New Synthesis of 1-β-D-Arabinofuranosyl-aminoimidazoles and of Related Purine Nucleosides

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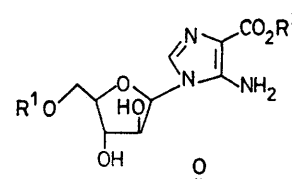
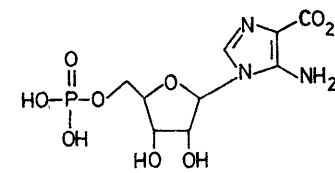
Summary Ethyl 5-amino-1-β-D-arabinofuranosylimidazole-4-carboxylate has been prepared by condensation of 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride with ethyl 5-aminoimidazole-4-carboxylate and hydrogenation of the tri-*O*-benzyl derivative so formed with palladium on barium sulphate; the structure of the imidazole nucleoside was confirmed by conversion into the known 9-β-D-arabinofuranosyl hypoxanthine.

As part of a study[1] designed to prepare inhibitors of enzymes involved in the *de novo* biosynthesis of purine nucleotides we have earlier recorded[2] the synthesis and preliminary inhibition studies of 5-amino-1-β-D-arabinofuranosyl imidazole-4-carboxylic acid 5′-phosphate (**1a**), an analogue of the ribonucleotide CAIR (**2**), which is a central intermediate in the pathway. However the arabinosyl nucleoside ester (**1b**) from which the nucleotide (**1a**) was obtained could only be obtained in low yield by condensation of the arabinofuranosylamine (**3**) with the formimidate[3] (**4**), the major product being the α-anomer. In addition the total yield of nucleosides in this reaction was further diminished by O → N benzoyl migration in the amine (**3**) and by *O*-alkyl fission during the exceptionally difficult removal of the benzoyl groups in (**1b**) with methanolic sodium methoxide. The interesting enzyme inhibitory activity of the arabinose nucleotide (**1a**) has prompted us to examine alternative syntheses of this substance since we require large amounts both for further enzyme studies and for appropriate biological tests.

Earlier attempts to synthesise aminoimidazole nucleosides by direct condensation of a sugar derivative with an imidazole have proved very unrewarding. Various heavy metal salts of the nitro imidazole ester (**5**) with acylated glycosyl halides gave mixtures of 1- and (mainly) 3-glycosides with the required 1-isomer being produced in very low yield.[4,5]



(1) a; $R^1 = (HO)_2P(O)-$, $R^2 = H$
b; $R^1 = H$, $R^2 = Et$



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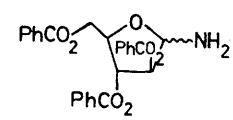

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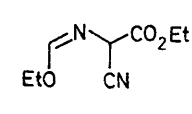

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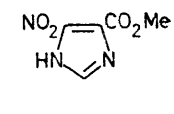
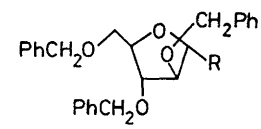
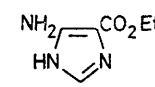


(5)



(6) a; R = Cl
b; R = Br
c; R = I



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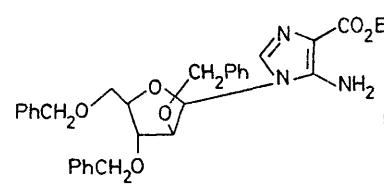
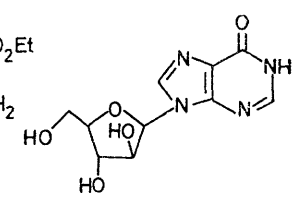


(8)



(9)

A similar fusion reaction[6] of the nitroimidazole (**5**) with tetra-*O*-acetyl-β-D-ribofuranose gave only the 3-isomer. In our hands several attempts to condense heavy metal or silyl derivatives of various aminoimidazole derivatives with tri-*O*-benzoylribofuranosyl or arabinofuranosyl halides produced only traces of condensation products and similar results were obtained with a variety of fusion reactions. These results contrast sharply with the results obtained from most purines or pyrimidines when generally good yields of nucleosides are readily produced by fusion reactions or the use of silyl derivatives and glycosyl halides.

We now report a simple improved synthesis of the required arabinosyl nucleoside (**1b**).

2,3,5-Tri-*O*-benzyl-α-D-arabinofuranosyl chloride[7] (**6a**) with the aminoimidazole ester[8] (**7**) in hot acetonitrile containing triethylamine reacted rapidly (the reaction appears to be complete in < 1 h) to produce, after evaporation and washing a dichloromethane solution with alkali, ethyl 5-amino-1-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-imidazole-4-carboxylate (**8**) which rapidly crystallised without chromatography in pure form (24% yield) m.p. 93 °C. The structure assigned was confirmed by reaction with excess of formamidine acetate in hot acetonitrile to produce the arabinosyl hypoxanthine, which, after hydrogenolysis of the benzyl groups, gave the deblocked nucleoside (**9**) as a crystalline solid identical with an authentic specimen[9] (mixed m.p., i.r., u.v.). The imidazole nucleoside (**8**) could also be deblocked (90% yield) by hydrogenation over palladium–charcoal to produce the required nucleoside (**1b**). The reaction allows the ready production of relatively large amounts of the required nucleoside without chromatography. The same nucleoside derivative (**8**) was also obtained by reaction in dichloromethane at room temperature or from a silyl derivative, prepared from the aglycone (**7**) and hexamethyldisilazane and the arabinosyl chloride (**6a**), but in each case much lower yields of product were obtained.†

In sharp contrast to the ease of reaction of the chloride (**6a**) with the aglycone (**7**), similar reaction of the arabinosyl bromide (**6b**) or iodide (**6c**) (prepared, like the chloride, from the 1-*O*-*p*-nitrobenzoate and hydrogen halide) only gave, even after long heating, traces of the nucleoside (**8**).

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† Satisfactory analytical t.l.c. and spectral data were obtained for all new compounds.

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