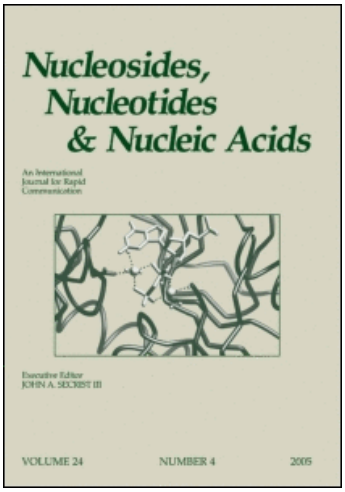

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Synthesis of Some Novel 1-(5-Thio-ß-D-glucopyranosyl)-6-azauracil Derivatives - Thiosugar Nucleosides

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SYNTHESIS OF SOME NOVEL 1-(5-THIO-β-D-GLUCOPYRANOSYL)-6-AZAURACIL DERIVATIVES - THIOSUGAR NUCLEOSIDES

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Abstract. The chemical syntheses of 1-(2,3,4,6-tetra-O-acetyl-5-thio-β-D-glucopyranosyl)-6-azauracil (4) and the 5-bromo analogue 6 are described. Deblocking of 4 and 6 with sodium methoxide afforded the free nucleosides 5 and 7, respetively. Treatment of 6 with benzylmercaptan in basic medium led to the formation of 6-benzylthio-1-((2,3,4,6-tetra-O-acetyl-5-thio-β-D-glucopyranosyl)-6-azauracil (8), in good yield, which was deblocked to 9 on treatment with sodium methoxide. Reaction of 6 with benzlamine gave 5-benzylamino-1-(5-thio-β-D-glucopyranosyl)-6-azauracil (10).

A great variety of nucleosides, in general, have been used among other compounds as broad spectrum antiviral, antibacterial, and antitumor agents[1]. Various nucleosides containing interchanged nitrogen and carbon atoms in their base moities have shown considerable activity as antimetabolic agents[2,3]. 6-Azauridine 5'-monophosphate[4-8], the first reported example containing a nitrogen atom in the 6-position, was found to act as a competitive inhibitor of orotidine 5'-

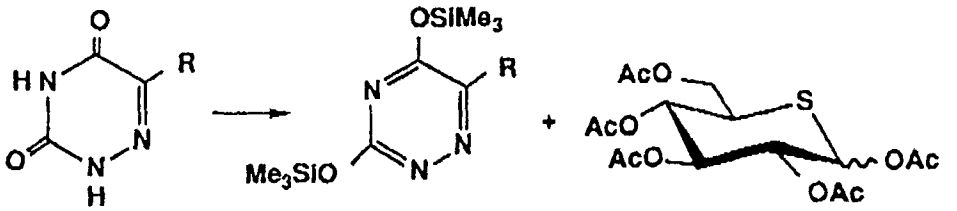
phosphate decarboxylase[10-12]. Furthermore the high reactivity at the ring carbon atoms led to the preparation of a number of 6-azauracil nucleoside derivatives[13-17], the structure and properties of which have been discussed in comparison to the uracil nucleoside analogues.

As part of our program to develop new antitumor and antiviral agents, respectively, as well as to look for enzyme inhibitors, we report now the synthesis of a new type of 6-azauracil nucleosides carrying a 5-thio-β-D-glucopyranosyl moiety from the fact that 5-thio-D-glucose[18] itself acts as an active antimetabolite[19-21].

SYNTHESES

Glycosylations of 6-azauracil (1) and 5-bromo-6-azauracil (2) were performed by the Hilbert-Johnson-Birkofer method[22] treating the trimethylsilyl derivatives 3 and 4, respectively, with 1,2,3,4,5,6-penta-O-acetyl-5-thio-D-glucopyranose (5) under trimethlsilyl triflate catalysis[23] in boiling 1,2-dichloroethane to give the N-1 nucleosides 6 and 8 in 70% and 61% yield, respectively. These products were purified by chromatography to remove traces of the α-anomers. The free nucleosides 7 and 9 were obtained in good yields on treatment of 6 and 8 with sodium methoxide in MeOH solution for a few hours.

