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Syntheses of β-iodourea derivatives of carbohydrates and glycosylamino-oxazolines*

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ABSTRACT

Syntheses of *N*-(β-D-glycopyranosyl)-*N'*-(*trans*-2-iodocyclohexyl)ureas (**3**–**7**), *N*-(β-D-glucopyranosyl)-*N'*-(2-iodo-3,3-dimethylbutyl)ureas (**8** and **9**), *N*-(2-iodo-1,1-diphenylethyl)-*N'*-(β-D-xylopyranosyl)-urea (**10**), 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-[3-(*trans*-2-iodocyclohexyl)ureido]-α- (**11**) and -β-D-glucopyranoses (**12**), 2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamino)-*cis*-3a,4,5,6,7,7a-hexahydrobenzoxazole (**15**), and 4,4-diphenyl-2-(β-D-xylopyranosylamino)-2-oxazoline (**16**) are reported.

INTRODUCTION

β-Iodoureas are useful intermediates in the syntheses of derivatives of imidazole and oxazole[1–5]. Few β-iodoureas have been identified[1–4,6] and carbohydrate derivatives of this type are unknown. We now describe preparations of the simple *N*-*p*-bromophenyl-*N'*-β-iodoalkylureas **1** and **2**, as model compounds for spectroscopic studies, and some β-iodourea derivatives (**3**–**12**) of carbohydrates.

β-Iodoureas can undergo intramolecular S_N2 displacement of the iodine substituent by the neighbouring urea group[4]. The resulting 2-amino-2-oxazolines have numerous pharmaceutical applications, such as stimulators of the central nervous system, regulators of blood pressure, antinociceptives[2,7–9], *etc.* This type of reaction has been performed on **1** and **2**, to give the 2-*p*-bromophenyloxazolines **13** and **14**, respectively, as model compounds. The synthesis of the 2-glycosylamino-2-oxazoline derivatives **15** and **16** from the corresponding *N*-glycosyl-*N'*-(β-iodoalkyl)ureas (**6** and **10**) is also described. Although the preparation of some 2-glycosylamino-2-thiazoline derivatives has been reported and β-halothioureas are postulated as reaction intermediates[10,11], there are no examples of similar reactions to give glycosylamino-oxazolines and there are few examples of glycosylamino derivatives of the oxazoles[12].

* Dedicated to Professor Grant Buchanan on the occasion of his 65th birthday.
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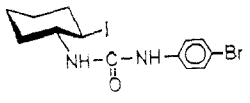

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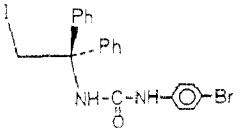

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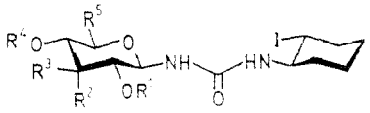
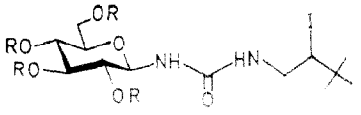
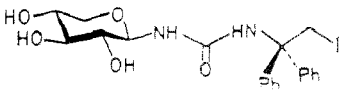


	R^1	R^2	R^3	R^4	R^5
3	H	H	OH	H	CH_2OH
4	H	H	OH	H	H
5	H	OH	H	H	H
6	Ac	H	OAc	Ac	CH_2OAc
7	Ac	H	OAc	Ac	H



8 R = H
9 R = Ac



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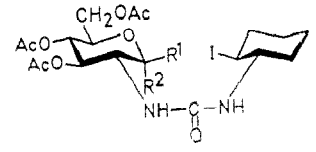
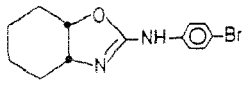


11 R^1 = H, R^2 = OAc
12 R^1 = OAc, R^2 = H



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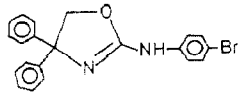

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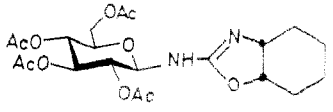

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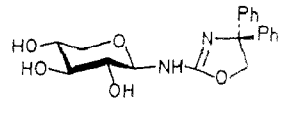

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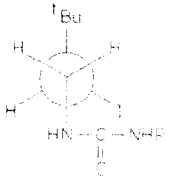

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RESULTS AND DISCUSSION

N-*p*-Bromophenyl-*N'*-(*trans*-2-iodocyclohexyl)urea (**1**) and *N*-*p*-bromophenyl-*N'*-(2-iodo-1,1-diphenylethyl)urea (**2**) were prepared by reaction of the corresponding *vic*-iodoisocyanates[13] and *p*-bromoaniline. The structures of **1** and **2** were assigned on the basis of analytical, u.v., i.r., ^{1}H- and ^{13}C-n.m.r., and m.s data (see Experimental).

Compound **1** showed $J_{1,2}$ and $J_{2,3ax}$ values (10.6 Hz) in the range for antiperiplanar protons, indicative of a chair conformation with the iodine atom and the urea group equatorial. No ^{13}C-n.m.r. data for β-iodoureas appear to have been reported. A signal at ~153.7 p.p.m. was assigned to the urea group[14]. The chemical shifts of the rest of the signals agreed with those expected from the deshielding effect of the N atom and the shielding effect of the I atom[14]. The mass spectrum of **1**, but not that of **2**, contained a peak for M^+, indicated losses variously of I, HI, and IPh, and reflected the facility for elimination of the iodine substituent (see below).

Reactions of *trans*-2-iodocyclohexyl[13], 2-iodo-3,3-dimethylbutyl[3], and 2-iodo-1,1-diphenylethyl[13] isocyanates with glycosylamines[15,16] or aminodeoxy sugar hydrochlorides[17,18] gave the β-iodoalkylurea derivatives **3**–**12**. When *trans*-2-iodocyclohexyl isocyanate was used, *N*-(β-D-glycopyranosyl)-*N'*-(*trans*-2-iodocyclohexyl)ureas (**3**–**5**) and 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-[3-(*trans*-2-iodocyclohexyl)ureido]-α- (**11**) and -β-D-glucopyranose (**12**) were isolated as crystalline 1:1 mixtures of diastereomers. The diastereomers had the same chromatographic properties and, except for **4** and **12**, no spectroscopic differences were observed. The ^{1}H- and ^{13}C-n.m.r. data for **3**–**5**, **11**, and **12** were consistent with those for **1** and supported the same conformation for the cyclohexane ring. The $J_{1,2}$ values for **11** (3.4 Hz) and for **3**, **4**, and **12** (8.9–9.3 Hz) confirmed the α and β configurations, respectively. The $^3J_{H,H}$ values for **3**, **4**, **11**, and **12** showed that the $^4C_1$(D) conformation preponderated in solutions in chloroform or methyl sulphoxide. The chemical shifts of the resonances of the sugar carbons for **3**–**5**, **11**, and **12** confirmed the α- (**11**) and β-glycopyranosyl (**3**–**5** and **12**) structures[19]. The resonances of C-1/5 in **12**, compared to those in **11**, showed downfield shifts in accord with published data for pairs of anomers[19–21].

