Chiroptical Studies. Part 92[1] The Circular Dichroism of Strained, Bridged-ring, and Other Ketones

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The systematic empirical re-evaluation of c.d. data ($n \longrightarrow \pi^*$) for ketones. which in earlier papers has covered extended decalones. hexahydroindanones. and cyclopentanone derivatives. is now continued to include bridged-ring ketones and miscellaneous ketones with strained or conformationally mobile structures. Carbon–carbon bonds which are particularly strained by the molecular structure generally make c.d. contributions which are larger in the consignate ('octant') sense than those of similarly placed unstrained bonds. Data for a wide variety of ketones ranging from essentially unstrained to very highly strained structures have been used to derive an approximate empirical relationship between the strain energy in a bond and the contribution which the bond makes to the total value of $\Delta\varepsilon$.

Approximate values of $\Delta\varepsilon$ for many ketones can be derived from the torsion angles ω_H and ω_C between the carbonyl bond and the C_α–H and C_α–C_β bonds. respectively. by using functions of the form $k \sin^2\omega$. Six bonds need to be included in calculations, all ketones being treated as acetone derivatives. Coefficients k_H and k_C are used for C_α–H and C_α–C_β bonds. respectively. The numerical value of k_C is widely variable. depending upon the amount and distribution of bond strain in the molecule. The complete empirical equation for the total contributions of C_α–H and C_α–C_β bonds to $\Delta\varepsilon$ is (i). Application of this equation. and addition of the estimated contribu-

$$\delta\Delta\varepsilon = \Sigma k_H \sin^2\omega_H + \Sigma k_C \sin^2\omega_C \tag{i}$$

tion of any extended 'primary zig-zag' of C–C bonds. permits the derivation of approximate values of $\Delta\varepsilon$ for rigid ketones of diverse types. including strained bicyclo- and tricyclo-alkanones. Some non-rigid ketones (*e.g.* pregnan-20-ones and cycloheptanone analogues) can also be treated in this way if conformer populations are known.

Recommendations are offered to organic chemists wishing to use the data and methods in this and preceding papers in connection with problems involving chiroptical properties of ketones.

THREE previous papers in this series [2-4] have been concerned with a re-evaluation of chiroptical data ($n \longrightarrow \pi^*$ transition; *ca.* 290 nm) for ketones. The Octant Rule [5] has served organic chemists well as a basis for the interpretation of o.r.d. and c.d. data for ketones, and as an aid to the assignment of structure and conformation to new compounds. Recent developments, however, had shown that although the Octant Rule in its original form [5] is valid for many types of structure, apparent exceptions to 'Octant' behaviour can arise for some patterns of either alkyl [6,7] or heteroatom [8,9] substitution.

With the benefit of accumulated data from these and other laboratories for several hundred ketones, we under-

took a systematic analysis of c.d. data in order to establish, more definitively than in any previous investigation, the main features of the relationships between the molecular structures and the c.d. ($n \longrightarrow \pi^*$) of ketones. Our recent studies have been concerned almost wholly with ketones having saturated hydrocarbon frameworks, to avoid the complications of remote unsaturation or of heteroatoms either in rings or as substituents. Those aspects are being dealt with by Hudec and his co-workers [8,10-12] in particular.

[1] Part 91, J. Hudec and D. N. Kirk, *Tetrahedron*, 1976, **32,** 2475.

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

[3] D. N. Kirk and W. Klyne, *J.C.S. Perkin I*, 1976, 762.

[4] D. N. Kirk, *J.C.S. Perkin I*, 1976, 2171.

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

[6] H. J. C. Jacobs and E. Havinga, *Tetrahedron*, 1972, **28,** 135.

[7] C. Coulombeau and A. Rassat, *Bull. Soc. chim. France,* 1971, 516.

[8] J. Hudec, *Chem. Comm.*, 1970, 2678; M. T. Hughes and J. Hudec, *ibid.*, 1971, 805; G. P. Powell and J. Hudec, *ibid.*, p. 806.

[9] M. M. Cook and C. Djerassi, *J. Amer. Chem. Soc.*, 1973, **95,** 3678.

[10] E. E. Ernstbrunner and J. Hudec, *J. Amer. Chem. Soc.*, 1974, **96,** 7106.

[11] G. P. Powell, R. N. Totty, and J. Hudec, *J.C.S. Perkin I,* 1975, 1015.

[12] J. Hudec, *J.C.S. Perkin I*, 1975, 1020.

Our strategy has been to analyse data for compounds in increasing order of structural and conformational complexity, beginning with the large accumulation of data for *trans*-decalones and their extended analogues,[2] since these, generally with ' all-chair 'conformations, offered the most clearly defined and regular structural and conformational patterns. Conclusions regarding the contributions of component bonds to the total c.d. ($\Delta\varepsilon$), and equally important the identification of parts of structures, defined by bonding patterns, which made *no* significant contribution to $\Delta\varepsilon$, enabled us to bring *cis*-decalones[2] for the first time into a comprehensive treatment of compounds of essentially ' diamond network ' type, based upon a cyclohexanone ring. In the next stage of our study[3] compounds with a hexahydroindan-1-one or -2-one component were analysed. Special consideration was given to the cyclopentanone ring itself because of its inherent chirality in hexahydroindanones.[13] In other respects, however, the conclusions from this study could be correlated with those arising from decalone analogues. A few ketones with a bicyclo[4.2.0]-octan-7-one component of structure, containing a fused cyclobutanone ring, were also fitted into the general pattern.[3]
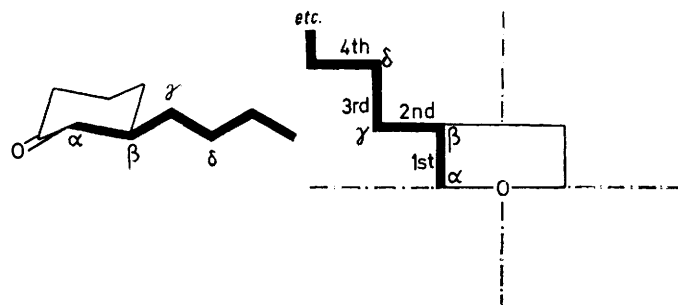
The third paper of this group[4] focused further attention on the chiral cyclopentanone ring itself. Data obtained from hexahydroindanones were used to derive a novel interpretation of the sign and magnitude of $\Delta\varepsilon$ for twisted rings in terms of torsion angles about the C_α–C(:O) bonds, and ' dissignate '[14] contributions from C_α–H bonds. The treatment was extended, with satisfactory results, to a few compounds of decalone type which are thought to have the cyclohexanone component held in a ' twist ' conformation by non-bonded interactions.

We now present the final part of our present analysis, in which we attempt to interpret c.d. characteristics of a wide variety of ' miscellaneous ' ketones, including many with dissymmetric bridged-ring structures, by further application of the ' torsion angle ' concept. We also discuss the very important contribution of bond strain to the c.d. behaviour of ketones.

Summary of Previous Results and Conclusions.—The main findings in our three previous papers are summarised here for reference in the discussion which follows.

(a) *Decalones and extended analogues.*[2] The largest or ' first-order ' contribution, always consignate, comes from what we have termed ' primary zig-zags ' of C–C bonds (Figure 1). The contribution of a normal primary zig-zag can be up to *ca.* ± 3 units of $\Delta\varepsilon$ (1 mol^{-1} cm^{-1}), depending upon its length.

Second-order effects (up to *ca.* ± 1 unit) can arise when a primary zig-zag carries alkyl substituents or equivalent ring fragments. If these are of ' β '-axial or ' γ '-equatorial type their contributions may be dissignate. ' Front octant ' effects[2,5,15-18] may also have to be considered. ' Calculated ' total values of $\Delta\varepsilon$ usually agree with experimental values to within ± 0.2 unit; deviations of >0.5 unit are often associated with bond strain (see below).

(b) *Hexahydroindanones.*[3] The largest contribution to $\Delta\varepsilon$ normally comes from the chiral cyclopentanone component. ' β '-Axial methyl substituents may make second-order contributions which are consignate, zero, or dissignate, according to the particular class of hexahydroindanone. The empirical equation (i) was introduced[3] to express the dependence of ' α '-methyl substituent

FIGURE 1 Primary zig-zag of C–C bonds (heavy lines), and octant projection

effects on the torsion angle (ω) between the C=O and C_α–Me bonds.

$$\delta\Delta\varepsilon = k \sin^2\omega \qquad (i)$$

The value of the coefficient k was estimated as *ca.* 1.9 when C_α is quaternary or *ca.* 1.6 when C_α is tertiary. The equation was used only to calculate the *difference* between the contributions of a C–H bond and a C–Me bond in the same location.

(c) *Chiral cyclopentanones.*[4] The contribution of a chiral cyclopentanone ring to $\Delta\varepsilon$ is given approximately by the sum of $\delta\Delta\varepsilon$ values from two equations of type (ii), one each for the torsion angles (ω) between the two C_α–C_β bonds and the C=O bond.

$$\delta\Delta\varepsilon = \pm 1.9 \sin^2\omega - 5.4 \sin^2\omega \qquad (ii)$$

The positive sign for the first term in equation (ii) is

[13] W. Klyne, *Tetrahedron*, 1961, **13**, 29; *Bull. Soc. chim. France*, 1960, 1396.

[14] W. Klyne and D. N. Kirk, *Tetrahedron Letters*, 1973, 1483.

[15] D. N. Kirk, W. Klyne, and W. P. Mose, *Tetrahedron Letters*, 1972, 1315.

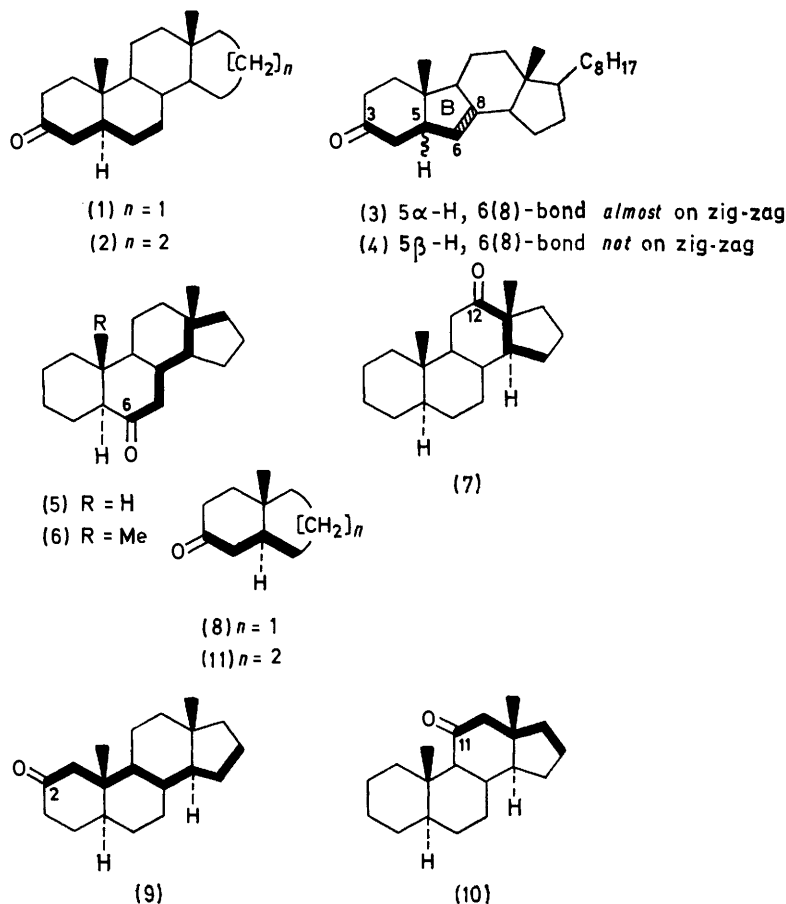[16] D. A. Lightner and D. E. Jackman, *J. Amer. Chem. Soc.*, 1974, **96**, 1938.

[17] 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.

[18] T. D. Bouman and D. A. Lightner, *J. Amer. Chem. Soc.*, 1976, **98**, 3145.

used when ω is negative, and *vice-versa*, to allow for the loss of sign information when sin ω is squared. Unlike equation (i), the empirical equation (ii) gives an estimate of the *absolute* magnitude of the combined contributions of one set of C_α–C_β with its associated pair of C_α–H bonds to the total value of Δε for a chiral cyclopentanone ring. It was proposed [4] that the *separate* absolute contributions

A further feature found to be inseparable from a discussion of many compounds of bridged-ring type (*e.g.* camphor) is the special significance of strained bonds, in c.d. terms. Abnormal Δε values can occur [2] when one or more of the bonds of a primary zig-zag is unusually strained [19] by its environment.

We begin by a further examination of our previous

(1) *n* = 1
(2) *n* = 2

(3) 5α-H, 6(8)-bond *almost* on zig-zag
(4) 5β-H, 6(8)-bond *not* on zig-zag

(5) R = H
(6) R = Me

(7)

(8) *n* = 1
(11) *n* = 2

(9)

(10)

of the C_α–C_β and C_α–H bonds may be estimated from a modified equation (i), where *k* is replaced by $k_C = -1.9$ for the C_α–C_β bond of cyclopentanone, or by $k_H = -6.2$ for each C_α–H bond. These negative values correspond to separate *octant-dissignate* [14] effects of the C_α–C_β and C_α–H bonds, the latter having the larger magnitude.

No theoretical basis was claimed for the foregoing conclusions, which serve solely as an empirical means for ' predicting ' Δε for new ketones.

Present Work

A reassessment of c.d. data for bridged ring ketones was undertaken partly for its intrinsic value to organic chemists who use chiroptical methods as an aid to structure determination or assignment of absolute configurations, and partly to examine further the implications and applicability of equations of types (i) and (ii). Both the dependence of c.d. characteristics on C_α–C(:O) torsion angles (ω), and the concept of octant-dissignate effects of C_α–H bonds, gain support from the present work.

data [2] for those extended decalone derivatives which give anomalous Δε values because of strain associated with the presence of a five-membered ring. The suggestion [2] that strained bonds give more-consignate effects compared with similarly placed unstrained bonds is then developed to explain anomalies which became apparent when attempts were made to calculate Δε values for bridged-ring ketones by use of the torsion angle concept expressed in equations (i) and (ii). The implications of these results are next examined for a variety of other types of ketones, including some (*e.g.* cycloheptanones and acyclic ketones) with non-rigid conformations. Finally it will be shown that an approximate (empirical) numerical relationship exists between the strain in a C–C bond, as expressed by the elevation of its bond energy as compared with normal values, and its effect on the chiroptical properties of a ketone.

Compounds containing Five-membered Rings: Evidence

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

of a Relation between Bond Strain and Enhanced Consignate Effects of C–C *Bonds.*—When a ketone contains a cyclopentane ring which is not linked to the carbonyl group through a periplanar zig-zag of C–C bonds, the effect of ring size on c.d. is generally negligible. A 3-oxo-5α-steroid (1) and its D-homo-analogue (2), for example, gave [2] identical values of Δε, within the limits of experimental error. Abnormal Δε values are found, however, for steroidal ketones in which a five-membered ring contributes one or more of the bonds of a primary zig-zag.[2] Such bonds are strained, and appear to give enhanced consignate contributions. The term 'strain' is used

bonds in question: the magnitude of the strain effect in the 12-oxo-compound is distinctly smaller than this, and strangely appears not to include any notable enhancement of the effect of the ' first ' (13,14-) bond of the zig-zag. No explanation or precise treatment of the transmission of strain effects through zig-zags was possible from this limited evidence.

The search for regularities seemed complicated by a few additional compounds (Table 1) for which c.d. data *do not* reveal effects of strain. The reported o.r.d. amplitude for 8-methyl-*trans*-hexahydroindan-5-one (8) is identical with that of its decalone analogue (11). The bicyclic

TABLE 1

Effects of bond-strain on Δε for steroidal ketones in which bonds of a five-membered ring lie on a primary zig-zag

| | Δε [a](MeOH or EtOH) | | | Effect of ring strain | |
	For compound with five-membered ring (indicated in parentheses) (a)	For corresponding compound with a six-membered ring (b)	Location of strained bond(s) on primary zig-zag [b]	δΔε [(a) − (b)]	Sign predicted from octant occupied by strained bonds
Compounds showing evidence of strain					
B-Nor-5α-cholestan-3-one (3)	+2.5 (B)	+1.2	2nd, 3rd	+1.3	+
B-Nor-5β-cholestan-3-one (4)	−1.3 (B)	−0.5	2nd	−0.8	−
5α-Estran-6-one (5)	−1.4 (D)	(−0.4)	3rd, 4th	(−1.0)	−
5α-Androstan-6-one	−1.3 (D)	−0.6	3rd, 4th	−0.7	−
5α-Androstan-12-one (7)	+1.5 (D)	+2.4	1st, 2nd	−0.9	−
Compounds not showing evidence of strain					
8-Methyl-*trans*-hexahydroindan-5-one (8)	+1.2 (B)	+1.2	2nd, 3rd	0.0	+
2-Oxo-5α-steroid (9)	+2.2 (D)	+2.3	5th, 6th	−0.1	+
5α-Androstan-11-one (10)	+0.1 (D)	+0.2	2nd, 3rd	−0.1	+

[a] To nearest 0.1 unit; italicised entries are estimates based on o.r.d. amplitudes: Δε = a/40.28 (*cf.* ref. 2). [b] The C_α–C_β bond is regarded as the ' first ' bond of a primary zig-zag. [c] Calc. value (ref. 2); compound not available.

TABLE 2

Recommended coefficients k_C for use in equation (iii) (with $k_H = −6.2$)

| | For sec. or tert. C_α | | For quaternary C_α | |
C_α–C Bond type	Substitution increment (δk_C) * relative to C_α–H	k_C (abs. value †)	Substitution increment (δk_C) * relative to C_α–H	k_C (abs. value †)
Unstrained (*e.g.* C_α–Me, or C_α–C_β in a cyclohexanone)	+1.6	−4.6	+1.9	−4.3
Strained, as C_α–C_β in a cyclopentanone	+4.3	−1.9	+4.9	−1.3

* Substitution increment (δk_C), *i.e.* effect of replacing a C_α–H bond by a C_α–C bond of the type indicated: the positive sign corresponds to a *consignate* substituent effect. † The absolute (k_C) and the relative (δk_C) coefficients are related by: $δk_C = k_C − k_H = k_C + 6.2$.

here whenever molecular geometry causes marked deviations from normal bond angles or torsion angles (see p. 2145, where an approximate empirical correlation between strain and c.d. data is proposed).

Data for the five steroids (3)—(7) which have no further complicating features are summarised in the first part of Table 1. The Table presents a direct comparison between c.d. data for each steroid with a five-membered ring and its homologue with a six-membered ring. The difference between Δε values for each pair corresponds to enhanced consignate behaviour of a bond or bonds of the five-membered ring: δΔε ranges between 0.7 and 1.3 unit, showing no clear correlation with structure. Excepting the 12-oxo-steroid (7), strain effects appear very roughly to double the normal consignate contributions [2] of the

compound, however, is less strained than a B-nor-5α-steroid (3), where *trans*-fusion of rings B and C further distorts the five-membered ring. The 2-oxo-5α- (9) and 11-oxo-steroids (10) also show negligible differences between the parent compounds and their D-homo-analogues. Models of each of these compounds show that a five-membered ring D forces the terminal bond of the primary zig-zag out of coplanarity. It seems likely that the c.d. contribution of the terminal bond is reduced by this distortion, and that this reduction happens to compensate for any increase which might be expected as a consequence of bond strain. The 11-oxo-steroid (10) is also the only compound of the group possessing a ' β '-axial methyl substituent on a primary zig-zag. Since the contribution of a ' β '-axial methyl group depends

critically [2] upon the nature of the primary zig-zag on which it lies, the 11-oxo-compound is not typical.

