Facile Synthesis of Novel 3-Quinoxalinyl-1,5-benzodiazepines *via* Ring Transformation. Stable Tautomers in the 1,5-Benzodiazepin-2-one Ring System [1]

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Novel 3-quinoxalinyl-1,5-benzodiazepines **4**, **5**, **6**, **9**, **10** were synthesized *via* the ring transformation of 3-(*N,N*-dimethylcarbamoyl)furo[2,3-*b*]quinoxaline hydrochloride (**1**). The 3-quinoxalinyl-1,5-benzodiazepine hydrochlorides **4** and **6** are the tautomers of the $N^{1'}$-H (or N^5-H) form and the C^3-H form, respectively, which are stable in solid and solution. However, **4** (NH form) was found to be converted into **6** (C^3-H form) by refluxing in acetic acid. The individual spectral evidences and different reactivity of these tautomers are described.

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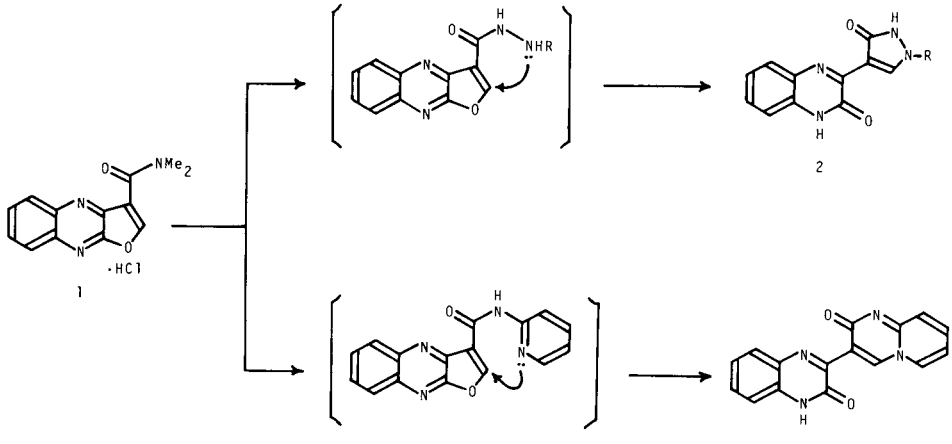
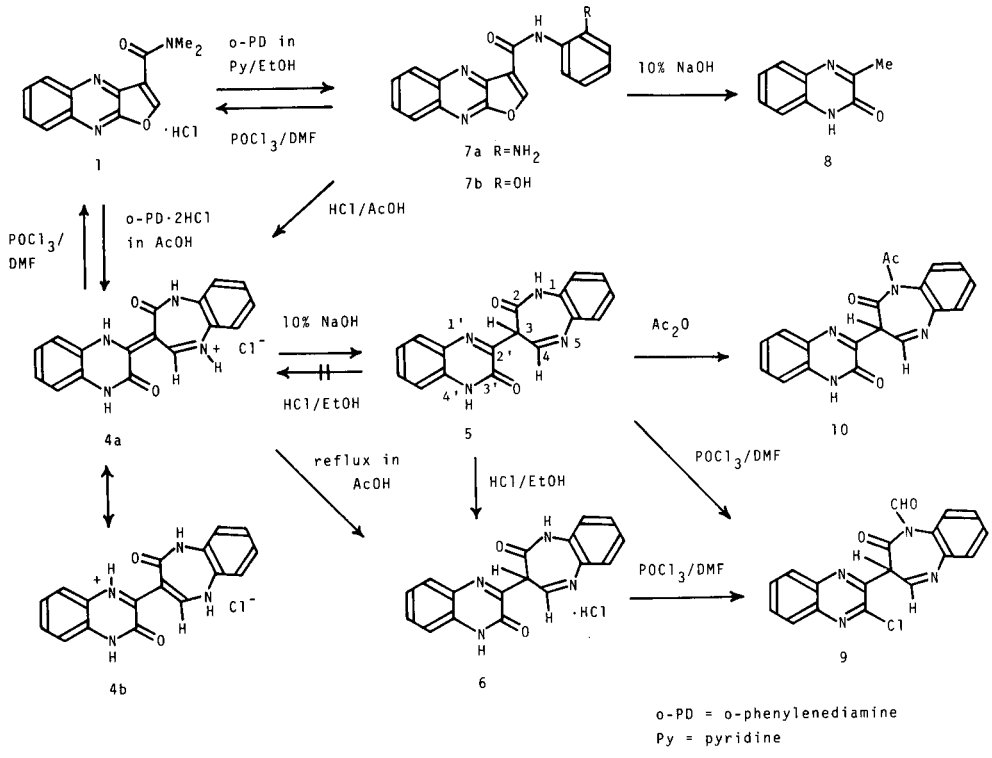
In previous papers [2,3], we reported that the reactions of 3-(*N,N*-dimethylcarbamoyl)furo[2,3-*b*]quinoxaline hydrochloride (**1**) with hydrazines and 2-aminopyridine resulted in ring transformations to give the quinoxalinylpyrazolones **2** and the quinoxalinylpyridopyrimidine **3**, respectively (Scheme 1). From these results, it is obvious that C^2, C^3 and carbonyl-C of **1** are furnished as three carbon source. Accordingly, a use of an ambident reagent such as *o*-phenylenediamine in place of hydrazines and 2-aminopyridine was expected to effect the ring transformation into a 3-quinoxalinyl-1,5-benzodiazepine, which would become an intermediate to analogues of pharmacologically active heteroepines [4]. Thus, we undertook the synthesis of novel 3-quinoxalinyl-1,5-benzodiazepines *via* the ring transformation. Furthermore, we could isolate two stable 1,5-benzodiazepin-2-one tautomers, whose spectral evidences were independently obtained. This paper also describes a different reactivity of these two tautomers.