Conventional acetylation of **3** and **4** gave **6** and **7**, respectively, the ^{1}H- and ^{13}C-n.m.r. spectra of which contained different signals for the diastereomers. The $^3J_{H,H}$ values confirmed the β configuration and $^4C_1$(D) conformation ($CDCl_3$). The magnitude of $J_{5a,5b}$ in the pentopyranosyl derivatives is dependent on the orientation of the 4-*O*-acyl group[22,23] (axial, 13 Hz; equatorial, 11 Hz). The $J_{5a,5b}$ value (11.3 Hz) for **7** accorded with the assigned conformation.

The mass spectra of **6**–**7** contained peaks for M^+, and losses of I and HI were the primary fragmentations. In contrast, **11** and **12** gave no peaks for M^+ and no simple losses of I and HI. Fragmentations started with the loss of an acetyl group, acetoxyl radical, or acetic acid, followed by the elimination of I and HI, and the characteristic losses (acetic acid, acetic anhydride, and ketene) of acetylated sugars[24,25]. The fragment with *m/z* 334.01078 ($C_{11}H_{15}IN_2O_2$) indicated that cleavages at the sugar ring were more favorable than the loss of HI.

The *N*-(β-D-glucopyranosyl)-*N'*-(2-iodo-3,3-dimethylbutyl)urea (**8**) was a hygroscopic syrup which was acetylated (→**9**) in order to confirm the structure. Signals for both diastereomers at C-2 were observed in the ^{1}H- and ^{13}C-n.m.r. spectra, which agreed with those for *N*-(2-iodo-3,3-dimethylbutyl)urea[9], supported the conformation (C-1–C-2 bond) shown in **17** as the major conformation in a solution in chloroform, and confirmed the β configuration ($J_{1',2'}$ 9.2 Hz) and $^4C_1$(D) conformation. The mass spec-

trum showed a fragmentation pathway similar to that of **6**, but there was no peak for $M^{+\cdot}$.

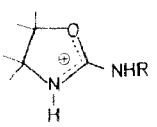
N-(2-Iodo-1,1-diphenylethyl)-*N'*-(β-D-xylopyranosyl)urea (**10**) was an unstable solid, the structure of which was confirmed by the characteristic[24] i.r. absorption for C=O at ~1650 cm^{-1} and by transformation into the oxazoline derivative **16** (see below).

On heating **1** in water–ethanol (4:1) and **2** in water, the 2-(*p*-bromophenylamino)-2-oxazoline derivatives **13** and **14**, respectively, were obtained. The cyclisation of **2** was easier than for **1**, and some **14** was obtained during the recrystallisation of **2**. This difference in behaviour is attributed to the anchimeric assistance of the neighbouring phenyl group. The shorter reaction time diminished the thermolysis of **2** and the hydrolysis and polymerisation of the protonated oxazoline[5,25], and increased the yield.

The structures of **13** and **14** were confirmed by analytical and spectroscopic data. The i.r. band at 1680 cm^{-1} is characteristic[4] of 2-arylamino-2-oxazolines. The $^3J_{H,H}$ values of **13** were different from those for **1**, indicative of a change in conformation on formation of the bicyclic system. The C-7a signal for **13** showed a significant downfield shift (39.6 p.p.m.) compared to the signal for C-2 in **1**. Similarly, the resonance for C-5 in **14** was shifted downfield (58.4 p.p.m.) compared to that for C-2 in **2**. These results accord with the replacement of the iodine substituent by the oxygen of the urea group. The chemical shift (~156 p.p.m.) of the resonances for C-2 in **13** and **14** also accorded with data for related amino-oxazolines[4]. The mass spectrum of **13** showed losses of 43 (C_3H_7) and 56 (C_4H_8) and prominent fragments that contained the *p*-bromophenyl group. Compound **14** underwent loss of CH_2O as described for 5-unsubstituted oxazolines[25]. The displacement of the iodine substituent in **1** and **2** by oxygen rather than by nitrogen can be explained by the stability of the respective resulting cations. The amino-oxazolinium cation (**18**) is stabilised by participation of π bonding and non-bonding electrons of the heteroatoms[26]. Such participation would not be possible in **19**.

On heating **3** with dry *N*,*N*-dimethylformamide at 80° and acetylation of the product, 2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamino)-*cis*-3a,4,5,6,7,7a-hexahydrobenzoxazole (**15**, 64%) was obtained as a pair of diastereomers. However, 4,4-diphenyl-2-(β-D-xylopyranosylamino)-2-oxazoline could be prepared (73%) upon heating **4** with water. In the latter reaction, 2-amino-4,4-diphenyl-2-oxazoline was formed also, probably due to partial hydrolysis of **16** in the acid medium (see Experimental).

Some unprotected glycosylaminoheterocycles that contain the unit **20** have been reported[28] to mutarotate, and some derivatives of 2-amino-4,4-diphenyl-2-oxazoline show a tautomeric equilibrium in solution in chloroform[25]. This behaviour was not observed for a solution of **16** in methyl sulphoxide during 12 h.



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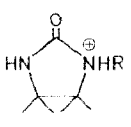

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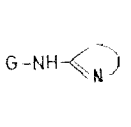

