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SYNTHESIS OF 1,3,4,6-TETRA-*O*-ACETYL-2-[3-ALKYL(ARYL)-THIOUREIDO]-2-DEOXY-α-D-GLUCOPYRANOSES AND THEIR TRANSFORMATION INTO 2-ALKYL(ARYL)AMINO-(1,2-DIDEOXY-α-D-GLUCOPYRANO)[2,1-*d*]-2-THIAZOLINES*

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ABSTRACT

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-isothiocyanato-α-D-glucopyranose, produced from 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranose hydrochloride, thiophosgene, and calcium carbonate, was condensed with alkyl- and arylamines in ether to afford the crystalline 1,3,4,6-tetra-*O*-acetyl-2-[3-alkyl(aryl)-thioureido]-2-deoxy-α-D-glucopyranoses (**2**). Compounds **2** and the β anomers **3** were converted in high yield into 2-alkyl(aryl)amino-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano)[2,1-*d*]-2-thiazoline hydrobromides (**4**) by hydrogen bromide-promoted cyclisation. The *O*-deacetylated thiazoline hydrobromide **5** was also isolated and converted into 2-[*N*-(4-methoxyphenyl)acetamido]-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano)[2,1-*d*]-2-thiazoline (**8**). Conformational studies of **4** and **8** were made by ^{1}H-n.m.r. spectroscopy.

INTRODUCTION

Isothiocyanates and thioureas are valuable intermediates in the construction of heterocyclic compounds[1], and the glycosyl derivatives have been widely used in the synthesis of *N*-nucleosides and glycosylaminoheterocycles[2–12]. However, very little attention has been directed to the transformation of isothiocyanates and thioureas of 2-amino-2-deoxyaldoses into heterocyclic derivatives[13,14] and *C*-nucleosides[15–17]. The preparation of several thioureas by the reaction of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose with aryl isothiocyanates has been described[18] and treatment of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-isothiocyanato-β-D-glucopyranose (**1b**) with alkyl(aryl)amines afforded new thioureas[19–21]. We have

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described[22] the synthesis of thioureas from 2-amino-2-deoxy-D-*glycero*-α-L-*gluco*-heptopyranose.

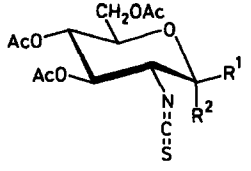
We now report the preparation of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-isothiocyanato-α-D-glucopyranose (**1a**) and the synthesis of several 1,3,4,6-tetra-*O*-acetyl-2-[3-alkyl(aryl)thioureido]-2-deoxy-α-D-glucopyranoses (**2**), followed by a cyclisation reaction to afford 2-alkyl(aryl)amino-α-D-glucopyrano[2,1-*d*]-2-thiazolines **4** and **5**.

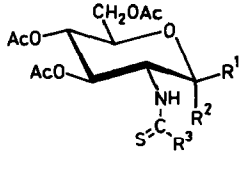
There have been few publications on glycopyrano[2,1-*d*]-2-thiazolines. Ito[23] described the preparation of 2-methylthio-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano)[2,1-*d*]-2-thiazoline by cyclisation of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-[(methylthio)thiocarbonylamino]-β-D-glucopyranose. The synthesis of 2-methyl-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano)[2,1-*d*]-2-thiazoline by intramolecular nucleophilic substitution of chloride by sulfur in 3,4,6-tri-*O*-acetyl-2-deoxy-2-thioacetamido-α-D-glucopyranosyl chloride has been reported[24].

RESULTS AND DISCUSSION

Following a procedure similar to that described[19,22], 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-isothiocyanato-α-D-glucopyranose (**1a**) was prepared by reaction of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranose hydrochloride[25] with thiophosgene in chloroform–water in the presence of calcium carbonate.

The reaction of **1a** variously with benzylamine, cyclohexylamine, diethylamine, 4-methoxyaniline, 4-bromoaniline, and 1-naphthylamine gave the corresponding 1,3,4,6-tetra-*O*-acetyl-2-[3-alkyl(aryl)thioureido]-2-deoxy-α-D-glucopyranoses (**2**). The structures of **1** and **2** were demonstrated by elemental analyses and spectral data. The ^{1}H-n.m.r. assignments (Table I) are based on the results of D_2O-interchange, double resonance, and Eu(fod)$_3$-shift experiments. The *J* values were not affected by the addition of the shift reagent, and are indicative of the





1a R^1 = H, R^2 = OAc
1b R^1 = OAc, R^2 = H

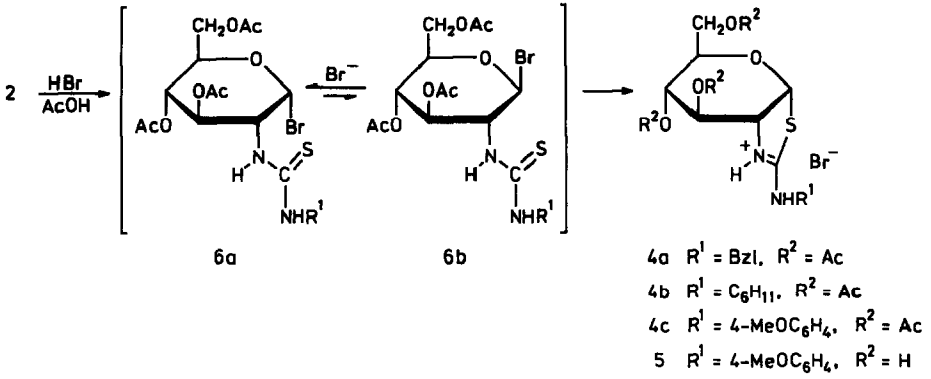
2a R^1 = H, R^2 = OAc, R^3 = BzlNH
2b R^1 = H, R^2 = OAc, R^3 = $C_6H_{11}NH$
2c R^1 = H, R^2 = OAc, R^3 = Et_2N
2d R^1 = H, R^2 = OAc, R^3 = 4-$MeOC_6H_4NH$
2e R^1 = H, R^2 = OAc, R^3 = 4-BrC_6H_4NH
2f R^1 = H, R^2 = OAc, R^3 = 1-$C_{10}H_7NH$
3a R^1 = OAc, R^2 = H, R^3 = BzlNH
3b R^1 = OAc, R^2 = H, R^3 = $C_6H_{11}NH$

