# Syntheses with Partially Benzylated Sugars. IX.[1] Synthesis of a 5-Hexulosonic Acid (5-Ketohexonic Acid) Derivative and Inversion of Configuration at C-5 in an Aldose

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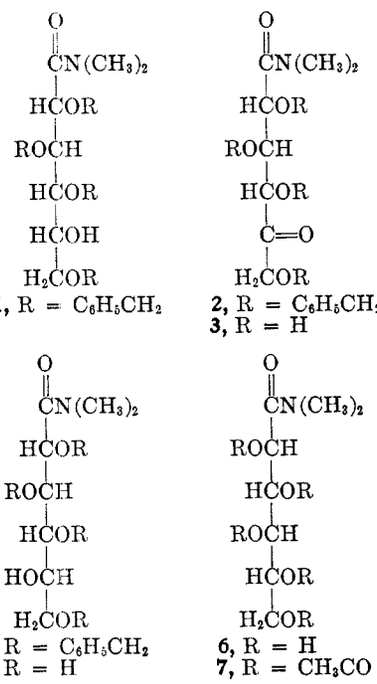
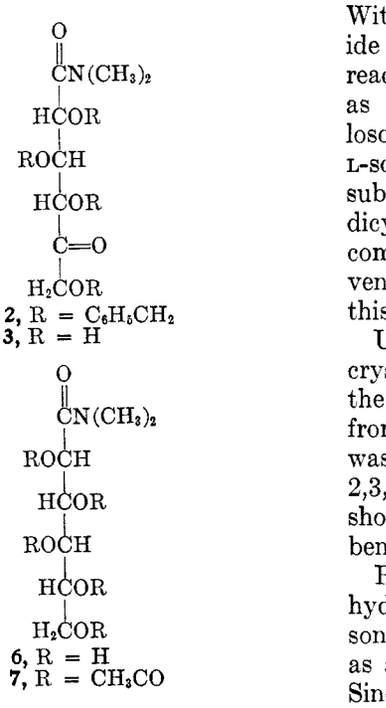
The utility of partially benzylated derivatives of sugars for the synthesis of 5-ketoaldonic acids and for the inversion of the configuration of C-5 in an aldose has been investigated using 2,3,4,6-tetra-*O*-benzyl-*N*,*N*-dimethyl-D-gluconamide (**1**). With dimethyl sulfoxide–acetic anhydride, **1** is readily oxidized at C-5, the product (**2**) being an amorphous, unstable derivative of L-sorburonic acid. Catalytic debenzylation of **2** yields crystalline *N*,*N*-dimethyl-D-*xylo*-hex-5-ulosamide (**3**) which mutarotates in aqueous solution and is comparatively resistant to acidic hydrolysis, indicating that it probably exists as a cyclic hemiacetal. Reduction of **2** with sodium borohydride gives largely 2,3,4,6-tetra-*O*-benzyl-*N*,*N*-dimethyl-L-idonamide (**4**); this substance was debenzylated and identified by comparison with authentic *N*,*N*-dimethyl-D-idonamide (**6**). The reduction of **4** with 2 moles of lithium aluminum hydride gives 2,3,4,6-tetra-*O*-benzyl-L-idose (**8**) which was identified by conversion to **10** and **11**.

In an earlier paper,[1] we have shown that a pyranose sugar, fully benzylated except at C-1 and C-5 (2,3,4,6-tetra-*O*-benzyl-D-glucopyranose), may readily be converted into an acyclic derivative, 2,3,4,6-tetra-*O*-benzyl-*N*,*N*-dimethyl-D-gluconamide (**1**), in which all groups except the hydroxyl group at C-5 are masked. We wish now to show how this type of derivative may be used as an intermediate in the synthesis of substituted 5-hexulosonic acids (= 5-ketohexonic acids) as well as for the inversion of the configuration of C-5 in an aldose. Such transformations are of potential utility in the synthesis of otherwise difficultly accessible (and, particularly, labeled) sugar derivatives.



