Synthesis of Acylated Thioureylenedisaccharides

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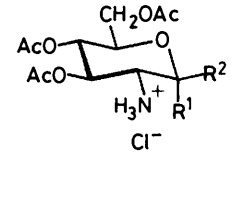
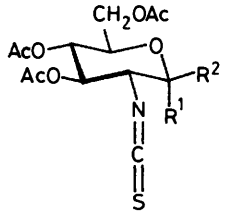
Thioureylenedisaccharides have been prepared from sugar isothiocyanates and aminosugars. Thus, a thiourea bridge connects the (C-1)–(C-2) or (C-2)–(C-2) positions of some pentose, hexose, and heptose frameworks with different anomeric patterns in compounds (**16**)—(**28**). With this aim, several C-2-functionalised derivatives of compound (**7**) have been synthesized. A (*Z,Z*)-conformation is proposed for thioureylenedisaccharides in solution.

Many biologically important products have two sugar units joined through an atom (as oxygen in disaccharides) or group of atoms (as phosphate in dinucleotides and agrocinopines[1]). The replacement of these classical bridges gives rise to compounds of great structural analogy with natural products, and which may be used as enzyme inhibitors. For this reason, much effort has been directed toward the synthesis of such compounds. Thus, *S*-,[2] *N*-,[3] and *C*-disaccharides[4] are already known. Pseudodisaccharides with disulphide[5] and hydrazine[6] bridges, and pseudodinucleotides with carbonate,[7] methylphosphonate,[8] carbamate,[9] thiocarbamate,[10] thiophosphate,[11] phosphoramidate,[12] and diphenylsilane[13] bridges have been also synthesized. Sugars joined by urea or thiourea groups, non-ionic isosteric bridges of phosphates, have been studied to some extent. These bridges are present in a few natural products such as glycocinnamoylspermidines,[14] a family of broad-spectrum antibiotics. The condensation of monosaccharides with urea,[15] the benzoylation of glycosylureas,[16] the addition of water[17] and hydrogen sulphide[18] to diglycosylcarbodi-imides, and the reaction of glycosyl isothiocyanates with glycosylamines[19] produced 1,3-diglycosylureas and 1,3-diglycosylthioureas, respectively. The same compounds were also obtained as side-products in several reactions of glycosyl isocyanates[20] and glycosyl isothiocyanates.[21] On the other hand, two 2-deoxy-2-glycosylureidosugars have been synthesized,[10,22] and Jochims and Seeliger[23] have described the only urea and thiourea derivatives in which both nitrogen atoms are joined to non-anomeric carbon atoms.

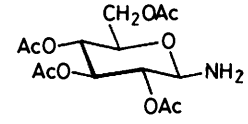
In this paper we report on the preparation of a wide set of thioureas in which the HN–CS–NH group links the aldopyranose frameworks that have different anomeric patterns, through the reaction of the free amino group of one aminosugar with a sugar isothiocyanate.



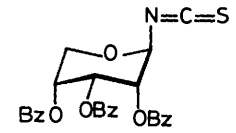
(**1**) R^1 = OAc, R^2 = H
(**2**) R^1 = H, R^2 = OAc



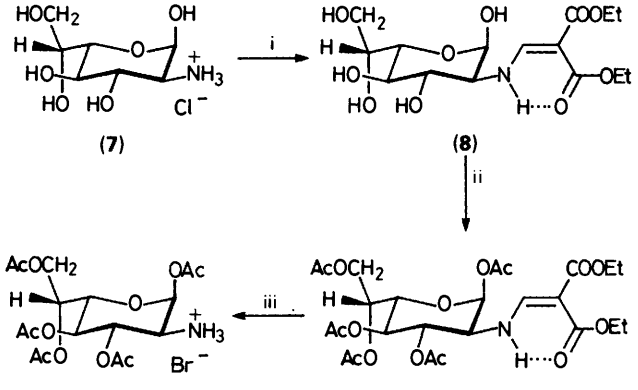
(**3**) R^1 = OAc, R^2 = H
(**4**) R^1 = H, R^2 = OAc



(**5**)



(**6**)



(**7**) (**8**) (**9**) (**10**)

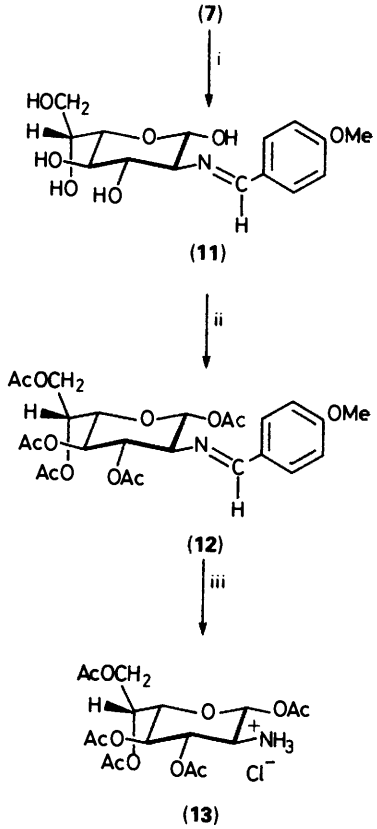
Scheme 1. *Reagents:* i, $EtOCH{=}C(COOEt)_2$; ii, Ac_2O–pyridine; iii, Br_2–$CHCl_3$–water

Results and Discussion

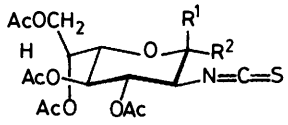
Synthesis of Precursors.—Starting compounds (**1**),[24] (**2**),[25] (**3**),[26] (**4**),[23] (**5**),[19] and (**6**)[27] have been prepared by methods described in the literature. The synthesis of several *O*-acyl derivatives of 2-amino-2-deoxy-D-*glycero*-α-L-*gluco*-heptopyranose hydrochloride[28] (**7**)† and their use as intermediates for the synthesis of sugar thioureas is now described. The reaction of compound (**7**) with diethyl ethoxymethylenemalonate gave compound (**8**). Conventional acetylation of (**8**) afforded penta-acetate (**9**) which led to the amine (**10**) through *N*-deprotection with bromine in humidified chloroform. This alternative synthesis follows with greater total yield (82%) that was previously reported[29] (Scheme 1).

