UDC 547.829.07

152. Bunsuke Umezawa : Studies on Tertiary Amine Oxides. VI. Comparisons of the Reactivity of 1-(2-Pyridylmethyl)-, 1-(1-Oxido-2-pyridylmethyl)-, and 1′-Methyl-1,2′-methylenebis-pyridinium Salt.

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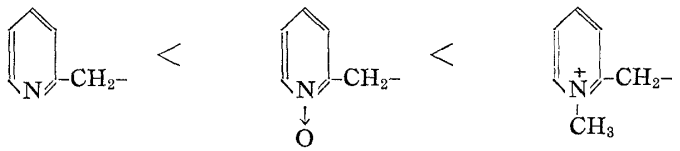
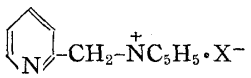
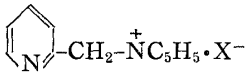
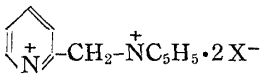
Recently, the preparation of 1-(1-oxido-2-pyridylmethyl)pyridinium iodide[1] by the King's method was reported and it was suggested that the electron-attracting power of the pyridine ring in 1-(2-pyridylmethyl)pyridinium salt was markedly enhanced by deriving the ring nitrogen to N-oxide or methiodide in the order shown below. The suggestion seems to be supported by the fact that 2-picoline failed to undergo the King reaction,[2]



while its N-oxide or methiodide was smoothly converted to the corresponding pyridinium salt[1,3] in the yield of 40.1% or 73%, respectively.

In order to confirm the suggestion, 1-(2-pyridylmethyl)- (I), 1-(1-oxido-2-pyridylmethyl)pyridinium- (II), and 1′-methyl-1,2′-methylenebis-pyridinium salt were compared in regard to the formation of nitrone, cyano-anil, and hydroxyethylpyridinium salt, and their behavior towards alkali. The result are shown in Table I.

Table I.

$R-CH_2-\overset{+}{N}C_5H_5\cdot X^-$	$ON-Ph-NMe_2$ CN^-	$ON-Ph-NMe_2$ OH^-	OH^-	PhCHO OH^-
 (I)	+ (68)	—	− (17)[a]	− (22.3)
 (II)	+ (64;68)	+ (80)	− (36.6)	− (36)
 (III)	+	+ (100)	+ (71)[b]	+[c]

Yields are given in parentheses.

a) (I) ⟶ 2-pyridinemethanol + pyridine (at 100°).

b) 1-Methyl-2(1*H*)-pyridone.

c) 1-Methyl-2(1*H*)-pyridone + $H_5C_5\overset{+}{N}-CH_2CH(OH)C_6H_5\cdot X^-$.

While (II) and (III) gave both cyano-anil and nitrone[1,4] (I) only gave cyano-anil.[2] The formation reaction of nitrone and cyano-anil from pyridinium salt has been reported to be a kind of aldol condensation,[4] the initial step of the reaction being the attack of base on the hydrogen atom of active methylene group in pyridinium salt as shown in Chart 1.

*1 Katakasu, Fukuoka (梅沢文輔).

1) M. Hamana, B. Umezawa, Y. Gotoh, K. Noda : This Bulletin, 8, 692(1960).
2) F. Kröhnke, K. F. Gross : Chem. Ber., **92**, 22(1959).
3) J. A. Berson, T. Cohen : J. Am. Chem. Soc., **78**, 416(1956).
4) F. Kröhnke, H. Leister, I. Vogt : Chem. Ber., **90**, 2792(1957).

