NITROSATION OF 1-ALKYLISOQUINOLINES AND THEIR N-OXIDES AND CONFIGURATIONAL ASSIGNMENTS OF THEIR OXIMES

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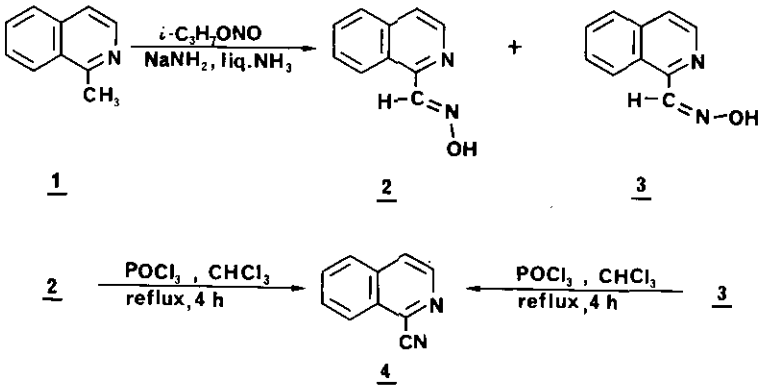
Abstract——Nitrosation of 1-methyl-, 1-ethylisoquinoline and their N-oxides with alkyl nitrite was studied under various conditions, and the following three systems, (t-BuONO and t-BuOK in THF), (t-BuONO and t-BuOK in liq. NH_3) and (t-BuONO and n-BuLi-t-BuOK in THF), were found to be generally effective for nitrosation of not only isoquinolines but also pyridine and quinoline derivatives. The $\delta_{OH} - \delta_{CH=N}$ and δ_{OH} values were shown to be reliable criterions for assigning configurations of aldoximes and methyl ketoximes in these series. The semi-empirical molecular orbital calculations (MNDO method) about the reactivity of isoquinoline derivatives and the stability of ketoximes were in good qualitative agreement with the experimental results.

The reaction with alkyl nitrite and alkali amide in liquid ammonia has been extensively utilized for nitrosation of active methyl and methylene groups of N-heteroaromatics such as pyridine, quinoline and their N-oxides[1]. However, no reports are available on isoquinoline derivatives. We now investigated the nitrosation of 1-alkylisoquinolines and their N-oxides with alkyl nitrite in some detail and obtained interesting results including finding of new effective procedures. Further, it was found that the magnitude of $\delta_{OH} - \delta_{CH=N}$ and δ_{OH} values can be used as the reliable criterions for assigning the configurations of aldoximes and methyl ketoximes, in pyridine, quinoline and isoquinoline series. We also describe the theoretical approach to the reactivity of some isoquinoline derivatives and the stability of oximes.

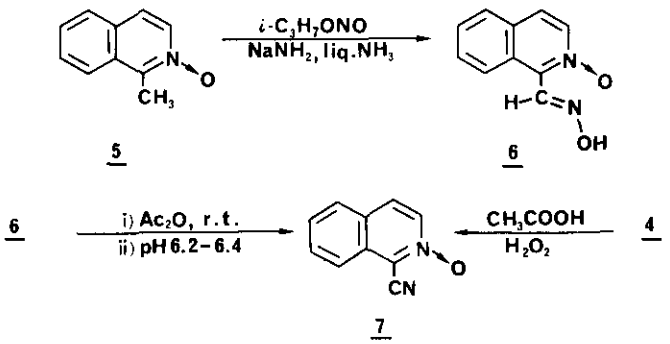
We first tried nitrosation of 1-methylisoquinoline **1**[2] with isopropyl nitrite (i-C_3H_7ONO) and sodium amide ($NaNH_2$) in liquid ammonia (liq. NH_3) (Method A) according to the procedure reported by Kato and Goto[1], and obtained (E)-1-iso-

quinolinecarboxaldehyde oxime 2 and the Z isomer 3 in 31 and 18% yields, respectively (Scheme 1).



Scheme 1

Though 2 was reported to form by oximation of the corresponding aldehyde[3], no evidence was offered for its configuration. We now established the configurations of 2 and 3 by means of ^{1}H-nmr spectroscopy[4] (see below). It is interesting that the OH proton signal of 3 appears in surprising low field (δ_{OH} = 17.3 ppm in $CDCl_3$) compared with the usual OH proton signal of oxime (δ_{OH} = 9-12 ppm). Both 2 and 3 were converted almost quantitatively to 1-cyanoisoquinoline 4[5] upon heating with phosphoryl chloride ($POCl_3$) as expected (Scheme 1). Nitrosation of 1-methylisoquinoline 2-oxide 5 [6] under the same conditions afforded (E)-1-isoquinolinecarboxaldehyde 2-oxide oxime 6 as a sole product in a high yield of 85% (Scheme 2).

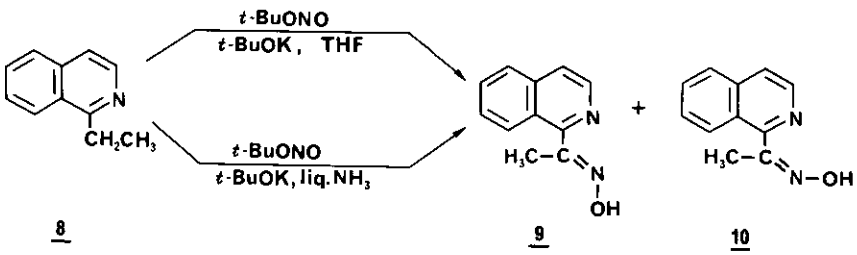


Scheme 2

It is well known that the acetate of (Z)-aldoxime gives the corresponding nitrile under hydrolytic conditions using a weak base whereas that of E isomer undergoes hydrolysis to the original oxime[7]. In order to confirm chemically the E-configuration of 6 determined by the spectroscopic method described later, we

attempted acetylation of 6 but could not obtain the expected oxime acetate and only 1-cyanoisoquinoline 2-oxide 7[5] was isolated. Compound 7 was identified with a specimen prepared by N-oxidation of 4 (Scheme 2).

