

Chiroptical Studies. Part LXXXIX.¹ An Empirical Analysis of the Circular Dichroism of Hexahydroindanones, Bicyclo[4.2.0]octan-7-ones, and their Polycyclic Analogues

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An empirical analysis of c.d. data for five-membered ring ketones of the hexahydroindanone type, including androstan-15-ones, -16-ones, and -17-ones and similar compounds, has established the main features of the relationships between Cotton effects and structural and conformational types in this series. The analysis has been extended to a few compounds of steroid-like structure which include a cyclobutanone ring (bicyclo[4.2.0]octan-7-ones). Five stereochemical types of hexahydroindanone are recognised, three for hexahydroindan-1-ones and two for hexahydroindan-2-ones.

In the first stage of the analysis, estimates of c.d. contributions ($\delta\Delta\epsilon$) are obtained from experimental data for the following units: (a) the bicyclic systems, (b) angular methyl groups, and (c) 'third rings'. Estimates of the contribution of the 'second' (cyclohexane) ring to the total value of $\Delta\epsilon$ for each of the bicyclic systems are then obtained by regarding the effects of individual bonds of the 'second' ring as equivalent to those of C-Me bonds at ' α ' or ' β ' positions of the cyclopentanone ring. The $\delta\Delta\epsilon$ values obtained in this way for 'second' rings are used to derive $\delta\Delta\epsilon$ values for the chiral cyclopentanone rings themselves. The values confirm earlier suggestions that the sign and magnitude of the Cotton effect is controlled largely by the chirality of the cyclopentanone ring itself, although other major contributions may come from any ' α '-quasi-axial substituents present at the ring junction. Effects of alkyl substituents elsewhere on the cyclopentanone ring are discussed briefly.

A PREVIOUS paper² presented the results of an empirical analysis of c.d. data ($n \rightarrow \pi^*$) for decalones and their extended polycyclic analogues. By analysing data for a wide variety of compounds of the *trans*- and *cis*-decalone types (including many steroidal ketones) we were able to establish the general additivity of contributions ($\delta\Delta\epsilon$) of

suitably chosen structural features to the total value of $\Delta\epsilon$. We were also able to identify instances of disignate³ behaviour, as well as deviations from acceptable additivity of group contributions, for certain recognisable structural types. The data were first analysed by inspection to evaluate the contributions associated with parti-

¹ Part LXXXVIII, P. M. Johnson, T. E. Michaelson, and P. M. Scopes, *Scand. J. Immunol.*, 1975, **4**, 113.

² D. N. Kirk and W. Klyne, *J.C.S. Perkin I*, 1974, 1076.

³ W. Klyne and D. N. Kirk, *Tetrahedron Letters*, 1973, 1483.

cular carbocyclic rings fused to the parent *trans*- or *cis*-decalone, or contributions due to the presence of alkyl substituents (usually methyl) in the vicinity of the carbonyl chromophore. Further examination showed that the observed value of $\Delta\epsilon$ for a ring system could be related directly to the length of a particular coplanar zig-zag of C-C bonds in a polycyclic structure: the bonds concerned are those of the type illustrated in Figure 1,* which make up a 'primary zig-zag'. In order to predict the value of $\Delta\epsilon$ for a ketone of the 'extended decalone' class, without polar substituents and free from excessive strain, it is necessary only to consult tables of data² listing the



FIGURE 1 Primary zig-zag of coplanar bonds

contributions of ring systems (or alternatively the contributions of zig-zag chains of different lengths), and to add algebraically the contributions of any alkyl groups in the vicinity of the carbonyl group. Our subsequent use of the data for a variety of ketones of the decalone type, examined since the completion of that analysis, has generally given estimates in satisfactory agreement with observed values of $\Delta\epsilon$.

We now report an extension of our general empirical method of data analysis to the available compounds of the hexahydroindan-1-one, hexahydroindan-2-one, and bicyclo[4.2.0]octan-7-one series. Previous efforts in the hexahydroindanone field⁴⁻⁸ have been limited in scope, although the sign of the Cotton effect is known to follow the sense of twist of the cyclopentanone ring,⁵ corresponding to consignate behaviour³ of out-of-plane carbon atoms (Figure 2). This is an example of dissymmetry in the 'second sphere'.⁹

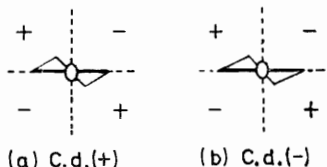


FIGURE 2 Octant projections of twisted cyclopentanone rings

In the present work, c.d. data were collected for all available compounds of the 'extended hexahydroindan-1-one' or '-2-one' classes, making use, as in the decalone series,² of as many of the four solvents (hexane, dioxan, acetonitrile, and methanol) as solubilities and limited supplies of ketones permitted. Where ketones were not available, data from earlier investigations were used, from these laboratories or from the literature. When no c.d. data could be traced for an important type of com-

* Bonds drawn as broken lines, in perspective drawings and 'octant' projections, lie in the direction away from the observer, and are not necessarily indications of α -configurations.

⁴ P. M. Bourn and W. Klyne, *J. Chem. Soc.*, 1960, 2044.

⁵ W. Klyne, *Tetrahedron*, 1961, **13**, 29; *Bull. Soc. chim. France*, 1960, 1396; *Anales real Soc. españ. Fis. Quím.*, 1966, 371.

pound, we used the less satisfactory conversion of o.r.d. data, according to the relationship $\Delta\epsilon = a/40.28$;¹⁰ values of $\Delta\epsilon$ obtained in this way for our study of decalones were seen to be reasonably reliable where a direct comparison with experimental values of $\Delta\epsilon$ was possible. The analysis is in terms of $\Delta\epsilon$ (in l mol⁻¹ cm⁻¹), as in the previous study.²

Classification of Ring Systems.—The system of classification of rings which greatly simplified our analysis of extended decalones² was adopted, with only minor modifications, for hexahydroindanones and bicyclo[4.2.0]octan-7-ones. The parent bicyclic structures are coded as either *trans* (*t*) or *cis* (*c*), prefixed by a number (5 or 4) to indicate the size of the ring containing the carbonyl function. (The six-membered ketonic ring in decalones would be indicated by *6t* or *6c*.) The location of the second (cyclohexane) ring in relation to the carbonyl group is then indicated for hexahydroindanones by a digit (2 or 3) representing the carbon atom of the cyclopentanone ring to which the nearest bond of the second ring is attached; where necessary (for class *5c2* only) the conformation of that bond relative to the cyclopentanone ring is then denoted by either *ax* or *eq*, representing quasi-axial or quasi-equatorial respectively. Bicyclo[4.2.0]octan-7-ones are treated similarly, although the bond designated must be at C-2 of the cyclobutanone ring. The resulting symbolism closely resembles that used for the decalones. It divides the hexahydroindan-1-ones into three stereochemical types (Figure 3a), and the hexahydroindan-2-ones into two types (Figure 3b). Bicyclo[4.2.0]octan-7-ones fall into one of three classes (Figure 3c). Third and subsequent rings are coded in the manner used for extended decalones.²

As with decalones, the absolute configuration of the bicyclic structure is indicated by the use of unprimed or primed digits. In the present series of compounds, unprimed digits are used when carbon atoms C-1, C-2, and C-3 run clockwise when viewed in projection down the O=C axis. Primed digits are used when these atoms form an anticlockwise series. For hexahydroindanones, in which the cyclopentanone ring is itself chiral, the use of un-primed digits (2 or 3) implies that the cyclopentanone ring has positive chirality (Figure 2a), whereas primed digits are required when the cyclopentanone chirality is negative (Figure 2b). The structures depicted in Figure 3 (a and b) all have unprimed digits (positive helicity of cyclopentanone ring); their enantiomers would be designated by the use of 2' or 3' instead of 2 and 3, respectively.

Hexahydroindanones of class *5c3* are peculiar in possessing chirality dependent upon conformation. The two conformers of the unsubstituted bicyclic compound are enantiomeric. We shall distinguish them as *5c3* or

⁶ P. Crabbé, 'Applications de la Dispersion Rotatoire Optique et du Dichroïsme Circulaire Optique en Chimie Organique,' Gauthier-Villars, Paris, 1968, pp. 172, 251.

⁷ M. J. Brienne, A. Heymes, J. Jacques, G. Snatzke, W. Klyne, and S. R. Wallis, *J. Chem. Soc. (C)*, 1970, 423.

⁸ C. Emeis and L. J. Oosterhoff, *J. Chem. Phys.*, 1971, **54**, 4809.

⁹ G. Snatzke, *Tetrahedron*, 1965, **21**, 413.

¹⁰ S. F. Mason, *Quart. Rev.*, 1963, **17**, 20.

5c3' by citing the locant (3 or 3') of that ring carbon atom which carries an equatorial C-C bond; the other location at the ring junction necessarily carries an axial C-C bond.

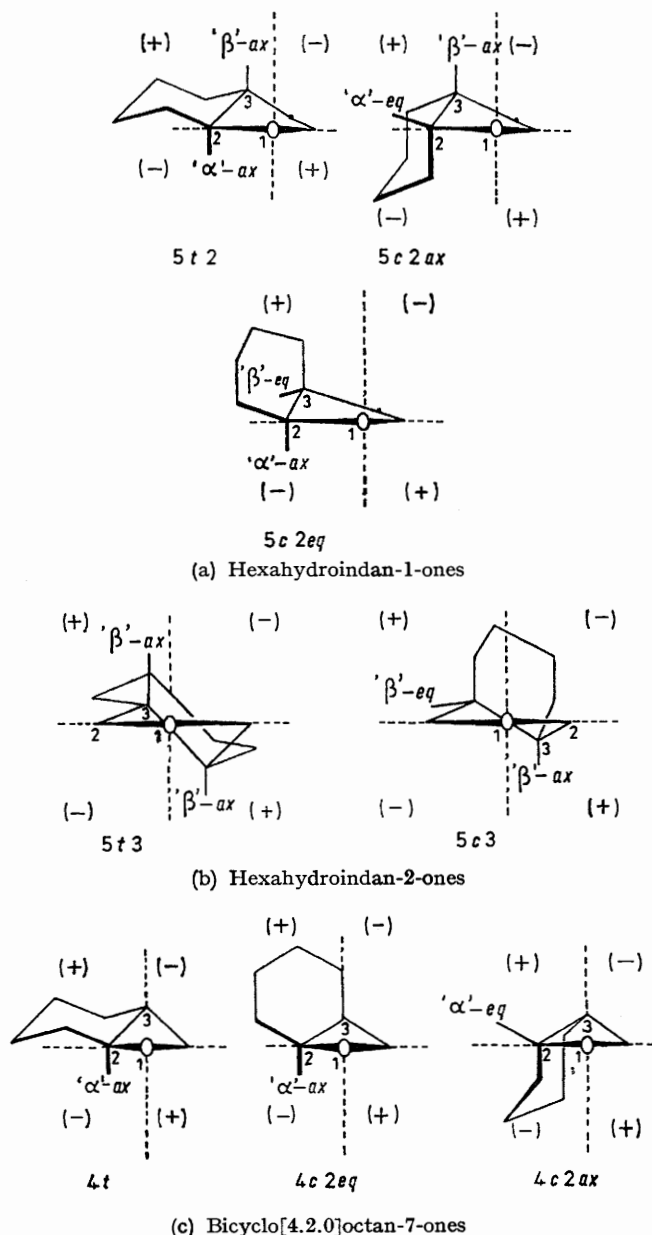


FIGURE 3 Conformational classes of hexahydroindanones and bicyclo[4.2.0]octan-2-ones

Analysis of C.d. Data for Hexahydroindanones.—The available data for the c.d. of extended hexahydroindanones, classified under the five structural types represented in Figure 3, are presented in Tables 1, 3, 5, and 6. Values of $\Delta\epsilon$ derived from o.r.d. data are given in italics, to indicate their lower reliability. Com-

¹¹ L. Velluz, M. Legrand, and M. Grosjean, 'Optical Circular Dichroism,' Verlag Chemie, Academic Press, New York, 1965, p. 196.

¹² N. S. Bayliss and E. G. McRae, *J. Phys. Chem.*, 1954, **58**, 1002.

ments² about the shapes and other characteristics of curves for decalones apply for the most part in the present work, with the exception that vibronic fine structure tends to be more pronounced for some compounds of hexahydroindanone type, particularly in hexane solution. This may represent evidence for relative conformational rigidity in some hexahydroindanones, but did not occur with sufficient regularity to suggest any useful correlation with structure. As before,² the $\Delta\epsilon$ values used are those of the strongest component band, whenever fine structure is pronounced. Wavelengths of c.d. maxima show the usual dependence on solvent polarity;^{2,11,12} maxima in methanol are usually within the range 295–300 nm, compared with a wider range (289–299 nm) found for decalone analogues.² The difference is more noticeable in hexane solution, especially for those c.d. curves which show pronounced fine structure:^{12,13} hexahydroindanones often give maxima at 324, 313, 302, and 291 (each ± 2) nm, the band at 313 nm generally being the most intense. Corresponding values for decalones are about 316, 306, and 296 nm with the last-named band usually dominant. All measurements were made at room temperature; some earlier studies^{7,14} have shown significant variations of $\Delta\epsilon$ with temperature, but the causes (conformational flexibility, possible changes in solvation) are not well understood. *trans*-Hexahydroindan-2-one shows little variation of c.d. behaviour with temperature down to -196°C .⁸

Our first objective was to establish reliable contributions to $\Delta\epsilon$ from the various fused ring systems and their separate cyclic components, as well as from angular methyl groups, whose geometry is determined within fairly narrow limits by the nature and conformation of the ring junction. We therefore excluded from the Tables any data which refer to compounds bearing either polar substituents in the vicinity of the carbonyl group, or substituents in the cyclopentanone ring which might be expected to cause significant changes in the conformation of the ring.

