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116. Masatomo Hamana, Bunsuke Umezawa, Yoshinobu Gotoh, and Kanji Noda: Studies on Tertiary Amine Oxides. III. King Reaction of 2-Picoline 1-Oxide.

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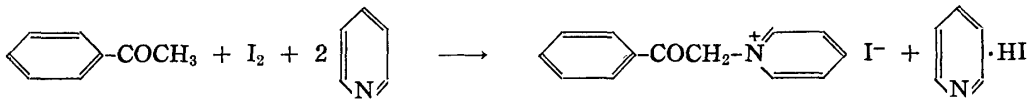
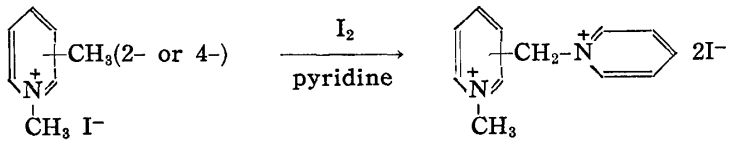
Early in 1944, King[1] reported that aryl methyl ketone reacted directly with iodine and pyridine to give 1-aroylmethylpyridinium iodide; for example, acetophenone gave 1-phenacylpyridinium iodide.

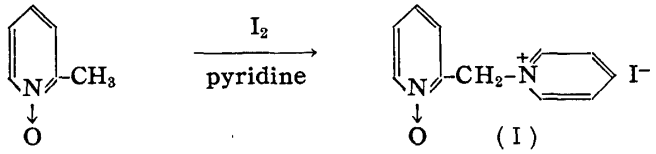


Since then, this reaction was shown to be widely applicable for various types of compounds containing active hydrogen.[2] Among methylpyridines and analogous N-heterocycles, the following substances have been reported to undergo this reaction: 1-Methyl-2- or -4-picolinium iodide,[3] quinaldine,[4] lepidine,[5] 6-methylquinaldine,[5] and 1-methylisoquinoline.[4] Recently, Kröhnke[5] stated that 2- or 4-picoline could not yet be transformed into 1-(2- or 4-pyridylmethyl)pyridinium iodide, while 1-methyl-2- or -4-picolinium iodide could be so converted.



This fact clearly shows that the reactivity of the methyl group in 2- or 4-picoline is not so high as to undergo this reaction, but can be enhanced by quaternisation of the original base. However, the effect of N-oxidation in this case has never been reported. Much interest was felt in clarifying the influence of N-oxide function and the King reaction of 2-picoline 1-oxide was investigated with following results.

On refluxing a mixture of 2-picoline 1-oxide with equivalent mole of iodine and excess of pyridine, the desired pyridinium iodide, 1-(1-oxido-2-pyridylmethyl)pyridinium iodide (I), m.p. 180~181°(decomp.), was obtained in a moderate yield (40.1%), and formed a dipicrate, m.p. 142~143°.



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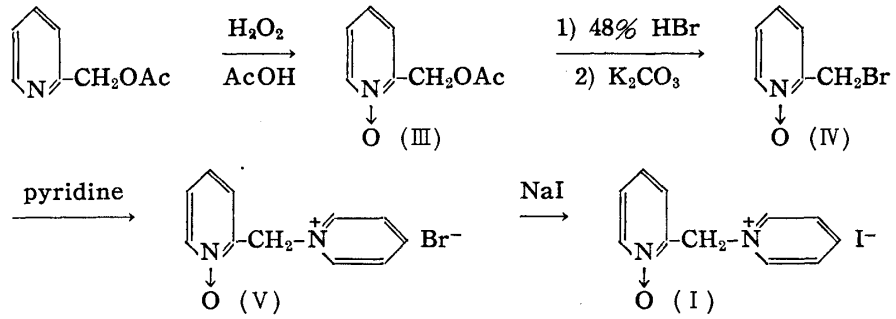
1) L. C. King: J. Am. Chem. Soc., **66**, 894 (1944).
2) *Idem*: *Ibid.*, **66**, 1612(1944), **67**, 2089(1945), **68**, 716(1946), **70**, 289(1948); J. L. Hartwell, S. R. L. Kornberg: *Ibid.*, **68**, 863, 1131(1946); L. I. Smith, V. A. Englehardt: *Ibid.*, **71**, 2676(1949); R. H. Baker, E. N. Squire: *Ibid.*, **70**, 1487(1948); J. Schmutz, R. Hirt, H. Lauener: Helv. Chim. Acta, **35**, 1168(1952); D. I. Sapper, P. L. Southwick: J. Org. Chem., **21**, 105(1956); W. Reid, H. Bender: Chem. Ber., **89**, 1893(1956).
3) J. A. Berson, T. Cohen: J. Am. Chem. Soc., **78**, 416(1956); F. Kröhnke, H. Leister, I. Vogt: Chem. Ber., **90**, 2793(1957).
4) L. C. King, S. V. Abramo: J. Org. Chem., **23**, 1609(1958). King reaction of quinaldine and lepidine methiodide is also reported in this literature.
5) F. Kröhnke, K. F. Gross: Chem. Ber., **92**, 22(1959).

