AMINATION AND NITROSATION OF QUINOLINES AND THEIR N-OXIDES

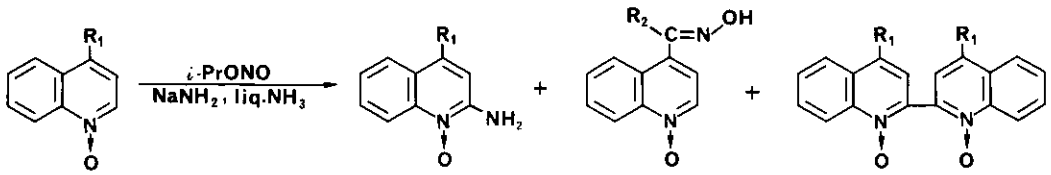
Yoshinobu Tagawa, Toshio Yoshida, Noriko Honjo, and Yoshinobu Goto*

Faculty of Pharmaceutical Sciences, Fukuoka University, Nanakuma, Jonan-ku, Fukuoka 814-01, Japan

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 agents[1], 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).



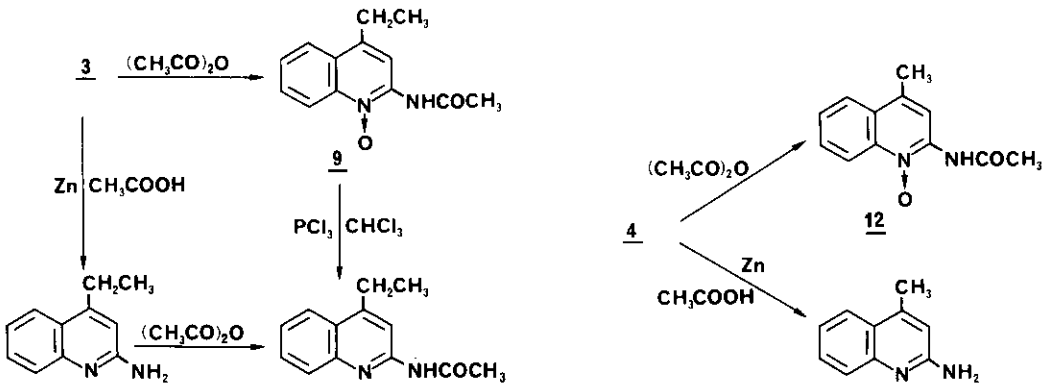
1: R_1=CH_2CH_3
2: R_1=CH_3

3: R_1=CH_2CH_3, 30%
4: R_1=CH_3, 49%

5: R_2=CH_3, 12%
6: R_2=H, 2%

7: R_1=CH_2CH_3, 8%
8: R_1=CH_3, 1%

Scheme 1



Scheme 2

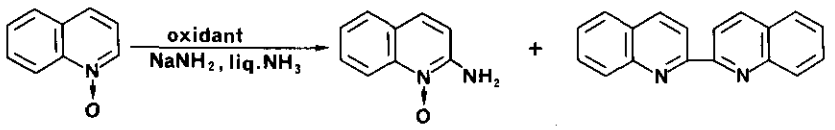
This result is very significant in view of the fact that the reaction of lepidine 1-oxide 2 using amyl nitrite instead of i-PrONO under similar conditions brought about much resinification and gave only trace amounts of aldoxime 6, the corresponding nitrile and amide[3]. Apparently, i-PrONO acts mainly 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

	Yield (%)						Recovery (%)	
Oxidant	3	4	5	6	7	8	1	2
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 15[5] 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.

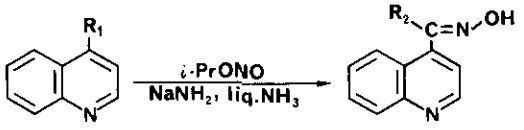
Table II. Reactions of Quinoline 1-Oxide 14 with $NaNH_2$-liq. NH_3 in the Presence of Oxidants



14 15 16

Oxidant	Yield (%) 15	16
i-PrONO	66	12
$i\text{-PrONO}_2$	44	16
$KMnO_4$	11	16
KNO_3	17	12
$K_2S_2O_8$	17	3
$K_3Fe(CN)_6$	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 °C[6]. On the other hand, the reaction of 4-ethylquinoline 17[7] and lepidine 18 under the same conditions gave only nitrosation products, (E)-methyl 4-quinolyl ketone oxime 19[8] and (E)-4-quinolinecarboxaldehyde oxime 20[3] respectively, no amination products being obtained (Scheme 3).

