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MIXED-ACETAL GLYCOSIDES. THE PREPARATION AND CONFIGURATIONAL ASSIGNMENT OF (*R*)- AND (*S*)-2-BROMO-1-METHOXYETHYL α-D-GLUCOPYRANOSIDE AND DERIVATIVES THEREOF

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ABSTRACT

By proton-catalyzed transacetalation with 2-bromoacetaldehyde dimethyl acetal as the substrate and 2,3,4,6-tetra-*O*-acetyl-D-glucose as the acceptor, a mixture of diastereoisomeric, mixed-acetal glycosides was obtained. α-Glycosides preponderated, and could be separated by chromatography into (*R*)- and (*S*)-2-bromo-1-methoxyethyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside. Structural assignment was achieved *via* the intramolecular, nucleophilic-cyclization products (6*S*)- and (6*R*)-6-methoxy-(3,4,6-tri-*O*-acetyl-α-D-glucopyrano)-[1,2-*b*]-1,3-dioxane. Several derivatives could be prepared by functionalizing the aglycon group.

INTRODUCTION

Glycosides[1] of mixed acetals constitute a new type of glycoside that has thus far not attracted much attention. They can be readily prepared under thermodynamically controlled conditions by heating protected sugar derivatives (having a free lactol group) in dialkoxy acetals of acetaldehyde**. Recent publications by Tietze and Fischer[2] described the preparation of several mixed-acetal glycosides by a different method. The usefulness of glycosides of mixed acetals as substrates in continuous enzyme-assays has been demonstrated[1]. Further use could be made of such compounds were the aglycons of the acetal glycosides to carry groups that allow diverse functionalization. Of interest would be, for instance, the attachment of glycosidic ligands to compounds of low molecular weight, or to polymeric matrices of various types, such as enzymes, transport proteins, and carriers for affinity chromatography. As acetals of bromoacetaldehyde are commercially available, the dimethyl acetal*** was applied for our purposes.

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**Mixed-orthoester glycosides may be similarly prepared with trialkyl orthoformate.

***The diethyl derivative may also be used, but its relatively high boiling point complicates the isolation procedure.

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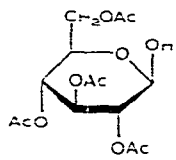
RESULTS AND DISCUSSION

The most striking feature of the thermodynamically controlled glycosidation of 2,3,4,6-tetra-*O*-acetyl-β-D-glucose (**1**) with acetaldehyde diethyl acetal is its stereoselectivity. Of the four diastereomers theoretically possible (depicted in Fig. 1),



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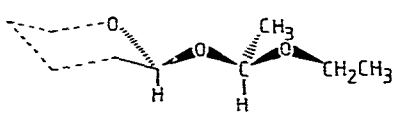
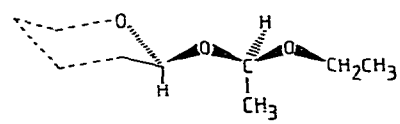
form D could be isolated crystalline from the mixture in almost 60% yield. This is, no doubt, mainly because of the "anomeric effect" exerted by the double acetal grouping, which favors the ideal helical arrangement possible in C and D. In D, unlike C, this arrangement is undisturbed by an adverse, nonbonded 1,3-interaction between the *C*-methyl group and the ring-oxygen atom.

As might be expected, the corresponding transacetalation with **1** and 2-bromoacetaldehyde dimethyl acetal also yields α-glycosides preponderantly under thermodynamically controlled conditions*. The excess of bromoacetaldehyde dimethyl acetal was removed by distillation, the syrupy mixture of products was deacetylated, and the resulting mixture treated in phosphate buffer, pH 6.8, with β-D-glucosidase



A



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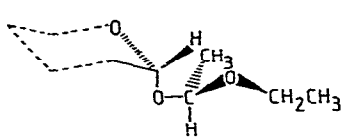

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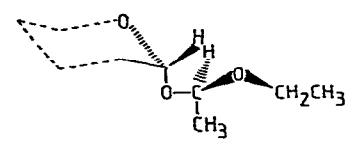


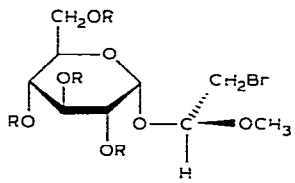
D

Fig. 1. The four diastereoisomers: 1-ethoxyethyl tetra-*O*-acetyl-β- and -α-D-glucopyranoside.

