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ACETONATION OF SOME PENTOSES WITH 2,2-DIMETHOXYPROPANE–*N*,*N*-DIMETHYLFORMAMIDE–*p*-TOLUENESULFONIC ACID*

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ABSTRACT

D-Xylose, D-arabinose, and D-ribose were each treated with 2,2-dimethoxypropane in *N*,*N*-dimethylformamide containing a trace of *p*-toluenesulfonic acid. D-Xylose gave 3,5-*O*-isopropylidene-D-xylofuranose, 1,2:3,5-di-*O*-isopropylidene-α-D-xylofuranose, 1,2-*O*-isopropylidene-α-D-xylopyranose, and two acyclic di-*O*-isopropylidene derivatives. D-Arabinose gave the known 3,4-*O*-isopropylidene-β-D-arabinopyranose and 1,2:3,4-di-*O*-isopropylidene-β-D-arabinopyranose. D-Ribose gave 2,3-*O*-isopropylidene-D-ribofuranose almost exclusively.

INTRODUCTION

A mixture of 2,2-dimethoxypropane, *N*,*N*-dimethylformamide, and *p*-toluenesulfonic acid is known to be a unique acetonating reagent for the preparation of a variety of isopropylidene derivatives[2–9], and in the amino sugar field, it has found new potential utility in our recent studies[10–12]. In the immediately preceding paper[1], we reported that D-glucose reacts with this reagent to give various products that reflect the pyranose–furanose equilibria in the reaction solution.

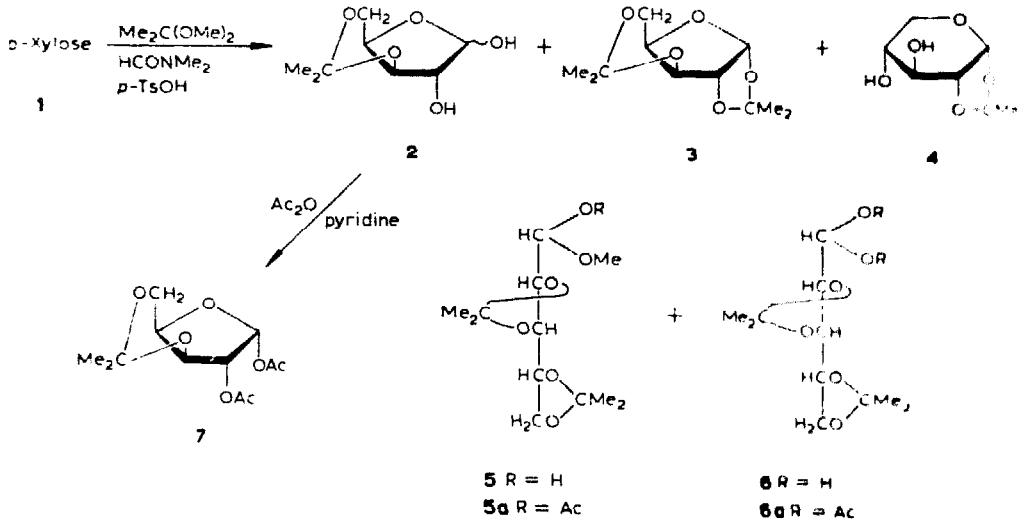
We now describe the reaction of some pentoses with this reagent, and discuss the reaction mechanism for D-xylose.

RESULTS AND DISCUSSION

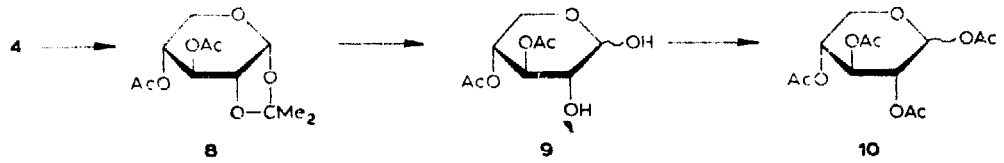
Treatment of D-xylose (**1**) with ~3.0 mole-equivalents of 2,2-dimethoxypropane in dry *N*,*N*-dimethylformamide in the presence of a trace of *p*-toluenesulfonic acid at 40–45° gave a mixture from which four fractions (**A–D**) were separated by column chromatography. Fraction **A** yielded the known 1,2:3,5-di-*O*-isopropylidene-α-D-xylofuranose (**3**) as a single product, and the specific rotation and melting point were

