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Structure and Reactivity of Glycosides: IV.[1] Koenigs–Knorr Synthesis of Aryl β-*D*-Glucopyranosides Using Phase-Transfer Catalysts

A. E. Pavlov, V. M. Sokolov, and V. I. Zakharov

St. Petersburg State Institute of Technology, St. Petersburg, Russia

Research and Production Association of Pulp-and-Paper Industry, St. Petersburg, Russia

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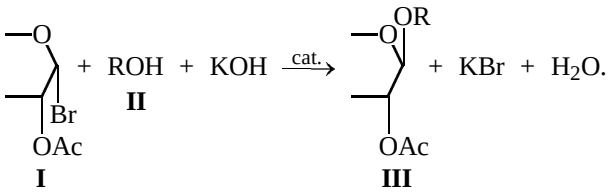
Abstract—A series of acetylated aryl β-*D*-glucopyranosides were prepared in 12–63% yields from tetra-*O*-acetyl-α-*D*-glycopyranosyl bromide and phenols containing acyl, formyl, and hydroxy substituents, and also from sterically hindered phenols in the two-phase system chloroform–aqueous alkali in the presence of triethylbenzylammonium chloride. Hydroxyethylated sucrose and dibenzo-18-crown-6 do not behave as phase-transfer catalysts in glycosylation of phenols.

One of the main routes to acetylated 1,2-*trans*-glycosides is the Koenigs–Knorr procedure based on the reaction of appropriate 1,2-*cis*-halo derivatives of protected sugars (mainly bromides) with phenols in solution of an alkali in aqueous acetone [2]. The reaction is accompanied by inversion of the glycoside center configuration and yields exclusively 1,2-*trans* isomers. In several studies, glycosylation of phenols with bromo derivatives of benzylated and acetylated sugars was performed with phase-transfer catalysts [3–7]. Such a modification of the Koenigs–Knorr procedure allows not only synthesis of known 1,2-*trans*-arylglucopyranosides in high yields, but also preparation of previously unknown derivatives. Furthermore, the synthesis and workup procedure is very simple.

Proceeding with studies on synthesis of arylglycosides, we faced serious problems with glycosylation of complex and sterically hindered phenols with tetra-*O*-acetyl-α-acetyl-α-*D*-glucopyranosyl bromide **I** under classical conditions of the Koenigs–Knorr reaction. Phenols with acyl, formyl, and hydroxymethyl substituents, as well as phenols with other hydroxyl-containing substituents and phenols containing *o*-substituents in the aromatic ring, did not react with α-acetylbromoglucose **I**, and only in a few cases the corresponding acetylated aryl β-*D*-glucopyranosides were isolated in very low yields. Our attempts to prepare glycosides of complex and sterically hindered phenols by their glycosylation with full acetates of sugars (Helferich reaction) in the presence of Brønsted and Lewis acids (*p*-toluenesulfonic, sulfuric, and orthophosphoric acids, tin tetrachloride, zinc chloride, etc.) failed also.

Low yields of aryl glycosides prepared by the Koenigs–Knorr reaction of bromide **I** with phenols are probably due to degradation of **I** in aqueous acetone under the action of alkalis and lability of phenols with oxygen-containing substituents under the reaction conditions.

In this connection, we examined the possibility of preparing glycosides of some natural phenols by the Koenigs–Knorr reaction using phase-transfer catalysts:



I **II** **III**

R is substituted phenyl; cat. is phase-transfer catalyst.

The initial tetra-*O*-acetyl-α-*D*-glucopyranosyl bromide **I** was prepared by treatment of penta-*O*-acetyl-α- and β-*D*-glucopyranose with a solution of hydrogen bromide in glacial acetic acid [8]. Because of instability of **I**, it was stored for no more than 1–2 days in a vacuum desiccator in the dark. As phase-transfer catalysts we tested hydroxyethylated sucrose **IV**, dibenzo-18-crown-6 **V**, and triethylbenzylammonium chloride **VI**. Hydroxyethylated sucrose containing seven hydroxyethyl groups per hydroxy group of sucrose was prepared by treatment of sucrose with oxirane in dimethyl sulfoxide [9]. Triethylbenzyl-

[1] For communication III, see [1].

