Synthesis, Ring Opening, and Glycosidic Bond Cleavage of 3-Methyl-2′-deoxyadenosine

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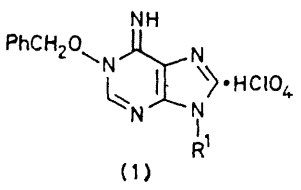
Summary Methylation of *N*′-benzyloxy-1-(2-deoxy-β-D-ribofuranosyl)-5-formamidoimidazole-4-carboxamidine (**2a**) followed by hydrogenolysis of the *N*′-benzyloxy-group and cyclization produced the hitherto unknown 3-methyl-2′-deoxyadenosine (**5a**), which was readily hydrolysed to 3-methyladenine (**6**) in H_2O at pH ⩽7 0 and to (**6**) and the imidazole-(2-deoxy)riboside (**4a**) at pH 8·98

THE 3-methyl-2′-deoxyadenosine structure (type **5a**) has been assumed to occur in DNA's which had been treated with various methylating agents [1] Because of the extraordinary instability its glycosidic bond to acid hydrolysis at the polynucleotide level,[2] it is of prime importance to study this part-structure at the nucleoside level We now record the first synthesis of 3-methyl-2′-deoxyadenosine (**5a**), which has enlarged the scope of our general method[3] for the synthesis of 3,9-disubstituted adenines, as well as its behaviour toward hydrolysis

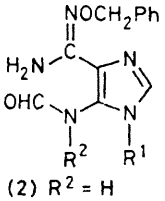
In general agreement with previous results,[4] the reaction of 2′-deoxyadenosine 1-oxide[5] with $PhCH_2Br$ in $AcNMe_2$ and treatment of the benzylated product with $NaClO_4$ gave the 1-benzyloxy-derivative (**1a**),† m p 143 5—144 5 °C (decomp), in 85% yield The perchlorate (**1a**) was converted into the free base by the use of Amberlite IRA-402 (HCO_3^-) and the base was treated with H_2O at 3—4 °C for 8 days to furnish the formamidoimidazole (**2a**) $\frac{1}{4}H_2O$ (70% yield), m p 138—139 °C (decomp) Methylation of (**2a**) with anhydrous K_2CO_3 and MeI in $HCONMe_2$ at room temperature afforded the *N*-methylformamido-derivative (**3a**) (69% yield), m p 141—142 °C (decomp), which was hydrogenolysed with Raney Ni and H_2 (1 atm, room temperature, 90 min) in H_2O in the presence of a mol equiv of toluene-*p*-sulphonic acid (TsOH) The crude (**4a**) TsOH that formed was treated with a little Et_3N in MeOH at −18 °C for 3 days to produce the desired compound (**5a**) TsOH [19% yield from (**3a**)], m p *ca* 120 °C (decomp), λ_{max} (95% EtOH) 272 nm (unstable), λ_{max} (H_2O) (pH 1 or 13) unstable, λ_{max} (H_2O) (pH 7) 271 nm (ε 16900) (unstable), δ [$(CD_3)_2SO$] 2 28 (3H, s, CMe), 4 19 (3H, s NMe), 8 63 and 8 71 (1H each, s, purine protons), and 9 15 and 9 23 (2H, $=NH_2^+$ or 2 NH)

The (**5a**) TsOH thus obtained was found to be very unstable When treated with boiling MeOH for 30 min, it gave 3-methyladenine (**6**)[6] in 99% yield It underwent hydrolysis to (**6**) much faster in an aqueous acidic solution and rate constants of 0 25 min^{-1} (half life 2 7 min), 0 039 min^{-1} (18 min), and 0 02 min^{-1} (35 min) were determined for the hydrolyses at pH 3 34 and 25 °C, pH 5 00 and 37 °C, and pH 7 00 and 37 °C, respectively In contrast the hydrolysis of methylated DNA at 37 °C at pH 5 0 or 7 0 was reported to liberate (**6**) at a rate of 1 0 × 10^{-3} min^{-1} (half life 11 5 h) or 4 8 × 10^{-4} min^{-1} (24 h) [2a] We also found that the rate constant for the hydrolysis of the furanosyl-analogue (**5b**) TsOH[3b] at pH 3 34 and 25 °C was 6 9 × 10^{-4} min^{-1} (half life 17 h) Interestingly, the replacement of the ribosyl-group in (**5b**) TsOH by the 2-deoxyribosyl-group to give

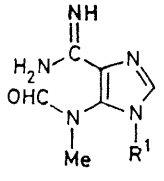
† Satisfactory spectral data and/or elemental analyses were obtained for all the new compounds described



(1)



(2) R^2 = H
(3) R^2 = Me



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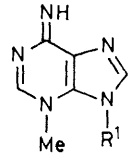
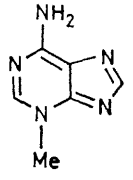
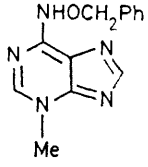


(5)



(6)



(7)

a; R^1 = 2-deoxy-β-D-ribofuranosyl
b; R^1 = β-D-ribofuranosyl
c; R^1 = H

(**5a**) · TsOH made the glycosidic bond cleavage 360 times faster. In H_2O at pH 8·98 and 25 °C, (**5a**) · TsOH was slowly converted into (**6**) in 45 h, during which time the temporary formation of the ring-opened derivative (**4a**) was observed. Although the ring opening of (**5a**) · TsOH was similar to that reported[3b] for (**5b**) · TsOH, the observed hydrolytic cleavage of the glycosidic bond in alkaline solution was quite notable.

The glycosidic bond of the imidazole-derivative (**3a**) was also unstable in aqueous acidic solution. On treatment with 0·1 N aq. HCl at room temperature for 3·5 h, (**3a**) provided (**3c**) (61% yield) as a glass. The ribosyl-analogue (**3b**)[3b] was stable under similar conditions. The structure of (**3c**) was confirmed by its cyclization with HCl–EtOH to yield (**7**), m.p. 180—181 °C, identical with a sample synthesized from 3-methyl-6-methylthiopurine[6] and benzyloxyamine, and by its hydrogenolysis using Raney Ni and H_2 and spontaneous cyclization to give (**6**) in 84% yield.

We acknowledge support of this work by a Grant-in-Aid for Special Project Research from the Ministry of Education, Science and Culture, Japan.

(*Received, 12th May* 1980; *Com.* 509.)

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