Tetrahedron Vol. 49, No. 34, pp. 7579-7592, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

Synthesis of some Novel 1-(5-Thio-β-D-xylopyranosyl)-lumazine and -pyrimidine Nucleosides

Najim A. Al-Masoudi[a)]* and Wolfgang Pfleiderer[b)]

a) Dept. of Chemistry, College of Science, University of Basrah, Basrah / Iraq;

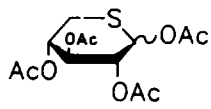
b) Fakultät für Chemie, Universität Konstanz, Postfach 5560, D-7750 Konstanz / Germany.

(*Received in UK* 27 *November* 1991; *accepted* 2 *July* 1993)

Abstract: 1,2,3,4-Tetra-O-acetyl-5-thio-D-xylopyranose (1) reacts with the silylated lumazine bases (2-5) under trimethylsilyl trifluoromethylsulfonate catalysis to give the nucleosides 6, 8, 10, and 12 respectively, which face deblocking with potassium carbonate in dry methanol to yield the free nucleosides 7, 9, 11, and 13 respectively. The synthesis of 1-(2,3,4-tri-O-acetyl-5-thio-β-xylopyranosyl)-thymine (17) and its free nucleoside 18 have been improved and in a similar manner reacted the silylated pyrimidine bases 15 and 16 to the 5-iodo- (19) and 5-fluoro- (21) analogues. Deacylation afforded the free nucleosides 20 and 22, respectively.

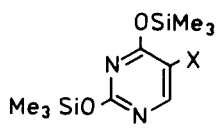
Introduction

Several nucleosides have been proven to be effective against viral infections. For AIDS, 3'-azido-3'-deoxy-thymidine (AZT)[1] is so far the only approved drug on the market to treat HIV-1 infected patients chemotherapeutically. Recently, new types of 2',3'-dideoxy[2-4] and 2',3'-didehydro-2',3'-dideoxynucleosides[5-9] have been reported among the most potent and selective inhibitors of HIV-1 replication in vitro. Likewise, various 3'-fluoro-2',3'-dideoxy nucleosides[10-18] were discovered to be effective and selective anti-HIV agents. The structural similarity between lumazine-N-1 nucleosides[19-21] and the pyrimidine nucleosides prompted us to synthesize a novel type of lumazine nucleosides carrying a thio-sugar moiety as the striking structural feature. Examination of the literature revealed that few examples of thio-sugar nucleosides have been reported[22,23], among which the 4-thio-β-D- and β-L-ribofuranosyl[23], 4-thio-β-D-xylofuranosyl[24], and 4-thio-β-D-arabinofuranosyl adenines[24] and some 4-thio-D-ribofuranosyl- and 5-thio-β-D-xylopyranosylpyrimidine nucleosides[25] are the best-known representatives. Recently some complex thiosugar-nucleosides have been discovered, of which the albomycine antibiotics[26,27] contain as a sub-unit the 6-amino-6-deoxy-4-thio-L-glycero-α-L-idoheptyfuranoronic acid moiety. We have concentrated our efforts on the glycosylation reactions of various pyrimidines and lumazines with



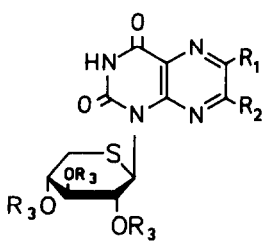
(1)

	R_1	R_2
2	H	p-Cl-C_6H_4
3	p-Cl-C_6H_4	H
4	H	p-Br-C_6H_4
5	p-Br-C_6H_4	H

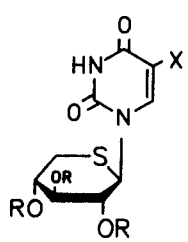


	X
14	CH_3
15	I
16	F

$CF_3SO_3SiMe_3$ / $ClCH_2CH_2Cl$



$CF_3SO_3SiMe_3$ / $ClCH_2CH_2Cl$



	R_1	R_2	R_3
6	H	p-Cl-C_6H_4	Ac
7	H	p-Cl-C_6H_4	H
8	p-Cl-C_6H_4	H	Ac
9	p-Cl-C_6H_4	H	H
10	H	p-Br-C_6H_4	Ac
11	H	p-Br-C_6H_4	H
12	p-Br-C_6H_4	H	Ac
13	p-Br-C_6H_4	H	H

	X	R
17	CH_3	Ac
18	CH_3	H
19	I	Ac
20	I	H
21	F	Ac
22	F	H

1,2,3,4-tetra-O-acetyl-5-thio-D-xylose[28,29] as promising new biologically active nucleosides.

Results and Discussion

5-Thio-D-xylose[28,30] was the first sulphur-in-ring pentose to be synthesized and encountered dome biological interest as a xylodase inhibitor[31]. Its synthetic availability prompted us to use this thio-sugar as a starting material in glycosylation reactions of the Hilbert-Johnson-Birkofer type[32]. Thus trimethylsilylated derivatives of 6- and 7-p-chloro- and p-bromophenyl-lumazines (2-5) respectively were condensed with 1,2,3,4-tetra-O-acetyl-5-thio-D-xylopyranose (1) in presence of trimethylsilyl trifluoromethylsulfonate as catalyst[33] and 1,2-dichloroethane as solvent. The reaction proceeded well at room temperature to give the crystalline 6- and 7-p-chloro- and p-bromophenyl-1-(2,3,4-tri-O-acetyl-5-thio-β-D-xylopyranosyl)-lumazines (6, 8, 10, 12) in yields of 21-40 %. Deacetylation to the free nucleosides (7, 9, 11, 13) was achieved by transesterification in MeOH in presence of catalytic amounts of potassium carbonate.

