Structure and the Optical Rotatory Dispersion of Saturated Ketones

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Symmetry principles permit the deduction of a simple octant rule, which relates the sign and amplitude of the Cotton effect exhibited by saturated ketones to the disposition of atoms in space about the carbonyl groups of the ketones. The octant rule should find utility in studies of structure and absolute configuration.

Recent theoretical studies[2] of the process of light absorption by chromophores situated in an asymmetric environment provide a basis for the suggestion that certain simple relationships may be expected between the optical rotatory dispersion of ketones[3] in the region of their long wave length absorption, and the disposition of groups in space about the carbonyl group.

Consider a carbonyl group (Fig. 1), lying along the z-axis, with its attached groups a and b lying in plane yz, of a coördinate system of three mutually perpendicular planes, xy, xz and yz, its midpoint at the origin. These are nodal and symmetry planes of the orbitals involved in the relatively weak $n \rightarrow \pi^*$ transition associated with the absorption of carbonyl compounds in the 270–310 mμ region.[4] Consequently, we may expect that the effect of an atom at any point P (x, y, z) in inducing asymmetry in the electronic processes associated with long wave length carbonyl absorption will be equal in magnitude and opposite in sign to that induced by the same atom situated at the reflection of P through any of the planes xy, yz and xz, and will vanish identically when P lies in any one of those planes. We may further assume that the effect will be characteristic of the particular perturbing atom, and that it will be additive with the effects of other atoms.[5] These relationships lay the foundation for a very simple *octant rule: the sign of the contribution which a given atom at point P (x, y, z) makes to anomalous rotatory dispersion will vary as the simple product, $x \cdot y \cdot z$, of its coördinates.*[6]

The availability in recent years of a large body of experimental data[3] on the optical rotatory dispersion of ketones of known, fixed, geometry and absolute configuration permits us to put the octant rule to simple, direct test. Since these substances are cyclohexanones whose conformation is essentially fixed by the fusion of further rings, or by the presence of large, equatorially disposed groups, it is important first to consider the geometry of the cyclohexanone ring (I). While no direct measurements

I
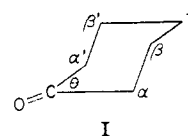
of the relevant parameters are available, we may assume with confidence that the bonds $\alpha\beta$, $\alpha'\beta'$, $\beta\gamma$ and $\beta'\gamma$ are of the normal length, 1.545 Å.,[7] and that the bonds Cα and Cα', involving the trigonal carbon atom, are shortened to 1.50 Å.[7,8] We are on less firm ground in assessing the internal carbonyl angle, θ; a direct measurement of the corresponding parameter in acetone has given a value of 116°,[9] and this choice seems consistent with those observed for a number of acetyl compounds.[8] The use of those parameters leads to the important conclusion that *the backbone system, α–β–γ–β'–α', of any cyclohexanone is only very slightly distorted from normal cyclohexane geometry.*[10] The detailed comparison of

(1) The late Professor Moffitt's contributions to this work were of primary importance. His death on December 19, 1958, unfortunately prevented his participation in the preparation of the present account, and the other authors must bear alone the responsibility for its deficit in the elegance and theoretical rigor he would have contributed.

(2) W. Moffitt and A. Moscowitz, Abstracts of Papers, 133rd Meeting of the American Chemical Society, April, 1958, p. 27Q; W. Moffitt and A. Moscowitz, *J. Chem. Phys.*, **30**, 649 (1959).

(3) *Cf.* C. Djerassi, "Optical Rotatory Dispersion; Applications to Organic Chemistry," McGraw–Hill Book Co., New York, N. Y., 1960; C. Djerassi, *Rec. Chem. Progress*, **20**, 101 (1959).

(4) J. W. Sidman, *Chem. Revs.*, **58**, 689 (1958). This statement is strictly true for the yz plane, which is nodal for the π^* orbital, a relatively diffuse antibonding molecular orbital involving both the carbon and the oxygen atoms, and the xz plane, which is nodal for the n orbital, a non-bonding $2p$ orbital of the oxygen atom. The second nodal surface of the π^* orbital certainly does not pass precisely through the midpoint of the C–O bond, and indeed is not strictly a plane. Present theory does not permit precise definition of the latter situation, and the simplifying assumption inherent in the use, as a symmetry plane, of the xy plane defined above, is adequate for our present qualitative purposes.

