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Influence of Intramolecular Hydrogen-Bonding on the Conformational Properties of Sugar Thioureas

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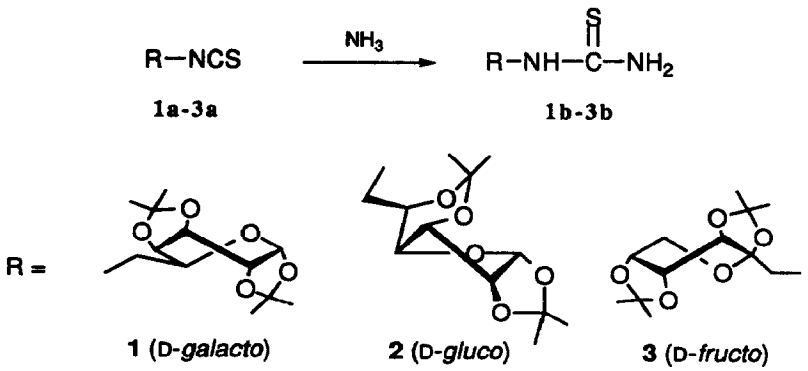
Abstract: Reaction of deoxyisothiocyanato derivatives of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose, 1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranose, and 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose with ammonia afforded the corresponding sugar thioureas. Both the *Z* and *E* stereoisomers around the NH-C(=S) bond were observed in the ^{1}H and ^{13}C NMR spectra of the later in the low temperature range, their relative proportions being a function of the sugar configuration. Experimental evidence for the existence of seven-membered NH····O intramolecular hydrogen bonds in the *E* isomers of thioureas has been obtained from DNMR experiments, rotational barrier height calculations, measurements of temperature coefficients for the ^{1}H chemical shifts of the NH signals, and study of the influence of the solvent polarity in the rotameric ratio.

Thioureido sugars are important intermediates in synthetic approaches to nucleoside analogues. In addition, the structural analogy of the thiourea group with other functional groups commonly found in naturally occurring carbohydrate derivatives, such as amide, urea, or phosphate, make sugar thioureas interesting from a biological point of view. For this reason, much effort has been directed to the synthesis of such compounds.[1] However, works dealing with the configuration and conformation of sugar thioureas are scarce,[1d,e] in spite of the influence that these structural aspects may have on both the chemical and biological properties.

Previous studies concerned exclusively the particular case of a thioureido group linked to a secondary carbon atom of an acylated aldopyranose. The conformational rigidity of the sugar ring simplifies the structural analysis of these molecules. We now report the synthesis and conformational properties of some thioureido sugars in which the functional group is linked to a primary carbon atom. The existence of two slow-rotating pseudo amide bonds in these compounds makes the structural analysis more complex as compared to the homologous thioamides[2]. On the other hand, the sharing of delocalized π electrons leads to much lower energy barriers suitable to study by using dynamic NMR techniques.[3] The possibility of hydrogen bonding as a consequence of the relative flexibility of the thioureidomethyl group and its role in the stabilization of certain conformers as a function of the sugar configuration have been studied.

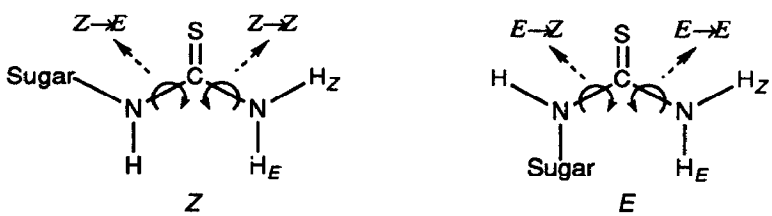
RESULTS AND DISCUSSION

6-Deoxy-1,2:3,4-di-*O*-isopropylidene-6-thioureido-α-D-galactopyranose (**1b**), 6-deoxy-1,2:3,5-di-*O*-isopropylidene-6-thioureido-α-D-glucofuranose (**2b**), and 1-deoxy-2,3:4,5-di-*O*-isopropylidene-1-thioureido-β-D-fructopyranose (**3b**) were prepared by reaction of the corresponding sugar isothiocyanate[4] **1a-3a** with ammonia (Scheme 1).



