Notes

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Tautomeric Character of 3-Heteroarylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxalines[1)]

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The proton nuclear magnetic resonance (^{1}H-NMR) spectra of some 3-(1,3,4-oxadiazol-5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines and 3-(1,2,4-triazol-5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines were measured in dimethylsulfoxide-d_6 (DMSO-d_6), trifluoroacetic acid (TFA), and TFA-d_1. The spectra in DMSO-d_6 indicated that **2**, **3**, **4**, and **5** existed as the two tautomers A and B, and **6**, **7**, and **8** as a single tautomer. From the spectra of **2**, **3**, **4**, and **5** in DMSO-d_6, it was elucidated that tautomer A was predominant over tautomer B at low temperature, while the ratio of the tautomer B gradually increased with increase of the temperature. The spectra in TFA indicated that **2** occurred as the three tautomers C, D, and E, while **3**, **4**, and **5** existed as a single tautomer, D. Compounds **6** and **7** also appeared to isomerize in TFA, that is, **6** existed as the two tautomers C and E, while **7** existed as two of the three tautomers C, E, and G. Compound **8** was predominantly present in the form of tautomer C or E.

Keywords——3-(1,3,4-oxadiazol-5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline; 3-(1,2,4-triazol-5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline; 3-(α-hydroxy-1,3,4-oxadiazol-5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline; 3-(4-allyl-α-hydroxy-3-methylsulfinyl-4*H*-1,2,4-triazol-5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline; 3-(α-hydroxyimino-4-methyl-4*H*-1,2,4-triazol-5-ylmethyl)-2-oxo-1,2-dihydroquinoxaline; prototropy; protonation; isomerization

The tautomerism of 3-methoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (**1a**) and related compounds (**1b**—**e**) has been studied by means of nuclear magnetic resonance (NMR) and ultraviolet (UV) spectroscopies by Mondelli and Merlini.[2)] Namely, the proton nuclear magnetic resonance (^{1}H-NMR) spectra in dimethylsulfoxide-d_6 (DMSO-d_6) demonstrated that two tautomers A and B of **1a**, **1b**, and **1c** coexist, while the tautomer A predominates in the cases of **1d** and **1e**, as shown in Chart 1 and Table I. In addition, the ^{1}H-NMR spectra in trifluoroacetic acid (TFA) indicated that **1a** and **1b** existed as the tautomer B, while **1c**, **1d**, and **1e** existed as the tautomer A. Thus, compounds **1a**—**e** exist predominantly as the single tautomer A or B in TFA.

In previous studies,[3-6)] we also synthesized compounds of type **1** having various heteroaryl groups at the 3-methylenic carbon, such as 3-(1,3,4-oxadiazol-5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines (**2a**,[3)] **2b**,[3)] **2c**[4)]), 3-(2,3-dihydro-2-thioxo-1,3,4-oxadiazol-

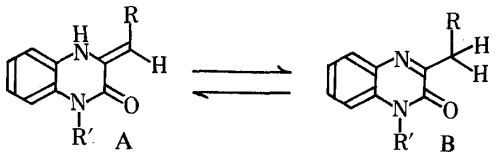
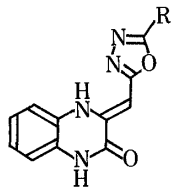


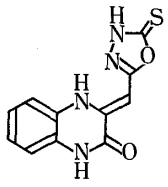
Chart 1. Equilibria of **1** in DMSO or TFA

TABLE I. Tautomers of **1** Assigned on the Basis of ^{1}H-NMR Spectral Data

No.	Compound R	R′	Tautomers in DMSO-d_6	Tautomers in TFA
1a	COOMe	H	A B	B
1b	COOEt	H	A B	B
1c	CN	H	A B	A
1d	COMe	H	A	A
1e	COCOOEt	Me	A	A



2a : R=H
2b : R=Me
2c : R=SMe



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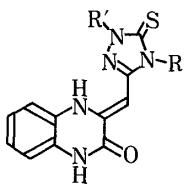
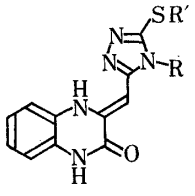
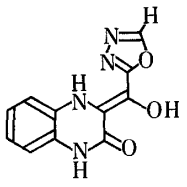


4a : R=allyl, R′=H
4b : R=allyl, R′=Me
4c : R=Me, R′=H



5a : R=allyl, R′=Me
5b : R=allyl, R′=COC_6H_5
5c : R=Me, R′=COC_6H_5



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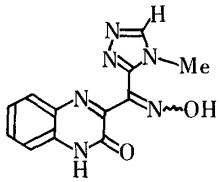

