[CONTRIBUTION FROM WAYNE STATE UNIVERSITY AND THE STATE UNIVERSITY OF IOWA]

The Preparation of 3,5-Di-*O*-methyl-D-glucose and 2,3,5-Tri-*O*-methyl-D-glucose*

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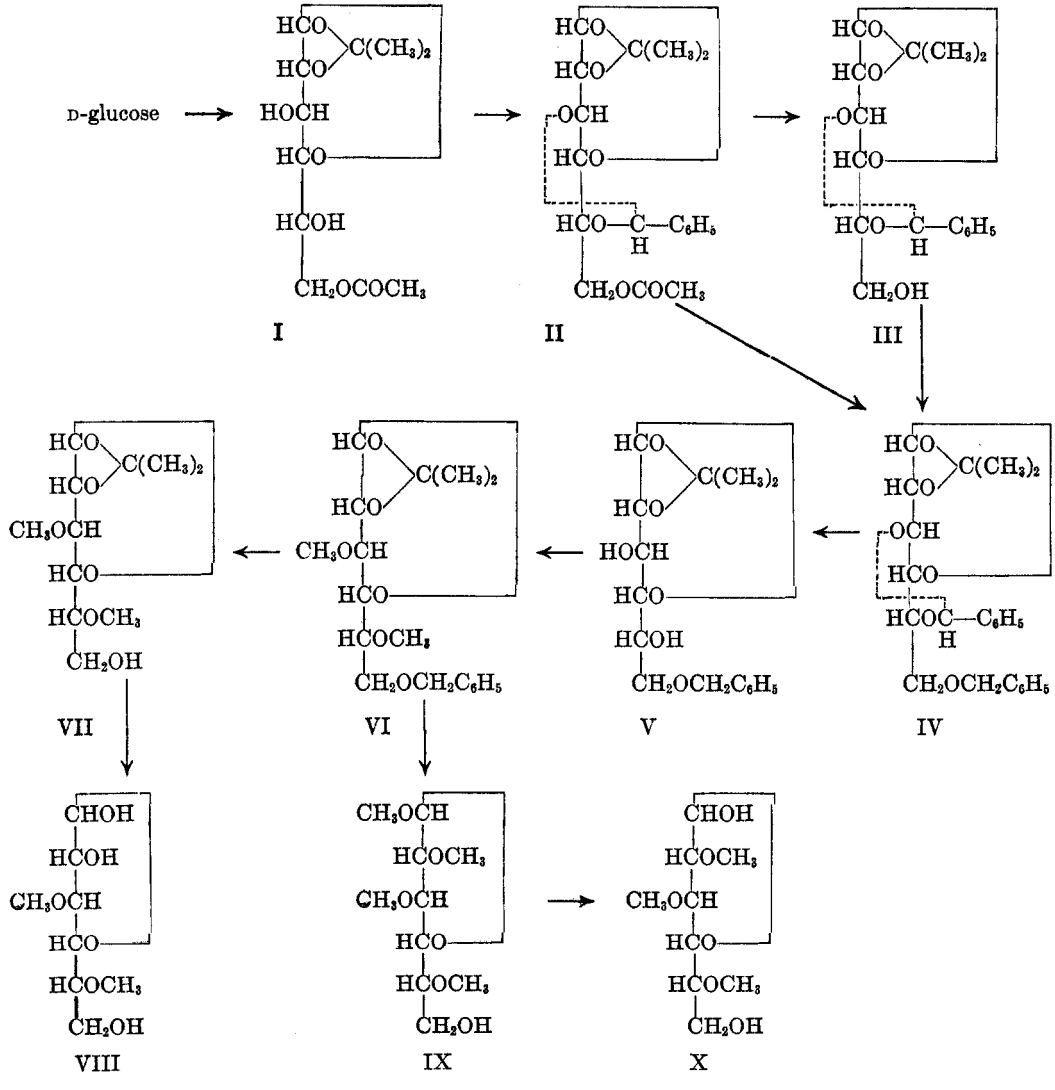
3,5-Di-*O*-methyl-D-glucose (VIII) has been prepared by the hydrogenolysis and hydrolysis of crystalline 6-*O*-benzyl-1,2-*O*-isopropylidene-3,5-di-*O*-methyl-D-glucose (VI). Methanolysis of the latter compound followed by methylation and hydrogenolysis formed a crystalline methyl 2,3,5-tri-*O*-methyl-D-glucoside, (IX).

