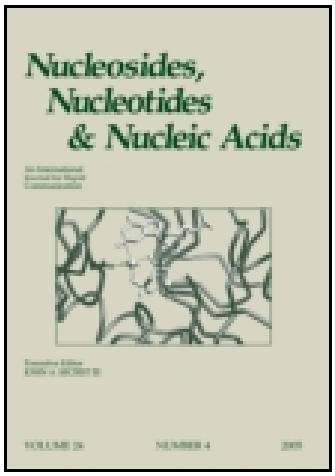

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Chemistry and Dynamics of Interaction of Nucleosides with Pentafluoropyridine

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CHEMISTRY AND DYNAMICS OF INTERACTION OF NUCLEOSIDES WITH PENTAFLUOROPYRIDINE

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▫ *Interaction of pentafluoropyridine with hydroxyl groups of thymidine, uridine, adenosine, and deoxyadenosine at room temperature leads to the formation of aryl ethers of nucleosides with a high yield. Under severe conditions, one more tetrafluoropyridine residue is attached to pyrimidine fragments of T and U, while purine heterocycle in A remains intact. Nucleoside derivatives are formed with a quantitative yield and can be used in situ as intermediates for, as an example, molecular design of arene analogs of nucleic acids. The reaction with thymidine is a successive-parallel process, the limited stage being arylation of the secondary hydroxyl group. The presence of the vicinal hydroxyl group in pentose results in the opposite rate ratio of the formation of primary and secondary tetrafluoropyridyl ethers of adenine and uridine.*

Keywords Nucleosides, Arylation, S_NAr, Pentafluoropyridine

INTRODUCTION

Elaboration of new methods of functionalization of key biopolymer fragments is of great interest for fundamental and applied bioorganic chemistry, molecular biology, biotechnology, etc.[1–5]

S_NAr reactions used, for example, for introduction of aryl groups into nucleosides[6] can be employed for this purpose. We believe that for the successful modification of nucleophilic centers of nucleosides these reagents can be involved in reactions with pentafluoropyridine bearing several selectively substituting halogen atoms. This approach allows further multiple transformations of the introduced pentafluoropyridine fragments. Revelation of chemical characteristics of nucleosides as polynucleophilic targets in S_NAr reactions is also of interest.

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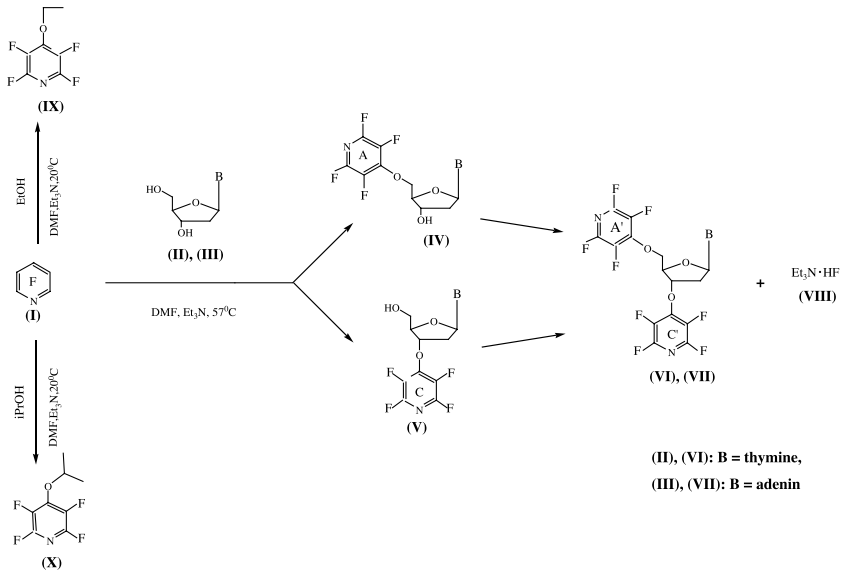
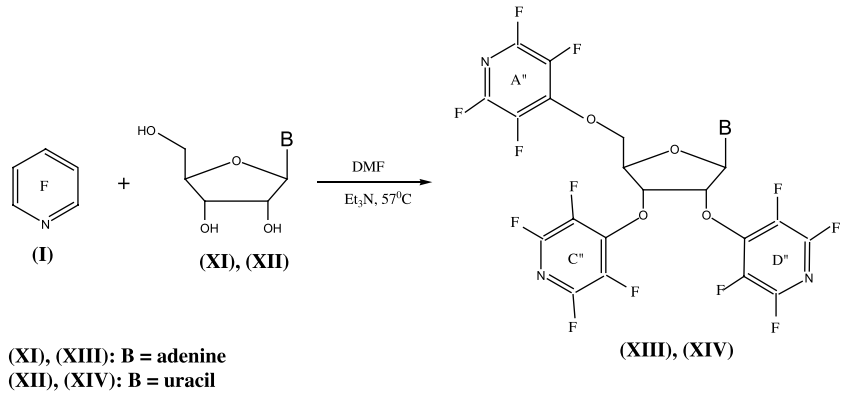


