SYNTHESIS OF THE GLYCOSIDES OF SEVERAL STEROIDS

G. V. Elyakov, N. I. Uvarova, and G. I. Oshitok

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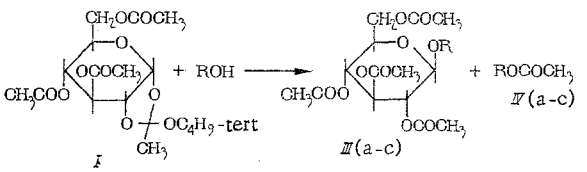
We previously reported the synthesis of glycosides of condensation of 1,2-ethylorthoacetyl-3,4,6-tri-O-acetyl-α-D-glucopyranose with lanosterol, β-sitosterol, cholesterol, and panaxadiole [1]. The highest yield of glycoside was observed for cholesterol (45%), while the lowest yield was observed for panaxadiole (18.8%). The synthesis of the glycosides of the cholesterol and β-sitosterol was complicated by a side reaction to form the ethers of these alcohols. The conditions for obtaining the glycosides were drastic for the synthesis of the acetate of panaxadiole glycoside since the latter underwent partial alteration to more polar products.

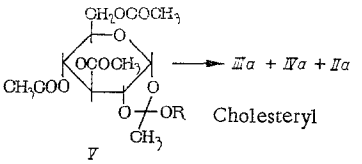
The aim of this work was the further study of the conditions for the synthesis of the glycosides of the polycyclic alcohols cholesterol (IIa), β-sitosterol (IIb), and 16-dehydropregnenolone (IIc) by reaction with 1,2-tert-butylorthoacetyl-3,4,6-tri-O-acetyl-α-D-glucopyranose (I).

The glycosylation of monosaccharide derivatives with glucose tert-butylorthoacetate, realized by Kochetkov and co-workers [2, 3], made it possible to obtain disaccharides in high yields. We used this method to synthesize the glycosides of the indicated alcohols (IIa-c), during which the best yields were obtained with doubled amounts (0.02 mmole) of the catalyst – 2,6-lutidine perchlorate. In all cases, in addition to the target products (IIIa-c), we observed the formation of side products (IVa-c) – the acetates of the starting alcohols – the formation of which was not observed during synthesis of the disaccharides [2, 3]. The side reaction consists in the formation of the acetates of the glycosides of the lower alcohols formed during conversion of the starting ortho ester. In addition, depending on the nature of the solvent and catalyst, the reaction may proceed with the formation of a new ortho ester (transesterification) [4, 5].



I

We assume that the development of side products in our case is associated with the transesterification of I by the steroids (IIa-c) introduced into the reaction, which apparently proceeds parallel to the glycosylation reaction. The ortho ester formed in the process may subsequently be the source of the acetates of alcohols IVa-c. This assumption was confirmed by an experiment in which 1,2-cholesterylorthoacetyl-3,4,6-tri-O-acetyl-α-D-glucopyranose (V), synthesized by the method in [4], was treated with 0.2 and 0.004 mmole of catalyst under the synthesis conditions. Cholesterol acetate, the acetate of cholesterylglycoside, and cholesterol (see Fig. 1) were identified in the reaction products by thin-layer chromatography.



V

Institute of Biologically Active Substances, Vladivostok. Translated from Khimiko-Farmatsevticheskii Zhurnal, No. 10, pp. 7-9, October, 1971. Original article submitted April 7, 1970.

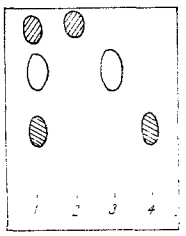


Fig. 1. Chromatogram in a thin layer of aluminum oxide. Chloroform–methyl–ethyl–ketone system (98.5 : 1 : 1.5). Detection via concentrated sulfuric acid: 1) reaction mixture; 2) cholesterol acetate; 3) acetate of cholesteryl-β-D-glucopyranoside; 4) cholesterol.

Changes in the catalyst concentration (0.002, 0.01, and 0.05 mmole) led to a decrease in the yield of the target products during the synthesis of cholesterol and β-sitosterol glycosides.

Increasing the reaction time (by a factor of two) and introduction of excess glucose tert-butylorthoacetate caused a decrease in the formation of the major products (III).

The yields of β-sitosterol and 16-dehydropregnenolone glycosides were lower than that of cholesterol glycoside. Consequently, to exclude losses during treatment of the reaction mass, the latter was subjected to acetylation after removal of chlorobenzene. The yields of IIIb and IIIc, however, remained the same.