*The Behavior of Some Aldoses with 2,2-Dialkoxypropane–*N*,*N*-Dimethylformamide–*p*-Toluenesulfonic Acid, Part V. For Part IV, see ref. 1.

identical with those reported[13]. Fraction **B** gave a single spot in t.l.c., but acetylation of the material yielded two syrupy esters, **5a** and **6a**. The n.m.r. spectrum of **5a** showed the presence of one acetyl, one methoxyl, and two isopropylidene groups, whereas that of **6a** revealed two acetyl and two isopropylidene groups. The chemical shifts of the signals for H-1 (δ 5.9 for **5a**, and 6.98 for **6a**) were strongly indicative of the presence of one, or two, acetoxyl group(s) at C-1. Their mass spectra showed the parent peaks at *m/e* 289 (**5a**) and 317 (**6a**), respectively, which were assigned to the $M^+ - \cdot CH_3$ ions. The treatment of fraction **B** with 60% aqueous acetic acid, in addition, gave crystals identified as D-xylose. Thus, the most probable structures of **5a** and **6a** are 1-*O*-acetyl-2,3:4,5-di-*O*-isopropylidene-1-*O*-methyl-(D-xylose aldehydrol) and 1,1-di-*O*-acetyl-2,3:4,5-di-*O*-isopropylidene-(D-xylose aldehydrol), respectively; and, therefore, the two components of fraction **B** are 2,3:4,5-di-*O*-isopropylidene-1-*O*-methyl-(D-xylose aldehydrol) (**5**) and 2,3,4,5-di-*O*-isopropylidene-(D-xylose aldehydrol) (**6**).



Fraction **C** gave a crystalline product which did not reduce Fehling solution. Its n.m.r. spectrum indicated that the product was a single anomer having one isopropylidene group; the chemical shift (δ 5.29) and the coupling constant ($J_{1,2}$ 2.8 Hz) for H-1 are strongly indicative of an α-pyranoid structure. This acetal was acetylated, the diacetate (**8**) deacetonated, and the product (**9**) acetylated to compound **10**, whose spectral data agreed with those of 1,2,3,4-tetra-*O*-acetyl-D-xylopyranose synthesized by the direct acetylation of D-xylose (**1**). Thus, it is evident that the component of fraction **C** is 1,2-*O*-isopropylidene-α-D-xylopyranose (**4**). The n.m.r. data for **4** (see Experimental section) indicate that the $^1C_4$(D) conformer preponderates in chloroform-*d*, and this preponderance was also found for the 3,4-diacetate **8**. However, as compound **10** exists in the $^4C_1$(D) conformation, the $^1C_4$(D) conformation must be caused by the 1,2-*O*-isopropylidene ring.

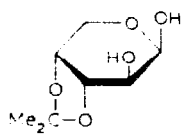


8 9 10

The main product was obtained from fraction **D** in 32% yield. Its n.m.r. spectrum showed the presence of one isopropylidene group, and two anomeric protons were observed at δ 5.67 and 5.2 as a narrow doublet ($J_{1,2}$ 3.8 Hz) and a singlet ($J_{1,2}$ ~0 Hz), respectively, strongly indicative of a furanoid structure. This compound reduced Fehling solution, and consumed one mole of periodate per mole. Acetylation introduced two acetyl groups, to give a single, crystalline ester (**7**); the structure shown for **7** was confirmed by n.m.r. analysis (using decoupling techniques), indicating that the main mono-*O*-isopropylidene product is 3,5-*O*-isopropylidene-D-xylofuranose (**2**).

Treatment of D-arabinose (**11**) with the 2,2-dimethoxypropane reagent at room temperature gave a single product in almost quantitative yield (85%); the melting point and specific rotation were in accord with those of the known 3,4-*O*-isopropylidene-β-D-arabinopyranose[14–16] (**12**). However, when this reaction was performed at 80°, the well known 1,2,3,4-di-*O*-isopropylidene-β-D-arabinopyranose[14,17] (**13**) was formed almost exclusively (88%).

Acetonation of D-ribose (**14**) with this reagent at room temperature afforded 2,3-*O*-isopropylidene-D-ribofuranose[16,18,19] (**15**) in almost quantitative yield (91%). Acetylation of **15** gave 1,5-di-*O*-acetyl-2,3-*O*-isopropylidene-β-D-ribofuranose; its structure was analyzed by n.m.r. spectroscopy.



