TAUTOMERISM AND ISOMERISM OF HETEROCYCLES [1]

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Abstract - This review describes the various tautomerism and isomerism of diverse heterocyclic compounds in solution and solid state, which are classified into several sections as shown in the subject contents.

This review includes the following contents.

[I] Introduction

[II] Tautomerism

(II-1) Annular Tautomerism

II-1-a. Dihydropyrazolo[5,1-*c*][1,2,4]triazin-4-ones

II-1-b. Spiro[benzoxazole-2',4(6*H*,3'*H*)-pyrazolo[5,1-*c*][1,2,4]triazines]

II-1-c. Dihydropyrazolo[1,5-*a*]pyrimidin-7-ones

II-1-d. Dihydropyridazino[3,4-*b*]quinoxalines

II-1-e. Cyclopenta[*c*]quinoline

II-1-f. 1,2-Diazepino[3,4-*b*]quinoxalines

II-1-g. 5,14-Methano-16-oxo-1,5,6-benzoxadiazonino[3,4-*b*]quinoxalines

II-1-h. 1,3,4-Thiadiazoles

II-1-i. 6-Formyloctahydropyrido[2,1-*b*]quinazolin-11-ones

(II-2) Ring-Chain Tautomerism

II-2-a. Quinazoline-2,4-dione
II-2-b. Furo[3,4-*b*]pyridine
(II-3) Keto-Enol Or Amino-Imino Tautomerism In Side Chain
II-3-a. 4,6-Dinitrobenzofuroxan
II-3-b. Pyrazolo[1,5-*a*]pyrimidine
II-3-c. 1,2,4-Thiadiazoles
[III] Isomerism
(III-1) E-Z Isomerization In Side Chain
III-1-a. Pyrazoles
III-1-b. Pyridines
(III-2) Valence Isomerization With Or Without Prototropy
III-2-a. 1,2,4-Thiadiazoline
III-2-b. 1,2-Dithiolo[3,4-*b*]pyridine And Isothiazolo[5,4-*b*]pyridine-3-thione
(III-3) Epimerization
III-3-a. Ribo-Xylo Interconversion Of 6,5'-Cyclopyrimidine Nucleosides

[I] Introduction

The studies on the tautomeric structure of heterocyclic compounds have been very important theoretically and practically for every chemists and biochemists, and many research groups have reported numerous papers on the tautomerism of various heterocyclic compounds. These important works on the tautomerism have been collected and published as monographs[1-4] and reviews[5,6] in the past four decades. Our previous review[7] has also dealt with the tautomerism of side-chained quinoxalines between the enamine and methylene imine forms and between the hydrazone imine and diazenyl enamine forms together with the isomerism of multifarious quinoxaline derivatives. This review describes the tautomerism and isomerism of manifold heterocyclic compounds mainly reported in the past two decades.

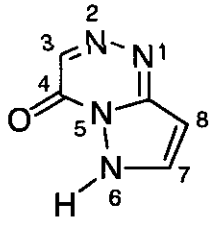
[II] Tautomerism

(II-1) Annular Tautomerism

II-1-a. Dihydropyrazolo[5,1-*c*][1,2,4]triazin-4-ones

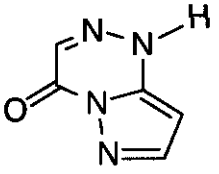
There are three possible tautomers in the dihydropyrazolo[5,1-*c*][1,2,4]triazin-4-ones, including the 4,6-dihydro A, 1,4-dihydro B, and 4-hydroxy C forms (Chart 1). The NOE spectral data of the 3-quinoxalinyldihydropyrazolo[5,1-*c*][1,2,4]tri-

Chart 1



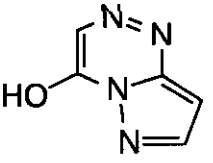
A

4,6-Dihydro Form



B

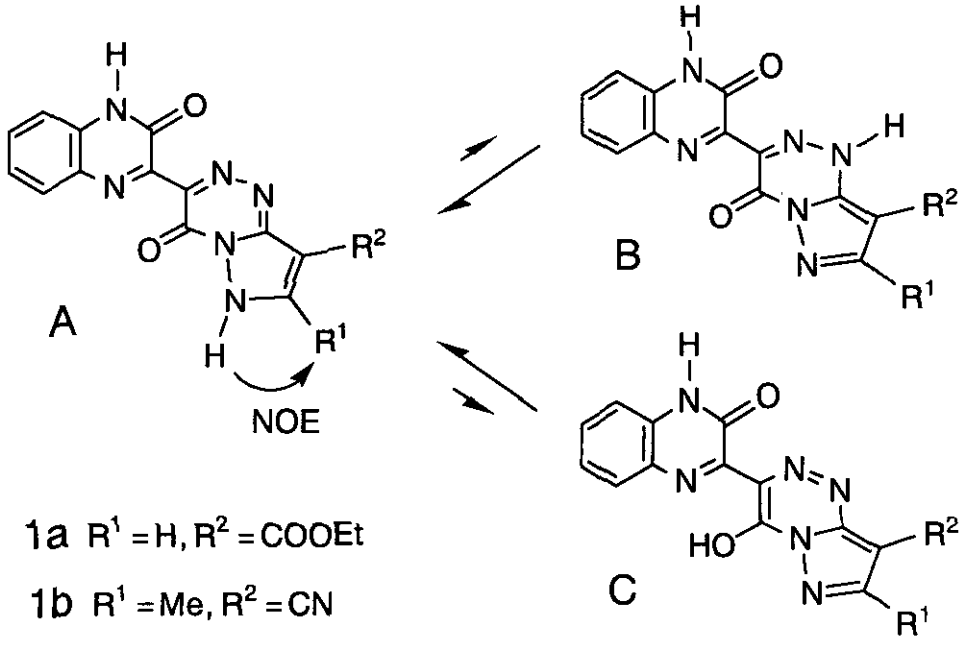
1,4-Dihydro Form



C

4-Hydroxy Form

Scheme 1



1a R^1 = H, R^2 = COOEt

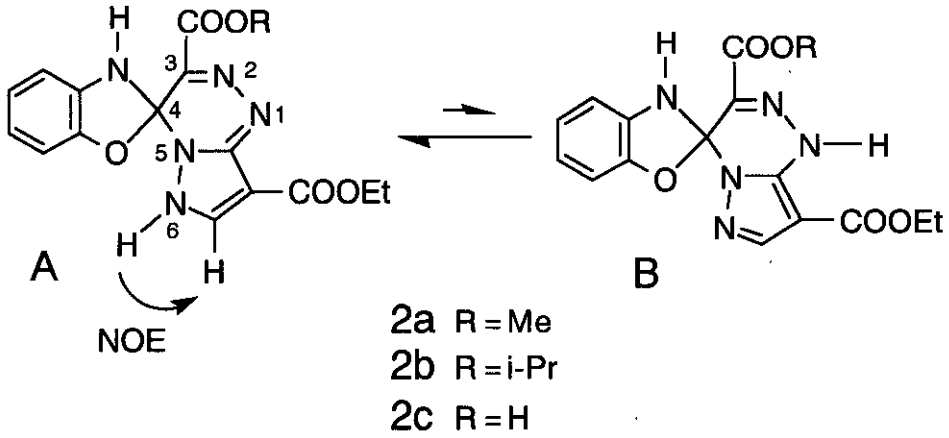
1b R^1 = Me, R^2 = CN

azin-4-ones (**1a**)[8] and (**1b**)[9] in DMSO-d_6 showed the existence as the 4,6-dihydro form **A** rather than as the 1,4-dihydro **B** and 4-hydroxy **C** forms[10] (Scheme 1).

