Tetrahedron Vol. 38, No. 1, pp. 3 to 26, 1982
Printed in Great Britain.

0040-4020/82/010003-24$12.00/0
Pergamon Press Ltd.

TETRAHEDRON REPORT NUMBER 119

CIRCULAR DICHROISM AND STEREOCHEMISTRY OF CHIRAL CONJUGATED CYCLOHEXENONES

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(*Received* 25 *April* 1981)

Abstract—An empirical analysis of CD spectra of variety of cyclohexenones, including variable temperature and solvent studies, reveals the presence of up to three Cotton effects in the 260–185 nm region, in addition to the well-recognized n-π^* Cotton effect at 300–350 nm. The long-wavelength band I and band II Cotton effects are ascribed respectively to the first (allowed) and second (formally forbidden) π-π^*-transitions. The third (band III) Cotton effect at below 200 nm is of different nature and is attributed to the n-σ^* transition in the CO group.

It is shown that CD spectra of cyclohexenones not only are influenced by the conformation of the chromophore but also reflect the presence of allylic axial substituents (n-π^* and band I), the absolute configuration of the cyclohexenone ring (band II), and the presence of axial alkyl groups in α' or β' positions (band III).

The optical activity of α,β-unsaturated ketones has been a subject of long standing interest and numerous theoretical and experimental studies, especially since development in CD instrumentation allowed to penetrate the strongly absorbing π–π^* region.

For structural reasons chiroptical studies focussed on polycyclic conjugated cyclohexenones, including steroid and terpene derivatives. These studies were directed toward relationship between CD or ORD and molecular structure or conformation, yet the CD technique was capable of uncovering transitions not seen in the isotropic absorption spectra (*vide infra*). As the interest in chiroptical properties of conjugated unsaturated systems continues to grow, partly in connection with such important problems as for example structure-biological activity of steroid hormones and macrocyclic antibiotics, we have chosen to review the relationship between structure of conjugated cyclohexenones and their chiroptical properties, with the aim to demonstrate new generalizations useful in structural investigations.

Presently existing generalizations, or rules, mainly cover the n–π^* transition and in the past decade there appeared several excellent reviews on the n–π^* Cotton effects of α,β-unsaturated ketones by Snatzke,[1–4] Crabbé,[5] and Legrand.[6,7] In this Report emphasis is placed upon the optical activity of cyclohexenones in the π–π^* region for which the situation is definitely more complex, mainly due to overlapping bands in the CD spectra and partially unknown nature of the Cotton effects. A reassignment of these bands will be proposed and the relation between structure and observed Cotton effects will be discussed. The CD data on n–π^* transition Cotton effects will also be presented and discussed in terms of previously published rules. In this Report an attempt is made to show that analysis of Cotton effects in the π–π^* region provides more information about cyclohexenone structure and conformation than interpretation of the n–π^* Cotton effect taken alone.

Summary of previous advances. Unlike saturated ketones, or isolated olefins, conjugated ketones fall into a class of inherently dissymmetric chromophores.[8] Basically no sector rules are applicable, except for cases where the chromophore is planar (see Ref. 9).

The earliest structural correlation came from ORD studies of steroidal enones by Whalley[10] and Djerassi *et al.*[11] They have correlated the sign of the n–π^* (R-band) and π–π^* (K-band) Cotton effect of *trans*-enones with the sense of helicity of an inherently dissymmetric chromophore (Fig. 1). Later Snatzke found empirically that more skewed *trans*-enones are characterized by higher $\Delta\epsilon$ values for the n–π^* transition.[1,2,12] For a coplanar enone system, a sector rule for the n–π^* transition has been proposed,[1–3,12] with sign pattern opposite to that applicable to saturated ketones. Subsequent theoretical calculations on skewed acrolein model gave somewhat conflicting results. Hug and Wagniere used SCF-CNDO-CI method and found good agreement with the helicity rule[11] for *trans*- as well as *cis*-acrolein. They have also

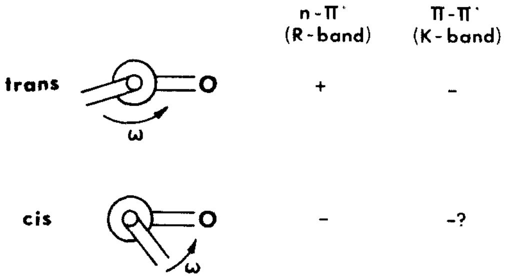

Fig. 1. Skewed ($\omega < 0$) cyclohexenone Cotton effects.

found maximum of rotational strength of the $\pi-\pi^*$ transition for orthogonal arrangement of the C=C and C=O orbitals.[13] Calculations of Aoyama and Yamakawa gave similar results for *trans*-acrolein but were less predictive for *cis*-acrolein.[14] Eyring *et al.* obtained in the semiempirical LCAO–MO–SCF calculation minimal rotational strength of the $\pi-\pi^*$ transition for acrolein molecule twisted at 90°, with differing results for zeroth-order calculation and for calculations incorporating CI.[15]

As early as the CD measurements down to 200 nm became routine another optically active transition was recognized in the region 200–220 nm, having no corresponding band in the isotropic absorption spectrum.[16,17] In some cases a strong Cotton effect associated with this transition obscured the $\pi-\pi^*$ Cotton effect. This made the verification of the $\pi-\pi^*$ Cotton effect with the prediction of the helicity rule difficult. At that time no assignment of the new band was attempted.

Further work on the $\pi-\pi^*$ region Cotton effects indicated apparent break-down of the enone helicity rule when a hetero-atom is present in the allylic axial position[18] (R′ in Fig. 2). In addition, the deviations from the helicity rule for $\pi-\pi^*$ transition found frequently among *cis*-enones has led Burgstahler *et al.* to a new experimental rule, according to which the sign of the $\pi-\pi^*$ Cotton effect is controlled primarily by the asymmetric perturbations of the double bond components of the chromophore with allylic axial bonds ("allylic axial chirality rule", R and R′ in Fig. 2).[19a,b] At the same time these authors have proposed that the sign of the short-wavelength (200–220 nm) Cotton effect reflects the chirality of the system: CO group–α'-axial bond (R″ in Fig. 2).[19a] This proposal has not been supported by the more recent studies of Burnett and Kirk.[20]

Totty and Hudec have proposed that the sign of the 220–260 nm $\pi-\pi^*$ Cotton effect is due to an overriding contribution of the γ-transoid allylic axial substituent (R′ in Fig. 2). When the substituent R′ is of the type inducing strong quadrant behaviour in α-axial or β-equatorial substituted cyclohexanones (e.g. Me, Cl, Br, J, SAc), it also changes the sign of the n-π^* Cotton effect.[21] Beecham has recognized particularly strong allylic axial chirality contributions of oxygen substituents.[22] According to Snatzke, allylic axial bonds plus the chromophore form a chiral first sphere and the chirality of the part with $\pi-\sigma$ conjugation overcomes that of the part with $\pi-\pi$ conjugation.[2]

Present work. We have surveyed the CD data for about one hundred cyclohexenone derivatives. The CD data were either collected in our laboratory or, if the compounds were not available, taken from the relevant publications. Obviously, the scope of this Report does not allow for including all the data, yet we tried to include as many diverse structures as possible to make the content of this work more representative. This work is limited to the analysis of recognizable structural effects on the CD spectra of cyclohexenones: a detailed empirical analysis of the CD of α,β-unsaturated ketones is to be published elswhere.[23]

Transitions. For the purpose of the present review it is highly desirable to discuss briefly the nature of observed bands in the UV and CD spectra and to compare matching of their maxima within the given class of compounds.

The maximum of the broad n–π^* band appears both in CD and UV spectra between 370 and 290 nm, being blue shifted in solvents of higher polarity. At shorter wavelengths we have labelled the observed

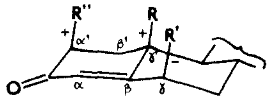

Fig. 2. Allylic axial chirality contributions (R,R′) to the 220–260 nm π-π^* Cotton effect (R″ determines the sign of the 200–220 nm Cotton effect[19a]).

CD bands in the 260–185 nm region in the order of increasing energies, with latin numerals I, II, and III. Band I appears both in CD and UV spectra between 220 and 260 nm and undoubtedly belongs to the allowed π–π^* transition (K–band). Band II appears in the CD spectra within the 200–220 nm spectral range and as mentioned earlier usually has no corresponding UV maximum. Both CD bands frequently overlap and in some cases one of them is merely seen as a shoulder or it is completely obscured by the other one. In such cases where the shape of the curve or position of the CD maxima indicated overlapping bands the experimental curve was resolved into the component Gaussian curves. Since band I dominates the UV spectrum the position of the maximum of this band was taken directly from the UV spectrum† and the experimental CD curve was resolved to fit the band I maximum (Fig. 3).

The nature of band II remained highly speculative until recently Allinger and Liljefors published the results of the VESCF-CI calculations on conformations and electronic absorption spectra of α,β-unsaturated ketones and aldehydes.[24,25] Their calculations strongly indicate that the broad UV absorption band observed for α,β-unsaturated ketones and aldehydes is generally made up of two π–π^* transitions. These transitions are predicted to lie close together if the doubly excited configurations are included in calculations. The recent linear and circular dichroism studies of a number of steroidal α,β-unsaturated ketones confirmed the presence of an additional π–π^* transition around 200 nm, correlated well with the calculations including all singly and doubly excited configurations.[26]

In our analysis we sought experimental means for identifying the Cotton effects below 220 nm as well as for relating the sign and magnitude of these Cotton effects to the structure.

The results of our study of the solvent effect on the Cotton effects of some steroidal enones are exemplified in Tables 4–6 (entries **A1, A2, A12, A13, B1, B9, C1, E1**). It is evident that in addition to the n–π^* Cotton effect the two bands I and II are present in the CD spectra in all cases, except where band I Cotton effect is obscured by the strong band II Cotton effect. Moreover, in many cases there is another Cotton effect observed at higher excitation energy (below 200 nm), here assigned as band III Cotton effect.

As a rule, the n–π^* Cotton effect undergoes blue shift when the polarity of the solvent is increased. Solvent effects upon the magnitude of the n–π^* Cotton effect appear to be highly sensitive to the enone

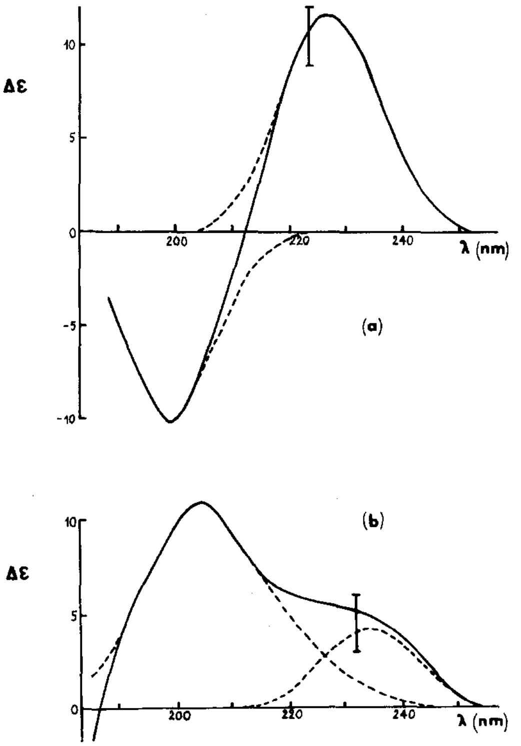

Fig. 3. Resolution of the experimental CD curves (——) into Gaussian components (– – – –): (a) bands I and II of opposite sign, weakly overlapping (**B1**); (b) bands I and II of the same sign with significant overlap (**A1**). Bars indicate position of the UV maximum.

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†The vibronic structure is usually insignificant and does not interfere with the analysis.

structure, as already observed for saturated ketones.[27] Noteworthy is a particularly strong effect of hexafluoroisopropanol which is again highly structural dependent. For unhindered enones, such as steroidal 4-en-3-ones (**A1**, **A2**), 1-en-3-one (**B1**), and 5-en-4-one (**E1**) blue shifts of the magnitude of 36 to 45 nm and *ca.* 3-fold increase of rotational strength are observed on changing the hydrocarbon solvent to hexafluoroisopropanol. We note that a similar large increase of the n–π* Cotton effect in hexafluoroisopropanol is observed for saturated ketones of unhindered structural type.[28]

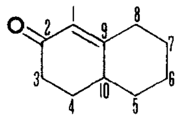
The maxima of bands I and II shift progressively bathochromically with the increase of solvent polarity. The magnitudes of Cotton effects are also affected to some extent, yet in less predictable manner, accounted for in part by varying separation of bands I and II. Usually both bands are better separated in non-polar solvents, indicating a larger bathochromic shift of band II maximum with an increase of solvent polarity. The particular position of bands I and II is strictly related to cyclohexenone substitution pattern. For each structural type (**A–F**, see below) we have obtained a set of characteristic positions of band I and II maxima, utilizing the resolved CD curves and the UV maxima. In planar or nearly planar enones the second π–π* transition is forbidden and it does not contribute to the experimental UV curve.† Since it usually cannot be observed directly in the isotropic electronic absorption spectra, we have included in Table 1 for comparison the difference for the positions of the two UV π–π* transitions, calculated from data of Ref. 25.

