[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

1,2:4,6-Di-*O*-benzylidene-α-D-glucopyranose and Improvements in the Preparation of 4,6-*O*-Benzylidene-D-glucopyranose

BY HARRY B. WOOD, JR., HARRY W. DIEHL AND HEWITT G. FLETCHER, JR.

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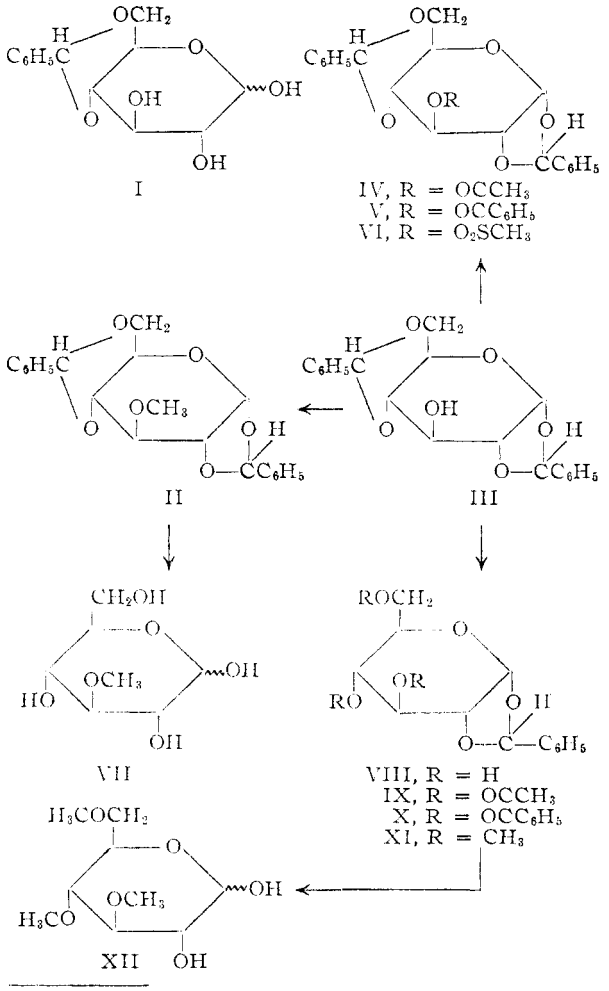
As a by-product in an improved preparation of 4,6-*O*-benzylidene-D-glucopyranose, a di-*O*-benzylidene-D-glucose was obtained. Evidence that this substance is 1,2:4,6-di-*O*-benzylidene-α-D-glucopyranose is described.

The cyclic acetal 4,6-*O*-benzylidene-D-glucopyranose (I) which was first described by Zervas in 1931[1] has proved a valuable intermediate for syntheses in the hands of a number of workers. However, despite the utility of this substance, the process which Zervas used to make it has seen little improvement and his yield, about 12% of pure material, leaves much to be desired although the reactants, D-glucose, benzaldehyde and zinc chloride are relatively inexpensive. Since relatively large quantities of 4,6-*O*-benzylidene-D-glucopyranose were needed in this Laboratory, we have restudied Zervas' preparation and have found that changes in the proportions of reactants, reaction time and method of purification of the product result in a yield of 42% of pure product. Under the new reaction conditions the 4,6-*O*-benzylidene-D-glucopyranose is accompanied in 6% yield by a non-reducing di-*O*-benzylidene-D-glucose. A further modification of the reaction conditions led to a decreased yield (17%) of 4,6-*O*-benzylidene-D-glucopyranose but a slightly improved (11%) yield of the di-*O*-benzylidene-D-glucose. The by-product thus obtained melted at 161–162° and rotated $[\alpha]^{20}D$ +107° in chloroform and $[\alpha]^{20}D$ +92.7° in pyridine.



