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1. Yutaka Kawazoe and Misako Tachibana : Studies on Chemical Carcinogens. II.*1 Syntheses of Some Derivatives of 4-Nitro and 4-Hydroxyaminoquinoline 1-Oxide.

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Many 4-nitroquinoline 1-oxides and the corresponding 4-hydroxyamino derivatives were prepared in connection with their carcinogenic activity.

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Since the carcinogenic activity of 4-nitroquinoline 1-oxide (4-NQO) was demonstrated by Nakahara, Fukuoka and Sugimura in 1957,[1] many studies were reported on the carcinogenic mechanism of 4-NQO and its related compounds.[2~22] Thus, 2-methyl, 2-ethyl, 6-chloro[4] and 6-carboxyl[3,19] derivatives of 4-NQO were proved to induce malignant tumor by subcutaneous injection or painting on the skin of mouse and rat. Shirasu and Ohta[12,14] found in 1963 that 4-hydroxyaminoquinoline 1-oxide (4-HAQO), which was shown by Okabayashi to be one of the reduction products of 4-NQO in the microorganisms,[8,9] induced fibrosarcoma and carcinoma locally at the site of the injection or the painting as 4-NQO did. The same finding was reported

*1 Part I : This Bulletin, **13**, 1103 (1965).
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1) W. Nakahara, F. Fukuoka, T. Sugimura : Gann, **48**, 129 (1957).
2) T. Okabayashi : Yakugaku Zasshi, **73**, 964 (1953).
3) F. Fukuoka, T. Sugimura, S. Suzuki : Gann, **48**, 263 (1957).
4) W. Nakahara, F. Fukuoka, S. Sakai : *Ibid.*, **49**, 33 (1958).
5) H. Endo : *Ibid.*, **49**, 151 (1958).
6) W. Nakahara, F. Fukuoka : *Ibid.*, **50**, 1 (1959).
7) W. Nakahara : Progr. Exptl. Tumor Res., **2**, 158 (1961).
8) T. Okabayashi : This Bulletin, **10**, 1127 (1962).
9) T. Okabayashi, A. Yoshimoto : *Ibid.*, **10**, 1221 (1962).
10) Al-Kassab, B. Boyland, K. Williams : Biochem. J., **87**, 5 (1963).
11) T. Okamoto, M. Itoh : This Bulletin, **11**, 785 (1963).
12) Y. Shirasu, A. Ohta : Gann, **54**, 221 (1963).
13) H. Endo, F. Kume : *Ibid.*, **54**, 443 (1963).
14) Y. Shirasu : *Ibid.*, **54**, 487 (1963).
15) H. Endo, F. Kume : Naturwiss., **50**, 525 (1963).
16) C. Nagata, A. Imamura, K. Fukui, H. Saitoh : Gann, **54**, 401 (1963).
17) W. Nakahara : Arzneimittel Forsch., **14**, 842 (1964).
18) H. Endo, F. Kume : Gann, **56**, 261 (1965).
19) T. Kawachi, Y. Hirata, T. Sugimura : *Ibid.*, **56**, 415 (1965).
20) T. Sugimura, K. Okabe, H. Endo : *Ibid.*, **56**, 489 (1965).
21) C. Nagata, M. Kodama, Y. Tagashira, A. Imamura : Biopolymers, **4**, 409 (1966).
22) H. Hoshino, F. Fukuoka, K. Okabe, T. Sugimura : Gann, **57**, 71 (1966).

also by Endo and Kume.[13,15] Since then, many efforts have been focussed on clarification of the metabolic pathway of 4-NQO and 4-HAQO *in vivo*[20,22] and also on correlation of the biological activities with the chemical reactivities of these and related compounds. The results so far obtained indicate that either nitro or hydroxyamino group at position 4, in addition to N-oxide group, is necessary for the carcinogenicity of the quinoline compound and that the essential carcinogen may be either 4-NQO, 4-HAQO or one of their metabolic intermediates such as 4-nitrosoquinoline 1-oxide, etc. It can be considered that the cell cancerization is caused by chemical reactions of one of these metabolites with biological substances and that an alternative possibility may be in its reductive or oxidative metabolic process in the biological system.

