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Facile Synthesis and Ring Transformations of a Spiro-[cyclobutene-1,2′(1*H*)-quinoxaline][1)]

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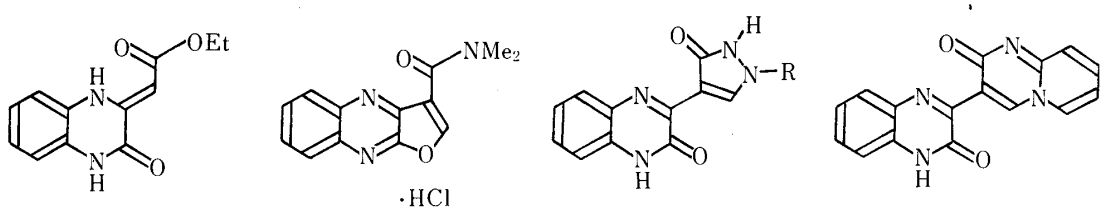
The reaction of 3-(*N,N*-dimethylcarbamoyl)furo[2,3-*b*]quinoxaline (**2**) with ethyl cyanoacetate in sodium ethoxide–ethanol occurred with ring transformation to give 4-cyano-2-ethoxycarbonyl-3-hydroxy-3′-oxo-3′,4′-dihydrospiro[2-cyclobutene-1,2′(1*H*)-quinoxaline] (**5**). When **5** was refluxed in acetic acid and in *N,N*-dimethylformamide, it afforded 2-cyano-3-hydroxy-3′-oxo-3′,4′-dihydrospiro[2-cyclobutene-1,2′(1*H*)-quinoxaline] (**6**) and 7-cyano-5,6-dihydro-6,10-dioxo-8-hydroxy-10*H*-pyrido[1,2-*a*]quinoxaline (**9**), respectively. Refluxing of **5** with hydrazine dihydrochloride and with *o*-phenylenediamine dihydrochloride in acetic acid also induced ring transformation to produce 6-(3-oxo-3,4-dihydroquinoxalin-2-yl)-3-amino-5-hydroxy-7-oxo-1,2-dihydro-1,2-diazepine hydrochloride (**12a**) and 16-amino-1,8-dioxo-1,2,8,10-tetrahydroquinoxalino[1′,2′:1,2]pyrido[4,3-*b*][1,5]benzodiazepine hydrochloride (**13a**), respectively.

Keywords——hydrazine dihydrochloride; hydrazine hydrate; *o*-phenylenediamine dihydrochloride; ethyl cyanoacetate; pyrido[1,2-*a*]quinoxaline; quinoxalinyl-1,2-diazepine; quinoxalino[1′,2′:1,2]pyrido[4,3-*b*][1,5]benzodiazepine

In previous papers, we reported that the reaction of 3-ethoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (**1**)[2)] with the Vilsmeier reagent [phosphorus oxychloride–*N,N*-dimethylformamide ($POCl_3$–DMF)] gave 3-(*N,N*-dimethylcarbamoyl)furo[2,3-*b*]quinoxaline hydrochloride (**2**),[3,4)] which reacted with hydrazines and 2-aminopyridine to afford quinoxalinylpyrazolones (**3**)[3,4)] and quinoxalinylpyridopyrimidine (**4**),[5,6)] respectively (Chart 1).



1 2 3 4

Chart 1

These results show that the 3-carbonyl and C_2 carbons of **2** are susceptible to attack by nucleophiles.[7)] Besides the above N-nucleophiles, a C-nucleophile such as a carbanion was also expected to attack either the 3-carbonyl or C_2 carbon of **2**. In fact, the reaction of **2** with the carbanion generated from ethyl cyanoacetate induced a ring transformation to furnish a spiro[homocycle-quinoxaline] derivative. Among spiroquinoxalines, many spiro[heterocycle-quinoxaline] derivatives have been synthesized by various methods,[8)] but few reports have been presented on the synthesis and conversion of spiro[homocycle-quinoxaline] derivatives,

possibly because the carbon–carbon bond formation is a critical step in the construction of the spiro-homocycle moiety. However, we have found a facile method for the synthesis of a spiro[2-cyclobutene-1,2′(1*H*)-quinoxaline] derivative by the ring transformation of **2**. Moreover, this spiro[2-cyclobutene-1,2′(1*H*)-quinoxaline] derivative was found to be a versatile intermediate leading to various novel quinoxaline derivatives. This paper describes the synthesis and ring transformations of this novel spiroquinoxaline.

