

CIRCULAR DICHROISM OF SOME STEROIDAL α -KETOLS AND THEIR ACETATES

J. R. BULL and P. R. ENSLIN

National Chemical Research Laboratory, South African Council for Scientific and Industrial Research,
Pretoria, Republic of South Africa

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Abstract—An examination of the CD spectra of certain steroidal α -ketols and their acetates revealed instances where the Cotton effect of the ketone $n \rightarrow \pi^*$ transition does not obey the octant rule. This was discussed in terms of the conformational preferences of the α -substituents. The relevance of these results to earlier configurational assignments on A-ring α -ketols in the cucurbitacin series was assessed.

An α -ketol grouping is present in many natural products. The configuration of the OH group in cyclic α -ketols may often be assigned with the aid of physical methods such as UV, IR and NMR spectroscopy where well-known shift rules have been developed¹ to discriminate between axial and equatorial substituents. However, as a result of non-bonded interactions across rings containing one or more trigonal C atoms, a definite assignment is often unreliable without information about the conformation of the ring containing the α -ketol function. The cucurbitacins exemplify this difficulty and recently CD measurements were made on two isomeric 3-hydroxy-2-ketones and one of two possible 2-hydroxy-3-ketones.² The amplitudes of their ketone $n \rightarrow \pi^*$ Cotton effects differed considerably, and this led to conclusions being drawn about the conformation of the A-ring and the configuration of the α -ketol OH-group in these compounds.

Previous studies^{3, 4} on the ORD of steroidal α -ketols have usually been carried out on the corresponding acetates, since the possibility that intramolecular H-bonding could lead to distortion of the shape of participating carbonyl orbitals, was recognised as a complicating factor in the free α -ketols.³ In this event it would be expected that strong solvent effects would be obtained. The consequent difficulty in interpreting Cotton effects of free α -ketols cannot however, be avoided by performing all measurements on the corresponding acetates instead, since no information is available on possible vicinal effects resulting from weak coupling between proximate ketone and acetoxy $n \rightarrow \pi^*$ transitions (cf. evidence for such coupling in the ultraviolet spectra of 4-acetoxyisopulegones⁵).

With this in mind we undertook a study of model steroidal α -ketols and their acetates in the cholestane series. The CD spectra were determined in a polar (methanol) and a non-polar (hexane) solvent for both the ketone and acetoxy $n \rightarrow \pi^*$ transitions. The spectra of all compounds were determined on the same instrument under strictly defined conditions. Steroidal C- and D-ring α -ketols were not considered because of conformational uncertainties in these compounds.^{3, 4}

The results are presented in Table 1. The absence of any major conformational distortions in the rings containing the ketol or ketol acetate function was evident from

the observed shifts in $\Delta\epsilon_{\max}$ of the ketone $n \rightarrow \pi^*$ transition. Thus in general, an axial OH-group caused a bathochromic shift greater than that of an axial OAc-group, while an equatorial OH-group caused a hypsochromic shift greater than that of an equatorial OAc-group. This is in accordance with the shift rules.¹ The contribution of the α -substituent of each compound to the ketone $n \rightarrow \pi^*$ Cotton effect is presented in the Table as $\Delta\Delta\epsilon_{\max}$ values.

