CONFORMATIONAL STUDIES ON PYRANOID SUGAR DERIVATIVES BY N.M.R. SPECTROSCOPY. CONFORMATIONAL EQUILIBRIA OF THE PERACETYLATED AND SOME PERBENZOYLATED METHYL D-ALDOPENTOPYRANOSIDES IN SOLUTION*†

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ABSTRACT

The method of averaging of spin-coupling was used to determine by n.m.r. spectroscopy the conformational populations of the eight methyl D-aldopentopyranoside triacetates and the corresponding tribenzoates having the β-D-*ribo*, β-D-*arabino*, α-D-*xylo*, β-D-*xylo*, and α-D-*lyxo* configurations. The α-D-*xylo* derivatives adopt the *C1*(D) conformation almost exclusively, and the β-D-*arabino* derivatives favor the *1C*(D) conformation very strongly; in solution, the other examples have substantial proportions of both chair conformers. The axial-directing effect of the methoxyl group at C-1 is greater than that of the acetoxy or benzoyloxy group, except when the axial 1-substituent would be *syn*-axial to the 3-substituent. The axial-directing effect of the methoxyl group at C-1 is enhanced by replacing acetoxy groups at C-2, 3, and 4 by benzoyloxy groups. The axial-directing effect of a 1-substituent is discussed in terms of polar and steric contributions. For methyl 2,3,4-tri-*O*-benzoyl-β-D-xylopyranoside, the proportion of the all-axial chair conformer was found to decrease with increasing polarity of the solvent; this behavior contrasts with that observed with some aldopentopyranose tetraacetates and tri-*O*-acetyl-β-D-xylopyranosyl chloride, for which the polarity of the solvent has little effect on conformational populations.

INTRODUCTION

As part of a general study of favored conformations and conformational populations for pyranoid sugar derivatives in solution, it has been of interest to evaluate the influence of the aglycon in determining conformational tendencies of multisubstituted tetrahydropyran ring-systems. The results of investigations on the axial-directing effect of the bromo[4], chloro[4], acetoxy[1,3], and benzoyloxy[1,3] substituents have already been reported. The present study of the axial-directing influence of an

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anomeric methoxyl group describes measurement of the conformational equilibria of the eight peracetylated methyl D-aldopentopyranosides (**1–8**) and five perbenzoylated methyl D-aldopentopyranosides (**9–13**) in solution. The eight peracetylated methyl D-aldopentopyranosides constitute all of the different stereochemical arrangements possible for a 3,4,5-triacetoxy-2-methoxytetrahydropyran, as the L-enantiomorphs would give identical equilibrium data.

METHODS AND MATERIALS

The methyl tri-*O*-acetyl-D-aldopentopyranosides having the α-*ribo* (**1**), β-*ribo* (**2**), β-*arabino* (**4**), α-*xylo* (**5**), α-*lyxo* (**7**), and β-*lyxo* (**8**) configurations were prepared by acetylating the corresponding methyl aldopentopyranosides with acetic anhydride in the presence of pyridine or sodium acetate. The methyl tri-*O*-acetyl-D-aldopentopyranosides having the α-*arabino* (**3**) and β-*xylo* (**6**) configurations were prepared by stirring, for several hours in the dark, a methanolic solution of the appropriate, thermodynamically "stable" tri-*O*-acetyl-D-aldopentopyranosyl bromide with fresh silver carbonate and "anhydrous" calcium sulfate (Koenigs–Knorr method[6]). The α-D-*ribo* (**1**) and β-D-*ribo* (**2**) derivatives are reported anomerically pure for the first time. The melting point of the β-D-*arabino* derivative (**4**), which gave a satisfactory elemental analysis, was about 10° lower than the value reported[7] for the L-enantiomorph; however, the numerical values of the specific rotations were in good agreement. The other methyl peracetylated aldopentopyranosides gave physical constants in good agreement with the literature values (see Experimental section).

The methyl tri-*O*-benzoyl-D-aldopentopyranosides having the β-*arabino* (**10**), α-*xylo* (**11**), β-*xylo* (**12**), and α-*lyxo* (**13**) configurations were prepared by benzoylating the corresponding methyl aldopentopyranosides with benzoyl chloride and pyridine. Methyl tri-*O*-benzoyl-β-D-ribopyranoside (**9**) was prepared according to the procedure of Jeanloz *et al.*[8]. The β-D-*ribo* (**9**), β-D-*arabino* (**10**), and β-D-*xylo* (**12**) derivatives had physical constants in good agreement with the literature values. The α-D-*xylo* (**11**) and α-D-*lyxo* (**13**) derivatives are reported for the first time.

Unless otherwise indicated, the n.m.r. spectra were measured at 100 MHz on 20% (w/v) solutions of the freshly prepared compounds in the appropriate, deuterated solvent containing 5% of tetramethylsilane. The chemical shifts recorded, given on the τ scale, were obtained by analysis of the spectra on a first-order basis, and are considered accurate to within ±0.005 p.p.m. The time-averaged, $J_{4,5}$ and $J_{4,5'}$ spin-couplings employed in the calculation of conformational populations were obtained by ABX analysis[9] of spectra measured at 100-Hz sweep-width; they are considered accurate to within ±0.1 Hz. All other coupling-constants recorded were obtained on a first-order basis as direct peak-spacings, from spectra measured at a sweep-width of 100 Hz, and are considered precise to within ±0.1 Hz. Spectral data for the thirteen compounds are tabulated in Tables I–VI. Partial n.m.r. spectra for compounds **1**, **7**, **12**, and **13** are given in Figs. 1–4, respectively.

For each of the methyl tri-*O*-acetyl-D-aldopentopyranosides (**1–8**) and methyl tri-*O*-benzoyl-D-aldopentopyranosides (**9–13**) in acetone-d_6 at 31°, the n.m.r. spectral

TABLE I

FIRST-ORDER CHEMICAL-SHIFTS[a] OF THE PERACETYLATED METHYL ALDOPENTOPYRANOSIDES IN ACETONE-d_6 AT 31°

Compound	*Configuration*	*Chemical shifts*[b] *(τ)*							
		H-1	*H-2*	*H-3*	*H-4*	[c]*H-5*	[c]*H-5′*	*OMe*	*Acetyl methyl*
1	α-D-*ribo*	5.29d	4.97t	4.58t	5.00m	6.05q	6.38o	6.61	7.99[d], 8.00
2	β-D-*ribo*	5.31d	5.09sx	4.67t	4.94m	6.03q	6.28q	6.63	7.98[d], 8.03
3	α-D-*arabino*[e]	5.66d	4.91q	4.97q	4.76o	5.97q	6.37q	6.52	7.88, 7.94, 7.99
4	β-D-*arabino*	5.09d	4.93o	4.70q	4.73m	6.03q	6.37q	6.63	7.91, 7.99, 8.06
5	α-D-*xylo*	5.13d	5.21q	4.58t	5.08m	6.23q	6.47t	6.63	8.00, 8.02[d]
6	β-D-*xylo*	5.49d	5.17q	4.83t	5.12sx	5.94q	6.54q	6.59	8.01[d], 8.04
7	α-D-*lyxo*[f]	5.31d	4.84q	4.78q	4.90sx	6.15q	6.42q	6.59	7.89, 7.97, 8.02
8	β-D-*lyxo*	5.29d	4.71q	4.92q	5.03o	5.91q	6.57o	6.60	7.95, 7.97, 8.03