Scheme 1

The ^1H (Table 1) and ^{13}C (Experimental) NMR spectra of the thioureas **1b-3b**, recorded at room temperature for $CDCl_3$ solutions, displayed broad signals, indicative of a relatively slow chemical exchange process. Variable temperature ^1H NMR spectra evidenced several coalescence phenomena. It must be considered that in thiourea derivatives both N-C(=S) rotations are restricted. Consequently, the hydrogen atoms at the NH_2 group become chemically and magnetically different in both the *Z* and *E* isomers. Hence, in addition to the chemical exchange associated to the *Z*/*E* configurational equilibrium, two degenerated processes involving the pro-*Z* (H_Z) and pro-*E* (H_E) protons must be considered.



The three coalescence phenomena were clearly perceived in the region of the NH resonances, with coalescence temperatures (T_c) of respectively 305, 268, and 252 ± 2 K for the *Z*→*E*/*E*→*Z*, *E*→*E*, and *Z*→*Z* exchanges (Figure 1). In the low temperature range, at least one of the resonances of the α-methylene protons

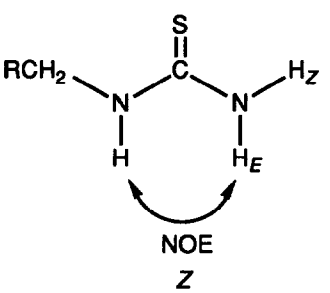
appeared at considerably lower field than the other one, suggesting a spacial proximity with respect to the sulphur atom. Therefore, the *Z* configuration was tentatively assigned to this isomer. Definitive evidence for this assignment was obtained from ROESY experiments at low temperatures, which, in addition, allowed identification of the signals for the diasterotopic NH_2 protons in both rotamers from the cross peaks indicated in the formulae.

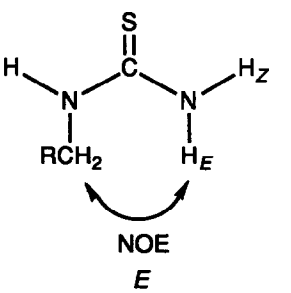
Table 1. ^{1}H NMR Data (300 MHz, $CDCl_3$) of Compounds **1b-3b**.

Comp.	Chemical shifts (δ, ppm)									
	H-1a	H-1b	H-2	H-3	H-4	H-5	H-6a	H-6b	NH	NH_2
1b[a]	—	5.53d	4.32dd	4.65dd	4.28dd	4.10bs	3.81bs	3.47ddd	6.82bs	6.16bs
1b*Z*[c]	—	5.56d	4.36m	4.64m	4.28bd	4.30-4.25m	3.99dd	3.45-3.34m	7.57t	6.48s
1b*E*	—	5.53d	4.36m	4.64m	4.23bd	3.84t	←—3.45-3.34m—→		7.36t	6.89s 6.70s
2b[b]	—	5.95d	4.55d	4.21d	4.28dd	←———	3.70 - 3.50m	——→	6.66t	6.22bs
2b*Z*[c]	—	6.05d	4.61d	4.26d	4.36dd	3.83m	4.08	3.70-3.50m	7.39t	6.48bs
2b*E*	—	6.04d	4.63d	4.26d	4.36dd	←—3.70-3.50m—→		3.43m	6.99t	6.77s 6.51s
3b[a]	←— 3.67bs —→		—	4.31d	4.62dd	4.23dd	3.92dd	3.76dd	6.82bs	6.16bs
3b*Z*[c]	4.05dd	3.94dd	—	4.46d	4.59dd	4.26m	3.85d	3.75d	7.44t	6.42s
3b*E*	3.56dd	3.35dd	—	4.29d	4.65dd	4.26m	3.92d	3.79d	7.56t	6.73s 6.68s