The key assumption, in this first stage, is that the conformation of the cyclopentanone ring remains essentially constant within each of the five classes of hexahydroindanone, provided that the cyclopentanone ring is unsubstituted other than at its points of fusion with the next ring. Dreiding models and published data on molecular geometries¹⁵⁻¹⁷ suggest that the conformation of the cyclopentanone ring falls into one of two groups, according to the class of hexahydroindanone, when viewed along the axis of the O=C bond. In hexahydroindan-2-ones (class 5t3 or 5c3) the ring appears to be essentially in or near the half-chair form, with C_2 symmetry, the two carbon atoms at the rear of the ring lying on opposite sides of the horizontal plane defined by the carbonyl group and the α - and α' -carbon atoms. Hexahydroindan-1-ones, in contrast, present a different projection when viewed along the O=C bond, the two rear carbon

¹³ O. Weigang, jun., *J. Chem. Phys.*, 1965, **43**, 3609.

¹⁴ K. M. Wellman, E. Bunnenberg, and C. Djerassi, *J. Amer. Chem. Soc.*, 1963, **85**, 1870; A. Moscovitz, K. Wellman, and C. Djerassi, *ibid.*, p. 3515.

TABLE 1

C.d. data for extended *trans*-hexahydroindan-1-ones (class 5*t*2); values in italics are calculated from o.r.d. data ($\Delta\epsilon = a/40.28$); * 'calculated' values are based on group contributions in Table 2

Compound	Ring code	Additional angular methyl groups at hexahydroindanone ring junction	$\Delta\epsilon$ in solvent indicated								Ref. †
			Hexane		Dioxan		Acetonitrile		Methanol		
			Obs.	Calc.	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.	
Bicyclic (8 <i>S</i> ,9 <i>R</i>)-8-Methylhexahydroindan-1-one (1)	5 <i>t</i> 2	' α '		+2.2	+2.2	+2.2		+2.2		+2.2	<i>a</i>
Tetracyclic and pentacyclic (based on 5 <i>t</i> 2, <i>t</i> 4 types)											
5 α -Androstan-17-one	5 <i>t</i> 2, <i>t</i> 4, <i>t</i> 2	' α '	+2.90	+3.0	-3.39	+3.2	+3.40	+3.3	+3.35	+3.4	
3 α -Hydroxy-5 α -androstan-17-one		' α '		+3.0	+3.46 ‡	+3.2	+3.38	+3.3	+3.25	+3.4	
3 β -Hydroxy-5 α -androstan-17-one		' α '		+3.0	+3.40 ‡	+3.2		+3.3	+3.48	+3.4	
3 β -Acetoxy-5 α -androstan-17-one		' α '	+3.06	+3.0	+3.20 ‡	+3.2	+3.49	+3.3	+3.44	+3.4	
5 β -Androstan-17-one	5 <i>t</i> 2, <i>t</i> 4, <i>c</i> 2 <i>eq</i>	' α '	+3.05	+3.0		+3.2	+3.13	+3.3		+3.4	
3 α -Hydroxy-5 β -androstan-17-one	5 <i>t</i> 2, <i>t</i> 4, <i>c</i> 2 <i>eq</i>	' α '			+3.41 ‡	+3.2		+3.3	+3.50	+3.4	
3-Hydroxygon-1,3,5(10)-trien-17-one (18-noroestrone)	5 <i>t</i> 2, <i>t</i> 4	None	+4.22	+4.3		+4.7	+4.85	+5.0		+5.3	<i>b</i>
3-Hydroxyoestra-1,3,5(10)-trien-17-one (oestrone) (2)	5 <i>t</i> 2, <i>t</i> 4	' α '			+3.28 ‡	+3.2	+3.40	+3.3	+3.07	+3.4	
3 β -Hydroxy-4,4,14 α -trimethyl-5 α -androstan-17-one	5 <i>t</i> 2, <i>t</i> 4, <i>t</i> 2	' α ' + ' β '	+1.65	+1.8		+2.2	+2.10	+2.5		+2.6	<i>c</i>
A-Nor-19-nor-5 α -oxo-steroid (3)		None		-4.3	-4.85	-4.7		-5.0		-5.3	<i>d</i>
A-Nor-5 α -3-oxo-steroid (4)		' β '		-3.1	-3.92	-3.7		-4.2		-4.7	<i>e</i>
5-Methyl-A-nor-5 α -cholestan-3-one (5)		' α ' + ' β '		-1.8		-2.2		-2.5	-2.8	-2.8	<i>f</i>
5-Methyl-A-nor-5 α -androstan-3-one (5)	5 <i>t</i> 2', <i>t</i> 4', <i>t</i> 2'	' α ' + ' β '	-1.66	-1.8		-2.2	-1.78	-2.5		-2.8	<i>e</i>
17 β -Hydroxy-5-methyl-A-nor-5 α -androstan-3-one (5)		' α ' + ' β '		-1.8	-2.6	-2.2		-2.5		-2.8	<i>g</i>
20,20-Ethylenedioxy-5-methyl-A-nor-5 α -pregnan-3-one (5)		' α ' + ' β '		-1.8	-2.35	-2.2		-2.5	-2.95	-2.8	<i>h</i>
4,23,24-Trinorlupan-3-one (6)	5 <i>t</i> 2', <i>t</i> 4', <i>t</i> 2', <i>t</i> 4'	' β '		-3.1		-3.7		-4.2	-4.9	-4.7	<i>i</i>
22,29,30-Trinor-17 β (<i>H</i>)-hopan-3-one (6)	5 <i>t</i> 2', <i>t</i> 4', <i>t</i> 2', <i>t</i> 4'	' β '		-3.1		-3.7		-4.2	-5.0	-4.7	<i>i</i>
Tetracyclic and pentacyclic (5 <i>t</i> 2, <i>t</i> 2, <i>t</i> 4 types)											
5 α -Androstan-15-one (7)	5 <i>t</i> 2, <i>t</i> 2, <i>t</i> 4	' β '	+2.5	+2.4	+2.98	+2.8	+2.93	+3.0	+3.05	+3.2	<i>j</i>
A-Nor-5 α -cholestan-1-one (8)	5 <i>t</i> 2', <i>t</i> 2', <i>t</i> 4'	' α '		-2.4		-2.3		-2.1	-1.5	-1.9	<i>k</i>
20,29,30-Trinor-18 α -lupan-19-one (9)	5 <i>t</i> 2', <i>t</i> 2', <i>t</i> 4', <i>t</i> 2'	' β '		-2.4		-2.8		-3.0	-3.3	-3.2	<i>l</i>

* Ref. 9. † In footnote references a name indicates the source of the sample, c.d. measurements being made in Westfield College; absence of a reference indicates our own data and sample. ‡ Ref. 11.

^a Ref. 19. ^b G. D. Searle and Co., Chicago. ^c G. R. Pettit, University of Maine, Orono. ^d J.-C. Bloch, Thesis, Strasbourg, 1964. ^e M. Audouin and J. Levisalles, *Bull. Soc. chim. France*, 1975, 695. ^f A. Romeo, Rome. ^g J. Bascoul and A. Crastes de Paulet, *Bull. Soc. chim. France*, 1969, 189. ^h D. Currotti, A. Romeo, and I. Torrini, *Gazzetta*, 1971, 101, 475. ⁱ G. V. Baddeley, T. G. Halsall, and E. R. H. Jones, *J. Chem. Soc.*, 1960, 1715. ^j Ref. 31. ^k H. P. Sigg and Ch. Tamm, *Helv. Chim. Acta*, 1961, 43, 1402. ^l Sir Ewart Jones, Oxford.

atoms (β and β') of the cyclopentanone ring lying usually on the same side of the C_{α} -CO- $C_{\alpha'}$ plane, although at different distances from this plane since the cyclopentanone ring is chiral. The boundary case between these two extreme projected types is an 'envelope' conformation of the cyclopentanone ring, in which four

¹⁵ C. Altona, H. J. Geise, and C. Romers, *Tetrahedron*, 1968, 24, 13.

¹⁶ N. L. Allinger and M. T. Tribble, *Tetrahedron*, 1972, 28, 1191.

carbon atoms, including that of the carbonyl group, are coplanar and only one of the ' β '-carbon atoms is out of plane; few hexahydroindanones, however, appear to have a true envelope conformation of the cyclopentanone ring.¹⁵⁻¹⁷ We found it convenient to distinguish between the two groups of projected conformations, which

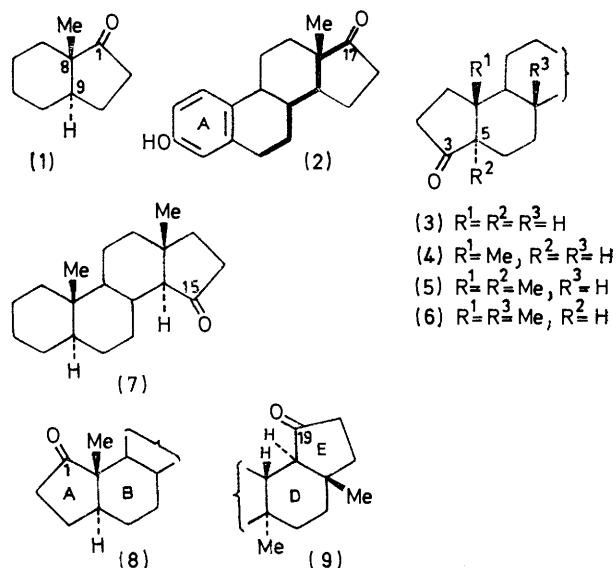
¹⁷ C. Romers, C. Altona, H. J. C. Jacobs, and R. A. G. De Graaff, in 'Terpenoids and Steroids,' ed. K. H. Overton, Chem. Soc. Specialist Periodical Report, London, 1974, vol. 4, p. 531.

lie on either side of the 'envelope,' by using the general terms 'twisted' (for C_2 -like forms) and 'folded' (for those in which both the rear carbon atoms lie on the same side of the C_α -CO- $C_{\alpha'}$ plane) (see also p. 733).

Assuming that each hexahydroindanone class has its cyclopentanone ring in an essentially fixed conformation, the chiroptical contributions of the chiral cyclopentanone ring itself, and of the hexahydroindanone unit, were expected to vary relatively little within each class of compound. On this basis estimates were made of the separate contributions of the hexahydroindanone component, and of 'third' rings, as well as those of methyl substituents, by pairwise comparisons of compounds in the manner which was successful in the decalone series.

Although data for key structures are less complete for the hexahydroindanones than for the decalones, the regularities observed² among decalones have been used, where necessary, to guide the derivation of group increments ($\delta\Delta\epsilon$) in the hexahydroindanones. In the analysis which follows, the reasonably regular trends in solvent effects,² the special characteristics associated with primary zig-zags,^{2,18} and the negligible contributions expected from rings not connected to the carbonyl group by a primary zig-zag,² have each been invoked in order to by-pass the absence of certain items of data. While this procedure must reduce the quantitative reliability of conclusions, we believe the qualitative features to be generally valid.

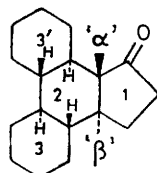
roughly into an arithmetic progression. This provides the convenient possibility of interpolating reasonable estimates of missing values of $\delta\Delta\epsilon$ provided that data are



available for at least two of the solvents. The expectation of a progression also affords some check on the likely reliability of $\Delta\epsilon$ values calculated from o.r.d. data, or

TABLE 2

Group increments for extended *trans*-hexahydroindan-1-ones (class 5*t*2); values of $\delta\Delta\epsilon$ refer to contributions of individual rings or methyl substituents, labelled as in the formula



Structural feature	Approximate $\delta\Delta\epsilon$			
	Solvent : Hexane	Dioxan	Acetonitrile	Methanol
Rings 1 + 2 (consignate)	+3.5	+3.7	+3.9	+4.1
Ring 3 (consignate)	+0.8	+1.0	+1.1	+1.2
Ring 3' (weakly con- or dis-signate in 'front' octant)	+0.2	+0.1	-0.1	-0.3
' α '-Methyl (consignate)	-1.3	-1.5 ^a	-1.7	-1.9
' β '-Methyl (dissignate)	-1.2	-1.0	-0.8	-0.6

^a Data given by Velluz *et al.*¹¹ for 3 α ,11 β -dihydroxy-5 β -androstan-17-one and its 18-nor-analogue indicate an ' α '-axial methyl contribution of -1.67 in dioxan.

trans-Hexahydroindan-1-ones.—Class 5*t*2 (Table 1). This class is the most widely represented of the hexahydroindanones. Some of these compounds show significant solvent effects, but few were available in sufficient quantity to allow study in three or four of the series of solvents. We have therefore made use of the observation, in our work on decalones, that $\delta\Delta\epsilon$ values for structural components, taken in the order of solvents hexane, dioxan, acetonitrile, methanol, tend to fall

taken from the literature and measured on different instruments.

