NMR Study on the Tautomeric Equilibria between the Hydrazone Imine and Diazenyl Enamine Forms in Side Chained Quinoxalines: Solvent Effects and Temperature Dependence

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The reaction of 7-chloro-4-ethoxycarbonylmethylene-4,5-dihydro-1,2,4-triazolo[4,3-*a*]quinoxaline **6** with 4-ethoxycarbonyl-1-methyl-1*H*-pyrazole-5-diazonium chloride or 4-cyano-1,3-dimethyl-1*H*-pyrazole-5-diazonium chloride gave 7-chloro-4-[α-(4-ethoxycarbonyl-1-methyl-1*H*-pyrazol-5-ylhydrazono)-ethoxycarbonylmethyl]-1,2,4-triazolo[4,3-*a*]quinoxaline **8a** or 7-chloro-4-[α-(4-cyano-1,3-dimethyl-1*H*-pyrazol-5-ylhydrazono)ethoxycarbonylmethyl]-1,2,4-triazolo[4,3-*a*]quinoxaline **8b**, respectively, while the reaction of 7-chloro-4-ethoxycarbonylmethylene-4,5-dihydrotetrazolo[1,5-*a*]quinoxaline 7 with 4-ethoxycarbonyl-1-methyl-1*H*-pyrazole-5-diazonium chloride or 4-cyano-1,3-dimethyl-1*H*-pyrazole-5-diazonium chloride provided 7-chloro-4-[α-(4-ethoxycarbonyl-1-methyl-1*H*-pyrazol-5-ylhydrazono)ethoxycarbonylmethyl]tetrazolo[1,5-*a*]quinoxaline **9a** or 7-chloro-4-[α–(4-cyano-1,3-dimethyl-1*H*-pyrazol-5-ylhydrazono)ethoxycarbonylmethyl]tetrazolo[1,5-*a*]quinoxaline **9b**, respectively. Compounds **8a,b** and **9a,b** showed the tautomeric equilibria between the hydrazone imine **C** and diazenyl enamine **D** forms in dimethyl sulfoxide and/or trifluoroacetic acid, and the effects of solvent and temperature on the tautomer ratios of **C** to **D** were studied by the nmr measurements in a series of mixed trifluoroacetic acid/dimethyl sulfoxide media (compounds **8a,b** and **9a,b**) and at various temperatures (compounds **8a,b**).

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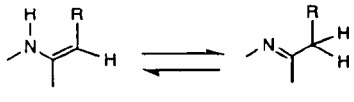
Some side chained quinoxaline derivatives **1a-c** [1,2] or **2a-d** [3-6] (Chart 1) have been reported to show interesting tautomeric equilibria between the enamine **A** and methylene imine **B** forms (compounds **1**) (Scheme 1) or between the hydrazone imine **C** and diazenyl enamine **D** forms (compounds **2**) (Scheme 2), respectively. The tautomeric equilibria between the **A** and **B** forms have been studied in detail by the nmr spectroscopy. Namely, compounds **1** existed as the **A** (major) and **B** (minor) forms in a dimetyl sulfoxide solution, while compounds **1** predominated as the tautomer **B** in a trifluoroacetic acid solution. Moreover, the ratios of the tautomer **B** in a dimethyl sulfoxide solution gradually increased with elevation of temperature.

Scheme 1



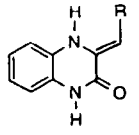
A Enamine Form ⇌ B Methylene Imine Form

Scheme 2

C Hydrazone Imine Form ⇌ D Diazenyl Enamine Form

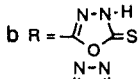
Recently, we have reported the synthesis of compounds **3** [7], whose nmr spectral data in trifluoroacetic acid clarify that the increase in the p*K*a values of the basic side chain moieties R augments the ratios of the tautomer **A** . Thus, the solvent effects, temperature dependence and p*K*a dependence have been reported for the tautomeric equilibria between the **A** and **B** forms. However, there have been few papers on the tautomeric equilibria between the **C** and **D** forms in connection with the solvent effects, temperature dependence or other factors. In the present investigation, we synthesized the pyrazolylhydrazones **8a,b** and **9a,b** by the diazotization of the esters **6** and **7** [8] (Scheme 3) obtained from the enol type acyl cyanides **4** and **5** [8] (Chart 2), respectively, and

