HETEROCYCLES, Vol. 41, No. 9, 1995

# TAUTOMERISM AND ISOMERISM OF HETEROCYCLES [2]

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**Abstract** - This review describes the tautomerism of various heterocyclic compounds between the enamine and methylene imine forms, between the enamine and enol imine forms, and between the azo and hydrazone forms together with the isomerism of some heterocycles.

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## I. Introduction

In a preceding review as the Part 1,[1] we introduced the tautomerism and isomerism of manifold heterocyclic compounds in solution or solid state. The present review as the Part 2 describes the tautomerism of diverse heterocyclic compounds between the enamine and methylene imine forms, between the enamine and enol imine forms, and between the azo and hydrazone forms along with the isomerism of several heterocycles.

## II. Tautomerism

### II-1. Tautomerism Between Enamine And Methylene Imine Forms

The tautomerism between the enamine **A** and methylene imine **B** (or azomethine **C**) forms (Scheme 1) has been reported since early 1960s for side-chained heterocyclic compounds including pyridines (1),[2,3] quinolines (2),[4-6] pyrazine (3),[7] pteridines (4),[8,9] and quinoxalines (5,6)[4,10,11] (Chart 1). A monograph[12] summarized the studies on the tautomerism of the above heterocyclic compounds reported in 1960-1973, and our review[10] introduced the papers on the tautomerism of quinoxalines published in 1966-1985. This review describes the various works, which are not involved in the above monograph and review.

Scheme 1

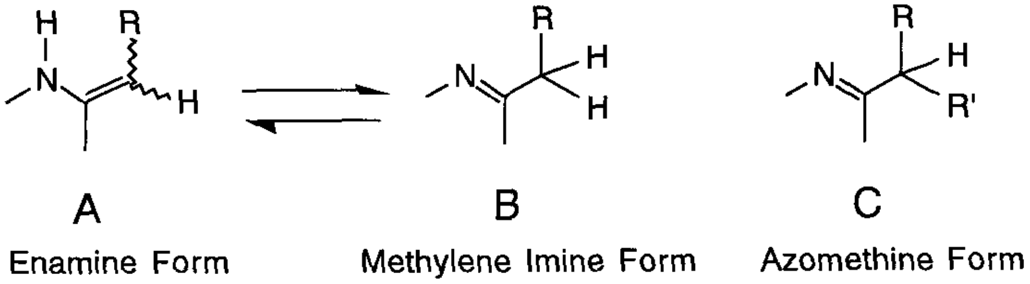
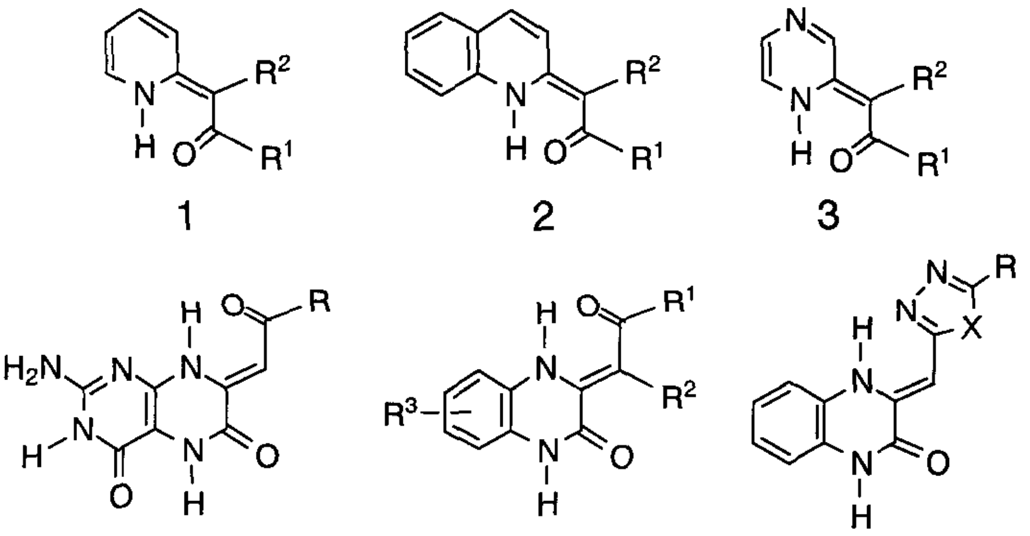


Chart 1



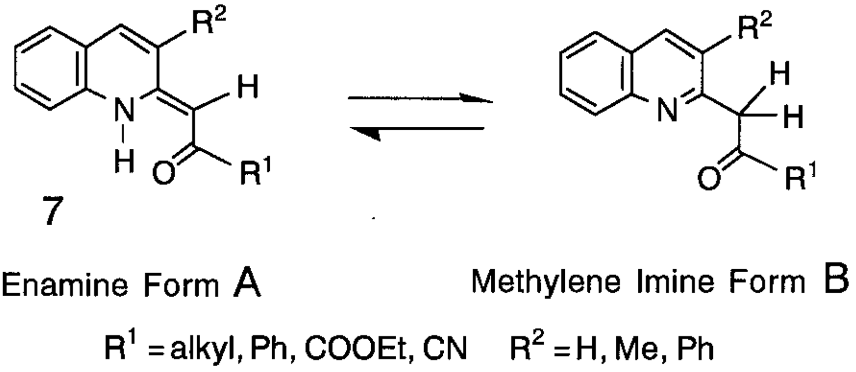
4 5

**6a** X = O, R = H, Me, SMe
**6b** X = NR', R = SMe

II-1-a. Quinolines

The quinaldyl ketones (7) (16 derivatives) coexisted as the enamine A and methylene imine B forms with a predominance of the A form, which was supported by the $^1$H-nmr spectral data in $CDCl_3$ or dioxane-$d_8$[13] (Scheme 2). In

Scheme 2



Scheme 3

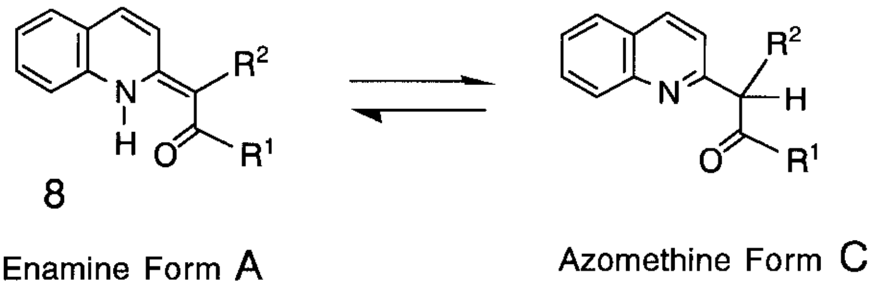


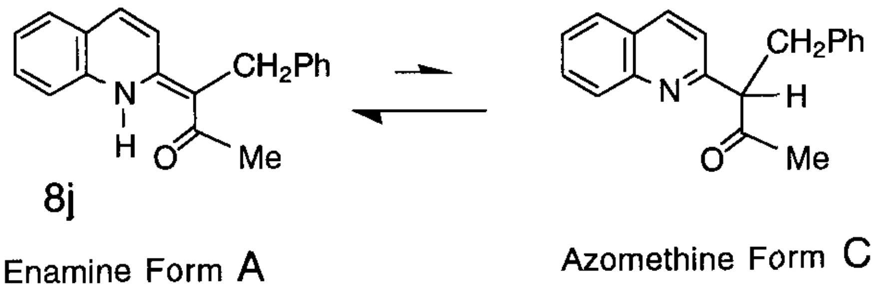
Table 1

| Compound | $R^1$ | $R^2$ | Tautomer Ratio A | Tautomer Ratio C |
|---|---|---|---|---|
| **8a** | Me | CN | 100 | 0 |
| **8b** | $CH_2Cl$ | CN | 100 | 0 |
| **8c** | $CH_2I$ | CN | 100 | 0 |
| **8d** | Ph | CN | 100 | 0 |
| **8e** | Me | COOEt | 100 | 0 |
| **8f** | Ph | COOEt | 100 | 0 |
| **8g** | *t*-Bu | Me | 0 | 100 |
| **8h** | Ph | Me | 0 | 100 |
| **8i** | Ph | $CH_2Ph$ | 0 | 100 |
| **8j** | Me | $CH_2Ph$ | 100 | 0 |

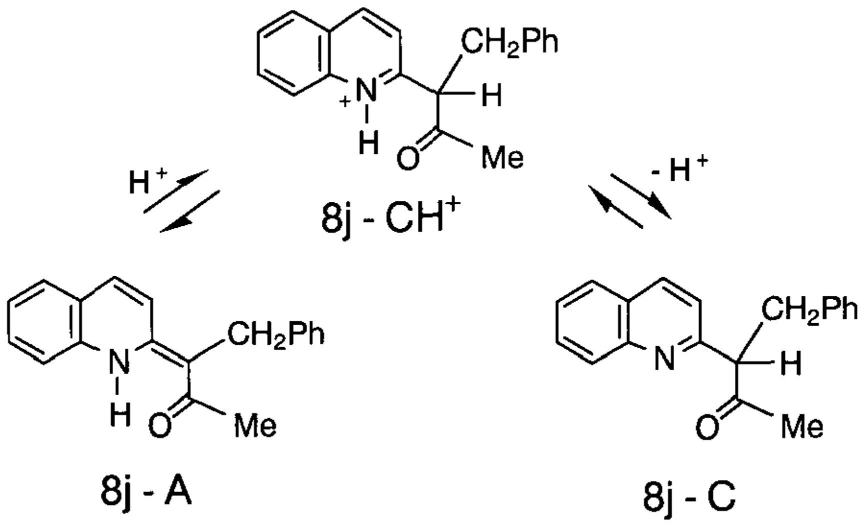
the α-substituted quinaldyl ketones (**8**), the tautomer ratios of the enamine form A to the azomethine form C depended on the kind of the substituents[13,14]

(Scheme 3, Table 1). When $R^2$ is a strong electron-withdrawing group, compounds occurred as the enamine form A (**8a-f**) in $CDCl_3$. To the contrary, when $R^2$ is alkyl and $R^1$ is phenyl or alkyl, compounds existed as the azomethine form C (**8g-i**) in $CDCl_3$. In contrast to the result of compound (**8i**), the quinaldyl ketone (**8j**) surprisingly occurred as the enamine form A, but not as the azomethine form C, in $CDCl_3$[15] (Scheme 4). When a trace of acid is present in the solution, compound (**8j**) equilibrates between the A and C forms in a ratio of 60 to 40, presumably *via* a protonated intermediate (**8j**-$CH^+$) (Scheme 5).

