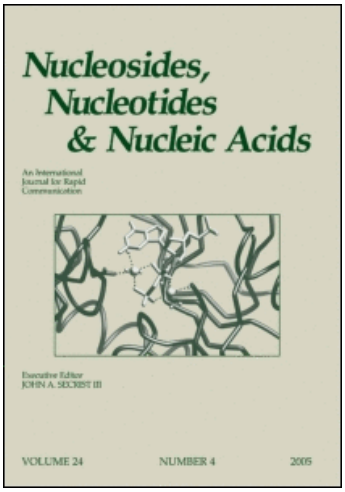

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Synthesis of 5'-H-Phosphonates of 3'-Substituted Purine Deoxynucleosides

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SYNTHESIS OF 5'-H-PHOSPHONATES OF 3'-SUBSTITUTED PURINE DEOXYNUCLEOSIDES

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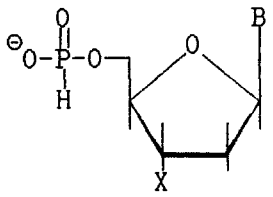
Abstract: H-Phosphonates of 3'-azido-2',3'-dideoxyadenosine, 3'-azido-2',3'-dideoxyguanosine and 3'-chloro-2',3'-dideoxyadenosine were synthesized and their antiviral activity in HIV-infected cell cultures was investigated.

As was shown recently 5'-H-phosphonate of AZT **1** blocked reproduction of HIV in MT4 and H9 cell cultures[1]. It had nearly the same activity and less toxicity as compared with parental AZT. Here we report the synthesis of H-phosphonates of purine 3'-substituted 2',3'-dideoxynucleosides **2-4**, because anti-HIV activity usually decreases for purine 3'-substituted 2',3'-dideoxynucleosides due to poor phosphorilation in cells.

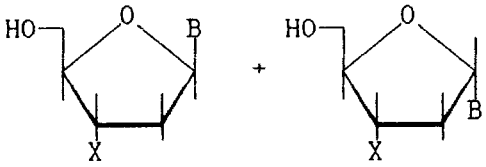


1 B=Thy X=N_3
2 B=Ade X=N_3
3 B=Gua X=N_3
4 B=Ade X=Cl

3'-Azido- and 3'-chloro derivatives of purine 2',3'-dideoxynucleosides were synthesized by transglicosidation of corresponding thymine derivatives[2] as well as by direct condensation of heterocyclic bases with 3-chloro- or 3-azido-2,3-dideoxy-5-O-toluyl-1-O-methylribosides[3]. In the case of transglicosidation of 3'-chlorothymidine the

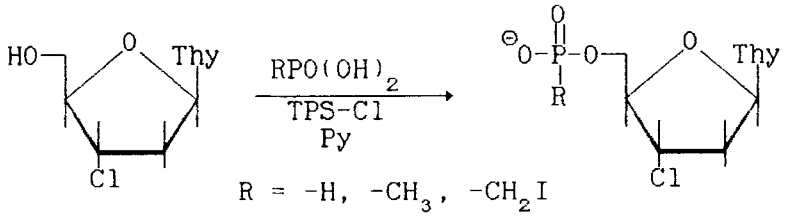
yield of 3'-chloroadenosine was 41%, α:β ratio was 2:3. The main results of direct glicosidation were follows:

B	X	Yield	α:β
Thy	N_3	52%	5:8
Cyt	N_3	37%	2:1
Ade	N_3	34%	0:1
Gua	N_3	29%	0:1
Thy	Cl	55%	1:1
Ade	Cl	48%	2:1



Phosphitilation was made with H_3PO_3 in the presence of DCC. H-Phosphonates **1-4** were isolated by ion-exchange chromatography on DEAE-Toyopearl with recleaning on LiChroprep RP 18 in water, average yield was 60%. The effectivity of inhibition of HIV-reproduction in MT4 and H9 cells by H-phosphonates **2** and **3** was comparable with that of corresponding nucleosides, whereas their toxicity was lower than that of nucleosides. Antiviral activity of **4** is under investigation.

Some phosphonates of 3'-chloro-2',3'-dideoxythymidine were also prepared by condensation of 3'-chloro-2',3'-dideoxythymidine with phosphorous or corresponding phosphonic acid. These compounds had no anti-HIV activity.



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