THERMAL TRANFORMATION OF CARDIAC GLYCOSIDES

II. ACIDLESS HYDROLYSIS OF LABILE GLYCOSIDES IN AQUEOUS ALCOHOLIC SOLUTIONS AND PROSPECTS FOR ITS UTILIZATION

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The thermal transformations of cardiac glycosides in neutral alcoholic solutions have been investigated. The kinetics of their acidless hydrolysis at 100 and 142°C and the activation energy of the process have been studied. The possibility has been shown of the stepwise hydrolysis of natural trisdigitoxosides with the production of difficulty available mono- and bisdigitoxosides. The following were used as the objects of investigation: convallatoxin, glucostrophanthidin, cheirotoxin, desglucocheirotoxin, erycordin, erysimin, erysimoside, digitoxin, and cymarin.

We have described the thermal transformations of cardenolides on dry heating [1]. The present communication is devoted to the thermal transformations of cardiac glycosides on their heating in neutral solutions. As solvents we have used mixtures of water and alcohols. Convallatoxin, glucostrophanthidin, cheirotoxin, glucocheirotoxin, erycordin, erysimin, erysimoside, digitoxin, and cymarin (for their structures, see [2]) have been investigated. The first five glycosides, in which the aglycons are linked with the carbohydrate components hydroxylated at C-2 scarcely changed on being heated to 140°C for 4 h each. Glycosides containing 2-deoxysugars, which are fairly labile under these conditions, underwent hydrolysis. Results characterizing the rate of hydrolysis of the glycosides of this group are given in Fig. 1 and Table 1. Chromatographic analysis showed that on their hydrolysis aglycons were formed that were not contaminated by other cardenolides, which can rarely be achieved with the aid of the usual acid hydrolysis. In view of this circumstance, we carried out the preparative acidless hydrolysis of erysimin and in this way obtained pure stropanthidin with a yield of 84%. We consider that this approach is promising both for the laboratory and the industrial preparation of the aglycons from the corresponding glycosides.

The rate of hydrolysis depended greatly on the presence of substituents in the sugar component. The presence of a methoxy group at C-3' in the D-digitoxose residue of erysimin sharply retarded hydrolysis. The rate of hydrolysis of 3'-O-methylerysimin (cymarin) fell by a factor of 9.5 in comparison with the unmethylated compound. The addition of a D-glucose residue at C-4' of erysimin likewise lowered the rate of hydrolysis. At 100°C, erysimoside was hydrolyzed 5.5 times more slowly than erysimin. The decrease in the rate of hydrolysis on the introduction of substituents into the sugar components is probably due to the steric hindrance so arising. As was to be expected, an increase in the distance from the substituents to the reaction center weakened the influence of a substituent (compare the hydrolysis of cymarin and erysimoside).

This influence of substituents on the rate of hydrolysis led us to the opinion that glycosides containing a chain of 2-deoxysugars should hydrolyze mainly by a stepwise process, beginning with the terminal unit. The partial acidless hydrolysis of digitoxin (digitoxigenin tridigitoxoside) was performed. This gave a mixture of three glycosides and digitoxigenin. The components of the mixture were isolated in the individual state by chromatography. They included digitoxin mono- and bisdigitoxosides. Chromatographic analysis showed that the hydrolysate of the compounds contained digitoxin (the initial compound), digitoxigenin bisdigitoxoside, digitoxigenin monodigitoxoside, and digitoxigenin in a ratio of 2:4:1.5:1.5. The presence of the bisglycoside as the main product showed that acid-free

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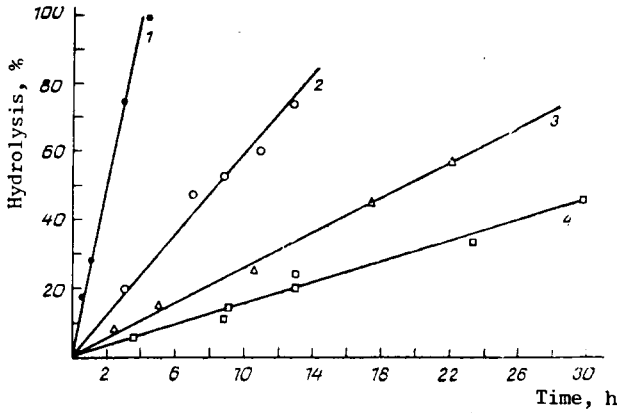

Fig. 1. Dependence of the degree of hydrolysis of the glycosides on the temperature and time of the process: 1) erysimoside at 142°C; 2) erysimin at 100°C; 3) cymarin at 142°C; 4) erysimoside at 100°C.