(5) The choice of *atoms*, rather than bonds or orbitals, as perturbing parameters has obvious analytical advantages. Further, since the above relations depend on symmetry considerations alone, the choice of any set of parameters which defines uniquely the geometry of the perturbing systems is justified.

(6) The sign associated with any asymmetry effect is of course always arbitrary. The coördinate system of Fig. 1 has been so chosen that the effect predicted for any atom from the octant rule will conform with generally accepted practice in the presentation of experimental results [*cf.* C. Djerassi and W. Klyne, *Proc. Chem. Soc.*, 55 (1957)]. It may be noted here that Cotton effects of sign in agreement with those observed have been deduced from a quantitative treatment of the octant rule [A. Moscowitz and L. C. Snyder, *Note Added in Proof* in A. Moscowitz, *Tetrahedron*, **13**, 48 (1961)], based upon the assumption that the dissymmetric perturbing potential which gives rise to anomalous rotatory dispersion is attributable to the coulomb fields of the incompletely shielded nuclei of the perturbing atoms [*cf.* E. U. Condon, W. Altar and H. Eyring, *J. Chem. Phys.*, **5**, 753 (1937); E. Gorin, J. E. Walter and H. Eyring, *ibid.*, **6**, 824 (1938); and W. J. Kauzmann, J. E. Walter and H. Eyring, *Chem. Revs.*, **26**, 339 (1940)].

(7) C. C. Costain and B. P. Stoicheff, *J. Chem. Phys.*, **30**, 777 (1959).

(8) L. C. Krisher and E. Bright Wilson, Jr., *ibid.*, **31**, 882 (1959).

(9) J. D. Swalen and C. C. Costain, *ibid.*, **31**, 1562 (1959).

(10) We wish to express our warm appreciation of the coöperation of Professor E. J. Corey in calculating the precise data, presented in Fig. 2, upon which this conclusion is based. It will be noted that our conclusion is at variance with that of previous discussions, in which no account has been taken of the shortening of the Cα and Cα' bonds, and θ has arbitrarily been assumed to be 120°. These choices lead to a substantial distortion from normal cyclohexane geometry [*cf.* E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **77**, 2505 (1955); and R. C. Cookson, *J. Chem. Soc.*, 282 (1954)]. For example, the new model indicates that the angle between the planes αCα' and $\beta\gamma\beta'$ of any cyclohexanone is only 3°6', as compared with 18°52' on the older model.
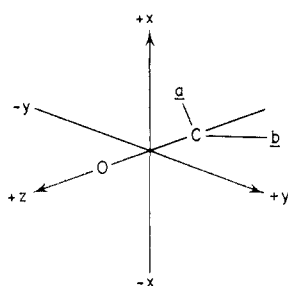
Fig. 1.

the two systems (Fig. 2) provides a firm basis for adopting cyclohexane geometry as a very close approximation to fact in making octant rule tests and predictions.

We shall limit our discussion here to cases in which the perturbing atoms are only saturated carbon atoms and hydrogen atoms, and shall neglect the effect of the latter.[11] We note first that the space around a carbonyl group, disposed in the coordinate system of Fig. 1, is divided by the mutually perpendicular planes into eight octants, and that the placement of an atom within four of these will make a *positive* contribution to anomalous rotatory dispersion, while the presence of a perturbing atom in the other four will make an opposite, *negative* contribution as shown

Octant	Contribution	Octant	Contribution
$+ x + y + z$	$+$	$+ x - y + z$	$-$
$+ x - y - z$	$+$	$+ x + y - z$	$-$
$- x + y - z$	$+$	$- x + y + z$	$-$
$- x - y + z$	$+$	$- x - y - z$	$-$

Viewed in projection on the xy plane, from $z = +$ ∞, these octants appear as

Further, we find that the angle which an α equatorial bond makes with the carbonyl plane is only 4°3′, as compared with the previous 14°36′. The case of *cis* β-decalone (*vide infra*, footnote 21) illustrates very clearly the importance of the use of the correct model in applying the octant rule.

