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## Nucleosides, Nucleotides and Nucleic Acids

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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'-AZIDOTHYMININE

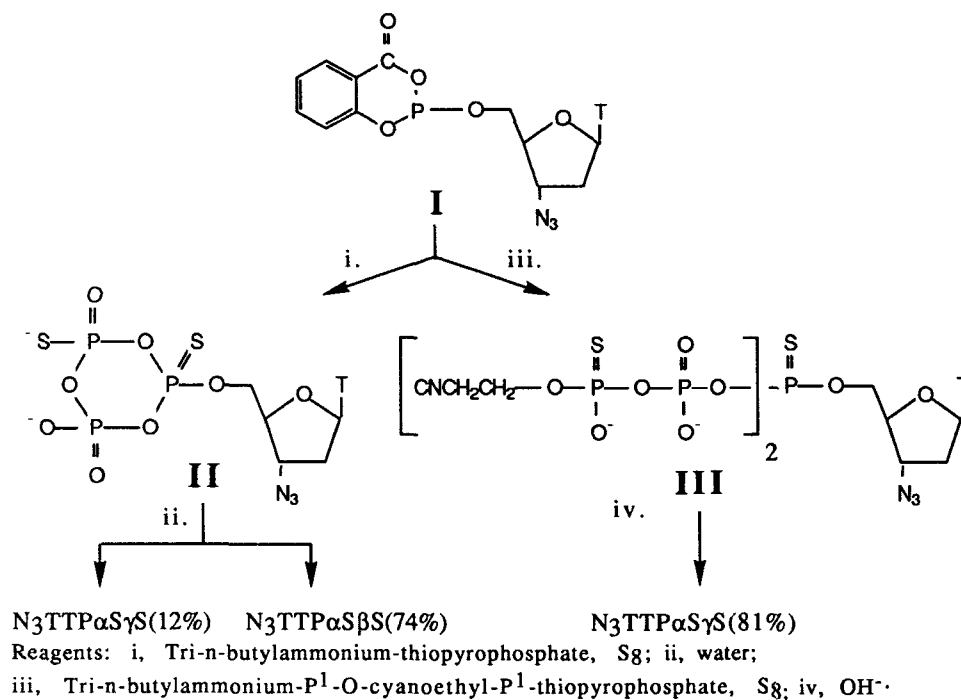
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**ABSTRACT:** An efficient synthesis of  $N_3TTP\alpha S\gamma S$  and  $N_3TTP\alpha S\beta S$  is described starting from 3'-deoxy 3'-azidothymidine.

The Sp-diastereomers of nucleoside 5'-O-( $\alpha$ -thiotriphosphates) are good substrates for RNA and DNA polymerases allowing the incorporation of phosphorothioate groups into RNA and DNA.<sup>1</sup> These triphosphate analogues are very slowly hydrolysed by enzymes which attack at the  $\alpha$ -phosphorus. Nucleoside 5'-O-( $\gamma$ -thiotriphosphates) are resistant to many enzymes which degrade nucleoside 5'-O-triphosphates from the  $\gamma$ -position. These  $\gamma$ -thio triphosphates are substrates of polymerases as well.<sup>1</sup> Nucleotide analogues containing phosphorothioate groups in the  $\alpha$  - as well the  $\gamma$  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, ( $N_3TTP\alpha S\gamma S$ ).

We have shown earlier that acyl phosphites (I) may serve as starting materials for an efficient synthesis of the  $\alpha$ -thiotriphosphates of nucleosides.<sup>2</sup> In this work we extended this approach to the synthesis of the  $\alpha,\gamma$ -dithio derivatives. In order to introduce the second P-S linkage thiopyrophosphate was employed instead of pyrophosphate. Thus phosphorylation 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-butylammonium-thiopyrophosphate in DMF and oxidation of the  $\alpha$  P with sulfur gave the nucleoside 5'-( $\alpha,\beta$ -dithiocyclotriphosphate) (II) as demonstrated by  $^{31}P$  NMR analysis.<sup>3</sup> Hydrolysis of this intermediate resulted in the formation of a 6:1 mixture of  $N_3TTP\alpha S\beta S$  and  $N_3TTP\alpha S\gamma S$ . This ratio reflects the greater reactivity of the  $\beta$  phosphoryl over the the  $\beta$  thiophosphoryl centre in II.



$\text{N}_3\text{TTP}\alpha\text{S}\gamma\text{S}$  was formed however as the only product when P<sup>1</sup>-O-cyanoethyl-P<sup>1</sup>-thio-pyrophosphate was employed in the reaction with I. The  $\beta$ -cyanoethyl group was selected because it can be removed under conditions where the product is completely stable. As <sup>31</sup>P NMR analysis indicated<sup>3</sup> a branched pentaphosphate derivative (III) was formed after the oxidation with sulfur. This compound hydrolyses exclusively by attack of water on the P( $\beta$ ) with formation of 3'-deoxy 3'-azidothymidine 5'-(1,3-dithio-(3-O-cyanoethyl)-triphosphate. The two diastereomers of  $\text{N}_3\text{TTP}\alpha\text{S}\gamma\text{S}$  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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