Optical Rotatory Dispersion and Circular Dichroism. Part LXIX.[1] Camphor Derivatives; 'Anti-Octant' Behaviour of Hydroxy- and Acetoxy-substituents

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C.d. and o.r.d. data are reported for the epimeric 3-hydroxy- and 3-acetoxy-derivatives of (+)-bornan-2-one [(+)-camphor], and the 2-hydroxy- and 2-acetoxy-derivatives of (−)-bornan-3-one [(−)-epi-camphor]. The observed contributions of hydroxy- or acetoxy-groups to amplitudes or $\Delta\varepsilon$ values are in the opposite sense to that predicted for alkyl groups by the Octant Rule.

THE Octant Rule [2] relates the Cotton effects due to the $n \to \pi^*$ transitions of saturated carbonyl compounds to the stereochemistry of the surroundings of the chromophore. Extensive studies have shown that alkyl groups of all kinds and halogen atoms (except fluorine) in a given Octant make contributions of the *same* sign to the Cotton effect.[3-5] The signs for the rear Octants are shown in Figure 1. A given substituent has the
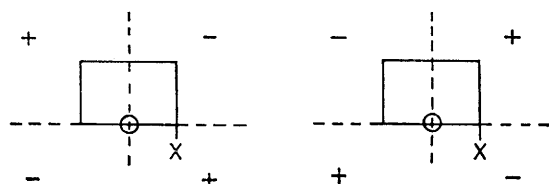

FIGURE 1 Normal Octant signs (for rear octants); – – – – nodal planes

FIGURE 2 Anti-Octant signs (for rear octants)

largest effect when it is in an axial position ' α ' to the carbonyl group of a cyclohexanone in a chair conformation (as X in Figures 1 and 2).

Recently many different theoretical treatments of the Octant Rule, which some authors suggest is more properly a Quadrant Rule, have appeared. A detailed account (with earlier references) is given by Höhn and Weigang;[6] a useful general survey of symmetry rules has been made by Schellman;[7] references are also collected by Snatzke.[8] (The significant discussion by Hudec [8a] appeared after this paper had been submitted for publication.)

A few examples known to Djerassi and colleagues [9] indicated that fluorine atoms gave contributions of *opposite* sign to alkyl (or chlorine or bromine). This behaviour has been termed ' Anti-Octant ' behaviour (see Figure 2).

Evidence has accumulated recently from various sources to suggest that oxygen- and nitrogen-containing substituents of several types in axial ' α '-positions (as X in Figures 1 and 2) make anti-Octant contributions to the o.r.d. curves (signs as in Figure 2). The origin of these effects is not yet clear. Anti-Octant contributions by nitrogen-containing substituents are discussed by Yamada and Kunieda [10] and by Höhn and Weigang;[6] apparent anomalies in the Cotton effects of some oxo-decahydroquinolines prepared in the Upjohn laboratories [11] may also be due to anti-Octant effects.

Early data regarding contributions by oxygen-containing substituents, previously collected by one of us,[12] now appear to be misleading. Studies on steroid ring A hydroxy- and acetoxy-ketones, which are being conducted by Enslin and his colleagues in Pretoria,[13] show apparent anti-Octant effects.

In this paper we present o.r.d. and c.d. data for solutions in three solvents for a series of hydroxy- and acetoxy-derivatives of (+)-bornan-2-one [(+)-camphor (I; $R^1 = R^2 = H$)] and (−)-bornan-3-one [(−)-epi-camphor (II; $R^1 = R^2 = H$)], which were prepared in

(I) (+)-Bornan-2-one [(+)-Camphor]

(II) (−)-Bornan-3-one [(−)-epi-Camphor]
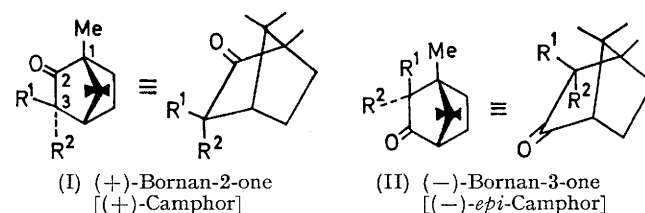
Stockholm; details of other physical properties, including n.m.r. data, have been given elsewhere.[14] These o.r.d. and c.d. results, together with data from Djerassi

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and his co-workers [15,16] for some related ring D steroid ketol acetates (Table 2), present a clear picture of apparent 'Anti-Octant' effects by oxygen-containing substituents.

