Correlation of Circular Dichroism and Conformation in γδ- and δε-Unsaturated Ketones

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C.d. spectra of a number of unsaturated ketones (several γδ- and one δε-) are discussed. The orientation of the C=C bond with respect to the C=O group in terms of the pathway *via* the intervening C–C bonds is important in determining the sign of the Cotton effect of the $n\rightarrow\pi^*$ transition, not the position of the double bond in a particular octant. Octant contribution can be expected only in those orientations of bonds which permit effective π back-donation from C=C *via* C–C bonds to the carbonyl group. Anomalous solvent effects on steroidal Δ^6-3-ketones are discussed.

We have reported [1] that both 5α-cholest-6-en-3-one (1) and 5α-androst-6-en-3-one (2) exhibit weak negative c.d. bands at *ca.* 296 nm in n-hexane solution corresponding to the $n\rightarrow\pi^*$ transition at 287 nm in the isotropic spectrum, and that this observation is in agreement with o.r.d. data for (1).[2] [A report [3] that (1) exhibits a double positive c.d. bond is in error,[1] the sample being contaminated with an isomer of (1).[4]] On the basis of the Octant Rule [5] both (1) and (2) would be expected to exhibit positive c.d. bands similar to those observed for the corresponding saturated ketones (3) and (4), as the relevant octant diagram (Figure 1) shows that the 6,7-double bond is clearly in a positive octant. In contrast to (1) and (2), 6-methylene-5α-cholestan-3-one (5) exhibits a weak positive c.d. band in the $n\rightarrow\pi^*$ region, although both 2α-methyl-5α-cholest-6-en-3-one (6) and 2,2-dimethyl-5α-cholest-6-en-3-one (7) exhibit negative c.d. bands.

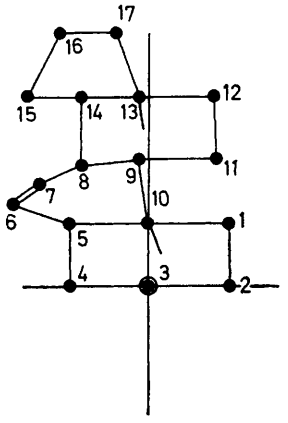
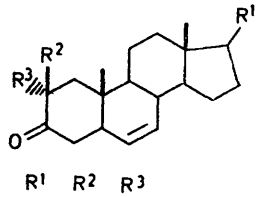


FIGURE 1 Octant diagram of 5α-cholest-6-en-3-one

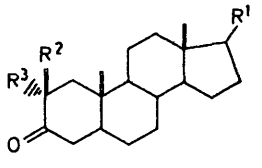
It might at first be assumed that this variation in chiroptical properties between the saturated and unsaturated 3-oxo-steroids is due to the inversion of ring A into a boat conformation caused by insertion of the 6,7-double bond.[2] However, the n.m.r. spectra indicate otherwise. The position of the 10-methyl resonance is very sensitive to molecular environment [6] and, as chemical shift values may be calculated on the basis of Zürcher's rules,[6,7] deviations from the calculated value reveal the extent to which the carbon skeleton, especially of ring A, is distorted.[8] Thus the 10-methyl resonances of (1) and (2) would be expected to be shifted upfield by 0·3 p.p.m. relative to (3) and (4); the actual shift of 0·06 p.p.m. indicates that ring A in (1) and (2) adopts a slightly flattened chair conformation. Similar comparison of the 10-methyl resonance of 2α-methyl-5α-cholestan-3-one with that of (6) shows that the latter also adopts a chair

[1] J. Hudec, *Chem. Comm.*, 1967, 539.
[2] F. Sondheimer, Y. Klibansky, Y. M. H. Haddad, G. H. R. Summers, and W. Klyne, *J. Chem. Soc.*, 1961, 767.
[3] J-C. Bloch and G. Ourisson, *Bull. Soc. chim. France*, 1964, 3018.
[4] G. Ourisson, personal communication.
[5] W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, 1961, **83**, 4013; *cf.* L. Velluz, M. Legrand, and M. Grosjean, 'Optical Circular Dichroism,' Academic Press, New York, 1965.
[6] N. S. Bhacca and D. H. Williams, 'Applications of NMR Spectroscopy in Organic Chemistry,' Holden-Day, San Francisco, 1964.
[7] R. F. Zürcher, *Helv. Chim. Acta*, 1963, **46**, 2054.
[8] R. Baker and J. Hudec, *Chem. Comm.*, 1967, 891.

