SOME TRANSFORMATIONS OF α-D-GLUCOSE (CHOLESTERYL ORTHOACETATE) UNDER THE CONDITIONS OF THE ORTHOESTER METHOD OF SYNTHESIZING GLYCOSIDES

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In the glycosylation of cholesterol and of β-sitosterol with α-D-glucose (ethyl orthoacetate) and with maltose (methyl orthoacetate) in nitromethane in the presence of $HgBr_2$ (modification 1, see Scheme), in addition to the glycosides of cholesterol and β-sitosterol, we isolated their ethers [1-3]. The glycosylation of cholesterol and β-sitosterol with D-glucose (tert-butyl orthoacetate) in chlorobenzene in the presence of 2,6-lutidinium perchlorate (modification 2, see Scheme) is also accompanied by the formation of by-products – the acetates of cholesterol and of β-sitosterol [4]. In the condensation of betulin and of 16-dehydropregnenolone with carbohydrate orthoacetates, the only by-products, both in the first and second modification of the glycosylation process, were the acetates of the initial alcohols [2, 5].

According to the equation of the glycosylation reaction of hydroxyl-containing compounds with sugar orthoacetates-ethers and acetates of the polycyclic alcohols are not formed [6-8]. Since the by-products arising remove the aglycone from the glycosylation reaction, it appeared desirable to study this reaction in more detail.

In a study of the condensation of cholesterol with glucose (ethyl orthoacetate) (modification 1), Kochetkov et al. [6] found that the reaction can take place in two directions (glycosylation or transesterification) depending on the solvent and the catalyst, which they explained by the ambident properties of the carbocation formed as an intermediate.

It has been shown previously [4] that a possible source of by-products, especially cholesteryl acetate, in the glycosylation of cholesterol (modification 2) may be glucose (cholesteryl orthoacetate) (I), which apparently arises in parallel with the desired product and undergoes complete transformation under the conditions of the experiment. A study of the process of the transformation of this orthoester during the synthesis is also closely connected with two-stage glycosylation (modification 3) [9-11], since the yield of glycoside depends on the completeness of the transformation of the orthoester (I), which is isomeric with the desired glycoside (IV). Consequently, we decided to investigate how the transformation of (I) takes place under various conditions of glycosylation by the orthoester method.

In fact, as follows from the experimental results (experiment 1), on treatment under the conditions of synthesis, (I) gives a series of transformation products (modification 1).

Somewhat unexpected is the formation of substance (III) which was not detected in the glycosylation of cholesterol with α-D-glucose (ethyl orthoacetate) [7]. Thus, when cholesterol was heated in the presence of $HgBr_2$ in control experiment 4, 1.6% of (II) was formed.

In an investigation of the process of conversion of (I) under other glycosylation conditions (modification 2), it was established that substance (III) is formed together with (IV) and (I) 30 min after the addition of the catalyst to the reaction mixture (modification 2). After 20 h, an appreciable amount of a

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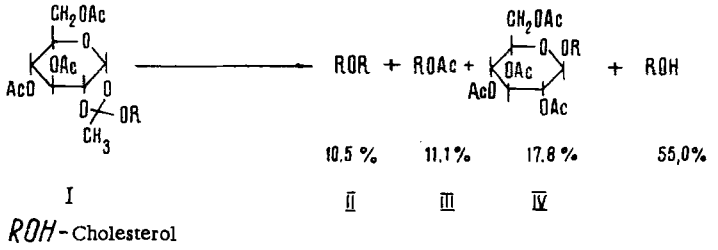
highly polar substance of sterol nature and traces of the initial orthoester (I) were detected in the reaction mixture.

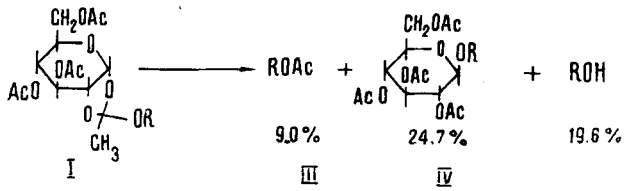
It can be seen from experiments 1 and 2 that (III) can arise from (I). The appearance of (II) cannot be explained solely by the decomposition of (I) (10.5%, experiment 1), since (II) can be formed also as the result of the dehydration of cholesterol.

