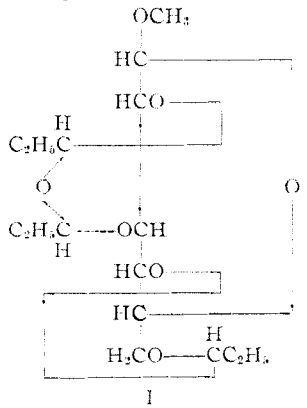
[CONTRIBUTION FROM THE NORTHERN REGIONAL RESEARCH LABORATORY[1]]

Some Cyclic Acetals of D-Glucose and its Derivatives

BY R. L. MELLIES, C. L. MEHLTRETTER AND C. E. RIST

Cyclic acetals have been prepared from carbohydrate substances by condensation with a large number of aldehydes including formaldehyde, acetaldehyde, furfural and benzaldehyde.[2] The present work extends the series of cyclic acetals obtained by reaction of aldehydes with D-glucose, methyl α-D-glucoside and D-sorbitol. Acetaldehyde, paraldehyde, propionaldehyde, butyraldehyde and isobutyraldehyde were found to condense smoothly with D-glucose to produce acetals. Stearaldehyde did not react with D-glucose but gave a monostearylidene derivative with D-sorbitol. The condensation of propionaldehyde with methyl α-D-glucoside yielded methyl 4,6-propylidene-α-D-glucoside and methyl 2,3-oxidodipropylidene-4,6-propylidene-α-D-glucoside. The structures of these two compounds were established by methods analogous to those used by Appel, *et al.*,[3] for determining the structure of the corresponding ethylidene derivatives. Methylation of methyl 4,6-propylidene-α-D-glucoside with methyl iodide and silver oxide followed by reaction with benzaldehyde and zinc chloride gave the known methyl 4,6-benzylidene-2,3-dimethyl-α-D-glucoside.[4] The assumption of the 4,6-structure for the monopropylidene derivative was therefore correct.

The oxido compound, by reaction with bromine in ether solution, yielded methyl 4,6-propylidene-α-D-glucoside. From the latter substance the oxido compound could be reformed by treatment with propionaldehyde in the presence of a trace of concentrated sulfuric acid. Ultimate analysis, molecular weight determination and failure to react with acetic anhydride in pyridine, which indicates absence of a free hydroxyl group, aided in the assignment to the oxido compound of the structure shown by (I).



I

The 4,6-acetal structure was assigned to a monobutylidene-D-glucose obtained from *n*-butyraldehyde and anhydrous D-glucose because methylation with dimethyl sulfate and alkali followed by reaction with benzaldehyde and zinc chloride gave a compound whose melting point, specific rotation and analytical values agreed with those recorded in the literature for methyl 4,6-benzylidene-2,3-dimethyl-β-D-glucoside. This method was used by Helferich and Appel[5] to prove the structure of 4,6-ethylidene-α-D-glucose.

Diethylidene-D-glucose and a low yield of crystalline monoethylidene-D-glucose were obtained when anhydrous D-glucose reacted with acetaldehyde and hydrochloric acid. The analysis and melting point of the monoethylidene derivative coincided with those of the known 4,6-ethylidene-α-D-glucose prepared by Helferich and Appel[5] from D-glucose, paraldehyde and sulfuric acid. For comparative purposes the ethylidene compound of these investigators was prepared. Its melting point and analytical data corresponded with those obtained for our product and the melting point of a mixture of the two was not depressed. The specific rotation was essentially that found by Helferich and Appel. The ethylidene-D-glucose was methylated with dimethyl sulfate and alkali to give the known methyl 4,6-ethylidene-2,3-dimethyl-β-D-glucoside.[5] The 4,6-acetal structure has accordingly been assigned to the compound from D-glucose and acetaldehyde.

Table I lists the diacetals of D-glucose prepared, together with their yields, analyses and physical properties. The calculated molar refractions show close agreement with the experimental values and in conjunction with the analytical data are further evidence for the structures represented.

The more highly acetalized compounds were generally non-crystallizable viscous oils or gums, soluble in nearly all classes of organic solvents and insoluble in water. Diethylidene- and dipropylidene-D-glucose were only slightly soluble in petroleum ether. As expected, the crystalline monoacetals, with the exception of monostearylidene-D-sorbitol, were less soluble in organic solvents and more soluble in water.

