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155. Yutaka Kawazoe, Masako Ohnishi, and Yuko Yoshioka : Studies on Hydrogen Exchange. VI.[*1] The Base-catalyzed Hydrogen Exchange of α-Hydrogens in Alkyl Groups substituted on Some Nitrogen-containing Heteroaromatic Rings.

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Hydrogen-deuterium exchange of α-hydrogens of the side-chain alkyl groups substituted in pyridine, quinoline, isoquinoline, their N-oxides and N-alkyl halides were carried out by heating their D_2O solutions containing sodium hydroxide or sodium carbonate. Exchange reactivities of these hydrogens were discussed in term of the electronic effect of the nitrogen function in these heteroaromatic rings.

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α-Hydrogens of alkyl grougs substituted in an electron-deficient aromatic rings can be expected to undergo a base-catalyzed hydrogen exchange reaction more easily than methyl hydrogens in toluene. This type of hydrogen exchange can be considered to be initiated by a nucleophilic attack of a base ion or molecule on hydrogen, resulting in heterolytic (protolytic) cleavage of C-H bond to yield a carbanion and a proton, just as in the dissociation process of the conventional acid molecules, as shown in Chart 1.[*3,1)] Since the rate-determining step might be regarded as formation of the carbanion, the ease of the hydrogen exchange must directly depend on the stability of the carbanion as the reaction intermediate. It may, therefore, be expected that the relative exchange reactivity must reflect, in principle, the hyperconjugative electron-releasing contribution of the alkyl group concerned. This may correspond to the π-bond order in the molecular orbital expression between the α-carbon atom bearing the hydrogen concerned and an aromatic carbon bonded to the alkyl group. As one of our serial studies on the reactivities of N-containing heteroaromatic compounds, this paper describes hydrogen-deuterium exchange of α-hydrogens of the side chain alkyl groups substituted in pyridine, quinoline, isoquinoline, their N-oxides, and N-alkyl halides, discussing in connection with the electronic effect of the nitrogen function in these heteroaromatic nuclei.

$$\text{R-COOH} \xrightarrow{\text{base}} \text{R-COO}^- + \text{H}^+$$

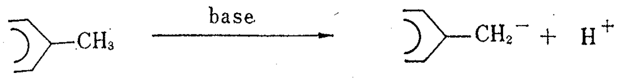

Chart 1.

Results and Discussion

Hydrogen-deuterium exchanges were carried out by heating the neutral or alkaline deuterium oxide solutions (with 1% NaOD or 1% Na_2CO_3) of the compounds examined[*4]

[*1] Part V : This Bulletin, **15**, 826 (1967).

[*2] Tsukiji, Chuo-ku, Tokyo (川添 豊, 大西柾子, 吉岡佑子).

[*3] The fact that the rate of exchange is limited by the rupture of the C-H bond was suggested by kinetic studies on hydrogen exchange of tritium and deuterium in the methylene group of fluorene in ammonia, establishing the isotope effect to be 1.9 (K_D/K_T).[2)]

[*4] The sample concentrations were about 30 mg. in 0.5 ml. of the solvent.

1) J.E. Hofmann, R.J. Muller, A. Schriesheim : J. Am. Chem. Soc., **85**, 3000, 3002 (1963), and literatures cited therein.

2) F.S. Yakushin, Y.G. Dubinskii, E.A. Yakovleva, A.I. Shatenshtein : Zh. Fiz. Khim., **33**, 2820 (1959) (Chem. Abstr., **55**, 12003).

