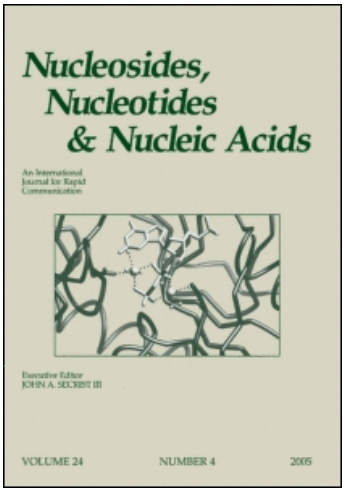

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Synthesis of Nucleosides Fluorinated in the Sugar Moiety. The Application of Diethylaminosulfur Trifluoride to the Synthesis of Fluorinated Nucleosides

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SYNTHESIS OF NUCLEOSIDES FLUORINATED IN THE SUGAR MOIETY. THE APPLICATION OF DIETHYLAMINOSULFUR TRIFLUORIDE TO THE SYNTHESIS OF FLUORINATED NUCLEOSIDES

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ABSTRACT. A survey is given of the different methods that have been used for the synthesis of nucleosides fluorinated in the carbohydrate moiety. In this article we describe the use of diethylaminosulfur trifluoride (DAST) as a fluorinating agent in the nucleoside field.

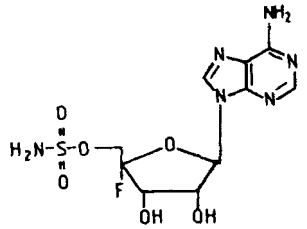
The introduction of a fluorine substituent in organic compounds has frequently led to a dramatic change in their biological activity. This is perhaps most clearly shown in the field of the anti-inflammatory steroids where inclusion of a fluorine atom, at either the 6α- or 9α-position, generally leads to a marked increase in their potency. A more recent example is the interesting development in the field of the antibacterial quinolones derived from nalidixic acid. The introduction of a fluorine atom in the 6-position has potentiated the antimicrobial activity and has broadened their antibacterial spectrum. A well known example in the carbohydrate field is 2-deoxy-2-[^{18}F]-D-fluoroglucose which is used for the study of the glucose metabolism and also as a diagnostic agent.

The interest of medicinal chemists in the construction of fluorine containing drugs is derived from the relative stability of the carbon-fluorine bond, both chemically and metabolically, and from the strong electronegative character of fluorine, which alter the electronic properties of a molecule. In most examples, fluorine has taken the place of a hydrogen atom. Fluorine and hydrogen have indeed similar Van der Waals radii, but they strongly differ in electronegative character. Physicochemically speaking, there are much more similarities between a fluoro group and an hydroxyl group; for example in their bond lengths to carbon and in the dipole moments of these bonds. In solution, the conformation of a fluorine compound often resembles that of the parent hydroxyl compound ra-

ther than that of the hydrogen analogue: for example 2'-fluoro-2'-deoxyribonucleosides[1a] and 2'-fluoro-2'-deoxyarabinonucleosides[1b]. In these examples, the conformation is strongly related to the electrostatic interactions between the fluorine substituent and the vicinal hydroxyl group[2]. These results are not always in conformity with crystallographic data. To explain these crystallographic data, it has been suggested that an alternative conformation can be stabilized by an intramolecular hydrogen bond (3'-OH...F)[3]. On the other hand, a fluoro group can only be a proton acceptor, while a hydroxyl group can function both as an acceptor and as a donor in the formation of hydrogen bonds. Therefore it seems very difficult to predict the molecule's biological behaviour when a C-H or a C-OH group has been displaced by a C-F group.

There is only a very small number of naturally occurring organic fluorine compounds, an example of which is "nucleocidin", 1, an antibiotic, isolated from Streptomyces clavus[4]. The compound's structure, 4'-fluoro-5'-O-sulfamoyladenosine, was elucidated in 1969[5] and its synthesis was described in 1971[6] and 1976[7].

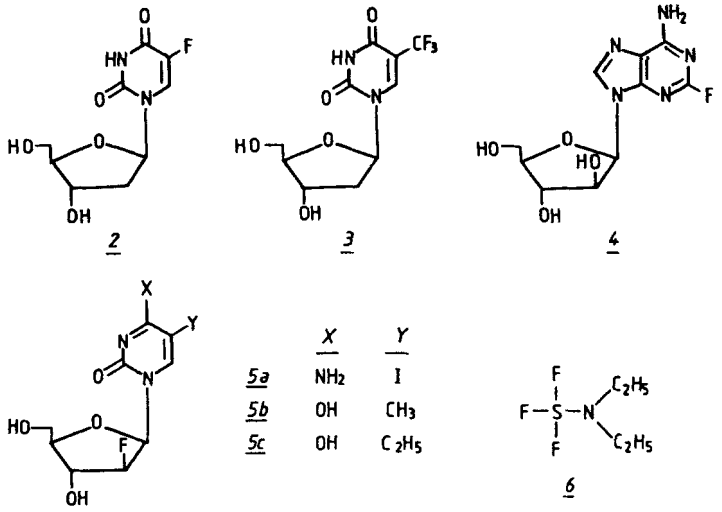
Still, the fluorinated nucleosides from synthetic origin are far more important. 5-Fluoro-2'-deoxyuridine, 2, (as 5-fluorouracil) is a widely used antitumor compound, which is either used single or in combination therapy for the treatment of different metastatic cancers. Trifluorothymidine, 3, is one of the oldest antiviral compounds, used in topical treatment of herpetic eye infections (acute keratitis). The introduction of a fluorine substituent in the 2-position of 9-β-D-arabinofuranosyladenine



1

enhances its stability towards enzymatic deamination. This compound, 9-β-D-arabinofuranosyl-2-fluoroadenine, 4[8], shows good activity against experimental animal cancers[9]. The 2'-fluoro-2'-deoxy-β-D-arabinofuranosylpyrimidine compounds 5a and 5b were found to be very active against the herpes

simplex virus type I and type II infections with very low cytotoxicity[10]. More recently, the 5-ethyl analogue 5c was described as a promising new antiherpes agent[11,12].



CHEMISTRY

Due to solvation, the fluoride ion is a relatively poor nucleophile in protic solvents. In polar aprotic solvents, however, only cations are strongly solvated and the nucleophilicity of the fluoride ion is significantly enhanced. Extremely nucleophilic fluoride ions have been obtained by the use of crown-ethers and of fluoride loaded exchange resins. Despite this, the synthesis of fluorinated nucleosides is still a difficult task. A frequently encountered problem is the fluoride ion catalysed elimination reaction. Frequently vigorous reaction conditions are required and even then, the yields of the desired compounds are low. In this article we'll give a literature survey of the nucleosides fluorinated in the sugar moiety, and we'll describe the use of diethylaminosulfur trifluoride (DAST), 6, for the synthesis of some selected compounds. This allows the preparation of these compounds in good yield, under very mild conditions and with normal glassware.

Three basic methods were used to synthesize nucleosides fluorinated in the sugar moiety :

- epoxide cleavage by fluoride ions,
- displacement of a sulfonyloxy group by fluoride ions,

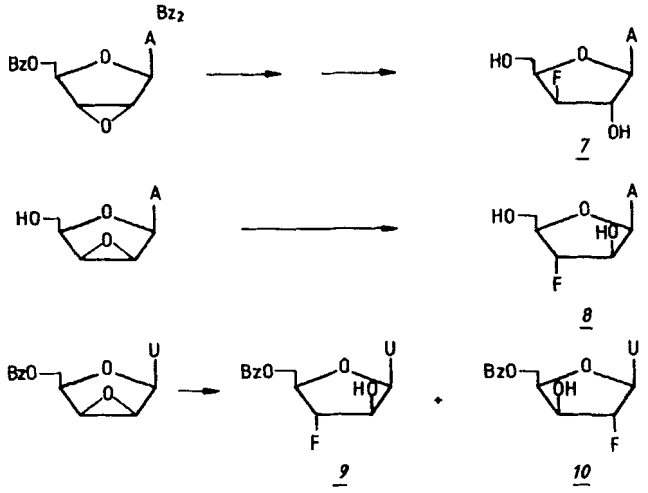
- opening of the anhydro bond formed by the sugar and the base part. The latter reaction is restricted to pyrimidine- and some related nucleosides.

All these reactions occur with inversion of configuration.

