[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY AND CHEMOTHERAPY, EXPERIMENTAL BIOLOGY AND MEDICINE INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

The Reaction of 2,3,4,6-Tetrabenzoyl-α-D-glucopyranosyl Bromide and 2,3,4,6-Tetrabenzoyl-α-D-mannopyranosyl Bromide with Methanol. Certain Benzoylated Derivatives of D-Glucose and D-Mannose

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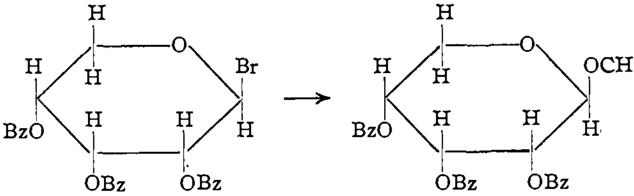
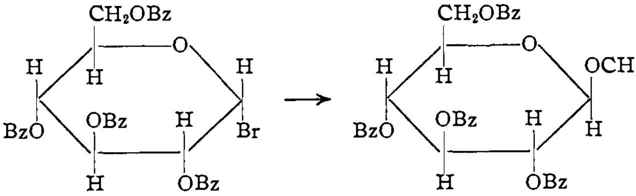
It has recently been shown[2] that 2,3,4-tribenzoyl-β-D-ribopyranosyl bromide (I) reacts directly with anhydrous methanol to give methyl β-D-ribopyranoside tribenzoate (II) in high yield. The present communication describes analogous reactions in the D-glucose and D-mannose series together with various benzoylated derivatives of these two sugars, whose preparation was incidental to the research.



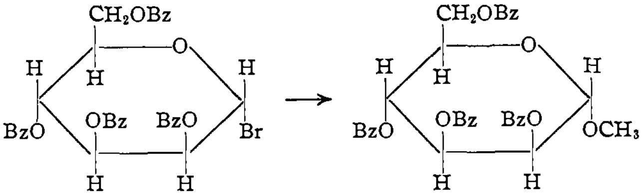
I
2,3,4-Tribenzoyl-β-D-ribopyranosyl bromide

II
Methyl β-D-ribopyranoside tribenzoate



III
2,3,4,6-Tetrabenzoyl-α-D-glucopyranosyl bromide

IV
Methyl β-D-glucopyranoside tetrabenzoate



V
2,3,4,6-Tetrabenzoyl-α-D-mannopyranosyl bromide

VI
Methyl α-D-mannopyranoside tetrabenzoate

2,3,4,6-Tetrabenzoyl-α-D-glucopyranosyl bromide (III), first prepared by Fischer and Helferich,[3] has been classed as a member of the α-series through comparison of its molecular rotation with those of other benzoylated glucose derivatives.[4] Like its D-ribose analog, 2,3,4,6-tetrabenzoyl-α-D-glucopyranosyl bromide (III) reacts readily with methanol, methyl β-D-glucopyranoside tetrabenzoate (IV) being formed in 90% yield and identified by comparison with authentic material. The reaction is therefore similar to that which Koenigs and Knorr[5] found for 2,3,4,6-tetraacetyl-α-D-glucopyranosyl bromide nearly half a century ago; in the older example, however, methyl β-D-glucopyranoside was the product isolated, the acetyl groups, less stable than benzoyl, being removed under the acidic conditions of the reaction.

When treated with hydrogen bromide in glacial acetic acid, β-D-mannopyranose pentabenzoate, first prepared by Fischer and Oetker,[6] gave 2,3,4,6-tetrabenzoyl-α-D-mannopyranosyl bromide (V) which could be obtained only as an amorphous solid possessing a specific rotation in chloroform of +11.7°. That this substance is, like its previously known analog of the acetyl series, a member of the α-series is made highly probable through a comparison of the molecular rotations of the acetylated and benzoylated D-mannopyranosyl halides (Table I).

Reaction of the amorphous 2,3,4,6-tetrabenzoyl-α-D-mannopyranosyl bromide (V) with anhydrous methanol gave, in 69% yield, the previously known methyl α-D-mannopyranoside tetrabenzoate (VI).

It is now to be noted that a fundamental difference appears to exist between the D-ribose and the D-mannose series on the one hand and the D-glucose series on the other in regard to the reaction between the benzoylated glycosyl halides and methanol. In the D-ribose series the benzoylated glycosyl bromide, which was tentatively classified in the β-series because of its strong levorotation,[7] reacts with methanol to give the tribenzoate of what has been established by periodate oxidation[8] to be methyl β-D-ribopyranoside; a β-D-halide thus leads to a β-D-glycoside and there is no over-all change in the configuration of carbon atom one. Likewise in the D-mannose series an α-D-halide, 2,3,4,6-tetrabenzoyl-α-D-mannopyranosyl bromide, gives rise to an α-D-

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[1] Senior Research Fellow, National Institutes of Health, 1948–1950.

[2] R. Jeanloz, H. G. Fletcher, Jr., and C. S. Hudson, THIS JOURNAL, **70**, 4055 (1948).

[3] E. Fischer and B. Helferich, *Ann.*, **383**, 68 (1911).

[4] C. S. Hudson, THIS JOURNAL, **46**, 462 (1924).

[5] W. Koenigs and E. Knorr, *Ber.*, **34**, 957 (1901).

[6] E. Fischer and R. Oetker, *ibid.*, **46**, 4029 (1914).

[7] R. Jeanloz, H. G. Fletcher, Jr., and C. S. Hudson, THIS JOURNAL, **70**, 4052 (1948).