II-1-b. Spiro[benzoxazole-2',4(6*H*,3'*H*)-pyrazolo[5,1-*c*][1,2,4]triazines]

The spiro[benzoxazole-2',4(6*H*,3'*H*)-pyrazolo[5,1-*c*][1,2,4]triazines] (**2a-c**)[11,12] were found to occur as the 4,6-dihydro form **A** rather than as the 1,4-dihydro form **B** from the NOE spectral data of compound (**2a**) (R = Me) in DMSO-d_6[10] (Scheme 2).

Scheme 2



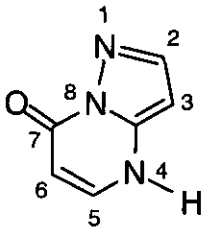
II-1-c. Dihydropyrazolo[1,5-*a*]pyrimidin-7-ones

There are three tautomeric structures for the dihydropyrazolo[1,5-*a*]pyrimidin-7-ones, involving the 4,7-dihydro-7-oxo **A**, 1,7-dihydro-7-oxo **B**, and 7-hydroxy **C** forms (Chart 2). The NOE spectral data of 6-quinoxalinyldihydropyrazolo[1,5-*a*]pyrimidin-7-ones (**3a-e**)[13,14] in DMSO-d_6 clarified the existence as the 4,7-dihydro-7-oxo form **A** (Scheme 3), while the study in the solid state indicated the occurrence as a mixture of the 1,7-dihydro-7-oxo **B** and 7-hydroxy **C** forms.[15]

II-1-d. Dihydropyridazino[3,4-*b*]quinoxalines

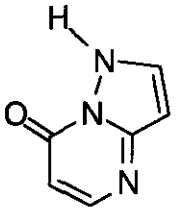
Dihydropyridazine[16] and dihydrocinnolines[17] have been known to exist as the 1,4-dihydro form **A** rather than as the 1,2-dihydro **B** and 3,4-dihydro **C** forms in

Chart 2



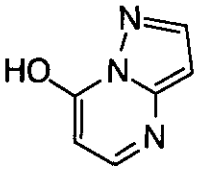
A

4,7-Dihydro-7-oxo Form



B

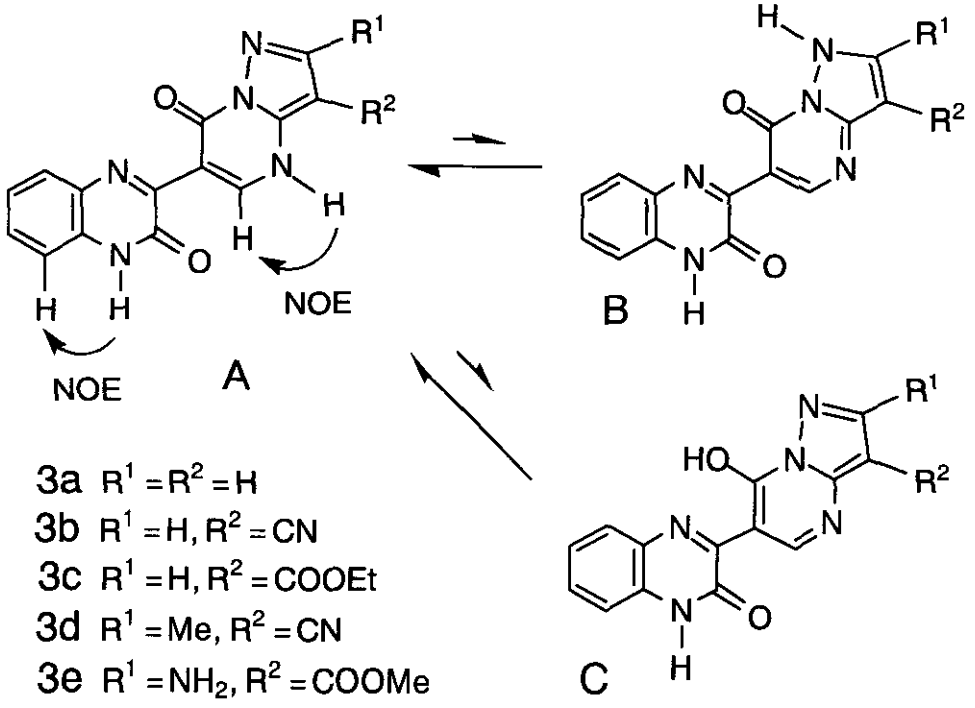
1,7-Dihydro-7-oxo Form



C

7-Hydroxy Form

Scheme 3

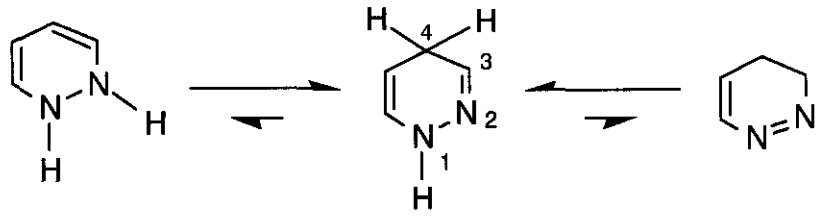


3a $R^1 = R^2 = H$
3b $R^1 = H, R^2 = CN$
3c $R^1 = H, R^2 = COOEt$
3d $R^1 = Me, R^2 = CN$
3e $R^1 = NH_2, R^2 = COOMe$

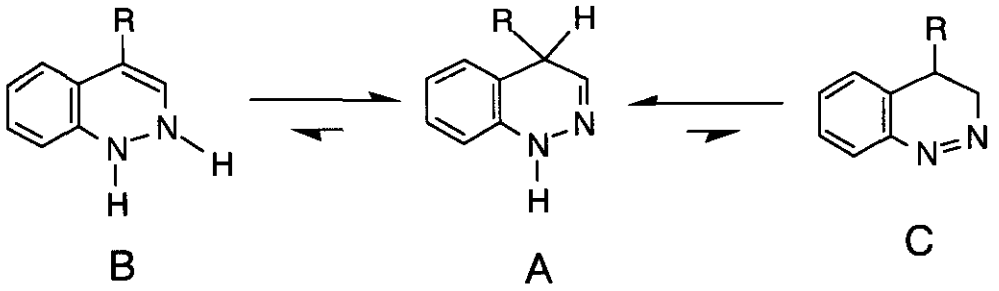
a solution (Schemes 4,5). However, the NOE spectral data of the dihydropyrid-

azino[3,4-*b*]quinoxalines (4a-c) in DMSO-d_6 or TFA/DMSO-d_6 exhibited the occurrence as the 1,5-dihydro form D rather than as the 1,4-dihydro A and 1,2-dihydro B forms[18] (Scheme 6).

