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Note

Structure of glycosylamines and diglycosylamines in the arabinose, mannose, and rhamnose series †

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Aldoses react with ammonia, generally to give cyclic products (glycosylamines), which may further undergo spontaneous transglycosylation to yield diglycosylamines. The reaction has been known since the pioneering work of Isbell and Frush[2], who assigned the anomeric configuration of a number of glycosylamines on the basis of their optical rotations. The structures of the corresponding diglycosylamines is, however, still uncertain. Furthermore, in some instances, anomerization reactions have been shown to occur upon *O*-acetylation[1]. In a previous paper[1], the structure of glycosylamines and diglycosylamines derived from D-glucose and D-xylose have been firmly assigned using ^1H and ^{13}C NMR spectroscopy. The results are now extended in the arabinose, mannose, and rhamnose series.

α-L-Arabinopyranosylamine was earlier prepared by Isbell and Frush[3], and its anomeric configuration assigned[2] on the basis of Hudson's isorotation rules. α-D-Arabinopyranosylamine (**1**) has now been prepared by the same procedure, and confirmation of its structure was provided by ^1H NMR spectroscopy (Table I). The $J_{1,2}$ and $J_{2,3}$ values for **1** of 8.7 and 9.6 Hz, respectively, indicated a *trans*-diaxial arrangement for these protons and, consequently, the α-anomeric configuration in the $^1C_4$(D) conformation with the amino group in an equatorial orientation. This structure was also found with the peracetylated derivative **2**, which showed a heteronuclear $J_{C\text{-}1,H}$ coupling constant of 158.11 Hz, similar to values reported for α-arabinopyranosides[4].

Di-L-arabinopyranosylamine had been previously prepared[2], however, its anomeric configuration was not assigned. The procedure has now been applied to di-D-arabinopyranosylamine. When α-D-arabinopyranosylamine, in methanolic solution, was heated under reflux in the presence of phenol for 1 h and the mixture

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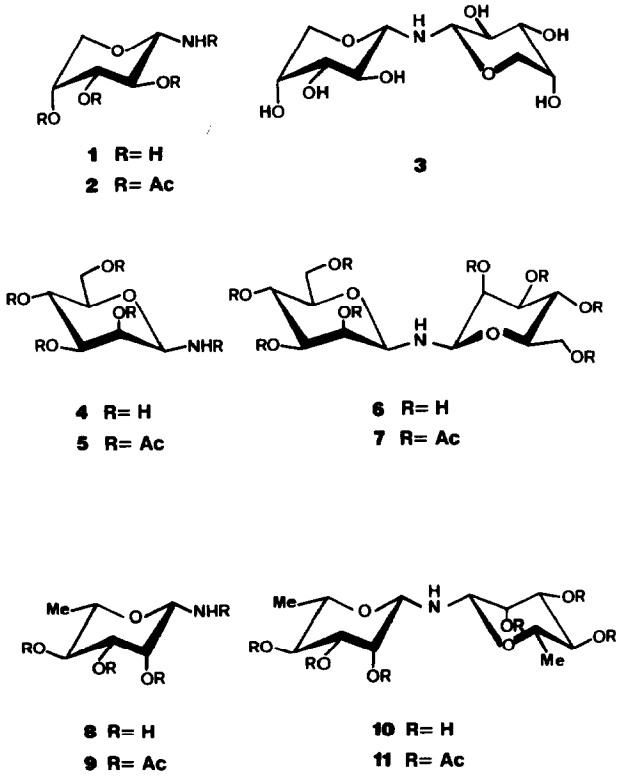
† Glycosylamines, Part 2. For Part 1, see ref 1.



Scheme 1.

cooled to room temperature[2], crystalline di-D-arabinopyranosylamine (**3**) was obtained in 35% yield. The ^{13}C NMR spectrum of the mother liquor showed that no other isomer had been formed in the transglycosylation process. The dimeric structure of **3** was inferred from its FAB mass spectrum, and the presence of six signals in its ^{13}C NMR spectrum indicated a symmetrical structure. From the $J_{1,2}$ and $J_{2,3}$ coupling constants (8.6 and 8.8 Hz, respectively), the anomeric configuration of **3** is α,α and the conformation $^1C_4$(D) for both pyranose rings. Interestingly, attempts to acetylate compound **3** in pyridine–acetic anhydride, following the procedure already applied to the D-glucose and D-xylose analogs[1] were unsuccessful, α-D-arabinopyranose tetraacetate being the only product recovered in the reaction.

