Glycoside Migration in Uracil and Thymine Derivatives

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O- → *N*-GLYCOSYL REARRANGEMENTS in derivatives of tautomeric heterocycles, including nucleic acid bases, have been much studied;[1] such rearrangements in monoglycosides are subject to general Lewis-acid catalysis.[2] We now report some novel results obtained with uracil derivatives, and a comparison with the corresponding thymine compounds.

The reaction of the silver salt of uracil with acetobromoglucose (ABG) in toluene gives a mixture of five products, of which four are new compounds. The products were identified as *N*(3)-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-uracil[3] (I; R = H), 2,6-bis-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)uracil (II; R = H, m.p. 222—223°), *N*(3),*O*(6)-bis-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)uracil (III; R = H, m.p. 267·5°—268·5° decomp.), *N*(1)-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)uracil (IV; m.p. 110—111°) and 1,3-bis-*N*-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)uracil (V; m.p. 122—123°).† The structure of these products was established on the basis of microanalytical and spectral data, degradation with ammonia, and comparison with known uracil derivatives.

By varying the time and temperature of the condensation reaction, and by studying the rearrangement of the *O*(2),*O*(6)- and the *N*(3),*O*(6)-bis-glucosides (either with mercuric bromide, or with silver bromide + ABG), the following reaction sequences were established.

$$(\text{II};\ R = H) \rightarrow (\text{I}) + (\text{III}) + (\text{IV}) + (\text{V})$$

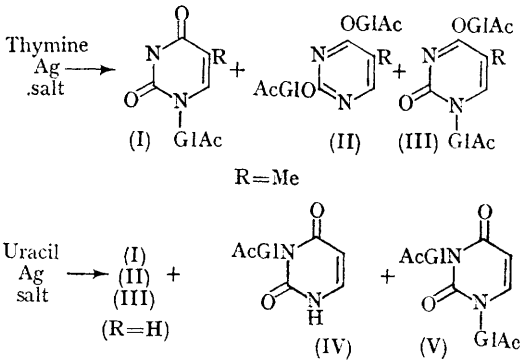
$$(\text{III};\ R = H) \rightarrow (\text{I}) + (\text{V})$$

When the reaction temperature is *lowered*, more of the *N*(3)-glucoside (I) and less of the *N*(3),*O*(6)-bis glucoside (III) are formed, which clearly indicates that (III) is not the only route to (I); the *N*(3)-glucoside may also be formed directly. The direct formation of pyrimidine *N*-glycosides in certain cases has previously been inferred by the failure to rearrange the corresponding *O*-glycosides.[4]

The *N*(1)-glycosyl derivative (IV; R = H) is formed in small amounts by rearrangement of the bis-*O*-glucoside (II) and may also be formed directly. This seems to be the first time that an *N*(1)-glycosyl derivative has been observed in a nucleoside synthesis from a pyrimidine.

A similar reaction with thymine gave the known compounds *N*(3)-(2,3,4,6,-tetra-*O*-acetyl-β-D-glucopyranosyl)thymine[5] (I; R = Me) and 2,6-bis-*O*-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thymine (II; R = Me), together with the previously uncharacterised[7] *N*(3),*O*(6)-bis-(2,3,4,6-tetra-*O*-acetyl β-D-glucopyranosyl)thymine (III; R = Me, m.p. 128—131°). Rearrangement studies confirmed the sequence[7] (II) → (III) → (I). No evidence for the formation of *N*(1)-glycosides was obtained.

The striking difference between the reactions of uracil and thymine derivatives is noteworthy. In the absence of the 5-methyl group, the reactivity of the two nitrogen atoms is almost equal.



AcGl =2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl

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† After heating under reflux for 20 min., the yield of crude products is 57% (based on uracil). The yield of pure recrystallised products (I)–(V) is 11, 1, 5, 4, and 5% respectively, but the proportions obtained vary with the time and temperature of the reaction, *e.g.* more of (II) and (III) are obtained if the reaction time is reduced.

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