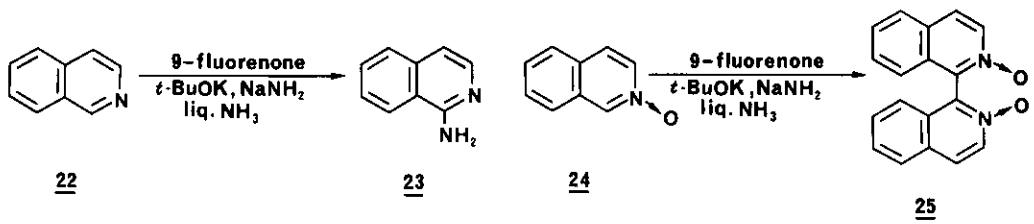


17: $R_1=CH_2CH_3$ 19: $R_2=CH_3$, 43%
18: $R_1=CH_3$ 20: $R_2=H$, 63%

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 oxidation[11] using 9-fluorenone as a hydrogen acceptor gave 1-aminoisoquinoline 23[12] 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).



22 23 24 25

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 Galvinoxyl : 1		Yield (%) 3	5	7	Recovery (%) 1
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 likely[13], 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-PrONa[14] and t-BuOK) were added to the reactants or when $NaNH_2$ 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 (%) 4	6
$NaNH_2$	49	2
MeONa, $NaNH_2$	0	94
EtONa, $NaNH_2$	0	91
i-PrONa, $NaNH_2$	9	87
t-BuOK, $NaNH_2$	11	82
MeONa	0	95
t-BuOK	0	95

These results together with those reported in the preceding paper[8] 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 $NaNH_2$ in liq. NH_3, 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 method[15] combined with geometrical optimization by the Davidon-Fletcher-Powell method[16]. 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 reaction[17]. 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).

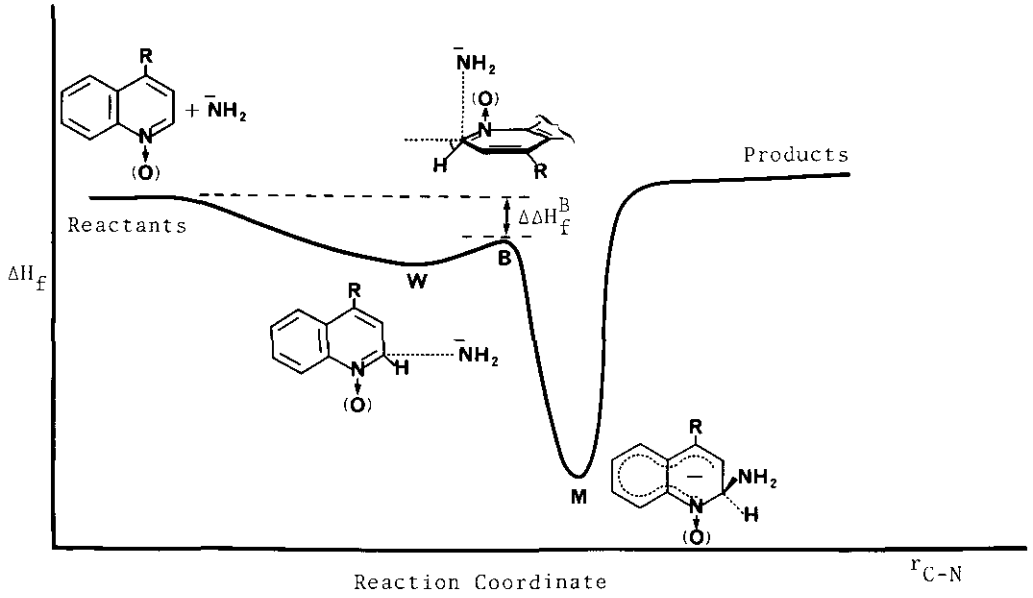


Figure 1. Reaction Profile of Quinoline Derivative with Amide Ion

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 equation[17].

