ADVANCES IN THE SYNTHESIS OF CARDENOLIDES

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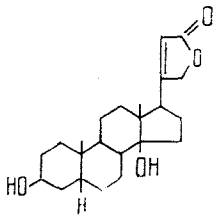
UDC 547.926

Cardenolides and their glycosides, sometimes called cardiac glycosides, are widely known because of their specific healing action on the cardiac muscle. They form a group of drugs which is one of the most important and most frequently used in clinical medicine. Cardenolides, usually in the form of glycosides, are found in various plants which still serve as the only source of their industrial production. Nevertheless, cardiotonic glycosides are not among the compounds that are widely distributed in the vegetable kingdom [1-3]. The species composition of plants elaborating glycosides of the cardiac group in the process of their vital activity is limited, and therefore the search for new methods for obtaining them is of no little importance.

In their chemical structure, the cardenolides belong to the class of steroids. They are characterized by the presence of an α,β-unsaturated butenolide ring attached at C-17, by the presence of hydroxy groups at C-3 and C-14, and by a cis linkage of rings C/D. The spatial arrangement of the substituents at C-14 and C-17 is of first-degree importance for cardiotonic activity — in all active natural aglycones they have the β orientation. The cardenolide with the simplest chemical structure, which is typical for the whole group, is digitoxigenin:



The high lability and strict stereospecific nature of the structural elements of the cardiosteroids formed an obstacle difficult to surmount on the route to their synthesis. Although the first investigations in this direction were undertaken at the beginning of the forties, appreciable advances have been achieved very recently [4, 5].

In the present review, an attempt is made to generalize and systematize scattered information on the synthesis of natural cardenolides. It does not consider methods for obtaining modified cardenolides or methods of synthesizing the bufadienolides — cardiosteroids with a six-membered α-pyrone lactone ring. The latter questions undoubtedly deserve special consideration.

Even in the early period of the development of the cardenolides after the elucidation of the main elements of their structure, attempts were made to find methods for synthesizing the cardiac genins and their analogs (for reviews of early work, see [6, 7]).

Starting from the assumption that cardiotonic activity is due to the presence of an α,β-unsaturated lactone ring, the authors directed their efforts to synthesizing various cyclic compounds containing such a substituent.

Among the first investigations in this field are those of Elderfield et al. [8, 9], who developed a method for obtaining β-substituted α,β-unsaturated butenolides. The scheme of synthesis was based on the Reformatsky condensation of ethyl bromoacetate with various ketones and ketols [10-13].

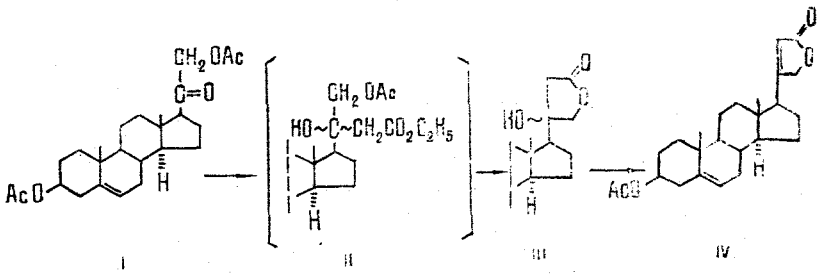
A similar method using acyloxymethyl ketones as the starting compounds was selected by Ruzicka et al., who were working in this direction simultaneously with Elderfield. Thus, for example, starting from the ketol acetate (I) (Scheme 1), via the hydroxylactone (III), which was dehydrated under severe conditions, the butenolide (IV) was obtained [14-16].

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR, Tashkent. Translated from Khimiya Prirodnykh Soedinenii, No. 3, pp. 283-299, May-June, 1978. Original article submitted December 1, 1977.

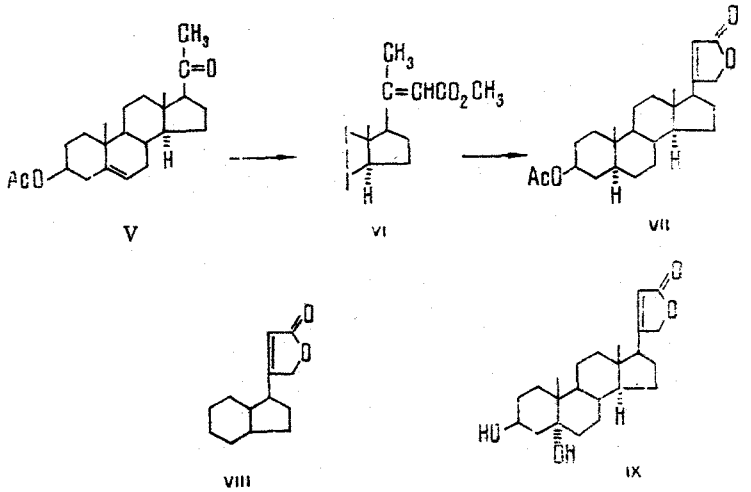
0009-3130/78/1403-0233$07.50

Another method for the synthesis of β-substituted butenolides is based on experiments by Elderfield, who showed that the oxidation of β-methyl-substituted α,β-unsaturated acids with selenium dioxide led to intramolecular cyclization with the formation of α,β-unsaturated lactones [17].

The Swiss chemists used this reaction to obtain various steroid lactones. Thus, pregnenolone acetate (V) (Scheme 2), after Reformatsky condensation with methyl bromoacetate, hydrogenation and the Δ^5 bond, and subsequent dehydration, was converted into the $\Delta^{20(22)}$-unsaturated derivative (VI), the allyl oxidation of which with selenium dioxide led to 14-deoxy-14α-uzarigenin acetate (VII) [18]:



