

Chiroptical Studies. Part 101.¹ An Empirical Analysis of Circular Dichroism Data for Steroidal and Related *transoid* $\alpha\beta$ -Unsaturated Ketones

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An empirical analysis of c.d. data for steroidal and related *transoid* $\alpha\beta$ -unsaturated ketones substantially confirms existing helicity 'rules' for the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ Cotton effects, and shows that the signs and magnitudes of $\Delta\epsilon$ depend essentially upon the structural class of the bicyclic component containing the chromophore. The third c.d. band, in the region 200—220 nm, has the characteristics expected for the olefinic $\pi_x \rightarrow \pi_y^*$ transition, and is relatively insensitive to the immediate environment of the carbonyl group.

EMPIRICAL analyses of c.d. data for compounds composed essentially of carbocyclic rings have enabled us recently to recognise relationships between structure and chiroptical behaviour which had previously escaped notice. The general procedure, applied to extensive series of compounds with a common chromophore, has been to evaluate the apparent contributions of individual rings, or groups of rings, by making pairwise comparisons of compounds and assuming additivity of contributions from individual rings, or other suitably chosen structural features. In this way we have already analysed c.d. data for saturated ketones (at both the '290 nm' ²⁻⁵ and the '190 nm' ⁶⁻⁸ c.d. bands), olefins,⁹ acetates and acetamides,¹⁰ and seven-membered lactams and lactones.¹¹ The chiral compounds studied were mainly of steroid or similar type. They were chosen deliberately to exclude derivatives in which major contributions were likely to come from the presence of hetero-substituents or unsaturation in the vicinity of the chromophore.

Many workers have discussed the chiroptical behaviour of $\alpha\beta$ -unsaturated ketones,¹²⁻²² which exhibit at least three and in some cases four c.d. bands in the region accessible to measurements in solution (400—185 nm). The two bands of lowest energy ($n \rightarrow \pi^*$, >300 nm; $\pi \rightarrow \pi^*$, ca. 230—260 nm) exhibit signs which were originally thought to be related only to the helicity of the enone moiety (Figure 1),¹⁶ but more recent studies of

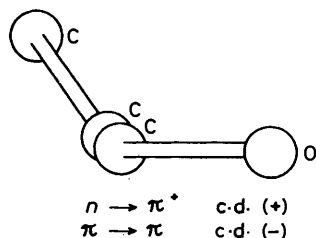


FIGURE 1 Helicity rule for *transoid* $\alpha\beta$ -unsaturated ketones: signs reversed for opposite helicity

steroidal 4-en-3-ones, in particular, have shown that γ -axial substitution (at $\beta\beta$) (Figure 2) can exert a dominant influence.¹⁹ 6β -Chloro- or 6β -bromo-substituents, for example, reverse the signs of the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ c.d. bands, compared with the corresponding unsub-

stituted 4-en-3-one, although apparently having only minor effects on the conformation.

The sign of the c.d. band in the region 200—220 nm. has been tentatively attributed¹⁸ to the 'axial-chirality' effect of axial H or a substituent at the α' -position, adjacent to the carbonyl group. A recent review²⁰ provided some confirmation of these various interpretations, but suggested that further study would be

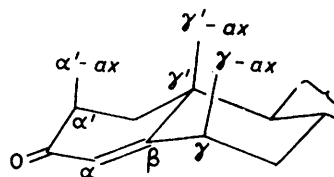


FIGURE 2 Designations of substituent positions in a steroidal 4-en-3-one or similar compound

appropriate, particularly in regard to the 200—220 nm band.

One of the main objectives of the present work has been to identify the structural features which control the 200—220 nm c.d. Accepting that large hetero-atom effects may mask smaller contributions from the structure and chirality of the carbocyclic framework, we have applied our general empirical procedure to analyse all available data for those $\alpha\beta$ -unsaturated ketones which contain no hetero-atoms or polar groups likely to dominate their c.d. The Table contains c.d. data for 52 compounds, most of which fall into easily recognisable classes according to the location of the enone system, and do not have rings which are seriously deformed from the normal chair or half-chair forms by their manner of ring fusion. The present study is limited to compounds of cyclohexenone type.

To aid discussion, the bicyclic fragment containing the $\alpha\beta$ -unsaturated ketone was classified by an extension of the method introduced^{2,3} for saturated ketones, and recently adapted to lactams and lactones.¹¹ With locants appropriate to the cycloalkenone ring (Figure 3), the configuration at the ring junction and the position of the second ring are indicated as if for the nearest corresponding decalone² or hexahydroindanone³ by *t* (*trans*) or *c* (*cis*) followed by the *lower* locant at the

