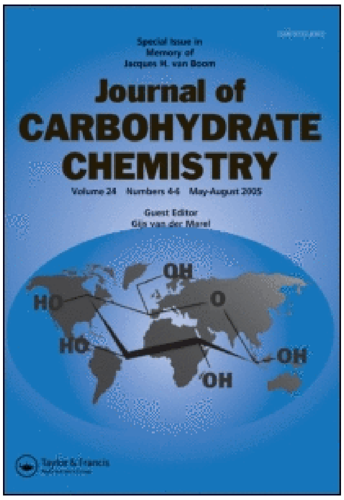

Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

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To cite this Article Ljevaković, Burdica , Horvat, Jaroslav , Klaić, Branimir and Tomić, Srdanka(1983) '1-Thioglycopyranosyl Esters of N-Acylamino Acids', Journal of Carbohydrate Chemistry, 2: 3, 263 — 278

To link to this Article: DOI: 10.1080/07328308308057873

URL: http://dx.doi.org/10.1080/07328308308057873

J. CARBOHYDRATE CHEMISTRY, 2(3), 263-278 (1983)

1-THIOGLYCOPYRANOSYL ESTERS OF *N*-ACYLAMINO ACIDS

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Received April 25, 1983

ABSTRACT

Fully protected 1-thioglycopyranosyl esters of *N*-acylamino acids (5, 6, and 7) were prepared by condensation of methyl 2,3,4-tri-*O*-acetyl-1-thio-β-*D*-glucopyranuronate (1), 2,3,4-tri-*O*-acetyl-1-thio-*L*-arabinopyranose (2), and 2,3,4-tri-*O*-acetyl-1-thio-*D*-arabinopyranose (3) with pentachlorophenyl esters of *N*-acylamino acids in the presence of imidazole.

The ^{13}C NMR chemical shifts of the starting 1-thio sugars and the 1-thiol ester products are reported.

INTRODUCTION

Thio sugars and their derivatives constitute an intensively studied class of carbohydrates. Rather marked contrasts are evident in the reactivities of thio sugar derivatives and their oxygen analogs[1] owing to important differences between sulfur and oxygen atoms.

Together with many attractive synthetic possibilities presented by sugars containing sulfur, there are also interesting potentialities for thio sugar

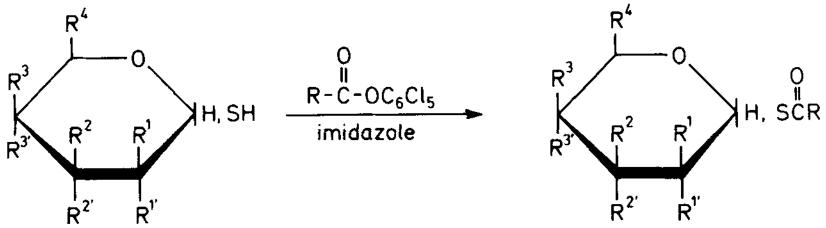
0732-8303/83/0203-0263$3.50/0

derivatives in the field of carbohydrate biochemistry. For example, certain 1-thioglycosides are effective inducers, although not substrates, for enzymes that catalyze hydrolysis of the corresponding oxygen glycosides; thio sugars may also act as antimetabolites by inhibiting certain enzymes that require the normal sugar derivative in an essential metabolic step.[2] Such compounds are of interest as biochemical probes for elucidating metabolic pathways and as potential therapeutic agents.

In contrast to 1-thioglycosides,[1] not much attention has been given to the chemistry and biochemistry of 1-thioglycosyl esters.[3] Various studies in this laboratory have been concerned with synthesis[4] of 1-thioglucosyl esters of amino acids and peptides, their reactivities relative to oxygen analogs,[5] and the mechanism of peptide forming aminolysis reactions[6] typical for these compounds. We now report on the synthesis and identification of some fully protected 1-thioglycosyl esters of N-acylamino acids having different 1-thio sugars linked by the thiol ester bond to various amino acids.