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

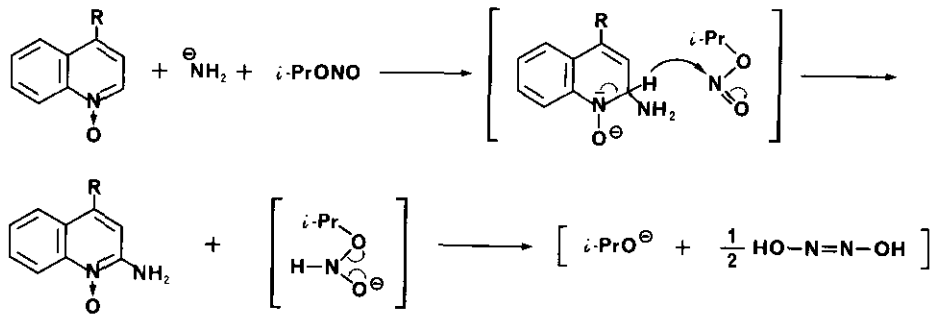
As can be seen in Figure 1, the reaction profile indicates that as amide anion approaches the substrate, the superion first stabilizes somewhat (point W), subsequently passes over the low energy barrier (point B) and then via Meisenheimer-type complex (point M) leads to the final amino compound. Accordingly, 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)
21	-4.395	-0.531
14	-7.235	-0.888
18	-5.455	-0.590
2	-7.756	-0.946
17	-2.306	-0.577
1	-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 functions[18]. Recently, the oxidative mechanism for the conversion of hemoglobin into methemoglobin by alkyl nitrite was kinetically investigated in detail[19]. 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 spectroscopy[6]. 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

leads to finally hyponitrous acid ($H_2N_2O_2$) via the electron transfer as shown in Scheme 5.

In the reaction of 2 with tert-butyl nitrite (t-BuONO) in place of i-PrONO as an oxidant and $NaNH_2$ in liq. NH_3, 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.

EXPERIMENTAL

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; ^{1}H-nmr spectra, Hitachi R-22 (90MHz), JEOL FX-100 (100MHz) and JEOL 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 ^{1}H-nmr spectra, 2D ^{1}H- ^{13}C chemical shift correlation spectra measured by GX-400 (400MHz) were utilized. High-performance thin layer chromatography (HPTLC) 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).

Preparation of 4-Ethylquinoline 1-Oxide 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 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 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 λ_{max}^{EtOH}nm(logϵ): 228(4.55). Ir ν_{max}^{KBr}cm^{-1}: 3220, 1270, 1210(N–O), 1160, 860, 750. ^{1}H-Nmr $\delta_{ppm}^{CDCl_3}$(90MHz): 1.36(3H,t,J=8.0Hz,CH_3), 3.04(2H,q,J=8.0Hz,CH_2), 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 $\delta_{ppm}^{CDCl_3}$(25.1MHz): 13.95(q,CH_3), 24.67(t,CH_2), 119.51(d,Ar), 120.42(d,Ar), 124.20(d,Ar), 128.41(d,Ar), 129.14(s,Ar), 129.87(d,Ar), 135.11(d,Ar), 140.22(s,Ar),

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 paper[3], 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(logϵ): 251(5.17). Ir ν_{max}^{KBr} cm^{-1}: 3400-3000, 1643(NH_2), 1270(NH_2), 1190(N→O), 750. ^{1}H-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(logϵ): 255(5.08). Ir $\nu_{max}^{KBr}$$cm^{-1}$: 2970, 1560, 1310, 1210(N→O), 880, 760, 740. ^{1}H-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 2[2]——The residue was chromatographed to give 4,4'-dimethyl-2,2'-biquinoline 1,1'-dioxide 8 (with $CHCl_3$-MeOH, 20:1), (E)-4-quinolinecarboxaldehyde 1-oxide oxime 6 (with $CHCl_3$-MeOH, 10:1) and 2-amino-4-methylquinoline 1-oxide 4 (with $CHCl_3$-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 $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.82; H, 5.90; N, 15.99. Uv λ_{max}^{EtOH}nm(logϵ): 250(5.15). Ir $\nu_{max}^{KBr}cm^{-1}$: 3300-3000, 1670(NH_2), 1270(NH_2), 1195(N→O), 747. ^{1}H-Nmr $\delta_{ppm}^{MeOH\text{-}d_4}$(90MHz): 2.58(3H,s,$CH_3$), 4.82(2H,s,$NH_2$), 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). ^{13}C-Nmr $\delta_{ppm}^{MeOH\text{-}d_4}$(25.1MHz): 18.52(q,$CH_3$), 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 $C_{11}H_{12}N_2O(M^+)$: 174.079. Found: 174.081. Compound 6[3] 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 $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 75.70; H, 5.18; N, 8.87. Uv λ_{max}^{EtOH}nm(logϵ): 255(5.14). Ir $\nu_{max}^{KBr}cm^{-1}$: 3400, 1560, 1340, 1205(N→O), 758. ^{1}H-Nmr $\delta_{ppm}^{pyridine\text{-}d_5}$(400MHz): 2.48(3H×2,s,$CH_3$×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'). ^{13}C-Nmr $\delta_{ppm}^{pyridine\text{-}d_5}$(100.5MHz): 17.74(q,$CH_3$), 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 $C_{20}H_{16}N_2O_2(M^+)$: 316.121. Found: 316.121.

