CHARACTERISTIC TAUTOMERISM AND ISOMERIZATION IN THE QUINOXALINE CHEMISTRY

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Abstract —— Various side-chained quinoxalines have been found to exhibit the interesting tautomeric equilibria between the enamine and methylene imine forms and between the hydrazone imine and diazenyl enamine forms by means of the various spectroscopies. Moreover, some of the quinoxaline derivatives have also been known to isomerize from one tautomer into the other stable tautomer without the tautomeric equilibria in the media. This review describes the above quinoxalines exhibiting the above tautomeric equilibria and isomerizations.

This review includes the following contents.

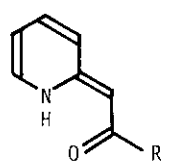
1. 3-Formyl-2-oxo-1,2-dihydroquinoxaline Chlorophenylhydrazones
2. 3-(α-Chlorophenylhydrazono)oxadiazolylmethyl-2-oxo-1,2-dihydroquinoxalines
3. 3-(α-Chlorophenylhydrazono)methoxycarbonylmethyl-2-oxo-1,2-dihydroquinoxalines

IV. Isomerization
1. 3-(α-Acetamido)ethoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline and 3-(α-Acetamido)ethoxycarbonylmethyl-2-oxo-1,2-dihydroquinoxaline
2. 2,4-Dihydrofuro[2,3-b]quinoxalin-2-ones
3. 3-Quinoxalinyl-1,5-benzodiazepines

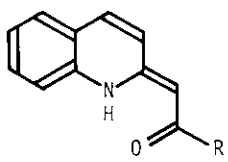
V. Qualitative Mechanistic Consideration in D-H Exchange

I. INTRODUCTION

There have been reported so far numerous works concerning the tautomerism of the various heterocyclic compounds by many researchers.[1] Among the heterocyclic compounds, the side-chained N-heterocyclic compounds have been found to exhibit interesting tautomeric equilibria in some kinds of solvents. For example, the side-chained pyridines 1,[2,3] quinolines 2,[4-6] pyrazine 3,[7] and pteridines 4[8,9] (Chart 1) showed the tautomeric equilibria between the enamine form A and the methylene imine form B (Scheme 1). Concerning the above type of side-chained quinoxalines, Iwanami[10] reported the synthesis of the 3-alkoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxalines 5 (Chart 2) from the reactions of substituted o-phenyl-



1 R=Me, Ph



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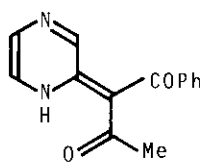

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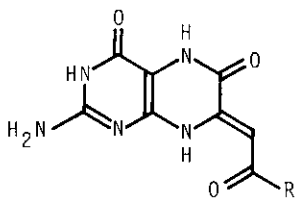


4 R=Me, Ph

CHART 1

enediamines with acetylenedicarboxylates, and the tautomeric equilibria of 5 and its related compounds were studied in detail by Chapman[11] and Mondelli and Merlini,[4] who clarified a great dependence of the ratios of the tautomers A and B on the kind of solvents. The author also synthesized the 3-heteroarylmethylene-2-oxo-1,2,3,4-

A enamine form ⇌ B methylene imine form

SCHEME 1

tetrahydroquinoxalines and related compounds (Chart 3),[12-15] and some of them exhibited the interesting tautomerism, which was due to the presence of the heteroaryl ring in the side-chain.[16,17] Moreover, the 3-(α-chlorophenylhydrazono)methyl-2-oxo-1,2-dihydroquinoxalines (Chart 4) were synthesized by the author,[18-22] and these

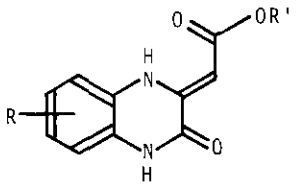
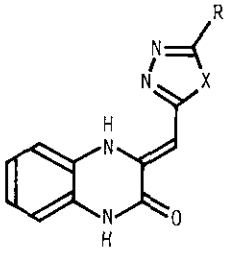


CHART 2



X=O, N-R'

CHART 3

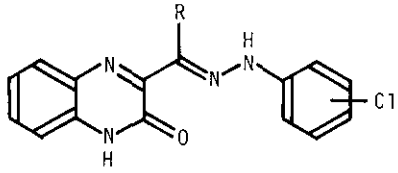
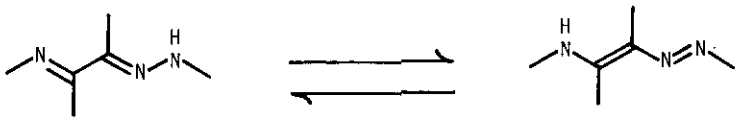


CHART 4

compounds were reported to show the tautomeric equilibria between the hydrazone imine form C and the diazenyl enamine form D (Scheme 2).[22-24] Besides the above compounds, there have been found some quinoxaline derivatives to isomerize from one tautomer to the other stable tautomer without the tautomeric equilibria in the media.[25-27] This review summarizes the above tautomeric equilibria and isomerization of the quinoxa-

line compounds.



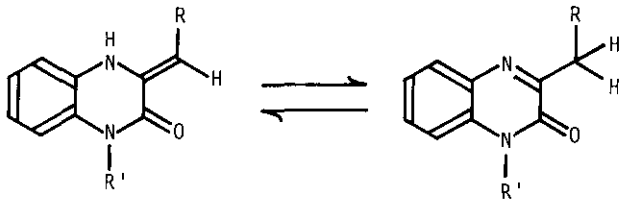
C hydrazone imine form ⇌ D diazenyl enamine form

SCHEME 2

II. TAUTOMERIC EQUILIBRIA BETWEEN ENAMINE AND METHYLENE IMINE FORMS

1. 3-ALKOXYCARBONYLMETHYLENE-2-OXO-1,2,3,4-TETRAHYDROQUINOXALINES AND RELATED COMPOUNDS

The tautomeric equilibria of the 3-alkoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxalines 5a,b and related compounds 5c-e (Scheme 3) have been investigated by



A ⇌ B

5	R	R'
a	COOMe	H
b	COOEt	H
c	CN	H
d	COMe	H
e	COCOOEt	Me
f	COOEt	Me

SCHEME 3 Tautomeric Equilibria of 5 in DMSO-d_6

means of the PMR and UV spectra, which are measured in $CDCl_3$, DMSO-d_6, and trifluoroacetic acid (TFA).[4,11] Namely, the PMR spectral data in DMSO-d_6 (Table 1) demonstrated that the two tautomers A and B coexisted in 5a,b,c, and the tautomer A was predominant in 5d,e. In addition, the PMR spectra in TFA indicated that 5a,b exist-

ed as the tautomer B, and 5c,d,e as the tautomer A. On the other hand, 5b,e predominated as the tautomer A in $CDCl_3$. Moreover, 3-ethoxycarbonylmethylene-1-methyl-2-oxo-1,2,3,4-tetrahydroquinoxaline 5f (R=COOEt, R'=Me) was found to exist as the tautomer A in $CDCl_3$ [δ 5.82 (vinyl), 3.54 (N_1-Me) ppm], as the tautomer B in TFA [δ 4.6 (methylene), 4.10 (N_1-Me) ppm], and as the tautomers A and B in $CDCl_3$/TFA [δ 5.82 (vinyl), 3.95 (methylene), 3.68, 3.57 (N_1-Me) ppm].[4]

Table 1-a. PMR Spectral Data (δ ppm) for 5

Compound	R	R'	DMSO-d_6		TFA		$CDCl_3$	
			vinyl	methylene	vinyl	methylene	vinyl	methylene
5a	COOMe	H	5.52	3.83	——	4.55		
5b	COOEt	H	5.52	3.84	——	4.5	5.72	——
5c	CN	H	5.03	4.25	6.20	——		
5d	COMe	H	6.01	——	6.52	——		
5e	COCOOEt	Me	6.70	——	7.42	——	7.04	——

Table 1-b. Tautomers for 5

Compound	Tautomer			
	in DMSO-d_6		in TFA	in $CDCl_3$
5a	A	B	B	
5b	A	B	B	A
5c	A	B	A	
5d	A		A	
5e	A		A	A

DMSO-d_6: deuteriodimethylsulfoxide

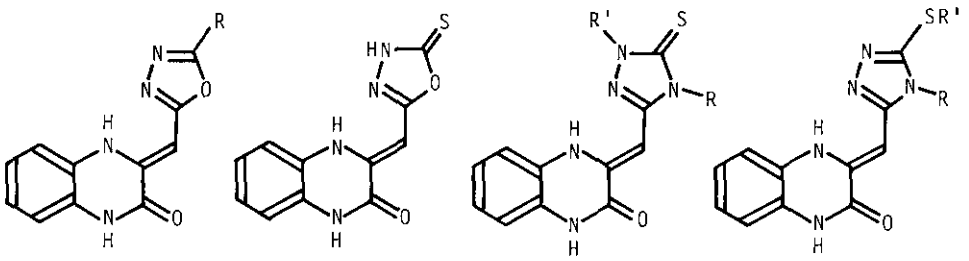
TFA: trifluoroacetic acid

$CDCl_3$: deuteriochloroform

2. 3-HETEROARYLMETHYLENE-2-OXO-1,2,3,4-TETRAHYDROQUINOXALINES

a. 3-OXADIAZOLYLMETHYLENE- AND 3-TRIAZOLYLMETHYLENE-2-OXO-1,2,3,4-TETRAHYDROQUINOXALINES

The tautomeric equilibria of the 3-oxadiazolylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxalines 6a-c, 7 and the 3-triazolylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxalines 8a-c, 9a-c (Chart 5)[12-15] are described in this section.



