*UDC 547.829.07*

# 118. **Masatomo Hamana, Bunsuke Umezawa, and Kanji Noda**: Studies on Tertiary Amine Oxides. XVIII.[*1] On the Reduction of 1-[(1-Oxido-2-pyridyl)methyl]pyridinium Salt.

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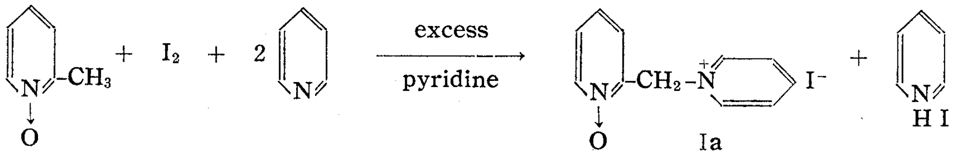
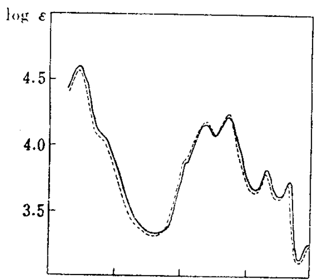
In an earlier paper,[1] the synthesis of 1-[(1-oxido-2-pyridyl)methyl]pyridinium iodide (Ia) by King reaction of 2-picoline 1-oxide and some of its reactions have been reported.



Excess of pyridine in the original King's procedure often caused a poor isolation of Ia. Therefore, in the hope of simplifying the procedure, reactions, in which the three reactants held the molecular ratio as shown in the formula (2-picoline 1-oxide-iodine-pyridine=1:1:2), were conducted in dioxane or xylene.

When the reaction was carried out in boiling dioxane, Ia was obtained only in a low yield (15%). However, in boiling xylene, the similar reaction gave an unexpected compound (II), yellow needles, m.p. 252~253°, with a trace of Ia. II was soluble in water, gave a precipitate of silver iodide with silver nitrate and formed a monopicrate. Moreover II displayed a violet fluorescence in dilute aqueous solution and its ultraviolet spectrum showed several absorption maxima (Fig. 1) characteristic of a polynuclear aromatic system.[2] From these facts and elemental analysis, II was assumed to be a polynuclear heteroaromatic compound containing a quaternary nitrogen atom of molecular formula $(C_{11}H_9N_2)^+I^-$. Its structure was finally confirmed as pyrido[1′,2′:3,4]imidazo[1,2-*a*]pyridinium iodide by the following synthesis; namely cyclization[3] of 2-bromopyridine with 2-bromomethylpyridine followed by anion exchange (Fig. 2).



$0.5\times10^{-4}M$ in 95% EtOH

Fig. 1. Ultraviolet Spectra

——— Pyrido[1′,2′:3,4]imidazo[1,2-*a*]pyridinium Iodide (II)

– – – – Pyrido[1′,2′:3,4]imidazo[1,2-*a*]pyridinium Bromide Monohydrate

When Ia was refluxed with pyridine hydroiodide or with iodine in xylene, II was obtained in the yield of 64% or 53% respectively. A trace of II was also obtainable on heating of Ia in xylene. No formation of II from 1-(2-pyridylmethyl)pyridinium bromide (III)[1] was observed under the same conditions. Therefore N-oxide group and

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[*1] Part XVII: Yakugaku Zasshi, **83**, 342 (1963).

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1) M. Hamana, B. Umezawa, Y. Gotoh, K. Noda: This Bulletin, **8**, 692 (1960).

2) L.C. King, S.V. Abramo: J. Org. Chem., **23**, 1926 (1958).

3) B.R. Brown, E.H. Wild: J. Chem. Soc., **1956**, 1158.

