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SYNTHESIS OF SUGAR *N*-(2-THIAZOLIN-2-YL)THIOUREAS

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ABSTRACT

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-isothiocyanato-α- or -β-D-glucopyranose (**4** or **5**) was condensed with 2-chloroethylamine hydrochloride in pyridine to afford *N,N'*-bis(1,3,4,6-tetra-*O*-acetyl-2-deoxy-α- or -β-D-glucopyranos-2-yl)-*N*-(2-thiazolin-2-yl)thiourea (**2** or **3**). When the reactions were carried out in ether, 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(2-thiazolin-2-yl)amino-α- and -β-D-glucopyranose (**6** and **7**) were isolated and converted into the mixed *N*-(2-thiazolin-2-yl)-urea and -thioureas (**9–12**) by reaction with iso(thio)cyanates. Bromine-promoted cyclisation of 1,3,4,6-tetra-*O*-acetyl-2-(*N'*-allylthioureido)-2-deoxy-α-D-glucopyranose (**13**) gave a mixture of the diastereomers 1,3,4,6-tetra-*O*-acetyl-2-[5(*R* and *S*)-5-bromomethyl-2-thiazolin-2-yl]amino-2-deoxy-α-D-glucopyranose hydrobromides (**14** and **15**), which was transformed into the analogous *N*-(2-thiazolin-2-yl)thioureas (**16–18**).

INTRODUCTION

The reaction of β-haloalkylamines with alkyl(aryl) isothiocyanates gives 2-alkyl(aryl)amino-2-thiazolines[1,2]. In the carbohydrate field, there is only one report on the reaction of sugar isothiocyanates with β-haloethylamines[3], which described the synthesis of *N*-nucleosides of the imidazolidine-2-thione by the addition of 2-chloroethylamine to acylated glycosyl isothiocyanates under basic conditions. We have corrected[4] the results reported by Ogura *et al.*[3]. Thus, treatment of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate with 2-chloroethylamine hydrochloride, under the conditions described[3], gave *N,N'*-bis(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*-(2-thiazolin-2-yl)thiourea (**1**). We now report further examples of this reaction and the bromine-promoted cyclisation of a sugar alkenylthiourea, a new starting material for the synthesis of heterocycles.

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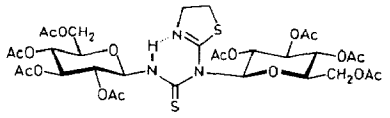

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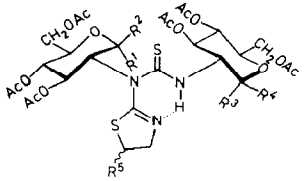
RESULTS AND DISCUSSION

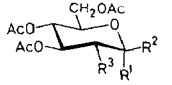
The reaction of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-isothiocyanato-α- or -β-D-glucopyranose (**4** or **5**) with 2-chloroethylamine hydrochloride in pyridine afforded the *N*-(2-thiazolin-2-yl)thiourea derivatives **2** or **3**. These reactions must involve the formation of a haloalkylthiourea, which undergoes intramolecular cyclization to give 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(2-thiazolin-2-yl)amino-α- or -β-D-glucopyranose (**6, 7**), and further addition of sugar isothiocyanates then affords **2** or **3**.

Compounds **2** and **3** had λ_{max} at 245 nm, as expected for the thiourea moiety[5,6], and ν_{max} at ~1550 cm^{-1} for the NH group. The $\nu_{C=N}$ for **2** and **3** showed a large shift toward lower wave numbers (~40–50 cm^{-1}) compared to simple thiazolines or aminothiazolines[7], which is indicative of diminution in double-bond character.

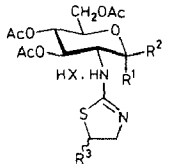
The ^{1}H-n.m.r. spectrum of **2** contained two signals for H-1 (H-1A at 6.09 p.p.m., H-1B at 6.14 p.p.m.), which indicates the presence of two sugar residues*. The signal for H-2B (m, 5.46 p.p.m.) is similar to that of H-2 of alkylthiourea



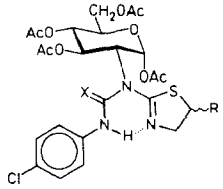
2 $R^1=R^3=OAc$, $R^2=R^4=H$, $R^5=H$
3 $R^1=R^3=H$, $R^2=R^4=OAc$, $R^5=H$
11 $R^1=R^4=OAc$, $R^2=R^3=H$, $R^5=H$
12 $R^1=R^4=H$, $R^2=R^3=OAc$, $R^5=H$
18 $R^1=R^3=OAc$, $R^2=R^4=H$, $R^5=CH_2Br$



