SOME CONFORMATIONAL PECULIARITIES OF CARDENOLIDES AND BUFADIENOLIDES

I. P. Kovalev and V. T. Chernobai

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In the partial synthesis of cardiac glycosides, and also in the production of a number of derivatives of the aglycones, it has been found [1] that the aglycones of the A/B-cis series differ considerably with respect to the reactivity of the hydroxy group at C_3 and the aldehyde group at C_{10} (glycosidation, acylation, reduction, oximation) from the aglycones of the A/B-trans series. For example, the partial synthesis of corotoxigenin 3-β-D-glucoside (A/B-trans series) takes place with a yield of 5–6% [1], while the yield of strophanthidin 3-β-D-glucoside under identical conditions amounts to 50% [2]. It has been suggested that the different reactivities of the aglycones is due to conformational peculiarities of these compounds.

To confirm the results obtained during chemical transformations and to elucidate some conformational features, the IR spectra were studied in the region of the stretching vibrations of the hydroxyl and carbonyl groups, and so were the optical-rotatory dispersion spectra of strophanthidin, corotoxigenin, and other compounds.

In neutral methylene chloride solution, strophanthidin exhibits a clear absorption band at 1718 cm^{-1} (Fig. 1), which is characteristic for an aldehyde group at C_{10}. In contrast to the spectrum of strophanthidin, that of corotoxigenin has a broad and diffuse maximum in the 1725–1705 cm^{-1} region. It is known that the presence of a diffuse maximum shows the formation of a hydrogen bond; however, in the region of the stretching vibrations of the hydroxyl group of corotoxigenin there is one band at 3608 cm^{-1} (table) belonging to the absorption of free hydroxyls.

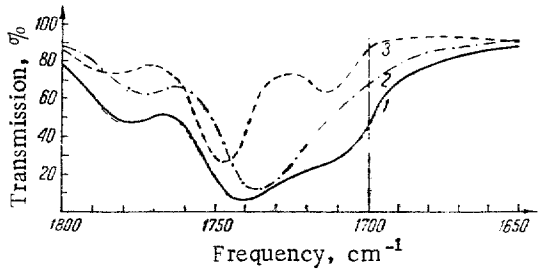
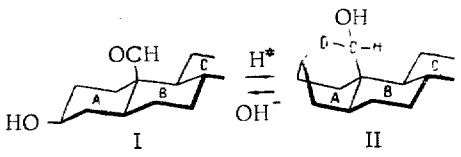


Fig. IR spectra. 1) Corotoxigenin (c = 0.005 M, l = 0.401 cm); 2) corotoxigenin in an acid medium (c = 0.0032 M, l = 0.401 cm); 3) strophanthidin (c = 0.0061 M, l = 0.40 cm) in methylene chloride solutions in the region of the C=O stretching vibrations.

It has previously been shown [1] that the reactivities of the hydroxyl group at C_3 and of the aldehyde group at C_{10} of corotoxigenin, unlike those of strophanthidin, depend on the pH of the medium to a considerable extent. For example, the aldehyde group of corotoxigenin is not reduced by sodium borohydride in an acid medium, while with strophanthidin this reaction takes place relatively readily. The results obtained permit the assumption that in anhydrous media of an acidic nature corotoxigenin is present completely or predominantly in the semiacetal form (II) while in solutions of a basic nature it is present in the aldehyde form (I):



The IR spectrum of corotoxigenin in an acid medium has no maximum corresponding to the aldehyde group at C_{10} (cf. Fig. 1). The disappearance of this maximum shows the presence of the semiacetal form at C_{19} (II). The IR spectrum of the 3-O-acetate of corotoxigenin may serve as a proof of the fact that the semiacetal form is produced from the hydroxyl group at C_3; this spectrum does not change in either neutral or acid media and has the maximum

characteristic for the aldehyde group. The IR spectra of corotoxigenin in basic and neutral media do not differ in the region of the stretching vibrations of the C=O of the aldehyde group.

