84. **Goro Kobayashi and Sunao Furukawa:** The Reactions of 2-Picoline 1-Oxide with Acid Anhydride.

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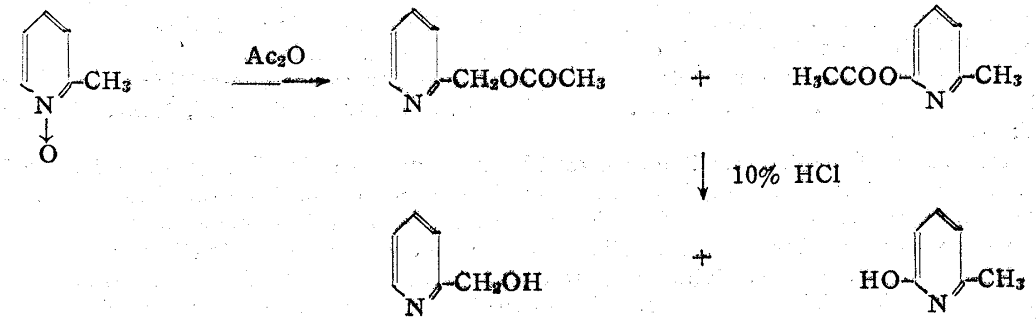
Previously, Katada[1] proved that pyridine 1-oxide reacts with acetic anhydride to yield 2-pyridone. 2-Picoline 1-oxide reacting with acetic anhydride, however, gave rise to 6-methyl-2-pyridone and 2-picolyl alcohol.

2-Picoline 1-oxide was warmed with acetic anhydride on a boiling water bath after which the reaction mixture was distilled under a diminished pressure. The whole reaction mixture, consisting of the acetate of 2-picolyl alcohol and 6-methyl-2-acetyloxypyridine, was distilled at b.p$_5$ 100~120°. After this distillate was hydrolyzed with 10% hydrochloric acid the base was again distilled under a diminished pressure resulting in two fractions, (A) b.p$_5$ 100~120°, and (B) b.p$_5$ above 120°.

The picrate of (A), m.p. 156~158°, was identified to be the picrate of 2-picolyl alcohol by mixed melting-point determination.

(B) was crystalized from acetone, m.p. 163~165°. Analysis of this material agreed with that of 6-methyl-2-pyridone.

The oily (A) was oxidized to picolinic acid with potassium permanganate, converted to 2-picolyl chloride by phosphorus trichloride, and to acetic ester by acetic anhydride. This ester was reduced to 2-picoline by the catalytic reduction using Pd-charcoal. From above experiments, it is considered to be certain that (A) is 2-picolyl alcohol. The course of reactions is shown below.



The formation ratio of 2-picolyl alcohol and 6-methyl-2-pyridone was about 5:2. Furthermore, it was proved that 6-methyl-2-acetyloxypyridine was considerably stable to hydrolysis, differing from normal pyridones.

This reaction, differing from that of pyridine 1-oxide, is assumed to occur even at a considerably lower temperature. The relationship between yield, reaction period, and temperature is shown in the table.

Reaction Time (hr.)	Temperature (°C)	Yield (%) (2-Picolyl alcohol)
8~10	60	40~45
6	90~100	45~50
1	100	45~50
1	130~140	45~50
One week	20~25	20 (Some material was recovered)

In this Table, results using acetic anhydride is given but this reaction was also carried out with benzoic anhydride but resulted in the decrease of the yield. However, succinic anhydride did not react even at 150~160°.

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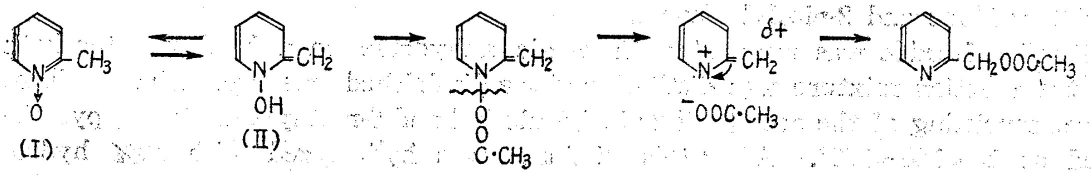
[1] M. Katada: J. Pharm. Soc. Japan, 67, 15(1947).

