. of 35% H_2O_2 added in small lots, and the mixture was warmed at 80~90° for 12 hours. The 1-oxide thereby formed was fractionally distilled and 25 g. of b.p$_4$ 128~133° was obtained, giving a picrate,

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7) E. Ochiai, M. Ikehara: J. Pharm. Soc., Japan, 70, 265(1950).
8) E. Ochiai, *et al.*: *Ibid.*, 71, 1385(1951).

m.p. 140°, of 2,4-lutidine 1-oxide. A solution of 25 g. of this oxide dissolved in 250 cc. $CHCl_3$ was chilled to 0° to 5°, and 70 g. of PCl_3 was added in drops during 5 hours. After allowing the mixture to stand for 4 hours, the reaction mixture was poured into ice water, the base was separated, and fractionally distilled to give 20 g. of a fraction boiling at 157°. The base was derived to the picrate of m.p. 181°, dissolved in 10% NaOH with warming, and the oil that separated out was extracted with ether, giving 13 g. of 2,4-lutidine, b.p. 157°.

Purification of γ-Picoline, 2,6-Lutidine, α-Picoline, and Pyridine—γ-Picoline was obtained in the same manner as in the case of β-picoline 1-oxide, from the foregoing γ-picoline 1-oxide, m.p. 182°. This was derived to its oxalate, recrytsallized, and the liberated base was distilled before use.

Yawata 2,6-Lutidine (v.s.) was dissolved in dehydrated acetone, EtOH saturated with HCl gas was added, and the hydrochloride thereby obtained was recrystallized from EtOH. The liberated base was then distilled before use.

α-Picoline and pyridine were distilled with the Fenske column before use.

Reaction of Pyridines with Benzyl Chloride—An equimolar mixture of the foregoing pyridines and benzyl chloride, when heated at 100~180°, becomes cloudy, gradually separates into two layers, and then merges into a viscous, single layer, indicating the formation of a quaternary ammonium salt. The salts thereby formed show following m.ps.

N-Benzylpyridinium chloride, hygroscopic
N-Benzyl-α-picolinium chloride, m.p. 99~100°(acetone-EtOH)
N-Benzyl-β-picolinium chloride, m.p. 220°(acetone)
N-Benzyl-γ-picolinium chloride, m.p. 78~82°(acetone-EtOH)
N-Benzyl-2,4-lutidinium chloride, m.p. 212°(acetone)
N-Benzyl-2,6-lutidinium chloride, m.p. 220°(acetone)

The result is the same whether these salts are taken out and recrystallized or whether the thermal reaction product is used, *per se*, for the next reaction.

Copper bronze is added to the salt in 10% amount, and the temperature is gradually raised by which, as in the case of 2,6-lutidine, the mixture begins to reflux, or as in the case of 2,4-lutidine, the quaternary ammonium chloride sublimes. The bath temperature is raised to 240~270° by the end of the reaction, requiring about 5~7 hours.

After the reaction mixture is cool, it is poured into 10% HCl solution, the insoluble resinous matter removed, and the HCl-soluble base is separated. After liberation with NaOH, the separated oil is taken up in ether and ethereal residue is separated into the monobenzyl and dibenzyl compounds by fractional distillation. The boiling points and yields are shown in Table VII.

TABLE VII. Boiling Point and Yield of the Reaction Products of Pyridines and Benzyl Chloride

Original Material	Monobenzyl Compound	Dibenzyl Compound	Recovered Pyridines
Pyridine 25 g. $PhCH_2Cl$ 40 g.	b.p. 265~285° 18.2 g. (I, II)[a]	b.p$_9$ 200~230° 6.6 g. (III)	4.9 g.
α-Picoline 23 g. $PhCH_2Cl$ 32 g.	b.p. 265~270° 14.8 g. (IV) b.p. 272~275° 6.6 g. (V)	b.p$_6$ 216~218° 3.1 g. (VI)	5.0 g.
γ-Picoline 15 g. $PhCH_2Cl$ 21.5 g.	b.p. 270~275° 8.8 g. (VIII)	b.p. 300~320° 1.3 g. (IX)	3.2 g.
2,6-Lutidine 10 g. $PhCH_2Cl$ 12 g.	b.p. 240° 3 g. (X)	b.p$_4$ 200~230° 1 g. (X)	5.0 g.
2,4-Lutidine 15 g. $PhCH_2Cl$ 18 g.	b.p$_6$ 140~150° 10 g. (XII)	b.p$_6$ 200~240° 2 g. (XIIIa, b)	4.0 g.
β-Picoline 15 g. $PhCH_2Cl$ 21.5 g.	b.p$_6$ 135~160° 7 g. (XIV, XV, XVI)[b]	b.p$_6$ 207° 3 g. (XVII)	5.0 g.

