Carbohydrate Research, 29 (1973) 209–222

THE BEHAVIOR OF SOME ALDOSES WITH 2,2-DIMETHOXYPROPANE–*N*,*N*-DIMETHYLFORMAMIDE–*p*–TOLUENESULFONIC ACID. I. AT ROOM TEMPERATURE (~25°)

AKIRA HASEGAWA* AND HEWITT G. FLETCHER, JR.

National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare, Bethesda, Maryland 20014 (U. S. A.)

(Received February 21st, 1973; accepted February 28th, 1973)

ABSTRACT

When treated at room temperature with a small excess of 2,2-dimethoxypropane in *N*,*N*-dimethylformamide solution in the presence of a trace of *p*-toluenesulfonic acid, 2-acetamido-2-deoxy-D-glucose, 2-acetamido-2-deoxy-D-mannose, 2-acetamido-2-deoxy-D-galactose, and D-glucose yield the corresponding 4,6-*O*-isopropylidenealdopyranoses. D-Mannose, however, gives the known 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose.

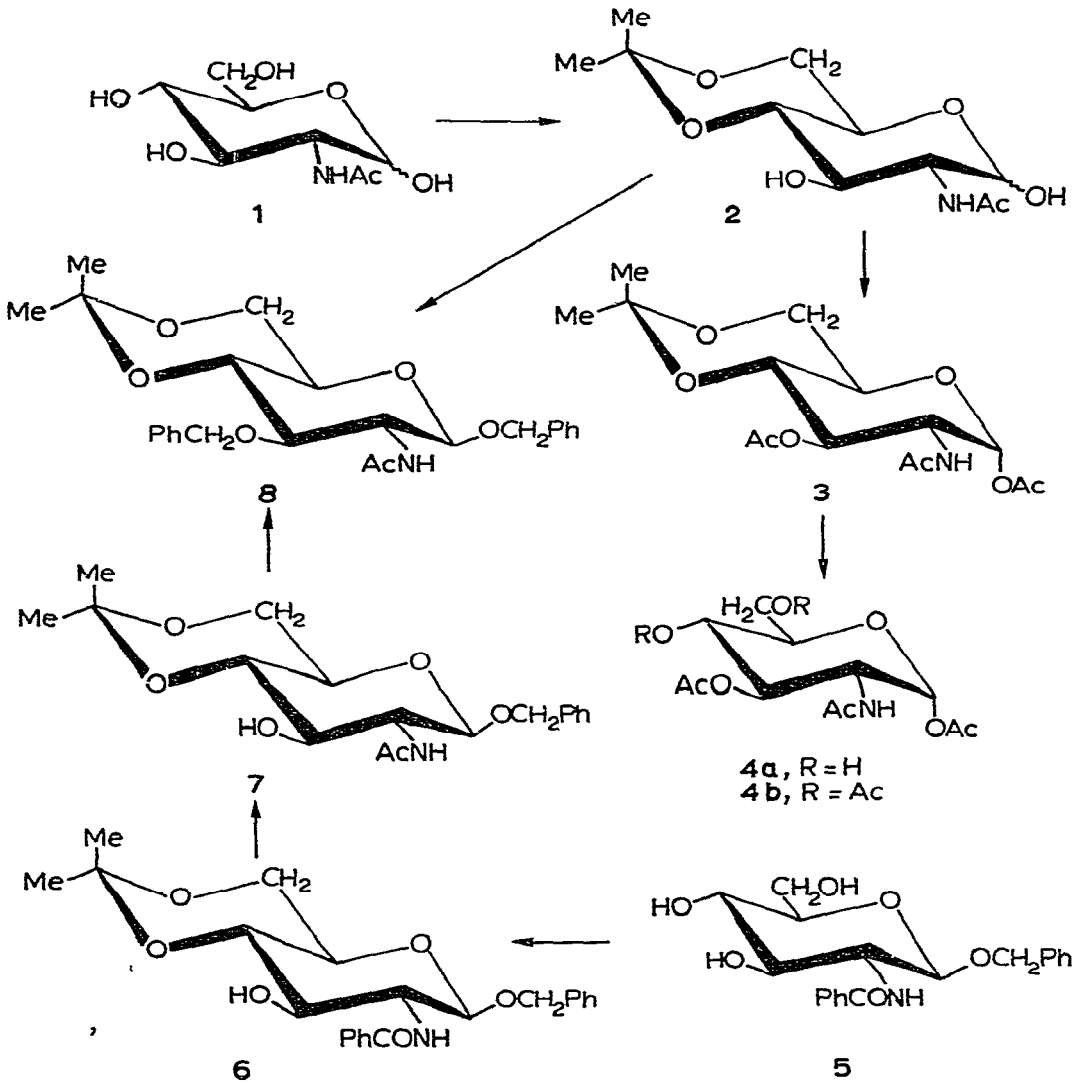
INTRODUCTION

In the course of some studies involving the use of 2-acetamido-2-deoxyaldohexoses as intermediates in syntheses, we found it of interest to investigate the formation of isopropylidene derivatives from these compounds and, for this purpose, used a mixture of 2,2-dimethoxypropane, *N*,*N*-dimethylformamide, and *p*-toluenesulfonic acid. This combination of reagents has recently been shown to effect the insertion of strained, and otherwise inaccessible, isopropylidene acetal moieties in methyl α-D-glucopyranoside[1,2] and in certain *N*-substituted 2-deoxystreptamine derivatives[3], but its action on free aldoses has not hitherto, to the best of our knowledge, been examined. The behavior of 2-acetamido-2-deoxy-D-glucose (**1**) with this mixture of reagents will be described first.

RESULTS

When 2-acetamido-2-deoxy-D-glucose (**1**) (see Scheme I) was stirred for 2 h at room temperature with ~3.6 mole-equivalents of 2,2-dimethoxypropane in a large excess of dry *N*,*N*-dimethylformamide containing a trace of *p*-toluenesulfonic acid, reaction appeared to be complete (as shown by t.l.c.) and, subsequently, a crystalline

