1. Steroids with branched side chains are more active than steroids with additional tetrahydropyran-4-one and -2-one rings E. The most active in this series are 20-ketosteroids containing in the side chain such polar groupings as a β-diketonic or an epoxyethyl grouping.

2. Steroids with a spirotetrahydrofuran ring at C(17) exhibit activities greater than those of their pyranoside analogs.

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OXIMES AND NITRILES OF CARDENOLIDES

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The influence of the oximation of cardenolides and the production of 10-cyanocardenolides on their biological activity has been studied. The prefered conformation of strophanthidin 19-aldoxime has been established; it has chelate fragment as the result of the orientation in the same direction of the nitrogen atom of the oxime group and the hydroxy groups at C-3 and C-5.

We have previously [1] established that strophanthidin 19-aldoxime has a biological activity three times greater than that of the natural cardiac aglycone. In attempting to investigate the influence of oximation and some other types of transformation of cardenolides on the change in their biological activity more widely, we have synthesized oximes both of aglycones (II, IV, VI) and also of glycosides (VIII, X, XII), and also 10-cyanocardenolides (XIII, XIV). For oximation we used substances each containing an angular aldehyde group, so obtaining the corresponding 19-aldoximes. Digitoxigenin 3-ketoxime (VI) was also synthesized.

Treatment of the oximes with dehydrating reagents and, in particular, heating with them in a mixture of acetic anhydride and pyridine, yielded the 10-cyanocardenolides (XIII) and (XIV). The nitrile derivatives of some cardiac glycosides were known previously [2, 3], but information on their biological activity was lacking.

The structures of the compounds obtained were confirmed by the results of elementary analysis and IR and PMR spectroscopy. The IR spectra of the oximes have bands in the 1610-1630 cm^{-1} region due to the C=N bond, which are usually accompanied by the absorption bands of double C=C bonds of the butenolide ring, increasing their intensity. In the PMR spectra there are signals with a chemical shift of 7.65 ppm belonging to the proton of the $-CH=N-$

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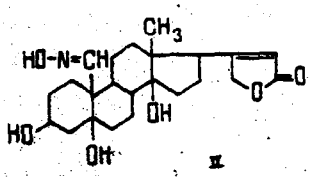
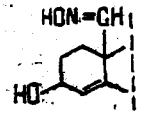
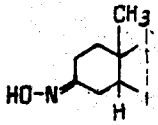
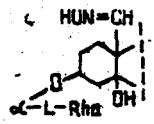
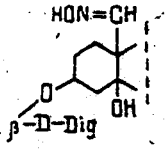
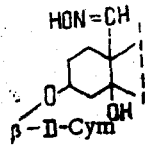
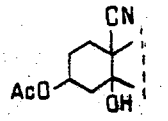
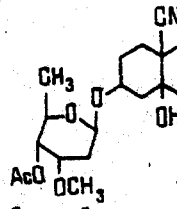
TABLE 1. Biological Activities of Cardenolide Oximes and Nitriles

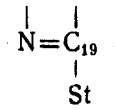
Substance	Biological activity according to Hatcher (mg/kg wt. of the cat)	Structures of the oximes and nitriles
I. Strophanthidin	0,32 [4]	
II. Strophanthidin 19-aldoxime	0,11	II
III. Securigenin	0,90 [4]	
IV. Securigenin 19-aldoxime	0,30±0,025	IV*
V. Digitoxigenin	0,44 [5]	
VI. Digitoxigenin 3-ketoxime	1 67±0.18	VI
VII. Convallatoxin	0,079 [6]	
VIII. Convallatoxin 19-aldoxime	0,112±0,009	VIII
IX. Erysimin	0,095 [6]	
X. Erysimin 19-aldoxime	0,180±0,007	X
XI. Cymarin	0,11 [6]	
XII. Cymarin 19-aldoxime	0,128±0,002	XII
XIII. 3-O-Acetyl-10-cyanostrophanthidin	1,63±0,058	 XIII
XIV. 4'-O-Acetyl-10-cyanocymarin	2,0±0,088	 XIV

*The illustration of part of a structural formula means that its remainder is constructed as in the case of the oxime (II).

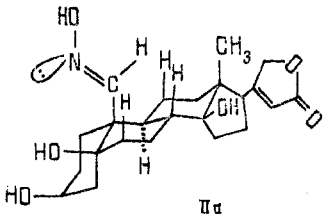
grouping. The nitrile group is detected from its weak but well-resolved absorption band in the 2240 cm^{-1} region of the IR spectrum.

