Synthesis and Tautomeric Behavior of 3-(Pyrazolylhydrazonomethyl)-2-oxo-1,2-dihydroquinoxalines. Specification of Hydrazone Imine and Diazenyl Enamine Forms

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3-(Pyrazolylhydrazonomethyl)-2-oxo-1,2-dihydroquinoxalines were synthesized, and their tautomer ratios between hydrazone imine and diazenyl enamine forms were specified by pmr spectral data.

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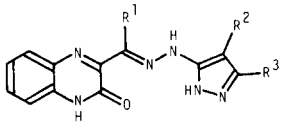
In a previous paper [2], we reported the synthesis and tautomerism of 3-[α-(4-ethoxycarbonyl-1*H*-pyrazol-5-ylhydrazono)methoxycarbonylmethyl]-2-oxo-1,2-dihydroquinoxaline **1** (Chart 1), wherein we could not specify two tautomers, hydrazone imine **A** and diazenyl enamine **B** forms, existing in a ratio of 22 *versus* 3 (or 3 *versus* 22) in deuteriodimethyl sulfoxide (DMSO-d_6). In order to clarify the tautomer ratio for the **A** and **B** forms of **1**, various 3-(pyrazolylhydrazonomethyl)-2-oxo-1,2-dihydroquinoxalines were synthesized in the present investigation. As the result, 3-[(4-ethoxycarbonyl-1*H*-pyrazol-5-ylhydrazono)-methyl]-2-oxo-1,2-dihydroquinoxaline **2** was found to exist as only one tautomer in DMSO-d_6, and the pmr spectral data of **2** enabled us to specify two tautomeric forms **A** and **B** of **1** existing in the ratio of 22 *versus* 3 (or 3 *versus* 22). Moreover, 3-[α-(4-cyano-3-methyl-1*H*-pyrazol-5-ylhydrazono)methoxycarbonylmethyl]-2-oxo-1,2-dihydroquinoxaline **3** showed the interesting tautomeric equilibrium when the pmr spectra were measured in DMSO-d_6 and in DMSO-d_6/deuterium oxide. This paper describes the synthesis and tautomeric behavior of 3-(pyrazolylhydrazonomethyl)-2-oxo-1,2-dihydroquinoxalines, especially the specification of the tautomers **A** and **B** and the effect of solvent on the tautomeric equilibrium.

Chart 1

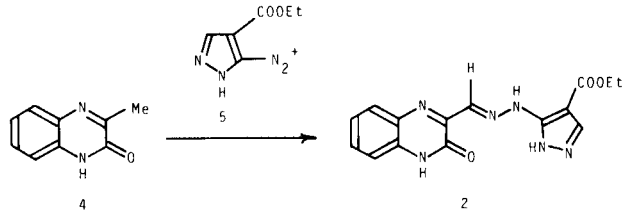


1 R^1=COOMe, R^2=COOEt, R^3=H
2 R^1=H, R^2=COOEt, R^3=H
3 R^1=COOMe, R^2=CN, R^3=Me

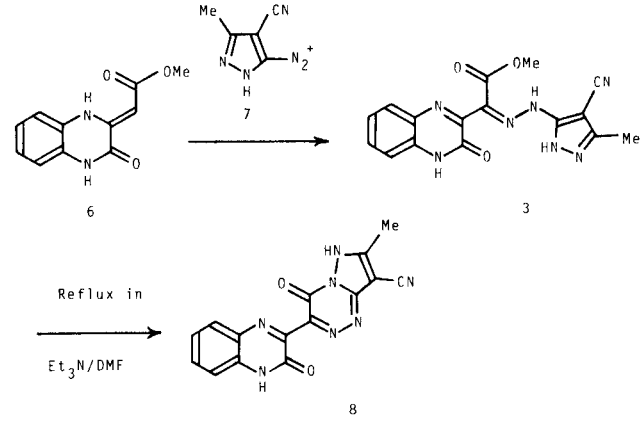
Synthesis.

The reaction of the quinoxaline **4** with the pyrazole-5-diazonium salt **5** afforded the hydrazone **2** (Scheme 1). The reaction of the quinoxaline **6** with the pyrazole-5-diazonium salt **7** furnished the hydrazone **3**, whose refluxing in triethylamine and *N*,*N*-dimethylformamide resulted in cyclization to give 8-cyano-7-methyl-4-oxo-3-(3-oxo-3,4-dihydroquinoxalin-2-yl)-4,6-dihydropyrazolo[5,1-*c*][1,2,4]-triazine **8** (Scheme 2).