6 7 8 9

a, R=H
b, R=Me
c, R=SMe

a, R=allyl R'=H
b, R=allyl R'=Me
c, R=Me R'=H

a, R=allyl R'=Me
b, R=allyl R'=COC_6H_5
c, R=Me R'=COC_6H_5

CHART 5

The PMR spectra of 6a-c in DMSO-d_6 exhibited the vinyl and methylene proton signals together with pairs of the C_2,-H, C_2,-Me, and C_2,-SMe proton signals (Table 2).[16,17] Similarly, the spectra of 7, 8a-c, 9a-c in DMSO-d_6 showed the vinyl and methylene proton signals, and the pairs of the N-Me or S-Me proton signals were observed in 8b,c, 9a,c (Table 3). These results support the tautomeric equilibria between the A and B forms (Scheme 4). When the spectra of 6a,b, 8c, 9a-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 tautomer A predominated over the tautomer B at low temperature, but the ratio of the tautomer B gradually increased with elevation of the temperature (Table 4).

Table 2. PMR Spectral Data for 6

Solvent	Compound	Chemical Shift (δ ppm)		
		vinyl	methylene	$C_{2'}$-H, -Me, -SMe
DMSO-$\underline{d}_6$	6a	6.12	4.47	9.20 9.13 ($C_{2'}$-H)
	6b	6.02	4.37	2.50 2.49 ($C_{2'}$-Me)
	6c	6.00	4.39	2.71 2.66 ($C_{2'}$-SMe)
TFA	6a	6.63 6.03	4.97	a) a) 8.44 ($C_{2'}$-H)
	6b	6.52 5.97	4.93	2.92 2.80 2.62 ($C_{2'}$-Me)
	6c	6.47 5.92	4.93	2.88 2.84 2.73 ($C_{2'}$-SMe)
TFA-$\underline{d}_1$	6a	—— ——	——	9.05 8.97 8.47 ($C_{2'}$-H)
	6b	—— ——	——	2.95 2.88 2.65 ($C_{2'}$-Me)
	6c	—— ——	——	2.93 2.86 2.73 ($C_{2'}$-SMe)

a) overlapping with TFA hydrogen

Table 3. PMR Spectral Data for 7, 8, and 9

Solvent	Compound	Chemical Shift (δ ppm)		
		vinyl	methylene	methyl
DMSO-$\underline{d}_6$	7	5.86	4.29	
	8a	5.88	4.18	
	8b	5.87	4.18	3.79 3.76 ($N_{2'}$-Me)
	8c	5.93	4.27	3.53 3.50 ($N_{4'}$-Me)
	9a	5.97	4.23	2.63 2.58 ($C_{3'}$-SMe)
	9b	6.42	4.56	
	9c	6.42	4.56	3.60 3.56 ($N_{4'}$-Me)

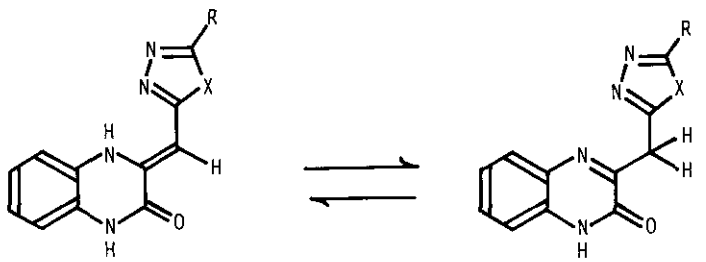
Table 3. PMR Spectral Data for 7, 8, 9 (continued)

Solvent	Compound	Chemical Shift (δ ppm)		
		vinyl	methylene	methyl
TFA	7	——	4.72	
	8a	——	4.90	
	8b	——	a)	2.73 (N_2,-Me)
	8c	——	4.83	3.90 (N_4,-Me)
	9a	——	4.90	2.90 (C_3,-SMe)
	9b	——	5.26	
	9c	——	5.25	3.88 (N_4,-Me)
TFA-$\underline{d}_1$	7	——	——	
	8a	——	——	
	8b	——	——	2.73 (N_2,-Me)
	8c	——	——	3.83 (N_4,-Me)
	9a	——	——	2.87 (C_3,-SMe)
	9b	——	——	
	9c	——	——	3.87 (N_4,-Me)

a) overlapping with allylic hydrogen

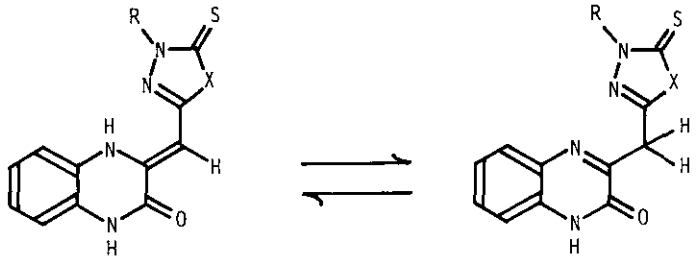
Table 4. Integral Ratios of Vinyl-Methylene Proton Signals in DMSO-$\underline{d}_6$ at Various Temperatures (°C)

Compound	Temperature	Vinyl-Methylene		Compound	Temperature	Vinyl-Methylene	
6a	30	4	1	9a	70	7	1
	50	4	1		90	3	1
	90	2	1		110	2	1
6b	30	3	1	9b	30	9	2
	50	5	2		50	5	2
	90	1	1		90	17	10
8c	30	10	7	9c	30	4	1
	50	10	8		50	3	1
	90	10	23		90	2	1



A B

6 X=O
9 X=NR'



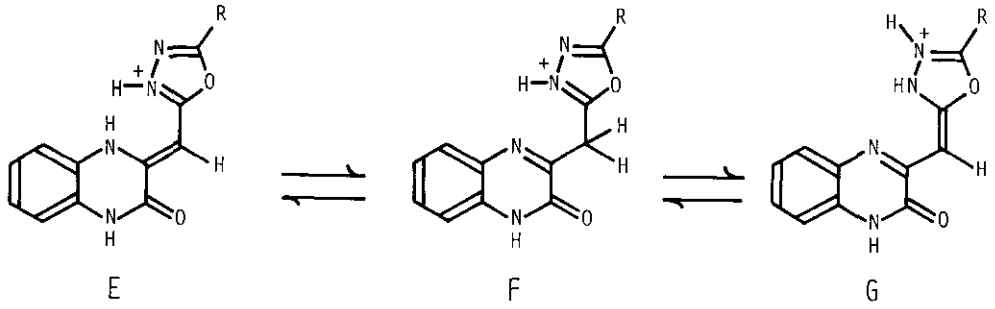
A B

7 X=O
8 X=NR'

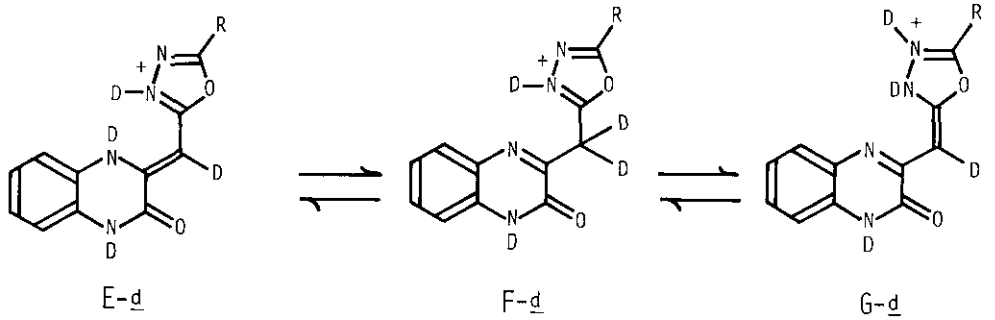
SCHEME 4 Tautomeric Equilibria of 6, 7, 8, and 9 in DMSO-$\underline{d}_6$

The PMR spectra of 5a,b (section II. 1.) in TFA showed the methylene proton signals at δ 4.55 and 4.5 ppm, respectively, lacking the vinyl proton signals. To the contrary, the spectra of 6a-c in TFA exhibited the two vinyl and one methylene proton signals together with the respective three C_2,-H, C_2,-Me, and C_2,-SMe proton signals (Table 2), indicating the occurrence of the three tautomers E, F, and G (Scheme 5). Furthermore, the spectra of 6a-c in TFA-$\underline{d}_1$ showed the respective three C_2,-H, C_2,-Me, and C_2,-SMe proton signals with disappearance of the vinyl and methylene proton signals (Table 2), supporting the tautomeric equilibria among the deuterized species E-$\underline{d}$, F-$\underline{d}$, and G-$\underline{d}$ (Scheme 6).

In contrast to the tautomeric behaviors of 6a-c in TFA and TFA-$\underline{d}_1$, the PMR spectra of 7, 8a-c, and 9a-c in TFA showed the respective single methylene proton signals without the vinyl proton signals (Table 3), while the methylene proton signals also



SCHEME 5 Tautomeric Equilibria of 6 in TFA



SCHEME 6 Tautomeric Equilibria of 6 in TFA-$\underline{d}_1$

disappeared in the spectra measured in TFA-$\underline{d}_1$. These data indicated that 7, 8a-c, and 9a-c occurred as the tautomers F in TFA and the deuterized tautomers F-$\underline{d}$ in TFA-$\underline{d}_1$ (Chart 6).

The above tautomers are summarized in Table 5.