Table 1 gives information on the biological activities of the oximes and nitriles in comparison with the initial glycosides and aglycones from which these compounds were obtained. Attention is attracted above all to the opposite effects of oxime groups on the biological activities of the aglycones and the glycosides. While for the aglycones it increases, for the glycosides it falls somewhat. The increase in the biological activities of the aldoximes of the aglycones are so considerable (three times) that this demands both an explanation and, if possible, practical utilization.

Assuming that the cause must be sought on the basis of the fine chemical structures of these compounds, we attempted first of all to evaluate the stereostructures by using Stuart–Briegleb molecular models. This showed the following facts. In the first place, of the two isomer due to the configurations of the oxime group, only one, the E isomer,



is possible. The Z isomer is excluded from steric considerations. In the second place, the rotation of an oxime group around the C_{10}–C_{19} bond is inhibited. It is prevented by the 1βH, 6βH, 8βH, and 11βH hydrogen atoms and by the 5β-OH group. As a result, only two stable conformers must be expected. In one of them the C=N bond is directed towards the oxygen atom at C-3, and in the other it is directed opposite to the C_7–Hα bond. Of these conformers, the first, represented by formula (IIa) is preferred. A confirmation of this is, in particular, the fact that strophanthidin 19-aldoxime forms complexes with a number of metal ions. A particularly strong, green, complex soluble in organic solvents is formed with copper salts.* We assume that in this case the chelate fragment of the molecule formed by the nitrogen atom and the hydroxyls at C-3 and C-5 are involved. Furthermore, in the PMR spectrum of the oxime (II) the signal of the angular methyl group 18-CH_3 appears in the 0.74 ppm region, i.e., shifted upfield, which is apparently connected with the spatial screening of the influence of the 19C–H proton on this group. The spatial approach of the 19C–H and 18-CH_3 group can be well seen on molecular models, but it is difficult to show graphically by ordinary formulas of type (IIa)



IIα

It must be mentioned that a similar restriction of rotation is experienced by the aldehyde group at C-10, which explains the existence of a Cotton effect in the optical rotatory dispersion spectra of cardenolides and bufadienolides with a 19-aldehyde group. The oxygen atom of the –CH=O is group is obviously orientated in the direction of the OH group at C-3 and the hydrogen atom in the direction of the 18-CH_3 group, since in the PMR spectrum of strophanthidin, just as in that of the oxime (II), the signal of the methyl group appears in the low-field region – at 0.73 ppm.

We may consider that it is precisely the chelate groupings in the aldoximes of the aglycones that are responsible for such a substantial rise in biological activity. Such structures apparently permit the cardenolide to interact more strongly with the functional groups of the receptors in the organism than the natural aglycones.

The proposed explanation does not exclude others, as well. In particular, thanks to the presence of chelate groupings the aldoximes of aglycones are possibly selective carriers of calcium ions through the membranes of the myofibrillar cells and thereby increase biological activity, since it is known [8-10] that calcium ions intensify the contractility of the myofibrils. It is also not excluded that both these effects take place in the living organism.

*A special communication will be devoted to these investigations.

In relation to the ketoxime (VI), it can be said that the decrease in its biological activity in comparison with digitoxigenin is normal, since it lacks the 3β-OH group that is important for the cardiotonic action of the aglycones and does not have the chelate structure discussed above.

The 10-cyanocardenolides proved to have little biological activity.

EXPERIMENTAL

IR spectra were taken on a IR-27G spectrometer and PMR spectra of BF-497, 100 MHz, spectrometer. Elementary analyses were performed on a Hewlett-Packard automatic C—H—N analyzer; the analyses of all the compounds corresponded to the calculated figures. Melting points were determined on a Kofler block. The purifies of the substances and the course of the reaction were monitored by paper chromatography using the following solvent systems: methyl ethyl ketone—m-xylene (1:1)/formamide and chloroform—tetrahydrofuran (1:1)/formamide. In determining biological activity by Hatcher's method, the working solutions were the following dilutions of the substances: (VI) and (XIV), 1:10,000; (IV), 1:50,000; (II) and (XIII), 1:100,000; and (VIII), (X), and (XII), 1:200,000.

The oximes of the glycosides and the aglycones were obtained by known methods (see, for example, [7]) and they were crystallized from water and recrystallized from ethanol.

Strophanthidin 19-aldoxime, $C_{23}H_{33}O_6N$, mp 255-265°, $[\alpha]_D^{20}$ +47.8 ± 2° (c 1.0; methanol—chloroform (2:1).

Securigenin 19-aldoxime, $C_{23}H_{31}O_5N$, mp 249-254°, $[\alpha]_D^{20}$ +53.6 ± 2° (c 1.0; methanol).

Digitoxigenin 3-ketoxime, $C_{23}H_{33}O_4N$, mp 130-135°, $[\alpha]_D^{21}$ +45.4 ± 2° (c 1.0; methanol).