C.d. results for the bornanone series in hexane are summarized in Table 1; values for solutions in hexane

TABLE 1

C.d. of bornanone derivatives: summary of $\Delta\varepsilon$ values and differences ($\Delta\Delta\varepsilon$)

Solvent, Hexane. Principal c.d. maxima only are shown. Signs for $\Delta\Delta\varepsilon$ are 'Anti-Octant' in every case.

	λ/nm	$\Delta\lambda$/nm	$\Delta\varepsilon$	$\Delta\Delta\varepsilon$
Hydroxy-groups				
Bornan-2-one	303		+1·50	
endo-3-OH	320 [a]	+17	+0·31 [a]	−1·19
exo-3-OH	304	+1	+1·85	+0·35
Bornan-3-one	306		−1·46	
endo-2-OH	317 [b]	+11	−0·76 [b]	+0·70
exo-2-OH	304	−2	−2·07	−0·61
Acetoxy-groups				
Bornan-2-one	303		+1·50	
endo-3-OAc	325 [c]	+22	+0·36 [c]	−1·14
exo-3-OAc	304	+1	+2·18	+0·68
Bornan-3-one	306		−1·46	
endo-2-OAc	327 [d]	+21	−0·23 [d]	+1·23
exo-2-OAc	308	+2	−2·34	−0·88

[a–d] Additional maxima of opposite sign at shorter wavelength, as follows:

	$\Delta\varepsilon$	λ/nm		$\Delta\varepsilon$	λ/nm
a	−0·20	288	c	−0·09	283
b	+0·16	283	d	+0·35	292

are most appropriately considered as reference values, since hexane is non-polar and essentially non-associating. The o.r.d. results are closely related to the c.d. results in the expected fashion; since the c.d. results are essentially simpler, we concentrate our attention on these.

All the c.d. substituent differences ($\Delta\Delta\varepsilon$ values) for solutions in hexane shown in Table 1 are of 'Anti-Octant' sign. Although the magnitudes of the differences vary, the *endo*-isomer in each pair produces the larger effect. The patterns of effects for solutions in dioxan and in methanol (Table 3) are generally similar to those in hexane, except that *endo*-2-hydroxybornan-3-one shows a small 'Octant' substituent effect in methanol: its *exo*-2-hydroxy-epimer shows a negligible effect in methanol. Four compounds, indicated by footnotes in Table 1, show double c.d. maxima of opposite signs at *ca.* 320 and *ca.* 290 nm; further comment is made later.

The differences in wavelength of the principal c.d.

maxima caused by the substituents follow a simple pattern. In hexane $\Delta\lambda$ for *endo*-substituents is large: +11 to +17 nm for OH, +21 to +22 nm for OAc; $\Delta\lambda$ for *exo*-substituents is negligible or small. From Dreiding models (*e.g.* of the 3-acetoxycamphors) it appears that substituents adjacent to the carbonyl group are in semi-axial or 'bisectional' positions, where the torsion angle in the O=C–C–X system is *ca.* 60°. *X*-Ray crystal structure determinations on 3-*endo*-bromo-

TABLE 2

O.r.d. data for steroid ring D ketol acetates

All data from ref. 16.
Solvent, dioxan.

Ketone or acetoxy-ketone	a	Δa for OAc
14α-Configuration		
17-CO	+132	
17-CO; 16α-OAc	+176	+44
17-CO; 16β-OAc	+85	−47
16-CO	−264	
16-CO; 17α-OAc	−313	−49
16-CO; 17β-OAc *	−202	+62
14β-Configuration		
17-CO	+35	
17-CO; 16α-OAc	+51	+16
17-CO; 16β-OAc	−57	−92
16-CO	+110	
16-CO; 17α-OAc	+96	−14
16-CO; 17β-OAc	+194	+84

* Note also 16-CO; 17β-OH; a, −232; Δa, for OH, +32).

camphor and other derivatives confirm this.[17,18] C.d. measurements on bromocamphor have been reported by Cookson.[19]

Unsubstituted Bornanones.—The Cotton effects of the unsubstituted ketones, (+)-bornan-2-one (I; $R^1 = R^2 = H$) and (−)-bornan-3-one (II; $R^1 = R^2 = H$) have been discussed elsewhere by Cookson,[19] and also by Coulombeau and Rassat[20] in an intensive study of solvent effects on ketones. The contribution of C-7 and its two substituent methyl groups appears to be dominant.[19] The magnitudes of these Cotton effects (either o.r.d. or c.d.) show only small differences between solutions in the three solvents studied. If o.r.d. and c.d. data for the same compound are compared, the values of $a/\Delta\varepsilon$ are near to the theoretical value[21] of 40. Details of previous measurements, with which ours are in fair agreement, are given in footnotes to Table 3.

