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Synthesis of Some Substituted Nucleoside Analogs

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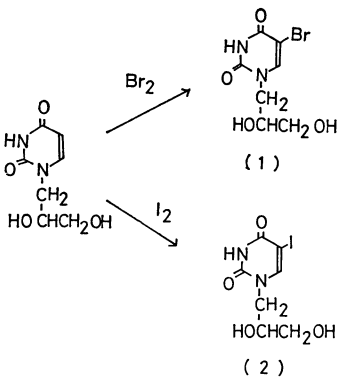
Polymers which contain nucleic acid bases in their main chain or in side groups present many interesting problems with respect to their physicochemical properties. But the water-insolubility of polymers was often encountered and was unsuitable for the study of physicochemical properties. This problem was solved by the introduction of phosphoric ester group into the main chain of polymer.[1-2] The authors have synthesized, further, water-soluble polymers particularly paying attention to the new structural analogs of nucleic acid.[3] Takemoto *et al.* reported on the derivatives of nucleic acid bases.[4]

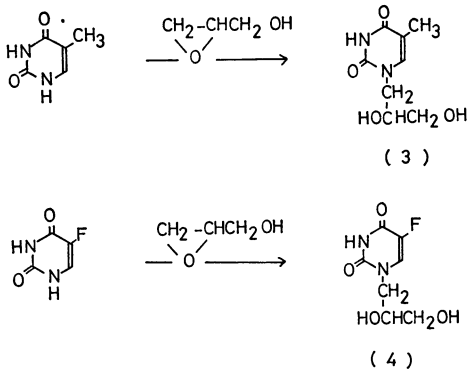
In this paper we describe the synthesis of 5-substituted uracil. The oligomers and polymers obtained from compounds of these types may provide a mean of studying chemotherapeutic applications. One of the most interesting utilization may be the incorporation of 5-halouracils into polymer, especially of the most important anti-cancer material, 5-fluorouracil.

Bromination of 1-(2′,3′-dihydroxypropyl)-uracil was carried out using bromine in mixture of 0.5 M nitric acid and *p*-dioxane to give 1-(2′,3′-dihydroxypropyl)-5-bromouracil (**1**). When 1-(2′,3′-dihydroxypropyl)-uracil was refluxed with iodine under similar condition described above, the 1-(2′,3′-dihydroxypropyl)-5-iodouracil (**2**) was formed in good yield. The position of substitution of bromine or iodine atom was confirmed by ultraviolet absorption. The ultraviolet absorption spectra of **1** and **2** are shifted toward longer wavelength than that of 1-(2′,3′-dihydroxypropyl)-uracil. The position of halogen atom was also checked by the absence of absorption peak at τ 4.2 corresponding to H-5 of uracil ring.



Scheme 1.

Thymine was treated with glycidol in DMF containing a trace of anhydrous potassium carbonate at 60—70 °C. Chromatography of reaction mixture on silica gel using benzene–ethanol as solvent gave the 1-(2′,3′-dihydroxypropyl)-5-methyluracil (**3**). Also the reaction of 5-fluorouracil with equimolar glycidol was carried out under similar condition to give 1-(2′,3′-dihydroxypropyl)-5-fluorouracil (**4**).



Scheme 2.

Experimental

The IR spectra were run on a JASCO Model IR-G Spectrometer. The UV spectra were measured by a Hitachi Recording Spectrometer Model ESP-3T. The NMR spectra were recorded with a Hitachi-Perkin-Elmer apparatus, Model R-20.

*1-(2′,3′-Dihydroxypropyl)-5-bromouracil (**1**).* A solution of 1-(2′,3′-dihydroxypropyl)-uracil (1.86 g, 10 mmol) dissolved in a mixture of 0.5 M nitric acid (20 ml) and *p*-dioxane (80 ml) was added to a solution of bromine (2.4 g, 15 mmol) in 20 ml of carbon tetrachloride, and the solution was stirred at room temperature for 3 hr. The reaction mixture was evaporated under reduced pressure to dryness. The oil residue is dissolved in ethanol, and the solution was evaporated to dryness. The obtained precipitate was recrystallized from ethanol to give **1** (2.5 g, (85%)) as colorless needles.

Mp 202—204°C, UV: $\lambda_{max}^{H_2O}$ 211 mμ (ε=9800), 283 mμ (ε=9100), IR: 3300 (OH), 1700, 1650 (bromouracil ring) and 1090, 1030 (primary and secondary alcohol C–O); NMR (DMSO-d_6) τ −1.15 (br s, 1, N_3–H), 2.0 (s, 1, C_6–H), 5.5 (br s, 2, $C_{2',3'}$–OH), 5.8—6.5 (m, 3, $C_{2',3'}$–H), 6.65 (br s, 2, C_1, –H); Found: C, 31.69; H, 3.48; N, 10.49%. Calcd for $C_7H_9N_2O_4Br$: C, 31.71; H, 3.42; N, 10.56%.

