Synthesis of 6-Quinoxalinyldihydropyrazolo[1,5-*a*]pyrimidin-7-ones by a Ring Transformation. Tautomeric Structure of Dihydropyrazolo[1,5-*a*]pyrimidin-7-ones in a Solution [1].

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The reaction of 3-(*N*,*N*-dimethylcarbamoyl)furo[2,3-*b*]quinoxaline hydrochloride **1** with the 5-aminopyrazoles **6a-e** gave 6-quinoxalinyldihydropyrazolo[1,5-*a*]pyrimidin-7-ones **7a-e**, respectively. Compounds **7a-e** were found to predominate as the 4,7-dihydro-7-oxo form in a solution based on the NOE data.

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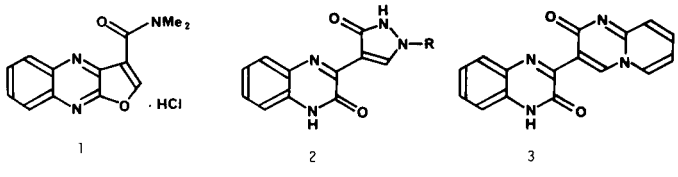
In previous papers [3-6], we reported that the reaction of 3-(*N*,*N*-dimethylcarbamoyl)furo[2,3-*b*]quinoxaline hydrochloride **1** with hydrazines, 2-aminopyridine, *o*-phenylenediamine hydrochloride and ethyl cyanoacetate resulted in ring transformation to give compounds **2-5**, respectively (Chart 1). In continuation of these works, we studied the

Chart 1



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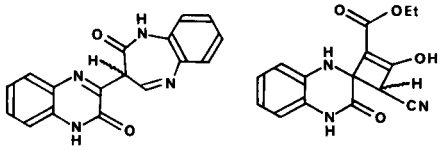

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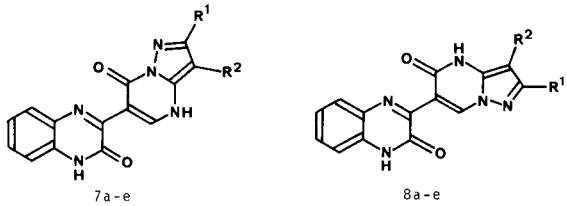
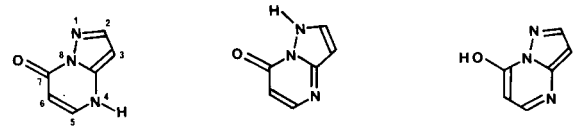
Chart 2



7a-e 8a-e

ring transformation of **1** with the 5-aminopyrazoles **6a-e** in the present investigation, because it was interesting to clarify whether this ring transformation produced the 6-quinoxalinyldihydropyrazolo[1,5-*a*]pyrimidin-7-ones **7a-e** or 6-quinoxalinyldihydropyrazolo[1,5-*a*]pyrimidin-5-ones **8a-e** (Chart 2). Moreover, it was important to determine either tautomeric structure of **7a-e** or **8a-e** in a solution, because there were few papers concerning the tautomeric structure of dihydropyrazolo[1,5-*a*]pyrimidin-7-ones [7] and dihydropyrazolo[1,5-*a*]pyrimidin-5-ones [8] in solution. The nmr spectral data of the products manifested that the above ring transformation furnished the 6-quin-

