PART-I

AUTOXIDATION STUDIES ON β -AMYRONE: INVESTIGATIONS ON THE STEROCHEMISTRY OF 2-ACETOXY-3-KETO- β -AMYRIN AND 3-ACETOXY-2-KETO- β -AMYRIN.

PART-I

CHAPTER-I

A review on optical rotatory dispersion and its application in stereochemical assignments in Organic Chemistry.

Section A: Optical Rotatory Dispersion:

A wave of plane -polarised light may be considered to be made up of two types of "circularly polarised light": one right circularly polarised wave and one left circularly polarized wave[1]. A "circularly polarized wave" is one whose plane of polarisation rotates continuously and in the same sense around the axis of propagation of the wave. Thus the electric field of a right circularly polarised wave may be described as a right-handed screw or helix twisting round the direction of propagation (Fig. 1), whereas a left circularly polarised wave describes a left-handed screw. Fig. 2 shows how the electric vector of a right circularly polarised wave (E_R) and that of a left circularly polarised wave (E_L) combine to give the vector of a plane-polarised wave (E), which starting out with a maximum value, decreases to zero and then to a minimum and grows again to zero and back to the maximum. Circularly polarised light may actually be produced by passing plane polarised light through a specially cut glass prism known as "Fresnel's rhomb".

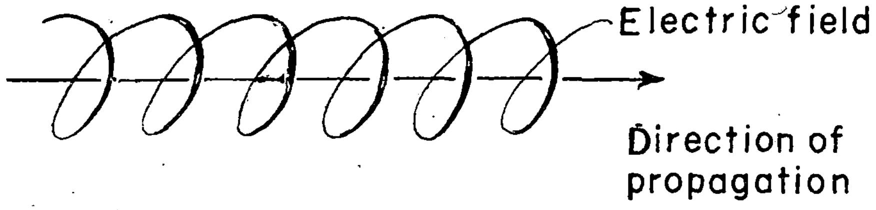


Fig -1. Right circularly polarized light wave

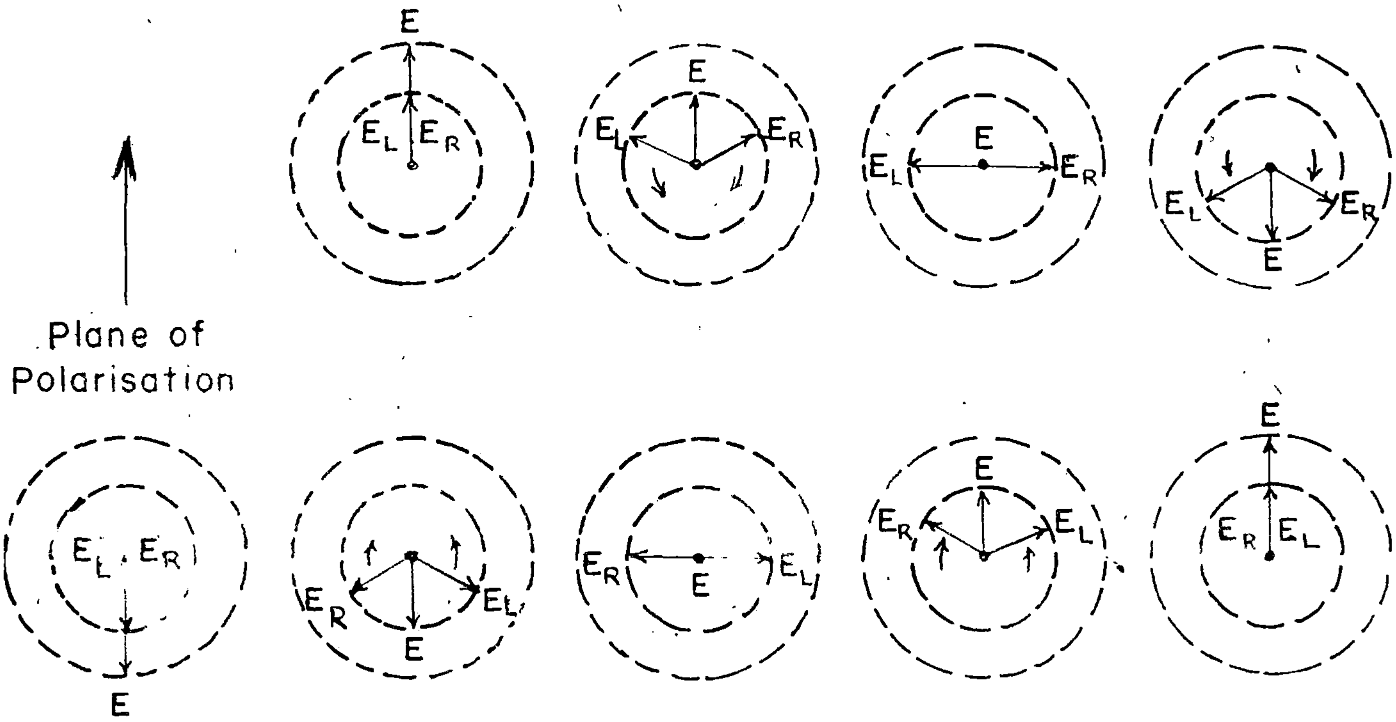


Fig -2.

The important feature of an optically active substance is that it is "circularly birefringent" i.e. that it has unequal refractive indices for right and left circularly polarised light. Since the velocity of light in a medium is given by $v = c/n$, where c is the velocity of light in vacuo and n is the refractive index of the medium, the result of circular birefringence is an unequal velocity of propagation of the left and right circularly polarised rays. If the right circularly polarised ray E_R travels faster than the left circularly polarised one E_L, the result will be as shown in Fig. 3. The resultant wave will still pulsate in a plane i.e. be plane-polarised but the plane of polarisation will no longer be the x-plane but will make an angle α' with the x-plane; in other words the circularly birefringent medium has rotated the plane of polarisation by an angle α'. If the right circularly polarised wave travels faster, α' is positive and the medium is dextrorotatory, whereas if the left circularly polarised wave is faster, α' is negative and the medium is levorotatory.

The variation of optical activity with the wave length gives an optical rotatory dispersion curve. For a compound containing no chromophore (a substance which does not absorb light in the region of wavelength in which it is being examined) the optical activity progressively decreases in magnitude as the wave length increases. A plain positive or plain negative dispersion curve is obtained, depending upon whether it rises or falls with decreasing wave length. For a compound presenting one or several optically

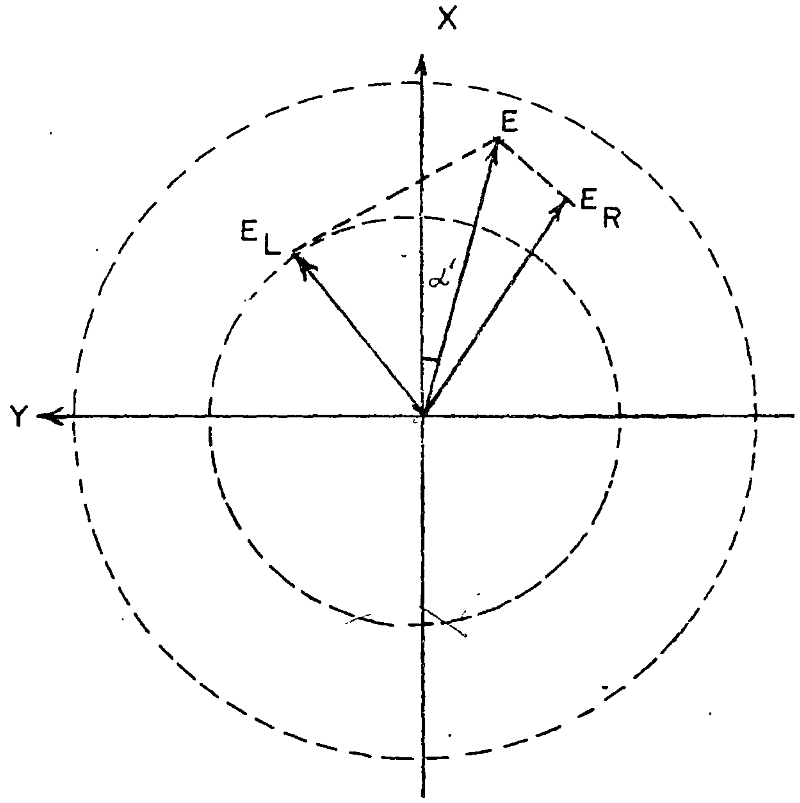


Fig – 3

active absorption bands within the spectral range under experimental observation, the dispersion curve is anomalous and shows one or several "extrema" (peaks or troughs) in the spectral region in which the chromophore absorbs.

Section B: Circular Dichroism:

After passing through an optically active medium, both constituents (E_L and E_R) of a circularly polarised ray not only show circular birefringence, but they are also differentially absorbed. As a result, the two vectors E_L and E_R (Fig 2) are unequal in length and their resultant, instead of decreasing or increasing in a given plane (the plane of polarisation) actually sweeps out in an elongated ellipse. The plane polarised light passing through a dissymmetric medium therefore becomes elliptically polarised. This phenophenon is known as "Circular Dichroism"[2].

Section C : Cotton Effect:

The combination of unequal absorption and unequal velocity of transmission of left and right circularly polarised light in the region in which optically active absorption bands are observed is a phenomenon called the "Cotton Effect". Cotton[3,4] observed that an optically active compound showed in this spectral region an abnormal behaviour of its rotatory power. Thus the basic information which can be deduced from rotatory dispersion and circular dichroism curves is obtained most easily in the immediate vicinity of the spectral region of maximal absorption.