Scheme 4



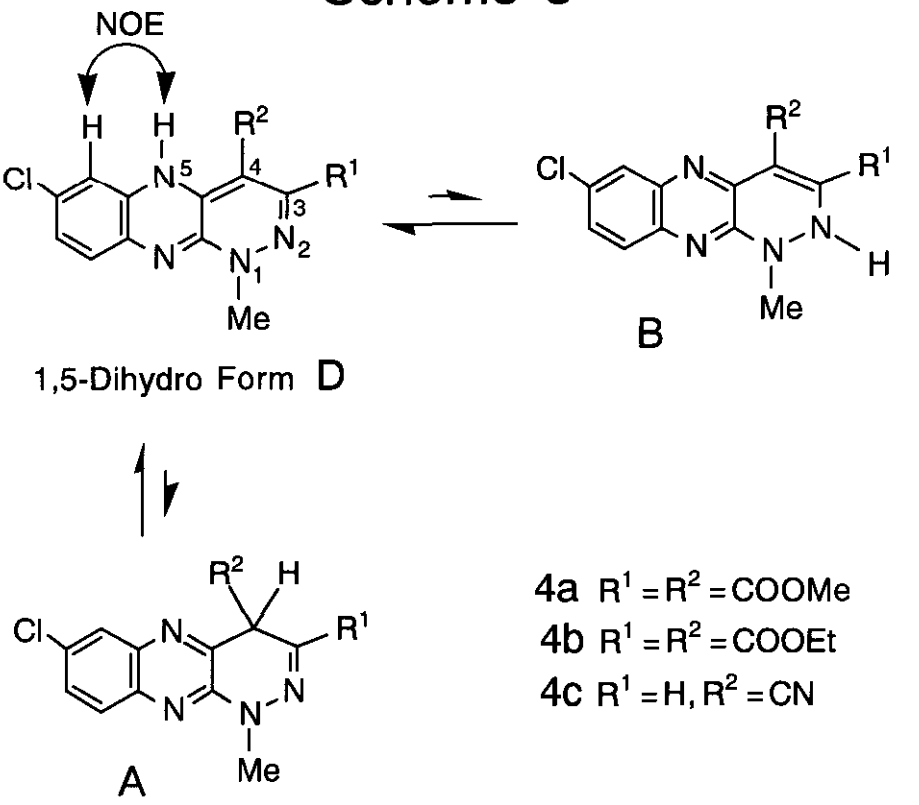
Scheme 5



II-1-e. Cyclopenta[*c*]quinoline

Cyclopenta[*c*]quinoline (5) was found to exist as the NH form A under a neat condition [ir (NH) 3300 cm^{-1}], but compound (5) coexisted as the C_3-H form B and C_1-H form C in $CHCl_3$ or CCl_4, which was supported by the nmr spectral data[19] (Scheme 7, Table 1).

Scheme 6



Scheme 7

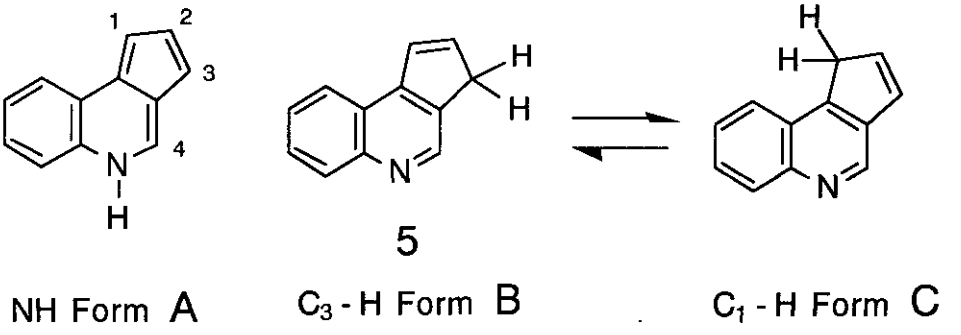


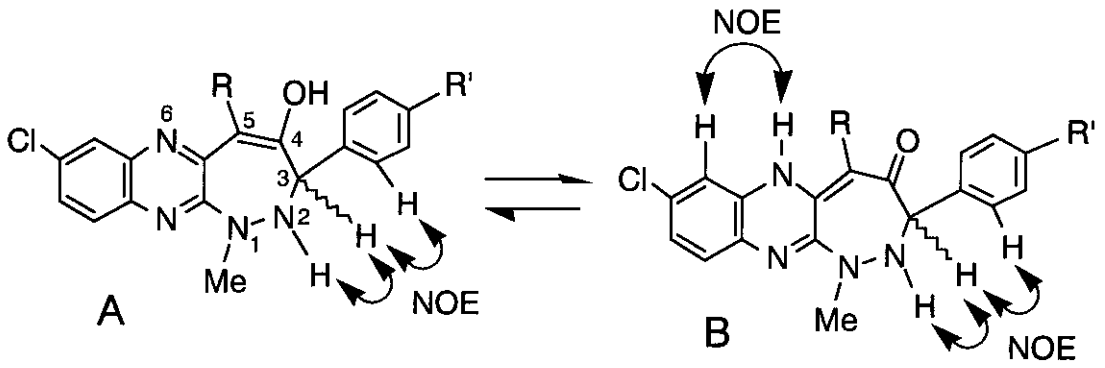
Table 1

Tautomer	Ratio	Chemical Shift (δ ppm) Methylene	C_4-H
B	2	3.64	8.97
C	1	3.75	8.99

II-1-f. 1,2-Diazepino[3,4-*b*]quinoxalines

The tautomeric structure of the 1,2-diazepino[3,4-*b*]quinoxalines depended on the kind of the C_5-substituents (Scheme 8, Table 2). Namely, the 5-cyano series of compounds (**6a,b**) occurred as the 2,3-dihydro-4-hydroxy form **A** in DMSO-d_6, while the 5-alkoxy series of compounds (**7a,b-9a,b**) favored the 2,3,4,6-tetrahydro-4-oxo form **B** in DMSO-d_6.[20,21] The 5-cyano series of compounds (**10a,b**) (Chart 3) also existed as the 2,3-dihydro-4-hydroxy form **A**, which was support-