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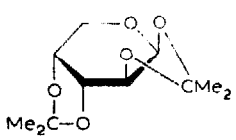

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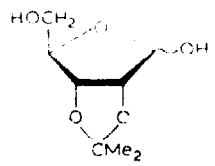

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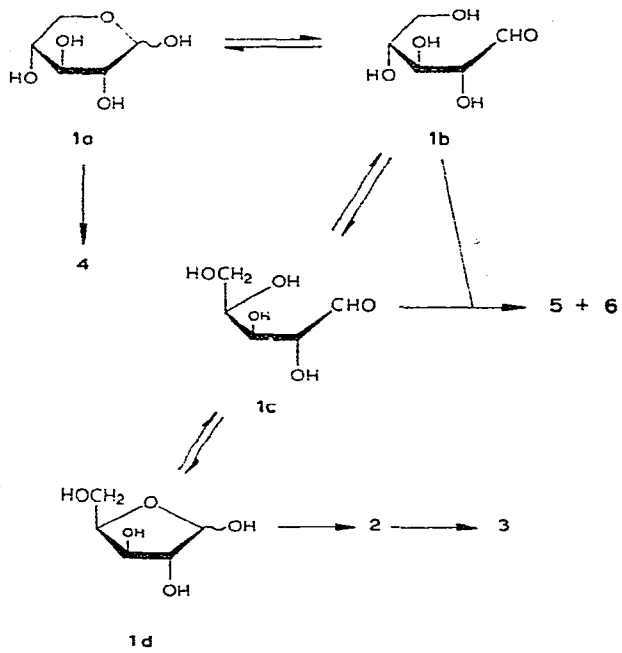
The behavior of D-xylose (**1**) with the 2,2-dimethoxypropane reagent is summarized in Scheme 1. The existence of such equilibria in the reaction solution explains the variation of products, as with D-glucose[1]. It is considered that the products (**2** and **3**) and (**5** and **6**) are formed *via* the furanoid (**1d**) and aldehydo (**1b** and **1c**) forms, respectively, by stepwise acetonation, with favored, initial attack by the reagent at the primary hydroxyl group. The production of **4**, however, indicates simultaneous occurrence of attack by the reagent at secondary hydroxyl groups, in contrast to the case of D-glucose[1]. This result is presumably attributable to the fact that D-xylopyranose (**1a**) has no primary hydroxyl group, and that *cis*-isopropylidene acetal formation is only possible at the 1- and 2-hydroxyl groups in **1a**.



Scheme 1.

EXPERIMENTAL

General methods. — See ref. 1.

Acetonation of D-*xylose* (**1**). — To a stirred solution of D-xylose (**1**) (4.0 g, 26.6 mmoles) in *N,N*-dimethylformamide (50 ml) were added *p*-toluenesulfonic acid monohydrate (60 mg) and then 2,2-dimethoxypropane (10 ml, 3.04 moles/mole of **1**). The mixture was stirred for 2 to 3 h at 40–45°, and then treated with Amberlite IRA-410 (OH^-) ion-exchange resin to remove the acid; the resin was filtered off, and washed with methanol. The combined filtrate and washings were evaporated *in vacuo* (~60° bath), and the syrupy residue was chromatographed on a column (4 cm, diam.) of silicic acid (160 g) with benzene and then two benzene–methanol mixtures. The benzene eluate yielded **3** (980 mg, 16%), and the 100:1 benzene–methanol eluate yielded a syrupy mixture of **5** and **6** (1.5 g, 23%), which could not be separated from each other by re-chromatography. The 50:1 benzene–methanol eluate yielded **4** (800 mg, 16%) and **2** (1.6 g, 32%), whose R_F values in t.l.c. are very close.

*3,5-*O*-Isopropylidene-*D*-xylofuranose* (**2**). — Compound **2** had $[\alpha]_D^{20}$ +19.2° (*c* 0.5, methanol); ν_{max}^{film} 3370 (OH) and 840 cm^{-1} (Me_2C); n.m.r. data at 60 MHz: δ 1.45 (Me_2C), 3.5 (OH), 3.8–4.4 (m, ring protons), 5.2 (s, $J_{1,2}$ ~0 Hz, H-1β), and 5.67 (d, $J_{1,2}$ 5.8 Hz, H-1α).

