[Chem. Pharm. Bull. 26(8)2435—2441(1978)]

UDC 547.821.3.04 : 547.339.2.04

Reaction of N-Methoxyquinolinium Methosulfate with Malononitrile in Dimethylsulfoxide[1)]

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(Received February 9, 1978)

The reaction of N-methoxy quinolinium methosulfate with malononitrile in dimethylsulfoxide afforded 2- and 4-dicyanomethylene-quinoline (II and III), N-methoxy-2- and 4-dicyanomethylene-quinoline (IV and V) in addition to quinoline and quinoline-1-oxide. The reaction at the higher temperature (100—110°) gave anomalous products (VI and VII). The assumed reaction mechanism was offered.

Keywords——N-alkoxy-quinolinium salt; malononitrile; dimethylsulfoxide; carbanion; heteroaromatic substitution reaction; temperature effect

In the previous papers of this series,[3)] it has been shown that, N-alkoxy-pyridinium and quinolinium salts react with nucleophile to afford 2- and/or 4-substituted pyridine and quinoline derivatives in a variety of the reaction conditions.

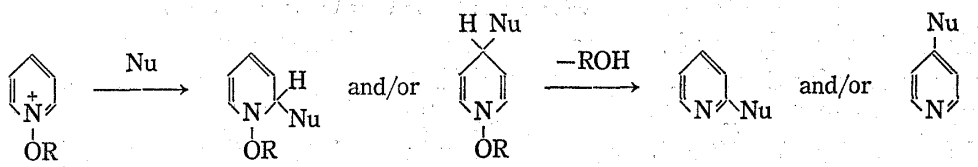

Chart 1. Reaction Pathway of N-Alkoxypyridinium Salt with Nucleophiles (Nu)

The authors have further studied the reactions of N-alkoxy-pyridinium and quinolinium derivatives in order to introduce carbon side chain into pyridine and quinoline nucleus, and here, we wish to describe that N-methoxy-quinolinium methosulfate (I) reacts with malononitrile in dimethylsulfoxide (DMSO) to give 2- and 4-dicyanomethylquinoline, N-methoxy-2- and -4-dicyanomethylene-quinoline, coupled with the interesting temperature effects and the side reactions.

We took as a substrate the fairly hygroscopic but thermally stable N-methoxyquinolinium methosulfate, which can be prepared from the reaction of quinoline-1-oxide with dimethylsulfate in good yield. The reactions of I with malnonitrile in DMSO were carried out at 60—70 °C (i) and 100—110 °C (ii).

i) A mixture of I and malononitrile in DMSO was heated at 60—70 °C for 2 hr. After removal of DMSO under a reduced pressure, the reaction mixture was poured into water and extracted with chloroform, Alumina column chromatographic separation of the residue obtained from chloroform extracts, resulted in the formation of yellow plumlet (II), mp 295—297° (dec.) and yellow needles (III) mp 324° (dec.) besides quinoline-1-oxide. Purification of the chloroform soluble portion of the aq. layer, after neutralized with sodium bicarbonate,

1) This forms Part VIII of "Reaction of N-Alkoxypyridinium Derivatives."

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3) T. Okamoto and H. Tani, *Chem. Pharm. Bull.* (Tokyo), **7**, 130, 925, 930 (1959); W.E. Feely, and Beavers, *J. Am. Chem. Soc.*, **81**, 4008 (1959); O. Cervinka, *Chem. Ind.* (London), **1960**, 1482; T. Okamoto and H. Takayama, *Chem. Pharm. Bull.* (Tokyo), **11**, 514 (1963); H. Takayama and T. Okamoto, *ibid.*, **26**, 2422 (1978).

gave two products; yellow needles, mp 176—177° (dec.) (IV), deep yellow needles, mp 210° (dec.) (V) in addition to quinoline.

ii) On the other hand, when the reaction was carried out at 100—110° for 3 hr and the reaction mixture was treated with the same procedure as the reaction (i), II, III, and quinoline-1-oxide were again obtained from the chloroform layer, but new products; colorless needles, mp 145—147° (dec.) (VI), colorless needles, mp 128—130° (VII) in addition to quinoline were obtained from the aqueous layer instead of IV and V resulted from the reaction (i).