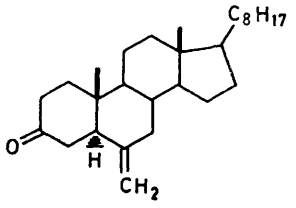
conformation. However, the 10-methyl resonance of (7) is shifted upfield by 0·29 p.p.m. in comparison with that of 2,2-dimethyl-5α-cholestan-3-one (9), and clearly



	R¹	R²	R³
(1)	C_8H_{17}	H	H
(2)	H	H	H
(6)	C_8H_{17}	H	Me
(7)	C_8H_{17}	Me	Me



	R¹	R²	R³
(3)	C_8H_{17}	H	H
(4)	H	H	H
(8)	C_8H_{17}	H	Me
(9)	C_8H_{17}	Me	Me
(10)	C_8H_{17}	Br	Me



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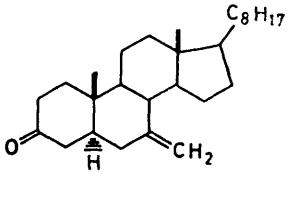

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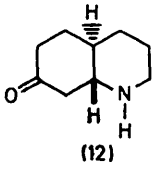


(12)

indicates that ring A in (7) is inverted into a boat conformation, in a similar manner to ring A of 2α-bromo-2β-methyl-5α-cholestan-3-one (10).[9] The 10-methyl resonance of (10) is similarly shifted upfield from the expected

TABLE 1

Chemical shift values (δ) for 10-methyl signals [a]

5α-Cholest-6-en-3-one	(1)	0·96 [b]
5α-Androst-6-en-3-one	(2)	0·98 [b]
5α-Cholestan-3-one	(3)	1·02 [b]
5α-Androstan-3-one	(4)	1·03 [c]
6-Methylene-5α-cholestan-3-one	(5)	0·90 [b]
2α-Methyl-5α-cholest-6-en-3-one	(6)	1·03
2,2-Dimethyl-5α-cholest-6-en-3-one	(7)	0·79
2α-Methyl-5α-cholestan-3-one	(8)	1·03
2,2-Dimethyl-5α-cholestan-3-one	(9)	1·08
2α-Bromo-2β-methyl-5α-cholestan-3-one	(10)	0·72
7-Methylene-5α-cholestan-3-one	(11)	1·14 [b]

[a] Me_4Si internal reference; $CDCl_3$ solution; mean of 4—7 scans. [b] Ref. 8. [c] Calculated.

value (calc. 1·12 p.p.m.[6,7]). For the 3-oxo-steroids with exocyclic double bonds, (5) and (11), the shielding effect of the double bond on the 10-methyl resonance is less predictable; however, both compounds apparently have ring A in a chair conformation.[8]

It is clear therefore, that except for (7), the 'anti-octant' behaviour of the Δ⁶-3-oxo-steroids cannot be attributed to conformational inversion of ring A, and as the signs of the c.d. bands of other conformationally rigid γδ-unsaturated ketones, (5), (22), and (24), are those predicted by the Octant Rule, it thus appears that the precise orientation of the double bond with respect to the carbonyl group plays a crucial role in determining the sign of the c.d. band. A mechanism similar to that proposed to account for the unusual chiroptical properties of amino-ketones [10] may be advanced to show how this occurs.