TABLE I

^{1}H-N.M.R. DATA[a] FOR COMPOUNDS **1** AND **2**

Compound	*Chemical shifts (δ)*									*First-order coupling constants (Hz)*							
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*	*GNHCSNHR*[g]	*GNHCSNHR*[g]	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	$J_{2,NH}$
1a[b]	6.28d	3.98dd	5.49t	5.06t		4.42–4.05m				3.7	10.0	10.0	10.0	3.9[e]	2.0[e]	−12.0[e]	
1b[b,d]	5.68d	3.83[e]	5.28t	4.98t	4.00–3.75m	4.30dd	3.98dd[e]			10.0	10.0[e]	10.0	10.0	5.0	3.0	−12.0	
2a[b]	6.29d		5.35–4.95m			4.35–3.80m		7.27	5.97d	3.3	9.0[e]	10.0[e]	9.0[e]	4.0[e]	2.3[e]	−12.0[e]	7.3
2b[b]	6.43d		5.50–4.95m		3.74m	4.35dd	4.09dd	6.50d	6.00d	3.3[e]				4.3[e]	2.3[e]	−12.7[e]	8.0[e]
2c[b]	6.54d		5.45–5.10m		4.00m	4.30dd	4.05dd		5.57d	2.7[f]				4.6[f]	2.7[f]	−12.7[f]	8.0
2d[c]	6.31d		5.30–5.10m		3.93m	4.25dd	4.03dd	7.97s	5.73d	2.8			8.9	3.7	2.1	−11.1	8.0
2e[b]	6.34d		5.40–4.95m		3.96m	4.28dd	4.03dd	8.47s	6.00d	2.7[e]				4.3[e]	2.3[e]	−12.7[e]	8.0[e]
2f[b]	6.27d		5.30–4.85m		3.75m	4.17dd	3.93dd	8.69s	5.58d	3.3[e]		9.7[e]	9.7[e]	4.0[e]	2.7[e]	−12.7[e]	8.0[e]

[a]Recorded for solutions in $CDCl_3$. [b]At 90 MHz. [c]At 200 MHz. [d]The data for **1b** are taken from ref. 22. [e]Values obtained after addition of Eu(fod)$_3$. [f]Measured on D_2O-interchanged spectrum. [g]G = Sugar moiety.



preponderance of the $^4C_1$(D) conformations in solution. The small values (2.7–3.7 Hz) of $J_{1,2}$ for **1a** and **2** accord with the α configuration. However, the large value (10 Hz) for **1b** is indicative of the β configuration. Table III gives the ^{13}C chemical shifts of the thioureas **2a, 2b**, and **2d**; C-1 was more deshielded than the other ring carbons. The C-6 signals were assigned on the basis of APT spectra, and C-2 was assigned to the peak that appeared at ~56 p.p.m. The thiocarbonyl carbons resonated at ~181 p.p.m. and the signals for C-3,4,5 were assigned by comparison with those for C-3,4,5 in 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranose[26] (**11**).

When **2a** and **2b** were treated with hydrogen bromide–acetic acid, crystalline 2-benzylamino- and 2-cyclohexylamino-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano)[2,1-*d*]-2-thiazoline hydrobromides **4a** and **4b**, respectively, were obtained in high yields (~90%); AcO-1 is replaced by Br since the glycosyl bromide **6** is required for the formation of the thiazolines. Under the reaction conditions, the more stable α-anomer **6a** should rapidly equilibrate with **6b** in the presence of bromide ion[27,28]. The S_Ni displacement of bromine by sulfur of the thiourea moiety gave **4a** and **4b** through the β-anomer **6b**, since the S_N2 mechanism for the reaction of glycosyl bromides with thioureas is well established[29]. However, an S_N1 mechanism through an oxocarbonium ion is also possible[26,27].

The structures of **4** were indicated by the following data. The i.r. absorption between 3200 and 2700 cm^{-1} was typical of the NH stretching of an ammonium salt, and that at ~1630 cm^{-1} was assignable to the C=N$^+$ stretching vibration of a protonated thiazoline[30,31] and was coincident with that described for glucopyrano[2,1-*d*]-2-oxazoline hydrochlorides[32]. The u.v. spectra had no λ_{max} above 200 nm, as would be expected[33–35] (~245 nm) for the thiourea moiety of **6** and for the imidazolidine-2-thione moiety of **7**. Only bromine-containing fragments were recognisable in the lower *m/z* range of the mass spectra, due to HBr^+, Br^+, and Br^{2+} in accord with a hydrobromide structure. The *J* values in the ^1H-n.m.r. spectra of **4a** and **4b** (see Table II) are different from those for **2** and **3**, indicative of a large conformational change consequent on the formation of the thiazoline ring. The ^{13}C-n.m.r. data for **4a** and **4b** (Table III) supported the formation of a thiazoline

TABLE II

^{1}H-N.M.R. DATA[a] FOR COMPOUNDS **4** AND **8**

Compound	*Chemical shifts (δ)*							*First-order coupling constants (Hz)*						
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*	$J_{1,2}$	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$
4a[b]	6.63d	4.66m	5.37dd	4.88dd	3.96m	4.21m		6.7	3.5	<0.3	3.2	9.2	5.0	4.2
4b[b]	6.59d	4.63dd	5.43dd	4.85dd	3.86m	4.19m		6.9	4.4	<0.3	3.2	8.7	4.6	4.1
4c[b]	6.63d	4.61dd	5.42dd	4.88dd	4.06m	4.22m		6.7	4.3	<0.3	2.8	9.0	4.3	4.3
8[c]	6.08d	4.23ddd	5.34dd	4.88m	3.74m	4.17m		7.4	4.2	1.3	2.3	9.5	4.7	4.0

[a]Recorded at 200 MHz. [b]In $(CD_3)_2SO$. [c]In $CDCl_3$.