4 $R^1=OAc$, $R^2=H$, $R^3=NCS$
5 $R^1=H$, $R^2=OAc$, $R^3=NCS$
8 $R^1=OAc$, $R^2=H$, $R^3=NH_2$
13 $R^1=OAc$, $R^2=H$, $R^3=NHC(=S)NHCH_2CH=CH_2$



6 $R^1=OAc$, $R^2=R^3=H$, $X=Cl$
7 $R^1=R^3=H$, $R^2=OAc$, $X=Cl$
14,15 $R^1=OAc$, $R^2=H$, $R^3=CH_2Br$, $X=Br$



9 $R=H$, $X=O$
10 $R=H$, $X=S$
16,17 $R=CH_2Br$, $X=O$

*A and B denote the sugar residues joined to N and N′, respectively.

derivatives of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranose[4,5] (**8**). However, the signal for H-2A was shifted markedly upfield (3.49 p.p.m.). The diastereotopic thiazolinic protons gave four individual multiplets, namely, for =N–CH_x, =N–CH_y, –S–CH_u, and –S–CH_v at 4.95, 4.30, 3.13, and 3.03 p.p.m., respectively. Finally, the NH signal at 12.07 p.p.m. indicated the presence of an intramolecular hydrogen bond, as observed in other heterocyclic thioureas[8,9] and some sugar keto-enamines having a chelated structure[10,11], and which makes the thiazolinic protons anisochronous.

In the ^{13}C-n.m.r. spectrum of **2**, the resonance of C-2B appeared at 55.98 p.p.m., as in other sugar thioureas[4,5], but that of C-2A was shifted markedly downfield (66.99 p.p.m.) due to the presence of the 2-aminothiazoline ring. The thiourea bridge was indicated by the thiocarbonyl signal at 180.92 p.p.m., and the upfield signal at 161.08 p.p.m. was attributed to the N=C–S group of the thiazoline ring. The other thiazoline carbons resonated at 55.41 and 25.00 p.p.m., which is analogous to those in simple aminothiazolines[12].

Alternative syntheses of **6** and **7** as hydrochlorides were carried out by the reaction of **4** and **5** with ethereal 2-chloroethylamine. Compound **7** was an amorphous and hygroscopic solid, and was used without purification. Crystalline **6**, which can also be obtained easily by reaction of **4** with 2-chloroethyl isothiocyanate, had no absorption above 210 nm, in accord with other sugar 2-alkylamino-2-thiazoline hydrobromides[6]. The i.r. bands for ammonium salt (3270–2820 cm^{-1}) and for C=N^+ (1645 cm^{-1})[5,6,13] are also given by 2-alkyl(aryl)amino-D-glucopyrano[2,1-*d*]-2-thiazoline[5,6] and -D-glucopyrano[2,1-*d*]-2-oxazoline hydrobromides[14]. The chemical shifts of the ^{1}H and ^{13}C resonances of **6** were similar to those of ring A in **2**. The upfield shift of the NH resonance (10.83 p.p.m.), compared to that for **2**, is noteworthy. Likewise, thiazolinic protons are magnetically more equivalent, and they gave multiplets at 3.98 and 3.56 p.p.m.

Compound **6** was characterised further by the preparation of the *N'*-(4-chlorophenyl)-*N*-(1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranos-2-yl)-*N*-(2-thiazolin-2-yl)urea (**9**) and its analogous thiourea **10**. An outstanding feature of these compounds is an intramolecular hydrogen bond which is indicated by the strong downfield shift of the NH resonance (11.82 p.p.m. in **9**, 14.00 p.p.m. in **10**).

Condensation of **6** with the isothiocyanate **4** afforded **2** and confirmed the proposed mechanistic pathway. On the other hand, reactions of **6** with **5**, and **7** with **4**, led to the mixed anomeric thioureas **11** and **12**, which cannot be obtained directly from sugar isothiocyanates.

The ^{1}H- and ^{13}C-n.m.r. data of the complex thioureas **3, 11,** and **12** were analogous to those for **2**. Assignments were confirmed by spin–spin decoupling, APT, DEPT experiments, and 2D ^{1}H–^{13}C shift correlations.

On the other hand, treatment of 2-amino-2-deoxy-α-D-glucopyranose tetraacetate (**8**) with allyl isothiocyanate in dichloromethane afforded **13**, bromine-promoted cyclisation of which gave a mixture of the diastereomers 1,3,4,6-tetra-*O*-acetyl-2-[5(*R* and *S*)-5-bromomethyl-2-thiazolin-2-yl]amino-2-deoxy-α-D-gluco-

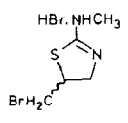
pyranose hydrobromide (**14** and **15**). Compounds **14** and **15** had spectral characteristics similar to those of **6**, although in their ^{1}H-n.m.r. spectra H-2 was deshielded (0.7 p.p.m.). In the ^{13}C-n.m.r. spectrum, the resonance of C-2 was shifted upfield (−4.4 p.p.m.), compared to that of **6**.