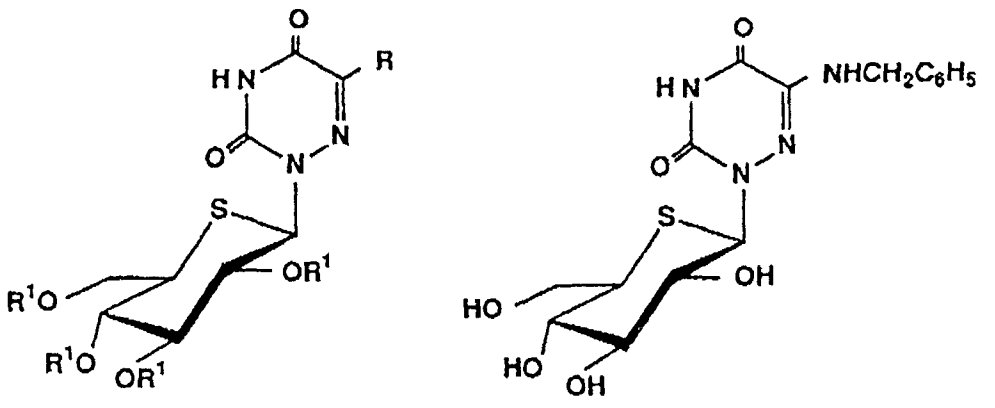
The high reactivity of 5-halo-6-azauracils towards nucleophiles[15,16,24] allowed the displacement of the bromo atom in 8 by a benzylmercaptan/triethylamine mixture to give 10 in 94% yield as well as by benzylamine to form under simultaneous aminolysis 12 in 75% yield. Deacetylation of 10



	R
1	H
2	Br

	R
3	H
4	Br

5



12

	R	R^1
6	H	Ac
7	H	H
8	Br	Ac
9	Br	H
10	$SCH_2C_6H_5$	Ac
11	$SCH_2C_6H_5$	H

worked well by the transesterification method of Zemplen[25] applying sodium methoxide in MeOH. The 5-benzylthio-1-(5-thio-β-D-glucopyranosyl)-6-azauracil (11) was isolated in 77% yield as colorless crystals.

PHYSICAL PROPERTIES

The UV spectra and pk_a data of the newly synthesized compounds are summarized in table 1. The 6-azauracil-N-1-thioglucosides are relatively acidic compounds being ionized to a large extent at physiologic pH. It is also noteworthy that monoanion formation is associated with a hypsochromic shift of the long wavelenth band, which is also reflected partially in the MeOH spectra of the acylated and free nucleosides. ^{1}H-NMR specttra (Table 2) reveal a series of fine structureal properties as the β-configuration of the glycosidic linkage from the large coupling constants of H-1′ ($J_{1'.2'}$ 10 Hz) and the $^4C_1$ conformation derived again from the large coupling constants of the residual pyranose ring protons ($J_{2.3} = J_{3.4} = J_{4.5} = 9.5$ 10.0 Hz). The analysis of the proton assignments in the nucleosides (7, 9, 11, and 12) were performed by decoupling experiments which showed, after D_2O exchange, a clear shift of the H-3′ and H-4′ signals towards higher field.

E X P E R I M E N T A L

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. UV spectra were measured on a perkin Elmer spectrophotometer Lambada 5; ^{1}H-NMR spectra were recorded at 250 MHz on a Bruker WM-250 high resolution

Table 1 - Physical Data of 6-Azauracil-N-1-Thioglucosides

	pK_a in H_2O	UV - Absorption Spectra λ_{max} (nm)	(lg ε)	pH Solvent	Molecular Form
6		263	3.87	MeOH	o
7		265	3.96	MeOH	o
	6.07	266	3.54	4.0	o
		261	3.55	8.0	-
8		274	3.92	MeOH	o
9		274	3.85	MeOH	o
	5.32	282	3.82	3.1	o
		272	3.77	7.0	-
10		[215] [233] 309	[4.33] [4.12] 3.94	MeOH	o
11		[216] [234] 309	[4.35] [4.16] 3.93	MeOH	o
	5.94	211 233 315	4.25 4.02 3.87	4.0	o
		[215] [242] 305	[4.23] [3.97] 3.81	8.0	-
12		275	3.94	MeOH	o
	5.18	282	3.98	3.1	o
		272	3.92	7.0	-

[ ] = Shoulder; o = neutral form; - = monoanion.

Table 2 - ^{1}H-NMR Data of the Sugar Protons of the 6-Azauracil-N-1- Thioglucosides