*1,2:3,5-Di-*O*-isopropylidene-α-*D*-xylofuranose* (**3**). — Compound **3** had m.p. 44–45° and $[\alpha]_D^{20}$ +13.0° (*c* 0.5, water), in agreement with those reported[13]; ν_{max}^{Nujol} 900–

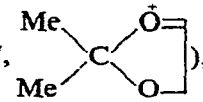
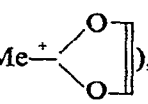
800 cm^{-1} (Me_2C); n.m.r. data at 60 MHz: δ 1.3, 1,36, 1.42, and 1.47 (4 s, Me_2C), 3.8–4.2 (m, H-4,5), 4.26 (d, $J_{3,4}$ 2.3 Hz, H-3), 4.48 (d, $J_{1,2}$ 3.8 Hz, $J_{2,3}$ ~0 Hz, H-2), and 5.94 (d, $J_{1,2}$ 3.8 Hz, H-1).

Anal. Calc. for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.11; H, 7.85.

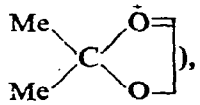
1,2-O-Isopropylidene-α-D-xylopyranose (**4**). — The crude crystals of **4** were recrystallized from benzene, to give colorless needles, m.p. 74–75°; ν_{max}^{Nujol} 3380, 3320 (OH), and 845 cm^{-1} (Me_2C); n.m.r. data at 90 MHz: δ (before D_2O treatment) 1.39 and 1.6 (2 s, Me_2C), 2.91 (d, $J_{3,OH}$ 4.3 Hz, 3-OH), 3.12 (d, $J_{4,OH}$ 10 Hz, 4-OH), 3.43–3.72 (double m, H-4), 3.75 (double d of d, J_{gem} 12 Hz, $J_{4,5}$ 3.1 Hz, four-bond coupling 1.0 Hz, H-5), 3.93 (d of d, J_{gem} 12 Hz, $J_{4,5'}$ 2.2 Hz, H-5'), 3.95 (m, $J_{1,2} \simeq J_{2,3}$ 2.8 Hz, four-bond coupling 1.0 Hz, H-2), 4.19 (m, $J_{3,OH} \simeq J_{3,4}$ 4.3 Hz, $J_{2,3}$ 2.8 Hz, H-3), and 5.29 (d, $J_{1,2}$ 2.8 Hz, H-1).

Anal. Calc. for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found: C, 50.64; H, 7.39.

1-O-Acetyl-2,3:4,5-di-O-isopropylidene-1-O-methyl-(D-xylose aldehydrol) (**5a**) *and 1,1-di-O-acetyl-2,3:4,5-di-O-isopropylidene-(D-xylose aldehydrol)* (**6a**). — The syrupy fraction (600 mg) containing **5** and **6** was acetylated with acetic anhydride in pyridine solution. The reaction mixture was evaporated *in vacuo*, and the syrupy residue was chromatographed on a column of silicic acid with 100:1 benzene–methanol, to give **5a** (320 mg) and **6a** (260 mg) as syrups.

Compound **5a** had $[\alpha]_D^{20}$ −9.2° (c 0.5, methanol); n.m.r. data at 60 MHz: δ 1.3–1.6 (2 Me_2C), 2.15 (s, AcO), 3.5 (s, MeO), 3.8–4.3 (m, H-2,5), and 5.9 (m, H-1); mass-spectral data: *m/e* 289 (15, $M^+ - Me$), 245 (3, $M^+ - AcO$), 231 (11, 289 − Me_2CO), 203 (3, $M^+ - 101$), 101 (17, ), 85 (12, ), 59 (14, $Me_2\overset{+}{C}OH$), and 43 (100, $Me\overset{+}{C}O$).

Anal. Calc. for $C_{14}H_{24}O_7$: C, 55.25; H, 7.95. Found: C, 55.43; H, 8.12.

Compound **6a** had $[\alpha]_D^{20}$ −24.3° (*c* 0.5, methanol); n.m.r. data at 60 MHz: δ 1.3–1.6 (2 Me_2C), 2.1 (s, 2 AcO), 3.7–4.4 (m, H-2,5), and 6.98 (d, $J_{1,2}$ 4 Hz, H-1); mass-spectral data: *m/e* 317 (24, $M^+ - Me$), 259 (12, 317 − Me_2CO), 231 (11, M^+ − 101), 201 (4.4, $M^+ - 2$ AcO), 157 (12), 149 (12), 139 (16), 101 (33, ), 85 (9.3), 59 (12, $Me_2\dot{C}OH$), and 43 (100, $Me\dot{C}O$).

