

ON THE OPTICAL ACTIVITY OF α,β -UNSATURATED KETONES

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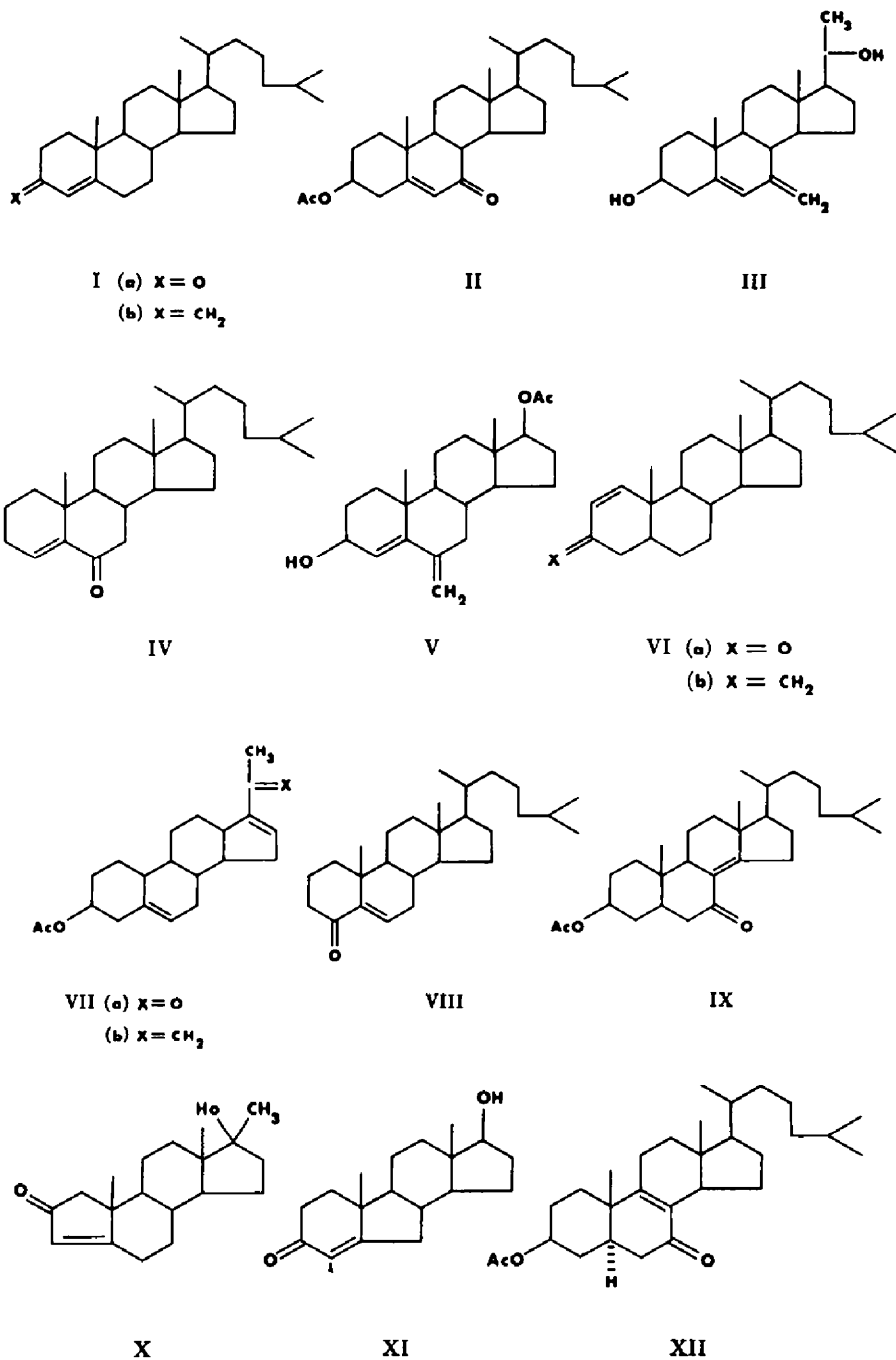
Abstract—The ORD curves of several α,β -unsaturated ketones are compared with those of structurally related dienes and the similarities and differences discussed. A determination of the CD curves of a number of α,β -unsaturated ketones revealed the presence of a new very strong optically active transition close to that of the $\pi \rightarrow \pi^*$ transition. The sign of the Cotton effect associated with the $\pi \rightarrow \pi^*$ transition as determined by ORD measurements is sometimes obscured by the overlapping new transition. The CD curves of a number of α,β -unsaturated ketones were determined in a study of the effect of ring size on the sign and magnitude of the optical activity of these transitions.