**1**, R = $C_6H_5CH_2$



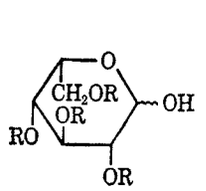
**2**, R = $C_6H_5CH_2$
**3**, R = H

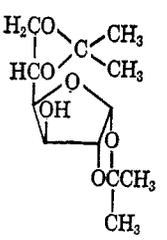


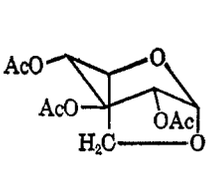
**4**, R = $C_6H_5CH_2$
**5**, R = H



**6**, R = H
**7**, R = $CH_3CO$







**8**, R = $C_6H_5CH_2$
**9**, R = H

**10**

**11**

The facile oxidation of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose with dimethyl sulfoxide–acetic anhydride[3] apparently ceases, as described earlier,[1] with the formation of 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone, the lactone ring effectively protecting C-5. With 2,3,4,6-tetra-*O*-benzyl-*N*,*N*-dimethyl-D-gluconamide (**1**), however, this combination of reagents readily attacks C-5.[4] The product (**2**) may be named as 2,3,4,6-tetra-*O*-benzyl-*N*,*N*-dimethyl-D-*xylo*-5-hexulosonamide or, alternatively, as 1,3,4,5-tetra-*O*-benzyl-L-sorburonic acid *N*,*N*-dimethylamide. The same substance may be obtained using dimethyl sulfoxide–dicyclohexylcarbodiimide[5] as an oxidant, but this combination of reagents proved somewhat less convenient than dimethyl sulfoxide–acetic anhydride for this purpose.

Unfortunately, all attempts to obtain **2** in pure or crystalline form were unsuccessful and, indeed, none of the usual reagents for ketones gave a solid derivative from it, although the 2,5-dichlorophenylhydrazone was obtained as an analytically pure syrup. Like 2,3,4,6-tetra-*O*-benzyl-5-*O*-methyl-*aldehydo*-D-glucose,[1,2] **2** shows a certain degree of instability, slowly evolving benzaldehyde on storage.[6]

Removal of the benzyl groups from **2** by catalytic hydrogenolysis yielded *N*,*N*-dimethyl-D-*xylo*-5-hexulosonamide (**3**), a derivative of "5-ketogluconic acid," as a crystalline solid which reduced Fehling solution. Since the substance shows only amide carbonyl absorption and mutarotates in aqueous solution, it presumably exists in the furanose form **3a**. However, the magnitude of the rotational change is small and speculation as to the anomeric form of the crystalline substance must be regarded as unwarranted. The

(1) Paper VIII of this series: H. Kuzuhara and H. G. Fletcher, Jr., *J. Org. Chem.*, **32**, 2531 (1967).

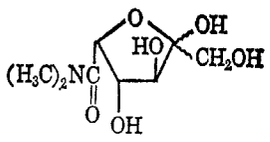
(2) Fellow in the Visiting Program of the National Institutes of Health, 1965–1967.

(3) J. D. Albright and L. Goldman, *J. Am. Chem. Soc.*, **87**, 4214 (1965).

(4) This fact supports our earlier suggestion (ref 1, footnote 12) that the methyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate isolated by K. Onodera, S. Hirano, and N. Kashimura [*J. Am. Chem. Soc.*, **87**, 4651 (1965)] was actually formed by the methanolysis of 2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone during the isolation process. Had methyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate been formed in the oxidation mixture, it would (like **1**) have been attacked at C-5.

(5) K. E. Pfitzner and J. G. Moffatt, *ibid.*, **87**, 5670 (1965).

(6) Reference 1, footnote 14.



3a

stability of the amide linkage toward acidic hydrolysis is marked; in this respect it resembles 2,3,4,6-tetra-*O*-benzyl-5-*O*-methyl-*N*,*N*-dimethyl-D-gluconamide[1] and stands in marked contrast to **1** and to 5-*O*-methyl-*N*,*N*-dimethyl-D-gluconamide[1] which hydrolyze readily. With these latter two amides, the hydroxyl groups which they have at C-5 and C-4, respectively, presumably attack C-1 under acidic conditions to yield the corresponding lactones. It is probable that the cyclic form (**3a**) postulated for **3** prevents approach of a hydroxyl group at C-1.

