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Reactions of D-lyxose and D-xylose with 2-methoxypropene under kinetic conditions*

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ABSTRACT

D-Lyxose (**1**) undergoes acetonation under kinetic conditions with 2-methoxypropene to give 2,3-*O*-isopropylidene-α-D-lyxofuranose (**2**) in high yield, further characterized as its 1,5-diacetate **3**, thus affording a preparative route to **2**. Forcing conditions are required to bring D-xylose (**5**) into reaction, leading to 39% of 3,5-*O*-isopropylidene-α,β-D-xylofuranose (**7**, further characterized as its 1,2-diacetate **9**), 33% of 1,2:3,5-di-*O*-isopropylidene-α-D-xylofuranose (**6**), and 20% of 2,3:4,5-di-*O*-isopropylidene-*aldehydo*-D-xylose (**8**, further characterized as its aldehydrol diacetate **10**). The results are all readily rationalized within the framework of the general principles earlier advanced for kinetic acetonation of sugars.

INTRODUCTION AND DISCUSSION

Previous papers in this series have surveyed several aspects of the acetonation of various sugars under kinetic control[1]. Among the aldopentoses, results with D-ribose and D-arabinose have been already reported[2]. The present report complements these findings and details the comparative behavior of the aldopentoses in this reaction, as previously[1] summarized in a general survey of the reaction.

The principal ring form of each of the four aldopentoses is pyranoid, and thus the established[1], most-favored mode of initial attack of 2-methoxypropene at a primary hydroxymethyl group is not possible (except for minor proportions of the furanoid tautomers as observed in the reaction with D-ribose[2]). The second-most-favored mode of attack, that between *cis*-disposed secondary hydroxyl groups, takes place in the case of arabinose to give the 3,4-acetal of the pyranoid sugar in high yield. D-Ribose likewise gives the pyranoid 3,4-acetal, but together in this instance (as the three hydroxyl groups are mutually *cis*) with the 2,3-acetal, which predictably rearranges to the more stable furanoid tautomer.

In the case of D-lyxose, acetonation between positions 3 and 4 is disfavored as these hydroxyl groups are *trans*-disposed, but the *cis*-disposed 2,3-diol group reacts and leads to the 2,3-diacetal in high (80–85%) yield. This product is isolated as the α-furanose form **2**, but its formation may be considered to result from pyranose→furanose tautomerization *after* acetonation.

* Taken in part from the doctoral dissertation of Joelle Barbat, Université de Clermont-Ferrand, 1985.

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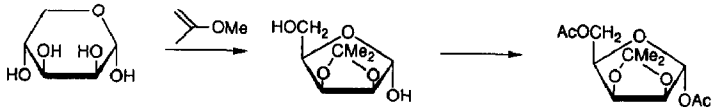
Thus the action of 2 equivalents of 2-methoxypropene on a solution of D-lyxose (**1**) in *N,N*-dimethylformamide at 0° gives 2,3-*O*-isopropylidene-α-D-lyxofuranose (**2**) in excellent yield, readily identified by n.m.r. spectroscopy and by conversion into its diacetate **3**. The yield of compound **2** reaches 80–85% if the product is isolated directly, in a form that would be suitable for further synthetic transformation; purification of the product on a column of silica gel permits isolation of ~65% of pure compound **2**.



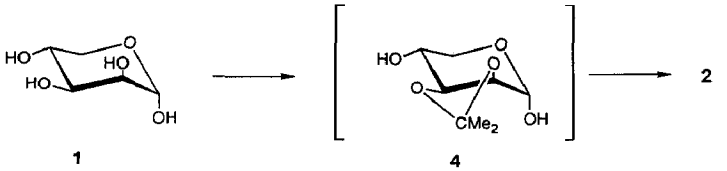
1 **2** **3**

The ^{1}H-n.m.r. spectrum of compound **2** indicates it to be a monoisopropylidene acetal, and its behavior in methyl sulfoxide solution shows, in particular, exchangeable signals at 4.58 p.p.m. as a triplet corresponding to a hydroxyl proton on a primary hydroxymethyl group, and a sole doublet at 6.23 p.p.m. corresponding to a hydroxyl group at the anomeric position of one anomer only. After deuteration, the anomeric signal at δ 5.12 collapses into a very narrow doublet ($J < 0.5$ Hz). These results establish that the compound is the pentofuranose derivative, a structural attribution consolidated by detailed examination of the ^{1}H-n.m.r. spectrum.