The structures of the newly synthesized lumazine nucleosides were determined on the basis of their UV and ^{1}H-NMR spectra. The UV spectra are very similar to those of the 6- and 7-chlorophenyl-1-(β-D-ribofuranosyl)-lumazines[19]. The small bathochromic shift of the spectra on anion formation at pH 13 indicates that the site of attachment of the sugar moiety is undoubtedly the N-1 atom.

Table 1 - Physical Data of Lumazine and Pyrimidine 5'-Thio-β-D-xylopyranosides

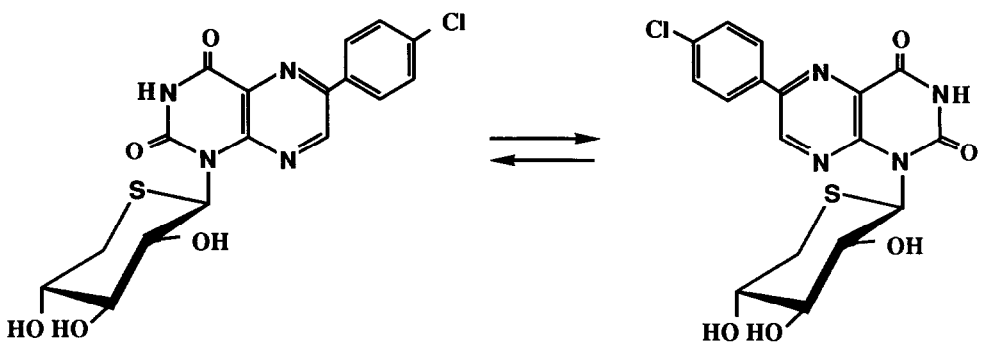
Compound	UV-Absorption Spectra in MeOH						Compound	UV-Absorption Spectra in MeOH				
	λ_{max} (nm)			lg ε				λ_{max} (nm)		lg ε		
6	217	280	351	4.11	4.46	3.98	17	214	266	3.93	4.04	
7	[217]	281	254	[4.14]	4.44	3.95	18	[215]	267	[4.50]	4.00	
8	[218]	281	352	[4.18]	4.44	3.96	19	213	282	4.15	3.99	
9	[217]	282	354	[4.16]	4.41	3.94	20	210	284	4.17	3.92	
10	[219]	283	353	[4.14]	4.52	4.00	21	206	266	4.09	4.02	
11	[218]	281	350	[4.11]	4.50	3.97	22	208	269	4.09	4.02	
12	[218]	280	354	[4.13]	4.42	3.98						
13	[219]	282	353	[4.18]	4.43	3.96						

