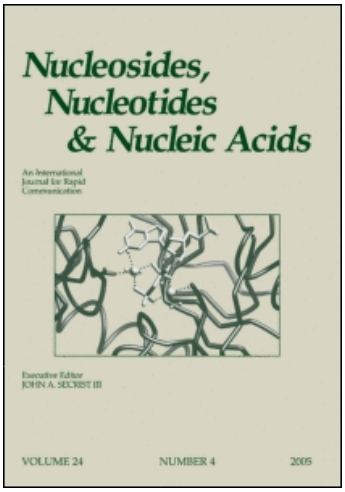

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Synthesis of 5'-Dithiotriphosphate Derivatives of 3'-Deoxy 3'-Azidothymidine

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SYNTHESIS OF 5′-DITHIOTRIPHOSPHATE DERIVATIVES OF 3′-DEOXY 3′-AZIDOTHYMIDINE

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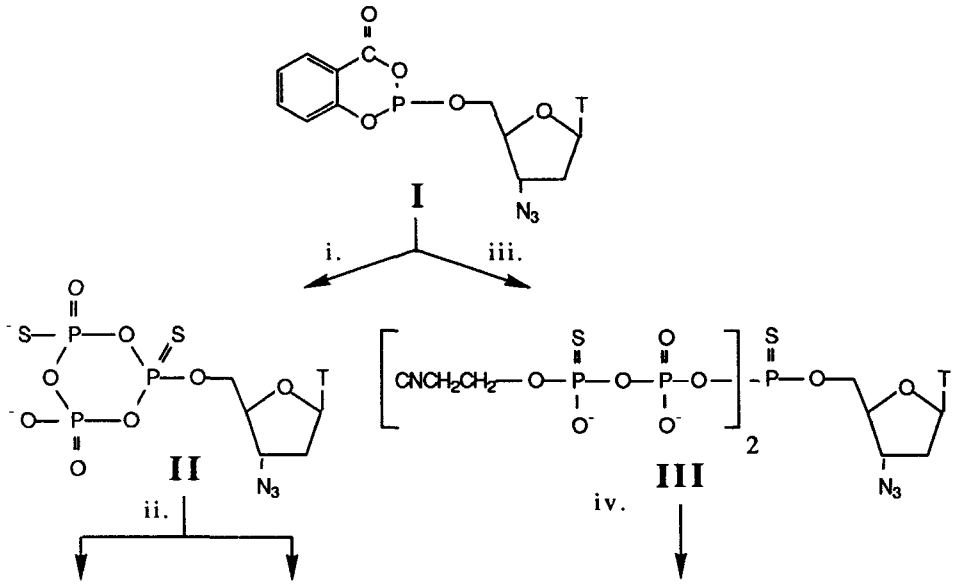
ABSTRACT: An efficient synthesis of N3TTPαSγS and N3TTPαSβS is described starting from 3′-deoxy 3′azidothymidine.

The Sp-diastereomers of nucleoside 5′-O-(α-thiotriphosphates) are good substrates for RNA and DNA polymerases allowing the incorporation of phosphorothioate groups into RNA and DNA.[1] These triphosphate analogues are very slowly hydrolysed by enzymes which attack at the α-phosphorus. Nucleoside 5′-O-(γ-thiotriphosphates) are resistant to many enzymes which degrade nucleoside 5′-O-triphosphates from the γ-position. These γ-thio triphosphates are substrates of polymerases as well.[1] Nucleotide analogues containing phosphorothioate groups in the α - as well the γ position should be stable against both type of hydrolytic enzymes. We report here the synthesis of such a dithiotriphosphate derivative of 3′-deoxy 3′-azidothymidine, (N3TTPαSγS).

We have shown earlier that acyl phosphites (**I**) may serve as starting materials for an efficient synthesis of the α-thiotriphosphates of nucleosides.[2] In this work we extented this approach to the synthesis of the α,γ-dithio derivatives. In order to introduce the second P-S linkage thiopyrophosphate was employed instead of pyrophosphate. Thus phospitylation of 3′-deoxy 3′-azidothymidine in pyridine-dioxane with equimolar amounts of 2-Chloro-4H-1,3,2-benzodioxaphosphorin-4-one, followed by reaction with bis-tri-n-butylammmonium-thiopyrophosphate in DMF and oxidation of the α P with sulfur gave the nucleoside 5′-(α,β-dithiocyclotriphosphate) (**II**) as demonstrated by ^{31}P NMR analysis.[3] Hydrolysis of this intermediate resulted in the formation of a 6:1 mixture of N3TTPαSβS and N3TTPαSγS. This ratio reflects the greater reactivity of the β phosphoryl over the the β thiophosphoryl centre in **II**.



$N_3TTP\alpha S\gamma S$(12%) $N_3TTP\alpha S\beta S$(74%) $N_3TTP\alpha S\gamma S$(81%)

Reagents: i, Tri-n-butylammonium-thiopyrophosphate, S_8; ii, water;
iii, Tri-n-butylammonium-P^1-O-cyanoethyl-P^1-thiopyrophosphate, S_8; iv, OH^-.

$N_3TTP\alpha S\gamma S$ was formed however as the only product when P^1-O-cyanoethyl-P^1-thio-pyrophosphate was employed in the reaction with **I**. The β-cyanoethyl group was selected because it can be removed under conditions where the product is completely stable. As ^{31}P NMR analysis indicated[3] a branched pentaphosphate derivative (**III**) was formed after the oxidation with sulfur. This compound hydrolyses exclusively by attack of water on the P(β) with formation of 3′-deoxy 3′-azidothymidine 5′-(1,3-dithio-(3-O-cyanoethyl)-triphosphate. The two diastereomers of $N_3TTP\alpha S\gamma S$ are formed in 81% yield after removal of the protecting group by alkaline hydrolysis and DEAE-Sephadex purification. The diastereomers could be separated by reverse phase HPLC.

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