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Ring Transformation of 4-Amino-1*H*-1,5-benzodiazepine-3-carbonitrile. II.[1] Formation of Ring-opened Hydrazine Adducts

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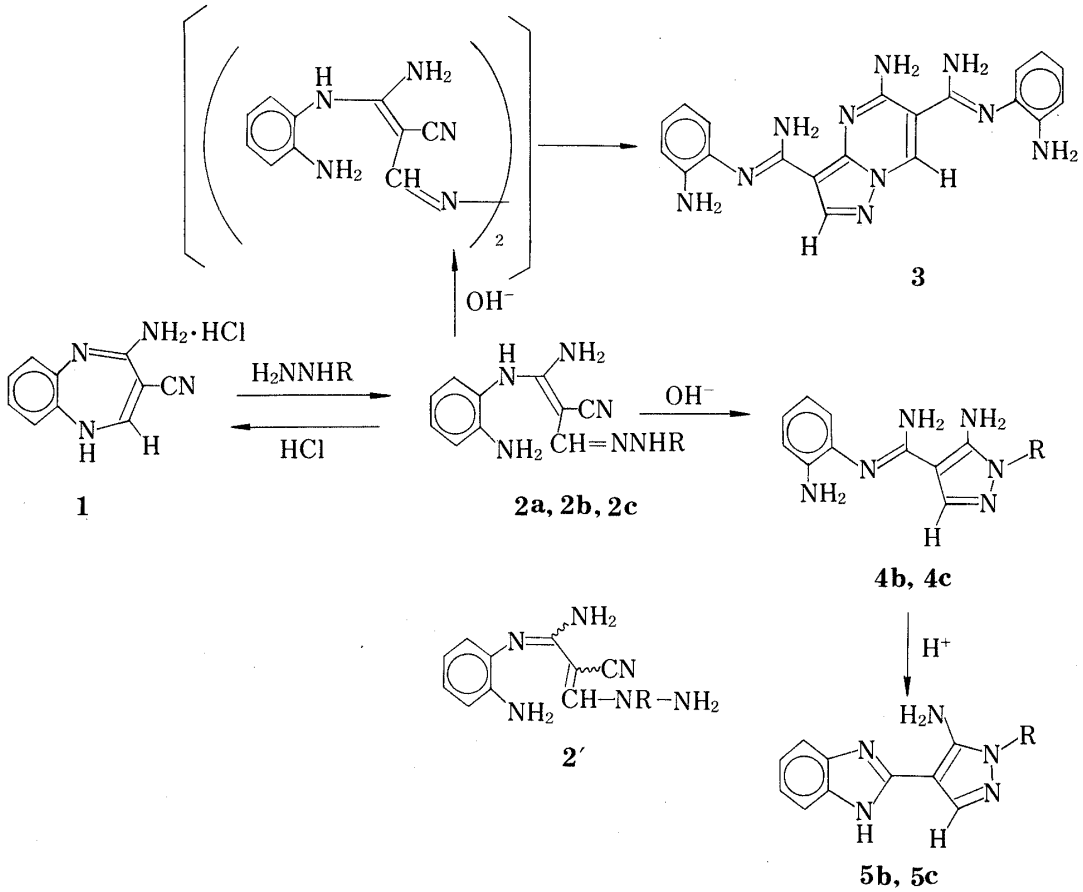
Hydrazines readily reacted with 4-amino-1*H*-1,5-benzodiazepine-3-carbonitrile (**1**) to afford ring-opened hydrazine adducts (**2**) which were recyclized to compounds **3**, **4** and **9** by treatment with aqueous sodium hydroxide solution. Compound **4** was converted to **5** by loss of ammonia in good yield. All the reactions described here were carried out in water.