TABLE

C.d. data for *transoid* $\alpha\beta$ -unsaturated ketones ^a

Compound	Solvent ^b	$n \rightarrow \pi^*$	$\pi \rightarrow \pi^*$	$\Delta\epsilon(\lambda/\text{nm})$	
				200—220 nm band	4th band
Class 6t3/6c3					
19-Nor-4-en-3-one types					
17 β -Hydroxyoestr-4-en-3-one (1)	M	-1.6 (318)	+6.6 (240)	+6.9 (ca. 215)	
17 β -Acetoxyoestr-4-en-3-one (2)	M	-2.0 (320)	+7 (240)	+6 (200)	
<i>ent</i> -18-Nor-D-homoandrost-13(17a)-en-17-one (3)	M	-2 (318)	+7 (238)	+5 (215)	
Tricyclic compound (4) ^c	M	-2.8 (319)	+9.9 (238)	{ +5.8 (ca. 213br)	
	H	-1.9 (325 & 338)	+15.2 (229)	{ +4.1 (200sh) +9.9 (217sh) +3.1 (199)	
17 β -Hydroxy-2 β ,17 α -dimethyloestr-4-en-3-one (5) ^d	M	-0.9 (322)	-5.3 (243)	+5.4 (210)	
17 β -Hydroxy-2,2,17 α -trimethyloestr-4-en-3-one (6) ^d	M	-2.05 (322)	+1.3 (240)	+9.8 (210)	
17 β -Hydroxy-6 β -methyloestr-4-en-3-one (7) ^c	E	-0.9 (321)	+4.0 (235)	+1.8sh (206)	
	T	-1.6 (304)	+3.6 (230)	+2.9sh (208)	-2.1 (186)
4-En-3-one types					
Cholest-4-en-3-one (8)	H	-1.6 (339)	+4.7 ^f (231)	+11.1 (206)	ca. 0 (185)
	E	-1.5 (320)	+3.4 ^f (241)	+13.2 (215)	ca. 0 (185)
	T	-2.4 (302)	+4.4sh (248)	+12.8 (223)	+5.8 (200) -3.4! (184)
	1% TFA-H	-1.4 (294)		+5.6 (220)	
17 β -Hydroxyandrost-4-en-3-one (9)	M	-2 (320)	+7 (240)	+11 (220)	
17 β -Acetoxyandrost-4-en-3-one (10)	M	-1.5 (317)	+6.5 ^f (240)	+10.2 (215)	
2 α Methylcholest-4-en-3-one (11)	H	-2.2 (325)	+10.1 (228)	+14 (198)	
* 17 β -Hydroxy-8-methylandrost-4-en-3-one (12)	H	+0.08 (352) -0.51 (312)	-1.65 (248)	+9.9 (212)	
17 β -Acetoxy-4-methylandrost-4-en-3-one (13)	H	-1.4 (326)	+9.8 (240)	+4.9 (212)	-2.5 (192)
	E	-1.5 (321)	+8.4 (246)	+5.1sh (213)	ca. -8 (195)
	T	-2.7 (307)	+8.1 (254)	+5.3sh (220)	+3.3sh (200) -5.3 (185)
6 α -Methylcholest-4-en-3-one (14)	H	-1 (338)	+4 (230)	+8 (210)	
	M	-1 (316)	+3 (235)	+8 (218)	
	E	-1.2 (317)	+5.4sh (233)	+9.7 (211)	
* 2,2-Dimethylcholest-4-en-3-one (15)	{ H	-1.7 (337)	+0.2 (248)	-0.8 (226)	+15.2 (193)
	{ E	-2.1 (323)	-0.6 (244)	+12.3 (209)	
* 2 β -Methylcholest-4-en-3-one (16) ^e	H	+1 (335)	-33 (233)	+14 (198)	
	M	+1 (321)	-29 (246)	+13 (211)	
* 6 β -Methylcholest-4-en-3-one (17)	{ H	0	{ -0.2 (255) +1.8 (230)	+5.8 (214)	
	{ M	+0.7	{ -1.6 (253) +2 (236)	+6 (220)	
Miscellaneous					
* Pentacyclic 4'-en-3'-one (18)	H	-0.75 (336)	+6.7 (231)	-3.8 (209)	
	T	-2.6 (300)	+7.4 (250)	-2.6 (216)	+3.7 (192)
<i>ent</i> -9 β ,10 α -Ergosta-4,22-dien-3-one (19)	H	{ +0.2 (373, 363) -1.0 (322)	+21.6 (235)	+7.7 (200)	
<i>ent</i> -9 β ,10 α -Androst-4-en-3-one (20)	M	{ +0.1 (352) -0.9 (309)	+12.5 (239)	+11 (210)	
5-Methyl-19-nor-5 α -cholest-1(10)-en-2-one (21)	M	ca. -1.2 (313)	ca. +11 (ca. 235)	?	
5-Methyl-19-nor-5 α -androst-1(10)-en-2-one (22)	M	ca. -1.1 (331)	+12.6 (232)	?	
Class 6t4					
<i>ent</i> -17 β -Acetoxy-5 α -androst-3-en-2-one (23) ^a	H	(+)	-10.8 (229)	+7.2 (202)	-2.2 (188)
D-Homo-5 α -androst-17(17a)-en-16-one (24)	H	+0.9 (348)	-7 (228)	+9 (204)	-9 (186)
<i>ent</i> -5 α -Cholest-1-en-3-one (25)	{ H	+0.8 (350)	-8.7 (227)	+7.1 (198)	
	{ M	+0.9 (340)	-8.0 (236)	+5 (204)	
	{ T	+2.0 (322)	-12.1 (242)	+9.3 (206)	
	{ M	+1.4 (336)	-5.4 (232)	+3.5 (202)	
<i>ent</i> -17 β -Hydroxy-5 α -androst-1-en-3-one (26)	{ H	+0.9 (337)	-6.65 (230)	+3.0 (201)	
<i>ent</i> -17 β -Acetoxy-5 α -androst-1-en-3-one (27)	{ M	+1.6 (337)	-15.4 (232)	+11.8 (200)	
	{ H	+1.1 (349)	-13.7 (228)	+10.6 (200)	
<i>ent</i> -17 β -Acetoxy-1-methyl-5 α -androst-1-en-3-one (28)	M	+3.2 (330)	-13.5 (242)	+7.6 (210)	
<i>ent</i> - Δ^1 -3-Oxo-derivative (29) from manoyl oxide ^f	H	+2.5 (351)	-18 (229)	+11.6 (207)	-13.0 (191)
* Friedel-1-en-3-one (30)	H	-0.7 (338)	-9.6 (230)	+13.6 (204)	
Class 6t5					
5 α -Cholest-2-en-4-one (31)	M	-2 (322)	0	+7.3 (195)	
<i>ent</i> -D-Homo-5 α -androst-16-en-17a-one (32)	M	-0.8 (326)	0	+6.6 (207)	
<i>ent</i> -3 β -Acetoxy-17-methyl-D-homo-5 α -androst-16-en-17a-one (33)	M	-0.5 (324)	+0.6sh (237) +1.2sh (223)	+9.2 (194)	
	H	-0.45 (342 & 329)	+1.1 (233)	+12.5 (200)	
17 β -Acetoxy-5 α -androst-2-en-1-one (34)	H	-1.8 (345)	0	+29.7 (198)	
Δ^2 -1-Oxomanoyl oxide derivative (35) ^f	H	-2.3 (343)	+1.3sh (225)	+29.8 (197)	

