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THE PROTECTION OF HYDROXYL GROUPS IN DIRIBONUCLEOSIDE PHOSPHATES

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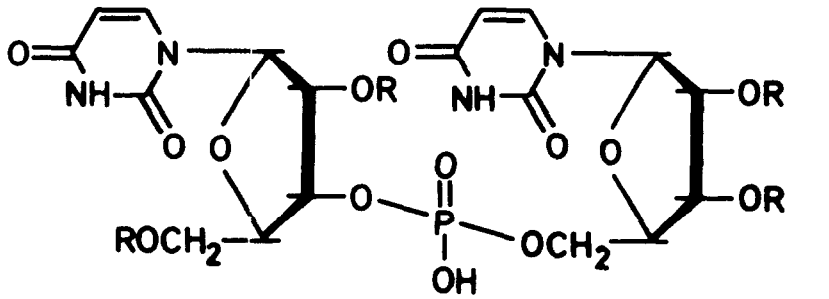
The internucleotidic linkage in the ribose series is readily split both in alkaline and in acid media[1]. In an acid medium the hydrolysis of the phosphodiester bond is accompanied by isomerization to the 2′,5′-phosphodiester[2]. This exceptional lability of the phosphodiester bond is known to be due to the presence of a cis-vicinal hydroxyl.

It was of interest to establish whether this cis-vicinal hydroxyl can be protected without causing cleavage or isomerization of the internucleotidic linkage. The model used for studying this problem was uridylyl-(3′→5′)-uridine (I). The course of the reaction of this compound with ethylvinyl ether and with dihydropyrane under acid catalysis and further the course of acetylation under various conditions was studied.

It was found that the compound I gives through a reaction with ethylvinyl ether in a dimethylformamide solution in the presence of trifluoroacetic acid a quantitative yield of 2′,5′-di-O-ethoxyethyluridylyl-(3′→5′)-2′,3′-di-O-ethoxyethyluridine (II). Because of blocking of the vicinal hydroxyl, the internucleotidic bond of substance II is resistant to pancreatic ribonuclease. After the removal of the ethoxy groups (20% acetic acid, 50°, 20 min) substance I is regenerated. Quantitative cleavage of this regenerated substance indicates that no isomerization took place either during the blocking of the $C^{2'}$-hydroxyl or during the removal of the protecting groups. Compound I reacted analogously with dihydropyrane giving rise to III. In this case, too, no isomerization of the internucleotide bond was observed.

Reaction of substance I with acetic anhydride differed in dependence on the conditions used. In the presence of triethylamine, acetic anhydride converted substance I quantitatively to 2′,5′-di-O-acetyluridylyl-(3′→5′)--2′,3′-di-O-acetyluridine (IV) resistant to pancreatic ribonuclease. After cleavage of acetyl groups with ammonia the compound IV yields the starting substance I where a quantitative splitting by ribonuclease indicated that during acetylation under the given conditions no isomerization of the internucleotidic bond took place. Acetylation in the presence of tetraethylammonium acetate proceeded in an identical manner.

On the other hand, when acetic anhydride acted on compound I in pyridine, 30% of the internucleotidic bond were split and uridylyluridine regenerated from the peracetyl derivative thus obtained was found to contain 21% of the 2′,5′-diester. Acetic anhydride in the presence of hydrogen chloride cleaves compound I by 50% and the regenerated uridylyluridine contains 43% of the 2′,5′-isomer.



I (R=H) II (R=—CH(OC$_2$H$_5$)CH$_3$) III (R=tetrahydropyranyl)

IV (R=—COCH$_3$)

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