Scheme 8



6a,b R = CN **8a,b** R = OCH_2CH_2OH **a** R' = Cl

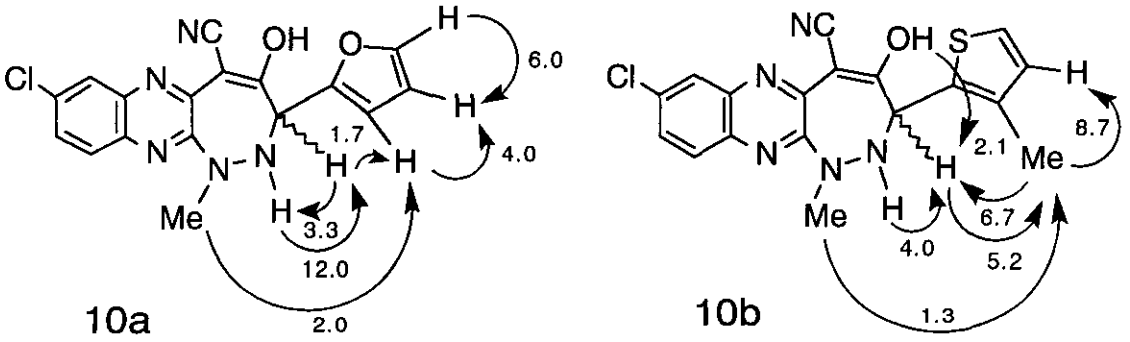
7a,b R = OEt **9a,b** R = $OCH_2C{\equiv}CH$ **b** R' = Br

ed by the NOE spectral data in DMSO-d_6.[22] The C_4=O carbon signals of compounds (**7a,b-9a,b**) were observed at δ 166.5-168.5 ppm.

Table 2

Compound	R	Ratio A	Ratio B
6a,b	CN	100	0
7a,b	Alkoxy	0	100
8a,b	Alkoxy	0	100
9a,b	Alkoxy	0	100
10a,b	CN	100	0

Chart 3

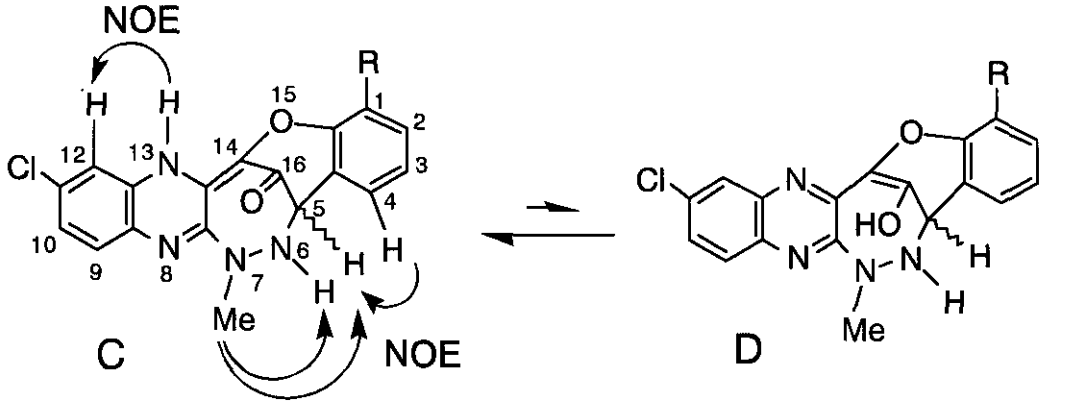


NOE Spectral Data (%) for Compounds (**10a**) and (**10b**)

II-1-g. 5,14-Methano-16-oxo-1,5,6-benzoxadiazonino[3,4-*b*]quinoxalines

The structure of 5,14-methano-16-oxo-1,5,6-benzoxadiazonino[3,4-*b*]quinoxalines (**11a,b**)[23,24] is similar to that of compounds (**7a,b-9a,b**), since compounds (**11a,b**) have the oxygen function in a similar position to that of compounds (**7a,b-9a,b**). As was expected, compounds (**11a,b**) occurred as the 5,6,7,13-tetrahydro-16-oxo form C in DMSO-d_6, which was confirmed by the NOE spectral data (Scheme 9) and the chemical shifts for the C_{16}=O carbon signals observed at δ 162.5-165.0 ppm.

Scheme 9



5,6,7,13-Tetrahydro-16-oxo Form 5,6-Dihydro-16-hydroxy Form

11a R=H, **11b** R=OMe

II-1-h. 1,3,4-Thiadiazoles

There have been many papers on the tautomerism between the thione **A** *and* thiol **B** forms,[25] and the thione structure **A** has frequently been supported by some spectroscopies. The 1,3,4-thiadiazoles (**12a-d**) also existed as the thione form **A** in DMSO-d_6[26] (Scheme 10). The C_5=S carbon signals of compounds (**12a-d**) were observed at δ 181.2-184.0 ppm, which corresponded to the typical chemical shifts for the C_5=S of compounds (**13a**,[26] **13b-d**,[27] **13e**[28]) (δ 180.2-

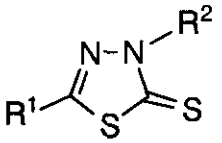
Scheme 10

2-Amino-5-thione Form 2-Amino-5-thiol Form

12a R=Me **12c** R=C_6H_4-o-Me
12b R=Ph **12d** R=C_6H_4-o-Cl

189.2 ppm) (Chart 4, Table 3).

Chart 4



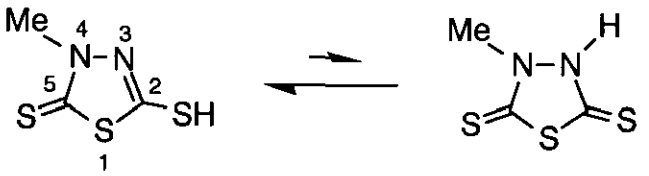
13

Table 3

Compound	R^1	R^2	δC_5=S
13a	NH_2	H	181.2
13b	SMe	H	189.2
13c	SMe	Me	186.3
13d	SH	Me	180.2
13e	NHMe	H	181.1

The 1,3,4-thiadiazole (**14**) favored the 2-thiol-5-thione form C in DMSO-d_6 (Scheme 11), which was supported by the comparison of the carbon chemical shifts between compound (14) and its thiomethyl derivative[29] (Chart 5).

