A NEW METHOD FOR SYNTHESIZING THE ANTINEOPLASTIC NUCLEOSIDES 1-(2-AZIDO-2-DEOXY-β-D-ARABINOFURANOSYL)CYTOSINE (CYTARAZID) AND 1-(2-AMINO-2-DEOXY-β-D-ARABINOFURANOSYL)CYTOSINE (CYTARAMIN) FROM URIDINE[1)]

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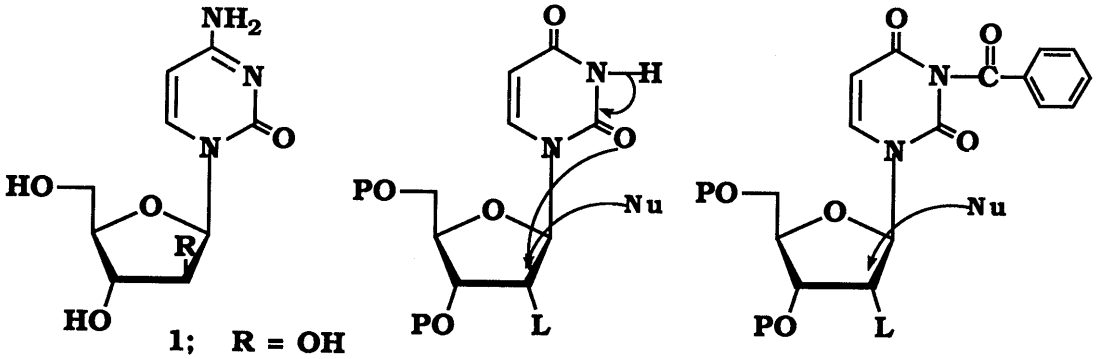
A new method was developed for synthesizing of antineoplastic nucleosides 1-(2-azido-2-deoxy-β-D-arabinofuranosyl)cytosine (**2**) and 1-(2-amino-2-deoxy-β-D-arabinofuranosyl)-cytosine (**3**) from uridine. The reaction of N3-benzoyluridine derivative (**5**) with DPPA, triphenylphosphine and diethyl azodicarboxylate gave the desired 2'-azido-arabinosyl derivative (**6**), which was subsequently transformed to lead **2** and **3**.

KEYWORDS cytarazid; cytaramin; uridine; N3-benzoyluridine; diethyl azodicarboxylate; diphenylphosphorazide; intermolecular nucleophilic substitution; 1-(2-azido-2-deoxy-β-D-arabinofuranosyl)cytosine; 1-(2-amino-2-deoxy-β-D-arabinofuranosyl)cytosine

1-(2-Azido-2-deoxy-β-D-arabinofuranosyl)cytosine (**2**, cytarazid) and 1-(2-amino-2-deoxy-β-D-arabino-furanosyl)cytosine (**3**, cytaramin) have been synthesized by Bobek *et al.*[2,3)] as analogs of 1-(β-D-arabino-furanosyl)cytosine (**1**, araC), one of the clinically useful anticancer drugs. These nucleosides are significantly antileukemic to mouse leukemia L1210, human T-cell acute lymphoblastic leukemia Molt 4F and HeLa cells *in vitro* at concentrations of 7 X 10^{-8} to 3 X 10^{-5} M. Also **2** and **3** are significantly antileukemic against L1210 *in vivo* when administrated at 40 and 75 mg/Kg, respectively, twice daily for 2 days, with over 120-day, long-term survivors. It is noteworthy that these nucleosides were resistant to cytidine deaminase, which converts araC to a chemotherapeutically inactive araU.

The original synthesis method for **2** involved a multistep synthesis of anomeric 3-*O*-acetyl-5-*O*-benzoyl-2-azido-2-deoxy-D-arabinofuranosyl chlorides from D-glucose to be condensed with a base.[2-5)] The desired β-nucleoside was obtained in only 37% by this method, along with the formation of the α-anomer

