Tautomeric Structure of 1-Methyldihydropyridazino-[3,4-*b*]quinoxalines in Solution

Yoshihisa Kurasawa* and Atsushi Takada

School of Pharmaceutical Sciences, Kitasato University,
Shirokane, Minato-ku, Tokyo 108, Japan

Ho Sik Kim

Department of Chemistry, Hyosung Women's University,
Gyongsan 713-900, Korea

Yoshihisa Okamoto

Department of Chemistry, College of Liberal
Arts and Sciences, Kitasato University,
Kitasato, Sagamihara, Kanagawa 228, Japan

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The reaction of 6-chloro-2-(1-methylhydrazino)quinoxaline 4-oxide **1** with ethyl 2-ethoxymethylene-2-cyanoacetate or ethoxymethylenemalononitrile gave 6-chloro-2-[2-(2-cyano-2-ethoxycarbonylvinyl)-1-methylhydrazino]quinoxaline 4-oxide **3a** or 6-chloro-2-[2-(2,2-dicyanovinyl)-1-methylhydrazino]quinoxaline **3b**, respectively. The reaction of **3a** with a base afforded 7-chloro-1-methyl-1,5-dihydropyridazino[3,4-*b*]quinoxaline **4**. From the NOE spectral data, the 1-methyldihydropyridazino[3,4-*b*]quinoxalines **2a**, **2b** and **4** were found to exist as the 1,5-dihydro form in a dimethyl sulfoxide or trifluoroacetic acid/dimethyl sulfoxide solution.

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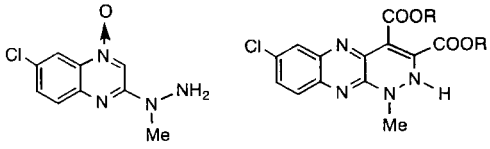
In previous papers [1,2], we reported that the 1,3-dipolar cycloaddition reaction of 6-chloro-2-(1-methylhydrazino)-quinoxaline 4-oxide **1** with dimethyl or diethyl acetylenedicarboxylate gave dimethyl or diethyl 7-chloro-1-methyl-1,2-dihydropyridazino[3,4-*b*]quinoxaline-3,4-dicarboxylate **2a** or **2b**, respectively (Chart 1). The nmr spectral data for

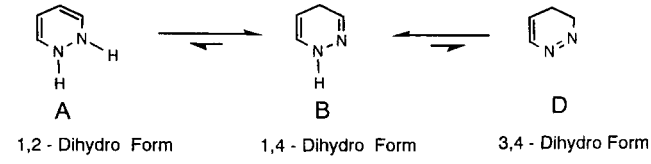
Chart 1



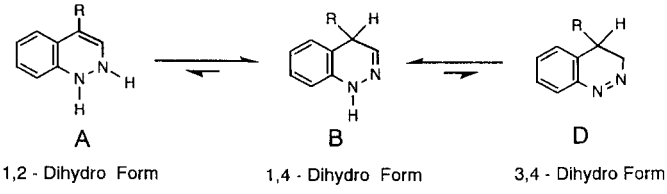
1 2a R = Me 2b R = Et

compounds **2a** and **2b** supported the 1-methyldihydropyridazino[3,4-*b*]quinoxaline structure, but these data were not adequate for the assignment of the 1-methyl-1,2-dihydropyridazino[3,4-*b*]quinoxaline structure. Namely, there are three possible tautomers such as the 1,2-dihydro form **A**, 1,4-dihydro form **B** and 1,5-dihydro form **C** in compounds **2a** and **2b** (Scheme 1). In the literature, dihydropyridazine [3] (Scheme 2) and dihydrocinnolines [4] (Scheme 3) have been reported to predominate both as the 1,4-dihydro form **B**. Accordingly, the 1,2-dihydro form **A** would not be suitable for the tautomeric structure of compounds **2a** and **2b** in a solution, and hence the preferred tautomeric structure was examined in this paper.