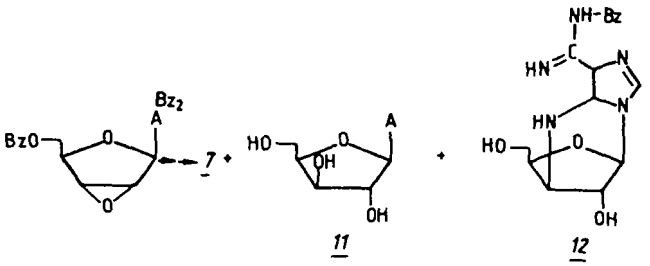
A. Nucleophilic oxirane ring opening with fluoride ion

Fluoride ring opening of oxiranes has been used for the synthesis of 9-(3-fluoro-3-deoxy-β-D-xylofuranosyl)adenine[13] (7) ($Et_4N^+F^-$ in acetonitrile, 63 %) and of 9-(3-deoxy-3-fluoro-β-D-arabinofuranosyl)adenine[14] (8) (KHF_2 in ethylene glycol, 41 %). In the case of 7 and 8, regiospecificity was reported and no other isomers were mentioned. Nevertheless, when 1-(5-O-benzoyl-2,3-epoxy-β-D-lyxofuranosyl)uracil was treated with 10 % HF in dioxane[15], the two isomers 9 (25 %) and 10 (11 %) were isolated, together with uracil and 1-β-D-xylofuranosyluracil.

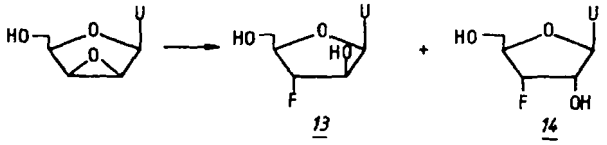
These methods are subject to several drawbacks related to the vigorous reaction conditions which are needed for the ring opening. With KHF_2[14] or HF[15], decomposition occurred and respectively adenine or uracil were formed. The method with tetraethylammonium fluoride[13] suffers from the disadvantage of the strictly anhydrous conditions required for the reaction. The problems associated with the drying of tetraalkylammonium fluoride and the stability of this reagent under the conditions mentioned were studied by Sharma et al.[16] When we repeated the synthesis of 7 following the literature procedure, the fluorinated nucleoside was isolated in a 40 % yield. The two other compounds, isolated after debenzoylation with methanol saturated with ammonia, are 9-β-D-xylofuranosyladenine, 11, and 5-amino-1-(3-deoxy-β-D-xylofuranosyl)imidazole-4-(N-benzoyl)carboxamide-$N^5 \rightarrow 3'$-cyclonucleoside, 12.



Bz = benzoyl



The formation of 11 was also reported in the original manuscript and results from traces of moisture which are introduced into the reaction mixture. The N-benzoyl group of the cyclonucleoside 12, which is formed via an attack of N^3 on the epoxide followed by ring opening[13], is stable against mild debenzoylation conditions (MeOH, NH_3). A rather strange re-

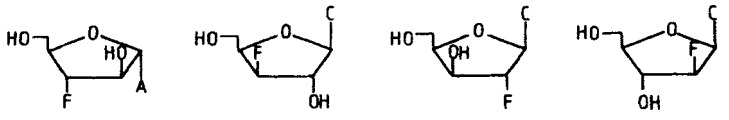


sult was obtained by ring opening of the epoxide, 1-(2,3-epoxy-β-D-lyxofuranosyl)uracil, with liquid hydrogen fluoride (10 %) in dioxane[17]. Together with the expected 3'-fluoro-3'-deoxyarabinouridine, 13 (13 %) and uracil, 3'-fluoro-3'-deoxyuridine, 14, (11 %) was obtained.

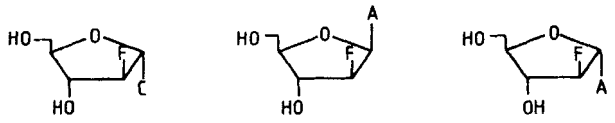
The latter was formed from 13 during the reaction. The authors didn't speculate on a possible reaction mechanism. Epoxide opening of the same product in analogous reaction conditions[18] gave 13 in 3 % yield together with two other unidentified products containing fluorine. This demonstrated that in such vigorous reaction conditions it is very difficult to obtain reproduceable results.

The ring opening of epoxides (KHF_2 in ethylene glycol) on carbohydrates has also been used by Wright et al. in their total synthesis of 7 and 15[19,20], in their synthesis of the cytidine analogues 16, 17, 18 and 19[19-23] and for the synthesis of the 2'-fluoro analogues of 9-(β-D-arabinofuranosyl)adenine, 20, and the α-analogue 21[23]. Normally, the opening of epoxides is very easy with HF in the presence of an organic base, such as

tetrahydrofuran or dioxan. This is to be attributed to the increased dissociation of the hydrofluoric acid[24] and its most important application



15 16 17 18



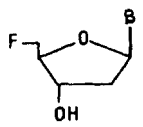
19 20 21

can be found in the steroid field. Potassium hydrogen fluoride, however, gave better results on carbohydrates[20]. Besides, high HF-concentrations are incompatible with the acid sensitive glycosidic bond of nucleosides.

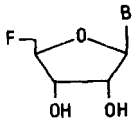
B. Nucleophilic displacement of sulfonates by fluoride ion

This reaction has been used most often for the introduction of a fluorine atom in the 5'-position of different nucleosides because the displacement of primary sulfonates in a reaction with fluorine is more easily achieved than the same reaction on a secondary carbon. The reaction was carried out on, either mesylates, or tosylates with potassium fluoride in ethylene glycol (or methanol) (130-150°C) or with tetrabutylammonium fluoride in dimethylformamide at 50°C. Yields then range from 15 % to 92 %. The reaction with hydrofluoric acid in dioxane, however, was reported to give better yields[25]. Scheme I gives a clear view of the compounds synthesized by this method. Some of the ribo-analogues were opened between the 2'- and 3'-position by treatment with $NaIO_4$ in water[40].

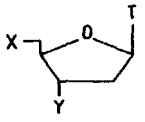
To introduce fluorine on a secondary carbon atom, a more reactive leaving group is preferred. The use of triflate as leaving group has allowed a good yield-preparation of fluorine containing nucleosides and this under very mild conditions ($Bu_4N^+F^-$, THF, 0°C). A lot of publications have dealt with the synthesis of 2'-deoxy-2'-fluoroadenosine, 22a[41-46]. The tetrahydrofuranyl group[42] proved to be more suitable than the tetrahydropyranyl group for protection of the 3'- and 5'-hydroxyl group because it is more readily removed. 2'-Deoxy-2'-fluoroguanosine, 22b, has been synthesized in the same manner ($Bu_4N^+F^-$, THF, R.T.) from 2-N-isobutyryl-3',5'-di-O-tetrahydrofuranyl-9-ß-D-arabinofuranosylguanine in a 40 % yield.[47] Ni-



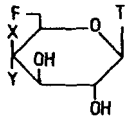
T (27) (28) (33)
(35) (36) (38)
C (27)
U (27) (36)
A (27)
5 - fluoro U (27)



different bases (39)
C (30)
U (30) (37)
5 - fluoro U (26)



X = F ; Y = F (32)
X = F ; Y = N_3 (31)
X = F ; Y = H (29)

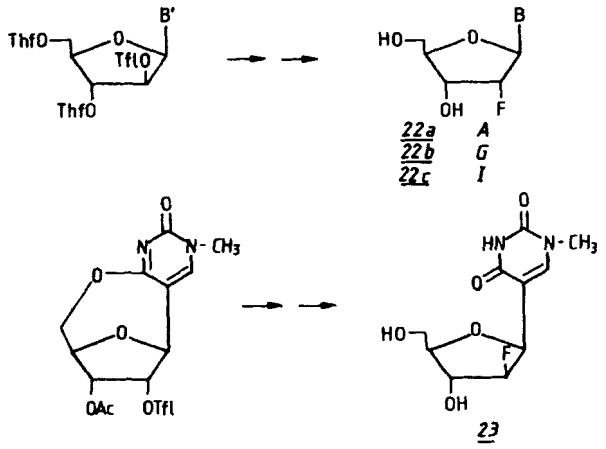


X = OH ; Y = H (34)
X = H ; Y = OH (34)

SCHEME I

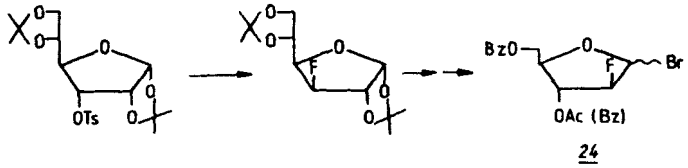
trite deamination of 22a resulted in 2'-deoxy-2'-fluoroinosine 22c.[48,49] A useful alternative, which has only recently found its application in the nucleoside field[50], is the use of tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)[51] on trifluoromethanesulfonyl derivatives. The reaction has been reported on C-nucleosides, 23[50]. Still, the reaction on a N-nucleoside[50] was unsuccessful. The difficulties encountered with a direct introduction of the fluorine atom in the 2'-"up" position of N-nucleosides could be caused by the unfavorable interaction between the approaching nucleophile and the anomeric substituents. Another factor might be the bond length of the C-N bond which is shorter than that of the C-C bond.

