HYDROLYSES OF INTERMEDIATE ACETOXONIUM IONS DERIVED FROM D-GLUCOSE*

W. E. DICK, JR.
Northern Regional Research Laboratory†, Peoria, Illinois 61604 (U. S. A.)
(Received June 28th, 1971; accepted in revised form, August 9th, 1971)

ABSTRACT

The effects of solution acidity and structural differences on the relative proportions of 1-OH and 2-OH forms produced by hydrolysis were determined for tetra-*O*-acetyl-β-D-glucopyranosyl chloride (**1a**), 2,3-di-*O*-acetyl-4,6-*O*-ethylidene-β-D-glucopyranosyl chloride (**2a**), and hepta-*O*-acetyl-β-maltosyl chloride (**3a**), tri-*O*-acetyl-1,2-*O*-(ethoxyethylidene)-α-D-glucopyranose (**1b**) and hexa-*O*-acetyl-1,2-*O*-(methoxyethylidene)-α-maltose (**3b**). Formation of a 2-OH derivative was promoted in strongly acidic solutions; however, the extent to which a given reactant formed a 2-OH product also was determined by structural features at sites remote from the reaction center. Control of solution acidity led to yields of the 2-OH form varying from 10 to 75% in series **1**, from 51 to 95% in series **2**, and from 9 to 40% in series **3**. To demonstrate the usefulness of such product mixtures in syntheses of 2-*O*-substituted derivatives. 2-methyl ethers were prepared from 1,3-di-*O*-acetyl-4,6-*O*-ethylidene-α-D-glucose and 1,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-α-maltose. N.m.r. spectral data were obtained.

INTRODUCTION

For most syntheses of 2-*O*-substituted carbohydrates, a partially substituted, 2-hydroxy intermediate is required. Numerous methods are available for preparing such intermediates from D-glucose, notably the selective acylation of specific glucosides[1–4], reaction of peracetates with piperidine[5,6] or phosphorus trichloride[7], and hydrolyses of acetylated α-D-glucosyl bromides[8,9], acetylated β-D-glucosyl chlorides[10,11], or 1,2-*O*-acetoxonium-3,4,6-tri-*O*-acetyl-α-D-glucopyranose tetrafluoroborate[12]. Although crystalline 2-hydroxy derivatives of cellobiose[13–15] and maltose[16] had been prepared by application of some of these methods, yields were low and often the syntheses were difficult. A more facile synthesis of 2-hydroxy disaccharide derivatives is needed if their synthetic utility is to be fully exploited.

In a series of investigations with dioxolenium (including acetoxonium) ions

*Presented before the Division of Carbohydrate Chemistry at the 160th National Meeting of the American Chemical Society, Chicago, Illinois, September 1970.
†This is a laboratory of the Northern Marketing and Nutrition Research Division, Agricultural Research Service, U.S. Department of Agriculture.

anchored to condensed ring-systems—such as, *trans*-decalins and steroids—King and Allbutt[17] found that dioxolenium ions bridging vicinal, *cis*-hydroxyl groups will react with water, under conditions of kinetic control, to form preferentially the product that contains an axial ester and an equatorial hydroxyl group. For D-glucose, their findings predict that, when such ions bridge O-1 and O-2, an α-1-*O*-acetyl-2-hydroxy derivative will be the major product formed by hydrolysis. The yield of 2-hydroxy derivative will thus depend upon the ability of the reactant to form an acetoxonium ion and upon subsequent hydrolytic conditions that favor a selective ring-opening of that ion. Therefore, hydrolyses of α-D-glucosyl bromides or chlorides would not be expected to produce high yields of 2-hydroxy derivatives, whereas hydrolyses of β-D-glucosyl halides should. A relationship between the ease with which an acetoxonium ion is formed and the yield of a 2-hydroxy product can be seen in the hydrolyses of D-glucosyl halides[8–15], all of which predate the work of King and Allbutt[17].

A series of three β-D-glucosyl chloride derivatives and two α-D-glucose orthoesters was subjected to hydrolyses by water at 25° to devise a simple, general procedure for producing the maximum yield of a transitory acetoxonium ion and subsequent 2-hydroxy derivative. Since aqueous solutions of D-glucosyl chlorides generate hydrochloric acid and become too acidic for use with many compounds, the effects of controlling acidity with co-solvents or buffer salts were evaluated. The relative yields of 1- and 2-hydroxy derivatives were determined by g.l.c. of their monotrimethylsilyl (Me_3Si) ethers. In addition, the effects of structural changes at sites remote from the ionic center were evaluated.