[a]Data from spectra measured at 100 MHz. [b]Observed multiplicities: d, doublet; m, complex multiplet; o, octet; q, quartet; sx, sextet; t, triplet. [c]The proton on C-5 giving the higher field signal is designated H-5′. [d]6-Proton singlet. [e]In chloroform-*d*. [f]Measured at 220 MHz at 23°.

TABLE II

COUPLING CONSTANTS OF METHINE AND METHYLENE PROTONS FOR PERACETYLATED METHYL ALDOPENTOPYRANOSIDES IN ACETONE-d_6 AT 31°

Compound	*Configuration*	*Coupling constants*[a] *(Hz)*					
		$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	[b,c]$J_{4,5}$	[b,c]$J_{4,5'}$	$J_{5,5'}$
1	α-D-*ribo*[d]	3.3	3.4	3.3	7.7	3.9	−11.6
2	β-D-*ribo*[e]	4.0	3.6	3.4	3.0	5.2	−12.5
3	α-D-*arabino*[f]	6.1	9.0	3.7	3.1	1.7	−13.1
4	β-D-*arabino*	3.2	11.7	3.3	1.3	1.8	−13.2
5	α-D-*xylo*	3.5	9.3	9.2	5.7	11.1	−10.9
6	β-D-*xylo*	7.2	8.6	8.6	5.0	9.3	−11.7
7	α-D-*lyxo*-[g]	2.2	3.4	9.7	5.1	9.5	−11.0
8	β-D-*lyxo*-[h]	2.2	3.2	7.9	3.8	7.1	−12.0

[a]Data taken from spectra measured at 100 MHz at a sweep width of 100 Hz. [b]Coupling constants calculated by ABX analysis. [c]The proton on C-5 giving the higher field signal is designated H-5′. [d]$J_{3,5} = 0.6$ Hz. [e]$J_{2,4} = 0.8$ Hz. [f]In chloroform-*d*. [g]Measured at 220 MHz at 23°. [h]$J_{3,5} = 0.6$ Hz.

TABLE III

FIRST-ORDER CHEMICAL-SHIFTS[a] OF THE PERBENZOYLATED METHYL ALDOPENTOPYRANOSIDES IN ACETONE-d_6 AT 31°

Compound	*Configuration*	*Chemical shifts*[b] *(τ)*							
		H-1	*H-2*	*H-3*	*H-4*	[c]*H-5*	[c]*H-5′*	*OMe*	*Benzoyl*
9	β-D-*ribo*	4.92d	4.50sp	4.16t	4.36m	5.66q	5.89q	6.50	1.94–2.76
10	β-D-*arabino*	4.71d	4.24q	4.01q	4.15m	5.70q	5.99q	6.51	1.81–2.80
11	α-D-*xylo*	4.77d	4.62q	3.84t	4.49m	5.86q	6.10t	6.52	1.77–2.76
12	β-D-*xylo*	5.07d	4.58q	4.11t	4.56sx	5.55q	6.13q	6.49	1.99–2.72
13	α-D-*lyxo*[d]	4.96d	4.28q	4.10q	4.20sx	5.78q	6.02q	6.46	1.79–2.69

[a]Data taken from spectra measured at 100 MHz. [b]Observed multiplicities: d, doublet; m, complex multiplet; q, quartet; sp, septet; sx, sextet; t, triplet. [c]The proton on C-5 giving the higher field signal is designated H-5′. [d]Measured at 220 MHz at 23°.

TABLE IV

COUPLING CONSTANTS OF METHINE AND METHYLENE PROTONS FOR PERBENZOYLATED METHYL ALDOPENTOPYRANOSIDES IN ACETONE-d_6 AT 31°

Compound	*Configuration*	*Coupling constants*[a] *(Hz)*					
		$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	[b,c]$J_{4,5}$	[b,c]$J_{4,5'}$	$J_{5,5'}$
9	*β*-D-*ribo*[d]	2.8	3.8	3.7	2.4	3.4	−12.9
10	*β*-D-*arabino*	3.3	10.5	3.3	1.1	2.0	−13.3
11	*α*-D-*xylo*	3.4	9.8	9.8	5.8	11.1	−10.9
12	*β*-D-*xylo*	6.5	8.2	8.4	4.8	8.6	−11.9
13	*α*-D-*lyxo*[e]	2.0	3.2	9.5	5.1	9.8	−10.9

[a]Data taken from spectra measured at 100 MHz at a sweep width of 100 Hz. [b]Coupling constants calculated by ABX analysis. [c]The proton on C-5 giving the higher field signal is designated H-5′. [d]$J_{2,4} = 0.8$ Hz. [e]Measured at 220 MHz at 23°.

TABLE V

SOLVENT-DEPENDENCE OF THE CONFORMATIONAL EQUILIBRIUM FOR METHYL TRI-*O*-BENZOYL-*β*-D-XYLOPYRANOSIDE (**12**) AT 31°

Solvent	*ε*[b]	*Coupling constants*[a] *(Hz)*					
		$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	[c,d]$J_{4,5}$	[c,d]$J_{4,5'}$	$J_{5,5'}$
C_6D_6	2.3	5.7	7.6	7.6	4.6	7.8	−12.1
$C_6D_5CD_3$	2.4	5.7	7.6	7.6	4.6	7.8	−12.0
$CDCl_3$	4.8	5.6	7.2	7.4	4.3	7.4	−12.1
C_5D_5N	12.3	5.9	7.5	7.6	4.7	8.0	−12.0
$(CD_3)_2CO$	20.7	6.5	8.2	8.4	4.8	8.6	−11.9
$(CD_3)_2SO$	48.9	6.8	8.2	8.4	4.9	9.3	−11.6

[a]Data taken from spectra measured at 100 MHz at a sweep width of 100 Hz. [b]Values taken from A. A. MARYOTT AND E. R. SMITH, *Table of Dielectric Constants of Pure Liquids, National Bureau of Standards Circular 514*, U. S. Government Printing Office, Washington, D. C., 1951. [c]Coupling constants calculated by ABX analysis. [d]The proton on C-5 giving the higher field signal is designated H-5′.

