UDC 547.821.41

82. Tetsuzo Kato and Yoshinobu Goto : Synthesis of Methylpyridine Derivatives. XVI.*1 The Reaction of Picolines and their N-Oxides with Amyl Nitrite.

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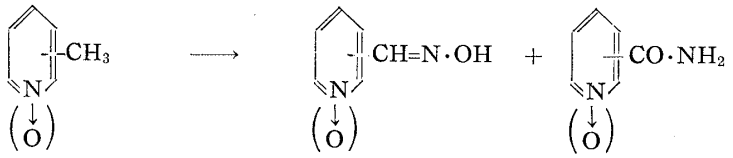
It is a well documented fact that amyl nitrite reacts with the active methylene or methyl group to yield the nitroso compound.[1] However, no previous work on the active methyl group of heterocyclic system such as methylpyridine or methylquinoline appears in literature. The present investigation is concerned with the reaction of picolines and their N-oxides with amyl nitrite in order to compare the reactivity of the methyl function of picolines with that of their N-oxides.

Although picoline or its N-oxide did not react with amyl nitrite under usual conditions reported in previous papers, the reaction was assumed to occur smoothly in liquid ammonia in the presence of metal amide or sodium hydroxide giving the corresponding aldoxime and acid amide.



2-Picoline 1-oxide reacted readily with amyl nitrite in liquid ammonia in the presence of sodium amide at room temperature to give picolinaldehyde 1-oxide oxime and picolinamide 1-oxide. Table I, which follows, summarizes the result of this reaction.

Table I. Reaction of 2-Picoline 1-Oxide at Room Temperature

N-Oxide (mol.)	$C_5H_{11}ONO$ (mol.)	$NaNH_2$ (mol.)	NH_3 (ml.)	Time (hr.)	Product (%)		
					Aldoxime	Acid amide	Recovery
0.01	0.011	0.021	10	1	36.9	3.6	12.8
0.01	0.011	0.02[a)]	15	2	37.6	2.1	12.8
0.01	0.011	0.021	10	48	38.4	3.6	9.1
0.01	0.021	0.021	10	5	51.4	5.8	—
0.01	0.021	0.021	10	24	40.5	10.8	—
0.01	0.021	0.021	10	48	39.8	10.8	—

a) Prepared freshly from sodium metal and liquid ammonia.

The reaction of 2-picoline 1-oxide at −33° in the presence of potassium amide (B-Method in Table II) increased the yield of the corresponding acid amide (16.6%). The reaction of 3-picoline 1-oxide under the same condition resulted in the recovery of the starting N-oxide. However, 4-picoline 1-oxide reacted easily in the presence of potassium amide at −33° to give 71% of the aldoxime, 10% of the amide and 2% of isonicotinonitrile 1-oxide which was only one nitrile obtained in this investigation.

Attempts were made to react three kinds of picoline instead of their N-oxides in order to know the difference of activity between picoline and its N-oxide. The reaction of 3-picoline resulted in the recovery of the starting material, but 2- and 4-picoline afforded the corresponding acid amide in the presence of sodium amide at room temperature. Treatment with potassium amide at −33° afforded the aldoxime. In these

*1 Part XV : T. Kato, Y. Goto, Y. Yamamoto : Yakugaku Zasshi, **82**, 1650 (1962).
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1) *e.g.* Organic Reactions, **VII**, 327 (1953).

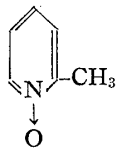
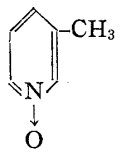
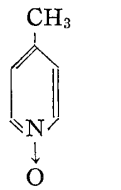
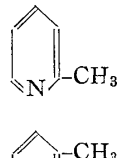
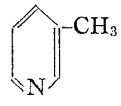
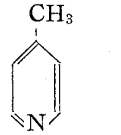
reactions the recovery of the starting material was always observed. Table II shows the summary of these reactions.

Based upon these results, it may be given as a conclusion that the methyl group of picoline N-oxide is much more reactive than that of picoline and that the 4-substituted methyl group is more reactive than the 2-isomer and the methyl group at 3-position of pyridine ring is almost unreactive toward amyl nitrite under these conditions.

