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Synthesis and reactions of 1-(5-azido-5-deoxy-3-*O*-*p* toluenesulfonyl-β-D-xylofuranosyl) derivatives of 5-alkyl- and 5-halo-pyrimidines

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Abstract

Chemical syntheses of 1-(2-*O*-acetyl-5-azido-5-deoxy-3-*O*-*p*-toluenesulfonyl-β-D-xylofuranosyl)-5-iodo-, -5-fluoro-, and -5-trifluoromethyl-uracil nucleosides (**11–13**) as well as the thymine analogue **10** were performed from a sugar precursor and the corresponding uracil bases. Partial deblocking of **10–13** gave the 5′-azido-5′-deoxynucleosides **14–17**. The 3′,5′-diazido-3′,5′-dideoxyribonucleosides were obtained in the same way. The 2′,3′-anhydro analogue **20** was prepared by treatment of **10** with potassium carbonate in methanol or a basic ion-exchange resin. Reaction of **10** with azide or methanethiolate ions gave 2′-azido- and 2′-thiomethyl-ribonucleosides, respectively. Similarly, **13** gave a 2′-thiomethylribonucleoside on treatment with methanethiolate ion. Treatment of **16** with phenoxythiocarbonyl chloride in basic medium afforded a 2′,3′-anhydro derivative and not the expected ester.

Keywords: 5-Alkyl- and 5-halo-pyrimidines; 5′-Azido-5′-deoxyxylonucleosides; 3′,5′-Diazido-3′,5′-dideoxyribonucleosides; 2′,3′-Anhydronucleosides; Glycosylation

1. Introduction

Several 3′- and 5′-azido and amino derivatives of 5-substituted pyrimidine 2-deoxyribonucleosides [1–8] have been synthesized in order to improve the antiviral

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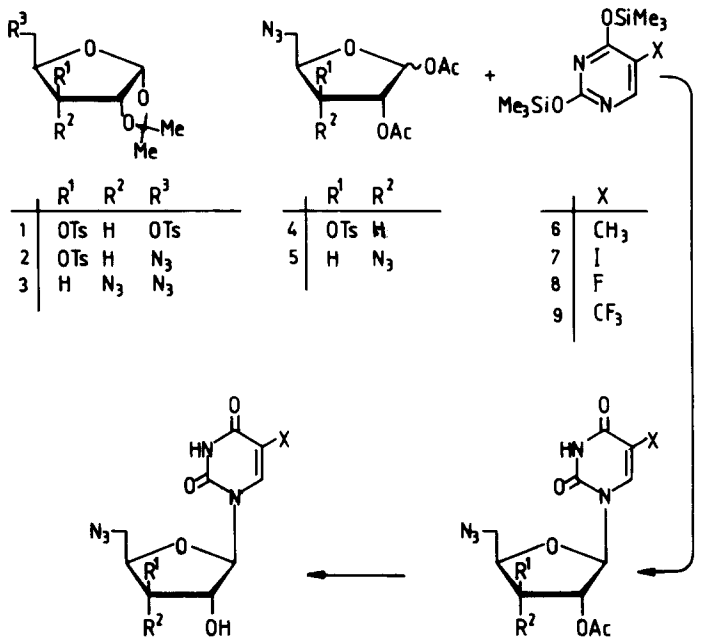
activity. 3′-Azido-3′-deoxythymidine (AZT), the only licensed drug for the treatment of AIDS [9,10], is among numerous examples of such nucleosides. We present here the synthesis of various 5′-azido-5′-deoxy derivatives of 5-alkyl- and 5-halo-pyrimidine nucleosides and describe the chemical behaviour of these nucleosides toward certain nucleophiles.