According to Moscowitz[1,5-8] optically active chromophores can be classified into two extreme types: (a) the inherently dissymmetric chromophore and (b) the inherently symmetric, but assymmetrically perturbed, chromophore.

The optical activity of compounds belonging to the first class is inherent in the intrinsic geometry of the chromophore, as for example hexahelicene[5] and twisted biphenyls[8,9]. In these compounds the molecular amplitude of the O.R.D. curve and the maximum value of the c.d curve are generally quite high in comparison with the corresponding quantities observed for the second type of chromophore.

A typical example of the second class is the carbonyl function. For an isolated carbonyl there are two orthogonal reflection planes of symmetry, and to a first approximation the chromophore should be optically <u>inactive</u>, as indeed it is in formaldehyde. Only when the chromophore is placed in some dissymmetric molecular environment e.g. in a terpene or steroid, do its transitions become~~s~~ optically active. Since this optical activity is induced in the chromophore by its environment, rather than being inherent, the magnitude of the associated Cotton effect is often considerably smaller than in the first type of chromophore.

The optical activity associated with the type (b) chromophore is typified by the presence of an as~~s~~ymmetric carbon atom.

In such instances, the inherently symmetric chromophore acts like a molecular probe with which to explore the extra chromophoric geometry, since the magnitude of the induced optical activity depends on the geometry of the extra chromophoric portion of the molecule relative to the symmetry elements of the chromophore. In conclusion, the Cotton effect associated with an optically active absorption band of a given compound manifests itself by a c.d. curve and an anomalous o.r.d. curve.

The rotatory dispersion curves can be divided into three different groups: plain curves, single Cotton effect curves, and multiple Cotton effect curves. Plain dispersion curves are called *positive* or *negative* according to their tendency toward more positive or more negative values with decreasing wavelength. When the peak occurs at higher wavelength than the trough, the curve is a positive *Cotton effect curve*. Conversely when the trough occurs first, the curve is a negative *Cotton effect curve*. The vertical distance between the peak and trough is called the molecular amplitude[10] *a*

$$a = \frac{[\Phi]_1 - [\Phi]_2}{100}$$, where $[\Phi]_1$ is the molecular rotation at the extremum (peak or trough) of longer wavelength and $[\Phi]_2$ molecular rotation at the extremum of shorter wavelength. The third type of dispersion curve is more complicated in the region of ultraviolet absorption in that it possesses two or more peaks with a corresponding number of troughs and therefore is called a *multiple*

Cotton effect curve. Such features are normally observed with $\alpha\beta$ -unsaturated ketone[11] and in these cases it is also necessary to distinguish between broad peaks and troughs, as well as between shoulders and inflections. Fig. 4

Section D : The Octant Rule:

The Octant Rule[12] relates the Cotton effects due to the $n \longrightarrow \pi^*$ transitions of saturated carbonyl compounds to the stereochemistry of the surroundings of the chromophore. The 290 mμ transition of the carbonyl group (in acetone) involves[13,14] roughly speaking the promotion of an electron from a non-bonding 2p orbital situated on the oxygen atom to an anti-bonding π orbital. Concerned with both the carbon and oxygen atoms of the carbonyl chromophore (Fig. 5). Whatever the perturbations the rest of the molecular framework may induce on the chromophoric electrons, they are not significant for the dipole strength of the transitions. However, while the rotational strength of a $n-\pi^*$ transition must be zero in a symmetrical molecule like acetone, this strength has some non-zero value when the carbonyl is asymetrically surrounded, as in a steroid or a terpene. Hence the rotational strength of a carbonyl function is quite sensitive to molecular environment and will reflect quantitatively the asymmetry around the chromophore[15,16].

As a result of the above concept, the carbonyl group or any symmetric chromophore whose associated optically active transitions are readily amenable to investigation, becomes an ideal

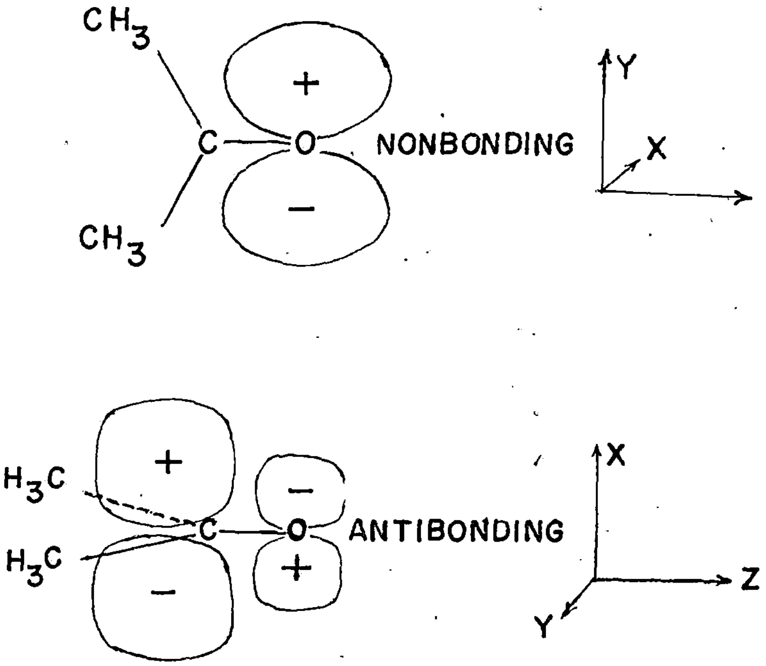

CH3
CH3
C
O
+
−
NONBONDING
Y
X
H3C
H3C
C
O
+
−
−
+
ANTIBONDING
X
Z
Y

Fig. 5

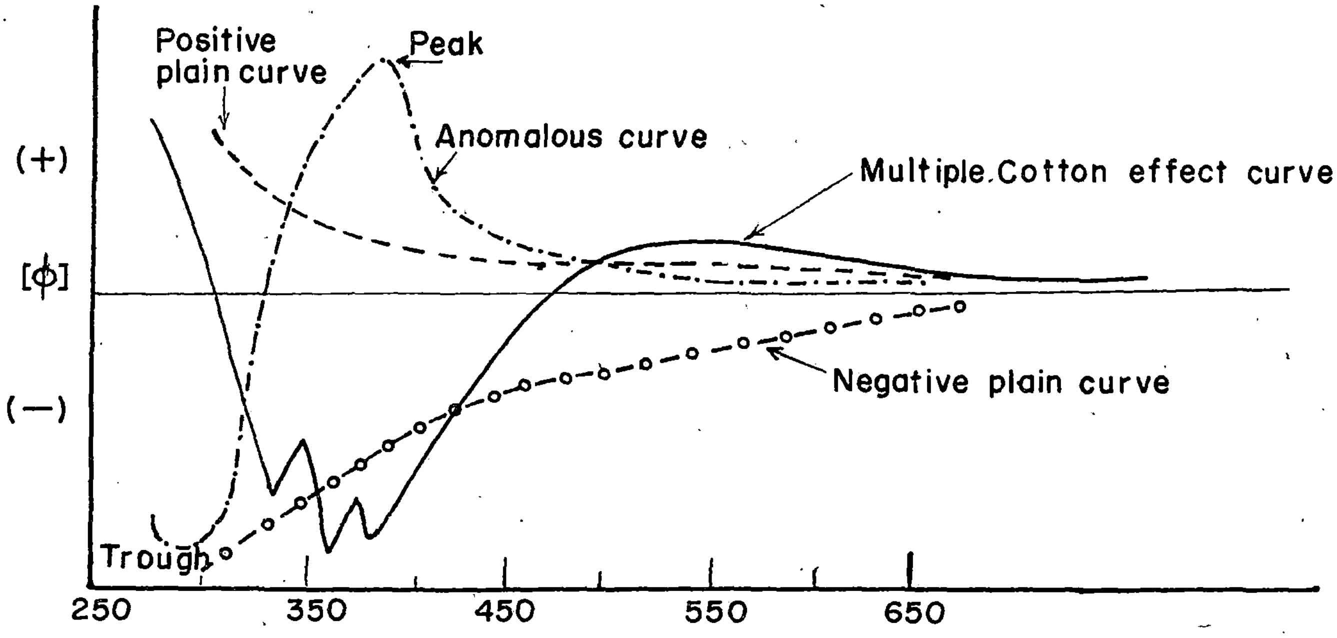

Positive plain curve
Peak
Anomalous curve
Multiple Cotton effect curve
(+)
[ϕ]
(−)
Negative plain curve
Trough
250
350
450
550
650

Fig- 4

probe with which to search out structural, configurational and conformational subtleties of a particular molecular framework.

It will be observed that when a carbonyl function is situated in a cyclohexane ring in the chair conformation, the $n \rightarrow \pi^*$ transition of the chromophore will result in a Cotton effect which is directly dependent upon the spatial orientation of the substituents in the ring system. The Octant rule[12] which is obtained from the symmetry principles, relates the sign and amplitude of the Cotton effect exhibited by an optically active saturated ketone to the spatial orientation of atoms about the carbonyl function. As a consequence, this rule permits prediction of the sign and semiquantitatively, the intensity of the Cotton effect exhibited by saturated ketones.

Taking the carbonyl chromophore as the reference point, a cyclohexane can be divided into eight Octants by means of three mutually perpendicular planes[12,17,18]. These are nodal and symmetry planes of the orbitals involved in the $n-\pi^*$ transition associated with the absorption of the carbonyl group. Here, cyclohexanone ring is used as an example as it is easy to visualise and discuss. However, the same concept is applicable to any ring system or side chain carrying a carbonyl function.

