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NMR SPECTRA OF CARDENOLIDES WITH AN OXYGEN-CONTAINING FUNCTION AT C_{10}

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In the majority of papers devoted to the NMR-spectroscopic study of the cardenolides [1-8], with a few exceptions [1-2], only steroid aglycones with methyl groups at C_{10} and C_{13} are considered. We give the results of an NMR-spectroscopic investigation with some cardenolides with oxygen-containing functions at C_{10}.

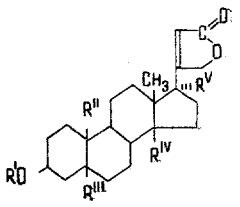
Chemical shifts of the angular C_{18} methyl group. If literature data on the acetates of periplogenin and strophanthidin [4-8] and the results that we have obtained for strophanthidin (I), strophanthidol (III), and 10β-hydroxyl-19-norperiplogenin (VIII) are compared, it can be seen that the values of the chemical shifts for the 18-methyl protons are almost the same in all cases, amounting to 9.10-9.13 τ. This means that substituents at C_{10} practically do not interact with the 18-methyl protons and do not affect the position of their signal in the spectrum. The introduction of a Δ^5 bond into the strophanthidin molecule causes slight screening of the C_{18} methyl group. Thus, for example, the signal of the C_{18} methyl group in pachygenin (IV) (table) shifts into the stronger field by 0.06 ppm ($\Delta\tau = \tau_{IV} - \tau_I = 0.06$ ppm). As was to be expected [6], in diffugenin (VI), because of the presence of a Δ^{14} bond, the screening effect appears far more ($\Delta\tau = \tau_{VI} - \tau_I = 0.25$ ppm). The trans linkage of the A and B rings and the absence of a hydroxyl group at C_5 in corotoxigenin (V) leads to only a small displacement of the signal of the C_{18} methyl group to the stronger field ($\Delta\tau = \tau_V - \tau_I = 0.08$).

The introduction of an OH group into the 17α position has a considerable influence on the chemical shift of the C_{18} methyl group. Thus, in the 19-norpentahydroxycardenolide **X** and its acetate **XI** and in the acetate of 17α-hydroxystrophanthidin (XII), the chemical shift of the C_{18} methyl changes in the narrow range of 8.95-8.88 ppm and is displaced into the weaker field as compared with the field of the C_{18} methyl of strophanthidin by 0.18-0.24 ppm.

Signals of the protons of the butenolide ring. The protons of the C_{21} methylene group of the butenolide ring form an AB system which interacts weakly with the vinyl proton at C_{22} [2]. In the spectra of strophanthidin (I) and its acetate (II) and of strophanthidol (III) and 10β-hydroxy-19-norperiplogenin (VIII) and its acetate (IX), the signals of the C_{21} methylene protons appear in the form of a well-resolved quartet. It follows from the figures in the table that a change in the substituent at C_{10} is not reflected in the chemical shift of the C_{21} protons. The introduction of a double bond in the C_5 position (IV) or a change in the linkage of the A and B rings (V) also has little effect on the shift of the signals of the C_{21} protons. However, a double bond located at C_{14} (VI) and (VII) shifts the signals of the C_{21} protons in the high-field direction by 0.25 and 0.38 ppm. At the same time, the nature of the signals of the AB quartet of these compounds shows that the chemical shifts of the C_{21} protons are extremely close.

A 17α-hydroxyl descreens the C_{21} protons, which shifts their signal into a weaker field.

The signal of the C_{22} vinyl proton, which generally appears in the form of a poorly resolved triplet [6], resonated in the 4.02-4.06 τ region in the cardenolides that we studied. It follows from the table that only the introduction of a 17α-hydroxyl (compounds **X-XIII**), which displaces this signal to the weaker field by 0.56-0.58 ppm, has a marked effect on the shift of this proton.



Signal of the proton at C_{17}. It is known [4, 6] that the signal of the proton at C_{17} appears in the form of a broad multiplet and its chemical shift for the 19-methylcardenolides is 7.14-7.17 τ. In the cardenolides that we studied, the 17α-proton resonates at 7.32-7.37 τ. The position of its signal is almost independent of the nature of this substituent at C_{10}, the linkage of the A/B rings, and the presence of double bonds at C_5 and C_{14}.

Signals of the protons of a C_{19} oxygen-containing substituent. As was to be expected, in all the compounds with a carbonyl function at C_{10} (I, II, IV-VII, XII), the aldehyde proton resonates in a very weak field in the form of a sharp

NMR Spectra of Cardenolides with Oxygen-Containing Functions at C_{10} (τ scale).