The β-anomer (**13**)‡ was easily available (total yield 47%) through the *N*-protection of compound (**7**) with 4-methoxy-

† *Correct name:* 2-amino-2-deoxy-β-D-*glycero*-L-*gluco*-heptopyranose.
‡ *Note:* the text uses α, β to describe the stereochemistry of the anomeric centre with respect to that at C-5, for comparative purposes homomorphous sugars. The *strictly correct* (IUPAC) nomenclature for the heptopyranoses should show the reverse anomeric configurational prefix (see Experimental section).



Scheme 2. *Reagents:* i, 4-$MeOC_6H_4CHO$–1M-NaOH; ii, Ac_2O–pyridine; iii, 5M-HCl–acetone



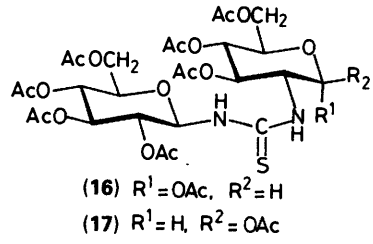
(**14**) R^1 = OAc, R^2 = H

(**15**) R^1 = H, R^2 = OAc

benzaldehyde (Scheme 2). The Schiff derivative (**11**) was then acetylated to give penta-acetate (**12**), which showed a high value of $J_{1,2}$ (8.3 Hz), in accord with a β-configuration. A similar anomeric anchorage has been observed in the D-glucosamine series.[25] Isothiocyanates (**14**)[30] and (**15**) were prepared from amines (**10**) and (**13**) with thiophosgene in a two-phase reaction system.

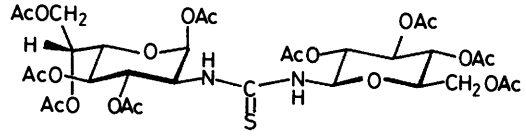
Synthesis of Thioureylenedisaccharides and Analogues.—Anomeric and C-2 carbons of different sugars have been linked by a thiourea group in the reaction of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine (**5**) with 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-isothiocyanato-α- and -β-D-glucopyranose,[23,26] (**3**) and (**4**) respectively, to give products (**16**) and (**17**). From the heptopyranose (**14**) the thiourea (**18**) was obtained. In the same way, 2,3,4-tri-*O*-benzoyl-β-D-ribopyranosyl isothiocyanate (**6**) was linked to the sugar residues of 2-deoxy-β-D-glucopyranose and 2-deoxy-D-*glycero*-β-L-*gluco*-heptopyranose in the thioureas (**19**) and (**20**) by reaction with the amines (**2**) and (**13**), respectively. On the other hand, in compounds (**21**)—(**28**) the thiourea bridge connects the C-2 atoms of hexose–hexose, heptose–heptose, and hexose–heptose frameworks with different anomeric patterns.

All these reactions were performed with equimolar amounts of aminosugar and isothiocyanate in pyridine at room

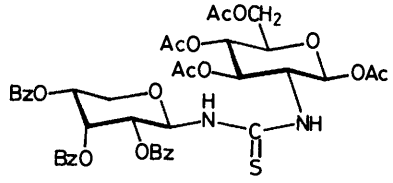


(**16**) R^1 = OAc, R^2 = H

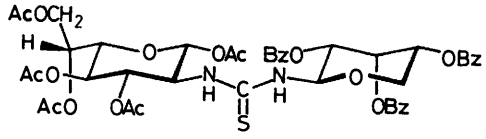
(**17**) R^1 = H, R^2 = OAc



(**18**)

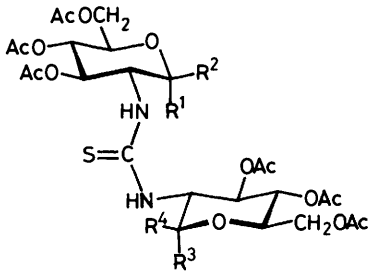


(**19**)

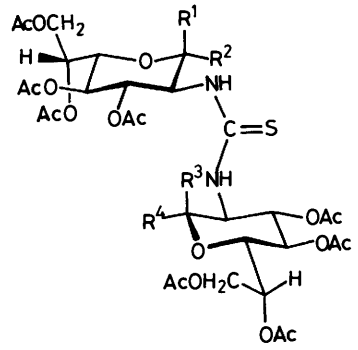


(**20**)

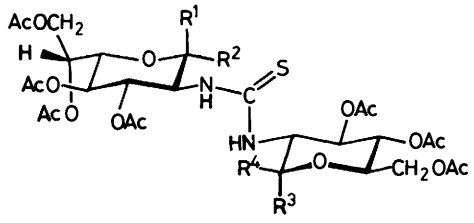
temperature. Structures of new compounds were demonstrated by elemental analyses and spectral data. The u.v. spectra showed $\lambda_{max.}$ at 243—249 nm, as would be expected, for the thiourea moiety, and the i.r. spectra showed characteristic absorption bands of NH at 3 390—3 300 and ~1 540 cm^{-1}. ^1H and ^{13}C n.m.r. spectra of products (**16**)—(**28**) show some analogies with those other thioureas already described,[19,26,30,31] although the presence of two sugar rings made their interpretation difficult. Molecular symmetry of compounds (**21**) and (**22**) simplified their spectra and thus they served as model compounds. Resonances of compound (**23**) were coincidental with those of (**21**) and (**22**), as might have been expected. The thioureas (**24**)—(**26**) showed analogous n.m.r. spectra to their homomorphs (**21**)—(**23**), except for the presence of the 6-H proton and C-6 carbon signals. The ^1H n.m.r. spectra of the sugar moieties of unsymmetrical thioureas (**16**)—(**18**), (**27**), and (**28**) are almost superposable on those of symmetrical thioureas (**21**), (**22**), (**24**), (**25**), and (**29**)[19] when they have the same sugar framework. The ribopyranosyl residue of compounds (**19**) and (**20**) showed n.m.r. spectra analogous to that of the tri-*O*-benzoylribopyranosylamine[27] except for 1-H. This proton appears shifted downfield (~1.5—2.0 p.p.m.) in a similar way as for other thioureas with respect to its parent aminosugar.[19,27,30,31] All compounds described showed a $^4C_1$(D) conformation for hexose residues or a $^1C_4$(L) conformation for heptose residues. The $^4C_1$(D) conformation of the ribopyranosyl residues contrast with that [$^1C_4$(D)] of the parent isothiocyanate (**6**).[27] The β-anomeric configuration has been assigned on the basis of the large $J_{1,2}$ value (8.2—10.0 Hz), and the α-anomeric configurations are consistent with a small $J_{1,2}$ value (3.2—4.0 Hz) (see Table 2).