In general we see satisfactory matching of the respective positions of CD bands I and II and the two calculated lowest energy π–π* transitions, providing that the "ring closure effect"[25] is included. This, combined with the previously discussed solvent effect, strongly advocates that the two CD bands I and II belong to the two lowest π–π* transitions. Strictly speaking, some contribution of other transitions, e.g. of σ–π* character, to the band II Cotton effect cannot be ruled-out, however, on the basis of existing data.

Table 1. Typical positions of π-π* CD bands (in nm)

Class	Solvent [a]	Band I [b]	Band II [c]	Δλ /band I - band II/ [d]
A	h	230±2	206±2	
	m	240±2	214±2	13±2
B/C	h	223±2	198±2	
	m	230±2	204±2	12±4
D	h	/235/[e]	/203/[e]	
	m	253±2	215±3	24±6
E	h	236±2[f]	213±3	
	m	244±1	217±3	29
F	h	243±2	?	
	m	251±2	?	33

[a] h = hydrocarbon, m = methanol or ethanol. [b] From resolved c.d. curve and u.v. curve. [c] From resolved c.d. curve. [d] From the data of ref.25; class A-D ω=175±5°, class E,F ω=25°. [e] Based on one example. [f] Additional weak band of opposite sign frequently seen at ca. 250-260 nm.



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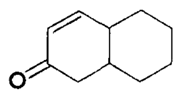

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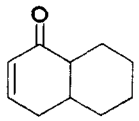

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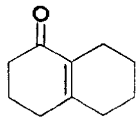

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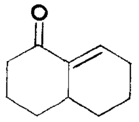

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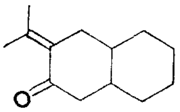

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†Weakly allowed second π–π* transition is calculated to occur in some highly alkylated s-*trans* enones.[25]

Simultaneous observation of both bands in the CD and UV spectra would provide additional evidence for their π–π^* character. Such cases are scarce, as they require a highly twisted chromophore (at $\omega = 90°$ the allowedness of the two lowest π–π^* transitions is reversed[25]). The recently published CD and UV data of steroidal 5–en–7–one with the abnormal configuration (**A62**)[29] (Table 4) indicate the two π–π^* transitions of this highly strained compound, in which the cyclohexenone ring probably exists in a skewed boat conformation. Another example could be the abnormal katonic acid derivative, but complete chiroptical data are not available.[30]

Considering band III observed occasionally in the CD spectra of chiral cyclohexenones we note that particularly strong Cotton effects are produced in the presence of alkyl substituents in the α' or to lesser extent in the β' axial positions (R and R′ in Fig. 4).

The position of band III maximum is found invariably in the region 185–195 nm (see Tables 4–6). Data of Tables 4–6 also point at zero or just a small blue shift of the maximum with the increase of solvent polarity. These spectral features suggests that band III Cotton effect results from the CO n–σ^* transition. Cotton effects of this type are observed in saturated ketones at *ca.* 195 nm,[31] and it is known that position of maximum for this type of transition is not affected by conjugation of the CO group with the olefinic bond.[32]

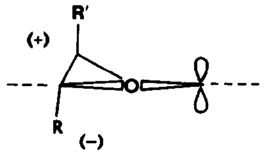


Fig. 4. Octant-like projection of 2-cyclohexenone ring in a sofa conformation (planar chromophore) with signs of contributions of the alkyl substituents to the n-σ^* transition (band III) Cotton effect.

SIMPLE CYCLOHEXENONES

Structural factors that affect the CD spectra of cyclohexenones are readily demonstrated for simple *trans*-enones **1** and **3** and *cis*-enones **2** and **4**. In addition to rigid enones **3** and **4** we will briefly discuss two cyclohexenones **1** and **2** with simple carbon frameworks, for which conformational equilibria need to be considered. Like 2-cyclohexenone itself, its (−)-(5*R*)-methyl derivative (**1**) is assumed to exist in the equilibrium of the two sofa or half-chair conformations (Fig. 5).

By lowering the temperature, the n–π^* Cotton effect at around 350 nm becomes more positive and the negative Cotton effect at 218 nm, corresponding to the UV maximum, increases significantly. The small pos-

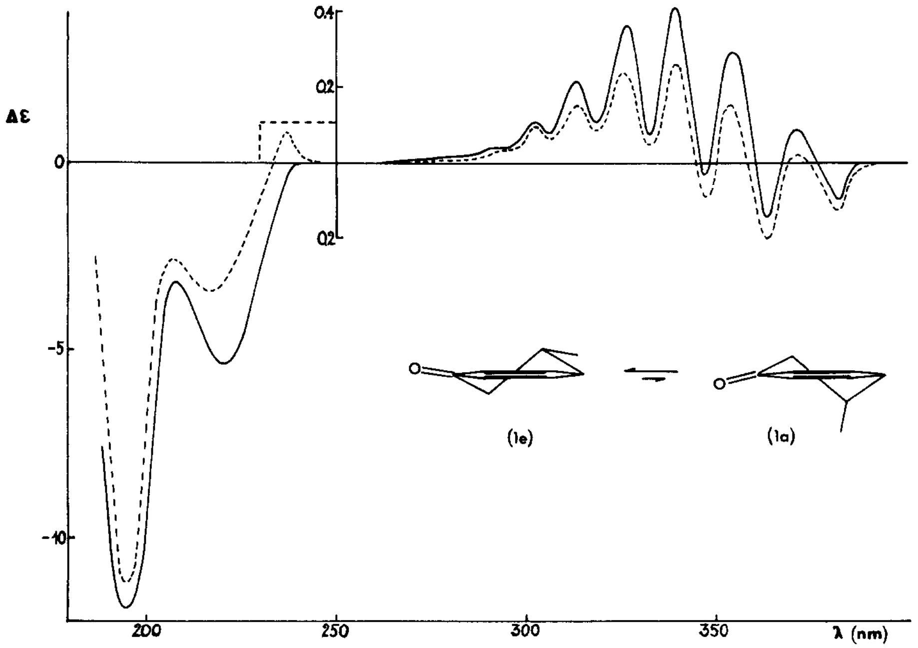
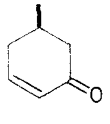


Fig. 5. Conformations and CD spectra of **1** at +20° (----) and at −150° (——) in methylcyclohexane-isopentane (4:1).

Table 2. CD and UV data for 1 and 2

No.	Compound	n-π*		Band I	Δε /λmax./ Band II	Band III	U.v. max.	Solvent[a]
1	/-/-/5R/-Methyl--2-cyclohexenone	-0.17 /363/	+0.33 /339/	-3.0 /212/	-11.8 /196/		213	p
		-0.18 /363/	+0.27 /339/	-3.4 /218/	-11.2 /195/		218	h
		-0.15 /356/	+0.14 /320/	-3.2 /221/	b		223	d
		-0.15 /351/	+0.13 /316/	-2.5 /222/	-7.2 /194/		224	a
		-0.17 /341/	+0.07 /300/	-2.5 /224/	-6.5sh /196/	-8[b] /192/	226	m
		-0.58 /310/	+0.05 /273/	+0.2 /246/ -0.7 /221/	-4 sh /204/	-4.9 /195/	234	f
2	/+/-Pulegone		+0.60 /332/	-3.0 /238/		+0.8 /210/ -4 /192/	245	h
			+0.66 /325/	-3.2 /245/		+1.4 /204/ -3[b] /190/	249	a
			+0.61 /320/	-2.3 /247/		+1.2 /203/ -2[b] /194/	253	m
			+0.65 /303/	-2.0 /259/		+2.0 /195/	265	f

[a] a = acetonitrile, d = dioxan, f = 1,1,1,3,3,3-hexafluoroisopropanol, h = hexane or cyclohexane, m = methanol or ethanol, p = perfluoromethylcyclohexane. [b] Maximum not reached.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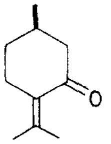
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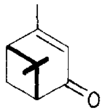
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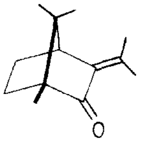
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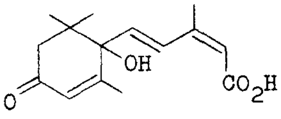
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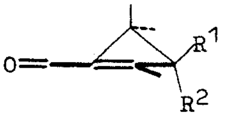

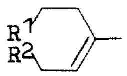
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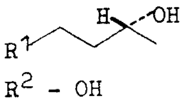

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itive hump, + 0.08 at 237 nm, disappears on lowering the temperature. The increase of the third Cotton effect at 195 nm is insignificant.

Our calculations based on the rotational strength of the n–π* Cotton effect at various temperatures point to 80–85% of **1e** in the equilibrium at room temperature in hydrocarbon solvents. The equilibrium (**1e**$\rightleftharpoons$**1a**) was previously studied by variable-temperature CD in the n–π* region in EPA solvent. At room temperature the equilibrium mixture was calculated to consist of 80% of **1e** with positive rotational strength ($\Delta G° = 0.8$ kcal/mol).[33] This reference also lists room temperature equilibria for **1a, b** in other solvents, calculated from rotational strengths of the n–π* Cotton effect and assuming its insensitivity to polarity of the solvent. We feel that such far-reaching assumptions should be made with caution, particularly if one considers the diverse Δε values for the *n*–π* Cotton effect of rigid steroidal enones, e.g. 5α-cholest-3-en-2-one (**B9**) (see also recent discussion of the effect of H-bonding on the position of n–π* transition of enones[34]).

Analysis of the low-temperature CD data on **1a, b** shows that for **1e** the n–π* Cotton effect is positive and the band I Cotton effect is negative. The opposite sign pattern holds for **1a**, the conformer apparently stabilized by polar solvents. Comparable change of the CD sign pattern among polycyclic enones is found in configurational isomers of 4-en-3-ones **A7** and **A3** (Table 4). It has been noted[33] that signs of the n–π* Cotton effect of **1e** and **1a** do not follow the octant rule for cyclohexenones with planar chromophores.[12] However, signs of both n–π* and π–π* Cotton effects are correctly predicted if one assumes the half-chair conformation with non-planar chromophore for either **1e** or **1a** and applies the enone helicity rule (Fig. 1). The negative Cotton effect at 195 nm is significantly broadened and its intensity is lowered in polar solvents. Although the CD curve resolution is poor, it is reasonable to assume that it is due to the presence of the two different transitions in this spectral region, both with negative rotational strength; i.e. band II, red shifted in polar solvents, and band III (due to the β′-axial Me group), blue shifted in polar solvents.

X-ray data indicate a sofa or slightly distorted sofa conformation in abscisic acid (**5**) and its *trans*, *trans*

Table 3. CD and UV data for other simple enones

No.	Compound	$\Delta\varepsilon$ and ε /λmax./ n-π*	Band I	Band II	Band III	Solvent[a]	Ref.
3	/+/-Verbenone	+3.50 /338/ 58 /338/	+1.0 /240/ 7,530 /240/	-	-3.4 /203/	h	
4	α-Isopropylidene-D-camphor	+0.60 /340/ 135 /340/	+9.1 /240/ 12,800 /240/	-	-8.5 /197/	h	
6	Isophorone 4,4-spiroderivative	+1.25 /348/	-3.4 /239/	-	+9.2 /201/	h	aa
7	Blumenol B	+1.01 /325/	-8.2 /250/	+11.4 /217/		m	bb

[a] See Table 2. [aa] A.G. Gonzalez, J. Darias, A. Diaz, J.D. Fourneron, J.D. Martin, and C. Perez, Tetrahedron Letters, 3051 /1976/. [bb] G. Weiss, M. Koreeda, and K. Nakanishi, Chem. Comm., 565 /1973/.

isomer.[35] The available CD data on analogous derivatives **6** and **7** of isophorone, di-substituted at C–4 (Table 3), are compatible with the preferred sofa conformation.

Noteworthy is that the preferred sofa conformation proposed here for **6** differs from that suggested originally and is of a type enantiomeric to the "normal" sofa conformation of Δ^4-3-keto steroids. Thus the n–π* and band I Cotton effects are of opposite sign to those of unsubstituted Δ^4-3-keto-steroids (e.g. **A1**). The enhanced band I Cotton effect of blumenol B (**7**) compared to **6** is due to the contribution of the allylic axial oxygen substituent (see p. 22). The short-wavelength region of the CD spectrum of **6** and **7** is dominated by the positive band III Cotton effect due to the β'-axial Me group.

