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# Influence of intramolecular hydrogen-bonding on the conformation of 3-deoxy-3-thioureido sugars [1]

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**Abstract**

3-Deoxy-3-thioureido derivatives of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose and 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose were prepared, and their conformational properties in chloroform-*d* solutions were studied by temperature variable $^1$H NMR spectroscopy. The whole results, which include temperature coefficient data for the exchangeable pseudoamide protons, support that the presence of the sugar NH–C(=S) *E*-rotamer for D-*gluco* *N*,*N*′-disubstituted derivatives can be essentially ascribed to the existence of an intramolecular hydrogen bond analogous to that characteristic of peptide γ-turns. © 1996 Elsevier Science Ltd.

*Keywords:* Sugar thioureas; Intramolecular hydrogen-bonding; Rotational isomerism; Chemical shift temperature coefficients; Pseudo-γ-turn

## 1. Introduction

A main interest of thioureido sugars lies in the structural analogy of the thiourea functionality with the phosphate, urea, or amide moieties which appear in a variety of

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[1] Dedicated to the memory of Professor F. Serratosa (CSIC, Spain).

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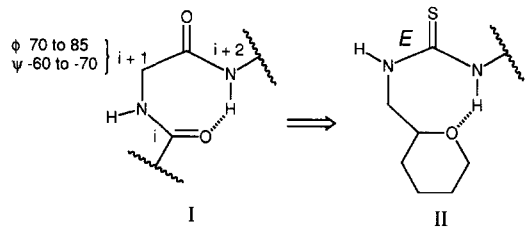



Fig. 1. Intramolecular hydrogen bonds in peptide γ-turns (stereostructure I) and in the *E*-isomer of 6-deoxy-6-thioureido aldopyranoses (stereostructure II). substituents at the carbon atoms are omitted. The designation of amino acid residues and the definition of the principal torsion angles in I are according to the IUPAC-IUB Commission on Biochemical Nomenclature [11]. See also ref. [10].

biologically important carbohydrates. Thus, neutral isosteres of oligo(glycosyl phosphate) [1] and polynucleotides [2], in which the phosphodiester groups have been replaced by thiourea bridges, have recently been reported. The use of thiourea linkers as replacement of such functionalities may result, however, in important differences in the conformational properties due, on the one hand, to the existence of two slow-rotating pseudoamide NH–C(= S) bonds and, on the other hand, to the strong hydrogen-bond donor character of the NH thiourea protons [3].

Dynamic NMR studies have shown that sugars bearing a thiourea group at a secondary carbon atom in a rigid pyranose framework exist exclusively in the NH–C(= S) low energy *Z*-configuration [4–6]. In contrast, both *Z*- and *E*-rotamers were found when the thioureido substituent was located at a primary position [7]. Recently, we have reported the synthesis of $\alpha,\alpha'$-trehalose-based macrocycles incorporating thiourea spacers at the primary position of the glucopyranose subunits, which revealed restricted conformational adaptability arising from the hindered rotational processes about the N–C partial double bonds [8]. Results have been rationalised [7,8] on the basis of a stabilisation of the *E*-rotamer by an NH · · · O hydrogen bond structurally related with that frequently encountered in peptide chains fitting γ-turn loops [9,10] (Fig. 1), and receiving support from temperature coefficient measurements and rotational barrier calculations.

Taking into consideration the dramatic influence that the conformational properties of thioureas have in both their biological activity [12] and their complexing properties [13,14], it appears important to quantify the effect of intramolecular hydrogen-bonding in the rotameric equilibrium of thioureido sugars. With this aim, we have now designed rigid sugar thiourea models which could allow the ring-O · · · HN stabilisation and examined their conformational behaviour in solution.

## 2. Results and discussion

Two series of isomeric 3-deoxy-3-thioureido sugars having, respectively, D-*allo* (**1–4**) and D-*gluco* (**5–8**) configurations were considered. The presence of the 1,2-*O*-isopropylidene group in both series provides a rigid furanose framework in the $^3T_4$ (D)

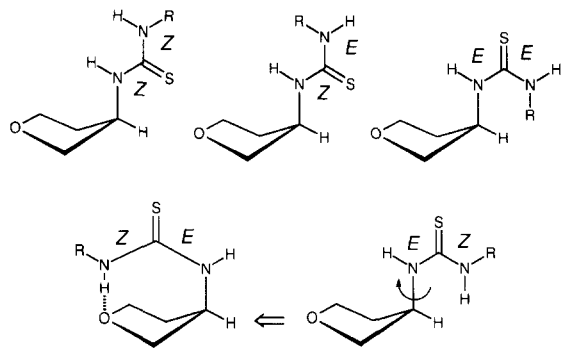
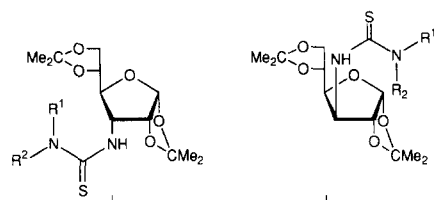