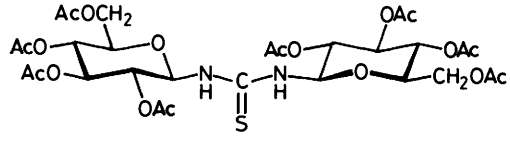
(21) $R^1=R^3=OAc$, $R^2=R^4=H$
(22) $R^1=R^3=H$, $R^2=R^4=OAc$
(23) $R^1=R^4=OAc$, $R^2=R^3=H$



(24) $R^1=R^3=OAc$, $R^2=R^4=H$
(25) $R^1=R^3=H$, $R^2=R^4=OAc$
(26) $R^1=R^4=OAc$, $R^2=R^3=H$

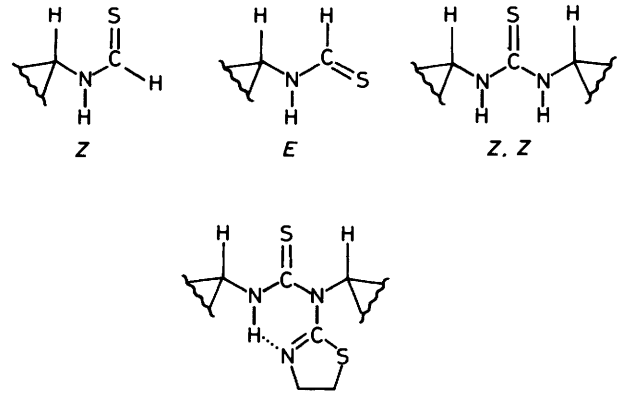


(27) $R^1=R^3=OAc$, $R^2=R^4=H$
(28) $R^1=R^3=H$, $R^2=R^4=OAc$



(29)

Generally, 1,3-disubstituted alkylthioureas exist in solution as an equilibrium mixture of three conformational isomers: (*Z*,*Z*), (*Z*,*E*), and (*E*,*Z*). The free-energy barrier to the internal rotation for thioureas[32–37] is ~50 kJ mol^{-1}. The (*E*,*E*)-isomer has not been detected.[38] The chemical shifts of 1-H or 2-H protons joined to the thiourea bridge are similar to those of the corresponding protons of the *Z*-isomer in sugar thioformamides,[39] and coincide with the chemical shifts of sugar protons



Z *E* *Z*, *Z*

Figure.

joined to the unsubstituted nitrogen of *N*,*N*′-bis(glycosyl)-*N*-(2-thiazolin-2-yl)thioureas.[40] In these latter compounds the (*Z*,*Z*)-conformations are fixed by an internal hydrogen bond. On the other hand, the large couplings $J_{1,NH}$ or $J_{2,NH}$ observed agree with an antiperiplanar disposition between these protons. For these reasons, we propose a (*Z*,*Z*)-assignment to the major isomer of compounds (**16**)—(**18**) in $CDCl_3$ solution at room temperature (see Figure). This assumption was confirmed by means of low-temperature n.m.r. experiments for compound (**21**). The ^1H and ^{13}C n.m.r. spectra at 193 K and 298 K are closely similar (see Tables 1 and 3), showing the presence of only a single conformer at both temperatures.

Experimental

General Methods.—M.p.s were determined using a Gallenkamp apparatus, and are uncorrected. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. T.l.c. was performed on silica gel GF_{254} (Merck) with detection by u.v. light or iodine vapour. I.r. spectra (KBr discs) were recorded with a Perkin-Elmer 399 spectrometer, and u.v. spectra (ethanol solutions) with a Pye-Unicam SP8-250 or a Beckman 50 instrument. ^1H n.m.r. spectra were obtained with Perkin-Elmer R-32 (90 MHz), Bruker AC 200-E, and Varian XL-200 (200 MHz) instruments. ^{13}C N.m.r. spectra were recorded on a Bruker AC 200-E or a Varian XL-200 (50.2 MHz) spectrometer. For n.m.r. experiments at low temperature, the spectrometer was fitted with a variable-temperature accessory capable of maintaining temperature to within ±1 K, and spectra were recorded in [$^2H_6$]acetone solution at 298, 273, 243, 213, and 193 K. Elementary analyses were performed using a Perkin-Elmer 240C analyser.

2-*Deoxy*-2-{[2,2-*bis*(*ethoxycarbonyl*)*vinyl*]*amino*}-β-D-glycero-L-gluco-*heptopyranose* (**8**).—To a suspension of compound (**7**) (29.5 g, 120.2 mmol) in methanol (600 ml) were added triethylamine (42 ml) and diethyl ethoxymethylenemalonate (26.0 ml, 130.0 mmol) and the mixture was refluxed for 5 min. Crystals obtained by cooling (31.0 g) were washed with 1:1 ethanol–ether and then with ether. Concentration of mother liquors, followed by refrigeration, afforded two additional crops (total yield 41.3 g, 91%). Recrystallisation from methanol gave the *title compound* as needles, m.p. 193—195 °C (decomp.); $[\alpha]_D^{17}$ −139°, $[\alpha]_{578}^{17}$ −147°, $[\alpha]_{546}^{17}$ −170.5°, $[\alpha]_{436}^{17}$ −318°, and $[\alpha]_{365}^{17}$ −581° (*c* 1.0, pyridine); $\lambda_{max.}$ 277 nm (ε 21 900); $\nu_{max.}$ 3 380—3 100 (OH and NH), 1 680, 1 650 (C=O), 1 605 and 790 cm^{-1} (C=C) (Found: C, 47.1; H, 7.0; N, 3.9. $C_{15}H_{25}NO_{10}$ requires C, 47.49; H, 6.64; N, 3.69%).

