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REACTION OF D-*ribo*-HEXOS-3-ULOSE AND OF 1,2:5,6-DI-*O*-ISOPROPYLIDENE-α-D-*ribo*-HEXO-1,4-FURANOS-3-ULOSE 3-HYDRATE WITH METHANOL–HYDROGEN CHLORIDE. A PREPARATION OF D-*ribo*-3-HEXULOSE

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ABSTRACT

The reaction of D-*ribo*-hexos-3-ulose (**1**) with methanol–hydrogen chloride yielded as major products methyl (methyl β-D-*ribo*-hexo-1,4-furanosid)-β-D-3-ulo-3,6-furanoside (**4**), and methyl (methyl α-D-*ribo*-hexo-1,4-furanosid)-β-D-3-ulo-3,6-furanoside (**5**). Similar treatment of 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexo-1,4-furanos-3-ulose 3-hydrate (**2**) afforded **4** and **5** together with methyl (1,2-*O*-isopropylidene-α-D-*ribo*-hexo-1,4-furanos)-β-D-3-ulo-3,6-furanoside (**3**). Compounds **3**, **4**, and **5** were all partially hydrolyzed to methyl α,β-D-*ribo*-hexo-1,4-furanos-β-D-3-ulo-3,6-furanoside (**6**). Catalytic hydrogenation of **6** gave methyl β-D-*ribo*-3-hexulo-3,6-furanoside (**7**), which was hydrolyzed to D-*ribo*-3-hexulose (**8**). The preparation of **8** by partial reduction of **1** does not appear to be practicable.

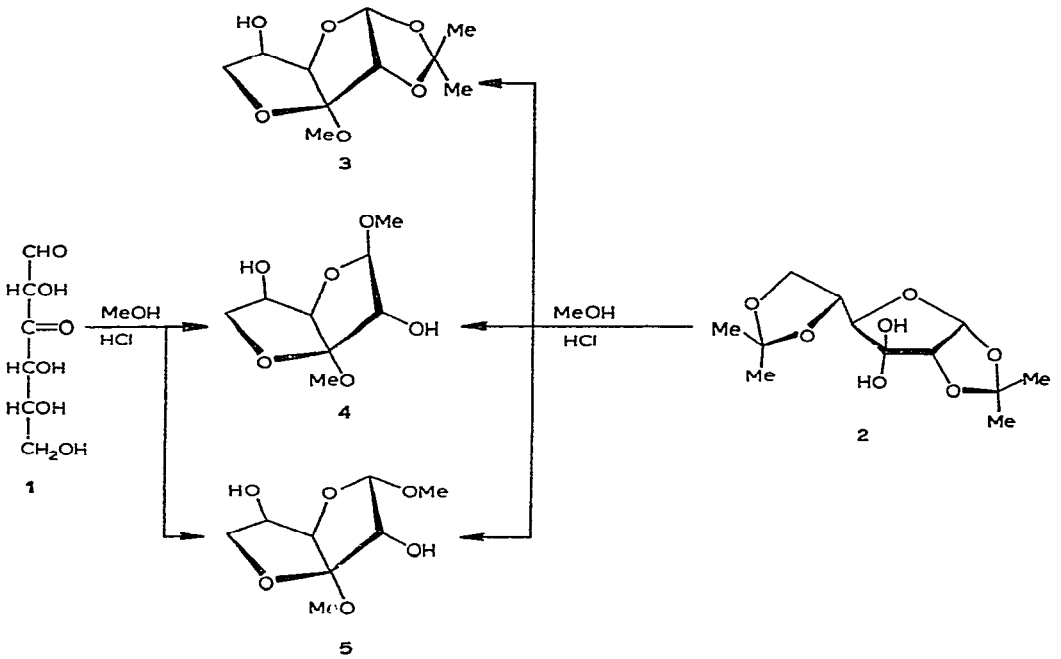
INTRODUCTION

A previous paper[1] examined the possibility of synthesizing glucopyranosid-2-uloses by the treatment of D-*arabino*-hexosulose (D-glucosone) with methanol–hydrogen chloride at room temperature. However, *gem*-dimethyl acetals were the main reaction products, and the furanoside modification was favored over the pyranoside. As an extension to the 3-keto series, the results of reaction of D-*ribo*-hexos-3-ulose (**1**) and of 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexo-1,4-furanos-3-ulose 3-hydrate (**2**) with methanol–hydrogen chloride are now reported. Compound **2** was used as it was more readily available than **1**. A similar technique has previously been employed[2] for the methanol–hydrogen chloride treatment of D-*manno*-hexodialdose.

