THE CHEMISTRY OF CARDIAC GLYCOSIDES IN THE SOVIET UNION

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Advances in the chemistry of the cardiac glycosides are connected above all with their practical significance. After the Scottish physician and botanist Withering had published a tract on the remarkable healing properties of the foxglove in 1785 [1], the search for plants containing substances of a cardiotonic nature proceeded with unabated interest.

For Russia, this period began approximately 100 years ago. At this time, our country had practically only one plant species Digitalis purpurea L. (common foxglove) possessing cardiac activity. However, even then it was clear that plants possessing a strong action on the heart were not rare. In 1865, E. V. Pelikan [2] reported that the arrow poison obtained from the seeds of the plant ine or onazh growing in West Africa (later, this plant acquired the name of Strophanthus kombé Oliv.) was characterized by a pronounced cardiotonic action. A year later he reported the toxicological effect of Nerium oleander L. (common oleander) [3]. To N. A. Bubnov [4] is due the honor of introducing into scientific medicine preparations of Adonis vernalis L. (spring adonis). A year later, I. V. Troitskii [5] and N. P. Bogoyavlenskii [6] recommended for the treatment of organic cardiac defects the use of the flowers of Convallaria majalis L. (lily-of-the-valley). É. A. Leman [7] isolated from Periploca graeca L. (Greek silk-vine) the glycoside periplocin and gave its first chemical characteristics. The discoveries of Russian physicians and pharmacologists have enriched scientific medicine with galenical preparations which even at the present time have not lost their importance. These discoveries have greatly promoted a deeper study of the flora of the country for its content of cardiac glycosides.

Knowledge of the pharmacological properties and therapeutic action of the cardiotonic glycosides outstripped purely structural investigations for a long time not only in the USSR but throughout the world. The chemistry of the cardiac glycosides developed slowly. The first successes were reported only in the mid thirties of the 20th century, when, under conditions excluding the destruction of the main nucleus, anhydrouzarigenin was converted into 5α-etianic acid [8] and digitoxigenin into 5β-etianic acid [9]. This showed that the cardiac aglycones were steroid compounds.

Soviet scientists took part in the investigation and determination of the chemical structures of the cardiac glycosides in the fifties. In the first stage (1950-1957), investigations of a purely practical nature predominated. The urgent need for cardiotonic preparations, especially the fast-acting ones of the type of strophanthin-K made it necessary above all to deal with the isolation of individual substances that were known and adequate supplies of which were ensured by the raw materials basis. Thus, cymarin was obtained from Apocynum cannabinum L. [10], oleandrin (folinerin, neriolin) from Nerium oleander L. [11], hellebrin (corelborin P) and desglucohellebrin (corelborin C) from Helleborus caucasicus A. Br. and H. purpurascens Waldst and Kit. [12], and convalloside from Convallaria majalis L. [13]. Investigations similar to those described promoted the creation in the Soviet Union of a domestic industry of cardiotonic preparations and served as the starting point for further directed searches.

The glycosides of the cardiac group are not among the compounds distributed throughout the vegetable kingdom. At the present time, they have been found reliably in representatives of thirteen families

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of flowering plants: Liliaceae, Moraceae, Ranunculaceae, Cruciferae, Leguminosae, Meliaceae, Euphorbiaceae, Celastraceae, Tiliaceae, Sterculaceae, Apocynaceae, Asclepiadaceae, and Scrophulariaceae. In some of the families mentioned (for example, Euphorbiaceae, Tiliaceae, Scrophulariaceae) only one genus is capable of synthesizing compounds with cardiac activity in the process of its vital activity. Consequently, it is not surprising that plants in which glycosides of the group of interest to us have been found amount to only 0.35% of the total number of species in the flora of the USSR. (For a review of the floristic composition of plants of the USSR in which cardiac glycosides have been found, see [14].)

On the taxonomic level, we are obviously close to a complete recording of the terrestrial flora for its content of cardiotonic glycosides, since in recent years reports of the presence of such glycosides in new plant genera have appeared only rarely.

The weightiest contribution of the Soviet school has been made to the study of the glycosides of plants of the family Cruciferae. The report by Jaretzky and Wilke [15] that plants of three genera of this family – Erysimum, Cheiranthus, and Sisymbrium* – contained substances stopping the action of the frog heart in a state of systole attracted the attention of a large number of workers. Later, a similar effect was found in plants of the genus Syrenia [16].

Of the species of Erysimum cultivated in the Soviet Union, the most active has proved to be E. canescens Roth (hoary erysimum). A chemical study of this plant was begun as early as 1943 and led to the production of a crystalline substance – erysimolactone [17] which, however, was not a glycoside. The first authentic glycoside – erysimin – was isolated from E. canescens by V. V. Feofilaktov and P. M. Loshkarev [18]. Erysimin had the properties characteristic for cardiotonic glycosides and on acid hydrolysis it was split into aglycone and sugar moieties. The structure of the aglycone (erisimidin, erysimolactone) and that of the sugar could not be determined immediately. Erysimin proved to be an effective cardiotonic preparation [9] and was introduced into officinal medicine.

Almost at the same time, N. P. Maksyutina and D. G. Kolesnikov [20], studying the leaves of Cheiranthus Allionii hort. [synonym: E. x. marschallii (Stark ex Moore) Bois.] found two crystalline glycosides – alleoside A and alleoside B in them, while in the herb Syrenia angustifolia (Ehrh.) Rchb. they found the glycoside syreniotoxin. The aglycone moiety of alleoside A and of syreniotoxin was identified as strophanthidin by paper chromatography. Alleoside B was probably a mixture of two glycosides with different genins – strophanthidin and digitoxigenin.

Reichstein et al. [21] found in previously fermented seeds of E. crepidifolium Rchb. and E. helveticum (Jacq.) DC a monoglycoside giving on hydrolysis strophanthidin (XIII) and D-digitoxose. Consequently, the glycoside was strophanthidin 3-β-D-digitoxoside (XIV). On comparing the properties of the glycoside that they had obtained with those of erysimin [18] and alleoside A [20], the Swiss workers put forward the hypothesis that all three compounds were identical. But since the discoverers of erysimin considered that its glycone (erisimidin) was different from strophanthidin, the glycoside found in E. crepidifolium and E. helveticum was given the name of helveticoside. Independently of the Swiss authors, the structure of strophanthidin 3-D-digitoxoside was ascribed to the glycoside erysimotoxin from E. cheiranthoides [22]. The fact that erysimin has a similar structure was shown somewhat later [23]. At the present time, it has been firmly established that one and the same compound has been described under the names of erysimin, alleoside A (in later papers, allioside A), syreniotoxin, helveticoside, and erysimotoxin. In our view, priority is due to the name erysimin, and we shall make use of this name subsequently.

