Synthesis and Hydrolysis of 3-Methyladenosine

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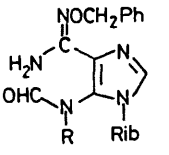
Summary Methylation of *N'*-benzyloxy-5-formamido-1-β-D-ribofuranosylimidazole-4-carboxamidine (**1**) followed by hydrogenolysis of the *N'*-benzyloxy group and cyclization gave the hitherto unknown 3-methyladenosine (**4**), which was easily hydrolysed to 3-methyladenine (**6**) in 0·1 N aq. HCl and to the imidazole ribosides (**3**) and (**5**) under basic conditions.

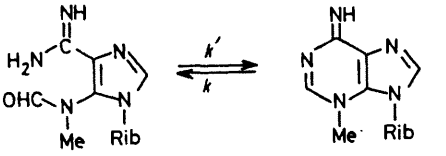
3-SUBSTITUTED adenosines are among the four possible *N*-monosubstituted adenosine isomers, and they have been prepared as modified cyclonucleoside derivatives with[1] or without[2,3] extra N^6-substituents. Although 3-methyladenosine (**4**) is the simplest member in this series, it still remains to be synthesized whereas the other three *N*-methyladenosines[4] are already known. We now report the first synthesis of (**4**), which represents an extension of our recent general method[5] for the synthesis of 3,9-dialkyladenines to the nucleoside series.

Treatment of the formamidoimidazole (**1**),[6] the readily isolable intermediate in the Dimroth rearrangement of 1-benzyloxyadenosine,[7] with MeI in $HCONMe_2$ in the presence of anhydrous K_2CO_3 at room temperature for 9 h furnished the *N*-methylformamido derivative (**2**),† m.p. 160—161 °C, in 86% yield. Removal of the *N'*-benzyloxy group from (**2**) was then effected by hydrogenolysis using Raney Ni and H_2 (1 atm, room temp., 70 min) in H_2O in the presence of 1 mol equiv. of toluene-*p*-sulphonic acid (TsOH), and the crude (**3**)·TsOH that resulted was treated with a little Et_3N in MeOH at room temperature for 48 h, giving the desired compound (**4**)·TsOH [53% yield from (**2**)], m.p. *ca.* 150 °C (decomp.); λ_{max} (95% EtOH) 272 nm (ε 16,500); λ_{max} (H_2O) (pH 1) unstable; λ_{max} (H_2O) (pH 7) 270 nm (ε 17,400); λ_{max} (H_2O) (pH 13) unstable; δ [$(CD_3)_2SO$] 2·28 (3H, s, CMe), 4·19 (3H, s, NMe), 8·59 and 8·74 (1H each, s, purine protons), and 9·12 and 9·21 (2H, $=NH_2^+$ or 2 × NH).

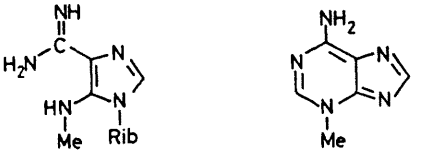
As in the case of 3,9-dialkyladenine salts,[5] (**4**)·TsOH was found to be unstable under basic conditions: treatment of its aqueous solution with Amberlite CG-400 (OH^-) at room temperature resulted in the ring opening of the purine unit, and the methylaminoimidazole (**5**) was isolated in the form of (**5**)·2HCl·H_2O (87% yield), m.p. 99—102 °C (decomp.). In 0·1 M aq. $NaHCO_3$ (pH 8·32) at 25 °C, 3-methyladenosine (**4**) equilibrated with (**3**), and the pseudo-first-order rate constants and equilibrium constant for the ring opening and cyclization were determined to be $k = 6{\cdot}6 \times 10^{-3}$ min^{-1}, $k' = 6{\cdot}9 \times 10^{-3}$ min^{-1}, and $K = k/k' = 0{\cdot}96$.



(1) R = H
(2) R = Me



(3) (4)



(5) (6)

Rib = β-D-ribofuranosyl

In contrast to the inertness of 3,9-dialkyladenine salts in aqueous acidic solution, (**4**)·TsOH underwent hydrolysis to afford 3-methyladenine (**6**)[8] (92% yield) on treatment with 0·1 N aq. HCl at room temperature for 1 h. For the hydrolysis [(**4**)·TsOH → (**6**)] at pH 1 and 25 °C a rate constant of $4{\cdot}0 \times 10^{-2}$ min^{-1} and a half life of 17 min were obtained. Adenosine itself was completely stable under similar conditions, and Venner[9] reported that the rate constant for its hydrolysis at pH 1 and 37 °C was $2{\cdot}16 \times 10^{-5}$ min^{-1}. Interestingly, the introduction of the methyl group into adenosine at the 3-position thus made the glycosidic bond cleavage some thousand times easier under acidic conditions.

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† Satisfactory microanalytical and/or spectroscopic data have been obtained for all new compounds described.

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