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Mercuration of Quinoline N-Oxide

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Mercurations of quinoline N-oxide with various reagents under different conditions were investigated using gas chromatographic analysis of the bromoquinolines derived from the reaction products. Mercuration in acetic acid or perchloric acid gave 8-mercurichloride as a main product and small amounts of 3-, 5-, 6- and 7-isomers. The reaction with mercuric sulfate without solvent gave all of the isomers, although the total yield was poor.

A great many investigations have already been carried out on the electrophilic substitution reaction of aromatic N-oxides.[2] Among the electrophilic reactions, aromatic mercuration of pyridine N-oxide has been studied by Ukai and his coworkers,[3] who reported the formation of 4-substituted derivative as the result of the reaction. Upon reinvestigation of the reaction, Ammers and Hertog[4] corrected the observation of Ukai, *et al.* by demonstrating that the main product was invariably 2-substituted compound, and further showed that the yields of 3- and 4-mono and 2,6-di-substituted derivatives obtained as by-products varied with the nature of reagent as well as the reaction conditions. Since comparable studies have not been made on mercuration of quinoline N-oxide except for the formation of 8-mercurichloride,[3] more detailed examination of this reaction appears to be mandatory. The results of our investigation on the mercurations of quinoline N-oxide with various reagents under different conditions are summarized in this report.

In view of the readily expected occurrence of a mixture of various isomers as the reaction products, it is imperative first of all to establish the method of analysis of these isomers. Such analysis may be accomplished best by gas chromatographic determination of a mixture of bromoquinolines readily obtainable from the reaction products through the corresponding chloromercuriquinoline N-oxides and then bromoquinoline N-oxides, in the same manner as described by Ammers and Hertog on the analysis of the reaction mixture of mercuration of pyridine N-oxide.

Gas chromatographic behavior of standard samples of seven kinds of bromoquinoline isomers was investigated using XE-60, QF-1 and SE-30 column packings. The retention times and column conditions are shown in Table 1. Good separation was generally obtained on the XE-60 column packing, except the separation of 3- and 4-isomers, which were separated by QF-1 or SE-30 phase. Close retention times were observed for 2- and 7-isomers on QF-1 phase, and for 4- and 5-isomers on both QF-1 and SE-30 phases. Qualitative and quantitative analysis of bromoquinoline mixtures were thus accomplished by obtaining gas chromatograms on at least two column packings.

The reactions were carried out essentially by the same procedure as that reported by Ukai[3] and Ammers.[4] The reaction mixture was treated with sodium chloride solution and then brominated with potassium bromide and bromine in chloroform. After de-oxygenation

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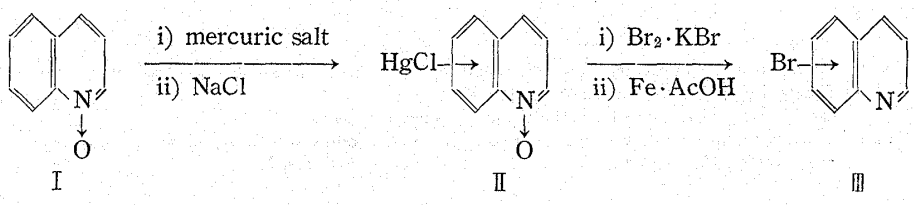
2) E. Ochiai, "Aromatic Amine Oxides," Elsvier Publishing Company, Amsterdam, 1967.
3) T. Ukai, Y. Yamamoto, and S. Hirano, *Yakugaku Zasshi*, 73, 823 (1953).
4) M. van Ammers, and H.J. Den Hertog, *Rec. Trav. Chem.*, 77, 340 (1958); 81, 124 (1962).

