Synthesis of Novel 3-(α-Arylhydrazono-1,3,4-oxadiazol-2-ylmethyl)-2-oxo-1,2-dihydroquinoxalines and Their Characteristic Tautomerism between the Hydrazone Imine and Diazenyl Enamine Forms

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The reactions of 3-(α-arylhydrazono)hydrazinocarbonylmethyl-2-oxo-1,2-dihydroquinoxalines **1a,b** with triethyl orthoesters resulted in the intramolecular cyclization to give the 3-(α-arylhydrazono-1,3,4-oxadiazol-2-ylmethyl)-2-oxo-1,2-dihydroquinoxalines **4a-d**, but not the 1,2,4,5-tetrazepinylquinoxalines **5a-d**. The cyclization mode into the 1,3,4-oxadiazole ring was confirmed by the alternate syntheses of **4a,c** from the reactions of 3-(1,3,4-oxadiazol-2-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines **6a,b** with *o*-chlorophenyl diazonium salts, respectively. Moreover, **4a-d** exhibited an interesting tautomerism between the hydrazone imine form A and diazenyl enamine form B.

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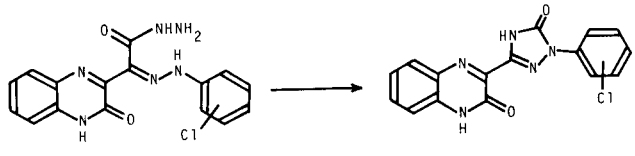
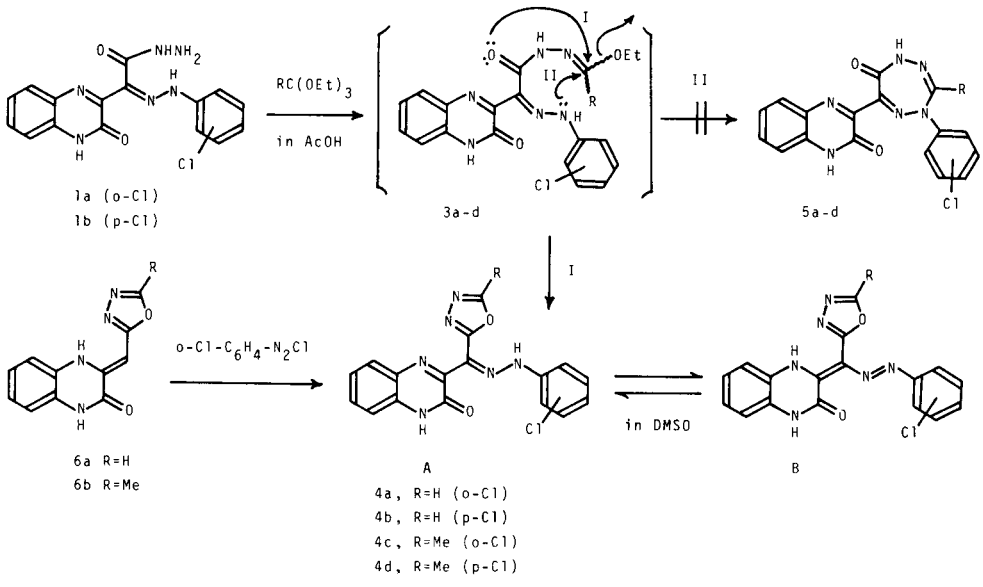
In a previous paper [1], we reported the conversions of 3-(α-arylhydrazono)hydrazinocarbonylmethyl-2-oxo-1,2-dihydroquinoxalines **1** into the 1-aryl-3-quinoxalinyl-1,2,4-triazol-5-ones **2** (Scheme 1) as a part of our series of studies on the synthesis of azole-conjugated quinoxalines [2-6]. In continuation of the above work, we undertook the intramolecular cyclization of **1** with triethyl orthoesters for the purpose of an additional ring construction, since there were at least two cyclization possibilities in intermediary hydrazonic esters **3a-d** (Scheme 2). As the result, these reactions were found to effect cyclizations into the 1,3,4-oxadiazole ring, but not into the tetrazepine ring, giving the novel 3-(α-arylhydrazono-1,3,4-oxadiazol-2-ylmethyl)-2-oxo-1,2-dihydroquinoxalines **4a-d**. Moreover, **4a-d** were found to exhibit an interesting tautomeric equilibria between the hydrazone imine form **A** and diazenyl enamine form **B** (Schemes 2,3). This paper describes the synthesis of the novel 1,3,4-oxadiazoles **4a-d** and their tautomeric equilibria between the **A** and **B** forms.