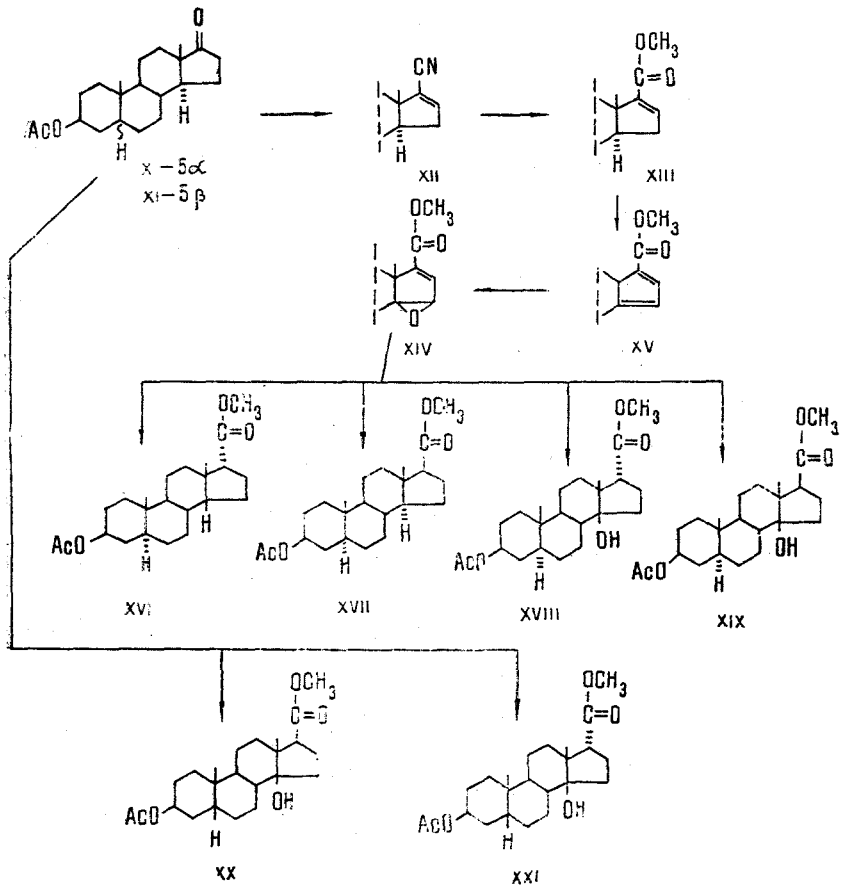
Scheme 1



Scheme 2

The American [8-13] and Swiss [18-28] workers synthesized various α,β-unsaturated butenolides by the methods described above. However, neither the simplest derivatives [of type (VIII)] nor closer analogs [for example, (VII) and (IX)] possessed cardiotonic activity. It is obvious that this is due mainly to trans linkage of the C/D rings and to the absence of a hydroxy group at C-14, which distinguishes these compounds from the cardiac aglycones.

The next approach to the synthesis of the natural cardenolides was the development of methods of introducing a hydroxy group in the C-14 position. Systematic investigations in this field were undertaken in 1946-1947 [29, 30]. The 5α-androstan-17-one (X, Scheme 3) selected as the starting compound, on reaction with HCN, readily formed the cyanohydrin, which, after dehydration, was converted into the unsaturated nitrile (XII). This substance was hydrolyzed, acetylated, and esterified with diazomethane, after which the 17-carboxylic acid methyl ester (XIII) was obtained. Allyl bromination with N-bromosuccinimide of the olefin (XIII) followed by the splitting out of hydrogen bromide permitted passage to the diene (XV) [29], which, on reaction with one molecule of perbenzoic acid, formed the 14β,15β-epoxysteroid (XIV). Hydrogenation of the epoxide (XIV) over a platinum catalyst gave, in addition to the hydrogenolysis products (XVI and XVII), two isomeric compounds containing a 14-hydroxy group. The steroid (XVIII) — the 14β,1/α isomer — was obtained with a yield of about 40%. The 14β,17β epimer (XIX), which is more suitable for the synthesis of cardenolides, was formed in lower yield — about 25% [30].



Scheme 3

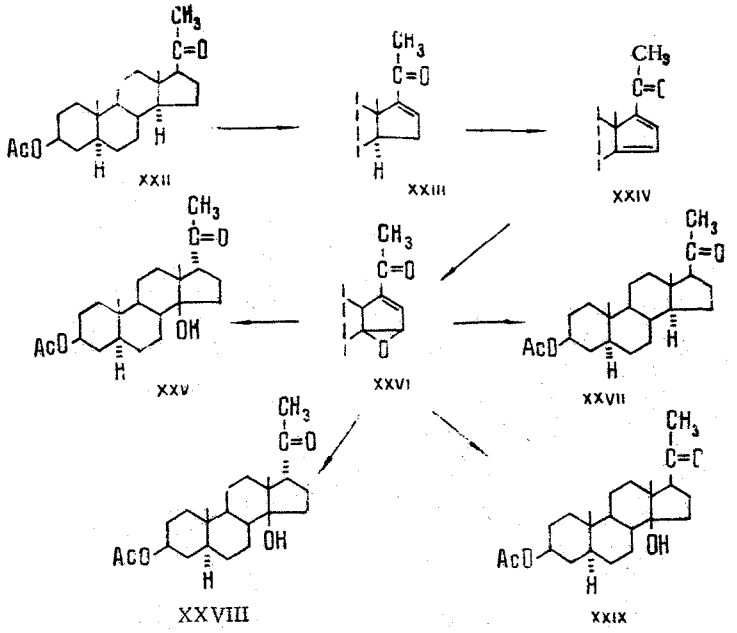
The same series of transformations, with slight modifications, was applied to the compounds of the 5β series (XI) [31, 32], but the yield of the 14β,17β steroid (XX) did not exceed 25% while that of its 14β,17α isomer (XXI) reached 70% [32]. Compound (XX) was subsequently used by Sondheimer et al. [33, 34] for the synthesis of digitoxigenin.

The possibility of introducing a 14β-hydroxy group into pregnan-20-ones or into 21-hydroxypregnan-20-ones is attractive from the point of view of cardenolide synthesis. Detailed investigations were carried out by Swiss chemists at the same time. The initial substance for obtaining 14-hydroxypregnan-20-ones was 5α-pregnan-20-one 3-acetate (XIII, Scheme 4). This compound was brominated and was then converted by dehydrobromination into pregn-16-ene (XXIII) [35]. The epoxide (XXVI) was obtained by the usual route from the pregnene (XXIII) via the diene (XXIV). Hydrogenation of the epoxide (XXVI) with the aid of a palladium catalyst led to the 14-deoxy compounds (XXV and XXVII) and to the 14β-hydroxy steroids (XXVIII and XXIX), and in this case the yield of the 17α epimer (XXVIII) (40%) was much greater than that of the 17β isomer (XXIX) (10%) [35].