The displacement of primary and secondary sulfonates has also been used for the preparation of fluorocarbohydrates which function as starting material for the synthesis of nucleosides by a sugar-base condensation reaction. The most relevant example is the synthesis of the 2-deoxy-2-fluoro-D-arabinofuranose derivative 24[52]. This compound has been used for the preparation of many analogues of FIAC 5a. The synthesis described is suitable for large scale preparations. The reason for this total synthesis lies in the facile neighbouring group participation reaction of the C-2



Thf = tetrahydrofuranyl; Ac = acetyl; Tfl = triflate

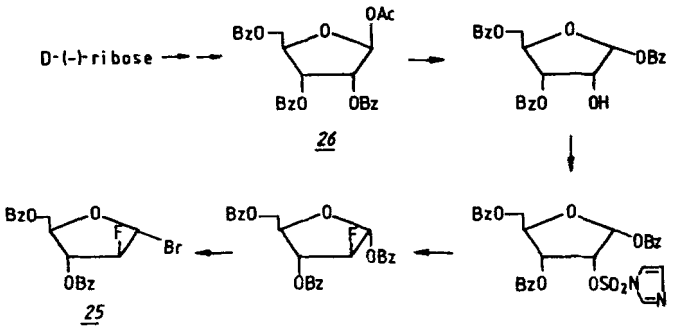
carbonyl group with a leaving group in the 2'-position, which prevents direct introduction of a fluoro group in the 2'"up" position. The key step in this reaction sequence is the direct displacement of a secondary sulfonyloxy group by a fluorine atom with potassium fluoride in acetamide in a 65 % yield. The reaction sequence leading to 24 proceeds with an overall yield of 25 %.



3-O-acetyl-5-O-benzoyl-2-deoxy-2-fluoro-D-arabinofuranosylbromide 24, was condensed with several trimethylsilylated bases. Deprotection with ammonia in methanol provided the β-nucleosides in good yield[11,12,21,52-64]. Other analogues were made by modification of the base[59-70] or the sugar moiety[71] after condensation.

An alternative procedure for the synthesis of the same sugar (25) was published by Tann et al.[72,73] They started with 1,3,5-tri-O-benzoyl-α-D-ribofuranose (26)[74], used imidazolylsulfonates[75] as leaving group and suggested a sulphonylfluoride (SO_2F) as reactive intermediate. We compared the two methods. The method of the Bristol-Myers group was indeed more

straightforward than the lengthy procedure carried out by Reichman et al.[52] The Sloan-Kettering procedure could be reproduced exactly as described in the described yields. When we used the method of P.R. Brodfuehrer[74] and C.H. Tann[72], we didn't follow the fluorination with KHF_2 by HPLC but after 1 hour, 52 % cyrstalline material was obtained (literature 63 %).

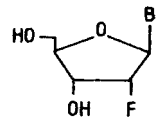


C. Nucleophilic attack on anhydro bonds

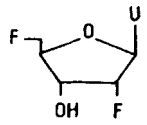
This is the most widely used method for the introduction of a fluorine atom into the carbohydrate moiety of nucleosides. The method is restricted to pyrimidine nucleosides. Elimination as a side reaction is most pertinent in the deoxy series. A kaleidoscope of examples exists for the introduction of fluorine in the 2'- and the 3'-position.

a) Introduction of fluorine in the 2'-position by opening of the O^2,2'-bond

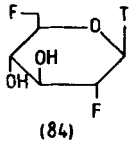
Attack of fluoride ion occurs on the sugar carbon atom. Normally about 10 % HF in dioxane, at an elevated temperature, was used[76-81]. A yield optimization study has been carried out for the work with [18]F[82]. Yields ranging from 10 to 50 % dependent on reaction time and reaction temperature were obtained. In some cases AlF_3 was used as a catalyst[30,84]. The use of potassium fluoride in the presence of crown ethers[85] appeared to be the best method for the synthesis of the cytosine analogue. Simple heating of O^2,2'-anhydro-1-β-D-arabinofuranosylcytosine hydrofluoride in dimethylformamide[86] gave lower yields. Scheme II gives an overall view of the nucleosides synthesized by this method.



T (76)
C (83) (85) (86)
U (76-82) (87)
5 - fluoro U (76)

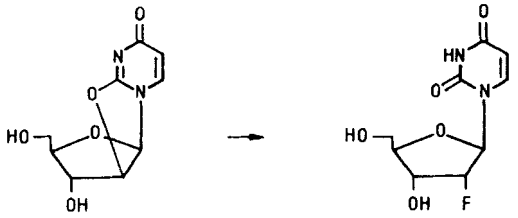


(30)



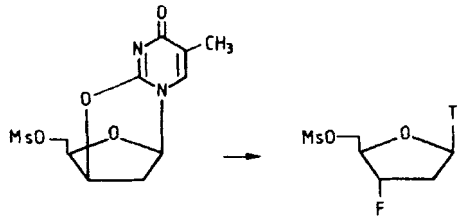
(84)

SCHEME II

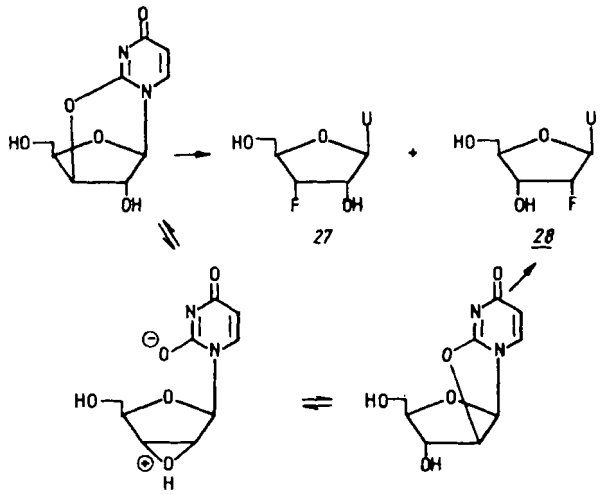


b) Opening of the O^3,3'-bond of cyclonucleosides

This reaction was used for the synthesis of 2',3'-dideoxynucleosides. Only two other examples exist. Reaction of O^2,3'-anhydro-1-β-D-xylofuranosyluracil with 1 % HF in dioxane in the presence of AlF_3 afforded two fluorine containing nucleosides[87]: 27 (31 %) and 28 (47 %). The formation of the latter has been explained through a rearrangement of the starting material to the thermodynamically more stable O^2,2'-anhydronucleoside (Scheme III). In the other example[17], 2'-O-tritylation apparently prevents this rearrangement and 3'-fluoro-3'-deoxyuridine was obtained in good yield (66 %). This compound is the only example of a 3'-fluoro-3'-deoxy-β-D-ribofuranose-nucleoside described in literature.

