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Preparation and Hydrolysis of 4-Amino-1*H*-1,5-benzodiazepine-3-carbonitrile[1)]

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In the presence of hydrochloric acid, *o*-(2,2-dicyanovinyl)aminoaniline is easily converted into 4-amino-1*H*-1,5-benzodiazepine-3-carbonitrile, which can be hydrolyzed with various bases to other diazepine, triazepine or benzimidazole derivatives. Ethyl 4-amino-1*H*-1,5-benzodiazepine-3-carboxlate and other 1,5-benzodiazepine derivatives were also obtained from similar reactions. A remarkable tautomeric nature of compound (IX) is also reported.

Recently, many investigations have been reported on the chemistry of benzodiazepine derivatives.[3)] It has been well known that *o*-phenylenediamine is a useful starting material for the synthesis of 1,5-benzodiazepines.[4)] However, there has been no report concerning the synthesis of 1,5-benzodiazepines from the reaction of *o*-phenylenediamine with ethoxymethylenemalononitrile. One of the reasons should be that *o*-(2,2-dicyanovinyl)aminoaniline (IIIa), prepared from *o*-phenylenediamine and ethoxymethylenemalononitrile, is easily converted to benzimidazole on heating.[5a),5b)] This report describes in detail the synthesis of 4-amino-1*H*-1,5-benzodiazepine-3-carbonitrile hydrochloride (Va) and related compounds and also their behavior in hydrolytic reaction.

Our previous paper[6)] described that N^1-(2-cyanoethyl)benzamidine hydrochloride (I) was cyclized to 6-amino-4,5-dihydro-2-phenylpyrimidine hydrochloride (II) on being refluxed in ethanol. On the basis of this finding, we attempted, at first, the synthesis of a hydrochloride (IVa) of *o*-(2,2-dicyanovinyl)aminoaniline. Treatment of IIIa with 10% hydrochloric acid afforded colorless powder which was characterized as IVa by analysis. Compound IVa is slightly soluble in water or ethanol, and fairly stable in hydrochloric acid.

When the salt IVa was refluxed in ethanol for 2 hr, orange needles were obtained in 92% yield. Its structure was elucidated as 4-amino-1*H*-1,5-benzodiazepine-3-carbonitrile hydrochloride (Va) from the data of nuclear magnetic resonance (NMR) and infrared (IR) spectra, mass and elementary analyses. The method for synthesizing Va could be applied to the synthesis of 4-amino-8-chloro-1*H*-1,5-benzodiazepine-3-carbonitrile hydrochloride (Vc), ethyl

1) A Part of this work was reported by Y. Okamoto and T. Ueda, in *J. C. S. Chem. Comm.*, 367 (1973).
2) Location: *Shirokane, Minato-ku, Tokyo 108, Japan.*
3) G.A. Archer and L.H. Sternbach, *Chem. Rev.*, **68**, 747 (1968).
4) For example, A. Takamizawa, and K. Hirai, Japan Patent 18950 (1966) [*C.A.*, **66**, 37969*m* (1967)].
5) *a*) K.S. Sardesai and S.V. Sunthankar, *J. Sci. Ind. Res.*, (India), **B18**, 158 (1959); *b*) P.H. Stahl, R. Barchet, and K.W. Merz, *Arzneimittelforsch.*, **18**, 1214 (1968).
6) Y. Okamoto, T. Tsuji, and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **17**, 2273 (1969).

