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THE ACID-CATALYSED CONDENSATION OF D-XYLOSE WITH BENZALDEHYDE IN THE PRESENCE OF ALCOHOLS. TWO DIASTEREOISOMERIC 1,2:3,5-DI-*O*-BENZYLIDENE-α-D-XYLOFURANOSES

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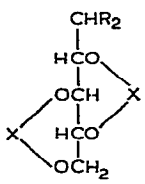
INTRODUCTION

Reaction of D-xylose with benzaldehyde–methanol mixtures in the presence of an acid catalyst affords 2,4:3,5-di-*O*-benzylidene-D-xylose dimethyl acetal[1] (**1**; R = OMe, X = CHPh), which can also be prepared in high yield by mercury-catalysed solvolysis of 2,4:3,5-di-*O*-benzylidene-D-xylose diethyl dithioacetal (**1**; R = SEt, X = CHPh) in methanol[2,3]. Although it has been used on many occasions to characterise D-xylose, and also in the quantitative determination of this sugar[1,4], the dimethyl acetal has apparently not found other use; the related 2,4-*O*-benzylidene-D-xylose dimethyl acetal, prepared after partial hydrolysis of the thioacetal (**1**; R = SEt, X = CHPh), has, however, been employed in the synthesis of 3-*O*-β-D-xylopyranosyl-D-xylose[3].



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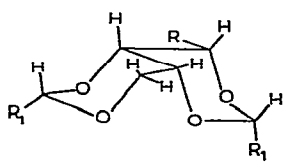

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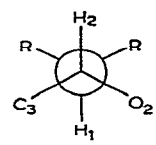

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We now report on experiments designed to provide a route to a series of di-*O*-benzylidene-D-xylose dialkyl acetals and, from them, to D-xylose dialkyl acetals, which were required for comparison with compounds detected amongst the products of alcoholysis of this pentose[5].

RESULTS AND DISCUSSION

The use of ethanol, propyl alcohol, butyl alcohol, and isobutyl alcohol in place of methanol in the initial condensation afforded the corresponding 2,4:3,5-di-*O*-benzylidene-D-xylose dialkyl acetals (**1**; R = OEt, OPr, OBu, OBu^i X = CHPh) in good yield, each of which, together with the dimethyl compound (**1**; R = OMe, X = CHPh), gave syrupy D-xylose dialkyl acetals on hydrogenolysis in 2-methoxyethanol; these were

characterised by conversion into crystalline bis(benzeneboronic) esters (**1**; R=O-alkyl, X=BPh). Previously[6], the methyl and ethyl acetals had been prepared by lengthier procedures from D-xylose diethyl dithioacetal. With ethylene glycol, under the same conditions, a cyclic ethylene acetal derivative was obtained from which the benzylidene groups were removed to give crystalline D-xylose ethylene acetal.

The 60-MHz nuclear magnetic resonance (n.m.r.) spectra of the dibenzylidene dialkyl acetals (**1**; R=O-alkyl, X=CHPh) were closely similar, except for the normal variations in the alkyl-group resonances, and were consistent with "*O*-inside", *cis*-decalin conformations [**2**; R=CH(O-alkyl)$_2$, R$_1$=Ph; $J_{4,5}$ and $J_{4,5'}$, *ca.* 2 Hz] as was expected, since (*a*) in this conformation, the group at C-2 is equatorial, and (*b*) this is the ring shape adopted by the parent bicyclic compound[7] (**2**; R=R^1=H)* and by 1,3:2,4-di-*O*-benzylidene-D-threitol[8] (**2**; R=H, R$_1$=Ph)*. Each spectrum showed two singlets for benzylic protons, with separations that increased with the size of the alkyl groups [dimethyl acetal, τ4.37, 4.37 (unresolved); diethyl acetal, 4.38, 4.41; dipropyl acetal, 4.38, 4.43; dibutyl acetal, 4.36, 4.42; di-isobutyl acetal, 4.36, 4.43], which suggests that large alkyl groups cause small, specific shieldings of the nearer benzylic protons. Alternatively, both alkyl groups on each compound showed identical resonance patterns (with tetra-*O*-acetyl-D-xylose diethyl dithioacetal, the signals from each ethyl group can be recognised[5]), suggesting that free rotation occurs about the C-1–C-2 bonds. This conclusion is supported by the finding that the H-1 splitting of 7.5 Hz observed near τ 5.15 for each dibenzylidene dialkyl acetal is unaffected by raising the temperature to 60°, and so it most probably is a weighted mean value of the sort that is observed for the ethyl group (6.7–7.2 Hz)[9], rather than a coupling constant derived from the most stable rotamer (**3**) with H-1 and H-2 opposed.