TABLE (continued)

Compound	Solvent ^b	$n \rightarrow \pi^*$	$\Delta\epsilon(\lambda/\text{nm})$		4th band
			$\pi \rightarrow \pi^*$	200–220 nm ^c band	
Middle ring enones (<i>t4</i> + <i>t2</i>)					
3 β ,17 β -Diacetoxyoestr-5(10)-en-6-one (36)	H	+0.3 (356)	{ -0.5 (255) +1.6 (236)	+6.4 (206)	
3 β -Acetoxy-5 α -cholest-8-en-7-one (37)	T	+0.9 (321)	-1.2 (262)	+5.8 (206)	-7.5 (186)
	H	+0.2 (351)	-8 (241)	+6.6 (210)	+5.7 (194)
	M	+1.5 (328)	-8 (253)	+4.6 (217)	
<i>ent</i> -3 α -Acetoxy-5 β -androst-8-en-11-one (38) ^j	E	+0.9 (335)	-6.3 (252)	+5.2 (212)	
<i>ent</i> -3 β -Acetoxy-4,4-dimethyl-5 α -cholest-8-en-11-one (39) ^k	H	+0.6 (342)	-9.1 (242)	+10.85 (212)	-3.6! (198)
	M	+1.6 (334)	-7.9 (252)	+5.9 (217)	
<i>ent</i> -3 β -Acetoxy-des-D-13 β (H)-androst-5-en-7-one (40)	H	-1.5 (340)	+12.4sh (226)	+20.1 (204)	
	M	{ +0.5 (360) -0.6 (308)	+7.2sh (233)	+11.5 (210)	
<i>ent</i> -3 β -Acetoxy-5 α -cholest-7-en-6-one (41)	D	-4.3 (329)	+20 (241)	-0.7 (213) +1.1 (202)	
	H	-1.7 (339)	+17.6sh (228)	+25.1 (203)	
<i>ent</i> -3 β -Acetoxycholest-5-en-7-one (43) ^l	M	-1 (330)	+3 (240)	+15 (220)	
	E	-2.5 (340)	+6 (240)	+11 (215)	
3 β ,17 β -Dihydroxy-18-nor-D-homoandrost-12-en-11-one (44) ^m	H	-2.0 (340)	+14.8 (230)	+9 (198)	-11 (183)
	E	-2.2 (328)	+11 (236)	+5 (206)	
3 β -Acetoxy-5 α ,25R-spirost-9(11)-en-12-one (46)	H	-1.8 (348)	+15.6 (232)	+9.6 (194)	
	M	-2.3 (326)	+14.7 (238)	+6sh (ca. 215)	
Methyl-11-oxo-18 α -methyl oleanolate 3-acetate (47)	M	-0.4 (305)	+2.9 (250)	+6.1 (216)	
<i>Enones with a cis ring junction</i>					
5 β ,25R-Spirost-3-en-2-one (48) ⁿ	D	-1.2 (335)	-5.5 (235)	+2! (210)	
* 5 β -Cholest-1-en-3-one (49) ^m	E	0	+19 (235)	-10! (200)	
5 β ,25R-Spirost-1-en-3-one (50) ⁿ	D	+0.3 (360)	+19 (235)	?	
		-0.15 (320)			
3 α -Hydroxy-5 β ,14 β -androst-8-en-11-one (51) ^j	M	-0.3 (311)	+8 (245)	-12 (205)	
3 β -Acetoxy-4,4-dimethyl-5 α ,14 β -cholest-8-en-11-one (52) ^k	H	+0.37 (340)	+7.35 (238)	-10.1 (205)	
	M	-0.51 (330)	+5.9 (245)	-5.4 (209)	

* Compound with unusual c.d. features which suggest moderate or severe distortion from the normal conformation.

^a For compounds prefixed by '*ent*-' the signs of $\Delta\epsilon$ have been reversed to correspond to the enantiomer of the natural compound; ! Indicates a limit of measurement, not a maximum. ^b Solvents: M = methanol; H = hexane; E = ethanol; T = 2,2,2-trifluoroethanol; TFA = trifluoroacetic acid; D = dioxan. ^c Sample from Prof. M. Fetizon, Palaiseau, France. ^d J. Nedelec, J. C. Gasc, and R. Bucourt, *Tetrahedron*, 1974, **30**, 3263. ^e Sample from Dr. J. A. Edwards, Syntex, California. ^f $\Delta\epsilon$ Obtained from experimental curve by use of a Du Pont curve resolver. ^g Sample from Prof. W. Reusch, Michigan. ^h Data supplied by Dr. J. K. Gawronski, A. Mickiewicz University, Poznan, Poland. ⁱ Sample from Prof. R. E. Corbett, Otago, N.Z. ^j Personal communication from Dr. R. Viennet, Roussel-Uclaf, Romainville, France. ^k Sample from Dr. R. B. Boar, Chelsea College, London. ^l Refs. 15 and 17. ^m Ref. 15. ⁿ K. Takeda, G. Lukacs, and F. Yasuda, *J. Chem. Soc. C*, 1968, 1041.

junction (*t2* and *t3* assume that the two rings each have the chair or half-chair forms closest to those of the

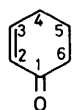


FIGURE 3 Locants for cyclohexenone ring

corresponding saturated bicyclic system; where the resemblance is to a *cis*-fused pair of rings, *c2* or *c3* would be used). The size of the ring carrying the carbonyl group is indicated by a prefix (e.g. 6 for cyclohexenones). Additional rings may be indicated in similar fashion where necessary (cf. extended decalones²).