As one of our serial studies on chemical carcinogens, this paper describes syntheses of various 4-NQO derivatives and the corresponding 4-HAQO derivatives. Bioassay for their carcinogenicity in mice is now being pursued, intending to correlate the carcinogenicity with their structures and chemical reactivities.

Table I. 4-Nitroquinoline 1-Oxides Tested for Carcinogenic Activity in Mice

Compounds	m.p. (°C)	References	
		for Synth.	for Carcinogenicity
4-NQO	153~154	23)	1)
2-Methyl-4-NQO	157	24)	4)
3-Methyl-4-NQO	179~180		
5-Methyl-4-NQO	174~175		
6-Methyl-4-NQO	184~186	25)	
7-Methyl-4-NQO	164~165	*a*)	
8-Methyl-4-NQO	153~154	*a*)	
3-Chloro-4-NQO	159~160		
3-Bromo-4-NQO	159	26)	
5-Chloro-4-NQO	145~146		
6-Chloro-4-NQO	193~195	25)	4)
7-Chloro-4-NQO	219 (decomp.)	27)	
6,7-Dichloro-4-NQO	191		
4,5-Dinitro-QO	260~262	28)	
4,6-Dinitro-QO	218 (decomp.)	28)	17)
4,7-Dinitro-QO	195~196		
4,8-Dinitro-QO	222~223 (decomp.)	28)	17)
3-Methoxy-4-NQO	196		
3-Diethylmalonyl-4-NQO	101~102	29)	
6-Carboxy-4-NQO	305~307 (decomp.)	30)	19)
4,6,8-Trinitro-QO	189~191 (〃)	28)	17)

a) These compounds were reported by G. Buchmann on their fungistatic and bacteriostatic effects but we could not find the reference for their preparation (G. Buchmann: Pharmazie, **17**, 283 (1962); Wiss. Z. Tech. Hochsch. Chem. Leuna-Merseburg, **4**, 213 and 219 (1962)).

23) E. Ochiai, M. Ishikawa, Z. Sai: Yakugaku Zasshi, **63**, 280 (1943).
24) M. Ishikawa: *Ibid.*, **65B**, 99 (1945).
25) T. Okamoto: *Ibid.*, **71**, 727 (1951).
26) *Idem*: *Ibid.*, **70**, 376 (1950).
27) S. Yoshida: *Ibid.*, **66B**, 158 (1946).
28) M. Ishikawa: Proc. Imp. Acad. (Tokyo), **20**, 599 (1944). E. Ochiai, T. Okamoto: Yakugaku Zasshi, **70**, 384 (1950).
29) H. J. Richter, N. E. Rustad: J. Org. Chem., **29**, 3381 (1964).
30) E. Ochiai, S. Suzuki, Y. Utsunomiya, T. Oomoto, N. Nagatomo, M. Itoh: Yakugaku Zasshi, **80**, 339 (1960).

4-Nitroquinoline 1-oxide derivatives

The derivatives synthesized are shown in Table I. Many 4-NQO derivatives listed have been already synthesized by Ochiai and Okamoto and their coworkers and seven compounds newly prepared are underlined in the table. Their structures were verified by changing them to the corresponding 4-chloro derivatives by nucleophilic replacement of 4-nitro group with hydrochloric acid. It is a reasonable assumption that only 4-nitro group can undergo this replacement under such a mild reaction condition as chosen in our experiment. A further unequivocal evidence for their structural identities was given by proton magnetic resonance spectrum analysis. Nitration was carried out by the treatment of the parent 1-oxide with 1.2 equivalents of potassium nitrate in rather concentrated sulfuric acid at an appropriate temperature. In order to obtain 4-nitro derivative in as high yield as possible, sulfuric acid should not be too concentrated and the reaction temperature should be rather high. These conditions were recommended and discussed by Ochiai and Okamoto[31,25] and Ochiai and Satake[32] in the papers concerning the mechanism of nitration of the N-oxides, and later this was further discussed by Hamana, *et al.*[33] in nitration of 6-substituted quinoline 1-oxides. In Table II are summarized the melting points and the elemental analyses of 4-nitro derivatives newly prepared. Table III shows those of 4-chloro derivatives derived by

