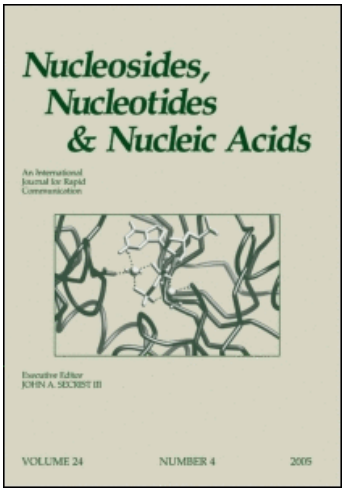

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis and Properties of Novel NTP Derivatives

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To cite this Article Padyukova, N. Sh. , Dixon, H. B. F. , Efimtseva, E. V. , Ermolinsky, B. S. , Mikhailov, S. N. and Karpeisky, M. Ya.(1999) 'Synthesis and Properties of Novel NTP Derivatives', Nucleosides, Nucleotides and Nucleic Acids, 18: 4, 1013 — 1014
To link to this Article: DOI: 10.1080/15257779908041633
URL: http://dx.doi.org/10.1080/15257779908041633

NUCLEOSIDES & NUCLEOTIDES, 18(4&5), 1013–1014 (1999)

SYNTHESIS AND PROPERTIES OF NOVEL NTP DERIVATIVES

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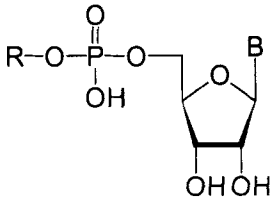
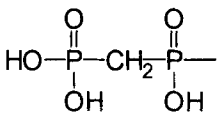
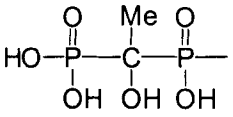
ABSTRACT: Simple method for the preparation of anhydrides of nucleoside-5′-monophosphoric acid and with 1-hydroxyethane-1,1-diylbis(phosphonic acid) has been developed.

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[1]. The substitution of the P-O-P fragment in NTP with P-CR_1R_2-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_3^--form using concentration gradient of ammonium bicarbonate solutions. The isolated yields of I were usually high (65-75%).



I R = 

II R = 

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)	^{31}P NMR spectra in D_2O (pD 5.6) at 298 °K		
			P_α ($J_{P\alpha,P\beta}$, Hz)	P_β	P_γ ($J_{P\gamma,Pb}$, 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_3COO^--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[2]. 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 ^{1}H and ^{31}P NMR spectroscopy (Table 1). ^{31}P NMR spectra of the known I (B=Ade) is in accordance with the published one[3]. Hydrolytic stability of P-O-P bond of NTP analogs obtained was shown to be higher for -CH_2-derivatives (I) in comparison with -CMe(OH)- derivatives (II) at pH 3 - 9.

Financial support from MBC Research Inc. is gratefully acknowledged.

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