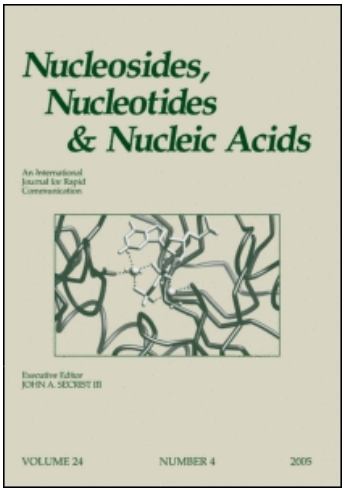

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The Synthesis of 2-Fluoropurine Nucleosides

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THE SYNTHESIS OF 2-FLUOROPURINE NUCLEOSIDES

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Abstract: 2-Aminoadenosine, obtained by silylation-amination from guanosine, is readily converted by KNO_2/ HF/Pyridine in up to 80% yield into 2-fluoradenosine, which is a convenient starting material for the preparation of 9(β-D-arabinofuranosyl)-2-fluoroadenine 5'-phosphate (Fludara). N^6,N^6-Pentamethylene-2-aminoadenosine and guanosine afford likewise the corresponding 2-fluoropurine nucleosides in high yields.

The potent antileukemia drug Fludarabine Phosphate (Fludara) **6**[1] has been synthesized by coupling of 2,6-dichloropurine **2** with 2,3,5-tri-O-benzyl-D-arabinosyl chloride **1** to 9-(2,3,5-tri-O-benzyl-β-D-arabinofuranosyl)-2,6-dichloropurine **3**, conversion to the protected 2,6-diaminopurine nucleoside **4** and finally Schiemann reaction to the corresponding 2-fluoro-6-amino derivative **5**. Reductive removal of the O-benzyl groups[2] and 5'-O-phosphorylation[1] gave finally Fludarabine Phosphate (Fludara) **6** (Scheme I). Since this route as well as later routes e. g. employing 2,6-diaminopurine[3][4] instead of **2** all involve high cost nucleoside coupling of purine-bases with the relatively expensive 2,3,5-tri-O-benzyl-D-arabinofuranosyl chloride, we investigated alternative routes.

Starting from the inexpensive guanosine **7**, silylation-amination[5][6] (Scheme II) can be readily performed on a 100-250 kg scale to give 2-aminoadenosine **8** in ca. 85-95% yield. Since the 2',3',5'-tri-O-acetate **9** of 2-aminoadenosine **8** had been converted by Robins et al.[7] in 85% yield into 2-fluoroadenosine-2',3',5'-tri-O-acetate **10** employing tert.-butyl nitrite / 60% HF-pyridine, we tried a variety of acylation conditions to transform **8** into **9**. But in accordance with Montgomery et al.[2] we invariably obtained mixtures of the corresponding tetra- and pentaacetates. Since the described routes of Montgomery[8][9] and Robins[10] to con-