TABLE 1. Kinetics of the Hydrolysis of 2'-Deoxyglycosides

Glycoside	Temperature of heating the solution, °C	Half-reaction time	Rate constant, moles/liter·s
Erysimin,	100	8 h40 min	$4{,}7\cdot10^{-8}$
Erysimoside,	100	48 h	$4{,}3\cdot10^{-9}$
Erisimoside	142	2 h	$1\cdot10^{-7}$
Cymarin	142	19 h	$1{,}11\cdot10^{-8}$

hydrolysis did actually take place mainly in stepwise fashion. Thus, this method of hydrolysis is more selective than acid hydrolysis and expands the possibilities of obtaining a number of difficultly accessible mono- and bisdigitoxosides. A study of the occurrence of acidless hydrolysis in time has shown that the rate of the reaction in highly dilute solutions does not depend on the concentration of the glycosides, i.e., formally the reaction has zero order with respect to the concentration of the glycosides and is determined essentially by the temperature factor. Raising the temperature sharply accelerates the reaction. Thus, with a rise in the temperature from 100 to 142°C the rate of hydrolysis of erysimoside increased by a factor of 24. The activation energy of the process is 98 kJ/mole.

EXPERIMENTAL

Elementary analysis was carried out with the aid of an automatic C—H—N analyzer. Melting points were determined on a Kofler block. The purity of the substances was checked by paper chromatography using methyl ethyl ketone—m-xylene (1:1)/formamide.

Acidless Hydrolysis of 2'-Deoxyglycosides. Solutions of the glycosides at a concentration of $1.5\cdot10^{-3}$ M in 50% propan-1-ol with pH 6.85-6.90 were sealed into glass containers and were kept at one of two temperatures: 100 ± 1°C and 142 ± 1°C. The semiquantitative analysis of the reaction products was carried out by thin-layer chromatography on Silufol in the solvent systems chloroform—ethanol (9:1) and chloroform—methanol—water (84:15:1).

Preparative Acidless Hydrolysis of Erysimin. A solution of 2 g of erysimin in 40 ml of 50% propan-1-ol was heated in a sealed glass vessel at 140°C for 5 h. The solution was concentrated in vacuum to an aqueous residue. The crystals that had deposited were separated off and were recrystallized from aqueous methanol. This gave 1.27 g of the aglycon strophanthidin, mp 144-147/230-242°C; $[\alpha]_D^{20}$ +43.0 ± 2° (c 1.0; methanol).

Partial Hydrolysis of Digitoxin: Production of Digitoxigenin Mono- and Bisdigitoxosides. A solution of 1.5 g of digitoxin in 60 ml of 50% propan-1-ol was heated in a sealed glass container at 125 ± 1°C for 70 min and was then evaporated in vacuum. The mixture of substances so obtained was chromatographed on a column of silica gel activated at 120°C.

Methylene chloride and methylene chloride–ethanol in mixtures of increasing polarity were used as eluents. The ratio of adsorbent to the mixture to be separated was 150:1. The three glycosides so obtained were crystallized from acetone, and the aglycon from ethanol. As a result, the following were obtained in the individual state: digitoxigenin, mp 235-239/250-256°C; digitoxin, mp 263-273°C; digitoxigenin bisdigitoxoside, mp 226-230°C, $[\alpha]_D^{21}$ +7.1 ± 2° (c 0.70; methanol), found, %: C 66.01, H 8.59 ($C_{35}H_{54}O_{10}$); and digitoxigenin monodigitoxoside, mp 195-200°C, $[\alpha]_D^{20}$ −5.6 ± 2° (c 0.65; methanol), found, %: C 68.86, H 8.72 ($C_{29}H_{44}O_7$).

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SYNTHESIS AND ANTICHOLINESTERASE PROPERTIES OF NEW DERIVATIVES OF LUPININE AND ELILUPININE

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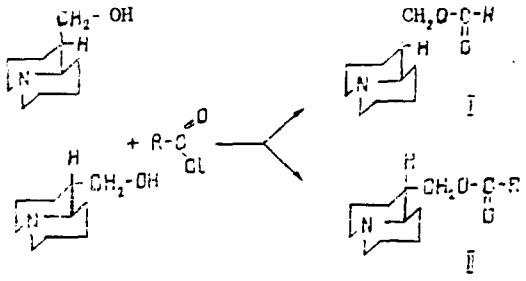
Esters of lupinine and epilupinine have been obtained by their acylation with isovaleroyl, cinnamoyl, trichloroacetyl, and trimethylacetyl chlorides. The methiodide derivatives of these esters have been investigated in reactions with the blood cholinesterases of warm-blooded animals. The interaction has a reversible nature, and the inhibition of the activity of the enzyme is both quantitative and qualitative in dependence on the structure of the acid taken and the conformational properties of the lupinine epimers.

Continuing investigations begun earlier [1], we have synthesized some new esters of lupinine (I) and epilupinine (II) and have studied the kinetics of the interaction of the compounds obtained with such blood enzymes of warm-blooded animals as acetylcholinesterase (ACE) and butyrylcholinesterase (BuCE). The scheme of the synthesis is given below:



where R = $-C(CH_3)_2$ (Ia, IIa); $-CH_2CH(CH_3)_2$ (Ib, IIb); $-CH=CH-C_6H_5$ (Ic, IIc); $-CCl_3$ (Id, IId)

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