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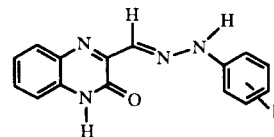
The *p*- and *m*-substituted 3-(arylhydrazono)methyl-2-oxo-1,2-dihydroquinoxalines **1a-i** and **2a-d** exhibited tautomeric equilibria between the hydrazone imine **A** and diazenyl enamine **B** forms in a series of mixed dimethyl sulfoxide/trifluoroacetic acid media. The substituent and solvent effects on the tautomer ratios of **A** to **B** in a series of mixed media were studied for compounds **1a-i** and **2a-d** by the nmr spectroscopy. The linear correlation of the Hammett σ_p and σ_m values with the tautomeric equilibrium constants K_T ($[A]/[B]$) was found in the dimethyl sulfoxide media of compounds **1a-i** and **2b-d**. On the other hand, the linear correlation of the Hammett σ_p and σ_m values with the $\log C'(A:B = 1:1)$ was also observed in a series of mixed media of compounds **1a-h** and **2a-c**, wherein $C'(A:B = 1:1)$ indicated the concentrations of trifluoroacetic acid (mol/l) giving 1:1 tautomer ratios in a series of mixed media. The increase in the Hammett σ_p or σ_m values decreased the K_T values in dimethyl sulfoxide media and augmented the $C'(A:B = 1:1)$ values in a series of mixed media. The Hammett σ_p or σ_m values controlled the electron density of the side chain nitrogen atom, which influenced the $C'(A:B = 1:1)$ values. In the K_T value temperature dependence, the higher temperature provided the larger K_T values in dimethyl sulfoxide media regardless of the Hammett σ_p or σ_m values.

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In previous papers [1,2], we reported that the nmr spectra of the *p*-substituted 3-(arylhydrazono)methyl-2-oxo-1,2-dihydroquinoxalines **1a-i** (Chart 1) in dimethyl sulfoxide or a series of mixed dimethyl sulfoxide/trifluoroacetic acid media showed tautomeric equilibria between the hydrazone imine **A** and diazenyl enamine **B** forms (Schemes 1, 2). Moreover, the linear correlation of the Hammett σ_p values with the tautomeric equilibrium constants K_T ($[A]/[B]$) was found in the dimethyl sulfoxide media of compounds **1a-i** (Table 2, Figure 5) [1], while the linear correlation of the Hammett σ_p values with the $\log C'(A:B = 1:1)$ values was found in a series of mixed dimethyl sulfoxide/trifluoroacetic acid media of compounds **1a-h** (Table 2, Figure 6) [2], wherein $C'(A:B = 1:1)$ provided a mean of the concentration of trifluoroacetic acid (mol/l) giving a 1:1 tautomer ratio in a series of trifluoroacetic acid/dimethyl sulfoxide media. In the present investigation, the *m*-substituted 3-(arylhydrazono)methyl-2-oxo-1,2-dihydroquinoxalines **2a-d** (Chart 1) were synthesized in order to study the correlation of the Hammett σ_p and σ_m values with the tautomeric equilibrium constants K_T or with the $\log C'(A:B = 1:1)$ values. This paper describes the nmr spectral data of compounds

2a, **2b** [3], **2c** and **2d** in a series of mixed dimethyl sulfoxide/trifluoroacetic acid media and the correlation of the Hammett σ_p and σ_m values with the tautomeric equilibrium constants K_T or with the $\log C'(A:B = 1:1)$ values.

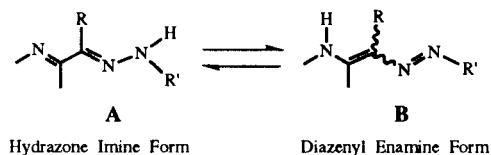
Chart 1



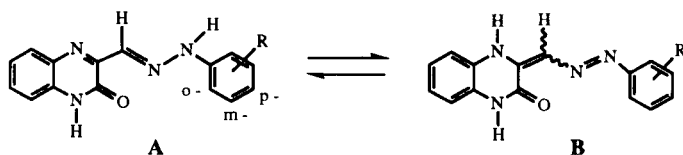
- | | |
|---|-----------------------------|
| 1a R = <i>p</i> -NO ₂ | 1f R = <i>p</i> -F |
| 1b R = <i>p</i> -CN | 1g R = <i>p</i> -H |
| 1c R = <i>p</i> -SO ₂ NH ₂ | 1h R = <i>p</i> -Et |
| 1d R = <i>p</i> -COOEt | 1i R = <i>p</i> -Me |
| 1e R = <i>p</i> -Cl | |
| 2a R = <i>m</i> -CN | 2c R = <i>m</i> -OMe |
| 2b R = <i>m</i> -Cl | 2d R = <i>m</i> -Et |

