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Note

Synthesis of a new class of D-aldopentofuranosylamines, the 5-*O*-trityl-D-aldopentofuranosylamines

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The general utility of aldofuranosylamines in nucleoside and drug syntheses[1–3] has been limited to the isopropylidene acetals of the furanosylamines of ribose and xylose, as other important aldopentoses, *e.g.*, D-arabinose or 2-deoxy-D-*erythro*-pentose, do not afford analogously useful furanosylamine derivatives. Synthesis of aldofuranosylamines by catalytic reduction of 2,3,5-tri-*O*-acyl-D-aldopentofuranosyl azides[4] is tedious, emphasizing the absence of efficient routes to these synthetically important compounds. As an alternative method for the general preparation of aldofuranosylamines, we have now examined the conversion of the readily available 5-*O*-trityl-D-aldopentofuranoses[5] into a new class of compound, the corresponding 5-*O*-tritylaldofuranosylamines. We further report on their synthetic utility by the preparation of the pyridine coenzyme precursor, 1-D-ribofuranosylnicotinamide.

The 5-*O*-trityl-D-aldopentofuranosylamines **5–8** were synthesized in quantitative yield from the corresponding 5-*O*-trityl-D-aldopentofuranoses (**1–4**) by treatment with methanolic ammonia, as shown in Scheme 1. All of the products (**5–8**) gave a positive ninhydrin test, characteristic of primary amines, and a deep-red color with 3-carbamoyl-1-(2,4-dinitrophenyl)pyridinium chloride[6]. The formation of the furanosylamine was monitored by natural-abundance, ^{13}C-n.m.r. spectroscopy. The chemical shifts for the 5-*O*-trityl-D-aldopentofuranoses and their furanosylamine derivatives are listed in Tables I and II, and representative spectra are shown in Fig. 1. The assignments of the resonances are in accord with the recent results of Kam *et al.*[7]. The anomeric configurations assigned were based on the criterion that C-1 of *cis*-1,2 cyclic compounds is shielded relative to that of the corresponding *trans*-1,2 derivatives[8]. A definitive assignment of the anomeric configuration of the 2-deoxy-D-*erythro*-pentofuranose derivatives (**4** and **8**) could not, however, be made, as their C-1 resonances fortuitously coincide. The ^{13}C-n.m.r. spectra provided no

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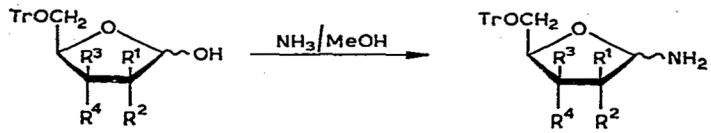
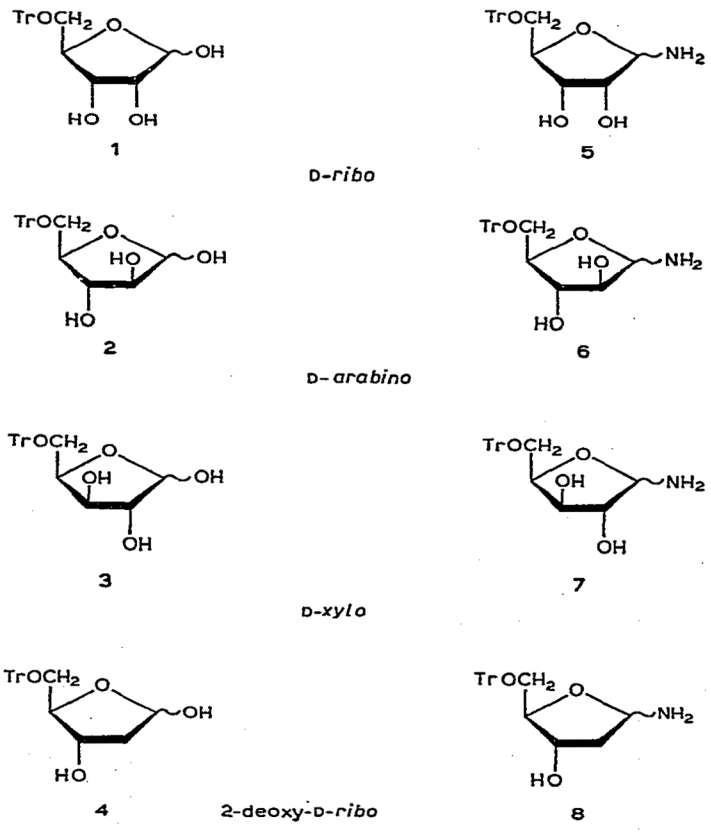