The reaction of **2** with a 5-fold molar excess of ethyl cyanoacetate in sodium ethoxide–ethanol gave **1** and 4-cyano-2-ethoxycarbonyl-3-hydroxy-3′-oxo-3′,4′-dihydrospiro[2-cyclobutene-1,2′(1*H*)-quinoxaline] (**5**). Refluxing of **5** in acetic acid resulted in hydrolysis and decarboxylation to afford 2-cyano-3-hydroxy-3′-oxo-3′,4′-dihydrospiro[2-cyclobutene-1,2′(1*H*)-quinoxaline] (**6**). The structural assignment of **5** was based on the analytical and spectral data. The infrared (IR) spectrum of **5** showed an absorption band due to a nitrile group at 2225 cm^{-1}, suggesting incorporation of ethyl cyanoacetate into **2**. Moreover, mass specral (MS) and microanalytical data indicated the molecular formula $C_{15}H_{13}N_3O_4$ (**5**), which was consistent with three possible structures of **5** (Chart 2). However, the structures **5a** and **5b** (Chart 3) were excluded by the formation of **6** from **5**. The nuclear magnetic resonance (NMR) spectrum of **6** exhibited a singlet signal due to methylene protons at δ 3.98 ppm, which disappeared in dimethylsulfoxide-d_6 (DMSO-d_6)–D_2O. The above results supported the validity of the structures of **5**, **6**, and the species **7** (Chart 2). If **6a** or **6b** (Chart 3) were

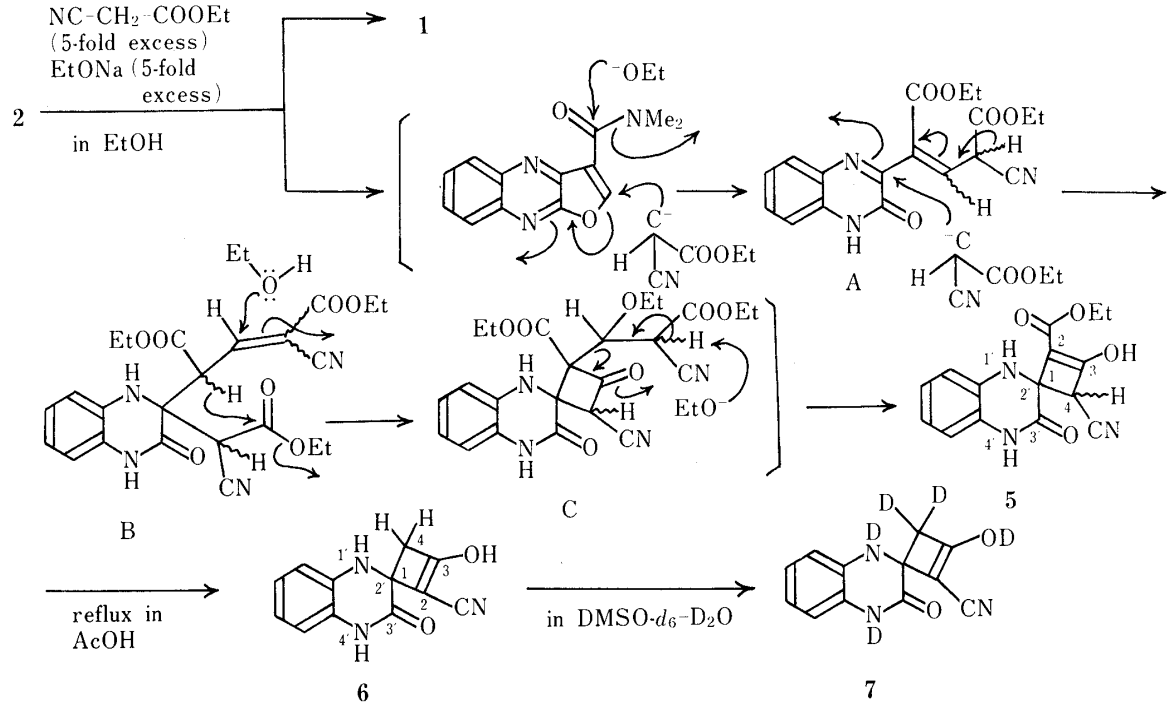
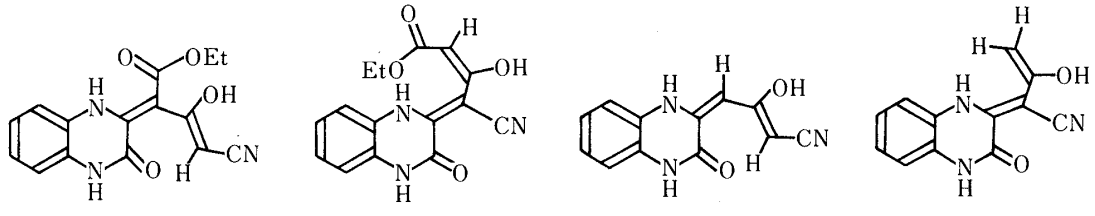