The reactions of **1a,b** (**a** = *o*-Cl, **b** = *p*-Cl) with triethyl orthoesters (R = H, Me) would provide intermediary hydrazonic esters **3a-d** [2], whose cyclizations were expected to furnish the oxadiazole ring and/or tetrazepine ring by the I and/or II routes, respectively. However, these reactions were clarified to afford a sole product by the route I cyclization. Namely, the pmr spectral data of the above cyclization products supported the structures of the 3-(α-arylhydrazono-1,3,4-oxadiazol-2-ylmethyl)-2-oxo-1,2-dihydroquinoxalines **4a-d**, but not the 1,2,4,5-tetrazepinylquinoxalines **5a-d**, as described later. Furthermore, the structural establishment of **4a-d** was accomplished by the alternate syntheses, that is, the reactions of 3-(1,3,4-oxadiazol-2-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines **6a,b** (**a**, R = H, **b**, R = Me) with *o*-chlorophenyl diazonium salt resulted in the diazotization at the methylenic carbon [1] to give the α-arylhydrazones **4a** and **4c**.

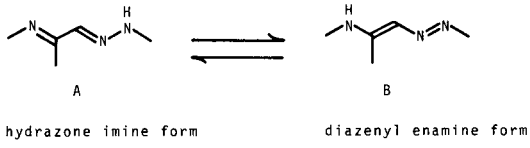


SCHEME 1

Our previous paper [7] reported the tautomeric equilibria of 3-formyl-2-oxo-1,2-dihydroquinoxaline chlorophenylhydrazones between the hydrazone imine form **A** and diazenyl enamine form **B** by means of the pmr spectral data in dimethylsulfoxide (DMSO), wherein the hydrazone CH proton signals (δ 7.87-7.73 ppm) appeared at a higher magnetic field than the diazenyl enamine CH proton signals (δ 8.40-8.37 ppm), and the hydrazone NH and N_4-H proton signals appeared at δ 14.73-14.45 ppm and δ 11.33-11.26 ppm, respectively. Based on these data, the pmr spectral data of **4a-d** also suggested the tautomeric equilibria between the hydrazone imine form **A** and diazenyl enamine form **B** in DMSO. Namely, the pmr spectrum of **4a** exhibited the hydrazone NH (δ 14.35 ppm) and N_4-H (δ 12.45 ppm) proton signals, together with the two $C_5'-H$ [δ 9.30 (due to **A** form), 9.47 (due to **B** form) ppm] proton signals. The spectrum of **4b** also showed the two $C_5'-H$ [δ 9.27 (due to **A** form), 9.42 (due to **B** form) ppm] proton signals, whose values were similar to those of **4a**. In case of **4b**, hydrazone NH and N_4-H proton signals were observed at δ 11.45 and 11.97 ppm, respectively. The spectra of **4c** and **4d** represented the hydrazone NH [δ 14.22 (**4c**), 11.18 (**4d**) ppm] and N_4-H [δ 12.42 (**4c**), 11.95 (**4d**) ppm] proton signals at similar magnetic fields to those observed in **4a** and **4b**, respectively. The $C_5'-Me$ proton signals of the **A** and **B** forms were observed at the same magnetic fields in **4c** (δ 2.57 ppm) and **4d** (δ 2.59 ppm). Moreover, the ^{13}C-nmr spectrum of **4c** ex-



SCHEME 2



SCHEME 3

hibited the thirty-six carbon signals due to the **A** (eighteen carbons) and **B** (eighteen carbons) forms of **4c**, wherein the $C_{5'}$-Me carbon signals were observed at δ 10.67 and 10.48 ppm. The ^{13}C-nmr spectrum of **4d** also showed the thirty-two carbon signals due to the **A** (eighteen carbons) and **B** (eighteen carbons) forms of **4d**, wherein the $C_{5'}$-Me carbon signals were observed at δ 10.71 and 10.50 ppm.

The tautomer ratios of the **A** form versus the **B** form in **4a-d** were 2:1, 5:1, 1:1 and 4:1, respectively, when calculated from the integral curves of the hydrazone NH, N_4-H and $C_{5'}$-H proton signals.

Thus, **4a-d** have been clarified to be the compounds exhibiting the characteristic tautomeric equilibria between the hydrazone imine and diazenyl enamine forms by means of the pmr and ^{13}C-nmr spectral data.

General Procedure.

All melting points are uncorrected. Infrared (ir) spectra were recorded from potassium bromide discs on a JASCO IRA-1 spectrophotometer. Mass spectra (ms) were determined with a JMS-01S spectrometer (JEOL). The pmr and

Table 1

The PMR Spectral Data for **4a-d**

Compound	Tautomer Ratio [a] A	B	Chemical Shift δ (ppm) NH	$C_{5'}$-H or -Me	aromatic
4a	2	1	14.35 (s, 2/3 H, C=N-NH-) [b] 12.45 (s, 1/3 H, N_4-H) [c] 12.80 (s, 1H, N_1-H)	9.30 (s, 2/3 H, $C_{5'}$-H) [b] 9.47 (s, 1/3 H, $C_{5'}$-H) [c]	8.03-6.80 (m, 8H)
4b	5	1	11.45 (s, 5/6 H, C=N-NH-) [b] 11.97 (s, 1/6 H, N_4-H) [c] 12.80 (s, 1H, N_1-H)	9.27 (s, 5/6 H, $C_{5'}$-H) [b] 9.42 (s, 1/6 H, $C_{5'}$-H) [c]	8.07-7.10 (m, 8H)
4c	1	1	14.22 (s, 1/2 H, C=N-NH-) [b] 12.42 (s, 1/2 H, N_4-H) [c] 12.77 (s, 1H, N_1-H)	2.57 (s, 3H, $C_{5'}$-Me)	8.00-6.93 (m, 8H)
4d	4	1	11.18 (s, 4/5 H, C=N-NH-) [b] 11.95 (s, 1/5 H, N_4-H) [c] 12.76 (s, 1H, N_1-H)	2.59 (s, 3H, $C_{5'}$-Me)	8.07-7.17 (m, 8H)

[a] Calculated from the integral curves of the hydrazone NH, N_4-H and $C_{5'}$-H proton signals. [b] Signals due to the tautomer **A**. [c] Signals due to the tautomer **B**.