RESULTS AND DISCUSSION

Compound **2** gave three major products when treated with 4M hydrogen chloride in methanol for 1 h at room temperature; one product (**3**) retained an isopropylidene group, and two (**4** and **5**) were isomeric methyl glycosides. In addition,

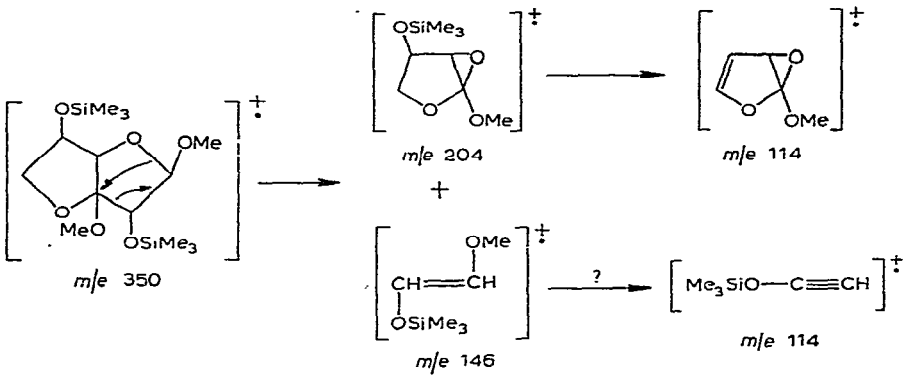
some 1,2-*O*-isopropylidene-α-D-*ribo*-hexo-1,4-furanos-3-ulose was produced by hydrolysis, and some minor components obtained were not identified. Treatment of **1** under similar conditions gave **4** and **5** as the major products, and a change in concentration of the acid reactant to 1M caused no significant change in the reaction pattern.



Preliminary results showed that, after treatment of **2** for 1 h at 100°, or 10 h at room temperature, the proportion of **3** decreased markedly, and some new, minor products appeared. Compounds **4** and **5** were major products, but darkening of the solution occurred and was extensive after 45 h at room temperature.

Compound **3** was crystalline (m.p. 80–81°). Its n.m.r. spectrum (in chloroform-*d*) showed C-methyl proton signals at τ 8.43 and 8.63 in the ratio of 1:1, and a doublet for H-1 at τ 4.12 (*J* 4 Hz). These data are characteristic of the 1,2-*O*-isopropylidene group and H-1 in such compounds as 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose and **2**. A signal at τ 6.63 was ascribed to a glycosidic methoxyl group. Mass spectrometry supported the proposed identity of **3** as methyl (1,2-*O*-isopropylidene-α-D-*ribo*-hexo-1,4-furanos)-β-D-3-ulo-3,6-furanoside, giving a top-mass peak at *m/e* 217 ($M-CH_3$), and a peak at 157 ($M-CH_3-CH_3COOH$), these being characteristic breakdowns for isopropylidene acetals. Other peaks, at 201 and 143, may be associated with the loss of the glycosidic methoxyl group followed by elimination of acetone. On steric grounds, it is unlikely that a *trans*-fused furo[3,2-*b*]furan system should form, and hence, *cis*-fusion is postulated as shown in **3**. No trace was found of any product in which the 5,6-*O*-isopropylidene residue had been retained; this behavior parallels that of **2** in aqueous acid[3].