Table II. 4-Nitroquinoline 1-Oxides

Compounds	Appearance	Formula	Analysis					
			Calcd.			Found		
			C	H	N	C	H	N
3-Methyl-4-NQO	yellow needles	$C_{10}H_8O_3N_2$	58.77	3.92	13.71	58.99	3.70	13.59
5-Methyl-4-NQO	yellow prisms	〃	58.77	3.92	13.71	58.82	3.49	13.41
8-Methyl-4-NQO	yellow needles	〃	58.77	3.92	13.71	58.50	3.97	13.94
3-Chloro-4-NQO	pale yellow needles	$C_9H_5O_3N_2Cl$	48.09	2.23	12.47	48.01	2.34	12.63
5-Chloro-4-NQO	〃	〃	48.09	2.23	12.47	48.25	2.28	12.44
6,7-Dichloro-4-NQO	yellow prisms	$C_9H_4O_3N_2Cl_2$	41.69	1.54	10.81	41.59	1.57	11.02
3-Methoxy-4-NQO[a)]	yellow needles	$C_{10}H_8O_4N_2$	54.50	3.63	12.72	54.64	3.56	12.72

a) This compound was synthesized also by T. Okamoto's group of University of Tokyo. They examined the nitration of 3-methoxyquinoline 1-oxide in much more details than we did, which will be reported by them in near future.[42] Thanks are indebted to Professor T. Okamoto for identifying our sample with theirs.

Table III. 4-Chloroquinoline 1-Oxides

Compounds	m.p. (°C)	Appearance	Formula	Analysis					
				Calcd.			Found		
				C	H	N	C	H	N
3-Methyl-4-chloro-QO	215～217	white needles	$C_{10}H_8ONCl$	61.97	4.13	7.23	61.87	4.10	6.96
4-Chloro-5-methyl-QO	149～150	〃	〃	61.97	4.13	7.23	62.06	3.70	7.32
4-Chloro-8-methyl-QO	140～141	〃	〃	61.97	4.13	7.23	62.32	4.60	7.27
3,4-Dichloro-QO	162～163	〃	$C_9H_5ONCl_2$	50.46	2.34	6.54	50.54	2.55	6.79
4,5-Dichloro-QO	164～165	〃	〃	50.46	2.34	6.54	50.67	2.87	6.25
4,6,7-Trichloro-QO	200	〃	$C_9H_4ONCl_3$	43.46	1.61	5.63	43.30	1.79	5.77

31) E. Ochiai, T. Okamoto : Yakugaku Zasshi, **70**, 384 (1950).
32) E. Ochiai, K. Satake : *Ibid.*, **71**, 1078 (1951).
33) M. Hamana, T. Nagayoshi : This Bulletin, **14**, 319 (1966).

chlorine-replacement of the corresponding 4-nitro groups. It is to be noted that 3- or 5-substituent is expected to have a serious steric effect on the nucleophilic reaction at the carbon 4 and on spectroscopic behaviors of these compounds because of resonance interruption by twisting of 4-nitro group. The ultraviolet (UV) spectra of each of these derivatives showed a considerable blue shift from that of 4-NQO as expected, as shown in Figs. 1 and 2.