2. Results and discussion

Reaction of the ditosylate **1** with 1.5 mol. equiv of sodium azide in *N,N*-dimethylformamide at 120°C gave the syrupy 5-azido-5-deoxy sugar derivative **2** in 98% yield. Acetolysis of **2** with a mixture of acetic acid, acetic anhydride, and sulfuric acid gave the diacetate **4** in 92% yield, isolated as an oil. The procedure of Hilbert–Johnson–Birkofer [11] was employed for ribosylation of the silylated uracil derivatives **6–9** with the 5′-azido-5′-deoxy sugar derivative **4** in dry 1,2-dichloroethane with trimethylsilyl trifluoromethanesulfonate as catalyst. This method showed a regioselective reaction toward N-1 substitution and resulted in the formation of the desired 5-substituted 1-(2-*O*-acetyl-5-azido-5-deoxy-3-*O*-*p*-toluenesulfonyl-β-D-xylofuranosyl)uracil nucleosides (**10–13**). Deacetylation of these protected nucleosides with methanolic ammonia afforded the corresponding nucleosides **14–17**.

We next prepared 1,2-di-*O*-acetyl-3,5-diazido-3,5-dideoxy-D-ribofuranose (**5**) from the ditosylate **1**, via the isopropylidene derivative **3**, by using the procedure of Krayevsky and co-workers [12]. Equimolar treatment of the silylated thymine **6** with the sugar precursor **5** in boiling 1,2-dichloroethane for 3 h under trimethylsilyl triflate catalysis led to the formation of the nucleoside **18** in 63% yield. The deacetylation of **18** with methanolic ammonia led to a good yield of **19**.

The action of nucleophilic reagents on compounds **10** and **16** was investigated. Thus, treatment of **10** with potassium carbonate in dry methanol for 48 h at room temperature gave, after chromatographic separation, a new compound that exhibited spectroscopic data in agreement with the expected structure **20** (52% yield). Analogous treatment of **10** with Dowex 1-X8-50 (OH^-) ion-exchange resin or sodium methoxide in dry methanol for 2–3 h resulted in the formation of **20** in 85 and 65% yields, respectively. Treatment of **10** with excess of a 3:2 mixture of sodium azide and ammonium chloride in DMF at 120°C for 2 h gave a crystalline product which was tentatively identified as **24**. Reaction of **10** or **13** with 1.2 mol equiv of sodium methanethiolate in boiling methanol afforded mainly crystalline **25** and **26**, respectively. These results might be explained in terms of the intramolecular displacments of the sulfonate groups at C-3′ in **10** and **13** to give the intermediates **20** and **21**, respectively, which are in equilibrium with the most favoured 2,2′-anhydrides **22** and **23**, respectively [13,14]. Then, both azide and methanethiolate ions are able to attack C-2′ in **22** to give **24** and **25**, respectively, while similar attack by methanethiolate ions on C-2′ in **23** would give **26**. These findings are in accordance with the results obtained by Sasaki et al. [15] during the reaction of some methanesulfonic esters of uracil derivatives with azide ions. They reported also [16] the formation of a triazolino-pyrimidine from the thermal reaction of 5′-azido-5′-deoxy-2′,3′-*O*-isopropylideneuridine with azide ions in methanol. In our case, there is no evidence that such an



	R^1	R^2	R^3
1	OTs	H	OTs
2	OTs	H	N_3
3	H	N_3	N_3

	R^1	R^2
4	OTs	H
5	H	N_3

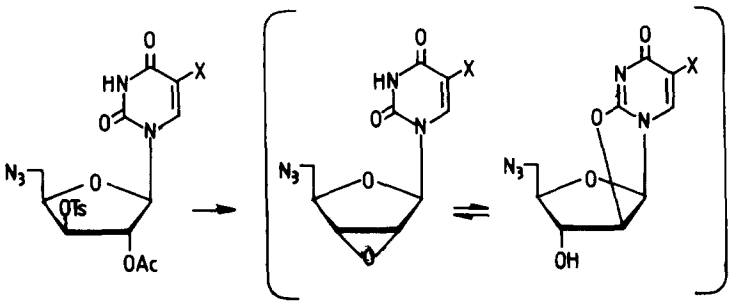
	X
6	CH_3
7	I
8	F
9	CF_3

	X	R^1	R^2	
14	CH_3	OTs	H	10
15	I	OTs	H	11
16	F	OTs	H	12
17	CF_3	OTs	H	13
19	CH_3	H	N_3	18

N-5′-C-6 bridge compound has been formed, since the ^{1}H NMR spectrum of **24** revealed a signal for H-6 at δ 7.52 as well as the appearance of a strong IR absorption at 2100 cm^{-1}, attributed to the azido group.

