

Synthesis of 9-(3-Deoxy-3-fluoro- β -D-ribofuranosyl)guanine, a New Potent Antiviral Agent

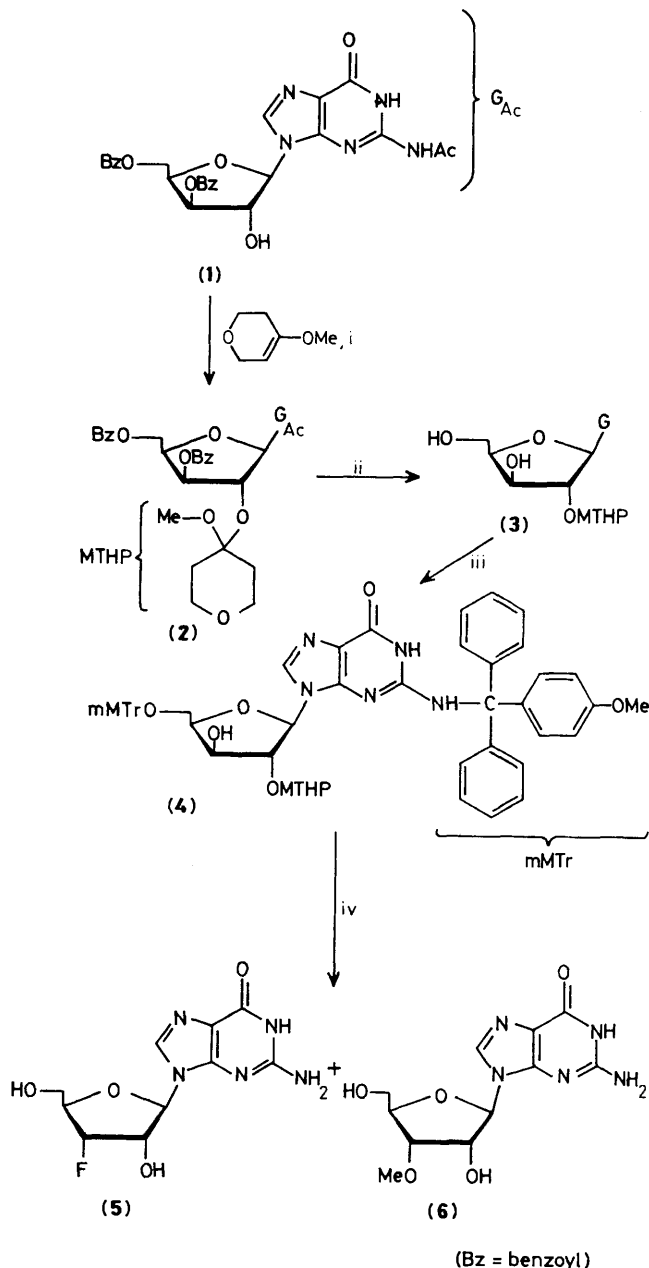
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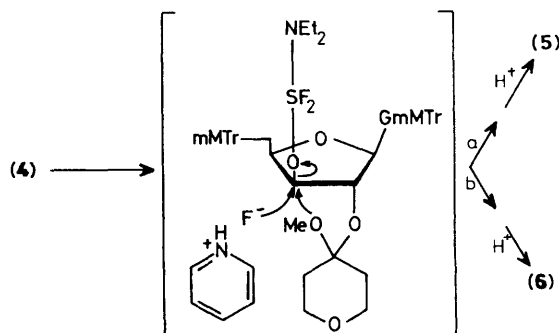
The title compound (**5**) was prepared by reacting a corresponding nucleoside of *xylo* configuration with (diethylamino)sulphur trifluoride (DAST).

Pyrimidine nucleosides fluorinated in the sugar moiety have been extensively investigated in the search for antiviral agents, and to date some 2'-*ara*-fluoro and 2'-deoxy-3'-*ribo*-fluoro analogues have actually displayed potent anti-herpes¹ and anti-human immunodeficiency virus² (anti-HIV) activities,

respectively. In contrast fluorinated purine nucleosides have been less explored, owing to the difficulty in their synthesis. For instance, in the 3'-*ribo*-fluoro series, only the adenine derivative has been prepared.³ The cytostatic potential of this compound together with the recently mentioned selective



Scheme 1. Reagents and conditions: i, TFA, CH₂Cl₂; ii, NH₃, MeOH; iii, mMTrCl, pyridine; iv, DAST, pyridine, CH₂Cl₂, followed by 1% TFA, CH₂Cl₂.