1,3,4,6,7-*Penta*-O-*acetyl*-2-*deoxy*-2-{[2,2-*bis*(*ethoxycarbonyl*)*vinyl*]*amino*}-β-D-glycero-L-gluco-*heptopyranose*

Table 1. ^{1}H N.m.r. chemical shifts of compounds (16)—(28)[a]

Compound	Ring[b]	1-H	2-H	3-H	4-H	5-H	5-H′	6-H	6-H′	7-H	7-H′	NH
(16)	A	6.28d	5.07m	5.3—5.2m		4.03m		4.29dd	4.08dd			6.64d
	B	5.69m	4.95t	5.35t	5.07t	3.85m		4.36dd	4.07dd			6.92d
(17)	A	5.80d	5.25—5.2m			3.85m		4.29dd	4.13dd			6.87d
	B	5.74t	4.98t	5.35t	5.05t	3.85m		4.37dd	4.07dd			6.89d
(18)	A	6.40m	5.1—5.0m	5.3—5.1m		4.04dd		5.3—5.1m		4.25dd	4.15dd	6.86d
	B	5.69m	4.90t	5.35t	5.03t	3.91m		4.32dd	4.2—4.0m			7.08d
(19)	A	5.74d	5.2—5.1m			3.78m		4.26dd	4.12dd			6.85d
	B	6.38d	5.44dd	6.22t	5.47m	4.3—4.1m						7.25d
(20)	A	5.63d	4.97m	5.3—5.1m		4.06m		5.3—5.1m		4.4—4.0m		6.80d
	B	6.38m	5.6—5.4m	6.31t	5.6—5.4m	4.4—4.0m						7.29d
(21)	A = B	6.28d	5.05m	5.3—5.1m		4.00m		4.26dd	4.07dd			6.50d
(21)[c]	A = B	6.28d	5.02m	5.29t	5.16t	4.15m		4.24dd	4.03dd			7.14d
(21)[d]	A = B	6.17d	4.91m	5.25t	5.18t	4.25m		4.25dd	3.84dd			7.65d
(22)	A = B	5.81d	5.2—4.9m	5.41t	5.2—4.9m	3.92m		4.3—4.1m				6.56d
(23)	A	6.34d	5.2—4.9m	5.3—5.2m		4.05m		4.29dd	4.07dd			6.48m
	B	5.76d	5.2—4.9m	5.3—5.2m	5.12m	3.88m		4.3—4.1m	4.1—4.0m			
(24)	A = B	6.27d	5.1—5.0m	5.3—5.1m		4.06dd		5.3—5.1m		4.26dd	4.13dd	6.14d
(25)	A = B	5.77d	5.2—5.0m	5.32t	5.08t	3.97dd		5.23m		4.33dd	4.19dd	6.54d
(26)	A	6.34m		5.3—5.0m		4.08dd		5.3—5.0m		4.27dd	4.12dd	6.25d
	B	5.67d		5.3—5.0m		3.88dd		5.3—5.0m		4.35dd	4.14dd	6.34m
(27)	A	6.27d	5.2—5.0m	5.3—5.2m		4.07dd		5.3—5.2m		4.24dd	4.13dd	6.42d
	B	6.27d	5.2—5.0m	5.3—5.2m		4.02m		4.27dd	4.08dd			6.43d
(28)	A	5.77d	5.2—5.0m	5.33t	5.06t	3.88dd		5.3—5.1m		4.31dd		6.56d
	B	5.81d	5.2—5.0m	5.38t	5.14t	3.95m		4.3—4.1m				6.53d

[a] In $CDCl_3$. [b] Rings A and B are the sugar moiety joined to N and N′ atoms respectively. [c] In [$^2H_6$]acetone at 298 K. [d] In [$^2H_6$]acetone at 193 K.

Table 2. ^{1}H N.m.r. coupling constants of compounds (16)—(19) and (21)—(28)[a]

Compound	Ring	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	$J_{6,7}$	$J_{6,7'}$	$J_{7,7'}$	$J_{1,NH}$	$J_{2,NH}$
(16)	A	4.0				4.2	4.8	13.2					8.8
	B	8.8	8.8	8.8	9.8	4.8	4.4	12.6				8.8	
(17)	A	9.0				4.0	3.0	13.0					10.0
	B	10.0	9.5	10.0	9.5	4.5	3.0	13.0				9.0	
(18)	A				8.0	2.2			5.1	6.9	12.3		8.6
	B		9.4	9.4	9.7	4.7		13.1				8.3	
(19)	A	9.2			8.0	4.7	2.2	12.5					10.0
	B	9.4	2.8	2.8								10.0	
(21)	A = B	3.6	9.5	9.5		4.0	2.0	14.0					8.8
(22)	A = B	8.2	10.0	10.0									9.2
(23)	A	4.0				4.0	2.0	13.0					
	B	8.2											
(24)	A = B	3.2	8.8	8.8	9.1	2.9			5.1	6.5	12.4		8.8
(25)	A = B	8.6	9.6	9.6	9.6	1.7			3.8	7.4	11.9		9.4
(26)	A				8.0	3.2			5.1	7.7	12.1		8.4
	B	8.3			9.4	1.7			4.5	7.7	11.7		
(27)	A	3.6			9.0	2.6			5.8	7.3	11.4		8.5
	B	3.6				4.2	2.2	13.4					8.5
(28)	A	8.6	9.6	9.6	9.6	1.7			3.9	7.4	11.8		9.3
	B	8.4	9.8	9.8	9.8								9.3

[a] In $CDCl_3$.