The rigid *trans*-cyclohexenone, (+)-verbenone (**3**), exists in a "frozen" sofa conformation imposed by the bicyclo[3.1.1]heptane skeleton. Since the chromophore is planar and the "double-sofa" is nearly symmetrical with respect to the plane of the chromophore, the band I Cotton effect is indeed small, reflecting minor effect of the remote gem-dimethyl substituent (Table 3). The large n–π* Cotton effect is of some interest, as it originates from the apparently "octant-like" contribution of the gem-dimethyl group.

From the n–π* region variable temperature CD spectra of the *cis*-enone, (+)-pulegone (**2**), $\Delta G^\circ = 1.1$ kcal/mol has been estimated for the equilibrium (**2e** ⇌ **2a**).[36] This corresponds to 87% of **2e** in the equilibrium at 20°. The full range CD spectrum at +20° and −150° is shown in Fig. 6.

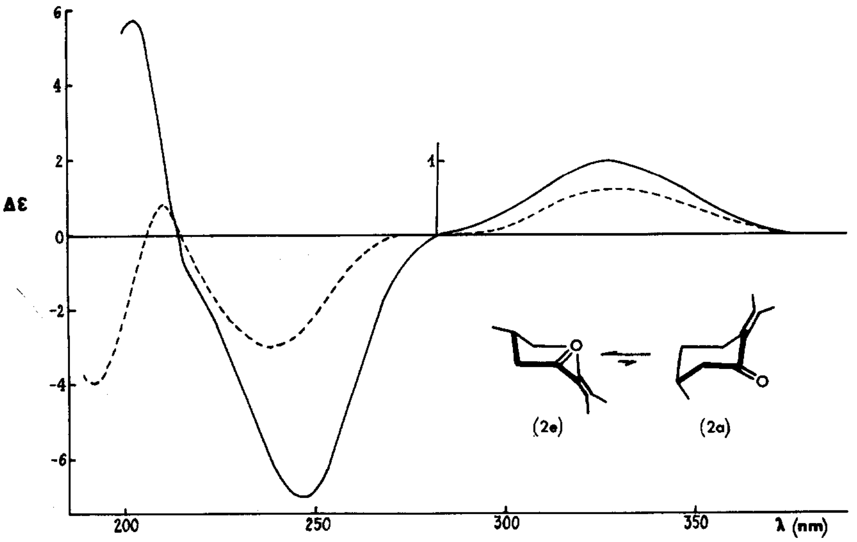


Fig. 6. Conformations and CD spectra of **2** at +20° (----) and at −150° (——) in methylcyclohexane-isopentane (4:1).

Our analysis shows that **2e** conformer contributes positive n–π* and negative π–π* (band I) Cotton effects; the opposite sign pattern is found for the **2a** conformer. Sign patterns for the n–π* transition Cotton effect follow the helicity rule (Fig. 1), for band I Cotton effect they are in accord with our experimental findings for other α-isopropylidenecyclohexanones (see p. 21), but they do not correlate with the original helicity rule.[11] Inspection of Table 2 and Fig. 6 locates two short-wavelength Cotton effects. One with a positive rotational strength which evidently belongs to the **2e** conformer is blue-shifted in polar solvents, a behavior not expected for band II (π–π^*) Cotton effect. The negative one is due to the **2a** conformer and is presumably a band III Cotton effect, related to the presence of a β'-axial Me group.

The isopropylidene derivative of (+)-*D*-camphor (**4**) displays three Cotton effects listed in Table 3. A similar CD pattern [$\Delta\epsilon$: + 0.5 to + 1.1 (n–π^*), + 5 to + 10 (band I), strong negative (band III)] show other alkylated derivatives of (1*R*, 4*S*)-3-methylenebicyclo[2.2.1]heptan-2-one.[37–40] All of these compounds have planar rigid *cis*-enone chromophore. Since the observed n–π^* and band I Cotton effects cannot be due to the inherent dissymmetry of the chromophore and Me substituents on the skeleton produce only minor effects, it is believed that the signs of these Cotton effects are governed by the absolute configuration of the bicyclo[2.2.1]heptane skeleton. The strong negative band III Cotton effect below 200 nm is probably due to the presence of the α'-pseudoaxial 1, 6-bond situated in the negative sector (Fig. 4) for the given (1*R*, 4*S*) absolute configuration.†

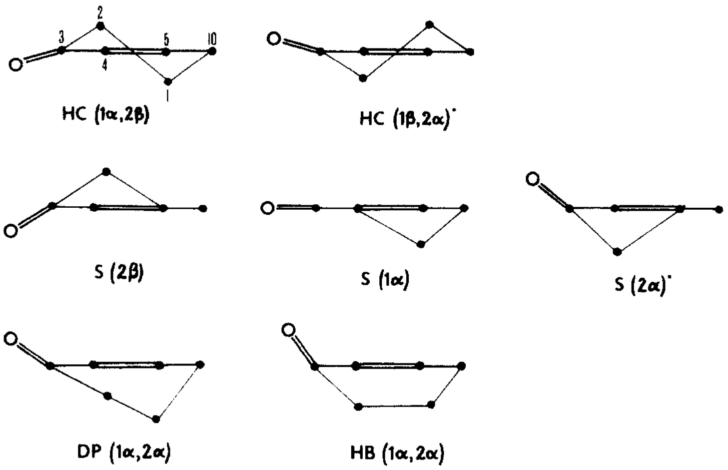
POLYCYCLIC ENONES

For convenience of discussion, enones with polycyclic skeletons are divided into structural classes **A–D** (*trans*-enones) and **E, F** (*cis*-enones). The important structural difference between cyclic *trans*- and *cis*-enones is readily noticeable on inspection of molecular models: in the absence of special conformational effects class **A–D** cyclohexenones assume sofa-half chair conformation, with nearly planar chromophore ($\omega_{\text{calc.}}$ 175–179°[25]), while the chromophore is significantly skewed ($\omega_{\text{calc.}}$ 23°[25]) in *cis*-enones (**E, F**). For this reason relatively small changes in conformation or substitution in allylic axial positions can bring about substantial changes in the CD spectra of *trans*-enones.‡ Such effects are discussed separately in the following sections.

Since the typical conformations of 2-cyclohexenone ring are not always consistently labelled we will use in our discussion the descriptions referring to idealized geometrical ring conformations. Some of these descriptions have been successfully in use for the presentation of the torsion angle notation.[41] Figure 7 should be helpful in defining the most frequently encountered conformations of ring A in steroidal 4-en-3-ones. To assist in further explanation Fig. 8 shows how these conformations are interrelated to each other by varying ring torsion angles.

Although a great deal of information have been collected by X-ray analysis on the detailed conformation of steroids in the solid state,[42, 43] it is generally accepted that such information should be used with caution with reference to the conformation in solution. In the foregoing discussion we use X-ray data, when available, merely to indicate general trends in conformation due to the structural modification, rather than to ascribe any importance to the exact values of torsional angles found in the solid state.

Derivatives of $\Delta^{1(9)}$*-octalin-2-one* (**A**). As mentioned earlier, in the absence of non-bonded interactions the most stable conformations of cyclohexenone ring in this class are half-chair or sofa. The preferred



HC (1α,2β) HC (1β,2α)*

S (2β) S (1α) S (2α)*

DP (1α,2α) HB (1α,2α)

Fig. 7. Schematic representation of idealized conformations of cyclohexenone ring in steroidal 4-en-3-ones (HC-halfchair, *s*-sofa, DP-1,3-diplanar, HB-half-boat; *-"inverted" conformations).

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†Similar negative n–σ^* Cotton effects are displayed by saturated bicyclo[2.2.1]heptan-2-ones of the same absolute configuration.

‡*cis*-Enones have not been studied extensively in this direction.

cyclohexenone conformation appears to be reflected by the band I Cotton effect. In many cases where the available X-ray data[42,43] (see also Appendix) suggest planar sofa conformation, the band I Cotton effect is weak, often seen as a shoulder on the strong band II Cotton effect of the same sign. The $n-\pi^*$ Cotton effect is of opposite sign to band I Cotton effect and its magnitude in $\Delta\epsilon$ units is typically around 1.5 (in methanol). Examples from Table 4 include steroidal 4-en-3-ones (**A1** and **A4**), 1(10)-en-2-one (**A18**), and 9(11)-en-12-one (**A21**), as well as their quasi-enantiomer, 5-en-7-one (**A12**). By similar reasoning, in the half-chair conformation the band I Cotton effect is stronger ($\Delta\epsilon$ often around 10) and the band II Cotton effect is decreased, due to the increased skew angle of the chromophore. The examples are: 4-methyl-4-en-3-one (**A2**), 19-nor-4-en-3-one (**A3**), anthrasteroid (**A14**), 12(13)-en-11-one (**A19**), and glycyrrhetic acid derivative (**A20**); they also include the quasi enantiomers: a retrosteroid (**A7**), des-A-steroid (**A15**), and 7-en-6-one (**A22**).

Table 4. CD data for class **A** cyclohexenones

No.	Compound	Configurational type	$\Delta\varepsilon$/λmax./ $n-\pi^*$	Band I	Band II	Band III	ε/λmax./ Band I	Solvent^a	Ref.
A1	Cholest-4-en-3-one	P	-1.41 /337/	+5.5sh /230/	+11.0 /207/		16,630 /232/	h	
			-1.31 /326/	+4.9sh /236/	+11.0 /214/		15,870 /239/	a	
			-1.48 /316/	+4.2sh /240/	+11.0 /217/		16,100 /242/	m	
			-4.10 /292/	i	+11.7 /233/		15,830 /256/	f	
A2	4-Methylcholest-4-en-3-one	P	-1.31 /338/	+7.3 /242/	+5.3 /213/	-1.3 /195/	15,880 /243/	h	
			-1.52 /326/	+6.4 /247/	+6.0 /215/	-1.2 /194/	15,600 /248/	a	
			-1.78 /317/	+6.1 /250/	+6.2 /219/	/-/^{c}	15,420 /251/	m	
			-4.18 /300/	+5.6sh /260/	+7.6 /231/	-3.8 /186/	15,350 /262/	f	
A3	17β-Hydroxyestr-4-en-3-one	P	-1.95 /316/	+8.2 /238/	+6.7 /219/			m	
A4	17β-Hydroxyandrost-4-en-3-one	P	-1.50 /315/	+8.3sh /240/	+11.5 /216/			m	
A5	17β-Hydroxy-10α-estr-4-en-3-one	M	-2.29 /323/	+1.8 /245/	b			m	aa
A6	17β-Hydroxy-10α-androst-4-en-3-one	M	-1.9 /331/	-0.4 /251/	-11.3 /212/			m	bb
A7	17β-Hydroxy-9β,10α-estr-4-en-3-one	M	+1.7 /315/	-10.6 /240/	/-/^{c}			m	cc
A8	17β-Hydroxy-9-methyl-9β,10α-estr-4-en-3-one	M	+2.2 /315/	-15.8 /243/	b			m	dd
A9	17β-Hydroxy-17α-methyl-9β-estr-4-en-3-one	P	+1.26 /325/	-8.7 /244/	b			m	ee
A10	17β-Hydroxy-8α-estr-4-en-3-one	P	+0.95 /320/	+2.6 /250/	+4.7 /210/			m	bb
A11	17α-Hydroxy-8α,13α,14β-androst-4-en-3-one	P	-1.7 /320/	+12.0 /239/	/+/^{c}			m	bb
A12	Cholest-5-en-7-one	M	-0.13 /383/						
			+1.49 /337/	-14.5sh /227/	-21.0 /204/	+6.4 /185/	14,640 /230/	h	
			-0.10 /373/						
			+1.35 /333/	-12.0sh /232/	-16.0 /214/	+4.0 /186/	13,940 /236/	a	
			+1.18 /324/	-11.5sh /236/	-15.1 /218/	/+/^{c}	13,860 /239/	m	
			-0.37 /338/						
			+0.63 /305/	-8.9sh /245/	-14.9 /224/	+4.0 /186/	12,500 /248/	f	
A13	4,4-Dimethylcholest-5-en-7-one	M	-1.04 /368/	+1.1 /250/	-18.1 /213/	+10.0 /188/	13,400 /233/	h	
			-3.78 /325/	+5.2 /261/	-11.2 /227/	+6.0 /184/	12,000 /252/	f	
A14	17β-Hydroxy-9-methyl-1/10+6αH/abeo-9β-estr-4-en-3-one	P	-1.04 /311/	+10.0 /242/	b			m	ff
A15	17β-Hydroxy-des-A-estr-9-en-5-one	M	+0.37 /310/	-7 /240/	+2 /215/			m	cc
A16	17β-Hydroxy-des-A-androst-9-en-5-one	M	-0.38 /340/	-3.5 /245/	+1/220-215/			m	cc
A17	Methyl 13-oxopodocarp-8/14/-en-18-oate	P	-2.50 /319/	+13.6 /238/	+6.9sh/220/			m	
A18	5α-Methylcholest-1/10/-en-2-one	P	-1.3 /312/	+8.5sh /245/	+11.2 /231/			m	gg
A19	18-Nor-D-homo-3α,17β-dihydroxyandrost-12/13/-en-11-one	P	-2.3 /339/	+5.8 /239/	+10.5 /212/			m	bb
A20	Methyl glycyrrhetate 3-acetate	P	+0.30 /345/	+7.9 /236/				m	