The structure of (I) was confirmed unequivocally by the following synthetic route.



From this result, it can be concluded that N-oxide function is able to noticeably activate the methyl at 2-position of pyridine ring in the King reaction.

As (I) was obtained easily, some of its chemical properties were studied. (I) showed anomalous behavior towards acid and acetic anhydride as shown in Table I. The major product of this reaction was the deoxygenated compound of (I); i.e. 1-(2-pyridylmethyl)-pyridinium compound (VI), accompanied with a few by-products in some cases. Being not crystalline, (VI) was isolated and characterized as a dipicrate, m.p. 169~170°, in all cases. The structure of (VI) was also confirmed by synthesis as shown in Chart 1.

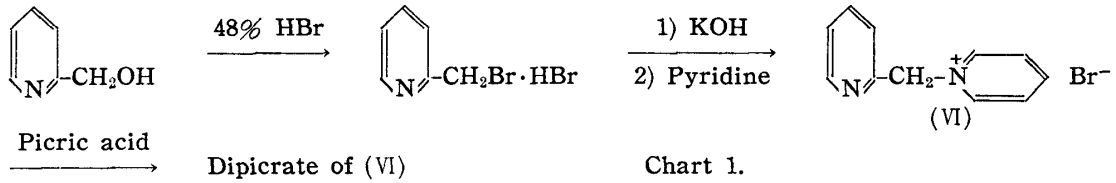
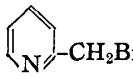
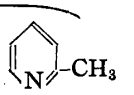


Chart 1.

Table I.

Reagent	Condition	Product (%) (VI)			
HCl	90°	85	—	—	—
48% HBr	refluxed	30	—	—	—
〃	sealed tube, 155~160°	21.5	8.3	10.2	—
HBr/AcOH	〃	trace	—	7.7	+*
Ac_2O	refluxed	12.5	—	—	—

* Unseparable mixture of 2-picoline and pyridine was obtained. When 1-(1-oxido-2-pyridylmethyl)pyridinium perchlorate was used as the starting material, pure 2-picoline was obtained.

Heating of the hydrochloride of (I) alone or boiling (I) with 48% hydrobromic acid gave (VI) as the sole product in 85% or 30% yield, repectively. Heating of (I) with 48% hydrobromic acid in a sealed tube at 155~160° gave (VI) together with a small amount of pyridine and ω-bromo-2-picoline as by-products, the latter of which was characterized by its conversion with sodium acetate and acetic acid to 2-pyridylmethyl acetate. These by-products may have been produced from the nucleophilic attack of bromide ion on the intervening methylene carbon atom of (VI). Attempt to increase the yield of ω-bromo-2-picoline with acetic acid saturated with dry hydrogen bromide failed and 2-picoline was unexpectedly obtained. It is most probable that a small amount of hydriodic acid formed during the reaction might have reduced ω-bromo-2-picoline or (VI).

Usually, aromatic N-oxides undergo rearrangement on heating with acetic anhydride.[6]

6) E. Ochiai : J. Org. Chem., **18**, 534(1953); K. Thomas, D. Jerchel : Angew. Chem., **70**, 719(1958).

Refluxing of (I) with this reagent, however, caused no rearrangement and only (VI) was obtained, quite analogous to the cases mentioned above.

Considering the stability of aromatic N-oxides,[7] it seems rather curious that (I) is readily deoxygenated by acid reagents. The mechanism of this deoxygenation might be illustrated as shown in Chart 2.

