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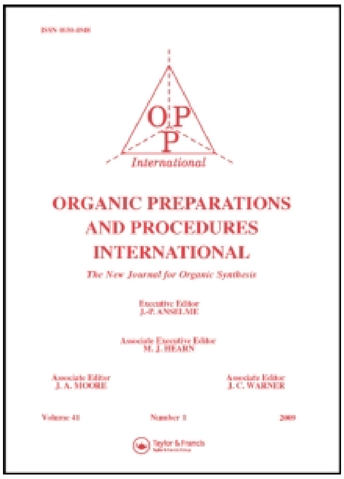

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THE PREPARATION OF 1,2:5,6-Di-O-Cyclohexylidene-α-D-Gulofuranose

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ORGANIC PREPARATIONS AND PROCEDURES 2(2), 83-87 (1970)

THE PREPARATION OF 1,2:5,6-Di-O-Cyclohexylidene-α-D-Gulofuranose.

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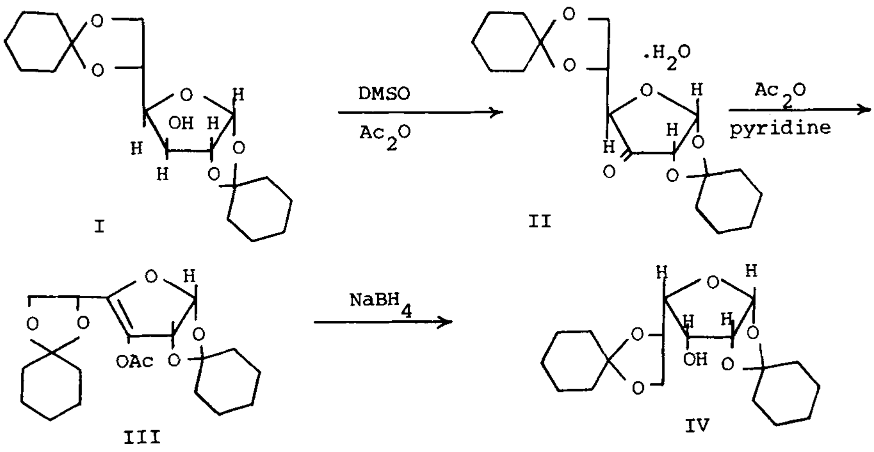


1,2:5,6-Di-O-cyclohexylidene-α-D-glucofuranose (I) was oxidized with dimethylsulfoxide and acetic anhydride to 1,2:5,6-di-O-cyclohexylidene-α-D-ribo-3-ulofuranose monohydrate (II) which was acetylated to D-glucofuranose-3-enol acetate (III). Reduction of (III) with $NaBH_4$ yielded 1,2:5,6-di-O-cyclohexylidene-D-gulofuranose (IV). It is important to add $NaBH_4$ to III in order to avoid hydrolysis of the alkali-labile cyclohexylidene group in the 5,6 position of III. This route was chosen for the preparation of IV, since sterochemical considerations of the structure of d-gulose indicated the possible formation of two derivatives following the introduction of protective groups into free gulose. One derivative protected in the 1,2:5,6 positions and the second one in the 2,3:5,6 positions of the carbon chain, analogous to the acetonation of D-talose[1] may be formed.

Reckendorf was the first to describe this general route for the preparation of D-gulose using 1,2:5,6-di-O-isopropylidene D-glucofuranose as the starting compound.[2a,b.] The preparation of 1,2:5,6-di-O-cyclohexylidene-D-ribo-3-ulofuranose (II), reported by James et.al., was modified and it was noted that the melting point, optical rotation and TLC R_f values of II differed from those reported.[3] Compound II crystallized with one mole of water. The cyclohexylidene derivatives of D-glucose, D-mannose, and D-gulose may be purified by sublimation.

EXPERIMENTAL[4]

1,2:5,6-Di-O-cyclohexylidene-α-D-glucofuranose (I).

The procedure was adapted from that described by Hockett et.al,[5]. Powdered anhydrous D-glucose (45g., 0.25 mole) was added to a cooled solution of 100 ml redistilled cyclohexanone and 6.5 ml of concentrated sulfuric acid. The reaction mixture was shaken at room temperature for 16 hrs. Then, 250 ml of *n*-heptane was added and the mixture was heated on a water bath until two liquid layers were formed. The *n*-heptane layer contained I, which crystallized on cooling. The crude product was filtered, dissolved in 200 ml of acetone. Reprecipitation by the addition of 200 ml of water gave 24.8g(29.2%), m.p. 134-136°, $[\alpha]_D^{25}$ + 2° (*c* 1, chloroform), R_f 0.31 in solvent *2*. [lit.[5] 131.4-132.4(cor.)]. The material was sublimed *in vacuo* at 18 mm. without a change in its physical constants.

1,2:5,6-Di-O-cyclohexylidene-α-D-ribo-3-ulofuranose monohydrate (II).