TABLE VI

SOLVENT-DEPENDENCE OF FIRST-ORDER CHEMICAL-SHIFTS FOR METHYL TRI-*O*-BENZOYL-*β*-D-XYLOPYRANOSIDE (**12**)[a]

Solvent	*Chemical shifts*[b] *(τ)*							
	H-1	*H-2*	*H-3*	*H-4*	[c]*H-5*	[c]*H-5′*	*OMe*	*Benzoyl*
C_6D_6	5.47d	4.29q	3.97t	4.58sx	5.74q	6.60q	6.79	1.84–3.20
$C_6D_5CD_3$	5.50d	4.38q	4.06t	4.66sx	5.75q	6.61q	6.75	1.90–3.19
$CDCl_3$	5.26d	4.60q	4.20t	4.67sx	5.56q	6.29q	6.47	1.94–2.78
C_5D_5N	5.02d	4.23q	3.84t	4.37sx	5.48q	6.11q	6.54	1.87–2.90
$(CD_3)_2CO$	5.07d	4.58q	4.11t	4.56sx	5.55q	6.13q	6.49	1.99–2.72
$(CD_3)_2SO$	5.01d	4.61q	4.08t	4.58m	5.62q	6.10q	6.50	2.00–2.66

[a]Data taken from spectra measured at 100 MHz. [b]Observed multiplicities: d, doublet; m, complex multiplet; q, quartet; sx, sextet; t, triplet. [c]The proton on C-5 giving the higher field signal is designated H-5′.

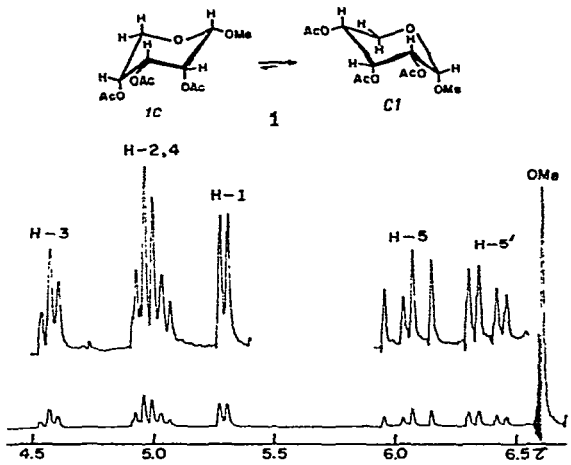


Fig. 1. Partial n.m.r. spectrum of methyl tri-*O*-acetyl-α-D-ribopyranoside (**1**) in acetone-d_6, at 100 MHz.

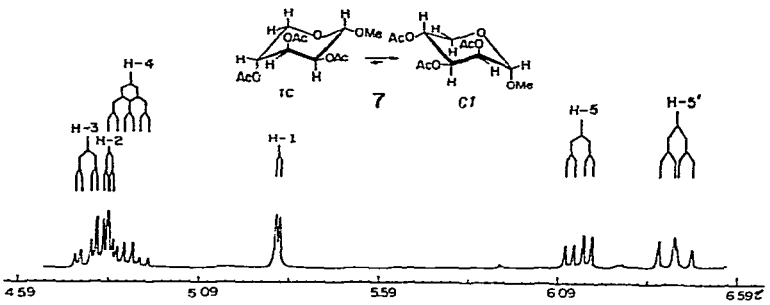


Fig. 2. Partial n.m.r. spectrum of methyl tri-*O*-acetyl-α-D-lyxopyranoside (**7**) in acetone-d_6, at 220 MHz.

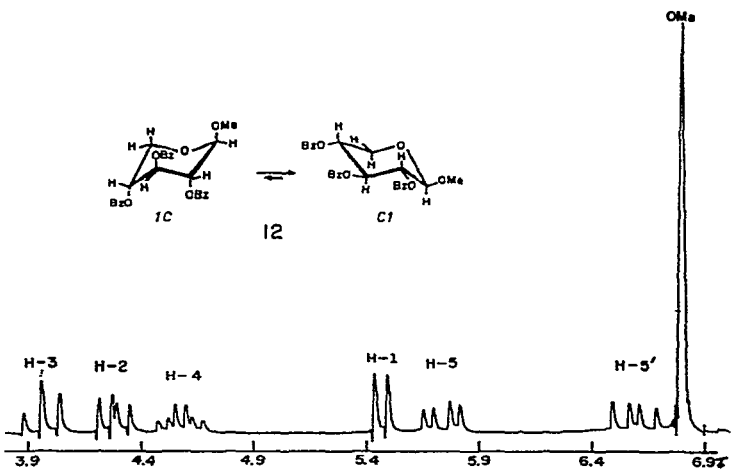


Fig. 3. Partial n.m.r. spectrum of methyl tri-*O*-benzoyl-β-D-xylopyranoside (**12**) in benzene-d_6, at 100 MHz.

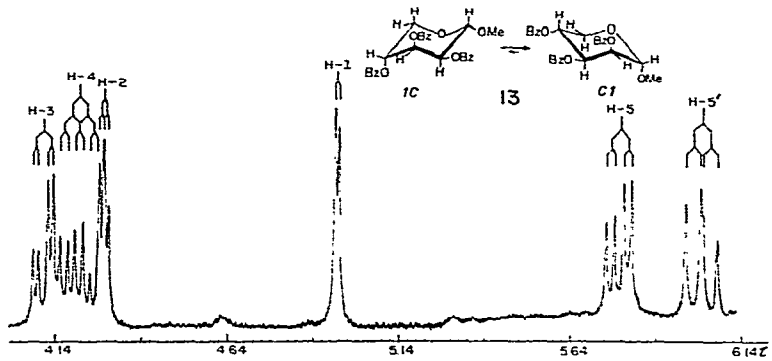


Fig. 4. Partial n.m.r. spectrum of methyl tri-*O*-benzoyl-α-D-lyxopyranoside (**13**) in acetone-d_6, at 220 MHz.

method of averaging of spin coupling[10] was used, by procedures already detailed[11], to determine the proportions of the *1C*(D) and *C1*(D) conformers present at equilibrium. Chloroform-*d* was used as the solvent for compound **3**, in order to provide an easily interpreted spectrum.

