ELUCIDATION OF THE REACTION PATH FOR THE NITROSATION OF 2- AND 4-METHYLPYRIDINE 1-OXIDES WITH ALKYL NITRITE IN LIQUID AMMONIA**

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Abstract - The reaction path for the nitrosation of 2- and 4-methylpyridine 1-oxides with alkyl nitrite in the presence of $NaNH_2$ in liquid NH_3 was elucidated experimentally, and theoretically by the use of a semiempirical molecular orbital method (PM3 method). In the case of the nitrosation of 4-methylpyridine 1-oxide at room temperature, only 4-pyridinecarboxamide 1-oxide was obtained, while at -33℃ a thermodynamically unstable aldoxime, (Z)-4-pyridinecarbaldehyde 1-oxide oxime, which was easily transformed into E-form by heating, was obtained. On the other hand, the nitrosation of 2-methylpyridine 1-oxide gave only a thermodynamically stable aldoxime, (E)-2-pyridinecarbaldehyde 1-oxide oxime, both at room temperature and at -33℃. These results were reasonably explained by PM3 method.

It is well known that the oximes are easily obtained in rather good yield by the nitrosation of an active alkyl group of the heterocyclic compounds with alkyl nitrite in the presence of sodium amide ($NaNH_2$) in liquid ammonia (liq. NH_3).[1] In 1963 Kato and Goto reported[1a] that the reaction of 4-methylpyridine 1-oxide (1) with isoamyl nitrite ($C_5H_{11}ONO$) in the presence of $NaNH_2$ in liq. NH_3 gave only 4-pyridinecarboxamide 1-oxide (5) at room temperature and at -33℃ a thermodynamically stable aldoxime, (E)-4-pyridinecarbaldehyde 1-oxide oxime (3E) in good yield, on the other hand in the case of the reaction of 2-methylpyridine 1-oxide (2) under the same conditions a thermodynamically

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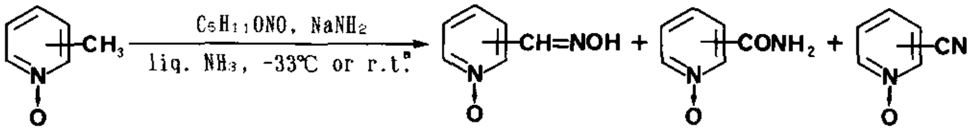
** Dedicated to Emeritus Professor Masatomo Hamana on the occasion of his 75th birthday.

stable aldoxime, (E)-2-pyridinecarbaldehyde 1-oxide oxime (4E) was obtained both at room temperature and at -33℃.

In this report, we would like to present the results of a careful reinvestigation of the work described above to elucidate the reaction path using a semiempirical molecular orbital method (PM3 method[2]) as well as the experimental study.

The most part of the results is the same as that by Kato and Goto, but it is noteworthy that the reaction of 1 with $C_5H_{11}ONO$ in the presence of $NaNH_2$ in liq. NH_3 at -33℃ gave not 3E but only (Z)-4-pyridinecarbaldehyde 1-oxide oxime (3Z) in 50% yield. The configurations of 3Z and other oximes were confirmed by the ^1H-nmr spectrum,[3] which was measured without further purification other than water washing of the product immediately after the evaporation of NH_3 from the reaction mixture. The spectral data of these oximes were identical with those of the authentic samples.[4] It is conceivable that 3Z obtained by Kato and Goto was isomerized by the post-treatment of the product such as heating or purification(Table I).