The preparation of this compound was adapted from the general method of Sowa and Thomas.[6] To a solution of 3.4g (10 mmole) of I in 30 ml of dimethylsulfoxide, 20 ml of acetic anhydride was added and the solution was allowed to stand at room temperature for 24 hours. The solution was evaporated at 40°C *in vacuo* until the odor of methyl sulfide could no longer be detected, and then concentrated at 40° under high vacuum. The residue was dissolved in ether (200 ml) and the solution washed with water (4 x 100 ml), saturated sodium hydrogen carbonate (4 x 100 ml) and water (4 x 100 ml). Evaporation of the ether gave a syrup which crystallized partly on standing for 30 minutes. Further crystallization was achieved by refluxing the contents of the flask with wet ether for a period of 15 min. One additional crystallization from ether yielded 2.08g (67%) of II, m.p. 123°, $[\alpha]_D^{25}$ + 37.4 (*c* 1, chloroform), R_f 0.36 in solvent *1*. [lit. m.p. 65-67°, $[\alpha]_D^{20}$ + 119.2° (*c* 1, chloroform), R_f 0.63 in solvent *1*].

Anal. Calcd. for $C_{18}H_{28}O_7$ C,60.66; H,7.92.

Found: C,60.60; H,8.04.

IR (Nujol) no CO but bonded OH frequency 3.00 μ.

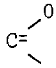
A small amount of II was dehydrated over phosphorus pentoxide *in vacuo* (18 mm, 65°). A noncrystalline solid was obtained m.p. 107°, which converted to the higher melting form on exposure to moist air. The hydrated and dehydrated form of II gave the same R_f. (TLC, solvent *1*)

1,2:5,6-Di-O-cyclohexylidene-D-glucofuranose-3-enol acetate (III).

To a solution of 6.5 g (18 mmole) of II in 40 ml of dry pyridine was added 20 ml of acetic anhydride. The solution was held at 75° for 16 hours, then concentrated *in vacuo*. The resulting syrup was added dropwise with rapid mechanical stirring to 200 ml of ice and water. The product was extract with 5 x 100 ml. of petroleum ether (b.p. 40-60°C) and the extract was washed with 2 x 50 ml. of 1% sodium hydrogen carbonate and 2 x 50 ml. of water. The extract was dried over anhydrous sodium sulfate and concentrated in vacuo. The solid obtained was recrystallized from methanol-water to give 3.5g (48%), m.p. 73-74°; $[\alpha]_D^{25}$ - 29.3 (c 1, chloroform), R_f 0.43 in solvent 1. Identified by means of UV light, since the compound did not char with sulfuric acid.

Anal. Calcd. for $C_{20}H_{28}O_7$; C,62.85; H,7.40.

Found: C,62.52; H,7.30.

IR (Nujol) 

$\mathrm{C}\overset{\diagup\mathrm{O}}{\underset{\diagdown}{=}}$, 5.7 μ

1,2:5,6-Di-O-cyclohexylidene-D-gulofuranose (IV).

A solution of 1g (26.3 mmole) of $NaBH_4$ in 50 ml. of methanol was added dropwise to a solution of 3.5g (9.3 mmole) of III in 50 ml. of methanol in a 300 ml. boiling flask. The resulting mixture was stirred at room temperature for 30 minutes, then concentrated to dryness in vacuo at 40°. The residue was dissolved in 100 ml. of water and the product was extracted with 3 x 100 ml. of ether. The ethereal extract was washed with water, dried over anhydrous sodium sulfate and concentrated to a solid, which crystallized on standing to give 0.79g (25%), m.p. 146-148°, $[\alpha]_D^{25}$ + 10° (c 1, chloroform). R_f 0.26 in solvent 1.

Anal. Calcd. for $C_{18}H_{25}O_6$; C,63.68; H,8.01.

Found: C,63.20; H,8.56.

A sample of IV was hydrolyzed to D-gulose by heating with 10% trifluoroacetic acid at 100° for 2 hr. The migration on TCL was identical with the migration of an authentical sample of D-gulose[9]. R_f 0.63 in solvent 3.

Paper electrophoresis was carried out according to Bourne et.al.,[10] D-gulose migrated toward the anode the same distance an authentical sample of D-gulose[9].

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4. Carbon-hydrogen analyses were performed by George I. Robertson, Florham Park, N.J.

   All melting points were obtained on a Fisher-Jones melting point apparatus and are uncorrected.

   Thin layer chromatography (TLC) was carried out on 250 micron thick layers of silica gel Whatman Chromedia SG-41, employing a Chromaflex Sandwich Technique Apparatus (Kontes Glass Co., Vineland, N.J.). Solvent systems used were: Solvent 1: benzene:methanol (95:5 v/v)[6], Solvent 2: ethyl acetate:pentane (1:3 v/v)[7] and Solvent 3: methyl ethyl ketone:acetic acid:methanol (60:20:20 v/v)[8]. R_f of the solvent front was designated as 1. Detection of compounds on TLC plates was accomplished by either spraying the plates with 30% sulfuric acid followed by heating at 100-110°C for 20 minutes, or by observation under ultraviolet light. All reagents and solvents were dried and distilled.

   Electrophoresis was carried out at pH_5 and 10 v/cm on Whatman No. 3 paper in 0.9 m molybdate buffer for 90 minutes[10]. 3% p-anisidine HCL was employed for the detection of gulose on the paper strip.

   Infrared spectra obtained as Nujol mulls were carried out by Crobaugh Laboratories, Cleveland, Ohio.

   Sublimation was carried out at *in vacuo* at 18 mm. pressure.

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