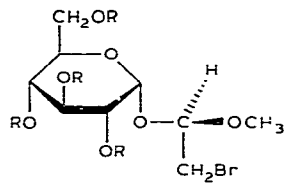
*The 5% proportion of β-D-glycosides in the deacetylated product-mixture was determined by hydrolysis with β-D-glucosidase and enzymic determination of free bromoacetaldehyde[1].

from sweet-almond emulsin. The free D-glucose formed was then removed by flash chromatography[3] on silica gel. The glycoside fraction crystallized, and was recrystallized from ethanol. It was homogeneous by t.l.c., and completely hydrolyzable by α-D-glucosidase from yeast.

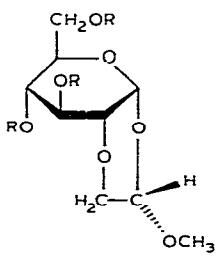
However, the ^{13}C-n.m.r. spectrum of the product in water indicated the presence of two products in about equal proportions. Reacetylation yielded a crystalline product barely separable into two components by t.l.c. in 3 : 1 (v/v) petroleum ether–ethyl acetate. The R_F values were ~0.1, with ~10% difference between the spots. The slower-migrating compound seemed to be preponderant. Preparative separation was achieved by flash chromatography, to yield two crystalline compounds, **2** and **4**. Both were deacetylated, to give crystalline **3** and **5**.



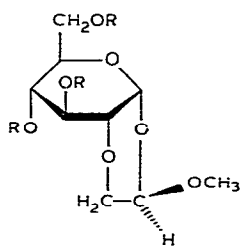
2 R = Ac
3 R = H



4 R = Ac
5 R = H



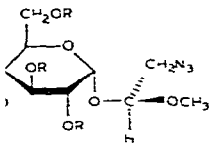
6 R = H
7 R = Ac



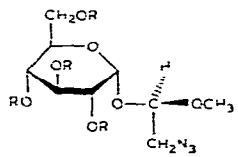
8 R = H
9 R = Ac

Separate treatment of **3** and **5** with sodium *tert*-butoxide in *tert*-butyl alcohol afforded, in each case, one product (**6** and **8**, respectively) in good yield (and containing no bromine); acetylation gave products (**7** and **9**, respectively) containing three *O*-acetyl groups according to the ^{1}H-n.m.r. spectra. The 2-hydroxyl groups in **6** and **8** had evidently displaced the bromine on the corresponding aglycons, forming, in each instance, a fused-ring system. The signals for the three protons on the former aldehyde skeletons clearly showed couplings corresponding to one synclinal and one antiperiplanar relationship for **7**, and two synclinal relationships for **9**. Interestingly, the anomeric proton in **9** is shifted downfield by 0.29 p.p.m., because of the proximity of the axial methoxyl group. The asymmetric carbon atom of the mixed acetal group of **2** and **4** therefore has the (*S*) and (*R*) configuration, respectively.

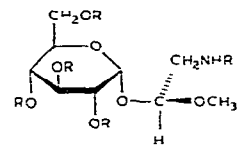
The bromine atom in the acetates **2** and **4** may be replaced by azide, yielding crystalline **10** and **12** in good yields. This result demonstrates the ease of further functionalization of mixed acetal groups. The deacetylated products (**11** and **13**) from the azides **10** and **12** yielded the free amines **14** and **16** by hydrogenation in ethanol with Adams' catalyst. The peracetylated glycosides **15** and **17** were correspondingly obtained from **14** and **16**. The results of preliminary experiments indicated that all of the non-*O*-acetylated α-D-glucosides described herein are susceptible to hydrolysis by α-D-glucosidase (maltase) from yeast.



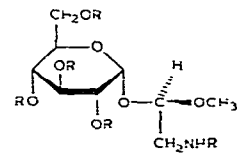
10 R = Ac
11 R = H



12 R = Ac
13 R = H



14 R = H
15 R = Ac



16 R = H
17 R = Ac

EXPERIMENTAL

General. — Melting points are uncorrected. Optical rotations were measured with a Perkin–Elmer 141 polarimeter. I.r. spectra were recorded with a Perkin–Elmer 1320 i.r. spectrophotometer. T.l.c. was performed on silica gel F_{254} (Merck) with *A*, 4:1 ether–light petroleum (b.p. 40–65°); and *B*, 25:14:7 ethyl acetate–2-propanol–water for compounds having free hydroxyl groups. Detection was effected by charring with sulfuric acid. ^{13}C-N.m.r. spectra were recorded with a Bruker WP 100 at 25.18 MHz. and ^{1}H-n.m.r. spectra at 250 MHz, with a Cameca spectrophotometer. Assignments were confirmed by double irradiation, or the INDOR technique. The chemical shifts are reported in δ relative to an internal standard of Me_4Si, or to acetone for unacetylated compounds, and the coupling constants (in brackets) are in Hz.

