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102. Yutaka Kawazoe and Masako Ohnishi : Studies on Hydrogen Exchange. V.*1 Electrophilic Deuteration of Quinoline and Its 1-Oxide.

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The reactivity toward acid-catalyzed deuterium substitution was compared with each other position of quinoline and its 1-oxide. Discussion was made in connection with other electrophilic reactivities in nitration and so on. Many selectively deuterated derivatives were synthesized on the course of the present study.

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Acid-catalyzed aromatic hydrogen exchange can be considered to involve an electrophilic attack at the initial stage of the reactions, as nitration, sulfonation, halogenation and other electrophilic reactions.[1~7] Studies on hydrogen exchange, which can be done by using deuterated or tritiated reactants and/or reaction medium, have a great advantage for fundamental studies on the reactivities of aromatic compounds toward electrophiles, because proton or hydroxonium cation (H_3O^+) is a simplest electrophile in its spatial size and its electronic character. Thus, it is allowed us to neglect not only steric effect which may act an important role in other electrophilic reactions, but also electronic effect of the deuterium incorporated on a subsequent attack by another deuterium cation.

As one of our serial studies on hydrogen exchange of a wide variety of organic compounds in the presence of acidic or basic catalysts, discussions will be made, in this paper, on the acid-catalyzed deuterium substitutions of quinoline 1-oxide derivatives in connection with the electronic effect of 1-oxide group. The results could be conveniently applied to syntheses of the selectively deuterated (probably tritiated) compounds. Deuterated compounds thus synthesized were identified by NMR spectroscopy.

Results

Quinoline and its 1-oxide were deuterated by active deuterium cations in deuterated sulfuric acid solutions. Thus, the sample examined was dissolved in D_2SO_4-D_2O mixture, acid-concentration ranging from 45% to 96.5%.*3 The prepared solution was sealed in an tube and heated at an appropriate reaction temperature in an oil bath which was thermo-controlled within ± one degree. The sample concentrations were about 5%. The positions deuterated were determined by the NMR spectra of the sample recovered from the reaction mixture. The details of the procedures for spectral analyses will be described in a subsequent paragraph of this paper. The results are summerized in Table I, II and III. The deuteration reactions were carried

*1 Part IV : This Bulletin, **15**, 391 (1967).
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*3 96.5% Acid was commercially available "concentrated sulfuric acid-d_2."

1) F.A. Long, M.A. Paul : Chem. Rev., **57**, 935 (1957).
2) A.J. Kresge, Y. Chiang : J. Am. Chem. Soc., **83**, 2877 (1961).
3) V. Gold, R.M. Lambert, D.P.N. Satchell : J. Chem. Soc., **1960**, 2461.
4) J. Schulze, F.A. Long : J. Am. Chem. Soc., **86**, 322, 331 (1964).
5) F.A. Long, J. Schulze : *Ibid.*, **86**, 327 (1964).
6) A.R. Katritzky, B.J. Ridgewell : J. Chem. Soc., **1963**, 3753.
7) A.R. Katritzky, B.J. Ridgewell, A.M. White : Chem. & Ind., **1964**, 1576.

out in 45, 70, 80, 90 and 96.5% sulfuric acid-d_2 solutions and at three different reaction temperatures, 150°, 200° and 250° for each examined sample. Table I shows the results from the treatment at 150° for 25 hr. The sign "−" means "no deuterium exchange" and "+" means "exchange started." The sign "卌" means "complete replacement by deuterium." Table II and III show the results from the treatments at 200° and 250° for 8 hr., respectively.