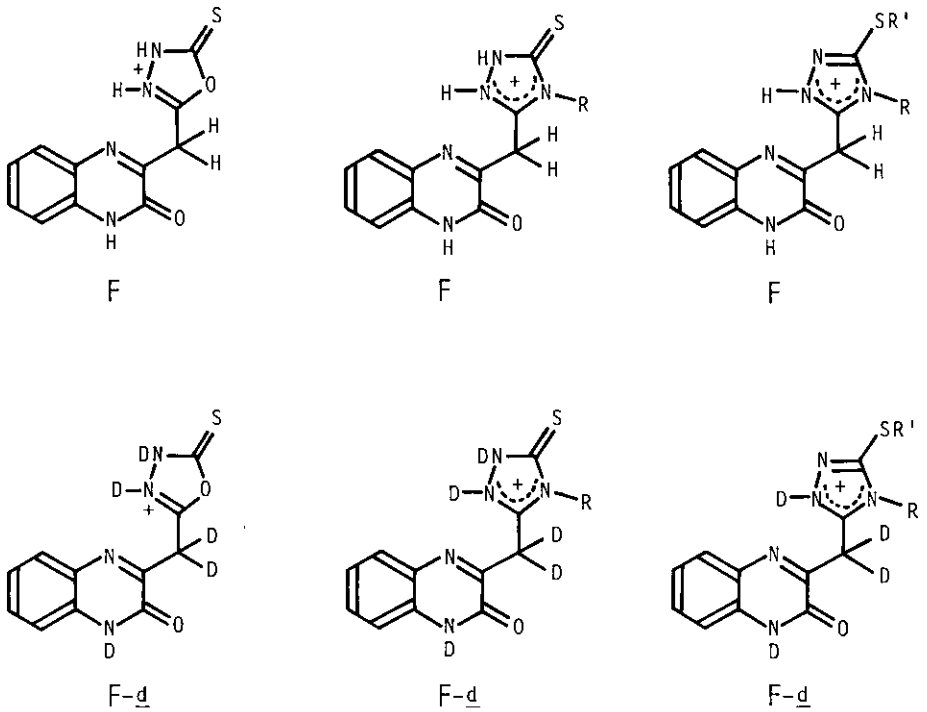


CHART 6 Tautomers of 7, 8, and 9 in TFA and TFA-$\underline{d}_1$

b. 3-BENZIMIDAZOLYLMETHYLENE-2-OXO-1,2,3,4-TETRAHYDROQUINOXALINES AND ITS HYDROCHLORIDE

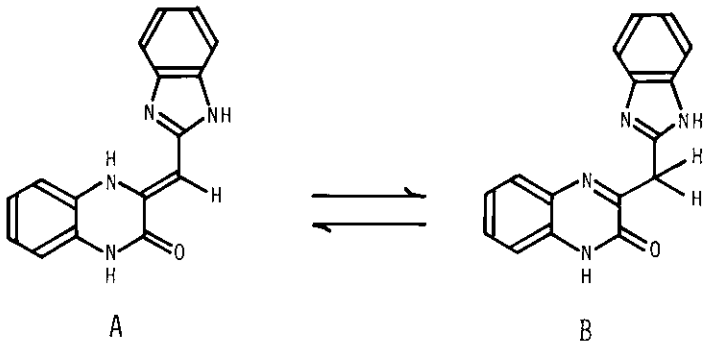
The PMR spectra of 3-(benzimidazol-2-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline 10 and its hydrochloride 11 in DMSO-$\underline{d}_6$ exhibited the vinyl and methylene proton signals (Table 6), indicating the tautomeric equilibria between the A and B forms (Scheme 7) and the E and F forms (Scheme 8), respectively.[28] The integral ratios of the vinyl versus methylene proton signals were 9:1 in 10 and 1:1 in 11 at 30 °C, that is, the ratio of the tautomer B against the tautomer A was larger in the hydrochloride 11 than in the free base 10. In addition, the spectra of 10 and 11 in DMSO-$\underline{d}_6$/D_2O provided the quite different results, namely, the vinyl and meth-

Table 5. Tautomers for 6, 7, 8, and 9

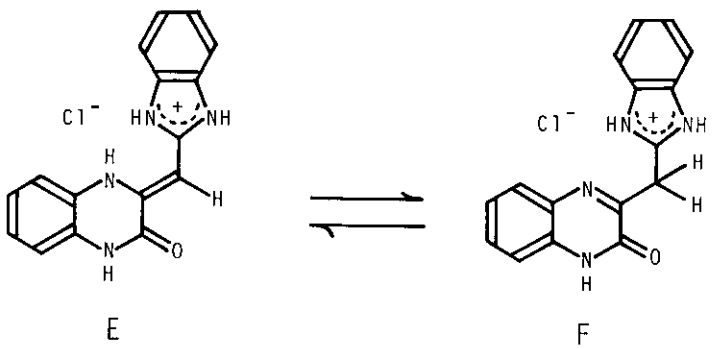
Compound	Tautomer	
	in DMSO-$\underline{d}_6$	in TFA
6a	A B	E F G
6b	A B	E F G
6c	A B	E F G
7	A B	F
8a	A B	F
8b	A B	F
8c	A B	F
9a	A B	F
9b	A B	F
9c	A B	F

Table 6. Tautomers for 10 and 11

Compound	Solvent	Chemical Shift (δ ppm)		Tautomer	
		vinyl	methylene		
10	DMSO-$\underline{d}_6$	6.24	4.55	10A	10B
	DMSO-$\underline{d}_6$/D_2O	6.24	4.55	10A-$\underline{d}$	10B-$\underline{d}$
	TFA	——	5.12		10F
	TFA-$\underline{d}_1$	——	——		10F-$\underline{d}$
11	DMSO-$\underline{d}_6$	6.41	4.78	11E	11F
	DMSO-$\underline{d}_6$/D_2O	——	——	11E-$\underline{d}$	11F-$\underline{d}$
	TFA	——	5.21		11F
	TFA-$\underline{d}_1$	——	——		11F-$\underline{d}$

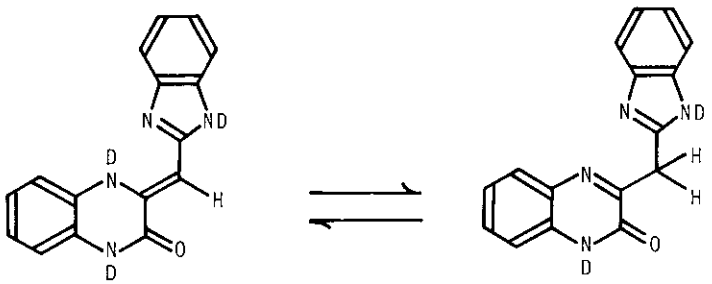


SCHEME 7 Tautomeric Equilibria of 10 in DMSO-$\underline{d}_6$

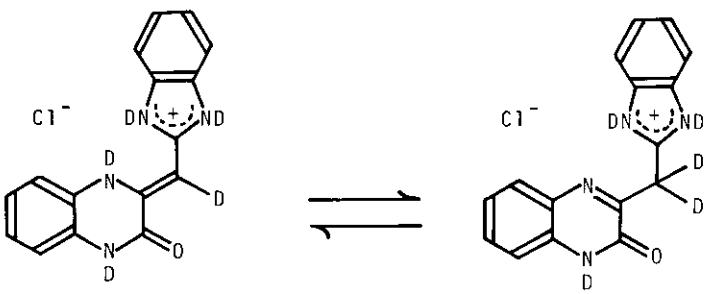


SCHEME 8 Tautomeric Equilibria of 11 in DMSO-$\underline{d}_6$

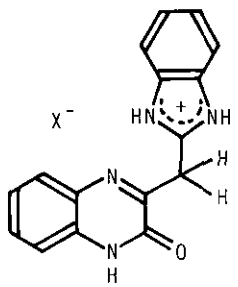
ylene proton signals were observed in 10, while the both signals disappeared in the spectra of 11, supporting the tautomeric equilibria between the deuterized A-d and B-d (Scheme 9) and the deuterized E-d and F-d (Scheme 10). Furthermore, the spectra of 10 and 11 in TFA exhibited the methylene proton signals without the vinyl proton signals, while the both signals disappeared in TFA-d_1, indicating the predominance of the species F and the deuterized F-d (Chart 7).