In the laboratory directed by the author, a new steroid diglycoside, erysimoside, has been found in the seeds of Erysimum diffusum Ehrh. [24]. Its structure has been established by stepwise hydrolysis. Under the action of β-glucosidase, which is present in an enzyme preparation from the seeds of E. diffusum, or under the action of the pancreatic juice of the snail Helix plectotropis, erysimoside splits off D-glucose and is converted into a monoside – desglucoerysimoside. The latter is decomposed by the action of mineral acids into strophanthidin (XIII) and D-digitoxose, and is therefore identical with erysimin (XIV). The direct acid hydrolysis of erysimoside gave strophanthidin (XIII) and a disaccharide with constants corresponding to digilanidobiose. This biose is present in the sugar component of the genuine glycosides of Digitalis and has the structure of 4-O-(β-D-glucopyranosyl)-D-digitoxopyranose [25]. Thus, erysimoside is

*In the laboratory directed by the author, plants of the genus Sisymbrium have been investigated repeatedly but in not one of them, including S. Loeselii L., an extract from which causes the systolic stoppage of the heart according to Jaretzky and Wilke, have glycosides of the cardiac group been found.

strophanthidin 3-O-β-D-glucosyl-(1→4)-β-digitoxopyranoside, and its structure corresponds to formula (XX). The β form of the glycosidic link between the strophanthidin and the D-digitoxose, and also between the two sugars was established from molecular rotation differences. This glycoside possesses a high cardiotonic activity and has been introduced into officinal medicine as a cardiac preparation used perorally [26].

The names E. diffusum Ehrh. and E. canescens Roth must be regarded as synonyms. But since the first name was assigned five years before the second [F. Ehrhart. Beitr., 7 (1792); A. Roth, Catalecta botan., 1 (1797)], it must be given preference. In this plant, in addition to erysimin and erysimoside, another seven individual glycosides have been found. In the qualitative composition of the glycosides no insignificant part is apparently played by the ecological and geographical conditions of growth of the plant. Thus, Czech workers [27] have isolated from E. canescens the glycosides erycanoside (XXIV) and eryscenoside (XXV), containing 2-deoxyglucose and 2-deoxygalactose, respectively. In spite of numerous investigations on plants cultivated in the territory of the USSR, no glycosides of similar structure have been found.

Apart from E. diffusum, the glycosides of E. cheiranthoides, E. gypsaceum, and E. x. marschallii have been studied in most detail (see below).

Plants of the Family Cruciferae and Their Glycosides

Name of the plant	Glycosides isolated*
The genus Erysimum L.	
E. Altaicum C.A.M. [32]	Erysimin (XIV), erysimoside (XX)
E. cheiranthoides L. [22, 33-35]	Glucodigifucoside (II), desglucoerycordin (IX), erycordin (X), erysimotoxin = erysimin (XIV), corchoroside A (XV), erychroside (XIX), erysimoside (XX), erythriside (XXVI), helveticosol (XXIX), erychrosol (XXX), erysimosol (XXXI).
E. crepidifolium Rchb. [21, 36]	Helveticoside = erysimin (XIV), erysimoside (XX)
E. cuspidatum (M. B.) DC [32]	Erysimin (XIV), erysimoside (XX) (cuspidoside)
E. diffusum Ehrh. (synonym: E. canescens Roth) [17, 18, 23, 24, 27, 32]	Erysimin (XIV), desglucocheirotoxin (XVII), erysimoside (XX), cheirotoxin (XXIII), erycanoside (XXIV), eryscenoside (XXV), canescein (XXXVII), glucocanescein (XXXVIII), (erydiffuside)
E. gypsaceum Botsch. et Vved. [37]	Erysimin (XIV), erychroside (XIX), erysimoside (XX), gypsobioside (XL), gypsotrioside (XLI), 17α-gypsobioside (XLIII)
E. helveticum (Jacquin) A.P. DC [21]	Helveticoside = erysimin (XIV) (glucoside z)
E. marschallianum Andrz. [31, 32, 38]	Allioside A = erysimin (XIV), corchoroside A (XV), erysimoside (XX), (sinapoyl-glucoerysimoside)
E. x. marschallii (Stark ex Moore) Bois (synonym: Cheiranthus x allionii hort.) [20, 38-41]	Allionin = glucodigifucoside (II), cheiroside A (V), cheiranthoside (VII), desglucoerycordin (IX), erycordin (X), alliotoxin (XII), allioside A = erysimin (XIV), desglucocheirotoxin (XVII), erysimoside (XX), glucoerysimoside (XXVII), helveticosol (XXIX), erysimosol (XXXI), glucoerysimosol (XXXII), alliside (XXXIV), glucoalliside (XXXV), (violin).
E. nuratensae M. Pop. [32]	Erysimin (XIV), erysimoside (XX).
E. perofskianum Fisch. et Mey [44]	Helveticoside = erysimin (XIV), corchoroside A (XV), cabuloside (XVI), perofskoside (XVIII), erysimoside (XX), eryperoside (XXI), erycorchoside (XXII).
E. repandum L. [17]	Erysimin (XIV), erysimoside (XX), cheirotoxin (XXIII).
E. violascens M. Pop. [32]	Erysimin (XIV), erysimoside (XX), gypsobioside (XL).
The genus Syrenia Andrz.	
S. dolychostylos Klok. [46]	Allioside A = erysimin (XIV), erychroside (XIX), erysimoside (XX).

S. siliculosa M.B. Andrz [32, 46]	Allioside A = erysimin (XIV), corchoroside A (XV), cabuloside (XVI), erychroside (XIX), erysimoside (XX), (C-5 and C-6 glycosides).
S. ucrainica Klok. (synonyms: S. angustifolia (Ehrh) Rchb and S. cana auct. fl. ucr. et ross) [46]	Syreniotoxin = allioside A = erysimin (XIV), erychroside (XIX), erysimoside (XX), (C-5, C-6, and C-9 glycosides).

The genus Cheiranthus (L.) R. Br.