Reaction of 4-Ethylquinoline 17——After the residue was enough extracted with $CHCl_3$, the $CHCl_3$ 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 $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.60; H, 5.59; N, 14.57. Uv λ_{max}^{EtOH}nm(logϵ): 231(4.91). Ir $\nu_{max}^{KBr}cm^{-1}$: 2850, 1590, 995, 770. ^{1}H-Nmr $\delta_{ppm}^{DMSO\text{-}d_6}$(90MHz): 2.33(3H,s,$CH_3$), 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}C-Nmr $\delta_{ppm}^{DMSO-d_6}$(25.1MHz): 15.23(q,CH_3), 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 $C_{11}H_{10}N_2O$(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 20[3], colorless prisms, 1.08 g (63% yield).

General Procedure for the Reaction of Amino Compound with Ac_2O——A mixture of amino compound (2.5 mmol) and Ac_2O (5 ml) 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 Ac_2O, the solvent was evaporated to dryness.

Reaction of 3——The residue was recrystallized from ether to give 2-acetylamino-4-ethylquinoline 1-oxide 9, colorless prisms, mp 149-150°C, 0.29 g (50% yield). Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.99; H, 6.15; N, 12.03. Uv λ_{max}^{EtOH}nm(logε): 262(5.16). Ir ν_{max}^{KBr}cm^{-1}: 3190, 1705(C=O), 1580(NH), 1500(NH), 1315, 1270(N→O), 1110, 760. ^{1}H-Nmr $\delta_{ppm}^{CDCl_3}$(90MHz): 1.40(3H,t,J=7.0Hz,C$\underline{H}_3$CH$_2$), 2.37(3H,s,CH_3), 3.09(2H,q,J=7.0Hz,CH_2), 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}C-Nmr $\delta_{ppm}^{CDCl_3}$(25.1MHz): 14.19(q,$\underline{C}H_3CH_2$), 25.22(t,CH_2), 25.22(q,CH_3), 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 $C_{13}H_{14}N_2O_2$(M^+): 230.105. Found: 230.105.

Reaction of 10 (vide infra)——The residue was recrystallized from ether-acetone to give 2-acetylamino-4-ethylquinoline 11, colorless prisms, mp 182-183 °C, 0.26 g (48% yield). Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.90; H, 6.66; N, 13.06. Uv λ_{max}^{EtOH}nm(logε): 246(5.14). Ir ν_{max}^{KBr}cm^{-1}: 3280, 1680(C=O), 1580(NH), 1500, 1430, 1360, 1250, 745. ^{1}H-Nmr $\delta_{ppm}^{CDCl_3}$(90MHz): 1.40(3H,t,J=7.0Hz,C$\underline{H}_3$CH$_2$), 2.22(3H,s,CH_3), 3.13(2H,q,J=7.0Hz,CH_2), 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}C-Nmr $\delta_{ppm}^{CDCl_3}$(25.1MHz): 14.13(q,$\underline{C}H_3CH_2$), 24.79(q,CH_3), 25.58(t,CH_2), 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 $C_{13}H_{14}N_2O$(M^+): 214.111. Found: 214.111.