R^1 and R^3 = H, or OH; R^2 and R^4 = OH, or H
(R^1 = R^2 = H for 4 and 8)



Scheme 1

evidence for an aldimine (Schiff base) structure. The C-1 resonances show the upfield shift caused by the replacement of the 1-hydroxyl group by the (less electronegative) 1-amino group[9], rather than the strong deshielding expected for an sp^2-hybridized carbon atom (C-1); furthermore, a planar, sp^2-hybridized C-1 atom could not give rise to two distinct anomeric forms.

As a further proof of the glycosylamine structure of derivatives **5–8**, and as a demonstration of their synthetic utility, we prepared 1-D-ribosylnicotinamide

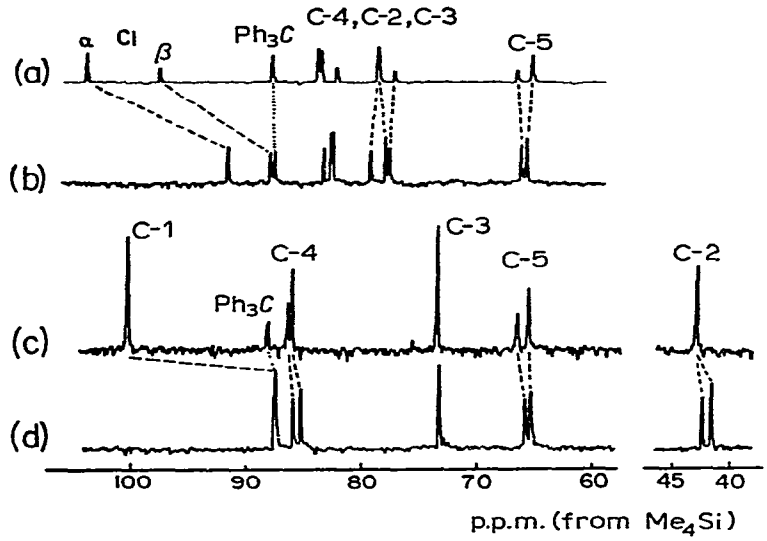


Fig. 1. Portions of the natural-abundance, ^{13}C-n.m.r. spectra of the 5-trityl ethers (**2** and **4**) of D-arabinose and 2-deoxy-D-*erythro*-pentose and 1-amines (**6** and **8**) in CD_3OD. [(a) Compound **2**, (b) **6**, (c) **4**, and (d) **8**.]

TABLE I

^{13}C CHEMICAL SHIFTS OF 5-*O*-TRITYL-D-ALDOPENTOFURANOSES[a]

Compound		*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-Ph*$_3$
1	α	98.0	72.8	72.8	83.7	65.3	87.7
	β	103.1	77.1	72.6	82.8	66.5	
2	α	103.3	83.5	78.7	83.8	65.4	87.7
	β	97.2	78.7	77.3	82.2	66.7	
3	α	97.7	79.3	77.6	82.2	64.2	88.0
	β	104.3	78.2	77.2	82.5	64.6	
4		99.6	42.9	73.4	86.1	65.5	87.8
					85.8	66.5	

[a]Chemical shifts are recorded in p.p.m. from internal Me_4Si.

