Substituent Effects on the Tautomer Ratios between the Hydrazone Imine and Diazenyl Enamine Forms in 3-(Arylhydrazono)methyl-2-oxo-1,2-dihydroquinoxalines. Correlation of the Hammett Constants σ_p with the Tautomeric Equilibrium Constants K_T

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The 3-(arylhydrazono)methyl-2-oxo-1,2-dihydroquinoxalines **1a-e** and **2a-i** showed tautomeric equilibria between the hydrazone imine **A** and diazenyl enamine **B** forms in dimethyl sulfoxide media. The substituent effects on the tautomer ratios of **A** to **B** in compounds **1a-e** and **2a-i** were studied by the nmr spectroscopy. The electron-donating or electron-withdrawing *p*-substituents R^1 in compounds **2a-i** represented a tendency to increase the ratios of the tautomer **A** or the tautomer **B**, respectively, exhibiting the linear correlation of the Hammett constants σ_p (-0.17 to +0.78) with the tautomer ratios of **A** to **B** or the tautomeric equilibrium constants K_T. However, the presence of the ester group R^2 in compounds **1a-e** induced the exclusive existence of the tautomer **A** regardless of the nature of the *p*-substituents R^1. In the tautomeric thermodynamic study, the elevating temperature increased the ratios of the hydrazone imine tautomer **A** in compounds **2a-i**. The tautomeric thermodynamic parameters ΔG°, ΔH° and ΔS° were derived from the van't Hoff plots for compounds **2a,b,h,i**, wherein the entropy term dominated the free-energy difference between the **A** and **B** tautomers.

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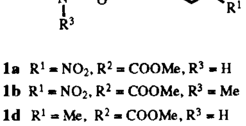
In a previous paper [1], we reported the synthesis of the 3-(arylhydrazono)methyl-2-oxo-1,2-dihydroquinoxalines **1a,b,d,e** and **2a,d,h,i** (Chart 1), whose nmr spectra in dimethyl sulfoxide showed the tautomeric equilibria between the hydrazone imine **A** and diazenyl enamine **B** forms (Schemes 1,2). Moreover, the presence of the electron-withdrawing *p*-substituents R^1 [**2a** (NO_2), **2d** (COOEt)] or electron-donating *p*-substituents R^1 [**2h** (Et), **2i** (Me)] exhibited a tendency to increase the ratios of the tautomer **B** or the tautomer **A**, respectively, while the presence of the ester group R^2 in compounds **1a,b,d,e** effected the exclusive existence of the tautomer **A** regardless of the nature of the *p*-substituents R^1. In order to explain the above results concretely, we inspected the correlation of the tautomer ratios of **A** to **B** with the Hammett constants σ_p reflecting the nature of the *p*-substituents R^1. Accordingly, additional compounds **1c** and **2b,c,f,g** were synthesized to cover the various Hammett constants σ_p (-0.17 to +0.78). As the result, we found the linear correlation of the Hammett constants σ_p with the tautomer ratios of **A** to **B** or the tautomeric equilibrium constants K_T in compunds **2a-i** (Table 1, Figures 1,2). Furthermore, the elevation of temperature was found to augment the ratios of the hydrazone imine tautomer **A** in all of compounds **2a-i** (Table 2). This paper describes the synthesis of compounds **1c** and **2b,c,f,g** and the linear correlation of the Hammett constants σ_p with the tautomer ratios of **A** to **B** or the tautomeric equilibrium constants K_T in compounds **2a-i**. The tautomeric equilibrium constant temperature dependence and the thermodynamic consideration are also provided for compounds **2a,b,h,i**.