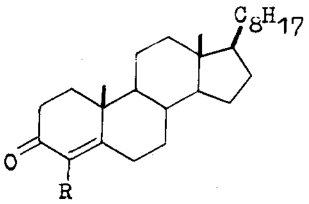
Table 4. (*Contd*)

No.	Compound	Configurational type	$n-\pi^*$	Δε/λmax./ Band I	Band II	Band III	ε/λmax./ Band I	Solvent[a]	Ref.
A21	Methyl 3α-hydroxy-12-keto-5β-chol-9/11/enoate	P	-2.20 /333/ -1.94 /318/	+3.5 /242/ +3.2 /248/	 +6.1 /215/	+15.5 /197/ +7.8 /192/	10,100 /239/ 9,900 /247/	a f	
A22	3β-Acetoxy-5β-ergosta-7,22-diene-6-one	M	+2.24 /336/	-9.1 /240/	/+/			d	hh
A23	Ecdysone	M	+1.43 /340/	-4.2 /245/	+3.0 /220/			d	ii
	Substituted cholest-4-en-3-ones								
A24	6α-Hydroxy	P	-1.50 /319/	+7.9 /242/	+9.0 /203/			m	
A25	6α-Acetoxy	P	-1.46 /319/	+3.7sh /230/	+5.5 /205/			m	jj
A26	6α-Bromo	P	-1.05 /337/	+6.6sh /230/	+13.8 /210/			h	
A27	6α-Azido	P	-1.29 /342/	+5.2 /230/	+12.0 /198/			h	
A28	6α-Nitro[d]	P	-0.88 /345/	+3.0 /231/	+13.0 /204/			h	
A29	6β-Hydroxy	P	-0.70 /321/	-5.3 /250/	+10.7 /215/			m	
A30	6β-Acetoxy	P	-1.31 /348/	-1.6 /239/	+14.9 /210/			h	
A31	6β-Azido[e]	P	-0.55 /347/	-9.7 /240/	+11.4 /210/			h	
A32	6β-Acetamido	P	-0.98 /323/	-3.6 /248/	+24.4 /215/			m	
A33	6β-Methoxysulfonyl	P	+0.83 /348/	-9.5 /245/	+6.5 /218/			a	
A34	6β-Bromo	P	+2.00 /353/	-19.9 /249/	+9.8 /218/			h	
A35	6β-Nitro	P	- f	+4.2 /240/	+8.0sh/211/			h	
	Substituted 4-en-3-ones								
A36	17β-Hydroxy-6β,17α-dimethylandrost-4-en-3-one	P	+0.70 /333/	-1.8 /248/	+5.8 /221/			m	
A37	6β,17β-Dihydroxyestr-4-en-3-one	P	-1.47 /323/	-5.2 /242/	+4.7 /210/			m	jj
A38	17β-Acetoxy-6β-bromoestr-4-en-3-one	P	+0.80 /341/	-10.5 /246/	+2.7 /215/[c]			d	jj
A39	10β,17β-Dihydroxyestr-4-en-3-one	P	-1.65 /321/	+6.8 /235/	+5.5 /210/			m	jj
A40	17β-Hydroxy-1α-methylandrost-4-en-3-one	P	-2.60 /330/	+16.6 /239/	i	-7.0 /187/		a	
A41	17β-Hydroxy-1α-methylestr-4-en-3-one	P	-3.1 /320/	+14.0 /243/	i			m	kk
A42	11β-Hydroxy-1β-methyl-17α,20,20,21-bismethylenedioxypregn-4-en-3-one	P	+1.50 /321/	-19.2 /248/	+10.8 /212/			m	kk
A43	17β-Hydroxy-1β-methylestr-4-en-3-one	P	+1.3 /325/	-21.5 /245/	i			m	kk
A44	17β-Acetoxy-2α-methylandrost-4-en-3-one	P	-2.75 /315/	+12.4 /235/	+10.8 /213/			m	
A45	17β-Hydroxy-2α,17α-dimethylestr-4-en-3-one	P	-3.0 /320/	+12.2 /239/	+14.5sh/225/			m	kk
A46	2α-Bromocholest-4-en-3-one	P	-1.40 /326/	+13.0 /235/	+5.4 /210/			h	ll
A47	17β-Hydroxy-2β-methylandrost-4-en-3-one	P	+1.3 /322/	-21.7 /243/	+12 /210/			m	kk
A48	17β-Hydroxy-2β,17α-dimethylestr-4-en-3-one	P	-0.94 /322/	-5.3 /243/	+5.4 /210/			m	mm
A49	2β-Bromocholest-4-en-3-one	P	-1.06 /338/	-3.9 /239/	+10.0 /213/			h	ll
A50	4-Bromocholest-4-en-3-one	P	-0.64 /322/	+7.0 /256/				h	ll
A51	4-Methoxycholest-4-en-3-one	P	-1.84 /310/	+2.8 /254/	+4.7 /209/			m	
A52	11β-Hydroxy-9α-methyl-17α,20,20,21-bismethylenedioxypregn-4-en-3-one	P	-2.30 /317/	+19.0 /242/	i			m	
A53	9α-Bromo-11β,17β-dihydroxy-17α-methylandrost-4-en-3-one	P	-2.50 /320/	+21.2 /245/	i			m	
A54	9α,11β,17β-Trihydroxy-17α-methylandrost-4-en-3-one	P	-2.50 /310/		+21.0 /225/			m	
A55	17β-Hydroxy-17α-methyl-B-norandrost-4-en-3-one	P	+5.20 /323/	-24.5 /242/	+12.0 /205/			m	
	Bicyclic enones								
A56	/S/-7a-Methyl-7,7a-dihydro-1,5/6H/-indandione	P	+2.30 /337/	-29.9 /240/	+20.8 /215/[g]			d	nn
A57	/S/-8a-Methyl-3,4,8,8a-tetrahydro-1,6/2H,7H/-naphtalenedione	P	-0.98 /335/	-1.6 /249/	+5.4 /220/[h]			d	oo
A58	1,1-Ethylenedioxy-analog of enantiomer-A56	M	-1.35 /324/	+11.7 /248/	b				pp

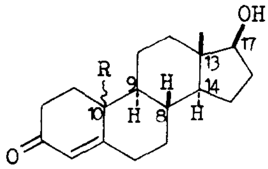
Table 4. (*Contd*)

No.	Compound	Configu-rational type	n-π^*	$\Delta\varepsilon/\lambda$max./ Band I	Band II	Band III	ε/λmax./ Band I	Solvent[a]	Ref.
A59	1,1-Ethylenedioxyderivative of A57	P	-1.00 /339/	+6.3 /231/	+6.0sh/215/			h	rr
A60	15-Nor-7β/H/-eudesma-4,11-dien-3-one	P	+0.4 /361/	i	+19.0 /201/		13,500 /235/	h	ss
A61	11-Acetoxy-15-nor-4-eudesmen-3-one	P	-0.70 /338/	+12.0 /228/	+7.5sh/209/		16,900 /230/		tt
A62	3β-Acetoxy-9β-lanost-5-en-7,11-dione	P	-4.92 /341/	-5.8 /255/	+12.2 /230/[j]		6,000 /255/ 6,400 /239/[k]	a	uu

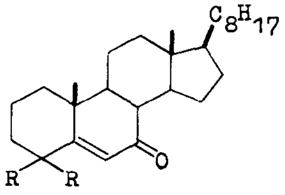
[a] See Table 2. [b] Not reported. [c] Maximum not reached. [d] Additional Cotton effect /$\Delta\varepsilon$=+1.23 at 281 nm/ due to the n-π^* transition in $-NO_2$. [e] Additional Cotton effect /$\Delta\varepsilon$=-1.0 at 288 nm/ due to the n-π^* transition in $-N_3$. [f] Cotton effect is partially obscured by the n-π^* Cotton effect of the $-NO_2$ chromophore /$\Delta\varepsilon$=-9.6 at 284 nm/. [g] Additional n-π^* Cotton effect /$\Delta\varepsilon$=+8.2 at 308 nm/ due to the β,γ-unsaturated ketone. [h] Additional n-π^* Cotton effect /$\Delta\varepsilon$=+1.54 at 295 nm/ due to the β,γ-unsaturated ketone. [i] Not observed. [j] Saturated ketone $\Delta\varepsilon$+3.69 /291 nm/. [k] Band II u.v. max. [aa] M.Debono, E.Farkas, R.M.Molloy, and J.M.Owen, *J. Org. Chem.*, 34, 1447 /1969/. [bb] Ref. 16. [cc] V.Delaroff and R.Viennet, *Bull. Soc. chim. France*, 277 /1972/. [dd] J.R.Bull, J.Floor, and A.Tuinman, *Tetrahedron*, 31, 2157 /1975/. [ee] E.Farkas, J.M.Owen, and D.J.O'Toole, *J. Org. Chem.*, 34, 3022 /1969/. [ff] J.R.Bull and A.Tuinman, *Tetrahedron*, 29, 1101 /1973/. [gg] G.Habermehl and W.Walz, *Z. Naturforsch.*, 31b, 983 /1976/. [hh] H.Scherrer, *Helv. Chim. Acta*, 52, 2428 /1969/. [ii] T.Takemoto, Y.Hikino, H.Hikino, S.Ogawa, and N.Nishimoto, *Tetrahedron*, 25, 1241 /1969/. [jj] Ref. 18. [kk] Ref. 58. [ll] J.Gawroński, *Roczniki Chem.*, 51, 1525 /1977/. [mm] L.Nédélec, J.C.Gasc, and R.Bucourt, *Tetrahedron*, 30, 3263 /1974/. [nn] Z.G.Hajos and D.R.Parrish, *J. Org. Chem.*, 39, 1615 /1974/. [oo] J.Gutzwiller, P.Buchschacher, and A.Fürst, *Synthesis*, 167 /1977/. [pp] D.Bondon, Y.Piétrasanta, and B.Pucci, *J. Chem. Res.*, 112 /1980/. [rr] Sample kindly supplied by Prof. T.Kametani; T.Kametani, K.Suzuki, and H.Nemoto, *Chem. Comm.*, 1127 /1979/. [ss] D.C.Humber, A.R.Pinder, and S.R.Wallis, *J. Chem. Soc.* /C/, 2941 /1968/. [tt] Sample kindly supplied by Prof. D.Caine; D.Caine, Pi-Chang Chen, A.S.Frobese, and J.T.Gupton, *J. Org. Chem.*, 44, 4981 /1979/. [uu] Ref. 29.