In the case of 1-ethylisoquinoline 8[8] no reaction occurred under the above conditions. We therefore examined the reaction conditions, especially the application of various alkoxides as bases, and found that the use of potassium tert-butoxide (t-BuOK) instead of $NaNH_2$ is very effective for the reaction to proceed. Thus, treatment of 8 with tert-butyl nitrite (t-BuONO) and t-BuOK in THF (Method B) gave (E)-methyl 1-isoquinolyl ketone oxime 9 and the Z isomer 10 in 45 and 12% yields, respectively. The reaction with t-BuONO and t-BuOK in liq. NH_3 (Method C) proceeded more effectually to afford 9 and 10 in 78 and 16% yields, respectively (Scheme 3).

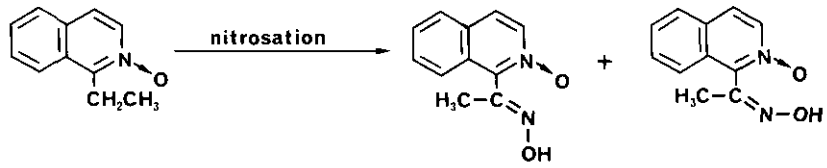


Scheme 3

It was early reported that 1-acetylisoquinoline reacted with hydroxylamine (NH_2OH) to give a single oxime of unestablished configuration[9], which was now unambiguously proved to be the Z isomer 10 on the basis of ^1H- and ^{13}C-nmr spectra[4, 10]. It is of interest that the above nitrosation of 8 gave both isomers, 9 and 10, with preferential formation of 9, and oximation of the ketone yielded only the isomer 10. These experimental results indicate that t-BuOK as proton-abstracting base is suitable for the nitrosation of 8 rather than $NaNH_2$, although in general $NaNH_2$ seems to be stronger base than t-BuOK.

Although 1-ethylisoquinoline 2-oxide 11 [8] resisted the reaction under the conditions of Methods A and B, nitrosation was successively realized with t-BuONO under various conditions summarized in Table I. Apparently, the conditions of run 1 (Method C) and run 4 (Method D) are most efficient. In run 4 involving treatment with t-BuONO in the presence of n-BuLi and t-BuOK in THF, the superbasic character of the so-called LiCKOR reagents[11] seems to be operative. The use of thiourea (H_2NCSNH_2), which is a very active catalyst for N-nitrosation[12], was not fruitful at all against our expectation (run 2). Further, oximation of

Table I.



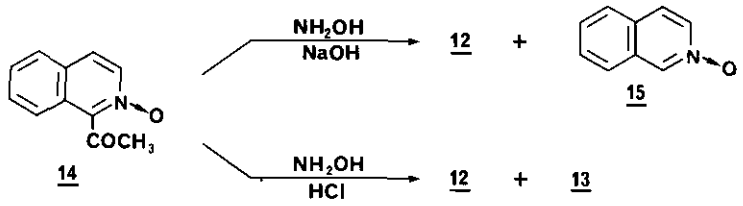
11 12 13

Nitrosation of 11 under the Various Types of Nitrosation Conditions

Run	Nitrite	Base	Other Component	Solvent	Temp.(°C)	Time(h)	Yield(%)[a]
1	t-BuONO	t-BuOK	——	liq.NH_3	-33	2	74
2	t-BuONO	t-BuOK	H_2NCSNH_2	liq.NH_3	-33	2	24
3	t-BuONO	LDA	——	THF	-78→r.t.	12	11
4	t-BuONO	n-BuLi t-BuOK	——	THF	0	2	74
5	t-BuONO	n-BuLi t-BuOK	——	liq.NH_3	-33	2	36

a) Yield(%) contains both 12 and 13.

1-acetylisoquinoline 2-oxide 14[13] with NH_2OH was explored, and it was found that a single oxime, (E)-methyl 2-oxido-1-isoquinolyl ketone oxime 12 (20%), was formed accompanied with isoquinoline 2-oxide 15 (59%) in the reaction in basic media (NaOH), while the reaction in acidic media (HCl) gave 12 as well as the Z isomer, (Z)-methyl 2-oxido-1-isoquinolyl ketone oxime 13[13] in the ratio of 1:1 (80% yield) (Scheme 4).



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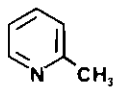
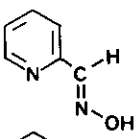
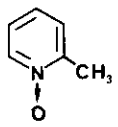
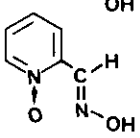
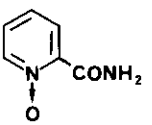
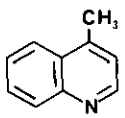
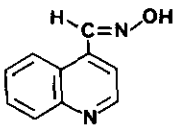
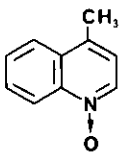
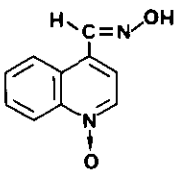
Scheme 4

The formation of 15 by the hydrolytic cleavage of the 1-acetyl group of 14 by hydroxide anion is apparently facilitated by the electron-withdrawing effect of N-oxide function as the hydrolysis of 2-acyl-3-quinoxalinone 1-oxides with KOH[14].

The above-mentioned results demonstrate that methods using t-BuOK as a base (Methods B, C and D) are effective for nitrosation of 1-alkylisoquinolines and

their N-oxides. In exploring the utility of these methods for nitrosation of heteroaromatics other than isoquinoline, we carried out nitrosation of some pyridine and quinoline derivatives under the conditions of Methods B and D and compared with that by Method A (Tables II and III).

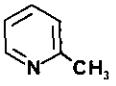
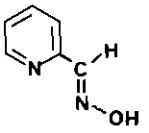
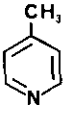
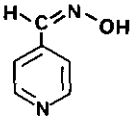
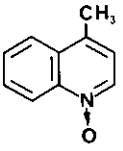
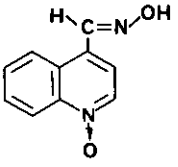
Table II. Nitrosation of 2-Picoline, Lepidine and Their N-Oxides under the Conditions of Method A and Method B

Run	S.M.[a]	Product	Method B		Method B	Method A
			Temp.(°C)	Time(h)	Yield(%)	Yield(%)
6			r.t.	12	9	23[1a]
7			r.t.	2	57	57[1a]
					12	17[1a]
8			r.t.	0.5	92	67[1b]
9			-78	3	32	trace[1a]

a) S.M. means starting material.