(11) Undoubtedly, hydrogen atoms must be taken into account in any refinement of the octant rule, particularly in a quantitative direction; indeed, that they can be ignored without serious difficulty in the essentially qualitative discussion of this paper is probably as much a consequence of widespread automatic cancelling of effects of opposite sign as it is the result of a small perturbative effect of hydrogen atoms. The extent to which induction of asymmetry by an atom *in a given position* varies with the nature of the atom can only be assessed empirically, in the absence of a detailed quantitative theory of perturbing interactions. Though insufficient carefully determined data are as yet available in apposite cases to permit detailed development of the topic, it is clear that various atoms may be arranged on what may be described as a scale of *specific rotativity:*

	Rotativity	Atomic refractivity[a]
Iodine ⎫		13.90
Bromine ⎬	Strongly positive[b,c]	8.87
Chlorine ⎭		5.97
Carbon	Positive	2.42
Hydrogen	Small	1.10
Fluorine	Negative[c]	0.95

[a] "Handbook of Chemistry," 8th Ed., p. 1421, Handbook Publishers, Inc., Sandusky, Ohio, 1952. [b] C. Djerassi, I. Fornaguera and O. Mancera, *J. Am. Chem. Soc.*, **81**, 2383 (1959). [c] C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, *ibid.*, **80**, 1216 (1958).

It will be noted that the order of the atoms on this scale parallels that of their atomic refractivities. Further, note may be taken of the fact that the strong positive rotativity of the halogen atoms (other than fluorine) lies at the basis of the *axial haloketone rule* of Djerassi and Klyne [*J. Am. Chem. Soc.*, **79**, 1506 (1957)], which may now be seen to be a special case of the octant rule.

$$+ x - y - z \mid + x + y - z$$
$$\underline{\qquad + \qquad \mid \qquad - \qquad}$$
$$- \qquad \mid \qquad +$$
$$- x - y - z \mid - x + y - z$$

Back octants

$$+ x - y + z \mid + x + y + z$$
$$\underline{\qquad - \qquad \mid \qquad + \qquad}$$
$$+ \qquad \mid \qquad -$$
$$- x - y + z \mid - x + y + z$$

Front octants

The use of such projections greatly clarifies the evaluation of the effects produced by variously placed atoms, and further simplification can be brought about through the use of *octant diagrams*, in which only perturbing atoms are shown, with numerical designation, in the appropriate octant. In order to obviate the necessity for separate representation of back and front octants, we use a single projection, with the following arbitrary conventions: (i) In full projections, bonds in back octants are drawn with solid lines, while those in front octants are drawn with dotted lines; if bonds of opposite type overlap in projection, a dashed line is used. (ii) In octant diagrams, ordinary Arabic numerals designate atoms in back octants, and italic numerals are used for atoms in front octants. This protocol may now be illustrated for the simple case of 3-methylcyclohexanone (II).[12] It is at once apparent that C.2, C. 6 and C.4, lying as they do in nodal planes, make no contribution to anomalous dispersion, and that the contributions of C.3 and

obsd. sign and molecular amplitude [A][13] of Cotton effect: +25

II
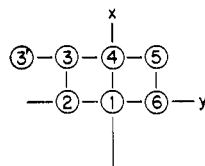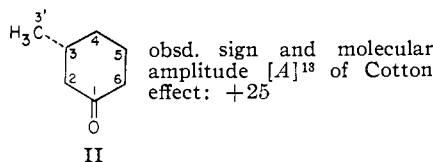
coördinate system as in Fig. 1; full projection on *xy* plane; viewed from $z = + ∞$[14]
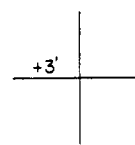
simplified octant diagram, showing only perturbing atoms

C.5, being equal and opposite, cancel; the entire, *positive*, Cotton effect is associated with C.3′ alone.

We may now consider other simple cyclohexanones whose conformation may be regarded as essentially fixed. In *trans*-3,6-dimethylcyclohexanone (III),[15] the α-equatorial substituent attached at C.6 lies very nearly in a nodal plane, and makes no substantial contribution to the anomalous

(12) C. Djerassi and G. W. Krakower, *J. Am. Chem. Soc.*, **81**, 237 (1959).

