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A GENERAL METHOD OF SYNTHESIS AND ISOLATION, AND AN N.M.R.-SPECTROSCOPIC STUDY, OF TETRA-*O*-ACETYL-D-ALDOPENTO-FURANOSES

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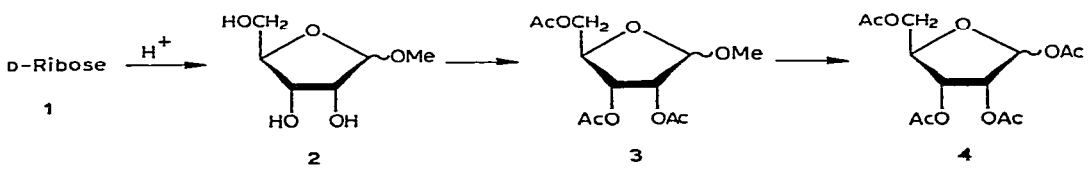
ABSTRACT

The Guthrie–Smith method for the synthesis of tetra-*O*-acetyl-β-D-ribofuranose has been successfully generalized to apply to the D-aldopentofuranose series. Treatment of a D-aldopentose with acidic methanol, followed by acetylation and acetolysis, led to the peracetylated derivatives in good yields. All compounds were characterized, and their structures established. Isolation of products is described, and their ^{1}H- and ^{13}C-n.m.r. spectra are discussed.

INTRODUCTION

Peracetylated D-aldopentofuranoses have been prepared by various methods[1–8]. Generally, isolation of the intermediates is required, except in the Guthrie–Smith method[7] for the synthesis of D-ribofuranose derivatives. This method involves three steps, the most important being the formation of the methyl D-ribofuranosides (**2**) as intermediates (see Scheme 1). The analogous methyl glycosides of D-arabinose[9]



1 2 3 4

Scheme 1

and D-xylose[10] have been obtained under similar conditions. It was, therefore, reasonable to assume that D-lyxose would undergo the same reaction. On this basis, we successfully applied the Guthrie–Smith method to all four of the D-aldopentoses,

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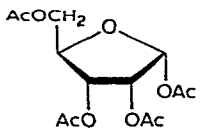
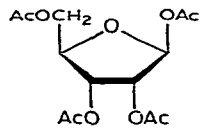
and now report a general method of synthesis and isolation of, and the ^{1}H- and ^{13}C-n.m.r. data for, the tetra-*O*-acetyl-D-aldopentofuranoses.

RESULTS AND DISCUSSION

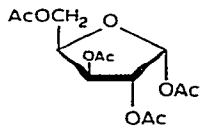
Treatment of a D-aldopentose in methanol with sulfuric acid at room temperature gave the corresponding methyl D-aldopentofuranosides. Direct acetylation of the latter, followed by acetolysis of the methyl group, gave the respective tetra-*O*-acetyl-D-aldopentofuranose (**4**–**7**) in a total yield of ~70%. Except for the tetra-*O*-acetyl-D-arabinofuranoses (**7α,β**), both anomers were isolated, for the first time, by column chromatography. All compounds were characterized, and identified, either as pure anomers or mixtures, in comparison with the literature data, depending upon the nature of the known compounds. The results were then substantiated by n.m.r.-spectral analysis of the products.



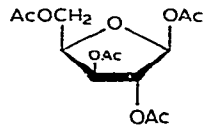
4α



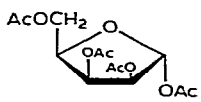
4β



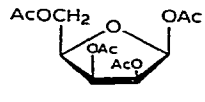
5α



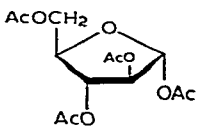
5β



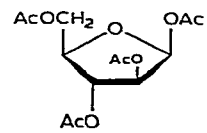
6α



6β



7α



7β

Compound **4β**, obtained by recrystallization, proved to be identical to tetra-*O*-acetyl-β-D-ribofuranose described by Guthrie and Smith[7]. Compound **4α** had a specific rotation of $[\alpha]_D^{20}$ +75.6°, different from those of the pyranose tetraacetates

