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Ring Transformation of 4-Amino-1*H*-1,5-benzodiazepine-3-carbonitrile. The Use of Hydroxylamines as Nucleophile

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The reaction of 4-amino-1*H*-1,5-benzodiazepine-3-carbonitrile hydrochloride (**1**) with hydroxylamine gave a ring-opened compound, 3-amino-3-(*o*-aminoanilino)-2-cyano-2-propenaloxime (**5**). Compound **5** was converted to 5-(*o*-aminoanilino)-4-cyanoisoxazole (**6**) on treatment with hydrochloric acid. Compound **1** was also reacted with methoxyamine to give 2-(1′-cyano-2′-methoxyaminovinyl)benzimidazole (**8**). On the other hand, hydrolysis of **1** at pH 1 gave 2-cyanomethylbenzimidazole hydrochloride (**12**).

Keywords——NMR; acid hydrolysis; nucleophilic reaction; 2-cyanomethylbenzimidazole; 5-(*o*-aminoanilino)-4-cyanoisoxazole; 2-(1′-cyano-2′-methoxyaminovinyl)benzimidazole

Ring transformations of 1,5-benzodiazepines have been extensively studied by several groups.[2–6] In a previous paper,[7] we reported a facile synthesis of 4-amino-1*H*-1,5-benzodiazepine-3-carbonitrile hydrochloride (**1**) by the reaction of *o*-phenylenediamine with ethoxymethylenemalononitrile. This diazepine was found to be easily hydrolyzed to 2,4-diamino-3*H*-1,5-benzodiazepine (**2**), 2-hydroxy-4-methyl-3*H*-1,3,5-benzotriazepine (**3**), and 2-(1′-cyano-2′-hydroxyvinyl)benzimidazole (**4**) under basic conditions. We report here ring transformations of **1**, which involve ring opening in the diazepine nucleus by nucleophilic attack of hydroxylamines, and also describe the hydrolysis of **1** to 2-cyanomethylbenzimidazole hydrochloride (**12**).

Aqueous sodium hydroxide solution (10%) was gradually added to a hot solution of **1** and hydroxylamine hydrochloride. The reaction mixture (pH 8.5) became colorless and clear when heated for 10 min on a water bath. From this solution, 3-amino-3-(*o*-aminoanilino)-2-cyanopropenaloxime (**5**) and 5-(*o*-aminoanilino)-4-cyanoisoxazole (**6**) were obtained in 66% and 14% yields, respectively. The formation of **6** should depend upon the acidity of the solution. In fact, the reaction of the free base of **1** with hydroxylamine under basic conditions gave only **5** as crystals in 33% yield, and **5** was converted to **6** on treatment with hydrochloric acid. Therefore, a certain amount of **5** would have been converted to **6** in the first experiments, where the acidity was maintained until the solution was neutralized. The structures of **5** and **6** were determined on the basis of nuclear magnetic resonance (NMR), infrared (IR), mass spectral (MS) and elementary analysis data. As shown in Fig. 1, **5** showed ion peaks at *m/e* 217 (M^+), 200, 183, 156, 129 and 103, and **6**, at *m/e* 200 (M^+), 183, 156, 155, 129 and 103 in the mass spectra. These results and elementary analyses data indicate that **5** is a hydroxylamine adduct of the free base of **1**, and **6** is the deammonia com-

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2) J. Thiele and G. Steimming, *Chem., Ber.*, **40**, 955 (1907).
3) D. Lloyd, R.H. McDougall, and D.R. Marshall, *J. Chem. Soc.*, **1965**, 3785.
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pound of **5**. Qualitative analysis of **5** and **6** was also carried out. When a suspension of **5** in aqueous ammonia containing silver nitrate was boiled in a test tube for a few minutes, Ag^+ was reduced to Ag. This indicates the presence of a reductive group such as –CH=N–OH (or =CH–NH–OH) in **5**. However, no reduction occurred when **6** was examined under the same conditions. In the NMR spectrum, **5** showed a broad signal due to amino protons at