TABLE III

^{13}C-N.M.R. CHEMICAL SHIFTS[a]

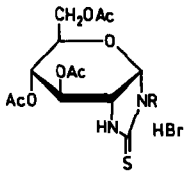
Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C=S*	*N=C$^{S}_{N}$*	*C=O*	*CH_3*		*Ar*	*Alkyl*		*OCH_3^-*
										OAc	*NAc*		*CH_2*	*CH*	
2a[b]	90.1	56.0	70.8[d]	69.3[d]	67.1	61.4	182.4		171.8	20.6		136.3 (1c)	48.0	51.6	
									170.6	20.5		128.7 (2c)			
									168.8	20.5		127.7 (1c)			
									168.3	20.3		127.0 (2c)			
2b[b]	90.4	55.8	71.0[d]	69.4[d]	67.1	61.4	180.6		171.8	20.7			32.3 (2c)	51.6	
									170.6	20.6			25.0		
									168.8	20.5			24.4 (2c)		
									168.3	20.3					
2d[b]	90.0	55.7	70.4[d]	69.4[d]	67.0	61.2	181.2		171.0	20.5		159.0 (1c)			55.7
									170.4	20.4		127.6 (3c)			
									168.7	20.3		114.7 (2c)			
									168.4	20.2					
4a[c]	84.2	59.8	67.5	67.7	69.1	62.6		168.1	170.1	20.8		135.3 (1c)	48.1		
									169.4	20.7		128.8 (2c)			
									169.2	20.6		128.1 (1c)			
												127.7 (2c)			
4b[c]	83.8	59.3	67.5	68.9	69.1	62.7		166.1	170.0	20.8			31.2	54.4	
									169.3	20.7			31.1		
									169.1	20.6			24.6		
													24.2		
													24.1		
5[c]	86.7	72.0	68.2	63.8	76.8	61.1		158.4				158.4 (1c)			55.6
												129.0 (1c)			
												126.4 (2c)			
												115.0 (2c)			
8[b]	87.1	68.8[d]	68.3[d]	70.7[d]	68.9[d]	63.4		159.7	171.7	20.9	24.6	159.5 (1c)			55.5
									170.7	20.8 (2c)		132.9 (1c)			
									169.3 (2c)			129.6 (2c)			
												114.8 (2c)			

[a]For clarity, numbering is based on thioureas. [b]In $CDCl_3$. [c]In $(CD_3)_2SO$. [d]Assignments may be interchanged.

ring when they were compared with data for **2a** and **2b**. The spectra of **4a** and **4b** showed a characteristic downfield shift for the C-2 signal, and the C=S resonance was replaced by a signal at ~167 p.p.m. which was assigned to -N=C(S-)N- of the 2-aminothiazoline ring. These shifts are similar to those described for 2-oxazolines[26,36]. However, the signals for C-1 were shifted upfield (~ +6 p.p.m.), compared to the corresponding signals in **2a** and **2b**, whereas the signals for C-1 in 2-oxazolines[26] are shifted downfield (~ −8.5 p.p.m.) compared to that for C-1 in **11**. This difference (~14.5 p.p.m.) accords with the replacement of the oxygen of **11** by the sulfur in **4a** and **4b**. The signals for C-3,4,5 showed only slight variations.

Treatment of **2d** with HBr/AcOH yielded **4c** which could not be purified; when **4c** was treated with ethanol, the deacetylated product **5** was obtained in near quantitative yield and had i.r. absorptions for OH and ammonium salt (between 3500 and 2500 cm^{-1}) and for $C=N^+$ (1630 cm^{-1}). The ^{13}C-n.m.r. spectrum of **5** showed characteristics similar to those for **4a** and **4b**. The downfield shift (7.70 p.p.m.) of the signal for C-5 reflects the lack of a β-effect of the acetyl groups, present in **4a** and **4b**. The pyranoid structure of **5** was established by the preparation of **8** (also obtained from **4c**), which showed i.r. absorption at 1690 cm^{-1} (acetamide C=O and thiazoline C=N). The isomeric structure **9** was ruled out because the chemical shift of the signal of H-2 (4.23 p.p.m.) accords with those observed[26,37] for analogous bicyclic systems with an endocyclic double-bond. An acetylated heterocyclic nitrogen linked to C-2, as in **9**, would cause a large deshielding (~0.7 p.p.m.)[38]. The same effect (~0.55 p.p.m.) has been observed in glycofurano[2,1-*d*]imidazolidine-2-thiones[39]. The mass spectrum of **8** showed a peak at *m/z* 452 arising by cleavage of the N-Ac bond with loss of ketene. This ion is not indicative of the position of the N-Ac group, because a McLafferty rearrangement is possible in both structures (**8** and **9**) with formation of the same ion.