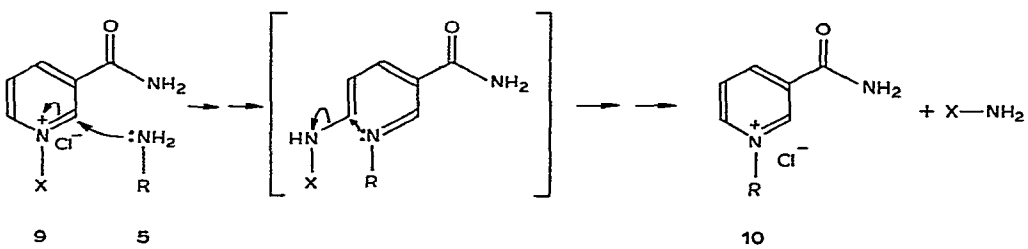
chloride by using a method, developed by Atkinson *et al.*[10], in which the pyridinium moiety is generated by attack of the primary glycosylamine on 3-carbamoyl-1-(2,4-dinitrophenyl)pyridinium chloride[6,11] (**9**) to give **10**, as shown in Scheme 2. Note that this occurs with retention of the configuration of C-1 of the furanosylamine. Subsequent removal of the trityl group by treatment with 1% aqueous HCl yielded the fully characterized[12,13] anomeric forms of 1-D-ribosylnicotinamide

TABLE II

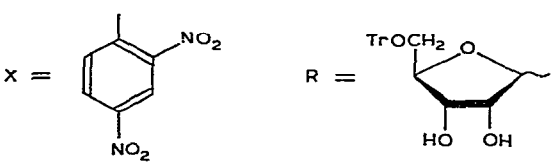
^{13}C CHEMICAL SHIFTS OF 5-*O*-TRITYL-D-ALDOPENTOFURANOSYLAMINES[a]

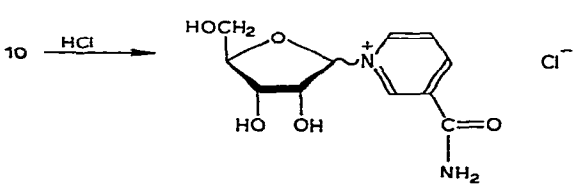
Compound		*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-Ph₃*	cis:trans
5	α	87.7	77.0	72.5	82.8	65.7	87.7	1:1.30
	β	91.1	73.5	72.7	81.7	66.0		
6	α	91.5	82.6	78.1	83.4	65.8	87.6	1:1.32
	β	87.9	79.4	77.8	82.7	66.3		
7	α	87.9	79.8	77.5	81.7	64.3	87.6	1:1.15
	β	93.3	78.1	77.5	82.7	64.7		
8		87.7	42.2 43.0	73.7	86.2 85.6	65.8 66.3	87.7	1:1.15

[a]Chemical shifts are recorded in p.p.m. from internal Me_4Si.



9 5 10





Scheme 2 11

chloride (**11**) in the same ratio as for the starting 5-*O*-trityl-D-ribofuranosylamine. Therefore, based upon the demonstrated synthetic utility of furanosylamines[1–3], the 5-*O*-tritylfuranosylamines should have wide applicability in nucleoside chemistry.

EXPERIMENTAL

General methods. — Specific rotations were determined with a Perkin–Elmer 141 polarimeter. Natural-abundance, ^{13}C-n.m.r. spectra were recorded at 25.2 MHz with a Varian XL-100 n.m.r. spectrometer equipped with a Nicolet Technologies Fourier-transform system; CD_3OD was used as the solvent, with Me_4Si as the internal reference standard. Plates of silica gel (Baker-flex) were used for t.l.c., with 1:4 MeOH–$CHCl_3$ as the solvent. Compounds were detected either with a u.v. lamp or an aerosol spray of ninhydrin.

