Carbohydrate Research
Elsevier Publishing Company, Amsterdam
Printed in Belgium

Note

Anomeric methyl 4-*O*-alkyl-D-glucopyranosides

J. N. BeMiller, Carol L. Collins, Elaine R. Doyle, and R. E. Wing*
Department of Chemistry, Southern Illinois University, Carbondale, Illinois 62901 (U. S. A.)
(Received July 2nd, 1970)

The method used for preparing malto-oligosaccharides[1] substituted at only one hydroxyl group of the nonreducing end-unit has now been applied to synthesis of methyl 4-*O*-alkyl-α,β-D-glucopyranosides. The reaction sequence was as follows: (a) perbenzylation of amylose to give tri-*O*-benzylamylose, (b) methanolysis of tri-*O*-benzylamylose to give methyl 2,3,6-tri-*O*-benzyl-α,β-D-glucopyranosides, (c) alkylation at the unsubstituted hydroxyl group, (d) separation by preparative t.l.c. of the anomers of methyl 4-*O*-alkyl-2,3,6-tri-*O*-benzyl-D-glucopyranoside, and (e) debenzylation of the individual anomers to give the methyl 4-*O*-alkyl-D-glucopyranosides. These compounds are potential model compounds for starch and cellulose, and their preparation is another indication of the general utility of this procedure[1].

EXPERIMENTAL

Tri-*O*-benzylamylose[1] (10 g) was dissolved in anhydrous chloroform (300 ml) in a 1-l round-bottomed flask. A solution (0.8M) of hydrogen chloride in methanol (prepared by adding 18 ml of acetyl chloride to 100 ml of anhydrous methanol at ~25°) was added, and the mixture was boiled for 120 h under a reflux condenser (drying tube); an additional 118 ml of methanolic hydrogen chloride was added after each 24-h period, except the last. The extent of methanolysis was monitored by t.l.c. on Silica Gel H with 5:1 (v/v) petroleum ether (b.p. 30–60°)–acetone (solvent *A*)[2]. The mixture was cooled to ~25°, made neutral with Amberlite IR-45 (OH^-) ion-exchange resin, and the suspension was filtered. The resin was washed with chloroform, and the filtrate and washings were combined and evaporated under diminished pressure to a syrup (10.25 g) consisting of methyl 2,3,6-tri-*O*-benzyl-α,β-D-glucopyranosides contaminated with small amounts of methyl 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranosides (from the nonreducing end-units) and traces of mono- and di-substituted D-glucopyranosides.

A column (3 × 33 cm) was packed dry with a mixture of 50 g of acetic acid-washed Magnesol (Waverly Chemical Co., Inc., Mamaroneck, N. Y.) and 10 g of

*Present address: Northern Regional Laboratory, A.R.S., U.S.D.A., Peoria, Illinois 61604, U. S. A.

Celite 545 (Johns–Manville Company, New York, N.Y.), and distilled, dry benzene was passed through the column under diminished pressure. A portion (2–3 g) of the methanolysis product was dried onto a sample (2 g) of the column packing material by evaporating a benzene solution of it in the presence of the adsorbent in a round-bottomed flask on a rotary evaporator under diminished pressure. The adsorbate was then powdered and added to the prepared column, with light packing.

The column was developed with distilled, dry benzene, with collection of 100-ml fractions that were evaporated to dryness and examined by t.l.c. on Silica Gel H with solvent *A*. The first components to be eluted (~1 day) consisted of the methyl 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranosides and were discarded. The second components, the desired methyl 2,3,6-tri-*O*-benzyl-α,β-D-glucopyranosides, were eluted as a single, pure fraction after 16–24 h; elution was continued for >80 h; yield ~2 g. Fractions containing both the tetra- and tri-substituted components were saved for rechromatography.

The methyl 2,3,6-tri-*O*-benzyl-α,β-D-glucopyranosides were dissolved in 50 ml of *N*,*N*-dimethylformamide (predried over sodium hydride) in a round-bottomed flask fitted with a drying tube. To the solution was added ether-washed sodium hydride, and the mixture was stirred for 1 h at ~25°. An alkyl halide was then added, and the mixture was stirred at ~25°; for the amounts and reaction times, see Table I. Methanol was added to decompose the excess of sodium hydride, chloroform was added, the mixture was centrifuged, and the precipitate was washed with chloroform. The filtrate and washings were combined and evaporated to dryness under diminished pressure.

