

AMINATION AND NITROSATION OF QUINOLINES AND THEIR N-OXIDES

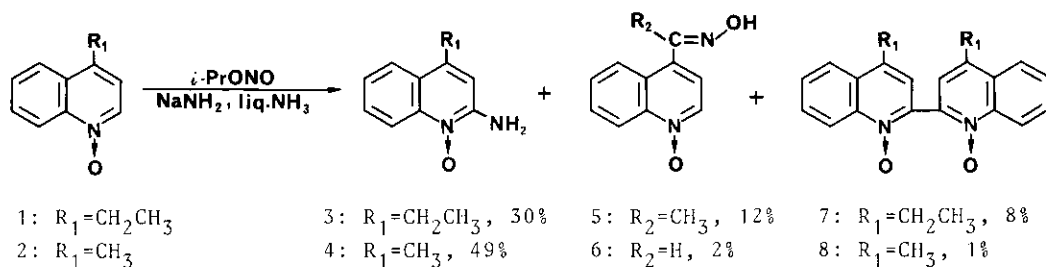
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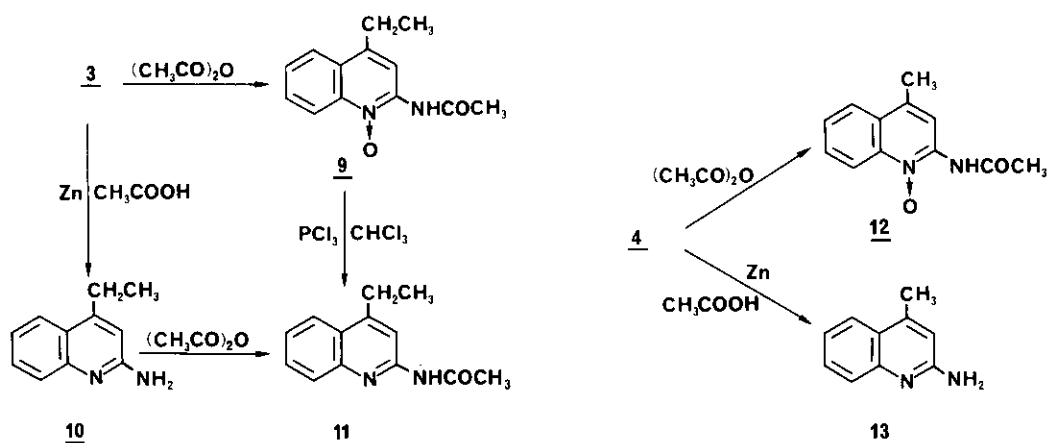
Abstract—4-Ethylquinoline 1-oxide reacted with isopropyl nitrite and sodium amide in liquid ammonia to give 2-amino-4-ethylquinoline 1-oxide as the main product. Similar amination occurred also with lepidine 1-oxide and quinoline 1-oxide, but only the corresponding oximes were formed from reactions of 4-ethylquinoline and lepidine under the same conditions. Isopropyl nitrite was shown to be most potent as oxidant compared with other oxidants used in such amination. The difference of reactivity between quinoline 1-oxides and quinolines was explained in terms of $\Delta\Delta H_F^B$ and LUMO energies, calculated by semi-empirical molecular orbital calculation (MNDO method).

In the course of our investigation on the reactions of methyl N-oxido-pyridyl, -quinolyl and -isoquinolyl ketoximes with acylating agents¹, we happened to find that treatment of 4-ethylquinoline 1-oxide with isopropyl nitrite (i-PrONO) and sodium amide (NaNH_2) in liquid ammonia (liq. NH_3), which has been so far regarded as the typical nitrosation conditions, gives 2-amino-4-ethylquinoline 1-oxide as the main product instead of the expected oxime. We investigated this amination reaction in some detail and obtained the following results.

4-Ethylquinoline 1-oxide **1** reacted with i-PrONO and NaNH_2 in liq. NH_3 at -33°C to afford 2-amino-4-ethylquinoline 1-oxide **3** as the main product together with small amounts of the expected (E)-ketoxime **5**^{1b} and the 4,4'-diethyl-2,2'-biquinoline 1,1'-dioxide **7**. The reaction of lepidine 1-oxide **2**² proceeded in essentially the same way to give the 2-amino derivative **4**, the (E)-aldoxime **6**³ and the biquinoline dioxide **8** (Scheme 1). The structures of **3** and **4** were established on the basis of their spectral data and the following chemical reactions (Scheme 2).



Scheme 1



Scheme 2

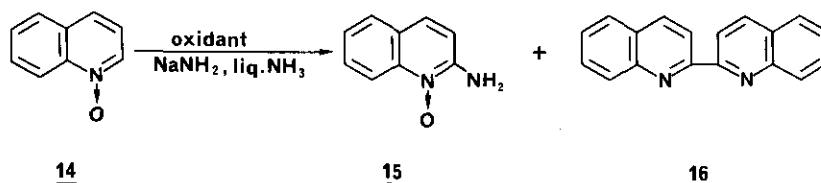
This result is very significant in view of the fact that the reaction of lepidine 1-oxide 2 using amyl nitrite instead of *i*-PrONO under similar conditions brought about much resinification and gave only trace amounts of aldoxime 6, the corresponding nitrile and amide³. Apparently, *i*-PrONO acts mainly as an oxidant in the amination. In evaluating the oxidizing potency of *i*-PrONO, we examined reactions of 1 and 2 using KMnO_4 ⁴, which is known as a useful oxidant in amination of *N*-heteroaromatics in liq. NH_3 , and NaNO_2 (Table I), and found *i*-PrONO is superior to KMnO_4 and NaNO_2 as oxidant in the present amination.