ALTHOUGH a theoretical treatment relating the sign of the Cotton effect associated with the $\pi \rightarrow \pi^*$ transition (220–260 m μ) of α,β -unsaturated ketones with stereochemistry was published in 1962,¹ very little experimental work on the ORD and CD of this chromophore has appeared in the literature. The use of the sign of this effect in assigning absolute stereochemistry has been limited by the fact that Dreiding models of most α,β -unsaturated ketones appear quite flexible and therefore could be expected to shift easily from a conformation associated with a positive effect to that with a negative Cotton effect. The recent work by Bloch and Wallis,² however, can be interpreted to show that the conformation of these unsaturated ketones (or the position of the conformational equilibrium) is not as sensitive to structural changes as might have been supposed. Their work indicated that although various substituents (halogen, alkyl, and others) on the conjugated system changed the sign of the Cotton effect associated with the $n \rightarrow \pi^*$ transition, the sign of the $\pi \rightarrow \pi^*$ transition was constant except for some small variation in magnitude.

In this investigation of the optical activity of α,β -unsaturated ketones, the optical activity associated with the $\pi \rightarrow \pi^*$ transition has been compared with the activity associated with the isoelectronic long wavelength (220–260 m μ) $\pi \rightarrow \pi^*$ transition of conjugated dienes. In addition to this comparison and the consequences thereof a preliminary study of the effect of ring size on the magnitude and sign of this effect has been made.

As no quantitative calculations of the optical activity of α,β -unsaturated ketones have been published, the optical activity (ORD curves) of these compounds was compared with that of conjugated dienes for which calculations of the ORD curves

as a function of skew angle exists.³ In order to minimize extraneous effects, we chose a group of steroidal α,β -unsaturated ketones and converted the carbonyl to a methylene group. In this way the $\pi \rightarrow \pi^*$ transitions occur at similar wavelengths and it was hoped that the conformations of the two steroids would be quite similar.



Comparisons of the ORD curves of five pairs of α,β -unsaturated ketones with the appropriate dienes (Ia and Ib; II and III; IV and V; VIa and VIb; VIIa and VIIb) are given in Figs 1–5. The pair of compounds (Ia and Ib) shown in Fig. 1 appears to exhibit Cotton effects consistent with regard to sign and magnitude. However, the effect is not symmetric about the absorption band of the α,β -unsaturated ketone (absorption spectrum shown in insert) and CD measurements (Fig. 8) show the presence of two bands having the same sign but differing significantly in magnitude. A similar situation is noted in the pair of compounds shown in Fig. 2. Here the ORD curves have similar shapes and magnitudes, however, the ORD curve of the ketone displays a remarkable lack of symmetry about λ_{max} , 236 m μ (see absorption spectrum in insert). An equivalent situation is again noted in Fig. 3.

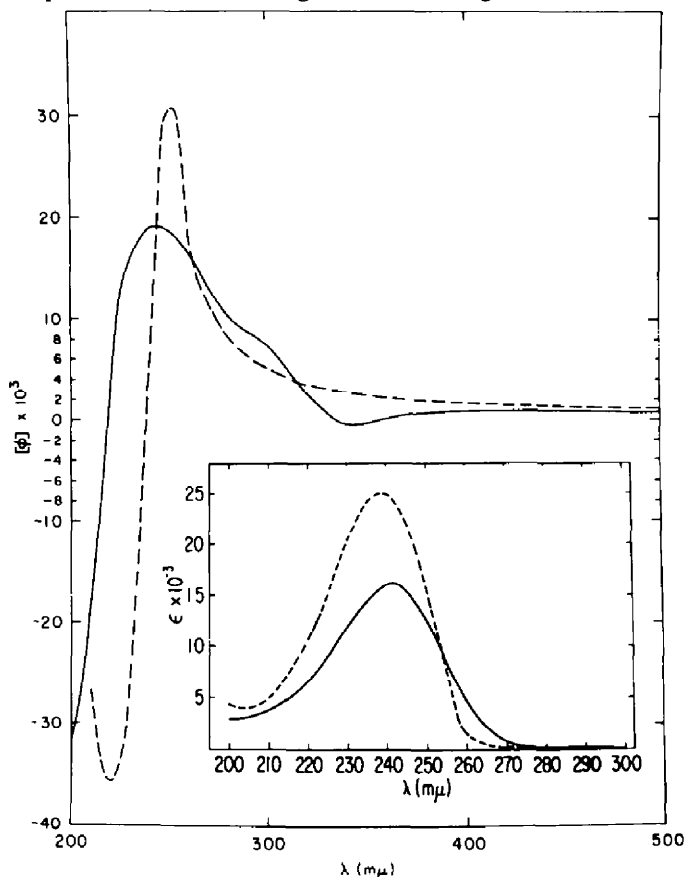


FIG. 1 ORD curves of Ia — and Ib ---. The UV spectra are shown in insert.