Keywords——ring transformation; 1,5-benzodiazepine; hydrazine adduct; 3-aminopyrazole; pyrazolo[1,5-*a*]pyrimidine; *N*-(2-amino-3-quinoxalinylmethylene)-*N'*,*N'*-dimethylhydrazine

Recently, we have synthesized 4-amino-1*H*-1,5-benzodiazepine-3-carbonitrile (**1**)[2] and studied the ring transformations of **1** by reaction with hydroxylamines[1] and by hydrolysis.[3] In continuation of these studies, we found that **1** readily reacts with hydrazines in water to give ring-opened hydrazine adducts (**2**) which are key intermediates in the preparation of pyrazole ring compounds. These results are different from those obtained by reaction of **1** with hydroxylamines[1] and by reaction of 1,5-benzodiazepines with hydrazines.[4,5]

As shown in Chart 1, reaction of **1** with hydrazine hydrate in water immediately gave a yellow powder of 3-amino-3-(*o*-aminoanilino)-2-cyano-2-propenal hydrazone (**2a**) in 75% yield. Similarly, reaction of **1** with phenylhydrazine in water afforded 3-amino-3-(*o*-aminoanilino)-2-cyano-2-propenal phenylhydrazone (**2c**) in 90% yield. Attempts to purify **2a** and **2c** failed because of the insolubility of **2a** in ordinary organic solvents and because of their instability to heat. Therefore, their structures were elucidated on the basis of spectral data. The structure **2'**, which could have arisen by nucleophilic attack of the secondary nitrogen of the substituted hydrazines at C-2 of **1**, was excluded, because **1** did not react with *N*,*N'*-dimethylhydrazine (*sym*) under the same conditions (pH 8.5) as used for the reaction of **1** with methylhydrazine. It should be noted that treatment of **2a** with hydrochloric acid affords **1** in 72% yield, while treatment of **2c** with hydrochloric acid affords **1** in 26% yield and the hydrochloride of 3-amino-4-[*N*-(*o*-aminophenyl)amidino]-2-phenylpyrazole (**4c**) in 44% yield. However, on treatment in alkaline media, **2a** was converted to 3,6-bis[*N*-(*o*-aminophenyl)-amidino]-pyrazolo[1,5-*a*]pyrimidine (**3**) in 84% yield, presumably *via* diazane as an intermediate. The structure **3** was determined on the basis of analytical data, especially the infrared (IR) spectrum (no absorption band in nitrile region) and the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum, which showed 20 signals (all the carbons of **3**). Treatment of **2c** in alkaline media afforded **4c** in 80% yield. Similarly, **4b** was obtained in 69% yield from the reaction of **1** with methylhydrazine in alkaline media, presumably *via* **2b**. The structures of **4b** and **4c** were determined by high resolution mass analyses (Fig. 1a and 1b). ^{13}C-NMR spectral analysis also supported the structure **4b**. Compounds **4b** and **4c** were converted to 2-(3-amino-2-methylpyrazol-4-yl)benzimidazole (**5b**) and 2-(3-amino-2-phenylpyrazol-4-yl)-benzimidazole (**5c**) by loss of ammonia, respectively. The structures of **5b** and **5c** were supported by the spectral data.



