Studies on Nucleosides Analogs. XVIII.¹ Synthesis of Pyrimido-[4,5-c]pyridazine Nucleoside Analogs²

HARUO OGURA,* MASAKAZU SAKAGUCHI, KENKO NAKATA, NOBUKO HIDA, and HISAKO TAKEUCHI

School of Pharmaceutical Sciences, Kitasato University, 5-9-1 Shirogane, Minato-ku, Tokyo 108, Japan

(Received August 19, 1980)

The reactions of 6-hydrazino-1,3-dimethyluracil (1) with aldoses (2a—e), d-fructose, and d-glucuronolactone gave hydrazones (3a—e, 6, and 8) in good yields, and these products were converted to pyrimido[4,5-c]pyridazine nucleoside analogs (4a—e, 7, and 9) by cyclodehydration.

Stereoisomers were isolated from the reaction mixtures of pyrimido[4,5-c]pyridazine derivatives, and were examined by CD spectroscopy.

On the other hand, the hydrazones (11a, b) of 1 with glycolaldehyde or (±)-glyceraldehyde were converted only to acetates (12a, b). Formation of the pyrimido[4,5-c]-pyridazine derivatives (13a, b) was not observed.

Keywords—6-hydradino-1,3-dimethyluracil; d-fructose; d-glucuronolactone; (±)-glyceraldehyde; glycolaldehyde; pyrimido[4,5-c]pyridazine nucleoside; CD; absolute configuration

As part of a series of synthetic studies of nucleoside analogs, we have reported the synthesis of theophylline and aminopyrazole[3,4-d]pyrimidine nucleoside analogs by the reaction of diamine and hydrazine derivatives with sugars.³,⁴ While several synthetic methods for nucleosides⁵ and nucleoside analogs⁶ by the reaction of hydrazine derivatives are known, they are not very convenient and produce nucleoside derivatives only in low yields.

In this paper, we describe the facile synthesis of pyrimido[4,5-c]pyridazine nucleoside analogs and the isolation of diastereomers from the reaction mixtures of 6-hydrazino-1,3-dimethyluracil (1) with sugars.


Chart 1
Hofmann, Wolfrom et al., and Mester et al. have reported the synthesis of acyclic sugar phenylhydrazones and acetylation of these hydrazones. By a similar procedure, hydrazones (3a–e) of 6-hydrazino-1,3-dimethyluracil (1) were obtained from refluxing mixtures of aldoses (2a–e) in good yields. These hydrazones (3a–e) were converted to the 1-acetyl-4-substituted pyrimido[4,5-c]pyrazidines (4a–e) by cyclodehydration with acetic anhydride containing pyridine at room temperature. As shown in Chart 1, 4a–e were converted to 1-acetyl-4-substituted pyrimido[4,5-c]pyrazidines (5a–e) in good yields by deacetylation with methanolic ammonia at 0°.

Me\(\text{N}^+\text{CH}_2\text{OH}
\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{O}
\)

\(\text{N}\)

\(\text{NH}_2\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)

\(\text{N}\)

\(\text{N}\)

\(\text{Me}
\)

\(\text{Me}
\)
Similarly, the reactions of 1 with D-fructose and D-glucuronolactone in methanol gave the hydrazones (6 and 8) in good yields, and these products were converted to pyrimido[4,5-c]-pyridazine derivatives (7 and 9) by cyclodehydration with acetic anhydride as shown in Chart 2.

On the other hand, the hydrazones (11a, b) prepared by the reaction of 1 with glycolaldehydes (10a) or (±)-glyceraldehyde (10b) were converted to acetylated pyrimidine derivatives (12a, b), and the desired pyrimido[4,5-c]pyrimidines (13a, b) were not obtained (Chart 3).