As an interesting sidelight to this investigation, we have found that the reaction of 2-picoline, 4-picoline and 4-picoline 1-oxide in the presence of sodium amide at room temperature (A-Method in Table II) resulted in the formation of corresponding acid amide, but 2-picoline 1-oxide was easily converted to picolinaldehyde 1-oxide oxime in 51.4% yield under the same condition, and that the aldoximes obtained in this reaction did not react with another mole of sodium amide in liquid ammonia, that is, the reaction of the aldoxime with sodium amide resulted in the recovery of the starting material. However, isonicotinonitrile 1-oxide was easily converted to the acid amide under the same condition.

It is reported that the *syn*-type aldoxime is more stable than the *anti*-type one which undergoes readily a catalyzed reaction with sodium amide to form the nitrile or

Table II.

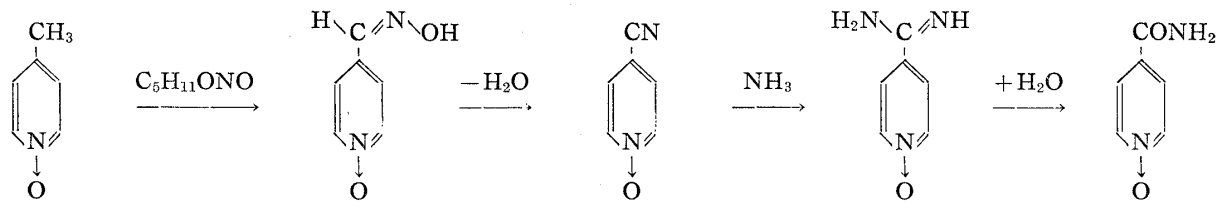
Starting material	Product (%) \ Method	A	B	C	D
	Aldoxime	51.4	57.2	45.7	22.5
	Nitrile	—	—	—	—
	Acid amide	5.8	16.6	8	5
	Recovery	—	—	13.7	26.6
	Aldoxime	—	—		
	Nitrile	—	—		
	Acid amide	—	—		
	Recovery	74.3	70		
	Aldoxime	—	71	50	
	Nitrile	—	2	—	
	Acid amide	41.3	10	5	
	Recovery	—	—	15.6	
	Aldoxime	—	22.9		
	Nitrile	—	—		
	Acid amide	2	—		
	Recovery	79.2	55.9		
	Aldoxime	—	—		
	Nitrile	—	—		
	Acid amide	—	—		
	Recovery	83.9	71		
	Aldoxime	—	65.9		
	Nitrile	—	—		
	Acid amide	18	5		
	Recovery	45.6	8		

a) A-Method : $NaNH_2$, room temperature. B-Method : KNH_2, −33°. C-Method : $NaNH_2$, −33°. D-Method : NaOH, room temperature.

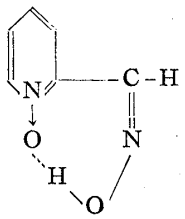
b) Starting material 0.01 mole, amyl nitrite 0.021 mole, alkali amide or hydroxide 0.011 mole, reaction time 2.5 hr.

c) Liquid ammonia 20 ml. at room temperature, 300 ml. at −33°.

the amidine.[2] In view of these results, it is considered that the aldoximes isolated in this reaction would be *syn*-type,[3] and the reaction at room temperature (A-Method in Table II) gave the *anti*-aldoximes which reacted easily with sodium amide to form the acid amides via the nitriles and amidines.



On the other hand, the *anti*-type picolinaldehyde 1-oxide oxime would be comparatively stable in order to form the hydrogen bond between the oxygen of N-oxide and the hydrogen of the oxime, and consequently this reaction resulted in the fromation of the corresponding aldoxime as a main product (51.4 %) with a small amount of the acid amide as a by-product (5.8 %).



Experimental

General Procedure

A-Method——To a mixture of 0.43 g. (0.011 mole) of $NaNH_2$ and 0.01 mole of methylpyridine or its N-oxide in 10 ml. of liq. NH_3 was added 2.46 g. (0.021 mole) of amyl nitrite in 10 ml. liq. NH_3 in a sealed pyrex glass tube,[4] and allowed to stand at room temperature for 2.5 hr. The reaction mixture was neutralized with a solution of 0.6 g. of NH_4Cl in 5 ml. of liq. NH_3.