We have found no information in the literature on the appearance of ethers in reactions of carbohydrate orthoacetates [6-8]. It must, however, be noted that cyclic orthoesters of carboxylic acids undergo transformations giving rise to ethers when they are heated in the presence of $FeCl_3$, BF_3, etc. [12-14].

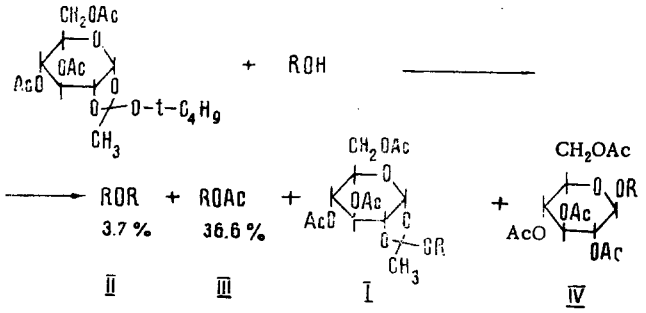
Modification 1



Modification 2



Modification 3



In the first stage of the transformation of (I) under the conditions of the two-stage method of glycosylation (modification 3) [8-11], the transesterification by the cholesterol of glucose (tert-butyl orthoacetate) takes place, and in the second stage the transformation of (I) arising into the isomeric glycoside takes place. The reaction is performed in dichloroethane (DCE) in the presence of 2,6-lutidinium perchlorate and p-toluenesulfonic acid (PTSA), and compounds (II), (III), (I), and (IV) are obtained (see Scheme). Cholesta-3,5-diene is also formed in very small amounts.

Heating cholesterol in DCE in the presence of PTSA and 2,6-lutidinium perchlorate gives substance (II) and a trace amount of cholesta-3,5-diene (experiment 5).

The results of this experiment and of experiments 1 and 2 agree in showing that the source of the formation of cholesteryl acetate is, in fact, (I). Compound II arises mainly by the decomposition of (I) and partially through the dehydration of cholesterol.

The incomplete transformation of glucose (cholesteryl orthoacetate) (I) under the conditions of the two-stage method of synthesizing glycosides leads to lower yields of desired products than the one-stage syntheses (modifications 1 and 2). The same incomplete conversion was observed by Bashkatova et al. [15] in the preparation of glycosyl glycerides through the isomeric orthesters.

EXPERIMENTAL

The catalysts, the solvents, and the sorbents were prepared as described in the literature [6, 8]. For thin-layer chromatography we used the following solvent systems: 1) chloroform–methyl ethyl ketone (98.5 : 1.5) (Al_2O_3); 2) petroleum ether–diethyl ether (98.5 : 1.5); and 3) petroleum ether–acetone (4 : 1) (on a nonfixed layer of silica gel). The reaction products were detected with the aid of concentrated H_2SO_4 or a saturated solution of $SbCl_3$ in chloroform.

In column chromatography, the fractions were eluted successively with petroleum ether, benzene, and chloroform. The melting points were determined on a Kofler block. The cholesta-3,5-diene [16], the dicholesteryl ether, the cholesteryl acetate, and the cholesteryl β-D-glucoside tetraacetate gave no depressions of the melting points in admixture with the respective authentic samples. The α-D-glucose (cholesteryl orthoacetate) was synthesized as described in the literature [6, 17], mp 98-102°C, $[\alpha]_D^{20}$ +2.2° (c 0.63; $CHCl_3$), and the acid test was positive. The yields are given for chromatographically homogeneous substances.