(13) All amplitudes used in this paper are defined as the difference between peak and trough values for [φ]/100 in standard Cotton effect curves [*cf.* C. Djerassi, W. Klyne, *Proc. Chem. Soc.*, 55 (1957), and ref. 3a, p. 17].

(14) The ketone can be placed within the coördinate system as shown, or rotated 180° about the z-axis. For comparison purposes, it is useful to adopt a consistent practice in this detail.

(15) C. Djerassi, L. A. Mitscher and B. J. Mitscher, *J. Am. Chem. Soc.*, **81**, 947 (1959).
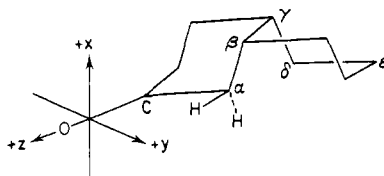
	x		y		z	
	Cyclohexane	Cyclohexanone	Cyclohexane	Cyclohexanone	Cyclohexane	Cyclohexanone
C	0	0	0	0	−0.610	−0.610
α	0	0	+1.262	+1.272	−1.502	−1.405
β	+1.262	+1.205	+1.262	+1.260	−2.394	−2.373
γ	+1.262	+1.157	0	0	−3.286	−3.253
δ	0	−0.153	0	0	−4.178	−4.073
ε	0	− .203	+1.262	+1.260	−5.070	−4.963
Equat. α-H	0	+ .077	+2.152	+2.123	−0.873	−0.729
Axial α-H	−0.890	− .924	+1.262	+1.344	−2.131	−1.975

Cyclohexane

All angles = 109°28′
All distances = 1.545 Å.

Cyclohexanone

O—< = 116°; all other angles = 109°28′

C-α ⎫
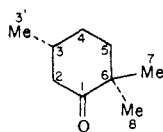C-α′⎬ = 1.500 Å.; all other distances = 1.545 Å.

Fig. 2.—Parameters of the *cis*-decalin system (all distances in Å.).

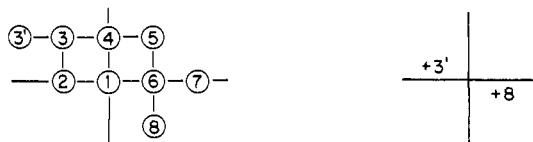dispersion of the ketone, which is essentially indistinguishable from that of 3-methylcyclohexanone
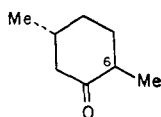
III, [A] = +25

(II). By contrast, the addition of the further α-axial substituent in 3,6,6-trimethylcyclohexanone (IV)[15] should, and


IV, [A] = +81

does, lead to a large added positive contribution to the Cotton effect. This case brings us face to face with the very important problem of estimating the relative magnitudes of the contributions made by differently placed atoms. This problem can become acute when atoms making contributions of opposite sign are present within the same molecule. Clearly, an important avenue to be followed is that of determining values for atoms in known positions empirically by careful studies on well-chosen cases. For example, the compounds just cited suggest that the amplitude contributed by carbon in an α-axial position is *ca.* ± 56, and in a β-equatorial position, *ca.* ± 26. This valuable ap-

proach has not as yet been developed *in extenso*, since the accuracy of many of the available determinations is not high and, further, since the amplitudes presently available should often be corrected, in unknown measure, for varying amounts of background dispersion.[16] Nonetheless, it may be hoped that when accurate values are available for a considerable number of known positions, a useful empirical relationship will be deduced which will permit the reliable estimation of the contribution to the molecular amplitude [A] provided by a given atom in any position from its coördinates.[17]

V
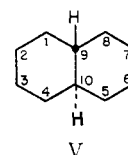
(16) A solution to the problem of correcting for background dispersion has been published elsewhere [A. Moscowitz, *Revs. Mod. Phys.*, **32** (2), 440 (1960)]. In this analysis it is shown that in compounds whose circular dichroism bands have comparable half-width, and for which the curvature of the background dispersion is not large, the molecular amplitudes serve as a rough measure of the relative rotational strength. These conditions obtain widely in ketones, and provide justification for using molecular amplitudes in a semi-quantitative manner.