Although Method B was much inferior to Method A in nitrosation of 2-picoline (run 6), and in nitrosation of 2-picoline 1-oxide essentially the same results were obtained under both conditions (run 7), better yields were obtained by Method B than by Method A in nitrosation of lepidine and its N-oxide[17] (runs 8 and 9). Method D was carried out particularly with 2-picoline and lepidine 1-oxide, those were beset by low yields under the conditions of Method B, and 4-picoline which has been so far difficult to form the Z aldoxime. In reaction of

Table III. Nitrosation of 2-, 4-Picoline and Lepidine 1-Oxide under the Conditions of Method D

Run	S.M.[a]	Product	Temp.(°C)	Time(h)	Yield(%) of (E)	Yield(%) of (Z)
10			-78→r.t.	12	20	16[15]
11			-78→r.t.	12	—	41[16]
12			-78→r.t.	12	60	—

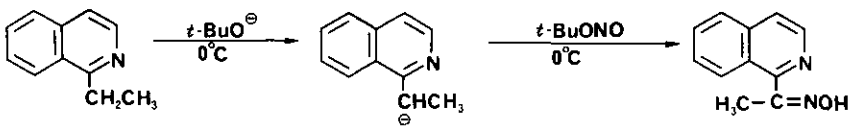
a) S.M. means starting material.

2-picoline and lepidine 1-oxide the respective aldoximes were obtained in higher yields (runs 10 and 12). Of particularly significant is the formation of Z aldoximes in reactions of 2-picoline and especially of 4-picoline (runs 10 and 11). Because of its chemotherapeutic interest[18], (Z)-4-pyridinecarboxaldehyde oxime has drawn special attention, but its yields remained to be poor in the reported reactions such as oximation of isonicotinaldehyde with NH_2OH[16] and photochemical isomerization of the E isomer[19]. It is notable that this Z aldoxime was selectively obtained in moderate yield in the present work (run 11). Nitrosation of lepidine 1-oxide is generally accompanied by side reactions[1b] and gives the corresponding aldoxime in rather poor yields. However, under the conditions of Method D, side reactions were appreciably surpressed and (E)-aldoxime was selectively obtained in reasonable yield (run 12). These outstanding characteristics of Method D for the nitrosation could likely be attributed to the superbase character contributing to proton-abstracting step and the fairly low temperature (-78 °C), which make it possible to form so-called unstable isomer and to perform the selective nitrosation suppressing side reactions. Accordingly, Method D as a nitrosation conditions could extensively be recom-

mendable for the nitrosation.

It is well known that conversion of pyridine and quinoline to their N-oxides increases their susceptibilities to nitrosation of their active methyl and methylene groups[1a]. However, as described above, the nitrosation under the conditions of Method B smoothly took place with 1-ethylisoquinoline 8 but did not proceed with its N-oxide 11. In order to interpret this result from a theoretical viewpoint, we performed the molecular orbital (MO) calculations using MNDO method[20] on the following assumptions used in MO study of nitrosation of the active methyl and methylene groups of pyridine and pyrimidine series[21].

1) The reaction proceeds by the following two-step sequence (Scheme 5), and MO calculation was performed on the first step, i.e., proton-abstracting step.



Scheme 5

2) Abstraction of hydrogen (H^1) occurs in a conformation shown in Figure 1 in the light of the stability of the anion produced.

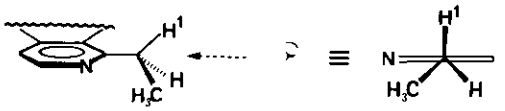


Figure 1. The Conformation of 8 and 11 for the Theoretical Calculations Using MNDO Method

Table IV contains Frontier electron density (Fr) of H^1 at LUMO, net charge of H^1 and energetic terms of Klopman-Salem equation calculated for 8 and 11, taking only frontier molecular orbital (FMO) into account. Energetic terms of Klopman-Salem equation were calculated on the assumption that 8 (or 11) and tert-butoxide anion interact at a distance of 2.72Å equal to the sum of respective van der Waals radii of hydrogen and oxygen atoms in THF (ϵ=7.4). Data in Table IV show that the reaction of 8 with tert-butoxide may proceed more favorably than that of 11, in accordance with the experimental result. Furthermore, the reaction may be conceivable to be governed by the Coulombic interaction in view of the energetic terms.

As for the configurational assignment of aldoximes and ketoximes, various types of spectroscopic methods have been reported[4,10,22]. Among these, the use of δ_{OH}

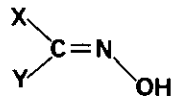
Table IV. Fr of H^1 atom at LUMO and Net Charge of H^1 in 8 and 11, and the Energetic Terms of Klopman-Salem Equation for the Reaction of 8 (or 11) with tert-Butoxide Anion Calculated by MNDO Method

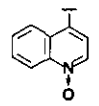
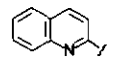
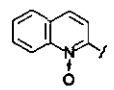
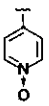
Compound	$Fr \times 10^{-2}$	Net Charge	Coulombic Term (eV)	Frontier Term (eV)	ΔE[a] (eV)
8	1.351	0.016	8.680×10^{-3}	3.035×10^{-3}	1.172×10^{-2}
11	1.195	0.015	8.228×10^{-3}	3.227×10^{-3}	1.146×19^{-2}

a) ΔE = Coulombic Term + Frontier Term.