Compounds **4** and **5**, both of which are colorless syrups, were deduced to be stereoisomeric difuranosides on the following evidence. They had mass spectra identical in *m/e* values, showing, *inter alia*, peaks at *m/e* 175 ($M-CH_3O$) and 133. The latter peak was very dominant, and is possibly due to loss of ketene from the 175 ion, but it is at this time not further rationalized. The mass spectra of the bis-(trimethylsilyl) ethers of **4** and **5** were also identical in *m/e* values; they showed small peaks that could be attributed to the molecular ion, *m/e* 350, and at 319 ($M-CH_3O$), 335 ($M-CH_3$), and 303 ($M-CH_3-CH_3OH$). The peaks at *m/e* 204, 146, and 114 may arise as shown in Scheme 1. A metastable peak at *m/e* ~64 supports



Scheme 1

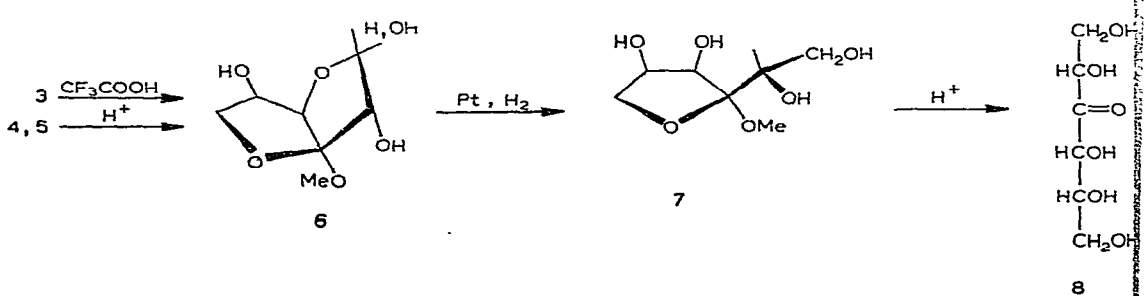
the fragmentation 204→114. The mobilities of **4** and **5** in thin-layer and paper chromatography were very similar. In g.l.c., their mobilities were almost identical, as were those of their bis(trimethylsilyl) ethers. Their n.m.r. spectra (in chloroform-*d*) were similar to each other, each having two signals in the methoxyl region at τ 6.54 and 6.68 (**4**), and τ 6.51 and 6.62 (**5**). In the anomeric-proton region, however, **4** showed a singlet at τ 4.99, and **5**, a doublet signal at τ 4.90 (J 4 Hz). It was subsequently found that the common product (**6**) of their partial hydrolysis had retained the glycosidic methoxyl group at C-3; hence, the n.m.r. data indicate that **4** and **5** are anomeric at C-1. The H-1 multiplicity and the value of the coupling constant indicate[4] the β and α configurations, respectively, at C-1 of **4** and **5**. This conclusion was further supported by the large difference in optical rotation (**4**, −58°; **5**, +89°). The compounds may be named methyl (methyl β-D-*ribo*-hexo-1,4-furanosid)-β-D-3-ulo-3,6-furanoside (**4**) and methyl (methyl α-D-*ribo*-hexo-1,4-furanosid)-β-D-3-ulo-3,6-furanoside (**5**). Compound **4** was further characterized as its crystalline 2,5-di-*p*-toluenesulfonate.

A semi-quantitative inspection by t.l.c. indicated that the extents of formation of **4** and **5** from **2** were approximately equal. Compound **5** was, however, recovered in lower yield than **4**, owing to the contamination, during chromatography, of the slower-moving **5** by **6**, which formed on the column. Thus, after collection of a small quantity of pure **5**, a large amount of a mixture of **5** and **6** was collected from the column.

It is notable that, in the present case, in contrast to that of D-glucosone[1], no *gem*-dimethyl acetals were encountered; moreover, no appreciable proportions of glucosid-3-uloses were formed; this is presumably attributable to the stability of the 1,4:3,6-difuranoside structure. Compounds having a *cis*-fused furo[3,2-*b*]furan system have been shown to be formed readily, and they are favored over the *trans*-fused form. For example, the 1,4:3,6-dianhydrides of D-glucitol, D-mannitol, and D-iditol are more readily formed than those of the other hexitols[5].

