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Reaction of Isoquinoline 2-Oxides with Methylsulfinylmethyl Carbanion

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7-Methoxy-3-methylsulfonyl-3*H*-benz[*d*]azepine (5) and 2-deuterio-3-(methyl-d_3)-sulfonyl-3*H*-benz[*d*]azepine (14) were obtained from the reaction of the corresponding isoquinoline 2-oxides with methylsulfinylmethyl carbanion. A revised reaction mechanism is proposed on the basis of the results obtained by use of deuterated dimethyl sulfoxide-d_6.

Keywords benz[*d*]azepine; isoquinoline 2-oxide; 1,6-naphthyridine 6-oxide; methylsulfinylmethyl carbanion; methylation; nucleophilic reaction

Reactions of pyridine, quinoline, isoquinoline,[1] and their *N*-oxides[2] with methylsulfinylmethyl carbanion have already been reported, and the products were methylated compounds except for the pyridine and pyridine 1-oxide. The authors have reported that isoquinoline 2-oxide (**1**), benzo[*f* or *h*]quinoline *N*-oxide, and mono *N*-oxides of phenanthrolines did not give ordinarily methylated compounds but their *N*-oxides gave naphthalene (from **1**), phenanthrene (from benzo[*f* or *h*]quinoline *N*-oxide), and benzoquinolines (from mono *N*-oxides of phenanthrolines) through the liberation of the *N*-oxide group.[3] Further, compound **1** gave 3-methylsulfonyl-3*H*-benz[*d*]azepine (**2**).[4] We examined here whether or not similar reactions occur with substituted isoquinoline 2-oxides and 1,6-naphthyridine 6-oxide. To elucidate the reaction mechanism, the reaction using dimethyl sulfoxide-d_6 (DMSO-d_6) was carried out.

When 7-methoxy- (**4**) and 7-hydroxy-isoquinoline 2-oxide (**6**) were allowed to react with sodium hydride in DMSO at 70 °C for 15 min, the 7-methoxybenzazepine derivative (**5**) was obtained from **4**, but **6** afforded only 1-methyl-7-hydroxyisoquinoline 2-oxide (**7**) in 14% yield. The 5-NO_2, 8-NO_2, 4-CN, and 4-$CONH_2$ substituted isoquinoline 2-oxides always gave decomposition products, even when the reaction time was reduced to 5 min. Similarly, 1,6-naphthyridine 6-oxide (**8**) and 1-oxide afforded decomposition products. In the case of **8** the reaction under mild conditions (−5 °C and 5 min) gave 5-methyl-1,6-naphthyridine 6-oxide (**9**). From these results, it is deduced that in the case of a compound having an electron-attracting group a ring-opening reaction occurs to give decomposition products. On the other hand, the ring-opening reaction does not take place in the case of a compound possessing an electron-donating group such as a hydroxy group.

With regard to 4-isoquinolinecarbonitrile (**10**) and 7-methoxyisoquinoline (**12**), which are compounds without an *N*-oxide moiety, the reactions at 70 °C for 15 min yielded compounds **11** and **13** with a methyl group at the 1-position, respectively. In the case of 7-hydroxyisoquinoline, however, the raw material was recovered.

In order to examine the reaction mechanism, the reaction of **1** was carried out in DMSO-d_6. Although a deuterated azepine derivative (**14**) was obtained, deuterated naphthalene could not be isolated from the reaction mixture because of the small scale of the experiment.

