Cleavage with Phenol.—The same procedure was followed as for naphthalene, using 257 g. (2.7 moles) of phenol, 150 g. (1 mole) of benzyl *n*-propyl ether and 34 g. (0.5 mole) of boron fluoride. Distillation gave 159 g. of unreacted phenol and a fraction which distilled at 161–165° at 5 mm. After crystallization from petroleum ether this product melted at 83–84°, checking the melting point of *p*-benzylphenol.[9] The yield was 87.7 g. (47.7%).

Cleavage with both Benzene and Acetic Acid.—To a solution of 95 g. of benzene (1.2 moles) and 80 g. of acetic acid (1.4 moles) was added 31 g. (0.45 mole) of boron fluoride. One mole (150 g.) of benzyl *n*-propyl ether was added slowly and the mixture refluxed for two hours before being washed and dried. Distillation yielded 51 g. (50%) of *n*-propyl acetate, 34.5 g. (20.6%) of benzylbenzene, and 37 g. (28.6%) of dibenzylbenzene. These products were identified as in the preceding experiments.

Cleavage with both Benzene and Acetic Anhydride.—The procedure was the same as in the preceding experiment. The amounts of reagents were as follows: 312 g. (4 moles) of benzene, 204 g. (2 moles) of acetic anhydride, 48 g. (0.7 mole) of boron fluoride, and 150 g. (1 mole) of benzyl *n*-propyl ether. Yields were 66 g. (64.7%) of *n*-propyl acetate, 81 g. (48.3%) of benzylbenzene, and 30 g. (23.2%) of dibenzylbenzene.

Reaction with Ethyl Acetoacetate.—Boron fluoride was passed into a solution of 262 g. (2 moles) of ethyl acetoacetate and 150 g. (1 mole) of benzyl *n*-propyl ether until 32.3 g. (0.48 mole) was absorbed. After treatment as above distillation yielded 147 g. distilling at 48–60° at 5–8 mm., $n^{20}D$ 1.4398 to 1.4845 (identified as a mixture of unreacted ethyl acetoacetate and benzyl *n*-propyl ether); 22.2 g. at 125–135° at 3 mm., $n^{20}D$ 1.4998 to 1.5178 (which yielded, from ammonium hydroxide in acetone solution, leaflet crystals[10] melting at 97–100°); 19.3 g. at 140–160° at 3 mm., $n^{20}D$ 1.5248 to 1.5291 (which gave no solid derivative with ammonium hydroxide in acetone or with ammonia). When the experiment was repeated without the benzyl *n*-propyl ether fractions were obtained distilling at 123–130° at 3 mm., $n^{20}D$ 1.5040 to 1.5135 (which yielded, from ammonium hydroxide in acetone solution, leaflet crystals melting at 97–99°); and at 140–170° at 3 mm., $n^{20}D$ 1.5085 (which gave no solid product with ammonium hydroxide in acetone solution or with liquid ammonia).

(9) Zincke and Walter, *Ann.*, **334**, 367 (1904).

(10) Ethyl α-benzylacetoacetate boils at 155–167° at 12 mm. and yields an amide, m. p. 149–150° (ref. 5).

NOTRE DAME, INDIANA RECEIVED MARCH 5, 1941

Summary

The alkylation of acetic acid, acetic anhydride, benzene, naphthalene and phenol with benzyl *n*-propyl ether in the presence of boron fluoride has been studied. Ethyl acetoacetate did not alkylate under the conditions employed.

A mechanism for the alkylation reactions has been suggested based on the cleavage of the benzyl *n*-propyl ether into a positive benzyl fragment and a negative *n*-propoxyl ion.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

Synthesis of the Epimer of Cellobiose (4-[β-D-Glucopyranosido]-D-mannose)[1]

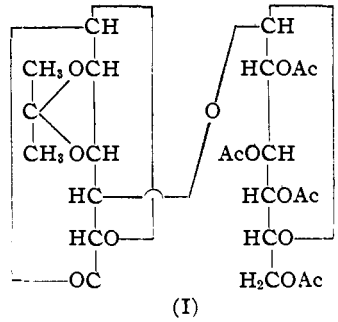
BY W. T. HASKINS, RAYMOND M. HANN AND C. S. HUDSON