The results of both reactions (i) and (ii) are summarized in Table I.

Table I. Yields in the Reaction of I with Malononitrile in DMSO

	II	III	IV	V	VI	VII	Quinoline	Quinoline 1-oxide	Total yield	Product ratio in reaction (i)
mp (dec.) (°C)	295—297	324	176—177	210	145—147	128—130	—	—		$\frac{(II)+(IV)}{(III)+(V)}=3.5$
Yield (%) in reaction (i)	3.9	0.4	5.8	2.4	—	—	14.0	15.9	42.4	
Yield (%) in reaction (ii)	5.2	0.7	—	—	4.8	1.0	32.6	25.5	69.8	$\frac{(IV)+(V)}{(II)+(III)}=1.9$

Concerning the Structures of Compound (II), (III), (IV), (V), (VI), and (VII)

The elementary analyses of both compound (II) and (III) were in good agreement with the calculated value for $C_{12}H_7N_3$. The infrared (IR) spectrum of II showed ν_{NH} at 3200 cm^{-1}, ν_{CN} at 2190, 2215 cm^{-1} (KBr). The ultraviolet (UV) spectrum of II, whose absorption maxima in ethanol (286, 398 nm) shifted hypsochromically in a dilute NaOH solution (276, 293, 303, 379 nm in 2N NaOH), but remained unchanged in a dilute acidic solution, suggested the basicity of quinoline nitrogen was remarkably weaken.

Whereas the cyano group of II strongly resisted to alkaline hydrolysis (II was recovered unchanged after refluxing in 20% NaOH aqueous ethanol solution for 10 hr), II was successfull hydrolyzed by prolonged refluxing in 17% HCl solution to give a colorless oil, which was identified with quinaldine. The formation of quinaldine thus indicates that the primary product in this hydrolysis is quinaldyl-α,α'-dicarboxylic acid. Actually, the structure of II was determined as 2-dicyanomethylquinoline by mixed melting point determination with the authentic sample prepared from the reaction of quinoline 1-oxide with malononitrile in acetic anhydride.[4] Similarly, IR spectrum of III showed ν_{NH} at 3200 cm^{-1}, ν_{CN} at 2180, 2205 cm^{-1} (KBr), which were quite similar to those of II. However, the UV spectrum was remarkably different from that of II suggesting that III was an isomer of II. Hydrolysis of III on refluxing

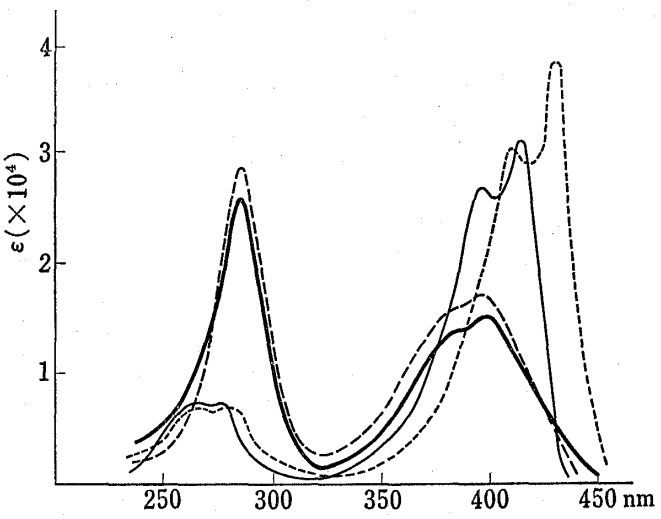

Fig. 1. UV Spectra of II, III, IV, V, in EtOH
——: II, ——— : III, ——— : IV, ---------: V.