The reaction of 3-methyl-2-oxo-1,2-dihydroquinoxaline with *m*-cyano-, *m*-methoxy- or *m*-ethylbenzenediazonium salt gave 3-(*m*-cyanophenylhydrazono)methyl-2-oxo-1,2-dihydroquinoxaline **2a**, 3-(*m*-methoxyphenylhydrazono)-

Scheme 1



Scheme 2



Scheme 3

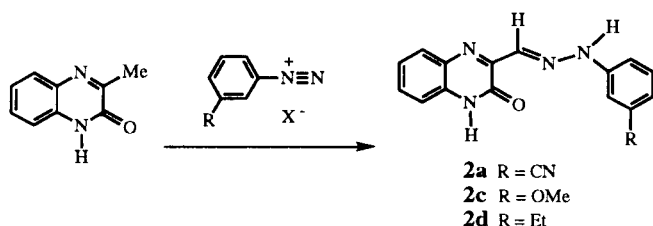
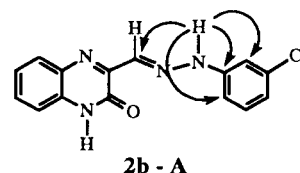


Chart 2



Hydrazone NH (δ 14.4)
 Hydrazone C (δ 123.5)
 Benzene C₁ (δ 144.9)
 o-C (δ 112.6, 113.4)

HMBC Spectral Data for Compound **2b**

methyl-2-oxo-1,2-dihydroquinoxaline **2c** and 3-(*m*-ethylphenylhydrazono)methyl-2-oxo-1,2-dihydroquinoxaline **2d**, respectively (Scheme 3). The synthesis of *m*-chloro derivative **2b** has already been reported in a previous paper [3,4].

The nmr spectra of compounds **2a-d** were measured in dimethyl sulfoxide and a series of mixed trifluoroacetic acid/dimethyl sulfoxide media. In order to specify the proton signals due to the tautomer **A** or **B**, the ¹³C-¹H coupling data were obtained from the HMBC and HMQC spectra of compound **2b** (Chart 2). As the result, the hydrazone NH, N₄-H, hydrazone CH, diazenyl CH and

Table 1

Data of the Tautomers **A** and **B** for Compounds **2a,b,c,d**

Compound	TFA % in DMSO	Tautomer Ratio		Chemical Shift (δ ppm)		C ₅ -H	
		A	B	Hydrazone CH	Diazenyl CH	A Form	B Form
				A Form	B Form		
2a (<i>m</i> -CN)	0	54	46	7.76	8.37	8.16	7.80
	10	56	44	7.79	8.37	8.13	7.74
	25	50	50	7.74	8.28	7.96	7.88
	50	26	74	7.66	8.16	[b]	[b]
	75	0	100	—	8.00	—	7.63
	100	0	100	—	8.16	—	7.71
2b (<i>m</i> -Cl)	0	53	47 [a]	7.74	8.34	8.13	7.80
	10	51	49	7.75	8.33	8.07	7.86
	20	48	52	7.74	8.28	7.98	7.88
	25	44	56	7.73	8.26	7.99	7.89
	50	21	79	7.67	8.18	7.74	7.92
	75	0	100	—	7.91	—	7.54
2c (<i>m</i> -OMe)	100	0	100	—	8.11	—	7.68
	0	60	40	7.71	8.33	8.04	7.79
	10	50	50	7.71	8.25	7.98	7.88
	25	36	64	7.68	8.18	7.83	7.90
	40	16	84	7.61	8.11	7.65	7.86
	60	0	100	—	7.99	—	7.67
2d (<i>m</i> -Et)	75	0	100	—	7.89	—	7.53
	100	0	100	—	8.14	—	7.80
	0	67	33	7.68	8.33	8.00	7.77
	10	52	48	7.70	8.25	7.97	7.90
	25	29	71	7.65	8.17	7.82	7.90
	50	0	100	—	8.06	—	7.80
75	0	100	—	7.84	—	7.48	
100	0	100	—	7.98	—	7.56	

[a] Tautomer ratio based on the hydrazone CH, diazenyl CH, C₅-H and other CH proton signals. See references [3,4].