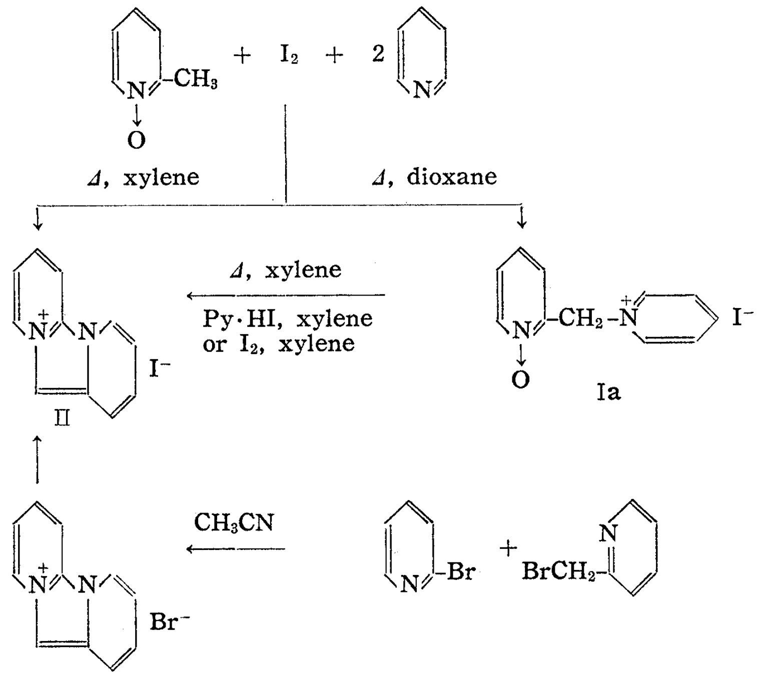


Chart 1. Formation and Synthesis of II

pyridine hydroiodide might have played an essential role for the formation of II and the reaction would have proceeded through the following course; namely usual King reaction of 2-picoline 1-oxide gave Ia together with pyridine hydroiodide and the former was converted to II by the catalytic action of the latter at high temperature.

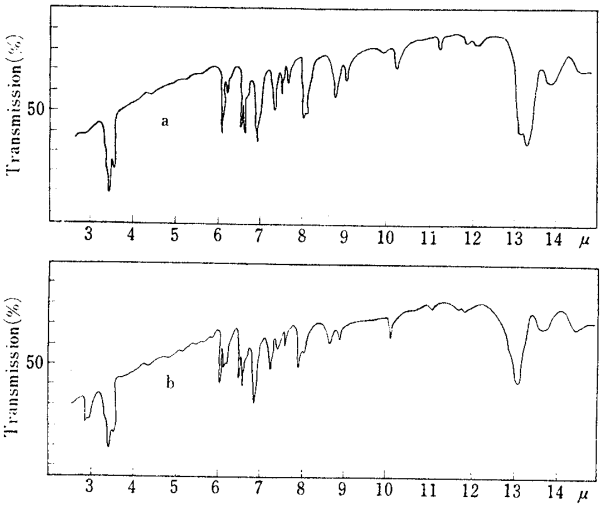
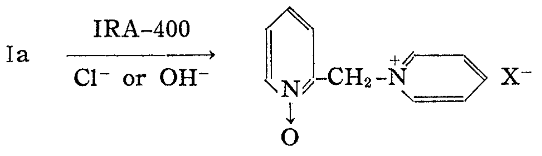


Fig. 2. Infrared Absorption Spectra (Nujol)

a : Pyrido[1′,2′:3,4]imidazo[1,2-*a*]pyridinium Iodide (II)
b : Synthetic Pyrido[1′,2′:3,4]imidazo[1,2-*a*]pyridinium Bromide Monohydrate

As Ia had two reduciable groups, one was N-oxide and the other pyridinium, the selective reduction of these two was studied under a variety of conditions. Throughout the catalytic reduction, anion exchange (from iodide to chloride or hydroxide) was effected through chromatography on Amberlite IRA-400.



Ia : X=I
Ib : X=Cl
Ic : X=OH

Raney-nickel was reported as the most specific catalyst for the deoxygenation of N-oxide group.[4] In consideration of this fact, Ib and Ic were subjected to reduction with Raney-nickel in neutral, basic or acidic medium to give the result in Table I.