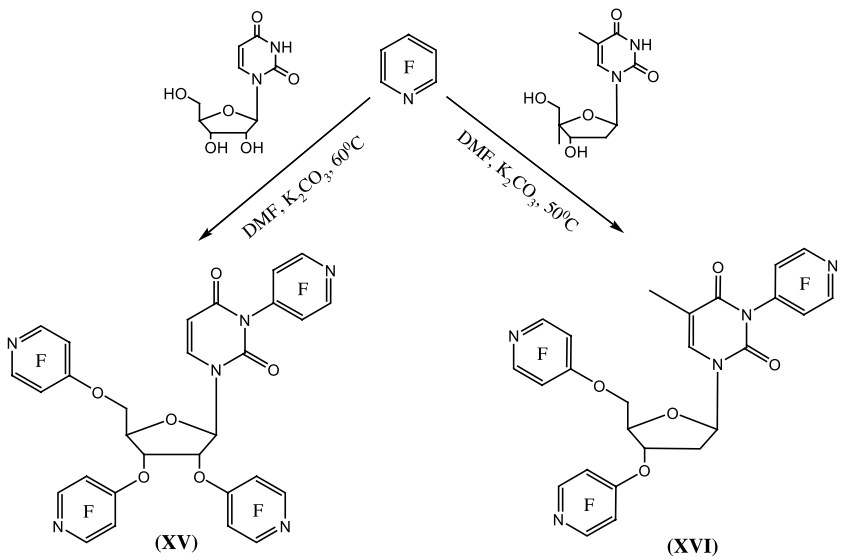
SCHEME 1

RESULTS AND DISCUSSION

We have studied the interaction of thymidine, T (II), uridine, U (XII), adenosine, A (XI), and deoxyadenosine, dA (III) with pentafluoropyridine (I) bearing at least three fluoroatoms capable of successive nucleophilic substitution (Schemes 1, 2, and 3). Noncatalytic synthesis of ethers is known to occur via the interaction of activated arenes with previously prepared alcoholates of alkali metals in the media of corresponding alcohols. This variant of Williamson synthesis is hardly applicable to arylation of nucleosides for several reasons. They are, for example, the high activity of atomic hydrogen forming upon preparation of



SCHEME 2



SCHEME 3

alcoholates, the low solubility of polyalcoholates in solvents usually used in S_NAr reactions, and complication of preparation of nucleoside alcoholates. Therefore, the synthesis of arene derivatives VI, VII, XIII–XVI and the study of some ethers formation were carried out in situ when nucleophiles were generated via reactions of their precursors with bases–triethylamine (Schemes 1 and 2) and K_2CO_3 (Scheme 3). Although the reaction rate is higher in the presence of K_2CO_3, a part of pentafluoropyridine in this case is wasted for the formation of γ-hydroxyl-α,β,α′,β′-tetrafluoropyridine. The most efficient media for such reactions, DMF, appears to be the most acceptable solvent in our case, too. The reaction conditions were chosen so that only one–the most mobile–fluorine atom in γ-position of pentafluoropyridine[7] was substituted in the reaction with nucleosides. As a result, arylation products VI, VII, XIII, and XIV were prepared as individual compounds with high yields. Products preserving several mobile halogen atoms sustain more severe conditions (57°C, 54 h); this stipulates a possibility of using them in situ as intermediates for the consecutive modification of S_NAr type.

To assign signals of polyfluorinated fragments attached to the primary or secondary hydroxyl groups in arylation products IV–VII, ^{19}F NMR spectra of ethers IX and X formed in reactions of pentafluoropyridine with ethanole and *iso*-propanole were initially registered (Scheme 1, Figure 1). Multiplet assigned to β,β′-2F (c) of ethyl ether IX is shifted to the higher field (3.84 ppm; here and then chemical shifts correspond to the centers of symmetric multiplets) compared to that for *iso*-propyl derivative X (4.86 ppm) (Figure 1d). Signals of fluorine atoms in 2, 6 positions of pyridine rings of primary ether IX are also disposed in higher field compared to secondary ether X (see Experimental). These data indicate that