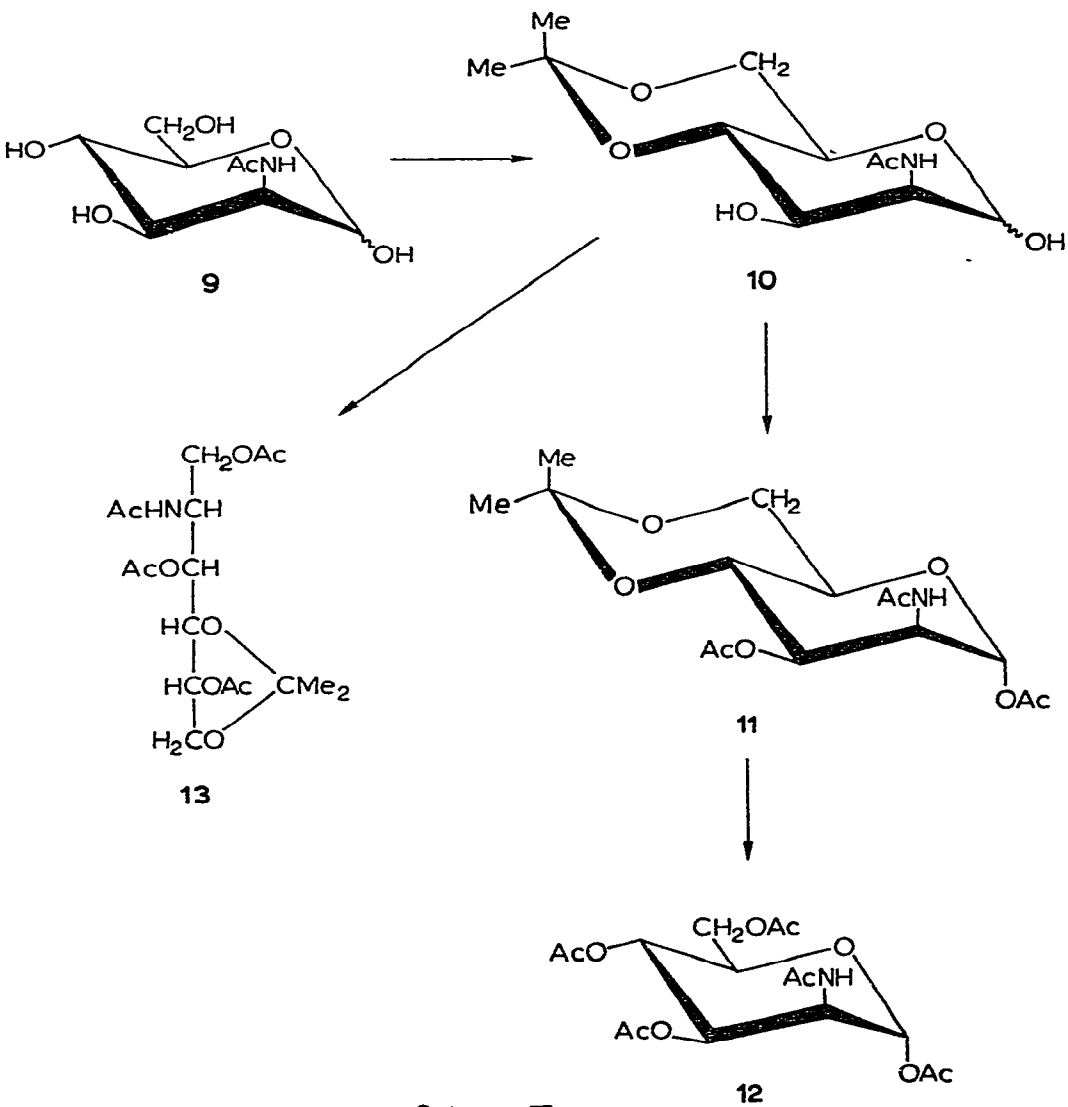
*Visiting Scientist, National Institutes of Health, 1971–1972. Present address: Department of Agricultural Chemistry, Faculty of Agriculture, Gifu University, Kakamigahara, Gifu, Japan.



Scheme I

derivative was isolated in 91% yield. The elemental composition and n.m.r. spectrum of the product indicated that a single isopropylidene group had been introduced and that the acetamido group was unalterated; the rapid reduction of warm Fehling solution showed that C-1 was unsubstituted. Acetylation of this derivative introduced two more acetyl groups, giving a crystalline ester from which the isopropylidene group could be cleaved under comparatively mild, acidic conditions; further acetylation of the crystalline product thus obtained afforded 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-decxy-α-D-glucopyranose (**4b**) in high yield. It is evident, then, that the parent com-

pound is 2-acetamido-2-deoxy-3,4-(or 4,6)-*O*-isopropylidene-D-glucopyranose. In order to obtain further structural evidence, the known benzyl 2-benzamido-2-deoxy-*β*-D-glucopyranoside[4–6] (5) was converted into a crystalline isopropylidene derivative by using the 2,2-dimethoxypropane–*N*,*N*-dimethylformamide–*p*-toluenesulfonic acid mixture. The *N*-benzoyl group was then removed through the use of strong alkali, and was replaced by an *N*-acetyl group; the remaining hydroxyl group was masked with a benzyl group, giving a crystalline product. The same compound was obtained through the direct benzylation of the 2-acetamido-2-deoxy-*O*-isopropylidene-D-glucopyranose. By analogy with the acetonation of methyl *α*-D-glucopyranoside[1,2], the product from