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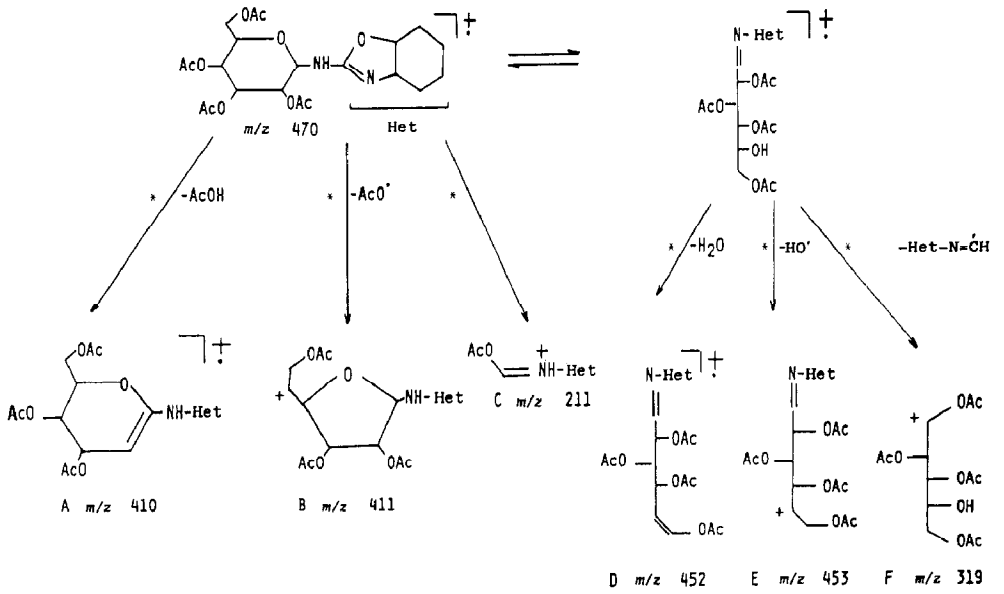
The structures of the glycosylamino-oxazolines **15** and **16** were based on analytical and spectroscopic properties. The i.r., ^{1}H-n.m.r., and ^{13}C-n.m.r. data were consistent with those for **13** and **14**, respectively. Different signals for the two *cis*-diastereomers of **15** were not observed. The $J_{1',2'}$ values for **15** (9.7 Hz) and **16** (8.6 Hz) established the β configuration. The $^3J_{H,H}$ values were consistent with the $^4C_1$(D) conformation for solutions in chloroform (**15**) or methyl sulphoxide (**16**). The ^{13}C-n.m.r. assignments accorded with those reported for D-gluco- and D-xylo-pyranosides[19,21] and glycosylaminothiazolines[11].

The high-resolution mass spectrum of **15** contained a weak peak for M^+. Scheme 1 summarises the primary fragments and the various pathways of fragmentation. The structures assigned to fragments A and B are similar to those reported for acetylated glycosylamines[29]. Fragmentation of M^+ according to the J-fragmentation pattern[30,31] gives C (base peak), which undergoes losses of CO and ketene. Fragments D–F can be explained by an acyclic ⇌ pyranoid equilibrium. Peaks B and E undergo losses mainly of AcOH, CH_2O, Ac_2O, or RNHCHO. Although no mass-spectral data for glycosylaminoheterocycles are available, these results agree with those reported for acetylated *N*-acetyl(methyl)glycosylamines[29,32] and acyclic aminodeoxy sugar derivatives[33].



Scheme 1.

EXPERIMENTAL

General methods. — Melting points are uncorrected. Optical rotations were measured at 22° ± 1°, using 1- and 10-cm cells. I.r. spectra were recorded for KBr discs. Assignments of the ^{1}H-n.m.r. (200.13 MHz) spectra were confirmed by decoupling and H/D exchange experiments. ^{13}C-N.m.r. (50.3 MHz) spectra were obtained for solutions in $CDCl_3$ and $(CD_3)_2SO$. Proton-decoupled APT[34] (attached proton test) spectra were used to assist in the assignment of signals. E.i.-mass spectra (70 eV) were recorded with a Kratos MS-80RFA instrument, with an ionising current of 100 μA, an accelerating voltage of 4 kV, and a resolution of 1000 (10% valley definition). The elemental composition of the ions was determined with a resolution of 10000 (10% valley definition). Metastable peaks in the field-free region were obtained on the same instrument; fragment-ion and precursor-ion scans were used. Preparative chromatography was performed on Silica Gel 60 (Merck, 230 mesh).

N-(p-*Bromophenyl*)-N′-(*2-iodoalkyl*)*ureas* (**1** *and* **2**). — A solution of *p*-bromoaniline (4.7 mmol) in ether (5 mL) was added to a solution of the 2-iodoalkyl isocyanate[13] (4.7 mmol) in ether (15 mL). The mixture was kept at room temperature for *t* h, then at 0° overnight. The crystalline product was collected and crystallised from ethanol at 50–60°. The following compounds were prepared in this manner.

N-(*p*-Bromophenyl)-*N*′-(*trans*-2-iodocyclohexyl)urea (**1**; 1.60 g, 78%; *t* 1 h), m.p. 145–146°; $\lambda_{max}^{CH_2Cl_2}$ 243 nm (ε_{mM} 24.4); ν_{max} 3305 (NH), 1640 (CO), 1590 (C=C aromatic), 1570 (NH), and 825 cm^{-1} (CH aromatic). N.m.r. data [$(CD_3)_2SO$]: ^{1}H, δ 8.60 (s, 1 H, NH), 7.38 (s, 4 H, aromatic), 6.39 (d, 1 H, $J_{1',NH}$ 9.8 Hz, N′H), 4.24 (td, 1 H, $J_{1',2'}$ 10.6, $J_{2',3'ax}$ 10.6, $J_{2',3'eq}$ 4.0 Hz, H-2′), 3.70 (m, 1 H, H-1′), and 2.80–1.10 (m, 8 H, 4 CH_2); ^{13}C, δ 153.8 (CONH), 139.8–112.2 (6 C, Ph), 54.9 (C-1′), 38.6 (C-3′), 38.2 (C-2′), 32.8 (C-6′), 29.6 (C-4′), and 24.0 (C-5′). Mass spectrum: *m/z* 424, 422 (2%, M^+), 297, 295 (9, $M^+ - I$), 296, 294, (43, $M^+ - HI$, peak A), 253, 251 (48, $A - C_3H_6^+$), 199, 197 (73, $BrPhNCO^+$), 240, 238 (5, $A - C_4H_8^+$), 173, 171 (100, $BrPhNH^+$), 128 (62, HI^+), 90 (40), 81, 79 (70, Br^+), and 54 (50).

Anal. Calc. for $C_{13}H_{16}BrIN_2O$: C, 36.90; H, 3.81; N, 6.62. Found: C, 37.09; H, 3.90; N, 6.83.

N-(*p*-Bromophenyl)-*N*′-(2-iodo-1,1-diphenylethyl)urea (**2**; 1.74 g, 71%; *t* 2 h), m.p. 170–172°; $\lambda_{max}^{CH_2Cl_2}$ 246 and 228 nm (ε_{mM} 11.5 and 8.5); ν_{max} 3320, 3300 (NH), 1655 (CO), 1600, 1580 (C=C aromatic), 1550 (NH), 830, 745, and 700 cm^{-1} (CH aromatic). N.m.r. data [$(CD_3)_2SO$]: ^{1}H, δ 9.13 (s, 1 H, N′H), 7.56–7.13 (m, 15 H, 2 Ph, C_6H_4, and NH), and 4.83 (s, 2 H, CH_2); ^{13}C, δ 153.6 (CONH), 143.6–112.3 (18 C, 2 Ph and C_6H_4), 63.1 (C-1), and 19.0 (C-2). Mass spectrum: *m/z* 395, 393 (2%, $M^+ - I$), 394, 392 (65, $M^+ - HI$, peak A), 318, 316 (30, $M^+ - IPh$), 317, 315 (100, $A - Ph^+$), 195 (70, $A - OCNC_6H_4Br^+$), 194 (49), 180 (40, $^+CH_2Ph_2$), 165 (70, fluorenyl cation), and 91 (40, $C_7H_7^+$).