Scheme 1



Scheme 2

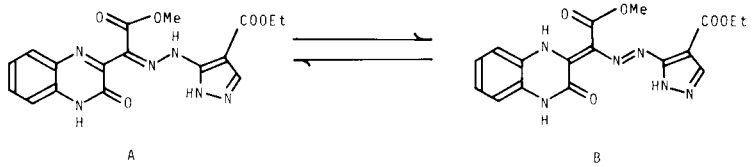


Tautomerism.

The pmr spectrum of **2** in DMSO-d_6 showed the signals due to a single tautomeric species **A** (Scheme 3, Table 1). The $C_{3'}$-H and hydrazone CH proton signals of **2** were observed at δ 7.85 and 7.82 ppm, respectively, and the aromatic proton signals were observed at δ 8.20-7.25 ppm. Since the hydrazone CH (**A**) and diazenyl CH (**B**) proton signals have already been known to appear at δ 7.87-7.73

Scheme 3. Tautomerism of 2 in DMSO-d_6.

Scheme 4. Tautomerism of 1 in DMSO-d_6.



(**A**) and 8.40-8.37 (**B**) ppm [3], respectively, the signal at δ 7.82 ppm of **2** is assigned as the hydrazone CH proton signal, supporting the presence of the tautomer **A** and the absence of the tautomer **B** in the solution of **2** in DMSO-d_6.

The pmr spectrum of **1** in DMSO-d_6 exhibited the signals due to two tautomeric species **A** and **B** (Scheme 4, Table 1). The aromatic proton signals of **1** due to the tautomers **A** and **B** were observed at δ 8.20-7.35 and 6.92-6.47 ppm, respectively. Since the aromatic proton signals of **2** due to the tautomer **A** were observed at δ 8.20-7.25 ppm, the assignment for the aromatic proton signals of **1** were considered to be reasonable. From the integral curve of the aromatic proton signals, the ratio of the tautomers **A** and **B** was determined as 15% *versus* 85%.

The pmr spectrum of **3** in DMSO-d_6 showed the signals due to two tautomeric species **A** and **B** (Scheme 5, Table 1). Since the aromatic proton signals due to the tautomer **A** were found to appear in a lower magnetic field than those due to the tautomer **B** in compound **1**, the signal assignment was very easy in compound **3**. The aromatic proton signals of **3** due to the tautomers **A** and **B** were observed at δ 7.86-7.32 and 6.91-6.48 ppm in the ratio of 95% *versus* 5%, respectively. The NH and $C_{3'}$-methyl proton signals of **3** due to the tautomers **A** and **B** were also observed as the paired peaks in the ratio of 95% *versus* 5%, while the ester methyl proton signal was observed as a single peak. In contrast to the cases of **1** and **2**, the pmr spectrum of **3** in DMSO-d_6/deuterium oxide altered the ratio of the tautomers **A** and **B**. Namely, the aromatic and $C_{3'}$-methyl proton signals due to the tautomers **A** and **B** were observed in the ratio of 37% *versus* 63% in this solvent system.

The ^{13}C-nmr spectrum of **3** in DMSO-d_6 showed the paired ester methyl and $C_{3'}$-methyl proton signals at δ 52.43 and 12.66 (due to **A**) and 52.38 and 10.18 (due to **B**) ppm, respectively. These signals due to the tautomers **A** and **B** could be assigned from the peak height alteration influenced by the solvent effect in DMSO-d_6 and in DMSO-d_6/deuterium oxide.

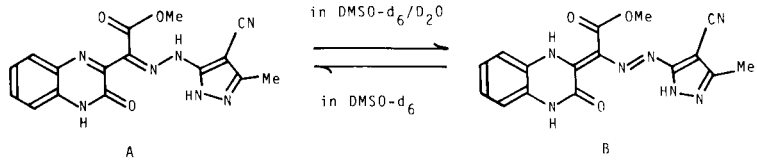
Table 1

PMR Spectral Data for **1**, **2** and **3**

Compound	Solvent	Tautomer Ratio A	Tautomer Ratio B	Chemical Shift (δ) Aromatic	Chemical Shift (δ) $C_{3'}$-Me
2	DMSO-d_6	100	0	8.20-7.25 (4H) [**A**]	
1	DMSO-d_6	15	85	8.20-7.35 (0.6H) [**A**] 6.92-6.47 (3.4H) [**B**]	
3	DMSO-d_6	95	5	7.86-7.32 (3.8H) [**A**] 6.91-6.48 (0.2H) [**B**]	2.35 (2.85H) [**A**] 2.17 (0.15H) [**B**]
	DMSO-d_6/D_2O	37	63	7.84-7.32 (1.5H) [**A**] 6.91-6.48 (2.5H) [**B**]	2.35 (1.1H) [**A**] 2.17 (1.9H) [**B**]

[**A**]: Signals due to the tautomer **A**. [**B**]: Signals due to the tautomer **B**.

Scheme 5. Tautomerism of 3 in DMSO-d_6 and DMSO-d_6/D_2O.



