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44. Masatomo Hamana and Tsuyoshi Nagayoshi: Studies on Tertiary Amine Oxides. XXVI.*1 Nitration of 6-Substituted Quinoline 1-Oxides.

(*Faculty of Pharmaceutical Sciences, Kyushu University**2)

In 1950, Ochiai and Okamoto[1] have found that nitration of quinoline 1-oxide is markedly temperature-dependent; that is, the polar effect of the N-oxide function does not appear at low temperatures and 5- and 8-nitro derivatives are formed just as in quinoline, but the orienting effect of the N-oxide function becomes apparent above 40° and 4-nitroquinoline 1-oxide is produced as the main product with potassium nitrate and conc. sulfuric acid at 65~70°. Further, Okamoto[2] has described that a similar temperature effect exists also in nitration of 6-substituted quinoline 1-oxides and showed that the relative order of the 6-substituents and the N-oxide group with respect to the orienting effect in the reaction at 110~120° is as follows: CH_3O>Cl>Br~N-oxide>CH_3>NO_2.

During a synthetic study of 4-hydroxyaminoquinoline 1-oxide derivatives, it was required to prepare a somewhat large amount of 4-nitro-6-chloroquinoline 1-oxide (IIa). Although nitration of 6-chloroquinoline 1-oxide (Ia) gives IIa only in a poor yield of 16%, the other routes to IIa, *e.g.* that through 4.6-dinitroquinoline 1-oxide, seem to be more circuitous and less promising. These situation prompted us to re-examine the nitration of Ia.

Ochiai and Satake[3] have examined the nitration of quinaldine 1-oxide with potassium nitrate and sulfuric acid in some detail, and not only confirmed the existence of temperature effect but also found that 86% sulfuric acid gives a better effect on the yield of 4-nitro derivative than 96% acid. The latter observation seems very significant, but no comparable study is available. Therefore, we examined at first the effect of the concentration of sulfuric acid upon the nitration of Ia.

At the constant temperature of 110~120°, 6-chloroquinoline 1-oxide (Ia) was treated with 1.4 equivalents of potassium nitrate in sulfuric acid of various concentrations. Separation of nitro derivatives was achieved by chromatography on an alumina column with mixtures of carbon tetrachloride and chloroform. 4-Nitro derivative (IIa) was obtained from the first eluate, 5-nitro derivative (IIIa) from the second. The results obtained (Table I) clearly showed that the concentration of sulfuric acid has a very important effect on the reaction course; that is, the amount of IIa increased and that

*1 Part XXV. M. Hamana, K. Shimizu: Yakugaku Zasshi, **86**, 59 (1966).
*2 Katakasu, Fukuoka (浜名政和, 永吉 剛).
1) E. Ochiai, T. Okamoto: Yakugaku Zasshi, **70**, 384 (1950).
2) T. Okamoto: *Ibid.*, **71**, 727 (1951).
3) E. Ochiai, K. Satake: *Ibid.*, **71**, 1078 (1951).

of IIIa correspondingly decreased as the concentration of the acid became smaller to some extent, and 4-nitro derivative (IIa) was produced by use of 85% acid in the best yield of 62.4%, accompanied with a very small amount of IIIa (4.0%). This observation is similar to that obtained by Ochiai and Satake,[3] but the change of the relative order of activity between the 4- and 5-positions is much more remarkable.

It was subsequently examined the influence of the temperature on the nitration of Ia with potassium nitrate in 85% sulfuric acid. The temperature effect was slightly noticed also in this case, but the main product was always IIa, and above 60° the yield of IIa remained almost constant (Table I).

These results suggest that the concentration of sulfuric acid may be much more important rather than the reaction temperature in nitration of quinoline 1-oxide derivatives. In order to confirm this suggestion, similar studies were carried out with 6-bromo-, 6-methyl-, and 6-methoxy-quinoline 1-oxides and the results were compared with those reported by Okamoto.[2] Table I involves all results thus obtained and also some representatives of Okamoto's data[2] for reference.

When 6-bromoquinoline 1-oxide (Ib) was treated with potassium nitrate in 85% sulfuric acid, the activity of the 4-position was markedly enhanced and a nitro group was introduced predominantly into the 4-position; above 70° 4-nitro derivative (IIb) was obtained as a sole product and even at room temperature 5-nitro derivative (IIIb) was formed merely as a minor product, IIb remaining the main.

In nitration of 6-methylquinoline 1-oxide (Ic), it was also observed that 85 or particularly 80% acid was more effective than the conc. acid for the formation of 4-nitro derivative (IIc). Although the effect of the concentration of the acid was a little smaller and conversely the temperature effect was more noticeable in this case as compared with those of Ia and Ib, still the former effect was larger than the latter for the direction of the reaction.

