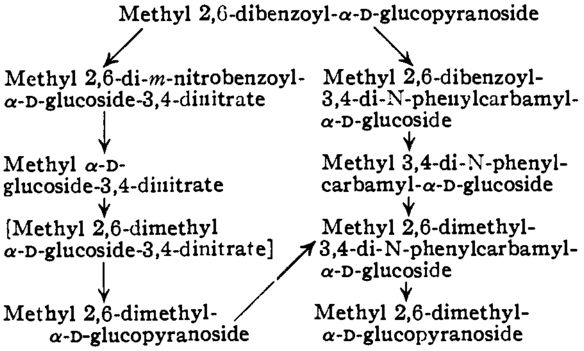
[CONTRIBUTION FROM THE SOUTHERN REGIONAL RESEARCH LABORATORY[1]]

Methyl 2,6-Dimethyl-α-D-glucopyranoside

BY RICHARD E. REEVES

In connection with current work an alkali-stable glucopyranoside substituted in positions 2 and 6 was desired; accordingly, the preparation of methyl 2,6-dimethyl-α-D-glucoside was undertaken. The β-form of this glucoside has been prepared by Bell and Synge.[1a] The α-glucoside was obtained by two different routes, as shown in the diagram below. All substances except the starting material are previously unreported; the compound enclosed in brackets was not characterized.



The glucoside has not yet been obtained in the crystalline state, but the preparations from the two series exhibited almost identical rotatory values and gave satisfactory analyses. The nature of the reactions employed allows the belief that the α-pyranoside structure persisted throughout both series. This view is supported by the high positive rotation of the final glucoside, and by its quantitative reconversion to the crystalline methyl 2,6-dimethyl-3,4-di-N-phenylcarbamyl-α-D-glucoside.

The nitrate series of reactions is of significance with regard to the assignment of structure to the final product because, as Bell and Synge[2] have pointed out, nitrate groups do not migrate.

Nitration of methyl 2,6-dibenzoyl-α-D-glucopyranoside at positions 3 and 4 proceeded smoothly with simultaneous nitration of the benzoyl radicals. The di-m-nitrobenzoyl derivative, obtained in fair yield, was a satisfactory intermediate.

N-Phenylcarbamyl derivatives (phenylurethans, carbanilates) are extensively used to characterize alcohols, and they have been so employed in the sugar series.[3] They have also been used by Hearon, Hiatt and Fordyce[4] to block certain positions, taking advantage of their relatively great resistance against acid catalyzed alcoholysis to allow the selective removal of acyl radicals at other positions.

Methyl 2,6-dimethyl-α-D-glucopyranoside in cuprammonium hydroxide solution was found to be strongly dextrorotatory as expected from the study of other cuprammonium-glucoside complexes. The rotatory shift (sp. rot. cupra − sp. rot, water) was approximately +950°. The corresponding value previously found[5] for methyl 2-methyl-β-D-glucopyranoside (+1054°) was attributed to complex formation at the 3-4 position although in that instance there was some uncertainty due to the presence of a free hydroxyl group at position 6. The present glucoside, having the 6 position blocked by a methyl group, allows no doubt as to its site of complex formation being the 3-4 position. It is intended to discuss in a later communication the significance of the properties of various cuprammonium–glycoside complexes with regard to conformation of the pyranoside ring.

Experimental

All melting points were observed between crossed polaroids by means of a Fisher–Johns melting point apparatus, drilled to allow the passage of a 1 mm. beam of light.

Except where the mercury blue line is specifically mentioned, the optical rotations were measured with the sodium D line. The mercury blue line (436 mμ) was isolated for aqueous solutions by Corning filters 511 and 038; for cuprammonium solutions, by filter 038 only. All rotations were measured at 25°.

The cuprammonium contained 15 g. copper, 240 g. ammonia and 1 g. glycerol per liter.

Methyl 2,6-dibenzoyl-α-D-glucopyranoside, m. p. 141.5–142°, was prepared in small lots by the method of Lieser and Schweizer.[6]

The Nitrate Series

Methyl 2,6-Di-m-nitrobenzoyl-α-D-glucoside 3,4-Dinitrate.—Methyl 2,6-dibenzoyl-α-D-glucopyranoside, 1.4 g., was dissolved in a mixture of 49 ml. of chloroform and 21 ml. of 100% nitric acid, previously cooled to 0°. The solution was kept for fifteen minutes in an ice-bath after which ice water was added and the chloroform layer extracted, washed with ice water, cold potassium bicarbonate solution, water and dried over calcium chloride. Removal of solvent *in vacuo* left a sirup which yielded 1.6 g. of crystals from alcohol. After two recrystallizations from alcohol the product melted at 148–149°, sp. rot. +167° ± 3° ($CHCl_3$, *c*, 1.1).