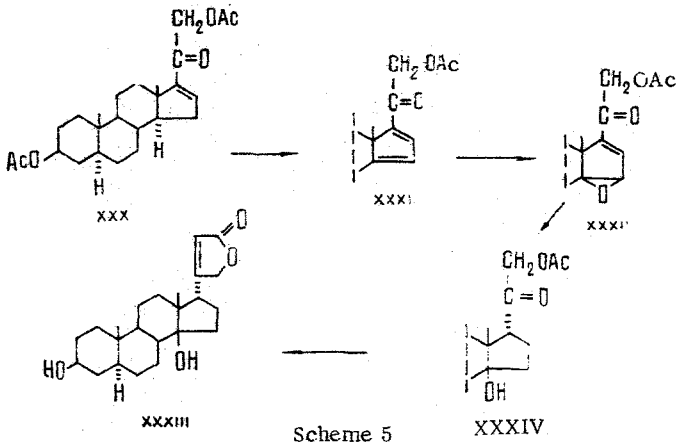
For the synthesis of pregnane-14,21-diols, the initial pregnene (XXX) (Scheme 5) was converted via the diene (XXXI) into the 14β,15β-epoxide (XXXII). But when the epoxide (XXXII) was reduced with the aid of a palladium catalyst, it was possible to isolate only the 14β-hydroxy-17α isomer (XXXIV), and the 14β-hydroxy-17β-pregnane corresponding to it was not obtained at all [36].

Swiss authors synthesized the physiologically inactive 17α-uzarigenin (XXXIII) from compound (XXXIV) by adding on a lactone ring with the aid of the Reformatsky reaction [37].

This communication, as it were, completed a series of notable investigations by Ruzicka and Plattner, and their colleagues on obtaining analogs of cardiac genins. Although the



Scheme 4



Scheme 5

authors had not synthesized any natural cardenoline, thanks to their investigations the probable routes had been marked out and the possibility of such synthesis had been shown.

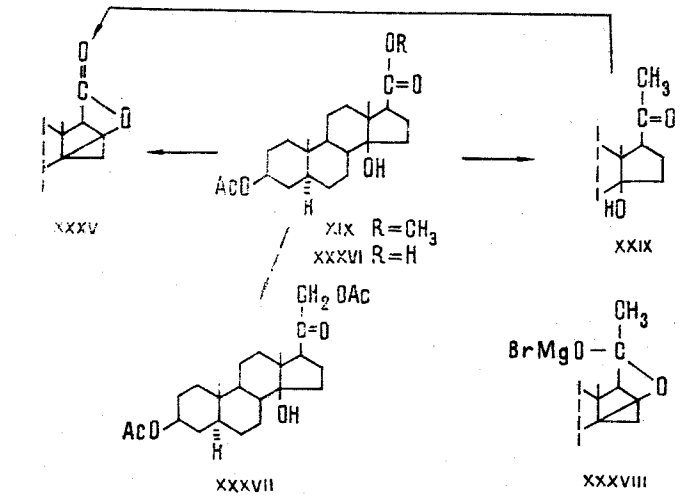
No publications appeared on the production of cardiosteroids for a long time, until in 1962 Sondheimer et al. [33] reported the synthesis of a native cardiac aglycone — digitoxigenin. This was the next important step in this field..

In preliminary experiments in which steroids of the 5α series were used, it was planned [4], after having constructed the side-chain of the 14β-hydroxy-17β-carboxylic acid side chain (XXXVI) obtained by the method of Ruzicka et al. [29, 30] (see Scheme 3), to pass to the diacetate of 3β,14β,21-trihydroxy-5α-pregnan·20-one (XXXVII). Such a passage from a 17-carboxylic acid via the acid chloride and a diazoketone to the corresponding ketol in the absence of a hydroxy group at C-14 was widely used in the work of Elderfield [9, 12, 13] and of Ruzicka [19-22]. However, in the present case when an attempt was made to obtain the acid chloride, the 14β-hydroxy acid (XXVI) always gave only the 14 → 20-lactone (XXXV) [4]. This high tendency of the compound (XXVI) to undergo lactonization forced the authors to seek different methods for adding on the side chain.

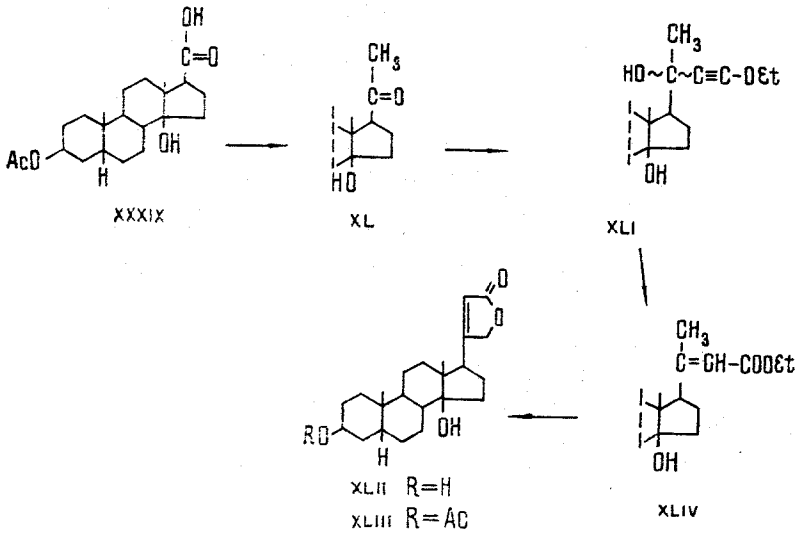
Thus, in another series of experiments, the carboxylic acid (XXXVI) was condensed with

methyllithium in tetrahydrofuran [4]. However, the ketone (XXIX) obtained in this way, which was identical with the 5α-pregnan-20-one (see Scheme 4) synthesized previously by Ruzicka et al. [35], when oxidized with lead tetraacetate again gave the lactone (XXXV) in place of the expected ketol (XXXVII) [4].

Subsequently, to add on the C-22 and C-23 carbon atoms an attempt was made to condense the ketone (XXIX) with ethoxyethynylmagnesium bromide. The reaction was expected to give an ethoxyethynyl carbinol, which, in a weakly acid medium, could be rearranged into an α,β-unsaturated ether. Unfortunately, the reaction did not take place in the expected direction, since on the addition of ethoxyethynylmagnesium bromide a compound to which the structure (XXXVIII) was assigned deposited as a precipitate.