RESULTS AND DISCUSSION

The imidazole-promoted active ester method elaborated for the preparation of the fully protected 1-O-(N-acylaminoacyl)-D-glucopyranose,[7] the corresponding 1-thio analogs,[4] and the fully protected 1-O-(N-acylaminoacyl)-D-glucopyranuronates,[8,9] was successfully applied to the synthesis of protected 1-thioglycopyranosyl esters of various N-acylamino acids. Thus, treatment of methyl 2,3,4-tri-O-acetyl-1-thio-ß-D-glucopyranuronate (1), 2,3,4,-tri-O-acetyl-1-thio-L-arabinopyranose (2), and 2,3,4-tri-O-acetyl-1-thio-D-arabinopyranose (3), with N-acylamino acid pentachlorophenyl esters in the presence of one equivalent of imidazole, afforded 1-thioglycopyranosyl esters 5, 6, or 7, respectively (Scheme 1). Analytical and physical data for the methyl 2,3,4-tri-O-acetyl-1-S-(N-acylaminoacyl)-1-thio-ß-D-glucopyranuronates 5 are reported in Table 1, while Table 2 gives data for 2,3,4-tri-O-acetyl-1-S-(N-acylaminoacyl)-1-thio-α-L-(6) and α-D-arabinopyranoses (7). The rate at which the 1-thioglycopyranosyl ester forms depends on the type of 1-thio sugar used in synthesis. Thus, com-



1 - 4 5 - 8

1ß, 5ß $R^{1'} = R^2 = R^{3'} = OAc$; $R^1 = R^{2'} = R^3 = H$; $R^4 = CO_2Me$
2, 6α $R^{1'} = R^2 = R^3 = OAc$; $R^1 = R^{2'} = R^{3'} = R^4 = H$
3, 7α $R^1 = R^{2'} = R^{3'} = OAc$; $R^{1'} = R^2 = R^3 = R^4 = H$
4ß, 8ß $R^{1'} = R^2 = R^{3'} = OAc$; $R^1 = R^{2'} = R^3 = H$; $R^4 = CH_2OAc$
RCO = amino acid residue

SCHEME 1

TABLE 1

Analytical Data for Methyl 2,3,4-Tri-O-acetyl-1-S-(N-acylaminoacyl)-1-thio-ß-D-glucopyranuronates

Compound	RCO	Yield (%)	m.p.[a] (°C)	$[\alpha]_D$[b]	Formula	Anal.							
						Calc. (%)				Found (%)			
						C	H	N	S	C	H	N	S
5a	Z-Gly-[c]	46	119-121	0	$C_{23}H_{27}NO_{12}S$	51.01	5.03	2.59	5.92	50.92	5.01	2.31	5.86
5b	Z-Ala-	51	105-107	-3.0	$C_{24}H_{29}NO_{12}S$	51.89	5.26	2.52	5.77	51.71	5.59	2.65	5.49
5c	Z-D-Ala-	54	108-110	+11.0	$C_{24}H_{29}NO_{12}S$	51.89	5.26	2.52	5.77	51.65	5.48	2.39	5.74
5d	Boc-Ala-	61	131-133	-10.2	$C_{21}H_{31}NO_{12}S$	48.36	5.99	2.69	6.15	48.53	6.07	2.39	6.37
5e	Boc-D-Ala-	61	183-185	+15.6	$C_{21}H_{31}NO_{12}S$	48.36	5.99	2.69	6.15	48.13	5.76	2.66	6.00
5f	Z-Phe-	77	158-159	-32.3	$C_{30}H_{33}NO_{12}S$	57.04	5.27	2.22	5.08	56.89	5.40	2.05	4.99
5g	Boc-Phe-	46	164-166	-33.7	$C_{27}H_{35}NO_{12}S$	54.27	5.90	2.34	5.36	53.98	5.09	2.43	5.24

a. From di(2-propyl)ether-light petroleum. b. In chloroform at 24-26°C. c. Z = $PhCH_2OCO$; Boc = Me_3COCO