[8] (a) J. Minsaas, *Ann.*, **512**, 286 (1934); (b) E. L. Jackson and C. S. Hudson, THIS JOURNAL, **63**, 1229 (1941).

TABLE I

ACETYLATED AND BENZOYLATED α-D-MANNOPYRANOSYL HALIDES

	Chloride	Bromide	Iodide
M. p. tetrabenzoate, °C.	Amorph.	Amorph.	Amorph.
$[\alpha]^{20}\text{D}$ tetrabenzoate, (dry $CHCl_3$)	−30.5°	+11.7°	+44.8°
$[M]^{20}\text{D}$ tetrabenzoate	−18,800	+ 7,720	+31,650
$[M]^{20}\text{D}$ tetraacetate	+32,970	+54,120	+87,290

TABLE II

ACETYLATED AND BENZOYLATED α-D-GLUCOPYRANOSYL HALIDES

	Chloride	Bromide	Iodide
M. p. tetrabenzoate, °C.	116–118	129–131	139–140
$[\alpha]^{20}\text{D}$ tetrabenzoate, (dry $CHCl_3$)	+109°	+123.6°	+139.5°
$[M]^{20}\text{D}$ tetrabenzoate	+67,000	+81,500	+98,600
$[M]^{20}\text{D}$ tetraacetate	+60,900	+81,300	+108,800

glycoside, methyl α-D-mannopyranoside tetrabenzoate, and the configuration of carbon atom one is retained. In the D-glucose series, however, an α-D-halide, 2,3,4,6-tetrabenzoyl-α-D-glucopyranosyl bromide, reacts with methanol to give the β-D-glucoside, a Walden inversion having taken place at carbon atom one. As a tentative explanation of this apparent anomaly it might be suggested that the 2,3,4,6-tetrabenzoyl-α-D-glucopyranosyl bromide reacts with methanol to form methyl α-D-glucopyranoside tetrabenzoate as an initial product which, under the acidic conditions of the reaction, subsequently anomerizes to the β-D-glucopyranoside tetrabenzoate. Such appears, however, not to be the fact since methyl α-D-glucopyranoside tetrabenzoate was found to be stable in methanolic hydrogen bromide solution under the conditions of the experiment. Further research on the mechanism of the reaction of benzoylated glycosyl halides with methanol is currently under way in this Laboratory.

While 2,3,4,6-tetrabenzoyl-α-D-glucopyranosyl bromide, as mentioned above, has been prepared previously, neither the corresponding chloride nor the iodide has been reported. Reaction of either of the anomeric D-glucopyranose pentabenzoates with titanium tetrachloride in absolute chloroform[9] gave the desired 2,3,4,6-tetrabenzoyl-α-D-glucopyranosyl chloride while treatment of β-D-glucopyranose pentabenzoate with hydrogen iodide in glacial acetic acid yielded the corresponding iodide. The physical constants of these crystalline halides are listed in Table II; their molecular rotations closely parallel those of their acetyl analogs and this fact, together with the fact that the molecular rotations progress in the positive direction from the chloride to the bromide to the iodide confirms the assignment of these substances to the α-D-series. As was to be expected, considerable difference exists between the stabilities of these two new halides; the iodide tends to decompose spontaneously at room temperature while the chloride was found to be only 48% converted to methyl β-D-glucopyranoside tetrabenzoate after sixteen hours in boiling methanol.

While much research has been devoted in the past to the interconversion of the anomeric forms of the sugar acetates through such reagents as zinc chloride in acetic anhydride,[10] sulfuric acid in acetic acid–acetic anhydride,[11] stannic chloride in chloroform[12] and sodium hydroxide in ether or dioxane,[13] apparently no attempt has been made to carry out a similar interconversion using sugar benzoates. In the course of the present work two reagents have been found practicable for such purposes. Heating a solution of β-D-glucopyranose pentabenzoate in anhydrous chloroform with stannic chloride afforded a small yield (8%) of the α-D-pentabenzoate; fusion of the β-D-pentabenzoate with zinc chloride and benzoic acid gave a somewhat higher yield (25%) of pure α-D-glucopyranose pentabenzoate.

β-D-Mannopyranose pentabenzoate was prepared in a fashion similar to that originally used by Fischer and Oetker[6]; the α-D-anomer, hitherto unreported, was obtained by two methods. In the first of these, a solution of D-mannose was heated in dry pyridine solution prior to benzoylation to yield a mixture of the α-D-anomer (40%) and the β-D-anomer (6.3%). In the second procedure methyl α-D-mannopyranoside tetrabenzoate was fused with a mixture of anhydrous zinc chloride, benzoic anhydride and benzoic acid, giving a 61% yield of the desired α-D-mannopyranose pentabenzoate.

Attempts to make 2,3,4,6-tetrabenzoyl-α-D-mannopyranosyl chloride and iodide led to amorphous materials; specific rotations shown by the partially purified halides are given in Table I. As in the D-glucose series the molecular rotations of these halides progress in the positive direction in the order chlorine–bromine–iodine, as is to be expected of α-halides of the D-series.

Reaction of 2,3,4,6-tetrabenzoyl-α-D-mannopyranosyl bromide with slightly damp methanol was found to give, in addition to methyl α-D-mannopyranoside tetrabenzoate as mentioned above, a quantity of another crystalline material which subsequently was shown to be identical with 2,3,4,6-tetrabenzoyl-D-mannose, prepared through the reaction of 2,3,4,6-tetrabenzoyl-α-D-

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[9] E. Pacsu, *Ber.*, **61**, 1508 (1928). G. Zemplén and Z. Csürös [*ibid.*, **62**, 993 (1929)] mentioned that D-glucose pentabenzoate reacts normally with titanium tetrachloride but gave no experimental details.