Fig. 2. Rotamers about the N–C( = S) bonds for 3-deoxy-3-thioureido glucofuranose derivatives in the $^3T_4$ conformation (substituents at the furanose ring are omitted). The sterically favoured *anti* conformers at the C-3–N bond are represented. Rotation about this bond for the *E,Z*-isomer, allowing formation of a N′H · · · O-4 hydrogen bond, is shown.

conformation [15]. Consequently, the thioureido substituent at C-3 adopts a quasi-equatorial (in **1–4**) or a quasi-axial disposition (in **5–8**). In the first case, this orientation precludes the formation of an efficient intramolecular hydrogen bond involving the ring oxygen atom (O-4) and an N′H thiourea proton, which is instead allowed in their C-3 epimers provided they adopt the sterically unfavourable *E*-configuration at the sugar NH–C( = S) pseudoamide bond and the *syn*-conformation at the C-3–N bond (Fig. 2). If the presence of the *E*-isomer is exclusively related to the formation of the above hydrogen bond, it should not be present in solutions of D-allose thiourea derivatives, while its proportion should be significant for D-glucose isomers having an N′H hydrogen-bond donor.



| | $R^1$ | $R^2$ |
|---|---|---|
| **1** | H | H |
| **2** | H | Me |
| **3** | H | Ph |
| **4** | Et | Et |

| | $R^1$ | $R^2$ |
|---|---|---|
| **5** | H | H |
| **6** | H | Me |
| **7** | H | Ph |
| **8** | Et | Et |

For purposes of comparison with previous data for 6-deoxy-6-thioureidoaldose derivatives [7], we were initially interested in analogs bearing an NH–C( = S)–$NH_2$ substituent at C-3. Compounds **1** and **5** were easily obtained by condensation of the corresponding 3-deoxy-3-isothiocyanato sugar [16] with ammonia. However, their lack

Table 1
$^1$H NMR data [a] for compounds **1**–**8**

| Compound | Chemical shifts ($\delta$ in ppm) | | | | | | | Coupling contants ($J$ in Hz) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | H-1 | H-2 | H-3 | H-4 | H-5 | H-6 | H-6′ | $J_{1,2}$ | $J_{2,3}$ | $J_{3,4}$ | $J_{4,5}$ | $J_{5,6}$ | $J_{5,6'}$ | $J_{6,6'}$ |
| **1** [b,d] | 5.79d | 4.64t | 4.57bs | 4.02t | 4.24td | 3.95td | 3.82t | 3.5 | 3.5 | 7.7 | 7.7 | 2.7 | 7.7 | 7.7 |
| **2** [c,e] | 5.84d | 4.73t | 4.64td | 3.99dd | 4.36m | 4.18dd | 4.00dd | 3.6 | 3.6 | 8.9 | 6.3 | 6.7 | 4.2 | 8.2 |
| **2***Z,Z* [c,f] | 5.96d | 4.79m | 4.74m | 4.11dd | 4.54m | 4.27t | 4.10dd | 3.6 | – | 8.3 | 6.0 | 7.2 | 2.7 | 7.2 |
| **2***Z,E* [c,f] | 5.90d | ⟵4.89—4.69⟶ | | 4.08m | 4.52m | 4.23t | 4.08m | 3.6 | – | – | – | – | – | – |
| **3** [c] | 5.82d | 4.79dd | 4.70ddd | 3.84dd | 4.33td | 4.14dd | 3.95dd | 3.8 | 5.0 | 9.6 | 4.4 | 6.6 | 6.6 | 8.4 |
| **4** [c,e] | 5.84d | 4.81dd | 4.85m | 3.97dd | 4.39td | 4.18dd | 4.01dd | 3.6 | 4.9 | 9.4 | 4.1 | 6.7 | 6.7 | 8.3 |
| **5** [b,d] | 5.81d | 4.48d | 4.67m | 4.09dd | 4.22q | 3.97dd | 3.82dd | 3.7 | 0 | 3.6 | 6.9 | 6.9 | 6.9 | 8.3 |
| **6** [c,e] | 5.87d | 4.70d | 4.41bs | 4.09dd | 4.27m | 4.13dd | 3.92dd | 3.7 | 0 | 4.2 | 7.4 | 6.2 | 6.0 | 8.6 |
| **6***E,Z* [c,f] | 5.98d | 4.72d | 4.05m | ⟵4.35—3.70m⟶ | | | | 3.7 | 0 | – | – | – | – | – |
| **6***Z,E* [c,f] | 5.90d | 4.88d | 4.81m | ⟵4.35—3.70m⟶ | | | | 3.7 | 0 | – | – | – | – | – |
| **6***Z,Z* [c,f] | 5.81d | 4.81m | 4.81m | ⟵4.35—3.70m⟶ | | | | 3.7 | – | – | – | – | – | – |
| **7** [c,e] | 5.78d | 4.87d | 4.82bs | 4.19dd | ⟵4.05m⟶ | | 3.80m | 3.6 | 0 | 3.3 | 6.9 | – | – | – |
| **7***Z,E* [c,g] | 5.85d | 5.00d | 4.81dd | 4.24dd | 4.18q | 4.11dd | 3.76dd | 3.8 | 0 | 3.7 | 6.0 | 6.0 | 6.0 | 7.2 |
| **7***E,Z* [c,g] | 6.19d | 4.94d | 4.31dd | – | – | – | – | 3.8 | 0 | 3.7 | – | – | – | – |
| **8** [c] | 5.81d | 4.83d | 4.95dd | 4.22dd | 4.30dd | 4.15dd | 3.87dd | 3.7 | 0 | 3.5 | 6.5 | 5.9 | 6.5 | 8.3 |