Chart 2



5a **5b** **6a** **6b**

Chart 3

produced from **5a** or **5b**, respectively, the above NMR spectral data would not be obtained. In addition, the ester C=O absorption band of **5** was observed at a lower wavenumber (1680 cm^{-1}) than that of ordinary ester C=O absorption bands (above 1700 cm^{-1}), providing confirmation of the α,β-unsaturated ester in **5**. Compound **5** was assumed to be produced *via* intermediates A, B, and C, as shown in Chart 2, and the formation of **1** from **2** was reported in our previous papers.[3,4]

Furthermore, the reaction of **5** with an excess of hydrazine hydrate afforded 3-hydrazinocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (**8**),[9] presumably *via* intermediates D and E (Chart 4). Interestingly, moreover, the reaction of **5** with the Vilsmeier reagent induced ring transformation to provide **2**, possibly through **1** as an intermediate,[3,4] by a similar mechanism to that proposed for the production of **8**. Refluxing of **5** in DMF and pyridine–butanol caused ring transformation to give 7-cyano-5,6-dihydro-6,10-dioxo-8-hydroxy-10*H*-pyrido[1,2-*a*]quinoxaline (**9**) and the pyridinium salt of **9** (**10**), respectively, probably *via* an intermediate F, whose four-membered ring should open thermally.[10] The structural assignments of **9** and **10** were based on the analytical and spectral data. The MS and microanalytical data afforded the molecular formulae $C_{13}H_7N_3O_3$ (**9**) and $C_{13}H_7N_3O_3 \cdot C_5H_5N$ (**10**). In the NMR spectrum of **9**, the C_1–H proton signal appeared at a much lower magnetic field (δ 9.18 ppm) than the three other aromatic proton signals (δ 7.37—6.90 ppm), presumably due to anisotropy of the C_{10}=O group. The NMR spectrum of **10** exhibited the α-, β-, and γ-proton signals of pyridine near ordinary magnetic fields (δ 8.68, 7.40, 7.87 ppm); these were easily distinguishable from the other signals. The reaction of **5** with an excess of methyl iodide in sodium ethoxide–ethanol resulted in N_4-methylation to afford 4-cyano-2-ethoxycarbonyl-3-hydroxy-4′-methyl-3′-oxo-3′,4′-dihydrospiro[2-cyclobutene-1,2′(1*H*)-quinoxaline] (**11**), but C_3–O methylation did not occur. An attempt to obtain the C_3–O-tosylated compound by the reaction of **5** with *p*-toluenesulfonyl chloride

