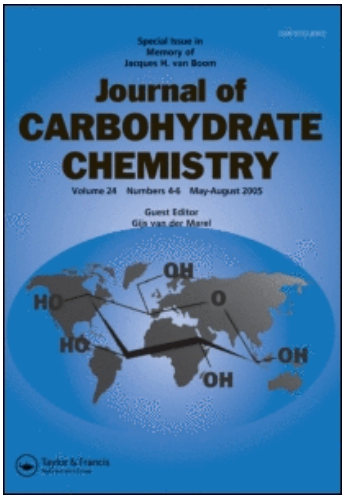

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NMR STUDIES OF CONFIGURATION AND CONFORMATION IN *N*-ACYL-D-RIBOSYLAMINES

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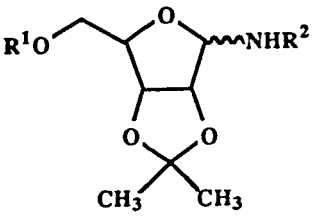
ABSTRACT

Configurational assignments for a series of *N*-acyl-D-ribofuranosylamines have been established unequivocally using a set of NMR criteria. The conformation of the *exo*-cyclic substituents is determined.

INTRODUCTION

N-Acylglycosylamines have an important function in the biosynthesis of glycoproteins and may be intimately involved in the immune process.[1] We have synthesised a range of *N*-acyl-D-ribosylamines as part of a program to investigate immunosuppressant activity in these compounds and related nucleosides. Since biological function is related to configuration and conformation we have made a detailed study of the stereochemistry of a series of *N*-acyl derivatives of 2,3-*O*-isopropylidene-D-ribofuranosylamine 1, with or without a blocking group at the 5-position. Configurational assignments in this series are not trivial and we discuss the best approach to anomeric assignment. It should be emphasised that we were interested in developing an unequivocal but routine method using standard proton and carbon data which would find wide applicability to *N*-glycosides (of D-ribofuranose) of type 1. With that objective in mind a range of criteria have been examined and the final assignment in any one case is made on the basis of the best fit to the set of criteria rather than reliance



	R^1	R^2
1	H	H
2	COMe	COMe
3	H	$COCF_3$
4	COPh	COPh
5	H	$COCH_2CO_2Et$
6	$COCMe_3$	$COCH_2CONH_2$
7	H	$COC(=NOH)CO_2Et$
8	COMe	$COC(=NOH)CONH_2$
9	COMe	$COCHNH_2CONH_2$

on a single parameter. This approach overcomes the common difficulties associated with spectral complexity, the availability of only one anomer, or the breakdown of any one criterion in a particular case.

The choice of criteria is discussed below but we have deliberately excluded as a general procedure, the determination of nuclear Overhauser enhancements. The effectiveness of NOE in verifying the close proximity of particular protons is well established but it is a time consuming task to obtain high quality results. Futhermore, in the case of **1** and related sugars the interpretation of NOE results can be seriously complicated by the existence of severe second order coupling, the near coincidence of some chemical shifts, the presence of exchangeable protons, and the conformational mobility of the ring and sidechain.

RESULTS AND DISCUSSION

The proton and carbon NMR data for the series **2** - **9** are given in Tables 1 and 2. Some compounds were examined as complex mixtures of isomers and limited data are available.

The conformation of the 5-substituent is discussed in terms of the usual conformational labels,[2] ϕ_+ (torsion angle O-5,C-5,C-4,C-3 = 60°), ϕ_a (180°), and ϕ_-(−60°). In all cases H-5 was taken as downfield of H-5' and the conformer populations were estimated from the vicinal coupling constants using the standard parameters J_t 11.0 Hz and J_g 1.5 Hz.[2]

The normal labels (*syn* and *anti*) for the conformation of the glycosidic bond in nucleosides are not used for the *N*-acyl compounds. Since the nitrogen atom is protonated there is a closer analogy with amino acids. Extensive investigations[3] of peptides have shown that only three conformations are likely for the peptide bond and thus in the case of the