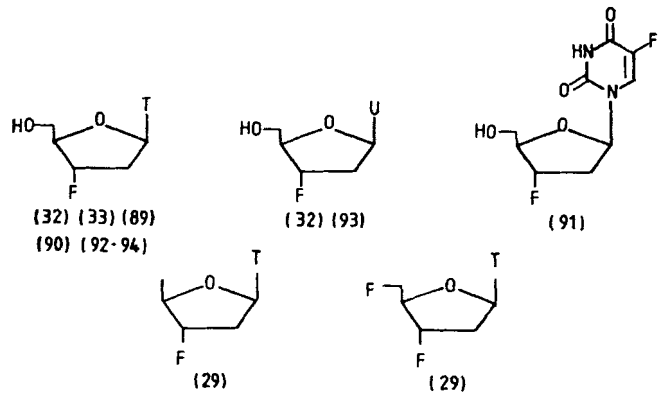


29 30

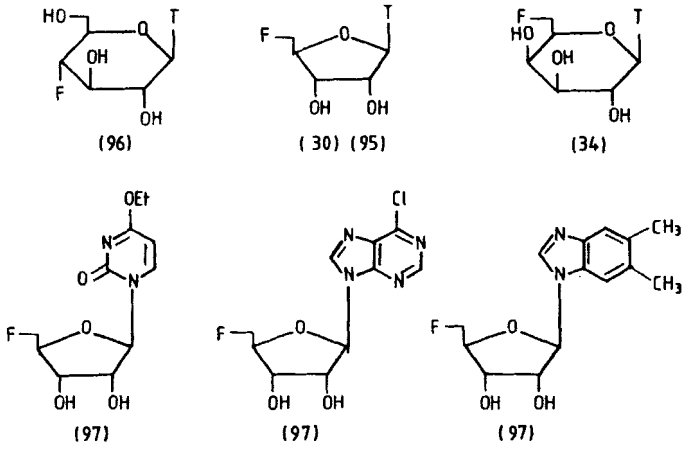


SCHEME III

As mentioned before, the group of P. Langen concentrated on the 2'-deoxypyrimidine nucleosides. The introduction of a fluorine atom in the 3'-position was carried out successfully (30 % yield) with HF in dimethylformamide or in dioxan on the 5'-O-mesylate, 29[88]. The mesylate group of 30 can be easily removed because of the possibility that an intermediate O^2,5'-anhydro bond forms. The use of 5'-O-tritylated or 5'-O-unprotected O^2,3'-anhydro compounds give lower yields of the 3'-fluoro analogue[88,89]. The same authors introduced the use of an electrophilic catalyst, such as AlF_3, for the opening of the anhydro bond. In these circumstances, the concentration of the needed HF could be lowered. Also HF excesses could be reduced (e.g. 0.1 % HF, AlF_3, dioxane or DMF, 150-200°C)[29,32,33,90-94]. The 5'-O-mesylated-3'-fluorothymidine, 30, was obtained in 66 % yield[30,94]. The 5'-O-mesylate group could be removed by heating with potassium acetate in acetic anhydride[94]. This reaction may also be carried out without the 5'-O-mesylate group[29,33,90,91]. Nevertheless, the AlF_3's solubility in dioxane is very low and its exact function is not very clear. Another alternative is the application of KHF_2 or NH_4F in diethylene glycol[33,89,90] onto O^2,3'-anhydro-1-(2-deoxy-β-D-threo-pentofuranosyl)thymine and 3'-O-mesyl-2'-deoxythymidine. The products synthesized by these methods are summarized in Scheme IV. The reaction also works on pyranoses[84].



SCHEME IV



SCHEME V

c) Opening of the O^2,5'-bond of cyclonucleosides

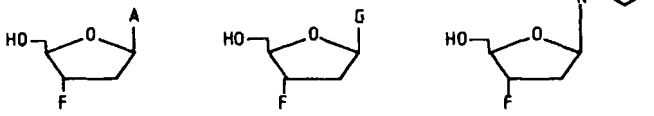
These anhydronucleosides can function as reactive intermediates during the synthesis of 5'-fluoropyrimidines. They were rarely used as starting material for the synthesis of such compounds.[37,95]

D. Miscellaneous methods

A lot of fluorinated nucleosides have been synthesized by condensation of fluorinated carbohydrates with purine or pyrimidine bases. Most of these fluorocarbohydrates have been synthesized by one of the methods described herebefore. A discussion of their synthesis is beyond the scope of this short review. Of the non-mentioned products, only a tabular review is given (Scheme V).

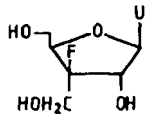
Further modifications of the known fluorinated nucleosides, either in the base, or in the sugar part have led to compounds depicted in Scheme VI. The 4-thio analogues were synthesized as intermediates in the conversion of an uracil base into a cytosine base. The inosine analogues were obtained by enzymatic deaminase of the adenine counterpart. The base modified 2'-fluoro-2'-deoxyarabinonucleosides are not mentioned. Many of them are described in patent literature as for instance under ref. 56 and 59. Some compounds (31 and 32) were constructed by a gradual build up of the base part, starting from the appropriate sugar (Scheme VII).

Because the formation and opening of anhydro bonds is impossible for naturally occuring purine nucleosides, the 3'-fluoro-2',3'-dideoxynucleosides with adenine, 33[110a], guanine, 34[110b], or benzimidazole, 35[111], as base part have been synthesized by transglycosylation of a fluorinated pyrimidine nucleoside with the silylated purine base.



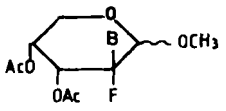
33 34 35

Only one example exists of a branched chain fluoronucleoside: 1-(3-deoxy-3-fluoro-3-C-hydroxymethyl-β-D-xylofuranosyl)uracil, 36. It was synthesized by a sugar-base condensation reaction[112].



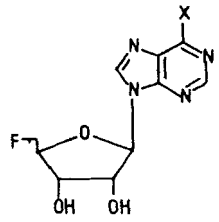
36

Bobek et al. synthesized several 2'-fluorinated pyrimidine isonucleosides, 37, by means of a nucleophilic displacement on gem-difluoro-carbohydrates[113,114].

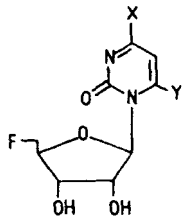


37

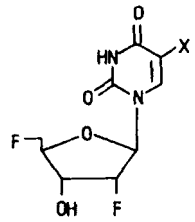
B: uracil, thymine, 5-fluorouracil, cytosine



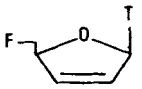
X = H, SH, NH_2 (97)
X = OH (103)



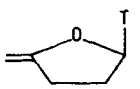
X = OH ; Y = H (97)
X = NH_2; Y = H (30)(97)
X = OH ; Y = CN, COOH (106)



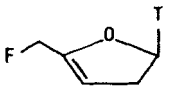
X = H, I (30)



(98)



(32)



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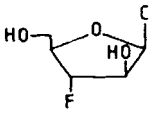

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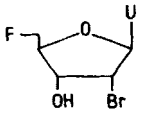
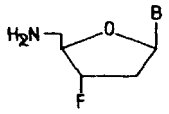
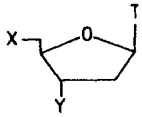


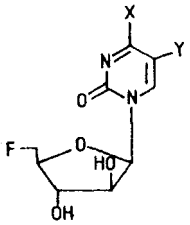
(30)



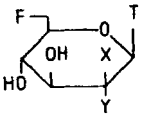
U,C,T (108)



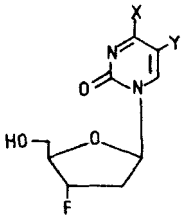
X = F ; Y = Cl (29)
X = I ; Y = F (32)



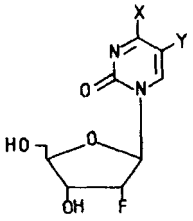
X = OH, NH_2 ; Y = H (30)
X = OH; Y = Br (30)



X = H ; Y = Br, I, Cl, F, H, (84
X = OH ; Y = H (84)

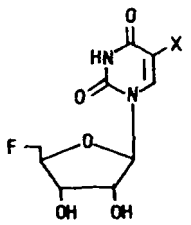


X = SH, SMe ; Y = H (32)
X = OH ; Y = F (101)
X = NH_2 ; Y = H (32)



X = SH, SMe ; Y = H (99)
X = NH_2; Y = I (61)
X = OH ; Y = F, Cl, Br, I, SCN (107)
X = NH_2; Y = H (1a) (99)

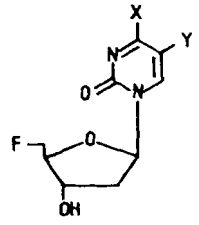
SCHEME VI



X = Br, I (30)

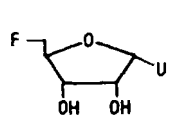
X = Br, OH, NH_2, NHMe, NHBu, NHBn, morpholino, piperidino, pyrrolo (37)

X = CH=O; CH_2OH; CH_2OMe, CH_2OBu, CH_2OAllyl, $CH_2\beta$ (104)
X = perfluoroalkyl (102)

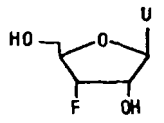


X = SH, NH_2; Y = H, Me, F (105)
X = OH; Y = H (30) (100) (102)
X = OH; Y = I (27)
X = OH; Y = Br (100)
X = OH; Y = Perfluoroalkyl (102)

SCHEME VI (continued)



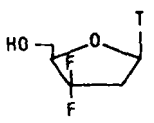
31 (109)



32 (87)

SCHEME VII

Recently, publications have mentioned two examples where nucleosides were substituted by a gem-difluoro group. 2',3'-Dideoxy-3',3'-difluorothymidine, *38*,[115] has been synthesized from the 3'-keto derivative with diethylaminosulfur trifluoride. Different 2',2'-difluoro-2'-deoxynucleosides *39* were synthesized by the Eli Lilly Research group[116] and by Merrell Dow Pharmaceuticals[117]. Both started with the appropriate base and with ethyl 2-bromo-2,2-difluoroacetate. The 5-halogeno-, 5-halogenovinylpyrimidines[116] and different purine analogues[117] are also mentioned.