- $\delta_{CH=N}$ and δ_{OH} values seems to be reliable criterions for assigning the configurations of aldoximes of analogous structures and those of methyl ketoximes, even if only one isomer is obtainable. For example, it was reported the magnitude of $\delta_{OH} - \delta_{CH=N}$ is around 3 ppm for E isomers and around 4 ppm for Z isomers in E-Z pairs of aliphatic aldoximes[4], and the syn-methyl aromatic and heteroaromatic ketoximes (E-form) exhibit their δ_{OH} values from 10.12 to 10.21 ppm, while those of the anti-methyl ketoximes (Z-form) are found in the range of 10.05 to 10.08 ppm[4]. Further, as the more recent example, it is known that in the sulfur derivatives of 2-oxopropanal oxime the E isomer has the magnitude of $\delta_{OH} - \delta_{CH=N}$ = 5.02 - 5.46 ppm[23]. We chose this method and examined the ^{1}H-nmr spectra in DMSO-d_6 of seventeen aldoximes of known configuration of pyridine, quinoline, isoquinoline and their N-oxides and tabulated δ_{OH}, $\delta_{CH=N}$ and $\delta_{OH} - \delta_{CH=N}$ values in Table V, and also listed δ_{OH} values of fourteen methyl ketoximes of known configuration in Table VI. Oximes other than those obtained in the present work were prepared according to the reported procedures (see Tables V and VI). In aldoximes series, $\delta_{OH} - \delta_{CH=N}$ values ranged from 3.16 to 3.77 ppm (average 3.53 ppm) for E isomers and from 4.36 to 5.33 ppm (average 4.78 ppm) for Z isomers (Table V), and it could be noticed that there was a definite difference (average 1.25 ppm) of $\delta_{OH} - \delta_{CH=N}$ values between E and Z isomers. Thus, it has proved possible to use $\delta_{OH} - \delta_{CH=N}$ values as a reliable means for assigning the configurations of aldoximes in these series, the separate use of δ_{OH} or/and $\delta_{CH=N}$ being not applicable (Table V). Although we obtained only one aldoxime 6 from 1-methylisoquinoline 2-oxide 5 and our attempt to assign chemically its configuration failed as mentioned above, we may resonably conclude that 6 is the E aldoxime based on the magnitude of $\delta_{OH} - \delta_{CH=N}$ = 3.51. As can be seen in Table VI, δ_{OH} values of methyl ketoximes ranged from 11.30 to 11.90

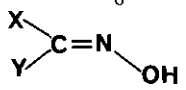
Table V. δ_{OH}, $\delta_{CH=N}$ and $\delta_{OH} - \delta_{CH=N}$ Values (in ppm) for N-Containing Heteroaromatic Aldoximes and Their N-Oxides in DMSO-d_6

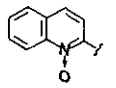
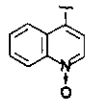
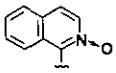
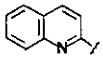
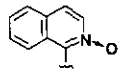
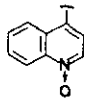


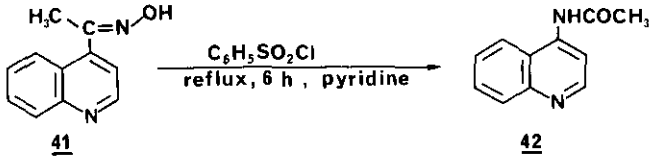
Compd.	X	Y	δ_{OH}	$\delta_{CH=N}$	$\delta_{OH}-\delta_{CH=N}$	Compd.	X	Y	δ_{OH}	$\delta_{CH=N}$	$\delta_{OH}-\delta_{CH=N}$
16		H	11.71	8.11	3.60[1a]	24		H	11.94	8.78	3.16[1b]
17		H	12.13	8.53	3.60[1a]	25		H	11.98	8.28	3.70[1b]
18		H	11.83	8.35	3.47[7]	26		H	12.33	8.80	3.53[1b]
19		H	12.17	8.70	3.47[7]						
20		H	11.61	8.22	3.39[24]	27	H		12.40	7.57	4.83[15]
21		H	11.86	8.19	3.67[1a]	28	H		12.33	7.97	4.36[25]
22		H	11.76	8.17	3.59[1a]	29	H		12.23	7.54	4.69[16]
2		H	11.97	8.54	3.43	30	H		12.18	7.50	4.68[25]
23		H	12.01	8.24	3.77[1b]	3	H		13.68	8.35	5.33

ppm (average 11.65 ppm) for E isomers and from 10.66 to 10.97 ppm (average 10.82 ppm) for Z isomers. The difference of such definite magnitude (average 0.83 ppm) is also enough for the configurational assignment of methyl ketoximes in these cases. Previously, we obtained only one isomer in nitrosation of 4-ethylquinoline by Method A[26]. Now we determined this isomer to be (E)-methyl 4-quinolyl ketone oxime 41 on the basis of δ_{OH} = 11.67 ppm. This configuration was further confirmed by the formation of 4-acetylaminoquinoline 42[27], though in poor yield, from the Beckmann rearrangement under forced conditions using benzenesulfonyl

Table VI. δ_{OH} Value (in ppm) for N-Containing Heteroaromatic Ketoximes and Their N-Oxides in DMSO-d_6



Compd.	X	Y	δ_{OH}	Compd.	X	Y	δ_{OH}
31		CH_3	11.52[1c]	36		CH_3	11.73[13]
32		CH_3	11.53[1c]	37		CH_3	11.79[13]
33		CH_3	11.90[7]				
34		CH_3	11.30[7]	38	CH_3		10.91[1c]
9		CH_3	11.69	39	CH_3		10.66[7]
12		CH_3	11.74	10	CH_3		10.72
35		CH_3	11.67[13]	13	CH_3		10.97[13]
				40	CH_3		10.82[13]



Scheme 6

chloride, while application of trimethylsilyl polyphosphate (PPSE) or phosphorus pentachloride (PCl_5) was also tried but no rearrangement was noticed (Scheme 6). Next, to examine the effect of N-oxide function on chemical shifts of OH and

CH=N hydrogens, we surveyed the ^{1}H-nmr spectra shown in Tables V and VI. Only in E aldoximes having oxime group adjacent to N-oxide group, there were noticed low field shifts by average 0.35 ppm for δ_{OH} and by average 0.37 ppm for $\delta_{CH=N}$ due to the electron-withdrawing effect of N-oxide group (17-16, 19-18, 26-25, 6-2). However, no significant informations could not be obtained in other aldoximes and ketoximes.