Table I. Deuteration of Quinoline and Its 1-Oxide at 150° for 25 hr. in D_2SO_4–D_2O Mixture at Various Acid-concentrations[a]

Position / Acid-concentration (%)	Quinoline							Quinoline 1-oxide						
	2	3	4	5	6	7	8	2	3	4	5	6	7	8
45	−	−	−	−	−	−	−	−	−	−	−	−	−	−
70	−	−	−	(±)	(±)	−	卌	−	−	−	(±)	(±)	−	卌
80	−	−	−	(±)	(±)	−	卌	−	−	−	(±)	(±)	−	卌
90	−	−	−	+	+	−	卌	−	−	−	+	+	−	卌
96.5	−	−	−	卌	卌	−	卌	−	−	−	卌	卌	−	卌

a) Acid-concentrations are shown by w/w %. The sign 卌 means that the deuteration was completed.

Table II. Deuteration of Quinoline and Its 1-Oxide at 200° for 8 hr. in D_2SO_4–D_2O Mixture at Various Acid-concentrations[a]

Position / Acid-concentration (%)	Quinoline							Quinoline 1-oxide						
	2	3	4	5	6	7	8	2	3	4	5	6	7	8
45	−	−	−	−	−	−	−	−	−	−	−	−	−	−
70	−	(±)	−	卌	卌	(±)	卌	−	(±)	−	卌	卌	(±)	卌
80	−	(±)	−	卌	卌	(±)	卌	−	(±)	−	卌	卌	(±)	卌
90	−	(±)	−	卌	卌	(±)	卌	−	(±)	−	卌	卌	(±)	卌
96.5[b]	/	/	/	/	/	/	/	−	(±)	−	卌	卌	+	卌

a) Acid-concentrations are shown by w/w %. The sign 卌 means that the deuteration was completed.
b) Quinoline was sulfonated under this reaction condition.

Table III. Deuteration of Quinoline and Its 1-Oxide at 250° for 8 hr. in D_2SO_4–D_2O Mixture at Various Acid-concentrations[a]

Position / Acid-concentration (%)	Quinoline							Quinoline 1-oxide						
	2	3	4	5	6	7	8	2	3	4	5	6	7	8
45	−	−	−	−	−	−	−	−	−	−	−	−	−	−
70	−	卄	−	卌	卌	卌	卌	−	+	−	卌	卌	卌	卌
80	−	卄	−	卌	卌	卌	卌	−	+	−	卌	卌	卌	卌
90	−	卌	−	卌	卌	卌	卌	−	卄	−	卌	卌	卌	卌
96.5[b]	/	/	/	/	/	/	/	/	/	/	/	/	/	/

a) Acid-concentrations are shown by w/w %. The sign 卌 means that the deuteration was completed.
b) These compounds were sulfonated under this reaction condition.

From these data some conclusions could be derived, as follows :

i) There exists no serious difference in acid-catalysed deuterium substitution reactivity between quinoline and its 1-oxide. Thus, 1-oxide group causes no effect at all on the reactivities of any position on the benzene moiety and only makes position-3 on the pyridine moiety slightly inactive compared with the same position of quinoline free base.

ii) Deuteration proceeds more easily in higher acid-concentration media and at higher reaction temperature.

iii) Positions-2 and -4 are completely inactive toward acid-catalyzed deuteration. This is interesting in contrast to high reactivity of the same positions toward electrophilic nitration reaction.

iv) The relative reactivities in either quinoline or the 1-oxide decreased in the following order of positions :

$$8>5,\ 6>7,\ 3>2,\ 4$$

Now, although it became valid from the above data that 45% acid-concentration was not enough for acid-catalyzed deuteration of these compounds, we treated these compounds with more diluted acid medium and, moreover, with neutral and alkaline media, realizing that 1-oxide group might exert its electron donating resonance effect on the π-electron system in these media to bring about a serious effect on the deuteration reactivity. From our study already reported on the deuterium exchange of aromatic hydrogens of pyridine and its 1-oxide,[8] it could be expected that position-2 of quinoline derivatives must be reactive toward base-catalyzed deuterium exchange. The results are summarized in Table Ⅳ. Only position-2 took place for deuterium

Table Ⅳ. Deuteration of the Position-2 of Quinoline and Its 1-Oxide in Alkaline and Acidic Aqueous Solutions at Various Reaction Conditions