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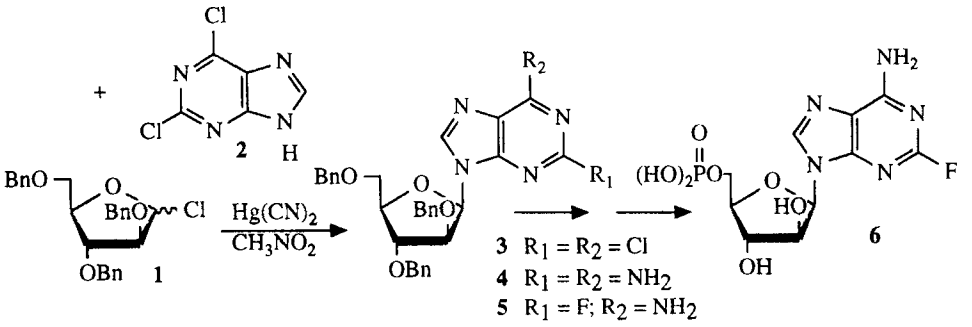
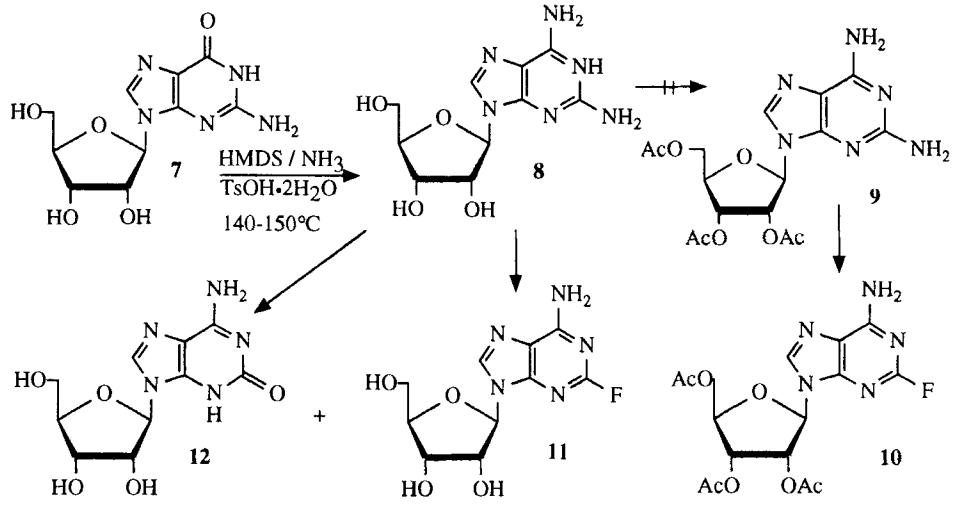
Dedicated to the memory of the late R. K. Robins.

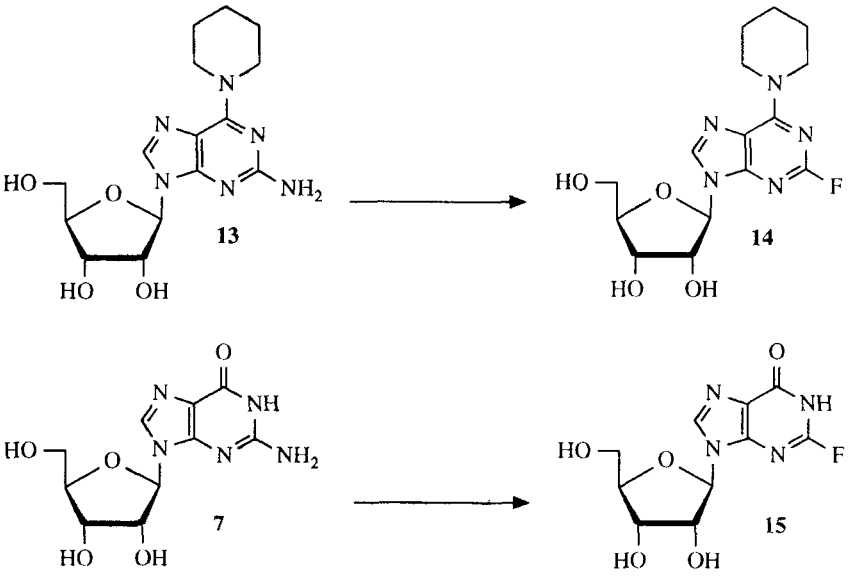


Scheme I



Scheme II

vert guanosine **6** via its corresponding 6-chloro- and 6-azido-2',3',5'-tri-O-acetyl-derivatives into **9** involved many steps, including some awkward and dangerous ones from a technical point of view, we wondered whether the O-acetyl-protecting groups in **9** were necessary for the Schiemann reaction. Although Montgomery et al.[8] had only obtained a 16% yield of 2-fluoroadenosine **11** on Schiemann reaction of 2-aminoadenosine in aqueous solution, we reacted unprotected 2-aminoadenosine **8** in 60% HF/pyridine with tert.-butyl nitrite and obtained after workup with an icecold suspension of $CaCO_3$ and filtration of the $CaF_2/CaCO_3$ slurry 2-fluoroadenosine **11** in ca. 80% yield besides traces of isoguanosine[11] **12** and unreacted 2-aminoadenosine **8**, which were readily removed on crystallization from ethanol/water.