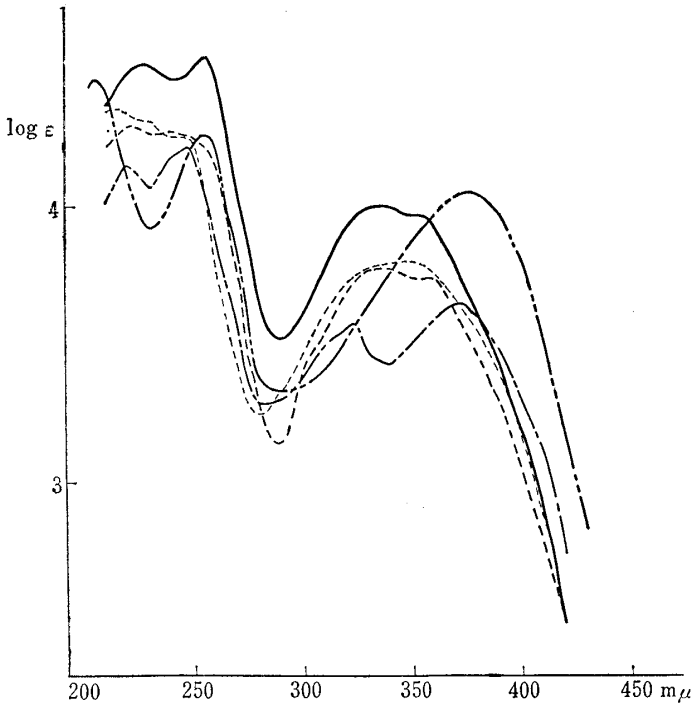

Fig. 1. Ultraviolet Spectra of 3-Substituted-4-nitroquinoline 1-Oxides

The nuclear magnetic resonance (NMR) spectrum of 3-methyl-4-NQO also suggested that the nitro group at the position 4 is considerably twisted to result in less mesomeric interaction of the nitro group with the ring π-electron system. This could become evident by comparing the chemical shift of proton-5 resonance with that of 4-NQO. Thus, spectral analysis of 4-NQO[34] tells that protons 5 and 8 resonate at about 0.8 to 0.9 p.p.m. lower field than protons 6 and 7. This may be mainly due to the neighboring magnetic effect of NO_2 and N^+–O^- groups on protons 5 and 8, respectively. But it was observed that introduction of a bulky methyl group to position 3 affected one of the lower signals to shift by about 0.8 p.p.m. higher, no remarkable change being observed with other signals. This could be reasonably understood by the fact that anisotropy effect of nitro group on proton 5 was changed to a great extent by twisting of NO_2 group from the plane including aromatic ring, quantitative treatment of the effect being now under investigation using some appropriate model compounds.

4-Hydroxyaminoquinoline 1-oxide derivatives

4-HAQO was originally obtained in 1944 by Ochiai and Naito[35] by the catalytic reduction of 4-NQO but it had been misformulated as 4,4′-hydrazoquinoline 1,1′-dioxide until 1957, when Ochiai and Ohta established its true structure.[36] Lately, Ochiai and Mitarashi reported that 4-HAQO was easily prepared by treatment of 4-NQO with phenylhydrazine in a almost quantitative yield.[37,38] The latter method is superior to the catalytic reduction both in the reaction yield and in the purity of 4-HAQO produced. The same authors reported in the subsequent paper[39] that this method

34) Y. Kawazoe, M. Ohnishi, N. Kataoka : This Bulletin, **13**, 396 (1965).
35) E. Ochiai, T. Naito : Yakugaku Zasshi, **64**, 204 (1944).
36) E. Ochiai, A. Ohta, H. Nomura : This Bulletin, **5**, 310 (1957).
37) E. Ochiai, H. Mitarashi : Ann. Rept. ITSUU Lab., **13**, 19 (1963).
38) *Idem* : This Bulletin, **11**, 1084 (1963).
39) *Idem* : Ann. Rept. ITSUU Lab., **14**, 17 (1964).

