Chemistry

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Abstract

Full Text

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Synthesis of Disaccharides

Recently we proposed a new method for constructing the glycosidic bond, based on the reaction of sugar ortho esters with the corresponding alcohols ([1]), which may be called the orthoester method for the synthesis of glycosides. The possibilities of this method, demonstrated earlier on several examples ([1–3]), are now being studied by us in greater detail in the synthesis of oligosaccharides. Extension of the method in this direction appears to be very important, since oligosaccharides, widely distributed in animal and plant tissues, are also products of the fragmentation of carbohydrate-containing biopolymers and model the principal type of linkage in polysaccharides. The present article sets forth the results obtained by us in using the orthoester method for the synthesis of disaccharides with glycopyranosidic linkages.

By this method we synthesized derivatives of 6-O-(β-*D*-glucopyranosyl)-*D*-galactose (1), 6-O-(β-*D*-galactopyranosyl)-*D*-galactose (2), 6-O-(α-*L*-rhamnopyranosyl)-*D*-glucose (rutinose) (3), 6-O-(β-*D*-glucopyranosyl)-*D*-glucose (gentiobiose) (4), 2-O-(β-*D*-glucopyranosyl)-*D*-glucose (sophorose) (5), and 5-O-(β-*D*-glucopyranosyl)-*D*-glucose (6) (see scheme). This choice of objects made it possible for us, under the conditions of glycoside synthesis, to examine the reactivity of ortho esters of three different monosaccharides (I, IV, VI) and of three types of sugar hydroxyls: a primary one at $C_{(6)}$, an equatorial secondary one at $C_{(2)}$, and an exocyclic secondary hydroxyl at $C_{(5)}$.

To obtain comparable data, all syntheses were carried out under very similar conditions. These average conditions cannot be regarded as optimal for each particular case, and therefore the yields obtained are apparently not maximal. The typical procedure consisted in treating the alcohol component with an alkyl orthoacetate of the second sugar in boiling nitromethane in the presence of catalytic amounts of $HgBr_2$, with azeotropic distillation of the liberated methanol or ethanol. The condensation conditions and the yields of the corresponding derivatives are presented in Table 1.

Table 1

Conditions of synthesis and yields of disaccharide derivatives

Scheme showing condensation reactions of protected monosaccharide derivatives I-XIII, with elimination of ethanol or methanol, and products labeled III, V, VIII, IX, XI, and XIII. Reactions are numbered (1)-(6).

Figure 1: Scheme showing condensation reactions of protected monosaccharide derivatives I-XIII, with elimination of ethanol or methanol, and products labeled III, V, VIII, IX, XI, and XIII. Reactions are numbered (1)-(6).

Ortho ester,[a] mmoles	Alcohol,[a] mmoles	CH_3NO_2, ml	$HgBr_2$, mmoles	Reaction duration, h	Condensation product,[a] yield,[b] %	Molar ratio: ortho ester : alcohol : $HgBr_2$
I([5]), 2.71	II([6]), 1.81	15	0.10	1.5	III[b], 51.5	1.5 : 1.0 : 0.055
IV([5]), 3.63	II([6]), 2.68	20	0.085	1.5	V[b], 64	1.35 : 1.0 : 0.032
VI([7]), 1.00	VII([8]), 1.00	10	0.03	3	VIII[b], 45	1.0 : 1.0 : 0.03
I([5]), 1.50	VII([8]), 1.00	10	0.03	1.5	IX[b], 35	1.5 : 1.0 : 0.03
I([5]), 5.35	X([9]), 4.22	25	0.13	3.5	XI[r], 20.5	1.26 : 1.0 : 0.03
I([5]), 1.86	XII([10]), 1.31	5	0.093	2.5	XIII[b], 9.6	1.42 : 1.0 : 0.071

[a] See scheme. [b] Yield of a chromatographically homogeneous preparation. [c] Analysis of the reaction mixture and homogeneity of the obtained preparation in system A. [d] Same in system B.

The specific rotations of the derivatives obtained, as well as the absence of condensation by-products in chromatographic analysis of the reaction mixtures in systems that resolve anomeric pairs (4), make it possible

Scheme

to assert that the condensation proceeds stereospecifically. Judging from the yields obtained, the orthoesters of the three monosaccharides studied

(*D*-glucose, *D*-galactose, and *L*-rhamnose) possess approximately the same reactivity, whereas the activity of the sugar hydroxyl decreases in the order $C_{(6)} > C_{(2)} > C_{(5)}$.

In the synthesis of the sophorose derivative we found two condensation products, one of which was identified as 2-O-(2,3,4,6-tetra-O-acetyl-β-*D*-glucopyranosyl)-4,6-O-benzylidene-α-methyl-*D*-glucopyranoside (XI). The second substance is the product of glucosylation of the C_{(3)} hydroxyl of X, i.e., a derivative of laminaribiose*.

The results obtained testify to the stability, under condensation conditions, of the protecting groups most widely used in sugar chemistry (acetyl, benzylidene, isopropylidene, methyl glycosidic). This makes it possible to use a broad range of sugar derivatives as the alcohol component in the orthoester method for the synthesis of glycosides, opening new and broad prospects for it.

Experimental Part

CH_3NO_2: the commercial solvent is distilled at 100–200 mm over urea and then twice over P_2O_5. Al_2O_3 neutral, activity grade III according to Brockmann. Thin-layer chromatography on Al_2O_3 in the systems $CHCl_3$—MeCOEt (98.5 : 1.5) (A) and $CHCl_3$—Me_2CO (9 : 1) (B). Paper chromatography, Goznak paper, in the system Bu—Py—W (6 : 4 : 3) (C). Melting points are corrected.

