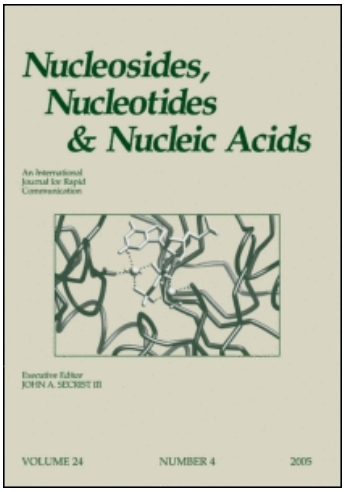

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Synthesis and Evaluation of Antiviral Activity of 3'-C-Cyano-3'-Deoxynucleosides

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SYNTHESIS AND EVALUATION OF ANTIVIRAL ACTIVITY OF 3'-C-CYANO-3'-DEOXYNUCLEOSIDES

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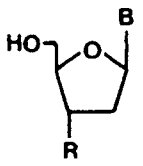
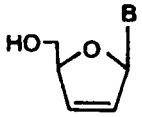
ABSTRACT. A series of 3'-C-cyano-3'-deoxy and 3'-C-cyano-2',3'-dideoxy-nucleoside analogues of thymidine, uridine, cytidine and adenosine have been prepared. Their antiviral activity was assessed in various assay systems and while none of the compounds proved specifically active against human immunodeficiency virus, some compounds had marked activity against other viruses.

An increasing number of sugar-modified nucleosides show antiviral activity.[1] The 2',3'-dideoxynucleosides, such as **1-3**, are among the most potent and selective inhibitors of human immunodefiency virus (HIV) described so far.[2,3] Other arabino, acyclic and carbocyclic nucleoside derivatives show significant activities against a variety of viruses.[4] The branched-chain sugar nucleosides represent a group of derivatives, of which some members show antiviral, anticancer and enzyme-inhibitory activities.[5-7] This prompted us to synthesize and evaluate a series of branched-chain sugar nucleoside derivatives of adenosine, cytidine, uracil and thymidine in which the 3'-OH group was replaced by a 3'-C-CN branch.

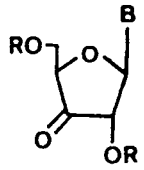
Reaction of 2',5'-di-O-(t-butyldimethylsilyl)-3'-ketonucleoside derivatives of adenosine **(4a)**,[8] 4-N-acetylcytosine **(4d)**, thymidine **(4t)**,[9] and uridine **(4u)**,[8] with sodium cyanide gave in each case, a mixture of the two epimeric nucleoside 3'-cyanohydrins. These cyanohydrins were deoxygenated at 3'-position by reaction with phenyloxythiocarbonyl chloride and, then, with tributyltin hydride in the presence of AIBN, to afford stereoselectively 3'-C-cyano-3'-deoxy-β-D-xylo-pentofuranosyl nucleosides **5a, 5d, 5t** and **5u.**



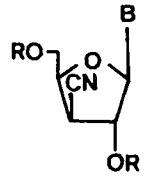
1a,c,g,t ; R=H
2g,t ; R=N3



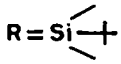
3c,t



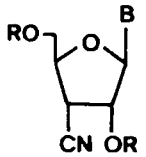
4a,d,t,u



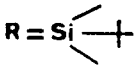
5a,d,t,u



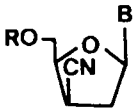
6a,c,d,t,u;R=H



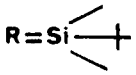
7a,c,t,u



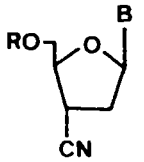
8a,c,d,u;R=H



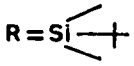
9t,



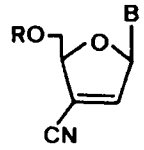
10t ; R=H



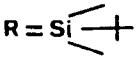
11t,



12t ; R=H



13t.