In figure 6 plane A is vertical passing through C-1 and C-4. The only substituents in this plane are the ones attached to C-4. The Plane B is horizontal and encompasses the carbon atom bearing the carbonyl group (C-1) and its two adjacent atom (the C-atom C-2 to the right called R_2 and the carbon atom C-6 to the

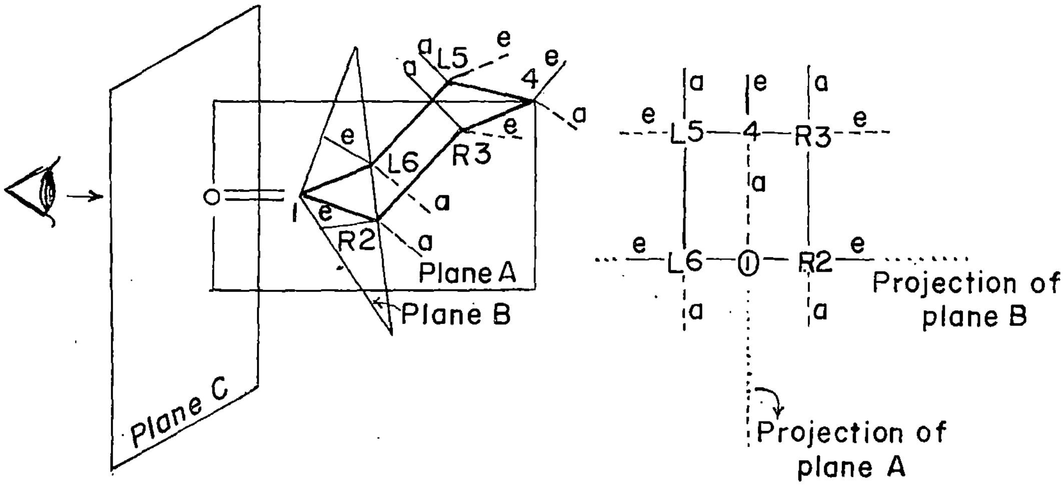
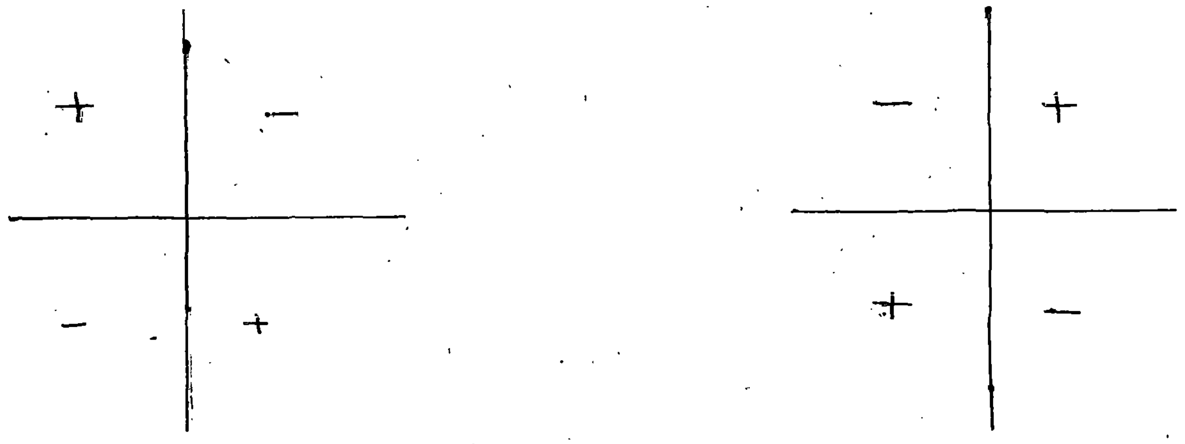

Plane C
O
1
L6
R2
L5
R3
4
a
e
Plane A
Plane B
L5
4
R3
L6
O
R2
Projection of plane B
Projection of plane A

Fig-6

left, called L-6). The equatorially oriented substituents attached to these carbon-atoms C-2 and C-6 lie nearly in the nodal plane B. Thus, the planes A and B correspond to the nodal planes xz and yz of the orbitals mentioned in <u>Fig. 6</u>. The planes A and B provide four Octants, the back Octants (Fig. 6). A third plane C, perpendicular to plane A and dissecting the oxygen-carbon atom (C-1) bond produces four additional Octants, called front Octants. It should be pointed out that the exact nature and position of plane C are still uncertain. The four back Octants defined by planes A and B are the most important ones for practical purposes (Fig. 7).

The Octant rule states that substituents lying in planes A and B make no contribution to the Cotton effect associated with the carbonyl. This includes the equatorial substituents on carbon atoms C-2 and C-6 provided that they are exactly in the plane and both substituents on carbon atom C-4.



Back Octants

Front Octants

Fig. 7

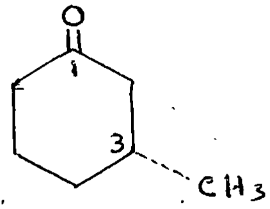
The atoms or groups of atoms situated in an axial configuration on C-2 (lower right Octant) as well as axial and equatorial substituents on C-5 (upper left Octant) make a positive contribution to the Cotton effect. And the substituents located in an axial configuration on carbon C-6 (lower left Octant) as well as the axial and equatorial substituents on carbon C-3 produce a negative Cotton effect.

Extensive studies have shown that alkyl group of all kinds and halogen atoms (except fluorine) in a given Octant make contributions of the same sign to the Cotton effect[18,19,20]. The signs of the rear Octant are shown in <u>Fig. 7</u>. A given substituent produces the largest effect when it is in an axial position α to the carbonyl group of a cyclohexanone in a chair conformation.

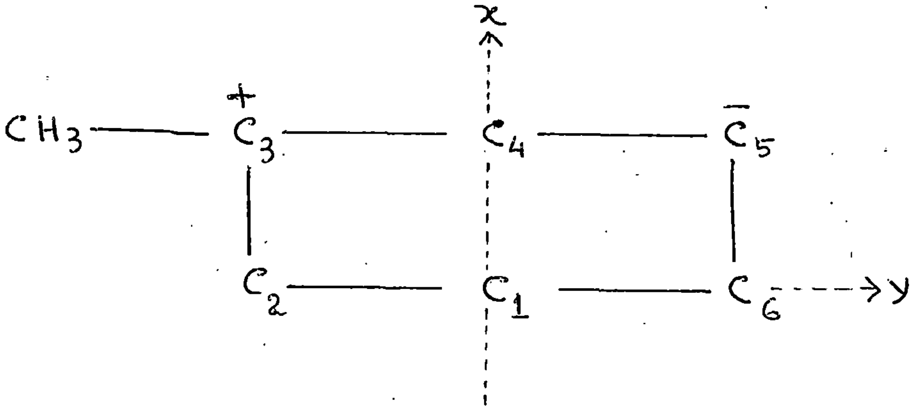
<u>Section E</u>: <u>Applications of the Octant Rule</u>:

The main utility of the Octant rule is as follows: If the absolute configuration[21] of a ketone is known, its conformation can be determined. Conversely, if the conformation of the compound is established, its correct absolute configuration can be assigned[22-28].

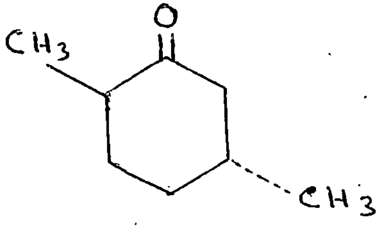
The study of the Cotton effect associated with (+) 3-methyl cyclohexanone <u>1</u> clearly illustrates the Octant Rule. The carbon atoms C-2, C-4 and C-6 lie in nodal planes and thus make no contribution to the Cotton effect. The contributions due to C-3 and C-5 cancel each other, being equal and opposite.



1



However, the methyl groups on C-3, being on a positive Octant, is alone responsible for the positive Cotton effect of this substance. The molecular amplitude of the O.R.D. curve of (+) 3-methylcyclohexanone is a = +25.



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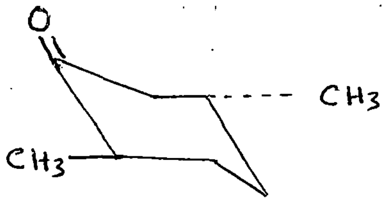
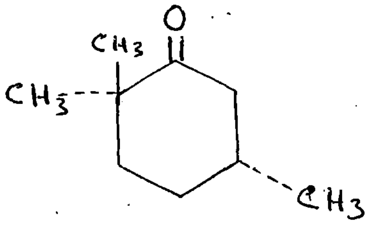


2a



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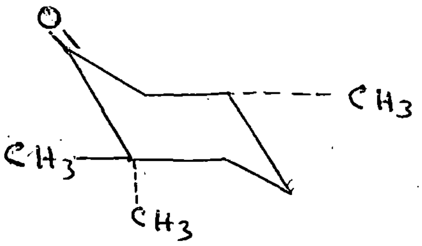
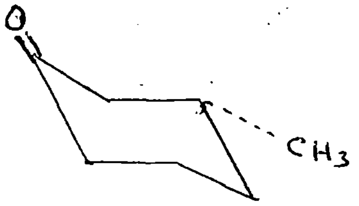


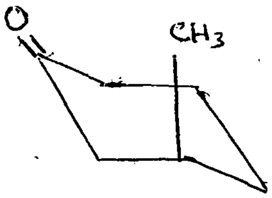
3a

In (+)-trans-3,6-dimethyl cyclohexanone 2 the equatorial methyl at C-6 2a lies in plane B and makes no contribution to the Cotton effect. Hence the compound shows the same positive Cotton effect as 1 (a = +28). But in compound (+) 3,6,6-trimethyl cyclohexanone 3 one axial methyl group is introduced, which being in a positive Octant enhances the positive Cotton effect (a = +81).