Scheme 2

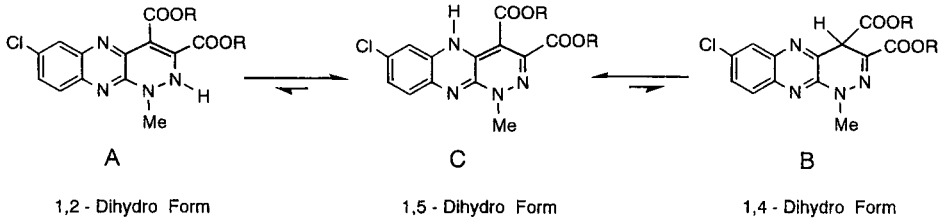


Scheme 3



The nmr spectrum of compound **2a** or **2b** showed the NH proton signal at δ 9.90 or 10.35 ppm, respectively, but not the methine proton signal. These data evidently excluded the 1,4-dihydro form **B**. Therefore, the NOE spectra were measured by radiation at the NH proton signal (δ

Scheme 1



9.90 or 10.35 ppm), since the NOE between the NH and N_1-methyl proton signals or between the NH and C_6-H proton signals would determine the 1,2-dihydro form **A** or 1,5-dihydro form **C**, respectively. As a result, the NOE spectral data (Table, Chart 2) indicated that compounds **2a** and **2b** existed as the 1,5-dihydro form **C** in a solution.

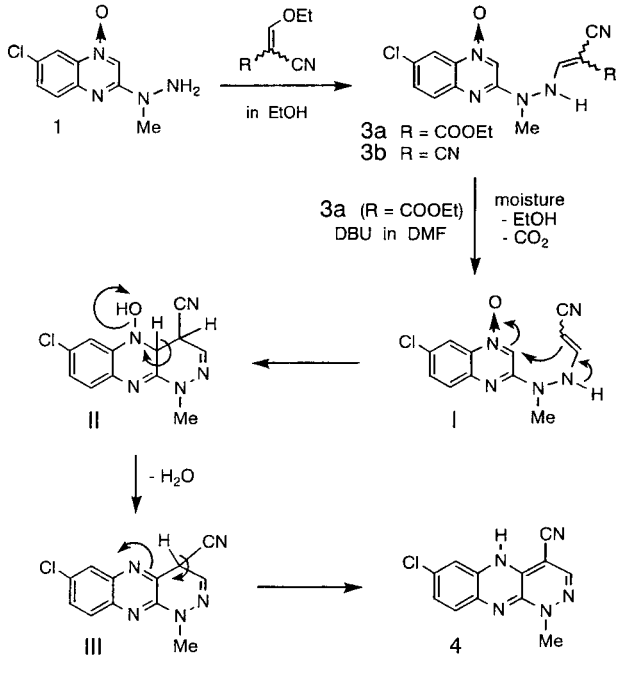
Table

NOE Spectral Data for Compounds **2a**, **2b** and **4**

Compound	Solvent	Radiation	NOE	
2a	DMSO-d_6 [a]	N_5-H	C_6-H	(15.2%)
		C_6-H	N_5-H	(5.7%)
2b	DMSO-d_6	N_5-H	C_6-H	(13.9%)
		C_6-H	N_5-H	(5.9%)
2a	TFA/DMSO-d_6 [b]	N_5-H	C_6-H	(1.8%)
		C_6-H	N_5-H	(1.8%)
2b	TFA/DMSO-d_6	N_5-H	C_6-H	(2.3%)
		C_6-H	N_5-H	(1.7%)
4	TFA/DMSO-d_6	C_6-H	N_5-H	(2.4%)

[a] Deuteriodimethyl sulfoxide. [b] Trifluoroacetic acid/deuteriodimethyl sulfoxide (4:1).