Table I. Relative Retention Times of Bromoquinolines

Quinoline	1.5% XE-60 1.00 (4.0 min)	2.0% QF-1 1.00 (4.15 min)	1.5% SE-30 1.00 (3.75 min)
2-Br	5.4	3.2	3.7
3-Br	3.0	2.0	3.05
4-Br	3.0	2.2	3.2
5-Br	3.4	2.3	3.2
6-Br	4.2	2.75	3.5
7-Br	4.8	3.1	3.9
8-Br	9.5	5.1	5.0
Column temp.	100°	100°	117°
Carrier gas(N_2) flow rate	60 ml/min	60 ml/min	40 ml/min

of bromoquinoline N-oxides with iron powder in acetic acid, the bromoquinolines thus obtained were identified and determined quantitatively by gas chromatographic analysis using three kind of column packings. Gas chromatograms of the products obtained from the reactions with mercuric acetate and with mercuric sulfate at 130° were shown in Fig. 1 and 2, respectively. Further identification of each component was effected by collecting the corresponding gas chromatographic effluent and by comparison of the fingerprint region of its IR spectrum with that of an authentic sample.



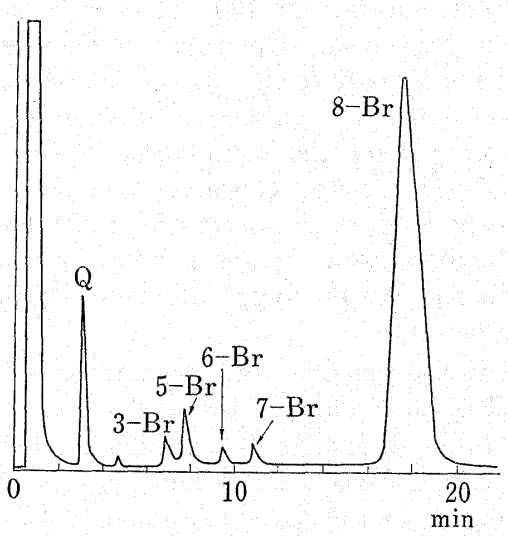


Fig. 1. Gas Chromatogram of Bromoquinolines Mixture derived from the Reaction Product of Quinoline N-Oxide with Mercuric Acetate at 130°

2.0% QF-1 on Gas Chrom P; 105°; N_2 flow rate, 60 ml/min

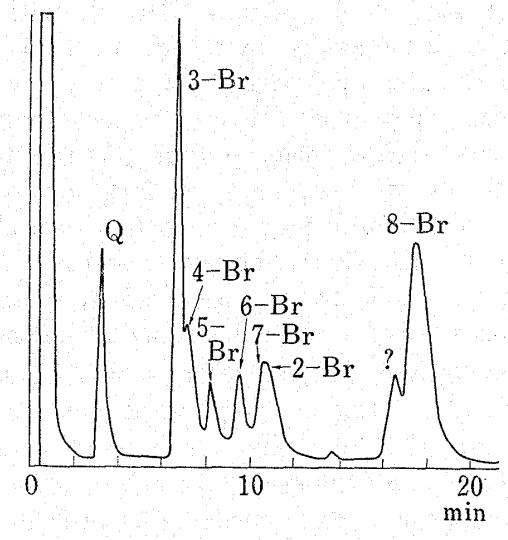


Fig. 2. Gas Chromatogram of Bromoquinolines Mixture derived from the Reaction Product of Quinoline N-Oxide with Mercuric Sulfate at 130°

2.0%QF-1 on Gas Chrom P; 105°; N_2 flow rate, 60 ml/min

The reaction conditions and the yields of mercuration and also those of the bromoquinolines derived from the reaction products are shown in Table II. The structure of dibromide which was formed in a small amount and the unknown compounds A, B, and C listed in Table

II have not yet been investigated. Formation of 4-bromoquinoline was observed only when mercuric sulfate was used. Since a small amount of 4-isomer might possibly decompose during gas chromatographic detection owing to its thermal instability, the accurate amount of 4-isomer could not be determined.