Compound	R^{I}	R^{II}	R^{III}	R^{IV}	R^{V}	C_3-H m	$C_{17}-H$ m	$C_{18}-CH_3$ s	$C_{19}-H$	$C_{21}<^{H}_{H}$ centers of the doublets (J = = 18 Hz)	$C_{22}-H$*	Other protons
Strophanthidin (I)	H	CHO	OH	OH	H	5.71	7.34	9.13	−0.26; s	4.83 5.13	4.02	—
Strophanthidin acetate (II)	Ac	CHO	OH	OH	H	4.91	7.34	9.13	−0.28; s	4.83 5.13	4.02	C_3—Ac; 8.17
Strophanthidol (III)	H	CH_2 OH	OH	OH	H	5.76	7.32	9.12	5.63; d (J=10 Hz) 6.23; q (J_1=10 Hz) (J_2=3 Hz)	4.82 5.14	4.02	—
Pachygenin (IV)	H	CHO	Δ^5	OH	H	6.25	7.36	9.19	0.31; s	4.85 5.16	4.04	C_6—H; 4.30; m
Corotoxigenin** (V)	H	CHO	H	OH	H	6.25	7.36	9.20	0.02; s	4.85 5.16	4.04	
Diffugenin [9] (VI)	H	CHO	OH	Δ^{14}	H	5.73	7.34	9.38	−0.28; s	5.16 5.37	4.06	C_{15}—H; 4.84*
Diffugenin acetate (VII)	Ac	CHO	OH	Δ^{14}	H	4.87	7.37	9.40	−0.31; s	5.18 5.39	4.06	C_3—Ac; 8.16; s C_{15}—H; 4.87*
10β-Hydroxy-19-norperiplogenin [10] (VIII)	H	OH	OH	OH	H	5.80	7.32	9.11	—	4.84 5.14	4.04	—
10β-Hydroxy-19-norperiplogenin acetate (IX)	Ac	OH	OH	OH	H	4.91	7.33	9.08	—	4.82 5.13	4.02	C_3—Ac; 8.16; s
19-Norpentahydroxycardenolide (X)	H	OH	OH	OH	OH	5.79	—	8.88	—	4.46 4.94	3.46	
19-Norpentahydroxycardenolide acetate [11] (XI)	Ac	OH	OH	OH	OH	4.91	—	8.89	—	4.46 4.95	3.47	C_3—Ac; 8.11; s
17α-Hydroxystrophanthidin acetate [12] (XII)	Ac	CHO	OH	OH	OH	4.86	—	8.95	−0.31; s	4.48 4.95	3.46	C_3—Ac; 8.17; s

*Broadened singlet

**Rings A and D in the trans-linkage

s) singlet; d) doublet; m) multiplet; q) quadruplet.

singlet. The formation of a Δ^{14} bond or even the introduction of a 17α-hydroxy group has no appreciable influence on the position of this signal. Conversely, a double bond at C_5 and a change in the linkage of the A/B ring (compounds IV and V) shift the signal into a weaker field by 0.57 and 0.28 ppm, respectively.

It is an interesting fact that in the NMR spectrum of strophanthidol (III), because of the nonequivalence of the methylene protons of the C_{19}—CH_2OH group, a one-proton quadruplet is found at 6.23 τ(J_1 = 10 Hz and J_2 = 3 Hz) and also a one-proton doublet at 5.36 τ (J = 10 Hz). When the signals of the hydroxy groups are displaced by means of CF_3COOH, the methylene protons of the C_{19}—CH_2OH group form a well-defined AB system.

Signals of the protons at C_3. In the NMR spectra of the acetates of the compounds that we studied, the protons of the acetyl groups form a narrow singlet at 8.11–8.17 τ. In the cardenolides themselves, the proton at C_3 attached to the same carbon atom as the hydroxyl group is generally descreened and is located in the 5.7–6.3 τ region. On passing to the acetates, it undergoes a paramagnetic shift by 0.9–1.0 ppm [2]. It is known [2] that axial protons attached to the same atom of carbon as an acetate or hydroxyl group resonate in a stronger field than the corresponding equatorial protons in the epimeric compounds. As can be seen from the table, in pachygenin (IV) and corotoxigenin (V) the 3α-axial proton resonates in a stronger field than the 3α-equatorial protons in the 5β-cardenolides. Moreover, the 3α-axial protons in compounds IV and V are subject to diaxial and axial-equatorial interaction with the protons at C_2 and C_4, which leads to a very broad signal with $\Delta f_{1/2}$ = 15–23 Hz. Conversely, the signal of the 3α-equatorial proton is fairly narrow and sharp ($\Delta f_{1/2}$ = 8–9 Hz).

Signals of the protons at the Δ_5 and Δ_{14} bonds. In pachygenin (IV), the resonance signals of the proton at C_6 appears at 4.37τ and has the form of a broad multiplet. The olefinic proton at C_{15} in compounds VI and VII resonates in the 4.84–4.87 τ region in the form of a signal with a half width of 7 Hz, which shows its weak interaction with the protons at C_8 and C_{16}.

Experimental

The spectra were recorded on a JNM-4H-100 instrument with a working frequency of 100 MHz in deuteropyridine. HMDS was used as the internal standard, its signal being taken as 10 (τ-scale). The displacement of the signals of the hydroxyl group was made with the aid of CF_3COOH.

Conclusions

The NMR spectra of 12 cardenolides with oxygen-containing functions at C_{10} has been studied. The chemical shifts of the signals of the protons of the C_{18} angular methyl group, a butenolide ring, and some other protons have been discussed as functions of the structural features of the individual compounds.

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