Scheme **III**

To test the generality of this method, we converted also 2-amino-N^6,N^6-pentamethyleneadenosine **13**[5] as well as guanosine **7** into 2-fluoro-N^6,N^6-pentamethylene-adenosine **14** and 2-fluoroinosine **15** in ca. 70-80% yield. On attempted recrystallization from ethanol-H_2O, 2-fluoroinosine **15** was partially saponified to xanthosine so that no analytical sample of **15** could as yet be obtained. 2-fluoroinosine **15** has previously been prepared by Schiemann reaction of the O^6-benzyl derivative of guanosine in aqueous solution followed by hydrogenation of the O^6-benzyl group in ca. 19% overall yield[12] (Scheme **III**).

Since tert.-butyl nitrite turned out to be a potential explosive[13], we subsequently replaced tert.-butyl nitrite by a concentrated aqueous solution of potassium nitrite without any decrease in yield of 2-fluoroadenosine **11**. The use of solid sodium or potassium nitrite is also feasable but the addition of solid salts is, however, more difficult to control and leads to increased foaming.

We anticipate that heterocyclic amino groups in other types of unprotected nucleosides can likewise be converted into the corresponding fluoronucleosides without cleavage of the nucleoside bond.

The further conversion of 2-fluoroadenosine **11** e. g. via its corresponding crystalline[14] 3',5'-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-derivative[15-20] followed by inversion of the 2'-hydroxy group[21-24], desilylation and 5'-phosphorylation into Fludarabine-phosphate (Fludara) **6** is straightforward and is therefore not dealt with here.

EXPERIMENTAL

^{1}H-NMR spectra were recorded on a Bruker WH 300 instrument. Thin layer (TLC) and column-chromatography were carried out on silica plates (E. Merck) and silica gel No. 10757 E. Merck, containing 40% H_2O using the systems: A: upper phase of n-butanol-acetic acid - H_2O = 4:1:5, System B: upper phase of ethyl-acetate-2-methoxyethanol-H_2O = 4:1:2, System C: ethanol-25% NH_3.

2-Fluoroadenosine **11**

To a stirred solution of 15 g (53,14 mmol) 2-aminoadenosine **8** in 50 ml 56% HF/pyridine, which was cooled from +14°C to -11°C, a concentrated solution of 4.9 g KNO_2 (57.6 mmol) in 3 ml H_2O was added dropwise at -11°→ -6°C within 1h, whereupon gas evolution was observed. After continued stirring for 1h at -6°→ -8°C the solution became turbid and TLC (system A) showed that practically all of the 2-aminoadenosine **8** had reacted. After a further hour at +3°C, the reaction mixture was poured on a stirred ice cold slurry of 100 g of powdered $CaCO_3$ in 200 ml H_2O, containing ca. 0.5 ml n-butanol to suppress any excess foaming. After 3h at +6°C and 16h at +24°C, the slightly basic solution (P_H = 7.5-8) was filtered, the $CaF_2/CaCO_3$ cake washed with 120 ml H_2O and 150 ml ethanol - H_2O (1:1) and the combined filtrates concentrated at 45°C/35-40 mbar, whereupon a voluminous yellowish precipitate of 2-fluoroadenosine **11** formed on standing overnight. After filtration, washing with 50 ml H_2O followed by 50 ml 95% ethanol and finally by 30 ml methyl-tert.-butyl ether, the pink precipitate was dried at 60°C in vacuo to give a first crop of 7.98 g of **11**. On concentration of the combined mother liquors three further crops of 1.7 g, 1.7 g and 0.8 g of **11** were obtained (combined yield = 12.18 g = 80.3%), which were homogeneous on TLC (System A, R_f = 0.63). TLC of the mother liquor (System A) demonstrated the presence of minor amounts of the starting material 2-aminoadenosine **8** and isoguanosine **12** besides 2-fluoroadenosine **4** as the major spot. The 2-fluoroadenosine **11** gave on recrystallization from ethanol-H_2O with added charcoal a gel-like product, which solidified on washing with ethanol followed by methyl-tert.-butyl ether to give the analytical sample of **11**. ^{1}H-NMR (DMSO-D_6) δ: 3.50-3.70 (m, 2H, H-5') 3.93 (m, 1 H, H-4'), 4.13 (m, 1H, H-3'), 4.52 (m, 1H, H-2'), 5.78 (d, J = 6 Hz, H-1'), 8.34 (s, 1H, H-8) Anal. calcd for $C_{10}H_{12}N_5O_4F$ (285.25) C, 42.11; H, 4.24; N, 24.55; F, 6.66. Found: C, 41.94; H 4.38; N 24.35; F, 6.77

