

Synthesis of 2',3',5'-Tris-*O*-acetyl-8-fluoroadenosine¹

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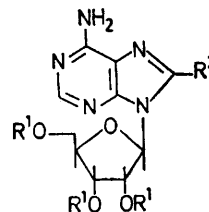
Summary 2',3',5'-Tri-*O*-acetyl-8-fluoroadenosine has been synthesized from the 8-bromo compound using the crown ether 18-crown-6.

PYRIMIDINE nucleosides having fluorine at the 5-position are well known to have anti-tumour activity. Since position-5 of the pyrimidine nucleoside and position-8 of the purine nucleoside are not involved in the Watson-Crick base-pairing site, the synthesis of 8-fluoropurine nucleosides is of interest. Previous attempts to synthesize 8-fluoroadenosine from 8-halogenoadenosines using metal fluorides were unsuccessful.²

Application of crown ethers in the synthesis of aryl fluorides from aryl halides has been reported.³ We now report a synthesis of 2',3',5'-tri-*O*-acetyl-8-fluoroadenosine from the corresponding bromide using 1,4,7,10,13,16-hexaoxacyclo-octadecane (18-crown-6).

2',3',5'-Tri-*O*-acetyl-8-bromoadenosine² (**1**) and dry KF, in the presence of 18-crown-6,³ with dry MeCN as solvent were shaken in a stainless steel tube (120 °C, 48 h), and 2',3',5'-tri-*O*-acetyl-8-fluoroadenosine (**3**) was obtained after chromatography on silica gel with CHCl₃-BuOH (20:1) as eluant; 25% yield, m.p. 99–102 °C (from EtOAc-hexane), one spot on t.l.c. [silica gel with CHCl₃-EtOAc (4:1) as eluant], λ_{max} (tetrahydrofuran) 249 nm (log ε 4.12) [250 (4.15) with alkali, 251 nm (4.13) with acid]; δ (¹H) 2.1 and 2.13 (9H, Ac), 4.4 (3H, 4'- and 5'-H), 5.76 (1H, 3'-H), 6.0 (2H, 1'- and 2'-H), 6.3 (2H, 6-NH₂), and 8.3 (1H, 2-H); ¹⁹F n.m.r. spectrum +44 (s) p.p.m.; † *m/e* 411 (*M*⁺), 259 (sugar residue), 154 (base residue + 2H), and 153 (base residue + H); high resolution, *m/e* 411.120 (calc. 411.119). ‡

Treatment of (**3**) with NaSH in dimethylformamide gave 2',3',5'-tri-*O*-acetyl-8-mercaptoadenosine (**4**), as shown by its u.v. spectrum and t.l.c. behaviour.² Dissolution of (**3**) in MeOH containing a few drops of aqueous 0.1N NaOH gave 8-methoxyadenosine (**5**) (90%), m.p. 204–206 °C (decomp.) (from EtOH), λ_{max} (pH 1) 261 and 259 nm. ‡



- (1) R¹ = Ac, R² = Br (2) R¹ = H, R² = Br
(3) R¹ = Ac, R² = F (4) R¹ = Ac, R² = SH
(5) R¹ = H, R² = OMe

Compound (**4**) was also obtained from (**1**) in a similar manner, while (**5**) was synthesized by the treatment of (**2**) with NaOMe in MeOH.⁴ As shown, compound (**3**) is highly reactive compared with other halogeno-derivatives. Compound (**5**) was also obtained by addition of 10% HCl to a solution of (**3**) in MeOH. The chemical and physical properties of (**3**) are different from those reported previously^{2,5} for the compound obtained by Schiemann reaction of 8-amino-tri-*O*-acetyladenosine. The 2',3',5'-tri-*O*-acetyl-8-fluoroadenosine obtained by us is very unstable in acidic or alkaline media and seems to be unable to withstand the

† From PhCF₃ as internal standard.

‡ Satisfactory elemental analyses were obtained [F for (**2**); C, H, and N for (**4**)].

reaction condition used previously. Since ^{19}F n.m.r. data and elemental analyses for fluorine were not included in the previous report, we conclude that the compound obtained previously was not 8-fluoroadenosine.

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