Acetylation of compound **2** gives the pure α-diacetate **3**, in which the H-1 signal appears as an apparent singlet ($J_{1,2} < 0.5$ Hz) at 6.08 p.p.m.

Modification of the reaction conditions, such as reaction at very low temperature, termination of the reaction before consumption of all of the lyxose, or utilization of solvents other than *N,N*-dimethylformamide did not give any stable, detectable product other than the acetal **2**. As this compound was obtained[3,4] in only 10–20% yield by conventional acetonation of lyxose under thermodynamic conditions as with acetone in the presence of copper sulfate, the kinetic acetonation procedure constitutes a major improvement in the access to compound **2**.

D-Lyxose crystallizes as the α-pyranose form and exists essentially as the pyranose tautomers in water and methyl sulfoxide solution[5]. It is proposed that the acetonation reaction leads inititally to the 2,3-pyranose acetal **4** through favored reaction at the accessible *cis*-diol group at positions 2 and 3. The remaining possible diol groups are either exclusively trans (3,4) or would involve the anomeric hydroxyl group. It is already established that the kinetic acetonation reaction is specifically disfavored at the anomeric position. Furthermore, the α-pyranose form, having the 1,2-diol group in *trans*-antiparallel disposition in the favored conformation, is the principal tautomer, and would need to anomerize to make O-1 sterically accessible.



1 **4**

As soon as the 2,3-acetal is formed, it can be expected to undergo tautomerization to the furanose form **2** because of the greater stability of the fused [3.3.0]bicyclic system in comparison with the [4.3.0] isomer. It is noteworthy that this behavior of D-lyxose parallels exactly that of the 6-deoxyhexose homomorph L-rhamnose (6-deoxy-L-mannopyranose), which likewise[6] gives in high yield the homomorphous product, 6-deoxy-2,3-*O*-isopropylidene-L-mannofuranose.

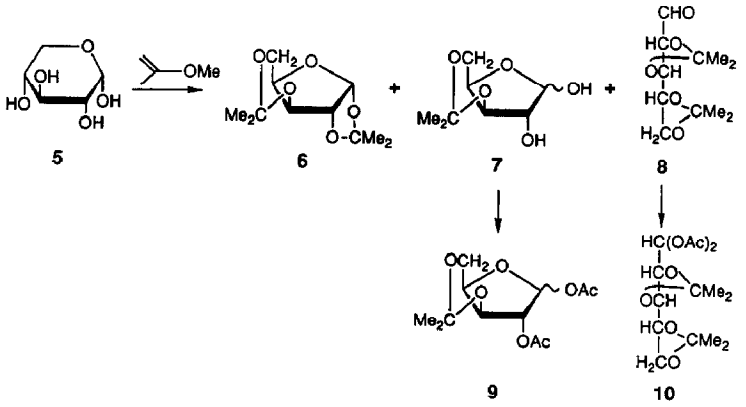
Attempts to effect further reaction of the furanoid monoacetal **2** with the acetonation reagent under a range of forcing conditions did not lead to any further acetonation, as by bridging between the hydroxyl groups at positions 5 and 1. This result contrasts with the behavior observed with D-ribose, where the initital 2,3-*O*-isopropylidene-D-ribofuranose could be subsequently converted into a 1,5:2,3-di-isopropylidene acetal. The failure of this reaction may be attributed to the fact that the lyxose derivative exists, even at mutarotational equilibrium, essentially exclusively as the α anomer, having the hydroxyl group at C-1 *trans*-disposed to the substituent at positions 2 and 3. This is in contrast with the situation in the corresponding 2,3-*O*-isopropylidene-D-ribofuranose analog, which is essentially exclusively the β anomer and in which therefore the stereochemical arrangement is suitable for formation of the 1,5-bridged derivative when the conditions of reaction are sufficiently vigorous to overcome the general reluctance of the reagent to react with the anomeric hydroxyl group.