2-Fluoro-N^6,N^6-pentamethyleneadenosine **14**

To a solution of 0.7 g (2mmol) of finely powdered 2-amino-N^6,N^6-pentamethyleneadenosine **13** in 7 ml 50% HF/pyridine was added 0.412 g (2 mmol) tert-butyl nitrite at -25°C within 5 min with stirring. After 30 min at -25° the reaction mixture was poured on an ice cold and stirred suspension of 25 g $CaCO_3$. After filtering and washing the powdered CaF_2/CO_3 cake with ethanol-water, evaporation of the filtrate in vacuo gave 0.89 g crude product. This material dissolved in 20 ml methanol and evaporated with 15 g silica gel (40%

H_2O). The resulting mixture was placed on top of a column containing additional 15 g silica gel (40% H_2O) that was then eluted with the upper phase of System B: ethyl acetate-2-methoxyethanol-H_2O = 4:1:2 to give after a 25 ml forerun with the subsequent 125 ml 0.64 g (90%) of yellowish, crystalline 2-fluoro-N^6,N^6-pentamethyleneadenosine **14**, which was recrystallized from ethyl acetate to afford the analytical sample, mp 164°C. ^{1}H-NMR (DMSO-D_6) δ: 1.52-1.75 (m, 6H, $(CH_2)_3$), 3.91-3.98 (m, 1H, H-4'), 4.10-4.18 (m, 1H, H-3'), 4.45-4.52 (m, 1H, H-2'), 5.82 (d, J = 6 Hz, 1H, H-1'), 8.38 (s, 1H, H-8). Anal. calcd for $C_{15}H_{20}N_5O_4F$ (353.37) C 50.99; H 5.7; N 19.82; F 5.38. Found: C 50.79; H 5.85; N 19.67; F 5.30

2-Fluoroinosine **15**

1.41 g (5 mmol) guanosine-dihydrate **7** were dissolved in 20 ml 50% HF/pyridine, treated at -25°C with 1.108 g (5 mmol) tert.-butyl nitrite, kept for an additional 60 min at -30°C and worked up with ice cold $CaCO_3$. After washing the $CaF_2/CaCO_3$ cake with 150 ml H_2O and evaporating the filtrate in vacuo, the residue (0,9 g), which sometimes crystallizes spontaneously from ethanol-H_2O, was dissolved in 10 ml H_2O and evaporated with 10 g silica gel (40% H_2O). The resulting mixture was placed on top of a column containing additional 20 g silica gel (40% H_2O) that was then eluted with the upper phase of TLC system A n-butanol-acetic acid - H_2O = 4:1:5 the first 50 ml gave rise to impurities. Further elution with 50 ml afforded 0.46 g (80,4%) of **15**, which was homogenous on TLC (System A, R_f=0.37) after washing with 96% ethanol. After dissolving the substance in ca 4-5 ml H_2O pure 2-fluoroinosine **15** crystallized out, mp 250°C (dec.), and TLC (System C) of the mother liquor indicated besides 2-fluoroinosine (R_f=0.42) the presence of xanthosine (R_f=0.26). ^{1}H-NMR (DMSO-D_6) δ: 3.91-3.98 (br, H-4'), 4.1-4.21(br, H-3'), 4.48-4,6 (br, H-2'), 5.76-5.85 (br, H-1'), 8.15-8.45 (br, H-8); ^{19}F-NMR (DMSO-D_6) δ: 110.5 ppm (br) (C_6F_6 as internal standard = 0 ppm); UV (H_2O) λ_{max} 253 nm (11.900)

