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Behavior of free sugar thiosemicarbazones toward heterocyclization reactions

Miriam A. Martins Alho, Norma B. D'Accorso *

CIHIDECAR (CONICET)-Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, 3° Piso, Pabellón II-Ciudad Universitaria, CP 1428 Buenos Aires, Argentina

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Abstract

The heterocyclization reaction on thiosemicarbazones having the D-galacto, D-gluco and D-manno configuration was studied. We applied two different acetylating conditions, and the reaction products obtained were identified, spectroscopically characterized, and conformationally analyzed. Using experimental data, we discuss a possible mechanistic pathway for heterocyclization and evaluate the influence of several factors, including starting material configuration, pH of reaction medium, and reaction time.

Keywords: Sugar thiadiazolines; Sugar thiosemicarbazones; Acetylation; Heterocyclization; pH influence

1. Introduction

The synthesis of (+)- and (−)-5-acetamido-3-*N*-acetyl-2-(1,2,3,4,5-penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)-1,3,4-thiadiazoline [(+)-**1** and (−)-**1**] from penta-*O*-acetyl-*aldehydo*-D-galactose thiosemicarbazone under two different acetylating conditions has been described by Somogyi [1]. In a further publication, El Ashry et al. [2] reported the synthesis of the dextrorotatory isomer by direct acetylation of D-galactose thiosemicarbazone (**2**). All our attempts to synthesize the analogous compounds from D-glucose or D-mannose thiosemicarbazone (**3** and **4**) using this method failed, and in addition, the results for compound **2** itself were not reproducible. According to these observations, we decided to study the reaction products of **2**, **3** and **4** under different acylation conditions. The products were isolated and characterized in each case. Using the experimental data, we attempted a mechanistic explanation for our observations.

2. Results

For our purposes we applied two different acetylating procedures. Procedure A used an acetylating mixture of acetic anhydride and pyridine at room temperature during 24 h, while Procedure B was carried out by heating the thiosemicarbazones with boiling acetic anhydride.

By carrying out Procedure A on compound **2**, we could isolate, in several cases, (+)-**1** as a main product, a small proportion of (−)-**1**, as well as acetylated pyranose structures, which were separated and characterized as 4-*N*-acetyl-1-*N*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)thiosemicarbazide (**5**), and 1,4-*N*,*N*-diacetyl-1-*N*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)thiosemicarbazide (**6**).

* Corresponding author. Tel./fax: +54-11-45763346.
E-mail address: norma@qo.fcen.uba.ar (N.B. D'Accorso).

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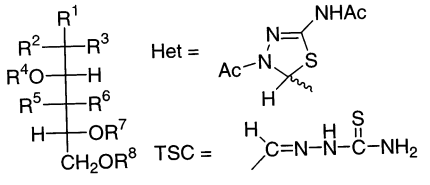
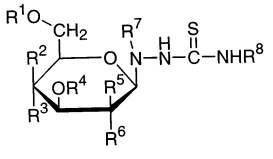
In addition, we obtained spectroscopic evidence of 1-*N*-acetyl-1-*N*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)thiosemicarbazide (**7**). In other cases, when we applied the same procedure on another batch of **2**, no heterocyclic compounds were found, and the main isolated products were **5** and **6**.

An explanation of this behavior was given by the ^{13}C NMR spectra of different batches of compound **2**, which showed that it can crystallized as a single pyranose form or as a mixture of this pyranose and an open-chain structure, according to its reaction and crystallization conditions, in a variable ratio (see Section 4). When the C=N bond was not present in the starting material, thiadiazoline derivatives could not be obtained by this procedure.



	R1	R2	R3	R4	R5	R6	R7	R8
(±)-1	Het	H	OAc	Ac	OAc	H	Ac	Ac
2	TSC	H	OH	H	OH	H	H	H
(-)-12	Het	H	OAc	Ac	H	OAc	Ac	Ac
(±)-13	Het	OAc	H	Ac	H	OAc	Ac	Ac



	R1	R2	R3	R4	R5	R6	R7	R8
2	H	OH	H	H	H	OH	H	H
3	H	H	OH	H	H	OH	H	H
4	H	H	OH	H	OH	H	H	H
5	Ac	OAc	H	Ac	H	OAc	H	OAc
6	Ac	OAc	H	Ac	H	OAc	OAc	OAc
7	Ac	OAc	H	Ac	H	OAc	OAc	H
8	Ac	H	OAc	Ac	H	OAc	OAc	H
9	Ac	H	OAc	Ac	H	OAc	H	OAc
10	Ac	H	OAc	Ac	H	OAc	OAc	OAc
11	Ac	H	OAc	Ac	OAc	H	H	OAc

Scheme 1.

