GLYCOSYLATION OF CARDIOSTEROIDS

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The review considers methods of glycosylating cardiosteroids with the aim of obtaining compounds possessing a specific action on the cardiac muscle.

The synthesis of cardiac glycosides includes two successive operations: 1) the preparation by one method or another of a steroid compound of cardenolide or bufadienolide nature; and 2) its glycosylation with a suitable sugar. The first part of the problem — the preparation of the aglycone — has been considered to be the most difficult to resolve [1]. At the same time, an experimenter who has been given the aim of introducing a sugar residue into a given steroid compound is sometimes faced with no small difficulties. Complications arise when it is necessary to obtain not a simple glycoside with any sugar but a compound of given structure.

The first synthesis of cardiac glycosides was carried out in 1943 [2]. Subsequently, investigations in this field were carried out fairly intensively.

In the initial period, partial syntheses of cardenolide glycosides were usually performed either with the aim of confirming the correctness of a structure established by another method or in order to study the link between the nature of the sugar residue and cardiac activity. Here, efforts were made largely to obtain compounds close to natural ones. In the following years a different tendency predominated — to synthesize not natural glycosides but close analogues of them. Endeavors were made to obtain such substances as, while retaining an inotropic action, would possess definite advantages in comparison with existing drugs of plant origin: the possibility of peroral administration, controllable cumulativeness, lower toxicity, and greater breadth of therapeutic action. The methods developed for the glycosylation of cardenolides and bufadienolides are not infrequently being used in work with other steroid compounds.

The present review covers the literature up to the end of 1982. Our main attention has been devoted to investigations of recent years. Earlier publications have been discussed fairly fully in a review paper by Zorbach and Bhat [3].

Main Methods of Forming the O-Glycosidic Bond

An important role in obtaining cardiosteroid glycosides has been played by the Koenigs—Knorr reaction [4]. It is based on the condensation of an acylhalogenose (I) with a hydroxyl-containing compound in the presence of silver oxide or carbonate. Because of the combined participation of the neighboring acyloxy groups and the formation of an intermediate acyloxonium ion, the halide reacts with the hydroxyl-containing compound to form a 1,2-trans-glycoside (II). The silver compounds not only bind the hydrogen halide formed but also catalyze the Koenigs—Korr reaction. [See scheme on next page.]

The water liberated during the reaction causes a number of undesirable side reactions [5, 6]. Depending on the method of eliminating the water, two varieties of practical performance of this reaction are distinguished. In one of them, condensation is carried out at room temperature with the stirring of a reaction mixture consisting of the initial aglycone, and acylhalogenose, silver oxide or carbonate, and a desiccant. According to the other method (Meystre and Miescher [7]), the reaction is carried out in the presence of the silver at the boiling point of the solvent and the water is eliminated by azeotropic distillation. It has been proposed to use for the elimination of water both azeotropic distillation of the solvents and a reliable desiccant simultaneously [8].

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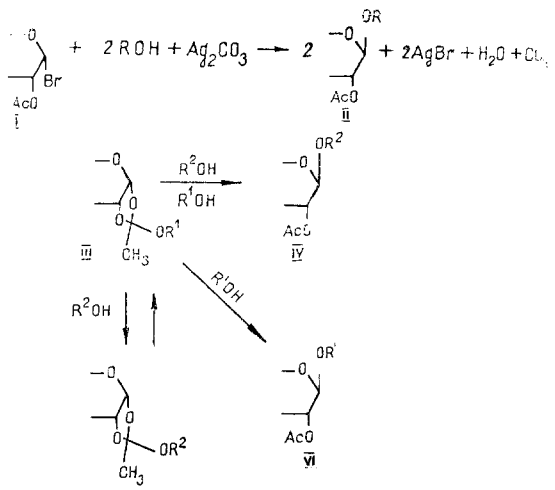


In addition to the classical variant of the Koenigs—Knorr reaction, modifications are used in the synthesis of cardiosteroid glycosides that differ by the hydrogen halide acceptor employed. Thus, the Helferich method [9], in which the soluble mercuric cyanide is introduced into the reaction is widely known. The reaction in the presence of the mercury salt sometimes gives a mixture of the 1,2-trans- and 1,2-cis-glycosides.

The orthoester method developed by N. K. Kochetkov et al. [10, 11] consists of the condensation of a sugar orthoester (III) with an alcohol in an inert solvent in the presence of acidic catalysts (for example, $HgBr_2$, 2,6-lutidinium perchlorate). The yield of the glycoside (IV) synthesized in the optimum variant may be lowered by two side reactions: 1) transesterification, leading to a new orthoester (V), isomeric with the desired glycoside (IV); and 2) the glycosylation of the lower alcohol R'OH split out by the initial orthoester, leading to the formation of the glycoside (VI) isomeric with the initial orthoester (III). The direction of the reaction (glycosylation or transesterification) depends on the solvent and the nature and amount of the catalyst. Azeotropic distillation is usually used to suppress the second side reaction.

The Koenigs—Knorr reaction and the orthoester method usually form 1,2-trans-glycosides.

Lemieux et al. [12] have proposed an interesting method for the synthesis of 1,2-cis-glycosides. It consists in the *in situ* anomerization of 1,2-cis-glycosyl halides the hydroxy groups of which have nonparticipating protective substituents. The anomeric bromides react with the alcohol with reversal of the configuration. The 1,2-trans- anomer is more reactive, which explains the predominant formation of the 1,2-cis-glycoside. This method has been used for the synthesis of anomers of digitoxigenin digitoxosides [13].

Other methods of glycosylation have not come into wide use as applied to cardiosteroids. A fairly full characterization of the methods of forming the O-glycosidic bond has been given in reviews [14-16].

Features of the Synthesis of Cardiosteroid Glycosides

An obligatory element of the structure of the cardenolides is a hydroxy group at C-14 of the steroid nucleus. This tertiary hydroxyl may undergo elimination in an acid medium [17]. Under the influence of an alkali, however, the cardenolides undergo an irreversible transformation [18] into the iso-compounds. If cardiac aglycones with an aldehyde group at C-10 take part in the reaction, then on prolonged contact of solutions of such compounds with atmospheric oxygen this group is gradually oxidized to a carboxy group [19-22].

In the orthoester method of synthesing strophanthidol rhamnosides in the presence of mercury bromide, 8,19-epoxy compounds with the 17α-configuration of the butenolide ring are obtained [23]. It is important that compounds of this type are found fairly frequently as by-products when the glycosylation of cardiosteroids capable of forming internal ethers is carried out in the presence of mercury salts.

In the case of resibufogenin, which has a 14,15-epoxy group, the epoxide ring undergoes cleavage under the conditions of the classical variant of the Koenigs—Knorr method, together with other changes caused by the hydrogen bromide liberated during glycosylation [24, 25].