[10] E. Erwig and W. Koenigs, *Ber.*, **22**, 1464 (1889); C. S. Hudson and J. M. Johnson, THIS JOURNAL, **37**, 1270 (1915).

[11] L. Maquenne and W. Goodwin, *Bull. soc. chim. France*, [3] **31**, 854 (1904); E. Montgomery and C. S. Hudson, THIS JOURNAL, **56**, 2463 (1934).

[12] E. Pacsu, *Ber.*, **61**, 137 (1928).

[13] M. L. Wolfrom and D. Husted, THIS JOURNAL, **59**, 364 (1937).

mannopyranosyl bromide with moist acetone and silver carbonate.

Acknowledgment.—We are indebted to Mr. William C. Alford, Mrs. Margaret M. Ledyard and Mrs. Evelyn G. Peake for analytical determinations incident to this research.

Experimental[14]

α-D-Glucopyranose Pentabenzoate.—By a procedure similar to that employed previously for the preparation of β-D-ribopyranose tetrabenzoate,[7] anhydrous α-D-glucose was benzoylated at 0–4°. The crude product (50% yield) obtained from absolute ethanolic solution showed m. p. 179–188° and rotated +128.5° in chloroform; recrystallized twice from a warm mixture of 58 parts of acetone and 34 parts of water the α-D-glucopyranose pentabenzoate melted at 190–191° and rotated +136.8° in chloroform (*c*, 2.1). Further recrystallization failed to change these values. Levene and Meyer[15] reported a melting point of 187° and a rotation in chloroform of +138.5° for this substance.

β-D-Glucopyranose Pentabenzoate.—A procedure similar to that reported previously for the preparation of α-D-arabinopyranose tetrabenzoate[16] was used. Twenty grams of D-glucose in 240 ml. of dry pyridine was heated on the steam-bath for thirty minutes and on cooling 80 ml. of benzoyl chloride was added. The reaction flask was heated for one hour at 60°; 10 ml. of water was added to the cooled contents and ten minutes later an additional 100 ml. of water, after which the mixture was immediately poured into 2 l. of cold water. On kneading the resulting gum in fresh water, it crystallized; the pulverized material, soaked overnight in 75 ml. of methanol, yielded 74 g. (96%) of dry product which showed a rotation in chloroform of +57°. Recrystallization from ten parts of glacial acetic acid afforded a 61% recovery of almost pure β-D-glucopyranose pentabenzoate rotating in chloroform +25.4°. A second recrystallization from aqueous acetone gave the pure compound showing a rotation in chloroform of +24.2° (*c*, 2.6); further recrystallization failed to change this value. After drying at 120°, the substance sintered at 160° and melted at 185–192°; upon heating at 150° overnight, it melted at 189–192° without preliminary sintering. Fischer and Freudenberg[17] reported that β-D glucopyranose pentabenzoate sintered slightly at 155°, melted completely at 187° and showed a rotation of +24.03° in chloroform. Levene and Meyer[15a] obtained a similar rotation but found the melting point to be 157°.

α-D-Glucopyranose Pentabenzoate from β-D-Glucopyranose Pentabenzoate. (a) Using Stannic Chloride in Chloroform Solution.—Three grams (0.0043 mole) of β-D-glucopyranose pentabenzoate, dissolved in 16 ml. of freshly prepared absolute chloroform, was treated with 0.50 ml. (0.0043 mole) of stannic chloride and heated at reflux temperature for five hours. The solution was then washed successively with ice water, sodium bicarbonate solution and ice water, dried over sodium sulfate and, after treatment with carbon, concentrated *in vacuo* (45° bath) to a sirup. Solution of this residue in 85 ml. of warm methanol led to the spontaneous crystallization of 1.55 g. of material melting at 123–134° and showing a rotation of +105° in absolute chloroform. Recrystallization, first from 10 parts of 96% aqueous acetic acid and then from 33 parts of 80% aqueous acetone, gave 0.23 g. (8%) of pure α-D-glucopyranose pentabenzoate m. p. 190–191° and rotating +139° in chloroform. A mixed melting point with authentic material was undepressed.

(b) By Fusion with Anhydrous Zinc Chloride and Benzoic Acid.—Two grams of zinc chloride (Merck reagent grade, "95% minimum assay") was fused in a lightly corked flask and, at a temperature of 130–150°, 20 g. of benzoic acid was dissolved therein. Twenty grams of pure β-D-glucopyranose pentabenzoate was then added and heating continued for thirty minutes at 125–132°. The dark reddish-brown reaction mixture was dissolved in 70 ml. of pyridine and the crude product precipitated by the addition of 400 ml. of water. After standing for thirty minutes the crystalline product was washed successively with water, half-saturated aqueous sodium bicarbonate solution and again with water; recrystallization from 1 liter of hot absolute ethanol with the use of decolorizing carbon gave 11.25 g. (56%) of material rotating +110° in chloroform. Repeated fractional recrystallization of this material from aqueous acetic acid and aqueous acetone gave 4.95 g. (25%) of pure α-D-glycopyranose pentabenzoate rotating +136° in chloroform and melting at 190–191° either alone or when mixed with authentic α-D-glucopyranose pentabenzoate.