## Scheme 4

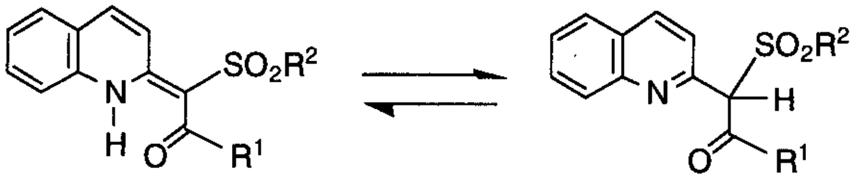


## Scheme 5



The quinaldyl disulfones (**9a,b**) existed as the azomethine form C in DMSO-$d_6$, and compounds (**9e,f**) having an excellent electron-withdrawing group (CN, keto) occurred as the enamine form A in $CDCl_3$[16] (Schemes 6,7, Table 2). In compounds

Scheme 6



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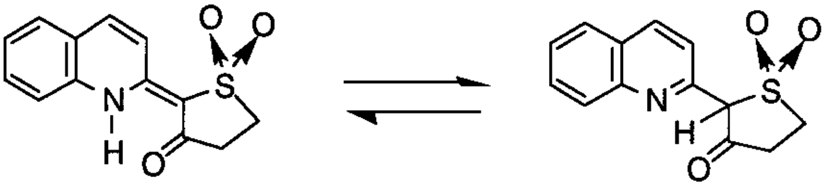
Enamine Form A

Azomethine Form C

Scheme 7



9f

Enamine Form A

Azomethine Form C

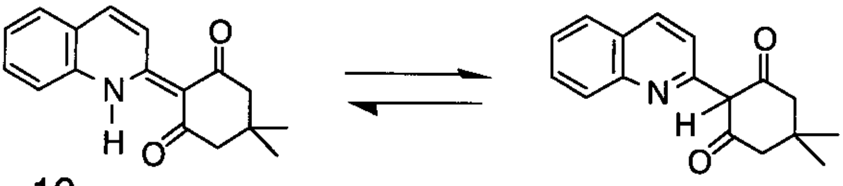
Table 2

| Compound | $R^1$ | $R^2$ | Solvent | Tautomer Ratio A | Tautomer Ratio C |
|---|---|---|---|---|---|
| **9a** | $SO_2Me$ | Me | DMSO-$d_6$ | 0 | 100 |
| **9b** | $SO_2Ph$ | Ph | DMSO-$d_6$ | 0 | 100 |
| **9c** | COOEt | Me | $CDCl_3$ | 0 | 100 |
| **9d** | COOMe | Ph | $CDCl_3$ | 35 | 65 |
| **9e** | CN | Me | $CDCl_3$ | 100 | 0 |
| **9f** | --- | --- | $CDCl_3$ | 100 | 0 |

(9c,d) possessing the ester group, the azomethine form C predominated over the enamine form A in $CDCl_3$. The methine proton signals were observed at δ 5.38-5.66 ppm.

The quinoline (10) coexisted as the enamine A (80%) and azomethine C (20%) forms in $CDCl_3$[17] (Scheme 8).

Scheme 8



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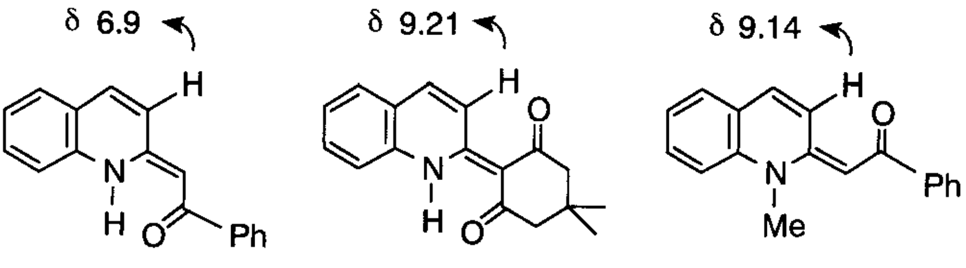
Enamine Form A

Azomethine Form C

The enamine form A of the quinaldyl ketone (7a) occurred in the *cis-s-cis* conformation, while the *N*-methyl derivative (11) existed in the *trans-s-cis* conformation, which was supported by the $^1$H-nmr spectral data for the $C_3$-H proton signals of compounds (7a, 10, and 11) in $CDCl_3$[18,19] (Chart 2). The anisotropy due to the C=O group is eminent in compounds (10) and (11).

Chart 2



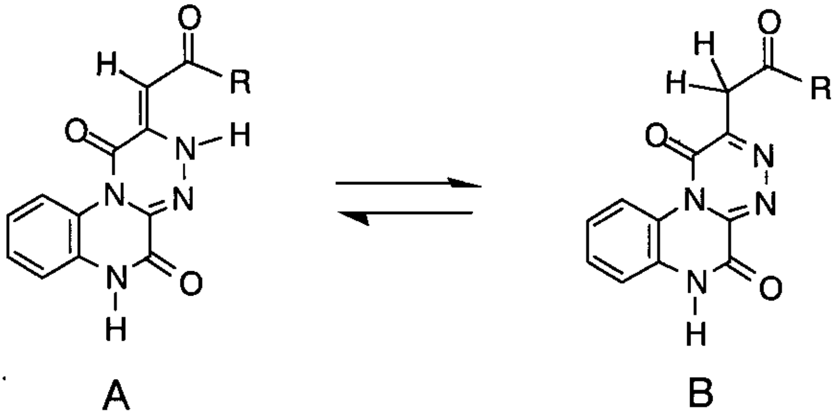
7a 10 11

Besides the above investigations, there have been some theoretical studies dealing with the tautomeric equilibrium constants $K_T$,[18,20,21] p*Ka* values,[18,20] and some other factors.[21]

### II-1-b. 1,2,4-Triazino[4,3-*a*]quinoxalin-5-ones

The tautomeric structure of the 1,2,4-triazino[4,3-*a*]quinoxalin-5-ones (**12**) was clarified to be solvent dependent from the $^1$H-nmr and ir spectral data. Compounds (**12a,b**) occurred as the enamine form A in DMSO-$d_6$, while compounds (**12a,b**) existed as the methylene imine form B in nujol [ir ν (C = O) 1715, 1680 (**12a**), 1712, 1680 (**12b**)][22] (Scheme 9).

Scheme 9



**12a** R = Ph, **12b** R = $C_6H_4$-*p*-OMe

### II-1-c. 1,2,4-Triazolo[4,3-*a*]quinoxalines And Tetrazolo[1,5-*a*]quinoxalines

The $^1$H-nmr spectral data of the 1,2,4-triazolo[4,3-*a*]quinoxaline (**13**) and tetrazolo[1,5-*a*]quinoxaline (**14a**) in DMSO-$d_6$ or TFA exhibited the tautomeric equilibria among the enamine A, methylene imine B, and enamine A' forms[23] (Scheme 10, Table 3). The A' form was supported by the NOE between the $N_5$-H and vinyl proton signals, but the ratio of A to A' could not be obtained.

Scheme 10

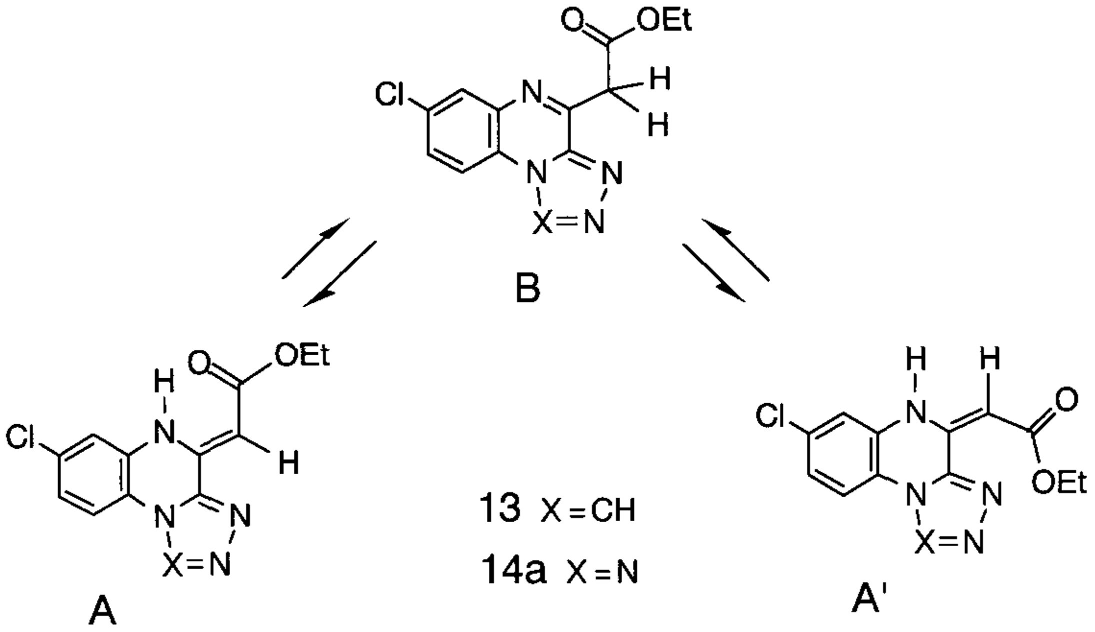


Table 3

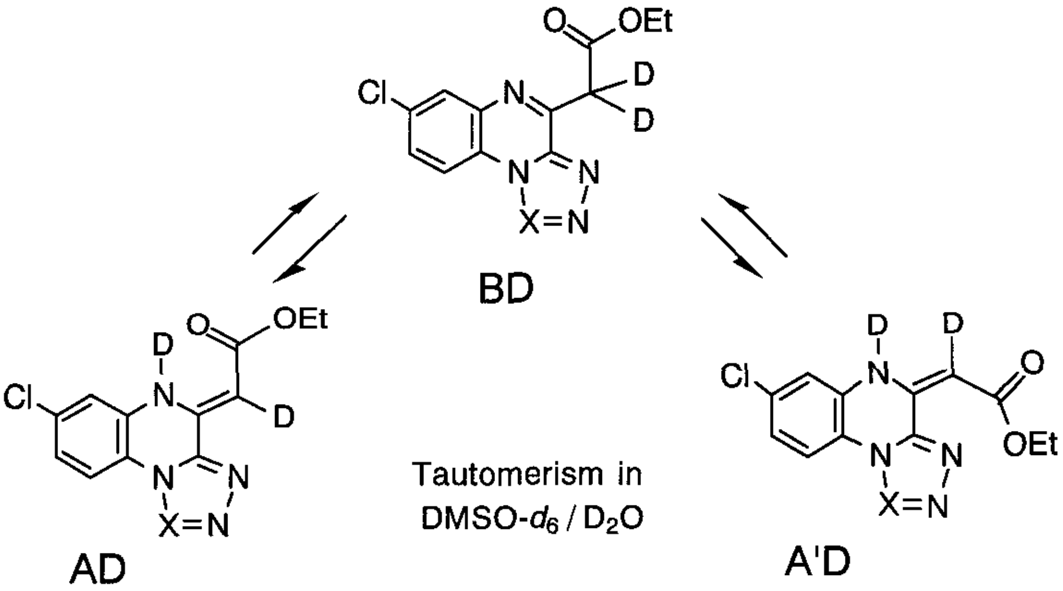
| Compound | Solvent | Tautomer Ratio A[a] | B |
|---|---|---|---|
| **13** | DMSO-$d_6$ | 89 | 11 |
| | D-T (1:4)[b] | 80 | 20 |
| | TFA-$d_1$ | 67 | 33 |
| **14a** | DMSO-$d_6$ | 91 | 9 |
| | D-T (1:4)[b] | 67 | 33 |
| | TFA-$d_1$ | 50 | 50 |

a - Ratio including the **A'** form
b - DMSO-$d_6$/TFA (1:4)

Moreover, the NH, vinyl, and methylene protons of compounds (**13**) and (**14a**) were deuterized in DMSO-$d_6$/$D_2O$ (Scheme 11). The formation of the species AD and BD would be due to an electron-donating nature of the $N_{10}$ atom as shown in

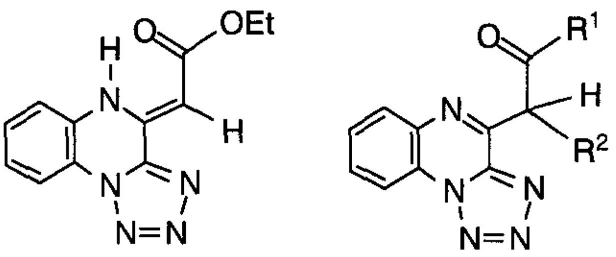
Scheme 12. This mechanism may be supported by the results displayed in Scheme 13, wherein only NH protons are deuterized in DMSO-$d_6$/$D_2O$.[4,10,11]

Scheme 11



The tautomers of the tetrazolo[1,5-*a*]quinoxalines (**14b-e**) (Chart 3) were clarified as shown in Table 4.[24]