The inductive withdrawal of electrons from the carbonyl group of the Δ⁶-3-oxo-steroids (1) and (2) by the double bond (σ withdrawal) *via* the intervening bonds leads to the 'anti-octant' negative c.d. for the $n\rightarrow\pi^*$ transition. Electron donation from the *p*-orbital of the double bond at C-6 (termed π donation [11] or back donation [10]) *via* the 4,5-bond, which would decrease the 'anti-octant' character, cannot take place because of the incorrect orientation of the orbitals involved. The correct orientation can result in a significant octant-like contribution (Table 3). For (5) the double bond is also incorrectly oriented for π donation to the carbonyl group *via* the 4,5-bond, and the σ withdrawal of electrons by the exocyclic methylene group decreases the rotatory strength of (5) relative to that of (3). In this manner, the contribution of the exocyclic methylene group of (5) may be termed 'anti-octant.' In contrast, 7-methylene-5α-cholestan-3-one (11) exhibits a c.d. band which is enhanced relative to that of (3). The exocyclic methylene group of (11) is now in a position (favourable extended **W** orientation [11]) relative to the carbonyl group such that π back-donation can take place effectively. The strong negative c.d. of (7) is consistent with the adoption of a boat conformation of ring A [*cf.* (10) [9]].

(4a*S*,8a*S*)-*trans*-Decahydroquinolin-7-one (12) [12]† affords a structural parallel with the Δ⁶-3-oxo-steroids; σ withdrawal by the nitrogen atom might be expected to be paramount as the axial, and perhaps even the equatorial, lone pair of the nitrogen atom is not favourably oriented for back-donation, thus leading to an 'anti-octant' contribution which is reflected in the negative c.d. band observed in alcoholic solvents.

The trends observed in the Δ⁶-3-oxo-steroids are also to be found in other γδ-unsaturated ketones (Table 3). An anti-octant effect, comparable in magnitude to that of Δ⁶-3-oxo-compounds, is also shown by (18) and the 'enantiomeric' (20). The compounds in this group have an anti-octant δΔε increment of *ca.* 1·2—1·5 [$\delta\Delta\varepsilon^{EtOH}$ = Δε(unsat. ketone) − Δε(sat. ketone)]. The other extreme is represented by (22) and (24), both of which have an octant δΔε increment of *ca.* 1·6—2·0. This octant increment drops to *ca.* 0·6 in (11) when an extra C–C bond is introduced into the chain connecting the double bond and the carbonyl group. The inter-

† We thank Dr. R. A. Johnson for a gift of this compound and Professor W. Klyne for the measurement of the c.d. spectra.

[9] C. Djerassi, N. Finch, and R. Mauli, *J. Amer. Chem. Soc.*, 1959, **81**, 4997.

[10] J. Hudec, *Chem. Comm.*, 1970, 829.

[11] R. Ditchfield, J. E. Del Bene, and J. A. Pople, *J. Amer. Chem. Soc.*, 1972, **94**, 703.

[12] R. A. Johnson, H. C. Murray, L. M. Reineke, and G. S. Fonken, *J. Org. Chem.*, 1968, **33**, 3207.

mediate group of compounds is represented by the already discussed (5), which shows only a small anti-octant increment, and by (14) and (16), which show a very weak octant increment.

The comparison of the nearly identical chromophoric systems in (1) or (2) and in (24) is particularly instructive with regard to the conformational requirements for π back-donation (Figure 2). The introduction of the exocyclic double bond into the BC ring system in (23) hardly affects the chair–chair conformation of rings B and C in (24). However, the introduction of the endocyclic double bond into ring B at Δ^6 of (3) [or (4)] results in flattening of ring A[8,13] in (1) [or (2)] which reduces the overlap of the *p* orbitals on C-6 and C-3 with the orbitals forming the 4,5-bond to such an extent that π back-donation cannot take place. In contrast, the orbitals of the 8,9-bond in (24) are well oriented to overlap with *p* orbitals on C-7 and C-11, thus allowing π back-donation.