Experimental

Preparation of Diacetals of D-Glucose.—Diethylidene- and dibutylidene-D-glucose were prepared by treating 2 moles of acetaldehyde or *n*-butyraldehyde with 0.2 mole of anhydrous D-glucose. The condensations were carried out in the presence of 2.5 ml. (0.03 mole) and 10 ml. (0.12 mole), respectively, of concentrated hydrochloric acid at temperatures not above 45°. For the synthesis of dipropylidene- and diisobutylidene-D-glucose a ratio of 1 mole of the appropriate aldehyde to 0.2 mole of D-glucose was used, with 2.5 ml. of concentrated hydrochloric acid. In a typical run the reaction mixture from 58 g. (1 mole) of propionaldehyde, 36 g. (0.2 mole) of anhydrous D-glucose and 2.5 ml. of concentrated hydrochloric acid was stirred 3 hours at room temperature. After standing overnight it was neutralized with aqueous sodium bicarbonate solution and ex-

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(2) For recent reviews on cyclic acetals see Owen, *Ann. Repts. on Progress Chem. (Chem. Soc. London)*, **40**, 119 (1943); Jones, *ibid.*, **43**, 183 (1946); Hurd, *Ann. Rev. Biochem.*, **14**, 100 (1945); Purves, *J. Wash. Acad. Sci.*, **36**, 65 (1946).

(3) Appel, Haworth, Cox and Llewellyn, *J. Chem. Soc.*, 793 (1938).

(4) Evans, Levi, Hawkins and Hilbert, *Can. J. Research*, **20B**, 175 (1942).

(5) Helferich and Appel, *Ber.*, **64**, 1811 (1931).

TABLE I

CYCLIC DIACETALS OF D-GLUCOSE

Compound, -D-glucose	Empirical formula	Crude yield, %	Boiling point °C.	Mm.	$[\alpha]^{25}D$[a]	c	d^{25}_4	$n^{25}D$	Molar refraction Calcd.	Found	Analyses, % Carbon Calcd.	Found	Hydrogen Calcd.	Found
Diethylidene-[c]	$C_{10}H_{16}O_6$	46	200–205	0.1–0.2	+ 5.8	5.02	1.2812	1.4805	51.52	51.54	51.7	52.0	6.9	6.7
Diethylidene-[d]	$C_{10}H_{16}O_6$	68	175–182	.005–0.01	+11.0	4.86	1.2808	1.4768	51.52	51.21	51.7	52.0	6.9	7.3
Dipropylidene-	$C_{12}H_{20}O_6$	79	195–200	.01–0.02	+17.8	3.36	1.2031	1.4747	60.76	60.88	55.4	55.4	7.8	7.8
Dibutylidene- (A)[b]	$C_{14}H_{24}O_6$	..	193–196	.01	+16.5	3.48	1.1619	1.4700	69.99	69.24	58.3	58.2	8.4	8.8
Dibutylidene- (B)[b]	$C_{14}H_{24}O_6$	..	215–220	.005	+15.2	3.08	1.1569	1.4710	69.99	69.66	58.3	58.4	8.4	8.4
Diisobutylidene-	$C_{14}H_{24}O_6$	89	195–200	.005–0.01	+17.5	4.07	1.1477	1.4700	69.99	70.09	58.3	58.6	8.4	8.5

[a] Optical rotations measured in chloroform. [b] Isomeric fractions from the same preparation. [c] From acetaldehyde. [d] From paraldehyde.

tracted with benzene. The benzene layer was dried and concentrated *in vacuo* to remove solvent and excess aldehyde. The viscous residue was purified by high vacuum distillation. Dibutylidene-D-glucose differed from the other diacetals in that two isomeric fractions, A and B in Table I, were obtained by this treatment.

4,6-Ethylidene-α-D-glucose.—The aqueous layer from the preparation of diethylidene-D-glucose from acetaldehyde and D-glucose was concentrated *in vacuo* to dryness and extracted with warm dioxane. The sirup obtained by evaporation of the dioxane solution was crystallized from chloroform and yielded 1.7 g. (4%) of a crude monoethylidene-D-glucose, m.p. 164–166° (dec.). Two recrystallizations from acetone–ethanol (5:1) gave microscopic white needles which melted at 179–182° (dec.); $[\alpha]^{25}D$ +47.3° (after 2 minutes), changing to −0.2° in 4 hours (*c*, 1.79; water).

Anal. Calcd. for $C_8H_{14}O_6$: C, 46.6; H, 6.8. Found: C, 46.6; H, 7.0.

Helferich and Appel[5] reported the preparation of 4,6-ethylidene-α-D-glucose from D-glucose, paraldehyde and sulfuric acid. The melting point was 179–182° (dec.), but the $[\alpha]^{22}D$ value was +66.4° (after 3 minutes), changing to −2.36° in 4 hours (*c*, 8; water).