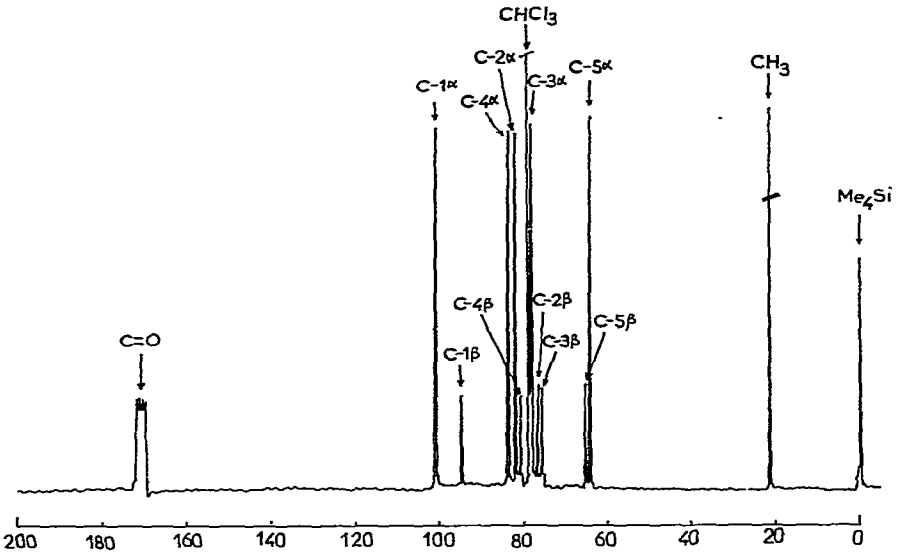


Fig. 1. ^{13}C-N.m.r. spectrum of tetra-*O*-acetyl-D-arabinofuranoses (**7**) in $CHCl_3$.

described by Zinner[4]. The ^{1}H-n.m.r. spectrum of the mixture **5αβ** corresponds to that of the mixed tetra-*O*-acetyl-D-xylofuranoses reported by Magnani and Mikuriya[11]. Purification of **6** gave, in addition to the α and β anomers, a third, crystalline product identical to tetra-*O*-acetyl-α-D-lyxopyranose[12]. Whereas the specific rotation of **6α** is similar to that of tetra-*O*-acetyl-α-D-lyxofuranose[12], that of **6β** differs from that of 1,2,3,4-tetra-*O*-acetyl-β-D-lyxopyranose[12]. The specific rotation of **7** agreed with those of the tetra-*O*-acetyl-D-arabinofuranoses obtained by Kuszmann and Vargha[6]; in addition, its ^{13}C-n.m.r. spectrum (see Fig. 1) indicated that we had obtained a mixture of the pure anomers.

In order to provide more information on this series, and then to correlate the chemical shifts to the problems of stereochemistry, and the values of the coupling constants to the structures, the ^{1}H- and ^{13}C-n.m.r. spectra of all of the compounds were analyzed.

(a) ^{1}H-N.m.r. analysis

Except for those of **7α** (ref. 8), few ^{1}H-n.m.r. data for peracetylated D-aldopentofuranoses have been reported[11,13], because of supposed difficulties in isolating the anomers.

These derivatives being available to us, it was then interesting to examine their n.m.r. spectra, recorded either at 100 or 250 MHz. Chemical shifts were assigned on the basis of spin decoupling. The difference in chemical shifts between H-1, H-2, and H-3,H-4 was sufficiently larger than the corresponding values of coupling constants to justify a first-order analysis of H-1, H-2, and H-3. Surprisingly, H-4, H-5, and H-5′ were strongly coupled, forming a degenerated ABC system. A first-order analysis was made possible either by high-resolution, n.m.r. analysis at 250

TABLE I

^{1}H-N.M.R. CHEMICAL SHIFTS[a] OF TETRA-*O*-ACETYL-D-ALDOPENTOFURANOSES

Tetra-acetate	*Solvent*	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-5'*
4α	C_6D_6	6.61	5.24	5.30	4.34	4.15	3.97
	$CDCl_3$	6.41					
4β	$CDCl_3$	6.18	5.34	5.36	4.39	4.34	4.15
5α	$CDCl_3$	6.41	5.30	5.54	4.63	4.26	4.10
5β	C_6D_6	6.36	5.35	5.40	4.50	4.34	4.21
	$CDCl_3$	6.15					
6α	$CDCl_3$	6.28	5.37	5.61	4.59	4.31	4.17
6β	$CDCl_3$	6.36	5.29	5.63	4.52	4.34	4.21
7α	$CDCl_3$	6.21	5.21	5.35		4.50–4.00 (3H)	
7β	$CDCl_3$	6.35	5.05 (2H)				

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

TABLE II

VALUES OF ^{1}H-N.M.R. COUPLING-CONSTANTS (IN Hz)

Anomer	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$
4α	4.3	6.8	2.8	3.2	4.4	12
4β	0.8	4.8	5.1	3.4	4.8	11.4
5α	4.6	6.4	6.4	4.8	4.6	12
5β	0.4	1.6	5.6	6.0	6.1	11.6
6α	2.1	5.1	5.4	4.8	7.2	11.9
6β	4.6	5.4	4.7	5.3	7.3	11.6

MHz of **4**, or by a change of solvent ($CDCl_3$, C_6D_6) for the other derivatives. The corresponding values of coupling constants, namely, $J_{4,5}$, $J_{4,5'}$, and $J_{5,5'}$, were substantiated by iterative fitting of the observed spectra, using the LAOCN program. The results are listed in Tables I and II.