Attention was recently[2] directed to the possibility of using 2,3-isopropylidene-D-mannosan-<1,5>β<1,6> (or, in short, acetone-D-mannosan) for the synthesis of disaccharides which are linked through carbon atom four of D-mannose. The present article describes the synthesis of the epimer of cellobiose, namely, 4-[β-D-glucopyranosido]-D-mannose, the disaccharide which was first prepared synthetically from cellobiose through cellobial by Bergmann and Schotte.[3] Acetobromo-D-glucose, by slight modification of the conditions for disaccharide synthesis described by Reynolds and Evans, condenses with acetone-D-mannosan to form in about 25 to 30% yield the crystalline 2,3-isopropylidene-4-[2,3,4,6-tetraacetyl-β-D-glucosido]-D-mannosan<1,5>β<1,6> (I), which upon treatment with boiling 80% acetic acid loses the isopropylidene residue and forms 4-[2,3,4,6-β-tetraacetyl-D-glucosido]-D-mannosan (II). The latter compound readily acetylates by usual methods to form 2,3-diacetyl-4-[2,3,4,6-tetraacetyl-β-D-glucosido]-D-mannosan<1,5>β<1,6> (III). The 1,6-mannosan ring of this anhydro disaccharide is readily ruptured, with concurrent acetylation on carbon atoms one and six, upon treating the compound with an acid acetylating mixture, the product being the well known α-octaacetate of 4-β-D-glucopyranosido-D-mannose (IV). The octaacetate upon deacetylation with barium methylate yields the parent disaccharide, 4-β-D-glucopyranosido-D-mannose, in the form of the known well characterized monohydrate of the alpha form.

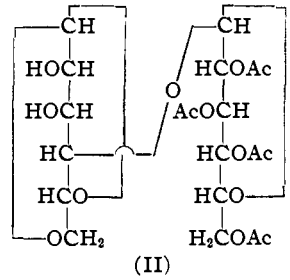
(1) Publication authorized by the Surgeon General, U. S. Public Health Service. (Not copyrighted.)

(2) Knauf, Hann and Hudson, THIS JOURNAL, **63**, 1447 (1941).

(3) Bergmann and Schotte, *Ber.*, **54**, 1564 (1921).



(I)



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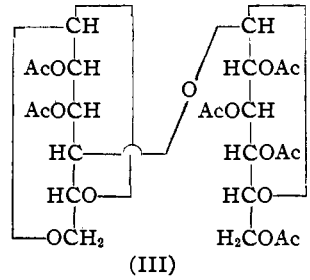
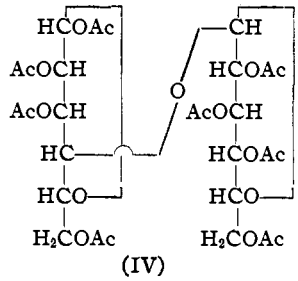


(III)



(IV)

We express our appreciation to Dr. Arthur T. Ness for performing the microchemical analyses in connection with this work.

Experimental

2,3-Isopropylidene-4-[2,3,4,6-tetraacetyl-β-D-glucosido]-D-mannosan<1,5>β<1,6>.—The coupling of 2,3-isopropylidene-D-mannosan<1,5>β<1,6> and acetobromoglucose was accomplished by the general method of Reynolds and Evans.[4] A number of modifications were studied and it was found that the best yields were obtained with the following procedure. A solution of 10.1 g. (0.05 mole) of isopropylidene-D-mannosan in 100 cc. of dry alcohol-free chloroform, 50 g. of "Drierite," 25 g. of silver oxide and 35 g. of glass beads (4 mm. diameter) in a brown 500-cc. glass-stoppered bottle were shaken on a machine for one hour to assure drying of the reagents; 2.5 g. of solid iodine and a solution of 20.6 g. (0.05 mole) of acetobromoglucose in 50 cc. of chloroform were then added and shaking resumed in a 20° constant temperature room; after five days of shaking, tests indicated no further decrease in ionizable halogen and the reaction mixture was filtered; the filtrate was concentrated *in vacuo* to a thick sirup which, upon solution in methyl alcohol and reconcentration, crystallized in fine needles; the solid mass was recrystallized from 35 cc. of methyl alcohol and yielded 6.5 to 8.5 g. (24 to 32%) of a product melting at 170–174° (cor.); recrystallization from ten parts of methyl alcohol gave a pure product melting at 176° (cor.) and rotating[5] −50.0° in chloroform (*c*, 0.8; *l*, 4); the pure compound, as would be expected from its mannosan structure, did not reduce boiling Fehling solution.

