SYNTHESIS AND TRANSFORMATIONS OF CARBOHYDRATE DERIVATIVES.

1. SYNTHESIS OF FURAN AND 5-NITROFURAN DERIVATIVES OF SOME THIOSEMICARBAZONES AND THIOSEMICARBAZIDES OF D-GLUCOSE AND L-ARABINOSE

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N-Glycopyranosylthiosemicarbazones and their acetates were synthesized by the reaction of tetraacetylglycopyransyl isothiocyanates with hydrazones of furan and nitrofuran aldehydes and also by reaction with hydrazine hydrate and subsequent treatment with the aldehydes. Acetates of glycopyranosyl-5-R-furoylthiosemicarbazides were obtained by acetylation of glycopyranosylthiosemicarbazides with furan- and 5-nitrofuranocarboxylic acid chlorides. The structures of the synthesized compounds were confirmed by thin-layer chromatography and the IR and PMR spectra and by the results of elementary analysis.

In order to increase the selectivity of the action, decrease the toxicity, and increase the solubilities in water of biologically active furan and 5-nitrofuran compounds [1, 2] we synthesized carbohydrate-containing derivatives of furan and 5-nitrofuran that are connected by means of thiosemicarbazide and thiosemicarbazone fragments.

We studied the reactions of 1-deoxy-2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate (I) and 1-deoxy-2,3,4-tri-O-acetyl-L-arabinopyranosyl isothiocyanate (XIV) with hydrazine hydrate, hydrazones of 2-R-substituted formylfurans (R = H, NO_2), and hydrazides of 5-R-substituted furan-2-carboxylic acids (R = H, NO_2).

Compounds I and XIV were obtained by the action of ammonium thiocyanate or silver thiocyanate on the acetobromo sugar in an inert medium [3, 4]. They are readily identified from the characteristic absorption bands in the IR spectra at 2060-2140 cm^{-1} (—N=C=S) and at 1750 and 1240 cm^{-1} ($OCOCH_3$).

Acetylglycosylthiosemicarbazides II and XV are formed in good yields when the glycosylisothiocyanates are treated in the cold with hydrazine hydrate, while partial deacetylation of the desired products occurs in the presence of excess hydrazine hydrate. Two absorption bands at 3315-3465 cm^{-1}, which are related to the symmetrical and asymmetrical stretching vibrations of the amino group, are observed in the IR spectra of II and XV. In the PMR spectra of II and XV the protons of the amino group give a singlet at 4.6 ppm (2H), while the remaining NH protons of the thiosemicarbazide part give singlets at 8.3 (1H) and 9.6 ppm (1H).

Glycosylthiosemicarbazide acetates II and XV form formylfuran and 5-nitroformylfuran glycosylthiosemicarbazone acetates (V-VIII and XVII-XXI) with formylfuran and 5-nitroformylfuran in alcohol media in the presence of acids (method A). The band that is characteristic for the amino group vanishes in the IR spectra of these compounds, and a band of an azomethine group appears at 1470-1485 cm^{-1}. In addition, NH (3320-3340 cm^{-1}) and CSNH (1680 cm^{-1}) stretching vibrations and vibrations of the furan ring at 1510 and 1595 cm^{-1} are observed in the spectra. Symmetrical vibrations of the C—O—C bond of the furan ring are observed at 1025-1035 cm^{-1}, while the asymmetrical vibrations are overlapped by the vibrations of the O—C group in the acetates. The nitro group in VII, VIII, XX, and XXI gives two characteristic intense absorption bands at 1360 and 1530-1560 cm^{-1}. The bands of the acetate groups of the carbohydrate ring appear at 1750 (C=O) and 1240 cm^{-1} (O—C). The pyranose ring in V-VIII and XVIII-XXI is characterized by an absorption band at 910-925 cm^{-1}. The deformation vibrations of the $C_{(1)}$—H bond at 885-894 cm^{-1} are due to the β configuration of the aglycone.