A further suggestion of enhanced consignate effects from strained C–C bonds emerged from our analysis of c.d. data for cyclopentanone rings.[3,4] An ' α '-methyl

derived as the *absolute* value appropriate for a C_α–C_β bond of a cyclopentanone, and the coefficient ($k_H = -6.2$) for a C_α–H bond.[4] The numerical value of k_H is assumed at present not to vary significantly.† The *relative* coefficients δk_C derived for a somewhat strained C_α–C_β

TABLE 3

Attempts to calculate Δε for some bi- and tri-cycloalkanones by use of equation (iii)

Ketone	Δε (obs.)	Torsion angles (ω)	Calculations based upon $k_H = -6.2$		Calculations based upon $k_H = 0$	
			Values examined for k_C (see text, p. 2128)	Δε (calc.)	Values examined for k_C (see text, p. 2128)	Δε (calc.)
Bicyclo[3.2.1]-octan-6-one (13)	−2.3	H_{exo}, +60°; H_{endo}, −60°; C-1, 180°; H-5, −30°; C-4, +90°; C-8, −155°	(a) −4.6	−2.2	(g) +1.6	+1.3
			(b) −4.6 (for C-4) −1.9 (for C-8)	−2.7	(h) +1.6 (for C-4) +22.4 (for C-8)	−2.3
			(c) −1.9	0.0	(i) −2.9	−2.3
			(d) −4.6 (for C-4) −3.6 (for C-8)	−2.3		
			(e) −4.8	−2.3		
			(f) −4.6 (for C-4) −2.0 (for C-8)	−2.6		
Bicyclo[2.2.1]heptan-2-one (12)	−0.5	H_{exo}, +60°; H_{endo}, −60°; C-1, 180°; H-1, −20°; C-6, +105°; C-7, −145°	(a) −4.6	−2.1	(g) +1.6	+1.0
			(b)(c) −1.9	−0.4	(h) +1.6 (for C-6) +6.1 (for C-7)	−0.5
			(d) −1.9 (for C-6) −1.7 (for C-7)	−0.5	(i) −0.8	−0.5
			(e) −2.0	−0.5		
			(f) −1.9 (for C-6) −0.4 (for C-7)	−0.9		
Bicyclo[3.2.1]octan-2-one (14)	−2.0	H-1, 0°; C-7, −120°; C-8, +120° H_{exo} −10°; H_{endo} +110° C-4, −130°	(a) −4.6	−2.6	(g) +1.6	−0.9
			(b) −4.6 (for C-4) −1.9 (for C-7 and C-8)	−2.6	(i) +3.4	−2.0
			(c) −1.9	−4.2		
			(d) −4.6 (for C-4) −1.9 (for C-7) −1.1 (for C-8)	−2.0		
			(e) −5.6	−2.0		
			(f) −4.6 (for C-4) −1.9 (for C-7) −2.0 (for C-8)	−2.7		
Tricyclo[4.4.0.0^{3,8}]-decan-2-one (' twistan-2-one ') (79)	+10.6	H-1, H-3, −25°; C-4, C-10, +95°; C-6, C-8, −145°	(a)(b) −4.6	−3.9	(g) +1.6	+2.1
			(c) −1.9	−0.3	(i) +8.0	+10.6
			(d) −4.6 (for C-6, C-8) +2.7 (for C-4, C-10)	+10.6		
			(e) +6.3	+10.6		
			(f) −4.6 (for C-6, C-8) −0.25 (for C-4, C-10)	+4.8		
Tricyclo[4.4.0.0^{3,8}]-decan-4-one (' twistan-4-one ') (80)	−0.88	H-3, 20°; C-8, +105°; C-2, −140° H-5eq. −30°; H-5ax, +90°; C-6, 150°	(a)(b) −4.6	−4.6 *	(g) +1.6	+1.1
			(c) −1.9	−3.2 *	(i) +0.7	+0.9
			(e) +15.6	+0.9 *		
			(f) −4.6 (for C-2, C-8) −0.25 (for C-6)	−5.6 *		

* Calculated with normal allowance for the 8,9-bond, as the second bond of a primary zig-zag. Introduction of ' strain ' and ' orientation ' factors for the 8.9-bond gives greatly improved values of Δε; see p. 2147.

substituent on a cycloalkanone ring makes a consignate contribution, relative to hydrogen, which is given approximately [3] by equation (i). The coefficient k is now replaced by δk_C, which expresses the difference between the coefficients k_C for ' α '-methyl and k_H for ' α ' hydrogen. In a cyclohexanone ring δk_C has the value 1.9 for a methyl substituent on quaternary carbon, or 1.6 for methyl on tertiary carbon (Table 2).[2] The value of the substituent coefficient δk_C for the C_α–C_β bonds of a chiral cyclopentanone ring is estimated as *ca.* 4.3. This value is the difference between the coefficient ($k_C = -1.9$)

cyclopentanone bond and for an unstrained C_α–Me (or a cyclohexanone C_α–C_β) bond are therefore in the ratio *ca.* 2.4 : 1. This enhancement of δk_C in a cyclopentanone, attributed to bond strain, agrees well with the tentatively doubled contribution of a strained C–C bond on a primary zig-zag (see above, and p. 2145).

Bridged-ring Compounds.—An attempt was next made

† It is recognised that this assumption is questionable on theoretical grounds (J. Hudec, personal communication). No empirical method is yet available for evaluating k_H in different situations, but the use of a single value for calculations of the present type seems justified by the results.

to bring data for the heterogeneous collection of ketones based on bridged bicycloalkane and tricycloalkane frameworks into one comprehensive pattern with the more regular structures examined earlier. Typical $\Delta\varepsilon$ values were derived, wherever possible, from compounds lacking the complicating features of polar substituents or unsaturation. No simple procedure of pairwise comparisons

that the parent bicyclo[3.2.1]octan-6-one (13) would have a $\Delta\varepsilon$ value of *ca.* —2.3 (*cf.* p. 2128). Table 6 gives data for a few compounds of the bicyclo[3.2.1]octan-2-one type (14).

Conventional octant diagrams for bicyclo[3.2.1]octan-6-one (13) and bicyclo[2.2.1]heptan-2-one (12), each illustrated here as the enantiomer with a *negative* Cotton
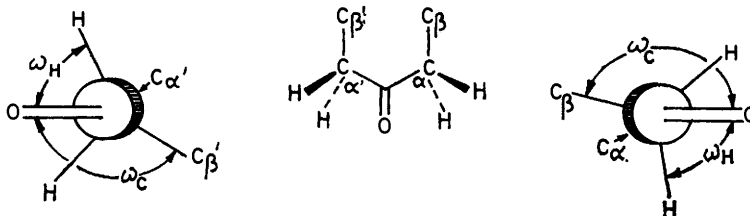
Figure 2 Torsion angles (ω): Newman projections of C(:O)—C$_\alpha$ bonds of a ketone

seemed likely to bring order into these complex series of bridged-ring compounds, so a different approach was adopted. The empirical method of calculation of $\Delta\varepsilon$ based on application of equations of type (i) was tested for these compounds, following its success when used for twisted cyclopentanone and cyclohexanone analogues.[4]

The present set of calculations of $\Delta\varepsilon$ (Table 3) was based upon the more general equation (iii), which gives

$$\delta\Delta\varepsilon = \Sigma k_H \sin^2\omega_H + \Sigma k_C \sin^2\omega_C \qquad (iii)$$

an estimate of the combined contributions of all bonds of C_α–H or C_α–C_β type to the total value of $\Delta\varepsilon$. The coefficients k_H and k_C were initially given values (Table 2) taken from earlier work.[4] Their negative signs correspond to dissignate behaviour, which is more pronounced for a C_α–H than for a C_α–C bond; values chosen for k_C depended only upon substitution type and ring size. Additional values of k_C, corresponding to altered strains, were later derived for bonds in particularly strained situations. The angles ω_H and ω_C are the torsion angles between the C=O bond and the respective C_α–H or C_α–C bonds, usually estimated from Dreiding models. Summations included terms for all six bonds radiating from the two ' α '-carbon atoms of the ketone, regarded as an acetone derivative. Pairs of Newman projections were used to illustrate the sets of torsion angles (Figure 2). Signs allotted to terms for individual bonds corresponded to those of their torsion angles ω (clockwise, +; anticlockwise, —); this is equivalent to giving each term the sign appropriate for the ' rear ' octant in which the C_α–H or C_α–C bond is assumed to lie.[4]

Equation (iii) takes account only of bonds originating at C_α. Additional allowance [2] was made for any extended primary zig-zag present in the structure, and for ' α '-axial or ' β '-equatorial substitution when present.

Bicyclo- and Tricyclo-alkanones (Bridged-ring Ketones). —C.d. data (Table 5) are available for bicyclo[2.2.1]heptan-2-one (12) ($\Delta\varepsilon$ —0.5 [7,20]) and some of its derivatives. Bicyclo[3.2.1]octan-6-one (13) is not itself available, but forms part of the molecular framework of various polycyclic compounds including kaurane, beyerane, and gibberellane derivatives (Table 4). Inspection suggests

effect, reveal the inadequacy of a simple ' Octant Rule ' treatment, as has long been appreciated.[13,19] In each case c.d. effects are seemingly dominated by the out-of-plane atoms or bonds of the cyclopentanone components, despite the ' α '-quasi-axial character of the C(5)–C(4) and C(1)–C(6) bonds, respectively. The ' upper ' and
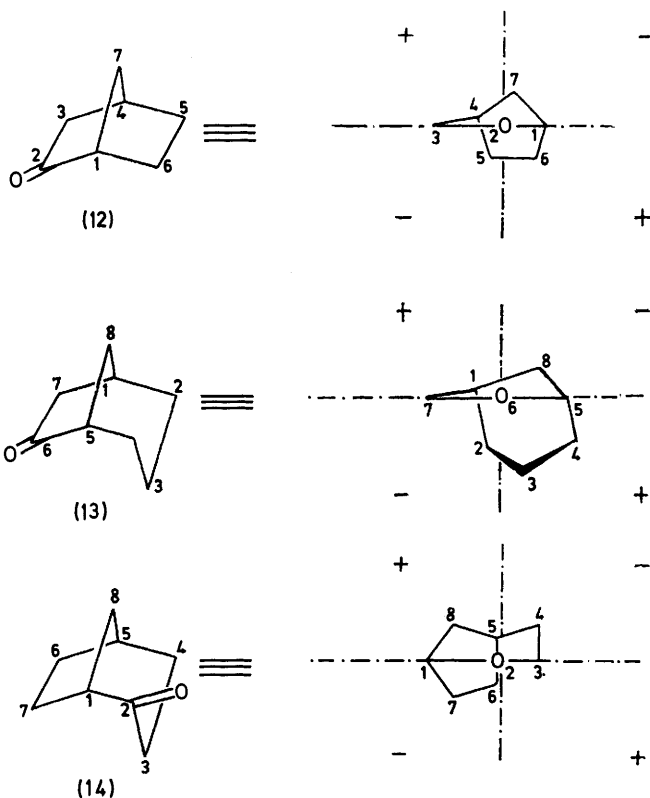
' lower ' parts of bicyclo[2.2.1]heptan-2-one (12) apparently make almost compensating contributions, leaving only a small net value of $\Delta\varepsilon$ (*ca.* —0.5). In bicyclo[3.2.1]octan-6-one (13), however, the bonds of the cyclopentanone ring appear more strongly dominant, even

[20] C. Coulombeau and A. Rassat, *Bull. Soc. chim. France,* 1966, 3752.

though the 'lower right' part of the carbonyl environment is relatively more occupied than in bicyclo[2.2.1]-heptan-2-one (12). The explanation of these apparent anomalies appears to lie in the more-consignate effects of strained as compared with unstrained C–C bonds.[19] The 'anomalies' disappear if the bonds comprising the strained one-carbon (methylene) bridge in each case are allotted contributions which are relatively more consignate than usual.† Calculations based upon equation (iii), for the sets of bonds which originate at C_α in each of these bicycloalkanones, can be made to give approximately correct values of $\Delta\varepsilon$ if the C_α–C_β bonds of the methylene bridges are assigned less negative k_C values, corresponding to bond contributions which are relatively more consignate than those hitherto employed (Table 2).

The various classes of bicycloalkanones, and some other strained bridged structures, are discussed individually. Attention is focused in each case on the C_α–C_β and any C_α–H or C_α–Me bonds, with additional consideration of any periplanar 'primary zig-zags' of C–C bonds which extend beyond the C_α–C_β bonds. 'β'-Axial substituents are also taken into account in the few cases where they occur. All the other parts of a saturated hydrocarbon framework which lie in rear octants are ignored in the present analysis, since they seemed to make little if any contribution in the ketones studied previously.[2,3] Small 'front-octant' effects may occur in isolated cases, but appear generally to be insignificant as compared with contributions from the set of bonds originating at C_α.

The following discussion includes an exploration of the changes in coefficients k_C which are required in order to reproduce observed values of $\Delta\varepsilon$ for bicyclo- and tricyclo-alkanones. The results for bicyclo[2.2.1]heptan-2-one and bicyclo[3.2.1]octan-6-one and -2-one are summarised in Table 3, which lists trial values of k_C and the derived values of $\Delta\varepsilon$ calculated by use of equation (iii). Torsion angles (ω) taken from Dreiding models are expected to contain errors of perhaps ±5°, insufficient to affect the *qualitative* significance of conclusions. The principal set of calculated values of $\Delta\varepsilon$ in Table 3 assumes $k_H = -6.2$ (dissignate, as derived from our analysis of data for cyclopentanones).[4] For comparison, Table 3 also contains the results of an alternative set of calculations which assumed $k_H = 0$, *i.e.* ignored contributions of C–H bonds, as in all previous work. The erratic nature of this latter set of results reinforces the view that the dissignate effect of C_α–H bonds expressed by the negative value of k_H is real, since neglect of C_α–H bonds (Table 3, final two columns) forces the adoption of k_C values some of which seem highly improbable.

Trial values of k_C (when $k_H = -6.2$) included: (a) −4.6, *i.e.* $\delta k_C = +1.6$ relative to k_H: this is the consignate substitution increment used previously for unstrained C_α–C bonds in cyclohexanone systems, when C_α is secondary or

tertiary; (b) −4.6 (as above) for C_α–C bonds in a cyclohexane, and −1.9 for C_α–C bonds in a cyclopentane ring: this distinction recognises the probably unequal distribution of strains within some bicycloalkane systems, and allots a relatively more consignate value of k_C to the bonds of a cyclopentane ring; (c) −1.9 for *all* C_α–C bonds (*i.e.* assuming that *all* C_α–C bonds are as strained as in a cyclopentanone); (d) the *optimum* value (*i.e.* the one which best reproduces the experimental value of $\Delta\varepsilon$ for the compound in question) for any C_α–C bond which is part of a one-carbon (methylene) bridge, assumed to be the most strained part of the molecular framework: other bonds are assigned 'normal' k_C values as in (b); (e) the single *optimum* value for the structure as a whole, calculated on the assumption that strain is equally distributed between all C–C bonds irrespective of ring size: this value of k_C was obtained as the solution of equation (iii) with insertion of measured values of ω, the experimental value of $\Delta\varepsilon$, and $k_H = -6.2$; (f), for strained 'bridge' bonds, the 'calculated' value taken from Table 10 (see p. 2146): other bonds are given their 'normal' k_C values as in (b).

For calculations to examine the alternative assumption that C_α–H bonds could be neglected (*i.e.* that $k_H \approx 0$), the values of k_C examined were: (g) +1.6, being the coefficient used previously [2] to evaluate the effects of substitution of α-H by α-Me at secondary or tertiary carbon [*cf.* trial (a)]; (h) +1.6 for unstrained bonds of a cyclohexane ring, and the *optimum* value of k_C for strained C_α–C bonds [*cf.* trial (d)]; (i) the *optimum* value calculated on the assumption that strain is evenly distributed [*cf.* trial (e), but with $k_H = 0$].

The results are presented in Table 3, and discussion of their significance follows.

Bicyclo[3.2.1]*octan*-6-*ones* (*Table* 4). Values of $\Delta\varepsilon$ for the bicyclo[3.2.1]octan-6-one analogues without 'special structural features' fall within a narrow range of *ca.* 2—2.5 units (mean *ca.* 2.3). Some compounds with 'special structural features' show wider deviations. Allowance [2] for the four-bond primary zig-zag in the *ent*-kauran-15-ones (21) and (22) brings these compounds more into line with others of the series. The contributions of the other 'special features' listed can only be assessed empirically by pairwise comparisons. Tricyclo-[4.3.1.0³,⁷]decan-4-one (38) has its 7,8-bond on a primary zig-zag in a 'positive' octant, accounting for the slightly enhanced $\Delta\varepsilon$ value of +2.7. It appears that the conformation (chair or boat) imposed on the cyclohexane ring component of a bicyclo[3.2.1]octan-6-one by its mode of fusion to additional rings has no appreciable effect on its chiroptical properties.

Application of equation (iii) to the parent bicyclo-[3.2.1]octan-6-one (see Table 3) generally gave $\Delta\varepsilon$ values of the correct sign and order of magnitude when k_H was taken to be −6.2; neglect of C–H bonds ($k_H = 0$) either resulted in $\Delta\varepsilon$(calc.) having the wrong sign, or required the use of highly improbable values of k_C. Sets of coefficients (b) or (d) probably have the best validity, and imply that a more-consignate (or less-dissignate) coefficient for the strained bonds comprising the methylene

† There is a problem of concise terminology here: the *absolute* contributions of the bonds in question are smaller than usual in the *dissignate* sense, *i.e. tend towards* being consignate. Expressions like 'relatively more consignate' are therefore used. Consignate effects in the absolute sense arise only for very highly strained bonds.