When 36 g. (0.2 mole) of anhydrous D-glucose, 88 g. of paraldehyde (equivalent to 2 moles of acetaldehyde) and 2.5 ml. of concentrated hydrochloric acid reacted by our method, 31.6 g. (68%) of a colorless gum was obtained. It was isomeric with the diethylidene-D-glucose prepared from D-glucose and acetaldehyde (Table I). No monoethylidene-D-glucose was isolated.

To establish conclusively the identity of our monoethylidene-D-glucose with the 4,6-ethylidene-α-D-glucose prepared by Helferich and Appel, the compound was prepared by their method.

A mixture of 25 g. of anhydrous D-glucose, 90 g. of paraldehyde and 0.22 ml. of concentrated sulfuric acid was stirred for 24 hours at room temperature in a flask from which atmospheric moisture was excluded. The mixture was filtered and the precipitate washed with ether. Upon dissolving the precipitate (9.7 g., 32%) in sufficient hot dioxane, filtering and cooling, two crops of white crystals (6.2 g.), melting at 158–161° and 151–154°, respectively, were obtained. (H. and A. added petroleum ether to the dioxane solution to induce crystallization.) Fractional crystallization from acetone–ethanol (1:1), followed by recrystallization from acetone–ethanol (5:1) of a crop melting at 174–176° (dec.) gave 0.7 g. of the pure product; m.p. 179.5–182.5° (dec.); $[\alpha]^{25}D$ +56.9° (after 5 minutes), changing to −2.47° after 4 hours (*c*, 5.74; water).

Anal. Calcd. for $C_8H_{14}O_6$: C, 46.6; H, 6.8. Found: C, 46.7; H, 6.7.

A mixed melting point taken with the compound prepared earlier showed no depression.

Methyl 4,6-Ethylidene-2,3-dimethyl-β-D-glucoside.—Various crops of impure 4,6-ethylidene-α-D-glucose were combined (3.7 g.), dissolved in 25 ml. of water and the solution kept at 15–18° while adding, during one-half hour, 3.5 ml. of redistilled dimethyl sulfate and 1.5 ml. of 30% sodium hydroxide solution. The solution was slightly alkaline at all times. During the next 2 hours, while the temperature was gradually raised to 65–70°, 26.5 ml. of dimethyl sulfate and 29 ml. of 30% sodium hydroxide were added. The mixture, from which some solid had already precipitated, was heated for fifteen minutes at 70° and then on the steam-bath for one-half hour. The solution was chilled and filtered from 2.3 g. of crystals. An additional 2 g. was recovered by extraction of the mother liquor with chloroform. Several recrystallizations from petroleum ether gave the pure product; m.p. 109.5–110.5°; $[\alpha]^{25}D$ −47.4° (*c*, 1.13; chloroform). H. and A. gave m.p. 109.5–111°; $[\alpha]^{21.5}D$ −47.8° in chloroform.

Anal. Calcd. for $C_{11}H_{20}O_6$: C, 53.2; H, 8.1. Found: C, 53.1; H, 8.0.

4,6-Butylidene-α-D-glucose.—Three ml. of concentrated hydrochloric acid was added to a mixture of 18 g. (0.1 mole) of anhydrous D-glucose and 15 g. (0.21 mole) of redistilled *n*-butyraldehyde. The mixture was shaken for fifteen minutes and the crystalline acetal that formed was suspended in acetone, filtered and washed with acetone. The yield was 11.5 g. (49%). After two recrystallizations from water and one from *n*-butanol, the white needles melted at 164–165°; $[\alpha]^{25}D$ +5.0° (after 10 minutes), changing to +1.7° in 2 hours (*c*, 2.13; water).

Anal. Calcd. for $C_{10}H_{18}O_6$: C, 51.3; H, 7.7. Found: C, 51.0; H, 7.8.

Methyl 4,6-Butylidene-2,3-dimethyl-β-D-glucoside.—To a solution of 4.7 g. of 4,6-butylidene-α-D-glucose in 60 ml. of water at 15–18° was added during one-half hour, 3.5 ml. of dimethyl sulfate and 3.0 ml. of 30% sodium hydroxide solution. In the next 2 hours, while the temperature was gradually raised to 60°, 25.5 ml. of dimethyl sulfate and 27 ml. of sodium hydroxide solution were added. The mixture was heated for 15 minutes at 60° and then on the steam-bath for 1 hour, before cooling and filtering from 3.4 g. of crystals.

Two recrystallizations from petroleum ether and 2 from water–ethanol (2:1) gave the pure product; m.p. 93–94°; $[\alpha]^{17}D$ −36.1° (*c*, 1.06; chloroform).