Scheme II

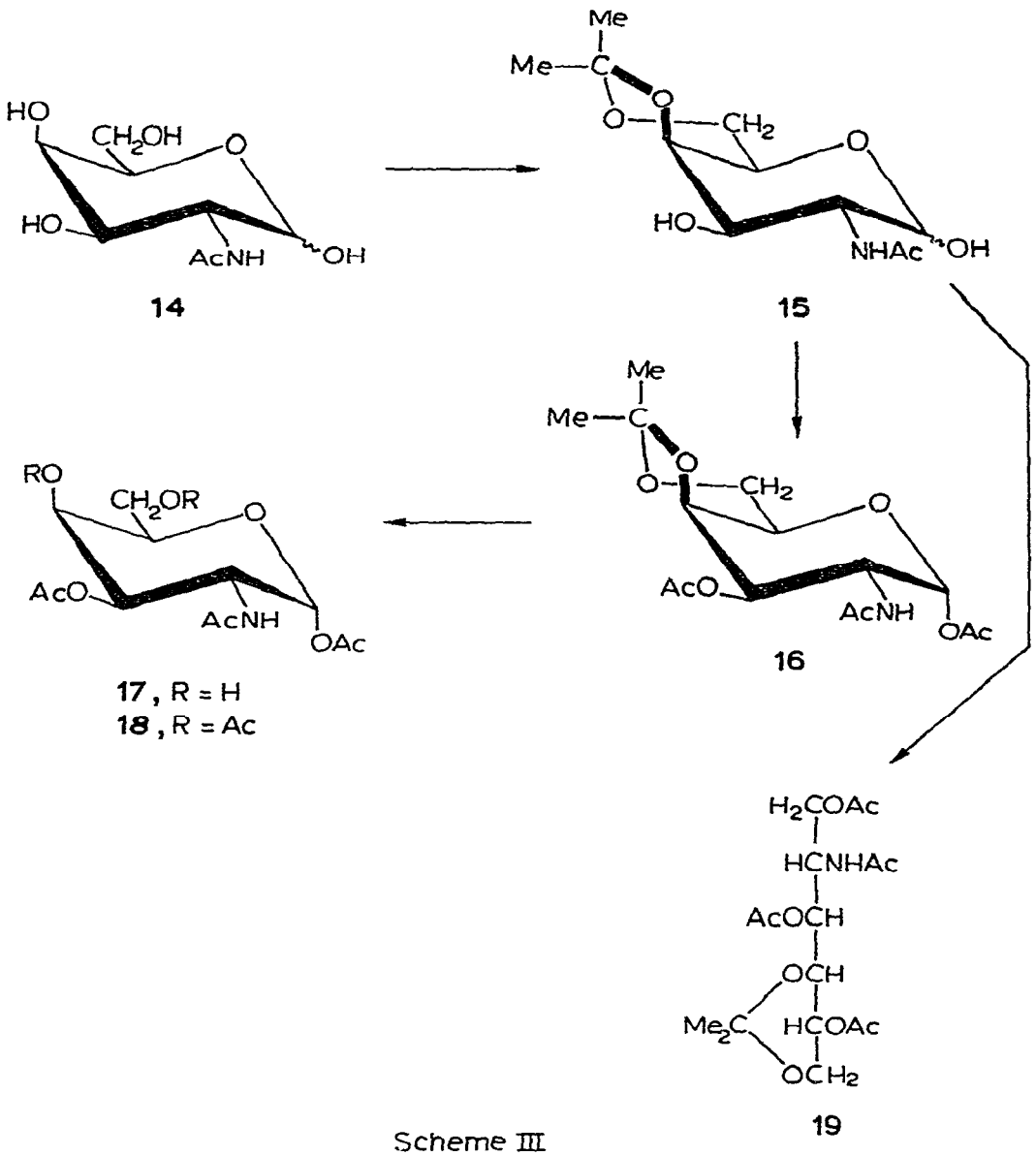
5 may be designated as benzyl 2-benzamido-2-deoxy-4,6-*O*-isopropylidene-β-D-glucopyranoside (**6**) and, from this, through structures **7** and **8**, the product in question may be regarded as **2**, namely, 2-acetamido-2-deoxy-4,6-*O*-isopropylidene-D-glucopyranose.

2-Acetamido-2-deoxy-D-mannose (**9**, Scheme II) also gave a crystalline monoisopropylidene derivative in good yield. Although the product from the acetylation of this derivative was syrupy, its n.m.r. spectrum indicated that it was substantially a single anomer. Hydrolytic removal of the isopropylidene group, followed by further acetylation, gave a syrupy product of $[\alpha]_D^{20} + 50°$ (*c* 1.0, chloroform) which was identified through its n.m.r. spectrum as 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-mannopyranose[7] (**12**). It was, therefore, evident that the isopropylidene derivative from **9** has a pyranoid ring. Further evidence bearing on its structure was obtained through reduction with sodium borohydride, followed by acetylation, which afforded a crystalline compound having an elementary composition corresponding to that calculated for an acetamido-tri-*O*-acetyl-deoxy-*O*-isopropylidenehexitol. Following de-*O*-acetylation, this product was found to be stable to the action of aqueous sodium metaperiodate, showing the absence of vicinal hydroxyl groups.

Spectral evidence clearly showed that the isopropylidene derivative from **9** had a free acetamido group. For the pyranose ring there remain, then, only three feasible cyclic acetal bridges, namely 3,4, 3,6, and 4,6. Of these, only the 4,6-isomer would, on reduction, give an alditol having no vicinal hydroxyl groups. It was, therefore, concluded that the product in question is **10**, namely 2-acetamido-2-deoxy-4,6,*O*-isopropylidene-D-mannopyranose.

The acetonation of 2-acetamido-2-deoxy-D-galactose (**14**, Scheme III) gave similar results. A crystalline monoisopropylidene derivative, obtained in 72% yield, clearly retained an unaltered acetamido group, and was further characterized through the preparation of a crystalline di-*O*-acetyl derivative. Cleavage of the isopropylidene group from this diacetate was performed under mild conditions, to give an amorphous product having an elemental composition corresponding to that calculated for an acetamido-di-*O*-acetyl-deoxyhexose; acetylation of it afforded the known, crystalline 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-galactopyranose (**18**); the pyranoid ring-structure was therefore, established. Reduction of the 2-acetamido-2-deoxy-*O*-isopropylidene-D-galactopyranose with sodium borohydride, followed by acetylation, gave a crystalline product having the elemental composition of an acetamido-tri-*O*-acetyl-deoxy-*O*-isopropylidenehexitol; de-*O*-acetylation thereof afforded a product that proved to be stable to sodium metaperiodate. We therefore concluded that the initial product from **14** is 2-acetamido-2-deoxy-4,6-*O*-isopropylidene-D-galactopyranose (**15**).