The reaction of **1** with *o*-phenylenediamine dihydrochloride in acetic acid resulted in the ring transformation to afford 3-(3-oxo-1,2,3,4-tetrahydroquinoxalin-2-ylidene)-1,2-dihydro-2-oxo-3*H*-1,5-benzodiazepine hydrochloride (**4a**) or 3-(3-oxo-3,4-dihydroquinoxalin-2-yl)-1,2-dihydro-2-oxo-5*H*-1,5-benzodiazepine hydrochloride (**4b**) (72%), whose structure was established on the basis of mass, ^{1}H-nmr, ir spectral and elemental analytical data (Scheme 2). In the ^{1}H-nmr spectrum of **4**, the C^4-H proton signal was observed as a singlet at δ 8.42 ppm. Since there have been reported some cases that the coupling of vicinal -N*H*-C*H*= protons does not appear [5], the structure **4b** can not be eliminated. Treatment of **4** with 10% sodium hydroxide provided the free base 3-(3-oxo-3,4-dihydroquinoxalin-2-yl)-1,2-dihydro-2-oxo-3*H*-1,5-benzodiazepine (**5**) (91%). The ^{1}H- and ^{13}C-nmr spectra supported the structure **5**, that is, the C^3-H and C^4-H proton signals were observed as the doublets ($J_{3,4}$ = 15 Hz) at δ 7.46 and 8.55 ppm, respectively, and the tertiary C^3-carbon signal was observed as the doublet at δ 108.92 ppm. Further treatment of **5** with ethanolic hydrogen chloride did not furnish the hydrochloride **4**, but formed 3-(3-oxo-3,4-dihydrquinoxalin-2-yl)-1,2-dihydro-2-oxo-3*H*-1,5-benzodiazepine hydrochloride (**6**) (98%). In the ^{1}H-nmr spectrum of **6**, the coupling was also observed between the C^3-H and C^4-H protons ($J_{3,4}$ = 15 Hz). The hydrochloride **6** was also obtained by



Scheme 1



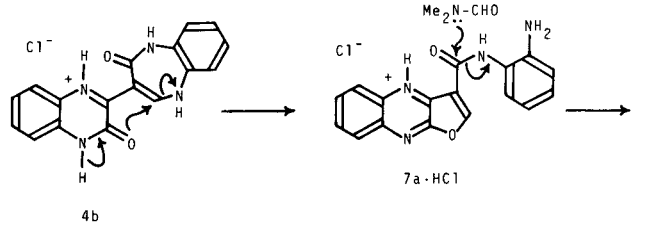
Scheme 2

refluxing of the hydrochloride **4** in acetic acid (73%).