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Table 1. Aryl tetra-*O*-acetyl-β-*D*-glucopyranosides

Comp. no.	Aryl	Yield, %	mp, °C	$[\alpha]_D^{20}$ (*c* 1, $CHCl_3$), deg	Found, %		Formula	Calculated, %	
					C	H		C	H
IIIa	4-Acetylphenyl	42	168–169	–27	56.49	5.41	$C_{22}H_{26}O_{11}$	56.65	5.65
IIIb	4-Propionylphenyl	44	158–159	–13	57.19	5.68	$C_{23}H_{28}O_{11}$	57.50	5.87
IIIc	2-Propionylphenyl	12	164–165	–9.5	57.28	5.84	$C_{23}H_{28}O_{11}$	57.50	5.87
IIId	2-Methoxy-4-propionylphenyl	63	158–159	–38.5	58.20	6.58	$C_{24}H_{30}O_{12}$	56.47	5.92
IIIe	2-Formylphenyl	35	138–139	–29	54.97	5.35	$C_{21}H_{23}O_{11}$	55.75	5.35
IIIf	2-Methoxy-5-formylphenyl	50	140–141	–25	55.45	5.67	$C_{22}H_{25}O_{12}$	54.77	5.43
IIIg	4-Hydroxymethylphenyl	39	168–169	–12	54.83	5.79	$C_{21}H_{25}O_{11}$	55.50	5.77
IIIh	4-(1-Hydroxypropyl)-2-methoxyphenyl	35	[a]	–5.5	53.98	6.08	$C_{24}H_{32}O_{12}$	56.24	6.29
IIIi	2,6-Dimethylphenyl	25	91–92	0	54.58	6.02	$C_{22}H_{28}O_{10}$	58.40	6.24

[a] Syrupy substance.

ammonium chloride was prepared from benzyl chloride and triethylamine [10].

The catalytic activity of **IV** and **V** in glycosylation was tested using as an example the reaction of **I** with 4-acetylphenol **IIa** in the system acetone–solid KOH at room temperature. The reaction completion was judged from attainment of the constant optical rotation angle of the reaction mixture. We found that the reaction is complete in approximately 45 h, giving 4-acetylphenyl tetra-*O*-acetyl-β-*D*-glucopyranoside **IIIa** in 7–13% yield depending on the initial amount of the catalyst. In the absence of **IV** and **V**, the results were similar.

The pattern was quite different when the reaction was performed in the system chloroform–aqueous KOH in the presence of triethylbenzylammonium chloride. Preliminary experiments with varied initial amounts of reactants and catalyst **VI** showed that the highest yields of the target product **III** are attained with the molar ratio of phenol, α-acetylbromoglucose **I**, and triethylbenzylammonium chloride of 2 : 1 : 1. This ratio is close to that used by Dess *et al.* [6] in syntheses of glycosides of the simplest phenols. For example, we prepared glycoside **IIIa** in 42% yield by refluxing the reaction mixture for 3 h. Glycosylations of other phenols containing acyl, methoxy, formyl, and hydroxyalkyl substituents in various positions of the benzene ring, and also of sterically hindered phenols are complete in 3–5 h. Thus, we prepared various acetylated aryl β-*D*-glucopyranosides **IIIa**–**IIIi** in 12–63% yields (Table 1). Unprotected aryl β-*D*-glucopyranosides **VIIa**–**VIIg** were prepared by Zemplén deacetylation of the corresponding acetates with catalytic amounts of sodium methylate in methanol [2]. The product purity was confirmed by elemental analysis, optical rotation, and ^{13}C NMR spectroscopy (Tables 1–3).