Table I . Reaction of 2- and 4-Methylpyridine 1-Oxides with $C_5H_{11}ONO$ in the Presence of $NaNH_2$ in Liquid NH_3



1 = 4-CH_3
2 = 2-CH_3

3E and 3Z = 4-CH=NOH
4E and 4Z = 2-CH=NOH

5 = 4-$CONH_2$
6 = 2-$CONH_2$

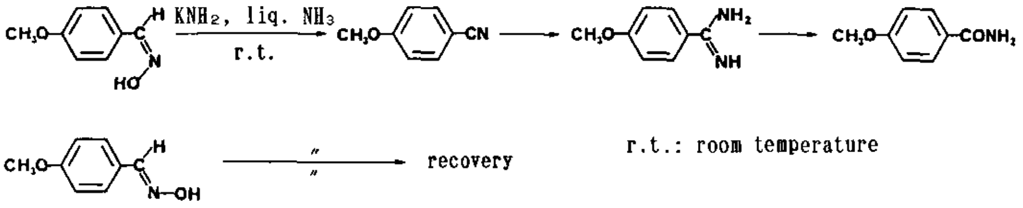
7 = 4-CN
8 = 2-CN

Reactant	Temperature	Product(%)								Recovery(%)
		aldoxime				amide		nitrile		
		3E	3Z	4E	4Z	5	6	7	8	
1	r.t.[a]	--	--			41.3		--		--
1	-33℃	--	50			5		--		15.6
2	r.t.[a]			51.4	--		5.8		--	--
2	-33℃			45.7	--		8		--	13.7

a)room temperature

In 1941 Vermillion and Hauser[5] reported that in the presence of KNH_2 in liq. NH_3 at room temperature, (Z)-p-anisaldehyde oxime changed via nitrile and amidine into the corresponding amide, while under similar conditions (E)-p-anisaldehyde oxime was mostly recovered, being partly decomposed (Scheme 1).

Taking into account this report by Vermillion and Hauser, the fact that only 5 was obtained in the nitrosation of 1 with $C_5H_{11}ONO$ in the presence of $NaNH_2$ in liq. NH_3 at room



r.t.: room temperature

Scheme 1

temperature strongly indicates that 5 was formed via originally thermodynamically unstable Z-isomer 3Z. This suggestion was made first by Kato and Goto and this estimation was now confirmed through the following experimental and theoretical studies.

The corresponding Z- and E-isomers of aldoxime which are obtained by nitrosation of 1 and 2 were treated under the same conditions as those of the nitrosation to afford the results as shown in Table II. When 3Z was treated with $NaNH_2$ in the presence of $C_5H_{11}ONO$ and $C_5H_{11}OH$ in liq. NH_3 at room temperature, the corresponding amide and nitrile were obtained in 22 and 20% yields, respectively, with the recovery of a small amount of 3Z and 3E isomerized from 3Z. Since the nitrile is quantitatively converted into the amide in liq. NH_3, this result is compatible with the previous experimental fact that only 5 was obtained in 41% yield as shown in Table I. At -33℃, 3Z was recovered in 84% yield with very small amounts of amide and nitrile. In the case of the reaction of 3E, both at room temperature and at -33℃ 3E was recovered nearly quantitatively. On the other hand, the reaction of (Z)-2-pyridinecarbaldehyde 1-oxide oxime (4Z) at room temperature gave the corresponding amide (6) in 40% yield and nitrile (8) in 14% yield with deoxygenated amide in 5% yield and 4E isomerized from 4Z in 12% yield, while at -33℃ 4Z isomerized mostly to the stable isomer 4E accompanied with the corresponding amide(6)in 18% yield and no 4Z was recovered. In the reaction of 4E both at room temperature and at -33℃, 4E was recovered nearly quantitatively.