The reduction of 2,3,4,6-tetra-*O*-benzyl-*N*,*N*-dimethyl-D-*xylo*-5-hexulosonamide (**2**) with sodium borohydride in methanol afforded a mixture of **1** and 2,3,4,6-tetra-*O*-benzyl-*N*,*N*-dimethyl-L-idonamide (**4**) in which the latter predominated and from which it could be separated in crystalline form in 32% yield; the D-gluconic acid analog (**1**) was isolated in 19% yield. Catalytic debenzylation of **4** gave *N*,*N*-dimethyl-L-idonamide (**5**); the enantiomorph (**6**) was made from cadmium D-idonate–cadmium bromide monohydrate[7] for purposes of comparison and was itself further characterized through its tetraacetate (**7**).

We have earlier shown[1] that 2,3,4,6-tetra-*O*-benzyl-*N*,*N*-dimethyl-D-gluconamide is cleanly reduced to 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose through the action of 2 moles of lithium aluminum hydride. This process has now been applied to the L-idonamide analog **4** and 2,3,4,6-tetra-*O*-benzyl-L-idose (**8**) obtained as a chromatographically pure syrup in 53% yield. The free sugar, L-idose, has never been obtained in crystalline form; to confirm the identity of **8**, the benzyl groups were removed and the resulting L-idose was converted to the known 1,2:5,6-di-*O*-isopropylidene-β-L-idofuranose (**10**).[8,9] The L-idose prepared from **8** was also converted into 2,3,4-tri-*O*-acetyl-1,6-anhydro-β-L-idopyranose (**11**) which was compared with its known enantiomorph[10] by gas–liquid partition chromatography. Attempts to invert the configuration of C-5 in **1** through the use of a conventional SN2 displacement procedure were unsuccessful; this topic is currently the object of further investigation.

## Experimental Section[11]

**Crude 2,3,4,6-Tetra-*O*-benzyl-*N*,*N*-dimethyl-D-*xylo*-5-hexulosonamide (2).**—To a solution of 2,3,4,6-tetra-*O*-benzyl-*N*,*N*-dimethyl-D-gluconamide (**1**, 2.0 g) in dimethyl sulfoxide (12 ml) was added acetic anhydride (8 ml) and the mixture was stored at room temperature overnight. It was then poured into water (80 ml) and the aqueous layer decanted. The syrupy product was washed with two 50-ml portions of water and then dissolved in chloroform (50 ml); moisture was removed with sodium sulfate; and the solution was concentrated *in vacuo* to give a pale yellow syrup (1.6 g). Thin layer chromatography on silica gel using benzene–ether (1:1, v/v) revealed a major component, together with a minor and slightly faster moving one; column chromatography using the same solvent system failed to effect further purification of the product, infrared absorption (neat) at about 1735 (two peaks, C=O) and 1645 $cm^{-1}$ (amide). The substance proved to be somewhat unstable, slowly evolving benzaldehyde on storage.

A mixture of **2** (3.3 g) and 2,5-dichlorophenylhydrazine (1.1 g) in 2-propanol (35 ml) was boiled under reflux for 16 hr and then concentrated *in vacuo* to give a brown syrup (4.4 g) which was chromatographed on a column of silica gel using benzene–ether (8:1, v/v). While chromatographically homogeneous, the product (2.9 g, 69%) could not be induced to crystallize, $[\alpha]^{20}D$ +16.7° (*c* 3.12, $CHCl_3$).

*Anal.* Calcd for $C_{42}H_{43}Cl_2N_3O_5$ (740.74): C, 68.10; H, 5.85; Cl, 9.57; N, 5.67. Found: C, 67.96; H, 5.82; Cl, 9.30; N, 5.57.