(9).—Conventional treatment of compound (8) (40.0 g, 105.0 mmol) with pyridine (300 ml) and acetic anhydride (240 ml) overnight at room temperature gave the *title compound* (9) (59.1 g, 95%). Recrystallised from aq. ethanol, it showed m.p. 120—122 °C; $[\alpha]_D^{22}$ −83.5°, $[\alpha]_{578}^{22}$ −88°, $[\alpha]_{546}^{22}$ −101°, $[\alpha]_{436}^{22}$ −189°, and $[\alpha]_{365}^{22}$ −347° (*c* 1.0, chloroform); $\lambda_{max.}$ 275 nm (22 300); $\nu_{max.}$ 3 280—3 100 (NH), 1 740, 1 670, 1 630 (C=O), 1 600 and 795 cm^{-1} (C=C); δ_H ($CDCl_3$) 1.25 (3 H, t, Me), 1.30 (3 H, t, Me), 2.00 (9 H, s, 3 × OAc), 2.08 (3 H, s, OAc), 2.25 (3 H, s, OAc), 3.80 (1 H, m, 5-H), 4.15 (2 H, q, CH_2), 4.22 (2 H, q, CH_2), 4.00—4.40 (4 H, m, 2-H, 6-H, and 7-H_2), 5.10 (1 H, t, *J* 9.3 Hz, 4-H), 5.36 (1 H, t, *J* 9.3 Hz, 3-H), 6.26 (1 H, d, *J* 4.0 Hz, 1-H), 7.92 (1 H, d, *J* 13.3 Hz, CH=C), and 9.05 (1 H, dd, *J* 9.7, 13.3 Hz, NH) (Found: C, 51.3; H, 6.2; N, 2.3. $C_{25}H_{35}NO_{15}$ requires C, 50.93; H, 5.98; N, 2.37%).

1,3,4,6,7-*Penta*-O-*acetyl*-2-*amino*-2-*deoxy*-β-D-glycero-L-gluco-*heptopyranose Hydrobromide* (10).—To a solution of diester (9) (24.8 g, 42.1 mmol) in chloroform (60 ml) was added gradually a solution of bromine (7.0 g, 43.8 mmol) in chloroform (150 ml) containing water (0.75 ml). Crystallisation of free amine (10) began at room temperature and was completed by dilution with ether (19.9 g, 95%). Compound (10) decomposes above 185 °C without melting (lit.,[29] 180—182 °C).

2-*Deoxy*-2-(4-*methoxybenzylidene*)*amino*-α-D-glycero-L-gluco-*heptopyranose* (11).—To a solution of compound (7)

Table 3. ^{13}C N.m.r. chemical shifts of compounds (**16**)—(**28**)[a,b]

Compound	Ring	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C=S
(**16**)	A	90.28	55.68	70.62	67.26	69.54	61.52		183.92
	B	82.61	71.00	73.62	68.22	72.62	61.77		
(**17**)	A	92.23	57.15	72.96	68.08	72.64	61.57		184.67
	B	82.51	70.51	73.25	67.63	72.64	61.48		
(**18**)	A	89.60	55.61	70.64	66.38	69.87	66.38	62.00	184.15
	B	82.35	70.33	73.14	67.99	72.45	61.64		
(**19**)	A	94.01	57.36	72.81	67.49	72.40	61.60		185.12
	B	80.54	69.24	69.15	67.09	62.97			
(**20**)	A	92.80	57.24	73.03	67.30	73.03	66.47	62.33	185.59
	B	80.88	69.69	69.56	66.47	63.04			
(**21**)	A = B	90.46	55.92	70.96	67.42	69.72	61.68		183.55
(**21**)[c]	A = B	90.78	56.52	71.06	68.70	70.57	62.33		185.20
(**21**)[d]	A = B	90.46	55.65	70.79	67.00	69.60	61.48		184.29
(**22**)	A = B	92.91	57.33	72.45	68.55	72.13	61.53		183.97
(**23**)	A	89.85	57.32	70.41	67.23	69.60	61.57		183.78
	B	92.74	57.54	72.70	67.61	72.61	61.38		
(**24**)	A = B	90.28	55.65	71.03	66.53	69.87	66.37	62.13	183.53
(**25**)	A = B	93.27	57.52	73.02	67.28	73.02	66.58	62.85	184.30
(**26**)	A	89.78	55.22	72.75	66.29	69.75	65.65	62.06	183.73
	B	92.83	57.17	72.93	66.29	70.43	65.65	62.09	
(**27**)	A	90.13	55.48	70.70	66.32	69.35	66.32	61.36	183.78
	B	90.25	55.48	70.85	67.15	69.49	61.88		
(**28**)	A	93.02	57.45	73.09	67.14	72.38	66.48	61.70	184.27
	B	93.02	57.63	73.30	68.57	72.84	62.72		

[a] Assignments of C-3, C-4, and C-5 resonances may be interchanged. [b] In $CDCl_3$. [c] In [$^2H_6$]acetone at 298 K. [d] In [$^2H_6$]acetone at 193 K.

(31.5 g, 128.0 mmol) in 1M-sodium hydroxide (150 ml) was added 4-methoxybenzaldehyde (23.0 ml, 189.0 mmol). The mixture was stirred vigorously at room temperature; a white solid crystallised out, and was separated and washed successively with cold water, ethanol, and ether to give *compound* (**11**) (26.2 g, 62%), m.p. 190—192 °C; $[\alpha]_D^{28}$ −46°, $[\alpha]_{578}^{28}$ −48.5°, $[\alpha]_{546}^{28}$ −55°, $[\alpha]_{436}^{28}$ −105.5°, $[\alpha]_{365}^{28}$ −103° (starting value), $[\alpha]_D^{28}$ −55°, $[\alpha]_{578}^{28}$ −57.5°, $[\alpha]_{546}^{28}$ −66.5°, $[\alpha]_{436}^{28}$ −129.5°, and $[\alpha]_{365}^{28}$ +724.5° (final value, 6 days) (*c* 1.0, pyridine); $\nu_{max.}$ 3 460—3 160 (OH), 1 635 (C=N), 1 600, 1 510, and 830 cm^{-1} (aromatic) (Found: C, 54.4; H, 6.5; N, 4.2. $C_{15}H_{21}NO_7$ requires C, 55.04; H, 6.47; N, 4.28%).