Table 2 - ^{1}H-NMR Data of Lumazine-5'-thio-β-D-xylopyranosides in D_6-DMSO

Compound	N-H	H-C(1') $J_{1',2'}$	H-C(2') $J_{2',3'}$	H-C(3') $J_{3',4'}$	h-C(4') $J_{4',5'}$	H-C(5') $J_{4',5''}$	H-C(5'') $J_{5',5''}$	6-Subst.	7-Subst.	Acetyl
6 a	12.24s	6.73d 10.0	6.33t 9.5	5.29dd 9.5	5.04m 9.8	3.40dd 5.5	2.97dd 12.5	9.52s	8.24d 7.68d	2.01 1.98, 1.76
b	12.11s	6.43d 10.4	6.05t 9.1					9.39s	8.20d 7.62d	2.01 1.96, 1.68
120°	11.60s	6.50d 9.0	5.21t 9.5	5.18dd 10.0	5.10dd 10.0	3.13		9.34s	8.18d 7.60d	2.02, 2.01 1.81
7 a	12.14s	6.13d 9.8	4.57t	3.58	2.98t 9.0	2.78dd 5.5	2.54dd 10.0	9.42s	8.19d 7.64d	
b	12.14s	5.96d 9.8	4.43t 9.4					9.35s	8.15d 7.60d	
120°	11.55s	6.03d 9.0	4.50m	3.52m	3.12dd 10.0	2.78dd 5.0	2.65dd 11.0	9.25s	8.18d 7.58d	
8 a	12.24s	6.73d 10.4	6.33t 9.6	5.28dd 9.3	5.05m 10.0	3.37dd 4.0	2.96dd 13.0	8.26d 7.65d	9.25s	2.01 1.95, 1.76
b	12.12s	6.43d 10.4	6.06t 9.5					8.19d 7.62d	9.39s	2.01 1.93, 1.67
120°	11.75s	6.59d 9.5	6.17t 9.5	5.21t 9.8	5.06dt 10.0	3.11		8.20d 7.63d	9.29s	2.01, 1.97 1.69
9 a	12.11s	6.13d 9.8	4.56t	3.56m	3.02m	2.74dd 4.8	2.62dd 11.0	8.21d 7.64d	9.42s	
b	12.09s	5.73d 9.5	4.38t 9.4					8.18d 7.61d	9.40s	
120°	11.61s	6.02d 9.0	4.54m	3.57m	3.08dd 10.0	2.77dd 5.0	2.66dd 12.0	8.16d 7.56d	9.28s	
10 a	12.15s	6.65d 9.7	6.31d 9.5	5.24dd 9.5	5.19m 9.3	3.28dd 5.0	3.01dd 13.0	9.61s	8.19d 7.59d	2.03 2.02, 1.86
b	12.02s	6.52d 10.0	6.11d 9.5					9.34s	8.17d 7.54d	2.82, 2.02 1.97, 1.71
120°	11.60s	6.59d 9.3	6.12t 9.2	5.26dd 9.0	5.09dd 9.2	3.48-3.10m		9.31s	8.16d 7.54d	2.03 1.98, 1.85
11 a	12.08s	6.21d 9.5	4.72t 9.0			3.11-2.78m		9.47s	8.28d 7.79d	
b	13.04s	6.01d 9.0	4.53t 9.0					9.42s	8.27d 7.77d	
120°	11.32s	6.18d 9.2	4.69t 9.2	3.69m	3.05dd 9.8	2.80-2.62m		9.34s	8.26d 7.78d	
12 a	12.23s	6.72d 10.3	6.39t 9.5	5.31dd 9.4	5.02dd 9.0	3.24m 3.4	2.89dd 13.0	8.20d 7.60d	9.63s	2.05 1.95, 1.73
b	12.12s	6.42d 10.3	6.09t 9.7					8.14d 7.57d	9.39s	1.98 1.95, 1.65
120°	12.19s	6.56d 10.2	6.14t 9.5	5.29t 9.5	5.01dd 9.5	3.19m		8.15d 7.54d	9.49s	2.02 1.95, 1.71
13 a	12.12s	6.17d 9.8	4.59t	3.54m	3.19m	2.98dd 5.3	2.71dd 11.5	8.15d 7.69d	9.42s	
b		5.79d 9.2	4.41t 9.5					8.16d 7.74d	9.40s	
120°	12.09s	5.98d 9.0	4.49m	3.56m	3.27dd 9.5	2.99dd 6.0	2.78dd 12.5	8.13d 7.72d	9.27s	

a and b = syn- and anticonformers measure at 20°C; s = singlet; d = doublet; dd = doublet of doublet; t = triplet; dt = doublet of triplet; m = multiplet.

The ^{1}H-NMR spectra taken at room temp. (table 2) revealed complex patterns, which are best explained as compositions of mixtures of syn- and anti-rotamers. This phenomenom has already been recognized and identified in the lumazine- and isopterin-ß-D-glucopyranosides series[34,35] some time ago showing especially the H-1' signals as two doublets $J_{1',2'}$ = 9.5-10.4 Hz) in the region of δ 6.13-6.72.



At higher temperatures coalescence takes place and at 120° the time-averaged spectra were obtained, which are in full agreement with the proposed structures. The large coupling constants between H-1', H-2', H-3', H-4', and H-5' prove the $^4C_1$ conformation of the sugar moiety as well as the ß-configuration of the glycoside linkage in these molecules.

A similar series of reactions was performed with three different uracils. Thus, a solution of 1,2,3,4-tetra-O-acetyl-5-thio-D-xylopyranose (1) in dry dichloroethane was boiled with the trimethylsilylated uracils (14-16) under trimethylsilyl triflate catalysis[33] to produce the ß-anomeric nucleosides 17, 19, and 21 in yields of 50, 52, and 46 %, respectively. These reactions are thermodynamically controlled and form by neighbouring participation of the 2-O-acetyl group almost exclusively the ß-anomers. Deacetylation worked best with potassium carbonate in dry methanol at room temperature to give the known free nucleoside 18 in 82 % yield[25] and 20 and 22 in 76 and 50 % yield, respectively. The UV spectra (Table 1) of these compounds coincide with their ribofuranoside counterparts proving the N-1 substitution. The ^{1}H-NMR spectra (Table 3) can be considered as an additional structural characterization, since they all showed a close pattern of signals. The large coupling constant ($J_{1',2'}$ ∿