TABLE 4

C.d. data for compounds containing a bicyclo[3.2.1]octan-6-one component

	Absolute configuration of bicyclo-[3.2.1.]-octan-6-one component [cf. formula (13)]	Δε(obs.)	Special structural features	Δε(calc.) [a]	Refs.[b]
ent-17-Norkauran-16-one (15)	ent-(13)	+2.4		+2.3	aa, bb
ent-18-Hydroxy-17-norkauran-16-one (16)	ent-(13)	+2.2		+2.3	bb
ent-16-Oxo-17-norkauran-18-oic acid (17)	ent-(13)	+2.3		+2.3	bb
ent-Methyl 16-oxo-17-norkauran-18-oate (18)	ent-(13)	+2.0, 2.2		+2.3	cc
ent-Methyl 3β-acetoxy-16-oxo-17-norkauran-18-oate (19)	ent-(13)	+1.9		+2.3	cc
' Epoxynorcafestanone ' (20)	ent-(13)	+2.4		+2.3	aa
ent-(16S)-kauran-15-one (21)	(13)	−0.51 −0.4	2nd—4th bonds of zig-zag in ' positive ' octant; ' α '-Me in ' negative ' octant [c,d]	−0.7	dd, ee
ent-(16R)-kauran-15-one (22)	(13)	+0.79	2nd—4th bonds of zig-zag and ' α ' Me in ' positive ' octant [c,d]	+1.7	dd
Beyeran-16-one (23)	ent-(13)	+2.3		+2.3	cc
17-Norbeyeran-16-one (24)	ent-(13)	+2.4		+2.3	aa, cc
ent-Methyl 16-oxobeyeran-18-oate (' isosteviol ') (25)	(13)	−2.45		−2.3	cc
Beyeran-15-one (26)	(13)	−2.9	10β-methyl overhanging oxo-group in ' negative ' front octant [e]	ca. −3	cc
(16R)-16-Methyl-17-norbeyeran-15-one (27)	(13)	−2.82	16β-Me in ' negative ' octant [d]	−3.5	dd
(16S)-16-Methyl-17-norbeyeran-15-one (28)	(13)	−2.05 −1.9	16α-Me in ' positive ' octant [d]	−1.1	dd ff
13-Methyl-16-oxo-17,19,20-trinor-6αH,-9β-gibberella-1,3,5(10)-trien-7-oic acid (29)	(13)	−2.4	Aromatic ring A [f]	−2.4	aa
3β,10-Dihydroxy-13-methyl-16-oxo-17,20-dinor-6αH,9β-gibberellane-7,19-dioic acid 19,10-lactone (30)	(13)	−2.05		−2.4	aa
9α-Isomer (31) of (30)	(13)	−2.1	' Boat ' conformation? [g]	−2.4	aa
ent-3α,10,13-Trihydroxy-17,20-dinor-gibberellane-7,19-dioic acid 7-methyl ester 19,10-lactone (32)	ent-(13)	+1.9	13-OH;[f] ' boat ' conformation? [g]	+2.4	aa
13-Hydroxy-16-oxo-17,19,20-trinor-6αH-gibberella-1,3,5(10)-trien-7-oic acid (33)	(13)	−0.25	Aromatic ring A;[f] 13-OH;[f] ' boat ' conformation? [g]	?	gg
Methyl ester of (33)	(13)	−0.25	Aromatic ring A;[f] 13-OH;[f]' boat ' conformation? [g]	?	gg
13-Methyl-16-oxo-17,19,20-trinor-gibberella-1,3,5(10)-trien-7-oic acid (gibberic acid) (34)	(13)	−1.73 −2.5	Aromatic ring A [f]	−2.4	gg, hh
Methyl ester of (34) (' methyl gibberate ')	(13)	−1.7	Aromatic ring A [f]	−2.4	gg
ent-Methyl 13-hydroxy-16-oxo-17,20-dinor-6βH,9β-gibberella-1,3,5(10)-trien-7-oate (35)	ent-(13)	+1.1	Aromatic ring A; [f] 13-OH [f]	+2.4	gg
3β,5-(1-oxoethano)-5β-cholestane (36)	(13)	−3.7		−2.4	cc
3β-Hydroxy-3α 5-(2-oxoethano)-5α-cholestane (37)	(13)	−1.4	10β-Me, ' β '-equatorial bond in ' positive ' octant [h]	−1.3	cc
Tricyclo[4.3.1.0³,⁷]decan-4-one (38)	ent-(13)	+2.7	Boat conformation of cyclohexanone ring; ' β '-equatorial 7,8-bond	+2.9	jj

[a] Calculated on the basis of $\delta\Delta\varepsilon = \pm2.3$ for the parent bicyclo[3.2.1]octan-6-one unit, with increments for ' special structural features,' where these can be estimated. [b] Footnote references. [c] 2nd—4th bonds of primary zig-zag, $\delta\Delta\varepsilon = +2.8$, including ' orientation factor ' of 1.7 for the primary zig-zag ($\omega \approx 90°$; see p. 2146). ' α '-Me at $\omega = \pm60°$, $\delta\Delta\varepsilon \approx \pm1.2$. [d] The 16-Me effect, here taken as $\delta\Delta\varepsilon = \pm1.6 \sin^2 60° = \pm1.2$ (ref. 3), appears to be an overestimate. [e] Front octant contribution probably in the range −0.5 to −1.0 (refs. 15—17). [f] No increment included. [g] A model suggests that a ' boat ' conformation of the cyclohexanone ring may be enforced by the cis-stereochemistry at C-8 and C-9. [h] $\delta\Delta\varepsilon = 0.6 \times 1.7$ (orientation factor—cf. footnote c) = +1.0.

[aa] Ref. 23. [bb] P. R. Jeffries, W. Australia (Westfield College measurement). [cc] Ref. 33. [dd] J. MacMillan and E. R. H. Walker, J.C.S. Perkin I, 1972, 986. [ee] Sir Ewart R. H. Jones, Oxford (Westfield College measurement). [ff] P. S. Rutledge, Auckland (Westfield College measurement). [gg] K. Mori, M. Matsui, and Y. Sumiki, Tetrahedron Letters, 1970, 429. [hh] J. F. Grove, I.C.I. (Westfield College measurement). [jj] Ref. 48.

bridge improved the calculated value of Δε. Only minor changes from ' normal ' values of k_C were needed, however, so evidence of strain is slight.

For bicyclo[3.2.1]octan-6-one (13), but not for the other compounds in Table 3, a simplified quantitative treatment also gave satisfactory results, again indicating that the framework is not grossly strained (see also bicyclo[3.2.1]octan-2-ones, below). Dreiding models suggest that the conformation of the ' cyclopentanone ' component is near the ' envelope ' form, giving $\delta\Delta\varepsilon$ ca. −4.0
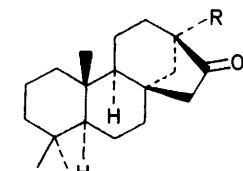
units [3] as the dominant contribution. The ' α '-quasi-axial C–C bond can be allotted a substituent contribution [3] of +1.6 units (1.6 sin² 90°) of opposite sign, if
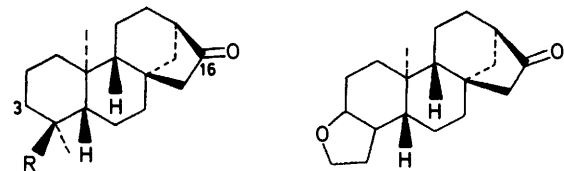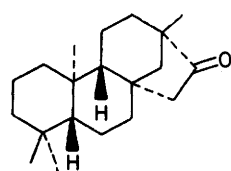

(15) R = Me
(16) R = CH₂OH
(17) R = CO₂H
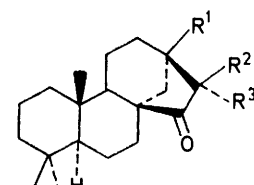(18) R = CO₂Me
(19) R = CO₂Me, with 3α-OAc

(20)
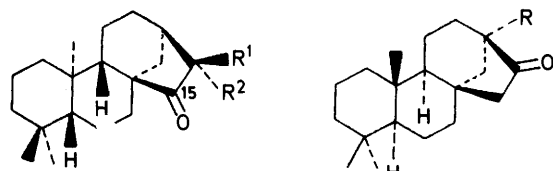
(21) R¹ = Me, R² = H
(22) R¹ = H, R² = Me

(23) R = Me
(24) R = H

(25)

(26) R¹ = Me,   R² = R³ = H
(27) R² = Me,   R¹ = R³ = H
(28) R¹ = R² = H,   R³ = Me

strain in this bond is assumed to be negligible. The net Δε value of −2.4 units, estimated on this very simple basis, provides excellent agreement with experimental data. A Dreiding model, however, fails to simulate the torsional strain which is largely responsible for an isolated cyclopentanone ring adopting the ' twisted ' conformation (C_2 symmetry). A model of bicyclo[3.2.1]octan-6-one (13) shows that tension in the three-carbon bridge is minimised when the cyclopentanone ring is in the relatively high-energy ' folded ' conformation.[3] The three-carbon bridge is only slightly strained when the cyclopentanone ring is in the ' envelope ' conformation but strain in the bridge increases sharply if the cyclopentanone component is forced towards the ' twist ' (C_2) conformation (39) which represents the energy minimum for

[21] C. Ouannes and J. Jacques, *Bull. Soc. chim. France*, 1965, 3601.

an isolated cyclopentanone ring.[21,22] A rough calculation suggests that the ' twist ' conformation (39) would result in a Δε value similar to that of the form (13) containing the ' envelope ' cyclopentanone [δΔε for ' twist ' form of the isolated cyclopentanone ring *ca.* −5.5 units; [3,4] ' α '-quasiaxial substituent contribution,[2,3]
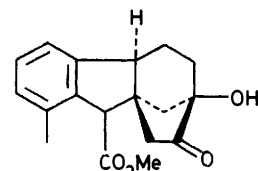
(29) 9β-H, R = Me
(33) 9α-H, R = OH
(34) 9α-H, R = Me
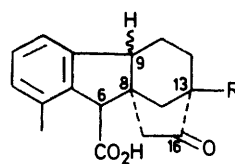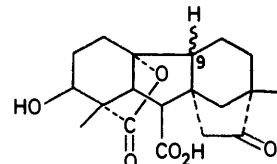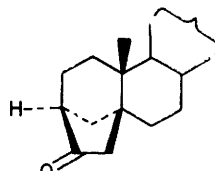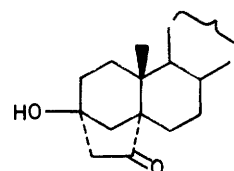
(30) 9β-H
(31) 9α-H
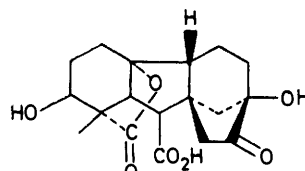
(32)
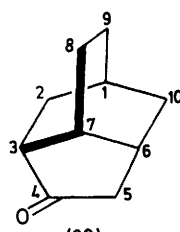
(35)
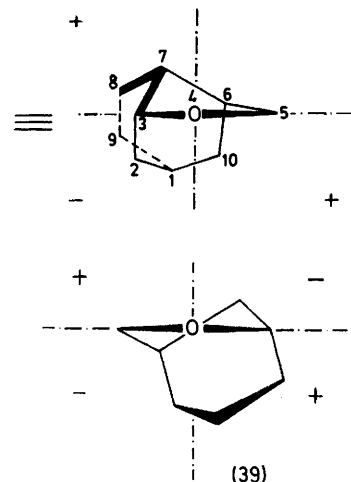
(36)

(37)

(38)

(39)

assumed to be doubled by increased strain, *ca.* 3.2 units: net effect −2.3 units]. The narrowness of the range of Δε values for compounds of bicyclo[3.2.1]octan-6-one

[22] N. L. Allinger, M. T. Tribble, and M. A. Miller, *Tetrahedron*, 1972, **28**, 1173.

type may well be a consequence of this mutual compensation of changes in the contributions from bonds of the five- and six-membered rings over a range of minor conformational variations, although fine structure evident in some c.d. curves determined in dioxan [23] perhaps

group increments here (mean value *ca.* ± 0.5 unit) are smaller than would be predicted $(1.6 \sin^2 60° = 1.2)$.[3] The reason is not clear, but could lie in differing flexibilities of various ring systems, permitting different degrees of conformational adjustment to substitution.

TABLE 5(a)

C.d. data for bicyclo[2.2.1]heptan-2-one (' norbornanone ') and its methylated derivatives

	Solvent: hexane or cyclohexane		Solvent: methanol or ethanol			
	$\Delta\varepsilon$	λ/nm	$\Delta\varepsilon$	λ/nm	$\Delta\varepsilon$ (' calc.')	Ref.
(1S,4R)-Bicyclo[2.2.1]heptan-2-one (12)	$-0.44,$ -0.55	306	$\{-0.25$ $\{+0.15$	305 280	-0.5	*a, b*
Derivatives [*cf.* Figure 3 for structures of compounds (40—(50)]						
(1S,4R)-1-Me (40)	-0.25		-0.25		-0.3	*b*
(1S,4R)-3,3-Me$_2$ (α-camphenilone) (41)	$\{-0.14, -0.18$ $\{+0.32$	318 288	$\{-0.05$ $\{+0.7, +0.53$	315 284	$+0.5$ *	*a, b*
(1R,4R)-5,5-Me$_2$ [(+)-β-fenchocamphorone] (42)	-0.75	307	$\{-0.53$ $\{+0.15, +0.18$	305 275	-0.5	*a, b*
(1S,4S)-7,7-Me$_2$ (α-fenchocamphorone) (43)	$-1.6, -1.97$	304	$-1.45, -1.8$	294	-1.8	*a, b*
(1S,4R)-1,3,3-Me$_3$ [(+)-fenchone] (44)	$+0.76$	292	$+1.07$	289	$+0.7$ *	*b*
(1R,4R)1,5,5-Me$_3$ [(+)-isofenchone] (45)	$\{-0.25$ $\{+0.19$	316 282	$\{-0.07$ $\{+0.44$	311 280	-0.3	*a, b*
(1S,4S)-1,7,7-Me$_3$ [(−)-camphor] (46)	-1.69	302	$-1.6, -1.54$	292—295	-1.6	*a, b, c*
(1S,4R)4,6,6-Me$_3$ (epi-isofenchone) (47)	-0.52	306	$\{-0.15$ $\{+0.22$	307 280	-0.5	*a, b*
(1S,4S)-4,7,7-Me$_3$ [(−)-epicamphor] (48)	-1.86	304	-1.81	294	-1.8	*a, b*
(1S,4S)-1,3-*endo*,7,7-Me$_4$ [(−)-3-*endo*-Me-camphor] (49)	-1.0				-1.1 *	*c*
(1S,4R)-1,3,3,7,7-Me$_5$ [(−)-3,3-Me$_2$-camphor] (50)	-1.25		-1.25		-0.6 *	*c*
ent-' Longicamphor ' (1,3-*exo*,7,7-tetrasubstituted) (51)			-1.2		-0.4	*d*
' Longicamphenilone ' (3,3,7-*syn*-trisubstituted) (52)			-1.3		-1.1 *	*d*

* These ' calculated ' values include allowances for a twisting deformation; see Table 5(b).

[a] Ref. 20.   [b] Ref. 7.   [c] Ref. 19.   [d] Ref. 27: $\Delta\varepsilon$ calculated from o.r.d. of enantiomer ($\Delta\varepsilon = a/40.28$).

TABLE 5(b)

Methyl group increments ($\delta\Delta\varepsilon$) used to ' calculate ' values of $\Delta\varepsilon$ for bicyclo[2.2.1]heptan-2-one derivatives (see text p. 2132)

Structural feature	$\delta\Delta\varepsilon$
(1S,4R)-Bicyclo[2.2.1]heptan-2-one	-0.5
Substituents	
1-Me	$+0.2$
3-*endo*-Me	$+0.5$ †
3,3-Me$_2$	$+1.0$ †
4-Me	0
5,5-Me$_2$	0
6,6-Me$_2$	0
7,7-Me$_2$	-1.3
7-*syn*-Me	$+0.6$?
7-*anti*-Me	-1.9 ?

† These values include an allowance for twisting of the ring system (p. 2132).

suggests rather rigid molecular conformations with well defined vibrational levels.

Table 4 contains little if any evidence of a significant effect of 5-methyl (' α '-) substitution in bicyclo[3.2.1]-octan-6-ones. Any consignate effect of the methyl group itself is probably compensated by a slightly more-consignate contribution from the 4,5-bond, resulting from the quaternary nature of C-5.[2] Methyl substitution at C-7, however (*e.g.* in 16-methyl-17-norbeyeran-15-ones), results in rather small changes in $\Delta\varepsilon$ corresponding to consignate effects of methyl groups. The methyl

Bicyclo[2.2.1]heptan-2-ones (*norbornan-2-ones*). C.d. data for a series of these compounds (*e.g.* camphor and fenchone) are listed in Table 5. Their o.r.d. or c.d. characteristics have been discussed previously by several groups,[7,13,19,24,25] but no attempt at a quantitative treatment has hitherto succeeded in integrating this group of compounds into a comprehensive pattern of ketone behaviour.

The parent bicyclo[2.2.1]heptan-2-one (12) ($\Delta\varepsilon$ *ca.*

[23] A. I. Scott, F. McCapra, F. Comer, S. A. Sutherland, D. W. Young, G. A. Sim, and G. Ferguson, *Tetrahedron*, 1964, **20**, 1339.

[24] L. Bartlett, D. N. Kirk, W. Klyne, S. R. Wallis, H. Erdtman, and S. Thorén, *J. Chem. Soc.* (C), 1970, 2678.

[25] H. P. J. M. Dekkers and L. E. Closs, *J. Amer. Chem. Soc.*, 1976, **98**, 2210.

−0.5) resembles bicyclo[3.2.1]octan-6-one except in comprising two fused five-membered rings instead of a five- and a six-membered ring. It therefore seemed appropriate to use equation (iii) with $k_C = -1.9$ for *each* of the two strained C_α–C_β bonds; the result [$\Delta\varepsilon = -0.4$; Table 3, entry (b)] was very satisfactory, as are the slightly modified calculations listed as entries (d)—(f).

The smaller negative value of $\Delta\varepsilon$ as compared with that for bicyclo[3.2.1]octan-6-one evidently results from a more-consignate (or less-dissignate) contribution from the ' α ' quasiaxial C_α–C bond in the lower right rear octant, which is more strained in the norbornanone series.

The other bicyclo[2.2.1]heptan-2-ones in Table 5 have methyl or similar substituents. The following discussion, like Table 5, refers to each compound in the absolute configuration corresponding to (1*S*,4*R*)-bicyclo-[2.2.1]heptan-2-one (12) as the parent compound. A 1-methyl group (40) makes C_α quaternary, and from previous conclusions [2,3] would cause the contributions of the 1,6- and 1,7-bonds to become somewhat more consignate, as well as introducing its own small consignate substitution increment ($-1.9 \sin^2 20° = -0.2$). A k_C value of −1.3 for the 1,6- and 1,7-bonds is required in order to obtain a total value of $\Delta\varepsilon = -0.3$ for the 1-methyl derivative, in agreement with experiment. The small change, in the consignate direction, from k_C *ca.* −1.9 for secondary or tertiary carbon to k_C *ca.* −1.3 for quaternary carbon in a strained cyclopentane ring seems reasonable, since it roughly parallels the corresponding difference (−4.6 *vs.* −4.3) required for cyclohexanone derivatives.[2]

The other positions of substitution covered by Table 5 need individual discussion (Figure 3). Data [25] are complicated by instances of bisignate [26] curves. There are
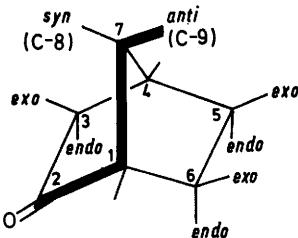

FIGURE 3 (1*S*,4*R*)-Bicyclo[2.2.1]heptan-2-one: substitution pattern

also changes of magnitude and even occasionally of sign of $\Delta\varepsilon$ with solvent. The following discussion makes no attempt to accommodate solvent effects,[25] but refers mainly to data in a hydrocarbon solvent.

A Dreiding model indicated that substituents at C-4 or at the 5-*exo*-position would be without effect, since they neither strain the molecular framework nor lie on a primary zig-zag.