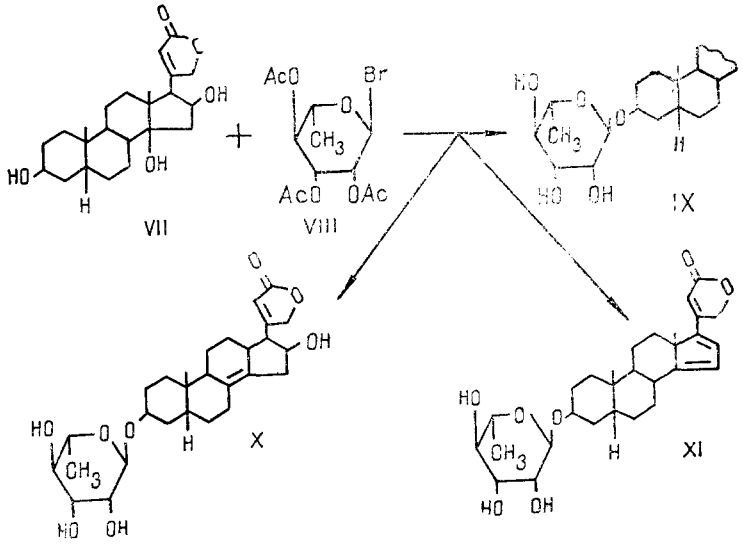
In view of the circumstances mentioned, the lability of the cardiosteroids means that careful attention to the choice of hydrogen halide acceptor is required.

The fact that in the Koenigs–Knorr reaction, in addition to the usual glycosides, glycosides of anhydroaglycones are formed was reported by Reichstein et al. [26]. By performing the condensation of strophanthidin with acetobromoglucose, these authors obtained an anhydrostrophanthidin glucoside tetraacetate (it was impossible to establish accurately the position of the double bond in the steroid part of the molecule). The yield of the anhydrostrophanthidin glycoside amounted to 42% when silver oxide was used and 24% when silver carbonate was used.

Later, other workers [27], in the condensation of digitoxigenin with acetobromorhamnose obtained, in place of evomonoside, Δ^{14}-anhydrodigitoxigenin α-L-rhamnoside.

By replacing the acetobromorhamnose with the less reactive benzoylate rhamnose derivative, Zorbach et al. [28] succeeded in increasing the yield of evomonoside to 6% by the Meystre-Miescher method using silver carbonate and to 44% by the Helferich method (using mercury cyanide as the hydrogen halide acceptor). The elimination of the 14-OH group was also observed in the coupling of 3,4,6-tri-O-p-nitrobenzoyl-2-deoxy-α-D-arabinohexosyl bromide with digitoxigenin in the absence of an acid-acceptor [29].

In the condensation of ditoxigenin (VII) with acetobromorhamnose (VIII) [30], $\Delta^{8(14)}$-enhydrogitoxigenin α-L-rhamnoside (X) and $\Delta^{14,16}$-dianhydroditoxigenin α-L-rhamnoside (XI) were obtained in addition to ditoxigenin α-L-rhamnoside (IX).



In the synthesis of digitoxigenin 2'-deoxy-β-D-allopyranoside an unusual by-product — digitoxigenone — was isolated [31].

In the opinion of Reichstein et al. [26], silver carbonate is a better hydrogen halide acceptor than silver oxide. Thus, in the synthesis of convallatoxin by the Meystre–Meischer method using silver oxide the yield was 11%, and using silver carbonate it was 44%. In a study of the conditions for condensing acetobromoglucose with strophanthidin, it was confirmed that the use of silver carbonate gave a higher yield than silver oxide or mercury cyanide [20]. Other authors have stated, conversely, that the replacement of silver carbonate by mercury cyanide gives better results [28]. Albrecht [32] has performed glycosylation at the tertiary hydroxy group of cardenolides branched at C-3 in the presence of mercury cyanide. The use of silver carbonate under otherwise the same conditions did not give the desired product.

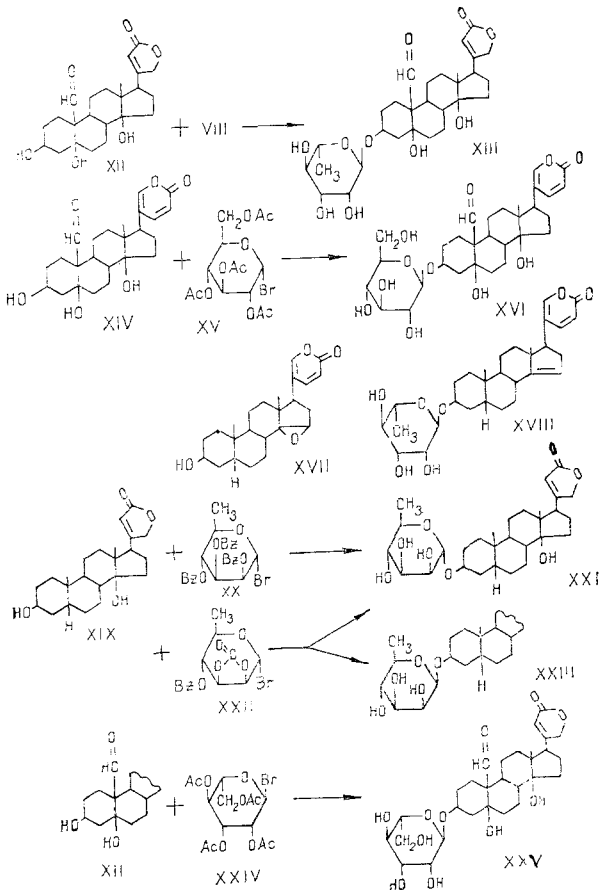
Hartenstein and Satzinger [33, 34] proposed Fetison's reagent [35], i.e., finely dispersed silver carbonate on Celite, as hydrogen halide acceptor. The large surface of contact with the silver carbonate ensures a rapid occurrence of the glycosylation reaction, so that the side reactions are reduced to a minimum. Under the Meystre–Miescher conditions, the reaction is complete in a few minutes and no formation of appreciable amounts of anhydroglycosides or of other by-products is observed.

However, other workers [36], have reported that syntheses using Fetison's reagent are not reproducible. Thus, the condensation of digitoxigenin with acetobromoglucose led predominantly to the 14-anhydroglucoside, while the yield of the expected digitoxigenin β-D-glucoside ranged within the limits. These authors proposed as a more effective catalyst; a combination of mercury salts — the cyanide and the bromide — with Fetison's reagent. They also emphasized the advantages of the innovation, such as the rapidity of the reaction, the high yield, and the absence of by-products. In our view, these conclusions are not completely convincing. In particular, digitoxigenin glucoside was obtained with a yield of only 14% and the synthesis of digitoxigenin rhamnoside was effected by using Fetison's reagent alone.