Two non-reducing di-*O*-benzylidene-D-glucoses have been reported in the literature. In 1937, Papadakis[2] obtained one such substance through the action of benzaldehyde and zinc chloride on 6-*O*-benzoyl-D-glucose diethyl thioacetal; very shortly thereafter Wolfrom and Tanghe[3] published a study of the preparation of this substance. Although the melting point recorded by these authors, 163–165°,[3] is close to that of our substance, the rotation in pyridine, $[\alpha]^{24}D$ +35°,[3] clearly shows that the two products are not identical. Through the action of benzaldehyde and phosphorus pentoxide on 4,6-*O*-benzylidene-D-glucose, Papadakis[2] obtained a second non-reducing di-*O*-benzylidene-D-glucose which melted at 163°, rotated [α] +116° in chloroform[4] and depressed the melting point of the isomeric substance derived from 6-*O*-benzoyl-D-glucose diethyl thioacetal. As none of this material has survived,[5] its identity with our present product cannot be established, although we are inclined to believe that the earlier preparation was quite probably identical with ours.[6]

The structure of the di-*O*-benzylidene-D-glucose was demonstrated in the following manner. Methylation afforded a crystalline methyl ether which was hydrogenolyzed to give the well-known crystalline 3-*O*-methyl-D-glucose (VII), demonstrating that a hydroxyl at C_3 in the substance is unsubstituted. Partial hydrogenolysis afforded a mono-*O*-benzylidene-D-glucose which was stable to Fehling solution and not identical with the 1,2-*O*-benzylidene-α-D-glucofuranose which Sowden and Kuenne[7] had isolated as a by-product in the preparation (Zervas' procedure) of 4,6-*O*-benzylidene-D-glucopyranose. Methylation of the new mono-

(1) L. Zervas, *Ber.*, **64**, 2289 (1931).

(2) P. Papadakis, THIS JOURNAL, **59**, 841 (1937).

(3) M. L. Wolfrom and L. J. Tanghe, *ibid.*, **59**, 1597 (1937).

(4) We are indebted to Professor Papadakis for this rotatory value which was obtained by him after publication of reference 2.

(5) Personal communication from Professor Papadakis.

(6) Condensation of 4,6-*O*-benzylidene-D-glucose with benzaldehyde in the presence of zinc chloride has, in our hands, afforded the di-*O*-benzylidene-D-glucose having $[\alpha]^{20}D$ +107° in chloroform. However, the low yield (never over 12%) as well as the lability of acetal rings in the presence of acidic catalysts render such a preparation of doubtful value in structural studies.

(7) J. C. Sowden and D. J. Kuenne, THIS JOURNAL, **74**, 686 (1952); see also B. Helferich and A. Porck, *Ann.*, **582**, 233 (1953).

O-benzylidene-D-glucose, followed by hydrogenolytic removal of the benzylidene residue, led to the isolation of crystalline 3,4,6-tri-*O*-methyl-D-glucose (XII); it is plain, then, that the parent substances are 1,2-*O*-benzylidene-D-glucopyranose (VIII) and 1,2:4,6-di-*O*-benzylidene-D-glucopyranose (III). The steric requirements of the 1,3-dioxolane ring as well as the strong dextrorotation of both III and VIII appear to justify the assumption that both are α-anomers.

A number of bicyclic acetals derived from the condensation of D-glucose with ketones has been prepared; their ring structure is typified by 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, a substance which has played an important role in carbohydrate chemistry. Bicyclic acetals from D-glucose and aldehydes have not, however, been much investigated save in the case of the product from formaldehyde which was shown[8,9] to be 1,2:3,5-di-*O*-methylene-α-D-glucofuranose. Whether other analogous products[10] have the same ring structure or the different one reported here has not been ascertained, but the fact that III is obtained in low yield under all conditions thus far tried may possibly signify that this ring system is not the preferred one.[11]

Experimental[12]

