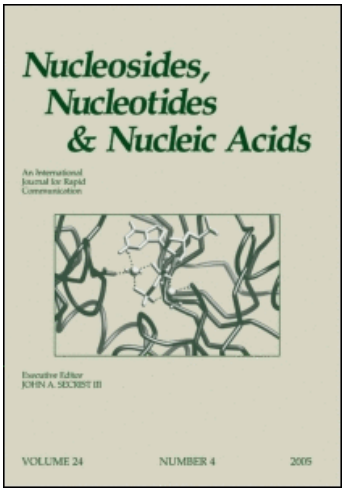

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Synthesis and Biological Evaluation of 3-Chloro-4-(D-Ribofuranosyl)-Pyridine and 3-(D-Ribofuranosyl)-2- Pyridone

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SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-CHLORO-4-(D-RIBOFURANOSYL)-PYRIDINE AND 3-(D-RIBOFURANOSYL)-2-PYRIDONE.

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Abstract : Condensation of 2-fluoro-3-lithio pyridine and 3-chloro-4-lithio pyridine with 2,4:3,5-di-O-benzylidene-aldehydo-D-ribose gives the corresponding D-allo- and D-altro-addition products. These were converted into the corresponding mesylates and cyclized to the ribofuranosyl nucleosides with an overall yield of 60-70 %. Both nucleosides did not show any inhibitory effect on L_{1210}-cells.

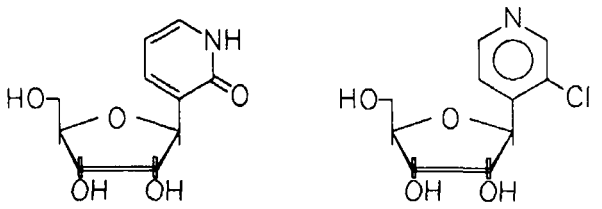
INTRODUCTION

The observation that the active form of the cytostatic C-nucleoside tiazafurin was the corresponding NAD^+-analog[1], initiated a project aiming at the synthesis of isosteric NAD^+-analogs. Therefore, the synthesis of a series of pyridine-C-nucleosides is investigated[2,3,4].

In this paper we wish to discuss the synthesis of 3-chloro-4-(D-ribofuranosyl)-pyridine and 3-(D-ribofuranosyl)-2-pyridone (FIG. 1).

RESULTS AND DISCUSSION

Since it is known that monohalopyridines can be lithiated in good to excellent yields by LDA[5] at -78°C, these lithio products were used as starting material for a



1 2

FIG. 1.

coupling reaction with 2,4:3,5-di-O-benzylidene-aldehydo-D-ribose. The lithiation occurs with a high regioselectivity at the ortho position with regard to the halogen atom. In the case of 3-chloro-pyridine, the lithiation appears to be 95 % regioselective at the C_4-position. This is expected, since the relative kinetic acidity of the protons in pyridine have the following sequency (4>3>2).

The addition reactions were performed by adding a solution of 2,4:3,5-di-O-benzylidene-aldehydo-D-ribose in THF to the lithioderivatives at -78°C. In both cases we obtained D-allo/altro mixtures which were not separated. These addition products were converted into the mesylates using methanesulphonic acid chloride in dry pyridine. On treatment of these mesylates with 1 N hydrochloric acid for 50 minutes at reflux temperature, we obtained a crude reaction mixture of both nucleosides 1 and 2 (see FIG. 2). Purification was done by affinity chromatography on an Affigel boronate column. Analysis of the reaction mixture resulting from the cyclisation of D-allo- and D-altro-2-fluoro-3-(1-O-mesyl-2,4:3,5-di-O-benzylidene-pentitol-1-yl)-pyridine by DLI/LC-MS revealed the presence of 3-(D-ribo-furanosyl)-2-pyridone instead of 2-fluoro-(D-ribofuranosyl)-3-pyridine. This conclusion was based upon the occurance of a protonated molecular ion $[MH]^+$ at a m/z-value 2 amu below the expected value for the fluoro-compound. the replacement

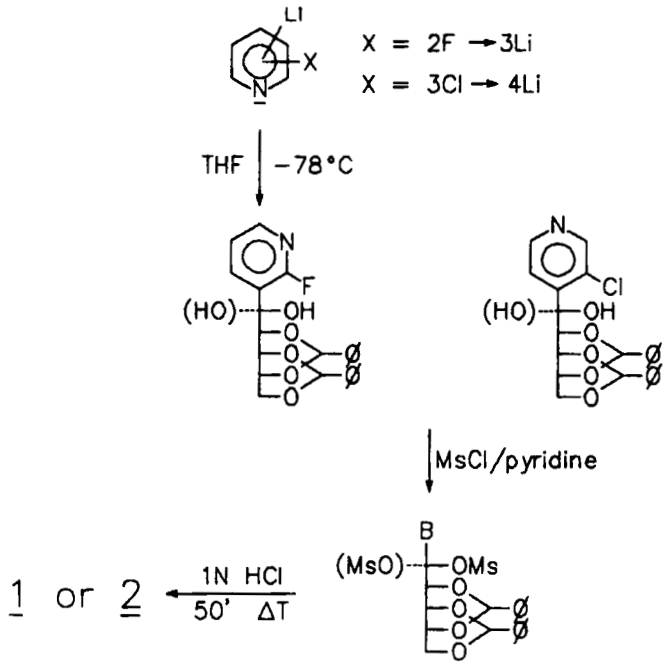


FIG. 2.

of the fluorine atom by a hydroxyl group was also confirmed by N.M.R. spectroscopy. A more detailed paper, together with N.M.R.-data and anti-viral screening results is in progress.

Achnowledgement

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