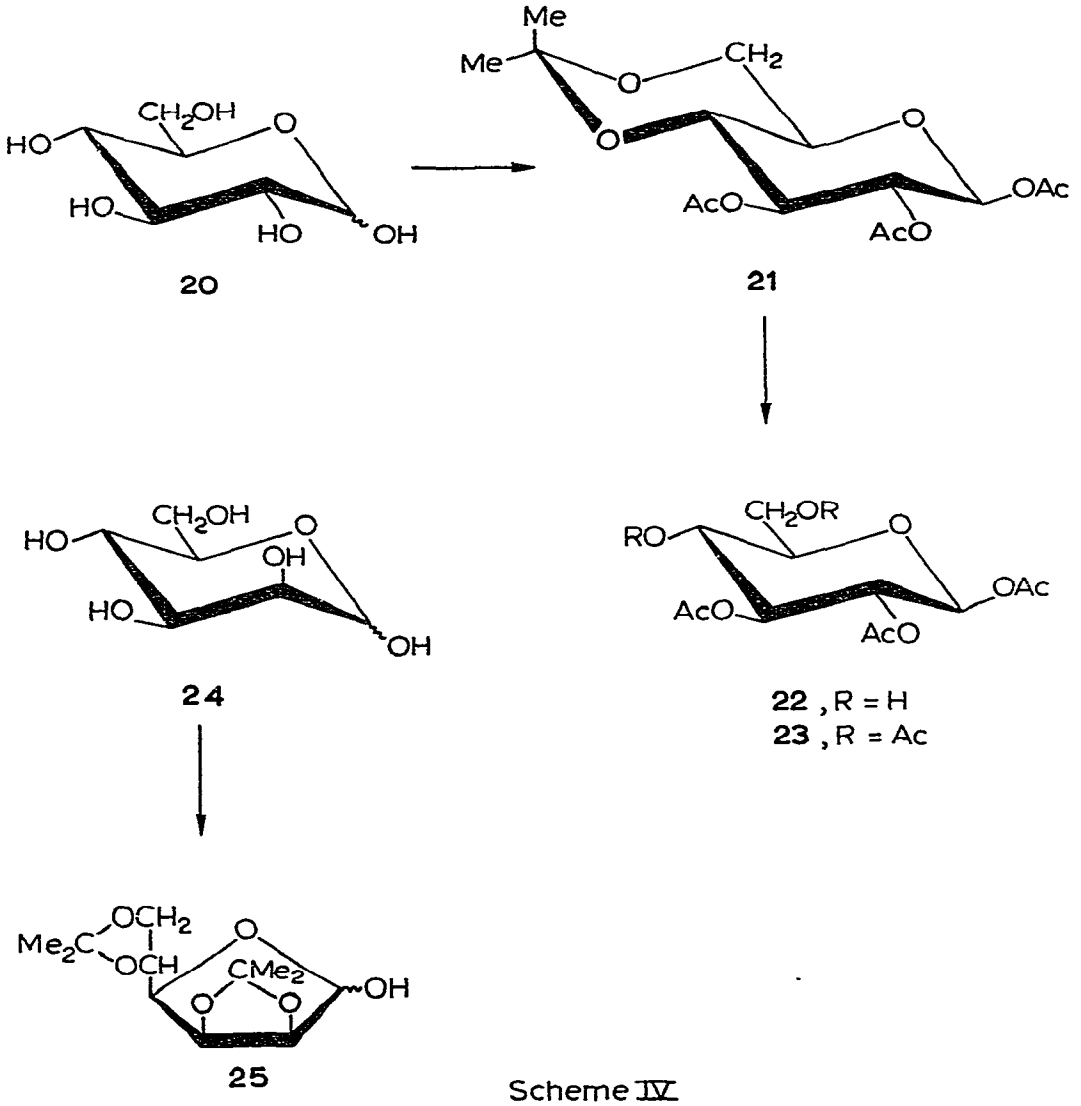
Although our primary interest concerned the 2-acetamido-2-deoxyaldoses, the behavior of two non-nitrogenous aldoses with 2,2-dimethoxypropane–*N*,*N*-dimethylformamide–*p*-toluenesulfonic acid was also studied. D-Glucose (**20**) gave an amorhous mixture of products; acetylation of this mixture, followed by column chromatography, led to the isolation of a crystalline tri-*O*-acetyl-*O*-isopropylidene-D-glucose in



Scheme III

an overall yield of 42%. The compound reduced Fehling solution, and was levorotatory, $[\alpha]_D^{20}$ −34° (*c* 1.0, chloroform); its n.m.r. spectrum included a doublet (H-1, $J_{1,2}$ 8.5 Hz), centered at τ 4.25. These data were consistent with structure **21** (see Scheme IV). Hydrolytic removal of the isopropylidene group under mild conditions gave a syrupy product having an elemental composition and an n.m.r. spectrum consistent with structure **22**. This material was stable to aqueous sodium metaperiodate and, on acetylation, gave β-D-glucopyranose pentaacetate (**23**) in high yield. We concluded

that the original crystalline material, obtained from D-glucose *via* isopropylidenation and subsequent acetylation, is, most probably, 1,2,3-tri-*O*-acetyl-4,6-*O*-isopropylidene-β-D-glucopyranose (**21**). In passing, it may be noted that the hydrolysis product, 1,2,3-tri-*O*-acetyl-β-D-glucopyranose (**23**) has been prepared by another route by other researchers[8,9], but that the compound has not previously been characterized.



Scheme IV

The isopropylidenation of D-mannose (**24**) with the trio of reagents gave, in 54% yield, the known, crystalline 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose[10,11] (**25**).

DISCUSSION

As far as we are aware, the only prior study of the acetonation of a 2-acylamido-2-deoxyaldose is that of Konstas, Photaki, and Zervas[12], who found that treatment of 2-benzamido-2-deoxy-D-glucose with acetone containing hydrogen chloride gives (1,2-dideoxy-5′,6′-*O*-isopropylidene-α-D-glucofurano)-[2′,1′:4,5]-2-phenyl-2-oxazoline; this fact stands in sharp contrast to the behavior of 2-acetamido-2-deoxy-D-glucose with the acetonating agent used in the present study. Even more impressive is the case of D-glucose. As is well known[11], the condensation of this aldose with acetone in the presence of any of a variety of catalysts gives preponderantly 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose. Indeed, the only recognizably "normal" product obtained in the course of the present study is 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**25**), as this compound is also obtained by the condensation of D-mannose with acetone in the presence of sulfuric acid[10,11]. Special note should be taken of the fact that none of the products in this admittedly limited study were found to bear an isopropylidene group at O-1, and it seems likely that the mechanism of isopropylidenation by this trio of reagents may be notably different from that which is involved in conventional acetonations. As *N*,*N*-dimethylformamide dimethyl acetal is, presumably, a potential component of the reagent mixture, and as it is known to react with vicinal diols to form highly labile (dimethylamino)methylene acetals[13,14], it is possible that some functional groups in these aldoses are masked by protecting groups that permit insertion of isopropylidene groups in abnormal positions but are themselves spontaneously removed during the isolation process. Irrespective of mechanistic considerations, the impression conveyed by earlier communications[1–3], namely that 2,2-dimethoxypropane–*N*,*N*-dimethylformamide–*p*-toluene sulfonic acid is an acetonating agent that may give unexpected and potentially useful products, appears to be amply supported by the results here described. The behavior of some aldoses with this reagent under more vigorous conditions (80°) is described in the paper immediately following this one.[15]

EXPERIMENTAL

General methods. — Melting points recorded are equivalent to corrected values. T.l.c. was performed on Silica Gel GF (Analtech, Inc.) with the solvent systems specified; components were detected by heating after spraying with a 3.3% solution (w/v) of ammonium vanadate in 50% sulfuric acid. Preparative chromatography was performed on 100-mesh silicic acid (Mallinckrodt Chem. Works) with the solvent systems specified. Chloroform was U.S.P. grade, and proportions of liquids are given by volume. N.m.r. spectra were recorded at 60 MHz for solutions in chloroform-*d* unless otherwise noted. *N*,*N*-Dimethylformamide (Aldrich Chem. Co.) was dried over molecular sieve 4A; 2,2-dimethoxypropane (Aldrich Chem. Co.) was used as received.