The conformational arrangement of the extended chromophore in (24) should also give rise to a ' σ-coupled transition ' at higher energy[14] which has the opposite chirality to the $n\rightarrow\pi^*$ transition in the case of β-aminoketones with a correctly oriented lone pair on the N atom.[1,15] Indeed, a strong positive Cotton effect is observed at 203 nm where neither the parent ketone (23)[16] nor the 7-methylene steroid[17] have any Cotton

TABLE 2

U.v. and c.d. spectra (λ in nm) of Δ^6-3-oxo-steroids and related compounds

	Hexane				Ethanol				2,2,2-Trifluoroethanol			
	u.v.		c.d.		u.v.		c.d.		u.v.		c.d.	
Solvent	$\lambda_{max.}$	ε	$\lambda_{max.}$	Δε	$\lambda_{max.}$	ε	$\lambda_{max.}$	Δε	$\lambda_{max.}$	ε	$\lambda_{max.}$	Δε
											307	−0·10
5α-Cholest-6-en-3-one (1)	287	21	297	−0·47	282	27	307	−0·18	380	36	277	+0·40
							309	−0·17			336	+0·03
5α-Androst-6-en-3-one	287	23	296	−0·41	281	31	279	+0·02			304	−0·08
							257	−0·01			278	+0·18
5α-Cholestan-3-one (3)	288	17	297	+0·84	283	23	290	+1·32	276	44	283	+2·24
5α-Androstan-3-one (4)	289	18	296	+0·83	282	30	289	+1·47	276	39	282	+2·18
6-Methylene-5α-cholestan-3-one (5)	286	16	296	+0·28	278	25	288	+0·59				
2α-Methyl-5α-cholest-6-en-3-one (6)			296	−0·42			308	−0·18				
2,2-Dimethyl-5α-cholest-6-en-3-one (7)	280	75	297	−1·25	282	95	295	−1·37				
2α-Bromo-2β-methyl-5α-cholestan-3-one (10)	315	132	316	−4·15	309	128	312	−3·54				
7-Methylene-5α-cholestan-3-one (11)			296	+1·26			290	+1·91				
			a				*a, b*					
(4a*S*,8a*S*)-*trans*-Decahydroquinolin-7-one (12)	285	18	324	−0·02	286	19	320	−0·01			287	−0·06
			318	+0·01			288	+0·01			225	+0·14!
			313	−0·01								
			307	+0·03			219	+0·15			286 [c]	−0·22
			297	+0·03			210	−0·62!				
			289	+0·02								
			226	+0·71								
			209	−1·19!								

[a] Ref. 13. [b] In methanol. [c] On addition of strong acid.

TABLE 3

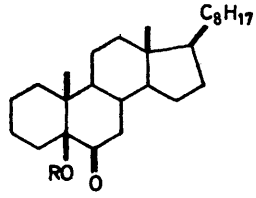
U.v. and c.d. spectra (λ in nm) of some γδ-unsaturated ketones and related compounds

	Hexane				Ethanol			
	u.v.		c.d.		u.v.		c.d.	
Solvent	$\lambda_{max.}$	ε	$\lambda_{max.}$	Δε	$\lambda_{max.}$	ε	$\lambda_{max.}$	Δε
5-Hydroxy-5β-cholestan-6-one (13)	284	48	284	−4·54	284	59	286	−4·86
5-Hydroxy-5β-cholest-2-en-6-one (14) [a]	283	59	289	−5·05	283	68	287	−5·12
5-Acetoxy-5β-cholestan-6-one (15)	287	51	292	−2·88	287	49	291	−3·70
5-Acetoxy-5β-cholest-2-en-6-one (16) [a]	291	56	292	−3·10	289	69	289	−3·87
5α-Cholestan-6-one (17)					290	39	293	−1·55
5α-Cholest-2-en-6-one (18)					289	46	293	−2·72
3,3;20,20-Bisethylenedioxy-5α-pregnan-11-one (19) [b]				+0·24				
3,3;20,20-Bisethylenedioxy-5α-pregn-5-en-11-one (20) [b]				+1·50				
(1*R*,6*R*,8*R*)-9,9-Dimethyltricyclo [6,2,1,$_0$1,6]undecan-10-one (21) [c]					293	28	294	−1·66
(1*R*,6*R*,8*R*)-9,9-Dimethyl-5-methylenetricyclo [6,2,1,0^{1,6}]undecan-10-one (22)	303	40	302	−2·40	295	48	296	−3·14
3β-Acetoxyergostan-11-one (23)					237	38	299	+0·26
3β-Acetoxy-7-methylene-ergostan-11-one (24) [d]	318	35	314	−1·66	300	46	302	−1·87
	308	39	305	−1·76				
	295	38					203	+11·5