The resulting syrup was dissolved in 2:1 (w/w) benzene–absolute ethanol, the solution was evaporated to dryness under diminished pressure, and the syrup was subjected to preparative t.l.c. by use of Silica Gel H and petroleum ether (b.p. 30–60°)–acetone in the ratio indicated in Table I. In this way, the anomers of the substituted D-glucosides were separated. Two distinct bands were visible while the t.l.c. plate was wet; these bands were also visible when the dried plate was irradiated with u.v. light of long wavelength. Methyl 4-*O*-alkyl-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside was the faster-moving component (see Table II). These compounds were then separately eluted from the adsorbent with chloroform.

After thorough removal of the chloroform, each of the D-glucosides was separately suspended in absolute ethanol and transferred, with washing, to a Parr hydrogenation flask (see Table III). About 2 g of freshly activated Raney nickel (active enough to burn filter paper in ~30 sec) was added, together with sufficient absolute ethanol to afford a volume of ~250 ml. After the flask had been flushed with hydrogen, hydrogenolysis of the benzyl groups was accomplished during 48 h at 60° with hydrogen at a pressure of 65 lb. in^{-2}. After release of the pressure, the catalyst was filtered off and washed with absolute ethanol. The filtrate and washings were combined, and evaporated to dryness, and the resulting syrup was dissolved in water; the solution was washed with chloroform to remove any partially benzylated material remaining. Nickel ions were removed by saturating the solution with

TABLE I

ALKYLATION OF METHYL 2,3,6-TRI-*O*-BENZYL-α,β-D-GLUCOPYRANOSIDES

4-O-Alkyl derivative	*Starting material (g)*	*Alkyl halide used*	*Volume (ml) of halide*	*Reaction time (h)*	*NaH (g)*	*Pet. ether (b.p. 30–60°)–acetone ratio for prep. t.l.c.*	*Yield (g)*	
							α-D	β-D
Methyl	5.2	methyl iodide	30	4	10.0	100:4	1.72 [a]	1.11 [b]
Ethyl	2.1	ethyl bromide	20	16	5.6	100:3		
1-Propyl	3.6	propyl iodide	25	16	9.6	100:4	1.61	0.81 [c]
2-Propyl	4.1	isopropyl chloride	[d]	336	16	100:3	1.19	0.90 [e]
1-Butyl	4.0	butyl bromide	20	3.5	6.8	100:3	0.66	1.235
2-Methylpropyl	4.0	*sec*-butyl bromide	[f]	155	22	100:2	0.83	0.95
1-Octyl	4.0	octyl iodide	20	18	10	100:2	0.85	0.98

[a]Undetermined. [b]Undetermined, m.p. 62.5–63° from ethanol. [c]M.p. 68.5–70°, crystallized syrup. [d]20 ml initial; 20 ml after 2 h; 30 ml/day over 14 days, to a total of 460 ml. [e]M.p. 58–59.5°, crystallized syrup. [f]20 ml initial; 10 ml at regular intervals as checked for product formation, to a total of 190 ml.

TABLE II

R_F VALUES[a] OF METHYL 4-*O*-ALKYL-D-GLUCOSIDES ON SILICA GEL H

	2,3,6-Tri-O-benzyl derivatives[b] *Ratio (v/v) of petroleum ether (b.p. 30–60°)–acetone*				*Debenzylated compounds, with 9:6:3:1 BuOH–HOAc–Et_2O–H_2O*
	20:3	*20:4*	*20:5*	*20:6*	
4-O-Alkyl substituent of methyl α-D-glucosides					
Methyl	0.30 ±0.03	0.36 ±0.02	0.52 ±0.04	0.56 ±0.04	0.42 ±0.06
Ethyl	0.32 ±0.04	0.37 ±0.01	0.56 ±0.05	0.58 ±0.04	0.48 ±0.02
1-Propyl	0.35 ±0.03	0.40 ±0.02	0.58 ±0.06	0.60 ±0.04	0.53 ±0.04
2-Propyl	0.34 ±0.02	0.39 ±0.02	0.56 ±0.06	0.58 ±0.04	0.51 ±0.04
1-Butyl	0.38 ±0.03	0.44 ±0.04	0.60 ±0.06	0.62 ±0.04	0.56 ±0.04
2-Methylpropyl	0.39 ±0.03	0.43 ±0.03	0.60 ±0.06	0.63 ±0.02	0.56 ±0.04
1-Octyl	0.43 ±0.03	0.50 ±0.03	0.67 ±0.06	0.69 ±0.02	0.65 ±0.04
4-O-Alkyl substituent of methyl β-D-glucosides					
Methyl	0.35 ±0.01	0.44 ±0.03	0.57 ±0.04	0.65 ±0.06	0.46 ±0.02
Ethyl	0.38 ±0.01	0.47 ±0.02	0.60 ±0.04	0.66 ±0.05	0.52 ±0.01
1-Propyl	0.42 ±0.01	0.51 ±0.02	0.64 ±0.05	0.67 ±0.05	0.60 ±0.02
2-Propyl	0.42 ±0.04	0.47 ±0.01	0.62 ±0.04	0.66 ±0.06	0.58 ±0.02
1-Butyl	0.43 ±0.03	0.52 ±0.04	0.65 ±0.05	0.67 ±0.06	0.64 ±0.01
2-Methylpropyl	0.44 ±0.03	0.49 ±0.02	0.65 ±0.05	0.66 ±0.04	0.62 ±0.01
1-Octyl	0.49 ±0.04	0.54 ±0.02	0.72 ±0.06	0.71 ±0.06	0.68 ±0.02