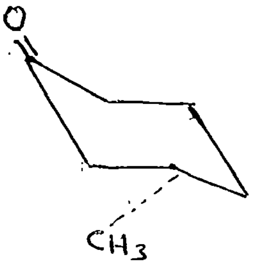
(+) 3-methyl cyclohexanone (1) can exist in two inter convertible conformations represented by 1a and 1b. Since the ketone showed positive Cotton effect; the conformation 1a represents the correct stereochemistry[29].



1a



1b

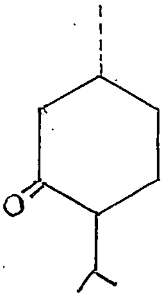


1c

The Cotton effect should be negative for conformation 1b and 1c also would be expected to show a -ive Cotton effect, thus confirming indirectly the absolute configuration 1a assigned to (+) 3-methyl cyclohexanone.

Absolute Configuration of monoterpenes (-)-menthone 4 and (+) isomenthone 5:

(-) menthone 4 shows a weak positive Cotton effect curve[22,23,28,30] whose amplitude is similar to that of trans, 3,6-dimethyl cyclohexanone 2. This can best be explained by the preferred conformation 4a in which both the alkyl groups are equatorially oriented (as in 2a).



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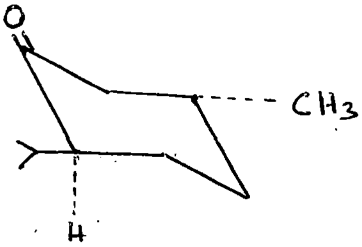
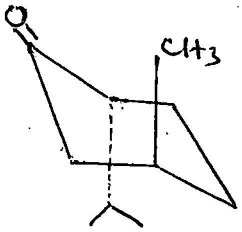
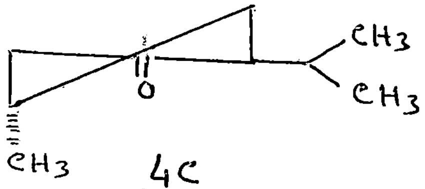


4a

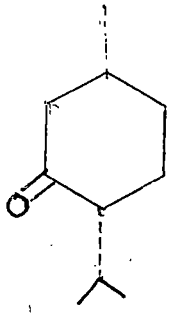


4b



4c

Isomerisation of (-) menthone 4a leads to (+)-isomenthone 5, for which two chair conformations 5a and 5b can be drawn. Since the Octant rule predicts a positive Cotton effect for conformation 5a and negative Cotton effect for 5b, the latter could be excluded.



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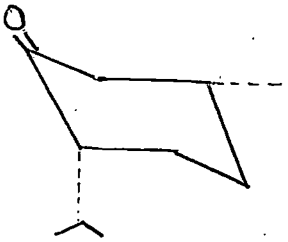
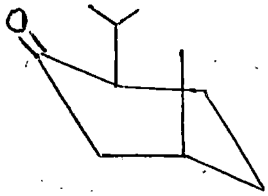
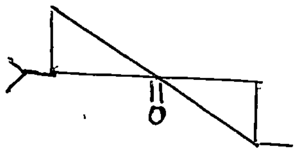


5a



5b

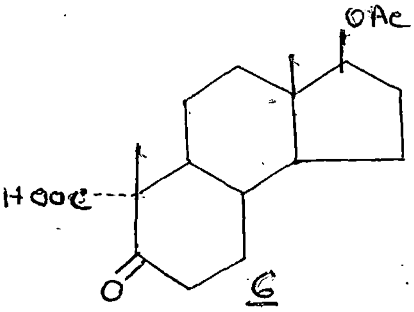


5c

Quantitative study[24] of the Cotton effect associated with (+)-isomenthone 5 indicates that there are contributions from conformers other than 5a. Although the twist form 5c would be expected to show a strongly positive Cotton effect[25], its participation together with conformer 5a can be excluded *a priori*[24].

Quantitative studies of the Cotton effect associated with α-equatorial alkyl cyclohexanones have indicated that in such cases an equatorial methyl[26], isopropyl[24] and t-butyl[27] group does not lie exactly in the nodal plane. In these cases, the equatorial alkyl substituent makes a positive contribution to the Cotton effect when situated on the right side next to the carbonyl.

The c.d of axial alkylated compounds 6 to 11 has also been measured. It was observed[31] in agreement with the Octant rule that an axial methyl group in α-position with respect to the carbonyl group has a *major influence* on the intensity and sometimes the sign of the Cotton effect.



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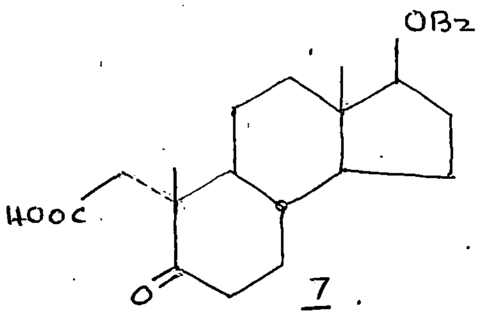

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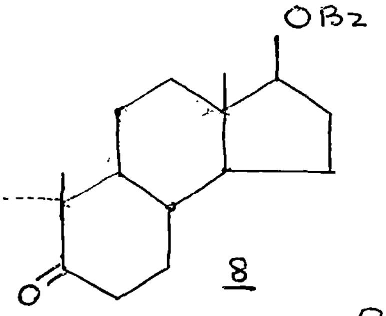

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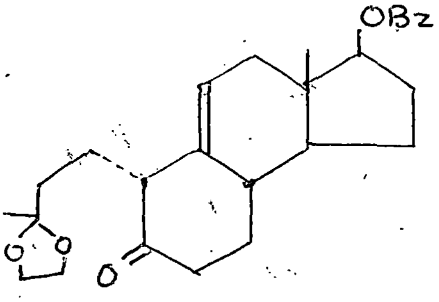

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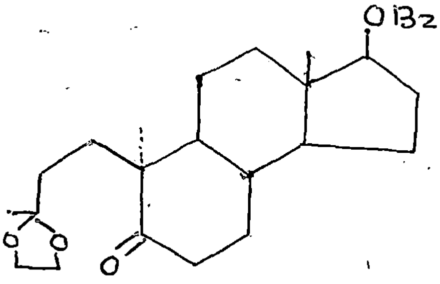

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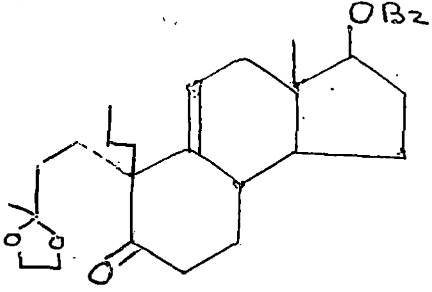

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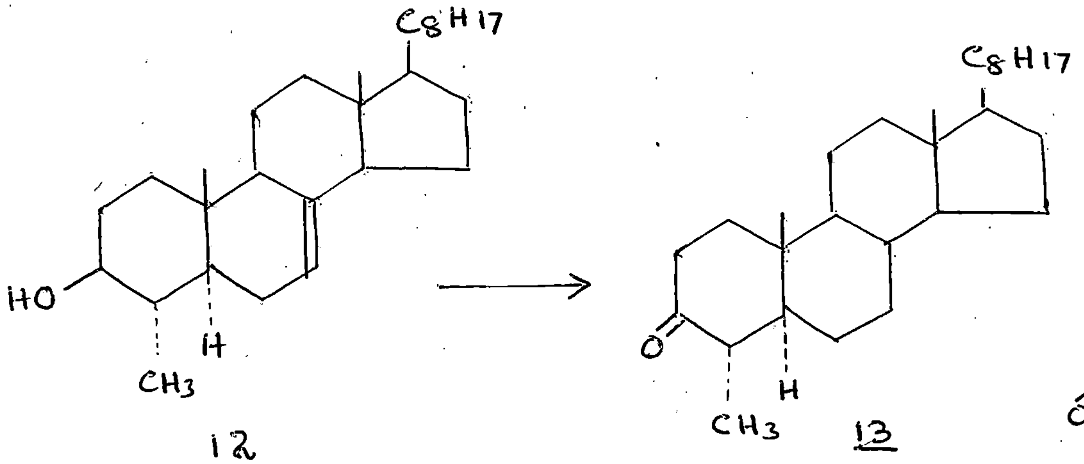
For example, in cases of acids 6 and 7 it has been pointed out[31] that, as expected, the introduction of an axial methyl group at C-10 has a positive effect on the c.d. maximum. However, the positive increment is higher than would be expected for a methyl group. In order to release the newly introduced 1,3-interactions between the 10β-methyl and the 6β, 8β and 11β-hydrogen atoms, the cyclohexanone ring probably partially adopts a boat or twist conformation.

Lophenol: The presence of adjacent alkyl groups was also shown[32] to have a strong inhibitory effect upon (hemi) ketal formation and advantage of this was taken in the structure elucidation[33] of lophenol 12, a novel type of biogenetically important plant sterol.