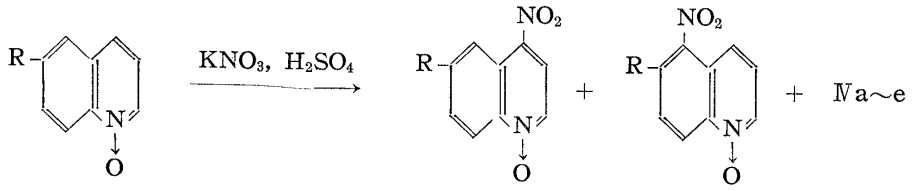
Nitration of 6-methoxyquinoline 1-oxide (Id) has been shown to result in the predominant formation of 5-nitro derivative (IIId), sometimes accompanied with 4,5-dinitro derivative (IVd), and no 4-nitro derivative (IId) has ever been detected.[2,4] In fact, IIId was produced always as the main product also in our experiments; nevertheless, we succeeded to isolate IId, although in a very poor yield (9.5%), in addition to IIId (40.1%) from the reaction with potassium nitrate in 70% sulfuric acid at 70~80°. This is particularly surprising in view of the strong electron-releasing effect of methoxyl group,*3 and very interesting for its theoretical implication.

4-Nitro-6-methoxyquinoline 1-oxide, IId, was crystallized from ethanol as yellow needles of m.p. 204~205° and its structure was established by the following sequence of reactions. Namely, IId was converted by heating with conc. hydrochloric acid on a water-bath into 4-chloro-5-methoxyquinoline 1-oxide,[7] followed by catalytic reduction with hydrogen and Raney nickel[8] to 4-chloro-6-methoxyquinoline, which

*3 Though no comparable study with 2-alkoxyquinoline 1-oxide is available, nitration of 2-methoxy-[5] and 2-ethoxy-pyridine 1-oxides[6] has been shown to result in overwhelming formation of the corresponding 4-nitro derivative, which fact indicates that the orienting effect of the N-oxide function is larger than that of alkoxyl group in the nitration of pyridine 1-oxide series. This fact, however, can not be applied directly to the case of Id, because of different position of methoxyl group in Id from that in 2-alkoxypyridine 1-oxide; in the former the substituent is located in the benzene ring, and on the other hand in the latter that is present in the same ring with N-oxide group.

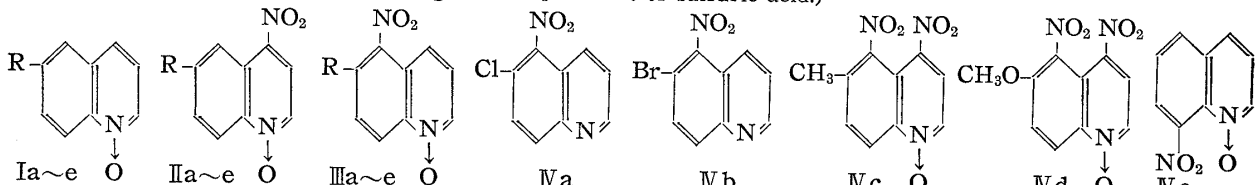
4) M. O. Ishikawa : *Ibid.*, **65A**, 102 (1945).
5) H. J. den Hertog, C. Jouwersma, A. A. van der Wal, E. C. C. Wellenbrands-Schogt : Rec. Trav. Chim., **68**, 433 (1949).
6) H. J. den Hertog, C. R. Kolder, W. P. Combé : *Ibid.*, **70**, 598 (1951).
7) T. Okamoto : Yakugaku Zasshi, **71**, 297 (1951).
8) E. Hayashi, H. Yamanaka, K. Shimizu : This Bulletin, **7**, 141, 146 (1959).