Unfortunately the parent bicyclic ketone, unlike those in the decalone series, was not available for study. The contributions estimated for the bicyclic structure are therefore based upon what we consider to be reasonable allowances for 'third' rings in the available 5*t*2,4 and 5*t*2,2 classes, together with the one $\Delta\epsilon$ value calculated from published o.r.d. data (in dioxan) for (8*S*,9*R*)-*trans*-8-methylhexahydroindan-1-one (1).¹⁹ The aromatic ring

¹⁸ The first recognition of the significance of zig-zag patterns of bonds in chiroptical phenomena appears to have been by J. H. Brewster, *Tetrahedron*, 1961, **18**, 106.

¹⁹ C. Djerassi, B. Riniker, and R. Riniker, *J. Amer. Chem. Soc.*, 1956, **78**, 6362.

A of oestrone (2) does not affect any bonds of a primary zig-zag [heavy lines in (2)], and makes no significant contribution; Δ^5 -unsaturation also has no appreciable effect on the $\Delta\epsilon$ values of 17-oxo-steroids.

The numerical values are larger in the present series than for the decalones, but the spatial relationship of the 'third' ring to the chromophore in a 5*t*2,14 unit [cf. (2)] is not dissimilar to that found in the corresponding ex-

TABLE 3
C.d. data for extended *cis*-hexahydroindan-1-ones (classes 5*c*2*eq* and 5*c*2*ax*)

Compound	Ring code	Angular methyl substituents at hexahydroindanone ring junction	$\Delta\epsilon$ (solvent in parentheses) *		
			Obs.	'Calc.' †	Ref. ‡
(a) Class 5 <i>c</i> 2 <i>eq</i>					
Bicyclic					
(8 <i>S</i> ,9 <i>S</i>)-8-Methyl- <i>cis</i> -hexahydroindan-1-one (10)	5 <i>c</i> 2 <i>eq</i>	' α '- <i>ax</i>	+0.5 § (M)	+0.5 § (M)	<i>a</i>
Tetracyclic and pentacyclic structures based on 5 <i>c</i> 2 <i>eq</i> ,14 (12)					
A-Nor-5 β -cholestan-3-one	5 <i>c</i> 2 <i>eq</i> ,14,12	' β '- <i>eq</i>	+3.08 (D)	+3.3 (D)	<i>b</i>
3-Oxo-A-nor-5 β -cholan-24-oic acid		' β '- <i>eq</i>	+3.3 (M)	+3.2 (M)	<i>c</i>
14 α -Methyl-A-nor-5 β -cholestan-3-one		' β '- <i>eq</i>	+2.9 (M)	+3.2 (M)	<i>d</i>
17 β -Hydroxy-14 α -methyl-A-nor-5 β -androstan-3-one		' β '- <i>eq</i>	+3.4 (M)	+3.2 (M)	<i>e</i>
17 β -Hydroxy-5-methyl-A-nor-5 β -oestrane-3-one		' α '- <i>ax</i>	+0.6 (D)	+0.8 (D)	<i>e</i>
5-Methyl-A-nor-5 β -cholestan-3-one		' α '- <i>ax</i> + ' β '- <i>eq</i>	+1.54 (H)	+1.6 (H)	<i>f</i>
17 β -Hydroxy-5-methyl-A-nor-5 β -androstan-3-one		' α '- <i>ax</i> + ' β '- <i>eq</i>	+1.53 (D)	+1.4 (D)	<i>b</i>
4,23,24-Trinor-5 β -lupan-3-one	5 <i>c</i> 2 <i>eq</i> ,14,12,14	' β '- <i>eq</i>	+1.15 (D)	+1.4 (D)	<i>e</i>
'Backbone-rearranged' 14 β -methyl-18-nor-17-ketone (13)	5 <i>c</i> 2 <i>eq</i> ,14,12	' β '- <i>eq</i>	+2.95 (M)	+3.2 (M)	<i>g</i>
22,29,30-Trinor-17 α (<i>H</i>)-hopan-21-one (14)	5 <i>c</i> 2 <i>eq</i> ,14,12,14	' β '- <i>eq</i>	+3.1 (M)	+3.2 (M)	<i>h</i>
Structures based on 5 <i>c</i> 2 <i>eq</i> ,12					
3 β -Acetoxy-20,29,30-trinor-18 β -lupan-19-one (15)	5 <i>c</i> 2 <i>eq</i> ,12,14,12	' β '- <i>eq</i>	+2.0 (D)	+2.4 (D)	<i>i</i>
5 α ,14 β -Androstan-15-one (16)	5 <i>c</i> 2' <i>eq</i> ,12',14'	' β '- <i>eq</i>	-2.29 (M)	-2.5 (M)	<i>j</i>
3 β -Acetoxy-5 α ,14 β -androstan-15-one (16)		' β '- <i>eq</i>	-2.6 (M)	-2.5 (H)	<i>k</i>
14-Methyl-5 α ,14 β -androstan-15-one (17)		' β '- <i>eq</i>	-2.46 (H)	-2.5 (H)	<i>k</i>
17-Oxo-13 α -steroids:		' α '- <i>ax</i> + ' β '- <i>eq</i>	-2.30 (M)	-2.5 (M)	<i>l</i>
3 β -Acetoxy-18-nor-5 α ,13 α -androstan-17-one (18)	5 <i>c</i> 2' <i>eq</i> ,14',12'	None	-0.64 (H)	-0.6 (H)	<i>l</i>
5 α ,13 α -Androstan-17-one (19)		' α '- <i>ax</i>	-0.51 (M)	-0.6 (M)	<i>m</i>
3 β -Acetoxy-5 α ,13 α -androstan-17-one (19)		' α '- <i>ax</i>	-2.86 (H)	-2.9 (H)	<i>m</i>
3 β -Hydroxy-13 α -androstan-17-one (19)		' α '- <i>ax</i>	-2.34 (M)	-2.4 (M)	<i>n</i>
3-Hydroxy-13 α -oestra-1,3,5(10)-trien-17-one (19)		' α '- <i>ax</i>	-0.87 (H)	-1.0 (H)	<i>n</i>
14-Methyl-18-nor-13 α -17-one (20)		' β '- <i>eq</i>	-0.67 (M)	-0.5 (M)	<i>n</i>
(b) Class 5 <i>c</i> 2 <i>ax</i>					
Bicyclic					
(6 <i>R</i> ,8 <i>R</i> ,9 <i>R</i>)-6-Isopropyl-8,9-dimethyl- <i>cis</i> -hexahydroindan-1-one ('norvaleranone') (11)	5 <i>c</i> 2 <i>ax</i>	' α '- <i>eq</i> + ' β '- <i>ax</i>	-0.6 (M)	-0.5 (M)	<i>o</i>
Tetracyclic					
5 α ,14 β -Androstan-17-one (21)	5 <i>c</i> 2' <i>ax</i> ,14',12'	' α '- <i>eq</i>	+0.53 (H)	+1.3 (M)	<i>p</i>
3 β -Acetoxy-5 α ,13 α -androstan-15-one (22)	5 <i>c</i> 2' <i>ax</i> ,12',14'	' β '- <i>ax</i>	+1.0 (M)	+2.0 (M)	<i>r</i>
5 α ,13 α -Androstan-15-one (22)	5 <i>c</i> 2' <i>ax</i> ,12',14'	' β '- <i>ax</i>	+0.96 (M)	+2.0 (M)	<i>s</i>
			+1.8 (M)	+2.0 (M)	<i>r</i>
			+2.18 (M)	+2.0 (M)	<i>s</i>

* M = methanol, D = dioxan, H = hexane or cyclohexane. † Calculated from group contributions $\delta\Delta\epsilon$ given in Table 4; values in dioxan estimated as slightly smaller than calculated values in hexane. ‡ See footnote references (see also Table 1, †) § Observed $\Delta\epsilon$ value estimated from incomplete o.r.d. data—see text: 'Calculated' value assumes the 5*c*2*eq* conformation: the calculated value for 5*c*2*ax* would be +1.3. ¶ 'Calculated' for 5*c*2*ax* (probably the preferred conformation) by assuming that the isopropyl group contributes -0.95 unit, by providing the third and fourth bonds of a primary zig-zag (see Table 12 in ref. 2). The 'calculated' value for 5*c*2*eq* would be -1.3.

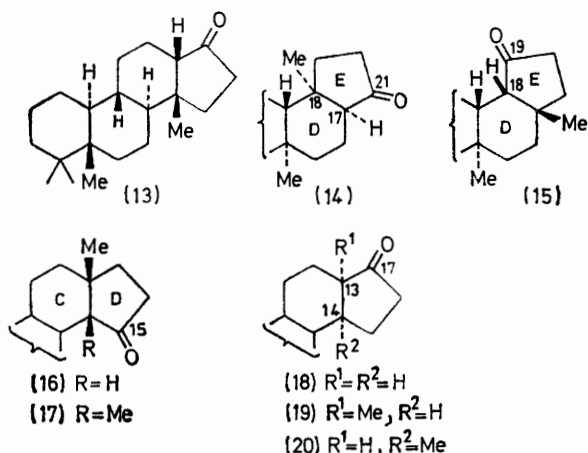
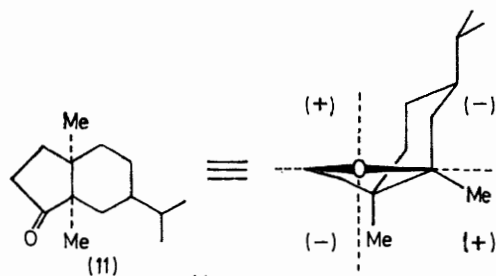
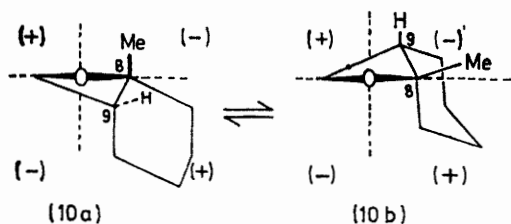
¶ Ref. 20. † M. Audouin and J. Levisalles, *Bull. Soc. chim. France*, 1975, 695. † Ref. 19. † J.-C. Bloch, Thesis, Strasbourg, 1964. † J. Bascoul and A. Crastes de Paulet, *Bull. Soc. chim. France*, 1969, 189. † I. Morelli and S. Catalano, *Gazzetta*, 1972, 102, 572. † T. G. Halsall, Oxford. † R. C. Sheppard, Liverpool. † C. Djerassi, J. Osiecki, and W. Closson, *J. Amer. Chem. Soc.*, 1959, 81, 4587. † Ref. 31. † Ch. Tamm, Basel. † G. D. Meakins, Oxford. † J. T. Pinhey, Sydney; see also J. T. Chapman and J. C. Pinhey, *Austral. J. Chem.*, 1974, 27, 2421 ($\Delta\epsilon$ -2.2 in MeOH). † C. M. Hol, Thesis, Leiden 1970. † M. Fétizon, Orsay. † Ref. 11. † F. Šorm, Prague. † T. Nambara, H. Hosoda, M. Usui, and L. Y. Ng, *Chem. and Pharm. Bull. (Japan)*, 1971, 19, 2555. † I. M. Clark and G. D. Meakins, Oxford.

Table 2 lists the structural components considered to contribute to $\Delta\epsilon$, and the increments ($\delta\Delta\epsilon$) tentatively assigned to them for each of the four solvents.

tended decalones: moreover the third ring extends a coplanar zig-zag of bonds closely analogous to the 'primary zig-zags' identified in the decalone series. The

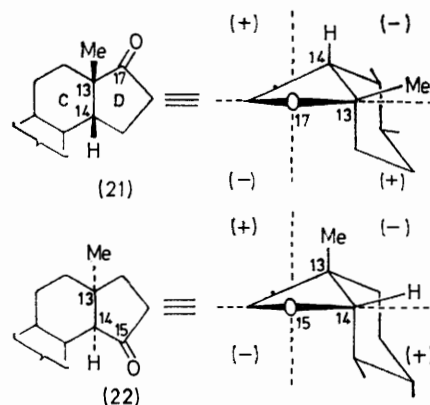
set of values allotted to 'ring 3' was therefore selected so as to form a series rising in proportion to the set of $\Delta\epsilon$ values found² for similar third rings in the corresponding extended decalones (6/2,4). Fourth rings are ignored in view of their general insignificance in the decalone series.² The 'front octant' contributions estimated for 'ring 3' are derived from consideration of the effect of ring B in 5 α -androstan-15-one (7), by making suitable allowance for the hexahydroindanone component (rings D and C) with a β '-axial methyl substituent: any small contribution due to the remote ring A is ignored.

Table I includes $\Delta\epsilon$ values 'calculated' by appropriate summation of group contributions ($\delta\Delta\epsilon$) taken from Table 2. Agreement with the available $\Delta\epsilon$ values is satisfactory, although the nature of the approximations



necessary in evaluating group contributions makes it unlikely that values for compounds not included in this study will show the very good agreement which has

generally been found for decalone analogues. Deviations of up to ± 0.5 unit might be expected in this hexahydroindanone series of compounds.



cis-Hexahydroindan-1-ones (Table 3).—The parent (bicyclic) *cis*-hexahydroindan-1-one was not available for study. Even had it been available, it would not be expected to exist wholly in either the *5c2eq* or the *5c2ax* conformation. The two conformations are calculated¹⁶ to be of approximately equal enthalpy, so the conformational preference, if any, will depend upon entropies, which are not known. It would be desirable to have for c.d. study a pair of isomeric *cis*-hexahydroindan-1-ones with a bulky substituent so placed in the six-membered ring as to favour the *5c2eq* and the *2c5ax* conformations, respectively, while itself exerting no measurable influence on the c.d.