As it was observed for D-glucose-4-tolylthiosemicarbazone [3], thiosemicarbazones **3** and **4** are β-pyranose structures, even in aqueous solution, we could not synthesize them in any other form than these cyclic structures (determined by ^{13}C NMR, see Section 4). As a consequence of that, application of Procedure A on these compounds allowed us to isolate and characterize only some acetylated pyranose products, but no thiadiazoline derivatives. These pyranose products were 1-*N*-acetyl-1-*N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiosemicarbazide (**8**), 4-*N*-acetyl-1-*N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiosemicarbazide (**9**), 1,4-*N*,*N*-diacetyl-1-*N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiosemicarbazide (**10**), and 1-*N*-acetyl-1-*N*-(2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl)thiosemicarbazide (**11**). These compounds are summarized in Scheme 1. ^1H NMR data for compounds **5**–**11** are listed in Table 1, and ^{13}C NMR data assignments were made using model compounds (Table 2)[1].

When we applied Procedure B on compound **2** (in the pure pyranose form), we obtained a reproducible result: the main compound was (−)-**1**. Other isolated products were penta-*O*-acetyl-β-D-galactopyranose and 2-acetamido-5-methyl-1,3,4-thiadiazole. In addition we had spectroscopic evidence of the formation of some acetylated derivatives of (galactopyranosyl)hydrazine by losses of the thiocarbamoyl moiety. In the literature there is a similar degradation reported for penta-*O*-acetyl-*aldehydo*-D-galactose semicarbazone, which in presence of acetic anhydride and pyridine loses a carbamoyl group, affording the corresponding *N*,*N*-diacetylhydrazine [4]. Application of Procedure B to **3** gave the same result as that observed in the case of compound **2**: only one thiadiazoline, (−)-5-acetamido-3-*N*-acetyl-2-[1,2,3,4,5-penta-*O*-acetyl-D-*gluco*-pentitol-1-yl]-1,3,4-thiadiazoline [(−)-**12**], peracetylated glucopyranose, and the above-mentioned thiadiazole with other degradation products. As expected, Procedure B applied to compound **4** gave both possible thiadiazolines, (+)- and (−)-5-

[1] For display of the NMR data, the carbohydrate part is shown with primed numbers.

Table 1
^{1}H NMR data for compounds **5**, **6** and **8**–**11**

Chemical shifts (δ, ppm)	Compounds					
	5	**6**	**8**	**9**	**10**	**11**
H-1′	5.14	5.89	5.84	4.45	5.95	4.68
H-2′	5.15	5.07	5.03	4.90	4.80	5.61
H-3′	4.52	5.15	5.39	5.22	5.03	5.15
H-4′	5.43	5.32	5.04	4.97	5.33	5.25
H-5′	3.89	3.99	3.84	3.58	3.76	3.68
H-6′a	4.21	3.99	4.36	4.19	4.16	4.31
H-6′b	4.04	3.99	4.08	4.00	4.13	4.10
N*H*-1	6.41			6.39		6.26
N*H*-2	7.15	8.90	8.21	7.27	9.21	7.67
N*H*-4	10.10	12.10	6.64, 6.28	10.07	12.06	10.17
Coupling constants (J, Hz)						
$J_{1',2'}$	9.0	8.8	9.1	8.8	9.5	<1
$J_{2',3'}$	10.2	10.2	9.3	9.1	9.6	2.8
$J_{3',4'}$	2.2	3.1	9.5	9.3	9.6	9.8
$J_{4',5'}$	1.0	<1	10.1	9.8	9.5	9.0
$J_{5',6'a}$	7.0		2.2	5.4	6.7	6.3
$J_{5',6'b}$	6.3		4.5	2.5	5.4	2.5
$J_{6'a,6'b}$	11.1		12.6	12.3	12.1	12.1