Scheme 4



Moreover, we synthesized an additional 1-methyldihydropyridazino[3,4-*b*]quinoxaline in order to extend an example of the 1-methyl-1,5-dihydropyridazino[3,4-*b*]quinoxaline as follows.

The reaction of compound **1** with ethyl 2-ethoxymethylene-2-cyanoacetate or ethoxymethylenemalononitrile afforded 6-chloro-2-[2-(2-cyano-2-ethoxycarbonylvinyl)-1-methylhydrazino]quinoxaline 4-oxide **3a** or 6-chloro-2-[2-(2,2-dicyanovinyl)-1-methylhydrazino]quinoxaline 4-oxide **3b**, respectively (Scheme 4). The reaction of compound **3a** with 1,8-diazabicyclo[5.4.0]-7-undecene in *N,N*-dimethylformamide effected hydrolysis with moisture, decarboxylation and then dehydrative cyclization to provide 7-chloro-1-methyl-1,5-dihydropyridazino[3,4-*b*]quinoxaline-4-carbonitrile **4**, presumably *via* intermediates **I-III**, while compound **3b** was not converted into a pyridazino[3,4-*b*]quinoxaline ring under a similar reaction condition to the above. Compound **4** was insoluble in deuteriodimethyl sulfoxide or other ordinary solvents, and hence the nmr spectra of compound **4** were measured in trifluoroacetic acid/deuteriodimethyl sulfoxide. The NOE spectral data (Table, Chart 3, Scheme 5) showed that compound **4** also predominated as the 1,5-dihydro form **C** in a solution.

Chart 2

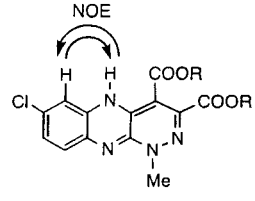
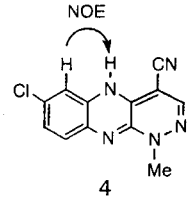
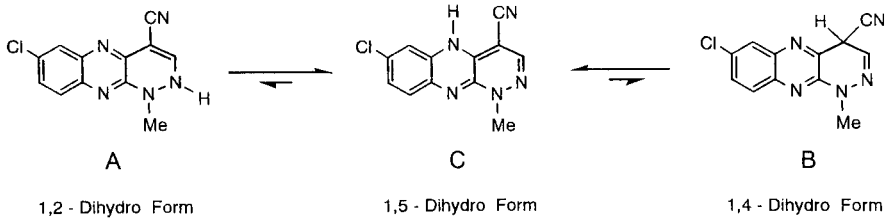


Chart 3



Scheme 5



In conclusion, the 1-methyldihydropyridazino[3,4-*b*]-quinoxalines **2a, 2b** and **4** were found to exist as the 1,5-dihydro form **C** in a solution, which was different from dihydropyridazine (Scheme 2) or dihydrocinnolines (Scheme 3) predominating as the 1,4-dihydro form **B** in a solution.

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. The mass (ms) spectra were determined with a JEOL JMS-01S spectrometer. Elemental analyses were preformed on a Perkin-Elmer 240B instrument.

6-Chloro-2-[2-(2-cyano-2-ethoxycarbonylvinyl)-1-methylhydrazino]quinoxaline 4-Oxide **3a**.

A solution of compound **1** (5 g, 22.3 mmoles) and ethyl 2-ethoxymethylene-2-cyanoacetate (5.66 g, 33.5 mmoles) in ethanol (350 ml) was refluxed on a boiling water bath for 3 hours to precipitate yellow needles **3a**. After the reaction mixture was cooled to room temperature, the yellow needles **3a** were collected by suction filtration and washed with ethanol to obtain an analytically pure sample (5.94 g). The filtrate was evaporated *in vacuo* afforded yellow needles **3a**, which were collected by suction filtration (1.06 g), total yield, 7.0 g (90%).