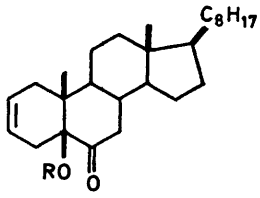
[a] Sample kindly donated by Professor A. T. Rowland. [b] G. Snatzke and D. Bechar, *Tetrahedron*, 1964, **20**, 1921; solvent methylcyclohexanol–isopentane (1 : 3). [c] Sample kindly donated by Professor C. A. Cupas. [d] Starting material kindly donated by Dr. J. Elks, Glaxo Laboratories.

[13] R. Baker and J. Hudec, *Chem. Comm.*, 1967, 479.
[14] R. C. Cookson, J. Henstock, and J. Hudec, *J. Amer. Chem. Soc.*, 1966, **88**, 1060.
[15] E. E. Ernstbrunner and J. Hudec, in preparation.
[16] D. N. Kirk and W. Klyne, *J. Chem. Soc.*, 1974, 1076.
[17] D. N. Kirk and J. Hudec, in preparation.

effect. The exact nature of this transition is as yet uncertain.[1,18]



(13) R = H
(15) R = Ac



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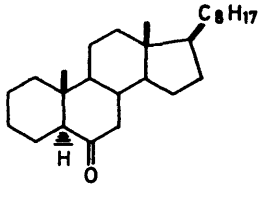

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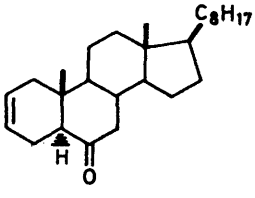

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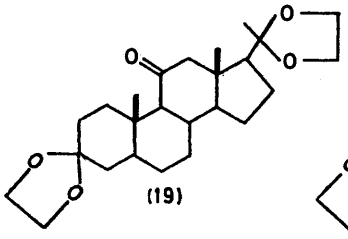

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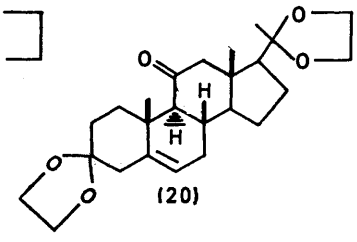

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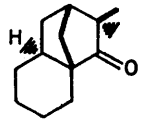

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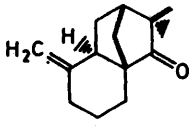

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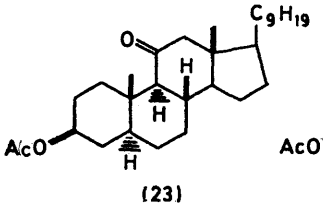

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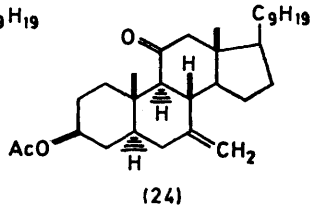
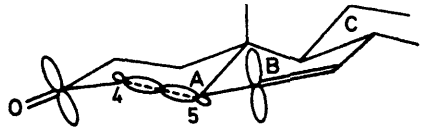
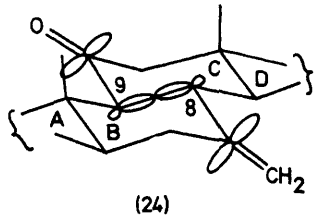