On the other hand, the reactions of **1** with *o*-phenylenediamine and *o*-aminophenol in pyridine/ethanol did not result in the ring transformation, but effected only substitution to give 3-(*N*-2-aminophenylcarbamoyl)furo[2,3-*b*]-quinoxaline (**7a**) (82%) and 3-(*N*-2-hydroxyphenylcarbamoyl)furo[2,3-*b*]quinoxaline (**7b**) (98%). The structural assignments of **7a** and **7b** were based on the further reactions as well as the spectral data, which were quite different from those of **5**. Heating of **7a** and **7b** in 10% sodium hydroxide afforded 2-methyl-3-oxo-3,4-dihydroquinoxaline (**8**) [6] (46% from **7a**, 46% from **7b**). The mechanism similar to the reactions of **7a** and **7b** to **8** has already been reported in our previous paper [2]. Furthermore, refluxing of **7a** in hydrogen chloride-saturated acetic acid for 20 minutes provided the hydrochloride **4** (39%) and the prolonged refluxing for 2 hours furnished the isomerized hydrochloride **6** (65%). The reactions of **7a** and **7b** with the Vilsmeier reagent gave **1** (22% from **7a**, 69% from **7b**).

Interestingly, the NH tautomer **4** represented the different reactivity from that of the C^3-H tautomer, **5**, **6**. Namely, the reaction of **4** with the Vilsmeier reagent formed **1** (55%), while the reactions of **5** and **6** with the same reagent produced 3-(3-chloroquinoxalin-2-yl)-1,2-dihydro-1-formyl-2-oxo-3*H*-1,5-benzodiazepine (**9**) (26% from **5**, 68% from **6**). A similar N^1-acylation was induced in the reaction of **5** with acetic anhydride, giving 3-(3-oxo-3,4-dihydroquinoxalin-2-yl)-1-acetyl-1,2-dihydro-2-oxo-3*H*-1,5-benzodiazepine (**10**) (50%). The structural establishments of **9** and **10** were mainly based on the ^{1}H-nmr spectral data. That is, the couplings between the C^3-H and C^4-H protons were observed in **9** and **10** (both $J_{3,4}$ = 15 Hz). Moreover, one of the eight aromatic protons in **4**, **5**, **6**, and **10** were observed at a lower magnetic field than the seven other aromatic protons. On the contrary, the eight aromatic protons in **7a**, **7b**, and **9** were observed separately as two groups of five and three protons. This difference would be due to whether the quinoxaline ring was aromatized or not.

From the above results, the reaction mechanism from **4** to **1** may be formulated as shown in Scheme 3.



Scheme 3

There have been reported many examples on the tautomerism of the 1,5-aryldiazepin-2-one ring system, wherein

the most of compounds predominate as the C^3-H form **A** rather than the N^5-H form **B** [7], as depicted in Scheme 4. Among our compounds, **5, 6, 9,** and **10** are the C^3-H form, which is confirmed by the presence of the coupling between the C^3-H and C^4-H protons. Interestingly, furthermore, the NH tautomer **4** was enough stable in solid and solution to obtain its own spectral data, and it did not isomerize easily into the C^3-H tautomer **6** without refluxing in acetic acid. The ^{1}H-nmr spectrum of **4** in DMSO-d_6 exhibited the singlet signal for the C^4-H proton, elucidating the presence of the quaternary C^3-carbon, and the C=O absorption bands of **4** and **6** appeared at the different wave number areas [1680 cm^{-1} (**4**); 1740, 1680 cm^{-1} (**6**)]. The stability of the NH form of **4** would depend on the presence of the quinoxaline ring, which also supported the resonance structures of **4a** and **4b**.

A B

Scheme 4

EXPERIMENTAL

All melting points are uncorrected. Infrared (ir) spectra were recorded from potassium bromide discs on a JASCO IRA-1 spectrophotometer. Nuclear magnetic resonance (nmr) spectra were measured with an EM-390 spectrometer at 90 MHz using tetramethylsilane as an internal reference. Chemical shifts are given in the δ scale, relative to the internal reference. Mass spectra (ms) were determined with a JMS-01S spectrometer (JEOL).

