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5-Fluorouracil Derivatives. II.[1] A Convenient Synthesis of 5-Fluoro-2′-deoxyuridine

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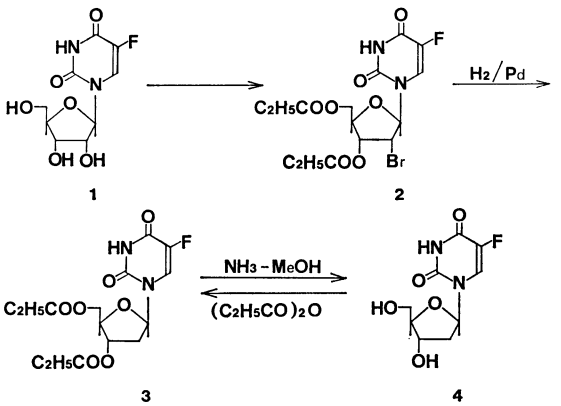
Synopsis. The reaction of 5-fluorouridine with propionyl bromide in acetonitrile afforded 3′,5′-di-*O*-propionyl-2′-bromo-5-fluoro-2′-deoxyuridine (**2**). Compound **2** was then hydrogenated, using Pd–C as the catalyst, to afford 3′,5′-di-*O*-propionyl-5-fluoro-2′-deoxyuridine (**3**). Compound **3** was deacylated with methanolic ammonia to give 5-fluoro-2′-deoxyuridine (FUDR). In this way, FUDR, a good antitumor agent, can easily be prepared from 5-fluorouridine by three steps in a 48.9% total yield.

5-Fluoro-2′-deoxyuridine (FUDR, **4**) was first prepared by enzymic procedures[2] and then by the chemical condensation method using a mercury-process.[3] In the latter process, methyl 2-deoxy-D-ribofuranoside was converted to the 3,5-di-*O*-*p*-toluoyl derivative, which was treated with HCl to give 3,5-di-*O*-*p*-toluoyl-2-deoxy-D-ribosyl chloride. 5-Fluorouracil-mercury was synthesized from 5-fluorouracil and mercury(II) acetate. The condensation of 3,5-di-*O*-*p*-toluoyl-2-deoxy-D-ribosyl chloride with 5-fluorouracil-mercury and the subsequent deacylation of the condensation product yielded **4** in a 30.8% total yield. Autitumor activities of **4** were demonstrated in several experimental tumors[4,5] and by clinical studies.[6]

Compound **4**, an approved drug for clinical use, has a remarkable anti-tumor activity with low toxicity. Unfortunately, this material was too expensive, because an industrial synthetic method had not yet been found.

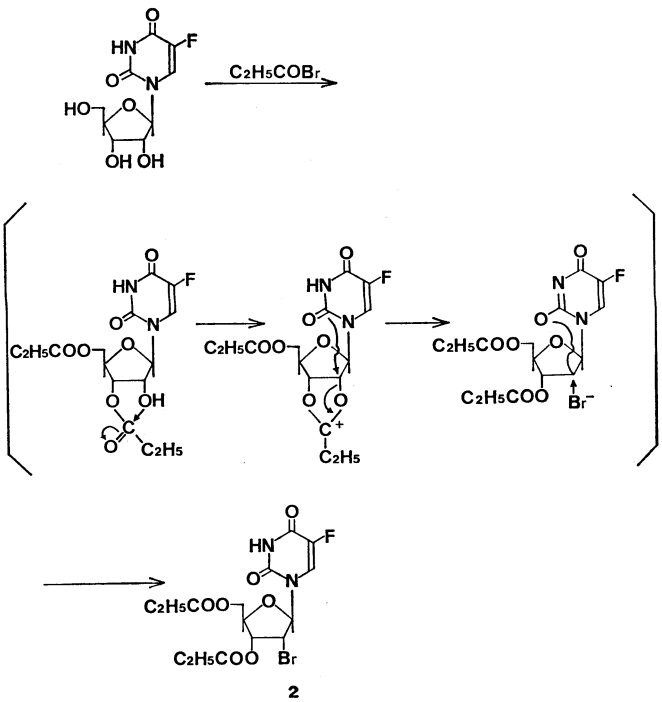
In this paper, we wish to report a convenient and industrial method for the synthesis of **4** starting from 5-fluorouridine (**1**), which can be prepared[7,8] easily from trimethylsilylated 5-fluorouracil and 1-acetyl-2,3,5-tribenzoylribose.

2′-Deoxyuridine was synthesized by Marumoto *et al.*[9] from uridine. When this synthetic procedure was applied to 5-fluorouridine (**1**), **4** was obtained from **1** *via* three steps in a 48.9% total yield. The synthetic route is illustrated in Scheme 1.



Scheme 1.