*2-Acetamido-2-deoxy-4,6-*O*-isopropylidene-*D*-glucopyranose* (**2**). — To a solution of 2-acetamido-2-deoxy-D-glucose (**1**, Pfanstiehl Laboratories, Inc., 10.0 g, 45.2

mmoles) in dry *N,N*-dimethylformamide (200 ml) were added 2,2-dimethoxypropane (20 ml, 3.6 moles/mole of **1**) and *p*-toluenesulfonic acid monohydrate (150 mg). The mixture was stirred at room temperature while the progress of the reaction was monitored by t.l.c. with 15:1 chloroform–methanol; after ~2 h, the starting material was no longer detectable, and the acid present was then removed by stirring for 15 min with Amberlite IR-45 (OH^-) ion-exchange resin (~10 g). After filtration, the colorless solution was evaporated *in vacuo* at 60–70° (bath). Crystallization was spontaneous, and when evaporation had ceased, the mass was cooled, and stirred with absolute ethanol; after further cooling, the product was removed by filtration and dried. Recrystallization from hot, absolute ethanol (~23 ml/g) gave 10.8 g (91%) of 2-acetamido-2-deoxy-4,6-*O*-isopropylidene-D-glucopyranose (**2**) as fine needles having m.p. 189–190° (sample introduced at 180°, 2°/min, dec.) and $[\alpha]_D^{20}$ +57.5° (*c* 0.99, equil. in methanol).

Anal. Calc. for $C_{11}H_{19}NO_6$: C, 50.57; H, 7.33; N, 5.36. Found: C, 50.29; H, 7.53; N, 5.19.

The 220-MHz p.m.r. spectrum of a solution of the compound in methanol-d_4 showed signals at τ 4.85 (doublet, $J_{1,2}$ 3.5 Hz), 7.97 (AcN), and 8.46 and 8.57 (Me_2C).

*2-Acetamido-1,3-di-*O*-acetyl-2-deoxy-4,6-*O*-isopropylidene-α-*D*-glucopyranose* (**3**). — The cyclic acetal **2** (300 mg) was acetylated with pyridine–acetic anhydride at room temperature in the usual way and the product was crystallized from ether to give 290 mg (73%) of **3**, m.p. 137–138°, $[\alpha]_D^{20}$ +73° (*c* 1.0, chloroform). The i.r. spectrum of the compound (Nujol) showed absorption at 3330 (NH), 1750, 1720, 1250–1220 (ester), 1660, 1530 (amide), and 855 cm^{-1} (Me_2C). Its n m r. spectrum included a doublet centered at τ 3.87 ($J_{1,2}$ 3.5 Hz), and three-proton signals at τ 7.82 (axial acetyl), 7.91 (equatorial acetyl), and 8.06 (equatorial AcNH).

Anal. Calc. for $C_{15}H_{23}NO_8$: C, 52.17; H, 6.71; N, 4.06. Found: C, 51.98; H, 6.42; N, 3.87.

*2-Acetamido-1,3-di-*O*-acetyl-2-deoxy-α-*D*-glucopyranose* (**4a**). — A solution of compound **3** (40 g) in 60% aqueous acetic acid (450 ml) was heated for 3 h at 50°, and evaporated *in vacuo*, and the residue was crystallized from chloroform to give **4a**; wt. 34.1 g (96%), m.p. 172–173°, $[\alpha]_D^{20}$ +80° (*c* 1.0, methanol). In a Nujol mull, it showed i.r. absorption at 3500 (OH), 3330 (NH), 1750, 1720, 1230 (ester), 1670, and 1540 cm^{-1} (amide). In solution in methanol-d_4, it afforded ^1H signals that included a doublet at τ 3.92 ($J_{1,2}$ 3.5 Hz) and three-proton signals at 7.83 (axial Ac), 7.94 (equatorial Ac), and 8.10 (equatorial AcNH). In solution in methyl sulfoxide-d_6, the 100-MHz, n.m.r. spectrum included a doublet at τ 4.09 ($J_{1,2}$ 3.0 Hz), a signal at 4.54 (secondary OH), one at 6.61 (primary OH), and three-proton signals at 7.84 (axial AcO), 7.98 (equatorial AcO), and 8.20 (equatorial AcN).

Anal. Calc. for $C_{12}H_{19}NO_8$: C, 47.21; H, 6.27; N, 4.59. Found: C, 47.06; H, 6.49; N. 4.44.

A sample (300 mg) was heated with a mixture of pyridine (5 ml) and acetic anhydride (2 ml) for 3 h at 60°. The solvents were removed *in vacuo*, and the residue was crystallized from ethanol–ether to give 340 mg (89%) of **4b**; m.p. 139°, $[\alpha]_D^{20}$ +94°

(*c* 1.0, chloroform); the n.m.r. spectrum of the product thus obtained was identical with that of an authentic specimen obtained in the usual way by the direct acetylation of 2-acetamido-2-deoxy-D-glucose

Benzyl 2-benzamido-2-deoxy-4,6-O-isopropylidene-β-D-glucopyranoside (**6**).—The glycoside **5** was prepared, in 90% yield, as described by Weidmann and co-workers[5], and was found to have m.p. 210–211°, $[\alpha]_D^{20}$ −21.9° (*c* 0.93, methanol), $[\alpha]_D^{20}$ −41.3° (*c* 1, pyridine), and the appropriate elemental composition. Gross and co-workers[4] reported m.p. 236° and $[\alpha]_D^{20}$ −44° (pyridine) for this glycoside. A solution of **5** (2.0 g) in a mixture of *N,N*-dimethylformamide (30 ml) and 2,2-dimethoxypropane (10 ml) was treated with *p*-toluenesulfonic acid monohydrate (50 mg). The mixture was stirred for 3 h at room temperature and then freed of acid through the addition of Amberlite IR-45 (OH^-) ion-exchange resin. After removal of the resin, the solution was evaporated *in vacuo* at 70–80°, to give a crystalline product; this was recrystallized from ethanol to give needles (1.63 g, 74%); m.p. 203.5–204°, $[\alpha]_D^{20}$ −71.6° (*c* 1.61, chloroform).

Anal. Calc. for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.39. Found: C, 66.75; H, 6.59; N, 3.47.

Benzyl 2-acetamido-2-deoxy-4,6-O-isopropylidene-β-D-glucopyranoside (**7**). — To a solution of **6** (500 mg) in methanol (20 ml) was added sodium hydroxide (2.5 g), and the mixture was boiled under reflux and stirred for 40 h. It was then cooled to 0° and stirred, while the major part of the alkali was neutralized through the cautions addition of 3 M hydrochloric acid. The pH was finally brought to 1 through the addition of M hydrochloric acid. Amberlite IR-45 (OH^-) ion-exchange resin was added until the pH was 5–6, and the suspension was then filtered and the filtrate evaporated to dryness. The residue was dissolved in methanol (30 ml), acetic anhydride (3 ml) was added, and the solution was boiled for 5 min. It was then evaporated *in vacuo* to a crystalline solid (400 mg, 84%), which was recrystallized from ethanol–hexane to give needles of m.p. 173.5–175.5° and $[\alpha]_D^{20}$ −60.0° (*c* 0.57, chloroform).

