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NUCLEOSIDES LXXXVI. A DIRECT SYNTHESIS OF 2'-UNSUBSTITUTED PYRIMIDINE RIBONUCLEOSIDES BY USE OF A SUGAR 1,2-KETAL [1]

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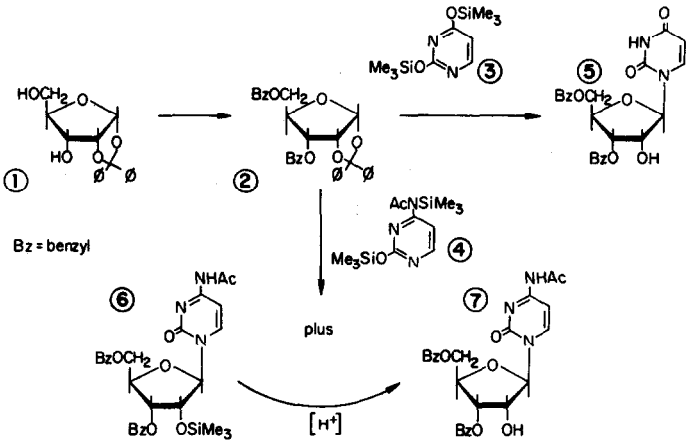
The synthesis of protected nucleosides selectively unsubstituted at position 2' has hitherto been achieved [2] by tritylation of ribonucleosides. Mixtures of 2',5'- and 3',5'-ditritylated nucleosides were formed from which the 3',5' derivatives were obtained only after laborious chromatography in yields lower than 35%. We now report a direct and facile synthesis of crystalline 3',5'-protected pyrimidine nucleosides from the 3,5-di-O-benzyl derivative of 1,2-diphenylmethylidene-α-D-ribofuranose(1), a sugar 1,2-ketal previously reported from this laboratory [3].

Benzylation of 1 with benzyl chloride and KOH [4] afforded crystalline (from cyclohexane) 3,5-di-O-benzyl-1,2-O-diphenylmethylidene-α-D-ribofuranose (2) in nearly quantitative yield, mp 105-106°, δ ($CDCl_3$); 5.9 (1H, d, $J_{1,2}$ = 4 Hz, H-1). The benzyl blocking group was chosen in preference to acyl protecting groups in order to avoid any possible migration during or after nucleoside formation. Reaction of 2 mmol dibenzylated ketal (2) with 3 mmol 2,4-bis-trimethylsilyloxy-pyrimidine (3) in dichloroethane with 3 mmol of $SnCl_4$ [5] gave crystalline 3',5'-di-O-benzyluridine (5), mp 81-83° in 60% yield (from benzene/pet. ether), λ_{max} (MeOH) at 264 nm (ε = 8300); δ ($CDCl_3$): 5.32 (1H, d, H5), 5.94 (1H, d, $J_{1',2'}$ = 3.5 Hz, H-1'), 7.32 (10H, broad s, benzyl H), 7.76 (1H, d, H6). Treatment of 5 with H_2 and 10% Pd/charcoal catalyst in ethanol afforded uridine.

Reaction of the ketal (2) with the trimethylsilyloxy derivative of N^4-acetylcytosine (4) under similar conditions afforded two products which showed different mobilities on tlc. The less polar component was isolated directly from the crude reaction mixture by crystallization from ether and was characterized as 3',5'-di-O-benzyl-2'-O-trimethylsilyl-N^4-acetylcytidine (6) mp 156-157° (ether); λ_{max} (MeOH) 249, 302 nm (ε, 9800, 5800); δ ($CDCl_3$): 0.21 (9H, broad s, silyl methyls), 2.28 (3H, s, N^4-acetyl methyl), 5.81 (1H, s, H-1'), 7.08 (1H, d, H-5), 7.21 (10H,



broad s, benzyl H), 8.49 (1H, d, H-6), 10.4 (1H, broad s, N-H). Treatment of 6 with 1:1 mixture of ethanol and 40% aqueous HOAc at room t° overnight afforded the second, more polar product which was identified as the expected 3',5'-di-O-benzyl-N^4-acetylcytidine (7), mp 75-76° (EtOH/pet ether): λ_{max} (MeOH) 249, 301 nm, (ϵ = 10,300, 6000); δ ($CDCl_3$): 2.21 (3H, s, N^4-acetyl methyl), 5.92 (1H, d, $J_{1',2'}$ = 1.5 Hz, H-1'), 7.11 (1H, d, H-5), 7.22 (10H, broad s, benzyl H), 8.33 (1H, d, H-6), 9.8 (1H, broad s, NH). When the reaction mixture, after removal of the tin salts, was treated with HOAc as described above, nucleoside 7 was obtained as the sole product in 60% yield. (No attempts were made to maximize the yields of these reactions).

α-Nucleosides were not detected in the reaction mixtures from condensation of 3 or 4 with α-ketal (2). The exclusive formation of β-anomers (5,6,7) in these reactions is consistent with a mechanism involving an SN_2 attack of the silylated pyrimidine on C-1 of ketal (2). A similar reaction was attempted using 3,5,6-tri-O-benzyl-1,2,-O-isopropylidene-α-D-glucofuranose and 4. With this latter ketal, the formation of nucleoside product was not observed. These data suggest that complex formation between the Lewis acid ($SnCl_4$) and the phenyl groups of ketal (2) may be an important factor in the condensation reaction with silylated pyrimidines.

To our best knowledge, these data represent the first example of the use of a sugar 1,2-ketal for nucleoside condensation reactions. The newly synthesized 2'-unsubstituted pyrimidine ribonucleosides should be useful intermediates for the preparation of 2'-substituted derivatives, such as 2'-O-methyl nucleosides which have been isolated from natural sources [6] and which have

been synthesized by alternate methods [7].

We have also examined the use of the cyclic ketal (2) for the preparation of purine nucleosides. The best results were obtained by a fusion reaction [8] of (2) with 2,6-dichloropurine without catalyst. (Addition of any acid catalyst increased the number of side products considerably). The major products obtained in 65% yield after chromatography was a mixture of two isomers which could not be separated by chromatographic methods. This mixture exhibited a uv spectrum similar to that for 9-substituted 2,6-dichloropurine and gave an nmr spectrum with two signals for H-1' ($J_{1',2'} \sim 4$ Hz for each) and H-8. Reaction of ketal (2) with 6-chloropurine or N^6-benzoyladenine under similar conditions failed to yield nucleosidic products.

The use of ketal (2) for the synthesis of selectively blocked nucleosides employing other heterocycles and under various conditions is worthy of further investigation.

Proper elemental analyses have been obtained for compounds 2,5,6,7.

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