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Studies on the Reactions of Heterocyclic Compounds. XI.[1] Methylation of Heteroaromatic N-Oxides[2]

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N-Oxides of quinoline, isoquinoline, and benzo[*f*]quinoline were methylated with sodium methylsulfinylmethylide. Methyl group was introduced into the α-position to the N-oxide group in each case, regardless of the charge densities. Reaction mechanism is proposed upon these results.

In synthetic chemistry it is very important to find how to introduce carbon-substituent to a heterocyclic ring, such as in quinoline and isoquinoline, and there have been many attempts to achieve it. Among them, Russel, *et al.*[4] and Nozaki, *et al.*[5] succeeded in methylation of aromatic compounds with methylsulfinyl methylide anion. Russel suggested that a methyl group was introduced to the position expected from the charge density of aromatic compounds.

We tried to apply this method to heteroaromatic N-oxides, and found that a methyl group was introduced to heterocycles. In this case, the reaction occurred at α-position to the N-oxide group, regardless of the charge densities or other parameters calculated by molecular orbital theory. These results will be discussed in detail and in comparison with those of unoxidized heterocyclic compounds.

Sodium methylsulfinylmethylide, obtained by dissolving sodium hydride in dimethylsulfoxide at 70° under atmosphere of dry nitrogen, was used for the reaction with heteroaromatic N-oxides and the results are shown in Table I.

Table I

Starting material	Product	Yield
Pyridine 1-oxide	no reaction	
Quinoline 1-oxide	quinaldine 1-oxide	40%
Isoquinoline 2-oxide	1-methylisoquinoline 2-oxide	19%
Benzo[*f*]quinoline 4-oxide	3-methylbenzo[*f*]quinoline 4-oxide	45%

Pyridine 1-oxide did not undergo this reaction, like pyridine itself. Quinoline 1-oxide gave quinaldine 1-oxide, namely, methyl group was introduced to 2-position. This was in a striking contrast to the result of quinoline, where methyl group was introduced to 4-position of the ring. Isoquinoline 2-oxide gave 1-methylisoquinoline 2-oxide, just as isoquinoline gave 1-methylisoquinoline.

These results seemed to suggest that a methyl group is introduced selectively to the α-position of N-oxide group when the reaction proceeds. To confirm this point, methylation of benzo[*f*]quinoline was carried out, since the compound is known to show quite peculiar reactivity; most heterocyclic N-oxides give α-cyano compound by the so-called Reissert

1) Part X: Y. Kobayashi, I. Kumadaki, Y. Sekine, and T. Kutsuma, *Chem. Pharm. Bull.* (Tokyo), **21**, 1118 (1973).
2) Presented at the 91th Annual Meeting of Pharmaceutical Society of Japan, Fukuoka, April 1971.
3) Location: *Kitashinjuku 3-chome, Shinjuku-ku, Tokyo, 160, Japan.*
4) G.A. Russel and S.A. Weiner, *J. Org. Chem.*, 31, 248 (1966).
5) H. Nozaki, Y. Yamamoto, and R. Noyori, *Tetrahedron Letters*, **1966**, 1123.

reaction, but benzo[*f*]quinoline N-oxide gives γ-cyano compound. In this case, methylation again occurred at α-position to N-oxide group, giving 3-methylbenzo[*f*]quinoline 4-oxide, which was identified by comparison of infrared (IR) spectra and mixture melting point with the authentic sample obtained by oxidation of 3-methylquinoline. Benzo[*f*]quinoline itself gave 5-methylbenzo[*f*]quinoline.

The charge densities of quinoline and benzo[*f*]quinoline N-oxides are shown in Fig. 1.[6] In each case, the charge density of α-position is not the largest, but still this methylation proceeded at α-position to N-oxide group. This means that reaction occurred regardless of the charge density, in contrast to the results of other compounds without N-oxide groups. This difference may be explained by some kind of coordination of sodium ion to N-oxide group and methylide anion, as shown in Chart 1 taking quinoline 1-oxide as an example.