Anal. Calcd. for $C_{28}H_{32}O_{14}$: C, 51.88; H, 6.06; CH_3CO, 32.3; combined acetone, 10.9. Found: C, 51.81; H, 6.09; CH_3CO, 32.2; combined acetone, 11.0.

4-[2,3,4,6-Tetraacetyl-β-D-glucosido]-D-mannosan<1,5>β<1,6>.—A solution of 5.0 g. of 2,3-isopropylidene-4-[2,3,4,6-tetraacetyl-β-D-glucosido]-D-mannosan in 100 cc. of 80% acetic acid was heated for one hour on the steam-bath, during which period its rotation changed from −53° to a constant value of −72°. The solution was concentrated *in vacuo* to spontaneous crystallization, the crystalline magma dried by successive addition and evaporation of two 25-cc. portions of absolute alcohol, and then dissolved in 15 cc. of warm alcohol. Upon cooling the solution the desired deacetonated compound crystallized readily in a yield of 4.2 g. (91%). The material was recrystallized from four parts of alcohol or ten parts of water and separated in clusters of colorless needles which melted at 192–193° (cor.) and showed a rotation of −68.9° (*c*, 0.8; *l*, 4) in chloroform. The substance is slightly soluble in ether, petroleum ether, cold methyl or iso-amyl alcohols, toluene, or water, but dissolves readily in boiling methyl alcohol, toluene, or water. Its aqueous solution is devoid of reducing action on boiling Fehling solution.

Anal. Calcd. for $C_{20}H_{28}O_{14}$: C, 48.78; H, 5.73; CH_3CO, 35.0. Found: C, 48.95; H, 5.79; CH_3CO, 35.1.

2,3-Diacetyl-4-[2,3,4,6-tetraacetyl-β-D-glucosido]-D-mannosan<1,5>β<1,6>.—(1) A solution of 1.3 g. of 4-[2,3,4,6-tetraacetyl-β-D-glucosido]-D-mannosan in a mixture of 2 cc. of pyridine and 2 cc. of acetic anhydride was allowed to stand at room temperature overnight. The reaction mixture was then poured over crushed ice and the sirup which first separated gradually crystallized; yield, 0.7 g. The aqueous acetic acid solution was extracted with chloroform in the usual manner and yielded a further 0.7 g. of crystalline material; total yield 1.4 g. (93%). (2) A mixture of 4 g. of the tetraacetate, 1 g. of fused sodium acetate and 8 cc. of acetic anhydride was heated for one hour on the steam-bath, cooled and poured over crushed ice; 2.7 g. of crystalline material separated di-

(4) Reynolds and Evans, THIS JOURNAL, **60**, 2559 (1938).

(5) All rotations are specific rotations at 20° for sodium light; *c* is the concentration in grams in 100 cc. of solution; *l* is the tube length in decimeters; all substances were recrystallized to constant specific rotation.

rectly and the chloroform extract of the aqueous acetic acid yielded a further 1.8 g.; total yield, 4.5 g. (96%). The compound was recrystallized by solution in six parts of absolute alcohol and gradual addition of ten parts of isopentane; it separated in fine cottony needles which melted at 131–132° (cor.) and showed a rotation of −69.8° (*c*, 0.8; *l*, 4) in chloroform. The substance resembled the other mannosan compounds in its inability to reduce Fehling solution.

Anal. Calcd. for $C_{24}H_{32}O_{16}$: C, 50.00; H, 5.60; CH_3CO, 44.8. Found: C, 49.99; H, 5.71; CH_3CO, 45.1.