The structure **14** was determined by ^{1}H-NMR spectral examination, as in the case of 3*H*-1,3-benzazepines.[5] In the undeuterated compound (**2**), two equivalent olefinic protons resonating at lower magnetic field (δ 5.91) were assigned to α positions ($C_{2,4}$-H) and those at higher magnetic field (δ 5.48) were assigned to ($C_{1,5}$-H). In the ^{1}H-NMR spectrum of the deuterated **14** a proton signal at lower magnetic field disappeared and a singlet proton signal appeared at δ 5.48. In the mass spectrum (MS), fragment

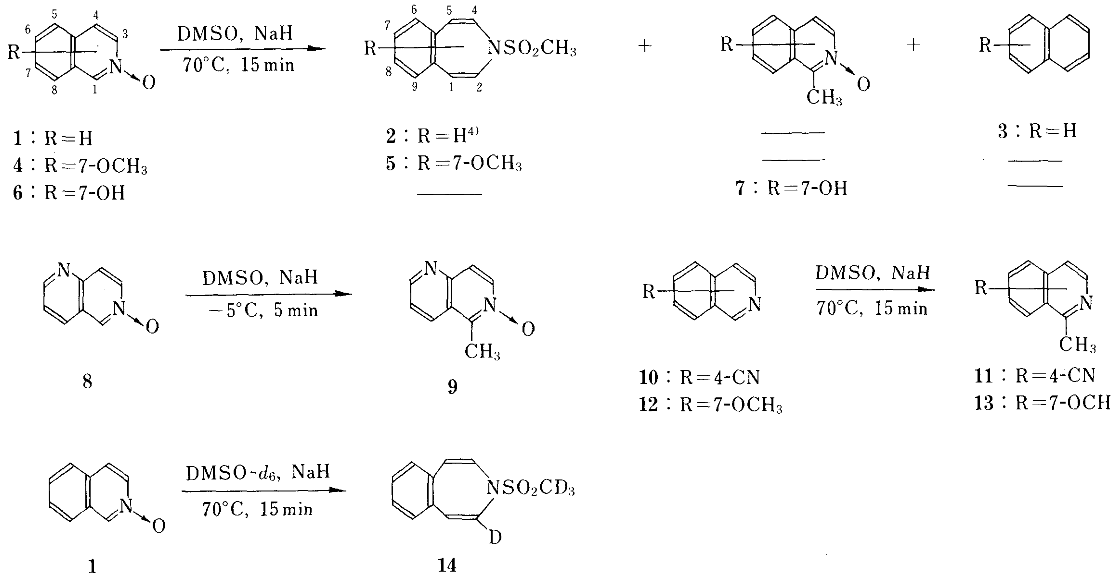

Chart 1

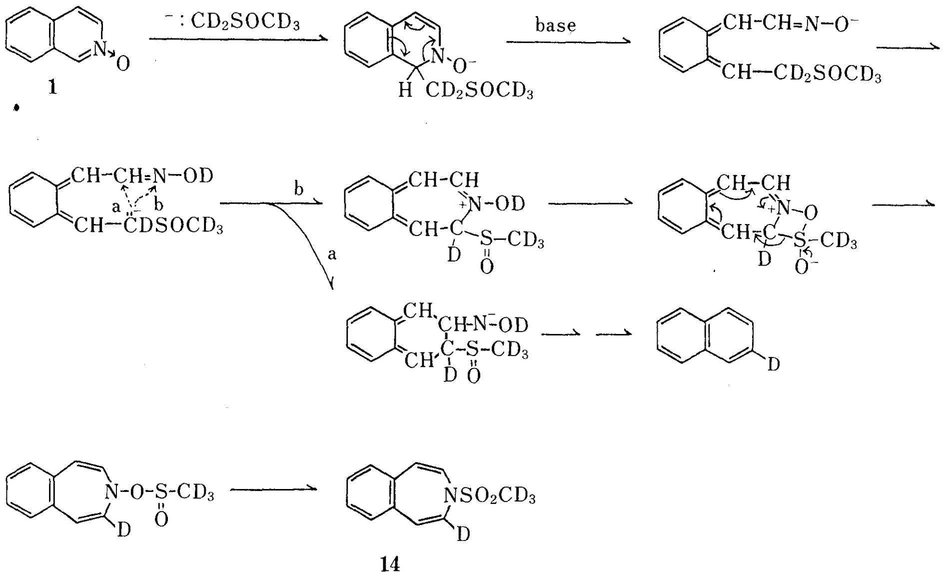

Chart 2

ions of m/z 116 (143−HCN) and 115 (143−DCN) were observed with similar ratio, and the fragment ions were identified by high-resolution MS. These facts show that one deuterium exists at the α position with respect to ring nitrogen. Previously, a reaction mechanism has been proposed for the ring closure.[4] The reaction mechanism involved a proton shift, so that the mono- and di-deuterated products should have been formed in equal quantities. However, only the monodeuterated compound (**14**) was obtained.