	Coupling constants (*J*, Hz)										
	$J_{1a,1b}$	$J_{1a,NH}$	$J_{1b,NH}$	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$	$J_{6a,NH}$	$J_{6b,NH}$
1b	—	—	—	4.9	2.4	7.8	1.8	—	4.9	13.0	—	8.0
1b*Z*	—	—	—	4.9	—	7.8	—	—	—	13.6	6.0	6.0
1b*E*	—	—	—	4.9	—	7.8	—	6.3	6.3	—	6.2	6.2
2b	—	—	—	3.7	0	4.0	7.1	—	—	—	5.5	5.5
2b*Z*	—	—	—	3.7	0	3.9	7.3	5.1	—	13.0	5.1	5.1
2b*E*	—	—	—	3.7	0	3.9	7.3	—	—	—	6.0	6.0
3b	14.0	6.0	6.0	—	—	1.8	8.0	1.4	0.6	13.2	—	—
3b*Z*	14.0	5.5	5.5	—	—	1.8	8.0	—	—	13.2	—	—
3b*E*	14.8	6.8	6.8	—	—	1.8	8.0	—	—	13.6	—	—

[a]At 323 K. [b]At 313 K. [c]At 263 K.





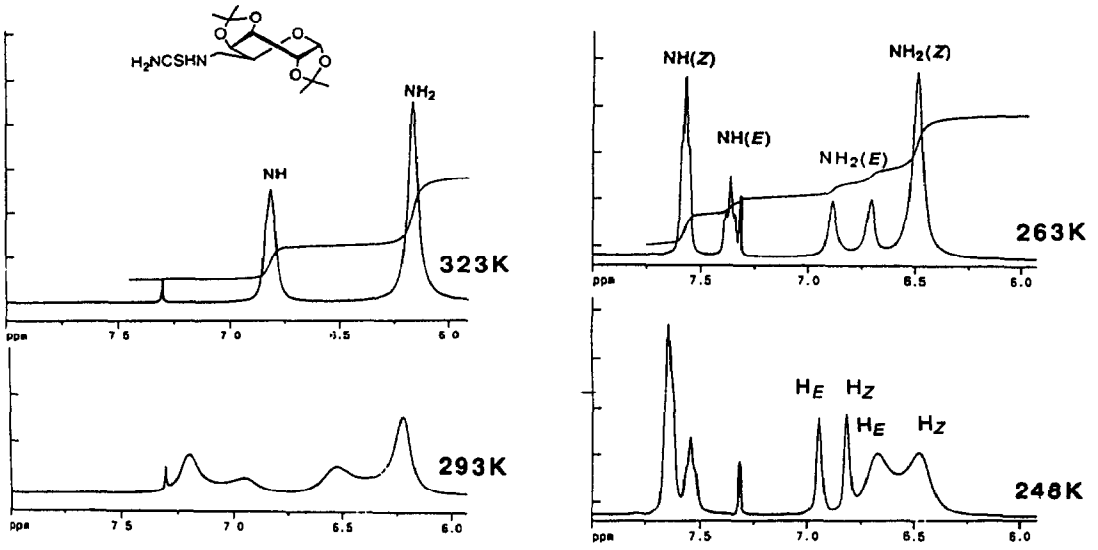
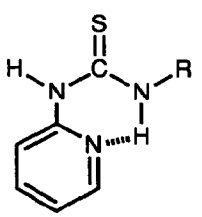


Figure 1. Partial (NH resonance region) ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of compound **1b** at different temperatures.

The following rules, arising from comparative analysis of the ^{13}C NMR spectra, were of diagnostic value: $\delta_{\alpha CH2(Z)} > \delta_{\alpha CH2(E)}$, $\delta_{C=S(Z)} > \delta_{C=S(E)}$. The relative proportion of *Z/E* isomers for **1b-3b** did not change significantly with temperature, the *Z:E* rotameric ratios being 1:0.48, 0.73:1, and 0.41:1, respectively. These unexpected high percentages of *E* rotamers cannot be satisfactorily explained exclusively in terms of steric effects.