Compound **3a** had mp 224-225°; ir: ν cm^{-1} 2210, 1685, 1610; ms: m/z 347 (M^+), 349 ($M^+ + 2$); pmr (deuteriodimethyl sulfoxide): 10.65 (s, 1H, NH), 8.53 (s, 1H, C_3-H), 8.28 (d, J = 2.0 Hz, 1H, C_5-H), 8.08 (s, 1H, vinylic H), 7.85 (d, J = 9.0 Hz, 1H, C_8-H), 7.81 (dd, J = 2.0 Hz, J = 9.0 Hz, 1H, C_7-H), 4.15 (q, J = 7.0 Hz, 2H, CH_2), 3.33 (s, 3H, CH_3), 1.21 (t, J = 7.0 Hz, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{14}ClN_5O_3$: C, 51.81; H, 4.06; Cl, 10.19; N, 20.14. Found: C, 51.87; H, 4.11; Cl, 10.28; N, 19.86.

6-Chloro-2-[2-(2,2-dicyanovinyl)-1-methylhydrazino]quinoxaline 4-Oxide **3b**.

A solution of compound **1** (5 g, 22.3 mmoles) and ethoxymethylenemalononitrile (4.09 g, 33.5 mmoles) in ethanol (250 ml) was refluxed on a boiling water bath for 2 hours to give a clear solution. The solvent was evaporated *in vacuo* to give reddish brown needles **3b**, which were collected by suction filtration and washed with ethanol (6.17 g, 92%). Recrystallization from *N,N*-dimethylformamide/ethanol/water afforded reddish brown needles, mp 146-147°; ir: ν cm^{-1} 3220, 3040, 2220, 2200, 1610; ms: m/z 300 (M^+), 302 ($M^+ + 2$); pmr (deuteriodimethyl sulfoxide): 11.12 (s, 1H, NH), 8.63 (s, 1H, C_3-H), 8.29 (d, J = 2.0 Hz, 1H, C_5-H), 8.08 (s, 1H, vinylic H), 7.86 (d, J = 9.0 Hz, C_8-H), 7.81 (dd, J = 2.0 Hz, J = 9.0 Hz, 1H, C_7-H), 3.33 (s, 3H, CH_3).

Anal. Calcd. for $C_{13}H_9ClN_6O$: C, 51.93; H, 3.02; Cl, 11.79; N, 27.95. Found: C, 52.03; H, 3.04; Cl, 11.98; N, 27.78.

7-Chloro-1-methyl-1,5-dihydropyridazino[3,4-*b*]quinoxaline-4-carbonitrile **4**.

A solution of compound **3a** (5 g, 14.4 mmoles) and 1,8-diazabicyclo[5.4.0]-7-undecene (1 ml) in *N,N*-dimethylformamide (150 ml) was refluxed in an oil bath for 2 hours to give a clear solution. The solvent was evaporated *in vacuo* to afford crystals, which were triturated with water (100 ml)/acetic acid (2 ml) and then collected by suction filtration (2.81 g, 76%). Recrystallization from *N,N*-dimethylformamide/ethanol/water provided yellow needles, mp above 310°; ir: ν cm^{-1} 2210, 1620, 1600, 1540, 1515; ms: m/z 257 (M^+), 259 ($M^+ + 2$); pmr (trifluoroacetic acid/deuteriodimethyl sulfoxide, 4:1): 9.35 (s, 1H, N_5-H), 7.31 (s, 1H, C_3-H), 6.68 (d, J = 8.5 Hz, 1H, C_9-H), 6.66 (d, J = 2.0 Hz, 1H, C_6-H), 6.63 (dd, J = 8.5 Hz, J = 2.0 Hz, 1H, C_8-H), 3.41 (s, 3H, CH_3).

Anal. Calcd. for $C_{12}H_8ClN_5$: C, 55.93; H, 3.13; Cl, 13.76; N, 27.18. Found: C, 55.64; H, 3.13; Cl, 13.73; N, 27.30.

REFERENCES AND NOTES

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