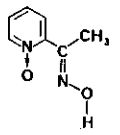
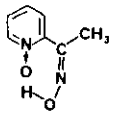
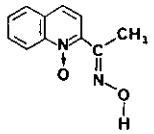
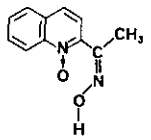
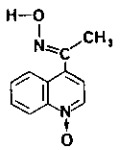
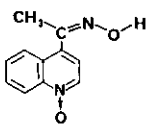
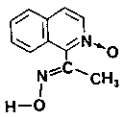
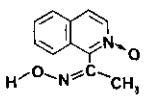
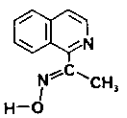
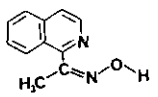
It is well established that the favourable steric arrangement of aromatic aldoximes is E configuration[28]. This is also the case for aldoximes given in Table V and E isomers surpassed Z ones with respect to the availabilities and yields. On the other hand, such a general trend as observed in aromatic aldoximes seems to have not been still confirmed in aromatic and heteroaromatic methyl ketoximes, to our knowledge. However, it is evident that E isomers also surpassed Z ones with respect to the availabilities and yields as shown in Table VI. In order to evaluate the stabilities of these ketoxime isomers, we performed the MO calculation using MNDO method for ketoximes in which both isomers are obtainable, by assuming the coplanarity of the heteroaromatic ring and the oxime group from the following reasons.

1) In the uv spectra of a series of alkyl phenyl ketoxime O-methyl ethers, both λ_{max} and ϵ values decrease with bulk of alkyl group, and phenyl group is shown to be likely conjugated with C=N bond when alkyl group is hydrogen or methyl on the basis of their λ_{max} and ϵ values[29].

2) *Crystallographic studies of 4-pyridinecarboxaldehyde oximes* (E and Z isomers) and 4-pyrimidinecarboxaldehyde oximes (E and Z isomers) demonstrate that the oxime group and heteroaromatic ring are nearly coplanar in each case[30].

In fact, the theoretical calculation of benzaldoxime was achieved on the basis of this assumption[31]. Table VII contains the most stable structures, which are the optimized geometries calculated by MNDO method for E and Z isomers, total energies (E_T) and E-Z energy differences (ΔE_T) [32]. Thus, it was found that E isomer is the preferred form compared with Z isomer as anticipated. It should be considered that this difference of stability between E and Z isomers might be at least partly attributed to the no effective hydrogen bonding between the oxygen of N-oxide group or the ring nitrogen and the hydrogen of hydroxyl group in Z isomers, and the steric compression effect between CH_3 and hydroxyl groups in E isomers.

Table VII. The Most Stable Structures, Total Energies (E_T) and E-Z Energy Differences (ΔE_T) in N-Containing Heteroaromatic Ketoximes and Their N-Oxides Calculated by MNDO Method

Compd.	Structure	Type of Isomer	E_T(eV)	ΔE_T(kcal/mol) E-Z
32		E	-2062.839	
				-11.230
38		Z	-2062.352	
36		E	-2602.004	
				-3.690
43		Z	-2601.844	
37		E	-2601.846	
				-5.373
40		Z	-2601.613	
12		E	-2601.628	
				-5.627
13		Z	-2601.384	
9		E	-2282.303	
				-4.174
10		Z	-2282.122	

EXPERIMENTAL

Melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. Spectral data were recorded on the following spectrometers : ultraviolet (uv) spectra, Hitachi 150-20 ; infrared (ir) spectra, JASCO IR-810 ; ^{1}H-nmr spectra, JEOL FX-100 (100MHz); ^{13}C-nmr spectra, JEOL FX-100 (25MHz); mass spectra (ms), JEOL JMS-DX300. 2D ^{1}H-^{13}C chemical shift correlation spectra measured by JEOL GX-400 were utilized for the assignments of ^{1}H- and ^{13}C-nmr spectra. High-performance thin layer chromatography (hptlc) about the yields shown in Tables I and III was conducted on a Shimadzu high speed thin layer chromatoscanner (CS-920) with the detector set at uv 254nm. Column chromatography was carried out with Kieselgel 60 (70-230 mesh, Merck).

Nitrosation of 1-Methylisoquinoline 1 in Liq. NH_3 ——Reaction was carried out as described in the previous paper[1], using 1 (1.0 g, 7 mmol) and isopropyl nitrite (1.37 g, 15.4 mmol) instead of amyl nitrite. The residue from the reaction mixture was chromatographed to give (Z)-1-isoquinolinecarboxaldehyde oxime 3, starting material (S.M.) (with $CHCl_3$) and (E)-1-isoquinolinecarboxaldehyde oxime 2 (with $CHCl_3$-MeOH, 20:1). The mixture of 3 and S.M. was washed with petrol. ether to separate into two components. S.M. (0.3 g, 30%) was recovered. Compound 2 was recrystallized from ether to give colorless prisms, mp 184-185.5 °C (lit[3]. 171-172 °C), 0.37 g (31%). Anal. Calcd for $C_{10}H_8N_2O$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.67; H, 4.77; N, 16.01. Uv λ_{max}^{EtOH}nm(logϵ): 222(4.53). Ir ν_{max}^{KBr}cm^{-1}: 2738, 1502, 1345, 993, 825. ^{1}H-Nmr $\delta_{ppm}^{DMSO-d_6}$: 7.20-8.14(4H,m,Ar-H), 8.31-8.63(1H,m,H-3), 8.54(1H,s,-C<u>H</u>=NOH), 9.00(1H,d,J=8.6Hz,H-5), 11.97(1H,s,OH). ^{13}C-Nmr $\delta_{ppm}^{DMSO-d_6}$: 121.22(d,C-4), 125.51(s,C-9), 126.46(d,C-5). 127.22(d,C-7), 128.28(d,C-8), 130.26(d,C-6), 136.14(s,C-10), 141.93(d,C-3), 150.33(s,C-1), 151.03(d,-<u>C</u>H=NOH). Ms m/z(rel.int.): 172(M^+,99), 155(19), 129(44), 115(100). High-resolution ms Calcd for $C_{10}H_8N_2O$(M^+): 172.064. Found: 172.064. Compound 3 was recrystallized from ether to give yellow prisms, mp 98-99°C, 0.22 g (18%). Anal. Calcd for $C_{10}H_8N_2O$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.71; H, 4.70; N, 16.16. Uv λ_{max}^{EtOH}nm(logϵ): 222(4.41). Ir ν_{max}^{KBr}cm^{-1}: 2600, 1590, 1317, 949, 829. ^{1}H-Nmr $\delta_{ppm}^{DMSO-d_6}$: 7.43-8.23(5H,m,Ar-H), 8.35(1H,s,-C<u>H</u>=NOH), 8.56(1H,d,J=6.0Hz,H-5), 13.68(1H,s,OH). ^{13}C-Nmr $\delta_{ppm}^{DMSO-d_6}$: 121.89(d,C-4), 125.24(s,C-9), 125.72(d,C-5), 127.07(d,C-7), 128.07(d,C-8), 130.84(d,C-6), 135.77(s,C-10), 140.28(d,-<u>C</u>H=NOH), 142.05(d,C-3), 151.37(s,C-1). Ms m/z(re-