Anal. Calc. for $C_{15}H_{24}O_8$: C, 54.21; H, 7.28. Found: C, 54.33; H, 7.25.

1,2-Di-O-acetyl-3,5-O-isopropylidene-α-D-xylofuranose (**7**). — Compound **2** was acetylated with acetic anhydride in pyridine solution, and the solution evaporated *in vacuo*, to give crystalline **7**, which was recrystallized from benzene–hexane, m.p. 64–65°, $[\alpha]_D^{20}$ +77.2° (*c* 0.5, methanol); ν_{max}^{Nujol} 1760 (AcO), 1245, 1215 (ester), and 850–800 cm^{-1} (Me_2C); n.m.r. data at 90 MHz: δ 1.39 and 1.41 (2 s, Me_2C), 2.05–2.09 (2 s, AcO), 3.37 (d of d, J_{gem} 12.5 Hz, $J_{4,5}$ 3.6 Hz, H-5), 4.05 (d of d, J_{gem} 12.5 Hz, $J_{4,5'}$ 3.6 Hz, H-5'), 4.19 (near q, $J_{3,4} \simeq J_{4,5} \simeq J_{4,5'}$ 3.6 Hz, H-4), 4.35 (d of d, $J_{2,3}$

1.8 Hz, $J_{3,4}$ 3.6 Hz), 5.19 (d of d, $J_{1,2}$ 4.3 Hz, $J_{2,3}$ 1.8 Hz), 6.47 (d, $J_{1,2}$ 4.3 Hz, H-1); mass-spectral data: *m/e* 259 (20, $M^+ - Me$), 215 (11, $M^+ - AcO$), 173 (12, 259 – 2 MeCO), 157 (8.6), 139 (14, 259 – 2 AcOH), 131 (5.0), 115 (11), 97 (12), 59 (15, $Me_2\dot{C}OH$), and 43 (100, $Me\dot{C}O$).

Anal. Calc. for $C_{12}H_{18}O_7$: C, 52.55; H, 6.62. Found: C, 52.64; H, 6.60.

3,4-Di-O-acetyl-1,2-O-isopropylidene-α-D-xylopyranose (**8**). — Compound **4** was acetylated with acetic anhydride in pyridine solution, and the reaction mixture was evaporated *in vacuo* to a syrupy residue, which was chromatographed on a column of silicic acid with chloroform, to give **8** as a syrup; $[\alpha]_D^{20}$ +23.7° (*c* 0.43, methanol); n.m.r. data at 90 MHz: δ 1.38 and 1.6 (2 s, Me_2C), 2.08 and 2.1 (2 s, AcO), 3.75–3.95 (m, H-5), 4.03 (m, $J_{1,2}$ 3.9 Hz, $J_{2,3}$ 3.0 Hz, four-bond coupling 1.0 Hz, H-2), 4.78 (m, $J_{3,4}$ 3.1 Hz, $J_{4,5}$ 3.2 Hz, four-bond coupling 1.0 Hz, H-4), 5.25 (near t, $J_{2,3}$ 3.0 Hz, $J_{3,4}$ 3.1 Hz, H-3), and 5.38 (d, $J_{1,2}$ 3.9 Hz, H-1).

Anal. Calc. for $C_{12}H_{18}O_7$: C, 52.55; H, 6.62. Found: C, 52.35; H, 6.72.

1,2,3,4-Tetra-O-acetyl-D-xylopyranose (**10**). — A solution of compound **8** (200 mg) in 70% aqueous acetic acid was stirred for 3–4 h at 60°; this reaction is very slow. The solution was evaporated *in vacuo* (~50° bath) to a syrupy residue, which was acetylated with acetic anhydride in pyridine solution. The reaction mixture was evaporated *in vacuo*, and the residue was extracted with ether; the extract was dried, and evaporated to syrup, which was chromatographed on a column of silicic acid with chloroform, to give **10** (170 mg, 69%) as a syrup. An authentic sample of **10** was synthesized from D-xylose (**1**) by direct acetylation with acetic anhydride in pyridine solution. The i.r. and n.m.r. spectra of both samples of **10** were in agreement with each other, although the anomeric ratios were slightly different. The n.m.r. signals for H-1 were observed at δ 5.7 (d, $J_{1,2}$ 6.7 Hz, H-1β) and 6.23 (d, $J_{1,2}$ 3.7 Hz, H-1α).

