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

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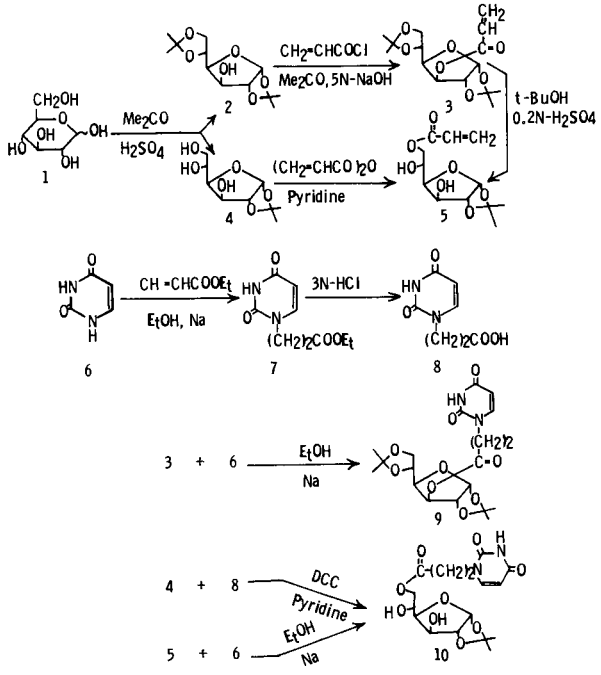
It has been reported that 5-fluorouracil not only has remarkable antitumor activity but also has strong side-effects (1-2). In order to counter the latter effects, 1-(tetrahydro-2-furanyl)-5-fluorouracil (futraful) (3) and 5-fluorouridine (4) were synthesized.

In order to provide non-toxic models of 5-fluorouracil and the pharmacons of polymeric drugs, 1,2:5,6-di-*O*-isopropylidene-3-*O*-[3-(uracil-1-yl)propionoyl]-α-D-glucofuranose (**9**) and 1,2-mono-*O*-isopropylidene-6-*O*-[3-(uracil-1-yl)propionoyl]-α-D-glucofuranose (**10**) were synthesized *via* the synthetic routes in Scheme 1.

Scheme 1



We have approached the synthesis of **9** by the following three methods: (i) the direct condensation reaction of **2** with 3-(uracil-1-yl)propanoic acid (**8**) by using dicyclohexylcarbodiimide (DCC) as a condensing agent; (ii) the Michael addition reaction of 1,2:5,6-di-*O*-isopropylidene-3-*O*-acryloyl-α-D-glucofuranose (**3**) with uracil (**6**); and (iii) the reaction of the sodium salt of **2** with the acid chloride of **8**. It was found that method (ii) allowed the best yields and the greatest ease of isolation. Compound **10** was prepared by the following two methods: (i) the direct condensation reaction of **4** with **8** by using DCC and (ii) Michael addition of 1,2-mono-*O*-isopropylidene-6-*O*-acryloyl-α-D-glucofuranose (**5**) with **6**.

EXPERIMENTAL

Melting points were recorded on a Yanagimoto micro melting point apparatus and are uncorrected. The ir spectra were recorded on a JASCO A-202 spectrophotometer and the nmr spectra were measured with a JEOL PMX-60 spectrometer using tetramethylsilane as the internal standard. The mass spectra were obtained on a JEOL JMS-01SG spectrometer. Optical rotations were determined with a Union Digital PM-101 polarimeter. The reactions were monitored *via* tlc with Merck F_{254} silica gel plates, which were developed with petroleum ether-1-butanol (9:1 v/v) for compounds **2**, **3** and **9**, and 1-butanol-ethanol-water (4:1:1 v/v) for compounds **4**, **5** and **10**.

1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (**2**), 1,2-Mono-*O*-isopropylidene-α-D-glucofuranose (**4**), and 3-(Uracil-1-yl)propanoic Acid (**8**).

Compounds **2**, **4** and **8** were prepared according to conventional methods. Compound **2** was obtained in a yield of 41%, mp 110°, lit (5) 110°. Compound **4** was obtained in a yield of 21%, mp 158-160°, lit (5) 160°. Compound **8** was obtained in a yield of 84%, mp 189-191°, lit (6,7) 191°.

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

A 5*N* solution of sodium hydroxide (5 ml) was added to a solution of **2** (1 g, 3.85 mmoles) in acetone (5 ml) and then acryloyl chloride (1 ml) was added dropwise to the mixture with stirring in an ice bath. After additional stirring at 0° for 1 hour, the reaction mixture was diluted with water (10 ml) and extracted with chloroform. The organic layer was washed several times with water to remove the salt and unreacted materials and dried over anhydrous sodium sulfate. The drying agent was filtered off and the filtrate was evaporated under reduced pressure to give a crude sirup. Crystallization of the sirup was induced in petroleum ether to give the needles, 0.59 g (49%), mp 76.5-77.0°; ^{1}H-nmr (carbon tetrachloride): δ 1.2-1.5 (m, 12H, $4CH_3$), and 5.9-6.3 (m, 3H, CH_2=CH); ir (potassium bromide): 2980 (CH), 1710 (ester C=O) and 1625 (C=C) cm^{-1}; $[\alpha]_D^{21}$ -58° (c 0.1, methanol).

Anal. Calcd. for $C_{15}H_{22}O_7$: C, 57.31; H, 7.05. Found: C, 57.14; H, 7.03.