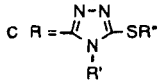
Chart 1

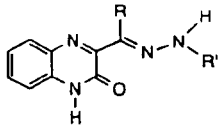


1

a R = COOR'

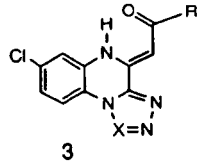
b R = 

c R = 



2

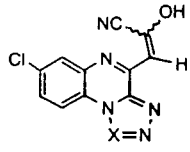
a R = H, R' = C_6H_4Cl
b R = COOMe, R' = C_6H_4Cl
c R = Oxadiazolyl, R' = C_6H_4Cl
d R = COOMe, R' = Pyrazolyl



3

X = N, CH
a R = OEt
b R = NHC_6H_4Me
c R = NHC_6H_4OH
d R = NH-Pyridyl

Chart 2



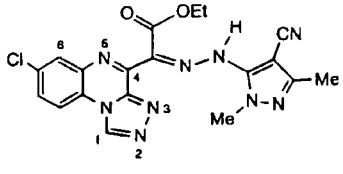
4 X = CH
5 X = N

relation to the solvent effect and temperature dependence.

The reaction of 7-chloro-4-ethoxycarbonylmethylene-4,5-dihydro-1,2,4-triazolo[4,3-*a*]quinoxaline **6** with 4-ethoxycarbonyl-1-methyl-1*H*-pyrazole-5-diazonium chloride or 4-cyano-1,3-dimethyl-1*H*-pyrazole-5-diazonium chloride gave 7-chloro-4-[α-(4-ethoxycarbonyl-1-methyl-1*H*-pyrazol-5-ylhydrazono)ethoxycarbonylmethyl]-1,2,4-triazolo[4,3-*a*]quinoxaline **8a** or 7-chloro-4-[α-(4-cyano-1,3-dimethyl-1*H*-pyrazol-5-ylhydrazono)ethoxycarbonylmethyl]-1,2,4-triazolo[4,3-*a*]quinoxaline **8b**, respectively, while the reaction of 7-chloro-4-ethoxycarbonylmethylene-4,5-dihydrotetrazolo[1,5-*a*]quinoxaline **7** with 4-ethoxycarbonyl-1-methyl-1*H*-pyrazole-5-diazonium chloride or 4-cyano-1,3-dimethyl-1*H*-pyrazole-5-diazonium chloride afforded 7-chloro-4-[α-(4-ethoxycarbonyl-1-methyl-1*H*-pyrazol-5-ylhydrazono)ethoxycarbonylmethyl]tetrazolo[1,5-a]quinoxaline **9a** or 7-chloro-4-[α-(4-cyano-1,3-dimethyl-1*H*-pyrazol-5-ylhydrazono)ethoxycarbonylmethyl]tetrazolo[1,5-*a*]quinoxaline **9b**, respectively (Scheme 3).

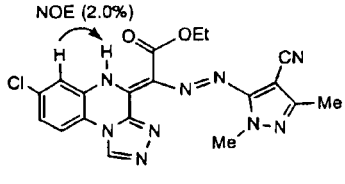
In order to examine the solvent effects on the tautomer ratios of **C** to **D**, the pmr spectra of compounds **8a,b** and **9a,b** were measured in a series of mixed trifluoroacetic acid/dimethyl sulfoxide media, and the tautomer ratios of **C** to **D** were calculated from the ratios of the integral curves due to the C_6-H, C_8-H and C_9-H proton signals (Tables 1-4). The integral ratios due to the C_1-H, *N*-methyl, pyrazole C_3-methyl or pyrazole C_3-H proton signals were also helpful to calculate the tautomer ratios of **C** to **D**. The NOE spectral data between the N_5-H and C_6-H

