Synthesis of β-*D*-xylofuranosyl- and 2,2′-anhydro-1-β-*D*-lyxofuranosylpyrimidine nucleosides

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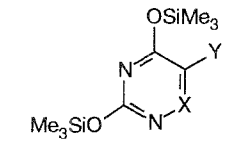
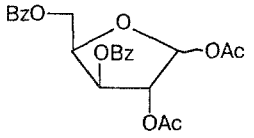
β-*D*-Xylofuranosylpyrimidines were obtained by condensation of silyl derivatives of pyrimidines with 1,2-di-O-acetyl-3,5-di-O-benzoyl-*D*-xylofuranose with subsequent deprotection of the sugar fragment. Refluxing 2-O-tosyl derivatives of nucleosides with NaI results in the formation of 2,2'-anhydro-compounds.

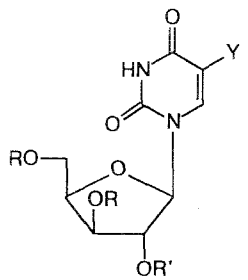
Key words: 1,2-di-O-acetyl-3,5-di-O-benzoyl-*D*-xylofuranose, β-*D*-xylofuranosylpyrimidines, 2,2′-anhydro-1-β-*D*-lyxofuranosyluracils, 2,3-didehydro-3-deoxythymidine, 3-β-*D*-xylofuranosyl-6-methyluracil.

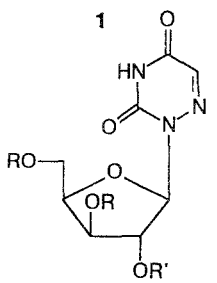
Xylofuranosyl nucleosides are known to exhibit high antitumor and antiviral activities.[1,2] In addition, nucleosides containing *D*-xylofuranose as the sugar fragment are suitable for obtaining compounds with valuable properties.[3—5] For example, the drug azidothymidine (AZT), which is effective against the human immunodeficiency virus (HIV), has been obtained in several stages using β-*D*-xylofuranosylthymine as the starting material.[6] In this connection the synthesis of 5- and 6-substituted xylofuranosylpyrimidines is of obvious interest, as is the investigation of the possibility of functionalizing both the pyrimidine ring and the sugar fragment.



X = CH, N
Y = H, Me, Hal







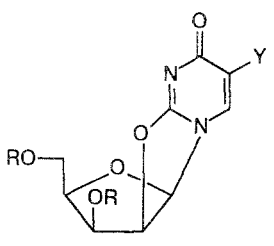
7: R = Bz, R' = Ac
13: R = R' = H

R = Bz, R' = Ac, Y = H(**2**), Me(**3**), Br(**4**), F(**5**), I(**6**)
R = R' = H,Y = H(**8**), Me(**9**), Br(**10**), F(**11**), I(**12**)
R = Bz, R' = H, Y = Br(**14**), F(**15**), I(**16**)
R = Bz, R' = Ts,Y = Br(**17**), F(**18**), I(**19**) ,Me(**20**), H(**21**)

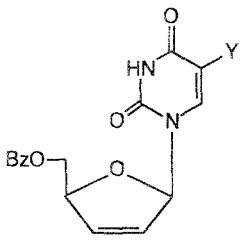
Silyl derivatives of 5-halouracils, 6-aza- and 6-methyluracil[7] were introduced into the condensation reaction with 1,2-di-O-acetyl-3,5-di-O-benzoyl-*D*-xylofuranose (**1**) (see ref. 8) in 1,2-dichloroethane in the presence of $SnCl_4$. Under these conditions only N(1)-xylofuranosylpyrimidines (**2—7**) were formed (Table 1). The protective groups in compounds **2—7** were removed with 0.1 *N* MeONa in MeOH to give the respective 1-(β-*D*-xylofuranosyl)pyrimidines (**8—13**). The UV spectra of these compounds in neutral and alkaline solutions show slight differences in positions of the maxima,[9] which are characteristic of N(1)-substituted nucleosides.

Deacetylation of compounds **4—6** with H_2SO_4 in aqueous acetonitrile gives 1-(3,5-di-O-benzoyl-β-*D*-xylofuranosyl)pyrimidines (**14—16**). Their tosylation in pyridine at room temperature affords 1-(2-O-tosyl-3,5-di-O-bensoil-β-*D*-xylofuranosyl)pyrimidines (**17—19**) in high yield (Table 1).