	Solvent / Condition	Free Base		Bisulfate				
		1% NaOD	D_2O	D_2O	5% D_2SO_4	10% D_2SO_4	20% D_2SO_4	45% D_2SO_4
Quinoline	200°, 3 hr.	/[a]	/	—	—	—	—	—
	250°, 3 hr.	/	/	##	—	—	—	—
Quinoline 1-oxide	100°, 1 hr.	##	—	—	—	—	—	—
	200°, 3 hr.	##	##	##	—	—	—	—
	250°, 3 hr.	##[b]	##	##	##	##	+	—

a) Quinoline free base is not soluble in these media but it can be expected from the data of pyridine and its 1-oxide that proton-2 might be replaced by deuterium under these conditions.
b) Position-3 and -4 were also deuterated in part under this condition.

exchange in these media except for position-3 and -4 in more strongly alkaline medium and at high reaction temperature above 200°. The results indicate that the 1-oxide was much more reactive than quinoline under these conditions and that the deuteration mechanism in these media may be not the acid-catalyzed but the base-catalyzed hydrogen abstruction process.*4 Benzene ring hydrogens did not undergo deuterium exchange at all in alkaline media, even in 5% NaOD solution at above 250°.

Hereupon, it may be worth to summarize these acid- and base-catalyzed deuteration reactions from the standpoint of syntheses of deuterium-(or, maybe, tritium-)labelled

*4 The details of the base-catalysed hydrogen exchange of these heteroaromatic bases are now under investigation in connection with the isotope effect of these reactions.

8) Y. Kawazoe, M. Ohnishi, Y. Yoshioka : This Bulletin, **12**, 1384 (1964).

compounds. Chart 1 includes some examples for stepwise deuterations of quinoline and the 1-oxide.