Chart 3



**14b**

**14c** $R^1$ = OEt, $R^2$ = Ph
**14d** $R^1$ = OEt, $R^2$ = Me
**14e** $R^1$ = $NHCH_2CH_2OH$, $R^2$ = H

## Scheme 12

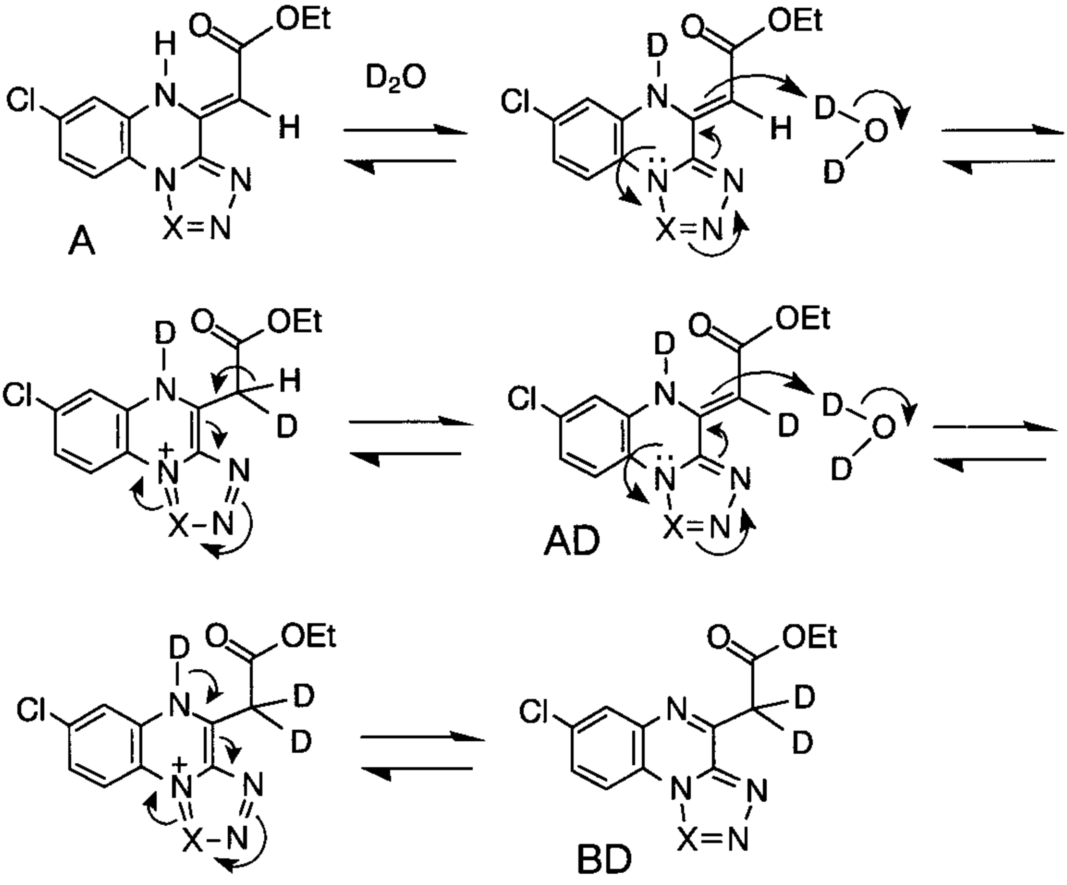
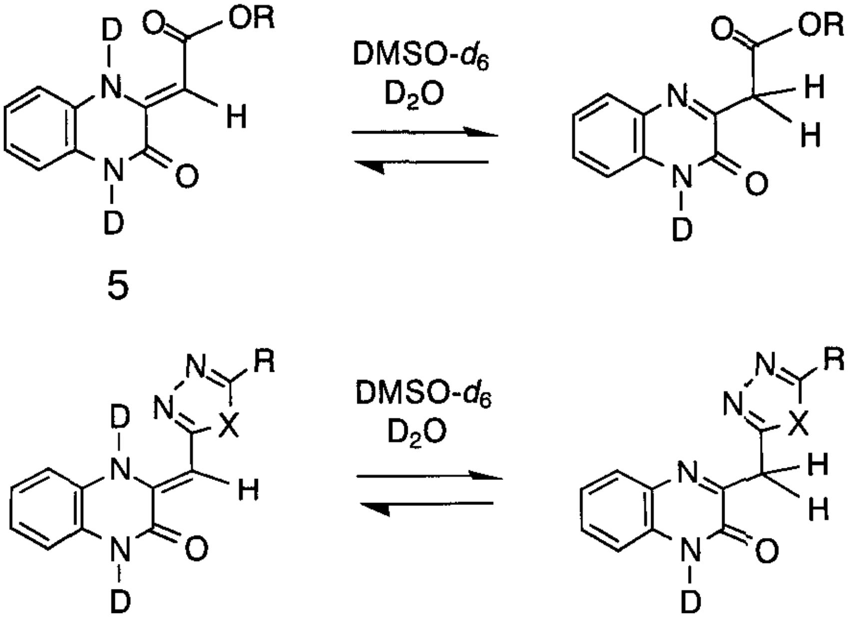


Table 4

| Compound | Tautomer | Spectroscopy |
|---|---|---|
| **14b** | A[a] | $^1$H-nmr |
| **14c** | C | ir |
| **14d** | C | ir |
| **14e** | B | ir |

a - **A** (90%)

Scheme 13

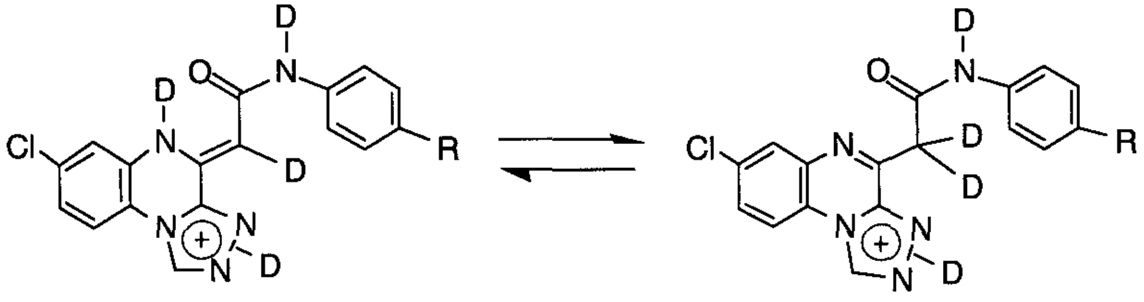


**5**

**6a** X = O, R = H, Me, SMe
**6b** X = NR', R = SMe

The 4-carbamoylmethylene-1,2,4-triazolo[4,3-*a*]quinoxalines (**15a,b**) and 4-carbamoylmethylenetetrazolo[1,5-*a*]quinoxalines (**16a-c**) coexisted as the AD$^+$ and

Scheme 14



AD$^+$ BD$^+$

**15a** R = Me, **15b** R = OD

BD$^+$ forms in TFA-$d_1$[25] (Schemes 14,15, Tables 5,6). The data of Table 6 indicate that the tautomer ratios of AD$^+$ to BD$^+$ depend on the p*Ka* of the parent amines in the side chain carbamoyl moiety.

Scheme 15

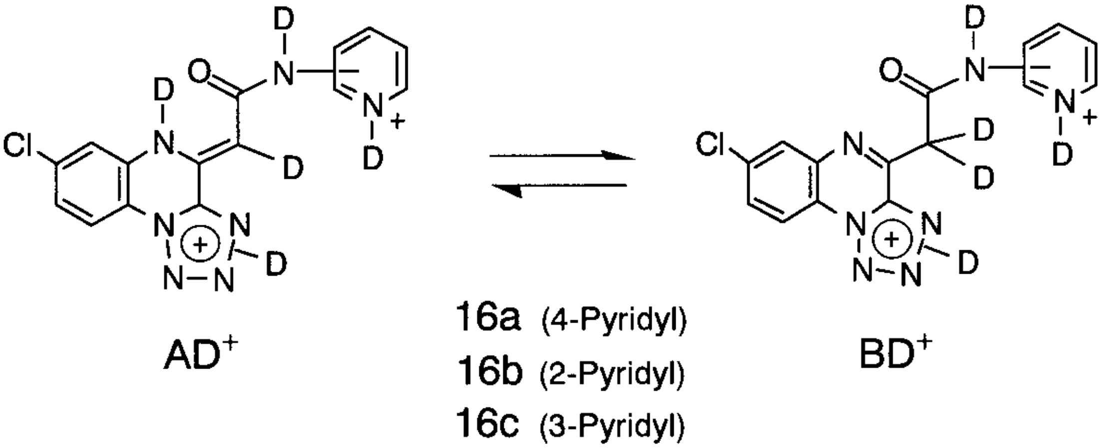


Table 5

| Compound | Tautomer Ratio AD$^+$ | Tautomer Ratio BD$^+$ |
|---|---|---|
| **15a** | 79 | 21 |
| **15b** | 76 | 24 |

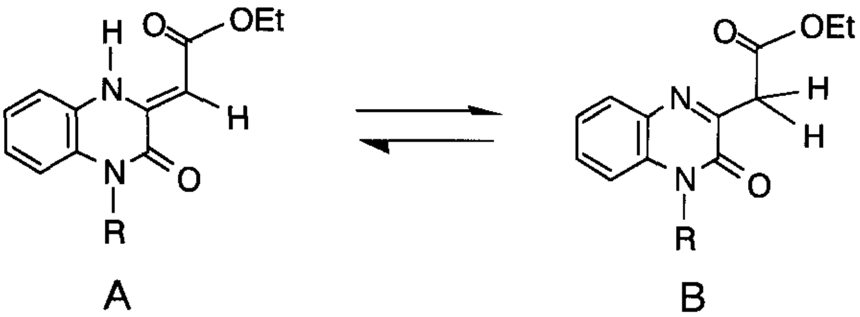
Table 6

| Compound | Tautomer Ratio AD$^+$ | Tautomer Ratio BD$^+$ | Parent Amine in Side Chain (p*Ka*) |
|---|---|---|---|
| **16a** | 100 | 0 | 4-Aminopyridine (9.17) |
| **16b** | 83 | 17 | 2-Aminopyridine (6.86) |
| **16c** | 68 | 32 | 3-Aminopyridine (5.98) |

### II-1-d. Quinoxalines

The tautomer ratios of the enamine form A to the methylene imine form B have been shown to depend on temperature or solvent from the nmr spectral data of the side-chained quinoxalines such as 5 and 6 (section II-1, Chart 1), which are measured in DMSO-$d_6$, TFA, or $CDCl_3$.[4,10] Moreover, there have been the theoretical studies concerning the solvent effects on the tautomeric equilibrium constants $K_T$ ([B]/[A]) catalyzed by acid or base in compound (5a)[26] (Scheme 16, Table 7) and concerning the determination of the $K_T$ and ΔH values by the $^1$H-nmr spectral data of compounds (5a,b).[27] The *p*- and *m*-substituted 3-aryl-