C.d. Data.—All data in this paper are presented in respect of that enantiomer which, in the absence of any major deformations produced by substituents, would be predicted from Dreiding models to have the cyclohexenone ring essentially in the absolute configuration which permits it to adopt conformations of the type illustrated in Figure 4. The sense of ring twist is such that the 2,3- and 5,6-bond directions define a positive (clockwise) helix, as viewed across the ring. Those experimental data presented with c.d. signs reversed to conform to this standard type are prefixed by '*ent*' in the Table. It will become evident that a few compounds are forced by substituents to adopt configurations different from that represented by Figure 4. It must also be emphasised that the adoption of a standard

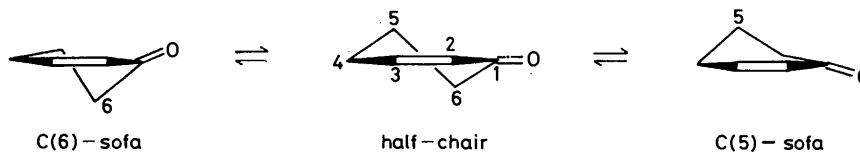


FIGURE 4 Standard configuration of cyclohexenone ring adopted for discussion, with positive ring chirality: three of the possible conformations are illustrated

configuration for the cyclohexenone ring does not imply any particular helicity for the enone moiety; enone helicity is determined by the preferred ring conformation, as indicated in Figure 4.

Compounds containing a cyclohexenone fused to a cyclohexane ring fall into four classes according to the location of the chromophore (Figure 5). Most of the

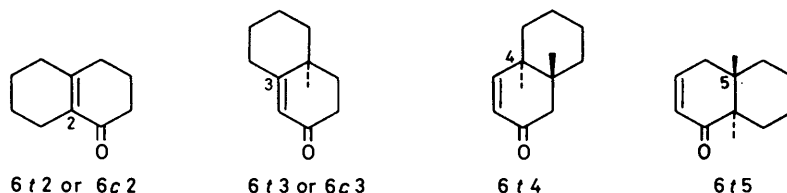


FIGURE 5 Classification of bicyclic systems

compounds are coded here as belonging to the 't' series, except where there are clear indications to the contrary. Some of the formulae are drawn in an unconventional manner to assist in comparisons of related types. Within each class there are general regularities with regard to signs of c.d. bands in each of the three wavelength ranges above 200 nm. Numerical values of $\Delta\epsilon$ cluster about a norm in some cases, but show fairly wide variations in others. Some of the more extreme values can be attributed to special patterns of substitution (e.g. 4,4-dimethyl) which would be expected to cause conformational changes. The following sections deal first with those compounds where the enone is in a terminal ring and then with those where it forms part of a 'middle' ring of a polycyclic system.

Class 6t3 (including Steroidal 4-En-3-ones).—The normal pattern comprises a rather weak negative c.d. band ($\Delta\epsilon$ ca. -1 to -2) above 300 nm ($n \rightarrow \pi^*$), a strong positive c.d. band near 240 nm ($\Delta\epsilon$ ca. $+4$ to $+10$), and another strong positive band ($\Delta\epsilon$ ca. $+5$ to $+13$) which lies in the range 220–200 nm, and is often not clearly resolved from the 240 nm band. In some cases a fourth c.d. band of negative sign is observed below 200 nm.

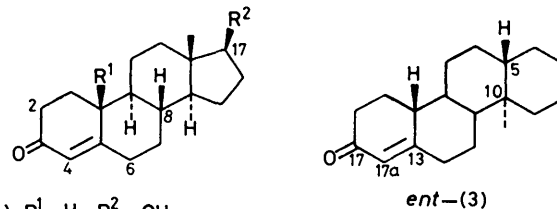
There are a few gross departures from this norm, which are associated with alkyl substitution.

The $n \rightarrow \pi^*$ Band.—The 2 β -methyl (16) and 6 β -methyl (17) derivatives of cholest-4-en-3-one, and the one 8 β -methyl compound (12) show bisignate or weakly positive c.d. bond attributable to flattening of ring A, to accommodate the β -face compression of methyl groups. 2 β -Methylcholest-4-en-3-one (16) would be expected to exist at least partly in the inverted (6c3) conformation already established^{23,24} for a 2 β -acetoxy-4-en-3-one. The positive $n \rightarrow \pi^*$ c.d. band confirms this. A recent X-ray crystallographic analysis²⁵ of 6 β -methylcholest-4-en-3-one (17) has shown that the enone system is close to planar, with ring A forced into a conformation of '1 α -sofa' type by 6 β ,19-interaction. Such a distortion was inferred from o.r.d. data for 6 β -methyltestosterone in 1958,²⁶ and is not shown by the 6 β -methyl-19-nor-analogue (7). 8 β -Methyltestosterone (12) is also close to the '1 α -sofa' conformation (in the crystal²⁴).

All the data are entirely compatible with the view¹⁶ that enone helicity controls the c.d. at the $n \rightarrow \pi^*$ band, in the absence of strongly electron-donating or withdrawing γ -axial substituents.¹⁹ It has not yet been possible to attempt a quantitative correlation of experimentally determined values of $\Delta\epsilon$ (in solution) with enone torsion angles or other conformational features,

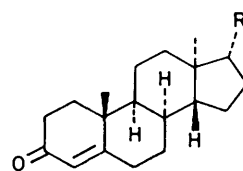
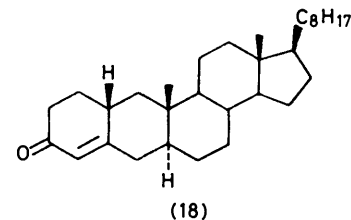
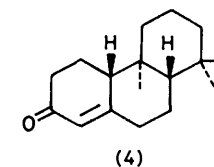
which are not necessarily identical with those determined by X-ray study of the crystal.