An attempt to prepare the 2′-deoxy analogue of compound **16**, using the method of Robins et al. [17], has been examined. However, reaction of the latter compound with phenoxythiocarbonyl chloride, in the presence of 4-dimethylaminopyridine (DMAP), gave a crystalline product whose physical properties agreed with structure **27** and not **28** as expected. This result is due to the basic action of DMAP, and generation of the alkoxide ion in **16**, leading to the formation of the 2′,3′-anhydro derivative **27**. Repetition of the above experiment in the presence of only DMAP also afforded **27**, in 48% yield.

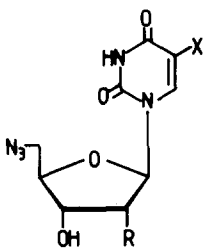
Physical properties.—All compounds were fully characterized by elemental analyses or accurate mass determinations, UV spectra (Table 1), and ^{1}H NMR spectra which were found to be consistent with the assigned structures. The formation of N-1 nucleosides was confirmed from UV spectral comparison with the proven structures of



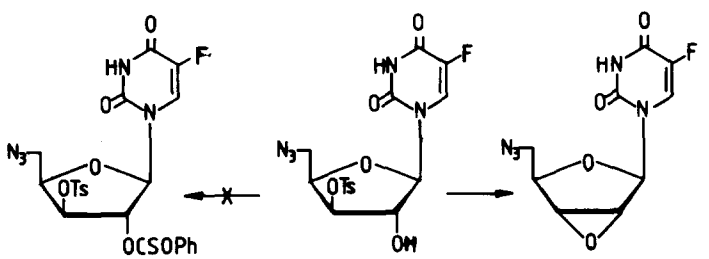
	X
10	CH_3
13	CF_3

	X
20	CH_3
21	CF_3

	X
22	CH_3
23	CF_3



	X	R
24	CH_3	N_3
25	CH_3	SMe
26	CF_3	SMe



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most familiar pyrimidine nucleosides prepared previously (references cited in the introduction). The ^{1}H NMR data of the new compounds are summarized in Tables 2 and 3 and show a common pattern of spectral features. The chemical shifts of H-1′ in compounds **10–13** (δ 5.99, 5.40, 5.93, and 5.94) with the corresponding $J_{1',2'}$ values (3.0, 2.4, 2.5, and 2.2 Hz, respectively) clearly indicated that these compounds have the β configuration and are in agreement with the N-type conformation of the sugar moiety.

The signals at δ 5.83, 5.10, 5.51, and 5.21, respectively, as pseudo-triplets were attributed to H-2′ ($J_{2',3'}$ 2.0, 2.0, 2.1, and 1.9 Hz, respectively) while the signals at δ 5.01, 5.06, 5.04, and 5.10, with J values of 4.0, 3.8, 4.0, and 3.9 Hz, respectively, were assigned to H-3′. These data established also the D-*xylo* configuration of these compounds. The ^{1}H NMR spectrum of **20** (Tables 2 and 3) also confirmed the D-*ribo* configuration of this compound and there was no evidence for the formation of the expected 2,2′-anhydro analogue since there was a singlet at δ 9.45 belonging to the NH group. The structures of **24–26** followed from their ^{1}H NMR spectra. The observed couplings for H-1′ ($J_{1',2'}$ 5.8, 5.5, and 5.0 Hz, respectively) are close to that of 1-(2-azido-5-*O*-benzoyl-2-deoxy-β-D-ribofuranosyl)uracil [14]. The assignments of the hydroxyl groups in these compounds were determined from D_2O exchange as well as the irradiation experiments which revealed a clear decoupling with the H-3′ multiplet signals and, as a result of this irradiation, the latter protons in **24–26** were enhanced to doublets of doublets ($J_{3',4'}$ 6.2, 5.9, and 6.5 Hz), respectively. These data proved that these compounds possessed the *ribo* configuration.