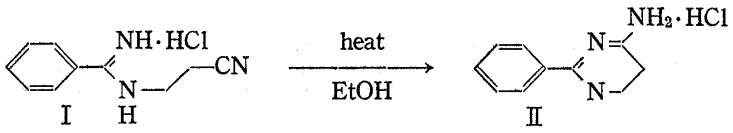

Chart 1

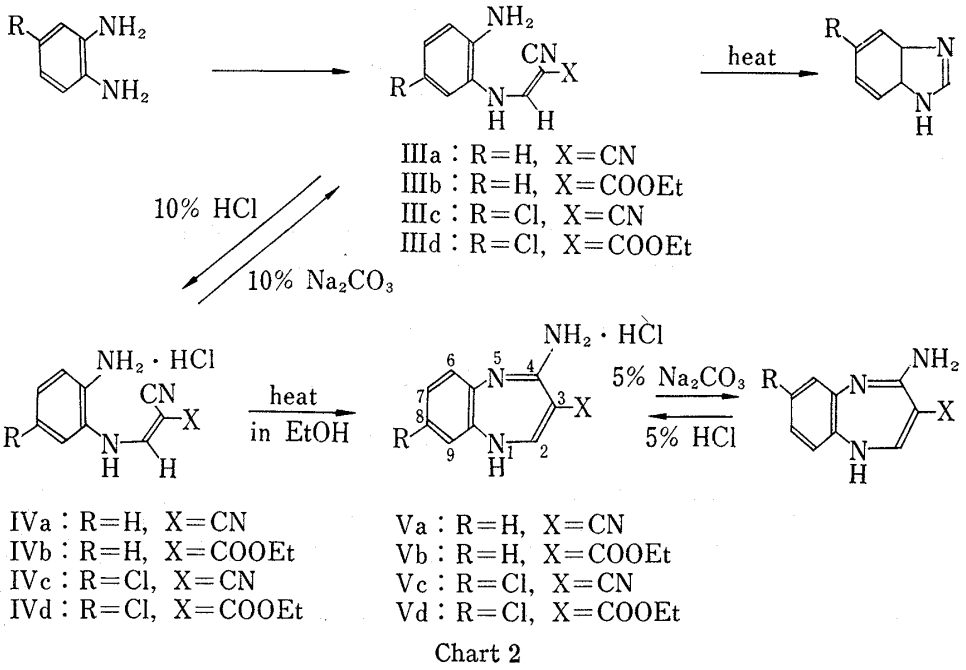

Chart 2

4-amino-1*H*-1,5-benzodiazepine-3-carboxylate hydrochloride (Vb) and its chloro derivative (Vd).

Since the structure of Va may be regarded as an *o*-aminonitrile, it may be transformed into a variety of condensed heterocyclic systems.[7] In an attempt to obtain a condensed benzodiazepine (VI), guanidine was added to a hot aqueous solution of Va, but 2,4-diamino-3*H*-1,5-benzodiazepine (VII) was obtained in 30% yield instead of the expected condensation product VI. A similar result was also obtained with methylguanidine. Apparently, Va underwent base-catalyzed hydrolysis. Namely, reaction of Va (1 g) with excess sodium hydroxide (1.4 g) in 50 ml of water on a water-bath for 15 min gave VII in 50% yield. On the other hand, hydrolysis of Va (1 g) with 0.36 g of sodium hydroxide in 100 ml of water (pH 8.5) afforded another hydrolysis product, 2-hydroxy-4-methyl-3*H*-1,3,5-benzotriazepine (IX), in 47% yield, and 2-(1′-cyano-2′-hydroxyvinyl)benzimidazole (VIII) was obtained by treatment with aqueous ammonia or 2-aminopyrimidine. Heating of an aqueous solution of Va for 3 hr yielded also VIII. From these results, we proposed a mechanism shown in Chart 3, involving cleavage of either a C-C bond (a) or a C-N bond (b) of diazepine ring in Va. Which cleavage occurs probably depends on the basicity of the base used.

In contrast, compound Vb was not converted to products similar to those described above under the same conditions, the free base of Vb being obtained exclusively. These differences between Va and Vb in hydrolysis seemed to depend on whether or not a hydrogen bond could be formed in the molecules. *o*-Aminocarboxylate moiety in Vb might form a six-membered ring by intramolecular hydrogen bonding, whereas *o*-aminonitrile in Va could not form such a bond and, moreover, a cyano group should be more electron-withdrawing than a carboxylate group. These might promote hydrolysis of Va more effectively than Vb.

Spin systems for aromatic protons are shown in Fig. 1. Although spectra of these compounds showed symmetrical four spin systems, they are different from each other. Compounds

7) E.C. Taylor and A. McKillop, *Adv. Org. Chem.*, 7, 286 (1970).