Chart 3



8b C Form

C_8 - H (δ 8.34 ppm)
Hydrazone NH (δ 14.33 ppm)

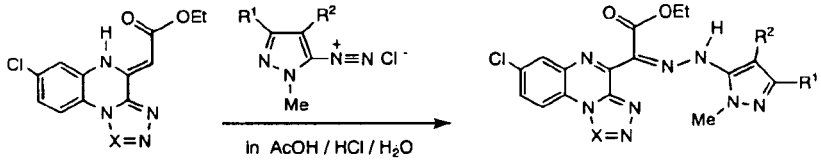


8b D Form

C_6 - H (δ 8.10 ppm)
N_5 - H (δ 11.80 ppm)

studied the fluctuation tendency for the tautomer ratios of **C** to **D** in a series of mixed trifluoroacetic acid/dimethyl sulfoxide media (compounds **8a,b** and **9a,b**) or at various temperatures (compounds **8a,b**). This paper describes the synthesis of novel pyrazolylhydrazones **8a,b** and **9a,b** and the nmr study on the tautomeric equilibria between the hydrazone imine **C** and diazenylenamine **D** forms in

Scheme 3



6 X = CH
7 X = N

in AcOH / HCl / H_2O

8a X = CH, R^1 = H, R^2 = COOEt
8b X = CH, R^1 = Me, R^2 = CN
9a X = N, R^1 = H, R^2 = COOEt
9b X = N, R^1 = Me, R^2 = CN

proton signals of compound **8b** (Chart 3) ascertained the assignment of the aromatic proton signals in Tables 1-4, exhibiting that the C_6-H proton signal (δ 8.34 ppm) of the tautomer **C** appeared in a lower magnetic field than the C_6-H proton signal (δ 8.10 ppm) of the tautomer **D**. The above NOE spectral data also supported the assignment of

Table 1

NMR Spectral Data for Compound **8a**

Chemical Shift in δ [a]

Solvent	Tautomer (%)	C_6-H	C_8-H	C_9-H	C_1-H	N-CH_3	Pyrazole C_3-H	NH	Ester CH_2	Ester CH_3
DMSO-d_6*	**C** (67)	8.58	8.00	8.51	10.20	4.08	7.74	14.28	4.37, 4.30	1.31, 1.26
	D (33)	8.20	7.96	8.52	10.20	4.04	7.76	12.85	4.35, 4.31	1.34, 1.22
25% TFA	**C** (68)	8.58	7.92	8.49	10.17	4.06	7.68	——	4.35, 4.28	1.29, 1.24
	D (32)	8.14	7.90	8.50	10.18	4.02	7.71	——	4.35, 4.28	1.31, 1.20
50% TFA	**C** (33)	8.68	7.68	8.15	10.00	3.90	7.93	——	4.22-4.09	1.11, 1.05
	D (67)	8.01	7.66	7.91	9.96	3.90	7.93	——	4.22-4.09	1.12, 1.03
75% TFA	**C** (32)	8.76	7.70	8.14	10.00	3.90	8.00	——	4.23-4.10	1.08, 0.98
	D (68)	7.97	7.63	8.10	10.04	3.90	8.03	——	4.23-4.10	1.08, 0.98
TFA-d_1*	**C** (41)	8.80	7.73	8.12	10.00	4.00	8.12	——	4.30-4.17	1.11, 1.10
	D (59)	8.00	7.65	8.07	10.19	4.00	8.02	——	4.30-4.17	1.11, 1.10

[a] Coupling constants: C_6-H (2.0 Hz), C_8-H (2.0, 9.0 Hz), C_9-H (9.0 Hz), ester CH_2 (7.0 Hz), ester CH_3 (7.0 Hz).* DMSO-d_6: deuteriodimethyl sulfoxide; TFA-d_1: deuteriotrifluoroacetic acid.

