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## Nucleosides, Nucleotides and Nucleic Acids

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### Synthesis and Properties of Novel NTP Derivatives

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## SYNTHESIS AND PROPERTIES OF NOVEL NTP DERIVATIVES

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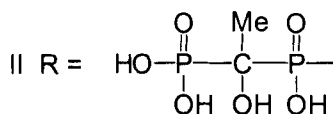
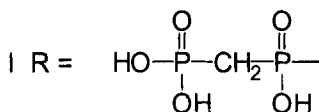
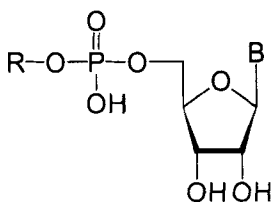
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**ABSTRACT:** Simple method for the preparation of anhydrides of nucleoside-5'-monophosphoric acid and with 1-hydroxyethane-1,1-diylbis(phosphonic acid) has been developed.

Unique properties of phosphonate analogs of the natural phosphoric acid derivatives make them exceptionally suitable for the use in a continuously increasing variety of applications<sup>1</sup>. The substitution of the P-O-P fragment in NTP with P-CR<sub>1</sub>R<sub>2</sub>-P enhanced the stability of phosphoanhydride bond of these analogs towards hydrolytic cleavage.

Anhydrides of nucleoside-5'-monophosphoric acid and methylenebis(phosphonic acid) (I) were prepared by activation of NMP with *N,N'*-carbonyldiimidazole (CDI) followed by condensation with methylenebis(phosphonic acid). The separation of products was carried out on DEAE-cellulose in HCO<sub>3</sub><sup>-</sup>-form using concentration gradient of ammonium bicarbonate solutions. The isolated yields of I were usually high (65-75%).



Analogous condensation of nucleotide imidazolides with 1-hydroxyethane-1,1-diylbis(phosphonic acid) gave II in poor yield due to instability of modified triphosphate

Table 1. Physico-chemical properties of NTP derivatives.

Compound	Yield, (%)	HPLC* RT (min)	<sup>31</sup> P NMR spectra in D <sub>2</sub> O (pD 5.6) at 298 °K		
			P <sub>α</sub> (J <sub>Pα,Pβ</sub> , Hz)	P <sub>β</sub>	P <sub>γ</sub> (J <sub>Pγ,Pβ</sub> , Hz)
I B=Hyp	74	7.20	-10.10 d (25.0)	9.82 dd	15.32 d (7.0)
I B=Ade	67	9.91	-10.76 d (25.9)	9.04 dd	14.68 d (7.5)
II B=Hyp	84	8.98	-9.31 d (32.0)	12.70 dd	17.72 d (30.1)
II B=Ade	70	9.54	-9.26 d (32.4)	12.90 dd	17.90 d (29.3)
II B=Ura	75	3.49(16.2**)	-9.21 d (31.7)	12.82 dd	17.83 d (33.7)
II B=Cyt	43	3.28(10.7**)	-9.40 d (33.0)	12.72 dd	17.52 d (32.1)

\*Nucleosil C-18 5 μ column (4 x 250 mm) using a MeCN concentration gradient (0-4% MeCN over 20 min) in 0.1M triethylammonium acetate, pH 6.8 (flow rate 1ml/min).

\*\*RT of 2',3'-cyclocarbonate derivative

residue during isolation of the product. Much better yields were obtained when the product separation was carried out under slightly acidic conditions, using column chromatography on DEAE-cellulose in CH<sub>3</sub>COO<sup>-</sup>-form in gradient concentration of lithium acetate (pH 4.6). It is known that the reaction of NMP-5' with CDI gave 2',3'-O-cyclic carbonates, which were sensitive to alkaline treatment<sup>2</sup>. In the preparation of pyrimidine NTP derivatives the corresponding 2',3'-O-cyclic carbonates of II were obtained in good yield. Mild treatment with 0.5% aqueous triethylamine at room temperature for 0.5 h followed by HPLC isolation gave desired derivatives (II) in a high overall yield. Their structure was proved by <sup>1</sup>H and <sup>31</sup>P NMR spectroscopy (Table 1). <sup>31</sup>P NMR spectra of the known I (B=Ade) is in accordance with the published one<sup>3</sup>. Hydrolytic stability of P-O-P bond of NTP analogs obtained was shown to be higher for -CH<sub>2</sub>-derivatives (I) in comparison with -CMe(OH)- derivatives (II) at pH 3 - 9.

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