	NH	H-1' $J_{1',2'}$	H-2' $J_{2',3'}$	H-3' $J_{3',4'}$	H-4' $J_{4',5'}$	H-5' $J_{5',6'}$	H-6' $J_{5',6''}$	H-6'' $J_{6',6''}$
6	8.96s	5.84d (10.0)	5.84t (10.0)	5.62t (10.0)	5.27t (10.0)	5.16dt (3.0)	4.09dd (5.0)	4.27dd (12.0)
7	11.20s	5.46d (10.0)	3.70pt (9.0)	3.06pt (8.5)	3.27pt (10.5)	2.75m (4.5)	3.28dd (6.0)	3.75dd (11.5)
8	9.19s	5.81d (9.5)	5.59t (9.5)	5.29t (9.5)	5.17t (9.5)	3.40ddd (3.5)	4.10dd (5.5)	4.28dd (12.0)
9	10.90s	5.45d (10.0)	3.69pt (9.5)	3.05pt (8.5)	3.27pt (11.0)	2.78m (2.5)	3.76dd (6.5)	3.51dd (11.0)
10	8.85s	5.81d (10.0)	5.71t (10.0)	5.27t (10.0)	5.14t (10.0)	3.35ddd (3.5)	4.28dd (6.0)	4.08dd (12.0)
11	11.80s	5.49d (10.0)	3.96pdt (9.5)	3.14pddd (8.0)	3.31pddd (10.5)	2.87m (3.0)	3.80ddd (7.0)	3.53ddd (11.5)
12	11.09s	5.44d (10.0)	3.69pt (9.5)	3.07pt (8.5)	3.27pt (10.0)	2.83m (3.0)	3.78dd (6.5)	3.59dd (11.0)

s = Singlet; d = doublet; dd = doublet of doublet; t = triplet;
dt = doublet of triplet; ddd = doublet of doublet of doublet;
pt = pseudotriplet; pddd = pseudo-doublet of doublet of doublet;
pdt = pseudo-doublet of triplet; m = multiplet. Coupling constants (Hz).

Table 2 - ^{1}H-NMR Data for the 6-Azauracil-N-1 Nucleosides (Continuation)

	OH-Groups	Sugar	5 - Subst.		
	2', 3', 4', 6', 6"	acetate	H-5	CH_2	Phenyl Protons
6	-	2.01, 1.98, 1.94, 1.86	7.43s	-	-
7	4.65-3.84m, 3.44d (6.0)	-	7.42s	-	-
8	-	2.02, 1.98, 1.94, 1.88	-	-	-
9	+ 4.44 - 3.79m +	-	-	-	-
10	-	2.02, 1.99, 1.95, 1.88	-	4.26s	7.43-7.22m
11	+ 5.03-4.98m + 4.02d (5.5)	-	-	4.05, 3.99 J_{gem} 13.5 Hz	7.44-7.21m
12	+ 5.41-4.50m + 3.51t	-	-	4.03s	7.44-7.33m

s = Singlet; d = doublet; m = multiplet; t = triplet.

spectrometer with tetramethylsilane as an internal standard and on a δ-scale in ppm. The pk_a valuse were determined spectrophotometrically[27]. Thin layer chromatography was performed on silica gel sheets F 1550 LS 254 of schleicher & schull.

1-(2,3,4,6-Tetra-O-acetyl-5-thio-β-D-glucopyranosyl) 6-azauracil (6). A suspension of 6-azauracil (1) (0.25 g, 2.21 mmole) in hexamethyldisilizane (15 ml) with a few crystals of $(NH_4)_2SO_4$ was heated under reflux for 6 h. After cooling, the solution was evaporated in vacuum to give the silylated base 3. A solution of 1,2,3,4,6-penta-O-acetyl-5-thio-D-glucopyranose (5) (0.80; 1.97 mmole) in dry 1,2-dichloroethane (15 ml) was added to a stirred solution of 3 in dichloroethane (15 ml), followed by addition of trimethylsilyl triflate catalyst (0.49 g; 0.40 ml). The mixture was heated under reflux for 5 h and then evaporated to dryness. The residue was partitioned between an aqueous solution of $NaHCO_3$ (20 ml) and chloroform (2x20 ml) and the combined extracts were dried (Na_2SO4), filtered and evaporated to dryness to give a crude product (0.89 g). This product was put onto a silica gel column (40 g) for chromatography with $CHCl_3$/MeOH (100:1) to give on subsequent evaporation a colorless material (0.75 g). Recrystallization from EtoH afforded 6 (0.63 g; 70 %; m.p. 204-206°C).

Anal. Calc. for $C_{17}H_{21}N_3O_{10}S$ (459.4): C, 44.44; H, 4.57; N, 9.01. Found: C, 44.52; H, 4.57; N, 8.79.

1-(5-Thio-β-D-glucopyranosyl)-6-azauracil (7). A solution of 6 (100 mg; 0.22 mmole) in sodium methoxide solution

[from Na (6.5 mg) and methanol (13 ml)] was stirred at room temperature for 7 h. The solution was neutralized with AcOH to pH 5 and then evaporated to dryness. The residue was partitoned between water (20 ml) and ether (10 ml) and the aqueous layer was evaporated to dryness. Recrystallization of the residue from aqueous methanol gave compound 7 (50 mg; 80; m.p. 175-180°C, decomp.).

Anal. Calc. for $C_9H_{13}N_3O_6S \cdot H_2O$ (327.3): C, 32.02; H, 5.23; N, 12.84. Found: C, 31.72; H, 5.19; N, 13.01.