[a]An average of 3 values from 3 different plates. [b]45-min equilibration.

TABLE III

METHYL 4-*O*-ALKYL-D-GLUCOPYRANOSIDES FROM METHYL 4-*O*-ALKYL-2,3,6-TRI-*O*-BENZYL-D-GLUCOPYRANOSIDES

	Wt. of perbenzylated material used (g)	*Yield of purified material (g)*	*M.p. (degrees)*	*Calc.*		*Found*	
				C, %	*H, %*	*C, %*	*H, %*
4-O-Alkyl substituent of methyl α-D-glucosides							
Methyl[a]	0.30	0.12	—	—	—	—	—
Ethyl	0.85	0.18	—	48.63	8.18	43.77	7.33
1-Propyl	0.90	0.18	—	50.82	8.55	50.67	8.46
2-Propyl[b]	0.93	0.31	—	50.82	8.55	50.76	8.64
1-Butyl	0.66	0.45	—	52.77	8.88	52.51	8.73
2-Methylpropyl	0.59	0.26	—	52.77	8.88	49.71	8.26
1-Octyl	0.76	0.05[c]	—	—	—	—	—
4-O-Alkyl substituent of methyl β-D-glucosides							
Methyl	1.03	0.42	97–102[d]	—	—	—	—
Ethyl	0.81	0.29	127.5–129	48.63	8.18	48.46	8.28
1-Propyl	0.76	0.30	95.5–100	50.82	8.55	50.80	8.68
2-Propyl	0.93	0.34	61–66[e]	50.82	8.55	50.66	8.46
1-Butyl	0.67	0.19	—	52.77	8.88	52.82	8.93
2-Methylpropyl	0.91	0.33	—	52.77	8.88	52.62	8.82
1-Octyl	0.99	0.09[c]	—	—	—	—	—

[a]Crystallized from 2-butanone and from ethyl acetate by Whistler *et al.*[4], m.p. 94–95°. [b]Previously prepared by Hook and Lindberg[5]. [c]Yields are much higher, but it is difficult to purify. Number represents weight purified. [d]Reported[6] m.p. 102–103°. [e]Crystallized syrup; reported[5] m.p. 69–72° (from ethyl acetate–light petroleum).

hydrogen sulfide at pH 6, removing the precipitate of nickel(II) sulfide, and rendering the filtrate neutral with an ion-exchange resin in the hydroxyl form. After evaporation, most of the products were obtained as syrups (see Table I), but others were white solids. The yields are given Table III.

The products may be chromatographed on Silica Gel H by use of 9:6:3:1 (v/v) butyl alcohol–acetic acid–ether–water (see Table II).

ACKNOWLEDGMENT

This study was supported by Agricultural Research Service, U. S. Department of Agriculture, Grant No. 12-14-100-9139(71), administered by the Northern Utilization Research and Development Division, Peoria, Illinois, whose support is gratefully acknowledged.

REFERENCES

1 J. N. BeMiller and R. E. Wing, *Carbohyd. Res.*, 6 (1968) 197.
2 R. E. Wing, C. L. Collins, and J. N. BeMiller, *J. Chromatogr.*, 32 (1968) 303.
3 G. H. Hay, B. A. Lewis, and F. Smith, *J. Chromatogr.*, 11 (1963) 479.
4 R. L. Whistler, E. G. Linke, and S. Kazeniac, *J. Amer. Chem. Soc.*, 78 (1956) 4704.
5 J. E. Hook and B. Lindberg, *Acta Chem. Scand.*, 20 (1966) 2363.
6 D. I. McGilvray, *J. Chem. Soc.*, (1952) 3748.