D-Xylose (**5**) is exceptional among the aldopentoses in that it has no *cis*-diol group present, apart from the 1,2-diol of the α-pyranose tautomer, and it is to be expected[1] that reactivity at position 1 would be low under the kinetic acetonation conditions used here. Classic thermodynamic acetonation leads[7] to 1,2:3,5-di-*O*-isopropylidene-α-D-xylofuranose (**6**).

The reaction of 1.8–2.0 equivalents of 2-methoxypropene with **5** under the general conditions used with the other aldopentoses[2] led to a complex mixture of monoacetals and rather unstable products containing acyclic acetal groups; no single stable acetal is formed in high yield. At the same time, a considerable proportion of the starting sugar remained unreacted. The reaction was repeated employing a larger excess of reagent (3 equivalents). This led to complete conversion of the starting material, and t.l.c. of the product mixture indicated a larger proportion of diacetal products. Column chromatography of this mixture led to diacetal **6** in 33% yield, to **8** in ~20% yield (a compound of low stability), and monoacetal **7** in 39% yield. These compounds were identified by ^{1}H-n.m.r. spectroscopy and by comparison with the literature; furthermore, from compound **7** the α and β diacetates **9** and for **8** the aldehydrol diacetate **10** were prepared.

Numerous repetitions of this reaction indicate significant difficulties in exact reproduction of all results and the formation of the isolated products in the same proportion. Furthermore, other products of low stability (probably aldehydo forms) also appear to be formed in the mixture.

D-Xylose (**5**) is known[5] to exist exclusively in the pyranose form in solution; neither furanose forms nor the aldehydo form can be expected to be present to any significant extent at the outset of the reaction. The results of the present work may be interpreted as proceeding through initial attack on the most reactive hydroxyl group

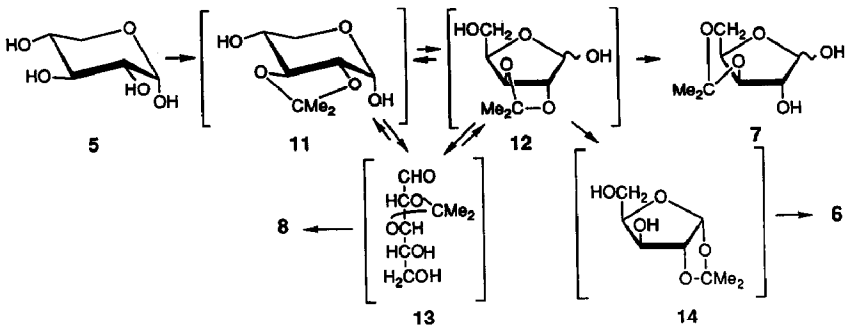


(O-2) with possible ring-closure under the forcing conditions in the *trans*-disposition to form the unstable pyranoid 2,3-acetal **11**, which may tautomerize to the likewise unstable furanoid form **12** or, more probably, to the aldehydo form **13**, which would then present a ready opportunity for acetonation between the primary position 5 and position 4 to give the aldehydo diacetal **8**. Alternatively, the furanoid acetal **12** may isomerize by a classic acid-catalyzed mechanism to either the stable furanoid 3,5-acetal **7**, which was the preponderant product isolated, or to the furanoid 1,2-monoacetal **14**. The latter was not isolated; this compound can be expected to display high reactivity initiated at the primary hydroxymethyl group with rapid ring-closure at the accessible O-3 position to give the furanoid 1,2:3,5-diacetal **6** actually isolated.