The '240 nm' ($\pi \rightarrow \pi^*$) Band.—The norm for $\Delta\epsilon$ lies in the range $+4$ to $+10$. The exceptions, which include

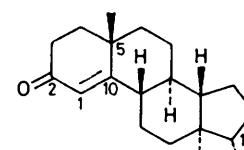


- (1) $R^1 = H, R^2 = OH$
- (2) $R^1 = H, R^2 = OAc$
- (5) as (1), with 2 $\beta, 17\alpha$ -Me₂
- (6) as (1), with 2, 2, 17 α -Me₃

- (7) as (1), with 6 β -Me
- (8) $R^1 = Me, R^2 = C_8H_{17}$
- (9) $R^1 = Me, R^2 = OH$
- (10) $R^1 = Me, R^2 = OAc$
- (11) as (8), with 2 α -Me
- (12) as (9), with 8 β -Me
- (13) as (10), with 4-Me
- (14) as (8), with 6 α -Me
- (15) as (8), with 2, 2-Me₂
- (16) as (8), with 2 β -Me
- (17) as (8), with 6 β -Me



- ent-(19) $R = C_9H_{17}$
ent-(20) $R = OH$

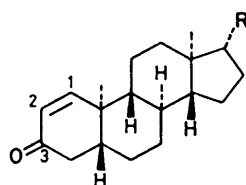
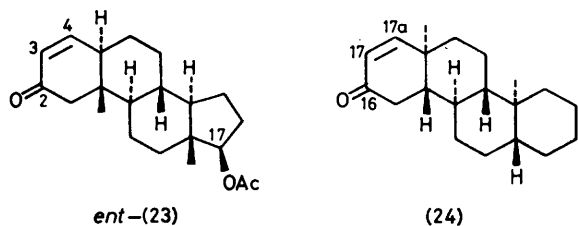


- ent-(21) $R = C_8H_{17}$
ent-(22) $R = H$

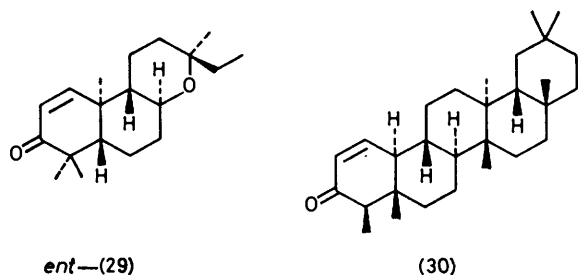
instances of sign reversal, comprise the 2β -, 6β -, and 8β -methyl-4-en-3-ones, presumably for the reasons discussed above, and two 2,2-dimethyl derivatives which are also likely to be conformationally distorted. Apart from these very clear exceptions, there is no evident correlation between values of $\Delta\epsilon$ and patterns of substitution.

The 220–200 nm Band.—A positive sign occurs almost universally, although the magnitude of $\Delta\epsilon$ includes extreme values of *ca.* +2 and +14 units. The only evident structural correlation among the undistorted compounds lies in the high values (*ca.* 10–14) for normal steroids containing the γ' -axial 10β -methyl group, compared with their 19-nor analogues ($\Delta\epsilon$ *ca.* 5–6 units). The 6β -methyl-*estr*-4-en-3-one (7) has the weakest Cotton effect ($\Delta\epsilon < +2$) in this region (see Discussion). The pentacyclic analogue (18) of a steroidal 4-en-3-one is the one clear exception, giving a negative sign without obvious reason.

Probably the most noteworthy feature of the c.d. in



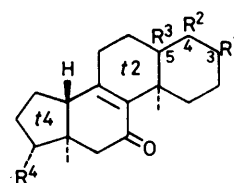
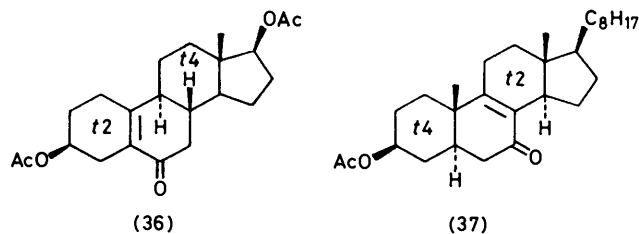
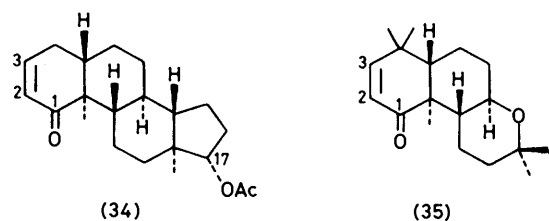
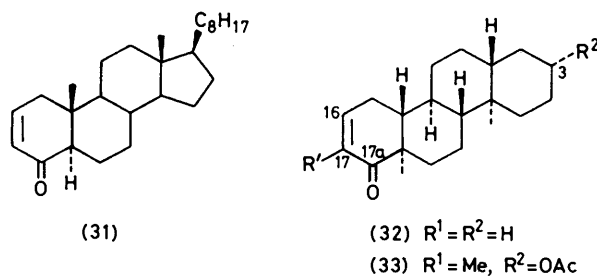
- ent* — (25) R = C₈H₁₇
ent — (26) R = OH
ent — (27) R = OAc
ent — (28) R = OAc, with 1-Me



this region is the absence of any deviation from the normal positive sign even among those 2β -, 6β -, and 8β -substituted compounds which show major deviations or sign inversions at the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ bands. Steroidal 2β -acetoxy-4-en-3-ones also exhibited a positive 220 nm band,²³ despite being known from X-ray and

n.m.r. data to have the 'inverted half-chair' conformation (6c3) in ring A, even in solution. The significance of these findings in relation to the problem of assigning the 200–220 nm c.d. band is discussed below.

Class 6t4.—Data for most of the compounds of this



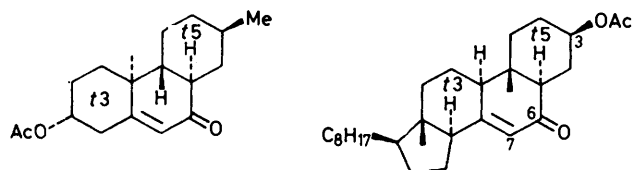
- ent* —(38) R¹ = —OAc, R² = R⁴ = H, R³ = ---H
ent —(39) R = ---OAc, R² = Me₂, R³ = —H, R⁴ = C₈H₁₇

series are presented in respect of their enantiomers, in order to match the standard cyclohexenone configuration represented in Figure 4. Regularities with regard to signs are obvious from the Table, although there are wide variations in magnitudes of $\Delta\epsilon$.