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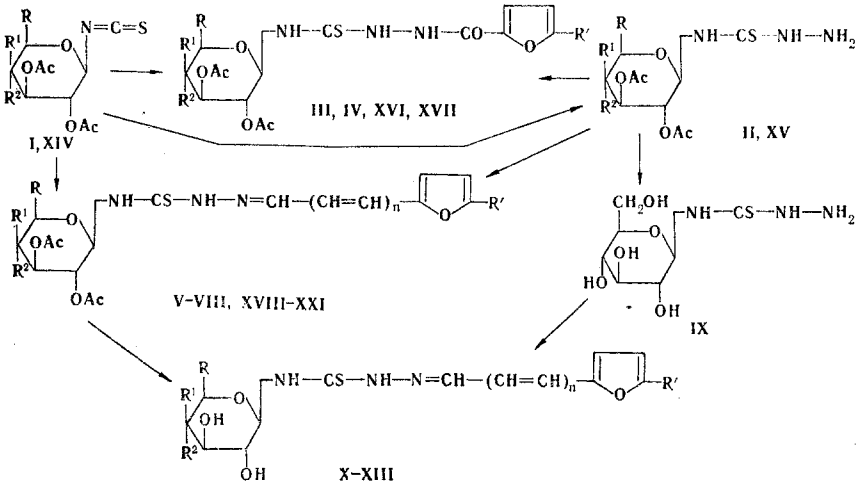


I R=CH_2OAc, R^1=H, R^2=OAc; II R=CH_2OAc, R^1=H, R^2=OAc; III R=CH_2OAc, R^1=H, R^2=OAc, R′=H; IV R=CH_2OAc, R^1=H, R^2=OAc, R′=NO_2; V R=CH_2OAc, R^1=H, R^2=OAc, R′=H, n=0; VI R=CH_2OAc, R^1=H, R^2=OAc, R′=H, n=1; VII R=CH_2OAc, R^1=H, R^2=OAc, R′=NO_2, n=0; VIII R=CH_2OAc, R^1=H, R^2=OAc, R′=NO_2, n=1; X R=CH_2OH, R^1=H, R^2=OH, R′=H, n=0; XI R=CH_2OH, R^1=H, R^2=OH, R′=H, n=1; XII R=CH_2OH, R^1=H, R^2=OH, R′=NO_2, n=0; XIII R=CH_2OH, R^1=H, R^2=OH, R′=NO_2, n=1; XIV R=R^2=H, R^1=OAc; XV R=R^2=H, R^1=OAc; XVI R=R^2=H, R^1=OAc, R′=H; XVII R=R^2=H, R^1=OAc, R′=NO_2, n=0; XVIII R=R^2=H, R^1=OAc, R′=H, n=0; XIX R=R^2=H, R^1=OAc, R′=H, n=1; XX R=R^2=H, R^1=OAc, R′=NO_2, n=0; XXI R=R^2=H, R^1=OAc, R′=NO_2, n=1

In contrast to glycosylureas and N-glycosides [5], the anomeric proton shows up in the form of a triplet (J = 8.5-10 Hz) in the PMR spectra of derivatives V-VIII and XVIII-XXI. This splitting is a consequence of spin–spin coupling of the anomeric proton with the protons attached to the $C_{(2)}$ atom and the 4′-N atom. The signal of the $N'_{(4)}$–H proton is observed in the form of a broad doublet due to the quadrupole moment of the nitrogen atom. The magnitude of the $J_{1,2}$ value of the proton anomers confirms the β configuration of the aglycone vis-à-vis the glycoside center for glycosylthiosemicarbazones V–VIII, XVII-XXI, and X-XIII [6]. The signals of the H_β and $H_{\beta'}$ protons of the furan ring in V, VI, X, XI, XVIII, and XIX give doublets at 6.7-7.0 ppm. In the spectra of compounds that contain a nitro group in the 5 position (VII, VIII, XII, XIII, XX, and XXI) these signals are shifted to weaker field (7.40-7.80 ppm) due to its electronegative character, in agreement with the data in [7].

The use of diacetates instead of unstable formylfuran and 5-nitroformylfuran in the reaction with glycosylthiosemicarbazides II, XV, and IX in acidic media gives thiosemicarbazones V-XIII and XVIII-XXI in good yields. When the reaction is carried out at pH 2-3 with acetylglycosylthiosemicarbazides, it leads to partial deacetylation of the reaction products.

Glycosylthiosemicarbazones V-VIII and XVII-XXI were also obtained by the reaction of acetylglycosyl isothiocyanates I and XIV with furfural and 5-nitrofurfural hydrazones (method B). The yields of the compounds were higher by method B than by method A.

The acetyl protective groups of VII, VIII, XX, and XXI are removed in absolute methanol in the presence of $HClO_4$ or HCl. However, we were unable to remove the protective groups by the Zemplen method [8] in absolute methanol in the presence of sodium methoxide because of the instability of the nitrofuran ring.