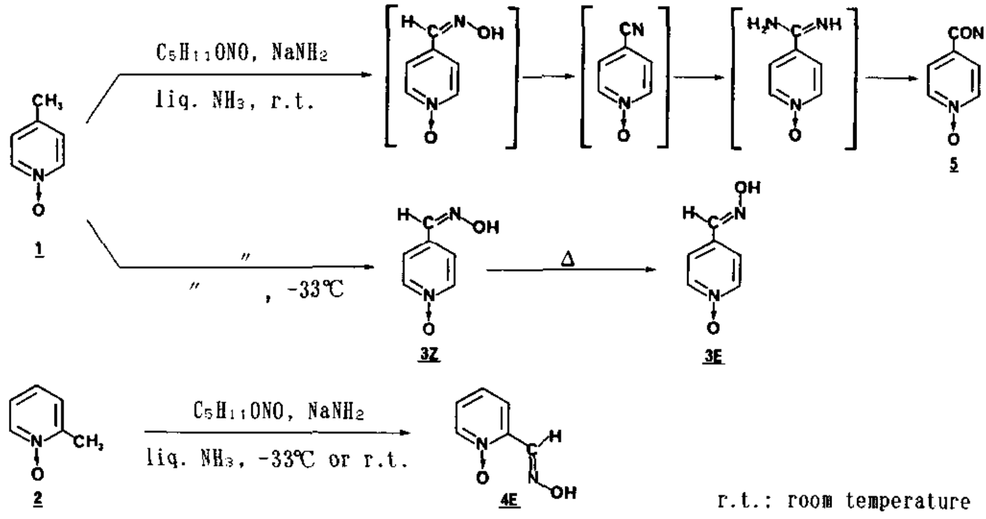
Table II. Reaction of Pyridinecarbaldehyde 1-Oxide Oximes with $NaNH_2$ in the Presence of $C_5H_{11}ONO$ and $C_5H_{11}OH$ in Liquid NH_3

Reactant	Temperature	Product(%)				Recovery(%)	Isomer(%)[a]			
		amide		nitrile						
		5	6	7	8		3E	3Z	4E	4Z
3E	r.t.[d]	3		3		90		--		
3E	-33℃	--		--		quant[b]		--		
3Z	r.t.[d]	22		20		4	7			
3Z	-33℃	4		4		84	--			
4E	r.t.[d]		5.5		--	90				--
4E	-33℃		--		--	quant[b]				--
4Z	r.t.[d]		40+5[c]		14	--			12	
4Z	-33℃		18		--	--			47	

a)isomerized aldoxime b)quantitative recovery c)deoxygenated amide
d)room temperature

Besides, under the reaction conditions of Vermillion and Hauser, i.e., the reaction of 3Z with $NaNH_2$ in liq. NH_3 at room temperature for a day gave only 5 in 57% yield, whereas that of 3E resulted in 31% recovery with a small amount of 5 in 5% yield. The reaction of 4E and 4Z under the same conditions described above led to almost resinification.

These experimental results described above indicate obviously that in the nitrosation of 1 at room temperature the thermodynamically unstable Z-isomer 3Z could be first formed and then via nitrile and amidine it could be converted into amide eventually, and at -33℃ only 3Z is formed, which is isomerized by post-treatment such as heating, on the other hand, in the nitrosation of 2 both at room temperature and at -33℃ only the thermodynamically stable E-isomer 4E is formed (Scheme 2).



r.t.: room temperature

Scheme 2

Next, a semiempirical molecular orbital study (PM3 method) was carried out about the nitrosation of 1 and 2 with methyl nitrite (CH_3ONO) as a simpler model instead of $C_5H_{11}ONO$. The reaction coordinate system assumed for another hydrogen abstraction by NH_2^- from the complex of 1-oxido-4-pyridomethide anion, which occurs by one hydrogen abstraction from active methyl group of 1, and CH_3ONO is shown in Figure 1 in the case of the nitrosation of 1 and the system could be regarded as a supermolecule.

The enthalpies of formation of supermolecules were calculated by PM3 method, and the change of the energies along the reaction path was investigated. The reaction profile for the reaction of the complex of 1-oxido-4-pyridomethide anion and CH_3ONO with NH_2^- is shown in Figure 2. The enthalpy of formation is plotted as ordinate and the distance between N5 and H4 (vide infra) as abscissa, i.e., as the *reaction coordinate* (r_{N-H}).