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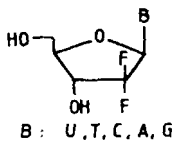
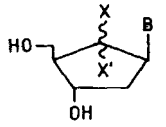


B: U, T, C, A, G

39

The synthesis of nucleocidine, 1,[6,7] was accomplished via an addition reaction of iodine fluoride (AgF, I_2) on the 4',5'-unsaturated nucleoside. Some other 4'-C-fluoronucleosides, as for example the uracil[118,119] and the thymine[119] analogue of nucleocidine, and the 5'-amino- and 5'-deoxy-analogue of 4'-C-fluoroadenosine[119], have been described by the same group. AgF in pyridine has also been used for the introduction of a fluorine atom in the 5'-position of uridine with iodine as leaving group[89]. The O^2,5'-anhydro compound was suggested as reactive intermediate.

Finally, several 4-fluorinated carbocyclic nucleosides were described in a Syntex patent[121].



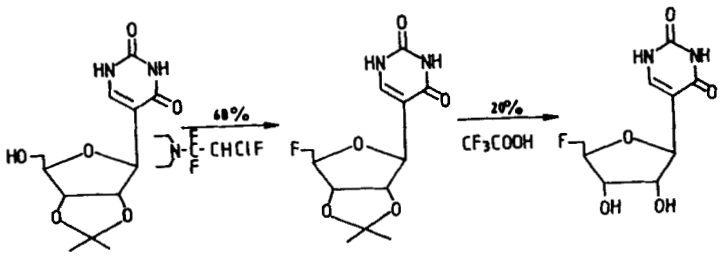
X ; H, F ; X': F

E. Reaction of a free hydroxyl group with diethylaminosulfur trifluoride

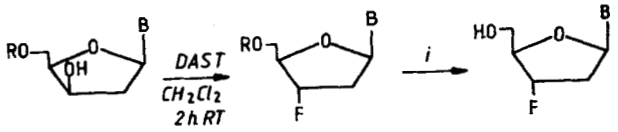
Dialkylaminosulfur trifluoride, 6,[122,123] shows the same chemical characteristics as sulfur(IV)fluoride. Markovskij and Middleton introduced it in organic chemistry for the synthesis of, among others, gem-difluoroalkanes[124] and acid fluorides[124,125]. The reagent has been successfully applied for the replacement of a hydroxyl group by a fluorine atom[126] and for the replacement of an anomeric hydroxyl group in the preparation of glycosyl fluorides[127,128]. It also reacts easily with tertiary alcohols (for example ref. 126,129,130). DAST has been extensively used for the introduction of fluorine into carbohydrates[131].

The reaction with DAST affords products resulting from Walden inversion. Nevertheless, there are a few examples in which the reaction proceeds with retention of configuration. An elimination reaction was not often encountered, although problems still exist when trans-elimination can easily take place[132]. DAST offers the advantage that it can be used for direct displacement of a hydroxyl group by fluorine. Very mild conditions suffice for the alcohol-fluoride conversion with DAST. Moreover, DAST can be used on acid sensitive substances and the reaction can be carried out with normal laboratory glass equipment. This direct introduction of a fluorine starting with an alcohol has been done in the past with several other reagents, for example: 2-chloro-1,1,2-trifluorotriethylamine[133] and diphenyltrifluorophosphorane and analogues[134]. In spite of

this, only the first reagent has been used for the synthesis of a fluorinated nucleoside, namely the 5'-fluoro derivative of pseudouridine[135a]. The reaction on thymidine with the same reagent but in different circumstances gave the O^2,3'-anhydro compound[135b].



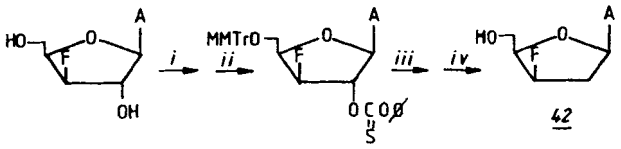
The synthesis of 3'-fluoro-2',3'-dideoxynucleosides resorts under P. Langen et al.'s work. Their synthesis is restricted to pyrimidine nucleosides[32,33,88-94]. The purine analogues were obtained by a trans-glycosylation procedure[110,111]. In order to find a more generally applicable method, we tested the reaction of diethylaminosulfur trifluoride on 5-O-protected-2-deoxy-1-β-D-threo-pentofuranosyl-nucleosides. The reactions with pyrimidine nucleosides are summarized in Scheme VIII. Except for the use of distilled dichloromethane, dried on $CaCl_2$, no special precautions were taken and apart from the uridine analogue, syntheses are described in a previous paper[136]. No attempts were made to optimize the described yields. The synthesis of 3'-fluoro-2',3'-dideoxyuridine is analogous to the one described for the thymidine derivative. Dichloromethane can be used as solvent for all the nucleosides



B: thymin-1-yl; uracil-1-yl; 5-ethyluracil-1-yl; cytosin-1-yl; adenin-9-yl; N-trityl-2,6-diaminopurin-9-yl; guanin-9-yl

i) when R = trityl: 80 % HOAc, 100°C; when R = monomethoxytrityl 2 % p-toluenesulfonic acid, RT, $CHCl_3$-MeOH (4:1)

SCHEME VIII



i) monomethoxytrityl chloride pyridine; ii) phenoxythiocarbonyl chloride, DMAP, CH_3CN; iii) AIBN, tributyltin hydride, toluene; iv), p-toluenesulfonyl chloride, $CHCl_3$, MeOH.

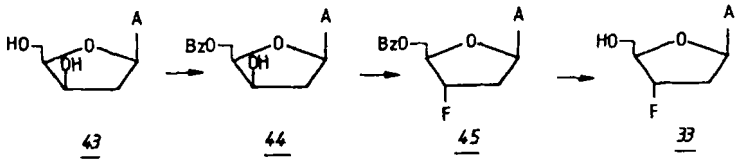
SCHEME IX

The same reaction was also carried out on different purines. The reactions with adenine[137] and guanine[138] as base were described earlier. It is noteworthy to say that the protection of an amino group of adenine or cytosine with a benzoyl group gives complex reaction mixtures. In all cases, only some traces of elimination products were detected. The synthesis of 9-(2-fluoro-2,3-dideoxy-β-D-erythro-pentofuranosyl)adenine, 40, and 9-(2'-fluoro-2',3'-dideoxy-β-D-threo-pentofuranosyl)adenine, 41, was also described[137]. The purification of the latter was arduous and the yield was low (10 %). Fox et al.'s[52] method is still the method to be chosen when greater amounts of a compound with the 2'-up configuration are needed.

40 41

A partical problem is the synthesis of the adenosine analogue with a fluoro group in the 3'-"up" configuration 42. This product could not be obtained by reaction of DAST with 5'-O-protected-2'-deoxyadenosine because of the attack of nitrogen in position-3 on the activated C-3'. This problem was resolved as shown in Scheme IX[137]. The starting material for this synthesis, 9-(3-fluoro-3-deoxy-β-D-xylofuranosyl)adenine, 7, can be obtained with DAST (see further).

The compounds 40 and 41 were also described by Marquez et al.[139] For the synthesis of 40, they used the nucleophilic substitution of a triflate with tetra-n-butylammonium fluoride. For the synthesis of 41, an analogous reaction sequence was used as in that of Scheme IX.

