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Photochemical Reactions of 5-Fluoropyrimidine Bases with Alcohols

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Abstract: Photochemical reactions of 5-fluorocytosine with primary alcohols led to 5-alkoxycytosines and 6-alkoxycytosines as the main photoproducts. These products are formed *via* reactive intermediates 6-alkoxy-5-fluoro-5,6-dihydrocytosines, whereas photochemical reactions of 5-fluorouracil with alcohols led to stable 6-alkoxy-5-fluoro-5,6-dihydrouracils.

The photochemistry of 5-halogenopyrimidine bases has received particular attention due to the pronounced photoreactivity of 5-halogenopyrimidine-substituted nucleic acids and the potential use of photochemical cross-linking of such nucleic acids and proteins to probe contact positions located in nucleoprotein complexes.[1] Although there is ample literature on photocross-linking of proteins to 5-halogenopyrimidine-substituted nucleic acids, detailed information on the chemical structures of the conjugates and reaction mechanisms involved in their formation is often lacking.[2,3] In this study, we have focused on the hydroxyl group functionality which is present in the side-chains of amino acids serine and threonine. We report herein our results on the isolation and characterization of products obtained from photochemical reactions of 5-fluorocytosine and 5-fluorouracil with primary alcohols.

Irradiation of 5-fluorocytosine (**1**) in methanol with 254 nm ultraviolet light yields initially 5-fluoro-6-methoxy-5,6-dihydrocytosine (**2a**), which is unstable thermally and photochemically and undergoes quickly conversion to cytosine (**4**), 6-methoxycytosine (**5a**) and 5-methoxycytosine (**6a**) *via* unstable 5,6-dihydro-5,6-dimethoxycytosine (**3a**).[4]

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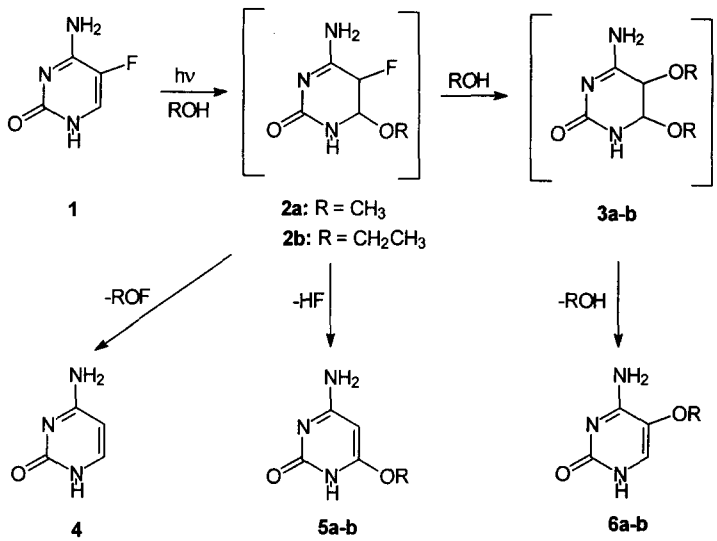
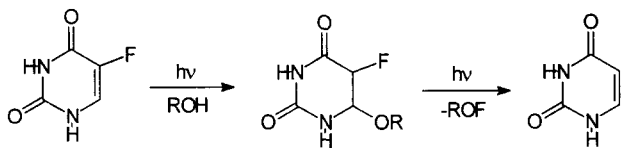


The photoreaction was monitored by high performance liquid chromatography (HPLC) equipped with photodiode array detector (PAD).[5] It was possible to isolate compound **2a** by HPLC and obtain its UV spectrum[6] using PAD. The spectrum shows no absorption band with maximum at 276 nm characteristic for the pyrimidine chromophore of 5-fluorocytosine. This indicates that saturation of the double bond C(5)=C(6) occurred. In the case of compound **3a**, which decomposed to **6a** more slowly, UV spectrum and mass spectrum were recorded.[7] The structures of stable products **4**, **5a** and **6a** were established on the basis of UV, MS, and NMR data.[8] The photoreaction of 5-fluorocytosine with ethanol proceeds similarly.