TABLE I. Nitration of 6-Substituted Quinoline 1-Oxides

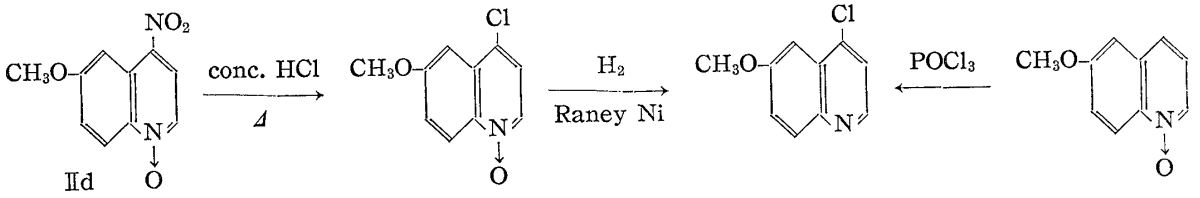


Exp. No.	Ia~e (R)	Concentration of H_2SO_4 (%)	Reaction temp. (°C)	Reaction time (hr.)	Yields of products (%) IIa~e	IIIa~e	Va~e
1	Cl	95	110~120	1	36.0	17.6	2.5
2	〃	90	110~120	1	52.0	9.6	—
3	〃	85	110~120	1	62.4	4.0	2.5
4	〃	80	110~120	1	51.2	—	—
	〃	(conc.	110~120	1	16.0	32.0	2.9[a]
	〃	(〃	ice-cooling room temp.	5 48	—	73.5	—)[a]
5	〃	85	80	1.5	64.8	5.6	—
6	〃	85	60	2	64.8	4.8	—
7	〃	85	20~ 25	14	23.7	35.7	—
8	Br	85	110~120	1	50.8	—	—
9	〃	85	70~ 80	1	68.3	—	—
10	〃	85[b]	20~ 25	14	43.3	14.2	—
	〃	(95	110~120	1	25	25	4.4[a]
	〃	(95	ice-cooling room temp.	5 24	—	66.5	—)[a]
11	CH_3	85	110~120	1	49.1	11.3	—
12	〃	85	70~ 80	1	37.4	34.3	—
13	〃	85[b]	20~ 25	14	—	68.7	—
14	〃	80	110~120	1	42.9	—	—
15	〃	80	70~ 80	1	49.5	—	—
16	〃	80[b]	20~ 25	14	7.9	28.7	—
	〃	(95	60~ 70	2	35.0	26.0	—)[a]
	〃	(95	ice-cooling room temp.	5 24	—	35.0	2.4)[a]
17	CH_3O	85	70~ 80	1	—	43.3	4.6
18	〃	80[c]	70~ 80	1	—	50.0	—
19	〃	75[b]	70~ 80	1	—	67.3	—
20	〃	75[b]	20~ 25	5 days	—	90.1	—
21	〃	70[b]	70~ 80	1	9.5	40.1	—
	〃	(95	110~120	1	—	53.0	—)[a]
	〃	(95	ice-cooling room temp.	5 24	—	47.5	6.6)[a]
22	H	90	room temp.	15	17.3	22.4	17.7
23	〃	85	〃	15	42.8	8.3	2.9
24	〃	80	〃	15	10.5	—	—
25	〃	80	〃	5 days	60.0	—	—

a) Okamoto's data.[2] *b*) 15 ml. of H_2SO_4 was used. *c*) 10 ml. of H_2SO_4 was used.
(One g. of Ia~e was treated with 1 g. of KNO_3 in 6 ml. of sulfuric acid.)



a : R=Cl b : R=Br c : $R=CH_3$ d : $R=CH_3O$ e : R=H



was proved to be identical with a sample prepared from 6-methoxyquinoline 1-oxide and phosphorus chloride[9] by the admixture and infrared examination.

Finally, nitration of quinoline 1-oxide (Ie) at room temperature was examined with potassium nitrate in sulfuric acid of various concentrations, and a similar effect of the concentration of sulfuric acid was shown to exist also in this case. The activity of the 4-position toward nitration appeared already in the reaction using 90% sulfuric acid, and when 85% acid was employed 4-nitro derivative (IIe) became the main product, 5- and 8-nitro derivatives being formed only as minor products; furthermore, the use of 80% acid resulted in overwhelming production of IIe.

As a consequence of the experiments described above it may be now concluded that the most important factor influencing the direction of nitration of quinoline 1-oxide derivatives is not the reaction temperature but the concentration of sulfuric acid. Accordingly, nitration of quinoline 1-oxide derivatives must be re-examined by varying the concentration of sulfuric acid. Such studies may possibly open a route for the preparation of some 4-nitroquinoline 1-oxide derivatives not obtainable hitherto or improve the yields of those available only in poor yields. The correlation between the concentration of sulfuric acid and the directive effect of N-oxide function in nitration of quinoline 1-oxides is not yet clear.

Experimental*4

General Procedure of Nitration——The concentration of sulfuric acid, the reaction temperature and the reaction time are given in Table I. To a solution of Ia~e (1 g.) dissolved in H_2SO_4 (6 ml.) was added KNO_3 (1 g.) at the constant temperature, and the whole was kept at the same temperature for the given period. The reaction mixture was poured onto ice-water (ca. 100~150 ml.) and extracted with $CHCl_3$. The residual acidic solution was made alkaline with Na_2CO_3 and again extracted with $CHCl_3$. Both extracts were dried over anhyd. Na_2SO_4 and evaporated on a water-bath to afford fraction (A) and (B), respectively. Fraction (A) and (B) were separately submitted to further treatment. Products obtained, except 4-nitro-6-methoxyquinoline 1-oxide (IId), were identified by comparison with samples prepared by Okamoto's procedure.[2]

Nitration of 6-Chloroquinoline 1-Oxide (Ia) (Exp. 1~7)——Fraction (A) was dissolved in a mixture of CCl_4-$CHCl_3$ (3:1) and chromatographed on an alumina column using combinations of CCl_4 and $CHCl_3$ (3:1, 2:1, 1:1) for elution to separate two or three fractions. The first was 5-nitro-6-chloroquinoline (IVa),[2] pale yellow needles, m.p. 127~128° (*n*-hexane), (Exp. 1 and 3); the second was 4-nitro-6-chloroquinoline 1-oxide (IIa),[2] yellow needles, m.p. 193° (acetone); the third was 5-nitro-6-chloroquinoline 1-oxide (IIIa),[2,10] yellow needles, m.p. 213° (acetone).

