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Studies on Nucleosides and Nucleotides. V. Selective Aroylation of 5'-Hydroxyl Group of Uridine and Adenosine

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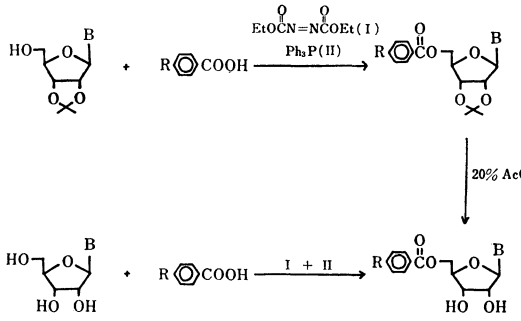
Synopsis. When uridine was allowed to react with diethyl azodicarboxylate, triphenylphosphine and either benzoic or *p*-nitrobenzoic acid at room temperature, 5'-*O*-aroyluridines were selectively obtained in good yields. Similarly, adenosine gave 5'-*O*-aroyladenosine. In this case, however, a small amount of N^3,5'-cycloadenosine was formed.

In a previous paper, the selective acylation of the 5'-hydroxyl group of thymidine by the use of diethyl azodicarboxylate (I) and triphenylphosphine (II) was described.[1] We now report selective aroylation of 5'-hydroxyl group of uridine and adenosine with a similar system.

When 2',3'-*O*-isopropylideneuridine was allowed to react with *p*-nitrobenzoic acid, I and II in dioxane containing a small amount of hexamethylphosphoric triamide (HMPA)[2] at room temperature overnight, 2',3'-*O*-isopropylidene-5'-*O*-(*p*-nitrobenzoyl) uridine (IIIb) was isolated in a 65% yield. Similarly, 2',3'-*O*-isopropylidene-5'-*O*-benzoyluridine (IIIa) and 2',3'-*O*-isopropylidene-5'-*O*-(*p*-nitrobenzoyl) adenosine (IVb) were obtained. The 2',3'-*O*-isopropylidene group of IIIa, IIIb and IVb was removed in the usual manner giving the corresponding 5'-*O*-aroylnucleosides (IIIc, IIId and IVd).

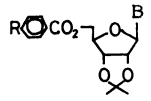
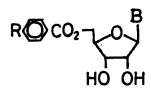
The reaction of uridine with I, II and either benzoic or *p*-nitrobenzoic acid under the same conditions as above also led to the formation of the corresponding 5'-*O*-aroyluridines (IIIc and IIId) in good yields. Examination of the crude reaction mixture on paper chromatography in four solvent systems revealed the presence of uridine and a nucleosidic product which have the same R_f values as the corresponding 5'-*O*-aroyluridine prepared from the 2',3'-*O*-isopropylideneuridines. In spite of an apparently clean reaction as judged by paper chromatographical analysis (IIIc, 83%; IIId, 80%), the isolated yields of the products were about 50%. Structures of the isolated IIIc and IIId were confirmed by elemental analyses, UV spectra and positive *cis*-diol test.[3] The total analysis thus gave assurance that the reaction of uridine with I, II and either benzoic or *p*-nitrobenzoic acid brings about selective aroylation of the 5'-hydroxyl group of uridine without any accompanying 2'- and/or 3'-*O*-aroylated products.



Following the method described above, 5'-*O*-(*p*-nitrobenzoyl)adenosine (IVd) was isolated in a 43% yield. The homogeneity of the isolated product was determined by paper chromatography in four solvent systems. The results are summarized in Table 1.

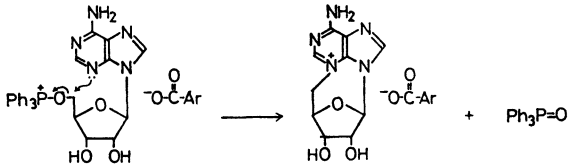
In the case of the aroylation of adenosine, however, the formation of a small amount of a side product was observed by examination of the reaction mixture with paper chromatography. The ultraviolet spectral characteristics of the side product indicated a chromophore similar to N^3, 5'-cycloadenosine (VI, λ_{max} 272