RESULTS AND DISCUSSION

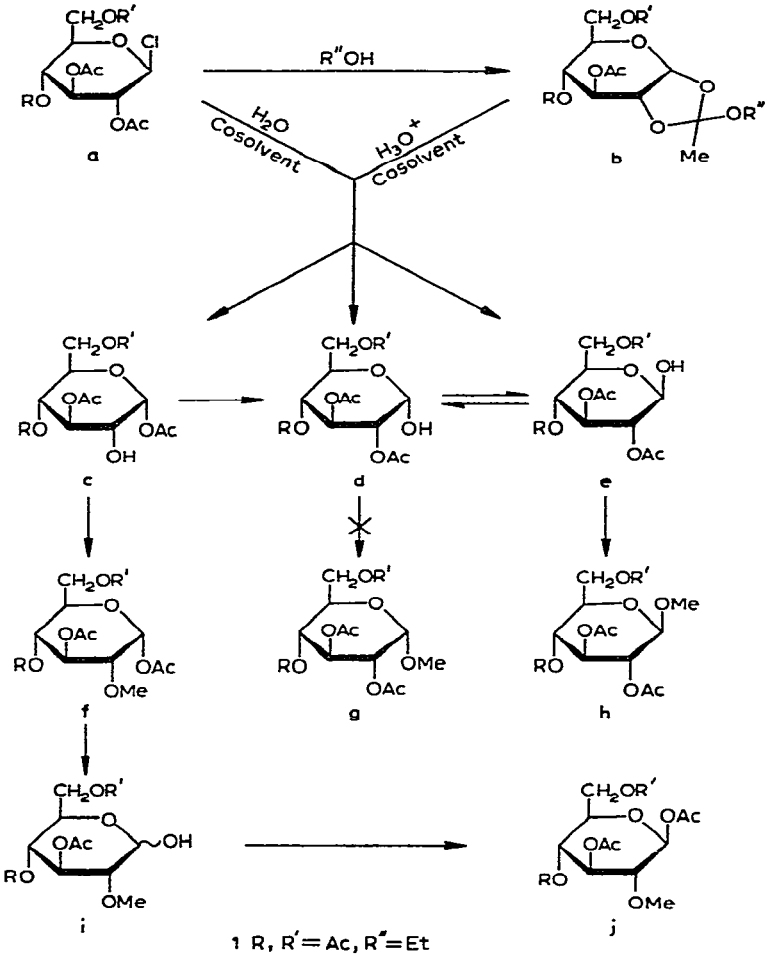
Two classes of compounds were selected for the comparative hydrolyses: 2-*O*-acetyl-β-D-glucopyranosyl chlorides and 1,2-*O*-alkoxyalkylidene-α-D-glucoses.

The β-chlorides selected included tetra-*O*-acetyl-β-D-glucopyranosyl chloride (**1a**), 2,3-di-*O*-acetyl-4,6-*O*-ethylidene-β-D-glucopyranosyl chloride (**2a**), and hepta-*O*-acetyl-β-maltosyl chloride (**3a**). Evidence for intermediate formation of an acetoxonium ion was obtained by reduction with sodium borohydride to the corresponding 1,2-*O*-ethylidene-α-derivatives[18] in pyridine or *N*,*N*-dimethylformamide (DMF).

The orthoesters, 3,4,6-tri-*O*-acetyl-1,2-*O*-(ethoxyethylidene)-α-D-glucose (**1b**) and 3,6,2′,3′,4′,6′-hexa-*O*-acetyl-1,2-*O*-(methoxyethylidene)-α-maltose (**3b**), presumably also form a transient acetoxonium-ion in acidic solutions[19].

All five compounds undergo hydrolysis to give a mixture of three mono-hydroxy derivatives, **c**, **d**, and **e** (Scheme I). The major products are **c** and **d**; **e** arises primarily by mutarotation of **d**. Rearrangements of the acetoxonium ion before collapse with solvent, as reported by Paulsen and coworkers for compounds having different anions[12], were sought but were not detected.

Preliminary hydrolyses of **1a**, **2a**, and **3a** in aqueous acetic acid confirmed the need for control of the hydrogen chloride to permit isolation of acid-sensitive products in high yields. Although Lemieux and his coworkers[10,20], who prepared **1c**



SCHEME I

from **1a** in aqueous acetic acid, added silver acetate to destroy HCl as it was formed, other methods for control of HCl have not been reported. Furthermore, the effects of decreased acidity or of silver salts on product ratios in such hydrolyses have not been determined. To gauge the influence of acidity on product ratios, two methods for attenuating the acidity were tested, complexing the HCl with a basic co-solvent, and buffering the solution with alkaline salts. Four aqueous co-solvents were selected for conducting hydrolyses of the β-chlorides: DMF, pyridine, acetone, and dichloromethane–acetic acid. In DMF and pyridine, HCl forms a complex that lowers the overall acidity of the solution. Comparative hydrolyses were conducted in the other two solvents, neither of which combines with hydrolytically generated HCl. In the second method for attenuating acidity, the solution was buffered with alkali-metal salts of acetic or trifluoroacetic acid.

TABLE I

HYDROLYSES OF *O*-ACETYLATED-β-D-GLUCOPYRANOSYL CHLORIDES AT 25°

Aqueous solvent	*Solute*	*Compound*					
		1		**2**		**3**	
		1-OH	*2-OH*	*1-OH*	*2-OH*	*1-OH*	*2-OH*
Pyridine[a]		80	20	42	58	88	12
	HOAc	69	31	31	69	86	14
	DMF	76	24	41	59	85	15
	NaCl	78	22				
	LiCl	80	20				
	$NaCOCF_3$	81	19	44	56	88	12
	$LiCOCF_3$	79	21				
	AgOAc	87	13	49	51	92	8
	NaOAc	86	14	46	54	89	11
	LiOAc	90	10				
$HCONMe_2$		30	70	7	93	63	37
	HOAc	31	69	7	93	65	35
	NaCl	34	66				
	LiCl	35	65				
	$NaCOCF_3$	46	54	13	87	83	17
	$LiCOCF_3$	40	60				
	AgOAc	79	21	32	68	91	9
	NaOAc	79	21	37	63	93	7
	LiOAc	87	13				
	Pyridine	68	32	32	68	88	12
Acetone[a]		31	69	6	94	60	40
	HOAc	27	73	6	94	62	38
	$HCONMe_2$	28	72	6	94	60	40
	NaCl	31	69				
	LiCl	30	70				
	$NaCOCF_3$	47	53	11	89	89	11
	$LiCOCF_3$	38	62				
	AgOAc	75	25	31	69	91	9
	NaOAc	74	26	30	70	91	9
	LiOAc	78	22				
	Pyridine	74	26	34	66	84	16
CH_2Cl_2–HOAc[b]		28	72	7	93	63	37
	$HCONMe_2$	25	75	5	95	64	36
	$NaCOCF_3$	44	56	7	93	84	16
	AgOAc	43	57	12	88	87	13
	NaOAc	54	46	12	88	89	11
	Pyridine	68	32	26	74	87	13

[a]Ratio of a:solvent:H_2O, 1:10:1 w/v/v; [b]Ratio of a:CH_2Cl_2:aqueous HOAc (90%), 1:10:4 *w/v/v*.