Table 2

NMR Spectral Data for Compound **8b**

Chemical Shift in δ [a]

Solvent	Tautomer (%)	C_6-H	C_8-H	C_9-H	C_1-H	N-CH_3	Pyrazole C_3-CH_3	NH	Ester CH_2	Ester CH_3
DMSO-d_6	**C** (42)	8.34	8.03	8.58	10.25	4.00	2.21	14.33	4.38	1.25
	D (58)	8.10	7.89	8.47	10.17	3.82	2.21	11.80	4.29	1.23
25% TFA	**C** (60)	8.17	7.80	8.45	10.09	3.97	2.44	——	4.25	1.18
	D (40)	7.90	7.70	8.37	10.04	3.85	2.41	——	4.25	1.16
75% TFA	**C** (58)	8.03	7.69	8.16	10.01	3.91	2.47	——	4.18	1.03
	D (42)	7.99	7.65	8.13	9.80	3.89	2.46	——	4.14	0.97
TFA-d_1	**C** (57)	8.12	7.79	8.18	9.89	4.03	2.56	——	4.22	1.05
	D (43)	8.08	7.74	8.16	10.23	3.83	2.30	——	4.22	1.05

[a] Coupling constants: same as the data in Table 1.

Table 3

NMR Spectral Data for Compound **9a**

Chemical Shift in δ [a]

Solvent	Tautomer (%)	C_6-H	C_8-H	C_9-H	N-CH_3	Pyrazole C_3-H	NH	Ester CH_2	Ester CH_3
DMSO-d_6	**C** (100)	8.78	8.12	8.68	4.11	7.80	14.52	4.42, 4.36	1.31, 1.29
25% TFA	**C** (50)	8.80	7.95	8.55	4.07	7.66	——	4.36, 4.26	1.30-1.19
	D (50)	8.24	7.91	8.55	4.07	7.66	——	4.36, 4.26	1.30-1.19
50% TFA	**C** (48)	8.76	7.76	8.38	4.04	7.69	——	4.26, 4.15	1.17, 1.12
	D 52)	8.07	7.72	8.37	4.03	7.71	——	4.24, 4.21	1.18, 1.09
75% TFA	**C** (28)	8.60	7.64	8.23	3.95	8.00	——	4.19, 4.13	1.06, 1.01
	D (72)	8.01	7.62	8.24	3.95	8.03	——	4.17, 4.14	1.08, 0.95
TFA-d_1	**C** (24)	8.74	7.85	8.44	4.11	8.14	——	4.41, 4.31	1.21, 1.14
	D (76)	8.17	7.83	8.46	4.11	8.25	——	4.35, 4.32	1.26, 1.12

[a] Coupling constants: same as the data in Table 1.

Table 4

NMR Spectral Data for Compound **9b**

Chemical Shift in δ [a]

Solvent	Tautomer (%)	C_6-H	C_8-H	C_9-H	N-CH_3	Pyrazole C_3-CH_3	NH	Ester CH_2	Ester CH_3
DMSO-d_6	**C** (33)	8.62	8.16	8.74	3.90	2.23	—	4.46	1.31
	D (67)	8.31	8.04	8.62	3.68	2.23	12.01	4.34	1.27
25% TFA	**C** (41)		8.58-7.92		3.82	2.14	—	4.22	1.20
	D (59)		8.58-7.92		3.65	2.14	—	4.22	1.20
50% TFA	**C** (52)		8.40-7.60		3.67	2.05	—	4.22	1.09
	D (48)		8.40-7.60		3.72	2.05	—	4.22	1.09
75% TFA	**C** (76)	8.01	7.67	8.31	3.70	1.97	—	4.15	1.00
	D (24)	[b]	[b]	8.04	3.75	2.10	—	4.18	1.02
TFA-d_1	**C** (100)	8.20	7.86	8.48	3.90	2.35	—	4.29	1.10

[a] Coupling constants: same as the data in Table 1. [b] Overlapped with other signals.