Table I. Effect of Oxidants on the Yields of 3-8

Oxidant	Yield (%)						Recovery (%)	
	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>	<u>1</u>	<u>2</u>
<i>i</i> -PrONO	30	49	12	2	8	1	-	-
KMnO_4	14	15	-	-	2	2	57	59
NaNO_2	-	3	-	-	-	3	94	75
none	-	4	-	-	-	-	63	89

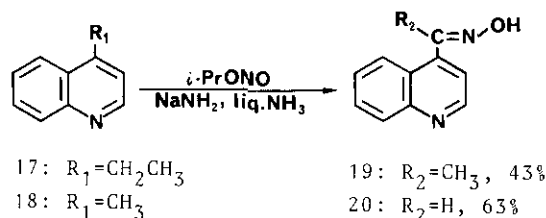
Subsequently amination of quinoline 1-oxide 14 with NaNH_2 in liq. NH_3 was carried out in the presence of various types of oxidants (Table II). In all attempted reactions, 2-aminoquinoline 1-oxide 15⁵ and deoxygenated 2,2'-biquinoline 16 were formed, and 15 was obtained in the highest yield from the reaction using *i*-PrONO. Thus, it was proved that *i*-PrONO is highly effective as oxidant for amination with NaNH_2 in liq. NH_3 in a series of quinoline 1-oxides.

Table II. Reactions of Quinoline 1-Oxide 14 with NaNH_2 -liq. NH_3 in the Presence of Oxidants



Oxidant	Yield (%)	
	<u>15</u>	<u>16</u>
<i>i</i> -PrONO	66	12
<i>i</i> -PrONO ₂	44	16
KMnO ₄	11	16
KNO ₃	17	12
K ₂ S ₂ O ₈	17	3
K ₃ Fe(CN) ₆	trace	1
none	22	10

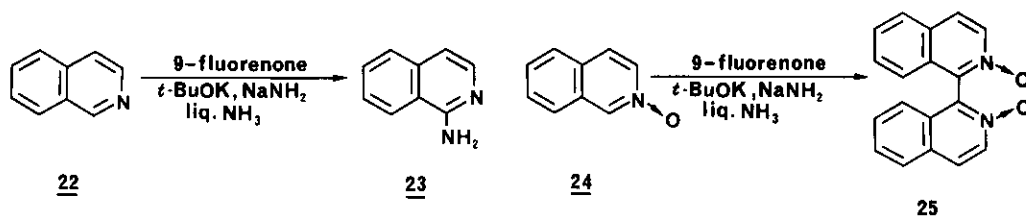
In this reaction, the reason why no 4-amino isomer was obtained probably would be attributable to the well-known dependency of the position of addition of the amide ion on the temperature in the Chichibabin amination of azaaromatics, in fact in the amination of 1,5-naphthyridine the σ adduct at 2-position was converted into the σ adduct at 4-position as ranging from -40°C to $+10^\circ\text{C}$ ⁶. On the other hand, the reaction of 4-ethylquinoline 17⁷ and lepidine 18 under the same conditions gave only nitrosation products, (*E*)-methyl 4-quinolyl ketone oxime 19⁸ and (*E*)-4-quinolinecarboxaldehyde oxime 20³ respectively, no amination products being obtained (Scheme 3).



Scheme 3

The amination scarcely occurred also with quinoline 21 under these conditions, although it was reported that 2-aminoquinoline and/or 4-aminoquinoline were obtained from the reaction of 21 with KNH_2 and KNO_3 or KMnO_4 in liq. NH_3 ^{9,10}. From these results, it was disclosed that the N-oxide function is indispensable for the amination of quinoline derivatives. A theoretical approach to this aspect will be later described.

We also tried the amination of isoquinoline 22 and its N-oxide 24 with *i*-PrONO and NaNH_2 in liq. NH_3 , but no amination occurred in both cases. In this connection, we examined the reaction of 22 and 24 with NaNH_2 in the presence of various oxidants in liq. NH_3 and found that modified Oppenauer oxidation¹¹ using 9-fluorenone as a hydrogen acceptor gave 1-aminoisoquinoline 23¹² in 20% yield from 22, but in the case of 24 1,1'-biisoquinoline 2,2'-dioxide 25 was produced in 40% yield (Scheme 4).



Scheme 4

The formation of 25 is apparently the same pattern with the formation of 2,2'-biquinoline 1,1'-dioxides, 7 and 8 from 1 and 2 respectively, and such an oxidative coupling would be conceivable to follow the course involving radical species. To explore this possibility, the first-mentioned reaction of 1 was examined using Galvinoxyl as a radical scavenger, but against our anticipation any effects were not observed on the proportion and yields of product. Thus, a radical process was ruled out (Table III).

Table III. Effect of Galvinoxyl on the Yields of 3, 5 and 7

Run	Molar Ratio of		Yield (%)			Recovery (%)
	Galvinoxyl : <u>1</u>		<u>3</u>	<u>5</u>	<u>7</u>	<u>1</u>
1	0	100	30	12	8	-
2	5	100	31	14	9	26
3	15	100	31	11	12	26

Although the details of the mechanism is not clear yet, the following ionic pathway seems more likely¹³, i.e., the α -proton of the N-oxide is abstracted

with a base, followed by nucleophilic attack of the so-formed carbanion center at the α -position of the another N-oxide molecule to give a 1,2-dihydroquinoline intermediate which is oxidized with *i*-PrONO to the product.

It was further found that, in the original reaction of lepidine 1-oxide 2, nitrosation smoothly proceeded as the main process when alkoxides (MeONa, EtONa, *i*-PrONa¹⁴ and *t*-BuOK) were added to the reactants or when NaNH₂ was replaced by alkoxides, giving the aldoxime 6 in very high yields with no visible sign of resinification (Table IV).

Table IV. Effect of Various Alkoxides on the Yields of 4 and 6 in the Reaction of 2 with *i*-PrONO

Base	Yield (%)	
	<u>4</u>	<u>6</u>
NaNH ₂	49	2
MeONa, NaNH ₂	0	94
EtONa, NaNH ₂	0	91
<i>i</i> -PrONa, NaNH ₂	9	87
<i>t</i> -BuOK, NaNH ₂	11	82
MeONa	0	95
<i>t</i> -BuOK	0	95

These results together with those reported in the preceding paper⁸ suggest that the use of alkoxides as bases seems to be promising for this kinds of nitrosation.