Table I shows the relative amounts of 1-OH derivatives (**d**+**e**) and 2-OH derivative (**c**) present at the end of each hydrolysis. The 1-OH:2-OH ratio remained constant throughout the entire reaction, although mutarotation of **d** to **e** was generally observed. No changes in the ratio of products were observed for hydrolyses of **1a** or **3a** when the water content was doubled or halved, or when the hydrolyses were

performed at ice-bath temperature. However, the rate of hydrolysis decreased sharply as the temperature or water content was lowered. Compound **2a** was not tested under these changed conditions.

In general, the product ratio (1-OH:2-OH) depends on the reaction conditions and the structure of the reactant. More 2-OH derivative was always formed in those solutions that were highly acidic at the end of the reaction, and less when the solution acidity was decreased. Partial decomposition of reactant and products occurred during hydrolyses conducted at high acidity. Losses were greatest for **2** but could be held to 5–10% in aqueous DMF, presumably because an HCl complex was formed. Addition of a small quantity of DMF to the acetone or dichloromethane–acetic acid solutions decreased losses to the level obtained in aqueous DMF alone.

No decomposition losses were noted when pyridine or the buffer salts were added, but yields of **c** relative of **d** always dropped. Qualitatively, decrease in content of **c** varied directly with decrease in acidity of the solution. Lower proportions of **c** were formed whenever pyridine was present.

When buffer salts were added, **c** increased proportionately to the strength of the secondary acid that was formed. Thus more **c** was formed with trifluoroacetate salts than with acetate salts. As expected, the addition of a common-ion salt, a chloride, did not alter the ratio of products substantially.

Comparative hydrolyses with sodium and lithium salts showed that the cation of the added salt did not affect the product ratio significantly. Even though the rate of hydrolysis increased when silver ions were added, for a given anion the product compositions did not change.

Since fixed conditions were followed, the yields shown in Table I are not necessarily the maximum or minimum values that might be obtained under different reaction conditions.

Hydrolyses of the orthoesters, **1b** and **3b**, gave product ratios that closely matched those obtained with **1a** and **3a**. Samples were hydrolyzed in solutions of

TABLE II

HYDROLYSES OF ORTHOESTERS[a]

Solvent	*Aqueous hydrolyst*	*Compound*			
		1		**3**	
		1-OH	*2-OH*	*1-OH*	*2-OH*
$HCONMe_2$	CF_3CO_2H	29	71	64	36
	HCl	26	74	62	38
	HOAc	72	28	85	15
Acetone	CF_3CO_2H	25	75	62	38
	HCl	26	74	61	39
	HOAc	47	53	74	26
CH_2Cl_2	HOAc	43	57	73	27

[a]Ratio of b:solvent:aqueous acid, 1:10:1 *w/v/v* for molar trifluoroacetic acid or HCl, 1:10:4 for aqueous HOAc (90%, *v/v*).

DMF, acetone, or dichloromethane with molar solutions of HCl, trifluoroacetic acid, and aqueous acetic acid (90% *v/v*). The results are summarized in Table II.

Highest yields of **1c** or **3c**, within the limitations imposed by structural factors, were again obtained in strongly acidic solutions (trifluoroacetic acid or HCl). In DMF–acetic acid, the least acidic mixture, yields of **1c** or **3c** were lowest of the series, and the reaction time was 30 times longer than that measured in mixtures of acetone or dichloromethane with acetic acid.

Although the hydrolysis of an orthoester is more rapid in a strongly acidic solution than hydrolysis of the corresponding β-chloride, both classes of compound give equivalent 1-OH:2-OH ratios, and the orthoester must be prepared from the β-chloride. For syntheses of a 2-hydroxy derivative on a large scale, hydrolysis of the β-chloride is, therefore, the method of choice.

The effects of structural factors are readily seen in Tables I and II. For example, in aqueous DMF the yield of **c** from the three β-chlorides varies from 93% (**2c**) to 37% (**3c**). In a similar fashion, an acidic solution of **1b** in DMF gave a 71–74% yield of **1c**, whereas **3b** gave **3c** in only 36–38% yield. Similar effects were observed with other hydrolytic systems.

Although the hydrolysis of a 2-*O*-acetyl-β-D-glucopyranosyl chloride or a 1,2-*O*-alkoxyethylidene-α-D-glucopyranose can be presumed to pass through successive acetoxonium and orthoacid intermediates[17,18], the relative importance of factors such as rigidity of the pyranoid ring, charge distribution and separation in the acetoxonium ion-pair, and the extent and importance of O-5 protonation in the orthoacid, cannot now be evaluated in terms of the ratio of 1-OH and 2-OH products formed in a given hydrolysis.

In hydrolyses of the maltose derivatives (**3a**, **3b**), the 1-OH forms preponderated under all conditions of acidity tested, although shifts in the 1-OH:2-OH ratio, related to conditions of changed acidity, followed the trend observed with **1** and **2**. Since solutions of **3a** or **3b** can form an acetoxonium ion as easily as derivatives of **1** and **2**, apparently the 4-*O*-α-D-glucopyranosyl substituent of **3** adversely affects the pattern of collapse of the acetoxonium ion when conditions that usually favor formation of the **c** form are used.

