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Abstract

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ON GLYCOSIDATION WITH 2-*O*-TRICHLOROACETYL-3,4,6-TETRAACETYL-β-*D*-GLUCOPYRANOSYL CHLORIDE

The synthesis of β-glucosides, as well as of other 1,2-trans-glycopyranosides, has now been well developed on the basis of the Koenigs–Knorr reaction ([1]). By contrast, α-glucosides and other 1,2-cis-glycopyranosides still remain rather inaccessible compounds because of the absence of a general stereospecific method for their synthesis. This applies in particular to the synthesis of glycosides of complex natural aglycones, since in this case the matter is substantially complicated by the lability of the latter. It therefore seems entirely justified to search for such a variant of the Koenigs–Knorr reaction as would lead to the formation of 1,2-cis-glycosides. The chief obstacle to this is the "neighboring-group participation effect" of the 2-*O*-acyl group, as a result of which, irrespective of the configuration of the acyl halogenose, glycosides with the 1,2-trans configuration are formed ([2]). To eliminate the "neighboring-group participation effect," it is necessary to replace the 2-*O*-acyl group by a substituent that is incapable of participating in the substitution reaction at the glycosidic center. In this case, substitution of the halogen atom in a 1,2-trans-halogenose should lead to a 1,2-cis-glycoside.

One substituent of this kind, showing only a very weak tendency toward "participation," is the trichloroacetyl group ([2]). Hickinbottom ([3]), carrying out reactions of 2-*O*-trichloroacetyl-3,4,6-tri-*O*-acetyl-β-*D*-glucopyranosyl chloride (I) with methanol and ethanol under the conditions of the Koenigs–Knorr reaction, found preferential formation of the α-glucosidic linkage. However, the possibility of using this reaction for the stereospecific or directed synthesis of 1,2-cis-glycosides of complex aglycones remained unclear, since the synthesis conditions here are quite different, inasmuch as the reaction must be conducted not in an alcohol medium but in an inert solvent. In order to clarify this question, which is important for the synthesis of complex natural glycosides, we investigated the interaction of 2-*O*-trichloroacetyl-3,4,6-tri-*O*-acetyl-β-*D*-glucopyranosyl chloride (I) with cholesterol (II), and also with the methyl ester of oleanolic acid (III), which were taken as compounds modeling typical natural aglycones. The reaction conditions, close to those of the Koenigs–Knorr reaction, were varied within rather wide limits (see Table 1). The reaction products, without isolation

in pure form, were subjected to deacylation with sodium methoxide followed by acetylation, and the outcome of the reaction was determined from the amount and ratio of the resulting α- and β-anomers of the full acetates.

[reaction scheme]

Ac = CH_3CO-, R = residue of cholesterol or of the methyl ester of oleanolic acid

In the main experiment, the α- and β-anomers of the glucoside of cholesterol were separated preparatively; in the other experiments they were determined by means of thin-layer ···

Table 1

Interaction of 2-O-trichloroacetyl-3,4,6-tri-O-acetyl-β-D-glucopyranosyl chloride (I) with cholesterol (II) and methyl oleate (III)[1]

No. of experiment	Reaction conditions	HCl acceptor	Ratio I : II or III	Yield and steric result of the reaction
1	$C_6H_5\dot{C}H_3$, 140°, 10 h.[3]	Ag_2CO_3	2 : 1	38% (75% α- and 25% β-)
2	$C_6H_5CH_3$, 140°, 6 h.[3]	$PbCO_3$	2 : 1	4% ($\alpha + \beta$)
3	$C_6H_5CH_3$, 140°, 4 h.[2]	–	1 : 2	4.3% $\alpha + \beta$
4	CH_3NO_2, 80–90°, 10 h.[3]	Ag_2CO_3	2 : 1	10.8% $\alpha + \beta$
5	$CHCl_3$, 20°, 16 days[3]	Ag_2O	1 : 2	13.7% $\alpha + \beta$
6	CH_3NO_3, 105°, 12 h.[4]	Ag_2CO_3	2 : 1	25% $\alpha + \beta$

[1] Nos. 1–5: interaction of I with II; No. 6–I with III. [2] Removal of water by azeotropic distillation. [3] Removal of H_2O with $CaSO_4$. [4] Removal of H_2O with $MgSO_4$.

thin-layer chromatography on aluminum oxide* (Fig. 1). The results obtained are summarized in Table 1, from which it is evident that in all cases the interaction of chloride I with compounds II and III leads to a mixture of α- and β-anomers with a significant predominance of the α-anomer.

Thus, the reactions with I did not proceed stereospecifically. Among the possible causes responsible for the formation of β-anomers, the following may be mentioned first of all: 1) occurrence of the reaction by the S_N1 mechanism;

2) participation of the 2-O-trichloroacetyl group; 3) anomerization of the initial halogenose I under the reaction conditions; and 4) anomerization of the glucoside formed.