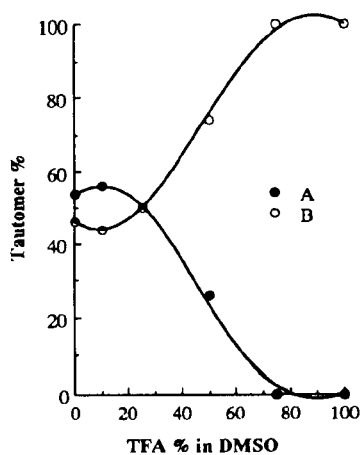
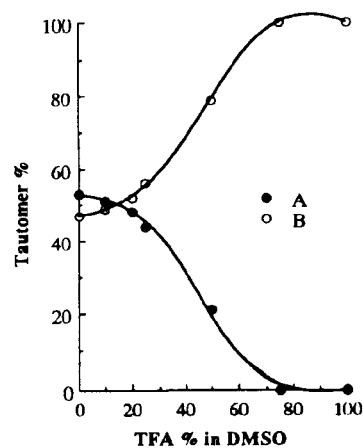
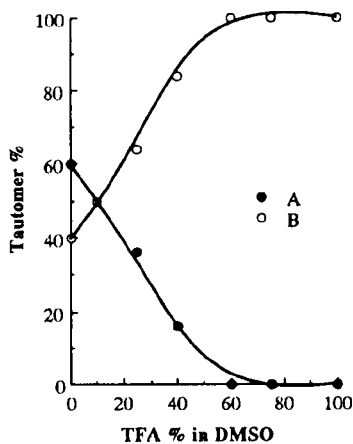
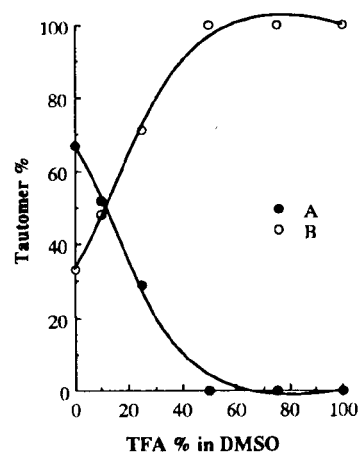
[b] Overlapped with other signals.

Table 2

Data of the Tautomeric Equilibrium Constants K_T , $C(A:B = 1:1)$ [a], $C'(A:B = 1:1)$ and $\log C'(A:B = 1:1)$ Values for Compounds **1a-i** [b] and **2a-d**

Compound	σ Value [c]	K_T [d]	$C(A:B = 1:1)$ (v/v %)	$C'(A:B = 1:1)$ (mol/l)	$\log C'(A:B = 1:1)$
1a	+0.78 (<i>p</i> -NO ₂)	0.43	57	7.70	0.89
1b	+0.66 (<i>p</i> -CN)	0.67	42	5.67	0.75
1c	+0.58 (<i>p</i> -SO ₂ NH ₂)	0.79	35	4.73	0.67
1d	+0.45 (<i>p</i> -COOEt)	0.85	25	3.38	0.53
1e	+0.23 (<i>p</i> -Cl)	1.17	13	1.76	0.25
1f	+0.06 (<i>p</i> -F)	1.50	9	1.22	0.09
1g	0.00 (<i>p</i> -H)	1.63	7	0.95	-0.02
1h	-0.15 (<i>p</i> -Et)	2.03	5	0.68	-0.17
1i	-0.17 (<i>p</i> -Me)	2.03	—	—	—
2a	+0.56 (<i>m</i> -CN)	(1.17) [e]	25	3.38	0.53
2b	+0.37 (<i>m</i> -Cl)	1.13	15	2.03	0.31
2c	+0.10 (<i>m</i> -OMe)	1.50	11	1.49	0.17
1g	0.00 (<i>m</i> -H)	1.63	7	0.95	-0.02 [b]
2d	-0.08 (<i>m</i> -Et)	2.03	12	1.62	(0.21) [e]