By comparison, preliminary hydrolytic studies indicate that a 4-*O*-β-D-glucopyranosyl substituent, present in cellobiose derivatives, does not depress yields of the corresponding **d** product. A product ratio (1-OH:2-OH) of 31:69 was observed for a solution of the β-chloride in aqueous DMF.

Although it is easy to prepare a reaction mixture that contains a substantial amount of 2-hydroxy derivative (**c**), isolation of pure material can be difficult. The **c** products are unstable and readily rearrange to form the isomeric **d** product in neutral or slightly basic media[10,21]. However, instability can be minimized by control of acidity whenever **c** is isolated or converted into a more stable derivative. The high yields of **c** and the ease with which it is prepared offset other advantages that may be gained by more difficult syntheses which generate a more stable anomer of **c**, the β-1-*O*-acetyl-2-hydroxy derivative[7,16].

TABLE III

N.M.R. PARAMETERS FOR DERIVATIVES OF 2 AND 3[a]

Compound	*Chemical shift, τ*									
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6′*	*CH_3–CH–*	*CH_3–CH–*	*OCH_3*
2c[b]	3.87d	6.25m	4.75t	6.61t	6.23m	5.90dd	6.54t	5.34q	8.71d	
2d[b]	4.62t	5.17dd	4.52t	6.62t	6.03m	5.88m	6.51t	5.32q	8.68d	
2f[b]	3.66d	6.60	4.66t	6.65	6.24m	5.90dd	6.55t	5.35q	8.70d	6.62
	H-1	*H-1′*	*H-2*	*H-2′*	*H-3*	*H-3′*	*H-4*	*H-4′*	*H-5*	*OCH_3*
3f[c]	3.59d	4.35d	7.08dd	4.89dd	4.25	4.16t	5.98	4.62t		7.04
3j[c]	4.34d	4.46d	6.97dd	4.94dd	4.64t	4.21dd	6.07t	4.64t	6.97m	6.81
	Coupling constants, J (Hz)									
	$J_{1,2}$	$J_{1',2'}$	$J_{2,3}$	$J_{2',3'}$	$J_{3,4}$	$J_{3',4'}$	$J_{4,5}$	$J_{4',5'}$	J_{CH_3-CH-}	
2c[b]	3.9		9		10		9.5		5	
2d[b]	3.8		10		9.5		9.5		5	
2f[b]	3.9		9.5		10		9.5		5	
3f[c]	3.6	4	9.5	10.5	9.5	9.5		10		
3j[c]	7.8	3.9	9.5	10.5	9.5	9.5	9.5	9.5		

[a]100 MHz; d = doublet, dd = doublet of doublets, m = multiplet, q = quartet, t = triplet, [b]In chloroform-*d*. [c]In benzene-d_6.

Two of the three **c** products, **1c** and **2c**, were isolated by fractional crystallization. The yield of **1c** from an improved synthesis exceeded that reported in the literature[10]. Although crystalline **2c** probably had been isolated earlier by Korytnyk and Mills[22] from a hydrolysis of **2a** in a mixture of acetone, silver carbonate, and silver nitrate, they tentatively assigned **2d** as the structure. However, the properties they reported closely match those of **2c** and, furthermore, do not agree with those found for an authentic sample of **2d**, prepared by isomerization of **2c** on preparative t.l.c. plates. The structures of **2c** and **2d** were established by n.m.r. spectroscopy (Table III) and because only **2c** forms 2-*O*-methyl-α,β-D-glucose after methylation and hydrolysis.

Efforts to crystallize **3c** were unsuccessful. A technique as mild as preparative t.l.c., which Koeppen [16] used to purify the more stable anomer of **3c**, 1,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-β-maltose, could not be used since the silica gel on hand could be expected to isomerize **3c** as readily as it had isomerized **2c**. A similar rearrangement of **1c** may explain why hydrolysis of 1,2-*O*-acetoxonium-3,4,6-tri-*O*-acetyl-α-D-glucopyranose tetrafluoroborate when followed by preparative t.l.c. gave only **1d** (Ref. 23), whereas similar hydrolysis without t.l.c. gave **1c** (Ref. 12). It was necessary, therefore, to prepare a stable derivative of **3c**, the previously unknown 2-methyl ether (**3f**), before attempting any purification procedures.

Although most acylation reactions of **c** can be accomplished without causing a rearrangement before the derivative is formed, such rearrangements are often observed during alkylations[21,24]. However, a notable exception is the methylation reagent of Mastronardi and coworkers[25]—a cold mixture of diazomethane and boron trifluoride etherate in dichloromethane.

When pure samples of **1c**, **2c**, **1e**, and **3e** were methylated under these conditions, the corresponding 2-methyl ethers or methyl β-D-glucosides were isolated in crystalline yields greater than 90%. No products that could have arisen by rearrangements were observed. During the methylation, only trace amounts of **1d**, **2d**, or **3d** are converted into methyl α-D-glucosides (**g**), and the presence of **d** does not inhibit the methylation of other forms. When a crude preparation of **3c** was methylated, the major component in the mixture, **3d**, was unaffected by the reagent. The methylated products, a mixture of **3f** and **3h**, were separated from the unreacted material on a column of silica gel.

The methylated products were separated from one another by treating the product mixture with piperidine, a procedure that selectively deacetylates **3f** at C-1 without affecting **3h**, and by chromatographing the product mixture on a column of silica gel. The overall yield of 3,6,2,′3′,4′,6′-hexa-*O*-acetyl-2-*O*-methylmaltose (**3i**), which was isolated as a solid mixture of both anomers, was 30% (based on **3a**). Acetylation of **3i** produced a pure, crystalline form, 1,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-2-*O*-methyl-β-maltose (**3j**). A different synthesis of **3j** was reported[26] after this work had been completed.

