Studies on Glycosylation. III.¹⁾ A Novel, Stereospecific Synthesis of 1-O-Acyl- and 1-Aryl- β -D-glucopyranose Tetraacetates *via* the 1,2-*t*-Butyl-orthoacetate

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1-O-Acyl- β -D-glucopyranose tetraacetates (I—IX) were obtained in high yields by the condensation of acetylated α -D-glucopyranose 1,2-*t*-butyl orthoacetate) with carboxylic acids in chlorobenzene under reflux. The similar reaction with some phenols and *p*-nitrothiophenol provided the corresponding aryl- β -D-glucoside derivatives (X—XII).

1-O-Acyl glucoses have rarely distributed in Nature. However, some examples have hitherto been reported.³⁾ Quilico, *et al.* isolated the so-called periplanetin from the secretion of the cockroaches and determined the structure to be 1-O-benzoyl- β -D-glucopyranose.^{3a)} Tschesche, *et al.* obtained two 1-O-acyl- β -D-glucopyranoses, tuliposide-A and -B, from tulip, which are biologically active.^{3b)}

The preparation of acetylated 1-O-acyl- β -D-glucoses is usually based on the following reactions; the condensation of α -acetobromoglucose with a carboxylic acid silver salt⁴⁾ and the condensation of 2,3,4,6-tetra-O-acetyl- β -D-glucose with an acyl halide.⁵⁾

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The orthoester method for synthesis of glycosides, including oligo and polysaccharides, has been developed by Kochetkov and his co-workers.⁶⁾ Recently, Volkova, *et al.* have employed the stereospecific synthesis of β -D-glucopyranosyl phosphate by use of glucose 1,2-alkyl orthoacetate and dibenzyl phosphate.⁷⁾ However, application of the orthoester method to the synthesis of 1-O-acyl derivatives have not been reported.

To prepare acetylated 1-O-acyl- β -D-glucopyranoses, we employed a reaction by use of glucose 1,2-(*t*-butyl orthoacetate). As shown in Chart 1, the reaction of the orthoacetate with several free aromatic and aliphatic carboxylic acids in chlorobenzene under reflux afforded the corresponding 1-O-acyl- β -D-glucopyranose tetraacetates (I—IX) in good yield. Moreover, synthesis of aryl glucosides (X—XII) by similar reaction was also carried out.

Experimental

General Procedure—Melting points were determined on a H₂SO₄ bath and are uncorrected. $[\alpha]_D$ values were determined on a Yanagimoto OR 50 and optical rotatory dispersion (ORD) spectra on a Jasco model ORD/UV-5 polarimeter. Nuclear magnetic resonance (NMR) spectra were recorded on a Hitachi R-22 apparatus using tetramethyl silane (TMS) as an internal standard. Thin-layer chromatography (TLC) was performed on Silica gel F 254 (Merck Co. Ltd.) with benzene–MeOH (100:2) throughout this experiment.

Materials—The carboxylic acids used were obtained from commercial sources. 3,4,6-Tri-O-acetyl- α -D-glucopyranose 1,2-(*t*-butyl orthoacetate) was prepared by the method of Kochetkov, *et al.*^{6a)}

Preparation of 1-O-Acyl- β -D-glucopyranose Tetraacetates (I—IX)—A solution of 3,4,6-tri-O-acetyl- α -D-glucopyranose 1,2-(*t*-butyl orthoacetate) (200 mg, 0.5 mmole) and each carboxylic acid (0.6 mmole) in chlorobenzene (10 ml) was refluxed for 1 hr. The solution was evaporated under reduced pressure and the residue was crystallized from ethanol. The recrystallization from the same solvent gave the respective 1-O-acyl- β -D-glucopyranose tetraacetate as colorless needles in 70–90% yields.

Preparation of Aryl- β -D-glucopyranoside Tetraacetates (X—XII)—A solution of 3,4,6-tri-O-acetyl- α -D-glucopyranose 1,2-(*t*-butyl orthoacetate) (320 mg, 0.8 mmole) and each phenol (1.0 mmole) in chlorobenzene (10 ml) was refluxed for 1–2 hr. The solution was evaporated under reduced pressure and the residue was crystallized from ethanol. The recrystallization from the same solvent gave the respective glucoside derivative as colorless needles.