Table 2
^{13}C NMR data for compounds **5**, **6** and **8**–**11**

Chemical shifts (δ, ppm)	Compounds					
	5	**6**	**8**	**9**	**10**	**11**
C-1′	90.3	81.1	80.7	89.7	80.4	88.5
C-2′	68.1	66.7[a]	67.6	70.7	67.4	68.0
C-3′	71.0	70.5	74.1	72.6[a]	73.7	70.7
C-4′	67.1	67.0[a]	68.4	68.5	69.3	66.4
C-5′	71.5	72.4	72.4	72.8[a]	73.7	73.4
C-6′	61.1	61.0	61.0	61.7	62.2	62.3
C-3 (C=S)	184.4	183.5	184.9	184.3	182.3	184.4

[a] These values may be exchanged.

acetamido-3-*N*-acetyl-2-[1,2,3,4,5-penta-*O*-acetyl-D-*manno*-pentitol-1-yl]-1,3,4-thiadiazoline [(+)-**13** and (−)-**13**], in addition to peracetylated mannopyranose, 2-acetamido-5-methyl-1,3,4-thiadiazole and degradation products analogous to those observed for compound **2** and **3**. ^{1}H and ^{13}C NMR data for compounds (+)-**1**, (−)-**1**, (+)-**12**, (−)-**12**, (+)-**13** and (−)-**13** are listed in Tables 3 and 4. Assignments of ^{13}C NMR signals of compounds (+)-**1** and (−)-**1** were made by heteronuclear COSY experiments, which confirmed our previous assignments using model compounds.

Thiadiazolines derived from D-galactose and D-mannose thiosemicarbazone [(+)-**1**, (−)-**1**, (+)-**13** and (−)-**13**] showed a planar zigzag extended chain as the main conformation in solution, as was deduced using the ^{1}H NMR first-order analysis coupling constant. Using the same procedure we determined that (−)-**12** showed a deviation from the planar zigzag extended chain, which corresponded to ${}_1G^-$ using the convention of Angyal et al. [5].

The assigned conformations for these compounds are shown in Fig. 1. Despite the fact that all spectra were very clear, the absolute configuration of the heterocyclic C-2 could not be assigned on the basis of potential interactions between the heterocyclic ring and the

Table 3
^{1}H NMR data for compounds (+)-**1**, (−)-**1**, (−)-**12**, (+)-**13** and (−)-**13**

Chemical shifts (δ, ppm)	Compounds				
	(+)-**1**	(−)-**1**	(−)-**12**	(+)-**13**	(−)-**13**
H-2	5.79	6.06	5.97	5.94	6.09
H-1′	4.99	5.63	5.52	5.52	5.30
H-2′	5.39	5.43	5.35	5.37	5.70
H-3′	5.29	5.29	5.26	5.44	5.41
H-4′	5.25	5.22	4.96	5.11	4.97
H-5′a	4.19	4.21	4.13	4.20	4.22
H-5′b	3.77	3.81	3.98	4.00	4.03
–N*H*–$COCH_3$	8.14	8.43	8.91	8.27	9.49
Coupling constants (J, Hz)					
$J_{2,1'}$	9.8	1.6	2.3	1.8	5.6
$J_{1',2'}$	1.4	1.9	7.3	9.2	9.1
$J_{2',3'}$	9.9	9.6	3.4	2.0	1.8
$J_{3',4'}$	1.9	1.9	7.9	9.4	8.9
$J_{4',5'a}$	4.8	4.9	4.3	4.9	4.9
$J_{4',5'b}$	7.5	7.1	3.4	2.7	2.7
$J_{5'a,5'b}$	11.6	11.6	12.5	12.5	12.5

Table 4
^{13}C NMR data for compounds (+)-**1**, (−)-**1**, (−)-**12**, (+)-**13** and (−)-**13**

Chemical shifts (δ, ppm)	Compounds				
	(+)-**1**	(−)-**1**	(−)-**12**	(+)-**13**	(−)-**13**
C-2	62.2	67.2	65.1	66.9	64.7
C-5 (C=N)	148.2	147.3	146.5	147.9	147.6
C-1′	70.6	67.5	67.8[a]	67.3[a]	68.8
C-2′	66.4	67.7	70.5	67.6[a]	67.8[a]
C-3′	67.4	68.0	68.0[a]	67.3[a]	67.7[a]
C-4′	67.4	68.1	68.3	67.9[a]	68.1[a]
C-5′	62.0	62.1	61.2	61.9	61.5

[a] These values may be exchanged.