Benzylideneation of D-Glucose.—A mixture of 10 g. of powdered anhydrous D-glucose (which had been dried *in vacuo* at 60°), 40 g. of freshly fused and powdered zinc chloride and 200 ml. of freshly distilled benzaldehyde was shaken at room temperature (28°) for 4 hr., cooled and diluted with 250 ml. of cold water. After 0.5 hr. at 0° the resulting crystalline mass was filtered off and washed, first with cold water (2 × 25 ml.) and then with pentane (2 × 25 ml.). Dried in the air, the crude 4,6-*O*-benzylidene-D-glucose (7.5 g.) melted at 140–150° and rotated in methanol $[\alpha]^{20}D$ +30.8° → +19.3° (*c* 3.4). The aqueous layer of the mother liquor and washings was extracted with ether (2 × 100 ml.). The ether extracts were added to the organic phase and the aqueous solution was filtered through 30 g. of Darco G-60 and discarded. The decolorizing carbon, washed with 100 ml. of water, was heated with 100 ml. of dioxane, filtered off and washed with 50 ml. more warm dioxane. Concentration of the dioxane extracts *in vacuo* afforded a crystalline residue; recrystallization from a mixture of 10 ml. of warm dioxane and 50 ml. of chloroform afforded a second batch (1.8 g., m.p. 155–161°) of 4,6-*O*-benzylidene-D-glucose rotating $[\alpha]^{20}D$ −2.5° (MeOH, *c* 4.0).

Combined crops of 4,6-*O*-benzylidene-D-glucose were recrystallized from dioxane–chloroform and then from water in the following fashion. To the nearly pure product (8.2 g.) was added 90 ml. of boiling water containing 9 drops of aqueous ammonia. The mixture was shaken for not more than one minute, filtered through a very thin layer of decolorizing carbon and the filtrate cooled as rapidly as possible,[13] finally to 0°. The pure **4,6-*O*-benzylidene-D-glucose** (I, 6.3 g., 42%) melted at 186–187° and showed $[\alpha]^{20}D$ −4.9° (final, methanol, *c* 2.6).

The original organic phase and combined ether extracts were concentrated *in vacuo*, first at a water-pump and then at *ca.* 1 mm. and a bath temperature of 60–70°. The residual, heavy sirup gave, from 15 ml. of absolute alcohol at −5°, 1.1 g. (6%) of crystalline product melting at 160–161° and rotating $[\alpha]^{20}D$ +107° in chloroform (*c* 1.3). Recrystallization from methanol gave pure **1,2:4,6-di-*O*-benzylidene-α-D-glucopyranose (III)** as minute needles melting at 161–162° and rotating $[\alpha]^{20}D$ +107° in chloroform (*c* 1.3); in pyridine (*c* 1.47) it showed $[\alpha]^{20}D$ +92.7°. The substance was unaffected by hot Fehling solution.

Anal. Calcd. for $C_{20}H_{20}O_6$: C, 67.40; H, 5.66. Found: C, 67.69; H, 5.64.

When the amount of zinc chloride in the above procedure was reduced to 10 g., the yield of the diacetal rose to 11%, but that of the monoacetal fell to 17%.

3-*O*-Acetyl-1,2:4,6-di-*O*-benzylidene-α-D-glucose (IV).—One gram of 1,2:4,6-di-*O*-benzylidene-α-D-glucopyranose was acetylated with acetic anhydride in pyridine[14] in the usual manner to yield 0.92 g. (82%) of crystalline product melting at 177–178°. Recrystallization from 20 parts of 1-propanol gave the pure ester as fine needles melting at 178° and rotating $[\alpha]^{20}D$ +81.0° in chloroform (*c* 0.97).

Anal. Calcd. for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 66.17; H, 5.71.

1,2:4,6-Di-*O*-benzylidene-3-*O*-methylsulfonyl-α-D-glucopyranose (VI).—The acetal (1 g.) was treated with mesyl chloride in pyridine solution to yield 1.13 g. (93%) of crude product. Recrystallization from 130 parts of 1-propanol gave, with little loss, the pure ester as needles melting with decomposition at 177° and rotating +79.2° in chloroform (*c* 1.01).

Anal. Calcd. for $C_{21}H_{22}O_8S$: C, 58.05; H, 5.11; S, 7.38. Found: C, 58.02; H, 5.16; S, 7.44.