The preparation and isolation of 2-*O*-methyl derivatives of **1**, **2**, and **3** demonstrated the utility of this general synthesis of 2-hydroxy derivatives of D-glucose and homologous compounds. Furthermore, the separation procedure devised for 2-*O*-methylmaltose showed that it is not necessary to isolate a pure 2-hydroxy inter-

mediate before preparing a derivative from it. These combined techniques should allow the preparation of a wide variety of 2-*O*-substituted derivatives of D-glucose.

EXPERIMENTAL

General. — N.m.r. spectra were measured at 100 MHz on a Varian* HA-100 spectrometer with Me_4Si ($\tau = 10.0$) as the internal standard. Chemical shifts and coupling constants are first-order, measured directly from spectral spacings. An F & M research chromatograph, Model 700 equipped with a Disc integrator, was employed for g.l.c. Hydroxyl compounds were converted into Me_3Si ethers approximately 18 h before injection. Columns of 1/8-inch o.d. stainless-steel tubing were packed as follows: (*A*) 4 ft, 1:1 (*w/w*) mixture[27] of 20% BDS and 20% Apiezon M separately coated on Chromosorb W (60–80 mesh); (*B*) 6 ft, 3% OV-17 on Gas Chrom Q (80–100 mesh); (*C*) 2.5 ft, 3% OV-17 on Gas Chrom Q (80–100 mesh); (*D*) 4 ft, 3% 8BP on Chromosorb W (80–100 mesh); (*E*) 6 ft, 3% JXR on Gas Chrom Q (100–120 mesh); (*F*) 12 ft, 15% Carbowax 20M on Gas Chrom Q (80–100 mesh).

Column programming was isothermal with helium as the carrier gas and with flame-ionization detection. Melting points were determined in capillary tubes and are corrected. Optical rotations were measured in a 1-dm tube. Pyridine was removed from organic phases by repeated washing with 5% aqueous cupric sulfate, and acetic acid was removed with aqueous $NaHCO_3$. Solutions were evaporated below 40° under diminished pressure. Precoated plates of Silica Gel F-254 (E. Merck, Darmstadt, Germany) were used for t.l.c. For column chromatography, Baker Analyzed Silica Gel (J. T. Baker Chemical Co., Phillipsburg, N. J.) was used without pretreatment. Solvents were proportioned on a *v/v* basis. Calcium hydride was used to dry DMF, pyridine, and dichloromethane.

O-*Acetyl-β*-D-*glucopyranosyl chlorides.* — *A.* Tetra-*O*-acetyl-*β*-D-glucopyranosyl chloride (**1a**) was prepared by the following modification of a published procedure[28]. A 500-ml Erlenmeyer flask that contained a mixture of 60 g of *β*-D-glucose pentaacetate and 13 g of powdered aluminum chloride in 300 ml of dichloromethane was stoppered and stirred for 45 min. The solution was poured into 600 ml of chloroform, washed three times with a slurry of ice and water, and dried over calcium chloride. The solvent was evaporated and the residue dissolved in 200 ml of ethyl ether. Evaporation gave **1a** (50 g) pure enough for most uses. One crystallization from ethyl ether gave 45 g of **1a** (80%); m.p. 96–98° (lit.[28] 99–100°).

*B. 2,3-Di-*O*-acetyl-4,6-*O*-ethylidene-β*-D-*glucosyl chloride* (**2a**). Prepared as above from 1,2,3-tri-*O*-acetyl-4,6-*O*-ethylidene-*β*-D-glucose[29] and crystallized once; it had m.p. 165–167° (lit.[22] 170–171°).

*C. Hepta-*O*-acetyl-β-maltosyl chloride* (**3a**). The method of Korytnyk and Mills[22] was used.

Orthoesters. — 3,4,6-Tri-*O*-acetyl-1,2-*O*-(ethoxyethylidene)-α-D-glucose (**1b**)

*The mention of firm names or trade products does not imply that they are endorsed or recommended by the Department of Agriculture over other firms or similar products not mentioned.

and hexa-*O*-acetyl-1,2-*O*-(methoxyethylidene)-α-maltose (**3b**) were prepared by published methods[30,31].

1,3,4,6-Tetra-O-*acetyl*-α-D-*glucose* (**1c**). — A solution containing 10 g of **1a** in 100 ml of acetone was treated with 4 ml of DMF and 10 ml of water. The reaction was complete after 2.5 h at 25°, as judged by t.l.c. (ether). Pyridine (4 ml) was added and the solution was evaporated at 30° to a volume of 30–40 ml. The concentrate was dissolved in 600 ml of ethyl acetate, washed twice with water, freed of residual pyridine, and finally dried and evaporated. Crystalline **1c** was obtained from ether: hexane (5.6 g, 60%), m.p. 95–97° (lit.[10] 98–100°, 110–111°).

1,3-Di-O-*acetyl-4,6*-O-*ethylidene*-α-D-*glucose* (**2c**). — Prepared from 18 g of **2a** as described for **1a**, crystalline **2c** was obtained from ether; yield, 9 g, m.p. 140–141°, $[\alpha]_D^{20}$ +117° (*c* 1, chloroform). For n.m.r. data see Table III.

Anal. Calc. for $C_{12}H_{18}O_8$: 49.7; H, 6.3. Found: C, 49.9; H, 6.5.

G.l.c. analysis showed that the mother liquors (7 g) contained 85% of **2d**.