1,2-Mono-*O*-isopropylidene-6-*O*-acryloyl-α-D-glucofuranose (**5**).

Compound 5 was synthesized by two methods.

Synthesis from Compound **4**.

To a solution of **4** (0.54 g, 2.46 mmoles) in pyridine (10 ml), acrylic

anhydride (0.26 ml) was added dropwise at -15°. The mixture was stirred for 4 hours at -15° and then was poured into a large amount of water to decompose the excess acrylic anhydride. Compound **5** was extracted with chloroform. The organic layer was washed with water and dried over anhydrous sodium sulfate. The drying agent was filtered and the filtrate was evaporated under reduced pressure below 40°. Consequently, the pale yellow sirup was obtained in good yield. This product was dissolved in a mixture of methanol-petroleum ether-ether, and cooled to crystallize as needles, 0.25 g (40%).

Synthesis from Compound **3** (Rearrangement of the Acryloyl Group from the 3 Position to the 6 Position of the Furan Ring).

Sulfuric acid (15 ml, 0.2*N*) was added to a solution of **3** (1 g, 3.18 mmoles) in *t*-butyl alcohol (5 ml) and allowed to react at room temperature for 24 hours with stirring. The reaction mixture was neutralized with barium carbonate. After filtration, the filtrate was lyophilized to give crude powder, which was subjected to column chromatography on silica gel. The isolated products were recrystallized from petroleum ether-methanol-ether to give colorless needles, 0.38 g (44%), mp 132-133°; ^{1}H-nmr (DMSO-d_6): δ 1.2-1.4 (d, 6H, $2CH_3$), 5.8-6.2 (m, 3H, CH_2=CH); ir (potassium bromide): 3460 (OH), 2980 (CH), 1700 (ester C=O) and 1620 (C=C) cm^{-1}; $[\alpha]_D^{21}$ -0.1° (c 1.0, methanol).

Anal. Calcd. for $C_{12}H_{18}O_6$: C, 52.51; H, 6.62. Found: C, 52.74; H, 6.51.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-[3-(uracil-1-yl)propionoyl]-α-D-glucofuranose (**9**).

Ethyl alcohol (70 ml) was distilled with benzene (9 ml) to separate water contained in the ethyl alcohol as an azeotrope of benzene. Into the distillate (30 ml) collected at 79-80°, metallic sodium (0.005 g) and uracil (0.53 g, 4.78 mmoles) were added. After evolution of hydrogen ceased, **3** (1.54 g, 4.78 mmoles) was added to the solution. The reaction mixture was refluxed in an oil bath until the system became homogeneous. The reactant was evaporated under reduced pressure to give the crude product as a sirup. The residual sirup was subjected to column chromatography on silica gel. Elution with benzene-methanol (49:1 v/v) afforded the desired product as a sirup. The product was lyophylized to give a white powder, 0.87 g (46%), mp 37.0-42.0°; ^{1}H-nmr (carbon tetrachloride): δ 1.3-1.5 (m, 12H, $4CH_3$), 5.6 (d, 1H, uracil ring) and 7.4 (d, 1H, uracil ring); ^{13}C-nmr (DMSO-d_6): δ 167 (C=O, ester), 105 (5-C, uracil ring), 73 (5′-C, furan), 65 (6′-C, furan); ir (potassium bromide): 3320 (NH), 2980 (CH), 1720 (ester C=O) and 1680 (amide C=O) cm^{-1}; $[\alpha]_D^{21}$ -24° (c 0.1, methanol); ms: m/e 426 (M^+).

Anal. Calcd. for $C_{19}H_{26}N_2O_9$: C, 53.52; H, 6.10; N, 6.57. Found: C, 53.91; H, 6.25; N, 6.23.

1,2-Mono-*O*-isopropylidene-6-*O*-[3-(uracil-1-yl)propionoyl]-α-D-glucofuranose (**10**).

Direct Condensation Reaction by DCC.

A solution of **4** (1.3 g, 5.76 mmoles), **8** (2.0 g, 10.86 mmoles) and DCC (2.2 g, 10.86 mmoles) in pyridine (25 ml) was stirred at 0° for 3 hours and continued for a further 3 hours at room temperature. After additional stirring for 30 minutes with water (30 ml), the mixture was extracted with chloroform and the extract was dried over anhydrous sodium sulfate. The drying agent was removed by filtration and the filtrate was evaporated under reduced pressure. The sirup obtained was subjected to thin layer chromatography on silica gel. The desired product was lyophilized to give a white powder, 0.40 g (19%).

Michael Addition Reaction.

Compound **10** could be obtained by the same procedure described above, using **5** and **6** as the starting materials, 0.29 g (14%), mp 102-104°; ^{1}H-nmr (DMSO-d_6): δ 1.1-1.3 (d, 6H, $2CH_3$), 5.4 (d, 1H, uracil ring), 7.4 (d, 1H, uracil ring); ir (potassium bromide): 3550 (OH), 3230 (NH), 1720 (ester C=O) and 1680 (amide C=O) cm^{-1}; $[\alpha]_D^{21}$ -0.1° (c 0.1, methanol).

Anal. Calcd. for $C_{16}H_{22}N_2O_9$: C, 49.73; H, 5.75; N, 7.25. Found: C, 49.77; H, 6.04; N, 6.99.

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