Scheme 16



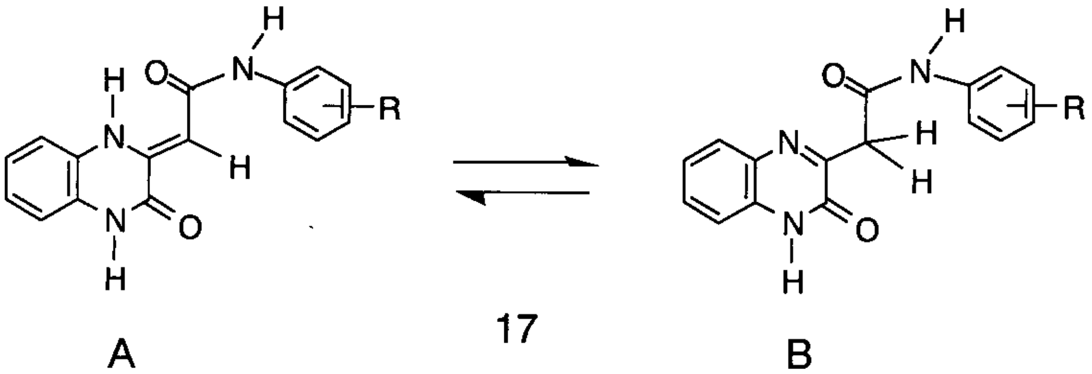
5a R = Me , 5b R = H

Table 7

| Solvent | Catalyst | $K_T$ ([B]/[A]) |
|---|---|---|
| MeOH | AcOH | 2.95 |
| | $NEt_3$ | 3.05 |
| $CHCl_3$ | AcOH | 1.3 |
| PhMe | AcOH | 0.4 |
| $C_6H_{12}$ | $NEt_3$ | 0.24 |

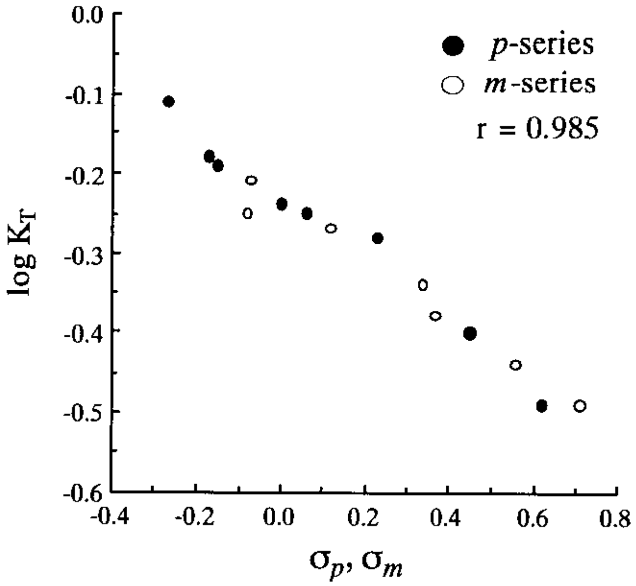
carbamoylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxalines (**17**) (Scheme 17) have recently been elaborated, and their tautomeric equilibrium constants $K_T$ ([B]/[A]) were obtained by the $^1$H-nmr spectral data in DMSO-$d_6$ or DMSO-$d_6$/TFA (2:1).[28] As the result, the log$K_T$ values were found to correlate with the Hammett $\sigma_p$ and $\sigma_m$ values in DMSO-$d_6$/TFA (2:1) (correlation coefficient r = 0.985) (Figure 1). The $\sigma_p$ and $\sigma_m$ values lie between +0.62 and -0.27 and between +0.71 and

Scheme 17



R : *p*- and *m*-Substituents

Figure 1

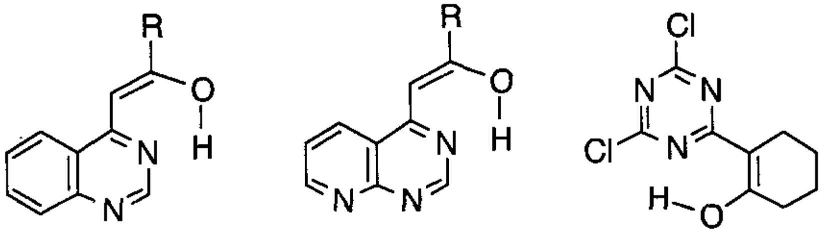


-0.08. These data indicated that the larger σ values effected a decrease in the $K_T$ ([B]/[A]) values, namely, an increase in the ratios of the tautomer A. These results mean that the smaller p*Ka* of a base in the side chain increases the ratio of the tautomer A in compounds (**17**), which opposes the results of compounds (**16a-c**) in TFA-$d_1$. This discrepancy would be due to the structural and/or functional difference between compounds (**17**) and (**16**), which was caused by the condensed tetrazole ring of compounds (**16**). The solvents were also different in both systems [**17** in TFA-$d_1$, **16** in DMSO-$d_6$/TFA (2:1)].

### II-2. Tautomerism Between Enamine And Enol Imine Forms

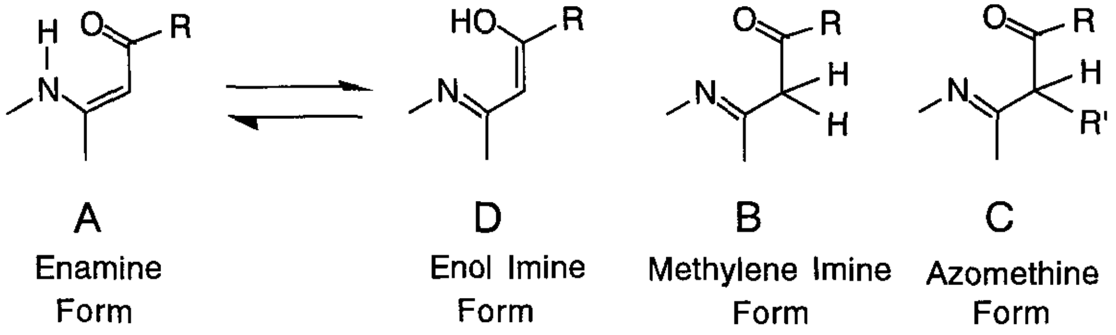
There have been several side-chained heterocycles (**18-20**) (Chart 4) exhibiting

Chart 4



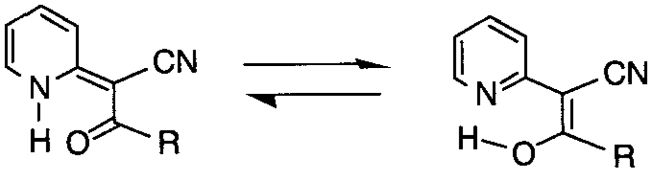
18 19 20

Scheme 18



the tautomerism between the enamine A and enol imine D forms, which do not involve the methylene imine B or azomethine C form[12,29-32] (Scheme 18). The quinazolines (18)[29] and pyrido[2,3-*d*]pyrimidines (19)[30] were found to occur as the enol imine form D from the ir (KBr), uv (in EtOH), and nmr (in $CDCl_3$) spectral data, and the 1,3,5-triazine (20) was also reported to predominate as the enol imine form D.[12,31] On the other hand, the pyridines (21) existed as the enol imine form D in $CDCl_3$ (nmr), $CHCl_3$ (ir), aqueous base (uv), but occurred as the enamine form A in aqueous acid (uv) and MeOH (uv) (Scheme 19).

Scheme 19



21

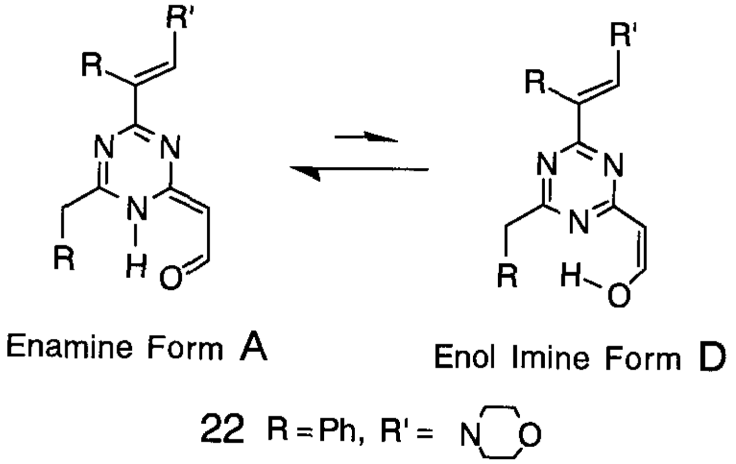
Enamine Form A

Enol Imine Form D

II-2-a. 1,3,5-Triazines

The $^1$H-nmr spectral data of the 1,3,5-triazines (22, 23, and 24a-f) in $CDCl_3$ revealed the existence as the enamine form A[33] (Schemes 20-22, Table 8), while the 1,3,5-triazine (25) occurred as the enol imine form D (Scheme 23). The X-ray crystal structure analysis for compound (24c) clarified the existence as the enamine form A, but not as the enol imine D and azomethine C (Chart 5) forms. The number of the enol or enamine units in the molecule exerted a great influence on the tautomerism.

## Scheme 20



## Scheme 21

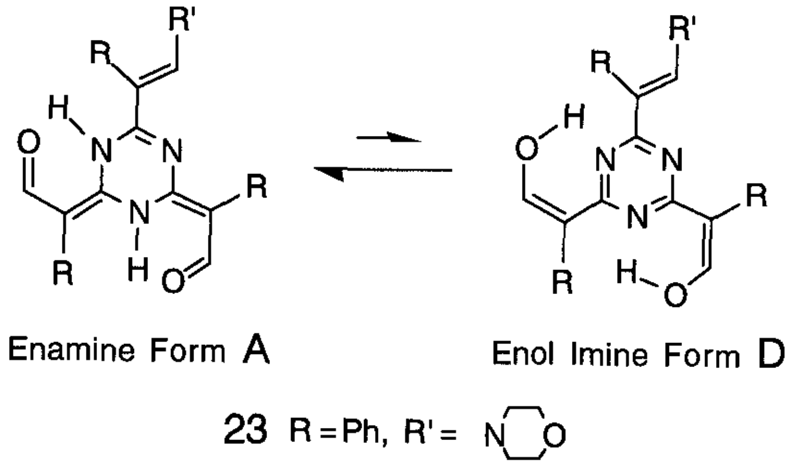
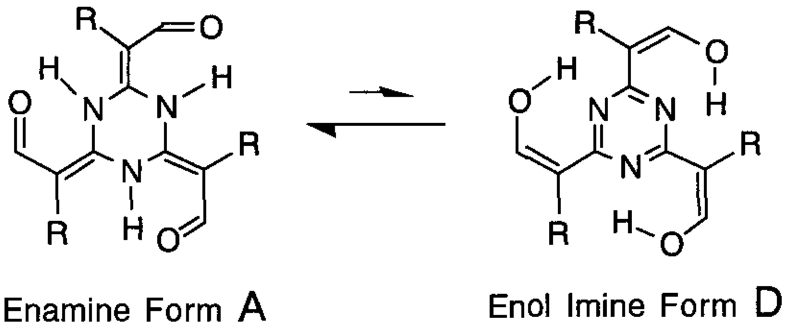


Table 8

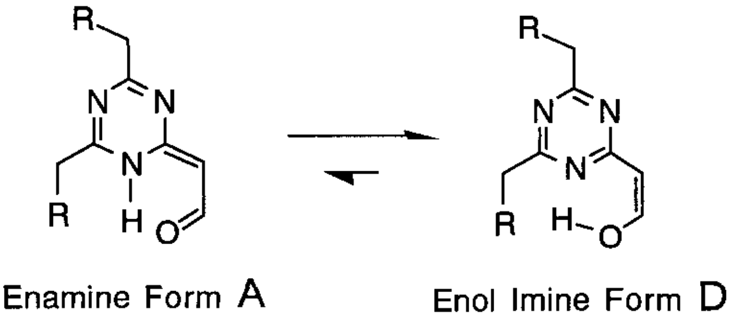
| | | Chemical Shift (δ ppm) in $CDCl_3$ | | | |
|---|---|---|---|---|---|
| | | Enamine Form A | | Enol Imine Form D | |
| Compound | Tautomer | CHO | NH | Vinyl | OH |
| 22 | A | 8.25 | 12.60 | --- | --- |
| 23 | A | 8.77 | 13.40 | --- | --- |
| | | 8.80 | 14.20 | --- | --- |
| 24a | A | 8.87 | 13.40 | --- | --- |
| 24b | A | 8.55 | 13.90 | --- | --- |
| 25 | D | --- | --- | 8.41 | 11.2 |