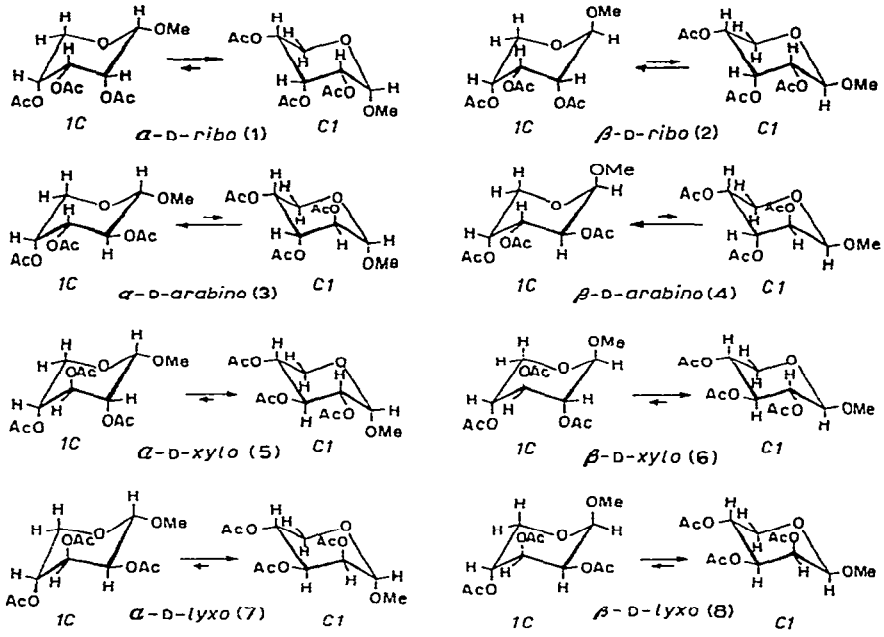
Analysis of the signals of H-4 and the two protons at C-5 as ABX spin-systems[9] gave $J_{4,5}$ and $J_{4,5'}$ values for the peracetylated and perbenzoylated methyl aldopentopyranosides that are weighted time-averages for the two chair conformers in rapid equilibrium. Conformational populations at 31° were determined from the observed coupling of H-4 with the *trans*-disposed proton at C-5, taken in conjunction with values for $J_{4e,5e}$ and $J_{4a,5a}$ that had been obtained from model compounds. The model compounds chosen for $J_{4a,5a}$ were methyl tri-*O*-acetyl-α-D-xylopyranoside (**5**) and methyl tri-*O*-benzoyl-α-D-xylopyranoside (**11**). The vicinal spin-couplings for these two derivatives remained unchanged as the temperature was lowered to −50°, and

TABLE VII

CONFORMATIONAL EQUILIBRIA OF PERACETYLATED METHYL ALDOPENTOPYRANOSIDES IN ACETONE-d_6 AT 31°

Compound	*Configuration*	*Equilibrium data*			$\Delta G°_{31}$ (*kcal.mole*$^{-1}$) *for* 1C(D)⇌C1(D)
		% C1	% 1C	K = C1/1C	
1	α-D-*ribo*	65	35	1.8	−0.36 ±0.29
2	β-D-*ribo*	39	61	0.63	+0.28 ±0.28
3	α-D-*arabino*[a]	17	83	0.20	+0.98 ±0.40
4	β-D-*arabino*	3	97	0.03	+2.1 ±1.1
5	α-D-*xylo*	>98	<2	>50[b]	<−2.4
6	β-D-*xylo*	81	19	4.3	−0.89 ±0.37
7	α-D-*lyxo*[c]	83	17	5.0	−0.95 ±0.39
8	β-D-*lyxo*	58	42	1.4	−0.20 ±0.28

[a]In chloroform-*d*. [b]Almost exclusively *C1*(D) at 31°. [c]Determined at 220 MHz at 23°.



Scheme 1

TABLE VIII

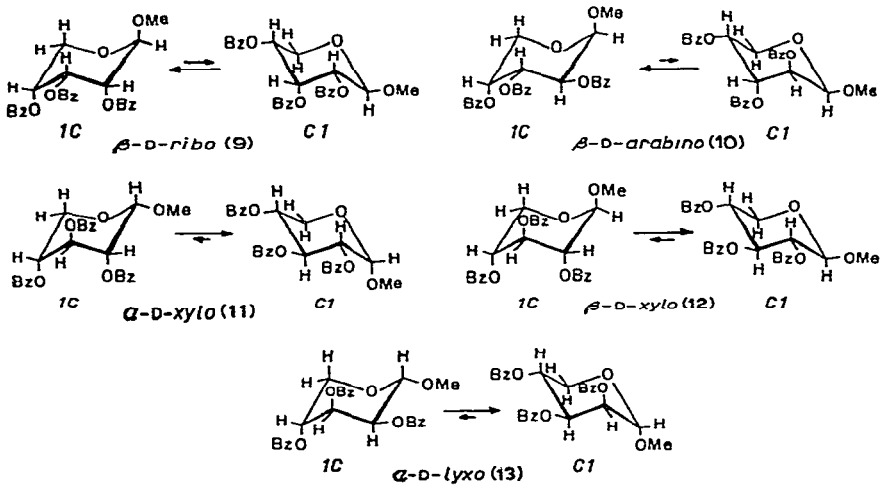
CONFORMATIONAL EQUILIBRIA OF PERBENZOYLATED METHYL ALDOPENTOPYRANOSIDES IN ACETONE-d_6 AT 31°

Compound	*Configuration*	*Equilibrium data*			$\Delta G°_{31}$ (*kcal.mole*$^{-1}$) *for* 1C(D)⇄C1(D)
		% C1	%1C	K = C1/1C	
9	β-D-*ribo*	20	80	0.25	+0.85 ±0.36
10	β-D-*arabino*	5	95	0.05	+1.8 ±0.9
11	α-D-*xylo*	>98	<2	>50[a]	<−2.4
12	β-D-*xylo*	74	26	2.8	−0.63 ±0.32
13	α-D-*lyxo*[b]	86	14	6.4	−1.10 ±0.44

[a]Almost exclusively *C1*(D) at 31°. [b]Determined at 220 MHz at 23°.

it was thus concluded that both **5** and **11** are essentially all in the *C1*(D) conformation at 31°. Accordingly, the $J_{4,5a}$ value of 11.1 Hz measured for both **5** and **11** was taken as the magnitude of $J_{4a,5a}$ for each peracetylated and perbenzoylated methyl aldopentopyranoside. The model compounds chosen for $J_{4e,5e}$ were methyl tri-*O*-acetyl-β-D-arabinopyranoside (**4**) and methyl tri-*O*-benzoyl-β-D-arabinopyranoside (**10**). The $J_{4,5'}$ values for both compounds decreased to a limit of 1.5 Hz at low temperatures, and this value was used throughout as the magnitude of $J_{4e,5e}$ for each peracetylated and perbenzoylated methyl aldopentopyranoside. From the conformational populations determined from the spin-coupling data, the equilibrium constants (*K*) and

free-energy differences ($\Delta G°$) for the *1C*(D)⇄*C1*(D) equilibria given in Tables VII and VIII were calculated. The limits of accuracy for the calculations were determined from the uncertainty of ±0.1 Hz in the experimental values of the time-averaged couplings, in conjunction with a conservative estimate (±0.5 Hz) of the extent to which the "model" coupling-values actually differ from the true couplings for the separate conformers of each compound. The positions of the conformational equilibria are illustrated qualitatively in Schemes 1 and 2.



