A FACILE SYNTHESIS OF
1-(2-TETRAHYDROFURYL)-5-FLUOROURACIL (FTORAFUR)

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1-(2-Tetrahydrofuryl)-5-fluorouracil (1), a potent
anti-tumor agent, was conveniently synthesized by the
the condensation of 5-fluorouracil (2) with vari-
ous 2-alkoxy-2,3,4,5-tetrahydrofurans (3a-j), and the
best yield of 1, by this method was obtained in the
reaction of 2-t-butoxy analog (3h).

1-(2-Tetrahydrofuryl)-5-fluorouracil (1, Ftorafur) is a clinica-
ly effective anti-tumor agent which functions a nucleic acid anta-
gonist. There are many reports on the synthesis of 1,1,2 and we also
examined a simple preparation of this compound. Now we wish to
report an alternative synthesis of 1.

The Hilbert-Johnson procedure has been a representative method
to prepare pyrimidine nucleosides, and applied by Russian chemist1)
to the first synthesis of 1 by the reaction of 2-chlorotetrahydro-
furan (4) with 2,4-bis(trimethylsilyloxy)-5-fluorouracil (5). The mercury salt of 2 was also used instead of 5. Although several kinds of alternative syntheses of 5 by a reaction of some 2-alkoxy-2,3,4,5-tetrahydrofurans with 5 or 2 in the presence of acidic catalysts, were widely investigated, these methods have some defects in which unstable material was an intermediate and the process needed a severe condition.

Scheme 1

\[ \text{TMS=trimethylsilyl} \]

In order to explore a simplified synthesis of 5, we examined a condensation of 2 with various 2-alkoxy-2,3,4,5-tetrahydrofurans (3a-j)\(^{3}\) without using any catalysts. Heating 2 (1 g, 7.7 m mol) and 3a-j (11.6 m mol) at 150 - 165\(^{\circ}\) in dimethylformamide for 4 - 5 hr afforded successfully 5 (mp 164 - 165\(^{\circ}\); lit.,\(^{2}\) mp 164 -
165°) by simple work-up, namely evaporation of the solvent, followed by recrystallization. Among several 2-alkoxytetrahydrofurans (3a-j), the highest yield of 1 was obtained in case of 2-t-butoxytetrahydrofuran (3h).

Scheme 2

Table 1 The Yield of the Reaction of 2 with 3a-j

<table>
<thead>
<tr>
<th>Starting furans (3a-j)</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>e</th>
<th>f</th>
<th>g</th>
<th>h</th>
<th>i</th>
<th>j</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yield of 1 (%)</td>
<td>2.5</td>
<td>12.3</td>
<td>13.0</td>
<td>15.0</td>
<td>9.1</td>
<td>7.8</td>
<td>15.6</td>
<td>67.0</td>
<td>8.1</td>
<td>5.2</td>
</tr>
</tbody>
</table>

This reason would be due to the t-butoxy group of 3h which is more susceptible to its elimination than those of the others. However, the reaction of 2 with 3h in the presence of Lewis acid...
(AlCl$_3$) gave a less yield of 1 ($25\%$). Prolongation of the reaction time and addition of more excess of 3 in these reactions improved the yield of 4, but the best yield of 4 was again observed with using 4h. A detailed investigation of these reaction products revealed that a small amount of 2,4-bis(2-tetrahydrofuryl)-5-fluorouracil [5, mp 104 – 106$^\circ$; mass (m/e) 270 (M$^+$)] was also obtained. Hydrolysis of 5 by means of acetic acid yielded 4 quantitatively.

Thus, a facile synthesis of 4 is now available. The application of this procedure would provide a new class of preparative method of pyrimidine nucleosides.

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REFERENCES

3) These compounds were easily prepared by the addition of the

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