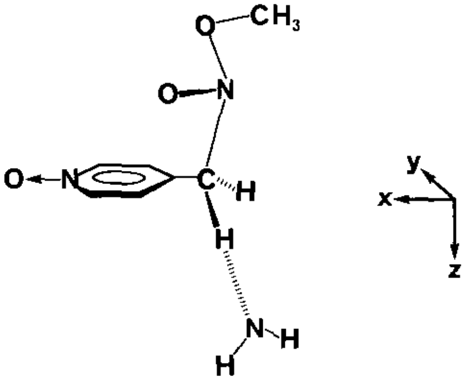


Figure 1. Coordinate System Assumed for Hydrogen Abstraction by NH_2^- from the Complex of 1-Oxido-4-pyridomethide Anion and CH_3ONO

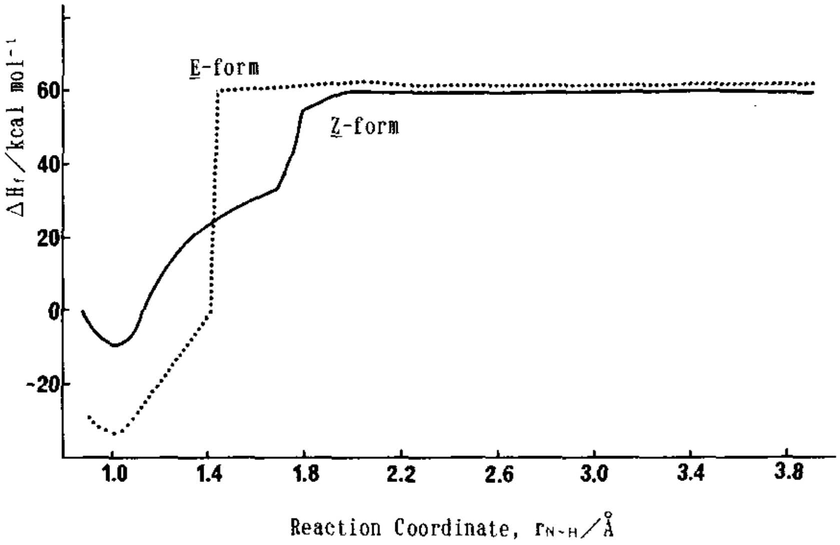
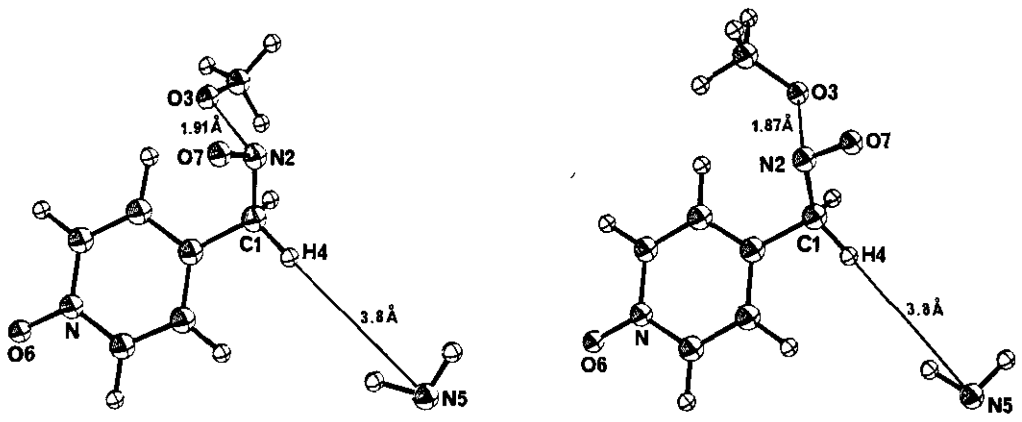


Figure 2. Reaction Profile for Nitrosation of 4-Methylpyridine 1-Oxide with CH_3ONO

In the solid line of formation of Z-isomer a steep drop in energy is observed at the distance r_{N-H} between 1.80～1.70 Å, and at *this point the distance* N2-O3 changes fairly from 2.02 to 4.68 Å with almost accomplished formation of 3Z. In the dotted line of formation of E-isomer a steep drop in energy is observed ultimately at the distance r_{N-H} between 1.50-1.40 Å, and at the same time the distance N2-O3 changes remarkably from 1.99 to 16.28 Å.