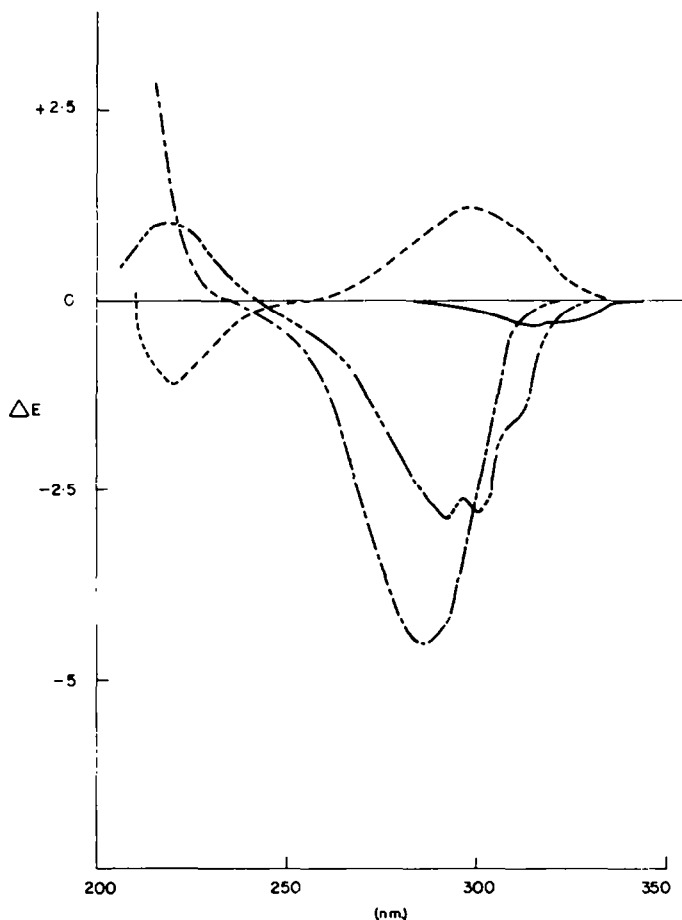


FIG. 1 CD spectra in hexane solution, ——— 5-hydroxy-5 β -cholestan-4-one, - - - - 5-acetoxy-5 β -cholestan-4-one, - · - · - 5-hydroxy-5 β -cholestan-6-one, - - - - 5-acetoxy-5 β -cholestan-6-one

The octant rule⁶ dictates that an α -substituent will make a significant contribution to the ketone $n \rightarrow \pi^*$ Cotton effect only when in an axial orientation, and the sign of this contribution will be determined by the sign of the octant in which the substituent falls. Since equatorial α -substituents lie near a symmetry plane their contributions will be insignificant.

The results for three α -ketols with axial OH-groups, *viz.*, the 5 α -hydroxy-4-one, the 5 β -hydroxy-4-one and the 5 α -hydroxy-6-one, show that in each case the α -substituent makes a significant contribution of the predicted sign.

Anomalous results were obtained for two α -ketols with equatorial OH-groups. In hexane solution where strong intramolecular H-bonding is expected, the spectra of 3 β -hydroxy-5 α -cholestan-4-one and the 5 β -hydroxy-6-one revealed an unmistakable contribution due to the equatorial substituent. This effect in methanol, where the polar nature of the solvent would be expected to weaken intramolecular hydrogen bonds, was no longer significant in the 3 β -hydroxy-4-one, but was still apparent in the 5 β -hydroxy-6-one. The influence of intramolecular H-bonding is also evident as strong end absorption at 210–215 nm in the CD spectra of these compounds, particularly in hexane solution. The presence of this end absorption in the equatorial α -ketols studied here appears to be diagnostic for intramolecular H-bonding.

Significant changes were observed in the corresponding OAc-derivatives where H-bonding is no longer a consideration. The axial OAc-group of the 5 α - and 5 β -acetoxy-4-ones and the 3 α -acetoxy-2-one makes a strong contribution to the ketone Cotton effect, but of a sign opposite to that predicted by the octant rule (anti-octant contribution). The sign of the ketone Cotton effect in the 5 α -acetoxy-6-one accords with prediction, but the magnitude of the effect is strongly reduced by comparison with that of the corresponding OH-compound. The effect of this anti-octant behaviour of axial OAc-groups is demonstrated forcefully in the case of 5-hydroxy-5 β -cholestan-4-one where acetylation of the tertiary OH-group leads to reversal of the sign of the ketone $n \rightarrow \pi^*$ Cotton effect (Fig. 1).

The CD spectra of 3 β -acetoxy-5 α -cholestan-2-one and 3 β -acetoxy-5 α -cholestan-4-one and the data reported in the literature^{3, 4, 7} for various A-ring equatorial α -ketol acetates are in agreement with the octant rule since these OAc-groups contribute insignificantly to Cotton effects of the corresponding parent ketones. The result reported here on the 5 β -acetoxy-6-one is however, an important exception since this equatorial OAc-group makes a demonstrable positive contribution in both hexane and methanol solutions.

The results obtained for the acetate $n \rightarrow \pi^*$ transitions are also presented in Table 1. The ORD spectra of various steroidal acetates have been reported by Jennings *et al.*,⁸ but no data on amplitudes are yet available for comparison with the CD results presented here. Furthermore, it is evident that the conformation of the OAc-group relative to the attached ring should differ in isolated acetates and α -ketol acetates since steric and dipole–dipole interactions will influence this functional group in the latter class of compounds. In this study the compounds containing an equatorial OAc-group showed, with one exception (q.v.), only end absorption, but the axial α -ketol acetates exhibited clear maxima for the acetate $n \rightarrow \pi^*$ transition. A striking result is the unexpectedly high $\Delta\epsilon$ value (+2.4) observed for the 5 α -acetoxy-4-one in methanol.