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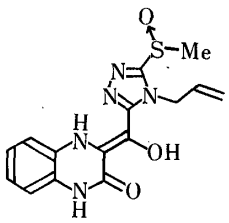

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Chart 2

5-ylmethylene)-2-oxo-1,2,3-4-tetrahydroquinoxaline (**3**),[4] 3-(3,4-dihydro-3-thioxo-2*H*-1,2,4-triazol-5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines (**4a**—**c**),[5,6] 3-(4*H*-1,2,4-triazol-5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines (**5a**,[5,6] **5b**,[6] **5c**,[6]), 3-(α-hydroxy-1,3,4-oxadiazol-5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline (**6**),[3b] 3-(α-hydroxyimino-4-methyl-4*H*-1,2,4-triazol-5-ylmethyl)-2-oxo-1,2-dihydroquinoxaline (**7**),[5,6] and 3-(4-allyl-α-hydroxy-3-methylsulfinyl-4*H*-1,2,4-triazol-5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline (**8**),[6] as shown in Chart 2. In contrast to the above tautomerism of **1**, some of compounds **2**—**8** were found to exhibit interesting tautomeric behavior. That is, they existed as two or more tautomers in TFA and as two tautomers in DMSO-d_6. These tautomeric properties in TFA are presumably due to the presence of the heterocycles conjugated with the 3-methylenic carbon in place of the carbonyl or nitrile group of **1**. This paper describes the tautomeric behavior of 3-(1,3,4-oxadiazol-5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines and 3-(1,2,4-triazol-5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines in DMSO-d_6, TFA, and TFA-d_1 based on ^{1}H-NMR spectral analyses.

Tautomeric Equilibria of 2, 3, 4, and 5

The ^{1}H-NMR spectrum of **1a** in DMSO-d_6 exhibited vinyl and methylene proton signals due to the tautomers A and B at δ 5.52 and 3.83 ppm, respectively. The spectra of **2a**, **2b**, and **2c** in DMSO-d_6 also showed the vinyl and methylene proton signals together with pairs of $C^{2'}$-H, $C^{2'}$-Me, and $C^{2'}$-SMe proton signals (Table II). Similarly, the spectra of **3**, **4a**—**c**, and **5a**—

TABLE II. ^{1}H-NMR Spectral Data for **2**

Solvent	Compound	Chemical shift δ (ppm) Vinyl		Methylene	$C^{2'}$-H, Me, SMe		
DMSO-d_6	**2a**	6.12		4.47	9.20	9.13	($C^{2'}$-H)
	2b	6.02		4.37	2.50	2.49	($C^{2'}$-Me)
	2c	6.00		4.39	2.71	2.66	($C^{2'}$-SMe)
TFA	**2a**	6.63	6.03	4.97	—[a]	—[a]	8.44 ($C^{2'}$-H)
	2b	6.52	5.97	4.93	2.92	2.80	2.62 ($C^{2'}$-Me)
	2c	6.47	5.92	4.93	2.88	2.84	2.73 ($C^{2'}$-SMe)
TFA-d_1	**2a**	—	—	—	9.05	8.97	8.47 ($C^{2'}$-H)
	2b	—	—	—	2.95	2.88	2.65 ($C^{2'}$-Me)
	2c	—	—	—	2.93	2.86	2.73 ($C^{2'}$-SMe)

a) Overlapping with TFA hydrogen.

TABLE III. ^{1}H-NMR Spectral Data for **3**, **4**, and **5**

Solvent	Compound	Chemical shift δ (ppm) Vinyl	Methylene	Methyl	
DMSO-d_6	**3**	5.86	4.29		
	4a	5.88	4.18		
	4b	5.87	4.18	3.79	3.76 ($N^{2'}$-Me)
	4c	5.93	4.27	3.53	3.50 ($N^{4'}$-Me)
	5a	5.97	4.23	2.63	2.58 ($C^{3'}$-SMe)
	5b	6.42	4.56		
	5c	6.42	4.56	3.60	3.56 ($N^{4'}$-Me)
TFA	**3**	—	4.72		
	4a	—	4.90		
	4b	—	—[a]	2.73 ($N^{2'}$-Me)	
	4c	—	4.83	3.90 ($N^{4'}$-Me)	
	5a	—	4.90	2.90 ($C^{3'}$-SMe)	
	5b	—	5.26		
	5c	—	5.25	3.88 ($N^{4'}$-Me)	
TFA-d_1	**3**	—	—		
	4a	—	—		
	4b	—	—	2.73 ($N^{2'}$-Me)	
	4c	—	—	3.83 ($N^{4'}$-Me)	
	5a	—	—	2.87 ($C^{3'}$-SMe)	
	5b	—	—		
	5c	—	—	3.87 ($N^{4'}$-Me)	

a) Overlapping with allylic H.