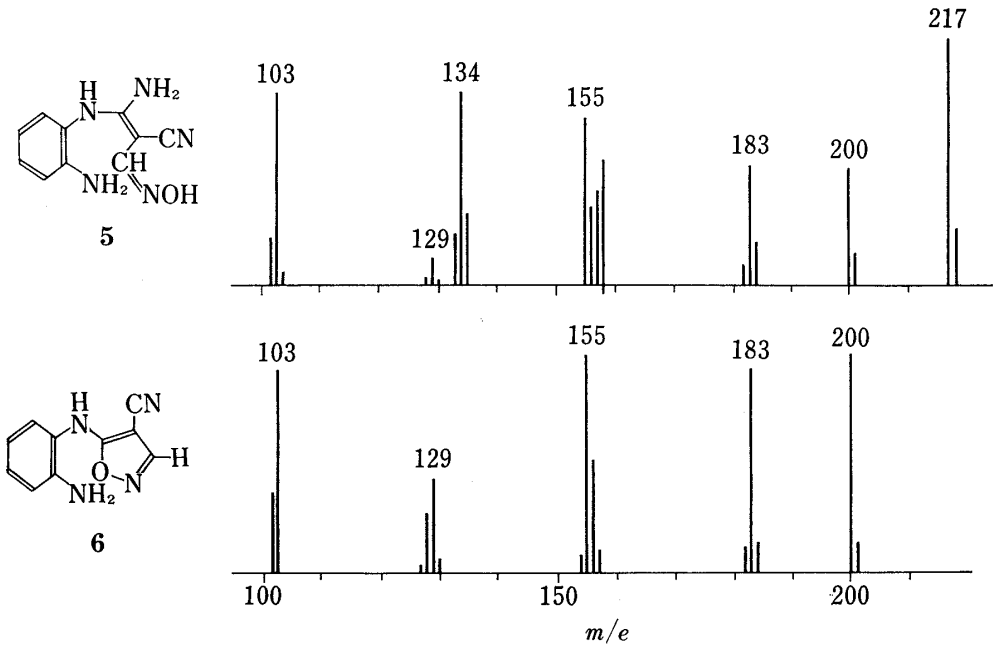

Fig. 1. Mass Spectra of Compounds **5** and **6**

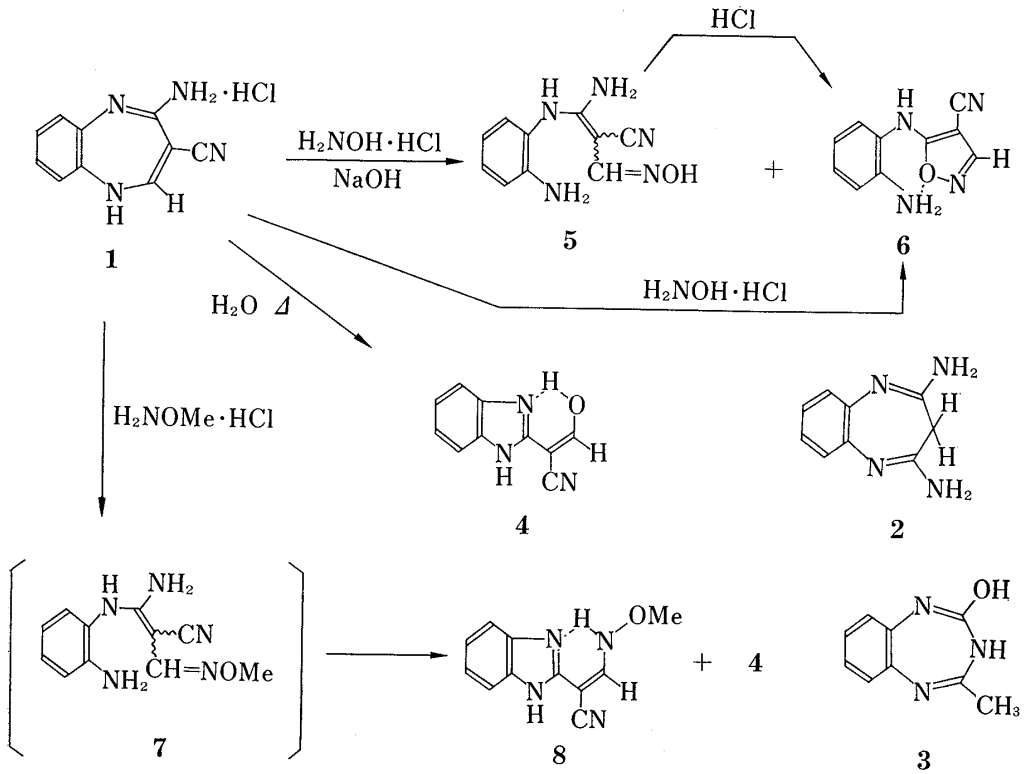

Chart 1

4.97 ppm, a broad signal due to aromatic amino protons at 6.35 ppm, multiplet signals due to aromatic, olefinic and aromatic amino (–NH–) protons at 6.40—7.10 ppm, and a broad signal due to a hydroxyl proton at 10.33 ppm. On the other hand, **6** showed a broad signal due to an aromatic amino (–NH–) proton at 6.32 ppm, multiplet signals due to aromatic protons at 7.00—7.60 ppm, and a broad signal due to aromatic amino protons at 12.17 ppm. Both **5** and **6** showed a cyano absorption band in the IR spectra. On the basis of these data, we proposed the reaction pathways shown in Chart 1, which involve nucleophilic attack of hydroxylamine at the 2-position of **1** to give the ring-opened adduct **5**, followed by liberation of ammonia from **5** to afford **6**. A hydrogen bond may exist between the amino proton and oxygen of the isoxazole ring, because the signal for aromatic amino protons was observed at lower magnetic field (12.17 ppm).

The reaction of **1** with methoxyamine hydrochloride gave a mixture of 2-(1′-cyano-2′-methoxyaminovinyl)benzimidazole (**8**) (36%) and **4** as a by-product (4%). N-Methylhydroxylamine (both the hydrochloride and the free base), however, did not react with **1** under the same conditions. The reason for this might be slight steric hindrance of the methyl group. As shown in Chart 1, **8** should be produced when ammonia is liberated from a presumed intermediate (**7**). In the NMR spectrum of **8**, coupling between a methoxyamino proton and an olefinic proton was observed. The constant is $J_{NH-CH}=16$ Hz, which indicates they are in a *trans* relation. The signal for the methoxyamino proton was observed at 9.62 ppm. This may indicate the formation of a hydrogen bond with the nitrogen of the heterocycle. Competition between the nucleophile and water may be responsible for the low yield of **8** and the formation of the by-product **4**. In fact, **4** was obtained by hydrolysis of **1** in the absence of base.[8]