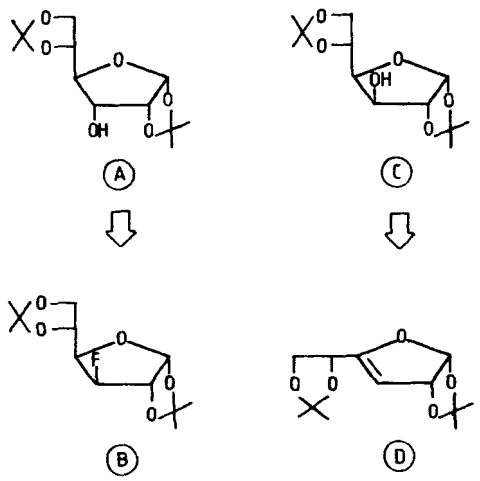


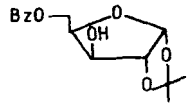
43 44 45 33

SCHEME X

In all previous cases, the trityl- or monomethoxytrityl group was used for the 5'-protection, the reason therefore lies in the selective introduction of this protecting group at a primary hydroxyl group. In case of a monomethoxytrityl group, some detritylation was always taking place during the reaction. Therefore, we suggest the 5'-O-benzoyl group as a useful alternative (Scheme X). Also the yields are better with this protecting group. Monobenzoylation of 9-(2-deoxy-β-D-threo-pentofuranosyl)-adenine, 43, with 1 equivalent of benzoyl chloride (added dropwise in pyridine at 0°C), afforded the 5'-O-benzoylated derivative 44 in an 80 % yield. This compound was treated with 3 equivalents of DAST in dichloromethane for 1.30 h. After the normal work-up procedure and the chromatographic purification, the 3'-fluoro compuond 45 was obtained in an 80 % yield. Debenzoylation with ammonia in methanol gave 9-(3-fluoro-2,3-dideoxy-β-D-erythro-pentofuranosyl)adenine, 33, in a 91 % yield.

The most observed side reaction during the introduction of a fluorine atom by a nucleophilic substitution reaction is the fluoride catalyzed elimination reaction. The extent to which this side reaction occurs is determined by the stereochemical configuration of the substrate. A very interesting example is the fluorination of 1,2:5,6-di-O-isopropylidene-α-D-allofuranose (A). The reaction with DAST[132] yields the product from the nucleophilic displacement (B). The same results are obtained with other fluorinating reagents (Amberlyst A26/F^-)[140], Bu_4NF[141], TASF[142]) after 3-O-activation. The fluoride attack occurs from the exo-side of the bicyclo-[3.3.0]octane ring system. In the opposite situation, 3'-O-activated 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (C) is strongly resistent to the nucleophiles' attack. Elimination with the favorably disposed C-4 hydrogen is the predominant reaction (D) (DAST[132], Bu_4NF[141], TASF[142]). The same results were obtained on the 5-O-benzoylated (or tritylated) derivative 46 (with DAST on the alcohol, with Bu_4NF or CsF on the 3-O-triflate or 3-O-tosylate)[143]. So, each sugar exhibits a unique reactivity pattern.

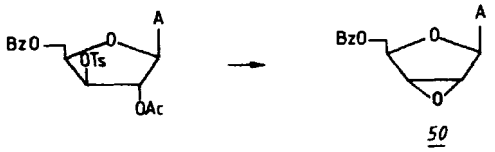




46

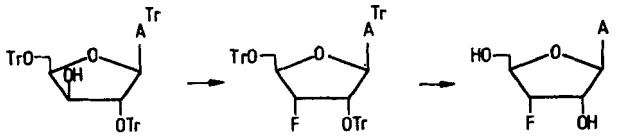
It is well known that changes in the conformation of the ribose ring upon protection may alter the course of the reaction. Therefore the reaction with DAST was tested on tritylated 9-β-D-xylofuranosyladenine, 47. This reaction yielded the expected 3'-fluoro compound 48 well (78 %) (Scheme XI). The yield of the deprotection step was rather disappointing (46 %).

The importance of the use of a non-participating protecting group in 2'-position may be illustrated by the reaction of 9-(5-O-benzoyl-3-O-tosyl-2-O-acetyl-β-D-xylofuranosyl)adenine with tetra-butylammonium fluoride in a mixture of tetrahydrofuran-acetonitrile which gave the epoxide 50 in a 63 % yield[143].



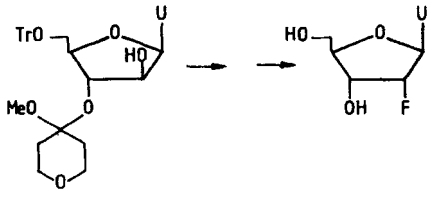
50

The synthesis of fluorinated nucleosides with this reagent is also applicable to other nucleosides as illustrated by the preparation of 2'-deoxy-2'-fluorouridine (Scheme XII). The product was found to be identical



47 48 49

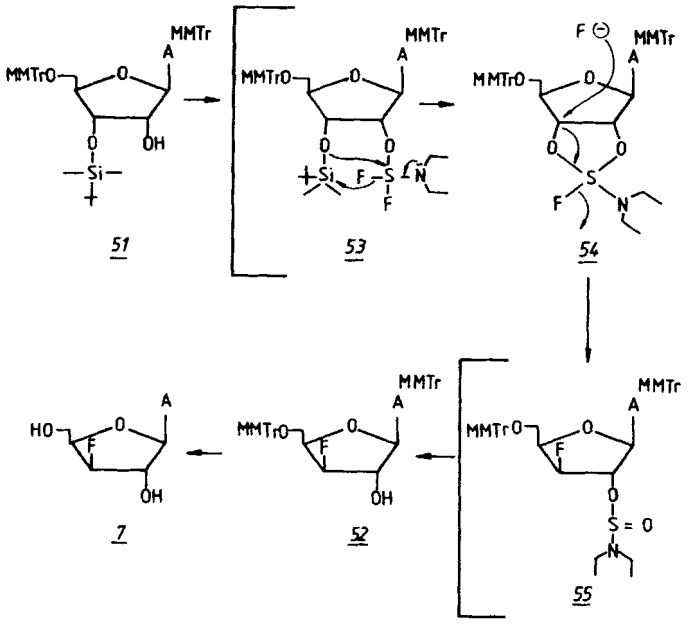
SCHEME XI



SCHEME XII

with that described by Cushley et al.[18] The choice of the 3'-O-protecting groups was arbitrary.

A rather strange observation was made when 6-N,5'-O-di(monomethoxytrityl)-3'-O-tert-butyldimethylsilyl-adenosine, 51, obtained as side compound in our synthesis of the 2'-O-silyl derivative[137], was treated with DAST (5 h, RT, CH_2Cl_2). The reaction mixture was fairly complex, but only one fluorinated compound, 52, was isolated (30 % yield). This product was detritylated. The non-introduction of a fluorine substituent in 2'-position follows from the coupling constants in the ^1H NMR- and ^{13}C NMR spectrum. The isolated compound has the same mp, UV, ^1H NMR spectrum, ^{13}C NMR spectrum and Rf in TLC as 9-(3-fluoro-3-deoxy-β-D-xylofuranosyl)adenine. An analogous observation was made by S. Roberts with adenosine protected on 3' and 5' with the tetraisopropyldisiloxane group[144]. The theoretical possibility that DAST first cleaves the silylether moiety and only thereafter converts di(monomethoxytrityl)adenosine into 7, was ruled out by the observation that the reaction did not give the same results when starting from 6-N,5'-O-ditrityladenosine. The following reaction mechanism is proposed (Scheme XIII). Due to its very electrophilic nature, diethylaminosulfur trifluoride first reacts with the hindered 2'-OH group. It thus generates the intermediate 53. Removal of the silyl protecting group with an

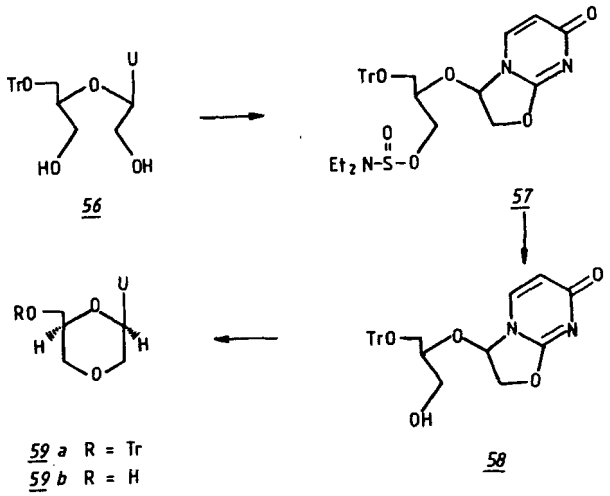


SCHEME XIII

concomitant attack of the alkoxyde, generated from this fluoride induced desilylation, on sulphur gives a cyclic intermediate, 54, which gives rise to the 3'-fluoro-2'-sulfinate, 55, after attack of fluoride ion on the less hindered 3'-position. This intermediate is unstable and is hydrolyzed during work-up by attack on sulphur.

