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## Nucleosides, Nucleotides and Nucleic Acids

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## The Synthesis of $\alpha\beta$ Imidothymidine Diphosphate

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THE SYNTHESIS OF  $\alpha\beta$  IMIDOTHYIMIDINE DIPHOSPHATE

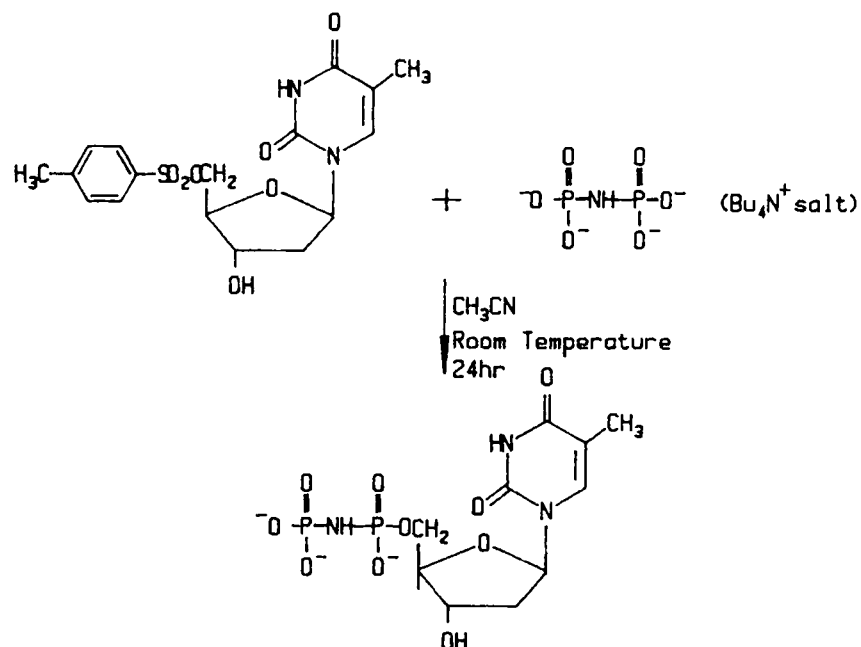
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It has been shown by many workers that nucleotides containing an  $\alpha\beta$  methylene link have interesting biochemical properties compared to those containing an  $\alpha\beta$  oxo linkage.<sup>1</sup> In our laboratory  $\alpha\beta$  methylene thymidine triphosphate has been shown to be a more powerful inhibitor of thymidine kinase than thymidine triphosphate but a weaker inhibitor of ribonucleotide reductase and cytidine deaminase.<sup>2</sup> We have been interested in examining the properties of the  $\alpha\beta$  imido analogue. Several routes to prepare the unknown  $\alpha\beta$  imidothymidine triphosphate were unsuccessfully tried:

- a) Reaction of 3'-O-Acetylthymidine with the tributylammonium salt of dicyclohexylcarbodiimide.
- b) Reaction of 5'-O-tosylthymidine with the tributylammonium salt of imidodiphosphoric acid in hot dimethylacetamide.<sup>3</sup>

Dixit and Poulter<sup>4</sup> have developed milder conditions for the latter type of reaction which have proved successful in this case. Two equivalents of the tetrabutylammonium salt of imidodiphosphoric acid were reacted with 5'-O-tosylthymidine in dry acetonitrile for 24 hours. (Longer reaction times cause decomposition of the product). A large number of by-products are however produced. It has not been possible to purify the product to greater than about 80% purity by either ion-



exchange chromatography on DEAE-Sephadex using triethylammonium bicarbonate as buffer or on silica using a mixture of aqueous ammonia and n-propanol as eluant.

The <sup>31</sup>p nmr spectrum gives two singlets. Over a period of days the product decomposes to the phosphoramidate of thymidine monophosphate. Recently Ma, Babbitt and Kenyon have published a synthesis of αβ imidoadenosine diphosphate using the same procedure.<sup>5</sup>

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