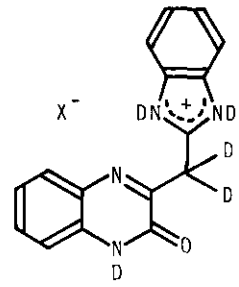
SCHEME 9 Tautomeric Equilibria of 10 in DMSO-d_6/D_2O



SCHEME 10 Tautomeric Equilibria of 11 in DMSO-d_6/D_2O



F

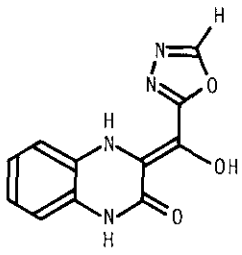


F-d

CHART 7 Species of 10 and 11 in TFA and TFA-d_1

3. 3-(α-HYDROXY)HETEROARYLMETHYLENE-2-OXO-1,2,3,4-TETRAHYDROQUINOXALINES AND RELATED COMPOUNDS

The PMR spectral data of the 3-(α-hydroxy)heteroarylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxalines 12,[12b] 13,[15] and related compounds 14, 15[29] in DMSO-d_6 indicated the occurrence of the tautomer A shown in Chart 8 (Table 7).[17]



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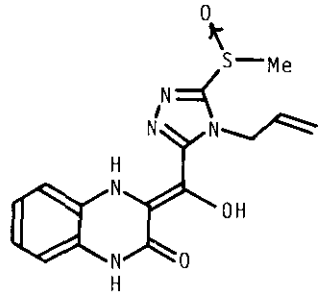

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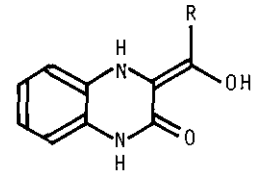
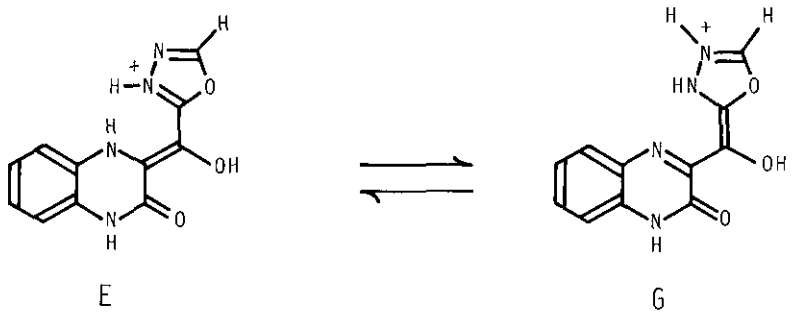


14 R=COOMe

15 R=H

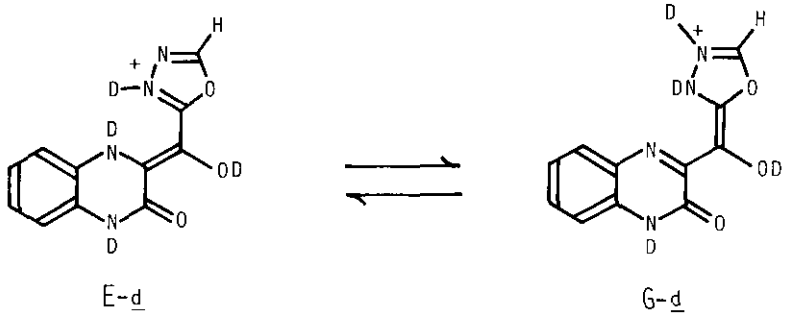
CHART 8

However, these compounds displayed the quite different behaviors in TFA and TFA-$\underline{d}_1$. That is to say, the PMR spectra of 12 in both TFA and TFA-$\underline{d}_1$ exhibited the two C_2,-H proton signals, indicating the tautomeric equilibria between the E and G forms (Scheme 11) and the E-$\underline{d}$ and G-$\underline{d}$ forms (Scheme 12), respectively.[17] On the contrary,



E G

SCHEME 11 Tautomeric Equilibria of 12 in TFA



E-$\underline{d}$ G-$\underline{d}$

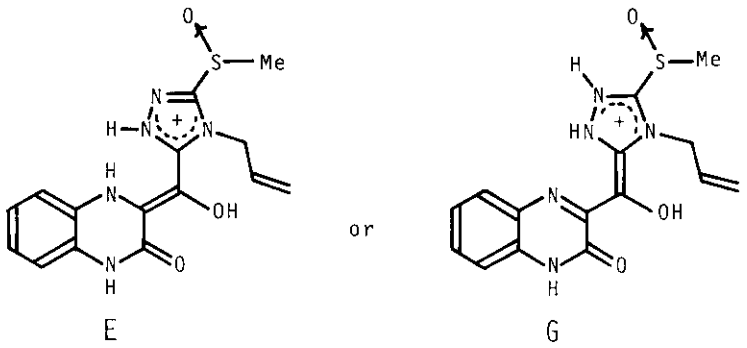
SCHEME 12 Tautomeric Equilibria of 12 in TFA-$\underline{d}_1$

the spectra of 13 in both TFA and TFA-$\underline{d}_1$ showed a single $C_{3'}$-SOMe proton signal, supporting the occurrence of the protonated species E or G (Chart 9) and the deuterized species E-$\underline{d}$ or G-$\underline{d}$ (Chart 10), respectively. Moreover, the PMR spectrum of 14 in TFA exhibited the methine proton signal, which did not disappear even if measured in TFA-$\underline{d}_1$, indicating the predominance of the species B and B-$\underline{d}$ (Chart 11).[29] Compounds 12 and 13 did not isomerize into the tautomers F (Chart 12) such

Table 7. PMR Spectral Data for 12, 13, 14, and 15

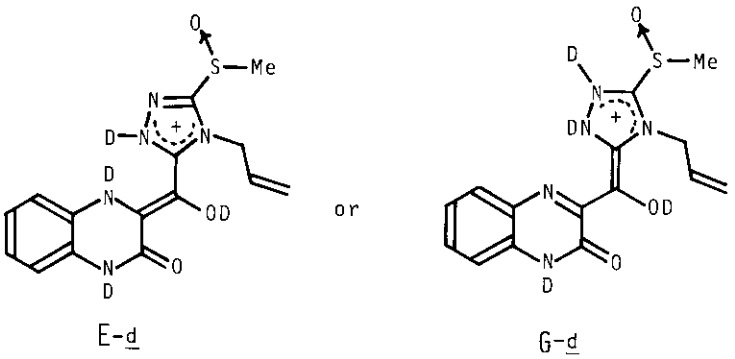
Compound	Solvent	Chemical Shift (δ ppm)	Tautomer
12	DMSO-$\underline{d}_6$	9.34 ($C_{2'}$-H)	A
	TFA	9.02 8.53 ($C_{2'}$-H)	E and G
	TFA-$\underline{d}_1$	8.97 8.54 ($C_{2'}$-H)	E-$\underline{d}$ and G-$\underline{d}$
13	DMSO-$\underline{d}_6$	3.20 ($C_{3'}$-SOMe)	A
	TFA	3.47 ($C_{3'}$-SOMe)	E or G
	TFA-$\underline{d}_1$	3.45 ($C_{3'}$-SOMe)	E-$\underline{d}$ or G-$\underline{d}$
14	DMSO-$\underline{d}_6$	—— (no methine)	A
	TFA	4.23 (methine)	B
	TFA-$\underline{d}_1$	4.22 (methine)	B-$\underline{d}$
15	DMSO-$\underline{d}_6$	4.63 (vinyl)	A
	TFA	3.08 (methylene)	B
	TFA-$\underline{d}_1$	—— (no methylene)	B-$\underline{d}$

as the species 14B, which would be due to the facile migration of their methine protons onto the nitrogen atoms of the azole rings of 12 and 13. On the other hand, the spectra of 15 in TFA showed the methylene proton signal, while its spectra in TFA-$\underline{d}_1$ exhibited no methylene proton signal, supporting the occurrence of the species B and B-$\underline{d}$ (Chart 13).



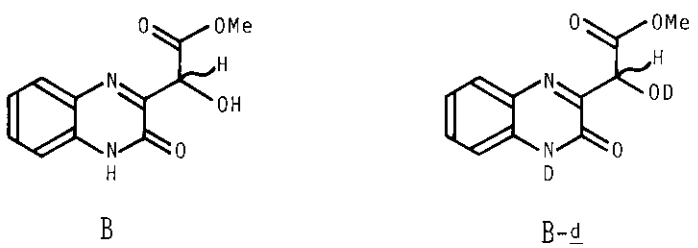
E G

CHART 9 Protonated Species of 13 in TFA



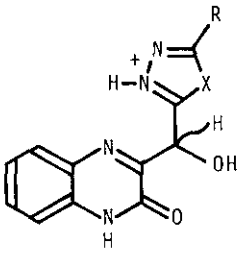
E-d G-d

CHART 10 Deuterized Species of 13 in TFA-d_1



B B-d

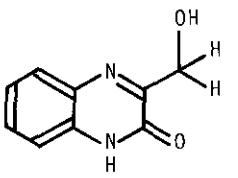
CHART 11 Species of 14 in TFA and TFA-d_1



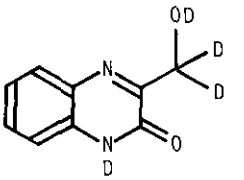
[F]

X=O, NR'

CHART 12



B

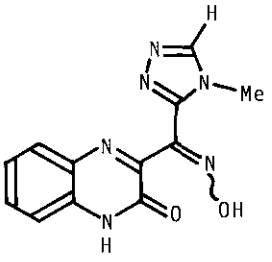


B-d

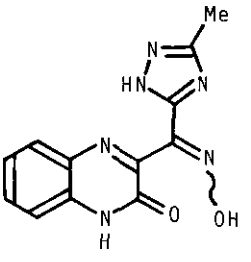
CHART 13 Species of 15 in TFA and TFA-d_1

4. 3-(α-HYDROXYIMINO)TRIAZOLYLMETHYL-2-OXO-1,2-DIHYDROQUINOXALINES

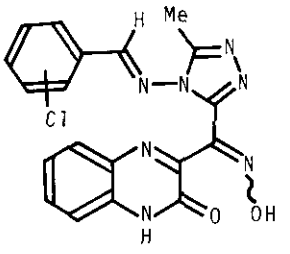
The PMR spectral data of the 3-(α-hydroxyimino)triazolylmethyl-2-oxo-1,2-dihydroquinoxalines 16a,[14,15] 16b-d[30] in DMSO-d_6 supported the predominance of the only one species shown in Chart 14 (Table 8).[17]