2,3,4,6-Tetra-O-*acetyl*-β-D-*glucose* (**1e**). — A 5-g sample of **1e** was prepared by the method of McCloskey and Coleman[32]. A 1-g portion was dissolved in 50 ml of 90% aqueous acetone, kept for 48 h, and then evaporated. The residue, a mixture of **1d** and **1e**, served as a g.l.c. standard.

2,3-Di-O-*acetyl-4,6*-O-*ethylidene*-α-D-*glucose* (**2d**). — A 2-g sample of **2c** was streaked on four preparative t.l.c. plates, irrigated once with ether, and recovered. G.l.c. analysis of the syrupy extract (1.9 g) showed that the major component was **2d**, with traces of **2c** and **2e**. The syrup crystallized after long standing at room temperature. Pure **2d** was obtained from ether; yield, 1.5 g, m.p. 148–150°, $[\alpha]_D^{20}$ +72° (*c* 1.1, chloroform). For n.m.r. data see Table III.

Anal. Calc. for $C_{12}H_{18}O_8$: C, 49.7; H, 6.3. Found: C, 49.9; H, 6.1.

A 0.1-g sample of **2d**, after equilibration in aqueous acetone, served as a g.l.c. standard.

2,3,6,2',3',4',6'-Hepta-O-*acetyl*-β-*maltose* (**3e**). — A 1-g sample of **3a** was added to a solution containing 10 ml of pyridine and 1 ml of water. The solution was kept 18 h at room temperature and then was poured into 250 ml of ethyl acetate. Pyridine was removed and the residue was crystallized from ethanol; yield, 0.7 g, m.p. 187–188° (lit.[33] 188°).

A 0.1-g sample was equilibrated in aqueous acetone and served as a g.l.c. standard.

Aqueous hydrolyses. — General procedure. A 4-dram screw-capped bottle that contained a 0.5-g sample of **a** or **b** dissolved in 5 ml of solvent was used in each case. Each solution was treated with an indicated amount of water or aqueous solution, and the reaction was allowed to proceed at room temperature unless otherwise noted. Mixtures that were not homogeneous were shaken vigorously during the reaction period, and samples that contained silver salts were protected from light. Each reaction was monitored by t.l.c. (ethyl ether, R_F **c**<R_F **d** or **e**), and 0.2 ml samples were removed at intervals for g.l.c. analysis and quenched in a solution of pyridine (1 ml), hexamethyldisilazane (1 ml), and chlorotrimethylsilane (0.5 ml). The ratio of

hydrolytic products at the end of each reaction was expressed as 1-OH:2-OH (**d**+**e**:**c**) in Tables I and II.

A. A series of **1a** samples was prepared for each of three solvents: acetone, 11 samples per series; DMF, 10 samples; pyridine, 10 samples. The first sample in each series was treated with water (0.5 ml); the second and third with aqueous sodium (or lithium) trifluoroacetate (0.5 ml, 0.4 g/ml); the fourth and fifth with aqueous sodium (or lithium) acetate (0.5 ml per 0.2 g/ml); the sixth and seventh with aqueous sodium (or lithium) chloride (0.5 ml per 0.2 g/ml); the eighth with a mixture of water (0.5 ml) and silver acetate (0.2 g); the ninth with 90% aqueous acetic acid (2 ml); the tenth with aqueous DMF (0.5 ml, 0.2 g); and the eleventh with aqueous pyridine (0.5 ml, 0.2 g). Sample 10 was omitted from the DMF series and sample 11 from the pyridine series. Hydrolyses were complete within 2.5–3 h (see Table I).

B. Hydrolyses of **2a** and **3a** were performed as described for **1a**, but samples containing lithium salts were omitted. Hydrolyses of **2a** were complete in less than 1 h; **3a** required 1.5–2.5 h.

C. Six samples of **1a**, **2a**, or **3a** in dichloromethane were prepared. The first sample in each series was treated with 2 ml of 90% aqueous acetic acid, and the other samples with a mixture of 2 ml of 90% aqueous acetic acid and one of the solutes, in pure form, described in *A*. Reactions were complete within 0.5–1.5 h. Rapid decomposition of **2a**, **2c**, **2d**, and **2e** was noted in mixtures that did not contain pyridine, silver acetate, or sodium acetate.

D. Duplicate samples of **1a** or **3a** were dissolved in acetone, DMF, or pyridine. Each sample was treated with 0.5 ml of water and the first member of each pair was placed in an ice bath whereas the other was kept at room temperature. The samples kept cold were hydrolyzed two to four times more slowly than their counterparts at room temperature. For each pair, the 1-OH:2-OH ratios were identical (±1%) at completion, and matched the corresponding value in Table I.

E. Four samples of **1a** or **3a** were dissolved in DMF or pyridine. The ratio of a:solvent:water was varied by changing the water content as follows: 0.1 ml, 1:10:0.2, 0.25 ml, 1:10:0.5; 0.5 ml, 1:10:1; and 1 ml, 1:10:2. As the water content decreased, the time of hydrolysis increased sharply. The 1-OH:2-OH ratio was identical (±1%) for each series member, and equal to the corresponding 1:10:1 *w/v/v* values of Table I.

F. Three samples of **1b** or **3b** were dissolved in either DMF or acetone, and a single sample of each was dissolved in dichloromethane. The first sample in each series was treated with 2 ml of 90% aqueous acetic acid. The reaction in acetone and dichloromethane was complete within 2 h; in DMF the reaction required approximately 60 h. The second sample in the DMF and acetone series was treated with 0.5 ml of M HCl, and the third sample was 0.5 ml of M trifluoroacetic acid. Reactions were complete within 20 min. Results are shown in Table II.