Scheme 6



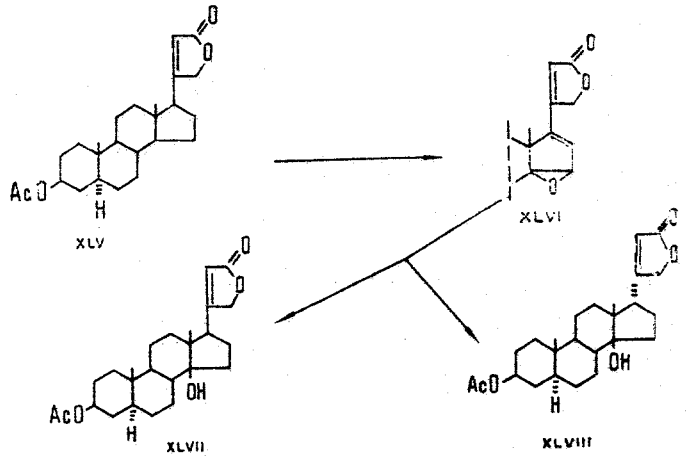
Scheme 7

The formation of a precipitate, interfering with the further occurrence of the reaction, was most probably connected with the poor solubility of the Grignard derivative. The authors of the present paper have shown [38, 39] that when ethoxyethynyllithium is used in place of ethoxyethynylmagnesium bromide, the condensation takes place smoothly and in the desired direction.

Subsequently, Sondheimer et al. [33, 34] used steroids of the 5β series for the synthesis of cardenolides (Scheme 7). The acetate of the 14β-hydroxy carboxylic acid (XXXIX) obtained by Ruzicka's method [31, 32], on being condensed with methyllithium, formed 3β,14β-dihydroxy-5β-pregnan-20-one (XL). Condensation of the ketone (XL) with ethoxyethynyllithium gave the ethoxyethynyl carbinol (XLI), which rearranged in an acid medium into the α,β-unsaturated

ester (XLIV). Oxidation of this compound with selenium dioxide led to the closure of a lactone ring and the formation of digitoxigenin acetate (XLIII), the saponification of which gave digitoxigenin (XLII). Although, reckoning from the acid (XXXIX), the intermediate products were obtained in appreciable amounts, the synthesis of 14β-hydroxy acid (XXXIX) itself is a multistage one [30, 32] and takes place with a low yield. The introduction of a 14β-hydroxy group obviously required a different approach.

Using a method different from that described above, Japanese chemists [40], who synthesized another cardiac aglycone — uzarigenin — used the steroid (XL) as the key compound (Scheme 8). The latter already contained a butenolide ring. However, the synthesis that they performed cannot be regarded as strictly sterospecific. Oxidation of the trienolide (XLV), obtained on the basis of Ruzicka and Plattner's well-known work [18, 27, 41], with 1 mole of perbenzoic acid led to the epoxide (XLVI). In this case, as in other investigations of a similar type [29, 32, 36], the action of the peroxy acid on 14,16-dienes takes place by a β attack and the epoxide formed has the 14β,15β configuration. The hydrogenation of the Δ^{16}-epoxy compound (XLVI) in the presence of palladium on coal led to a mixture of 17α-uzarigenin and uzarigenin acetates (XLVIII and XLVII, respectively) with yields of 9.7 and 3.4%, calculated on compound (XL).

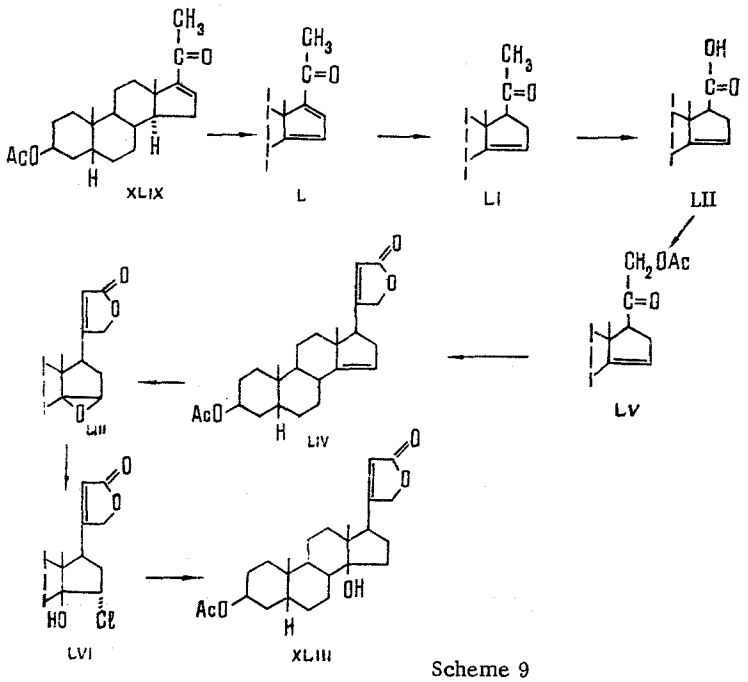


Scheme 8

The acetates of digitoxigenin and its 17α isomer were obtained by an analogous method starting from $\Delta^{14,16}$-dianhydrodigitoxigenin [42].

An interesting method of synthesizing digitoxigenin was described in 1964 by Engel and Bach [43]. Rejecting the method developed previously for introducing 14β-hydroxy group, the authors proposed a scheme of synthesis in which the key compound was β-anhydrodigitoxigenin acetate (LIV, Scheme 9). First the dienone (L) was obtained by the allyl bromination of pregnenolone acetate (XLIX) with N-bromosuccinimide [28, 35, 41, 44-46] followed by dehydrobromination. Compound (L) was then reduced with sodium in propanol [47] to pregn-14-en-20-one, which was then oxidized at the 20-hydroxy group. This gave the 5β-pregnen-20-one (LI), which was transformed by haloform cleavage into the 17β acid (LII). The latter was converted via the acid chloride and the diazoketone into 21-acetoxypregnene (LV). β-Anhydrodigitoxigenin acetate (LIV) was obtained from (LV) by the Reformatsky reaction. The reaction of the anhydro compounds (LIV) with N-bromosuccinimide in dioxane in the presence of perchloric acid [43] or in aqueous acetone [43, 48] led to the bromohydrin which, on chromatographic purification by passage through alumina, formed the 14β,15β-epoxide (LIII). Cleavage of the epoxide (LIII) with hydrogen chloride led to the 14β-hydroxy-15α-chloro compound (LVI). Under the action of Raney nickel, this compound was converted in low yield (22%) into digitoxigenin acetate (XLIII).

Fritsch et al. [49, 50] have developed a method for introducing a lactone ring by the esterification of a 21-hydroxysteroid with malonic acid followed by intramolecular condensation. By making use of this method, the German authors have performed syntheses of digitoxigen [51, 52], uzarigenin [53], and canarigenin [54].



