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.

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[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 monographs1-4 and reviews5,6 in the past four decades. Our previous review7 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](image)

**Scheme 1**

![Scheme 1](image)

1a \( R^1 = H, R^2 = \text{COOEt} \)

1b \( R^1 = \text{Me}, R^2 = \text{CN} \)
Azin-4-ones (1a) and (1b) 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 (Scheme 1).

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

The spiro[benzoxazole-2',4(6H,3'H)-pyrazolo[5,1-c][1,2,4]triazines] (2a-c) 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-$d_6$ (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) 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.

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

Dihydropyridazine and dihydrocinnolines 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

4,7-Dihydro-7-oxo Form

1,7-Dihydro-7-oxo Form

7-Hydroxy Form

Scheme 3

a solution (Schemes 4,5). However, the NOE spectral data of the dihydropyrid-
azino[3,4-b]quinoxalines (4a-c) in DMSO-\textsubscript{d\textsubscript{6}} or TFA/DMSO-\textsubscript{d\textsubscript{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\textsuperscript{18} (Scheme 6).

\begin{center}
\textbf{Scheme 4}
\end{center}

\begin{center}
\begin{tikzpicture}
\node (B) at (0,0) {B};
\node (A) at (1.5,0) {A};
\node (C) at (3,0) {C};
\draw[->] (B) -- node[above] {1,2-Dihydro Form} (A);
\draw[->] (A) -- node[above] {1,4-Dihydro Form} (C);
\draw[->] (B) -- node[below] {3,4-Dihydro Form} (C);
\end{tikzpicture}
\end{center}

\begin{center}
\textbf{Scheme 5}
\end{center}

\begin{center}
\begin{tikzpicture}
\node (B) at (0,0) {B};
\node (A) at (1.5,0) {A};
\node (C) at (3,0) {C};
\draw[->] (B) -- node[above] {B} (A);
\draw[->] (A) -- node[above] {A} (C);
\draw[->] (B) -- node[below] {C} (C);
\end{tikzpicture}
\end{center}

II-1-e. Cyclopenta[c]quinoline
Cyclopenta[c]quinoline (5) was found to exist as the NH form A under a neat condition [\textit{ir} (NH) 3300 cm\textsuperscript{-1}], but compound (5) coexisted as the C\textsubscript{3}-H form B and C\textsubscript{1}-H form C in CHCl\textsubscript{3} or CCl\textsubscript{4}, which was supported by the nmr spectral data\textsuperscript{19} (Scheme 7, Table 1).
Scheme 6

1,5-Dihydro Form D

4a \( R^1 = R^2 = \text{COOMe} \)
4b \( R^1 = R^2 = \text{COOEt} \)
4c \( R^1 = H, R^2 = \text{CN} \)

Scheme 7

NH Form A

C\(_3\) - H Form B

C\(_1\) - H Form C
Table 1

<table>
<thead>
<tr>
<th>Tautomer</th>
<th>Ratio</th>
<th>Methylene (δ ppm)</th>
<th>C₄-H (δ ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>2</td>
<td>3.64</td>
<td>8.97</td>
</tr>
<tr>
<td>C</td>
<td>1</td>
<td>3.75</td>
<td>8.99</td>
</tr>
</tbody>
</table>

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 C₅-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-d₆, while the 5-alkoxy series of compounds (7a,b-9a,b) favored the 2,3,4,6-tetrahydro-4-oxo form B in DMSO-d₆.²⁰,²¹ 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

![Scheme 8 diagram](image-url)

2,3-Dihydro-4-hydroxy Form 2,3,4,6-Tetrahydro-4-oxo Form

6a,b R = CN 8a,b R = OCH₂CH₂OH  a R' = Cl
7a,b R = OEt 9a,b R = OCH₂C≡CH  b R' = Br
ed by the NOE spectral data in DMSO-d6.22 The C4=O carbon signals of compounds (7a,b-9a,b) were observed at δ 166.5-168.5 ppm.

Table 2

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a,b</td>
<td>CN</td>
<td>100</td>
</tr>
<tr>
<td>7a,b</td>
<td>Alkoxy</td>
<td>100</td>
</tr>
<tr>
<td>8a,b</td>
<td>Alkoxy</td>
<td>100</td>
</tr>
<tr>
<td>9a,b</td>
<td>Alkoxy</td>
<td>100</td>
</tr>
<tr>
<td>10a,b</td>
<td>CN</td>
<td>100</td>
</tr>
</tbody>
</table>

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-d6, which was confirmed by the NOE spectral data (Scheme 9) and the chemical shifts for the C16=O carbon signals observed at δ 162.5-165.0 ppm.
There have been many papers on the tautomerism between the thione A and thiol B forms, 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- $d_6$ (Scheme 10). The C=S carbon signals of compounds (12a-d) were observed at $\delta$ 181.2-184.0 ppm, which corresponded to the typical chemical shifts for the C=S of compounds (13a, 13b-d, 13e) ($\delta$ 180.2-
189.2 ppm) (Chart 4, Table 3).

