Synthesis of Novel 3-Substituted 1,5-Benzodiazepine Derivatives

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This paper describes an improved method for the synthesis of 3-(3-chloroquinoxalin-2-yl)-1,2-dihydro-1-formyl-2-oxo-3*H*-1,5-benzodiazepine (**2**) and its conversions into novel 3-substituted 1,5-benzodiazepine derivatives (**3a,b** and **4a,b**).

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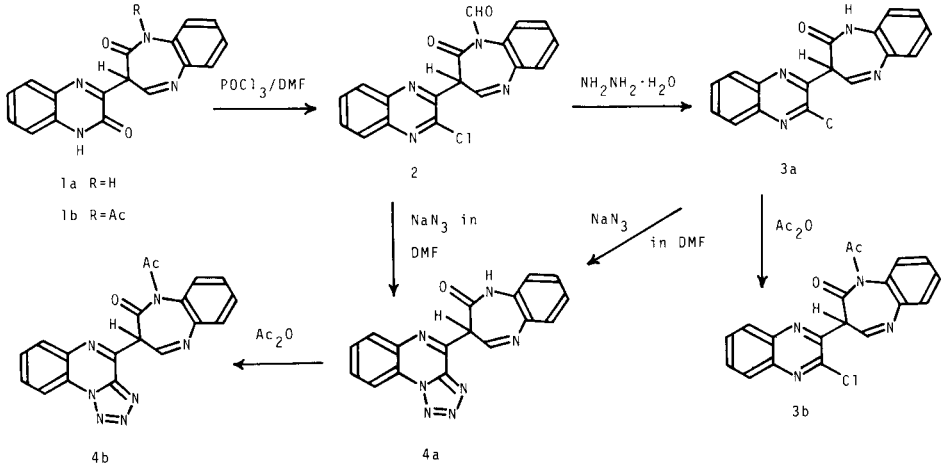
In previous papers [1], we reported that the reaction of 3-(3-oxo-3,4-dihydroquinoxalin-2-yl)-1,2-dihydro-2-oxo-3*H*-1,5-benzodiazepine (**1a**) (1 g) with the Vilsmeier reagent [phosphorus oxychloride (50 ml)/DMF (50 ml)] gave 3-(3-chloroquinoxalin-2-yl)-1,2-dihydro-1-formyl-2-oxo-3*H*-1,5-benzodiazepine (**2**) in low yield (26%). Because of this low yield, the structural assignment of **2** had to depend on comparison of the ^{1}H-nmr spectral data of **2** with those of the related compounds. In the present investigation, however, we have found that decrease in the amount of the Vilsmeier reagent to react with **1a** considerably improves the yield of **2** (73%). This improved method enabled us to prepare novel 3-substituted 1,5-benzodiazepine derivatives **3a,b** and **4a,b** from **2**. Moreover, ir spectral data of **3a,b** and **4a,b** supplied an additional evidence to support the structure of **2**. We wish to report herein the improved method for the synthesis of **2**, its conversions into **3a,b** and **4a,b**, and the ir spectral data to support the structure of **2**.

The reaction of **1a** (10 g) with the Vilsmeier reagent [phosphorus oxychloride (50 ml)/DMF (50 ml)] precipitated **2** as yellow needles, which were easily isolated by treatment of the reaction mixture with ice. This reaction condition needs no extraction procedure previously reported by us [1b]. Compound **2** obtained by the above manner were derivatized as follows.

Treatment of **2** with hydrazine hydrate effected deformylation to afford 3-(3-chloroquinoxalin-2-yl)-1,2-dihydro-3-oxo-3*H*-1,5-benzodiazepine (**3a**), whose acetylation with acetic anhydride provided 3-(3-chloroquinoxalin-2-yl)-2-acetyl-1,2-dihydro-2-oxo-3*H*-1,5-benzodiazepine (**3b**). The reaction of **3a** with sodium azide produced 3-(tetrazolo[4,5-*a*]-quinoxalin-4-yl)-1,2-dihydro-2-oxo-3*H*-1,5-benzodiazepine (**4a**), which was also obtained directly from the reaction of **2** with sodium azide. Acetylation of **4a** with acetic anhydride gave 3-(tetrazolo[4,5-*a*]quinoxalin-4-yl)-1-acetyl-1,2-dihydro-2-oxo-3*H*-1,5-benzodiazepine (**4b**).

