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

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6-Quinoxalinyldihydropyrazolo[1,5-*a*]pyrimidin-7-ones **4a-d** were synthesized by the ring transformation of 3-(*N,N*-dimethylcarbamoyl)furo[2,3-*b*]quinoxaline hydrochloride **5**. Compounds **4a-d** were found to exist as the 4,7-dihydro-7-oxo form **E** in dimethyl sulfoxide based on the nmr spectral data.

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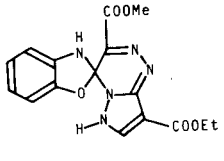
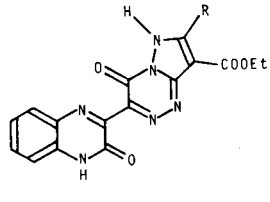
In a previous paper [2], we reported that the dihydropyrazolo[5,1-*c*][1,2,4]triazines **1,2** (Chart 1) synthesized by us [2,3,4] predominated as the 4,6-dihydro form **A**, but not the 1,4-dihydro form **B**, in the deuteriodimethyl sulfoxide (DMSO-d_6) solution (Chart 2). On the other hand, the dihydropyrazolo[1,5-*a*]pyrimidin-7-ones **3** (Chart 1) were reported to exist as a mixture of the 1,7-dihydro-7-oxo form **C** and 7-hydroxy form **D** (Chart 3) in the solid state [5]. However, there have been few papers concerning the tautomeric structure of dihydropyrazolo[1,5-*a*]pyrimidin-7-ones in a solution. In continuation of the above works, we found that the 6-quinoxalinyldihydropyrazolo[1,5-*a*]-pyrimidin-7-ones **4a-d** (Scheme 1) synthesized by the ring transformation of 3-(*N,N*-dimethylcarbamoyl)furo[2,3-*b*]-quinoxaline hydrochloride **5** [6] were predominant as the 4,7-dihydro-7-oxo form **E** (Chart 3) in the DMSO-d_6 solution. This paper describes a convenient synthesis of novel 6-quinoxalinyldihydropyrazolo[1,5-*a*]pyrimidin-7-ones **4a-d** and their tautomeric structure in the solution.