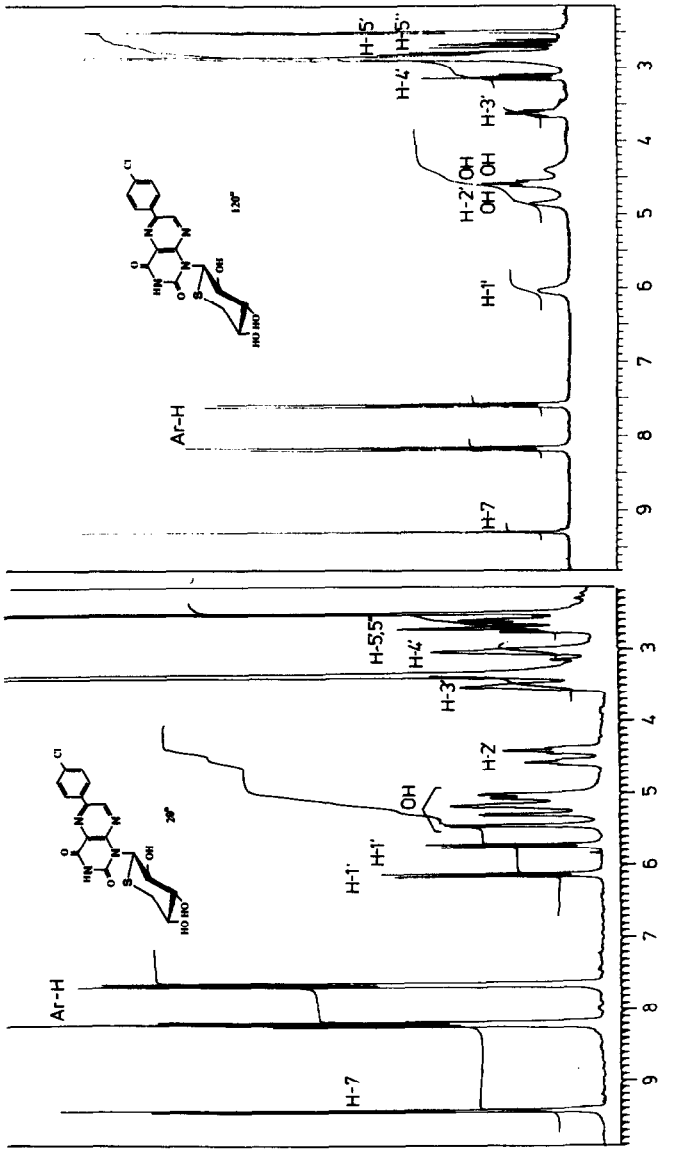

H-7
Ar-H
H-1'
H-1''
OH
H-2'
H-3'
H-4'
H-5,5''
H-7
Ar-H
H-1''
OH
OH
H-2''
H-3'
H-4'
H-5'
H-5''

Table 3 - ^{1}H-NMR Data of Uracil-5'-thio-β-D-xylopyranosides in $CDCl_3$* or D_6-DMSO

Compound	N-H	H-C(1')	H-C(2')	H-C(3')	H-C(4')	H-C(5')	H-C(5")	5-Subst.	6-Subst.	Acetyl or OH Groups		
		$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'}$	$J_{4',5"}$	$J_{5',5"}$					
17*	8.93s	5.85d 10.7	5.38t 9.15	5.22t 9.46	5.08m 10.4	2.99dd 4.8	2.89dd 13.5	1.94s	7.27s	2.06	2.03	1.96
18	11.33s	5.39d 5.2	5.32m 9.0	3.07m	3.43m	2.62m		1.77s	7.51s	5.19	5.13	3.67
19*	8.67s	5.79d 10.0	5.33t 9.6	5.22t 9.5	5.08m 10.4	3.02dd	2.89dd		7.75s	2.06	2.03	1.98
20	11.80s	5.51d 5.20	5.32m	3.08t 11.6	3.46m	2.75m			8.02s	5.50	5.10	3.75
21*	8.58s	5.81d 11.8	5.31t 9.5	5.22t 9.5	5.07m 9.4	3.01dd 3.6	2.89dd 13.8		7.41d 5.5	2.06	2.04	1.99
22	11.64s	5.51d	5.42m	3.05t 8.5	3.44m	2.64m			8.08d 7.0	5.43	5.15	3.70

s = singlet; d = doublet; dd = doublet of doublet; t = triplet, m = multiplet.

11.0 Hz) revealed the β-configuration of the N-1 nucleosides, whereas the large values of $J_{2',3'}$, and $J_{4',5'}$ (∿ 9-11 Hz) in 18, 20, and 22 are consistent with the $^4C_1$ conformation of the sugar moiety. The anomeric protons in the free nucleosides showed some decreased $J_{1',2'}$ values (∿ 5.20 Hz), which may reflect a less rigid chair conformation of the sugar part.

EXPERIMENTAL PART

The melting points were taken on a Büchi apparatus, model Dr. Tottoli, not corrected. The UV spectra were recorded on a spectrometer of Applied Physics Corp., model 118. ^{1}H-NMR spectra were determined in a Bruker WM-250 and Bruker AM-250: δ in ppm relative to TMS. TLC: precoated silica-gel thin layer sheets F 1500 LS 254 from Schleicher & Schüll. Prep. TLC: silica-gel 60 F_{254} (Merck). Column chromatography: silica-gel Merck 60 (0.063-0.2 mesh).

