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# Nucleosides, Nucleotides and Nucleic Acids

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# Synthesis and Evaluation of Acyclic Nucleotide Analogs

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### SYNTHESIS AND EVALUATION OF ACYCLIC NUCLEOTIDE ANALOGS

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ABSTRACT. Acyclic nucleotide analogs derived from antiviral 9-(2-phosphonylmethoxyethyl) adenine by modification at the side chain or by alternation of the heterocyclic base were synthesized and investigated for their antiviral activity.

The antiviral activity of 9-(2-phosphonylmethoxyethyl)adenine (PMEA) (I) directed towards DNA viruses and retroviruses1) prompted us to investigate additional acyclic nucleotide analogs bearing no hydroxyl group at the side chain. The first part of this study was aimed at the modification at the side chain in the series of adenine derivatives: 9--(phosphonylmethoxyalkyl)adenines (V) were synthesized by the reaction of sodium alkoxides of 9-(\omega-hydroxyalkyl)adenines (III) or their N-benzoyl derivatives with the synthon II2). The reaction proceeded in DMF, affording the diesters IV which were isolated by silica gel chromatography. Treatment of compounds IV with bromotrimethylsilane in acetonitrile2) followed by hydrolysis, desalting and anion-exchange chromatography affords the phosphonyl derivatives V. The isomeric 9-(2-phosphonylmethoxypropyl) derivative VI was obtained from 9-(RS)-(2-hydroxypropyl)adenine, and 9-[(2--phosphonylmethoxyethoxy)methylladenine (VII) from the adenine analog of acyclovir.

 $A-CH_2CH_2OCH_2P(0)(OH)_2$   $TsOCH_2P(0)(OC_2H_5)_2$  I II

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> A-CH2(CH2)nOH III

 $A-CH_2(CH_2)_nOCH_2P(0)(OC_2H_5)_2$ IV

V n=2,3,4

 $A-CH_2(CH_2)_nOCH_2P(O)(OH)_2$   $A-CH_2CH(CH_3)-OCH_2P(O)(OH)_2$ VΙ

A-CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>P(O)(OH)<sub>2</sub> VII

A-CH2OCH2P(O)(OH)2 VIII

A... adenin-9-yl residue, Ts... tosyl residue

9-(Phosphonylmethoxymethyl)adenine (VIII) was synthesized by alkylation of adenine with diethyl chloromethoxymethylphosphonate followed by cleavage of ester groups.

The preparation of  $9-(\omega-phosphonylalkyl)$  adenines (XI) makes use of the Arbuzow reaction: 9-(ω-halogenoalkyl)adenines (IX) easily accessible from compounds III by triphenylphosphine/CX4 reaction, reacted with triethyl phosphite at the reflux temperature to form the diesters X. Using the above procedure of ester cleavage, phosphonates XI were isolated in fair yields. The isomer of PMEA, compound XII, was synthesized by the same route from 9-(2-hydroxyethoxymethyl)adenine. The parent compound of the series, 9-phosphonylmethyladenine (XIII), resulted from alkylation of adenine with the synthon II followed by ester cleavage reaction.

The structural variations in the heterocyclic base of PMEA are based on (a) base-catalyzed alkylation of the heterocyclic base with an appropriate phosphorus-containing

> A-CH2(CH2)nX IX X=C1.Br

A-CH<sub>2</sub>(CH<sub>2</sub>)<sub>n</sub>P(O)(OR)<sub>2</sub>X R=C2H5 XI R=H n=1,2,3

A-CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>P(O)(OH)<sub>2</sub> XII

A-CH<sub>2</sub>P(O)(OH)<sub>2</sub> IIIX

XCH2CH2OCH2P(0)(OC2H5)2

XIVa X=OTs XIVb X=C1

B-CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>P(0)(OR)<sub>2</sub> ΧV R=C2H5 IVX R≖H

synthon or (b) subsequent transformation of the preformed N--(2-phosphonylmethoxyethyl)derivative at the heterocyclic moiety. The former alternative utilizes synthons of the type XIV of which the tosyloxy derivative XIVa was already used for the synthesis of PMEA<sup>3</sup>. The distillable 2-chloro derivative XIVb can be easily obtained from 2-chloroethanol by chloromethylation followed by reaction of the resulting chloromethoxyethyl chloride with triethyl phosphite. The easy availability of the synthon XIVb makes its use preferable to the tosyl derivative XIVa. The diesters XV obtained by silica gel chromatography are subsequently cleaved to the PME-derivatives XVI by the above technique.

The compounds XVI prepared by this reaction encompass 1-substituted pyrimidine (uracil, thymine, cytosine, 5-methyl-cytosine) derivatives, as well as 9-substituted purine analogs (e.g. 2-amino-, 2,6-diamino-, 6-hydrazino-, 6-methyl-and 6-methylthiopurine, 3-deazaadenine). The guanine compounds were obtained via 2-amino-6-chloropurine intermediates followed by acid hydrolysis. Additional compounds were prepared by modification of PMEA (hypoxanthine, 1,6-ethenoadenine derivative).

ANTIVIRAL ACTIVITY. All the compounds were tested against selected RNA and DNA viruses (including TK<sup>-</sup> mutants) under in vitro conditions. None of the PMEA analogs modified at the side chain exhibited any significant antiviral activity thus demonstrating the narrow margin of the PMEA structure. Of the base-modified PMEA analogs (XVI), the pyrimidine derivatives are devoid of antiviral effect. However, in the purine series, several compounds (guanine, 2,6-diaminopurine) showed activity superior to PMEA or comparable (2-aminopurine, 6-hydrazinopurine) with the parent compound. The effect is directed against herpesviruses (HSV 1,2, CMV, VZV)<sup>4</sup>) and, most interestingly, against MSV and HIV<sup>5</sup>). However, the cytotoxicity of these compounds is also significantly higher than that of PMEA.

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