Although the literature[1] indicates that 2-amino-2-thiazolines are protonated at the exocyclic nitrogen, the structures **4** and **5** are preferred to **10**, on the basis of i.r. and ^{13}C-n.m.r. data. The $\nu_{C=N}$ for **4** and **5** showed a large shift toward lower wave numbers compared to that for **8**, which is indicative of diminution in double-bond character. This feature accords with protonation at the heterocyclic nitrogen that is the origin of the resonance structures of Scheme 1. The protonation of the exocyclic nitrogen should increase $\nu_{C=N}$ since the charge cannot be delocalised. An



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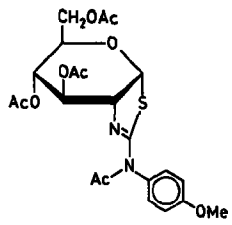

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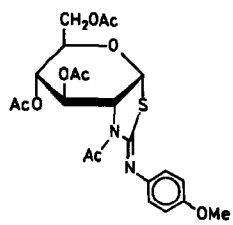

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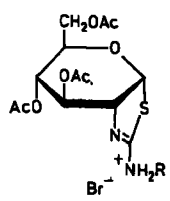

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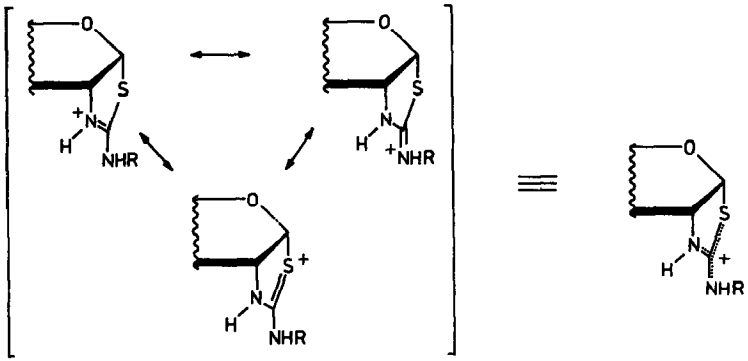

Scheme 1.

TABLE IV

VICINAL-PROTON TORSION ANGLES (°) FOR **4** AND **8** DEDUCED FROM ^{1}H-N.M.R. DATA[a]

Torsion angle	*Equation (ref.)*	*Compound*			
		4a[d]	**4b**[d]	**4c**[d]	**8**[e]
$\Phi_{1,2}$ (H1–C1–C2–H2)	*b*	25 (148)	23 (150)	25 (148)	18 (154)
	c	30	27	30	18
$\Phi_{2,3}$ (H2–C2–C3–H3)	*b*	47 or 128	42 or 134	42 or 133	43 or 133
	c	38 or 114	31 or 120	32 or 119	33 or 119
$\Phi_{3,4}$ (H3–C3–C4–H4)	*b*	120 (55)	126 (49)	124 (52)	120 (55)
	c	128	135	132	128
$\Phi_{4,5}$ (H4–C4–C5–H5)	*b*	177	166	171	*f*

[a]As derived from the observed spacings. [b]Calculated by using the expression proposed by Coxon[46]. [c]Calculated by using the expression proposed by Altona *et al.*[47]. [d]$(CD_3)_2SO$. [e]$CDCl_3$. [f]No solution is given by equation *b* for $J_{4,5}$ 9.5 Hz; ~180° estimated for $\Phi_{4,5}$.

TABLE V

VICINAL-PROTON TORSION ANGLES (°) FOR SEVERAL POSSIBLE CONFORMATIONS OF **4** AND **8**[a]

Torsion angle	*Conformations*					
	$^4H_5$	$^{0,3}B$	$B_{2,5}$[b]	$^oS_2$	$^oH_5$	$^4C_1$[c]
$\Phi_{1,2}$	5	0	25	30	15	30
$\Phi_{2,3}$	135	70	85	50	120	142
$\Phi_{3,4}$	170	65	120	85	140	160
$\Phi_{4,5}$	165	130	180	150	180	180

[a]Obtained from Dreiding models. [b]Distorted $B_{2,5}$, ring flattened at C-1. [c]Distorted $^4C_1$, ring flattened at C-2.

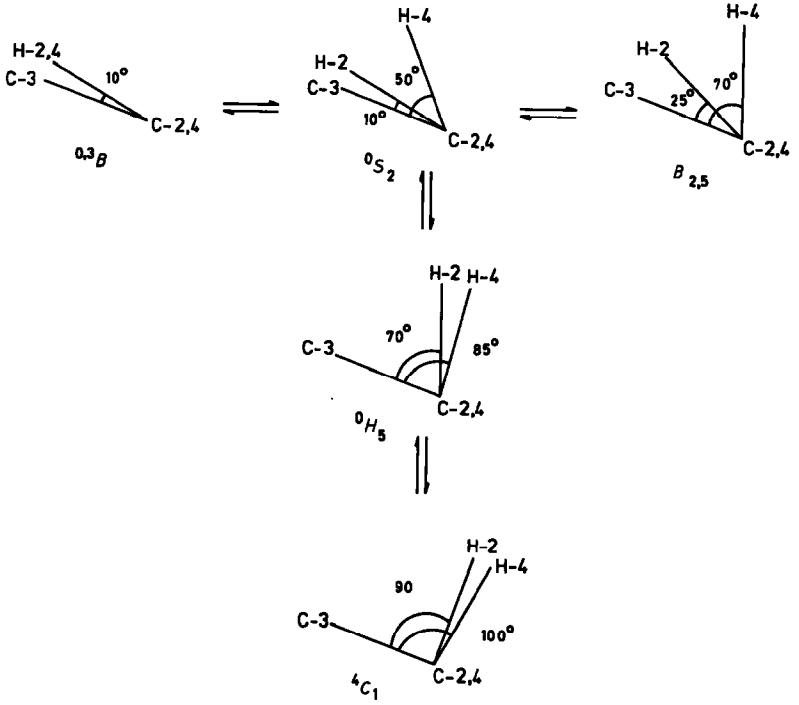

Fig. 1. Approximate variations of dihedral angles made by the H-2/C-2 and H-4/C-4 bonds with the plane determined by C-2,3,4 (from Dreiding models).

analogous effect is evident in glycopyrano[2,1-*d*]-2-oxazolines and their hydrochlorides[32]. The downfield shift of the signal for C-2 caused by *N*-protonation of the thiazoline ring is similar to that encountered for other heterocycles[40].