1,3,4,6,7-*Penta*-O-*acetyl*-2-*deoxy*-2-(4-*methoxybenzylidene*)*amino*-α-D-glycero-L-gluco-*heptopyranose* (**12**).—Conventional treatment of compound (**11**) (25.8 g, 78.9 mmol) with pyridine (120 ml) and acetic anhydride (97 ml) at room temperature for 12 h gave penta-acetate (**12**) (33.1 g, 78%) as needles, m.p. 188—190 °C (from ethanol); $[\alpha]_D^{18}$ −58°, $[\alpha]_{578}^{18}$ −61.5°, $[\alpha]_{546}^{18}$ −74°, $[\alpha]_{436}^{18}$ −170°, $[\alpha]_{365}^{18}$ −418° (*c* 0.6, chloroform); $\lambda_{max.}$ 269 nm (20 400); $\nu_{max.}$ 1 730 (C=O ester), 1 625 (C=N), 1 595, 1 495, and 815 cm^{-1} (aromatic); δ_H ($CDCl_3$) 1.88, 2.07, and 2.11 (each 3 H, each s, 3 × OAc), 2.02 (6 H, s, 2 × OAc), 3.48 (3 H, s, OMe), 3.47 (1 H, t, *J* 9.6 Hz, 2-H), 3.68 (1 H, dd, *J* 2.3, 9.7 Hz, 5-H), 4.00 (1 H, dd, *J* 7.7, 13.3 Hz, 7-H′), 4.38 (1 H, dd, *J* 5.7, 13.3 Hz, 7-H), 5.13 (1 H, t, *J* 9.7 Hz, 4-H), 5.27—5.41 (1 H, m, 6-H), 5.42 (1 H, t, *J* 10.0 Hz, 3-H), 5.88 (1 H, d, *J* 8.3 Hz, 1-H), and 8.18 (1 H, s, CH=) (Found: C, 55.8; H, 6.0; N, 2.7. $C_{25}H_{31}NO_{12}$ requires C, 55.86; H, 5.81; N, 2.61%).

1,3,4,6,7-*Penta*-O-*acetyl*-2-*amino*-2-*deoxy*-α-D-glycero-L-gluco-*heptopyranose Hydrochloride* (**13**).—A boiling solution of compound (**12**) (20.0 g, 37.2 mmol) in acetone (100 ml) was treated with 5M-hydrochloric acid (8.5 ml); immediately, a white solid was formed. Crystallisation was completed by dilution with ether (100 ml) and further refrigeration (16.6 g, 98%). This *product* decomposes above 209 °C without melting; $[\alpha]_D^{17}$ −5.5°, $[\alpha]_{578}^{17}$ −4.6°, $[\alpha]_{546}^{17}$ −6°, $[\alpha]_{436}^{17}$ −10.5°, and $[\alpha]_{365}^{17}$ −16° (*c* 0.6, pyridine); $\nu_{max.}$ 3 180—2 500 (NH_3^+), 1 745 (C=O ester), and 1 570 and 1 495 cm^{-1} (NH_3^+); δ_H [$(CD_3)_2SO$] 1.96, 2.00, 2.02, 2.04, and 2.21 (each 3 H, each s, 5 × OAc), 3.57 (1 H, t, *J* 9.7 Hz, 2-H), 3.96—4.32 (3 H, m, 5-H and 7-H_2), 4.91 (1 H, t, *J* 9.7 Hz, 4-H), 5.10—5.30 (1 H, m, 6-H), 5.42 (1 H, t, *J* 9.7 Hz, 3-H), 5.96 (1 H, d, *J* 9.0 Hz, 1-H), and 9.03 (1 H, m, NH) (Found: C, 44.7; H, 6.0; N, 3.1. $C_{17}H_{26}ClNO_{11}$ requires C, 44.79; H, 5.75; N, 3.07%).

1,3,4,6,7-*Penta*-O-*acetyl*-2-*deoxy*-2-*isothiocyanato*-α-D-glycero-L-gluco-*heptopyranose* (**15**).—To a mixture of compound (**13**) (5.4 g, 12.0 mmol), chloroform (90 ml), calcium carbonate (4.1 g, 40.8 mmol), and water (40 ml) was added thiophosgene (15 ml, 19.0 mmol). The mixture was stirred vigorously for 48 h and then filtered. The organic layer was washed with water, dried ($CaCl_2$), and evaporated to dryness. The residue was crystallised from ether (3.6 g, 65%). Recrystallisation from ether gave the *title isothiocyanate*, m.p. 136—138 °C, $[\alpha]_D^{22}$ −23°, $[\alpha]_{578}^{22}$ −25°, $[\alpha]_{546}^{22}$ −29°, $[\alpha]_{436}^{22}$ −53.5°, and $[\alpha]_{365}^{22}$ −90° (*c* 1.0, chloroform); $\lambda_{max.}$ 246 nm (7 300); $\nu_{max.}$ 2 100 (NCS) and 1 740 cm^{-1} (C=O ester); δ_H ($CDCl_3$) 2.01, 2.05, 2.09, 2.11, and 2.20 (each 3 H, each s, 5 × OAc), 3.93 (1 H, dd, *J* 2.2, 10.0 Hz, 5-H), 4.00 (1 H, dd, *J* 8.6, 9.2 Hz, 2-H), 4.10 (1 H, dd, *J* 8.0, 12.0 Hz, 7-H′), 4.27 (1 H, dd, *J* 6.0, 12.0 Hz, 7-H), 5.00 (1 H, t, *J* 10.0 Hz, 4-H), 5.28 (2 H, m, 3- and 6-H), and 5.65 (1 H, d, *J* 8.6 Hz, 1-H) (Found: C, 47.25; H, 5.1; N, 2.8. $C_{18}H_{23}NO_{11}S$ requires C, 46.85; H, 5.02; N, 3.03%).

General Procedure for the Preparation of Compounds (**16**)—(**28**).—To a solution of a sugar isothiocyanate (1.3 mmol) in pyridine (6 ml) was added the appropriate aminosugar (1.3 mmol). The solution was stored at room temperature for 24 h and then poured into ice–water; the resulting white solid was collected. If the precipitation failed, the aqueous solution was extracted with dichloromethane (3 × 50 ml). The extracts were repeatedly washed with 2M-hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and water, dried ($MgSO_4$), and evaporated to dryness. The residue was crystallised from an appropriate solvent. According to this general procedure, the following products were prepared.