The addition of a carbohydrate fragment to the formylfuran and 5-nitroformylfuran thiosemicarbazones increases their solubility in water.

The bands of an acetate group (1750 cm^{-1}) vanish in the IR spectra of X-XIII, and a broad absorption band of a hydroxy group appears at 3350-3490 cm^{-1}.

A method for the preparation of 4-(acetyl-N-glycopyranosyl)-1-furoyl-3-thiosemicarbazides by direct reaction of glycosyl isothiocyanates with furan-2-carboxylic acid hydrazide is known [9]. We demonstrated that the compounds indicated above and 4-(acetylglycopyranosyl)-1-(5-nitro-2-furoyl)-thiosemicarbazides can be obtained by acylation of glycosylthiosemicarbazide acetates II and XV with furan- or 5-nitrofurancarboxylic acid chlorides in an inert solvent.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp, °C	R_f (system)	n_D^{20} (°C), in $CHCl_3$	Found, %				Empirical formula	Calc., %				Yield, %
				C	H	N	S		C	H	N	S	
I	111—112	0,52 (A)	+2 (5,0)	46,1	4,8	3,5	8,0	$C_{15}H_{19}NO_9S$	46,3	4,9	3,6	8,2	80
II	169—171	0,40 (C)	—	42,5	5,3	9,6	7,5	$C_{15}H_{23}N_3O_9S$	42,8	5,5	10,0	7,6	87
III	149—151	0,56 (A)	+3 (2,0)	45,6	4,8	8,0	6,0	$C_{20}H_{24}N_3O_{11}S$	45,8	5,0	8,0	6,1	82
IV	126—129	0,74 (B)	−11 (2,5)	42,6	4,3	9,9	5,7	$C_{20}H_{24}N_4O_{13}S$	42,9	4,3	10,0	5,7	87
V	126—127	0,59 (B)	−48 (2,0)	47,8	5,1	8,6	6,3	$C_{20}H_{25}N_3O_{10}S$	48,1	5,0	8,4	6,4	92
VI	168—169	0,78 (B)	−69,5 (2,3)	50,0	5,2	7,9	5,8	$C_{22}H_{27}N_3O_{10}S$	50,3	5,1	8,0	6,1	96
VII	202—204	0,39 (C)	−102 (2,5)	44,2	4,5	10,0	5,8	$C_{20}H_{24}N_4O_{12}S$	44,1	4,4	10,3	5,9	73
VIII	228—230	0,53 (A)	−31 (2,7)	46,2	4,5	9,4	5,5	$C_{22}H_{26}N_4O_{12}S$	46,3	4,6	9,8	5,6	96
IX	184—186	0,31 (C)	− (2,3)*	33,0	6,0	16,4	—	$C_7H_{15}N_3O_5S$	32,4	6,0	16,6	—	91
X	147—149	0,42 (C)	−23 (2,1)*	43,3	5,2	12,7	9,4	$C_{12}H_{17}N_3O_6S$	43,5	5,1	12,7	9,7	88
XI	176—177	0,62 (C)	−14 (2,0)*	46,8	5,2	11,5	8,8	$C_{14}H_{19}N_3O_6S$	47,1	5,3	11,8	9,0	74
XII	172—174	0,71 (C)	+4 (2,5)*	51,0	3,3	11,8	6,7	$C_{12}H_{16}N_4O_8S$	51,3	3,4	11,7	6,7	81
XIII	187—189	0,59 (C)	−76 (3,1)*	41,7	4,4	13,8	7,8	$C_{14}H_{18}N_4O_8S$	41,8	4,5	13,9	7,9	78
XIV	Syrup	0,46 (B)	—	54,3	4,8	4,5	9,8	$C_{12}H_{15}NO_7S$	45,4	4,7	4,4	10,1	56
XV	Syrup	0,30 (C)	+42 (2,1)	41,1	5,5	12,1	9,1	$C_{12}H_{19}N_3O_7S$	41,3	5,4	12,0	9,2	83
XVI	194—195	0,27 (B)	+105 (1,0)	45,4	4,7	9,2	9,1	$C_{17}H_{21}N_3O_9S$	45,4	4,9	9,4	7,1	73
XVII	124—126	0,63 (A)	+92 (1,9)	41,7	4,0	11,5	6,4	$C_{17}H_{20}N_4O_{11}S$	41,8	4,1	11,5	6,6	79
XVIII	186—187	0,52 (A)	−43 (2,0)	47,6	4,7	9,2	7,4	$C_{17}H_{21}N_3O_8S$	42,8	4,9	9,8	7,5	75
XIX	134—136	0,68 (A)	−29,5 (1,8)	50,4	4,9	9,1	7,0	$C_{19}H_{23}N_3O_8S$	50,3	5,1	9,3	7,1	86
XX	221—223	0,71 (C)	−58 (1,2)	43,1	4,1	11,7	6,5	$C_{17}H_{20}N_4O_{10}S$	43,2	4,2	11,9	6,8	84
XXI	230—233	0,39 (A)	−44 (2,4)	45,6	4,2	11,1	6,3	$C_{19}H_{22}N_4O_{10}S$	45,8	4,4	11,2	6,4	89