β-D-Mannopyranosylamine (**4**) was prepared by Isbell and Frush[2] and the anomeric configuration was assigned according to Hudson's rules. Confirmation of this structure has now been provided from ^1H and ^{13}C NMR spectra. The δ (^{13}C) value for C-5 (78.32 ppm, Table II) is in agreement with the β-anomeric configuration, as inferred from the results of Voelter and Breitmaier[5]. This was confirmed by the $J_{1,2}$ coupling constant (1.2 Hz, Table I) since corresponding values of 1.1 and 1.9 Hz, respectively, have been reported[6] for β and α anomers of D-manno-

TABLE I

^{1}H NMR spectral data for glycosylamines **1**, **2**, **4**, **5**, **8**, and **9** and diglycosylamines **3**, **6**, **7**, **10**, and **11**

Compound	Chemical shift (δ)									Coupling constants									
	H-1	H-2	H-3	H-4	H-5	H-5′	H-6	H-6′	NH	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	$J_{1,NH}$
1	3.98d	3.41t	3.65q		3.85q	3.66q				8.7	9.6	3.5	2.3		13.1				
2 [a]	5.11m	5.14m		5.31o	3.98q	3.78q			6.58			3.4	2.0	1.3	13.4				
3	4.15d	3.53t	3.70q	3.97o	3.65q	3.88q				8.6	8.8	3.5	1.0	2.3	13.0				
4	4.34d	3.88q	3.64q	5.53t	3.36o		3.90q	3.68q		1.20	3.30	9.60	9.60			2.40	6.50	12.10	
5 [b]	5.50d	5.31q	5.07q	5.16t	3.75o		4.24q	4.03q	6.6d	1.24	3.24	10.1	9.99			5.10	2.25	12.43	9.47
6	4.54d	3.97q	3.66q	3.55t	3.34o		3.90q	3.71q		1.25	3.30	9.70	9.70			2.30	6.10	12.10	
7 [c]	4.57o	5.38q	5.06q	5.21t	3.66o		4.26q	4.09q		0.90	3.37	9.9	10.1			5.33	5.77	12.3	
8	4.34d	3.88q	3.61q	3.43–3.30m			1.28d			1.10	3.41	9.36	9.38			5.92			
9 [d]	5.50q	5.36q	5.07q	5.00t	3.68		1.25d		6.88d	1.10	3.10	8.92	9.00			6.13			9.30
10	4.45d	3.92q	3.57q	3.31t	3.36m		1.25d			1.13	3.45	9.50	9.30			5.61			
11 [e]	4.51d	5.30q	5.03m	5.00m	3.51s		1.25d			1.15	3.60	9.00	9.37			6.19			

[a] Additional signals at δ 2.11, 2.03, 1.99, and 1.95 for CH_3CO. [b] CH_3CO at δ 2.16, 2.06, 1.99, 1.94, and 1.91. [c] CH_3CO at δ 2.18, 2.11, 2.09, and 1.99. [d] CH_3CO at δ 1.97, 1.99, and 2.06. [e] CH_3CO at δ 1.99, 2.06, and 2.10.

TABLE II

^{13}C NMR chemical shifts for glycosylamines **1**, **2**, **4**, **5**, **8**, and **9**, and diglycosylamines **3**, **6**, **7**, **10**, and **11**

Compound	Chemical shift							
	C-1	C-2	C-3	C-4	C-5	C-6	C=O	$CH_3(CO)$
1	87.1	73.2	74.2	70.0	68.3			
2	78.8	68.4	70.5	68.1	65.8		171.0	23.1
							170.4	20.7
							169.9	20.6
							169.5	20.4
3	88.8	71.5	74.3	69.8	68.1			
4	83.69	72.49	75.03	68.09	78.32	62.39		
5	75.7	69.7	71.3	65.0	73.8	62.1	170.40	22.9
							170.10	20.6
							169.55	20.5
							169.50	20.4
								20.3
6	86.31	72.81	74.95	68.10	78.31	62.36		
7	83.0	70.3	71.4	66.4	73.2	62.5	170.7	20.7
							170.4	20.6
							169.9	20.5
							169.5	
8	83.4	72.4	74.5	74.2	73.1	18.0		
9 [a]	75.4	69.9	71.3	69.9	71.9	17.2	170.1	22.8
							169.7	20.5
							169.7	20.3
							169.6	20.6
10	86.0	72.7	74.5	73.9	73.2	18.0		
11	82.6	70.6	71.4	70.7	71.4	17.5	170.5	20.7
							170.0	20.6
							169.8	