TABLE 2

Analytical Data for 2,3,4-Tri-O-acetyl-1-S-(N-acylaminoacyl)-1-thio-α-L- (and α-D-)arabinopyranoses[a]

Compound	RCO	Sugar config.	Yield (%)	$[\alpha]_D$[b]	Formula	Anal. Calc. (%) C	H	N	S	Found (%) C	H	N	S
6a	Z-Ala-[c]	L	64	-35	$C_{22}H_{27}NO_{10}S$	53.11	5.47	2.64	6.44	53.21	5.50	2.81	6.33
6b	Z-D-Ala-	L	67	-10	$C_{22}H_{27}NO_{10}S$	53.11	5.47	2.64	6.44	52.88	5.63	2.82	6.25
6c	Z-Phe-	L	69	-23	$C_{28}H_{31}NO_{10}S$	58.63	5.45	2.44	5.59	58.45	5.41	2.37	5.59
6d	Boc-Phe-	L	85	-24.5	$C_{25}H_{33}NO_{10}S$	55.64	6.16	2.60	5.94	55.41	6.40	2.78	5.97
7a	Z-Phe-	D	62	-39.5	$C_{28}H_{31}NO_{10}S$	58.63	5.45	2.44	5.59	58.59	5.61	2.39	5.71
7b	Boc-Phe-	D	76	-38.5	$C_{25}H_{33}NO_{10}S$	55.64	6.16	2.60	5.94	55.77	6.21	2.81	5.75

a. 5a (m.p. 161-163°C) and 5c (m.p. 62-65°C) were crystalline; all other compounds were amorphous solids. b. In chloroform at 24-26°C. c. Z = $PhCH_2OCO$; Boc = Me_3COCO.

pounds 6 and 7 formed in a relatively short time (~ 1 h), and 1-thiol esters 5 needed longer periods (~ 4 h), while the formation of 2,3,4,6-tetra-O-acetyl-1-S-(N-acylaminoacyl)-1-thio-β-D-glucopyranoses (8)[4] proceeded at even slower rates (4-12 h). Yields were always relatively high (50-80%), and were not influenced by prolongation of reaction times.

As previously reported,[4] optical rotation values and ^{1}H NMR data of the fully acetylated 1-thioglucopyranosyl esters 8 indicated the β-D-configuration of these compounds.

The 90-MHz ^{1}H NMR data (in chloroform-d) of peracetylated methyl 1-thioglucopyranuronate esters 5 revealed the O-acetyl group signals in the δ 1.95-2.07 range, the chemical shift values corresponding closely to those observed for the fully acetylated 1-thioglucopyranosyl esters 8.[4] The methyl ester group in 1-thio esters 5 resonates as a singlet at δ 3.71-3.76, while the signal for the anomeric proton is obscured by other ring proton signals. A clear doublet at δ 4.16 ($J_{4,5}$ 9.3 Hz) could be found in all spectra of 5, and it was assigned to H-5. It is known that the position and the pattern of the H-5 signal in the spectra of D-glucosiduronic acid derivatives might provide useful information about the anomeric configuration of these compounds.[10,11] The signal for H-5 in acetylated methyl D-glucopyranuronates[8,9,12] and methyl D-glucopyranosiduronates[10,11] usually appears as a doublet in the range of δ 4.30-4.40 ppm ($J_{4,5}$ ~ 10 Hz) for α-D-anomers, and at higher fields (δ 4.04-4.18 ppm, $J_{4,5}$ 9.5 Hz) for ß-D-anomers. Therefore, the position of doublets assigned to H-5 in the ^{1}H NMR spectra of acetylated methyl 1-thio-D-glucopyranuronates 5 indicates the ß-D-configuration for these compounds.