***N*,*N*-Dimethyl-D-*xylo*-5-hexulosonamide (3).**—To a solution of chromatographed **2** (2.0 g) in a mixture of freshly distilled dioxane (40 ml) and water (5 ml) was added palladium black, freshly made by the reduction (with hydrogen in methanol) of palladium chloride (1.5 g). The suspension was shaken with hydrogen at room temperature until absorption of the gas had ceased (2 hr). After removal of the catalyst, the solution was concentrated *in vacuo* to give a syrup (900 mg) which contained two minor contaminants (tlc, 2-propanol–water, 4:1, v/v). Crude **3** (3.0 g), prepared in this fashion, was chromatographed on a column of silica gel (200 g) using 2-propanol–water (4:1, v/v) and a main fraction (1.8 g, 71%) obtained which crystallized when rubbed with a little of the eluent mixture of solvents. It was recrystallized from absolute ethanol (100 ml) and dried under high vacuum at 80°: mp 151–152°; $[\alpha]^{20}D$ −40.8° (10 min) → −44.0° (23 hr, constant, *c* 2.63, water). The substance (**3**) readily reduces hot Fehling solution and shows no ketone carbonyl absorption in its infrared spectrum.

*Anal.* Calcd for $C_8H_{15}NO_6$ (221.22): C, 43.44; H, 6.83; N, 6.33. Found: C, 43.67; H, 6.50; N, 6.28.

The stability of **3** toward acid was investigated by stirring an aqueous solution of it with several equivalents of Amberlite IR-120 ($H^+$) for 2 hr at 80° and by storing a solution of it in 20% hydrochloric acid at room temperature for 6 hr. Thin layer chromatography (2-propanol–water, 4:1, v/v) showed in both cases that **3** was largely unattacked under these conditions.

**2,3,4,6-Tetra-*O*-benzyl-*N*,*N*-dimethyl-L-idonamide (4).**—A solution of unchromatographed **2** (7.5 g) in methanol (80 ml) was treated with sodium borohyride (530 mg) and the mixture stored at room temperature overnight. Amberlite IR-120 ($H^+$) (4 g) was added and the suspension stirred for 10 min; the solution was then filtered and concentrated *in vacuo* to a syrup from which four batches of methanol were distilled. The residue crystallized spontaneously; tlc showed the presence of a major component, a minor component, and three substances present in traces only. By comparison with authentic material, the minor component was identified as **1**; the three trace impurities were not identified. The residue was dissolved in hot methanol (50 ml) and the solution stored (after seeding) at 5°; the crystals of **4** thus obtained (2.4 g, 32%) were recrystallized from a mixture of ethyl acetate (10 ml) and pentane (15 ml) and then from methanol. The product was dried at 80° for 2 hr under high vacuum: mp 120°; $[\alpha]^{20}D$ +23.1° (*c* 1.77 $CHCl_3$); infrared absorption at (Nujol) 3400 ± 5 (OH) and 1630 ± 5 $cm^{-1}$ (C=O).

*Anal.* Calcd for $C_{36}H_{41}NO_6$ (583.74): C, 74.07; H, 7.08; N, 2.40. Found: C, 74.07; H, 7.21; N, 2.43.

The original mother liquor was concentrated and then stored at 5° for more than 1 week to give 1.4 g (19%) of 2,3,4,6-tetra-*O*-benzyl-*N*,*N*-dimethyl-D-gluconamide (**1**), mp 103–104°. Its chromatographic behavior (tlc) and infrared spectrum were identical with those of authentic **1**.

***N*,*N*-Dimethyl-L-idonamide (5) from 2,3,4,6-Tetra-*O*-benzyl-*N*,*N*-dimethyl-L-idonamide (4).**—Palladium black, made by the reduction (with hydrogen in methanol solution) of palladium chloride (700 mg), was added to a solution of **4** (1.9 g) in methanol (70 ml) and the suspension was shaken with hydrogen at room temperature until absorption of the gas had ceased (30 min). After removal of the catalyst, the solution was concentrated *in vacuo* to give a crystalline mass, 700 mg (96%). Recrystallization from methanol (20 ml) afforded cubic prisms which were chromatographically homogeneous (tlc, 2-propanol–water, 4:1, v/v): mp 161° dec; $[\alpha]^{20}D$ −26.4° (*c* 2.19, water). The chro-

