

Circular Dichroism of Cardenolides [1]

Helmut Ripperger, Claus Lindig¹⁾, and Günther Snatzke^{†, 2)}

Halle/Saale, Institute of Plant Biochemistry

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Abstract. The relationship between structure and circular dichroism was studied for a series of cardenolides including

some compounds with saturated lactone ring.

The chiroptical properties of a few cardenolides have already been studied [2–6]. The syntheses of a large variety of such compounds gave the opportunity to investigate the relationship between structure and circular dichroism (CD) in detail. As problematic positions and shapes of the nodal surfaces of the relevant molecular orbitals of enones in five-membered rings have to be considered, application of the qualitative MO theory of the CD [7] of cardenolides with a planar butenolide ring seems to be very difficult. Furthermore, the CD is the weighed sum of the Cotton effects of all conformations differing by the torsional angle C-13, C-17, C-20, C-22, whose ratios in turn may be determined by the substituents at C-12, C-16, C-17 *etc.* Therefore, we have to confine ourselves to a publication of our experimental results omitting detailed theoretical considerations. Such data are useful for empirical comparisons with new structures [8]. The present publication was delayed, firstly, because of industrial interests inhibiting the cooperation of the authors and, secondly, by the death of one of the authors.

Cardenolides show an $n \rightarrow \pi^*$ Cotton effect around 240 nm and a $\pi \rightarrow \pi^*$ effect around 220 nm (Table 1). In general, compounds of the digitoxigenin type possess a positive $n \rightarrow \pi^*$ effect ($\Delta\epsilon$ ca +4) and a negative $\pi \rightarrow \pi^*$ effect ($\Delta\epsilon$ ca -1) (cf. **1** – **3**, **5**, **6**). If an acetoxy group is present, then it contributes also to the CD at 220 nm. Usually this effect is small ($|\Delta\epsilon_{\max}| < 1.5$, e.g. for 3β -acetoxy- 5β -steroids $\Delta\epsilon_{\max} = -0.17$ at 212 nm in methanol) [9], and since one cannot separate these two Cotton effects, differences in the CD at 220 nm of two compounds smaller than ± 1.5 cannot in this case be taken into account.

The technique of low-temperature CD measurement has been introduced to study conformational equilibria. Investigations with digitoxigenin 3-acetate (**1**) revealed (Table 1) that the size of the $n \rightarrow \pi^*$ CD does not change between +20 °C and -140 °C. Such an independence of CD of temperature can be explained at least in two ways: (1) Either only one conformer is present (or predominant strongly) or (2), two (or more)

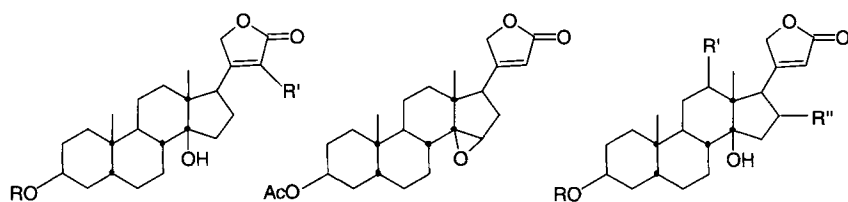
Table 1 CD Data of Cardenolides

Compound	λ_{\max} [nm] ($\Delta\epsilon_{\max}$)	solvent ^{a)} (temp. ^{b)})
1	239 (+3.80)	
	242 (+3.43), 206 (-3.2 °)	EPA ^{d)} (+20 °C)
	239 (+3.06), 207 (-5.5 °)	EPA ^{d)} (-60 °C)
	240 (+3.34), 213 (-5.9 °)	EPA ^{d)} (-100 °C)
	239 (+3.42), 208 (-5.3 °)	EPA ^{d)} (-140 °C)
2	241 (+4.53), 221 (-1.2)	
3	238 (+3.40), 216 (-1.6)	
4	217 (+5.3)	
5	241 (+2.96), 214 (-2.3)	
6	239 (+2.82), 217 (-0.9)	
7	219 (+3.8)	
8 [14]	219 (+4.0)	
9	216 (+5.6)	
10 [14]	227 (-2.8)	
11 [15]	223 (-2.9)	
12	241 (+1.73), 209 (-4.2)	
13	243 (-1.97), 205 (-7.2)	
14	248 (-1.65), 221 (+1.5)	
15 [15]	225 (-3.7)	
16	223 (-2.4)	
17	239 (-4.39), 216 (+2.7)	
18	239 (+2.59), 217 (-2.7)	
20	242 (+7.75), 220 (-1.1)	
21	244 (+2.62), 212 (+1.9)	
22	242 (+6.11), 210 (+3.8)	
23	209 (+13.3)	
24	217 (+4.7)	
25	210 (-11.3)	
26	258 (-0.72), 216 (+13.3)	
27	249 (+1.73), 212 (-11.6)	
28	215 (-0.9)	
29	218 (+0.9)	