1,2,3,4-Tetra-O-acetyl-5-thio-D-xylopyranose (1). - This compound was prepared according to the procedure of Adely and Owen.[28] A mixture of 1,2-O-isopropylidene-5-O-tosyl-α-D-xylofuranose (11.5 g; 0.05 mole) in DMF (200 ml) containing potassium thioacetate (11.4 g; 0.1 mole) was heated at 100°C for 4.5 h under N_2. The mixture was cooled and evaporated to dryness. The residue was partitioned between $CHCl_3$ and H_2O, the organic extract dried (Na_2SO_4), filtered and evaporated to dryness to give mainly 1,2-O-isopropylidene-5-thioacetyl-α-D-xylofuranose and some of the 3-O-acetyl analogue (7.0 g). This mixture was dissolved in MeOH (100 ml), sodium methoxide (1 g) added and heated under reflux for 1 h under N_2. The solution was then evaporated to dryness to give the 1,2-O-isopropylidin-5-thio-5-deoxy-α-D-xylofuranose (4.5 g, 72 %), m.p. 79-81°, reported[28] 80-82°C, in addition to a small quantity of the corresponding disulfide compound. The free thio sugar was obtained by hydrolysis with 0.05 N H_2SO_4 (50 ml) on boiling under N_2 for 1 h. The mixture was neutralized with Amberlite IR-4S (OH^-) resin, filtered and evaporated to dryness to give the 5-thio-D-xylose (3 g, 83 %), m.p. 129-129°C (from EtOH/H_2O); lit.[28] 122-123°C. The 5-thio-D-xylose was acetylated in the normal way to give the tetraacetate 1 (5.5 g, 91 %), which was used directly for the glycosylation reactions.

7-(p-Chlorophenyl)-1-(2,3,4-tri-O-acetyl-5-thio-β-D-xylopyranosyl)-lumazine (6). - 7-(p-Chlorophenyl)-lumazine (1.0 g, 3.6 mmole) was heated under reflux in hexamethyldisilazane (HMDS) (20 ml) in the presence of a few crystals of ammonium sulfate for 24 h to afford 7-(p-chlorophenyl)-2,4-(trimethylsilyl-oxy)-pteridine 2. The HMDS was evaporated to dry-

ness and the residue was dissolved in dry CH_2Cl_2 (25 ml). A solution of 5-thio-D-xylose tetraacetate (1) (0.7 g, 2.09 mmole) in dry CH_2Cl_2 (20 ml) was added, followed by dropwise addition of the catalyst trimethylsilyl trilfuoromethanesulfonate (0.6 ml). The reaction mixture was stirred at room temperature for 7 h and then treated with an aqueous solution of $NaHCO_3$ for neutralization. The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness to give a yellowish amorphous solid (0.95 g). The product was dissolved in a small volume of $CHCl_3$ and passed through a silica-gel column (50 g) in $CHCl_3$/MeOH 99:1. The main fraction was evaporated and the residue recrystallized from $CHCl_3$/hexane to give the pure nucleoside 6 (found: C 49.84; H 3.80; N 9.69. $C_{25}H_{21}ClN_4O_8S$ (348.9) requires: C 50.34; H 3.85; N 10.20 %) as colorless crystals; m.p. 265-266°; yield 0.24 g (40 %).

7-p-Chlorophenyl-1-(5-thio-β-D-xylopyranosyl (7). - A solution of 6 (130 mg, 0.23 mmole) in abs. MeOH (30 ml) and a catalytic amount of potassium carbonate (62 mg) was stirred at room temperature for 20 h. The solid (70 mg) was filtered off, dissolved in hot H_2O and neutralized with dil. acetic acid to pH 5 to give the free nucleoside 7 (found: C 46.00; H 3.65; N 12.29. $C_{17}H_{15}ClN_4O_5S$. (H_2O) (440.8) requires: C 46.31; H 3.88; N 12.71 %) as colorless crystals; m.p. 297°C (decomp.); yield 60 mg (65 %).

6-(p-Chlorophenyl)-1-(2,3,4-tri-O-acetyl-5-thio-β-D-xylopyranosyl)-lumazine (8). - A solution of 6-(p-chlorophenyl)-lumazine (1 g, 3.6 mmole) in hexamethyldisilazane (25 ml) was heated under reflux for 28 h with a catalytic amount of ammonium sulfate and then evaporated to dryness. The residue (3) was dissolved in CH_2Cl_2 (20 ml) and then united with a solution of the thio sugar 1 (0.9 g, 2.7 mmole) in dry CH_2Cl_2 (20 ml). The mixture was stirred with the triflate catalyst (1.0 ml) for 6 h at room temperature. After working up in the usual manner a brown solid (1.23 g) was obtained. The product was purified by chromatography on a column of silica-gel (50 g) and elution with $CHCl_3$/MeOH (99:1) gave 8 (0.7 g). Reprecipitation from $CHCl_3$/n-hexane led to a pure sample (found: C 50.37; H 3.95; N 9.99. $C_{23}H_{21}ClN_4O_8S$ (548.9) requires: C 50.34; H 3.84; N 10.20 %) as colorless powder; m.p. 235-239°; yield 0.6 g (40 %).

6-p-Chlorophenyl-1-(5-thio-β-D-xylopyranosyl)-lumazine (9). - The nucleoside 8 (210 mg, 0.38 mmole) in abs. MeOH (35 ml) was stirred with K_2CO_3 (100 mg) at room temperature for 20 h. Evaporation to dryness, solution in hot H_2O, and neutralization by AcOH to pH 5 afforded 9 (found: C 44.29; H 4.41; N 11.52. $C_{17}H_{15}ClN_4O_5S$. 1/2 H_2O (439.5) requires: C 44.49; H 4.12; N 12.20 %) as a colorless powder; m.p. 290°C (decomp.);

yield 0.11 g (67 %).