*1-(2′,3′-Dihydroxypropyl)-5-iodouracil (**2**).* Into a solu-

1) T. Seita, K. Yamauchi, M. Kinoshita, and M. Imoto, This Bulletin, **45**, 926 (1972).

2) T. Seita, K. Yamauchi, M. Kinoshita, and M. Imoto, *Makromol. Chem.*, **154**, 255 (1972).

3) T. Seita, K. Yamauchi, M. Kinoshita, and M. Imoto *ibid.*, **154**, 263 (1972).

4) a) K. Kondo, M. Miyata, and K. Takemoto, This Bulletin, **44**, 2554 (1971). b) N. Ueda. T. Kawabata and K. Takemoto, *J. Heterocyclic Chem.*, **8**, 827 (1971).

tion of 1-(2′,3′-dihydroxypropyl)-uracil (0.86 g, 10 mmol) in a mixture of 0.5 M nitric acid (20 ml) and *p*-dioxane (80 ml), iodine (5.1 g, 20 mmol) was added and the solution was refluxed for 3 hr. After allowing to cool to room temperature, the solvent was evaporated under reduced pressure. The residue was recrystallized from ethanol to give **2** (2.18 g, (80%)) as colorless needles.

Mp. 196—198°C, UV: $\lambda_{max}^{H_2O}$ 219 mμ (ε=12000), 292 mμ (ε=9800), IR; 3350 (OH), 1690, 1660 (iodouracil ring) and 1090, 1020 (primary and secondary alcohol C–O); NMR (DMSO-d_6) τ −1.15 (br s, 1, N_3–H), 1.9 (s, 1, C_6–H), 5.6 (br s, 2, $C_{2',3'}$–OH), 5.9—6.4 (m, 3, $C_{2',3'}$–H), 6.5 (br s, 2, $C_{1'}$–H); Found: C, 26.86; H, 2.90; N, 8.62%. Calcd for $C_7H_9N_2O_4I$: C, 26.93; H, 2.90; N, 8.97%.

*1-(2′,3′-Dihydroxypropyl)-5-methyluracil (**3**).* Thymine (1.25 g, 10 mmol) and glycidol (0.74 g, 10 mmole) in DMF (50 ml) containing a trace amount of anhydrous potassium carbonate was stirred at 60—65°C for 8 hr. The solvent was evaporated to dryness under reduced pressure. The residue was chromatographed over silica gel using a mixture of benzene and ethanol (4 : 1) as solvent. The obtained product was recrystallized from benzene–ethanol (7 : 1) to give the compound **3** (0.8 g, (40%)) as colorless needles.

Mp. 145—146°C, UV: $\lambda_{max}^{H_2O}$ 210 mμ (ε=13500), 273 mμ (ε=12000), IR: 3500 (OH), 1660 (thymine ring) and 1090, 1040 (primary and secondary alcohol C–O); NMR (DMSO-d_6) τ −1.15 (br s, 1, N_3–H), 8.2 (s, 3, N_5–CH_3), 2.8 (s, 1, C_6–H), 5.6 (br s, 2, $C_{2',3'}$–OH), 5.9—6.5 (m, 3, $C_{2',3'}$–H), 6.6 (br s, 2, $C_{1'}$–H); Found: C, 47.81; H, 5.89; N, 13.87%. Calcd for $C_8H_{12}N_2O_4$: C, 48.02; H, 6.04; N, 13.99%.

*1-(2′,3′-Dihydroxypropyl)-5-fluorouracil (**4**).* 5-Fluorouracil (1.29 g, 10 mmol) and glycidol (0.74 g, 10 mmol) was reacted in the way described in the case of **3**. The obtained product was recrystallized from a mixture of benzene–ethanol (9 : 1) to give the compound **4** (0.76 g, (38%)) as colorless needles.

Mp. 147—149°C; UV $\lambda_{max}^{H_2O}$ 210 mμ (ε=9800), 275 mμ (ε=9000), IR: 3350 (OH), 1720, 1650 (fluorouracil ring) and 1070, 1020 (primary and secondary alcohol C–O); NMR (DMSO-d_6) τ −1.18 (br s, 1, N_3–H), 2.2 (d, 1, C_6–H), 5.2 (br s, 2, $C_{2',3'}$–OH), 6.0—6.6 (m, 3, $C_{2',3'}$–H), 6.7 (br s, 2, $C_{1'}$–H); Found: C, 41.42; H, 4.51; N, 13.76%. Calcd for $C_7H_9N_2O_4F$: C, 41.18; H, 4.44; N, 13.72%.