A partial-hydrolysis product, namely, methyl α,β-D-*ribo*-hexo-1,4-furanos-β-D-3-ulo-3,6-furanoside (**6**), was produced from **4** and from **5** in aqueous acid, and also from **3** by treatment with 90% trifluoroacetic acid; the latter reagent has been shown[6] to remove isopropylidene residues, but probably not glycosidic residues. Hence, it was established that the methoxyl group in **6** is attached to C-3. The difference in reactivity of the methoxyl groups on C-1 and C-3 of **4** and **5** under hydrolyzing conditions is not surprising, as hydrolysis at C-3 would normally require the formation of a carbonium ion at a bridge-head carbon atom. No great difference in reactivity between the anomeric C-1 methoxyl groups of **4** and **5** was noted on hydrolysis. Under the conditions employed [aqueous solution, with Dowex 50 (H^+) at 50°], both **4** and **5** were slowly hydrolyzed during several hours, the optimal time for isolation of the product of partial hydrolysis being about ten hours. The n.m.r. spectrum of **6** in methanol-d_4 had two, very closely spaced, methoxyl signals (at τ 6.67 and 6.69), due, perhaps, to the existence of two furanose anomers and, hence, of two slightly different environments for the C-3 methoxyl groups. In the anomeric-proton region, there were three signals (τ 4.64, 4.70, and 4.73), further indicating an anomeric mixture.

Catalytic hydrogenation of **6** yielded methyl β-D-*ribo*-3-hexulo-3,6-furanoside (**7**), having a high, negative, optical rotation (~ −80°; *cf.* methyl β-D-fructofuranoside, $[\alpha]_D$ −172.1° in water[7], and its α-D anomer, +46.5° in water[8]). The n.m.r. spectrum of **7** (in methanol-d_4) showed, *inter alia*, a singlet signal at τ 6.72 (OCH_3) and no signal in the anomeric-proton region. The C-3 methoxyl group of **7**, being no longer at a point of ring fusion, was readily removed by treatment with dilute acid, to give D-*ribo*-3-hexulose (**8**, $[\alpha]_D^{22}$ −9°). Indeed, when **6** was reduced with sodium borohydride, the brief treatment with acid necessary during the processing of the crude product was sufficient to cause hydrolysis of **7** to **8**.



A sample of **8** was reduced with sodium borohydride, and the product was acetylated with acetic anhydride–pyridine. By a standard, g.l.c. analysis, the product was shown to be comprised of approximately equal amounts of the hexaacetates of a glucitol and allitol, confirming the identity of **8**. The pentaacetate of the *keto*-form of **8** has been prepared[9], and the 1,2,5,6-tetra-*O*-acetyl-4-*O*-formyl derivative has been reported[10].

On paper chromatography, both the free sugar **8** and its methyl glycoside gave a very distinctive, bright-yellow spot when sprayed with the resorcinol reagent and heated; the color changed to green after one day. Thus, this 3-hexulose may readily be distinguished from the 2-hexuloses, which give red spots.

The possibility of obtaining **8** by partial reduction of **1** has been examined. The reduction of D-glucosone with zinc and acetic acid is known to give mainly D-fructose[11], a fact which may be explained by the assumption that the hexosulose exists in aqueous solution in the 2,5-furanose form, with a free carbonyl group at C-1. This suggestion was made[1] because methyl *β*-D-*arabino*-hexosulofuranoside 1,1-(dimethyl acetal) had been isolated after treatment of D-glucosone with methanol–hydrogen chloride. In the present work, as **4** and **5** have the furo[3,2-*b*]furan structure, it seemed possible that **1** has this structure, and that preferential reduction might occur. However, the conditions employed by Fischer[11] caused extensive degradation of **1**, and no significant amount of D-glucose, D-allose, or D-*ribo*-3-hexulose was detected. Reduction of **1** with an equimolar amount of sodium borohydride in water gave a mixture of an allose and a glucose, in which the former preponderated, together with a smaller proportion of the corresponding alditols; virtually no **8** was formed. This result suggests that either (*a*) the difuranose modification of **1** is not favored, or (*b*) if it is, the 1,4-ring is the more stable. In situation *a*, a 1,4-furanose or 1,5-pyranose structure, having a free carbonyl group at C-3, might be present. As regards possibility *b*, it may be mentioned that the 3,6-acetal ring in compounds **4** and **5** is particularly stable to hydrolysis, because of the difficulty in forming a bridge-head carbonium ion, whereas, in the 1,4:3,6 difuranose form of **1**, opening of the 3,6-hemiacetal ring would not require formation of such an ion, and, consequently, reduction might occur preferentially at C-3.