[a] Assignation by 2D heteronuclear correlation.

pyranose. The $^4C_1$(D) conformation for **4** was furthermore confirmed from the large $^3J_{3,4}$ and $^3J_{4,5}$ coupling constant (9.6 Hz, Table I), indicative of a *trans*-diaxial arrangement for these protons. The same conformation and anomeric configuration is also found for the peracetylated derivative **5**, as deduced from a comparison of the NMR data for both compounds (Table I).

Di-β-D-mannopyranosylamine (**6**) had previously been prepared[2] without establishing the configuration of the *N*-glycosyl bond. The ^{13}C NMR spectrum of **6** has now been found to exhibit six different carbon signals, pointing to a symmetrical molecule, since the FABMS of **6** confirmed its dimeric structure. The δ values for C-5 (78.31 ppm) and the anomeric coupling constant (1.25 Hz) are both in agreement with a β,β anomeric configuration for **6**, the $^4C_1$(D) conformation being maintained in both mannopyranosyl sites ($^3J_{3,4}$ 9.7 Hz). Acetylation of **6** in 2:1 pyridine–acetic anhydride[2] afforded bis(2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl)amine (**7**) as a syrup. A small amount of penta-*O*-acetyl-α-D-mannopyranose was formed during the acetylation process, which could be removed by column chromatography. The presence of six signals in the ^{13}C NMR spectrum of **7**, in the

resonance range for sugar carbon atoms, indicated that the molecule was still symmetrical. The $^3J_{1,2}$ $^3J_{2,3}$, $^3J_{3,4}$, and $^3J_{4,5}$ coupling constants in the ^{1}H NMR spectrum (Table I) confirmed that the β,β-anomeric configuration and the $^4C_1$(D) conformation were retained.

β-L-Rhamnopyranosylamine (**8**) was prepared long ago by Lobry de Bruyn and Van Leent[7] without any structural characterization. Its proof of structure has now been provided by ^{1}H NMR spectroscopy. The value of the coupling constants (Table I) suggests[8] that the compound has the β-anomeric configuration and the $^1C_4$(L) conformation. Acetylation of **8** in pyridine–acetic anhydride yielded the crystalline peracetylated derivative **9**, which showed almost no change in the vicinal coupling constant of its ^{1}H NMR spectrum as compared to **8** (Table I).

Transglycosylation of β-L-rhamnopyranosylamine (**8**), by boiling it in anhydrous methanol, afforded a crystalline dimeric product **10** (FABMS) which, taking into account the NMR parameters, should have the di-β-L-rhamnopyranosylamine structure **10**. This point was further corroborated by the value for the heteronuclear anomeric coupling constant which was found identical in **8** and **10** ($J_{C\text{-}1,H}$ 154.2 ± 1 Hz). *O*-Acetylation of **10** in pyridine–acetic anhydride gave a single per-*O*-acetylated derivative which, as inferred from the FABMS, ^{1}H (Table I) and ^{13}C NMR (Table II) data, had the structure **11**.

The aforementioned results thus further indicate that the favored structure of aldosylamines, and dialdosylamines, have the amino group at the anomeric position in equatorial. This is agreement with the fact that the expected anomeric effect would be small with these structures and that any positive charge on the nitrogen atom would furthermore result in an inverse anomeric effect, with increased stabilization of the anomeric group in equatorial orientation. Anomerization reactions, which have been found previously to occur[1] upon *O*-acetylation of β,β-diglucosylamine and β,β-dixylosylamine, and were ascribed to interactions of equatorial 2-*O*-acetyl groups with the equatorial interglycosidic glycosylamine linkage, have not been presently encountered in the mannose and rhamnose series where such parallel interactions are obviously missing. It is noteworthy that such an unfavorable arrangement is present in di-α-D-arabinopyranosylamine (**3**), and this may explain why attempts to acetylate this compound have been unsuccessful.