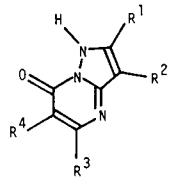
Chart 1



1

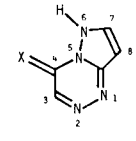


2 R=H,Me



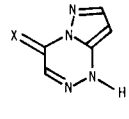
3 R^1=Me
R^2=H,COOEt
R^3=Me,Ph
R^4=H,CN

Chart 2



A

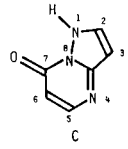
4,6-Dihydro Form



B

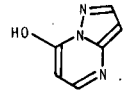
1,4-Dihydro Form

Chart 3



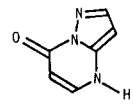
C

1,7-Dihydro-7-oxo Form



D

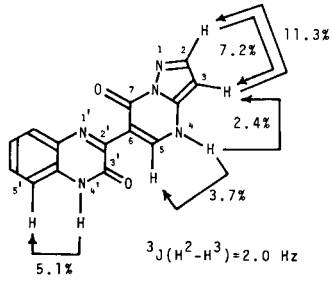
7-Hydroxy Form



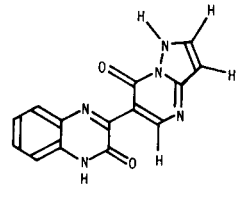
E

4,7-Dihydro-7-oxo Form

Chart 4



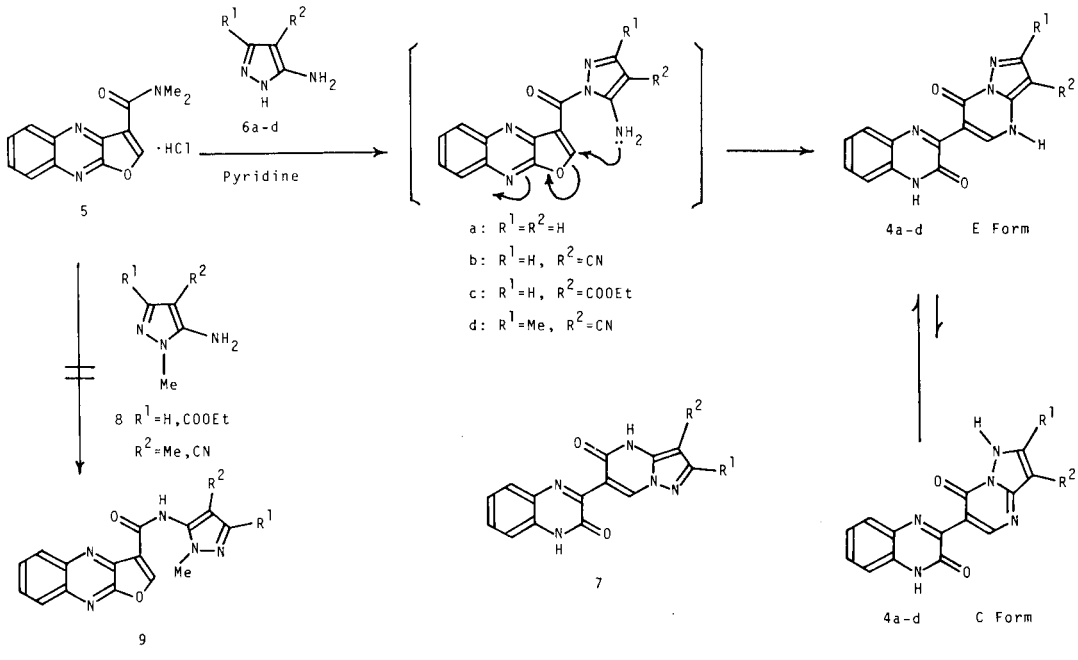
4a E Form



4a C Form

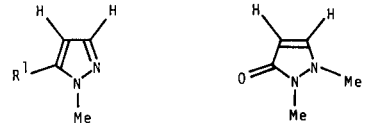
The reaction of 3-(*N,N*-dimethylcarbamoyl)furo[2,3-*b*]-quinoxaline hydrochloride **5** with the 5-amino-1*H*-pyrazoles **6a-d** in the presence of pyridine gave the 6-quinoxalinyldihydropyrazolo[1,5-*a*]pyrimidin-7-ones **4a-d**, respectively, but not the 6-quinoxalinyldihydropyrazolo[1,5-*a*]pyrimidin-5-ones **7** (Scheme 1). The formation of **7** was eliminated by the following results. Namely, the reaction of **5** with the 5-amino-1-methylpyrazoles **8** in

Scheme 1



the presence of pyridine did not afford 3-[*N*-(1-methylpyrazol-5-yl)carbamoyl]furo[2,3-*b*]quinoxalines **9**, but recovered the free base of **5**. Moreover, the one dimensional nOe different spectrum of **4a** in DMSO-d_6 supported the structure **4**, especially the 4,7-dihydro-7-oxo form **4E** (Scheme 1, Chart 3). The radiation at the N_4-H and $N_{4'}$-H proton signals (both observed at δ 12.50 ppm) showed the 2.4%, 3.7% and 5.1% nOe to the C_3-H, C_5-H and $C_{5'}$-H proton signals (δ 6.29, 8.32 and 7.35 ppm), respectively, but exhibited no nOe to the C_2-H proton signal (δ 7.96 ppm) (Chart 4), excluding the tautomeric structure of the 1,7-dihydro-7-oxo form **4C** (Scheme 1, Chart 3). The radiation at the C_2-H and C_3-H proton signals showed the 7.2% and 11.3% nOe to the C_3-H and C_2-H proton signals, respectively. The coupling constant between the C_2-H and C_3-H protons in the pyrazole ring of **4a** was 2.0 Hz, which was a similar value to that of the 1*H*-pyrazoles **10** (1.9-2.0 Hz) [7] (Chart 5), but not to that of the 1,2-dimethylpyrazolones **11** (3.50-3.60 Hz) [8], furnishing an additional evidence for the tautomeric structure **E**, but not **C**. The signals due to the C_2, C_{3a}, C_5, C_6 and C_7 carbons were similar among compounds **4a-c** (Table). These data indicated that the 6-quinoxalinyldihydropyrazolo[1,5-*a*]pyrimidin-7-ones **4a-d** existed as the 4,7-dihydro-7-oxo form **E** in a solution.

Chart 5



10 11

$^3J(H^3\text{-}H^4)$ 1.9-2.0 Hz

$^3J(H^3\text{-}H^4)$ 3.50-3.60 Hz

Table

^{13}C-NMR Spectral Data for Compounds **4a-c** [a]

Carbon	Compound **4a**	Compound **4b**	Compound **4c**
C_2	143.47 (dd, J = 184.0, J = 4.5)	145.38 (d, J = 194.3)	143.42 (d, J = 190.0)
C_3	89.96 (dd, J = 179.0, J = 10.5)	76.31 (d, J = 10.5)	97.57 (d, J = 10.0)
C_{3a}	141.39 (ddd, J = 9.0, J = 3.5, J = 8.5)	145.59 (dd, J = 10.0, J = 5.0)	142.86 (dd, J = 9.0, J = 4.5)
C_5	140.45 [b]	142.33 [b]	141.28 (d, J = 184.0)
C_6	105.30 (d, J = 2.5)	108.03 (d, J = 2.5)	108.57 (d, J = 2.0)
C_7	154.86 (d, J = 8.3)	154.16 (d, J = 8.5)	154.00 (d, J = 8.0)
$C_{2'}$	153.94 (d, J = 3.5)	152.69 (d, J = 3.5)	152.86 (d, J = 3.5)
$C_{3'}$	154.31 (s)	154.16 (s)	154.19 (s)

[a] Measured in DMSO-d_6. [b] Confirmed by COSY spectra.

EXPERIMENTAL

All melting points were determined on an 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 deuteriodimethyl sulfoxide 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 **4a**, 6-(3-Oxo-3,4-dihydroquinoxalin-2-yl)-3-cyano-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-7-one **4b** and 6-(3-Oxo-3,4-dihydroquinoxalin-2-yl)-3-cyano-2-methyl-4,7-dihydropyrazolo-[1,5-*a*]pyrimidin-7-one **4d**.

General Procedure.

A suspension of **5** (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 **4a**, brick red needles **4b** or orange needles **4d**, respectively, which were collected by suction filtration. Trituration with hot ethanol gave analytically pure samples, yield, **4a** (3.31 g, 66%), **4b** (4.45 g, 81%), **4d** (4.03 g, 70%).

Compound **4a**.

This compound 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 **4b**.

This compound 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 **4d**.

This compound 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 **4c**.

A solution of **5** (5 g, 18.0 mmoles) and the pyrazole **6c** (4.19 g, 27.0 mmoles) 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 **4c**, which were triturated with ethanol and then collected by suction filtration. Recrystallization from *N,N*-dimethylformamide/ethanol afforded yellow needles (4.54 g, 74%), 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.

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REFERENCES AND NOTES

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