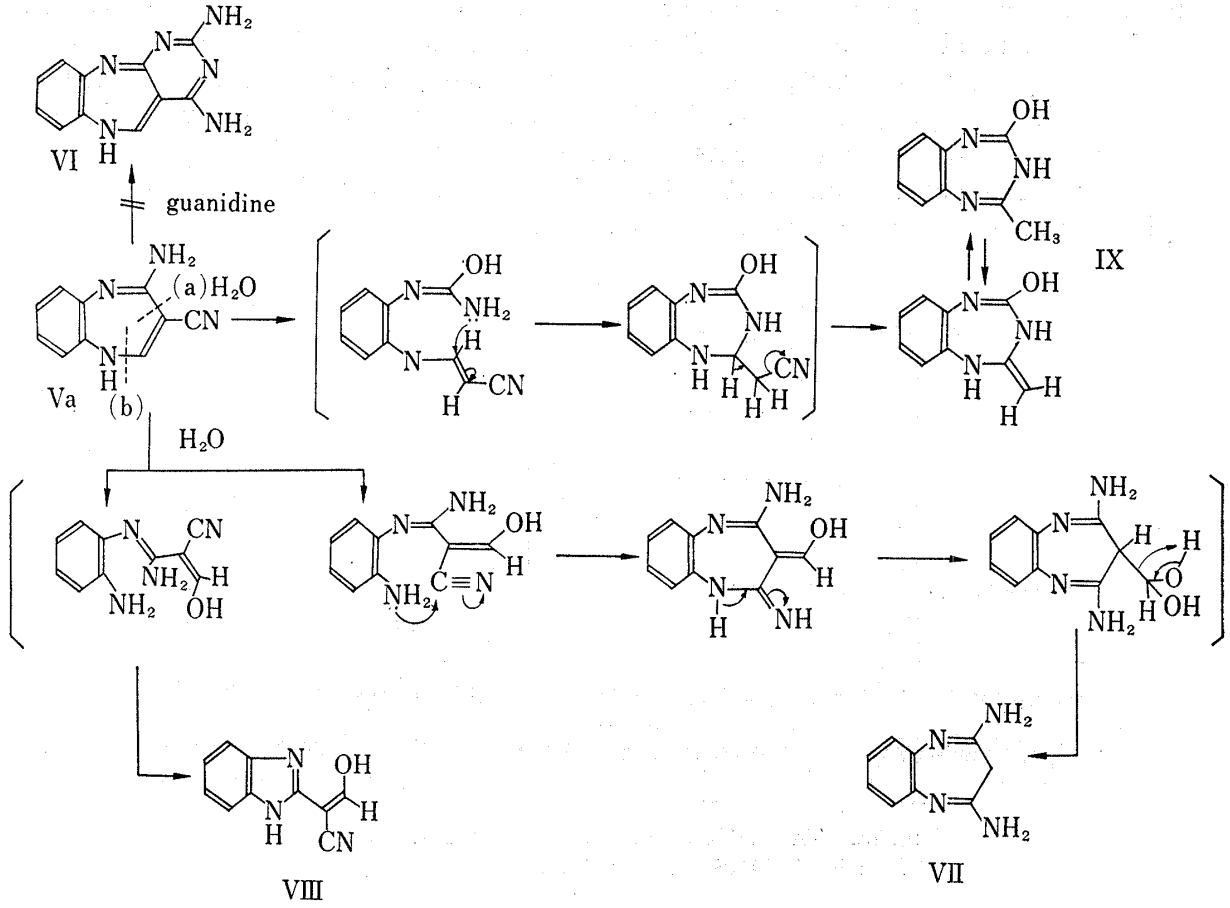

Chart 3

Va and VIII showed A_2B_2 (or AA'BB') patterns and compounds VII and IX showed A_2A_2' and A_4 patterns, respectively. Thus, the signal patterns might be due not only to circumstances around aromatic protons but a $\Delta\nu/J$ ratio, where $\Delta\nu$ is the chemical shift difference in (Hz) between aromatic protons.[8] The singlet appearance of the aromatic protons of VII and IX in NMR spectra seemed to be due to the small $\Delta\nu/J$ ratio.[9] As shown in Fig. 2, compound