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REFERENCES

1) *Drugs of the Future* (1993) **18**, 80 and *ibid.* (1991) **16**, 78
2) Montgomery, J.A.; Hewson, K.; *J. Med. Chem.* (1969) **12**, 498
3) Montgomery, J.A.; Clayton, S.D.; Shortnacy, A.T.; in: *Nucleic Acid Chemistry III* (1986) 156; edited by L. B. Townsend and R. S. Tipson, John Wiley/New York
4) Markovac, A.; LaMontagne, M.P.; Eur. Pat. Appl. EP 461.407, *Chem. Abstr.* (1992) **116**, 194798,
5) Vorbrüggen, H.; Krolikiewicz, K.; *Liebigs Ann. Chem.* (1976) 745
6) Robins, M.J.; Hansske, F.; Bernier, S.E.; *Can. J. Chem.* (1981) **59**, 3360

7) Robins, M.J.; Uznański, B.; *Can. J. Chem.* (1981) **59**, 2608
8) Montgomery, J.A.; Hewson, K.; *J. Amer. Chem. Soc.* (1960) **82**, 463
9) Montgomery, J.A.; Hewson, K.; *J. Org. Chem.* (1968) **33**, 432
10) Robins, M.J.; Uznański, B.; *Can. J. Chem.* (1981) **59**, 2601
11) Davoll, J.; *J. Amer. Chem. Soc.* (1951) **73**, 3174
12) Gerster, J.F.; Robins, R.K.; *J. Amer. Chem. Soc.* (1965) **87**, 3752; *J. Org. Chem.* (1966) **31**, 3258
13) Lopez, F.; *Chem. Eng. News* (1992), Dec. 21, 2
14) 2-Fluoroadenosine **11** was reacted with TIPS-Cl in pyridine to give after evaporation and filtration of the crude product in CH_2Cl_2 over a short column of SiO_2 the crystalline TIPS-derivative of **11** in 80% yield, mp 210°C (from methanol).
15) Markiewicz, W.T.; *J. Chem. Res.* (1979), (S) 24
16) Fukukawa, K.; Uedao, T.; Hirano, T.; *Chem. Pharm. Bull.* (1983) **31** (5), 1582
17) Biggadike, K. Borthwick. A.D.; Evans, D.; Exall, A.M.; Kirk, B.E.; Roberts, S.M.; Stephenson, L.; Youds, P.; Slawin, A.M.Z.; Williams, D.J.; *J. Chem. Soc., Chem. Comm.* (1987) 251
18) Marriott, J.H.; Mottahedeh, M.; Reese, C.B.; *Carbohyd. Res.* (1991) **216**, 257
19) Matsuda, A.; Takenuki, K.; Tanaka, M.; Sasaki, T.; Ueda, T.; *J. Med. Chem.* (1991) **34**, 812
20) Robins, M.J.; Hawrelak. S.D.; Hernández, A.E.; Wnuk, S.F.; *Nucleosides & Nucleotides* (1992) **11**, 821
21) Fukukawa, K; Ueda, T.; Hirano, T.; *Chem. Pharm. Bull.* (1981) **29**, 597
22) Samano, V.; Robins, M.J.; *J. Org. Chem.* (1990) **55**, 5186
23) Lubineau, A.; Bienaymé, H.; *Carbohyd. Res.* (1991) **212**, 267
24) Binkley, R.W.; *J. Org. Chem.* (1991) **56**, 3892

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