The fact that only the *Z* isomer of sugar thioureas has been detected up to now probably means that the 1,3-parallel interaction between the sugar substituent and H_E is sterically unfavourable with respect to the sugar/sulphur *cis* arrangement. Intramolecular hydrogen bonding has been invoked in the case of *N*-(2-pyridyl)thioureas (**2**) to explain a similar stabilization of the *E*-isomer.[5] Analogously, an NH····O intramolecular hydrogen bond involving the NH_2 group in the *E* configuration would explain the observed experimental rotameric ratios for **1b-3b**.



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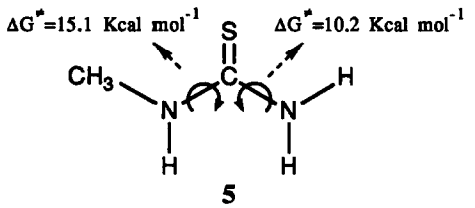
To support the above hypothesis, three type of experiments were carried out: (a) calculation of the activation free energies ($\Delta G^{\neq}$) for the hindered rotations about the N-C(=S) bonds, (b) measurements of the temperature coefficients of the NH chemical shifts, and (c) study of the influence of the solvent polarity on the relative proportion of *Z*/*E* isomers.

(a) Although total line shape analysis is by far the most reliable method to obtain $\Delta G^{\neq}$ values, the use of approximate equations based on spectral parameters usually provides accurate enough values for comparative purposes in the case of two-site chemical exchange processes.[4] Application of eq (1), where ΔW is the line widening due to chemical exchange,[6] and substitution of the rate constants obtained in Eyring's equation (2) results on the $\Delta G^{\neq}$ values[7] for the $Z \rightarrow E/E \rightarrow Z$, $E \rightarrow E$, and $Z \rightarrow Z$ exchanges showed in Table 2. The reliability of these data was confirmed by a magnetization transfer experiment[8] carried out on compound **3b** at 273 K, involving the $NH_2(Z)$ and $NH_2(E)$ singlets (see Experimental). The values of $\Delta G^{\neq}_{Z \rightarrow E}$ (15.1 ± 0.2 Kcal mol^{-1}) and $\Delta G^{\neq}_{E \rightarrow Z}$ (14.7 ± 0.2 Kcal mol^{-1}) obtained by this methodology reasonably approached those obtained from eq (1) and (2).

$$k = \pi\Delta W \qquad (1)$$

$$\Delta G^{\neq} = RT(\ln k_B/h - \ln \pi\Delta W/T) \qquad (2)$$

Comparison of data from Table 2 with reported data[9] for *N*-methylthiourea (**5**) revealed that, whereas the barrier heights associated to the $Z \rightarrow E/E \rightarrow Z$ and $Z \rightarrow Z$ processes in **1b**-**3b** were very similar to those for rotations about the corresponding bonds in *N*-methylthiourea, $\Delta G^{\neq}_{E \rightarrow E}$ values were significantly higher than $\Delta G^{\neq}$ for rotation about the NH_2-C(=S) bond in **5**, and even higher than the reported value for thiourea itself[9] (**6**).



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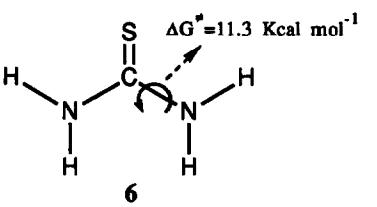

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Table 2. Gibbs energies of activation to hindered rotations of the sugar thioureas **1b**-**3b**.