Scheme 9

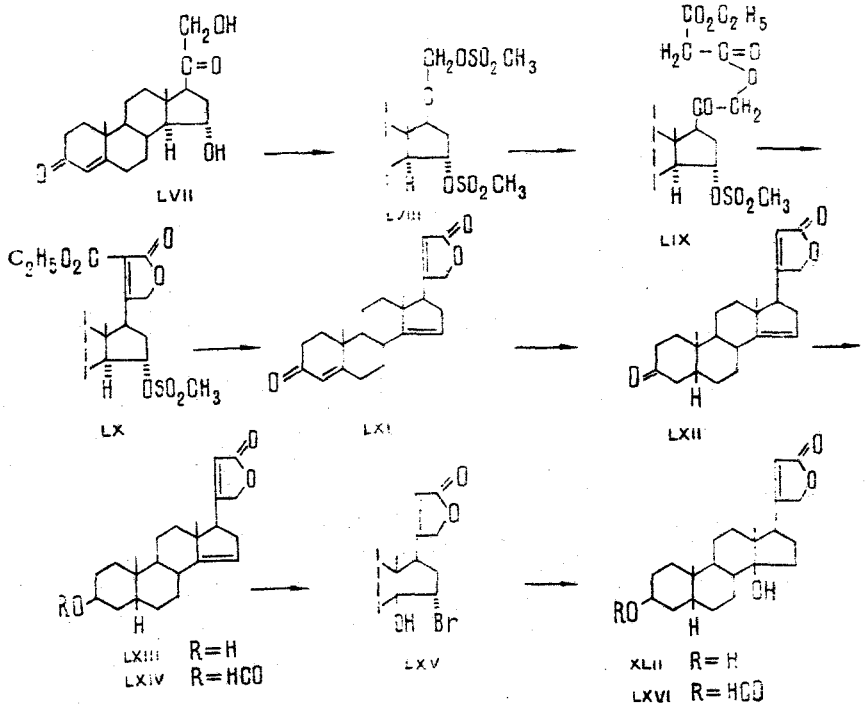
The original synthesis of digitoxigenin was described in 1969 [51]. While retaining the basic principles of the initial scheme, the same authors later reported a far more effective route [52]. The synthesis, consisting of 10 stages, was carried out with an overall yield of 21%.

The initial compound in the synthesis of digitoxigenin was 15α-hydroxycortexone (LVII) (Scheme 10), obtained by the microbiological oxidation of cortexone [55, 56]. Reaction of compound (LVII) with methanesulfonyl chloride led to the 15,21-dimesylate (LVIII), which, under the action of the potassium salt of monoethyl malonate, formed the 21-malonate (LIX). This intermediate substance partially underwent spontaneous intramolecular condensation with conversion into the butenolide (LX), this process taking place better under the action of piperidine acetate. Compound (LX), on treatment with collidine with the addition of p-toluenesulfonic acid, was converted into the Δ^{14}-butenolide (LXI). Hydrogenation of the unsaturated ketone (LXI) under carefully selected conditions over $Pd/CaCO_3$ in the presence of pyridine made it possible to pass to the 5β-3-oxo butenolide (LXII) in good yield. Reduction of 3-oxo group by the method of Haddad et al. [57] in isopropanol in the presence of trimethylphosphine gave the β-anhydrodigitoxigenin (LXIII), from the formate of which (LXIV) the bromohydrin (LXV) was obtained. The reductive debromination of compound (LXV) with Raney nickel gave digitoxigenin formate (LXVI). Saponification of (LXVI) led to digitoxigenin (LXII).

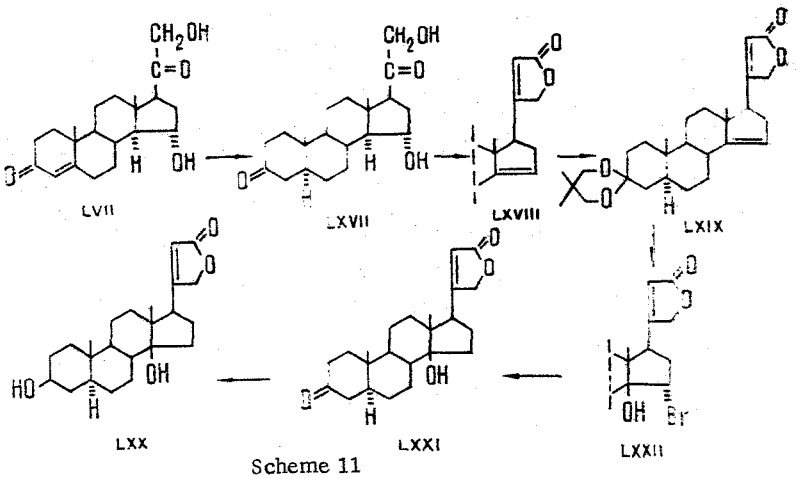
The synthesis of digitoxigenin from another product of the microbiological oxidation of cortexone — 14α-hydroxycortexone — was proposed by Italian chemists in 1974 [58]. The scheme of synthesis does not differ essentially from that described above, only the sequence of the individual stages being changed.

The possibility of obtaining compounds not only of the 5β but also of the 5α series by the reduction of a Δ^3-oxo grouping enabled German chemists [53] to us 15α-hydroxycortexone for the synthesis of uzarigenin. Hydrogenation of compound (LVII) (Scheme 11) over a palladium catalyst gave a mixture of 5α and 5β isomers, from which the 5α steroid (LXVII) was isolated with a yield of 42%. Under conditions similar to those described above, this ketone was converted into the butenolide (LXVIII). After the formation of the ketal (LXIX), the introduction of a 14β-hydroxy group via the bromohydrin (LXXII), and the removal of the ketal protection, uzarigenone (LXXI) was obtained. Reduction of uzarigenone with the aid of lithium tris(tert-butoxy)hydroaluminate led to uzarigenin (LXX).