Anal. Calcd. for $C_{21}H_{18}O_{16}N_4$ (582.38): C, 43.31; H, 3.11; N, 9.62. Found: C, 43.18, 43.25; H, 3.11, 3.20; N, 9.52, 9.55 (micro Dumas).

Methyl α-D-Glucoside 3,4-Dinitrate.—Two grams of the substance described above was dissolved in 6 ml. of absolute methanol containing 2.5 mg. of sodium. The solution turned slightly yellow and deposited crystals within a very short time. When crystallization appeared

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(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(1a) D. J. Bell and R. L. M. Synge, *J. Chem. Soc.*, 833–836 (1938).

(2) D. J. Bell and R. L. M. Synge, *ibid.*, 836–838 (1938).

(3) M. L. Wolfrom and D. E. Pletcher, THIS JOURNAL, **62**, 1151–1153 (1940).

(4) W. M. Hearon, G. D. Hiatt and C. R. Fordyce, *ibid.*, **66**, 995–997 (1944).

(5) R. E. Reeves, *J. Biol. Chem.*, **154**, 49–55 (1944).

(6) Th. Lieser and R. Schweizer, *Ann.*, **519**, 271–278 (1935).

to be complete the solution was filtered and the crystals rinsed with cold methanol. After drying in a vacuum desiccator the crystals weighed 935 mg. and melted at 77–78°, alone or mixed with an authentic sample of methyl *m*-nitrobenzoate (m. 77–78°). The yield amounts to 74% of the theoretical amount of methyl *m*-nitrobenzoate.

The combined filtrate and washings were acidified with a trace of glacial acetic acid. Removal of solvent in a current of air left 1.3 g. of crystals. Two recrystallizations from benzene gave 0.86 g. of product, m. p. 132–134°, sp. rot. +183° ± 4° (methanol, *c*, 0.85).

Anal. Calcd. for $C_7H_{12}O_{10}N_2$ (284.18): C, 29.58; H, 4.27; N, 9.86. Found: C, 30.08, 29.85; H, 4.42, 4.33; N, 9.46, 9.52 (micro Dumas).

Methyl 2,6-Dimethyl-α-D-glucopyranoside.—The dinitrate described above, 1.075 g., was dissolved in 25 ml. of methyl iodide and refluxed with 5 g. of silver oxide and 2 g. of anhydrous calcium sulfate for eight hours. The solution was then filtered, the salts washed with boiling chloroform, and the combined filtrate and washings evaporated to dryness *in vacuo*. The sirupy product, weighing 1.09 g., consisted largely of methyl 2,6-dimethyl-α-D-glucoside 3,4-dinitrate.

Anal. Calculated for $C_9H_{16}O_{10}N_2$ (312.24): OCH_3, 29.82. Found: OCH_3, 31.1.

Since the above sirup did not seem amenable to further purification the entire sample was dissolved in 10 ml. of glacial acetic acid and warmed with iron dust and a few magnesium turnings. A violent reaction occurred and nitrogen oxide gases were evolved. In a few moments the diphenylamine test for nitrate became negative and the solution was then filtered. The salts were extracted with acetone and acetic acid. The filtrate and extracts were concentrated to dryness *in vacuo* and the residue was once taken to dryness with water, and once with absolute alcohol. The residue was extracted with warm acetone, filtered, and the filtrate transferred to a micro-distillation outfit. The solvent was removed in a current of air and the residue was distilled at 130–140° and approximately 0.01 mm. pressure. The distillate amounted to 333 mg. It was a viscous, almost colorless, sirup. Its specific rotation was as follows: D line +156° ± 2° (water, *c*, 1.44); Hg blue line +285° ± 3° (water, *c*, 1.44); Hg blue line +1230° ± 12° (cupra., *c*, 0.45). The substance was very hygroscopic; it was dried at 55° in vacuum over phosphorus pentoxide for analysis. The analytical values are in agreement with those required for a methyl dimethylglucoside.

Anal. Calcd. for $C_9H_{18}O_6$ (222.23): C, 48.64; H, 8.16; OCH_3, 41.89. Found: C, 48.12, 48.19; H, 8.22, 8.21; OCH_3, 41.7.

The N-Phenylcarbamate Series

Methyl 2,6-Dibenzoyl-3,4-di-N-phenylcarbamyl-α-D-glucoside.—Methyl 2,6-dibenzoyl-α-D-glucopyranoside, 4.02 g. was dissolved in 20 ml. of anhydrous pyridine and 40 ml. of anhydrous benzene. Five ml. (100% excess) of freshly distilled phenyl isocyanate was added and the solution was refluxed one and one-half hours, being protected from atmospheric moisture with a calcium chloride tube. The solvent and excess reagent were removed *in vacuo*. The residue was dissolved in alcohol and yielded crystals on cooling. After two recrystallizations from alcohol, 3 g. of product, m. p. was 202–203°, sp. rot. +103° ± 1° ($CHCl_3$, *c*, 2.8), was obtained.

