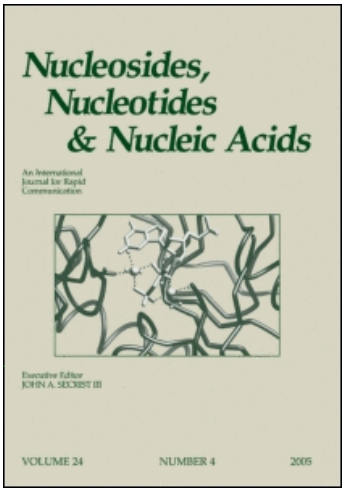

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REACTIONS OF PURINE NUCLEOSIDES WITH AQUEOUS ALKALIES: THE EFFECT OF THE C6 SUBSTITUENT ON THE KINETICS OF THE MULTISTAGE PATHWAY

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Abstract: Kinetics of the reactions of 6-substituted 9-(β-D-ribofuranosyl)purines with aqueous alkalies have been studied liquid chromatographically.

LC analyses indicate that the main reaction pathway for the cleavage of 6-chloro-, 6-methyl- and 6-methylthio-9-(β-D-ribofuranosyl)purines in aqueous alkali is analogous to that described previously[1] for their unsubstituted counterpart. Accordingly, an attack of hydroxide ion on C8 leads to opening of the imidazole ring, and the resulting 5-formamido-4-(β-D-ribofuranosyl)aminopyrimidines are rapidly anomerized to a mixture of furanoid and pyranoid derivatives. The carbonyl carbon of the formamido group is subsequently attacked by hydroxide ion, and the tetrahedral intermediate formed undergoes a base-catalyzed breakdown to formate ion and 5-amino-4-ribosylaminopyrimidine. Which one of these steps is rate-limiting depends on the polar nature of the 6-substituent. Finally, 5-amino-4-ribosylaminopyrimidines are hydrolyzed to 4,5-diaminopyrimidines. The latter reaction may be assumed to involve an attack of hydroxide ion on the anomeric carbon of the acyclic Schiff base form and a breakdown of the carbinolamine formed. With 6-methyl and 6-methylthio derivatives the reaction sequence is further complicated by partial recyclization of the 5-formamidopyrimidine intermediates to isomeric nucleosides, mainly to β-D-ribopyranosyl derivatives.

The cleavage of adenosine is also initiated by opening of the imidazole ring. However, intramolecular cyclizations to anomeric adenine nucleosides and N^6-ribosyladenines competes with the subsequent deformylation. A base-catalyzed hydrolysis of N^6-ribosyladenines finally gives adenine. Adeno-

sine and 6-chloro- and 6-methylthio-purine ribosides are also partly converted to inosine, the proportion of this reaction ranging from 2 to 15 %.

The initial opening of the imidazole ring and the subsequent deformylation are both accelerated by electron-withdrawal of a polar group at C6, the susceptibility being considerably higher in the former step. This is understandable on the basis of the mechanism presented. An electron-withdrawing group facilitates the attack of hydroxide ion on both the C8 atom of the purine ring and the carbonyl carbon of the formamido group. However, at the same time the $\underline{N}^5$H becomes more acidic, and the increased concentration of the unreactive $\underline{N}^5$-monoanion partly cancels the accelerating effect of the diminished electron density at the carbonyl carbon. The final step, viz. the rupture of the $\underline{N}$-glycosidic bond, is not markedly susceptible to the polar nature of the 6-substituent. Consequently, the three consecutive reactions are kinetically fairly well separated when the 6-substituent is electronegative, but overlap severely when it becomes electropositive.

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