In 1970, the authors of the present paper reported the synthesis of uzarigenin [38, 39] starting from the readily accessible steroid compound 3β-acetoxy-5α-pregn-16-en-20-one (XXIII)



Scheme 10

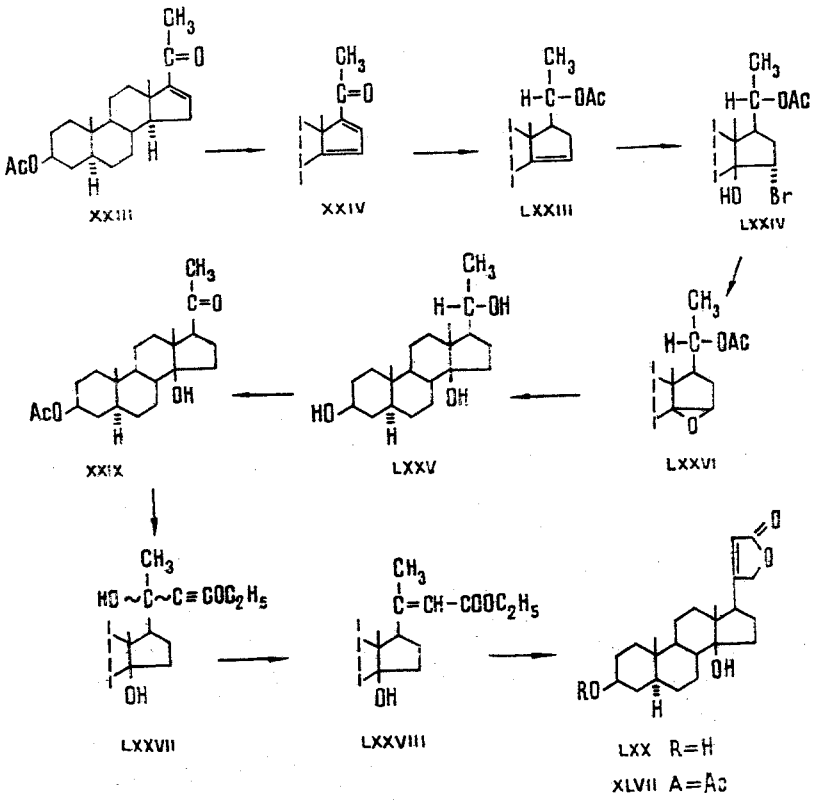


Scheme 11

(Scheme 12). This substance is readily obtained by the oxidative cleavage of tigogenin [59, 60] — a frequently found steroid sapogenin. The proposed synthesis of uzarigenin consists of three main steps: 1) passage from Δ^{16} steroids to Δ^{14} compounds, 2) the introduction of a 14β-hydroxy group, and 3) the construction of the lactone ring.

5α-Pregnenolone acetate (XXIII) was subjected to allyl bromination with N-bromosuccinimide followed by dehydrobromination with sodium iodide in acetone. This gave a good yield of the dienone (XXIV), from which by reduction with sodium in propanol and acetylation, the Δ^{14} steroid (LXXIII) was obtained [61].

The next stage of the synthesis consisted in the introduction of the 14β-hydroxy group. For this purpose, the Δ^{14}-diene diacetate (LXXIII) was subjected to the action of N-bromoacetamide in the presence of perchloric acid, which led to the bromohydrin (LXXIV). Heating (LXXIV) with potassium acetate in ethanol gave the epoxide (LXXVI). In order to open the oxide ring, compound (LXXVI) was reduced with lithium tetrahydroaluminate. This gave a 90% yield of the 3β,14β,20α-triol (LXXV). The selective acetylation of the triol (LXXV) at the



Scheme 12

3β-hydroxy group followed by oxidation led to the 14β-hydroxy-20-oxo steroid (XXIX) in good yield. This ketone had previously been obtained by Ruzicka et al. [35], but in low yield, by the hydrogenation of the corresponding 14β,15β-epoxide (see Scheme 4).

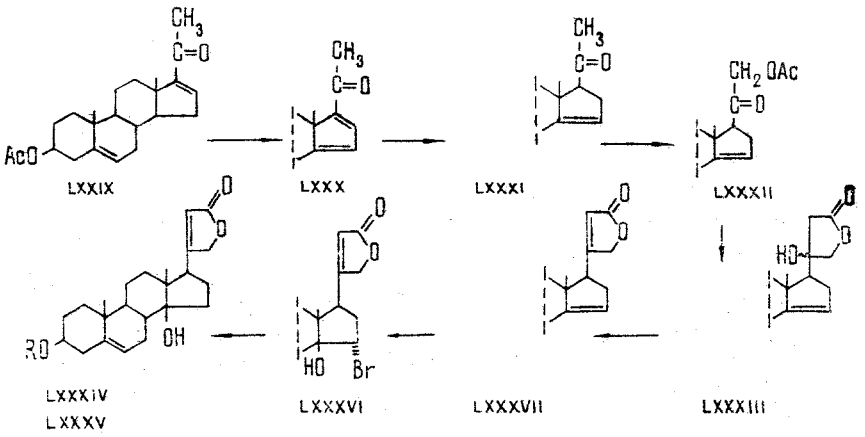
In order to carry out that part of the synthesis involving the construction of a lactone ring, the ketone (XXIX) was condensed with ethoxyethynyllithium. Rearrangement in an acid medium of the ethoxy carbinol (LXXVII) obtained led to the formation of the α,β-unsaturated ester (LXXVIII). Oxidation of the ester (LXXVIII) with simultaneous closure of the lactone ring gave uzarigenin acetate (XLVII). Saponification of the acetate gave uzarigenin (LXX).

A group of Japanese chemists [62, 63] has recently effected the synthesis of xysmalogenin — a cardiac aglycone containing a Δ^5 bond. One of the advantages of this scheme is the development of a new method for the selective reduction of the Δ^{16} bond in pregna-14,16-dien-20-ones.

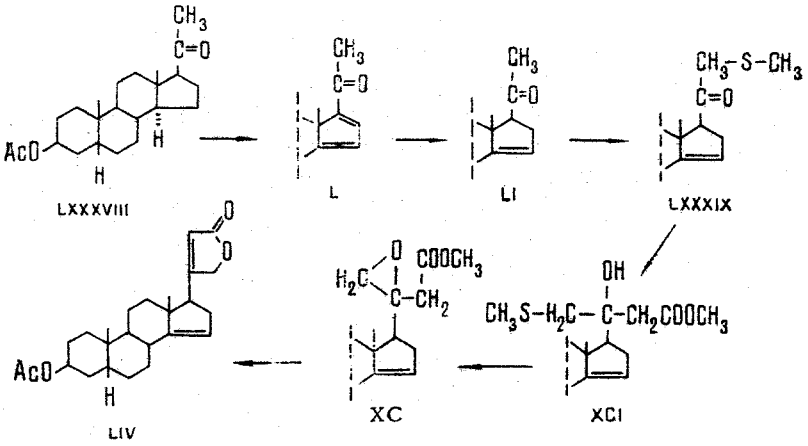
In the synthesis under consideration the initial compound was 3β-hydroxypregna-5,16-dien-20-one (LXXIX) (Scheme 13). This compound, which is also known under the name of 16-dehydropregenolone, is one of the most accessible substances in the synthesis of hormones and their analogs. It is obtained by the oxidative cleavage of diosgenin.