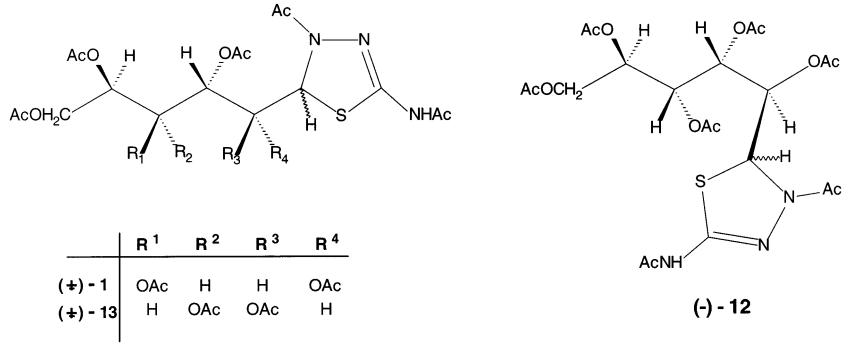


Fig. 1. Conformation of acyclic-sugar derivatives (±)-**1**, (−)-**12** and (±)-**13**.

carbohydrate chain. All efforts to obtain crystals for X-ray diffraction were unsuccessful. Thus this configuration could not be assigned. However, we carried out molecular calculations which led us to formulate an hypothesis about their absolute configuration (see Section 3).

All acetylated pyranose structures showed the $^4C_1$ as the main conformation in solution that was determined by ^{1}H NMR first-order analysis of the coupling constants, selective irradiation, as well as by ^{1}H NMR spectral simulations [6].

3. Discussion

Comparing the behavior of **2**, **3** and **4** toward Procedure A, we can conclude that heterocyclization occurs only if the starting material has a C=N bond. When we studied the same thiosemicarbazones with Procedure B, we found that even in the case where the substrate has a single pyranosidic form, thiadiazolines could be obtained.

The main differences between the two methods are the pH and the temperature. Taking in account that a pyranosidic form is a hemiacetal, acidic media in Procedure B can promote pyranose ring opening, which allows the heterocyclization reaction to proceed. Obtaining 2-acetamido-5-methyl-1,3,4-thiadiazole under these conditions is a direct consequence of the loss of the nitrogen-containing part. A similar loss was described in the transglycosylation of glycosylamines [7], and it occurs probably by formation of D-hexopyranosylium ion. According to this theory, the possibility of obtaining the α- and the β-per-*O*-acetyl hexopyranose from that intermediate is the same, but we could isolate only the β anomer. When we applied Procedure B to compound **6**, using GC with corresponding standards, we found that both anomers were formed. Isolation of only one of them may be a direct consequence of separative procedures, which includes further crystallization that may favor the isolation of a single annomer.

As mentioned above, Procedure B carried out on **2** and **3** gave only one of the two possible thiadiazolines, but **4** gave both, and it can be concluded that the inversion of the configuration on C-2 has a strong influence on the products obtained.

When we studied the consequences of heating time on compounds **3** and **4**, we found that for compound **3**, the results of a longer reaction time was an increase in the yield of heterocyclic products. Meanwhile for compound **4**, this increase in yield was parallel to a loss of (−)-**13**. This fact could indicate that an excess of energy could effect a conversion of one isomer into the other. Thus (−)-**13** could be a kinetic product that can be converted into the thermodynamic (+)-**13**.

Taking in account that (+)-**1** was synthesized by the lowest energy procedure, we assume that (+)-**1** could be the kinetic product, and (−)-**1** the thermodynamic one. In order to estimate the conversion time between two isomers, we applied Procedure B on pure (+)-**1** and found using ^{1}H NMR that at 30 min both thiadiazolines were present. So we investigated the reaction product of thiosemicarbazone **2** by Procedure B at 30 min, and we found, that even when the reaction was very incomplete, the two corresponding thiadiazolines were present in a 1:1 ratio.

Summing up these experimental data we can conclude the following:

1. The cyclization of free sugar thiosemicarbazones can be made in either acidic or basic media.
2. If the reaction is carried out in basic media, the thiadiazolines can be obtained only if the C=N is present, but not with the cyclic form of thiosemicarbazones.
3. If the reaction is carried out in acidic media, these conditions promote pyranose ring opening, and the cyclation yields both thiadiazolines.
4. One of these thiadiazolines might be a kinetic product and the other the thermodynamic one.
5. Isolation of both thiadiazolines depends on the carbohydrate under reaction and the interconversion speed between the kinetic and thermodynamic products.