Interest in the di-*O*-methyl-D-glucoses as reference compounds and as intermediates has led previously to the preparation of all but two of the normal structural isomers; these are 3,5-di-*O*-methyl-D-glucose and 4,5-di-*O*-methyl-D-glucose.

The synthesis of 3,5-di-*O*-methyl-D-glucose has now been carried out and in connection with the proof of structure of the various compounds involved in the synthesis 2,3,5-tri-*O*-methyl-D-glucose was prepared by a new method and a crystalline methyl 2,3,5-tri-*O*-methyl-D-glucoside obtained.



2,3,5-Tri-*O*-methyl-D-glucose had been prepared previously by two different pathways. Smith[3] in 1944 reported the synthesis of this compound from

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(3) F. Smith, *J. Chem. Soc.*, 571 (1944).

the methyl furanoside *via* the 6-*O*-trityl derivative. Dimler, Davis, and Hilbert[4] prepared the same compound by methylation and hydrolysis of 1,6-anhydro-β-D-glucofuranose, a new anhydride of glucose which had been isolated from the mixture of products resulting from the vacuum pyrolysis of starch.

The present syntheses were based on 6-*O*-benzyl-1,2-*O*-isopropylidene-D-glucose (V). This compound had previously been prepared by Ohle and Tessmar[5] from 5,6-anhydro-1,2-*O*-isopropylidene-D-glucose. The development of a simplified method for the preparation of 6-*O*-acetyl-1,2-*O*-isopropylidene-D-glucose (I) utilizing 3.5 mole quantities of reactants made possible the ready preparation of V *via* the 3,5-*O*-benzylidene derivatives II and IV. Methylation of V formed the crystalline 6-*O*-benzyl-1,2-*O*-isopropylidene-3,5-di-*O*-methyl-D-glucose (VI). By the hydrogenolysis of (VI) 1,2-*O*-isopropylidene-3,5-di-*O*-methyl-D-glucose (VII) was obtained as a sirup. For additional characterization of this compound a crystalline derivative, the *p*-phenylazobenzoate was prepared. Hydrolysis of VII formed the sirupy 3,5-di-*O*-methyl-D-glucose (VIII). As a further confirmation of structure, as well as an illustration of the versatility of these compounds as intermediates, compound VI, 6-*O*-benzyl-1,2-*O*-isopropylidene-3,5-di-*O*-methyl-D-glucose, was subjected to methanolysis followed by hydrogenolysis with palladium charcoal catalyst, then methylation and final hydrolysis to yield the known compound 2,3,5,6-tetra-*O*-methyl-D-glucose.[6]

Using a different sequence of similar reactions with compound VI, methanolysis was followed by methylation and then hydrogenolysis to remove the benzyl group. The product formed was a crystalline methyl 2,3,5-tri-*O*-methyl-β-D-glucofuranoside (IX). Hydrolysis of IX formed sirupy 2,3,5-tri-*O*-methyl-D-glucose (X) which was identified by oxidation to the gluconic acid and preparation of the known phenylhydrazide.