Ch. cheiri L. [48-50]	Cheiroside A (V), cheirotoxin (XXIII).

*Compounds whose structures have not been completely determined are given in brackets.

Among the glycosides isolated from Erysimum, the sugar components of erychroside (XIX) and gypsobiosides (XL) proved to be unusual.

At the beginning of the sixties, on the basis of a generalization of the experimental material an idea was gained of the limited nature of the structural schemes for the carbohydrate moieties of the cardiac glycosides [28-30]. Only three types of structure were known:

1. Aglycone–hexamethylose–D-glucose–D-glucose.
2. Aglycone–3 molecules of a hexamethylose–D-glucose.
3. Aglycone–D-glucose–D-glucose.

One of the two terminal D-glucose molecules may be absent. The hexamethylose is represented by a methylpentose (L-rhamnose, D-gulomethylose, D-allomethylose, etc.) or by a 2-deoxymethylpentose (D-digitoxose, D-cymarose, D-boivinose, etc.). Such well-known glycosides as k-strophanthoside, periplocin, and convalloside and the overwhelming majority of di- and triglycosides are constructed in accordance with the first scheme; the main glycosides of Digitalis, lanatosides A, B, and C, digitoxin, gitoxin, and digoxin with the second; and a small group of glycosides of the type of uzarin with the third.

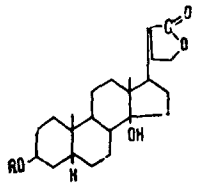
T. Reichstein, the author of numerous papers in the field of cardiac glycosides, has summarized the specific features of the structure of the sugar moiety of the cardiac glycosides in the following way [30]: "If we compare the sugar components of the digitaloid lactones (and also two small groups of related substances)* with other similar natural glycosides of higher plants, a striking difference is observed: the non-digitaloid glycosides almost always contain as a structural component one or more of eight sugars: D-glucose, D-glucuronic acid, D-xylose, L-arabinose, D-galactose, D-galacturonic acid, L-fucose, or L-rhamnose. The oligosaccharide moiety almost always contains the hexose 'internally,' i.e., attached directly to the aglycone, and the pentoses and methylpentoses 'externally.' An oligosaccharide moiety with a number of sugars greater than two frequently proves to be branched. In the cardiac glycosides (and in the two small groups of substances closely related to them) of these eight sugars only D-glucose and L-rhamnose are found frequently. Together with these, other sugars, particularly hexamethyloses, are found very frequently. An oligosaccharide moiety always contains a hexose (D-glucose) 'externally.' An oligosaccharide moiety consisting of more than two sugars always has a linear structure."

Erychroside (XIX) and gypsobioside (XL), which are found in plants of the family Cruciferae, do not come under this general rule. As in the majority of glycosides constructed on the "classical" pattern, D-digitoxose is attached directly to the aglycone, but the most "external" sugar is not D-glucose but D-xylose. This pentose, although extremely widely distributed in the vegetable kingdon, had never previously been found in cardiac glycosides. As will be shown below, D-xylose also forms part of the sugar moiety of securidaside (LVI) – a glycoside from Securigera securidaca (family Leguminosae). But, in contrast to the glycosides mentioned above, in securidaside the D-xylose fulfills the role not of "external" but of "internal" sugar. In recent years, several more glycosides the structure of whose sugar moiety falls outside the limits of generally known schemes have been found. In this connection a report by N. P. Maksyutina [31] on the presence in plants of the family Cruciferae of triglycosides acylated with sinapic acid is interesting. Unfortunately, experimental results that would confirm this discovery have not subsequently appeared in print.

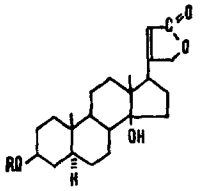
*The reference is to the bufadienolide and pregnane glycosides.

The total number of cardiac glycosides the structures of which are known that have been isolated from plants of the family Cruciferae (not counting aglycones) is 32 (see below).

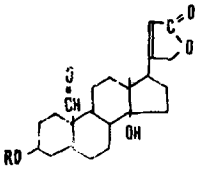
Cardenolides Found in Plants of the Family Cruciferae*



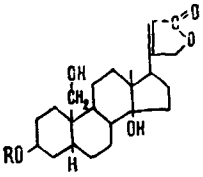
I. Digitoxigenin, $C_{23}H_{34}O_4$, R = H
II. Glucodigifucoside [34, 51], $C_{35}H_{54}O_{13}$, R = β-D-glucosyl-(1→4)-β-D-fucosyl→



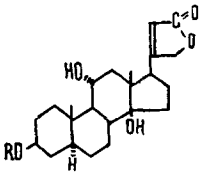
III. Uzarigenin, $C_{23}H_{34}O_4$, R = H
IV. Desglucocheiroside A [50], $C_{29}H_{44}O_8$, R = β-D-fucosyl→
V. Cheiroside A [40, 50], $C_{35}H_{54}O_{13}$, R = β-D-glucosyl-(1→4)-β-D-fucosyl→



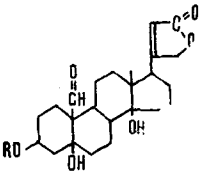
VI. Cannogenin, $C_{23}H_{32}O_5$, R = H
VII. Cheiranthoside [40], $C_{29}H_{42}O_9$, R = β-D-gulomethylosyl→



VIII. Cannogenol, $C_{23}H_{34}O_5$, R = H
IX. Desglucoerycordin [33], $C_{29}H_{44}O_9$, R = β-D-gulomethylosyl→
X. Erycordin [33], $C_{35}H_{54}O_{14}$, R = β-D-glucosyl-(1→4)-β-D-gulomethylosyl→



XI. Alliotoxigenin (11α-hydroxyuzarigenin) [40], $C_{23}H_{34}O_5$, R = H
XII. Alliotoxin [40], $C_{29}H_{44}O_9$, R = α-L-rhamnosyl→



*The glycosides discovered by Soviet workers are underlined.