7-(p-Bromophenyl)-1-(2,3,4-tri-O-acetyl-5-thio-β-D-xylopyranosyl)-lumazine (10). - 7-(p-Bromophenyl)-lumazine (1.0 g, 4.09 mmole) was trimethylsilylated to give 7-(p-bromophenyl)-2,4-bis(trimethylsilyloxy)-pteridine (4) in the usual manner. A solution of sugar 1 (0.6 g, 1.79 mmole) in dry 1,2-dichloroethane 825 ml) was added to a stirred solution of compound 4 in dry $ClCH_2CH_2Cl$ (20 ml) at room tmeperature followed by dropwise addition of the triflate catalyst (0.7 ml). The reaction mixture was stirred for 24 h and then worked up as usual to give a mixture of products (0.79 g), which was separated by column chromatography on silicagel (50 g) with $CHCl_3$/MeOH 99:1 to give compound 10 (found: C 96.21; H 3.32; N 9.00. $C_{23}H_{21}BrN_4O_8S$ (593.4) requires: C 46.55; H 3.56; N 9.44 %) as colorless crystals from $CHCl_3$/hexane; m.p. 177-181°C; yield 0.32 g (30 %).

7-p-Bromophenyl-1-(5-thio-β-D-xylopyranosyl)-lumazine (11). - The nucleoside 10 (200 mg, 0.33 mmole) was stirred at room temperature with abs. MeOH (30 ml) containing potassium carbonate (100 mg) for 20 h. The solvent was evaporated to dryness, the residue was dissolved in hot H_2O and then neutralized with AcOH to pH 5 to give compound 11 (found: C 41.80; H 3.30; N 11.19. $C_{17}H_{15}BrN_4O_5S \cdot H_2O$ (485.3) requires: C 42.07; H 3.53; N 11.54 %) as a colorless solid; m.p. 292°C (decomp.); yield 0.1 g (60 %).

6-(p-Bromophenyl)-1-(2,3,4-tri-O-acetyl-5-thio-β-D-xylopyranosyl)-lumazine (12). - 6-(p-Bromophenyl)-lumazine (0.8 g, 2.18 mmole) was trimethylsilylated to give compound 5, which was dissolved after evaporation to a sirup in dry $ClCH_2CH_2Cl$ (20 ml). A solution of the sugar 1 (0.6 g, 1.79 mmole) in the same solvent was added, followed by dropwise addition of trimethylsilyl trifluoromethanesulfonate (0.6 ml). The reaction mixture was stirred at room temperature for 48 h and then partitioned with a dilute solution of $NaHCO_3$. The organic extract was dried (Na_2SO_4), filtered and evaporated to dryness to give a crude product (1 g). This material was dissolved in $CHCl_3$ and passed through column of silica (70 g) by elution with $CHCl_3$/MeOH (00:1) to give the nucleoside 12 (0.32 g). Reprecipitation from $CHCl_3$/n-hexane gave pure 12 (found: C 46.11; H 3.69; N 9.34. $C_{23}H_{21}BrN_4O_8S$ (593.4) requires: C 46.55; H 3.56; N 9.44 %) as a colorless powder; m.p. 165-167°C; yield 0.28 g (26 %).

6-p-Bromophenyl-1-(5-thio-β-D-xylopyranosyl)-lumazine (13). - A solution of the nucleoside 12 (215 mg, 0.39 mmole) in abs. MeOH (35 ml) containing potassium carbonate (102 mg) was stirred at room temperature for 20 h. The solution was evaporated to dryness, the residue dissolved in hot H_2O, and AcOH added till pH 5 to give 13 (found: C 40.22; H 3.84;

N 10.94. $C_{17}H_{15}BrN_4O_5S$. 2 H_2O (503.3) requires: C 40.56; H 3.81; N 11.13 %) as a colorless solid; m.p. 280°C (decomp.): yield 0.147 g (80 %).

1-(2,3,4-Tri-O-acetyl-5-thio-β-D-xylopyranosyl)-thymidine (17). - Thymine (0.5 g, 3.9 mmole) was heated under reflux in HMDS (25 ml) in the presence of a few crystals of ammonium sulfate for 18 h. It was evaporated in vacuo to a sirup, which was dissolved in abs. $ClCH_2CH_2Cl$ (30 ml), then united with a solution of the sugar 1 (1.0 g, 2.99 mmole) in abs. $ClCH_2CH_2Cl$ (30 ml) and followed by the addition of the triflate catalyst (1.2 ml). After refluxing for 3.5 h, the solution was partitioned with a diluted solution of $NaHCO_3$, the organic extract was dried (Na_2SO_4), filtered and evaporated to dryness to give a solid product (0.69 g). The product was treated with hot ether, filtered off, to give the nucleoside 17 (found: C 47.97; H 5.04; N 7.04. $C_{16}H_{20}N_2O_8$ (400.4) requires: C 47.99; H 5.03; N 6.99 %) as a colorless solid; m.p. 145-150°C; yield 0.59 g (50 %).