Serratke et al.\textsuperscript{10)} determined the configuration of acyclic sugar derivatives of benzothiazole and benzothiazoline by measuring the circular dichroism (CD) spectra. We also studied the relation of the stereochemistry of nucleoside analogs to the CD spectra by means of X-ray analysis.\textsuperscript{11)} From these data, nucleoside analogs having $S$ configuration at the anomeric position give positive CD bands at around 250—260 nm and 210 nm, and negative ones at around 290 nm and 230 nm. Compounds having $R$ configuration at the anomeric position give negative CD bands at around 250—260 nm and 210 nm, and positive ones at around 290 nm and 230 nm. We obtained a pair of diastereomers (4d), 4-\textit{R} and 4-\textit{S}, from the reaction mixture of hydrazone (3d) with acetic anhydride after column chromatography and recrystallizations. These isomers showed symmetrical CD curves, as summarized in Table I.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Configuration at C-4</th>
<th>Sugar</th>
<th>CD maxima ([θ]×10\textsuperscript{-3})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>I</td>
</tr>
<tr>
<td>4a</td>
<td>R</td>
<td>D-Arabinose</td>
<td>208(-37.9)</td>
</tr>
<tr>
<td>4b</td>
<td>S</td>
<td>L-Arabinose</td>
<td>207(+51.7)</td>
</tr>
<tr>
<td>4c</td>
<td>R</td>
<td>D-Glucose</td>
<td>213(-29.9)</td>
</tr>
<tr>
<td>(4d)</td>
<td></td>
<td>(D-Mannose)</td>
<td></td>
</tr>
<tr>
<td>4d</td>
<td>S</td>
<td>D-Mannose</td>
<td>211(+29.9)</td>
</tr>
<tr>
<td>7</td>
<td>S</td>
<td>D-Fructose</td>
<td>202(-16.0)</td>
</tr>
<tr>
<td>9</td>
<td>S</td>
<td>D-Glucuronolactone</td>
<td>207(+47.2)</td>
</tr>
<tr>
<td>5c</td>
<td>R</td>
<td>D-Glucose</td>
<td>203(+4.3)</td>
</tr>
<tr>
<td>(5d)</td>
<td></td>
<td>(D-Mannose)</td>
<td></td>
</tr>
<tr>
<td>5d</td>
<td>S</td>
<td>D-Mannose</td>
<td>215(+21.4)</td>
</tr>
</tbody>
</table>

On the basis of the data in Table I, compound (4d), having positive (260 nm)—positive (210 nm) Cotton effects, was considered to be 4-S, and the compound having negative (260 nm)—negative (210 nm) Cotton effects was considered to be 4-R.

From the reaction mixture of the hydrazone of d-glucose (3c) with acetic anhydride, only the 4-\textit{R} compound (4c) was isolated; 4c was confirmed to be the same compound as 4d, which was obtained from the hydrazone of d-mannose (3d), by mixed melting point determination and comparison of infrared (IR), nuclear magnetic resonance (NMR), and ultraviolet (UV) spectrum data.

In the case of other sugar hydrazones (3a, b, c, 6, and 8), only one compound (4-R or 4-S isomer) could be isolated. The CD data for these compounds are summarized in Table I.

From the CD data for these acyclic sugar-pyrimido[4,5-c]pyridazine derivatives (4a—e, 7, and 9), their configurations at C-4 were assigned as shown in Table I.

**Experimental**

All melting points are uncorrected. NMR spectra were measured with a Varian T-60 or a JEOL PS100 spectrometer, and Me\textsubscript{4}Si was used as an internal standard. Mass spectra (MS) were determined with a JEOL 01S spectrometer equipped with a direct inlet system at 75 eV. IR and UV spectra were obtained with a
JASCO IR A2 spectrometer and a Hitachi 340 spectrometer, respectively. CD curves were obtained on a JASCO J-20 spectropolarimeter in 1 mm and 0.1 mm cells; the concentration and length were adjusted to obtain the maximum signal.