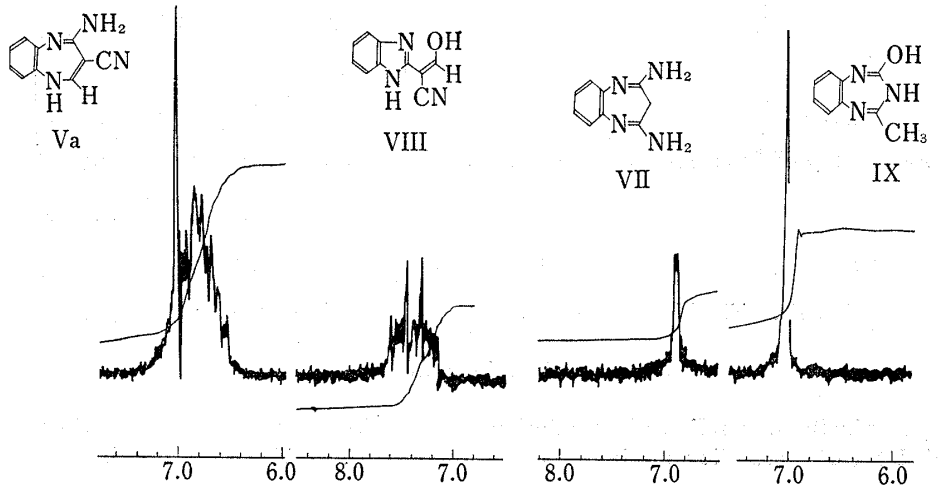

Fig. 1. The NMR Spectra of Free Bases Va, VII, VIII, and IX

8) F.A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," ed., Academic Press, New York, N.Y., 1969, p. 91.
9) S.S. Danyluk, *Can. J. Chem.*, **41**, 387 (1963).

IX forms tautomeric systems. A similar tautomerism of diazepine derivatives has been reported by Israel and others.[10] It is difficult to asign the signals of NH or OH proton, but signals of methyl protons at 2.25, aromatic protons at 7.00 and olefinic protons at 6.80 ppm are recognized. Methyl protons and olefinic protons could be exchanged with duterium oxide. The exchange for methyl protons was not so rapid, and the signal disappeared entirely 20 min after addition of duterium oxide. From these results, it should be noted that methyl-methylene tautomerism might exist in compound IX.

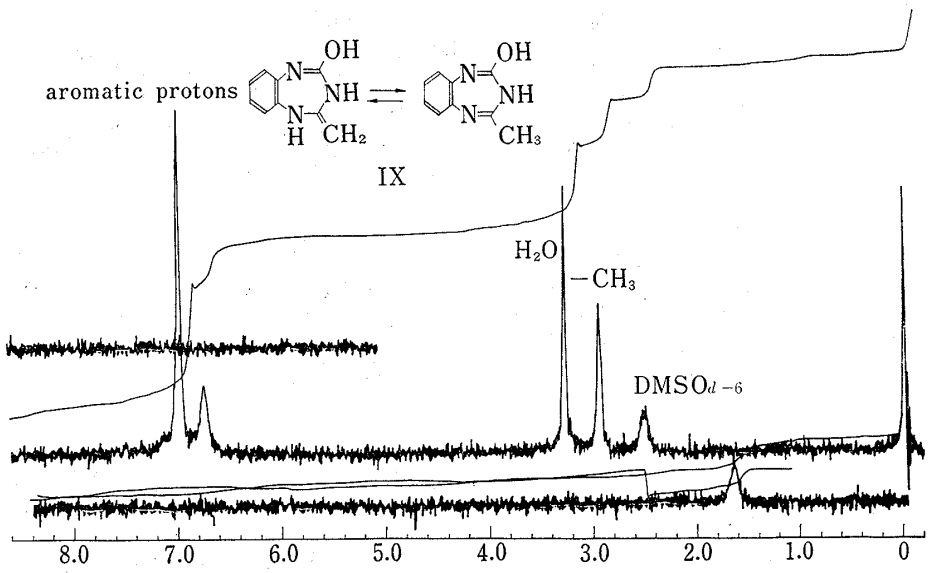

Fig. 2a. The NMR Spectrum of Compound IX (10% Solution in DMSO $_{d-6}$, 60 MHz)