3-*O*-Benzoyl-1,2:4,6-di-*O*-benzylidene-α-D-glucopyranose (V).—Benzoylation of a sample (0.5 g.) of 1,2:4,6-di-*O*-benzylidene-α-D-glucopyranose with benzoyl chloride in pyridine solution using the standard procedure afforded, from absolute ethanol, 0.60 g. (93%) of fine needles melting at 181–182° and showing $[\alpha]^{20}D$ +41.8° in chloroform (*c* 1.26). Further recrystallization did not alter these constants.

Anal. Calcd. for $C_{27}H_{24}O_7$: C, 70.42; H, 5.25. Found: C, 70.63; H, 5.30.

Wolfrom and Tanghe[3] reported m.p. 156–156.5° and $[\alpha]^{26}D$ +15° ($CHCl_3$, *c* 4) for the benzoate of their non-reducing di-*O*-benzylidene-D-glucose.

1,2:4,6-Di-*O*-benzylidene-3-*O*-methyl-α-D-glucopyranose (II).—One-gram portions of silver oxide were added at 0.5-hr. intervals to a boiling solution of 2 g. of 1,2:4,6-di-*O*-benzylidene-α-D-glucopyranose in 50 ml. of methyl iodide until 8 g. had been added. Half an hour after the last addition, the solution was cooled, treated with 0.5 g. of Darco G-60, filtered and concentrated to give a crystalline mass. Recrystallization from 14 ml. of absolute ethanol afforded 2.0 g. (96%) of fine needles, m.p. 115–117°, $[\alpha]^{20}D$ +81.0° ($CHCl_3$, *c* 1.20). Recrystallization from ethanol–pentane gave the pure ether, m.p. 117–119° and $[\alpha]^{20}D$ +81.1° ($CHCl_3$, *c* 0.92).

Anal. Calcd. for $C_{21}H_{22}O_6$: C, 68.09; H, 5.99. Found: C, 68.08; H, 5.96.

3-*O*-Methyl-D-glucose (VII) from 1,2:4,6-Di-*O*-benzylidene-3-*O*-methyl-α-D-glucopyranose (II).—A solution of the methyl ether (1.6 g.) in dioxane (40 ml.) was shaken with palladium black (0.5 g.) and hydrogen at room temperature. After 2.5 hr., absorption of hydrogen had ceased. The catalyst was removed and the solution concentrated to a clear, colorless sirup; from a mixture of 20 ml. of absolute ethanol and 20 ml. of pentane the product separated as fine needles: 0.4 g. (48%), m.p. 162–163°. Recrystallization from the same solvent mixture gave, with little loss, pure 3-*O*-methyl-D-glucose rotating $[\alpha]^{20}D$ +92.4° (2 min.) → +55.5° (H_2O, *c* 1) and melting at 163–164° either alone or in admixture with authentic 3-*O*-methyl-D-glucose. A final rotation in water of $[\alpha]^{20}D$ +55.5° previously has been recorded[15] for 3-*O*-methyl-D-glucose.

(8) O. T. Schmidt, A. Distelmaier and H. Reinhard, *Chem. Ber.*, **86**, 741 (1953).

(9) W. P. Skyluk, J. Honeyman and T. E. Timell, *Can. J. Chem.*, **33**, 1202 (1955).

(10) For instance see R. L. Mellies, C. L. Mehltretter and C. E. Rist, This Journal, **73**, 294 (1951).

(11) Using a zinc chloride–glacial acetic acid catalyst [H. B. Wood, Jr., H. W. Diehl and H. G. Fletcher, Jr., *ibid.*, **78**, 4715 (1956)], we have obtained a second di-*O*-benzylidene-D-glucose, the structure of which is under investigation in this Laboratory.

(12) Melting points are corrected.

(13) Speed is imperative at this stage since prolonged heating of the solution results in greatly diminished yields of product.

(14) Although 1,2:4,6-di-*O*-benzylidene-α-D-glucopyranose rapidly dissolves in anhydrous pyridine, the solution thus obtained tends (if not too dilute) to precipitate what appears to be simply a solvated crystalline form. The substance was not investigated further except to demonstrate that 1,2:4,6-di-*O*-benzylidene-α-D-glucopyranose could be recovered from it unchanged.