Numerous communications[26,37,41–45] have dealt with the conformation of six-membered rings 1,2-*cis*-fused to a five-membered ring. The torsion angles between the vicinal ring protons of compounds **4** and **8** (Table IV) were calculated from the observed ^3J values using the equation proposed by Coxon[46] and that parametrised with the electronegativity corrections of Altona *et al.*[47]. The large values for $J_{4,5}$ are indicative of a near antiperiplanar orientation for H-4,5 ($\Phi_{4,5}$ 170–180°). If the thiazoline rings were planar, the available conformations would be the half-chair $^4H_5$ and the boat form $^{0,3}B$. However, the $\Phi_{1,2} \neq 0$ value suggested slightly puckered thiazoline rings, and the available conformations for **4** and **8** would be limited to the following fragment of the pseudorotational sphere: $B_{2,5} \rightleftarrows {}^0S_2 \rightleftarrows {}^0H_5 \rightleftarrows {}^4C_1$. The dihedral angles, estimated for each conformation from Dreiding molecular models, are given in Table V.

The values for $\Phi_{2,3}$ and $\Phi_{3,4}$ (~120°) suggest that C-3 is nearly eclipsed with C-2 and C-4, and are consistent with $^0H_5$ conformations. However, the $J_{2,4}$ value 1.3 Hz indicates a planar W arrangement for **8**, consistent with an $^0S_2$ conformation ($\Phi_{2,3}$ ~45°) and not with a $^4C_1$ chair conformation flattened around the thiazoline ring fusion (Fig. 1). Also, the $B_{2,5}$ conformation is not consistent with the data in Table IV.

It is proposed that several conformations of the pyranose ring in **4** and **8** are present in a dynamic equilibrium in which the coupling constants are time-averages and the contributions of the $^{o}S_2$ forms give rise to long-range $J_{2,4}$ couplings.

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 (10 cm, 5-mL cell). I.r. spectra (KBr discs) were recorded 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 ethyl acetate–ethanol (3:1) or benzene–ether (3:2), using detection with u.v. light or iodine vapor.

^{1}H-N.m.r. spectra were recorded with a Perkin–Elmer R-32 (90 MHz, c.w.) and a Varian XL-200 spectrometer (200 MHz, F.t.). Assignments were confirmed by double-resonance experiments and overlapping signals were resolved by incremental additions of $Eu(fod)_3$. ^{13}C-N.m.r. spectra (50 MHz) were recorded with a Varian XL-200 spectrometer. Assignments were confirmed by APT and off-resonance experiments. E.i.-mass spectra (70 eV) were obtained with an AEI MS-30 mass spectrometer, using a direct-insertion probe heated at 30° below the m.p. for solids.

*1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-isothiocyanato-α-*D*-glucopyranose* (**1a**). — To a mixture of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranose hydrochloride[25] (6.0 g, 15.0 mmol), chloroform (60 mL), calcium carbonate (15.0 g, 50.0 mmol), and water (30 mL) was added thiophosgene (5 mL). The mixture was stirred vigorously for 48 h and then filtered, and the organic layer was washed with water, dried ($CaCl_2$), filtered, and concentrated. Treatment of the residue with ether (10 mL) at 0° gave **1a** (3.4 g, 54%). Recrystallisation gave material having m.p. 65–66°, $[\alpha]_D$ +142°, $[\alpha]_{578}$ +148°, $[\alpha]_{546}$ +167°, $[\alpha]_{436}$ +281°, $[\alpha]_{365}$ +433° (*c* 1, chloroform); λ_{max}^{EtOH} 259 nm (ε_{mM} 17.50); ν_{max} 2050 (N=C=S) and 1740 cm^{-1} (C=O ester). The most significant ^{1}H-n.m.r. data are given in Table I.

Anal. Calc. for $C_{15}H_{19}NO_9S$: C, 46.27; H, 4.91; N, 3.59. Found: C, 46.40; H, 5.08; N, 3.65.

*1,3,4,6-Tetra-*O*-acetyl-2-[3-alkyl(aryl)thioureido]-2-deoxy-α-*D*-glucopyranose.* — To a solution of **1a** (1.0 g, 26.0 mmol) in ether (15 mL) was added alkyl(aryl)amine (26.0 mmol). The mixture was kept at room temperature for 24 h when the 2-alkyl(aryl)thioureido derivative crystallised. The following compounds were prepared in this way.

1,3,4,6-Tetra-*O*-acetyl-2-(3-benzylthioureido)-2-deoxy-α-D-glucopyranose (**2a**, 70%), m.p. 135–136° (from ethanol–light petroleum), $[\alpha]_D$ +96°, $[\alpha]_{578}$ +100°, $[\alpha]_{546}$ +113°, $[\alpha]_{436}$ +176°, $[\alpha]_{365}$ +222° (*c* 1, chloroform); λ_{max}^{EtOH} 245 nm (ε_{mM} 16.40); ν_{max} 3380–3280 (NH), 1750 (C=O ester), 1545 (NH), 740 and 700 cm^{-1} (phenyl). The most significant ^{1}H- and ^{13}C-n.m.r. data are given in Tables I and III.

Anal. Calc. for $C_{22}H_{28}N_2O_9S$: C, 53.22; H, 5.68; N, 5.64. Found: C, 53.49; H, 5.81; N, 5.64.

1,3,4,6-Tetra-*O*-acetyl-2-(3-cyclohexylthioureido)-2-deoxy-α-D-glucopyranose (**2b**, 83%), m.p. 174–175° (from ethanol), $[\alpha]_D$ +85°, $[\alpha]_{578}$ +89°, $[\alpha]_{546}$ +100°, $[\alpha]_{436}$ +159°, $[\alpha]_{365}$ +215° (*c* 1, chloroform); λ_{max}^{EtOH} 244 nm (ε_{mM} 16.3); ν_{max} 3350 and 3320 (NH), 2930 and 2840 (CH_2), 1750 and 1735 (C=O ester), and 1535 cm^{-1} (NH). The most significant ^1H- and ^{13}C-n.m.r. data are given in Tables I and III.