Scheme 2

RESULTS AND DISCUSSION

Effect of configuration and substitution on the relative axial-directing influence of the acetoxy, benzoyloxy, and methoxyl groups. — From an inspection of the conformational equilibrium data for the peracetylated and perbenzoylated methyl D-aldopentopyranosides given in Tables VII and VIII, the data for the D-aldopentopyranose tetraacetates and tetrabenzoates[3], and those for the 1,2-*trans* 2,3,4-tri-*O*-acetylaldopentopyranosyl benzoates and 2,3,4-tri-*O*-benzoylaldopentopyranosyl acetates[1], it may be seen that the strength of the axial-directing influence of the C-1 methoxyl group, as compared with that of the acetoxy and benzoyloxy groups, depends on whether or not the axial C-1 substituent has a *syn*-axial group at C-3. If such a *syn*-diaxial arrangement is absent, the axial-directing influence of the methoxyl group is stronger than that of the acetoxy or benzoyloxy group. Thus, in the β-D-*ribo* and α-D-*lyxo* series, where the C-1 substituent does not have a *syn*-axial group at C-3, the peracetylated methyl aldopentopyranosides have a greater equilibrium proportion of that chair conformer having the anomeric substituent axial than do the corresponding tetraacetates or 2,3,4-tri-*O*-acetylaldopentopyranosyl benzoates. For example, the *C1*(D) conformer is present to the extent of 83% at equilibrium for methyl tri-*O*-acetyl-α-D-lyxopyranoside (7) (anomeric substituent axial) and 71% for

α-D-lyxopyranose tetraacetate. The difference in the conformational populations for the tetraacetate and the peracetylated methyl aldopentopyranoside depends on the stereochemistry at the other three positions of the pyranoid ring-system. Thus, the change in the free-energy differences is ~0.1 kcal.mole^{-1} for the β-D-*ribo* derivatives and ~0.4 kcal.mole^{-1} for the α-D-*lyxo* derivatives.

On the other hand, if the C-1 substituent does have a *syn*-axial group at C-3, the axial-directing influence of the methoxyl group is weaker than that of the acetoxy and benzoyloxy groups. Thus, in the α-D-*ribo*, α-D-*arabino*, β-D-*xylo*, and β-D-*lyxo* series, where the C-1 substituent is *syn*-diaxial to an acetoxy group at C-3, the equilibrium proportion of that chair conformer having the anomeric substituent axial is less for the peracetylated methyl aldopentopyranosides than for the analogous tetraacetates or 2,3,4-tri-*O*-acetylaldopentopyranosyl benzoates. For example, the *1C*(D) conformer (C-1 and C-3 substituents axial) is present only to the extent of 42% for methyl tri-*O*-acetyl-β-D-lyxopyranoside (**8**), whereas 61% of the *1C*(D) conformer is present in the solution of β-D-lyxopyranose tetraacetate. The shifts in the positions of the conformational equilibria are, again, a function of the total stereochemistry of the sugar; the change in the free-energy differences for the peracetylated methyl aldopentopyranoside and the corresponding tetraacetate is ~0.4 kcal.mole^{-1} in the α-D-*ribo* series, ~0.2 kcal.mole^{-1} in the α-D-*arabino* series, ~0.3 kcal.mole^{-1} in the β-D-*xylo* series, and ~0.5 kcal.mole^{-1} in the β-D-*lyxo* series; these changes are all in the direction opposite from that observed when an axial methoxyl group at C-1 is not *syn*-diaxial to the 3-substituent.

Since the axial-directing effect of the benzoyloxy group was found to be stronger than that of the acetoxy group for those configurations that have a *syn*-diaxial relationship between the C-1 and C-3 substituents[1], the difference in the axial-directing influence between the methoxyl and benzoyloxy groups is larger than that between the methoxyl and acetoxy groups. Thus, the $\Delta\Delta G°$ value for methyl tri-*O*-acetyl-β-D-xylopyranoside (**6**) and β-D-xylopyranose tetraacetate is 0.3 kcal.mole^{-1} (the axial-directing effect of the acetoxy group exceeding that of the methoxyl group), whereas the $\Delta\Delta G°$ value between **6** and tri-*O*-acetyl-β-D-xylopyranosyl benzoate is larger (0.6 kcal.mole^{-1}). A similar effect is observed in the α-D-*arabino* series.

The five perbenzoylated methyl D-aldopentopyranosides investigated exhibit behavior similar to that of the peracetylated methyl D-aldopentopyranosides. The axial-directing influence of the methoxyl group is stronger than that of the acetoxy or benzoyloxy groups by ~0.1 kcal.mole^{-1} in the β-D-*ribo* series and by ~0.5 kcal.mole^{-1} in the α-D-*lyxo* series. In the β-D-*xylo* series (where an axial 1-substituent is *syn*-diaxial to the 3-substituent), the axial-directing influence of the methoxyl group is weaker than that of the acetoxy group by 0.55 kcal.mole^{-1}, and that of the benzoyloxy group, by 0.64 kcal.mole^{-1}.

As was observed for the benzoyloxy and acetoxy substituents at the anomeric position[1], the axial-directing influence of the methoxyl group depends on the nature of the substituents on O-2, O-3, and O-4. Changing the 2,3,4-substituents from acetates to benzoates results in an enhancement of the axial-directing influence of

the methoxyl group, with the exact amount being dependent on the total stereochemistry. The $\Delta\Delta G^\circ$ value is 0.57 kcal.mole^{-1} for the *β*-D-*ribo* configuration, 0.26 kcal.mole^{-1} for the *β*-D-*xylo* configuration, and 0.15 kcal.mole^{-1} for the *α*-D-*lyxo* configuration.

Factors determining the axial-directing influence of a polar C-1 substituent. — The net axial-directing influence of a polar C-1 substituent in a polysubstituted tetrahydropyran ring-system is the resultant of a polar and a steric contribution. The polar contribution, termed the anomeric effect[1,2], is positive, in the sense that axial orientation of the anomeric substituent is favored because of favorable dipolar interactions. The steric contribution can be considered as comprised of two factors, one positive and the other negative. The negative factor favors equatorial orientation of the C-1 substituent, because of the relief in non-bonded interactions between this substituent and the *gauche*-disposed ring atoms (C-3 and C-5) and any *syn*-axial substituent at C-3. The second (positive) factor only enters in when the substituents at C-1 and C-2 are in *trans*- arrangement[2]. With such an arrangement, the 1,2-di-equatorial conformer is destabilized by a non-bonded, gauche interaction between the substituents at C-1 and C-2. However, as the alternative, 1,2-diaxial conformer has considerably more steric destabilization because of gauche and *syn*-diaxial interactions, the resultant of the two steric factors is usually negative, and equatorial disposition of the C-1 group is still favored.