2,3,4,6-Tetrabenzoyl-α-D-glucopyranosyl Bromide (III).—A procedure similar to that employed by Fletcher and Hudson[18] for the preparation of the D-xylose analog was used. Pure α-D-glucopyranose pentabenzoate (5.65 g.) was dissolved in 6 ml. of ethylene dichloride and treated with 5.8 ml. of glacial acetic acid which had previously been saturated with hydrogen bromide at 0°. After two hours at room temperature, the reaction mixture was diluted with 40 ml. of toluene and then concentrated *in vacuo* (45–50° bath). The toluene treatment was repeated and then 20 ml. of dry ether was evaporated *in vacuo* from the mixture to give a sticky crystalline mass which, recrystallized from a mixture of 50 ml. of ether and 75 ml. of pentane at 0°, gave 4.76 g. (90%) of needle-shaped material melting at 129–130°. Recrystallization from a mixture of 27 parts of ether and 74 parts of pentane gave with negligible loss a pure product with the same melting point and a rotation in dry chloroform of +123.6° (*c*, 2.15). Its rotation in toluene of +149.3° (*c*, 2.14) is in agreement with that obtained by Maurer and Böhme.[15b] The β-D-anomer served equally well for this preparation.

Methyl β-D-Glucopyranoside Tetrabenzoate (IV) from 2,3,4,6-Tetrabenzoyl-α-D-glucopyranosyl Bromide (III).—Pure 2,3,4,6-tetrabenzoyl-α-D-glucopyranosyl bromide (2.50 g.) was dissolved in 300 ml. of commercial anhydrous methanol by warming gently for a few minutes and then held at 0°. After two days some of the bromide which had crystallized out was redissolved by warming and a further 50 ml. of methanol added. On the third day, seeding with authentic methyl β-D-glucoside tetrabenzoate caused crystallization to begin. After four days a total of 2.08 g. (90%) of material was obtained in the form of needles melting at 161–162°[19]; recrystallized twice from 5 parts of alcohol and then from a 1:10 acetone–ether mixture, the methyl β-D-glucopyranoside tetrabenzoate showed a rotation in chloroform of +29.1° (*c*, 2.02) and melted at 163–164° either alone or in admixture with authentic methyl β-D-glucopyranoside tetrabenzoate.[17b,20]

Stability of Methyl α-D-Glucopyranoside Tetrabenzoate (IV) in Methanolic Hydrogen Bromide at 20°.—Methyl α-D-glucopyranoside tetrabenzoate was prepared through the benzoylation of methyl α-D-glucopyranoside; the compound was found to melt at 105–108° and show a rotation of +84° in chloroform (*c*, 0.95). Helferich and Becker[21] reported a melting point of 105° for the substance but apparently did not measure its specific rotation.

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(14) Melting points were taken with an Anschütz-type thermometer completely immersed in the bath liquid. Rotations are specific rotations for the D line of sodium at 20°; concentration is expressed in g. of substance per 100 ml. of solution.

(15) (a) P. A. Levene and G. M. Meyer, *J. Biol. Chem.*, **76**, 513 (1928); (b) K. Maurer and R. Böhme, *Ber.*, **69**, 1399(1936).

(16) H. G. Fletcher, Jr., and C. S. Hudson, THIS JOURNAL, **69**, 1145 (1947).

(17) (a) E. Fischer and K. Freudenberg, *Ber.*, **45**, 2709 (1912); (b) E. Fischer and B. Helferich, *Ann.*, **383**, 68 (1911).

(18) H. G. Fletcher, Jr., and C. S. Hudson, THIS JOURNAL, **69**, 921 (1947).

(19) On one occasion, clear rhombohedral plates formed among the needles; these rotated +29.8° in chloroform and on recrystallization yielded only the needles characteristic of methyl β-D-glucopyranoside tetrabenzoate.

(20) K. Josephson, *Ber.*, **62**, 317 (1929).

(21) B. Helferich and J. Becker, *Ann.*, **440**, 1 (1924).

In view of the low solubility of methyl α-D-glucopyranoside tetrabenzoate in pure methanol, a mixture of 1,4-dioxane and methanol in the proportion of 1:9 was employed in ascertaining the stability of the substance toward methanolic hydrogen bromide. The methyl α-D-glucopyranoside tetrabenzoate (0.4752 g.) was dissolved in 5.00 ml. of purified 1,4-dioxane and diluted to 50.0 ml. with 0.0178 *N* hydrogen bromide in methanol. The resulting concentration of hydrogen bromide was of the same order of magnitude as that produced when an equivalent quantity of 2,3,4,6-tetrabenzoyl-α-D-glucopyranosyl bromide is allowed to react with methanol under similar circumstances. The first polarimetric observation yielded a calculated specific rotation of +95°; over a period of four weeks at 20° no change was observable polarimetrically.

In an experiment comparable with the above, 0.5133 g. of 2,3,4,6-tetrabenzoyl-α-D-glucopyranosyl bromide was dissolved in 5.00 ml. of purified 1,4-dioxane, the solution made up to 50.0 ml. with methanol, and observed polarimetrically at 20°. A plot of the observed rotation of the resulting solution against time gave a curve which showed the reaction to be of the pseudo-unimolecular type and indicated that conversion to methyl β-D-glucopyranoside tetrabenzoate was 90% complete after fifty hours under these conditions.