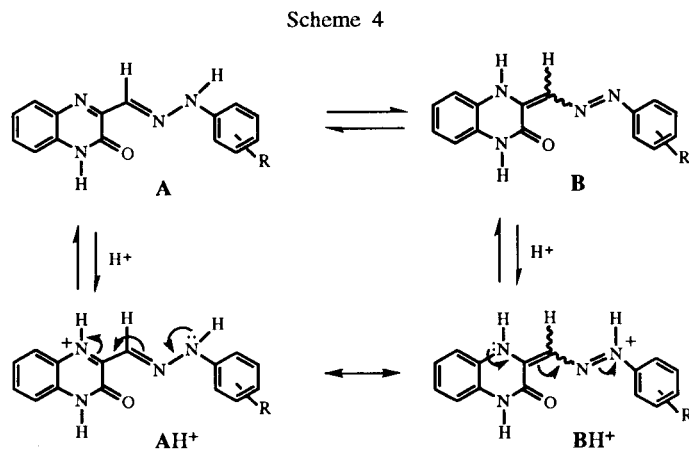
[a] $C(A:B = 1:1)$ means the concentration of trifluoroacetic acid in dimethyl sulfoxide giving the 1:1 tautomer ratio of A to B. [b] Already reported in references [1,2] and listed again in this paper. [c] The σ values shown herein were picked up from several literatures. [d] $K_T = [\text{hydrazone imine form}]/[\text{diazenyl enamine form}]$ or $[A]/[B]$ in dimethyl sulfoxide media. [e] The data in parentheses were not incorporated in Figures 5 and 6.

Figure 1. Plots of Tautomer Ratios A/B for Compound **2a**.Figure 2. Plots of Tautomer Ratios A/B for Compound **2b**.Figure 3. Plots of Tautomer Ratios A/B for Compound **2c**.Figure 4. Plots of Tautomer Ratios A/B for Compound **2d**.

C_5 -H proton signals due to tautomer **A** or **B** in a series of mixed trifluoroacetic acid/dimethyl sulfoxide media were easily assigned, and the tautomer ratios of **A** to **B** were calculated from the integral ratios of the hydrazone CH, diazenyl CH, C_5 -H and other CH proton signals (Table 1). The data of the tautomer ratios of **A** to **B** in compounds **2a-d** provided the tautomeric equilibrium constants K_T in dimethyl sulfoxide and the $\log C'(A:B = 1:1)$ values in a series of mixed trifluoroacetic acid/dimethyl sulfoxide media (Table 2), wherein the $\log C'(A:B = 1:1)$ values were derived from the $C'(A:B = 1:1)$ (mol/l) and $C(A:B = 1:1)$ (v/v%) values obtained from the intersections of the tautomer fluctuation curves in Figures 1-4.

The correlation of the Hammett σ_p and σ_m values with the tautomeric equilibrium constants K_T ($[A]/[B]$) in dimethyl sulfoxide is shown in Figure 5 (correlation coefficient, $r = 0.958$), wherein the σ_p and σ_m values are between +0.78 and -0.17 and between +0.37 and -0.08, respectively (Table 2). The data of *m*-cyano derivative **2a** was not plotted in Figure 5, because its K_T value (1.17) did not fit the correlation. On the other hand, the correlation of the Hammett σ_p and σ_m values with the $\log C'(A:B = 1:1)$ values is exhibited in Figure 6 (correlation coefficient, $r = 0.984$), wherein the σ_p and σ_m values lie between +0.78 and -0.15 and between +0.56 and 0, respectively (Table 2). The data of the *m*-ethyl derivative **2d** was not plotted in Figure 6, since its $\log C'(A:B = 1:1)$ value (0.21) did not fit the correlation. These data indicate that compounds having the higher Hammett σ_p or σ_m values provide the smaller K_T values in dimethyl sulfoxide [1] and the larger $\log C'(A:B = 1:1)$ values in a series of mixed trifluoroacetic acid/dimethyl sulfoxide media [2].