3. Experimental

General.—Melting points were measured on a Buchi apparatus, model Dr Tottoli, with no correction. UV spectra were recorded on a Perkin–Elmer spectrometer Lambda 5; λ_{max} in nm (log ϵ). ^{1}H NMR spectra were recorded with a Bruker WM-250 spectrometer; δ relative to internal Me_4Si. TLC: precoated silica gel thin-layer sheets F 1500 LS 254 from Schleicher and Schüll; precoated silica gel thin-layer sheets (without fluorescence) from Merck.

Table 1
Physical data of pyrimdine N-1 nucleosides

Compound	UV absorption spectra			
	λ_{max} (nm)		log ϵ	
10	223	263	4.29	3.96
11	222	281	4.24	3.82
12	225	260	4.15	3.94
13	228	273	4.36	4.01
14	221	261	4.15	3.85
15	220	272	4.21	3.81
16	220	[255]	4.31	[3.86]
17	220	268	4.21	3.98
18	[226]	262	[4.21]	3.82
19	[224]	264	[4.08]	3.98
20	228	262	3.72	3.88
24	230	[246]	3.91	[3.97]
25	212	263	3.72	3.63
26	[227]	252	[3.79]	3.79
27	[224]	252	[3.76]	3.80

Table 2
^{1}H NMR chemical shift data (δ) for the sugars and pyrimidine N-1 nucleosides [a]

Compound	NH	H-1′	H-2′	H-3′	H-4′	H-5′a	H-5′b	OH	5-subst.	6-subst.	Me-$ArSO_2$	OAc	$ArSO_2$	Other signals
2	—	5.91d	4.53dd	5.09dd	4.30dt	3.63dd	3.61dd	—	—	—	2.50s	—	7-90–7.38m	1.51, 1.32 $(CMe)_2$
4	—	5.92d	4.68dd	4.79dd	4.28ddd	3.54dd	3.68dd	—	—	—	2.47s	1.48, 1.29	7.82d, 7.44d	
10	9.47s	5.99d	5.83dd	5.01dd	4.31ddd	3.74dd	3.68dd	—	1.88d	7.18s	2.46s	2.07s	7.82d, 7.39d	
11	8.69s	5.80d	5.10pt	5.06dd	4.36ddd	3.74dd	3.59dd	—	—	7.12s	2.10s	2.07s	7.73d, 7.27d	
12	8.73s	5.93pt	5.51pt	5.04dd	4.34ddd	3.75dd	3.62dd	—	—	8.35d ($J_{6,F}$ 4.9 Hz)	2.21s	2.09s	7.83d, 7.40d	
13	8.74s	5.94d	5.21pt	5.10pt	4.41ddd	3.76dd	3.67dd	—	—	7.67s	2.21s	2.11s	7.80d, 7.39d	
14	10.09s	6.07d	4.44t	5.14pt	3.99m	3.36dd	3.22dd	3.07d	1.81d	7.12s	2.10s	—	7.73d, 7.27d	
15	8.49s	6.33d	4.27pt	5.28pt	4.22m	3.43dd	3.20dd	5.35d	—	7.87s	2.44s	—	7.50d, 7.7.09d	
16	8.65s	6.32d	4.22pt	5.33pt	4.25ddd	3.44dd	3.26dd	3.30bs	—	8.35d ($J_{6,F}$ 4.9 Hz)	2.21s	—	7.47d, 7.11d	
17	8.71s	6.43d	4.33pt	5.27pt	4.23pt	3.40dd	3.35dd	6.07d	—	8.06s	2.27s	—	7.47d, 7.10d	
18	9.82s	6.13d	5.72pt	4.49dd	4.38ddd	3.77dd	3.58dd	—	1.90d	7.19s		2.12s		
19	9.71s	6.17d	4.65–4.33m			3.75dd	3.52dd	3.12d	1.87d	7.17s				
20*	9.45s	6.24d	3.83dd	3.82–3.44m		3.25dd	3.23dd	—	1.88d	7.11s				
24*	10.12s	6.22d	4.87dd	4.70m	4.03dt	3.45dd	3.38dd	5.81d	1.89d	7.52s				
25*	10.12s	6.68d	5.25dd	4.32m	4.23ddd	3.45dd	3.15dd	6.07d	—	8.14s				1.99 (SMe)
26*	9.66s	6.43d	4.92dd	4.41m	4.20ddd	3.62dd	3.26dd	6.12d	—	8.12bs				1.88 (SMe)
27	8.95s	6.19d	3.95dd	3.58t	3.49ddd	3.31dd	3.21dd	—	7.87bs					

[a] All spectra were measured in $CDCl_3$ unless otherwise stated (*, Me_2SO-d_6). s, singlet; d, doublet; bs, broad singlet; dd, doublet of doublets; pt, pseudo-triplet; t, triplet; m, multiplet; ddd, doublet of doublet of doublets.