a : R=H, **b** : R=CH_3, **c** : R=phenyl

Chart 1

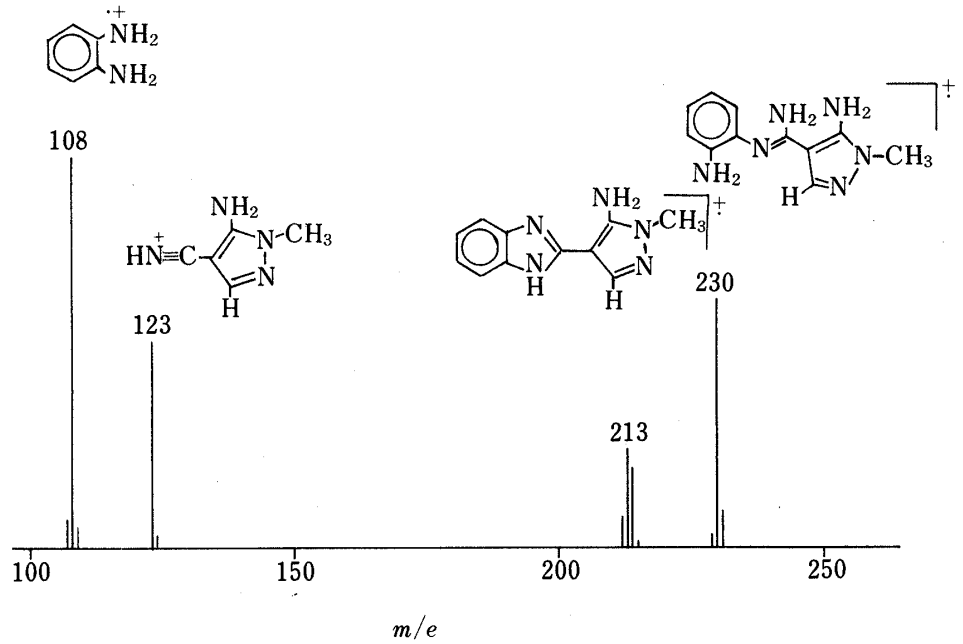


Fig. 1a. MS of 4b

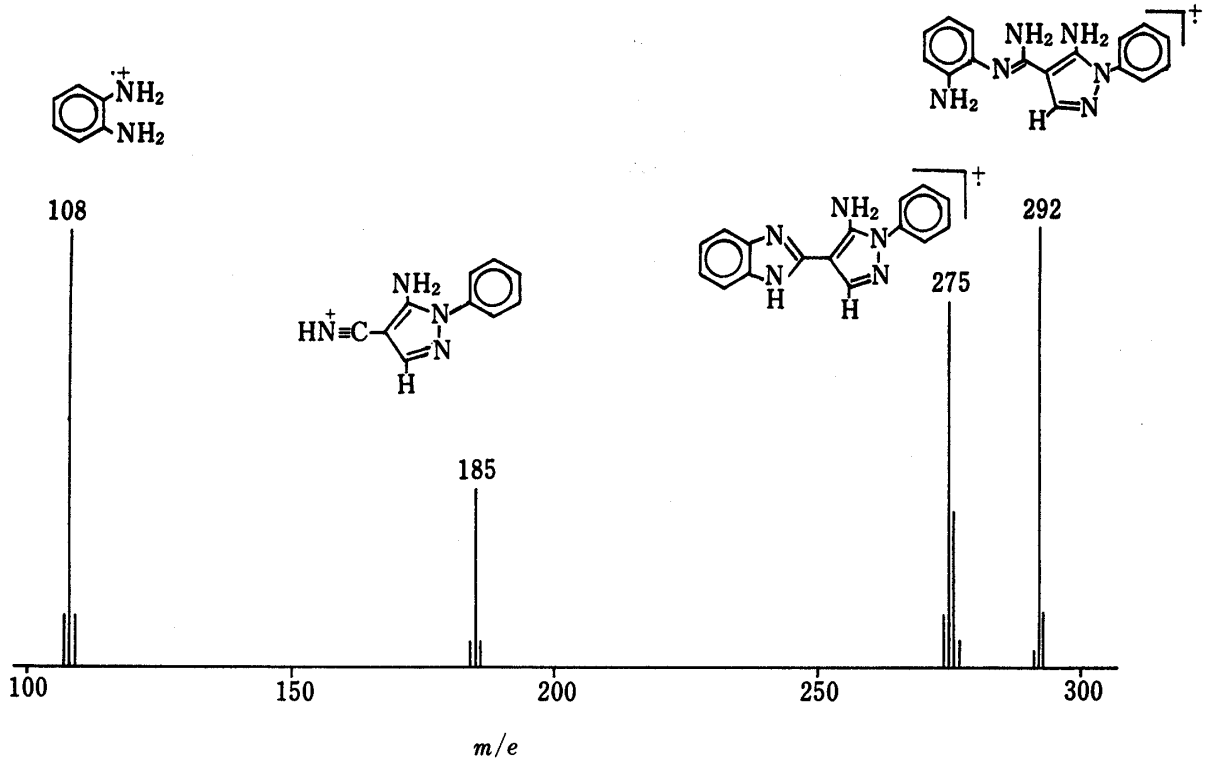


Fig. 1b. MS of 4c

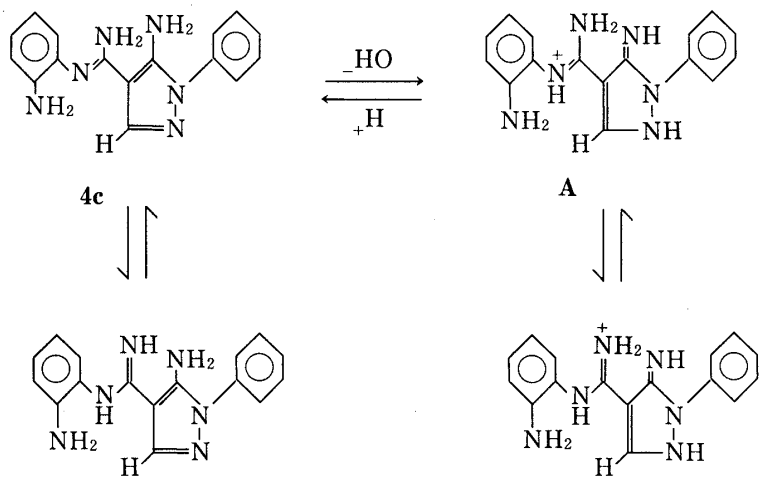


Chart 2

Reaction of **1** with hydrazine hydrate in ethanol also gave **2a** in 80% yield, but reaction of **1** with phenylhydrazine in ethanol gave fine needles of the hydrochloride of **4c** in 85% yield. This difference might be due to solubility differences in ethanol; **2a** is almost insoluble, but **2c** is soluble. The hydrochloride of **4c** obtained from the above reaction contained ethanol in the crystals even after the crystals were dried in a vacuum desiccator over P_2O_5 at 40°C for 3 h. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of the crystals showed signals at 4.20 ppm due to amino protons, 6.47 due to amidino protons, 8.40 due to pyrazole NH, and 10.10 ppm due to imino protons. In contrast, the ^{1}H-NMR spectrum of **4c** showed signals at 4.37 and 6.77 ppm due to two amino protons, and 5.88 ppm due to amidino protons. From these results, it may be concluded that **4c** is protonated at amidino nitrogen to give A