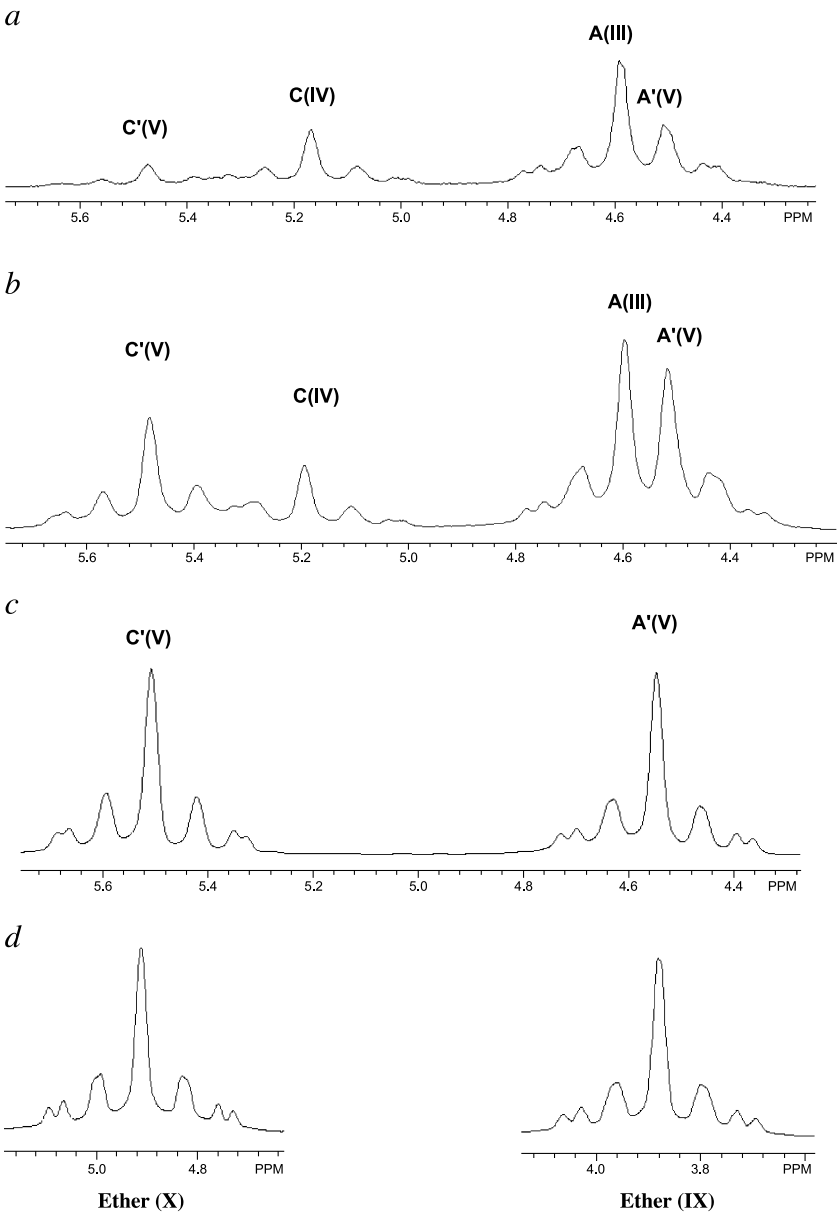


FIGURE 1 Fragments of ^{19}F NMR spectra of the reaction mixtures (Scheme 1) that correspond to [β],[β]′-fluorine atoms of pyridyl rings A, C, A′, and C′ of (III), (IV), and (V). The spectra are registered after 0.75 (a), 3 (b), and 16 (c, final) h after the beginning of the reaction; (d), fragments of ^{19}F NMR spectra of the reaction mixtures containing [β],[β]′-fluorine atoms of pyridyl rings of ethers (VII) and (VIII).

multiplets in lower fields corresponding to products V–VII belong to fluorine atoms in β,β′-positions of rings C and C′ of ethers at the secondary carbon atoms, while multiplets in higher fields correspond to analogous halogen atoms of rings A and A′ of the primary ethers. The other reason for such assignment can be significantly higher rate of the formation of ethers IV and IX in comparison with that of ethers V and X, respectively.

In general, arylation of nucleoside hydroxyl groups with pentafluoropyridine is carried out with comparable rates (Figures 1a, b; 2;3b, d). Maximum accumulation of monoethers IV and V, for example, amounts to 18 and 7% in 3 h, respectively (Figure 2); by this time, 13% of the final product VI is already formed.

Like diethers VI and VII, the quantitative formation of triethers XIII and XIV is observed (Scheme 2). Signals of fluorine atoms at β,β′ positions of the isolated products consist also of two multiplets (Figure 3a, c). Analogously, multiplets in the higher field can be assigned to fragments at the 5′ oxygen atoms (A rings), and combined multiplets in the lower field can be attributed to corresponding fragments of the secondary ethers (C and D) with twice the intensity.

The nitrogen atoms of the pyrimidine cycle can be brought into the reaction at higher temperatures using the excess of pentafluoropyridine and K_2CO_3 as a condensing agent. As a result, the formation of tri- and tetrafluoropyridyl derivatives