Acetylation of 2,3,4-tri-O-acetyl-1-thio-L-arabinopyranose (2) produced the peracetylated 1-thio-L-arabinopyranose derivative (9). Its optical rotation value and ^{1}H NMR spectra are in accordance with data previously reported for the α-L-anomer.[3] It is well documented that peracetylated 1-thio-α-L-arabinopyranose and its oxygen analog[13] exist mostly in the $^{4}C_{1}$ conformation, whereas their α-D-enantiomers are essentially all in the $^{1}C_{4}$ conformation.[3,13] Both forms have substituents on C-1, -2, and -3 in equatorial positions and on C-4 in an axial position, giving thus, identical ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectra of the fully acetylated 1-thioarabinopyranosyl esters 6 and 7 revealed the O-acetyl group signals at 2.0-2.1 ppm. The H-1 signal could not be measured owing to overlap with other ring protons. In all ^{1}H NMR spectra of compounds 6 and 7 the H-5 protons (H-5 giving the higher field signals and H-5′ giving the lower field signals) appeared as two sets of two closely spaced pairs of signals (centered at $\delta \sim 3.8$ and ~ 4.1 ppm), which is the typical pattern for the AB portion of an ABX system,[14] X in this case being H-4. The signals for H-4 appear at lower field and overlap with other ring protons. Chemical shifts and coupling constants

($J_{5,5'}$ ~ 12.5 Hz, $J_{4,5}$ ~ 2.5 Hz, and $J_{4,5'}$ ~ 4.5 Hz) of signals assigned to H-5 protons are in accordance to those reported for 1-thio-α-L- (or α-D-) arabinopyranose tetraacetates.[3] However, the values of $J_{4,5}$ and $J_{4,5'}$ did not allow unambiguous differentiation of equatorial and axial H-5 signals.

Assignment of signals of carbon atoms in the sugar moieties in the ^{13}C NMR spectra of the fully protected 1-thio-glycosyl esters 5, 6, 7, and 8 (Table 3) was established on the basis of data reported for peracetylated 1-thio-D-glucopyranosides,[15,16] some peracetylated glycopyranosides,[16-18] and acetylated glycopyranoses.[17,19]

For the anomeric carbon atoms in all carbohydrate moieties introduction of a sulfur atom instead of oxygen produces a large upfield shift (12-16 ppm) owing to the acompanying decrease in electronegativity. A number of other influences on ^{13}C shielding may be ascribed to the replacement of oxygen by sulfur.[15] For example, in 2,3,4,6-tetra-O-acetyl-1-thio-ß-D-glucopyranose (4) and its fully acetylated derivative 10, the C-3 and C-5 resonate 1.0-4.3 ppm downfield of those of oxygen analogs,[19] whereas the chemical shifts of C-4 and C-6 remain essentially the same. These results are comparable to those previously reported for methyl and ethyl 1-thio-ß-D-glucopyranosides, their peracetylated derivatives, and oxygenated analogs.[15]

The TLC homogeneity and ^{13}C NMR spectra of the starting 1-thio sugars revealed the exclusive ß-configuration of methyl 2,3,4-tri-O-acetyl-1-thio-D-glucopyranuronate (1) and 2,3,4,6-tetra-O-acetyl-1-thio-D-glucopyranose (4), while 2,3,4-tri-O-acetyl-1-thio-L- (2) and D-arabinopyranose (3) exist as anomeric mixtures, with α-L- and α-D-anomers largely predominating (∼ 90% by TLC). ^{13}C NMR chemical shifts for 1-thio sugars 1, 2α, 2β, and 4 (Table 3) were determined by comparison to some oxygen analogs.[17,20]

In comparison to the starting 1-thio sugars (1, 2, 3, and 4), the anomeric carbon atom is generally deshielded (0.5-1.5 ppm) in all three series of esterified products (5, 6, 7, and 8). In contrast to that of C-1, the C-2 signal was found to be displaced upfield (2.5-4.6 ppm). The chemical shifts for C-3, -4, and -6 in the methyl 1-thio-D-glucopyranuronate (5) and 1-thio-D-glucopyranosyl (8) classes of compounds remain unchanged regardless of substitution on C-1. Fully acetylated 1-thio-L- (and D-) arabinopyranosyl esters (6 and 7) exhibit a slight upfield shift for C-3 (1.2-1.6 ppm) and C-5 (0.7-1.6 ppm), whereas the signal for C-4 remains unshifted.