The mixture of **14** and **15** showed only one set of n.m.r. signals. However, h.p.l.c. of the mixture revealed a ~1:1 composition. Furthermore, when the mixture was condensed with 4-chlorophenyl isocyanate, the mixture of diastereomers **16** and **17** was obtained in the ratio ~2:1 (^{1}H-n.m.r. spectrum). The ^{13}C-n.m.r. spectrum contained two sets of signals with almost coincident chemical shifts ($\Delta\delta$ <1.0 p.p.m.). The spectral data for **16** and **17** were similar to those of **9**.

In contrast, on reaction of the mixture of **14** and **15** with **2**, **18** was isolated as the only diastereomer. The absolute configuration of the new chiral centre in **18** has not yet been determined but the spectral data were identical to those of **2**, except for those of the heterocyclic ring. The resonances of the $=N-CH_xH_y$ protons had similar chemical shifts (4.78 and 4.69 p.p.m.), having the typical AB pattern of an $ABMX_2$ system. The -S–CH- group gave a complex multiplet that overlapped the resonances of both H-5 protons. The $BrCH_2$- group gave a doublet at 3.51 p.p.m. In the ^{13}C-n.m.r. spectrum, the resonances of heterocyclic carbons had chemical shifts analogous to those of 5-bromomethyl-2-methylamino-2-thiazoline hydrobromide[15] (**19**) (see Table III).

Each of the compounds described had a $^4C_1$(D) conformation, and the $J_{1,2}$ values of the α and β compounds were in the appropriate ranges (3.0–3.8 and 8.1–8.5 Hz, respectively). Likewise, the large $J_{2,NH}$ values for **2**, **3**, **11**, **12**, and **18** are consistent with an antiperiplanar arrangement between the corresponding protons. The intramolecular hydrogen bond confers rigidity on the thioureas **2**, **3**, **10–12**, and **18**, and ureas **9**, **16**, and **17**, and anchors the *E,Z* conformation. The upfield chemical shift of the H-2 resonance in ring A is similar to that of the *E* conformer in the C-2-substituted D-glucopyranose thioformamides[16] (**20**). Hence, it is proposed that **21** is the more stable conformer in solution for these compounds.

The mass spectra of **9** and **10** showed the higher mass peak at *m/z* 432, which is attributed to the concerted loss of an isocyanate or isothiocyanate from [M$^+$] (not observed) (Scheme 1). This dominant fragmentation is favoured strongly by the presence of the intramolecular hydrogen bond. Other fragmentations are due to the further loss of ketene, acetyl, acetoxyl groups, and acetic acid in a manner similar to that of acetylated sugar derivatives[5]. The aryliso(thio)cyanate ion is the base peak.



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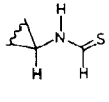

E

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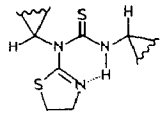
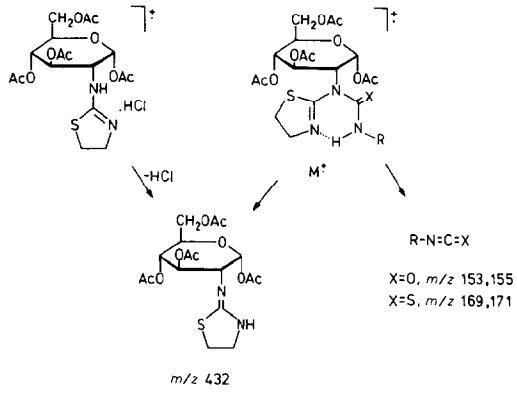


E,Z

21



Scheme 1. Mass-spectral fragmentation pathway.

EXPERIMENTAL

General methods. — Solutions were concentrated *in vacuo* at <50°. Melting points were determined with a Gallenkamp apparatus, and are uncorrected. Optical rotations were measured at 20 ±5° with a Perkin–Elmer 141 polarimeter, i.r. spectra (KBr discs) with a Perkin–Elmer 399 spectrophotometer, and u.v. spectra with a Pye–Unicam SP8-250 instrument. T.l.c. was conducted on Silica Gel GF_{254} (Merck) with benzene–acetone (5:1) and benzene–methanol (5:1 or 5:2), with detection by u.v. light or iodine vapour. Preparative t.l.c. was performed on Silica Gel PF_{254} with benzene–acetone (5:1). ^{1}H-N.m.r. spectra were recorded with a Varian XL-200 (200 MHz) and a Bruker WM-360 (360 MHz) spectrometer, ^{13}C-n.m.r. spectra (50.2 MHz) with a Varian XL-200 spectrometer, and 2D shift correlations at room temperature with a Bruker-IBM AC-200 spectrometer (200 MHz). E.i.-mass spectra (35 and 70 eV) were obtained with a Kratos MS-80RFA mass spectrometer, using a direct-insertion probe heated at 30° below the m.p. for solids. H.p.l.c. involved a Waters instrument, using a reverse-phase C-18 column, detection at 254 nm, and acetonitrile as the eluant (h.p.l.c. grade) which was degassed immediately prior to use. Elemental microanalyses were performed on a Perkin–Elmer 240C analyser.