3-(3-Oxo-1,2,3,4-tetrahydroquinoxalin-2-ylidene)-1,2-dihydro-2-oxo-3*H*-1,5-benzodiazepine Hydrochloride (**4a**) or 3-(3-Oxo-3,4-dihydroquinoxalin-2-yl)-1,2-dihydro-2-oxo-5*H*-1,5-benzodiazepine Hydrochloride (**4b**).

A suspension of **1** (10 g, 36.0 mmoles) and *o*-phenylenediamine dihydrochloride (9.77 g, 54.0 mmoles) in acetic acid (300 ml) was refluxed for 1 hour to precipitate **4** as a red powder, which was collected by suction filtration (7.65 g, 72%). Washing of the red powder with cold aqueous ethanol (1:1, v/v) gave an analytically pure sample, 266-267°; ms: m/z 304 (M^+) (M^+ of the free base due to thermal dissociation in the inlet system of a mass spectrometer); ir: ν cm^{-1} 1680, 1635; ^{1}H-nmr (DMSO-d_6): 12.67 (s, 1H, NH), 11.50 (br s, 1H, NH), 9.67 (s, 1H, NH), 8.42 (s, 1H, C^4-H), 7.69 (d, dd, J_{ortho} = 9.0 Hz, J_{meta} = J_{para} = 1.0 Hz, 1H, aromatic), 7.57-6.83 (m, 7H, aromatic), 6.50 (br s, 1H, =$^+$NH-).

Anal. Calcd. for $C_{17}H_{13}ClN_4O$: C, 59.92; H, 3.84; Cl, 10.40; N, 16.44. Found: C, 59.64; H, 3.84; Cl, 10.34; N, 16.14.

3-(3-Oxo-3,4-dihydroquinoxalin-2-yl)-1,2-dihydro-2-oxo-3*H*-1,5-benzodiazepine (**5**).

Ten percent sodium hydroxide was added to a suspension of **4** (5 g) in water (10 ml) and ethanol (300 ml) with stirring on a boiling water bath to precipitate yellow crystals, which were dissolved by addition of ethanol. The solution was filtered and acetic acid (10 ml) was added to this filtrate to precipitate **5** as yellow needles (4.2 g, 94%). Recrystallization from ethanol afforded analytically pure yellow needles, mp 325-326° dec; ms: m/z 304 (M^+); ir: ν cm^{1-} 1735, 1680, 1650; ^{1}H-nmr (DMSO-d_6): 12.33 (s, 1H, NH), 11.27 (s, 1H, NH), 8.55 (d, J = 15 Hz, 1H, C^4-H) [8], 7.73 (dd, J_{ortho} = 9 Hz, J_{meta} = 1.8 Hz, 1H, aromatic), 7.46 (d, J = 15 Hz, 1H, C^3-H) [8], 7.67-7.00 (m, 7H, aromatic); ^{13}C-nmr (DMSO-d_6): 155.42 (s, 1C), 154.06 (s, 1C), 153.63 (s, 1C), 133.19 (s, 1C), 132.12 (s, 1C), 129.99 (d, 1C), 129.99 (d, 1C), 129.79 (s, 1C), 128.77 (d, 1C), 128.29 (s, 1C), 124.16 (d, 1C), 124.01 (d, 1C), 122.36 (d, 1C), 116.00 (d, 1C), 110.91 (d, 1C), 110.52 (d, 1C), 108.92 (d, 1C).

Anal. Calcd. for $C_{17}H_{12}N_4O_2$: C, 67.09; H, 3.98; N, 18.41. Found: C, 66.85; H, 3.97; N, 18.19.

3-(3-Oxo-3,4-dihydroquinoxalin-2-yl)-1,2-dihydro-2-oxo-3*H*-1,5-benzodiazepine Hydrochloride (**6**). Method A.