A different situation is encountered in the pair of compounds in Fig. 4. Here the ORD curve for the ketone is symmetrical about λ_{max} for the $\pi \rightarrow \pi^*$ transition; however, the sign of the ORD curve is opposite to that of the diene. The magnitude of the ORD curve of the diene which is less than half of that of the ketone can be rationalized in a simple way. Dreiding models of the diene indicate that conformations expected to exhibit positive and negative Cotton effects are possible and only

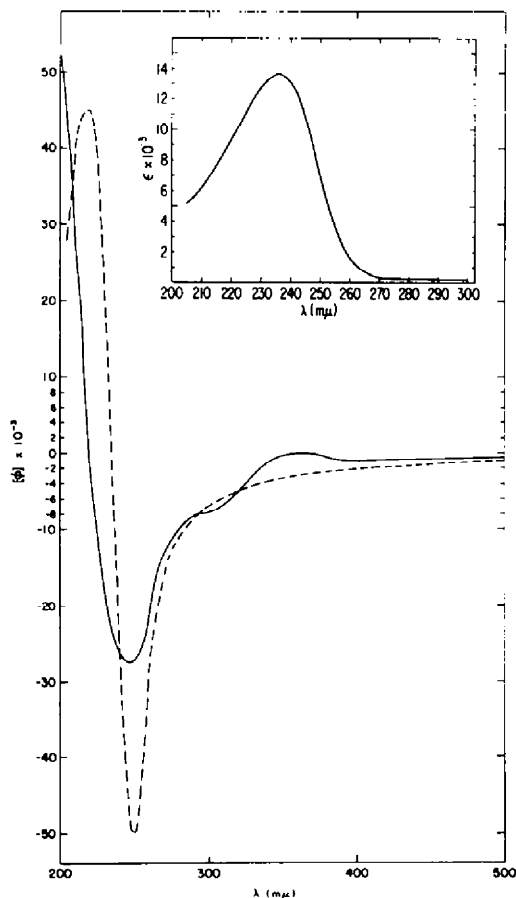


FIG. 2 ORD curves of II — and III ---, UV spectrum of II in insert.

a very small energy barrier between the two conformations could be expected. The reduced optical activity of the diene might therefore be the result of a conformational equilibrium between two such conformations. The curves from compounds VIIa and VIIb (Fig. 5) indicate that here the diene is associated with a positive Cotton effect while CD measurements of the ketone show the presence of a negative Cotton effect. An investigation by Wellman and Djerassi⁴ of the temperature dependence of the CD curves of saturated 20-keto steroids revealed that the optical activity of these compounds showed large temperature dependencies. In VIIa and VIIb the conjugated double bond favors those rotomers where conjugation is greatest. The effective size of the methylene group in VIIb, however, is greater than that of the carbonyl and therefore the difference in the sign of the two Cotton effects may merely reflect a different rotomer distribution.

The broadness and lack of symmetry of the ORD curves for a number of the unsaturated ketones (Ia, II, IV) prompted us to examine the CD curves of these compounds (Figs 6-8). These curves reveal the existence of a previously unreported

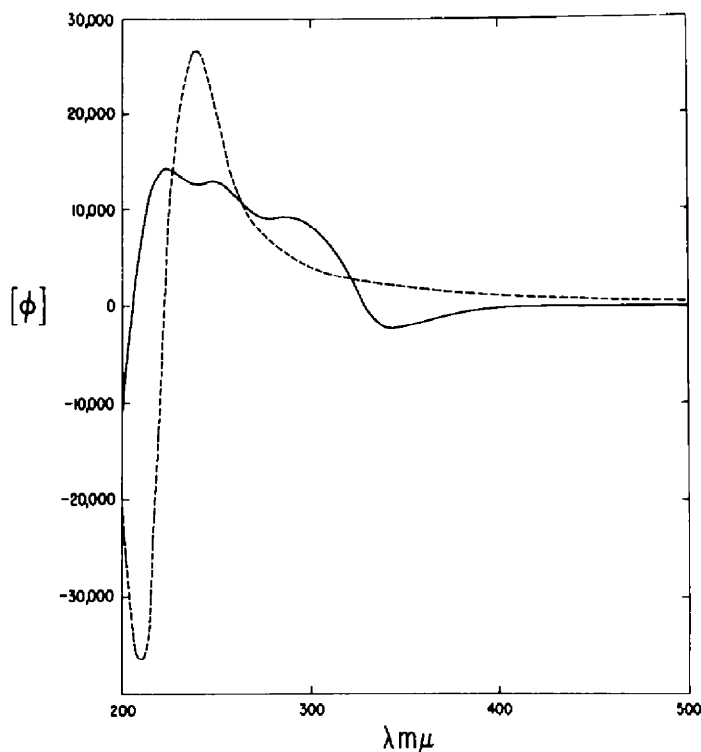


FIG. 3 ORD curves of IV ——— and V - - - -.

strong to very strong optically active band in the range of 200–220 $m\mu$.^{*} Examination of the UV absorption spectra (shown in Figs 9 and 10) indicates, in several cases, presence of small shoulders on the short wavelength side of the principal absorption bands. These new optically active bands may or may not (see Figs 6–8) have the same sign as those associated with the $\pi \rightarrow \pi^*$ transitions. The sign of the Cotton effect in the ORD curves of the ketones in Figs 1, 2, 3 and 5 is that of this band and NOT necessarily that associated with the $\pi \rightarrow \pi^*$ transition. These results raise several fundamental questions. (1) Are the above curves truly representative of α,β -unsaturated ketones or is this new transition unusual in these compounds? (2) If this new transition is commonly present in unsaturated ketones, how good is the experimental verification of the theory relating the skew sense of the chromophore to the sign of the Cotton effect at 220–260 $m\mu$? (3) What is the origin of this new, strong optically active transition? The following represents an effort to answer some of these questions.