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to an appropriate temperature for an appropriate period. The relative reaction rates were determined by the quantitative analysis of the areal intensity of NMR signals due to the alkyl hydrogens concerned. In order to trace the time-dependent intensity-decrease of the signal, the reactions were conveniently carried out in a sealed NMR sample tube, the spectrum being measured at certain time intervals and the signal intensity was then integrated. The results are summarized in Table I for pyridine derivatives, in Table II for quinoline derivatives, and in Table III for isoquinoline derivatives. Comparison in the exchange reactivity, *i.e.*, the acidity of the hydrogens concerned was made with monomethyl derivatives; 2-, 3-, and 4-methylpyridines, 2-, 3-, 4-, 6-, 7-, and 8-monomethylquinolines, and 1- and 3-monomethylisoquinolines, and their N-oxides and N-methiodides.

TABLE I. Deuterium Exchange of Methyl Hydrogens of Monomethylpyridines and their N-Oxides and N-Methiodides in 1% NaOD-D_2O Solutions

Compound	Started[a]	Completed[b]
2-Me-pyridine	180°, 1 hr.	180°, 3 hr.
3-Me-pyridine	>200°	[c]
4-Me-pyridine	130°, 2 hr.	180°, 1 hr.
2-Me-pyridine N-O	100°, 1 hr.	100°, 3 hr.
3-Me-pyridine N-O	150°, 1 hr.	180°, 1 hr.
4-Me-pyridine N-O	100°, 1 hr.	100°, 3 hr.
2-Me-pyridine N^+-CH_3	22°, 0 hr.	22°, <1 hr.
3-Me-pyridine N^+-CH_3	100°, 1 hr.	150°, 1 hr.
4-Me-pyridine N^+-CH_3	22°, 0 hr.	22°, 1 day

a) The conditions under which hydrogen exchange was detected to start.
b) The conditions under which hydrogen exchange was completed.
c) The exchange did not complete at 200° for 3 hr.

TABLE II. Deuterium Exchange of Methyl Hydrogens of Monomethylquinoline and their N-Oxides and N-Methiodides

Compound	Solvent	Started[a]	Completed[b]
2-Me-quinoline	1% NaOD D_2O-dioxan[c]	100°, 1 hr.	180°, 3 hr.
4-Me-quinoline	1% NaOD D_2O-dioxan[c]	100°, 1 hr.	150°, 8 hr.
6-Me-quinoline	1% NaOD D_2O-dioxan[c]	not started at 200° for 8 hr.	
7-Me-quinoline	1% NaOD D_2O-dioxan[c]	not started at 200° for 8 hr.	
8-Me-quinoline	1% NaOD D_2O-dioxan[c]	not started at 200° for 8 hr.	
2-Me-quinoline N-O	1% NaOD D_2O-dioxan[c]	22°, 1 day	50°, 1 hr.
3-Me-quinoline N-O	1% NaOD D_2O-dioxan[c]	180°, 1 hr.	>200°
4-Me-quinoline N-O	1% NaOD D_2O-dioxan[c]	50°, 1 hr.	50°, 8 hr.
6-Me-quinoline N-O	1% NaOD D_2O-dioxan[c]	200°, 1 hr.	>200°
7-Me-quinoline N-O	1% NaOD D_2O-dioxan[c]	130°, 1 hr.	>200°
2-Me-quinoline N^+-CH_3	D_2O	100°, 1 hr.	100°, 8 hr.
4-Me-quinoline N^+-CH_3	D_2O	130°, 1 hr.	130°, 8 hr.
6-Me-quinoline N^+-CH_3	D_2O	not started at 200° for 8 hr.	
7-Me-quinoline N^+-CH_3	D_2O	not started at 200° for 8 hr.	
8-Me-quinoline N^+-CH_3	D_2O	accompanied by decomposition.	
2-Me-quinoline N-O	D_2O	not started at 100° for 8 hr.	
4-Me-quinoline N-O	D_2O	not started at 180° for 1 hr.	

a) The conditions under which hydrogen exchange was detected to start.
b) The conditions under which hydrogen exchange was completed.
c) One to one mixture (v/v).