[a] At 300 MHz, excepting **4** (500 MHz).
[b] In $Me_2SO$-$d_6$.
[c] In $CDCl_3$.
[d] At 323 K.
[e] At 313 K.
[f] At 233 K.
[g] At 250 K.

of solubility in chloroform-*d* prevented this comparative analysis. Nevertheless, the $^1$H NMR spectrum of **5**, recorded at 10 °C in dimethyl sulfoxide-$d_6$ containing 5% of chloroform, showed a beginning of decoalescence for the $NH_2$ resonance which was absent in the spectrum of **1**. Taking into consideration that the free activation energy ($\Delta G^{\neq}$) for rotation about the $NH_2$–(C = S) bond has been found to be 1–3 kcal mol$^{-1}$ lower than $\Delta G^{\neq}$ for rotation about the sugar NH–(C = S) bond [7], this result probably indicates the presence of the *E*-rotamer in the conformational equilibrium of **5**.

A confirmation was obtained from variable temperature $^1$H and $^{13}$C NMR spectra (Table 1 and Experimental section) of the *N'*-methyl derivatives **2** and **6**, obtained from the corresponding 3-amino-3-deoxy sugar derivatives or the corresponding hydrochlorides [16] by reaction with methyl isothiocyanate. The low temperature range spectra of the D-*allo* derivative **2** showed two sets of signals which could be assigned to the *E*- and *Z*-rotamers at the MeNH–C(= S) bond on the basis of NOE experiments. Both isomers kept the *Z*-configuration at the sugar NH–C(= S) bond, displaying extended conformations with the NH and H-3 protons in *anti* relative disposition, in agreement with the large $J_{3,NH}$ value. Further X-ray data for the *Z,Z*-rotamer confirmed this structural arrangement (see Experimental section for supplementary material). A $^1$H NMR spectrum at −10 °C, recorded immediately after dissolution of the crystalline material in chloroform-*d*, showed signals only for the *Z,Z*-isomer of **2**, allowing unequivocal assignment of the NMR parameters. After 2 h at room temperature, the *Z,Z*/*Z,E* thermodynamic equilibrium was attained. In contrast, the NMR data of the D-*gluco* counterpart **6** showed the presence of three rotameric forms in chloroform-*d* solution, namely the *E,Z*- (major), *Z,Z*-, and *Z,E*-rotamers (Table 2). As a general rule, the resonances of C*H* protons vicinal to the thiourea group [i.e., N'H*Me* for the N'H–C(= S) bond and H-3 for the sugar NH–C(= S) bond] (Table 1 and Experimental section) were strongly deshielded in the *Z*-rotamer at the corresponding bond as compared to the *E*-rotamer [17]. No signal arising from the *E,E*-rotamer could be detected as expected from the unfavourable 1,3-parallel arrangement of the carbon substituents (Fig. 2).

According to our original hypothesis, the presence of the *E,Z*-conformer of **6** must be related to the existence of a N'H · · · O-4 hydrogen bond which features a pseudo-γ-turn. To support this point, the temperature coefficients of the NH and N'H $^1$H NMR chemical shifts were measured over the range 233–263 K, as summarised in Table 3. A

Table 2
Temperature coefficients ($-d\delta/dT \times 10^3$ ppm K$^{-1}$) for the pseudoamide NH protons in compounds **2**, **3**, **6**, and **7**

| Compound | Rotamer | | | | | |
|---|---|---|---|---|---|---|
| | *Z,Z* | | *Z,E* | | *E,Z* | |
| | NH | N'H | NH | N'H | NH | N'H |
| **2** | −5.0 | 11.1 | 6.1 | 15.3 | | |
| **3** | | | 2.9 | 15.0 | | |
| **6** | −3.9 | 8.2 | 18.3 | 13.9 | 13.9 | 1.1 |
| **7** | | | 7.9 | 20.2 | 16.3 | 1.7 |

Table 3
Rotamer populations (%) for compounds **2**, **3**, **6**, and **7** in $CDCl_3$ [a]

| Compound | Rotamer | | |
|---|---|---|---|
| | *Z,Z* | *Z,E* | *E,Z* |
| **2** | 55 | 45 | |
| **3** | | 100 | |
| **6** | 21 | 26 | 53 |
| **7** | | 94 | 6 |

[a] Obtained by digital integration of $^1$H NMR signals at 233 K.

decrease in temperature susceptibility has been commonly accepted as an indicator of decreased interaction with solvent, due either to intramolecular H-bonding, steric hindrance (crypticity), or both, in polypeptides [10] as well as carbohydrates [18]. Results revealed that the N′H proton temperature coefficient for the *E,Z*-conformer of **6** was about one order of magnitude lower as compared with those for the other pseudoamide protons. Indeed, the coefficient was almost identical with those which are characteristic for amide protons in γ-turns [19,20].