Consequently, the reaction mechanism should be revised as shown in Chart 2. The sulfinic ester produced after the formation of the azepine ring is transformed to the thermodynamically more stable sulfone.[6] Although deuterated naphthalene was not isolated, its formation could be explained by the existence of a common intermediate (Chart 2).

Experimental

^{1}H-NMR spectra were recorded using a JEOL JNM PS-100 spectrometer. Chemical shifts are given in ppm from tetramethylsilane (TMS) as an internal standard and coupling constants in Hz (s, singlet; d, doublet; dd, double doublet; m, multiplet). MS were taken with a Hitachi GC-MS M-52 spectrometer and high-resolution MS were taken with a Hitachi GC-MS M-80 spectrometer.

General Procedure Sodium hydride (2.64 g, 0.11 mol, 60% dispersion in oil) was dissolved in 80 ml of dry DMSO at 70 °C under a nitrogen atmosphere, and a solution of isoquinoline 2-oxide (0.02 mol) in DMSO (20 ml) was dropped into the solution. The reaction mixture was kept at 70 °C and stirred for 15 min. The mixture was poured into a large excess of water and the brownish yellow solid that separated from the solution was collected by filtration. The reaction products were purified by column chromatography.

8-Methoxy-3-methylsulfonyl-3*H*-benz[*d*]azepine (5) Compound **5** was prepared from **4** according to the general procedure. The residue was purified by column chromatography (silica gel, benzene : $CHCl_3$ = 5 : 1) and recrystallized from benzene : cyclohexane (1 : 1) to give **5** (0.35 g, 7%) as yellow plates, mp 148—150 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.97 (3H, s, SO_2CH_3), 3.70 (3H, s, OCH_3), 5.38 (1H, d, J = 9.2 Hz, C_1-H), 5.42 (1H, d, J = 9.2 Hz, C_5-H), 5.76 (1H, d, J = 9.2 Hz, C_2-H), 5.88 (1H, d, J = 9.2 Hz, C_4-H), 6.45 (1H, dd, J = 8.2, 2.6 Hz, C_8-H), 6.65 (1H, d, J = 8.2 Hz, C_9-H), 6.72 (1H, d, J = 2.6 Hz, C_6-H). *Anal.* Calcd for $C_{12}H_{13}NO_3S$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.46; H, 5.11; N, 5.34. MS m/z (%): 251 (M^+, 13), 172 ($M^+-SO_2CH_3$, 100), 145 (172−HCN, 42).

2-Deuterio-3-(methyl-d_3)-sulfonyl-3*H*-benz[*d*]azepine (14) Sodium hydride 0.26 g (0.011 mol), **1** (0.29 g, 0.002 mol), and dry DMSO-d_6 (10 ml) were employed in the general procedure, except for the use of deuterium oxide (5 ml) for decomposition of methylsulfinylmethyl carbanion. The residue was purified by column chromatography (silica gel, benzene : $CHCl_3$ = 5 : 1) and recrystallized from benzene : cyclohexane (1 : 1) to give **14** (25 mg, 6%) as yellow plates. ^{1}H-NMR ($CDCl_3$) δ: 5.48 (1H, s, C_1-H), 5.48 (1H, d, J = 9.0 Hz, C_5-H), 5.94 (1H, d, J = 9.0 Hz, C_4-H), 6.73—7.08 (4H, m, C_{6-9}-H). *Anal.* Calcd for $C_{11}H_7D_4NO_2S$: C, 58.64; H, 4.92; N, 6.22. Found: C, 58.55, H, 4.96; N, 6.07. MS m/z (%): 225 (M^+, 9), 144 (17), 143 ($M^+-SO_2CD_3$, 100), 116 (143−HCN, 60), 115 (143−DCN, 48). High-resolution MS m/z: Calcd for $C_{11}H_7D_4NO_2S$ (M^+): 225.0761. Found: 225.0775. Calcd for C_9H_6D (143−HCN): 116.0610. Found: 116.0602. Calcd for C_9H_7 (143−DCN): 115.0547. Found: 115.0559.