As mentioned above, it was evident that there was a great difference in behavior between quinolines and the corresponding N-oxides in the reaction with *i*-PrONO and NaNH₂ in liq. NH₃, i.e., nitrosation of an alkyl substituent occurred in the former cases and the 2-amination was the main reaction in the latter cases. Therefore, in order to rationalize such different behaviour, the calculations of the heats of formation (ΔH_f) and the LUMO energies were performed using a semi-empirical molecular orbital (MO) method, i.e., MNDO method¹⁵ combined with geometrical optimization by the Davidson-Fletcher-Powell method¹⁶. It was reported recently by our group that $\Delta \Delta H_f^B$ would be useful as a chemical reactivity index for the nucleophilic substitution reaction¹⁷. The minimized energy pathways for nucleophilic attack at 2-position of quinoline nucleus, i.e., 1, 2, 14 and their parent compounds by amide anion were determined on the basis of the calculation which was carried out regarding the distance between the carbon atom

at 2-position of quinoline nucleus and the nitrogen atom of amide anion as the reaction coordinate in view of so-called complex "superion" which consists of quinoline derivative and amide anion (Figure 1).

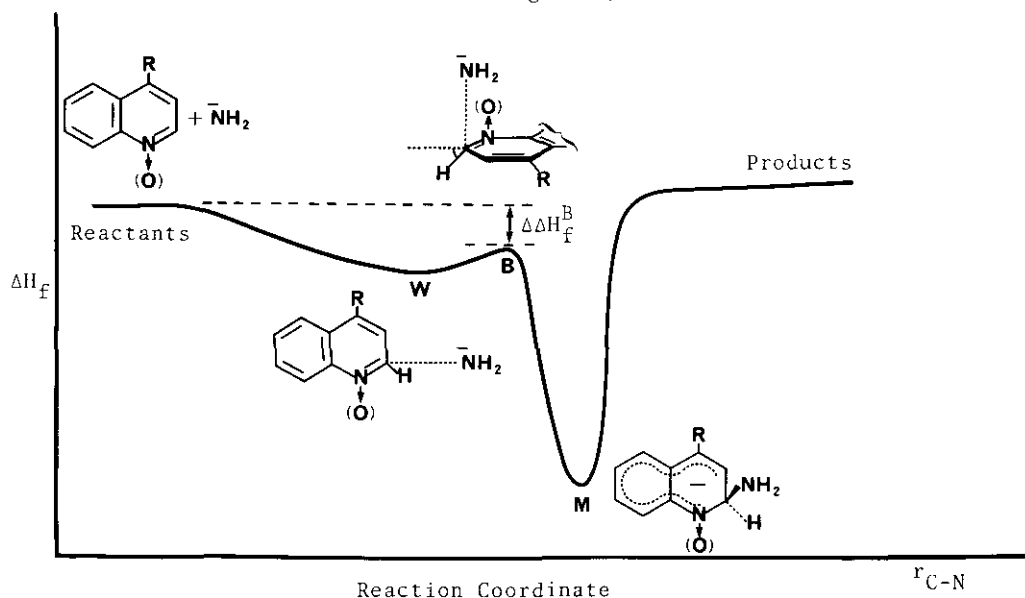


Figure 1. Reaction Profile of Quinoline Derivative with Amide Ion

The chemical reactivity index $\Delta\Delta H_f^B$ is defined as the difference between ΔH_f of superion at the point B in Figure 1 and that of reactants which involve amide anion and quinoline derivative, as shown in the following equation¹⁷.

$$\Delta\Delta H_f^B = \Delta H_f(\text{superion at the point B}) - \Delta H_f(\text{reactants})$$

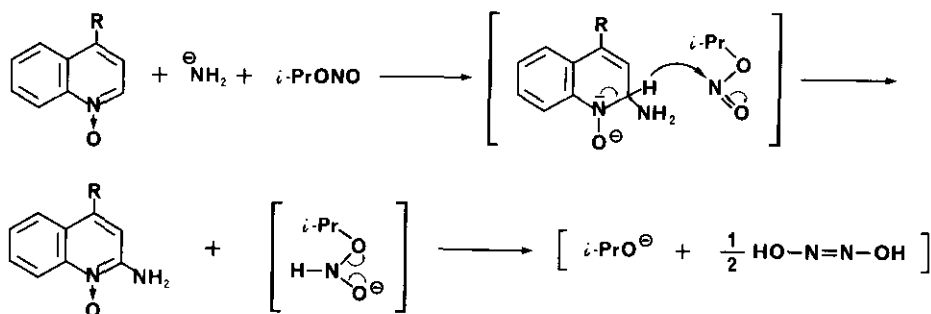
As can be seen in Figure 1, the reaction profile indicates that as amide anion approaches the substrate, the superion first stabilizes somewhat (point W), subsequently passes over the low energy barrier (point B) and then via Meisenheimer-type complex (point M) leads to the final amino compound. Accordingly, as expected readily, the reactivity in nucleophilic substitution reaction would be in inverse ratio to the $\Delta\Delta H_f^B$ involved in each process. Table V shows the $\Delta\Delta H_f^B$ in the each intermolecular distance as well as the LUMO energy of the substrate. It is evident from Table V that the $\Delta\Delta H_f^B$ of the compound with N-oxide group is invariably smaller than that of the corresponding parent compound and the LUMO energy level of the compound with N-oxide is lower than that of the corresponding parent compound. These results of theoretical calculation suggest

that the amination of heterocycles with N-oxide group is preferable to that of heterocycles without N-oxide group, and this fact is in good agreement with the experimental results mentioned above.