Chart 1



1a $R^1 = NO_2$, $R^2 = COOMe$, $R^3 = H$
1b $R^1 = NO_2$, $R^2 = COOMe$, $R^3 = Me$
1d $R^1 = Me$, $R^2 = COOMe$, $R^3 = H$
1e $R^1 = Me$, $R^2 = COOMe$, $R^3 = Me$

2a $R^1 = NO_2$, $R^2 = R^3 = H$
2d $R^1 = COOEt$, $R^2 = R^3 = H$
2h $R^1 = Et$, $R^2 = R^3 = H$
2i $R^1 = Me$. $R^2 = R^3 = H$

Table 1

Data of the Hammett Constants σ_p, Tautomer Ratios of **A** to **B** and Tautomeric Equilibrium Constants K_T for Compounds **1** and **2** [a]

Compound	R^1	R^2	R^3	σ_p [b]	Tautomer Ratio A	B	K_T [c]
1a	NO_2	COOMe	H	+0.78 (*p*-NO_2)	100	0	
1b	NO_2	COOMe	Me	+0.78 (*p*-NO_2)	100	0	
1c	H	COOMe	Me	0 (*p*-H)	100	0	
1d	Me	COOMe	H	-0.17 (*p*-Me)	100	0	
1e	Me	COOMe	Me	-0.17 (*p*-Me)	100	0	
2a	NO_2	H	H	+0.78 (*p*-NO_2)	30	70	0.43
2b	CN	H	H	+0.66 (*p*-CN)	40	60	0.67
2c	SO_2NH_2	H	H	+0.58 (*p*-SO_2NH_2)	44	56	0.79
2d	COOEt	H	H	+0.45 (*p*-COOEt)	46	54	0.85
2e	Cl	H	H	+0.23 (*p*-Cl)	54	46	1.17
2f	F	H	H	+0.06 (*p*-F)	60	40	1.50
2g	H	H	H	0 (*p*-H)	62	38	1.63
2h	Et	H	H	-0.15 (*p*-Et)	67	33	2.03
2i	Me	H	H	-0.17 (*p*-Me)	67	33	2.03

[a] The nmr spectra were measured in deuteriodimethyl sulfoxide at 25°. [b] The values shown herein were picked up from several literatures. [c] K_T = [hydrazone imine form]/[diazenyl enamine form] or [**A**]/[**B**].

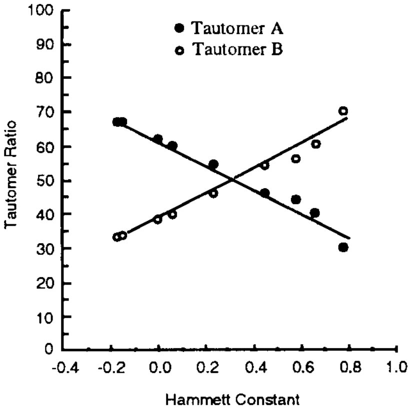


Figure 1. Correlation of the Hammett Constants σ_p with the Tautomer Ratios.

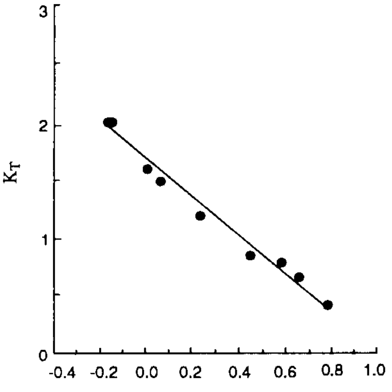


Figure 2. Correlation of the Hammett Constants σ_p with the Tautomeric Equilibrium Constants K_T.

Table 2

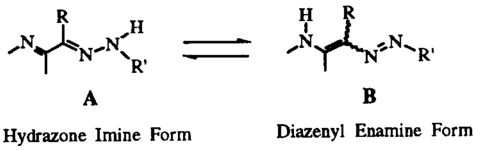
Tautomeric Equilibrium Constant Temperature Dependence and Tautomeric Thermodynamic Parameters for Compounds **2a,b,h,i**

Compound	Temperature °K	K_T [a]	ΔG° (kcal/mol)	ΔH° (kcal/mol)	ΔS° (cal/mol deg)
2a	298	0.43	0.50	1.97	4.93
(*p*-NO2)	323	0.56	0.37		4.95
	348	0.69	0.26		4.92
	373	0.85	0.12		4.96
2b	298	0.67	0.24	1.30	3.57
(*p*-CN)	323	0.79	0.15		3.56
	348	0.92	0.06		3.57
	373	1.04	-0.03		3.56
	398	1.17	-0.12		3.58
2h	298	2.03	-0.42	1.44	6.25
(*p*-Et)	323	2.45	-0.58		6.25
	348	2.85	-0.72		6.23
	373	3.35	-0.90		6.27
2i	298	2.03	-0.42	1.17	5.35
(*p*-Me)	323	2.33	-0.54		5.31
	348	2.70	-0.69		5.35
	373	3.00	-0.81		5.33
	398	3.35	-0.96		5.35