Anal. Calcd. for $C_{35}H_{32}O_{10}N_2$ (640.63); C, 65.62; H, 5.04; N, 4.37. Found: C, 65.71, 65.61; H, 5.15, 5.05; N, 4.14, 4.33 (micro Kjeldahl).

Methyl 3,4-Di-N-phenylcarbamyl-α-D-glucoside.—Preliminary experiments indicated that the benzoyl groups could not be selectively saponified from the preceding compound using alcoholic alkali solutions. However, the following procedure was successfully employed: Two and five-tenths grams of the above substance was placed in a glass-stoppered flask with 20 ml. of absolute methanol containing 1% anhydrous hydrogen chloride. The flask was kept in an incubator at 40° with occasional shaking. After five days the substance had passed into solution, and after two more days the hydrogen chloride was removed with a cold solution of ethereal diazomethane, and the solvents removed *in vacuo*. The residue recrystallized from alcohol, melted at 213–218°, sp. rot. +128° ± 4° (acetone, *c*, 0.52), weighed 0.9 g.

Anal. Calculated for $C_{21}H_{24}O_8N_2$ (432.42): C, 58.33; H, 5.59; N, 6.48. Found: C, 58.42, 58.13; H, 5.54, 5.59; N, 6.38, 6.48 (micro Dumas).

Methyl 2,6-Dimethyl-3,4-di-N-phenylcarbamyl-α-D-glucoside.—Five and three-tenths grams of the preceding substance was dissolved in 50 ml. of alcohol-free acetone and 50 ml. of methyl iodide. The solution was stirred under reflux at 40–45° with 5 g. of silver oxide and 2 g. of anhydrous calcium sulfate. Fifteen grams more silver oxide was added during the reaction, which was allowed to continue for twenty-two hours. The mixture was filtered and the salts washed with boiling chloroform. The solvents were removed and the residue, dissolved in alcohol, slowly deposited 1.2 g. of crystals, m. p. 225–227. After recrystallization to constant m. p. from dilute alcohol the substance melted at 235–236°, and showed a sp. rot. of +87° ± 2° ($CHCl_3$, *c*, 0.72).

Anal. Calcd. for $C_{23}H_{28}O_8N_2$ (460.47): C, 59.99; H, 6.13; N, 6.09; OCH_3, 20.22. Found: C, 59.80, 59.88; H, 6.10, 6.09; N, 6.35, 6.08 (micro Dumas); OCH_3, 20.15.

Methyl 2,6-Dimethyl-α-D-glucopyranoside.—Two hundred and thirty mg. of the preceding product dissolved in alcohol was warmed under reflux. On adding 10 ml. of 0.39 *N* barium hydroxide solution through the condenser a white precipitate gradually formed. Refluxing was continued for four hours; then carbon dioxide was passed through the solution to remove the excess barium. The precipitate was removed by filtration and the solution evaporated to dryness *in vacuo*. The residue, amounting to 106 mg., was transferred to a micro distillation outfit and distilled at 120–140° at approximately 0.01 mm. The product, a colorless, viscous, sirup, showed approximately the same properties as the sample prepared from the nitrate series: sp. rot. D line, +152° ± 2° (water, *c*, 1.57); Hg blue line, +1240° ± 12° (cupra., *c*, 0.52).

Anal. Calcd. for $C_9H_{18}O_6$ (222.23): OCH_3, 41.89. Found: OCH_3, 41.22.

Di-N-phenylcarbamate of Methyl 2,6-Dimethyl-α-D-glucoside from the Nitrate Series.—Sixty-three mg. of glucoside was dissolved in 1.5 ml. of dry pyridine and 1 ml. of dry benzene containing 220 mg. of phenyl isocyanate. The solution was sealed in a small glass tube and kept at 100° for twenty hours. The tube was then cooled, opened and the volatile material removed under vacuum. The crystalline residue was treated with chloroform, filtered and the filtrate made up to 4-ml. volume. This solution showed an optical rotation of +1.45° (0.5 dm.) corresponding to 133 mg. of product of sp. rot. +87°. (The theoretical yield would be 131 mg.) The chloroform was removed in a current of air; and after two recrystallizations from dilute alcohol, 37 mg. of crystals m. p. 233–235°, sp. rot. +95° ± 3° ($CHCl_3$, *c*, 0.80), was obtained. The melting point of this preparation was not depressed when mixed with the corresponding substance from the N-phenylcarbamate series.

Acknowledgments.—The micro carbon–hydrogen and Dumas nitrogen analyses were performed by Lawrence E. Brown, and the Zeisel methoxyl analyses by L. W. Mazzeno, Jr.

Summary

Methyl 2,6-dimethyl-α-D-glucopyranoside has been synthesized by two different methods. Its optical rotations in water and cuprammonium hydroxide solution are given.

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