The $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ Bands.—The $n \rightarrow \pi^*$ Cotton effect is consistently positive, except in the case of the friedelin derivative (30) which carries 4,5-dimethyl substitution. Even the friedelin derivative is no exception to the negative sign observed throughout the

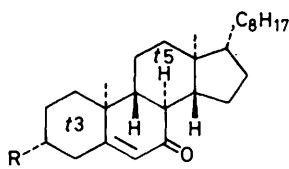
series for the $\pi \rightarrow \pi^*$ band. Taken together, these results seem to imply a helicity of the enone system which is the reverse of that in class 6*t*3, although the cyclohexenone ring configuration chosen for discussion belongs to the same enantiomeric set. Magnitudes of $\Delta\epsilon$ vary widely at the $\pi \rightarrow \pi^*$ band (ca. -5 to -14), without obvious reason.

The 200–220 nm Band.—As for class 6*t*3, this band is



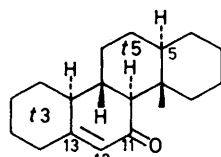
ent-(40)

ent-(41)

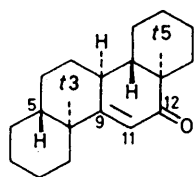


ent-(42) R=H

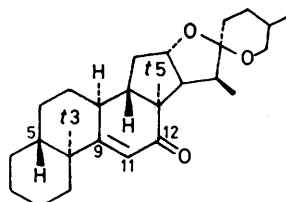
ent-(43) R=OAc



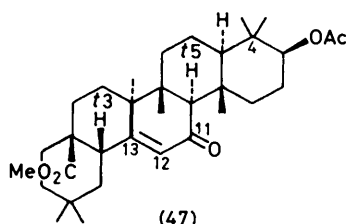
(44)



(45)



(46)



(47)

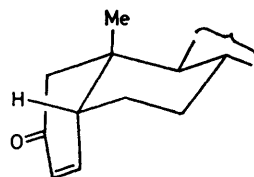
of positive sign, despite the reversed enone helicity implied by the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ c.d. bands. Values of $\Delta\epsilon$ again vary too widely for any trend to be perceptible.

The fourth c.d. band, where it is observed, is again of negative sign (cf. class 6*t*3).

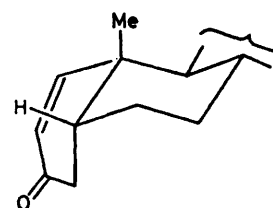
*Class 6*t*5.*—The remarkable feature of c.d. for this group of compounds is the absence, or near absence, of

the usual strong band in the $\pi \rightarrow \pi^*$ region. The $n \rightarrow \pi^*$ band is consistently negative, suggesting enone helicity similar to that found in class 6*t*3, although this helicity is at best weakly reflected in the $\pi \rightarrow \pi^*$ region by the small positive c.d. bands for compounds (33) and (35).

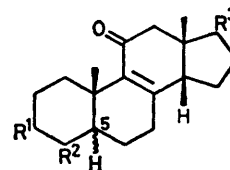
A strongly positive c.d. band appears in the 200 nm region, but is blue-shifted by comparison with class 6*t*3, to 200 ± 7 nm. It is not clear whether this is a composite of two bands, including the unassigned one which sometimes appears below 200 nm. Two 2-en-1-ones (34) and (35) give exceptionally large values of $\Delta\epsilon$ (ca. $+30$), which may perhaps include a positive contribution from the forward-projecting ('front



(48)



(49) (cholestane)

(50) (25*R*-spirostan)(51) $R^1 = \alpha\text{-OH}$, $R^2 = R^3 = \text{H}$, $5\beta\text{-H}$ (52) $R^1 = \beta\text{-OAc}$, $R^2 = \text{Me}_2$, $R = \text{C}_8\text{H}_{17}$, $5\alpha\text{-H}$

octant') ring c. The angular methyl group (α' -axial) is not responsible, for its effect is negligible in the D-homoenone (33).

Middle-ring transoid Enones.— $\alpha\beta$ -Unsaturated steroid ketones with the carbonyl group in ring B or C fall into two groups according to the locations of the adjoining rings. Structures may be either of 't4 + t2' type, or 't3 + t5', and are tabulated under these headings.

Class 't4 + t2'.—These ketones (36)—(39) show the pattern of c.d. signs and magnitudes typical of class 6*t*4 (above), suggesting that the 2,3-fused ring makes little if any contribution. Unfortunately we had no 'terminal ring' $\alpha\beta$ -unsaturated ketones of class 6*t*2, which would have enabled us to check their c.d. characteristics. [Such structures would include steroidal 19-nor-5(10)-en-1-ones or 5(10)-en-4-ones.] We infer that they would show relatively weak Cotton effects.

Class 't3 + t5'.—*Compounds (40)—(47).* Here the pattern of signs seems to be dominated by the t3 component. This must apply particularly in the $\pi \rightarrow \pi^*$ region, where class 6*t*5 shows very weak effects, if any.

On the other hand the very large '200—220 nm' band for class 6*t*5 appears to be reflected in some unusually strongly positive Cotton effects ($> +15$) among the middle-ring compounds of class 't3 + t5'.

Compounds with cis-Fused Rings.—Only five such compounds (48)—(52) were available. C.d. data are insufficient for a systematic empirical analysis. The negative Cotton effects at both lower-energy c.d. bands for the 3-en-2-one (48) provide apparently contradictory evidence as to enone helicity.

The 5 β -1-en-3-ones (49) and (50) are remarkable in apparently having a planar enone (very weak $n \rightarrow \pi^*$ band) but showing exceptional $\pi \rightarrow \pi^*$ c.d. ($\Delta\epsilon + 19$) and a strong negative band near or below 200 nm (see Discussion).