could be applicable to 2-methyl-4-NQO and 3-NQO to give the corresponding hydroxyamino derivatives. So, we attempted to derive the 4-NQO derivatives synthesized for carcinogenicity test to their corresponding hydroxyamino derivatives by the above method. Thus, 4-nitro derivatives were treated with a large excess of phenylhydrazine in ethanol solution at an appropriate temperature described in the experimental part. 5-, 6-, 7-, and 8-Monomethyl-4-NQO readily afforded the corresponding 4-HAQOs in fairly good yields. With regard to halogeno 4-NQOs, 6- and 7-monohalogeno and 6,7-dihalogeno derivatives similarly gave the corresponding 4-HAQOs. 6- and 7-Nitro-4-HAQOs could also be prepared by the same method in fair yield.*[3] Table Ⅳ shows 4-HAQO derivatives newly prepared by this method,

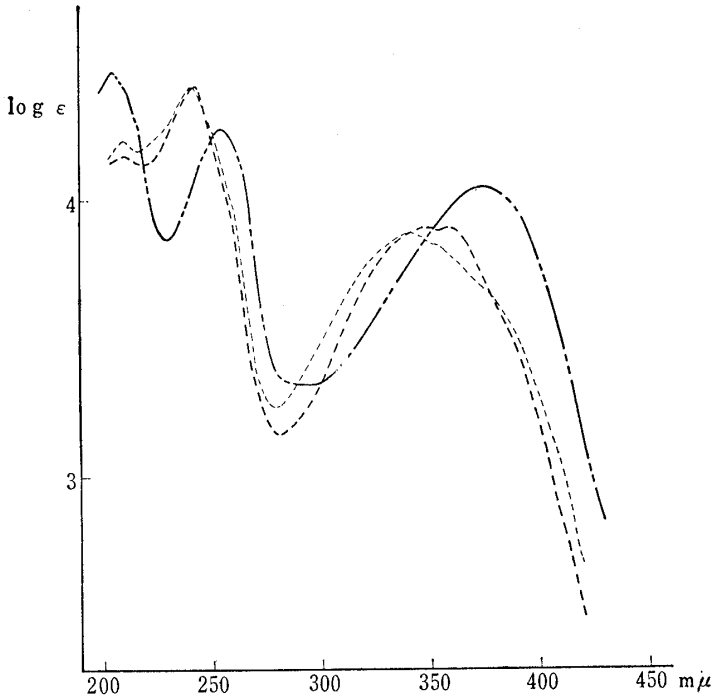

Fig. 2. Ultraviolet Spectra of 5-Substituted-4-nitroquinoline 1-Oxides

- - - - - - 5-methyl-4-NQO
— — — — 5-chloro-4-NQO
—·····— 4-NQO

Table Ⅳ. 4-Hydroxyaminoquinoline 1-Oxides

Compounds	m.p. (℃) (decomp.)		Formula	Analysis of HCl Salts (%)					
				Calcd.			Found		
	Free Base	HCl Salt		C	H	N	C	H	N
5-Methyl-4-HAQO	173～180	195～198	$C_{10}H_{10}O_2N_2 \cdot HCl$	52.95	4.85	12.35	52.92	5.11	12.40
6-Methyl-4-HAQO	212～213	221.5～223	〃	52.95	4.85	12.35	53.24	4.98	12.54
7-Methyl-4-HAQO	205	243～245	〃	52.95	4.85	12.35	53.21	4.93	12.54
8-Methyl-4-HAQO	146	189～190	〃	52.95	4.85	12.35	53.25	4.94	12.75
6-Chloro-4-HAQO	199～200	223	$C_9H_7O_2N_2Cl \cdot HCl$	43.72	3.24	11.33	43.80	3.35	11.86
7-Chloro-4-HAQO	233	207	〃	43.72	3.24	11.33	43.68	3.15	11.43
6,7-Dichloro-4-HAQO	233	219～220	$C_9H_6O_2N_2Cl_2 \cdot HCl$	38.37	2.49	9.95	38.17	2.59	9.95
6-Nitro-4-HAQO	210	202～203	$C_9H_7O_4N_3 \cdot HCl$	41.92	3.11	16.30	42.31	3.19	16.17
7-Nitro-4-HAQO	207	197～198	〃	41.92	3.11	16.30	41.77	3.25	16.20