(17) For the present, we note only that atoms at considerable remove from the carbonyl group still exert an appreciable effect, and that the effect of an atom at a given distance is not constant, but varies according to the asymmetry of its position in respect to the nodal surfaces of the *n* and π* orbitals. Some factors which must be kept in mind in developing the octant rule in a quantitative direction, and may represent occasions for some difficulty are: (i) the inclusion of the effects of hydrogen atoms; (ii) possible very difficultly assessable asymmetric effects of solvent; (iii) uncertainties in atomic positions as a result of skeletal distortions induced by steric repulsions and other factors; and (iv) ambiguity about the appropriate contour and placement of the third nodal surface, here approximated by the *xy* plane [cf. footnote 4]. It is of much interest that the quantitative theoretical treatment mentioned earlier (ref. 6) has given results in good agreement with observation for the reduced rotational strengths of a number of saturated ketones.
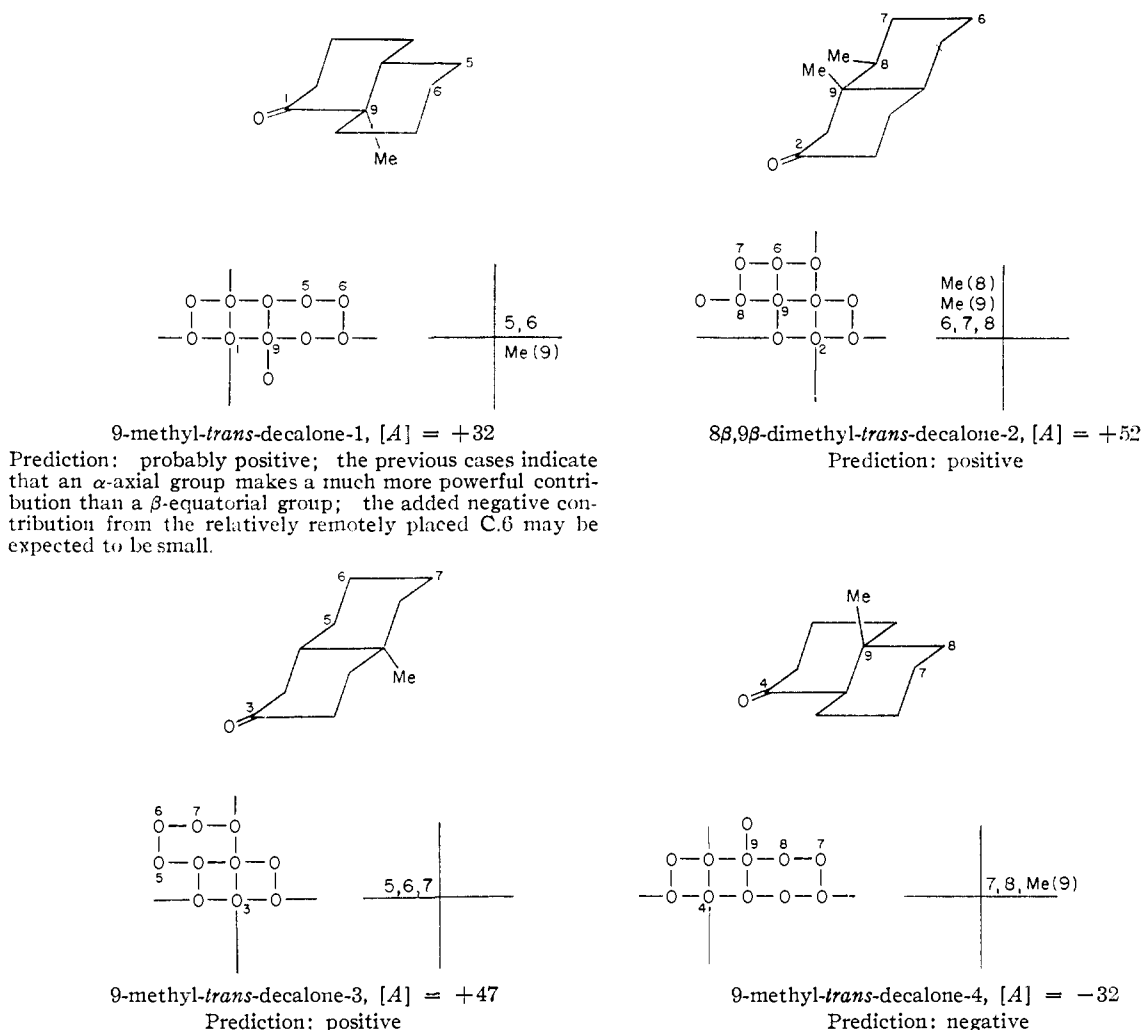
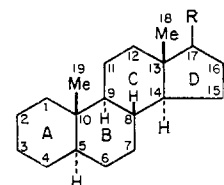9-methyl-*trans*-decalone-1, [A] = +32