Table V. $\Delta\Delta H_f^B$ and LUMO Energy Level of N-Containing Heterocycles Calculated by MNDO Method

Compd. No.	$\Delta\Delta H_f^B$ (kcal/mol)	LUMO (ev)
<u>21</u>	-4.395	-0.531
<u>14</u>	-7.235	-0.888
<u>18</u>	-5.455	-0.590
<u>2</u>	-7.756	-0.946
<u>17</u>	-2.306	-0.577
<u>1</u>	-4.377	-0.942

As for the oxidative function of *i*-PrONO in the amination, the nitrites generally have the amphoteric character that involves both oxidative and reductive functions¹⁸. Recently, the oxidative mechanism for the conversion of hemoglobin into methemoglobin by alkyl nitrite was kinetically investigated in detail¹⁹. In the amination of azaaromatics in the presence of the conventional oxidant in liq. NH_3 , the formation of anionic 1:1 σ adduct, which is formed between azaaromatics and amide anion, was fully confirmed by use of nmr spectroscopy⁶. Based on these previous findings, the oxidation mechanism by *i*-PrONO in the amination of heterocycles with N-oxide group could be reasonably considered in the following way (Scheme 5).



Scheme 5

The nucleophilic attack at 2-position of quinoline nucleus by amide anion takes place first, via the electron transfer as shown in Scheme 5 the hydride ion eliminates and the amino compound forms, essentially in a similar way as the mechanism of Chichibabin amination. On the other hand, the reduced nitrite

Preparation of 4-Ethylquinoline 1-oxide $\bar{1}$ —To a solution of 4-ethylquinoline (10.0 g, 64 mmol) in acetic acid (130 ml), 35% aqueous hydrogen peroxide (21 g, 216 mmol) was added and the mixture was heated at 70-80°C for 12 h. The reaction mixture was concentrated $\bar{in vacuo}$, the residue was basified by sat. K_2CO_3 aqueous solution and extracted with $CHCl_3$. The residue from the $CHCl_3$ extract was chromatographed with $CHCl_3$ -ether (1:1) to give 4-ethylquinoline 1-oxide $\bar{1}$, colorless needles (from ether-acetone), mp 91-92°C, 6.3 g (57% yield). Anal. Calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.25; H, 6.33; N, 8.04. $UV \lambda_{EtOH}^{max} (log \epsilon)$: 228(4.55). $IR \nu_{KBr}^{max} (cm^{-1})$: 3220, 1270, 1210(N-O), 1160, 860, 750. $^1H-NMR \delta_{CDCl_3}^{ppm}$ (90MHz): 1.36(3H,t,J=8.0Hz,CH₂), 3.04(2H,q,J=8.0Hz,CH₂), 7.11(1H,d,J=6.0Hz,H-3), 7.50-7.86(2H,m,H-6 and H-7), 7.90-8.10(1H,m,H-5), 8.44(1H,d,J=6.0Hz,H-2), 8.70-8.90(1H,m,H-8). $^{13}C-NMR \delta_{CDCl_3}^{ppm}$ (25.1MHz): 128.41(d,Ar), 129.14(s,Ar), 129.87(d,Ar), 135.11(d,Ar), 140.22(s,Ar), 13.95(q,CH₃), 24.67(t,CH₂), 119.51(d,Ar), 120.42(d,Ar), 124.20(d,Ar).

Melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. Spectral data were recorded on the following spectrophotometers and spectrometers: ultraviolet (uv) spectra, Hitachi 556; infrared (ir) spectra, JASCO IR-810; ^1H-NMR spectra, Hitachi R-22 (90MHz), JEOL FX-100 spectra, JASCO GX-400 (400MHz); $^{13}C-NMR$ spectra FX-90Q (22.5MHz), JEOL FX-100 (25.1MHz) and JEOL GX-400 (100.5MHz); mass spectra (ms), JEOL JMS-DX300. As regards the assignment of ^1H-NMR spectra, 2D $^1H-^{13}C$ chemical shift correlation spectra measured by GX-400 (400MHz) were utilized. High-performance thin layer chromatography (HPLC) about the yields shown in Tables I, II 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).

EXPERIMENTAL

In the reaction of $\bar{2}$ with tert-butyl nitrite (t-BuONO) in place of t-PrONO as an oxidant and $NANH_2$ in liq. NH_3 , $\bar{4}$ was obtained in 21% yield and the potency of other alkyl nitrites as oxidant in similar reaction systems will have to be explored further.

Scheme 5.

Leads to finally hypnitrous acid ($H_2N_2O_2$) via the electron transfer as shown in

141.08(s,Ar). Ms m/z (rel.int.): 173(M^+ ,66), 158(100). High resolution ms Calcd for $C_{11}H_{11}NO(M^+)$: 173.084. Found: 173.083.

General Procedure for the Reaction of N-Heterocycle with i-PrONO in Liq. NH_3

—Reaction was carried out as described in the previous paper³, using quinoline or isoquinoline derivative (10 mmol) and i-PrONO (1.96 g, 22 mmol) instead of amyl nitrite. After standing overnight until liq. NH_3 completely evaporated, the residue was respectively post-treated in the manner as shown below.