Table I. Catalytic Hydrogenation of I with Raney-nickel

| No. | Starting material | X | Catalyst | Medium | $H_2$ (equimol.) absorbed | Product | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | Ib | Cl | deactivated Ni | neutral | 1 | III | 43 |
| 2 | 〃 | 〃 | 〃 | 4% AcOH | 1 | III | 41 |
| 3 | Ic | OH | Ni($W_1$) | neutral | 4 | IV | 71 |
| 4 | 〃 | 〃 | 〃 | 1% NaOH | 4 | IV | 91 |
| 5 | Ib | Cl | 〃 | neutral | 4 | IV | 74 |
| 6 | 〃 | 〃 | 〃 | 2% AcOH | 4 | IV | 91 |

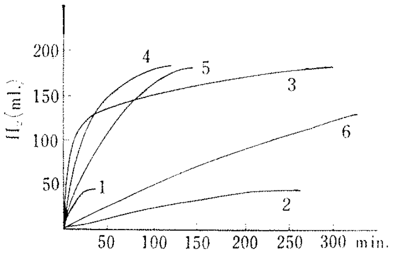
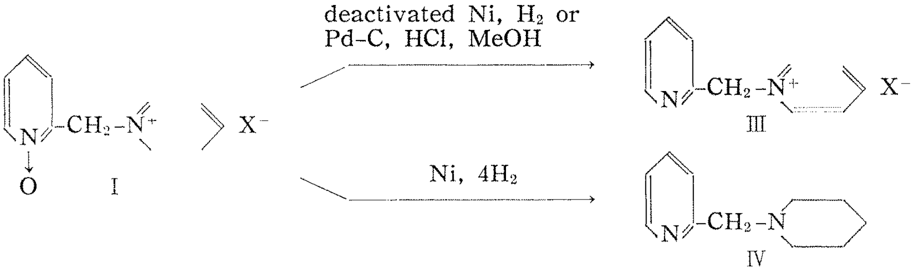


Fig. 3. Hydrogen Absorption Curves of I

The hydrogen absorption curve, in every case, was one with a smoothly rising slope indicating no stepwise reduction of N-oxide or pyridinium group and showed that the rate of reduction was dependent on the basicity of the medium; *i.e.* in the retarding order of basic>neutral>acidic (Fig. 3). By this method, N-(2-pyridylmethyl) piperidine (IV) was always obtainable in a good yield. However, with deactivated Raney-nickel,



the selective reduction of N-oxide giving 1-(2-pyridylmethyl)pyridiniumsalt (III) was achieved in a considerable yield, when the reduction mixture was treated immediately after absorption of one equimole of hydrogen. Therefore, Raney-nickel was confirmed to be more specific to N-oxide group than to pyridinium.

Catalytic reduction of Ib with palladium on charcoal in acidic medium also furnished III in the yield of 68%.

In order to reduce the pyridinium moiety selectively, Ia was first treated with sodium borohydride to yield 2-[(1,2,3,6-tetrahydro-1-pyridyl)methyl]pyridine 1-oxide (V). With palladium on charcoal in neutral medium, V afforded the desired piperidine derivative, 2-piperidinomethylpyridine 1-oxide (VII). Although palladium on charcoal showed specificity to N-oxide group in acidic medium, its selectivity in neutral medium seemed greater to ethylenic linkage than to N-oxide.[5]

Treatment of V with phosphorus trichloride gave 1-(2-pyridylmethyl)-1,2,3,6-tetrahydropyridine (VI) which was convertible to IV. With Raney-nickel, V was fully reduced

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[4] E. Hayashi, H. Yamanaka, K. Shimizu: This Bulletin, 7, 141 (1959).

[5] E. Hayashi, H. Yamanaka, C. Iijima, S. Matsushita: This Bulletin, 8, 649 (1960).

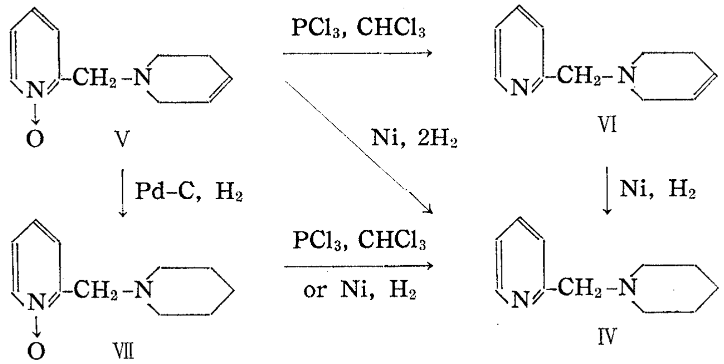


Chart 2. Reduction of V

to IV which was also obtainable from VII with phosphorus trichloride or Raney-nickel (Chart 2).

All reduction products of I, except V, were identified with authentic specimens prepared by the reaction of 2-bromomethylpyridine or its N-oxide with pyridine,1) piperidine, or $\Delta^3$-piperideine6) as shown in Chart 3.