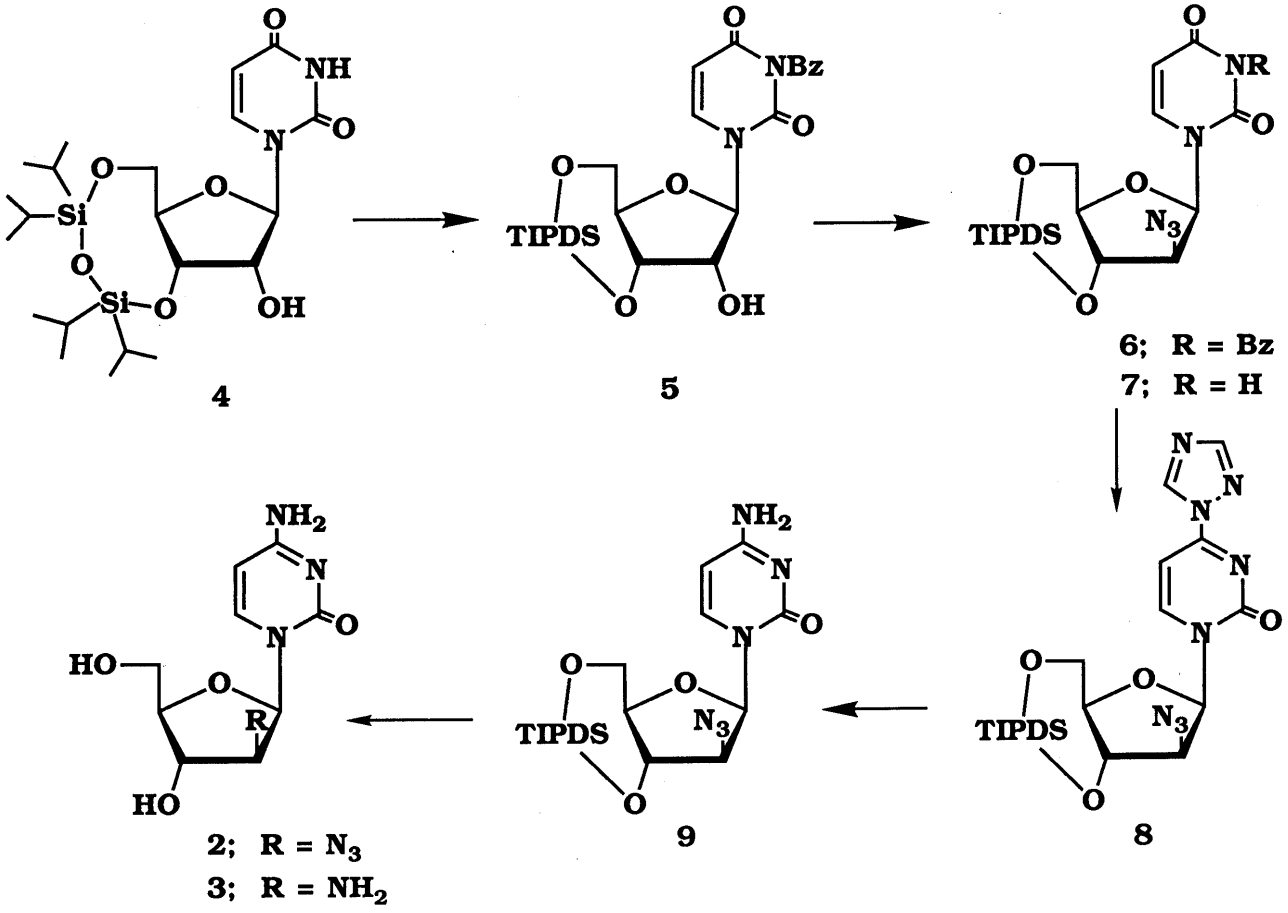


1; R = OH
2; R = N_3
3; R = NH_2

Chart 1

(10%).[6] Therefore, further evaluation of **2** and **3** depends on the availability of these compounds. It seems worthwhile to develop a synthetic route from ready accessible pyrimidine nucleosides such as uridine or cytidine. However, it has been generally recognized that the intramolecular nucleophilic attack of the 2-carbonyl group of the uracil base on the 2' position having a leaving group in the uridine derivative is predominant rather than the intermolecular nucleophilic substitution (Chart 1). For example, treatment of TIPDS-uridine with triflic anhydride afforded the 2,2'-anhydrouridine derivative only as an isolable product.[7] Loibner and Zbiral reported that 3'-azido-3'-deoxy-β-D-xylofuranosyluracil was obtained when 2',5'-di-*O*-trityluridine was treated with a combination of hydrogen azide, triphenylphosphine, and diethyl azodicarboxylate, without formation of the 2,3'-anhydrouridine derivative. However, when this procedure was applied to 3',5'-di-*O*-trityluridine, the product was the 2,2'-anhydrouridine derivative, and 2'-azido-2'-deoxy-β-D-arabino-furanosyluracil was not obtained at all.[8] If the nucleophilicity of the 2-carbonyl oxygen could be reduced, the direct SN2 reaction at the 2'-position of uridine would be realized. After several attempts, we found a benzoyl group as a choice of the N3-protection. In this communication we describe a new simple method for synthesizing **2** and **3** from N3-benzoyl-uridine derivative.