1-Methyl-7-hydroxyisoquinoline 2-Oxide (7) Compound **7** was prepared from **6** according to the general procedure. The reaction mixture was poured into water and neutralized with AcOH. The solution was evaporated *in vacuo* and the residue was extracted with hot benzene. The benzene solution was evaporated and the residue was purified by column chromatography (silica gel, $CHCl_3$), and recrystallized from benzene to give **7** (0.49 g, 14%) as yellow needles, mp 257—258 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.70 (3H, s, CH_3), 7.25 (1H, d, J = 8.0 Hz, C_6-H), 7.27 (1H, s, C_8-H), 7.72 (1H, d, J = 5.2 Hz, C_3-H), 7.85 (1H, d, J = 8.0 Hz, C_5-H), 8.06 (1H, d, J = 5.2 Hz, C_4-H). MS m/z (%): 175 (M^+, 48), 159 (M^+-O, 100), 158 (M^+-OH, 69), 131 (40), 130 (16), 103 (18). *Anal.* Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.37; H, 5.20; N, 7.76.

5-Methyl-1,6-naphthyridine 6-Oxide (9) Sodium hydride (0.26 g, 0.011 mol) was dissolved in dry DMSO (10 ml) and tetrahydrofuran (THF) (20 ml) at 70 °C under a nitrogen atmosphere, and the reaction mixture was chilled to −5 °C. A solution of 1,6-naphthyridine 6-oxide[7] (0.29 g, 2 mmol) in DMSO (5 ml) was dropped into the above solution. The reaction mixture was kept at −5 °C and stirred for 5 min. The mixture was poured into a large excess of water and the solution was neutralized with AcOH, then evaporated *in vacuo*. The residue was extracted with hot $CHCl_3$ and the extract was evaporated. The resultant residue was purified by column chromatography (silica gel, $CHCl_3$: Me_2CO = 5 : 1), and recrystallized from benzene to give **9** (0.05 g, 16%) as colorless needles, mp 145—147 °C (lit.,[7] mp 158—159 °C). Picrate 215—216 °C (dec.) (from EtOH, lit.,[7] mp 216—219 °C). ^{1}H-NMR ($CDCl_3$) δ: 2.88 (3H, s, CH_3), 7.57 (1H, dd, J = 9.0, 4.4 Hz, C_3-H), 7.83 (1H, d, J = 7.2 Hz, C_8-H), 8.28 (1H, dd, J = 9.0, 4.4 Hz, C_4-H), 8.40 (1H, d, J = 7.2 Hz, C_7-H), 8.92 (1H, dd, J = 4.4, 1.6 Hz, C_2-H). MS m/z (%): 160 (M^+, 97), 144 (M^+-O, 100), 143 (M^+-OH, 92), 117 (144−HCN, 33), 116 (143−HCN, 57). *Anal.* Calcd for $C_{15}H_{11}N_5O_8$: C, 46.28; H, 2.85; N, 17.99. Found: C, 46.32; H, 2.69; N, 17.59.