Anal. Calc. for $C_{21}H_{18}BrIN_2O$: C, 48.38; H, 3.48; N, 5.37. Found: C, 48.13; H, 3.55; N, 5.05.

(*1*R,*2*R)- *and* (*1*S,*2*S)-N(N′)-(*β*-D-*glycopyranosyl*)-N′(N)-(trans-*2-iodocyclohe-*

xyl)ureas (**3–5**). — A solution of the glycosylamine[15,16] (4.7 mmol) in water (5 mL) was added to a solution of 2-iodocyclohexyl isocyanate[13] (4.7 mmol) in acetone (15 mL). The mixture was kept at room temperature for 30 min. The resulting solid was crystallised from ethanol. The following compounds were prepared in this manner.

(1′*R*,2′*R*)- and (1′*S*,2′*S*)-*N*-(β-D-glucopyranosyl)-*N*′-(*trans*-2-iodocyclohexyl)-urea (**3**; 1.8 g, 88%), m.p. 143–144°, $[\alpha]_D^{22}$ 0° (*c* 0.55, pyridine); ν_{max} 3480 (OH), 3310 (NH), 1640 (CO), and 1575 cm^{-1} (NH). N.m.r. data [$(CD_3)_2SO$]: ^1H, δ 6.46 (d, 1 H, $J_{1,NH}$ 8.3 Hz, NH), 6.20 (d, 1 H, $J_{1',N'H}$ 8.0 Hz, N′H), 5.00–4.80 (m, 4 H, 4 OH), 4.60 (td, 1 H, $J_{1',2'}$ 9.3, $J_{2',3'ax}$ 9.3, $J_{2',3'eq}$ 4.2 Hz, H-2′), 4.50 (bs, 1 H, H-1), 4.19 (m, 1 H, H-1′), 3.30–2.80 (m, 6 H, H-2,3,4,5,6a,6b), and 2.50–1.10 (m, 8 H, 4 CH_2); ^{13}C, δ 156.1 (CONH), 83.0, 81.1 (C-1), 77.7 (C-5), 77.6 (C-3), 72.9, 72.8 (C-2), 69.9 (C-4), 60.8 (C-6), 54.7, 53.6 (C-1′), 38.2 (C-3′), 38.0 (C-2′), 32.6 (C-6′), 26.5, 26.4 (C-4′), and 23.9 (C-5′).

Anal. Calc. for $C_{13}H_{23}IN_2O_6$: C, 36.28; H, 5.39; N, 6.51. Found: C, 36.10; H, 5.41; N, 6.32.

(1*R*,2*R*)- and (1*S*,2*S*)-*N*-(*trans*-2-iodocyclohexyl)-*N*′-(β-D-xylopyranosyl)urea (**4**; 1.2 g, 64%), m.p. 154–156° $[\alpha]_D^{22}$ +79° (*c* 0.75, pyridine); ν_{max} 3405 (OH), 3305 (NH), 1640 (CO), and 1580 cm^{-1} (NH). N.m.r. data [$(CD_3)_2SO$]: ^1H, δ 6.47 (d, 1 H, $J_{1',N'H}$ 9.0 Hz, N′H), 6.26 (d, 1 H, $J_{1,NH}$ 9.0 Hz, NH), 5.04, 4.93, 4.90 (3 d, each 1 H, $J_{H,OH}$ 5.1 Hz, 3 OH), 4.51 (t, 1 H, $J_{1',2'}$ 9.0 Hz, H-1′), 4.19 (td, 1 H, $J_{1,2}$ 10.3, $J_{2,3ax}$ 10.3, $J_{2,3eq}$ 4.4 Hz, H-2), 3.60 (m, 2 H, H-1,3′), 3.35–2.85 (m, 3 H, H-4′,5′a,5′b), 3.00 (m, 1 H, H-2′), and 2.50–1.10 (m, 8 H, 4 CH_2); ^{13}C, δ 155.9 (CONH), 81.7 (C-1′), 77.4 (C-3′), 72.5 (C-2′), 69.6 (C-4′), 66.7 (C-5′), 54.6 (C-1), 38.5 (C-3), 38.1 (C-2), 32.5 (C-6), 26.5 (C-4), and 23.7 (C-5).

Anal. Calc. for $C_{12}H_{21}IN_2O_5$: C, 36.00; H, 5.29; N, 7.00. Found: C, 35.72; H, 5.13; N, 6.77.

(1*R*,2*R*)- and (1*S*,2*S*)-*N*-(*trans*-2-iodocyclohexyl)-*N*′-(β-D-ribopyranosyl)urea (**5**; 1.52 g, 81%), m.p. 126–128°, $[\alpha]_D^{22}$ −24° (*c* 0.5, pyridine); ν_{max} 3470 (OH), 3310 (NH), 1640 (CO), and 1570 cm^{-1} (NH). N.m.r. data [$(CD_3)_2SO$]: ^1H, δ 6.37 (d, 1 H, $J_{1',N'H}$ 9.5 Hz, N′H), 6.22 (d, 1 H, $J_{1,NH}$ 8.2 Hz, NH), 5.13 (bs, 1 H, OH), 4.82 (td, 1 H, $J_{1,2}$ 10.1, $J_{2,3ax}$ 10.1, $J_{2,3eq}$ 3.6 Hz, H-2), 4.78 (bs, 1 H, OH), 4.65 (bs, 2 H, H-1′ and OH), 4.20 (m, 1 H, H-1), 3.80–3.10 (m, 5 H, H-2′,3′,4′,5′a,5′b), and 2.50–1.00 (m, 8 H, 4 CH_2); ^{13}C, δ 156.6, 156.5 (CONH), 78.1, 78.0 (C-1′), 71.1 (C-2′), 70.1 (C-3′), 67.4 (C-4′), 64.1 (C-5′), 54.9 (C-1), 38.4 (C-3), 38.3 (C-2), 32.8 (C-6), 26.9 (C-4), and 24.0 (C-5).

