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Radical Methylation and Radical Hydroxymethylation of N-Substituted Quinoline Derivatives[1]

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N-substituted quinoline derivatives such as $\rangle N^+$–Me, $\rangle N^+$–O^-, $\rangle N^+$–NH^- were derived to methyl substituted compound at C-2 and/or C-4 by radical methylation and by radical hydroxymethylation.

In the case of radical methylation and radical hydroxymethylation of quinoline 1-oxides, carbon at C-2 was preferentially nucleophilic than at C-4.

Useful way to synthesize the alkyl substituted derivatives at C-2 selectively was to proceed the alkylation after forming N-oxide.

Keywords——radical methylation; radical hydroxymethylation; 1-methylquinolinium salts; 1-aminoquinolinium salts; quinoline 1-oxide

Previously, Itokawa *et al.* have reported nucleophilic substitution of hydroxy alkyl radicals which were formed from alcohols used as solvent through the action of OH radical produced by hydroperoxide and the metals having reducing character (Fe^{2+}, Cu^+, Cr^{2+}, *etc.*).[3]

The authors wish to apply this reactions to other various N-substituted derivatives.

In this paper, it will be described about the radical hydroxylations of various N-substituted derivatives, *e.g.* $\rangle N^+$–Me, $\rangle N^+$–O^-, $\rangle N^+$–NH^-.

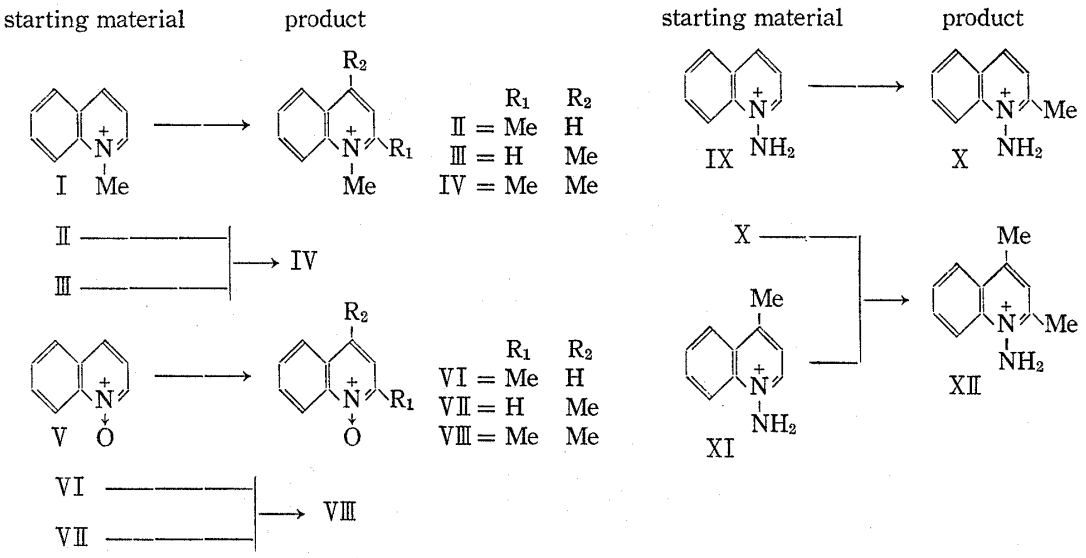

Chart 1

1) Presented at the 94th Annual Meeting of Pharmaceutical Society of Japan, Sendai, April, 1974.
2) Location: *a) 1432-1, Horinouchi, Hachioji, Tokyo, 192-03, Japan; b) 3-1, Tanabedori, Mizuho-ku, Nagoya, 467, Japan; c) 5-1-1, Tsukiji, Chuo-ku, Tokyo, 104, Japan.*
3) H. Itokawa, Sh. Kameyama, T. Inaba, T. Tazaki, S. Mihashi, and Y. Kawazoe, *Chem. Pharm. Bull.* (Tokyo), 23, 487 (1975).

1) Radical Methylation of 1-Methylquinolinium Salts, Quinoline-1-oxides and 1-Aminoquinolinium Salts

t-Butylperoxide was used as methyl radical source and $FeSO_4 \cdot 7H_2O$ was used as metal salts.