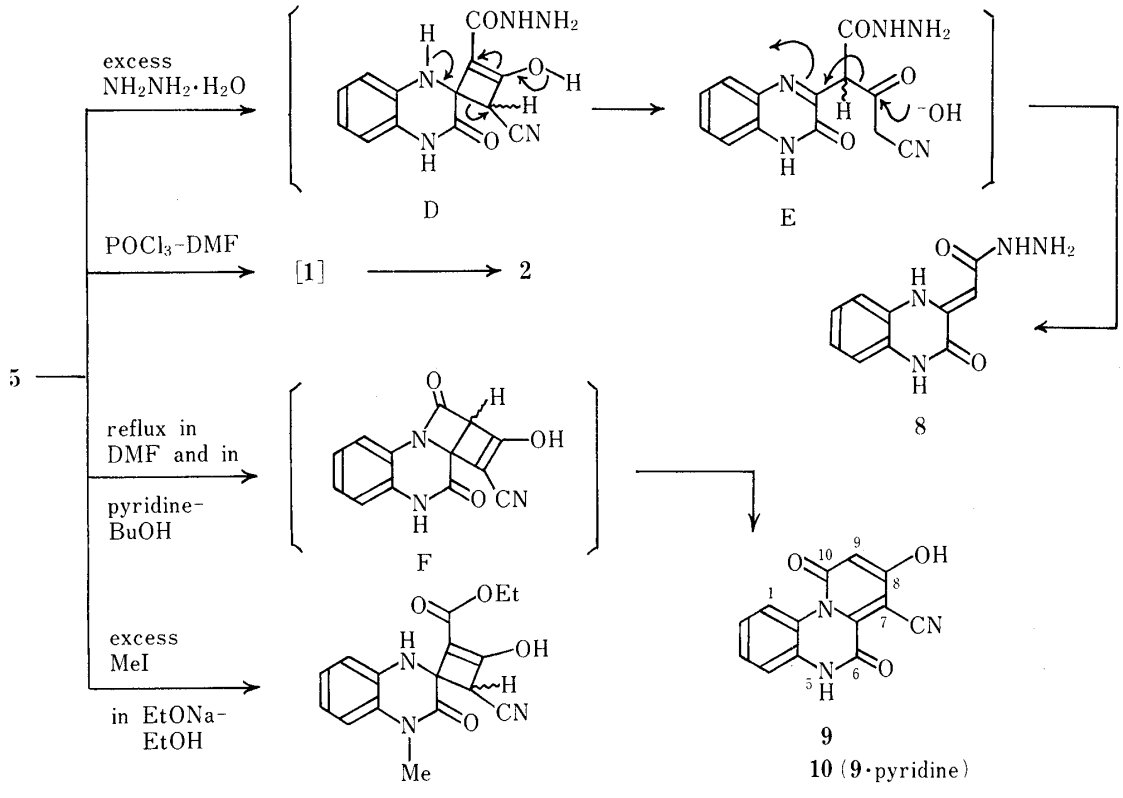


Chart 4

in pyridine also failed. The $N_{4'}$–Me proton signal of **11** was observed at δ 3.52 ppm in DMSO-d_6, with disappearance of the $N_{4'}$–H proton signal observed at δ 11.92 ppm in **5**, while the N_1–Me proton signal of 1-methyl-3-methoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline[11] appeared at δ 3.68 ppm in DMSO-d_6. These data for the $N_{4'}$–Me and N_1–Me proton signals supported the structural assignment of **11**.

Furthermore, the above ring transformation of **5** into **9** was also provoked by refluxing **5** with guanidine hydrochloride and *o*-hydroxyaniline hydrochloride in acetic acid (**6** was also formed as a by-product), whereas the presence of phenylhydrazine hydrochloride, pyridine hydrochloride, and ammonium chloride did not produce **9**, but did provide **6**. These results are shown in Chart 5 and Table I. Moreover, the reactions of **5** with hydrazine dihydrochlo-

$$\mathbf{5} \xrightarrow[\text{in AcOH}]{\text{hydrochloride of base}} \mathbf{6}+\mathbf{9}$$

Chart 5

TABLE I. Conversion of **5** into **6** and/or **9**[a]

Hydrochloride of base	Product (Yield, %)	
	6	**9**
Guanidine·HCl	10.5	46.5
o-Hydroxyaniline·HCl	50.1	17.7
$C_6H_5NHNH_2$·HCl	30.5	—
Pyridine·HCl	76.4	—
NH_3·HCl	26.3	—

a) A 5-fold molar excess of HCl-salt was used.

ride and *o*-phenylenediamine dihydrochloride in acetic acid resulted in ring transformation to give 6-(3-oxo-3,4-dihydroquinoxalin-2-yl)-3-amino-5-hydroxy-7-oxo-1,2-dihydro-1,2-diazepine hydrochloride (**12a**) and 16-amino-1,8-dioxo-1,2,8,10-tetrahydroquinoxalino-[1′,2′ : 1,2]pyrido[4,3-*b*][1,5]benzodiazepine hydrochloride (**13a**), respectively. Treatments of **12a** with pyridine in butanol and of **13a** with 10% sodium carbonate in ethanol afforded the free base (**12b**) and the ethanol complex (**13b**), respectively. The structural elucidations of **12** and **13** were based on the analytical and spectral data. The microanalytical and MS data provided the molecular formulae $C_{13}H_{11}N_5O_3$·HCl (**12a**), $C_{13}H_{11}N_5O_3$ (**12b**), $C_{19}H_{13}N_5O_2$·HCl (**13a**), and $C_{19}H_{13}N_5O_2$·EtOH (**13b**). In the NMR spectrum, **13a** exhibited the C_6–H proton signal at a lower magnetic field (δ 7.93 ppm) than the seven other aromatic proton signals (δ 7.50—6.67 ppm), presumably due to the anisotropy of the C_8=O group, and this anisotropic effect became rather remarkable in **13b** [C_6–H (δ 8.34 ppm), seven other aromatic H (δ 7.13—6.67 ppm)]. The NMR spectrum of **13b** showed the signals due to ethanol near ordinary magnetic fields; these signals were easily distinguishable from others. In addition, the C_9–H proton signals of the hydrochloride **13a** and the ethanol complex **13b** were observed at δ 7.72 and 6.59 ppm, respectively, and this significant difference might be due to susceptibility of the adjacent N_{10} atom to pH variation in the medium. The above data are consistent with the ring system of **13a** and **13b**. On the other hand, the anisotropy observed in **9**, **13a**, and **13b** did not appear in the NMR spectra of **12a** and **12b**. Since the reaction of **5** with hydrazine hydrate induced opening of the cyclobutene ring, the production of the 1,2-diazepine ring was considered to be reasonable. The postulated reaction mechanism *via* intermediates G, H, and I[12] is shown in Chart 6.