N,N′-*Bis(1,3,4,6-tetra*-O-*acetyl-2-deoxy-α*-D-*glucopyranos-2-yl)*-N-*(2-thiazolin-2-yl)thiourea* (**2**). — To a solution of **4** (1.0 g, 2.6 mmol) in pyridine (7.5 mL) was added 2-chloroethylamine hydrochloride (0.4 g, 3.1 mmol). The mixture was kept at room temperature for 24 h, then poured into ice–water, and extracted with chloroform (3 × 25 mL). The combined extracts were washed with 2M hydrochloric acid, saturated aq. sodium hydrogencarbonate, and water, dried ($MgSO_4$), and concentrated to dryness. The syrupy residue was crystallised from ethanol to give **2** (0.7 g, 65%). Recrystallisation from ethanol gave white needles, m.p. 174–175° (dec.), $[\alpha]_D$ +159°, $[\alpha]_{578}$ +167°, $[\alpha]_{546}$ +192°, $[\alpha]_{436}$ +350°, $[\alpha]_{365}$ +715.5° (*c* 0.9,

TABLE I

^{1}H-N.M.R. CHEMICAL SHIFTS (δ) FOR COMPOUNDS **2, 3, 6,** AND **9–18**

Compound	*Ring*[a]	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6′*	*N-H*	*=NCHxHy*	*=NCHxHy*	*-S-CHuHv*	*-S-CHuHv*	*-S-CH*	*CH_2Br*	*Allyl*
2[b]	A	6.09d	3.49dd	5.29t	5.09t	3.97m	4.25dd	4.01dd	12.07d	4.95m	4.30m	3.13m	3.03m			
	B	6.14d	5.46m	5.2–5.1m		3.88m	4.21dd	4.00dd								
3[b]	A	5.92d	3.36dd	5.60t	5.16t	4.00m	4.37dd	4.14dd	11.96d	4.81m	4.39m	3.15m	3.08m			
	B	6.10d	5.04m	5.63t	5.19t	3.97m	4.31dd	4.10dd								
6[b]		6.31d	3.73dd	5.43t	5.12t	4.1–4.0m	4.37dd	4.1–4.0m	10.83m	3.98m			3.56m			
9[b]		6.17d	3.47dd	5.62t	5.15t	4.13m	4.17dd	4.02dd	11.82s	4.30m	4.25m		3.20m			
10[b]		6.22d	3.57dd	5.57t	5.19t	4.14t	4.34dd	4.07dd	14.00s	4.96m	4.60m		3.24m			
11[b]	A	6.32d	3.52dd	5.67t	5.19t	4.13m	4.34dd	4.12dd	11.91d	4.87m	4.60m		3.18t			
	B	5.81m	5.4–5.3m		5.18t	3.95m	4.32dd	4.06dd								
12[b]	A	5.62d	3.37dd	5.58t	5.18t	4.38m	4.40dd	4.06dd	11.55d	4.95m	4.39m	3.18m	3.09m			
	B	6.67d	4.92m	5.46t	5.12t	3.97m	4.26dd	4.04dd								
13[b]		6.37d	5.09m	5.4–5.2m		3.99m	4.28dd	4.07dd	6.24m							5.84m
									6.97m							5.18m
																4.04m
14, 15[c]		6.22d	4.43m	5.25t	5.02t		4.1–3.9m		10.08d	4.1–3.9m				4.1–3.9m		
16[b]		6.18d	3.53dd	5.70t	5.23t	4.0–3.8m	4.23dd	4.08dd	11.71s	4.47dd	4.37dd			4.0–3.8m	3.6–3.4m	
17[b]		6.34d	3.49dd	5.68t	5.21t	4.0–3.8m	4.21dd	4.09dd	11.76s	4.64dd	4.35dd			4.0–3.8m	3.6–3.4m	
18[b]	A	6.13d	3.52dd	5.38t	5.17t	4.0–3.8m	4.33dd	4.08dd	12.04d	4.78dd	4.68dd			4.0–3.9m	3.51d	
	B	6.20d	5.51m	5.3–5.2m		4.0–3.8m	4.27dd	4.06dd								

[a]Rings A and B refer to the sugar residues joined to N and N′, respectively. [b]In $CDCl_3$. [c]In $(CD_3)_2SO$.