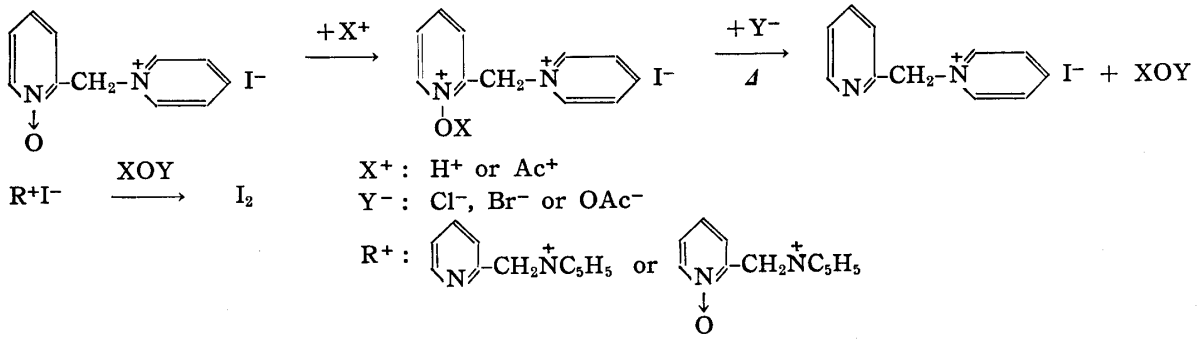
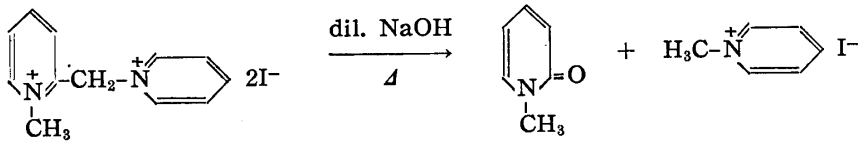


Chart 2. Mechanism of Deoxygenation

At first, proton or acetylium cation attacks the N-oxide oxygen to leave a positive charge at the nitrogen atom. Thus, the resulting molecule has two positive centers, only a short distance from each other. It would be conceivable that this state of a molecule might not be stable enough and the molecule will tend to abandon one of the two positive charges at an elevated temperature. Comparing the two bonds attached to each of the positive charges, the N–O bond would be weaker than the C–N bond, and the former is likely to be severed. This view seems to be supported by the formation of iodine, which was visible in a few cases.

Treatment of 1-(1-alkyl-2-pyridylmethyl)pyridinium diiodide with alkali affords N-alkyl-2-pyridone and N-methylpyridinium compound.[3~5]



In order to examine the posibility of an approach to 2-hydroxypyridine 1-oxide from (I), reaction with alkali was carried out. Treatment of (I) with potassium carbonate or dilute sodium hydroxide solution, either at room temperature or on a water bath, failed to cause any change in the cationic moiety, which was proved by the identity of picrates of the product and the starting material.

A more severe condition, i.e. refluxing (I) with sodium hydroxide solution or sodium ethoxide in ethanol, merely caused resinification.

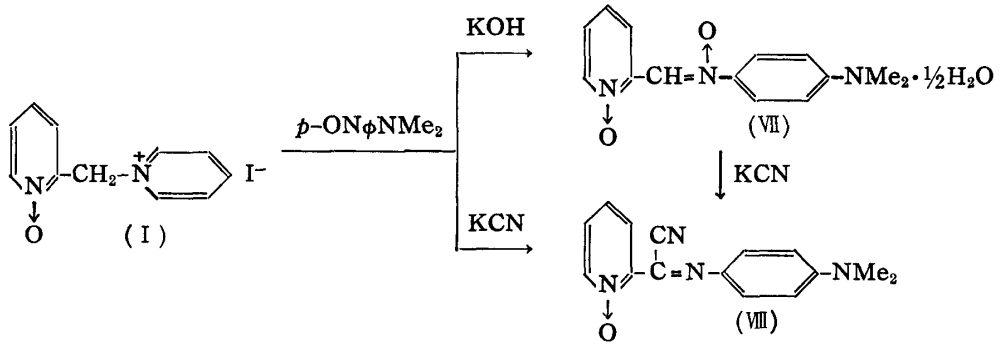
While the behavior of (I) towards acid reagents and alkali was noticeably unusual, as mentioned above, the conversion to nitrone and cyano-anil occurred smoothly by the usual method.[8] The reaction of *p*-nitroso-N,N-dimethylaniline and potassium hydroxide with (I) afforded fine red crystals of N-(*p*-dimethylaminophenyl)-α-(1-oxido-2-pyridyl)nitrone hemihydrate (VII), m.p. 160~161°, in 80% yield. The presence of one-half mole of water of crystallization was confirmed by analysis and infrared spectrum. By drying over phosphorus pentoxide or repeated recrystallization from ethyl acetate, the water of crystallization was lost gradually and the red color of (VII) faded to yellow, but