3-Methyl substitution, ' α ' to carbonyl, introduces a

[26] W. Klyne and D. N. Kirk in ' Fundamental Aspects and Recent Developments in Optical Rotatory Dispersion and Circular Dichroism,' ed. F. Ciardelli and P. Salvadori, Heyden, London, 1973, pp. 89—107.

direct substituent effect. Data for compounds (41), (44), (49), and (50) (Table 5), compared in each case with those for the corresponding compound lacking C-3 substitution, show *positive* substitution increments. However, an undistorted model suggests that 3,3-dimethyl substitution should have no effect, since the C–Me bonds lie at torsion angles of equal magnitude but opposite sign with respect to the carbonyl group. Moreover a 3-*endo*-methyl substituent alone would be expected to make a *negative* contribution.

A 3-*endo*-methyl group would be expected to deform the molecule to relieve its compression with C-5. Equally a 5-*endo*-substituent would be expected to cause distortion. The precise nature of the deformation is
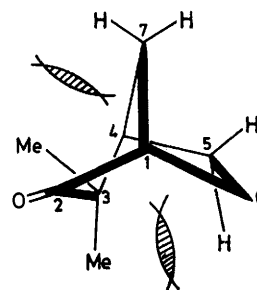

FIGURE 4 3,3-Dimethylbicyclo[2.2.1]heptan-2-one: proposed twisting to minimise non-bonded interactions

difficult to predict, but seemed likely to contain the explanation of the unexpected c.d. effects of C-3 substitution.

Calculations [equation (iii)] for the 3,3-dimethyl derivative showed that a small twisting distortion in the sense which gives the bicyclo[2.2.1]heptane framework *M*-helicity (Figure 4) whould result in a more positive value of $\Delta\varepsilon$, by altering torsion angles (ω). Analogous twisting is well established for bicyclo[2.2.2]octanes (p. 2136). The proposed twisting would be assisted to some extent by relief of torsional strains about the 2,3- and 5,6-bonds, and would permit simultaneous movement of the 3-*endo*-methyl group away from the 5-*endo*-H, and of the 3-*exo*-methyl group away from the 7-*syn*-H. The alternative sense of twist (*P*-helicity), while having a similar effect in relieving the *endo,endo*-interaction, would introduce 3-*exo*,7-*syn* compression.

Although further evidence to support the proposed deformation is lacking, this hypothesis provides a consistent explanation of c.d. data for the 3,3-dimethyl- and 3-*endo*-methyl-substituted compounds. The required degree of twist (*M*-helicity) to account for a change of +1 unit in $\Delta\varepsilon$ as a result of 3,3-dimethyl substitution is estimated to be 7° about the 1,4-axis ($\delta\Delta\varepsilon \approx 0.15$ unit per 1° of twist), which can be accommodated without difficulty by a Dreiding model, but is less than the allowed twist (*ca.* 12°) of a bicyclo[2.2.2]-octane (p. 2136). ' *ent*-Longicamphor ' (51),[27] a compound of sesquiterpenoid structure based upon bicyclo-[2.2.1]heptane, but with an extra bridge, is the only

[27] G. Jacob, G. Ourisson, and A. Rassat, *Bull. Soc. chim. France*, 1959, 1374.

2133

example of 3-*exo*- without 3-*endo*-substitution. The experimental value of $\Delta\varepsilon$ is more negative than that calculated, which assumes an undistorted bicyclo[2.2.1]-heptan-2-one unit. The assumption that the ' bridge ' is equivalent to 3-*exo*-methyl substitution is probably not valid.

The effects of 5,5-dimethyl substitution (Table 5) are solvent-dependent and cannot be analysed simply. Since neither methyl group lies on a primary zig-zag, $\Delta\varepsilon$ should match that of the parent compound, in the absence of distortion. Deviations from the expected values of $\Delta\varepsilon$ for the 5,5-dimethyl (42) and 1,5,5-trimethyl (45) derivatives may be due to twisting distortions similar but opposite in sign to that suggested for the 3,3-dimethyl compound. The lack of consistency with regard to signs of increments suggests the need for further examination of these compounds, particularly in respect of solvent sensitivity.[24]

4,6,6-Trimethyl substitution (47) causes no significant change in $\Delta\varepsilon$. The 6-*exo*-methyl group alone should exert a positive effect, as part of a rather unusually aligned primary zig-zag, but if this effect exists it appears to be compensated by a negative (dissignate) effect of the 6-*endo*-methyl group, which tends towards ' β-axial ' character.[2] In the absence of either 6-monomethyl derivative, these contributions cannot be separately evaluated.

The other major substituent effect (consignate) appears as a consequence of 7-*anti*-methyl substitution (C-9). Hudec[8] has demonstrated large contributions from heteroatom substitution at C-9, associated with the periplanar zig-zag pattern of bonding between C-9 and the carbonyl group. A 7-*syn*-methyl substituent (C-8), in contrast, may exert a dissignate effect, compatible with its spatial orientation which closely resembles that of a ' β '-axial methyl substituent in a hexahydroindan-1-one (class 5*t*2; cyclopentanone ring in ' envelope ' conformation).[3] The total effect of 7,7-dimethyl substitution (43) averages −1.3 unit, from experimental data. The only 7-*syn*-monosubstituted compound available is ' longicamphenilone ' (52), where the apparent contribution of the 7-*syn*-substituent (−CMe$_2$−, as part of the bridge) is *ca*. +0.6 unit (dissignate). This value is not necessarily typical of a methyl group in the same location, but a significant dissignate (positive) effect is indicated. The 7-*anti*-methyl substituent must therefore be assigned an exceptionally large consignate (negative) contribution of perhaps 1.3—1.9 units (*cf*. p. 2147).

Table 5 contains ' calculated ' values of $\Delta\varepsilon$ based upon the increments discussed above, which are collected for convenience in part (b) of the Table.

Bicyclo[3.2.1]*octan-2-ones* (*Table* 6). The bicyclo-[3.2.1]octan-2-one unit (14) probably comprises a chair-like cyclohexanone ring, distorted and rendered chiral by the two-carbon bridge, which creates an additional five-

membered ring. Calculated[28] strain energies for the two conformers of the hydrocarbon bicyclo[3.2.1]octane show a large preference (5.3 kcal mol^{-1}) for the form

with a chair cyclohexane ring. The alternative conformation (59) with the cyclohexanone ring in a twist-boat shape is known (*X*-ray data)[29] to exist in the 9β-bromo-derivative (60) of the 15-nor-8-ketone (58) derived from (+)-2,5-di-*epi*-β-cedrene, but this compound is probably abnormal in that the chair form would be strongly destabilised by Br,C-14 compression (see below).

A Dreiding model of bicyclo[3.2.1]octan-2-one with the cyclohexanone ring in the chair conformation (14) suggests that the cyclopentane ring is approximately bisected by the ' horizontal ' nodal plane of the carbonyl group. The torsion angles ω for the 1,7- and 1,8-bonds are therefore assumed to be nearly equal and of opposite sign. To a first approximation the cyclopentane component should be without chiroptical effect. The observed c.d. should therefore be dominated by the contributions of those bonds which originate at C-3.

The limited data available for compounds of bicyclo-[3.2.1]octan-2-one type (Table 6) seem best interpreted on the assumption that the parent bicyclic ketone (14) has a $\Delta\varepsilon$ value of −2.0 units. A smaller value (−0.7) has been reported[30] for the parent compound, but no proof of the optical purity of the sample has been reported: it was made to establish the *sign* of its o.r.d. curve. The three methylated derivatives (53)—(55) provide a consistent set of data,[13] each compound essentially comprising the parent compound with a ' β '-axial and a ' β '-equatorial methyl substituent. After making allowances of 0.1 unit (dissignate)[2] and 0.6 unit (consignate)[2] respectively for these methyl groups, we are

[28] E. M. Engler, J. D. Andose, and P. von R. Schleyer, *J. Amer. Chem. Soc.*, 1973, **95**, 8005.

[29] T. Norin, S. Sundin, B. Karlsson, P. Kierkegaard, A.-M. Pilotti, and A.-C. Wiehager, *Tetrahedron Letters*, 1973, 17.

[30] H. M. Walborsky, M. E. Baum, and A. A. Yousseti, *J. Amer. Chem. Soc.*, 1961, **83**, 988; H. M. Walborsky, personal communication (to Professor W. Klyne, 1976).
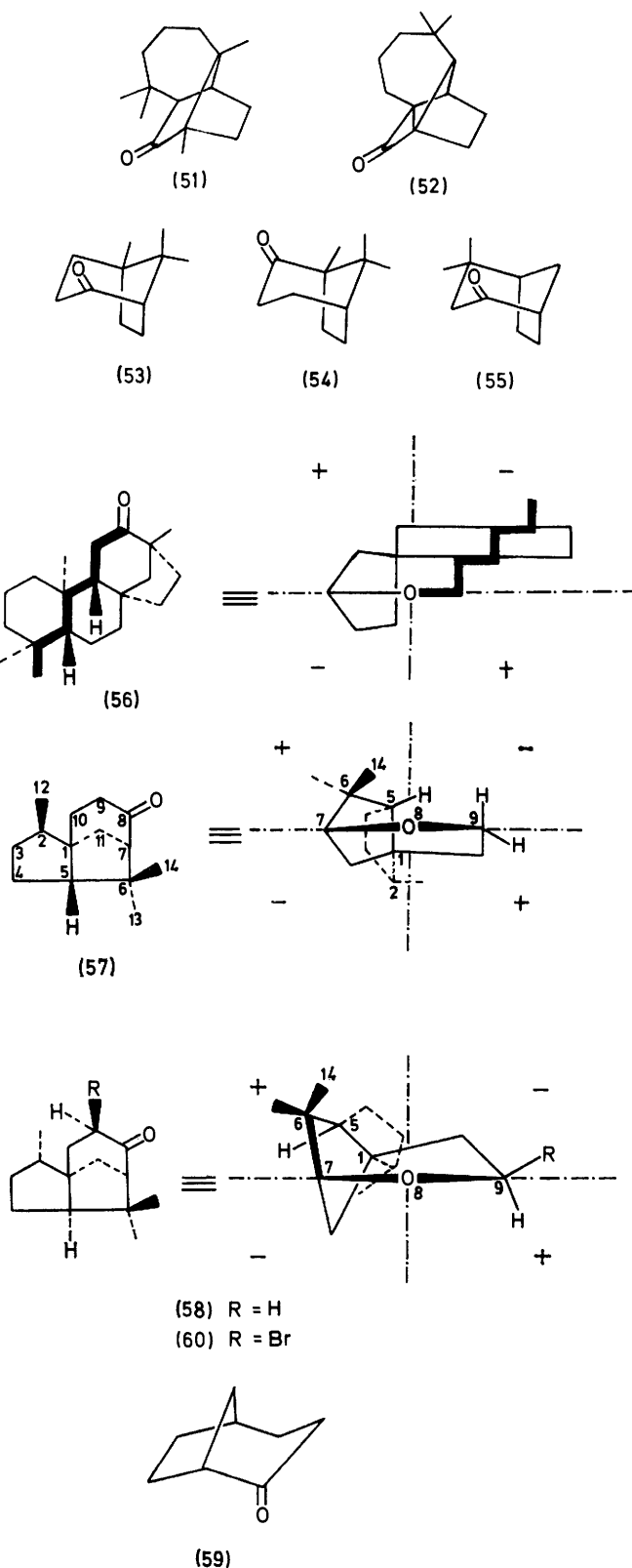
left with 2.0—2.1 units for the parent compound in each case. The *sign* of Δε corresponds to a consignate contribution from the 1,7-bond, which is quasiaxial to the cyclohexanone ring, in close agreement with the effect of an ordinary ' α '-axial methyl substituent. This agreement may be a consequence of strains in the 1,7- and 1,8-bonds making roughly equal and opposite contributions to Δε.

Among the few extended derivatives of bicyclo[3.2.1]-octan-2-one, *ent*-beyeran-12-one (56) (Δε —2.6) [31] contains an extended ' primary zig-zag ' ; normal allowances [2] for the latter and for ' γ '-substituents would leave a residual contribution of only —1.3 units for the bicyclo-ketone, suggesting some additional strain or distortion which cannot be reliably assessed. The nor-ketone (57) [32] from (+)-β-cedrene contains a ' bicyclo[3.2.1]-octan-2-one ' unit which is additionally strained by fusion to a further cyclopentane ring, so that it cannot be used to derive a reliable value of Δε for the parent bicyclic ketone. This is even more true of the 2,5-di-*epi*-isomer (58),[29] which probably contains a twisted cyclohexanone ring (see below).

Attempts (Table 3) to calculate Δε for the parent bicyclo[3.2.1]octan-2-one on the basis of equation (iii) gave a value of —2.0; the 1,8-bond of the strained methylene bridge was given a k_C value (—1.1) which is only slightly more consignate (less dissignate) than the normal cyclopentane value. [A more extreme value of k_C (+0.6), indicative of high strain, would be needed to reproduce Δε = —0.7, reported for the parent ketone of uncertain optical purity; this is a further reason for preferring to adopt the Δε value of —2.0, derived above.]

Further comment is now possible on the nor-ketones (57) and (58) from (+)-β-cedrene [32] and its 2,5-di-*epi*-isomer.[29] In view of the report,[29] based on *X*-ray crystallography, that the 9β-bromo-derivative (60) of the latter compound has its cyclohexanone ring in the twist-boat conformation, values of Δε were calculated by use of equation (iii) for both the ' chair ' and the ' twist-boat ' conformation of each of the unsubstituted ketones. With the assumption that the *gem*-dimethyl groups (C-14 and C-13, respectively) of ' β '-axial and ' β '-equatorial character) contribute a total of +0.6 unit, as in the ' homocamphor ' series discussed above, both nor-ketones were calculated to have Δε = +3.2 in their ' chair ' conformations. The ' twist-boat ' conformations gave Δε = —0.1 for the β-cedrene derivative (57) and Δε = —2.8 for the 2,5-di-*epi*-compound (58). The difference results from different torsion angles (ω), imposed by the configurations at C-5. These results support the view that the β-cedrene derivative (57) (found: Δε +2.0) exists largely if not wholly with its cyclohexanone ring in the chair conformation. A Dreiding model shows that compression between 9β-H and the nearer 6-methyl group (C-14) is not a serious destabilising factor in this isomer. The 2,5-di-*epi*-compound (58) (Δε —0.7), how-

[31] G. Hugel, L. Lods, J. M. Mellor, and G. Ourisson, *Bull. Soc. chim. France*, 1965, 2894.

[32] M. Fétizon, Y. Le Bigot, and J. Rens, *Tetrahedron*, 1973, **29**, 2815.

ever, appears to have a substantial proportion in the ' twist-boat ' conformation, corresponding to the preferred conformation of the 9β-bromo-derivative, as a

(51)

(52)

(53)

(54)

(55)

(56)

(57)

(58) R = H
(60) R = Br

(59)

result of the strong compression between 9β-H and C-14 in the chair conformation (H · · · H distance <1.3 Å, from a Dreiding model).

Miscellaneous Ketones.—Discussion so far has been limited to ketones which satisfy the two essential requirements for a detailed empirical analysis: (1) they belong to classes represented by a reasonably large number of compounds with different substitution patterns; and (2) their structures ensure reasonably rigid conformations, so that pairwise comparisons offer a good prospect of providing useful ' group increments '. Many ketones exist, however, which do not fulfil either of these requirements. These miscellaneous ketones served as useful tests of the validity and scope of the generalisations reached in our systematic analysis covering the main groups of compounds. Moreover, the study of a number of ketones with different degrees of strain led to a new empirical (and approximate) correlation amongst the varying numerical values of k_C, needed for calculation of $\Delta\varepsilon$, and the strain energies of molecular frameworks.

The examples given below were found in Crabbé's compilation of chiroptical data,[33] or in the more recent literature, or come from our own measurements. The compounds were chosen to contain neither unsaturation nor heteroatoms sufficiently close to the carbonyl chromophore to cause major additional perturbation.

Uncertainty as to conformer populations was the main difficulty affecting studies of, for example, acyclic ketones and ketones in rings of seven or more carbon atoms (*e.g.* A-homo- or B-homo-steroids). Bicyclo[2.2.2]octan-2-ones (69) and bicyclo[3.3.1]nonanones (62) are among bridged-ring ketones which are more flexible than the classes discussed above, by virtue of the sizes of their component rings. Compounds with sufficient regularity of structure are treated by the simplest method of summing increments [2,3] due to ' α '- and ' β '-substituents or primary zig-zags. Where this simple treatment is inadequate, the ' torsion angle ' concept expressed in equation (iii) is used, with additional allowance for extended zig-zags as required.

Ketones treated by simple summation of group increments. The examples which follow illustrate the range of applicability of simple calculations of the types described in previous papers, when strain effects are likely to be small. Only conclusions with brief comments are presented here. More detailed discussion of topics indicated by an asterisk is available as Supplementary Publication No. SUP 22087 (9 pp.).†

Bicyclo[3.2.1]octan-3-one: * the 9-oxo-norcedrane derivative (61); Δε —0.46;[32] Δε (calc.) —0.5 (β-equatorial 1,2-bond [2]).

Bicyclo[3.3.1]nonan-2-one (62): * 2β-hydroxyclovan-9-one[34] (63), $a = -77$,[35] whence Δε ≈ —1.9; Δε(calc.) —1.9 (' α '-axial C–C bond [2]).

† For details of Supplementary Publications see Notice to Authors no. 7, in *J.C.S. Perkin I*, 1976, Index issue.

[33] P. Crabbé, 'Application de la Dispersion Rotatoire Optique et du Dichroïsme Circulaire Optique en Chimie Organique,' Gauthier-Villars, Paris, 1968, ch. 5.

Bicyclo[3.3.1]nonan-9-one: * A-nor-3(5 ⟶ 6)*abeo*-steroids (64).[36] Values of Δε seem wholly due to effects of β-substitution (at C-3) by polar groups, paralleling those of adamantanone derivatives.[37] Rings C and D are without measurable effect. There is no extended primary zig-zag of bonds.

(61)

(62)

(63)

(64)
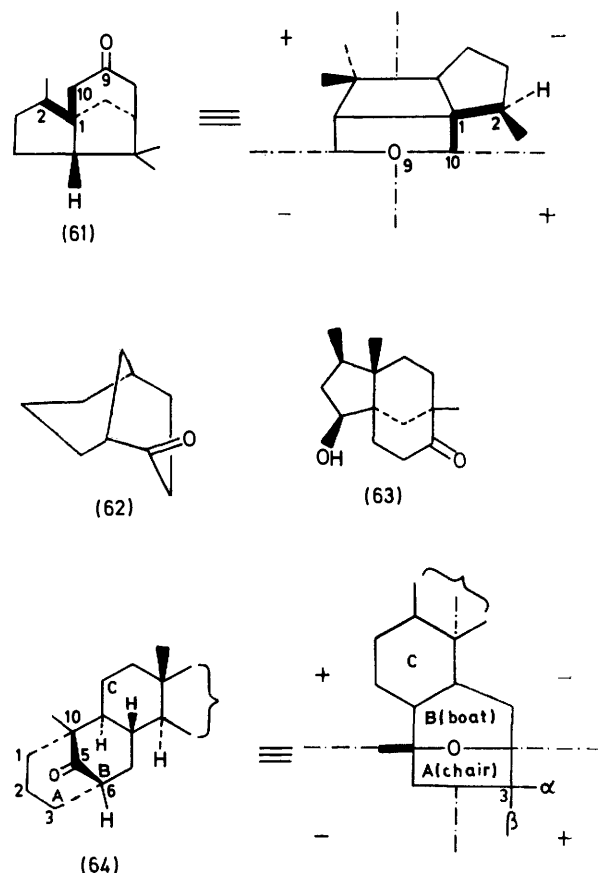
(1S,4S,7R,10S)-*Tricyclo[5.2.1.0⁴,¹⁰]decan-2-one* * (65) (Δε +2.9):[38] if a planar cyclopentanone ring is assumed, the substituent effect of the 1,9-bond is calculated as +1.2 (1.6 sin² 60°). A twisted conformation (66) with P-helicity would give enhanced positive c.d., and appears to be less strained than either the planar or M-helical form.