Anal. Calc. for $C_{18}H_{25}NO_6$: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.15; H, 7.20; N, 4.15.

Benzyl 2-acetamido-3-O-benzyl-2-deoxy-4,6-O-isopropylidene-β-D-glucopyranoside (**8**). — (*A*) *From 2-acetamido-2-deoxy-4,6-O-isopropylidene-D-glucopyranose* (**2**). The procedure employed was patterned after that used earlier[16] for the benzylation of **1**. To a stirred solution of **2** (500 mg) in *N,N*-dimethylformamide (10 ml) held at 0° were added benzyl bromide (3 ml), barium oxide (3.0 g of freshly ground, lump BaO), and barium hydroxide octahydrate (1.2 g). The mixture was stirred for 2 h at 0 to −10° and then for 18 h at room temperature. Dichloromethane (50 ml) was added, and the mixture was filtered, the residue being washed with more dichloromethane. The filtrate and washings were combined and washed three times with water, dried (sodium sulfate), and evaporated *in vacuo* to a syrup which was chromatographed on a column (2.0 cm i.d.) of silicic acid (30 g) with benzene and then with chloroform. The chloroform eluate afforded 575 mg (68%) of product; recrystallization from ethanol–hexane gave needles, m.p. 152–153° and $[\alpha]_D^{20}$ −21.0° (*c* 1.1, chloroform); on

admixture of the product with a specimen prepared from **7** as described next, the m.p. was undepressed.

Anal. Calc. for $C_{25}H_{31}NO_6$: C, 68.01; H, 7.08; N, 3.17. Found: C, 67.65; H, 7.07; N, 3.12.

(*B*) *From benzyl 2-acetamido-2-deoxy-4,6-O-isopropylidene-β-D-glucopyranoside* (**7**). Compound **7** (400 mg) was benzylated in essentially the same way as described in (*A*), to yield 360 mg (72%) of chromatographed **8**; on crystallization from ethanol–hexane, the product had m.p. 152–153°.

2-Acetamido-2-deoxy-4,6-O-isopropylidene-D-mannopyranose (**10**). — To a solution of 2-acetamido-2-deoxy-D-mannose (**9**, 2.0 g of the monohydrate, Pfanstiehl Laboratories, Inc.) in *N,N*-dimethylformamide (50 ml) were added 2,2-dimethoxypropane (4 ml) and *p*-toluenesulfonic acid monohydrate (20 mg). The mixture was stirred for 90 min at room temperature and then treated with Amberlite IR-45 (OH^-) ion-exchange resin to remove the acid. The solution was evaporated *in vacuo* (80° bath) to a syrupy product which was crystallized from chloroform–ether. Recrystallization from ethyl acetate gave pure **10** (1.6 g, 73%) as needles, m.p. 128–129.5°; $[\alpha]_D^{20} - 10°$ (*c* 1.0, methanol). The i.r. spectrum of a Nujol mull of the product showed absorption at 3400 (NH, OH), 1665, 1650, and 1540 (amide), and 862 cm^{-1} (Me_2C). The n.m.r. spectrum of a solution of **10** in methanol-d_4 included a one-proton signal at τ 5.0 ($J_{1,2}$ 1.5 Hz) and three-proton signals at τ 7.97 (AcN), 8.45, and 8.62 (Me_2C).

Anal. Calc. for $C_{11}H_{19}NO_5$: C, 50.57; H, 7.33; N. 5.36. Found: C, 50.14; H, 7.36; N, 5.33.

2-Acetamido-1,3-di-O-acetyl-2-deoxy-4,6-O-isopropylidene-α-D-mannopyranose (**11**). — A sample of **10** (100 mg) was acetylated overnight at room temperature with pyridine–acetic anhydride. The product was chromatographed on a column (1.6 cm) of silicic acid (10 g) with 50:1 chloroform–methanol to give the di-*O*-acetyl derivative (**11**) as a syrup· wt. 110 mg (83%), $[\alpha]_D^{20} + 38.5°$ (*c* 1, chloroform). The i.r. spectrum of the syrup (neat) showed absorption at 3400 (NH), 1752 and 1320 (ester), and 860 cm^{-1} (Me_2C); the n.m.r. spectrum included the following signals: τ 4.0 (broad singlet, H-1), three-proton signals at 7.83 (axial AcO), 7.94 and 7.96 (axial AcN and equatorial AcO), 8.48 and 8.59 (Me_2C).

Anal. Calc. for $C_{15}H_{23}NO_8$: C, 52.17; H, 6.71; N, 4.06. Found: C, 51.91; H, 6.50; N, 3.80.

A solution of **11** (120 mg) in 50% aqueous acetic acid was heated for 90 min at 60–70°; it was then evaporated under diminished pressure (50° bath) to a syrup which was acetylated by heating with pyridine (3 ml) and acetic anhydride (1 ml) for 2 h at 60°. The reagents were removed by evaporation *in vacuo*, and the residue was chromatographed on a column of silicic acid (10 g) with 50:1 chloroform–methanol to give 130 mg (96%) of syrupy 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-mannopyranose (**12**) having $[\alpha]_D^{20} + 50°$ (*c* 1.0, chloroform); n.m.r. signals appeared at τ 3.96 ($J_{1,2}$ 2.0 Hz), 7.82 (3 H, axial AcO), 7.91 (3 H), 7.99 (3 H), and 7.93 (6 H) (three equatorial AcO, one axial AcN). These signals agree very closely with those reported

recently[7] for a specimen of highly purified **12**, prepared through the direct acetylation of **9**, that showed $[\alpha]_D^{20}$ +63.9° (*c* 0.78, chloroform).

Anal. Calc. for $C_{16}H_{23}NO_{10}$: C, 49.36; H, 5.95; N, 3.60. Found: C, 48.99; H, 5.96; N, 3.32.

*2-Acetamido-1,3,5-tri-*O*-acetyl-2-deoxy-4,6-*O*-isopropylidene-*D*-mannitol* (**13**). — A solution of **10** (150 mg) in water (1.5 ml) was added dropwise at room temperature to a stirred solution of sodium borohydride (40 mg) in water (1.0 ml). After 15 min, the residual reagent was decomposed through the addition of acetic acid. The solution was diluted with water to a volume of 30 ml, treated with Amberlite IR-45 and with Amberlite IRC-50 ion-exchange resins, and then evaporated *in vacuo* at 30°. The residual syrup was acetylated by heating for 4 h at 50–60° with pyridine (5 ml) and acetic anhydride (1 ml), and the product was chromatographed on a column of silicic acid (15 g) with 50:1 chloroform–methanol to give 180 mg (81%) of **13**; after recrystallization from ether, this was obtained as needles, m.p. 122° and $[\alpha]_D^{20}$ −11.5° (*c* 1.0, chloroform). The i.r. spectrum of the product (Nujol mull) showed absorption at 3350 (NH), 1750 and 1225 (ester), 1650 and 1540 (amide), and 855 cm^{-1} (Me_2C); n.m.r. signals, all three-proton singlets, were observed at τ 7.88, 7.93, 7.95, 8.00 (AcO and AcN), 8.50 and 8.53 (Me_2C).