All optimized geometries of the supermolecules in the case of formation of Z- and E-isomers are shown in Figure 3(a) and 3(b), respectively, which are optimized at the distance 3.8 Å between the nitrogen atom N5 of NH_2^- and the hydrogen atom H4 of CH_2 group of 1-oxido-4-pyridomethide anion.



(a)Formation of (b)Formation of E-Isomer

Figure 3. ORTEP Drawing of the Supermolecule Composed of 1-Oxido-4-pyridomethide Anion, CH_3ONO and NH_2^- at the Distance 3.8 Å between N5 and H4

It is obvious that the atoms N5, C1, N2 and O3 in Figure 3(a) lie on the same plane, i.e., the reaction should proceed easily with this conformation. In contrast with the case of Figure 3(a), when N5 approaches H4 as shown in Figure 3(b), i.e., the reaction takes place, the atoms N5, C1, N2 and O3 should lie on the same plane, but to do so the methoxyl group has to be rotated around the axis C1-N2 and consequently is brought so closely to the pyridine nucleus that the reaction to form 3E could be more difficult to occur than the one to form 3Z. From these results, it can be considered that 3Z is more preferentially produced than 3E in the nitrosation of 1.

On the other hand, in the case of the nitrosation of 2 the formation of 4E is likely to be more preferable to that of 4Z, judging from the reaction profile of the reaction of 2 with CH_3ONO energically (Figure 4). As shown in Figure 4, in the solid line of the formation of 4E when N5 approaches H4 at the distance r_{N-H} between 2.7-2.6 Å, the energy lowers remarkably and concurrently the distance N2-O3 changes from 1.99 to 4.87 Å, whereas in the dotted line of the formation of 4Z the reaction proceeds with more difficulty than the case of the formation of 4E and at the distance r_{N-H} between 1.50-1.40 Å a steep drop in energy is observed and at the same time the distance N2-O3 changes from 2.02 to 5.06 Å.

All optimized geometries of the supermolecules in the case of formation of Z- and E-isomers are shown in Figure 5(a) and 5(b), respectively, which are optimized at the distance 3.8 Å between the nitrogen atom N5 of NH_2^- and the hydrogen atom H4 of CH_2 group of 1-oxido-2-pyridomethide anion (Figure 5(a) and 5(b)).