14t ; R=H

a, B = Adenin-9-yl; **c**, B = cytosin-1-yl;
d, B = 4-N-acetylcytosin-1-yl; **g**, B = guanin-9-yl
t, B = thymin-1-yl; **u**, B = uracil-1-yl

These β-D-xylo-nucleosides were epimerized to the corresponding β-D-ribo epimers **7a-u** by treatment with a methanolic NaOH solution up to pH 9. Treatment of the 2',5'-di-O-(t-butyldimethylsilyl)-protected nucleosides **5** and **7** with tetrabutylammonium fluoride gave the corresponding 3'-C-cyano-3'-deoxy-β-D-xylo and ribo deprotected nucleosides **6** and **8**, respectively.

The β-D-xylo-thymidine **6t** was transformed to the β-D-threo-thymidine **10t** by selective 5'-O-silylation with t-butyldimethylsilyl chloride, 2'-deoxygenation with phenyloxythiocarbonyl chloride in pyridine and tributyltin chloride/AIBN, and deprotection with 0.1 N HCl.

The β-D-threo-thymidine derivatives **9t** and **10t** were epimerised to the β-D-erythro-thymidines **11t** and **12t** by treatment with a solution of NaOH in methanol up to pH 9.

Table 1. Antiviral activity of 3'-C-cyano-3'-deoxynucleosides in different assay systems

	HIV/MT-4		MSV/C3H		VV/PRK		SV/Vero	
Compound	MIC (μM)	SI	MIC (μg/ml)	SI	MIC (μg/ml)	SI	MIC (μg/ml)	SI
6a	> 1.6	< 1.8	6.6	6	4	50	10	20
6t	> 250	< 0.9	> 250	1	150	3	150	1.3
6u	> 400	1	260	1.5	> 200	1	> 200	< 2
8a	> 1.6	< 2.4	8.5	4.7	4	25	10	10
8c	> 10	< 2.3	43	> 4.7	40	2.5	> 100	< 1
8u	> 80	< 1.8	> 200	1	> 200	1	> 100	2
10t	> 250	1	> 250	1	> 400	1	> 400	1
12t	> 16	< 1.9	> 16	< 5	20	5	> 10	1
14t	> 50	< 0.5	191	> 1.3	> 100	< 2	> 100	1

Reaction of 1-[5'-O-(t-butyldimethylsilyl)-3'-C-cyano-3'-deoxy-β-D-xylo-pentofuranosyl]thymine with phenyloxythiocarbonyl chloride and 4-dimethylaminopyridine, a stronger base than the pyridine used before for the 2'-deoxygenation of **6t**, did not afford the expected 2'-O-thiocarbonyl derivative, but the 3'-C-cyano-2',3'-unsaturated thymidine derivative **13t**. Treatment of the latter with a 0.1 N solution of HCl in methanol afforded the deprotected unsaturated nucleoside **14t**.

The absolute configuration at C-3' of nucleosides **5-12** was unequivocally determined by NOE experiments.

The 3'-C-cyano-3'-deoxynucleosides were evaluated for their antiviral activity in various assay systems (Table 1) : against human immunodeficiency virus (HIV) in human MT-4 limphocytes, against murine (Moloney) sarcoma virus (MSV) in murine C3H fibroblasts, against vaccinia virus (VV) in primary rabbit kidney (PRK) cells, and against Sindbis virus (SV) in African green monkey kidney (Vero) cells. The minimum inhibitory concentration (MIC), required to reduce virus-induced cytopathogenicity by 50 %, as well as the minimum cytotoxic concentration for the host cells were determined, and the ratio of the

minimum cytotoxic concentration to the minimum antiviral concentration was defined as the selectivity index (SI). From the results presented in Table 1 is is evident that none of the 3'-C-cyano-3'-deoxynucleosides exhibited a selective inhibitory effect on HIV replication. However, compounds **6a** and **8a** caused a marked and selective inhibition of VV and SV replication. They also demostrated some selectivity in their effects against MSV, and so did **8c** against MSV and **12t** against VV.

Based on the antiviral results obtained here for the 3'-C-cyano-3'-deoxy-β-D-xylo-pentofuranosyl (**6a**) and 3'-C-cyano-3'-deoxy-β-D-ribo-pentofuranosyl (**8a**) derivatives of adenine, it would seem justified to further explore these compounds for their antiviral potential and mode of action.

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