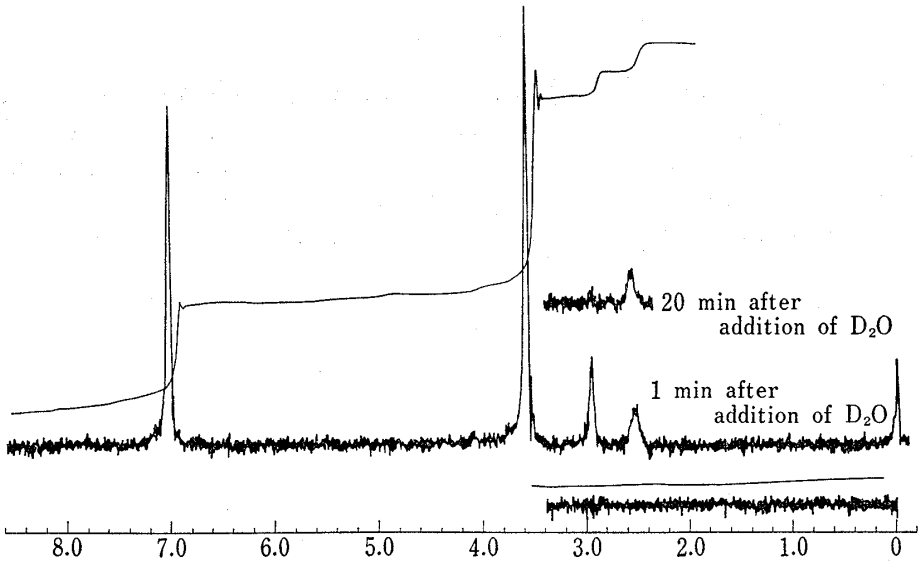

Fig. 2b. The NMR Spectrum of Compound IX (DMSO $_{d-6}$ +D_2O)

Experimental[11]

***o*-(2,2-Dicyanovinyl)aminoaniline Hydrochloride (IVa)**——To a 10% solution of HCl in 100 ml of cold water was added 1 g of *o*-(2,2-dicyanovinyl)aminoaniline (IIIa).[5b] The salts obtained were washed with

10) M. Israel, L.C. Jones, and E.J. Modest, *J. Heterocyclic Chem.*, 4, 659 (1967).

11) All melting points are uncorrected. The IR spectra were recorded on a Japan Spectroscopic Model IRA-1 spectrometer. The NMR spectra were obtained on a Varian T 60 spectrometer with tetramethylsilane as reference. Mass spectra were obtained on a JMS-O1S spectrometer (Japan Electron Optics Laboratory Co., Ltd.).

100 ml of water and 50 ml of ethanol, and dried. This gave 1.1 g of IVa (95% yield), mp 230°. *Anal.* Calcd. for $C_{10}H_9N_4Cl$: C, 54.43; H, 4.11; N, 25.39. Found: C, 54.19; H, 4.09; N, 25.64.

(IVb), (IVc), and (IVd) were also yielded quantitatively by the same procedure described above, and exerted to next step without recrystallization.

4-Amino-1*H*-1,5-benzodiazepine-3-carbonitrile Hydrochloride (Va) and Its Chloro Derivative (Vc)——Compound IVa (1 g) was refluxed for 2 hr in 100 ml of ethanol. Orange needles were obtained and filtered by suction. Recrystallization from water gave 0.92 g (92% yield) of Va. mp 280° (decomp.). *Anal.* Calcd. for $C_{10}H_9N_4Cl$: C, 54.43; H, 4.11; N, 25.39. Found: C, 54.45; H, 4.02; N, 25.61. Mass Spectrum *m/e*: 184 (M^+). IR cm^{-1}: $\nu_{C\equiv N}$ 2223 (KBr). NMR (10% solution in $DMSO_{d-6}$) δ: 7.02 (4H, multiplets, aromatic protons), 7.37 (1H, singlet, olefinic proton), 9.30—10.93 (three broad peaks, NH protons).

To a solution of 0.2 g of Na_2CO_3 in 50 ml of water was added 1 g of Va under cooled conditions. Red powder was obtained, and washed with water and ethanol to give 0.78 g (95% yield) of free bases of Va. mp 203° (decomp.). *Anal.* Calcd. for $C_{10}H_8N_4$: C, 65.21; H, 4.38; N, 30.42. Found: C, 65.15; H, 4.60; N, 30.22.

Under the same conditions described above, IVc (1 g) was converted to Vc (0.6 g), which was changed to free bases of Vc, and the free bases were recrystallized from ethanol to give red powder mp 205° (decomp.).

Anal. Calcd. for $C_{10}H_7N_4Cl$: C, 54.93; H, 3.23; N, 25.62. Found: C, 54.90; H, 3.31; N, 25.72. Mass Spectrum *m/e*: 220 (M^++2), 218 (M^+). IR cm^{-1}: $\nu_{C\equiv N}$ 2180 (KBr).