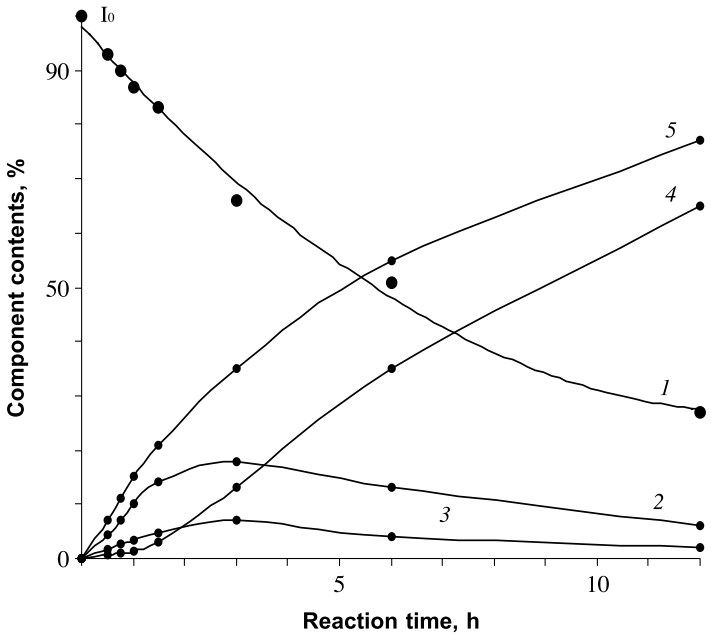


FIGURE 2 Kinetic curves of arylation of thymidine with pentafluoropyridine. The relative content of components of the reaction mixture is considered as (I_i/I_0) 100%, where I_i and I_0 are the integral intensities of fluorine resonances of the reaction components and the initial pentafluoropyridine, respectively: 1, substrate (I); 2, intermediate (III); 3, intermediate (IV); 4, diether (V); 5, the overall content of ethers (III)–(V) and triethylamine hydrofluoride (VI).

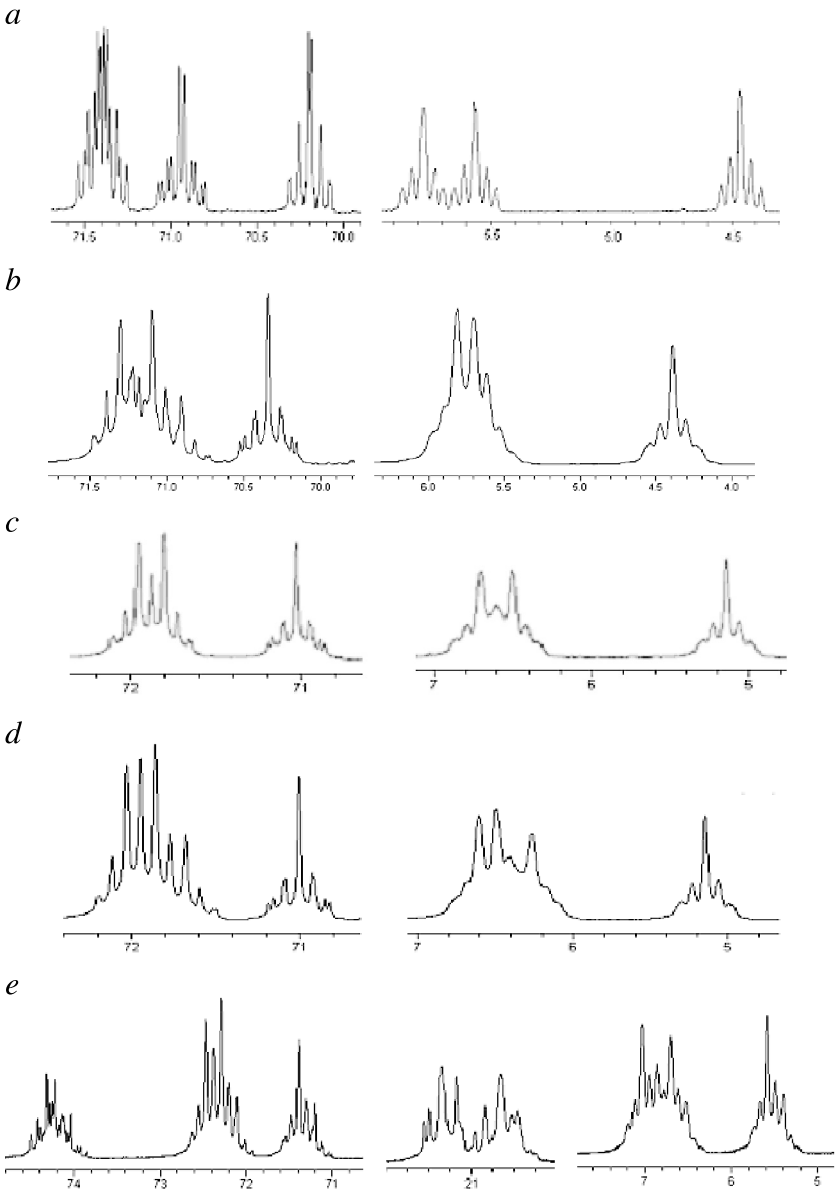


FIGURE 3 Fragments of ^{19}F NMR spectra of the reaction mixtures containing α,β-fluorine atoms of pyridyl rings of ethers (XIII), (XIV), and (XV). Presented spectra: (a), isolated ether (XIV); (b), ether (XIV) on the initial portion of the kinetic curve; (c), isolated ether (XIII); (d), ether (XIII) on the initial portion of the kinetic curve; (f), isolated ether (XV).

of T (XVI) and U (XV) is observed (Scheme 3). ^{19}F NMR spectra are presented on Figure 3f. Signals of all fluorine atoms of pyridyl fragments attached to the nitrogen atom are observed in lower field. Multiplets of fluorine atoms in α, α′ positions (73 ppm) have a more complicated structure and more components as compared to hydroxyl derivatives. Signals of β,β′ fluorine atoms in XV appear as two approximate multiplets (center at 21 ppm) of equal intensity, multiplets of XVI being overlapped. These signals are broadened, which is stipulated by the additional interaction of fluorine atoms with pyrimidine nitrogen. The individual products have no absorption bands of protons at nitrogens in IR and PMR spectra. The data confirm the attachment of the forth substrate molecule to nitrogen, but not to the other nucleophilic centers of pyrimidine. Purine base in XIII is not modified under the conditions of arylation of pyrimidine fragment.