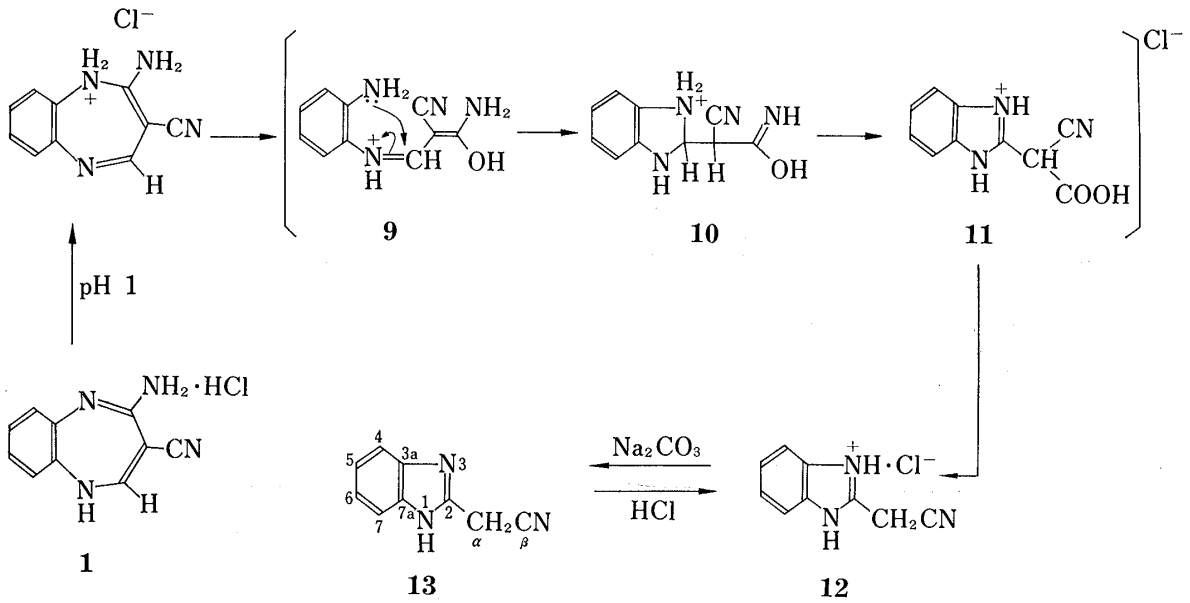

Chart 2

We attempted to react **1** with an amino acid, valine or alanine, in place of hydroxylamine. However, the reaction gave complicated products resulting from the hydrolysis of **1**. Thus, we used the hydrochlorides of the amino acids. Compound **1** and valine hydrochloride were dissolved in water, and the solution was heated on a water bath for 5 hr to give 2-cyanomethylbenzimidazole hydrochloride **12** (final pH 2—3). Thiele and Steimming[2] have reported

8) When a solution of **1** in water was heated on a water bath for 3 hr, a small amount of **4** precipitated.

ring transformations of 1,5-benzodiazepines to benzimidazole derivatives in mineral acids, so we examined the acid hydrolysis of **1**. Upon heating a solution of **1** under acidic conditions (pH 1), **12** was obtained in good yield. Thus, **12** was a product of acid hydrolysis of **1**. The structure was deduced from the analytical data, and the compound was identical with an authentic sample prepared by the method of Copeland and Day.[9] It is worth noting that no absorption band was observed in the C≡N region in its IR spectrum, but the free base of **12** showed the band at 2256 cm^{-1}. Since **4** was not changed to **12** by heating at pH 1, we propose a mechanism (Chart 2) in which **12** is formed by C_4–N_5 bond cleavage, followed by formation of the benzimidazoline nucleus (**10**), and finally oxidation and decarboxylation.

Experimental[10]

3-Amino-3-(*o*-aminoanilino)-2-cyano-2-propenaloxime (**5**)——a) A solution of 10 ml of 10% aq. NaOH was gradually added to a hot solution of 1 g of **1** and $NH_2OH \cdot HCl$ (1.39 g) in 50 ml of water, and the mixture (pH 8.5) was heated on a water bath for 10 min. After standing overnight, prisms of **5** (0.65 g, 66%) and a powder of **6** (0.13 g, 14.3%) were precipitated. Recrystallization of the former from ethanol gave colorless needles of **5** (0.37 g, 37%), mp 193—194°. NMR ppm (10% solution in DMSO-d_6): 4.97 (2H, s, NH_2), 6.35 (2H, s, aromatic NH_2), 6.40—7.10 (6H, m, aromatic, olefinic, aromatic NH), 10.33 (1H, s, oxime-OH). IR ν_{max}^{KBr} cm^{-1}: 2200 (C≡N). UV λ_{max}^{MeOH} nm (log ε): 211 (4.16), 220 (4.15), 245 (4.12), 264 (4.21), 294 (3.79). MS *m/e*: 217 (M^+). *Anal.* Calcd for $C_{10}H_{11}N_5O$: C, 55.29; H, 5.10; N, 32.24. Found: C, 55.40; H, 5.24; N, 32.45. The powder was slightly soluble in ethanol, and was characterized as **6** after recrystallization from DMF–ethanol.

b) A solution of 1 g of **1** in 50 ml of water was treated gradually with a solution of 10 ml of 10% aq. NaOH at room temperature. The free base of **1** (red powder) was precipitated. Next, 1.4 g of $NH_2OH \cdot HCl$ was added to the above suspension, then the mixture was heated on a water bath for 30 min, and allowed to stand overnight to precipitate colorless prisms of **5** (0.33 g, 33%).