N-(1,3,4,6-*Tetra*-O-*acetyl*-2-*deoxy*-α-D-*glucopyranosan*-2-*yl*)-N′-(2,3,4,6-*tetra*-O-*acetyl*-β-D-*glucopyranosyl*)-*thiourea* (**16**). From compounds (**3**) and (**5**) (73%), m.p. 206—208 °C (decomp.) (from ethanol); $[\alpha]_D^{22}$ +58°, $[\alpha]_{578}^{22}$ +60°, $[\alpha]_{546}^{22}$ +68°, $[\alpha]_{436}^{22}$ +112.5°, and $[\alpha]_{365}^{22}$ +176.5° (*c* 1.0, chloroform); $\lambda_{max.}$ 249 nm (11 300); $\nu_{max.}$ 3 350 (NH), 1 745 (C=O), and 1 530 cm^{-1} (NH) (Found: C, 47.6; H, 5.7; N, 3.7. $C_{29}H_{40}N_2O_{18}S$ requires C, 47.28; H, 5.47; N, 3.80%).

N-(1,3,4,6-*Tetra*-O-*acetyl*-2-*deoxy*-β-D-*glucopyranosan*-2-*yl*)-N′-(2,3,4,6-*tetra*-O-*acetyl*-β-D-*glucopyranosyl*)-*thiourea* (**17**). From compounds (**4**) and (**5**) (86%), m.p. 175—176 °C (lit.,[10] 178 °C).

N-(1,3,4,6,7-*Penta*-O-*acetyl*-2-*deoxy*-β-D-glycero-L-gluco-*heptopyranosan*-2-*yl*)-N′-(2,3,4,6-*tetra*-O-*acetyl*-β-D-*glucopyranosyl*)*thiourea* (**18**). From compounds (**14**) and (**5**) (59%), m.p. 126—128 °C (from ethanol); $[\alpha]_D^{28}$ −24.5°, $[\alpha]_{578}^{28}$ −25°, $[\alpha]_{546}^{28}$ −27.5°, $[\alpha]_{436}^{28}$ −30.5°, and $[\alpha]_{365}^{28}$ +17.5° (*c* 1.0, chloroform); $\lambda_{max.}$ 245 nm (11 100); $\nu_{max.}$ 3 350 (NH), 1 745 (C=O), and 1 530 cm^{-1} (NH) (Found: C, 47.8; H, 5.5; N, 3.3. $C_{32}H_{44}N_2O_{20}S$ requires C, 47.52; H, 5.48; N, 3.46%).

N-(1,3,4,6-*Tetra*-O-*acetyl*-2-*deoxy*-β-D-*glucopyranosan*-2-*yl*)-N′-(2,3,4-*tri*-O-*benzoyl*-β-D-*ribopyranosyl*)-*thiourea* (**19**). From compounds (**6**) and (**2**) (57%), m.p. 203—205 °C (decomp.) (from ethanol); $[\alpha]_D^{28}$ −3.5°, $[\alpha]_{578}^{28}$ −3°, $[\alpha]_{546}^{28}$ −3.5°, $[\alpha]_{436}^{28}$ ~0°, and $[\alpha]_{365}^{28}$ +29° (*c* 1.0, chloroform); $\lambda_{max.}$ 249 nm (12 000); $\nu_{max.}$ 3 390 (NH), 1 765 (C=O), and 1 540 cm^{-1} (NH) (Found: C, 57.75; H, 5.0; N, 3.2. $C_{41}H_{42}N_2O_{16}S$ requires C, 57.88; H, 4.98; N, 3.29%).

N-(1,3,4,6,7-*Penta*-O-*acetyl*-2-*deoxy*-α-D-glycero-L-gluco-*heptopyranosan*-2-*yl*)-N′-(2,3,4-*tri*-O-*benzoyl*-β-D-*ribopyranosyl*)*thiourea* (**20**). From compounds (**6**) and (**13**) (99%), m.p. 177—179 °C (decomp.) (from aqueous methanol); $[\alpha]_D^{28}$ +17°, $[\alpha]_{578}^{28}$ +19°, $[\alpha]_{546}^{28}$ +22.5°, $[\alpha]_{436}^{28}$ +56°, and $[\alpha]_{365}^{28}$ +158° (*c* 0.5, chloroform); $\lambda_{max.}$ 247 nm (19 600); $\nu_{max.}$ 3 370 (NH), 1 765, 1 740 (C=O), and 1 550 cm^{-1} (NH) (Found: C, 57.35; H, 5.0; N, 2.9. $C_{44}H_{46}N_2O_{18}S$ requires C, 57.26; H, 5.02; N, 3.03%).

N,N′-*Bis*-(1,3,4,6-*tetra*-O-*acetyl*-2-*deoxy*-α-D-*glucopyranosan*-2-*yl*)*thiourea* (**21**). From compounds (**3**) and (**1**) (51%), m.p. 219—220 °C (decomp.) (from ethanol); $[\alpha]_D^{23}$ +82°, $[\alpha]_{578}^{23}$ +86°, $[\alpha]_{546}^{23}$ +97°, $[\alpha]_{436}^{23}$ +147.5°, and $[\alpha]_{365}^{23}$ +179° (*c* 1.0, chloroform); $\lambda_{max.}$ 248 nm (8 000); $\nu_{max.}$ 3 320 (NH), 1 760, 1 740 (C=O), and 1 545 cm^{-1} (NH) (Found: C, 47.7; H, 6.0; N, 3.5. $C_{29}H_{40}N_2O_{18}S \cdot \frac{1}{2}C_2H_5OH$ requires C, 47.43; H, 5.70; N, 3.69%).

N,N′-*Bis*-(1,3,4,6-*tetra*-O-*acetyl*-2-*deoxy*-β-D-*glucopyranosan*-2-*yl*)*thiourea* (**22**). From compounds (**4**) and (**2**) (82%), m.p. 175—177 °C (lit.,[23] 172—173 °C).