EXPERIMENTAL

General. — T.l.c. was performed on plates of Silica Gel G, with elution by 19:1 benzene–methanol (solvent *a*), 1:1 ethyl acetate–carbon tetrachloride (solvent *b*), or ethyl acetate (solvent *c*). Paper, cellulose-column, and preparative thick-paper (Whatman 3MM paper) chromatography were all conducted with 10:3:5 butyl alcohol–ethanol–water as eluant, unless otherwise stated. Bisulfite buffer[12] (pH 4.7) was employed at 50° for electrophoresis. Chromatograms and electrophoretograms were visibilized with the following standard reagents: *p*-anisidine hydrochloride (*d*), *p*-anisidine hydrochloride followed by methanol–hydrogen chloride[13] (*e*), silver nitrate–sodium hydroxide (*f*), (2,4-dinitrophenyl)hydrazine (*g*), and resorcinol (*h*).

N.m.r. spectra were recorded with a Perkin–Elmer IR-12 spectrometer at 60 MHz, with tetramethylsilane as the internal standard. Chemical shifts are given on the τ-scale. Mass spectra were recorded on a Perkin–Elmer 270 spectrometer. G.l.c. measurements were made on a column of OV 17 in a Perkin–Elmer 800 instrument. Melting points are corrected.

1,2:5,6-Di-O-isopropylidene-α-D-ribo-hexo-1,4-furanos-3-ulose 3-hydrate (**2**). — This compound was prepared essentially as described by Beynon *et al.*[14]. By the use of an excess of potassium periodate and potassium carbonate, complete oxidation was effected, as judged by t.l.c. [R_F (solvent *a*) of **2**, 0.66; of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, 0.41]. D-*ribo*-Hexos-3-ulose (**1**) was prepared from **2** by the method of Christensen and Goodman[6], and was purified by chromatography on a cellulose column.

Treatment of **2** *with methanol–hydrogen chloride; separation of the products.* — After preliminary, small-scale investigations, compound **2** (1 g) was treated with hydrogen chloride in methanol (4M, 30 ml) at room temperature. After 1 h, the starting material had largely disappeared, and t.l.c. showed the presence of at least six new compounds (spray *e*). The reaction was stopped by the addition of solid sodium hydrogen carbonate, the resulting slurry was filtered, and the filtrate was evaporated to yield a brownish solid, much of which consisted of sodium salts. The solid was extracted with chloroform, and the extract (620 mg) was placed on a column (2.5 × 60 cm) of silicic acid and eluted with solvent *b*. Four pure fractions were obtained: *A* (7 mg), R_F (solvent *b*) 0.92; *B* (2 mg), R_F (*b*) 0.67; *C* (65 mg), R_F (*b*) 0.61; and *D* (6 mg), R_F (*c*) 0.83. Elution with solvent *c* then provided three further fractions: *E* (47 mg), R_F (*c*) 0.80; *F* (229 mg), R_F (*c*) 0.70; and *G* (8 mg), R_F (*c*) 0.57. Subsequently ~200 mg of material was eluted, which contained mainly the same material as fraction *G*, together with a compound later found to be a partial-hydrolysis product (**6**) that was not present before chromatography.