**Chart 4**

![Chart 4](image)

**Table 3**

<table>
<thead>
<tr>
<th>Compound</th>
<th>R¹</th>
<th>R²</th>
<th>δ C₅=S</th>
</tr>
</thead>
<tbody>
<tr>
<td>13a</td>
<td>NH₂</td>
<td>H</td>
<td>181.2</td>
</tr>
<tr>
<td>13b</td>
<td>SMe</td>
<td>H</td>
<td>189.2</td>
</tr>
<tr>
<td>13c</td>
<td>SMe</td>
<td>Me</td>
<td>186.3</td>
</tr>
<tr>
<td>13d</td>
<td>SH</td>
<td>Me</td>
<td>180.2</td>
</tr>
<tr>
<td>13e</td>
<td>NHMe</td>
<td>H</td>
<td>181.1</td>
</tr>
</tbody>
</table>

The 1,3,4-thiadiazole (14) favored the 2-thiol-5-thione form C in DMSO-d₆ (Scheme 11), which was supported by the comparison of the carbon chemical shifts between compound (14) and its thiomethyl derivative²⁹ (Chart 5).

**Scheme 11**

![Scheme 11](image)
The tautomeric structure of the 1,3,4-thiadiazoles (15a,b) was dependent on the kind of the substituent R attached to the C2-amino group. Compound (15a) (R = n-butyl) existed as the 2-amino-5-thione form E in DMSO-d6, while compound (15b) (R = phenyl) preferred the 2-imino-5-thione form F in DMSO-d6\(^2\) (Scheme 12, Table 4). The structural distinction was based on the NH proton signals.

**Scheme 12**

![Chart 5](chart.png)

Values in $\delta$ ppm

186.5 153.1 185.0 156.0

**Table 4**

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>E</th>
<th>F</th>
<th>$\delta$ NH</th>
</tr>
</thead>
<tbody>
<tr>
<td>15a</td>
<td>n-Bu</td>
<td>100</td>
<td>0</td>
<td>7.69(t)</td>
</tr>
<tr>
<td>15b</td>
<td>Ph</td>
<td>0</td>
<td>100</td>
<td>10.2(s)</td>
</tr>
</tbody>
</table>
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 comparison 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) (\(\delta\) 165.0-166.7 ppm) are evidently different from those of 5-imino compounds (17a,b) (\(\delta\) 159.7-160.9 ppm).

**Scheme 13**

```
R\(^1\)
\(\text{H} \ 5\) \(\equiv \text{N} \ 4\)
\(\ 1\) \(\equiv \text{S} \ 3\)
\(\text{H}_2\text{N} \ 2\)
\(\equiv \text{N} \ \equiv \text{N} \ \equiv \text{N} \)
\(\text{R}^2\)

5-Amino Form  \(\rightarrow\)  5-Imino Form

16a,b  \(R^1 = \text{Alkyl}\),  17a,b  \(R^1 = \text{Ph}\)
```

**Table 5**

<table>
<thead>
<tr>
<th>Compound</th>
<th>R(^1)</th>
<th>R(^2)</th>
<th>G</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>16a</td>
<td>Et</td>
<td>SMe</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>16b</td>
<td>CH(_2)Ph</td>
<td>SMe</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>17a</td>
<td>Ph</td>
<td>SMe</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>17b</td>
<td>Ph</td>
<td>NMe(_2)</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>
II-1-i. 6-Formyloctaahydropyrido[2,1-b]quinazolin-11-ones

The $^1$H- and $^{13}$C-nmr spectral data of 6-formyloctaahydropyrido[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
of the A form\(^30\) (Scheme 14). The formyl proton signal in a relatively high magnetic field \([\delta \ 8.58 \ (19a), 8.77 \ (19b) \text{ ppm}]\) pointed to a mobile tautomeric equilibrium between the A and B forms. The observation of the N\(_5\)-H proton signal at \(\delta \ 14.59 \ (19a)\) and 14.60 \( (19b)\) ppm excluded the formyl imine form C (Chart 7).