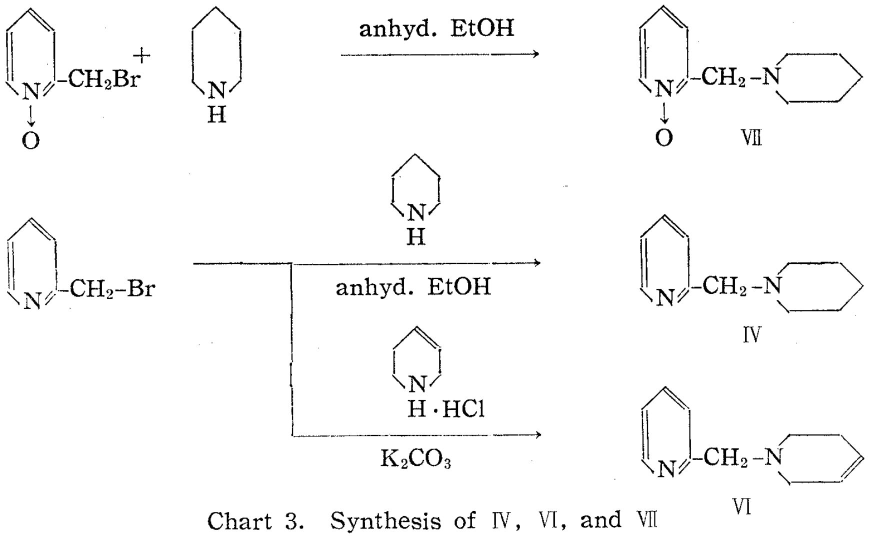
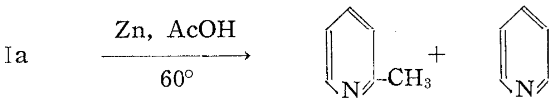


Chart 3. Synthesis of IV, VI, and VII

For the sake of the considerable activity of the methylene group in Ia, Ia was expected to suffer reductive cleavage with zinc dust in glacial acetic acid.7) In fact, Ia was cleaved to yield 2-picoline and pyridine.



## Experimental[*3]

Distillation under reduced pressure was carried out in a collar flask and boiling points showed the bath temperature. Catalytic reductions were performed at atmospheric pressure.

**King Reaction of 2-Picoline 1-Oxide in Dioxane**——A solution of 11 g. of 2-picoline 1-oxide, 16 g. of pyridine, and 26 g. of $I_2$ in 30 ml. of dioxane was refluxed for 5 hr. On standing of the reaction mixture overnight in a refrigerator, crystals were precipitated. Treatment of the crystals with activated charcoal and recrystallization from EtOH gave pale yellow needles of Ia, m.p. 180~181°(decomp.), 5 g. (16%).

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[*3] All melting points were uncorrected.

6) R. Lukés, J. Pliml : Chem. Listy, **48**, 49 (1954). [C. A. **49**, 1720 (1955)].

7) F. Kröhnke : Ber., **67**, 656 (1934).

**King Reaction of 2-Picoline 1-Oxide in Xylene**——A solution of 11 g. of 2-picoline 1-oxide, 26 g. of $I_2$, and 16 g. of pyridine in 10 ml. of xylene was refluxed for 5 hr. to give a crystalline mass. After decanting off the solvent, the mass was purified through chromatography (elution with $Me_2CO$) over $Al_2O_3$-celite (2:1). Recrystallization from EtOH afforded yellow needles Ⅱ, m.p. 252~253°, 1.5 g. (5%). *Anal.* Calcd. for $C_{11}H_9N_2I$ : C, 44.61; H, 3.39; N, 9.46. Found : C, 44.33; H, 3.04; N, 9.81.

Picrate, m.p. 217~218°, yellow needles(from MeOH). *Anal.* Calcd. for $C_{11}H_9N_2 \cdot C_6H_2N_3O_7$ : C, 51.38; H, 2.77; N, 17.62. Found : C, 51.36; H, 2.83; N, 17.60.

Ⅱ or its picrate was identified by mixed fusion with an authentic sample of pyrido[1′,2′:3,4]imidazo-[1,2-*a*]pyridinium iodide or its picrate respectively.