7) E. Ochiai : Proc. Imp. Acad. (Tokyo), **19**, 307(1943); E. Ochiai, T. Naito, M. Katada : *Ibid.*, **19**, 574(1943).

8) F. Kröhnke : Angew. Chem., **65**, 605(1953).

readily recovered on exposure to air.

The action of either potassium cyanide and *p*-nitrosodimethylaniline on (I) or potassium cyanide alone on (Ⅶ) afforded wine red needles of α-(*p*-dimethylaminophenylimino)-2-pyridineacetonitrile 1-oxide [cyano-anil] (Ⅷ), m.p. 183°, in 64~68% yield.



According to the recent paper of Kröhnke[5] on 1-(2-pyridylmethyl)pyridinium salt and its methiodide, the former gives cyano-anil alone, while the latter gives both nitrone and cyano-anil. Judging from these results, N-oxide function of (I) is clearly acting as an electron-attractor as quaternary N-methyl group. However, the acidifying power of the former might be reduced to some extent owing to its inherent $+M$ effect. The failure of the attempted synthesis of pyridinium ethanol[8] from (I) seems to endorse this fact. Examinations are being made on the effect of deriving the ring nitrogen to N-oxide or methiodide upon the active methylene in 1-(2-pyridylmethyl)pyridinium salt. The result will be published in the near future.

Experimental*2

King Reaction of 2-Picoline 1-Oxide—A solution of 109 g. (1 mole) of 2-picoline 1-oxide and 254 g. (1 mole) of iodine in 500 cc. of pure pyridine was refluxed for 5 hr. in an oil bath (bath temp., 140°). The reaction mixture was allowed to stand over night in a refrigerator and the crystals that precipitated were collected. Treatment with activated charcoal and recrystallization from EtOH afforded light yellowish white needles, m.p. 180~181° (decomp.) (Ⅱ), 126 g. (40.1% yield). Picryl chloride test[8]: Blue. *Anal.* Calcd. for $C_{11}H_{11}ON_2I$: C, 42.05; H, 3.53; N, 8.92. Found: C, 41.87; H, 3.66; N, 8.78.

This gave a yellow picrate (Ⅱ), m.p. 142~143° (from EtOH). It was confirmed that (I) and (Ⅱ) are identical with an authentic specimen of 1-(1-oxido-2-pyridylmethyl)pyridinium iodide and its picrate respectively by mixed fusion (see below).

1-(1-Oxido-2-pyridylmethyl)pyridinium Iodide—To a solution of 20 g. of 2-picolyl acetate in 150 cc. of AcOH, 30 cc. of 30% H_2O_2 was added. After maintaining this solution at 70~80° for 3 hr. on a water bath, 20 cc. of 30% H_2O_2 was added again. The whole was warmed for further 9 hr. under the same condition. AcOH and excess of H_2O_2 were distilled off under reduced pressure. A small amount of water was added to this residue and the base was taken up in $CHCl_3$ as usual. Recystallization of the product from a mixture of AcOEt and MeOH afforded white needles (Ⅲ), m.p. 142~143°; 12 g. (54% yield). *Anal.* Calcd. for $C_8H_9O_3N$: C, 57.41; H, 5.38; N, 8.37. Found: C, 57.23; H, 5.58; N, 8.63.