16 a



16 b



16 c o-Cl
16 d p-Cl

CHART 14 Species of 16 in DMSO-d_6

Table 8. PMR Spectral Data for 16a-d

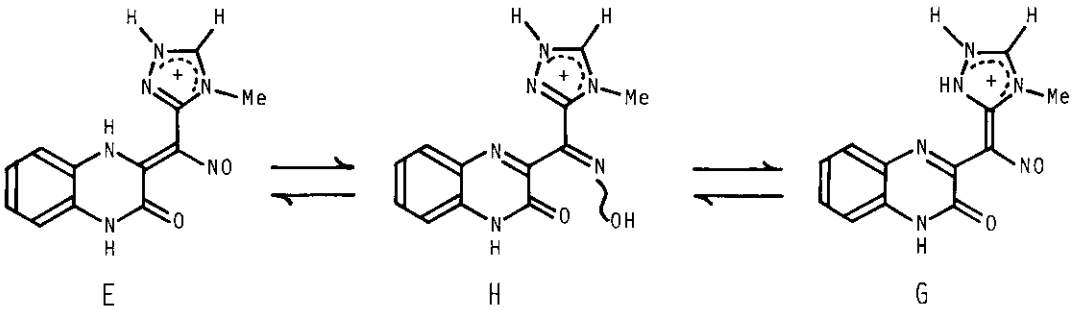
Compound	Solvent	Chemical Shift (δ ppm)
16a	DMSO-$\underline{d}_6$	8.57 (C_3,-H) 3.87 (N_4,-Me)
	TFA	9.60 9.52 (C_3,-H) 4.32 4.13 (N_4,-Me)
	TFA-$\underline{d}_1$	9.60 9.52 (C_3,-H) 4.32 4.13 (N_4,-Me)
16b	DMSO-$\underline{d}_6$	2.33 (C_3,-Me)
	TFA	2.97 2.93 (C_3,-Me)
	TFA-$\underline{d}_1$	2.98 2.94 (C_3,-Me)
16c	DMSO-$\underline{d}_6$	2.55 (C_3,-Me) 9.43 (N_4,-N=CH-)
	TFA	3.06 (C_3,-Me) 9.57 (N_4,-N=CH-)
	TFA-$\underline{d}_1$	3.04 (C_3,-Me) 9.57 (N_4,-N=CH-)
16d	DMSO-$\underline{d}_6$	2.50 (C_3,-Me) 9.00 (N_4,-N=CH-)
	TFA	2.99 (C_3,-Me) 8.97 (N_4,-N=CH-)
	TFA-$\underline{d}_1$	2.99 (C_3,-Me) 8.97 (N_4,-N=CH-)

The spectra of 16a in both TFA and TFA-$\underline{d}_1$ represented the respective two C_3,-H and N_4,-Me proton signals, indicating the presence of two of the tautomers E, G, and H (Scheme 13) and E-$\underline{d}$, G-$\underline{d}$, and H-$\underline{d}$ (Scheme 14). Moreover, the spectra of 16b in both TFA and TFA-$\underline{d}_1$ exhibited the two C_3,-Me proton signals,[31] similarly providing a proof for the occurrence of two of the tautomers E, G, and H (Scheme 15) and E-$\underline{d}$, G-$\underline{d}$, and H-$\underline{d}$ (Scheme 16).[31] However, the spectra of 16c,d in both TFA and TFA-$\underline{d}_1$ showed the respective one C_3,-Me and N_4,-N=CH- proton signals,[31] supporting the predominance of the species H and H-$\underline{d}$ (Chart 15).[31]

III. TAUTOMERIC EQUILIBRIA BETWEEN HYDRAZONE IMINE AND DIAZENYL ENAMINE FORMS

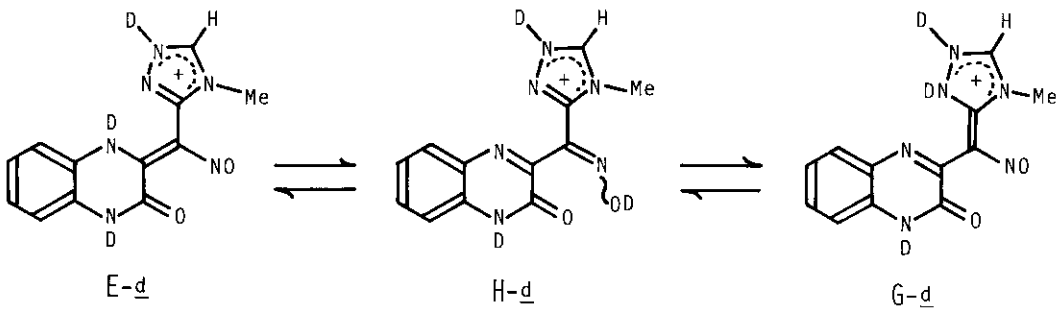
1. 3-FORMYL-2-OXO-1,2-DIHYDROQUINOXALINE CHLOROPHENYLHYDRAZONES

The PMR spectrum of the 3-formyl-2-oxo-1,2-dihydroquinoxaline chlorophenylhydrazone



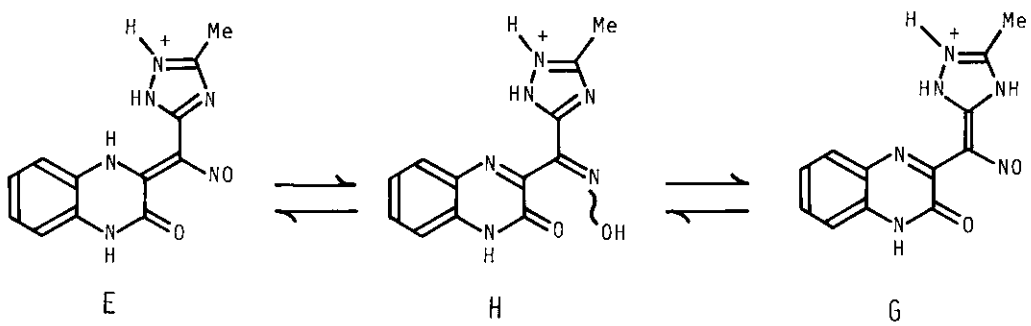
E H G

SCHEME 13 Tautomeric Equilibria of 16a in TFA
(Tautomers in Medium — Two of E, G, H)



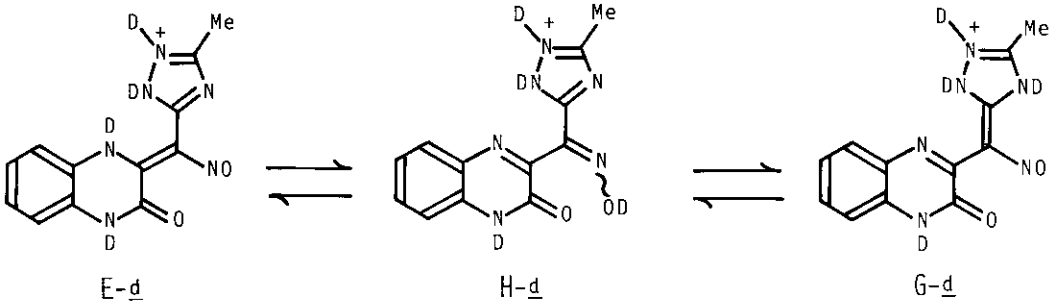
E-d H-d G-d

SCHEME 14 Tautomeric Equilibria of 16a in TFA-d_1
(Tautomers in Medium — Two of E-d, G-d, H-d)



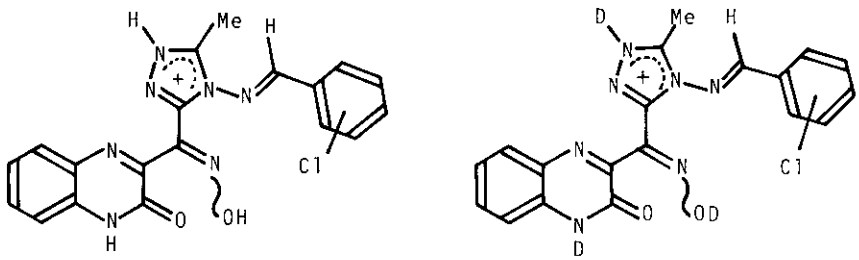
E H G

SCHEME 15 Tautomeric Equilibria of 16b in TFA
(Tautomers in Medium — Two of E, G, H)



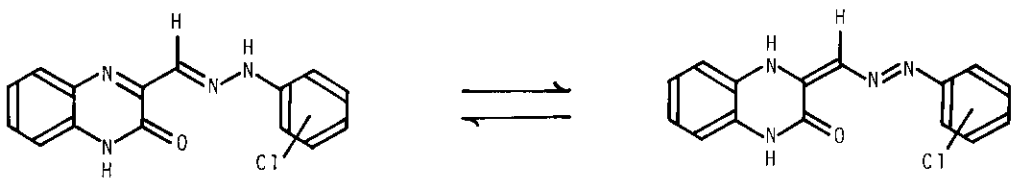
E-d H-d G-d

SCHEME 16 Tautomeric Equilibria of 16b in TFA-$\underline{d}_1$
(Tautomers in Medium — Two of E-$\underline{d}$, G-$\underline{d}$, H-$\underline{d}$)



H H-d

CHART 15 Species of 16c,d in TFA and TFA-$\underline{d}_1$



C D

17 a, $\underline{o}$-Cl
b, $\underline{m}$-Cl
c, $\underline{p}$-Cl

SCHEME 17 Tautomeric Equilibria of 17a-c in DMSO-$\underline{d}_6$

17a in DMSO-d_6 represented the hydrazone CH and hydrazone NH proton signals (Table 9), supporting the predominance of the tautomer C (Scheme 17).[23,24] However, the