In order to determine whether other unsaturated ketones exhibit this new Cotton effect, the CD of compounds VIII–XII were investigated; the results are shown in Figs 6, 7 and 8. Every one of these compounds showed the two effects, and

^{*} In their discussion of CD and UV of β,γ -unsaturated ketones, Cookson *et al.*⁵ point out that the $n \rightarrow \pi^*$ transition of the CO group could couple with a $\pi \rightarrow \pi^*$ transition of the olefin. The location of the $n \rightarrow \sigma^*$ transition as well as other possible transitions in α,β -unsaturated ketones has not been determined.

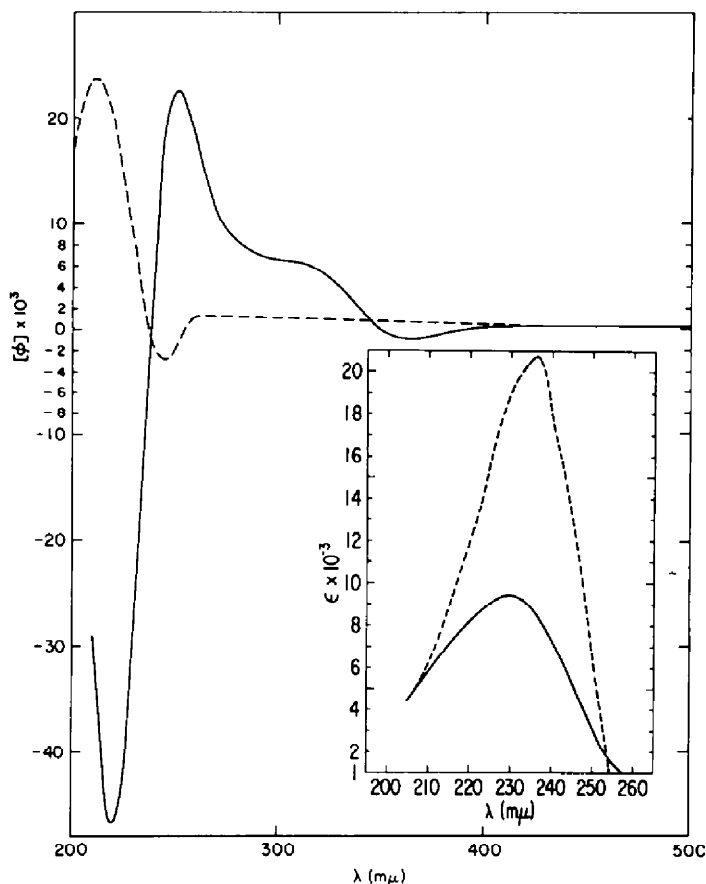


FIG. 4 ORD curves of VIa — and VIb ····. The UV spectra are given in the insert.

the signs of the two effects may or may not be the same. The intensities of the two effects also vary in such a way as to make it extremely difficult to determine the sign of the Cotton effect from the ORD curves. Since the compounds shown in Figs 6, 7 and 8 all contain this new optically active band, the necessity of answering the second question now becomes important. A partial answer is given by the CD curve of Ia (Fig. 8). Although the ORD curve of this compound itself was not used in the experimental verification of the chirality rule, the signs of the ORD curves of a number of its derivatives were used as examples to support the rule. The wavelength of the strongest band in the CD curve of Ia is centered at ~ 215 m μ . A much weaker band of the same sign appears at ~ 240 m μ and this latter band coincides with λ_{\max} of the compound. It is therefore apparent that the ORD curve given in Fig. 1 only accidentally yielded the correct sign of the $\pi \rightarrow \pi^*$ transition and that the sign of the ORD curve was associated with the new band centered at ~ 215 m μ . The CD curve of II exhibits roughly the mirror image relationship to that of I. The CD curve of IX, which is one of the less flexible non-planar unsaturated ketones, exhibits a relatively strong Cotton effect for the $\pi \rightarrow \pi^*$ transition. The band at shorter wavelength is only poorly defined and of opposite sign. This is not the case, however, with IV and