*G. 1,3,6,2',3',4',6'-Hepta-*O*-acetyl-α-maltose* (**3c**). A 25-g portion of **3a** was dissolved in a mixture of acetone (200 ml) and DMF (10 ml) and then was treated with 25 ml of water. The reaction was kept for 1.5 h at room temperature, treated

with pyridine (10 ml), and worked up as described for **1c**. The final syrup (24 g, 62:38 1-OH:2-OH) was methylated immediately.

H. Korytnyk–Mills hydrolysis[22] *of* **2a**. A solution of **2a** (0.5 g) in acetone (5 ml) was treated with a mixture of silver carbonate (0.5 g) and silver nitrate (0.1 g) and shaken vigorously. Samples (0.2 ml) were removed at $t+7$ min and $t+20$ min, quenched, and analyzed. The 1-OH:2-OH ratio was 35:65 for each sample. Crystalline **2c** was obtained from ether.

G.l.c. analyses. — The products of each hydrolysis, as monotrimethylsilyl ethers, were eluted in the order: **d**, **e**, and **c**. Often the peaks overlapped those of one or more of their methylated counterparts, **f**, **g**, and **h**.

A. Analyses of hydrolyzates. Compounds **1a** or **1b**, columns *A* (190°), *B* (180°, **d** overlapped **e**), and *D* (170°); **2a**, columns *B* (155°) and *D* (145°); **3a** or **3b**, column *C* (230°, **d** partially overlapped **e**).

B. Methylated products **f**, **g**, *and* **h**. Compound **1**, column *A* (195°, **f** overlapped **h**); **2**, column *B* (165°); **3**, column *C* (235°, **g** overlapped **h**).

Methylation. — *A. Reagents.* A solution of diazomethane in dichloromethane was prepared in a stoppered flask fitted with a bottom drain. A simplified Arndt[34] procedure was employed, with dichloromethane as a substitute for ether (2.5:1 *v/v*). The stock solution of boron trifluoride etherate contained 2 ml of etherate diluted to 50 ml with dichloromethane.

B. The methylation procedure of Mastronardi and coworkers[25] was modified slightly. A solution of pure compound or mixture in dichloromethane (1 g per 5–10 ml) was chilled in an acetone–solid CO_2 bath. Reaction was initiated by adding 1–3 ml of boron trifluoride solution, and then diazomethane solution was added until a faint yellow color persisted. The reaction mixture was kept at the bath temperature at all times. If the initial quantity of diazomethane was not immediately decolorized, additional boron trifluoride solution was added until evolution of gas was noted. For normal reactions, a second addition of boron trifluoride (1–3 ml) and diazomethane completed the reaction (yellow color persisted), as judged by the onset of polymer formation and by t.l.c. (ether). Reaction time was 10–15 min overall. Pyridine and Celite were added and the mixture was filtered. The filtrate was washed to remove pyridine and water-soluble substances.

C. A 1-g mixture of **1c** (10%), **1d** (73%), and **1e** (17%) was methylated and analyzed by g.l.c. The product mixture contained **1f** (12%), **1g** (4%), and **1h** (18%). The remainder was **1d**.

D. Samples (1 g) of **1e** and **3e** were separately methylated and analyzed by g.l.c. A single product was formed each time, **1h** or **3h**, and all starting materials were consumed.

E. Methylation of 1.2 g of **1c** gave **1f** as the only product. Crystalline **1f** (1.1 g, m.p. 104–106°, lit.[25] (107–108°) was obtained from 2-propanol.

*F. 1,3-Di-*O*-acetyl-4,6-*O*-ethylidene-2-*O*-methyl-α-*D*-glucose* (**2f**). A 6-g sample of **2c** was methylated. Crystalline **2f** (6 g, 95%) was obtained from 2-propanol; m.p. 107–108°, $[\alpha]_D^{20}$ +118° (*c* 0.96, chloroform). For n.m.r. data see Table III.

Anal. Calc. for $C_{13}H_{20}O_8$: C, 51.3; H, 6.6; OMe, 10.2. Found: C, 51.3; H, 6.7; OMe, 10.5.

G. Crude 1,3,6,2',3',4',6'-hepta-O-acetyl-2-O-methyl-α-maltose (**3f**). A 24-g mixture of **3c** (38%), **3d** (55%), and **3e** (7%) was methylated, and a 0.2-ml sample was removed. Analysis showed **3d** (53%), **3e** (4%), **3g**+**3h** (5%), and **3f** (38%). The mixture was fractionated on a 60 × 750 mm column of silica gel (chloroform:acetone 9:1). The fraction containing **3f**, **3g**, and **3h** weighed 11 g. Pure **3f** (600 mg) was separated from 1 g of the mixture by preparative t.l.c. (methyl cyclopentane:acetone 7:3, two ascents); $[\alpha]_D^{20}$ +139° (*c* 0.8, chloroform). For n.m.r. data, see Table III.

Anal. Calc. for $C_{27}H_{38}O_{11}$: C, 49.8; H, 5.9. Found: C, 49.6; H, 5.8.

3,6,2',3',6'-Hexa-O-acetyl-2-O-methyl-α,β-maltose (**3i**). — A 10-g portion of these methylated products was dissolved in 40 ml of tetrahydrofuran and treated with 9 ml of piperidine. The reaction mixture was kept for 3 h at room temperature and then poured into a solution that contained 10 ml of glacial acetic acid in 1,500 ml of ethyl acetate. The mixture was washed twice with water and then was freed of acetic acid. G.l.c. analysis showed that 95+% of the **3f** initially present had been converted into **3i**. Column chromatography with silica gel (chloroform:acetone 9:1) gave pure **3i** (7.4 g, 32%). A crystalline mixture that contained both anomers was obtained from 2-propanol (6.7 g, 29%); m.p. 126–128°.