Reaction of 4-Ethylquinoline 1-Oxide 1—

The residue was chromatographed with $CHCl_3$ -MeOH (20:1) to give 4,4'-diethyl-2,2'-biquinoline 1,1'-dioxide 7, (E)-methyl 1-oxido-4-quinolyl ketone oxime 5 and 2-amino-4-ethylquinoline 1-oxide 3, in turn. Compound 3 was recrystallized from acetone-MeOH to give pale yellow scales, mp 217-218°C, 0.56 g (30% yield). Compound 3 is susceptible to sunlight to turn brown from yellow in the appearance. Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.21; H, 6.44; N, 14.79. Uv λ_{max}^{EtOH} nm(log ϵ): 251(5.17). Ir ν_{max}^{KBr} cm^{-1} : 3400-3000, 1643(NH_2), 1270(NH_2), 1190($N=O$), 750. 1H -Nmr $\delta_{ppm}^{DMSO-d_6}$ (90MHz): 1.24(3H,t,J=8.0Hz, CH_3), 2.96(2H,q,J=8.0Hz, CH_2), 6.98(1H,s,H-3), 7.31(2H,br s, NH_2), 7.39(1H,t,J=7.0Hz,H-6), 7.69(1H,t,J=7.0Hz,H-7), 7.93(1H,d,J=8.0Hz,H-5), 8.40(1H,d,J=8.0Hz,H-8). ^{13}C -Nmr $\delta_{ppm}^{DMSO-d_6}$ (22.5MHz): 13.42(q, CH_3), 23.41(t, CH_2), 109.13(d,Ar), 116.97(d,Ar), 121.46(s,Ar), 123.07(d,Ar), 123.90(d,Ar), 129.16(d,Ar), 139.11(s,Ar), 139.55(s,Ar), 146.86(s,Ar). Ms m/z (rel.int.): 188(M^+ ,100), 173(31), 130(25), 99(17). High resolution ms Calcd for $C_{11}H_{12}N_2O(M^+)$: 188.095. Found: 188.095. Compound 5^{1b} was recrystallized from acetone to give yellow prisms, 0.24 g (12% yield). Compound 7 was recrystallized from acetone-MeOH to give yellow fine needles, mp 239-240°C (decomp.), 0.14 g (8% yield). Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.71; H, 5.87; N, 8.25. Uv λ_{max}^{EtOH} nm(log ϵ): 255(5.08). Ir ν_{max}^{KBr} cm^{-1} : 2970, 1560, 1310, 1210($N=O$), 880, 760, 740. 1H -Nmr $\delta_{ppm}^{DMSO-d_6}$ (100MHz): 1.34(3H*2,t,J=7.1Hz, CH_3 *2), 3.13(2H*2,q,J=7.1Hz, CH_2 *2), 7.66(1H*2,s,H-3 and H-3'), 7.78-7.98(2H*2,m,H-6',H-6',H-7 and H-7'), 8.20-8.33(1H*2,m,H-5 and H-5'), 8.61-8.71(1H*2,m,H-8 and H-8'). ^{13}C -Nmr $\delta_{ppm}^{DMSO-d_6}$ (22.5MHz): 13.32(q, CH_3), 23.26(t, CH_2), 119.32(d,Ar), 121.51(d,Ar), 124.19(d,Ar), 128.38(d,Ar), 129.21(d,Ar), 136.72(s,Ar), 137.79(s,Ar), 140.67(s,Ar), 142.96(s,Ar). Ms m/z (rel.int.): 344(M^+ ,40), 327(16), 311(15), 299(100), 285(22), 269(25). High resolution ms Calcd for $C_{22}H_{20}N_2O_2(M^+)$: 344.152. Found: 344.153.

Reaction of 4-Methylquinoline 1-Oxide 2²——The residue was chromatographed to give 4,4'-dimethyl-2,2'-biquinoline 1,1'-dioxide 8 (with CHCl₃-MeOH, 20:1), (E)-4-quinolinecarboxaldehyde 1-oxide oxime 6 (with CHCl₃-MeOH, 10:1) and 2-amino-4-methylquinoline 1-oxide 4 (with CHCl₃-MeOH, 1:1). Compound 4 was recrystallized from acetone-MeOH to give pale yellow prisms, mp 257-258°C, 0.85 g (49% yield). Compound 4 is susceptible to sunlight to turn brown from yellow in the appearance. Anal. Calcd for C₁₀H₁₀N₂O : C, 68.95; H, 5.79; N, 16.08. Found: C, 68.82; H, 5.90; N, 15.99. Uv $\lambda_{\max}^{\text{EtOH}}$ nm(log ϵ): 250(5.15). Ir ν_{\max}^{KBr} cm⁻¹: 3300-3000, 1670(NH₂), 1270(NH₂), 1195(N-O), 747. ¹H-Nmr $\delta_{\text{ppm}}^{\text{MeOH-d}_4}$ (90MHz): 2.58(3H,s,CH₃), 4.82(2H,s,NH₂), 6.93(1H,s,H-3), 7.42(1H,t,J=7.0Hz,H-6), 7.76(1H,t,J=7.0Hz,H-7), 7.89(1H,d,J=8.0Hz,H-5), 8.33(1H,d,J=8.0Hz,H-8). ¹³C-Nmr $\delta_{\text{ppm}}^{\text{MeOH-d}_4}$ (25.1MHz): 18.52(q,CH₃), 112.42(d,Ar), 117.29(d,Ar), 124.07(s,Ar), 125.33(d,Ar), 126.06(d,Ar), 132.10(d,Ar), 140.00(s,Ar), 142.24(s,Ar), 149.79(s,Ar). Ms m/z(rel.int.): 174(M⁺,100), 158(43), 130(39). High-resolution ms Calcd for C₁₁H₁₂N₂O(M⁺): 174.079. Found: 174.081. Compound 6³ was recrystallized from MeOH to give pale yellow prisms, 0.04 g (2% yield). Compound 8 was recrystallized from acetone to give pale yellow needles, mp 269-270°C (decomp.), 0.016 g (1% yield). Anal. Calcd for C₂₀H₁₆N₂O₂: C, 75.93; H, 5.10; N, 8.86. Found: C, 75.70; H, 5.18; N, 8.87. Uv $\lambda_{\max}^{\text{EtOH}}$ nm(log ϵ): 255(5.14). Ir ν_{\max}^{KBr} cm⁻¹: 3400, 1560, 1340, 1205(N-O), 758. ¹H-Nmr $\delta_{\text{ppm}}^{\text{pyridine-d}_5}$ (400MHz): 2.48(3H*2,s,CH₃*2), 7.61(1H*2,t,J=8.3Hz,H-6 and H-6'), 7.70(1H*2,t,J=8.3Hz,H-7 and H-7'), 7.72(1H*2,s,H-3 and H-3'), 7.85(1H*2,d,J=8.3Hz,H-5 and H-5'), 9.09(1H*2,d,J=8.3Hz,H-8 and H-8'). ¹³C-Nmr $\delta_{\text{ppm}}^{\text{pyridine-d}_5}$ (100.5MHz): 17.74(q,CH₃), 120.69(d,Ar), 124.34(d,Ar), 125.32(d,Ar), 128.94(d,Ar), 129.78(d,Ar), 130.27(s,Ar), 131.65(s,Ar), 142.16(s,Ar). Ms m/z(rel.int.): 316(M⁺,24), 271(100), 115(23). High-resolution ms Calcd for C₂₀H₁₆N₂O₂(M⁺): 316.121. Found: 316.121.