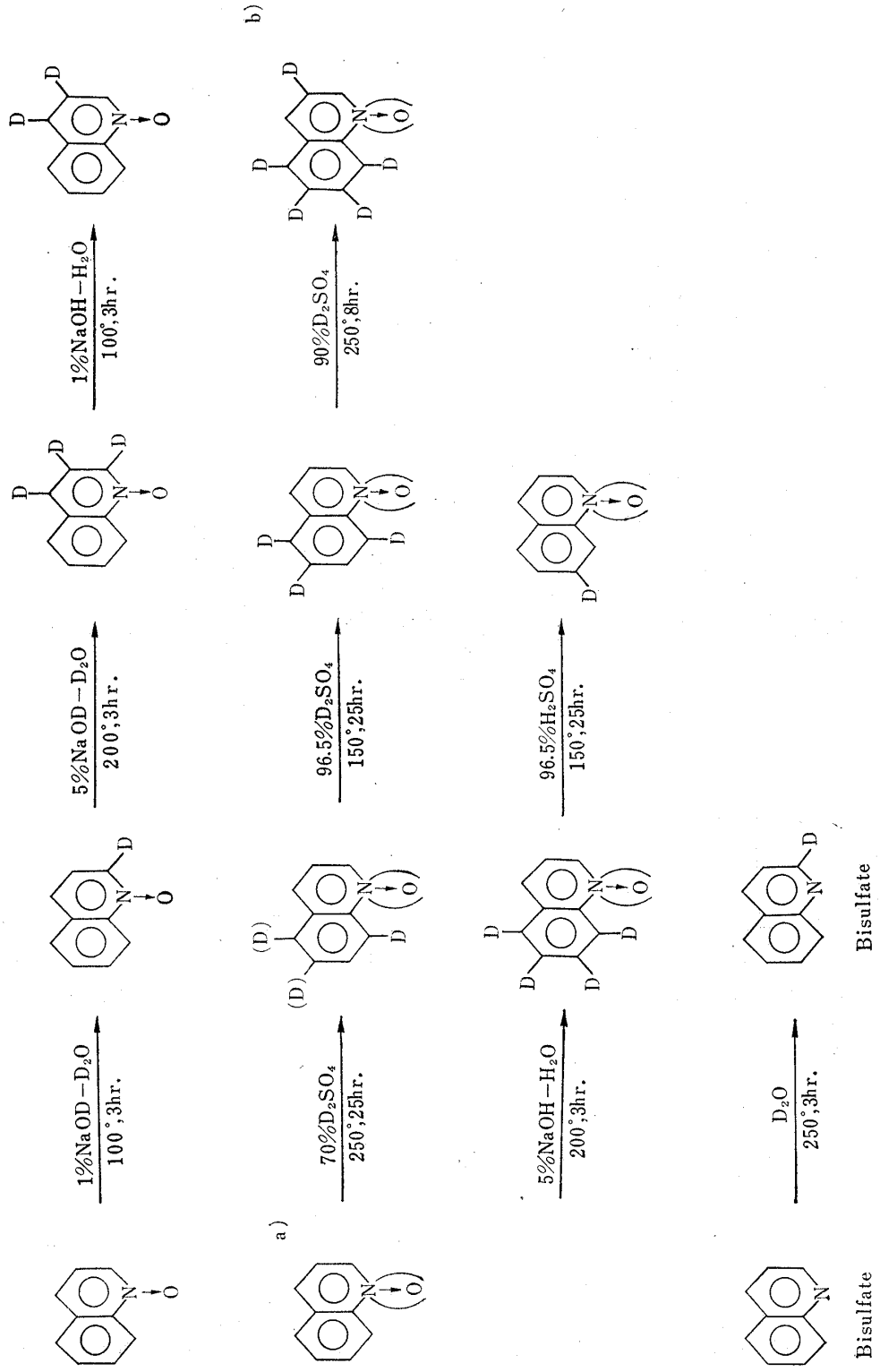


Chart 1.

a) Either quinoline or its 1-oxide undergoes deuteration reaction under the reaction condition indicated to give the corresponding deuterated derivatives.
b) Position-3 of the 1-oxide was incompletely deuterated in some experimental runs.

Spectral Analyses of Deuterated Quinoline and Its 1-Oxide

NMR spectra of quinoline[9] and its 1-oxide[10,11] were already analyzed by several authors. In Fig. 1 are reproduced spectra of deuterated derivatives of quinoline and

9) P. J. Black, M. L. Heffernan : Australian J. Chem., **17**, 558 (1964).
10) K. Tori, M. Ogata, H. Kano : This Bulletin, **11**, 681 (1963).
11) Y. Kawazoe, M. Ohnishi, N. Kataoka : *Ibid.*, **13**, 396 (1965).