Replacement of the *N′*-methyl group by phenyl dramatically changed the composition of the respective rotameric populations (Table 3). It is known that *N*-aryl thioureas have a high tendency to adopt the *E*-configuration at the corresponding pseudoamide linkage [21–23], probably through π-type intramolecular hydrogen-bonding [24], therefore forcing the *N*-substituent to adopt the *Z*-orientation. Thus, the D-allose phenylthiourea derivative **3** was in the exclusive *Z,E*-configuration in chloroform-*d* solution. In contrast, low temperature $^1$H NMR spectra for its D-*gluco* diastereomer **7** showed the existence of an equilibrium mixture between the *Z,E*- (major) and *E,Z*- (minor) rotamers (Table 2). Furthermore, the temperature coefficient for the N′H proton of the latter also agreed with the expected value for a hydrogen-bonded pseudoamide proton (Table 2). When formation of this bond was prevented by the absence of a H-donor, as in **4** and **8**, no *E*-rotamer was detected neither for the D-*allo* nor for the D-*gluco* derivative.

In conclusion, these results strongly support the idea that intramolecular hydrogen-bonding is the main factor involved in the overall stabilisation of the sugar NH–C(=S) *E*-rotamer in **6** and **7**, overcoming the gain of energy in going from *Z* to *E* and from *anti* to *syn* dispositions, and even forcing, to some extent, the *N′* aromatic substituent in **7** to adopt the *Z*-orientation. This lets us assume that the observed proportion of *E,Z*-rotamer actually corresponds to the proportion of pseudo-γ-turn conformation in solution. In connection with the recent use of pseudoglycopeptides to mimic the structural properties of peptides [25], oligosaccharides [26,27], and glycopeptides [28], sugar thioureas offer the possibility of designing pseudo-γ-turn loops by judicious choice of the sugar template and substituents as well as restriction of the conformational freedom, e.g. by cyclisation. Identification of the spectral parameters arising from rotamers at this bond would then allow a direct evaluation of this structural feature in compounds carrying thiourea spacers as amide or phosphate surrogates.

## 3. Experimental

*General methods.*—Melting points were determined with a Gallenkamp apparatus and are uncorrected. A Perkin–Elmer Model 141 MC polarimeter, 1 cm tubes, at room temperature, were used for measurement of specific rotations. $^{1}H$ and $^{13}C$ NMR spectra were recorded at 500 (125.7) and 300 (75.5) MHz with, respectively, Bruker 500 AMX and Bruker 300 AMX spectrometers. Chemical shifts are given in ppm with reference to tetramethylsilane as internal standard. Assignments of $^{1}H$ and $^{13}C$ signals were assisted by 2D COSY, NOE, and HETCOR experiments. Temperature measurements were based on the chemical-shifts separation of the protons of a sample in methanol and the use of known temperature-shift correlations [29]. EIMS were taken on a Kratos MS-80 RFA instrument. Operating conditions were: ionizing energy 35 eV, ionizing current 100 $\mu$A, accelerating voltage 4 kV, resolution 1000 (10% valley definition). TLC was performed with E. Merck precoated TLC plates, Silica Gel 30F-245, with visualisation by UV light and by charring with 10% $H_2SO_4$. Flash and column chromatography were carried out with Silica Gel 60 (E. Merck, 230–400 mesh). Microanalyses were performed by the Departamento de Química Analítica (University of Sevilla) and by the Instituto de Química Orgánica General (CSIC) in Madrid.