**Chart 7**

![Chart 7](image)

Formyl Imine Form

(II-2) Ring-Chain Tautomerism

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

The \(^1\text{H-nmr}\) 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 \(\text{ir}\) 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 \(\text{ir}\) 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

Scheme 16

(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$_6$ (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**

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**
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**

![Scheme 19](image)

**Table 7**

<table>
<thead>
<tr>
<th>Tautomer</th>
<th>Ratio</th>
<th>Chemical Shift (δ ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Methylene</td>
</tr>
<tr>
<td>C</td>
<td>31.5</td>
<td>4.50</td>
</tr>
<tr>
<td>D</td>
<td>68.5</td>
<td>----</td>
</tr>
</tbody>
</table>

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 CDC$_3$ (Chart 8, Table 8). Namely, the C$_3$
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).
Isomerism

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

III-1-a. Pyrazoles

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

**Chart 9**

![Chart 9](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ratio E</th>
<th>Z</th>
<th>Chemical Shift ((\delta) ppm) in DMSO-(d_6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E</td>
<td>Z</td>
<td>Vinyl</td>
</tr>
<tr>
<td>28a</td>
<td>25</td>
<td>75</td>
<td>8.57</td>
</tr>
<tr>
<td>28b</td>
<td>20</td>
<td>80</td>
<td>8.37</td>
</tr>
<tr>
<td>28c</td>
<td>17</td>
<td>83</td>
<td>8.55</td>
</tr>
</tbody>
</table>

Table 9
in Table 10. 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>
<thead>
<tr>
<th>Compound</th>
<th>Isolated Yield (%)</th>
<th>Isolated Ratio</th>
<th>Chemical Shift (δ ppm) in DMSO-d6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E</td>
<td>Z</td>
<td>E</td>
</tr>
<tr>
<td>28c</td>
<td>47</td>
<td>6</td>
<td>89</td>
</tr>
<tr>
<td>28d</td>
<td>24</td>
<td>31</td>
<td>44</td>
</tr>
</tbody>
</table>

III-1-b. Pyridines
Fusion of 2-aminopyridines with ethyl ethoxymethyleneacyanoacetate afforded the pyridin-2-ylaminoacrylates (29a–c) composed of the E and Z isomers (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

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction Condition</th>
<th>Ratio</th>
<th>Chemical Shift (δ ppm) in CDCl₃</th>
<th>E Form</th>
<th>Z Form</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>°C</td>
<td>min</td>
<td>E</td>
<td>Z</td>
<td>Vinyl</td>
</tr>
<tr>
<td>29a</td>
<td>100</td>
<td>15</td>
<td>66</td>
<td>34</td>
<td>9.20</td>
</tr>
<tr>
<td></td>
<td>150</td>
<td>120</td>
<td>100</td>
<td>0</td>
<td></td>
</tr>
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<td></td>
<td>180</td>
<td>120</td>
<td>100</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>29b</td>
<td>100</td>
<td>15</td>
<td>55</td>
<td>45</td>
<td>9.22</td>
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<td>180</td>
<td>120</td>
<td>100</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>29c</td>
<td>110</td>
<td>10</td>
<td>54</td>
<td>46</td>
<td>9.16</td>
</tr>
<tr>
<td></td>
<td>115</td>
<td>30</td>
<td>54</td>
<td>46</td>
<td></td>
</tr>
</tbody>
</table>

### Table 12

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Reaction Condition</th>
<th>Ratio</th>
<th>Solvent</th>
<th>min</th>
<th>E</th>
<th>Z</th>
</tr>
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<tbody>
<tr>
<td>29a E</td>
<td>EtOH</td>
<td>30</td>
<td>66</td>
<td>34</td>
<td></td>
<td></td>
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<td>38</td>
<td>62</td>
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<td>HClᵇ/H₂O (1:1)</td>
<td>30</td>
<td>100</td>
<td>0</td>
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</table>

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'-dityhelcarbodiimide gave the 5-guanidino-1,2,4-thiadiazoline (31) (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 1H-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

\[
\begin{align*}
\text{Scheme 21} \\
30 & \quad \xrightarrow{\text{heat}} \quad 31 \\
& \quad \xrightarrow{\text{cool}} \quad 32 \\
\text{Ar} = \text{p-Tolyl}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Condition</th>
<th>Solvent</th>
<th>Temp °C</th>
<th>Ratio in Solution (%)</th>
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</thead>
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<tr>
<td>1</td>
<td>CDCl₂CDCl₂</td>
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<tr>
<td>2</td>
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<td>90 10 0</td>
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<tr>
<td>3</td>
<td>CDCl₂CDCl₂</td>
<td>120</td>
<td>35 39 26</td>
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<td>4</td>
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<td>20</td>
<td>69 31 0</td>
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<tr>
<td>5</td>
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<td>21 21 58</td>
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<tr>
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<td>CD₃CN</td>
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<td>80 20 0</td>
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<tr>
<td>9</td>
<td>CD₃CN</td>
<td>20</td>
<td>70 30 0</td>
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</table>
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

**Equilibrium in Polar Solvents**

**Table 14**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical Shift ((\delta) ppm) in CDCl(_3)</th>
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<tbody>
<tr>
<td></td>
<td>NCH(_2)</td>
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<tr>
<td>33</td>
<td>3.40</td>
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<td>34</td>
<td>4.40</td>
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**(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)\(^1\) (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**

![Scheme 23](image)

**REFERENCES**

16. Reference 3, p 78.


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