The mechanism of the isomerization between the tautomers **A** and **B** in dimethyl sulfoxide and acidic media is summarized in Scheme 4, which would be supported by the following results. Namely, the tautomer **A** is predominant in the dimethyl sulfoxide media of compounds with the electron-donating substituents [$R = p$ -Me, *p*-Et; K_T ($[A]/[B]$) = 2.03] (Table 2), and the protonation of the tautomer **A** would give the species AH^+ [5,6]. The electron-donating substituents increase the electron density of the side chain nitrogen atom, which promotes the isomerization of the species AH^+ into the resonance isomer BH^+ . Subsequently, the $C(A:B = 1:1)$ values are lower in compounds with the electron-donating substituents. To the contrary, the tautomer **B** is predominant in the dimethyl sulfoxide media of compounds with the electron-withdrawing substituents [$R = p$ -NO₂, *p*-CN; K_T ($[A]/[B]$) = 0.43, 0.67] (Table 2), and the protonation of tautomer **B** would afford the species BH^+ [5,6]. Since the electron-withdrawing substituents decrease the electron density of the side chain nitrogen atom, the higher acid concentration is required for the protonation of this nitrogen atom.



Behavior of Compounds 1 and 2 in Dimethyl Sulfoxide or Acidic Media

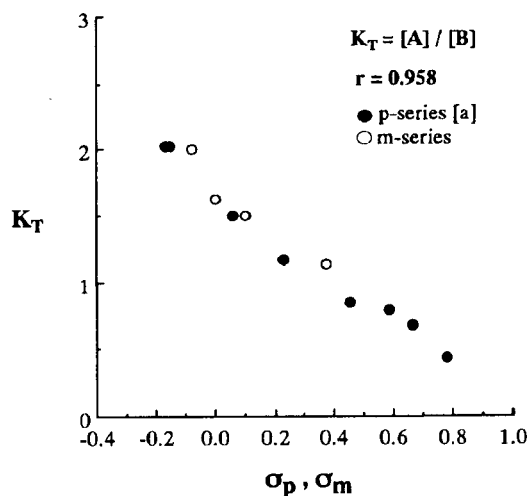


Figure 5. Correlation of the Hammett σ_p and σ_m Values with the Tautomeric Equilibrium Constants K_T . [a] Already reported in reference [1].

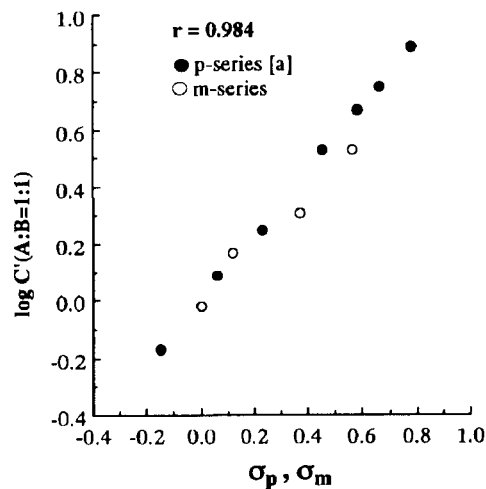


Figure 6. Correlation of the Hammett σ_p and σ_m Values with the $\log C'(A:B = 1:1)$ Values. [a] Already reported in reference [2].

Consequently, the C(A:B = 1:1) values are higher in compounds with the electron-withdrawing substituents. For example, the C(A:B = 1:1) values of the *p*-nitro derivative **1a** (57 v/v %) is higher than that of the *p*-ethyl derivative **1h** (5 v/v %) (Table 2). Accordingly, the nature of the *p*- or *m*-substituent R controls the electron density of the side chain nitrogen atom [6b], which influences the C(A:B = 1:1) values.

In *m*-substituted compounds **2a,b,d**, the increasing temperature elevated the ratios of tautomer A leading to the augment of the K_T value in dimethyl sulfoxide media (Table 3). The results of these *m*-substituted compounds coincided with those of *p*-substituted compounds **1a,b,h,i** increasing the K_T ([A]/[B]) values with rise in temperature [1].