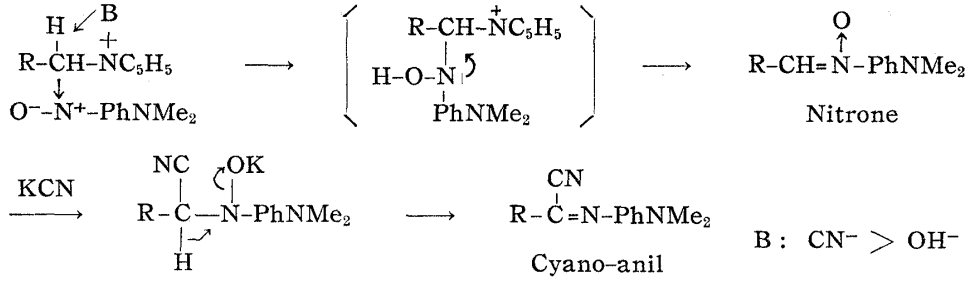


Chart 1. Formation Mechanism of Nitrone and Cyano-anil

The reaction, therefore, must be dependent both on the electron-attracting power of R in Chart 1 and on the nature of catalyst, cyanide or hydroxide ion, of which the former is more powerful than the latter. The fact that (I) gave cyano-anil but failed to give nitrone appears to be ascribable to the nature of the catalyst and the fact that (II) or (III) gave nitrone, while (I) failed to, seems to indicate R in (II) or (III) to be more effective electron-attractor than that in (I).

When an aqueous solution of (III) was treated with dilute sodium hydroxide at room temperature, a blood-red color appeared and 1-methyl-2(1*H*)-pyridone[3] was obtained. It is stated that this color shows the presence of an intermediate, anhydro base.[3] On treatment of (I) or (II) similarly, a light red or an orange color developed and only the starting material was recovered.

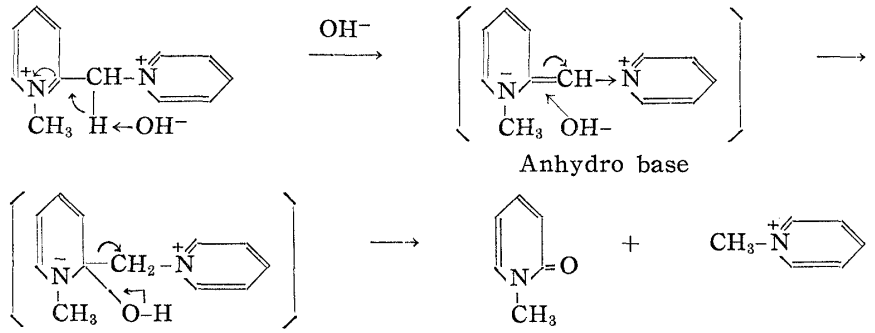
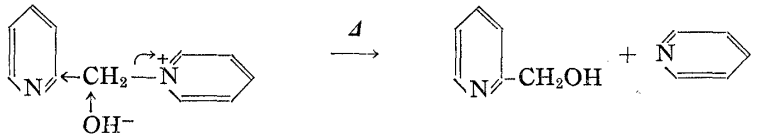


Chart 2.

At elevated temperature, however, the other type of reaction with alkali took place. Refluxing of (I) in dilute alkali gave 2-pyridinemethanol and pyridine. Their formation must have been caused by the attack of hydroxide ion on the carbon atom of the methylene group as shown below. On the other hand, (II) was recovered unchanged when warmed



with alkali. It appears to be most probable that +M effect of N-O group, promoted at elevated temperature,[5] diminishes the cationic nature of the carbon atom in methylene group and thus the nucleophilic attack of hydroxide ion is not favored.

From the fact that (I) or (II) was not affected by dilute sodium hydroxide, the condensation of (I) or (II) with benzaldehyde[6] did not seem to take place and this assumption was confirmed. Owing to the enhanced activity of hydrogen atom in the methylene group

5) E. Ochiai, T. Okamoto : Yakugaku Zasshi, **70**, 384(1950).
6) F. Kröhnke : Angew. Chem., **65**, 605(1953).

by the co-operative inductive effect of two pyridinium moieties, the condensation of (III) with benzaldehyde seemed possible. Addition of dilute sodium hydroxide to hydrous ethanolic solution of benzaldehyde gave 1-methyl-2(1*H*)-pyridone and 1-(β-hydroxyphenethyl)pyridinium salt. Two alternative routes were assumed, one involving first splitting of (III) into 1-methyl-2(1*H*)-pyridone and 1-methylpyridinium salt, which was able to react with benzaldehyde,[7] and the other an aldol-type condensation of (III) and benzaldehyde followed by cleavage as shown in Chart 3. However, because of the appearance of the blood-red color in the reaction mixture showing the presence of anhydro base,[3] the former route would be more favorable.