Synthesis of Glycosides Including Sugars with 2-Hydroxy Groups — Hexoses, Pentoses, and Methylpentoses

As already mentioned, the first partial syntheses of glycoside were performed by Uhle and Elderfield in 1943 [2]. By condensing strophanthidin with acetobromosugars they obtained crystalline completely acetylated strophanthidin α-L-arabinoside, β-D-xyloside, β-D-galactoside, and β-D-glucoside. These authors showed that only the secondary hydroxy group at C-3 was glycosylated, and the tertiary hydroxy groups at C-5 and C-14 remained free. After the saponification of the acetates, strophanthidin β-D-glucoside, β-D-xyloside, and α-L-arabinoside were obtained in crystalline form. In their paper they posed for the first time the question of the influence of sugars on the cardiac activity of the glycosides. It was shown that, in spite of the fact that the bearer of the cardiac activity is the aglycone, sugars are capable of changing the effect of their action within fairly wide limits. Later, the same authors obtained the β-D-glucosides of other cardiac aglycones: digitoxigenin, digoxigenin, and periplogenin [37]. The glycosides mentioned had not yet been found in plants.

A natural cardiac glycoside — convallatoxin (XIII) — was first synthesized in 1950, by condensing acetobromorhamnose (VIII) with strophanthidin (XII) [26]. Later, convallatoxin was obtained with a better yield by other workers [8, 34, 38, 39]. Strophanthidin α-D-lyxoside was obtained by the reaction of strophanthidin (XII) with amorphous acetobromolyxose [40].



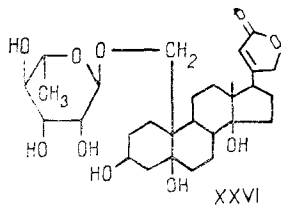
In the bufadienolide series, the reaction of hellebrigenin (XIV) with acetobromoglucose (XV) in the presence of silver carbonate yielded hellebrigenin 3-β-D-glucoside (XVI) [41].

We have already mentioned that the direct glycosylation of resibufogenin (XVII) led to the opening of the epoxy group. Haede et al. [24] succeeded in getting round this difficulty. They first very successfully achieved the synthesis of 14-anhydrobufalin rhamnoside (XVIII), and then converted compounds (XVIII) via the bromohydrin into resibufogeninrhamnoside.

When digitoxigenin (XIX) was condensed with the bromide (XX), digitoxigenin α-D-rhamnoside (XXI) was obtained [28]. Since the activity of this compound proved to be considerably lower than that of its aglycone, it was concluded that the α-glycosidic bond in a cardenolide containing a D-sugar residue led to a molecular conformation unfavorable for cardiotonic activity. For confirmation, they obtained strophanthidin α-D-mannopyranoside and α-D-rhamnopyranoside [42]. They also had a low activity. As is known, in the overwhelming majority of natural glycosides sugars of D- series are attached to the aglycone by β- bonds, and sugars of the L- series by the α- anomeric configuration [43].

In another paper [44], an attempt to synthesize digitoxigenin and strophanthidin β-D-rhamnosides was considered. The natural cardiac glycosides are α-L-rhamnosides. In order to prevent the participation of the neighboring acyloxy group, leading to the production of 1,2-trans-glycosides, the benzoyl derivative of rhamnose (XXII) was used as the glycosylating component. However, the main product of the condensation of the bromide (XXII) with digitoxigenin (XIX) proved to be the digitoxigenin α-D-rhamnoside (XXI) obtained previously, and the yield of the β-D-rhamnoside (XXIII) amounted to only 13%. The condensation of the same bromide (XXII) with straphanthidin (XII) led to strophanthidin β-D-rhamnoside with a yield of only 6%.

Zorbach et al. [42] have directed attention to the fact that a decrease in the number of hydroxy groups in the sugar moiety leads to a fall in activity. Since the most active natural glycoside is convallatoxin (0.79 mg/kg in the cat), it was decided to replace the methyl group of the rhamnose residue by a hydroxymethyl group. The condensation of tetra-O-acetyl-α-L-mannosyl bromide (XXIV) with strophanthidin (XII) followed by the elimination of the protective groups led to strophanthidin α-L-mannopyranoside (XXV). The activity of compound (XXV) was the highest among the cardenolides (0.069 mg/kg in the cat) and, as the authors expected, it exceeded the activity of convallatoxin (XII).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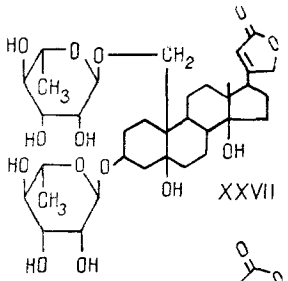
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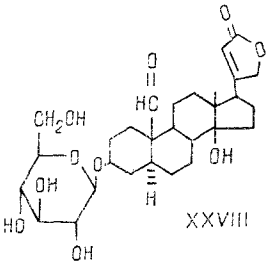
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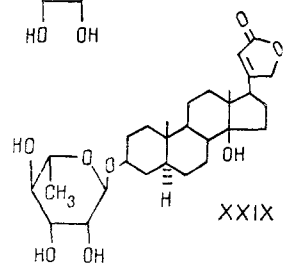
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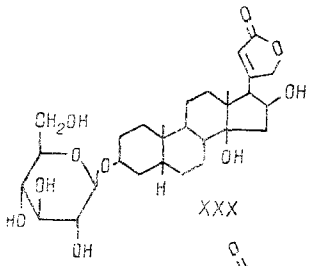
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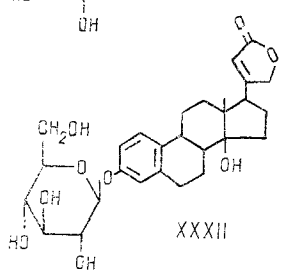
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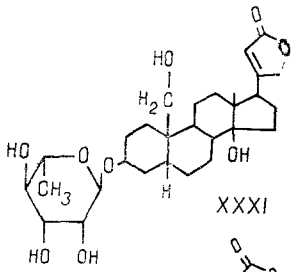
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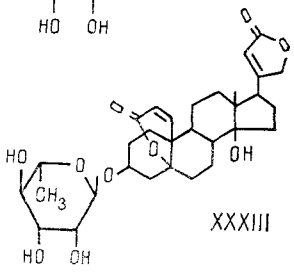

XXXIII

V. T. Chernobai decided to investigate the influence of a sugar component in the C-19 position of a steroid nucleus on the activity of the glycoside. With this aim, he performed syntheses of strophanthidol 19-O-α-L-rhamnoside (XXVI) and strophanthidol 3,19-bis-O-α-L-rhamnoside (XXVII). Compound (XXVI) had no cardiotonic activity whatever.

In the literature, in the main, it is partial syntheses of glycosides the aglycones of which have the cis-A/B ring linkage that have been described. The synthesis of corotoxigenin β-D-glucoside (XXVIII) has been undertaken [47]. In this aglycone, rings A/B are linked in the trans position. The yield of glycosylation product proved to be an order of magnitude less than for the glycosides of the cis-A/B series. Later [48], syntheses of other cardiac glycosides of the trans-A/B series — uzarigenin β-D-glucoside and α-L-rhamnoside (XXIX) — were effected and it was observed that the latter compound was the most active among uzarigenin glycosides (0.315 mg/kg body weight of the cat).