Examination of fractions *A* and *D* by combined g.l.c.–mass spectrometry did not afford any conclusive results. Fraction *B* was found to be unchanged **2**, and *E* to consist of 1,2-*O*-isopropylidene-α-D-*ribo*-hexo-1,4-furanos-3-ulose (by comparison with the authentic compound by g.l.c.–mass spectrometry, or by t.l.c. in a number of solvent systems.)

Fraction *C* yielded crystalline *methyl (1,2-O-isopropylidene-α-D-ribo-hexo-1,4-furanos)-β-D-3-ulo-3,6-furanoside* (**3**), m.p. 80–81°, after two recrystallizations from ethanol; $[\alpha]_D^{22}$ +20.5° (*c* 0.3, chloroform); mass spectrum: *m/e* 29 (54% base peak), 43 (100), 85 (40), 98 (27), 100 (43), 132 (30), 157 (2.5), 173 (2.9), 201 (1.9), 217 (6.3).

Anal. Calc. for $C_{10}H_{10}O_6$: C, 51.7; H, 6.9. Found: C, 51.6; H, 6.9.

Fraction *F* was a colorless syrup that was distilled *in vacuo* to give the *dimethyl difuranoside* **4**, $[\alpha]_D^{22}$ −58° (*c* 0.2, methanol); mass spectrum: *m/e* 45 (34%), 73 (40), 75 (40), 133 (100), 156 (5.7), 175 (2.9), 188 (1.4); trimethylsilyl derivative: 28 (75), 32 (16), 73 (33), 75 (21), 89 (18), 114 (25), 146 (100), 159 (11), 204 (21), 217 (25), 303 (22), 319 (14), 335 (8.3), 350 (15). A portion of **4** was converted into the di-*p*-

toluenesulfonate, which, after purification on a column of silicic acid, and recrystallization from ethanol, had m.p. 122°.

Anal. Calc. for $C_{22}H_{26}O_{10}S_2$: C, 51.4; H, 5.07. Found: C, 51.4; H, 5.05.

Fraction *G* was a colorless syrup, considered to be the dimethyl difuranoside **5**, $[\alpha]_D^{22}$ +89° (*c* 0.75, methanol). The mass spectra of **5** and its trimethylsilyl derivative had the same *m/e* values as **4** and its corresponding derivative.

The g.l.c. retention times for **4** and **5** were 8.8 min (155°), 20 min (140°), and 46 min (120°), and, for their trimethylsilyl derivatives, 10.5 min (180°) and 16.2 min (170°). Admixtures of **4** and **5**, or of their trimethylsilyl derivatives, could not be resolved by g.l.c.

When M instead of 4M hydrogen chloride in methanol was used, an identical pattern of products was obtained. Treatment of **1** with methanol–hydrogen chloride for 1 h at room temperature gave only **4** and **5** as the major products.

Partial hydrolysis of **3**, **4**, *and* **5**. — Compound **4** (15 mg) was stirred in water (1.5 ml) with Dowex 50 (H^+) ion-exchange resin (about 600 mg of damp resin) at room temperature. By paper chromatography, two products were observed, having R_{Fru} 1.9 and 1.1. The slow-moving product was shown by paper chromatography and electrophoresis to be **1**. The concentration of the faster-moving product (**6**) always exceeded that of **1**, until it reached a maximum at about 10 h. Compound **6** could be visibilized on the chromatogram with spray *d* (yellow-brown spot), *f*, or *g* (strong orange spot).

A similar hydrolysis of **5** gave the same products. In each experiment, the starting material appeared to react at about the same rate.

When treated at room temperature with 9:1 trifluoroacetic acid–water (1 ml), a sample (5 mg) of **3** gave **6** and **1**, compound **6** preponderating.