Reaction of 4———The residue was chromatographed with $CHCl_3$ to give 2-acetylamino-4-methylquinoline 1-oxide 12, colorless prisms (from ether-acetone), mp 183-184°C, 0.28 g (52% yield). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.63; H, 5.74; N, 12.87. Uv λ_{max}^{EtOH}nm(logϵ): 262(5.21). Ir $\nu_{max}^{KBr}cm^{-1}$: 3190, 1700(C=O), 1570(NH), 1495, 1325, 1260(N—O), 770. ^{1}H-Nmr $\delta_{ppm}^{CDCl_3}$(90MHz): 2.37(3H,s,CH_3), 2.70(3H,s,$COCH_3$), 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). ^{13}C-Nmr $\delta_{ppm}^{CDCl_3}$(25.1MHz): 18.76(q,CH_3), 25.16(q,$CO\underline{C}H_3$), 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 $C_{12}H_{12}N_2O_2$(M^+): 216.090. Found: 216.089.

Reaction of Quinoline 1-Oxide 14———The residue was chromatographed with $CHCl_3$ to give 2,2'-biquinoline 16 and 2-aminoquinoline 1-oxide 15 in turn. Compound 16[20] was recrystallized from acetone to give colorless scales, 0.31 g (12% yield). Compound 15[5] was recrystallized from CH_3COOEt-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 $MgSO_4$ 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 $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.62; H, 7.02; N, 16.22. Uv λ_{max}^{EtOH}nm(logϵ): 238(5.09). Ir $\nu_{max}^{KBr}cm^{-1}$: 3480(NH_2), 3120, 1640(NH_2), 1610(NH_2), 1430, 1410, 755(NH_2). ^{1}H-Nmr $\delta_{ppm}^{CDCl_3}$(90MHz): 1.31(3H,t,J=7.0Hz,CH_3), 2.96(2H,q,J=7.0Hz,CH_2), 4.94(2H,br s,NH_2), 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). ^{13}C-Nmr $\delta_{ppm}^{CDCl_3}$(25.1MHz): 13.64(q,CH_3), 24.91(t,CH_2), 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(rel.int.): 172(M^+,100), 171(24), 157(14), 130(15). High-resolution ms Calcd for $C_{11}H_{12}N_2$(M^+): 172.100. Found: 172.099.

Deoxygenation of 4———The residue was recrystallized from benzene to give 2-amino-4-methylquinoline 13[21], 0.28 g (90% yield).

Deoxygenation of 9 with PCl_3———PCl_3 (0.55 g, 4 mmol) in $CHCl_3$ (5 ml) was added dropwise to a solution of 9 (0.46 g, 2 mmol) dissolved in $CHCl_3$ (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 $CHCl_3$. The residue from the $CHCl_3$ extract was recrystallized from ether-acetone to give 11, 0.23 g (54% yield).

Reaction of 1 (or 2) with $NaNH_2$ in the Presence of an Oxidant in Liq. NH_3———Reaction was carried out as described in general procedure for the reaction of 1 (or 2) with i-PrONO in liq. NH_3 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 F_{254} precoated (Merck); solvent system, $CHCl_3$:MeOH = 10:1. The yield of respective compound was as follows.

$KMnO_4$ (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).

$NaNO_2$ (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 $NaNH_2$ in the Presence of an Oxidant in Liq. NH_3———Carried out as described for reaction of 1 (or 2) with $NaNH_2$ in the presence of an oxidant in liq. NH_3 but using the solvent system (CH_3COOEt:C_6H_6 = 5:1) as concerns the determination of 16. The yield of the respective compound was as follows.

i-$PrONO_2$ (2.31 g, 22 mmol) as an oxidant: 15 0.70 g (44% yield) and 16 0.41 g (16% yield).

$KMnO_4$ (3.48 g, 22 mmol) as an oxidant: 15 0.18 g (11% yield) and 16 0.41 g (16% yield).

KNO_3 (2.22 g, 22 mmol) as an oxidant: 15 0.27 g (17% yield) and 16 0.31 g (12% yield).

$K_2S_2O_8$ (5.95 g, 22 mmol) as an oxidant: 15 0.27 g (17% yield) and 16 0.08 g (3% yield).