General Procedure for the Reaction of Hydrazones (3a—e, 6, and 8) of Sugars with 6-Hydrazino-1,3-dimethyluracil (I)—6-Hydrazino-1,3-dimethyluracil (I) (0.01 mol) was added to a solution of a sugar (0.01 mol) in MeOH (80 ml), and the mixture was refluxed for 3 to 5 hr. After cooling, the separated crystalline products were collected by filtration, washed with EtOH, and recrystallized from 90% EtOH to give white or pale yellow crystals of the hydrazone (3a—e, 6, and 8). The results are summarized in Tables II and III.

1-Acetyl-4(R)-(o-erythro-triacectoxypropyl)-6,8-dimethylpyrimido[4,5-c]pyridazine-5,7-dione (4a)—A solution of 0.61 g (0.002 mol) of 3a in 10 ml of pyridine was treated with 10 ml of acetic anhydride at room temperature for 16 hr. The clear reaction solution was then concentrated to one-third of its original volume.

### Table II. Yields and Analysis Results of Hydrazones (3a—e, 6, 8, and 11a, b)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>Formula</th>
<th>Analysis (%)</th>
<th>Calcd</th>
<th>Found</th>
<th>C</th>
<th>H</th>
<th>N</th>
<th>C</th>
<th>H</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>93</td>
<td>183</td>
<td>C₂₇H₂₂N₆O₅</td>
<td></td>
<td>43.70</td>
<td>6.00</td>
<td>18.54</td>
<td>18.60</td>
<td>43.84</td>
<td>5.74</td>
<td>18.60</td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>93</td>
<td>178</td>
<td>C₂₇H₂₂N₆O₅</td>
<td></td>
<td>43.70</td>
<td>6.00</td>
<td>18.54</td>
<td>18.74</td>
<td>43.59</td>
<td>6.07</td>
<td>18.74</td>
<td></td>
</tr>
<tr>
<td>3c</td>
<td>94</td>
<td>165</td>
<td>C₂₇H₂₂N₆O₅</td>
<td></td>
<td>43.37</td>
<td>6.07</td>
<td>18.66</td>
<td>18.66</td>
<td>43.37</td>
<td>6.06</td>
<td>18.66</td>
<td></td>
</tr>
<tr>
<td>3d</td>
<td>87</td>
<td>192</td>
<td>C₂₇H₂₂N₆O₅</td>
<td></td>
<td>43.37</td>
<td>6.07</td>
<td>18.66</td>
<td>18.66</td>
<td>43.37</td>
<td>6.08</td>
<td>18.66</td>
<td></td>
</tr>
<tr>
<td>3e</td>
<td>93</td>
<td>175</td>
<td>C₂₇H₂₂N₆O₅</td>
<td></td>
<td>43.37</td>
<td>6.07</td>
<td>18.66</td>
<td>18.67</td>
<td>43.34</td>
<td>5.87</td>
<td>18.67</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>93</td>
<td>181</td>
<td>C₂₇H₂₂N₆O₅</td>
<td></td>
<td>43.37</td>
<td>6.07</td>
<td>18.66</td>
<td>18.63</td>
<td>43.38</td>
<td>6.04</td>
<td>18.63</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>94</td>
<td>157</td>
<td>C₂₇H₂₂N₆O₅</td>
<td></td>
<td>43.90</td>
<td>4.91</td>
<td>17.07</td>
<td>17.04</td>
<td>43.92</td>
<td>4.90</td>
<td>17.04</td>
<td></td>
</tr>
<tr>
<td>11a</td>
<td>71</td>
<td>159</td>
<td>C₂₇H₂₂N₆O₅</td>
<td></td>
<td>45.28</td>
<td>5.70</td>
<td>26.40</td>
<td>26.70</td>
<td>45.22</td>
<td>5.63</td>
<td>26.70</td>
<td></td>
</tr>
<tr>
<td>11b</td>
<td>74</td>
<td>192</td>
<td>C₂₇H₂₂N₆O₅</td>
<td></td>
<td>44.62</td>
<td>5.83</td>
<td>23.13</td>
<td>23.37</td>
<td>44.63</td>
<td>5.85</td>
<td>23.37</td>
<td></td>
</tr>
</tbody>
</table>