The net, axial-directing effect of a polar, C-1 substituent in a polysubstituted tetrahydropyran ring-system can, therefore, be defined as follows: (1) "axial effect" $= E_p + E_{s(g2)} - E_{s(syn)} - E_{s(g3)} - E_{s(g5)}$, where, for the axial 1-substituent, E_p is the polar term, and the E_s values are steric terms, $E_{s(g2)}$ denoting gauche interaction with the 2-substituent, $E_{s(syn)}$ the interaction with an axial 3-substituent, and $E_{s(g3)}$ and $E_{s(g5)}$ the gauche interactions with C-3 and C-5. When the substituents at C-3 and C-5 are hydrogen atoms, the equation reduces to (2) "axial effect" $= E_p - [E_{s(g3)} + E_{s(g5)}] + E_{s(g2)}$, where $[E_{s(g3)} + E_{s(g5)}]$ = the classical "A-value". Thus, "axial effect" = "anomeric effect" $+ E_{s(g2)}$, because the "anomeric effect" $= E_p - [E_{s(g3)} + + E_{s(g5)}]$. When the substituents at C-1 and C-2 are gauche in each chair conformer, the "axial effect" = "anomeric effect", assuming that the gauche interactions are the same in each conformer.

The magnitude of the polar term appears to be a function of the nature of the substituents at the other positions of the tetrahydropyran ring-system. It has been demonstrated that the axial-directing effect is enhanced by increasing the electronegativity of the substituents at these positions, with the exact amount being a function of the total stereochemistry[1–5].

The observation that the axial-directing influence of the methoxyl group is stronger than that of the acetoxy group in the aldopentopyranoid configurations that have the axial C-1 substituent gauche to C-3 and C-5 but not *syn*-diaxial to a 3-substituent can be partly explained from steric considerations, since the conformational free-energy ("A-value") of the methoxyl group is 0.16 kcal.mole^{-1} smaller than that of the acetoxy group[13]. Such a difference in the "A-values", and the close

similarity of the "A-values" for the acetoxy and benzoyloxy groups[14], could cause a greater proportion of that chair conformer having the C-1 substituent axial to be present in the solutions of the methyl tri-*O*-acyl-β-D-ribo- and α-D-lyxopyranosides than in the corresponding tetra-*O*-acylpentopyranoses.

Those aldopentopyranoid configurations in which the axial-directing influence of the methoxyl group is weaker than that of the acetoxy or benzoyloxy group have the axial C-1 substituent *syn*-diaxial to the acyloxy substituent at C-3, and gauche to C-3 and C-5. No simple relationship exists between the magnitude of the individual, conformational free-energies of two groups X and Y and the magnitude of the *syn*-diaxial interaction between them. Therefore, although the magnitude of the equatorial conformational tendency for the methoxyl group (from steric considerations) is smaller than that of the acetoxy group[13], it does not necessarily follow that the 1,3-interaction between the methoxyl and acetoxy groups is smaller than that between two acetoxy groups. In fact, from an n.m.r. spectroscopic study of the conformational equilibria of various methyl di-*O*-acyl-3-deoxy-β-L-*erythro*-pentopyranosides, Lemieux and Pavia[15] found that the 1,3-interaction between the methoxyl and acetoxy groups was larger than that between two acetoxy groups. The electrostatic repulsions between the C-2 and C-4 oxygen atoms were observed to be weaker when these oxygen atoms were linked to electron-withdrawing acyl groups than when they were linked to the electron-releasing methyl group. The greater proportion of the chair conformer having the C-1 and C-3 substituents axially disposed (observed in the present studies for the D-aldopentopyranose tetraacylates having the α-*ribo*, α-*arabino*-, β-*xylo*, and α-*lyxo* configurations) than for the corresponding methyl tri-*O*-acyl-D-aldopentopyranosides probably results in part from this difference in *syn*-diaxial interactions.

Of the four aldopentopyranoid configurations in which an axial C-1 substituent has a *syn*-axial group at C-3, the β-*xylo* and α-*arabino* derivatives have the C-1 and C-2 substituents antiparallel in one of the chair conformers and gauche in the other, whereas the α-*ribo* and β-*lyxo* derivatives have these groups gauche in both chair forms. The larger $\Delta\Delta G^\circ$ values observed on comparing the peracetylated methyl D-aldopentopyranoside with the corresponding D-aldopentopyranose tetraacetates in the α-*ribo* and β-*lyxo* configurations than the values for those pairs having the β-*xylo* and α-*arabino* configurations probably result from a larger gauche interaction present between the methoxyl and acetoxy groups than that between two acetoxy groups. This difference presumably acts as a counterbalance to the increase in the 1,3-interaction in the same direction[2]. This difference in gauche interactions probably also plays a role in determining the relative conformational populations of the β-*ribo* and α-*lyxo* derivatives (in which the C-1 and C-2 substituents are antiparallel in one of the chair conformers).

Conformational equilibrium and its solvent dependence. — That solvent polarity does not in any regular manner affect the position of conformational equilibria for tetrasubstituted tetrahydropyran ring-systems has already been demonstrated from a study of the solvent dependence of the conformational populations of solutions of

β-D-ribopyranose tetraacetate[3], β-D-xylopyranose tetrabenzoate[3], and tri-*O*-acetyl-β-D-xylopyranosyl chloride[4]. The solvent dependence of the conformational equilibrium for methyl tri-*O*-benzoyl-β-D-xylopyranoside (**12**) has now been investigated. In Table V are given, as a function of the dielectric constant, the $J_{1,2}$, $J_{2,3}$, $J_{3,4}$, and $J_{4,5}$, couplings for **12**. These couplings provide a measure of the equilibrium constant, since they represent a time-average between a diaxial arrangement of the coupled protons in the *C1*(D) conformer and a diequatorial orientation in the *1C*(D) conformer. Although, again, there exists no simple relationship between the solvent polarity and the conformational population, the results for **12** show a more regular increase in the equilibrium proportion of that chair form having the anomeric substituent equatorial with an increase in the dielectric constant of the solvent than did those for the three tetrasubstituted tetrahydropyran derivatives previously reported[3,4]. Thus, there is a difference of 1.5 Hz between the $J_{4,5}$, coupling for **12** in methyl sulfoxide-d_6 (9.3 Hz; ε 48.9) and in benzene-d_6 (7.8 Hz; ε 2.3), the minor, all-axial conformer being less favored in the more-polar solvent.