Frequencies, Half-Widths, and Intensities of the Bands of the Stretching Vibrations of the Hydroxyl Groups of Some Cardenolides

Compound	ν_{max}	$\Delta\nu^1/_2$	mole^{-1} · l · · cm^{-1}	B, 10^4 · mole^{-1} · · l · cm^{-2}
	cm^{-1}			
Strophanthidin	3610	52	110	2.3
	3488	110	102	4.3
Periplogenin	3610	55	112	2.2
	3500	110	99	4.2
Corotoxigenin 3-O-acetate	3600	53	67	0.9
Corotoxigenin	3608	52	98	1.6

The production of the semiacetal form of corotoxigenin (II) is also confirmed by the optical rotatory dispersion spectra (Fig. 2). In a neutral medium, corotoxigenin, and also its 3-O-acetate, have a curve with a shape typical for steroids of the A/B-trans series with an aldehyde group at C_{10}, while in an acid medium the flat shape of the optical rotatory dispersion curve shows the disappearance of the chromophoric grouping causing the Cotton effect. The very high value of the specific rotation at long waves above 340 mμ shows the appearance of a new asymmetric center at C_{19} (II).

We have also obtained the IR spectra of bovogenin (in neutral and acid media), which differs from corotoxigenin only in the size of the lactone ring at C_{17}. In the IR spectrum of bovogenin, the band of the carbonyl group of the six-membered lactone ring is split into two bands: one at 1742 cm^{-1} and the other at 1721 cm^{-1}. The frequency of band 2 almost coincides with the frequency of the maximum of the absorption band of the aldehyde group at C_{10}. Only the decrease in the intensity of the second band 570 mole^{-1} · l · cm^{-1} in a neutral medium and 400 mole^{-1} · l · cm^{-1} in an acid medium, can serve as an independent proof of the production of the semiacetal form.

A semiacetal form produced by the hydroxyl group of the carbohydrate part and the aldehyde group of the aglycone part of glucobovoside "A" has been found by Tshesche et al., [3].

In contrast to compounds of the A/B-trans series, the IR spectra of strophanthidin (A/B-cis series) taken in neutral, acid, and basic media exhibit no changes whatever in the region of the stretching vibrations of the aldehyde group. The optical rotatory dispersion spectra of strophanthidin obtained in the same media are identical and have a curve-shape which is characteristic for steroid compounds of the A/B-cis series with an aldehyde group at C_{10} (Fig. 3).

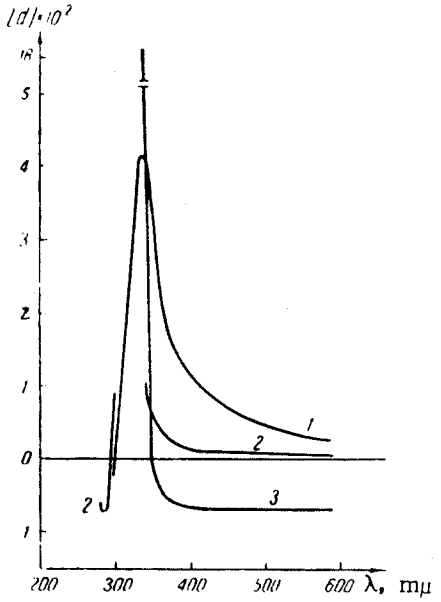


Fig. 2. Optical rotatory dispersion spectra. 1) Corotoxigenin acetate (c = 0.12, 25° C; methanol); 2) corotoxigenin (c = 0.2, 24 ; methanol); 3) corotoxigenin in an acid medium (c = 0.2, 25° C; methanol).

Djrassi et al., [4] also show that strophanthidin and its acetate have distinct optical rotatory dispersion curves differing from corotoxigenin acetate. The authors state that on the basis of a small number of data it is impossible to decide whether this difference is explained by the trans- or cis-linkage of rings A/B or by a hydrogen bond between the 5-β-OH group and the aldehyde group of strophanthidin.

We have attempted to determine whether a hydrogen bond could be formed between the aldehyde group of strophanthidin and the hydroxyl groups at C_3 and C_5.