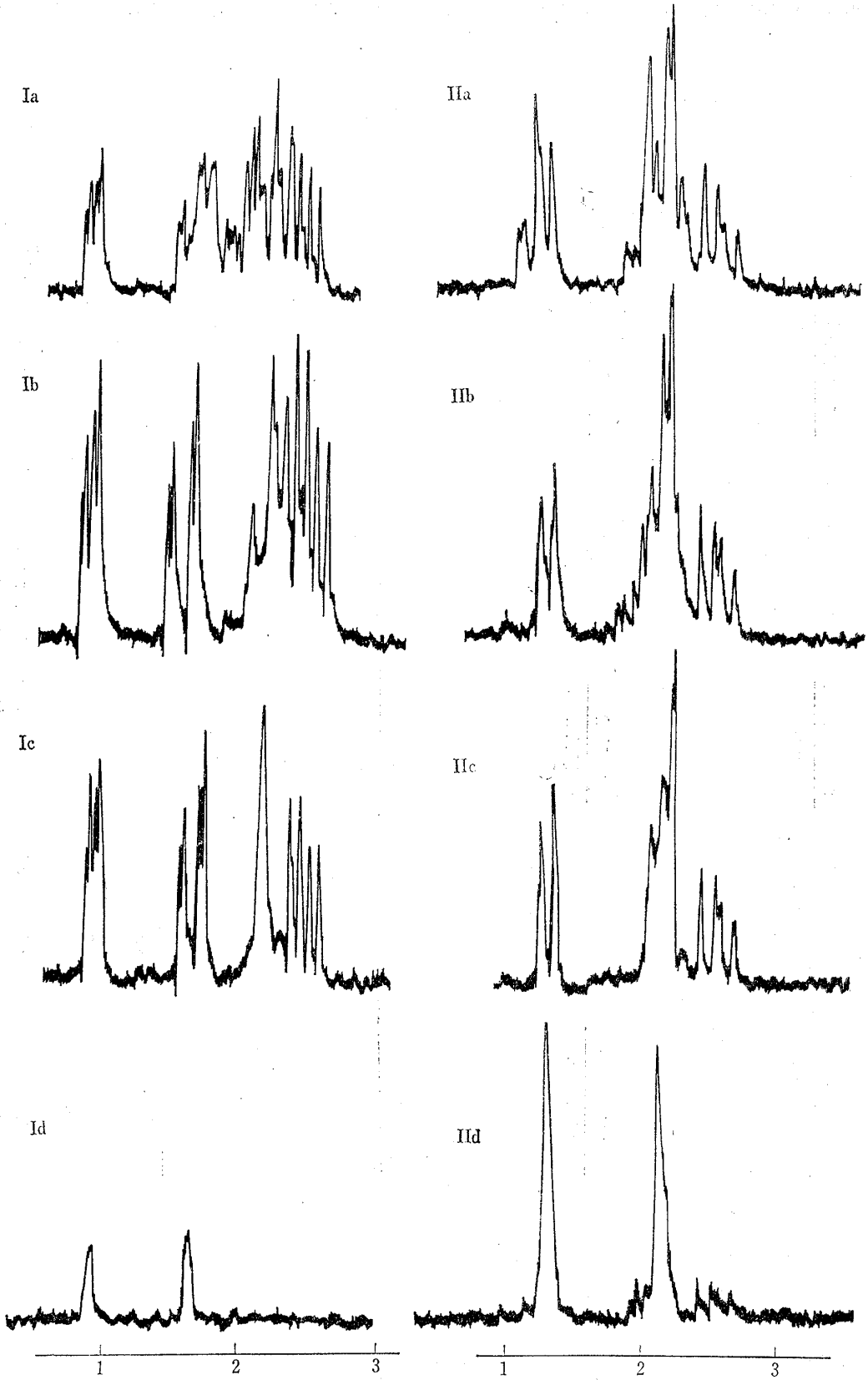


Fig. 1. The NMR Spectra of Quinolines and Their 1-Oxides measured in Dioxan, Chemical Shifts being presented by τ-Values

Ia: quinoline; Ib: 8-deuterated quinoline;
Ic: 5,6,8-trideuterated quinoline; Id: 3,5,6,7,8-pentadeuterated quinoline;
IIa: quinoline 1-oxide; IIb: 8-deuterated quinoline 1-oxide;
IIc: 5,6,8-trideuterated quinoline 1-oxide; IId: 3,5,6,7,8-pentadeuterated quinoline 1-oxide.

its 1-oxide measured in dioxan. The signals due to protons-2, -3, -4 and -8 were isolated from others and easily assignable in the spectrum measured in dioxan with a help of inspection of signal pattern changes. In order to obtain informations of deuteration at position-5, -6 and -7 of the 1-oxide, the product from the reaction mixture was led to the corresponding 4-nitroquinoline 1-oxide.*5 The spectra of some of them are reproduced in Fig. 2. Proton-5 and -8 resonate at about 0.8 to 0.9 p.p.m. lower field than proton-6 and -7. In order to establish the structure of 5,6,8-trideutero derivative, excluding the possibility of 5,7,8-trideutero isomer, it was led to 5-nitroquinoline 1-oxide, where proton-6 must be more deshielded by an adjacent nitro group than proton-7. The spectrum reproduced in Fig. 3b indicates that a remained singlet other than proton-3 and -4 could be assigned to the second highest triplet (just below the highest quartet due to proton-3) of Fig. 3a. Since proton-6 could not resonate at higher field than proton-7, this remained singlet can be assigned to proton-7.