B-Method——In a 500 ml. three necked flask equipped with a stirrer and a dry ice condenser was placed 300 ml. of liq. NH_3, and was added 0.43 g. (0.011 mole) of K with a small amount of $FeCl_3$ as a catalyst. As soon as a blue coloration had disappeared, 0.01 mole of methylpyridine or its N-oxide and 2.46 g.(0.021 mole) of amyl nitrite were added. After stirring for 2.5 hr., 0.6 g. of NH_4Cl was added.

C-Method——In a 500 ml. three necked flask a mixture of 0.43 g. (0.011 mole) of powdered $NaNH_2$ and 0.01 mole of methylpyridine or its N-oxide in 300 ml. of liq. NH_3 was placed, and 2.46 g. (0.021 mole) of amyl nitrite were added. After stirring for 2.5 hr., 0.6 g. of NH_4Cl was added.

D-Method——In a sealed tube a mixture of 0.44 g. (0.011 mole) of powdered NaOH and 0.01 mole of 2-picoline 1-oxide in 10 ml. of liq. NH_3 was placed, and 2.46 g. of amyl nitrite were added to this mixture.

Reaction of 2-Picoline 1-Oxide

A-Method——After evaporation of liq. NH_3, a small amount of H_2O was added. The residue, which was sparingly soluble in H_2O, was recrystallized from EtOH to yield 0.51 g. of white fine needles, m.p. 215~216° (decomp.), which was identical with picolinaldehyde 1-oxide oxime[5] by the admixture test and comparison of IR spectrum with an authentic sample. The H_2O soluble fraction was condensed under a diminished pressure, and the resulted residue was extracted with 1) $CHCl_3$ and 2) hot EtOH. 1) After drying with Na_2SO_4, the $CHCl_3$ solution was chromatographed on neutral alumina, using $CHCl_3$ and EtOH as eluent. From the $CHCl_3$ eluted fraction 0.08 g. of m.p. 161~162° was obtained, white needles from MeOH, which was identical with picolinamide 1-oxide[6] by the admixture test. Yield, 5.8 %. From the EtOH eluted fraction 0.01 g. of the oxime was obtained. 2) The EtOH extract was purified by recrystallization from H_2O to give 0.19 g. of the oxime. The total yield of picolinaldehyde 1-oxide oxime was 0.71 g. (51.4 %).

B-Method——After evaporation of liq. NH_3, the residue was treated similarly as described above. Total yield of the oxime was 0.78 g. (57.2 %) and that of the acid amide was 0.23 g. (16.6 %).

C-Method——After evaporation of NH_3, the residue was extracted with 1) $CHCl_3$ and then with 2) hot EtOH. 1) The $CHCl_3$ extract was distilled under a diminished pressure to give a pale yellow liquid

2) G. Vermillion, C. Hauser : J. Org. Chem., **6**, 507 (1941).
3) M. Hamana *et al.* : Yakugaku Zasshi, **80**, 1519 (1960).
4) K. Shimo : "Ekian Yūkikagaku (Organic Chemistry in Liquid Ammonia)" (Gihodo) **1957**, 18.
5) D. Jerchel *et al.* : Ann., **613**, 153 (1958).
6) M. Shimizu *et al.* : Yakugaku Zasshi, **72**, 1474 (1952).

of $b.p_5$ 130~140° (bath temp.), which was identical with 2-picoline 1-oxide by the admixure test of its picrate. Yield, 0.15 g. (13.7 %).

The residue was recrystallized from MeOH to give 0.11 g. of picolinamide 1-oxide. Yield, 8%. 2) The hot EtOH extract was recrystallized from H_2O to give 0.63 g. of the aldoxime (45.7%).

D-Method——After allowing to stand for 2.5 hr. at room temperature., liq. NH_3, was evaporated. The residue was extracted with $CHCl_3$ and treated similarly as above C-Method to give 0.31 g. of the aldoxime (22.5 %), 0.07 g. of the acid amide (5 %) and 0.29 g. of the starting N-oxide (26.6 %).