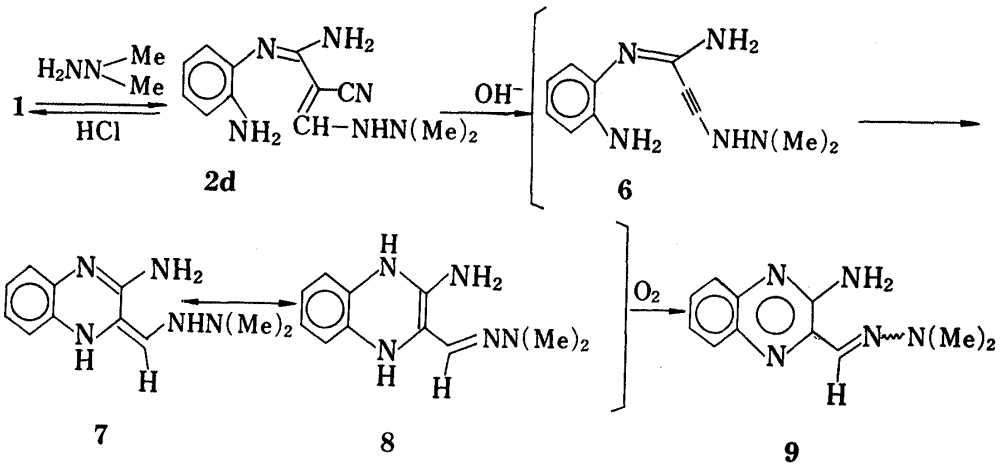


Chart 3

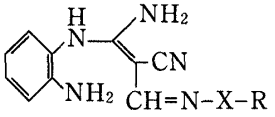


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Chart 4

or B which bears an imino group at the 3 position of the pyrazole ring instead of an amino group (Chart 2). It is worth noting that reaction of **1** with *N*,*N*-dimethylhydrazine in alkaline media gave *N*-(2-amino-3-quinoxalinylmethylene)-*N'*,*N'*-dimethylhydrazine (**9**) in 32% yield. The reaction pathways are shown in Chart 3; the ring-opened hydrazine adduct (**2d**) is formed first, then loss of hydrogen cyanide gives (**6**), whose intramolecular cyclization affords (**7**). Compound **7** and its tautomer (**8**) are readily oxidized by air to give **9**.

In conclusion, the ring-opened adducts (**10**) obtained from **1** react in different orientations when treated with acidic or alkaline solution, or when heated. The results depend on the nature of X and R where X=NH, NCH_3, or O, and R=H or R≠H (Chart 4).

Experimental

Melting points were determined using a Yamato Scientific stirred liquid apparatus and are uncorrected. IR and ultraviolet (UV) spectra were recorded on a Japan Spectroscopic model IRA-1 spectrometer and a Hitachi model 200-20 spectrophotometer. NMR and mass spectra were obtained on Varian T-60, EM-390, and ^{13}C-JMS-PS-100 spectrometers with tetramethylsilane as an internal standard, and on JMS-O1S and DX-300 (with JMA-3100) spectrometers (Japan Electron Optics Laboratory Co., Ltd.), respectively. Elementary analyses were performed on a Perkin-Elmer model 240B machine.

3-Amino-3-(*o*-aminoanilino)-2-cyano-2-propenal Hydrazone (**2a**)——Method A: Hydrazine hydrate (0.3 g, 6 mmol) was added to a solution of **1** (0.5 g, 2.3 mmol) in 25 ml of water with stirring, and the mixture was stirred at room temperature for 1 h. The yellow powder that precipitated was collected, washed with water and ethanol, and dried in a vacuum desiccator. Yield, 0.3 g (75.6%), mp 170°C (dec.). MS: *m/e* 216 (M^+), *m/e* (199 (M^+-17). IR cm^{-1}: $\nu_{C\equiv N}$ 2260 (KBr). ^{1}H-NMR ($(CD_3)_2SO$) δ: 5.03 (2H, s, NH_2), 8.03 (1H, s, =CH–), 6.37—7.53 (4H, m, aromatic; 2H, s, NH_2; 1H, s, –NH–), 10.73 (1H, s, –NH–).

Method B: When ethanol (25 ml) was employed as the reaction solvent in the above reaction, **2a** was obtained as a yellow powder in 80% yield (0.39 g), mp 170°C (dec.). MS and IR were checked.

3-Amino-3-(*o*-aminoanilino)-2-cyano-2-propenal Phenylhydrazone (**2c**)——Phenylhydrazine (2 g, 18.4 mmol) was added to a solution of **1** (2 g, 8 mmol) in 150 ml of water with stirring. After stirring for 2 h, the precipitates were filtered off by suction, washed with water, and dried in a vacuum desiccator to give **2c** as a yellow powder in 90.9% yield (2.4 g), mp 149.5°C (dec.). High resolution mass, Calcd for $C_{16}H_{16}N_6$: 292.146. Found: 292.143. IR cm^{-1}: $\nu_{C\equiv N}$ 2170 (KBr). ^{1}H-NMR ($(CD_3)_2SO/CDCl_3$=1/1) δ: 4.90 (2H, s, NH_2), 6.00 (2H, s, NH_2), 6.47—7.33 (9H, m, aromatic), 7.75 (1H, s, –NH–), 7.62 (1H, s, =CH–), 9.13 (1H, s, –NH–).