Anal. Calc. for $C_{21}H_{32}N_2O_9S$: C, 51.63; H, 6.60; N, 5.73. Found: C, 51.52; H, 6.72; N, 5.63.

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(3,3-diethylthioureido)-α-D-glucopyranose (**2c**, 84%), m.p. 96–97° (from ethanol), $[\alpha]_D$ +82°, $[\alpha]_{578}$ +85°, $[\alpha]_{546}$ +96°, $[\alpha]_{436}$ +152.5°, $[\alpha]_{365}$ +201° (*c* 1, chloroform); λ_{max}^{EtOH} 239 nm (ε_{mM} 21.50); ν_{max} 3390 and 3350 (NH), 1750 (C=O ester), 1535, 1510, and 1500 cm^{-1} (NH). The most significant ^1H-n.m.r. data are given in Table I.

Anal. Calc. for $C_{19}H_{30}N_2O_9S$: C, 49.34; H, 6.53; N, 6.05. Found: C, 49.43; H, 6.74; N, 6.00.

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-[3-(4-methoxyphenyl)thioureido]-α-D-glucopyranose (**2d**, 68%), m.p. 165–166° (from ethanol), $[\alpha]_D$ +80°, $[\alpha]_{578}$ +83°, $[\alpha]_{546}$ +95°, $[\alpha]_{436}$ +161°, $[\alpha]_{365}$ +267° (*c* 1, chloroform); λ_{max}^{EtOH} 245 nm (ε_{mM} 17.6); ν_{max} 3380, 3360, and 3200 (NH), 2840 (OMe), 1750 (C=O ester), 1610 (aromatic), 1545 and 1515 cm^{-1} (NH). The most significant ^1H- and ^{13}C-n.m.r. data are given in Tables I and III.

Anal. Calc. for $C_{22}H_{28}N_2O_{10}S$: C, 51.55; H, 5.50; N, 5.46. Found: C, 51.61; H, 5.62; N, 5.35.

1,3,4,6-Tetra-*O*-acetyl-2-[3-(4-bromophenyl)thioureido]-2-deoxy-α-D-glucopyranose (**2e**, 80%), m.p. 158–159° (from ethanol), $[\alpha]_D$ +102°, $[\alpha]_{578}$ +108°, $[\alpha]_{546}$ +122°, $[\alpha]_{436}$ +212°, $[\alpha]_{365}$ +367° (*c* 0.8, chloroform); λ_{max}^{EtOH} 292, 281, and 271 nm (ε_{mM} 6.8, 8.8, and 8.1); ν_{max} 3370 and 3300 (NH), 1750 (C=O ester), 1585 (aromatic), 1540 and 1500 cm^{-1} (NH). The most significant ^1H-n.m.r. data are given in Table I.

Anal. Calc. for $C_{21}H_{25}BrN_2O_9S$: C, 44.92; H, 4.49; N, 4.99. Found: C, 44.89; H, 4.59; N, 4.85.

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-[3-(1-naphthyl)thioureido]-α-D-glucopyranose (**2f**, 95%), m.p. 152–153° (from ethanol), $[\alpha]_D$ +113°, $[\alpha]_{578}$ +118°, $[\alpha]_{546}$ +133°, $[\alpha]_{436}$ +222.5°, $[\alpha]_{365}$ +342° (*c* 0.7, chloroform); λ_{max}^{EtOH} 243 nm (ε_{mM} 15.50); ν_{max} 3330 and 3160 (NH), 1750 (C=O ester), 1600 (aromatic), 1540 and 1500 cm^{-1} (NH). The most significant ^1H-n.m.r. data are given in Table I.

Anal. Calc. for $C_{25}H_{28}N_2O_9S$: C, 56.39; H, 5.30; N, 5.26. Found: C, 56.39; H, 5.27; N, 5.16.

*2-Alkyl(aryl)amino-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano)[2,1-d]-2-thiazoline hydrobromide.* — Compound **2** (1 mmol) was added to a saturated solution of hydrogen bromide in glacial acetic acid (12.5 mL) and the mixture was

kept at room temperature for 2 h. The following compounds were prepared in this manner.

2-Benzylamino-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano)[2,1-*d*]-2-thiazoline hydrobromide (**4a**, 98%), m.p. 235–236° (from ethanol), $[\alpha]_D$ +44°, $[\alpha]_{578}$ +67.5°, $[\alpha]_{546}$ +76°, $[\alpha]_{436}$ +136° (*c* 1, pyridine); ν_{max} 3200–2700 (NH^+), 1750 and 1740 (C=O ester), 1635 ($C{=}NH^+$), 1545 (NH), 750 and 700 cm^{-1} (phenyl). The most significant ^1H- and ^{13}C-n.m.r. data are given in Tables II and III. Mass spectrum: *m/z* 437 (1%, M + H^+), 436 (2, M^+), 232 (50), 106 (35), 91 (100, $PhCH_2^+$), 82 (30, $H^{81}Br^+$), 81 (15, $^{81}Br^+$), 80 (30, $H^{79}Br^+$), 79 (15, $^{79}Br^+$), and 43 (95).

Anal. Calc. for $C_{20}H_{25}BrN_2O_7S$: C, 46.43; H, 4.87; N, 5.41. Found: C, 46.72; H, 4.96; N, 5.42.

Compound **4a** (75%) was also prepared from **3a** in a similar way.