4) M. Hamana and M. Yamazaki, *Chem. Pharm. Bull.* (Tokyo), **11**, 415 (1963).

Chart 2

in 17% HCl afforded oily material which was identified with lepidine. By analogy, the structure of III can be assigned as 4-dicyanomethyl-quinoline. Actually, methylation with diazomethane of III afforded N-methyl-4-dicyanomethylene-quinoline[5] whose structure was determined unequivocally by the separate synthesis.

Further, the elementary analyses of both compound(IV) and (V) were in agreement with the calculated value for $C_{13}H_9N_3O$, which corresponded to the methanol addition products of II and III respectively. The IR spectra of IV and V exhibited ν_{CN} at 2200 cm^{-1} and 2180, 2200 cm^{-1} (KBr) respectively. The pattern of UV spectrum of IV had a very close resemblance to that of II and also that of V to III (Fig. 1). The cyano group of IV and V again stubbornly resisted to hydrolysis in both alkaline and acidic media, but fortunately, the reaction of IV and V with a strong base such as 10% NaOH ethanolic solution proceeded smoothly to give II and III respectively. Therefore, the structures of IV and V were proved to be N-methoxy-2-dicyanomethylene-quinoline and N-methoxy-4-dicyanomethylene-quinoline, respectively.

Finally, the compound(VI), $C_{14}H_{13}N_2OS$, containing a sulfur atom, obtained only from the reaction at the higher temperature, was somewhat unstable in standing in air. Upon both an alkaline and acidic hydrolysis, catalytic hydrogenation with paladium charcoal in neutral medium, or, desulfurization with Raney Nickel in boiling ethanol, VI gave 2-aminoquinoline (VII). These evidences suggested that VI is 2-animoquinoline derivative. Further, on the pyrolysis of VI, VII and dimethylsulfide were detected by GLPC. Reaction of VI in a mixture of 30% H_2O_2 and acetic acid resulted in the formation of dimethylsulfone, mp 112°, and allowing to stand VI in a mixture of 30% H_2O_2 and ethanol at room temperature afforded 2-carboxyamino-quinoline, which was rather unstable and gave VII by decarboxylation under a mild condition. From these chemical evidences, coupled with the spectral data [NMR($CDCl_3$) τ: 7.1 (6H, s, CH_3–$\overset{+}{S}$–CH_3), IR(KBr) cm^{-1}: ν_{NH} 3500, ν_{CN} 2175], it can be concluded that VI could have the structure as depicted in Chart 2.

Concerning the Reaction Mechanism

The formation of the compounds II, III, IV, and V, coupled with the fact that the acidity of the reaction mixture increased gradually as the reaction proceeded, suggested the following mechanism. i) Methylsulfate anion as a base, attacks malononitrile to produce $\bar{C}H(CN)_2$ with liberation of CH_3SO_4H. DMSO could assist this process. ii) Malononitrile anion thus produced, attacks the 2- and 4-position of N-methoxyquniolinium ring to give N-methoxy-1,2-dihydro-2-dicyanomethyl-quinoline and N-methoxy-1,4-dihydro-4-dicyanomethyl-quinoline intermediates. iii) Elimination of a methanol from each of the presumed intermediate, then affords either II or III. The key step of such elimination would be the abstraction by bases (X^-) of a proton from the allylic hydrogen atom. On the contrary, if the hydrogen atom is substracted as a hydride (DMSO is capable to act as hydride acceptor[6]), the compound IV and V would result. This assumption was further supported by the fact that the total yield (8.2%) of the dehydrogenation products (IV+V) was substantially larger than that (4.2%) of the demethoxylation products (II+III), attributing to the acidity difference between two types of hydrogen being attacked by bases. Although in our present studies, we have no proof to decide in which step DMSO involved in the reaction, the major pathway of the formation of VI may be considered as shown in Chart 3. iv) The malononitrile anion or its ambident anion reacts with DMSO to give a complex nitranion, which would then attack the 2-position of N-methoxyquinolinium ring affording N-methoxy-2-substituted-1,2-dihydro intermediate, followed by liberation of methanol to

5) N.J. Leonard, *J. Am. Chem. Soc.*, 74, 2110 (1952). He supposed this compound to be 4- substituted quinoline without any chemical evidence. The cyano group of the compound strongly resisted to hydrolysis in acidic and alkaline aqueous media in our experiments.