The authors concerned converted the diene (LXXIX) into the triene (LXXX) by allyl bromination followed by dehydrobromination. When the triene (LXXX) was heated with triphenylstannane or with certain alkyl- and alkoxysilanes [62-64], reduction of the Δ^{16} bond took place leading in good yield to pregn-14-en-20-one (LXXXI). This compound was oxidized with lead tetraacetate to the 21-acetoxy derivative (LXXXII), which, on Reformatsky condensation, formed the hydroxylactone (LXXXIII). It is interesting to note the ease with which the dehydration of the β-hydroxy-γ-lactone (LXXXIII) takes place. Even during chromatography on alumina, it is converted into the acetate of anhydroxysmalogenin (LXXXVII). The introduction of the 14β-hydroxy group, effected via the bromohydrin (LXXXVI) followed by reduction with Raney nickel, led to xysmalogenin acetate (LXXXV). Saponification of (LXXXV) gave xysmalogenin (LXXXIV).

In the synthesis of xysmalogenin that has been described, the stage of the oxidation of the 21-methyl group in compound (LXXXI) with lead tetraacetate took place with the lowest yield. In view of this weak aspect of the synthesis, Yoshii and his colleagues [63] developed



Scheme 13

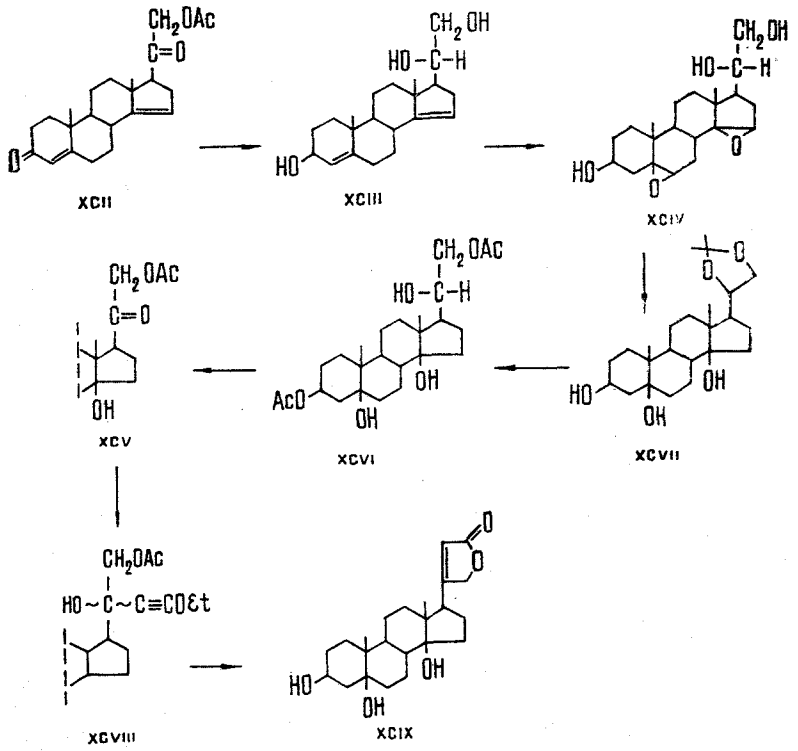


Scheme 14

an alternative method of constructing the lactone ring, and this has been used in the synthesis of β-anhydrodigitoxigenin.

By bromination followed by dehydrobromination, pregnan-20-one (LXXXVIII) (Scheme 14) was converted into the 14,16-dien-20-one (L), from which, by reduction with the aid of triphenylstannane or triethylsilane, passage was effected to pregn-14-en-20-one (LI). Compound (LI) was condensed with diethyl oxalate. On reaction with methyl thiotosylate the crude α-oxo ester obtained gave a good yield of the 21-methylthio derivative (LXXXIX). This substance was subjected to the Reformatsky reaction with methylbromoacetate, which gave an 85% yield of the 20-hydroxy-21-methylthio-24-norcholenate (XCI). The product of the Reformatsky reaction (XCL) was then methylated with trimethyloxonium tetrafluoroborate to the corresponding methylsulfonium salt, which, under the action of sodium hydroxide, was converted into the epoxy ester (XC). When the epoxy compound (XC) was chromatographed through alumina, β-anhydrodigitoxigenin acetate (LIV) was obtained in good yield [63].

The only natural cardenolide with the hydroxy group at C-5 that has been synthesized up to the present time is periplogenin [5, 65]. The starting substance was 14-dehydrocortexone acetate (XCII) (Scheme 15), which is the product of the dehydration of 14α-hydroxycortexone or of the microbial oxidation of 14-dehydroprogesterone [66]. Compound (XCII) was reduced with lithium tetrahydroaluminate to the triol (XCIII), the triacetate of which, under the action of N-bromoacetamide, formed a dibromohydrin which was then converted by the action of alkali into the diepoxide (XCIV). After the introduction of an isopropylidene protective group into the 20,21 position, the acetonide of compound (XCIV) was reduced with lithium tetrahydroaluminate to the 3β,5β,14β-trihydroxy acetonide (XCVII). This compound was acetylated at the C-3 hydroxyl, and after the elimination of the protective isopropylidene grouping it was again selectively acetylated, but now at the primary 21-hydroxy group. The diacetate (XCVI) was oxidized with chromium trioxide to the ketol (XCV). The lactone ring was attached