Tricyclo[7.2.1.0¹,⁵]undecan-2-one: * represented by the ketone (67) ($a = -104$; Δε *ca.* —2.6), which was derived from zizanoic acid (68).[39] The compound (67) can be regarded as a *trans*-hexahydroindan-1-one with an ' α '-axial substituent. The calculated value of Δε is —2.2 (—3.7 for the hexahydroindanone and +1.5 for the ' α '-axial substituent [3]).

Ketones requiring consideration of torsion angles and

[34] D. H. R. Barton and A. Nickon, *J. Chem. Soc.*, 1954, 4665.
[35] Measured in this Department; sample kindly provided by Professor Sir Derek Barton, F.R.S.
[36] G. Snatzke and K. Kinsky, *Tetrahedron*, 1972, **28**, 289.
[37] G. Snatzke and G. Eckhardt, *Tetrahedron*, 1970, **26**, 1143.
[38] L. A. Paquette, W. B. Farnham, and S. V. Ley, *J. Amer. Chem. Soc.*, 1975, **97**, 7273.
[39] F. Kido, H. Uda, and A. Yoshikoshi, *Tetrahedron Letters*, 1968, 1247.

bond strain. (i) *Bicyclo*[2.2.2]*octan-2-ones* (69).[40,41] Simple substituted derivatives as well as bridged steroid and diterpene ketones with this structural component are known (Table 7); Δε values are generally rather small (0.2—0.7 units).

TABLE 7

C.d. data for compounds containing a
bicyclo[2.2.2]octan-2-one unit

	Δε	Ref.
(1S,2S,4R)-2-Carboxymethylbicyclo[2.2.2]-octan-6-one (70)	+0.6	a
19-Oxo-3β,19-methylene-5α-androstane-3α,17β-diol (71)	−0.2	b
17-Noratisan-15-one (72)	−2.0	c, d
17-Noratisan-16-one (73)	+0.7	c, d
ent-17-Noratisan-16-one (74)	−0.28	e
ent-Methyl 16-oxo-17-noratisan-18-oate (75)	−0.51	e
ent-Methyl 3β-acetoxy-16-oxo-17-noratisan-18-oate (76)	−0.48	e
17-Noratisan-13-one (77)	ca. +0.8 *	d
Methyl 13-oxo-17-noratisan-18-oate (78)	ca. +0.8 *	d

* Only first extrema (o.r.d.; $[\phi]_{308}$) reported: estimates here are $2 \times [\phi]_{308}/40.28$.

a Refs. 46 and 47. *b* Ref. 41. *c* Ref. 33, p. 242. *d* Ref. 40. *e* Ref. 33, p. 190.

The bicyclo[2.2.2]octane framework has no clearly defined energy minimum, but appears able to oscillate between two twisted conformations with torsion angles *ca.* ±12° about the CH_2–CH_2 bonds.[42,43] Bicyclo[3.2.2]-nonane, and other hydrocarbons with bridges of two or

Table 7, apparently does little to confer rigidity. It is generally difficult or impossible to decide, by inspection of a model, which is likely to be the energetically preferred conformation.

Calculations for bicyclo[2.2.2]octan-2-one (69) itself, based upon equation (iii) with $k_C = -4.6$ (*i.e.* assuming no significant strain) indicate that each 1° of clockwise rotation of bonds at C-4 with respect to those at C-1, as viewed from C-1 (*P*-helicity), would produce a c.d. increment of *ca.* −0.3 unit. This value is little affected by using a strain-modified value of k_C (*cf.* p. 2147). Conformational uncertainties concerning actual compounds preclude an experimental check on this result at present.

One diterpenoid compound, 17-noratisan-15-one (72) (Δε −2.0) deserves comment (*cf.* Crabbé[45]). The structure of the 15-one includes a ' primary zig-zag ', which extends for three bonds outside the ' bicyclo[2.2.2]octan-2-one ' component. Irrespective of any twist of the bicyclo-octanone unit, the zig-zag (3rd, 4th, and 5th bonds) lies in a ' negative ' octant, and from data for extended decalones[2] should contribute Δε *ca.* −1.6. The residual part of the experimental value, amounting to *ca.* −0.4 unit, agrees in magnitude with values for other bicyclo[2.2.2]octan-2-ones (Table 7) which are not extended by a primary zig-zag. The sign and magnitude of this residual part of the c.d. effect for the 15-oxo-compound (72) appear to correlate with a preference for

(65)   (66)

(67)   (68)
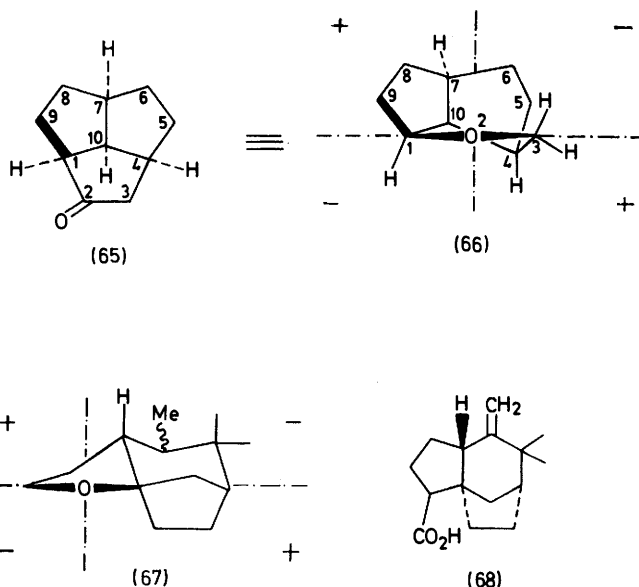
more carbon atoms[44] also appear to be free to twist (*cf.* also bicyclo[2.2.1]heptane derivatives; p. 2132). The ketone bicyclo[2.2.2]octan-2-one (69) should similarly have no clear conformational preference.[22] Even fusion to other ring systems, as in the steroid and terpenoids in

the twisted conformation with *P*-helicity (Figure 5), which seems from a model to minimise compression of the 10β-methyl group. This may be an erroneous conclusion, however, for the isomeric 16-oxo-compound (73) appears to require the same sense of twist to minimise internal strain, yet gives a positive c.d. curve. The need

[40] P. Crabbé, L. H. Zalkow, and N. N. Girotra, *J. Org. Chem.*, 1965, **30**, 1678.
[41] F. M. Hauser, A. Philip, and F. I. Carroll, *J. Org. Chem.*, 1973, **38**, 3696.
[42] O. Ermer and J. D. Dunitz, *Chem. Comm.*, 1968, 567; *Helv. Chim. Acta*, 1969, **52**, 1861.

[43] A. Yokozeki, K. Kuchitsu, and Y. Morino, *Bull. Chem. Soc. Japan*, 1970, **43**, 2017.
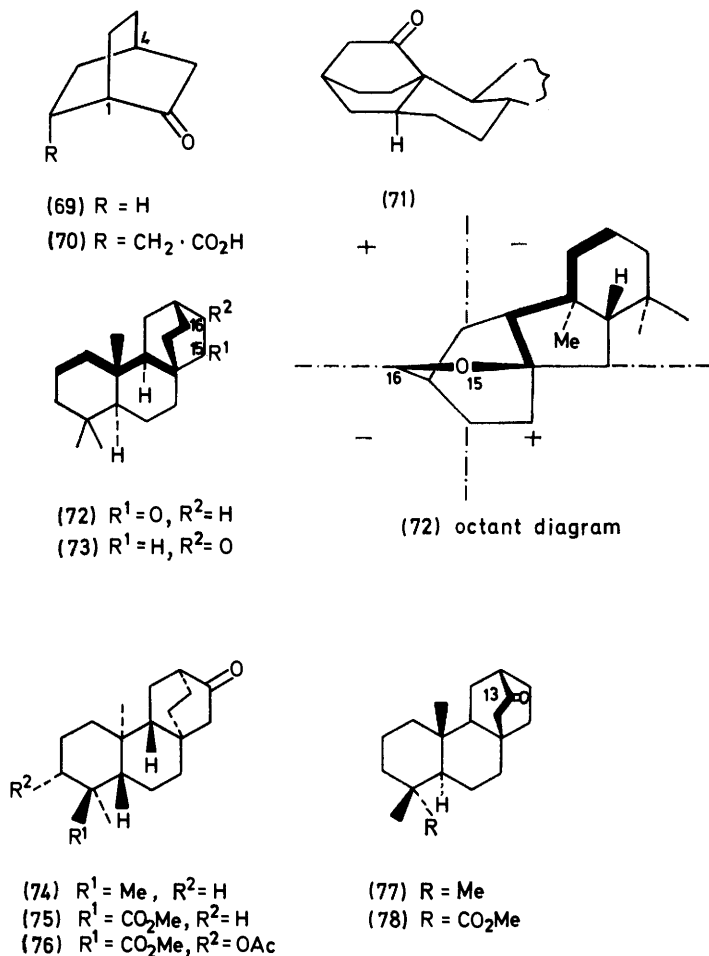[44] E. M. Engler, L. Chang, and P. von R. Schleyer, *Tetrahedron Letters*, 1972, 2525.
[45] Ref. 33, pp. 242—243.

for further study of these and related compounds is indicated.

(ii) *Tricyclo*[4.4.0.0³,⁸]*decan*-2-*one* [' twistan-2-one ' (79); Δε +10.6].[46] The twistane framework is a rigid one. Calculations [equation (iii)] of Δε for twistan-2-one,

respect to the twisted ring. A model suggests that the bonds in the two-carbon bridges are highly strained, despite being formally parts of six-membered rings. Not surprisingly, values of Δε (Table 3) calculated on the basis of either no strain ($k_H = -4.6$) or slight strain (k_C

(69) R = H
(70) R = CH₂·CO₂H

(71)

(72) R¹ = O, R² = H
(73) R¹ = H, R² = O

(72) octant diagram

(74) R¹ = Me, R² = H
(75) R¹ = CO₂Me, R² = H
(76) R¹ = CO₂Me, R² = OAc

(77) R = Me
(78) R = CO₂Me

which has C_2 symmetry, were therefore included in Table 3. The very large positive value of Δε does not correlate with the helicity of the central twisted cyclohexanone
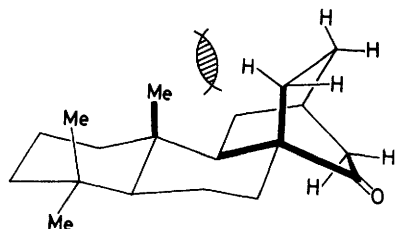

FIGURE 5   Twisting (P-helicity) of the ' bicyclo[2.2.2]octan-2-one ' unit of 17-noratisan-15-one (72) to minimise non-bonding interactions

ring, so must be derived[47,48] largely from the two (3,4- and 1,10-) bonds which are of ' α '-quasiaxial character with

= −1.9) [entries (a)—(c)] were negative, as implied by the helicity of the central cyclohexanone ring. Positive values of k_C [entries (d) and (e)] were required to generate the experimental value of Δε from equation (iii). The implication is that the two ' α '-quasiaxial C–C bonds are highly strained, their positive k_C values being among the largest consignate bond effects yet found, either relative to hydrogen or in absolute terms. Entry (d) ($k_C = +2.7$ for C-4 and C-10) represents a consignate substituent effect (δk_C) relative to hydrogen of 8.9 units, larger even than those estimated[4] for ' α '-axial amino- or iodo-substituents (see discussion, p. 2147).

(iii) *Tricyclo*[4.4.0.0³,⁸]*decan*-4-*one* [' *twistan*-4-*one* ' (80); Δε +0.88].[49] This isomer lacks the symmetry of the 2-oxo-compound, and presented a major problem.

[46] K. Adachi, K. Naemura, and M. Nakazaki, *Tetrahedron Letters*, 1968, 5467; for revised absolute configuration of twistan-2-one, see refs. 47 and 48.
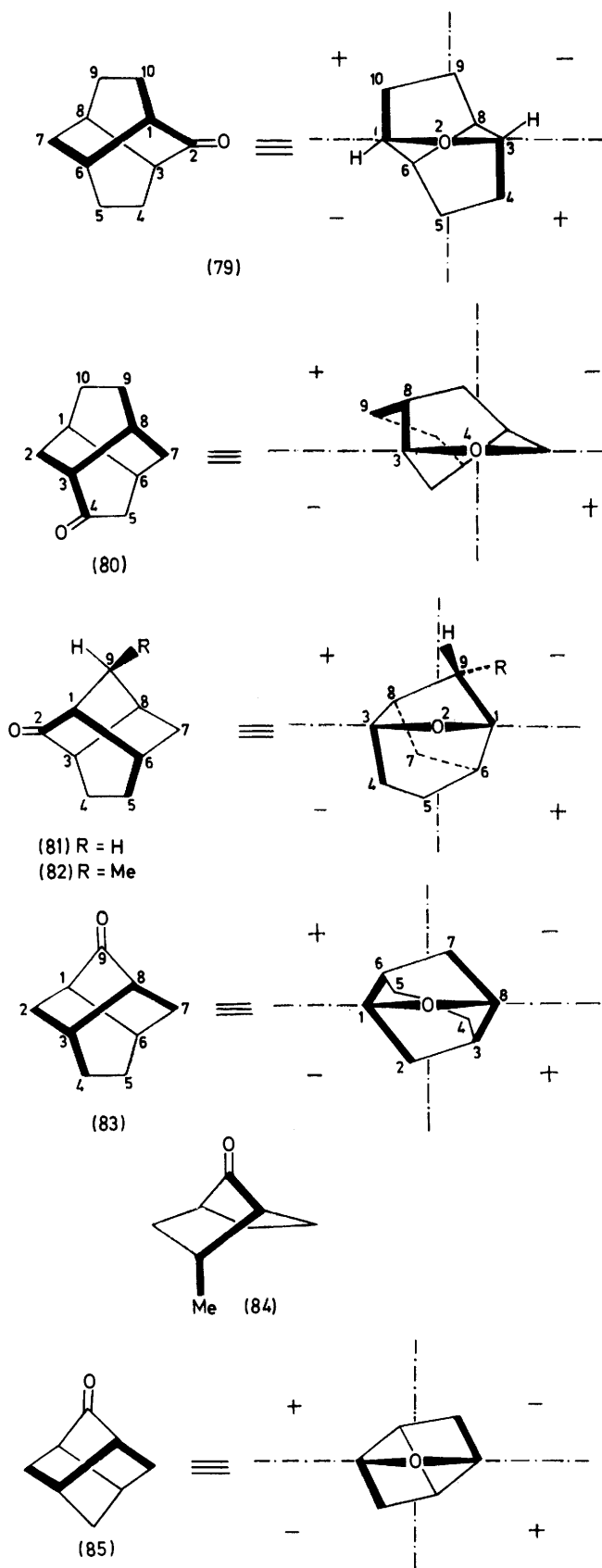
[47] G. Snatzke and F. Werner-Zamojska, *Tetrahedron Letters*, 1972, 4275.

[48] M. Nakazaki, K. Naemura, and S. Harita, *Bull. Chem. Soc. Japan*, 1975, 48, 1907.

[49] M. Tichý, *Coll. Czech. Chem. Comm.*, 1974, 39, 2673.

Calculated values of $\Delta\varepsilon$ (Table 3) failed to reproduce the experimental value even when the assumptions regarding strain distribution in twistan-2-one were adopted. An unreasonably large positive value for k_C was required to generate the only positive value of $\Delta\varepsilon$ listed [entry (d)]. The main factor not so far evaluated for this compound is the effect of the high degree of strain in the 8,9-bond, which is part of one of the two-carbon bridges, and was included in calculations of $\Delta\varepsilon$ as the second bond of a primary zig-zag extending into a 'positive' octant. It seems necessary to allot an unusually large positive 'β'-substituent contribution of ca. $+4$ units (instead of $+0.7$ unit [2]) to the 8,9 bond in order to 'calculate' a positive value of $\Delta\varepsilon$ matching that found experimentally. Some justification for this extra large substituent effect is presented on p. 2147.

(iv)   (1R,3R,6S,8R)-Tricyclo[4.3.0.0^{3,8}]nonan-2-one [(−)-twist-brendan-2-one (81); $\Delta\varepsilon$ −4.5].[50] This ketone has a 'nor-twistane' skeleton, and must be subject to even greater strains than twistan-2-one. Like the latter compound, the sign of its Cotton effect is contrary to expectation on the basis of the P-helicity of the 'central' cyclohexanone component, but instead reflects major consignate contributions from the outer bridging parts of the structure.[48] A calculation [equation (iii)] using torsion angles estimated from a Dreiding model gave $\Delta\varepsilon = -3.6$ when k_C was allotted the same strongly consignate value of $+2.7$ as had been required to generate the correct value of $\Delta\varepsilon$ for twistan-2-one. An even larger value of k_C ($+3.8$) gave the correct value of $\Delta\varepsilon$ (-4.5) for twist-brendan-2-one, consistent with the enhanced strain in this compound. The 9-(anti-) methyl derivative (82) of twist-brendan-2-one, however ($\Delta\varepsilon$ −2.4),[48] unexpectedly implies a positive increment for the methyl substituent, despite its being almost ideally placed on a zig-zag path in a 'negative' octant. No explanation is apparent.

(v)   (1R,3R,6R,8R)-Tricyclo[4.3.0.0^{3,8}]nonan-9-one-[twist-brendan-9-one (83); $\Delta\varepsilon$ −0.6].[48] This presents an octant diagram resembling that for a cycloheptanone ring, held firmly in an exaggerated twist-chair conformation (cf. p. 2140) by the two methylene bridges. As a cycloheptanone of P-helicity, its Cotton effect might be expected to be strongly positive (cf. p. 2141). The strained and quasiaxial C_α–C_β bonds (1,2- and 8,7-bonds) of the two 'bridges', however, lie in 'negative' octants, and their consignate effects clearly outweigh the positive contribution of the cycloheptanone ring. In this case, equation (iii) with a very small positive value of k_C (ca. $+0.6$) gives the correct small negative value of $\Delta\varepsilon$.