Anal. Calc. for $C_{12}H_{21}IN_2O_5$: C, 36.00; H, 5.29; N, 7.00. Found: C, 35.88; H, 5.12; N, 6.73.

*(1*R,2R)- *and (1*S,2S)-N-(trans-*2-iodocyclohexyl*)-N′-(*poly*-O-*acetyl*-β-D-*glyco-pyranosyl)ureas* (**6–7**). — Conventional treatment of **3** or **4** (0.72 mmol) with pyridine (0.3 mL) and acetic anhydride (0.3 mL, 3.18 mmol) gave the corresponding acetylated derivative.

(1*R*,2*R*)- and (1*S*,2*S*)-*N*-(*trans*-2-iodocyclohexyl)-*N*′-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)urea (**6**; 0.40 g, 93%), m.p. 114–118° (from ethyl ether–hexane), $[\alpha]_D^{22}$ −8.6° (*c* 0.58, dichloromethane); $\lambda_{max}^{CH_2Cl_2}$ 231 nm (ε_{mM} 0.64); ν_{max} 3320 (NH), 1750 (CO ester), 1650 (CO urea), 1560 (NH), and 1240 cm^{-1} (C–O–C ester). N.m.r. data ($CDCl_3$): ^1H, δ 5.57, 5.53 (2 d, 1 H, $J_{1',N'H}$ 9.4 Hz, N′H), 5.31, 5.29 (2 t, 1 H, $J_{1',2'}$ 9.4 Hz, H-1′), 5.21,

5.13 (2 t, 1 H, $J_{2',3'}$ 9.4, $J_{3',4'}$ 9.4 Hz, H-3'), 5.12, 5.00 (2 d, 1 H, $J_{1,NH}$ 8.4 Hz, NH), 5.05, 5.03 (2 t, 1 H, $J_{4',5'}$ 9.4 Hz, H-4'), 4.33, 4.31 (2 dd, 1 H, $J_{6'a,6'b}$ 12.7, $J_{5',6'a}$ 2.8 Hz, H-6'a), 4.21, 3.92 (2 td, 1 H, $J_{1,2}$ 11.2, $J_{2,3ax}$ 11.2, $J_{2,3eq}$ 4.0 Hz, H-2), 4.07, 4.05 (2 dd, 1 H, $J_{5',6'b}$ 2.5 Hz, H-6'b), 3.82 (m, 1 H, H-5'), 3.65, 3.60 (2 m, 1 H, H-1), 2.60–1.10 (m, 8 H, 4 CH_2), 2.06, 2.05, 2.01, and 1.99 (4 s, each 3 H, 4 Ac); ^{13}C, δ 171.1, 170.6, 169.7, 169.5 (4 $COCH_3$), 155.4, 155.0 (CONH), 80.1, 79.9 (C-1'), 73.1 (C-3'), 72.8, 72.7 (C-5'), 70.6, 70.5 (C-2'), 68.2 (C-4'), 61.8 (C-6'), 56.8, 56.0 (C-1), 39.4, 39.0 (C-3), 37.0, 35.9 (C-2), 34.1, 33.2 (C-6), 27.7, 27.5 (C-4), 24.5, 24.4 (C-5), 21.0, 20.8, 20.6, and 20.5 (4 CH_3CO). Mass spectrum: *m/z* 598.0861 (1%, M^+), 471.1784 (8, $M^+ - I$), 470.1839 (10, $M^+ - HI$, peak A), 411.1651 (28, A – AcO^+), 169.0687 (76), 145.0525 (73, Ac_2O^+), 140 (19, $C_6H_{10}NHCONH_2^+$), 128 (80, HI^+), 127 (45, I^+), 97 (38, $C_6H_{11}N^+$), 81 (43), and 43 (100, Ac^+).

Anal. Calc. for $C_{21}H_{31}IN_2O_{10}$: C, 42.14; H, 5.22; N, 4.68. Found: C, 41.98; H, 5.20; N, 4.72.

(1*R*,2*R*)- and (1*S*,2*S*)-*N*-(*trans*-2-iodocyclohexyl)-*N'*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)urea (**7**; 0.31 g, 82%), obtained as an amorphous solid by preparative t.l.c. (ether–hexane 3:1), had $[\alpha]_D^{22}$ −17° (*c* 0.53, dichloromethane); $\lambda_{max}^{CH_2Cl_2}$ 231 nm (ε_{mM} 3.7); ν_{max} 3320 (NH), 1750 (CO ester), 1645 (CO urea), 1555 (NH), and 1245 cm^{-1} (C–O–C ester). ^1H-N.m.r. data ($CDCl_3$): δ 5.83 (d, 1 H, $J_{1,NH}$ 9.5 Hz, N'H), 5.30, 5.29 (2 t, 1 H, $J_{1',2'}$ 9.5 Hz, H-1'), 5.08 (t, 1 H, $J_{2',3'}$ 9.5 Hz, H-2'), 5.00 (m, 1 H, H-4'), 4.88 (t, 1 H, $J_{3',4'}$ 9.5 Hz, H-3'), 4.10, 3.99 (2 td, 1 H, $J_{1,2}$ 10.3, $J_{2,3ax}$ 10.3, $J_{2,3eq}$ 4.3 Hz, H-2), 4.08 (dd, 1 H, $J_{5',6'b}$ 11.3, $J_{4',5'a}$ 5.6 Hz, H-5'a), 3.80 (m, 1 H, H-1), 3.47 (dd, 1 H, $J_{4',5'b}$ 10.8 Hz, H-5'b), 2.60–1.10 (m, 8 H, 4 CH_2), 2.03, 2.02, 2.01 (3 s, each 3 H, 3 Ac). Mass spectrum: *m/z* 526 (1%, M^+), 399 (2, $M^+ - I$), 3.98 (3, $M^+ - HI$, peak A), 339 (10, A – AcO^+), 128 (40, HI^+), 127 (20, I^+), 97 (30, $C_6H_{11}N^+$), 81 (27), 79 (31), 60 (30, $AcOH^+$) and 43 (100, Ac^+).

Anal. Calc. for $C_{18}H_{27}IN_2O_8$: C, 41.07; H, 5.17; N, 5.32. Found: C, 41.27; H, 4.91; N, 5.33.