**Pyrido[1′,2′:3,4]imidazo[1,2-*a*]pyridinium Iodide (II)**——A solution of 2-bromomethylpyridine (prepared from 2.5 g. of its hydrobromide) and 7 g. of 2-bromopyridine in 30 ml. of $CH_3CN$ was refluxed for 20 hr. On distilling off the solvent, the residue was purified through chromatography (elution with $Me_2CO$-EtOH=4:1 by volume) over $Al_2O_3$-celite (2:1). Recrystallization from $Me_2CO$ gave pyrido[1′,2′:3,4]imidazo[1,2-*a*]pyridinium bromide monohydrate, m.p. 150~152°, pale brownish yellow needles, 470 mg. (18%). *Anal.* Calcd. for $C_{11}H_9N_2Br \cdot H_2O$ : C, 49.43; H, 4.12; N, 10.49. Found : C, 49.51; H, 4.12; N, 10.73.

Picrate, yellow needles, m.p. 217~218°(from MeOH).

A solution of 130 mg. of the above bromide and 300 mg. of NaI in 40 ml. of $Me_2CO$ was refluxed for 4 hr. Usual treatment gave Ⅱ, m.p. 252~253°, pale yellow needles (from EtOH), 120 mg. (100% yield).

**Refluxing of Ia in Xylene**——A suspension of Ia in 10 ml. of xylene was refluxed for 5 hr. Treatment as above gave a small amount of Ⅱ, m.p. 252~253°.

**Refluxing of Ia with Pyridine Hydriodide**——A suspension of 800 mg. of Ia and 520 mg. of pyridine HI in 10 ml. of xylene was refluxed for 5 hr. Usual treatment gave Ⅱ, m.p. 252~253°, 500 mg. (64%).

**Refluxing of Ia with Iodine**——A suspension of 500 mg. of Ia and 700 mg. of $I_2$ in 10 ml. of xylene was refluxed for 5 hr. Treating usually gave Ⅱ, m.p. 252~253°, 300 mg. (53%).

**Refluxing of 1-(2-Pyridylmethyl)pyridinium Bromide (III) with Pyridine Hydriodide**——A suspension of Ⅲ (prepared from 500 mg. of 2-bromomethylpyridine·HBr and 1 ml. of pyridine) and 350 mg. of pyridine hydriodide in 10 ml. of xylene was refluxed for 5 hr. Treatment as above gave a brown oil. The oil was converted to a picrate, yellow needles, m.p. 169~170°(from MeOH), which was identical with Ⅲ picrate.

**Anion Exchange of Ia**——A solution of 630 mg. of Ia in a small amount of 80% MeOH was poured on a column of activated IRA-400 (ca. 20 ml. of dried resin, $Cl^-$ or $OH^-$ type), and the column was eluted with the same solvent. The first fraction (ca. 40 ml.) was subjected directly to the following catalytic reduction.

**Raney-Ni ($W_1$)**——Raney-Ni ($W_1$) was prepared from 0.6 g. of alloy. Its deactivation was achieved by keeping in MeOH for 2 days at room temperature.