Previously we pointed out[10] that the analogous thymine and uracil tosylates **20** and **21** form 2,2′-anhydrocompounds (**22, 23**) and unsaturated benzoates (**24, 25**) on heating with NaI in 1,2-di-



R=Bz,Y=Me(**22**),H(**23**),Br(**26**),F(**27**),I(**28**)
R = H, Y = Br(**29**), F(**30**),I(**31**)



24: Y = Me
25: Y = H

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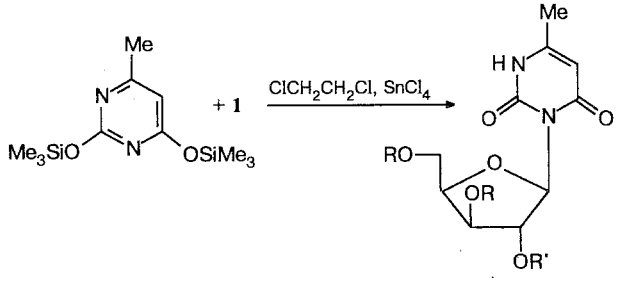
Table 1. Yields, melting points or R_f values, and UV spectra of compounds **4—33**

Compound	Yield (%)	M.p./°C or R_f*	UV spectrum		
			Solvent**	λ_{max}/nm	λ_{min}/nm
4	69	0.38	A	228.4; 274.2	250.4
5	74	0.37	A	229.4; 267.0	250.2
6	84	0.38	A	228.4; 284.2	251.1
7	70	0.34	A	236.2; 260.0	253.4
10	74	189—192	B	279.0	242.4
		(EtOH)	C	277.0	250.6
11	82		B	269.6	234.2
			C	269.5	247.6
12	85	170—173	B	284	250.0
		(EtOH)	C	278.3	252.4
13	80	206—208	B	261.2	230.4
		(EtOH)	C	255.0	223.3
14	72	94—97	A	228.6; 275.0	251.6
		($CHCl_3$)			
15	74	81—84 ($CHCl_3$)	A	227.8; 264.4	249.4
16	79	198—202 ($CHCl_3$)	A	227.6; 280.4	254.8
17	73	167—169 (Et_2O)	A	228.4; 274.0	251.6
18	79	0.35	A	227.7; 269.2	234.6
19	79	0.36	A	227.8; 280.1	253.0
26	39	0.10	A	227.6; 269.1	238.1
27	35	0.10	A	229.6; 260.0	239.0
28	34	0.10	A	230.6; 272.8	235.4
29	70	246—247 (MeOH)	B	234.0; 267.0	243.7
30	69	257—260 (MeOH)	B	221.3; 255.4	234.3
31	50	230—232 (MeOH)	B	231.8; 273.0	251.6
32	66	0.34	A	230.6; 266	250.5
33	70	205—207	B	264.8	234.1
		(MeCOMe)	C	289.9	248.9

* R_f were determined in MeCN/MeOH, 95/5.
* Solvents A — MeCN, B —H_2O, C— 0.1 *N* aqueous NaOH.

methoxyethane. However, under these conditions tosylates **17—19** form only 2,2′-anhydro-1-(3,5-di-O-benzoyl-1-β-*D*-xylofuranosyl)pyrimidines (**26—28**).

Condensation of bis(trimethylsilyl)-6-methyluracil with 1,2-di-O-acetyl-3,5-di-O-benzoyl-*D*-xylofuranose was also carried out under the conditions described above. However, in this case the reaction product was 3-(2-O-acetyl-3,5-di-O-benzoyl-*D*-xylofuranosyl)-6-methyluracil (**32**). The UV spectrum of nucleoside (**33**) in an alkaline medium (0.1 *N* NaOH) exhibits a strong bathochromic shift of the maximum (Δ 25.1 nm), which is characteristic of N(3)-substituted nucleosides.[9]



32: R = Bz, R' = Ac,
33: R = R' = H

Experimental

^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, on a Bruker AM-300 instrument (TMS as the internal standard). Chemical shifts are given in δ. Specific rotation was measured on a Perkin-Elmer 241 MC polarimeter. UV spectra were recorded on a Shimadzu 365 UV spectrophotometer. Silica gel LS 40/100 μ was used for chromatography. The purity of the products was checked by TLC on Silufol UV 254 plates (Czechoslovakia). The yields and physicochemical constants of the obtained compounds are given in Tables 1—3.