TABLE II

^{1}H-N.M.R. COUPLING CONSTANTS (Hz) FOR COMPOUNDS **2, 3, 6,** AND **9–18**

Compound	*Ring*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,6'}$	$J_{5,6'}$	$J_{2,NH}$	$J_{Hx,Hu}$	$J_{Hx,Hv}$	$J_{Hx,Hy}$	$J_{Hy,Hu}$	$J_{Hy,Hv}$	$J_{Hu,Hv}$
2[a]	A	3.6	9.9	9.7	9.8	4.1	2.4	−12.6	9.3	7.2	4.0	−12.0	4.0	7.0	−11.0
	B	3.6				4.1	2.3	−12.4							
3[a]	A	8.1	9.6	9.7	9.8	4.2	2.0	−12.5	8.4	7.0	4.5	−12.0	4.3	7.0	−11.5
	B	8.5	9.5	10.5	9.7	4.3	2.1	−12.5							
6[a]		3.8	9.8	9.8	9.6	3.4		−12.2							
9[a]		3.7	10.0	9.8	10.0	6.0	2.1	−12.0		5.9	4.2	−12.7			−11.1
10[a]		3.6	10.0	9.8	9.7	4.0	3.0	−12.0		8.0	6.0	−12.0			
11[a]	A	3.7	10.0	9.7	9.9	3.2	2.1	−12.5	9.0	6.4		−12.1		7.5	
	B			9.1	10.0	3.1	2.4	−12.4							
12[a]	A	8.2	8.6	10.0	10.0	4.4	1.3	−12.4	7.0	6.8	3.6	−11.3	3.5	7.3	−11.0
	B	3.5		9.4	10.0	4.3	2.3	−13.0							
13[a]		3.0				4.2	2.4	−12.6							
14, 15[b]		3.0		9.6	9.8				10.0						
16[a]		3.7	9.4	9.8	10.0	5.7	2.8	−12.3		3.3		−12.2	3.8		
17[a]		3.7	9.4	9.8	9.9	4.7	2.8	−11.3		2.3		−12.1	3.8		
18[a]	A	3.8	9.4	9.4	9.4	4.2	2.6	−12.4	10.8	6.8		−12.4	6.4		
	B	3.4				4.2	2.6	−12.7							

[a]In $CDCl_3$. [b]In $(CD_3)_2SO$.

TABLE III

^{13}C-N.M.R. CHEMICAL SHIFTS (P.P.M.) FOR COMPOUNDS **2, 3, 6,** AND **9–18**[a]

Compound	*Ring*	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C=S*	*C=O*	*C=N*	*=N–C*	*-S–C*	*CH_2Br*
2[b]	A	91.20	66.99	71.51	67.87	69.09	61.64	180.92		161.08	55.41	25.00	
	B	90.12	55.98	70.78	67.61	69.01	61.46						
3[b]	A	92.81	67.78	73.31	67.12	72.25	61.36	181.14		161.01	55.07	24.78	
	B	92.81	57.44	72.50	67.06	71.53	61.36						
6[b]		88.64	60.05	71.02	67.51	69.27	61.07			161.12	48.97	31.22	
9[b]		90.03	65.86	71.47	67.35	69.70	61.44		150.24	161.02	48.48	25.86	
10[b]		90.01	66.10	71.53	67.36	69.94	61.43	182.66		161.33	54.41	25.02	
11[b]	A	92.97	65.52	72.60	68.01	71.59	61.44	181.14		161.19	55.21	24.74	
	B	88.72	57.74	71.79	67.43	69.19	61.29						
12[b]	A	93.10	67.70	74.20	68.84	69.40	61.52	180.87		161.30	55.33	24.73	
	B	88.51	56.65	71.93	68.20	68.92	61.29						
13[b]		90.09	55.86	70.71	67.02	69.35	61.30	182.42					
14, 15[c]		88.80	55.65	70.15	67.23	69.11	61.02			169.02	51.96	48.26	35.22
16[b]		90.06	65.95	71.47	67.19	70.06	61.38		150.00	158.90	51.92	42.07	31.86
17[b]		89.62	65.51	71.38	67.27	70.20	61.38		150.22	159.12	61.48	42.94	32.64
18[b]	A	91.03	66.77	71.51	67.68	69.07	61.50	180.85		159.00	58.74	41.52	31.96
	B	90.22	55.94	70.93	67.45	68.99	61.49						
19[c]										168.53	51.59	48.44	35.53

[a]Assignments of C-3, C-4, and C-5 resonances may be interchanged. [b]In $CDCl_3$. [c]In $(CD_3)_2SO$.

chloroform); λ_{max}^{EtOH} 274 and 244 nm (ε_{mM} 17.4 and 12.4); ν_{max} 3120–2930 (NH, CH), 1745 (C=O ester), 1610 (C=N), and 1550 cm^{-1} (NH). The ^1H- and ^{13}C-n.m.r. data are given in Tables I–III.

Anal. Calc. for $C_{32}H_{43}N_3O_{18}S_2$: C, 46.77; H, 5.27; N, 5.11. Found: C, 46.97; H, 5.29; N, 4.95.