c in DMSO-d_6 showed the vinyl and methylene proton signals, and pairs of methyl proton signals were observed in **4b**, **4c**, **5a**, and **5c** (Table III). These results are shown in Chart 3. Furthermore, the spectra of **2a**, **2b**, **4c**, and **5a**—**c** were measured at various temperatures in order to estimate changes in the distribution of the tautomers A and B in DMSO-d_6. The results are shown in Table IV; it is clear that tautomer A predominates over tautomer B at low temperature, but the ratio of tautomer B gradually increased with elevation of the temperature.

On the other hand, the spectrum of **1a** in TFA showed the methylene proton signal at δ 4.55 ppm, lacking the vinyl proton signal. Interestingly, however, the spectra of **2a**—**c** in TFA showed two vinyl and one methylene proton signals together with three $C^{2'}$-H, $C^{2'}$-Me,

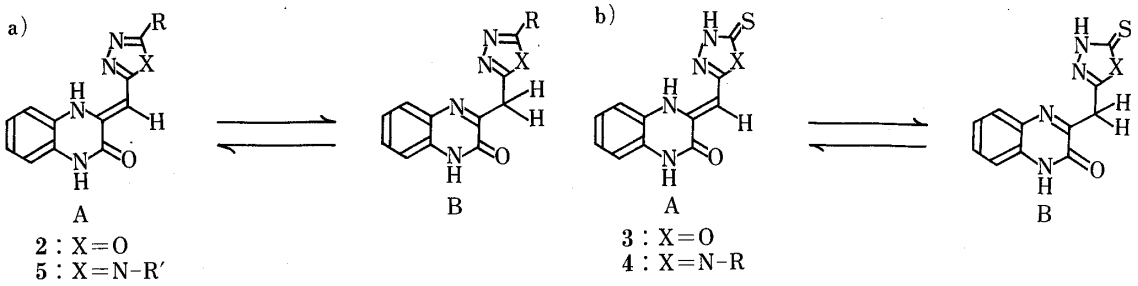


Chart 3. Equilibria of **2**, **3**, **4**, and **5** in DMSO

TABLE IV. Integral Ratios of Vinyl–Methylene Signals in DMSO-d_6 at Various Temperatures

Compound	Temperature (°C)	Vinyl–methylene	
2a	30	4	1
	50	4	1
	90	2	1
2b	30	3	1
	50	2.5	1
	70	2	1
	90	1	1
4c	30	1	0.7
	50	1	0.8
	70	1	1.3
	90	1	2.3
	110	1	2.5
5a	70	7	1
	90	3	1
	110	2	1
5b	30	4.5	1
	50	2.5	1
	70	2	1
	90	1.7	1
	110	1	1
5c	30	4	1
	50	3	1
	70	2	1
	90	2	1
	110	1.5	1

and $C^{2'}$-SMe proton signals (Table II). These data indicate that **2a**—**c** occur as three tautomers, possibly as the protonated species[7] in TFA. As regards protonated azoles in TFA, 1,2,4-triazole,[8] imidazole,[8] oxazole,[9] and 1,2-benzoisothiazole[10] derivatives have already been reported, as shown in Chart 4. In particular, protonations of 1,2,4-triazoles give cations stabilized by amidinium resonance, and the downfield shift of the proton conjugated with the positively charged carbon is larger than that of the other proton.[8] However, the $C^{2'}$-H proton signals of **2a** in TFA did not show a downfield shift compared with the $C^{2'}$-H proton signal in DMSO-d_6, while the methylene proton signals of **2a**—**c** in TFA appeared at lower magnetic fields than those in DMSO-d_6. The shift differences of the methylene proton signals are δ 0.5—0.6 ppm. These results support the occurrence of protonation on $N^{4'}$ of **2a**—**c** in TFA. Moreover, taking prototropy into consideration, the species C, D, and E are proposed as the tautomers of **2** in TFA, as shown in Chart 5. In tautomer E, protonation was assumed to