Table 3

Temperature Dependence of the Tautomeric Equilibrium Constants K_T [a] in Dimethyl Sulfoxide Media of Compounds **2a,b,d**

Compound	Temperature	Tautomer Ratio		K_T
		A	B	
2a (<i>m</i> -CN)	25	54	46	1.17
	50	58	42	1.38
	75	63	37	1.70
2b (<i>m</i> -Cl)	25	53	47	1.13
	50	57	43	1.33
	75	58	42	1.38
	100	67	33	2.03
2d (<i>m</i> -Et)	25	67	33	2.03
	50	68	32	2.13
	75	70	30	2.33
	100	77	24	3.21

[a] Tautomeric equilibrium constant, $K_T = [\text{hydrazone imine form A}]/[\text{diazenyl enamine form B}]$.

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 spectral data shown in Tables 1 and 2 were obtained at 25° with a VXR-300 spectrometer at 300 MHz. The HMBC and HMQC spectra were measured with an XL-400 spectrometer at 400 MHz. The following solvents were used for the measurement of the nmr spectra in a series of mixed media: 0 v/v % TFA — deuteriodimethyl sulfoxide; 10 to 75 v/v % TFA — trifluoroacetic acid and deuteriodimethyl sulfoxide; 100 v/v % TFA — deuteriotrifluoroacetic acid. Chemical shifts are given in the δ scale. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

3-(*m*-Cyanophenylhydrazono)methyl-2-oxo-1,2-dihydroquinoxaline **2a**.

A solution of sodium nitrite (1.56 g, 22.6 mmol) in water

(50 ml) was added to a solution of *m*-cyanoaniline (2.67 g, 22.6 mmol) in acetic acid (50 ml) with stirring in an ice-water bath to give a brown solution, which was added to a solution of 3-methyl-2-oxo-1,2-dihydroquinoxaline (3.00 g, 18.8 mmol) in acetic acid (50 ml)/water (50 ml). The mixture was heated with stirring on a boiling water bath for 30 minutes to precipitate red crystals **2a**, which were collected by suction filtration and washed with ethanol and then *n*-hexane (2.89 g, 53%). Recrystallization from *N,N*-dimethylformamide/ethanol afforded red needles, mp 336-337°; ir: ν cm^{-1} 2230, 1660; ms: m/z 289 (M^+); pmr (deuteriodimethyl sulfoxide): (hydrazone imine form A) 14.42 (s, hydrazone NH), 12.52 (br, N_1 -H), 8.16 (dd, $J = 1.0$ Hz, $J = 8.0$ Hz, C_5 -H), 7.76 (s, hydrazone CH); (diazenyl enamine form B) 12.52 (br, N_1 -H), 11.43 (s, N_4 -H), 8.37 (s, diazenyl CH), 7.80 (dd, $J = 1.0$ Hz, $J = 8.0$ Hz, C_5 -H). Other proton signals were observed at 7.84-7.72 ppm and 7.56-7.24 ppm.

Anal. Calcd. for $C_{16}H_{11}N_5O$: C, 66.43; H, 3.83; N, 24.21. Found: C, 66.35; H, 3.95; N, 23.97.

3-(*m*-Methoxyphenylhydrazono)methyl-2-oxo-1,2-dihydroquinoxaline **2c**.