Calculated strain energies¹⁶ for 8-methyl-*cis*-hexahydroindan-1-one suggest that the *5c2eq* conformer (10a), with the methyl group equatorial to the cyclohexane ring, is marginally the more stable (by 0.2 kcal mol⁻¹), although entropy effects are again unknown. A positive Cotton effect is reported²⁰ (first extremum only, $[M]_{314} + 1.040^\circ$) for (8*S*)-8-methyl-*cis*-hexahydroindan-1-one (10), and a similar finding for the (5*S*)-5-hydroxy-derivative. Models show that the positive sign is compatible with either the *5c2eq* (10a) or the *5c2ax* (10b) conformation. From data given below, the rather small magnitude of the Cotton effect ($\Delta\epsilon$ ca. +0.5, if the second extremum of the o.r.d. curve is of comparable magnitude to the first) implies a preference for the *5c2eq* conformation, which was favoured by the original authors.²⁰

The only other bicyclic compound of this class for which data are available is (6*R*,8*R*,9*R*)-6-isopropyl-8,9-dimethyl-*cis*-hexahydroindan-1-one ('norvalerانون')(11). Here the 6-isopropyl group would be expected to prefer the equatorial location, so holding the molecule mainly in the *5c2ax* conformation. The rather strongly negative Cotton effect ($\Delta\epsilon -2.1$) is compatible with this conclusion, for the isopropyl group extends a primary zig-zag in a negative octant; a relatively small proportion of the *5c2eq* form would reduce the numerical value of $\Delta\epsilon$ without changing its sign.

Class 5c2eq [Table 3, section (a)]. Three groups of

²⁰ W. Acklin and V. Prelog, *Helv. Chim. Acta*, 1959, **42**, 1239.

polycyclic compounds belonging to this class were available for c.d. study, but quantities were too limited to allow measurements to be made in four solvents. Where solvent comparisons were possible $\Delta\epsilon$ values in methanol were generally smaller than those in hexane or dioxan. Estimates of group contributions $\delta\Delta\epsilon$ have been made for the solvents methanol and hexane: dioxan should give values close to those in hexane.

Pairwise comparisons afforded the group contributions listed in Table 4. The assumption was made that ring 3

Class *5c2ax* [Table 3, section (b)]. Examples of this class are very limited and are insufficient to allow a full analysis by pairwise comparisons. On the evidence provided by one of the compounds, a 17-oxo-14 β -steroid (21), the solvent effect may be appreciable, but generally data were available only for methanol as solvent. Large positive values of $\Delta\epsilon$ are presumably dominated by the ' α '-axial bond, in a manner similar to that found in *cis*-1-decalones of class *6c2ax*.² In the absence of more compounds of this class it is impossible to evaluate

TABLE 4
Group contributions, $\delta\Delta\epsilon$, for extended *cis*-hexahydroindan-1-ones

Solvent:	Class <i>5c2eq</i> (Figure 4)		Class <i>5c2ax</i> (Figure 5)
	Hexane $\delta\Delta\epsilon$	MeOH $\delta\Delta\epsilon$	MeOH $\delta\Delta\epsilon$ ^a
Rings 1 + 2	2.9	2.4 (consignate ^b)	ca. 1.8 (dissignate ^b)
Ring 3	0	0	ca. 0
Ring 3'	1.0	0.7 (front-octant consignate)	ca. 0.4 (front-octant consignate)
' α '-Methyl	(<i>ax</i>) 1.9	1.9 (consignate)	(<i>eq</i>) 0.5 (consignate)
' β '-Methyl	(<i>eq</i>) 0.6	0.8 (consignate)	(<i>ax</i>) 0.6 (dissignate)

^a Tentative estimates—see text. ^b Consignate or dissignate with respect to the chirality of the cyclopentanone ring—see text.

makes no contribution in compounds of type *5c2eq,t4* (Figure 4), being remote from the carbonyl group and

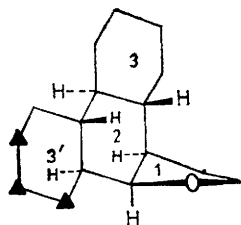


FIGURE 4 Positions of 'third' rings in compounds of classes *5c2eq,t4* (ring 3) and *5c2eq,t2* (ring 3') (▲ = carbon atom in front octant)

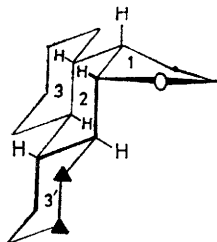


FIGURE 5 Positions of 'third' rings in compounds of classes *5c2ax,t4* (ring 3) and *5c2ax,t2* (ring 3') (▲ = carbon atom in front octant; thick lines indicate a primary zig-zag of C-C bonds)

not connected to it by an antiperiplanar 'primary zig-zag' of C-C bonds. The 'third' ring in structures of type *5c2eq,t2* (ring 3' in Figure 4) lies in a front octant²¹ and appears to make a significant contribution of appropriate sign.

'Calculated' values of $\Delta\epsilon$ for compounds in Table 3, section (a), are those obtained by summation of appropriate group contributions taken from Table 4. The correlation with experimental values is generally satisfactory.

accurately the effects of individual methyl groups at the ring junction, or of third rings, but approximate and tentative estimates of the c.d. contributions (in methanol) associated with the *5c2ax* structure were obtained by assuming: (a) that 'third' rings in a *5c2ax,t4* system make a negligible contribution (Dreiding models, and the criteria concerning significant bonds established in the decalone series, suggest that this is a reasonable assumption); (b) that the contribution of a ' β '-axial methyl group to $\Delta\epsilon$ may be taken as 0.6 unit (dissignate), since the cyclopentanone ring has a 'folded' conformation approximating to that found in class *5t2*, where the corresponding ' β '-axial methyl group makes a dissignate contribution of 0.6 unit (*cf.* Table 2); and (c) that the contribution of an ' α '-quasi-equatorial methyl group to $\Delta\epsilon$ is about 0.5 unit (consignate). [This last assumption is based upon a semi-quantitative relationship between the magnitude of $\delta\Delta\epsilon$ for the methyl group and the O=C-C-Me torsional angle (see p. 775)].

The best derived value of $\delta\Delta\epsilon$ at present for the bicyclic ketone *5c2ax* is 1.8 unit, with sign corresponding to consignate behaviour of the ' α '-quasi-axial bond. A small 'front-octant consignate' contribution (0.4 unit) is assigned to ring 3' (Figure 5). The values of $\delta\Delta\epsilon$ are tentatively entered into Table 4 and give reasonable 'calculated' $\Delta\epsilon$ values for the compounds listed in Table 3 (b).

Hexahydroindan-2-ones.—Class *5t3* (Table 5). This class includes the 16-oxo- (29) and 2-oxo-A-nor-steroids (27) which provided the first example of 'quasi-enantiomeric' behaviour to be recognised¹⁹ during early o.r.d. studies. They were also the first compounds for which twisting of the cyclopentanone ring itself (Figure 2) was suggested⁵ as the dominant factor causing chiroptical

²¹ W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, 1961, **83**, 4013.

behaviour. The bicyclic compounds with and without an angular methyl group have been examined,⁴ and show no significant difference in o.r.d. behaviour. Further rings present in 2-oxo-A-nor-5 α -steroids (27) and in androstan-16-ones (29) likewise appear to make no

formational changes attending the presence of one ' β '-axial methyl group (see p. 774).

A mean value of $\Delta\epsilon = 5.5 (\pm 0.5)$ appears to be characteristic of the 5 β 3 class of hexahydroindanones. The presence of one angular substituent has no noticeable

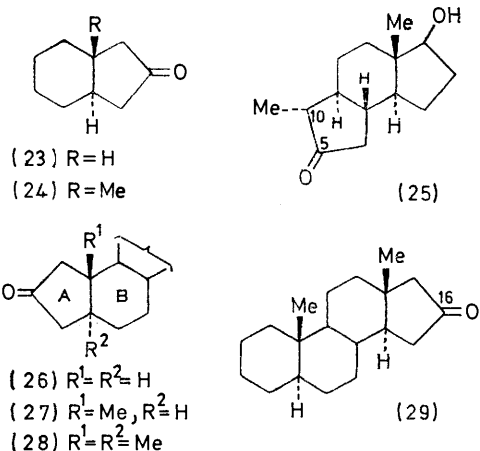
TABLE 5
C.d. data for extended *trans*-hexahydroindan-2-ones (class 5 β 3)

Compound	Ring code	$\Delta\epsilon$ (solvent in parentheses) *	Ref. †
Bicyclic			
(8 <i>R</i> ,9 <i>R</i>)- <i>trans</i> -Hexahydroindan-2-one (23)	5 β 3'	-5.0 (H), -5.5 (M)	a
(8 <i>R</i> ,9 <i>R</i>)-8-Methyl- <i>trans</i> -hexahydroindan-2-one (24)	5 β 3'	-5.5 (M)	b
Tricyclic			
17 β -Hydroxy-des-A-B-nor-10 β (H)-androstan-5-one (25)	5 β 3,t1	+5.9 (M)	c
Tetracyclic			
2-Oxo-A-nor-5 α -steroids:			
A-Nor-5 α -oestrane-2-one (26)	5 β 3,t1,t4	+5.4 (M)	d
17 β -Hydroxy-A-nor-5 α -oestrane-2-one (26)		+5.9	e
17 β -Acetoxy-A-nor-5 α -oestrane-2-one (26)		+5.97 (H), +5.36 (A)	f
17 β -Hydroxy-A-nor-5 α -androstan-2-one (27)		+5.58 (A), +5.30 (M)	
17 β -Acetoxy-A-nor-5 α -androstan-2-one (27)		+5.48 (H), +5.35 (A)	
A-Nor-5 α -cholestan-2-one (27)	+5.55 (M)	b, e	
5-Methyl-A-nor-5 α -cholestan-2-one (28)	+5.8 (M)		
		+6.8 (H), +6.55 (A)	g
		+6.2 (M), +6.8 (D)	
16-Oxo-steroids:			
5 α -Androstan-16-one (29)	5 β 3',t1',t4'	-5.45 (H), -5.9 (M)	h
3 β -Hydroxy-5 α -androstan-16-one		-5.15 (A)	i
3 β -Acetoxy-5 α -androstan-16-one		-6.40 (H), -5.45 (D), -5.5 (A), -5.19 (M)	j
3-Hydroxyoestra-1,3,5(10)-trien-16-one		-6.12 (D)	

* See Table 3, *; A = acetonitrile. † See footnote references (see also Table 1, †).

^a Ref. 4. ^b Ref. 19. ^c Sir Ewart Jones, Oxford. ^d F. Sondheimer, Cambridge. ^e Ref. 6, pp. 234—235. ^f S. Szpilfogel, N. V. Organon, Oss, Netherlands. ^g A. Romeo, Rome; data in methanol from D. Curotti, A. Romeo, and I. Torrini, *Gazzetta*, 1971, **101**, 475; in dioxan from M. Audouin and J. Levisalles, *Bull. Soc. chim. France*, 1975, 695. ^h D. W. Mathieson, Bradford. ⁱ D. K. Fukushima, Sloan-Kettering Institute, New York. ^j Ref. 11.

significant contribution to chiroptical properties; the third and fourth rings extend a periplanar zig-zag of bonds, but this lies almost in the horizontal nodal plane



of the carbonyl group and so should make little if any contribution. Values of $\delta\Delta\epsilon$ throughout this series of compounds lie generally within the range 5.0—6.0 units. The only compound to fall clearly outside this range is 5-methyl-A-nor-5 α -cholestan-2-one (28); the presence of two ' β '-axial angular methyl groups appears to enhance $\Delta\epsilon$ values by ca. 1 unit, although a single ' β '-axial methyl group produces no measurable effect. This apparent anomaly may be a consequence of minor con-

formational changes attending the presence of one ' β '-axial methyl group (see p. 774).

formational changes attending the presence of one ' β '-axial methyl group (see p. 774). A mean value of $\Delta\epsilon = 5.5 (\pm 0.5)$ appears to be characteristic of the 5 β 3 class of hexahydroindanones. The presence of one angular substituent has no noticeable effect, but two such groups introduce a consignate contribution amounting to ca. 1 unit (*i.e.* 0.5 for each methyl group). Solvent effects are not clearly defined, but $\Delta\epsilon$ values in hexane are often larger than those in methanol. ^{*} Class 5c3 (Table 6). Four types of tetracyclic (steroidal) compounds were available in this group. Solvent effects may be appreciable but cannot be evaluated from available data. Values of $\Delta\epsilon$ for 2-oxo-A-nor-5 β -steroids (30a) span a wide range, but come from diverse sources: their mean (-3.3) is close in numerical value of $\Delta\epsilon$ to that for the quasi-enantiomeric 16-oxo-18-nor-13 α -compound (32) (+3.39), suggesting that the ' β '-equatorial angular methyl group makes little if any contribution. By contrast, the ' β '-axial methyl groups in A-nor-5 α ,10 α -cholestan-2-one (31) and 5 α ,13 α -androstan-16-one (33) appear to exert small dissignate effects, averaging about 0.5 unit.