$K_3Fe(CN)_6$ (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. NH_3——In the general procedure for the reaction of N-heterocycle with i-PrONO in liq. NH_3, when Na was converted completely into $NaNH_2$,(in the reaction using t-BuOK, t-BuOK (3.37 g, 30 mmol) was added to the liq. NH_3 solution in this time and then after stirring for 30 min) quinoline or isoquinoline derivative (10 mmol) was added to the liq. NH_3 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 NH_4Cl. After standing overnight until liq. NH_3 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 $CHCl_3$ to give 1-aminoisoquinoline 23[12], 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 $CHCl_3$) and 1,1'-biisoquinoline 2,2'-dioxide 25 (with $CHCl_3$-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 $C_{18}H_{12}N_2O_2$: 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 $\nu_{max}^{KBr}cm^{-1}$: 3460, 3070, 1329, 1235,(N→O), 1133, 742. ^{1}H-Nmr $\delta_{ppm}^{DMSO-d_6}$(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). ^{13}C-Nmr $\delta_{ppm}^{DMSO-d_6}$(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(rel.int.): 288(M^+,29), 271(21), 255(41), 128(19), 44(100). High resolution ms Calcd for $C_{18}H_{12}N_2O_2(M^+)$: 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. NH_3 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. MeONa+$NaNH_2$:6 1.77 g (94% yield). EtONa+$NaNH_2$: 6 1.71 g (91% yield). i-PrONa+$NaNH_2$: 4 0.16 g (9% yield) and 6 1.64 g (87% yield). t-BuOK+$NaNH_2$: 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).

ACKNOWLEDGEMENT

The authors thank Mrs. M. Yukawa of Fukuoka University for her helpful advices on the theoretical calculations and the Computation Center of Fukuoka University for the use of FACOM M780/10S computer. Thanks are also due to the staffs of the Analytical Center of the Faculty of Pharmaceutical Sciences, Fukuoka University, for elemental analyses and spectral measurements.

REFERENCES AND NOTES

1. a) Y. Tagawa, N. Honjo, Y. Goto, T. Chiba, and T. Kato, Chem. Pharm. Bull., 1983, 31, 2269; b) Y. Tagawa, N. Honjo, and Y. Goto, Chem. Pharm. Bull., 1986, 34, 564; c) Y. Tagawa, N. Honjo, and Y. Goto, Chem. Pharm. Bull., 1986, 34, 4984.
2. E. Ochiai and H. Tanida, Pharm. Bull., 1957, 5, 621.
3. T. Kato, Y. Goto, and M. Kondo, Yakugaku Zasshi, 1964, 84, 290.
4. A. T. M. Marcelis, H. Tondijs, and H. C. van der Plas, J. Heterocyclic.

Chem., 1988, 25, 831.

5. H. Tanida, Yakugaku Zasshi, 1959, 79, 1063.
6. H. J. W. van den Haak, H. C. van der Plas, and B. van Veldhuizen, J. Org. Chem., 1981, 46, 2134.
7. Blaise and Maire, Bull. Soc. Chim. France, 1908, [4]3, 658.
8. Y. Tagawa, H. Arakawa, and Y. Goto, Heterocycles, in press.
9. F. W. Bergstrom, J. Org. Chem., 1937, 2, 411.
10. H. Tondys, H. C. van der Plas, and M. Woźniak, J. Heterocyclic. Chem., 1985, 22, 353.
11. E. W. Warnhoff and P. Reynolds-Warnhoff, J. Org. Chem., 1963, 28, 1431.
12. E. Ochiai and Y. Kawazoe, Chem. Pharm. Bull., 1957, 5, 606.
13. A. R. Katritzky and J. M. Lagowski, " Chemistry of the Heterocyclic N-Oxides, " Academic Press, Inc., London, 1971, p. 345.
14. N. Fisher and S. M. McELvain, J. Am. Chem. Soc., 1934, 56, 1766.
15. M. J. S. Dewar and W. Thiel, J. Am. Chem. Soc., 1977, 99, 4899.
16. a) R. Fletcher and M. J. D. Powell, Comput. J., 1963, 6, 163; b) W. C. Davidon, ibid., 1968, 10, 406.
17. M. Yukawa, T. Niiya, Y. Goto, T. Sakamoto, H. Yoshizawa, A. Watanabe, and H. Yamanaka, Chem. Pharm. Bull., 1989, 37, in press.
18. K. Jones, " Comprehensive Inorganic Chemistry, " Pergamon Press Ltd., Oxford, 1973, p. 366.
19. M. P. Doyle, R. A. Pickering, T. M. DeWeert, J. W. Hoekstra, and D. Pater, J. Biol. Chem., 1981, 256, 12393.
20. This compound is available from Aldrich Chemical Co., Inc., Milwaukee.
21. I. A. Kaye, J. Am. Chem. Soc., 1949, 71, 2322.

Received, 10th May, 1989