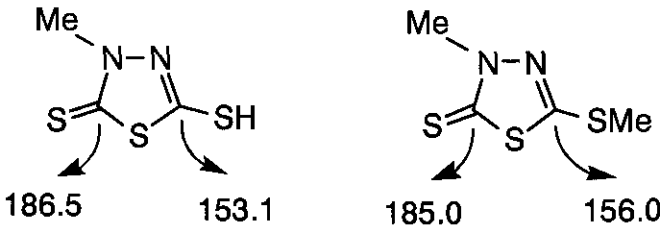
Scheme 11



14

2-Thiol-5-thione Form C 2,5-Dithione Form D

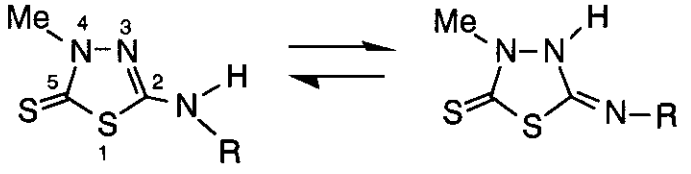
Chart 5



Values in δ ppm

The tautomeric structure of the 1,3,4-thiadiazoles (**15a,b**) was dependent on the kind of the substituent R attached to the C_2-amino group. Compound (**15a**) (R = *n*-butyl) existed as the 2-amino-5-thione form E in DMSO-d_6, while compound (**15b**) (R = phenyl) preferred the 2-imino-5-thione form F in DMSO-d_6[29] (Scheme 12, Table 4). The structural distinction was based on the NH proton signals.

Scheme 12



E
2-Amino-5-thione Form

F
2-Imino-5-thione Form

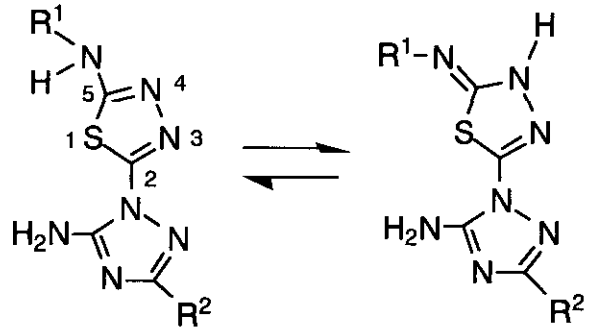
15a R = n-Bu, **15b** R = Ph

Table 4

Compound	R	Ratio E	Ratio F	δ NH
15a	*n*-Bu	100	0	7.69(t)
15b	Ph	0	100	10.2(s)

Similarly, compounds (**16a,b**) (R^1 = alkyl) occurred as the 5-amino form G in DMSO-d_6, whereas compounds (**17a,b**) (R^1 = phenyl) favored the 5-imino form H in DMSO-d_6[29] (Scheme 13, Table 5). These tautomers were assigned in compari-

Scheme 13



G 5-Amino Form H 5-Imino Form

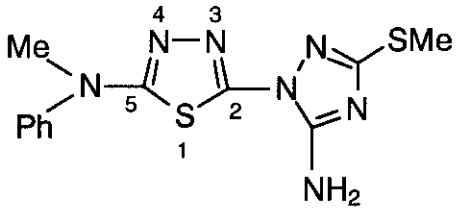
16a,b R^1 = Alkyl, **17a,b** R^1 = Ph

Table 5

Compound	R^1	R^2	Ratio G	Ratio H
16a	Et	SMe	100	0
16b	CH_2Ph	SMe	100	0
17a	Ph	SMe	0	100
17b	Ph	NMe_2	0	100

son of the chemical shifts for the C_2 and C_5 carbons among compounds (**16a,b**, **17a,b** and **18**) (Chart 6, Table 6). Namely, the C_2 carbon signals of 5-amino compounds (**16a,b** and **18**) (δ 165.0-166.7 ppm) are evidently different from those of 5-imino compounds (**17a,b**) (δ 159.7-160.9 ppm).

Chart 6



18

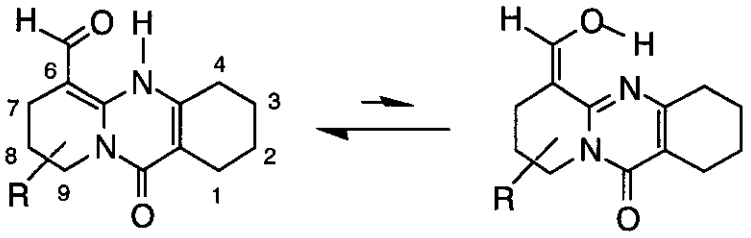
Table 6

	16a,b G Form	17a,b H Form	18 G Form
δ C_2	165.0-165.2	159.7-160.9	166.7
δ C_5	150.5-150.6	151.7-152.7	150.9

II-1-i. 6-Formyloctahydropyrido[2,1-*b*]quinazolin-11-ones

The ^{1}H- and ^{13}C-nmr spectral data of 6-formyloctahydropyrido[2,1-*b*]quinazolin-11-ones (**19a,b**) in $CDCl_3$ provided an evidence for the tautomeric equilibria between the formyl enamine **A** and enol imine **B** forms with the predominance

Scheme 14



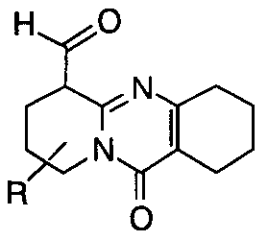
A Formyl Enamine Form

B Enol Imine Form

19a R=H, **19b** R=9-Me

of the A form[30] (Scheme 14). The formyl proton signal in a relatively high magnetic field [δ 8.58 (**19a**), 8.77 (**19b**) ppm] pointed to a mobile tautomeric equilibrium between the A and B forms. The observation of the N_5-H proton signal at δ 14.59 (**19a**) and 14.60 (**19b**) ppm excluded the formyl imine form C (Chart 7).

Chart 7



C

Formyl Imine Form

(II-2) Ring-Chain Tautomerism

II-2-a. Quinazoline-2,4-dione

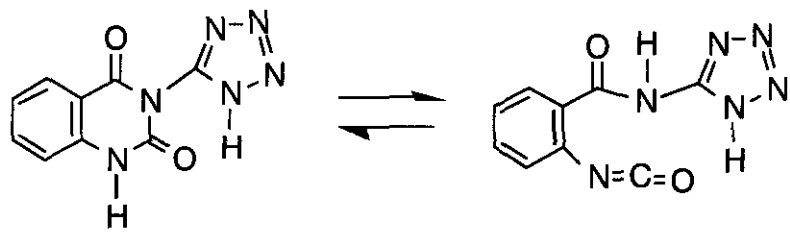
The ^{1}H-nmr spectrum of the 3-tetrazolylquinazoline-2,4-dione (**20**) in DMSO-d_6 showed the ring-chain tautomerism[31] (Scheme 15). The equilibrium mixture of the species (**20**) and (**20'**) could account for the nmr spectrum. However, the ir spectrum of compound (**20**) in DMSO failed to show an appreciable absorption band in the isocyanate region.