### Table III. Physical Data for Hydrazones (3a—e, 6, 8, and 11a, b)

<table>
<thead>
<tr>
<th>Compound</th>
<th>IR ν(κmax) cm⁻¹</th>
<th>NMR (in DMSO-d₆) δ</th>
<th>UV λ(κmax) nm (log ε)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OH, C=O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>3350, 1685</td>
<td>3.13 (3H, s, NMe), 3.37 (3H, s, NMe), 3.58—5.10 (9H, m, sugar-H), 5.35 (1H, s, 5-H), 7.72 (1H, d, d, =N=CH—), 10.12 (1H, s, NH)</td>
<td>220 (4.23)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>289 (4.22)</td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>3350, 1685</td>
<td>3.17 (3H, s, NMe), 3.38 (3H, s, NMe), 3.50—5.05 (9H, m, sugar-H), 5.40 (1H, s, 5-H), 7.78 (1H, d, d, =N=CH—), 10.17 (1H, s, NH)</td>
<td>220 (4.11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>288 (4.15)</td>
<td></td>
</tr>
<tr>
<td>3c</td>
<td>3350, 1680</td>
<td>3.17 (3H, s, NMe), 3.37 (3H, s, NMe), 3.35—5.35 (11H, m, sugar-H), 5.40 (1H, s, 5-H), 5.60 (1H, d, d, =N=CH—), 7.85 (1H, s, NH)</td>
<td>200 (4.22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>265 (4.25)</td>
<td></td>
</tr>
<tr>
<td>3d</td>
<td>3350, 1680</td>
<td>3.17 (3H, s, NMe), 3.37 (3H, s, NMe), 3.50—5.23 (11H, m, sugar-H), 5.43 (1H, s, 5-H), 7.77 (1H, d, d, =N=CH—), 10.20 (1H, s, NH)</td>
<td>200 (4.20)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>268 (4.22)</td>
<td></td>
</tr>
<tr>
<td>3e</td>
<td>3350, 1680</td>
<td>3.17 (3H, s, NMe), 3.40 (3H, s, NMe), 3.00—5.40 (11H, m, sugar-H), 5.42 (1H, s, 5-H), 7.77 (1H, d, d, =N=CH—), 10.10 (1H, s, NH)</td>
<td>218 (4.26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>250 (3.59)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3350, 1680</td>
<td>3.10 (3H, s, NMe), 3.30 (3H, s, NMe), 3.50—5.00 (12H, m, sugar-H), 5.33 (1H, s, 5-H), 8.20 (1H, s, NH)</td>
<td>207 (3.99)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>225 (4.03)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>3350, 1800</td>
<td>3.16 (3H, s, NMe), 3.35 (3H, s, NMe), 4.30—5.90 (8H, m, 5-H and sugar-H), 7.80 (1H, d, d, =N=CH—), 10.27 (1H, s, NH)</td>
<td>220 (4.24)</td>
</tr>
<tr>
<td></td>
<td>1680</td>
<td></td>
<td>288 (4.21)</td>
</tr>
<tr>
<td>11a</td>
<td>1685</td>
<td>3.10 (3H, s, NMe), 3.33 (3H, s, NMe), 4.07 (2H, m, CH₂), 5.10 (1H, m, OH), 5.30 (1H, s, 5-H), 7.67 (1H, t, d, =N=CH—), 10.00 (1H, bs, NH)</td>
<td>240 (4.24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>288 (4.30)</td>
<td></td>
</tr>
<tr>
<td>11b</td>
<td>1685</td>
<td>3.20 (3H, s, NMe), 3.40 (3H, s, NMe), 3.58 (2H, dd, CH₂O), 4.17 (1H, m, CH₂), 4.78 (1H, t, CH₂OH), 5.30 (1H, d, OH), 5.40 (1H, s, 5-H), 7.52 (1H, d, =N=CH—), 10.17 (1H, s, NH)</td>
<td>240 (4.21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>288 (4.27)</td>
<td></td>
</tr>
</tbody>
</table>
at 35—40° under reduced pressure, and the resulting syrup was poured into 100 ml of ice-water under stirring.