In the case of the ethylene compound (**1**; R=OCH$_2^-$, X=CHPh), the benzylic protons resonate unexceptionally at τ 4.34 and 4.37, and the other spectral features are consistent with those of the derivatives of the alkyl acetals, apart from the H-1 signal which appears as a doublet (splitting, 7.0 Hz) at τ 4.70. The deshielding of H-1 is attributed to the influence of the unshared electrons on the adjacent oxygen atoms held in the dioxolane ring in orbitals eclipsed with the C-1–H bond; this may also explain, to some extent, why benzylidene acetal protons on dioxolane rings resonate at lower fields than those on 1,3-dioxane rings[10].

Attempts to repeat the condensation reactions by using benzaldehyde together with secondary or tertiary alcohols (isopropyl alcohol, *sec*-butyl alcohol, *tert*-butyl alcohol) resulted in the isolation of crystalline, non-reducing products devoid of alkyl groups, and identified by n.m.r. spectroscopy as mixtures of di-*O*-benzylidene-D-xyloses. Thin-layer chromatography revealed the presence of two components (*A* and *B*) which were isolated after separation on a column of alumina, and had m.p 132–133°, $[\alpha]_D$+25° (chloroform), and m.p. 155–156°, $[\alpha]_D$+27° (chloroform), respectively. The only products of direct condensation of benzaldehyde and a xylose previously reported

*In these papers, 1,3:2,4-di-*O*-methylene-and 1,3:2,4-di-*O*-benzylidene-L-threitol were examined, and the conformations of the enantiomers are inferred.

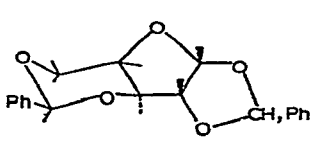
have m.p. 132°, $[\alpha]_D$ +26° (chloroform)*[11], and m.p. 130°, $[\alpha]_D$ +37.5° (methanol)**[12], respectively.

Partial hydrolysis of a mixture of isomers *A* and *B* afforded a mixture (n.m.r. analysis; see below) of monobenzylidene-D-xyloses, which did not reduce Fehlings' solution or sodium metaperiodate, and from which, on methylation and removal of the second benzylidene group, 3,5-di-*O*-methyl-D-xylose alone was obtained. The monobenzylidene compounds were consequently diastereoisomeric 1,2-*O*-benzylidene-D-xylofuranoses, and compounds *A* and *B* were 1,2:3,5-di-*O*-benzylidene-D-xylofuranoses.