The starting nucleoside, 1-(3,5-tetraisopropyldisiloxan-1,3-diyl)-β-D-ribofuranosyl-N3-benzoyluracil (**5**) in 69% yield, was obtained by treating of compound (**4**) with benzoyl chloride (1.1 mol eq) in the presence of triethylamine in dichloromethane. When nucleoside **5** was treated with a mixture of hydrogen azide, triphenylphosphine and diethyl azodicarboxylate[7] in tetrahydrofuran at room temperature, the desired 2'-"up"-azidouridine derivative (**6**) was obtained in 62% yield as a foam after purification over a silica gel column. The ^{1}H-NMR spectrum of **6** showed a doublet (6.9 Hz) for H-1' at 6.24 ppm. This shows that the 2'-substituent is oriented to *cis* to the glycosyl linkage. Compound **6** was then deprotected to the free nucleoside, 1-(2-azido-2-deoxy-β-D-arabinofuranosyl)uracil, whose physical properties are clearly different from those of the known 1-(2-azido-2-deoxy-β-D-ribofuranosyl)uracil.[9] Thus, it is clear that the



intermolecular nucleophilic substitution of **5** by azide ion overcomes the intramolecular attack of the 2-carbonyl nucleophile by protecting the N3-position of uridine with the benzoyl group. To avoid using toxic hydrogen azide, we then examined diphenylphosphorazide (DPPA).[10] In the combination with DPPA, triphenylphosphine and diethyl azodicarboxylate,[11] we obtained the best result from **5** to yield **6** in 74%. This is, to our knowledge, the first indication that the intermolecular nucleophilic substitution is superior to the intramolecular displacement of the 2-carbonyl nucleophile of uridine to the 2'-position.

Compound **6** was then treated with NH_4OH in MeOH to afford a crystalline **7** (94% yield),[12] which was a key intermediate to cytarazid and cytaramin. Compound **7** was converted to the 4-triazolide (**8**) by treatment with phosphoryl oxychloride, triethylamine and 1,2,4-triazole in acetonitrile,[13] which was then converted to the cytidine derivative (**9**) by treatment with NH_4OH. Subsequently, compound **9** was deblocked by treatment with tetrabutylammonium fluoride to give cytarazid (**2**) in 80% yield as HCl salt.[14] Cytarazid (**2**) was hydrogenated over Pd-carbon in HCl/MeOH to furnish cytaramin (**3**), obtained as 2HCl salt in 94% yield.[15]

The overall yield of **2** from uridine was 33% and this method seems superior to the current condensation procedure.

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12) mp 156-157°C (MeOH); ^{1}H-NMR ($CDCl_3$) δ: 1.07 (28H, m, iso-Pro), 3.83-4.32 (5H, m, 2',3',4',5',5''-H), 5.71 (1H, d, 5-H, $J_{5,6}$ = 8.1 Hz), 6.25 (1H, d, 1'-H, $J_{1',2'}$ = 6.1 Hz),7.63 (1H, d, 6-H, $J_{5,6}$ = 8.1 Hz), 8.36 (1H, brs, NH); IR(nujol) 2190 cm^{-1}.
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14) mp 165°C (eff. H_2O-EtOH); ^{1}H-NMR (DMSO-d6 + D_2O) δ: 3.64-3.87 (3H, m, 4',5',5''-H), 3.97 (1H, dd, 3'-H, $J_{2',3'}$ = 5.6, $J_{3',4'}$ = 5.9 Hz), 4.31 (1H, dd, 2'-H, $J_{1',2'}$ = 5.9, $J_{2',3'}$ = 5.6 Hz), 5.74 (1H, d, 5-H, $J_{5,6}$ = 7.6 Hz), 6.14 (1H, d, 1'-H, $J_{1',2'}$ = 5.9 Hz), 7.71 (1H, d, 6-H, $J_{5,6}$ = 7.6 Hz).
15) mp 192°C (H_2O-MeOH); ^{1}H-NMR (D_2O) δ: 3.85 (1H, dd, 5'-Ha, $J_{4',5'a}$ = 3.3, $J_{5'a,5'b}$ = 12.8 Hz), 3.99 (1H, dd, 5'-Hb, $J_{4',5'b}$ = 2.2 Hz), 4.19 (1H, ddd, 4'-H, $J_{3',4'}$ = 5.5 Hz), 4.23 (1H, t, 3'-H, $J_{2',3'}$ = $J_{3',4'}$ = 5.5 Hz), 4.48 (1H, t, 2'-H, $J_{1',2'}$ = $J_{2',3'}$ = 5.5 Hz), 6.22 (1H, d, 1'-H), 6.29 (1H, d, 5-H, $J_{5,6}$ = 7.9 Hz), 8.20 (1H, d, 6-H, $J_{5,6}$ = 7.9 Hz).

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