Ethyl 4-Amino-1*H*-1,5-benzodiazepine-3-carboxylate (Vb) and Its Chloro Derivative (Vd)——*o*-Phenylenediamine (1 g) and ethyl ethoxymethylenecyanoacetate (1.5 g) were dissolved in 100 ml of ethanol, and the mixture was heated for 10 min on a water-bath. After the mixture had been cooled, HCl gas (0.4 g) was passed into the flask, and then the mixture was refluxed for 3 hr. Orange needles were precipitated, filtered by suction and washed with ethanol to give 1.7 g (80% yield) of Vb, mp 230° (decomp.). *Anal.* Calcd. for $C_{12}H_{14}O_2N_3Cl$: C, 53.84; H, 5.27; N, 15.70. Found: C, 53.44; H, 5.19; N, 15.48. Mass Spectrum *m/e*: 231 (M^+).

Vd was also obtained from the reaction of *p*-chloro-*o*-phenylenediamine (356 mg) with ethyl ethoxymethylenecyanoacetate (423 mg) under the same procedure described above. Recrystallization from water gave Vd (400 mg, 58.9% yield), mp 223° (decomp.). *Anal.* Calcd. for $C_{12}H_{13}O_2N_3Cl_2$: C, 47.70; H, 4.34; N, 13.91. Found: C, 47.91; H, 4.21; N, 13.88. Mass Spectrum *m/e*: 267 (M^++2), 265 (M^+).

2,4-Diamino-3*H*-1,5-benzodiazepine (VII)——To a 2.7% solution of NaOH in 50 ml of water was added 1 g of Va, and the mixture was heated for 15 min on a water-bath. Crystals were precipitated and filtered by suction. Re-precipitation with 5% HCl and 5% Na_2CO_3 solution gave pure compound of VII in 50.6% yield (0.4 g). mp>260°. *Anal.* Calcd. for $C_9H_{10}N_4$: C, 62.05; H, 5.79; N, 32.17. Found: C, 61.84; H, 5.87; N, 31.80. Mass Spectrum *m/e*: 174 (M^+). NMR (10% solution in $DMSO_{d-6}$) δ: 2.65 (2H, singlet, $-CH_2-$), 6.17 (4H, broad peak, $(-NH_2)_2$), 6.88 (4H, $A_2A'_2$, aromatic protons).

Compound VII (1 g) was dissolved in 10% solution of HCl in 10 ml of water. Removal of water under reduced pressure gave crystals, which were recrystallized from ethanol to give dihydrochlorides of VII in 95% yield. mp>260°. *Anal.* Calcd. for $C_9H_{12}N_4Cl_2$: C, 43.74; H, 4.49; N, 22.67. Found: C, 43.64; H, 5.03; N, 22.65. Mass Spectrum *m/e*: 174 (M^+).

2-(1′-Cyano-2′-hydroxyvinyl)benzimidazole (VIII)——Compound Va (0.5 g) was added to a solution of 2-aminopyrimidine (0.43 g) in 30 ml of water. The mixture was heated for 1 hr on a water-bath. and allowed to stand overnight. Precipitated crystals were filtered by suction, and recrystallized from ethanol to give 0.15 g of VIII (36% yield). mp>267°. *Anal.* Calcd. for $C_{10}H_7ON_3$: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.23; H, 3.67; N, 22.77. Mass Spectrum *m/e*: 185 (M^+). NMR (10% solution in $DMSO_{d-6}$) δ: 7.28 and 7.52 (4H, A_2B_2, aromatic protons), 9.03 (1H, singlet, olefinic protons), 13.00 (1H, broad peak, –OH). IR cm^{-1}: $\nu_{C\equiv N}$ 2220 (KBr).

2-Hydroxy-4-methyl-3*H*-1,3,5-benzotriazepine (IX)——Sodium hydroxide (0.36 g) was dissolved in 100 ml of water, and Va (1 g) was added into the solution. The mixture was heated to dissolve on a water-bath for 20 min, and filtered immediately. The filtrate was allowed to stand at room temperature overnight. Colorless crystals were precipitated, filtered by suction, and recrystallized from ethanol-water to give colorless powder in 38% yield (0.3 g). mp 261° (decomp.). *Anal.* Calcd. for $C_9H_9ON_3$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.59; H, 5.38; N, 23.79. Mass Spectrum *m/e*: 175 (M^+). NMR (10% solution in $DMSO_{d-6}$) δ: 2.93 (singlet, $-CH_3$), 6.75 (singlet, olefinic protons), 7.00 (singlet, aromatic protons), 9.97 (broad peak, NH or OH).

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