*3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-thioureido-α-*D*-allofuranose* (**1**).—Dry (KOH) ammonia was bubbled into a solution of 3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-isothiocyanato-α-D-allofuranose [16] (0.6 g, 1.99 mmol) in ether (25 mL) at 0 °C for 10 min, and then at room temperature for 20 min. The resulting crystalline product was collected and washed with cold $Et_2O$ to give **1** (0.62 g, 98%), mp 192–194 °C (dec, from $Et_2O$); $[\alpha]_D$ +137° (*c* 0.6, $Me_2SO$); UV ($Me_2SO$) 259 nm ($\varepsilon_{mM}$ 11.0); IR (KBr) 3449, 3337, 3304, 1620, 1553, and 1067 $cm^{-1}$; NMR: $^{1}H$ (300 MHz, $Me_2SO$-$d_6$, 323 K) Table 1 and δ 7.43 (d, 1 H, $J_{3,NH}$ 8.1 Hz, NH), 7.18 (s, 2 H, $NH_2$), 1.50, 1.34, 1.30, and 1.26 (4 s, each 3 H, 4 Me); $^{13}C$ (75.5 MHz, $Me_2SO$-$d_6$, 323 K): δ 183.2 (C = S), 111.5, 108.5 (2 $CMe_2$), 103.7 (C-1), 78.4 (C-4), 77.3 (C-3), 74.7 (C-4), 63.5 (C-6), 57.1 (C-3), 26.6, 26.2, 26.1, and 25.1 (4 Me); EIMS *m/z* 318 (5%, $M^{+\cdot}$), 303 (50, $M^+ - Me^{\cdot}$), 242 (100, $M^+ - NH_2CSNH_2$), and 184 (40, 242 − $Me_2CO$). Anal. Calcd for $C_{13}H_{22}N_2O_5S$: C, 49.04; H, 6.96; N, 8.80; S, 10.07. Found: C, 49.18; H, 7.17; N, 8.98; S, 9.95.

*3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-(3-methylthioureido)-α-*D*-allofuranose* (**2**).—To a solution of 3-amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose hydrochloride [16] (0.5 g, 1.69 mmol) in dry pyridine (10 mL) was added methyl isothiocyanate (0.12 g, 1.69 mmol). The mixture was stirred at room temperature for 15 h, then concentrated. Column chromatography (1:3 hexanes–EtOAc) and crystallisation from EtOH gave **2** (0.53 g, 95%), mp 202–204 °C (dec, from EtOH), $[\alpha]_D$ +110° (*c* 1, MeOH); UV (MeOH) 240 nm ($\varepsilon_{mM}$ 13.6); IR (KBr) 3360, 3291, 1561, and 1065 $cm^{-1}$; NMR: $^{1}H$ (300 MHz, $CDCl_3$, 313 K) Table 1 and δ 6.67 (q, 1 H, $J_{Me,N'H}$ 4.5 Hz, N′H), 6.17 (bs, 1 H, NH), 3.00 (d, 3 H, N′H*Me*), 1.56, 1.44, 1.35, and 1.34 (4 s, each 3 H, 4 Me); 233 K, *Z,Z*-conformer, δ 6.57 (q, 1 H, $J_{Me,N'H}$ 5.0 Hz, N′H), 5.92 (d, 1 H, $J_{3,NH}$ 8.1 Hz, NH), 2.92 (d, 3 H, N′H*Me*), 1.59, 1.51, 1.37, and 1.36 (4 s, each 3 H, 4 Me); 233 K, *Z,E*-conformer, δ 7.45 (q, 1 H, $J_{Me,N'H}$ 3.8 Hz, N′H), 6.92 (m, 1 H, NH), 3.08 (d, 3 H, N′H*Me*), 1.57, 1.51, 1.37, and 1.36 (4 s, each 3 H, 4 Me); $^{13}C$ (75.5 MHz,

$CDCl_3$, 313 K): δ 183.0 (C = S), 112.6, 109.5 (2 $CMe_2$), 104.1 (C-1), 79.6 (C-4), 78.9 (C-2), 75.4 (C-5), 65.0 (C-6), 58.1 (C-3), 30.4 (NHMe), 26.5, 26.2, 26.1, and 25.0 (4 Me); EIMS *m/z* 332 (5%, $M^{+\cdot}$), 317 (50, $M^+ - Me^\cdot$), 274 (25, $M^+ - Me_2CO$), 256 (100, $M^+ - NH_2CSNHMe$), and 198 (19, 256 − $Me_2CO$). Anal. Calcd for $C_{14}H_{24}N_2O_5S$: C, 50.57; H, 7.27; N, 8.43; S, 9.64. Found: C, 50.47; H, 7.27; N, 8.39; S, 9.50.

Compound **2** was also prepared in 95% yield by treatment of 3-amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (0.66 g, 2.55 mmol) with methyl isothiocyanate (0.18 g, 2.55 mmol) in $CH_2Cl_2$ (30 mL) in the presence of $Et_3N$ (0.5 mL) at room temperature for 24 h.