Table 3
^{1}H NMR coupling constants (Hz) [a]

Compound	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'a}$	$J_{4',5'b}$	$J_{5'a,5'b}$	OH
2	3.5	0.5	3.5	5.2	2.7	10.8	—
4	3.5	1.0	2.0	6.7	2.8	13.0	—
10	3.0	2.0	4.0	6.0	6.4	13.0	—
11	2.4	2.0	3.8	5.8	6.7	13.0	—
12	2.5 ($J_{1',F}$ 1.5 Hz)	2.1	4.0	6.0	6.2	13.8	
13	2.2	1.9	3.9	5.8	6.0	13.0	—
14	4.9	1.5	5.3	7.3	3.3	11.9	7.0
15	5.8	1.8	5.2	5.0	6.4	13.4	4.5
16	5.8	2.0	5.0	6.5	5.8	13.0	—
17	5.5	1.2	5.5	5.0	6.0	13.0	4.3
18	3.2	5.0	2.0	4.8	5.2	13.0	—
19	4.2	—	—	—	5.0	12.5	4.5
20*	5.2	6.7	—	—	4.5	13.0	—
24*	5.8	2.0	—	6.4	8.0	13.0	5.7
25*	5.5	3.0	—	3.5	7.2	13.8	5.5
26*	5.0	3.5	—	4.0	6.5	12.5	5.0
27	5.0	5.8	3.5	5.5	6.0	12.0	—

[a] For chemical shift data, see Table 2.

*5-Azido-5-deoxy-1,2-*O*-isopropylidene-3-*O*-p-toluenesulfonyl-α-*D*-xylofuranose* (**2**). —A mixture of the ditosylate **1** (4.0 g, 8.54 mmol) and NaN_3 (0.83 g, 12.77 mmol) in *N,N*-dimethylformamide (50 mL) was heated at 120°C for 2 h. Solvent was evaporated and the residue was partitioned between $CHCl_3$ (2 × 50 mL) and water (50 mL). The organic extracts were dried (Na_2SO_4), filtered, and evaporated to dryness to give **2** (3.10 g, 98%) as syrup, $[\alpha]_D$ −19° (*c* 1.5, $CHCl_3$). Mass spectrum: *m/z* 369.0880 ($C_{15}H_{19}N_3O_6S$ calcd: 369.0995).

*1,2-Di-*O*-acetyl-5-azido-5-deoxy-3-*O*-p-toluenesulfonyl-*D*-xylofuranose* (**4**).—To a suspension of **2** (3.0 g, 8.13 mmol) in a mixture of glacial AcOH (20 mL) and Ac_2O (14 mL) was added conc. H_2SO_4 (0.13 mL) slowly with stirring for 18 h at room temperature. The mixture was added slowly to vigorously stirred dil aq $NaHCO_3$ (100 mL). After 2 h of stirring, the solution was partitioned with $CHCl_3$ (3 × 50 mL) and the combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to dryness to give **4** (3.1 g, 92%) as an oil, $[\alpha]_D$ +60° (*c* 1.0, $CHCl_3$). Mass spectrum: *m/z* 413.0804 ($C_{16}H_{19}N_3O_8S$ calcd: 413.0893).