N,N'-*Bis(1,3,4,6-tetra*-O-*acetyl-2-deoxy-β*-D-*glucopyranos-2-yl)*-N-*(2-thiazolin-2-yl)thiourea* (**3**). — To a solution of **5** (0.5 g, 1.3 mmol) in pyridine (4.0 mL) was added 2-chloroethylamine hydrochloride (0.2 g, 1.5 mmol). The mixture was processed, as described for the preparation of **2**, to give **3** (0.4 g, 73%), which, after recrystallisation from ethanol, had m.p. 191–193° (dec.), $[\alpha]_D$ +37°, $[\alpha]_{578}$ +39°, $[\alpha]_{546}$ +43°, $[\alpha]_{436}$ +41.5°, $[\alpha]_{365}$ −218° (*c* 1, chloroform); λ_{max}^{EtOH} 276 and 246 nm (ε_{mM} 12.8 and 8.8); ν_{max} 3100–2860 (NH, CH), 1740 (C=O ester), 1605 (C=N), and 1550 cm^{-1} (NH). The ^1H- and ^{13}C-n.m.r. data are given in Tables I–III.

Anal. Calc. for $C_{32}H_{43}N_3O_{18}S_2$: C, 46.77; H, 5.27; N, 5.11. Found: C, 46.71; H, 5.32; N, 5.13.

1,3,4,6-Tetra-O-*acetyl-2-deoxy-2-(2-thiazolin-2-yl)amino-α*-D-*glucopyranose hydrochloride* (**6**). — (*a*) To a stirred solution of 2-chloroethylamine hydrochloride (2.2 g, 20 mmol) in water (20 mL) were added ether (25 mL) and M sodium hydroxide (25 mL). The organic layer was decanted and the aqueous solution was extracted with ether (3 × 25 mL). The combined extracts were dried ($MgSO_4$) and concentrated to one-third volume, and **4** (3.0 g, 7.7 mmol) was added. After 24 h at room temperature, the solvent was evaporated and the residue was recrystallised from acetone or ethanol–light petroleum to give **6** (2.8 g, 79%), m.p. 213–214° (dec.), $[\alpha]_D$ +57.5°, $[\alpha]_{578}$ +60.5°, $[\alpha]_{546}$ +68°, $[\alpha]_{436}$ +108°, $[\alpha]_{365}$ +150° (*c* 0.6, chloroform); ν_{max} 3270–2820 (NH^+), 1760, 1745, and 1730 (C=O ester), 1645 ($C{=}NH^+$), and 1525 cm^{-1} (NH). The ^1H- and ^{13}C-n.m.r. data are given in Tables I–III. Mass spectrum: *m/z* 432 (3%), 415 (0.6), 414 (0.6), 389 (17), 373 (65), 313 (52), 271 (53), 253 (15), 241 (13), 199 (32), 181 (21), 168 (57), 157 (36), 145 (100), 127 (41), 115 (15), 103 (83), 97 (24), and 40 (33).

Anal. Calc. for $C_{17}H_{25}ClN_2O_9S$: C, 43.54; H, 5.37; N, 5.97. Found: C, 43.32; H, 5.37; N, 5.70.

(*b*) To a solution of **8** (5.6 g, 16.1 mmol) in acetone (35 mL) was added 2-chloroethyl isothiocyanate (1.5 mL, 16.1 mmol). The mixture was kept at room temperature, when **6** (3.6 g, 48%) crystallised.

N'-*(4-Chlorophenyl)*-N-*(1,3,4,6-tetra*-O-*acetyl-2-deoxy-α*-D-*glucopyranos-2-yl)*-N-*(2-thiazolin-2-yl)urea* (**9**). — To a solution of **6** (0.5 g, 1.1 mmol) in pyridine (7 mL) was added 4-chlorophenyl isocyanate (0.2 g, 1.1 mmol). The mixture was processed as described above for **2**, to yield **9** (0.3 g, 54%). Recrystallisation from ethanol gave needles, m.p. 155–156°, $[\alpha]_D$ +95.5°, $[\alpha]_{578}$ +100°, $[\alpha]_{546}$ +114.5°, $[\alpha]_{436}$ +205.5°, $[\alpha]_{365}$ +349.5° (*c* 0.6, chloroform); λ_{max}^{EtOH} 257, 250, and 228 nm (ε_{mM} 13.4, 14.1, and 11.7); ν_{max} 3140–2840 (NH, CH), 1735 (C=O ester), 1680 (C=O urea), 1615 (C=N), 1585 and 820 (aromatic), and 1540 cm^{-1} (NH). The ^1H- and ^{13}C-n.m.r. data are given in Tables I–III. Mass spectrum: *m/z* 432 (1%), 389 (7),

373 (20), 313 (17), 271 (17), 199 (11), 168 (18), 155 (37), 153 (100), 145 (39), 125 (25), 103 (23), and 45 (22).

