Synthesis of 1,2:5,6-Di-*O*-isopropylidene-3-*O*-[3-(5-fluorouracil-1-yl)-propionoyl]-α-D-glucofuranose and its Antitumor Activity

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In order to provide a less toxic 5-fluorouracil derivative, 1,2:5,6-di-*O*-isopropylidene-3-*O*-[3-(5-fluorouracil-1-yl)-propionoyl]-α-D-glucofuranose, which was the derivative of 5-fluorouracil combining indirectly to 3-position of diacetoneglucose, was synthesized, and its antitumor activity was tested.

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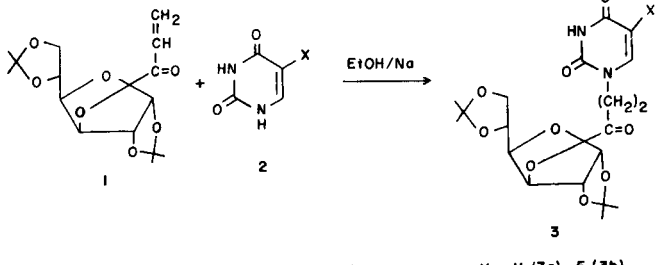
It has been reported that 5-fluorouracil has not only remarkable antitumor activity but also has strong side-effects [1,2]. In order to reduce the latter effects, 1-(tetrahydro-2-furanyl)-5-fluorouracil (ftorafur) [3] and 5-fluorouridine [4] were synthesized.

In the previous paper [5], as a non-toxic model of 5-fluorouracil, we synthesized 1,2:5,6-di-*O*-isopropylidene-3-*O*-[3-(uracil-1-yl)]-α-D-glucofuranose (**3a**), which did not contain a fluoro group at the 5-position of uracil. The present paper is concerned with the synthesis of 1,2:5,6-di-*O*-isopropylidene-3-*O*-[3-(5-fluorouracil-1-yl)propionoyl]-α-D-glucofuranose (**3b**), which is expected to hold a remarkable antitumor activity, *via* the synthetic route shown in Scheme 1.

Scheme 1



1 2 3

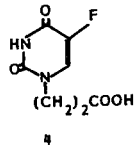
X = H (2a), F (2b) X = H (3a), F (3b)

We have synthesized **3b** by the Michael addition of 1,2:5,6-di-*O*-isopropylidene-3-*O*-acryloyl-α-D-glucofuranose (**1**) with 5-fluorouracil (**2**), according to the method established in the previous paper [5].

Table 1

Antitumor Activities of **3b** and **4**

Doses Tested (mg/kg)	T/C (%) **3b**	**4**
240	122	100
120	113	—
60	108	101
30	104	100



4

EXPERIMENTAL

Melting points were determined in capillary tubes on a warm plate and are uncorrected. The ir spectrum was recorded on a JASCO A-202 spectrophotometer, and the ^{1}H-nmr spectrum was measured with a JEOL PMX-60 spectrometer using tetramethylsilane as the internal standard. The ^{13}C-nmr spectrum was obtained on a JEOL JNM-PS-100 spectrometer equipped with a JNM-PET-100 Fourier transform accessory. The mass spectrum was obtained on a JEOL JMS-01SG spectrometer. Optical rotation was determined with a Union Digital PM-101 polarimeter. The reaction was monitored *via* tlc with Merck F_{254} silica gel plate, which was developed with petroleum ether-butanol (9:1 v/v).

1,2:5,6-Di-*O*-isopropylidene-3-*O*-acryloyl-α-D-glucofuranose (**1**) and 5-Fluorouracil (**2b**).

Compound **1** was prepared by the reaction of Schotten-Bauman of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose with acryloyl chloride in 5*N* sodium hydroxide solution, according to the method reported in the previous paper [5], mp 76.5-77.0°.

5-Fluorouracil (**2b**) of commercial reagent grade was used without further purification.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-[3-(5-fluorouracil-1-yl)propionoyl]-α-D-glucofuranose (**3b**).

Metallic sodium (0.10 g) and **2b** (0.20 g, 1.5 mmoles) were added into dried ethanol (10 cm^3). After evolution of hydrogen ceased, **1** (0.47 g, 1.5 mmoles) was added to the solution. The reaction mixture was refluxed in oil bath until the system became homogeneous. The reactant was evaporated under reduced pressure to give the crude product as a syrup. The residual syrup was subjected to column chromatography on silica gel. Elution with benzene-methanol (49:1 v/v) afforded the product as a white powder. The crude product was purified by reversed phase chromatography on C^{18}-ODS (eluting agent: water-methanol) (50:50 v/v), 0.39 g (58%), mp 103.5-104.8; ^{1}H-nmr (deuteriochloroform): δ 1.4-1.5 (t, 12H, $4CH_3$), 5.8 (d, 1H, H-1'), 7.7 (d, 1H, H-6 uracil ring), 10.0 (broad, 1H, NH); ^{13}C-nmr (deuteriochloroform): δ 170 (C=O, ester), 130 (5-C, uracil ring), 72.5 (5'-C, furan), 67 (6'-C, furan); ms: m/e 429 ($M^+ - 15$); uv (methanol): λ max 270.5 nm; ε max 9280; ir (potassium bromide): 3180 (NH), 2980 (CH), 1710 (ester C=O) and 1680 cm^{-1} (amide C=O); $[\alpha]_D^{25}$ −22° (c 0.1, methanol).

Anal. Calcd. for $C_{19}H_{25}FN_2O_9$: C, 51.35; H, 5.67; N, 6.30; F, 4.28. Found: C, 50.98; H, 5.68; N, 6.16; F, 4.46.

Antitumor Activity.

The antitumor effect of compound **3b** obtained was tested *in vivo* against P-388 leukemia in mice according to a typical NCI protocol [6]. Compound **3b** has anticancer activity, as shown in Table 1. However, it

was not at such a high level. On the contrary, 5-fluorouracil-1-propionic acid (**4**) has practically no activity under the same testing conditions, as shown in Table 1.

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