2,3,4,6-Tetrabenzoyl-α-D-glucopyranosyl Chloride.—A procedure similar to that employed by Pacsu[9] for the preparation of acetylated glycosyl chlorides was employed. β-D-Glucopyranose pentabenzoate[22] (16 g.) was dissolved in 90 ml. of absolute chloroform and treated with a solution of 2.5 ml. (1 molar equivalent) of titanium tetrachloride in 5 ml. of absolute chloroform. After four hours at 60°, the orange-colored solution was diluted with ethylene dichloride and washed successively with ice water, sodium bicarbonate solution and water. After removal of water with sodium sulfate, and concentration *in vacuo* (45° bath) to a thick sirup, the material was dissolved in 70 ml. of absolute ether and the solution brought to supersaturation with pentane. On seeding,[23] 10.8 g. (77%) of crystalline material melting at 114–117° was obtained. Recrystallization from 1:1 ether–pentane gave, with negligible loss, large radial masses of needles melting at 116–118° and showing in absolute chloroform a rotation of +109° (*c*, 0.98).

2,3,4,6-Tetrabenzoyl-α-D-glucopyranosyl chloride is soluble in ether, acetone, benzene, ethyl acetate, chloroform and carbon tetrachloride, slightly soluble in methanol and practically insoluble in water and petroleum ether.

Anal. Calcd. for $C_{34}H_{27}O_9Cl$: C, 66.39; H, 4.43; Cl, 5.77. Found: C, 66.65; H, 4.76; Cl, 6.01.

Methyl β-D-Glucopyranoside Tetrabenzoate (IV) from 2,3,4,6-Tetrabenzoyl-α-D-glucopyranosyl Chloride.—A solution of 1.01 g. of 2,3,4,6-tetrabenzoyl-α-D-glucopyranosyl chloride in 20 ml. of methanol was boiled under reflux for sixteen hours, care being taken to exclude atmospheric moisture. On seeding the cooled solution, 0.504 g. (48%) of material with a rotation of +33° ($CHCl_3$) crystallized out. Two recrystallizations from methanol and one from alcohol gave 0.38 g. (38%) of methyl 2,3,4,6-tetrabenzoyl-β-D-glucoside, identified by its rotation in chloroform of +30° (*c*, 1.19) and the fact that its melting point of 161–162° was undepressed when the substance was mixed with authentic material.

2,3,4,6-Tetrabenzoyl-α-D-glucopyranosyl Iodide.—A solution of 4.32 g. of β-D-glucopyranose pentabenzoate in 10 ml. of ethylene dichloride was treated with 10 ml. of a cold solution of hydrogen iodide in glacial acetic acid which had been made by the cautious addition of 26.4 ml. of hydriodic acid (55–58%, sp. gr. 1.7) to 100 ml. of cold acetic anhydride. After one hour at room temperature the solution was diluted with ethylene dichloride and washed successsively with ice water, cold saturated sodium bicarbonate solution, aqueous sodium thiosulfate and finally ice water. After desiccation with sodium sulfate and removal of solvent under reduced pressure (35° bath) the material was dissolved in absolute ether and reconcentrated to a volume of about 20 ml. When crystallization had begun, an equal volume of pentane was added; the first crop of material thus obtained (3.34 g.) was augmented by a second slightly less pure fraction, making the total yield of crude product 3.68 g. or 84%. The first crop was dissolved in dry chloroform, concentrated *in vacuo* to a sirup and dissolved in 20 ml. of absolute ether. The needle-like crystals which formed melted at 141–142° and showed a rotation in dry chloroform of +139.5° (*c*, 1.00). A second recrystallization did not alter these constants.

The iodide is readily soluble in chloroform, acetone, ethyl acetate and benzene, less soluble in carbon tetrachloride and glacial acetic acid, very slightly soluble in ether and methanol and insoluble in petroleum ether and water. When stored over sodium hydroxide at −5°, it showed no sign of decomposition over the course of a month; at room temperature, however, it gradually darkened.

Anal. Calcd. for $C_{34}H_{27}O_9I$: C, 57.80; H, 3.85; I, 17.97. Found: C, 57.99; H, 3.66; I, 17.88.

β-D-Mannopyranose Pentabenzoate.—β-D-Mannose was benzoylated at −10 to −5° in pyridine solution in a manner similar to that employed by Fischer and Oetker[6] to give pure β-D-mannopyranose pentabenzoate (86% yield) melting at 161–162° and showing in chloroform a specific rotation of −82.0° (*c*, 2.8). Fischer and Oetker reported a melting point of 161–161.5° and rotations in chloroform of −80.44° and −80.7° for β-D-mannopyranose pentabenzoate.

α- and β-D-Mannopyranose Pentabenzoates.—The benzoylation of 5 g. of D-mannose in dry pyridine solution with 20 ml. (6.2 moles) of benzoyl chloride was conducted in a manner similar to that used for the preparation of β-D-glucopyranose pentabenzoate. After the methanol treatment, 18.4 g. (95%) of material having a specific rotation in chloroform of −34.1° was obtained. The isolation of α-D-mannopyranose pentabenzoate from this crude material was accomplished by dissolving 5 g. in a mixture of 10 ml. of acetone and 10 ml. of methanol. After standing overnight the mixture was diluted with 10 more ml. of methanol and two hours later 2.3 g. of crude crystalline α-D-mannopyranose pentabenzoate, melting at 150–152° and showing a rotation of −19.3° in chloroform, was removed by filtration. The filtrate gave spontaneously a second fraction (0.46 g.) of the impure α-D-isomer. After treatment with an additional 12 ml. of methanol the mother liquor afforded a third fraction (0.56 g.) showing a rotation in chloroform of −67°. Recrystallization of the first fraction from 35 parts of absolute alcohol yielded 2.08 g. (corresponding to a yield of 40%) of pure α-D-mannopyranose pentabenzoate melting at 152–153° and showing a rotation in chloroform of −18.6° (*c*, 1.6). The compound is soluble in chloroform, acetone, ethyl acetate and benzene, slightly soluble in carbon tetrachloride and glacial acetic acid, difficultly soluble in alcohol and ether and practically insoluble in water and petroleum ether.