As we previously noted, the absolute configuration of the heterocyclic C-2 in thiadiazoline derivatives could not be determined. Attempting to build some theoretical supposi-

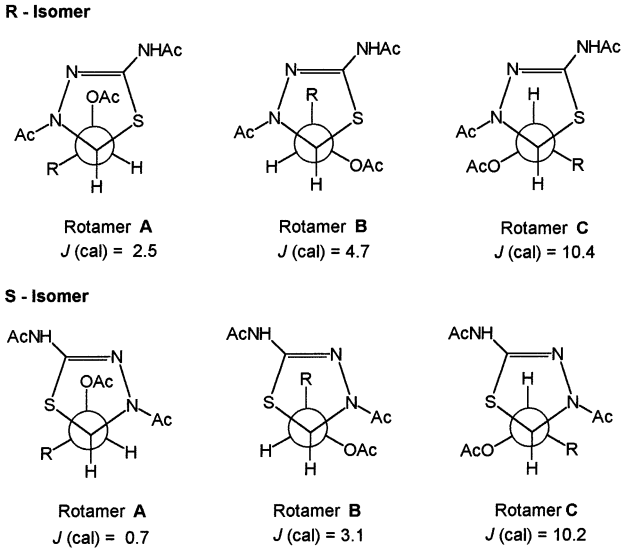


Fig. 2. Rotamers for (2*R*)-**1** and (2*S*)-**1**.

tions and applying an approximation used before [8], we calculated the lowest energy conformation for both isomers of compound **1** using molecular mechanics and semiempirical methods [9]. As the result of both calculations, we came to the same conclusion: the lowest energy conformation for the 2R and 2S isomers of compound **1** show a *gauche* relationship between heterocyclic H-2 and H-1′. According to this calculation, they might have a small coupling constant, but (+)-**1** has a $J_{2,1'}$ value of 9.8 Hz that indicates an *anti* relationship. As the observed $J_{2,1'}$ is an average between coupling constants of closer rotamers (in regard to the energetic level), we must to suppose that there is a greater contribution to the rotameric equilibrium of an *anti* form, which could not be avoided.

In regard to that, we used PCMODEL™ [9], which can calculate a theoretical coupling constant for each pair of protons, and we performed the minimization of three rotamers for 2R and 2S isomer of **1**. We arrived at the following conclusions:

For the R isomer, rotamer **B** is the lowest energy structure (see Fig. 2), but the difference of energy with rotamer **C** is about 1 kcal/mol, while the difference with rotamer **A** is about 4 kcal/mol. Thus rotamers **B** and **C** must make the major contribution to the equilibrium mixture. Taking into account that rotamers **B** and **C** have a $J_{2,1'}$ bigger than (−)-**1** (1.6 Hz), the R configuration on C-2 might be attributed to compound (+)-**1**.

Similar calculations performed with the S isomer show that rotamers **A** and **B** have an energetic difference of only 0.5 kcal/mol, while the difference with rotamer **C** is near 3 kcal/mol, and the configuration on C-2 of compound (−)-**1** which has a $J_{2,1'}$ of 1.6 Hz, could be assigned to the S isomer.

4. Experimental

General methods.—^{1}H and ^{13}C NMR spectra were recorded at 200 or 300 MHz and 50 or 75 MHz, respectively, in $CDCl_3$ with Me_4Si as internal standard. Mass spectra were performed with a Shimadzu QP-5000 by electron-impact ionization and fast-atom bombardment mass spectra (FABMS) in a ZAB-SEQ4F. Optical rotations were recorded at 20 °C, and the melting points are uncorrected. Elemental analyses were performed at the UMYMFOR, Facultad de Ciencias Exactas y Naturales, University of Buenos Aires, Buenos Aires, Argentina. Chromatographic purification was performed on Silica Gel G using mixtures of benzene and EtOAc as the eluent.

Procedure A.—Aldose thiosemicarbazone (1 g, 3.95 mmol) was suspended in 125 mL of pyridine, and 25 mL of Ac_2O were added. The mixture was stirred for 24 h at rt, at the end of which time the reaction was stopped by addition of EtOH. The mixture was concd under diminished pressure to a thick syrup, with occasional addition of water and toluene to eliminate all AcOH residues.