On the basis of a report [49] on the high activity of digicorin — a glycoside from *Digitalis purpurea*, the aglycone of which is ditoxigenin 3-acetate and the sugar moiety digicuronic acid, attached to the 16-OH group of the aglycone, I. F. Makarevich et al. synthesized ditoxigenin glycosides at the C-16 OH group [50]. The condensation of ditoxigenin with acetobromoglucose led to the formation of small amounts of ditoxigenin 3,16-di-O-β-D-glucoside and its 16-O-β-D-glucoside but the main reaction product (49% yield) proved to be ditoxigenin 3β-O-β-D-glucoside (XXX). The last-mentioned compound possessed a comparatively high cardiotonic activity (0.25 mg/kg body weight in the cat), but the diglycoside and the monoglucoside at the C-16 hydroxy group possessed no specific action on the cardiac muscle.

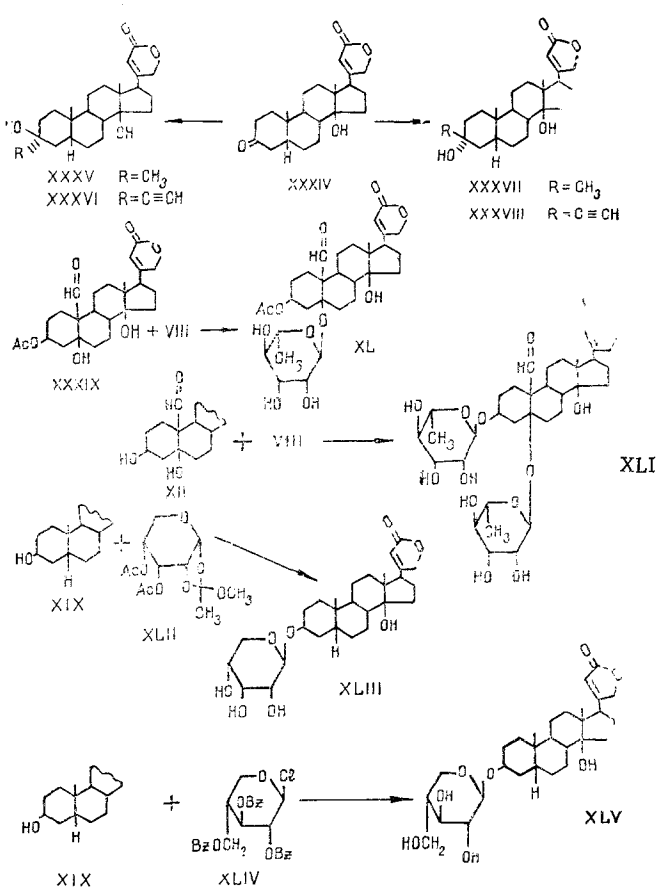
To confirm the structure of a natural compound — evonoloside — cannogenol 3-O-β-L-rhamnoside (XXXI) was synthesized [51]. Syntheses have also effected the strophanthidin α-L- and α-D-arabinosides [52] and of digitoxigenin α-L-rhamnoside [53].

The synthesis of a glycoside with an aromatic ring A has been described [54]. This type of compound is not found in nature, and the genin used in this investigation was obtained by Kupchan et al. [55] from strophanthidin by a microbiological method. The reaction of 3,14β-dihydroxy-19-norcard$\Delta^{1,3,5(10),20(22)}$-tetraenolide with acetobromoglucose in quinoline in the presence of silver oxide followed by saponification yielded the glucoside (XXXII). Unfortunately, the paper gives no information on the activity of this compound.

The reaction of 3β,14-dihydroxy-5,19-epoxycarbonylmethylene-5β,14β-card-20(22)-enolide with acetobromorhamnose (VIII) followed by saponification with methanolic ammonia yielded compound (XXXIII) [56]. This compound was twice as active as R-strophanthin.

By the reaction of digitoxigenone with organolithium compounds LiR where R = CH_3, C_2H_5, $CH{=}CH_2$, and C_6H_5, and with $NaC{\equiv}CH$, Albrecht and Kunz [57] obtained two series of cardenolides branched at C-3. The series differed in the configuration of the hydroxy group at C-3: β-OH (examples being (XXXV) and (XXXVI)) and α-OH (examples being (XXXVII) and (XXXVIII)). In comparison with digitoxigenin (XIX), the compounds synthesized possessed a greatly weakened cardiotonic activity. Some of the branched cardenolides (XXXV-XXXVIII) were glycosylated with 2,3,4-tri-O-benzoyl-α-L-rhamnopyranosyl bromide or 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide in the presence of mercury(II) cyanide [32, 58]. After the splitting out of the protective groups, the free glycosides were obtained with yields of 50-60%. Albrecht's observation of the dependence of the course of the reaction on the quality of the glycosyl bromide used is an important one. Thus, the aglycone (XXXV) began to react with freshly prepared acetobromoglucose only after an induction period of 24-30 h. If, however, the acetobromoglucose contained traces of hydrogen bromide, the reaction was complete after 8 h. In order to decrease the induction period, mercury(II) bromide or hydrogen bromide was added to the reaction mixture. (See scheme on next plate.)

The authors of the present review have studied the possibility of glycosylating the tertiary hydroxy group at C-5 of strophanthidin [59]. The reaction of strophanthidin acetate (XXXIX) with acetobromorhamnose (VIII) under the conditions of the Koenings–Knorr reaction followed by hydrolysis with potassium bicarbonate gave strophanthidin 5-O-α-L-rhamnopyranoside 3-O-acetate (XL). The condensation of strophanthidin (XII) with acetobromorhamnose (VIII) under the same conditions gave strophanthidin 3,5-bis-O-rhamnoside (XLI). The yields of compounds (XL) and (XLI) amounted to 10-14%. It was later found that if the condensation of strophanthidin with acetobromorhamnose was carried out in dichloroethane in the presence of mercury cyanide, i.e., under the conditions given by Albrecht [32], the yield of strophanthidin 3,5-bis-O-rhamnoside (XLI) could be raised to 50%. The activities of compounds (XL) and (XLI)



were somewhat lower than convallatoxin but were fully comparable with those of natural glycosides [60].

We have also used for the synthesis of cardenolide glycosides one of the variants of the orthoester method: the reaction of sugar orthoesters with aglycones in nitromethane in the presence of mercury bromide. Thus, by the reaction of 3,4-di-O-acetyl-β-L-rhamnopyranose 1,2-O-(methyl orthoacetate) with digitoxigenin (XIX), with strophanthidin (XII), with periplogenin, and with strophanthidol we have obtained evomonoside, convallatoxin (XIII), periplogenin 3-O-α-L-rhamnoside, and strophanthidol 3,19-bis-O-α-L-rhamnoside (XXVII) with yields of 35-55% [23, 61]. The reaction of an orthoester of fucose with periplogenin [62] gave periplogenin β-D-fucoside, identical with the natural glycoside ledienoside [63], in a yield of 65%. By the reaction of the ribose orthoester (XLII) with strophanthidin (XII) and with digitoxigenin (XIX), strophanthidin β-D-riboside and digitoxigenin β-D-riboside (XLIII) have been synthesized with yields of 75 and 51%, respectively [64].