After extraction with CHCl₃, the extract was dried over MgSO₄ and evaporated to dryness under reduced pressure to yield 0.63 g (69%) of a pale yellow syrup. Crystallization from EtOH gave 0.30 g (33%) of 4a (4-R-form) as colorless needles, mp 150°C. Further recrystallization from EtOH gave colorless needles, mp 150°C. UV λmax nm (log e): 206 (4.5), 244 (4.0), 260 (4.0). MS m/z: 524 (M⁺). IR νmax cm⁻¹: 1735, 1700 (C=O). NMR (CDCl₃): δ 1.82—2.12 (9H, s × 3, OAc × 3), 2.57 (3H, s, NAc), 1.33 (3H, s, NMe), 1.35 (9H, s, NMe), 3.43 (3H, s, NMe), 4.00—5.60 (6H, m, 4-H and sugar protons), 5.80 (1H, d, 3-H). Anal. Calcd for C₂₃H₃₃NO₄: C, 50.58; H, 5.38; N, 10.68. Found: C, 50.59; H, 5.38; N, 10.73.

1-Acetyl-4(S)-(1-erythro-triacetoxypropyl)-6,8-dimethylpyrimido[4,5-c]pyridazine-5,7-dione (4S) —

According to the method described above, 3a (0.66 g, 0.002 mol) in 10 ml of pyridine was treated with 10 ml of acetic anhydride to give crude 4c (0.72 g, 69%) as a gummy precipitate. Crystallization from EtOH yielded 0.45 g (38%) of pure 4c (R-form) as colorless needles, mp 215°C. UV λmax nm (log e): 206 (4.3), 241 (4.1), 260 (4.0). MS m/z: 524 (M⁺). IR νmax cm⁻¹: 1735, 1700 (C=O). NMR (CDCl₃): δ 1.82—2.05 (12H, s × 4, OAc × 4), 2.63 (8H, s, NAc), 3.38 (3H, s, NMe), 3.43 (3H, s, NMe), 4.00—5.60 (6H, m, 4-H and sugar protons), 5.80 (1H, d, 3-H). Anal. Calcd for C₂₃H₃₃NO₄: C, 50.58; H, 5.38; N, 10.68. Found: C, 50.59; H, 5.38; N, 10.73.

1-Acetyl-4(R)-(4'-lipo-tetraacetoxybutyl)-6,8-dimethylpyrimido[4,5-c]pyridazine-5,7-dione (4E) —

According to the method described above, 3d (0.66 g, 0.002 mol) in 10 ml of pyridine was treated with 10 ml of acetic anhydride to give crude 4e (0.75 g, 72%) as a gummy precipitate. Crystallization from EtOH yielded 0.37 g (36%) of 4e-S (S-form) as colorless prisms, mp 200°C. UV λmax nm (log e): 204 (4.4), 240 (3.9), 260 (3.9). MS m/z: 524 (M⁺). IR νmax cm⁻¹: 1730, 1705 (C=O). NMR (CDCl₃): δ 1.82—2.05 (12H, s × 4, OAc × 4), 2.57 (3H, s, NAc), 3.35 (3H, s, NMe), 3.55 (3H, s, NMe), 3.80—6.20 (7H, m, 3-H, 4-H, and sugar protons). Anal. Calcd for C₂₃H₃₃NO₄: C, 50.38; H, 5.38; N, 10.68. Found: C, 50.22; H, 5.32; N, 10.61.