Considering the reaction mechanism, 2-picoline 1-oxide, having constitution of (II) by prototropy, is acetylated to (III). To the nitrogen cation center caused by fission of the nitrogen-oxygen bond, the methylene double bond shifted, and acetyloxy group undergoes rearrangement to the carbonium cation. This reaction is assumed to be a kind of anionotropy. Further research of the reaction mechanism is being continued.

The authors are indebted to Prof. Dr. E. Ochiai and Mr. K. Hasegawa for their invaluable advices.



Experimental

1) **Reaction of 2-picoline 1-oxide and acetic anhydride**—Ten g. of 2-picoline 1-oxide was mixed with 15 cc. of acetic anhydride and after warming for 1~2 minutes on a boiling water bath, a violent reaction started which soon subsided. The reaction mixture turned dark green. Further heating was continued for 1 hour after which excess of acetic anhydride was distilled off in vacuum, 5 cc. of water was added, and then distilled to dryness in vacuum. The residue was distilled under a diminished pressure. The distillate of b.p$_5$ 100~120° weighed 12~13 g. The oily material was refluxed with 30 cc. of 10% hydrochloric acid for 15~20 minutes. This acid solution was distilled to dryness in vacuum. The residue was neutralized by potassium carbonate and extracted with chloroform. The chloroform residue was fractionated in vacuum into two parts; (A) b.p$_5$ 100~120°, yield, 5.0~5.5 g., and (B) b.p$_5$ above 120°, yield, 1.5~2.0 g.

(A) was rectified again and a fraction of b.p$_5$ 98~105°, weighed 4.5~5.0 g. This fraction was almost pure 2-picolyl alcohol. The picrate formed yellow prismatic crystals, m.p. 156~158° (from methanol). *Anal.* Calcd. for $C_{12}H_{10}O_8N_4$: N 16.56. Found: N, 16.72.

It was identified as the picrate of 2-picolyl alcohol by admixture.

(B) was crystallized from acetone and recrystallized from acetone-methanol to white prismatic crystals, m.p. 163~165°. *Anal.* Calcd. for C_6H_7ON: C, 66.05; H, 6.46; N, 12.84. Found: C, 66.36; H, 6.43; N, 13.04.

2) **Reaction of 2-picoline 1-oxide and benzoic anhydride**—Five g. of 2-picoline 1-oxide was mixed with 15 g. of benzoic anhydride and heated at 150~170° for 8 hours. When cool, the reaction mixture was extracted with 5% hydrochloric acid, the separated benzoic acid filtered off, and the acid solution was washed with ether. The clear solution was concentrated in vacuum and neutralized with potassium carbonate. The separated oily layer was extracted with chloroform and was distilled under a diminished pressure. The distillate of b.p$_7$ 150~170° weighed 5~6 g. This oily base was hydrolyzed and treated in the same manner as in (1). Yield of 2-picolyl alcohol was 1.0~2.0 g. of 6-methyl-2-pyridone, 0.8~1.0 g.

3) **Reaction of 2-picolyl alcohol and phosphorus trichloride**—Into a solution of 0.5 g. 2-picolyl alcohol in 10 cc. dry benzene was added a solution of 1.5 g. phosphorus trichloride in 5 cc. dry benzene. After warming for 5 minutes on a water bath, ice was added, and neutralized slowly with aqueous ammonia while cooling. The benzene layer was separated and dried with sodium sulfate. The benzene residue was a very irritant oil, and weighed 0.5 g. The picrate formed yellow columnar crystals, m.p. 143~145° (from methanol). *Anal.* Calcd. for $C_{12}H_9O_7N_4Cl$: C, 40.38; H, 2.54; N, 15.66. Found: C, 40.81; H, 2.82; N, 15.54.