*3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-(3-phenylthioureido)-α-*D*-allofuranose* (**3**).—An analogous reaction of the above allose-derived amine hydrochloride (0.5 g, 1.69 mmol) or the free base (0.5 g, 1.93 mmol) with phenyl isothiocyanate (0.20 mL, 1.69 mmol or 0.23 mL, 1.93 mmol) and further column chromatography (1:1 hexanes–EtOAc) of the reaction mixture gave **3** (0.56 g, 83% or 0.68 g, 90%), mp 156–158 °C (from EtOAc), $[\alpha]_D$ +87.5° (*c* 1, $CHCl_3$); UV ($CHCl_3$) 269 nm ($\varepsilon_{mM}$ 14.9); NMR: $^1H$ (300 MHz, $CDCl_3$, 313 K) Table 1 and δ 8.42 (s, 1 H, N′H), 7.33 (m, 5 H, Ph), 6.47 (d, 1 H, $J_{3,NH}$ 8.1 Hz, NH), 1.37, 1.34, 1.30, and 1.27 (4 s, each 3 H, 4 Me); $^{13}C$ (75.5 MHz, $CDCl_3$, 313 K): δ 180.0 (C = S), 135.8 (C-1 Ph), 129.9 (C-3,5 Ph), 127.1 (C-4 Ph), 124.6 (C-2,6 Ph), 112.4, 109.6 (2 $CMe_2$), 104.3 (C-1), 78.5 (C-2), 78.2 (C-4), 75.4 (C-5), 65.2 (C-6), 58.8 (C-3), 26.2 (3 C), and 25.0 (4 Me); EIMS *m/z* 394 (5%, $M^{+\cdot}$), 379 (25, $M^+ - Me^\cdot$), 336 (18, $M^+ - Me_2CO$), and 318 (25, $M^+ - NH_2CSNHPh$). Anal. Calcd for $C_{19}H_{26}N_2O_5S$: C, 57.85; H, 6.64; N, 7.02; S, 8.13. Found: C, 57.91; H, 6.51; N, 7.00; S, 8.10.

*3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-(3,3-diethylthioureido)-α-*D*-allofuranose* (**4**).—To a solution of the corresponding 3-isothiocyanate derivative (0.4 g, 1.33 mmol) in ether (15 mL) was added diethylamine (0.14 g, 0.2 mL, 1.99 mmol). The mixture was stirred at room temperature for 30 min, then concentrated, and the residue purified by column chromatography (2:3 hexanes–EtOAc) to yield **4** (0.40 g, 80%), mp 87–89 °C (from $CHCl_3$–*n*-hexane), $[\alpha]_D$ +106° (*c* 0.9, $CHCl_3$); UV ($CHCl_3$) 254 nm ($\varepsilon_{mM}$ 14.9); IR (KBr) 3442, 3119, 1532, and 1069 $cm^{-1}$; NMR: $^1H$ (500 MHz, $CDCl_3$, 313 K) Table 1 and δ 5.75 (d, 1 H, $J_{3,NH}$ 7.4 Hz, NH), 3.67 (m, 4 H, 2 C$H_2$CH$_3$), 1.54 (3 H), 1.43 (3 H), 1.34 (6 H) (3 s, 4 Me), and 1.25 (t, 6 H, $^3J_{H,H}$ 7.0 Hz, 2 $CH_2CH_3$); $^{13}C$ (125.7 MHz, $CDCl_3$, 313 K): δ 180.3 (C = S), 112.4, 109.4 (2 $CMe_2$), 104.3 (C-1), 79.0 (C-4), 78.4 (C-2), 75.5 (C-5), 65.1 (C-6), 59.2 (C-3), 46.0, 45.4 (2 $CH_2CH_3$), 26.4, 26.3 (2 C), 26.2 (4 Me), and 12.4 (2 C, 2 $CH_2CH_3$); EIMS *m/z* 374 (5%, $M^{+\cdot}$), 359 (40, $M^+ - Me^\cdot$), 316 (30, $M^+ - Me_2CO$), and 286 (30, 359 − $Et_2NH$). Anal. Calcd for $C_{17}H_{30}N_2O_5S$: C, 54.52; H, 8.07; N, 7.48; S, 8.56. Found: C, 54.79; H, 8.10; N, 7.54; S, 8.62.

*3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-thioureido-α-*D*-glucofuranose* (**5**).—Through a solution of 3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-isothiocyanato-α-D-glucofuranose [16] (0.6 g, 1.99 mmol) in $Et_2O$ (25 mL) was bubbled dry ammonia, as above described for **1**, yielding **5** (0.60 g, 97%), mp 145–147 °C (dec, from $Et_2O$), $[\alpha]_D$ −37° (*c* 0.8, $Me_2SO$); UV ($Me_2SO$) 257 nm ($\varepsilon_{mM}$ 5.7); IR (KBr) 3389, 3329, 3216, 1649, 1589, and 1078 $cm^{-1}$; NMR: $^1H$ (300 MHz, $Me_2SO$-$d_6$, 323 K) Table 1 and δ 7.62 (d, 1 H, $J_{3,NH}$

8.5 Hz, NH), 7.03 (s, 2 H, $NH_2$), 1.48, 1.30, 1.26, and 1.25 (4 s, each 3 H, 4 Me); $^{13}C$ (75.5 MHz, $Me_2SO$-$d_6$, 323 K): δ 183.1 (C = S), 111.0, 108.5 (2 $CMe_2$), 104.0 (C-1), 84.2 (C-2), 78.5 (C-4), 71.9 (C-5), 66.1 (C-6), 59.6 (C-3), 26.6, 26.4, 26.0, and 25.3 (4 Me); EIMS *m/z* 318 (5%, $M^{+\cdot}$), 303 (25, $M^+ - Me^\cdot$), 242 (15, $M^+ - NH_2CSNH_2$), and 184 (15, 242 − $Me_2CO$). Anal. Calcd for $C_{13}H_{22}N_2O_5S$: C, 49.04; H, 6.96; N, 8.80; S, 10.07. Found: C, 49.21; H, 7.11; N, 8.66; S, 10.10.