Reaction of 4-Ethylquinoline 17——After the residue was enough extracted with CHCl₃, the CHCl₃ solution was evaporated to dryness. The resulting residue was extracted with ether to give the starting material, 0.22 g (14% recovered) from the ether solution and (E)-methyl 4-quinolyl ketone oxime 19 from the residue. Compound 19 was recrystallized from ether-acetone to give colorless needles, mp 156-157°C, 0.80 g (43% yield). Anal. Calcd for C₁₁H₁₀N₂O: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.60; H, 5.59; N, 14.57. Uv $\lambda_{\max}^{\text{EtOH}}$ nm(log ϵ): 231(4.91). Ir ν_{\max}^{KBr} cm⁻¹: 2850, 1590, 995, 770. ¹H-Nmr $\delta_{\text{ppm}}^{\text{DMSO-d}_6}$ (90MHz): 2.33(3H,s,CH₃), 7.51(1H,d,J=4.0Hz,H-3), 7.50-7.90(2H,m,H-6 and H-7), 8.10(1H,d,J=7.5Hz,H-5),

8.24(1H,d,J=7.5Hz,H-7), 8.94(1H,d,J=4.0Hz,H-2), 11.67(1H,s,OH). $^{13}\text{C-Nmr}$ $\delta_{\text{ppm}}^{\text{DMSO-d}_6}$ (25.1MHz): 15.23(q,CH₃), 120.12(d,C-3), 125.12(s,C-10), 125.78(d,C-8), 126.70(d,C-6), 129.19(d,C-7), 129.38(d,C-5), 143.39(s,C-4), 148.26(s,C-9), 150.03(d,C-2), 152.59(s,C=N). Ms m/z(rel.int.): 186(M⁺,100), 169(93), 128(59), 101(35). High resolution ms Calcd for C₁₁H₁₀N₂O(M⁺): 186.079. Found: 186.080.

Reaction of 4-Methylquinoline 18——The residue was washed with water and the insoluble substance was recrystallized from MeOH to give 4-quinolinecarboxaldehyde oxime 20³, colorless prisms, 1.08 g (63% yield).

General Procedure for the Reaction of Amino Compound with Ac₂O——A mixture of amino compound (2.5 mmol) and Ac₂O (5ml) was heated at 60-70°C to dissolve the compound, if necessary, then stood at room temperature for several hours. After MeOH was added to the mixture in order to decompose Ac₂O, the solvent was evaporated to dryness.

Reaction of 3——The residue was recrystallized from ether to give 2-acetyl-amino-4-ethylquinoline 1-oxide 9, colorless prisms, mp 149-150°C, 0.29 g (50% yield). Anal. Calcd for C₁₃H₁₄N₂O₂: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.99; H, 6.15; N, 12.03. Uv $\lambda_{\text{max}}^{\text{EtOH}}$ nm(log ϵ): 262(5.16). Ir $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3190, 1705(C=O), 1580(NH), 1500(NH), 1315, 1270(N→O), 1110, 760. $^1\text{H-Nmr}$ $\delta_{\text{ppm}}^{\text{CDCl}_3}$ (90MHz): 1.40(3H,t,J=7.0Hz,CH₃CH₂), 2.37(3H,s,CH₃), 3.09(2H,q,J=7.0Hz,CH₂), 7.40-7.87(2H,m,H-6 and H-7), 7.96(1H,d,J=8.0Hz,H-5), 8.46(1H,s,H-3), 8.67(1H,d,J=8.0Hz,H-8), 10.44(1H,br s,NH). $^{13}\text{C-Nmr}$ $\delta_{\text{ppm}}^{\text{CDCl}_3}$ (25.1MHz): 14.19(q,CH₃CH₂), 25.22(t,CH₂), 25.22(q,CH₃), 111.53(d,Ar), 119.39(d,Ar), 124.20(d,Ar), 124.63(s,Ar), 126.46(d,Ar), 130.53(d,Ar), 138.70(s,Ar), 141.26(s,Ar), 142.47(s,Ar), 169.40(s,C=O). Ms m/z(rel.int.): 230(M⁺,26), 188(100), 173(19), 130(12). High resolution ms Calcd for C₁₃H₁₄N₂O₂(M⁺): 230.105. Found: 230.105.

Reaction of 10 (vide infra)——The residue was recrystallized from ether-acetone to give 2-acetyl-amino-4-ethylquinoline 11, colorless prisms, mp 182-183°C, 0.26 g (48% yield). Anal. Calcd for C₁₃H₁₄N₂O: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.90; H, 6.66; N, 13.06. Uv $\lambda_{\text{max}}^{\text{EtOH}}$ nm(log ϵ): 246(5.14). Ir $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3280, 1680(C=O), 1580(NH), 1500, 1430, 1360, 1250, 745. $^1\text{H-Nmr}$ $\delta_{\text{ppm}}^{\text{CDCl}_3}$ (90MHz): 1.40(3H,t,J=7.0Hz,CH₃CH₂), 2.22(3H,s,CH₃), 3.13(2H,q,J=7.0Hz,CH₂), 7.30-7.73(2H,m,H-6 and H-7), 7.80(1H,d,J=8.0Hz,H-5), 7.96(1H,d,J=8.0Hz,H-8), 8.29(1H,s,H-3), 8.82(1H,br s,NH). $^{13}\text{C-Nmr}$ $\delta_{\text{ppm}}^{\text{CDCl}_3}$ (25.1MHz): 14.13(q,CH₃CH₂), 24.79(q,CH₃), 25.58(t,CH₂), 112.87(d,Ar), 123.47(d,Ar), 124.81(d,Ar),

125.66(s,Ar), 128.16(d,Ar), 129.44(d,Ar), 146.80(s,Ar), 151.12(s,Ar), 152.83(s,Ar), 169.03(s,C=O). Ms m/z(rel.int.): 214(M⁺,47), 172(100), 130(11). High resolution ms Calcd for C₁₃H₁₄N₂O(M⁺): 214.111. Found: 214.111.