l.int.): 172(M^+,89), 154(34), 129(53), 115(100). High resolution ms Calcd for $C_{10}H_8N_2O(M^+)$: 172.064. Found: 172.064.

Reaction of 2 (or 3) with $POCl_3$——$POCl_3$ (0.54 g, 3.5 mmol) in $CHCl_3$ (5 ml) was added dropwise to a solution of 2 (or 3, 0.2 g, 1.2 mmol) in $CHCl_3$ (10 ml) under ice-cooling. The mixture was heated under reflux for 4 h, treated with ice water, and the resulting precipitate (recovered S.M.) was filtered. The filtrate was basified with 28% ammonia and then extracted with $CHCl_3$. The residue from the $CHCl_3$ extract was chromatographed with $CHCl_3$ to give 1-cyanoisoquinoline 4[5], 0.17 g (95%) (in the case of 3, 0.16 g, 92%).

Nitrosation of 1-Methylisoquinoline 2-Oxide 5 in Liq. NH_3——Reaction was carried out as described in the previous paper[1], using 5 (1.0 g, 6.3 mmol) and isopropyl nitrite (1.23 g, 13.9 mmol) instead of amyl nitrite. The residue from the reaction mixture was washed with water and the insoluble product was recrystallized from 99% EtOH to give (E)-1-isoquinolinecarboxaldehyde 2-oxide oxime 6, pale yellow prisms, mp 230-231 °C (decomp.), 1.0 g (85%). Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.71; H, 4.22; N, 14.75. Uv λ_{max}^{EtOH}nm(logϵ): 268(4.38). Ir $\nu_{max}^{KBr}cm^{-1}$: 3300-2400, 1498, 1299, 1203, 963, 765. ^{1}H-Nmr $\delta_{ppm}^{DMSO\text{-}d_6}$: 7.46-7.86(2H,m,H-6 and H-7), 7.86-8.06(1H,m,H-8), 7.97(1H,d,J=7.0Hz,H-4), 8.26(1H,d,J=7.0Hz,H-3), 8.49-8.80(1H,m,H-5), 8.73(1H,s,-CH=NOH), 12.24(1H,s,OH). ^{13}C-Nmr $\delta_{ppm}^{DMSO\text{-}d_6}$: 124.47(d,C-5), 124.66(d,C-4), 127.22(s,C-9), 127.40(d,C-8), 128.04(d,C-7), 129.90(d,C-6), 136.53(d,C-3), 137.75(s,C-10), 143.18(d,-CH=NOH). Ms m/z(rel.int.): 188(M^+,50), 171(100), 154(42), 128(69). High resolution ms Calcd for $C_{10}H_8N_2O_2(M^+)$: 188.059. Found: 188.060.

Reaction of 6 with Ac_2O——A mixture of 6 (0.28 g, 1.5 mmol) and Ac_2O (7 ml) was heated at 50-60 °C to dissolve 6 and kept at room temperature for several hours. After addition of ice water, the mixture was made pH 6.2-6.4 with 10% Na_2CO_3 solution and then extracted with $CHCl_3$. The residue from the $CHCl_3$ extract was recrystallized from ether-acetone to give 1-cyanoisoquinoline 2-oxide 7[5], 0.24 g (70%).

General Procedure for the Reaction of N-Heterocycle with t-BuONO in the Presence of t-BuOK in anhydrous THF (Method B)——N-Heterocycle (10 mmol) in anhyd. THF (20 ml) was added dropwise to a solution of t-BuOK (2.24 g, 20 mmol) in anhyd. THF (20 ml) with stirring under ice-cooling, and the mixture was stirred for 1-2 h under ice-cooling. Then, t-BuONO (3.09 g, 30 mmol) was added dropwise to the

reaction mixture under ice-cooling, followed by stirring overnight at room temperature. The solvent was evaporated to dryness.

Reaction of 1-Ethylisoquinoline 8——The residue was chromatographed to give (E)-methyl 1-isoquinolyl ketone oxime 9 (with $CHCl_3$) and (Z)-methyl 1-isoquinolyl ketone oxime 10 (with ether). Compound 9 was recrystallized from benzene to give colorless needles, mp 148-149°C, 0.84 g (45%). Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.16; H, 5.44; N, 14.85. Uv λ_{max}^{EtOH} nm(log ϵ): 220(4.62). Ir ν_{max}^{KBr} cm^{-1} : 3254, 1559, 1251, 994, 931, 835, 677. ^{1}H-Nmr $\delta_{ppm}^{DMSO-d_6}$: 2.37(3H,s,CH_3), 7.37-8.00(4H,m,H-4,H-7,H-8 and H-6), 8.34-8.71(2H,m,H-3 and H-5), 11.69(1H,s,OH). ^{13}C-Nmr $\delta_{ppm}^{DMSO-d_6}$: 13.64(q,CH_3), 120.73(d,C-4), 125.60(s,C-9), 126.88(d,C-7), 127.37(d,C-5), 127.55(d,C-8), 130.05(d,C-6), 136.32(s,C-10), 141.32(d,C-3), 154.66(s,C-1), 155.14(s,-C=NOH). Ms m/z(rel. int.): 186(M^+,100), 169(50), 154(54), 128(62). High resolution ms Calcd for $C_{11}H_{10}N_2O$(M^+): 186.079. Found: 186.080. Compound 10 was recrystallized from ether-acetone to give colorless prisms, mp 205°C (decomp.) (lit[9]. 212-214°C), 0.22 g (12%). Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.24; H, 5.46; N, 14.94. Uv λ_{max}^{EtOH} nm(logϵ): 218(4.73). Ir ν_{max}^{KBr} cm^{-1}: 3300-2600, 1556, 1249, 1144, 1021, 932, 825. ^{1}H-Nmr $\delta_{ppm}^{DMSO-d_6}$: 2.23(3H,s,CH_3), 7.43-8.17(5H,m,Ar-H), 8.54(1H,d,J=5.7Hz,H-3), 10.72(1H,s,OH). ^{13}C-Nmr $\delta_{ppm}^{DMSO-d_6}$: 20.16(q,CH_3), 120.36(d,C-4), 124.51(s,C-9), 126.58(d,C-7), 126.76(d,C-5), 127.49(d,C-8), 130.29(d,C-6), 135.29(s,C-10), 141.93(d,C-3), 151.92(s,C-1), 156.85(s,-C=NOH). Ms m/z(rel.int.): 186(M^+,100), 169(51), 154(76), 128(78). High resolution ms Calcd for $C_{11}H_{10}N_2O$(M^+): 186.079. Found: 186.081.