1-Acetyl-3-acetoxyethyl-4(S)-(1-propano-l-tetraacetoxybutyl)-6,8-dimethylpyrimido[4,5-c]pyridazine-5,7-dione (7) —

According to the method described above, 6 (0.66 g, 0.002 mol) in 15 ml of pyridine was treated with 15 ml of acetic anhydride to give crude 7 (0.75 g, 70%) as a gummy precipitate. Crystallization from EtOH yielded 0.40 g (38%) of 7 as colorless prisms, mp 141°C. UV λmax nm (log e): 204 (4.5), 240 (4.0), 260 (3.9). MS m/z: 524 (M⁺). IR νmax cm⁻¹: 1740, 1700 (C=O). NMR (CDCl₃): δ 1.35—2.20 (12H, s × 4, OAc × 4), 2.83 (3H, s, NAc), 3.38 (3H, s, NMe), 3.45 (3H, s, NMe), 4.20—5.18 (6H, m, sugar protons), 6.10 (1H, d, 4-H). Anal. Calcd for C₂₃H₃₃NO₄: C, 50.38; H, 5.38; N, 10.68. Found: C, 50.33; H, 5.40; N, 10.62.

1-Acetyl-4(S)-(4'-o-threeo-2',3'-di-O-acetyl-1'-ketouranoranyl)-6,8-dimethylpyrimido[4,5-c]pyridazine-5,7-dione (9) —

According to the method described above, 8 (0.66 g, 0.002 mol) in 15 ml of pyridine was treated with 15 ml of acetic anhydride to give crude 9 (0.54 g, 61%) as a gummy precipitate. Recrystallization from EtOH yielded 0.29 g (33%) of 9 (S form) as pale yellow prisms, mp 204°C. UV λmax nm (log e): 207 (4.4), 245 (3.9), 262 (4.0). MS m/z: 456 (M⁺). IR νmax cm⁻¹: 1800 (lactone), 1745, 1700 (C=O). NMR (CDCl₃): δ 1.87 (6H, s, OAc), 2.23 (6H, s, OAc), 2.62 (3H, s, NAc), 3.38 (3H, s, NMe), 3.50 (3H, s, NMe), 5.28 (1H, d, 2'-H), 5.43—5.53 (2H, m, 3'-H and 4'-H), 5.90 (1H, m, 4-H), 6.40 (1H, d, 3-H). Anal. Calcd for C₂₃H₃₃NO₄: C, 49.55; H, 4.82; N, 12.85. Found: C, 49.89; H, 4.85; N, 12.80.

General Procedure for the Reaction of Hydrazones (11a, b) of Glycolaldehyde (10a) or (±)-Glyceraldehyde (10b) with 6-Hydroxy-1,3-dimethyluracil (1) — Compound 1 (0.01 mol) was added to a solution of glycolaldehyde (10a) (0.01 mol) or (±)-glyceraldehyde (10b) (0.01 mol) in MeOH (80 ml), and the mixture was refluxed for 3 hr. The mixture was concentrated and the residue was treated with 30 to 50 ml of EtOH. The separated crystalline powder was collected by filtration, washed with warm ETOH, and recrystallized from ETOH to give pale yellow crystals of the hydrazone (11a, b). The results are summarized in Tables II and III.

Acetylation of Hydrazones (11a) — According to the method described above, 11a (0.42 g, 0.002 mol)
in 10 ml of pyridine was treated with 10 ml of acetic anhydride to give crude 12a (0.53 g, 79%) as a pale yellow crystalline powder. Recrystallization from 95% EtOH yielded 0.42 g (63%) of 12a as pale yellow prisms, mp 120°. UV λmax (nm (log e)): 204 (4.4), 240 (3.9), 260 (3.8). MS m/z: 338 (M+). IR νmax cm⁻¹: 1740, 1700 (C=O). NMR (CDCl₃) δ: 2.00–2.13 (6H, s × 2, 5-Ac and OAc), 2.72 (3H, s, NAc), 3.35 (3H, s, NMe), 3.48 (3H, s, NMe), 4.63 (2H, d, CH₂), 6.80 (1H, t, -N=CH-). **Anal.** Calcd for C₁₁H₁₅N₂O₄: C, 49.70; H, 5.36; N, 16.56. Found: C, 49.80; H, 5.33; N, 16.54.