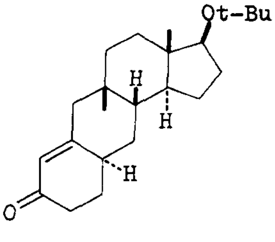
A1 R=H
A2 R=Me



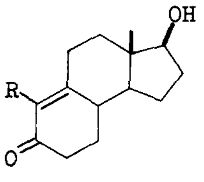
A3 R=β-H
A4 R=β-Me
A5 R=α-H
A6 R=α-Me
A7 R=α-H,9β-H
A8 R=α-H,9β-Me
A9 R=β-H,9β-H,17α-Me
A10 R=β-H,8α-H
A11 R=β-Me,8α-H,13α-Me,14β-H /17β-OH/



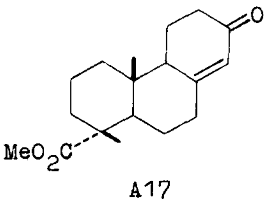
A12 R=H
A13 R=Me



A14



A15 R=H
A16 R=Me



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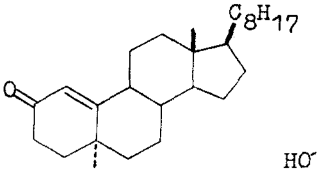

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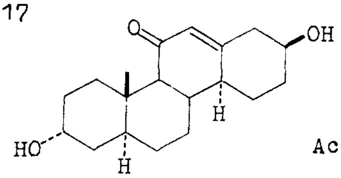

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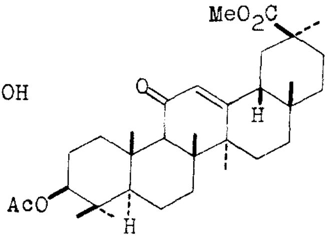

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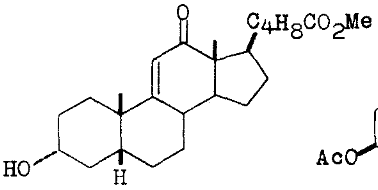
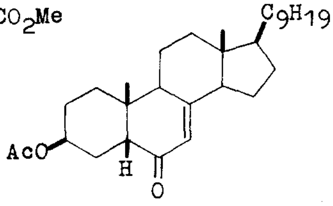


A21



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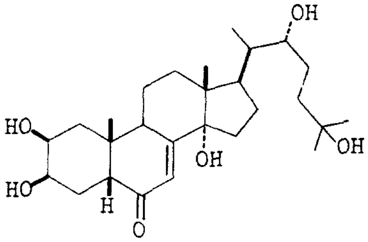

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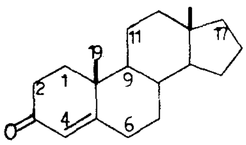
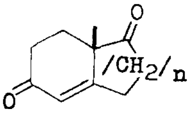


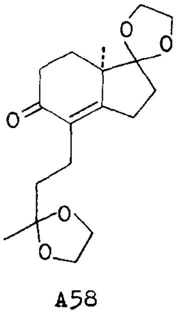
A24 to A35 - all 17β-C_8H_{17}

A24	6α-OH
A25	6α-OAc
A26	6α-Br
A27	6α-N_3
A28	6α-NO_2
A29	6β-OH
A30	6β-OAc
A31	6β-N_3
A32	6β-NHAc
A33	6β-SO_3Me
A34	6β-Br
A35	6β-NO_2
A36	6β-Me, 17α-Me, 17β-OH
A37	19-nor, 6β-OH, 17β-OH
A38	19-nor, 6β-Br, 17β-OAc
A39	19-nor, 10β-OH, 17β-OH
A40	1α-Me, 17β-OH
A41	19-nor, 1α-Me, 17β-OH
A42	1β-Me, 11β-OH, 17=BMD
A43	19-nor, 1β-Me, 17β-OH
A44	2α-Me, 17β-OAc
A45	19-nor, 2α-Me, 17α-Me, 17β-OH
A46	2α-Br, 17β-C_8H_{17}
A47	2β-Me, 17β-OH
A48	19-nor, 2β-Me, 17α-Me, 17β-OH
A49	2β-Br, 17β-C_8H_{17}
A50	4-Br, 17β-C_8H_{17}
A51	4-OMe, 17β-C_8H_{17}
A52	9α-Me, 11β-OH, 17=BMD
A53	9α-Br, 11β-OH, 17α-Me, 17β-OH
A54	9α-OH, 11β-OH, 17α-Me, 17β-OH
A55	B-nor, 17α-Me, 17β-OH



A56 n = 1

A57 n = 2



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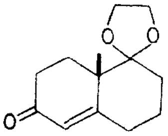
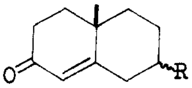
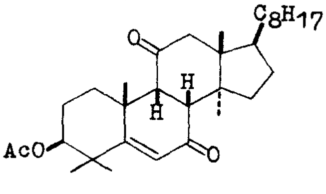


A59



A60 R = α-C/Me/=CH_2

A61 R = β-CMe_2OAc



A62

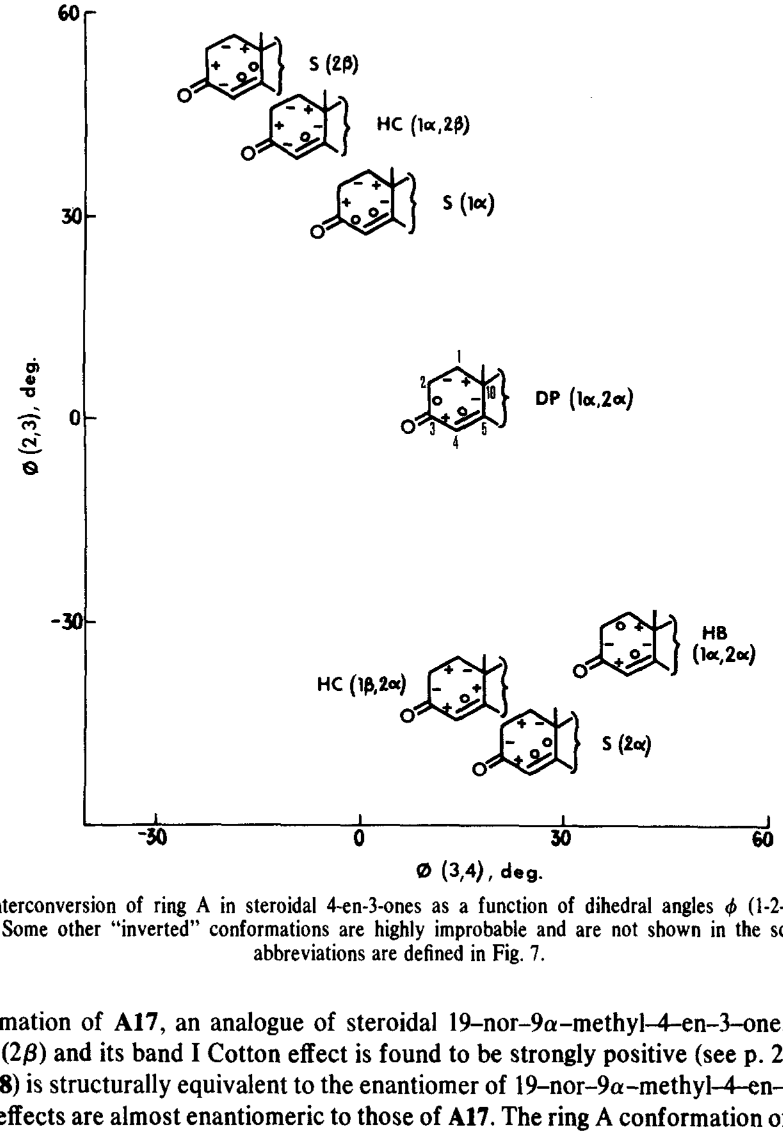


Fig. 8. Interconversion of ring A in steroidal 4-en-3-ones as a function of dihedral angles ϕ (1-2-3-4) and ϕ (2-3-4-5). Some other "inverted" conformations are highly improbable and are not shown in the scheme. The abbreviations are defined in Fig. 7.

The conformation of **A17**, an analogue of steroidal 19–nor–9α–methyl–4–en–3–one, is described as equivalent to $s(2\beta)$ and its band I Cotton effect is found to be strongly positive (see p. 23). Likewise, the retrosteroid (**A8**) is structurally equivalent to the enantiomer of 19–nor–9α–methyl–4–en–3–one and its reported Cotton effects are almost enantiomeric to those of **A17**. The ring A conformation of the retrosteroid (**A8**) is close to HC(1β, 2α). Retrosteroids indeed have ring A and B torsional angles of opposite sign to those of normal steroids, as determined by X-ray analysis.[42,44]

The enone **A16** (des–A steroid) most probably exists in an equilibrium of the two conformations (e.g. normal and "inverted" HC, see conspiciously low $\Delta\epsilon$ values).

The configurational isomers of steroidal 4–en–3–ones (**A5**, **A6** and **A9–A11**), having non-chair cyclohexane rings in the skeleton, deserve separate mentioning. In the 10α-isosteroids (**A5** and **A6**) ring B cannot accommodate a chair form and takes up one of the flexible conformations. Inversion of configuration at C–10 leads to the inversion of the ring A conformation, i.e. to the $s(1\beta)$ conformation. This is the most probable conformation of ring A in **A6** which displays π–π^* region Cotton effects of opposite sign to those typical for $s(1\alpha)$ (see for example **A1** Cotton effects). The incomplete CD data for **A5** point to a more complex conformational equilibrium.

Twist-boat forms were found by X-ray analysis for rings B and C of a 9β-iso-steroid,[45] structurally related to **A9**. The CD data of **A9** point to the ring A conformation close to DP(1α, 2α) and the X-ray data disclose positive $\emptyset(3,4)$ angle† for a 9β-iso-steroid.[45]

Flexible forms for rings B and C are also expected for 8α-iso-steroids, such as **A10** and **A11**. Nevertheless CD data indicate the presence of the normal HC(1α, 2β) conformation of ring A in **A11** (see X-

---

†The enone skew angle ω is related to the endocyclic torsional angle $\emptyset$ by the following approximation: $\omega = \emptyset - 180$ for $\emptyset > 0$, $\omega = 180 + \emptyset$ for $\emptyset < 0$.

ray data on a similar 8α–system[46]). The CD data of a more strained **A10** are less conclusive, probably due to the contributions of more than one conformer.

Considering the signs of band II Cotton effects of class A cyclohexenones, we find that they are consistently governed by the absolute configuration of the $\Delta^{1(9)}$–octalin–2–one system. Enones belonging to the P configurational family (Fig. 9) display a positive band II Cotton effect, while enantiomeric M type derivatives give negative band II Cotton effect (Table 4). The case of the two enones (**A12** and **A13**) is particularly interesting as it shows that change of the sign of n–π^* and band I Cotton effects due to the allylic substituents (4, 4-dimethyl group) is not accompanied by the change in the sign of band II Cotton effect.

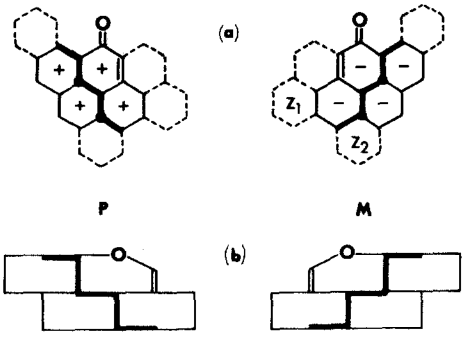


Fig. 9. Correlation of absolute configuration and the sign of cyclohexenone band II Cotton effect: (a) in-plane projection of the extended ring skeleton (rings contributing most significantly are marked with signs and heavy lines for common C–C bonds); (b) octant-like projection of the skeleton with cyclohexenone ring in a sofa conformation.

In certain cases the band II Cotton effect is relatively weak and obscured by the band I Cotton effect of the same sign (e.g. **A20**), or the CD data are incomplete (Table 4).

Figure 9 shows the generalized structural dependence of the sign of band II Cotton effect. Four rings in the extended arrangement, drawn in full lines, are found to contribute most significantly to the band II Cotton effect. It is easily seen that the structures involving cyclohexenone ring and any one of the three other important rings produce at least three C–C bond zig-zag arrangement (shown with bold lines) which in fact may be reasonable for the appearance of the band II Cotton effect. Further support for this hypothesis is found for enones of other classes discussed below.

As an exception, the enones **A15**, **A16** (des-A steroids), and 7–en–6–one **A23** display weak positive band II Cotton effects, although they belong to the configurational M-type. There is no obvious reason for this lack of consistency, although it can be related to the exceptional structure of these enones, bearing a 5-membered ring in place of either of the 6-membered rings Z^1 or Z^2 shown in Fig. 9(a).

In the case of 9(11)–en–12–one (**A2**) a strong positive band is observed at short wavelengths (below 200 nm) in acetonitrile. Data of Table 5 show unambigously that in the more polar solvent, hexafluorisopropanol, this CD band splits into two components— one shifted to the red side (band II at 215 nm) and the other—to the blue side (band III at 192 nm). The assignments of the two components are made on the basis of the expected solvent shifts for π–π^* and n–σ^* transitions, respectively. The band II Cotton effect follows the configurational rule mentioned earlier and the positive band III Cotton effect appears to reflect the presence of an α'-axial Me group (structural type enantiomeric to that shown in Fig. 4).

Derivatives of Δ^1-octalin–3–one (**B**) *and Δ^2-octalin–1–one* (**C**). Enones of these classes have endocyclic C=C bond and unlike class **A** enones their common feature is the opposite sign of band I and band II Cotton effects. The CD data for derivatives of **B** and **C** are limited in number, the majority of them being for steroid compounds. The steroidal 1–en–3–ones (**B1–B6**) are the most common examples. The conformation of cyclohexenone ring in this series is probably sofa (5α). It can be deformed in some cases, for example due to the interaction between substituent at C–1 and 11α–H, leading to increase of the $\phi(2, 3)$ torsional angle. In fact, X-ray data for (**B2**)[47a] and its 17α-methylderivative[47b] are helpful in showing that remote structural changes can bring about substantial changes in the conformation of 1–en–3–one chromophore, at least in the solid state—the $\phi(2, 3)$ torsional angle is found respectively as +2.9°[47a] and −10.7°[47b].