5-Methyl-A-nor-5 β -cholestan-2-one (30b) is the only compound in this class showing a major discrepancy between observed and calculated values of $\Delta\epsilon$. It is also the only compound with two angular methyl groups at the hexahydroindanone ring junction. A model suggests that the increased torsional strain about the C(5)-C(10) bond may force ring A into a more 'twisted' conformation than is common in this series of compounds, and so enhance $\Delta\epsilon$ (p. 773), giving an apparent consignate contribution of the 5 β -methyl group (' β '-axial) [*cf.* the corresponding 5 α -compound (28)].

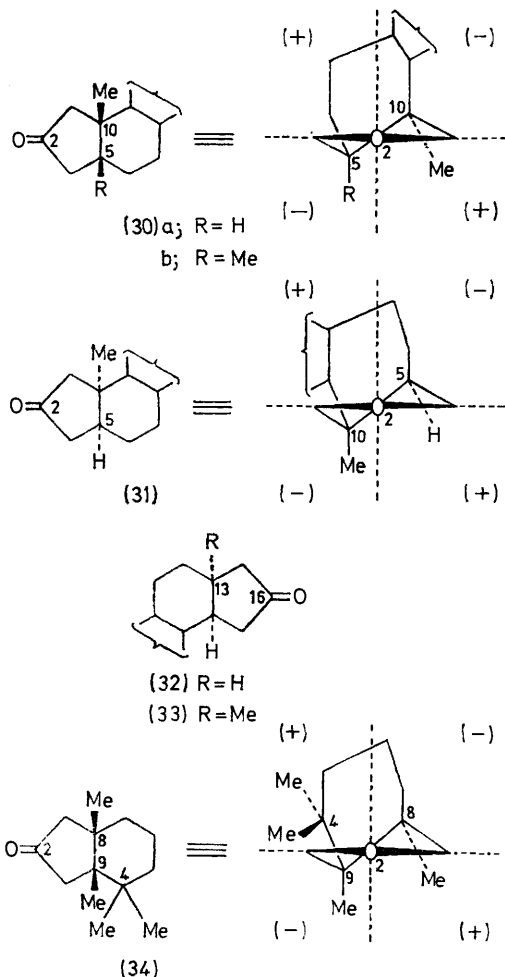
TABLE 6
C.d. data for extended *cis*-hexahydroindan-2-ones (class 5c3)

Compound	Ring code	$\Delta\epsilon$ (solvent in parentheses) *	$\Delta\epsilon$ (calc.†)	Ref.‡
2-Oxo-A-nor-5 β -steroid (30a)	5c3',t1',t4'	-3.55 (D)	-3.4	a
Methyl 2-oxo-A-nor-5 β -cholan-24-oate		-3.8 (M)	-3.4	b
17 β -Hydroxy-A-nor-5 β -androstan-2-one		-3.5 (M)	-3.4	a
		-3.09 (E)	-3.4	c
A-Nor-5 β -cholestan-2-one		-3.53 (I)	-3.4	c
		-2.99 (I)	-3.4	c
5-Methyl-A-nor-5 β -cholestan-2-one (30b)	5c3',t4',t1'	-2.74 (E)	-3.4	c
A-Nor-5 α ,10 α -cholestan-2-one (31)		-3.92 (D)	-2.9	d
		-3.0 (H)	-2.9	e
		-2.95 (M)	-2.9	e
3 β -Hydroxy-18-nor-5 α ,13 α -androstan-16-one (32)	5c3,t4,t1	+3.39 (D)	+3.4	f
5 α ,13 α -Androstan-16-one (33)	5c3,t4,t1	+2.71 (E)	+2.9	g

* H = hexane, I = iso-octane, D = dioxan, M = methanol, E = ethanol. † 'Calculated' from $\delta\Delta\epsilon$ values in Table 8, without regard to solvent. ‡ See footnote references (also Table 1, †).

§ J.-C. Bloch, Thesis, Strasbourg, 1964. ¶ Ref. 19. * L. Lábler and Ch. Tamm, *Helv. Chim. Acta*, 1972, **55**, 886. † M. Audouin and J. Levisalles, *Bull. Soc. chim. France*, 1975, 695. * P. D. Gardner, Austin, Texas. † Ref. 11. ‡ J. C. Gramain, Clermont-Ferrand; we thank Dr. Gramain for this unpublished result.

The fundamental bicyclic unit is assigned a mean contribution of 3.4 units, the sign corresponding to the sense of twist of the cyclopentanone ring. 'Third' rings are



A single bicyclic compound expected to exist mainly in the 5c3' conformation gave a $\Delta\epsilon$ value (-2.6 in methanol) which agrees acceptably with the 'calculated' value (-2.9). The compound is (8S,9S)-4,4,8,9-tetramethyl-*cis*-hexahydroindan-2-one (34);²² the alternative 5c3 conformation appears from a Dreiding model to be significantly more strained, having one of the methyl groups at C-4 overhanging the cyclopentanone ring.

Bicyclo[4.2.0]octan-7-ones (Figure 3c).—Cyclobutane rings are usually puckered by an angle which has been variously estimated²³ within the range 20–30°, rather than being planar. Fusion to a rigid cyclohexane ring will determine the sense of folding of a cyclobutanone, for the bonds exocyclic to the six-membered ring will adopt directions as near as possible to their normal axial or equatorial character. The molecule must then assume the conformation which is the best compromise, energetically, between the separate preferences of the two rings. Unlike a cyclopentanone, the carbon atoms of the cyclobutanone ring itself cannot adopt a chiral conformation, chirality being entirely due to associated substituents and rings.

C.d. data are available for four compounds of class 4c2eq, but for only one of each of the classes 4t and 4c2ax (Table 7). Additional data are provided by three compounds (41)–(43) of the *cis*-bicyclo[3.2.0]heptan-6-one type, although the conformational characteristics imposed by fusion of a cyclobutanone to a five-membered ring are not identical with those involving a six-membered ring. A Dreiding model of such a bicycloheptanone suggests that the bonds 'α' to carbonyl are of approximately 'bisectonal' type rather than quasi-axial or -equatorial. The symbol 4c2b is used for their classification (b = bisectonal).

Class 4c2eq. Values of $\Delta\epsilon$ average 1.1 unit for the three compounds (36)–(38) lacking a methyl group 'α' to carbonyl. Locations of 'third' rings have no significant effect, consistent with the criteria established during our study of those *cis*-decalones which lack extended primary

ignored, since they do not extend primary zig-zags of bonds. Values of $\delta\Delta\epsilon$ are collected in Table 8.

²² T. Norin, *Acta Chem. Scand.*, 1963, **17**, 738.

²³ R. M. Moriarty, *Topics Stereochem.*, 1973, **8**, 271.

TABLE 7

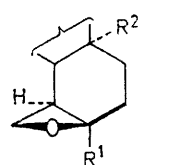
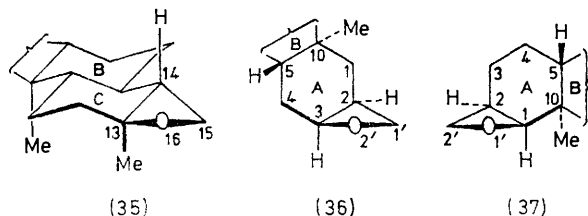
C.d. data for compounds containing a fused cyclobutanone ring ('Bicyclo[4.2.0]octan-7-ones')

Compound	Ring code	$\Delta\epsilon$ (solvent in parentheses *)	Ref.†
<i>trans</i> -Bicyclo[4.2.0]octan-7-one			
3 β -Methoxy-D-nor-5 α -androstan-16-one (35)	4 <i>t</i> ,4 <i>t</i> ,2	+0.85 (D)	a
<i>cis</i> -Bicyclo[4.2.0]octan-7-ones			
Class 4 <i>c</i> 2 <i>eq</i>			
2 α ,3 α -(Oxoethano)-5 α -cholestane (36)	4 <i>c</i> 2 <i>eq</i> ,3,4,2	+0.76 +0.73 (D) +1.13 (H)	b c
1 α ,2 α -(Oxoethano)-5 α -cholestane (37)	4 <i>c</i> 2' <i>eq</i> ,2',2',4'	-0.98 (H) -0.8 (D)	c
3 α ,4 α -(Epoxyethano)-5 α -cholestane (38)	4 <i>c</i> 2' <i>eq</i> ,4',2',4'	-1.16 (H) -0.83 (D)	c
3 β -Methoxy-D-nor-5 α ,13 α -androstan-16-one (39)	4 <i>c</i> 2' <i>eq</i> ,4',2'	+0.58 (D)	a
Class 4 <i>c</i> 2 <i>ax</i>			
2 α ,3 α -(Oxoethano)-5 α -cholestane (40)	4 <i>c</i> 2 <i>ax</i> ,3,2,4	-3.6 -4.26 (D)	b c
<i>cis</i> -Bicyclo[3.2.0]heptan-6-ones			
Class 4 <i>c</i> 2 <i>b</i>			
2 α ,3 α -(Oxoethano)-A-nor-5 α -cholestane (41)	4 <i>c</i> 2' <i>b</i> ,5 <i>t</i> 3',2',4'	-1.25	d
2 β ,3 β -(Oxoethano)-A-nor-5 α -cholestane (42)	4 <i>c</i> 2 <i>b</i> ,5 <i>t</i> 3,2,4	+0.94	d
Keto-ester (43) derived from β -bourbonene	4 <i>c</i> 2 <i>b</i>	+2.5 (M)	e

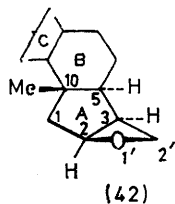
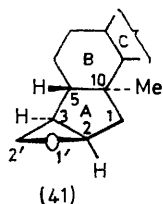
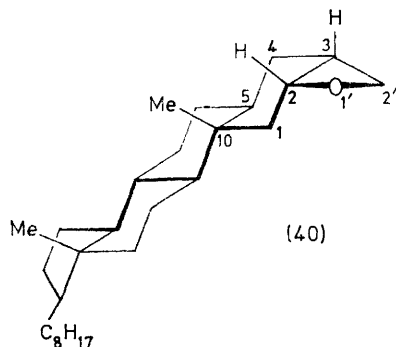
* M = methanol, D = dioxan, H = hexane. † See footnote references (see also Table 1, †).

^a G. Quinkert, G. Cimbollek, and G. Buhr, *Tetrahedron Letters*, 1966, 4573. ^b A. Hassner and V. R. Fletcher, *Tetrahedron Letters*, 1970, 5053. We thank Dr. Fletcher for information about solvents used. ^c G. M. L. Cragg, Pretoria, South Africa [$\Delta\epsilon$ values in dioxan from G. M. L. Cragg, *J. Chem. Soc. (C)*, 1970, 1829]. ^d Y. Tsuda, T. Tanno, A. Ukai, and K. Isobe, *Tetrahedron Letters*, 1971, 2009. ^e J. Křepinský, Z. Samek, F. Šorm, D. Lamparský, P. Ochsner, and Y.-R. Naves, *Tetrahedron*, 1966, Suppl. 8. 53.

zig-zags.² Comparison of the D-nor-13 α -androstan-16-one (39)²⁴ with the geometrically similar compound (38) gives a contribution $\delta\Delta\epsilon$ of +1.7 for the 13 α -methyl



(38) R¹ = H, R² = Me
(39) R¹ = Me, R² = H



group (' α' -quasi-axial) in the former compound. This value is close to that found for ' α' -axial methyl groups

in 1-decalones or hexahydroindan-1-ones, and appears to be characteristic of the steric relationship of the methyl group to the chromophore, irrespective of ring size. We therefore adopt $\delta\Delta\epsilon$ values of 1.1 and 1.7 (each consignate) for the parent 4*c*2*eq* ring system and the ' α' -quasi-axial methyl group, respectively.

*Class 4*t**. The one compound for which $\Delta\epsilon$ is available, a D-norandrostan-16-one (35),²⁴ gives a consignate contribution of 2.5 units for the ring system when allowance ($\delta\Delta\epsilon$ -1.7) is made for the 13 β -methyl group. The 13,12- and 12,11-bonds form a primary zig-zag, so the enhanced effect of the second ring compared with class 4*c*2*eq* is reasonable.