(2'R)- and (2'S)-N-(*β-D-glucopyranosyl*)-N'-(*2-iodo-3,3-dimethylbutyl*)*urea* (**8**) *and* (2R)- *and* (2S)-N-(*2-iodo-3,3-dimethylbutyl*)-N'-(*2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl*)*urea* (**9**). — A solution of D-glucopyranosylamine (4.7 mmol) in water (5 mL) was added to a solution of 2-iodo-3,3-dimethylbutyl isocyanate[5] in acetone (15 mL). The mixture was kept at room temperature for 2 h and then concentrated to dryness, to give **8** (1.38 g, 69%) as a hygroscopic syrup, which was treated conventionally with pyridine (1.5 mL) and acetic anhydride (1.5 mL, 16 mmol) to yield **9** (1.54 g, 80%) after preparative t.l.c. (ether–hexane 3:1). The 1:1 mixture of diastereomers **9** had $[\alpha]_D^{22}$ −6° (*c* 1, dichloromethane); $\lambda_{max}^{CH_2Cl_2}$ 231 nm (ε_{mM} 2.4); ν_{max} 3365 (NH), 1750 (CO ester), 1650 (CO urea), 1555 (NH), and 1230 cm^{-1} (C–O–C ester). N.m.r. data ($CDCl_3$): ^1H, δ 5.63, 5.60 (2 d, 1 H, $J_{1',NH}$ 9.2 Hz, N'H), 5.32, 5.31 (2 t, 1 H, $J_{1',2'}$ 9.2 Hz, H-1'), 5.16, 5.15 (2 t, 1 H, $J_{2',3'}$ 9.2, $J_{3',4'}$ 9.2 Hz, H-3'), 5.09 (t, 1 H, $J_{4',5'}$ 9.2 Hz, H-4'), 5.04 (bs, 1 H, NH), 4.95, 4.94 (2 t, 1 H, H-2'), 4.36, 4.34 (2 dd, 1 H, $J_{6'a,6'b}$ 12.5, $J_{5',6'a}$ 4.3 Hz, H-6'a), 4.26, 4.16 (2 dd, 1 H, H-2), 4.11, 4.09 (2 dd, $J_{5',6'b}$ 2.5 Hz, H-6'b), 3.90, 3.82 (2 ddd, 1 H, $J_{1a,1b}$ 15.2, $J_{1a,NH}$ 5.6, $J_{1a,2}$ 2.5 Hz, H-1a), 3.86–3.76 (m, 1 H, H-5'), 3.21, 3.15 (2 ddd, 1 H, $J_{1b,2}$ 10.6, $J_{1b,NH}$ 4.4 Hz, H-1b), 2.10, 2.09, 2.04, 2.03 (4 s, each 3 H, 4 Ac), and 1.13 (s, 9 H, ^{t}Bu); ^{13}C, δ 171.0, 170.6, 169.8, 169.5 (4 $COCH_3$), 155.8, 155.7 (CONH), 80.1 (C-1'), 73.1 (C-3'), 72.7 (C-5'), 70.4, 70.3

(C-2'), 68.1, 68.0 (C-4'), 61.6, 61.5 (C-6'), 58.2, 58.0 (C-1), 45.4, 45.3 (C-2), 35.0, 35.4 (C-3), 28.4 [3 C, $(CH_3)_3C$], 20.8, 20.7, 20.5, and 20.5 (4 CH_3CO). Mass spectrum: *m/z* 473.2008 (5%, $M^+ - I$), 472.1924 (7, $M^+ - HI$, peak A), 457.1819 (12, $A - CH_3^+$), 413.2048 (84, $A - AcO^+$), 353.1631 (40, $A - AcOH - AcO^+$), 169.0459 (100), 143 (50), 115 (40), 109 (45), 81 (30), 60 (30, $AcOH^+$), and 43 (81, Ac^+).

Anal. Calc. for $C_{21}H_{33}IN_2O_{10}$: C, 42.43; H, 4.58; N, 4.71. Found: C, 42.38; H, 4.60; N, 4.55.

N-(*2-Iodo-1,1-diphenylethyl*)-N'-(*β*-D-*xylopyranosyl*)*urea* (**10**). — A solution of D-xylopyranosylamine[16] (4.7 mmol) in water (5 mL) was added to a solution of 2-iodo-1,1-diphenylethyl isocyanate[13] in acetone (15 mL). The reaction mixture was kept at room temperature for 20 min, then concentrated to dryness, and the resulting syrup (1.42 g, 78%) was dissolved in ethanol–ether. Compound **10** was obtained as an amorphous and unstable solid which had ν_{max} 3320 (OH and NH), 1655 (CO), 1580 (C=C, aromatic), 1545 (NH), 760 and 700 cm^{-1} (CH aromatic). The structure was confirmed by its transformation into **16**.

(*1'*R,*2'*R)- *and* (*1'*S,*2'*S)-*1,3,4,6-tetra*-O-*acetyl-2-deoxy-2-[3-(*trans-*2'-iodocyclohexyl)ureido]-α-* (**11**) *and -β*-D-*glucopyranoses* (**12**). — A solution of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-α[17](or β[18])-D-glucopyranose hydrochloride (4.7 mmol) in water (5 mL) was neutralised with sodium hydrogencarbonate (4.7 mmol) and added to a solution of 2-iodocyclohexyl isocyanate[13] (4.7 mmol) in acetone (15 mL). The mixture was kept at room temperature for 30 min. The solid product was collected and crystallised from ethanol. The following compounds were prepared in this manner.

(1'*R*,2'*R*)- and (1'*S*,2'*S*)-1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-[3-(*trans*-2'-iodocyclohexyl)ureido]-α-D-glucopyranose (**11**; 2.3 g, 83%), m.p. 139–141°, $[\alpha]_D^{22}$ +28° (*c* 0.54, pyridine); λ_{max}^{EtOH} 259 nm (ε_{mM} 1.0); ν_{max} 3330 (NH), 1735 (CO ester), 1650 (CO urea), 1550 (NH), and 1225 cm^{-1} (C–O–C ester). N.m.r. data [$(CD_3)_2SO$]: ^1H, δ 6.24, 6.16 (2 d, 1 H, $J_{1',N'H}$ 9.1 Hz, N'H), 6.02, 5.98 (2 d, 1 H, $J_{2,NH}$ 9.8 Hz, NH), 5.97, 5.91 (2 d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 5.11 (t, 1 H, $J_{2,3}$ 9.5, $J_{3,4}$ 9.5 Hz, H-3), 4.99 (t, 1 H, $J_{4,5}$ 9.5 Hz, H-4), 4.20–3.90 (m, 5 H, H-2,5,6a,6b,2'), 3.60 (m, 1 H, H-1'), 2.50–1.10 (m, 8 H, 4 CH_2), 2.17, 2.01, 1.99, and 1.96 (4 s, each 3 H, 4 Ac); ^{13}C, δ 169.9, 169.8, 169.1, 169.0 (4 CH_3CO), 156.3, 156.0 (CONH), 90.6, 90.4 (C-1), 70.4 (C-3), 69.1, 69.0 (C-5), 67.7 (C-4), 63.1 (C-6), 54.9 (C-1'), 50.7, 50.4 (C-2), 38.6 (C-3'), 38.3, 38.2 (C-2'), 33.0, 32.6 (C-6'), 26.9, 26.6 (C-4'), 23.9, 23.8 (C-5'), 20.8, 20.7, 20.4 and 20.4 (4 CH_3CO). Mass spectrum: *m/z* 427.1662 (13%, $A - Ac^+$), 411.1764 (30, $A - AcO^+$), 410.1707 (10, $A - AcOH^+$), 376.0262 (19), 334.0178 (26, peak E), 206.1041 (12, $E - HI^+$), 169 (25), 141 (40), 128 (55, HI^+), 81 (60), and 60 (100, $AcOH^+$).

