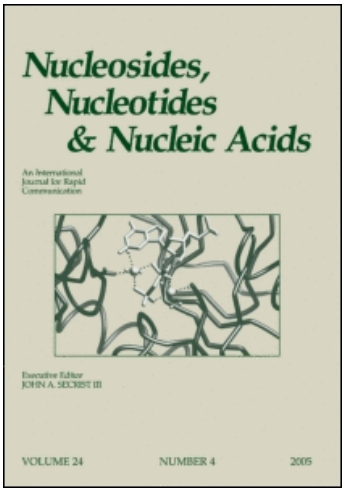

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New Prodrugs of 9-(2-Phosphonomethoxyethyl)adenine [PMEA]: Synthesis and Stability Studies

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NEW PRODRUGS OF 9-(2-PHOSPHONOMETHOXYETHYL) ADENINE [PMEA]: SYNTHESIS AND STABILITY STUDIES

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Abstract: The synthesis, and stability in different media of new PMEA prodrugs, with S-acyl-thioethyl (SATE) as enzyme-labile phosphonate protecting groups, are described in comparison with the already known Bis(POM)- and Bis(DTE)PMEA.

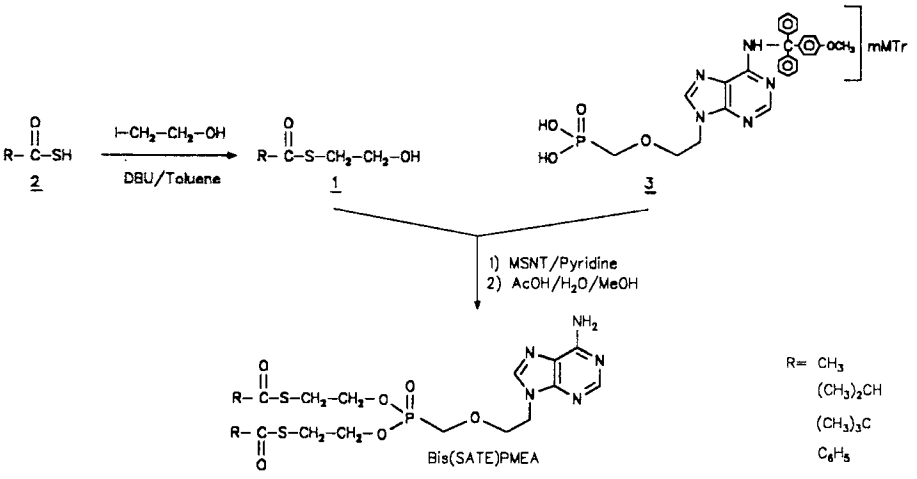
INTRODUCTION

The 9-(2-phosphonomethoxyethyl)adenine (PMEA) has demonstrated *in vitro* antiviral activity against several retroviruses, including human immunodeficiency virus (HIV), and against a broad spectrum of DNA viruses, including herpes viruses[1]. Its antiviral activity has also been proved in several animal models[1].

However, the cellular uptake as well as the oral bioavailability (< 1% in monkeys[2] and 11% in rats[3]) of PMEA are relatively poor[4], owing to its charged phosphonate function. Masking the latter may allow the passage of PMEA through membranes and thus increase its therapeutic potency. In this regard, we report here the synthesis of new neutral prodrugs of PMEA, with S-acyl-thioethyl (SATE) as enzyme-labile phosphonate protecting groups. Data on their stability in different media, compared with the already known Bis(POM)-[5,6] and Bis(DTE)PMEA[7] are also reported.

SYNTHESIS

The S-acyl-thioethanol reagents **1** have been prepared by reaction of 2-iodoethanol with the corresponding thioacids **2** and then condensed with the N^6-(4-monomethoxytrityl)-9-(2-phosphonomethoxyethyl)adenine **3**[7], to give after acidic treatment the Bis(SATE) derivatives (Scheme).



Scheme

STABILITY STUDIES

These studies indicated that the new Bis(SATE)PMEA prodrugs are more stable than the already known Bis(POM)- and Bis(DTE)PMEA derivatives in water, at pH 2 and 7, and in human gastric juice.

CONCLUSION

If we consider that three of the Bis(SATE)PMEA prodrugs are crystalline, and that they show a greater stability compared to Bis(POM)PMEA (this latter having even so demonstrated an improved oral bioavailability [5]), we can conclude that this new class of compounds merit further exploration

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