XIII. Strophanthidin, $C_{23}H_{32}O_6$, R = H

XIV. Erysimin [18, 20-23], $C_{29}H_{42}O_9$, R = β-D-digitoxosyl→

XV. Corchoroside A [54], $C_{29}H_{42}O_9$, R = β-D-boivinosyl→

XVI. Cabuloside [44], $C_{29}H_{42}O_{10}$, R = β-2-deoxy-D-gulosyl→

XVII. Desglucocheirotoxin [50], $C_{29}H_{42}O_{10}$, R = β-D-gulomethylosyl→

XVIII. Perofskoside [44], $C_{29}H_{42}O_{10}$, R = β-2-deoxy-D-glucosyl→

XIX. Erychroside [33], $C_{34}H_{50}O_{13}$, R = β-D-xylosyl-(1→4)-β-D-digitoxosyl→

XX. Erysimoside [24], $C_{35}H_{52}O_{14}$, R = β-D-glucosyl-(1→4)-β-D-digitoxosyl→

XXI. Eryperoside [44], $C_{35}H_{52}O_{14}$, R = α-D-glucosyl-(1→4)-β-D-digitoxosyl→

XXII. Erycorchoside [44], $C_{35}H_{52}O_{14}$, R = α-D-glucosyl-(1→4)-β-D-boivinosyl→

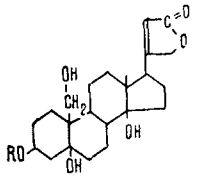
XXIII. Cheirotoxin [50], $C_{35}H_{52}O_{15}$, R = β-D-glucosyl-(1→4)-β-D-gulomethylosyl→

XXIV. Erycanoside [27], $C_{35}H_{52}O_{15}$, R = β-D-glucosyl-(1→4)-β-2-deoxy-D-glucosyl→

XXV. Eryscenoside [27], $C_{35}H_{52}O_{15}$, R = β-D-glucosyl-(1→4)-β-2-deoxy-D-galactosyl→

XXVI. Erythriside [33], $C_{40}H_{60}O_{18}$, R = β-D-glucosyl-(1→4)-β-D-xylosyl-(1→4)-β-D-digitoxosyl→

XXVII. Glucoerysimoside [31, 40, 42], $C_{41}H_{62}O_{19}$, R = β-D-glucosyl-(1→4)-β-D-glucosyl-(1→4)-β-D-digitoxosyl→



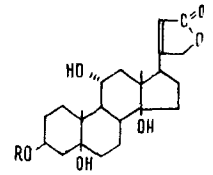
XXVIII. Strophanthidol, $C_{23}H_{34}O_6$, R = H

XXIX. Helveticosol [42, 43], $C_{29}H_{44}O_9$, R = β-D-digitoxosyl→

XXX. Erychrosol [34], $C_{34}H_{52}O_{13}$, R = β-D-xylosyl-(1→4)-β-D-digitoxosyl→

XXXI. Erysimosol [42, 43], $C_{35}H_{54}O_{14}$, R = β-D-glucosyl-(1→4)-β-D-digitoxosyl→

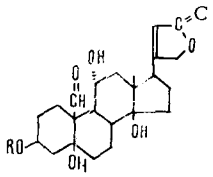
XXXII. Glucoerysimosol [40], $C_{41}H_{64}O_{19}$, R = β-D-glucosyl-(1→4)-β-D-glucosyl-(1→4)-β-D-digitoxosyl→



XXXIII. Bipindogenin, $C_{23}H_{34}O_6$, R = H

XXXIV. Alliside [41], $C_{29}H_{44}O_{10}$, R = α-L-glucomethylosyl→

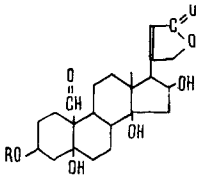
XXXV. Glucoalliside [40], $C_{35}H_{54}O_{15}$, R = β-D-glucosyl-(1→4)-α-L-glucomethylosyl→



XXXVI. Nigrescigenin, $C_{23}H_{32}O_7$, R = H

XXXVII. Canescein [23, 45], $C_{29}H_{42}O_{11}$, R = β-D-gulomethylosyl→

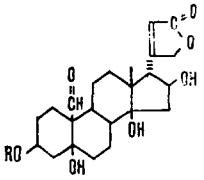
XXXVIII. Glucocanescein [23, 45], $C_{35}O_{52}H_{16}$, R = β-D-glucosyl-β-D-gulomethylosyl→



XXXIX. Strophadogenin, $C_{23}H_{32}O_7$, R = H

XL. Gypsobioside [37], $C_{34}H_{50}O_{14}$, R = β-D-xylosyl-(1→4)-β-D-digitoxosyl→

XLI. Gypsotrioside [37], $C_{40}H_{60}O_{19}$, R = β-D-glucosyl-β-D-xylosyl-(1→4)-β-D-digitoxosyl→



XLII. 17α-Strophadogenin, $C_{23}H_{32}O_7$, R = H

XLIII. 17α-Gypsobioside [37], $C_{34}H_{50}O_{14}$, R = β-D-xylosyl-(1→4)-β-D-digitoxosyl→

There is a qualitative and quantitative predominance of the glycosides of strophanthidin (XIII) and genins of similar structure – strophanthidol (XXVIII), strophadogenin (XXXIX), nigrescigenin (XXXVI), cannogenin (VI), and cannogenol (VIII). Cardenolides with a cis linkage of rings A/B and an oxidized angular group at C_{10} are more characteristic of plants of this family. The most widespread glycosides are erysimin (XIV) and erysimoside (XX). They have been found in all the species of Erysimum and Syrenia investigated and will therefore be regarded as a taxonomic index of these two close plant genera. Curiously, erysimoside has proved to be the third most important glycoside of Strophanthus kombé [42] after k-strophanthoside and k-strophanthin-β.

Of the other plants used as raw material for the industrial production of cardiotonic preparations, the most interesting and promising is jute – Corchorus olitorius L. and Corchorus capsularis L. (family Tiliaceae). Strictly, jute cannot be regarded as a plant of the domestic flora, but in the postwar years it has been widely sown in the central Asian republics as a raw material for fibers and has become adapted to the natural climatic conditions of the USSR.

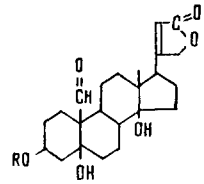
Although the first information concerning the toxic effect of an extract of jute seeds goes back to the end of the preceding century, for a long time there was no single opinion concerning the chemical nature of the substances responsible for this effect. Up to the time when Soviet workers began to study jute, only the presence in the seeds of the plant of a monoglycoside – corchoroside A (XV) – and its aglycone strophanthidin (XIII) was reliably known [52-54].