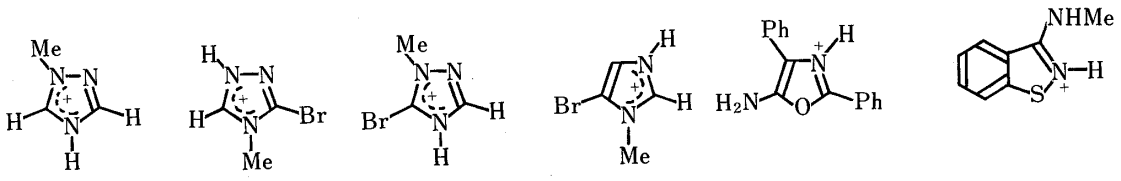


Chart 4

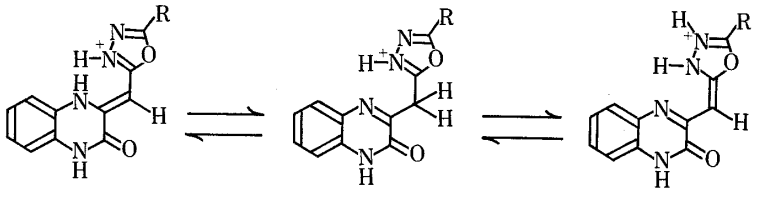


Chart 5. Equilibria of **2** in TFA

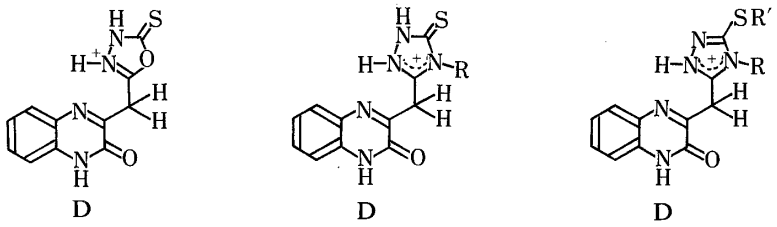


Chart 6. Tautomers of **3**, **4**, and **5** in TFA

occur on the $N^{3'}$ atom on the basis of the relative basicity of the $N^{3'}$ and $N^{4'}$ atoms. In the literature,[2] the vinyl and methylene proton signals of **1** in TFA were reported to be at lower

TABLE V. Tautomers of **2**, **3**, **4**, and **5** Assigned on the Basis of ^{1}H-NMR Spectral Data

Compound	Tautomers in DMSO-d_6	Tautomers in TFA
2a	A B	C D E
2b	A B	C D E
2c	A B	C D E
3	A B	D
4a	A B	D
4b	A B	D
4c	A B	D
5a	A B	D
5b	A B	D
5c	A B	D

magnetic fields than those in DMSO-d_6, and the shift differences between the solvents were δ 0.4—1.1 ppm in the vinyl proton signals and δ 0.6—0.7 ppm in the methylene proton signals. Accordingly, it was assumed that the vinyl proton signals [δ 6.63 (**2a**), 6.52 (**2b**), 6.47 (**2c**) ppm] were due to tautomer C, the methylene proton signals [δ 4.97 (**2a**), 4.93 (**2b**), 4.93 (**2c**) ppm] were due to tautomer D, and the remaining vinyl proton signals [δ 6.03 (**2a**), 5.97 (**2b**), 5.92 (**2c**) ppm] were due to tautomer E. In addition, the vinyl and methylene proton signals of **2a**—**c** disappeared on measurement in TFA-d_1,[2,11] while the $C^{2'}$-H proton signals of **2a** did not

TABLE VI. ^{1}H-NMR Spectral Data for **6**, **7**, and **8**

Compound	Solvent	Chemical shift δ (ppm)	
6	DMSO-d_6	9.34 ($C^{2'}$-H)	
	TFA	9.02 8.53 ($C^{2'}$-H)	
	TFA-d_1	8.97 8.54 ($C^{2'}$-H)	
7	DMSO-d_6	8.57 ($C^{3'}$-H)	3.87 ($N^{4'}$-Me)
	TFA	9.60 9.52 ($C^{3'}$-H)	4.32 4.13 ($N^{4'}$-Me)
	TFA-d_1	9.60 9.52 ($C^{3'}$-H)	4.32 4.13 ($N^{4'}$-Me)
8	DMSO-d_6	3.20 ($C^{3'}$-SMe)	
	TFA	3.47 ($C^{3'}$-SMe)	
	TFA-d_1	3.45 ($C^{3'}$-SMe)	

