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ACETYL MIGRATION IN DERIVATIVES OF 3β-D-XYLOSYLURACIL

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Acyl ribonucleoside derivatives are being studied extensively as model systems for aminoacyl-transfer RNA (1,2,3,4). Acyl migrations are well known in partially acylated sugars (5) and studies on acyl migrations in ribonucleoside derivatives have yielded much valuable information on the orientation of aminoacyl-transfer RNA and the detailed mechanism of protein biosynthesis (6,7,8,9). Interest is also high in the chemistry and biological activity of nucleosides with sugar moieties other than ribofuranose (10,11) and it has been suggested that acetylated derivatives of such nucleosides might be more useful than the parent nucleoside as antitumor agents (12).

This communication reports the preparation of 2'-, 3'- and 5'-O-acetyl-3β-D-xylosyluracil and acetyl migration studies on these esters together with some observations on the partial acetylation of 3β-D-xylosyluracil.

2'-O-Acetyl-3β-D-xylosyluracil (VIII, m.p. 137-8°. Found: C, 46.3; H, 4.8; N, 10.2% $C_{11}H_{14}O_7N_2$ requires C, 46.2; H, 4.9; N, 9.8%) was prepared from 3',5'-O-isopropylidene-3β-D-xylosyluracil (III, 13) by treatment with acetic anhydride in pyridine solution for 4 hr. at 25°, followed by careful acid hydrolysis with HBr in acetic acid for 15 min. at 25°. The

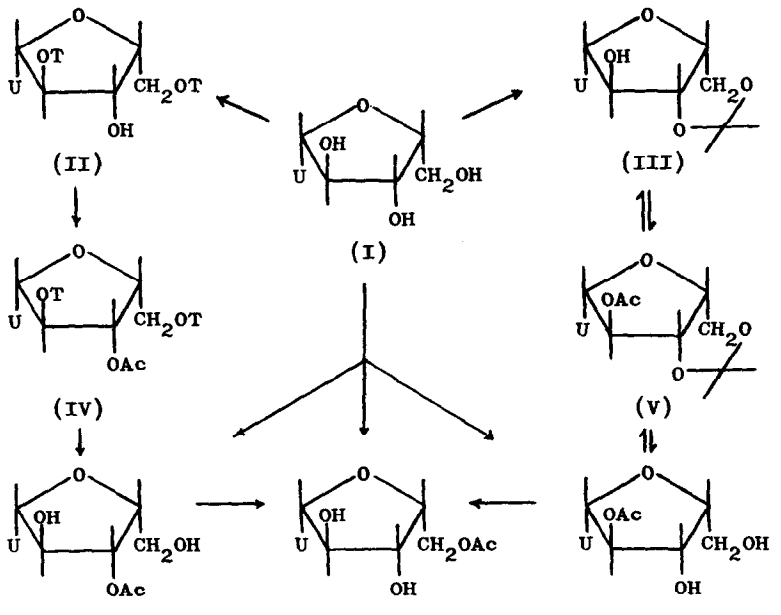
isopropylidene derivative (V) was formed in good yield by treatment of (VIII) in acetone containing traces of HCl, indicating that (VIII) was relatively pure 2' ester.

3'-O-Acetyl-3β-D-xylosyluracil (VI, m.p. 158-9°. Found: C, 46.6; H, 5.0; N, 9.7%) was prepared from 2',5'-di-O-trityl-3β-D-xylosyluracil (II, 13) by a similar acetylation procedure, followed by hydrolysis in 80% aqueous acetic acid at 60° for 30 min. Treatment of (VI) with HCl-acetone failed to yield an isopropylidene derivative. Both (VI) and (VIII) were stable to aqueous sodium periodate (14) for 24 hr.

The acidic conditions employed for removal of the isopropylidene and trityl protecting groups in the above preparations did not result in any apparent acetyl migration. Thus these esters (VI and VIII) are considerably less mobile than corresponding ribonucleoside esters, e.g. 2'- and 3'-O-acetyluridine derivatives (9). This may be an important factor contributing to the biological properties of 2',3'-trans nucleoside derivatives (e.g. xylosyl and arabinosyl derivatives of adenine and uracil), whose 2' and 3' esters, lacking the neighbouring cis hydroxyl group present in ribonucleosides, would be expected to be less mobile and more stable to external nucleophilic attack than corresponding ribonucleoside esters.

Refluxing either the 2' (VIII) or 3' ester (VI) in pyridine solution for 1 hr. gave a different ester (m.p. 163-5° depressed on admixture with either starting material. Found: C, 45.9; H, 4.8; N, 9.7%) identified as 5'-O-acetyl-3β-D-xylosyluracil (VII), since it reacted with one equivalent of periodate at a rate similar to that observed for 3β-D-xylosyluracil (14,15) and did not form an isopropylidene derivative. The isomeric esters (VI, VII and VIII) were hydrolysed by base to 3β-D-xylosyluracil (I) which was chromatographically and electrophoretically pure in a number of systems.

Acyl groups attached to carbohydrate derivatives tend to migrate from more hindered secondary to primary positions subject to steric and hydrogen-bonding considerations (5) and those attached to glycosides tend to migrate away from the glycosidic link (16). The above 2'(3')→5'acetyl migration conforms to this general pattern.



U = uracil T = trityl Ac = acetyl

Partial acetylation of 3β-D-xylosyluracil (I) with 1 mole of acetic anhydride in pyridine solution for 1 hr. at 25°, followed by column chromatography of the product on silicic acid, gave, in addition to starting material (eluted with 25% methanol-chloroform), an oil (eluted with 5% methanol-chloroform) which resisted crystallisation, analysed for a monoacetyl derivative, consumed 0.23 equivalents of periodate during 18 hr., and afforded the isopropylidene derivative (V) in approximately 55% yield on treatment with HCl-acetone. This oil was thus a mixture of acetyl derivatives with the 2' ester (VIII) predominating. Refluxing the oil in pyridine solution for 1 hr. gave crystalline 5'-O-acetyl-3β-D-xylosyluracil (VII) in good yield.

Acetylation of the 2' hydroxyl group predominating over acetylation of the 3' hydroxyl group in 3β-D-xylosyluracil is in accord with observations concerning reactions at the 2' and 3' positions in ribonucleosides.

Thus sulphonylation of 5'-substituted derivatives of adenosine and uridine yields mainly 2'-O-sulphonates (17), tritylation of uridine yields mainly 2',5'-di-O-trityluridine (18), and methylation of adenosine (19) and uridine (20) yields 2'-O-methylated products. Acylation of ribonucleosides is complicated by subsequent rapid acyl migration (9) and further investigations are being undertaken to clarify this situation and to relate these observations to the *in vivo* acylation of the terminal adenosine residue of transfer RNA by enzyme-bound aminoacyladenylates (21).

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