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CARBON-13 NUCLEAR MAGNETIC RESONANCE SPECTRA OF CARDENOLIDES

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It has been demonstrated recently that natural-abundance ^{13}C NMR spectroscopy is extremely useful for investigating stereochemical and mechanistic problems in steroid chemistry (1). Although several papers have presented correlations of structure with ^{13}C NMR spectra for steroids having various types of ring junctions, such studies have not yet been made for biologically important cardenolides (2). In this paper, we report a complete ^{13}C NMR analysis (3) for the carbons of several cardenolides (I-X). Cardenolides all occur as plant glycosides, and therefore, the present ^{13}C NMR spectroscopic data will be useful for determining their structure and sequence, and also those of related natural products, without hydrolytic or enzymatic cleavage of their sugar moieties (4).†

Application of chemical shift theory (5), single-frequency off-resonance decoupling (SFORD), and noise off-resonance decoupling, and comparison with the spectra of structurally related compounds led to the assignments shown in the TABLE.

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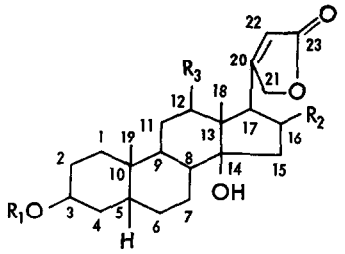
† Partially-relaxed-Fourier-transform experiments on some steroidal trisaccharides indicated that relaxation times in a mixed solvent of $CDCl_3$ and CD_3OD (1.5 : 1) are markedly shorter than those reported for a disaccharide at comparable concentrations in an aqueous solution (6). Detailed results will be presented in a forthcoming paper.



I, $R_1 = R_2 = R_3 = H$: digitoxigenin

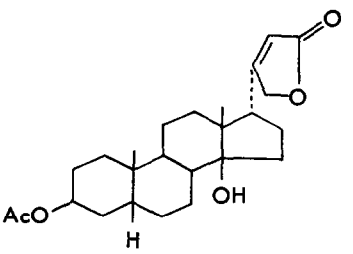
II, $R_1 = R_3 = H$; $R_2 = OH$: gitoxigenin

III, $R_1 = R_3 = H$; $R_2 = OAc$

IV, $R_1 = Ac$; $R_2 = OAc$; $R_3 = H$

V, $R_1 = Ac$; $R_2 = R_3 = H$

IX, $R_1 = R_2 = H$; $R_3 = OH$: digoxigenin



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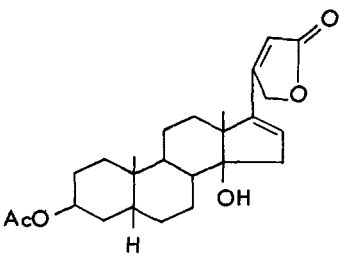
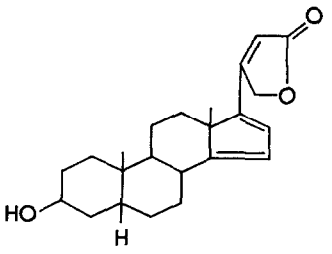
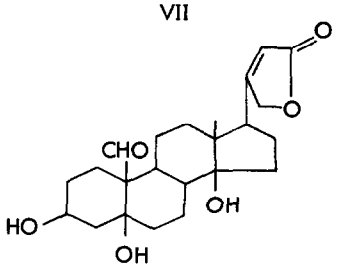


VII



VIII



X: strophanthidin

Compared with A/B-cis C/D-trans steroids (1b, 1c), the major ^{13}C NMR differences for the cardenolides are the expected shieldings for C-7, C-9, and C-16 and deshieldings for C-8, C-13, C-14, and C-15. The upfield shifts for the C-7 and C-9 signals are due to steric interaction between the axial hydrogens at these carbons and the C(14)-C(15) bond. Due to the equatorial β-effect of the C-14β hydroxyl group, the highest-field methine carbon signal does not arise from C-8 as in other steroids (1).