Anal. Calcd. for $C_{13}H_{24}O_6$: C, 56.5; H, 8.8. Found: C, 56.9; H, 8.7.

Methyl 4,6-Benzylidene-2,3-dimethyl-β-D-glucoside.—A mixture of 2.4 g. of the 4,6-butylidene derivative just described, 16 ml. of redistilled benzaldehyde and 3.5 g. of pulverized anhydrous zinc chloride was heated at 60–70° for 7 hours with occasional shaking. (An experiment conducted at room temperature was unsuccessful.)

The solution was treated with 20% sodium bisulfite solution until all the benzaldehyde had dissolved and then extracted with three 100-ml. portions of ether. The combined ether extract was washed with sodium bisulfite solution, cold saturated sodium bicarbonate solution and water before drying over sodium sulfate. Concentration of the filtrate gave 2.3 g. of crystals, which were recrystallized twice from petroleum ether and once from ethanol. The white crystals melted at 133–134°; $[\alpha]^{25}D$ −62.2° (*c*, 1.02; ethanol). Helferich and Appel[5] found m.p. 133.5–134°, $[\alpha]^{17}D$ −60° (ethanol).

Anal. Calcd. for $C_{16}H_{22}O_6$: C, 61.9; H, 7.1. Found: C, 61.5; H, 7.1.

Methyl 2,3-Oxidodipropylidene-4,6-propylidene-α-D-glucoside.—Upon stirring a mixture of 19.4 g. (0.1 mole) of methyl α-D-glucoside, 17.4 g. (0.3 mole) of redistilled propionaldehyde and 1.5 ml. of concentrated hydrochloric acid the solid dissolved and white needles gradually appeared. The suspension was stirred for 2 hours, water added and the mixture filtered. The precipitate (14.4 g.; 47%) was recrystallized from ethanol–water (2:1) to a constant melting point of 142.5–143.5°; $[\alpha]^{25}D$ +73.2° (*c*, 2.48; chloroform).

An attempt to acetylate the product in acetic anhydride–pyridine was unsuccessful, indicating that no free hydroxyl groups are present.

Anal. Calcd. for $C_{16}H_{28}O_7$: C, 57.9; H, 8.5; OCH_3, 9.3; mol. wt., 332. Found: C, 58.0; H, 8.1; OCH_3, 9.1; mol. wt. (isopiestic method in benzene against azobenzene), 330.

The product was converted to methyl 4,6-propylidene-α-D-glucoside as follows: 1.2 g. was boiled for 30 minutes with 100 ml. of ether containing a few drops of bromine. The excess bromine was destroyed by adding 5% sodium thiosulfate solution. The mixture was then made alkaline with 5% sodium bicarbonate solution and the ether removed with a stream of air. The aqueous mixture was filtered from 0.3 g. of the starting compound and the filtrate concentrated to dryness *in vacuo*. Extraction of the gummy residue with carbon tetrachloride yielded 0.8 g. of sirup which partly crystallized on standing. The mixture was dissolved in hot benzene, treated with decolorizing carbon and filtered. Addition of petroleum ether to the filtrate gave white needles (0.5 g.) which were recrystallized from petroleum ether–benzene (5:1) to yield methyl 4,6-propylidene-α-D-glucoside; m.p. 101.5–103°, not depressed by admixture with an authentic sample.

The oxido compound was also prepared from methyl 4,6-propylidene-α-D-glucoside (4.8 g.) by reaction with propionaldehyde (35 g.) and 4 drops of concentrated sulfuric acid at room temperature. After ten minutes the mixture was extracted with benzene, the benzene layer washed with sodium bicarbonate solution and water and dried over calcium chloride. Concentration of the benzene solution gave 3.2 g. of a white gummy solid, which after two recrystallizations from ethanol melted 141.5–142°; unchanged by mixing with the oxido compound.

Methyl 4,6-Propylidene-α-D-glucoside.—The combined filtrate and washings left after separation of the oxido compound obtained from methyl α-D-glucoside and propionaldehyde was neutralized with sodium bicarbonate and concentrated to dryness *in vacuo*. The residue was taken up in benzene, filtered, concentrated to dryness and triturated with ether. The insoluble crystals (5.5 g., 23%) were recrystallized from benzene–ether and from benzene–petroleum ether to yield microscopic white needles, m.p. 102–103.5°; $[\alpha]^{25}D$ +122.1° (*c*, 1.83; chloroform).

Anal. Calcd. for $C_{10}H_{18}O_6$: C, 51.3; H, 7.7; OCH_3, 13.3. Found: C, 51.5; H, 7.8; OCH_3, 13.2.