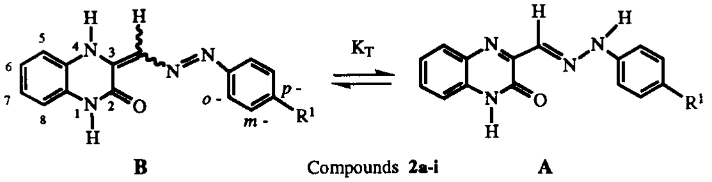
[a] K_T = [hydrazone imine form]/[diazenyl enamine form] or [**A**]/[**B**].

The reaction of 3-methoxycarbonylmethylene-1-methyl-2-oxo-1,2,3,4-tetrahydroquinoxaline **3** or 3-methyl-2-oxo-1,2-dihydroquinoxaline **4** with benzenediazonium salt gave 1-methyl-3-[α-(phenylhydrazono)-methoxycarbonylmethyl]-2-oxo-1,2-dihydroquinoxaline **1c** or 2-oxo-3-(phenylhydrazono)methyl-1,2-dihydroquinoxaline **2g**, respectively (Scheme 3). The reaction of 3-methyl-2-oxo-1,2-dihydroquinoxaline **4** with *p*-cyano-, *p*-aminosulfonyl- and *p*-fluorobenzenediazonium salts afforded 3-(*p*-cyanophenylhydrazono)methyl-2-oxo-1,2-dihydroquinoxaline **2b**, 3-(*p*-aminosulfonylphenylhydra-

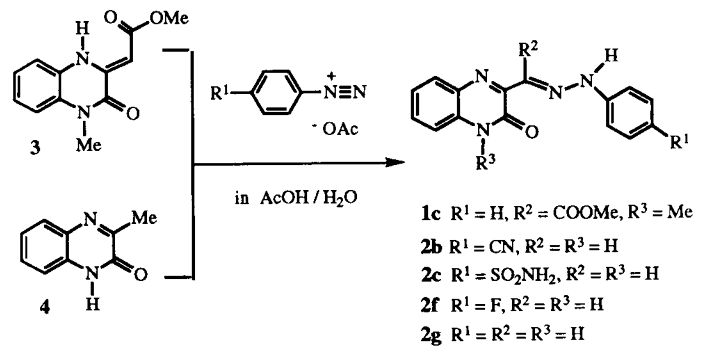
Scheme 1



Scheme 2



Scheme 3

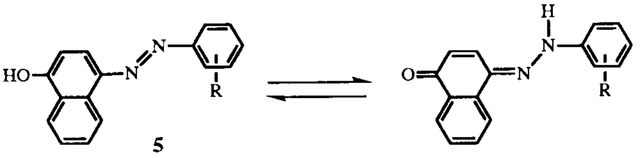


zono)methyl-2-oxo-1,2-dihydroquinoxaline **2c** and 3-(*p*-fluorophenylhydrazono)methyl-2-oxo-1,2-dihydroquinoxaline **2f**, respectively. The synthesis of the *p*-chloro derivative **2e** has already been reported in a previous paper [2,3].