a) Separation of (I) and (II) is possible by the fractional distillation and recrystallization of the picrate (cf. Footnote 2b) but the yield of each is more accurate when back-calculated from (Ia) and (IIa) isolated by the chromatography of the oxidation products (Ia and IIa).

b) The isolation of (XIV), (XV), and (XVI) is effected by the recrystallization of their respective picrates with subsequent liberation of the bases.

Permanganate Oxidation of the Monobenzyl and Dibenzyl Compounds—When the pyridine nucleus is substituted with phenethyl, methyl, or benzyl group, more time is required for oxidation with the increasing number of substituted groups. The foregoing groups are oxidized to COOH or COC_6H_5 but in general, the pyridine nucleus is resistant to oxidation and remains intact. However, when there are many substituents in the ring, oxidation requires a long period of time during which there is a possibility of the destruction of the pyridine nucleus.

In the case of one substituent (benzylpyridine, (I) and (II)) or two (dibenzylpyridine (III), benzylmethylpyridine (IV), (V), (VIII)), benzoylpyridine (Ia, IIa), dibenzoylpyridine (IIIa), and benzoylpyridine-carboxylic acid (IVb, Va, VIIIa) were obtained in a comparatively good yield. Therefore, benzoic acid was obtained for the first time by the oxidation of a compound substituted with the phenethyl group. For example, approximately equimolar amounts of benzoic acid and benzoylpyridine-carboxylic acid were obtained from benzylphenethylpyridine (VI, IX). When there were three substituents, such as in benzyldimethylpyridine (XII), a long period of time was required for the permanganate oxidation and benzoic acid was obtained as a by-product besides benzoylpyridine-dicarboxylic acid (XIIa). This benzoic acid was formed from the benzyl group by the destruction of the pyridine nucleus. In the case of benzylmethylphenethylpyridine (XI, XIIIa and b), the amount of benzoic acid formed was far larger than that of benzoylpyridine-dicarboxylic acid, showing the facile destruction of the pyridine nucleus.

2-Benzoylpyridine (Ia) and 4-Benzoylpyridine (IIa)—To a suspension of 7.5 g. of a mixture of benzylpyridines (I and II) in 300 cc. of water, while stirring on a water bath, 19 g. of $KMnO_4$ was added gradually. After about 6 hours, the oily product was extracted with benzene and 6.8 g. of the oxidation product was obtained. This product was passed through an alumina column as a benzene solution and eluted with benzene by which 2-benzoylpyridine (Ia) eluted out first and then 4-benzoylpyridine (IIa), giving 2.33 g. of (IIa), m.p. 70∼71°, and 3.17 g. of (Ia) as an oil. Yield, 66%.

2,4-Dibenzoylpyridine (IIIa) and 2,6-Dibenzoylpyridine—The oxidation was carried out as in the foregoing on 4.3 g. of 2,4-dibenzylpyridine (III) with 15 g. of $KMnO_4$, and 3 g. (63%) of (IIIa), m.p. 89∼90°, was obtained.

A mixture of 10 g. of 4-benzylpyridine (II) and 7.5 g. of benzyl chloride was heated to 150°, and the salt thereby formed was heated at 260° for 5 hours with copper bronze. The base was fractionally distilled from which 2.5 g. of the original base, b.p$_7$ 130∼138°, and 0.6 g. of b.p$_7$ 200∼210° were obtained. Oxidation of the latter with $KMnO_4$ gave 0.2 g. of crystals melting at 89∼90° which were identical with the above (IIIa).