	$\Delta G^{\neq a}$ (T^b)			
	$\Delta G^{\neq}_{E \rightarrow E}$	$\Delta G^{\neq}_{E \rightarrow Z}$	$\Delta G^{\neq}_{Z \rightarrow E}$	$\Delta G^{\neq}_{Z \rightarrow Z}$
1b	13.9 (263)	14.2 (293)	14.6 (293)	12.1 (248)
2b	13.2 (263)	14.3 (293)	14.0 (293)	11.8 (248)
3b	13.8 (263)	14.7 (303)	14.2 (303)	11.3 (283)

[a] In Kcal mol^{-1}. Calculated according to eq (1) and (2). The estimated errors do not exceed ±0.3 Kcal mol^{-1}. See ref 7. [b] In K.

This result is in agreement with the involvement of $NH_2(E)$ in an intramolecular hydrogen bond in compounds **1b-3b** which would partially anchor the *E* configuration, resulting in higher rotational barriers. The differences between $\Delta G^{\neq}_{E\rightarrow E}$ and $\Delta G^{\neq}_{Z\rightarrow Z}$ (~2 Kcal mol^{-1}) would represent the hydrogen bond stabilization energy, assuming that differences arising from other stereoelectronic interactions are irrelevant.

(b) Additional experimental evidence for the existence of these hydrogen bonds was obtained from temperature coefficient measurements for the NH chemical shifts (Table 3). It has been reported[10] that protons involved in efficient intramolecular hydrogen bonding have temperature coefficients at least one order of magnitude lower than protons which are not. In our case, the low values obtained for the pro-*E* NH_2 proton in the *E* isomers of **1b-3b**, as compared with values for the other nitrogen-bound protons, strongly support the above hypothesis. It is noteworthy that the NH proton in **1b**(*Z*) also has a lower temperature coefficient value, which may suggest a competition between two different hydrogen bonds in this molecule. This fact could explain the inversion in the *Z*/*E* populations observed for the D-*galacto* derivative **1b** as compared with the D-*gluco* (**2b**) and D-*fructo* (**3b**) thiourea derivatives.

Table 3. Temperature coefficients (ppm K^{-1}) for the N*H* chemical shifts of **1b-3b**.

	1b	**2b**	**3b**
NH (*Z*)	-0.005	-0.017	-0.015
NH (*E*)	-0.011	-0.014	-0.013
NH_2 (*E*)[a]	-0.002	-0.002	-0.001
NH_2 (*E*)[b]	-0.011	-0.014	-0.011

[a]pro-*E*. [b]pro-*Z*.

(c) Accepting that the existence of intramolecular hydrogen bonds is the main driving force in the stabilisation of the *E* isomers in $CDCl_3$ solutions of the sugar thioureas **1b-3b**, the position of the respective *E*/*Z* equilibria should be strongly influenced by modification of the solvent polarity. Increasing of this parameter by using mixtures of $CDCl_3$-Me_2SO-d_6 resulted in a progresive increase of the relative proportion of the *Z* at the expenses of the *E* isomer (Figure 2). A competition between intra- and inter-molecular hydrogen bonding probably explains this result. Binding of the NH protons to dimethyl sulphoxide molecules would break the intramolecular hydrogen bond. Steric factors then favour the *Z* configuration.

In conclusion, all commented data strongly support the original hypothesis of hydrogen bonding stabilization of the *E* isomers. Molecular models of **1b-3b**, taken into consideration that the sugar rings kept the rigid conformations already discussed for amides and thioamides[2], showed that seven-membered NH···O bonds can be easily formed involving the pro-*E* proton of the NH_2 group in the *E*-isomers and O-5 in the case of **1b** and **2b** or O-6 in the case of **3b**, but not in the *Z* isomers. Similar seven-membered hydrogen bond interactions have been found to be responsible for configurational stabilization in *N*-(α-hydroperoxyalkyl)amides[11] and macrocyclic polypeptides.[12] It is noteworthy that formation of these hydrogen bonds keep the thioureido group in *anti* disposition with respect to C-4 (**1b** and **2b**) or C-3 (**3b**), the most favourable arrangement in terms of steric interactions.[13]