The assignment of the nmr signals due to the tautomers **A** and/or **B** using ^{13}C-^{1}H coupling data and the subsequent calculation of the tautomer ratios of **A** to **B** in compounds **1a,b,d,e** and **2a,d,h,i** have already been reported in a previous paper [1]. In this study, the tautomer ratios of **A** to **B** in compounds **1c** and **2b,c,e,f,g** were also calculated from the integral curves of the signals due to the ester methyl, hydrazone CH, diazenyl CH, C_5-H, *p*-substituent or other CH proton signals [1]. Table 1 summarizes the Hammett constants σ_p, the tautomer ratios of **A** to **B** and the tautomeric equilibrium constants K_T for compunds **1a-e** and **2a-i**. Compounds **1a-e** exclusively existed as the tautomer **A** regardless of the nature of the *p*-substituents R^1 (Hammett σ_p values, -0.17 to +0.78), and hence there was no correlation of the Hammett constants σ_p with the tautomer ratios. However, compounds **2a-i** occurred as the tautomers **A** and **B**, and the stepwise decrease in the Hammett σ_p values gradually increased the ratios of the tautomer **A**, suggesting the correlation of the Hammett constants σ_p with the tautomer ratios of **A** to **B** or the tautomeric equilibrium constants K_T. The plots shown in Figures 1 and 2 present the linear correlation of the Hammett constants σ_p with the tautomer ratios (correlation coefficient, r = 0.994) and the tautomeric equilibrium constants K_T (correlation coefficient, r = 0.995), respectively.

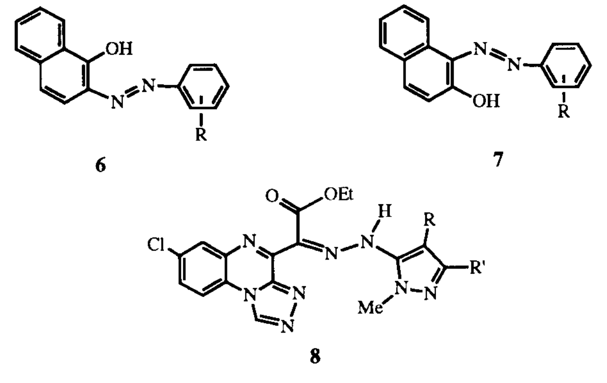
Korewa *et al.* [4] reported the effects of the substituents R on the ratios of the azo tautomer C in the 4-arylazo-1-naphthols 5 (Scheme 4) in various solvents. Since the substituents of compunds **5** were the *o*-, *m*-, *p*-chloro, *o*-, *m*-, *p*-nitro and *o,o*-, *o,m*-, *o,p*-dichloro groups, the results obtained from these substituent effects did not provide a clear-cut situation representing the correlation of the Hammett constants with the tautomeric equilibrium constants K_T. In addition, the electron-withdrawing substituents stabilize the hydrazone form **D** in the 4-arylazo-1-naphthols **5** and 2-arylazo-1-naphthols **6** (Chart 2) [4]. These results show the opposite effect to that observed in our compounds **2**, whose hydrazone form **A** is stabilized by the electron-donating *p*-substituents R^1.

Scheme 4



Azo Form **C** Hydrazone Form **D**

Chart 2



Saeva [5] reported the effect of temperature on the tautomer ratios of **C** to **D** together with the tautomeric thermodynamic parameters ΔG°, ΔH° and ΔS° in the 4-arylazo-1-naphthol **5** (R = *p*-OMe) and 1-arylazo-2-naphthol **7** (R = *p*-OMe), showing that the elevating temperature augmented the ratios of the azo tautomer **C**. These results are similar to those in our previous paper [6] reporting the tautomeric behavior of the 4-[α-(5-pyrazolylhydrazono)ethoxycarbonylmethyl]-1,2,4-triazolo[4,3-*a*]quinoxalines 8 (Chart 2). In the present investigation, we also measured the nmr spectra of compounds **2a-i** at various temperature (25-125°) to study the tautomeric equilibrium constant temperature dependence. In all of compounds

2a-i, the increasing temperature augmented the ratios of the hydrazone imine tautomer **A**, giving the opposite results to those of compounds **6**, **7**, **8**. On the other hand, the tautomeric thermodynamic parameters $\Delta G°$, $\Delta H°$ and $\Delta S°$ (Table 2) were derived from the van't Hoff plots for compounds **2a,b,h,i,** (Figure 3), wherein the entropy term was found to govern the free-energy difference between the hydrazone imine **A** and diazenyl enamine **B** tautomers.