Acetonation of D-arabinose (**11**). — (*a*) *At* ~20°. To a stirred solution of compound **11** (4 g) in *N,N*-dimethylformamide (50 ml) were added *p*-toluenesulfonic acid monohydrate (60 mg) and then 2,2-dimethoxypropane (10 ml, 3.04 moles/mole of **11**). The mixture was stirred for 2 h at room temperature, and then treated with Amberlite IRA-410 (OH^-) ion-exchange resin to remove the acid; the resin was filtered off and washed with dry *N,N*-dimethylformamide. The combined filtrate and washings were evaporated *in vacuo* (~60° bath), and the syrupy residue was chromatographed on a column (4 cm diam.) of silicic acid (120 g) with benzene and then 50:1 benzene–methanol. The latter eluate yielded a crystalline mass of 3,4-*O*-isopropylidene-β-D-arabinopyranose (**12**) (4.3 g, 85%), which was recrystallized from ether to give colorless needles of **12**, m.p. 84–85° (lit.[15] m.p. 82–85°, lit.[16] m.p. 82–84°); $[\alpha]_D^{20}$ −111.1° (*c* 0.5, water) (lit.[14,16] −111°); ν_{max}^{Nujol} 3360 (OH) and 840 cm^{-1} (Me_2C); n.m.r. data at 60 MHz: δ 1.35 and 1.53 (2 s, Me_2C), and 5.16 (d, $J_{1,2}$ 3 Hz, H-1).

Anal. Calc. for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found: C, 50.39; H, 7.28.

(*b*) *At* 80°. To a stirred solution of compound **11** (4 g) in *N,N*-dimethylformamide (50 ml) were added *p*-toluenesulfonic acid monohydrate (60 mg) and then 2,2-dimethoxypropane (10 ml). The mixture was stirred for 2.5 h at 80°, cooled, and

treated as described in reaction (*a*), to give a syrupy residue which was chromatographed on a column (4 cm diam.) of silicic acid (120 g) with benzene and then 50:1 benzene–methanol. The latter eluate yielded crystalline 1,2:3,4-di-*O*-isopropylidene-β-D-arabinopyranose (**13**) (5.4 g, 88%), which was recrystallized from ether–hexane; m.p. 39.5–40.5° (lit.[14] m.p. 40–41°, lit.[16] m.p. 41–42°); $[\alpha]_D^{20}$ −4.0° (*c* 0.5, water) (lit.[14] −4.0°, lit.[16] −5°). The n.m.r. spectrum was identical with that reported[17].

Anal. Calc. for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.19; H, 8.00.

Acetonation of D-*ribose* (**14**). — A solution of compound **14** (2 g), *p*-toluenesulfonic acid monohydrate (30 mg), and 2,2-dimethoxypropane (5 ml) in *N*,*N*-dimethylformamide (25 ml) was stirred for 3 h at room temperature, and then treated as described for the acetonation of **11**. The syrupy residue obtained was chromatographed on a column of silicic acid (60 g) with chloroform and then 50:1 chloroform–methanol. The latter eluate yielded 2,3-*O*-isopropylidene-D-ribofuranose (**15**) (2.3 g, 91%), $[\alpha]_D^{20}$ −37° (*c* 0.53, acetone) (lit.[16] −42° in acetone, lit.[18] −27° in acetone*).

Compound **15** (1 g) was treated with acetic anhydride (5 ml) in dry pyridine (10 ml), and the mixture was kept overnight at room temperature, and then evaporated *in vacuo* to a syrupy residue which was chromatographed on a column of silicic acid (30 g) with chloroform, to give 1,5-di-*O*-acetyl-2,3-*O*-isopropylidene-β-D-ribofuranose (1.4 g, 97%) as a syrup; ν_{max}^{Nujol} 1740 (AcO), 1220 (ester), and 860 cm^{-1} (Me_2C); n.m.r. data at 90 MHz: δ 1.28 and 1.42 (2 s, Me_2C), 1.99 and 2.03 (2 s, AcO), 4.0–4.2 (H-5), 4.42 (d of d, $J'_{3,4}$ ~0 Hz, $J_{4,5}$ 6.4 and 7.6 Hz, H-4), 4.7 (H-2,3), and 6.2 (s, $J_{1,2}$ ~0, H-1).

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