Investigations performed in the laboratory directed by the author led to this discovery in the seeds of C. olitorius and C. capsularis of a new bioside – olitoriside [55]. It was shown by stepwise hydrolysis that it has the structure strophanthidin 3-[O-β-D-glucosyl-(1→4)-β-D-boivinoside] (XLIV) (see below).

Cardenolide Glycosides First Found in Other Plants of the Flora of the USSR (apart from the family Cruciferae)

Corchorus olitorius L.

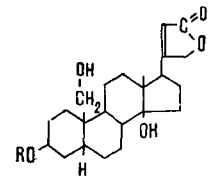
Corchorus capsularis L.



XIII. Strophanthidin, $C_{23}H_{32}O_6$, R = H

XLIV. Olitoriside [55], $C_{35}H_{52}O_{14}$, R = β-D-glucosyl-(1→4)-β-D-boivinosyl→

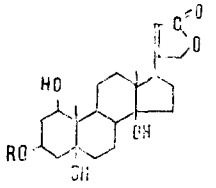
Evonymus europae L. (auct)



VIII. Cannogenol, $C_{23}H_{34}O_5$, R = H

XLV. Evonoloside [57], $C_{29}H_{44}O_9$, R = α-L-rhamnosyl→

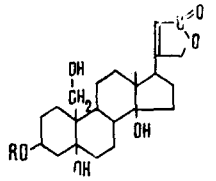
XLVI. Glucoevonoloside [57], $C_{35}H_{54}O_{14}$, R = β-D-glucosyl→α-L-rhamnosyl→



XLVII. Evonogenin [57], $C_{23}H_{34}O_6$, R=H

XLVIII. Glucoevonogenin [57], $C_{29}H_{44}O_{11}$, R=β-D-glucosyl→

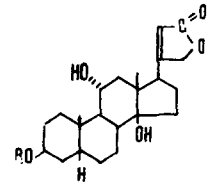
Convallaria majalis L.



XXVIII. Strophanthidol, $C_{23}H_{34}O_6$, R=H

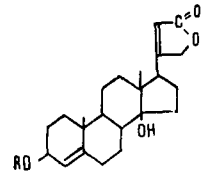
XLIX. Convallotoxoloside [58], $C_{35}H_{54}O_{15}$, R=β-D-glucosyl-(1→4)-α-L-rhamnosyl→

Ornithogalum magnum Krasch. et Schischk.



L. Sarmentogenin, $C_{23}H_{34}O_5$, R=H

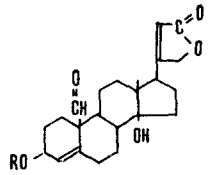
LI. Ornithagoloside [60], $C_{28}H_{42}O_9$, R=α-L-arabinosyl→



LII. Canarigenin, $C_{23}H_{32}O_4$, R=H

LIII. Ornithogalin [60], $C_{29}H_{42}O_9$, R=β-D-glucosyl→

Securigera securidaca (L.) Degen et Dorfler.
Coronilla hyrcana Prilipko

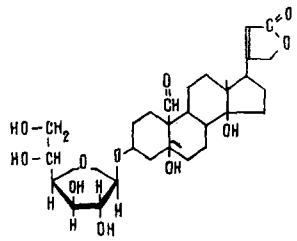


LIV. Securigenin (hyrcanogenin) [63], $C_{23}H_{30}O_5$, R=H

LV. Securiside (desglucohyrcanoside) [62-64], $C_{28}H_{38}O_9$, R=β-D-xylosyl→

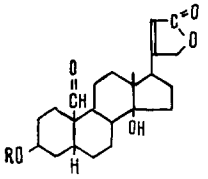
LVI. Securidaside (hyrcanoside) [62-64], $C_{34}H_{48}O_{14}$, R=β-D-glucosyl-(1→4)-β-D-xylosyl→

Coronilla scorpioides (L.) Koch



LVII. Scorpioside [65], $C_{29}H_{42}O_{11}$

Apocynum androsaemifolium L.



VI. Cannogenin, $C_{23}H_{32}O_5$, R = H

LVIII. Apobioside [74], $C_{36}H_{54}O_{13}$, R = β-D-glucosyl-(1→4)-β-D-cymarosyl→

Olitoriside has proved to be a valuable cardiotonic preparation; it is widely used in medicine at the present time [56].

A few new glycosides have been isolated from Evonymus europae L. (European euonymus, central Russian race). In the seeds of this plant, in addition to the known glycoside evomonoside, which is a L-rhamnoside of digitoxigenin, the following new glycosides have been found: evonoloside (XLV), glucoevonoloside (XLVI), and glucoevonogenin (XLVIII) [57]. The first two are glycosides of cannogenol (VIII) and the third is a β-D-glucoside of an aglycone of unknown structure which has been called evonogenin. It has been shown with a high degree of probability that evonogenin has the structure of 1β,3β,5,14-tetrahydroxy-5β,14β-card-20(22)-enolide (XLVII).

Of the family Liliaceae in the Soviet Union, the cardenolides of Convallaria majalis L., C. keiskei Miq., and Ornithogalum magnum Krasch. et Schischk. have been studied in most detail. The lily-of-the-valley is one of the best-known plants containing substances with a cardiotonic action. No less than ten individual cardiac glycosides have been found in it. Nevertheless, in this plant yet another diglycoside of strophanthidol (XXVIII) – convallotoxoloside (XLIX) – has been detected and its structure has been established [58].