6) G.A. Russel, *J. Am. Chem. Soc.*, 84, 2652 (1962).

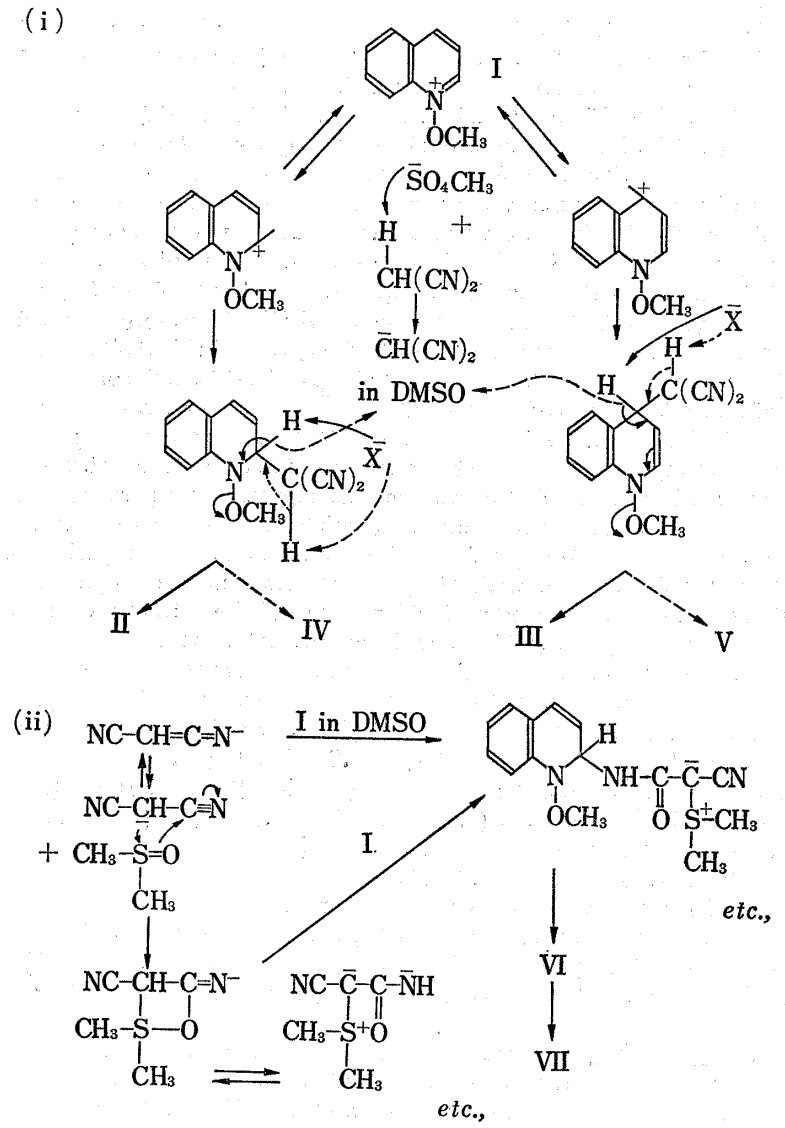

Chart 3

give VI. v) Formation of VII from VI can reasonably be explained under these conditions.