## Scheme 22



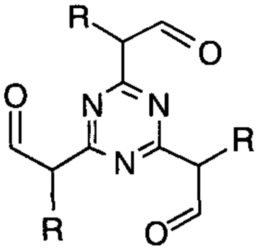
**24** R = Ph (a), Et (b), Me (c), *n*-Pr (d), $C_6H_4$-*p*-Cl (e), $C_6H_4$-*p*-OMe (f)

## Scheme 23



**25** R = Et

## Chart 5

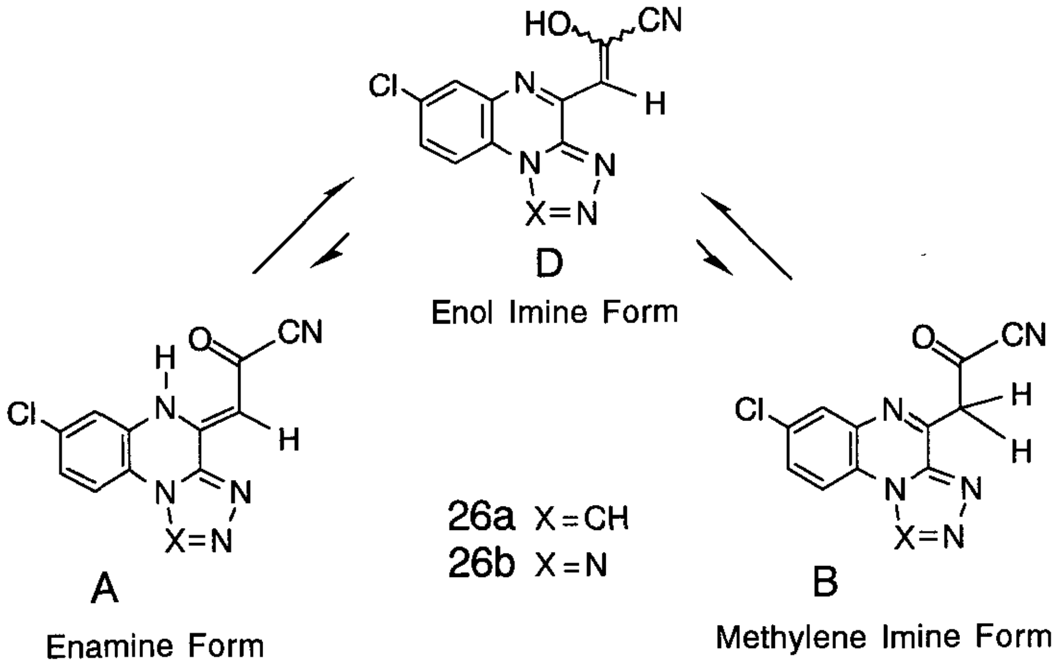


Azomethine Form C

### II-2-b. 1,2,4-Triazolo[4,3-*a*]quinoxaline And Tetrazolo[1,5-*a*]quinoxaline

The 1,2,4-triazolo[4,3-*a*]quinoxaline (**26a**) and tetrazolo[1,5-*a*]quinoxaline (**26b**) existed as the enol imine form D in DMSO-$d_6$[23] (Scheme 24). The enamine form A was denied from the $^{13}$C-nmr spectral data for the $C_4$, $C_{1'}$, and $C_{2'}$ carbons (Chart 6), and the methylene imine form B was excluded by the $^1$H-nmr spectral data.

Scheme 24



D
Enol Imine Form

A
Enamine Form

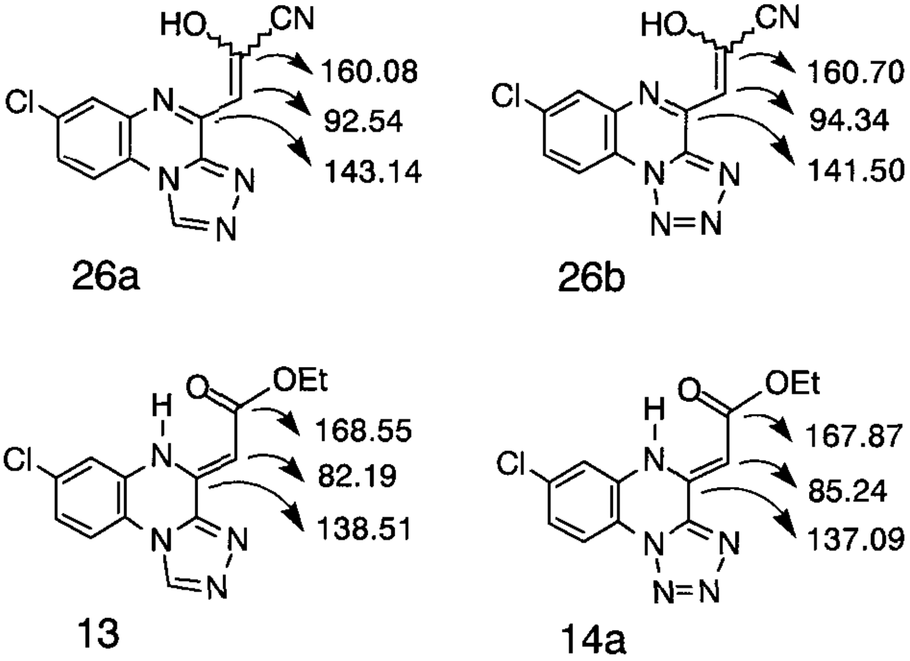
26a X=CH
26b X=N

B
Methylene Imine Form

### II-3. Tautomerism Between Azo And Hydrazone Forms

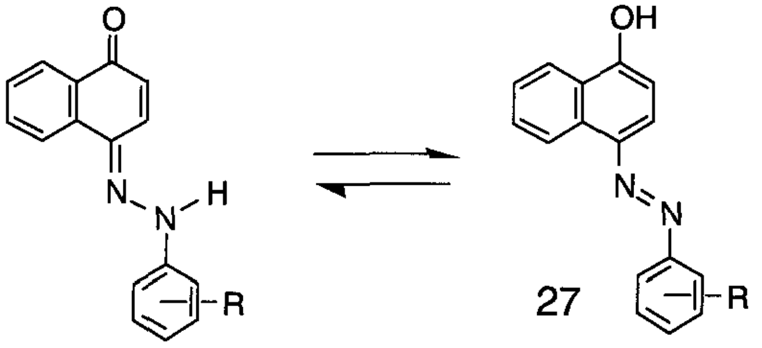
The tautomerism between the hydrazone A and azo B forms has been reported since early 1880s,[34] and the tautomeric characters of 4-arylazo-1-naphthol (27) (Scheme 25), 2-arylazo-1-naphthol (28), 1-arylazo-2-naphthol (29), 2-arylazo-3-naphthol (30) (Chart 7), and many other related compounds are summarized in monographs,[35] which introduce the extensive theoretical studies.

## Chart 6



Values in δ ppm

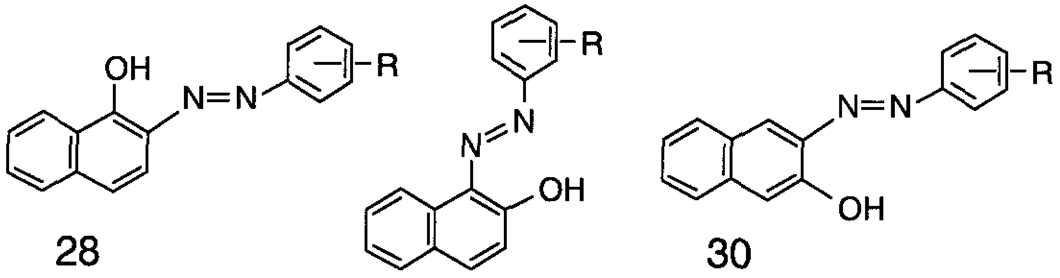
## Scheme 25



Hydrazone Form A

Azo Form B

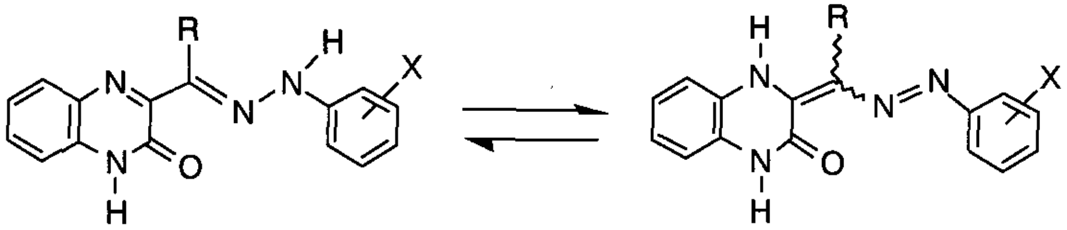
Chart 7



28 29 30

Concerning the heterocyclic compounds, our previous review described the tautomerism of quinoxalines (31) between the hydrazone imine A and diazenyl enamine B forms[10] (Scheme 26), and a monograph represented the tautomeric character of pyridine and pyrazole derivatives.[36] This review introduces some works published after the above monographs and review.

Scheme 26



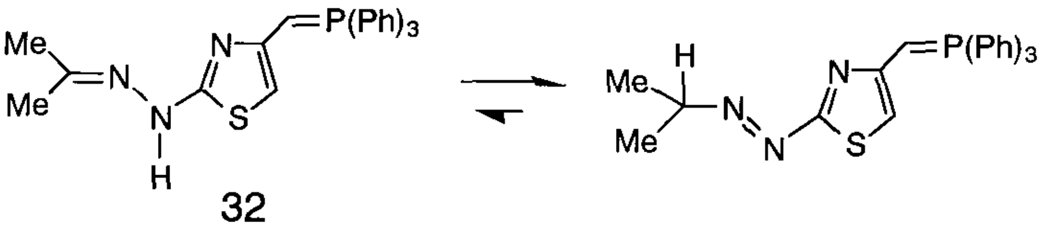
Hydrazone Imine Form **A** Diazenylenamine Form **B**

31 R = H, COOMe, X = *o*-, *m*-, *p*-Cl

II-3-a. Thiazole

The $^1$H-nmr spectral data of the 2-isopropylidenehydrazinylthiazole (32) manifested the occurrence as the azo form **B** in DMSO-$d_6$[37] (Scheme 27). This result is

Scheme 27



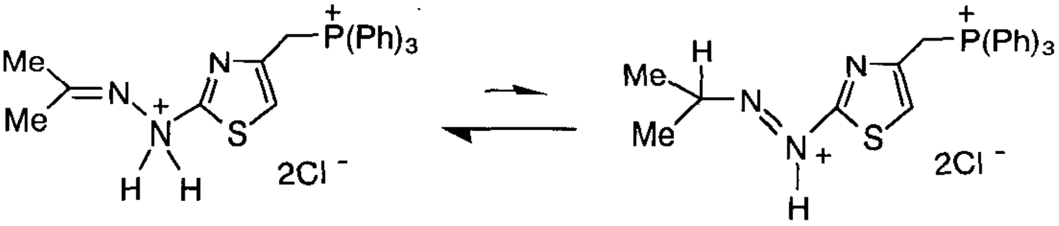
32

Hydrazone Form A

Azo Form B

consistent with the O'Connor's conclusion[38] that the freshly prepared phenylhydrazones of aliphatic ketones and aldehydes exist as the hydrazone form A, which rapidly tautomerizes into the azo form B. However, the dihydrochloride (32-H$^+$) favored the hydrazone form (32-AH$^+$) (Scheme 28).