Enzymic reactions. — α-D-Glucosidase (maltase, α-D-glucoside glucohydrolase, EC 3.2.1.20) from yeast and β-D-glucosidase (β-D-glucoside glucohydrolase, EC 3.2.1.21) from sweet almonds were purchased from Boehringer, and used without purification. All enzyme reactions were performed at 25° in 0.05M sodium phosphate buffer, pH 6.8. Substrate concentrations were 10mM, and enzyme concentrations were 1 mg per 100 mL. The reaction was monitored by t.l.c. in solvent *B*. Experimental data for compounds **2–17** are given in Tables I, II and III.

*Reaction of 2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranose* (**1**) *with bromoacetaldehyde dimethyl acetal.* — Compound **1** (10 g) in bromoacetaldehyde dimethyl acetal (50 mL) containing acetic acid (0.5 mL) was kept at 100°. After 18 h, the bath temperature was raised to 140–150°, and the volatile constituents, mainly methanol, were allowed to distil off during ~3 h. T.l.c. analysis (solvent *A*) then indicated almost complete disappearance of **1**. The excess of bromoacetaldehyde dimethyl acetal was

TABLE I

PROTON NUCLEAR MAGNETIC RESONANCE DATA[a] FOR *O*-ACETYLATED GLYCOSIDES IN CHLOROFORM-*d*

Compound	*H-1* $J_{1,2}$	*H-2* $J_{2,3}$	*H-3* $J_{3,4}$	*H-4* $J_{4,5}$	*H-5* $J_{5,6a}$ $J_{5,6b}$	*H-6a* $J_{6a,6b}$	*H-6b*	*H-5'a*	*H-5'b* $J_{5'a,5'b}$	*H-6'* $J_{5'a,6'}$ $J_{5'b,6'}$	*OMe*	*OAc*	*NH*
2	5.39d (3.5)	4.94dd (10.5)	5.52dd (10)	5.09t (10)	4.29m (4.5) (—)	4.26dd (12)	4.10m*	3.44m	(13)	4.77t (5) (5)	3.47	2.02; 2.04 2.07; 2.09	
4	5.34d (4)	4.94dd (10.5)	5.50dd (10)	5.08t (10)	4.29m (5) (2)	4.25dd (12)	4.12m*	3.49dd	3.45dd (12)	4.84t (5.5) (5.5)	3.39	2.02; 2.04 2.06; 2.09	
7	5.13d (3)	3.71dd (10)	5.72t (10)	5.09t (10)	4.28m (4) (2)	4.32dd (12)	4.13m*	3.62dd	3.53dd (12)	4.7dd (8.5) (3)	3.54	2.03; 2.06 2.09	
9	5.42d (3.5)	3.82dd (10)	5.75t (10)	5.10t (10)	4.16o (4) (2)	4.32dd (12)	4.10dd	3.98dd	3.49d (13)	4.8dl (~0) (2)	3.48	2.04; 2.08 2.10	
10	5.34d (4)	4.91dd (10.25)	5.49dd (10)	5.06t (10)	4.24m		4.08m*	3.43dd	3.23dd (13)	4.63t (5.5) (5.5)	3.48	2.01; 2.03 2.06; 2.09	
12	5.35d (4)	4.93dd (10)	5.50t (10)	5.07t (10)	4.11m (5) (2)	4.24dd (12)	4.11m*	3.42dd	3.34dd (13)	4.73t (5) (5)	3.43	2.03; 2.05 2.08; 2.11	
15	5.30d (4)	4.96dd (10.25)	5.50dd (9.5)	5.05t (9.5)	4.23m		4.08m*	3.53o	3.31s (14)	4.62dd (5) (5.5)	3.45	2.01; 2.02 2.05; 2.08 2.09	5.91
17	5.31d	4.91dd	5.48t	5.0t	4.1m	4.22dd	4.1m	3.45q		4.68t (5.5) (5.5)	3.38	2.0; 2.01 2.03; 2.04 2.09	5.96

[a]Abbreviations: d, doublet; dd, double doublet; m, multiplet; o, octet; q, quadruplet; s, sextuplet; t, triplet; l, large; * second-order effect.