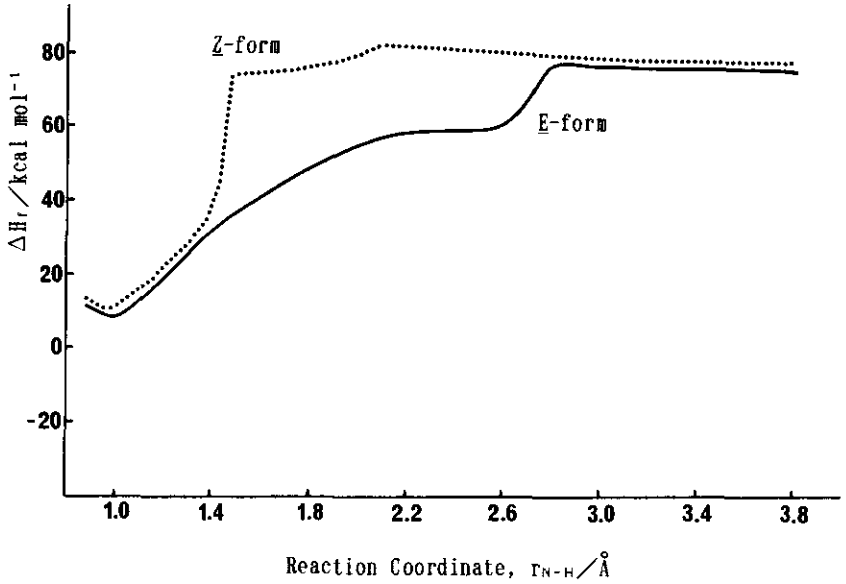
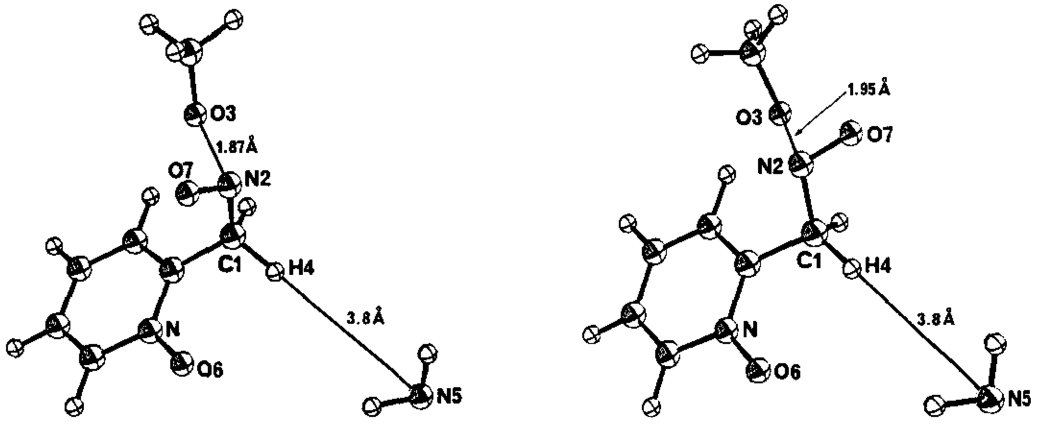


Figure 4. Reaction Profile for Nitrosation of 2-Methylpyridine 1-Oxide with CH_3ONO



(a)Formation of Z-Isomer (b)Formation of E-Isomer

Figure 5. ORTEP Drawing of the Supermolecule Composed of 1-Oxido-2-pyridomethide Anion, CH_3ONO and NH_2^- at the Distance 3.8 Å between N5 and H4

It is remarkable feature that the negative charge localizes on the atoms O3, O6 and O7 in both supermolecules and the distance between O6 and O7 in Figure 5(a) is far closer than that in Figure 5(b). As the result the electron repulsion between the atoms O6 and O7 in Figure 5(a) could be relatively larger than that in Figure 5(b) and therefore the conformation of Figure 5(b) is preferable to that of Figure 5(a), i.e., in the nitrosation of 2 the formation of E-isomer could be of greater advantage than the formation of Z-isomer. This also means that while the steric hindrance between methoxyl group and pyridine nucleus in the case of Figure 5(b) would be also observed in a similar manner as the case of Figure 3(b), the nitrosation of 2 is siginificantly responsive to the electron repulsion between O6 and O7 rather than the steric hindrance between methoxyl group and pyridine nucleus.

In conclusion, it has become apparent that in the nitrosation of 1 in liq. NH_3, Z-isomer 3Z is first formed both at room temperature and at -33℃ and transformed easily into E-isomer 3E by heating, whereas in the reaction of 2 under the same conditions as those of the reaction of 1, E-isomer 4E is always obtained and these experimental results are successfully explained by PM3 method.

In relation to the present nitrosation of 1 and 2, it is the typical reaction which should show the influence from the interaction of the molecular orbitals of the starting materials, rather than the influence from relative thermodynamical stabilities of the two possible Z- and E-aldoximes.

EXPERIMENTAL

Melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. Spectral data were recorded on the following spectrophotometer and spectrometer: ir spectra, JASCO IR-810; ^1H-nmr spectra, JEOL FX-100 (100 MHz). Hptlc was conducted on a Shimadzu high speed thin layer chromatoscanner (CS-920) with detector set at uv 254nm. Column chromatography was carried out with Kieselgel 60 (70-230 mesh, Merck).