The n.m.r. spectrum of compound *B* comprised a phenyl signal (10 protons), a doublet at τ 3.80 (H-1, $J_{1,2}$ 4.0 Hz), two benzylidene-acetal singlets (τ 4.10 and 4.54), a doublet at τ 5.31 (H-2, $J_{2,3}$ 0.5 Hz), and a doublet at τ 5.49 (H-3, $J_{3,4}$ 2.2 Hz) which overlapped the low-field part of the H-4, H-5e, H-5a ABC system. This was analysed by reference to computer-calculated, theoretical spectra[13], and $J_{4,5e} \simeq J_{4,5a} \simeq 2$ Hz and $J_{5a,5,e} \simeq 12$ Hz were thus obtained. The assignments were uncomplicated, except for H-3, and H-4 (τ 5.84), and were confirmed by a spin-decoupling experiment in which secondary irradiation at τ 5.8 caused decoupling of the assigned H-3 and H-5e signals. Compound *A* gave a spectrum differing in only two respects from that of *B*: (*a*) the low-field benzylidene resonance occurred at τ 3.83, instead of 4.10, and (*b*) H-3 gave a signal at τ 5.37. All other spectral features were alike; chemical shifts were within 3 Hz of the corresponding signals in the spectrum of isomer *B*, and the splittings were identical. Partial hydrolysis of both isomers exclusively removed the high-field benzylidene acetal signals (τ 4.51 and 4.54), indicating that they were derived from a common six-membered 3,5-ring, so that the two di-*O*-benzylidene-D-xyloses differ only in stereochemistry at the acetal centre of the 1,2-ring.

Since benzylic protons on dioxolane rings fused directly to five-membered cyclic systems are deshielded when *endo*[14], compounds *A* and *B* are assigned the H-*endo* and H-*exo* configurations, respectively. Consistent with this are the observations that, under kinetic control, preponderant proportions of isomer *B* are formed, whereas, at equilibrium, the compound with the phenyl groups *exo* is preponderant[14], and that H-3 is specifically shielded when the phenyl group on the dioxolane ring is *endo* (*B*).

It may be assumed, on the basis of extensive studies of benzylidene acetals[15], that the phenyl group on the 1,3-dioxane ring is equatorial in both isomers, but, since the compounds can exist with this ring in either of two slightly distorted chair conformations (**4**, "*O*-inside"; **5**, "H-inside"), this assumption does not permit a configu-



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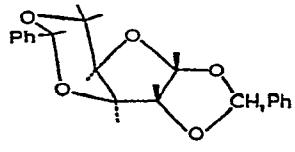

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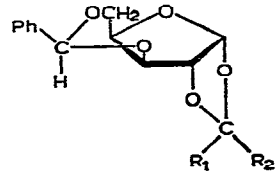

6 R_1 = H, R_2 = Ph
7 R_1 = Ph, R_2 = H

*This compound was described as the L enantiomer.

**The enantiomeric form was not indicated, but it has been assumed[11] to be L.

rational assignment at the second benzylidene centre. The H-4 and H-5 signals in the n.m.r. spectra of compounds *A* and *B*, however, allow a clear choice to be made in favour of structure **4**, since a large $J_{4,5a}$ value would be observed for conformation **5**, in which the C-4–H/C-5a–H angle is near 150°. A 4,5a splitting of 2 Hz precludes this possibility. In keeping with the "O-inside" assignment, $J_{2,3}$ is found to be < 1 Hz, and the measured dihedral angle is *ca.* 90°, whereas the coupling constants would be about 7 Hz for the alternative conformation (measured angle, *ca.* 150°).

Compounds *A* and *B* are assigned structures **6** and **7**. D-Xylose reacts with benzaldehyde, therefore, as with ketones to give 1,2:3,5-diacetals, which, on mild hydrolysis with acid, preferentially lose the six-membered ring, and, as has been found elsewhere with benzylidene derivatives[14,16], diastereoisomerism occurs only on the dioxolane system. The "O-inside" conformation adopted by those carbohydrate diacetals having a *cis*-decalin type of ring system[7,8,14] is also favoured by the oxygenated *cis*-hydrindanes.

EXPERIMENTAL

Analytical n.m.r. spectra were measured at 60 MHz and the double-resonance and elevated-temperature experiments at 100 MHz, with deuterated chloroform as solvent and tetramethylsilane as internal standard.

