A new method for the synthesis of N^3-alkylated analogs of 5-fluorouracil

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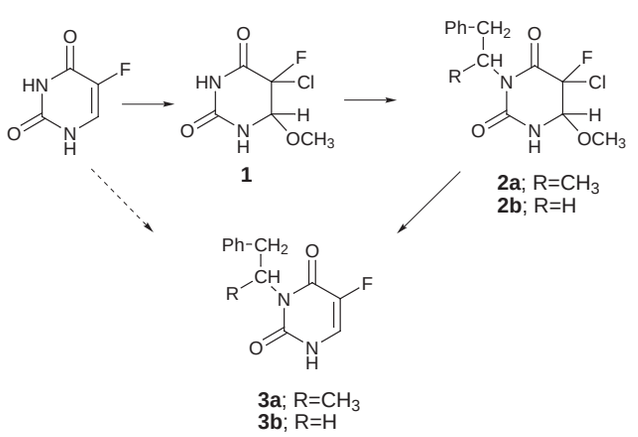
5-Fluorouracil has been converted to 5-chloro-5-fluoro-6-methoxy-5,6-dihydrouracil 1. Compound 1 was condensed with alcohols using a Mitsunobu reaction to give N^3-alkylated products 2a,b, which were hydrogenated in the presence of palladium on activated carbon to afford N^3-alkyl-5-fluorouracils 3a,b.

Since 5-fluorouracil is a potent anticancer agent,[1] many 5-fluorouracil derivatives have been prepared. Baker and Jackson reported that reaction of halogenoalkanes with excess amounts of 5-fluorouracil gave the 3-alkylated product, but yields from halogenoalkanes are limited to about 20% because of formation of the dialkylated product.[2] Recently, N^3-alkylation of uracil and derivatives *via* N^1-protected congeners has been reported.[3] However, it appeared more difficult to introduce a secondary alkyl group at N^3 of 5-fluorouracil. That prompted us to develop a novel method of N^3-alkylation of 5-fluorouracil. In this report synthesis of N^3-alkyl-5-fluorouracils by Mitsunobu reaction[4] of a 5-fluorouracil adduct with alcohols followed by reduction of the products is presented.

Reaction of 5-fluorouracil with *N*-chlorosuccinimide in methanol was carried out in a similar manner to that described by Miyashita *et al.*[5] to give 5-chloro-5-fluoro-6-methoxy-5,6-dihydrouracil **1** (91%). The product was proved to be one regioisomer by thin-layer and high-pressure liquid chromatography (HPLC). As reported in the literature,[5] Cl and OMe groups of the product were assumed to be *trans* to each other. Compound **1** was treated with 1-phenylpropan-2-ol in the presence of diisopropyl azodicarboxylate and triphenylphosphine in dry THF to give **2a** as a syrup (60%) (Scheme 1). The spectroscopic



Scheme 1

data suggested that the product **2a** was a condensate. Then compound **2a** was treated with palladium on activated carbon (5%) under H_2 atmosphere to give 5-fluoro-N^3-(1-phenyl-2-propyl)uracil **3a** (81%). The mechanism of reaction could be explained as follows. Catalytic reduction of **2a** affords 5-fluoro-6-methoxy-N^3-(1-phenyl-2-propyl)-5,6-dihydrouracil as an unstable intermediate, elimination of which affords **3a**.[6] The UV absorption of **3a** in alkaline solution was similar to that of 5-fluoro-N^3-alkyluracils,[2] indicating that N^3-alkylation on the 5,6-dihydrouracil ring had occurred. Thus the structure of **2a** was determined as 5-chloro-5-fluoro-6-methoxy-N^3-(1-phenyl-2-propyl)-5,6-dihydrouracil.

Compound **1** was also subjected to Mitsunobu reaction with phenethyl alcohol to give **2b**, from which 5-fluoro-N^3-(2-phenethyl)uracil **3b** was obtained (44% from **1**). Condensation of 5-fluorouracil with phenethyl alcohol was also examined, but only a trace of **3b** was observed on HPLC (3.7% conversion).

As a result of the current study, a novel method to synthesize N^3-alkylated analogs of 5-fluorouracil was developed.

Experimental

5-Chloro-5-fluoro-6-methoxy-5,6-dihydrouracil 1

To a suspension of 5-fluorouracil (3.90 g, 30 mmol) in methanol (210 ml) was added *N*-chlorosuccinimide (7.98 g, 60 mmol) and the solution was stirred at 50 °C overnight, then concentrated to dryness. The residue was crystallized from 50% EtOH to give a white crystalline solid (5.36 g, 91%), mp 208–210 °C (Found: C, 30.78; H, 3.13; N, 14.00. $C_5H_6ClFN_2O_3$ requires C, 30.55; H, 3.08; N, 14.25%); *m*/*z* 196, 198 (M^+), 165, 167 ($M^+ - CH_3O$), 165, 167 ($M^+ - CH_3OH$); δ_H ([$^2H_6$]-DMSO) 11.20 (1H, br s, N^3-H), 9.23 (1H, br, N^1-H), 5.00 (1H, dd, *J* 4.9, 1.1, 6-H), 3.36 (3H, s, OCH_3).