Investigation was performed in 7% sulphulic acid solution.

The result of methylation of 1-methylquinolinium salts,[4] quinoline-1-oxides[5] and 1-aminoquinolinium[6] salts are as follows: (Chart 1)

Table I. Recoveries of Reaction Products

N-Substituent	Substituent	Product Yield (%) Position 2	Position 3	Position 2,4	Recovery	Other product
Methyl	I —	II 14.7	III 8.9	IV 17.2	4.3	—
	II 2Me		IV 29.5		59.7	—
	III 4Me	IV 38.6			51.4	—
Oxy	V —	VI 37.7	VII 3.0	VIII 3.6	38.6	Quinoline trace Quinaldine 13.2
	VI 2Me		VIII 7.7		43.0	Not-detected
	VII 4Me	VIII 57.1			21.3	Not-detected
Amino	IX —	X 18.4	—	—	16.3	Quinoline 45.5 Quinaldine 6.2 Lepidine 3.6
	X 2Me		XII 34.8		38.0	Quinaldine 22.7 2,4-di Me quinoline 9.9
	XI 4Me	XII 40.3			34.1	Lepidine 8.2 2,4-di Me-quinoline 5.6

Nuclear magnetic resonance (NMR), gas liquid chromatography (GLC) and weight methods were used for quantitative determination of these compounds. Substitution on benzene ring at C-3 position and also at side chain such as methyl groups was not observed.

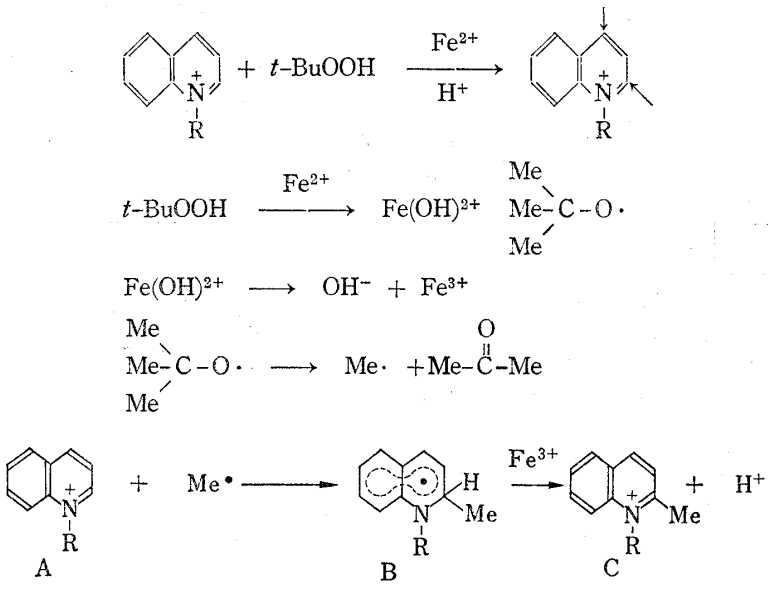

Chart 2

4) E. Ochiai, "Zikken Kagaku Koza," Vol. 21 (III), Maruzen, Tokyo, 1958, p. 290.
5) E. Ochiai, "Zikken Kagaku Koza," Vol. 21 (III), Maruzen, Tokyo, 1958, p. 335.
6) T. Okamoto, M. Hirobe, and T. Yamazaki, *Chem. Pharm. Bull.* (Tokyo), 14, 512 (1966).

From these results, methylation was assumed to be nucleophilic to the ring, and it was suggested that C-2 position of quinoline 1-oxide was more active than C-4 position to nucleophilic reagents.

Reaction mechanism shown in chart 1 indicated that *t*-butoxy radical (*t*-BuO·) was formed from *t*-butylperoxide and ferrous ion (Fe^{2+}) and further produced methyl radical and acetone. $Fe(OH)^{2+}$ formed in this case produced hydroxyl group (OH^-) and ferric ion (Fe^{3+}): (Chart 2).

Consequently, intermediate (B) was formed from starting compound (A) by nucleophilic attack of methyl radical, and further (B) was assumed to give product (C) through one electron oxidation by ferric ion (Fe^{3+}).