Convallatoxin 19-aldoxime, $C_{29}H_{43}O_{10}N$, mp 183-185°, $[\alpha]_D^{20}$ +5.2 ± 2° (c 1.0; methanol).

Erysimin 19-aldoxime, $C_{29}H_{43}O_9N$, mp 243-247°, $[\alpha]_D^{21}$ +35.1 ± 3° (c 1.0; methanol—chloroform (2:1)).

Cymarin 19-aldoxime, $C_{30}H_{45}O_9N$, mp 185-190°, $[\alpha]_D^{20}$ +43.9 ± 2° (c 1.0; methanol).

4'-O-Acetyl-10-cyanocymarin. A solution of 0.4 g of cymarin 19-aldoxine in 12 ml of absolute pyridine was treated with 3 ml of acetic anhydride, and the mixture was heated on the boiling water bath for 3 h. Then it was diluted with water containing ice (100 ml) and left for 2 h. The reaction product was extracted with chloroform—ethanol (3:1; 3 × 100 ml), and the extract was washed with water (7 × 30 ml) and evaporated in vacuum. The resulting compound (XIV) was crystallized from methanol and was then recrystallized from a mixture of methanol and diethyl ehter. Yield 0.27 g, mp 254-258°C, $[\alpha]_D^{20}$ +56.6 ± 2° (c 1.0; methanol—chloroform (1:1)); molecular formula $C_{32}H_{45}O_9N$.

3-O-Acetyl-10-cyanostrophanthidin. This was synthesized similarly from strophanthidin 19-aldoxime and had the molecular formula $C_{25}H_{33}O_6N$, mp 283-288°C, $[\alpha]_D^{20}$ +38.97 ± 2° (c 1.0; methanol—chloroform (9:1)).

SUMMARY

Oxime and nitrile derivatives of cardiac glycosides and aglycones have been obtained. Their biological activities have been determined – the 19-aldoximes of aglycones are approximately three times more active than the initial natural substances; the 10-cyano compounds proved to be only weakly active. It has been shown that the 19-aldoximes of aglycones have a chelate chemical structure; it is assumed that the enhancement of their biological activities is connected with this fact.

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TERPENE AMINES.

V. SYNTHESIS AND STUDY OF THE STRUCTURE OF N-SUBSTITUTED TETRAHYDROIONYLAMINES

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UDC 547.233.2.3

The catalytic hydroamination of a mixture of α- and β-ionones by aliphatic nitriles and amines has been studied. A scheme of the occurrence of the reaction has been put forward. It has been established that the reaction forms in each case a mixture of secondary amines containing two pairs of diastereomers. The optimum conditions for the performance of the process have been determined.

It is known that substituted ionylamines and their derivatives are effective plant growth regulators [1]. However, there is little information in the literature [2, 3] on the synthesis and stereochemistry of amino derivatives of α- and β-ionones. In view of this, the study of known methods for their preparation, the development of new ones, and the synthesis from them of amines of this series that have not previously been described are of great importance. We have shown previously [4] that catalytic hydroamination is an extremely convenient method for synthesizing difficultly accessible amines from unsubstituted monocyclic terpene ketones. On expanding our initial investigations, we have included among the oxygen-containing terpene compounds participating in the hydroamination reaction ionone (cyclocitrylideneacetone), which contains a mixture of two isomers α (I) and β (II) in a ratio of 40:60.

In the present paper we consider the synthesis of N-substituted 1-methyl-3-(2,6,6-trimethylcyclohexyl)propylamines (tetrahydroionylamines) by the reductive amination of ionol with nitriles or amines. During the work we pursued two aims: in the first place, to determine the optimum conditions for the performance of this reaction; and, in the second place, to synthesize secondary amines of the tetrahydroionone series not previously described and to study their properties and structures.

The reaction was performed in the vapor phase in the temperature interval of 210-270°C under a pressure of hydrogen of 10-20 atm. in the presence of a copper-aluminum oxide catalyst modified with lithium hydroxide. An investigation of the reductive amination of ionone by aliphatic nitriles or amines at various temperatures, pressure of hydrogen, and space velocities of the passage of the reaction mixture enabled us to determine the optimum conditions for its performance. The maximum yields of the desired reaction products — the secondary amines (III-VI) — were achieved at a temperature of 250°C, a hydrogen pressure of 15 atm, and a space velocity of 0.2 h^{-1}. The catalyst used contained 15% of copper and 6% of lithium hydroxide deposited on industrial γ-alumina. A further rise in the temperature of the reaction was accompanied by an increased formation of by-products. An increase in the pressure had a favorable influence on the yield of desired products but somewhat lowered the selectivity

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