DISCUSSION

In an attempt to resolve certain anomalies in the experimental results, space-filling models (Courtauld Atomic Models) of the above α -ketols and their acetates were examined. This led to some interesting observations pertaining to the rotational abilities of the α -substituents. Free rotation of the OH-groups of all the α -ketols is possible; but in axial cases, 1,3-diaxial interactions suggest some conformational preference. This preference must be strengthened by the known, albeit weak OH \cdots π -C H-bond.⁹ In those compounds with an equatorial OH-group the strong OH \cdots n-O H-bond⁹ should result in a pronounced conformational preference.

TABLE I

Compound	CD in Methanol			CD in Hexane		
	$\Delta\epsilon$ (nm)	Shift* (nm) of ketone $n \rightarrow \pi^*$ band	$\Delta\Delta_{\max}$ contribution ^b	$\Delta\epsilon_{\max}$ (nm)	Shift* (nm) of ketone $n \rightarrow \pi^*$ band	$\Delta\Delta_{\max}$ contribution ^b
3 β -OAc-5 α -cholestan-2-one ^{d, e}	+3.2 (289)		O	+2.25 (300)		O
	-1.1 (210 ^f)			+2.35 (292)		
3 α -OAc-5 α -cholestan-2-one ^{d, e}	+1.45 (300)		AO	-1.0 (210 ^f)		AO
	-1.0 (215 ^g)			+1.0 (314)		
5 α -cholestan-4-one ^d				+1.05 (305)		
	-2.1 (291)			-1.0 (215 ^g)		
				-1.0 (315)		
				-1.6 (304)		
3 β -OH-5 α -cholestan-4-one	-1.95 (289)	2 ⁻	+0.15	-1.6 (296)	14 ⁻	-0.65
	+0.35 (215 ^g)			-2.25 (286)		
3 β -OAc-5 α -cholestan-4-one	-2.1 (291)	0	0.0	+0.5 (215 ^g)	5 ⁻	0.0
	+1.25 (210 ^f)			-1.5 (299)		
5-OH-5 α -cholestan-4-one	-0.85 (302)	11 ⁺	+1.25, O	-1.2 (210 ^f)	6 ⁺	+0.5, O
	-2.9 (294)	3 ⁺	-0.8, AO	-1.1 (306)	1 ⁻	-0.7, AO
5 β -cholestan-4-one ^d	+2.4 (214)			-2.3 (299)		
	+0.20 (284)			+1.2 (222)		
5-OH-5 β -cholestan-4-one	-0.9 (306)	22 ⁺	-1.1, O	+0.25 (307)	19 ⁺	-0.55, O
				+0.25 (297)		
				-0.25 (326sh)		
				-0.30 (316)		

5-OAc-5 β -cholestan-4-one	+1.05 (297) -1.2 (220)	13 ⁺	+0.85, AO	+1.2 (300) -1.05 (220)	2 ⁺	+0.95, AO
5 α -cholestan-6-one	-1.60 (292)			-0.7 (315) -1.2 (305)		
5-OH-5 α -cholestan-6-one	-2.55 (303)	11 ⁺	-0.95, O	-1.1 (296)	8 ⁺	-0.25, O
5-OAc-5 α -cholestan-6-one	-1.9 (293) -0.8 (220)	1 ⁺	-0.3, O	-1.45 (308) -1.2 (302sh) -1.35 (296)	1 ⁻	-0.15, O
5 β -cholestan-6-one	-4.2 (294)			-0.55 (222) -3.2 (308)		
5-OH-5 β -cholestan-6-one	-5.1 (288) +2.45 (215 ^c)	6 ⁻	-0.9	-3.4 (299) -4.4 (286)	17 ⁻	-1.2
5-OAc-5 β -cholestan-6-one	-3.7 (293) +0.95 (220)	1 ⁻	+0.5	+2.9 (215 ^c) -2.6 (300) -2.75 (293)	7 ⁻	+0.65
4,4,14 α -trimethyl-19(10 \rightarrow 9 β)abeo-10 α -pregn-5-en-2,11,20-trione	+6.45 (297)			+1.15 (220)		
4,4,14 α -trimethyl-19(10 \rightarrow 9 β)abeo-10 α -pregn-5-en-3,11,20-trione	+6.65 (295) +12.0 (214)					
Anhydro-22-deoxocurbitacin D	+4.15 (302) +16.0 (216)					

^a bathochromic + hypsochromic -.

^b "O" octant contribution, "AO" anti-octant contribution.

^c end absorption.

^d supplied by Prof. W. Klyne and Dr. C. H. Robinson.