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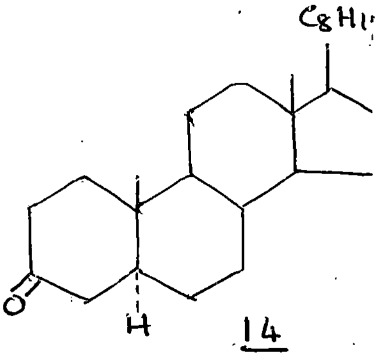

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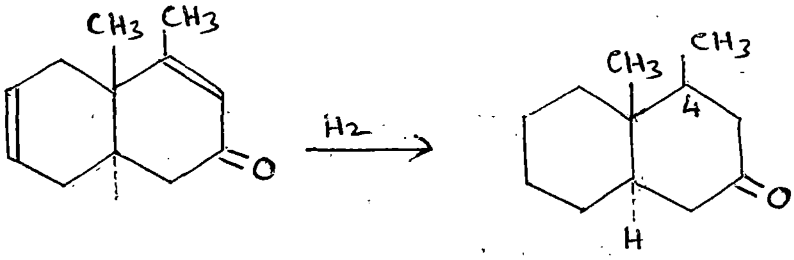
Reduction of the 6-7 double bond followed by oxidation gave lophanone 13, whose o.r.d. curve was similar to that of cholestanone 14, except that there was noted only a slight reduction in amplitude upon the addition of hydrochloric acid, in contrast to the marked one (64%) suffered by cholestan-3-one 14 . This observation strongly suggested the presence of a methyl group adjacent to the oxygen function and this helped greatly in the identification of lophanone 13 as 4α-methyl-cholestan-3-one.

Determination of stereochemistry of a Methyl group:

In connection with their work[34] in the eremophilone series Djerassi and coworkers, carried out the optical rotatory dispersion curve of the ketone 16 obtained by hydrogenation of 15 in methanol and noted that the curve underwent a marked reduction in amplitude upon addition of hydrochloric acid, which would only be compatible with an equatorial orientation of the C-4 methyl group. The axial isomer would almost certainly have inhibited the formation of the (hemi) ketal.



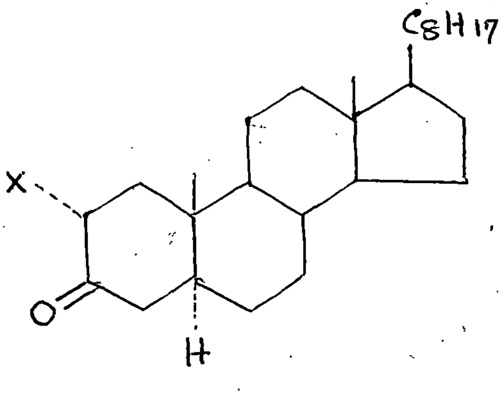
15 16

Section F: α-Halo Ketones:

The results accumulated[35] with U-V spectroscopic measurements demonstrated that the maximum associated with an isolated carbonyl group in a six membered ring is subjected to a hypsochromic shift of about 5 mμ by an adjacent equatorial bromine atom (i.e. to shorter wave length) but an axial bromine produces a bathochromic shift (i.e. to a longer wavelength) of 28 mμ. It is to be expected that corresponding shifts should be observed in the rotatory dispersion peaks (or troughs) of α-halo cyclohexanones as compared with those of halogen free precursors[36,37].

Equatorial halogen:

It will be observed from Table I that by comparison with cholestan-3-one 17 introduction of equatorial F(18), Cl(19), or Br(20) produces a slight bathochromic shift of practically the same amplitude (2 to 3 mμ) whereas an iodine atom causes a somewhat larger change (8 mμ)



17, X = H
18, X = F
19, X = Cl
20, X = Br
21, X = I.

Table I[37]

Substance	R.D. peak mμ	Mol. rot. MeOH	U.V. max for MeOH mμ
Cholestan-3-one 17	307	3710°	286 +
2α-Fluoro 18	309	2650°	280
2α-Chloro 19	310	3130°	279 +
2α-bromo 20	310	3190°	282 +
2α-Iodo 21	315	4400°	258

..+.. in ethanol

From the above table (Table I) it will be seen that with the exception of 21 (X = I), the range of wavelength shifts is comparable with that observed in the corresponding U-V spectra (hypsochromic shift of 4-7 mμ). Thus a slight bathochromic shift (+ 3 mμ) is observed in going from 17 to 20 (2α-bromo). A second characteristic feature associated with the equatorial halogen atom is that the rotatory dispersion amplitude of the parent ketone is not affected to a marked extent.

Axial Halogens:

Rotatory dispersion measurements of α-axial halogen substituted cyclohexanones exhibited a move to a higher wavelength[36] of 20+5 mμ (Table II), and the r.d. amplitude is greatly increased.

Axial Iodine caused a shift to a higher wavelength of 32 mμ.

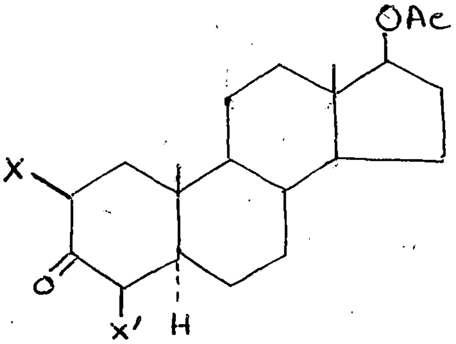
Table II[36]

Substance	R.D. first extremum	Wavelength shifts of axial halogen			
		Iodine	Br	Cl	F
Cholestan-2-one	310				
3 α-iodo	342	+ 32			
Friedelin	315				
2 α-bromo	335		+ 20		
4 α-bromo	335		+ 20		
Cholestan-3-one	307				
2 β-chloro	327			+ 20	
11-keto progesterone					
3,20-bisketal	321.5				
9 α-fluoro	340.0				+ 18.5

Section G: The Axial Halo Ketone Rule:[38] Its applications in Organic Chemistry:

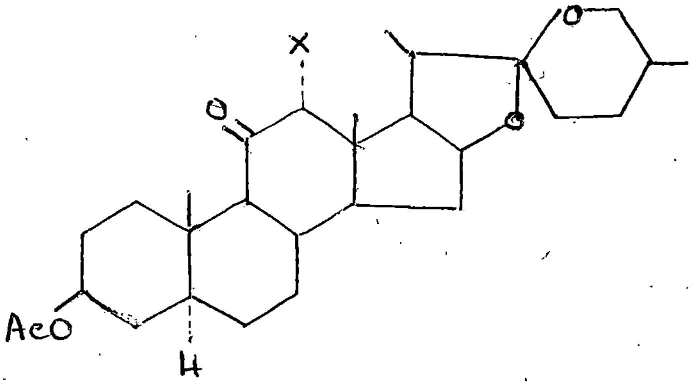
The sign of the Cotton effect associated with a given cyclohexanone is not altered by introduction of an equatorial bromine atom on either side of the keto group. On the other hand, this does not apply when the halogen atom exhibits an axial orientation, because in that event a reversal in sign may occur. The effect of an axial halogen atom is highly dependent on the site of the substitution.

Thus 2β-bromo androstan~~e~~-17β-ol-3-one acetate <u>22</u> shows a strongly positive and 4β-bromo androstan-17β-ol-3-one-acetate <u>23</u> a strongly negative Cotton effect. Numerous other examples of this phenomenon have been recorded in the literature[39] and this also applies to axial chlorine. Thus 5α-spirostan-3β-ol-11-one-acetate <u>24</u> has a positive and its 12α-chloro derivative <u>25</u>, a negative Cotton effect. It should be noted, however, that axial fluorine behaves anomalously and that the generalisations stated below applies to axial bromine, chlorine and probably also iodine, but not to fluorine.



<u>22</u>, X = Br, X' = H

<u>23</u>, X' = Br, X = H



<u>24</u>, X = H

<u>25</u>, X = Cl

The "axial halo ketone rule" states the matter as follows: (1) Introduction of equatorial halogen in either adjacent position of a keto group in a cyclohexanone does not alter the sign of the Cotton effect of the halogen free ketone.(2) The effect of introducing an axial chlorine, or bromine (and probably Iodine) atom next to the keto group of a ketone may affect the sign of the Cotton effect of the parent ketone.

The Cotton effect of the α-halocyclohexanone may be predicted by viewing along the O = C axis in a model so placed that the carbonyl group occupies the head of the chair (or boat) closest to the observer. If the halogen is now on the left of the line of view(Fig. 8)the compound will exhibit a negative Cotton effect (a) but if it is on the right, a positive Cotton effect will be observed (Table III).

Table III

Axial α-halo Ketone	Cotton Effect	
	Halogen free Ketone	α-Halo Ketone
3 α-Bromo androstan-2-one-17 β-ol propionate	+	+
7 α-Bromo cholestane-3 β,5 α-diol-6 one-3 acetate	-	+
7 α-Bromo cholestane-3 β,5 α,3 - diol-6one 3,5-diacetate	-	+

Contd..

Table III (Contd.)

Axial α-halo Ketone	Cotton Effect Halogen free Ketone	 α-Halo Ketone
6β-Bromo cholestan-3β-ol-7-one-acetate	-	+
9α-Bromo ergostan-3β-ol-11-one-acetate	+	+
12α-Bromo ergostan-3β-ol-11-one acetate	+	-
12α-Chloro-11-keto tigogenin acetate	+	-
12α, 23-Dibromo-11-Keto tigogenin acetate	+	-
Methyl 11β-bromo-3α-acetoxy-12 Keto cholanate	+	-
2α-Bromo friedelin	-	-
4α-Bromo friedelin	-	+

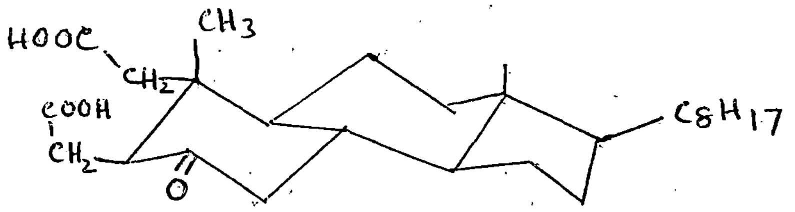
(a) Negative Cotton Effect (b) Positive Cotton Effect.