5-(*o*-Aminoanilino)-4-cyanoisoxazole (**6**)——a) A mixture of 1 g of **1** and 0.5 g of $NH_2OH \cdot HCl$ in 50 ml of water was heated on a water bath for 5 hr. Brown crystals of **6** (0.85 g, 93.7%) were precipitated. Recrystallization from ethanol gave prisms of **6**, mp 263° (dec.). NMR ppm (10% solution in DMSO-d_6): 6.32 (1H, s, NH), 7.00—7.60 (5H, m, aromatic), 12.17 (2H, s, NH_2). IR ν_{max}^{KBr} cm^{-1}: 2190 (C≡N). UV λ_{max}^{MeOH} nm (log ε): 204 (3.90), 219 (4.22), 255 (4.05), 312 (4.33). MS *m/e*: 200 (M^+). *Anal.* Calcd for $C_{10}H_8N_4O$: C, 59.99; H, 4.02; N, 27.99. Found: C, 59.71; H, 4.11; N, 27.83.

b) A suspension of 1 g of **5** in 50 ml of water was treated with 1 ml of 10% HCl solution at room temperature. After 20 min, needles of **6** (0.89 g, 98%) were precipitated.

2-(1′-Cyano-2′-methoxyaminovinyl)benzimidazole (**8**)——A solution of 1 g of **1** in 50 ml of water was treated with 0.7 g of $CH_3ONH_2 \cdot HCl$, and the mixture was heated on a water bath for 3 hr. Colorless powder was precipitated. The same compound was also obtained by concentration of the filtrate to a half volume under reduced pressure. Recrystallization from CH_3CN–$CHCl_3$ gave **8** as a powder (0.35 g, 36%), mp 199—201°. NMR ppm (10% solution in DMSO-d_6): 3.85 (3H, s, CH_3), 6.88 (4H, m, aromatic), 7.00 (1H, d, J_{CH-NH}=16 Hz, olefinic), 7.78 (1H, s, ring NH), 9.62 (1H, d, J_{NH-CH}=16 Hz, NH). IR ν_{max}^{KBr} cm^{-1}: 2223 (C≡N). UV λ_{max}^{MeOH} nm (log ε): 207 (4.39), 223 (4.48), 259 (4.09), 266 (4.15), 281 (4.28), 288 (4.29), 318 (4.44), 327 (4.44). MS *m/e*: 214 (M^+). *Anal.* Calcd for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.70; N, 26.15. Found: C, 61.60; H, 4.51; N, 25.93.

2-Cyanomethylbenzimidazole Hydrochloride (**12**)——A solution of 5 g of **1** in 200 ml of 0.1 N HCl was heated for 5 hr on a water bath, then the solvent was concentrated to a half volume under reduced pressure. Neutralization with 10% Na_2CO_3 gave a yellow powder, which was dissolved in diluted HCl. After removal of the solvent, crystals were obtained. Recrystallization from ethanol gave prisms of **12** (3 g, 70%), mp 240.5—242° (dec.). Free base, mp 209—210° (lit. 9, mp 209.7—210.7°). NMR ppm (10% solution in DMSO-d_6): 4.40 (2H, s, CH_2), 7.10—7.70 (4H, m, aromatic). ^{13}C-NMR ppm (DMSO-d_6): 145.08 (C_2), 138.68 (C_{3a}, C_{7a}), 122.99 (C_5, C_6), 116.68 (C_β), 115.42 (C_4, C_7), 18.35 (C_α). UV λ_{max}^{MeOH} nm (log ε): 207 (4.11), 242 (3.72), 248 (3.68), 265 (3.58), 271 (3.70), 278 (3.70), 313 (2.90). MS *m/e*: 157 (M^+). *Anal.* Calcd for $C_9H_8ClN_3$: C, 55.82; H, 4.16; N, 21.70. Found: C, 56.10; H, 4.23; N, 21.92.

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10) Melting points were determined using a Yamato Scientific stirred liquid apparatus and are uncorrected. IR and UV spectra were recorded on a Japan Spectroscopic IRA-1 spectrometer and a Hitachi 200-20 spectrophotometer, respectively. NMR spectra were obtained on Varian T-60 and ^{13}C-JMS-PS-100 spectrometers with Me_4Si as an internal standard. MS spectra were obtained on a JMS-01S spectrometer (Japan Electron Optics Laboratory Co., Ltd.). Indicator paper (pH-Box, Merck) was used for pH measurement.