Nitration of 6-Bromoquinoline 1-Oxide (Ib) (Exp. 8~10)——Fraction (A) was treated similarly as described above to afford 4-nitro-6-bromoquinoline 1-oxide (IIb),[2] yellow needles, m.p. 200~202° (acetone) and 5-nitro-6-bromoquinoline 1-oxide (IIIb),[2,10] yellow prisms, m.p. 215° (acetone). Fraction (B) gave no definite product.

Nitration of 6-Methylquinoline 1-Oxide (Ic) (Exp. 11~16)——Similarly, 4-nitro-6-methylquinoline 1-oxide (IIc),[2] yellow needles, m.p. 183° (acetone), and 5-nitro-6-methylquinoline 1-oxide (IIIc),[2] yellow needles, m.p. 184~185° (acetone) were obtained from fraction (A). From fraction (B) Ic was recovered (4.1% in Exp. 13; 5.1% in Exp. 14; 36.8% in Exp. 16).

Nitration of 6-Methoxyquinoline 1-Oxide (Id) (Exp. 17~21)——1) (Exp. 21): One gram of KNO_3 was added to a solution of 6-methoxyquinoline 1-oxide (1 g.) in 70% H_2SO_4 (15 ml.) warmed at 70~80° on

*4 All melting points were uncorrected.

9) G. B. Bachman, D. E. Cooper: J. Org. Chem., **9**, 302 (1944).
10) T. Naito: Yakugaku Zasshi, **68**, 209 (1948).

a water-bath. The whole was kept for 1 hr. at the same temperature, and then poured onto ice-water (ca. 150 ml.) and extracted with $CHCl_3$, which on evaporation gave fraction (A). The residual acidic solution from $CHCl_3$-extraction was made alkaline with Na_2CO_3 and again extracted with $CHCl_3$, which on evaporation gave fraction (B). Fraction (A) was dissolved in CCl_4-$CHCl_3$ (3:1) and chromatographed on an alumina column using mixtures of CCl_4 and $CHCl_3$ (3:1, 2:1, 1:1) to afford successively 4-nitro-6-methoxyquinoline 1-oxide (IId) and 5-nitro-6-methoxyquinoline 1-oxide (IIId).[2,11] IId was recrystallized from EtOH to yellow needles of m.p. 204~205°. *Anal.* Calcd. for $C_{10}H_8O_4N_2$: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.50; H, 3.33; N, 12.53. IIId was recrystallized from acetone to yellow needles of m.p. 182~184°. Fraction (B) gave a small amount of Id.

2) 4-Chloro-6-methoxyquinoline from 4-nitro-6-methoxyquinoline 1-oxide (IId): A mixture of IId (0.1 g.) and conc. HCl (1 ml.) was heated for 1 hr. on a water-bath, and then concentrated *in vacuo*. The residue was made alkaline with an Na_2CO_3 solution and extracted with $CHCl_3$. The extract was dried over Na_2SO_4, followed by evaporation to give white crystals, which was recrystallized from acetone to yield 0.057 g. of 4-chloro-6-methoxyquinoline 1-oxide, m.p. 172~175°. The latter (0.05 g.) was reduced in MeOH over Raney nickel.[8] After absorption of 1 mole of H_2, the reaction mixture was worked up in the usual way to give ca. 0.015 g. of 4-chloro-6-methoxyquinoline, colorless needles, m.p. 71~72° (petr. ether). This was identified with an authentic sample[9] prepared from Id and $POCl_3$ by admixture and IR examination.

Nitration of Quinoline 1-Oxide (Ie) (Exp.22~25)——Experiments were carried out and processed as described by Ochiai and Okamoto.[1]

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Summary

Nitrations of 6-chloro-, 6-bromo-, 6-methyl-, 6-methoxy-quinoline and quinoline 1-oxides with potassium nitrate in sulfuric acid were re-examined by varying the concentration of the acid and the reaction temperatures. The orientation of reaction was found to be more markedly dependent upon the concentration of sulfuric acid rather than the reaction temperature; generally, the activity of the 4-position toward nitration became most remarkable by use of 75~85% sulfuric acid.

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11) M. O. Ishikawa: Yakugaku Zasshi, **65**(3), 5 (1945).