TABLE 1. ^{1}H Chemical Shifts and Coupling Constants for Compounds 2 - 9[a]

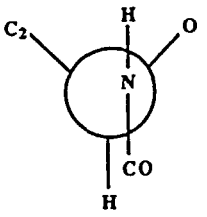
		H-1	H-2	H-3	H-4	H-5	H-5'	Me[b]	Me[b]	NH	$CONH_2$	CH[c]	$J_{2,3}$
2a	α	5.836	4.665	4.702	4.236	4.168	4.140	1.378	1.561	6.48		2.066	6.2
2b	β	5.539	4.704	4.636	4.305	4.350	4.090	1.334	1.530	6.79			6.4
3a	α	5.840	4.780	4.952	4.200	3.850	3.695	1.395	1.570				6.2
3b	β	5.882	4.630	4.895	4.412	3.915	3.888	1.335	1.532	8.46			6.0
4	β	5.831	4.943	4.828	4.567	4.702	4.385	1.380	1.580	7.31			6.2
5a	α	5.878	4.745	4.805	4.15	3.80	3.66	1.395	1.598	8.30		3.381	6.2
5b	β	5.732	4.658	4.865	4.290	3.8	3.8	1.330	1.530	8.27		3.322	6.2
6	α	5.855	4.705	4.720	4.312	4.205	4.138	1.38	1.59	7.72	5.80, 6.95	3.26	
6[d]	α	5.715	4.675	4.728	4.13	4.11	4.01	1.30	1.45	8.51	7.15, 7.60	3.15	6.2
7a	α	5.90						1.32	1.48	7.78			
7b	α	5.94						1.41	1.53	9.68			
7c	β	5.90								9.30			
8a[d]	α	5.684						1.324	1.465	7.58	7.66, 7.90		
8b[d]	β	5.484						1.27	1.44	8.70	7.62, 7.83		
8c[d]	α	5.734						1.27	1.44	8.55	7.38, 7.46		
8d[d]	β	5.400						1.27	1.44	9.07	7.38, 7.46		
9a	α	5.765	4.74	4.71	4.3	4.18	4.15	1.39	1.601	8.92	5.61, 7.60	4.105	6.5
e									1.607		5.61, 7.57	4.120	
9a[d]	α	5.584	4.735	4.71				1.30	1.47	8.56	7.41, 7.39	3.920	
e		5.598	4.740								7.45, 7.50	3.908	
9b	β	5.697	4.655	4.70	4.39	4.270	4.135	1.34	1.55	8.58	5.75, 7.53	4.079	5.7
e		5.649	4.635		4.37	4.285	4.140			8.52	5.75, 7.61	4.060	6.1
9b[d]	β	5.40	4.7	4.7				1.28	1.43	8.7	7.32, 7.43	3.810	
e		5.42										3.822	

a. In $CDCl_3$ relative to TMS. Only restricted data were accessible for the three and four component mixtures. Other couplings are given in Table 3. *b*. Isopropylidene methyl group *c*. β-Carbon of the N-substituent. *d*. In DMSO. *e*. Double entries are for distinguishable protons in diastereoisomeric mixtures.

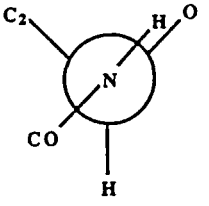
TABLE 2. ^{13}C NMR Chemical Shifts[a] for Compounds 2 - 9