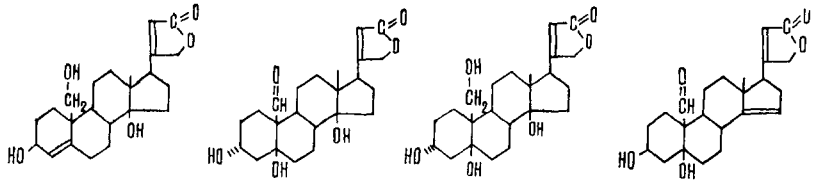
In the genus Ornithogalum, glycosides of the group of interest to us have been found comparatively recently [59]. About 30 species of plants of this genus grow in the USSR. From the pods of the Caucasian species O. magnum have been isolated rohdexin A (sarmentogenin L-rhamnoside) and two new cardenolide glycosides: ornithogaloside (LI) and ornithogalin [60]. The first of them has been ascribed the structure of sarmentogenin L-arabinoside (L). The presence of L-arabinose in cardiac glycosides is an unusual fact and apparently requires the confirmation of partial synthesis. Ornithogalin (LIII) proved to be the β-D-glucoside of a rare aglycone – canarigenin (LII). It was assumed previously that in the family Leguminosae, only the genus Coronilla contained glycosides of the cardiac group. Consequently, a report by Indian workers [61] on the components of Securigera securidaca was not given attention for a long time. The investigations of V. V. Zatula et al. [62] have shown that the main glycoside of this plant is securidaside (LVI), consisting of the aglycone securigenin (LIV), D-xylose, and D-glucose. The structure of the sugar moiety of securidaside – securidabiose – was established by exhaustive methylation. It proved to be O-β-D-glucopyranosyl-(1→4)-β-D-xylopyranose. A monoglycoside – securiside (LV) – was also found in the plant; it proved to be securigenin xyloside. The aglycone was found to contain a butenolide ring, an aldehyde group, two hydroxy groups, and an isolated double bond. The presence of the aldehyde group was confirmed by the reduction of securigenin to securigenol (LIX). The structure of securigenin (LIV) was shown by the independent synthesis from strophanthidin (XIII) of securigenol (LIX). The conformation of the aglycone has also been determined [63].

Precisely the same cardenolides as in the case of S. securidaca have been found in Coronilla hyrcana [64]. They were named, respectively, hyrcanoside (LVI), desglucohyrcanoside (LV), and hyrcanogenin (LIV). Both plants belong to the family Leguminosae, and the presence in them of the same glycosides is of interest from the point of view of plant taxonomy.

A glycoside of unusual structure has been found in Coronilla scorpioides [65]. As a rule, the sugars present in cardiac glycosides exist in the pyranose form. Strophanthidin β-D-glucopyranoside has been reported repeatedly. The presence in the plant mentioned, in addition to known glycosides, of scorpioside (LVII) – strophanthidin β-D-glucofuranoside – was unexpected.

Of the genus Digitalis (foxglove), the species D. purpurea L., D. lanata Ehrh., D. grandiflora Mill., D. ferruginea L., and D. thapsi L. have been studied most thoroughly in respect of their cardenolide composition. In the Soviet Union, in order to broaden the raw-materials basis, a systematic investigation for their content of glycosides, especially lanatosides A, B, and C, has been made of several other species of foxglove [66]. Some of them have been introduced into cultivation. The following glycosides have been isolated in the individual state from the endemic Caucasian species D. ciliata Trautv.: acetyldigitoxin α, digitoxin, acetylgitoxin α, and gitoxin [67].

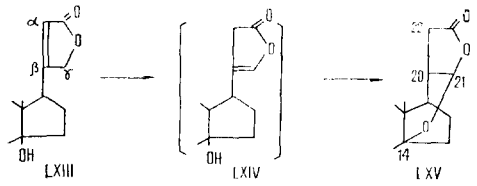
In addition to securigenin, Soviet authors have shown the structure of another five aglycones: alliotoxigenin (XI) [40], evonogenin (XLVII) [57], 3-epistrophanthidin (LX), 3-epistrophanthidol (LXI) [68], and diffugenin (LXII) [69].



LIX LX LXI LXII

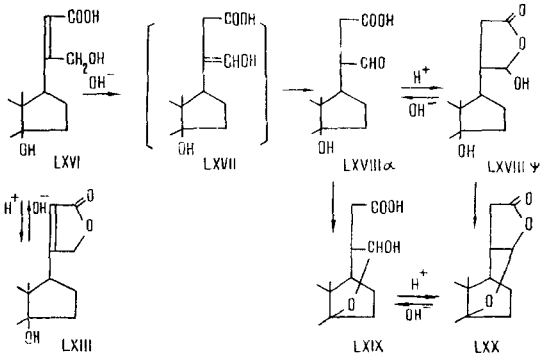
The native status of the last-mentioned compound has not been established strictly. Glycosides of 14-anhydrocardenolides have not yet been found in plants. The formation of an aglycone containing no hydroxy group at C_{14} has permitted the mechanism of the isomerization of the cardenolides to be shown more fully. The capacity of cardiac glycosides for isomerization is used to determine the spatial configuration of the lactone ring at C_{17} and is, as it were, a chemical test predetermining the existence of cardiac activity. The mechanism of this reaction was discussed repeatedly until Elderfield et al. [70] put forward the hypothesis that in the first stage of this reaction under the catalytic influence of alkali there is an irreversible shift of the double bond from the α,β (LVIII) to the β,γ position (LXIV). Then there is a simple intramolecular addition of the alcohol group at C_{14} to the double bond of the hypothetical intermediate LXIV with the formation of a new cyclic 14,21-oxido compound (LXV) (scheme A).

Scheme A



LXIII LXIV LXV

Scheme B



LXVI LXVII LXVIIIα LXVIIIψ LXIII LXIX LXX

Experiments on diffugenin (LXII) have shown that the isomerization of the cardenolides has a more complex nature (scheme B) [69]. The formation of the iso compound (LXV) is necessarily preceded by the hydrolysis of the butenolide ring. The α,β-unsaturated γ-hydroxy acid (LXVI) so produced undergoes ring closure again when the solution is acidified to form the initial lactone (LXIII). Under the more prolonged action of alkali, the reaction becomes irreversible, and the acid (LXVI) isomerizes into the vinyl alcohol (LXVII), which instantaneously rearranges into the aldolactone tautomeric system of the aldehydo acid

(XLIIIα) – the γ-lactol (LXVIIIψ). Both these forms are capable of giving internal semiacetals. The sterically close oxygen functions at C_{14} and C_{21} promote the formation of a 14,21-oxide ring. In an alkaline medium the iso acid (LXIX) deposits from the solution in the form of a salt, while in acidic and neutral media the equilibrium shifts in the direction of formation of the iso compound (LXX = LXV).

Of investigations relating to the sugar moiety, one relating to the biogenesis of the cardiac glycosides has proved to be interesting. The question arose in connection with a search in plants of the domestic flora for the medically important cardiotonic diglycoside k-strophanthin-β. The hypothesis was expressed that k-strophanthin-β should be sought in those plants where its simplest fragment – the monoside cymarin – has been found. Such plants were Apocynum androsaemifolium L., Apocynum cannabinum L., and Adonis chrysocyathus Hook f. et Thom [71].