Anal. Calc. for $C_{24}H_{28}ClN_3O_{10}S$: C, 49.19; H, 4.82; N, 7.17. Found: C, 49.46; H, 4.85; N, 7.20.

N'-(4-Chlorophenyl)-N-(1,3,4,6-tetra-O-acetyl-2-deoxy-α-D-glucopyranos-2-yl)-N-(2-thiazolin-2-yl)thiourea (**10**). — Treatment of **6** (0.5 g, 1.1 mmol) in pyridine (7 mL) with 4-chlorophenyl isothiocyanate (0.2 g, 1.1 mmol), as described for **9**, gave **10** (0.4 g, 55%). Recrystallisation from ethanol gave needles, m.p. 119–121°, $[\alpha]_D$ +119.5°, $[\alpha]_{578}$ +125°, $[\alpha]_{546}$ +144°, $[\alpha]_{436}$ +276°, $[\alpha]_{365}$ +353° (*c* 0.8 chloroform); λ_{max}^{EtOH} 282 and 272 nm (ε_{mM} 14.8 and 15.0); ν_{max} 3000–2770 (NH, CH), 1740 (C=O ester), 1605 (C=N), 1585 and 825 (aromatic), and 1545 cm^{-1} (NH). The ^1H- and ^{13}C-n.m.r. data are given in Tables I–III. Mass spectrum: *m/z* 432 (2%), 389 (18), 373 (51), 331 (11), 313 (43), 271 (40), 253 (12), 211 (17), 199 (27), 181 (18) 171 (25), 169 (80), 157 (29), 145 (73), 127 (35), 111 (19), 103 (67), 97 (19), 73 (13), 40 (44), and 43 (100).

Anal. Calc. for $C_{24}H_{28}ClN_3O_9S_2$: C, 47.88; H, 4.69; N, 6.98. Found: C, 47.70; H, 4.84; N, 6.69.

N-(1,3,4,6-Tetra-O-acetyl-2-deoxy-α-D-glucopyranos-2-yl)-N'-(1,3,4,6-tetra-O-acetyl-2-deoxy-β-D-glucopyranos-2-yl)-N-(2-thiazolin-2-yl)thiourea (**11**). — To a solution of **6** (1.0 g, 2.1 mmol) in pyridine (12 mL) was added **5** (0.8 g, 2.1 mmol). The mixture was processed as described for the preparation of **2**. Preparative t.l.c. gave amorphous **11** (0.6 g, 68%), $[\alpha]_D$ +77°, $[\alpha]_{578}$ +80.5°, $[\alpha]_{546}$ +91°, $[\alpha]_{436}$ +139°, $[\alpha]_{365}$ +75.5° (*c* 0.9, chloroform); λ_{max}^{EtOH} 274 and 246 nm (ε_{mM} 18.0 and 12.5); ν_{max} 3140–2820 (NH, CH), 1750 (C=O ester), 1610 (C=N), 1560 and 1550 cm^{-1} (NH). The ^1H- and ^{13}C-n.m.r. data are given in Tables I–III.

Anal. Calc. for $C_{32}H_{43}N_3O_{18}S_2$: C, 46.77; H, 5.27; N, 5.11. Found: C, 46.32; H, 5.31; N, 4.85.

N'-(1,3,4,6-Tetra-O-acetyl-2-deoxy-α-D-glucopyranos-2-yl)-N-(1,3,4,6-tetra-O-acetyl-2-deoxy-β-D-glucopyranos-2-yl)-N-(2-thiazolin-2-yl)thiourea (**12**). — To a solution of 2-chloroethylamine in ether, obtained from 2-chloroethylamine hydrochloride (0.7 g, 6.4 mmol) as described in the preparation of **6**, was added **5** (1.0 g, 2.6 mmol). After 24 h at room temperature, the solvent was evaporated to give **7**. To a solution of **7** in pyridine (12 mL) was added **4** (1.0 g, 2.6 mmol). The mixture was kept for 24 h at room temperature and then processed as described for the preparation of **2**. Preparative t.l.c. gave amorphous **12** (0.2 g, 18%), $[\alpha]_D$ +80°, $[\alpha]_{578}$ +83°, $[\alpha]_{546}$ +93°, $[\alpha]_{436}$ +144°, $[\alpha]_{365}$ +83° (*c* 0.5, chloroform); λ_{max}^{EtOH} 270 and 246 nm (ε_{mM} 22.0 and 12.0); ν_{max} 3180–2820 (NH, CH), 1755 (C=O ester), 1615 (C=N), and 1550 cm^{-1} (NH). The ^1H- and ^{13}C-n.m.r. data are given in Tables I–III.