*In H_2O.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The ^{1}H NMR spectra of the compounds were obtained with a Brucker WH-90DS spectrometer with hexamethyldisiloxane (HMDS) or DSS as the internal standard; the chemical shifts were measured relative to HMDS with an accuracy of ±0.02 ppm. The melting points were determined with a Boetius apparatus. The course of the reaction and the purity of the compounds obtained were monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates in toluene–acetone (2:1) (A), toluene–acetone (3:1) (B), and chloroform–ethanol–acetone (2:1:1) (C) systems (see Table 1). The plates were developed in UV light or by heating.

1-Deoxy-2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl Isothiocyanate (I). A 1.90-g (25 mmole) sample of dry ammonium thiocyanate was added to a solution of 4.11 g (10 mmole) of 1-deoxy-2,3,4,6-tetra-O-acetylglucopyranosyl bromide [10] in 25 ml of absolute acetonitrile, and the mixture was stirred at 50°C for 1 h. The solvent was removed by distillation, the residue was dissolved in chloroform, and the solution was washed with water. The chloroform layer was dried over $CaCl_2$ and evaporated to dryness in vacuo, and the residue was crystallized from ether–hexane (2:1). 1-Deoxy-2,3,4-tri-O-acetyl-L-arabinopyranosyl isothiocyanate was similarly obtained from 1-deoxy-2,3,4-tri-O-acetyl-L-arabinopyranosyl bromide.

4-(2',3',4',6'-Tetra-O-acetyl-β-D-glucopyranosyl)-3-thiosemicarbazide (II). A 0.5-g (10 mmole) sample of a 99.5% solution of hydrazine hydrate was added with vigorous stirring to a solution of 3.89 g (10 mmole) of I in 60 ml of absolute dioxane, and the mixture was stirred for 40 min. The solvent was evaporated at reduced pressure, and the resulting syrup was dissolved in alcohol at 50°C. The precipitated crystals were removed by filtration, washed with ether, and recrystallized from methanol. 4-(2',3',4'-Tri-O-acetyl-L-arabinopyranosyl)-3-thiosemicarbazide (XV) was obtained by a similar method.

Formylfuran and 5-Nitroformylfuran 4-(2',3',4',6'-Tetra-O-acetyl-β-D-glucopyranosyl)-3-thiosemicarbazones (V-VIII). A) A 10-mmole sample of the corresponding 5-R-formylfuran and 1 ml of glacial acetic acid were added to a solution of 10 mmole of glucopyranosylthiosemicarbazide II in 60 ml of methanol, and the reaction mixture was refluxed for 40 min. It was then evaporated until half the solvent had been removed, and the concentrate was allowed to stand in the cold for 12 h. The precipitated crystals were removed by filtration, washed with alcohol, and recrystallized from methanol.

B) A 10-mmole sample of the corresponding formylfuran hydrazone [11, 12] in an inert solvent was added to a solution of 3.89 g (10 mmole) of I in 50 ml of absolute dioxane, and the mixture was stirred at 50°C for 10 min. The solvent was evaporated, and the residue was dissolved in chloroform. The product was precipitated by the addition of hexane or petroleum ether to the solution and was recrystallized from methanol.