EXPERIMENTAL[7]

6-O-Acetyl-1,2-O-isopropylidene-D-glucofuranose[8-10] (I). Anhydrous glucose (640 g.) and 220 g. of boric acid were added to a solution prepared by adding 256 ml. of concentrated sulfuric acid to 8 l. of cold acetone. The mixture was stirred 4–5 hr. until the glucose had gone into solution, then cooled in an ice bath and 790 ml. of pyridine added slowly with stirring. After a few minutes the pyridine sulfate was allowed to settle and the acetone solution decanted from the sirupy residue. The acetone solution was stirred for 3 hr. with 250 g. of anhydrous potassium carbonate, decanted from the salts, and concentrated on a steam bath. Sodium acetate (250 g.) was added to the residue, the mixture cooled in an ice bath and 700 ml. of acetic anhydride added. After stirring a short time the mixture was heated for 20 min. on a steam bath and then 2 kg. of ice was added followed by 3 l. of water. The resulting solution was extracted with 600 ml. of a mixture (3:1) of benzene and ligroin (b.p. 60–70°), followed by a second extraction with 300 ml. of the benzene-ligroin mixture. The aqueous solution was saturated with sodium chloride by stirring with an excess of rock salt. The use of rock salt was found to be desirable as it facilitated separation of the product in the following steps. The crystals that formed were filtered off and dried. The dry material was extracted with 5 l. of hot chloroform from which I separated on cooling. The crystals were filtered off and the filtrate concentrated to one fourth the volume to obtain a second crop. The combined yield was 330 g. (35.2%) m.p. 145–146° (lit.[9] m.p. 145.5°).

6-O-Acetyl-3,5-O-benzylidene-1,2-O-isopropylidene-D-glucose (II) was prepared by the method of Freudenberg and Hüll.[10] From 125 g. of I, 500 ml. of benzaldehyde and 125 g. of powdered anhydrous zinc chloride, after 5 hr. of shaking, dilution with 2 l. of water, and concentration under reduced pressure, there was obtained after recrystallization of the residue from ethanol 125 g. of II, m.p. 125–127° (uncorr.) (lit.[9] 126–127°).

3,5-O-Benzylidene-1,2-O-isopropylidene-D-glucofuranose (III). Compound II was deacetylated by dissolving 100 g. in 150 ml. of dioxane, adding 150 ml. of methanol containing sodium methoxide from 1.5 g. of sodium, heating to reflux, and allowing the reaction mixture to stand overnight. Water was added to the solution and III crystallized out in nearly quantitative yield, m.p. 149–150° (uncorr.) (lit.[10] 148.5–150°).

6-O-Benzyl-3,5-O-benzylidene-1,2-O-isopropylidene-D-glucose (IV). A mixture of 100 g. of III (II was also used) and 125 g. of powdered potassium hydroxide was added in four portions with vigorous stirring to 500 ml. of benzyl chloride heated on a steam bath. Following the first addition, each successive addition was made after the reaction mixture had thinned from the previous addition. After 5 hr. most of the excess benzyl chloride was removed by distillation under reduced pressure and the residual mixture subjected to steam distillation until no more benzyl chloride came over. The aqueous layer was decanted. The residue solidified on standing overnight and was washed to remove salts. A crude yield of 128 g. (99%) was obtained. For analysis, a sample was crystallized from ligroin, b.p. 60–70°, and then from ether by cooling in an ice bath. $[\alpha]_D^{25}$ −1.3° (c 2, U.S.P. $CHCl_3$), m.p. 83.5–84°.

Anal. Calcd. for $C_{23}H_{26}O_6$: C, 69.33; H, 6.58. Found: C, 69.64; H, 6.73.

6-O-Benzyl-1,2-O-isopropylidene-D-glucofuranose (V). A solution of 100 g. of IV in 1 l. of acetone, 40 ml. of water, and 4 ml. of concentrated hydrochloric acid was refluxed for 75 min. The solution was neutralized with silver carbonate, filtered, saturated with hydrogen sulfide, and filtered through a charcoal mat. The filtrate was mixed with 200 ml. of water and evaporated to a sirup. The residue was dried by adding 50 ml. of toluene and reconcentrating to a residue which solidified on standing. It was recrystallized from a mixture of ethyl acetate and ligroin, (b.p. 60–70°) to yield 60 g. (80%), m.p. 78.5–79° (uncorr.) (lit.[5] 78.5–79°), b.p. 172°/0.16 mm.