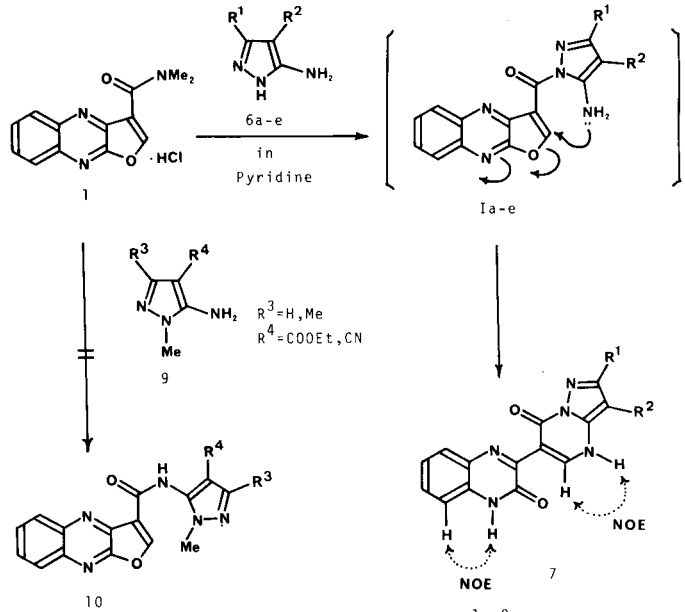
Chart 3



A B C

4,7-Dihydro-7-oxo Form | 1,7-Dihydro-7-oxo Form | 7-Hydroxy Form

Scheme 1



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

oxalinyldihydropyrazolo[1,5-*a*]pyrimidin-7-ones **7a-e** (Scheme 1), which existed as the 4,7-dihydro-7-oxo form **A** in solution (Chart 3). This paper describes the synthesis of 6-quinoxalinyldihydropyrazolo[1,5-*a*]pyrimidines **7a-e** and their tautomeric structure in solution together with the antifungal screening data of **7a-e**.

The reaction of **1** with the 5-amino-1*H*-pyrazoles **6a-e** in the presence of pyridine gave the 6-quinoxalinyldihydropyrazolo[1,5-*a*]pyrimidin-7-ones **7a-e** presumably *via* intermediates **Ia-e**, respectively (Scheme 1). The formation of intermediates **Ia-e** may be supported by the results that the reaction of **1** with the 5-amino-1-methylpyrazoles **9** does not afford 3-[*N*-(1-methylpyrazol-5-yl)carbamoyl]furo-[2,3-*b*]quinoxalines **10**, but recovered the free base of **1**. Moreover, the NOE data between the N_4-H and C_5-H protons of **7a-e** ascertained the formation of intermediates **Ia-e** and the tautomeric structure of the 4,7-dihydro-7-oxo form **A** (Table 1, Chart 3). The N_4-H and $N_{4'}$-H proton signals of **7a-d** appeared in the same magnetic field, and hence the radiation at the NH proton signal showed the NOE to both the C_5-H and $C_{5'}$-H proton signals (Table 1). The signals due to the C_2-C_7, $C_{2'}$ and $C_{3'}$ carbons were easily assigned from the ^{1}H-^{13}C coupling constant and ^{1}H-^{13}C COSY spectral data in compounds **7a-d** (Table 2).

Table 1
NOE Data for Compounds **7a-e**

		Compound				
Radiation	NOE	**7a**	**7b**	**7c**	**7d**	**7e**
N_4-H	C_5-H	3.7	5.5	3.5	2.3	2.5 [a]
$N_{4'}$-H	$C_{5'}$-H	5.1	8.2	5.8	3.6	4.2

[a] Expressed in %.

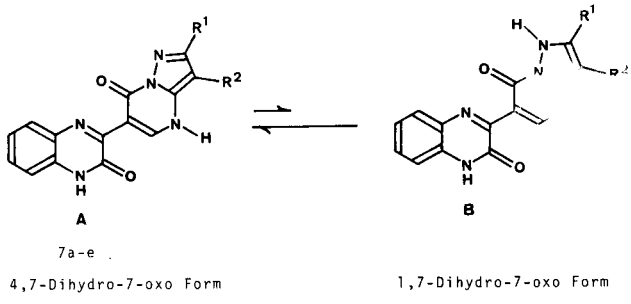
Table 2
^{13}C-NMR Spectral data for Compounds **7a-d** [a]

Carbon	Compound **7a**	Compound **7b**	Compound **7c**	Compound **7d**
C_2	143.46	145.38	143.42	145.73
C_3	89.96	76.31	95.57	76.34
C_{3a}	141.39	145.59	142.86	141.74
C_5	140.45	142.33	141.28	141.74
C_6	105.30	108.03	108.57	108.04
C_7	154.86	154.16	154.00	154.41
$C_{2'}$	153.94	152.69	152.86	152.53
$C_{3'}$	154.31	154.16	154.19	154.03