Reaction of 2-Picoline——The residue was chromatographed with $CHCl_3$-MeOH (30:1) to give S.M. and (E)-2-pyridinecarboxaldehyde oxime[1a], 0.11 g (9%).

Reaction of 2-Picoline 1-Oxide——The residue was chromatographed with ether to give 2-pyridinecarboxamide 1-oxide[1a], 0.15 g (12%) and (E)-2-pyridinecarboxaldehyde 1-oxide oxime[1a], 0.72 g (57%).

Reaction of Lepidine——The residue was chromatographed with $CHCl_3$-MeOH (20:1) to give (E)-4-quinolinecarboxaldehyde oxime[1b], 1.1 g (92%).

Reaction of Lepidine 1-Oxide——The residue was chromatographed with $CHCl_3$-MeOH (20:1) to give S.M. (0.22 g, 22%) and (E)-4-quinolinecarboxaldehyde 1-oxide oxime[1b], 0.4 g (32%).

General Procedure for the Reaction of 8 or 1-Ethylisoquinoline 2-Oxide 11 with t-BuONO in the Presence of t-BuOK in Liq. NH_3 (Method C)——In a 200 ml three

necked flask equipped with a stirrer and a Dry Ice-acetone condenser was placed liq. NH_3 (100 ml), and t-BuOK (1.68 g, 15 mmol) was added to liq. NH_3. After stirring for 15 min, 8 (or 11) (5 mmol) was added and the mixture was further stirred for 1 h. Then t-BuONO (1.13 g, 11 mmol) was added dropwise to the reaction mixture which was stirred for 2 h, and liq. NH_3 was evaporated.

Reaction of 8——The residue was treated as described for reaction of 8 with t-BuONO in the presence of t-BuOK in anhyd. THF to give 9 (0.73 g, 78%) and 10 (0.15 g, 16%). The final yield was determined by using a high speed thin layer chromatoscanner. Hptlc conditions: Hptlc plate, Silica gel 60 F_{254} precoated (Merck); solvent system, CH_3COOEt.

Reaction of 11——The residue was chromatographed with $CHCl_3$-MeOH (20:1) to give the mixture of (E)-methyl 2-oxido-1-isoquinolyl ketone oxime 12 (0.37 g, 37%) (vide infra) and (Z)-methyl 2-oxido-1-isoquinolyl ketone oxime 13[13](0.37 g, 37%). The mixture was separated by fractional recrystallization from acetone into the each isomer. The final yield was determined by using a high speed thin layer chromatoscanner. Hptlc conditions: Hptlc plate, Silica gel 60 F_{254} precoated (Merck); solvent system, benzene:MeOH = 10:1.

General Procedure for the Reaction of N-Heterocycle with t-BuONO in the Presence of t-BuOK and n-BuLi in Anhydrous THF (Method D)——To a solution of t-BuOK (2.24 g, 20 mmol) in anhyd. THF (80 ml) cooled with Dry Ice-acetone (in the case of 11, ice-cold water) under nitrogen, n-BuLi (1.6 M solution 12.5 ml, 20 mmol) was added dropwise with stirring for 10 min. After stirring for 30 min, a solution of N-heterocycle (10 mmol) in anhyd. THF (10 ml) was added dropwise over 20 min, and the resulting mixture was further stirred for 1 h. A solution of t-BuONO (3.09 g, 10 mmol) in anhyd. THF (10 ml) was added dropwise for 10 min, and the reaction mixture was further stirred for 2 h. The reaction mixture was allowed to reach room temperature overnight with stirring and THF was evaporated off at as low temperature as possible, and the residue was neutralized with 10% HCl solution and extracted with $CHCl_3$. Water was evaporated off at as low temperature as possible, provided the oxime was involved in the aqueous layer. The residue combined with the $CHCl_3$ extract was subjected to column chromatography. The final yields of oxime and S.M. were determined by thin layer chromatoscanner.

Reaction of 11——Work-up of the residue was carried out as described for reaction of 11 with t-BuONO in the presence of t-BuOK in liq. NH_3. 12+13 :

1.49 g (74%).

Reaction of 2-Picoline——The residue was chromatographed to give (Z)-2-pyridinecarboxaldehyde oxime[15] (with benzene-$CHCl_3$, 1:1), 0.20 g (16%), and (E)-2-pyridinecarboxaldehyde oxime[1a] (with $CHCl_3$-MeOH, 20:1), 0.24 g (20%). HPTLC conditions: Hptlc plate, Hptlc NH_2 F_{254s} (Merck); solvent system, CH_3COOEt:$CHCl_3$ = 1:1.

Reaction of 4-Picoline——The residue from the $CHCl_3$ extract was washed with ether and was recrystallized from ether-acetone to give (Z)-4-pyridinecarboxaldehyde oxime[16], 0.5 g (41%). Hptlc conditions: Hptlc plate, Silica gel 60 F_{254} (Merck); solvent system, $CHCl_3$:MeOH = 10:1.

