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# PROTECTION OF THE INTERNUCLEOTIDIC BOND AFTER ITS SYNTHESIS. AN APPROACH TO THE SYNTHESIS OF OLIGONUCLEOTIDIC CHAINS.

J. Smrt
Institute of Organic Chemistry and Biochemistry,
Czechoslovak Academy of Sciences, Prague

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The most frequent synthesis of the ribooligonucleotidic chain comprises condensation of the protected ribonucleoside 3'-phosphate with the $C^{5'}$-hydroxylic function of the second component, deblocking of the $C^{5'}$-hydroxylic group in the diribonucleoside phosphate formed, and an additional condensation with the protected ribonucleoside 3'-phosphate[1-6]. The phosphodiester bond on the chain to be lengthened is known to interfere in the synthesis of an additional internucleotidic bond. The unfavourable effect of the acidic function of the phosphodiester bond is eliminated in the triester synthesis of the internucleotidic bond. A nucleoside alkyl phosphate, the alkyl group of which may be readily removed is involved as the active component in the triester synthesis[7-11]. In the ribo series, however, the cumulation of the bulky protecting groups at the phosphodiester component has been shown to lower considerably the reactivity of this component for the formation of the triester[12].

An approach has been therefore investigated which would combine the advantageous features of the diester and triester synthesis. The internucleotidic bond is formed by the use of a sterically more favourable and more reactive phosphomonoester and the internucleotidic bond obtained is protected *in situ* by the 2-cyanoethyl group. The material for the next step of the chain synthesis thus contains a free hydroxylic function as the single reactive group.

2',3'-Di-O-benzoyluridine (2 mmol) is condensed with the triethylammonium salt of 2'-O-tetrahydropyranyl-5'-O-dimethoxytrityluridine 3'-phosphate (I) (1 mmol) in pyridine (5 ml) by the action of 2,3,5-triisopropylbenzenesulfonyl chloride (5 mmol). The reaction mixture is kept at room temperature for 20 hours and then treated with 2-cyanoethanol (10 mmol). After additional 20

hours, the crude 5′-O-dimethoxytrityl-2′-O-tetrahydropyranyluridylyl-(3′→5′)-2′,3′-di-O-benzoyluridine [P-(2-cyanoethyl)ester] is isolated by thin layer chromatography on silica gel. Removal of the dimethoxytrityl group with 90% acetic acid at 0°C leads to a 55% yield of 2′-O-tetrahydropyranyluridylyl-(3′→5′)-2′,3′-di-O-benzoyluridine [P-(2-cyanoethyl)ester] (HO-$U^{THP}_{p(ce)}$-$UBz_2$; II). An analogous reaction sequence is then used in the synthesis of HO-$U^{THP}_{p(ce)}$-$U^{THP}_{p(ce)}$-$UBz_2$ by reaction of compound II with I and 2-cyanoethanol (yield,48%). In another series of experiments, 5′-O-dimethoxytrityl-2′-O-acetyluridine 3′-phosphate was used to prepare stepwise the di-, tri-, and tetranucleotide derivatives with 60%, 55% and 45% yields.

As shown by preliminary experiments, the yields of the present procedure at the stage of the tri- and tetranucleotide are at least twice as high as those obtained by the synthesis without protecting of the internucleotidic bond.

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