(7) E. Fischer and I. W. Fay, *Ber.*, **28**, 1975 (1895).
(8) N. Baggett and R. W. Jeanloz, *J. Org. Chem.*, **28**, 1845 (1963).
(9) K. Iwadare, *Bull. Chem. Soc. Japan*, **19**, 27 (1944).
(10) E. Sorkin and T. Reichstein, *Helv. Chim. Acta*, **28**, 1 (1945).
(11) Melting points are corrected. Thin layer chromatography was conducted on silica gel G (E. Merck AG, Darmstadt) using the solvent systems specified, components being detected by spraying with 10% sulfuric acid and heating at 100°. Column chromatography was carried out with silica gel (0.05–0.20 mm) of E. Merck AG.

matographic behavior and infrared absorption spectrum of the product were indistinguishable from those of *N,N*-dimethyl-D-idonamide (see below).

*Anal.* Calcd for $C_8H_{17}NO_6$ (223.23): C, 43.04; H, 7.68; N, 6.28. Found: C, 43.07; H, 7.49; N, 6.33.

***N,N*-Dimethyl-D-idonamide (6).**—A solution of cadmium D-idonate–cadmium bromide monohydrate[7] (6 g, $[\alpha]^{20}D$ −3.9°, water) in water (200 ml) was passed through a column of Amberlite IR-120 ($H^+$) (120 g) and then stirred with silver carbonate (20 g) for 2 hr. After removal of the insoluble silver salts, the solution was treated with hydrogen sulfide, filtered, and concentrated *in vacuo*, giving syrupy D-idonolactone (2.2 g) with broad carbonyl absorption at 1750–1790 $cm^{-1}$. A mixture of methanol (200 ml) and anhydrous dimethylamine (5 ml) was added and the reaction mixture stirred at room temperature for 30 min. A crystalline powder was obtained on concentration *in vacuo*. It was recrystallized from methanol (50 ml): 2.2 g (65%); mp 159–160° dec. One further recrystallization from methanol gave pure *N,N*-dimethyl-D-idonamide: mp 161° dec; $[\alpha]^{20}D$ +26.3° (*c* 2.46, water); infrared absorption (Nujol) at 3650–3400 (four peaks, OH) and 1635 $cm^{-1}$ (C=O).

*Anal.* Calcd for $C_8H_{17}NO_6$ (223.23): C, 43.04; H, 7.68; N, 6.28. Found: C, 43.17; H, 7.45; N, 6.11.

**2,3,4,5,6-Penta-*O*-acetyl-*N,N*-dimethyl-D-idonamide (7).**—A sample of **6** (700 mg) was acetylated with acetic anhydride (4 ml) in pyridine (10 ml) in conventional fashion to yield, after removal of the excess reagents, a colorless syrup (1.2 g, 88%) which crystallized spontaneously. Recrystallization from a mixture of ethyl acetate (5 ml) and pentane (15 ml) gave the pure penta-acetate (**7**): mp 135–137°; $[\alpha]^{20}D$ +13.9° (*c* 1.32, $CHCl_3$).

*Anal.* Calcd for $C_{18}H_{27}NO_{11}$ (433.42): C, 49.88; H, 6.28; N, 3.23. Found: C, 50.10; H, 6.28; H, 3.33.

**2,3,4,6-Tetra-*O*-benzyl-L-idopyranose (8).**—A solution of 2,3,4,6-tetra-*O*-benzyl-*N,N*-dimethyl-L-idonamide (**4**, 2.0 g, 3.4 mmoles) in anhydrous tetrahydrofuran (30 ml) was cooled at 0° and stirred while a suspension of lithium aluminum hydride (264 mg, 6.96 mmoles) in anhydrous tetrahydrofuran (20 ml) was added. The mixture was stirred at 0° for 3 hr and then 5% sulfuric acid (80 ml) was added dropwise. The product was extracted with ether (200 ml) and the extract, after washing with water, dried over magnesium sulfate and concentrated *in vacuo* yield a colorless syrup (1.5 g). Thin layer chromatography (benzene–ether, 2:1, v/v) revealed a major component migrating at a rate close to that of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose as well as two minor, slower moving components. The crude product was chromatographed on a column of silica gel (150 g), using benzene–ether (2:1, v/v), to give a chromatographically pure syrup (980 mg, 53%) which showed no carbonyl absorption (infrared) but could not be induced to crystallize or give an acceptable elemental analysis; it was characterized through the preparation of **10** and of **11**, the latter being identified by glpc.