Prediction: probably positive; the previous cases indicate that an α-axial group makes a much more powerful contribution than a β-equatorial group; the added negative contribution from the relatively remotely placed C.6 may be expected to be small.

8β,9β-dimethyl-*trans*-decalone-2, [A] = +52

Prediction: positive

9-methyl-*trans*-decalone-3, [A] = +47

Prediction: positive

9-methyl-*trans*-decalone-4, [A] = −32

Prediction: negative

Fig. 3.

We consider next a series of substituted *trans*-decalins (V)[18]; in each of these simple basic cases, we present a perspective drawing, as well as the corresponding projection on the xy axis from $z = + \infty$, and the octant diagram (Fig. 3).

The steroid ketones present a rich array of carbonyl groups in differing asymmetric environments. There follow the observed Cotton effect,[18,19] the octant diagram, and the predicted effect, for a number of substances, illustrative of all available examples. It will be observed that there are no discrepancies between the observed and predicted effects.

Two steroid ketones have not been included in the above summaries, since they are worthy of special comment. It is a simple consequence of the octant rule that ketones containing in some octants substituents whose effects are quantitatively balanced by those of other, differently situated groups, will give plain dispersion curves, *even though the opposing*
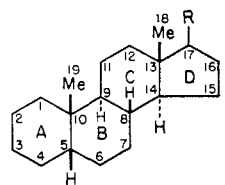
5α-derivatives, A/B *trans*

Ketone	[A]	Octant diagram	Prediction
Cholestanone-2 R = C₈H₁₇	+121	7, 19 / rings C, D	Pos.
Cholestanone-3 R = C₈H₁₇	+65	6, 7, 15, 16	Pos.
Cholestanone-4 R = C₈H₁₇	−94	19 rings C, D	Neg.
3β-Acetoxy-cholestanone-6 R = C₈H₁₇	−76	12, 18 / 19 ring D	Neg.

(18) C. Djerassi, R. Riniker and B. Riniker, *J. Am. Chem. Soc.*, 78, 6362 (1956); C. Djerassi and D. Marshall, *ibid.*, 80, 3986 (1958).

(19) C. Djerassi, W. Closson and A. E. Lippman, *ibid.*, 78, 3163 (1956); C. Djerassi and W. Closson, *ibid.*, 78, 3761 (1956); C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, *ibid.*, 80, 1216 (1958); C. Djerassi, O. Halpern, V. Halpern, O. Schindler and C. Tamm, *Helv. Chim. Acta*, 41, 250 (1958).
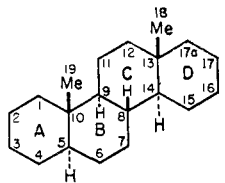
3β-Acetoxy-
cholestanone-7 −16
R = C₈H₁₇

	2, 3
15, 16	

Neg.

5α-Androstanone-11 +16
R = H

16, 18	6
	2

Pos.

3β-Acetoxy-5α-
ergostanone-12 +42
R = C₉H₁₉

2, 3, 4, 5, 6	
	18
	side chain

Pos.

5β-derivatives, A/B *cis*

Methyl 1-keto-
5β-etianate −136
R = COOMe

	6
rings C, D	

Neg.

Coprostanone-3 −27
R = C₈H₁₇

	6
	15, 16

Neg.

Coprostanone-4 +3
R = C₈H₁₇

7, 8, 9, 11, 12	
13, 14, 15	
16, 17, 18, 19	

Pos,

Coprostanone-6 −77
R = C₈H₁₇

	12, 18
19	D ring
3, 4	

Neg.