^{a)} No specification means ethanol (96%); ^{b)} No specification means room temperature; ^{c)} Noise > 10% of the signal; ^{d)} Ether-isopentane-ethanol (5:2:2)

¹⁾ Former coworker of the Central Institute of Molecular Biology, Academy of Sciences of the GDR, Berlin-Buch

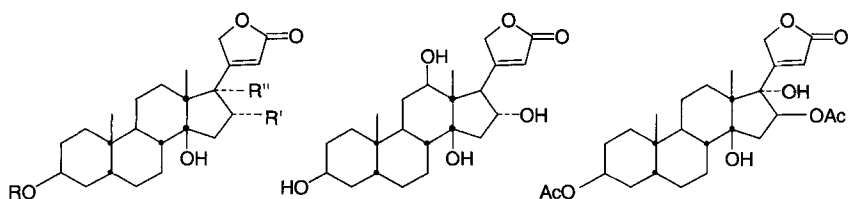
²⁾ Former professor at the Department of Structure Chemistry, University of Bochum



1 R = Ac, R' = H
2 R = H, R' = Me

3

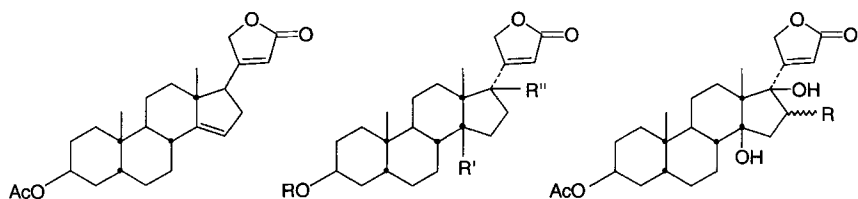
4 R = Ac, R' = OAc, R'' = H
5 R = Ac, R' = H, R'' = OAc
6 R = H, R' = OH, R'' = H
7 R = H, R' = OH, R'' = OH
8 R = Me, R' = H, R'' = OMe
9 R = H, R' = H, R'' = OH



10 R = Me, R' = OMe, R'' = H
11 R = H, R' = OH, R'' = H
12 R = Ac, R' = OAc, R'' = H
13 R = Ac, R' = OAc, R'' = OH
14 R = Ac, R' = H, R'' = OH

15

16



17

18 R = H, R' = OH, R'' = H
19 R = H, R' = H, R'' = H
20 R = Ac, R' = OH, R'' = OH

21 R = α -OAc
22 R = β -OAc

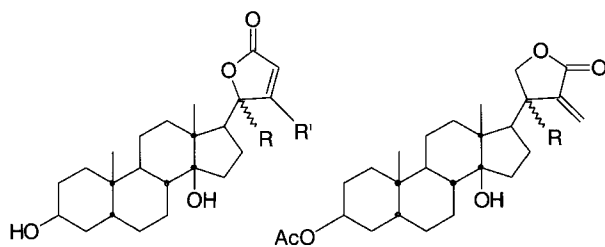
conformers exist which all have the same energy. Much less probable is the case of two conformations of different energy, whose CDs are of the same magnitude. NOE measurements (A. Porzel, H. Ripperger, unpublished results) strongly advocate for the first explanation [torsional angle C-13, C-17, C-20, C-22 approximately -100°]. Concerning the short wavelength effect the high signal to noise ratio made the interpretation of the apparent increase of the negative CD by lowering the temperature less reliable. In addition the conformation of the acetoxy group might play a role.