Anal. Calc. for $C_{21}H_{31}IN_2O_{10}$: C, 42.15; H, 5.22; N, 4.68. Found: C, 41.98; H, 5.20; N, 4.69.

(1'*R*,2'*R*)- and (1'*S*,2'*S*)-1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-[3-(*trans*-2'-iodocyclohexyl)ureido]-β-D-glucopyranose (**12**; 2.0 g, 72%), m.p. 155–158°, $[\alpha]_D^{22}$ +26° (*c* 0.84, pyridine); $\lambda_{max}^{CH_2Cl_2}$ 255 nm (ε_{mM} 1.8); ν_{max} 3310 (NH), 1750 (CO ester), 1650 (NH), and 1220 cm^{-1} (C–O–C ester). N.m.r. data ($CDCl_3$): ^1H, δ 5.66 (d, 1 H, $J_{1,2}$ 8.9 Hz, H-1), 5.16 (t, 1 H, $J_{3,4}$ 8.5, $J_{4,5}$ 8.5 Hz, H-4), 5.08 (t, 1 H, $J_{2,3}$ 8.5 Hz, H-3), 4.51 (d, 1 H, $J_{1',N'H}$ 9.0 Hz, N'H),

4.40 (d, 1 H, $J_{2,NH}$ 9.0 Hz, NH), 4.28 (dd, 1 H, $J_{5,6a}$ 4.6, $J_{6a,6b}$ 12.5 Hz, H-6a), 4.11 (dd, 1 H, $J_{5,6b}$ 2.2 Hz, H-6b), 4.10 (m, 1 H, H-2), 3.97 (td, 1 H, $J_{1,2}$ 10.7, $J_{2,3ax}$ 10.7, $J_{2,3eq}$ 4.2 Hz, H-2'), 3.75 (m, 2 H, H-5,1'), 2.60–1.10 (m, 8 H, 4 CH_2), 2.14, 2.10, 2.06, and 2.04 (4 s, each 3 H, 4 Ac); ^{13}C, δ 171.1, 170.7, 169.5, 169.3 (4 $COCH_3$), 156.1 (CONH), 93.0 (C-1), 72.7 (C-3), 72.6 (C-5), 68.1 (C-4), 61.7 (C-6), 56.4 (C-1'), 53.9 (C-2), 39.5 (C-3'), 37.3 (C-2'), 34.1 (C-6'), 27.8 (C-4'), 24.7 (C-5'), 21.3, 20.8, 20.7, and 20.5 (4 CH_3CO). Mass spectrum: *m/z* 427 (10%, A – Ac^+), 411 (17, A – AcO^+), 410 (10, A – $AcOH^+$), 376 (5), 334 (5, peak E), 206 (2, E – HI^+), 128 (28, HI^+), 127 (22, I^+), 81 (30), and 60 (100, $AcOH^+$).

Anal. Calc. for $C_{21}H_{31}IN_2O_{10}$: C, 42.15; H, 5.22; N, 4.68. Found: C, 42.20; H, 5.28; N, 4.41.

2-(p-*Bromophenylamino*)-cis-*3a,4,5,6,7,7a-hexahydrobenzoxazole* (**13**). — A suspension of **1** (0.33 g, 0.78 mmol) in water–ethanol (4:1, 25 mL) was boiled under reflux until dissolution was complete (4 h). The solution was cooled to room temperature and aqueous 50% potasium hydroxide was added to give **13** (0.16 g, 64%), m.p. 168–169° (from ethanol); $\lambda_{max}^{CH_2Cl_2}$ 253 nm (ε_{mM} 19.2); ν_{max} 3430 (NH), 1680 (C=N), 1600, 1580 (C=C aromatic), 1545 (NH), 1230 (C–O–C), and 840 cm^{-1} (CH aromatic). N.m.r. data [$(CD_3)_2SO$]: ^1H, δ 7.33 (m, 4 H, aromatic), 7.14 (bs, 1 H, NH), 4.53 (q, 1 H, $J_{7,7a}$ 5.8, $J_{7,7a}$ 5.8, $J_{3a,7a}$ 5.8 Hz, H-7a), 3.78 (q, $J_{3a,4}$ 5.8, $J_{3a,4'}$ 5.8 Hz, H-3a), and 1.79–1.17 (m, 8 H, 4 CH_2); ^{13}C, δ 156.7 (C-2), 141.9–113.6 (6 C, Ph), 77.8 (C-7a), 56.1 (C-3a), 27.6 (C-4), 25.9 (C-7), 19.3 (C-6), and 19.1 (C-5). Mass spectrum: *m/z* 296, 294 (30%, M^+), 253, 251 (35, $M^+ - C_3H_7$), 240, 238 (5, $M^+ - C_4H_8$), 215 (5, $M^+ - Br$), 199, 197 (20), 173, 171 (30), 96 (19), 81,79 (45, Br^+), 69 (38), 56 (100, $C_4H_8^+$), and 55 (68).

Anal. Calc. for $C_{13}H_{15}BrN_2O$: C, 52.89; H, 5.12; N, 9.49. Found: C, 52.81; H, 5.06; N, 9.23.

2-(p-*Bromophenylamino*)-*4,4-diphenyl-2-oxazoline* (**14**). — A solution of **2** (0.68 g, 1.3 mmol) in water (150 mL) was processed as described above for **1**, to yield **14** (0.38 g, 75%), m.p. 177–179° (from ether–hexane); $\lambda_{max}^{CH_2Cl_2}$ 253 nm (ε_{mM} 20.7); ν_{max} 3440 (NH), 1680 (C=N), 1580 (C=C aromatic), 1545 (NH), 1240 (C–O–C), 835, 750, and 705 cm^{-1} (CH aromatic). N.m.r. data: ^1H ($CDCl_3$), δ 7.40–7.20 (m, 15 H, 2 Ph, C_6H_4, and NH) and 4.28 (s, 2 H, H-5a,5b); ^{13}C [$(CD_3)_2SO$], δ 155.4 (C-2), 147.2–112.6 (18 C, 2 Ph and C_6H_4), 77.4 (C-5), and 76.7 (C-4). Mass spectrum: *m/z* 394, 392 (10%, M^+), 237 (8), 364, 362 (10, $M^+ - H_2CO$), 317, 315 (100, $M^+ - Ph$), 208 (10), 194 (15), 180 (20), 165 (40, fluorenyl cation), 152 (3), 119 (10), 103 (25), 91 (40), and 77 (10).