The c.d. fine structure for solutions in the non-polar solvent hexane is not particularly pronounced; the splitting between maxima and/or inflections is *ca.* 1000—1400 cm^{-1}, which is typical for ketones.[19,20,22] The bathochromic solvent shift for camphor on changing from methanol to hexane is *ca.* 1000 cm^{-1}, equivalent to

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3 kcal mol⁻¹, which is typical for the strength of a hydrogen bond:[22,23]

Camphor (in methanol), c.d. max. 295 nm; $\tilde{v}$ *ca.* 34×10^3 cm⁻¹

Camphor (in hexane), c.d. max. 303 nm; $\tilde{v}$ *ca.* 33×10^3 cm⁻¹.

These facts have been accommodated [19,20] by assuming the compound to be solvated in methanol. The absence of strong fine structure in hexane suggests that there may be some interaction with solvent even in the non-polar medium.[24] Maxima in dioxan are much closer to those in hexane than to those in methanol, indicating only weak interaction between ketone and dioxan.

Hydroxy-ketones.—All the hydroxy-ketones exhibit very little or no fine structure in their c.d. curves even in hexane; this may be a consequence of intramolecular hydrogen-bonding between the hydroxy- and ketone groups in the non-polar solvent. Joris and Schleyer [25] have found evidence for moderately strong hydrogen-bonding in the i.r. spectra of some related hydroxy-ketones in carbon tetrachloride. This suggestion is supported in the case of the *exo*-hydroxy-ketones (I; R¹ = OH, R² = H) and (II; R¹ = OH, R² = H) by the absence of any appreciable bathochromic solvent shift between methanol and hexane; contrast the parent ketones, which show a pronounced shift on changing the solvent.

Acetoxy-compounds.—The acetoxy-ketones are in many ways analogous to the hydroxy-compounds, but with the unusual features exaggerated.

There is no certainty that the conformation of the acetoxy-group itself is fixed, although the preferred conformation of many other acetoxy-compounds [26] appears to be of the type found by Mathieson [27] for secondary acetoxy-groups, in which carbonyl is eclipsed with secondary hydrogen [as in projections (IIIa and b)].

(III)

(IIIa) 3β *exo*   (IIIb) 3α *endo*
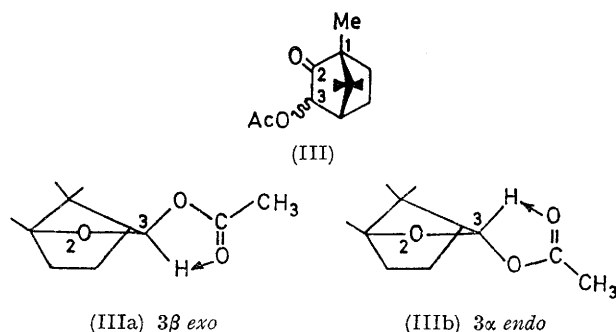
This should not be taken for granted in the present

series of compounds, because dipole–dipole interaction between the ketone and ester carbonyl groups may significantly alter the situation.

endo-Compounds. The *endo*-acetoxy-ketones (I; R¹ = H, R² = OAc) and (II; R¹ = H, R² = OAc) exhibit complex c.d. curves, possibly owing to solvation. Coulombeau and Rassat [20] have shown that the magnitude of $\Delta\varepsilon$ for the long-wavelength bands at about 325 nm (unsolvated carbonyl) increases in a linear manner with decreasing solvent polarity;[28] this is presumably due to an increase in the proportion of free, unsolvated form in the less polar solvents.

The observed magnitude of $\Delta\varepsilon$ should be treated with caution owing to the presence of overlapping bands of opposite sign (see later).

exo-Compounds. These acetoxy-compounds show simpler curves than their *endo*-epimers; neither shows c.d. maxima of opposite signs.

