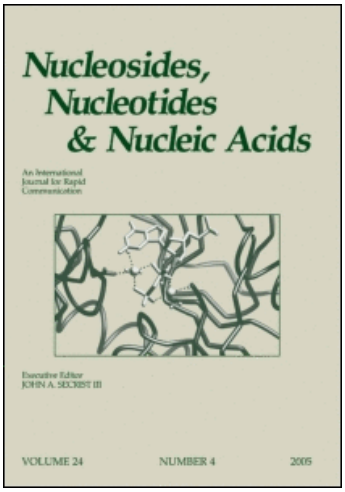

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Synthesis and Biological Evaluation of 2-Carbamoyl-5-D-Ribofuranosylpyridine

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SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-CARBAMOYL-5-D-RIBOFURANOSYLPYRIDINE.

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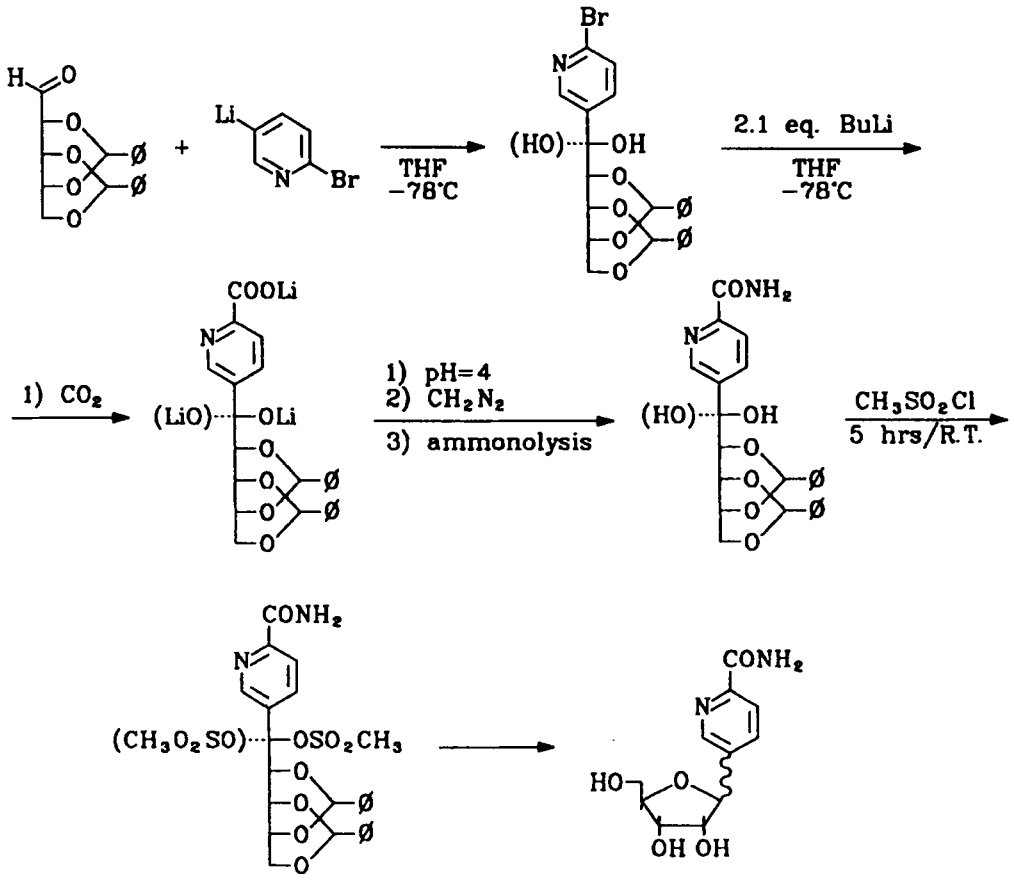
In order to study the influence of the position of both the carbamoyl- and the D-ribofuranosylmoiety on the biological activity of pyridine-C-nucleosides, the 2-carbamoyl-5-β-D-ribofuranosylpyridine was synthesized.