(15) L. v. Vargha, *Ber.*, **67**, 1223 (1934).

A sample of the 3-*O*-methyl-D-glucose was converted to the corresponding phenylosazone which was found to melt at 180–181°, again no depression being observed on admixture with authentic material.

Partial Hydrogenolysis of 1,2:4,6-*O*-Benzylidene-α-D-glucopyranose (III) to 1,2-*O*-Benzylidene-α-D-glucopyranose (VIII).—A solution of 10 g. of 1,2:4,6-di-*O*-benzylidene-α-D-glucopyranose in 300 ml. of ethyl acetate was shaken with 0.5 g. of palladium black and hydrogen at room temperature until two molar equivalents of hydrogen had been absorbed (7.5 hr.). The suspended material was then removed by filtration and digested with 15 ml. of methanol. On cooling, the methanolic solution gave 0.2 g. of crude 1,2-*O*-benzylidene-α-D-glucopyranose; a second crop (0.19 g.) was obtained by concentrating the mother liquor to dryness and adding 1 ml. of water to dissolve any glucose which might be present. Cooling the original ethyl acetate filtrate provided a third (0.4 g.) crop of material.[16] Recrystallization of the combined crops from 84 ml. of ethyl acetate gave 0.7 g. of pure 1,2-*O*-benzylidene-α-D-glucopyranose melting at 173–174° and rotating $[\alpha]^{20}D$ +90.6° in methanol (*c* 0.72). The acetal was unaffected by hot Fehling solution.

Anal. Calcd. for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01. Found: C, 57.93; H, 6.03.

3,4,6-Tri-*O*-acetyl-1,2-*O*-benzylidene-α-D-glucopyranose (IX).—The cyclic acetal (0.5 g.) was acetylated with acetic anhydride in pyridine solution using the usual technique to give from absolute ethanol 0.6 g. (82%) of crystalline product melting at 114–115°, a value unchanged by further recrystallization from alcohol. In chloroform (*c* 1) the pure product showed $[\alpha]^{20}D$ +47.5°.

Anal. Calcd. for $C_{19}H_{22}O_9$: C, 57.86; H, 5.62. Found: C, 57.96; H, 5.51.

3,4,6-Tri-*O*-benzoyl-1,2-*O*-benzylidene-α-D-glucopyranose (X).—1,2-*O*-Benzylidene-α-D-glucose (0.5 g.) was benzoylated with benzoyl chloride in pyridine in the usual fashion. The product (0.91 g., 84%) crystallized from alcohol; after recrystallization from the same solvent it melted at 138–139° and rotated $[\alpha]^{20}D$ −12° in chloroform (*c* 1.0).

Anal. Calcd. for $C_{34}H_{28}O_9$: C, 70.34; H, 4.86. Found: C, 70.45; H, 4.86.

1,2-*O*-Benzylidene-3,4,6-tri-*O*-methyl-α-D-glucopyranose (XI).—A stirred, boiling solution of 1.1 g. of 1,2-*O*-benzylidene-α-D-glucopyranose in a mixture of 20 ml. of methyl iodide and 10 ml. of dioxane was treated, at 0.5-hr. intervals with 1-g. batches of silver oxide until 6 g. of the latter had been added. The solution was then filtered and concentrated to a sirup which was methylated twice more in a similar fashion to give a sirup (1.2 g.) which showed no hydroxyl absorption in the infrared.