Table 5

Tautomer Ratios of **C** to **D** in a Dimethyl Sulfoxide Solution of Compound **8a** or **8b** at Various Temperatures

Temperature	Compound **8a** Tautomer (%)		Compound **8b** Tautomer (%)	
	C	**D**	**C**	**D**
25°	70	30	46	54
70°	63	37	42	58
90°	62	38	38	62
110°	57	43	31	69

the aromatic proton signals reported in previous papers [3-6]. Figures 1-4 constructed from the data of Tables 1-4 show that the tautomer ratios of **C** to **D** in compounds **8a,b** and **9a,b** fluctuate in a series of mixed trifluoroacetic acid/dimethyl sulfoxide media, and the fluctuation pattern is different in all compounds **8a,b** and **9a,b**, presumably due to the respective different p*K*a values resulting from four combinations of the triazole/tetrazole ring with the 4-ethoxycarbonyl-1-methylpyrazole/4-cyano-1,3-dimethylpyrazole ring. In addition, the Figures 1-4 indicate that an increase in the concentration of trifluoroacetic acid reverses the tautomer ratios of **C** to **D**, and suggest that there is a point or area giving the 1:1 tautomer ratio in the above mixed media .

Furthermore, the pmr spectra of compounds **8a,b** and **9a,b** were measured in dimethyl sulfoxide at various temperatures to examine the fluctuation tendency for the tau-

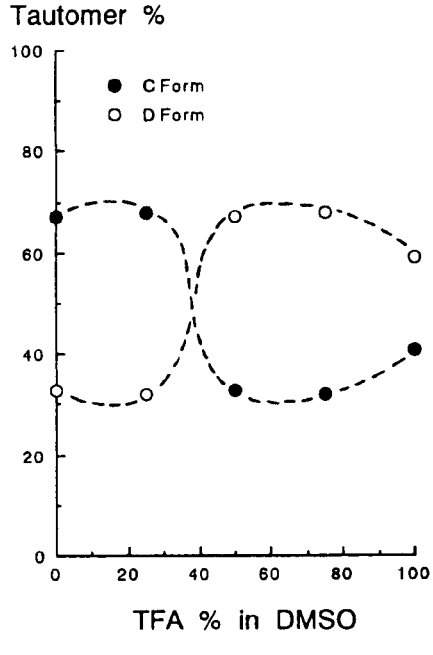


Figure 1. Plots of Tautomer Ratios C/D for Compound **8a**.

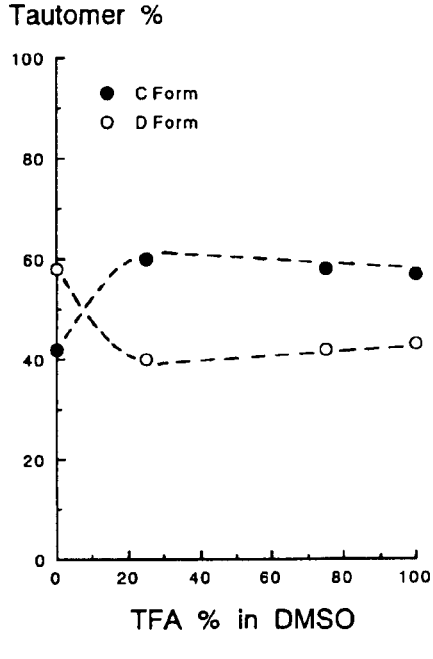


Figure 2. Plots of Tautomer Ratios C/D for Compound **8b**.