Reaction of Lepidine 1-Oxide——The residue was treated as described for reaction of lepidine 1-oxide with t-BuONO in the presence of t-BuOK in anhyd. THF to give (E)-4-quinolinecarboxaldehyde 1-oxide oxime[1b]. Hptlc conditions: Hptlc plate, Silica gel 60 F_{254} (Merck); solvent system, CH_3COOEt:MeOH = 5:1. (E)-4-quinolinecarboxaldehyde 1-oxide oxime: 1.13 g (60%). S.M.: 0.41 g (26%).

Reaction of 11 with t-BuONO in the Presence of t-BuOK and H_2NCSNH_2 in Liq. NH_3——To a solution of t-BuOK (2.24 g, 20 mmol) in liq. NH_3 (100 ml) was added 11 (1.73 g, 10 mmol) and the mixture was stirred for 1 h, then H_2NCSNH_2 (0.76 g, 10 mmol) was added. After stirring for 30 min, t-BuONO (3.09 g, 10 mmol) was added dropwise to the reaction mixture, followed by stirring for 2 h and then liq. NH_3 was evaporated. Work-up of the residue was carried out as described for reaction of 11 with t-BuONO in the presence of t-BuOK in liq. NH_3. 12+13: 0.48 g (24%). S.M.: 1.16 g (67%).

Reaction of 11 with t-BuONO in the Presence of LDA——To a solution of LDA in anhyd. THF (120 ml) prepared from diisopropylamide (2.02 g, 20 mmol) and n-BuLi (1.6 M solution 12.5 ml, 20 mmol) at -78 °C under nitrogen according to the usual method was added 11 (1.73 g, 10 mmol) and after stirring for 1 h t-BuONO (3.09 g, 30 mmol) was added dropwise to the reaction mixture. After stirring at -78 °C for 2 h, the reaction mixture was allowed to reach room temperature overnight with stirring and then THF was evaporated. The residue was neutralized with 10% HCl solution and the water was evaporated off in vacuo. Work-up of the residue was carried out as described for reaction of 11 with t-BuONO in the presence of t-BuOK in liq. NH_3. 12+13: 0.22 g (11%). S.M.: 0.87 g (50%).

Reaction of 11 with t-BuONO in the Presence of t-BuOK and n-BuLi in Liq. NH_3——n-BuLi (1.6 M solution 12.5 ml, 20 mmol) was added dropwise to a solution of t-

BuOK (2.24 g, 20 mmol) in anhyd. THF (90 ml) under ice-cooling and nitrogen and liq. NH_3 (90 ml) was introduced to the mixture. Compound 11 (1.73 g, 10 mmol) in anhyd. THF (30 ml) was added dropwise, and after stirring for 1 h, t-BuONO (3.09 g, 30 mmol) was added dropwise and the mixture was stirred for 2 h. After liq. NH_3 and THF were evaporated off, work-up of the residue was carried out as described for reaction of 11 with t-BuONO in the presence of t-BuOK in liq. NH_3. 12+13: 0.72 g (36%). S.M.: 1.01 g (60%).

Reaction of 1-Acetylisoquinoline 2-Oxide 14 with NH_2OH in Basic Media——NH_2OH·HCl (0.20 g, 2.8 mmol) was added to a solution of 14[13] (0.50 g, 2.6 mmol) in 20% NaOH solution (8 ml) and the mixture was stirred for 1 h at room temperature. The reaction mixture was adjusted to pH 8 with CO_2, and extracted with $CHCl_3$. The residue from the $CHCl_3$ extract was washed enough with ether, and the ether washings were concentrated. The residue was chromatographed with $CHCl_3$-MeOH (20:1) to give isoquinoline 2-oxide 15 (refined by sublimation, 1 mmHg at 80 °C), 0.23 g (59%). The residue insoluble in ether was recrystallized from acetone to give 12, colorless prisms, mp 244-246 °C, 0.10 g (19%). Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.45; H, 4.98; N, 13.84. Uv λ_{max}^{EtOH}nm(logϵ): 262(4.99). Ir ν_{max}^{KBr}cm^{-1}: 2832, 1323, 1203(N-O), 1135, 964, 811, 754. ^{1}H-Nmr$\delta_{ppm}^{DMSO-d_6}$: 2.15(3H,s,CH_3), 7.46-7.77(3H,m,Ar-H), 7.77-8.00(1H,m,Ar-H), 8.00(1H,d,J=7.2Hz,H-4), 8.24(1H,d,J=7.2Hz,H-3), 11.74(1H,s,OH). ^{13}C-Nmr $\delta_{ppm}^{DMSO-d_6}$: 13.25(q,CH_3), 123.96(d,Ar), 124.29(d,Ar), 127.03(d,Ar), 127.92(d,Ar), 128.19(s,Ar) 129.38(d,Ar), 136.87(d,Ar), 141.44(s,Ar), 148.84(s,Ar). Ms m/z(rel. int.): 202(M^+,41), 185(100), 154(43), 128(59). High resolution ms Calcd for $C_{11}H_{10}N_2O_2$(M^+): 202.074. Found: 202.076.

Reaction of 14 with NH_2OH in Acidic Media——NH_2OH·HCl (0.27 g, 3.9 mmol) was added to a solution of 14 (0.5 g, 2.6 mmol) in MeOH (14 ml) and the mixture was heated for 4 h under reflux. The solvent was evaporated and the residue was recrystallized from acetone to give a mixture of 12 and 13, 0.42 g (80%), in a ratio of 1:1 (from ^{1}H-nmr).

The Beckmann Rearrangement of Methyl 4-Quinolyl Ketone Oxime 41——A mixture of 41 (0.2 g, 1.1 mmol) in dry pyridine (10 ml) and $C_6H_5SO_2Cl$ (0.23 g, 1.3 mmol) was refluxed for 1.5 h. The solvent was evaporated and the residue was chromatographed with $CHCl_3$-MeOH (20:1) to give colorless powder, followed by basification with $NaHCO_3$ solution and then extraction with $CHCl_3$. The residue from the $CHCl_3$ extract was recrystallized from benzene to give 4-acetylaminoquinoline

42[27], 0.04 g (20%).

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