including the melting points and the elemental analysis data of their hydrochlorides. The products thus obtained were identified by the elemental analysis and infrared examination of the free bases and their hydrochlorides. No successful results have yet been obtained in reducing 3-substituted 4-NQO to 4-hydroxyamino 1-oxides by this reagent. Thus, 3-methyl- and 3-methoxy-4-NQO did not react at all under the same condition employed for other derivatives. 3-Bromo derivative afforded debrominated 4-HAQO itself. Catalytic reduction also has not been effective for these 3-substituted derivatives since further reductions proceeded beyond the HAQO stage. The

*[3] 6-Nitro- and 6-chloro-4-HAQO were also prepared by Hamana's group of Kyushu University. Our sincere thanks are indebted to Professor Masatomo Hamana for identification of our materials with theirs.

syntheses of 4-HAQO derivatives other than those described in Table Ⅳ are now being attempted and will be reported in near future.

Experimental

3-Methyl-4-nitroquinoline 1-Oxide——To a solution (warmed at 80°) of 0.95 g. of 3-methylquinoline 1-oxide*4 in 4 g. of 86% H_2SO_4 was added 0.87 g. of KNO_3 in small portions, and the reaction mixture was kept at the same temperature for 3 hr. The reaction mixture was poured into ice-water, and yellow precipitate was gathered, washed with water, and recrystallized from CH_3OH to give 0.80 g. of yellow needles (m.p. 178~180°, 77% yield), which is readily colored and decomposed on exposure to light.

5-Methyl-4-nitroquinoline 1-Oxide——Ninety hundredth g. of 5-methylquinoline 1-oxide (m.p. 121~123°[42]) was similarly treated at 92~93° for 2.5 hr. with 0.84 g. of KNO_3 in 5 g. of 79% H_2SO_4. The reaction mixture was poured into ice-water, extracted with $CHCl_3$, and $CHCl_3$ layer was washed with $NaHCO_3$ solution and dried with Na_2SO_4. After evaporation of the solvent *in vacuo*, yellow crystalline residue was chromatographed in benzene through an alumina column, eluted with benzene and then with $CHCl_3$. Twenty hundredth g. of yellow needles of 5-methyl-4-nitroquinoline 1-oxide was obtained from the benzene fractions, and recrystallized from CH_3OH (m.p. 174~175° (decomp.)). From $CHCl_3$ fractions was obtained 0.12 g. of yellow needles (m.p. 243~244° (decomp.)) of another mononitroquinoline 1-oxide, the structure of which is now under investigation.

8-Methyl-4-nitroquinoline 1-Oxide——Sixty eight hundredth g. of 8-methylquinoline 1-oxide was similarly treated at 90° for 2 hr. with 0.77g. of KNO_3 in 5 g. of 82% H_2SO_4. The $CHCl_3$ extract was dissolved in benzene and chromatographed through an alumina column. The first part of the benzene eluate gave 0.08 g. of 8-methyl-4-nitroquinoline (yellow needles, m.p. 78~79°. *Anal.* Calcd. for $C_{10}H_8O_2N_2$: C, 63.77; H, 4.25; N, 14.8. Found : C, 63.79; H, 4.07: N, 15.08. 10% yield). The next part of the eluate gave 0.23 g. of 8-methyl-4-nitroquinoline 1-oxide (24% yield).