The fact that all of these reactions leading to the three isolated products requires an initial step to liberate the hydroxymethyl group is in accord with the observation that, only when a large excess of reactant is used, is the xylose completely used up in the reaction.

The proposed initial acetal **11** might conceivably be converted into the pyranoid 1,2-acetal that has been observed in the reaction of D-xylose (**5**) with dimethoxypropane[8], but no evidence for the formation of 1,2-*O*-isopropylidene-α-D-xylopyranose under the present conditions with 2-methoxypropene was found. In support of the hypothesis of the transitory acetal **11**, it should be noted that concurrent work[9,10] has shown that 2-methoxypropene can effectively bridge a *trans*-diol group in a pyranoid ring under forcing conditions, if a more favorable arrangement for the initital reaction is not accessible*. It cannot be excluded that these transformations might also occur by way of transitory acyclic acetal derivatives.

* This is exemplified with the methyl α- and β-D-glucopyranosides, which readily react to form the 4,6-monoisopropylidene acetals and then under forcing conditions to give in high yield the 2,3:4,6-diacetals having the 2,3-*trans* configuration[9]; likewise the corresponding methyl α- and β-D-xylopyranosides react[1,10] to give a mixture of the 2,3- and 3,4-monoisopropylidene acetals having in each case the dioxolane ring *trans*-fused. In these glycoside examples, further tautomerization is not possible.



EXPERIMENTAL

General methods. — Chromatography was performed on Silica Gel 60 (E. Merck 5724) plates. Column purifications were performed on Silica Gel 60 (E. Merck 70–230 mesh) or with LiChroprep Si 60 on a Lobar (E. Merck) column. All solvents were dried and redistilled. ^{1}H-N.m.r. spectra at 60 MHz were recorded with a Varian T-60 spectrometer and those at 200 MHz with a Bruker WP-200 MHz spectrometer; chemical shifts are indicated in p.p.m. with reference to Me_4Si for solutions of ~20%; s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet. Optical rotations were recorded with a Perkin–Elmer 241 polarimeter for solutions of concentration 0.1. Melting points were recorded with a Büchi SMP-20 apparatus and are not corrected.

Action of 2-methoxypropene on D-*xylose.* — A solution of D-xylose (**5**, 4.5 g, 30 mmol) in anhydrous *N,N*-dimethylformamide (50 mL) was stirred at 0°. The 2-methoxypropene reagent (4.3 g, 60 mmol, 2 equiv.), dried over 4A molecular sieves, was slowly added together with catalytic quantities (~10 mg) of *p*-toluenesulfonic acid. After ~2 h, an extra equiv. of reagent was added. The course of the reaction was monitored by t.l.c. (EtOAc). After 5 h of reaction, the starting material had practically disappeared, and Na_2CO_3 (5 g) was added to the mixture, which was stirred for an additional 1 h. The mixture was filtered, and the filtrate was poured into a mixture of ice and water (50 mL). The resulting solution was extracted several times with CH_2Cl_2 (3 × 50 mL), and the organic extracts obtained were washed with water (4 × 20 mL), and then dried (Na_2SO_4). Evaporation of the solvent resulted in 4.4 g of a syrup composed principally of two products (t.l.c.), which were separated on a Lobar column (1:2 EtOAc–hexane) to afford two diacetals (**6** and **8**) pure in 33 and 20% yields, respectively. The aqueous phase and the aqueous extracts, after evaporation of the solvent under diminished pressure, were lyophilized to afford compound **7**, together with small quantities of impurities, which were removed by passage through a column of silica gel (EtOAc) to afford **7** in 39% yield. These compounds were identified by comparison with literature data and by ^{1}H-n.m.r. spectroscopy.