2,4:3,5-Di-O-benzylidene-D-xylose dialkyl acetals. — Freshly distilled benzaldehyde (20 ml) was added at 0° to a mixture of D-xylose (5 g) and dry alcohol (methanol, ethanol, propyl alcohol, butyl alcohol, isobutyl alcohol, or ethylene glycol; 100 ml) containing hydrochloric acid (4 ± 1%), and kept for 0.5 h at 0°. The heterogeneous mixtures were then allowed to warm to room temperature and kept for 2 days, after which they were again cooled to 0° and kept for a further 2 days. The crude acetals were removed by filtration, washed with water and methanol, and recrystallised from dichloromethane–methanol. The physical constants and analytical data are given in the Table, and the n.m.r. spectra were consistent with the assigned structures.

Parent acetal	*Yield* (%)	*M.p.* (*degrees*)	$[\alpha]_D$ (*degrees*) *in chloroform*	*Found, %* C	H	*Calc., %* C	H
Dimethyl[a]	70	209–210	−8	—	—	—	—
Diethyl[b]	60	185–186	−3	68.6	7.0	69.0	7.0
Dipropyl	60	168–170	−4	70.0	7.6	70.1	7.5
Dibutyl	50	160–161	−3	71.3	8.0	71.0	8.0
Di-isobutyl	30	158–159	+7	70.9	7.9	71.0	8.0
Ethylene	60	219–221	−22	67.9	6.0	68.1	6.0

[a]Lit.[1], m.p. 211–212°, $[\alpha]_D$ −9° (chloroform). [b]Lit.[6], m.p. 179°, $[\alpha]_D$ −2.8° (chloroform).

D-Xylose dialkyl acetals. — As a safeguard against acid-catalysed ring closure of the acetals, all processes, except the final evaporation, were carried out in the

presence of small amounts of basic resin (Deacidite FF, OH^-). The benzylidene acetals (1–2 g) in 2-methoxyethanol (300–500 ml) were hydrogenated at atmospheric temperature and pressure in the presence of a palladium catalyst (0.2–0.5 g, 10% on charcoal). After completion of the reaction (4 mol. of gas consumed; reaction times 0.5–3 h), the catalyst and solvent were removed to leave syrups that were taken up in water and extracted with carbon tetrachloride. The aqueous phases were taken to dryness, to give chromatographically pure products in yields of 80–95%. The $[\alpha]_D$ values (water) were: dimethyl acetal, +22° (lit.[6], +19.3°); diethyl acetal, +18° (lit.[6], +20.7°); dipropyl acetal, +18°; dibutyl acetal, +20°; di-isobutyl acetal, +18°; ethylene acetal, +1°. The last compound had m.p. 86.5–87.5° (Found: C, 43.3; H, 7.2. $C_7H_{14}O_6$ calc.: C, 43.3; H, 7.3%). The R_F values on chromatograms eluted with ethyl methyl ketone saturated with water were 0.13, 0.44, 0.78, 0.89, 0.87, and 0.10, respectively.

D-*Xylose dialkyl acetal bis(benzeneboronates)*. — The acetals (*ca.* 1 g) in *p*-dioxane (1%) were heated under reflux for 0.5 h with triphenylboroxole (0.66 mol.), and the majority of the solvent was then removed slowly by distillation. Final traces of *p*-dioxane were removed under vacuum, and the crystalline residues were recrystallized (light petroleum, b.p. 60–80°, for the dimethyl and diethyl compounds, b.p. 80–100°, for the dipropyl and ethylene compounds; aqueous methanol for the dibutyl compound) or sublimed (di-isobutyl compound).