Reaction of 4—The residue was chromatographed with CHCl₃ to give 2-acetyl-amino-4-methylquinoline 1-oxide 12, colorless prisms (from ether-acetone), mp 183-184°C, 0.28 g (52% yield). Anal. Calcd for C₁₂H₁₂N₂O₂: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.63; H, 5.74; N, 12.87. Uv λ_{max}^{EtOH}_{nm}(log ε): 262(5.21). Ir ν_{max}^{KBr}cm⁻¹: 3190, 1700(C=O), 1570(NH), 1495, 1325, 1260(N—O), 770. ¹H-Nmr δ_{ppm}^{CDCl₃}(90MHz): 2.37(3H,s,CH₃), 2.70(3H,s,COCH₃), 7.40-7.84(2H,m,H-6 and H-7), 7.93(1H,d,J=8.0Hz,H-5) 8.46(1H,s,H-3), 8.67(1H,d,J=8.0Hz,H-8), 10.37(1H,br s,NH). ¹³C-Nmr δ_{ppm}^{CDCl₃}(25.1MHz): 18.76(q,CH₃), 25.16(q,COCH₃), 113.06(d,Ar), 119.20(d,Ar), 124.63(d,Ar), 125.30(s,Ar), 126.51(d,Ar), 130.66(d,Ar), 136.69(s,Ar), 138.52(s,Ar), 140.95(s,Ar), 169.27(s,C=O). Ms m/z(rel.int.): 216(M⁺,29), 174(100), 130(34), 115(24). High resolution ms Calcd for C₁₂H₁₂N₂O₂(M⁺): 216.090. Found: 216.089.

Reaction of Quinoline 1-Oxide 14—The residue was chromatographed with CHCl₃ to give 2,2'-biquinoline 16 and 2-aminoquinoline 1-oxide 15 in turn. Compound 16²⁰ was recrystallized from acetone to give colorless scales, 0.31 g (12% yield). Compound 15⁵ was recrystallized from CH₃COOEt-MeOH to give colorless prisms, 1.06 g (66% yield).

General Procedure for Deoxygenation of N-Oxide Compound with Zn Dust—To a solution of N-oxide compound (2.0 mmol) in acetic acid (18 ml) Zn dust (2.1 g, 32 mmol) was added in small portions and the reaction mixture was heated at 50-60°C for 4 h with stirring. After the Zn dust was filtered, the filtrate was basified with 10% NaOH aqueous solution and extracted with ether. The ether layer was dried over MgSO₄ and the solvent was evaporated to dryness.

Deoxygenation of 3—The residue was recrystallized from petrol. ether to give 2-amino-4-ethylquinoline 10, colorless needles, mp 68 °C, 0.29 g (84% yield). Anal. Calcd for C₁₁H₁₂N₂: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.62; H, 7.02; N, 16.22. Uv λ_{max}^{EtOH}_{nm}(log ε): 238(5.09). Ir ν_{max}^{KBr}cm⁻¹: 3480(NH₂), 3120, 1640(NH₂), 1610(NH₂), 1430, 1410, 755(NH₂). ¹H-Nmr δ_{ppm}^{CDCl₃}(90MHz): 1.31(3H,t,J=7.0Hz,CH₃), 2.96(2H,q,J=7.0Hz,CH₂), 4.94(2H,br s,NH₂), 6.54(1H,s,H-3), 7.23(1H,t,J=8.0Hz,H-6), 7.50(1H,t,J=8.0Hz,H-7), 7.69(1H,d,J=8.0Hz,H-5), 7.80(1H,d,J=8.0Hz,H-8). ¹³C-Nmr δ_{ppm}^{CDCl₃}(25.1MHz): 13.64(q,CH₃), 24.91(t,CH₂), 109.89(d,Ar), 122.25(d,Ar), 123.17(d,Ar), 123.17(d,Ar), 123.17(s,Ar),

126.51(d,Ar), 129.19(d,Ar), 147.83(s,Ar), 151.37(s,Ar), 157.09(s,Ar). Ms m/z(re-l.int.): 172(M⁺,100), 171(24), 157(14), 130(15). High-resolution ms Calcd for C₁₁H₁₂N₂(M⁺): 172.100. Found: 172.099.

Deoxygenation of 4——The residue was recrystallized from benzene to give 2-amino-4-methylquinoline 13²¹, 0.28 g (90% yield).

Deoxygenation of 9 with PCl₃——PCl₃ (0.55 g, 4 mmol) in CHCl₃ (5 ml) was added dropwise to a solution of 9 (0.46 g, 2 mmol) dissolved in CHCl₃ (30 ml) under ice-cooling. The reaction mixture was heated under reflux on a water bath for 0.5 h, treated with ice water, the acid solution was basified with 28% ammonia and then extracted with CHCl₃. The residue from the CHCl₃ extract was recrystallized from ether-acetone to give 11, 0.23 g (54% yield).

Reaction of 1 (or 2) with NaNH₂ in the Presence of an Oxidant in Liq. NH₃

——Reaction was carried out as described in general procedure for the reaction of 1 (or 2) with i-PrONO in liq. NH₃ but using the oxidants described below instead of i-PrONO. After the residue was dissolved in MeOH and the insoluble materials were filtered out, the yield of each product in the filtrate was determined by using a high-speed thin layer chromatoscanner. Hptlc conditions: Hptlc plate, silica gel 60 F₂₅₄ precoated (Merck); solvent system, CHCl₃:MeOH = 10:1. The yield of respective compound was as follows.

KMnO₄ (3.48 g, 22 mmol) as an oxidant: 3 0.26 g (14% yield), 7 0.03 g (2% yield), and 1 0.99 g (57% recovery). 4 0.26 g (15% yield), 8 0.03 g (2% yield), and 2 0.94 g (59% recovery).