A mixture of 10 g. of 2-benzylpyridine (I) and 7.5 g. of benzyl chloride was reacted in the same manner and fractional distillation of the product gave 2.5 g. of the recovered material, b.p$_8$ 130∼132°, and 0.7 g. of a fraction of b.p$_8$ 200∼210°. Permanganate oxidation of the latter gave 0.4 g. of crystals which, when recrystallized from EtOH, separated into crystals of m.p. 106∼108° and of m.p. 89∼90°. The latter was identical with (IIIa) so that the former must be 2,6-dibenzoylpyridine. *Anal.* Calcd. for $C_{19}H_{13}O_2N$(2,6-Dibenzoylpyridine): N, 4.87. Found: N, 4.99.

4-Benzoylpyridine-2-carboxylic Acid (IVb) and 6-Benzoylpyridine-2-carboxylic Acid (Va)—Oxidation was carried out as before on 3 g. of (IV) with 15 g. of $KMnO_4$ for 8 hours. After the removal of MnO_2, the filtrate was concentrated, and acidified with HCl. The crystals that separated out were extracted with benzene and 2 g. of white crystals, m.p. 141∼142°, were obtained. This substance (IVb) was mixed with about an equal amount of copper bronze and heated under a reduced pressure by which an oil distilled out. This oil furnished a picrate of m.p. 159∼160° which was identical with the picrate of (IIa). When the heating period during oxidation with $KMnO_4$ is shortened in this reaction, 4-benzoyl-2-methylpyridine (IVa) is obtained with (IVb).

Oxidation was carried out on 3 g. of (V) with 15 g. of $KMnO_4$ by warming for 10 hours, and the reaction mixture separated from MnO_2 was shaken with benzene to remove the small amount of oily substance that floated on the surface. The aqueous layer was concentrated, acidified with HCl, and extracted with ether from which 0.6 g. of white crystals were obtained. Recrystallization from benzene furnished crystals of m.p. 134∼137° which was derived to (Ia) by heating with copper bronze.

4-Benzyl-2-phenethylpyridine (VI) and Its Oxidation Reaction—α-Picolinium lithium5) was prepared from 18.7 g. of α-picoline, 2.8 g. of lithium, and 31.4 g. of bromobenzene, and by reacting 25.32 g. of benzyl chloride, 16.2 g. of oily α-phenethylpyridine (VII), b.p$_{45}$ 185∼190°, was obtained. A mixture of 14 g. of (VII), 10 g. of benzyl chloride, and copper bronze was heated at 260∼270° for 4 hours and 0.5 g. of oil, b.p$_{11}$ 220∼230°, was obtained. This substance and the dibenzyl compound obtained by the reaction of α-picoline and benzyl chloride both give identical meconate of m.p. 165∼167° and corresponds to formula (VI).

Oxidation of 1.1 g. of (VI) with 10 g. of $KMnO_4$ was carried out by heating for 15 hours by which the oily substance disappeared completely. After the removal of MnO_2, the filtrate was concentrated under a reduced pressure, acidified with HCl, and the precipitate extracted with ether.

from which 0.3 g. of crystals were obtained. The crystals were treated with a small amount of ether and 0.07 g. of benzoic acid was obtained from the soluble portion. The portion sparingly soluble in ether was recrystallized from benzene and furnished 0.15 g. of (IVb), m.p. 140~142°.

2-Benzoylpyridine-4-carboxylic Acid (VIIIa)—A suspension of 3 g. of (VIII) in 300 cc. of water was warmed on a water bath, 15 g. of $KMnO_4$ added gradually, and heated for 15 hours by which the oily substance that floated on the surface entirely disappeared. After the removal of MnO_2 by filtration, the filtrate was concentrated, acidified with HCl, and the crystals that precipitated out were recrystallized from a mixture of alcohol and ligroine to crystals of m.p. 221~223° (VIIIa). A mixture of (VIIIa) and copper bronze was heated under a reduced pressure and (Ia) was obtained.