Experimental

Preparation of N-Methoxyquinolinium Methosulfate (I)——To a solution of 29 g (0.2 mol) of freshly distilled anhydrous quinoline 1-oxide in anhydrous benzene, 38 g (0.3 mol) of dimethyl sulfate was added slowly under cooling, then allowed to stand overnight at room temperature. The quaternary salt thus formed was extracted with water and the water extract was washed with benzene, concentrated to dryness, and dried in a vacuum desiccator until becoming solid. The crude quaternary salt was recrystallized from anhyd. methanol and acetone giving colorless needles, mp 155—157° (dec.) (I), 37 g (Yield, 68%). *Anal.* Calcd. for $C_{11}H_{13}NO_5S$: N, 5.17. Found: N, 5.28. Picrate (N-methoxyquinolinium picrate); yellow needles, mp 157—158° (dec.). *Anal.* Calcd. for $C_{16}H_{12}N_4O_8$: C, 49.49; H, 3.12; N, 14.43; Found: C, 49.74; H, 2.77; N, 14.03.

Reaction of N-Methoxyquinolinium Methosulfate (I) with Malononitrile in Dimethyl Sulfoxide——i) A mixture of 2.71 g (0.01 mol) of I, 0.66 g (0.01 mol) of malononitrile in 10 ml of DMSO heated on an oil bath at 60—70° for 2 hr. After removal of DMSO under a reduced pressure at below 70°, the residue was poured into water, extracted with chloroform and the chloroform solution was dried over anhydrous Na_2SO_4. After removing chloroform, the resulting oily materials were passed through alumina column and eluted with chloroform to give 230 mg of quinoline 1-oxide identified as its picrate, mp 143—145° (dec.), followed by yellow crystals, which were fractionally recrystallized from methanol to give 8 mg of III and 75 mg of II. III;

yellow needles, mp 324° (dec.). *Anal.* Calcd. for $C_{12}H_7N_3$: C, 74.60; H, 3.65; N, 21.76. Found: C, 73.98; H, 3.75; N, 21.67. UV λ_{max}^{EtOH} nm 226, 260, 270, 279, 397, 416, IR (KBr) cm^{-1} ν_{NH} 3200 (broad), ν_{CN} 2180, 2205. II; yellow plumlets, mp 295—297° (dec.). *Anal.* Calcd. for $C_{12}H_7N_3$: C, 74.60; H, 3.65; N, 21.76. Found: C, 74.28; H, 3.71; N, 22.16. UV λ_{max}^{EtOH} nm (ε) 286 (26100), 398 (15500). $\lambda_{max}^{0.1N\ NaOH}$ nm 276, 293, 303, 379. IR (KBr) cm^{-1}: $\nu_{C=C}$ 1640, ν_{CN} 2195, 2215. On the other hand, the aqueous solution obtained above, was neutralized with aq. $NaHCO_3$, extracted with chloroform and the chloroform solution was dried over anhyd. Na_2SO_4. After removal of chloroform, the residue was separated by passing through alumina column eluted with chloroform giving 180 mg of quinoline, identified as its picrate, mp 198—200° (dec.) and yellow crystals, which were fractionally recrystallized from methanol to afford 129 mg of IV and 54 mg of V. IV, yellow needles, mp 176—177° (dec.). *Anal.* Calcd. for $C_{13}H_9N_3O$: C, 69.94; H, 4.06; N, 18.83. Found: C, 70.35; H, 4.04; N, 18.78. UV: λ_{max}^{EtOH} nm: 218, 283, 380 (sh), 397. IR (KBr) cm: $\nu_{C=C}$ 1616, ν_{CN} 2200; V, deep yellow needles, mp 210° (dec.). *Anal.* Calcd. for $C_{13}H_9N_3O$: C, 69.94; H, 4.06; N, 18.83. Found: C, 70.07; H, 3.88; N, 18.89. UV: λ_{max}^{EtOH} nm: 227, 263, 273, 281, 411, 432. IR (KBr) cm^{-1} ν_{CN} 2180, 2200.