Experiment 1. Decomposition of α-D-Glucose 1,2-0-(Cholesteryl Orthoacetate) in Nitromethane in the Presence of $HgBr_2$ (Modification 1). After 0.716 g (0.001 mole) of (I) had been dissolved in 12 ml of CH_3NO_2, 2 ml of the solvent was distilled off, and 0.04 mmole of $HgBr_2$ in 4 ml of benzene was added. The mixture was heated with azeotropic distillation and with the volume of the reaction mixture kept constant. After boiling had continued for 30 min, a precipitate deposited. After the end of heating (2.5 h), the precipitate was filtered off and washed with methanol. This gave 0.083 g (10.5%) of dicholesteryl ether with mp 201-202°C. The reaction mixture was evaporated, and the residue was chromatographed on a column of Al_2O_3 (h = 10 cm, S = 3.14 cm). In this way, 0.04 g (11.1%) of cholesteryl acetate was isolated. The column was eluted with methanol, the solvent was distilled off, and the residue was treated with a mixture of pyridine and acetic anhydride to convert any cholesterol into its acetate (2 : 1, 24 h at 20°C). After the appropriate working up, the residue was again deposited on a column of Al_2O_3 and eluted. This gave 0.247 g (55.05%) of cholesteryl acetate with mp 113-114°C and 0.128 g (17.8%) of cholesteryl β-D-glucoside tetraacetate with mp 156-158°C.

Experiment 2. Decomposition of (I) in Chlorobenzene in the Presence of 2,6-Lutidinium Perchlorate (Modification 2). After 0.00002 mole of catalyst had been dissolved in 10 ml of DCE, 7 ml of the solvent was distilled off, the residue was added to a solution of 0.001 mole of (I) in 8 ml of chlorobenzene, and the mixture was heated for 1 h with azeotropic distillation of the solvent. Then the reaction mixture was left at room temperature for 12 h, since the acid test gave a positive reaction for unchanged orthoester (I). The chlorobenzene was evaporated off, and the residue was chromatographed on a column of Al_2O_3. This gave 0.040 g (9.03%) of cholesteryl acetate. After treatment of the residue as described in experiment 1, 0.084 g (19.6%) of cholesteryl acetate and 0.156 g (21.7%) of cholesteryl β-D-glucoside tetraacetate were isolated.

Experiment 3. Synthesis of Cholesteryl β-D-Glucoside Tetraacetate by Two-Stage Glycosylation in the Presence of 2,6-Lutidinium Perchlorate and PTSA. From a solution of 0.386 g (0.001 mole) of cholesterol and 0.404 g (0.001 mole) of α-D-glucose (tert-butyl orthoacetate) in 10 ml of DCE 2 ml of solvent was distilled off, and then 0.00002 mole of PTSA was added. Azeotropic distillation was performed for 1.25 h. Then 0.00002 mole of 2,6-lutidinium perchlorate was added, and heating with continuous boiling and distillation of the solvent was continued for 1.25 h. The reaction mixture was left for 12 h. The acid test for α-D-glucose (cholesteryl orthoacetate) was positive. The solvent was evaporated off, and the residue was separated by the usual method. This gave 0.0109 g (2.9%) of cholesta-3,5-diene, 0.013 g (3.7%) of dicholesteryl ether, 0.157 g (36.6%) of cholesteryl acetate, and 0.3 g of a mixture of the glucose orthoacetate (I) and cholesteryl β-D-glucoside tetraacetate (IV).

The mixture of (I) and (IV) was dissolved in 6 ml of acetone and 3 ml of 0.1 N H_2SO_4, and the solution was kept at 20°C for 2 h, neutralized with pyridine, and evaporated. After treatment as in experiment 1, 0.051 g (11.9%) of cholesteryl acetate and 0.145 g (20.2%) of cholesteryl β-D-glucoside tetraacetate were isolated.

Experiment 4. Under the conditions of experiment 1, 0.386 g of cholesterol was heated in nitromethane. This gave 0.006 g (1.6%) of dicholesteryl ether.

Experiment 5. A reaction under the conditions of experiment 3 was performed with 0.386 g of cholesterol. This gave 0.004 g (1.0%) of cholesta-3,5-diene and 0.055 g (14.3%) of dicholesteryl ether.

SUMMARY

1. The transformation of α-D-glucose (cholesteryl orthoacetate) has been studied under various conditions of glycosylation by the orthoester method.

2. It has been shown that cholesteryl acetate is formed from glucose (cholesteryl orthoacetate).

3. It has been established that under the conditions of the orthoester method for the glycosylation of cholesterol dicholesteryl ether can be obtained both from glucose (cholesteryl orthoacetate) and by the dehydration of cholesterol.

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