By the example of the reactions of bromide **I** with 4-hydroxymethylphenol **IIg** and 4-(1-hydroxypropyl)-2-methoxyphenol **IIh**, we demonstrated that glycosylation in the presence of triethylbenzylammonium chloride involves exclusively phenolic hydroxyl, yielding aryl glycosides **IIIg** and **IIIh**. The alcoholic hydroxyl is not involved. Furthermore, alcoholic hydroxyl is not involved even in attempted glycosylation with **I** of a compound containing no phenolic hydroxyl, 1-(3,4-dimethoxyphenyl)-1-propanol.

Our experimental data allowed evaluation of the relative effect of various substituents in the aromatic ring on the reactivity of phenols in glycosylation. It is seen that *o*-formyl and especially *o*-acyl substituents decrease the reactivity of phenols and the yield of the target products. The *p*- and *m*-substituents affect the yields of acetylated aryl β-*D*-glucopyranosides insignificantly (Table 1).

Thus, the reactivity of phenols in phase-transfer glycosylation with bromide **I** is determined by the presence and nature of oxygen-containing substituents in the *o*-position of the phenyl ring. This conclusion is consistent with Tulvitie's data [7]; however, we cannot agree with Tulvitie's statement that the suggested procedure is inapplicable to synthesis of glycosidues of sterically hindered phenols, as we managed to prepare 2,6-dimethylphenyl tetra-*O*-acetyl-β-*D*-glycopyranoside in 25% yield. Our results, along with the data of Klein *et al.* [11] who prepared acetylated aryl β-*D*-galactopyranosides by phase-transfer glycosyla-

Table 2. Aryl β-*D*-glucopyranosides

Comp. no.	Aryl	Yield, %	mp, °C	$[\alpha]_D^{20}$ (*c* 1, pyridine), deg	Electronic spectrum		Found, %		Formula	Calculated, %	
					λ_{max}, nm	log λ_{max}	C	H		C	H
VIIa	4-Acetylphenyl	56	188–189	–32	214, 264	4.032, 4.184	56.61	6.10	$C_{14}H_{18}O_7$	56.37	6.08
VIIb	4-Propionyl-phenyl	77	162–163	–30	214, 263	3.967, 4.180	55.85	6.23	$C_{15}H_{20}O_7$	57.69	6.45
VIId	2-Methoxy-4-propionylphenyl	89	175–176	–34	223, 265, 300	4.180, 4.042, 3.787	54.44	6.79	$C_{16}H_{22}O_8$	56.14	6.48
VIIe	2-Formylphenyl	62	185–186	–19	210, 253, 310	4.233, 4.024, 3.531	52.78	6.04	$C_{13}H_{16}O_7$	54.93	5.67
VIIf	2-Methoxy-5-formylphenyl	64	174–175	–21	226, 276, 300 sh	4.194, 4.075, 3.978	50.63	5.66	$C_{14}H_{18}O_8$	53.50	5.77
VIIg	4-Hydroxymeth-ylphenyl	70	169–170	–17.5	249	4.140	51.13	6.20	$C_{13}H_{18}O_7$	54.54	6.34
VIIh	4-(1-Hydroxy-propyl)-2-meth-oxyphenyl	15	182–183	+55	–	–	61.17	7.68	$C_{16}H_{24}O_8$	56.81	7.02

Table 3. ^{13}C NMR spectra of acetylated and unprotected aryl β-*D*-glucopyranosides (δ_C, ppm)