^e The results on these compounds should be compared with an ORD amplitude of $a = +121$ for the parent ketone in dioxan solution.⁴

A remarkable feature of the axial OAc-compounds is the almost complete restriction of rotation about the —C—O— bond of the OAc-group. In the equatorial OAc-compounds such rotation is also severely contained, but not to the same extent as axial cases. There is however, one notable exception, *viz.*, 5-acetoxy-5 β -cholestan-6-one, where rotation about the —C—O— bond of the equatorial (relative to the 6-ketone) α -substituent is completely frozen since this function is at a *cis*-ring junction and is therefore axial relative to the A-ring. Interestingly, this is also the one α -ketol acetate in which an equatorial OAc-group makes a significant contribution to the ketone $n \rightarrow \pi^*$ Cotton effect.

Due to the severe rotational barrier imposed upon OAc-groups in these compounds, two discrete conformers appear to be possible, in one of which the OAc-carbonyl group is orientated toward the ketone, and in the other, away. It is therefore feasible that in the former instance the proximity of the two optically active functions may lead to coupling of their respective $n \rightarrow \pi^*$ transitions. It is considered, however, that a more important factor may be perturbation of the ketone $n \rightarrow \pi^*$ transition by the lone pairs on the "ether" oxygen of the adjacent OAc-group and that the spatial orientation of these lone pairs relative to the ketone may be decisive in determining anomalous behaviour.

Since the models demonstrate that conformational preferences of the α -substituents exist, and further that the constrained orientation of the —C—O— oxygen lone pairs in each α -ketol acetate differs from that preferred in each corresponding α -ketol, this difference may well influence the amplitude and sign of the ketone $n \rightarrow \pi^*$ transition. Consequently, any factor which alters the lone pair orientation in a sterically restricted environment will result in an observable effect upon this transition whether the α -substituent is axial or equatorial. Before more is known about the exact nature of electronic perturbations of an optically active $n \rightarrow \pi^*$ transition by nearby lone pairs, the predictive aspects of this influence cannot be ascertained with certainty.

A pertinent result is that reported recently by Snatzke and Veithen,¹⁰ who observed a large difference in amplitude between the CD maxima of 5-amino-5 α -cholestan-6-one and its N-acetyl derivative. Here also, a difference in orientation of the nitrogen lone pairs of the two derivatives relative to the CO-group could play a role.

The findings presented here prompted a re-appraisal of the CD data on the three cucurbitacin α -ketols and their acetates reported in an earlier publication.² For comparison the CD spectra of the 2,11,20- and 3,11,20-triketones derived from cucurbitacin B¹¹ were determined (Table 1). The latter compound exhibited at 214 nm a strong band ($\Delta\epsilon$ 12.0) which was absent in the spectrum of the 2,11,20-triketone. This band is also present in the spectrum of anhydro-22-deoxocucurbitacin D, a 2-hydroxy- Δ^5 -3-one, and is ascribed to the olefinic $\pi \rightarrow \pi^*$ transition which is enhanced in amplitude by interaction with the 3-ketone.¹² This interaction in the β,γ -unsaturated ketone system must influence the $n \rightarrow \pi^*$ transition of the CO-group, and consequently the previous configurational assignment of the 2-OH-group in anhydro-22-deoxocucurbitacin D cannot yet be substantiated.

In the case of the two cucurbitacin-derived 3-hydroxy- Δ^5 -2-one epimers, the double bond is in the (x, z)-nodal plane of the CO-group and is therefore not expected to exert any direct influence upon the chromophore. An inspection of space-filling models of the proposed² structures, *viz.*, 3 α -acetoxy-2-one (A-ring in chair conformation) and 3 β -acetoxy-2-one (A-ring in twist conformation) shows that rotation about the

—C—O— bond in the two equatorial OAc-groups is restricted but not frozen. Furthermore, it was shown in the earlier study² that the amplitude of the ketone $n \rightarrow \pi^*$ transition in the free α -ketols did not change significantly when the products were acetylated. These data considered in conjunction with the present results do not contradict the earlier configurational assignments for the epimeric 3-hydroxy- Δ^5 -2-ketones. It is evident, however, that in view of the subtle influences exerted upon the ketone $n \rightarrow \pi^*$ transition by α -OH- and α -OAc-groups, conclusions based upon such results alone, do not constitute unequivocal proof of the configuration, and further work is clearly necessary.

EXPERIMENTAL

CD spectra were determined at 20°, in a 1 cm cell with a Jasco ORD/UV-5 instrument with CD attachment, at a scale factor of 0.01. 5 α -Cholestan-3-one was employed as a standard substance ($\Delta\epsilon$ in dioxan, +1.2), and the stability of the instrument was checked daily by running spectra of the standard before and after every batch of measurements. This was considered essential before any significance could be attached to small differences in amplitude between some of the compounds discussed.

Unless otherwise stated in the Table, the compounds investigated here were prepared by standard methods and their physical constants were in good agreement with those reported in the literature.

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