To simplify the spectral analysis, we considered two systems of three spins each, namely, H-1,H-2,H-3 and H-4,H-5,H-5'. The spin decoupling showed that, in all cases, H-2 resonates upfield of H-3 (see Table I). Generally, H-2 appears as a doublet of doublets, and H-3 is a triplet. On the other hand, not only are the anomeric protons of the *trans*-1,2 compounds more shielded than those of the corresponding *cis*-1,2 derivatives[14], but also, their values of coupling constants ($J_{1,2\text{-}trans}$) are less than 1.0 Hz, thus assigning their stereochemistry unambiguously[15].

TABLE III

^{13}C-N.M.R. CHEMICAL-SHIFTS[a] OF TETRA-*O*-ACETYL-D-ALDOPENTOFURANOSES

Tetra-acetate	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*
4α	94.07	69.98	69.78	81.64	63.30
4β	98.12	74.08	70.47	79.20	63.60
5α	92.81	75.25	73.84	75.40	61.59
5β	98.85	79.44	74.27	79.88	62.33
6α	98.04	75.01	70.57	77.01	62.43
6β	93.20	70.52	68.52	77.74	62.77
7α[b]	99.37	80.60	76.88	82.44	63.05
7β[b]	93.72	75.38	74.82	79.72	64.53

[a]Chemical shifts are given in p.p.m. from internal Me_4Si (in $CDCl_3$). [b]Recorded for a solution in $CHCl_3$ with a fluorine lock.

Although the values of the coupling constants of the *gem*-hydrogen atoms of the exocyclic methylene group are, in general, >11.0 Hz, those of the ring-hydrogen atoms are, in all cases, in the range of 0.0 to 7.0 Hz (see Table II); this result is consistent with the values of the coupling constants calculated by the Karplus equations[16] for a furanose ring, and therefore indicated that we had isolated the peracetylated D-aldopentofuranoses.

(*b*) *^{13}C-N.m.r. analysis*

Some ^{13}C-n.m.r.-spectral data for some D-aldopentofuranoses have been reported[17-20]. Although some data have been given for members of the pyranose tetraacetate series[21], none have been mentioned in the literature for the peracetylated D-aldofuranoses.

In order to provide more information on the latter series, we examined the ^{13}C-n.m.r. spectra of the compounds we had isolated. The spectra were recorded by using broad-band, homonuclear decoupling (to simplify their analysis). Chemical shifts were assigned according to the literature data[18,19]. The results are listed in Table III.

It is well known that the chemical shift of a carbon atom is extremely dependent upon the electronegativity of its substituents[19]. Accordingly, the carbon atoms of carbonyl groups are strongly deshielded and appear at $\delta > 160$ p.p.m., whereas those of methyl groups appear upfield, at $\delta < 30$ p.p.m. (for example, see the spectrum of **7**, given in Fig. 1).

As may be seen from Table III, carbon atoms substituted with *cis*-vicinal acetoxyl groups show a general shielding-effect over the corresponding *trans*-substi-

tuted atoms. Thus, C-1 and C-2 of *cis*-1,2 compounds appear upfield of those of the corresponding *trans*-1,2 derivatives, which confirms their stereochemistry. Similarly, the C-3 atoms of **4** and **6** are more shielded than those of **5** and **7**, where the acetoxyl groups are *trans*-2,3. These results agree with the contention that the chemical shift of a carbon atom is, also, extremely sensitive to steric hindrance, particularly by vicinal, oxygen substituents[22]; this is more or less true for C-4, for those atoms of *trans*-3,4 derivatives (**4** and **7**) are, in general, more deshielded than those of **5** and **6** (except for **6β**, C-4 of which is more deshielded than that of **4β**). However, in contrast to the vicinal-substituent effect, *cis*-1,3 substitution seems to result in deshielding of C-4 for each pair of anomers (see Table III).

For the exocyclic, methylene carbon atom, the reverse effect is observed within each pair of anomers, where C-5 is more shielded for those anomers for which the C-1,C-4 substitution is *cis*. In addition, it was found[20] that the chemical shift of C-5 depends upon the configuration of C-3. When the C-3–O bond is *endo* (*cis*-3,4), C-5 is more shielded than when the bond is *exo* (*trans*-3,4). Accordingly, we observed a general deshielding effect of C-5 of **4** and **7** compared to those to **5** and **6** (see Table III). It is interesting to compare the chemical shift of C-4 to that of C-2 of the peracetylated pyranose series[21]. In the latter series, in $CDCl_3$, C-2 is more deshielded than any other carbon atom, except C-1, and resonates, in general, at $\delta < 70$ p.p.m., whereas C-4 of the corresponding D-aldopentofuranoses appears at $\delta > 75$ p.p.m., independent of the nature or stereochemistry of the sugar. As these derivatives are readily soluble in chloroform, this difference is significant, and may be used to determine the pyranose or furanose structure, even if only one peracetylated D-aldopentose is isolated.