II-2-b. Furo[3,4-*b*]pyridine

The furo[3,4-*b*]pyridine (**21**) exhibited the ring-chain tautomerism (Scheme 16), which was supported by the comparison of the ir spectral data at room temperature (KBr disc) with that at 295°C (glc/ft ir).[32] Compound (**21**) had the sur-

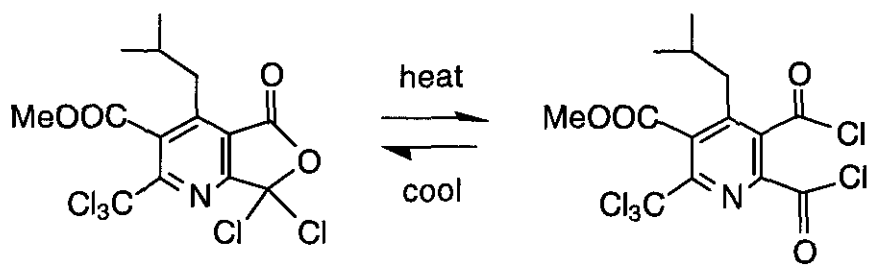
prisingly very broad melting point despite sharp, while its glc peak was single and its nmr spectrum was clear.

Scheme 15



20 20'

Scheme 16



21

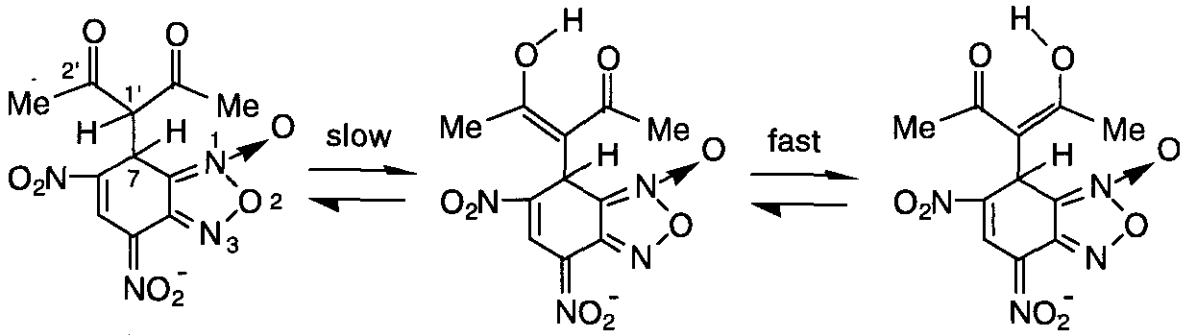
(II-3) Keto-Enol Or Amino-Imino Tautomerism In Side Chain

II-3-a. 4,6-Dinitrobenzofuroxan

The diketo form A of the ketonic σ complex (22) was initially confirmed by the ^{1}H-nmr spectral data in DMSO-d_6[33] (Scheme 17). The diketo form A then underwent a slow and partial conversion into the enol form B or B'. The doublet signal due to the C_7-H proton of the A form changed into a singlet signal due to the C_7-H proton of the B or B' form. An evidence for the fast equilibrium between the B and B' forms was based on the broad methyl proton signals. The equilibrium

was completed at 32°C, and the A and B (B') forms were present in a ratio of 30:70, which was essentially identical with that of 2,4-pentanedione in DMSO-d_6 at 32°C.

Scheme 17

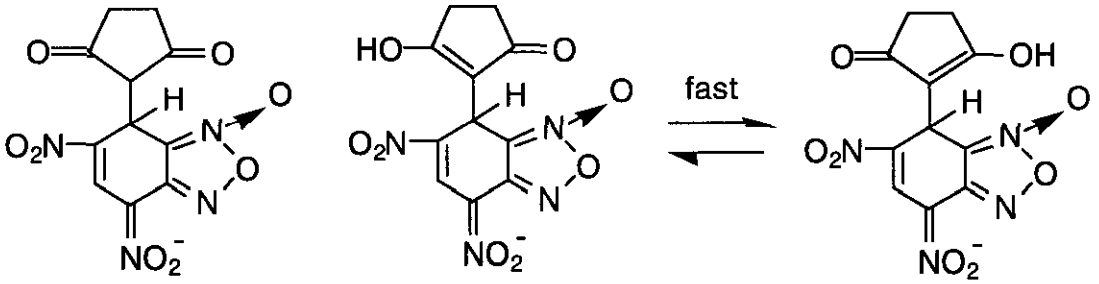


22

Diketo Form A Enol Form B Enol Form B'

On the other hand, the diketo form A of compound (23) did not exist in DMSO-d_6 when detected by the ^{1}H-nmr spectroscopy, and the rapid tautomeric equilibrium between the B and B' forms was confirmed in DMSO-d_6 at 32°C from the observation of the broad singlet signal due to the $C_{3'}$ and $C_{4'}$ methylene protons (δ 2.36 ppm) (Scheme 18).

Scheme 18



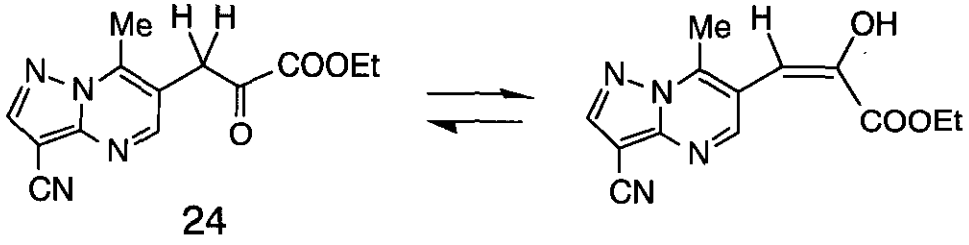
23

Diketo Form A Enol Form B Enol Form B'

II-3-b. Pyrazolo[1,5-*a*]pyrimidine

The ^{1}H-nmr spectral data of the pyrazolo[1,5-*a*]pyrimidin-6-ylpyruvate (**24**) exhibited the coexistence as the keto C and enol D forms with the predominance of the enol form D[34] (Scheme 19, Table 7). The reaction of compound (**24**) with acetic anhydride effected *O*-acetylation in the D tautomer to give enol acetate.

