Studies on Nucleosides and Nucleotides. XI.[1] Synthesis of 5′-Deoxypyrimidine Nucleosides

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Synopsis. When 2′,3′-*O*-(triphenylphosphoranediyl)-O^2,5′-cyclouridine and N^4-benzoyl-2′,3′-*O*-(triphenylphosphoranediyl)-O^2,5′-cyclocytidine were allowed to react with tributyltin hydride in the presence of azobisisobutyronitrile under reflux, 5′-deoxyuridine (84% yield) and N^4-benzoyl-5′-deoxycytidine (71% yield) were obtained.

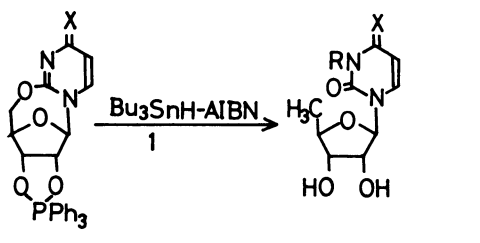
Tributyltin hydride (**1**) has been widely used as a reducing agent for organic compounds which include alkyl halides,[2a] nitro compounds,[2b] and xanthates.[2c]

In this paper we wish to report the reaction of 2′,3′-*O*-(triphenylphosphoranediyl)cyclonucleosides with **1**.

When 2′,3′-*O*-(triphenylphosphoranediyl)-O^2,5′-cyclouridine (**2**) was allowed to react with two molar amounts of **1** in the presence of azobisisobutyronitrile (AIBN) in THF under reflux for 6 h, 5′-deoxyuridine (**3**)[3] was obtained in 84% yield. When three molar amounts of **1** were used, a minor, more polar product was isolated by preparative layer chromatography ($CHCl_3$:MeOH=10:1). Based on ^{1}H-NMR spectroscopy, the structure of the side product was assigned to be N^3-methyl-5′-deoxyuridine (**4**) which would be formed during work-up. Thus, **2** was first reacted with **1** in THF as above, followed by addition of methanol, and the resulting solution was refluxed for 8 h. Compound **4** was expectedly isolated in 40% yield along with **3** (60%). Reduction of N^4-benzoyl-2′,3′-*O*-(triphenylphosphoranediyl)-O^2,5′-cyclocytidine (**5**) by the use of two molar amounts of **1** in the presence of AIBN afforded N^4-benzoyl-5′-deoxycytidine (**6**) in 71% yield. Products **3**, **4**, and **6** were readily converted into the corresponding acetonides, indicating that the 2′- and 3′-hydroxyl groups have the original cis configuration.

Contrary to the case of pyrimidine nucleosides, 3′,5′-*O*-(triphenylphosphoranediyl)adenosine or 2′,3′-*O*-(triphenylphosphoranediyl)-N^3,5′-cycloguanosine did not react with **1**.

From these results, it is proved that **1** does not react at the phosphoranediyl group but induces cleavage of the O^2,5′-anhydro bond of **2** or **5**.



2 X=O
5 X=NBz

3 X=O R=H
4 X=O R=Me
6 X=NBz R=H

We next examined the reaction of 2′,3′-*O*-isopropylidene-O^2,5′-cyclouridine (**7**) under the same conditions where 5′-deoxy-2′,3′-*O*-isopropylideneuridine was obtained in only 31% yield with 63% recovery of **7**. On the other hand, O^2-methyluridine, 5′-*O*-benzoyl-O^2,2′-cyclouridine, and O^2,2′-cyclocytidine hydrochloride were not reduced by **1** and starting materials were quantitatively recovered.

It is generally known that the O^2,2′-anhydro bond of pyrimidine nucleosides is more stable than the O^2,5′-anhydro bond.[4] The difference of reactivity between **2** and **7** might be due to 2′,3′-*O*-protecting group which exerts influence on the stability of O^2,5′-anhydro bond. Thus the phosphoranediyl group activate the O^2,5′-anhydro bond of **2** or **5** to some extent compared to isopropylidene group.