Previously, the opening of cyclic sulfates with fluoride ion by attack on carbon was described by Tewson et al.[145,146]. Nevertheless, the same reaction with cyclic sulfites was very slow and the yields were rather low[145].

The existence of a labile sulfinate as intermediate and the importance of the use of properly protected nucleosides for the introduction of a fluorine group can be illustrated by some reactions done on 2',3'-secouridine. Reaction of 5'-O-trityl-2',3'-secouridine, 56, with DAST at low temperature and interrupting the reaction so as to enable the isolation of the intermediate, produced only one spot in TLC. After a flash chromatography, however, a second compound appeared with a lower Rf on TLC. Both products were isolated and it was shown that the most apolar compound could be easily converted in the most polar compound, for example, by



SCHEME XIV

stirring in MeOH in the presence of silica. The unstable product was identified as 57, and the other compound as 58 (Scheme XIV). These products are the result of a neighbouring group participation reaction of the C-2 carbonyl groups on C-2'. When we tried to introduce a fluorine atom in the 2'-position with potassium fluoride and crown ether in monoglyme or dimethylformamide, in the presence of p-toluenesulfonic acid, the reaction mixture contained two products. The first was the starting material, the second 59a, resulted from a neighbouring group attack of the free HO-group on C-2'. Without p-toluenesulfonic acid, no such ring closure occurred. The product was further identified after detritylation to 59b.

When we compare the ^{1}H NMR and ^{13}C NMR spectra in DMSO-d_6 of the fluorinated β-adenosine analogues we can conclude as follows :

- When the 2'-fluorine atom is situated in the 2'"up" position, a long range coupling is found between the H-8 and fluorine in the ^{1}H NMR spectrum and between C-8 and fluorine in the ^{13}C NMR spectrum.
- When the fluorine atom is situated in the 3'"up" position, only the signal for C-8 is split into a doublet. No H-8,F coupling was found.
- With a fluorine atom in the 2'- or 3'"down" position, neither of the two occurred.

EXPERIMENTAL PART

Melting points were determined in capillary tubes with a Büchi-Tottoli apparatus and are uncorrected. Ultraviolet spectra were recorded with

a Beckman UV 5230 spectrophotometer. Mass spectra were determined with an AEI MS-12 apparatus. The ^{1}H NMR and ^{13}C NMR spectra were determined by means of a JEOL FX 90Q spectrometer with tetramethylsilane as internal standard (s = singlet, d = doublet, t = triplet, br = broad signal). Precoated Merck silica gel F254 plates were used for TLC, and the spots were examined with UV light and a sulphuric acid-anisaldehyde spray. Column chromatography was performed on Merck silica gel (0.063-0.200 mm). Anhydrous solvents were obtained as follows: pyridine was refluxed overnight in p-toluenesulfonyl chloride, distilled, refluxed overnight in potassium hydroxide, and distilled again; dichloromethane was stored for 1 week on anhydrous calcium chloride, filtered, and distilled.

3'-Fluoro-2',3'-dideoxyuridine

This product was described formerly[32], although with little physical constants. It was synthesized in the same way as described for the thymidine analogue[136], except that dichloromethane was used as solvent.

mp 183-184°C.

UV (MeOH) λ_{max} : 260 nm (ϵ 10,100).

MS (m/e) 230 (M^+).

^{1}H NMR (DMSO-d_6) δ : 2.00-2.63 (m, H-2', H-2"); 3.68 (m, H-5', H-5"); 4.17 (dt, $J_{4',F}$ = 27Hz, H-4'); 5.30 (m, $J_{3',F}$ = 54.5Hz, H-3'); 5.67 (m, 5'-OH, H-5); 6.20 (dd, J = 6.2Hz and 8.4Hz, H-1'); 7.84 (d, J = 7.9Hz, H-6); 11.3 (brs, NH).

^{13}C NMR (pyridine-d_5) : 38.8 (d, J = 20.9Hz, C-2'); 61.8 (d, J = 11.0Hz, C-5'); 85.6 (s, C-1'); 86.2 (d, J = 24Hz, C-4'); 95.6 (d, J = 175.9Hz, C-3'); 102.9 (s, C-5); 140.3 (s, C-6); 151.6 (C-2); 164.1 (C-4).

9-(3'-Fluoro-2',3'-dideoxy-β-D-erythro-pentofuranosyl)-2,6-diaminopurine

A solution of 1.5 g (2 mmol) of 9-(2-deoxy-5-O-trityl-β-D-threo-pentofuranosyl)-N-trityl-2,6-diaminopurine in 50 ml of anhydrous CH_2Cl_2 was treated with 1 ml of DAST for 75 min at room temperature. The mixture was poured in 40 ml of 10 % sodium bicarbonate. The organic layer was separated, dried, evaporated and purified by column chromatography to yield 1.17 g (78 %) of the 3'-fluoro compound.

^{1}H NMR ($CDCl_3$) δ : 1.91-2.80 (m, H-2', H-2"); 3.22 (m, H-5', H-5"); 4.21 (m, $J_{4',F}$ = 24Hz, H-4'); 4.93 (m, H-3', one part hidden by the NH_2 signal at 5.25 ppm); 5.72 (m, H-1'); 6.12 (NH); 6.87-7.64 (m, trityl).

The product was further identified after detritylation. Therefore, 1 mmol (0.75 g) was dissolved in 80 % acetic acid and heated for 25 min at 80°C. The mixture was evaporated, coevaporated with toluene and purified by co-

lumn chromatography ($CHCl_3$-MeOH, 95:5), thus yielding 145 mg (54 %) of the title compound which was crystallized from MeOH.

mp 192-193°C.

MS (m/e) 268 (M^+).

UV (H_2O) λ_{max} : 280 nm (ε 10,400), 256 nm (ε 9,700);
(0.1 N HCl) λ_{max} : 290 nm (ε 10,400), 252 nm (ε 12,000).

^1H NMR (CD_3OD) δ : 2.47-2.85 and 3.00-3.36 (m, 2x1H, H-2' and H2"); 3.82 (m, 2H, H-5' and H-5"); 4.35 (dt, 1H, $J_{4',F}$ = 27.5Hz, H-4'); 5.40 (dd, 1H, $J_{3',F}$ = 54.7Hz, H-3'); 6.30 (ddd, 1H, J = 5.9Hz, 9.2Hz and 0.6Hz, H-1'); 7.96 (s, NH, slowly exchangeable); 7.94 (d, J = 0.6Hz, H-8) ppm.

^{13}C NMR (CD_3OD) 39.0 (d, J = 20.75Hz, C-2'); 63.5 (d, J = 12.2Hz, C-5'); 87.3 (s, C-1'); 88.05 (d, J = 22.0Hz, C-4'); 96.50 (d, J = 175.8Hz, C-3'); 138.8 (s, C-8).

3'-Fluoro-3'-deoxyadenosine, 49

A mixture of 2 mmol of β-D-xylofuranosyladenine and 12 mmol of triphenylmethylchloride in anhydrous pyridine (30 ml) was heated for 2.5 days at 80°C. After cooling to room temperature and adding MeOH, we concentrated the mixture to 10 ml and then poured it into H_2O and extracted with $CHCl_3$. The organic layer was dried, evaporated and purified by column chromatography : 1) $CHCl_3$, 2) $CHCl_3$-MeOH (99:1). The product 47 crystallized from MeOH (1 mmol, 50 %, 1 g).

mp 240°C.

UV ($CHCl_3$) λ_{max} : 275 nm (ε 23,400).

^1H NMR ($CDCl_3$) δ : 3.50 (m, H-5', H-5"); 3.96 (dd, H-3'); 4.29 (m, H-4'); 4.57 (d, H-2'). The presence of three trityl groups was confirmed by integration of the multiplet at δ 7.30 and compared with the integration of the doublet at δ 5.45 (H-1'); 7.76 (s, purine H).