**Reduction of I on Raney-Ni**——1) A solution of 1-[(1-oxido-2-pyridyl)methyl]pyridinium chloride (Ib) in 40 ml. of 80% MeOH was shaken with deactivated Raney-Ni in $H_2$. After 20 min., when 47 ml. of $H_2$ was absorbed, reduction was interrupted and the catalyst was filtered off. The filtrate was concentrated *in vacuo* to leave a residue which was directly converted to a picrate. Recrystallization from MeOH gave 1-(2-pyridylmethyl)pyridinium (Ⅲ) picrate, yellow needles, m.p. 169~170°, 540 mg. (43%). 2) A solution of Ib in a mixture of 40 ml. of 80% MeOH and 2 ml. of AcOH was hydrogenated over deactivated Raney-Ni as above. It took 285 min. to absorb 45 ml. of $H_2$. Usual treatment gave Ⅲ-picrate, m.p. 168~170°(from MeOH), 520 mg. (41%). 3) A solution of 1-[(1-oxido-2-pyridyl)methyl] pyridinium hydroxide (Ic) in 40 ml. of 80% MeOH was hydrogenated over Raney-Ni for 290 min. to absorb 177 ml. of $H_2$. On filtering off the catalyst, filtrate was concentrated *in vacuo*, basified with $K_2CO_3$ and extracted with $CHCl_3$. From the $CHCl_3$ layer, an oil, b.p$_5$ 120~140°, 250 mg. (71%) was obtained. The oil gave a picrate, yellow plates, m.p. 180~182°(from MeOH). The picrate was identified as N-(2-pyridylmethyl)piperidine (Ⅳ) picrate by mixed fusion. 4) A solution of Ic in a mixture of 40 ml. of 80% MeOH and 5 ml. of 10% NaOH was hydrogenated over Raney-Ni for 105 min., when 178 ml. of $H_2$ was absorbed. Usual treatment gave Ⅳ, b.p$_4$ 100~125°, 320 mg. (91%); picrate, yellow plates, m.p. 180~182°. 5) A solution of Ib in 40 ml. of 80% MeOH was shaken with Raney-Ni in $H_2$. On removal of the catalyst, the filtrate was concentrated *in vacuo*, basified with 20% $K_2CO_3$ and extracted with $CHCl_3$. Usual treatment of the $CHCl_3$ layer gave Ⅳ, b.p$_4$ 100~115°, 260 mg. (74%); picrate, yellow plates, m.p. 180~182°. 6) A solution of Ib in a mixture of 40 ml. of 80% MeOH and 1 ml. of AcOH was hydrogenated over Raney-Ni. Usual treatment gave Ⅳ, b.p$_4$ 100~120°, 320 mg. (91%); picrate, yellow plates, m.p. 180~182°.

**Reduction of Ib on Pd-C**——A solution of Ib in a mixture of 40 ml. of 80% MeOH and 2 ml. of conc. HCl was shaken with 0.7 g. of Pd-C (30%) in $H_2$ under warming with infrared lamp. It took 240 min. to absorb 45 ml. of $H_2$. Treating as above gave Ⅲ. Picrate, yellow needles, m.p. 169~170°, 860 mg. (68%).

**Reduction of Ia with Zn-AcOH**——To a solution of 1.26 g. of Ia in 10 ml. of AcOH, 1.2 g. of Zn powder was added and the whole was warmed at 60° on a water bath for 3.5 hr. with occasional stirring. On removal of Zn powder, the filtrate was basified with dil. NaOH and extracted with $Et_2O$. From the $Et_2O$ layer, a liquid was obtained. Chromatography of the liquid over $Al_2O_3$ (elution with $Et_2O$-petr. ether (1:1)) gave first 2-picoline, picrate, yellow needles, m.p. 164~165°, 770 mg. (58%) and next pyridine, picrate, yellow needles, m.p. 165~167°, 650 mg. (51%), respectively.

**Reduction of Ia with $NaBH_4$**——To a solution of 3.14 g. of Ia in 20 ml. of $H_2O$, 410 mg. of $NaBH_4$ was added portionwise at room temperature and the whole was stood for 30 min. Basification of the reaction mixture with conc. NaOH, and extraction of the product with $CHCl_3$ followed by chromatography over $Al_2O_3$ (elution with $CHCl_3$) gave 2-[(1,2,3,6-tetrahydro-1-pyridyl)methyl]pyridine 1-oxide (V) as a faint yellow oil, 1.75 g. (92%); picrate, yellow prisms, m.p. 115~116° (from MeOH). *Anal.* Calcd. for $C_{17}H_{17}O_8N_5$: C, 48.69; H, 4.09; N, 16.69. Found: C, 48.79; H, 4.29; N, 16.67.

**Deoxygenation of V with $PCl_3$**——To a solution of V (prepared from 3.14 g. of Ia) in 25 ml. of $CHCl_3$, a solution of 1.4 g. of $PCl_3$ in 5 ml. of $CHCl_3$ was added under ice-cooling and the mixture was refluxed for 30 min. on a water bath. Usual treatment and distillation of the product under reduced pressure gave 1-(2-pyridylmethyl)-1,2,3,6-tetrahydropyridine (VI), b.p$_4$ 106~111°, 600 mg. (34%); picrate, yellow plates, m.p. 171~172° (from MeOH). The picrate showed no depression of melting point when mixed with an authentic specimen (see below).