C.d. Curves with Double Maxima.—Four compounds (indicated by footnotes in Table 1) show at shorter wavelength (*ca.* 290 nm) a second c.d. maximum of opposite sign to that of the main c.d. maximum at *ca.* 320 nm; in all cases this additional maximum shows an 'Anti-Octant' effect with respect to the parent compound's maximum at 303 nm. The four compounds which show double c.d. maxima of opposite signs are the *endo*-3-hydroxy-2-one and the *endo*-2-hydroxy-3-one (in hexane only), and the corresponding *endo*-acetoxy-ketones in all three solvents.

C.d. curves with maxima of opposite signs may arise from several different causes. The form of such curves (with apparent $\lambda_{\text{max.}}$ for c.d. separated by up to 30 nm, as a result of superposition of two simple curves whose maxima differ by only a few nm) has been discussed by Djerassi and his co-workers.[24] In some examples of this phenomenon [19,20] the two maxima are due respectively to the solvated form (shorter wavelength) and the un-solvated form (longer wavelength).

Conformational equilibria in the carbon framework can probably be excluded from consideration for relatively rigid structures such as the bornanones. A moderate degree of flexibility in substituted bornanes and related compounds has recently been demonstrated from X-ray studies,[29] but the possible distortions seem unlikely to alter significantly the octant dispositions of structural features in the present series of compounds, and should not afford two conformationally distinct species. There is, however, the possibility of two or more conformers about the C–OH or C–OAc bonds. We are not yet able to assess the possibility of such conformers affording c.d. maxima of opposite signs. A final possibility is that the

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[29] C. Altona and M. Sundaralingam, *J. Amer. Chem. Soc.*, 1970, **92**, 1995.

TABLE 3

Cotton effects of camphor and *epi*-camphor derivatives

Temperature, 22—24°.
Solvents: M, methanol; D, dioxan; H, hexane; polarities as measured by E_T values [28] are respectively 55·5, 36·0, and 30·9. $a/\Delta\varepsilon$ should be 40·28 in the theoretical case [21] of a perfect Gaussian c.d. curve. The experimental values are given to the nearest whole number.
Fine structure: O, none; W, weak; M, medium; S, strong; *cf.* ref. 22. The partial band of largest $\Delta\varepsilon_{max.}$ is shown in italics.
* $[\phi] \times 10^{-2}$ for single extremum.

Compound	Solvent	U.v. absorption λmax./nm; (εmax. in parentheses)	C.d. λ/nm	C.d. Δε	O.r.d. λ/nm of extrema	O.r.d. a	a/Δε	Fine structure (c.d.)
Bornan-2-one	M	290(30)	*295*	*+1·39*	314/276	+58	42	O
[(+)-Camphor]	D		*309*sh	*+1·04*				
			299	*+1·45*	315/275	+63	43	W
			*290*sh	*+1·20*				
	H	292(24)	*314*sh	*+1·01*				
			303	*+1·50*	320/277	+63	42	MW
			*294*sh	*+1·34*				
endo-3-Hydroxybornan-2-one	M		*314*	*+0·71*	330/294	+36	43	O
	D		*324*	*+0·61*				
			314	*+0·53*	323/300	+31	49	W
	H		*320*	*+0·31*	331/303	+19	52	O
			288	*−0·20*	303/273	−9	42	
exo-3-Hydroxybornan-2-one	M	303(34)	*307*	*+1·64*	328/287	+67	41	O
	D		*311*	*+1·70*	333/287	+69	41	O
	H	301(31)	*304*	*+1·85*	329/283	+86	46	O
endo-3-Acetoxybornan-2-one	M		333	−0·03	330 *,	−2 * pk		
			323	+0·06				W
			292	*−0·425*	306/270	−19	45	
	D		*323*	*+0·365*	330/306	+16	44	M
			312	+0·300				
			288	−0·155	306/270	−11	37	
	H	302(45)	*325*	*+0·36*	331/308	+17	47	MS
			313	+0·34				
			304sh	+0·10	303/263	−8		
			283	−0·09				
exo-3-Acetoxybornan-2-one	M		*305*	*2·15*	325/285	+95	44	O
	D		*307*	*2·23*	327/285	+103	46	O
	H	290(71)	*304*	*2·18*	328/285	+93	43	O
Bornan-3-one [(−)-*epi*-Camphor]	M		299sh	−1·58		−62	38	W
			295	*−1·65*	310/271			
	D		312sh	−1·04				
			303	*−1·52*	316/276	−64	42	W
			294sh	−1·36				
	H	295(27)	317sh	−0·93				
			306	*−1·46*	320/276	−62	42	M
			296sh	−1·34				
endo-2-Hydroxybornan-3-one	M		*313*	*−1·78*	329/289	−79	44	O
	D		329sh	−1·16				
			316	*−1·34*	331/297	−60	45	O
	H	300(19)	*317*	*−0·76*	330/297	−37	49	O
			283	+0·16				
exo-2-Hydroxybornan-3-one	M	303(37)	*307*	*−1·64*	325/281	−64	39	O
	D		*311*	*−1·80*	330/285	−72	40	O
	H	302(26)	*304*	*−2·07*	323/278	−82	40	O
endo-2-Acetoxybornan-3-one	M		333	+0·02	333	+7 *		
			325	−0·05				
			293	*+0·55*	310/272	+19	35	O
	D		325	−0·25	331/308	−16	64	
			315sh	−0·09				W
			291	*+0·38*	308/273	+17	45	
	H	304(54)	327	−0·23	332/311	−14	61	W
			316sh	−0·08				
			292	*+0·35*	311/269	+15	43	
exo-2-Acetoxybornan-3-one	M		*303*	*−2·40*	326/280	−122	51	O
	D		*308*	*−2·57*	330/285	−115	45	O
	H	304(48)	*308*	*−2·34*	332/284	−105	45	O