As depicted in scheme 1, 3,5-dibromopyridine (4.26 mmol dissolved in 20 cc THF) was treated with 4.32 mmol BuLi at -78°C for 7 min. As a result, 2-bromo-5-lithiopyridine was formed. To this solution 1 equivalent (4.26 mmol) 2,4:3,5-di-O-benzylidene-aldehyo-D-ribose (in 20 cc THF) was added. After 2 hours at -78°C the solution was allowed to warm up, overnight, to room temperature. The so formed D-allo/D-altro 2-bromo-(2,4:3,5-di-O-benzylidene-pentitol-1-yl)pyridine was not isolated. Instead, the reaction mixture was diluted with dry THF to a total volume of 80 cc and again cooled to -78°C. Then, 2.1 eq. of BuLi were added and after a reaction time of 3 min, the contents were poured on a large excess of dry ice (200 g). After evaporation of the CO_2, the residue was taken up in CH_2Cl_2 and treated with 500 cc of a buffer solution (pH = 4). The CH_2Cl_2 was evaporated and the resulting yellow foam was dissolved in a minimal amount of THF. The solution was cooled to -15°C and an excess CH_2N_2 was added. The resulting D-allo/D-altro 2-methoxycarbonyl-5-(2,4:3,5-di-O-benzylidene-pentitol-1-yl)pyridine was purified by circular chromatography (silica, eluent : CH_2Cl_2/ethylacetate 90/10) and isolated in 81% yield. Treatment of this methylester with a saturated methanolic ammonia solution for 20 hours gave D-allo/D-altro 2-carbamoyl-5-(2,4:3,5-di-O-benzylidene-pentitol-1-yl)pyridine (100% yield). In order to obtain the D-ribofuranosyl compounds, D-allo/D-altro-2-carbamoyl-5-(2,4:3,5-di-O-benzylidene-pentitol-1-yl)pyridine was converted into



Scheme 1.

the corresponding mesylate with the aid of a large excess of CH_3SO_2Cl in pyridine. The mesylation reaction was quenched after 5 hours by pouring the reaction mixture in a saturated $NaHCO_3$-solution. If longer reaction times were applied, we noticed the slow conversion of the carbamoyl function in a nitrile group[1].

The D-allo/D-altro 2-carbamoyl-5-(1-O-mesyl-2,4:3,5-di-O-benzylidene-pentitol-1-yl)pyridine was purified by circular thin layer chromatography on a Chromatotron^R (silica, eluent : CH_2Cl_2) and recristallised from CH_3OH (M.P. : 161°C, yield : 82%).