By application of this procedure to compounds **2**, **3** and **4** we could isolate, by chromatographic purification, compounds (±)-**1**, **5**, **6**, **8**, **9**, **10**, **11**, and obtained spectroscopic evidence for **7**.

Procedure B.—Aldose thiosemicarbazone (1 g, 3.95 mmol) was suspended in 44 mL of Ac_2O, and the mixture was stirred at reflux using a sand bath during a variable time period. The reaction was stopped by addition of EtOH. The mixture was concd under diminished pressure to a thick syrup, with occasional addition of water and toluene to eliminate all AcOH residues. The syrup was dissolved in EtOH and filtered to eliminate the

2-acetamido-5-methyl-1,3,4-thiadiazole. It was then concd, and the residue was purified by column chromatography.

By application of this procedure to compounds **2**–**4** we could isolate compounds (−)-**1**, (−)-**12**, (+)-**13**, (−)-**13**, 2-acetamido-5-methyl-1,3,4-thiadiazole, and the corresponding penta-*O*-acetyl-D-hexopyranose.

*(+)-5-Acetamido-3-*N*-acetyl-2-[1,2,3,4,5-penta-*O*-acetyl-*D*-galacto-pentitol-1-yl]-1,3,4-thiadiazoline* [(+)-**1**].—The yield of this compound was variable in accord with the proportion of the open-chain form. The better yield was 1.23 g (57.2%); mp 210–212 °C. (lit. 217 °C [1], 214 °C [2]); ^{1}H NMR ($CDCl_3$): δ 2.16–1.96 (7 s, 21 H, $-CH_3$); ^{13}C NMR ($CDCl_3$): δ 170.2–168.9 (4 s, C=O), 23.1–20.5 (4 s, CH_3-); EIMS: m/z 547 (M^+), 362, 331, 186, 144, 102 (100%).

*(−)-5-Acetamido-3-*N*-acetyl-2-[1,2,3,4,5-penta-*O*-acetyl-*D*-galacto-pentitol-1-yl]-1,3,4-thiadiazoline* [(−)-**1**].—By application of Procedure B over 4 h on D-galactose thiosemicarbazone in the pyranose form, 0.56 g (26%) of the title compound could be obtained; mp 234 °C (lit. 234 °C [2]); ^{1}H NMR ($CDCl_3$): δ 2.19–1.93 (7 s, 21 H, $-CH_3$); ^{13}C NMR ($CDCl_3$): δ 170.4–168.5 (7 s, C=O), 23.1–20.5 (6 s, $-CH_3$); EIMS: m/z 547 [M^+], 331, 186, 144, 102, 43 (100%).

D-*Galactose thiosemicarbazone* (**2**).—Synthesis was carried out in two different ways: (a) as described in the literature [10], and (b) by reflux a mixture of thiosemicarbazide and D-galactose in EtOH. In the first case, we could obtain the thiosemicarbazone **2** as a mixture of pyranose and open-chain form. When the second method was used, and the mixture was allowed to crystallize at rt, we obtained **2** only as a pyranose form.

Pyranose form: ^{13}C NMR (Me_2SO-d_6): δ 181.4 (C=S), 91.8 (C-1), 76.7 (C-5), 74.0 (C-3), 68.9 (C-2 or C-4), 68.8 (C-2 or C-4), 61.7 (C-6).

Open-chain form: ^{13}C NMR (Me_2SO-d_6): δ 178.2 (C=S), 148.6 (C=N, C-1), 71.7 (C-4), 70.3 (C-3 or C-5), 70.1 (C-3 or C-5), 69.4 (C-2), 63.4 (C-6).

D-*Glucose and* D-*mannose thiosemicarbazone* (**3**) *and* (**4**).—The title compounds were synthesized by both procedures cited earlier for compound **2**, but they could only be obtained in the pyranose form.

D-*Glucose thiosemicarbazone* (**3**).—^{13}C NMR (Me_2SO-d_6): δ 181.5 (C=S), 90.9 (C-1), 77.7 (C-3 or C-5), 77.2 (C-3 or C-5), 71.5 (C-2), 70.8 (C-4), 62.4 (C-6).

D-*Mannose thiosemicarbazone* (**4**).—^{13}C NMR (Me_2SO-d_6): δ 181.4 (C=S), 87.7 (C-1), 78.3 (C-5), 74.4 (C-3), 70.2 (C-2), 68.2 (C-4), 62.8 (C-6).