Table 2

The ^{13}C-nmr Spectral Data for **4c,d**

Compound	Chemical Shift δ (ppm)
4c	163.11, 163.07, 162.81, 162.34, 159.11, 154.22, 153.32, 151.62, 148.72, 139.05, 138.79, 132.54, 132.34, 131.82, 131.76, 131.53, 130.55, 129.67, 129.24, 128.59, 128.51, 128.15, 124.18, 124.09, 123.83, 123.54, 122.52, 122.27, 119.29, 118.54, 115.77, 115.19, 115.08, 95.50, 10.67, 10.48
4d	163.36, 162.65, 162.49, 154.20, 154.18, 153.80, 153.65, 151.81, 151.17, 142.53, 141.79, 132.80, 132.45, 132.11, 131.88, 131.71, 131.27, 129.40, 129.31, 129.13, 126.52, 125.26, 124.23, 123.75, 123.58, 121.01, 116.11, 115.69, 115.19, 95.52, 10.71, 10.50

^{13}C-nmr spectra were measured in deuteriodimethylsulfoxide at 34° with an EM-390 and an XL-400 spectrometers at 90 and 400 MHz, respectively, using tetramethylsilane as an internal standard.

Preparation of **4a,b**.

A solution of **1a** or **1b** [1,8] (10 g) and triethyl orthoformate (100 ml) in acetic acid (500 ml) was refluxed in an oil bath for 5 hours to precipitate crystals, which were excluded by suction filtration. Evaporation of the filtrate *in vacuo* afforded yellow crystals **4** [**a**, 5.17 g (55%), **b**, 5.94 g (63%)]. Recrystallization from *N,N*-dimethylformamide/ethanol provided yellow needles, mp 281-282° (**4a**), 270-271° (**4b**); ms: m/z 366 (M^+), 368 ($M^+ + 2$) (**4a,b**); ir: ν cm^{-1} 1660, 1607, 1590, 1570 (**4a**); 1670, 1605, 1590 (**4b**).

Anal. Calcd. for $C_{17}H_{11}ClN_6O_2$: C, 55.67; H, 3.02; Cl, 9.67; N, 22.91. Found: C, 55.45; H, 3.06; Cl, 9.65; N, 23.06 (**4a**). C, 55.48; H, 3.11; Cl, 9.41; N, 22.67 (**4b**).

Preparation of **4c,d**.

A solution of **1a** or **1b** (10 g) and triethyl orthoacetate (100 ml) in acetic acid (500 ml) was refluxed in an oil bath for 5 hours. Evaporation of the solvent *in vacuo* furnished yellow crystals **4** [**c**, 7.10 g (73%), **d**, 8.28 g (78%)]. Recrystallization from *N,N*-dimethylformamide/ethanol gave yellow needles, mp 276-277° (**4c**), 267-268° (**4d**); ms: m/z 380 (M^+), 382 ($M^+ + 2$) (**4c,d**); ir: ν cm^{-1} 1670, 1607, 1590, 1570 (**4c**); 1660, 1605, 1590, 1565 (**4d**).

Anal. Calcd. for $C_{18}H_{13}ClN_6O_2$: C, 56.78; H, 3.44; Cl, 9.31; N, 22.07. Found: C, 56.55; H, 3.44; Cl, 9.16; N, 22.28 (**4c**). C, 56.52; H, 3.50; Cl, 9.23; N, 22.14 (**4d**).

Alternate Synthesis of **4a,c**.

A solution of sodium nitrite (0.364 g, 5.27 mmoles) in water (10 ml) was added dropwise to a suspension of *o*-chloroaniline hydrochloride (0.864 g, 5.27 mmoles) in acetic acid (20 ml) with stirring in an ice-water bath to give a clear solution, which was added to a suspension of **6a** (1 g, 4.93 mmoles) in acetic acid (30 ml) and water (10 ml) with stirring in an ice-water bath. After stirring was continued for 30 minutes, the reaction mixture was heated on a boiling water bath for 1 hour with initial stirring to afford a clear solution and then to precipitate yellow crystals of **4a**, which were collected by suction filtration (0.64 g). Evaporation of the filtrate *in vacuo* afforded yellow crystals of **4a** (0.50 g), total yield, 1.14 g (71%).

Compound **4c** was obtained in a similar manner to the above (73%).

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[8] Compounds **1a,b** were obtained as hydrazinium salts [1], which were employed in the present investigation.