Anal. Calcd. for $C_{41}H_{32}O_{11}$: C, 70.28; H, 4.60. Found: C, 70.20; H, 4.88.

Recrystallization of the third fraction from 27 parts of absolute alcohol gave 0.33 g. (corresponding to a yield of 6.3%) of pure β-D-mannopyranose pentabenzoate which possessed a specific rotation of −81.0° in chloroform and melted at 160–161°. Both carbon tetrachloride and acetic acid were also used for the separation of the anomeric pentabenzoates but proved less satisfactory for this purpose than the acetone–methanol mixture.

α-D-Mannopyranose Pentabenzoate from Methyl α-D-Mannopyranoside Tetrabenzoate.—The methyl α-D-mannopyranoside tetrabenzoate, which was prepared in 93% yield through the direct benzoylation of methyl α-D-

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[22] Polarimetric observations at 20° indicate that the α-anomer reacts much more slowly with titanium tetrachloride than does the β-form.

[23] The first crystallization occurred while a sample of the sirup was being dissolved in warm methanol.

mannopyranoside,[24] melted at 136–137° and rotated in chloroform −67.5° (*c*, 3.1). To a mixture of 0.5 g. of freshly fused zinc chloride, 6.0 g. of benzoic anhydride and 3.0 g. of benzoic acid which had been heated at 145° until homogeneous and then cooled to 100°, 3.0 g. of the tetrabenzoate was added. After three hours at 100°, the dark, opaque melt was cooled, dissolved in a mixture of 20 ml. of pyridine and 10 ml. of water and heated on the steam-bath for twenty minutes to decompose the benzoic anhydride. Excess water was then added and the sirup thus precipitated was treated again with pyridine and water. After reprecipitation with water, the sirup was dissolved in 10 ml. of boiling absolute alcohol and the solution filtered through decolorizing carbon. Clear, rhombohedral prisms (2.08 g., 61%) melting at 147–149° and showing a rotation of −22.0° in chloroform, formed spontaneously within five minutes. Two recrystallizations from 18 parts of 1:5 acetone–methanol and one from 50 parts of absolute alcohol gave flat, elongated prisms which melted at 152–153° and showed a rotation in chloroform of −18.8° (*c*, 1.77). The melting point was undepressed upon admixture with a sample of α-D-mannopyranose pentabenzoate prepared directly from D-mannose.

2,3,4,6-Tetrabenzoyl-α-D-mannopyranosyl Bromide (V).—A solution of 4.0 g. of β-D-mannopyranose pentabenzoate[25] in 8 ml. of ethylene dichloride was treated with 8 ml. of a saturated solution of hydrogen bromide in glacial acetic acid and left for 2.5 hours at room temperature. The solution was then diluted with ethylene dichloride and washed, twice with ice water, once with cold sodium bicarbonate solution and again with ice water. Moisture was removed with sodium sulfate, the solution filtered through decolorizing carbon and the solvent removed *in vacuo* at 45°. Numerous attempts to obtain crystalline material from the residual sirup failed; on drying *in vacuo* over solid sodium hydroxide a sample of the material became an amorphous powder which showed in dry chloroform solution a specific rotation of +11.7° (*c*, 2.8).

Methyl α-D-Mannopyranoside Tetrabenzoate (VI) from β-D-Mannopyranose Pentabenzoate *via* the Amorphous 2,3,4,6-Tetrabenzoyl-α-D-Mannopyranosyl Bromide (V).—The initial part of the above preparation was repeated and the reaction mixture, after standing at room temperature for 2.5 hours, was diluted with 100 ml. of toluene. The solution was concentrated at 45° *in vacuo* and the sirup redissolved in 50 ml. of toluene and reconcentrated. This toluene treatment was repeated once again and the resulting sirup was dissolved at room temperature in 60 ml. of commercial anhydrous methanol. After sixteen hours at room temperature the solution was cooled in the refrigerator and the crystalline precipitate (2.40 g., 69%) removed by filtration. A second crop of less pure material (0.13 g.) was later obtained. Recrystallization of the first crop from 40 parts of methanol yielded 2.09 g. of pure methyl α-D-mannopyranoside tetrabenzoate rotating in chloroform −67.5° (*c*, 2.5) and melting at 134–136° either alone or in admixture with authentic material prepared through the benzoylation of methyl α-D-mannopyranoside.

On one occasion when the above preparation was carried out with methanol which apparently contained more water than usual, the yield of methyl α-D-mannopyranoside tetrabenzoate was only 44% and there was obtained in addition a 26% yield of crystalline material melting at 167–175°. After two recrystallizations from a mixture of benzene and pentane and two more from methanol, the substance was obtained as clear prismatic crystals rotating −81.9° (*c*, 1.16, $CHCl_3$) and melting at 182–184° either alone or in admixture with the authentic 2,3,4,6-tetrabenzoyl-D-mannopyranose whose preparation is described below.