Table II. Yields of Mercurations

Starting material	Quinoline N-oxide					Quinoline
Reagent[a]	$Hg(OAc)_2$	$Hg(ClO_4)_2$			$HgSO_4$	$Hg(OAc)_2$
Solvent	AcOH	AcOH	40% $HClO_4$	60% $HClO_4$		AcOH
Reaction temp.	130°	90°	90°	20°	130°	130°
Reaction time	5 hr	25 hr	6 hr	4 day	6 hr	5 hr
Yield of chloromercuri-quinoline N-oxide[b]	85%	20%	60%	25%	40%	30%
Compositions (%) of the bromo-quinoline obtained from the mixture of chloromercuric deriv.						
2-Br	—	—	—	—	6	—
3-Br	3	+	—	—	26	13
4-Br	—	—	—	—	7	—
5-Br	7	1	12	5	8	29
6-Br	3	—	10	4	8	12
7-Br	6	1	7	3	6	6
8-Br	81	88	67	86	30	40
Unknown[c]	—	10[a]	4[b]	2[b]	9[c]	—

a) The same molar equivalent of the reagent was used for the starting material, except for $HgSO_4$, which was used half molar equivalent.
b) The yield was calculated from the amount of mercuric salt.
c) Relative retention times of unknown compounds A, B, and C were 11.5, 5.1, and 8.6, respectively, using XE-60 column on the same conditions as in Table I.

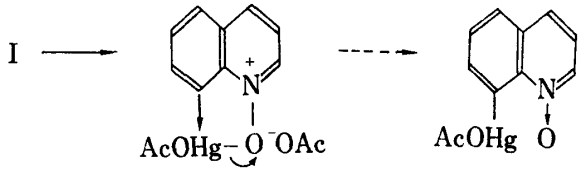
Mercuration of quinoline N-oxide with mercuric acetate at 130° gave 81% of the 8-derivative accompanied by 3—7% of 3-, 5-, 6- and 7-isomers. Upon reducing the temperature to 90°, the most part of the products was the 8-derivative, although the yield was poor. A similar temperature effect was also found when mercuric oxide was used in perchloric acid,[5] the 8-isomer being obtained as the main product together with considerable amounts of the 5-, 6- and 7-isomers. At 20°, however, 86% of the product was the 8-derivative. It is of interest to note that among the by-products the 5-isomer occupied a relatively large part compared with other minor components. The temperature effect on mercurations of nitrobenzene and toluene was discussed by Klapproth and Westheimer,[5] who reported that the orientation was less sharply defined at higher temperature.

Remarkably different results were obtained in the reaction with mercuric sulfate without solvent. Although total yield was poor, all of the isomeric bromoquinolines were obtained, and the predominant ones were 3- and 8-bromo derivatives. In order to explore the effect of N-oxide function, the mercuration of quinoline was undertaken. Ukai[6] reported the occurrence of 8-mercurichloride in a large amount and also a small amount of 3-isomer. When the 8-position was already substituted by a methyl group the reaction was shown to occur at the 5-position. In our experiment the yield of mercuration was about 30%, and the 8- and 5-bromo derivatives were formed together with small amounts of the 3-, 6- and 7-isomers. From these results the effect of N-oxide on mercuration appeared to be rather remarkable. However, as pointed out by Klapproth,[5] the mechanism of mercuration is not simple, showing anomalies, despite the fact that mercuration is an electrophilic substitu-

5) W.J. Klapproth and F.H. Westheimer, *J. Am. Chem. Soc.*, **72**, 4461 (1950).
6) T. Ukai, *Yakugaku Zasshi*, **51**, 72, 542 (1931).

tion. It is noteworthy that the composition of the products showed a considerable variation according to the mercuric salt employed and also the reaction conditions.

The fact that the mercuration in acetic acid or perchloric acid occurs predominantly at the 8-position might be possibly explained by the mechanism shown below. In the case of mercuric sulfate a different mechanism might be considered. The lack of orienting effect may be due to the reaction of the undissociated reagent and perhaps might be explained only by a radical mechanism.