1-Methyl-4-isoquinolinecarbonitrile (11) Compound **11** was prepared from **10** according to the general procedure. The residue was recrystallized from cyclohexane to give **11** (1.01 g, 30%) as colorless needles, mp 98—101 °C (lit.,[8] mp 100—101 °C). ^{1}H-NMR ($CDCl_3$) δ: 3.00 (3H, s,

CH_3), 7.52—7.92 (2H, m, $C_{6,7}$-H), 8.04—8.24 (2H, m, $C_{5,8}$-H), 8.67 (1H, s, C_3-H).

1-Methyl-7-methoxyisoquinoline (13) Compound **13** was prepared from **12** according to the general procedure. The reaction mixture was poured into a large excess of water and the solution was extracted with CH_2Cl_2. The extract was dried over $MgSO_4$, the solvent was evaporated off, and the residue was purified by column chromatography (silica gel, $CHCl_3 : Me_2CO = 5 : 1$) to give **13** (0.42 g, 12%) as a yellow oil, picrate mp 254—257 °C (from Me_2CO) (lit.,[9] mp 256—258 °C). ^{1}H-NMR ($CDCl_3$) δ: 2.73 (3H, s, CH_3), 3.70 (3H, s, CH_3O), 6.87 (1H, d, $J = 2.6$ Hz, C_8-H), 7.04 (1H, dd, $J = 8.6$, 2.6 Hz, C_6-H), 7.14 (1H, d, $J = 5.6$ Hz, C_4-H), 7.36 (1H, d, $J = 8.6$ Hz, C_5-H), 8.10 (1H, d, $J = 5.6$ Hz, C_3-H).

7-Methoxyisoquinoline 2-Oxide (4) A solution of **12** (1.6 g, 0.01 mol) and *m*-chloroperbenzoic acid (*m*-CPBA) (2.6 g 0.015 mol) in $CHCl_3$ (90 ml) was stirred at room temperature for 3 h. A solution of 5% Na_2CO_3 (60 ml) was added to the reaction mixture, and the whole was extracted with $CHCl_3$. The extract was dried over $MgSO_4$, the solvent was evaporated off, and the residue was purified by column chromatography (silica gel, benzene : $CHCl_3 = 1 : 1$) and recrystallized from benzene to give **4** (0.84 g, 48%) as colorless needles, mp 159—160 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.88 (3H, s, CH_3O), 6.88 (1H, d, $J = 2.0$ Hz, C_8-H), 7.13 (1H, dd, $J = 9.2$, 2.0 Hz, C_6-H), 7.52 (1H, d, $J = 7.6$ Hz, C_4-H), 7.58 (1H, d, $J = 9.2$ Hz, C_5-H), 7.96 (1H, d, $J = 7.2$ Hz, C_3-H), 8.61 (1H, s, C_1-H). MS *m/z* (%): 175 (M^+, 100), 159 ($M^+ - O$, 28), 148 ($M^+ - HCN$, 68), 133 (80), 132 (60). *Anal.* Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.66; H, 5.13; N, 7.83.

7-Hydroxyisoquinoline 2-Oxide (6) A solution of 7-hydroxyisoquinoline (1.45 g, 0.01 mol) and *m*-CPBA (2.6 g, 0.015 mol) in $CHCl_3$ (90 ml) was stirred at room temperature for 3 h. The resulting precipitate was collected and recrystallized from EtOH to give **6** (1.3 g, 81%) as colorless needles, mp 288—290 °C. ^{1}H-NMR (DMSO-d_6): 7.08 (1H, d, $J = 2.0$ Hz, C_8-H), 7.14 (1H, dd, $J = 9.2$, 2.0 Hz, C_6-H), 7.70—7.90 (3H, m, $C_{3,4,5}$-H), 8.73 (1H, s, C_1-H). MS *m/z* (%): 161 (M^+, 26), 145 ($M^+ - O$, 100), 144 ($M^+ - OH$, 33), 117 (28). *Anal.* Calcd for $C_9H_7NO_2$: C, 67.08; H, 4.38; N, 8.69. Found: C, 67.11; H, 4.55; N, 8.50.

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