All syntheses of disaccharides were carried out according to the following standard scheme. Into a flask equipped with a straight condenser are placed the orthoester, the alcohol, and CH_3NO_2. The mixture is heated to boiling and the solvent is distilled off, while fresh nitromethane is added dropwise so that the volume of the reaction mixture remains constant (this volume is indicated in Table 1 in the column CH_3NO_2, ml). These conditions are maintained throughout the entire reaction period. After distillation of 5 ml, $HgBr_2$ is introduced. At the end of the reaction, 1–2 ml of pyridine is added and the mixture is evaporated to dryness. The synthesis conditions and yields are presented in Table 1.

1. **1,2:3,4-Di-O-isopropylidene-6-O-(2,3,4,6-tetra-O-acetyl-β-*D*-glucopyranosyl)-α-*D*-galactopyranose (III) and 6-O-(β-*D*-glucopyranosyl)-*D*-galactose.**

III was isolated by chromatography on Al_2O_3. After recrystallization from Et_2O –C_6H_{14}, m.p. 140–142°, $[\alpha]_D - 54.5°$ ($CHCl_3$). Literature data ([11]): m.p. 141°, $[\alpha]_D - 52.6°$ ($Cl_2CHCHCl_2$).

Found, %: C 52.83; H 6.51

$C_{26}H_{38}O_{15}$. Calculated, %: C 52.89; H 6.48

From III, after saponification (0.02 N MeONa, 20°, 12 h) and hydrolysis (0.1 N H_2SO_4, 80°, 1.5 h), 6-O-(β-*D*-glucopyranosyl)-*D*-galactose is obtained, yield

90%; after reprecipitation with acetone from methanol, $[\alpha]_D + 9.4^\circ \rightarrow +14.0^\circ$ (H_2O), $R_{gl} = 0.38$ (system C). Literature data ([12]): $[\alpha]_D + 13.9^\circ$ (equilibrium, H_2O).

2. **1,2:3,4-Di-O-isopropylidene-6-O-(2,3,4,6-tetra-O-acetyl-β-*D*-galactopyranosyl)-α-*D*-galactopyranose (V) and 6-O-(β-*D*-galactopyranosyl)-*D*-galactose.**

V was isolated by chromatography on Al_2O_3. Syrup, $[\alpha]_D - 47^\circ$ ($CHCl_3$). Literature data ([12]): m.p. 101-102°, $[\alpha]_D - 44.7^\circ$ ($Cl_2CHCHCl_2$).

The entire obtained preparation is converted into 6-O-(β-*D*-galactopyranosyl)-*D*-galactose (as above), purified by partition chromatography; overall yield 43.5%. After reprecipitation with acetone from methanol, $[\alpha]_D + 39^\circ$ (equilibrium, H_2O), $R_{gl} = 0.26$ (system C). Literature data ([12]): $[\alpha]_D + 34.1^\circ$ (equilibrium, H_2O).

Found, %:	C 41.88; H 6.52
$C_{12}H_{22}O_{11}$. Calculated, %:	C 42.13; H 6.48

* Proof of the structure of this compound will be published by us later.

3. **1,2,3,4-Tetra-*O*-acetyl-6-*O*-(2,3,4-*O*-acetyl-α-*L*-rhamnopyranosyl)-β-*D*-glucopyranose (VIII).**

Isolated by chromatography on SiO_2 with subsequent crystallization from ethanol. M.p. 169-171°, $[\alpha]_D - 30.8^\circ$ ($CHCl_3$). Literature data ([13]): m.p. 168-169°, $[\alpha]_D - 29.66^\circ$ ($CHCl_3$).

Found, %:	C 50.64; H 5.95
$C_{26}H_{36}O_{17}$. Calculated, %:	C 50.33; H 5.85

4. **1,2,3,4-Tetra-*O*-acetyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-β-*D*-glucopyranose (IX).**

Isolated by twofold crystallization from Et_2O–C_6H_{14}, m.p. 191-193.5°, $[\alpha]_D - 4^\circ$ ($CHCl_3$). Literature data ([14]): m.p. 190°, $[\alpha]_D - 4^\circ$ ($CHCl_3$).

Found, %:	C 49.59; H 5.75
$C_{28}H_{38}O_{19}$. Calculated, %:	C 49.55; H 5.64

5. **2-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-*D*-glucopyranosyl)-4,6-*O*-benzylidene-α-methyl-*D*-glucopyranoside (XI).**

Isolated by crystallization from ethyl cellosolve. In the mother liquor, chromatography (system B) revealed significant amounts of XI (R_f 0.41) and of a substance with R_f 0.18. The obtained XI was recrystallized again from ethyl cellosolve. M.p. 221-224°, $[\alpha]_D + 45^\circ$ ($CHCl_3$).

A mixed sample with an authentic preparation gives no depression of the melting point. Literature data ([15]): m.p. 232°, $[\alpha]_D + 47°$ ($CHCl_3$); ([16]): m.p. 227-228°, $[\alpha]_D + 42.4°$ ($CHCl_3$).

6. **1,2-*O*-Isopropylidene-3,6-di-*O*-acetyl-5-*O*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-α-*D*-glucofuranose (XIII).**

Isolated by chromatography on Al_2O_3 with subsequent recrystallization from methanol and Et_2O, m.p. 170°, $[\alpha]_D - 26.3°$ ($CHCl_3$). Literature data ([10]): m.p. 173°, $[\alpha]_D - 28.8°$ ($CHCl_3$).

Found, %:	C 51.34; H 6.10
$C_{27}H_{38}O_{17}$. Calculated, %:	C 51.10; H 6.04

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Note: Figure translations are in progress. See original paper for figures.