The last assumption was rejected by a direct experiment, which showed that the acetates of α- and β-glucosides of cholesterol do not change under the reaction conditions. Experiments were also carried out on the anomerization of chloride I under conditions close to the reaction conditions; these showed that anomerization of I does indeed take place when HCl acceptors are used and may be one of the reasons for the formation of the β-glucoside. However, it is hardly the principal one, since even under those conditions in which anomerization does not occur (4-hour heating of I in toluene), the β-anomer is nevertheless formed (see Table 1, experiment No. 3). At the same time, the stability of chloride (I) in boiling toluene makes the occurrence of the process by the S_N1 mechanism highly unlikely. Thus, the principal reason for the non-stereospecificity of the reaction appears, evidently, to be the participation of the trichloroacetyl group in the reaction of the glycosidic center. The comparatively low yield of glucosides is probably associated with side transformations of chloride I under the action of HCl acceptors. Thus, upon interaction of I with Ag_2CO_3 in boiling toluene, the amount of labile chlorine decreases fivefold; moreover, after methanolysis, in the reaction products, paper chromatography revealed, in addition to β-methyl glucoside, spots with Rf 0.66 and 0.14 (see the experimental part; cf. (4)).

In conclusion, it should be noted that the preparation of α-glucosides by the method described in this article, despite the non-univocal character of the reaction, may in some cases be of preparative interest for the synthesis of certain glucosides with a complex aglycone.

Experimental Part

All melting points have been corrected. For the experiments, paper from the Leningrad Factory No. 2 named after Volodarsky, grade "B," was used. Al_2O_3 for chromatography was neutral ([5]), Brockmann activity grade III.

* Detailed data on the use of thin-layer chromatography for the identification of glucosides will be published by us elsewhere.

1. **2-O-Trichloroacetyl-3,4,6-tri-O-acetyl-β-D-glucopyranosyl chloride (I)** was prepared according to ([6]), m.p. 136–138°, $[\alpha]_D + 2.0 \pm 0.2^\circ$ (c 2.53, toluene).

2. **Reaction of 2-O-trichloroacetyl-3,4,6-tri-O-acetyl-β-D-glucopyranosyl chloride (I) with cholesterol (II).** A mixture of 4.0 g (10.4 mmoles) of cholesterol (m.p. 141° from alcohol, dried at 10^{-4} mm and 100°) and 3.5 g of freshly prepared Ag_2CO_3 in 40 ml of toluene is heated for 1 hr in the apparatus described previously ([7]), at a bath temperature of $140 \pm 2^\circ$. Then a solution of 5 g (10.7 mmoles) of I in 10 ml of toluene is added, the mixture is heated for 5 hr, a further 5 g of I and 3.5 g of Ag_2CO_3 are

added, and the mixture is heated for another 5 hr. The silver salts are filtered off, washed on the filter with toluene, the filtrate is evaporated in vacuo to dryness, the residue is treated with an excess of methanolic sodium methylate solution (12 hr at room temperature), diluted with water, and extracted with a butanol–toluene mixture (1 : 1; 5 times with 100 ml portions). The extracts are washed with water and evaporated to dryness. The residue is chromatographed on cellulose in the butanol–toluene system with an increase in the butanol concentration from 5 to 50%, monitoring the separation by paper chromatography (butanol–toluene 1 : 9). Fractions containing a mixture of glucosides (R_f 0.6) are combined and evaporated. Yield 2.19 g (38%).

Fig. 1. Thin-layer chromatography (Al_2O_3): 1 –tetraacetate of α-D-glucopyranoside II; 2 –tetraacetate of β-D-glucopyranoside II; 3 –mixtures of tetraacetates of α- and β-D-glucopyranosides II (experiments Nos. 1–5, Table 1); 4 –tetraacetate of β-D-glucopyranoside III; 5 –mixture of tetraacetates of α- and β-D-glucopyranosides III (experiment No. 6, Table 1).

300 mg of a mixture of cholesterol glucosides are acetylated with $(CH_3CO)_2O$ in pyridine (2 days, 20°), chromatographed on Al_2O_3 (chloroform–methyl ethyl ketone with an increase in the concentration of the latter from 0 to 1.5%). The separation of the tetraacetates of the α- and β-glucosides II is monitored by thin-layer chromatography on Al_2O_3 (Fig. 1). This gives 230 mg of the tetraacetate of α-glucoside II and 80 mg of the tetraacetate of β-glucoside II.

Tetraacetate of α-glucoside II: white needle crystals (from methanol), m.p. 195–197°, $[\alpha]_D + 88 \pm 1.8°$ (c 0.45, chloroform).

$C_{41}H_{64}O_{10}$.	Found % :	C 68.82; 68.78; H 8.91; 8.95
	Calculated % :	C 68.68; H 8.99

Literature data for the tetraacetate of cholesterol α-D-glucopyranoside: m.p. 195°, $[\alpha]_D + 88°$ (C 0.9, chloroform) ([8]).