		C-1	C-2	C-3	C-4	C-5	Me	OCO	CH	CO
2a	α	80.7	79.3	82.0	79.5	65.0	24.8, 26.3	113.3	23.6	170.1, 170.5
2b	β	87.8	85.3	81.3	83.5	64.5	25.3, 26.9	113.9	23.4	170.1, 171.0
3a	α	83.0	79.4	80.8	81.9	63.8	24.7, 26.2	113.0		155.9
3b	β	87.0	86.9	82.1	86.7	63.8	25.0, 26.6	113.1		156.5
4	β	89.7	86.2	81.5	84.6	65.4	25.3, 26.9	113.8		167.2, 166.8
6	α	81.0	79.4	82.1	79.7	65.5	24.8, 26.3	113.7	42.6	167.4, 168.9, 178.0
8a	α	81.4				64.0	24.6, 26.0	112.3	147.9	160.3, 162.4
8b[b]	β	85.8				64.1	24.7, 26.0	112.2	148.0	161.7, 163.2
8c[b]	α	81.5				64.0	25.1, 26.7	112.6	147.4	161.3, 162.7
8d[b]	β	85.3				64.4	25.1, 26.8	112.8	148.5	162.6
9a	α	82.0 82.1	81.0 80.9	79.6	79.5	65.0 65.0	25.0, 26.3 24.9	113.8 114.0	57.2	170.4, 170.5, 171.0
9b	β	87.3 87.5	85.6 85.9	83.4 83.3	81.7 81.8	65.0 65.2	25.3, 26.9 25.4	113.9 113.8	57.1	170.2, 170.8, 171.3 169.8, 170.6, 170.7

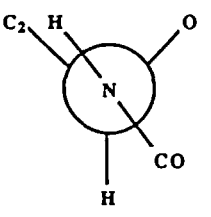
a. Relative to $CDCl_3$ (77.1 ppm). *b*. Assignment of some data to particular isomers is uncertain.



10 (ac)



11 (sc)



12 (ap)

C-1,N bond in the β-anomer we assume that only forms **10 - 12** contribute. Similar conformations can be considered for the α-anomer. The labels *ac*, *sc* and *ap* refer to the relationship of the acyl group to C-2. The orientation of the C-1 substituent can be examined directly using $J_{1,NH}$. Bystrov[3] has derived an empirical Karplus relation (equation 1) for proton coupling in the fragment NHCOCH3. This equation can be applied to *N*-acylribosides

$$^3J = 9.4\cos^2\theta - 1.1\cos\theta + 0.4 \qquad (1)$$

by inclusion of a suitable correction for the electronegativity effect of the ring oxygen atom according to the method of Altona.[4] Thus for the *ac* conformation ($\theta = 180°$) we calculate $J_{1,NH} = 9.4$ Hz, in both anomers. The *ap* and *sc* conformations have $\theta = -120°$ and $+120°$, respectively, and correspondingly $J_{1,NH} = 4.5$ Hz and 2.1 Hz for the β-anomer. These values are reversed for the *ap* and *sc* conformations in the α-anomer.

Collected in Table 3 are the data which determine the assignment of anomeric configuration. Some years ago Imbach[5] suggested that the methyl groups on the isopropylidene moiety had a consistently greater proton chemical shift separation Δ(H) in the β-anomer of ribosides. Typically Δ(H) was 0.2 - 0.3 ppm for the β-configuration compared to 0.0 - 0.1 ppm for the α-configuration. Later the carbon chemical shift separation Δ(C) for the isopropylidene methyl groups was taken as an even better means of discrimination for a range of ribosylamines[6]; the α-form had Δ(C) = 1.13 - 1.42 ppm compared to the β-form with Δ(C) = 1.64 - 1.86 ppm. Unfortunately, both these criteria require that the substituent at C-1 produce an anisotropic environment on the *exo* (lower) face of the ribose ring. The relatively simple substituents in the series **2 - 9** produce only small values of Δ(H) and Δ(C) for both α- and β-anomers (Table 3) and these criteria are unreliable.