*4-*N*-Acetyl-1-*N*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-galactopyranosyl)thiosemicarbazide* (**5**).—Yield: 0.30 g (16.5%); mp 122–123 °C (sealed capillary), $[\alpha]_D^{20}$ −73.6° (*c* 1, $CHCl_3$), λ_{max} = 272 nm (EtOH); ^{1}H NMR ($CDCl_3$): δ 2.45–1.93 (5 s, 15 H, $-CH_3$); ^{13}C NMR ($CDCl_3$): δ 178.9–170.0 (5 s, C=O), 25.7–20.6 (4 s, $-CH_3$); FABMS (glycerol): m/z 464 $[M+H]^+$; EIMS: m/z 463 [M^+], 404, 388, 331, 43 (100%); Anal. Calcd for $C_{17}H_{25}N_3O_{10}S$: C, 44.06; H, 5.40; N, 9.07; S, 6.91. Found: C, 43.77; H, 5.53; N, 8.75; S, 6.86.

*1,4-*N,N*-Diacetyl-1-*N*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-galactopyranosyl)thiosemicarbazide* (**6**).—Yield: 0.5 g (25.0%); mp 103–105 °C; $[\alpha]_D^{20}$ −14.8° (*c* 1, $CHCl_3$); λ_{max} = 276 nm (EtOH); ^{1}H NMR ($CDCl_3$): δ 2.19–1.91 (6 s, 18 H, $-CH_3$); ^{13}C NMR ($CDCl_3$): δ 172.5–169.8 (5 s, C=O), 24.0–20.6 (3 s, $-CH_3$); EIMS: m/z 505 [M^+], 331, 43 (100%); Anal. Calcd for $C_{19}H_{27}N_3O_{11}S$: C, 45.15; H, 5.35; N, 8.32; S, 6.34. Found: C, 45.34; H, 5.73; N, 8.63; S, 6.25.

*1-*N*-Acetyl-1-*N*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)thiosemicarbazide* (**8**).—Yield: 0.17 g (9.1%); mp 217 °C; $[\alpha]_D^{20}$ 67.7° (*c* 1, $CHCl_3$); λ_{max} = 216 and 250 nm (EtOH); ^{1}H NMR ($CDCl_3$): δ 2.12–2.04 (4 s, 15 H, $-CH_3$); ^{13}C NMR ($CDCl_3$): δ 173.4–169.1 (5 s, C=O), 20.8–20.4 (3 s, $-CH_3$); EIMS: m/z 463 [M^+], 331, 43 (100%); Anal. Calcd for $C_{17}H_{25}N_3O_{10}S$: C, 44.06; H, 5.40; N, 9.07. Found: C, 43.93; H, 5.72; N, 9.35.

*4-*N*-Acetyl-1-*N*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)thiosemicarbazide* (**9**).—Yield: 0.60 g (30.2%); mp 69–71 °C; $[\alpha]_D^{20}$ −71.9° (*c* 1, $CHCl_3$); λ_{max} = 226 and 268 nm (EtOH); ^{1}H NMR ($CDCl_3$): δ 2.41–1.94 (5 s, 15 H, $-CH_3$); ^{13}C NMR ($CDCl_3$): δ 178.5–169.5 (5 s, C=O), 25.3–20.5 (3 s, $-CH_3$); EIMS: m/z 463 [M^+], 331, 43 (100%); Anal.

Calcd for $C_{17}H_{25}N_3O_{10}S{\cdot}C_4H_8O_2$: C, 45.74; H, 5.99; N, 7.62. Found: C, 45.62; H, 5.72; N, 7.35.

*1,4-*N,N-*Diacetyl-1-*N-*(2,3,4,6-tetra-*O-*acetyl-β-*D-*glucopyranosyl)thiosemicarbazide* (**10**).—Yield: 0.85 g (42.8%); mp: 99–101 °C; $[\alpha]_D$ 14.6° (*c* 1, $CHCl_3$); $\lambda_{max} = 224$ and 274 nm (EtOH); ^{1}H NMR ($CDCl_3$): δ 2.16–1.34 (4 s, 18 H, –CH_3); ^{13}C NMR ($CDCl_3$): δ 170.9–169.3 (6 s, C=O), 26.8–20.6 (5 s, –CH_3); EIMS: *m/z* 505 [M^+], 331, 43 (100%); Anal. Calcd for $C_{19}H_{27}N_3O_{11}S{\cdot}C_4H_8O_2$: C, 46.54; H, 5.90; N, 7.08. Found: C, 46.50; H, 5.77; N, 6.77.