*General procedure for the synthesis of 5-*O*-trityl-*D*-aldopentofuranosylamines* (**5** *to* **8**). — A methanolic solution of 5-*O*-trityl-D-aldopentofuranose[5] (**1** to **4**) at 0° was saturated with ammonia, and kept[14] for 2 days at 0°. Methanol and ammonia were removed *in vacuo* at <40°, to give a quantitative yield of the corresponding 5-*O*-trityl-D-aldopentofuranosylamine as a foam; specific rotations: **5**, $[\alpha]_D^{24}$ +10.5° (*c* 1.15, MeOH); **6**, +11.1° (*c* 2.25, MeOH); **7**, −21.3° (*c* 1.45, MeOH), and **8**, +3.2° (*c* 1.25, MeOH).

Crystalline materials could be obtained from ethanol; however, the resulting compounds contained only half the expected nitrogen (by elemental analysis). The ^{13}C-n.m.r. spectra of the crystalline materials were distinct from that of the starting furanosylamine, and the compounds would not readily react with 3-carbamoyl-1-(2,4-dinitrophenyl)pyridinium chloride, suggesting that, under these conditions, the *O*-tritylaldofuranosylamines dimerize, as reported for D-ribopyranosylamine[14]. We have observed no evidence for these products when the *O*-tritylaldofuranosylamines are stored either in methanolic ammonia or as a foam. The lability of the glycosylamines to the high vacuum needed to remove all traces of solvent from the foams, and lack of crystalline salts, precluded acquiring definitive elemental analyses of the products.

*Synthesis of 3-carbamoyl-1-(5-*O*-trityl-α,β-*D*-ribofuranosyl)pyridinium chloride* (**10**). — Treatment of **5** (3.50 g, 12 mmol) with 3-carbamoyl-1-(2,4-dinitrophenyl) pyridinium chloride (**9**) (4.9 g, 12 mmol) in MeOH (100 mL) gave a yellow-orange solution after stirring for 5 h at room temperature. Ammonia was bubbled into the solution, cooled to 0°, in order to decompose any unreacted **9**, and then the methanol and ammonia were removed by evaporation. The residue was dissolved in the minimal volume of MeOH, and the product was precipitated with ethyl ether (250 mL, 3 times), to give **10** as a hygroscopic powder (3.65 g, 6.6 mmol; 55%); ^{1}H-n.m.r. data (Me_2SO-d_6): δ 9.47 (br s, 1 H, αH-2), 9.38 (br s, 1 H, βH-2), 9.16 (d, *J* 6.1 Hz, 1 H, α,βH-6), 9.07 (d, *J* 8.1 Hz, 1 H, α,βH-4), 8.23–8.13 (m, 1 H, α,βH-5), 7.40–7.34 (m, 15 H, α,βPh_3C), 6.70 (d, *J* 3.5 Hz, 1 H, αH-1′), 6.25 (d, *J* 3.0 Hz, 1 H,

βH-1'), 4.82–4.76 (m, 1 H, α,βH-2'), 4.50–4.10 (m, 2 H, α,β-H-3',4'), and 3.62–3.26 (m, 2 H, α,βH-5',5").

3-Carbamoyl-1-α,β-D-ribofuranosylpyridinium chloride (**11**). — A solution of powdery **10** in the minimal volume of MeOH was treated with 1% aqueous HCl (250 mL) for 15 min at room temperature. The precipitated tritanol was removed by filtration, and the filtrate was evaporated to dryness. The residue was dissolved in the minimal volume of water, and purified by chromatography in a C-2 reverse-phase column (Merck, 70–230 mesh) eluted with water, to give a quantitative yield of **11** (6.6 mmol, as determined spectrophotometrically, using the cyanide assay[15]) as a 1:1.3 mixture of the α and β anomers. The ^{1}H-n.m.r. spectrum was identical to that of the same mixture of the authentic nucleosides[13].

ACKNOWLEDGMENTS

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