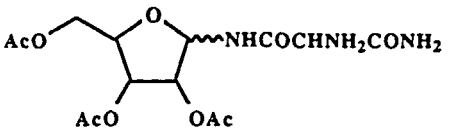
Chemical shifts of the nuclei at the anomeric site, Δ(H-1) and Δ(C-1) will be sensitive to the configuration but variation in the type of C-1 substituent can produce overlapping ranges for both these parameters. The (unassigned) anomers of compound **13** have H-1

TABLE 3. Criteria for configurational assignment in *N*-Acyl-D-ribosylamines

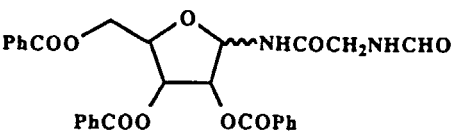
		Δ(H)[a]	Δ(C)[a]	δ(H-1)	δ(C-1)	$J_{1,2}$	$J_{3,4}$	$J_{1,NH}$
2a	α	0.18	1.5	5.836	80.66	3.9	1.1	9.4
2b	β	0.20	1.6	5.539	87.66	2.1	2.5	6.8
3a	α	0.17	1.6	5.84	83.0	4.5	1.5	9.0
3b	β	0.20	1.6	5.882	87.0	0.8	1.2	9.4
4	β	0.20	1.6	5.831	89.68	1.6	2.2	6.0
5a	α	0.20		5.878		4.4	1.2	9.0
5b	β	0.22		5.732		1.9	1.3	8.8
6	α	0.20	1.4	5.855	82.08			9.2
6[b]	α	0.15		5.715		4.1	1.1	9.5
7a	α_{anti}	0.16		5.90		4.4		9.5
7b	α_{syn}	0.12		5.94		4.2		9.0
7c	β_{syn}			5.90		1.0		8.8
8a[b]	α_{anti}	0.14	1.4	5.684	82.01	4.4		9.5
8b[b]	β_{syn}	0.16	1.7	5.484	87.29	2.2		8.9
8c[b]	α_{anti}	0.15	1.5	5.734	82.29	3.1		9.6
8d[b]	β_{syn}	0.17	1.7	5.400	87.47	2.2		8.5
9a	α	0.21	1.3	5.765	82.01	3.8	0.5	9.0
9a[b]	α	0.17		5.598		3.8		9.5
9b	β	0.21	1.6	5.697	87.29	2.0	2.1	8.9
9b[b]	β	0.15		5.40		2.0		

a. Separation of isopropylidene methyl groups. *b*. In DMSO.

chemical shifts of 5.67 and 5.62 ppm respectively.[7] The α- and β-anomers of compound **14** are reported[8] to have the anomeric protons at 5.4 and 5.7 ppm respectively, but that may be a wrong assignment. In imidazole nucleosides of D-ribofuranose[9,10] the anomeric proton is found in the range 5.80 - 6.12 ppm in the α-form and 5.60 - 5.83 ppm in the β-form. We find (Table 3) that the α-anomeric proton generally has a more downfield chemical shift in the series **2** - **9** but it is clear that this criterion must be used with caution.



13



14

There are no comparative carbon data for anomers of *N*-acylribofuranosylamines but for **1** and several related *N*-alkyl derivatives Δ(C-1) is in the range 86.9 - 91.2 ppm for

α-anomers and 91.7 -97.1 ppm for β-anomers.[6] This downfield shift of C-1 in the β-anomer is confirmed by our data (Table 3) and is probably a general feature of all ribofuranosyl glycosides. Overlap in the range of the C-1 chemical shift in α- and β-anomers might be a problem if only one anomer is available but otherwise the downfield shift of *ca.* 5 ppm is a good diagnostic for the β-configuration.