The presence of a 12β -hydroxy (**6**), 16β -acetoxy (**5**) or 22 -methyl group (**2**) or replacement of the 14β -hydroxy group by a $14\beta,15\beta$ -epoxy ring (**1**→**3**) does not change the CD considerably. This indicates that the substitutions do not appreciably change the preferred conformation of the side chain. For the 22 -methylcardenolide **2** this statement agrees with conclusions drawn from NOE measurements (A. Porzel, H. Ripperger, unpublished). Introduction of a 12β -acetoxy (**4**), 16α -hydroxy (**11**), 16α -methoxy (**10**), 16α -acetoxy (**12**), 16β -hydroxy (**9**), 16β -methoxy (**8**) or 17α -hydroxy group (**14**) causes a large change of the CD. The elimination of the 14β -hydroxy group and introduction of a 14 -double

bond (**1**→**17**) causes sign inversion of both Cotton effects. Introduction of a 17β -hydroxy group in $17\beta H$ -digitoxigenin (**18**→**20**) causes a large change of the CD, whereas replacement of the 14β -hydroxy group by hydrogen (**18**→**19**; peak of the optical rotatory dispersion curve of **19**, measured in dioxan: $[\Phi]_{260} = +1090^\circ$ [2]) did not change the sign of the $n \rightarrow \pi^*$ Cotton effect. A large change of the CD could be explained either by alteration of the C-13, C-17, C-20, C-22 torsional angle or by direct influence of the introduced substituent.

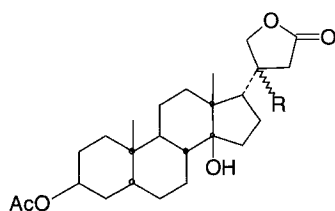
From three examples of pentenolides with allylic oxygen Beecham [10] concluded that the influence of this oxygen on the $\pi \rightarrow \pi^*$ CD is similar to that observed with related chromophors. This means, right-handed chirality in the allylic oxygen-olefinic double bond system O-C-C=C results in a strongly positive contribution to the CD and left-handed chirality in a strongly negative one. This should also be valid for the butenolides **23**–**25**, in which the allylic oxygen is located in the ring. The positive $\pi \rightarrow \pi^*$ CD of **23** and **24** and the corresponding negative effect of **25** indicated a quasi-equatorial conformation of the steroid nucleus with regard to the butenolide ring. The reduced size of the effect of **24** in

comparison with **23** is explained by the reduced dihedral angle of the C–O and C=C bonds by the presence of the β -methyl group of the butenolide **24**.



23 R = β -H, R' = H
24 R = β -H, R' = Me
25 R = α -H, R' = H

26 R = β -H
27 R = α -H



28 R = β -H
29 R = α -H

26 and **27** are α -methylene- γ -lactones with cisoid disposition of the carbonyl and olefinic double bonds opposed to the transoid disposition so far discussed. According to ref. [10] (cf. [11]), right-handed chirality of the chromophore corresponds to a positive $n \rightarrow \pi^*$ Cotton effect and left-handed to a negative one. The signs of the $n \rightarrow \pi^*$ Cotton effects of **26** and **27** indicated quasi-equatorial conformations of the steroid nuclei with regard to the lactone ring.

In saturated γ and δ -lactones, the chirality of the ring determines the sign of the $n \rightarrow \pi^*$ Cotton effect [12, 13] (cf. [11]). The negative sign for **28** and the positive for **29** were in

accordance with a quasi-axial conformation of the steroidal β -substituent of the lactone ring.

Experimental

The CD data were measured at concentrations of 0.1–0.2 mg/ml with the dichrograph model CD-185 from ISA-Jobin-Yvon-Jouan.

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Address for correspondence:

Dr. habil. H. Ripperger
 Institute of Plant Biochemistry
 Weinberg 3
 D-06120 Halle (Saale)