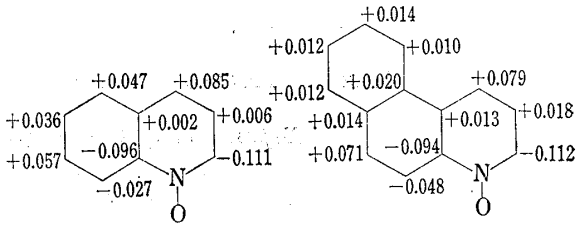

Fig. 1

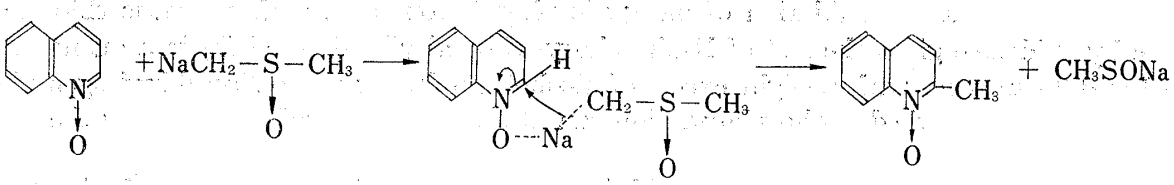

Chart 1

Experimental

General Procedure——Dimethyl sulfoxide (DMSO) (30 ml) was bubbled with dry nitrogen at 70° and NaH (0.5 g) was added under stirring. Stirring was continued for 5 hr at this temperature and under atmosphere of nitrogen.

After this solution was cooled to room temperature, amine N-oxide (1 g), which was azeotropically dehydrated with C_6H_6, if necessary, in DMSO (20 ml) was added dropwise and warmed at 20° for 2 hr.

The reaction mixture was poured on ice and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O to remove DMSO and dried over Na_2SO_4. The residue obtained by evaporation of $CHCl_3$ was treated as shown in each case.

Quinaldine 1-Oxide: The residue was dissolved in $CHCl_3$–CCl_4 (1: 4) and passed through Al_2O_3 column. The first effluent was recrystallized from EtOH–C_6H_6 to give yellow powder (0.4 g), mp 72°, which was identified with quinaldine 1-oxide 1/2 H_2O by comparison of IR spectra.

From the second effluent, quinoline 1-oxide (0.4 g) was recovered.

1-Methylisoquinoline 2-Oxide: The residue was dissolved in EtOH and EtOH–solution of picric acid was added to the above solution. The precipitates of picrate were filtered and shaken with 10% HCl. The picric acid was filtered off and the HCl–solution was neutralized with Na_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over Na_2SO_4 and concentrated. Nuclear magnetic resonance (NMR) spectrum of the residue did not show the peak of 1-H of isoquinoline ring, but a peak of CH_3 at δ 2.52 in $CDCl_3$. This is further derived to picrate (0.33 g), mp 142—145°. *Anal.* Calcd. for $C_{16}H_{12}O_8N_4$: C, 49.47; H, 3.12; N, 14.73. Found: C, 49.61; H, 3.10; N, 14.95.

3-Methylbenzo[*f*]quinoline 4-Oxide: The residue was dissolved in $CHCl_3$ and the solution was passed through SiO_2 column. The first effluent was recrystallized from acetone–H_2O to give pale yellow needles (0.48 g), mp 123—125° (after dehydration). Mass Spectrum *m/e*: 209 (M^+). This was identified with the authentic sample synthesized according to the literature by mixture melting point and comparison of IR spectra.

5-Methylbenzo[*f*]quinoline: Benzo[*f*]quinoline (0.54 g) was treated as in the case of N-oxide. The residue was dissolved in CCl_4 and passed through SiO_2 column. The second effluent was recrystallized from *n*-hexane to give colorless needles (57 mg, 10%), mp 101°. Mass Spectrum *m/e*: 193 (M^+). This was identified with the authentic sample obtained by photo reaction from β-methyl-β-(2-pyridyl)styrene.[7]

6) These values are obtained by Hückel method. Parameters used are: $\alpha_O=\alpha_C+0.8\beta$, $\alpha_N=\alpha_C+1.6\beta$. Inductive effect: $(1/3)^n h\alpha_N$.

7) Mamalis and V. Petrov, *J. Chem. Soc.*, **1950**, 703.