N-(1,3,4,6-*Tetra*-O-*acetyl*-2-*deoxy*-α-D-*glucopyranosan*-2-*yl*)-N′-(1,3,4,6-*tetra*-O-*acetyl*-2-*deoxy*-β-D-*glucopyranosan*-2-*yl*)*thiourea* (**23**). From compounds (**4**) and (**1**) (65%), m.p. 173—174 °C (from ethanol), $[\alpha]_D^{23}$ +43.5°, $[\alpha]_{578}^{23}$ +44°, $[\alpha]_{546}^{23}$ +49°, $[\alpha]_{436}^{23}$ +66°, and $[\alpha]_{365}^{23}$ +48° (*c* 1.0, chloroform); $\lambda_{max.}$ 248 nm (11 200); $\nu_{max.}$ 3 350 (NH), 1 755 (C=O), 1 550 and 1 540 cm^{-1} (NH) (Found: C, 47.0; H, 5.45; N, 3.5. $C_{29}H_{40}N_2O_{18}S$ requires C, 47.28; H, 5.47; N, 3.80%).

N,N′-*Bis*-(1,3,4,6,7-*penta*-O-*acetyl*-2-*deoxy*-β-D-glycero-L-gluco-*heptopyranosan*-2-*yl*)*thiourea* (**24**). From compounds (**14**) and (**10**) (51%), m.p. 179—181 °C (decomp.) (from aqueous methanol); $[\alpha]_D^{27}$ −46°, $[\alpha]_{578}^{27}$ −48°, $[\alpha]_{546}^{27}$ −53°, $[\alpha]_{436}^{27}$ −72.5°, and $[\alpha]_{365}^{27}$ −64.5° (*c* 1.0, chloroform); $\lambda_{max.}$ 243 nm (11 800); $\nu_{max.}$ 3 380 (NH), 1 765 (C=O), and 1 550 cm^{-1} (NH) (Found: C, 47.9; H, 5.6; N, 3.0. $C_{35}H_{48}N_2O_{22}S$ requires C, 47.73; H, 5.49; N, 3.18%).

N,N′-*Bis*-(1,3,4,6,7-*penta*-O-*acetyl*-2-*deoxy*-α-D-glycero-L-gluco-*heptopyranosan*-2-*yl*)*thiourea* (**25**). From compounds (**15**) and (**13**) (51%), m.p. 140—142 °C (from aqueous methanol); $[\alpha]_D^{26}$ +39°, $[\alpha]_{578}^{26}$ +40.5°, $[\alpha]_{546}^{26}$ +47°, $[\alpha]_{436}^{26}$ +94.5°, and $[\alpha]_{365}^{26}$ +195° (*c* 1.0, chloroform); $\lambda_{max.}$ 246 nm (11 200); $\nu_{max.}$ 3 340 (NH), 1 760 (C=O), and 1 550 cm^{-1} (NH) (Found: C, 47.4; H, 5.8; N, 3.1%).

N-(1,3,4,6,7-*Penta*-O-*acetyl*-2-*deoxy*-α-D-glycero-L-gluco-*heptopyranosan*-2-*yl*)-N′-(1,3,4,6,7-*penta*-O-*acetyl*-2-*deoxy*-β-D-glycero-L-gluco-*heptopyranosan*-2-*yl*)*thiourea* (**26**). From compounds (**15**) and (**10**) (51%), m.p. 176—178 °C (decomp.) (from aqueous methanol); $[\alpha]_D^{26}$ −5°, $[\alpha]_{578}^{26}$ −5.5°, $[\alpha]_{546}^{26}$ −5°, $[\alpha]_{436}^{26}$ +8.5°, and $[\alpha]_{365}^{26}$ +63.5° (*c* 1.0, chloroform); $\lambda_{max.}$ 245 nm (11 500); $\nu_{max.}$ 3 370 (NH), 1 755 (C=O), and 1 540 cm^{-1} (NH) (Found: C, 47.4; H, 5.6; N, 3.1%).

N-(1,3,4,6,7-*Penta*-O-*acetyl*-2-*deoxy*-β-D-glycero-L-gluco-*heptopyranosan*-2-*yl*)-N′-(1,3,4,6-*tetra*-O-*acetyl*-2-*deoxy*-α-D-*glucopyranosan*-2-*yl*)*thiourea* (**27**). From compounds (**3**) and (**10**) (48%), m.p. 212—213 °C (decomp.) (from ethanol); $[\alpha]_D^{26}$ +12.5°, $[\alpha]_{578}^{26}$ +12.5°, $[\alpha]_{546}^{26}$ +14.5°, $[\alpha]_{436}^{26}$ +26°, and $[\alpha]_{365}^{26}$ +45° (*c* 1.2, chloroform); $\lambda_{max.}$ 244 nm (11 000); $\nu_{max.}$ 3 380, 3 320 (NH), 1 760 (C=O), and 1 560 cm^{-1} (NH) (Found: C, 47.5; H, 5.5; N, 3.2. $C_{32}H_{44}N_2O_{20}S$ requires C, 47.52; H, 5.48; N, 3.46%).

N-(1,3,4,6,7-*Penta*-O-*acetyl*-2-*deoxy*-α-D-glycero-L-gluco-*heptopyranosan*-2-*yl*)-N′-(1,3,4,6-*tetra*-O-*acetyl*-2-*deoxy*-β-D-*glucopyranosan*-2-*yl*)*thiourea* (**28**). From compounds (**4**) and (**13**) (53%), m.p. 176—178 °C (decomp.) (from methanol); $[\alpha]_D^{26}$ +19.5°, $[\alpha]_{578}^{26}$ +20.5°, $[\alpha]_{546}^{26}$ +23.5°, $[\alpha]_{436}^{26}$ +42°, and $[\alpha]_{365}^{26}$ +69° (*c* 1.0, chloroform); $\lambda_{max.}$ 246 nm (10 600); $\nu_{max.}$ 3 360 (NH), 1 760 (C=O), and 1 555 cm^{-1} (NH) (Found: C, 47.7; H, 5.6; N, 3.4%).

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