Methyl 4,6-Benzylidene-2,3-dimethyl-α-D-glucoside from Methyl 4,6-Propylidene-α-D-glucoside.—Methyl 4,6-propylidene-α-D-glucoside (2.4 g.) was dissolved in 8 ml. of methanol, 16 ml. of methyl iodide added and the solution refluxed for 8 hours. During this period 14 g. of silver oxide was added in 3 portions.

The mixture was filtered and washed with hot methanol. Concentration *in vacuo* to dryness gave a sirup (2.7 g.), to which was added 16 ml. of redistilled benzaldehyde and 2.5 g. of pulverized anhydrous zinc chloride. The mixture was shaken for 48 hours. The solution obtained was then treated with 20% sodium bisulfite solution until the benzaldehyde had dissolved. Three 100-ml. portions of ether were used for extraction. The combined ether extract was washed with sodium bisulfite solution, dilute sodium hydroxide solution and water and dried over calcium chloride. Concentration *in vacuo* at 80–90° and 2 mm. left 2.4 g. of sirup, which crystallized on standing. The product was recrystallized twice from petroleum ether to give white needles; m.p. 121–122°, not depressed by admixture with an authentic sample of methyl 4,6-benzylidene-2,3-dimethyl-α-D-glucoside (m.p. 122–123°, prepared by Evans'[4] method); $[\alpha]^{25}D$ +96.9° (*c*, 1.51; chloroform). Appel[3] gives m.p. 120–121° and $[\alpha]^{25}D$ +96.2°, in chloroform.

Anal. Calcd. for $C_{16}H_{22}O_6$: C, 61.9; H, 7.1. Found: C, 62.0; H, 7.1.

Monostearylidene-D-sorbitol.—A mixture of 3.7 g. (0.02 mole) of D-sorbitol, 5.4 g. (0.02 mole) of stearaldehyde (m.p. 68–69°) and 0.1 g. of sulfosalicylic acid dihydrate was refluxed for 20 hours in 125 ml. of dioxane. All but a trace of the solid dissolved. Dioxane was removed *in vacuo* and the waxy residue was extracted with warm (35°) benzene to remove unreacted stearaldehyde. The residue was washed with water and filtered from 2.8 g. (32%) of an amorphous solid. Reprecipitation from ethanol and from ethanol–dioxane (4:1) gave a white, amorphous solid, melting at 133–137° to a clear gel which became liquid at 145°; $[\alpha]^{25}D$ −8.7° (*c*, 2.36; pyridine).

Anal. Calcd. for $C_{21}H_{40}O_6$: C, 66.6; H, 11.2. Found: C, 66.4; H, 10.6.

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Summary

Diethylidene-, dipropylidene-, dibutylidene- and diisobutylideneacetals of D-glucose have been prepared as sirupy compounds. Some of their physical properties have been determined. Monostearylidene-D-sorbitol has been obtained as an amorphous product.

The following crystalline cyclic acetals have been synthesized and their structures determined: 4,6-butylidene-α-D-glucose, methyl 4,6-butylidene-2,3-dimethyl-β-D-glucoside, methyl 4,6-propylidene-α-D-glucoside and methyl 2,3-oxidodipropylidene-4,6-propylidene-α-D-glucoside.

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The Reaction of Tribenzoyl-α-L-rhamnopyranosyl Bromide with Methanol. Various Benzoylated Derivatives of L-Rhamnose

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In a recent publication[2] it was shown that tetrabenzoyl-α-D-mannopyranosyl bromide reacts directly with anhydrous methanol in the absence of an acid acceptor to form methyl α-D-mannopyranoside tetrabenzoate in a 69% yield. This earlier work was carried out with amorphous tribenzoyl-α-D-mannopyranosyl bromide and since extensive attempts to crystallize this halide as well as the corresponding chloride and iodide were without success, it was deemed desirable to extend the study to the closely related L-rhamnose (6-desoxy-L-mannose) series in the hope that crystalline benzoylated halides might then be obtained and allow a confirmation of the results obtained in the D-mannose series. This hope has now been realized.

The complete benzoylation of α-L-rhamnose hydrate led only to an amorphous product showing $[\alpha]^{20}D$ +68° to +78° in chloroform. Similarly the complete benzoylation of β-L-rhamnose gave a sirupy tetrabenzoate of $[\alpha]^{20}D$ +138° in chloroform; doubtless these two products represent crude α- and β-L-rhamnopyranose tetrabenzoates, respectively. On treatment with hydrogen bro-

(1) Senior Research Fellow, National Institutes of Health, 1948–1950.

(2) R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, THIS JOURNAL, **72**, 2200 (1950).