(24)

Solvent Effects.—The ketones (1)—(4) show the expected red shift [19] of the wavelength maximum of the isotropic spectrum on changing solvent from ethanol to n-hexane, through solvents of intermediate polarity (Figure 3). However, whereas the c.d. wavelength maxima of (3) and (4) undergo the expected red shift,[20] those of (1) and (2) are subject to an unexpected blue shift on decreasing the polarity of the solvent. In the highly polar solvent 2,2,2-trifluoroethanol both (1) and



(1) [or (2)]



(24)

FIGURE 2 Conformation of $\gamma\delta$-unsaturated ketone unit in 5α-cholest-6-en-3-one and in 7-methylene-ergostan-11-one

(2) exhibit multiple c.d. bands in the $n\rightarrow\pi^*$ region. This anomalous solvent effect can be appreciated more readily by comparison of the c.d. spectra of (1) and (3) (Figure 4). The c.d. spectrum of (1) in n-hexane is an attenuated mirror image of that of (3), reproducing all fine structure and suggesting that all vibrational levels of the excited state have similar contributions in (1) and (3) but of opposite sign. In contrast the c.d. spectra of the two compounds in ethanol are no longer mirror images. The contributions of the lower energy vibrational levels of the

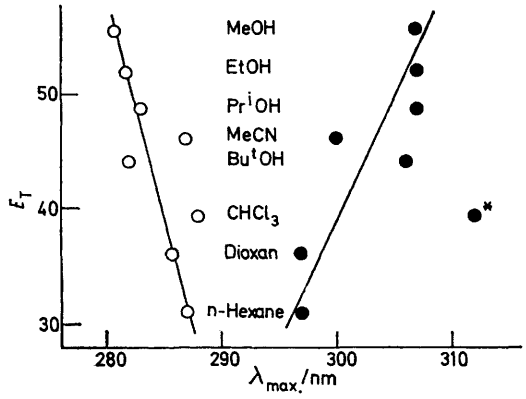


FIGURE 3 Effect of solvent polarity (E_T) (C. Reichardt, *Angew. Chem. Internat. Edn.*, 1965, **4**, 36) on the u.v. (○) and c.d. (●) spectra of 5α-cholest-6-en-3-one

* Proportional change in $\lambda_{max.}$ was also observed in CH_2Cl_2 and CCl_4 (c.d. only).

excited state of (1) are still of opposite sign to those of the corresponding levels of the excited state of (3), whereas the high energy vibrational levels of the excited state of

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[19] E. M. Kosower and G-S. Wu, *J. Amer. Chem. Soc.*, 1961, **83**, 3142; W. P. Hayes and C. J. Timmons, *Spectrochim. Acta*, 1964, **21**, 529; J. E. Dubois, E. Goetz, and W. A. Bienvenue, *ibid.*,

[20] J-C. Jacquesy and J. Levisalles, *Bull. Soc. chim. France* 1965, 1529

(1) do not contribute at all in the c.d. spectrum. [Hence zero rotational strength of (1) in ethanol from 235 to 285 nm although this region is within the envelope of the isotropic transition.] The situation for (2) in ethanol solution is the same as for (1) except that the high energy vibrational levels of the excited state of (2) now contribute with the same sign as those of the excited state of (4), leading to a double c.d. band with a weak positive

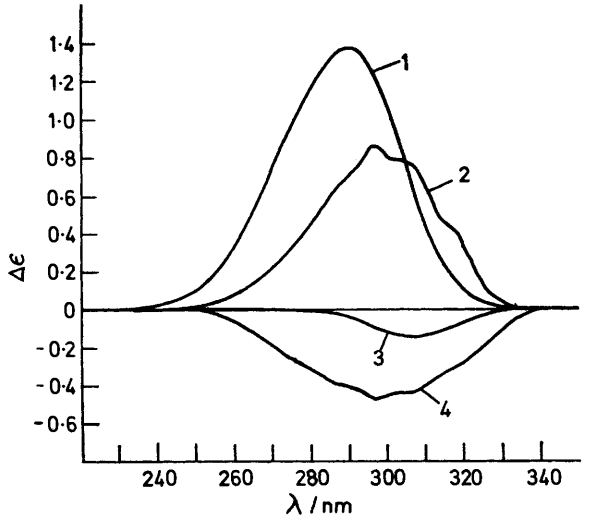

FIGURE 4 C.d. of 5α-cholestan-3-one: 1, in EtOH; 2, in n-hexane; and of 5α-cholest-6-en-3-one; 3, in EtOH; 4, in n-hexane