*3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-(3-methylthioureido)-α-*D*-glucofuranose* (**6**).—Reaction of 3-amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose hydrochloride [16] (0.8 g, 2.7 mmol) or the free base (0.8 g, 3.1 mmol) with methyl isothiocyanate (0.19 g, 2.7 mmol or 0.22 g, 3.1 mmol), as above described for **2**, gave **6** (0.76 g, 85% or 0.92 g, 90%) as an oil which crystallised on standing: mp 138–140 °C, $[\alpha]_D$ +9.5° (*c* 0.9, $CHCl_3$), UV ($CHCl_3$) 250 nm ($\varepsilon_{mM}$ 12.9); IR (KBr) 3333, 1541, and 1072 $cm^{-1}$; NMR: $^1H$ (300 MHz, $CDCl_3$, 313 K) Table 1 and δ 6.52 (q, 1 H, $J_{Me,N'H}$ 4.7 Hz, N'H), 6.41 (d, 1 H, $J_{3,NH}$ 7.4 Hz, NH), 3.04 (d, 3 H, N'H*Me*), 1.52, 1.44, 1.35, and 1.29 (4 s, each 3 H, 4 Me); 233 K, *E,Z*-conformer, δ 7.39 (d, 1 H, $J_{3,NH}$ 7.5 Hz, NH), 6.90 (q, 1 H, $J_{Me,N'H}$ 5.0 Hz, N'H), 2.81 (d, 3 H, N'H*Me*), 1.59, 1.51, 1.37, and 1.36 (4 s, each 3 H, 4 Me); 233 K, *Z,E*-conformer, δ 7.55 (q, 1 H, $J_{Me,N'H}$ 3.8 Hz, N'H), 6.51 (d, 1 H, $J_{3,NH}$ 5.7 Hz, NH), 3.05 (d, 3 H, N'H*Me*), 1.57, 1.51, 1.37, and 1.36 (4 s, each 3 H, 4 Me); 233 K, *Z,Z*-conformer, δ 7.26 (bs, 1 H, NH), 6.43 (bs, 1 H, N'H), 3.05 (d, 3 H, N'H*Me*), 1.59, 1.51, 1.37, and 1.36 (4 s, each 3 H, 4 Me); $^{13}C$ (75.5 MHz, $CDCl_3$, 313 K): δ 183.1 (C = S), 112.1, 109.9 (2 $CMe_2$), 104.1 (C-1), 84.4 (C-2), 78.4 (C-4), 72.5 (C-5), 67.2 (C-6), 60.3 (C-3), 31.3 (NHMe), 26.6, 26.3, 25.9, and 25.1 (4 Me); EIMS *m/z* 332 (19%, $M^{+\cdot}$), 317 (60, $M^+ - Me^\cdot$), 274 (60, $M^+ - Me_2CO$), 256 (30, $M^+ - NH_2CSNHMe$), and 198 (18, 256 − $Me_2CO$). Anal. Calcd for $C_{14}H_{24}N_2O_5S$: C, 50.57; H, 7.27; N, 8.43; S, 9.64. Found: C, 50.28; H, 7.37; N, 8.41; S, 9.51.

*3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-(3-phenylthioureido)-α-*D*-glucofuranose* (**7**).—An analogous reaction of the above glucose-derived amine (0.66 g, 2.55 mmol) with phenyl isothiocyanate (0.30 mL, 2.55 mmol) and further column chromatography (1:1 hexanes–EtOAc) of the reaction mixture gave **7** (1.1 g, 91%), $[\alpha]_D$ −46.1° (*c* 1, $CHCl_3$); UV ($CHCl_3$) 271 nm ($\varepsilon_{mM}$ 20.8); IR (KBr) 3374, 3304, 3227, 1597, 1528, and 1074 $cm^{-1}$; NMR: $^1H$ (300 MHz, $CDCl_3$, 313 K) Table 1 and δ 8.48 (s, 1 H, N'H), 7.33 (m, 5 H, Ph), 6.64 (d, 1 H, $J_{3,NH}$ 6.4 Hz, NH), 1.52, 1.32, 1.30, and 1.25 (4 s, each 3 H, 4 Me); 248 K, *Z,E*-conformer, δ 9.50 (s, 1 H, N'H), 7.33 (m, 5 H, Ph), 7.04 (d, 1 H, $J_{3,NH}$ 5.6 Hz, NH), 1.59, 1.51, 1.37, and 1.36 (4 s, each 3 H, 4 Me); 248 K, *E,Z*-conformer, δ 8.65 (s, 1 H, N'H), 8.04 (d, 1 H, $J_{3,NH}$ 9.0 Hz, NH), 7.33 (m, 5 H, Ph), 1.59, 1.51, 1.37, and 1.36 (4 s, each 3 H, 4 Me); $^{13}C$ (75.5 MHz, $CDCl_3$, 313 K): δ 180.8 (C = S), 136.5 (C 1 Ph), 129.9 (C-3,5 Ph), 126.8 (C-4 Ph), 124.2 (C-2,6 Ph), 112.4, 109.6 (2 $CMe_2$), 104.1 (C-1), 84.3 (C-2), 77.8 (C-4), 72.8 (C-5), 67.3 (C-6), 61.2 (C-3), 26.2 (3 C), and 25.0 (4 Me); EIMS *m/z* 394 (3%, $M^{+\cdot}$), 379 (15, $M^+ - Me^\cdot$), 336 (8, $M^+ - Me_2CO$), and 318 (4, $M^+ - NH_2CSNHPh$). Anal. Calcd for $C_{19}H_{26}N_2O_5S$: C, 57.85; H, 6.64; N, 7.02; S, 8.13. Found: C, 57.70; H, 6.39; N, 6.91; S, 8.07.

