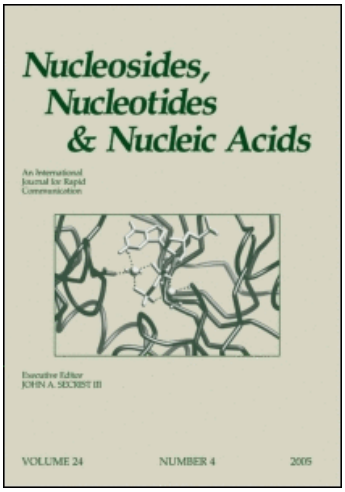

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NOVEL ACYCLIC DERIVATIVES OF AICA-RIBOSIDE (1-(β-D-RIBOFURANOSYL)5-AMINO-4-IMIDAZOLECARBOXAMIDE), POTENTIAL ANTIVIRAL AGENTS

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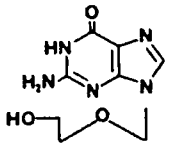
Abstract. A synthetic approach is described to obtain from AICA-riboside acyclic analogues of 2'-deoxyribosides in which the C(2')-C(3') bond is cleaved and the natural configuration (R) at the anomeric C (1')-position is retained.

During the last decade, the synthesis of an increasingly large number of acyclonucleosides has been reported, many with interesting biological activities[1]. The therapeutic utility of acyclic nucleoside analogues as antiviral agents is of particular interest. The two prototype drugs among this group of analogues are the widely used anti-herpes agent 9-(2-hydroxyethoxymethyl)guanine (acyclovir, 1) and 9-(1,3-dihydroxy-2-propoxymethyl)guanine (DHPG, 2), another anti-herpes agent useful in the treatment of human cytomegalovirus infections. Both drugs are sugar truncated derivatives of 2'-deoxyguanosine and interfere with viral DNA replication.



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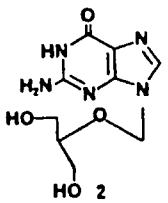

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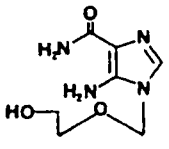
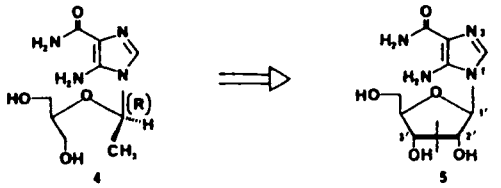


3

One analogue (3), in which the guanine of acyclovir was replaced by 5-amino-4-imidazolecarboxamide (AICA), was found to be completely inactive,[2] although it had the interesting potential of serving as a metabolic precursor of intracellular acyclovir nucleotides, since the 5'-

monophosphate of AICA-riboside (5) is an intermediate in the pathway of de novo purine biosynthesis. It appeared likely that the lack of biological activity could be due to the extensive structural modification involving both the sugar and the heterocyclic base. We decided to synthesize an acyclic AICA nucleoside analogue, in which all the carbons and OH-groups of the 2'-deoxyribose moiety are present. Thus, target compound 4 was designed and synthesized from AICA-riboside (5) by a series of chemical transformations.

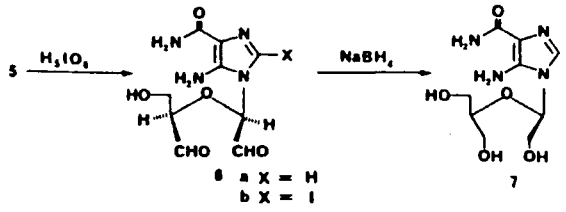


The following features of structure 4 should be noted: (1) the bond between the 2'-and 3-'position of the sugar is removed; (2) all 5 carbons of deoxyribose are present; (3) the analogous 2'-position is deoxy; (4) the natural R configuration at the 1'-position is retained.