A solution of 1.67 g. of (Ⅲ) in 15 cc. of 48% HBr was refluxed for 4 hr. in an oil bath. The solvent was distilled off under reduced pressure, a small amount of water was added to the residue, and the solution was made alkaline with K_2CO_3. After the $CHCl_3$ solution was dried over Na_2SO_4, the solvent was distilled off *in vacuo* in N_2 atmosphere to avoid decomposion. Residual light brown viscous oil (Ⅳ) weighed 1.2 g. (64% yield). Picrate: Yellow plates, m.p. 128.5~129.5° (from MeOH). *Anal.* Calcd. for $C_6H_6ONBr \cdot C_6H_3O_7N_3$: C, 34.54; H, 2.18; N, 12.43. Found: C, 34.81; H, 2.23; N, 13.32.

A solution of 1.16 g. of (Ⅳ) and 15 cc. of pure pyridine in 15 cc. of dehyd. EtOH was refluxed for 3 hr. EtOH and excess of pyridine were distilled off under reduced pressure. Recrystallization of the residual solid from a mixture of EtOH and AcOEt afforded yellow needles (V), m.p. 196~197°; 0.93 g. (56.5% yield). As these crystals were deliquescent, elementary analysis was impossible.

*2 All melting points are uncorrected.

Dipicrate : Yellow needles (from MeOH), m.p. 142~143°. *Anal.* Calcd. for $C_{11}H_{11}ON_2 \cdot C_6H_2O_7N_3 \cdot C_6H_3O_7N_3$: C, 42.86; H, 2.56; N, 17.40. Found : C, 42.61, 42.82; H, 2.81, 2.67; N, 17.30, 17.41.

A solution of 1 g. of (V) and 0.6 g. of NaI in a mixture of 30 cc. of dehyd. EtOH and 100 cc. of dehyd. Me_2CO was refluxed for 2 hr. on a water bath. The solution was concentrated to about 1/4 the original volume under a reduced pressure. The precipitated NaBr was filtered off and the filtrate was again concentrated in a similar way, giving yellowish crystals. Recrystallization from a mixture of dehyd. EtOH and AcOEt afforded light yellowish white needles, m.p. 180~181° (decomp.); 0.92 g. (78% yield).

Action of Hydrobromic Acid on (I)—a) Refluxing with 48% hydrobromic acid at atmospheric pressure : A solution of 0.5 g. of (I) in 2 cc. of 48% HBr was refluxed at 130~135° in an oil bath for 4 hr. Sublimed I_2 adhered to the inside wall of the cooler (I_2 identified by color test with starch test solution). After removal of the solvent, the residue was dissolved in a small amount of water, made slightly alkaline with K_2CO_3, and concentrated *in vacuo*. The residue was dried in a desiccator over night and extracted with dehyd. EtOH. A saturated solution of picric acid in EtOH was added to this EtOH extract and the picrate separated. Recrystallization from EtOH gave yellow needles, m.p. 169~170°; 0.3 g. (30% yield). This was identified by mixed fusion with an authentic specimen of 1-(2-pyridylmethyl)pyridinium dipicrate (see below). Refluxing a solution of 0.2 g. of (I) in 1 cc. of water for 4 hr. in an oil bath caused no change.

b) Refluxing with 48% hydrobromic acid in a sealed tube : A solution of 1 g. of (I) in 3 cc. of 48% HBr was heated at 155~160° in a sealed tube for 2 hr. On cooling to room temperature, liberated I_2 was filtered off and the filtrate was evaporated to dryness under a reduced pressure. A small amount of water was added to this residue and the solution was made alkaline with K_2CO_3. This solution was extracted first with Et_2O (A) and then with $CHCl_3$ (B). On saturating the aqueous solution with K_2CO_3 an oily substance (C) separated. The Et_2O solution of (A) was dried over Na_2SO_4 for 2 hr., Na_2SO_4 was filtered off, and to this filtrate 6 cc. of anhyd. AcOH and 0.2 g. of fused NaOAc were added. After Et_2O was distilled off, the residue was refluxed for 10 hr. On working up as usual, basic products distilled out at atmospheric pressure (A′) and under a reduced pressure (A″). (A′) was identified as pyridine, as its picrate, weighing 100 mg. (10.2% yield). (A″), $b.p_{20}$ 120~130° (bath temp.). Picrate : m.p. 166~167° (from EtOH); 100 mg. (8.3% yield). *Anal.* Calcd. for $C_8H_9O_2N \cdot C_6H_3O_7N_3$: C, 44.21; H, 3.16; N, 14.73. Found : C, 44.34; H, 3.35; N, 14.53.