Table II. Recoveries of Reaction Products

Substrate	Position 2	Position 4	Position 2,4	Recovery
Quinoline	32.4%	29.3%	14.6%	23.7%

1) Base: *t*-BuOOH=1:3. 2) Reaction time (30 min). 3) Temp. (15—20°).

It was not observed the distinguishable difference in yield between methyl substituents at C-2 and C-4 positions of 1-methylquinolinium salts and 1-aminoquinolinium salts as in the case of their proton derivatives (>NH).[7] (Table II.)

To introduce alkyl substituents at C-2 position selectively, it seems to be better method that at first $>N^+-H$ was transformed to N-oxide and then alkylation, followed deoxygenation.

The reaction of 1-aminoquinolinium salts with H_2O_2 in acetic acid was carried out to confirm if the deamino compound was formed by homolytic fission with methyl radical or by oxidation. Consequently, it was decided that deamination occured oxidatively, from the result of the good yields of deaminated products as shown in Chart 3, and Table III. In the case of 1-amino-4-methylquinolinium chloride, a dimer (XIII) was obtained, the structure of which was assumed by its analytical data.

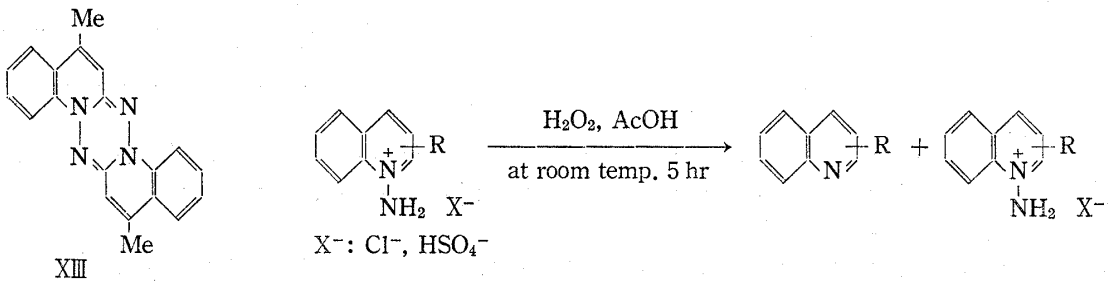

Chart 3

Table III. Recoveries of Reaction Product

Substituent	Base, H_2O_2 mole ratio	Deaminated product	Recovery	Other product
—	1 : 2	98.6%	0.6%	—
2-Methyl	1 : 2	48.2%	27.4%	—
4-Methyl	1 : 2	—	—	XIII 25.4%

7) F. Minisci, R. Galli, V. Malatesta, and T. Caronna, *Tetrahedron*, **26**, 4083 (1970).

2) Radical Hydroxymethylation of 1-Methylquinolinium Salts and Quinoline 1-Oxides

Hydroxymethyl radical was produced by the redox systems using 30% H_2O_2 and $FeSO_4 \cdot 7H_2O$ in 7% H_2SO_4 in methanol at 0°. The results of hydroxymethylation were shown as follows. (Chart 4) The mechanism was assumed to be the same as that of radical methylation.