6-O-Benzyl-1,2-O-isopropylidene-3,5-di-O-methyl-D-glucose (VI). A solution of 100 g. of V in 1 l. of acetone was methylated at 50° by the dropwise addition of 490 ml. of methyl sulfate and 826 ml. of 50% sodium hydroxide solution. After heating at 50° for 30 min., the temperature was raised to 70° until the acetone had distilled, 500 ml. of water was added, and the reaction mixture maintained at 70° for 1 hr. After standing overnight the solution was separated from the salts by decantation and extracted with one 400 ml. and

(4) R. J. Dimler, H. A. Davis, and G. E. Hilbert, *J. Am. Chem. Soc.*, **68**, 1377 (1946).

(5) H. Ohle and K. Tessmar, *Ber.*, **71**, 1843 (1938).

(6) C. G. Anderson, W. Charlton, and W. N. Haworth, *J. Chem. Soc.*, 1329 (1929).

(7) Melting points are corrected unless otherwise indicated. Boiling points are uncorrected.

(8) L. von Vorgha, *Ber.*, **66**, 706 (1933).

(9) D. J. Bell, *J. Chem. Soc.*, 859 (1936).

(10) K. Freudenberg and G. Hüll, *Ber.*, **74**, 237 (1941).

two 300 ml. portions of chloroform. The combined extracts were concentrated to a sirup and distilled, b.p. 127–128°/0.008 mm. The product has recrystallized from ligroin to give 43 g. (40%) of plates, m.p. 80.8–81.3°; $[\alpha]_D^{20}$ −41.65° (c 10, U.S.P. $CHCl_3$).

Anal. Calcd. for $C_{18}H_{26}O_6$: C, 63.88; H, 7.74. Found: C, 64.15; H, 7.80.

1,2-O-Isopropylidene-3,5-di-O-methyl-D-glucofuranose (VII). A solution of 25 g. of VI in 50 ml. of ethyl acetate was treated with hydrogen in the presence of palladium charcoal catalyst. After filtering off the catalyst, the filtrate was concentrated to a sirup and distilled under reduced pressure, b.p. 89–90°/0.011 mm., to give a nearly quantitative yield of sirup which did not crystallize on standing for several months. It formed a crystalline *p*-phenylazobenzoate which was recrystallized from ligroin, m.p. 93.2–93.5°.

Anal. Calcd. for *p*-phenylazobenzoyl: 45.83. Found: 45.64.

3,5-Di-O-methyl-D-glucofuranose (VIII). A solution of 6.5 g. of VII in 70 ml. of acetone and 96 ml. of water containing 5 ml. of concentrated hydrochloric acid was refluxed for 2 hr. The solution was neutralized as in the preparation of V and concentrated under reduced pressure to yield 13 g. of a sirup $[\alpha]_D^{20}$ −20.1° (c 1.37, H_2O).

Anal. Calcd. for $C_8H_{16}O_6$: C, 46.15; H, 7.75. Found: C, 46.11; H, 7.74.

2,3,5,6-Tetra-O-methyl-D-glucose. A solution of 15 g. of VI in 150 ml. of methanol containing 0.5% hydrogen chloride was refluxed for 3 hr. The solution was neutralized with silver carbonate, treated with charcoal, and filtered. The filtrate was shaken for 15 hr. under a hydrogen atmosphere in the presence of a palladium charcoal catalyst. After filtering off the catalyst and concentrating the filtrate to a sirup the residue was methylated with 68 ml. of methyl sulfate and 114 g. of 50% sodium hydroxide. The product was extracted with 400 ml. of chloroform and the chloroform distilled. The residue was refluxed for 5 hr. in a solution of 70 ml. of acetone, 70 ml. of water, and 5 ml. of concentrated hydrochloric acid. The solution was neutralized with sodium bicarbonate, filtered, and evaporated under reduced pressure. The sirupy residue was extracted with ether and the extract concentrated under reduced pressure to a sirup. $[\alpha]_D^{20}$ −30.0° (c 1.06, U.S.P. $CHCl_3$).