2-Cyclohexylamino-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano)[2,1-*d*]-2-thiazoline hydrobromide (**4b**, 87%), m.p. 240–241° (from ethanol), $[\alpha]_D$ −0.5°, $[\alpha]_{578}$ −1°, $[\alpha]_{546}$ −1.5°, $[\alpha]_{436}$ −4°, $[\alpha]_{365}$ −16° (*c* 1, pyridine); ν_{max} 3200–2600 (NH^+), 1750 (C=O ester), 1625 ($C{=}NH^+$), and 1535 cm^{-1} (NH). The most significant ^1H- and ^{13}C-n.m.r. data are given in Tables II and III. Mass spectrum: *m/z* 471 (1%, M + CH_3CO^+), 429 (8, M + H^+), 428 (2, M^+), 224 (100), 82 (85, $H^{81}Br^+$), 81 (35, $^{81}Br^+$), 80 (85, $H^{79}Br^+$), 79 (35, $^{79}Br^+$), 55 (90), and 43 (90).

Anal. Calc. for $C_{19}H_{29}BrN_2O_7S$: C, 44.82; H, 5.73; N, 5.49. Found: C, 44.42; H, 5.86; N, 5.63.

Compound **4b** (55%) was also prepared from **3b** in a similar way.

2-(4-Methoxyphenyl)amino-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano)[2,1-*d*]-2-thiazoline hydrobromide (**4c**, 83%) crystallised on treatment with ether but could not be recrystallised. It was homogeneous (n.m.r. and t.l.c.), and had ν_{max} 3500–2600 (NH^+), 1745 (C=O ester), 1630 ($C{=}NH^+$), and 1510 cm^{-1} (NH). The most significant ^1H-n.m.r. data are given in Table II.

2-(4-Methoxyphenyl)amino-(1,2-dideoxy-α-D-glucopyrano)[2,1-*d*]-2-thiazoline hydrobromide (**5**, 99%), m.p. 180–181° (dec.) (from aqueous ethanol), $[\alpha]_D$ +72.5°, $[\alpha]_{578}$ +76°, $[\alpha]_{546}$ +87°, $[\alpha]_{436}$ +166° (*c* 1, pyridine); λ_{max}^{EtOH} 252 and 226 nm (ε_{mM} 5.4 and 6.9); ν_{max} 3540–2500 (OH, NH^+), 1625 ($C{=}NH^+$), 1585 (aromatic), 1525 and 1505 (NH), 1250 (C–O–C), and 835 cm^{-1} (aromatic). ^1H-N.m.r. data [$(CD_3)_2SO$]: δ 7.20 (dd, 4 H, ArH), and 6.55 p.p.m. (d, 1 H, $J_{1,2}$ 6.6 Hz, H-1). The ^{13}C-n.m.r. data are given in Table III.

Anal. Calc. for $C_{14}H_{19}BrN_2O_5S$: C, 41.28; H, 4.70; N, 6.87. Found: C, 41.41; H, 4.82; N, 6.73.

*2-[N-(4-Methoxyphenyl)acetamido]-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano)[2,1-*d*]-2-thiazoline* (**8**). — (*a*) Conventional treatment of **5** (0.1 g, 0.3 mmol) with pyridine (1 mL) and acetic anhydride (0.5 mL) gave **8** (0.06 g, 40%), m.p. 64–65° (from ethanol), $[\alpha]_D$ −71°, $[\alpha]_{578}$ −75°, $[\alpha]_{546}$ −87°, $[\alpha]_{436}$ −174°, $[\alpha]_{365}$ −334° (*c* 1, chloroform); λ_{max}^{EtOH} 252 and 230 nm (ε_{mM} 14.0 and 15.0); ν_{max} 2830 (OMe), 1735 (C=O ester), 1690 (C=O amide and C=N thiazoline), 1590, 1500,

and 810 cm^{-1} (aromatic). The most significant ^1H- and ^{13}C-n.m.r. data are given in Tables II and III. Mass spectrum: *m/z* 494 (3%, M^+), 452 (13, $M^+ - CH_2CO$), 393 (15), 290 (9), 165 (12), and 43 (100).

Anal. Calc. for $C_{22}H_{27}N_2O_9S$: C, 53.43; H, 5.30; N, 5.66. Found: C, 53.30; H, 5.38; N, 5.51.

(*b*) Compound **8** (0.22 g, 47%) was also prepared from **4c** (0.5 g, 0.9 mmol) with pyridine (3.5 mL) and acetic anhydride (3.5 mL).