The solvent dependence of the first-order chemical-shifts for methyl tri-*O*-benzoyl-β-D-xylopyranoside is given in Table VI.

EXPERIMENTAL

General. — Evaporations were performed below 50° under diminished pressure. Melting points are uncorrected. Specific rotations were determined in a 1-dm, narrow-bore polarimeter tube. Microanalyses were made by W. N. Rond. T.l.c. was performed with 0.25-mm layers of Silica Gel G (E. Merck, Darmstadt, Germany), activated at 120°, as the adsorbent, and sulfuric acid as the indicator. Column chromatography was conducted with silica gel (7734, Merck) as the adsorbent, with 1 g of mixture to be separated per 30 g of adsorbent, and the compounds were eluted with the solvents specified.

N.m.r. spectra. — Spectra were recorded at 100 MHz with a Varian HA-100 n.m.r. spectrometer under the general conditions specified in Ref. 4. The two 220-MHz spectra were recorded by Dr. A. A. Grey of the Ontario Research Foundation, Sheridan Park, Ontario, Canada.

Preparation of the methyl 2,3,4-tri-O-acetyl-D-aldopentopyranosides

Methyl α-D-ribopyranoside. — The procedure of Reist *et al.*[16] was used. A solution of methyl 2-*O*-benzoyl-3,4-di-*O*-*p*-tolylsulfonyl-β-L-arabinopyranoside[16] in dry *N*,*N*-dimethylformamide was refluxed for two days. The reaction mixture was then processed as described[16], and the product was debenzoylated to give the title glycoside as a syrup contaminated by a trace of methyl β-L-lyxopyranoside.

Methyl tri-O-acetyl-α-D-ribopyranoside (**1**). — The syrupy methyl α-D-ribopyranoside was acetylated with acetic anhydride and pyridine, and then processed in the usual way. A solution of the residue in the minimal volume of dichloromethane was passed through a column of silica gel. Ether–dichloromethane (1:3) was used as

the eluant to separate the main product from traces of a faster-moving component (methyl tri-*O*-acetyl-β-L-lyxopyranoside). The fractions containing the slower-moving component were evaporated, and the residue was distilled under high vacuum to give **1** as a thick, colorless syrup; $[\alpha]_D^{18}$ +86.6° (*c* 1.61, chloroform); R_F 0.57 (3:1 dichloromethane–ether); λ_{max}^{film} 5.72 (C=O), 6.98, 7.31, 8.15, 8.86, 9.12, 9.31, 9.52, 10.15, and 11.30 μm.

Anal. for $C_{12}H_{18}O_8$: C, 49.65; H, 6.25. Found: C, 49.82; H, 6.28.

Methyl β-D-ribopyranoside. — A solution of methyl tri-*O*-benzoyl-β-D-ribopyranoside[8] (1.0 g, 2.1 mmoles) in dry methanol (50 ml) was treated with a catalytic amount of sodium and kept for 14 h at room temperature. A few drops of water were then added, carbon dioxide gas was bubbled through for 15 min, and the solution was concentrated to a syrup. Addition of ethyl acetate precipitated out the inorganic salts. After filtration of the mixture through a Celite pad, the filtrate was concentrated to a syrup; this was crystallized from anhydrous ether to give the title glycoside, yield 0.25 g (73%); m.p. 82–83° (lit.[17] m.p. 83°).

Methyl tri-O-acetyl-β-D-ribopyranoside (**2**). — Methyl β-D-ribopyranoside (1.0 g, 6.1 mmoles) was dissolved in dry pyridine (2.5 ml) with cooling in an ice-bath, and treated with acetic anhydride (2.0 ml, 20 mmoles). The resulting solution was kept overnight at 0° and then evaporated. The residue was coevaporated several times with toluene and finally with carbon tetrachloride. Distillation of the residue under high vacuum gave **2** as a thick, colorless syrup; yield 1.3 g (76%); $[\alpha]_D^{20}$ −88.1° (*c* 0.99, chloroform); R_F 0.63 (3:1 dichloromethane–ether); λ_{max}^{film} 3.41 (C–H), 5.71 (C=O), 6.98, 7.29, 7.88, 8.20, 8.82, 9.15, 10.20, 11.15, 12.03, and 12.68 μm.

Anal. Calc. for $C_{12}H_{18}O_8$: C, 49.65; H, 6.25. Found: C, 49.78; H, 6.29.

Methyl tri-O-acetyl-α-D-arabinopyranoside (**3**). — This compound was prepared by the Koenigs–Knorr method[6]. Anhydrous methanol (55 ml) was shaken with fresh silver carbonate (2.2 g) and "anhydrous" calcium sulfate (Drierite, 2.2 g) for 30 min. Tri-*O*-acetyl-β-D-arabinopyranosyl bromide[18] (2.0 g, 5.9 mmoles) was then added, and the mixture was shaken for 10 h in the dark at room temperature, and filtered through a Celite pad. The filtrate was evaporated, and the residue was dissolved in dichloromethane (55 ml). The solution was washed twice with an equal volume of cold, 3% aqueous ammonia (to remove traces of silver salts) and twice with cold water, dried by passage through a pad of anhydrous magnesium sulfate, and evaporated to a syrup, which was dissolved in the minimal volume of dichloromethane and passed through a column of silica gel. Ether–dichloromethane (1:3) was used as the eluant, to separate the main product from traces of a slower-moving component (probably a decomposition product of the bromide). The fractions containing the faster-moving component (**3**) were collected, and evaporated to a thick, colorless syrup; yield 1.3 g (77%); $[\alpha]_D^{20}$ −11.9° (*c* 1.85, chloroform) [lit.[19] $[\alpha]_D$ −17° (chloroform)]; R_F 0.67 (3:1 dichloromethane–ether); λ_{max}^{film} 5.73 (C=O), 7.00, 7.33, 8.19, 8.80, 9.17, 9.48, and 9.83 μm.

Methyl β-D-arabinopyranoside. — To a solution of D-arabinose (10 g) in abs. methanol (100 ml) was added some Amberlite IR-120 (H^+) resin, and the mixture

was boiled for 3 h under reflux and filtered. Upon evaporation of the filtrate, crystallization occurred. The crystals were filtered off and extracted with boiling ethyl acetate (to remove as much syrupy impurity as possible). Recrystallization from abs. ethanol gave the title glycoside, m.p. 169° (lit.[20] m.p. 168°).