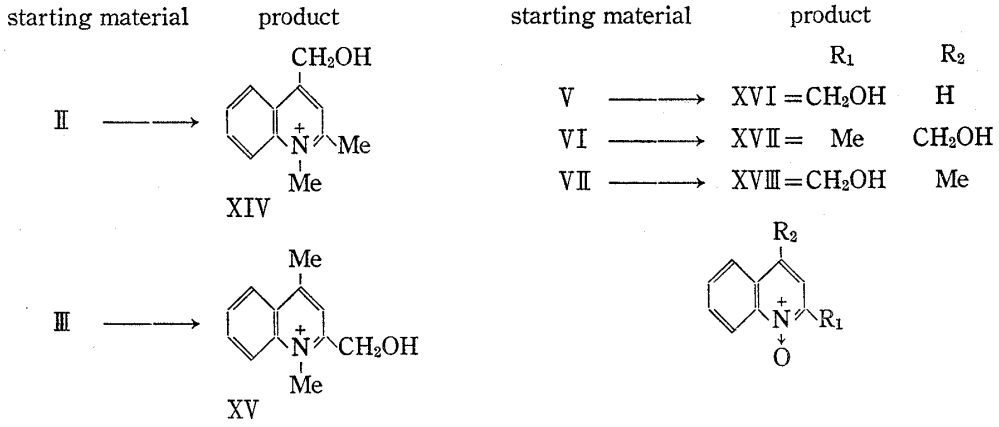

Chart 4

TABLE IV. Recoveries of Reaction Products

N-Substituent	Substituent	Product yield (%) Position 2	Position 3	Position 2,4	Recovery (%)	Other product	Total recovery
Methyl	II 2-Me		XIV 29.7		40.7	—	70.4
	III 4-Me	XV 32.2			61.5	—	93.7
Oxy	V —	XVI 26.5	—	—	30.6	Quinoline 1.5	58.6
	VI 2-Me		XVII 5.5		44.4	Quinaldine 8.6 4-hydroxymethyl-quinaldine	61.2
	VII 4-Me	XVIII 39.0			35.4	Lepidine 3.6	78.0

There was no relation with regard to variety of substituents for ring hydroxymethylation, as same as methylation. Moreover, in the case of quinoline-1-oxide there was observed more reactive at C-2 than C-4 position.

This suggested that the reactivity at C-4 position diminished by back donation of lone pair of oxygeon at N-oxide.

There was no remarkable differences in the yields of products of 1,2-dimethyl- and 1,4-dimethylquinolinium salts by radical methylation and radical hydroxymethylation (Chart 4).

TABLE V. Recoveries of Reaction Products

Substrate	Product yield (%) Position 2	Position 3	Position 2,4
Quinoline	30	20	1~2
Quinaldine		53	
Lepidine	55		

Comparing with >NH compounds illustrated in Table V, the yields of reaction products of 1-methylquinolinium salts and quinoline 1-oxides were relatively lower.

In conclusion, nucleophilic substitution at C-2 and C-4 position of N-substituted quinoline *e.g.* $>N^+-Me$, $>N^+-O^-$, $>N^+-NH^-$ occured by radical methylation and radical hydroxymethylation.

It was observed the regiospecificity of the substitution from higher activity at C-2 than C-4 in the case of radical methylation and radical hydroxymethylation of quinoline 1-oxides. In the case of radical methylation of 1-aminoquinolinium salts, there was no marked regiospecificity between at C-2 and C-4. Useful way to synthesize the alkyl substituted derivatives at C-2 selectively was to proceed the alkylation after forming N-oxide.

Experimental

1-Methylquinolinium Iodide (I)——CH_3J 15 g was added to a solution of quinoline 10 g in Me_2CO 20 ml, and stirred for about 1 hr. Then the resulting filtrates were collected by filtration, washed with Me_2CO and recrystallized from Me_2CO. Yellow crystalls (I) 16.6 g, mp 142—144° was obtained.

1,2-Dimethylquinolinium Iodide (II) and 1,4-Dimethylquinolinium Iodide (III)———A solution of quinaldine 5 g, Me_2CO 50 ml and CH_3J 5 ml was refluxed for 1—2 hr and then the resulting precipitates were collected by filtration, washed with Me_2CO and recrystallized from Me_2CO gave yellow crystalls (II).

Lepidine was also treated by same method as quinaldine, and gave yellow crystalls (III).