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Table Ⅲ. Deuterium Exchange of Methyl Hydrogens of Monomethylisoquinolines and their N-Oxides and N-Methiodides

Compound	Solvent	Started[a]	Completed[b]
1-Me-isoquinoline	1% NaOD D_2O-dioxan[c]	100°, 1 hr.	>200°
1-Me-isoquinoline N-O	1% NaOD D_2O-dioxan[c]	22°, 0 hr.	22°, 1 day
3-Me-isoquinoline N-O	1% NaOD D_2O-dioxan[c]	50°, 1 hr.	180°, 1 hr.
1-Me-isoquinoline N^+-CH_3	D_2O	22°, 1 day	100°, 1 hr.
3-Me-isoquinoline N^+-CH_3	D_2O	150°, 1 hr.	>200°
1-Me-isoquinoline N-O	D_2O	100°, 3 hr.	200°, 1 hr.
3-Me-isoquinoline N-O	D_2O	not started at 200° for 3 hr.	

a) The conditions under which hydrogen exchange was detected to start.
b) The conditions under which hydrogen exchange was completed.
c) One to one mixture (v/v).

It is evident from these data that N-quaternization or N-oxidation increased to a great extent the acidity of α-hydrogens of a substituent alkyl group, especially those on 2- and 4-positions of pyridine and quinoline, and on 1-position of isoquinoline, to result in promoting the hydrogen exchange. This might be a strong evidence for a predominant contribution of structures Ia, Ⅱa and Ⅲa in the resonance hybrids of these molecules as shown in Chart 2. A further evidence for this was provided by comparing the reactivity of 7-methylquinoline 1-oxide with that of 6-methyl derivative. Thus, the experimental result that 7-methyl hydrogens were more readily replaced by deuterium than 6-methyl ones, as shown in Table Ⅳ, strongly suggests a predominant

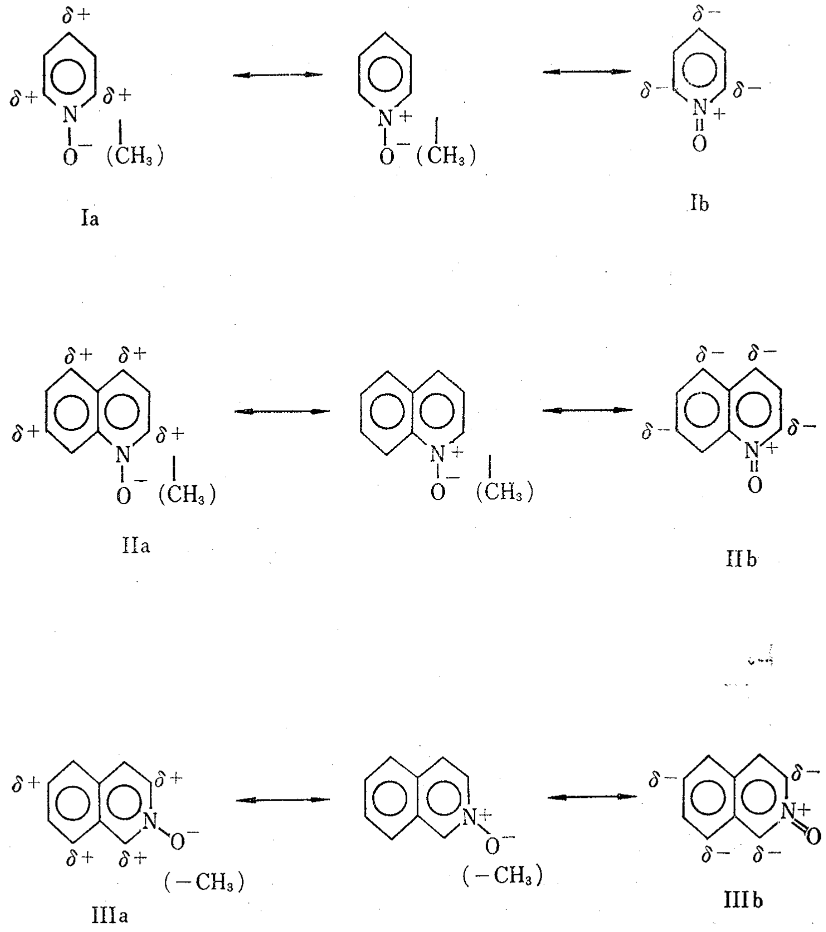

Chart 2.