It can be seen from the facts given that the yields of the final products obtained by the orthoester method are at the same level as the results obtained by the Koenigs–Knorr reaction.

Just like strophanthidol 19-O-α-L-rhamnoside (XXVI) [45], strophanthidol 3,19-bis-O-α-L-rhamnoside possessed none of the biological activity characteristic for cardiac glycosides. Tests on cats and on the inhibition of transport Na^+,K^+-ATPase gave similar results. On this basis, it was concluded that the introduction of a hydrophilic residue at the C-19 hydroxyl of the steroid nucleus led to a loss of cardiotonic activity [60]. The β-D-ribosides of strophanthidin and of digitoxigenin (XLIII) possessed an activity not inferior to that of the natural glycosides (50,000 frog activity units) [65].

So far, we have described syntheses of glycosides where, as in nature, the sugar residues had pyranose rings. Recently, the synthesis has been effected of cardenolide glycosides with a sugar residue in the furanose form. Arabinofuranosides of digitoxigenin [66] and of other cardenolides [67] have been obtained. Syntheses of strophanthidin α-L- and α-D-arabinopyranosides had been described previously [52]. The reaction of digitoxigenin (XIX) with 2,3,5-tri-O-benzoyl-α-L-arabinofuranosyl chloride (XLIV) in the presence of Fetison's reagent in a

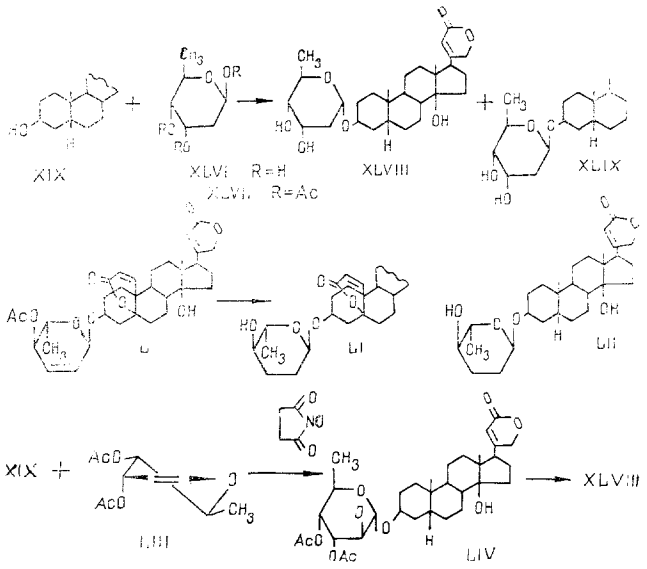
mixture of benzene and dioxane followed by saponification with methanolic ammonia has yielded digitoxigenin 3β-O-α-L-arabinofuranoside (XLV) [67]. The authors concerned reported that condensation of compounds (XIX) and (XLIV) in acetonitrile in the presence of mercury cyanide led to 14-anhydrodigitoxigenin 3β-O-α-L-arabinofuranoside tribenzoate. At a concentration of $4 \cdot 10^{-8}$ M, compound (XLIV) caused 50% inhibition of the Na^+,K^+-ATPase of porcine cardiac muscle, i.e., it was 2.5 times more active than digitoxigenin.

There are several patents on the partial synthesis of glucosides, rhamnosides, and galactosides of strophanthidin and of digitoxigenin [34, 39, 68]. In one of the patents in addition to syntheses of cardenolide glycosides, the preparation of glycosides of the bufadienolide series is described [38].

Cardenolides Containing 2-Deoxy- and 2,6-Dideoxy-Sugar Residues

In the preceeding section we have mainly considered syntheses of glycosides starting from acylhalogenoses having an acyl group at C-2, which ensures the stereochemical control of the reaction through the participation of the 2-acyloxy group. However, many of the cardiac preparations used in medicine contain 2,6-dideoxyaldoses (D-digitoxose, D-cymarose, D-boivinose, etc.) as the carbohydrate component. Increased attention is constantly being devoted to the serach for methods for obtaining such compounds, but the successes in this field have been less considerable.

The synthesis of a cardenolide glycoside containing a 2,6-dideoxysugar residue was effected as early as 1959 by Zorbach and Payne [69]. The reaction of digitoxigenin (XIX) with an excess of 3,4-di-O-p-nitrobenzoyl-2,6-dideoxy-β-D-ribohexosyl chloride in the absence of an acid acceptor led to digitoxigenin α-D-digitoxoside (XLVIII) in 45% yield. The activity of compound (XLVIII) amounted to 2/5 of the activity of the natural digitoxigenin β-D-digitoxoside — evantromonoside.



Later, by the direct condensation of digitoxose (XLVI) with digitoxigenin (XIX) in a mixture of dioxane and dichloromethane containing a small amount of hydrochloric acid the individual digitoxigenin α- and β-D-digitoxides (XLVIII) and (XLIX) were synthesized, but their yield did not exceed 5% [70].

Almost simultaneously, the same group of authors, by condensing 3,4,6-tri-O-p-nitrobenzoyl-2-deoxy-α-D-arabinohexosyl chloride with digitoxigenin in the presence of silver carbonate, obtained a mixture of anomers after the saponification of which and crystallization digitoxigenin 2-deoxy-β- and α-glucosides were obtained with yields of 19 and 15%, respectively [29].

By comparing with one another three glycosides of the same aglycone namely the β-D-glucoside, 2-deoxy-β-D-glucoside, and β-D-digitoxoside of digitoxigenin (XLIX), the authors [29] came to the conclusion that with a decrease in the number of hydroxy groups in the

sugar moiety the cardiotoxic activity fell. As has been shown in the preceeding section, on the basis of the same point of view the authors performed the synthesis of strophanthidin mannopyranoside, which, thanks to the increase in the number of hydroxy groups in the sugar moiety, proved to be more active than the known natural glycoside convallatoxin.

The synthesis of digitoxigenin 2-deoxy-β-D-allopyranoside has also been described [31].

A number of patents have been issued for the preparation of glycosides with oxide rings in the sugar moieties. The authors of a French patent [71] used acylated 1,2-glycals instead of acylglucosyl halides. Digitoxigenin 3-O-(2,3-anhydro-2-deoxy-L-arabinohexoside) and 3-O-(2,3-anhydro-2-deoxy-L-rhamnoside) were obtained with very good yields.

Acylated glycals have also been used for the synthesis of a number of 2,3-anhydroglycosides of cardenolides and of bufadienolides in a GFR patent [72].

There is a patent description of a method for obtaining digitoxigenin 3-O-(2,3-dideoxy-L-rhamnoside) by the reaction of digitoxigenin 12-O-acetate with 3,4-di-O-acetyl-L-rhamnal in tetrahydrofuran in the presence of $POCl_3$ followed by hydrogenation [73].