Oxidation of 2-Benzyl-4-phenethylpyridine (IX)—Oxidation of 1.3 g. of (IX) with 12 g. of $KMnO_4$ required heating for 10 hours. By treating the reaction mixture as above, 1 g. of an acid portion was obtained which was recrystallized from a mixture of benzene and alcohol to 0.2 g. of (VIIIa), m.p. 221~223°, and 0.57 g. of benzoic acid.

4-Benzoylpyridine-2,6-dicarboxylic Acid (Xa)—A mixture of 0.5 g. of (X), 3 g. of $KMnO_4$, and 300 cc. of water was heated on a water bath and it required 10 hours of heating until the floating oil disappeared. After the removal of MnO_2, the filtrate was extracted with benzene, and the aqueous solution was acidified with HCl. The crystals that separated out was extracted with ether and 0.3 g. of (Xa), m.p. 210°(decomp.), was obtained. Heating of (Xa) and copper bronze under a reduced pressure furnished (IIa).

Oxidation of 4-Benzyl-6-phenethyl-2-methylpyridine (XI)—Oxidation of 1 g. of (XI) was carried out with 5 g. of $KMnO_4$ by heating for 30 hours. After the removal of MnO_2, the filtrate was extracted with benzene, and the aqueous solution was neutralized with HCl. The acid substance that separated out was extracted with ether, and the ether residue was treated with petroleum ether from which 0.5 g. of benzoic acid was obtained from the soluble portion, and the petroleum ether-insoluble portion, when recrystallized from water, furnished 0.3 g. of (Xa), m.p. 210°.

6-Benzoylpyridine-2,4-dicarboxylic Acid (XIIa)—A mixture of 0.5 g. of (XII), 3 g. of $KMnO_4$, and 300 cc. of water was heated for 15 hours. After the removal of MnO_2, the filtrate was concentrated, acidified with HCl, and the crystals that precipitated were taken up in ether from which 0.03 g. of benzoic acid was obtained. Recrystallization of the residue from 1% HCl furnished 0.3 g. of (XIIa), m.p. 203°, which was derived to (Ia) upon heating with copper bronze.

Oxidation of 6-Benzyl-2-phenethyl-4-methyl- or 6-Benzyl-4-phenethyl-2-methyl-pyridine (XIIIa or XIIIb)—Oxidation of 1 g. of (XIIIa, b) with 5 g. of $KMnO_4$ and 150 cc. of water by heating for 35 hours and treatment of the product as before furnished 0.5 g. of benzoic acid and 0.05 g. of (XIIa).

4-Benzoylpyridine-3-carboxylic Acid (XIVa) and 6-Benzoylpyridine-3-carboxylic Acid (XVa)—Oxidation of 0.5 g. of (XIV) with 2 g. of $KMnO_4$ in 300 cc. of water by heating for 10 hours yielded 0.25 g. of (XIVa), m.p. 226°, which was derived to (IIa) when heated with copper bronze.

Oxidation of 0.5 g. of (XV) with 2 g. of $KMnO_4$ in 300 cc. of water, by heating for 8 hours, furnished 0.2 g. of (XVa), m.p. 167°, which was derived to (Ia) by heating with copper bronze.

4,6-Dibenzyl-3-methylpyridine (XVII)—A mixture of 2 g. of (XIV), 1.5 g. of benzyl chloride, and 0.05 g. of copper bronze was heated at 250° for 6 hours. The portion soluble in 3% HCl was alkalized with NaOH, extracted with ether, and 0.1 g. of a fraction of $b.p_6$ 200° was obtained, furnishing the picrolonate, m.p. 197°, of (XVII).

A mixture of 1.5 g. of (V), 1 g. of benzyl chloride, and 0.05 g. of copper bronze was heated at 250° for 7 hours and 0.1 g. of (XVII) was obtained. The picrolonate of (XVII) was identical with the picrolonate of the dibenzyl compound obtained by the reaction of β-picoline and benzyl chloride.