Synthesis of 1- and 3-(2-O-acetyl-3,5-di-O-benzoyl-*D*-xylofuranosyl)uracils (2—7, 32). 31.4 mmol of 5- or 6-substituted bis(trimethylsilyl)uracil and 29.8 mmol of 1,2-di-O-acetyl-3,5-di-O-benzoyl-*D*-xylofuranose were dissolved in 150 mL of 1,2-dichloroethane and 4.5 mL of $SnCl_4$ was added. The reaction mixture was left for 6 h at 20 °C. Then 40 g of dry $NaHCO_3$ and 15 mL of water were added, the suspension was stirred at 20 °C for 30 min, diluted with 200 mL of $CHCl_3$, and filtered, and the precipitate was washed with chloroform (2×20 mL). The combined filtrates were washed with water, 5 % aqueous $NaHCO_3$, water, and dried with Na_2SO_4. The solvent was evaporated under reduced pressure. The residue was chromatographed on a silica gel column, with $CHCl_3$ as the eluent.

Synthesis of β-*D*-xylofuranosylpyrimidines (8—13). 1 mmol of compound **2—7** was dissolved in 40 mL of 0.1 *N* methanolic

Table 2. ^{1}H NMR spectra of compounds **4—7**, **10—19**, **26—33**

Compound	Solvent*	H-1' ($J_{1',2'}$)	H-2' ($J_{2',3'}$)	H-3' ($J_{3',4'}$)	H-4'	H-5'a ($J_{5a,4}$)	H-5'b ($J_{5b,4}$)	H-5 H-6	J_{gem}
4	A	6.12 d (2.08)	5.41 dd (1.50)	5.75 dd (1.71)		4.70 m		8.05 s	
5	A	6.10 m (2.00, 1.66)	5.71 dd (3.40)	5.40 dd (4.80)	4.78 m	4.72 m		7.82	
6	A	6.08 d (1.91)	5.40 dd (1.44)	5.72 dd (3.49)		4.7 m		8.1 s	
7	A	6.25 d (3.83)	5.80 t (3.10)	5.72 dd (5.04)	4.80 q	4.60 dd (6.10)	4.70 dd (4.70)		−11.84
10	B	5.78 d (0.9)	4.10 m		4.28 m		3.92 m	8.15 s	
11	B	5.75 t (1.12)	4.10 d.t (1.25)	4.02 t.d (3.12)	4.20 dd	3.78 dd (4.00)	3.83 dd (5.37)	8.10 d (7.40)	−11.44
12	B	5.73 s	4.07 s	4.02 d (2.7)	4.20 m	3.75 dd (−11.45) (6.11)	3.85 dd (−11.45) (5.15)	8.20 s	
13	B	5.84 d (5.04)	4.08 m	4.41 dd	4.15 m	3.60 m	3.70 m	7.70 s	
14	B	5.60 d (1.5)	4.47 m	5.46 t (1.7)	4.90 m	4.82 m		8.3 s	
15	B	5.9 s	4.52 s	5.57 s	4.83 m	4.82 m		7.60	
16	C	6.02 d (1.34)	4.82 m	5.75 dd (1.26) (3.40)	5.15m	4.95 dd (4.00)	5.07 m (6.80)	8.44 s	−11.63
	D	6.02 d (1.59)	4.67 dd (1.41)	5.70 dd (3.28)	5.03 m	4.88 dd (3.63)	5.02 (6.73)	8.32 s	−11.19
17	A	6.10 d (3.17)	5.22 m (3.0)	5.83 dd (4.00)	4.85 m	4.62 dd −12.40 (4.20)	4.70 dd −12.40 (5.20)	7.82 s	
18	A	6.06 s	5.30 s	5.81 d	4.82 q	4.62 dd (3.98)	4.71 dd (5.37)		−12.4
19	A	6.02 d (3.09)	5.19 m (3.71)	5.82 dd (4.61)	4.86 q	4.63 dd (4.05)	4.69 dd (5.71)	7.90 s	−12.35
26	A	6.30 d (5.10)	5.70 t (5.85)	5.80 t (6.08)	4.84 m	4.42 dd −12.7 7.6	4.51 dd −12.7 5.3	7.78 s	
27	A	6.27 d (5.67)	5.72 t (5.90)	5.81 t (6.15)	4.92 dd	4.48 dd (7.73)	4.52 dd (5.02)		−12.28
28	A	6.30 d (5.60)	5.71 t (5.80)	5.70 t (6.00)	4.89 q	4.44 (7.71)	4.52 (4.09)	7.90 s	−12.27
29	B	6.20 d (5.90)	5.47 t (5.84)	4.57 dd (5.64)	4.23 m	3.65 m	3.54 m	8.41 s	
30	B	6.20 d (5.74)	5.48 t (5.30)	4.80 t (5.00)	4.20 q	3.41 m	3.58 m	8.30 dd (4.78) (0.80)	
31	B	6.12 d (5.85)	5.39 t (5.59)	4.50 q (5.79)	4.17 m	3.60 m 4.58	3.34 6.10	8.37 s	−12.4
32	A	6.34 d (5.16)	6.21 dd (2.54)	5.53 dd (1.10)	5.81 dd	4.70 dd (3.46)	4.72 (4.12)		−11.12
33	B	5.90 d (3.35)	4.40 dd (3.00)	5.55 d (0.6)	(3.90 − 3.60) m			8.30 s	