It should be noted that the signals of β,β′ fluorine atoms appear to be rather sensitive to the nature of γ-arene substituents. It can be used for both the interpretation of the interaction of polyfluorinated substrates with polynucleophilic molecules and various physicochemical investigations.

Kinetics of the process shown on Scheme 1 was followed by ^{19}F NMR spectra (Figures 1 and 2). Accumulation of ethers VI and V was determined by measuring integral intensities of signals of fluorine atoms of C′ and C rings, respectively. The content of ether IV, whose multiplet overlaps the signals of fragment A′ (Figure 1a, b), was calculated by dividing the integral intensity of signals of fluorine atoms in ring C′ (diether VI). The data in Figures 1 and 2 confirm the reactions drawn on Scheme 1. The substitution of γ-fluorine of pentafluoropyridine results in the exponential increase of signal intensity at 29.5 ppm (Figure 2, curve 1). At any time, decreasing the substrate in the reaction mixture is in accordance with the accumulation of the reaction products. Concentrations of monoethers IV and V increase from zero, achieve maximum, and decrease again to zero. The kinetic curve of diether VI formation goes through maximum in the region of the highest summary concentrations of monoethers IV and V; the tangent of the angle of slope values are equal to 0.6, 1.2, 1.4, 2.8, 1.8, and 1.5 in 1.5, 2.15, 2.65, 3.1, 3.6, and 4.05 h of the reaction, respectively. S-Like dependence 4 (Figure 2) also confirms its formation in the successive processes from its precursors (ethers IV and V), the rate of the former formation being three times higher (curves 2 and 3, respectively).

To reveal specific properties of polynucleophilic reagents, we compare the rates of arylation of primary and secondary hydroxyl groups in thymidine and in mononucleophiles—ethanol and *iso*-propanol (Scheme 1). The rate ratios of the formation of ethers IX and X as well as of primary and secondary thymidine ethers IV and V measured on the initial regions of kinetic curves give the following values:

$$\mathrm{IV/V} = 3.1\{1\}; \mathrm{IX/X} = 4.3\{2\}; \mathrm{IV/IX} = 2.2\{3\}; \mathrm{V/X} = 2.5\{4\}$$

The values {1} and {2} can be caused by higher ionization of the primary hydroxyl group in the presence of triethylamine and by lower steric hindrances as

compared to the secondary hydroxyl group. The ratios {3} and {4}, however, contradict the ratios {1} and {2} and the known data,[8] that an amplification of methylene groups in alcoholates leads to decreasing the reactivity of a nucleophile as it is in the ratios {1} and {2}, but not to an increase of that as in ratios {3} and {4}. Thus, thymidine hydroxyl groups attached to the relatively large pentose molecule appear to be more reactive than analogous nucleophilic centers in simpler molecules. The possible explanation of the revealed specificity of polynucleophilic molecules can be participation of the hydrogen atom of one of the hydroxyl groups in intermolecular solvataion, which causes an increase of concentration of the intermediate Meisenheimer σ-complex. Formation of the intermediate in the analyzing process is the limited stage, as it is for the reactions of activated arenes with anion reagents. The other distinguishing factor of polynucleophilic compounds making them more active reagents can be participation of the 5′- and 3′-hydroxyl groups in spiro-complex formation, the more stable intermediate than the classic Meisenheimer σ-complex. Therefore, one can assume that in the presence of vicinal hydroxyl groups in pentose, the role of the spiro-cyclic intermediate in changing ratios of arylation rates will be especially noticeable. Compounds of this type (for example, adducts of nucleosides with polynitroarenes) are well known.[9–12] Indeed, the kinetic investigation of the ethers XIII and XIV formation showed more rapid accumulation of the primary ethers than of the secondary ethers during all the process. The most characteristic example of the initial reaction stages is presented in Figure 3. Signals of individual ethers XIII, XIV, and their precursors are shown in Figure 3a, b and 3c, d, respectively. In the beginning of the reaction, a half of the integral multiplet intensity in low field (centers at $\sim$ 5.75 and 6.45 ppm) assigned to β,β′-fluorine atoms of the secondary esters exceeds by half the multiplet intensity of the primary ethers (4.45 and 5.15 ppm) (Figure 3b, d). Despite seven arylation products exist in the reaction mixture, multiplets at 4.4 ppm are symmetric and their chemical shift is not changed during all the process. Thus, there is no significant cross-impact of the substituents in 2′, 3′, and 5′-positions. The complicated signals at $\sim$ 5.75 and 6.45 ppm (Figure 3b, d) consist of three general, partly overlapping multiplets of the close intensity. These signals belong, apparently, to the mixture three secondary ethers in about equal proportion.