Chemical shift changes attendent with acetylation yielded the shift values for C-2, C-4, C-15, and C-17. Being unaffected by stereochemical changes, C-6, C-7, and C-11 varied little in their chemical shifts through most of the series. Of these signals, the C-6 signal is at the lowest field, whereas the C-7 and C-11 signals are undifferentiable in several compounds. While the axial hydrogens of C-11 and C-7 are

TABLE

^{13}C Chemical Shift Data on Cardenolides (δ in ppm downfield from TMS)

	I	II	III	IV	V	VI	VII	VIII	IX	X
C-1	30.0	30.0	30.0	30.7	30.8	30.8	30.8	30.7	30.0	24.8
C-2	28.0	28.0	27.9	25.2	25.4	25.3	25.4	27.9	27.9	27.4[a]
C-3	66.8	66.8	66.8	71.1	71.4	71.3	71.3	66.7	66.6	67.2
C-4	33.5	33.5	33.4	30.7	30.8	30.8	30.8	33.5	33.3	38.1
C-5	35.9[a]	36.4	36.4	37.2	37.4	37.4	37.3	36.8[a]	36.4	75.3
C-6	27.1	27.0	26.9	26.6	26.8	26.8	26.6	26.6	26.9	37.0
C-7	21.6[b]	21.4[a]	21.2[a]	20.9[a]	21.6	20.6[a]	20.2[a]	24.0	21.9	18.1[b]
C-8	41.9	41.8	41.8	41.6	41.8	41.5	41.2	36.7[a]	41.3	42.2[c]
C-9	35.8[a]	35.8	35.9	35.8	36.1	36.2	36.8	45.1	32.6	40.2[c]
C-10	35.8	35.8	35.6	35.4	35.8	35.5	35.4	36.2	35.5	55.8
C-11	21.7[b]	21.9[a]	21.3[a]	21.4[a]	21.6	21.2[a]	21.3[a]	21.4	30.0	22.8[b]
C-12	40.4	41.2	41.0	40.9	40.3	31.3	40.6	37.7	74.8	40.2
C-13	50.3	50.4	50.7	50.5	50.3	49.5	52.6	54.2	56.4	50.1
C-14	85.6	85.2	84.1	83.8	85.6	86.1	85.7	146.3[c]	85.8	85.3
C-15	33.0	42.6	39.5	39.3	33.0	31.3	38.8	108.3[d]	33.0	32.2
C-16	27.3	72.8	75.0	74.7	27.3	24.8	133.8	135.8[d]	27.9	27.5[a]
C-17	51.5	58.8	56.8	56.6	51.5	48.9	161.2	158.0[c]	46.1	51.4
C-18	16.1	16.9	16.1	16.1	16.0	18.5	16.6	20.1	9.4	16.2
C-19	23.9	23.9	23.9	23.8	23.9	24.0	24.1	24.0	23.8	195.7
C-20	177.1[c]	171.8[b]	171.5[b]	171.5[b]	177.1[a]	173.6[b]	172.8[b]	173.5[b]	177.1[a]	177.2[d]
C-21	74.5	76.7	76.8	76.5	74.7	74.8	72.6	72.1	74.6	74.8
C-22	117.4	119.6	121.3	121.1	117.4	116.6	111.7	119.5	117.0	117.8
C-23	176.3[c]	175.3[b]	175.8[b]	175.4[b]	176.3[a]	175.8[b]	176.3[b]	176.8[b]	176.3[a]	176.6[d]

$OCO\underline{C}H_3$, 21.3 ± 0.3; $O\underline{C}OCH_3$, 171.4 ± 0.4 ppm in III-VII.

[a, b, c, d] Values in any vertical column may be reversed.

involved in two 1,3-diaxial interactions, the C-6 axial hydrogen suffers steric compression only from the C-19 methyl group. The expected consequence of introduction of the C(14) : C(15) double bond in VIII and the C-12β hydroxyl group in IX differentiates the methine carbons, C-8, C-9, and C-5, the latter being unaffected. Differentiation of the signals of C-3, C-14, C-16, and C-23 depended on SFORD (1a) experiments and acetylation effects.

The ^{13}C NMR data on strophanthidin (X) are in consonance with assignments of the signals for the other compounds presented here. The C-5β hydroxyl group in X unsymmetrically deshields the C-4 and C-6 methylene carbons owing to differences between axial and equatorial β-effects, respectively. The assignment of these signals, as well as that of the C-3 signal, was made from comparison with those in the spectra of some glycosides.†

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