Parent acetal	*Yield* (%)	*M.p.* (*degrees*)	$[\alpha]_D$ (*degrees*) *in* p-*dioxane*	*Found*, % *C*	*H*	*B*	*Calc.*, % *C*	*H*	*B*
Dimethyl	74	168–169	+30	61.7	6.0	6.0	62.0	6.0	5.9
Diethyl	58	150–151	+28	64.1	6.7	5.6	63.7	6.6	5.4
Dipropyl	67	135–136	+22	64.8	6.9	5.2	65.1	7.1	5.1
Dibutyl	25	114–115	+25	66.4	7.3	5.0	66.4	7.6	4.8
Di-isobutyl	75	130–132	+23	66.2	7.6	5.0	66.4	7.6	4.8
Ethylene	70	180–181	+1	62.8	5.7	6.0	62.4	5.5	5.9

1,2:3,5-Di-O-*benzylidene*-D-*xylofuranoses*. — Reactions with isopropyl alcohol, *sec*-butyl alcohol, and *tert*-butyl alcohol were carried out in the same way as with the primary alcohols, and mixed products were obtained as follows:

Alcohol used	*Yield* (%)	*M.p.* (*degrees*)	$[\alpha]_D$ (*degrees*) *in chloroform*	% endo-*phenyl isomer*	*Found* % *C*	*H*	*Calc.*, % *C*	*H*
Isopropyl	32	136–137	+26 ±1	50	69.9	5.6	69.9	5.6
sec-Butyl	32	138–143	+26 ±1	78	—	—	—	—
tert-Butyl	55	140–142	+26 ±1	75	69.9	5.5	69.9	5.6

The yield of products obtained from *tert*-butyl alcohol was increased to 70% when anhydrous sodium sulphate was incorporated in the reaction mixture as a desiccant.

The mixture (2.0 g) obtained from isopropyl alcohol, and containing equal proportions of isomers (n.m.r. analysis), was resolved on a column of alumina (Camag M.F.C., neutral) by graded elution with light petroleum (b.p. 60–80°) and ether. The resolution was followed by t.l.c. on alumina, and two chromatographically pure fractions were obtained. Eluted first was (*1,2-endo-phenyl*)-1,2:3,5-di-*O*-benzylidene-α-D-xylofuranose* (0.24 g), m.p. 155–156°, $[\alpha]_{5890}$ +27° (chloroform), $[\alpha]_{4000}$ −138°, $[\alpha]_{2990}$ +95°, $[\alpha]_{2620}$ +285°, $[\alpha]_{2380}$ +605° (Found: C, 69.7; H, 5.6. $C_{19}H_{18}O_5$ calc.: C, 69.9; H, 5.6%). This was followed by (*1,2-exo-phenyl*)-1,2:3,5-di-*O*-benzylidene-α-D-xylofuranose* (0.13 g.), m.p. 132–133°, $[\alpha]_{5890}$ +25° (chloroform). $[\alpha]_{4000}$ +75°, $[\alpha]_{3080}$ +196°, $[\alpha]_{2380}$ +422° (Found: C, 69.9; H, 5.6%).

A mixture of di-*O*-benzylidene-D-xyloses (3 g, containing 78% of the higher-melting form) was kept in benzaldehyde (40 ml) containing hydrochloric acid (2.5%). Equilibration occurred within a few hours, and, after 48 h, the mixture was neutralised, and the isomers were analysed by n.m.r. spectroscopy, and found to be present in the ratio *endo*-phenyl–*exo*-phenyl, 1:2. Heating for 30 min at 100° prior to neutralisation caused no change.