*3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-(3,3-diethylthioureido)-α-*D*-glucofuranose* (**8**).—Treatment of the corresponding 3-isothiocyanate derivative (0.4 g, 1.33 mmol) in

ether with diethylamine, as above described, gave **8** (0.49 g, 98%), mp 76–78 °C (from $CHCl_3$–*n*-hexane), $[\alpha]_D$ −38.9° (*c* 0.9, $CHCl_3$); UV ($CHCl_3$) 254 nm ($\varepsilon_{mM}$ 17.1); IR (KBr) 3403, 3285, 1534, and 1071 $cm^{-1}$; NMR: $^1H$ (300 MHz, $CDCl_3$, 313 K) Table 1 and $\delta$ 5.88 (d, 1 H, $J_{3,NH}$ 6.1 Hz, NH), 3.78 (m, 2 H, $CH_2CH_3$), 3.72 (m, 2 H, $CH_2CH_3$), 1.54, 1.40, 1.35, 1.33 (4 s, each 3 H, 4 Me), and 1.22 (t, 6 H, $^3J_{H,H}$ 7.0 Hz, 2 $CH_2CH_3$); $^{13}C$ (75.5 MHz, $CDCl_3$, 313 K): $\delta$ 182.5 (C = S), 111.9, 109.6 (2 $CMe_2$), 103.9 (C-1), 84.6 (C-2), 77.5 (C-4), 73.1 (C-5), 67.4 (C-6), 61.3 (C-3), 44.7 (2 C, 2 $CH_2CH_3$), 26.4, 26.3 (2 C), 26.2 (4 Me), and 13.4 (2 C, 2 $CH_2CH_3$); EIMS *m/z* 374 (10%, $M^{+\cdot}$), 359 (20, $M^+ - Me^\cdot$), 316 (15, $M^+ - Me_2CO$), and 286 (45, 359 − $Et_2NH$). Anal. Calcd for $C_{17}H_{30}N_2O_5S$: C, 54.52; H, 8.07; N, 7.48; S, 8.56. Found: C, 54.59; H, 8.00; N, 7.58; S, 8.59.

*Crystal analysis for* **2** *(Z,Z-rotamer)*[3].—The compound crystallised as colourless prisms; orthorhombic; space group $P2_12_12_1$; $a = 9.813(1)$, $b = 11.089(3)$, and $c = 16.003(2)$ Å; $V = 1741.4(5)$ Å$^3$; $Z = 4$; $d_c = 1.268$ and $d_m = 1.24$ g $cm^{-3}$; $\mu = 0.198$ $mm^{-1}$; $F(000) = 712$; $T = 293$ K. Data collection: difractometer, Enraf–Nonius CAD-4; radiation Mo$K\alpha$ (0.7169 Å), 26 mA, 50 kV; monochromator, graphite; data collecting mode, $\omega$–2$\theta$ scan; data sets corrected for Lorentz and polarisation effects; extinction not applied; an empirical absorption correction following the DIFABS [30] procedure was applied to anisotropically refined data; maximum and minimum absorption corrections factors were 1.05 and 0.72, respectively. Crystal size 0.28 × 0.36 × 0.50 mm; 2$\theta$ range 2–50°; index range $0 < h < 13$, $0 < k < 15$, $0 < l < 22$; number of reflections, 2860 (independent), 1747 [$I > 3\sigma(I)$]. Structure analysis: solution direct methods using SIR92 [31]; method of refinement, full matrix least-squares; all calculations were carried out with the X-ray system [32]; anisotropic thermal parameters for non-H atoms and riding model for hydrogen atoms with fixed isotropic *U*. Number of parameters refined, 199; $R = 0.040$, $R\omega = 0.065$; final Fourier difference map 0.30 and −0.28 e Å$^{-3}$.

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