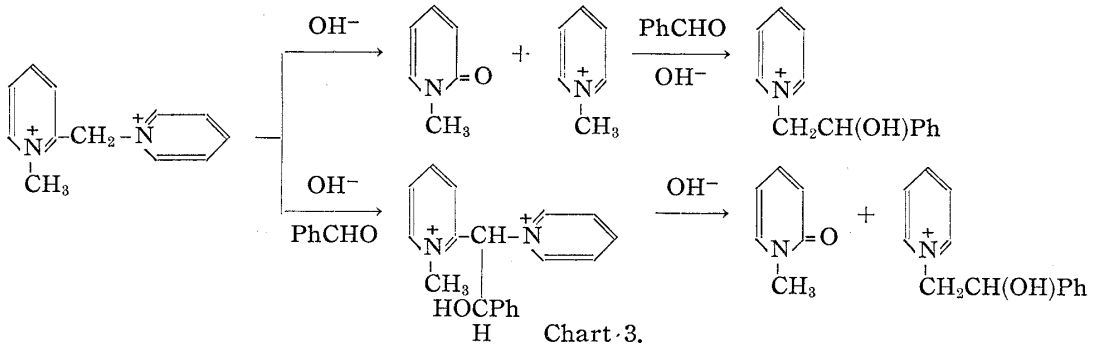


Chart 3.

It may therefore be concluded that the activity of hydrogen atom in the methylene group between pyridinium and pyridine rings in (I), (II), or (III) increases in the order of 1-(2-pyridylmethyl)pyridinium (I), 1-(1-oxido-2-pyridylmethyl)pyridinium salts (II), and 1'-methyl-1,2'-methylenebis-pyridinium salt.

Experimental*2

Syntheses of Starting Materials—1-(1-Oxido-2-pyridylmethyl)pyridinium iodide (II) and 1'-methyl-1,2'-methylenebis-pyridinium iodide (III) were prepared by the King's method. 1-(2-Pyridylmethyl)-pyridinium bromide hydrobromide*3 (I) was prepared by heating ω-bromo-2-picoline hydrobromide in excess of pure pyridine for 1 hr.

Reaction of (I) with Alkali—a) At room temperature : A solution of 500 mg. of (I) in 10 cc. of 10% NaOH was allowed to stand for 2 days. The solution was neutralized with 10 cc. of 10% HCl, concentrated to a small volume, and diluted with MeOH. Deposited NaCl was filtered off and the solution was treated with picric acid in EtOH. The picrate, m.p. 168°(from MeOH), 160 mg. (17% yield), was identical with (I) picrate.

b) At boiling temperature : A solution of 500 mg. of (I) in 10 cc. of 10% NaOH was gently refluxed for 1 hr. Extraction with $CHCl_3$ gave a brown oil which was fractionated by distillation. Fraction (A), boiling up to 140°(bath temp.), afforded a picrate, m.p. 167°, 230 mg. (49.7% yield), which was identified as pyridine picrate (m.p. 167°) by mixed fusion. Fraction (B), $b.p_6$ 100~115°(bath temp.), gave a picrate, m.p. 157~159°, 270 mg. (53% yield), which was identified as 2-pyridinemethanol picrate (m.p. 157~159°) by mixed fusion.

Base-catalysed Condensation of (I) with Benzaldehyde—To a solution of 500 mg. of (I) in 0.5 cc. of H_2O and 20 cc. of EtOH, 400 mg. of BzH and 0.15 cc. of 10*N* NaOH were added. The mixture was allowed to stand for 2 days at room temperature, acidified with 10% HCl, and treated as usual. A picrate, m.p. 168~169°(from MeOH), 210 mg. (22.3% yield), was identical with (I) picrate.