Table IV. Relative Rate of Deuterium Exchange of 6- and 7-Methylquinoline N-Oxides in 1% NaOD-D_2O Solutions[a]

Compound	Condition		
	130°, 1 hr.	180°, 8 hr.	200°, 8 hr.
6-Me-quinoline N-O	–	–	++
7-Me-quinoline N-O	+	++++	++++

a) The signs, +, ++, +++, and ++++, mean that deuteration proceeded in about 25, 50, 75, and more than 90% yield, respectively. The sign of – means no deuteration detected.

contribution of structure IIa over that of IIb. In comparing the exchange reactivity of methyl hydrogens of N-oxides with those of quaternary salts, the hydrogen of the former, where the nitrogen is also cationic as well, readily underwent exchange, but not so much as that of the quaternary salts. This must be due to partial neutralization of cationic charge of the aromatic ring by the electron-donating resonance effect of the N-oxide group, indicating the presence of a certain contribution of the structures Ib, IIb, and IIIb to the hybrid of the N-oxide molecules as shown in Chart 2.

Another interesting feature of the exchange reactivity is that, with regard to pyridine and quinoline derivatives, 4-methyl hydrogens are more reactive than 2-methyl ones in free bases, whereas the reverse order was demonstrated in the exchange rates of N-oxides and N-methiodides, as shown in Table V. It can be expected that there exists a parallelism between this order of the exchange reactivity and relative magnitude of the bond order, $P_{CH_3-C_{arom.}}$ Therefore, such basic parameters as coulomb integrals and resonance integrals, with which the bond orders are calculated, should be evaluated so as to be consistent with the order of the exchange reactivity experimentally obtained. This might be a great help in checking and improving the reliability of the parameters already chosen from other considerations, *i.e.*, electronic spectra, dipole

Table V. Comparison in the Deuterium Exchange Reactivity between α- and γ-Methyl Hydrogens of Pyridine, Quinoline, and Isoquinoline, Their N-Oxides, and N-Methiodides[b]

Compound	Solvent	Condition			
2-Me-pyridine	1% NaOD D_2O	170°, 1 hr.	++	180°, 1 hr.	+++
4-Me-pyridine	1% NaOD D_2O	170°, 1 hr.	++++	180°, 1 hr.	++++
2-Me-quinoline	1% NaOD D_2O-dioxan[a]	100°, 1 hr.	+	150°, 8 hr.	++++
4-Me-quinoline	1% NaOD D_2O-dioxan[a]	100°, 1 hr.	++++	150°, 8 hr.	completed
2-Me-pyridine N-O	1% Na_2CO_3 D_2O	100°, 1 hr.	+	100°, 8 hr.	+++
4-Me-pyridine N-O	1% Na_2CO_3 D_2O	100°, 1 hr.	–	100°, 8 hr.	++
2-Me-quinoline N-O	1% NaOD D_2O-dioxan[a]	22°, 1 day	++++	50°, 1 hr.	completed
4-Me-quinoline N-O	1% NaOD D_2O-dioxan[a]	22°, 1 day	–	50°, 1 hr.	++
1-Me-isoquinoline N-O	1% NaOD D_2O-dioxan[a]	22°, 1 day	completed		
3-Me-isoquinoline N-O	1% NaOD D_2O-dioxan[a]	22°, 1 day	–		
2-Me-pyridine N^+-CH_3	D_2O	120°, 3 hr.	++++		
4-Me-pyridine N^+-CH_3	D_2O	120°, 3 hr.	+		
2-Me-quinoline N^+-CH_3	D_2O	100°, 1 hr.	+++	100°, 8 hr.	completed
4-Me-quinoline N^+-CH_3	D_2O	100°, 1 hr.	–	100°, 8 hr.	+
1-Me-isoquinoline N^+-CH_3	D_2O	22°, 1 day	+	100°, 1 hr.	completed
3-Me-isoquinoline N^+-CH_3	D_2O	22°, 1 day	–	100°, 1 hr.	–

a) One to one mixture (v/v). b) See footnote (*a*) in Table IV.