Results and Discussion

According to the procedure shown in Chart 1, the reaction of 3,4,6-tri-O-acetyl- α -D-glucopyranose 1,2-(*t*-butyl orthoacetate) with carboxylic acids, including benzoic, salicylic, acetylsalicylic, aristrochic, *p*-nitrophenylacetic, cinnamic, hippuric, propionic, and stearic acids, was carried out in chlorobenzene under reflux without any catalyst and gave the corresponding 1-O-acyl-2,3,4,6-tetra-O-acetyl- β -D-glucopyranoses (I—IX) as colorless needles in good yields, (70–90%). The purity of each product was guaranteed by elemental analysis and TLC examination. The structures were confirmed by the NMR and analytical data, which were shown in Table I and II.

1-O-Acyl-glucose derivatives prepared were confirmed to be β -anomers on the basis of the following findings: 1) I—IX showed negative or positive low values in specific rotation and showed negative Cotton effect or negative plane curve on the ORD spectra.⁸⁾ 2) On the NMR spectra⁹⁾ signals of the anomeric proton were observed at 5.69–6.01 ppm as a doublet, $J=7$ –8 Hz, or a doublet as doublet, $J=6$ –7 Hz, which were shown in Table II. In the aromatic 1-O-acyl derivatives (I—IV) signals of the anomeric proton were complicated by additional small signals, which may be explained by the long-range coupling of the C-1 proton with the C-3 or other protons, caused with the effect of aromatic ring. As we would anticipate

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TABLE I. 1-O-Acyl- β -D-glucopyranose Tetraacetates

	R-CO-	Yield (%) ^{a)}	mp (°C)	[α] _D ^{25b)}	Formula	Analysis (%)		
						Calcd. (Found)	C	H N
I	benzoyl ^{c)}	79	144—145	−27°	C ₂₁ H ₂₄ O ₁₁	55.75 (56.00)	5.35 (5.13)	
II	salicyl ^{d)}	70	183—184	−35°	C ₂₁ H ₂₄ O ₁₂	53.85 (53.92)	5.16 (4.93)	
III	acetyl salicyl ^{e)}	73	174—175 ^{f)}	−55°	C ₂₃ H ₂₆ O ₁₃	54.12 (54.05)	5.13 (5.01)	
IV	aristlochyl	82	245	−235°	C ₃₁ H ₂₉ O ₁₆ N	55.44 (55.42)	4.35 (4.13)	2.08 (1.97)
V	<i>p</i> -nitrophenyl acetyl	83	135.5	−9°	C ₂₂ H ₂₅ O ₁₁ N	51.67 (51.57)	4.93 (4.78)	2.74 (2.56)
VI	cinnamyl	93	141—142	−29°	C ₂₃ H ₂₆ O ₁₆	57.74 (57.86)	5.48 (5.48)	
VII	hippryl ^{g)}	90	191—192	+2°	C ₂₃ H ₂₇ O ₁₂ N	54.22 (54.22)	5.34 (5.38)	2.75 (2.99)
VIII	propionyl ^{h)}	68	98	+4°	C ₁₇ H ₂₄ O ₁₁	50.49 (50.54)	5.98 (5.75)	
IX	stearyl ⁱ⁾	72	78	+3°	C ₃₂ H ₅₄ O ₁₁	62.52 (62.44)	8.85 (8.49)	

a) Based on the sugar used.

b) ($c=1.0$, CHCl₃)c) cf. lit.^{4a)} mp 143—146°, [α]_D²⁰ −28.1°d) cf. lit.^{4a)} mp 184°, [α]_D²⁰ −43.4°e) cf. lit.⁵⁾ mp 116—117°, [α]_D²⁰ −41.0°

f) This moistured at about 115° and completely melted at 174—174°.

g) cf. lit.^{4a)} mp 193—194°, [α]_D²⁰ +3.64°h) cf. lit.^{4c)} mp 102—103°, [α]_D²⁶ +5.3°i) cf. lit.^{4c)} mp 77°, [α]_D²⁶ +4.0°TABLE II. Spectral Data of 1-O-Acyl- β -D-glucopyranose Tetraacetates