2,3,4,6-Tetrabenzoyl-D-mannopyranose.—Amorphous 2,3,4,6-tetrabenzoyl-α-D-mannopyranosyl bromide (1.61 g.) was dissolved in a mixture of 16 ml. of acetone and 1.2 ml. of water. Silver carbonate (1.16 g.) was added and the suspension shaken mechanically for seventy-five minutes. The solution was filtered through a filter precoated with carbon and then concentrated *in vacuo* (30° bath) to a thick sirup which crystallized spontaneously when warmed with "Skellysolve E" (b. p. 100–140°). The crystalline material (1.0 g., 69%) melted at 179–183° and showed a rotation in chloroform of −84.4°. Two recrystallizations from 4.5 parts of methanol resulted in large, clear prisms melting at 182–184° and showing in chloroform a rotation of −82.6° (*c*, 1.04) (no mutarotation in seven days).

Anal. Calcd. for $C_{34}H_{28}O_{10}$: C, 68.45; H, 4.73. Found: C, 68.44; H, 4.91.

Methyl β-D-Mannopyranoside Tetrabenzoate.—Methyl β-D-mannopyranoside tetraacetate[26] (2.99 g., m. p. 161–162°, $[\alpha]^{20}\mathrm{D}$ −49.5° (chloroform, *c*, 1.1)) was dissolved in 20 ml. of warm anhydrous methanol, cooled and treated with 1.3 ml. of 2 *N* barium methoxide. After twenty-one hours at room temperature, the solution was concentrated *in vacuo* (35°) to a sirup which was then dissolved in 20 ml. of dry pyridine. This solution was cooled in an ice-bath, slowly treated with 12 ml. of benzoyl chloride and then held at 60° for 2.5 hours. Chloroform was added and the resulting solution washed successively with ice water, cold 3 *N* sulfuric acid, cold sodium bicarbonate solution and finally water. Moisture was removed with sodium sulfate, the solution filtered through decolorizing carbon and the light brown filtrate concentrated *in vacuo* at 45° to a sirup. Several 25-ml. batches of absolute alcohol were successively evaporated from the sirup and it was then dissolved in 50 ml. of methanol. Crystallization was spontaneous, the thin, elongated hexagonal plates (4.07 g., 81%) melting at 146–147° and showing a rotation in chloroform of −153° (*c*, 1.1). Subsequent recrystallizations from 13 parts of alcohol, from 10 parts of 1:2 acetone–pentane and from 33 parts of methanol did not significantly change the specific rotation, but increased the melting point to 148–149°.

Anal. Calcd. for $C_{35}H_{30}O_{10}$: C, 68.84; H, 4.95. Found: C, 68.94; H, 5.20.

2,3,4,6-Tetrabenzoyl-α-D-mannopyranosyl Chloride.—The method devised by Pacsu[9] for the preparation of acetylated aldosyl chlorides was employed. β-D-Mannopyranose pentabenzoate (5 g.) and titanium tetrachloride (0.79 ml.) dissolved in 23 ml. of dry chloroform were heated at 60° for six hours. The reaction mixture was then worked up in the usual manner to give a sirup which could not be induced to crystallize. In the vacuum desiccator, however, it became a friable, amorphous solid showing a rotation in dry chloroform of −30.5°. An attempt to prepare the substance by treating β-D-mannopyranose pentabenzoate with glacial acetic acid saturated with hydrogen chloride for three hours at room temperature led to the recovery of much unreacted pentabenzoate and no other crystalline product.

2,3,4,6-Tetrabenzoyl-α-D-mannopyranosyl Iodide.—A solution of 5 g. of β-D-mannopyranose pentabenzoate in 5 ml. of ethylene dichloride and 15 ml. of a solution of hydrogen iodide in glacial acetic acid (prepared as described above for the preparation of the D-glucose analog of this compound) was allowed to stand at room temperature for two hours. The product, purified in the same fashion as described for its D-glucose analog, was repeatedly precipitated from ether solution by the addition of pentane and then dried *in vacuo* to give an amorphous mass showing a rotation in dry chloroform of +45° (*c*, 0.71).

Summary

2,3,4,6-Tetrabenzoyl-α-D-glucopyranosyl bromide has been shown to react readily with meth-

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[24] W. T. Haskins, R. M. Hann and C. S. Hudson, THIS JOURNAL, **68**, 628 (1946).

[25] Polarimetric studies showed that, while the action of hydrogen bromide in glacial acetic acid on β-D-mannopyranose pentabenzoate is essentially complete in forty-five minutes, some fifteen hours are required before the rotation of the α-D-isomer becomes constant under these conditions.

[26] J. K. Dale, THIS JOURNAL, **46**, 1046 (1924).

anol to give methyl β-D-glucopyranoside tetrabenzoate in high yield, inversion of configuration having taken place at carbon atom one. In a similar fashion 2,3,4,6-tetrabenzoyl-α-D-mannopyranosyl bromide has been found to give methyl-α-D-mannopyranoside tetrabenzoate, without inversion at carbon one.

2,3,4,6-Tetrabenzoyl-α-D-glucopyranosyl chloride and iodide have been prepared in crystalline form.

Rearrangement of β-D-glucopyranose pentabenzoate to α-D-glucopyranose pentabenzoate has been carried out by the action of stannic chloride in absolute chloroform and through fusion with zinc chloride and benzoic acid.

Crystalline α-D-mannopyranose pentabenzoate has been prepared both by benzoylation of D-mannose which had been heated in dry pyridine and by fusion of methyl α-D-mannopyranoside tetrabenzoate with a mixture of anhydrous zinc chloride, benzoic anhydride and benzoic acid.