Quinoline 1-Oxide (V), 2-Methylquinoline 1-Oxide (IV) and 4-Methylquinoline 1-Oxide (VII)——A solution of quinoline 10 g, AcOH 50 ml and 30% H_2O_2 10 ml was heated for 3 hr, and further PtO_2 20 mg was added after cooled and allowed to stand at room temperature overnight. After concentration, the soln. was neutralized with Na_2CO_3, and treated with $CHCl_3$, $CHCl_3$ fr. was recrystallized with acetone–Et_2O to yield V. VI and VII were also obtained by the same method mentioned above. V; mp 58—60°; Mass Spectrum (MS) *m/e*; 145 (M^+); *Anal.* Calcd. for C_9H_7NO: C, 73.97; H, 5.48; N, 9.59. Found: C, 72.94; H, 4.91; N, 9.03. NMR ($CDCl_3$) ppm: 7.17—7.98 (m, 5H, aromatic proton); 8.56 (1H, d, ring proton at C-2); 8.77 (1H, d, ring proton at C-8). VI; mp 75—77°; MS *m/e*: 159 (M^+); NMR ($CDCl_3$) ppm: 2.74 (3H, s, ring-Me); 7.23—8.00 (5H, m, aromatic proton): 8.83 (1H, d, ring proton at C-8). VII: mp 114—115°; MS *m/e*: 159 (M^+). *Anal.* Calcd. for $C_{10}H_9NO$: C, 75.00; H, 6.25; N, 8.75. Found: C, 74.03; H, 5.81; N, 8.25. NMR ($CDCl_3$) ppm: 2.69 (3H, s, ring-Me); 7.03—8.16 (4H, m, aromatic proton); 8.47 (1H, d, ring proton at C-2); 8.83 (1H, d, ring proton at C-8).

1-Aminoquinolinium Sulfate (IX)——To a solution of quinoline 18.1 g (0.14 mmol) in MeOH 30 ml, NH_2OSO_3H 6.33 (0.056 mmol) was added by stirring and allowed to stand at room temperature for 2 days. The filtrate was evaporated to dryness, recrystallized from EtOH to give colorless needles, the yield was 25.4% (J^- salt: mp 178—179°).

1-Amino-2-methyl Quinolinium Sulfate (X)——NH_2OSO_3H 6.33 g (0.056 mmol) was added to a solution of quinaldine 20 g (0.14 mmol) in MeOH 30 ml, and treated same as mentioned above. The residue was recrystallized from EtOH to give colorless needles (3.6 g), the yield was 25.2%. mp 188—191°. UV (HCl–NaOH); mμ (ε): pH=5.8 λ_{max} 315 (8860.94), 230.5 (44493.83), λ_{min} 266 (1593.89); pH=1.8: λ_{max} 315 (8779.90), 231 (44250.69); λ_{min} 266 (1512.84); pH=12.3: λ_{max} 315 (8563.78), 232 (44196.66); λ_{min} 271 (1701.95).

1-Amino-4-methylquinolinium Sulfate (XI)——NH_2OSO_3H 6.33 g (0.056 mmol) was added to a solution of lepidine 20 g (0.14 mmol) in MeOH 30 ml and treated same as X. The residue was recrystallized from MeOH to give pale yellow needles, the yield was 20.1%. (Cl^- salt: mp 170—171.5°).

Methylation of 1-Methylquinolinium Iodide (I)——I 500 mg (1.85 mmol) was dissolved in 30% NaOH solution 20 ml, after extracted with $CHCl_3$, added conc. HCl, concentrated, added to 7% H_2SO_4 solution 30 ml, further $FeSO_4 \cdot 7H_2O$ 1.03 g was added. Further *t*-BuOOH 332.1 mg was added and stirred for 20 min after washed with $CHCl_3$, aq. layer was alkalified with NaOH solv. then was extracted with $CHCl_3$. II: NMR (D_2O) ppm: 2.60 (3H, s, C–Me); 4.00 (3H, s, N–Me); 7.50—8.70 (6H, m, aromatic proton). III: NMR (D_2O) ppm: 2.38 (3H, s, C–Me); 4.10 (3H, s, N–Me); 7.50—8.90 (6H, m, aromatic proton). IV: NMR (D_2O) ppm: 2.25 (3H, s, C–Me at C-4); 2.50 (3H, s, C–Me at C-2); 3.88 (3H, s, N–Me); 7.50—8.50 (m, 5H, aromatic proton).

Methylation of 1,2-Dimethylquinolinium Iodide (II) and of 1,4-Dimethylquinolinium Iodide (III)——IV was obtained by same procedure as methylation of I.