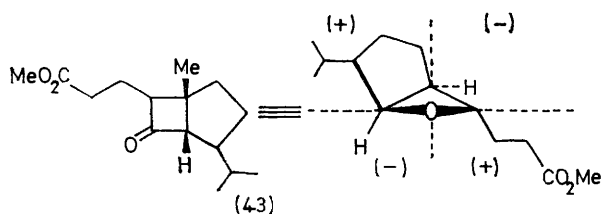
*Class 4*c*2*ax**. The only representative (40) has a series of bonds from C-15 to C-2 which form an extended primary zig-zag, although its orientation with respect to the carbonyl group differs from that recognised in decalone analogues. The large negative value of $\Delta\epsilon$ (-3.6) is to be expected, and is of the size associated with comparable polycyclic ketones of the 6*c*2*ax* class.

cis-Bicyclo[3.2.0]heptan-6-ones.—Class 4*c*2*b*. Two compounds (41) and (42) of quasi-enantiomeric type give $\Delta\epsilon$ values averaging 1.1 unit (consignate), identical with that associated with compounds of class 4*c*2*eq* (above). The bicyclic compound (43) shows an enhanced $\Delta\epsilon$ value (+2.5) as a result of the additional (α') alkyl substituent in a positive octant

The only C-C bond likely to make a significant contribution to the observed dichroism, either in 4*c*2*eq* or in 4*c*2*b* compounds, is the bond representing an ' α' -substituent on the cyclobutanone ring. The similarity of $\delta\Delta\epsilon$ values for these bicyclic structures probably implies that the ' α' C-C bond is not far from bisectonal in

²⁴ G. Quinkert, G. Cimbollek, and G. Buhr, *Tetrahedron Letters*, 1966, 4573.

character for both series. It seems reasonable to ascribe the $\delta\Delta\epsilon$ value of 1.1 unit almost wholly to the ' α ' C-C bond, for this value lies between those normally



associated with ' α '-axial (1.7—1.9) and ' α '-equatorial character (0.2 in decalones),² consistent with the intermediate orientation of the ' α ' C-C bond on the cyclopentanone (see further discussion on p. 775).

DISCUSSION

In our empirical analysis of c.d. data for decalones, the symmetry of the chair-form cyclohexanone ring itself with respect to the carbonyl group justified the empirical assignment of the observed Cotton effect to the contributions only of attached rings and alkyl substituents. Bicyclo[4.2.0]octan-7-ones also have local (C_s) symmetry within the cyclobutanone ring, so that only the substitution pattern of the cyclobutanone is important. Consideration of hexahydroindanones, however, is complicated by the chirality of the first (cyclopentanone) ring

The alternative possibility of assuming a fixed contribution for the skewed cyclopentanone, perhaps taken from data for monocyclic derivatives,²⁵ was clearly unjustifiable because of the known sensitivity of cyclopentanone conformation to substitution patterns.²⁵ No single value of $\delta\Delta\epsilon$ for a cyclopentanone ring should be generally applicable throughout the series of hexahydroindanones.

In order to 'calculate' second-ring contributions by summation of increments due to individual C-C bonds, it was first necessary to have reasonably reliable values of $\delta\Delta\epsilon$ for methyl substituents at the ' α '- and ' β '-positions of the cyclopentanone ring. Comparisons of group contributions derived for the five classes of hexahydroindanones (Table 8) revealed certain regularities, but also some apparent anomalies. A ' β '-axial methyl group, for example, has a dissignate effect of 0.5—0.6 unit in classes 5*t*2 and 5*c*3, but zero (or possibly weakly consignate) effect in class 5*t*3 (see p. 774). Another important substituent, a ' β '-equatorial methyl group, had been allotted a consignate effect of 0.6—0.8 unit in class 5*c*2*eq*, but its effect was negligible in class 5*c*3. Dreiding models suggested that the variations might be associated with differing conformations of the cyclopentanone ring, depending in particular upon the view of the ring obtained by looking down the O \rightarrow C axis of the carbonyl group.

TABLE 8
Structural-group increments ($\delta\Delta\epsilon$)^a for extended hexahydroindanone derivatives

Hexahydroindanone class	Cyclopentanone conformation class	Parent bicyclic structure $\delta\Delta\epsilon$	Third ring (rear) octant) ^b $\delta\Delta\epsilon$	Third ring (front) octant) ^b $\delta\Delta\epsilon$	Methyl substituents at ring junction positions			
					' α '-ax $\delta\Delta\epsilon$	' α '-eq $\delta\Delta\epsilon$	' β '-ax $\delta\Delta\epsilon$	' β '-eq $\delta\Delta\epsilon$
5 <i>t</i> 2	Folded	4.1 (con.)	1.2 (con.)	0.3 (f.o. dis.) ^c	1.9 (con.)		0.6 (dis)	
5 <i>t</i> 3	Twisted	5.5 (con.)	0.0				0.0 ^d	
5 <i>c</i> 2 <i>eq</i>	Folded	2.4 (con.)	0.0	0.7 (f.o. con.)	1.9 (con.)			0.8 (con.)
5 <i>c</i> 2 <i>ax</i> ^e	Folded	1.8 ^e (con.)	0.0 ^e	0.4 ^e (f.o. con.)		0.5 ^e (con.)	0.6 ^e (dis.)	
5 <i>c</i> 3	Twisted	3.4 (con.)	0.0				0.5 (dis.) ^f	ca. 0

^a $\delta\Delta\epsilon$ Values for methanol as solvent, or the best values available where solvent effects are small or uncertain: con. = consignate, dis. = dissignate, f.o. = front octant (see ref. 3). ^b See formula in Table 2, also Figures 4 and 5. ^c Apparently weakly consignate in solvents of low polarity—see Table 2. ^d Possibly a consignate effect of 0.5 unit when two ' α '-axial methyl groups are present (p. 770). ^e Tentative values from inadequate data for class 5*c*2*ax* (p. 769). ^f Possibly an apparent consignate effect when both ' β '-axial and ' β '-equatorial methyl groups are present (p. 770).

itself (Figure 2). Hexahydroindanone Cotton effects derived in the foregoing analysis therefore represent the sum of contributions from the first and the second rings. To divide the total value of $\Delta\epsilon$ into its separate parts due to individual rings requires some simplifying assumptions. The most hopeful possibility seemed to be to estimate the contribution associated with the 'second' ring, as was done previously for decalones,² by adding together the $\delta\Delta\epsilon$ values associated with those C-C bonds in the second ring which are expected to contribute significantly, according to the criteria established earlier. The residual part of the total dichroism could then be ascribed to the chiral cyclopentanone ring itself.

²⁵ C. Ouannès and J. Jacques, *Bull. Soc. chim. France*, 1965, 3601, 3611; C. Djerassi, R. Records, C. Ouannès, and J. Jacques, *ibid.*, 1966, 2378; R. E. Geiger and G. H. Wagnière, *Helv. Chim. Acta*, 1975, 58, 738.

Much has been written about the conformational features of cyclopentane rings, and different designations of 'pseudorotation phase,' or equivalent geometrical properties, have been used.^{15,25-27} The recent general treatment of ring-puckering co-ordinates by Cremer and Pople²⁷ allows exact descriptions of ring conformations, but is more elaborate than the present data would justify. We have adopted a very simple treatment, adequate for present purposes, which defines the conformation of a chiral cyclopentanone ring in terms of two independent parameters which are easily obtained by use

²⁶ K. S. Pitzer and W. E. Donath, *J. Amer. Chem. Soc.*, 1959, 81, 3213; J. B. Hendrickson, *ibid.*, 1961, 83, 4537; 1963, 85, 4059; E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis,' Wiley, New York, 1965, p. 200.

²⁷ D. Cremer and J. A. Pople, *J. Amer. Chem. Soc.*, 1975, 97, 1354 and 1358.

of Dreiding models. These are the torsional angles θ_1 and θ_5 observed by looking towards C-2 along the C(1)-C(2) bond, and towards C-5 along the C(1)-C(5) bond, respectively (Figure 6). A 'twisted' ring is one for which θ_1 and θ_5 have the same sign. The sum of θ_1 and θ_5 provides a convenient measure of the chirality of the ring. A 'folded' ring is one for which θ_1 and θ_5 have different signs, their algebraic sum giving a measure of the chirality of the ring. The intermediate 'envelope' conformation (p. 765), in which four carbon atoms are coplanar, is characterised by having a zero value for either θ_1 or θ_5 . The conformation of any particular cyclopentanone ring is designated from the point of view of the oxo-group, taken as C-1. A 16-oxo-steroid, for example, has a 'twisted' conformation when viewed along the O \rightarrow C axis; C-13 and C-14 lie on opposite sides of the plane defined by C-15, C-16, C-17, and the oxygen atom, with torsional angles about the C(15)-C(16) and C(16)-C(17) bonds roughly equal (*cf.* Figure 3b, class 5f3). A 17-oxo-steroid, in contrast, is described as having a 'folded' conformation with respect to the oxo-group because both C-14 and C-15 lie on the same side of the plane defined by C-13, C-16, C-17, and the

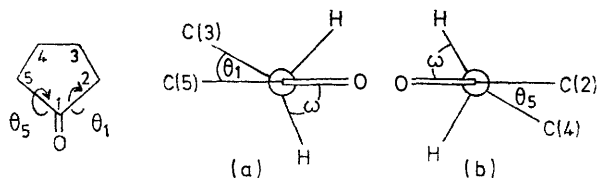


FIGURE 6 Newman projections showing torsion angles in the cyclopentanone ring: (a) θ_1 along C(1)-C(2) bond; (b) θ_5 along C(1)-C(5) bond; angle ω is the torsion angle for an ' α '-substituent with reference to carbonyl oxygen

oxygen atom (*cf.* Figure 3a, class 5f2). The present convention simplifies the discussion which follows.

Dreiding models suggested that the cyclopentanone ring in each of the three hexahydroindan-1-one types has a 'folded' (or possibly an 'envelope') conformation. This conclusion is consistent with X-ray data reported^{15,17} for 17-oxo-steroids, and also with data for any *cis*-hexahydroindan-1-ones having torsional angles close to those given by Allinger²⁸ for ring D of a 14 β -steroid. In contrast, a *trans*-hexahydroindan-2-one (5f3) has a 'twisted' conformation of the cyclopentanone ring^{15,17} and the same appears to be true of the *cis*-isomer (5c3) (*e.g.* a 16-oxo-14 β -steroid, based upon ring D geometry like that suggested for 14 β -steroids by Allinger²⁸).

The immediate importance of this conformational distinction lies in the differing spatial relationships of ' β ' substituents, in particular, to the carbonyl bond. A 'twisted' conformation causes a ' β '-equatorial bond to intersect the 'horizontal' nodal plane defined by the carbonyl group (Figure 7a), and the ' β '-equatorial bond contribution appears to be negligible, as is found in class 5c3. A 'folded' conformation puts the ' β '-equatorial bond at the ring junction clearly into one of the rear octants (Figure 7b), where its orientation in relation to

the carbonyl group resembles that of a ' β '-equatorial bond in a cyclohexanone, which is a part of a 'primary zig-zag'. A consignate effect is therefore found, as expected, and may be enhanced by further bonds

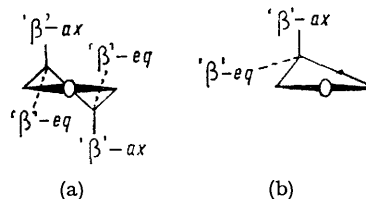


FIGURE 7 The different spatial characteristics of ' β '-*eq* and ' β '-*ax* substituents in cyclopentanones, depending on ring conformation; (a) twisted; (b) folded

approximating in geometry to those of a 'primary zig-zag'.

The apparently differing behaviour of ' β '-axial substituents is not so clearly related to conformational type but this is not surprising in view of the dichotomy of ' β '-axial methyl group behaviour in the decalone series.^{2,29} Estimates of effects of ' β '-axial C-C bonds are therefore subject to some uncertainty. A dissignate contribution of 0.6 unit is adopted for ' β '-axial C-C bonds in the 'folded' conformation (Figure 7b). When the cyclopentanone ring is in a 'twisted' conformation the situation is more complicated. A $\delta\Delta\epsilon$ value of 0.6 (dissignate) has been estimated in class 5c3, and values of 0.0 or 0.5 (consignate) for class 5f3 (Figure 7a), where the latter value is observed only if two ' β '-axial methyl groups are present. In attempting to explain this dichotomy, we note that *trans*-hexahydroindan-2-one (5f3) has C_2 symmetry when it possesses either no ' β '-axial substituents or two ' β '-axial methyl groups. The cyclopentanone ring should then have the perfect 'twisted' conformation, and make its maximum c.d. contribution (p. 773). One ' β '-axial methyl substituent, in contrast, destroys the C_2 symmetry, and creates unequal torsional strains about the two C_α - C_β bonds, so that some deviation from the symmetrically twisted conformation should result. The c.d. contribution of the cyclopentanone ring itself should then be slightly smaller (p. 776). We suggest that this reduction in value of $\Delta\epsilon$ compensates almost exactly for a small consignate effect of the single ' β '-axial methyl substituent. The consignate effect of the methyl group itself may be associated with its location as a substituent on an extended zig-zag chain of bonds, a feature similar to one which was noted but not explained in our analysis of ' β '-axial methyl group effects in extended decalones.²

A different argument was adopted to derive reasonable $\delta\Delta\epsilon$ values for methyl substituents at the ' α ' carbon atom. Contributions of ' α '-axial (or quasi-axial) methyl groups to $\Delta\epsilon$ in decalones,² hexahydroindanones, and bicyclo[4.2.0]octan-7-ones all lie in the region 1.7-1.9 units (in methanol). Furthermore a 'bis-sectional' ' α '-C- CH_2 bond in a fused cyclobutanone

²⁸ N. L. Allinger and F. Wu, *Tetrahedron*, 1971, **27**, 5093.