Change of the aglycon structure (from acetyl to an N-acylaminoacyl residue) did not influence the chemical shifts of the carbon atoms in any of the carbohydrate moieties, indicating that the 1-thio sugar configuration and conformation remain the same regardless of the aglycon structure in the fully acetylated 1-thio esters 5, 6, 7, and 8.

The CH$_3$ and CO resonances belonging to acetyls on

TABLE 3

^{13}C NMR Chemical Shifts of 1-Thio Sugars and 1-Thio Sugar Portions of Some Selected, Fully Protected 1-Thioglycopyranosyl Esters (in $CDCl_3$)

Compound	Chemical Shifts (δ_C, ppm)[a]					
	C-1	C-2	C-3	C-4	C-5	C-6
	1-Thioglucopyranuronate Moieties					
1	78.9	72.9	73.4	69.4	76.5	166.7
5f[b]	80.1	69.0[c]	73.3	69.4[c]	76.5	166.7
	1-Thioglucopyranosyl Moieties					
7	78.7	73.7	73.7	68.3	76.4	62.1
10	80.2	69.1	74.0	68.1	76.4	61.7
8b[b]	80.2	69.4	74.1	68.1	76.5	61.8
	1-Thioarabinopyranosyl Moieties					
2α	79.1	70.8	71.5	67.9	66.9	
2β	77.7	68.1	68.5	67.1	61.7	
9	80.2	68.1	70.0	67.2	65.5	
6c[b]	80.0	68.3	69.9	67.2	65.4	
7a[b]	80.1	68.1	70.1	67.2	65.8	

a. Chemical shifts of carbohydrate portion C-atoms remain unchanged regardless of the aglycon structure.
b. Aglycon = Z-Phe-. c. Assignments may be reversed.

the carbohydrate moieties occur as overlapped groups at $\delta_C \sim 20.5$ ppm and at ~ 169 ppm, respectively.

The signal of the SCO group occurs at typically low field (δ_C 191.8-199.4). Its position depends on the amino acid aglycon, and on the kind of its N-substitution (Ac, Z or Boc). It is also slightly but consistently affected by the configuration of the N-acylamino acid residues; compounds containing D-amino acids show SCO signals at lower fields than their L-analogs.

N-Acylamino acid aglycons in 5, 6, 7, and 8 give signals at same positions regardless of the sugar moiety (Table 4). These values, with some slight vari-

TABLE 4

^{13}C NMR Chemical Shifts for N-Acylaminoacyl Residues of the Fully Protected 1-Thioglycopyranosyl Esters 5, 6, 7, and 8 (in $CDCl_3$)

Group	δ (ppm)	Group	δ (ppm)
CH_2 (Gly)	50.5-50.9	OCO (Z,Boc)	154.7-156.2
CH (Ac Ala)	55.4	OCH_2 (Z)	67.2-67.5
CH (Boc Ala)	56.6	$O\underline{C}(CH_3)_3$ (Boc)	80.4-80.8
CH (Z Ala)	57.1	$OC(\underline{C}H_3)_3$ (Boc)	28.2
CH (Phe)	61.5-62.1	CH_3 (NAc)	22.9
CH_3 (Ala)	17.8-18.2	CO (NAc)	170
CH_2 (Phe)	37.6-38.0	CH_3 (SAc)	30.8
Ph (Phe,Z)[a]	127.3-129.3	CO (SCOR)	191.8-199.4
Ph (Phe,Z)[b]	135.0-136.1		

a. Protonated aryl c. b. Unprotonated aryl c.

ances caused by the proximity of the 1-thiol ester bond, are generally in accord with ^{13}C NMR data previously reported for N-acylamino acids.[21]