Methylation of Quinoline 1-Oxide (V)——$FeSO_4 \cdot 7H_2O$ 1.92 g (2 mol for starting material) was added to a solution of V 500 mg (3.45 mmol) in 7% H_2SO_4 aq. solution with stirring. To the solution was added *t*-BuOOH 620.7 mg (2 mol for starting material) for 20 min at room temperature under stirring for 20 min. The reaction mixture was extracted with $CHCl_3$, the aqueous layer acidified to pH=4—5 was extracted with $CHCl_3$ and further the aqueous layer was extracted with $CHCl_3$ after alkalified with NaOH sol. $CHCl_3$ layer was alkalified with NaOH sol., extracted with $CHCl_3$ and the fr. of $CHCl_3$ was submitted to column chromatography on alumina eluted with $CHCl_3$. VI, VII, VIII, and quinaldine were obtained. Production ratio

was measured by UV. VIII: NMR ($CDCl_3$) ppm: 2.60 (3H, s, C–Me at C-4); 2.85 (3H, s, C–Me at C-2); 7.10—9.10 (m, 5H, aromatic proton). Deoxy-derivative was identified with authentic sample.

Methylation of 2-Methylquinoline 1-Oxide (VI) and of 4-Methylquinoline 1-Oxide (VII)——VI and VII were methylated by the same procedure mentioned above as that of V.

Methylation of 1-Aminoquinolinium Sulfate (IX)——To a solution of IX 500 mg (2 mmol) in 7% H_2SO_4 aq. solution 30 ml was added $FeSO_4 \cdot 7H_2O$ 1.15 g (2 mol for starting material) under stirring by adding *t*-BuOOH 371.9 mg (2 mol for starting material) for 20 min. The reaction mixture was extracted with $CHCl_3$, the aqueous layer was neutralized to pH=6—7, and was extracted with ether the aqueous layer was extracted with $CHCl_3$ after alkalified with NaOH solution. Deaminoderivatives was identified with authentic sample by thin-layer chromatography (TLC) and NMR. Yield of amino derivative was determined by GLC: condition; column (1.5 m, 1.5% SE-30), column tem. 105°, inject temp. 200°, carrier gas N_2, 25 ml/min, H_2, 0.65; air 0.9. X: NMR (D_2O) ppm: 2.55 (3H, s, C–Me at C-2); 7.34—7.90 (5H, m, aromatic proton); 8.45 (1H, d, ring proton at C-4).

Methylation of 1-Amino-2-methylquinolinium Sulfate (X)——X was methylated by the same procedure as IX. Deaminoderivative was identified with authentic sample by TLC, NMR. XII: NMR (D_2O) ppm: 2.07 (3H, s, C–Me at C-4); 2.37 (3H, s, C–Me at C-2); 7.13—7.95 (5H, m, aromatic proton).

Methylation of 1-Amino-4-methylquinolinium Chloride (XI)——XI was methylated by same procedure as IX and obtained XI, XII, lepidine and 2,4-dimethylquinoline.

Oxidative Deamination of 1-Aminoquinolinium Sulfate (IX)——To a sol. of IX 500 mg (2.1 mmol) in AcOH 11 ml was added 35% H_2O_2 453.3 mg (2 mol for starting material). The mixed solution was stirred at room temp. for 5 hr. The sol. added conc. HCl was concentrated and extracted with $CHCl_3$ after alkalified with NaOH solution. Quinoline 337 mg, starting material 24 mg. They were identified with authentic samples by TLC and NMR.

Oxidative Deamination of 1-Amino-2-methylquinolinium Sulfate (X)——To a sol. of X 500 mg (1.95 mmol) in AcOH 11 ml and H_2O 0.5 ml was added 35% H_2O_2 442 mg (2 mol for starting material). The mixed solution was stirred at room temp. for 5 hr. The sol. added conc. HCl was concentrated and extracted with $CHCl_3$ after alkalified with NaOH solution. Yield: quinaldine (169 mg), starting material (104.2 mg). They were identified with authentic samples respectively.

Oxidative Deamination of 1-Amino-4-methylquinolinium Chloride (XI)——XI was treated by the same method as IX to give XIII 41.0 mg, mp 181—186° (dec.). MS *m/e*: 312 (M^+), UV (mμ): EtOH; λ_{max}, 235, 290 (s), 340, 355 (s), λ_{min} 310, pH=2: λ_{max}, 231 (s), 244 (s), 290, 332, 375 (s), λ_{min}, 273, pH=12: λ_{max}, 254, 365, λ_{min}, 240. IR_{max}^{KBr} cm^{-1}: 750, 1240 (C–N), 1380 (Me), 1500, 1590 (C=C), 1610 (C=N), 303 (C–H).