Experimental

Reactions——A general procedure of the mercuration was as follows. Quinoline N-oxide (5.0 g) and mercuric acetate (11 g) were heated with 5 ml of acetic acid for 5 hr at 130°. After removal of a precipitate, the filtrate was poured into a saturated solution of sodium chloride and the precipitate (11.1 g) was collected. Mercurichloride of quinoline N-oxide (0.28 g) thus obtained was shaken with 3 ml of chloroform and a solution of potassium bromide (0.24 g)–bromine (0.15 g) in 1 ml of water for 10 min in a separatory funnel. Then a solution of potassium bromide (0.36 g) and sodium carbonate (0.18 g) in 3 ml of water was added and the mixture was again shaken for 5 min. The chloroform layer was separated and washed with a solution of 0.1 g of potassium bromide, 0.1 g of sodium carbonate and 0.1 g of potassium thiosulfate in 3 ml of water. After drying over anhydrous sodium sulfate, the solvent was evaporated, and 0.1 g of oily substance was obtained. The reduction was carried out by heating with iron powder (0.04 g) in 1 ml of acetic acid for 1 hr. The reaction mixture was basified with sodium hydroxide solution and extracted with ether. The yield of bromoquinolines from chloromercuriquinoline N-oxides was about 70%.

A small amount of quinoline (5—7%), which was always detected by gas chromatography, may be formed during the process of reduction with iron.

Analysis of Products——Shimadzu Seisakusho model GC-1C gas chromatograph equipped with a hydrogen flame ionization detector was used in this study. The column consisted of U-type glass tube, 180 cm × 4 mm *i. d.* Column packings were prepared according to Horning, *et al.*[7] using Gas Chrom P, 80—100 mesh, as the support after washing with hydrochloric acid and silanization with dimethyldichlorosilane in toluene. Liquid phases used were 1.5% XE-60 (nitrile silicone, G.E.), 2.0% QF-1 (fluorinated alkyl silicone, Dow Chem. Co.), and 1.5% SE-30 (methyl silicone gum, G.E.).

For collection of gas chromatographic effluent, thermal conductivity detector and a column, 180 cm × 6 mm *i.d.*, packed with 5% QF-1 on Shimalite W, 60—80 mesh, were used. The effluent gas corresponding to the each peak was trapped in a U-shape glass tube inserted into the outlet and cooled by dry ice-acetone. The IR spectra of the fractions were obtained in CS_2 solution. The main peaks, cm^{-1}, in fingerprint region of bromoquinolines are as follows: 2-Br, 1125 (s), 1078 (s), 938 (m), 834 (m), 809 (s), 769 (s), 739 (s); 3-Br, 1189 (m), 1122 (m), 1071 (s), 944 (s), 885 (s), 836 (s), 773 (s), 742 (s); 5-Br, 1194 (m), 1186 (m), 1140 (w), 1122 (s), 1100 (w), 1071 (w), 1055 (m), 1038 (m), 949 (s), 936 (s), 881 (s), 838 (s), 791 (s), 748 (s); 6-Br, 1190 (w), 1179 (w), 1120 (w), 1060 (w), 1028 (w), 942 (w), 866 (w), 845 (w), 826 (s), 770 (s), 755 (s); 7-Br, 1186 (w), 1138 (m), 1122 (s), 1071 (m), 1055 (s), 1033 (m), 935 (s), 877 (s), 848 (s), 824 (s), 798 (w), 762 (w); 8-Br, 1197 (s), 1135 (m), 1121 (m), 1055 (s), 1025 (w), 960 (s), 946 (m), 814 (s), 803 (m), 777 (s), 750 (s).

Samples——Samples of 5- and 7-bromoquinolines were prepared by the method of Bradford.[8] 2-Bromo- and 6-bromoquinolines are the gift of Prof. M. Hamana, Kyushu University, 3-bromo- and 4-bromoquinolines are the gift of Prof. T. Okamoto, Tokyo University, and 8-bromoquinoline is the gift of Prof. E. Hayashi, Shizuoka Pharmaceutical College.

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7) E.C. Horning, W.J.A. VandenHeuvel, and B.G. Creech, "Methods of Biochemical Analysis," Vol. XI, D. Glick, ed., Interscience Publishers, New York, N.Y., 1963, p. 63.
8) L. Bradford, T.J. Elliott, and F.M. Rowe, *J. Chem. Soc.*, **1947**, 437.