Similarly, i.e., by the reaction of 5,19-epoxycarbonylmethylenedigitoxigenin with 3,4-di-O-acetyl-L-rhamnal, the 4-O-acetyl-2,3-didehydro-2,3-dideoxy-α-L-rhamnoside (L) was obtained [56]. The hydrogenation of this compound led to the 2,3-dideoxy-α-L-rhamnoside (LI) [74]. The 3β-O-(2,3-dideoxy-α-L-rhamnoside) of strophanthidin and of digitoxigenin (LII) were synthesized by the same method. It was shown [74] that compound (LII) was three times more active in relation to its inotropic action than digoxin and was well absorbed on internal administration. Compound (LII) possesses a therapeutically acceptable stability in acid media and the same duration of its effect as k-strophanthin. The authors assumed that compound (LII) can be used as oral strophanthin.

The preparation of a 2,6-dideoxyglycoside by the reaction of a 2-alkylthio-6-deoxyhexopyranosyl bromide with a genin has been reported [75]. The condensation of a mixture of 3,4-di-O-acetyl-2-S-benzyl-6-deoxy-2-thio-α- and β-D-altropyranosyl bromides with digitoxigenin in the presence of mercury cyanides followed by hydrogenation of the product has led to a syrupy mixture of 2',6'-dideoxy-α- and β-D-ribohexopyranosides of anhydrodigitoxigenins.

Recently, several new methods of obtaining digitoxosides of digitoxigenin, the synthesis of which was first effected by Zorbach et al. [69], have been proposed.

The reaction of digitoxose triacetate (XLVII) with digitoxigenin (XIX) in benzene in the presence of p-toluenesulfonic acid and 4 Å molecular sieve for 2 hours led to 25% of the α- and 35% of the β-D-digitoxosides of digitoxigenin (XLVIII) and (XLIX) [76].

Later, Thiem et al. [13] showed that under these conditions it is predominantly digitoxosides of 14-anhydrodigitoxigenin that are formed. They proposed a new method of condensation. By the reaction of D-digitoxal diacetate (LIII) with digitoxigenin (XIX) in acetonitrile in the presence of N-iodosuccinimide they obtained the α-D-glycoside (XLIV). This compound, after reductive dehalogenation and deacetylation was converted into digitoxigenin α-D-digitoxoside (XLVIII).

The condensation of α-acetobromodigitoxose obtained *in situ* with digitoxigenin in the presence of silver triflate in a mixture of nitromethane, toluene, dichloroethane (3:7:1) at −78° enabled them to obtain a mixture of the diacetates of digitoxigenin α- and β-D-digitoxosides with a yield of 51% [13]. The reaction products were saponified and were separated with the aid of chromatography into digitoxigenin β-D-digitoxoside (XLIX) and α-D-digitoxoside (XLVIII).

Uronic Acid Glycosides

Information on the influence of uronic acid residues on the activity of cardiac glycosides remained contradictory for a long time. As early as 1944, it was claimed [49] that a glycoside, digicorin, with a biological activity 100-1000 times exceeding the action of digitoxin had been isolated from *Digitalis purpurea*. The aglycone of digicorin was given as ditoxigenin and the sugar component, attached to the C-16 hydroxyl, was, in the opinion of the authors, D-digicuronic acid. The structure of the acid was not reliably established.

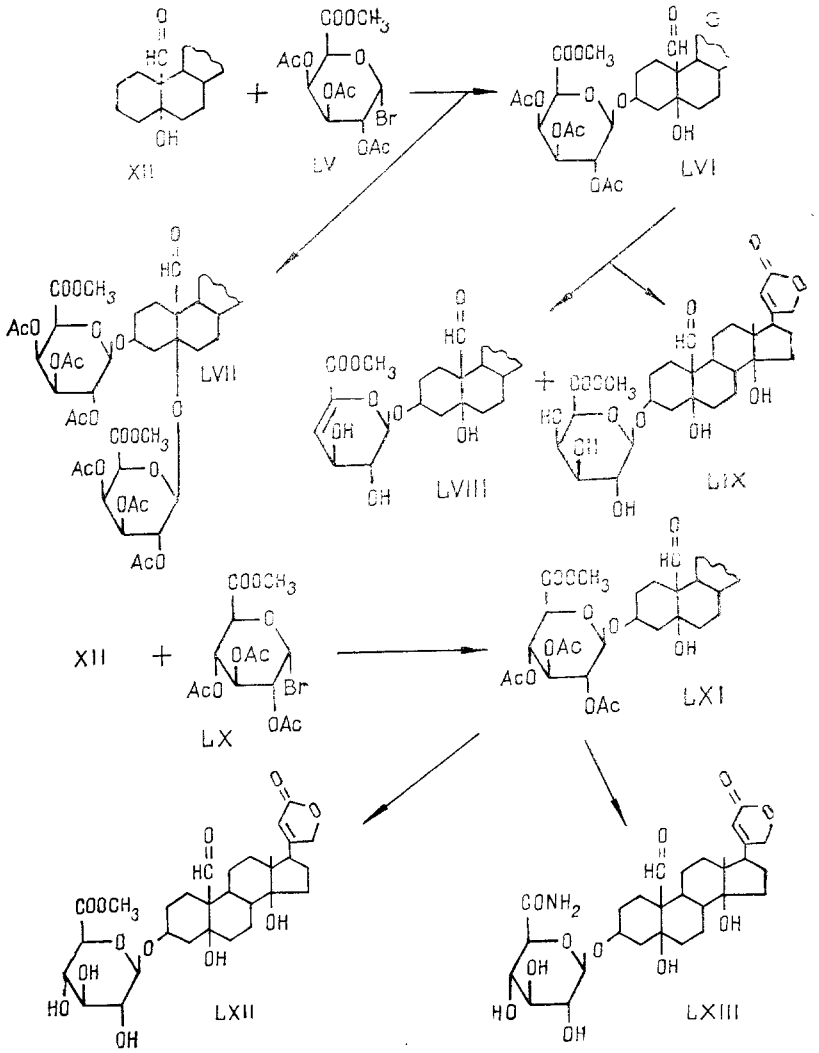
In spite of the intensive investigation of the cardiac glycosides of *Digitalis*, no one succeeded in confirming this report in subsequent years and, as recorded above, synthetic ditoxigenin 16-O-β-D-glucoside possessed no cardiotonic activity [50].

According to Repke's hypothesis [77, 78], in the liver of the animal organism the 3β-OH groups of cardenolides are epimerized to 3α-OH groups and, after conjugation with glucuronic acid, the glycosides are eliminated from the organism in the form of inactive compounds.

The first attempt to obtain glucuronosides of cardenolides was made by Zorbach et al. in 1962 [28]. They performed the condensation of digitoxigenin with the acetobromo derivative of methyl glucuronate and obtained the triacetate of the methyl ester of digitoxigenin glucosiduronic acid. All attempts to saponify this compound proved to be unsuccessful, and the question of activity remained unsolved.