Scheme 19



24

Keto Form C Enol Form D

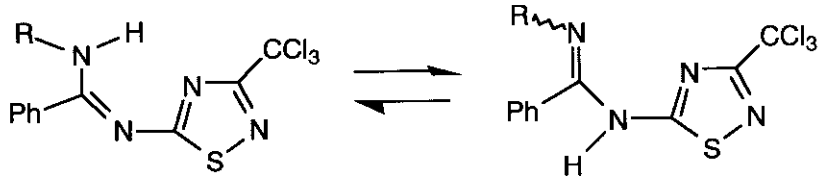
Table 7

Tautomer	Ratio	Chemical Shift (δ ppm) Methylene	Vinyl	C_7-Me
C	31.5	4.50	----	2.73
D	68.5	----	6.50	2.83

II-3-c. 1,2,4-Thiadiazoles

The ^{1}H-nmr spectral data of the 5-amidino-1,2,4-thiadiazoles (**25a,b**) in DMSO-d_6 indicated the presence of two tautomers E and F in the ratios of 6:4 (**25a**) and 1:2 (**25b**)[35] (Scheme 20). Moreover, the ^{13}C-nmr spectral data of compounds (**25a,b**) in DMSO-d_6 excluded the tautomeric structure G in comparison with those of compounds (**26**) and (**27**) in $CDCl_3$ (Chart 8, Table 8). Namely, the C_3

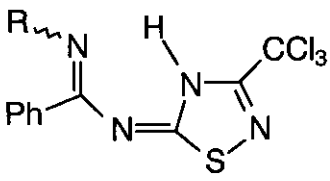
Scheme 20



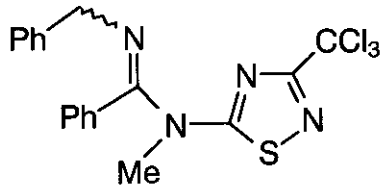
E F

25a R = Me, 25b R = CH_2Ph

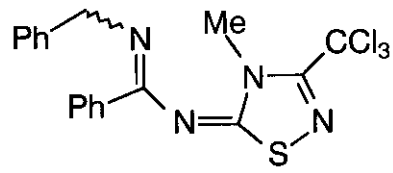
Chart 8



G



26



27

Table 8

Compound	Chemical Shift (δ ppm) C_3	C_5	Exocyclic N-C=N
25a F	164.8	175.8	153.6
25b F	164.9	175.9	153.9
26	164.7	176.9	156.6
27	148.9	170.6	162.2

and C_5 carbon signals of compound (27) structurally analogous to the G tautomer are obviously different from those of compounds (25a F, 25b F, and 26).

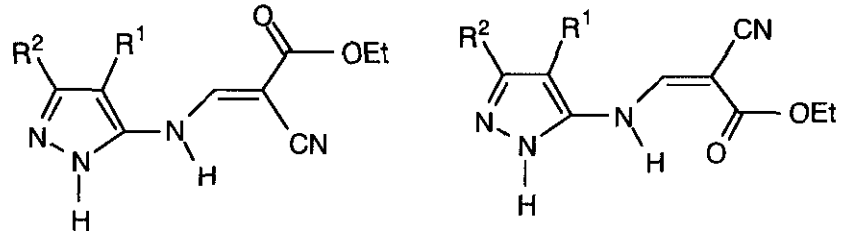
[III] Isomerism

(III-1) E-Z Isomerization In Side Chain

III-1-a. Pyrazoles

The reaction of 5-aminopyrazoles with ethyl ethoxymethylenecyanoacetate gave the pyrazol-5-ylaminoacrylates (**28a-c**), whose ^{1}H-nmr spectral data in DMSO-d_6 revealed the coexistence of the E (NH/COOEt, *trans*) and Z (NH/COOEt, *cis*) forms[36] (Chart 9, Table 9). The isolated ratios of E to Z for compounds (**28c,d**) are shown

Chart 9



E Form Z Form

28a $R^1 = CONH_2$, $R^2 = H$
28b $R^1 = CN$, $R^2 = H$
28c $R^1 = COOEt$, $R^2 = H$
28d $R^1 = COOEt$, $R^2 = Me$

Table 9

Compound	Ratio E	Ratio Z	Chemical Shift (δ ppm) in DMSO-d_6 E Form Vinyl	E Form C_5-NH	Z Form Vinyl	Z Form C_5-NH
28a	25	75	8.57	10.43	8.28	11.76
28b	20	80	8.37	10.87	8.21	11.52
28c	17	83	8.55	9.50	8.35	11.40

in Table 10.[37] The ratio of E to Z for compound (28c) is different between Tables 9 and 10, which is presumably due to the different reaction conditions.

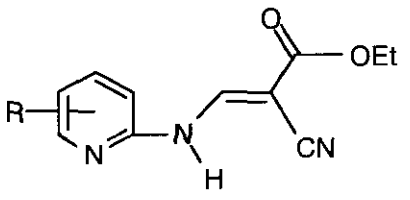
Table 10

Compound	Isolated Yield (%) E	Z	Isolated Ratio E	Z	Chemical Shift (δ ppm) in DMSO-d_6 E Form Vinyl	C_5-NH	Z Form Vinyl	C_5-NH
28c	47	6	89	11	8.48	9.40	8.28	11.42
28d	24	31	44	56	8.48	9.25	8.28	11.38

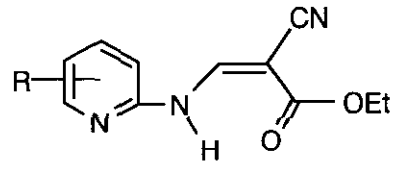
III-1-b. Pyridines

Fusion of 2-aminopyridines with ethyl ethoxymethylenecyanoacetate afforded the pyridin-2-ylaminoacrylates (29a-c) composed of the E and Z isomers[38] (Chart 10). The ratios of E to Z and reaction conditions are shown in Table 11. After the isolation of the E and Z isomers, the thermal interconversions between the E and Z forms were confirmed under several conditions (Table 12).

Chart 10



E Form



Z Form

29a R = H
29b R = 4-Me
29c R = 6-Me

Table 11

Compound	Reaction Condition °C	min	Ratio E	Z	Chemical Shift (δ ppm) in $CDCl_3$ E Form Vinyl	C_2-NH	Z Form Vinyl	C_2-NH
29a	100	15	66	34	9.20	9.20	8.71	10.89
	150	120	100	0				
	180	120	100	0				
29b	100	15	55	45	9.22	9.22	8.68	10.80
	150	120	100	0				
	180	120	100	0				
29c	110	10	54	46	9.16	9.09	8.73	10.83
	115	30	54	46				

Table 12

Starting Material	Reaction Condition Solvent	min	Ratio E	Z
29a E	EtOH	30	66	34
	EtOH	60	50	50
	Dowtherm A	10	unchanged	
	Fusion[a]	20	33	67
29a Z	EtOH	30	55	45
	EtOH	60	50	50
	Dowtherm A	10	50	50
	Fusion[a]	20	38	62
29b E	EtOH	30	46	54
	EtOH	60	46	54
	Dowtherm A	10	unchanged	
	Fusion[a]	20	0	100
29b Z	EtOH	30	unchanged	
	Dowtherm A	10	97	3
	Fusion[a]	20	unchanged	
29c E	EtOH	30	55	45
	Dowtherm A	10	24	76
	Fusion[a]	20	10	90
	HCl[b]/H_2O (1:1)	30	14	86
29c Z	EtOH	30	10	90
	Dowtherm A	10	41	59
	Fusion[a]	20	38	62
	HCl[b]/H_2O (1:1)	30	100	0