A solution of sodium nitrite (3.12 g, 45.1 mmol) in water (100 ml) was added to a solution of *m*-anisidine (5.56 g, 45.1 mmol) in acetic acid (20 ml)/10% hydrochloric acid (100 ml) with stirring in an ice-water bath to give a brown solution, which was added to a solution of 3-methyl-2-oxo-1,2-dihydroquinoxaline (6.00 g, 37.6 mmol) in acetic acid (200 ml). The mixture was heated with stirring on a boiling water bath at 40-50° for 3 hours to afford a violet solution. Evaporation of the solvent *in vacuo* provided an oily residue, which was treated with saturated sodium hydrogen carbonate to furnish brown crystals **2c**. The brown crystals were triturated with ethanol and then collected by suction filtration (5.18 g, 48%). Recrystallization from *N,N*-dimethylformamide/ethanol afforded brown needles, mp 269-270°; ir: ν cm^{-1} 1650; ms: m/z 294 (M^+); pmr (deuteriodimethyl sulfoxide): (hydrazone imine form A) 14.44 (s, hydrazone NH), 12.45 (br, N_1 -H), 8.04 (dd, $J = 1.0$ Hz, $J = 8.0$ Hz, C_5 -H), 7.71 (s, hydrazone CH), 7.53 (ddd, $J = 1.5$ Hz, $J = 8.0$ Hz, $J = 8.0$ Hz, C_7 -H), 3.79 (s, CH_3); (diazenyl enamine form B) 12.45 (br, N_1 -H), 11.20 (s, N_4 -H), 8.33 (s, diazenyl CH), 7.79 (dd, $J = 1.0$ Hz, $J = 8.0$ Hz, C_5 -H), 7.46 (ddd, $J = 1.5$ Hz, $J = 8.0$ Hz, $J = 8.0$ Hz, C_7 -H), 3.76 (s, CH_3). Other proton signals were observed at 7.37-7.16 ppm and 7.01-6.44 ppm.

Anal. Calcd. for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.04. Found: C, 64.98; H, 5.10; N, 18.75.

3-(*m*-Ethylphenylhydrazono)methyl-2-oxo-1,2-dihydroquinoxaline **2d**.

A solution of sodium nitrite (2.59 g, 37.6 mmol) in water (50 ml) was added to a solution of *m*-ethylaniline (4.56 g, 37.6 mmol) in acetic acid (50 ml) with stirring in an ice-water bath to give a red solution, which was added to a solution of 3-methyl-2-oxo-1,2-dihydroquinoxaline (5.00 g, 31.3 mmol) in acetic acid (100 ml)/water (50 ml). The mixture was heated with stirring on a boiling water bath for 1 hour to precipitate red crystals **2d**, which were collected by suction filtration and washed with ethanol and then *n*-hexane. Recrystallization from *N,N*-dimethylformamide/ethanol/water afforded orange needles (0.36 g, 3.9%); mp 282-283°; ir: ν cm^{-1} 1650; ms: m/z 292 (M^+); pmr (deuteriodimethyl sulfoxide): (hydrazone imine form A) 14.47 (s, hydrazone NH), 12.48 (br, N_1 -H), 8.00 (dd, $J = 1.0$ Hz, $J =$

8.0 Hz, C₅-H), 7.68 (s, hydrazone CH), 2.60 (q, J = 7.5 Hz, CH₂), 1.19 (t, J = 7.5 Hz, CH₃); (diazenyl enamine form **B**) 12.48 (br, N₁-H), 11.16 (s, N₄-H), 8.33 (s, diazenyl CH), 7.77 (dd, J = 1.0 Hz, J = 8.0 Hz, C₅-H), 2.56 (q, J = 7.5 Hz, CH₂), 1.17 (t, J = 7.5 Hz, CH₃). Other proton signals were observed at 7.52-7.14 ppm and 7.02-6.68 ppm.

Anal. Calcd. for C₁₇H₁₆N₄O: C, 69.84; H, 5.52; N, 19.17. Found: C, 70.08; H, 5.52; N, 19.07.

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[2] Y. Kurasawa, T. Hosaka, A. Takada, H. S. Kim, and Y. Okamoto, *J. Heterocyclic Chem.*, submitted.

[3] Y. Kurasawa, K. Yamazaki, S. Tajima, Y. Okamoto, and A. Takada, *J. Heterocyclic Chem.*, **23**, 957 (1986).

[4] The tautomer ratio **A/B** of compound **2b** (*m*-Cl) in deuteriodimethyl sulfoxide was calculated from the integral curves of the hydrazone NH and N₄-H proton signals in reference [3], which did not reflect the accurate tautomer ratio of **A** to **B**. The tautomer ratio of **A** to **B** in the present investigation was obtained from the integral curves of hydrazone CH, diazenyl CH, C₅-H or other CH proton signals, which provided the reliable tautomer ratios in a series of mixed media.

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