Preparation of (Z)-4-pyridinecarbaldehyde 1-oxide oxime (3Z) by nitrosation of 4-methylpyridine 1-oxide (1) in liq. NH_3 —— Reaction was carried out as described in the previous paper[1a] using 1 (1.0 g, 9.17 mmol) to give 3Z, 0.63 g (50% yield). The residue from the reaction mixture was washed with water and the ^1H-nmr spectrum of the insoluble product was measured immediately after drying. The magnitude of $\delta_{CH}-\delta_{CH=N}$ was in perfect accord with that of the authentic sample.[3] Furthermore, the mp and ir spectrum coincided with those of the authentic sample.[4]

Reaction of pyridinecarbaldehyde 1-oxide oximes with $NaNH_2$ in the presence of $C_5H_{11}ONO$ and $C_5H_{11}OH$ in liq. NH_3 —— Reaction was carried out as described in the previous paper[1a] using pyridinecarbaldehyde 1-oxide oxime (0.5 g, 3.62 mmol), $NaNH_2$ (0.16 g, 3.98 mmol), $C_5H_{11}ONO$ (0.42 g, 3.62 mmol), $C_5H_{11}OH$ (0.35 g, 3.98 mmol) and NH_4Cl (0.29 g, 5.43 mmol). The final yield of the products was determined by using a high speed thin layer chromatoscanner after the separation through silica gel column chromatography using a mixed solvent of CH_3Cl and CH_3OH as eluent. Hptlc conditions : Hptlc plate, silica gel 60 F_{254} precoated (Merck); solvent system, CH_3Cl:CH_3OH=10:1.

a) **Reaction of (E)-4-pyridinecarbaldehyde 1-oxide oxime (3E) at room temperature** ———— 5-15 mg (3% yield), 7-13 mg (3% yield) and 3E-450 mg (90% recovery).

b) **Reaction of 3E at -33℃** —— 3E-recovery quantitatively.

c) **Reaction of (Z)-4-pyridinecarbaldehyde 1-oxide oxime (3Z) at room temperature** ———— 5-112 mg (22% yield), 7-88 mg (20% yield), 3Z-20 mg (4% recovery) and 3E-34 mg (7% yield).

d) **Reaction of 3Z at -33℃** —— 5-20 mg (4% yield), 7-17 mg (4% yield) and 3Z-420 mg (84% recovery).

e) **Reaction of (E)-2-pyridinecarbaldehyde 1-oxide oxime (4E) at room temperature** ———— 6-27 mg (5.5% yield) and 4E-0.45 g (90% recovery).

f) **Reaction of 4E at -33℃** —— 4E-recovery quantitatively.

g) **Reaction of (Z)-2-pyridinecarbaldehyde 1-oxide oxime (4Z) at room temperature** ———— 6-196 mg (40% yield), 8-60 mg (14% yield), 2-pyridinecarboxamide-22 mg (5% yield) and 4E-62 mg (12% yield).

h) **Reaction of 4Z at -33℃** —— 6-88 mg (18% yield) and 4E-236 mg (47% yield).

Reaction of pyridinecarbaldehyde 1-oxide oxime with $NaNH_2$ in liq. NH_3 at room temperature (under the conditions of Vermillion and Hauser) —— Reaction was carried out as described in the previous paper[1a,5] using pyridinecarbaldehyde 1-oxide oxime (0.5 g, 3.62 mmol) and $NaNH_2$ (0.78 g, 20 mmol) with magnetic stirring for a day. The final yield of the products was determined by using a high speed thin layer chromatoscanner after the separation through silica gel column chromatography using a mixed solvent of CH_3Cl and CH_3OH as eluent.

a) **Reaction of 3E** —— 5-25 mg (5% yield) and 3E-155 mg (31% yield).

b) **Reaction of 3Z** —— 5-285 mg (57% yield). The mp and ir spectrum of 5 recrystallized from acetone-CH_3OH coincided with those of the authentic sample.[1a]

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