TABLE II

^{13}C-NUCLEAR MAGNETIC SHIFTS[a] FOR THE ANOMERIC CARBON ATOMS AND THE ASYMMETRIC CARBON ATOMS OF THE MIXED ACETAL GROUP

Compound[b]	*C-1*	*C-6'*	*Compound*[c]	*C-1*	*C-6'*
2	92.3	104.1	**3**	97.0	103.7
4	93.0	101.1	**5**	97.0	100.7
7	93.2	99.4	**6**	94.1	100.1
9	88.6	99.0	**8**	89.5	99.4
10	93.0	104.0	**11**	97.5	104.1
12	93.2	101.1	**13**	96.9	100.6
15	92.6	103.1	**14**	97.8	107.1
17	93.2	101.2	**16**	96.4	102.9

[a]Values are reported in δ. [b]$CDCl_3$ as the solvent, and Me_4Si as the internal standard. [c]D_2O as the solvent and Me_2CO as the internal standard.

recovered by distillation under diminished pressure at a bath temperature of ~100°, and a syrupy material (15 g) remained.

Isolation of (S)-*2-bromo-1-methoxyethyl 2,3,4,6-tetra*-O-*acetyl*-α-D-*glucopyranoside* (**2**) *and* (R)-*2-bromo-1-methoxyethyl 2,3,4,6-tetra*-O-*acetyl*-α-D-*glucopyranoside* (**4**). — The aforementioned syrup was deacetylated with 0.1M sodium methoxide in methanol, the solution made neutral with Amberlite IRA-120(H^+) resin, and evaporated, and the residue (8 g) treated with β-D-glucosidase in phosphate buffer. After 24 h at room temperature, the mixture was evaporated to dryness under diminished pressure, and the partly solid residue was taken up in the minimal volume of solvent *B* and submitted to flash chromatography on a column (7 × 20 cm) of silica gel with solvent *B*. The fractions containing the glycosides were collected, and evaporated to dryness. The resulting syrup (5.8 g) crystallized.

It was acetylated and the esters isolated conventionally; the resulting syrup (7.5 g) crystallized slowly. It was dissolved in the minimal volume of ethyl acetate, and submitted to flash chromatography on silica gel (same column dimensions as before). Pure fractions were collected, and these yielded **2** (2.3 g, 18%), and **4** (2.5 g, 19%). The remaining mixture (1.9 g) could be rechromatographed to increase the yields.

(S)-*2-Bromo-1-methoxyethyl* α-D-*glucopyranoside* (**3**) *and* (R)-*2-bromo-1-methoxyethyl* α-D-*glucopyranoside* (**5**). — Compounds **2** and **4** (2 g each) were separately deacetylated by the Zemplén procedure, to give **3** and **5** in almost quantitative yield.

(*6*S)-*6-Methoxy*-(*3,4,6-tri*-O-*acetyl*-α-D-*glucopyrano*)-[*1,2*-b]-*1,4-dioxane* (**6**) *and* (*6*R)-*6-methoxy*-(*3,4,6-tri*-O-*acetyl*-α-D-*glucopyrano*)-[*1,2*-b]-*1,4-dioxane* (**8**). — Compounds **3** and **5** (0.5 g each) were separately dissolved in *tert*-butyl alcohol (10 mL), and the solution stirred for 5 h at room temperature with potassium *tert*-