The structural assignments of **3a,b** and **4a,b** were based on their ir, ^{1}H-nmr, mass spectral, and microanalytical data. Concerning **4a,b**, the ir spectra lacked the azido group ($-N_3$) absorption bands, which were characterized by the strong asymmetric stretching band near 2100 cm^{-1} [2], suggesting the tetrazole ring structure. The ir spectra of the N_1-acetylated compounds **1b**, **3b**, and **4b** represented the two C=O absorption bands above 1700 cm^{-1}, respectively, while the ir spectra of the N_1-H compounds **1a**, **3a**, and **4a** exhibited the one C=O absorption band above 1700 cm^{-1}, respectively (Table 1). These data denied the C_2-O-acetylated structures for **3b** and **4b**. In addition, a possibility of the N_5-acetylations in **3b** and **4b** was also excluded by observation of their C_3-H proton signals as doublets in the ^{1}H-nmr spectra. On the other hand, the ir



Scheme 1

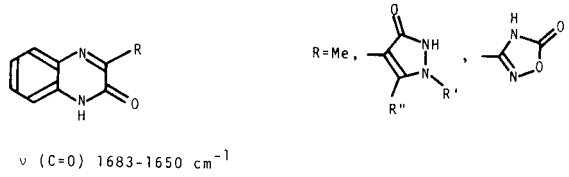
Table 1

IR Spectral Data for Compounds **1-4**

Compound	ν (potassium bromide) cm⁻¹ $C_2=O$, N_1-Acyl-C=O [a]	$C_{3'}=O$	Others
1a	1735	1665	1640, 1615, 1600
1b	1750, 1715	1600	1630
2	1750, 1725, 1700		1640, 1610
3a	1720		1630, 1615, 1605
3b	1735, 1715		1630, 1595
4a	1710		1630, 1595
4b	1740, 1720		1635, 1610, 1600

[a] A series ($C_2=O$), b series ($C_2=O$ and N_1-Acyl-C=O).

spectra of 3-substituted 2-oxo-1,2-dihydroquinoxalines [3] exhibited the quinoxaline-C=O absorption bands between 1683 and 1650 cm⁻¹, but not above 1700 cm⁻¹, as shown in Chart 1. The ir spectra of **1a,b** also represented the quinoxaline-C=O absorption bands at 1665 and 1660 cm⁻¹, respectively. The above ir spectral data support the $C_{3'}$-chloro-N_1-formyl structure of **2**, that is, **2**, **3a,b**, and **4a,b** exhibit the absorption bands above 1700 cm⁻¹, but no absorption band due to the $C_{3'}=O$ group.



ν (C=O) 1683-1650 cm⁻¹

CHART 1

EXPERIMENTAL

All melting points are uncorrected. Infrared (ir) spectra were recorded from potassium bromide discs on a JASCO IRA-1 spectrophotometer. The ir spectral data are shown in Table 1. Mass spectra (ms) were determined with a JMS-01S spectrometer (JEOL). ^{1}H-nmr spectra were measured with an EM-390 spectrometer at 90 MHz using tetramethylsilane as an internal standard. Chemical shifts are given in the δ scale, relative to the internal standard.

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

Phosphorus oxychloride (50 ml) was added dropwise to a suspension of **1a** (10 g) in DMF (50 ml) with stirring in an ice-water bath to give a clear solution. The solution was heated on a boiling water bath for 1 hour to precipitate yellow needles **2**. The reaction mixture was diluted with dioxane (200 ml) and then poured onto crushed ice to precipitate yellow needles **2**, which were collected by suction filtration. Recrystallization from chloroform/ethanol provided yellow needles (8.33 g, 73%), mp 246-248°. The ir spectrum of this sample coincided with that of an authentic sample [1].

3-(3-Chloroquinoxalin-2-yl)-1,2-dihydro-2-oxo-3*H*-1,5-benzodiazepine (**3a**).

A suspension of **2** (5 g, 14.25 mmoles) and hydrazine hydrate (1.78 g, 35.64 mmoles) in ethanol (50 ml)/chloroform (150 ml) was refluxed on a boiling water bath for 1 hour to precipitate yellow needles **3a**, which were collected by suction filtration (3.50 g, 76%). Trituration with hot chloroform gave an analytically pure sample, mp 277-278°; ms: m/z 322 (M^+), 324 ($M^+ + 2$); ^{1}H-nmr (DMSO-d_6): 11.50 (br s, 1H, NH), 8.42 (d, J = 14.4 Hz, 1H, C_4-H) [4], 7.35 (d, J = 14.4 Hz, 1H, C_3-H) [4], 8.20-7.00 (m, 8H, aromatic).