All (5α)–1–en–3–ones (**B1–B5**) and their tricyclic analog (**B7**) show negative n–π^* and strong positive band I Cotton effects. In 10β-methyl–1–en–3–ones (**B1** nd **B2**) the band I Cotton effect is smaller than in

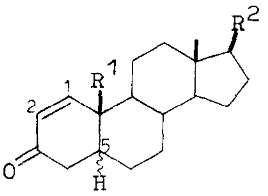
19–nor–analog (**B3**), presumably due to the *consignate* contribution of the allylic axial Me group, of the order of $\delta\Delta\epsilon = -10$. The n–π^* and band I Cotton effects of **B4** are enhanced due to the increased skew of the chromophore, imposed by the interaction of 1–Me and 11α–H.

B6 and **B8** are representative of Δ^1-octalin–3–ones with *cis*-ring fusion. The *s*(5β)–HC(4α, 5β) conformation of ring A and positive chirality of the allylic axial C9–C10 bond contribute to the strong positive

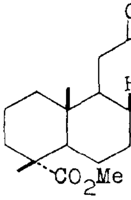
Table 5. CD data for classes B–D cyclohexenones

No.	Compound	Configurational type	n-π*	Band I	Δε/λmax./ Band II	Band III	ε/λmax./ Band I	Solvent[a]	Ref.
B1	5α-Cholest-1-en-3-one	M	-0.94 /349/	+11.6 /226/	-10.2 /199/		9,570 /223/	h	
			-1.04 /341/	+11.8 /233/	-10.4 /202/		9,200 /228/	a	
			-1.24 /335/	+11.8 /236/	-10.0 /203/		9,050 /231/	m	
			-3.38 /313/	+15.7 /248/	-10.2 /212/		9,000 /241/	f	
B2	17β-Acetoxy-5α-androst-1-en-3-one	M	-0.78 /348/	+11.9 /226/	-8.7 /199/			h	aa
B3	17β-Acetoxy-5α-estr-1-en-3-one	M	-0.65 /348/	+19.8 /223/	-14.9 /198/			h	aa
B4	17β-Hydroxy-1-methyl-5α-androst-1-en-3-one	M	-3.73 /323/	+16.2 /239/	-9.2 /206/			m	
B5	17β-Acetoxy-2-methyl-5α-androst-1-en-3-one	M	-1.32 /335/	+10.5 /242/	-7.9 /206/			m	
B6	17β-Acetoxy-5β-androst-1-en-3-one	M	+0.4 /342/						
			-0.4 /308/	+19.1 /229/	-10[b] /200/			m	bb
B7	Methyl 12-oxopodocarp-13-en-18-oate	M	-0.56 /331/	+11.6 /232/	-11.3 /205/			m	aa
B8	5β,25D-Spirost-3-en-2-one	P	-1.28 /336/	-5.1 /235/	+3[b] /210/			d	cc
B9	5α-Cholest-3-en-2-one	M	-0.16 /369/						
			+0.40 /344/	+10.8 /229/	-7.2 /202/	+2.2 /188/	8,700 /225/	h	
			-0.10 /357/						
			+0.20 /319/	+9.3 /236/	-4.3 /205/	+2.3 /189/	8,200 /229/	a	
			-0.15 /345/						
			+0.05 /310/	+8.7 /238/	-3.8 /207/	+2[b] /190/	8,320 /231/	m	
			-2.1 /310/	+9.9 /252/	-3.6 /218/	+1.8 /190/	8,240 /241/	f	
B10	6α-Acetoxyselin-3-en-11-ol-2-one	M	-1.7 /328/	+12.4 /241/	-3.7 /205/			m	dd
B11	α-Rotunol	M	-0.16 /361/						
			+0.15 /310/	-4.6 /242/				d	ee
B12	β-Rotunol	P	-1.05 /334/	+15.5 /236/	c	-15[b] /200/		d	ee
C1	5α-Cholest-2-en-1-one	P	+0.11 /392/						
			-1.72 /344/	-0.4 /229/		+28.0 /198/	8,200 /219/	h	
			-2.00 /321/	c	+12.3 /207/	+11.4 /191/	7,900 /230/	f	
C2	/6S,9S,10S/-6-Acetoxy-9-methyl-Δ^2-octalin-1-one	M	-0.20 /362/						
			+0.30 /338/	+0.25 /234/		-10.6 /195/		h	ff
			-0.14 /336/						
			+0.09 /308/	c	-2.7sh/204/	-3.6 /194/		f	
D1	3α,20-Dihydroxy-5α-pregn-8-en-7-one	P	+1.3 /333/	-6.4 /250/	+3.6 /209/			m	bb
D2	Methyl 3α-hydroxy-7-keto-5β-chol-8-enoate	P	+0.50 /318/	-2.2 /248/	+3.0 /210/			m	
D3	3β,11α,20-Triacetoxy-5α-pregn-8-en-7-one	P	+0.72 /375/	-2.1 /255/	d			d	gg
D4	3β,11α,15α-Triacetoxy-5α-pregn-8-en-7-one	P	+0.84 /362/	+14.4 /248/	-6.4 /218/			d	gg
D5	5α-Androst-8-en-11-one	M	-1.92 /335/	+9.0 /255/	-4.2 /220/			m	hh
D6	5α,14β-Androst-8-en-11-one	M	-0.74 /325/	+5.3 /248/	-3.4 /210/			m	hh
D7	3α-Hydroxy-5β-androst-8-en-11-one	M	-0.4 /314/	+8.1 /243/	-11.6 /203/			m	bb
D8	Methyl 11-oxo-13β-abiet-8-en-18-oate	M	-0.4 /325/	+10.8 /235/	-6.5 /203/			h	aa

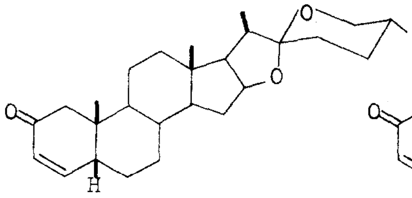
[a] See Table 2. [b] Maximum not reached. [c] Not observed. [d] Not reported. [aa] Data kindly provided by Prof. A.W.Burgstahler. [bb] Ref. 16. [cc] K.Takeda, G.Lukacs, and F.Yasuda, J. Chem. Soc. /C/, 1041 /1968/. [dd] J. de Pascual, I.S.Bellido, and M.S.González, Tetrahedron, 36, 371 /1980/. [ee] H.Hikino, K.Aota, D.Kuwano, and T.Takemoto, Tetrahedron, 27, 4831 /1971/. [ff] Table 4, footnote rr. [gg] E.J.Taylor and C.Djerassi, J. Org. Chem., 42, 3571 /1977/. [hh] D.G.Patterson, C.Djerassi, Y.Yuh, and N.L.Allinger, J. Org. Chem., 42, 2365 /1977/.



B1	R^1=Me,R^2=C_8H_{17} /5α/
B2	R^1=Me,R^2=OAc /5α/
B3	R^1=H,R^2=OAc /5α/
B4	R^1=Me,R^2=OH,1-Me /5α/
B5	R^1=Me,R^2=OAc,2-Me /5α/
B6	R^1=Me,R^2=OAc /5β/



B7



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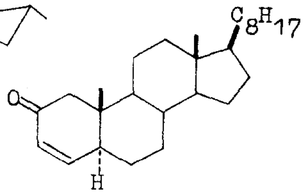
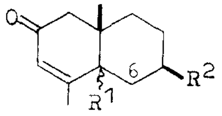
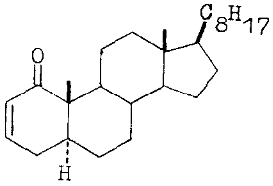


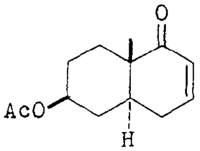
B9



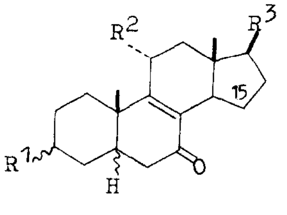
B10	R^1=α-H,R^2=CMe_2OH,6α-OAc
B11	R^1=α-OH,R^2=C/Me/=CH_2
B12	R^1=β-OH,R^2=C/Me/=CH_2



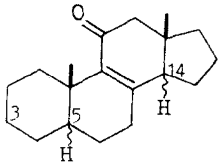
C1



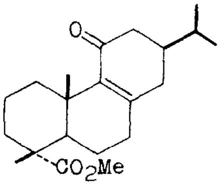
C2



D1	R^1=α-OH, R^2=H, R^3=CH/OH/Me /5α/
D2	R^1=α-OH, R^2=H, R^3=$C_4H_8CO_2Me$ /5β/
D3	R^1=β-OAc, R^2=OAc, R^3=CH/OAc/Me /5α/
D4	R^1=β-OAc, R^2=OAc, R^3=C_8H_{17}, 15α-OAc /5α/



D5	5α, 14α
D6	5α, 14β
D7	5β, 14α, 3α-OH



D8

band I Cotton effect in (5β)-1-en-3-one (**B6**). The $s(10\alpha)$ conformation of (5β)-3-en-2-one (**B8**) is equivalent to $s(5\beta)$ conformation of **B6** but presumably due to the lack of an allylc axial alkyl substituent in **B8** the band I Cotton effect is negative.

The cyclohexenone ring of (5α)-3-en-2-one (**B9**) and bicyclic 3-en-2-one (**B10**) can be compared structurally to that of **B3** and **1e**. Solvent studies reveal striking similarity of the $n-\pi^*$ Cotton effect in **B9** and **1e**, implying similar conformations of the cyclohexenone ring in both compounds. However, while the band I Cotton effect of **B9**, **B10**, and **B3** is positive, that of **1e** is negative (Tables 2 and 5). This leads to an estimate of the contribution of the allylic group with axial tertiary C–H bond as strong *dissignate* ($\delta\Delta\epsilon = +15$), after correction for the conformational effect in **B3**.

Enones **B1–B5**, **B7**, **B9**, and **B10** belong to the M-configurational type and accordingly they display negative band II Cotton effect (Table 5). In addition 3-en-2-one (**B9**) displays a weak positive Cotton effect at *ca.* 190 nm, consistent with the presence of a β'-axial Me group (band III Cotton effect, Fig. 4). The application of the configuration rule as shown in Fig. 9 to *cis*-fused ring A/B 1-en-3-one (**B6**) and 3-en-2-one (**B8**) is not obvious. It should be noted however that **B6** and **B2** have the same absolute configuration at allylic carbon C10 and both display negative band II Cotton effect, while (5β)-3-en-2-one (**B8**) and (5α)-3-en-2-one (**B9**) have opposite configurations at allylic carbon C5 and opposite band II Cotton effects.

For β-rotunol (**B12**) CD data appear to suggest a non-steroidal conformation of the *cis*-fused ring system. That is the strong positive band I Cotton effect, compared with the negative Cotton effect of **B8**, could be rationalized assuming a positive contribution of the allylic axial OH group. In addition, the strong negative band III Cotton effect of **B12** below 200 nm suggests a negative contribution of the β'-axial C9–C10 bond.

The case of 5α-cholest-2-en-1-one (**C1**) is of considerable interest. As expected for the sofa conformation of the cyclohexenone ring and lack of an allylic axial substituent, the band I Cotton effect is weak and the $n-\pi^*$ Cotton effect is of medium intensity. In heptane solution this compound shows an exceptionally strong CD band centered at 198 nm. As for **A21** the short-wavelength maximum splits into two components in hexafluoroisopropanol (Table 5). This correlates well with the P-type configuration (band II) and the presence of an α'-axial Me group (band III) in **C1**. The bicyclic enone (**C2**) is quasi-enantiomeric to C1 and so are the signs of the corresponding Cotton effects (note the separation of band II and III Cotton effects in hexafluoroisopropanol).