Partial hydrolysis of the di-*O*-benzylidene-D-xyloses (30 g, mixture containing 78% of 1,2-*endo*-phenyl isomer) was carried out in chloroform (150 ml) by adding methanolic hydrogen chloride (200 ml, 0.5%) and water (10 ml). After 2 days at 0°, the solution was neutralised with lead carbonate, filtered, and deionised with cationic and anionic resins. Water (100 ml) was added, and the bulk of the organic solvents removed under diminished pressure. The unhydrolysed acetals crystallised spontaneously and were removed by filtration (20 g), and the filtrate was taken to dryness. The syrupy residue was dissolved in chloroform (100 ml) and extracted with water (100 ml) to remove free D-xylose. The chloroform phase was taken to dryness to give a thick syrup (4.0 g), $[\alpha]_D$ +14° (ethanol), which solidified on trituration with light petroleum (b.p. 40–60°). T.l.c. and n.m.r. analysis showed it to contain mono-*O*-benzylidenexyloses exclusively. Similar treatment of the recovered diacetals afforded a further 4.3 g (total, 37%) of the partially hydrolysed products. They did not reduce Fehlings' solution, were not oxidised by sodium metaperiodate, and were shown by n.m.r. spectroscopy to contain two isomeric components in the ratio 78:22. Treatment with benzeneboronic acid in the usual way, with recrystallisation from light petroleum (b.p. 60–80°), afforded (*1,2-endo-phenyl*)-1,2-*O*-benzylidene-α-D-xylofuranose 3,5-benzeneboronate, m.p. 116–7°, $[\alpha]_D$ −6° (*p*-dioxane) (Found: C, 66.8; H, 5.5; B, 3.3. $C_{18}H_{17}BO_5$ calc.: C, 67.0; H, 5.25; B, 3.3%).

The mixed monoacetals (2.9 g) were treated with sodium hydride (1.5 g) in tetrahydrofuran (100 ml) for 3 h at room temperature, methyl iodide (30 ml) was added, and the mixture was kept for 18 h. After removal of the solids and the solvent, the residue was extracted with dichloromethane. Removal of this solvent gave a

*In the absence of an accepted rule, it is convenient to indicate the stereochemistry at the acetal carbon atom in these compounds by reference to the position of the phenyl group with respect to the fused-ring system.

syrup (2.7 g, 84%), $[\alpha]_D$ −8° (chloroform), which was homogeneous on thin-layer chromatograms and gave an n.m.r. spectrum consistent with that to be expected from 1,2-*O*-benzylidene-3,5-di-*O*-methyl-α-D-xylofuranoses. The dimethyl compound (2.5 g) was hydrogenolysed in 2-methoxyethanol (50 ml) in the presence of palladium-on-charcoal (1.7 g, 10%); 2 mol. of gas were consumed, and removal of the catalyst and solvent afforded 3,5-di-*O*-methyl-D-xylose (1.5 g, 90%, $[\alpha]_D$ +23° (water), +15° (chloroform) [lit.[17], +23° (water); +11° (chloroform)]. It was indistinguishable from 3,5-di-*O*-methylxylose on paper chromatograms, and reduced Fehlings' solution and sodium metaperiodate (1.0 mol., spectrophotometric determination[18]). Treatment of the free sugar (0.52 g) with triphenylboroxole (0.31 g, 0.33 mol.) in *p*-dioxane (30 ml), with slow removal of the solvent, gave a syrupy residue that, on distillation, afforded 3,5-di-*O*-methyl-α-D-xylofuranose 1,2-benzeneboronate (0.46 g, 60%), m.p. 53–54° [from light petroleum (b.p. 60–80°)], $[\alpha]_D$ −8° (*c* 1, *p*-dioxane) [lit.[17], m.p. 54–55°, $[\alpha]_D$ −9° (*p*-dioxane)]. The infrared spectrum was identical to that of an authentic sample and a mixed melting point was undepressed.

SUMMARY

D-Xylose condenses with benzaldehyde–primary alcohol mixtures to give 2,4:3,5-di-*O*-benzylidene-D-xylose dialkyl acetals from which the dialkyl acetals can be obtained by hydrogenolysis. Ethylene glycol affords the analogous ethylene acetal derivatives. With benzaldehyde–secondary or tertiary alcohol mixtures, two 1,2:3,5-di-*O*-benzylidene-D-xylofuranoses, which differ only in their stereochemistry at the new acetal centre on the 1,2-ring, are formed. The absolute configurations at the benzylidene positions are assigned, and the conformations of the six-membered 3,5-rings are found to be "*O*-inside".

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