²⁹ H. J. C. Jacobs and E. Havinga, *Tetrahedron*, 1972, **28**, 135

system contributes *ca.* 1.1 unit (p. 772) whereas an ' α '-equatorial C-C bond in a cyclohexanone is known to contribute *ca.* 0.2 unit.²

The orientation of any ' α '-C-C bond (whether C-CH₂ or C-Me) with respect to the carbonyl group is conveniently expressed in terms of the C-C _{α} -C=O torsion angle (ω) seen when the structure is viewed down the carbonyl-C _{α} bond (Figure 6). Values of ω vary from *ca.* 10–15° for equatorial 2-methylcyclohexanone to *ca.* 110–115° for axial 2-methylcyclohexanone. Dreiding models in conformations suggested by X-ray data^{15,17} indicate that ω is close to 90° for compounds of classes 5*t*2 (*e.g.* a 17-oxo-steroid) and 5*c*2*eq*; a value in the range 50–55° seems reasonable for bicyclo[4.2.0]octan-7-ones.

at that position. This value of $\delta\Delta\epsilon$ has been used above (p. 769 and Table 4).

Hexahydroindanones of classes 5*t*2 and 5*c*2*eq* include an ' α '-quasi-equatorial C-CH₂ bond in their second ring [Figure 8, C(7)-C(8) bonds].² Dreiding models suggest that ω takes values of *ca.* 25 and 30°, giving $\delta\Delta\epsilon$ *ca.* 0.4 and 0.5, respectively, for the bonds in question. These values are rough estimates, but probable errors come within the range considered acceptable, in view of the variations within the data being analysed.

The foregoing arguments provide estimates of numerical contributions $\delta\Delta\epsilon$ for all 'second ring' bonds originating at the ' α '- and ' β '-positions of hexahydroindanones. Only one other type of second ring C-C bond

TABLE 9
Estimates of c.d. contributions of individual rings in hexahydroindanones^a

Bicyclic class	Total $\Delta\epsilon$ (bicyclic)	'Second' (cyclohexane) ring	
		Contributing bonds ^b and $\delta\Delta\epsilon$ values	$\Delta\epsilon$ (total) for second ring
5 <i>t</i> 2	+4.1	' α '- <i>eq</i> , +0.4; ' β '- <i>eq</i> , +0.5	+0.9
5 <i>c</i> 2 <i>eq</i>	+2.4	' α '- <i>eq</i> , +0.5; ' β '- <i>ax</i> , -0.6	-0.1
5 <i>c</i> 2 <i>ax</i>	-1.8	' α '- <i>ax</i> , -1.9; ' β '- <i>eq</i> , +0.8; 2nd bond of 'primary zig-zag', -0.8 ^c	-1.9
5 <i>t</i> 3	+5.5	None	0.0
5 <i>c</i> 3	+3.4	' β '- <i>eq</i> , 0.0; ' β '- <i>ax</i> , -0.5	-0.5
			Cyclopentanone ring Estimated value of $\delta\Delta\epsilon$
			+3.2
			+2.5
			+0.1
			+5.5
			+3.9

^a See footnote *a* in Table 8; data refer to the enantiomers in Figure 3 (a) and (b). ^b For 5*t*2 and 5*c*2 classes see Figure 8 (thickened bonds): ' α ' bonds are C(7)-C(8); ' β ' bonds are C(4)-C(9). The second bond of a primary zig-zag in class 5*c*2*ax* is C(6)-C(7) (hexahydroindanone numbering). ^c See text, this page.

The estimated magnitudes of $\delta\Delta\epsilon$ for ' α '-methyl substituents vary with ω in a manner which agrees fairly well with the empirical equation (i). The sign of $\delta\Delta\epsilon$

$$\delta\Delta\epsilon = 1.9 \sin^2\omega \quad (i)$$

follows the Octant Rule (rear-octant consignate).

Equation (i) provided better agreement with the available data than a similar expression using $\sin \omega$ instead of its square. Some slight support for the use of equation (i) came from a comparison with the Karplus equation, which relates the spin-spin coupling between vicinal protons (H-C-C-H) to the torsion angle.³⁰ The Karplus equation is dominated by a term containing the square of the cosine of the angle in question, but the equations become strictly comparable if we consider the c.d. of the ' α '-substituted ketone to reach its maximum when the ' α '-alkyl group eclipses the *p* orbital at the carbonyl atom, *i.e.* when $\omega = 90^\circ$.

Equation (i) permits estimates to be made of the contributions of Me-C _{α} (or CH₂-C _{α}) bonds at various torsion angles to carbonyl. The assumption that C-Me and C-CH₂ bonds can be treated as almost equivalent was found satisfactory in dealing with decalones, and has now been extended to bonds of the second (*i.e.* six-membered) ring of hexahydroindanones, where strain effects² are unlikely to be excessive.

Measurements on a Dreiding model of a hexahydroindanone of class 5*c*2*ax* indicate that the torsion angle between the C=O bond and the ' α '-quasi-equatorial bond at the ring junction is about 30°, whence application of equation (i) gives $\delta\Delta\epsilon \approx 0.5$ for a methyl substituent

lies on a primary zig-zag, and would be expected to contribute significantly. This is the C(6)-C(7) bond in class 5*c*2*ax* (Figure 8c) (*cf.*² the corresponding bond in decalones of class 6*c*2*ax*). A contribution of 0.8 unit is tentatively assigned. This value is greater than the corresponding

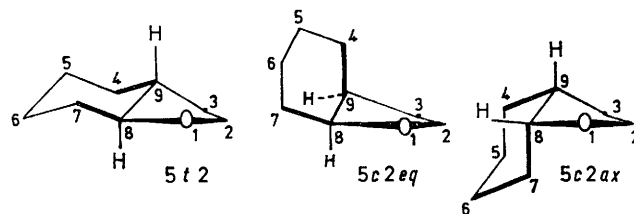


FIGURE 8 Hexahydroindan-1-ones, showing significant bonds of the 'second' ring (thickened lines)

value of 0.7 unit in a *cis*-1-decalone by the same ratio as that of values allotted to the 'first' bonds of zig-zags in these two systems (1.9:1.7; *cf.* p. 767).

Summations of $\delta\Delta\epsilon$ values for appropriate individual bonds of the second rings in each of the hexahydroindanone types are indicated in Table 9. The final two columns of Table 9 present the estimated contributions of the second (cyclohexane) ring, and the residual part of the total value of $\Delta\epsilon$, which is assigned to the chiral cyclopentanone ring.

In view of the multiplicity of approximations and assumptions used in its derivation, the estimate of $\delta\Delta\epsilon$ for the cyclopentanone ring in class 5*c*2*ax* cannot be

³⁰ N. S. Bhacca and D. H. Williams, 'Applications of NMR Spectroscopy in Organic Chemistry,' Holden-Day, San Francisco, 1964, p. 49.

considered as reliable, but the other values listed seem likely to have at least semiquantitative significance. The larger values are found for the cyclopentanones of classes 5 β 3 and 5 c 3, which are classified as 'twisted'; their conformations approximate to C_2 symmetry, and the chiroptical contributions of the 'rear' parts of the rings reinforce one another (θ_1 and θ_5 have the same signs). If the vanishingly small value of $\delta\Delta\epsilon$ estimated for the cyclopentanone ring in compounds of class 5 c 2 ax has any

Substituents at Other Positions in the Cyclopentanone Ring. Alkyl Groups.—Discussion so far has been concerned only with those hexahydroindanones which have no substituents in the cyclopentanone ring other than at ring-junction (' α ' and ' β ') positions. Data are also available for a few hexahydroindan-1-one analogues with alkyl substituents at C-2 and C-3 (the α' - and β' -positions), and for some hexahydroindan-2-ones with C-1 and C-3 (α - and α' -) substituents (Table 10).

TABLE 10

C.d. data for hexahydroindanone analogues: effects of alkyl substituents at ' α '- and ' β '-positions not at the ring junction

Entry no.	Compound	Ring code	ω (°) *	$\Delta\epsilon$ (total) †				Ref. ¶
				$\Delta\epsilon$ (total) †		$\delta\Delta\epsilon$ (substituent effect)		
				Obs.	Calc. ‡§	Obs.	Calc. §	
' α '-Substituents								
1	16 α -Methyl-5 α -androstan-17-one (44)	5 t 2,4,4	-45	+2.5 (D)	+2.5 (D)	-0.65	-0.7	
2	3 β -Hydroxy-16 β -methyl-5 α -androstan-17-one (45)	5 t 2,4,4	+75	+3.8 (M)	+4.9 (M)	+0.55	+1.5	<i>a</i>
3	17 β -Acetoxy-3 α -methyl-A-nor-5 α -androstan-2-one (46)	5 t 3,11,4	+50	+5.45 (M)	+6.4	-0.05	+0.9	<i>b</i>
4	3 β -Methyl analogue (47) of (46)		-70	+4.7 (M)	+4.1	-0.8	-1.4	<i>b</i>
5	1 β -Methyl analogue (48) of (46)		+50	+6.4 (M)	+6.4	+0.95	+0.9	<i>b</i>
6	1 β ,3 β -Dimethyl analogue (49) of (46)		+50, -70	+5.3 (M)	+5.0	-0.2	-0.5	<i>b</i>
7	1 β ,3 α -Dimethyl analogue (50) of (46)		+50, +50	+5.5 (M)	+7.3	0.0	+1.8	<i>b</i>
8	3,3-Dimethyl-A-nor-5 α -cholestan-2-one (51)		+50, -70	+5.5 (M)	+5.0	0.0	-0.5	<i>c</i>
9	3,3-Dimethyl-2-oxo-A-nor-diterpene analogue (51)	+50, -70	+4.2 (M)	+5.0	-1.2	-0.5	<i>d</i>	
10	1 α ,3,3-Trimethyl-2-oxo-analogue (52) of (51)	5 t 3,11,4	-70, +50, -70	+3.4 (M)	+3.5	-2.1	-2.0	<i>d</i>
11	1 β ,3,3-Trimethyl-2-oxo-analogue (53) of (51)	+50, +50, -70	+5.6 (M)	+5.9	+0.1	+0.4	<i>d</i>	
12	17 β -Methyl-5 α -androstan-16-one (54)	5 t 3',11',4'	-50	-5.55 (M)	-6.4	-0.15	-0.9	<i>b</i>
' β '-Substituents								
13	17 β -Methyl-5 α ,14 α -androstan-15-one (55)	5 t 2,4,4		+3.2 (M)		+0.15		<i>e</i>
14	17 β -Ethyl analogue (56) of (55)		+3.9 (M)		+0.85		<i>e</i>	
15	17 β -Isopropyl analogue (57) of (55)		+3.6 (M)		+0.55		<i>e</i>	
16	17 β -C ₈ H ₁₅ -analogue (58) of (55)	5 c 2' eq ,4',4'		+3.7 (M)		+0.65		<i>e</i>
17	17 β -Methyl-5 α ,14 β -androstan-15-one (59)		-3.0 (M)		-0.4		<i>e</i>	
18	17 β -Ethyl analogue (60) of (59)		-3.0 (M)		-0.4		<i>e</i>	
19	17 β -Isopropyl analogue (61) of (59)		-2.4 (M)		+0.2		<i>e</i>	
20	17 α -Methyl analogue (62) of (59)			-2.6 (M)		0.0		<i>e</i>

* Torsion angle between the C=O and C α -Me bonds (this page). † Solvent in parentheses: D = dioxan, M = methanol. ‡ Calculated values include $\Delta\epsilon$ for parent compound (from data in Tables 2 and 8) and 'calculated' substituent contribution (this Table). § Values calculated from $\delta\Delta\epsilon = 1.9 \sin^2\omega$ for substituents on quaternary carbon, or from $\delta\Delta\epsilon = 1.6 \sin^2\omega$ for substituents on tertiary carbon: signs according to the octant rule (rear-octant consignate); values for di- or tri-methyl derivatives are the algebraic sum of $\delta\Delta\epsilon$ values for individual methyl groups. ¶ See footnote references (see also Table 1, †).

^a P. de Ruggieri, Ormonoterapia Richter, Milan. ^b Ref. 7. ^c Sir Ewart Jones, Oxford. ^d P. Grant, Otago, New Zealand. ^e Ref. 31.

significance, it would appear to imply a 'folded' conformation with a very low degree of chirality (θ_1 and θ_5 similar in magnitude but of opposite sign). A Dreiding model shows that this is a possibility, but its validity cannot yet be tested.

The present conclusions concerning magnitudes of $\delta\Delta\epsilon$ for various hexahydroindanones confirm and refine earlier results⁵ which were used in an analysis of c.d. data for monocyclic cyclopentanones by Ouannès and Jacques.²⁵ The application of our own results to monocyclic compounds will be discussed in a separate paper.