2-Benzyl-3-methylpyridine (XVI)6)—A mixture of 3 g. of β-picoline and 2.5 g. of $NaNH_2$ was reacted in xylene and 2.5 g. of 2-amino-3-methylpyridine9), $b.p_{12}$ 102~104°, was obtained. This substance gave a picrate of m.p. 231° (from acetone). A mixture of 2 g. of this pyridine derivative and 9 cc. of 48% HBr was chilled to 0°, and 7 cc. of Br_2 was added. After the addition of 3 g. of $NaNO_2$ and 6 cc. of water, the mixture was allowed to stand, and 2.5 g of 2-bromo-3-methylpyridine10) (XVIII), $b.p_7$ 77~78°, was obtained.

To the ether solution of butyl lithium prepared from 0.12 g. of lithium and 1.2 g. of butyl bromide, chilled to −30°, a solution of 1.5 g. of (XVIII) dissolved in 1 cc. of ether was added, and then 0.62 g. of benzaldehyde was added to this mixture chilled to −15°. The mixture yielded 1 g. of (XX), $b.p_1$ 134~137°, which solidified on standing to crystals of m.p. 54~55°.

A mixture of 1 g. of (XX) and 6 cc. of benzene was warmed to below 25°, and 0.7 g. of $SOCl_2$ was added. After allowing the mixture to stand for 1 hour, the chloro compound was separated

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9) O. Seide: Ber., 57B, 1802 (1924).

10) R. P. Mariella, V. Kvinge: J. Am. Chem. Soc., 70, 3128 (1948).

and this was refluxed in acetic acid for 6 hours with 0.8 g. of zinc dust. The product was 0.3 g. of (XVI), b.p$_6$ 150°, which gave a picrate of m.p. 133°, and was identical with one of the monobenzyl compound obtained as the reaction product of β-picoline and benzyl chloride.

Summary

Pyridine, α-, β-, and γ-picoline, and 2,6- and 2,4-lutidine form salts when heated with benzyl chloride at 100∼150°. Raising of this temperature to 240∼270° results in the formation of compounds in which the benzyl group has entered the pyridine nucleus or the side-chain methyl. By the examination of the structure of these benzyl compounds formed, following conclusions were drawn. The chief reaction product is a monobenzyl compound in which the benzyl group has been substituted in the 2- or 4-position, and the dibenzyl compound is obtained as the by-product in around 5% yield. This dibenzyl compound is the one with the benzyl group substituted in the 2- and 4-positions of the pyridine nucleus in the case of pyridine and β-picoline. In the case of α- and γ-picoline, and 2,6- and 2,4-lutidine, one of the benzyl groups is substituted in the nuclear carbon and the other in the side-chain methyl carbon.

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75. **Yoshihisa Mizuno, Kikuo Adachi, and Kaname Nakamura:** Benzothiazoles. XII1). Studies on Reaction between 2-Chlorobenzothiazoles and Compounds possessing Reactive Methylene Groups.

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It has been well established that diethyl malonate readily reacts with alkyl halides in the presence of sodium, sodium amide, or sodium triphenylmethylate to give alkylated diethyl malonate, and this reaction is called malonic ester synthesis. It is also well known that the halogen atom at 2-position of benzothiazole is as reactive as that of saturated aliphatic halide toward nucleophilic reagents such as ammonia2), sodium alkoxides3), and piperidine4).

It has been our main objective to examine whether or not the malonic ester synthesis could be effected in 2-chlorobenzothiazole, using it as the reactive halide. A few investigations have been made in this direction by König and Fulda5), Doering6), Surrey7), Hartmann8), Kato9), and Nakayama10). Some of them reported successful results of the malonic ester synthesis, involving the nitrogenous aromatic halogen compounds chiefly using phenylacetonitrile as the reactive methylene compound. No reports, however, have been found dealing with the reaction involving 2-halobenzothiazoles, showing that it would be worth to try the malonic ester synthesis involving them.

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5) E. König, A. Fulda: Ber., **60**, 2106(1927).
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7) A. R. Surrey: *Ibid.*, **71**, 3378(1949).
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9) T. Kato: J. Pharm. Soc. Japan, **73**, 150(1953).
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