This was identified by mixed fusion with an authentic specimen of 2-picolyl acetate picrate.

(B) : As picrate, trace of 1-(2-pyridylmethyl)pyridinium dipicrate was detected.

(C) : Picrate, yellow needles (from EtOH), m.p. 169~170°, 0.43 g. (21.5% yield). This was identified by mixed fusion with an authentic specimen of 1-(2-pyridylmethyl)pyridinium dipicrate (see below).

c) Refluxing with HBr in AcOH in a sealed tube : A suspension of 2 g. of (I) in 10 cc. of dehyd. AcOH saturated with dry HBr was heated at 155~160° in a sealed tube for 2 hr. On working up as usual, trace of 1-(2-pyridylmethyl)pyridinium dipicrate, pyridine picrate (150 mg.), and a picrate melting at 150~160° were obtained. The latter was assumed to be a mixture of pyridine (m.p. 167°) and 2-picoline (m.p. 163°) picrate. When corresponding perchlorate instead of iodide was reacted under the same condition, pure 2-picoline picrate was obtained.

Action of Hydrochloric Acid on (I)—A solution of 0.5 g. of K_2CO_3 added to a solution of 0.2 g. of (I) in 1 cc. of water was acidified with 10% HCl, the solvent was distilled off *in vacuo*, and the residue was heated for 4 hr. at 90° on a water bath. During this period, iodine was liberated. On working up as usual, a picrate was obtained, as yellow needles (from MeOH), m.p. 169~170°. Yield, 0.34 g. (85%). This was identified by mixed fusion with an authentic specimen of 1-(2-pyridylmethyl)-pyridinium dipicrate.

Action of Acetic Anhydride on (I)—A suspension of 200 mg. of (I) in 5 cc. of Ac_2O was gently refluxed for 2 hr. On heating, the solution became red and gradually turned dark red, probably owing to liberated iodine. The solvent was distilled off *in vacuo* and the residue was extracted with warm water (resinous black substances remained). The orange yellow extract was concentrated to dryness *in vacuo*, leaving an oily residue. This was converted to a picrate (recrystallized once from MeOH), m.p. 167~169°, 50 mg. (12.5% yield). This was identified by mixed fusion with an authentic specimen of 1-(2-pyridylmethyl)pyridinium dipicrate.

Synthesis of 1-(2-Pyridylmethyl)pyridinium Dipicrate—63 cc. of 48% HBr was added dropwise to 255 cc. of Ac_2O under continuous stirring and ice-cooling. To this solution 6.0 g. of 2-picolyl alcohol was added and the whole was heated in a glass-autoclave on a boiling water bath for 4 hr. The solvent was distilled off *in vacuo* and recrystallization of the residue from a mixture of EtOH and AcOEt afforded colorless needles, m.p. 146°, 9.3 g. (72% yield). To a solution of 2.52 g. of ω-bromopicoline hydrobromide in a small amount of water, an aqueous solution of 1.1 g. of KOH was added and liberated ω-bromopicoline was extracted with $CHCl_3$. After drying over Na_2SO_4, $CHCl_3$ was distilled off *in vacuo* in N_2 atmosphere. To this residual reddish viscous oil, a solution of 5 cc. of pure

pyridine in 20 cc. of dehyd. EtOH was added and the whole was refluxed on a water bath for 3 hr. The solvent was distilled off *in vacuo* and the residue was converted directly to a picrate. Recrystallization from MeOH afforded yellow needles, m.p. 172~173°. Yield, 2.5 g. (40%). *Anal.* Calcd. for $C_{11}H_{11}N_2 \cdot C_6H_2O_7N_3 \cdot C_6H_3O_7N_3$: C, 43.94; H, 2.54; N, 17.83. Found: C, 43.75; H, 2.71; N, 17.70.