Fig. 8

The rule may be used in four ways:

1. If there is doubt whether an α-halogen is equatorial or axial, reversal of the Cotton effect upon halogenation proves location of the halogen. The converse is obviously not true. The halogen could be axial without reversing the Cotton effect, but even in this case it should be readily distinguishable from equatorial halogen through the bathochromic shift of the extrema and the increased amplitude[39].

2. If the configuration and conformation of the parent ketone are known and the α-halogen is axial (demonstrated as above (1) or by infra-red or U-V measurements) its location may be deduced from the sign of the Cotton effect of the haloketone. For example 2,3 -seco cholestan-6-one-2-3-dioic acid 26 upon bromination gives an axial α -bromo derevative which, a priori, could be the 5-or the 7-bromide. Since the Cotton effect for this bromide is negative, the haloketone rule implies that it is the 5-isomer.



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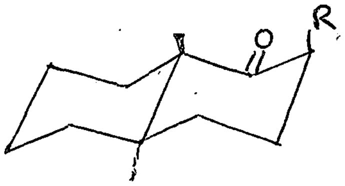
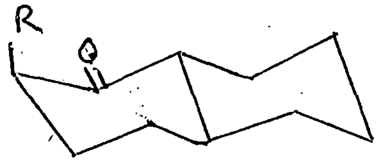
3. If the conformation of the ring system is fixed and the location of the axial α-halogen is known, the absolute configuration of the α-haloketone (and thus the parent ketone) may be deduced. An example is provided by (-) trans-1-decalone. This ketone may, a priori, have either configuration 27 or 28. Now bromination of trans-1-decalone gives, among other products, the



OR



27 R = H 28

29 R = Br 30

axial 2-bromo ketone. That the product is not the equatorial 2-bromo ketone may be deduced from I.R. as well as rotatory dispersion data as shown above; that it is not a 9-bromoketone follows from the fact that its reduction returns pure trans-1-decalone whereas the 9-bromo ketones-which are also formed in the bromination -upon reduction give the expected mixture of cis and trans-decalone[40]. When (-)-trans-1-decalone is brominated the product is (+)-2β-bromo-trans-1-decalone 29 or 30 which has a strong positive Cotton effect. According to the haloketone rule, this means that the dextrorotatory bromoketone has configuration 29 rather than 30. Therefore, (-) trans-1-decalone must have configuration 27 - thus providing an independent corroboration of the configurational assignment.

4. If the α-haloketone is axial and the position of the halogen and the configuration of the molecule are known, the conformation of the ring may be deduced. For example, chlorination of (+)-3-methyl cyclohexanone (absolute configuration as in Fig. 9) gives a mixture from which a pure crystalline isomer was isolated and shown, by chemical means, to be 2-chloro-5-methylcyclohexanone[41]. Two configurational isomers are possible, and each may exist in one or the other of two conformations as in Fig. 9 . The spectral properties of the crystalline chloroketone indicate that in octane solution it has axial halogen and the Cotton effect in octane is negative; this is compatible with configuration A but not with B. Hence the chloroketone is the trans-isomer. When the rotatory dispersion curve is measured in methanol, the Cotton effect is found to have become positive. This means that the trans isomer has changed from the diaxial conformation A to the diequatorial conformation A′, presumably because in methanol the dipole repulsion between the carbonyl group and the adjacent equatorial halogen is not so serious as in octane with its much lower dielectric constant.

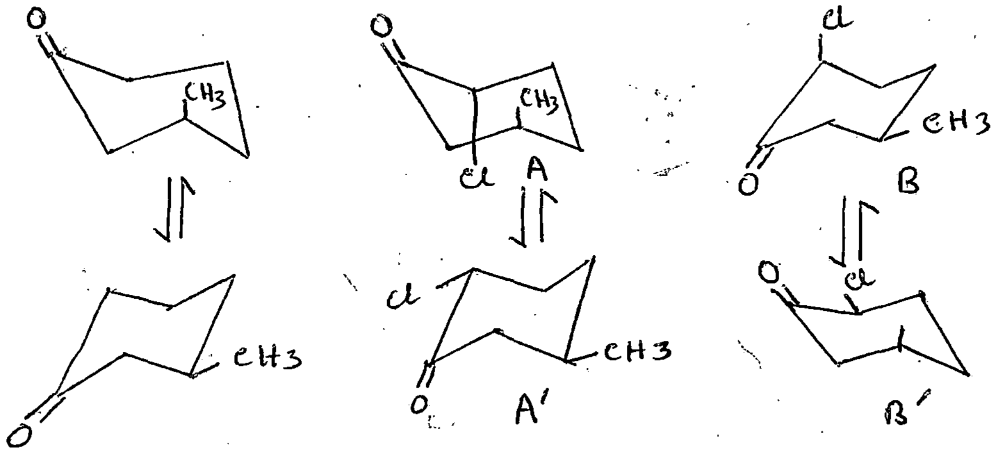
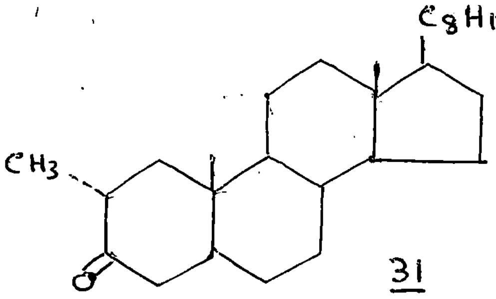


Fig. 9

Bromination of 2α-methyl cholestan-3-one: Boat Conformation of 2α-Bromo-2β-methyl cholestan-3-one.

Bromination of 2α-methyl cholestan-3-one 31 at the 2-position gave a 2-bromo-2-methyl-cholestan-3-one. I.R and U-V measurements[42] indicate that the bromine in this compound is axial and thus it appeared at first that the bromination product was - 2β-bromo-2α-methyl cholestan-3-one whose formation would have involved the usual axial attack of bromine in a kinetically controlled step. However, when the rotatory dispersion curve of the bromo ketone was recorded, it was found[43] that instead of the expected strong positive Cotton effect it shows a negative one. 2β-bromo-2α-methyl-3 keto steroids have been prepared[43] and they do indeed, show the expected strong positive Cotton effect. It, therefore, appears that the above discussed bromination product is 2α-bromo-2β-methyl cholestan-3-one and that its anomalous Cotton effect is due to the existence of the ring A in the boat form.



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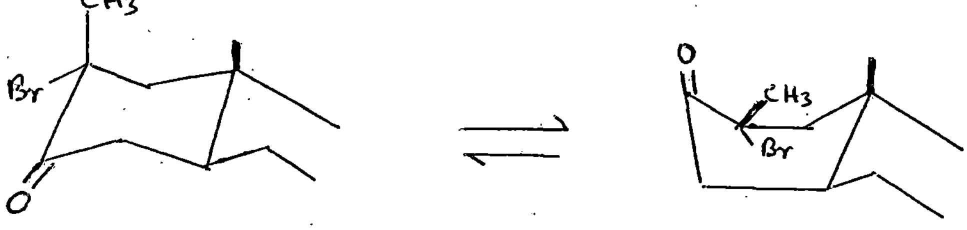


2α - bromo - 2β - methyl - Cholestan - 3 - one

In the chair form the bromine is equatorial and the Cotton effect should be unchanged from that of the parent ketone, this is not the case here.

Section H ; Effect of α-OH and α-acetoxy ketones: Anti Octant effect:

Information on the conformation of a ketone can generally be obtained from the sign, amplitude and position of its Cotton effect. With α-hydroxy ketones and α-acetoxy ketones, however, the situation is complicated by the fact that their circular dichroism (c.d), optical rotatory dispersion (o.r.d) spectra do not always follow the well known shift rules for U-V $n-\pi^*$ absorption bands of α-substituted ketones[35]. Thus it is known that the position of the $n - \pi^*$ bands in ultraviolet spectra is dependent on the nature and conformation of the α-substituent, and an axial hydroxyl group shows a bathochromic shift stronger than that of an axial acetoxy group, while on equatorial hydroxyl group shows a hypsochromic shift stronger than that of an equatorial acetoxy group[44]. Although most o.r.d and c.d. curves follow the same rule, exceptions[45] are known in steroids in α-ketal grouping in ring C (Table IV). This also appears to be true in some B-ring α-ketals[46].

Table IV

No.	Substance	Rotations dispersions, in Dioxan Solution	Δλe	Δλa
1.	11-keto-tigogenin	325 mμ	-	-
2.	12-α-hydroxy-11-keto-tigogenin	337.5 mμ		+12.5
3.	3-O-Acetyl-12α-acetoxy-11-keto tigogenin	340 mμ		+15
4.	12β-hydroxy-11-keto-tigogenin hydrate	315 mμ	-10	-10
5.	3-O-Acetyl-12β-acetoxy-11-keto-tigogenin	322.5 mμ	-2.5	
6.	3-O-Acetyl-hecogenin	312.5 mμ		
7.	3-O-Acetyl-11α-acetoxy-hecogenin	310 mμ	-2.5	
8.	3-O-Acetyl-23α-brom-11β-hydroxy-hecogenin	332.5 mμ		+20
9.	3-O-Acetyl-11β-acetoxy-23α-brom-hecogenin	335 mμ		+22.5

The deduction from the Octant rule that an equatorial OR group will have little influence on the Cotton effect, whereas an axial group will show a definite contribution applies in most cases[47] and leads

Table V α-Ketols and their acetates.