Anal. Calc. for $C_{17}H_{27}NO_9$: C, 52.43; H, 6.99; N, 3.60. Found: C, 52.55; H, 7.14; N, 3.42.

A sample (15 mg) of **13** was treated with methanol presaturated with ammonia and, after 18 h at room temperature, the solution was evaporated to dryness. Aqueous sodium metaperiodate was added; after 24 h, the quantity of periodate, as determined by titration, had not diminished.

*2-Acetamido-2-deoxy-4,6-*O*-isopropylidene-*D*-galactopyranose* (**15**). — To a solution of **14** (2.0 g, Pfanstiehl Laboratories, Inc.) in *N*,*N*-dimethylformamide (50 ml) were added 2,2-dimethoxypropane (4 ml) and *p*-toluenesulfonic acid monohydrate (20 mg). The mixture was stirred for 90 min at room temperature, and then treated with Amberlite IR-45 (OH^-) ion-exchange resin. After removal of the resin, the solution was evaporated *in vacuo* (80° bath) to a syrup which was crystallized from chloroform solution. Recrystallization from ethyl acetate gave 1.7 g (72%) of **15** as needles; m.p. 162–164° (dec.) and $[\alpha]_D^{20}$ +128.5° (*c* 1, methanol, equilibrium). In a Nujol mull, the product showed i.r. absorption at 3340 (NH, OH), 1665 and 1555 (amide), and 860 cm^{-1} (Me_2C); in methanol-d_4, its n.m.r. spectrum included signals at τ 4.80 (1 H, doublet, $J_{1,2}$ 3.5 Hz), 8.00 (3 H, AcNH), 8.50 (3 H) and 8 57 (3 H) (Me_2C).

Anal. Calc. for $C_{11}H_{19}NO_6$: C, 50.57; H, 7.33; N, 5.36. Found: C, 50.19; H, 7.45; N, 5.31.

*2-Acetamido-1,3-di-*O*-acetyl-2-deoxy-4,6-*O*-isopropylidene-α-*D*-galactopyranose* (**16**). — The acetal **15** (200 mg) was acetylated at room temperature with acetic anhydride–pyridine, and, after evaporation *in vacuo*, the mixture yielded a crystalline residue; on recrystallization from ether, the product (225 mg, 85%) was obtained as needles of m.p. 174.5–175.5° and $[\alpha]_D^{20}$ +148° (*c* 1.0, chloroform). In Nujol mull, the compound gave an i.r. spectrum which showed absorption at 3300 (NH), 1750, 1730,

1230–1250 (ester), and 855 cm^{-1} (Me_2C); the n.m.r. spectrum of the compound included signals at τ 3.7 (1 H, doublet, $J_{1,2}$ 3.0 Hz), 7.87 (6 H) and 8.05 (3 H) (AcO and AcN), 8.52 (3 H), and 8.57 (3 H) (Me_2C).

Anal. Calc. for $C_{15}H_{23}NO_8$: C, 52.17; H, 6.71; N, 4.06. Found: C, 51.93; H, 6.84; N, 3.85.

*2-Acetamido-1,3-di-*O*-acetyl-2-deoxy-*α*-*D*-galactopyranose* (**17**). — Cleavage of the isopropylidene group from **16** was accomplished by heating a sample (150 mg) in 50% aqueous acetic acid solution for 75 min at 60–70°. The mixture was evaporated *in vacuo* (50° bath), and the residual syrup was chromatographed on silicic acid (15 g) with 30:1 chloroform–methanol to afford 110 mg (83%) of **17** as a syrup having $[\alpha]_D^{20}+154°$ (*c* 1.0, methanol). The product (neat) showed absorption at 3350 (OH, NH), 1740 and 1230 (ester), 1650 and 1540 cm^{-1} (amide); its 100-MHz, n.m.r. spectrum in methyl sulfoxide-d_6 included an H-1 doublet, centered at τ 4.15 ($J_{1,2}$ 3.8 Hz), a doublet (J_{CHOH} 5.0 Hz) at 4.81, a poorly defined signal at 6.64 (CH_2OH), and other signals at 7.90 (3 H, axial AcO), 8.00 (3 H, equatorial AcO), and 8.23 (3 H, equatorial AcN).

Anal. Calc. for $C_{12}H_{19}NO_8$: C, 47.21; H, 6.27; N, 4.59. Found: C, 47.02; H, 6.14; N, 4.29.

A sample (150 mg) of **17** was acetylated by heating with acetic anhydride–pyridine for 2 h at 60°; the product was crystallized from ether; wt. 180 mg (94%), m.p. 178°, $[\alpha]_D^{20}+102°$ (*c* 1.0, chloroform). Admixture of this product with an authentic sample of 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-galactopyranose (**18**) did not depress its melting point; the i.r. and n.m.r. spectra of the product and of authentic **18** were indistinguishable.

*2-Acetamido-1,3,5-tri-*O*-acetyl-4,6-*O*-isopropylidene-2-deoxy-D-galactitol* (**19**). — A solution of **15** (300 mg) in water (3 ml) was added dropwise at room temperature to a stirred solution of sodium borohydride (80 mg) in water (2 ml). After 15 min, the excess of reagent was decomposed through the addition of acetic acid, and the solution was diluted with water to a volume of 30 ml. After treatment with Amberlite IR-45 and IRC-50 ion-exchange resins, the solution was evaporated *in vacuo* (30° bath) and the residual syrup was heated with acetic anhydride–pyridine for 3 h at 50°. Chromatography on silica gel with 50:1 chloroform–methanol gave **19** (350 mg, 78%); recrystallization from ether afforded needles of m.p. 114–115° and $[\alpha]_D^{20}-39.2°$ (*c* 1.0, chloroform). The i.r. spectrum of the compound in a Nujol mull showed absorption at 3300 (NH), 1750 and 1250 (ester), 1650 and 1550 (amide), and 855 cm^{-1} (Me_2C); the n.m.r. spectrum included signals at τ 7.88, 7.95, and 7.97 (all 3 H, AcO and AcN) and 8.54 (6 H, Me_2C).

Anal. Calc. for $C_{17}H_{27}NO_9$: C, 52.43; H, 6 99; N, 3.60. Found: C, 52.27; H, 7.19; N, 3.48.