Table 9. PMR Spectral Data for 17a-c in DMSO-d_6

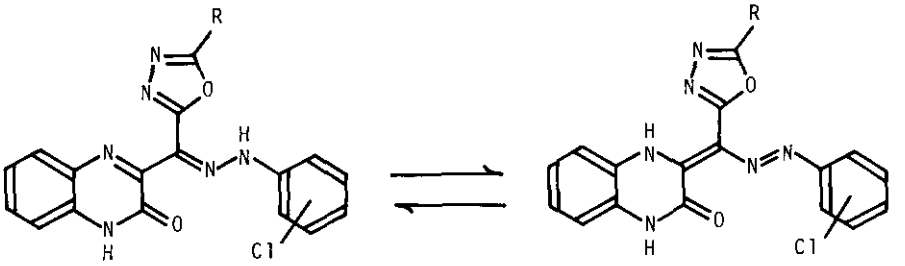
Compound	Tautomer Ratio C	D	Chemical Shift (δ ppm)	
17a	100	—	14.75 (s, 1H, =N-NH-)[a]	7.87 (s, 1H, -CH=N-N-)[a]
17b	67	33	14.45 (s, 2/3 H, =N-NH-)[a]	7.78 (s, 2/3 H, -CH=N-N-)[a]
			11.33 (s, 1/3 H, N_4-H)[b]	8.40 (s, 1/3 H, =CH-N=N-)[b]
17c	67	33	14.53 (s, 2/3 H, =N-NH-)[a]	7.73 (s, 2/3 H, -CH=N-N-)[a]
			11.26 (s, 1/3 H, N_4-H)[b]	8.37 (s, 1/3 H, =CH-N=N-)[b]

a) Signals due to the tautomer C
b) Signals due to the tautomer D

spectra of 17b,c in DMSO-d_6 exhibited the hydrazone CH and hydrazone NH proton signals due to the tautomer C together with the vinyl CH and N_4-H proton signals due to the tautomer D. The tautomer ratios of the C form versus the D form were 67:33 in both 17b and 17c.

2. 3-(α-CHLOROPHENYLHYDRAZONO)OXADIAZOLYLMETHYL-2-OXO-1,2-DIHYDROQUINOXALINES

The PMR spectral data of 3-(α-chlorophenylhydrazono)oxadiazolylmethyl-2-oxo-1,2-dihydroquinoxalines 18a-d in DMSO-d_6 also indicated the tautomeric equilibria between the C and D forms (Table 10, Scheme 18).[22,24] That is, the spectra of 18a,b in DMSO-d_6 showed the hydrazone NH and N_4-H proton signals together with the respective two C_2,-H proton signals. The spectra of 18c,d in DMSO-d_6 represented the hydrazone NH and N_4-H proton signals together with the respective single C_2,-Me proton signals. On the other hand, the ^{13}C-NMR spectra of 18c in DMSO-d_6 exhibited the



C D

18 a, R=H (o-Cl)
b, R=H (p-Cl)
c, R=Me (o-Cl)
d, R=Me (p-Cl)

SCHEME 18 Tautomeric Equilibria of 18a-d in DMSO-d_6

Table 10. PMR Spectral Data for 18a-d in DMSO-d_6

Compound	Tautomer Ratio C	D	Chemical Shift (δ ppm)	
18a	2	1	14.35 (s, 2/3 H, =N-NH-)[a]	9.30 (s, 2/3 H, C_2,-H)[a]
			12.45 (s, 1/3 H, N_4-H)[b]	9.47 (s, 1/3 H, C_2,-H)[b]
18b	5	1	11.45 (s, 5/6 H, =N-NH-)[a]	9.27 (s, 5/6 H, C_2,-H)[a]
			11.97 (s, 1/6 H, N_4-H)[b]	9.42 (s, 1/6 H, C_2,-H)[b]
18c	1	1	14.22 (s, 1/2 H, =N-NH-)[a]	2.57 (s, 3H, C_2,-Me)
			12.42 (s, 1/2 H, N_4-H)[b]	
18d	4	1	11.18 (s, 4/5 H, =N-NH-)[a]	2.59 (s, 3H, C_2,-Me)
			11.95 (s, 1/5 H, N_4-H)[b]	

a) Signals due to the tautomer C
b) Signals due to the tautomer D

thirty-six carbon signals due to the tautomer C (eighteen carbons) and the tautomer D (eighteen carbons), wherein the C_2,-Me carbon signals were observed at δ 10.67 and 10.48 ppm. The ^{13}C-NMR spectra of 18d in DMSO-d_6 showed the thirty-two carbon signals due to the tautomer C (eighteen carbons) and the tautomer D (eighteen carbons), wherein the C_2,-Me carbon signals were observed at δ 10.71 and 10.50 ppm. The ratios of the tautomer C were larger than those of the tautomer D in 18a,b,d.

3. 3-(α-CHLOROPHENYLHYDRAZONO)METHOXYCARBONYLMETHYL-2-OXO-1,2-DIHYDROQUINOXALINES

The PMR spectral data of 3-(α-chlorophenylhydrazono)methoxycarbonylmethyl-2-oxo-1,2-dihydroquinoxalines 19a-c in DMSO-d_6 were similar to those of 18a-d with respect to the chemical shifts of the hydrazone NH and N_4-H proton signals (Table 11), supporting the tautomeric equilibria between the C and D forms (Scheme 19).[24] The

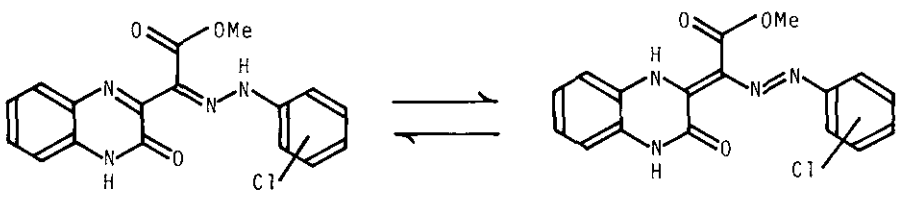
Table 11. PMR Spectral Data for 19a-c in DMSO-d_6

Compound	Tautomer Ratio C	D	Chemical Shift (δ ppm)	
19a	9	2	13.72 (s, 9/11 H, =N-NH-)[a]	3.83 (s, 3H, Me)
			12.53 (s, 2/11 H, N_4-H)[b]	
19b	10	1	11.15 (s, 10/11 H, =N-NH-)[a]	3.75 (s, 3H, Me)
			11.87 (s, 1/11 H, N_4-H)[b]	
19c	8	1	11.17 (s, 8/9 H, =N-NH-)[a]	3.73 (s, 3H, Me)
			11.90 (s, 1/9 H, N_4-H)[b]	

a) Signals due to the tautomer C
b) Signals due to the tautomer D

methyl proton signals due to the tautomers C and D coalesced at δ 3.83, 3.75, and 3.73 ppm in 19a-c, respectively. On the other hand, the ^{13}C-NMR spectra of 19a,b

in DMSO-$\underline{d}_6$ exhibited the thirty and thirty-two carbon signals, respectively, due to the tautomers C and D (total thirty-four carbons). The ester-Me carbon signals due to the tautomers C and D were observed at δ 52.50 and 52.31 ppm in 19a, while they coalesced at δ 52.16 ppm in 19b.



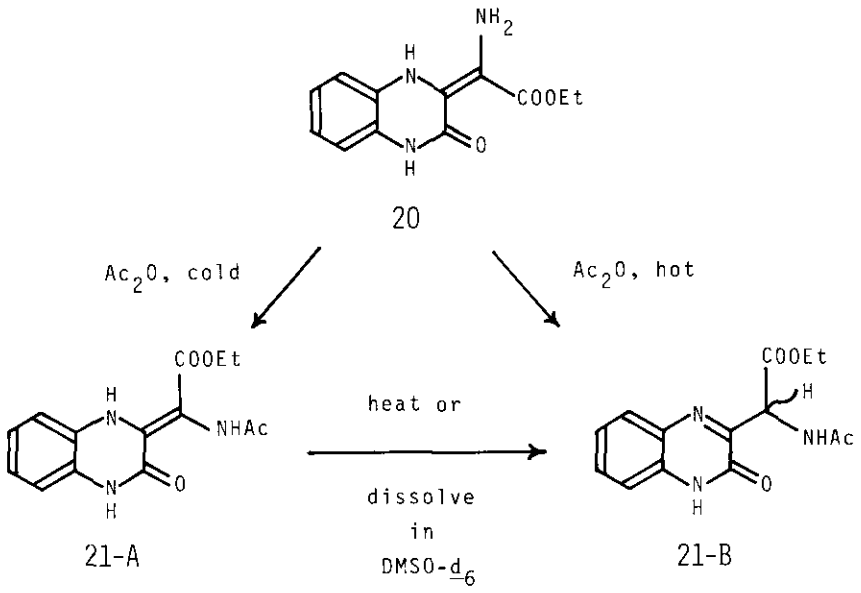
19 a, o-Cl
b, m-Cl
c, p-Cl

SCHEME 19 Tautomeric Equilibria of 19a-c in DMSO-$\underline{d}_6$

IV. ISOMERIZATION

1. 3-(α-ACETAMIDO)ETHOXYCARBONYLMETHYLENE-2-OXO-1,2,3,4-TETRAHYDROQUINOXALINE AND 3-(α-ACETAMIDO)ETHOXYCARBONYLMETHYL-2-OXO-1,2-DIHYDROQUINOXALINE

Chapman[25] studied the acetylation of 3-(α-amino)ethoxycarbonylmethylene-2-oxo-1,-2,3,4-tetrahydroquinoxaline 20 to clarify that 3-(α-acetamido)ethoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline 21-A (yellow crystals) was isolated by acetylation in the cold, and 3-(α-acetamido)ethoxycarbonylmethyl-2-oxo-1,2-dihydroquinoxaline 21-B (colorless crystals) was obtained by acetylation in the hot (Scheme 20). Moreover, the tautomer 21-A was elucidated to isomerize into the tautomer 21-B on dissolving in DMSO-$\underline{d}_6$. Accordingly, the PMR spectral data of 21-A and 21-B in DMSO-$\underline{d}_6$ were consistent with the structure of 21-B, and hence the structural differentiation of 21-A from 21-B was based on the IR spectral data and melting point measurements.