Scheme 28



32-AH$^+$

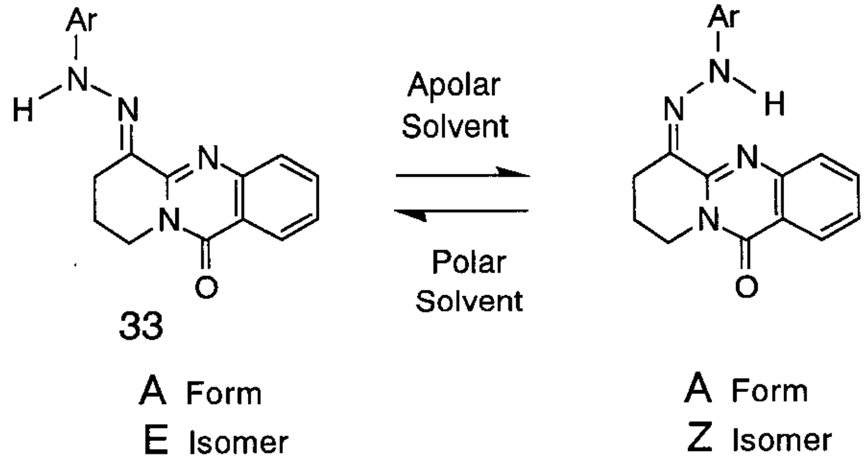
32-BH$^+$

II-3-b. Pyrido[2,1-*b*]quinazolines

The $^1$H- and $^{13}$C-nmr spectral data of the tetrahydropyrido[2,1-*b*]quinazolines (33) revealed the occurrence as the hydrazone imine form A, which was further found to predominate as the Z isomer in $CDCl_3$, but to prefer the E isomer in DMSO-$d_6$[39] (Scheme 29). In the octahydropyrido[2,1-*b*]quinazolines (34a-d), the

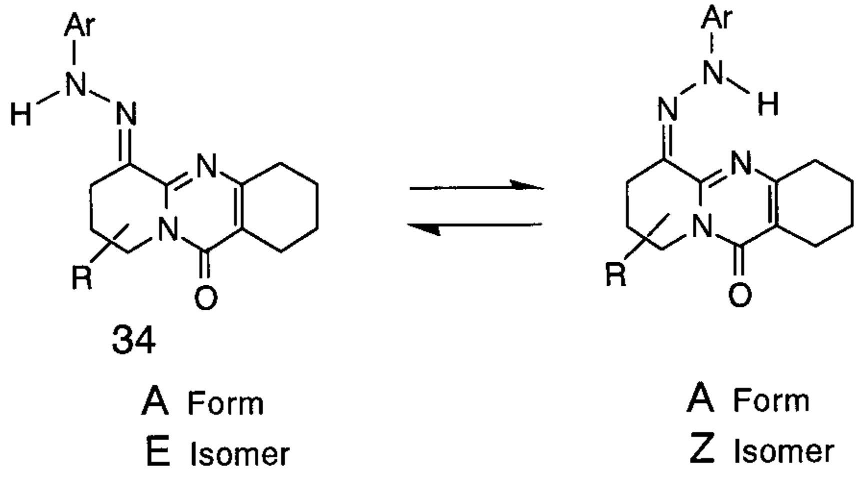
Z isomer was predominant in $CDCl_3$ and DMSO-$d_6$, and the ratio of the Z isomers were determined in $CDCl_3$ and DMSO-$d_6$[40] (Scheme 30, Table 9).

Scheme 29



33

Scheme 30



34

II-3-c. Quinoxalines

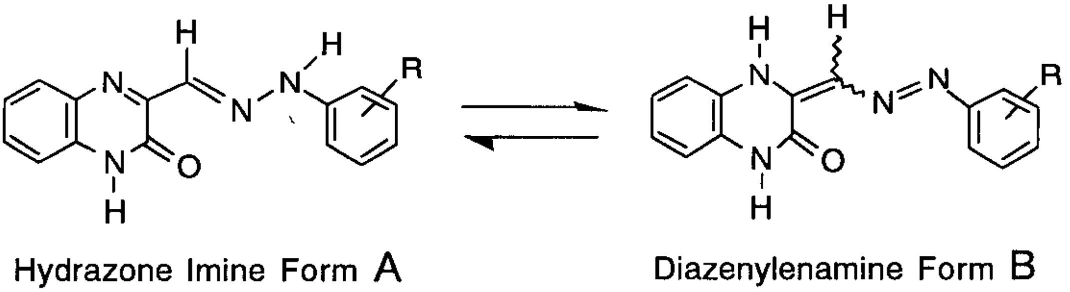
The *p*- and *m*-substituted 3-arylhydrazonomethyl-2-oxo-1,2-dihydroquinoxalines (35) coexisted as the hydrazone imine A and diazenylenamine B forms in

Table 9

| Compound | R | Ratio of Z Isomer in $CDCl_3$ | Ratio of Z Isomer in DMSO-$d_6$ |
|---|---|---|---|
| **34a** | H | 100 | 80 |
| **34b** | 9-Me | 95 | 70 |
| **34c** | 8-Me | 100 | 90 |
| **34d** | 7-Me | 100 | 100 |

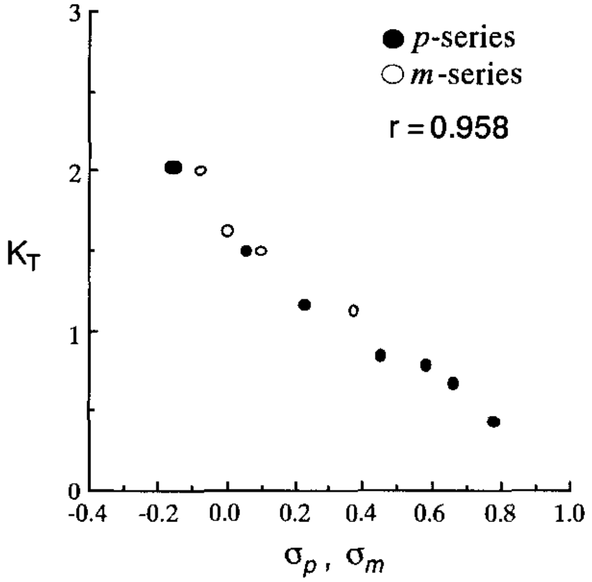
DMSO-$d_6$[41-43] (Scheme 31), wherein the *p*- and *m*-substituents excerted an influence on the tautomeric equilibrium constants. Namely, the Hammett $\sigma_p$ and $\sigma_m$ values were found to correlate with the tautomeric equilibrium constants $K_T$ ([A] /[B]) in DMSO-$d_6$ (correlation coefficient r = 0.958), wherein the $\sigma_p$ and $\sigma_m$ values were between +0.78 and -0.17 and between +0.37 and -0.08, respectively[42,43] (Figure 2). The larger Hammett $\sigma$ values (electron-withdrawing substituents) decreased the $K_T$ values, while the smaller Hammett $\sigma$ values (electron-donating substituents) increased the $K_T$ values. On the other hand, the tautomer ratios of A to B in compounds (**35**) fluctuated in TFA/DMSO-$d_6$.[43,44] The increase in the concentration of TFA increased the ratios of the B form, which exclusively

Scheme 31



**35** R = *p*- and *m*-Substituents

Figure 2



existed in TFA. As an example, the fluctuation curves of the *p*-H ($\sigma$ = 0) derivative is shown in Figure 3. The intersection of the fluctuation curves exhibits a TFA concentration giving a 1:1 tautomer ratio [C(A:B = 1:1)], which is observed in all compounds (35). The larger Hammett $\sigma$ values increased the C(A:B = 1:1) values, while the smaller $\sigma$ values decreased the C(A:B = 1:1) values. Thus, the Hammett $\sigma_p$ and $\sigma_m$ values were clarified to correlate with the log C(A:B = 1:1) values (correlation coefficient r = 0.984) (Figure 4). The Hammett $\sigma_p$ and $\sigma_m$ values lie between +0.78 and -0.15 and between +0.56 and 0, respectively.

The isomerization mechanism of compounds (35) between the tautomers A and B in DMSO-$d_6$ media and acidic media is summarized in Scheme 32. The tautomer A is predominant in DMSO-$d_6$ media of compounds with the smaller $\sigma$ values, and the protonation of the tautomer A gives the species $AH^+$. The electron-donating substituents increase the electron density of the side chain nitrogen atom, which promotes the isomerization of the species $AH^+$ into the resonance isomer $BH^+$. Subsequently, the C(A:B = 1:1) values are lower in

Figure 3

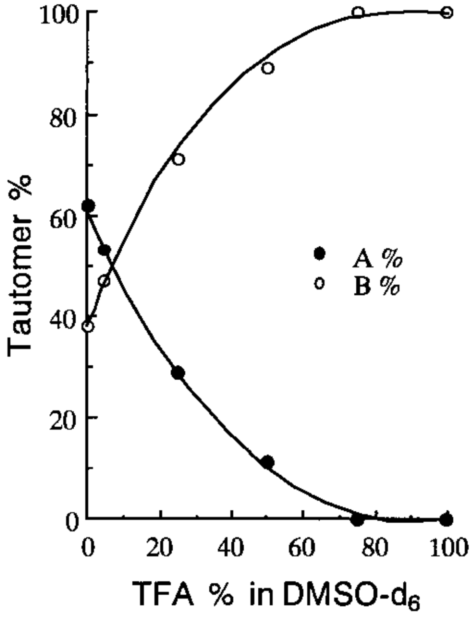
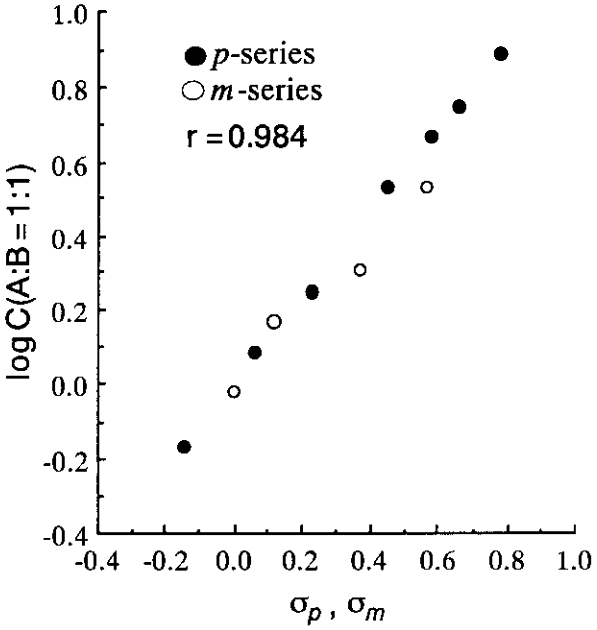
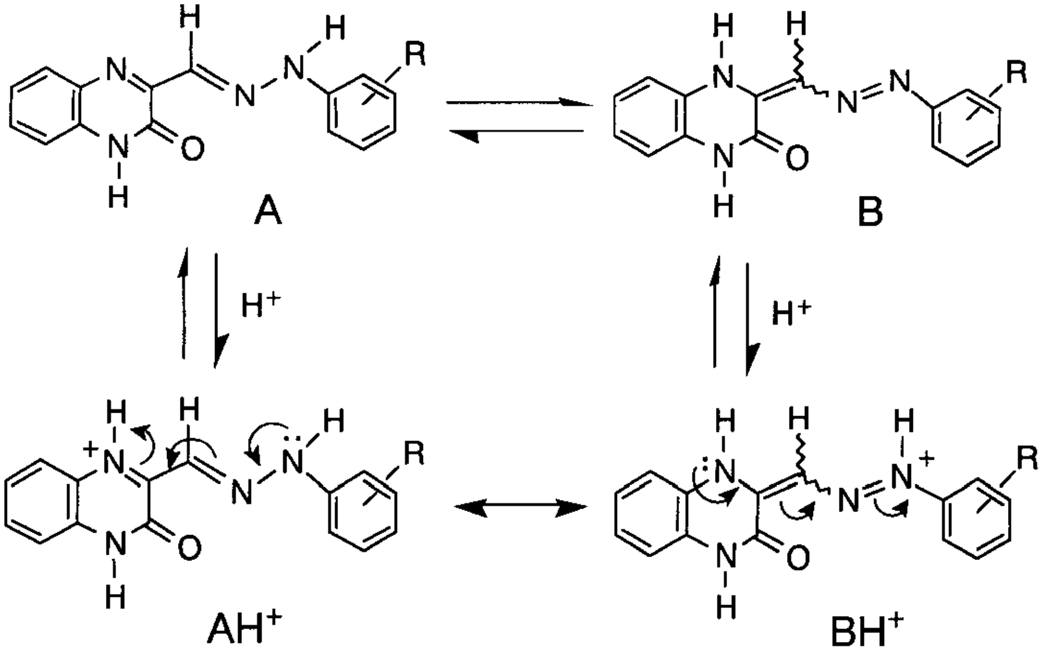