A solution of 1 mmol (993 mg) of this compound in anhydrous CH_2Cl_2 (50 ml) was treated with DAST (0.3 ml, 2 mmol) for 4 h at room temperature. The reaction mixture was poured into 50 ml of 10 % sodium bicarbonate, the organic layer was dried and evaporated. Column chromatographic purification ($CHCl_3$) yielded 720 mg (72 %) of tritylated 3'-fluoro-3'-deoxyadenosine, 48.

^1H NMR ($CDCl_3$) δ : 3.04 (m, H-5'); 3.30 (m, H-5" and one half of H-3'); 3.90 (brd, one half of H-3'); 4.23 (dt, $J_{4',F}$ = 27Hz, H-4'); 5.12 (ddd, $J_{2',F}$ = 21.5Hz, J = 3.7 and 7.5Hz, H-2'); 6.25 (d, J = 7.5Hz, H-1'); 7.32 (m, trityl); 7.82 and 7.86 (2xs, H-2 and H-8).

In comparison with the normal position of the H-3' proton, the H-3' proton

is situated at a much higher field. This suggests the situation of this proton in the shielding zone of an aromatic protecting group. An explanation by a close proximity of H-3' to the N-3 lone pair of electrons can be excluded because the same phenomenon was also observed for the thymine analogue (data not shown).

^{13}C NMR ($CDCl_3$) : 62.8 (d, J = 11.0Hz, C-5'); 74.5 (d, J = 15.9 Hz, C-2'); 82.5 (J = 23.2 Hz, C-4'); 86.7 (s, C-1'); 90.5 (d, J = 185Hz, C-3').

This compound (0.720 mmol, 716 mg) was diluted with 20 ml of 80 % acetic acid and stirred overnight at room temperature and 30 min at 100°C. We then evaporated the mixture, coevaporated it with toluene and purified it by column chromatography : 1) $CHCl_3$-MeOH (99:1), 2) $CHCl_3$-MeOH (90:10). The title compound 49 crystallized from MeOH : 70 mg (0.26 mmol, 46 %).

mp 164°C (dec).

UV (MeOH) λ_{max} : 259 nm (ε 15,070).

MS (m/e) 260 (M^+).

^1H NMR (DMSO-d_6) δ : 3.68 (m, H-5', H-5"); 4.32 (dt, $J_{4',F}$ = 27.2Hz, H-4'); 4.95 (ddd, J = 4.2 and 7.5Hz, $J_{2',F}$ = 25.0Hz, H-2'); 5.10 (dd, J = 4.2Hz, $J_{3',F}$ = 54.0Hz, H-3'); 5.95 (d, J = 7.5Hz , H-1'); 7.38 (brs, NH_2); 8.16 and 8.36 (2xs, H-8 and H-2).

^{13}C NMR (DMSO-d_6) : 61.2 (d, J = 11.0Hz, C-5'); 72.2 (d, J = 15.9Hz, C-2'); 84.1 (d, J = 22Hz, C-4'); 87.1 (s, C-1'); 93.2 (d, J = 181.9Hz, C-3'); 119.5 (s, C-5); 140.3 (s, C-8); 149.3 (s, C-4); 152.6 (s, C-2); 156.2 (s, C-6).

Elem. Anal. calculated C : 44.61 H : 4.49 N : 26.01
found C : 44.72 H : 4.64 N : 26.22.

5'-O-Trityl-O^2,2'-anhydro-2',3'-secouridine, 58

5'-O-Trityl-2',3'-secouridine (3 mmol, 1.46 g) was dissolved in 15 ml of CH_2Cl_2, cooled to -70°C, and 0.73 ml (6 mmol) of DAST was added. The reaction mixture was warmed up to -20°C over a period of 40 min, and poured into 5 % sodium bicarbonate solution, cooled in ice. The organic layer was separated, washed with water and dried. TLC revealed only one spot. After flash chromatography ($CHCl_3$-MeOH, 96:4) on silica gel, a second compound appeared with lower Rf. Both products were isolated in a total yield of approximately 60 %.

a) 5'-O-Trityl-3'-O-diethylaminosulfinyl-O^2,2'-anhydro-2',3'-secouridine, 57

MS (m/e) no molecular ion could be detected, high rel. intensity was found at 470 (M^+ - $SONEt_2$ + H) and 120 ($SONEt_2$).

^{1}H NMR ($CDCl_3$) δ : 1.08 (t, J = 7.1Hz, 2xCH_3); 3.12 (Q, $\underline{CH_2}CH_3$) and 3.16 (Q, $\underline{CH_2}CH_3$); 32.6 (m, H-5', H-5"); 3.52-4.24 (AB part from ABX spectrum, H-3', partially overlapped with H-4'); 4.63 (AB part of ABX spectrum, H-2', $J_{2',2"}$ = 10.4Hz, $J_{1',2'}$ = 2.6Hz, $J_{1',2"}$ = 5.7Hz); 5.75 (d, J = 7.5Hz, H-5); 6.06 (Q, J = 5.7 and 2.6Hz, H-1'); 7.3 (m, trityl and H-6).
^{13}C NMR ($CDCl_3$) : 13.6 (CH_3); 36.2 ($\underline{C}H_2CH_3$); 63.0 and 63.5 (C-2' and C-5'); 73.2 (C-3'); 79.5 (C-4'); 87.1 (C $_3$); 87.5 (C-1'); 109.5 (C-5); 127.0, 127.6, 128.2, 142.8 (trityl); 135.3 (C-6); 160.1 (C-2); 171.8 (C-4).

b) 5'-O-Trityl-O^2,2'-anhydro-2',3'-serouridine, 58
mp 181°C.
MS (m/e) 470 (M^+).
UV (MeOH) λ_{max} : 252 nm (sh.).
^{1}H NMR ($CDCl_3$) δ : 3.17 (m, H-5', H-5"); 3.62 (m, H-3', H-3"); 4.10 (m, H-4'); 4.65 (m, H-2', H-2"); 5.80 (d, J = 7.5Hz, H-5); 6.23 (t, J = 4Hz, H-1'); 7.47 (m, trityl); 7.57 (d, H-6).
^{13}C NMR ($CDCl_3$) 63.1 and 63.7 (C-2' and C-5'); 74.2 (C-3'); 82.4 (C-4'); 87.0 (C ϕ_3); 87.9 (C-1'); 109.2 (C-5); 136.4 (C-6); 160.5 (C-2); 172.8 (C-4). Other signals for the trityl groups are not mentioned.

1-(R)-[6-(R)-hydroxymethyl-1,4-dioxan-2-yl]uracil

Reaction of 5'-O-trityl-O^2,2'-anhydro-2',3'-secouridine, 58 (or the 3'-O-diethylsulfinate), with potassium fluoride (10 eq), [18]-crown-[6]-polyether, in monoglyme in the presence of p-toluenesulfonic acid anhydrous for 6 h at reflux temperature gave 48 % of the starting material and 30 % of the 1,4-dioxane derivative 59a. The yield of 59a is 60 % when the reaction is carried out in DMF at reflux overnight.
UV (MeOH) 260 nm.
^{1}H NMR ($CDCl_3$) δ : signals for H-3, H-5, H-6 and the $\underline{CH_2}$OTr protons are concentrated in one multiplet ranging from 2.9 to 4.2 ppm; 5.7 (d, H-5); 5.75 (dd, J = 2.8 and 9.4Hz, H-2'); 7.23 (trityl and H-6).
^{13}C NMR ($CDCl_3$) : 63.1 (CH_2OTr); 67.8 and 68.0 (CH_2OCH_2); 75.9 (C-6'); 78.7 (C-2'); 102.6 (C-5); 139.3 (C-6); 149.7 (C=O); 162.8 (C=O).
The product was further identified after detritylation with 80 % of acetic acid at 100°C for 25 min and isolated in 83 % yield after column chromatography ($CHCl_3$-MeOH, 97-3). This product, 59b, has been described previously[147,148].
mp 164-165°C.

UV (MeOH) λ_{max} : 260 nm (ε 9,700).

MS (m/e) 228 (M^+).

^{1}H NMR (CD_3COCD_3) δ : 3.3-4.15 (m, H-3', H-5', H-6' and $\underline{CH_2}OH$); 5.65 (d, J = 8Hz, H-5); 5.75 (dd, J = 9.7 and 2.9Hz, H-2'); 7.72 (d, H-6) ppm.

^{13}C NMR (CD_3COCD_3) : 61.6 ($\underline{C}H_2OH$); 67.2 and 67.6 (CH_2OCH_2); 77.9 and 78.9 (C-2' and C-6'); 102.0 (C-5); 140.5 (C-6); 150.3 (C=O); 162.8 (C=O).

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