Base-catalysed Condensation of (II) with Benzaldehyde—To a solution of 500 mg. of (II) in 10 cc. of EtOH and 0.5 cc. of H_2O, 500 mg. of BzH and 0.17 cc. of 10*N* NaOH were added. On standing the mixture at room temperature for 2 days, its yellow color gradually changed to pale red. Treatment of the product with picric acid gave a picrate, m.p. 140°, 370 mg. (36% yield), which was identical with (II) picrate. When Et_2NH or piperidine was used as the base, only the starting material was obtained.

*2 All m.p.s are uncorrected.

*3 These hydrobromides were too hygroscopic to show any clear m.p.

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

Base-catalysed Condensation of (III) with Benzaldehyde—To a solution of 500 mg. of (III) in 10 cc. of EtOH and 1 cc. of H_2O, 300 mg. of BzH and 0.13 cc. of 10*N* NaOH were added. The mixture was allowed to stand overnight at room temperature, concentrated *in vacuo*, extracted with $CHCl_3$, and $CHCl_3$ solution was evaporated to afford an oil. A picrate, m.p. 142°(from MeOH), 170 mg. (44.4% yield), was identified as 1-methyl-2(1*H*)-pyridone picrate.

A solution of 1 g. of (III) and 1 g. of BzH in EtOH solution containing 10*N* NaOH was allowed to stand for 2 days in a refrigerator, acidified with $HClO_4$, and concentrated to a small volume to give white crystals, m.p. 212～215°(from H_2O), 100 mg. (15.6% yield), which was identified as 1-(β-hydroxyphenylethyl)pyridinium perchlorate,[7] m.p. 212～215°, by mixed fusion.

The author expresses his deep gratitude to Prof. M. Hamana for his kind instruction.

Summary

The order of the activity of the active methylene of 1-(2-pyridylmethyl)- (I), 1-(1-oxido-2-pyridylmethyl)pyridinium salt (II) and 1′-methyl-1,2′-methylenebis-pyridinium salt (III) was determined.

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153. Takeo Ueda, Shigeshi Toyoshima, Kiyoshi Takahashi, Masako Muraoka, Hiroko Koibuchi, and Yoshiko Seto: Researches on Chemotherapeutic Drugs against Viruses. XXXI.*2 Synthesis and Antiviral Effect of 3-(Alkoxyphenoxy)-1,2-propanediols on Respiratory Virus.

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As can be seen from the summarized review written by Tamm[1] and by Horsfall and Tamm,[2] the search for effective chemotherapeutic drugs on respiratory viruses, particularly influenza virus, has been carried out by number of research workers, and many compounds have been reported to be effective on influenza virus in the experiment using chorioallantoic membrane culture or fertilized eggs, although all the substances except Caprochlorone[3] did not show any therapeutic effect on influenza in mice. On the contrary, search for chemotherapeutic agents on adenovirus has hardly been reported to date.

It was reported by Ueda[4] that 3-(alkyl- or alkanoylphenoxy)-1,2-propanediols, replacing the methyl group in Mephenesin with hydrophobic groups such as alkyl or alkanoyl group, exerted direct virus-inactivating action against poliomyelitis viruses, and moreover, certain compounds of these series were found to be fairly effective on the multiplication of the PR-8 strain of influenza virus in chorioallantoic membrane culture. It was considered, therefore, that the compounds formed by introduction of an active group into

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*2 This paper constitutes part of a series entitled "Researches on Chemotherapeutic Drugs against Viruses" by Takeo Ueda. Part XXX: This Bulletin, 8, 860(1960).

1) I. Tamm: "Viral and Rickettsial Infection of Man," 156(1952).
2) F. L. Horsfall, I. Tamm: Ann. Rev. Microbiol., **11**, 339(1957).
3) O. C. Liu, *et al.*: J. Immunol., **78**, 222(1957).
4) F. Ueda: This Bulletin, **7**, 823(1959).