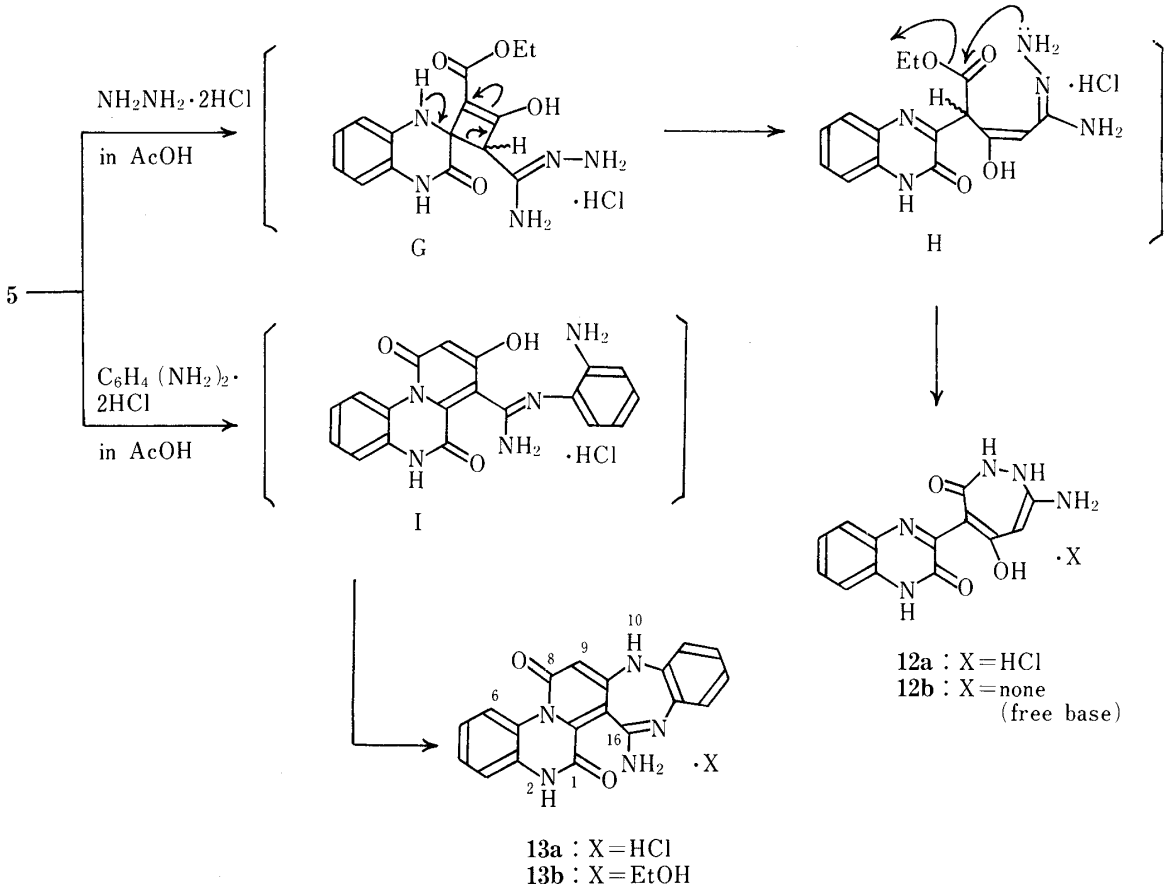


Chart 6

The ring transformations of **5** into **9** and **13** and the conversion of **5** into **8** excluded the structures **5a** and **5b**, respectively, and the above reactions could be well rationalized in terms of the structure **5**.