Twist-brendan-9-one (83) has also been compared[48] with 2-endo-methylbicyclo[2.2.1]heptan-7-one (84), which exhibits $\Delta\varepsilon$ $+0.6$,[16] following the simple Octant Rule. Here the methyl group is imperfectly located on a primary zig-zag bond path, so would be expected to make a positive contribution possibly rather less than that of a 'β'-equatorial methyl group in a cyclohexanone. A

(79)

(80)

(81) R = H
(82) R = Me

(83)

Me   (84)

(85)

[50] K. Naemura and M. Nakazaki, Bull. Chem. Soc. Japan, 1973, **46** 888.

slight twisting of the bicyclic framework, in the sense opposite to that enforced in twist-brendan-9-one, would partially relieve torsional and Me,6-*endo*-H strains, and may make a small contribution to the positive Cotton effect.

(vi) (−)-(1R,3R,5R,7R)-*Tricyclo*[3.3.0.0³,⁷]*octan-2-one* (85) (Δε −3.2).[51] This compound is related to twistan-2-one (79) but must be even more strained by having one- rather than two-carbon bridges across the twisted cyclohexanone ring. The negative sign of its Cotton effect was used by the original authors [51] to assign the absolute configuration, on the arbitrary basis that the Octant Rule is applicable to the ' outer ' rings as for twistan-2-one and twist-brendan-2-one, but not to the ' inner ' twisted cyclohexanone of any of this family of compounds. Application of equation (iii) gave the correct value of Δε when k_C was given the value +2.9; this is close to the value (+2.7) required for twistan-2-one but rather less than that (+3.8) for twist-brendan-2-one. Evidently the present correlation of k_C with the degree of strain suggested by Dreiding models is only approximate.

(vii) (1S,5S)-*Bicyclo*[3.3.0]*octan-3-one* (86) (Δε +7.0) [52] and (1S,5S)-*Bicyclo*[3.2.0]*heptan-3-one* (87) (Δε +9.9).[52,53] These ketones are related to *trans*-bicyclo[4.3.0]nonan-8-one [*trans*-hexahydroindan-2-one (88)] but have smaller rings fused to the cyclopentanone ring. Computed atomic co-ordinates [52] imply that twisting of the cyclopentanone ring increases as the adjoining ring is reduced in size. Dreiding models also reveal this trend, which is accompanied by considerably increased strain in the smaller-ring compounds. The large values of Δε reflect the increased twisting and strain, the combined effects

(86)   (87)

(88)
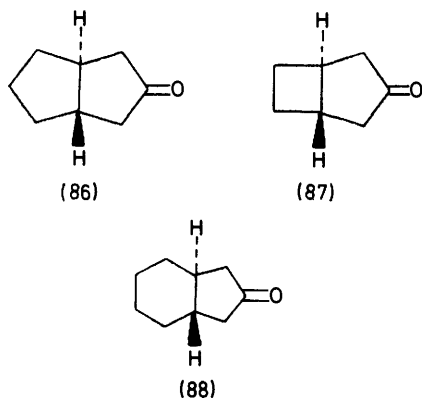
being almost to double the value of Δε for bicyclo-[3.2.0]heptan-3-one as compared with that of *trans*-hexahydroindan-2-one. Calculations of the type used in this paper failed to reproduce the experimental

values of Δε from the computed geometries of these molecules unless very large positive values were assigned to k_C.†

(viii) *Cyclobutyl ketones.** The cyclobutyl ketone unit is a component of a number of 4,5-ethano-steroids and related compounds of bicyclo[4.2.0]octan-2-one type (89)—(91); it is also found in the 2,19-cyclo-steroid (92) and the norpinane derivative (93), compounds of bicyclo-[3.1.1]heptan-2-one type (Table 8) (see also D-norpregnan-20-ones, p. 2144).

TABLE 8

C.d. data for cyclobutyl ketones

	Δε	Refs.
4α,5-Ethano-3-oxo-5α-steroid (89)	+0.64	a
4α,5-Ethano-3-oxo-5β-steroid (90)	+2.42	a
4β,5-Ethano-3-oxo-5β-steroid (91)	−0.9	a
2β,19-Cyclo-3-oxo-5α-steroid (92)	+0.5	b
(1R,5S)-6,6-Dimethylbicyclo[3.1.1]heptan-2- one (' nopinone ') (93)	+1.77	c

ᵃ Ref. 54.   *ᵇ* Ref. 33, p. 238.   *ᶜ* Ref. 55.

(89) 4α,5α
(90) 4α,5β
(91) 4β,5β

(92)

(93)
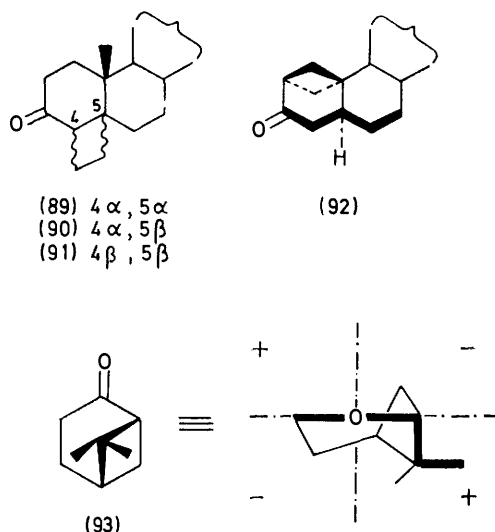
Examination of compounds (89)—(91) of bicyclo[4.2.0]-octan-2-one type is complicated by conformational ambiguities.‡ A 4α,5-ethano-3-oxo-5α-steroid (89) appears to be at least partly in the conformation with a twist or boat ring A, from n.m.r. evidence.[54] A 4α,5β-ethano-steroid (90) is very highly strained by the *trans*-fusion of cyclohexanone and cyclobutane rings. Very large values of Δε (up to +8 for some related compounds [54]) are in accordance with a highly twisted conformation, and extreme strain. Attempts at quantitative prediction of c.d. data were unrewarding.

(1R,5S)-6,6-Dimethylbicyclo[3.1.1]heptan-2-one (' nopinone ') (93) probably exists mainly in the conformation depicted, which would account for its positive c.d. (Δε +1.77).[55] The *exo*-methyl group is ' β '-quasiequatorial

[51] M. Nakazaki, K. Naemura, and N. Arashiba, *J.C.S. Chem. Comm.*, 1976, 678.

[52] J. C. A. Windhorst, Thesis, Leiden, 1975.

[53] J. C. A. Windhorst, *J.C.S. Chem. Comm.*, 1976, 331.

[54] G. R. Lenz, *Tetrahedron*, 1972, **28**, 2195.

[55] Westfield College measurement; sample provided by Dr. J. M. Coxon, Canterbury, New Zealand.

with respect to the cyclohexanone ring, and presumably makes a positive contribution. Calculations based upon equation (iii) give the correct value of $\Delta\epsilon$ if a large positive (highly consignate) value is adopted for k_C (ca. +4.2). The positive sign is compatible with the high strain in the cyclobutane ring, but since the conformation (93) may not be the only one present, the suggested value of k_C is regarded only as a crude estimate. The 2β,19-cyclo-3-oxo-5α-steroid (92) contains a bicyclo-[3.1.1]heptan-2-one unit quasienantiomeric with that of ' nopinone,' but additionally has a primary zig-zag running from C-4 to C-7 (three bonds). Calculation of $\delta\Delta\epsilon$ for the bicycloheptanone component by use of equation (iii), with $k_C = +3.5$ (p. 2146), gives $\delta\Delta\epsilon = -0.5$. Addition of the contribution [2] of a three-bond primary

normal orbital hybridisation in the four-membered ring.[56] Several attempts to interpret the chiroptical behaviour of cyclopropyl ketones have been reported.[57] These compounds give indisputable evidence of strong conjugation between the cyclopropyl and carbonyl systems, which is associated with the special character of the bonding and orbital hybridisation of the cyclopropane ring.[58] It proved impossible to bring cyclopropyl ketones within the present treatment, even by making allowances for high strain.

Ketones with non-rigid conformations. (i) *Cycloheptanone derivatives.* The cycloheptane ring exhibits pseudorotation between conformers which differ little in free energy.[59,60] Two pseudorotation sequences have been distinguished (Figure 6). The TC and TB conformations
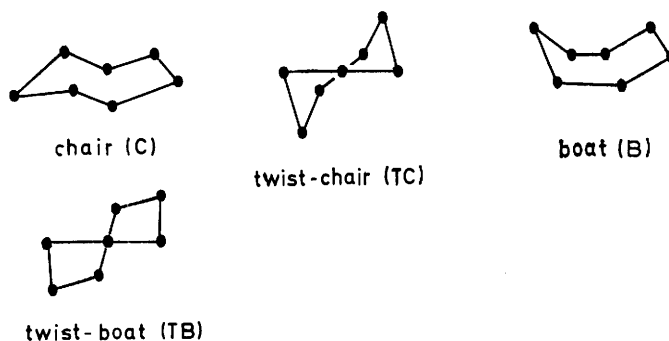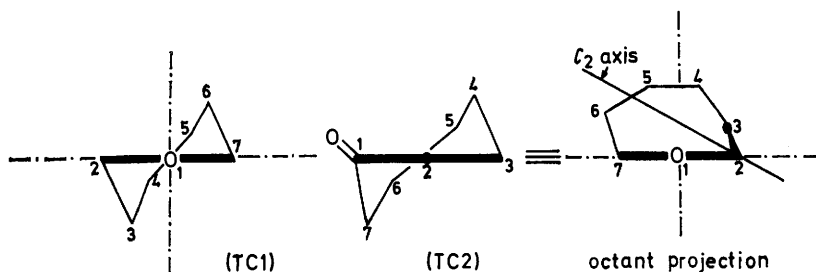

FIGURE 6 Conformations of cycloheptane

FIGURE 7 Minimum-energy conformations of cycloheptanone

zig-zag (ca. +1.6) would give $\Delta\epsilon = +1.1$. The zig-zag, however, has a somewhat ' flattened ' orientation with respect to the carbonyl group. Correction (cf. p. 2146) for this orientation gives a reduced zig-zag contribution of +1.1 unit (based on $\omega = +140°$; p. 2146), and a total value of $\Delta\epsilon = +0.6$ (found +0.5). The closeness of this agreement must be fortuitous, but the result helps to validate this treatment of bicyclo[3.1.1]heptan-2-ones. The use of a large positive value of k_C, corresponding to strongly consignate behaviour of bonds of the cyclobutane ring, seems justified, but attempts to calculate $\Delta\epsilon$ are useful only when the conformation is predictable.

Cyclobutyl ketones may share in some measure the peculiarities of cyclopropyl ketones, in view of the ab-

lie at energy minima for the respective sequences. For cycloheptane itself the TC conformation is estimated [59] to lie ca. 1—1.2 kcal mol⁻¹ below the C conformation, and ca. 0.6 kcal mol⁻¹ below TB.

Substituents, or fusion of a cycloheptane to further rings, may restrict pseudorotation to only a part of the circuit. Allinger and his co-workers [22] have calculated by the ' force-field ' method that the presence of a carbonyl group causes cycloheptanone to exist predominantly in those forms (TC_1 or TC_2) in which the carbonyl group is either at, or adjacent to, the ring position which lies on the two fold symmetry axis (Figure 7). We adopt the convention [61,62] that the twofold axis of a TC ring is

[56] R. M. Moriarty, *Topics Stereochem.*, 1974, **8**, 271.

[57] D. A. Lightner and D. E. Jackman, *Tetrahedron Letters*, 1975, 3051, and refs. therein.

[58] C. A. Coulson and W. E. Moffitt, *Phil. Mag.*, 1949, **40**, 1; P. J. Hay, W. J. Hunt, and W. A. Goddard, *J. Amer. Chem. Soc.*, 1972, **94**, 8293.

[59] D. F. Bocian, H. M. Pickett, T.-C. Rounds, and H. L. Strauss, *J. Amer. Chem. Soc.*, 1975, **97**, 687.

[60] N. M. J. Flapper and C. Romers, *Tetrahedron*, 1975, **31**, 1705.

[61] J. B. Jones, J. M. Zander, and P. Price, *J. Amer. Chem. Soc.*, 1967, **89**, 94.

[62] J. B. Hendrickson, *J. Amer. Chem. Soc.*, 1961, **83**, 4537; *Tetrahedron*, 1963, **19**, 1387.

denoted by a subscript (thus: TC_x) where x is the locant of that carbon atom which lies on the twofold axis. TC_1 was estimated [22] to be destabilised by only 0.25 kcal mol^{-1} relative to TC_2, so that both conformations should be substantially populated. Jones and his co-workers [61] reached a similar conclusion from study of chiroptical and other physical properties of some oxo-A-homo-steroids. As the energy barrier between TC_1 and TC_2 is small,[59] the instantaneous conformer population will be a broad distribution about the energy minima, rather than a concentration at the minima.

Attempts to calculate $\Delta\varepsilon$ for cycloheptanone derivatives were limited to the preferred TC conformations. Values of $\Delta\varepsilon$ calculated by use of equation (iii) for the full TC/C pseudorotation circuit of cycloheptanone itself are indicated in Figure 8. The narrow shaded zone between the two curves represents the uncertainty arising from use of the alternative values of -1.9 or -4.6 for k_O, assuming that the strain energy per bond lies between the values for a cyclopentanone and a cyclohexanone.[28]

The preferred conformations of TC_1, TC_2, or TC_7 type are contained within the vertical shaded strips of Figure 8. Because the free energies of these conformations [59] encompass a narrow band of only ca. 1 kcal mol^{-1}, the observed value of $\Delta\varepsilon$ cannot approach the positive or negative maxima indicated in Figure 8, but will be the
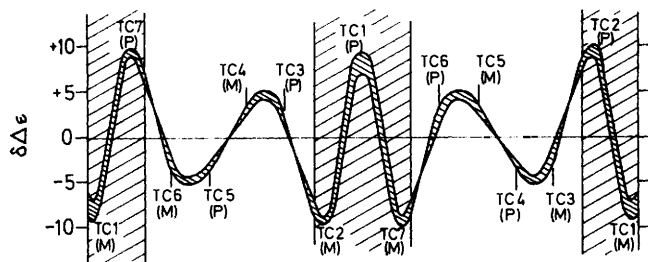

FIGURE 8 Calculated c.d. contributions ($\delta\Delta\varepsilon$) for cycloheptanone ring over the TC pseudorotation circuit (helicity of ring at each TC conformation indicated in parentheses); for explanation of shading, see text.

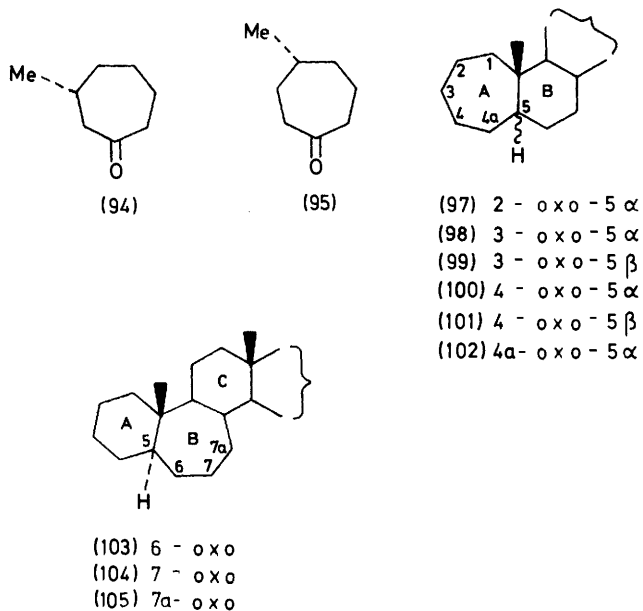weighted mean for the conformer distribution, and so of relatively small magnitude.

A-Homo- and B-homo-oxo-steroids (Table 9) were each examined in the single TC_1 conformation and in the two conformations of TC_2 type (cycloheptanone numbering; where it is helpful to indicate both cycloheptanone and steroid numbering, the latter is indicated by a subscript in parentheses: e.g. $TC_{1(3)}$ is used for that conformation of a 3-oxo-A-homo-steroid in which the oxogroup lies on the twofold axis of the TC ring).

Relative stabilities of TC_1 and TC_2 conformers can be influenced by several features not present in simple cycloheptanones.† The columns (Table 9) headed 'special features' indicate: (i) those structural features which tend to destabilise (or stabilise) the particular conform-

† See Supplementary Publication.

[63] C. Djerassi, B. F. Burrows, C. G. Overberger, T. Takekoshi, C. D. Gutsche, and C. Chang, *J. Amer. Chem. Soc.*, 1963, **85**, 949.

ation, and (ii) any additional ' β '-equatorial bonds or extended primary zig-zags for which allowance has been made in calculating $\Delta\varepsilon$. ' Octant ' diagrams (Figure 9) for compounds (97) and (103) illustrate the essential

(94) (95)

(97) 2 - o x o - 5 α
(98) 3 - o x o - 5 α
(99) 3 - o x o - 5 β
(100) 4 - o x o - 5 α
(101) 4 - o x o - 5 β
(102) 4a- o x o - 5 α

(103) 6 - o x o
(104) 7 - o x o
(105) 7a- o x o

difference between TC_1 and TC_2 conformations when viewed down the carbonyl axis.

The most significant conclusion from Table 9 is that the experimental value of $\Delta\varepsilon$ invariably has the same sign as that listed for the TC_1 conformation, although the magnitude is always much less than the value calculated for this conformation alone. Assuming for simplicity that each ketone is essentially distributed between the three conformers listed, irrespective of stabilising or destabilising factors, the experimental values of $\Delta\varepsilon$ can be reproduced tolerably well [' $\Delta\varepsilon$(calc.) '] by adopting an estimate that ca. $70 \pm 5\%$ is in the TC_1 conformation, and that the two TC_2 forms, which differ little in their calculated contributions, together account for the other $30 \pm 5\%$ of the material. This estimate, if correct, implies that the TC_1 conformer is on average ca. 0.9 kcal mol^{-1} more stable than either of the TC_2 forms, rather than 0.25 kcal mol^{-1} *less* stable, as calculated by Allinger.[22] The monocyclic $(3R)$-3-methyl-(5) and $(4R)$-4-methyl-cyclo-heptanone (96) [63] behave similarly (Table 9), although for these low-strain compounds the experimental values of $\Delta\varepsilon$ are rather better reproduced (entries in parentheses) by adopting a 65 : 35 ratio of TC_1 to $(TC_2 + TC_7)$, with an estimated free energy difference of only 0.75 kcal mol^{-1} in favour of TC_1.

(ii) *Acyclic ketones.* Uncertainties regarding conformations are greatest when the carbonyl group is in an alkyl chain which may oscillate between several conformations, e.g. in acetyl steroids, including pregnan-20-ones.[64,65] Calculations of $\Delta\varepsilon$ generally seem to have some validity

[64] Ref. 33, p. 264 *et seq.*
[65] K. M. Wellman and C. Djerassi, *J. Amer. Chem. Soc.*, 1965, **87**, 60.