Coupling constants for protons in the ribofuranose ring can be related to the anomeric configuration in nucleosides and nucleotides. The coupling $J_{1,2}$ can be less than 1 Hz in the β-anomer (if the torsion angle H-1,C-1,C-2,H-2 is ca. 90°) but is never less than 3 Hz in the α-anomer. Although the conformational mobility of the furanose ring is severely reduced by the 2,3-*O*-isopropylidene group there is still sufficient pseudorotational freedom to give rise to overlap in the ranges of $J_{1,2}$ for the two anomers. In β-nucleosides such as derivatives of adenine[2] $J_{1,2}$ can be as high as 5.2 Hz and in imidazole nucleosides this coupling is larger in the β-anomer (3.5 Hz) than in the α-anomer (3.2 Hz).[9] Thus whilst $J_{1,2}$ is potentially a good diagnostic of anomeric configuration it must be regarded with considerable caution especially if only one anomer is available. The data in Table 3 show that the *N*-acylribofuranosylamines have consistently larger values of $J_{1,2}$ for the α-anomers (mean 3.9 Hz) compared to the β-anomers (mean 1.8 Hz). The symmetry of the furanose ring should impose a trend in $J_{3,4}$ which is opposite to that observed in $J_{1,2}$. This coupling is usually more difficult to measure but the partial data in Table 3 confirm that a reversed trend is observed in most cases although $J_{3,4}$ has very limited value for configurational assignment.

The final two parameters which could be of diagnostic value in the particular case of the *N*-substituted ribofuranosylamines are the chemical shift δ(NH) and the coupling constant $J_{1,NH}$. The existence of intramolecular hydrogen bonding in some compounds obscures any relationship of δ(NH) to configuration and this parameter was disregarded. In contrast there does appear to be a consistent difference in $J_{1,NH}$ between the α- and β-anomers (Table 3). The α-anomers of series **2** - **9** are likely to populate largely the *ac* conformation with the NH bond over the *exo* face of the ribose ring. Unfavourable interaction of O-2 with either the NH or the carbonyl group will minimise the populations of the *ap* and *sc* conformers. The observed values of $J_{1,NH}$ are close to the value of 9.4 Hz calculated from equation (1). Greater conformational freedom is possible for the C-1 substituent in the β-anomers and inspection of models suggests that both *ac* and *sc* conformations at least, will contribute. Thus the coupling is smaller and variable (Table 3), and may be used to support the assignment of anomeric configuration.

The seven parameters listed in table 3 have been applied as a set of diagnostic criteria to the series **2** - **9**.

Treatment of 2,3-*O*-isopropylidene-D-ribofuranosylamine with acetyl chloride and triethylamine in chloroform affords a mixture of the *O,N*-diacetyl anomers **2**. These anomers were separated by column chromatography to give a fast running species **2a** and a slow running species **2b** which were assigned the α and β configurations, respectively, on the basis of the full set of criteria in Table 3. Extensive NOE measurements were also made on **2a** and **2b**. For the putative α-anomer irradiation of H-1 produced the largest enhancement at the H-2,H-3 multiplet and smaller and nearly equal effects at H-4, H-5, and H-5'. The $NHCOCH_3$ group was identified by a 5% enhancement relative to the $OCOCH_3$ group. For the ring protons the largest effect of irradiation at NH occured at H-4 and the *endo* isopropylidene methyl group had a small enhancement (0.5%) relative to the *exo* methyl group. Enhancements deriving from the irradiation of H-4 were ambiguous since the H-5,H-5' multiplet was also perturbed. The *exo* methyl group produces the largest NOE at the H-2,H-3 multiplet and smaller, similar effects at H-1, H-4,and NH sites. In contrast the *endo* methyl group has equal effects at NH and H-4 and much smaller enhancements at the H-2, H-3 multiplet. These results convincingly confirm that **2a** is the α-anomer.

A NOE investigation of **2b** was less effective principally because H-4 and H-5 have very similar chemical shifts. Irradiation of NH produces an enhancement at H-4, H-5 which is twice as large as that at H-3 and almost the same result is found for irradation of H-1. If we assume that the H-4, H-5 enhancement is largely attributable to H-5 in the first case and to H-4 in the second case then the β-configuration is confirmed.

The substituent at C-5 in the α-anomer shows the usual preference for the ϕ_+ form (41%) over the ϕ_a (34%) and ϕ_- (25%) forms, but in the β-anomer the ϕ_- form (57%) predominates over the ϕ_+ (16%) and ϕ_a (27%) forms, the result of the steric interaction between the *O*- and *N*-acetyl groups. The coupling $J_{1,NH}$ indicates an *ac* conformation for the C-1 substituent in the α-anomer as expected but this substituent in the β-anomer evidently exists in several conformations.