Reaction of 4-Picoline 1-Oxide

A-Method——After evaporation of NH_3, a small amount of H_2O was added. Recrystallization of the residue, which was sparingly soluble in H_2O, gave white crystals of m.p. 293~296° (decomp.). The IR spectrum was identical in every respect with isonicotinamide 1-oxide[6] and its elemental analyses were satisfactory for this compound. Yield, 0.3 g. The H_2O soluble fraction was condensed under a diminished pressure and the residual solid was recrystallized from EtOH to give 0.27 g. of the acid amide .Total yield of isonicotinamide 1-oxide was 0.57 g. (41.3 %).

B-Method——After evaporation of NH_3, the residue was extracted with 1) $CHCl_3$ and 2) hot EtOH. 1) Recrystallization of the $CHCl_3$ extract from EtOH gave 0.02 g. of m.p. 222~223° and 0.13 g. of m.p. 216~217°, which were identical with isonicotinonitrile 1-oxide[7] and isonicotinaldehyde 1-oxide oxime[8] by the admixture test and the comparison of IR spectrum with that of the corresponding authentic samples.

2) The hot EtOH extract was recrystallized from EtOH to yield 0.99 g. of crude crystals (m.p. 200~210°). The IR spectrum of this crystals contradicted the existence of CN group. This crude crystal was dissolved in Ac_2O and filtered. The insoluble crystal was collected and recrystallized from EtOH to give 0.1 g. of isonicotinamide 1-oxide. The filtrate was warmed on a steam bath to give isonicotinonitrile 1-oxide. Therefore, the crystals obtained from the hot EtOH extract (m.p. 200~210°) was assumed to be the mixture of the acid amide and the oxime which was converted to the nitrile by heating with Ac_2O. Yield of the oxime, acid amide and nitrile were respectively ca. 70 %, 10 % and 2 %.

C-Method——After evaporation of NH_3, the residue was treated similarly as C-Method of 2-picoline 1-oxide. The $CHCl_3$ soluble fraction was purified by chromatography on alumina using $CHCl_3$ and EtOH as eluent to give 0.17 g. of the starting N-oxide (15.6 %) and 0.01 g. of the aldoxime. Recrystallization of the $CHCl_3$ insoluble fraction from EtOH afforded 0.12 g. of the aldoxime. From the hot EtOH extract 0.54 g. of crude crystals of m.p. 213~216° was obtained. This crude crystal was treated with Ac_2O similarly as described above B-Method to give 0.06 g. of isonicotinamide 1-oxide from the Ac_2O insoluble fraction. The Ac_2O soluble fraction was heated on a steam bath to yield isonicotinonitrile 1-oxide. Total yield of the aldoxime was ca. 50 %.

Reaction of 2-Picoline

A-Method——After evaporation of NH_3, the residue was extracted with Et_2O. The Et_2O solution was condensed by the use of water-pump vacuum. The distillation was carried out by the use of an efficient condenser, and the distillate was bubbled into a receiver flask in which placed 10% HCl. From the distillate 2-picoline was recovered (Yield, 0.74 g., 79.5 %). The residue was distilled under a diminished pressure to give a white solid of $b.p_4$ 140~150° (bath temp.). Recrystallization from Et_2O-petr. ether afforded 0.02 g. of m.p. 104~105°, which was identical with picolinamide[9] by the admixture test with an authentic sample.

B-Method——After evaporation of NH_3, the residue was treated similarly described as above A-Method to give 1.79 g. (as picrate) of the starting picoline (55.9 %) and 0.28 g. of picolinaldehyde oxime[10] (22.9 %).

Reaction of 4-Picoline

A-Method——After evaporation of NH_3, the residue was extracted with 1) Et_2O and 2) hot $CHCl_3$. 1) The starting picoline was recovered from the Et_2O solution by the similar treatment as described above. Yield, 1.47 g. as its picrate, m.p. 169°, 45.6 %. Recrystallization of the residue from benzene-EtOH gave 0.2 g. of m.p. 156~157°, which was identical with isonicotinamide[11] by the admixture test with an authentic sample. 2) From the $CHCl_3$ extract 0.02 g. of the acid amide was obtained. Total yield of the acid amide was 0.22 g. (18 %).