3α-Hydroxy-7-
ketocholanic +29
acid
R = C₄H₈-
COOMe

	11	3, 4
	15, 16	

Pos.

5β-Andro- +15
stanone-11
R = H

16, 18	6
	3, 4

Pos.

Methyl 3α-acet- +10
oxy-12-keto-
cholanate
R = C₄H₈-
COOMe

2, 3, 4, 5, 6	
	18
	side chain

Pos.

D-homo derivatives, A/B *trans*

D-Homoandrostane-3β- −78
ol-17-one

	18, 12, 11,
	19, 1, 2, 3

Neg.

17aα-Methyl-D-homo- −21
androstane-3β-ol-17-
one

	18, 12, 11,
	19, 1, 2, 3
	Me(17aα)

Neg.

17aβ-Methyl-D-homo- −96
androstane-3β-ol-17-one

	18, 12, 11
	19, 1, 2, 3

Neg.

groups are not symmetrically disposed vis-a-vis the carbonyl function. Two cases in which this condition is approached are available in D-homoandrostane-3β-ol-17a-one (VI) and cholestanone-1 (VII),
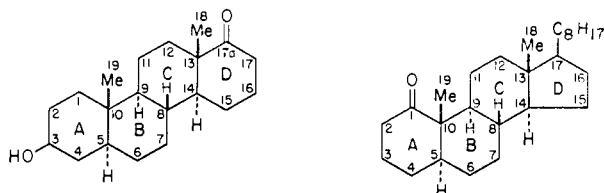

VI   VII
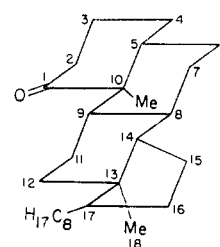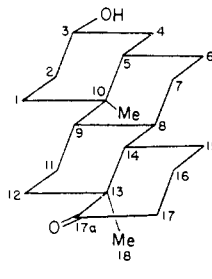
for which very small Cotton effects have been observed. In each case, comparison with 9-methyl-*trans*-decalone-1 ([A] = ±32, *vide supra*) shows that the effect of the axial α-methyl group should dominate those of the next most proximate non-vanishing groups—C.8 + C.9 in (VI), and C.6 + C.7 in (VII). To these latter, however, must be added, in the case of VI, the many, though relatively remote, atoms of rings A and B (C.1–7, C.10); similarly, in VII, atoms C.12, C.17 and those of the C₈H₁₇ side chain (note positions in a forward octant) swell the negative contributions of C.6 and C.7.

We have now tested the octant rule against a large number of substances of known, fixed, structure and conformation. The successful result of the test leads us to suppose that the octant rule will be of much value in providing structural and configurational information, and that, in particular, it is likely to prove of unique utility in studies of absolute configuration, and in establishing subtle conformational details. To exemplify the manner
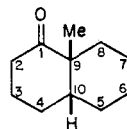
VIII, [A] = +51
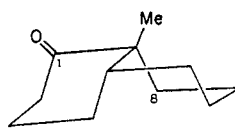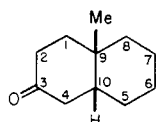

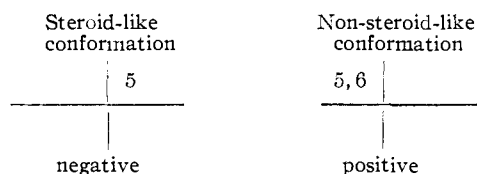| IX, steroid-like conformation	X, non-steroid-like conformation
	5, 6, 7
8	Me(9)
strongly negative	**positive**
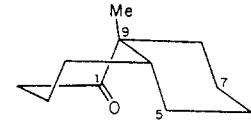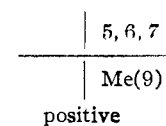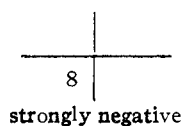
in which the rule can provide information not at present available from any other source, the 9-methyl-*cis*-decalones may be considered. *A priori*, any *cis*-decalin derivative may exist in one or the other of two alternative conformations. For example, 9-methyl-*cis*-decalone-1 (VIII) may take the forms IX or X.