*4-*N-*Acetyl-1-*N-*(2,3,4,6-tetra-*O-*acetyl-β-*D-*mannopyranosyl)thiosemicarbazide* (**11**).—Yield: 0.40 g (20.2%) (syrup); ^{1}H NMR ($CDCl_3$): δ 2.47–2.02 (5 s, 15 H, –CH_3); ^{13}C NMR ($CDCl_3$): δ 178.1–169.3 (5 s, C=O), 25.2–20.7 (5 s, –CH_3); EIMS: *m/z* 463 [M^+], 331, 43 (100%); Anal. Calcd for $C_{17}H_{25}N_3O_{10}S$: C, 44.06; H, 5.40; N, 9.07. Found: C, 44.32; H, 5.25; N, 8.93.

*(−)-5-Acetamido-3-*N-*acetyl-2-[1,2,3,4,5-penta-*O-*acetyl-*D-gluco-*pentitol-1-yl]-1,3,4-thiadiazoline* [(−)-**12**].—By application of Procedure B during 24 h on D-glucose thiosemicarbazone in the pyranose form, 0.69 g (32%) of the title compound was obtained; mp: 98–100 °C; $[\alpha]_D^{20}$ −152.1° (*c* 1, $CHCl_3$); $\lambda_{max} = 218$ and 286 nm (EtOH); ^{1}H NMR ($CDCl_3$): δ 2.14–1.93 (6 s, 21 H, –CH_3); ^{13}C NMR ($CDCl_3$): δ 170.7–168.7 (7 s, C=O), 23.2–20.5 (5 s, –CH_3); EIMS: *m/z* 186 (100%), 144, 102; Anal. Calcd for $C_{21}H_{29}N_3O_{12}S$: C, 46.07; H, 5.30; N, 7.68. Found: C, 46.34; H, 5.07; N, 7.82.

*(+)- and (−)-5-Acetamido-3-*N-*acetyl-2-[1,2,3,4,5-penta-*O-*acetyl-*D-manno-*pentitol-1-yl]-1,3,4-thiadiazoline* [(+)-**13** and (−)-**13**].—By using Procedure B for 2 h on D-mannose thiosemicarbazone, 0.50 g (23%) of the title compounds were obtained in a 2:1 ratio. At a reaction time of 4 h, the global yield rises to 0.65 g (30.1%) with a 4:1 ratio. After a reflux of 15 h, only (+)-**13** could be isolated in a 35% yield (0.76 g).

*(+)-5-Acetamido-3-*N-*acetyl-2-[1,2,3,4,5-penta-*O-*acetyl-*D-manno-*pentitol-1-yl]-1,3,4-thiadiazoline* [(+)-**13**].—Yield: 0.76 g (35%); mp: 115–117 °C; $[\alpha]_D^{20}$ 373.2° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.21–1.72 (7 s, 21 H, –CH_3); ^{13}C NMR ($CDCl_3$): δ 170.5–168.7 (7 s, C=O), 23.4–20.7 (3 s, 21 H, –CH_3); EIMS *m/z* 547 [M^+], 186, 144 (100%), 102, 43; Anal. Calcd for $C_{21}H_{29}N_3O_{12}S{\cdot}CH_4O$: C, 45.60; H, 5.70; N, 7.25. Found: C, 45.81; H, 5.44; N, 7.21.

*(−)-5-Acetamido-3-*N-*acetyl-2-[1,2,3,4,5-penta-*O-*acetyl-*D-manno-*pentitol-1-yl]-1,3,4-thiadiazoline* [(−)-**13**].—Yield: 0.17 g (7.8%); mp: 98–100 °C; $[\alpha]_D^{20}$ −121.9° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.22–2.04 (7 s, 21 H, –CH_3); ^{13}C NMR ($CDCl_3$): δ 170.6–168.9 (6 s, C=O), 23.0–20.5 (4 s, –CH_3); EIMS: *m/z* 186, 144 (100%), 102, 43; Anal. Calcd for $C_{21}H_{29}N_3O_{12}S{\cdot}C_4H_8O_2$: C, 47.24; H, 5.83; N, 6.61; S, 5.04. Found: C, 47.04; H, 5.66; N, 6.83; S, 4.81.

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