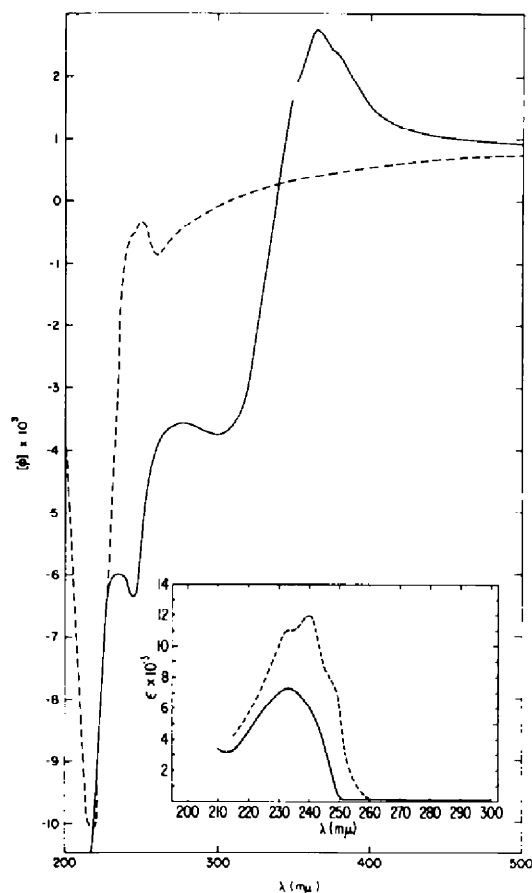


FIG. 5 ORD curves of VIIa — and VIIb ---. The UV spectra are given in the insert.

VIII, the latter used in demonstrating the rule. The CD curves of these compounds have a mirror image relationship as would be expected; their UV spectra shown in Fig. 9 are essentially identical. However, the shape of the CD curves indicates the presence of several overlapping bands. It is most easily seen in the CD curve of II that the sign of the observed ORD curve is determined by the sign of the band at shorter wavelength rather than the usual $\pi \rightarrow \pi^*$ transition.

These studies shed very little light on the third question as to what is the origin of the new band. The CD curves indicate that its rotational strength is comparable to that of the $\pi \rightarrow \pi^*$ transition, however, the UV absorption spectra indicate that the transition (dipole strength) is very weak. These observations require the magnetic transition moment to be large and suggest that the non-bonding electrons of the carbonyl oxygen may be involved. The actual nature of the transition is still unknown.

The experimental verification of the rule relating the chirality of the chromophore in α,β -unsaturated ketones with the sign of the Cotton effect of the $\pi \rightarrow \pi^*$ transition is exceedingly difficult because of the flexibility of this chromophore. Calculations by Charney³ for conjugated dienes have shown that the magnitude of the Cotton effect predicted by theory is dependent on the skew angle. As the theory is very

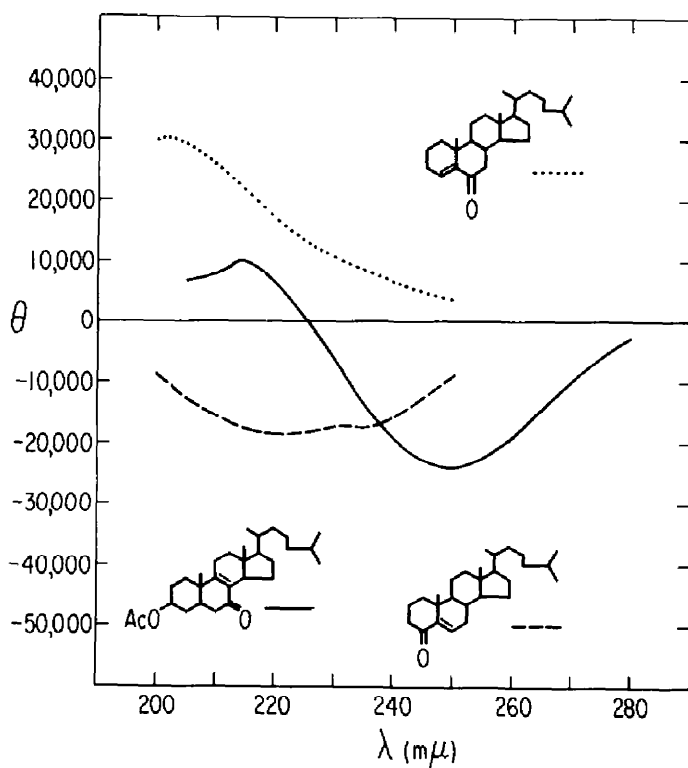


FIG. 6 CD curves of IV ····, and VIII ----, and XII ———.