In contrast to corotoxigenin, in which a single band at 3608 cm^{-1} belonging to the absorption of free hydroxyls appears in the region of the stretching vibrations of the hydroxyl groups, strophanthidin has two bands at 3610 and 3488 cm^{-1} (see table, Fig. 4). The band at 3488 cm^{-1} apparently relates to a hydroxyl group involved in an intra-

molecular hydrogen bond.

The appearance of an intermolecular bond is excluded, since a reduction in the concentration of the strophanthidin solution from 0.005 to 0.001 M (which generally favors the rupture of intermolecular bonds) leads to no change in the frequency or decrease in the intensity of the maximum.

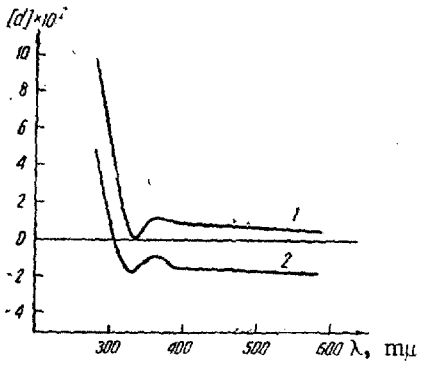


Fig. 3. Optical rotatory dispersion spectra. 1) Strophanthidin (c = 0.4; 25° C; dioxane); 2) cannogenin (c = 0.602; 25° C; dioxane).

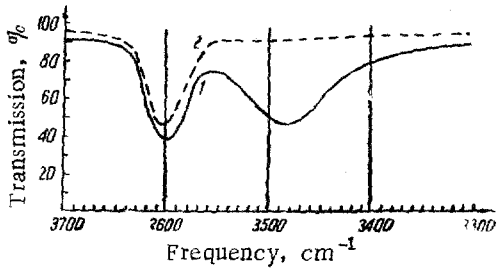
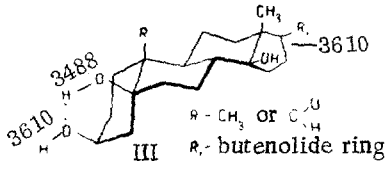


Fig. 4. IR spectra. 1) Strophanthidin (c = 0.0065 M, l = 0.509 cm); 2) corotoxigenin (c = 0.008 M, l = = 0.509 cm) in methylene chloride solutions in the region of the OH stretching vibrations.

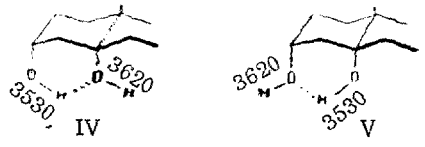
The aldehyde group of strophanthidin does not participate in the formation of an intramolecular hydrogen bond with the hydroxyl groups at C_3 and C_5 since the half-width values, the molar absorption coefficients, and the integral intensities of the bands at 3160 and 3488 cm^{-1} obtained for strophanthidin are almost the same as for periplogenin (see table), which differs from strophanthidin in the absence of the aldehyde group at C_{10}.



III

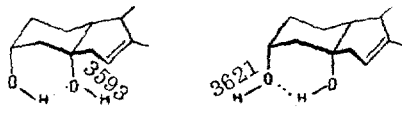
There is no intramolecular hydrogen bond between the hydroxyl group at C_{14} and the carbonyl at C_{10} or the lactone at C_{17}, since the spectra of corotoxigenin and its acetal derivative exhibit no band at 3500 cm^{-1}.

Consequently, it is most likely that the hydrogen bond in strophanthidin is located between the hydroxyl groups at C_3 and C_5 (III). This is also confirmed by the fact that cis-diols have a similar broad band at 3530 cm^{-1} which relates to a hydroxyl group involved in an intramolecular hydrogen bond [5-9]. It must be noted that cis-diols exhibit not only the band of bound hydroxyl groups (3530 cm^{-1}) but also bands of the "free" hydroxyl groups of the bound diols (3620 cm^{-1}). The hydroxyl groups of cis-diols have two forms of the bond (IV) and (V),



IV V

which are almost identical in spectral behavior. The existence of these forms is shown by the fact that Δ^7-diols have two "free" bands of hydroxyl groups: a band at 3593 cm^{-1} belonging to a 5-α-hydroxyl group oriented in the direction towards the 7,8-double bond (VI), and a band at 3621 cm^{-1} belonging to the 3-α-hydroxyl group (VII) [10, 11]:



VI VII

The reactivity of strophanthidin (acylation, glycosidation) shows that the 3-β-hydroxyl group is predominantly free.