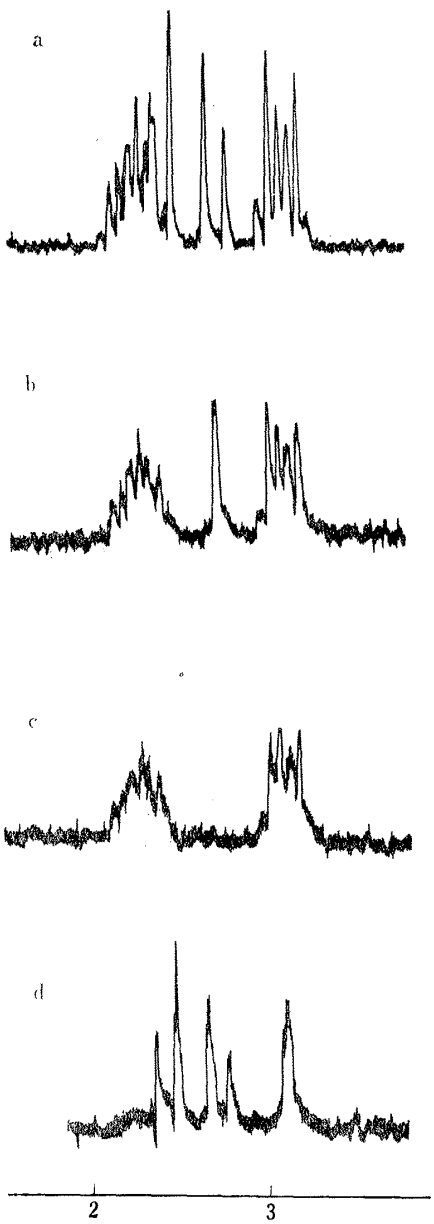


Fig. 2. The NMR Spectra of 4-Nitroquinoline 1-Oxide measured in Dioxan, Chemical Shifts being presented by τ-Values

a : 4-nitroquinoline 1-oxide;
b : 2-deuterated;
c : 2,3-dideuterated;
d : 5,6,8-trideuterated derivative.

Discussion

The organic electron theory predicts that quinoline is deactivated toward electrophilic attacks due to the strongly electronegative nature of the nitrogen atom compared with naphthalene molecules, whereas its 1-oxide is expected to undergo more easily electrophilic substitutions due to the electron donating resonance effect of 1-oxide group, as illustrated in Chart 2. However, in strongly acidic medium, where electrophilic reactions are usually carried out, the 1-oxide may take part in the reactions as its conjugate acid form like structure II in Chart 2. With regard to the 1-oxide, nitration, one of representative electrophilic substitution reaction, occurs at position-4 but many other electrophilic reactions proceed at position -3 or on the benzene moiety. Now, as far as the acid catalyzed-deuteration is concerned, it became evident from the present work*6 that the 1-oxide underwent it through the conjugate acid form. Thus, the result that the position-8 was most reactive could be understood by its high π-electron density and its naphthoidal reactivity. Second highest reactivity at position-5 and-6 can be explained by the facts that position-5 is α position of naphthoid system and that position-6 is less affected by the electronegative nitrogen function. The fact that position-7 strongly resisted deuterium replacement more than position-6 is an additional evidence for the fact that the N-O function interacts with

*5 It was made sure that no hydrogen exchange occurred during nitration procedure of quinoline 1-oxide.
*6 Katritzky, *et al.* derived the same conclusion from the kinetical works using pyridine 1-oxide.[7]