3-Methoxy-4-nitroquinoline 1-Oxide——Three g. of 3-methoxyquinoline 1-oxide was similarly treated at 90~95° with 2.5 g. of KNO_3 in 20 ml. of 79% H_2SO_4. After standing at this temperature for 2 hr., the reaction mixture was poured into ice-water. Yellow precipitate was gathered and washed with water. It was dissolved in benzene and chromatographed through an alumina column. Main fraction of the benzene eluate was recrystallized twice from acetone to give 2.5 g. of yellow needles (m.p. 196°, 66% yield). This mononitro derivative was identified as 3-methoxy-4-nitroquinoline 1-oxide, the structure of which was chemically established by Okamoto, *et al.*[42]

3-Chloro-4-nitroquinoline 1-Oxide——3-Chloroquinoline 1-oxide (m.p. 91~92°) was prepared by N-oxidation of 3-chloroquinoline obtained by Sandmeyer reaction of 3-aminoquinoline. Similarly, 0.54 g. of this N-oxide was treated at 70° for 2 hr. with 0.36 g. of KNO_3 in 2.5 ml. of 79% H_2SO_4. The reaction mixture was poured into ice-water. Yellow precipitate was gathered and washed with water. It was recrystallized from CH_3OH to give 0.2 g. of pale yellow needles (m.p. 159~160°, 42% yield). Thirteen hundredth g. of the starting material was recovered from the acidic filtrate.

6,7-Dichloro-4-nitroquinoline 1-Oxide——A mixture of 6,7- and 5,6-dichloroquinolines which were derived from 3,4-dichloroaniline by Skraup reaction was oxidized by an usual AcOH-H_2O_2 method to their 1-oxides. Four g. of this mixture of 1-oxides was dissolved in 25 ml. of 79% H_2SO_4 and warmed at 95°. To this solution was added 0.80 g. of KNO_3 in small portions, and then the mixture was kept at this temperature for 2.5 hr. The reaction mixture was poured into ice-water, yellow precipitate formed was gathered and washed with water. They were chromatographed in benzene through alumina column. Yellow crystal obtained from the benzene eluate was recrystallized from dioxane to give 1.01 g. of pure 6,7-dichloroquinoline 1-oxide (yellow prisms, m.p. 190.5~192°, 20% yield). Recrystallization from dioxane was so effective to eliminate 5,6-dichloro derivative and all nitro derivatives other than the 4-nitro compounds. From the acidic filtrate was recovered 1.65 g. of the starting material.

4-Chloroquinoline 1-Oxide Derivatives——General procedure : 50 mg. to 100 mg. of 4-nitroquinoline 1-oxides was dissolved in ca. 3 ml. of conc. HCl and warmed at 70° for 15 to 30 min. After evaporating the solvent *in vacuo*, the residue was made alkaline with $NaHCO_3$ and extracted with $CHCl_3$. Evaporation of the solvent gave 4-chloroquinoline 1-oxides which were recrystallized from CH_3OH. The melting points and the elemental analysis data are summarized in Table Ⅲ.

5-Methyl-4-hydroxyaminoquinoline 1-Oxide——To a solution of 0.10 g. of 5-methyl-4-NQO in 0.5 ml. of EtOH, 0.5 ml. of phenylhydrazine was added, and reaction mixture was kept at 70° for 20 min. to

*4 3-Methylquinoline was prepared by reduction[40] of *o*-nitrobenzaldehyde, followed by condensing with propionic aldehyde at 200° for 3 hr.

40) Org. Synth. Coll. Vol. Ⅲ, 56.

41) T. Yoshikawa : Yakugaku Zasshi, **81**, 1601 (1961).

42) T. Okamoto, *et al.* : This Bulletin, to be published.

deposit yellowish brown precipitate. Most of the solvent was removed *in vacuo*, ether was added and the precipitate was gathered and washed with ether. Fifty six thousandth g. of yellow powder thus obtained (60% yield) was recrystallized from CH_3OH containing a large excess of conc. HCl as the hydrochloride. (White needles, m.p. 195~198° (decomp.))