Klemer and Kohla[1] have reported the synthesis of the analog of **2a** without the *O*-protecting groups and of related *N*-acyl compounds (acyl = $COCH{=}CH_2$, $CO(CH_2)_3Cl$, $CO(CH_2)_2CN$, and $COCH_2CO_2Me$. In all cases the synthetic procedure could only give the α-anomer and the data for $J_{1,2}$ (4.0 - 4.5 Hz) and $J_{1,NH}$ (9.3 - 9.6 Hz) fit well with the criteria discussed above.

The trifluoracetyl derivative **3** was examined as the anomeric mixture obtained from the acylation reaction. The major component (78%) was assigned the β-configuration on the basis of δ(C-1) and $J_{1,2}$. This was the only compound where the $J_{1,2}$ was small enough to be an unequivocal diagnostic for the β-configuration. Those parameters which were measurable

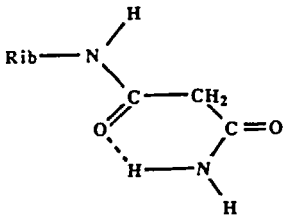
for the α-anomer (Table 3) illustrate strikingly the advantage of using a set of criteria. Only δ(C-1) and $J_{1,2}$ suggest an α-configuration, the other parameters giving ambiguous or contrary indications. The α-anomer has a predominance of the ϕ_+ form (65%) relative to the ϕ_a (21%) and ϕ_- (14%) forms of the C-5 group. The corresponding populations in the β-anomer are 42%, 32% and 26% suggesting a minimal interaction between the N-acyl and C-5 groups. This is confirmed by the value of $J_{1,NH}$ which indicates that only the *ac* conformation is populated in both anomers.

Benzoylation of **1** with excess benzoyl chloride gave the *N,O*-disubsituted derivative **4** as a single anomer, assigned the β configuration on the basis of δ(C-1) and the three coupling constants (Table 3). The CH_2OCH_2Ph group is mainly in the ϕ_- conformation (56%) with the other forms approximately equally populated. A very low value for $J_{1,NH}$ indicates a significant involvement of the *ap* conformation for the *N*-benzoyl group.

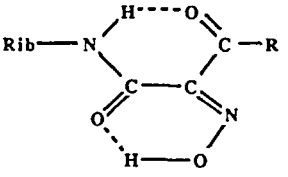
The ethylmalonyl derivative **5**, initially a complex mixture of species, was purified by reverse phase HPLC. Two fractions were obtained both α,β mixtures; the first fraction was predominantly the α-isomer (80%) and the second predominantly the β-anomer (77%). These configurations were determined from δ(H-1) and the three coupling constants. The α-anomer showed a normal preference for the ϕ_+ conformation (42%) over the ϕ_a (31%) and ϕ_- (27%) conformations at C-5 but the β-anomer had a much stronger bias to the ϕ_+ form (74%), possibly due to intramolecular hydrogen bonding of the 5-OH group with the C-1 substituent. In both anomers $J_{1,NH}$ indicates only a slight involvement of the *ap* or *sc* conformers.

The derivative **6** was formed as a single anomer. Although δ(H-1) and δ(C-1) suggested an α-configuration the diagnostic couplings were inaccessible due to virtual coincidence of protons H-2 and H-3 in $CDCl_3$ solution. However in DMSO the spectra gave values of $J_{1,2}$ and $J_{3,4}$ which confirm the assignment. It is notable that the NH_2 protons have widely separated chemical shifts ($\Delta\delta$ = 1.15 ppm) in $CDCl_3$, as would be expected for a hydrogen-bonded structure **15**, but in DMSO $\Delta\delta$ is only 0.45 ppm since hydrogen bonding to the solvent predominates. The blocking group on O-5 is large (Me_3CCO) but as expected the conformer distribution at C-5 shows the usual predominance of the ϕ_+ form (54%) relative to the ϕ_a (25%) and ϕ_- (21%) forms, typical of α-anomers. Furthermore, the acyl group is almost entirely in the *ac* conformation as indicate by the value of $J_{1,NH}$.