Table 6. CD data for classes E and F *cis*-enones

No.	Compound	Configu-rational type	n-π*	Δε/λmax./ Band I	Δε/λmax./ Band II	Δε/λmax./ Band III	ε /λmax./ Band I	Solvent[a]	Ref.
E1	Cholest-5-en-4-one	M	+1.08 /333/	+0.1 /260/ -7.1 /228/	-6.6sh /216/	-6.4 /189/	7,150 /234/	h	
			+1.43 /328/	+0.1 /268/ -7.7 /229/	-7.8 /218/		6,900 /240/	a	
			+1.76 /319/	b	-7.6 /222/		6,800 /243/	m	
			+3.60 /293/	-9.0 /248/	-8.2sh /229/		6,750 /254/	f	
E2	6-Methylcholest-5-en-4-one	M	+1.36 /335/	-8.0 /225/				h	aa
E3	A-Norcholest-5-en-3-one	M	-1.23 /337/	+0.55/251/ -1.5sh/236/	-5.2 /211/			h	
			-1.22 /327/	-5.3sh/242/	-5.6 /227/			m	
E4	Cholest-4-en-6-one	P	-1.2 /325/	+3.5sh/235/	+9.2 /210/			m	bb
E5	4-Methylcholest-4-en-6-one	P	-2.14 /331/	b	+12.9 /210/			h	aa
E6	3β-Acetoxy-5α-cholest-8/14/-en-7-one	P	c	-5.4 /260/	+5.2 /215/			m	cc
E7	3β-Acetoxy-5α-cholest-8/14/-en-15-one	P	+1.80 /350/	+3.7 /252/	+4.5 /223/			h	bb
E8	3β-Acetoxy-9α-hydroxy-5α-cholest-8/14/-en-15-one	P	+1.57 /355/	+8.4 /244/	b			h	dd
F1	2-Isopropylidene-5α-cholestan-3-one		+0.72 /332/	-2.2 /240/	+0.4 /211/	-7.5 /193/		h	
F2	Cuauhtemone		+1.25 /322/	-2.8 /252/	c			m	ee
F3	Chiloscyphone		-0.85 /356/	-14.0 /222/	c			h	ff

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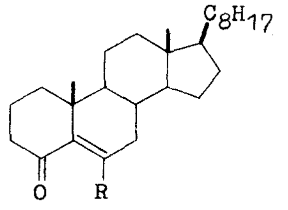
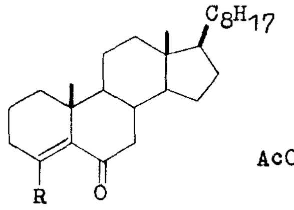
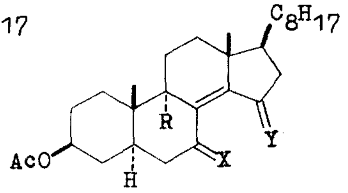
[a] See Table 2. [b] Not observed. [c] Not reported. [aa] J.R.Bull, J. Chem. Soc. /C/, 1128 /1969/. [bb] Ref. 19a. [cc] Ref. 17. [dd] Sample kindly provided by Dr. M.Anastasia. [ee] Ref. 49. [ff] A.Matsuo and S.Hayashi, Tetrahedron Letters, 1289 /1970/.



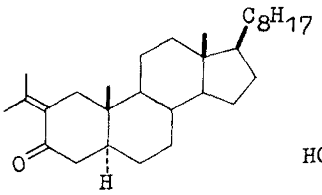
E1 R=H
E2 R=Me
E3 A-nor,R=H



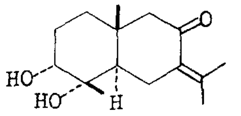
E4 R=H
E5 R=Me



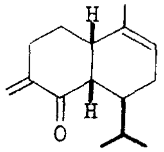
E6 R=H,X=O,Y=H_2
E7 R=H,X=H_2,Y=O
E8 R=OH,X=H_2,Y=O



F1



F2



F3

Derivatives of Δ^9*-octalin-*1*-one* (**D**). This class of enones with doubly endocyclic C=C bond is represented by relatively small number of examples (Table 5). If rings C and D in steroidal 8–en–7–ones (**D1–D4**) are neglected, the remaining A/B-ring system has mirror-image structure compared with steroidal 1–en–3–ones (class B). Cotton effects displayed by (**D1–D3**) are indeed of opposite sign to those of **B1–B5**, including band II Cotton effect. The enone (**D4**) has exceptional CD spectrum, apparently due to the peculiar effect of the 15α-acetoxy group situated in the immediate vicinity of the 7–keto–chromophore.

It is now clear that structurally class **D** enones can be reduced to class **B** enones, as the chiroptical properties of enones of both classes are quite similar. That is the additional ring fused to the C=C bond has only a minor effect on the CD spectra. The symmetrical setting of the C=C bond in the decalin skeleton in **D**-type enones can be responsible for their generally lower Cotton effects, *via* partial cancelling of vicinal contributions.

Further support for the above generalization comes from the analysis of chiroptical data on 8–en–11–ones **D5–D8**. These cyclohexenones are quasi-enantiomeric to **D1–D3** and hence of the same stereochemical type as steroidal 1–en–3–ones (class **B**), if rings A and B are neglected. Not unexpectedly the Cotton effects displayed by **D5–D8** are of the same sign as those of **B1–B5**. Band II Cotton effects are negative, just as required for the M configurational type. Except for some variations in the magnitudes of Cotton effects, the configurations at C–5 and C–14 do not appear to be essential for determining the signs of Cotton effects.

Derivatives of Δ^8*-octalin-*1*-one* (**E**). As mentioned earlier, *cis*-enones of this type have a highly skewed chromophore. For the 4–en–6–one (**E4**) $\omega = -31.36°$ was found from the X-ray crystal data.[48] With the notable exception of cyclopentanone derivatives (**E3**, **E7** and **E8**),[12] the n–π^* Cotton effect of other *cis*-enones is directly related to the helicity of the chromophore (Fig. 1). Despite significant non-planarity of the chromophore, available CD data (Table 6) indicate that inherent dissymmetry is not directly related to the sign of the band I cotton effect. In fact, the only *cis*-enone in Table 6 that conforms to the enone helicity rule[11] is 8(14)–en–7–one (**E6**), having $\omega < 0$ and a negative band I Cotton effect.

The 5–en–4–ones (**E1**, **E2**), A–nor–5–en–3–one (**E3**), and 4–en–6–ones (**E4**, **E5**), although related structurally, display diverse π–π^* region Cotton effects. The band I Cotton effects are small to medium intensity (Table 6) and when well-defined are of opposite sign to that predicted on the basis of the enone helicity rule.[11] In **E2** band I and II Cotton effects are not separated and in case of **E5** there is no indication of band I Cotton effect. Furthermore, **E1** and **E3** display peculiar bisignate band I Cotton effects in non-polar solvents.

The band II Cotton effects of **E1–E3** are negative and for the quasi-enantiomeric enones (**E4** and **E5**) are strongly positive. The signs and magnitudes of band II Cotton effects correlate well with those of *trans*-enones having their C=C bonds in the same position in the skeleton, i.e. **E1–E3** correlate with the

(A12) (M-configurational type) and **E4** and **E5** correlate with the **A1** (P-configurational type). *cis*-Enones with 8(14)–C=C bond, (**E6** and **E7**), also display band II Cotton effects in accordance with the configurational rule.

The above correlation is quite acceptable upon consideration of the transition moment direction. In stereochemically related enones (**E1** and **A12**) the directions of band II transition moment vectors form almost the same angle with the direction of the orientation axis (longitudinal axis of the steroid skeleton), as determined by recent linear dichroism studies.[26]

α-Alkylidene-decalones (**F**). Listed below are some comments on the very few CD data available on these highly skewed *cis*-enones with exocyclic C=C bond.

(i) The n–π* Cotton effects generally correlate with the enone skew angle, as defined by the helicity rule (Fig. 1).

(ii) The band I Cotton effects displayed by α-isopropylidene-ketone (**F1**) (Table 6), as well as by **2a** and **2e** have opposite signs to those predicted by the helicity rule,[11] as it was already seen in case of other *cis*-enones of **E**-type. The enone **F2** (cuauhtemone), although quasi-enantiomeric to **F1**, displays n–π* and band I Cotton effects very similar to those of **F1**. While no ready rationalization can be offered at present, it is suggested that additional support for the absolute configuration of **F2**, determined by Pr(dpm)$_3$-induced CD,[49] would be of great value. In contrast chiloscyphone (**F3**), a conformationally flexible *cis*-decalin derivative, displays both n–π* and band I Cotton effects in accordance with the helicity rule,[10, 11] if one assumes a non-steroidal conformer with the equatorial isopropyl substituent dominating the equilibrium.

(iii) Band II Cotton effect of **F1** is extremely weak (*cf* enone **2** CD data). A possible explanation is the unfavourable direction of the transition moment[26] with respect to the skeletal bonding pattern.

(iv) Below 200 nm **F1** displays a negative Cotton effect, tentatively assigned as band III Cotton effect (blue shift in hexafluoroisopropanol). The origin of this negative Cotton effect, as in case of **2e**, is not clear at present.

EFFECT OF ALLYLIC SUBSTITUTION

Remote substituents in polycyclic systems have little influence on the chiroptical properties of enone chromophore. For example there is essentially no difference between the CD spectra of steroidal 4-en-3-ones with or without side chain at C-17,[50,51] or with/without substituents at C-12, or C-11, or C-7.[50] Furthermore the configuration at C-13 is known not to alter CD spectra of 4-en-3-ones.[52] Understandably, in such cases the conformation of the cyclohexenone ring A remains essentially unchanged, as judged from the available X-ray data.[42,43a,b]

Equatorial substituents in the 6α-position [Table 4, **A24–A28**, *cf* **A1**] have little influence on the chiroptical properties of the 4-en-3-one chromophore, as noted by Hudec *et al.*[21] This is not surprising in view of an expected small conformational effect (*cf* NMR data[53,54]). In addition, the 6α-substituent is located close to the nodal plane of the enone chromophore.[21]

Polarizable bonds in the allylic axial position, especially those with good donor properties, have remarkable effects on band I Cotton effect and in some cases[19] on the n-π* Cotton effect (Table 4, **A29–A36**). Except for **A35** all other 6β-substituted 4-en-3-ones (**A29–A36**) exhibit negative band I Cotton effect that is attributed to the strong *consignate* allylic axial chirality contribution of a C–X bond. The estimated $\delta\Delta\epsilon$ contributions are listed in Table 7. The 6β C–N bond in the nitroenone (**A35**) is a poor donor and it does not contribute to the band I Cotton effect. In derivatives **A29–A32**, **A35**, and **A36** the 1,3-diaxial interaction between 10β-Me and 6β-substituent is relatively small and does not affect the ring B conformation significantly. However, some distortion of ring B is expected in 4-en-3-ones with bulky 6β-substituents (**A33**, **A34**), on the basis of NMR data.[50,53,54] This distortion is transmitted to ring A causing it to adopt a conformation with a more negative ω angle (the 4-en-3-one chromophore of 6β-bromoprogesterone is found by X-ray analysis to be nearly planar with a small negative ω angle.[55]) It can be concluded, in agreement with Hudec,[21] that the positive n-π* Cotton effect of 4-en-3-ones (**A33**, **A34** and **A36**) as well as negative band I Cotton effect of **A29–A34** and **A36** are primarily due to the chiral perturbation of the chromophore by the allylic axial 6β C–X bond.

Further evidence for the primarily non-conformational effect of substitution at 6β-position comes from comparison of the CD data on derivatives of 19-nortestosterone (**A37** and **A38**). Here, in the absence of 1,3-diaxial interaction, ring A adopts normal conformation of 19-nor-4-en-3-one,[54] yet the band I Cotton effect is negative.

On the other hand, scarce CD data[18] indicate that allylic axial substituents in 10β-position of steroidal

Table 7. Contributions of allylic axial 6β-substituents to the band I Cotton effect of steroidal 4-en-3-ones

Substituent	$\delta\Delta\varepsilon$	Reference compounds
OH	-9, -13	A29/A1, A37/A3
OAc	-7	A30/A1
NHAc	-8	A32/A1
N_3	-15	A31/A1
SO_3Me	-14	A33/A1
Br	-25, -19	A34/A1, A38/A3
Me	-10	A36/A4
NO_2	-1	A35/A1

4-en-3-ones do not influence significantly band I Cotton effect (e.g. **A39**, Table 4). The more significant contribution of the *heteroannular* allylic axial bond 6β compared with the *homoannular* allylic axial bond 10β evidently results from their relative positions with respect to the π-π^* (band I) transition moment direction in **A1**.[26]

Other substituted cyclohexenones (**A23**, **B11**, **B12**, and **E8**) also show the effect of allylic axial bond contribution to the band I Cotton effect. The positive (*consignate*) allylic C–O bond contribution is found by comparison of band I Cotton effects of **A22** and ecdysone **A23**, as well as of **E7** and **E8**. In α-rotunol (**B11**) the band I Cotton effect is negative while that of structurally related **B10** with no allylic OH-group is strongly positive. Similar sign inversion of the band I Cotton effect due to an allylic axial OH-group is shown by β-rotunol (**B12**, see p. 17).