NaNO₂ (1.52 g, 22 mmol) as an oxidant: 1 1.63 g (94% recovery). 4 0.05 g (3% yield), 8 0.05 g (3% yield), and 2 1.19 g (75% recovery).

no oxidant: 1 1.09 g (63% recovery). 4 0.07 g (4% yield), and 2 1.42 g (89% yield).

Reaction of 14 with NaNH₂ in the Presence of an Oxidant in Liq. NH₃——

Carried out as described for reaction of 1 (or 2) with NaNH₂ in the presence of an oxidant in liq. NH₃ but using the solvent system (CH₃COOEt:C₆H₆ = 5:1) as concerns the determination of 16. The yield of the respective compound was as follows.

i-PrONO₂ (2.31 g, 22 mmol) as an oxidant: 15 0.70 g (44% yield) and 16 0.41 g (16% yield).

KMnO₄ (3.48 g, 22 mmol) as an oxidant: 15 0.18 g (11% yield) and 16 0.41 g (16% yield).

KNO₃ (2.22 g, 22 mmol) as an oxidant: 15 0.27 g (17% yield) and 16 0.31 g (12% yield).

K₂S₂O₈ (5.95 g, 22 mmol) as an oxidant: 15 0.27 g (17% yield) and 16 0.08 g (3% yield).

K₃Fe(CN)₆ (7.24 g, 22 mmol) as an oxidant: 16 0.03 g (1% yield).

no oxidant : 15 0.35 g (22% yield) and 16 0.26 g (10% yield).

General Procedure for Modified Oppenauer Oxidation in Liq. NH₃———In the general procedure for the reaction of N-heterocycle with i-PrONO in liq. NH₃, when Na was converted completely into NaNH₂, (in the reaction using t-BuOK, t-BuOK (3.37 g, 30 mmol) was added to the liq. NH₃ solution in this time and then after stirring for 30 min) quinoline or isoquinoline derivative (10 mmol) was added to the liq. NH₃ solution and the reaction mixture was further stirred for 30 min. 9-Fluorenone (5.40 g, 30 mmol) which had been grained enough was added in small portions to the reaction mixture and then the reaction mixture was stirred for 2 h, finally followed by the addition of NH₄Cl. After standing overnight until liq. NH₃ completely evaporated, the residue was respectively post-treated in the manner as shown below.

Modified Oppenauer Oxidation of Isoquinoline 22———The residue was chromatographed with CHCl₃ to give 1-aminoisoquinoline 23¹², colorless prisms (from benzene), 0.19 g (13% yield) (in the reaction using t-BuOK, 0.29 g, 20% yield).

Modified Oppenauer Oxidation of Isoquinoline 2-Oxide 24———The residue was chromatographed to give starting material, 0.58g (40% recovery) (with CHCl₃) and 1,1'-biisoquinoline 2,2'-dioxide 25 (with CHCl₃-MeOH, 50:1). Compound 25 was recrystallized from acetone to give colorless prisms, mp 278-279°C (decomp.), 1.15 g (40% yield). Anal. Calcd for C₁₈H₁₂N₂O₂: C, 74.99; H, 4.20; N, 9.72. Found: C, 74.95; H, 4.21; N, 9.71. Uv λ_{max}^{EtOH}_{nm}(logε): 265(5.18). Ir ν_{max}^{KBr}cm⁻¹: 3460, 3070, 1329, 1235,(N→O), 1133, 742. ¹H-Nmr δ_{ppm}^{DMSO-d₆}(100MHz): 7.01(1H *2,d,J=8.6Hz,Ar-H), 7.31-7.77(2H*2,m,Ar-H), 7.93-8.49(3H*2,m,Ar-H). ¹³C-Nmr δ_{ppm}^{DMSO-d₆}(25.1MHz): 122.86(d,Ar), 125.45(d,Ar), 127.43(d,Ar), 127.88(s,Ar), 128.19(d,Ar), 128.61(s,Ar), 129.95(d,Ar), 136.32(s,Ar), 137.24(d,Ar). Ms m/z(re-1.int.): 288(M⁺,29), 271(21), 255(41), 128(19), 44(100). High resolution ms Calcd for C₁₈H₁₂N₂O₂(M⁺): 288.090. Found: 288.090.

Reaction of 1 with i-PrONO with and without Galvinoxyl——— Unless otherwise stated, all the reactions were carried out according to the general procedure for the reaction of N-heterocycle with i-PrONO in liq. NH₃ and the determination

conditions were the same as those used in reaction of 1 (or 2) with NaNH_2 in the presence of an oxidant in liq. NH_3 .

Run 1: This case refers to just the reaction of 1 with i-PrONO described already.

Run 2: Carried out as described for Run 1 but adding Galvinoxyl (0.21 g, 0.5 mmol) prior to adding 1. 3: 0.58 g (31% yield), 5: 0.28 g (14% yield), 7: 0.15 g (9% yield), and S.M.: 0.45 g (26% recovery).

Run 3: Carried out as described for Run 1 but adding Galvinoxyl (0.63 g, 1.5 mmol) prior to adding 1. 3: 0.58 g (31% yield), 5: 0.22 g (11% yield), 7: 0.21 g (12% yield), and S.M.: 0.45 g (26% recovery).

Reaction of 2 with i-PrONO in the Presence of Various Types of Base in Liq. NH_3

—Carried out as described for the reaction of 1 with i-PrONO with and without Galvinoxyl and in the case of using two kinds of bases, when Na was completely converted into NaNH_2 , the other base (20 mmol) was added to the reaction mixture and then after 15 min compound 2 was added to the reaction mixture. The yields of 4 and 6 were as follows. $\text{MeONa} + \text{NaNH}_2$: 6 1.77 g (94% yield). $\text{EtONa} + \text{NaNH}_2$: 6 1.71 g (91% yield). $\text{i-PrONa} + \text{NaNH}_2$: 4 0.16 g (9% yield) and 6 1.64 g (87% yield). $\text{t-BuOK} + \text{NaNH}_2$: 4 0.19 g (11% yield) and 6 1.54 g (82% yield). MeONa : 6 1.79 g (95% yield). t-BuOK : 6 1.79 g (95% yield).

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