The assumption arises that the intramolecular hydrogen bond between the hydroxyl groups of strophanthidin at C_3 and C_5 fix the position of ring A and prevent the appearance of the semiacetal form. To investigate this, we studied the IR spectrum of cannogenin, which differs from strophanthidin by the absence of a hydroxyl group at C_5 and from corotoxigenin only by the linkage of the A/B rings. It was found that cannogenin, just like strophanthidin, does not give a semiacetal form. The optical rotatory dispersion spectrum of cannogenin is characteristic for steroid compounds of the A/B-cis series with an aldehyde group at C_{10} (Fig. 3).

Thus, the aglycones of the A/B-cis series in neutral, acid, and basic media have the most stable chair–chair conformation of rings A and B.

In the aglycones of the A/B-trans series, ring A may be present in a chair–boat equilibrium, depending on the medium, because of which conditions are created for the production of a semiacetal form for compounds having an aldehyde group at C_{10}.

The capacity of the cardiac glycosides and aglycones of the A/B-trans series for undergoing conversion into the semiacetal form apparently has an influence on the process of their metabolism in the organism.

Experimental

The IR spectra were determined on a UR-10 spectrometer with prisms of LiF (3300–3700 cm^{-1}) and NaCl (1650–1800 cm^{-1}). The spectral slit widths were 5.7 cm^{-1} for a frequency of 3600, 4.3 cm^{-1} for 3500, 8.8 cm^{-1} for 1750 cm^{-1} and 8.7 cm^{-1} for 1720. The recording scale for the LiF prism was 50 mm/100 cm^{-1}, and for the NaCl prism it was 150 mm/100 cm^{-1}, the velocity of recording being 12 or 4 cm^{-1}/ min. The spectra were obtained with solutions in carefully purified and dried methylene chloride with a concentration of 0.008–0.001 M and with a cell thickness of 4.0–1.0 mm. The molar coefficients of rotation were calculated from the formula

$$\varepsilon = \frac{1}{cl} \log \left(\frac{T_0}{T} \right)_{\nu_{max}},$$

where C is the concentration, mole/l ; l is the layer thickness, cm; and $\log \left(\frac{T_0}{T} \right)_{\nu_{max}}$ is the optical density at the maximum of the band. The integral intensities were determined by Wilson and Wells's method as improved by Ramsay [12].

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When the spectra of the compounds were obtained in an acid medium, 2–3 drops of methylene chloride saturated at 0° C with dry hydrogen chloride were added to the solution, and then it was made up to the mark. To create a basic medium, 2–3 drops of methylene chloride saturated at 0° C with dry ammonia were added to the solution. The compounds investigated were dried under vacuum (10^{-2} mm Hg) at 115° C over phosphorus pentoxide for 3–4 hr.

The optical rotatory dispersion spectra were taken on a SPU-E spectropolarimeter in solutions in dioxane and methyl alcohol. The RD spectrum of corotoxigenin was taken with a layer thickness of 0.1 dm at a concentration of 0.2%. To obtain the RD spectrum of corotoxigenin in an acid medium, a drop of methanol saturated with hydrogen chloride was added to a solution of the substance in methyl alcohol.

Samples of bovogenin and cannogenin were given to us by A. A. Reznichenko and N. K. Abubakirov respectively.

Summary

1. The capacity of the cardenolides and bufadienolides of the A/B-trans series having an aldehyde group at C_{10} for giving a semiacetal form is due to the conformational features of ring A, which may be present in a chair–boat equilibrium.

2. The aldehyde group of strophanthidin does not participate in the formation of an intramolecular hydrogen bond with the hydroxyl group at C_3 and C_5; an intramolecular hydrogen bond occurs between the hydroxyl groups at C_3 and C_5.

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