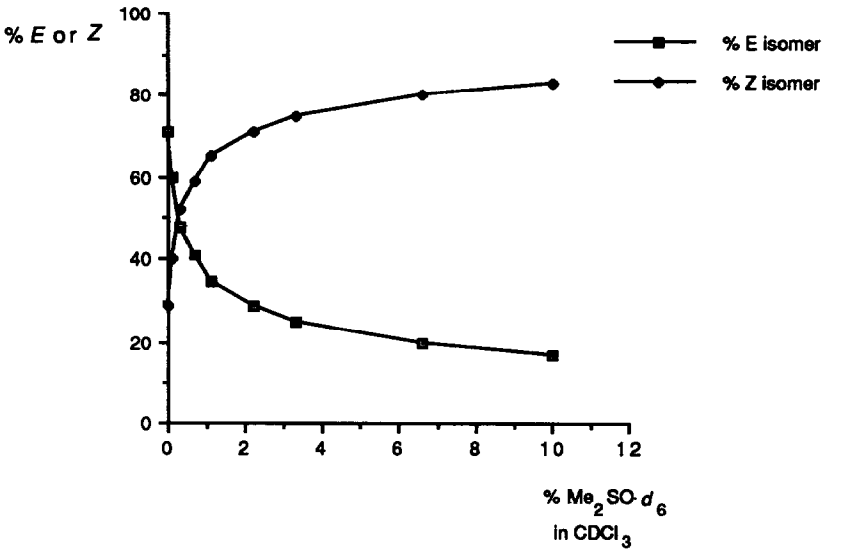
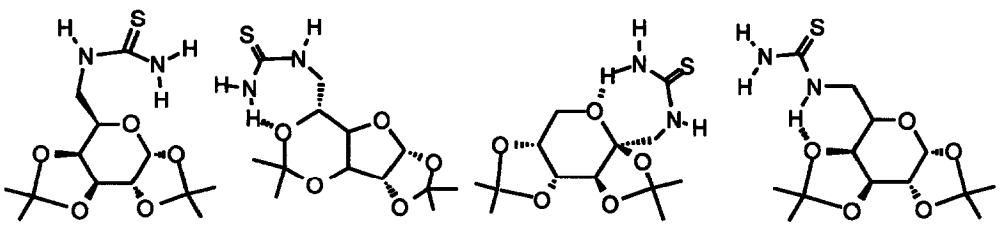


Figure 2. Plot of the relative proportions of the *Z*/*E* isomers of **3b** in mixtures of $CDCl_3$-Me_2SO-d_6 at 283 K. In neat Me_2SO-d_6 the *Z*:*E* ratio was 85:15. The concentration of **3b** was kept constant at $9 \cdot 10^{-5}$ M.

From these models, the NH····O-4 (**1b**, **2b**) or NH····O-3 (**3b**) shortest distances are of ~1.6, 2.1, and 2.7 Å, respectively. These differences explain the possibility of competition between the above mentioned seven-membered hydrogen bond and a six-membered hydrogen bond in the case of **1b**. Although this could exist in either the *Z* or *E* configuration, steric considerations would favour the *Z* isomer, in agreement with the experimental results.



1b *E* **2b** *E* **3b** *E* **1b** *Z*

EXPERIMENTAL SECTION

General methods. The General Methods reported in ref 2 were followed. The magnetization transfer experiment was carried out at 300 MHz for a $CDCl_3$ solution of **3b** at 273 K. A selective π pulse was applied at the frequency of resonance of the $NH_2(Z)$ protons. Spectra were recorded using exchange delays (τ_x) of 0.005, 0.01, 0.02, 0.03, 0.04, 0.06, 0.08, 0.1, 0.2, and 5 s (blank). Numerical analysis[14] of the changes in the peak heights of the NH_2 (*Z*) and NH_2 (*E*) signals as a function of the exchange delay (Table 4) yielded values of *Z*/*E* isomerization rate constants of 2.98 s^{-1} ($k_{E\rightarrow Z}$) and 7.08 s^{-1} ($k_{Z\rightarrow E}$), and a longitudinal relaxation time (T_1, assumed equal) of 0.26 s.