The 14 β -8-en-11-ones (51) and (52) present ambiguities with regard to conformation, since the *cis* C/D ring junction appears sufficiently flexible to adopt either of two alternative conformations. The signs of $\Delta\epsilon$ at the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ bands hint at a cyclohexenone conformation essentially of the type found in class 6*t*3 (*i.e.* as in Figure 2) which would permit the 17 β -side chain to be quasi-equatorial (Figure 6). The negative

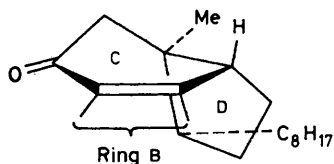


FIGURE 6 Probably conformation of rings c and d in a 14 β -cholest-8-en-11-one

c.d. band at *ca.* 205 nm, however, then requires explanation (see Discussion).

DISCUSSION

While the numerical values of $\Delta\epsilon$ found for each class among these *transoid* $\alpha\beta$ -unsaturated ketones span rather wide ranges for each wavelength region, the pattern of signs associated with the presence of particular rings is clear. Figure 7 presents an array of rings which includes all those discussed above except the few *cis*-fused examples. Each ring adjoining the cyclohexenone ring in Figure 7 contains the typical signs and the present best estimates of values of contributions to $\Delta\epsilon$ for each of the three main c.d. bands ($n \rightarrow \pi^*$, $\pi \rightarrow \pi^*$, and '200—220 nm', in that order). The contribution of the cyclohexenone ring itself is unknown, and probably varies according to its conformation, so is included in the values entered in the second rings. 'Third ring' estimates are not possible at present; signs alone are given in the Figure, for those rings which appear to make significant contributions.

The $n \rightarrow \pi^$ and $\pi \rightarrow \pi^*$ Bands.*—The signs associated with the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions presumably reflect enone helicity in solution as the dominant factor, according to previously established 'rules' (Figure 1). If this is the case, the compounds of class 6*t*4

must have reversed enone helicity, to account for the reversed signs of their Cotton effects. X-Ray crystallographic data for two 5 α -steroidal 1-en-3-ones²⁷ include one with a positive and one with a negative O=C—C=C helicity although the structures differ only in substitution at C-17, suggesting some flexibility in ring A. According

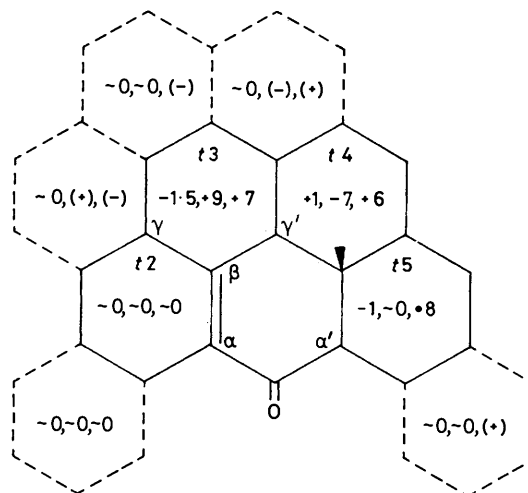


FIGURE 7 Estimated ring contributions for bicyclic systems: typical values of $\Delta\epsilon$ for $n \rightarrow \pi^*$, $\pi \rightarrow \pi^*$, and '200—220 nm' c.d. bands, respectively. 'Third ring' contributions are indicated only by signs

to the c.d. data, summarised here for the *ent*-series, negative enone helicity is generally dominant in solution for the *ent*-series, or positive helicity for steroidal 1-en-3-ones, implying a ring A conformation tending towards half-boat [*c.f.* (C(5)-sofa in Figure 3)].

No regular or pronounced alkyl substituent effects are apparent in $\Delta\epsilon$ values for either the $n \rightarrow \pi^*$ or the $\pi \rightarrow \pi^*$ c.d. band.

The '200—220 nm' Band.—This band is clearly insensitive to enone helicity, for it is almost invariably positive in the series of compounds discussed here despite wide variations in cyclohexenone geometry. The only clear exceptions are the pentacyclic enone (18) and compounds (49)—(52), with *cis*-ring fusions. Both enone helicity and α' -axial chirality¹⁸ are reversed when ring A of a 2 β -substituted 4-en-3-one adopts the 'inverted'

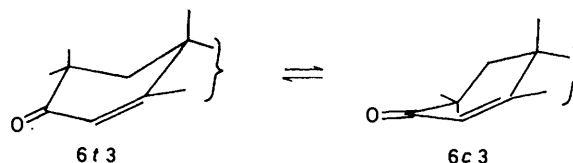


FIGURE 8 Quasi-enantiomeric forms of ring A in a steroidal 4-en-3-one

(6*c*3) conformation, with the 2 β -substituent equatorial to relieve 2 β /10 β -compression. This conformational change (Figure 8) results in ring A itself becoming quasi-enantiomeric with its more usual form, but the 200—220 nm c.d. bond remains positive. We are left with the conclusion²⁸ that the positive sign mainly expresses the

chirality of the surroundings of the olefinic bond, rather than of the carbonyl group. Such a conclusion is compatible with the recent proposal²⁹ that a second transition of $\pi \rightarrow \pi^*$ type ($\pi_x \rightarrow \pi_y^*$), lies in the 200–220 nm region, but is 'forbidden' in simple planar enones, so that it is rarely evident in the u.v. absorption spectrum alongside the very intense 240 nm band.

Some further features of the present observations support a $\pi \rightarrow \pi^*$ assignment.

(a) *Solvent effect.* The 200–220 nm band is generally red-shifted by 2–8 nm on changing from hexane to an alcohol. 2,2,2-Trifluoroethanol produces even larger red-shifts. Similar solvent effects have been noted for alkene c.d. bands,⁹ and are incompatible with a carbonyl transition of $n \rightarrow \sigma^*$ or $n \rightarrow 3s$ (Rydberg) type, which would be blue-shifted in strongly associating solvents.⁷

(b) The mean wavelength of the c.d. maximum is *ca.* 212 nm for the compounds of class 6*t*3, with a tri-substituted C=C bond, but *ca.* 202 nm for compounds of classes 6*t*4 and 6*t*5 with a disubstituted C=C bond. C.d. bands for mono-olefins show a similar trend with substitution levels.⁹

(c) Methyl substitution at the γ -axial or γ' -axial positions, particularly in class 6*t*3, has a significant effect on the numerical value of $\Delta\epsilon$. Thus the norm of *ca.* +6 units for a compound of 19-nor-4-en-3-one type is increased to *ca.* +10 to +12 units by the 10 β -methyl group in a normal steroid, or reduced to *ca.* +2 units by the 6 β -methyl substituent in compound (7). The two methyl group contributions balance out in 6 β -methyl-cholest-4-en-3-one (17). Values of $\Delta\epsilon$ in this region for classes 6*t*4 and 6*t*5, however, do not contain reliable evidence of γ' -substituent effects.

