SYNTHESES OF 3,9-DIALKYLADENINES AND 3-METHYLADENOSINE

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Alkylation of N′-alkoxy-1-alkyl-5-formamidoimidazole-4-carboxamidines, prepared by ring opening of 1-alkoxy-9-alkyladenines as reported previously, with alkyl halides in N,N-dimethylformamide (DMF) in the presence of NaH or anhydrous K_2CO_3 produced N′-alkoxy-1-alkyl-5-(N-alkylformamido)imidazole-4-carboxamidines (I) in good yields. Hydrogenolysis of I using hydrogen and Raney nickel as a catalyst in the presence of one molar equivalent of HCl afforded 1-alkyl-5-(N-alkylformamido)imidazole-4-carboxamidines (II). On treatment with Et_3N, HCl, or $HClO_4$ in ethanol or methanol, the amidines (II) cyclized to give 3,9-dialkyladenines (III), which were isolated as the HCl or $HClO_4$ salts.

Methylation of N′-benzyloxy-1-β-D-ribofuranosyl-5-formamidoimidazole-4-carboxamidine, obtained from 1-benzyloxyadenosine according to previously described procedure, with methyl iodide in DMF in the presence of anhydrous K_2CO_3 gave N′-benzyloxy-1-β-D-ribofuranosyl-5-(N-methylformamido)imidazole-4-carboxamidine (IV). The benzyloxy group of IV was removed by catalytic hydrogenolysis over Raney nickel in the presence of one molar equivalent of p-toluenesulfonic acid, and the resulting amidine (V) was treated with Et_3N in methanol to yield 3-methyladenosine (VI) as the p-toluenesulfonate.

3,9-Dialkyladenines (III) and 3-methyladenosine (VI) thus synthesized were found to be unstable in alkaline aqueous solution. In 0.1 M aqueous $NaHCO_3$, III and VI were equilibrated with their ring opened derivatives, II and V, and their equilibrium constants at 25 °C were determined. In addition, 3-methyladenosine (VI) was also unstable in acidic aqueous solution: it was readily hydrolyzed to 3-methyladenine, and the hydrolysis rate of the glycosidic linkage at pH 1 and 25 °C was determined to be 4.0×10^{-2} min^{-1}.