TABLE 3 (*Continued*)

Previous results in literature

	Solvent	λ/nm	$\Delta\varepsilon$
Bornan-2-one	EtOH (95%) [a]	296	+1·54
	Cyclohexane [a]	303	+1·69
	Me$_2$SO [a]	295	+1·68
	EtOH [b]	295	+1·55 †
	Cyclohexane [b]	302	+1·69 †
endo-3-Acetoxybornan-2-one	EtOH [b]	320	+0·10
		289	−0·39
	Cyclohexane [b]	325	+0·35
		285	−0·10
Bornan-3-one	EtOH (95%) [a]	296	−1·78
	Cyclohexane [a]	306	−1·82
	EtOH [b]	294	−1·81
	Cyclohexane [b]	305	−1·86
endo-2-Acetoxybornan-3-one	EtOH [b]	335	+0·03
		326	−0·03
		291	+0·42
	Cyclohexane [b]	328	−0·24
		294	+0·38

† After correction for optical purity.
[a] Ref. 19.   [b] Ref. 20.

'double-humped' curves represent permitted and forbidden branches of the same transition.[30]

Steroid Ring D *Ketol Acetates.*—Another series of acetoxy-ketones is that of the ring D steroid derivatives studied by Fishman and his co-workers,[16] by o.r.d.

(IV)   (V)
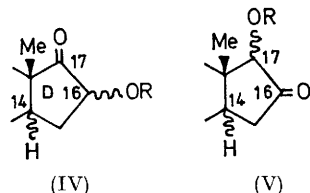
The Anti-Octant Δa values for OAc found in the bornanone series in methanol (mean value *ca.* ±60) agree remarkably well with values (Table 2) reported [16] for the steroid ketol acetates, (IV) and (V), where the acetoxy-groups are probably also close to 'bisectional' positions.

The possibility must always be borne in mind that substituents may cause conformational changes in cyclopentanones (*e.g.* in ring D of steroids); such changes could result in large differences in o.r.d. and c.d. curves. However, halogeno-substituents 'α' to carbonyl in ring D of steroids show 'normal' Octant effects on the o.r.d. and c.d. curves, and therefore they presumably

cause no major distortion of ring D. It thus seems reasonable to ascribe the 'Anti-Octant' behaviour of acetoxy-groups in ring D to some cause other than conformational change. This assumption is even more justified for the bornanones, which models show to be fairly rigid.

EXPERIMENTAL

C.d. curves were measured with a Jouan Dichrograph (model CD 185) for solutions in 1 cm cells, and o.r.d. curves with a Bellingham and Stanley/Bendix Polarmatic 62 spectropolarimeter, for solutions in 0·1, 0·2, or 1 cm cells; concentrations *ca.* 1 mg/ml, temperature 22—25°. The solvents, hexane, dioxan, and methanol were of commercial spectroscopic grade. U.v. absorptions were measured for solution in hexane with a Unicam SP 800 spectrophotometer.

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