In view of the clear indications that the 200–220 nm band is associated with the olefinic component of the enone system, we draw attention to a structural resemblance between the fragment comprising C(3), C(4), and

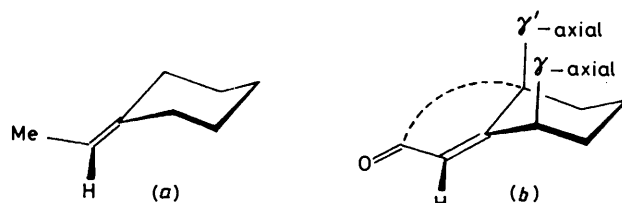


FIGURE 9 (a) Chiral ethylidenecyclohexane unit; (b) chiral cyclohexylidene-ethanal unit: each illustrated in the configuration which gives (+) c.d. at 200–210 nm, and (–) c.d. below 200 nm

ring B of a 4-en-3-one, and the chiral ethylidenecyclohexane moieties (3-ethylidene-5 α -cholestanes) for which we reported c.d. data in 1974.³⁰ We were able to demonstrate that the chiral ethylidenecyclohexane unit illustrated in Figure 9(a) is responsible for a strong positive band near 210 nm, and a negative band near 190 nm, seen also in oestr-4-enes which include an analogous structure. Signs are reversed for the enantiomeric

'ethylidenecyclohexane' unit. We therefore suggest that the 200–220 nm c.d. band of an $\alpha\beta$ -unsaturated ketone of 4-en-3-one type can be related to the chirality of the corresponding 'cyclohexylidene-ethanal' component of structure depicted in Figure 9(b), the remainder of ring A and the helicity of the enone system being unimportant. Steroidal 5-en-7-ones (42) and (43), considered here in their 'ent' forms, present the enantiomeric cyclohexylidene-ethanal fragment.

Enones of classes 6*t*4 and 6*t*5 do not include a cyclohexylidene-ethanal unit but comparisons may again be made with corresponding 5 α -steroidal olefins.⁹ The 200 nm c.d. band for simple 1-enes and 3-enes has the same sign as the 200–220 nm band for 5 α -steroidal 1-en-3-ones or 3-en-2-ones, and a similar sign correspondence exists between 5 α -steroidal 2-enes and the 200–220 nm band for 2-en-1-ones or 2-en-4-ones.

Further study of molecular models suggests that the 200–220 nm c.d. band is determined largely by γ -axial and γ' -axial chirality contributions of C–H or C–CH₃ (or C–CH₂) components.²⁸ Only the γ' -type can be present in enones of classes 6*t*4, 6*c*4, 6*t*5, or 6*c*5. Almost all the data in the Table can be explained qualitatively if: (i) a γ' -axial C–H bond exerts a consignate³¹ effect which is larger than that of a γ -axial C–H bond; (ii) methyl (or methylene) substitution results in a consignate effect which may be larger than or approximately equal to that of the corresponding C–H bond.

Thus 19-nor 4-en-3-ones give a positive Cotton effect (*ca.* +6) dominated by a large consignate effect of the γ' -quasi-axial C(10)–H bond. Methyl substitution at C(10) enhances the effect, whereas 6 β -methyl substitution introduces a counteracting negative contribution, as noted above.

Enones of type 6*t*4 show 200–220 nm c.d. controlled by the consignate effect of the γ' -axial C–H or C–CH₃ bond and those of class 6*t*5 listed in the Table show the consignate effect of the γ' -axial C–H bond [or C–CH₃ in the case of compound (35)]. Similar conclusions follow for the 'middle-ring' ketones.

In the *cis*-fused series, the 3-en-2-one (48) shows a consignate (positive) effect of the γ' -axial 5 β -H. The 5 β -1-en-3-ones would be expected to show a positive Cotton effect controlled by the γ' -quasi-axial C(10)–C(9) bond. Unfortunately neither the c.d. curve nor the compound was available to us, but we note that the negative maximum was apparently below 200 nm and the positive 235 nm band was exceptionally strong.¹⁵ Possibly the expected positive $\pi_x \rightarrow \pi_y^*$ band is concealed between the reported bands.

The conformation (Figure 6) predicted for 14 β -8-en-11-ones includes C(14)–H and C(14)–C(15) bonds which are neither quasi-axial nor quasi-equatorial, but a dominant C(14)–C(15) contribution would be of negative sign, as observed.

We therefore propose that (i) and (ii) above be provisionally regarded as 'rules' for the prediction of the sign of the 200–220 nm c.d. band.

Further work is in progress, involving comparisons of

solid-state and solution c.d., in an attempt to define more clearly the relationship between conformation and c.d. in $\alpha\beta$ -unsaturated ketones.

EXPERIMENTAL

C.d. measurements were made at ambient temperature (ca. 25 °C) on a Cary 61 instrument purged with a rapid flow of oxygen-free nitrogen. Solvents were of spectroscopic grade, except 2,2,2-trifluoroethanol and trifluoroacetic acid which were reagent grade. Solutions with concentrations in the range 0.2–0.5 mg ml⁻¹ were examined in a 10-mm cell for the $n \rightarrow \pi^*$ region, and in a 0.5-mm or 1-mm cell for the $\pi \rightarrow \pi^*$ region and down to 185 nm.

We thank colleagues who supplied c.d. data or samples of compounds (see footnotes to Table). C.d. curves from this laboratory were run by Mrs. M. W. Barrett.

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