In conclusion, the linear correlation of the Hammett constants σ_p with the tautomer ratios of **A** to **B** or the tautomeric equilibrium constants K_T was observed in the dimethyl sulfoxide media of the 3-(arylhydrazono)methyl-2-oxo-1,2-dihydroquinoxalines **2a-i**. In the tautomeric thermodynamic study, the increasing temperature augmented the ratios of the hydrazone imine tautomer **A** in compounds **2a-i**. The entropy term dominated the free-energy difference between the tautomers **A** and **B** in compounds **2a,b,h,i**.

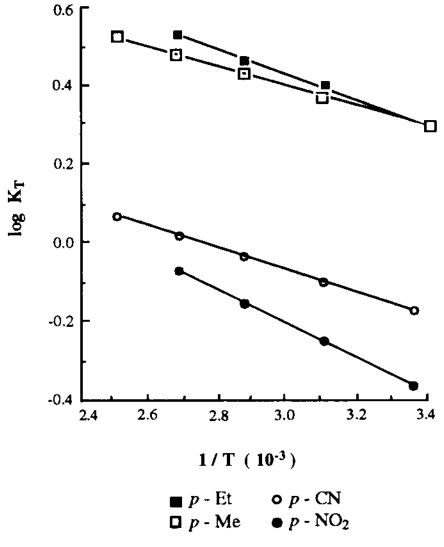


Figure 3. van't Hoff Plots for Compounds **2a,b,h,i**

EXPERIMENTAL

All melting points were determined on a Yazawa micro melting point BY-2 apparatus and are uncorrected. The ir spectra (potassium bromide) were recorded with a JASCO IRA-1 spectrophotometer. The mass spectra (ms) were determined with a JEOL JMS-01S spectrometer. The nmr spectra were measured in deuteriodimethyl sulfoxide with a VXR-300 spectrometer at 300 MHz. Chemical shifts are given in the δ scale. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

1-Methyl-3-[α-(phenylhydrazono)methoxycarbonylmethyl]-2-oxo-1,2-dihydroquinoxaline **1c**.

A solution of sodium nitrite (2.35 g, 32.3 mmoles) in water (30 ml) was added to a solution of aniline (3.01 g, 32.3 mmoles) in acetic acid (50 ml) with stirring in an ice-water bath to give a yellow clear solution, which was added to a suspension of 3-methoxycarbonylmethylene-1-methyl-2-oxo-1,2,3,4-tetrahydroquinoxaline (3 g, 12.9 mmoles) in acetic acid (50 ml). The mixture was heated with stirring on a boiling water bath for 1 hour to afford a brown solution. Evaporation of the solvent *in vacuo* provided oily residue, which was crystallized from ethanol to furnish orange needles **1c** (0.95 g, 22%), mp 179-180°; ir: ν cm^{-1} 1725; ms: m/z 336 (M^+); pmr: 10.95 (s, 1H, hydrazone NH), 7.92 (dd, J = 8.0 Hz, J = 1.5 Hz, 1H, C_5-H), 7.74 (ddd, J = 8.0 Hz, J = 8.0 Hz, J = 1.5 Hz, 1H, C_7-H), 7.65 (dd, J = 8.0 Hz, J = 1.5 Hz, 1H, C_8-H), 7.45 (ddd, J = 8.0 Hz, J = 8.0 Hz, J = 1.5 Hz, 1H, C_6-H), 7.29 (ddd, J = 8.0 Hz, J = 8.0 Hz, J = 1.0 Hz, 2H, *m*-H), 7.20 (dd, J = 8.0 Hz, J = 1.0 Hz, 2H, *o*-H), 6.95 (dddd, J = 8.0 Hz, J = 8.0 Hz, J = 1.0 Hz, J = 1.0 Hz, 1H, *p*-H), 3.71 (s, 3H, OCH_3), 3.66 (s, 3H, NCH_3).

Anal. Calcd. for $C_{18}H_{16}N_4O_3$: C, 64.28; H, 4.80; N, 16.66. Found: C, 64.54; H, 4.94; N, 16.45.

3-(*p*-Cyanophenylhydrazono)methyl-2-oxo-1,2-dihydroquinoxaline **2b**.