EXPERIMENTAL

General methods.—Methods reported in ref 1 were used, except that mass spectra were recorded with a Fisons, VG type ZAB-SEQ double focusing instrument, operating in FAB$^+$ ionisation mode with glycerol–thioglycerol matrix and NaI as cationizing agent, unless otherwise stated.

α-D-*Arabinopyranosylamine* (**1**).—Prepared as reported in ref 3 for the L enantiomer; mp 122–124°C; $[\alpha]_D^{25}$ −82.5° (*c* 2.0, H_2O, 2 min); lit.[3] mp 124°C, $[\alpha]_D$ +86.3° (*c* 2.0, H_2O, 5 min for the L enantiomer). FABMS: *m/z* 448.8 (6, $[M_3H]^+$), 413.1 (7, $[M_3H–H_2O]^+$), 320.9 (6, $[M_2Na]^+$), 280.0 (7, $[M_2–H_2O]^+$),

172.1 (33, $[MNa]^+$), 150.1 (32, $[MH]^+$), together with a signal at m/z 304 (8, $[M_2Na-NH_3]$) indicative of the possible presence of some di-arabinopyranosylamine (**3**).

N-*Acetyl-2,3,4-tri*-O-*acetyl-α*-D-*arabinopyranosylamine* (**2**).—Prepared according to ref 3 for the L enantiomer; mp 175°C; $[\alpha]_D^{25}$ −87.0° (*c* 2.0, $CHCl_3$); lit.[3] mp 177–178°C, $[\alpha]_D^{20}$ +89.6° (*c* 1.6, $CHCl_3$). FABMS (*m*-nitrobenzyl alcohol): m/z 657.2 (5, $[M_2Na]^+$), 635.2 (14, $[M_2H]^+$), 340.0 (36, $[MNa]^+$), 318.1 (100, $[MH]^+$), 259.1 (26, $[M-NHAc]^+$).

Di-α-D-*arabinopyranosylamine* (**3**).—Prepared as described in ref 2 for the "di-L" enantiomer; mp 143–144°C; $[\alpha]_D^{25}$ −52.0° (*c* 2.0, H_2O); lit.[2] mp 145°C, $[\alpha]_D$ +50.6° (*c* 1.6, H_2O). FABMS: m/z 304.0 (22, $[MNa]^+$), 282.0 (14, $[MH]^+$).

β-D-*Mannopyranosylamine* (**4**).—Prepared according to ref 2; mp 92–93°C; $[\alpha]_D^{25}$ −12.0 (*c* 2.0, H_2O, 2 min); lit.[2] mp 93–94°C, $[\alpha]_D$ −11.6° (*c* 2.0, H_2O). FABMS: m/z 381.0 (5, $[M_2Na]^+$), 359 (5, $[M_2H]^+$), 202.1 (55, $[MNa]^+$), 180.1 (100, $[MH]^+$), together with a signal at m/z 342 (4, $[M_2H-NH_3]^+$) indicative of the possible presence of some dimannopyranosylamine **6**.

N-*Acetyl-2,3,4,6-tetra*-O-*acetyl-β*-D-*mannopyranosylamine* (**5**).—Prepared according to ref 2; mp 186°C; $[\alpha]_D^{25}$ −15.5° (*c* 2.0, $CHCl_3$); lit.[2] mp 188–189°C, $[\alpha]_D^{20}$ −16.5° (*c* 2.0, $CHCl_3$). FABMS: m/z 412 (54, $[MNa]^+$), 390.1 (100, $[MH]^+$), 331 (17, $[M-NHAc]^+$).

Di-β-D-*mannopyranosylamine* (**6**).—Prepared according to ref 2; mp 160°C; $[\alpha]_D^{25}$ −35.5° (*c* 2.0, H_2O, 2 min); lit.[2] mp 157–158°C, $[\alpha]_D$ −36.8° (*c* 5.0, H_2O). FABMS: m/z 364.2 (37, $[MNa]^+$), 342.2 (54, $[MH]^+$).