4) **Reduction of acetic ester of 2-picolyl alcohol**—0.5 g. of 2-picolyl alcohol was mixed with 5 cc. of acetic anhydride and warmed for 0.5 hour on a boiling water bath. A small amount of water was added to the reaction mixture after which the solvent was distilled off in vacuum. The residue was distilled under a diminished pressure. Acetate of 2-picolyl alcohol distilled at b.p$_5$ 105~107°; picrate, yellow needles, m.p. 162~165° (from methanol). *Anal.* Calcd. for $C_{14}H_{12}O_9N_4$: N, 14.73. Found: N, 15.02. The solution of 0.5 g. of this ester in 10 cc. water was reduced catalytically using Pd-charcoal in hydrogen atmosphere. The absorption of hydrogen was about 80 cc. Pd-charcoal was filtered off, the filtrate acidified with hydrochloric acid, and concentrated in vacuum. The picrate, m.p. 165~166°, of the residue was identified as the picrate of 2-picoline by admixture.

5) **Acetylation of 6-methyl-2-pyridone**—0.5 g. of 6-methyl-2-pyridone was mixed with 3 cc. of acetic anhydride and warmed for 0.5 hour on a boiling water bath. The excess of acetic anhydride was decomposed by a small amount of water and distilled off in vacuum. The residue

was distilled under a diminished pressure. The oily 6-methyl-2-acetyloxypyridine, b.p$_4$ 118°, was hydrolyzed by hydrochloric acid to 6-methyl-2-pyridone.

Summary

It was proved that 2-picoline 1-oxide formed 2-picolyl alcohol and 6-methyl-2-pyridone through the action of acetic anhydride. The yield of 2-picolyl alcohol was 50% of the theoretical amount. It is assumed that this reaction is the best available for the preparation of 2-picolyl alcohol.

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85. **Masahiro Torigoe:** Reaction of Cysteine with Nitrogen Mustards and their N-oxides.*

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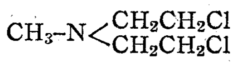
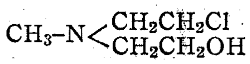
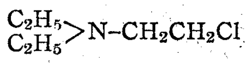
It is a well-known assumption that nitrogen mustard reacts chemically as an alkylating agent with active hydrogen atoms of some tumor cell constituents as a first step of its mitosis-inhibiting action upon proliferating cancer cells.

Experiments were carried out in order to compare the activities of nitrogen mustards with their N-oxides to combine with cysteine in bicarbonate buffer solution at an ordinary temperature. In the experiments, 10^{-3} mole of the compounds were added to the excess of cysteine dissolved in bicarbonate buffer and kept at 25° for a period, which was determined experimentally to be long enough for completion of the alkylating reaction; i.e. until no more increase in cysteine up-take was observed. After the reaction ceased, excess of cysteine was determined colorimetrically[1] with phosphotungstic acid[2], after treating with sodium amalgam[3] to reduce cystine, which appeared in the solution as a result of oxidation of cysteine by the N-oxide or air oxygen. The results of the experiments are summerized in Table I.

TABLE I. Cysteine Up-take of Nitrogen Mustards

	Nitrogen mustard concn. 10^{-3} Mol.	Cysteine-HCl concn. (Mole)	Time of reaction (hrs.)	Cysteine up-take (Mol. equiv.)
(I)	 $CH_3{-}N\Big<\begin{matrix}CH_2CH_2Cl\\CH_2CH_2Cl\end{matrix}$	4×10^{-3}	24	2.0
(II)	 $CH_3{-}N\Big<\begin{matrix}CH_2CH_2Cl\\CH_2CH_2OH\end{matrix}$	2×10^{-3}	24	0.93
(III)	 $\begin{matrix}C_2H_5\\C_2H_5\end{matrix}\Big>N{-}CH_2CH_2Cl$	2×10^{-3}	72	0.94

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* M. Ishidate, Y. Sakurai: Studies on Cancerocidal Substances. VII.

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[1] A. Schöberl, P. Rambacher: Biochem. Z., **295**, 377(1938).

[2] O. Folin, H. Trimble: J. Biol. Chem., **60**, 478(1924).

[3] I. M. Kolthoff, W. Strick: J. Am. Chem. Soc., **72**, 1952(1950).