B-Method——After evaporation of NH_3, the residue was extracted with 1) Et_2O, 2) $CHCl_3$ and then 3) hot EtOH. From 1) 8 % of 4-picoline (0.25 g. as its picrate) and 0.45 g. of isonicotinaldehyde oxime[10]

7) E. Ochiai *et al.* : Yakugaku Zasshi, **65B**, 435 (1945).
8) W. Mathes *et al.* : Ann., **618**, 152 (1958).
9) C. Engler : Ber., **27**, 1784 (1894).
10) S. Ginsburg *et al.* : J. Am. Cnem. Soc., **79**, 481 (1957).
11) L. Ternàjgò : Monatsh., **21**, 459 (1900).

(m.p. 130~132°, white prism from benzene) and 0.06 g. of isonicotinamide (5 %) were obtained. From 2) and 3) 0.15 g. and 0.17 g. of the aldoxime were respectively obtained. Total yield of the aldoxime was 0.8 g. (65.6 %).

N-Oxidation of Isonicotinaldehyde Oxime with Monoperphthalic Acid——To a solution of 0.22 g. of isonicotinaldehyde oxime in 10 ml. of Me_2CO, 6 ml. of Et_2O solution of monoperphthalic acid (0.0075 g. of active O_2 in 1 ml.) was added. The mixture was allowed to stand for a week in a refrigerator. After precipitated phthalic acid was removed by filtration, the filtrate was condensed. The residual solid was recrystallized from EtOH to white needles, m.p. 215~217° (decomp.). Yield, 0.18 g. (72 %). *Anal.* Calcd. for $C_6H_6O_2N_2$: C, 52.17, H, 4.38, N, 20.28. Found : C, 52.16, H, 4.40, N, 19.99.

Reaction of Isonicotinonitrile 1-Oxide with $NaNH_2$——To a mixture of 0.05 g. of isonicotinonitrile 1-oxide and 0.02 g. of $NaNH_2$ in 10 ml. of liq. NH_3, was added 0.05 g. of amyl nitrite and 0.05 g. of iso-amyl alcohol in 10 ml. of liq. NH_3. The reaction mixture was concentrated to 3 ml. After allowing to stand for 10 min. at room temperature., 0.04 g. of NH_4Cl in 5 ml. of NH_3 was added. Liq. NH_3 was evaporated and the residue was purified by recrystallization from EtOH to give 0.04 g. of isonicotinamide 1-oxide, m.p. 293~296° (decomp.).

A part of expenses for this work was defrayed by the Grant-in-Aid for Scientific Research from the Ministry of Education, which is gratefully acknowledged. Thanks are also due to Miss. H. Miyaji for elemental analyses and to Mr. T. Asano for infrared spectra.

Summary

The reactions of picolines and their N-oxides with amyl nitrite in the presence of metal amide or sodium hydroxide in liquid ammonia afforded the corresponding aldoximes and acid amides in comparatively good yields. It may be concluded that the methyl group of picoline is much less reactive than that of N-oxide and that the reactivity of methyl group in the pyridine ring increases in the order of 3-, 2-, and 4-position.

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83. Tatsuhiko Nakano,[*1] Masahisa Hasegawa,[*1] and Carl Djerassi[*2] : Bromination of 2-Oxo Steroids.[1]

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The most important and generally accepted views on the stereochemistry of the bromination of cyclohexanones in general and keto steroids in particular are attributed to Corey.[2] According to these generalizations, the kinetically controlled bromination product is always that in which the bromine atom assumes an axial orientation, since orbital overlap in the transition state is most favorable in such a geometric arrangement. If there exist no serious steric interactions between the axial bromine atom and other substituents, then the kinetic product is also the thermodynamically favored one.

*1 Yoshida-konoe-cho, Sakyo-ku, Kyoto (中野立彦, 長谷川昌久).
*2 Stanford, California, U. S. A. (Carl Djerassi).

1) Most of this work was done by one of us (T. N.) during the tenure of his postdoctorate fellowship at Stanford University while on leave from Kyoto University. For preliminary communication see C. Djerassi, T. Nakano, Chem. & Ind. (London), **1960**, 1385.

2) E. J. Corey : J. Am. Chem. Soc., **75**, 2301 (1953); *Ibid.*, **76**, 175 (1954); Experientia, **9**, 329 (1953).