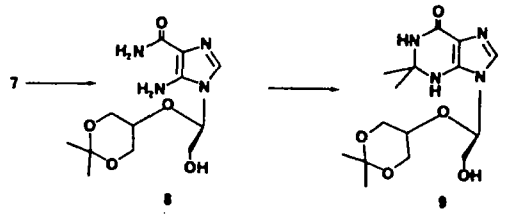
The use of AICA-riboside (5) as starting material has the advantage that the substitution is at the desired N_1-position of the imidazole ring and the right stereochemistry at the 1'-position is already established. In contrast, in the synthesis of 3, using AICA as starting material, alkylation of both nitrogens of the imidazole ring occurs, leading to a mixture of 1- and 3-substituted isomers[2].

In this paper we describe the approach used for the synthesis of 4 and discuss some of the preliminary biological results.

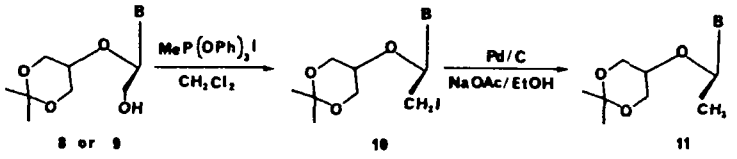
AICA-riboside (5) was oxidized with periodic acid to give the dialdehyde 6, which was reduced to the triol 7, using $NaBH_4$. Unexpectedly, the formation of the 2-iodo dialdehyde derivative (6b) also occured, which was favored by excess H_5IO_6 and longer reaction times. Thus, 6b was readily prepared in 65% yield in 16 hr using 1.2 equivalents of H_5IO_6. Both 6a and 6b were easily reduced by $NaBH_4$ in good yields either individually or together without prior separation

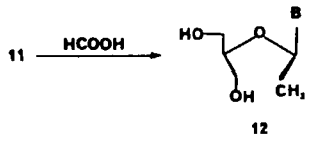


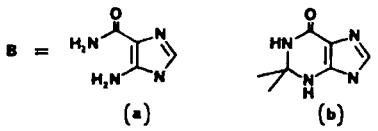
The 1,3-diol of 7 was converted to the acetonide 8 in acetone in the presence of toluenesulfonic acid and 2,2-dimethoxypropane. Prolonged reaction times lead to the formation of the diacetonide 9. After chromatographic separation, 8 and 9 were subjected to a parallel series of reactions to convert the $HOCH_2$-group to the desired CH_3-group at the C-1' position.



Treatment of 8 or 9 with Rydon's reagent gave in good yields iodomethyl derivatives 10a and 10b which were reduced by catalytic hydrogenation to the corresponding methyl derivatives 11a and 11b. Removal of the isopropylidene group from the glycerol derivatives was accomplished by treatment with 88% formic acid at room temperature for 5 and 30 min, respectively, to give 4 (12a) and 12b. The novel 2,2-dimethyl-dihydrohypoxanthine ring of 11b was stable under these conditions, so that selective deprotection of the diol could be achieved to give 12b in 66% yield.

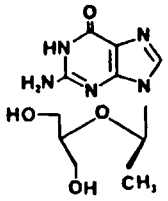






The AICA-derivative 11a could be converted to the corresponding guanine derivative 13 by established cyclization procedures.[3] Analogue

13 is the 1'-methyl derivative of DHPG (2). The guanine derivative 13 could not be prepared more directly from the 1'-iodomethyl intermediate 10 containing the guanine base in place of AICA, due to the ready alkylation of the N_3 position of the heterocyclic base. Thus, the method described is a general synthetic route to 1'-methyl acylonucleoside derivatives of purines, 2-substituted inosine analogues, in particular.



13

None of the new acyclic nucleoside derivatives (4, 12b and 13) showed activity in vitro against herpes viruses HSV1 and HSV2, and 13 was found to be inactive also against human cytomegalovirus (HCMV) in vitro. The lack of antiherpes activity of 4 is in agreement with the inactivity of 3, if one considers that the additional CH_3-group at the 1'-position is insufficient to confer biological activity to the analogue. The inactivity of 13, however, is more difficult to rationalize, since it is a simple homolog of DHPG (2). The presence of the CH_3-group at the 1'-position apparently eliminates biological activity. The molecular basis of this observation remains to be determined.

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