Anal. Calc. for $C_{25}H_{36}O_{17}$: C, 49.3; H, 6.0, OMe, 5.1. Found: C, 49.1; H, 6.1, OMe, 5.4.

G.l.c. analysis (column *F*, 215°) showed a deacetylated sample to be pure 2-*O*-methylmaltose.

1,3,6,2',3',4',6'-Hepta-O-acetyl-2-O-methyl-β-maltose (**3j**). — A 2.5-g sample of **3i** was acetylated at reflux in a mixture of acetic anhydride (10 ml) and sodium acetate (1 g). Crystalline **3j** was obtained from ethyl ether and a pure product (1.2 g, 48%) resulted after one recrystallization from methanol; m.p. 143–144.5°, $[\alpha]_D^{20}$ +86° (*c* 1.1, chloroform). For n.m.r. data see Table III.

Anal. Calc. for $C_{27}H_{38}O_{18}$: C, 49.8; H, 5.9; OMe, 4.8. Found: C, 49.8; H, 6.0; OMe, 4.8.

ACKNOWLEDGMENTS

Dr. D. Weisleder recorded the n.m.r. spectra and Mrs. B. Heaton, the microanalyses.

REFERENCES

1 R. W. Jeanloz and D. A. Jeanloz, *J. Amer. Chem. Soc.*, 79 (1957) 2579.
2 C. P. J. Glaudemans and H. G. Fletcher, Jr., *Carbohyd. Res.*, 7 (1968) 480.
3 E. J. Bourne, M. Stacey, C. E. M. Tatlow, and J. C. Tatlow, *J. Chem. Soc.*, (1951) 826.
4 E. J. Bourne, A. J. Huggard, and J. C. Tatlow, *J. Chem. Soc.*, (1935) 735.
5 J. E. Hodge and C. E. Rist, *J. Amer. Chem. Soc.*, 74 (1952) 1498.
6 A. Klemer, *Chem. Ber.*, 96 (1963) 634.
7 R. U. Lemieux and G. Huber, *Can. J. Chem.*, 31 (1953) 1040.

8 B. HELFERICH AND J. ZIRNER, *Chem. Ber.*, 95 (1962) 2604.
9 H. C. SRIVASTAVA AND K. V. RAMALINGAM, *Ind. J. Chem.*, 7 (1969) 1206.
10 R. U. LEMIEUX AND A. R. MORGAN, *Can. J. Chem.*, 43 (1965) 2190.
11 B. CAPON, *Chem. Rev.*, 69 (1969) 407.
12 H. PAULSEN, W.-P. TRAUTWEIN, F. G. ESPINOSA, AND K. HEYNS, *Chem. Ber.*, 100 (1967) 2822.
13 W. M. CORBETT, J. KIDD, AND A. M. LIDDLE, *J. Chem. Soc.*, (1960) 616.
14 B. HELFERICH AND J. ZIRNER, *Chem. Ber.*, 96 (1963) 385.
15 B. LINDBERG, O. THEANDER, AND M. S. FEATHER, *Acta Chem. Scand.*, 20 (1966) 206.
16 B. H. KOEPPEN, *Carbohyd. Res.*, 13 (1970) 193.
17 J. F. KING AND A. D. ALLBUTT, *Can. J. Chem.*, 48 (1970) 1754.
18 W. E. DICK, JR., D. WEISLEDER, AND J. E. HODGE, *Abstr. Papers Amer. Chem. Soc. Meeting*, 157 (1969) Carb. 13.
19 E. H. CORDES, in A. STREITWIESER AND R. W. TAFT (Eds.), *Progress in Physical Organic Chemistry*, Vol. 4, Interscience, New York, 1967, p. 1.
20 R. U. LEMIEUX AND C. BRICE, *Can. J. Chem.*, 33 (1955) 109.
21 W. A. BONNER, *J. Org. Chem.*, 24 (1959) 1388.
22 W. KORYTNYK AND J. A. MILLS, *J. Chem. Soc.*, (1959) 636.
23 K. IGARASHI, T. HONMA, AND J. IRISAWA, *Carbohyd. Res.*, 13 (1970) 49.
24 S. J. ANGYAL AND G. J. H. MELROSE, *J. Chem. Soc.*, (1965) 6501.
25 I. O. MASTRONARDI, S. M. FLEMATTI, J. O. DEFERRARI, AND E. G. GROS, *Carbohyd. Res.*, 3 (1966) 177.
26 H. ARITA, T. IKENAKA, AND Y. MATSUSHIMA, *J. Biochem.* (Tokyo), 69 (1971) 401.
27 L. R. SCHROEDER, J. W. GREEN, AND D. C. JOHNSON, *J. Chem. Soc. (B)* (1966) 447.
28 R. U. LEMIEUX, *Methods Carbohyd. Chem.*, 2 (1963) 224.
29 D. M. HALL AND O. A. STAMM, *Carbohyd. Res.*, 12 (1970) 421.
30 R. U. LEMIEUX AND J. D. T. CIPERA, *Can. J. Chem.*, 34 (1956) 906.
31 E. PASCU AND F. V. RICH, *J. Amer. Chem. Soc.*, 57 (1935) 587.
32 C. M. MCCLOSKEY AND G. H. COLEMAN, *Org. Syn., Coll. Vol.*, 3 (1955) 434.
33 R. M. ROWELL AND M. S. FEATHER, *Carbohyd. Res.*, 4 (1967) 486.
34 F. ARNDT, *Org. Syn., Coll. Vol.*, 2 (1943) 165.