Thus, the formation of secondary ethers for ribonucleosides having three hydroxyl groups is carried out faster than in the case of deoxyribonucleosides containing only two hydroxyl groups (Scheme 1). One of the reasons of the conversion of reactivity of two nucleophilic centers (5′>3′ for dioxy- and 3′>5′ for trioxy-derivatives) can be intensification of substitution at vicinal hydroxyl groups because of intermolecular nucleophilic substitution (Smiles rearrangement) carrying out via intermediate spiro-cyclic Meisenheimer σ-complex.[9–13] Formation of such an intermediate with participation of the 5′ and 3′ hydroxyls is also possible; the rate of its accumulation and its stability, however, must be significantly lower. It should be noted that the potentiality of anion σ-complexes in organic synthesis[13] is not expanded yet into nucleoside chemistry.

It should be noted that an increase of congenerous nucleophilic groups on the same molecule results in appreciable difference of their reactivity that can be utilized for the selective modification of biopolymers.

EXPERIMENTAL

^1H and ^{19}F NMR spectra were registered on Bruker WP 200 SY spectrometer (Germany) at 295 K and working frequencies of 200.13 and 188.28 MHz, respectively. The values of chemical shifts (δ, ppm) were measured relative to internal standards $SiMe_4$ for ^1H and C_6F_6 for ^{19}F NMR. The coupling constants J are given in Hz. Melting points were determined using Koefler S 30 A/G table (Germany).

The following chemicals were used: thymidine (Yamasa Shoyu Co., Ltd., Japan), adenosine and deoxyadenosine (Reanal, Hungary), and uridine (NPO Biokhimreaktiv, Russia). Pentafluoropyridine had no admixtures according to ^{19}F NMR spectrum. Silica gel (40–100 μm) was used for column chromatography. Solvents were purified according to known procedures[10] and stored over molecular sieves 4 Å.

The completeness of reactions and homogeneity of the resulting products were monitored by TLC and HPLC. TLC was carried out on Kieselgel 60F254 (Merck, Germany) in 10:1 (A), 20:1 (B), 5:1 (C) $CHCl_3$–MeOH mixtures and 10:1 (D) benzol–dioxane mixtures. Analytical HPLC was carried out on the microcolumn liquid chromatograph Milikchrom-1 (Nauchpribor, Russia) using a CHROM system for collection and analysis of chromatographic data,[11] a Nucleosil 100-5 C-18, 5-μm column (Macherey-Nagel, Germany) and elution during 20 min in a gradient of CH_3CN (70–90%) in 0.1% TFA at a flow rate of 100 μL/min.

Interaction of thymidine with pentafluoropyridine using the ^{19}F NMR. Pentafluropyridine (147 mg, 0.87 mmol) and triethylamine (96 mg, 0.95 mmol) were added to a solution of thymidine (100 mg, 0.41 mmol) in DMF (0.4 mL), and the reaction mixture was kept at room temperature, while registering ^{19}F NMR spectra in 0.5, 0.75, 1.0, 1.5, 3.0, 6.0, and 12 h after the beginning of the reaction. Relative contents of the products were determined according to integral intensities of resonances in the range of 1–6 ppm (Figures 1, 2).

Interaction of ethanol and isopropanol with pentafluoropyridine using the ^{19}F NMR. Triethylamine (97 mg, 0.95 mmol) and ethanol (44 mg, 0.95 mmol) or isopropanol (57 mg, 0.95 mmol) were added to a solution of pentafluropyridine (154 mg, 0.91 mmol) in DMF (0.4 mL), and the reaction mixtures were kept at room temperature, while registering ^{19}F NMR spectra in 10, 20, 30, and 40 h after the beginning of the reactions. Relative contents of the products IX and X were determined according to integral intensities of resonances in the range of 1–6 ppm.

3′,5′-O-bis(α,β,β′,α′-tetrafluoropyrid-γ-yl)thymidine (VI). Pentafluropyridine (166 mg, 0.98 mmol) and triethylamine (111 mg, 1.10 mmol) were added to a solution of thymidine (116 mg, 0.48 mmol) in DMF (0.5 mL), and the reaction mixture was kept for 16 h at 56–58°C. The completion of the reaction was registered by ^{19}F NMR by the absence of pentafluropyridine. The reaction mixture was poured into ice and water and neutralized with concentrated HCl. The resulting precipitate was filtered, washed with distilled water, and dried in air and then in vacuum over NaOH to give the product with a yield of 250 mg (96% to thymidine) with the purity of 91% (here and hereinafter, according to HPLC). The product with R_f 0.5 (A) was purified by column chromatography on silica gel (elution with $CHCl_3$). A portion of the product (100 mg) isolated by chromatography was recrystallized from 20% isopropanol in hexane to give (VI) (36 mg) with a purity exceeding 99%; mp 88–90°C; ^{1}H NMR (ÑDCl$_3$): 6 (3 H, s, CH_3), 2.48–2.79 (2 H, m, H2′), 4.60 (1 H, br. s, H4′), 4.80 (2 H, br. s, H5′), 5.52 (1 H, br. s, H3′), 6.30 (1 H, d., H1′), 7.17 (1 H, s, H6), and 9.59 (1 H, br. s, 3-NH); ^{19}F NMR (DMF): 4.58 [2 F, m, 5′-([β],[β]′-difluoropyrid-4-yl)], 5.55 [2 F, m, 3′-([β],[β]′-difluoropyrid-4-yl)], 70.69 [2 F, m, 5′-([α],[α]′-difluoropyrid-4-yl)], and 71.16 [2 F, m, 3′-([α],[α]′-difluoropyrid-4-yl)]. Found, %: C 44.12 and 45.31; H 2.29 and 2.42; N 10.43 and 10.25; F 28.36 and 28.59. $C_{20}H_{12}F_8N_4O_5$. Calc., %: C 44.46, H 2.24, N 10.37, F 28.13.