Bis(2,3,4,6-tetra-O-*acetyl-β*-D-*mannopyranosyl)amine* (**7**).—Prepared according to ref 2, this derivative did not crystallize upon attempted crystallization from hot EtOH as previously described[2]. From **6** (5 g), in a mixture of Ac_2O (25 mL) and pyridine (50 mL) at 20°C for 24 h, a crude product (8.1 g, 81.6%) was obtained which showed almost one component in ^{13}C NMR spectroscopy. Attempted crystallization from hot EtOH was unsuccessful, even with a preliminary purification step on a silica gel column (eluent 1:1 benzene–EtOAc). In the latter case, a colourless solid was obtained (5.2 g, 52.4%) which, after drying over P_2O_5, had $[\alpha]_D^{25}$ −27.0° (*c* 2, $CHCl_3$); lit.[2] mp 146–147°C; $[\alpha]_D^{20}$ −68.0° (*c* 2.0, $CHCl_3$). FABMS: m/z 700.1 (41, $[MNa]^+$), 678.2 (95, $[MH]^+$), 331 (52, $[Man\,Ac_4]^+$). Anal. Calcd. for $C_{28}H_{39}NO_{18}$: C, 49.6; H, 5.8; N, 2.1. Found: C, 49.7; H, 5.7; N, 2.0.

β-L-*Rhamnopyranosylamine* (**8**).—Prepared according to ref 7; mp 109–110°C; $[\alpha]_D^{25}$ +37° (*c* 2.0, H_2O, 2 min); lit.[7] mp 116°C, $[\alpha]_D$ +38° (water). FABMS: m/z 186.1 (39, $[MNa]^+$), 164.1 (47, $[MH]^+$), together with a signal at m/z 332 (77, $[M_2Na-NH_3]^+$) indicative of the presence of dirhamnopyranosylamine **10**.

N-*Acetyl-2,3,4-tri*-O-*acetyl-β*-L-*rhamnopyranosylamine* (**9**).—Prepared according to ref 7; mp 135°C; $[\alpha]_D^{25}$ +2.2° (c 2.0, $CHCl_3$); lit.[7] mp 135–137°C, $[\alpha]_D$ +6.2° ($CHCl_3$). FABMS (*m*-nitrobenzyl alcohol): m/z 685.3 (11, $[M_2Na]^+$), 663.3 (33, $[M_2H]^+$), 464 (10, $[MCs]^+$), 354.1 (56, $[MNa]^+$), 332.1 (100, $[MH]^+$), 273.1 (46, $[M-NHAc]^+$).

Di-β-L-rhamnopyranosylamine (**10**).—β-L-Rhamnopyranosylamine (**8**, 10 g) in dry MeOH (500 mL) was boiled under reflux with exclusion of external moisture while the course of the reaction was checked by TLC (5:1:1 MeOH–1,4-dioxane–heptane). After 1 h, the solution was concentrated until nucleation began and the crystallization continued at 0°C during 24 h. The crystalline dirhamnosylamine **10** (9 g, 47.5%) was filtered off and dried; mp 118°C (EtOH–Me_2CO), $[\alpha]_D^{25}$ +52.0° (*c* 2.0, H_2O, 2 min). FABMS: *m/z* 641.3 (6, $[M_2Na]^+$), 619.3 (4, $[M_2H]^+$), 332.1 (47, $[MNa]^+$), 310.2 (91, $[MH]^+$). Anal. Calcd for C_{12} H_{23} NO_8; C, 46.6; H, 7.5; N, 4.5. Found: C, 46.5; H, 7.6; N, 4.6.

Bis(2,3,4-tetra-O-acetyl-β-L-rhamnopyranosyl)amine (**11**).—A mixture of 1:2 Ac_2O–pyridine (135 mL) was added to di-L-rhamnosylamine **10** (9 g) and the solution was stirred for 24 h at 20°C. It was then poured into ice–water (500 mL), causing the crystallisation of **11** (5.5 g, 33.7%) which was filtered and dried; mp 153–155°C (H_2O–EtOH), $[\alpha]_D^{25}$ +23° (*c* 2, $CHCl_3$). FABMS (*m*-nitrobenzyl alcohol): *m/z* 584.2 (32, $[MNa]^+$), 562,2 (100, $[MH]^+$), 502.1 (10, $[MH-AcOH]^+$), 442.1 (7, $[MH-2AcOH]^+$), 273.1 (55, $[RhaAc_4]^+$). Anal. Calcd for C_{24} H_{35} NO_{14}: C, 51.3; H, 6.3; N, 2.5. Found: C, 51.2; H, 6.3; N, 2.4.

A ^{13}C NMR spectrum of the mother liquors resulting from the crystallization of **11** showed only the presence of residual **11**.

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