**Acetylation of Hydrazine (11b)**—According to the method described above, 11b (0.48 g, 0.002 mol) in 12 ml of pyridine was treated with 12 ml of acetic anhydride to give crude 12a (0.68 g, 84%) as a pale yellow crystalline powder. Recrystallization from 95% EtOH yielded 0.50 g (62%) of 12a as colorless prisms, mp 155°. UV λmax (nm (log e)): 204 (4.5), 240 (4.0), 260 (3.9). MS m/z: 410 (M+). IR νmax cm⁻¹: 1740, 1700 (C=O). NMR (CDCl₃) δ: 2.13 (9H, s × 3, OAc × 2 and 5-Ac), 2.73 (3H, s, NAc), 3.33 (3H, s, NMe), 3.47 (3H, s, NMe), 3.45–4.65 (2H, m, CH₂), 5.83 (1H, d, CH), 6.77 (1H, d, -N=CH-). **Anal.** Calcd for C₁₇H₂₄N₄O₄: C, 49.75; H, 5.40; N, 13.65. Found: C, 49.86; H, 5.41; N, 13.70.

1-Acetyl-4(R)-(n-arabino-tetrahydroxybutyl)-6,8-dimethylpyrimidino[4,5-c]pyridazine-5,7-dione (5c-R Form and 5d-R Form)—A suspension of 1.01 g (0.002 mol) of compound 4c (R form) or 4d (R form) in 100 ml of saturated NH₄-MeOH was stirred at 0° for 5 hr. The solvent was removed at 30–35° under reduced pressure, and the dried residue was mixed with 15 ml of EtOH. The insoluble material was filtered off, and crystallized from EtOH to yield 0.67 g (98%) of 5c (R form) as colorless needles, mp 252°. UV λmax (nm (log e)): 204 (4.4), 240 (3.8), 258 (3.8). MS m/z: 356 (M+). IR νmax cm⁻¹: 3400 (OH), 1700 (C=O). NMR (CDCl₃) δ: 2.68 (3H, s, NAc), 3.23 (3H, s, NMe), 3.37 (3H, s, NMe), 3.10–5.63 (11H, m, 3-H, 4-H, and sugar protons). **Anal.** Calcd for C₁₄H₂₀N₄O₇: C, 47.19; H, 5.66; N, 15.72. Found: C, 46.97; H, 5.62; N, 15.54.

1-Acetyl-4(S)-(n-arabino-tetrahydroxybutyl)-6,8-dimethylpyrimidino[4,5-c]pyridazine-5,7-dione (5d-S Form)—According to the method described above, 4d (S form) (1.01 g, 0.002 mol) was treated with 100 ml of saturated NH₄-MeOH to give crude 5d (S form) (0.66 g, 96%) as a white crystalline powder. Recrystallization from EtOH yielded 0.62 g (90%) of 5d (S form) as colorless needles, mp 201°. UV λmax (nm (log e)): 204 (4.4), 240 (3.9), 258 (3.9). MS m/z: 356 (M+). IR νmax cm⁻¹: 3400 (OH), 1700 (C=O). NMR (CDCl₃) δ: 2.57 (3H, s, NAc), 3.20 (3H, s, NMe), 3.37 (3H, s, NMe), 2.80–5.80 (11H, m, 3-H, 4-H, and sugar protons). **Anal.** Calcd for C₁₄H₂₀N₄O₇: C, 47.19; H, 5.66; N, 15.72. Found: C, 47.21; H, 5.44; N, 15.68.

**References and Notes**


2) This constitutes Part XXXVI of a series entitled "Studies on Heterocyclic Compounds," by H. Ogura.