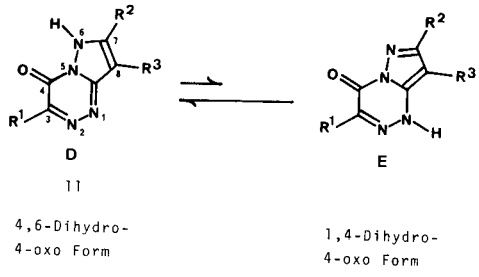
[a] Measured in DMSO-d_6.

Hori and others [7] reported that the dihydropyrazolo-[1,5-*a*]pyrimidin-7-ones predominated as a mixture of the 1,7-dihydro-7-oxo form **B** and the 7-hydroxy form **C** (Chart 3) in the solid state. Although there have been few papers concerning the tautomeric structure of the dihydropyrazolo[1,5-*a*]pyrimidin-7-ones in solution, we have just clarified that the dihydropyrazolo[1,5-*a*]pyrimidin-7-ones **7a-e** exist as the 4,7-dihydro-7-oxo form **A** in a solution (Scheme 2). Incidentally, our previous data [9] showed that the dihydropyrazolo[5,1-*c*] [1,2,4]triazin-4-ones **11** (Scheme 3) as an isostere of the dihydropyrazolo[1,5-*a*]pyrimidin-7-ones **7** were predominant as the 4,6-dihydro-4-oxo form **D**, but not the 1,4-dihydro-4-oxo form **E**, in solution. These results indicate that the tautomeric structure is completely changed when a ring nitrogen atom is replaced with a carbon atom (Scheme 4).

Scheme 2



Scheme 3



Scheme 4

Table 3
Antifungal Activity of Compounds **7a-e**

	Activity [a]		
Compound	P.d.	R.s.	P.o. [b]
7a	16	—	—
7b	—	22	16
7c	74	14	—
7d	23	11	12
7e	21	24	63

[a] Growth inhibition at a concentration of 100 ppm. [b] P.d.: *Pythium debaryanum*; R.s.: *Rhizoctonia solani*; P.o.: *Pyricularia oryzae*.

Compounds **7a-e** showed a weak antifungal activity against *Pythium debaryanum* (P.d.), *Rhizoctonia solani* (R.s.) and *Pyricularia solani* (P.s.) (Table 3), but exhibited no antibacterial activity against *Xanthomonas oryzae*, *Erwinia carotovara* and *Pseudomonas lachrmans*.

EXPERIMENTAL

All melting points were determined on a Ishii melting point apparatus and are uncorrected. The ir spectra (potassium bromide) were recorded with a JASCO IRA-1 spectrophotometer. The nmr spectra were measured in deuteriodimethylsulfoxide with a VXR-300 spectrometer at 300 MHz. Chemical shifts are given in the δ scale. The mass spectra (ms) were determined with a JEOL JMS-01S spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

6-(3-Oxo-3,4-dihydroquinoxalin-2-yl)-4,7-dihydropyrazolo[1,5-*a*]-pyrimidin-7-one **7a**, 6-(3-Oxo-3,4-dihydroquinoxalin-2-yl)-3-cyano-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-7-one **7b** and 6-(3-Oxo-3,4-dihydroquinoxalin-2-yl)-3-cyano-2-methyl-4,7-dihydropyrazolo[-1,5-*a*]pyrimidin-7-one **7d**.

General Procedure.

A suspension of **1** (5 g, 18.0 mmoles) and the appropriate pyrazole **6a** (2.24 g), **6b** (2.92 g) or **6d** (3.29 g) (27.0 mmoles, 1.5-fold) in pyridine (5 ml)/1-butanol (200 ml) was refluxed in an oil bath for 2 hours to precipitate yellow needles **7a**, brick red needles **7b** or orange needles **7d**, respectively, which were collected by suction filtration. Trituration with hot ethanol gave analytically pure samples, yields: **7a** (3.31 g, 66%), **7b** (4.45 g, 81%), **7d** (4.03 g, 70%).