Compound **6** had m.p. 43.5–45°, $[\alpha]_D^{21}$ +13° (water); lit.[8] m.p. 44–45°, $[\alpha]_D^{20}$ +13° (water); ^{1}H-n.m.r. ($CDCl_3$): δ 6.00 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 4.48 (d, 1 H, $J_{2,3}$ ~0 Hz,

H-2), 4.26 (d, 1 H, $J_{3,4}$ 2.3 Hz, H-3), 3.8–4.2 (m, 3 H, H-4,5,5'), and 1.3–1.5 (12 H, 2 CMe_2).

Compound **7** was a syrup, $[\alpha]_D^{21}$ +5.5° (MeOH), $[\alpha]_D^{21}$ +9.5° (water); lit.[8] $[\alpha]_D^{20}$ +19.2° (MeOH); ^{1}H-n.m.r. (Me_2SO-d_6): δ 5.95 and 5.55 (d, 1 H total, D_2O exchangeable, J 7.8 and 7.6 Hz, HO-1α and HO-β), 5.45 and 5.20 (d, 1 H total, D_2O exchangeable, J 4.2 and 4.8 Hz, HO-2α and HO-2β), 5.40 and 5.00 (d and s, 1 H total, $J_{1,2}$ 3.8 and ~0 Hz, H-1α and H-1β), 4.4–4.8 (m, 5 H, H-2,3,4,5,5'), and 1.40 (m, 6 H, CMe_2).

Compound **8** was a syrup, ^{1}H-n.m.r. ($CDCl_3$): δ 9.11 (d, 1 H, $J_{1,2}$ Hz, H-1), 4.4–4.9 (m, 5 H, H-2,3,4,5,5'), and 1.40–1.45 (m, 12 H, 2 × CMe_2).

The foregoing procedure was employed as the general method for acetonation under kinetic control of all mono- and oligo-saccharides employed in the remaining work concurrently described.

Formation of the acetates **9** *and* **10**. — A solution of diol **7** (or the aldehyde **8**) in pyridine at 0° was treated with twice the stoichiometric quantity of Ac_2O. After 24 h the solution was poured on ice and Na_2CO_3, and the mixture was extracted with CH_2Cl_2. The organic phase was washed with satd. aq. $NaHCO_3$ and then dried (Na_2SO_4). Evaporation gave the diacetate **9** (or the diacetate **10**) as a pure product after purification on a column of silica gel (1:1 EtOAc–hexane) as a syrup containing both anomeric forms.

Compound **9** was a syrupy 17:3 α:β mixture, $[\alpha]_D^{21}$ +58° ($CHCl_3$); lit.[8] m.p. 64–65°, $[\alpha]_D^{20}$ +77.2° for the pure α anomer; ^{1}H-n.m.r. ($CDCl_3$): δ 6.47 and 6.15 (d and s, 1 H total, $J_{1,2}$ 3.8 and ~0 Hz, H-1α and H-1β), (following signals for the α anomer only) 5.20 (dd, 1 H, $J_{2,3}$ 1.6 Hz, H-2), 4.35 (dd, 1 H, $J_{3,4}$ 3.6 Hz, H-3), 4.22 (m, 1 H, $J_{4,5}$ ~ $J_{4,5'}$ 3.6–3.8 Hz, H-4), 3.37 (q, 1 H, $J_{5,5'}$ 12.5 Hz, H-5), 4.05 (q, 1 H, H-5'), 2.09 and 2.05 (s, 6 H total, OAc), and 1.41, 1.39 (s, 6 H, CMe_2).

Compound **10** had $[\alpha]_D^{20}$ −21° (MeOH); lit.[3] $[\alpha]_D$ −24.3°; ^{1}H-n.m.r. ($CDCl_3$): δ 6.75 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 3.9–5.10, H-2,3,4,5,5'), 2.10 (s, 6 H, OAc), and 1.30–1.50 (m, 12 H, CMe_2).