Figure 4



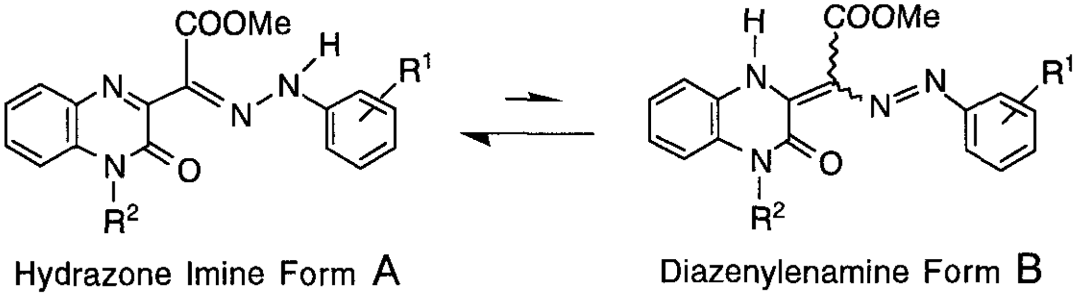
Scheme 32



compounds with the smaller σ values. To the contrary, the tautomer **B** is predominant in DMSO-$d_6$ media of compounds with the larger σ values, and the protonation of the tautomer **B** affords the species $BH^+$. Since the electron-withdrawing substituents decrease the electron density of the side chain nitrogen atom, the higher acid concentration is required for the protonation of this nitrogen atom. Consequently, the C(A:B = 1:1) values are higher in compounds with the larger σ values.

On the other hand, compounds (**36**) having the ester group on the hydrazone carbon exclusively occurred as the tautomer **A** in DMSO-$d_6$ regardless of the Hammett σ values of the substituent $R^1$ (Scheme 33).

Scheme 33



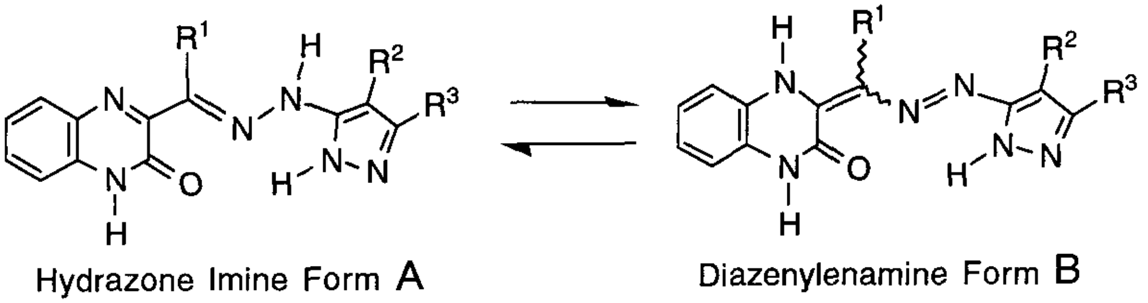
**36a** $R^1 = NO_2$, $R^2 = H$ **36d** $R^1 = Me$, $R^2 = H$

**36b** $R^1 = NO_2$, $R^2 = Me$ **36e** $R^1 = Me$, $R^2 = Me$

**36c** $R^1 = H$, $R^2 = Me$

However, 3-pyrazolylhydrazonomethyl-2-oxo-1,2-dihydroquinoxaline (**37a**) provided the different tendency in substituent effects from that of compounds (**36a-e**). Compound (**37a**) predominated as the tautomer **B** in DMSO-$d_6$ in spite of the presence of the ester group on the hydrazone carbon ($R^1$ = COOMe), while compounds (**37b,c**) preferred the tautomer **A** in DMSO-$d_6$[45] (Scheme 34, Table 10). Moreover, compound (**37c**) predominated as the tautomer **B** in DMSO-$d_6$/$D_2O$, which was reverse to the preference of the tautomer **A** in DMSO-$d_6$ (Table 10).

Scheme 34



**37a** $R^1$ = COOMe, $R^2$ = COOEt, $R^3$ = H
**37b** $R^1$ = H, $R^2$ = COOEt, $R^3$ = H
**37c** $R^1$ = COOMe, $R^2$ = CN, $R^3$ = Me

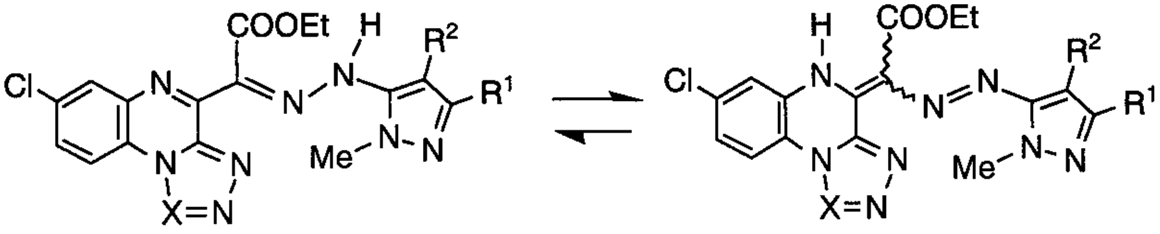
Table 10

| Compound | Solvent | Tautomer Ratio A | Tautomer Ratio B |
|---|---|---|---|
| **37a** | DMSO-$d_6$ | 15 | 85 |
| **37b** | DMSO-$d_6$ | 100 | 0 |
| **37c** | DMSO-$d_6$ | 95 | 5 |
| | DMSO-$d_6$/$D_2O$ | 37 | 63 |

### II-3-d. 1,2,4-Triazolo[4,3-*a*]quinoxalines And Tetrazolo[1,5-*a*]quinoxalines

The $^1$H-nmr spectral data of the side-chained 1,2,4-triazolo[4,3-a]quinoxalines (**38a,b**) and tetrazolo[1,5-*a*]quinoxalines (**39a,b**) manifested the coexistence as the hydrazone imine A and diazenylenamine B forms[46] (Scheme 35). The tautomer ratios of A to B in DMSO-$d_6$ or TFA-$d_1$ depended on the nature of the pyrazole ring, but not the condensed azole ring (Table 11). Namely, the tautomer A was predominant in DMSO-$d_6$ media of compounds (**38a**) and (**39a**) and in TFA-$d_1$ media of compounds (**38b**) and (**39b**). The predominant tautomer in DMSO-$d_6$ was reversed in TFA-$d_1$, and *vice versa*.

Scheme 35



Hydrazone Imine Form A

Diazenylenamine Form B

**38a** X = CH, $R^1$ = H, $R^2$ = COOEt
**38b** X = CH, $R^1$ = Me, $R^2$ = CN

**39a** X = N, $R^1$ = H, $R^2$ = COOEt
**39b** X = N, $R^1$ = Me, $R^2$ = CN

Table 11

| | Tautomer Ratio | | | |
|---|---|---|---|---|
| | in DMSO-$d_6$ | | in TFA-$d_1$ | |
| Compound | A | B | A | B |
| **38a** | 67 | 33 | 41 | 59 |
| **38b** | 42 | 58 | 57 | 43 |
| **39a** | 100 | 0 | 24 | 76 |
| **39b** | 33 | 67 | 100 | 0 |

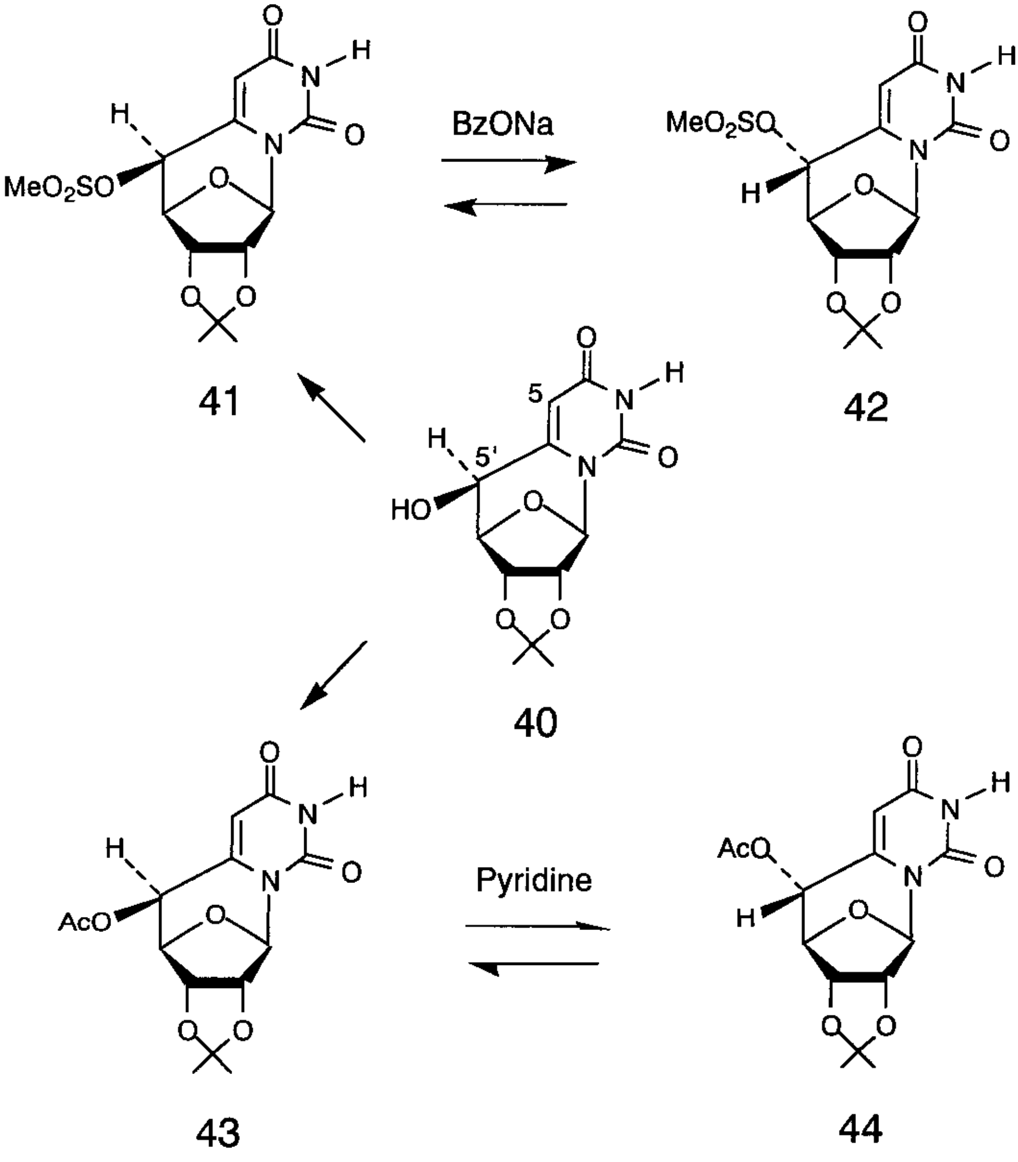
## III. Isomerism

### III-1. Epimerization

#### III-1-a. 6,5'(*R*)- And 6,5'(*S*)-Cyclouridines

The 5'(*S*)-mesyl derivative (**41**) and 5'(*S*)-acetyl derivative (**43**) were prepared from the 6,5'(*S*)-cyclouridine (**40**)[47] (Scheme 36). The 5'(*S*)-mesyl derivative (**41**) was stable in refluxing 2-butanone, but it rapidly equilibrated with the 5'(*R*)-mesyl derivative (**42**) on addition of sodium benzoate or triethylamine,