A sample (15 mg) of **19** was deacetylated at room temperature with methanolic ammonia; after removal of the methanol and ammonia, the product was dissolved in aqueous sodium mataperiodate. Over a period of 24 h, the titer of the periodate solution remained unchanged.

1,2,3-Tri-O-acetyl-4,6-O-isopropylidene-β-D-glucopyranose (**21**). — To a solution of anhydrous D-glucose (**20**, 4.0 g) in *N,N*-dimethylformamide (100 ml) were added 2,2-dimethoxypropane (8 ml) and *p*-toluenesulfonic acid monohydrate (20 mg). The mixture was stirred for 60 min at room temperature and then treated with Amberlite IR-45 ion-exchange resin to remove the acid. The suspension was filtered and the filtrate was evaporated *in vacuo* (70–80° bath) to a syrup which was dissolved in a mixture of acetic anhydride (10 ml) and pyridine (20 ml). The solution was kept overnight at room temperature and the acetylated product was then chromatographed on a column (2.8 cm diam.) of silicic acid (100 g) with chloroform, to give **21**. Recrystallized from ethanol, the product (3.25 g, 42%) was obtained as needles; m.p. 169° and $[\alpha]_D^{20} -34°$ (*c* 1.0, chloroform); i.r. absorption (Nujol mull) at 1775, 1200-1250 (ester), and 855 cm^{-1} (Me_2C); n.m.r. signals at τ 4.25 (doublet, H-1, $J_{1,2}$ 8.5 Hz), 7.93, 7.98, 8.00 (1 H each, Ac), 8.58 and 8.63 (3 H each, Me_2C). The compound gave a positive test with hot Fehling solution.

Anal. Calc. for $C_{15}H_{22}O_9$: C, 52.02; H, 6.40. Found: C, 51.78; H, 6.61.

Hydrolysis of **21** *and acetylation of the product.* — A solution of the acetal ester **21** (500 mg) in 50% aqueous acetic acid was heated for 60 min at 65 ±5° and then evaporated under diminished pressure; the residual syrup was chromatographed on a column of silicic acid (15 g) with 50:1 chloroform–methanol. The amorphous 1,2,3-tri-*O*-acetyl-β-D-glucopyranose (**22**) (350 mg, 79%) thus prepared showed $[\alpha]_D^{20} -26.6°$ (*c* 1.0, chloroform) and its n.m.r. spectrum in chloroform-*d* included a doublet, $J_{1,2}$ 8.0 Hz, centered at τ 4.25; two equatorial acetoxyl groups gave a signal at 7.90, and a third one, presumably that on C-1, appeared at 7.97. A sample (10 1 mg) of the ester was dissolved in 1.5 ml of 4.2M sodium metaperiodate; titration after 24 h at room temperature showed that the concentration of the oxidant was unchanged.

Anal. Calc. for $C_{12}H_{18}O_9$: C, 47.06; H, 5.92. Found: C, 46.88; H, 6.17.

Compound **22** (350 mg) was acetylated with pyridine–acetic anhydride to give colorless needles (400 mg, 90%; m.p. 132°) from ethanol solution. The n.m.r. spectrum of this product was identical with that of authentic 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (**23**); a mixed m.p. was undepressed.

2,3:5,6-Di-O-isopropylidene-D-mannofuranose (**25**). — To a solution of D-mannose (4.0 g) in *N,N*-dimethylformamide (100 ml) were added 2,2-dimethoxypropane (12 ml) and *p*-toluenesulfonic acid monohydrate (20 mg). The mixture was stirred for 110 min at room temperature and then treated with Amberlite IR-45 ion-exchange resin to remove the acid. The resin was removed by filtration, and the filtrate was evaporated *in vacuo* (60° bath) to give a syrup which was chromatographed on a column of silicic acid (100 g) with 50:1 chloroform–methanol. The crystalline product thus obtained was recrystallized from hexane as needles: wt. 3.1 g (54%), m.p. 122°, $[\alpha]_D^{20} +16°$ (*c* 1.0, ethanol). The n.m.r. spectrum of the product in methanol-d_4 showed a one-proton singlet at τ 4.76 (H-1) and signals from the isopropylidene methyl groups as follows: 8.60 (6 H), 8.67 (3 H), and 8.90 (3 H). For 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**25**), a m.p. of 122–123° and $[\alpha]_D^{16} +16°$ (*c* 2.6, ethanol) have been reported[10,11].

ACKNOWLEDGMENT

We are indebted to the staff of the Institute's Section on Microanalytical Services and Instrumentation for elemental analyses and n.m.r. spectra.

REFERENCES

1 M. E. EVANS AND F. W. PARRISH, *Tetrahedron Lett.*, (1966) 3805.
2 M. E. EVANS, F. W. PARRISH, AND L. LONG, JR., *Carbohyd. Res.*, 3 (1967) 453.
3 A. HASEGAWA, N. KURIHARA, D. NISHIMURA, AND M. NAKAJIMA, *Agr. Biol. Chem.* (Tokyo), 32 (1968) 1123.
4 P. H. GROSS, K. BRENDEL, AND H. K. ZIMMERMAN, JR., *Ann.*, 683 (1965) 175.
5 H. WEIDMANN, E. FAULAND, R. HELBIG, AND H. K. ZIMMERMAN, JR., *Ann.*, 694 (1966) 183.
6 P. A. GENT, R. GIGG, AND R. CONANT, *J. Chem. Soc., Perkin I*, (1972) 248.
7 N. PRAVDIĆ, B. ŽIDOVEC, AND H. G. FLETCHER, JR., *Croat. Chem. Acta*, 42 (1970) 523.
8 A. L. RAYMOND, *J. Biol. Chem.*, 113 (1936) 378.
9 D. MCGRATH, E. E. LEE, AND P. S. O'COLLA, *Carbohyd. Res.*, 11 (1969) 453.
10 J. C. IRVINE AND A. F. SKINNER, *J. Chem. Soc.*, (1926) 1089.
11 O. T. SCHMIDT, *Methods Carbohyd. Chem.*, 2 (1963) 318.
12 S. KONSTAS, I. PHOTAKI, AND L. ZERVAS, *Chem. Ber.*, 92 (1959) 1288.
13 J. ŽEMLIČKA, *Collect. Czech. Chem. Commun.*, 28 (1963) 1060.
14 J. ŽEMLIČKA AND A. HOLÝ, *Collect. Czech. Chem. Commun.*, 32 (1967) 3159.
15 A. HASEGAWA AND H. G. FLETCHER, JR., *Carbohyd. Res.*, 29 (1973) 223.
16 R. HARRISON AND H. G. FLETCHER, JR., *J. Org. Chem.*, 30 (1965) 2317.