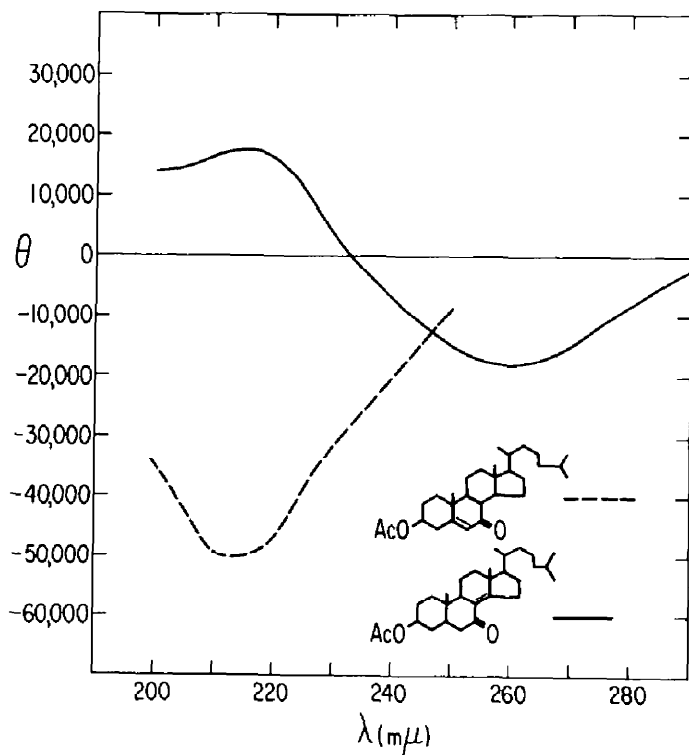


FIG. 7 CD curves of II ---- and IX ———.

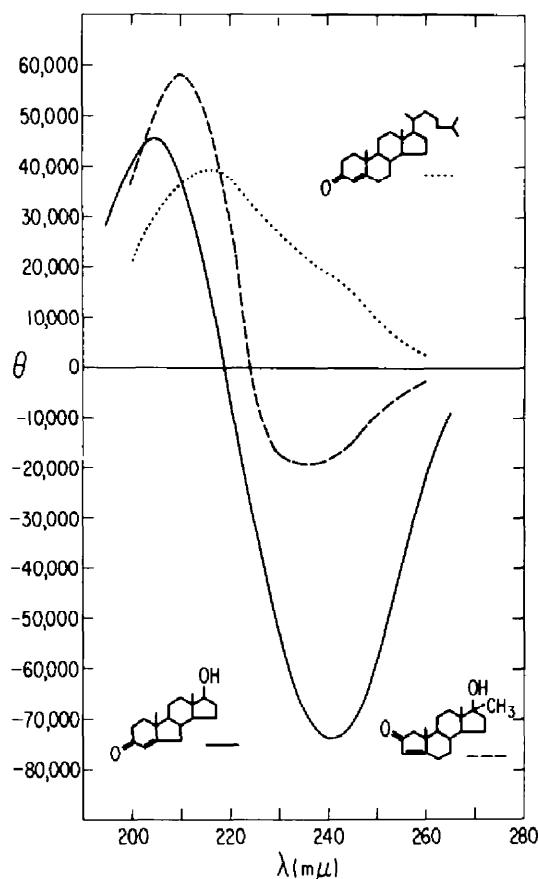


FIG. 8 CD curves of Ia ····, X ····, and XI ———.

similar for α,β -unsaturated ketones, the CD curves (Figs 6, 7 and 8) of the unsaturated ketones can be used to calculate the rotational strength associated with the $\pi \rightarrow \pi^*$ transition and to compare it with that expected from theory. The rotational strength to a good approximation is described by Eqs 1 and 2.

$$R_k = \frac{2.49 \times 10^{-39} \times \Delta\epsilon_{\max} \Delta\bar{\nu}}{\bar{\nu}} \quad (1)$$

$$\text{Reduced } R = 10^{40} R_k \quad (2)$$

Since Dreiding models indicate that IX is one of the less flexible non-planar unsaturated ketones, its reduced rotational strength (R) as well as that of the more flexible and less skewed Ia, has been calculated by means of the above equations. The values of reduced R are ~ 16.7 and 7.7 , respectively. These values are somewhat low but of the right order of magnitude for an inherently dissymmetric chromophore. The rotational strengths for the new transition would also be comparable. The pairs of compounds given in Figs 1–5 demonstrate that if the band at 220–260 $m\mu$ in unsaturated ketones can be completely described as a $\pi \rightarrow \pi^*$ transition, then the observed variances may reflect different preferred conformations of these unsaturated

TABLE I.

Compound	Rotation			Circular dichroism				Ref. source
	$[\Phi]_{\text{D}}^{\text{D}}$	$\lambda_{\text{D}}^{\text{D}}$	Solvent	Concentration g/100 ml	$[\Phi]$	λ	Solvent	Concentration g/100 ml
Ia	-527 8573 18,900	345 290 245	methanol	0.0700	39,300	215	ethanol	0.063
Ib	30,600	252	iso-octane	0.0160				
II	-1060 -58 -24,300	390 355 245	methanol	0.0220	-50,000	215	ethanol	0.0196
III	-50,000	252	methanol	0.0504				
IV	-2370 9111 13,000 14,500	345 290 250 225	methanol	0.0760	30,000	200	ethanol	0.0394
V	0 38,200 0 -47,700	205 240 225 205	methanol	0.0433	49,530	222	methanol	0.0452
VIa	-867 6400 22,500 -46,800	365 310 252 220	methanol	0.0444				
VIb	-3080 23,600	245 210	methanol	0.0112				

See Exper.