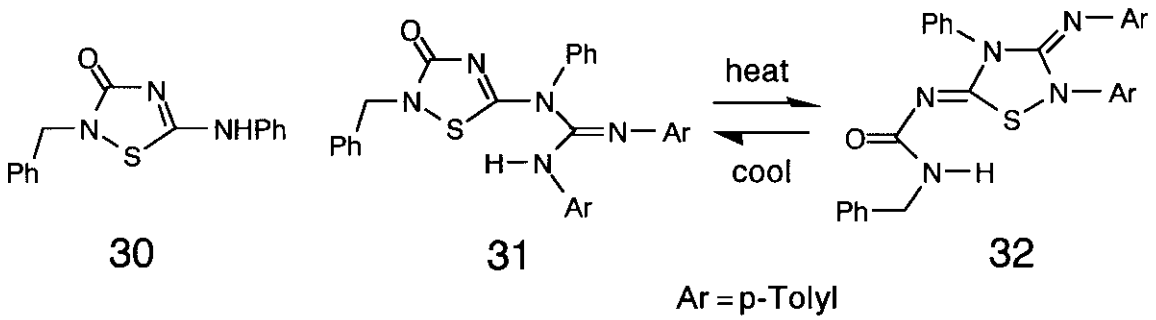
a - Fusion at 180°C; b - Concentrated HCl

(III-2) Valence Isomerization With Or Without Prototropy

III-2-a. 1,2,4-Thiadiazoline

The reaction of the 1,2,4-thiadiazoline (30) with *N,N'*-ditolylcarbodiimide gave the 5-guanidino-1,2,4-thiadiazoline (31)[39] (Scheme 21). Heating of compound (31) resulted in bond-switching rearrangement into the 5-carbamoylimino-1,2,4-thiadiazolidine (32), which was supported by the ^{1}H-nmr spectral data (Table 13). Compound (31) is stable under the conditions 1 and 7, and it isomerizes into compound (32) under the conditions 2, 4, 8, and 9. Compound (31) changed into compounds (32) and (30) at higher temperatures (conditions 3,5,6), but cooling

Scheme 21



30 31 32

Table 13

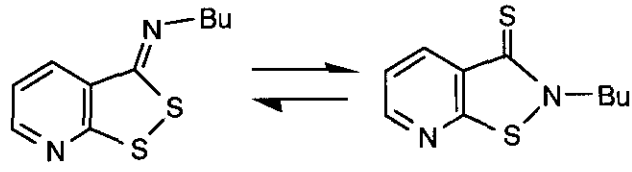
Condition	Solvent	Temp °C	Ratio in Solution (%) 31	32	30
1	$CDCl_2CDCl_2$	20	100	0	0
2		80	90	10	0
3		120	35	39	26
4	DMSO-d_6	20	69	31	0
5		70	39	34	27
6		110	21	21	58
7	C_6D_6	20	100	0	0
8	$CDCl_3$	20	80	20	0
9	CD_3CN	20	70	30	0

of the solution to room temperature increased the ratio of compound (31) with the expense of compounds (32) and (30).

III-2-b. 1,2-Dithiolo[3,4-*b*]pyridine And Isothiazolo[5,4-*b*]pyridine-3-thione

The pure 1,2-dithiolo[3,4-*b*]pyridine (33) rapidly establishes the equilibrium with the isothiazolo[5,4-*b*]pyridine-3-thione (34) in polar solvents such as DMSO, DMF, and acetone/water[40] (Scheme 22). Pure compound (34) also exhibited the same behavior. However, compound (33) or (34) did not isomerize in apolar solvents such as xylene. The NCH_2 proton signals and C_3 carbon signals were used for the structural differentiation of the isomers (33) and (34) (Table 14).

Scheme 22



33 34

Equilibrium in Polar Solvents

Table 14

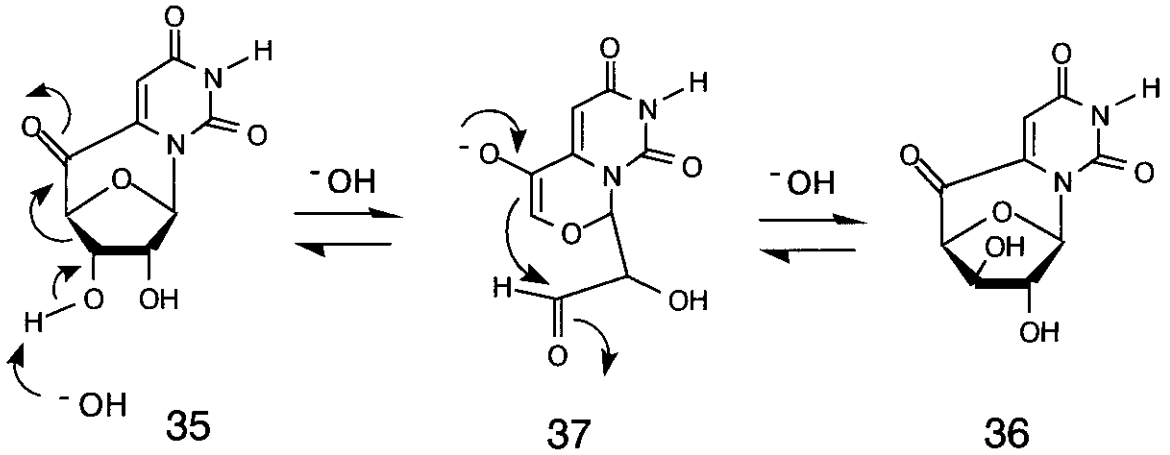
Compound	Chemical Shift (δ ppm) in $CDCl_3$ NCH_2	C_3
33	3.40	166.4 (C=N)
34	4.40	184.0 (C=S)

(III-3) Epimerization

III-3-a. Ribo-Xylo Interconversion Of 6,5'-Cyclopyrimidine Nucleosides

The ^{1}H-nmr studies show that 5'-oxo-6,5'-cyclouridine (35) rapidly isomerizes into 6,5'-cyclo-5'-oxo-1-(β-D-xylofuranosyl)uracil (36) at pH 8-9 *via* a pyrimido-[1,6-c][1,3]oxazine intermediate (37), wherein the equilibrium favors the xylo nucleoside (36)[41] (Scheme 23). To the contrary, compound (35) is stable in 1*N* NaOH, and the equilibrium between compounds (35) and (36) in 1*N* NaOD lies entirely in favor of the ribo isomer (35).

Scheme 23



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