Ten years later, a patent appeared on the production of substituted amides of digitoxigenin glycosiduronic acids. As the glycosylating component the authors used acetobromo-derivatives of methyl glucuronate, mannuronate, and galacturonate.

In contrast to Repke's hypothesis, it was shown that the substances obtained were very active compounds with a positive inotropic action on the cardiac muscle. Good enteral absorbability and a low capacity for cumulation were also reported. However, the absence of quantitative indices does not permit us to judge with complete confidence to what extent cardenolide glucuronosides approach the natural glycosides in activity.

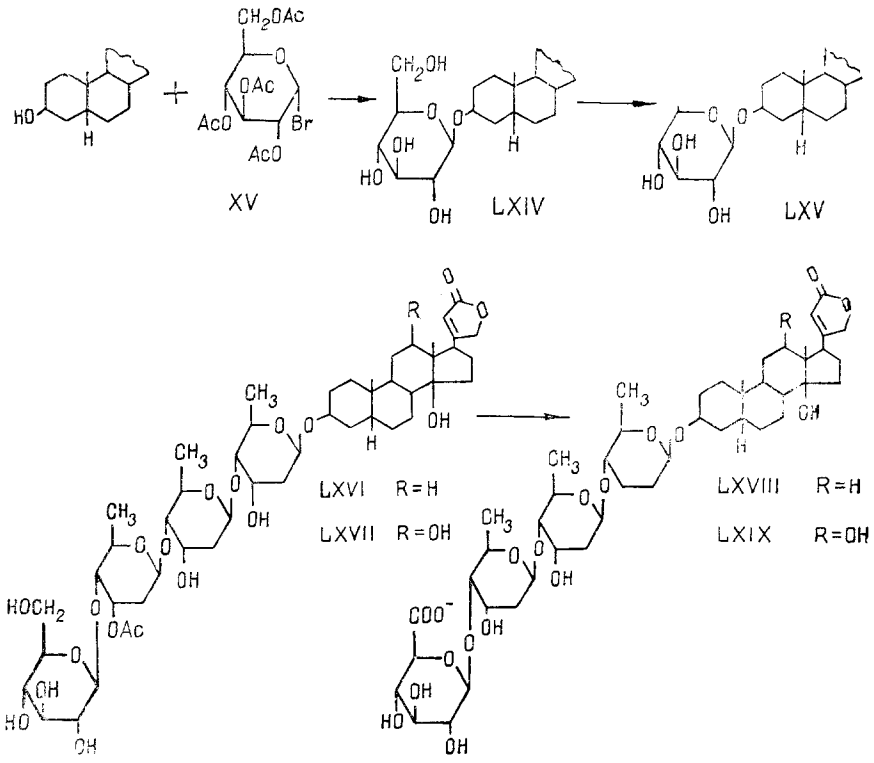


By the reaction of methyl 2,3,4-tri-O-acetyl-1-bromo-1-deoxy-α-D-galacturonate (LV) with strophanthidin (XII), the authors of the present review have synthesized the triacetate of the methyl ester of strophanthidin β-D-galactosiduronic acid (LVI) and the hexaacetate of the dimethyl ester of strophanthidin 3,5-bis-O-(β-D-galactosiduronic acid) (LVII) (yields 67 and 10%, respectively) [59, 80].

The Zemplen saponification of the triacetate (LVI) gave strophanthidin 3β-O(methyl α-L-threo-4'-hexenopyranosiduronate) (LVIII) and strophanthidin 3β-O(methyl β-D-galactopyranosiduronate) (LIX) [80].

The condensation of the acetobromo derivative of methyl glucuronate (LX) with strophanthidin (XII) gave the triacetate of strophanthidin (methyl β-glucosiduronate) (LXI) [81]. The action of a solution of ammonia in absolute ethanol on compound (LXI) gave the strophanthidin glucosiduronamide (LXIII), and the action of a methanolic solution of sodium methanolate on compound (LXI) gave strophanthidin (methyl glucosiduronate) (LXII).

The condensation of the bromide (LX) with periplogenin performed under the same conditions led to the triacetate of periplogenin (methyl β-glucosiduronate) and the hexaacetate of periplogenin 3,5-bis-O-(methyl β-glucosiduronate) [82]. The saponification of the acetates with a solution of sodium methanolate in absolute methanol yielded periplogenin (methyl β-D-glucosiduronate) and periplogenin 3,5-bis-O-(methyl β-glucosiduronate).



The cardiotonic effects of compounds (LXVIII) and (LIX) were tested on frogs. The efficacy of the first of these compounds corresponded to one half and that of the second to one third of the activity of k-strophanthidin-β. The derivatives of strophanthidin glucosiduronic acid proved to be even less active: The activity of the methyl ester (LXII) was 10% and that of the amide (LXIII) 2.5% of the activity of k-strophanthin-β. Trials on the inhibition of transport Na^+,K^+-ATPase from rat brain confirmed the low efficacy of compounds (LXI), (LXII), and (LXIII) [83]. In our opinion, the finding of highly active cardiac drugs among glycosides with uronic acid residues is unlikely, but they are of definite interest for the study of the metabolism of cardiac glycosides in the animal organism.

The synthesis of glucosiduronic acids can also be effected by a basically different method [84], namely, by the direct oxidation with oxygen in the presence of platinum of the hydroxymethyl groups of the glycosides (LXIV) to carboxy groups in compound (LXV). The initial glucosides themselves are obtained by the usual method — by the condensation of acetobromoglucose (XV) with the cardenolides. The lactone ring of the aglycone is not effected under these conditions.

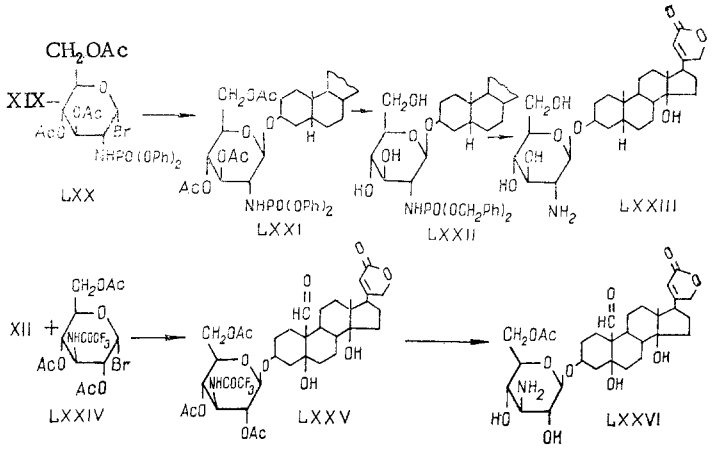
Glucosiduronic acids of digoxigenin, of digitoxigenin, of 3-epidigitoxigenin, and of digitoxigenin monodigitoxoside have been obtained in the form of their sodium salts by this method.