5-Bromo-1-(2,3,4,6-tetra-O-acetyl-5-thio-β-D-glucopyranosyl)-6-azauracil (8). A mixture of 5-bromo-6-azauracil (2) (0.82 g; 4.27 mmole), some crystals of $(NH_4)_2SO_4$ and hexamethldisilazane (25 ml) were boiled under reflux for 6 h. The mixture was evaporated to dryness and the resulting residue was dissolved in a solution of 1,2,3,4,6-penta-O-acetyl-5-thio-D-glucopyranose (5) (1.72g, 4.26 mmole) in dry 1,2-dichloroethane (30 ml). A solution of trimethylsilyl triflate (0.98 g; 0.80 ml) in dry 1,2-dichloroethane (10 ml) was added dropwise and the mixture was heated with stirring for 6 h under reflux. The reaction mixture was worked up as usual to give a crude crystalline product (1.70 g). This material was placed on a silica gel column (80 g) for chromatography with $CHCl_3$/MeOH (100:1) to give 8 as needles (1.40 g; 61 %; m.p. 246-248°C) (from ethanol).

Anal. Calc. for $C_{17}H_{20}Br_3O_{10}S$ (538.3) : C, 37.93; H, 3.47; N, 7.80. Found: C, 37.95; H 3.80; N, 7.85.

5-Bromo-1-(5-thio-β-D-glucopyranosyl)-6-azauracil (9). In dry methanol (15 ml) were dissolved 15 mg (0.67 mmole)

of Na and then 300 mg (0.56 mmole) of compound 8 added and stirred for 10 h at room temperature. The reaction mixture was neutralized with AcOH to pH 5, evaporated to dryness and the residue was partitioned between water (25 ml) and ether (15 ml). The aqueous layer was evaporated to dryness and the residue was recrystallized from aqueous methanol to yield compound 9 (180 mg; 80 %; m.p. 108-110°C).

Anal. Calc. for $C_9H_{12}BrN_3O_6S \cdot 2H_2O$ (406.3) : C, 26.60; H, 3.47; N, 10.34. Found: C, 26.98; H, 3.57; N, 10.09.

5-Benzylthio-1-(2,3,4-tetra-O-acetyl-5-thio-β-D-glucopyranosyl)-6-azauracil (10). A solution of 8 (0.37 g, 0.69 mmole) in dry ethanol (25 ml) containing triethylamine (1 ml) and benzyl mercaptan (0.16 ml, 1.33 mmole) was heated under reflux for 10 h. The solution was evaporated and the residue was partitioned between chloroform (25 ml) and water (25 ml). The organic extract was dried (Na_2SO_4), filtered and evaporated to give a crude product (0.60 g). This product was placed on a silica gel column (30 g) and elution with $CHCl_3$/MeOH (95:5) afforded the pure nucleoside 10 (0.35 g, 94%; m.p. 85-92°C) (recrystallized from ethyl acetate).

Anal. Calc. for $C_{24}H_{27}N_{10}S_2 \cdot H_2O$ (599.79): C, 48.06; H, 4.87; N, 7.00. Found: C, 47.93; H, 4.78; N, 6.51.

5-Benzylthio-1-(5-thio-β-D-glucopyranosyl)-6-azauracil (11). A solution of 10 (290 mg, 0.48 mmole) in sodium methoxide solution [from Na 16 mg, 0.69 mmole) and MeOH (15 ml)] was stirred at room temperature for 7 h. The solution was neutralized with AcOH to pH 5 and evaporated to dryness. The

residue was recrystallied from aqueous methanol to yield compound 11 (160 mg, 77%; 281-282°C).

Anal. Calc. for $C_{16}H_{18}N_3O_6S_2$. 1 1/2 H_2O (439.0): C, 43.92; H, 5.09; N, 9.48. Found: C, 43.77; H, 5.05; N, 9.57.

5-Benzylamino-1-(5-thio-β-D-glucopyranosyl)-6-azauracil (12). A solution of 8 (0.40 g, 0.66 mmole) in EtOH (15 ml) and benzylamine (0.16 ml, 1.48 mmole) was boiled under reflux for 4 h. The solution was evaporated and the residue was partitioned beween H_2O (25 ml) and ether (15 ml). The aqueous extract was evaporated to dryness and the residue was recrystallized from aqueous EtOH to give the free nucleoside 12 as colorless crystals (0.21 g, 72%; m.p. 139-145°C).

Anal. Calc. for $C_{16}H_{20}N_4O_6S$. $2H_2O$ (400.4): C, 47.99; H, 6.04; N, 13.99. Found: C, 47.65; H, 5.90; N, 14.23.

A C K N O W L E D G E M E N T

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