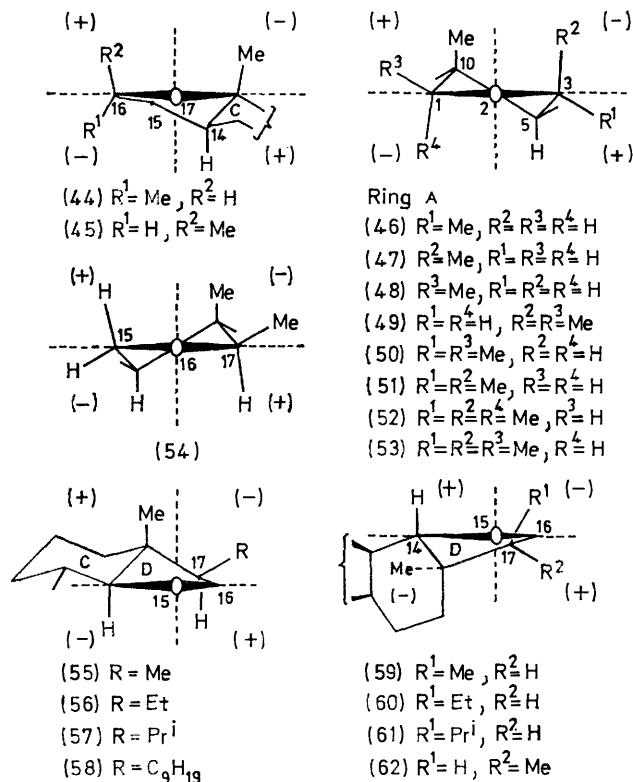
As a test of earlier conclusions, expected increments due to methyl substituents at the α - and α' -positions were calculated by use of equation (i) for methyl substitution at a quaternary carbon atom. For substitution at a tertiary carbon atom, equation (i) was modified to (ii). The adoption of the coefficient 1.6 for equation

$$\delta\Delta\epsilon = 1.6 \sin^2\omega \quad (\text{ii})$$

(ii), instead of 1.9 as in equation (i), was based upon the finding in our study of decalones that an ' α '-axial methyl substituent at tertiary carbon exerts a smaller

effect than one at quaternary carbon (see Table 3 in ref. 2). The average difference is about 0.3 unit, with slight variations according to solvent.

The angles ω required in the present work were estimated to the nearest 5° by use of Dreiding models, for those conformations thought to be the most probable in the absence of the alkyl substituents. The calculated increments $\delta\Delta\epsilon$ therefore represent expected contributions due to the substituents alone, and do not take into account any conformational changes of the cyclopentanone ring enforced by the presence of substituents. The effects of such conformational changes have been discussed previously for monocyclic compounds,²⁵ and for some of the methylated steroidal ketones listed in Table



10,⁷ but without the benefit of quantitative estimates of the direct effects of methyl substituents themselves.

'Calculated' $\Delta\epsilon$ values for hexahydroindanonones with α - or α' -substituents are listed in the first part of Table 10 (entries 1—12). Five of these show excellent agreement with observed values (deviations ≤ 0.3 unit), whereas moderate deviations (0.5—0.8 unit) occur in three cases (entries 4, 8, and 9).

Of the remaining four compounds, the 16β -methyl-17-ketone (entry 2; data converted from o.r.d.) may be somewhat distorted by 16β -Me, 13β -Me interaction. The other three compounds (entries 3, 7, and 12, all of class 5/3) have a common feature, a quasi-equatorial (3α - or 17β -) methyl substituent, on that side of the cyclopentanone ring which is remote from the 'third' ring, and is therefore not subject to steric interference by the 'third'

ring. All three compounds exhibit Cotton effects of lesser numerical magnitude than those calculated. Dreiding models suggest a possible explanation, if the assumption is accepted that steric and torsional effects will normally distort the cyclopentanone ring so that the methyl substituent tends to move 'outwards' (*i.e.* to become more nearly equatorial).²⁵ For the compounds in question, a model shows that the postulated distortion has two possibly significant features: (a) the change in geometry of the cyclopentanone ring bonds is in the sense which reduces the distortion of the adjoining cyclohexane ring enforced by fusion to the cyclopentanone, so gaining a little energetic assistance; (b) the cyclopentanone ring changes from a perfect or near-perfect 'twisted' conformation towards an 'envelope', so that a smaller Cotton effect would be predicted (p. 776).

Analogous conformational changes seem less probable in response to the other α - or α' -substituents listed. In the 2-oxo-A-nor-series (entries 3—11 inclusive), 'outward' movement of either a 1α - or a 3β -methyl group towards an equatorial conformation would be resisted by the still greater puckering which such a change would force upon ring B; 'outward' movement of a 1β -methyl group would be prevented by a different factor, *viz.* compression with C-11. Only the 3α -methyl-2-ketones (and the quasi-enantiomeric 17β -methyl-16-ketone) should therefore exhibit appreciable effects due to conformational distortion, consistent with the data listed.

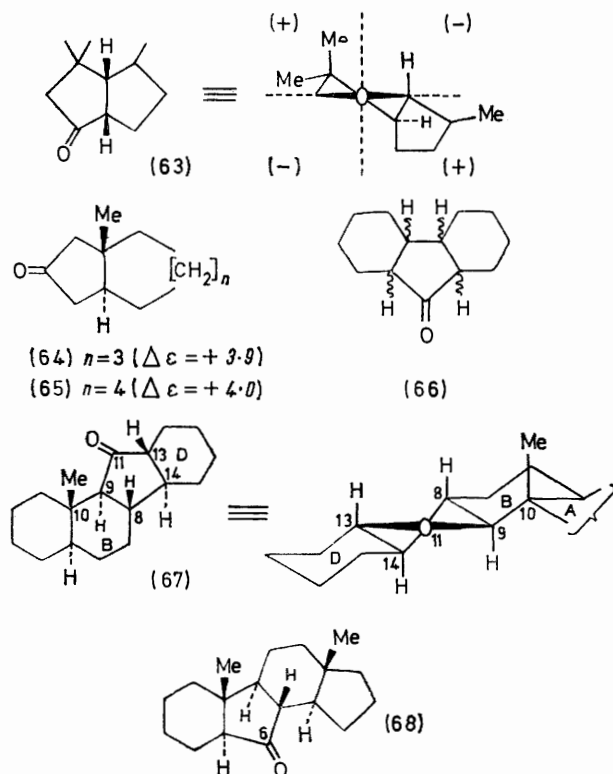
β' -Substituents at tertiary carbon can occur only in hexahydroindan-1-ones. The best compounds for comment are Djerassi's 17-substituted 14α - and 14β -androstan-15-ones (Table 10).³¹ The β' -carbon atom (C-17) is never far from the 'horizontal' nodal plane of the carbonyl group, assuming the 'folded' conformation discussed above. Models of both series of 17-substituted 15-ketones show that the 17β -alkyl substituents are fairly close to the nodal plane, but tend to project into a 'negative' octant. Nevertheless the rather small increments in $\Delta\epsilon$ when 17β -substituents are present are always positive in the 14α -series (55)—(58), and negligible or only weakly negative in the 14β -compounds (59)—(61). The absence of a direct consignate effect matches the behaviour of ' β' '-substituents at ring junction positions (dissignate or negligible effects). Dreiding models suggest that some relief of torsional strain between the 13β -methyl and 17β -alkyl groups is possible by conformational distortion of ring D,²⁸ the required sense of rotation of the 17β -substituent bond being 'forward' in the 14β - or 'backward' in the 14α -series. Each change tends to alter the ring conformation away from its relatively unstrained 'folded' form, in the direction tending towards a 'twisted' conformation. The corresponding c.d. change would be a slight enhancement of the magnitude of the Cotton effect, whether initially positive or negative. A very weakly dissignate (positive) contribution of the substituent itself, superimposed upon the small conformational contribution, would match the

³¹ A. R. Van Horn and C. Djerassi, *J. Amer. Chem. Soc.*, 1967, **89**, 651.

effects listed in Table 10. Zero effect of the one 17 α -methyl substituent listed (62) suggests that any weak torsional effects and direct dissignate effects exactly compensate each other.

Attempts at quantitative prediction of increments in $\Delta\epsilon$ due to alkyl substituents not at the ring junction can hardly be accurate, but the examples discussed above indicate the magnitudes and possible interplay of the separate indirect (conformational) and direct contributions of substituents.

Related Topics.—Monocyclic cyclopentanone derivatives will be discussed elsewhere.



A few bicyclic cyclopentanone derivatives other than hexahydroindanones have been described. Ketones [e.g. (63), $\Delta\epsilon +3.5$] of the *cis*-bicyclo[3,3,0]octan-2-one series, derived from the pipitzols,³² give $\Delta\epsilon$ values suggesting that the cyclopentanone ring is in a 'twisted' conformation; molecular models are too flexible to allow quantitative discussion. Bicyclic compounds with a seven- or eight-membered 'second' ring [(64) and (65), respectively] show reduced $\Delta\epsilon$ values, compared with the corresponding hexahydroindanone, suggesting that the cyclopentanone ring is less twisted when a large

³² F. Walls, J. Padilla, P. Joseph-Nathan, F. Giral, M. Escobar, and J. Romo, *Tetrahedron*, 1966, **22**, 2387.

³³ C. Djerassi and J. E. Gurst, *J. Amer. Chem. Soc.*, 1964, **86**, 1755.

³⁴ O. Wintersteiner and M. Moore, *Tetrahedron*, 1964, **20**, 1947; 1965, **21**, 779; *J. Org. Chem.*, 1964, **29**, 262.

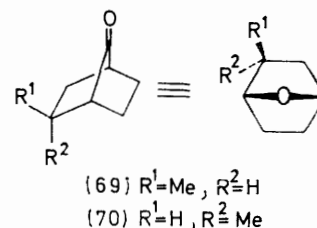
³⁵ T. Masamune, A. Murai, K. Orito, H. Ono, S. Numata, and H. Sugimoto, *Tetrahedron*, 1969, **25**, 4853; S. M. Kupchan and S. D. Levine, *J. Amer. Chem. Soc.*, 1964, **86**, 701; S. M. Kupchan and M. J. Abu El-Haj, *J. Org. Chem.*, 1968, **33**, 647.

second ring can adapt its conformation to minimise strains.³³

Perhydrofluoren-9-ones (66), represented by tetracyclic analogues of several types derived from steroids, show chiroptical properties which are qualitatively but not quantitatively predictable from the results of our hexahydroindanone analysis. The *trans,anti,trans*-perhydrofluoren-9-one system, for example, is represented by some rearranged steroids of the C-nor-D-homo-8 β ,9 α ,13 β ,14 α -11-oxo-type (67)^{34,35} with $\Delta\epsilon ca. -4.2$.³⁶ Dreiding models suggest that the cyclopentanone ring is of the 'twisted' type, and very similar to that found in hexahydroindanones of class 5t3, which have larger values of $\Delta\epsilon$ (*ca.* -5.5) for the cyclopentanone ring. Allowance for the six-membered rings B and D further increases the discrepancy between observed and 'predicted' $\Delta\epsilon$ values, so we conclude that additivity of group contributions is imperfect in these 'middle-ring' ketones, as it is for the analogous perhydrophenanthrene 'middle-ring' ketones.² Chiroptical data for the limited number of other perhydrofluoren-9-one types available support this conclusion, the $\Delta\epsilon$ values 'predicted' by analogy with the nearest classes of hexahydroindanones generally being rather larger than those observed [e.g. a 6-oxo-B-nor-5 α ,8 β ,9 α -steroid (68) (*trans,anti,trans*), $\Delta\epsilon ca. +3.2$;³⁷ a 6-oxo-B-nor-5 β ,8 α ,9 α -steroid (*cis,anti,cis*), $\Delta\epsilon ca. -3$;³⁷ a 6-oxo-B-nor-5 β ,8 β ,9 α -steroid (*cis,anti,trans*), $\Delta\epsilon ca. +1.1$;³⁷ and an 11-oxo-C-nor-D-homo-8 β ,9 α ,13 α ,14 α -steroid (*cis,syn,trans*), $\Delta\epsilon ca. -2.2$].^{34,35}

Two factors which probably contribute to the apparent deviations found in this group of compounds are uncertainty regarding conformation where *cis* ring junctions are involved, and the increase in strain generally attending the fusion of a cyclopentanone ring to two separate cyclohexane rings. Some of the possible effects of strain have been demonstrated in our analysis of data for decalones.²

Most bridged-ring compounds which include a cyclopentanone ring are also subject to strains, including abnormal bond angles, bond lengths, and torsion angles, and in some cases also steric compression. Recent



studies by Lightner³⁸ on 2-methylbicyclo[2.2.1]heptan-7-ones, (69) and (70), provide data for the effects of

³⁶ Unpublished data from this laboratory.

³⁷ J. Fajkoš, J. Joska, and F. Šorm, *Coll. Czech. Chem. Comm.*, 1964, **29**, 652.

³⁸ D. A. Lightner and D. E. Jackman, *J. Amer. Chem. Soc.*, 1974, **96**, 1938; see also D. A. Lightner and D. E. Jackman, *J.C.S. Chem. Comm.*, 1974, 344; D. A. Lightner and T. C. Chang, *J. Amer. Chem. Soc.*, 1974, **96**, 3017.

'front octant' and ' β '-equatorial methyl substituents in an otherwise symmetrical structure. The ' β '-equatorial methyl effect in compound (70) (0.6 unit, consignate) agrees well with our data for a 'folded' cyclopentanone (Table 8). Ketones of the bicyclo[2.2.1]-heptan-2-one series (*e.g.* camphor),³⁹ and bicyclo[3.2.1]-

octan-6-ones,⁴⁰ do not fit into the patterns established in this paper.

EXPERIMENTAL

C.d. measurements were made as previously.²

We thank Mrs. W. P. Mose and Mrs. B. M. Tracey for the measurements, numerous colleagues for samples (see footnotes to Tables) and the S.R.C. for a research grant (to W.K.).

[5/1322 Received, 4th July, 1975]

³⁹ D. E. Bays, G. W. Cannon, and R. C. Cookson, *J. Chem. Soc. (B)*, 1966, 885.

⁴⁰ Ref. 6, pp. 185—190, 240.