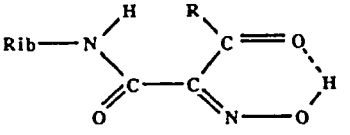
Oximation of the ester **5** and the amide **6** gave the corresponding oximes **7** and **8**. The oxime ester was purified by HPLC to give a sample containing three isomeric species as indicated by the severely overlapping NMR spectrum. The two major components **7a** (46%) and **7b** (32%) were assigned the α-configuration on the basis of $J_{1,2}$ whereas the third species **7c** is a β-anomer on the same basis. All three species have similar conformations at C-1 with



15



16



17

the *ac* conformer predominating. *Syn* and *anti* isomerism of the oxime hydroxyl group (defined with respect to the ribose ring) will result in four isomers in total and **7b** and **7c** are assigned the *syn* configuration **16** (R = OEt). This form has two strong hydrogen intramolecular bonds (the most stable of the possible conformations) and would experience a downfield shift for the NH proton (Table 1). Isomer **7a** has *anti* geometry **17** (R = OEt) as judged by the normal chemical shift for the NH proton in the absence of an intramolecular hydrogen bond.

The amide oxime **8** was a mixture of two pairs of α/β-anomers. Initially the proportion of these isomers was **8a** (24%), **8b** (31%), **8c** (23%), and **8d** (4%) (from the proton spectrum) but after several weeks some isomerisation had occurred to give proportions 50%, 17%, 19%, and 14% respectively. Assignment of the α configuration to **8a** and **8c** and the β configuration to **8b** and **8d** was supported by all available criteria ($J_{3,4}$ was inaccessible). These amides had to be examined in DMSO and thus the *syn* isomers **8c** and **8d** were not characterised by such lowfield chemical shifts for NH as found in the corresponding ester and the assignment of the oxime configuration is tentative. Exchange processes in these compounds is complex and one reflection of this is the observation that the NH proton in **8c** has a line width of 5 Hz at 20 °C compared to 2 Hz for the other species. Virtually only the *ac* form is populated by the C-1 substituent in the α-anomers but the β-anomers have up to 20% of *ap* or *sc* forms.

Reduction of the mixture of isomers of the oxime amide gave the corresponding aminoamide **9**. The crude product was purified by HPLC to give a fast running α-anomer **9a** and a slow running β-anomer **9b**. These configurations were assigned on the basis of δ(H-1) and δ(C-1) and the coupling $J_{1,2}$. Both anomers showed a doubling of some peaks in both ^1H and ^{13}C spectra in both $CDCl_3$ and DMSO solutions due to the existence of two diastereoisomers of each compound arising from the presence of a new chiral centre in the C-1 substituent. In the β-anomer nearly all the ribose ring protons were distinguishable in the diastereoisomers. The population distribution at C-5 was ϕ_+ (57%), ϕ_a (23%), and

ϕ_- (20%) in both diastereoisomers suggesting little interaction between C-1 and C-5 substituents. This is confirmed by $J_{1,NH}$ which indicates mainly an *ac* conformation for the *N*-acyl group with a structure of type **15** to account for the large difference in the NH_2 proton chemical shifts.

EXPERIMENTAL

Details of the synthetic methods for the *N*-acyl-D-ribofuranosylamines and the chromatographic procedures for their purification will be given elsewhere. The ^1H and ^{13}C spectra were obtained on a JEOL GX270 spectrometer using standard conditions with a data point resolution of 0.1 Hz. Where necessary chemical shift assignments were confirmed by decoupling and in the case of **2a** and **2b** the carbon assignments were confirmed by correlation with the proton spectrum. In all other cases carbon assignments were made by analogy with **2a** and **2b**.

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