Experimental

All melting points are uncorrected. IR spectra were recorded from KBr disks on a JASCO IRA-1 spectrophotometer. NMR spectra were measured with an EM-390 spectrometer at 90 MHz using tetramethylsilane as an internal standard. MS were determined with a JMS-01S spectrometer (Japan Electron Optics Laboratory Co., Ltd.).

4-Cyano-2-ethoxycarbonyl-3-hydroxy-3′-oxo-3′,4′-dihydrospiro[2-cyclobutene-1,2′(1*H*)-quinoxaline] (5)——Compound **2** (20 g, 72 mmol) was added to a solution of ethyl cyanoacetate (40.68 g, 360 mmol, 5-fold excess) and EtONa (360 mmol, 5-fold excess) in EtOH (600 ml), and the solution was refluxed for 6 h to precipitate NaCl. The NaCl was filtered off, and the filtrate was evaporated to give an oily residue. The residue was triturated with AcOH to yield **5** as yellow needles, which were collected by suction filtration and then washed with H_2O (18.50 g, 85.8%). Recrystallization from EtOH afforded yellow plates, mp 333—334 °C. MS *m/e*: 299 (M^+). IR ν_{max}: 3370, 2225, 1680 cm^{-1}. NMR (DMSO-d_6) δ: 11.92 (s, 1H, N_4–H), 10.77 (2, 1H, OH), 7.55 (m, 1H, C_5–H), 7.20—6.80 (m, 3H, aromatic), 6.07 (s, 1H, N_1–H), 4.24 (q, J=7 Hz, 2H, CH_2), 1.27 (t, J=7 Hz, 3H, Me). A signal due to C_4–H was not observed. *Anal.* Calcd for $C_{15}H_{13}N_3O_4$: C, 61.33; H, 4.83; N, 13.41. Found: 61.23; H, 4.72; N, 13.58.

Compound **1** precipitated in the above mother liquor (AcOH solution) as yellow needles, which were collected by filtration (2.0 g, 12%). The IR spectrum and melting point of this sample coincided with those of an authentic sample.[2)]

2-Cyano-3-hydroxy-3′-oxo-3′,4′-dihydrospiro[2-cyclobutene-1,2′(1*H*)-quinoxaline] (6)——A solution of **5** (3 g) in AcOH (150 ml) was refluxed for 5 h. The solution was filtered while hot, and compound **6** precipitated as yellow needles, which were collected by suction filtration (1.98 g). Evaporation of the mother liquor provided additional **6** (0.14 g). Total yield, 2.12 g (93%). Recrystallization from AcOH gave yellow needles, mp 248—250 °C. MS *m/e*: 227 (M^+). IR ν_{max}: 2270, 1690 cm^{-1}. NMR (DMSO-d_6) δ: 12.65 (s, 1H, OH), 11.90 (s, 1H, N_4–H), 7.43 (m, 1H, C_5–H), 7.33—6.97 (m, 3H, aromatic), 6.08 (s, 1H, N_1–H), 3.98 (s, 2H, CH_2). *Anal.* Calcd for $C_{12}H_9N_3O_2$: C, 63.43; H, 3.99;

N, 18.49. Found: C, 63.23; H, 3.81; N, 18.31.

3-Hydrazinocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (8)——A solution of **5** (500 mg) and hydrazine hydrate (5 g, excess) in EtOH (50 ml) was refluxed for 3 h, then evaporated to a small volume to precipitate **8** as colorless needles, which were collected by filtration (290 mg, 80%). The IR spectrum and melting point of this sample coincided with those of an authentic sample.[9]

7-Cyano-5,6-dihydro-6,10-dioxo-8-hydroxy-10*H*-pyrido[1,2-*a*]quinoxaline (9)——A solution of **5** (3 g) in DMF (60 ml) was refluxed for 2 h, then the solvent was evaporated off to afford an oily residue, which was dissolved in AcOH. The solution was refluxed for 2 h to precipitate **9** as yellow needles. The needles were collected by suction filtration (1.62 g, 63.8%). Recrystallization from AcOH provided yellow needles, mp above 340 °C. MS *m/e*: 253 (M^+). IR ν_{max}: 2255, 1695, 1665 cm^{-1}. NMR (DMSO-d_6) δ: 11.90 (s, 1H, N_5–H), 9.77 (br s, OH), 9.18 (m, $J_{1-3}=J_{1-4}=1.2$ Hz, $J_{1-2}=7.8$ Hz, 1H, C_1–H), 7.37—6.90 (m, 3H, aromatic, and 1H, C_9–H). *Anal.* Calcd for $C_{13}H_7N_3O_3$: C, 61.66; H, 2.79; N, 16.60. Found: C, 61.44; H, 2.75; N, 16.35.