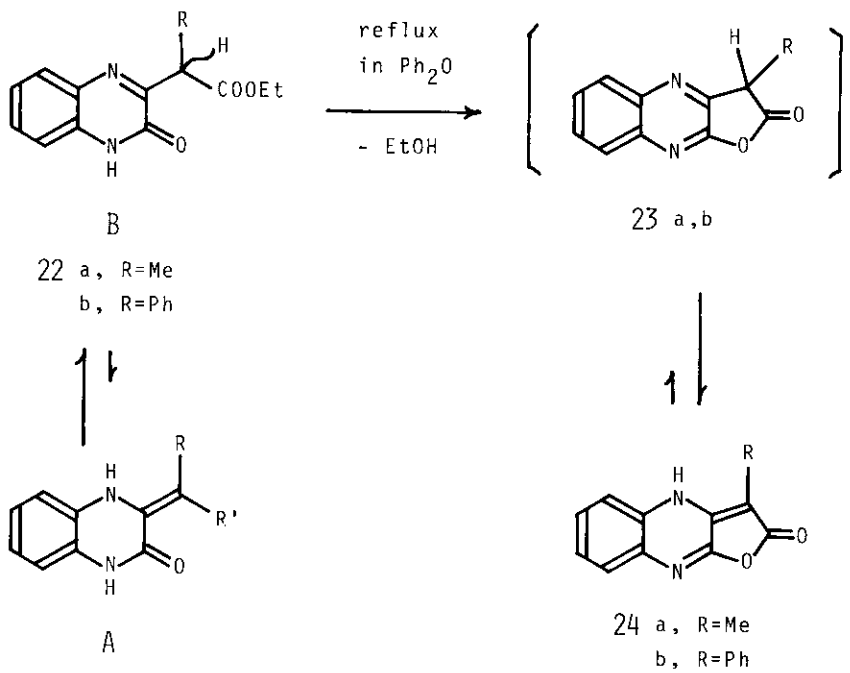
SCHEME 20

2. 2,4-DIHYDROFURO[2,3-b]QUINOXALIN-2-ONES

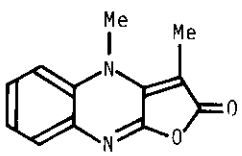
L'Italien et al.[32] and Chapman[11] reported that the 3-(α-substituted)ethoxycarbonylmethyl-2-oxo-1,2-dihydroquinoxalines 22a,b predominated as the tautomer B, but not the tautomer A, in solid and solution (Scheme 21). However, the intramolecular cyclizations of 22a,b in diphenyl ether would afford intermediary 2,3-dihydrofuro-[2,3-b]quinoxalin-2-ones 23a,b, which isomerized into the 2,4-dihydrofuro[2,3-b]-quinoxalin-2-ones 24a,b. The structural establishment of 24a,b was based on their PMR spectral data in DMSO-d_6 and the comparison of the UV spectral data of 24a with that of 24c (Chart 16) in ethanol.

3. 3-QUINOXALINYL-1,5-BENZODIAZEPINES

There have been reported many examples on the tautomerism of the fused 1,5-diazepin-



SCHEME 21



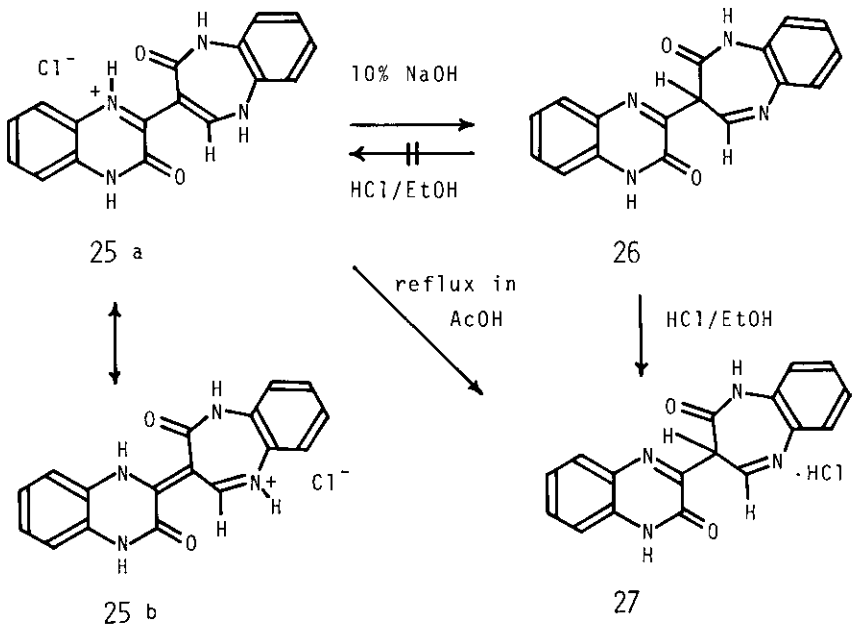
24 c

CHART 16

2-one ring system, wherein the most of compounds predominate as the C_3-H form rather than the N_5-H form (Scheme 22).[33]

C_3-H form $\quad$ N_5-H form

SCHEME 22



25 a $\quad$ 26

25 b $\quad$ 27

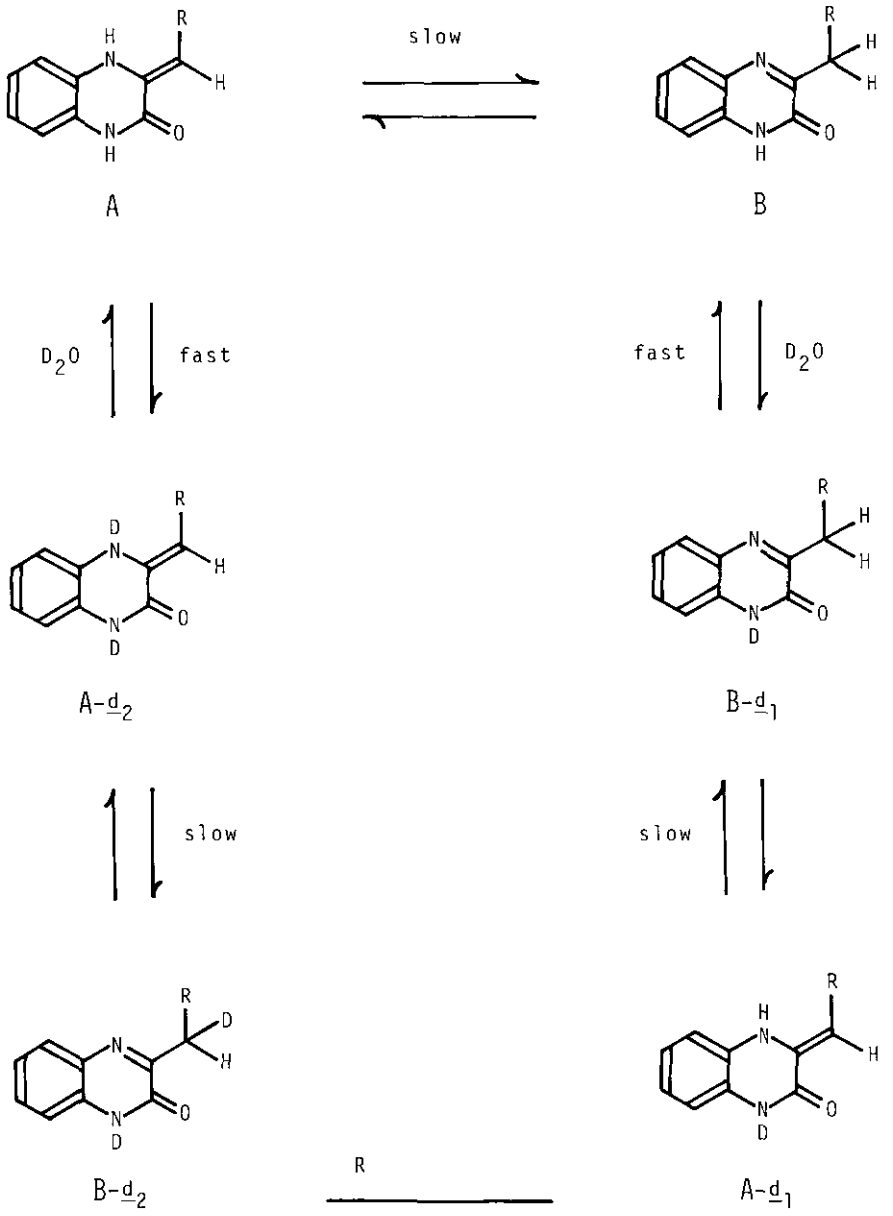
SCHEME 23

The reaction of 3-(N,N-dimethylcarbamoyl)furo[2,3-b]quinoxaline hydrochloride with o-phenylenediamine dihydrochloride provided the 3-quinoxalinyl-1,5-benzodiazepine hydrochloride 25a or its resonance isomer 25b, which was the N_5-H or $N_{1'}$-H form, respectively (Scheme 23).[26,27] Treatment of 25 with 10% NaOH resulted in isomerization to give the 3-quinoxalinyl-1,5-benzodiazepine 26, which was the C_3-H form. However, 26 (C_3-H form) did not isomerize into 25 (NH form) by treatment with HCl/-EtOH, but changed into the hydrochloride 27 (C_3-H form). The structural assignments of 25, 26, and 27 were based on the IR (KBr discs), PMR (in DMSO-d_6), and ^{13}C-NMR (in DMSO-d_6) spectral data as well as the mass spectral and microanalytical data. Thus, the NH and C_3-H isomers in the 1,5-benzodiazepin-2-one ring system were independently confirmed in the 3-quinoxalinyl-1,5-benzodiazepine hydrochlorides. However, the hydrochloride 25 (NH form) isomerized into the hydrochloride 27 (C_3-H form) under reflux in AcOH.

