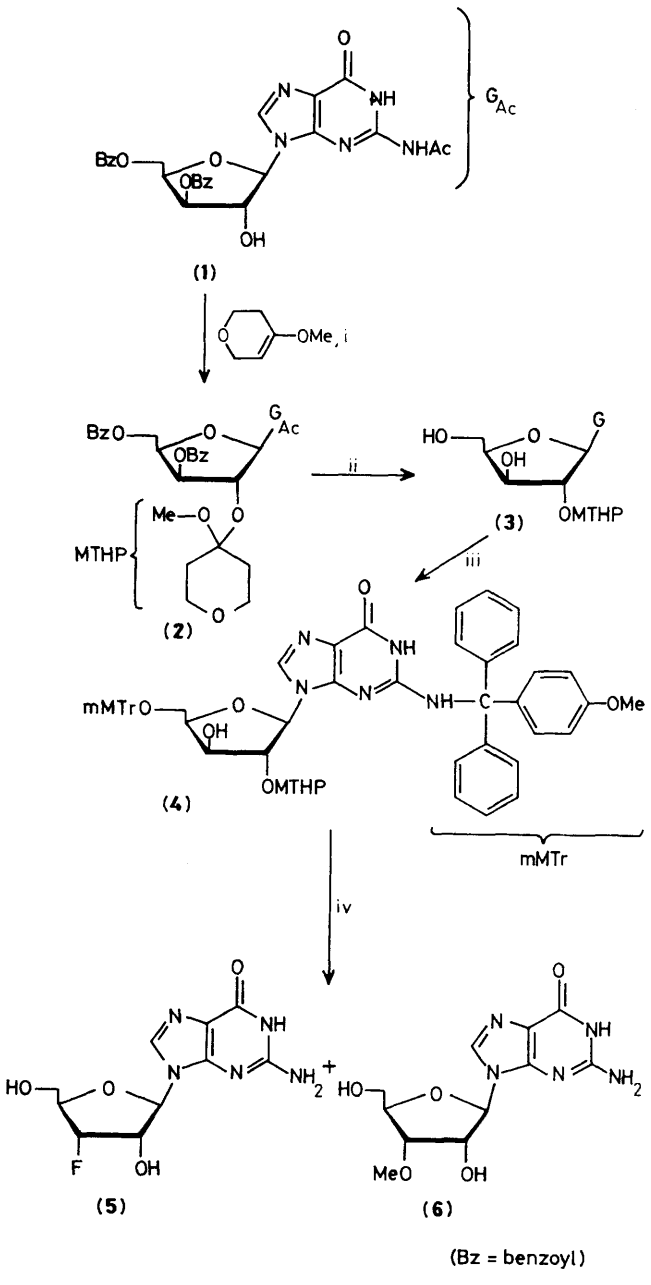
Synthesis of 9-(3-Deoxy-3-fluoro-β-D-ribofuranosyl)guanine, a New Potent Antiviral Agent

Frédéric Puech, Gilles Gosselin, and Jean-Louis Imbach*

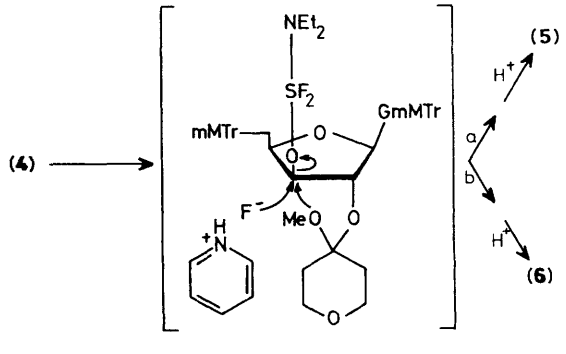
Université des Sciences et Techniques du Languedoc, Laboratoire de Chimie Bio-Organique, Case 008, UA nº 488 du C.N.R.S., Place E.-Bataillon, 34060 Montpellier Cédex 1, France

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-herpes[1] and anti-human immunodeficiency virus[2] (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, CH_2Cl_2; ii, NH_3, MeOH; iii, mMTrCl, pyridine; iv, DAST, pyridine, CH_2Cl_2, followed by 1% TFA, CH_2Cl_2.



Scheme 2. *Reagents and conditions*: Et_2N–SF_3, pyridine, CH_2Cl_2.

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 literature[5] 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 NH_2 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 reaction[7] (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 ^{1}H n.m.r., u.v., fast atom bombardment (f.a.b.) mass spectrometry and where appropriate, ^{19}F n.m.r. For (**5**): ^{1}H n.m.r. ([$^2H_6$]Me_2SO) δ (relative to [$^2H_5$]Me_2SO 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, NH_2), 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″); ^{19}F n.m.r. ([$^2H_6$]Me_2SO) δ (relative to $CFCl_3$) −198.64 (pq, F–3′; $J_{F,3'}$ 54.2 Hz, $J_{F,2'} \simeq J_{F,4'}$ 27 Hz); *m/z* (f.a.b. >O) (glycerol) 286 (*M* + H) and 152 (BH_2). 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.

The authors gratefully acknowledge financial support from CNRS and INSERM (PNR-SIDA) and Prof. E. De Clercq for the biological results.

Received, 11th February, 1989; Com. 9/00671K

References

1 J. J. Fox, K. A. Watanabe, T. C. Chou, R. F. Schinazi, K. F. Soike, I. Fourel, G. Hantz, and C. Trepo, in 'Fluorinated Carbohydrates, Chemical and Biochemical Aspects,' ed. N. F. Taylor, ACS Symp. Ser. 374, Washington, 1988, pp. 176—190.

2 (a) P. Herdewijn, J. Balzarini, M. Baba, R. Pauwels, A. Van Aerschot, G. Janssen, and E. De Clercq, *J. Med. Chem.*, 1988, **31**, 2040; (b) J. Balzarini, M. Baba, R. Pauwels, P. Herdewijn, and E. De Clercq, *Biochem. Pharmacol.*, 1988, **37**, 2847; (c) G. W. J. Fleet, J. C. Son, and A. E. Derome, *Tetrahedron*, 1988, **44**, 625; (d) E. Matthes, C. Lehmann, D. Scholz, H. A. Rosenthal, and P. Langen, *Biochem. Biophys. Res. Commun.*, 1988, **153**, 825; (e) P. Herdewijn, J. Balzarini, E. De Clercq, R. Pauwels, M. Baba, S. Broder, and H. Vanderhaeghe, *J. Med. Chem.*, 1987, **30**, 1270.

3 A. Van Aerschot, J. Balzarini, E. De Clercq, and P. Herdewijn, presented at the 8th International Round Table on 'Nucleosides, Nucleotides and Their Biological Applications,' 2—5 October, 1988, Orange Beach, Alabama, U.S.A. (To be published in *Nucleosides, Nucleotides*).

4 J. Balzarini, M. Baba, R. Pauwels, P. Herdewijn, S. G. Wood, M. J. Robins, and E. De Clercq, *Mol. Pharmacol.*, 1988, **33**, 243.

5 G. Gosselin, M-C. Bergogne, J. De Rudder, E. De Clercq, and J-L. Imbach, *J. Med. Chem.*, 1987, **30**, 982.

6 M. J. Robins, F. Hansske, and S. E. Bernier, *Can. J. Chem.*, 1981, **59**, 3360 and references cited therein.

7 T. J. Tewson and M. J. Welch, *J. Org. Chem.*, 1978, **43**, 1090.