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moment, pKa, etc. In addition to this, it is to be noted that the relative exchange reactivities of methyl hydrogens of N-oxides decrease in the following order as shown in Table VI: 1-Me-isoquinoline 2-oxide>2-Me-quinoline 1-oxide>4-Me-quinoline 1-oxide >2-Me-pyridine 1-oxide>4-Me-pyridine 1-oxide. It was revealed that 2- and 4-positions (or α and γ positions) of quinoline 1-oxides are more reactive than those of pyridine 1-oxides, whereas the 3-position (or β position) seems to be in the reverse order.[*5] 3-Methyl hydrogens of isoquinoline 2-oxide seem to be much less reactive than those of other methyls adjacent to the N-oxide group.

TABLE VI. Relative Rate of Deuterium Exchange of Methyl Hydrogens of Monomethylated Pyridine, Quinoline, and Isoquinoline N-Oxides in 1% NaOD Solutions[a]

Compound	Solvent	Condition				
		22°, 1 day	50°, 1 hr.	100°, 1 hr.	150°, 1 hr.	180°, 1 hr.
2-Me-pyridine N-O	D_2O	–	–	completed		
3-Me-pyridine N-O	D_2O		–	–	++	completed
4-Me-pyridine N-O	D_2O		–	+++	completed	
2-Me-quinoline N-O	D_2O-dioxan (1:1)	++++	completed			
3-Me-quinoline N-O	D_2O-dioxan (1:1)		–	–		++
4-Me-quinoline N-O	D_2O-dioxan (1:1)		++	completed		
1-Me-isoquinoline N-O	D_2O-dioxan (1:1)	completed				
3-Me-isoquinoline N-O	D_2O-dioxan (1:1)	–	+	+++	++++	completed

a) See footnote (a) in Table IV.

As a conclusion, it should be mentioned that the ease of the exchange reactivity reported in this paper must be explained in principle from consideration of the delocalization energies of the carbanions as the reaction intermediate and from the hyperconjugative contribution of the alkyl groups. Molecular orbital calculations concerning these are now in progress in our laboratory.

Another experiment was carried out to compare the exchange rate of methyl hydrogens with that of methylene hydrogens of ethyl group, which gave a strong support to the assumption that the reaction rate depends on the stability of the carbanion produced by abstraction of hydrogen by the base. Thus, metallation of α-position in toluene, ethylbenzene, and isopropylbenzene, the rate of which was postulated to depend on the stability of the protonized carbanions, give the proportions of the metallated products of 100, 50, and 13%, respectively.[3~5] Furthermore, the same sequence of the reactivity was found by measuring the rates of deuterium exchange with potassium amide in liquid deuteroammonia, the relative rate being 1: 0.14:0.029 for CH_3, CH_2, and CH, respectively.[6] Our experiment revealed that methyl hydrogens underwent deuterium exchange faster than methylene hydrogens in each position isomer, 2-, 3-, or 4-alkylpyridine 1-oxide, as shown in Table VII. Qualitative comparison was made by heating at 100° for 1 hr. the 1% NaOD solution of a mixture

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[*5] The rate of hydrogen exchange is, in general, a little faster in D_2O solution than in a mixtures of D_2O and dioxan. Therefore, an unequivocal conclusion should be drawn from the data in the same solvent system.

3) D. Bryce-Smith: J. Chem. Soc., **1954**, 1079.