Perhaps the most striking feature of the CD spectra of substituted steroidal 4-en-3-ones (**A24**–**A39**) is the persistently positive band II Cotton effect, also exhibited by unsubstituted enones (**A1**–**A4**), and previously correlated by Burgstahler *et al.* to the positive chirality contribution of the 2β-hydrogen.[19a] Here we wish to emphasize the insensitivity of the band II Cotton effect to allylic substitution and its dependence on the absolute configuration of the polycyclic skeleton (Fig. 9). The variations in magnitude and position of maximum of the band II Cotton effect are attributable primarily to the contributions from optically active transitions of substitutents at C-6 having absorption bands in the 220–200 nm region.

CONFORMATIONAL EFFECTS

The relatively flexible ring A of steroidal 4-en-3-ones is subject to conformational changes caused by substitution on rings A and B. These changes are followed by dramatic changes in the CD spectra, summarized in Table 8.

Table 8. Effect of ring A conformation on the CD of steroidal 4-en-3-ones

Predominant conformation	ϕ/3,4/	Position of methyl substituent	$\delta\Delta\varepsilon^a$ n-π^*	$\delta\Delta\varepsilon^a$ Band I	$\delta\Delta\varepsilon^a$ Band II	Source
S/2β/	-	1α or 9α	-0.8 to -1.6	+6 to +11	-10	A40, A41, A52
HC/1α,2β/	-	2α	-1.3 to -1.5	+4	ca.0	A44, A45
HC/1β,2α/	+	1β or 2β	+2.8 to +3	-27 to -30	ca.0	A42, A47
S/2α/	+	1β /19-nor/	+2.8	-30	-10	A43

[a] relative to $\Delta\varepsilon$ values for S/1α/ in A4

As mentioned earlier, the most stable conformation of ring A in 10β-methyl-4-en-3-ones, e.g. **A1**, **A4** is $s(1\alpha)$-HC(1α, 2β). In the absence of a 10β-Me group the ring A conformation approaches HC(1α, 2β). The CD spectra of the corresponding 19-nor-derivatives, such as **A3**, differ from that of **A4** by increased n-π^* and band I Cotton effects. This is consistent with the increased torsional angle $\phi(3,4)$ in HC(1α, 2β) compared to $s(1\alpha)$. It has to be mentioned, however, that X-ray data indicate a disorder in the crystal lattice, resulting from the presence of species with "inverted" HC(1β, 2α) conformation in 19-nortestosterone (**A3**).[56] Calculations show that while in testosterone (**A4**) the HC(1α, 2β) conformation is some 2.7 kcal/mol more stable than HC(1β, 2α), in 19-nortestosterone (**A3**) the difference is reduced to *ca.* 1 kcal/mol; thus there is considerable amount of HC(1β, 2α) in the equilibrium at room temperature.[57]

This is also confirmed by low-temperature CD studies of **A3**.[58] The normal HC($1\alpha, 2\beta$) conformation is stabilized by equatorial 2α-substituents, both in 19-nor and 10β-Me series, e.g. **A44–A46** (Table 8), and to some extent by 4-substituents, e.g. **A2**, **A50**, and **A51** (see changes in the n-π^* Cotton effects reported by Bloch and Wallis[59]).

Conformational changes of ring A in steroidal 4-en-3-ones as a function of torsional angles $\phi(2,3)$ and $\phi(3,4)$ are summarized in Fig. 8 and are substantiated by the results of the relevant X-ray analyses collected in the Appendix.

Data of Table 8 indicate the extent of change of the CD spectra of 4-en-3-ones upon changing ring A conformation. The $s(2\beta)$ conformation in 1α-substituted 4-en-3-ones (**A40** and **A41**), and in 9α-substituted 4-en-3-ones (**A52–A54**), with large negative torsional angle $\phi(3,4)$ and large negative n-π^* and positive band I Cotton effects, is a well-documented example. Other more strained conformations, i.e. DP($1\alpha, 2\alpha$), $s(2\alpha)$, and HC(1β, 2α) are obtained upon twisting $\phi(3,4)$ in the opposite direction, i.e. towards positive values (the half-boat HB(1α, 2α) conformation is less likely to occur, as it produces high strain in ring B due to the small ϕ(6-5-10-9) torsional angle). In $s(2\alpha)$, which is quasi-enantiomeric to $s(2\beta)$, e.g. in 1β-methyl-19-nor-4-en-3-one (**A43**), as well as in HC($1\beta, 2\alpha$), e.g. in 1β-methyl- (**A42**), or 2β-methyl-4-en-3-one (**A47**) the n-π^* Cotton effect is positive and the band I Cotton effect is strongly negative, owing to the significant positive torsional angle $\phi(3,4)$. The dipole–dipole repulsion between C=O and C–Br bonds is mainly responsible for the presence of the normal HC($1\alpha, 2\beta$) in addition to the "inverted" HC($1\beta, 2\alpha$) in **A49**.

In the DP($1\alpha, 2\alpha$) conformation the increased negative torsional angle ϕ(4-5-10-1) is the result of the decreased positive torsional angle ϕ(6-5-10-9). Examples of such specific ring B distortion include **A60**, and B-nor enones (**A55** and **A56**). The n-π^* Cotton effect is positive and the band I Cotton effect varies from nearly zero to strong negative in these enones, depending on the amount of DP($1\alpha, 2\alpha$)-conformer in the equilibrium. The exceptionally strong negative band I Cotton effect of **A56** is probably partly due to the contribution of the homo-conjugated CO substituent; see quasi-enantiomeric **A58** with decreased Cotton effects. The analogous effect is evident for **A57**, when compared to the ketal derivative **A59**. The CD data for bicyclic enone (**A61**) should serve as reference for the CD data of its distorted analogue (**A60**).

Inspection of the data of Table 8 leads to the conclusion that although the band II Cotton effect remains positive in the reported examples (in accordance with P-configurational type), its intensity varies in a regular manner. The high intensity band II Cotton effects are found in $s(1\alpha)$ and HC(1α, 2β) or HC(1β, 2α) conformations; they are least intense and practically not observed in highly skewed $S(2\beta)$ or $S(2\alpha)$ conformations (in these cases the band I Cotton effect dominates the CD curve but the presence of a hidden weak band II Cotton effect cannot be ruled out). This observation suggests that the magnitude of band II Cotton effect depends upon the angular relation of the transition moment to the C–C bond framework.

CONCLUDING DISCUSSION

We have shown that the π-π^* region (260–185 nm) CD spectra of α,β-unsaturated ketones are made-up of up to three Cotton effects, belonging to the three separate transitions: the first two (lowest energy) Cotton effects are correlated with the two lowest energy π–π^* transitions (red shift in polar solvents), the highest energy band is of n-σ^* type (blue shift in polar solvents).

In *trans*-enones the band I (π-π^*) Cotton effect is related to the conformation (skew angle of the chromophore). With Burgstahler *et al.*[17a,b] we conclude that the sign of the band I Cotton effect is also highly sensitive to the presence of allylic axial substituents, i.e. bonds in the plane orthogonal to the chromophore plane. The allylic axial bond contribution can be regarded as an octant contribution of a perturber with positive anisotropy, in a sector model recently developed by Weigang,[9] the direction of the transition moment being given by the linear dichroism measurements.[26]

From the limited data which are available it is seen that unlike for the n-π^* transition Cotton effect, no simple helicity rule can be applied to the band I Cotton effects of *cis*-enones. This apparent lack of correlation of the skew angle ω with enone rotational strength in the π-π^* transition band is of a paradoxical nature, as it is the *cis*-enone in 6-membered framework that is significantly skewed. This situation is also encountered when the rotational strength associated with the lowest energy π-π^* transition of *cis*-dienes is considered. Recent calculations have shown that computed rotatory strength associated with the *cis*-diene group itself is highly dependent upon small variations in structural parameters, strongly affecting the nearly orthogonal orientation of magnetic and electric transition moments. Thus the skewed *cis*-butadiene model, so successfully used in theoretical calculations, cannot be directly used as a basis for the "diene helicity rule" in more complex structures, such as cyclohexadiene.[60] It is reasonable that similar factors play a decisive role in determining the rotatory strength of the band I transition in isoelectronic *cis*-enones. Therefore there is little foundation for the belief that the theoretical "skewed acrolein model" would hold generally in case of cyclic *cis*-enones without reassessment of other structural effects, affecting the relative direction of the transition moments. One way of empirical correlation of the band I Cotton effect of *cis*-enones with structural factors is by looking at the important contributions of allylic axial substituents, as proposed by Burgstahler *et al.*[19a,b]

The finding that the band II (π-π^*) Cotton effect is primarily related to the absolute configuration of the 2-cyclohexenone ring (i.e. to the configuration at the allylic carbon C-4) can serve as a useful tool in stereochemical studies. This Cotton effect dominates the CD spectra of planar-chromophore cyclohexenones; in some highly skewed conformations, such as $s(2\alpha)$ or $s(2\beta)$ in steroidal 4-en-3-ones (Table 8) it is obscured by the strong band I Cotton effect. The "configurational rule" (Fig. 9) works with few exceptions for all enones with endocyclic C=C bond, including *cis*-enones of class E. In case of exocyclic C=C bond enones of class F the band II Cotton effect is absent or very weak, although more data are necessary for reliable conclusion.

The band II Cotton effect is not affected by substituents in the allylic axial positions; its presence can be related to the particular arrangement of C–C bonds constituting the ring framework (Fig. 9) with respect to the transition moment direction.[26] This rationale bears a resemblance to the Weigang's rule for conical contributions[9] which is explicitly applicable to the electric-dipole allowed transitions.

Our data reported here indicate that the third, band III, Cotton effect appearing in the CD spectra below 200 nm is particularly well defined if there is an α' or β' axial alkyl substituent present on the cyclohexenone ring. The alkyl substituents make consignate contributions according to the octant-like projection (Fig. 4) and the Cotton effect is related to the n-σ^* transition Cotton effect in saturated ketones.[31]

The present analysis of the CD spectra of α,β-unsaturated ketones is intended to show that, within the limits of available data, the full-range spectrum which is accessible with modern instruments can provide a wealth of structural information previously not expected from this type of measurement. Combined with the known rules for the n-π^* transition Cotton effect the rules for short wavelength transition Cotton effects can be useful for numerous stereochemical and structural studies (e.g. the determination of absolute configuration of chiral cyclohexenones obtained in asymmetric synthesis).

We expect that the rules be further developed for stereochemical studies of chiral cyclopentenones and hetero-cyclohexenones, such as α,β-unsaturated lactones and dihydropyranones.

EXPERIMENTAL

CD spectra were recorded with a Jobin-Yvon Dichrograph III equipped with a cryostat. Solutions were made with spectroscopic grade solvents at appropriate concentrations (usually 10^{-3} to 10^{-4} M). Cells with pathlength 0.01 cm to 1 cm were used.

We thank Mrs. J. Adamiec, M.Sc., for the measurements.
This work was done under Polish Academy of Sciences Grant MR 1-12.2.3.1.

Added in proof: R. D. Burnett and D. N. Kirk, *J. Chem. Soc.* Perkin I, 1460 (1981).

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Appendix. Ø/3, 4/ torsional angle of steroidal 4–en–3–ones as determined by X-ray analysis

Substituent	Ø/3,4/	References
Ring A and B unsubstituted	-8.7 to +3.5[a]	aa
19-nor	-10.9 to -1.5[b]	bb
2α-OAc	-9.7	cc
2β-OAc	+18.1 to +11.5	dd
2β-Me, 19-nor	-4.5 to -2.3	ee
6β-Br	+3.7	ff
9α-F,Cl,Br,OMe,Me	-20.9 to -6.1	gg

[a] Ø/4,5/ -1.7 to -12. [b] Ø/4,5/ -5 to -12. This broad range of Ø values is apparently due to the effect of crystal forces on molecular conformation /cf. P.Dauber and A.T.Hagler, Acc. Chem. Res., 13, 105 /1980/. [aa] Refs. 42 and 43; O.Dideberg, L.Dupont, and H.Campsteyn, Acta Cryst., B31, 637 /1975/; G.M.Sheldrick, E.Oesner, M.R.Caira, L.R.Nassimbeni, and R.A.Pauptit, ibid., B32, 1984 /1976/; P.J.Cox, P.D.Cradwick, and G.A.Sim, J.C.S.Perkin II, 110 /1976/; W.S.Sheldrick, Acta Cryst., B33, 177 /1977/; E.Surcouf, ibid., B33, 3891 /1977/; D.C.Rohrer, P.D.Strong, and W.L.Duax, ibid., B34, 2913 /1978/.

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