TABLE III

PROPERTIES OF COMPOUNDS **2–17**

Product	*Solvent for recrystallization*	*Yield (%)*	*Analysis for*	*Calc. (%)*	*Found (%)*	$[\alpha]_D^{22}$ *(c, 1.0) (degrees)*	*M.p. (°C)*
2	ether–pet. ether (50–60°) or ethanol–water	18	$C_{17}H_{25}BrO_{11}$	C, 42.07 H, 5.19 Br, 16.46	42.08 4.95 16.30	+119.5 ($CHCl_3$)	86
4	ether–pet. ether (50–60°)	19			41.86 5.12 16.20	+118.0 ($CHCl_3$)	100
3	ethanol	91	$C_9H_{17}BrO_7$	C, 34.08 H, 5.40 Br, 25.19	33.91 5.21 24.95	+142.8 ($CHCl_3$)	137
5	ethanol	92.5			33.92 5.21 24.94	+114.0 (ethanol)	125
6	methanol–benzene–pet. ether (50–60°) cryst., and drying at 80° *in vacuo*	100	$C_9H_{16}O_7 \cdot 0.5\ H_2O$ $C_9H_{16}O_7$	C, 44.08 H, 6.98 C, 45.75 H, 6.82	44.45 6.69 45.72 6.92	+205.0 (ethanol)	147
8	methanol–benzene–pet. ether (50–60°)	100			45.92 6.75	+2.8 (ethanol)	178
7	syrup	80					
9	ether–pet. ether (50–60°)	90	$C_{15}H_{22}O_{10}$	C, 49.72 H, 6.12	49.89 6.18	+51.5 ($CHCl_3$)	110
10	ether–pet. ether (50–60°) or ethanol–water	76	$C_{17}H_{25}N_3O_{11}$	C, 45.63 H, 5.63 N, 9.39	45.78 5.77 9.55	+119.0 ($CHCl_3$)	64
12	ether–pet. ether (50–60°) or ethanol–water	75		C, H, N,	45.84 5.55 9.68	+112.0 ($CHCl_3$)	80
11	acetone–pet. ether (50–60°)	85	$C_9H_{17}N_3O_7$	C, 38.63 H, 6.13 N, 15.04	38.49 5.80 15.26	+124.0 (ethanol)	109
13	syrup	100					
14	ethanol	92	$C_9H_{19}NO_7$	C, 42.68 H, 7.56 N, 5.53	42.59 7.34 5.42	+132.5 (ethanol)	160
16	syrup	100					
15	ether	86.3	$C_{19}H_{29}NO_{12}$	C, 49.24 H, 6.31 N, 3.02	49.43 6.01 3.14	+100.0 ($CHCl_3$)	112
17	toluene	90.6		C, 49.21 H, 6.05 N, 3.07		+112.0 ($CHCl_3$)	144–154

butoxide (0.5 g). The mixture was evaporated to dryness, and each product was acetylated, and the acetate isolated conventionally.

(6S)-α-D-*Glucopyrano*-[1,2-b]-6-*methoxy*-1,4-*dioxane* (**7**) *and* (6R)-α-D-*glucopyrano*-[1,2-b]-6-*methoxy*-1,4-*dioxane* (**9**). — Compounds **6** and **8** (0.5 g each) were separately deacetylated by the Zemplén method, to give **7** and **9**.

(S)-2-*Azido*-1-*methoxyethyl* 2,3,4,6-*tetra*-O-*acetyl*-α-D-*glucopyranoside* (**10**) *and* (R)-2-*azido*-1-*methoxyethyl* 2,3,4,6-*tetra*-O-*acetyl*-α-D-*glucopyranoside* (**12**). — Compounds **2** and **4** (1 g each) were separately heated for three days with dried sodium azide (1 g) in boiling, dry dimethyl sulfoxide (15 mL). The mixture was cooled, acetone (200 mL) was added, with stirring, the inorganic precipitate filtered off, and the filtrate evaporated under diminished pressure. The residue was taken up in water (100 mL), the suspension was extracted with ether (3 × 100 mL), and the extracts were combined, washed with water (100 mL), dried (calcium sulfate), and evaporated, to yield the crystalline products **10** and **12**, respectively.

(S)-2-*Azido*-1-*methoxyethyl* α-D-*glucopyranoside* (**11**) *and* (R)-2-*azido*-1-*methoxyethyl* α-D-*glucopyranoside* (**13**). — Compounds **10** and **12** were deacetylated by the Zemplén method, to yield crystalline **11** and **13**, respectively, in almost quantitative yield.

(S)-2-*Amino*-1-*methoxyethyl* α-D-*glucopyranoside* (**14**) *and* (R)-2-*amino*-1-*methoxyethyl* α-D-*glucopyranoside* (**16**). — Compounds **11** and **13** (0.5 g each) in ethanol (30 mL) were separately hydrogenated in the presence of Adams' catalyst (20 mg PtO_2). The reaction was complete after 2 h. The mixture was filtered, and the strongly basic filtrate was evaporated under diminished pressure, to yield, almost quantitatively, the amines **14** and **16**.

(S)-2-*Acetamido*-1-*methoxyethyl* 2,3,4,6-*tetra*-O-*acetyl*-α-D-*glucopyranoside* (**15**) *and* (R)-2-*acetamido*-1-*methoxyethyl* 2,3,4,6-*tetra*-O-*acetyl*-α-D-*glucopyranoside* (**17**). — Compounds **14** and **16** (0.5 g each) were conventionally acetylated with acetic anhydride (5 mL) in pyridine (10 mL). After 6 h, the mixtures were evaporated under diminished pressure, and traces of pyridine were removed from the residue by coevaporation with toluene. Compounds **15** and **17** were obtained as crystalline solids.

ACKNOWLEDGMENTS

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