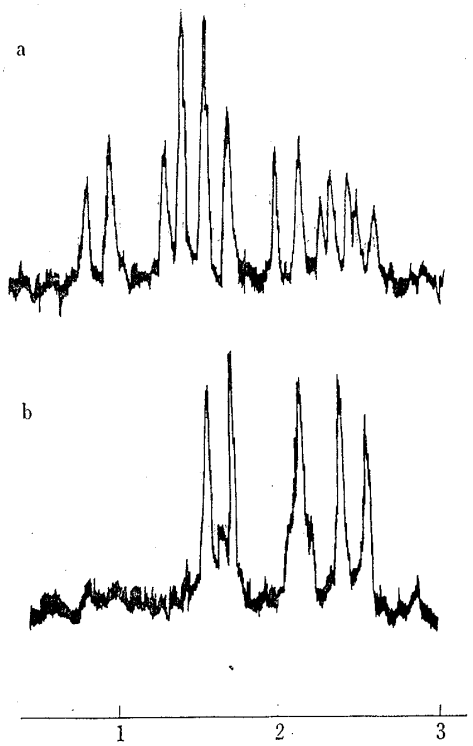
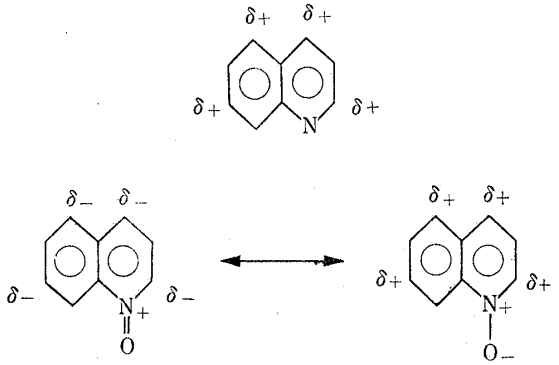


Fig. 3. The NMR Spectra of 5-Nitroquinoline 1-Oxide measured in $CDCl_3$, Chemical Shifts being presented by τ-Values

a : 5-nitroquinoline 1-oxide;
b : 6,8-dideuterated derivative.



I II

Chart 2.

π-electron system so as to withdraw electrons mesomerically from π-system. The discrepancy between deuteration and nitration may be probably due to the difference in the equilibrium constants of the following equation (Chart 3), that is, the difference in the affinity of the electrophiles to the substrate molecule to form the salts (II) or π-complexes (III).

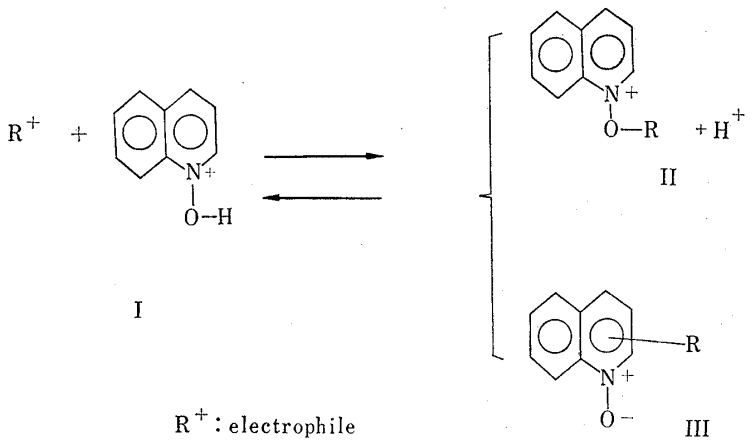


Chart 3.

Experimental

Compounds and Reagents

Quinoline and its 1-oxide were prepared by the authentic method and D_2SO_4 and D_2O were purchased from Showa Denko Co., Ltd., their isotope contents being 98 D-atom %.

NMR Spectra

The spectra were measured with a Japan Electron Optics Lab. Co.'s JNM-3H-60 spectrometer operating at 60 Mc.p.s.

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