Thus, glycosylation of the alcohols by means of I substantially raises the yields of glycosides as compared with glycosylation with glucose ethylorthoacetate, although it is also complicated by the side reaction – formation of the acetates of the starting alcohols.

EXPERIMENTAL

The catalyst, solvents, and sorbents were prepared in accordance with the literature [3, 4]; in addition to the systems previously mentioned [1, 2] for thin-layer chromatography on silica gel we also used a petroleum ether-diethyl ether system (95 : 5) and detection was achieved with concentrated sulfuric acid or a saturated solution of antimony trichloride in chloroform.

Cholesteryl β-D-Glucopyranoside Tetraacetate (IIIa). A mixture of 0.386 g (1 mmole) of cholesterol and 0.404 g (1 mmole) of I was refluxed in 10 ml of chlorobenzene by distilling and adding chlorobenzene in such a way that the volume of the reaction mixture remained constant. After removal of 3 ml of chlorobenzene, 0.02 mmole of 2,6-lutidine perchlorate in dichloroethane (~1.5 ml) was added and the mixture was refluxed for 0.5 h. Several drops of pyridine were added after cooling the reaction mass, and the mixture was evaporated to dryness. The dry residue (0.75 g) was dissolved in hot nitromethane. The precipitated crystals of IVa were filtered and crystallized from ethanol to give 0.11 g (25.8% based on the starting cholesterol) of IVa with mp 113-114.5° and $[\alpha]_D^{20}$ −40.3 ± 5° (c 0.124 in chloroform). The melting point was not depressed when this product was mixed with an authentic sample. According to the literature [6], IVa has mp 114.5-114.8° and $[\alpha]_D^{20}$ −47.4° in chloroform.

The mother liquor was evaporated and the residue was crystallized from methanol to give 0.44 g (61.38%) of IIIa with mp 156-157.5° and $[\alpha]_D^{20}$ −23.45 ± 5° (c 0.096 in chloroform). No melting point depression was observed when a sample of this product was mixed with an authentic sample. According to the literature [4], IIIa has mp 157-159° and $[\alpha]_D^{20}$ −25.0° (in chloroform).

β-Sitosteryl β-D-Glucopyranoside Tetraacetate (IIIb). The reaction mass obtained under the conditions of the previous experiment from 1 mmole (0.404 g) of I and 1 mole (0.414 g) of β-sitosterol was cooled and evaporated in the presence of pyridine. The residue (0.67 g) was introduced into a column with aluminum oxide (S = 7 cm^2, h = 12 cm) and eluted with petroleum ether. The eluate was evaporated and the IVc obtained (0.16 g, 35.08%) was crystallized from methanol to give a product with mp 123-124.0° and $[\alpha]_D^{20}$ −36.0 ± 5° (c 0.098 in chloroform). A sample mixed with an authentic sample melted without depression. According to the literature [7], IVc has mp 130-132.0° and $[\alpha]_D^{20}$ −42.5°. The IIIb was washed out of the column with chloroform, and the solution was evaporated. The residue (0.51 g) was crystallized from ethanol to give 0.28 g (37.6%) of IIIb with mp 165-167° and $[\alpha]_D^{20}$ −17.6 ± 5° (c 0.098 in chloroform). No depression of the melting point was observed with a sample mixed with an authentic sample. According to the literature [7], IIIb has mp 170-171° and $[\alpha]_D^{20}$ −24.2°.

16-Dehydropregnenolone β-D-Glucopyranoside Tetraacetate (IIIc). The reaction mass obtained as described above from 1 mmole (0.404 g) of I and 1 mmole (0.315 g) of 16-dehydropregnenolone was treated as in the previous experiment to give 0.12 g (33.6%) of IVc, which, after crystallization from alcohol, had mp 173-175° and $[\alpha]_D^{20}$ −27.5° (c 0.98 in chloroform). No melting point depression was observed when a sample of this product was mixed with an authentic sample. According to the literature [8], IVc has mp 176.0° and $[\alpha]_D^{20}$ −33° (in ethanol). IIIc was eluted with chloroform, and 0.56 g of dry residue was obtained

after removal of the solvent. Crystallization from ethanol yielded 0.16 g (25.8%) of IIIc with mp 231-233° and $[\alpha]_D^{20}$ −20.3° (c 0.296 in chloroform). According to the literature [9], IIIc has mp 234-237° and $[\alpha]_D^{20}$ −24° (c 1 in chloroform).

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