Table 1. Preparation of 5'-*O*-aroylnucleosides at room temperature

		B[a]	R	Yield[b] %	Mp °C	UV absorption Solvent	λ_{max} nm ($\varepsilon \times 10^{-4}$)		
	IIIa	Ur	H	43	145—146	95% EtOH	232 (1.50)	260	(1.01)
						THF		259	(1.32)
	IIIb	Ur	NO_2	65	214—215	THF		259	(2.58)
	IVb	Ad	NO_2	63	144—146	95% EtOH		259	(2.25)
						AcOH		260	(2.41)
	IIIc	Ur	H	56[c] (79.5) [20.2]	171—172	H_2O	234 (1.56)	263	(1.04)
	IIId	Ur	NO_2	50 (82.6) [15.2]	189—190	H_2O		262	(2.25)
	IVd	Ad	NO_2	43	229—230	THF		259.5	(2.67)

a) Ur=uracil, Ad=adenine. b) ( ): Yield estimated by paper chromatography. [ ]: Amount of recovered uridine estimated by paper chromatography. c) See Experimental.

nm, lit,[4] λ_{max} 273 nm). The formation of VI may be due to intramolecular displacement of an intermediate (V) of the present reaction.[5] When the reaction was carried out in *N,N*-dimethylformamide (DMF) at room temperature, the yield of VI was found to increase to 52% by paper chromatographical analysis.



5′-*O*-Aroyluridine and 5′-*O*-aroyladenosine were treated with methanolic ammonia (saturated at room temperature) at room temperature and the reaction was monitored by paper chromatography. While *p*-nitrobenzoyl group was completely removed within 1 h, it took 8 h for the complete removal of benzoyl group.

Experimental

Method. Paper chromatography was carried out by the ascending technique using Toyo Roshi No. 51A paper. Solvent systems were A, 1-butanol: 2 M HCl (3: 1); B, ethanol: 1 M ammonium acetate (7: 3); C, 1-butanol: acetic acid: water (5: 2: 3); D, 1-butanol: water (86: 14).

Table 2. Paper chromatography of different compounds

	R_f values in solvent system			
	A	B	C	D
Uridine	0.33	0.65	0.42	0.16
5′-*O*-Benzoyluridine	0.82	0.82	0.74	0.55
5′-*O*-*p*-Nitrobenzoyluridine	0.77	0.80	0.77	0.51
Adenosine	0.10	0.57	0.42	0.19
5′-*O*-*p*-Nitrobenzoyladenosine	0.50	0.73	0.71	0.51
N^3,5′-Cycloadenosine			0.32	

5′-O-Aroyluridine. A solution of 1.5 mmol each of benzoic acid and I in dioxane (1 ml) was added to a suspension of uridine (1 mmol) and II (1.5 mmol) in dioxane (1 ml) under vigorous stirring at room temperature over a period of 1 h. In the case of *p*-nitrobenzoylation, *p*-nitrobenzoic acid and I were dissolved in a mixture of dioxane (1 ml) and HMPA (0.5 ml). The mixture became clear within 1 h. After the solution was kept stirring overnight and the solvent was removed under reduced pressure, the residue was applied to a silica gel column (Wakogel C-300, 3.2 × 100 cm). The column was eluted with ethyl acetate giving the desired product, 5′-*O*-benzoyluridine (IIIc, 291 mg, 56%) or 5′-*O*-(*p*-nitrobenzoyl)uridine (IIId, 394 mg, 50%). In a large scale reaction, the isolated yield of IIIc increased to 77%.

5′-O-(p-Nitrobenzoyl)adenosine. The reaction was carried out in the same manner as described above. After removal of the solvent, the crude product was washed with methanol, and the remaining solid was suspended in water. The suspension was heated under reflux to dissolve unchanged adenosine. 5′-*O*-(*p*-Nitrobenzoyl)adenosine was left as insoluble solid (180 mg, 43%). The product was found to be homogeneous by paper chromatography and gave satisfactory results by elemental analysis. Paper chromatography of the crude reaction mixture indicated the presence of a small amount of N^3,5′-cycloadenosine (VI).

References

1) O. Mitsunobu, J. Kimura, and Y. Fujisawa, *Bull. Chem Soc. Jpn.*, **45**, 245 (1972).

2) HMPA was used in order to dissolve *p*-nitrobenzoic acid. The benzoylation of uridine was carried out in dioxane or THF.

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5) O. Mitsunobu and M. Eguchi, *Bull. Chem. Soc. Jpn.*, **44**, 3427 (1971); M. Wada and O. Mitsunobu, *Tetrahedron Lett.*, **1972**, 1279.