In the thirties, Arthur Stoll (Switzerland) – a great worker in the field of the chemistry of natural compounds – put forward the hypothesis that many cardiac glycosides are present in plants in the form of more complex compounds than those which are isolated. Specific enzymes accompanying the glycosides in plants destroy sugar-rich glycosides by splitting off part of the sugars on storage or in the process of extraction of the plant material. Consequently, most frequently only a simple fragment of a complex compound is obtained. Stoll called the glycosides originally present in the plants genuine glycosides [72].

On the basis of this hypothesis, it had to be assumed that to increase the yield of k-strophanthin-β the plant raw material must be treated in the freshest possible state, i.e., in that form in which the enzymatic processes of degradation have not yet affected the sugar-rich genuine glycosides. However, experiments showed the opposite. Regardless of the phase of development of the plant, freshly collected roots contained cymarin and only in isolated cases did they also contain traces of k-strophanthin-β. The situation was similar when the enzymes were previously deactivated. It was shown by special experiments [73] that k-strophanthin-β is synthesized from cymarin and the D-glucose which is always present in plants during the slow drying of the plant material, when the vital processes still continue to function for some time,

$$\underset{\text{cymarin}}{C_{30}H_{44}O_9} + \underset{\text{D-glucose}}{C_6H_{12}O_6} \overset{\text{enzyme}}{\rightleftarrows} \underset{\text{k-strophanthin-}\beta}{C_{36}H_{54}O_{14}} + H_2O.$$

The exact mechanism of this enzymatic reaction has not yet been determined. It is also difficult to state whether the transition from cymarin to k-strophanthin-β takes place with the aid of a specific glucosyl transferase enzyme or some one of the ordinary hydrolytic enzymes – carbohydrases – which, under the conditions used, catalyze the reverse process to the synthesis of the diglycoside, but undoubtedly this is one of the phenomena of the autoregulation of living organisms.

It is not excluded that the new glycoside apobioside (LVIII) found in A. androsaemifolium on a level with k-strophanthin-β and which has been shown to be cannogenin 3-[O-β-D-glucopyranosyl-(1→4)-cymaropyranoside] [74] is in a similar equilibrium system with apocannoside – cannogenin cymaroside.

Czech workers [75] have recently confirmed that in the process of drying the leaves of Digitalis lanata Ehrh. the relative amount of lanatosides A, B, and C, which Stoll included among the genuine glycosides increases sharply.

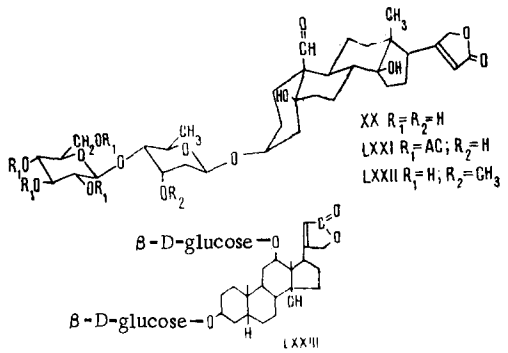
The separation of the glycosides into primary (genuine) and secondary has not been justified. The formation of glycosides cannot be considered as a statistical process. The steroid glycosides belong to the class of labile compounds, and, together with other, nonsteroid, glycosides of plants, including homoglycosides consisting of only sugars (of the type of sucrose), they take part in a wide range of metabolic reactions – in particular, in transglycosylation reactions. In view of their physiological role in vital phenomena, they are constantly in a state of variability, in a continuous process of inversion and reversion, decomposition and synthesis [76].

In addition to the plants mentioned, k-strophanthin-β has been detected in Adonis vernalis L. [77], Trachomitum (Apocynum) armenum Pobed., and Trachomitum (Apocynum) sarmatiense Voodson [78]. Bearing in mind the great practical importance of k-strophanthin-β in medicine, Soviet workers have performed several syntheses of this important glycoside from strophanthidin and acetobromo-D-glucose [79, 80].

An original method of obtained k-strophanthin-β has been described by I. F. Makarevich [81], who has studied the kinetics of the acetylation of equatorial and axial hydroxyls in the cardenolides. These investigations showed that equatorial hydroxyls acetylate 3-4 times faster than axial, not only in the aglycones

but also in the sugars, with the reservation that in the latter this rule remains valid only in the absence of voluminous substituents (for example, methoxy groups) in the cis position with respect to the OH group undergoing acetylation. Mainly on the basis of the rate of the acetylation reaction, the author determined the most stable conformational formulas of the 33 monosaccharides found in cardiac glycosides. He calculated that the majority of monosaccharides of the L series are present in the 1C form, while the monosaccharides of the D series are present in the C1 form. It was established that the glycosidic centers in the cardenolides are represented by all the possible types of conformational combinations, namely ee, ea, ae, and aa. It was considered previously that in the case of a voluminous aglycone the glycosidic bond could not be axial; i.e., the possibility of ae and aa linkages, especially in the case of L-sugars, was rejected.

The difference in the rates of acetylation of a- and e-hydroxyls was used by I. F. Makarevich in the partial synthesis of k-strophanthin-β. From the conformational formula of erysimoside (XX) it can be seen that in the sugar moiety of the glycoside – in the digilanidobiose – all the secondary OH groups of the D-glucose are equatorial, while the single hydroxyl of D-digitoxose has an axial nature. Those conditions were selected under which the acetylation of erysimoside could be stopped at the stage of the formation of the tetraacetate (LXXI). The remaining free axial hydroxyl was methylated. After the saponification of the acetate groups, k-strophanthin-β (LXXII) was obtained in 30% yield. Cymarin has been synthesized similarly from erysimin.