Compound **7a** had mp above 310°; ir: ν cm^{-1} 3280, 3220, 1675, 1605; ms: m/z 279 (M^+); pmr: 12.50 (s, 2H, N_4-H and $N_{4'}$-H), 8.32 (s, 1H, C_5-H), 7.96 (d, J = 2.0 Hz, 1H, C_2-H), 7.81-7.28 (m, 4H, aromatic), 6.29 (d, J = 2.0 Hz, 1H, C_3-H).

Anal. Calcd. for $C_{14}H_9N_5O_2$: C, 60.21; H, 3.25; N, 25.08. Found: C, 60.21; H, 3.45; N, 25.26.

Compound **7b** had mp above 310°; ir: ν cm^{-1} 3100, 3020, 2230, 1670, 1650; ms: m/z 304 (M^+); pmr: 12.60 (s, 2H, N_4-H and $N_{4'}$-H), 8.44 (s, 2H, C_5-H and C_2-H), 7.82-7.30 (m, 4H, aromatic).

Anal. Calcd. for $C_{15}H_8N_6O_2$: C, 59.21; H, 2.65; N, 27.62. Found: C, 59.01; H, 2.87; N, 27.38.

Compound **7d** had mp above 310°; ir: ν cm^{-1} 3170, 3120, 3060, 2230, 1680, 1670; ms: m/z 318 (M^+); pmr: 12.53 (s, 2H, N_4-H and $N_{4'}$-H), 8.44 (s, 1H, C_5-H), 7.82-7.29 (m, 4H, aromatic), 2.43 (s, 3H, CH_3).

Anal. Calcd. for $C_{16}H_{10}N_6O_2$: C, 60.38; H, 3.17; N, 26.40. Found: C, 60.10; H, 3.16; N, 26.13.

6-(3-Oxo-3,4-dihydroquinoxalin-2-yl)-3-ethoxycarbonyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-7-one **7c** and 6-(3-Oxo-3,4-dihydroquinoxalin-2-yl)-2-amino-3-methoxycarbonyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-7-one **7e**.

General Procedure.

A solution of **1** (5 g, 18.0 mmoles) and the pyrazole **6c** (4.19 g) or **6e** (4.21 g) (27.0 mmoles, 1.5-fold) in pyridine (5 ml)/*N,N*-dimethylformamide (100 ml) was refluxed in an oil bath for 3 hours. Evaporation of the solvent *in vacuo* afforded yellow crystals **7c** or **7e**, respectively, which were triturated with ethanol and then collected by suction filtration. Recrystallization from *N,N*-dimethylformamide/ethanol afforded yellow needles **7c** (4.54 g, 74%) or **7e** (2.10 g, 32%).

Compound **7c** had mp above 310°; ir: ν cm^{-1} 3260, 1680; ms: m/z 351 (M^+); pmr: 12.55 (s, 2H, N_4-H and $N_{4'}$-H), 8.30 (s, 1H, C_5-H), 8.27 (s, 1H, C_2-H), 7.79-7.33 (m, 4H, aromatic), 4.34 (q, J = 7 Hz, 2H, CH_2), 1.34 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{17}H_{13}N_5O_4$: C, 58.12; H, 3.73; N, 19.94. Found: C, 58.07; H, 3.75; N, 19.83.

Compound **7e** had mp 295-297°; ir: ν cm^{-1} 3440, 1650; ms: m/z 352 (M^+); pmr: 12.49 (s, 1H, $N_{4'}$-H), 12.12 (s, 1H, N_4-H), 8.05 (s, 1H, C_5-H), 7.82-7.29 (m, 4H, aromatic), 6.07 (s, 2H, NH_2), 3.83 (s, 3H, CH_3).

Anal. Calcd. for $C_{16}H_{12}N_6O_4 \cdot \frac{1}{2}H_2O$: C, 53.19; H, 3.63; N, 23.26. Found: C, 53.43; H, 3.82; N, 23.43.

Acknowledgement.

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