3′,5′-O-bis(α,β,β′,α′-tetrafluoropyrid-γ-yl)adenosine (VII). Pentafluropyridine (371.9 mg, 2.2 mmol) and triethylamine (253 mg, 2.5 mmol) were added to a solution of adenosine (251.3 mg, 1 mmol) in DMF (2 mL), and the reaction mixture was kept for 7 days at room temperature. The reaction was monitored and the product (VII) was isolated as described above for (VI) with a yield of 459 mg (83.6% to adenosine). A portion of the product was recrystallized from isopropanol; mp 120–123°Ñ. ^{1}H NMR (acetone – d_6): 3.26 (2 H, m, H2′); 4.85 (1 H, br. s, H4′); 5.04 (2 H, br. s, H5′); 5.98 (1 H, br. s, H4′); 6.64 (4 H, br. s, H2′, NH_2); 8.18 (2 Ì, d, H2, H8); ^{19}F NMR (DMF): 4.70 [2 F, m, 5′-([β],[β]′-difluoropyrid-4-yl)]; 5.71 [2 F, m, 3′-([β],[β]′-difluoropyrid-4-yl)]; 70.54 [2 F, m, 5′-([α],[α]′-difluoropyrid-4-yl)], and 71.06 [2 F, m, 3′-([α],[α]′-difluoropyrid-4-yl)]. Found, %: C 43.72 and 44.06; H 2.18 and 2.21; N 17.88 and 16.98; F 27.76 and 27.45. $C_{20}H_{11}F_8N_7O_3$. Calc., %: Ñ 43.73, H 2.02, N 17.85, F 27.66.

3′,5′-O-*tris*(α,β,β′,α′-tetrafluoropyrid-γ-yl)adenosine (XIII). Pentafluoropyridine (506 mg, 2.99 mmol) and triethylamine (331 mg, 3.28 mmol) were added to a solution of adenosine (250 mg, 0.94 mmol) in DMF (2 mL), and the reaction mixture was kept for 8 days at room temperature. The reaction was monitored and the product (XI) was isolated as described above for (V) with a guantitative yield (810 mg) and 97% purity. After recrystallization from propanol the purity of (XI) exceeded 99%; mp 81–83°C; ^{1}H NMR (ÑDCl$_3$): 4.78–5.00 (3 H, m, H5′, H4′), 5.92 (2 H, br. s, 6-NH), 6.12 (1 H, d., H3′), 6.34–6.40 (2 H, m, H1′ and

H2′), 7.91 (1 H, s, H8), and 8.18 (1 H, s, H2). ^{19}F NMR (DMF): 4.78 [2 F, m, 5′-([β],[β]′-difluoropyrid-4-yl)], 6.72 [2 F, m, 3′-([β],[β]′-difluoropyrid-4-yl)], 70.57 [2 F, m, 5′-([α],[α]′-difluoropyrid-4-yl)], and 71.51 [2 F, m, 3′-([α],[α]′-difluoropyrid-4-yl)]. Found, %: C 42.51 and 42.23; H 1.96 and 1.73; N 15.41; F 32.26 and 32.56. $C_{25}H_{10}F_{12}N_8O_4$. Calc., %: C 42.03, H 1.41, N 15.69, F 31.91.

2′,3′,5′-O-*tris*(α,β,β′,α′-tetrafluoropyrid-γ-yl)uridine (XIV). Pentafluropyridine (554 mg, 3.28 mmol) and triethylamine (363 mg, 3.58 mmol) were added to a solution of uridine (250 mg, 1.02 mmol) in DMF (2 mL), and the reaction mixture was kept for 6 days at room temperature. The product was isolated with a yield of 86% (709 mg, 86% purity) as described above. Purification by column chromatography on silica gel (elution with 49:1 $CHCl_3$-MeOH) yielded the product with Rf 0.5 (B), which was recrystallized from 7:3 propanol-water to give (XII) (315 mg, 99% purity); mp 78–80°C. ^{1}H NMR (N̂DCl_3): 4.76–5.00 (3 H, m, H5′ and H4′), 5.61 (2 H, br. s, H2′ and H3′), 5.77 (1 H, d., H5), 5.96 (1 H, s, H1′), 7.42 (1 H, d., H6), 9.52 (1 H, br. s, 3-NH). ^{19}F NMR (DMF): 4.82 [2 F, m, 5′-([β],[β]′-difluoropyrid-4-yl)], 6.18 [2 F, m, 3′-([β],[β]′-difluoropyrid-4-yl)], 70.64 [2 F, m, 5′-([α],[α]′-difluoropyrid-4-yl)], 71.52 [2 F, m, 3′-([α],[α]′-difluoropyrid-4-yl)]. Found, %: C 41.79 and 42.08; H 1.59 and 1.71, N 10.01, F 32.56 and 32.84. $C_{24}H_9F_{12}N_5O_6$. Calc., %: C 41.70, H 1.31, N 10.13, F 32.97.