*Methyl tri-*O*-acetyl-β-*D*-arabinopyranoside* (**4**). — Methyl β-D-arabinopyranoside was acetylated with acetic anhydride and sodium acetate, as described by Hudson and Dale[7] for the preparation of the corresponding L-enantiomorph, to give crystalline **4**, m.p. 75–77°, $[\alpha]_D^{22}$ −186.6° (*c* 1.16, chloroform) [lit.[7] values for the L-enantiomorph, m.p. 85°, $[\alpha]_D^{23}$ +182.0° (*c* 4.42, chloroform)]; R_F 0.71 (3:1 dichloromethane–ether); λ_{max}^{KBr} 5.73 (C=O), 6.95, 7.28, 8.16, 8.81, 9.37, 9.54, 9.93, 10.52, 11.18, 11.39, and 13.28 μm.

Anal. Calc. for $C_{12}H_{18}O_8$: C, 49.65; H, 6.25. Found: C, 49.89; H, 6.36.

Methyl α-D-xylopyranoside. — To a solution of D-xylose (20 g) in abs. methanol (200 ml) was added some Amberlite IR-120 (H^+) resin. The mixture was boiled under reflux for 6 h, and filtered, and the filtrate was evaporated to a thick syrup. On dissolving the syrup in isopropyl alcohol, crystalline methyl β-D-xylopyranoside was obtained. The mother liquor was processed as described by Hudson[21], to give the title glycoside, which was recrystallized twice from butanone; m.p. 90–91° (lit.[22] m.p. 90–92°).

*Methyl tri-*O*-acetyl-α-D-xylopyranoside* (**5**). — Methyl α-D-xylopyranoside was acetylated with acetic anhydride and sodium acetate by the procedure of Hudson and Dale[23], to give crystalline **5**, m.p. 85–86° (lit.[23] m.p. 86°).

*Methyl tri-*O*-acetyl-β-D-xylopyranoside* (**6**). — This compound was prepared by the Koenigs–Knorr method[6] from tri-*O*-acetyl-α-D-xylopyranosyl bromide[24] (3.0 g, 8.8 mmoles), by the procedure used for preparing **3**. The resulting solution was evaporated to a thick syrup, which was crystallized from abs. ethanol. Recrystallization from abs. ethanol gave **6**; yield 2.2 g (86%); m.p. 115° (lit.[25] m.p. 115°).

Methyl α-D-lyxopyranoside. — D-Lyxose (5 g) was refluxed for 4 h with abs. methanol (70 ml) containing 1.5% of hydrogen chloride. The mixture was then cooled, and processed by the method of Isbell and Frush[26], to give the crystalline, title glycoside, m.p. 107–108° (lit.[26] m.p. 108°).

*Methyl tri-*O*-acetyl-α-D-lyxopyranoside* (**7**). — Methyl α-D-lyxopyranoside was acetylated with acetic anhydride and pyridine according to the procedure of Phelps and Hudson[27], to give crystalline **7**, m.p. 96–97°, $[\alpha]_D^{20}$ +29.5° (*c* 1.12, chloroform) [lit.[27] m.p. 96°, $[\alpha]_D^{20}$ +29.4° (*c* 0.745, chloroform)]; R_F 0.78 (3:1 dichloromethane–ether).

*Methyl tri-*O*-acetyl-β-D-lyxopyranoside* (**8**). — The mother liquor remaining after removal of a second crystalline crop of methyl α-D-lyxopyranoside from the earlier preparation was evaporated to a thick syrup, which was acetylated with acetic anhydride and pyridine. After the usual processing, the residue was dissolved in the minimal volume of anhydrous ether and passed through a column of silica gel, with 1:1 ether–petroleum ether (b.p. 30–60°) as the eluant. The fractions containing the slowest moving component (identified as **8** from an authentic sample kindly supplied

by Dr. H. S. Isbell) were collected, and evaporated to a syrup which spontaneously crystallized. Recrystallization from ether–petroleum ether gave **8**, m.p. 89° (lit.[26] m.p. 88–89°); R_F 0.63 (3:1 dichloromethane–ether).

Preparation of the methyl 2,3,4-tri-O-benzoyl-D-aldopentopyranosides

Methyl tri-O-benzoyl-β-D-ribopyranoside (**9**). — Tri-*O*-benzoyl-β-D-ribopyranosyl bromide[28] (2.4 g, 4.6 mmoles) was dissolved in abs. methanol (25 ml) by boiling under reflux, with stirring, for several min. The solution was then refrigerated overnight, whereupon crystallization occurred. Recrystallization from ether–pentane gave **9**; yield 1.9 g (87%); m.p. 109–110°, $[\alpha]_D^{20}$ −69.8° (*c* 1.10, chloroform) [lit. [8] m.p. 109–110°; $[\alpha]_D$ −69.5° (*c* 0.820, chloroform)].

Methyl tri-O-benzoyl-β-D-arabinopyranoside (**10**). — Methyl β-D-arabinopyranoside was benzoylated with benzoyl chloride and pyridine according to the procedure of Fletcher and Hudson[29], to give crystalline **10**, m.p. 83–84° (lit.[29] m.p. 84–85°).

Methyl tri-O-benzoyl-α-D-xylopyranoside (**11**). — To a solution of methyl α-D-xylopyranoside (2.5 g, 15 mmoles) in anhydrous pyridine (10 ml) and dichloromethane (20 ml), cooled to 0° in an ice-bath, was added benzoyl chloride (10 ml) dropwise, with vigorous stirring. The mixture was kept for 45 min at 0° and then overnight at room temperature. After the usual processing, the resulting solution was evaporated to a thick syrup which was crystallized from 95% ethanol. Recrystallization from 95% ethanol gave **11**; yield 3.6 g (81%); m.p. 107–109°, $[\alpha]_D^{26}$ +56.3° (*c* 1.10, chloroform); λ_{max}^{KBr} 5.83 (C=O), 6.24, 6.95, 7.98, 8.51, 9.09, 9.68, 10.63, 11.69, 13.47, and 14.22 μm (aryl).

Anal. Calc. for $C_{27}H_{24}O_8$: C, 68.06; H, 5.08. Found: C, 67.97; H, 5.16.

Methyl tri-O-benzoyl-β-D-xylopyranoside (**12**). — Methyl β-D-xylopyranoside was benzoylated with benzoyl chloride and pyridine in the usual way, to give crystalline **12**, m.p. 93–95° (lit.[29] m.p. 95–96°).

Methyl tri-O-benzoyl-α-D-lyxopyranoside (**13**). — Methyl α-D-lyxopyranoside (1.2 g, 7.3 mmoles) was benzoylated with benzoyl chloride and pyridine in the usual way, to give **13** as an amorphous glass; yield 1.6 g (74%), $[\alpha]_D^{24}$ −141.5° (*c* 1.14, chloroform); λ_{max}^{KBr} 5.80 (C=O), 6.24, 6.92, 7.94, 8.57, 9.14, 9.37, 9.73, 11.55, and 14.15 μm (aryl).

Anal. Calc. for $C_{27}H_{24}O_8$: C, 68.06; H, 5.08. Found: C, 67.94; H, 4.94.

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