5-Fluorouridine (**1**) was suspended in acetonitrile, and the mixture was heated. Propionyl bromide was then added to the mixture at reflux to afford, after the usual work-up, 3′,5′-di-*O*-propionyl-2′-bromo-5-fluoro-2′-deoxyuridine (**2**) with a mp of 160—162 °C. This reaction may take place by means of the following mechanism,[9] even though no intermediate was isolated.



Compound **2** was hydrogenated on Pd–$BaSO_4$ as a catalyst at 1 atm 20 °C for 4 h to afford 3′,5′-di-*O*-propionyl-5-fluoro-2′-deoxyuridine (**3**) in a crystalline form in a 85.9% yield.

Compound **3** was also obtained by the reaction of authentic **4** with propionic anhydride, which was identical with the above sample. Compound **3** was deacylated with methanolic ammonia at 5 °C for 14 h to afford **4**. The structures of **2**, **3**, and **4** were confirmed by elemental analysis, IR, and NMR. The properties of the synthesized **4** were in good accord in all respects with those of an authentic **4** (obtained from PCR Inc. Gainesville, Florida, USA) and showed no depression in mixed mp. It may be concluded that this synthetic method is a convenient and inexpensive method to produce **4**.

Experimental

3′,5′-Di-O-propionyl-2′-bromo-5-fluoro-2′-deoxyuridine (2).

Into a boiling suspension of 5-fluorouridine (1310 mg, 5 mmol) in acetonitrile (60 ml), was added propionyl bromide (3 ml, 30 mmol) over a 30-min period. The stirring was then continued for a further 3 h. After the reaction mixture had been cooled, the solvent was evaporated, the residue was dissolved in methanol, and the solution was again evaporated to dryness. The residue was purified by column chromatography on silica gel using a benzene–methanol (4: 1) solvent. The crude product was crystallized from methanol to afford **2** (1764 mg, 80.8%): mp 160—161 °C. R_f=0.43 (benzene 4: methanol 1); IR (KBr) 3220, 3000, 1737 (s), 1710, 1475, 1392, 1357, 1289, 1270, 1212, 1180, 1162, 1098, 1068, 1040, 875, 812, cm^{-1}; NMR (60 MHz, CD_3OD) 1.12 (6H, t, J=7 Hz, CH_3), 2.44 (4H, q, J=7 Hz, CH_2), 4.36 (3H, m, OCH_2 and C_4'–H), 4.75 (CH_3O in CD_3OD+C_3'–H), 5.20 (1H, m, C_2'–H). Found: C, 40.96; H, 4.15; Br, 18.65; F, 4.25%. Calcd for $C_{15}H_{18}BrFN_2O_7$: C, 41.21; H, 4.15; Br, 18.28; F, 4.35%.

3′,5′-Di-O-propionyl-5-fluoro-2′-deoxyuridine (3). *a*): To a suspension of a 5% Pd–$BaSO_4$ catalyst (40 mg) in water (10 ml), was added a solution of **2** (169 mg, 0.364 mmol) and sodium acetate (89 mg, 1.09 mmol) in methanol (20 ml). The mixture was shaken in a hydrogen atmosphere at 1 atm and 23 °C for 4 h. The catalyst was then removed by filtration, and the filtrate was concentrated. The resulting sirup was mixed with water (10 ml) and extracted with chloroform. The chloroform layer was dried (Na_2SO_4) and evaporated. The residue was crystallized from ethanol to afford **3** (123 mg, 85.9%): mp 122—123 °C. TLC R_f=0.46 (benzene 4: methanol 1); IR (KBr) 3240, 3100, 3020, 1730 (s), 1685, 1470, 1372, 1290, 1280, 1260, 1200, 1180, 1142, 1076, 1012, 968, 927, 892, 866, 810, 789, 765 cm^{-1}. Found: C, 50.33; H, 5.38; F, 5.25; N, 7.71%. Calcd for $C_{15}H_{19}FN_2O_7$: C, 50.28; H, 5.34; F, 5.30; N, 7.82%.

b): A mixture of **4** (246 mg, 1 mmol), propionic anhydride (0.5 ml, 4 mmol), and anhydrous pyridine (20 ml) was heated at 110 °C for 2 h. The solvent was then evaporated *in vacuo*, and the residue was purified by column chromatography on silica gel (using 4: 1 benzene–methanol as the eluting solvent). Crude **3** was crystallized from ethanol to give pure **3** (277 mg, 77%): mp 122—123 °C.

5-Fluoro-2′-deoxyuridine (4). 3′,5′-Di-*O*-propionyl-5-fluoro-2′-deoxyuridine (218.6 mg, 0.61 mmol) in 20% methanolic ammonia (20 ml) was kept overnight at 5 °C. The reaction mixture was then concentrated to afford an oily substance. The oil was crystallized from methanol to afford **4** (177 mg, 70.5%); mp 150 °C. The sample was confirmed by IR, elemental analysis, and a mixed mp determination (150 °C) to be the same as the authentic **4**.

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