Action of Potassium Carbonate on (I)—a) To a solution of 0.2 g. of (I) in 1 cc. of water, 0.5 g. of K_2CO_3 was added. An oily substance separated. After removal of the solvent by distillation *in vacuo*, the residue was dried over night in a desiccator. The dried EtOH extract afforded a picrate (from EtOH), m.p. 142~143°, 0.15 g. (36.6% yield), which was identical with (II).

b) To a solution of 0.2 g. of (I) in 1 cc. of water, 0.5 g. of K_2CO_3 was added and the solution was acidified with dil. HCl. Removal of the solvent by distillation *in vacuo* or warming this solution at 80~90° on a water bath for 2.5 hr. left the starting material only, identified as its picrate of m.p. 142~143°, 0.38 g. (92.7% yield), or 0.34 g. (83% yield), respectively.

Action of Sodium Hydroxide on (I)—a) Warming: To a solution of (I) in 10 cc. of water an equivalent amount of 10*N* NaOH solution was added and the solution was allowed to stand over night or warmed on a water bath for 3 hr. This reaction mixture was made alkaline with 10% NaOH solution, extracted with $CHCl_3$ to remove organic impurities, and the residual alkaline solution was acidified with 10% HCl. Excess of HCl was removed carefully by distillation *in vacuo* on a water bath. To a portion of this residue a saturated solution of sodium picrate was added and the precipitated yellow picrate was recrystallized from MeOH, m.p. 141~143°, which was identical with (II).

b) Refluxing: A solution of 300 mg. of (I) in 10 cc. of 10% NaOH was refluxed for 1 hr. On heating, the yellowish solution turned brownish red. Working up as usual afforded only resinous substance in spite of all effort to find 1-hydroxy-2(1*H*)-pyridone.

Action of Sodium Ethoxide on (I)—300 mg. of (I) was added to a solution of 30 mg. of Na in 15 cc. of dehyd. EtOH. This solution was refluxed for 1 hr. on a water bath. The color changed to brownish red. Usual treatment afforded no identifiable substances.

N-(*p*-Dimethylaminophenyl)-*α*-(1-oxido-2-pyridyl)nitrone Hemihydrate (VII)—To a solution of 27 g. (1 mole) of (I) in 25 cc. of water, EtOH solution of 13 g. (1 mole) of *p*-nitroso-N,N-dimethylaniline was added and a solution of 6.5 g. (ca. 1.5 moles) of KOH in 130 cc. of water was added dropwise under stirring and ice-cooling. After a short time, red crystals began to precipitate out. This was collected and recrystallized from AcOEt, m.p. 160~161°, 18 g. (80% yield). *Anal.* Calcd. for $C_{14}H_{15}O_2N_3 \cdot \frac{1}{2}H_2O$: C, 63.14; H, 6.06; N, 15.28. Found: C, 63.46; H, 6.02; N, 15.61.

Infrared spectrum of this material clearly showed the presence of water of crystallization. IR λ_{max}^{Nujol} 2.898 μ (H_2O). On drying over P_2O_5 under a reduced pressure or repeated recrystallization from AcOEt, (VII) was dehydrated and the dehydrated product became light yellow, but soom became reddish on exposure to air.

***α*-(*p*-Dimethylaminophenylimino)pyridineacetonitrile 1-Oxide (VIII)**—a) From (I): To a solution of 1 g. of (I) in a mixture of 6 cc. of 95% EtOH and 3 cc. of water a mixture of 0.42 g. of KCN in 1 cc. of water and 0.5 g. of *p*-nitroso-N,N-dimethylaniline in 2 cc. of 95% EtOH was added at ordinary temperature. The solution turned deep wine red. More water was added and the whole was kept standing in a refrigerator for 2 hr., when red crystals began to precipitate. This was collected and washed with a large quanitity of water. Recrystallization from AcOEt afforded wine red needles, m.p. 183°, 0.54 g. (64% yield). *Anal.* Calcd. for $C_{15}H_{14}ON_4$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.53; H, 5.36; N, 20.73.

b) From (VII): The same product was also obtained by the action of KCN upon (VII) in aqueous EtOH (68% yield).

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Summary

1-(1-Oxido-2-pyridylmethyl)pyridinium iodide (I) was prepared by the King reaction of 2-picoline 1-oxide. Anomalous chemical poperties of (I) towards acid, which caused deoxygenation of (I) without difficulty, and alkali are presented. The formation of N-(*p*-dimethylaminophenyl)-*α*-(1-oxido-2-pyridyl)nitrone and *α*-(*p*-dimethylaminophenylimino)-2-pyridineacetonitrile 1-oxide is also described.

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