It is worth noting that photoreactions of 5-bromocytosine with alcohols yield cytosine as a main product. In this case, the cleavage of C(5)-Br bond takes place, which is weaker than C(5)-F bond. The photoreactions of 5-fluorocytosine with alcohols also differ from those of cytosine and 5-methylcytosine. In the case of 5-fluorocytosine nucleophilic attack of alcohols takes place at the C-6 position, whereas in the case of cytosine and 5-methylcytosine at the C-2 position, which leads to the cleavage of the C(2)-N(1) bond and formation of ring opened products: N-carboalkoxy-3-aminoacrylamidines.[9,10]

It should be noted that photoreactions of 5-fluorocytosine with alcohols can be employed for the synthesis of 5-alkoxycytosines and 6-alkoxycytosines.

Irradiation of 5-fluorouracil (**7**) in methanol with 254 nm ultraviolet light gives stable 5-fluoro-6-methoxy-5,6-dihydrouracil (**8a**) as a mixture of *cis* and *trans* isomers. Further irradiation of **8a** leads to slow formation of uracil (**9**). The photoreaction of 5-fluorouracil with ethanol proceeds similarly.



7 **8a:** R = CH_3 **9**

8b: R = CH_2CH_3

Compound **8a** was previously synthesized by fluorination of uracil with trifluoromethyl hypofluoride (CF_3OF) in methanol[11] and by treatment of 6-acetoxy-5-fluoro-5,6-dihydrouracil with methanol.[12,13]

The photoreactions of 5-bromouracil with alcohols yield uracil as a main product.[14] In this case the cleavage of weaker C(5)-Br bond takes place instead of photoaddition reaction.

Since the photoreactions of 5-fluorocytosine and 5-fluorouracil with alcohols are not photosensitized by acetone and presence of oxygen has no significant effect on the product formation, it is reasonable to assume, that they proceed with involvement of the singlet excited state.

Finally, our results suggest possible modes of photoinduced cross-linking between the alcoholic side chains of the amino acids serine and threonine, contained in proteins, and 5-fluoropyrimidine-substituted nucleic acids.

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References and Notes

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4. **General procedure for irradiations:** A solution of 5-fluoropyrimidine base (0.04 mmol) in alcohol (45 ml) was irradiated for 3 h in a cylindrical reactor using an immersed, water-cooled, 15 W low pressure mercury lamp (Heraeus, Germany) with a cylindrical Vycor light filter (2 mm thick). After removal of the solvent *in vacuo*, the products were isolated by preparative HPLC on Shiseido Capcell-Pak C_{18} reverse phase column (10 x 250 mm, 5 μm) using 5 mM aqueous lithium chloride as eluent. It was also possible to isolate the products by silica gel column chromatography using chloroform-methanol (50 : 1 v/v) as eluent. In the case of photoreaction of 5-fluorocytosine with methanol the products **4**, **5a** and **6a** were isolated in yields 9, 31 and 36%, respectively.

5. Analytical HPLC was carried out on a Shiseido Capcell-Pak C_{18} reverse phase column (4.6 x 250 mm, 5 μm) using 2 mM aqueous lithium chloride as eluent.

6. UV spectrum of **2a**: $\lambda_{max\,1}$ = 210 nm, $\lambda_{max\,2}$ = 243 nm (in 2mM aqueous lithium chloride).

7. UV spectrum of **3a**: $\lambda_{max\,1}$ = 214 nm, $\lambda_{max\,2}$ = 243 nm (in 2mM aqueous lithium chloride). Liquid secondary ion mass spectrum (LSIMS) of **3a**: (MH^+) 174 m/z.

8. Compound **5a**: UV (CH_3OH): λ_{max} = 277 nm. EIMS (high resolution): calcd for $C_5H_7N_3O_2$ 141.05383, found 141.05369. ^1H NMR (300 MHz, D_2O) δ: 3.67 (s, 3H, OCH_3), 5.19 (s, 1H, H-5). Compound **6a**: UV (CH_3OH): λ_{max} = 289 nm. EIMS (high resolution): calcd for $C_5H_7N_3O_2$ 141.05383, found 141.05391. ^1H NMR (300 MHz, D_2O) δ: 3.57 (s, 3H, OCH_3), 6.95 (s, 1H, H-6). ^{13}C NMR (75 MHz, D_2O) δ: 57.8 (q, OCH_3), 122.2 (s, C-5), 132.9 (d, C-6), 158.2 (s, C-2), 162.2 (s, C-4).

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