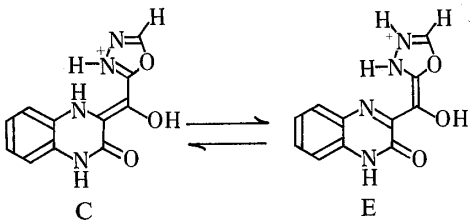


Chart 7. Equilibria of **6** in TFA

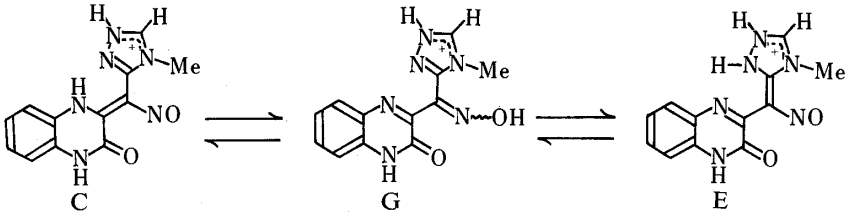


Chart 8. Equilibria of **7** in TFA

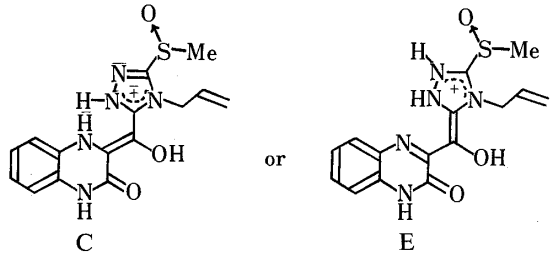
disappear, and the $C^{2'}$-Me proton signals of **2b** were observed as three singlet signals.

In contrast to the above tautomeric behavior of **2** in TFA, **3**, **4**, and **5** showed no vinyl proton signal, but showed a single methylene proton signal on measurement in TFA (Table III). Moreover, the methylene proton signals of **3**, **4**, and **5** disappeared on measurement in TFA-d_1, and the methyl proton signals of **4b**, **4c**, **5a**, and **5c** became singlets on measurements in TFA and in TFA-d_1. These data indicate that **3**, **4**, and **5** occur as tautomer D in TFA, as shown in Chart 6.

Thus, the compounds (**2**) having the 1,3,4-oxadiazole ring were found to exist in the three tautomers C, D, and E, while the compounds (**3**, **4**, **5**) possessing the 2,3-dihydro-1,3,4-oxadiazole, 2,3-dihydro-1,2,4-triazole, and 4*H*-1,2,4-triazole rings existed predominantly as tautomer D, as shown in Table V.

Tautomeric Equilibria of 6, 7, and 8

Compounds **2**, **3**, **4**, and **5** existed as the two tautomers A and B in DMSO-d_6, but compounds **6**, **7**, and **8** existed as only one species, as shown in Chart 2. However, **6** and **7** were found to isomerize in TFA (Table VI). Namely, the ^{1}H-NMR spectra of **6** in both TFA and TFA-d_1 exhibited two $C^{2'}$-H proton signals without the methine proton signal, excluding the D type of tautomer. In addition, the two $C^{2'}$-H proton signals in TFA did not show any downfield shift in comparison with the one $C^{2'}$-H proton signal in DMSO-d_6. These results indicate that tautomers C and E are present in the case of **6**, as shown in Chart 7. In the spectra of **7** in both TFA and TFA-d_1, two $C^{3'}$-H proton signals were observed together with



C E

Chart 9. Protonated Species of **8** in TFA

TABLE VII. Tautomers of **6**, **7**, and **8** in TFA Assigned on the Basis of ^{1}H-NMR Spectral Data

Compound	Tautomers
6	C and E
7	Two of C, E, and G
8	C or E

two $N^{4'}$-Me proton signals. Interestingly, the two $C^{3'}$-H proton signals in TFA appeared at lower magnetic fields than the one $C^{3'}$-H proton signal in DMSO-d_6, supporting protonation on the $N^{2'}$ atom of **7**. The above results provide evidence that **7** occurs as two tautomers. Two of the tautomers C, E, and G may be involved in this case, as shown in Chart 8. On the other hand, the spectra of **8** in both TFA and TFA-d_1 exhibited one methyl proton signal, indicating that **8** exists predominantly as the single tautomer C or E, as shown in Chart 9.

Thus, the isomerization in TFA was also confirmed to occur in **6** and **7**, which were functionalized with hydroxyl and hydroxyimino groups, respectively, at the 3-methylenic carbon. However, no data have yet been obtained to identify the one tautomer of **8**, although spectral measurement at high temperature could provide a clue. The above results are shown in Table VII.

Experimental

^{1}H-NMR spectra were measured with an EM-390 spectrometer at 90 MHz using tetramethylsilane as an internal reference. Accuracy in the chemical shifts is within 1—3 Hz. The spectra in TFA and TFA-d_1 were measured at near 30 °C. The concentrations of the samples in DMSO-d_6 varied between 4—10% because of poor solubility in some cases. No appreciable variation in chemical shifts in DMSO-d_6 was found within the range of temperatures measured.

The structural assignments of all samples employed were described previously.[3-6]

References and Notes

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