2′,3′,5′-O-3-*N*-*tris*(α,β,β′,α′-tetrafluoropyrid-γ-yl)thymidine (XVI). Pentafluropyridine (760.7 mg, 4.5 mmol) and K_2CO_3 (691 mg, 5 mmol) were added to a solution of thymidine (242.2 mg, 1 mmol) in DMF (3 mL), and the reaction mixture was kept for 5 days at 60°C. The completion of reaction was monitored by ^{19}F NMR. The reaction mixture was poured into ice water and neutralized with concentrated HCl. The resulting precipitate was filtered, washed with distilled water, and dried in air and then in vacuum over NaOH to give the product with a yield of 829 mg (78.8% to thymidine). Purification by column chromatography on silica gel (elution with $CHCl_3$) yielded the product with Rf 0.8 (C), which was recrystallized from propanol to give (XVI) 543 mg; mp 36–38°C. ^{1}H NMR (N̂DCl_3): 1.96 (3 H, s., CH_3); 2.62 (2 H, m., H2′); 4.57 (1 H, d, H3′); 4.75 (2 H, br. s, H5′); 5.44 (1 H, br. s, H4′); 6.30 (1 H, m., H1′); 7.18 (1 H, br. s, H6). ^{19}F NMR (DMF): 6.99 [2 F, m, 5′-([β],[β]′-difluoropyrid-4-yl)]; 7.35 [2 F, m, 3′-([β],[β]′-difluoropyrid-4-yl)]; 22.35 [2 F, m, N3-([β],[β]′-difluoropyrid-4-yl)]; 72.25 [2 F, m, 5′-([α],[α]′-difluoropyrid-4-yl)]; 73.33 [2 F, m, 3′-([α],[α]′-difluoropyrid-4-yl)]; 75.82 [2 F, m, N3-([α],[α]′-difluoropyrid-4-yl)]. Found, %: N̂ 43.31; H 1.56; N 9.77; F 33.10. $C_{29}H_8F_{16}N_6O_6$. Calc., %: N̂ 43.56, N 10.16; H 1.61; F 33.07.

2′,3′,5′-O-3-*N*-Tetra(α,β,β′,α′-tetrafluoropyrid-γ-yl)uridine (XV). Pentafluropyridine (1014.3 mg, 6 mmol) and K_2CO_3 (967.4 mg, 7 mmol) were added to a solution of uridine (242.2 mg, 1 mmol) in DMF (3 mL), and the

reaction mixture was kept for 6 days at 50°C. The product was isolated with a yield of 660 mg (78.57 to uridine) as described above. Purification by column chromatography on silica gel (elution with benzene) yielded the product with Rf 0.6 (D), which was recrystallized from ether-hexane to give (XV) (300 mg); mp 41–42°C. ^{1}H NMR ($\hat{N}DCl_3$): 4.91 (2 H, br. s, H5′); 5.55 (2 H, br. s, H2′, H3′); 6.00 (1 H, d., H5); 6.15 (1 H, s., H4′); 7.27 (1 H, s., H1′); 7.63 (1 H, d., H6). ^{19}F NMR (DMF): 4.80 [2 F, m, 5′-([β],[β]′-difluoropyrid-4-yl)]; 5.84 [2 F, m, 3′-([β],[β]′-difluoropyrid-4-yl)]; 6.17 [2 F, m, 2′-([β],[β]′-difluoropyrid-4-yl)]; 20.37 [2 F, m, N3-([β],[β]′-difluoropyrid-4-yl)]; 70.46 [2 F, m, 5′-([α],[α]′-difluoropyrid-4-yl)]; 71.38 [2 F, m, 3′,N3-([α],[α]′-difluoropyrid-4-yl)]; 73.3 [2 F, m, 2′-([α],[α]′-difluoropyrid-4-yl)]. Found, %: Ñ 41.64; H 0.91; N 9.89; F 36.27. $C_{29}H_8F_{16}N_6O_6$. Calc., %: Ñ 41.45, N 10.00; H 0.96; F 36.17.

γ-Ethoxy-α,β,β′,α′-tetrafluoropyridine (IX). ^{19}F NMR: 3.86 (2 F, m, F3, and F5), 70.41 (2 F, m, F2, and F6). The contents of (IX) at the above-mentioned time points were 66, 82, 87, and 91%, respectively.

γ-Isopropyloxy-α,β,β′,α′-tetrafluoropyridine (X). ^{19}F NMR: 4.89 (2 F, m, F3, and F5), 70.67 (2 F, m, F2, and F6). The contents of (X) at the above-mentioned time points were 13, 24, 35, and 43%, respectively.

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