Scheme 2. Reagents and conditions: Et₃N-SF₃, pyridine, CH₂Cl₂.

anti-HIV activity of 3'-fluoro-2',3'-dideoxyguanosine^{2a,4} prompted us to synthesize the hitherto unknown 3'-deoxy-3'-fluoroguanosine (5). In this Communication we report the synthesis of (5) with concomitant formation of the corresponding 3'-*O*-methyl ribonucleoside (6), by reaction with (diethylamino)sulphur trifluoride (DAST) of the free 3'-hydroxy function of a xylofuranonucleoside (4), in which the 2'-position was protected with the acid-labile methoxytetrahydropyranyl (MTHP) group (Scheme 1).

The starting *N*²-acetyl-9-(3,5-di-*O*-benzoyl-β-D-xylofuranosyl)guanine (1) was readily prepared according to the literature⁵ and treated with 5,6-dihydro-4-methoxy-2*H*-pyran and trifluoroacetic acid (TFA) in dichloromethane to give the fully protected intermediate (2) in 87% yield. Deacylation with saturated methanolic ammonia gave (3) (77%), of which the exocyclic NH₂ and 5'-hydroxy functions were simultaneously tritylated on reacting with three equivalents of 4-monomethoxytrityl chloride (mMTrCl) in pyridine for 48 h to afford (4) (84%).

Fluorination of (4) was effected using DAST (2 equiv.) in dichloromethane in the presence of pyridine (2 equiv.) at room temp. Examination of the crude reaction mixture by t.l.c. showed several new spots but all attempted purifications at this stage failed. The crude reaction mixture was therefore directly treated with TFA in dichloromethane in order to remove MTHP and monomethoxytrityl (mMTr) protecting groups.

Careful h.p.l.c. studies revealed guanine as a major compound and essentially two other compounds (5) and (6), which were isolated by h.p.l.c. (Scheme 1). Additional purification of (5) was made first by preparative t.l.c., then by crystallization from water (m.p. 275–277 °C). Structural assignments for the compounds (5) (2%) and (6) (4%) were based on their physical properties.†

Although no attempts were made to optimize the yields,‡ the disappointing yield for (5) can in part be explained by a *trans*-elimination side reaction⁷ (with the favourably disposed H-4') and/or degradation during the last deprotection step to give, finally, guanine. Regarding the unexpected formation of the 3'-*O*-methyl ether of guanosine (6), a plausible explanation can lie in the participation of the methoxy group of MTHP on the intermediate generated by reaction of DAST with the 3'-OH function (Scheme 2). Similar participations of the vicinal MTHP group have not been previously reported.

The title compound (5) was shown to be specifically effective against Reovirus 1, Sindbis virus, Coxsackie virus

† Selected spectroscopic data: Compounds (2)–(6) were characterised by ¹H n.m.r., u.v., fast atom bombardment (f.a.b.) mass spectrometry and where appropriate, ¹⁹F n.m.r. For (5): ¹H n.m.r. ([²H₆]Me₂SO) δ (relative to [²H₅]Me₂SO set at 2.51 p.p.m.) 10.7 (1H, br. s, NH-1), 7.91 (1H, s, H-8), 6.5 (2H, br. s, NH₂), 5.86 (1H, d, OH-2'; *J* 6.4 Hz), 5.72 (1H, d, H-1'; *J* 8.1 Hz), 5.25 (1H, t, OH-5'; *J* 5.5 Hz), 5.01 (1H, dd, H-3'; *J* 54.7 and 4.2 Hz), 4.73 (1H, dm, H-2'; *J*_{2',F} 26 Hz), 4.19 (1H, dpt, H-4'; *J*_{4',F} 27.5 Hz), 3.58 (2H, pt, H-5',5''); ¹⁹F n.m.r. ([²H₆]Me₂SO) δ (relative to CFCl₃) –198.64 (pq, F-3'; *J*_{F,3'}} 54.2 Hz, *J*_{F,2'}} = *J*_{F,4'}} 27 Hz); *m/z* (f.a.b. >O) (glycerol) 286 (*M* + H) and 152 (BH₂). Compound (6) has been reported previously.⁶

‡ Apart from the reasons in the text, the low yield obtained for (5) [and (6)] is also linked with experimental difficulties during the purification. The retention time (in h.p.l.c.) and *R*_f values (in t.l.c.) of (5) and (6) are very close.

B4, and Semliki forest virus in Vero cell cultures. It was not active against HIV-1 in MT4 cell cultures.

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