TABLE 9

C.d. data and conformations of compounds containing a cycloheptanone ring

Twist-chair conformations of cycloheptanone ring

Compound type	Δε Obs.	Δε Calc.*	Type TC₂ Helicity and conformation†	Type TC₂ Special features	δΔε (calc.)	Type TC₁ Helicity and conformation†	Type TC₁ Special features	δΔε (calc.)	Type TC₇ (or TC₇′) Helicity and conformation†	Type TC₇ (or TC₇′) Special features	δΔε (calc.)	Refs.
Monocyclic												
(3R)-3-Methylcycloheptanone (95)	+1.05	+2.1 (+1.2)‡	(M) TC₂	'β'-eq. Me	−10	(P) TC₁	'β'-eq. Me	+7	(M) TC₇	'β'-eq. Me	−9	a
(4R)-4-Methylcycloheptanone (96)	−1.2	−1.9 (−1.1)‡	(P) TC₂	None	+10	(M) TC₁	None	−7	(P) TC₇	None	+10	a
Steroids												
2-Oxo-A-homo-5α-steroid (97)	+2.3	+3.5	(M) TC₂₍₁₎	10β-Me,3β-H compression; 2nd—5th bonds of (−) primary zig-zag	−11	(P) TC₁₍₂₎	10β-Me,3β-H compression; 2nd—5th bonds of (+) primary zig-zag	+9	(M) TC₂₍₃₎	2nd—5th bonds of (+) primary zig-zag	−8	b
3-Oxo-A-homo-5α-steroid (98)	−1.5 to −2.5	−1.9	(P) TC₂₍₂₎	None	+10	(M) TC₁₍₃₎	None	−7	(P) TC₂₍₄₎	None	+10	c, d
3-Oxo-A-homo-5β-steroid (99)	+1.5	+1.9	(M) TC₂₍₂₎	None	−10	(P) TC₁₍₃₎	None	+7	(M) TC₂₍₄₎	4aα-H,9α-H compression	−10	c, d
4-Oxo-A-homo-5α-steroid (100)	+2.4 to +3.0	+2.8	(M) TC₂₍₃₎	2nd + 3rd bonds of (+) primary zig-zag	−8	(P) TC₁₍₄₎	2nd + 3rd bonds of (+) primary zig-zag	+8	(M) TC₂₍₄ₐ₎	Strained ring junction; 2nd + 3rd bonds of (−) primary zig-zag	−11	c, e, f
4-Oxo-A-homo-5β-steroid (101)	−1.5	−2.1	(P) TC₂₍₃₎	'α'-face compression; 'β'-eq. bond in (−) octant	+9	(M) TC₁₍₄₎	4aα-H,9α-H compression; 'β'-eq. bond in (−) octant	−7	(P) TC₂₍₄ₐ₎	Strained bond angles; 'β'-eq. bond in (+) octant	+10	d
4a-Oxo-A-homo-5α-steroid (102)	−1.8	−3.1	(P) TC₂₍₄₎	2nd—4th bonds of (−) primary zig-zag	+8	(M) TC₁₍₄ₐ₎	4β-H,10β-Me compression; 2nd—4th bonds of (−) primary zig-zag	−8	(P) TC₂₍₅₎	Unattainable without great strain; 2nd—4th bonds of (+) primary zig-zag. 1st +2nd bonds of (−) primary zig-zag	+9	e
6-Oxo-B-homo-5α-steroid (103)	+1.5	+2.5	(M) TC₂₍₅₎	7β-H,10β-Me compression; 1st + 2nd bonds of (+) primary zig-zag	+8	(P) TC₁₍₆₎	7β-H,10β-Me compression; 'β'-eq. 10,1-bond in (+) octant; 'α'-eq. 5,4a-bond	−7	(M) TC₂₍₇₎	'β'-eq. 10,1-bond in (+) octant	−9	g
7-Oxo-B-homo-5α-steroid (104)	−3.0	−3.9	(P) TC₂₍₆₎	2nd—4th bonds of (−) primary zig-zag	+8	(M) TC₁₍₇₎	2nd—4th bonds of (−) primary zig-zag	−9	(P) TC₂₍₇ₐ₎	Bond angles strained; 2nd + 3rd bonds of (−) primary zig-zag	+8	g
7a-Oxo-B-homo-5α-steroid (105)	+3.8	+2.7	(M) TC₂₍₇₎	'β'-eq. 9,11-bond	−9	(P) TC₁₍₇ₐ₎	Strained bond angles; 'β'-eq. 9,11-bond; 'α'-eq. 8,14-bond	+7	(M) TC₂₍₆₎	Strained bond angles; 1st—3rd bonds in (+) primary zig-zag	−6	g

* Calculated value of Δε based on the empirical generalisation of 70% TC₁ and 15% each of the TC₂ and TC₄ conformations (p. 2141). † TC conformations are described as having either (M) or (P) helicity with respect to the twofold axis of the seven-membered carbocyclic ring; (M) correlates with negative sign of Δε, (P) with positive sign of Δε. ‡ Values of Δε in parentheses were obtained by assuming 65% TC₁, and 17.5% each of TC₂ and TC₇; see text.

a Ref. 6.　b Ref. 6.　c M. Ephritikhine, J. Levisalles, and G. Teutsch, *Bull. Soc. chim. France*, 1971, 4335.　c M. Ephritikhine and J. Levisalles, *Bull. Soc. chim. France*, 1971, 4331.　d Ref. 61.　e I. Levisalles and G. Teutsch, *Bull. Soc. chim. France*, 1971, 263.　f G. Snatzke, B. Zech, and F. Müller, *Tetrahedron*, 1964, 20, 2937.　g L. Kohout and I. Faikos.

for such compounds, although any good agreements with experimental data are probably fortuitous.

The 3α- and 3β-acetyl-5α-cholestanes (106) and (107) [66] are not complicated by strained bonds. Carbonyl groups generally prefer to eclipse a C–C rather than a C–H bond,[67] so each 3-acetyl compound is expected to have a pair of preferred conformations, each with one of the ring C–C bonds eclipsed. The alternative conformations

bonds radiating from C-17 are calculated to total $\delta\Delta\varepsilon$ +1.8 [from equation (iii), with $k_C = -1.9$]. Addition of the normal increment for the second to fifth bonds of a primary zig-zag ($\delta\Delta\varepsilon$ +1.5 in hexane, +1.95 in methanol) gives a total of $\Delta\varepsilon$ +3.3 (hexane) or +3.75 (methanol). With added allowance for strain in the second bond of the zig-zag (13,14-bond) by doubling its normal contribution of 0.5 (hexane) or 0.7 (methanol) the total value of
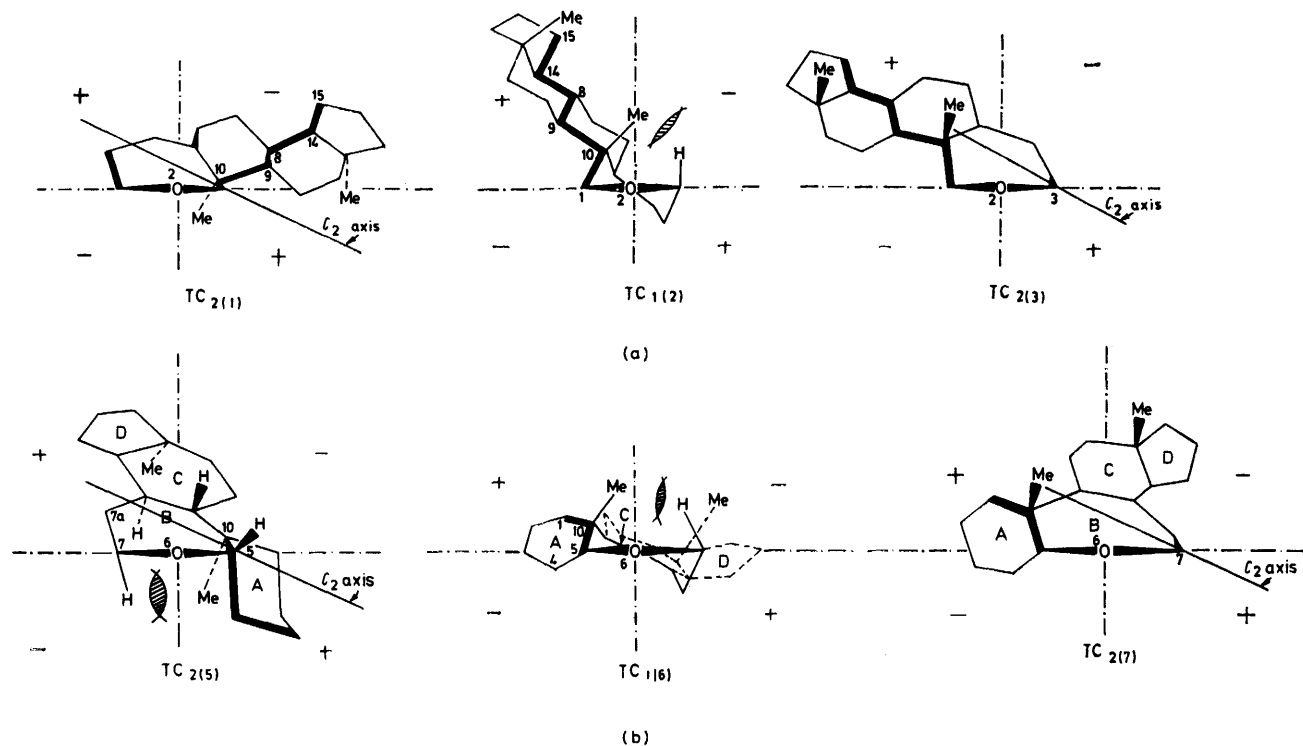

FIGURE 9   Octant diagrams for homo-steroid ketones as examples of alternative conformations for cycloheptanone rings: (a) 2-oxo-A-homo-5α-steroid (97): (b) 6-oxo-B-homo-5α-steroid (103)

(106a) and (106b) for the 3α-isomer each contain one C–C bond of ' α '-axial type (thickened), but no extended primary zig-zag. The populations of the two conformers must be closely similar, consistent with the very weak c.d. ($\Delta\varepsilon$ −0.12). The sign cannot be interpreted reliably. The two low-energy conformations (107a) and (107b) of the 3β-isomer, however, present primary zig-zags of different lengths (thickened bonds in diagrams). From published data for decalones (Table 12 in ref. 2) the calculated value of $\Delta\varepsilon$ for a 1 : 1 mixture of these conformers [107a; $\Delta\varepsilon$(calc.) = +2.85] and [107b; $\Delta\varepsilon$(calc.) = −2.1] would be +0.4, in excellent agreement with the experimental value (+0.38) (all values in hexane).

Pregnan-20-ones (108) [64,65] are complicated by having the acetyl side chain attached to a strained cyclopentane ring. Because of steric hindrance by the 13β-methyl group, however, they exist preferentially in one conformation, with the carbonyl oxygen almost but not exactly eclipsing C-16 (108a).[65,68,69] The effects of the three

Δε becomes +3.8 (hexane) or +4.45 (methanol). The 13β-methyl group approximates to ' β '-axial character; this would make only a small contribution and is therefore ignored. The calculated values of $\Delta\varepsilon$ represent upper limits, since they take no account of small populations of alternative conformations. They are therefore regarded as satisfactory by comparison with the experimental values ($\Delta\varepsilon$ +2.7 in hexane, or +3.4 in methanol). Measurements [65] at low temperature (−192°C) showed an increase (ca. 20%) in rotational strength as compared with that at +27 °C, as a consequence of ' freezing out ' of the preferred conformation.

An 18-norpregnan-20-one analogue (' 3β-acetoxy-hexanordammaran-20-one ') (109) exhibits [65] weak temperature-variable c.d. of negative sign ($\Delta\varepsilon$ ca. −0.2 at 25 °C; −1.2 at −192 °C) which has been correlated with a slight preference for the conformation (109a), although the alternative conformation [as (108a) without 13β-Me],

[66] D. N. Kirk and R. J. Mullins, *J.C.S. Perkin I*, 1974, 14.
[67] G. J. Karabatsos and D. J. Fenoglio, *Topics Stereochem.*, 1970, **5**, 167.

[68] N. L. Allinger, P. Crabbé, and G. Pérez, *Tetrahedron*, 1966, **22**, 1615.
[69] ' Atlas of Steroid Structures,' eds. W. L. Duax and D. A. Norton, Plenum, New York, 1975, p. 414.

is calculated to be of similar stability. The present method of calculation gives $\Delta\varepsilon = -3.2$ if oxygen exactly eclipses C-13 ($\omega_{13} = 0°$), falling to $\Delta\varepsilon = -0.1$ when $\omega_{13} = +30°$ [cf. (109a).] For the conformation with oxygen eclipsing C-16 ($\omega_{13} = +120°$) [cf. (108a)] a value of $\Delta\varepsilon$ ca. $+4.7$ is calculated, while at $\omega_{13} = +90°$, $\Delta\varepsilon$ is ca. $+2.7$. These latter values include allowance for the

17α-Pregnan-20-ones * (111) are similarly considered [68] to have a broad energy minimum, around a conformation of type (111a). Generally small negative values of $\Delta\varepsilon$ were calculated for $\omega_{16} > +60°$, and small positive values when $\omega_{16} < +60°$.* It has not yet been possible to reproduce the experimental value ($\Delta\varepsilon = -2.1$ in hexane, -2.6 in methanol) by calculation.
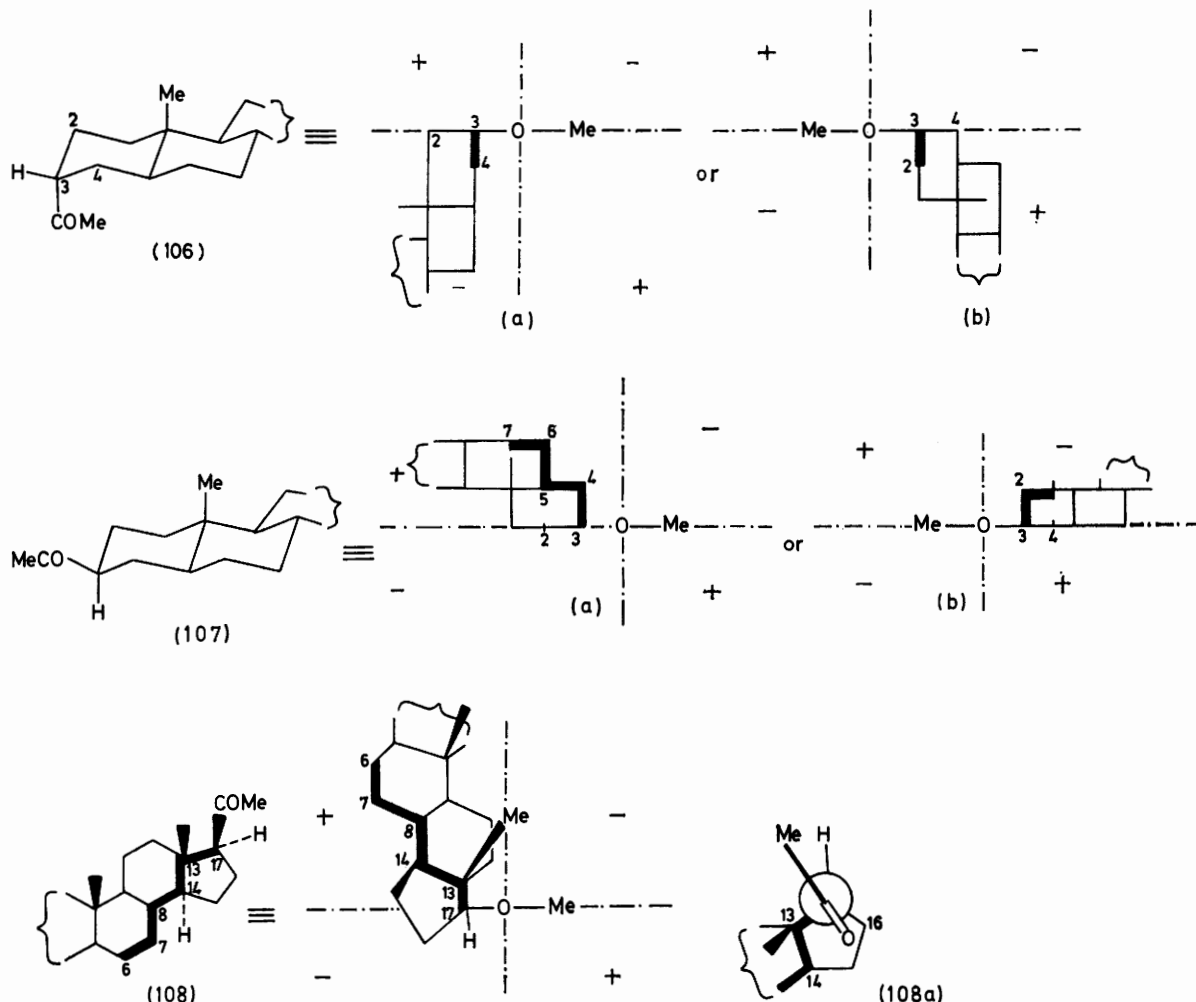
primary zig-zag extending from C-17 to C-6, which has the correct orientation only when the carbonyl oxygen is close to C-16. Clearly the present results support the earlier conclusion that (109a) is marginally the more stable conformation.

A 16β-methylpregnan-20-one * (110) gives a Cotton effect which is very weak and bisignate at room temperature, but becomes strongly negative ($\Delta\varepsilon$ ca. -1.6) at -192 °C.[70] The abnormal conformation (110a) [68] with a rather broad energy minimum, is calculated * to give small values of $\Delta\varepsilon$, which are rather sensitive to variations in ω_{13}.

14β-Pregnan-20-ones * of the 17β-series (112) exhibit positive c.d. curves ($\Delta\varepsilon$ ca. $+1.5$),[71] whereas those of the 17α-series (113) give negative Cotton effects ($\Delta\varepsilon$ ca. -1.8).[72] Dreiding models suggest that both systems should have an appreciable preference for conformations with the carbonyl oxygen close to C-16. Calculations * for the ' cyclopentyl methyl ketone ' component alone give essentially correct values of $\Delta\varepsilon$ for each isomer if ω_{16} is given values of -15 and $+15°$, respectively; the calculated magnitude of $\Delta\varepsilon$ is rather sensitive to ω.

D-Norpregnan-20-ones (114) [73] are cyclobutyl ketones, but were excluded from discussion under that heading (p.

* See Supplementary Publication.

[70] Ref. 33, p. 271—274.
[71] J. S. Baran, J. Org. Chem., 1964, 29, 527; W. Klyne, unpublished data; samples from Professor T. Reichstein, Basel.
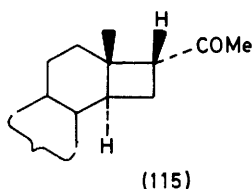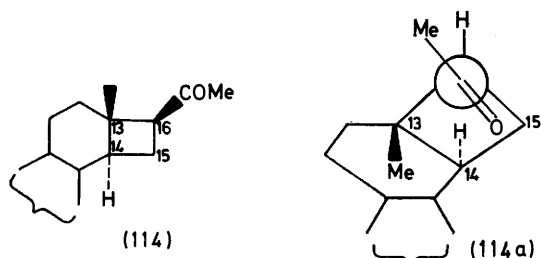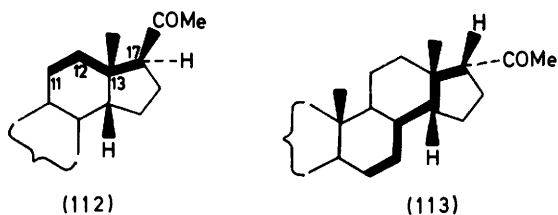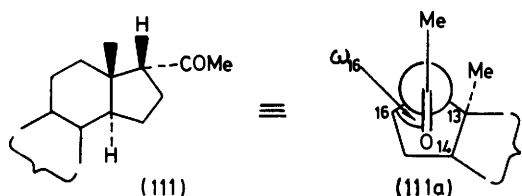
[72] H. Misuhashi, T. Nomura, and M. Fukuoka, Steroids, 1964, 4, 483; W. Klyne, unpublished data; samples from Professor T. Reichstein, Basel.
[73] Ref. 33, p. 284.

