Direct Synthesis of Pyrimidine Nucleosides: a Convenient Synthesis of 2-Thiocytidine

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OUR studies on the synthesis of uracil and thymine nucleosides[1] have recently led us to explore the possibility of synthesising pyrimidine nucleosides *directly*, *i.e.* by the reaction of the pyrimidine base with a glycosyl halide. The only syntheses of this type previously reported were with bases such as *N*-benzoylcytosine, soluble in organic solvents.[2]

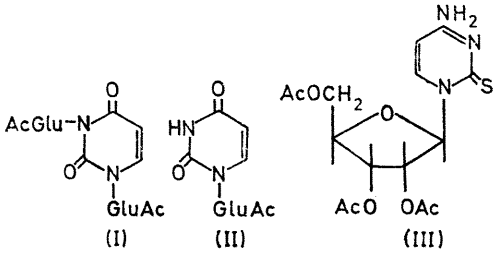
With uracil we found that nucleoside formation occurred when a suspension of the base was heated with a glycosyl halide and mercuric cyanide in a suitable solvent, and that whether the N^3-glycoside or N^1,N^3-bisglycoside was the main product could be controlled by choice of the reaction conditions:

(1) Uracil N^1,N^3-bisglucoside (I) is obtained in 50% yield from uracil, acetobromoglucose (ABG) and mercuric cyanide in toluene.

(2) Uracil N^3-glucoside (II) is obtained in 90% yield when reaction 1 is carried out in acetonitrile in the presence of molecular sieve, and triacetyluridine[3] (42% yield) can be obtained similarly.

We have established that the reaction sequence is uracil → N^3-glycoside → N^3,O^6-bisglycoside which, by rearrangement or cleavage, yields products like (I) and (II), respectively.

With cytosine, a triglycoside is formed in toluene, and *N*-acetylcytosine yields a mixture of the O^2- and N^3-glycosides. Satisfactory yields of cytosine N^3-nucleosides are obtained by using nitromethane as solvent, and as an example, we report a convenient synthesis of tri-*O*-acetyl-2-thiocytidine (III). 2-Thiocytidine has recently been found to be a component of transfer RNA.[4]



GluAc = 2,3,4,6-tetra-*O*-acetylglucopyranosyl.

2-Thiocytosine was treated with 2,3,5-tri-*O*-acetylribofuranosyl bromide[5] in refluxing nitromethane containing mercuric cyanide and molecular sieve. 2′,3′,5′-Tri-*O*-acetyl-2-thiocytidine (III) was isolated by preparative t.l.c. and crystallised from aqueous ethanol, m.p. 139—140°, in 29% yield. [λ_{max} 232, 279, 310 (sh) nm. (pH 1·0); 250, 272 (sh) nm. (pH 7·0)]. The structure of the product was confirmed by methylation and hydrolysis to cytidine.

Previous syntheses of 2-thiocytidine have involved multiple-stage routes giving poor yields.[6]

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