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 pmr and ^{13}C-nmr spectra were measured in deuteriodimethyl sulfoxide 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.

3-[(4-Ethoxycarbonyl-1*H*-pyrazol-5-ylhydrazono)methyl]-2-oxo-1,2-dihydroquinoxaline **2**.

A solution of sodium nitrite (12.94 g, 187.6 mmoles) in water (50 ml) was added to a solution of 5-amino-4-ethoxycarbonyl-1*H*-pyrazole (29 g, 187.6 mmoles) in acetic acid (100 ml)/10% hydrochloric acid (60 ml) with stirring in an ice-water bath for 10 minutes to give a clear solution, which was added to a suspension of the quinoxaline **4** (15 g, 93.8 mmoles) in acetic acid (400 ml)/10% hydrochloric acid (40 ml). After stirring in an ice-water bath for 10 minutes, the whole mixture was heated on a boiling water bath for 30 minutes with stirring to precipitate yellow crystals **2**, which were collected by suction filtration (24.7 g, 81%). Recrystallization from *N*,*N*-dimethylformamide/ethanol provided yellow needles, mp 291-292°; ir: ν cm^{-1} 3250, 1660, 1630, 1590; ms: m/z 326 (M$^+$); pmr: 14.96 (s, 1H, NH), 13.20 (br, 2H, NH), 8.20-7.25 (m, 4H, aromatic), 7.85 (s, 1H, $C_{3'}$-H), 7.82 (s, 1H, hydrazone CH), 4.33 (q, J = 7 Hz, 2H, CH_2), 1.32 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{14}N_6O_3$: C, 55.21; H, 4.32; N, 25.75. Found: C, 55.07; H, 4.61; N, 25.53.

3-[α-(4-Cyano-3-methyl-1*H*-pyrazol-5-ylhydrazono)methoxycarbonylmethyl]-2-oxo-1,2-dihydroquinoxaline **3**.

A solution of sodium nitrite (6.34 g, 91.9 mmoles) in water (20 ml) was added to a solution of 5-amino-4-cyano-3-methyl-1*H*-pyrazole (10.0 g, 92.9 mmoles) in acetic acid (180 ml) with stirring in an ice-water bath for 10 minutes to give a clear solution, to which the quinoxaline **6** (10 g, 45.9 mmoles) was added portionwise. After stirring in an ice-water bath for 10 minutes, the whole mixture was refluxed in an oil bath for 30 minutes to precipitate orange crystals **3**, which were collected by suction filtration (14.4 g, 89%). Recrystallization from *N*,*N*-dimethylformamide/ethanol gave orange needles, mp 290-291°; ir: ν cm^{-1} 3250, 2230, 1720, 1665; ms: m/z 351 (M$^+$); pmr: 12.92 (s, 0.95H, NH), 12.68 (s, 0.05H, NH), 12.58 (s, 0.95H, NH), 12.00 (s, 0.05H, NH), 11.66 (s, 0.95H, NH), 11.19 (s, 0.05H, NH), 7.86-7.32 (m, 3.8H, aromatic), 6.91-6.48 (m, 0.2H, aromatic), 3.72 (s, 3H, CH_3), 2.35 (s, 2.85H, $C_{3'}$-CH_3), 2.17 (s, 0.15H, $C_{3'}$-CH_3).

Anal. Calcd. for $C_{16}H_{13}N_7O_3$: C, 54.70; H, 3.73; N, 27.91. Found: C, 54.53; H, 3.73; N, 27.87.

8-Cyano-7-methyl-4-oxo-3-(3-oxo-3,4-dihydroquinoxalin-2-yl)-4,6-dihydropyrazolo[5,1-c][1,2,4]triazine **8**.

A solution of **3** (10 g) and triethylamine (1 ml) in *N*,*N*-dimethylformamide (200 ml) was refluxed in an oil bath for 4 hours. After addition of acetic acid (1 ml), evaporation of the solvent *in vacuo* afforded yellow crystals **8**, which were triturated with ethanol/hexane and then collected by suction filtration (7.79 g, 86%). Recrystallization from *N*,*N*-dimethylformamide/ethanol provided yellow needles, mp above 360°; ir: ν cm^{-1} 3480, 2230, 1710, 1660, 1615, 1605; ms: m/z 319 (M$^+$); pmr: 12.82 (s, 1H, NH), 7.88-7.34 (m, 4H, aromatic), 2.47 (s, 3H, C_7-CH_3). NH proton signal of the quinoxaline ring was unobservable presumably due to broadening.

Anal. Calcd. for $C_{15}H_9N_7O_2$: C, 56.43; H, 2.84; N, 30.71. Found: C, 56.23; H, 2.96; N, 30.57.

REFERENCES AND NOTES

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