Synthesis of 2′,3′,5′-Tris-*O*-acetyl-8-fluoroadenosine[1]

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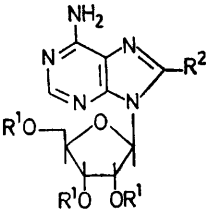
Summary 2′,3′,5′-Tri-*O*-acetyl-8-fluoroadenosine has been synthesized from the 8-bromo compound using the crown ether 18-crown-6.

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-bromoadenosine[2] (**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 $CHCl_3$–BuOH (20:1) as eluant; 25% yield, m.p. 99—102 °C (from EtOAc–hexane), one spot on t.l.c. [silica gel with $CHCl_3$–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 (^{1}H) 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-NH_2), and 8·3 (1H, 2-H); ^{19}F 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**) R^1 = Ac, R^2 = Br (**2**) R^1 = H, R^2 = Br
(**3**) R^1 = Ac, R^2 = F (**4**) R^1 = Ac, R^2 = SH
(**5**) R^1 = H, R^2 = 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 $PhCF_3$ 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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