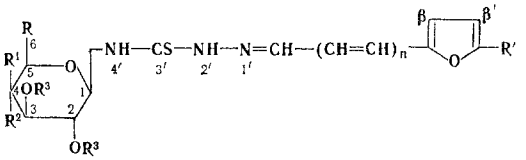
C) A 10-mmole sample of the diacetate of the corresponding aldehyde and 0.1 ml of concentrated HCl were added to a solution of 10 mmole of II in methanol, and the reaction mixture was refluxed for 1 h. It was then neutralized with sodium bicarbonate, and the solvent was evaporated. The precipitate was recrystallized from alcohol to give the product in 72-92% theoretical yield. Compounds XVIII-XXI were similarly obtained by methods A-C.

Formylfuran and 5-Nitroformylfuran 4-(β-D-Glycopyranosyl)-3-thiosemicarbazones (X-XIII). A solution of 5 mmole of acetate V-VIII in 60 ml of absolute methanol and 0.5 ml of 67% perchloric acid or concentrated HCl was refluxed for 2 h, after which it was treated with activated charcoal and filtered. Half the solvent was evaporated, and the concentrate was allowed to stand in the cold overnight. The precipitated crystals were removed by filtration, washed with dry acetone and ether, and recrystallized from aqueous alcohol. Compounds X-XIII were obtained from glucopyranosylthiosemicarbazide IX by methods A and B.

4-(Acetylglycopyranosyl)-1-(5-R-furoyl)thiosemicarbazides (III, IV, XVI, and XVII). A) Equimolar amounts of I or XIV and the corresponding 5-R-substituted furan-2-carboxylic acid hydrazide were refluxed in 35 ml of absolute dioxane for 2 h, after which the solvent was evaporated, and the residue was dissolved in chloroform and precipitated by the addition of hexane.

B) Triethylamine (14 ml) was added to a solution of 10 mmole of thiosemicarbazide II or XV in an inert solvent, and a solution of 10 mmole of the chloride of the corresponding furan-2-carboxylic acid [13] in an inert solvent was added gradually. The reaction mixture was stirred at 45°C for 35 min, after which the solvent was evaporated, and the residue was dis-

TABLE 2. PMR Spectra of the Synthesized Compounds



Compound	n	C_1—H, $J_{1,2}$ = 8—10 Hz	Chemical shift, ppm							Other protons	Solvent
			2-H	5-H, 6-H	$COCH_3$	N′(4)—H	N′(2)—H	β-H	β′-H		
III	—	5,65	5,45	4,00—3,75	1,90—2,10	8,60	9,55	6,60	7,05	9,80 $N_{(1)}H$	d_6-DMSO
II	—	5,85	5,40	4,15—3,80	1,90—2,05	8,25	9,95	—	—	4,65 NH_2	d_6-DMSO
IV	—	5,80	5,40	4,10—3,90	1,95—2,10	10,80	9,90	7,40	7,85	10,80 $N_{(1)}H$	d_6-DMSO
V	0	5,75	5,55	4,10—3,80	1,95—2,05	8,50	11,95	7,05	6,70	8,05 CH=N	d_6-DMSO
VI	1	5,75	5,60	4,10—3,90	1,95—2,00	8,45	11,86	7,05	6,75	8,10 CH=N	d_6-DMSO
VII	0	6,05	5,25	4,30—3,90	2,00—2,05	9,00	12,50	8,00	7,55	8,07 CH=N	
VIII	1	5,90	5,20	4,20—3,80	1,95—2,00	8,70	11,90	7,65	7,10	8,10 CH=N	
X	0	5,65	5,15	4,00—3,50	—	8,75	11,80	7,10	6,65	—	d_6-DMSO
XI	1	5,65	5,20	4,00—3,60	—	8,70	11,70	7,00	6,75	—	d_6-DMSO
XII	0	5,70	5,25	4,10—3,60	—	9,00	12,00	8,10	7,50	—	d_6-DMSO
XIII	1	5,75	5,30	4,10—3,80	—	8,95	12,10	8,00	7,35	—	d_6-DMSO
XVI	—	5,25	4,80	—3,70	1,95—2,05	7,90	8,40	7,15	6,50	9,30 $N_{(1)}H$	
XVII	—	5,60	4,80	—3,75	1,90—2,00	8,60	9,85	7,45	7,75	10,80 $N_{(1)}H$	d_6-DMSO
XVIII	0	5,60	5,05	—3,80	1,90—2,00	8.50	11,70	7,00	6,65	—	d_6-DMSO

solved in chloroform. The chloroform solution was washed with water, dried over $CaCl_2$, and evaporated, and the residue was recrystallized from alcohol.

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