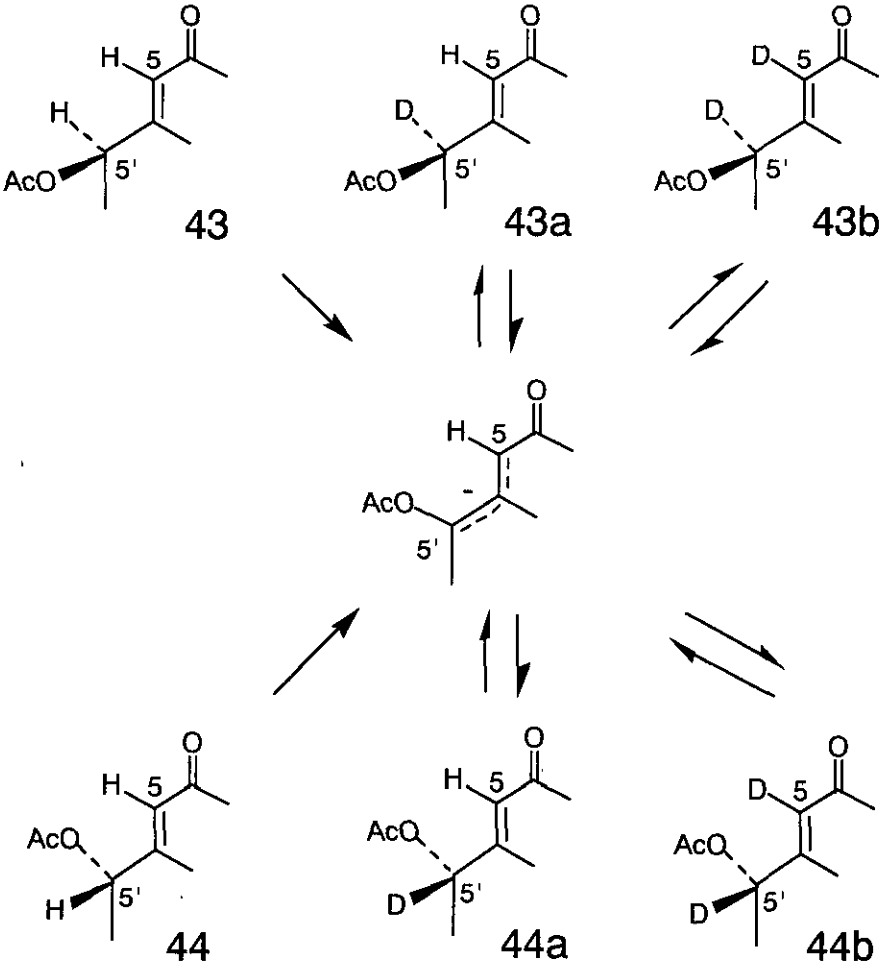
Scheme 36



which was confirmed by the nmr spectral data of the reaction mixture. The nmr study for the interconversion of the 5'(*S*)-acetyl derivative (43) and 5'(*R*)-acetyl derivative (44) in pyridine-$d_5$/$D_2O$ provided an evidence that the mechanism of the 5'-epimerization involved a resonance-stabilized carbanion intermediate (Scheme 37). At 80 °C, both the $C_5$ and $C_{5'}$ hydrogens of the *S* isomer (43) undergo exchange for deuterium with the rate of exchange at the allylic $C_{5'}$-

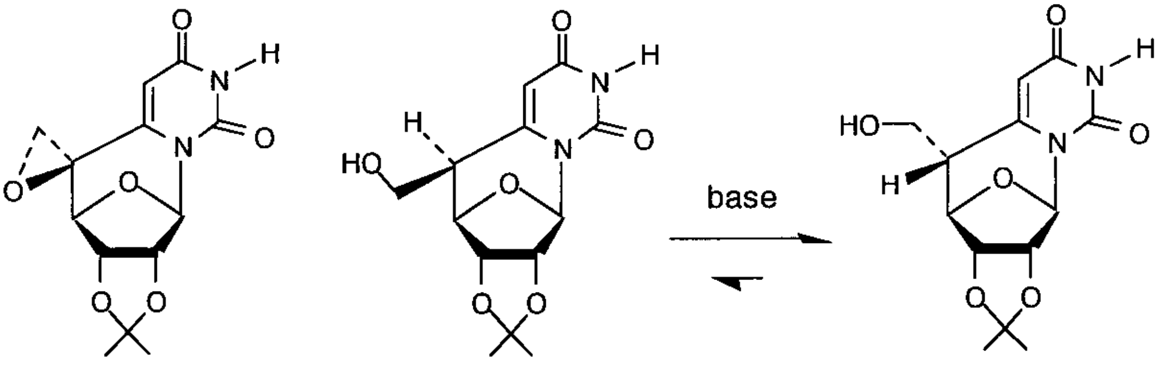
position exceeding that of the pyrimidine $C_5$-position, and the deuteration from the rear side of $C_{5'}$ (retention) predominates the deuteration from the front side (inversion). The *S*:*R* ratio reaches an equilibrium value of 2:1 at 40 hours. The *R* isomer (44) could undergo inversion to give the *S* isomers (43a) and (43b). Namely, the carbanion derived from compound (44) would undergo deuteration preferentially from the rear side (inversion) to afford compound (43a) and eventually (43b), and compound (43b) would be expected to reequilibrate with compound (44b).

Scheme 37



The reduction of the oxirane (45) gave the 5'-deoxy-5'-hydroxymethyl-6,5'(*R*)-cyclouridine (46) and 5'-deoxy-5'-hydroxymethyl-6,5'(*S*)-cyclouridine (47)[48] (Scheme 38). The structural assignment of the 5'*R* (46) and 5'*S* (47) isomers was based on the $J_{4',5'}$ values [5'*R* (46) $J_{4',5'} = 6.4$ Hz, 5'*S* (47) $J_{4',5'} = 0$ Hz]. The nmr studies in pyridine-$d_5$/$D_2O$ indicated that the isomerization proceeded *via* a resonance-stabilized carbanion (48) as shown in Scheme 39.

Scheme 38



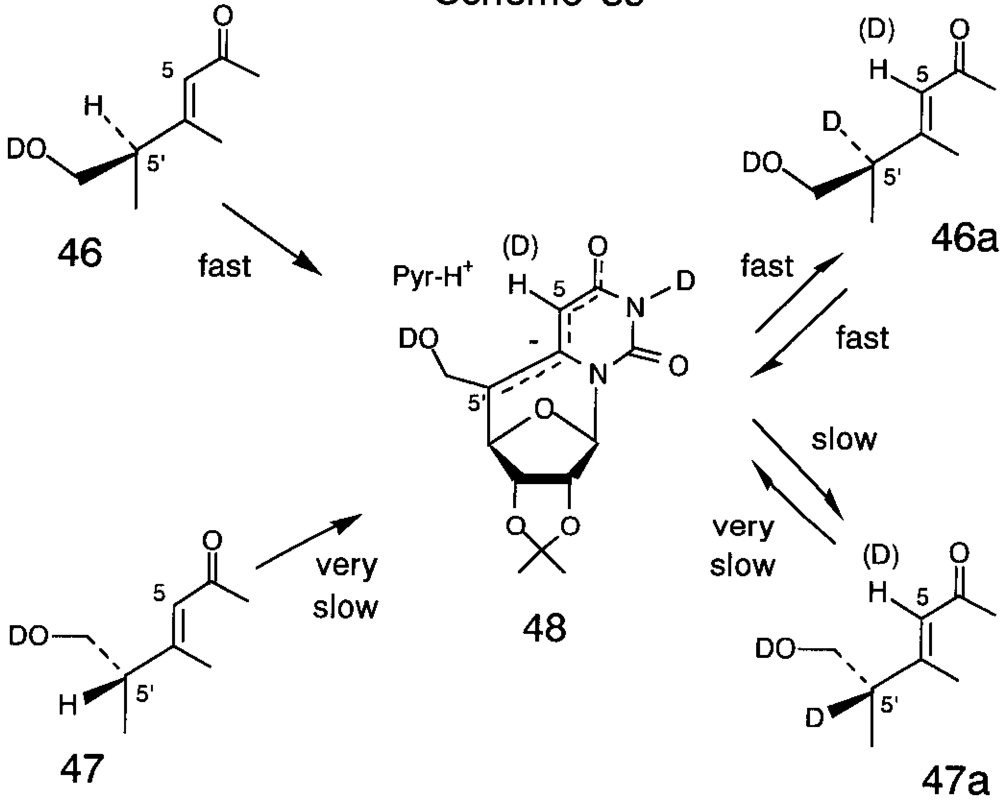
45 46 47

## III-2. Keto-Enol Isomerization

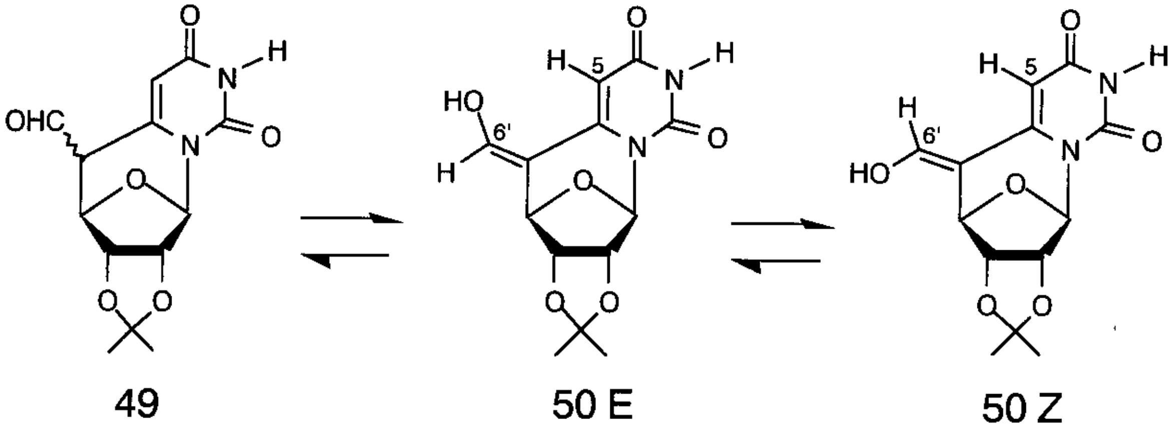
### III-2-a. 5'-Formyl-6,5'(*RS*)-cyclouridine

Irradiation of the oxirane (45) provided crystalline photoproduct, which was confirmed as the aldehyde (49).[48] It is not clear from the ir spectrum whether compound (49) crystallizes in the aldehyde or enol form, but this compound exists as two enols (50 E) and (50 Z) in a ratio of 1:1.33, which was confirmed by the $^1$H-nmr spectral data in DMSO-$d_6$ including the NOE spectral data between the $C_5$-H and $C_{6'}$-H protons (Scheme 40).

Scheme 39



Scheme 40



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Received, 9th May, 1995