3,6-Bis[*N*-(*o*-aminophenyl)amidino]-pyrazolo[1,5-*a*]pyrimidine (**3**)——A 10% sodium hydroxide solution (10 ml) was added to a suspension of **2a** (1 g, 4.6 mmol) in 90 ml of water. The mixture was heated on a water-bath for 2 h, then cooled. The yellow prisms that precipitated were filtered off and washed with water

and ethanol. Yield, 0.78 g (84%), mp >300°C. MS: *m/e* 400 (M^+). ^{1}H-NMR ($(CD_3)_2SO$) δ: 4.47 (4H, s, $2NH_2$), 6.40 (4H, s, $2NH_2$), 6.47—6.97 (8H, m, aromatic), 8.42 (1H, s, =CH–), 8.80 (2H, s, NH_2), 9.25 (1H, s, =CH–). ^{13}C-NMR ($(CD_3)_2SO$)[6]: δa (101.25), b (104.11), c (114.40), c′ (115.13), d (116.88), d′ (117.12), e (121.25), e′ (121.49), f (122.60), f′ (124.21), g (133.19), g′ (135.03), h (136.93), i (140.28), j (141.39), k (145.56), l (146.00), k′ (149.88), m (153.24), n (156.68). *Anal.* Calcd for $C_{20}H_{20}N_{10}$: C, 59.99; H, 5.03; N, 34.99. Found: C, 59.69; H, 4.95; N, 34.89.

3-Amino-4-[*N*-(*o*-aminophenyl)amidino]-2-methylpyrazole (4b)——Methylhydrazine (0.6 g, 13 mmol) was added to a suspension of **1** (1.1 g, 5 mmol) in 40 ml of ethanol with stirring. After 1.5 h, a clear solution was obtained, in which **1** was no longer present (checked by thin layer chromatography (TLC) over silica gel, chloroform/methanol=10/1). Then, a solution of 0.5 g of NaOH in 10 ml of water was added to the above solution, and the mixture was heated on a water-bath for 3 h. After evaporation of ethanol, the aqueous solution was allowed to stand overnight to give crystals, which were recrystallized from water–ethanol to afford prisms in 69.7% yield (0.8 g), mp 168—169°C. MS: *m/e* 230 (M^+). ^{1}H-NMR ($(CD_3)_2SO/CDCl_3=1/1$) δ: 3.55 (3H, s, CH_3), 4.33 (2H, s, NH_2), 5.73 (2H, s, NH_2), 6.47 (2H, s, NH_2), 6.53—6.77 (4H, m, aromatic), 7.68 (1H, s, =CH–). ^{13}C-NMR ($(CD_3)_2SO$)[6] δ: a (33.93), b (97.61), c (114.50), d (117.02), e (121.68), f (122.75), g (135.08), h (136.39), i (140.90), j (148.09), k (152.55). *Anal.* Calcd for $C_{11}H_{13}N_6$: C, 57.38; H, 6.13; N, 36.50. Found: C, 57.31; H, 6.11; N, 36.38.

3-Amino-4-[*N*-(*o*-aminophenyl)amidino]-2-phenylpyrazole (4c)——A solution of 1 g of NaOH in 20 ml of water was added to a suspension of 0.5 g of **2c** in 30 ml of water, and the mixture was heated on a water-bath for 2.5 h. The crystals that precipitated were filtered off and recrystallized from water–ethanol. Yield, 0.4 g (80%), mp 175—176°C (dec.). MS: *m/e* 292 (M^+). ^{1}H-NMR ($(CD_3)_2SO/CDCl_3=1/1$) δ: 4.37 (2H, s, NH_2), 5.88 (2H, s, NH_2), 6.77 (2H, s, NH_2), 6.47—6.80 (4H, m, *o*-aminophenyl), 7.23—7.73 (5H, m, phenyl), 8.00 (1H, s, =CH–). *Anal.* Calcd for $C_{16}H_{16}N_6$: C, 65.74; H, 5.52; N, 28.75. Found: C, 65.73; H, 5.47; N, 28.53.