ii) A mixture of 2.71 g (0.01 mol) of I, 0.66 g (0.01 mol) of malononitrile in 10 ml of DMSO was heated on an oil bath at 100—110° for 3 hr. After removal of DMSO under a reduced pressure at below 100°, the residue was poured into water, extracted with chloroform and the chloroform solution was dried over anhyd. Na_2SO_4. The extract was concentrated, the residue was separated by passing through alumina column to give 370 mg of quinoline 1-oxide, and yellow crystals, which were fractionally recrystallized from methanol to give 13 mg of yellow needles, mp 325° (dec.) identified with III by IR comparison, and 100 mg of yellow plumlets mp 295—297° (dec.) identified with II by IR comparison. The aqueous layer obtained above, was neutralized with aq. $NaHCO_3$, extracted with chloroform and the extract was dried over anhyd. Na_2SO_4, concentrated to give a reddish brown oil, which was chromatographed on alumina column eluted with chloroform. The eluted materials were 420 mg of quinoline, and newly formed viscous oil, which was crystallized by adding a small amount of ether, recrystallized from benzene to afford 130 mg of VI and 15 mg of 2-aminoquinoline (VII). VI, colorless needles, mp 145—147° (dec.). *Anal.* Calcd. for $C_{14}H_{13}N_3OS$: C, 61.99; H, 4.83; N, 15.50; O, 5.90; S, 11.81. Found: C, 62.23; H, 4.81; O, 5.97; N, 15.23; S, 11.87. UV: λ_{max}^{EtOH} nm (ε): 213 (25000), 243 (25700), 266 (28500), 324 (11500), 334 (10800), λ_{max}^{EtOH} nm (ε): 228 (17300), 252 (24200), 300 (5000), 331—332 (10600); $\lambda_{max}^{0.1N\ HCl}$ nm (ε): 253 (30800), 338 (18700), 348 (sh) (17900); IR (KBr) cm^{-1}: ν_{NH} 3500, ν_{CN} 2175, $\nu_{C=C}$ 1630. VII, colorless needles, mp 128—130° (dec.). *Anal.* Calcd. for $C_9H_8N_2$: C, 74.97; H, 5.59; N, 19.43. Found: C, 74.94; H, 5.69; N, 19.78.

Reaction of II with Diazomethane——To a suspension of 50 mg of II in methanol, was added diazomethane in ether and the reaction mixture was allowed to stand overnight affording, 35 mg of yellow needles, mp 253—254° (dec.), N-methyl-2-dicyanomethylene-quinoline. *Anal.* Calcd. for $C_{13}H_9N_3$: C, 75.34; H, 4.38; N, 20.28. Found: C, 74.99; H, 4.46; N, 20.61. UV: λ_{max}^{EtOH} nm: 285, 396. IR (KBr) cm^{-1}: $\nu_{C=C}$ 1620, ν_{CN} 2200, 2193.

Conversion of II into Quinaldine——A mixture of 100 mg of II, 3 ml of conc. HCl, and 3 ml of ethanol was refluxed for 25 hr. After removal of the solvents, the residue was diluted with a small amount of water and the aqueous solution was made alkaline, extracted with ether. The ether solution was dried over KOH. The oily material resulted from the ether solution, was added to the alcoholic picric acid solution to give 170 mg of quinaldine picrate, yellow prisms, mp 191—192° (dec.), after recrystallization from ethanol. Decomposition of the picrate by passing through basic alumina column gave quinaldine, identified by IR comparison with an authentic sample.

Conversion of III into Lepidine——A suspension of 100 mg of III in 3 ml of conc. HCl and 3 ml of ethanol was refluxed for 20 hr. After removal of the solvents, the residue was diluted with water, made alkaline, and extracted with ether. The ether solution was dried over KOH. The residual oil obtained after evaporation of ether, was added to alcoholic picric acid solution to give, 150 mg of lepidine picrate, yellow needles, mp 215—218° (dec.), which was passed through a basic alimina column, affording lepidine, identified by IR comparison with an authentic sample.