Compound	Solvent*	Me	NH	OH−2' (J)	OH−3' (J)	OH−5' (J)	ArH
4	A	2.20 s	8.70 s				7.30−8.00 m
5	A	2.22 s	9.03 s				7.4−8.1 m
6	A	2.10 s (OAc)	9.70 s				7.30−8.05 m
7	A	2.15 s					7.30−8.05 m
10	B		11.70 s	5.68 d (3.80)	5.30 d (3.00)	4.75 t (5.55)	
11	B		11.90 s	5.90 d (4.19)	5.60 d (3.45)	4.90 t (5.60)	
12	B		8.30 s				
13	B		12.40 s	5.67 d (4.80)	5.08 d (6.09)	4.52 t (5.30)	
14	B		11.80 s	6.40 d (4.60)			7.40−8.00 m
15	B		8.40 s	6.50			7.40−8.00 m
16	C		10.40 s	5.80 d (4.00)			7.60−8.18 m
	D		8.42 s	6.57 d (4.53)			7.60−8.20 m
17	A	2.35 s (OTs)	8.65 s				7.40−8.10 m
18	A	2.40 s	8.90 s				7.30−8.00 m
19	A	2.40 s	8.65 s				7.20−8.10 m
26	A						7.36−8.00 m
27	A						7.30−9.00 m
28	A						7.40−8.10 m
29	B				5.80 d (6.02)	4.78 t (5.20)	
30	B				5.70 s	4.53 s	
31	B				5.75 d (5.87)	4.74 t (5.12)	
32	A	2.02 s 2.12 s	9.30 s				
33	B	2.12 s					

* A — $CDCl_3$, B — DMSO-d_6, C — acetone-d_6, D — acetone-d_6 + DMSO-d_6.

Table 3. ^{13}C NMR spectra of xylofuranosylpyrimidines **5—7, 10—19, 26, 28, 32, 33** (δ, *J*/Hz)

Compound	C-1'	C-2'	C-3'	C-4'	C-5'	C-2	C-4	C-5	C-6	CO_2	C arom.	Me
5	88.96	75.07	79.53	79.93	61.41	148.48	156.18	142.09 (42)	123.00 (32)	166.18;164.86; 169.78	129.74;129.21;128.87;128.93; 130.56;130.16;134.22;134.17	20.65
6	89.02	79.95	74.93	79.53	61.39	149.80	159.76	69.36	143.73	166.06;164.70; 168.98	129.92;134.04;129.76;133.23; 129.20;128.91	20.54
7	88.90	77.81	75.67	77.98	62.27	147.70	155.37	136.27		165.12;165.53; 169.67	129.91;129.78;128.77;128.40; 133.80;133.24	20.60
10	91.18	80.34	74.36	84.04	59.03	149.75	159.11	94.58	141.04			
11	91.20	74.48	71.13	94.48	59.36	149.75	157.60	140.00	126.34			
12	91.11	80.54	74.39	83.81	58.90	150.79	161.29	68.39	145.86			
13	89.36	77.51	75.51	81.47	60.29	148.50	156.44	136.42				
14	91.14	78.72	77.66	77.27	61.94	149.62	159.05	95.82	139.22	165.46;165.48	129.33;129.13;129.20;128.51; 133.69;133.40	
15	90.66	77.43	77.43	78.44	62.12	149.03	157.10	140.00	124.8	164.57;165.42	129.31;129.18;129.17;128.54; 133.71;133.37	
16	93.51	80.98	78.84	80.29	63.13	151.37	161.10	69.08	145.45	166.11;166.78	129.80;130.14;130.68;130.90; 134.78;134.48	
17	87.62	83.00	74.11	78.70	61.55	149.36	158.77	97.83	138.29	165.91;164.61	128.70;128.10;129.66;130.00; 128.58;129.86;128.82;130.12; 134.06;133.47;132.29;145.96	21.67
18	87.99	74.36	78.96	83.11	61.53	148.22	159.00	141.00	123.40	166.00;164.65	128.75;128.15;129.58;130.22; 128.54;129.89;128.86;130.15; 134.28;133.77;132.29;146.08	21.74
19	87.87	83.00	74.12	78.77	61.60	149.53	159.73	69.32	143.43	165.98;164.62	130.90;130.17;129.18;130.16; 129.24;129.88;128.82;130.24; 134.14;133.23;132.29;146.04	21.76
26	89.69	78.45	71.41	81.46	61.97	159.62	166.56	107.94	135.09	165.68;164.97	127.99;128.73;128.46;129.15; 129.64;127.87;134.09;133.82	
28	89.44	81.29	78.49	82.64	61.99	160.38	167.77	71.40	140.12	165.86;164.39	129.94;129.15;129.73;127.99; 128.77;128.53;134.14;133.42	
32	85.45	77.29	76.40	77.74	62.91	151.18	162.71	100.54	163.07	166.36;166.01; 170.54	128.42;128.35;129.16;129.45 130.31;130.46;133.81;133.31	18.81