A solution of sodium nitrite (1.56 g, 22.6 mmoles) in water (50 ml) was added to a solution of *p*-cyanoaniline (2.67 g, 22.6 mmoles) in acetic acid (50 ml) with stirring in an ice-water bath to precipitate yellow crystals, to which a solution of 3-methyl-2-oxo-1,2-dihydroquinoxaline (3 g, 18.8 mmoles) in acetic acid (100 ml)/water (50 ml). The mixture was heated with stirring on a boiling water bath for 1 hour to precipitate yellow crystals **2b**, which were collected by suction filtration and washed with ethanol and then *n*-hexane (2.42 g, 45%). Recrystallization from *N,N*-dimethylformamide/ethanol afforded yellow needles, mp above 340°; ir: ν cm^{-1} 2200, 1660, 1600; ms: m/z 289 (M^+); pmr: (hydrazone imine form **A**) 14.45 (s, hydrazone NH), 12.45 (s, N_1-H), 8.10 (dd, J = 1.0 Hz, J = 8.0 Hz, C_5-H), 7.81 (s, hydrazone CH), 7.75 (d, J = 8.5 Hz, *m*-H), 7.54 (d, J = 8.5 Hz, *o*-H); (diazenyl enamine form **B**) 12.65 (s, N_1-H), 11.59 (s, N_4-H), 8.41 (s, diazenyl CH), 7.79 (dd, J = 1.0 Hz, J = 8.0 Hz, C_5-H), 7.69 (d, J = 8.5 Hz, *m*-H), 7.22 (d, J = 8.5 Hz, *o*-H). The C_6-H, C_7-H and C_8-H proton signals for the **A** and **B** forms were observed at 7.58-7.42 ppm and 7.37-7.26 ppm.

Anal. Calcd. for $C_{16}H_{11}N_5O$: C, 66.43; H, 3.83; N, 24.21. Found: C, 66.21; H, 3.95; N, 23.92.

3-(*p*-Aminosulfonylphenylhydrazono)methyl-2-oxo-1,2-dihydroquinoxaline **2c**.

A solution of sodium nitrite (1.56 g, 22.6 mmoles) in water (50 ml) was added to a suspension of sulfanylamide (3.89 g, 22.6 mmoles) in acetic acid (50 ml) with stirring in an ice-water bath to give a yellow solution, which was added to a suspension of 3-methyl-2-oxo-1,2-dihydroquinoxaline (3 g, 18.8 mmoles) in acetic acid (50 ml)/water (50 ml). The mixture was heated with stirring on a boiling water bath for 1 hour to precipitate a small amount of orange crystals. The solvent was evaporated *in vacuo* to afford orange crystals **2c**, which were triturated with ethanol/*n*-hexane and then collected by suction filtration (1.16 g, 18%). Recrystallization from *N,N*-dimethylformamide/ethanol provided orange needles, mp above 340°; ir: ν cm^{-1} 1650; ms: m/z 343 (M^+); pmr: (hydrazone imine form **A**) 14.50 (s, hydrazone NH), 12.63 (s, N_1-H), 8.08 (dd, J = 1.0 Hz, J = 8.0 Hz, C_5-H), 7.78 (s, hydrazone CH), 7.77 (d, J = 8.5 Hz, *m*-H), 7.54 (d, J = 8.5 Hz, *o*-H), 7.14 (s, SO_2NH_2); (diazenyl enamine form **B**)

12.42 (s, N_1-H), 11.49 (s, N_4-H), 8.41 (s, diazenyl CH), 7.73 (d, J = 8.5 Hz, *m*-H), 7.14 (s, SO_2NH_2). The other proton signals were observed at 7.82-7.73 ppm, 7.57-7.43 ppm and 7.37-7.18 ppm.

Anal. Calcd. for $C_{15}H_{13}N_5O_3S$: C, 52.47; H, 3.82; N, 20.40. Found: C, 52.45; H, 3.93; N, 20.51.

3-(*p*-Fluorophenylhydrazono)methyl-2-oxo-1,2-dihydroquinoxaline **2f**.