The accompanying octant diagrams enable us to predict that the alternative conformations should be associated with Cotton effects of opposite sign, and the observed[20] positive effect associated with the ketone of known absolute configuration (VIII) permits us to conclude that the non-steroid-like conformation (X) is preferred. Similarly, the two conformations which may be assumed by 9-methyl-*cis*-decalone-3 (XI)

XI, $[A] = -11$

Steroid-like conformation	Non-steroid-like conformation
5	5, 6
negative	positive

should be associated with Cotton effects of opposite sign[21]; in this case the observed negative value

(20) C. Djerassi and D. Marshall, *J. Am. Chem. Soc.*, **80**, 3986 (1958).

(21) The steroid-like conformer of XI provides an excellent example of the importance of the precise geometry used in applying the octant rule. In this molecule (Fig. i), if undistorted cyclohexane geometry obtains, all atoms except C.5 lie in nodal planes, or are reflected through a nodal plane; since C.5 lies in the negative $+ x + y - z$ octant, 1.26 Å. above the yz plane, a simple prediction of a negative Cotton effect is made. On the basis of the exact cyclohexanone model described above (*cf.* Fig. 2 and footnote 10), C.5 still lies in the $+ x + y - z$
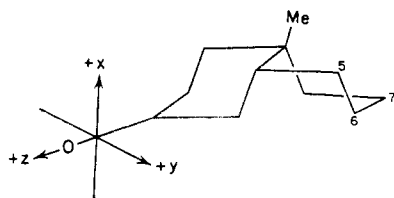

Fig. i

octant, now 1.16 Å. above the nodal plane yz, while atoms C.6 and C.7 lie, respectively, 0.15 and 0.20 Å. below the yz plane; the resulting

suggests that the steroid-like conformation is favored.[22] Finally, in the case of 9-methyl-*cis*-decalone-4 (XII), the observed weak positive effect indicates that the nonsteroid-like conformation is preferred.

XII, $[A] = +11$

Steroid-like conformation	Non-steroid-like conformation
Me(9) 6, 7, 8	Me(9) 5
strongly positive	weakly positive
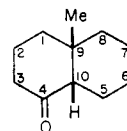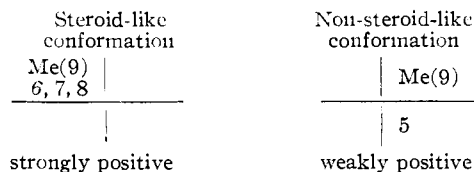
The octant rule has here been tested, and its use exemplified, through reference to cyclohexanones whose carbonyl group is situated within a cyclohexane ring in the chair conformation. The special symmetry of such systems, and the consequent frequent cancellation of the perturbative effects of many atoms, makes the application of the rule especially simple and unambiguous in those cases. On the other hand, there is no reason to suppose that the octant rule is not in principle entirely generally applicable, *e.g.*, to open-chain ketones,[23] to ketones containing six-membered rings in other than chair conformations,[24] and to five- and seven-membered ring ketones. Of course, in many such cases, prediction of the consequences of the rule may be difficult, or impossible, until further progress has been made in placing on a quantitative basis the manner in which the rotative contribution of an atom or group varies as it changes its position relative to the origin at the carbonyl group.

very small positive contributions of C.6 and C.7 should be insufficient to overcome the relatively strong negative effect of the much more asymmetrically placed C.5. By contrast, using the old cyclohexanone model (*cf.* footnote 10), C.6 and C.7 are found to be 0.77 and 1.06 Å. below plane yz, in the positive $- x + y - z$ octant, while C.5 is only 0.71 Å. above that same plane, and the cumulative effect of the positive contributions might be expected to be dominant.

(22) This conclusion, which was not expected on conformational analytical grounds, was reached earlier (*cf.* ref. 20) from special arguments based on rotatory dispersion measurements.

(23) C. Djerassi, I. Fornaguera and O. Mancera, *J. Am. Chem. Soc.*, **81**, 2383 (1959).

(24) C. Djerassi, N. Finch and R. Mauli, *ibid.*, **81**, 4997 (1959); C. Djerassi, N. Finch, R. C. Cookson and C. W. Bird, *ibid.*, **82**, 5188 (1960).