Table 4. Peak height variations for the N*H*$_2$ signals of **3b** (300 MHz, $CDCl_3$, 273 K) using different exchange delays (τ_x).

	Δ peak height[a] NH_2 (*E*)		Δ peak height[a] NH_2 (*E*)	
τ_x (s)	exptl	calcd[b]	exptl	calcd[b]
0.005	-15.52	-15.52	-100.00	-100.00
0.01	-16.71	-16.69	-95.14	-95.17
0.02	-18.73	-18.68	-86.33	-86.36
0.03	-20.36	-20.27	-78.55	-78.55
0.04	-21.61	-21.49	-71.64	-71.63
0.06	-23.22	-23.09	-60.05	-60.00
0.08	-23.88	-23.81	-50.85	-50.77
0.10	-23.92	-23.89	-43.44	-43.38
0.20	-19.61	-19.91	-22.61	-22.51
5	76.18		63.51	

[a]In arbitrary units. [b]According to ref 14.

General procedure for the preparation of deoxythioureido sugars (1b-3b). Dry (KOH) ammonia was bubbled into a solution of the corresponding isothiocyanato derivative[4] **1a-3a** (0.6 g, 1.99 mmol) in ether (30 mL) at 0°C for 10 min, and then at room temperature for 20 min. The crystalline product was collected, and washed with cold ether.

*6-Deoxy-1,2:3,4-di-*O*-isopropylidene-6-thioureido-α-D-galactopyranose* (**1b**). Yield 0.6 g (95%), mp 187-188°C (from ether), $[\alpha]_D$ -5.5 (*c* 1, CH_2Cl_2), λ_{max} 252 nm (ε_{mM} 5.7); ν_{max} 3415, 3329, 1617, 1553, and 1093 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): Table 1 and δ 1.45, 1.40, 1.30, 1.29 (4 s, 12 H, 4 Me). ^{13}C NMR (313 K): δ 184.2 (C=S), 109.4, 108.9 (2 *C*Me$_2$), 96.1 (C-1), 71.3 (C-4), 70.6 (C-3), 70.5 (C-2), 66.7 (C-5), 45.2 (C-6), 26.0, 25.8, 24.7, and 23.9 (4 Me); (263 K): δ 184.1 (C=S *Z*), 183.2 (C=S *E*), 109.4, 108.9 (2 *C*Me$_2$ *Z*,*E*), 96.0 (C-1 *Z*,*E*), 71.6 (C-4 *Z*), 70.6 (C-4 *E*), 70.2 (C-3 *Z*,*E*), 69.9 (C-2 *Z*,*E*), 66.8 (C-5 *E*), 66.4 (C-5 *Z*), 45.0 (C-6 *Z*), 44.3 (C-6 *E*), 26.0, 25.8, 24.7, and 23.9 (4 Me *Z*,*E*). EIMS: *m/z* 318 (20%, $M^{+\cdot}$), 303 (34, M^+-Me$^\cdot$), 113 (45, 4-methylidene-2,2-dimethyl-*m*-dioxolene cation), 100 (50, 2,2-dimethyl-*m*-dioxolene cation), 85 (30, 2-methyl-*m*-dioxolenium cation). *Anal.* Calcd for $C_{13}H_{22}N_2O_5S$: C, 49.04; H, 6.96; N, 8.80; S, 10.07. Found: C, 48.97; H, 6.95; N, 8.51; S, 10.11.