Acetonation of D-*lyxose to give 2,3-*O-*isopropylidene-*α-D-*lyxofuranose* (**2**). — To a solution of D-lyxose (**1**, 1.5 g, 10 mmol) in *N,N*-dimethylformamide (30 mL) at 0° was added 2 equiv. of 2-methoxypropene and a catalytic amount of *p*-toluenesulfonic acid. After 3 h at 0°, the mixture was made neutral. The filtrate was evaporated under diminished pressure at 40° to afford 2.0 g of crude product which was purified on a column of silica gel (EtOAc) to afford 1.3 g (68%) of **2**, identified by ^{1}H-n.m.r. spectroscopy. The compound had m.p. 80–82°, $[\alpha]_D^{21}$ +23 → +18° (final, H_2O); lit.[4] m.p. 81.5–82.5°, $[\alpha]_D^{22}$ +21.4 → 18.5° (10 min, H_2O); ^{1}H-n.m.r. (Me_2SO-d_6): δ 6.23 (d, 1 H, D_2O exchangeable, J 4.2 Hz, HO-1), 4.58 (t, 1 H, D_2O exchangeable, J 5.4 Hz, HO-5), 5.12 (d, 1 H, $J_{1,2}$ <0.5 Hz, H-1), 4.42 (d, 1 H, $J_{2,3}$ 6.0 Hz, H-2), 4.49 (dd, 1 H, $J_{3,4}$ 3.4 Hz, H-3), 3.3–3.8 (m, H-4,5,5'), 1.23 and 1.33 (s, 6 H, CMe_2).

*1,5-Di-*O*-acetyl-2,3-*O*-isopropylidene-*α-D-*lyxofuranose* (**3**). — Conventional acetylation of compound **2** with Ac_2O–pyridine with subsequent purification on a column of silica gel (1:1 EtOAc–hexane), gave the diacetate **3**, m.p. 48–50°, $[\alpha]_D^{21}$ +59.5° ($CHCl_3$); lit.[4] m.p. 49.5–50.5°, $[\alpha]_D$ +62.8° ($CHCl_3$); ^{1}H-n.m.r. (Me_2CO-d_6): δ 6.08 (s, 1

H, $J_{1,2}$ <0.5 Hz, H-1), 4.77 (d, 1 H, $J_{2,3}$ 5.8 Hz, H-2), 4.97 (dd, 1 H, $J_{3,4}$ 3.2 Hz, H-3), 4.0–4.4 (m, 3 H, H-4,5,5'), 2.03 (s, 6 H, OAc), 1.42 and 1.32 (s, 6 H, CMe_2).

REFERENCES

1 J. Gelas and D. Horton, *Heterocycles*, 16 (1981) 1587–1601.
2 J. Gelas and D. Horton, *Carbohydr. Res.*, 45 (1975) 181–195.
3 P. A. Levene and E. T. Stiller, *J. Biol. Chem.*, 102 (1933) 187–201; P. A. Levene and R. S. Tipson, *ibid.*, 115 (1936) 731–747.
4 R. Schaffer, *J. Res. Natl. Bur. Stand.*, 65A (1961) 507–512.
5 S. J. Angyal, *Adv. Carbohydr. Chem. Biochem.*, 42 (1984) 15–68; and references cited therein.
6 J. Barbat, J. Gelas, and D. Horton, *Carbohydr. Res.*, 116 (1983) 312–316.
7 K. Freudenberg and O. Svanberg, *Ber.*, 55 (1922) 3239–3242; W. N. Haworth and C. R. Porter, *J. Chem. Soc.*, (1928) 611–618; P. A. Levene and A. L. Raymond, *J. Biol. Chem.*, 102 (1933) 317–330.
8 M. Kiso and A. Hasegawa, *Carbohydr. Res.*, 52 (1976) 95–101.
9 J. L. Debost, J. Gelas, D. Horton, and O. Mols, *Carbohydr. Res.*, 125 (1984) 329–335.
10 J. L. Debost, J. Gelas, and D. Horton, unpublished observations.