4) P.D. Bartlett, S. Friedman, M. Stiles: J. Am. Chem. Soc., **75**, 1771 (1953).

5) H. Pines, V. Mark: *Ibid.*, **78**, 4316 (1956).

6) A.I. Shatenshtein, E.A. Izrailevich: Zh. Fiz. Khim., **32**, 2711 (1958) (Chem. Abstr., **53**, 13745).

Table VII. Relative Rate in Deuterium Exchange of α-Methyl and α-Methylene Hydrogens of Monomethyl and Monoethylpyridine N-Oxides in 1% NaOD-D_2O Solution[a]

Compound	Condition		
	100°, 1 hr.	100°, 3 hr.	180°, 1 hr.
2-Me-pyridine N-O	++++	completed	
2-Et-pyridine N-O	++	++++	
3-Me-pyridine N-O	—	—	completed
3-Et-pyridine N-O	—	—	++++
4-Me-pyridine N-O	+++	completed	
4-Et-pyridine N-O	+	+++	

[a] See footnote (a) in Table IV.

of 2-methyl- and 2-ethyl-pyridine 1-oxides and by integrating both signal intensities on the NMR spectrum of this mixture. Deuteration proceeded in 86% and 40% yields for CH_3 and CH_2, respectively.

Some examples of the experimental conditions for syntheses of partly deuterated derivatives are summarized in Chart 3 and 4.

In 1% NaOD D_2O solutions

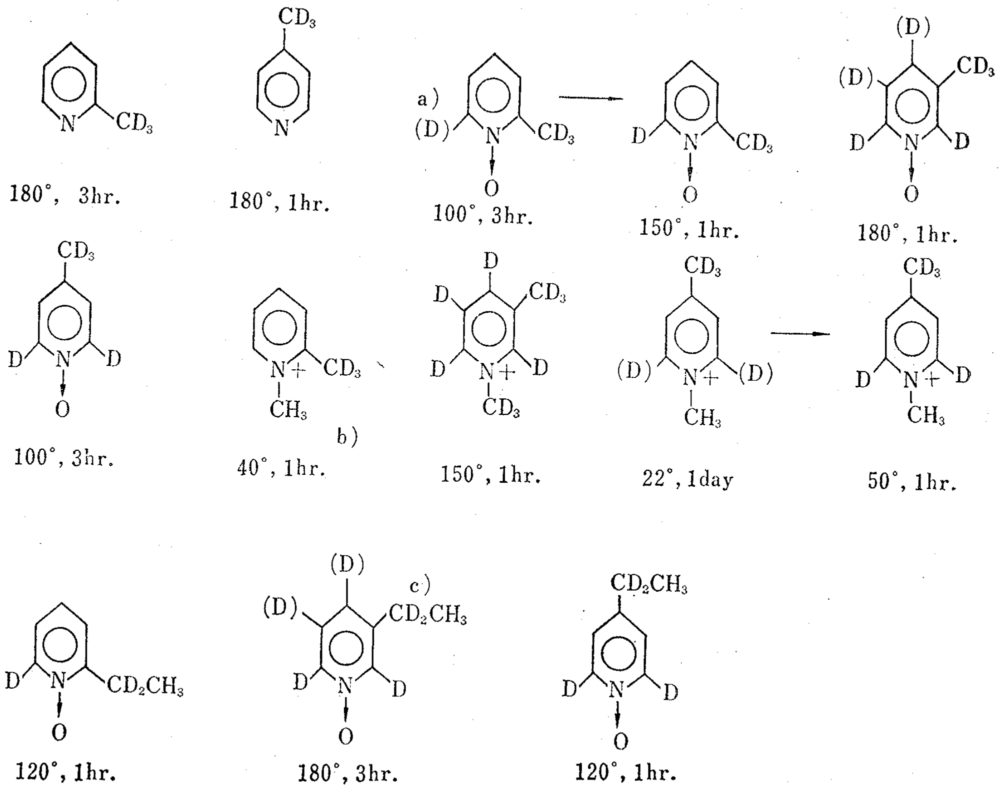

Chart 3. Some Deuterated Pyridine Derivatives prepared by Base-catalyzed Hydrogen Exchange (The condition chosen for syntheses are given under the formula.)

a) Deuterium in parantheses, (D) or (CD_3), were partly deuterated under the condition described.

b) 1% Na_2CO_3 was used instead of NaOD.

c) Almost completed.