1-(5-Thio-β-D-xylopyranosyl)-thymidine (18). - A solution of the nucleoside 17 (200 mg, 0.5 mmole) in abs. MeOH (20 ml) saturated by ammonia was kept at room temperature for 16 h with stirring. The solution was evaporated, the residue dissolved in MeOH, then acidified by AcOH, again evaporated and then the solid neutralized with HAc and the solution recrystallized from MeOH to give compound 18 (found: C 43.52; H 5.18; N 10.03. $C_{10}H_{14}N_2O_5S$ (274.2) requires: C 43.79; H 5.14; N 10.21 %) as colorless crystals; m.p. 296-298°C (decomp.); yield 0.112 g (82 %).

5-Iodo-1-(2,3,4-tri-O-acetyl-5-thio-β-D-xylopyranosyl)-uracil (19). - 5-Iodouracil (1.0 g, 4.2 mmole) was heated under reflux for 20 h in HMDS (30 ml) with a catalytic amount of $(NH_4)_2SO_4$. It was then evaporated in vacuo to give a sirup (15), which was dissolved in abs. $ClCH_2CH_2Cl$ (20 ml). A solution of the sugar 1 (1.0 g, 2.99 mmole) in the same solvent (20 ml) was added with stirring, followed by dropwise addition of the triflate catalyst (1.2 ml). The reaction mixture was heated under reflux for 6 h, then treated with dilute solution of $NaHCO_3$. The organic extract was dried (Na_2SO_4), filtered and evaporated to dryness. The residue was coevaporated several times with ether, then with n-hexane to give the chromatographically pure nucleoside 19 (found: C 35.38; H 3.35; N 5.62. $C_{15}H_{17}IN_2O_8S$ (512.2) requires: C 35.17; H 3.31; N 5.47 %) as a colorless solid; m.p. 137-139°C; yield 0.79 g (52 %).

5-Iodo-1-(5-thio-β-D-xylopyranosyl)-uracil (20). - The nucleoside 19 (0.65 g, 1.2 mmole) in 16 % methanolic ammonia (20 ml) was kept at room temperature over night. The solution was evaporated to a small volume, neutralized with AcOH and evaporated to give a crude solid (0.54 g).

Recrystallization from MeOH gave pure 20 (found: C 27.97; H 3.01; N 7.34. $C_9H_{11}IN_2O_5S$ (386.6) requires: C 27.99; H 2.87; N 7.25 %) as colorless crystals; m.p. 268-270°C; yield 0.32 g (76 %).

5-Fluoro-1-(2,3,4-tri-O-acetyl-5-thio-β-D-xylopyranosyl)-uracil (21). A solution of 5-fluorouracil (0.5 g, 3.8 mmole) in HMDS (25 ml) was heated under reflux for 18 h in the presence of a catalytic amount of $(NH_4)_2SO_4$. Evaporation of HMDS gave the silylated product 16, which was dissolved with the sugar 1 (1.0 g, 2.99 mmole) in dry $ClCH_2CH_2Cl$ (40 ml), and then the triflate catalyst (1.0 ml) was added dropwise. After reflux for 5 h the reaction mixture was treated with dilute $NaHCO_3$ solution, the organic layer dried (Na_2SO_4), evaporated and the residue refluxed in ether to give compound 21 (found: C 41.74; H 4.25; N 6.96. $C_{15}H_{17}FN_2O_8S$ (404.3) requires: C 44.55; H 4.24; N 6.92 %) as a colorless solid; m.p. 230-232°C; yield 0.56 g (46 %).

5-Fluoro-1-(5-thio-β-D-xylopyranosyl)-uracil (22). - The nucleoside 21 (0.22 g, 0.54 mmole) in abs. MeOH (30 ml) and K_2CO_3 (143 mg) were stirred at room temperature for 20 h. The solvent was evaporated, the residue dissolved in H_2O and neutralized with AcOH to pH 5 to give a brownish crystalline product (0.1 g). This material was stirred with ether for 20 h, filtered and dried to give 22 (found: C 36.24; H 4.33; N 8.94. $C_9H_{11}FN_2O_5S \cdot H_2O$ (278.2) requires: C 36.48; H 4.77; N 9.45 %) as a pale brownish solid; m.p. 260-263°C; yield 75 mg (50 %).

Acknowledgement

We thank the Alexander von Humboldt Foundation for a fellowship, the Fonds der Chemischen Industrie for financial support, and Mr. Krienitz for the measurements of the ^{1}H-NMR spectra at different temperatures.

REFERENCES

1. Mitsuya, H.; Weinhold, K.T.; Furman, P.A.; St.Clair, M.; Nusinoff-Lehrmann, S.; Gallo, R.C.; Bolognesti, D.; Bany, D.W.; Broder, S. Proc. Natl. Acad. Sci. USA 1985, 83, 7096.
2. Mitsuya, H.; Broder, S. Proc. Natl. Acad Sci. USA 1986, 83, 1911.
3. Baba, M.; Pauwels, R.; Herdewijn, P.; DeClercq, E.; Desmyter, J.; Vandeputte, M. Biochem. Biophys. Res. Commun. 1987, 142, 128.
4. Fiandor, J.; Huryn, D.M.; Sluboski, B.; Todaro, C.J.; Tamm, S. Nucleosides & Nucleotides 1989, 8, 1107.
5. Vial, J.M.; Agback, P.; Chattopadhyaya, J. Nucleosides & Nucleotides 1990, 9, 245.