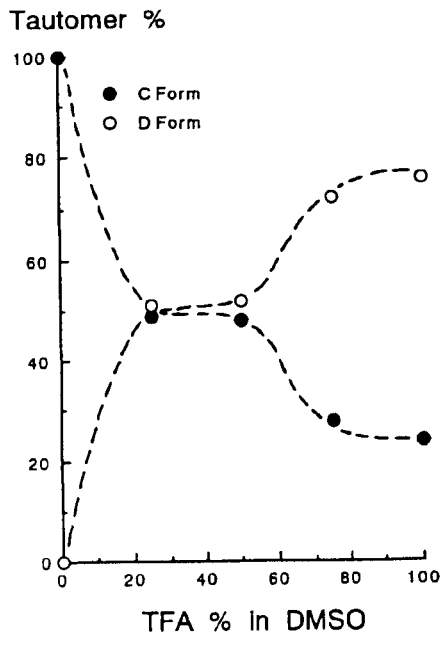


Figure 3. Plots of Tautomer Ratios C/D for Compound **9a**.

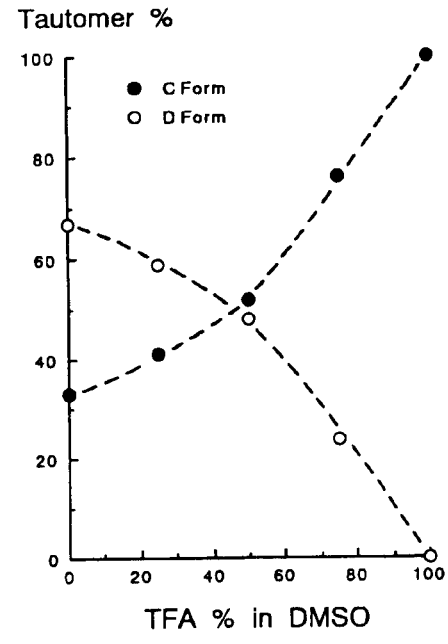


Figure 4. Plots of Tautomer Ratios C/D for Compound **9b**.

tomer ratios of **C** to **D**. The results are shown in Table 5, indicating that the tautomer ratios of **C** to **D** in compounds **8a** and **8b** change in our experimental temperature range of 25° to 110°. Moreover, an elevation of temperature augmented the ratios of the diazenyl enamine form **D**. In the spectra of compounds **9a** and **9b**, the tautomer ratios of **C** to **D** could not be calculated because of signal overlapping at high temperatures.

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 nmr spectra were measured with a VXR-300 spectrometer at 300 MHz. Chemical shifts are given in the δ scale. The mass spectra (ms) were determined with a JEOL JMS-01S spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

7-Chloro-4-[α-(4-ethoxycarbonyl-1-methyl-1*H*-pyrazol-5-ylhydrazono)ethoxycarbonylmethyl]-1,2,4-triazolo[4,3-*a*]quinoxaline **8a**.

A solution of sodium nitrite (1.78 g, 25.8 mmoles) in water (30 ml) was added to a solution of ethyl 5-amino-1-methyl-1*H*-pyrazole-4-carboxylate (4.37 g, 25.8 mmoles) in acetic acid (50 ml)/concentrated hydrochloric acid (3 ml) with stirring in an ice-water bath to give a clear solution, which was added to a solution of compound **6** (3 g, 10.3 mmoles) in acetic acid (50 ml)/concentrated hydrochloric acid (3 ml). The mixture was heated on a boiling water bath for 1 hour to furnish a clear solution. The solvent was evaporated *in vacuo* to afford yellow crystals **8a**, which were triturated with ethanol/water and then collected by suction filtration (4.10 g, 84%). Recrystallization from *N,N*-dimethylformamide/ethanol provided yellow needles, mp 261-262°; ir: υ cm^{-1} 3070, 2960, 1730, 1665; ms: m/z 470 (M^+), 472 ($M^+ + 2$).

Anal. Calcd. for $C_{20}H_{19}ClN_8O_4$: C, 51.01; H, 4.07; Cl, 7.53; N, 23.80. Found: C, 50.84; H, 4.06; Cl, 7.39; N, 23.98.

7-Chloro-4-[α-(4-cyano-1,3-dimethyl-1*H*-pyrazol-5-ylhydrazono)ethoxycarbonylmethyl]-1,2,4-triazolo[4,3-*a*]quinoxaline **8b**.