4-[β-D-Glucopyranosido]-D-mannose-α-octaacetate.—A solution of 3.6 g. of 2,3-diacetyl-4-[2,3,4,6-tetraacetyl-β-D-glucosido]-D-mannosan in 50 cc. of an acetolysis solution, prepared by adding 1 cc. of concd. sulfuric acid dropwise to an ice-cold mixture of 35 cc. of acetic anhydride and 15 cc. of acetic acid,[6] changed in rotation from +40.6° (after two minutes) to a constant value of +49.3° in two hours. The reaction mixture was poured into 200 g. of crushed ice and crystallization occurred almost at once; yield 3.8 g. (90%). The substance was recrystallized from thirty parts of methyl alcohol and separated in clusters of glistening needles which melted at 199–200° and showed a rotation of +36.5° (*c*, 0.8; *l*, 4) in chloroform. Brauns[7] reports a melting point of 202–203° and a rotation of +36.2° in chloroform. Isbell[8] reports a melting point of 203° and a rotation of +36.3°. A few crystals of the compound caused reduction of Fehling solution after boiling for four minutes.

Anal. Calcd. for $C_{28}H_{38}O_{19}$: C, 49.56; H, 5.64; CH_3CO, 50.7. Found: C, 49.59; H, 5.91; CH_3CO, 50.9.

4-[β-D-Glucopyranosido]-α-D-mannose Monohydrate.—A suspension of 3.0 g. of the octaacetate in 75 cc. of methyl alcohol was deacetylated by barium methylate in the usual manner. The disaccharide monohydrate was obtained in a yield of 1.5 g. (94%); it melted at 135–136° (cor.) and showed an equilibrium rotation of +5.8° (*c*, 2.0; *l*, 4) in water in agreement with the 137° and +5.9° reported by Isbell. Brauns gives a melting point of 139–140° and an equilibrium rotation of +5.8°. The course of its mutarotation is recorded in Table I.

Anal. Calcd. for $C_{12}H_{22}O_{11}\cdot H_2O$: C, 40.00; H, 6.71; H_2O, 5.00. Found: C, 40.07; H, 6.85; H_2O, 5.20.

(6) Hann and Hudson, THIS JOURNAL, **56**, 2465 (1934); Montgomery and Hudson, *ibid.*, **56**, 2463 (1934).

(7) Brauns, *ibid.*, **48**, 2784 (1926).

(8) Isbell, *J. Research Natl. Bur. Standards*, **5**, 1185 (1930).

TABLE I

MUTAROTATION OF 4-[β-D-GLUCOPYRANOSIDO]-α-D-MANNOSE MONOHYDRATE IN WATER

Concentration 0.5056 g. in 25 ml. of solution; tube length 4 dm.; $T = 20° \pm 0.5°$.

Time after making soln., min.	$[\alpha]^{20}D^{a}$ Monohydrate	Time, min.	$k_1 + k_2 \times 10^{-3}$
3	+11.1	0	..
4	10.9	1	16.7
5	10.7	2	17.1
10	10.1	7	13.0
15	9.4	12	14.0
20	8.8	17	14.5
25	8.3	23	14.2
30	8.1	27	13.4
45	7.3	42	13.0
60	6.6	57	14.4
90	6.0	87	16.3
120	6.0	117	..
∞	5.8	∞	Average 14.7

[a] Initial $[\alpha]^{20}D$ +11.8° (extrapolated). Reported values: Brauns, ref. 7, Initial (15′) +7.3 ⟶ +5.8°; Isbell, ref. 8, Initial (extrapolated) +14.64° ⟶ +5.88°; $k_1 + k_2 = 16.2 \times 10^{-3}$.

Summary

Acetobromo-D-glucose has been condensed with 2,3-isopropylidene-D-mannosan <1,5>β<1,6> to form 2,3-isopropylidene-4-[2,3,4,6-tetraacetyl-β-D-glycopyranosido]-D-mannosan <1,5>β<1,6>. The latter compound loses its acetone residue upon mild acid hydrolysis to yield 4-[2,3,4,6-tetraacetyl-β-D-glucopyranosido]-D-mannosan <1,5>β<1,6> which upon acetylation is converted to 2,3-diacetyl-4-[2,3,4,6-tetraacetyl-β-D-glucopyranosido]-D-mannosan <1,5>β<1,6>. Treatment of this hexaacetate with an acid acetylating mixture ruptures the 1,6-D-mannosan ring with an accompanying acetylation and produces the well known α-octaacetate of 4-β-D-glucopyranosido-D-mannose. The octaacetate, upon deacetylation, yields 4-β-D-glucopyranosido-D-mannose, the epimer of cellobiose.

WASHINGTON, D. C. RECEIVED APRIL 24, 1941