5-Chloro-5-fluoro-6-methoxy-N^3-(1-phenyl-2-propyl)-5,6-dihydrouracil 2a

To a mixture of 1-phenylpropan-2-ol (1.4 ml, 10 mmol) and **1** (0.98 g, 5 mmol) in dry THF (75 ml) was added triphenylphosphine (2.65 g, 10 mmol) and diisopropyl azodicarboxylate (1.1 ml, 5.1 mmol) and the solution was stirred at 50 °C overnight, then concentrated to a small volume. The residual solution was chromatographed on a column of silica gel G (3.0 × 55 cm) to give **2a** as a syrup (0.945 g, 60%), *m*/*z* 314.0817 (M^+, $C_{14}H_{16}ClFN_2O_3$ requires 314.0834); δ_H ($CDCl_3$) 7.15–7.30 (5H, m, Ph), 6.74 (1H, br s, N^1-H), 5.04 (1H, m, CH), 4.56 (1H, d, *J* 5.1, 6-H), 3.24–3.42 (4H, m, one of CH_2, OCH_3), 3.01 (1H, ddd, *J* 6.3, 12.1, 13.6, one of CH_2), 1.47 (3H, d, *J* 7.0, CH_3).

5-Fluoro-N^3-(1-phenyl-2-propyl)uracil 3a

A solution of **2a** (0.90 g, 2.86 mmol) in MeOH (50 ml) in the presence of palladium on activated carbon (5%, 0.20 g) was stirred vigorously under H_2 atmosphere at room temperature overnight. The catalyst was removed and the filtrate was concentrated to a small volume and chromatographed on a column of silica gel G (3.0 × 55 cm) to give a residue, which was crystallized from *n*-hexane (576 mg, 81%), mp 123.7–124.4 °C (Found: C, 62.69; H, 5.40; N, 11.24. $C_{13}H_{13}FN_2O_2$ requires C, 62.89; H, 5.28; N, 11.28%); *m*/*z* 248 (M^+); λ_{max} (MeOH)/nm 268; λ_{max} (0.1 M NaOH)/nm 300; δ_H ([$^2H_6$]-DMSO) 10.81 (1H, br s, N^1-H), 7.64 (1H, d, *J* 5.3, 6-H), 7.03–7.23 (5H, m, Ph), 5.06 (1H, m, CH), 3.25 (1H, dd, *J* 9.4, 13.3, one of CH_2), 2.95 (1H, dd, *J* 6.5, 13.3, one of CH_2), 1.35 (3H, d, *J* 6.8, CH_3).

5-Fluoro-N^3-phenethyluracil 3b

Compound **1** (0.98 g, 5 mmol) and phenethyl alcohol (1.2 ml, 10 mmol) were condensed as described in the preparation of **2a** to give **2b** (1.20 g); *m*/*z* 300.0663 (M^+, $C_{12}H_{14}ClFN_2O_3$ requires 300.0677); δ_H ($CDCl_3$) 7.21–7.32 (5H, m, Ph), 6.68 (1H, br s, N^1-H), 4.69 (1H, dd, *J* 5.1, 0.7, 6-H), 4.10 (1H, ddd, *J* 6.9, 8.8, 13.3, one of *N*-CH_2), 3.96 (1H, ddd, *J* 6.2, 8.8, 13.3, one of *N*-CH_2), 3.48 (3H, s, OCH_3), 2.90 (2H, m, CH_2Ph). The product was subjected to catalytic reduction to afford **3b** (44% from **1**), mp 158.8–161.5 °C (Found: C, 61.17; H, 4.75; N, 11.85. $C_{12}H_{11}FN_2O_2$ requires C, 61.53; H, 4.73; N, 11.96%); *m*/*z* 234 (M^+); λ_{max} (MeOH)/nm (log ε) 266 (3.76); λ_{max} (0.1 M NaOH)/nm (log ε) 297 (3.96); δ_H ([$^2H_6$]-DMSO) 8.88 (1H, br s, N^1-H), 7.84 (1H, d, *J* 5.5, 6-H), 7.17–7.36 (5H, m, Ph), 3.98 (2H, m, *N*-CH_2), 2.82 (2H, m, CH_2Ph).

5-Fluorouracil (0.65 g, 5 mmol) was subjected to Mitsunobu reaction with phenethyl alcohol (1.2 ml, 10 mmol) in a manner as described above and analyzed by HPLC. The ratio of 5-fluorouracil and **3b** was *ca*. 27 : 1, which showed 3.7% conversion of 5-fluorouracil to **3b**.

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