Anal. Calcd. for $C_{17}H_{11}ClN_4O$: C, 63.26; H, 3.44; N, 17.36. Found: C, 63.17; H, 3.37; N, 17.59.

3-(3-Chloroquinoxalin-2-yl)-1-acetyl-1,2-dihydro-2-oxo-3*H*-1,5-benzodiazepine (**3b**).

A solution of **3a** (2 g) in acetic anhydride (100 ml) was refluxed in an oil bath for 2 hours and the solution was filtered while hot. Cooling of the filtrate to room temperature precipitated yellow needles **3b**, which were collected by suction filtration (1.96 g, 91%). Recrystallization from acetic anhydride provided yellow needles, mp 233-234°; ms: m/z 348 (M^+), 350 ($M^+ + 2$); ^{1}H-nmr (DMSO-d_6): 8.40 (d, J = 15.0 Hz, 1H, C_4-H) [4], 7.68 (d, J = 15.0 Hz, 1H, C_3-H) [4], 8.43-7.00 (m, 8H, aromatic), 2.48 (s, 3H, Me).

Anal. Calcd. for $C_{19}H_{13}ClN_4O_2$: C, 65.43; H, 3.76; N, 16.06. Found: C, 65.21; H, 3.52; N, 16.30.

3-(Tetrazolo[4,5-*a*]quinoxalin-4-yl)-1,2-dihydro-2-oxo-3*H*-1,5-benzodiazepine (**4a**).

Method A.

A solution of **2** (5 g, 14.27 mmoles) and sodium azide (1.11 g, 17.13 mmoles) in DMF (100 ml) was refluxed in an oil bath for 2 hours to precipitate sodium chloride which was filtered off. The filtrate was evaporated *in vacuo* to give brown crystals **4a**, which were collected by suction filtration. Recrystallization from DMF/ethanol afforded brown needles (2.52 g, 54%), mp 238-239°; ms: m/z: 329 (M^+); ^{1}H-nmr (DMSO-d_6): 11.50 (br s, 1H, NH), 9.08 (d, J = 15.0 Hz, 1H, C_4-H) [4], 7.62 (d, J = 15.0 Hz, 1H, C_3-H) [4], 8.77-6.90 (m, 8H, aromatic).

Anal. Calcd. for $C_{17}H_{11}N_7O$: C, 62.00; H, 3.37; N, 29.77. Found: C, 61.71; H, 3.34; N, 30.03.

Method B.

A solution of **3a** (5 g, 15.49 mmoles) and sodium azide (1.21 g, 18.59 mmoles) in DMF (200 ml) was refluxed in an oil bath for 2 hours to precipitate sodium chloride which was filtered off. The filtrate was evaporated *in vacuo* to provide brown crystals **4a**. Recrystallization from DMF/ethanol afforded brown needles (2.82 g, 55%).

3-(Tetrazolo[4,5-*a*]quinoxalin-4-yl)-1-acetyl-1,2-dihydro-2-oxo-3*H*-1,5-benzodiazepine (**4b**).

A solution of **4a** (1 g) in acetic anhydride (50 ml) was refluxed in an oil bath for 2 hours. The solution was filtered while hot, and cooling of the filtrate to room temperature precipitated brown needles **4b**, which were collected by suction filtration (770 mg, 68%). Recrystallization from acetic anhydride provided brown needles, mp 248-249°; ms: m/z 371 (M^+); ^{1}H-nmr (DMSO-d_6): 9.67-7.00 (m, 8H, aromatic), 9.11 (d, J = 14.4 Hz, 1H, C_4-H) [4], 7.85 (d, J = 14.4 Hz, 1H, C_3-H) [4], 2.80 (s, 3H, Me); (trifluoroacetic acid): 10.25 (d, J = 14.4 Hz, 1H, C_4-H) [4], 8.93 (m, 1H, aromatic), 8.55 (d, J = 14.4 Hz, 1H, C_3-H) [4], 8.80-7.33 (m, 7H, aromatic), 2.97 (s, 3H, Me).

Anal. Calcd. for $C_{19}H_{13}N_7O_2$: C, 61.45; H, 3.53; N, 26.40. Found: C, 61.29; H, 3.45; N, 26.65.

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[4] These signals were checked by a decoupling procedure.