6. Lin, T.S.; Yang, J.H.; Gao, Y.S. Nucleosides & Nucleotides 1990, 9, 97.
7. Martin, J.C.; Mansuri, M.M.; Starrett, J.E.; Sommadossi, J.P.; Brankovan, V.; Ghazzouli, I.; Ho, H.T.; Hitchcock, Michael J.M. Nucleosides & Nucleotides 1989, 8, 841.
8. Vince, R.; Hua, M.; Brownell, J.; Lavelle, G.C.; Qualls, J.; Shannon, W.M. Nucleosides & Nucleotides 1989, 8, 1127.
9. Balzarini, J.; Pauwels, R.; Herdewijn, P.; DeClercq, E.; Coney, D.A.; Kang, G.J.; Dalal, M.; Joh, D.G.; Broder, S. Biochem. Biophys. Res. Commun. 1986, 140, 735.
10. Van Aerschot, A.; Balzarini, J.; Pauwels, R.; Kerremans, C.; DeClercq, E.; Herdewijn, P. Nucleosides & Nucleotides 1989, 8, 1121.
11. Van Aerschot, A.; Balzarini, J.; DeClercq, E.; Herdewijn, P. Nucleosides & Nucleotides 1989, 8, 1123.
12. Van Aerschot, A.; Balzarini, J.; Pauwels, R.; Widernick, P.; DeClercq, E.; Herdewijn, P. Nucleosides & Nucleotides 1989, 8, 1125.
13. Sterzycki, R.; Mansuri, M.; Brankovan, V.; Buroker, R.; Ghazzouli, I.; Hitchcock, M.; Sommadossi, J.P.; Martin, J.C. Nucleosides & Nucleotides 1989, 8, 1115.
14. Kim, C.H.; Marquez, V.E.; Broder, S.; Mitsuya, H.; Driscoll, J. J. Med. Chem. 1987, 30, 862.
15. Baba, M.; Pauwels, R.; Herdewijn, P.; DeClercq, E.; Desmyter, J.; Vandeputte, M. Biochem. Biophys. Res. Commun. 1987, 142, 128.
16. Herdewijn, P.; Balzarini, J.; DeClercq, E.; Pauwels, R.; Baba, M.; Broder, S.; Vandeputte, M. J. Med. Chem. 1987, 30, 1270.
17. Herdewijn, P.; Balzarini, J.; Baba, M.; van Aerschot, A.; Jansen, C.; DeClercq, E. J. Med. Chem. 1988, 31, 2040.
18. Horwitz, J.P.; Chua, J.; Noel, M. J. Org. Chem. 1964, 29, 2976.
19. Al-Masoudi, N.A.; Pfleiderer, W. Nucleosides & Nucleotides 1989, 8, 1485.
20. Al-Masoudi, N.A.; Pfleiderer, W. Pteridines 1990, 2, 9.
21. Ritzmann, G.; Ienaga, K.; Pfleiderer, W. Liebigs Ann. Chem. 1977, 1217.
22. Bloch, A. Proc. Am. Assoc. Cancer Res. 1985, 6, 6.
23. Reist, E.J.; Gueffroy, D.E.; Goodman, L. J. Am. Chem. Soc. 1964, 86, 5658.
24. Reist, E.J.; Fischer, L.V.; Goodman, L. J. Org. Chem. 1968, 33, 189.
25. Urbas, B.; Whistler, R.L. J. Org. Chem. 1966, 31, 813.
26. Benz, G.; Born, L.; Brieden, M.; Grosser, R.; Kurz, J.; Paulsen, H.; Sinnwell, V.; Weber, B. Liebigs Ann. Chem. 1984, 1408.

27. Paulsen, H.; Brieden, M.; Benz, G. Liebigs Ann. Chem. 1987, 565.
28. Adley, T.J.; Owen, N.L. Proc. Chem. Soc. 1961, 418.
29. Whistler, R.L.; Feather, M.S.; Ingles, D.I. J. Am. Chem. Soc. 1962, 84, 122.
30. Schwarz, J.C.P.; Yule, K.C. Proc. Chem. Soc. 1961, 417.
31. Claeyssens, M.; De Bruyne, C.K. Naturwissenschaften 1965, 52, 515.
32. Birkofer, L.; Ritter, A. Angew. Chem. 1965, 77, 414.
33. Vorbrüggen, H.; Höfle, G. Chem. Ber. 1981, 114, 1256.
34. Jochims, J.C.; Pfleiderer, W.; Kobayashi, K.; Ritzmann, R.; Hutzenlaub, W. Chem. Ber. 1973, 106, 2975.
35. Pfleiderer, W.; Ritzmann, G.; Harzer, K.; Jochims, J.C. Chem. Ber. 1973, 106, 2982.