component at low wavelength, similar to the c.d. spectra of (7) in the highly polar solvent 2,2,2-trifluoroethanol.

Kosower has shown that when lower vibrational levels of the excited state are coupled to the electronic transition, addition of the asymmetric interaction between the perturbing element and the coupled transition does not change the sign of the c.d. band, whereas when the higher vibrational states are coupled to the transition there is an interaction between the vibrational states and the perturbing element which can change the sign of the c.d. band, and furthermore that this latter effect is more apparent in polar solvents.[21] This treatment may be applied directly to the effects of solvent on the c.d. of the Δ^6-3-oxo-steroids, in that, as the vibrational modes of the four axial bonds on the α-carbon atoms couple with the vibrational modes of the excited state of the carbonyl group, the changed electron distribution in these bonds can alter not only the magnitude but also the sign of the rotatory contribution of the various levels of the excited state.

No unusual solvent effects were encountered in the spectra of the other γδ-unsaturated ketones.

EXPERIMENTAL

All compounds were prepared by standard literature methods and had physical properties in agreement with quoted values. C.d. spectra were measured with a Roussel-Jouan Dichrographe for solutions at a concentration of *ca.* 1 mg per ml and with a path length of 2 or 5 cm. The u.v. spectra were measured with a Perkin-Elmer 450 spectrophotometer.

(1R,6R,8R)-9,9-*Dimethyl*-5-*methylenetricyclo*[6.2.1.$0^{1,6}$]*undecan*-10-*one* (22).—This *compound* was prepared from the 5,10-diketone by treatment with an excess of methylenetriphenylphosphorane [22] in 33% yield after purification by preparative t.l.c. (silica; light petroleum–ether, 1 : 9) and subsequent micro-distillation (*ca.* 1·6 mmHg at bath temperature 160°). G.l.c. (E30, silicone oil; 202°) indicated >99·5% purity; M^+ 204 (Found: C, 82·0; H, 9·7. $C_{14}H_{20}O$ requires C, 82·3; H, 9·9%).

3β-*Acetoxy*-7-*methylene-ergostan*-11-*one* (24).—3β-Hydroxyergost-22-ene-7,11-dione (421 mg) by successive acetylation (acetic anhydride; reflux 1 h; usual work-up) and hydrogenation (10% Pd–C in ether–ethyl acetate, 4 : 1; usual work-up), followed by column chromatography (alumina; ether–benzene, 1 : 4) gave a crude sample of 3β-acetoxyergostane-7,11-dione (277 mg). This, with methylenetriphenylphosphorane (9·6 mol. equiv.) in boiling tetrahydrofuran (15 h), and work-up as described for (22), gave a yellow oil (470 mg). Elution with 15% ether–ethyl acetate on alumina gave 3β-hydroxy-7-methylene-ergostan-11-one as a white solid (132 mg), part of which (41 mg), upon acetylation (acetic anhydride–pyridine; overnight) gave, with the usual work-up, 3β-acetoxy-7-methylene-ergostan-11-one (17 mg), as needles (from ethanol), m.p. 105·5—106·5°, M^+ 470, $\nu_{max.}$ (Nujol) 1730s, 1705s, 1645m, 1245s,br, 1090m, 1030s, and 895m cm^{-1}, $\nu_{max.}$ (film) 3100w, 1735s, 1640m, 995m, 985m, 935m, 895m, and 850m cm^{-1}.

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