6-Methyl-4-hydroxyaminoquinoline 1-Oxide——A mixture of 0.3 g. of 6-methyl-4-NQO, 3 ml. of EtOH and 2 ml. of phenylhydrazine was warmed at 50° for 10 min. The same treatment of the reaction mixture as in the case of 5-methyl derivative gave 0.278 g. of yellow powder (quantitative yield). It was recrystallized from CH_3OH containing excess of conc. HCl as the hydrochloride. (White needles, m.p. 221.5~223° (decomp.))

7-Methyl-4-hydroxyaminoquinoline 1-Oxide——A mixture of 0.25 g. of 7-methyl-4-NQO, 2 ml. of EtOH and 1.5 ml. of phenylhydrazine was warmed at 50° for 10 min. Similar treatment of the reaction mixture gave 0.22 g. of yellow powder (95% yield). The hydrochloride was recrystallized from CH_3OH containing conc. HCl as white needles. (m.p. 243~245° (decomp.))

8-Methyl-4-hydroxyaminoquinoline 1-Oxide——A mixture of 0.20 g. of 8-methyl-4-NQO, 1 ml. of EtOH and 0.5 ml. of phenylhydrazine was warmed at 50° for 15 min. Similar treatment gave 0.065 g. of yellow powder (17% yield). The hydrochloride was recrystallized from CH_3OH containing conc. HCl as white needles. (m.p. 189~190° (decomp.))

6-Chloro-4-hydroxyaminoquinoline 1-Oxide——A mixture of 0.15 g. of 6-chloro-4-NQO, 2 ml. of EtOH and 1 ml. of phenylhydrazine was warmed at 40° for 15 min. Similar treatment gave 0.12 g. of yellow powder (85% yield). The hydrochloride was recrystallized from CH_3OH containing conc. HCl as white needles. (m.p. 223° (decomp.)

7-Chloro-4-hydroxyaminoquinoline 1-Oxide——Similar treatment of 0.15 g. of 7-chloro-4-NQO as in the case of 6-chloro derivative gave 0.11 g. of yellow powder (73% yield). The hydrochloride was recrystallized from CH_3OH containing conc. HCl as white needles. (m.p. 207° (decomp.))

6,7-Dichloro-4-hydroxyaminoquinoline 1-Oxide——A suspension of 0.20 g. of 6,7-dichloro-4-NQO in 2 ml. of EtOH was cooled in an ice-bath and 1 ml. of phenylhydrazine was added. The reaction mixture was kept standing at 0° for 4 hr. After most of the solvent was evaporated *in vacuo*, ether was added. The precipitate was gathered and washed with ether. Yellow powder thus obtained, 0.189 g. (quantitative yield) was recrystallized as the hydrochloride. (Orange needles, m.p. 219~220° (decomp.))

6-Nitro-4-hydroxyaminoquinoline 1-Oxide——Twenty hundredth g. of 4,6-dinitroquinoline 1-oxide was treated with 2 ml. of EtOH and 1 ml. of phenylhydrazine at 50° for 20 min. The violet precipitate was yielded. The same treatment of the reaction mixture as in the case of 5-methyl derivative gave 0.17 g. of violet powder of the corresponding hydroxyamino derivative (90% yield). The hydrochloride was recrystallized from CH_3OH containing conc. HCl as yellow needles. (m.p. 202~203° (decomp.))

7-Nitro-4-hydroxyaminoquinoline 1-Oxide——Twenty five hundredth g. of 4,7-dinitroquinoline 1-oxide was treated with 2 ml. of EtOH and 1 ml. of phenylhydrazine at 25° for 30 min. The red brown precipitate was yielded. The reaction mixture was similarly treated and gave 0.20 g. of red powder (85% yield). The hydrochloride was recrystallized from CH_3OH containing conc. HCl as deep red needles. (m.p. 197~198° (decomp.))

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