Compound **5** (440 mg) was added to ethanolic hydrogen chloride (300 ml) with stirring in an ice-water bath, and stirring was continued for 3 hours to precipitate **6** as a red powder, which was collected by suction filtration (280 mg). The filtrate was evaporated off to provide the additional product **6** (200 mg). Total yield, 480 mg (98%). Trituration with ethanolic hydrogen chloride under cooling in an ice-water bath gave an analytically pure sample, mp 292-293°; ms: m/z 304 (M^+) (M^+ of the free base due to the thermal dissociation in the inlet system of a mass spectrometer); ir: ν cm^{-1} 1740, 1680, 1620; ^{1}H-nmr (DMSO-d_6): 12.57 (br s, 1H, NH), 11.51 (s, 1H, NH), 8.77 (br s, 1H, -$^+$NH=), 8.75 (d, J = 15 Hz, 1H, C^4-H) [8], 7.80 (d, J = 7 Hz, 1H, aromatic), 7.55 (d, J = 15 Hz, 1H, C^3-H) [8], 7.73-7.00 (m, 7H, aromatic).

Anal. Calcd. for $C_{17}H_{13}ClN_4O_2$: C, 59.92; H, 3.84; Cl, 10.40; N, 16.44. Found: C, 59.81; H, 3.63; Cl, 10.59; N, 16.18.

Method B.

A solution of **4** (300 mg) in acetic acid (60 ml) was refluxed for 1 hour in an oil bath. Cooling of the solution to room temperature precipitated **6** as red needles, which were collected by suction filtration (220 mg, 73%).

3-(*N*-2-Aminophenylcarbamoyl)furo[2,3-*b*]quinoxaline (**7a**).

A suspension of **1** (5 g, 18.0 mmoles) and *o*-phenylenediamine (2.92 g, 27.0 mmoles) in pyridine (20 ml) and ethanol (400 ml) was refluxed on a boiling water bath for 1 hour to precipitate **7a** as orange needles, which were collected by suction filtration (4.5 g, 82%). Trituration with hot ethanol afforded an analytically pure sample, mp 205-208°; ms: m/z 304 (M^+); ir: ν cm^{-1} 3420, 3360, 1840, 1800, 1660, 1640; ^{1}H-nmr (DMSO-d_6): 8.62 (s, 1H, C^2-H), 8.00-7.40 (m, 5H, aromatic), 7.20-6.57 (m, 3H, aromatic), 5.67-3.33 (br, NH, NH_2, and water).

Anal. Calcd. for $C_{17}H_{12}N_4O_2$: C, 67.09; H, 3.98; N, 18.41. Found: C, 66.93; H, 4.08; N, 18.12.

3-(*N*-2-Hydroxyphenylcarbamoyl)furo[2,3-*b*]quinoxaline (**7b**).

A suspension of **1** (5 g, 18.0 mmoles) and *o*-aminophenol (2.94 g, 27.0 mmoles) in pyridine (20 ml) and ethanol (400 ml) was refluxed for 1 hour to precipitate **7b** as yellow needles, which were collected by suction filtration (4.36 g). Evaporation of the filtrate gave the additional product **7b** (1.04 g), total yield, 5.40 g (98%). Trituration with hot ethanol afforded an analytically pure sample, mp 269-270°; ms: m/z 305 (M^+); ir: ν cm^{-1} 1800, 1650, 1610, 1590; ^{1}H-nmr (DMSO-d_6): 10.73 (s, 1H,NH or OH), 8.92 (s, 1H, C^2-H), 8.00-7.30 (m, 5H, aromatic), 7.23-6.77 (m, 3H, aromatic), 4.27 (br s, NH or OH, H_2O).

Anal. Calcd. for $C_{17}H_{11}N_3O_3$: C, 66.88; H, 3.63; N, 13.77. Found: C, 66.76; H, 3.51; N, 13.83.

Conversion of **7a** and **7b** into **8**.

A solution of **7a** or **7b** (500 mg) in 10% sodium hydroxide (10 ml) and ethanol (30 ml) was refluxed for 1 hour on a boiling water bath. The reaction mixture was neutralized with 10% hydrochloric acid and the reaction product was extracted with chloroform. The chloroform layer was dried over sodium sulfate and removal of the solvent *in vacuo* provided **8** as yellow crystals [120 mg (46%) from **7a**, 100 mg (46%) from **7b**]. Recrystallization from ethanol gave yellow needles. The ir spectra and melting points of these samples coincided with those of an authentic sample [6].