*6-Deoxy-1,2:3,5-di-*O*-isopropylidene-6-thioureido-α-D-glucofuranose* (**2b**). Yield 0.62 g (98%), mp 165-166°C (from ether), $[\alpha]_D$ +4.5 (*c* 0.6, CH_2Cl_2), λ_{max} 259 nm (ε_{mM} 12.4); ν_{max} 3393, 3289, 1620, 1580,

and 1095 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): Table 1 and δ 1.46, 1.34, 1.30 (3 s, 12 H, 4 Me). ^{13}C NMR (313 K): δ 184.4 (C=S), 112.4 (*C*Me_2 dioxolane), 106.3 (C-1), 101.3 (*C*Me_2 dioxane), 83.9 (C-2), 79.8 (C-4), 74.9 (C-3), 71.4 (C-5), 47.1 (C-6), 27.1, 26.4, 24.2, and 23.8 (4 Me); (263 K): δ 183.1 (C=S *Z*), 182.8 (C=S *E*), 112.4 (*C*Me_2 dioxolane *Z,E*), 106.2 (C-1 *Z,E*), 101.3 (*C*Me_2 dioxane *Z,E*), 83.6 (C-2 *E*), 83.3 (C-2 *Z*), 80.7 (C-4 *Z*), 79.5 (C-4 *E*), 74.7 (C-3 *E*), 74.5 (C-3 *Z*), 72.2 (C-5 *E*), 70.3 (C-5 *Z*), 47.4 (C-6 *Z*), 46.5 (C-6 *E*), 27.1, 26.4, 24.2, and 23.8 (4 Me *Z,E*). EIMS: *m/z* 318 (5%, $M^{+\cdot}$), 303 (15, M^+-$Me^{\cdot}$), 229 (15, M^+-$CH_2NHCSNH_2^{\cdot}$), 171 (10, 229-Me_2CO), 113 (100, 2,2-dimethyl-*m*-dioxenium cation), 100 (20, 2,2-dimethyl-*m*-dioxolene cation), 85 (40, 2-methyl-*m*-dioxolenium cation). *Anal.* Calcd for $C_{13}H_{22}N_2O_5S$: C, 49.04; H, 6.96; N, 8.80; S, 10.07. Found: C, 48.83; H, 6.68; N, 8.84; S, 10.30.

1-Deoxy-2,3:4,5-di-O-*isopropylidene-1-thioureido-β-D-fructopyranose* (**3b**). Yield 0.61 g (97%), mp 111-113°C (from ether), $[\alpha]_D$ -47 (*c* 0.6, CH_2Cl_2), λ_{max} 253 nm (ε_{mM} 12.5); ν_{max} 3567, 3453, 3337, 1611, 1574, and 1092 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): Table 1 and δ 1.55, 1.44, 1.38 (3 s, 12 H, 4 Me). ^{13}C NMR (313 K): δ 184.3 (C=S), 109.1, 108.9 (2 *C*Me_2), 102.3 (C-2), 71.2 (C-3), 70.5 (C-5), 69.9 (C-4), 61.1 (C-6), 51.1 (C-1), 26.2, 25.9, 24.9, and 23.8 (4 Me); (233 K): δ 109.1, 108.9 (2 *C*Me_2 *Z,E*), 102.8 (C-2 *Z*), 102.1 (C-2 *E*), 71.3(C-3 *Z*), 70.1 (C-3 *E*), 69.9 (C-5 *Z*), 69.7 (C-5 *E*), 69.5 (C-4 *Z*), 69.3 (C-4 *E*), 60.9 (C-6 *E*), 60.4 (C-6 *Z*), 51.3 (C-1 *Z*), 49.2 (C-1 *E*), 26.2, 25.9, 24.9, and 23.8 (4 Me *Z,E*). EIMS: *m/z* 318 (5%, $M^{+\cdot}$), 303 (5, M^+-$Me^{\cdot}$), 229 (90, M^+-$CH_2NHCSNH_2^{\cdot}$), 171 (100, 229-Me_2CO), 113 (40, 4-methylidene-2,2-dimethyl-*m*-dioxolene cation), 85 (35, 2-methyl-*m*-dioxolenium cation). *Anal.* Calcd for $C_{13}H_{22}N_2O_5S$: C, 49.04; H, 6.96; N, 8.80; S, 10.07. Found: C, 48.70; H, 7.07; N, 8.62; S, 9.91.

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