2,3,4,6-Tetrabenzoyl-α-D-mannopyranosyl chloride and iodide have been obtained as partially purified amorphous solids and their specific rotations measured.

Methyl β-D-mannopyranoside tetrabenzoate and 2,3,4,6-tetrabenzoyl-D-mannose have both been obtained in crystalline form.

BETHESDA, MARYLAND RECEIVED NOVEMBER 21, 1949

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

β-Alkoxy- and Aryloxypropionates

BY C. E. REHBERG AND MARION B. DIXON

Earlier papers from this Laboratory described *n*-alkyl β-ethoxypropionates,[2] *n*-alkyl β-*n*-alkoxypropionates[3] and a group of β-alkoxypropionates of various types.[4]

The present paper, which concludes this series, describes the addition of various alcohols and phenols to the olefinic group in acrylic esters and the alcoholysis of some of the resulting ether-esters. Table I shows the new compounds and their characteristics.

It was of interest that phenols reacted better than most primary alkanols of comparable molecular weight.[3] Furfuryl alcohol and 2-ethoxyethanol also reacted satisfactorily.

From this and previously reported studies it may be concluded that most unhindered primary alkanols and phenols readily add to acrylic esters, the activity being less with compounds of higher molecular weight. Secondary alcohols are generally less reactive than the primary ones. Tertiary alcohols appear to be unreactive.

Alcoholysis of lower alkyl esters of ether-acids is a convenient way to prepare higher esters, as may be seen from the yields in Table I.

TABLE I

PREPARATION, PROPERTIES AND ANALYSES OF ESTERS, $ROCH_2CH_2COOR'$

R	R′	Yield, %	Boiling point °C.	Boiling point Mm.	n^{20}_D	d^{20}_4	Mol. refraction Calcd.	Mol. refraction Found	Sapn. equiv. Calcd.	Sapn. equiv. Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Methyl	Isobutyl	44^a	88	29	1.4128	0.9349	42.44	42.70	160.2	161.3	60.0	59.9	10.1	10.1
Methyl	3-Chloropropyl	78^b	82	2	1.4402	1.1207	42.69	42.50	...	...	46.5	47.0	7.3	7.5
Ethyl	3-Chloropropyl	75^b	80	1	1.4400	1.0843	47.31	47.33	...	...	49.3	49.0	7.8	7.8
Ethyl	2-Chloroallyl	84^b	45	0.4	1.4448	1.0952	46.85	46.84	192.6	182.7	49.9	49.7	6.8	6.7
Phenyl	Ethyl	53^a	92	.7	1.5002	1.0745	52.69	53.17	194.2	188.6	68.0	68.0	7.3	7.6
Phenyl	Methyl	59^a	85	.4	1.5071	1.1076	48.08	48.44	180.2	171.4	66.6	66.3	6.7	6.8
p-Cresyl	Methyl	37^a	91	.4	1.5061	1.0811	52.69	53.37	...	...	68.0	68.1	7.3	7.3
o-Cresyl	Methyl	52^a	92	.8	1.5042	1.0797	52.69	53.27	194.2	190.5	68.0	67.8	7.3	7.2
Methyl	2-Ethoxyethyl	86^a	92	6	1.4225	1.0094	44.08	44.40	176.2	175.5	54.5	54.4	9.1	8.9
Methyl	2-Phenoxyethyl	53^b	112	0.2	1.5010	1.1118	58.96	59.44	224.3	223.5	64.2	64.2	7.2	7.2
Methyl	Tetrahydrofurfuryl	68^b	74	0.3	1.4459	1.0796	46.50	46.47	188.2	189.2	57.4	56.6	8.6	8.5
Furfuryl	Methyl	30^a	127	12	1.4693	1.1278	45.57	45.52	184.2	191.5	58.7	58.5	6.6	6.5
2-Ethoxyethyl	Methyl	57^a	70	1.2	1.4232	1.0128	44.08	44.32	176.2	172.4	54.5	54.6	9.1	8.9
2-Ethoxyethyl	2-Ethoxyethyl	57^a	96	0.2	1.4307	1.0114	59.58	59.93	234.3	235.9	56.4	56.3		
n-Butyl	2-Methoxyethyl	87^b	68	.5	1.4253	0.9719	53.32	53.79	204.3	203.3	59.0	58.6	9.9	9.9
n-Butyl	2-Butoxyethyl	62^b	100	.5	1.4298	0.9415	67.17	67.54	246.3	244.5	63.4	63.4	10.6	10.3
Ethyl	2-(2-Chloroethoxy)-ethyl	79^b	96	.3	1.4451	1.1153	53.57	53.64	112.4	113.6	48.1	47.9	7.6	7.6

^{a} Made by the addition of alcohol to the acrylic ester. ^{b} Made by the alcoholysis of $ROCH_2CH_2COOR$ where R = CH_3, C_2H_5 or C_4H_9.

The detailed procedures used in the present work have been described in an earlier paper.[4]

Summary

Seventeen esters of β-alkoxy- and β-aryloxypropionic acids have been prepared by (a) addition

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[1] One of the Laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. Article not copyrighted.

[2] Dixon, Rehberg and Fisher, THIS JOURNAL, **70**, 3733 (1948).

[3] Rehberg, Dixon and Fisher, *ibid.*, **69**, 2966 (1947).

[4] Rehberg, Dixon and Fisher, *ibid.*, **68**, 544 (1946).