*1-(2-*O*-Acetyl-5-azido-5-deoxy-3-*O*-p-toluenesulfonyl-β-*D*-xylofuranosyl) derivatives of 5-alkyl- and 5-halo-pyrimidines* (**10–13**).—*General procedure.* A mixture of the substituted pyrimidine (5.0 mmol), a few crystals of $(NH_4)_2SO_4$, and hexamethyldisilazane (30 mL) was heated under reflux for 18 h. After cooling, the mixture was evaporated to dryness to give the silylated products **6–9**. These products were dissolved in dry 1,2-dichloroethane (20 mL) and then a solution of 1,2-di-*O*-acetyl-5-azido-5-deoxy-3-*O*-*p*-toluenesulfonyl-D-xylofuranose (**4**, 5.0 mmol) in dry 1,2-dichloroethane (20 mL) was added. The mixture was stirred for 48 h at room temperature after addition of

trimethylsilyl triflate (1.1 mL, 5.0 mmol), and then partitioned between $CHCl_3$ and dil aq $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered, and then evaporated to dryness to give a crude product, which was chromatographed on silica gel (20 g). Elution with 95:5 $CHCl_3$–MeOH afforded the desired nucleoside as a solid foam.

*1-(2-O-Acetyl-5-azido-5-deoxy-3-*O*-p-toluenesulfonyl-β-*D*-xylofuranosyl)thymine* (**10**).—Yield 1.94 g (81%), mp 65–69°C (found: C, 47.98; H, 4.49; N, 14.24. $C_{19}H_{21}N_5O_8S$ calcd: C, 47.60; H, 4.41; N, 14.61).

*1-(2-O-Acetyl-5-azido-5-deoxy-3-*O*-p-toluenesulfonyl-β-*D*-xylofuranosyl)-5-iodouracil* (**11**).—Yield 1.62 g (55%), mp 66–71°C (dec) (found: C, 36.09; H, 3.12; N, 12.26. $C_{18}H_{18}IN_5O_8S$ calcd: C, 36.56; H, 3.06, N, 11.84).

*1-(2-O-Acetyl-5-azido-5-deoxy-3-*O*-p-toluenesulfonyl-β-*D*-xylofuranosyl)-5-fluorouracil* (**12**).—Yield 1.23 g (51%), mp 92–96°C (found: C, 45.05; H, 3.75; N, 14.17. $C_{18}H_{18}FN_5O_8S$ calcd: C, 44.72; H, 3.75; N, 14.48).

*1-(2-O-Acetyl-5-azido-5-deoxy-3-*O*-p-toluenesulfonyl-β-*D*-xylofuranosyl)-5-trifluoromethyluracil* (**13**).—Yield 1.23 g (46%), mp 65–68°C (found: C, 42.73; H, 3.56; N, 13.03. $C_{19}H_{18}F_3N_5O_8S$ calcd: C, 42.78; H, 3.40; N, 13.12).

*1-(5-Azido-5-deoxy-3-*O*-p-toluenesulfonyl-β-*D*-xylofuranosyl) derivatives of 5-alkyl- and 5-halo-pyrimidines* (**14–17**).—*General procedure.* In a solution of 16% methanolic NH_3 (15 mL) was stirred the acetate (**10–13**; 0.40 mmol) for 3 h at room temperature. The solution was neutralized with Dowex 50-X2-200 (H^+) ion-exchange resin, filtered with washing of the resin with MeOH, and evaporated to dryness. The residue was stirred with $CHCl_3$ for 2 h and the solid was filtered off as the pure nucleoside.

*1-(5-Azido-5-deoxy-3-*O*-p-toluenesulfonyl-β-*D*-xylofuranosyl)thymine* (**14**).—Yield 0.15 g (86%), mp 154–156°C (dec) (found: C, 46.42; H, 4.40; N, 16.22. $C_{17}H_{19}N_5O_7S$ calcd: C, 46.67; H, 4.38; N, 16.01).

*1-(5-Azido-5-deoxy-3-*O*-p-toluenesufonyl-β-*D*-xylofuranosyl)-5-iodouracil* (**15**).—Yield 0.16 g (73%), mp 198–204°C (found: C, 34.59; H, 2.79; N, 13.29. $C_{16}H_{16}IN_5O_7S$ calcd: C, 34.98; H, 2.93; N, 12.75).

*1-(5-Azido-5-deoxy-3-*O*-p-toluenesulfonyl-β-*D*-xylofuranosyl)-5-fluorouracil* (**16**).—Yield 0.15 g (85%), mp 193–196°C (dec) (found: C, 43.38; H, 3.58; N, 15.94. $C_{16}H_{16}FN_5O_7S$ calcd: C, 43.54; H, 3.65; N, 15.83).