**Reduction of V on Pd-C**——A solution of crude V (prepared from 630 mg. of Ia) in 30 ml. of MeOH was shaken with 180 mg. of Pd-C (50%) in $H_2$ for 2 hr. when one equimol. of $H_2$ was absorbed. After usual treatment, the product was chromatographed over $Al_2O_3$ (elution with $CHCl_3$) to give IV; picrate, yellow plates, m.p. 180~182°, 82 mg. (6.3%), and 2-piperidinomethylpyridine 1-oxide (VII); picrate, yellow needles, m.p. 130~132°, 380 mg. (40%). The latter was identified with an authentic specimen by mixed fusion (see below).

**Reduction of V on Raney-Ni**——A solution of crude V (prepared from 314 mg. of Ia) in 30 ml. of MeOH was hydrogenated with $H_2$ over Raney-Ni ($W_1$) (from 300 mg. of alloy). Usual treatment gave IV, b.p$_6$ 130~140°, 30 mg. (17%); picrate, yellow plates, m.p. 180~182° (from MeOH).

**Reduction of VI on Raney-Ni**——A solution of 520 mg. of VI in 30 ml. of MeOH was hydrogenated with $H_2$ over Raney-Ni ($W_1$) (from 400 mg. of alloy). Usual treatment gave IV, b.p$_5$ 105~120°, 500 mg. (95%); picrate, yellow plates, m.p. 180~182°.

**Deoxygenation of VII with $PCl_3$**——To a solution of 100 mg. of VII in 5 ml. of $CHCl_3$, a solution of 70 mg. of $PCl_3$ in 1 ml. of $CHCl_3$ was added under ice-cooling and the mixture refluxed for 30 min. Usual treatment gave IV; picrate, yellow plates, m.p. 180~182°, 150 mg. (48%).

**Synthesis of 2-Piperidinomethylpyridine (IV)**——A solution of 2-bromomethylpyridine (freshly liberated from 2.5 g. of its hydrobromide) and 1.7 g. of piperidine in 20 ml. of anhyd. EtOH was refluxed for 1 hr. After evaporation of the solvent *in vacuo* and basification of the residue with 20% $K_2CO_3$, the product was extracted with $CHCl_3$. Usual treatment and distillation under reduced pressure gave IV, b.p$_4$ 100~110°, 1.7 g. (100%); picrate, yellow plates, m.p. 180~182° (from MeOH). *Anal.* Calcd. for $C_{23}H_{22}O_{14}N_8$: C, 43.26; H, 3.49; N, 17.77. Found: C, 43.63; H, 3.90; N, 17.62.

**Synthesis of 1-(2-Pyridylmethyl)-1,2,3,6-tetrahydropyridine (VI)**——A solution of 500 mg. of 2-bromomethylpyridine·HBr and 260 mg. of $\Delta^3$-piperideine·HCl in 20 ml. of $H_2O$ was basified with $K_2CO_3$ and the mixture was warmed for 30 min. on a water bath. Extraction with $CHCl_3$ and usual treatment gave VI, b.p$_4$ 100~120°, 220 mg. (63%); picrate, yellow plates, m.p. 170~171° (from MeOH). *Anal.* Calcd. for $C_{23}H_{20}O_{14}N_8$: C, 43.70; H, 3.16; N, 17.70. Found: C, 43.73; H, 4.45; N, 17.88.

**Synthesis of 2-Piperidinomethylpyridine 1-Oxide (VII)**——A solution of 2-bromomethylpyridine 1-oxide (freshly liberated from 2.7 g. of its hydrobromide) and 3.6 g. of piperidine in 30 ml. of anhyd. EtOH was refluxed for 3 hr. On evaporation of the solvent *in vacuo*, the residue was chromatographed over $Al_2O_3$ (elution with $CHCl_3$) to give VII, white prisms, m.p. 93~95° (from petr. benzin), 300 mg. (10%). *Anal.* Calcd. for $C_{11}H_{16}ON_2$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.79; H, 8.29; N, 14.42.

Picrate, yellow needles, m.p. 132~133° (from MeOH). *Anal.* Calcd. for $C_{17}H_{19}O_8N_5$: C, 48.45; H, 4.55; N, 16.62, Found: C, 48.58; H, 4.52; N, 16.53.

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## Summary

Modified King reaction of 2-picoline 1-oxide gave pyrido[1′,2′:3,4]imidazo[1,2-*a*]pyridinium iodide instead of 1-[(1-oxido-2-pyridyl)methyl]pyridinium iodide (Ia). Selective reduction of N-oxide or pyridinium group of Ia was investigated.

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