Position of Keto group	Series	α-Substituent OR	amplitude a	Contribution to O.R. Δa
3	5α-Cholestane	none	+58	
	2α-oAe(eq.)	2α-OAe(eq)	+66	+8
		2β-OAe(ax)	+166	+58
3	4,4'-dimethyl	none	-12	
	-5α-Cholestane	2α-OAe(eq)	+38	+50
		2β-OAe(ax)	+124	+136
4	5α-Cholestane	none	-95	-
		5α-OH(ax)	-45	+50
6	5α-Cholestane	none	-78	-
		5α-OH(ax)	-110	-32
		5α-OAe	-89	-11
11	5α-Spirostan	none	+43D	-
		12β-OH(eq)	+44D	+1 1
		12β-OAe(eq)	+42D	-1 1
		12α-OH(ax)	+42D	-1
		12α-OAe	+88D	+45
11	5β-Cholanate 12	none	-	-
		12β-OH(eq)	+14	
		12β-OAe(eq)	+28	
		12α-OAe(ax)	+73	
11	5α-Ergostane	none	+12	
		12α-OAe	+85	+73
	5α-Ergostane	none	+19	
		9α-OH(ax)	+68	+49
11	5β-Etianate	none	+10	
		12α-OH	+40	+30
		12α-OAe	+44	+34
		12β-OAe	+171D	+71
12	5α-Spirostan	none	-	
		11α-OAe(eq)	411D	
		11β-OH(ax)	+77D	
		11β-OAe(ax)	+162D	
13	5β-Cholanate	none	+10	
		11α-OH(eq)	+17	+ 7
		11β-OH(ax)	+39	+29

Table V (Contd)

Summary for α-Ketols

C = O	C-OH	Octant behaviour	
3(5α)	2	✓	Normal
4	5α	✓	
6	5α	✓	
11	9		
11	12	X	abnormal
12	11	X	

The above table showed that for the steriod α-ketols it is generally true that (a) eq. (OH) or acytoxy substituent have e ? little influence on the Cotton effect.

(b) axial (OH) or acetoxy substituents in ring A and B make large contribution to the Cotton effects of the same sign as chlorine or bromine in the same pattern.

(c) axial (OH) or acetoxy substituents in ring C makes large contribution to the Cotton effect of opposite sign to those given by chlorine or bromine in the same portion.

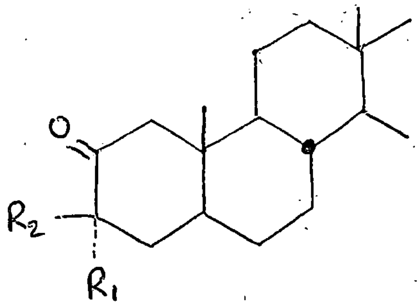
to the correct prediction of the Cotton effect of 4 β-acetoxy-cholestan-3-one[48], but not of 3 α-acetoxy cholestanone[48] or a 12 α-acetoxy-11-ketone or a 5 α-acetoxy-6-ketone, although no conformational change is to be expected. As shown in Table VI,

Table VI

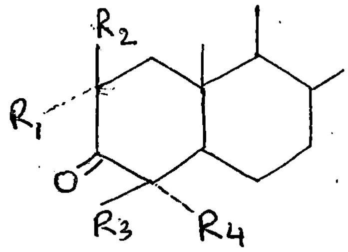
O.R.D

Compound	Peak	Trough	Molecular amplitude a
5 α-Cholestan-2-one	$[\Phi]_{310}$ $+6290^{\circ}$	$[\Phi]_{267}$ -5820°	$+121$
3 α-OH-5 α-Cholestan-2-one-acetate	$[\Phi]_{317}$ $+2540^{\circ}$	$[\Phi]_{257}$ -2330°	$+49$
3 β-OH-5 α-Cholestan-2-one-acetate	$[\Phi]_{305}$ $+6740^{\circ}$	$[\Phi]_{270}$ -5320°	$+120^{\circ}$
5 α-Cholestan-3-one	$[\Phi]_{307}$ $+3700^{\circ}$	$[\Phi]_{267}$ -2940°	$+55^{\circ}$
2 α-OH-5 α-Cholestan-3-one-acetate	$[\Phi]_{305}$ $+3450^{\circ}$	$[\Phi]_{265}$ -2790°	$+62$
2 β-OH-5 α-Cholestan-3-one-acetate	$[\Phi]_{290}$ $+1820^{\circ}$	$[\Phi]_{250}$ $+6201$	$+121$
4 α-OH-5 α-Cholestan-3-one-acetate	$[\Phi]_{300}$ $+1850^{\circ}$	$[\Phi]_{260}$ -2410°	$+43$
4 β-OH-5 α-Cholestan-3-one-acetate	$[\Phi]_{320}$ $+730$	$[\Phi]_{270}$ -970°	$+17$

3β-hydroxy-5α-cholestan-2-one-acetate 32c shows the same amplitude as 5α-cholestan-2-one in agreement with the Octant rule, since the equatorial acetoxy function lies in a nodal plane. The molecular amplitude of the 3α-acetoxy derivative 32b is considerably reduced when compared with the parent unsubstituted 5α-cholestan-2-one 32a. Since a 3α-axial substituent in ring A in the chair form would be expected to enhance the Cotton effect, it is suggested that this ring is distorted in 32b in order to release the non-bonded interactions between the 3α-substituent and the 1α- and 5α-axial hydrogen atoms. However, in a recent NMR study of axial and equatorial alcohols, it was indicated[48] that the coupling constant of the 3-equatorial proton in 32b is in perfect agreement with a normal chair conformation for Ring A. The unexpected o.r.d curve of 2β-acetoxy-cholestan-3-one 33b[48], on the other hand, has been taken as evidence for a twist conformation of ring A.



32a, $R_1 = R_2 = H$
32b, $R_1 = Ac$, $R_2 = H$
32c, $R_1 = H$, $R_2 = Ac$



33a, $R_1 = R_2 = R_3 = R_4 = H$

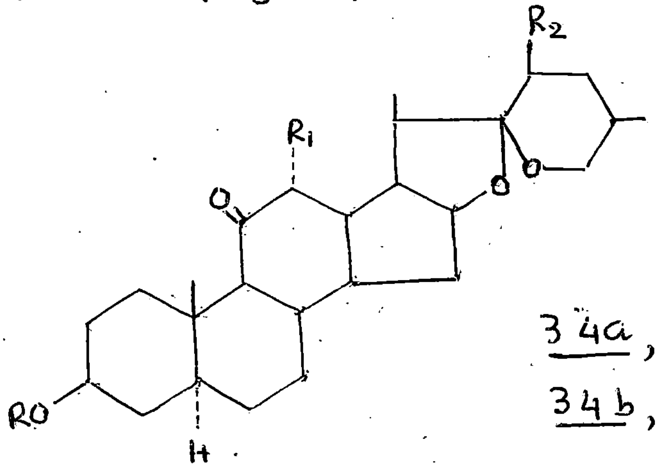
33b, $R_1 = R_3 = R_4 = H$; $R_2 = Ae$

33c, $R_1 = Ae$, $R_2 = R_3 = R_4 = H$

33d, $R_1 = R_2 = R_3 = H$, $R_4 = Ae$

33e, $R_1 = R_2 = R_4 = H$, $R_3 = Ac$

The 4β-acetoxy derivative 33e is also distorted in order to release 1,3-diaxial interactions between the 4β-acetoxy and the 10β-methyl groupings. The molecular amplitude of the 4α-isomer 33d, is somewhat decreased when compared with 33a. It has been suggested that this may be due to reorientation of the acetoxy group in 33d in order to avoid interactions with the 6α hydrogen atom. The acetoxy function is no longer in the nodal plane and makes a mild negative contribution to the Cotton effect. Djerassi and coworkers[49a and 49b] have shown that fluorine atoms gave contributions of opposite sign to alkyl (or chlorine or bromine) Fig 10. 11-keto tigogenin 34a is characterised by a weak positive single Cotton effect curve associated with 11-keto steroids and introduction of an axial bromine or chlorine atom at C-12 as 34b and 34c results in the anticipated increased amplitude and bathochromic shift as well as in an inversion of the sign of the Cotton effect. The latter observation is in accord with the empirical rule ~~49a~~ 49a already discussed. However, introduction of a fluorine atom at C-12 as in 12α-fluoro-11-keto tigogenin acetate 34d exhibits the same wavelength shifts as does the corresponding 12α-chloro analog 34c but the Cotton effect is of opposite sign. This grossly different behavior of axial fluorine is also observed in the case of 9α-fluoro-11-keto-progesterone-3-20-bisethylene ketal 35 which showed a negative Cotton effect in contrast to the 9α-bromo compound 36 where a positive single Cotton effect was observed. (Fig. 10)

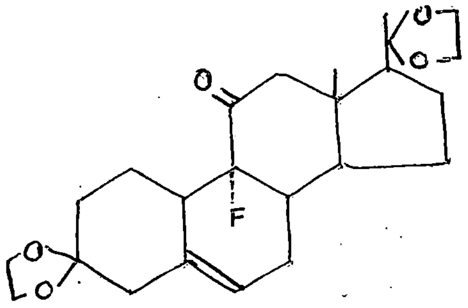


34a, $R = R_1 = R_2 = H$

34b, $R = Ac$, $R_1 = R_2 = Br$

34c $R = Ac$, $R_1 = Cl$, $R_2 = H$

34d $R = Ac$, $R_1 = F$, $R_2 = H$



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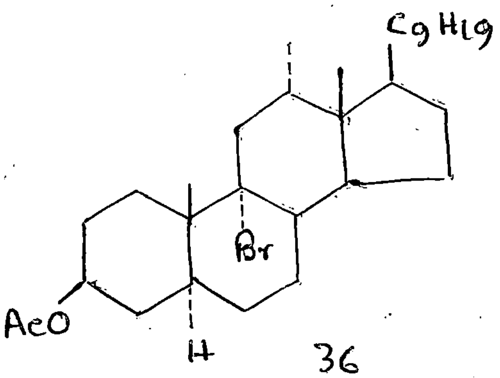