2-(3-Amino-2-methylpyrazol-4-yl)benzimidazole (5b)——A solution of **4b** (0.35 g, 1.5 mmol) in 10 ml of 1% HCl solution was heated on a water-bath for 1 h, then made alkaline by addition of 10% sodium carbonate solution with cooling. The precipitates were filtered off and washed with water to give crude **5b** in 90% yield (0.29 g). Recrystallization from water-ethanol gave colorless prisms of **5b** in 70% yield (0.22 g), mp 268—269°C. MS: *m/e* 213 (M^+). ^{1}H-NMR ($(CD_3)_2SO$) δ: 3.67 (3H, s, CH_3), 6.43 (2H, s, NH_2), 7.00—7.57 (4H, m, benzene), 7.77 (1H, s, =CH–), 11.67 (1H, s, –NH–). ^{13}C-NMR ($(CD_3)_2SO$)[6] δ: a (34.22), b (93.39), c (113.53), d (120.95), e (135.38), f (138.33), g (147.16), h (148.62). UV $\lambda_{max}^{methanol}$ nm (log ε): 235 (4.04), 263 (3.82), 272 (3.83), 302 (4.31), 312 (4.28). *Anal.* Calcd for $C_{11}H_{11}N_5$: C, 61.96; H, 5.20; N, 32.84. Found: C, 61.84; H, 5.15; N, 33.11.

2-(3-Amino-2-phenylpyrazol-4-yl)benzimidazole (5c)——A solution of **4c** (0.44 g, 1.5 mmol) in 10 ml of 1% HCl solution was heated on a water-bath for 1 h. The solution was made alkaline by addition of 10% sodium carbonate solution with cooling. The precipitates were filtered off and washed with water to give crude **5c** in 90.9% yield (0.38 g). Recrystallization from water–ethanol gave crystals of **5c** in 69.3% yield (0.29 g), mp 212—214°C. MS: *m/e* 275 (M^+). ^{1}H-NMR ($(CD_3)_2SO/CDCl_3=1/1$) δ: 6.33 (2H, s, NH_2), 6.90—7.71 (9H, m, benzene ring; 1H, s, –NH–), 8.07 (1H, s, =CH–). UV $\lambda_{max}^{methanol}$ nm (log ε): 240 (3.73), 263 (3.44), 272 (3.37), 303 (3.79), 313 (3.77). *Anal.* Calcd for $C_{16}H_{13}N_5$: C, 69.78; H, 4.76; N, 25.46. Found: C, 69.56; H, 5.02; N, 25.71.

Hydrochloride of 4c——A mixture of **1** (2 g, 9 mmol) and phenylhydrazine (2 g, 18.5 mmol) in 100 ml of ethanol was stirred at room temperature overnight. Colorless needles were precipitated. Recrystallization from chloroform–ethanol gave fine needles of the hydrochloride of **4c**. Yield, 2.53 g (84.9%), mp 99°C. An analysis sample was dried in a vacuum desiccator over P_2O_5 at 40°C for 3 h. This hydrochloride salt was converted to the free base **4c** quantitatively by addition of 1% alkaline solution. MS: *m/e* 292 (M^+). The^1 H-NMR ($(CD_3)_2SO/CDCl_3=1/1$) spectrum showed signals of ethanol (1.5 eq), which was still present in the sample. δ: 1.03 (4.5H, t, $J=6$ Hz, $1.5CH_3$), 3.43 (3H, q, $J=6$ Hz, $1.5CH_2$), 4.20 (2H, s, NH_2), 5.27 (1.5H, s, 1.5OH), 6.47 (3H, s, amidino), 6.50—7.20 (4H, m, aromatic), 7.50 (5H, s, phenyl), 8.10 (1H, s, =CH–), 8.40 (1H, s, –NH–), 10.10 (1H, s, =NH). *Anal.* Calcd for $C_{11}H_{13}N_6 \cdot HCl \cdot 1.5C_2H_5OH$: C, 57.35; H, 6.59; N, 21.12. Found: C, 57.04; H, 6.62; N, 20.82.