Comp. no.	Carbohydrate moiety								Aromatic ring						Other signals
	C^1	C^2	C^3	C^4	C^5	C^6	CH_3	CO	C^1	C^2	C^3	C^4	C^5	C^6	
IIIa	98.0	70.9	72.1	68.1	72.4	61.8	20.3	170.1, 169.8, 169.1, 168.9	160.1	116.2	130.2	132.3	130.2	116.2	26.1 (CH_3)
IIIb	98.0	70.9	72.0	68.0	72.9	61.7	20.2	170.1, 169.7, 169.0, 168.8	159.8	116.2	129.7	134.0	129.7	116.2	31.2 (CH_2), 8.0 (CH_3), 198.9 (CO)
IIId	99.5	70.8	71.8	68.1	72.1	61.6	20.1	169.9, 168.9, 168.9, 168.7	149.7	150.1	115.6	132.9	121.4	117.7	55.8 (OCH_3), 31.1 (CH_2), 8.1 (CH_3), 198.9 (CO)
IIIe	99.0	70.9	72.1	68.1	72.3	61.7	20.3	170.3, 169.8, 169.1, 168.9	158.6	126.6	128.1	123.4	135.4	116.0	188.8 (CHO)
IIIf	99.9	70.9	72.1	68.3	72.3	61.9	20.3	170.3, 169.8, 169.2, 168.9	146.4	155.4	111.7	128.4	129.9	117.4	56.0 (OCH_3), 189.9 (CHO)
IIIg	98.0	70.9	72.0	68.1	72.4	61.8	20.3	170.1, 169.8 169.1, 168.9	160.0	116.0	131.3	124.8	131.3	116.0	51.7 (CH_2)
IIIh	100.6	71.1	71.7	68.4	72.5	61.8	20.2	170.4, 170.0, 169.2	144.9	150.4	110.1	134.7	119.8	118.3	55.9 (OCH_3), 130.2 (α-CH), 125.0 (β-CH), 16.1 (CH_3)
IIIi	101.3	71.5	71.7	68.5	72.9	61.6	20.1	170.1, 168.1	152.6	127.4	128.9	124.8	128.9	127.4	16.6 (CH_3)
VIIa	99.9	73.3	76.7	69.8	77.8	60.8	–	–	161.3	116.1	130.2	131.1	130.2	116.1	26.7 (CH_3), 196.7 (CO)
VIIb	100.2	73.5	76.8	69.9	77.4	61.0	–	–	161.3	116.2	130.2	130.9	130.2	116.2	8.5 (CH_3), 31.2 (CH_2), 199.4 (CO)

tion of phenols with tetra-*O*-acetyl-α-*D*-galactopyranosyl bromide, demonstrate wide prospects for using this modification of the Koenigs–Knorr procedure for preparing glycosides of various phenols.

EXPERIMENTAL

The ^{13}C NMR spectra of acetylated aryl glycosides were recorded on a Varian CFT-20 spectrometer with 50% solutions in $CDCl_3$, and those of the unprotected compounds, with solutions in $(CD_3)_2SO$. The internal reference was TMS. The electronic absorption spectra of aryl-β-*D*-glycopyranosides were recorded on an SF-26 spectrophotometer with 10^{-4}–10^{-5} M aqueous solutions. The optical rotation angles of the acetylated compounds were measured in chloroform, and those of the unprotected derivatives, in pyridine, using an SU-3 universal saccharimeter.

Aryl 2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosides IIIa–IIIi. A solution of 20 mmol of tetra-*O*-acetyl-α-*D*-glucopyranosyl bromide **I** in 100 ml of chloroform was added to a solution or suspension of 40 mmol of appropriate phenol, 50 mmol of KOH, and 20 mmol of triethylbenzylammonium chloride in 40 ml of water. The mixture was refluxed with stirring for 3–5 h. At 30-min intervals, a 1-ml sample was taken, and the optical rotation angle was determined after dilution with 9 ml of chloroform. After a constant value of the rotation angle was attained, the mixture was cooled to room temperature, and the $CHCl_3$ solution was separated, washed with 1 M KOH (2 × 100 ml) and water (2 × 100 ml), and dried over sodium sulfate. The solvent was distilled off in a vacuum, and the syrupy residue was crystallized from a minimal amount of hot ethanol. The product was vacuum-dried at 60°C.

Aryl β-*D*-glucopyranosides VIIa–VIIh. A 5-mmol portion of appropriate acetylated aryl β-*D*-glucopyranoside was suspended in 10 ml of absolute methanol, and 1 ml of a 1 M NaOMe solution in absolute methanol was added. The deacetylated product started to crystallize within 10–15 min. The mixture was left overnight in a refrigerator, and the crystals were filtered off, washed with methanol (1 × 30 ml), and vacuum-dried at 60°C.

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