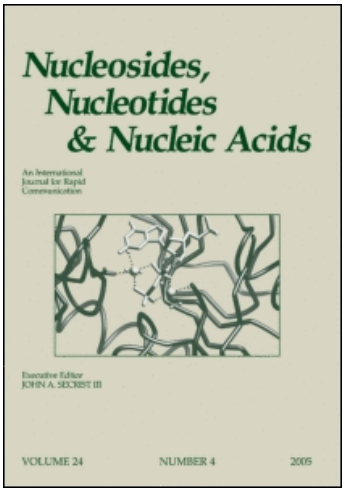

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2-Deoxy-D-Ribofuranosylation of Ethyl 5-Aminoimidazole-4-Carboxylate by Biotransformation and Chemical Methods

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2-DEOXY-D-RIBOFURANOSYLATION OF ETHYL 5-AMINOIMIDAZOLE-4-CARBOXYLATE BY BIOTRANSFORMATION AND CHEMICAL METHODS

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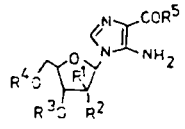
In our studies aimed at the synthesis of inhibitors of enzymes involved in the *de novo* biosynthesis of purine nucleotides, the arabinosyl nucleoside (1a), which is analogous to CAIR (1b), a central intermediate in the pathway, showed[1] significant inhibition and substrate activities. We were therefore interested to synthesize the related 2-deoxy-D-ribosyl nucleotide (1c) for further enzymological studies.

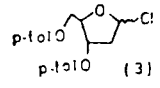
Previously reported routes to 2-deoxy-D-ribofuranosyl-aminoimidazole nucleosides have involved either degradation of purine nucleosides[2] or condensation[3] of 2-deoxyribofuranosyl halides with, such as, the nitro imidazole ester (2a) followed by hydrogenation.

We have earlier reported[4] the synthesis of the 1-β-D-arabinofuranosyl-5-aminoimidazole (1e) by direct condensation of the aminoimidazole (2b) with 2,3,5-tri-O-benzyl-α-D-arabinofuranosyl chloride in hot acetonitrile containing triethylamine. Using the same solvent conditions and imidazole (2b) we performed a comparable reaction using the 2-deoxyribofuranosyl halide (3)[5]. The reaction mixture revealed two U.V. and Bratton-Marshall[6] (diazotisable) spots on silica gel T.L.C. (ethyl acetate-toluene 1:1). Two fractions (A) and (B) were obtained from column chromatography (silica gel using ethyl acetate-toluene 3:7) of the reaction mixture, which corresponded to the two T.L.C. spots. Fraction (A) was found by NMR spectroscopy to contain the following isomeric mixture of nucleosides (20% base conversion) 55% α-N^1(4), 19% β-N^1(1d), 19% α-N^3 (5) and 7% β-N^3(6a). The components found to constitute fraction (B) (34% base conversion) were 77% α-N^3(5) and 23% β-N^3 (6a). The reaction was repeated in the absence of triethylamine. Two fractions (C) and (D) were again separated using the same chromatographic conditions but different isomeric ratios were obtained: fraction (C) (15% base conversion) contained 10% α-N^1(4) and 90% β-N^1(1d) whereas fraction (D) (35% base conversion) contained 80% α-N^3(5) and 20% β-N^3(6a).

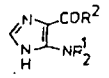
In light of the difficulties encountered in obtaining pure isomers of 2-deoxy-β-D-ribofuranosyl-5-aminoimidazole nucleosides, by chemical synthesis, an alternative route was investigated which involved biotransformation on encapsulated cells; a technique previously reported by Holy and Votruba[7]. The catalyst was composed of auxotroph thymine-

dependent Escherichia coli encapsulated in permeable alginate gel, and 2'-deoxyuridine, was the glycosyl donor. Such conditions were found to glycosylate the aminoimidazole ester (3) to give an isomeric mixture of two nucleosides (53% base conversion) containing 34% β-N^1(1f) and 66% β-N^3(6b) which were separated by HPLC [6% acetonitrile in 0.05M triethylammonium hydrogen carbonate pH7.5 (200 x 4 separon SG x 6μ)]. In contrast no reaction was observed with other azoles studied, namely, AICA, 4-cyano-5-hydroxyimidazole and 3-amino-4-ethoxycarbonylpyrazole. The ambiguity observed in the site of deoxyribosylation, by this biotransformation method, is contrary to results obtained[7] with pyrimidines and purines, so far studied, in which substitution takes place at sites N^1 and N^9 respectively.



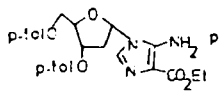


(3)

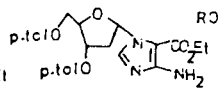


(1) a; R^1 = OH, R^2 = R^3 = H, R^4 = PO(OH)$_2$, R^5 = OEt
b; R^1 = R^3 = H, R^2 = R^5 = OH, R^4 = PO(OH)$_3$
c; R^1 = R^2 = R^3 = H, R^4 = PO(OH)$_3$, R^5 = OH
d; R^1 = R^2 = H, R^3 = R^4 = p-tol, R^5 = OEt
e; R^1 = OCH_2Ph R^2 = H R^3 = R^4 = CH_2Ph R^5 = OEt
f; R^1 = R^2 = R^3 = R^4 = H R^5 = OEt

(2) a; R^1 = O, R^2 = OMe
b; R^1 = H, R^2 = OEt



(4)



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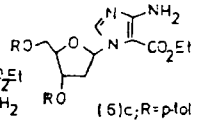

(6) c; R = p-tol
b; R = H

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