In addition to k-strophanthin-β, by means of the Koenigs–Knorr reaction, somewhat modified by V. T. Chernobai [80], partial syntheses have been effected of corotoxigenin 3-β-D-glucoside [80], erychroside (XIX) [82], cannogenol 3-α-L-rhamnoside (evonoloside) (XLV) [83], digoxigenin L-rhamnoside, D-xyloside, and D-glucoside [84], digitoxigenin 3-α-L-arabinoside [85], strophanthidin D- and L-arabinosides [86], gitoxigenin 3-β-D-glucoside, gitoxigenin 3,16-di-β-D-glucoside, and gitoxigenin 16-β-D-glucoside [87], strophanthidol 19-α-L-rhamnoside [80], strophanthidol 3,19-di-α-L-rhamnoside [80], and digoxigenin 3,12-di-β-D-glucoside (LXXIII) and digoxigenin 3,12-di-β-D-xyloside [84]. The structure of the last six compounds mentioned is somewhat unusual. In all plant cardenolides the sugar is attached to the aglycone through the hydroxy group at C_3. Monosides and diglycosides with the sugar residues in other positions of the steroid nucleus are not found in nature. It would appear that even the introduction of new glycosidic groups will open up wide possibilities in the creation of cardiotonic preparations of high activity. However, strophanthidol rhamnoside with the sugar residue in position 19 proved to be inactive [80], and the digoxigenin diglycoside (LXXIII), although it had a somewhat greater activity than the monoglycoside, did not surpass many known natural glycosides. Gitoxigenin 16-mono- and 3,16-diglucosides did not possess a specific action on the heart [87].

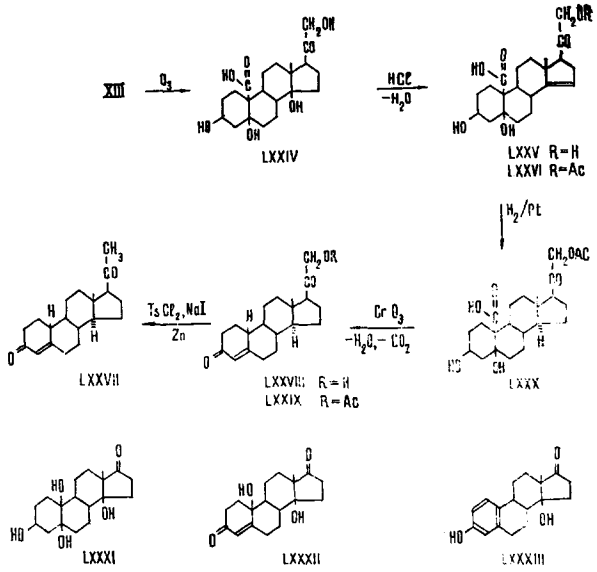
The aim of another series of synthetic investigations is to determine the possibility in principle of using cardiac aglycones to obtain steroid compounds with hormonal activity. The most suitable for the synthesis of analogs of hormonal substances proved to be strophanthidin. From this compound 19-nor-11-deoxycorticosterone (LXXVIII) and 19-norprogesterone (LXXVII) have been synthesized [88]. It is known that the first of these compounds is twice as active as the natural hormone deoxycorticosterone, while the second is eight times more active than progesterone.

In the first stage of the synthesis, the lactone ring of strophanthidin (XIII) was converted by ozonization into an α-ketol chain. Simultaneously, under the action of the ozone the aldehyde group at C_{10} was oxidized to a carboxy group, so that the final product of the reaction was 3β,5,14,21-tetrahydroxy-20-oxo-19-nor-5β,14β-pregnane-10β-carboxylic acid (LXXIV). The elimination of the hydroxy group at C_{14} was achieved by heating the acid (LXXIV) with a 1% solution of hydrogen chloride in methanol. The dehydration product –

the unsaturated ketol (LXXV) – was selectively acetylated at the C_{21} hydroxy group. Hydrogenation of the monoacetate (LXXVI) on a platinum catalyst gave compound (LXXX) with the trans linkage of rings C and D. Oxidation of the hydroxy group at C_3 to an oxo group, dehydration of the hydroxy group at C_5, and splitting out of the carboxy group at C_{10} were effected practically in one stage by the oxidation of compound (LXXX) with chromium trioxide and heating the oxidation product in glacial acetic acid. The 11-deoxy-19-norcorticosterone acetate (LXXIX) so formed was saponified to deoxynorcorticosterone (LXXVIII) and then, with the aid of p-toluenesulfonyl chloride, was converted into 19-norprogesterone (LXXVII).

While in the scheme of synthesis described above, the ready subjection of strophanthidin to the autooxidation reaction with the formation of strophanthidinic acid was taken into account [89], in another investigation a parallel autooxidation product – 10β-hydroxy-19-norperiplogenin was utilized. From this compound syntheses were performed [90] of 3β,5,10β,14-tetrahydroxy-19-nor-5β,14β-androstan-17-one (LXXXI), 10β,14β-dihydroxy-19-norandrost-4-ene-3,17-dione (LXXXII), and 14β-hydroxyestrone (LXXXIII). Compounds (LXXXI) and (LXXXII), of which this was the first synthesis, possess some anabolic activity.

The preparation of 17α-hydroxystrophanthidin has been described [91]. A stereodirected synthesis of the known cardiac aglycone uzarigenin (III) has been effected [92].



Interesting work has been performed on the use of instrumental methods of investigation for resolving structural problems. It has been shown that the halochromic spectra of aglycones and glycosides can be used for their identification and for the preliminary assignment of the aglycone and sugar moieties to known types of compounds [93]. IR spectra in the region of the stretching vibrations of hydroxy and carboxy groups and also optical rotatory dispersion spectra, have been used for determining the conformational features of strophanthidin and corotoxigenin [94, 95]. The NMR spectra of cardenolides with oxygen-containing functions at C_{10} have been studied [96].

In view of the fact that for a long time pharmacological investigations outstripped chemical studies, up to now biological methods for the quantitative determination of the cardiac glycosides have predominated. The photometric and spectrophotometric methods developed in recent years will enable a larger number of glycosides and the amounts of individual glycosides in plant raw material and medicinal forms to be determined with adequate accuracy [32, 97-100].

A characteristic feature of the Soviet school is the deep interpenetration of theoretical and practical studies. In no country does medicine have available such a rich selection of cardiotonic preparations as in the Soviet Union. In addition to galenical and nongalenical preparations, the following individual cardiac glycosides are used in the USSR: digitoxin, gitoxin, digoxin, lanatoside C (celanide), periplocin, hellebrin (corelborin P), oleandrin (neriolin), convallotoxin, k-strophanthin-β, cymarin, corchoroside, erysimin, gomphotin, olitoriside, erysimoside, and apobioside. The last five compounds were discovered by Soviet workers.

It goes without saying that the chemistry of the cardiac glycosides has developed in close connection with the corresponding divisions of pharmaceutical chemistry, pharmacology, pharmacognosy, the biology and introduction of medicinal plants, and technology. However, it did not appear to be possible to consider all related questions within the framework of the present review.

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