Anal. Calc. for $C_{32}H_{43}N_3O_{18}S_2$: C, 46.77; H, 5.27; N, 5.11. Found: C, 46.78; H, 4.95; N, 4.86.

1,3,4,6-Tetra-O-acetyl-2-(N'-allylthioureido)-2-deoxy-α-D-glucopyranose (**13**). — To a solution of **8** (2.5 g, 7.2 mmol) in dichloromethane (17 mL) was added allyl isothiocyanate (0.7 mL, 7.2 mmol). After 24 h at room temperature, the mixture

was concentrated to give an oil that crystallised from ether to give **13** (2.6 g, 80%), m.p. 150–151° (dec.), $[\alpha]_D$ +103°, $[\alpha]_{578}$ +107°, $[\alpha]_{546}$ +121°, $[\alpha]_{436}$ +191°, $[\alpha]_{365}$ +253° (*c* 0.5, chloroform); λ_{max}^{EtOH} 245 nm (ε_{mM} 9.0); ν_{max} 3340 (NH), 1740–1710 (C=O ester), 1635 (C=C), and 1530 cm^{-1} (NH). The ^1H- and ^{13}C-n.m.r. data are given in Tables I–III.

Anal. Calc. for $C_{18}H_{26}N_2O_9S$: C, 48.42; H, 5.87; N, 6.27. Found: C, 48.55; H, 6.03; N, 6.06.

*1,3,4,6-Tetra-*O*-acetyl-2-[5(*R *and* S*)-5-bromomethyl-2-thiazolin-2-yl]amino-2-deoxy-α-*D*-glucopyranose hydrobromide* (**14** *and* **15**). — To a solution of **13** (1.0 g, 2.2 mmol) in dichloromethane (12 mL) was added a 16% solution of bromine in carbon tetrachloride (2.3 mL). The mixture was stored in the dark at room temperature for 1 h, then concentrated to dryness, and the residue was crystallised from ethanol to give a mixture (1.0 g, 73%) of **14** and **15**; ν_{max} 3260–2800 (NH^+), 1755, 1730 (C=O ester), 1630 ($C=N^+$), and 1495 cm^{-1} (NH). The ^1H- and ^{13}C-n.m.r. data are given in Tables I–III.

Anal. Calc. for $C_{18}H_{26}Br_2N_2O_9S$: C, 35.66; H, 4.32; N, 4.62. Found: C, 35.75; H, 4.41; N, 4.39.

N-[*5(*R *and* S*)-5-Bromomethyl-2-thiazolin-2-yl*]-N′-*(4-chlorophenyl)*-N-*(1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-*D*-glucopyranos-2-yl)urea* (**16** *and* **17**). — To a solution of the above mixture (0.5 g, 0.8 mmol) of **14** and **15** in pyridine (7 mL) was added 4-chlorophenyl isocyanate (0.1 g, 0.8 mmol). After 24 h at room temperature, the mixture was poured into ice–water, and the resulting solid (0.5 g, 85%) was collected and recrystallised from ethanol to give a mixture of **16** and **17**; λ_{max}^{EtOH} 258 and 249 nm (ε_{mM} 17.9 and 17.6); ν_{max} 3280–2840 (NH, CH), 1740 (C=O ester), 1685 (C=O urea), 1615 (C=N), 1585 and 820 (aromatic), and 1540 cm^{-1} (NH). The ^1H- and ^{13}C-n.m.r. data are given in Tables I–III.

Anal. Calc. for $C_{25}H_{29}BrClN_3O_{10}S$: C, 44.23; H, 4.30; N, 6.19. Found: C, 44.27; H, 4.25; N, 6.32.

N-[*5(*R *or* S*)-5-Bromomethyl-2-thiazolin-2-yl*]-N,N′-*bis(1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-*D*-glucopyranos-2-yl)thiourea* (**18**). — To a solution of the mixture of **14** and **15** (0.2 g, 0.3 mmol) in pyridine (3.5 mL) was added **4** (0.1 g, 0.3 mmol). The mixture was processed as described for **2**, to yield **18** (0.1 g, 46%), which, after recrystallisation from ethanol, had m.p. 167–169° (dec.), $[\alpha]_D$ +95°, $[\alpha]_{578}$ +101°, $[\alpha]_{546}$ +116°, $[\alpha]_{436}$ +212°, $[\alpha]_{365}$ +430° (*c* 0.5, chloroform); λ_{max}^{EtOH} 272 and 238 nm (ε_{mM} 13.9 and 10.7); ν_{max} 3020–2800 (NH, CH), 1740 (C=O ester), 1610 (C=N), and 1540 cm^{-1} (NH). The ^1H- and ^{13}C-n.m.r. data are given in Tables I–III.

Anal. Calc. for $C_{33}H_{44}BrN_3O_{18}S_2$: C, 43.33; H, 4.85; N, 4.59. Found: C, 43.46; H, 4.90; N, 4.50.

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