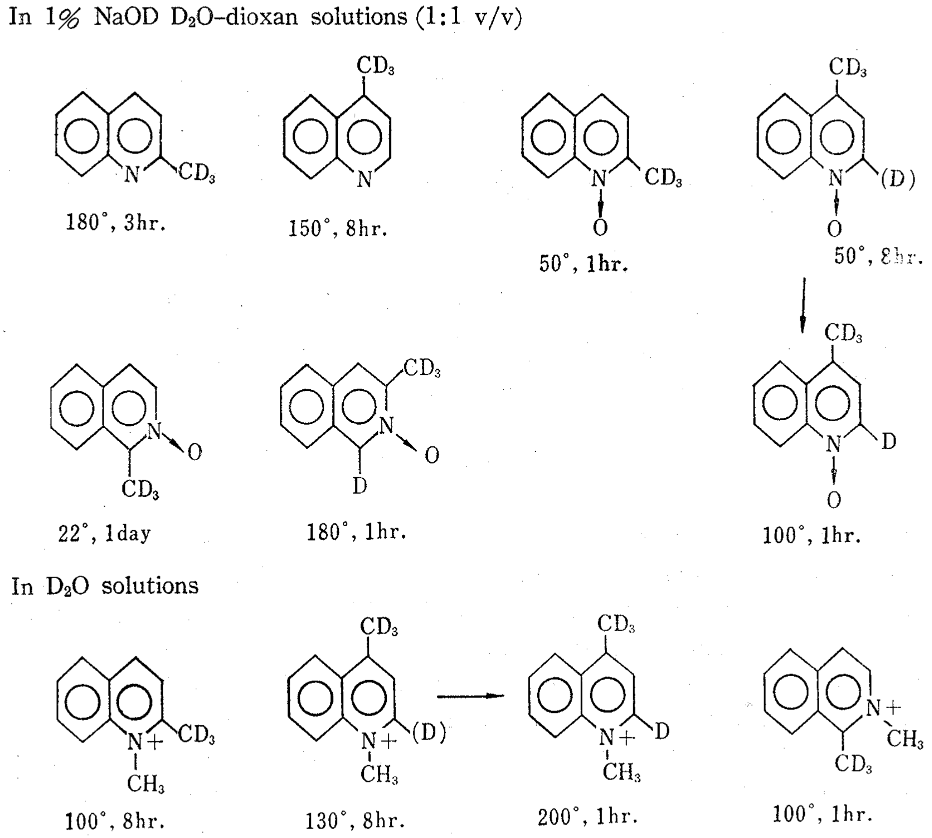

Chart 4. Some Deuterated Quinoline and Isoquinoline Derivatives prepared by Base-catalyzed Hydrogen Exchange (The conditions chosen for syntheses are given under the formula.)

Experimental

Compounds——Methyl and ethyl derivatives of pyridine, quinoline, and isoquinoline were purchased from Tokyo Kasei Co. and thier N-oxides and N-methiodides were prepared by authentic methods. Heavy water (99.9 D-atom%) was purchased from Merck Co. (Germany) and 98% D_2SO_4 (99 D-atom%) was purchased from Showa Denko Co. (Tokyo).

NMR Measurements——Spectra were measured with a JNM-3H-60 spectrometer (Japan Electron Optics Lab. Co.) operating at 60 Mcsp.

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