Compound **14** (17%) was also obtained from the mother liquor of **2**.

Anal. Calc. for $C_{21}H_{17}BrN_2O$: C, 64.13; H, 4.36; N, 7.12. Found: C, 63.85; H, 4.36; N, 6.89.

*2-(2',3',4',6'-Tetra-*O*-acetyl-β-*D*-glucopyranosylamino)*-cis-*3a,4,5,6,7,7a-hexahydrobenzoxazole* (**15**). — A solution of **3** (1 g, 1.16 mmol) in anhydrous *N,N*-dimethylformamide (5 mL) was kept at 80° for 30 min, then concentrated. A solution of the resulting syrup in water (50 mL) was neutralised with Amberlite IR-45(HO^-) resin (5 mL) and concentrated. The residue was dried over P_2O_5 and then acetylated conventionally (Ac_2O/Py). Preparative t.l.c. (ether–hexane, 3:1) of the product gave **15** as an amor-

phous solid (0.35 g, 64%), $[a]_D^{22}$ +10° (*c* 0.4, dichloromethane); $\lambda_{max}^{CH_2Cl_2}$ 226 nm (ε_{mM} 9.5); ν_{max} 3480, 3390 (NH), 1750 (CO), 1675 (C=N), 1540 (NH), and 1230 cm^{-1} (C–O–C). N.m.r. data ($CDCl_3$): ^1H, δ 5.24 (t, 1 H, $J_{2',3'}$ 9.7, $J_{3',4'}$ 9.7 Hz, H-3'), 5.17 (t, 1 H, $J_{4',5'}$ 9.7 Hz, H-4'), 5.05 (d, 1 H, $J_{1',2'}$ 9.7 Hz, H-1'), 5.03 (t, 1 H, H-2'), 4.42 (bs, 1 H, NH), 4.40–4.35 (m, 1 H, H-7a), 4.29 (dd, 1 H, $J_{6'a,6'b}$ 12.7, $J_{5',6'a}$ 4.7 Hz, H-6'a), 4.14 (dd, 1 H, $J_{5',6'b}$ 2.4 Hz, H-6'b), 3.84 (dd, 1 H, H-5'), 3.84–3.78 (m, 1 H, H-3a), 2.10, 2.04, 2.02, 1.99 (4 s, each 3 H, 4 Ac), and 1.18–1.10 (m, 8 H, 4 CH_2); ^{13}C, δ 171.3, 170.9, 170.6, 169.9 (4*C*OCH_3), 152.6 (CONH), 86.2 (C-1'), 76.9 (C-7a), 74.0 (C-3'), 73.8 (C-5'), 73.6 (C-2'), 69.0 (C-4'), 62.7 (C-6'), 54.4 (C-3a), 27.1 (C-4), 25.2 (C-7), 21.8, 21.7, 21.3, 21.2 (4 *C*H_3CO), 20.0 (C-6), and 19.8 (C-5). Mass spectrum: *m/z* 470.1894 (3%, M^+), 453.1885 (27, $M^+ - OH$), 452.1791 (10, $M^+ - H_2O$), 411.1764 (13, $M^+ - AcO\cdot$), 410.1674 (2, $M^+ - AcOH$), 393.1613 (41, $M^+ - OH - AcOH$), 392.1538 (9, $M^+ - H_2O - AcOH$), 319.0866 (27, Scheme 1), 243.0833 (12, Scheme 1), 211.1041 (100, $C_{10}H_{15}N_2O_3$), 183.1037 (27, $C_9H_{15}N_2O_2$), 169.0913 (76, $C_8H_{13}N_2O_2$), 141.0594 (41, $C_7H_9O_3$), and 81.0711 (32, $C_6H_9^+$).

Anal. Calc. for $C_{21}H_{30}N_2O_{10}$: C, 53.61; H, 6.43; N, 5.95. Found: C, 53.63; H, 6.30; N, 5.69.

*4,4-Diphenyl-2-(β-*D*-xylopyranosylamino)-2-oxazoline* (**16**). — A suspension of **10** (1.0 g, 1.66 mmol) in water (150 mL) was boiled under reflux until dissolution was complete (20 min). The solution was cooled to room temperature and aqueous 50% potassium hydroxide was added to give 2-amino-4,4-diphenyl-2-oxazoline (0.08 g). The aqueous solution was neutralised with aqueous 10% HCl and concentrated. The residue was dried (P_2O_5) and then extracted with hot ethanol. The extract was concentrated and the residue was treated with ether to give **16** (0.45 g, 73%) as an amorphous solid, $[a]_D^{22}$ +5.8° (*c* 0.52, methyl sulphoxide); λ_{max}^{EtOH} 251 nm (ε_{mM} 0.4); ν_{max} 3350 (OH), 1665 (C=N), 1595 (C–C aromatic), 1550 (NH), 755 and 710 cm^{-1} (CH aromatic). N.m.r. data [$(CD_3)_2SO$]: ^1H, δ 7.45–7.15 (m, 11 H, 2 Ph and NH), 5.35–5.20 (m, 3 H, 3 OH), 4.72 (m, 2 H, H-5a,5b oxazoline), 4.62 (d, 1 H, $J_{1',2'}$ 8.6 Hz, H-1'), 3.70 (td, 1 H, $J_{3',4'}$ 8.6, $J_{4',5'a}$ 8.6, $J_{4',5'b}$ 5.3 Hz, H-4'), 3.55–3.30 (m, 2 H, H-5'a,5'b), 3.20 (t, 1 H, $J_{2',3'}$ 8.6 Hz, H-3'), and 3.18 (t, 1 H, H-2'); ^{13}C, δ 159.2 (C-2), 147.8–126.2 (12 C, 2 Ph), 85.3 (C-1'), 78.5 (C-5), 77.6 (C-3'), 76.3 (C-4), 72.4 (C-2'), 69.7 (C-4'), and 67.2 (C-5').

Anal. Calc. for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.99; N, 7.56. Found: C, 64.70; H, 5.97; N, 7.32.

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