The IR spectra of the fully protected 1-thioglycosyl esters 5, 6, and 7 showed three well resolved bands in the carbonyl region; the thiolester carbonyl absorption (1710-1730 cm^{-1} in 5, 1730 cm^{-1} in 6 and 7) was clearly separated from absorptions exhibited by acetoxy (and the methyl ester group in 5) carbonyl groups (1750-1760 cm^{-1}). Urethane carbonyl absorptions appeared as sharp peaks at 1690 cm^{-1} in 5, and at 1710 cm^{-1} in the case of compounds 6 and 7. The starting 1-thio sugars 1, 2, and 3 displayed only one, broad band in the carbonyl region (1750 cm^{-1}), and a characteristic S-H stretching absorption at ~ 2550 cm^{-1}.

EXPERIMENTAL

General Procedures. Column chromatography was performed on Silica Gel (Merck 0.05-0.2 mm), and TLC on Silica Gel 60 (Merck). Solvents used were: A, benzene-ethyl acetate (2:1); B, ether-light petroleum (3:1). Detection on TLC plates was effected by charring with sulphuric acid, the ninhydrin reagent, or the chlorine-iodine reagent for peptides. IR spectra were recorded with a Perkin-Elmer 297 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded, at room temperature in 5 mm o.d. tubes, with a JEOL FX-90Q Fourier-transform spectrometer, operating at 90 and 22.5 MHz, respectively. The sweep width used was 1000 Hz (^{1}H) and 5200 Hz (^{13}C). The pulse width was 14 μs (^{1}H) and 5 μs (^{13}C), acquisition time was 15 s (^{1}H) and 2 s (^{13}C). Digital resolution was 0.0027 ppm (^{1}H) and 0.056 ppm (^{13}C). Chemical shifts were measured relative to Me_4Si as an internal standard.

Methyl 2,3,4-tri-O-acetyl-1-S-(N-acylaminoacyl)-1-thio-β-D-glucopyranuronates (5a-5g). To a solution of methyl 2,3,4-tri-O-acetyl-1-thio-β-D-glucopyranuronate[22,23] (1, 350 mg, 1 mmol) and the appropriate N-acylamino acid pentachlorophenyl ester[24] (1.1 mmol) in CH_2Cl_2 (15 ml), was added imidazole (68 mg, 1 mmol) at room temperature, and with shaking. The reaction mixture was kept (monitoring by TLC in solvent A) at room temperature for 4 h. Pentachlorophenol was filtered off, and the filtrate washed sequentially with water, 10% citric acid in water, water, aqueous $NaHCO_3$, and water, dried and concentrated. Purification of 1-thio-β-D-glucopyranuronate esters (5a-5g) was effected on silica gel columns with solvent A, followed by crystallization. The yields, and physical and analytical data of products 5 are given in Table 1.

2,3,4-Tri-O-acetyl-1-S-(N-acylaminoacyl)-1-thio-α-L- and α-D-arabinopyranoses (6a-6d, 7a, 7b). To a solution of 2,3,4-tri-O-acetyl-1-thio-L or D-arabinopyranose[25] (2, 235 mg, 0.8 mmol) and the appropriate N-acylamino acid pentachlorophenyl ester (0.8 mmol) in CH_2Cl_2 (10 ml), was added imidazole (55 mg, 0.8 mmol) at room temperature, and with shaking. The reaction mixtures were kept at room temperature for 1-2 h (monitoring by TLC in solvent A). Pentachlorophenol was filtered off, and the filtrate concentrated *in vacuo*. Purification of 1-thioarabinopyranosyl esters 6 and 7 was effected on silica gel columns (solvent B). The yields, physical and analytical data of compounds 6 and 7 are given in Table 2.

ACKNOWLEDGMENTS

The authors wish to thank Dr. D. Keglević and Dr. Š. Horvat for helpful suggestions and discussions, Mrs. A. Matijevac for technical assistance, Mrs. Lj. Sesartić for microanlyses, and Mrs. B. Metelko for IR, ^{1}H, and ^{13}C NMR measurements.

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