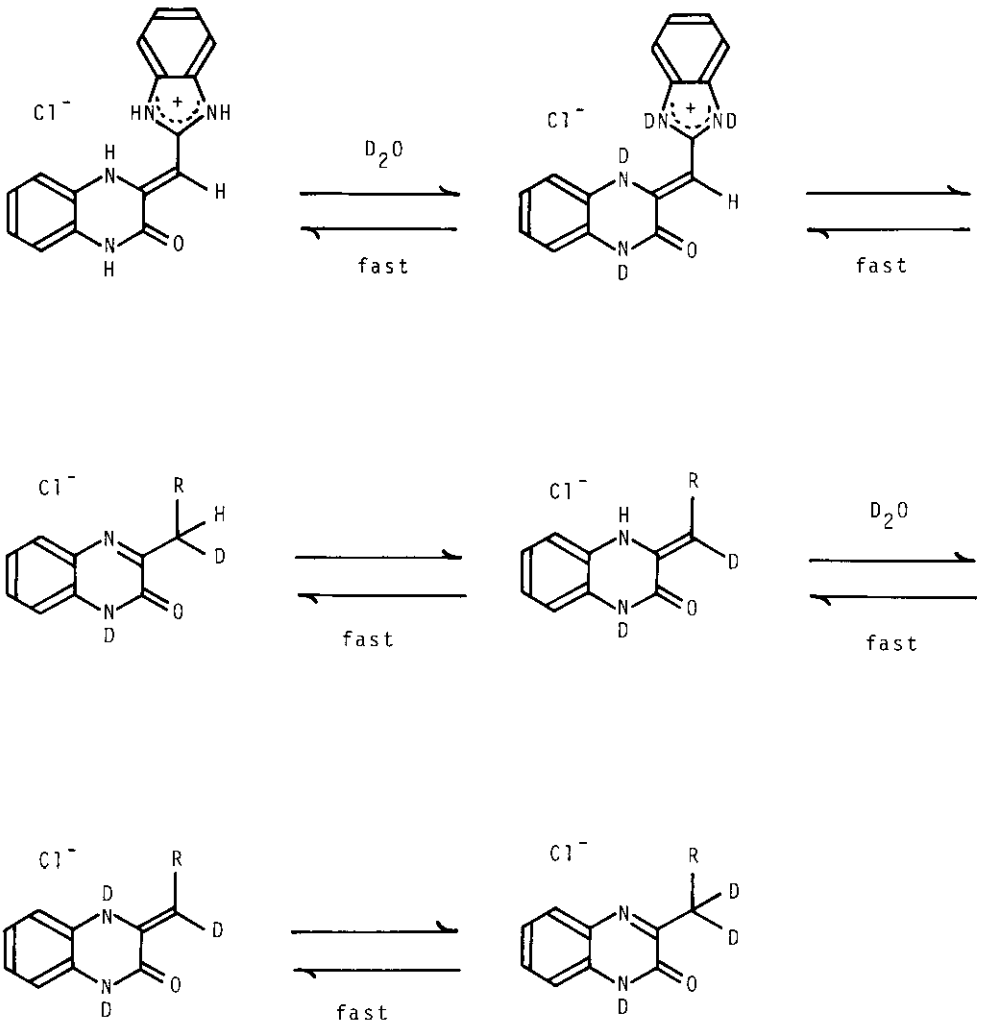
V. QUALITATIVE MECHANISTIC CONSIDERATION IN D-H EXCHANGE

When the PMR spectra of compounds 5a,b,6-10 were measured in DMSO-d_6/D_2O, the N_1- and N_4-H proton signals collapsed because of the D-H exchange, but the vinyl and methylene proton signals did not disappear. These results indicated the slow equilibria between the A and B forms (Scheme 24). Accordingly, there are few species A-d_1 and B-d_2, but the species A-d_2 and B-d_1 mainly remain in the medium.

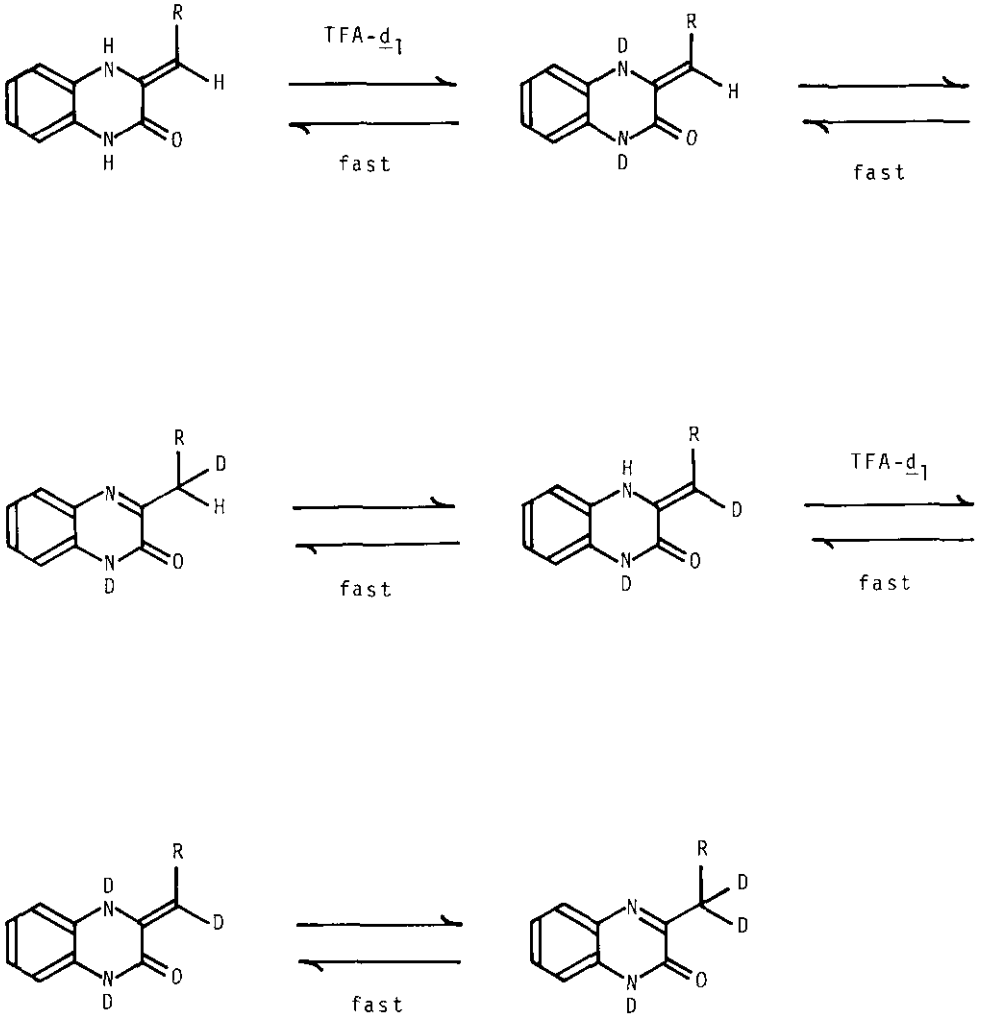
To the contrary, when the PMR spectrum of the hydrochloride 11 was measured in DMSO-d_6/D_2O, the vinyl and methylene proton signals disappeared as well as the N_1- and N_4-H proton signals, supporting the fast equilibria between the E and F forms (Scheme 25). The fast equilibria would be mediated or promoted by D^+Cl^- (or H^+Cl^-), but not halide anion, existing in the medium, since the presence of K^+Br^- did not effect the fast equilibria between the A and B forms.[34] The existence of the Brønsted acid seemed to act an important role for the above fast equilibria in consideration of the PMR spectral data of compounds 7-10 in TFA-d_1. The vinyl and methylene proton signals of these compounds rapidly disappeared in TFA-d_1, and hence the fast equilibria between the E and F forms were also suggested in these cases (Scheme 26).



SCHEME 24 Behaviors of 5a,b,6-10 in DMSO-$\underline{d}_6/D_2O$



SCHEME 25 Behavior of 11 in DMSO-$\underline{d}_6$/D_2O



R
oxadiazol-5-yl
triazol-5-yl
benzimidazol-2-yl

SCHEME 26 Behaviors of 7-10 in TFA-d_1

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