* Spectra of compounds **5—7**, **17—19**, **26**, **28** and **32** were recorded in $CDCl_3$, **10—16** and **33**, in DMSO-d_6.

MeONa and left at 20 °C for 24 h. The reaction mixture was neutralized with the cation-exchange resin KU-2-0.8 which had been prewashed with MeOH. The mixture was then filtered and the resin was washed with MeOH (2×20 mL). After the addition of 10 g of silica gel, the combined filtrate was evaporated to dryness *in vacuo*. Silica gel was transferred to a column and eluted with $CHCl_3$ (100 mL) and then with $CHCl_3/CH_3OH$ (85/15). Fractions containing nucleoside were concentrated *in vacuo*. In the case of compound **8**, after treating the reaction mixture with cation-exchange resin the combined filtrates were evaporated to dryness in vacuo and the residue was crystallized from ethanol.

Deacetylation of compounds (4—6). 10 mmol of compound **4—6** was heated for 18 h at 75 °C in 35 mL of acetonitrile and 5.5 mL of 1 *M* aqueous H_2SO_4. After cooling to 20 °C the reaction mixture was treated with Na_2CO_3, filtered, and concentrated to dryness under reduced pressure at 40 °C. Water and ethyl acetate were added to the residue, and the organic layer was washed with 5 % aqueous $NaHCO_3$ and water. The solvent was evaporated to dryness at 40 °C and the residue was recrystallized from $CHCl_3$ (15 mL) with the addition of 0.5—1 mL of water. After drying *in vacuo* at 40 °C the corresponding dibenzoates **14—16** were obtained.

Synthesis of tosylates (17—19). 3 mmol of compound **14—16** was dissolved in 16 mL of dry pyridine, 2.95 g (15 mmol) of toluene-*p*-sulfonyl chloride was added in three portions, and the reaction mixture was left for 24 h at 20 °C. Then the mixture was diluted with 10 mL of 50 % aqueous pyridine with ice cooling. The product was extracted with $CHCl_3$. The organic layer was washed with H_2O, 5 % aqueous $NaHCO_3$, and water, and dried with Na_2SO_4. After evaporating the solvent *in vacuo* at 30 °C the residue was chromatographed on a silica gel column (eluent, $CHCl_3$).

Synthesis of 2,2′-anhydro-1-(3,5-di-O-benzoyl-β-*D*-lyxofuranosyl)-5-halouracils (26—28). 2 mmol of tosylate **17—19** was refluxed for 39 h with 1.2 g (8 mmol) of NaI in 10 mL of 1,2-dimethoxyethane. The solvent was evaporated under reduced pressure, the residue was extracted with CH_2Cl_2 and filtered off, and the precipitate was washed with CH_2Cl_2 (2×20 mL). The combined filtrates were washed with water, 5 % aqueous sodium thiosulfate, and water, and dried with Na_2SO_4. After removing the solvent, the residue was chromatographed on a silica gel column (eluent, $CHCl_3$).

Synthesis of 2,2′-anhydro-1-β-*D*-lyxofuranosylpyrimidines

(29—31). 1 mmol of compound **26—28** was dissolved in 15 mL of 0.1 *N* MeONa in MeOH and left for 24 h. The precipitated white crystals were filtered off, washed with MeOH (2×1 mL), and dried *in vacuo*.

The results of elemental analysis of compounds **2—33** are consistent with the calculated data. Spectral characteristics of compounds **2**, **3**, **8**, **9**, **20—25** were reported in ref. 10.

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