Pyridinium Salt of 9 (10)——A solution of **5** (500 mg) in pyridine (10 ml) and BuOH (40 ml) was refluxed for 7 h, then evaporated to a small volume to precipitate **10** as analytically pure yellow needles. The product was collected by suction (120 mg, 21.6%), mp above 340 °C. MS *m/e*: 253 (M^+). IR ν_{max}: 2210, 1695, 1645 cm^{-1}. NMR (DMSO-d_6) δ: 12.82 (s, 1H, OH), 11.70 (s, 1H, N_5–H), 9.18 (d, $J_{1-2}=7.8$ Hz, C_1–H), 8.68 (m, 2H, C_2– and C_6–H of pyridine), 7.87 (m, 1H, C_4–H of pyridine), 7.40 (m, 2H, C_3– and C_5–H of pyridine), 7.33—6.70 (m, 3H, aromatic, and 1H, C_9–H). *Anal.* Calcd for $C_{18}H_{12}N_4O_3$: C, 65.05; H, 3.64; N, 16.86. Found: C, 65.01; H, 3.46; N, 16.75.

4-Cyano-2-ethoxycarbonyl-3-hydroxy-4′-methyl-3′-oxo-3′,4′-dihydrospiro[2-cyclobutene-1,2′(1*H*)-quinoxaline] (11)——A solution of **5** (1 g, 3.34 mmol) and MeI (1 ml, excess) in EtONa (16.7 mmol, 5-fold excess)–EtOH (50 ml) was refluxed for 2 h, and then neutralized with 10% HCl. The reaction product was extracted with $CHCl_3$, and the organic layer was washed with saturated $Na_2S_2O_3$ solution and then H_2O. After the solution was dried over Na_2SO_4, the solvent was evaporated off to provide yellow crystals (0.30 g, 28.6%). Recrystallization from EtOH afforded yellow needles, mp 205—207 °C. MS *m/e*: 313 (M^+). IR ν_{max}: 2220, 1690, 1660 cm^{-1}. NMR (DMSO-d_6) δ: 10.79 (s, 1H, OH), 7.57 (m, 1H, C_5–H), 7.42—6.93 (m, 3H, aromatic), 6.09 (s, 1H, N_1–H), 4.25 (q, $J=7$ Hz, 2H, CH_2), 3.52 (s, 3H, N_4–Me), 1.29 (t, $J=7$ Hz, 3H, Me). *Anal.* Calcd for $C_{16}H_{15}N_3O_4$: C, 61.33; H, 4.83; N, 13.41. Found: C, 61.23; H, 4.72; N, 13.58.

Reaction of 5 with Hydrochloride of Bases (Preparation of 6 and/or 9)——General procedure. A suspension of **5** (3 g, 10.0 mmol) and guanidine hydrochloride (4.78 g, 50.0 mmol) in AcOH (150 ml) was refluxed in an oil bath to give a clear solution. Refluxing was continued for 10 h to precipitate **9** as yellow needles, which were collected by suction filtration (1.18 g, 46.5%).

The above filtrate was evaporated to give crystals, which were triturated with H_2O to provide **6** as yellow needles. The needles were collected by suction (0.24 g, 10.5%).

The results using hydrochloride of other bases are shown in Table I.

6-(3-Oxo-3,4-dihydroquinoxalin-2-yl)-3-amino-1,2-dihydro-5-hydroxy-7-oxo-1,2-diazepine Hydrochloride (12a)——A suspension of **5** (3 g, 10.0 mmol) and hydrazine dihydrochloride (5.15 g, 50.0 mmol) in AcOH (150 ml) was refluxed for 10 h to precipitate yellow needles **12a**, which were collected by suction filtration (2.28 g, 70.4%). Recrystallization from EtOH–H_2O gave yellow needles, mp 297—298 °C. MS *m/e*: 285 (M^+). IR ν_{max}: 3440, 1690, 1660 cm^{-1}. NMR (DMSO-d_6) δ: 12.97 (s, 1H, OH), 11.42 (s, 1H, N_4–H), 10.67—8.33 (br, 2H, N_1– and N_2–H), 7.23 (s, 2H, NH_2), 7.03 (s, 1H, C_4–H), 7.03—6.87 (m, 4H, aromatic). No signal due to HCl was observed. *Anal.* Calcd for $C_{13}H_{12}ClN_5O_3$: C, 48.53; H, 3.76; N, 21.77. Found: C, 48.31; H, 3.86; N, 21.66.