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REFERENCES

1 T. S. Griffin, T. S. Woods, and D. L. Klayman, *Adv. Heterocycl. Chem.*, 18 (1975) 99–158.
2 I. Goodman, *Adv. Carbohydr. Chem.*, 13 (1958) 215–236.
3 A. Piskala and F. Sorm, *Collect. Czech. Chem. Commun.*, 29 (1964) 2060–2076.
4 T. Naito and M. Sano, *Chem. Pharm. Bull.*, 9 (1961) 709–714.
5 C. Ukita, A. Hamada, and M. Yoshida, *Chem. Pharm. Bull.*, 12 (1964) 454–459.
6 H. Ogura, H. Takahashi, and O. Sato, *Nucleic Acid Res., Symp. Ser.*, 6 (1979) s13–s16; *Chem. Pharm. Bull.*, 29 (1981) 2188–2192.
7 H. Takahashi, N. Nimura, and H. Ogura, *Chem. Pharm. Bull.*, 27 (1979) 1130–1136, 1143–1146, 1147–1152.
8 R. J. Suhadolnik, *Nucleoside Antibiotics*, Wiley–Interscience, New York, 1970.
9 H. Ogura and H. Takahashi, *Heterocycles*, 6 (1977) 1633–1638.
10 E. Stankevich, A. Dreimane, E. Liepins, A. Kemme, and J. Bleidelis, *Nucleosides Nucleotides*, 2 (1983) 155–173.
11 R. Bognar, L. Somogyi, L. Szilagyi, and Z. Györgydeak, *Carbohydr. Res.*, 5 (1967) 320–328.
12 J. Fuentes, M. C. Ortiz, and M. A. Pradera, *An. Quím., Ser. C*, 80 (1984) 48–53.
13 F. García-González, J. Fernández-Bolaños, and F. J. López Aparicio, in H. S. El Khadem (Ed.), *Synthetic Methods for Carbohydrates*, Am. Chem. Soc., Washington, 1976, pp. 207–226.
14 H. S. El Khadem, *Adv. Carbohydr. Chem. Biochem.*, 25 (1970) 351–405.
15 (*a*) J. Fernández-Bolaños, M. Repetto, J. Fuentes, and M. J. Martín, *An. Real Soc. Esp. Fís. Quím.*, 69 (1973) 771–774; (*b*) M. Repetto, J. Fernández-Bolaños, and M. J. Martín, *ibid.*, 64 (1968) 1013–1014.
16 J. Fuentes and J. M. Pareja, *An. Quím.*, 74 (1978) 975–978.
17 F. Rebolledo, Ph.D. Thesis, University of Extremadura, Badajoz, 1985.
18 C. J. Morel, *Helv. Chim. Acta*, 44 (1961) 403–412.
19 J. C. Jochims and A. Seeliger, *Tetrahedron*, 21 (1965) 2611–2616.
20 J. Fuentes and M. González, *An. Real Soc. Esp. Fís. Quím.*, 72 (1976) 996–997.
21 J. Fuentes, M. C. Ortiz, F. Segura, M. A. Pradera, and A. Cert, *An. Quím., Ser. C*, 79 (1983) 221–224.
22 J. Fuentes, M. Avalos, J. L. Jiménez, J. C. Palacios, and I. M. Gómez, *An. Quím., Ser. C*, 81 (1985) 239–243.
23 T. Ito, *Can. J. Chem.*, 44 (1966) 94–97.
24 N. V. Bovin, S. E. Zurabyan, and A. Ya, Khorlin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, (1981) 441–443; *Chem. Abstr.*, 95 (1981) 43486s.
25 A. Gómez, M. Gómez, and U. Scheidegger, *Carbohydr. Res.*, 3 (1967) 486–501.
26 V. K. Srivastava, *Carbohydr. Res.*, 103 (1982) 286–292.
27 R. U. Lemieux, K. B. Hendriks, R. V. Stick, and K. James, *J. Am. Chem. Soc.*, 97 (1975) 4056–4062.
28 R. U. Lemieux and H. Driguez, *J. Am. Chem. Soc.*, 97 (1975) 4063–4069.
29 K. L. Matta, R. N. Girotra, and J. J. Barlow, *Carbohydr. Res.*, 43 (1975) 101–109.

30 A. R. KATRITZKY AND A. P. AMBLER, *Phys. Methods Heterocycl. Chem.*, 2 (1965) 161–360.
31 A. S. DEUTSCH AND P. E. FANTA, *J. Org. Chem.*, 21 (1956) 892–895.
32 H. WEIDMANN, D. TARTLER, P. STÖCKL, L. BINDER, AND H. HÖMG, *Carbohydr. Res.*, 29 (1973) 135–140.
33 J. A. GALBIS PÉREZ, J. C. PALACIOS ALBARRÁN, J. L. JIMÉNEZ REQUEJO, M. AVALOS GONZÁLEZ, AND J. M. FERNÁNDEZ-BOLAÑOS, *Carbohydr. Res.*, 129 (1984) 131–142, 131 (1984) 71–82.
34 J. A. GALBIS PÉREZ, J. L. JIMÉNEZ REQUEJO, J. C. PALACIOS ALBARRÁN, M. AVALOS GONZÁLEZ, AND J. M. FERNÁNDEZ-BOLAÑOS, *An. Quím.*, 82 (1986) in press.
35 H. BEHRINGER AND H. MEIER, *Justus Liebigs Ann. Chem.*, 607 (1957) 67–73.
36 R. M. DAVIDSON, E. WHITE, S. A. GARGOLIS, AND B. COXON, *Carbohydr. Res.*, 116 (1984) 239–254.
37 M. A. NASHED, C. W. SLIFE, M. KISO, AND L. ANDERSON, *Carbohydr. Res.*, 82 (1980) 237–252.
38 C. F. HAMMER, R. A. LORANGER, AND P. S. SCHEIN, *J. Org. Chem.*, 46 (1981) 1521–1531.
39 M. AVALOS GONZÁLEZ, J. A. GALBIS PÉREZ, J. L. JIMÉNEZ REQUEJO, AND J. C. PALACIOS ALBARRÁN, *Carbohydr. Res.*, in press.
40 E. BREITMAIER AND W. VOELTER, *^{13}C-N.M.R. Spectrometry*, Verlag Chemie, Weinheim, 1974, pp. 182–185.
41 W. E. DICK, JR., D. WEISLEDER, AND J. E. HODGE, *Carbohydr. Res.*, 42 (1975) 65–72.
42 C. FOCES-FOCES, A. ALEMANY, M. BERNABÉ, AND M. MARTÍN LOMAS, *J. Org. Chem.*, 45 (1980) 3502–3506.
43 R. U. LEMIEUX AND O. HINDSGAUL, *Carbohydr. Res.*, 82 (1980) 195–206.
44 C. FOCES-FOCES, F. H. CANO, M. BERNABÉ, S. PENADES, AND M. MARTÍN LOMAS, *Carbohydr. Res.*, 135 (1984) 1–11.
45 F. H. CANO, C. FOCES-FOCES, A. ALEMANY, M. BERNABÉ, M. L. JIMENO, AND M. MARTÍN LOMAS, *Carbohydr. Res.*, 139 (1985) 65–73.
46 B. COXON, *Methods Carbohydr. Chem.*, 6 (1972) 513–519.
47 C. A. G. HAASNOOT, F. A. A. M. DE LEEUW, AND C. ALTONA, *Tetrahedron*, 36 (1980) 2783–2792.