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VIIa	1780	365	iso-octane	0.063	173	250	iso-octane	0.063	12
	-4760	300							
	-9080	240			-2595	232			
	-7350	230							
	-16,400	210							
VIIb	0	250	iso-octane	0.0504	4078	232	iso-octane	0.0504	7
	-10,300	215							
VIII	1010	348	methanol	0.0354	-17,100	235	methanol	0.0354	13
	-7390	290							
	-16,800	254							
	25,400	205							
	-2530	365	methanol	0.075	-17,700	260	ethanol	0.0398	12
IX	0	320			+17,300	215			
	-7340	282							
	25,800	230							
	-6030	335	methanol	0.0766	-18,900	235	ethanol	0.0502	*
	7640	287							
X	0	255							
	48,000	225							
	6190	357	ethanol	0.0282	-73,900	240	ethanol	0.0338	14
	-18,500	290			45,500	205			
	-45,300	257							
XII	71,500	222							
	912	360	methanol	0.087	-23,900	250	ethanol	0.0236	12
	-7450	305			+10,100	215			
	-16,800	272							
	19,100	230							

* This compound was obtained from the Cancer Chemotherapy National Service Center, National Cancer Institute, Bethesda, Maryland 20014.

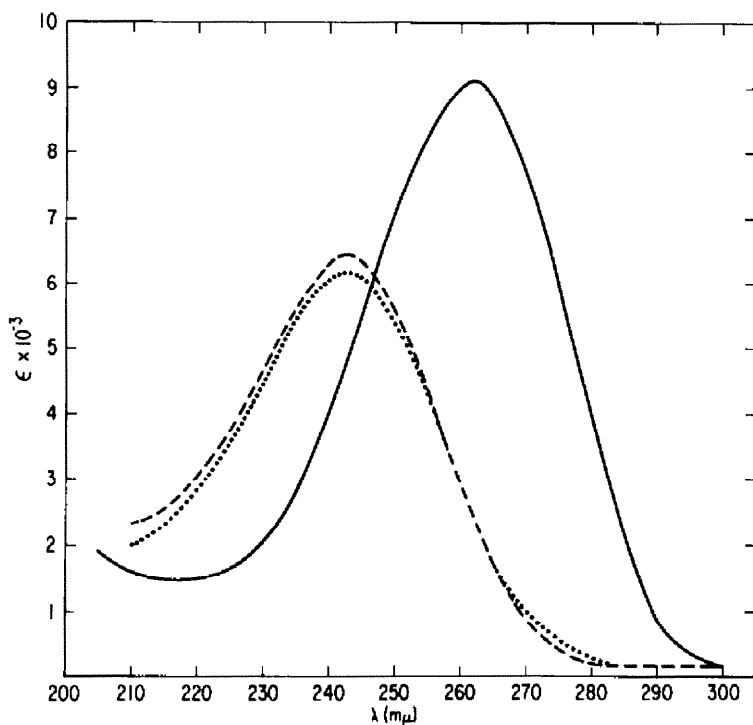


FIG. 9 UV spectra of IV ----, VIII ····, and IX ———.

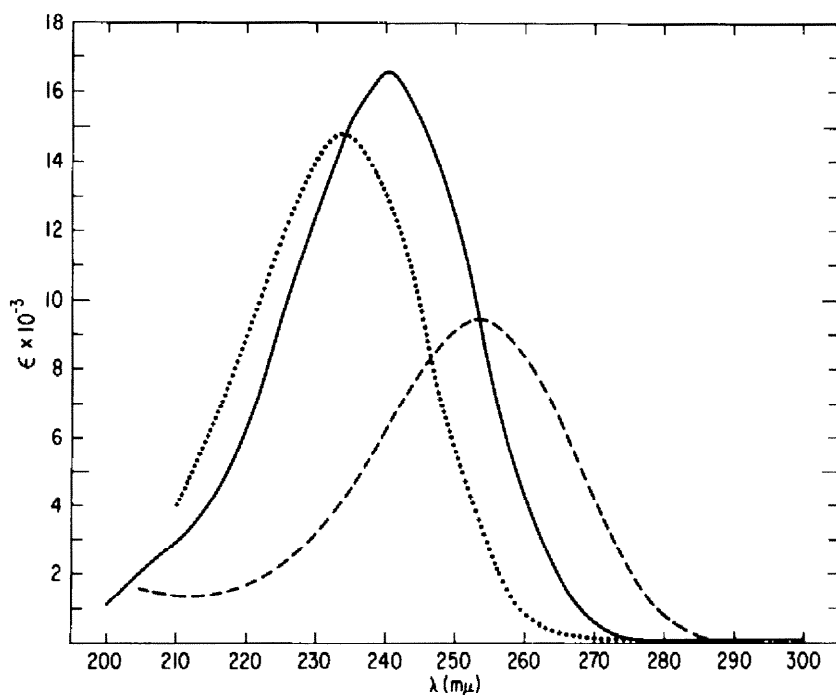


FIG. 10 UV spectra of X ····, XI ———, and XII ----.

ketones compared to the corresponding dienes. For example, the ketones may have a tendency to be more planar than the dienes. It is clear, however, that the spectroscopy of unsaturated ketones is more complex than that of dienes and if the description of the transition at 220–260 m μ is incomplete the chirality rule need not apply.