A solution of sodium nitrite (1.19 g, 17.2 mmoles) in water (20 ml) was added to a solution of 5-amino-1,3-dimethyl-1*H*-pyrazole-4-carbonitrile (2.34 g, 17.2 mmoles) in acetic acid (50 ml)/concentrated hydrochloric acid (3 ml) with stirring in an ice-water bath to give a clear solution, which was added to a solution of compound **6** (2 g, 6.88 mmoles) in acetic acid (50 ml)/concentrated hydrochloric acid (3 ml). The mixture was heated on a boiling water bath for 1 hour to provide a clear solution. The solvent was evaporated *in vacuo* to afford red crystals **8b**, which were collected by suction filtration. Recrystallization from ethanol/water gave red needles (1.55 g, 51%), mp 170-172°; ir: υ cm^{-1} 3440, 3360, 3080, 2970, 2940, 2220, 1720, 1625; ms: m/z 437 (M^+), 439 ($M^+ + 2$).

Anal. Calcd. for $C_{19}H_{16}ClN_9O_2$: C, 52.12; H, 3.68; Cl, 8.10; N, 28.79. Found: C, 52.33; H, 3.59; Cl, 8.23; N, 28.69.

7-Chloro-4-[α-(4-ethoxycarbonyl-1-methyl-1*H*-pyrazol-5-ylhydrazono)ethoxycarbonylmethyl]tetrazolo[1,5-*a*]quinoxaline **9a**.

A solution of sodium nitrite (1.19 g, 17.2 mmoles) in water (20 ml) was added to a solution of ethyl 5-amino-1-methyl-1*H*-pyrazole-4-carboxylate (2.91 g, 17.2 mmoles) in acetic acid (40 ml)/concentrated hydrochloric acid (2 ml) with stirring in an ice-water bath to give a clear solution, which was added to a

solution of compound **7** (2 g, 6.86 mmoles) in acetic acid (40 ml)/concentrated hydrochloric acid (2 ml). The mixture was heated on a boiling water bath for 1 hour to precipitate yellow needles **9a**, which were collected by suction filtration and washed with water and then ethanol to provide an analytically pure sample (2.67 g, 82%), mp 224-225°; ir: υ cm^{-1} 3060, 2960, 1730, 1665; ms: m/z 471 (M^+), 473 (M^++2).

Anal. Calcd. for $C_{19}H_{18}ClN_9O_4$: C, 48.36; H, 3.85; Cl, 7.51; N, 26.72. Found: C, 48.23; H, 3.78; Cl, 7.55; N, 26.83.

7-Chloro-4-[α-(4-cyano-1,3-dimethyl-1*H*-pyrazol-5-ylhydrazono)ethoxycarbonylmethyl]tetrazolo[1,5-*a*]quinoxaline **9b**.

A solution of sodium nitrite (1.19 g, 17.2 mmoles) in water (20 ml) was added to a solution of 5-amino-1,3-dimethyl-1*H*-pyrazole-4-carbonitrile (2.34 g, 17.2 mmoles) in acetic acid (40 ml)/concentrated hydrochloric acid (2 ml) with stirring in an ice-water bath to give a clear solution, which was added to a solution of compound **7** (2 g, 6.86 mmoles) in acetic acid (40 ml)/concentrated hydrochloric acid (2 ml). The mixture was heated on a boiling water bath for 1 hour to provide a clear solution. The solvent was evaporated *in vacuo* to furnish a red oily product, which was crystallized from ethanol/water to afford red needles (2.52 g, 84%). Recrystallization from ethanol/water gave red needles, mp 100-102°; ir: υ cm^{-1} 3070, 2870, 2220, 1720, 1610; ms: m/z 438 (M^+), 440 (M^++2).

Anal. Calcd. for $C_{18}H_{15}ClN_{10}O_2$: C, 49.27; H, 3.45; Cl, 8.08; N, 31.92. Found: C, 49.18; H, 3.55; Cl, 8.13; N, 31.88.

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