*1-(5-Azido-5-deoxy-3-*O*-p-toluenesulfonyl-β-*D*-xylofuranosyl)-5-trifluoromethyluracil* (**17**).—Yield 0.15 g (76%), mp 169–176°C (dec) (found: C, 41.89, H, 3.31; N, 13.80. $C_{17}H_{16}F_3N_5O_7S$ calcd: C, 41.55; H, 3.28; N, 14.25).

*1-(2-O-Acetyl-3,5-diazido-3,5-dideoxy-β-*D*-ribofuranosyl)thymine* (**18**).—A mixture of thymine (1.0 g, 8.19 mmol), some crystals of $(NH_4)_2SO_4$, and hexamethyldisilazane (20 mL) was stirred overnight under reflux. The mixture was evaporated to dryness under anhydrous condition and the residue was dissolved in dry 1,2-dichloroethane (20 mL) and added to a solution of sugar **5** (1.0 g, 3.5 mmol) in dry 1,2-dichloroethane (20 mL). A solution of trimethylsilyl triflate (0.64 mL, 3.52 mmol) was added dropwise and the mixture was stirred under reflux for 3 h. Solvent was evaporated to dryness and the residue was partitioned between $CHCl_3$ (3 × 20 mL) and dil aq $NaHCO_3$ (25 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was co-evaporated with ether (3 × 30 mL) and then stirred overnight to give

18 (0.78 g, 64%) as a colorless amorphous solid, mp 59–66°C (found: C, 41.47; H, 4.07; N, 31.62. $C_{12}H_{14}N_8O_5$ calcd: C, 41.14; H, 4.03; N, 31.99).

1-(3,5-Diazido-3,5-dideoxy-β-D-ribofuranosyl)thymine (**19**).—Compound **18** (220 mg, 0.71 mmol) was kept with 16% methanolic NH_3 (16 mL) at room temperature overnight. The solution was concentrated to 5 mL and neutralized with AcOH to pH 6. Evaporation of the solvent to dryness afforded a syrupy product (200 mg). The syrup was co-evaporated with $CHCl_3$ (3 × 15 mL) to yield amorphous nucleoside **19** (140 mg, 64%), mp 118–125°C (found: C, 39.25; H, 3.81; N, 36.18. $C_{10}H_{12}N_8O_4$ calcd: C, 38.95; H, 3.92; N, 36.35).

1-(2,3-Anhydro-5-azido-5-deoxy-β-D-ribofuranosyl)thymine (**20**).—(*a*) Compound **10** (0.49 g, 1.05 mmol) in dry MeOH (50 mL) was stirred with K_2CO_3 (0.08 g, 0.58 mmol) at room temperature for 48 h. The mixture was acidified with AcOH to pH 5, then evaporated to dryness to give a syrupy mixture (0.32 g). The syrup was chromatographed on silica gel (40 g) and elution with 99:1 $CHCl_3$–MeOH gave, first, the title compound **20** (0.16 g, 57%), mp 110–112°C (found: C, 45.52; H, 4.23; N, 26.14. $C_{10}H_{11}N_5O_4$ calcd: C, 45.28; H, 4.18; N, 26.40). Eluted second was the crystalline nucleoside **14** (0.04 g, 9%), mp, mixture mp, and other physical data identical with those of the authentic sample prepared in the above experiment.

(*b*) A solution of **10** (0.85 g, 1.77 mmol) in dry MeOH (30 mL) was stirred with Dowex 1-× 8-50 (OH^-) ion-exchange resin (2.0 g) for 2 h at room temperature. The resin was filtered off, washed with MeOH, and the filtrate was evaporated to give a crude product (0.50 g). This was purified on a short column of silica gel and elution with 99:1 $CHCl_3$–MeOH afforded **20** (0.36%, 77%), mp 111–112°C (from EtOH–ether).

(*c*) A solution of **10** (160 mg, 0.33 mmol) in dry MeOH (10 mL) was stirred with Na (8 mg, 0.34 mmol) at room temperature for 8 h. The solution was acidified with AcOH to pH 5 and the solvent was evaporated to dryness. The residue was partitioned between $CHCl_3$ and water. The organic extract was dried (Na_2SO_4), filtered, and evaporated to give **20** (66 mg, 75%), mp and mixture mp identical with those of the authentic sample from (*a*).