**Conversion of 8 into 1,2:5,6-Di-*O*-isopropylidene-β-L-idofuranose (10) *via* L-Idose (9).**—A suspension of 10% palladium on charcoal in a solution of chromatographically pure **8** (3.2 g) in a mixture of methanol (50 ml) and water (5 ml) was shaken with hydrogen at room temperature until absorption of the gas had ceased (2.5 hr). After removal of the catalyst, the solution was concentrated *in vacuo* to yield L-idose (**9**, 900 mg, 84%) as a syrup which strongly reduced Fehling solution. Anhydrous acetone (100 ml) and concentrated sulfuric acid (3 ml) were added to L-idose (2.2 g) prepared in this manner and the mixture was shaken for 3.5 hr. Anhydrous sodium carbonate (20 g) was then added and the suspension was stirred for 1 hr and filtered. The treatment with sodium carbonate was repeated twice more and the solution then concentrated *in vacuo* to give a semicrystalline mass which was extracted with hot benzene (100 ml). Concentration of the extract *in vacuo* afforded a partially crystalline product to which ether (30 ml) was added. The crystals were removed by filtration and washed with a little ether (1.25 g, 39%). Recrystallization from ethyl acetate–hexane yielded colorless prisms: mp 152–154°; $[\alpha]^{20}D$ −33.8° (*c* 3.44, acetone). Satisfactory elemental analyses were obtained. The substance was also purified by sublimation at 5–10-μ pressure and 80° (bath): mp 153–155°; $[\alpha]^{20}D$ −35.4° (*c* 1.41, water). Iwadare[9] reported mp 151–152.5° and $[\alpha]^{5}D$ +36° (*c* 2.01, acetone) for the enantiomorph of **10**; Baggett and Jeanloz[8] recorded mp 153–154°, $[\alpha]^{23}D$ −25° (*c* 0.55, acetone), and $[\alpha]^{22}D$ −22° (*c* 0.60, water) for 1,2:5,6-di-*O*-isopropylidene-β-L-idofuranose (**10**).

**Conversion of 9 into 2,3,4-Tri-*O*-acetyl-1,6-anhydro-β-L-idopyranose (11).**—A solution of **9** (256 mg) in 2.5% aqueous sulfuric acid was heated on a steam bath for 8 hr. Barium carbonate was then added in excess and the mixture heated and stirred for an additional 30 min. The solution was filtered and concentrated *in vacuo* to a syrup from which the 1,6-anhydro-β-L-idopyranose was extracted with methanol. The methanolic extract was concentrated *in vacuo* and the residue acetylated with acetic anhydride (1 ml) and pyridine (1 ml) at room temperature over night. The mixture was poured into ice water and the product was extracted with chloroform (30 ml). After being washed with 5% sulfuric acid, with aqueous sodium bicarbonate solution, and with water, the extract was dried over sodium sulfate and concentrated *in vacuo* to a yellow syrup. In pyridine solution, a sample of this product was applied to a column (0.25 in × 6 ft) of 3% SE 52 on Gas-Chrom A[12] at 175°. A single peak with a retention time identical with that of 2,3,4-tri-*O*-acetyl-1,6-anhydro-β-D-idopyranose was observed.

**Registry No.**—**1**, 13096-63-4; **2**, 13096-74-7; **3a**, 13096-75-8; **4**, 13096-76-9; **5**, 13096-77-0; **6**, 13096-78-1; **7**, 13096-79-2; **10**, 13100-30-6.

**Acknowledgment.**—We wish to thank the staff of the Section on Microanalytical Services and Instrumentation of this institute for elemental analyses and Dr. Nelson K. Richtmyer for an authentic sample of the enantiomorph of **11**.

(12) Applied Science Laboratories, Inc., State College, Pa.