Hydroxymethylation of 1,2-Dimethylquinolinium Iodide (II)——II 500 mg (1.75 mmol) was alkalified with NaOH sol. and extracted with $CHCl_3$. To the sol. was added conc. HCl and the solution was concentrated, to the concentrated solution was added under stirring conc. H_2SO_4 1 ml, MeOH 30 ml and $FeSO_4 \cdot 7H_2O$ 973 mg (2 mol for starting material). Further, to the above sol. was added 30% H_2O_2 396.7 mg (2 mol for starting material) under stirring at 0° for 20 min. After standing for 20 min under stirring, to the reaction mixture was added H_2O 20 ml, and the mixed solution was extracted with $CHCl_3$, aq. layer was alkalified with NaOH aq. sol. Then the sol. was extracted with $CHCl_3$. XIV: NMR (DMSO+TMS) ppm: 3.06 (3H, s, C–Me); 4.42 (3H, s, N–Me); 5.30 (2H, s, $-CH_2OH$); 7.26—8.26 (5H, m, aromatic proton).

Hydroxymethylation of 1,4-Dimethylquinolinium Iodide (III)——III was treated by same method as hydroxymethylation of II. XV: NMR (DMSO+TMS) ppm: 3.08 (3H, s, C–Me); 4.95 (3H, s, N–Me); 5.83 (2H, s, $-CH_2-OH$); 7.26—8.26 (5H, m, aromatic proton).

Hydroxymethylation of Quinoline 1-Oxide (V)——To the sol. of V 500 mg (3.44 mmol) in conc. H_2SO_4 1 ml and MeOH 30 ml sol. was added $FeSO_4 \cdot 7H_2O$ 1.9 g (2 mol for starting material). To the sol. was added 30% H_2O_2 779.7 mg (2 mol for starting material), and the mixed solution was treated by method III. Yield XV: 160.1 mg, starting material: 152.9 mg, quinoline: 6.6 mg. XV: mp 109—112°, colorless plate, MS *m/e*: 175 (M^+). *Anal.* Calcd. $C_{10}H_9NO_2$: C, 68.18; H, 5.68; N, 7.95. Found: C, 67.60; H, 5.00; N, 7.63. NMR ($CDCl_3$) ppm: 5.03 (2H, s, $-CH_2-OH$); 7.25—7.98 (5H, m, aromatic proton); 8.73 (1H, d, ring proton at C-8).

Hydroxymethylation of 2-Methylquinoline 1-Oxide (VI)——VI was treated by same method as hydroxymethylation of V. Yield: XVII: 32.7 mg, starting material: 221.9 mg, quinaldine: 38.8 mg, 2-methyl-4-hydroxymethyl-quinoline: 14.5 mg. XVII: mp 203—206°, colorless plate, MS *m/e*: 189 (M^+). *Anal.* Calcd. $C_{11}H_{11}NO_2$: C, 69.47; H, 6.31; N, 7.37. Found: C, 68.27; H, 5.64; N, 6.41. NMR (CD_3OD+TMS) ppm: 2.77 (3H, s, ring-Me); 5.13 (2H, s, $-CH_2OH$); 7.56—8.27 (4H, m, aromatic proton); 8.80 (1H, d, ring proton at C-8). Deoxyderivative was identified with authentic sample by TLC and NMR).

Hydroxymethylation of 4-Methylquinoline 1-Oxide (VII)——VII was treated by same method as hydroxymethylation of VI. XVIII: 231.9 mg, starting material: 177.0 mg, 4-methylquinoline: 16.0 mg. XVIII: mp 194—196°, colorless plate, MS *m/e*: 189 (M^+). *Anal.* Calcd. $C_{11}H_{11}NO_2$: C, 69.47; H, 6.31; N, 7.37. Found: C, 69.07; H, 5.65; N, 6.79. NMR (CD_3OD+TMS) ppm: 2.77 (3H, s, ring-Me); 5.10 (2H, s, $-CH_2OH$); 7.60—8.23 (4H, m, aromatic proton); 8.70 (1H, d, ring proton at C-8). Deoxyderivative was identified as lepidine.

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