Tetraacetate of β-glucoside II is recrystallized from methanol, m.p. 157–159°, $[\alpha]_D - 25 \pm 2°$ (C 2.34, chloroform). A mixed sample with an authentic specimen of the tetraacetate of β-D-glucopyranoside II, synthesized according to ([9]), gave no depression of the melting point. Literature data for the tetraacetate of cholesterol β-D-glucopyranoside: m.p. 158°, $[\alpha]_D - 26°$ ([9]).

α- and β-D-Glucopyranosides of cholesterol. The tetraacetates of the α- and β-D-glucopyranosides of cholesterol are deacetylated with a methanolic sodium methylate solution and, after reprecipitation with water from a pyridine solution, the α- and β-D-glucopyranosides of cholesterol are obtained. After drying (10^{-4} mm, 100°), the substances had the following constants: cholesterol α-D-glucopyranoside: m.p. 205–211°; $[\alpha]_D + 23 \pm 5°$ (C 1.3, pyridine).

$C_{33}H_{56}O_9 \cdot \frac{1}{2}H_2O$. Found, %: C 70.92; 71.01; H 9.93; 10.09. Calculated, %: C 71.05; H 10.30.

Cholesteryl β-*D*-glucopyranoside: m.p. 262-264°, $[\alpha]_D - 60 \pm 8°$ (c 2.48, pyridine).

$C_{33}H_{56}O_9 \cdot \frac{1}{2}H_2O$. Found, %: C 71.13; 71.17; H 10.33; 10.35. Calculated, %: C 71.05; H 10.30.

3. Reaction of 2-O-trichloroacetyl-3,4,6-tri-O-acetyl-β-*D*-glucopyranosyl chloride with the methyl ester of oleanolic acid. To 0.5 g of substance III, 1.0 g of substance I, 1.5 g of Ag_2CO_3, and 1.0 g of $MgSO_4$ are added 10 ml of nitromethane, and the mixture is heated for 12 hours at 105°. After the treatment described for the cholesteryl glucosides and analogous separation on cellulose, 0.17 g (25% of theory) of a colorless solid is obtained, which after recrystallization from aqueous alcohol had m.p. 161-162.5°, $[\alpha]_D + 51.5 \pm 7.5°$ (c 3.4, pyridine).

$C_{37}H_{61}O_8 \cdot \frac{1}{2}H_2O$. Found, %: C 69.15; 68.88; H 9.90; 9.62. Calculated, %: C 69.12; H 9.72.

The mixture of glucosides III is acetylated with $(CH_3CO)_2O$ in pyridine. The acetylation product on a thin-layer chromatogram on Al_2O_3 gave 2 spots (see Fig. 1), one of which is identical with the spot of the tetraacetate of β-*D*-glucopyranoside II, synthesized according to (10).

4. Anomerization of 2-O-trichloroacetyl-3,4,6-tri-O-acetyl-β-*D*-glucopyranosyl chloride (I).

a) 1.0 g of I is heated with 0.5 g of freshly prepared AgCl in toluene at 130° for 4 hours; the AgCl is filtered off, the filtrate is evaporated to dryness, and the residue is recrystallized from ether: $[\alpha]_D + 14.0 \pm 0.5°$ (c 1.74, toluene).

$C_{14}H_{16}O_9Cl_4$. Found, %: C 36.09; 36.13; H 3.61; 3.65; Cl 29.81; 29.85. Calculated, %: C 35.75; H 3.42; Cl 30.19.

b) 0.5 g of $PbCO_3$ (1.9 mmole) is covered with 10 ml of toluene, a weak stream (1.0 mmole) of dry HCl is passed through, the mixture is boiled for 30 min at 130° in a stream of dry nitrogen, and 1.0 g of I is added. After heating for 4 hours (130°), the lead salts are filtered off, the filtrate is evaporated, and the residue is recrystallized from ether: $[\alpha]_D + 2.5 \pm 0.3°$ (c 1.66, toluene).

$C_{14}H_{16}O_9Cl_4$. Found, %: C 36.09; 36.13; H 3.57; 3.62; Cl 29.57; 29.26. Calculated, %: C 35.75; H 3.42; Cl 30.19.

5. 1.2 g of 2-O-trichloroacetyl-3,4,6-tri-O-acetyl-β-*D*-glucopyranosyl chloride (I) and 2.0 g (7.3 mmole) of Ag_2CO_3 are heated in toluene in a stream of dry nitrogen for 30 min; a weak stream (4.0 mmole) of dry HCl is passed through and the mixture is heated for 4 hours at 140° in a stream of nitrogen. The silver salts are filtered off, evaporated, and part of the resulting syrup is treated with an excess of a methanolic solution of sodium methylate (10 hours, 20°). The

mixture is diluted with water, demineralized with EDE-10P anion exchanger and SG-1 cation exchanger, and chromatographed on paper in the butanol–ethanol–water system (5 : 1 : 4). To 1.411 g of the remaining syrup is added an excess of a solution of $AgNO_3$ in aqueous acetone. The precipitated AgCl is filtered off and dried; weight 8.7 mg, which corresponds to 21% of the amount of AgCl formed in the reaction of I with $AgNO_3$ under the same conditions.

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