2139) because of their conformational mobility. A Dreiding model suggests that the 16β-acetyl side chain should prefer the conformation (114a) in which the C=O

(109)   (109a)

(110)   (110a)

(111)   (111a)

(112)   (113)

(114)   (114a)

(115)
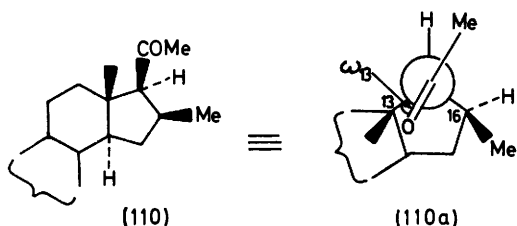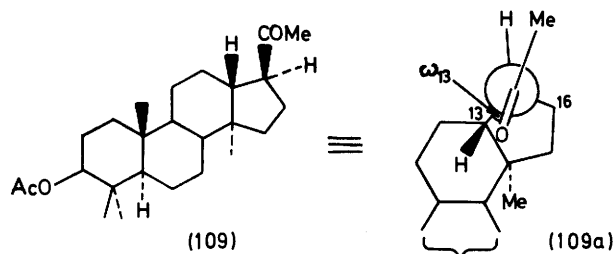
and 16,15-bonds are eclipsed, or nearly so [cf. (108)]. Calculation [equation (iii), with $k_C = +3.5$; p. 2146] gives $\Delta\varepsilon = +7$ (found: $\Delta\varepsilon = +4.5$), which again represents an upper limit since it ignores other conformers. The D-nor-16α-pregnan-20-one (115) ($\Delta\varepsilon = -2.3$)[73] appears to have a less pronounced preference for the conformation with the C=O and 16,15-bonds eclipsed (negative c.d.), which seems reasonable from a Dreiding model.

Chiroptical data are available [74] for various other acetyl-substituted compounds, including isomeric 2-acetyl and 3-acetyl A-nor-5α-steroids, and 13α-pregnan-20-ones. These compounds can be treated in the same manner as above, and in most cases give correct signs of $\Delta\varepsilon$, as they do by a conventional 'octant' treatment, but values of $\Delta\varepsilon$ cannot be calculated until conformer populations are known.

Calculations must be even less reliable for open-chain aliphatic ketones [75,76] because of their conformational complexity. Estimation of $\Delta\varepsilon$ will only be possible when conformer populations have been realiably computed.

Discussion: 'Strain' and its Effects.—Molecular strain [77] can appear in several forms; the best known are those encompassed in force-field calculations,[22,28,78] *viz.* bond stretching, bond angle bending, torsional effects, and van der Waals effects. To these must be added dipolar interactions in molecules with polar substituents. No attempt has been made in the present empirical study to distinguish amongst these various contributions to strain, although modern force-field computations allow separation of effects for chosen molecules, apparently with reasonable reliability.

In the present work, strain is assumed to accompany any deviation from the perfect geometry of a diamond framework, although it is more convenient in practice to use a cyclohexane (or cyclohexanone) ring as the strain-free reference system, neglecting the slight adjustments of geometry necessary to minimise its free energy. Unfortunately strain energies are available for only a very few of the ketones under discussion, although recent force-field calculations [22,28] have provided estimates of the total strain energies of many of the parent hydrocarbons. Where data for ketone and hydrocarbon have been compared [22] the differences are generally small as compared with the total strain energies.

In an attempt to correlate strain empirically with c.d. effects in ketones (as expressed by variations in numerical value of the coefficient k_C), the total strain energy [22,28] of the corresponding mono-, bi-, or tri-cyclic hydrocarbon framework was in each case divided by the

[74] Ref. 33, pp. 277—284.
[75] Ref. 33, pp. 262—264.
[76] L. Lardicci, P. Salvadori, C. Botteghi, and P. Pino, *Chem. Comm.*, 1968, 381.
[77] J. F. Liebman and A. Greenberg, *Chem. Rev.*, 1976, **76**, 311.
[78] J. D. Williams, P. J. Stang, and P. v. R. Schleyer, *Ann. Rev. Phys. Chem.*, 1968, **19**, 531; N. L. Allinger and M. T. Tribble, *Tetrahedron*, 1972, **28**, 1191; D. H. Wertz and N. L. Allinger, *ibid.*, 1974, **30**, 1579; C. Romers, C. Altona, H. J. C. Jacobs, and R. A.-G. de Graaft, in 'Terpenoids and Steroids,' Chem. Soc. Specialist Periodical Report, 1974, vol. 4, p. 531, and references therein.

number of C–C bonds comprising its fundamental structure, to obtain a crude estimate of the mean strain energy per bond ($\bar{S}$). Figure 10 presents a plot of k_C
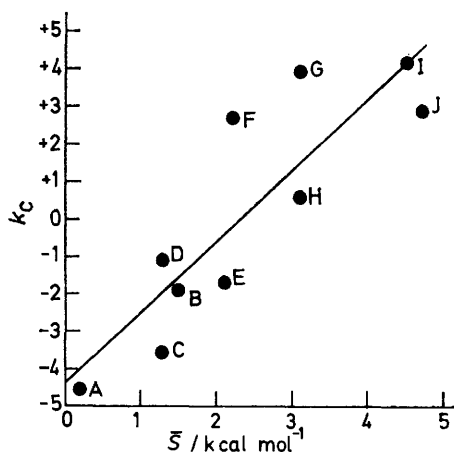

FIGURE 10 Empirical values of k_C for strained C_α–C_β bonds plotted against the mean strain energy ($\bar{S}$) per C–C bond (letters A–J refer to entries in Table 10); 'least-squares' line: $k_C = 1.9\ \bar{S} - 4.4$

values obtained in the foregoing analysis for the most strained C_α–C_β bonds in various cyclic compounds, against

10 are included in Table 10. These derived values of k_C were used in turn to obtain ' calculated ' values of $\Delta\varepsilon$, which are compared with experimental values (Table 10). The quantitative agreement is not good in every case. However, this empirical procedure may be useful in predicting approximate $\Delta\varepsilon$ values for strained and bridged-ring ketones of novel structure where no good analogy is available. Improvements in the present procedure can be expected if strain energies of individual bonds become available from force-field calculations on the molecules concerned.

Contributions of primary zig-zags. The effects of extended primary zig-zags (Figure 1) in compounds of extended-decalone type follow a consistent pattern, with $\Delta\varepsilon$ depending only upon the number of C–C bonds in the zig-zag, although being slightly modified in a predictable way by alkyl substitution.[2] The present study, however, includes compounds in which the orientation of a primary zig-zag with respect to the carbonyl group deviates markedly from the ' normal ' found in extended decalones (see below). Individual bonds of a primary zig-zag may also exert enhanced effects as a consequence of strain (p. 2125).

In order to generalise the present empirical procedure for calculation of $\Delta\varepsilon$, an attempt was made to estimate

TABLE 10

Relation between k_C [equation (iii)] and bond strain: ' strain factors ' and ' calculated ' values of $\Delta\varepsilon$

	Compound type	Mean strain per C–C bond[a] ($\bar{S}/$ kcal mol^{-1})	k_C Empirical value[b]	k_C ' Calculated ' value[c]	' Strain factor '[d] From empirical value of k_C	' Strain factor '[d] From ' calc.' value of k_C	$\Delta\varepsilon$ Obs.	$\Delta\varepsilon$ Calc.[e]
A	Cyclohexanone	0.2	−4.6	−4.0	1.0	1.4		
B	Cyclopentanone	1.5	−1.9	−1.6	2.7	2.9		
C	Bicyclo[3.2.1]octan-6-one (13)	1.3	−3.6	−2.0	1.6	2.6	−2.3	−2.6
D	Bicyclo[3.2.1]octan-2-one (14)	1.3	−1.1	−2.0	3.2	2.6	−2.0	−2.7
E	Bicyclo[2.2.1]heptan-2-one (12)	2.1	−1.7	−0.4	2.8	3.6	−0.5	−0.9
F	Tricyclo[4.4.0.0³,⁸]decan-2-one (' twistan-2-one ') (79)	2.2	+2.7	−0.3	5.6	3.7	+10.6	+4.8
G	Tricyclo[3.3.0.0³,⁸]nonan-2-one (' twist-brendan-2-one ') (81)	3.1	+3.8	+1.4	6.3	4.8	−4.5	−2.5
H	Tricyclo[4.3.0.0³,⁸]nonan-9-one (' twist-brendan-9-one ') (83)	3.1	+0.6	+1.4	4.3	4.8	−0.6	−1.4
I	Bicyclo[3.1.1]heptan-2-one [cf. (93)]	4.5	+4.2	+3.5	6.5	6.1	+1.8	+1.2
J	Tricyclo[3.3.0.0³,⁷]octan-2-one (85)	4.7	+2.9	+4.5	5.7	6.7	−3.2	−2.3

[a] Mean strain ($\bar{S}$) calculated from the total strain energy of the corresponding *hydrocarbon* (ref. 28), divided by the number of C–C bonds. [b] Value obtained for the most strained C_α–C_β bond by analysis of experimental data: see Table 3 and associated text. [c] From equation (iv); *cf.* Figure 10. [d] From equation (v). [e] By use of equation (iii), with the ' calculated ' value of k_C for strained C_α–C_β bonds.

the estimated mean strain energies per bond ($\bar{S}$). It is not surprising that there is no very close correlation between k_C and strain, in view of the many approximations employed, but the expected trend is evident, towards more positive values of k_C as strain increases. For the data incorporated into Figure 10, the best straight line (' least squares '), with $\bar{S}$ in kcal mol^{-1}, is given by equation (iv).

$$k_C = 1.9\ \bar{S} - 4.4 \qquad (iv)$$

Values of k_C calculated from $\bar{S}$ by use of equation (iv) for each of the compounds which contributed to Figure

the changes in zig-zag contributions which result from abnormal orientations and from strained bonds.

(i) *Orientation effects.* Data for primary zig-zags derived from extended decalones[2] refer to a cyclohexanone ring in its chair form, where the mean torsion angle of C_α–C_β with respect to C=O is normally about $\pm130°$. For other torsion angles (ω) it seems appropriate to apply an ' orientation factor ' of $\sin^2\omega/\sin^2 130°$, based on equation (i). This orientation factor may be expected to apply provided that ω is not too greatly different from $130°$ (perhaps between 90 and $180°$). If ω is much less than $90°$, however, the zig-zag may approach a region of ' front

' octant ' character, where $\delta\Delta\epsilon$ will undergo a sign reversal. No empirical provision for this situation seems possible at present.

(ii) *Strain effects*. Although the steroid examples discussed on p. 2125 suggested that strain may roughly double the contribution of a bond on a primary zig-zag, subsequent examples show that strain effects span a much wider range than is implied by the factor of 2 [$k_C \approx +3$, for example, used above for some tricycloalkanones, represents almost a six-fold enhancement of the substituent contribution of the bond, *i.e.* of the *difference* between k_C and k_H (-6.2), compared with that for a unstrained C–C bond of a cyclohexanone, where $k_C \approx -4.6$]. It is therefore proposed that the C_α–C_β bond should be treated in the normal way [equation (iii)] but that the contribution assigned to a strained bond on a primary zig-zag but more remote than the C_α–C_β bond, should be multiplied by an empirical ' strain factor ' given by the expression (v), where k_C has the value taken

$$\text{' strain factor '} = \frac{k_C - k_H}{k_C{}^0 - k_H} = \frac{k_C + 6.2}{1.6} \qquad \text{(v)}$$

from Table 2 or derived from equation (iv) for the fundamental strained molecular framework in question, and $k_C{}^0$ has the value (-4.6) appropriate for an unstrained C_α–C_β bond.

The ' strain factor ' calculated in this way is at best a rough guide to the increase in magnitude of the effect of a strained bond on a primary zig-zag. It has the value 2.7 for such a bond of a five-membered ring in a steroid (p. 2125), to be compared with the value of 2 estimated previously.

No distinction has been made above between (*a*) the contribution of a bond (other than the C_α–C_β bond) which is itself strained, and whose effect may be transmitted to the carbonyl group through a chain of essentially unstrained bonds [*e.g.* the 13,14-bond in a 6-oxo-steroid (Table 1)], and (*b*) the contribution of a bond which itself is essentially unstrained (*e.g.* a ' β-equatorial ' methyl substituent), but whose effect is transmitted to carbonyl through a strained C_α–C_β bond. Case (*b*) is exemplified by 7-*anti*-methyl or 6-*exo*-methyl substituents in a bicyclo-[2.2.1]heptan-2-one (p. 2133). In the absence of data for a considerable number of compounds of this type, we suggest that the 'strain factor ' calculated by equation (v) should be used here also, to obtain a rough estimate of the enhancement of the contribution of a bond which is on a primary zig-zag but beyond a strained C_α–C_β bond.

Two examples outside the steroid field illustrate applications of both ' strain ' and ' orientation ' factors. A 7-*anti*-methyl substituent in a bicyclo[2.2.1]heptan-2-one was estimated (p. 2133) to make a consignate contribution ($\delta\Delta\epsilon$) of about 1.3—1.9 units. The strain factor for the bicyclo[2.2.1]heptane skeleton may be 2.8 or 3.6 (Table 10), based respectively on the ' empirical ' and

' calculated ' k_C values listed in Table 10. The normal contribution allotted to the methyl substituent as the ' second ' bond of a zig-zag [2] (*ca.* 0.6 unit) is therefore increased to 1.7 or 2.2 units, respectively, in acceptable agreement with the observed increment. Further allowance for the unusual torsion angle in bicyclo[2.2.1]-heptan-2-one ($\omega \approx 145°$ for C-7) gives an ' orientation factor ' of 0.6, reducing the ' calculated ' 7-*anti*-methyl contribution to 1.0 or 1.3 units, respectively.

The 8,9-bond of ' twistan-4-one ' (p. 2137) may be treated similarly. The ' strain factor ' for twistane (5.6 or 3.7, *cf.* above, and Table 10) gives a strain-corrected contribution of 3.4 or 2.2 units, respectively, for the 8,9-bond. The torsion angle ω for the C_α–C_β bond (3,8-bond), which defines the orientation of the primary zig-zag, is *ca.* 105°. The correction factor is therefore estimated as 1.6, and the strain-adjusted increment for the 8,9-bond is further increased to 5.4 or 3.5 units, respectively, in fair agreement with the deficit of *ca.* 4 units provisionally attributed to the 8,9-bond (p. 2138).

The nature of the ' strain effects.' We have already offered [2] a simple pictorial rationalisation of the c.d. significance of bonds on ' primary zig-zags,' in terms of orbital interactions, and our conclusions have gained support from recent calculations (CNDO) by Bouman and Lightner.[18,‡] Perturbation theory (PMO) [79] shows that orbital interactions are largest when the energies of the orbitals are similar. Perturbation of the carbonyl *n* orbital (HOMO) by mixing with orbitals of σ or π type formally associated with adjacent hydrocarbon parts of the molecular framework will therefore be greater the higher the energy levels of these orbitals. The carbonyl π* orbital (LUMO) will likewise be most perturbed when it can mix with adjacent low-energy antibonding orbitals. The more strained a hydrocarbon molecular framework, within a series of related structures, the higher is the energy level associated with its HOMO, as is revealed by photoelectron spectroscopy,[80] and the lower should be the energy of the corresponding LUMO. Provided that the geometrical requirements for orbital interaction are satisfied, the carbonyl *n* and π* orbitals should therefore couple more strongly with orbitals of a strained framework than with those of a related unstrained system. This concept is equivalent to regarding the hydrocarbon framework of a ketone as an extension of the chromophore, the extended system being inherently chiral in a dissymmetric ketone. The precise natures of the extended orbitals can only be derived by calculation: according to Bouman and Lightner [18] the carbonyl *n* orbital in particular is highly delocalised into the hydrocarbon framework, with a considerable part of its electron density distributed among the atoms (or bonds) which constitute ' primary zig-zags.' From the PMO argument [80] it is to

‡ See also the results of calculations (M. R. Giddings, E. E. Ernstbrunner, and J. Hudec, *J.C.S. Chem. Comm.*, 1976, 954, 956; published after submission of this manuscript) which confirm the significance of zig-zag coupling paths between remote structural features and the carbonyl group.

[79] M. J. S. Dewar and R. C. Dougherty, ' The PMO Theory of Organic Chemistry,' Plenum, New York, 1975; I. Fleming, ' Frontier Orbitals and Organic Chemical Reactions,' Wiley–Interscience, London, 1976.
[80] M. J. S. Dewar and S. D. Worley, *J. Chem. Phys.*, 1969, **50**, 654; N. Bodor, M. J. S. Dewar, and S. D. Worley, *J. Amer. Chem. Soc.*, 1970, **92**, 19.

be expected that this delocalised part of the n orbital will become increasingly important the more closely the energy level of the formal HOMO of the hydrocarbon framework approaches that of the n-orbital of the carbonyl oxygen atom, as a result of molecular strain.

The assumption of additivity of group contributions is unlikely to be theoretically valid in such a situation, but the results of this and preceding papers confirm that it is a useful empirical approximation in dealing with the real structural problems encountered by organic chemists.

Conclusion and Recommendations.—With the three previous papers,[2-4] this reassessment of c.d. data has covered all the main groups of monofunctional saturated ketones. The stepwise analysis of data for compounds of increasing structural complexity has succeeded in defining the particular structural features which contribute most of the observed chiroptical behaviour, and in assessing their relative contributions. The results present theoreticians with an extensive range of data against which to test the various computational approaches to chiroptical properties.

For organic chemists who wish to use the data and procedures in our papers as aids to stereochemical and structural assignments, and to the interpretation of c.d. data for new compounds, we offer the following recommendations.

(1) For compounds of straightforward decalone or ' extended-decalone ' type, with no special features of strain, use the structural-group increments given in Part 82.[2] (2) For compounds of bicyclo[4.3.0]nonan-7-one or -8-one type(hexahydroindan-1-one and -2-ones) use the group-increments in Part 89,[3] but note that there are still major uncertainties regarding compounds of class $5c2ax$,[3] few of which were available for study. Compounds with a fused cyclobutanone ring (*e.g.* bicyclo-[4.2.0]octan-7-ones) are covered in the same paper. (3) Estimates of $\Delta\varepsilon$ for simple chiral cyclopentanones and twisted cyclohexanones [3,4] may usually be made on the basis of the empirical equations (i) or (ii), which have been generalised in the present paper into equation (iii). Appropriate values of k_H and k_C are given in Table 2. (4) For ketones with irregular or strained structures, rough estimates of $\Delta\varepsilon$ can be obtained by using equation (iii), with $k_H = -6.2$, and k_C having the most appropriate value selected from data in the present paper, bond strain being the most critical factor. (5) For conformationally mobile compounds, where more than one conformation is expected to be significant, the population-weighted mean of calculated $\Delta\varepsilon$ values should be used as the best estimate available.