Reaction of III with Diazomethane——A suspension of 50 mg of III in 2 ml of methanol was treated with ethereal diazomethane by usual way. After evacuation of the solvents, the resulting yellow material was recrystallized from methanol to afford 32 mg of N-methyl-4-dicyanomethylene-quinoline, yellow needles, mp 283—284° (dec.). *Anal.* Calcd. for $C_{13}H_9N_3$: C, 75.34; H, 4.38; N, 20.28. Found: C, 75.86; H, 4.53; N, 20.62. UV: λ_{max}^{EtOH} nm: 226, 262, 272, 281, 407, 425. IR (KBr) cm^{-1}: ν_{CN} 2180, 2200.

Conversion of IV to II——The compound (IV) was quantitatively recovered unchanged from refluxing IV in a mixture of 2 ml of ethanol and 1 ml of 30% $KHCO_3$ solution for 10 hr, and also in a mixture of 2 ml of ethanol and 1 ml of 30% K_2CO_3 solution for 5 hr. A solution of 50 mg of IV in a mixture of 2 ml of 20% NaOH solution and 2 ml of ethanol, was heated under refluxing for 3 hr. After removal of the solvents, the residue was diluted a small amount of water, neutralized with dil. HCl, extracted with ethyl acetate. The extract was dried over anhyd. Na_2SO_4 and concentrated to dryness giving 37 mg of yellow needles, mp 294—295° (dec.), which was identified with II by IR comparison.

Conversion of V into III——A solution of 50 mg of V in 2 ml of 20% NaOH solution and 2 ml of ethanol, was refluxed for 3 hr. After evacuation of the solvents, the residue was diluted with water, neutralized with dil. HCl, extracted with ethyl acetate. The extract was dried over anhyd. Na_2SO_4 and concentrated to

dryness affording 33 mg of yellow needles, mp 320° (dec.), which was identified with III by IR comparison.

Hydrolysis of VI to 2-Aminoquinoline (VII)——A solution of 100 mg of VI in 2 ml of 17% HCl was heated on a steam bath for 2 hr. The reaction mixture was made alkaline to give colorless precipitate, which was extracted with chloroform. The chloroform solution was dried over anhyd. Na_2SO_4 and concentrated to dryness. The residue obtained, was passed through alumina column eluted with chloroform to give 58 mg of 2-aminoquinoline, colorless needles, mp 128°.

Reaction of VI with Hydrogen Peroxide——i) To a solution of 100 mg of VI in acetic acid, 1 ml of 30% H_2O_2 was added. The mixture was heated on a steam bath for 2 hr, cooled, and treated with 10 mg of Pt black. After removing Pt black, the solution was evaporated, leaving a viscous oil, which was chromatographed on silica gel eluted with chloroform, giving 30 mg dimethylsulfone, mp 112° and 41 mg of VII.

ii) To a solution of 100 mg of VI in 2 ml of ethanol, 1 ml of 30% H_2O_2 was added. The mixture was allowed to stand overnight at room temperature. The colorless precipitate, mp *ca.* 120° (dec.). UV: λ_{max}^{EtOH} nm: 250, 318, 331. IR (KBr) cm^{-1}: $\nu_{C=O}$ 1680, ν_{OH} 2400—3200 (broad), was unstable and easily decomposed to VII.

Reaction of VI with Raney Nickel——To a solution of 100 mg of VI in 5 ml of ethanol, 500 mg of W-2 Raney Nickel was added. The mixture was heated under refluxing for 4 hr, ethanol and the nickel were removed, and the residue obtained was passed through alumina column eluted with chloroform to give 55 mg of VII.

Catalytic Hydrogenation of VI——A suspension of 135 mg of VI, 80 mg of 30% Pd–C in 10 ml of methanol was shaken under hydrogen atomosphere. After hydrogen absorption was completed, the catalyst and methanol were removed and the resulting residue was purified by passing through an alumina column to give 40 mg of VII.

Acknowledgement The authors wish to thank to the members of the Central Analytical Laboratories of this Faculty for the microanalyses and the measurements of UV, IR, and NMR spectra.