Free Base (12b)——A suspension of **12a** (1 g) in pyridine (10 ml) and BuOH (50 ml) was refluxed for 3 h to provide **12b** as yellow needles, which were collected by suction. Trituration of the yellow needles with hot EtOH gave analytically pure **12b** (720 mg, 81%), mp 318—320 °C. IR ν_{max}: 3460, 3400, 3380, 1705, 1690 cm^{-1}. MS *m/e*: 285 (M^+). NMR (DMSO-d_6) δ: 13.02 (s, 1H, OH), 11.46 (s, 1H, N_4–H), 10.67—8.33 (br, 2H, N_1– and N_2–H), 7.27 (s, 2H, NH_2), 7.07 (s, 1H, C_4–H), 7.03—6.67 (m, 4H, aromatic). *Anal.* Calcd for $C_{13}H_{11}N_5O_3$: C, 54.73; H, 3.89; N, 24.55. Found: C, 54.59; H, 3.88; N, 24.35.

16-Amino-1,8-dioxo-1,2,8,10-tetrahydroquinoxalino[1′,2′:1,2]pyrido[4,3-*b*][1,5]benzodiazepine Hydrochloride (13a)——A suspension of **5** (3 g, 10.0 mmol) and *o*-phenylenediamine dihydrochloride (3.62 g, 20.0 mmol) in AcOH (150 ml) was refluxed for 10 h to precipitate **13a** as brown needles, which were collected by suction filtration (1.69 g, 44.2%). Recrystallization from EtOH–H_2O gave brown needles, mp 320—322 °C. IR ν_{max}: 1705, 1675 cm^{-1}. MS *m/e*: 343 (M^+). NMR (DMSO-d_6) δ: 11.00—9.87 (br, 4H, NH, NH_2·HCl), 10.05 (s, 1H, NH), 7.93 (d, $J=7.5$ Hz, 1H, C_6–H), 7.72 (s, 1H, C_9–H), 7.50—6.67 (m, 7H, aromatic). *Anal.* Calcd for $C_{19}H_{14}ClN_5O_2$: C, 60.25; H, 3.46; N, 18.44. Found: 59.98; H, 3.76; N, 18.26.

The above filtrate was evaporated to afford crystals, which were triturated with H_2O to provide **6** as yellow crystals (820 mg, 36%).

Compound 13b——Na_2CO_3 (3 g) was added to a suspension of **13a** (500 mg) in EtOH (100 ml) and H_2O (30 ml), and the whole mixture was heated on a boiling water bath to give a clear solution. The solution was filtered, and compound **13b** precipitated as analytically pure orange needles (380 mg, 74%), mp 310—311 °C. IR ν_{max}: 1695, 1660 cm^{-1}. MS *m/e*: 343 (M^+). NMR (DMSO-d_6) δ: 11.00—8.00 (br, 3H, NH, NH_2), 9.08 (s, 1H, NH), 8.34 (d, $J=$

7.5 Hz, C_6–H), 7.13—6.97 (m, 3H, aromatic), 6.97—6.67 (m, 4H, aromatic), 6.59 (s, 1H, C_9–H), 4.13 (s, 1H, OH of EtOH), 3.42 (q, $J=7$ Hz, CH_2 of EtOH), 1.03 (t, $J=7$ Hz, Me of EtOH). *Anal.* Calcd for $C_{21}H_{19}N_5O_3$: C, 64.77; H, 4.92; N, 17.99. Found: C, 64.57; H, 4.81; N, 18.29.

Conversion of 5 into 2——$POCl_3$ (10 ml) was added dropwise to a suspension of **5** (1 g) in DMF (10 ml) with stirring in an ice-water bath. The suspension was heated on a boiling water bath to give a clear solution, which precipitated **2** as crystals. The mixture was cooled in an ice-water bath and then poured onto crushed ice to precipitate **2** as yellow crystals, which were collected by suction filtration (260 mg, 56.0%). The IR spectrum of this sample coincided with that of an authentic sample.[3,4]

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