In a large-scale preparation, **2** was treated with methanol–hydrogen chloride as already described, but the chromatography stage was replaced by a partition of the materials in the chloroform extract between chloroform and water. Minor products stayed in the chloroform, and **4** and **5** passed into the water layer. A mixture (600 mg) of **4** and **5**, thus obtained, was hydrolyzed with Dowex 50 (H^+) ion-exchange resin (20 g) in water (60 ml) for 12 h at room temperature. The suspension was filtered, and the filtrate was evaporated; the product was applied to a column (2.5 × 60 cm) of cellulose. Elution gave, first, methyl α-β-D-*ribo*-hexo-1,4-furanos-β-D-3-ulo-3,6-furanoside (**6**) (105 mg), isolated as a chromatographically homogeneous, colorless syrup, $[\alpha]_D^{22}$ −5.9° (*c* 1.7, methanol), $M_{vanillin}$ 0 (see Ref. 12). The n.m.r. spectrum showed signals at τ 4.64, 4.70, and 4.73 (anomeric mixture) and τ 6.67 and 6.69 (methoxyl H).

Reduction and hydrolysis of **6**. — A sample (34 mg) of **6** in ethanol was shaken in an atmosphere of hydrogen in the presence of palladium on charcoal. No change was observed after 4 h. When Adams' catalyst was used, n.m.r. spectroscopy showed about 20% reduction after 2 h, and complete reduction after 6 h, to methyl β-D-*ribo*-3-hexulo-3,6-furanoside (**7**), a colorless syrup, $[\alpha]_D^{22}$ ~−80° (*c* 0.4, methanol). Compound **7** had R_{Fru} 1.8, and showed as a brown spot with spray *d* or *e*, and, with

spray *h*, as a bright-yellow spot that turned green after one day. The n.m.r. spectrum (in methanol-d_4) showed a signal at τ 6.72 (methoxyl), but no signal in the H-1 region. A sample (5 mg) of **7** was highly, although not completely, converted into D-*ribo*-3-hexulose (**8**) by treatment with 0.5M sulfuric acid (1 ml) for 1 h at room temperature.

A solution of **6** (450 mg) in water (10 ml) was treated with sodium borohydride (500 mg) in water (10 ml) for 3 h. The solution was made neutral with acetic acid, treated with Dowex 50 (H^+) ion-exchange resin, and evaporated. The product was dried by repeated addition and evaporation of 4:1 benzene–ethanol, and boric acid was removed by repeated addition and evaporation of methanol. A portion (150 mg) of the product was purified by chromatography on thick paper, to yield **8** (33 mg) as a colorless syrup, $[\alpha]_D^{22}$ −9° (*c* 0.45, methanol). Compound **8** had R_{Fru} 1.0, and showed as a brown spot with spray *d* or *f*, a strong orange spot with spray *g*, and a bright-yellow spot (green after one day) with spray *h*. On electrophoresis, **7** had $M_{vanillin}$ 0 (see Ref. 12). The n.m.r. spectrum had no signal in either the methoxyl or the anomeric-proton region. A sample (5 mg) of **8** was reduced (sodium borohydride), and the product acetylated with acetic anhydride in pyridine. G.l.c. analysis of the acetate (on a 3% ECNSS column) showed it to consist of the acetates of a glucitol and allitol in approximately equal amounts.

Attempted partial reduction of **1**. — *Method A*. Compound **1** (40 mg) in water (2 ml) was treated with zinc dust[12] (400 mg), and acetic acid (120 mg) was slowly added during 1 h while the temperature was kept at 100° (boiling-water bath). After filtration, dissolved zinc was precipitated from the filtrate by passing hydrogen sulfide through the solution. The suspension was filtered, and the filtrate concentrated; the product was examined by paper chromatography in 3:1:1 ethyl acetate–acetic acid–water. At least seven components were detected (spray *d*); glucose, allose, and *ribo*-3-hexulose were present only in very minute amounts, if at all.

Method B. Compound **1** (50 mg) was reduced in the usual way with sodium borohydride (11 mg). Paper chromatography of the product by use of 3:1:1 ethyl acetate–acetic acid–water showed the presence of glucose, allose, and *ribo*-3-hexulose, but the last-named was present in only trace amount; an allose preponderated. The chromatogram also indicated the presence of alditols.

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