The product, *2,3,5,6-tetra-O-methyl-D-glucose* was oxidized with bromine to the 2,3,5,6-tetra-*O*-methyl-D-gluconic acid from which the phenylhydrazide was prepared, m.p. 135–135.5° (lit.[7,11,12] 136°).

Anal. Calcd. for $C_{16}H_{26}O_6N_2$: N, 8.18. Found: N, 8.05.

Methyl 2,3,5-tri-O-methyl-β-D-glucofuranoside (IX). A solution of 30 g. of VI in 300 ml. of methanol containing 0.5% hydrogen chloride was refluxed for 3 hr. The solution was neutralized with silver carbonate, concentrated, and the crude product methylated with 100 ml. of methyl sulfate and 170 ml. of 50% sodium hydroxide as described in the preparation of VI except that the methylation was started at 10° and then raised to 50°. The sirup produced was distilled and the product (25 g.) dissolved in ethyl acetate and shaken in a hydrogen atmosphere with palladium charcoal for 15 hr. After filtration and concentration to a sirup the residue was distilled, b.p. 81–84°/0.01 mm. The product crystallized on standing and was recrystallized from ligroin, b.p. 60–70°, m.p. 74–75°; $[\alpha]_D^{20}$ −69.7° (c 1.8; H_2O).

Anal. Calcd. for $C_{10}H_{20}O_6$: C, 50.87; H, 8.47. Found: C, 50.81; H, 8.48.

2,3,5-Tri-O-methyl-D-glucose (X). A solution of IX in 60 ml. of water and 5 ml. of hydrochloric acid was refluxed for 5 hr. The solution was neutralized as described in the preparation of V and concentrated to a sirup. The product was a hydroscopic liquid $[\alpha]_D^{20}$ −13.4 (c 2.14, H_2O).

Anal. Calcd. for $C_9H_{18}O_6$: C, 48.67; H, 8.10. Found: C, 48.75; H, 8.04.

Compound X was oxidized as described by Smith[1] and the 2,3,5-tri-*O*-methyl-D-gluconic acid identified by the preparation of its phenylhydrazide, m.p. 156–156.5° (lit,[1,2] 156°, 156–157°).

Anal. Calcd. for $C_{15}H_{24}O_6N_2$: N, 8.53. Found: N, 8.45.

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(11) W. N. Haworth and S. Peat, *J. Chem. Soc.*, 129, 3094 (1926).

(12) W. N. Haworth and C. W. Long, *J. Chem. Soc.*, 544 (1927).

[CONTRIBUTION FROM THE MERCK SHARP AND DOHME RESEARCH LABORATORIES)

Synthetic Antiviral Agents. I. 4-Arylmethyl-4-aryl-5-oxohexanoic Acids and Certain of Their Derivatives*,[1]

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A number of 4-arylmethyl-4-aryl-5-oxohexanoic acids were prepared by the following series of reactions: Various arylacetones were condensed with certain arylmethyl halides to give the corresponding 3,4-diphenyl-2-butanones. Cyanoethylation produced the 4-arylmethyl-4-aryl-5-oxohexanenitriles which upon hydrolysis yielded the corresponding 4-arylmethyl-4-aryl-5-oxohexanoic acids.

Several of the 4-arylmethyl-4-aryl-5-oxohexanoic acids were resolved through the brucine salts. Derivatives of some of the hexanoic acids were prepared. Among the derivatives were esters, amides, and enol-lactones. Many of the compounds described have been found to have antiviral activity against certain influenza viruses.

Interest in this group of compounds began with an observation by the virologists associated with this organization that 4,4-diphenyl-5-oxohexanoic acid markedly inhibited the multiplication of PR8 influenza virus in the allantoic cavity of the chicken embryo as measured by hemagglutinin production. This effect was also observed when the mouse served as the host and activity was measured by inhibition of lung lesions or by hemagglutinin formation. In the investigation that followed strong

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* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) A portion of the material contained in this paper was presented by the authors at the First Regional Meeting of the Delaware Valley Sections of the AMERICAN CHEMICAL SOCIETY, Feb. 16, 1956.