A solution of sodium nitrite (1.56 g, 22.6 mmoles) in water (50 ml) was added to a solution of *p*-fluoroaniline (2.51 g, 22.6 mmoles) in acetic acid (50 ml) with stirring in an ice-water bath to precipitate yellow crystals, to which a solution of 3-methyl-2-oxo-1,2-dihydroquinoxaline (3 g, 18.8 mmoles) in acetic acid (100 ml)/water (50ml) was added. The mixture was heated with stirring on a boiling water bath for 1 hour to precipitate orange crystals **2f**, which were collected by suction filtration and washed with ethanol and then *n*-hexane (1.99 g, 38%). Recrystallization from *N,N*-dimethylformamide/ethanol afforded orange needles, mp 320-321°; ir: ν cm^{-1} 1660; ms: m/z 282 (M^+); pmr: (hydrazone imine form **A**) 14.48 (s, hydrazone NH), 12.48 (br, N_1-H), 8.04 (dd, J = 1.0 Hz, J = 8.0 Hz, C_5-H), 7.68 (s, hydrazone CH), (diazenyl enamine form **B**) 12.48 (br, N_1-H), 11.21 (s, N_4-H), 8.31 (s, diazenyl CH), 7.75 (dd, J = 1.0 Hz, J = 8.0 Hz, C_5-H). The other proton signals were observed at 7.54-7.48 ppm and 7.35-7.10 ppm.

Anal. Calcd. for $C_{15}H_{11}FN_4O$: C, 63.82; H, 3.93; N, 19.85. Found: C, 63.54; H, 4.06; N, 19.71.

2-Oxo-3-(phenylhydrazono)methyl-1,2-dihydroquinoxaline **2g**.

A solution of sodium nitrite (1.56 g, 22.6 mmoles) in water (50 ml) was added to a solution of aniline (2.10 g, 22.6 mmoles) in acetic acid (50 ml) with stirring in an ice-water bath to give a yellow clear solution, which was added to a suspension of 3-methyl-2-oxo-1,2-dihydroquinoxaline (3 g, 18.8 mmoles) in acetic acid (50 ml)/water (50 ml). The mixture was heated with stirring on a boiling water bath for 30 minutes to precipitate orange needles **2g**, which were collected by suction filtration (620 mg, 12%). Recrystallization from *N,N*-dimethylformamide/ethanol afforded red needles, mp 303-304°; ir: ν cm^{-1} 1650; ms: m/z 264 (M^+); pmr: (hydrazone imine form **A**) 14.50 (s, hydrazone NH), 12.46 (br, N_1-H), 8.02 (dd, J = 8.0 Hz, J = 1.5 Hz, C_5-H), 7.70 (s, hydrazone CH), 6.99 (dddd, J = 7.0 Hz, J = 7.0 Hz, J = 1.5 Hz, J = 1.5 Hz, *p*-H), (diazenyl enamine form **B**) 12.46 (br, N_1-H), 11.21 (s, N_4-H), 8.33 (s, diazenyl CH), 7.76 (dd, J = 8.5 Hz, J = 1.5 Hz, C_5-H), 6.85 (dddd, J = 7.0 Hz, J = 7.0 Hz, J = 1.5 Hz, J = 1.5 Hz, *p*-H). The other proton signals were observed at 7.54-7.12 ppm.

Anal. Calcd. for $C_{15}H_{12}N_4O$: C, 68.17; H, 4.58; N, 21.20. Found: C, 68.22; H, 4.72; N, 21.15.

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[3] The tautomer ratio of **A** to **B** in compound **2e** (*p*-Cl) had to be calculated from the integral curves of the hydrazone NH and N_4-H proton signals in reference [2], because the nmr spectrum was measured with a 100 MHz instrument. Accordingly, the results in reference [2] did not reflect the accurate tautomer ratio of **A** to **B**. In the present investigation, the measurement of the nmr spectrum with a 300 MHz instrument afforded the accurate ratio of **A** to **B**, which was calculated from the integral curves of the hydrazone CH, diazenyl CH and C_5-H proton signals.

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