3-(3-Chloroquinoxalin-2-yl)-1,2-dihydro-1-formyl-2-oxo-3*H*-1,5-benzodiazepine (**9**). Method A.

A solution of **5** (1 g) in phosphorus oxychloride (50 ml) and DMF (50 ml) was heated on a boiling water bath for 5 hours. The solution was cooled in an ice-water bath and then poured onto crushed ice. The reaction product was extracted with chloroform and the chloroform layer was washed with water and then dried over sodium sulfate. Removal of the solvent by evaporation afforded **9** as yellow crystals (300 mg, 26%). Recrystallization from chloroform/ethanol provided yellow needles, mp 246-248°; ms: m/z 350 (M^+), 352 ($M^+ + 2$); ir: ν cm^{-1} 1750, 1725, 1700, 1640, 1610; ^{1}H-nmr (trifluoroacetic acid): 9.42 (s, 1H, CHO), 8.75 (d, J = 15 Hz, 1H, C^4-H) [8], 8.43-7.97 (m, 5H, aromatic), 8.02 (d, J = 15 Hz, 1H, C^3-H) [8], 7.70-7.23 (m, 3H, aromatic).

Anal. Calcd. for $C_{18}H_{11}ClN_4O_2$: C, 61.64; H, 3.16; Cl, 10.11; N, 15.97. Found: C, 61.53; H, 3.15; Cl, 10.23; N, 15.88.

Method B.

A solution of **6** (180 mg) in phosphorus oxychloride (5 ml) and DMF (5 ml) was heated on a boiling water bath for 2 hours to precipitate **9** as yellow crystals. The reaction mixture was cooled to room temperature and poured onto crushed ice. The yellow crystals **9** pecipitated were collected by suction filtration (140 mg, 68%).

3-(3-Oxo-3,4-dihydroquinoxalin-2-yl)-1-acetyl-1,2-dihydro-2-oxo-3*H*-1,5-benzodiazepine (**10**).

A solution of **5** (2 g) in acetic anhydride (50 ml) was refluxed in an oil bath for 30 minutes to precipitate **10** as yellow needles. After cooling to room temperature, the needles were collected by suction filtration (1.14 g, 50%). Recrystallization from acetic anhydride afforded analytically pure yellow needles, mp 276-277°; ms: m/z 346 (M^+); ir: ν cm^{-1} 1750, 1715, 1660, 1630, 1595; ^{1}H-nmr (DMSO-d_6): 12.50 (s, 1H, NH), 8.48 (d, J = 15 Hz, 1H, C^4-H) [8], 8.15 (dd, J = 7.2 Hz, J = 1.8 Hz, 1H, aromatic), 7.87-7.13 (m, 7H, aromatic), 7.62 (d, J = 15 Hz, 1H, C^3-H) [8], 2.68 (s, 3H, acetyl Me).

Anal. Calcd. for $C_{19}H_{14}N_4O_3$: C, 65.89; H, 4.07; N, 16.18. Found: C, 65.66; H, 4.07; N, 16.01.

Conversion of **7a** into **4** and **6**.

A suspension of **7a** (300 mg) in hydrogen chloride-saturated acetic acid (30 ml) was refluxed in an oil bath for 20 minutes to precipitate **4** as a red powder. While the solution was hot, the red powder was collected by suction filtration, and washed with hot ethanol, yield, 130 mg (39%).

A suspension of **7a** (500 mg) in hydrogen chloride-saturated acetic acid (300 ml) was refluxed in an oil bth for 2 hours to precipitate **6** as orange plates, which were collected by suction filtration (280 mg, 65%).

Conversion of **4**, **7a**, and **7b** into **1**.

A solution of **4**, **7a**, or **7b** (1 g) in phosphorus oxychloride (10 ml) and DMF (10 ml) was heated on a boiling water bath for 2 hours to precipitate yellow crystals. The reaction mixture was cooled to room temperature, and poured onto crushed ice to precipitate **1** as yellow needles, which were collected by suction filtration. Yield, 450 mg (55%) from **4**, 200 mg (22%) from **7a**, 570 mg (72%) from **7b**. The ir spectra of these samples coincided with the ir spectrum of an authentic sample [2].

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