Reaction of **10** *with azide ion.*—A mixture of **10** (0.48 g, 1.00 mmol), NaN_3 (0.39 g, 6.00 mmol), and NH_4Cl (0.22 g, 4.0 mmol) in DMF (15 mL) was stirred at 120°C. After 2 h, further amounts of NaN_3 (0.19 g, 2.92 mmol) and NH_4Cl (0.11 g, 2.06 mmol) were added and the reaction was continued for another 2 h at the same temperature. The mixture was cooled to 25°C, the salts were filtered off, and the filtrate was evaporated to a syrupy mixture (0.5 g). This syrup was chromatographed on silica gel (35 g) with $CHCl_3$ as eluent to give a syrupy compound tentatively characterized as 1-(2,5-diazido-2,5-dideoxy-β-D-ribofuranosyl)thymine (**24**). Crystallization from EtOH–petroleum ether gave 0.13 g of **24** (42%), mp 188–190°C (found: C, 39.25; H, 3.88; N, 36.11. $C_{10}H_{12}N_8O_4$ calcd: C, 38.96; H, 3.92; N, 36.35).

Reaction of **10** *with methanethiolate ion.*—A solution of **10** (103 mg, 0.22 mmol) in dry MeOH (10 mL) containing NaSMe (20 mg, 0.27 mmol) was boiled for 5 h. After cooling, the solvent was evaporated to dryness and the residue was taken into acetone (10 mL) and neutralized with AcOH to pH 6. The salt was filtered off and the filtrate was evaporated to dryness to give a crystalline compound (49 mg). Recrystallization from EtOH afforded 37 mg of a compound tentatively identified as 1-(5-azido-5-deoxy-

2-*S*-methyl-2-thio-β-D-ribofuranosyl)thymine (**25**) (51%), mp 155–160°C (dec) (found: C, 40.11; H, 5.01; N, 21.05. $C_{11}H_{15}N_5O_4S \cdot H_2O$ calcd: C, 39.87; H, 5.17; N, 21.13).

Reaction of **13** *with methanethiolate ion.*—A solution of **13** (150 mg, 0.28 mmol) in dry MeOH (12 mL) was boiled with NaSMe (29 mg, 0.41 mmol) for 3 h. The mixture was worked-up as in the previous experiment to give a crude product which recrystallized from EtOH to yield 1-(5-azido-5-deoxy-2*S*-methyl-2-thio-β-D-ribofuranosyl)-5-trifluoromethyluracil (**26**) (38 mg, 37%), mp 226–230°C (found: C, 36.28; H, 3.18; N, 18.86. $C_{11}H_{12}F_3N_5O_4S$ calcd: C, 35.97; H, 3.29; N, 19.06).

Reaction of **16** *with PTC-Cl in the presence of base.*—(*a*) Compound **16** (100 mg, 0.22 mmol) in toluene (15 mL) was stirred at room temperature for 5 h with phenoxythiocarbonyl chloride (PTC-Cl) (1 mL, 7.39 mmol) containing 4-dimethylaminopyridine (DMAP) (1 mL). The mixture was evaporated and the residue was partitioned between water (15 mL) and $CHCl_3$ (20 mL). The organic extract was dried (Na_2SO_4), filtered, and evaporated to dryness to yield a crystalline derivative. Recrystallization from EtOH gave 1-(2,3-anhydro-5-azido-5-deoxy-β-D-ribofuranosyl)-5-fluorouracil (**27**) (34 mg, 57%), mp 191–192°C (dec) (found: C, 39.88; H, 3.12; N, 26.20. $C_9H_8FN_5O_4$ calcd: C, 40.15. H, 2.99; N, 26.01).

(*b*) A solution of **16** (50 mg, 0.11 mmol) in toluene (7 mL) containing DMAP (0.5 mL) was stirred at room temperature for 6 h. The mixture was worked-up as in (*a*) to give **27** (28 mg, 48%), mp, mixture mp, and other physical data identical with those of the authentic sample prepared in (*a*).

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