Experimental

5′-Deoxyuridine (3) and N^3-Methyl-5′-deoxyuridine (4). A suspended solution of **2** (486 mg, 1 mmol),[5] **1** (582 mg, 2 mmol), and AIBN (40 mg) in THF (15 ml) was refluxed under nitrogen atmosphere for 6 h. As the reaction proceeded, the solution became homogeneous. The reaction solution was evaporated and 191 mg (84% yield) of the product **3** was obtained by column chromatography (Merck Kieselgel 60, solvent; $CHCl_3$: MeOH=5:1), followed by recrystallization from CH_3CN and had mp 187—189 °C (lit,[3] mp 182—184 °C); UV_{max}^{MeOH} 264 (ε 9800) nm; UV_{min} 232 nm. Found: C, 47.32; H, 5.30; N, 12.29%. Calcd for $C_9H_{12}O_5N_2$: C, 47.37; H, 5.30; N, 12.28%. NMR (DMSO-d_6) δ=1.28 (d, 3H, C$_{5'}$H), 5.63 (d, 1H, C$_5$H), 5.69 (d, 1H, C$_{1'}$H), and 7.55 ppm (d, 1H, C$_6$H).

Similarly, the reaction of **2** with three molar amounts of **1** in the presence of AIBN in THF was carried out under reflux for 6 h and methanol (20 ml) was added to the resulting mixture. The solution was successively refluxed for 8 h and evaporated. The products were separated by column chromatography (solvent; $CHCl_3$: MeOH=10:1) to give **3** and **4** in 60% and 40% yields, respectively. Compound **4** recrystallized from benzene had mp 107—109 °C; UV_{max}^{MeOH} 263 nm; UV_{min} 234 nm. Found: C, 49.48; H, 5.81; N, 11.55%. Calcd for $C_{10}H_{14}O_5N_2$: C, 49.48; H, 5.83; N, 11.57%. NMR ($CDCl_3$) δ=1.43 (d, 3H, C$_{5'}$H), 3.30 (s, 3H, CH_3), 5.65 (d, 1H, C$_{1'}$H), 5.78 (d, 1H, C$_5$H), and 7.43 ppm (d, 1H, C$_6$H).

N^4-Benzoyl-5′-deoxycytidine (6). The reaction of **5**[5] with two molar amounts of **1** in the presence of AIBN in THF under reflux for 6 h gave **6** in 71% yield. The **6** recrystallized from methanol had mp 201—202 °C; UV_{max}^{MeOH} 261 (ε 22200); 306 nm, UV_{min} 232, 287 nm. Found; C, 57.66; H, 5.12; N, 12.61%. Calcd for $C_{16}H_{17}O_5N_3$: C, 58.00; H, 5.17; N, 12.68%. NMR (DMSO-d_6) δ=1.39 (d, 3H, C$_{5'}$H) and 5.81 ppm (d, 1H, C$_{1'}$H).

N^3-Methyl-5′-deoxy-2′,3′-O-isopropylideneuridine. A solution of **4** in 2,2-dimethoxypropane-acetone in the presence of *p*-toluenesulfonic acid was stirred at room temperature for 5 h. The title compound was quantitatively iso-

lated as an oil by preparative TLC (developing solvent; ethyl acetate). NMR ($CDCl_3$) δ=1.38 (d, 3H, $C_{5'}H$), 1.32, 1.55 (s, 6H, $(CH_3)_2C$), 3.30 (s, 3H, CH_3), 5.56 (d, 1H, $C_{1'}H$), 5.70 (d, 1H, C_5H), and 7.20 ppm (d, 1H, C_6H).

N^4*-Benzoyl-5'-deoxy-2',3'-O-isopropylidenecytidine.* A solution of **6** in 2,2-dimethoxypropane-acetone in the presence of *p*-toluenesulfonic acid was stirred at room temperature for 2 h. The product was isolated in 61% yield by preparative TLC ($CHCl_3$:MeOH=10:1) and had mp 184—186 °C. NMR (DMSO-d_6) δ=1.38 (d, 3H, $C_{5'}H$), 1.31, 1.45 (s, 6H, $(CH_3)_2C$), and 5.83 ppm (d, 1H, $C_{1'}H$).

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