EXPERIMENTAL

General. — Melting points were determined on a Thomas–Hoover apparatus and are uncorrected. Specific rotations were determined with a Roussel–Jouan polarimeter. ^{1}H-n.m.r. spectra were recorded with a Varian HA-100 or a Caméca-250 n.m.r. spectrometer, and ^{13}C-n.m.r. spectra with a JEOL PG-100 n.m.r. spectrometer equipped with a Fourier-transform system. $CDCl_3$ or C_6D_6 was used as the solvent, with Me_4Si as the internal reference-standard. Merck silica gel $60F_{254}$ on aluminum plates was used for t.l.c., and compounds were detected either with iodine or by carbonization after spraying with 10% aqueous sulfuric acid. Merck silica gel 60 (230–400 mesh) was used for column chromatography. Analyses were performed by the C.N.R.S. Microanalysis Central Service of the E.N.S.C.M., Montpellier, France.

General procedure for the synthesis of tetra-O-acetyl-D-aldopentofuranoses. — Peracetylated D-aldopentofuranoses were synthesized by the method of Guthrie and Smith[7]. Anomers were isolated either by recrystallization, or by chromatography on a column of silica gel.

(*a*) *Tetra-O-acetyl-D-ribofuranoses* (**4**). Compound **4β** was obtained by re-

crystallization from ethanol[7]. The mother liquors were purified by column chromatography, with elution with 1:3 (v/v) cyclohexane–ethyl ether, to give more of **4β**, and **4α** as an oil; **4β**, yield 64.5%; m.p. 83–84° (lit.[7] m.p. 85°); R_F 0.62; **4α**, yield 10%; $[\alpha]_D^{20}$ +75.6° (*c* 1, MeOH); R_F 0.55.

Anal. Calc. for $C_{13}H_{18}O_9$: C, 49.06; H, 5.67. Found for **4α**: C, 48.98; H, 5.62.

(*b*) *Tetra*-O-*acetyl*-D-*xylofuranoses* (**5**). Compounds **5α** and **5β** were isolated by column chromatography, with elution with 1:3 (v/v) cyclohexane–ethyl ether, as oils, in 90% yield: **5α**, yield 44%; $[\alpha]_D^{20}$ +102.4° (*c* 1.25, $CHCl_3$); R_F 0.55; **5β**, yield 46%; $[\alpha]_D^{20}$ −16.2° (*c* 0.90, $CHCl_3$); R_F 0.50.

Anal. Calc. for $C_{13}H_{18}O_9$: C, 49.06; H, 5.67. Found for **5α**: C, 49.10; H, 5.60; for **5β**: C, 49.09; H, 5.62.

(*c*) *Tetra*-O-*acetyl*-D-*lyxofuranoses* (**6**). Compounds **6α** and **6β** were separated in 84% yield by column chromatography, with elution with 1:2 (v/v) pentane–ethyl ether. Compound **6α**, yield 60%; $[\alpha]_D^{20}$ +69.5° (*c* 1.35, $CHCl_3$) (lit.[12] $[\alpha]_D$ +73.0° ±0.7°); R_F 0.24; **6β**, yield 24%; $[\alpha]_D^{20}$ −38.5° (*c* 0.85, $CHCl_3$); R_F 0.18.

Anal. Calc. for $C_{13}H_{18}O_9$: C, 49.06; H, 5.67. Found for **6α**; C, 48.95; H, 5.70; for **6β**: C, 49.01; H, 5.53.

In addition, 1,2,3,4-tetra-*O*-acetyl-α-D-lyxopyranose was obtained, and crystallized from petroleum ether; yield 10%; m.p. 123–124°, $[\alpha]_D^{20}$ +22° (*c* 1.80, $CHCl_3$), (lit.[12] m.p. 124°, $[\alpha]_D$ +25°); ^{1}H-n.m.r. data ($CDCl_3$): δ 6.07 (d, 3.0 Hz, H-1).

(*d*) *Tetra*-O-*acetyl*-α,β-D-*arabinofuranoses* (**7**). Attempted separation of the anomers was unsuccessful. Compounds **7** were obtained as a syrupy mixture of the anomers, in 90% yield, by column chromatography; $[\alpha]_D^{20}$ +33.5° (*c* 1.65, $CHCl_3$) (lit.[6] $[\alpha]_D$ +29°).

Anal. Calc. for $C_{13}H_{18}O_9$: C, 49.06; H, 5.67. Found for **7**: C, 49.11; H, 5.53.

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