Compd. No.	ORD ^{a)} Trough (nm)	[α] _D ²² trough	NMR (CDCl ₃) ^{b)} : δ , Hz Anomeric proton
I	283	−88°	6.00, dd, $J=6$ and 2
II	243	−440°	5.97, dd, $J=6$ and 2
III	331	−364°	5.88, dd, $J=7$ and 2
IV	425	−542°	6.01, d, $J=8^c)$
V	300	−440°	5.69, d, $J=7.6$
VI	284	−750°	5.89, d, $J=8$
VII	256	−200°	5.85, d, $J=7$
VIII	negative plane		5.79, d, $J=7$
IX	negative plane		5.76, d, $J=7$

a) The ORD spectra were determined at a concentration of 0.1% in CHCl₃.b) Other signals of sugar moiety were commonly observed as follows. 2.00—2.10 (4×COCH₃), 3.80—4.00 (1H, m, C₅-H), 4.20—4.30 (2H, octet, C₄-H), 4.95—5.66 (3H, m, C_{2,3,4}-H).

c) But, this signal showed additional small signals between the strong outer lines like a multiplet.

from the results observed in the preparation of glycosides by the orthoester method,⁶⁾ acylation of glucose C-1 position *via* the 1,2-orthoester also exclusively provided 1,2-*trans*-anomers.

Analogous reaction of the glucose 1,2-(*t*-butyl orthoacetate) with phenols (*p*-nitrophenol, 7-hydroxycumarine) and *p*-nitrothiophenol were carried out. As shown in Table III, the product (X—XII) were obtained as colorless needles. They were compared with the literatural

TABLE III. 1-Aryl-2,3,4,6-tetra-O-acetyl- β -D-glucopyranosides

	R	Yield (%) ^{a)}	mp (°C)	[α] _D ^{25b)}	Formula	Analysis (%)		
						Calcd. (Found)		
						C	H	N
X	<i>p</i> -nitrophenyl ^{c)}	71	175—176	−36°	C ₂₀ H ₂₃ O ₁₂ N	51.18 (51.26)	4.94 (5.04)	2.98 (3.19)
XI	7-hydroxycumaryl ^{d)}	33	179—180	−38°	C ₂₃ H ₂₄ O ₁₂	56.10 (56.21)	4.91 (5.06)	
XII	<i>p</i> -nitrothiophenyl ^{e)}	35	180—181	−44°	C ₂₀ H ₂₃ O ₁₁ NS	49.48 (49.35)	4.77 (4.44)	2.86 (2.98)

a) Based on the sugar used.

b) (*c*=1.0, CHCl₃)c) cf. lit.^{8a)} mp 174—175°, [α]_D −41°d) cf. lit.^{8b)} mp 183—184°, [α]_D −63.3°e) cf. lit.^{8c)} mp 181—183°, [α]_D −34.1°

values in melting point and specific rotation,¹⁰⁾ and X was identical with the authentic sample prepared by the method previously reported.¹¹⁾ Further, they all showed negative Cotton effect on the ORD spectra, indicating all of the products to be β -D-configuration.

In the reaction with hydroxycarboxylic acid such as salicylic acid, the product obtained was predominantly the 1-O-acyl derivative (II), indicating that the condensation of the orthoester with carboxylic acid group proceeded more rapidly than phenol group.

The orthoesters are resistant toward alkali and very acid-sensitive. Consequently, it was assumed that the glycosylation by use of orthoesters without catalyst was affected by the acidity of the reactants. Thus, the reaction with carboxylic acids gave 1-O-acyl derivatives in high yields. However, the yields of 1-aryl products were dependent upon the degree of acidity of phenols. In the case of *p*-nitrophenol the yield (71%) of the product showed as high as those in carboxylic acids, but in other phenols the yields were lower than 40%. In the similar reaction in benzene under reflux, aromatic acids whose *pK_a* are lower than about 4 reacted with the orthoester to afford the corresponding products (I—V) in about 35—50% yields, which were lower than those in chlorobenzene, but aliphatic acids such as propionic and stearic acids, and phenols could not react at all.

It is well known that the orthoesters are useful starting materials in the stereospecific synthesis of 1-O-glycosides in the presence of suitable catalysts.⁶⁾ It was shown from our results that the orthoester method was successfully applied to the stereospecific synthesis of 1-O-acyl and some 1-aryl derivatives without any catalyst.

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