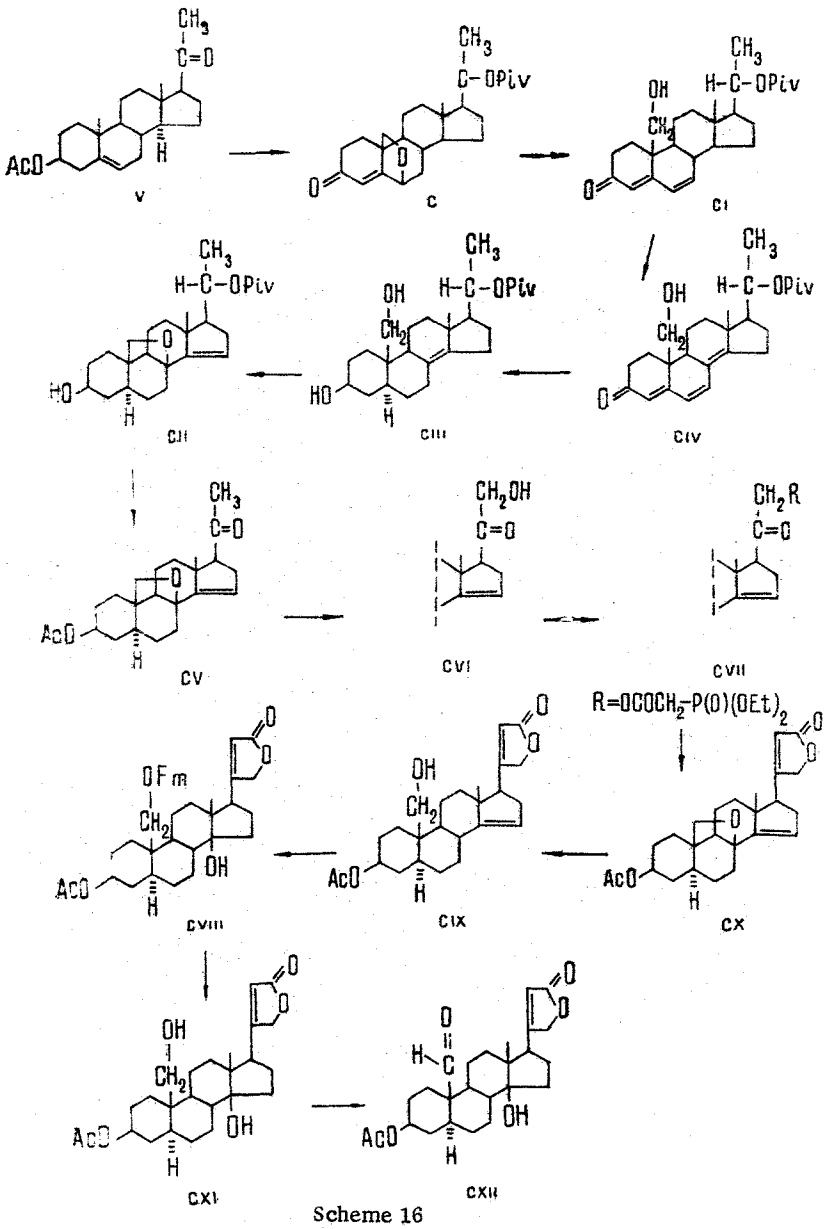
Scheme 15

by the condensation of the steroid (XCV) with ethoxyethynyllithium followed by isomerization of the carbinol (XCVIII) in an acid medium. As a result of the spontaneous cyclization taking place under these conditions, periplogenin (XCIX) was formed.

In 1974, Kruger performed an original synthesis of the acetates of corotoxigenin and coroglaucigenin — cardenolides containing an oxygen function at C-19 [67]. As the starting compound he selected pregnenolone (V) (Scheme 16), the Δ^5 bond of which was used to introduce the hydroxy group at C-19. The main stages of the synthesis consisted of the following transformations. Reduction of the oxo group at C-20 in (V) and preparation of the pivaloyl (trimethylacetyl) derivative and its conversion via the 5,6-chlorohydrin followed by oxidation with lead tetraacetate [68] enabled a steroid to be obtained with an oxygen bridge between C-6 and C-19 (C) [67, 69]. Under the action of p-toluenesulfonic acid [70], this compound gave the 19-hydroxydienone (CI). Enolization of (CI) with the aid of sodium methanolate followed by dehydrogenation with dichlorodicyanobenzoquinone led to the triene (CIV). Passage from (CIV) to the $\Delta^{8(14)}$ steroid (CIII) was effected by the reduction of (CIV) with sodium tetrahydroborate and catalytic hydrogenation of the 3β-hydroxy steroid so obtained. The introduction of a Δ^{14} bond required the formation of the 8,19-oxide (CII), which was achieved by the action of pyridinium bromide-perbromide on (CIII). After the elimination of the pivalic acid residue and oxidation of the 20-hydroxy group, the pregnen-20-one (CV) was obtained which, on oxidation with lead tetraacetate, formed the ketol (CVI). The latter product had all the necessary elements for the construction of a butenolide ring and the introduction of a 14β-hydroxy group.

The construction of the α,β-unsaturated butenolide ring was carried out by the method of Eberlein et al. [71] by esterifying the ketol (CVI) with diethoxyphosphinylacetic acid. The phosphinylacetate obtained (CVII) was converted by treatment with potassium hydroxide into the butenolide (CX). Subsequently, after the opening of the oxide ring the Δ^{14}-butenolide (CIX) in the form of the 19-formate was converted via the bromohydrin into the 14β-hydroxycardenolide (CVIII). Elimination of the formyl group led the authors to corogalucigenin 3-acetate (CXI). The oxidation of (CXI) with tert-butyl chromate gave corotoxigenin acetate (CXII).

The yields of the final products in this laborious and multistage synthesis were low. However, the very fact of the synthesis of such complex natural compounds as coroglaucigenin and corotoxigenin and the development in the course of the investigation of interesting methods for introducing a Δ^{14} bond and a 19-hydroxy group undoubtedly deserve attention.



Scheme 16

Recently, a number of analogs of cardiac glycosides with the cis linkage of rings C/D but containing no hydroxy group at C-14 have been synthesized. Although these compounds also possess a positive inotropic effect and block K^+,N^+-ATPase, their activities are considerably inferior to those of the natural cardenolides [72-75].

Definite advances have been achieved in the synthesis of the cardiac aglycones. From the first timid searches for a basic possibility of passing to cardenolides from other classes of steroid compounds to the directed synthesis of compounds with an oxygen-containing function at C-19 an enormous step has been made. Different variatons of the introduction of a 14β-hydroxy group and of the addition of the butenolide ring have been proposed, and original methods have been developed for the stereodirected synthesis of individual fragments of the molecule. And yet the problem of the synthetic production of cardiac aglycones cannot be regarded as completely solved. The possibilities of the synthesis of digoxigenin, strophanthidin, and ouabagenin — the aglycones and the glycosides which are most frequentlyl used in medicine — have not been investigated. The syntheses themselves have numerous stages and the particular reactions used in laboratory practice are difficult to realize under industrial conditions. An easy and accessible synthesis of cardenolides in a few stages is a task for

future work, a task which is all the more attractive since among the multiplicity of analogs that have been synthesized at the present time not one approaches the natural compounds in biological activity.

As is well known, in themselves the aglycones possess no high cardiotonic activity whatever. However, in combination with sugars they acquire properties that are most valuable in the treatment of cardiac diseases. Consequently, two interconnected problems are being solved in parallel: the synthesis of cardenolides and methods for their glycosylation. No little advances have also been achieved here (review [76]; investigations of recent years [77-83]), although not all the details of the introduction of the sugar component have been thoroughly worked out. The harmonius solution of both problems — so it appears to us — represents progress in this field of knowledge.

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