Reaction of 2a with Hydrochloric Acid——A 10% HCl solution (1 ml) was added to 1 g of **2a**, and the compound was well triturated. After 5 min, ethanol was added to the mixture and orange crystals of **1** that formed were filtered off, washed with ethanol and dried in a vacuum desiccator. The crystals were combined with orange needles which were obtained from the filtrate when it was allowed to stand. Yield, 0.74 g (72.5%), mp 280°C (dec.). MS and IR were checked.

Reaction of 2c with Hydrochloric Acid——A 10% HCl solution (1 ml) was added to a suspension of **2c** (0.5 g, 1.7 mmol) in 3 ml of water with stirring. Stirring was continued for 3 h, and the resulting orange crystals of **1** were filtered off by suction, washed with a small amount of ethanol, and dried in a vacuum desiccator. Yield, 0.1 g (26.5%), 280°C (dec.). The filtrate was evaporated to dryness under reduced pressure. Recrystallization from chloroform–ethanol gave 0.25 g (44.4% yield) of the hydrochloride of **4c** (checked by IR and MS), mp 99°C.

Reaction of 2d with Hydrochloric Acid——A suspension of 0.2 g of **2d** [mp 174°C (dec.); prepared in 45% yield by the same method as described for **2a**] in 0.1 ml of water was treated with 0.5 ml of 10% HCl solution, and the compound was well triturated. After 3 min, precipitated **1** was filtered off, washed with a small amount of ethanol and dried in a vacuum desiccator. Yield, 0.06 g (38%), mp 280°C (dec.). MS and IR were checked.

***N*-(2-Amino-3-quinoxalinylmethylene)-*N'*,*N'*-dimethylhydrazine (9)**——*N*,*N*-Dimethylhydrazine (5 ml) was added to a suspension of 1 g of **1** in 50 ml of ethanol, and the mixture was stirred at room temperature for 30 min. The solution was filtered, if necessary, and 10 ml of 5% NaOH solution was added to the filtrate. The mixture was heated on a water-bath for 3 h. The solution was concentrated to a third of the initial volume by distillation at 40°C under reduced pressure, and cooled in a refrigerator to give yellow needles of **9**. Yield, 0.31 g (32%), mp 203—204°C. MS: *m/e* 215 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 3.10 (6H, s, $2CH_3$), 6.90 (2H, s, NH_2), 7.25—7.90 (5H, m, aromatic and olefinic). ^{13}C-NMR ($(CD_3)_2SO/CDCl_3=2/1$; $CDCl_3$ was used as an internal standard).[6] δ: a (−1.31), b (38.638), c (47.860), d (48.016), e (48.539), f (48.974), g (52.138), h (55.672), i (62.661), j (67.224). *Anal.* Calcd for $C_{11}H_{13}N_5$: C, 61.38; H, 6.09; N, 32.54. Found: C, 61.38; H, 5.91; N, 32.53.

References and Notes

1) Part I: Y. Okamoto, K. Takagi and T. Ueda, *Chem. Pharm. Bull.*, **28**, 567 (1980).
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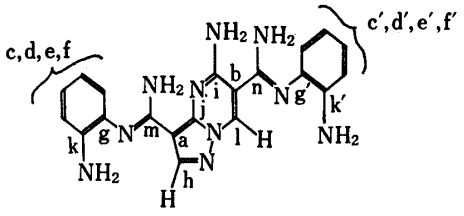
6) Assignments are as follows:



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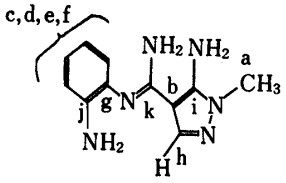
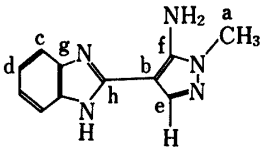


4b



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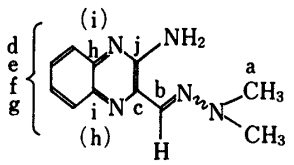

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