3,4,6-Tri-*O*-methyl-D-glucose (XII).—A portion (1.1 g.) of the sirup, prepared as described above, was dissolved in 20 ml. of ethanol and reduced with palladium black (0.5 g.) at room temperature to give 0.59 g. of a sirup which, diluted with ether at −5° and seeded, crystallized: 197 mg., m.p. 83–96°. The addition of pentane to the mother liquor afforded a second crop: 30 mg., m.p. 90–98°. Combined, the two crops were recrystallized from ether and then twice from isopropyl ether to give pure 3,4,6-tri-*O*-methyl-β-D-glucopyranose (70 mg.): m.p. 98–102°, $[\alpha]^{20}D$ +40.0° (7 min.) → +77.6° (24 hr., constant) (water, *c* 0.5). Sundberg, *et al.*,[17] reported m.p. 97–98° and $[\alpha]^{25}D$ +41.1° (2.5 min.) → +78.0° (constant) (H_2O, *c* 1.6) for this substance. A mixed melting point with authentic material was undepressed; in both borate ionophoresis and paper chromatography the substance behaved like authentic 3,4,6-tri-*O*-methyl-D-glucose.

Cautious addition of pentane to the combined mother liquors afforded 380 mg. of material (m.p. 62–70°) which, recrystallized from ether at −5°, was obtained as beautiful needles (164 mg.): m.p. 76–78°, $[\alpha]^{20}D$ +122° (extrapolated) → +77.7° (28 hr., constant, H_2O, *c* 1.0). While the final value here is in agreement with recorded values for 3,4,6-tri-*O*-methyl-D-glucose, the initial value lies some 30° higher than that recorded by Sundberg, *et al.*,[17] for the α-anomer. However, this new value leads to a 2A value which is quite close to that of D-glucose (Table I) and is, therefore, not unreasonable. Borate ionophoresis of this material gave a migration rate identical with that of authentic 3,4,6-tri-*O*-methyl-D-glucose.

TABLE I

	$[\alpha]^{20}D$ (H_2O)	$[M]^{20}D$	Difference (2A)
3,4,6-Tri-*O*-methyl-α-D-glucose	+122°	+27,100	17,970
3,4,6-Tri-*O*-methyl-β-D-glucose	+ 41.1°	+ 9,130	
α-D-Glucose	+112.2°	+20,210	16,840
β-D-Glucose	+ 18.7°	+ 3,370	

Acknowledgment.—Analyses were carried out in the Institutes' Microanalytical Laboratory under the direction of Dr. W. C. Alford.

(16) By selective adsorption on carbon the material remaining in the mother liquor was induced to yield a further 0.35 g. of 1,2-*O*-benzylidene-D-glucopyranose.

(17) R. L. Sundberg, C. M. McCloskey, D. E. Rees and G. H. Coleman, THIS JOURNAL, **67**, 1080 (1945).

BETHESDA 14, MD.

[CONTRIBUTION FROM THE FISHERIES RESEARCH BOARD OF CANADA, CHEMISTRY SECTION OF THE TECHNOLOGICAL STATION AT VANCOUVER, B. C.]

Marine Sterols. III. The Synthesis of 24-Methylenecholesterol and 25-Dehydrocholesterol

BY D. R. IDLER AND U. H. M. FAGERLUND

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A new sterol, 24-methylenecholesterol, recently isolated from several molluscs, has been synthesized from 24-ketocholesterol employing triphenylphosphinemethylene. The synthesis of 25-dehydrocholesterol is also reported and discrepancies in its properties with the products previously assigned this structure are discussed. Evidence is presented to support the conclusion that the earlier preparations are not 25-dehydrocholesterol and it is suggested that they are the previously undescribed 24-dehydrocholesterol. The broader implications of the use of triphenylphosphine alkylidene compounds in syntheses in the sterol side chain are outlined.

A new sterol, 24-methylenecholesterol, has recently been isolated from several species of shellfish.[1,2] The structure was established by chemical degradation and the present study was undertaken to confirm this structure by synthesis. Further, it was suggested that the biological reduction of 24-methylenecholesterol offered a possible explanation for the origin of C_{24}-epimeric 28-carbon sterols in nature and by a similar route fucosterol (24-ethyl-

(1) D. R. Idler and U. H. M. Fagerlund, THIS JOURNAL, **77**, 4142 (1955).

(2) U. H. M. Fagerlund and D. R. Idler, *J. Org. Chem.*, **21**, 372 (1956).