Digitoxin 16'-O-(β-D-glucosiduronic acid) (LXVIII) and digoxin 16'-O-(β-D-glucosiduronic acid) (LXIX) have been synthesized by the same way after the preliminary deacetylation of the natural glycosides lanatoside A (LXVI) and lanatoside C (LXVII).

All the compounds synthesized possessed a positive inotropic action. The introduction of a glucuronic acid residue roughly halved the toxic action of the cardiac glycosides (for example, the toxicity of digoxin on cats according to Hatcher is 0.33 mg/kg, and that of compound (LXIX) 0.71 mg/kg) [84].

Aminoglycosides

For a study of the influence of an amino group on the cardiotonic action of cardiac glycosides, digitoxigenin and strophanthidin 2'-amino-2'-deoxy-β-D-glucosides and strophanthidin 3'-amino-3'-deoxy-β-D-glucoside were prepared. The difficulty in the synthesis of the aminoglycosides consists in the fact that the amino group must be protected in such a way that it can be liberated after glycosylation without the aglycone moiety of the glycoside being affected in this process. Meyer zu Reckendorf et al. [85] used the N-diphenoxyphosphoryl group as the protective group for this purpose. The reaction of the bromine derivative (LXX) with digitoxigenin (XIX) in benzene in the presence of mercury cyanide led to compound (LXXI) in very good yield. Transesterification with a solution of ammonia in benzyl alcohol gave the derivative (LXXII). Then the benzyl residues were removed by catalytic hydrogenation over palladium in a neutral medium. The hydrolysis of the unstable phosphoramide group took place simultaneously with the formation of the free glycoside (LXXIII). Strophanthidin 2'-amino-2'-deoxy-β-D-glucoside was obtained similarly.



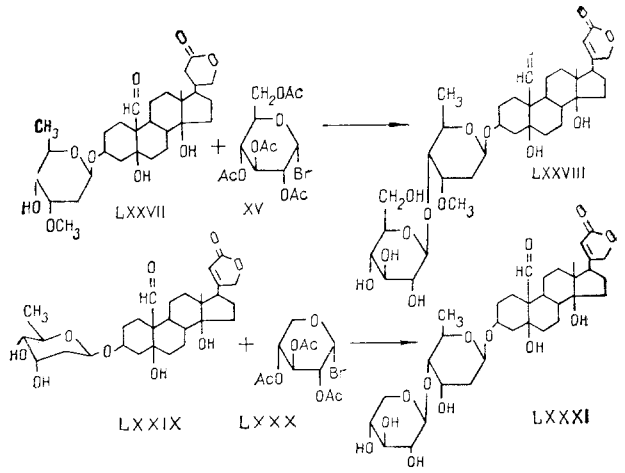
In the preparation of strophanthidin 3'-amino-3'-deoxy-β-D-glucoside (LXXVI) [86], the trifluoroacetyl group was selected as the protective group for the amino function. The condensation of strophanthidin (XII) with the bromide (LXIV) in the presence of mercury cyanide and bromide gave the glycoside (LXXV) in good yield. However, in subsequent Zemplen saponification and the following ammonolysis it was impossible to avoid losses and the glycoside (LXXVI) was obtained low yield. Unfortunately, the activities of the compounds synthesized were not reported in this paper.

Synthesis of Glycosides with Several Sugar Residues

The synthesis of diglycosides and triglycosides has been carried out by two methods: 1) the condensation of a suitable monoglycoside with an acylglycosyl halide, or 2) by the reaction of an aglycone with the bromine derivative of an acylated oligosaccharide.

N. K. Kochetkov et al. [87] have synthesized the cardiac diglycoside k-strophanthin-β. As the initial glycosides these authors selected cymarin, the sugar moiety of which has only one free hydroxy group. However, under these conditions of the Koenigs–Knorr reaction cymarin (LXXVII) did not react with acetobromoglucose. It was decided to perform the condensation in benzene using a special instrument in which the water eliminated by distillation was absorbed by metallic sodium. After the usual working up of the reaction products, k-strophanthin-β (LXXVIII) was obtained in very low yield. (See scheme on next plate.)

In a later investigation A. Ya. Khorlin and A. F. Bochkov [88] replaced the silver carbonate by lead carbonate and performed the condensation in boiling toluene. These changes permitted the yield of k-strophanthin-β to be raised to 17%.



V. T. Chernobai [89], studying the composition of the mixture formed in the condensation of cymarin (LXXVII) with acetobromoglucose (XV) came to the conclusion that the main product of this reaction is strophanthidin 3-O-β-D-glucoside, which arises as the result of the trans-glycosylation of the cymarin. Later, the same author proposed a method for obtaining k-strophanthin-β using as hydrogen bromide acceptor silver carbonate and camphor [90].

To confirm the structure of the diglycoside erychroside isolated from a plant, N. F. Makarevich synthesized it from erysimin (strophanthidin digitoxoside) (LXXIX) and acetobromo-xylose (LXXX) [91]. In the carbohydrate moiety of erysimin there are two hydroxy groups: equatorial at C-4 and axial at C-3. The reaction took place predominantly at the equatorial hydroxyl. The condensation was carried out at room temperature in dioxane with silver oxide and calcium oxide. Erychroside (LXXXI) was obtained with a 22% yield.

The condensation of digitoxigenin with acetobromo derivatives of gentiooligosaccharides had given glycosides with a chain of 1,6-linked D-glucose residues: in particular, digito-xigenin gentiobioside and gentiotrioside. As the authors showed, with an increase in the number of glucose residues the cardiac activity and the toxicity of the products rise [92].

Diglycosides in which sugar residues are attached to hydroxyls in different positions of the steroid nucleus have also been synthesized (some of them have been mentioned above): strophanthidol 3,19-di-O-α-L-rhamnoside (XXVII) [46, 23], digitoxigenin 3,12-di-O-β-D-xylo-side and 3,12-di-O-β-D-glucoside, ditoxigenin 3,16-di-O-β-D-glucoside [50], strophanthidin 3,5-di-O-α-L-rhamnoside and 3,5-di-O-(β-D-galactosiduronic acid) and periplogenin 3,5-di-O-(β-D-glucosiduronic acid).

In concluding this review, we come to the conclusion that the intensive investigations of the last few years have led to the development of a whole series of methods permitting sugars of various natures to be linked by a O-glycosidic bond with the nuclei of cardio-steroids. Completely satisfactory results have been obtained in glycosylation with hexoses, pentoses, and methylpentoses. The conditions for glycosylation with 2,6-dideoxy sugars have been studied inadequately. Because of this, there is a lack of methods of synthesizing the glycosides most frequently used in medicine such as digitoxin, digoxin, and strophantho-side not to speak of even more complex compounds such as lanatosides A, B, and C. As pre-viously, the demands of medicine for cardiac drugs is being satisfied exclusively from plant sources. In view of the intensification of studies on the pharmacokinetics and mechanism of the action of cardiac glycosides, the synthesis of model compounds identical with or similar to natural metabolites deserves attention.

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