The second part of the investigation, i.e. the effect of ring size on the sign of the Cotton effect, is shown in Fig. 8. Changes involved in making ring A a cyclopentenone or in maintaining the cyclohexenone system and converting ring B to a cyclopentanone alter the sign of the Cotton effects. It is interesting to note that in both X and XI the new Cotton effect is of opposite sign to that of the $\pi \rightarrow \pi^*$ transition, while the two effects have the same sign in Ia. The Dreiding models of these systems indicate that they are almost planar or can assume conformations associated with either positive or negative effects. It is therefore not clear what factors are influencing the increase in the rotational strength of the $\pi \rightarrow \pi^*$ transition in X and XI in comparison to Ia. The small shift to shorter wavelength of X compared to Ia (Fig. 10) is that expected in going from a cyclopentenone to a cyclohexenone.

Although the theoretical treatment of the longest wavelength absorption band of conjugated dienes should be transferable to the strong absorption band (220–260 m μ) of α,β -unsaturated ketones the above results indicate that in a fair number of cases a hitherto unsuspected absorption band is present in these compounds that severely complicates an analysis of the data. Progress in relating stereochemistry and structure to the sign and magnitude of these Cotton effects requires a theoretical analysis that takes into consideration the presence of the new band, its electronic nature, as well as more systematic studies of the effect of structural parameters, substituents, ring size, etc., on the optical activity.

EXPERIMENTAL

The ORD and CD measurements were made on a Cary Model 60 spectropolarimeter. The physical constants of the compounds investigated were in good agreement with those reported in the literature. The data are summarized in Table I.

3-Methylene- Δ^1 -cholestene (VIb). To a stirred soln of triphenylmethylphosphonium bromide (714 mg) in anhyd ether (12 ml), at room temp under argon, was added by syringe 1.4 ml n-BuLi in hexane (1.6N, Foote Mineral Co., Exton, Pa.). The mixture was stirred under argon for 2 hr, and a soln of 5 α - Δ^1 -cholesten-3-one (380 mg) in THF (20 ml) was added all at once. The ether was distilled off and replaced with THF and the reaction mixture was refluxed for 3 hr under argon, then cooled, diluted with water and extracted with ether. The ethereal extract was washed with water, dried (Na₂SO₄) and evaporated to give a solid residue which was extracted with pentane (3 \times 10 ml). The combined pentane extracts were concentrated to about 5 ml and applied to a column of alumina (Woelm, neutral, grade I). Elution with pentane gave 3-methylene- Δ^1 -cholestene (290 mg) which was crystallized from MeOH to give analytically pure VIb (209 mg), m.p. 89–90.5; $\lambda_{\text{max}}^{\text{MeOH}}$ 235 m μ (21,000); $\nu_{\text{max}}^{\text{KBr}}$ 1622, 1589, 878 cm⁻¹; NMR (CDCl₃) δ , 6.03 (S, C-1H and C-2H), 4.78 (S, C-3 CH₂=), 0.88 (S, C-19CH₃), 0.69 (S, C-18CH₃). (Found: C, 87.70; H, 11.73. Calc. for C₂₈H₄₆: C, 87.88; H, 12.12%).

17 β -Acetoxyl-6-methylene- Δ^4 -androst-3-en-3-ol. To a stirred soln of 6-methylene-testosterone acetate (100 mg, a gift from the British Drug Houses Ltd.) in 25 ml MeOH was added NaBH₄. After ~30 min several drops of AcOH were added and the soln concentrated on a rotatory evaporator. Water and CHCl₃ were added, the organic phase separated, dried (Na₂SO₄) and concentrated. The residue crystallized from 30–60 pet ether, m.p., 145–147; $\lambda_{\text{max}}^{\text{MeOH}}$ 220 (7240); $\nu_{\text{max}}^{\text{CHCl}_3}$ 1720 cm⁻¹; NMR (CDCl₃) δ , 5.60 (S,

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C-4H), 4.77 (D, J_{AB} 10 Hz, CH₂=), 2.03 (S, CH₃—C—O—) 1.13 (S, C-18 CH₃), 0.97 (S, C-19 CH₃). (Found: C, 76.04; H, 9.51. Calc. for C₂₇H₄₂O₃: C, 75.86; H, 9.70%).

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