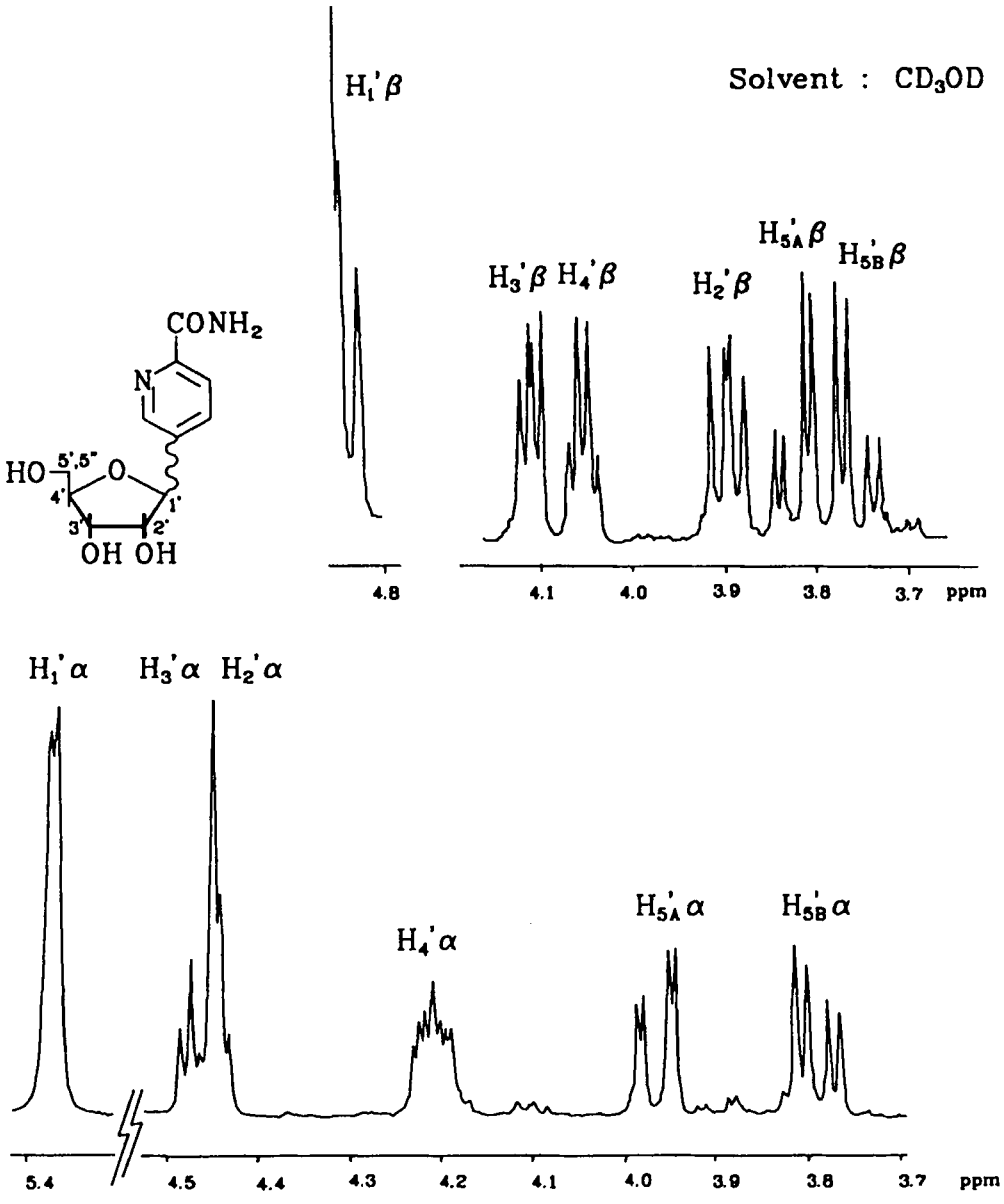


Fig. 1

In order to obtain the pyridine-C-nucleoside, the former compound was treated with CF_3COOH (20 cc CF_3COOH, 5 cc H_2O). After 15 min, the mixture was poured in 200 cc H_2O and extracted with CH_2Cl_2. The aqueous layer was evaporated, the residue redissolved in CH_3OH, neutralised with conc. NH_4OH and evaporated. The crude 2-carbamoyl-5-D-ribofuranosylpyridine was obtained and purified with the aid of reverse phase HPLC (Lichrosorb 10RP8, 25 cm x 9.4 mm I.D., H_2O/CH_3OH 99/1, flow rate: 5 cc/min). At the same time, The α,β-anomers could be separated (53% β, 47% α). The pure 2-carbamoyl-5-β-D-ribofuranosyl-pyridine was identified with the aid of 360 MHz ^{1}H-NMR (fig. 1).

BIOLOGICAL EVALUATION

2-Carbamoyl-5-β-D-ribofuranosylpyridine was evaluated against L-1210, FM3A, Raji, Molt/4F, VSV and HSV. No significant biological activity was observed (MIC_{50} > 200 or 400 μg/ml).

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