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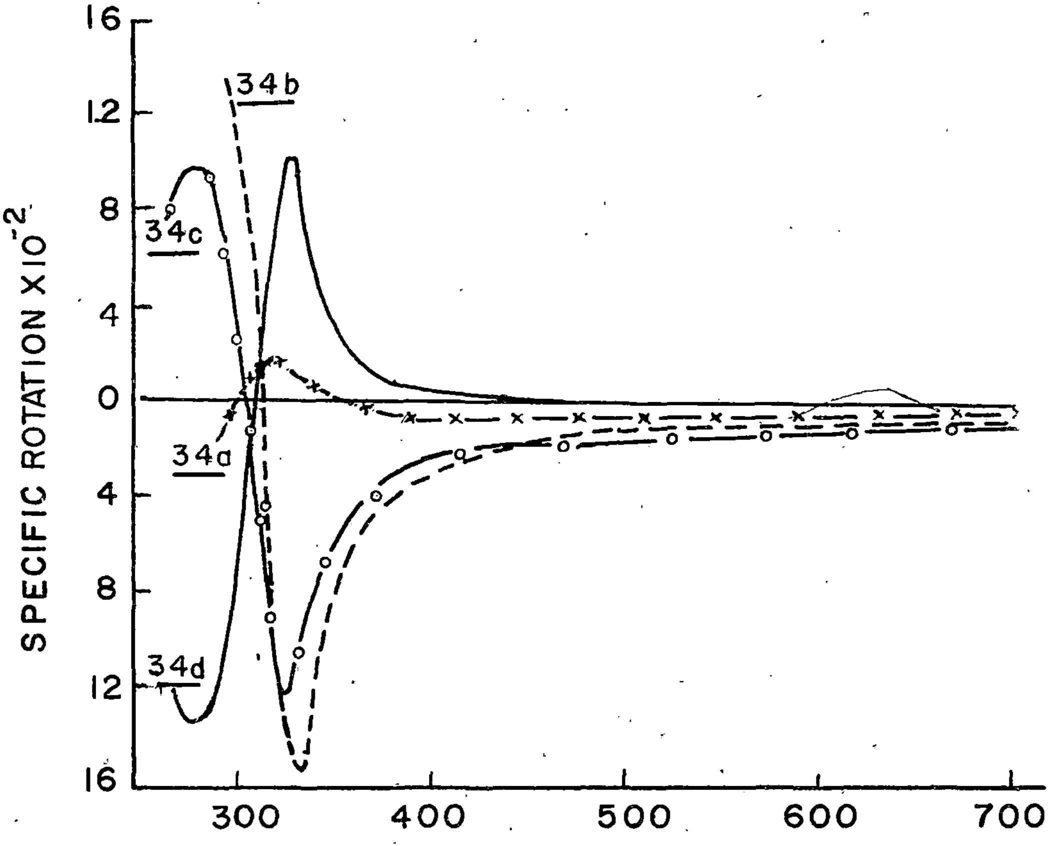
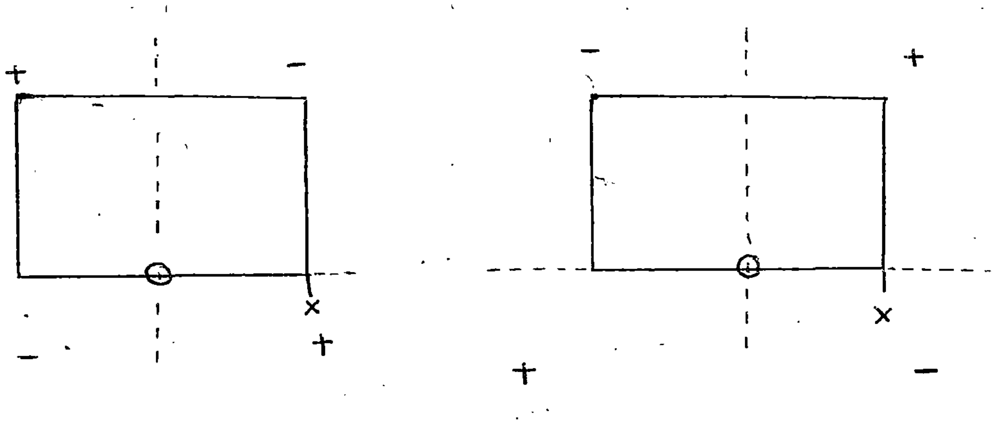

16
12
8
4
0
4
8
12
16
SPECIFIC ROTATION X10^{-2}
34b
34c
34a
34d
300
400
500
600
700
WAVE LENGTH (mμ)

Fig-10

This behaviour has been termed "Anti-Octant behaviour" (Fig. 11).



Normal Octant Sign
(for rear Octants)

Anti-Octant Signs (for rear
Octants)

.... nodal planes

Fig. 11

Recently, Enslin and his colleagues[50] carried out c.d. studies on ring A hydroxy and acetoxy-ketones and some of the results show anti-Octant effects. (Table VII[50]) (next page)

Table VII

Compound	CD in Methanol			CD in Hexane		
	$\Delta\epsilon$ (nm)	Shift[a] (nm) of ketone $n\to\pi^*$ band	$\Delta\Delta$max contribution[b]	$\Delta\epsilon_{max}$ (nm)	Shift[a] (nm) of ketone $n\to\pi^*$ band	$\Delta\Delta_{max}$ contribution[b]
3β-OAc-5α-cholestan-2-one[e]	+3.2(289) -1.1(210[c])		0	+2.25(300) +2.35(292) -1.0(210[c])		0
3α-OAc-5α-cholestan-2-one[e]	+1.45(300) -1.0(215[c])		AO	+1.0(314) +1.05(305) -1.0(215[c])		AO
5α-cholestan-4-one	-2.1(291)			-1.0(315) -1.6(304) -1.6(296)		
3β-OH-5α-cholestan-4-one	-1.95(289) +0.35(215[c])	2^{-}	+0.15	-2.25(286) +0.5(215[c])	14^{-}	-0.65
3β-OAc-5α-cholestan4-one	-2.1(291) +1.25(210[c])	0	0.0	-1.5(299) -1.6(291) +1.2(210[c])	5^{-}	0.0
5-OH-5-αcholestan-4-one	-0.85(302)	11^{+}	+1.25,0	-1.1(306)	6^{+}	+0.5,0

Table VII (Contd.)

Compound	CD in Methanol			CD in Hexane		
	$\Delta\epsilon$ (nm)	Shift[a] (nm) of ketone $n \rightarrow \pi^*$ band	$\Delta\Delta$ max contribution[b]	$\Delta\epsilon$ (nm) max	Shift[a] (nm) of ketone $n \rightarrow \pi^*$ band	$\Delta\Delta$ max contribution[b]
5-OAc-5α-Cholestan-4-one	$-2.9(294)$ $+2.4(214)$	3^+	-0.8,AO	$-2.3(299)$ $+1.2(222)$	1^-	-0.7,AO
5β-cholestan-4-one	$0.20(284)$			$+0.25(307)$ $+0.25(297)$		
5-OH-5β-cholestan-4-one	$-0.9(306)$	22^+	$-1.1,0$	-0.25(326sh) $-0.30(316)$	19^+	$-0.55,0$
5-OAc-5β-cholestan-4-one	$+1.05(297)$ $-1.2(220)$	13^+	$+0.85$,AO	$+1.2(300)$ $-1.05(220)$	2^+	$+0.95$,AO
5α-cholestan-6-one	$-1.60(292)$			$-0.7(315)$ $-1.2(305)$ $-1.1(296)$		
5-OH-5α-Cholestan-6-one	$-2.55(303)$	11^+	$-0.95,0$	$-1.45(308)$	8^+	$-0.25,0$
5-OAc-5α-cholestan-6-one	$-1.9(293)$ $-0.8(220)$	1^+	$-0.3,0$	-1.2(302sh) $-1.35(296)$ $-0.55(222)$	1^-	$-0.15,0$
5β-cholestan-6-one	$-4.2(294)$			$-3.2(308)$ $-3.4(299)$		
5-OH-5β-cholestan-6-one	$-5.1(288)$ $+2.45(215^c)$	6^-	-0.9	$-4.4(286)$ $+2.9(215^c)$	17^-	-1.2

Table VII (Contd.)

Compound	CD in Methanol			CD in Hexane		
	Δε(nm)	Shift[a] (nm) of ketone n ⟶ π* band	ΔΔmax contribution[b]	Δε(nm) max	Shift[a] (nm) of ketone n ⟶ π* band	ΔΔmax contribution[b]
5-OAc-5β-cholestan-6-one	-3.7(293) +0.95(220)	1^-	+0.5	-2.6(300) -2.75(293) +1.15(220)	7^-	+0.65
4,4,14α-trimethyl-19(10→9β) abeo-10α-pregn-5-en-2,11,20-trione	+6.45(297)					
4,4,14α-trimethyl-19(10→9β) abeo-10α-pregn-5-en-3, 11,20-trione	+6.65(295) +12.0(214)					
Anhydro-22-deoxocucurbitacin D	+ 4.15(302) +16.0(216)					

a bathochromic + hypsochromic -.
b "O" Octant contribution, "AO" anti-octant contribution.
c end absorption.
e The results on these compounds should be compared with an ORD amplitude of a = +121 for the parent ketone in dioxan solution.

The results of three α-ketals with axial OH-group viz. the 5α-hydroxy-4-one, the 5β-hydroxy-4-one and the 5α-hydroxy-6-one show that in each case the α-substituent makes a significant contribution of the predicted sign.

Anomalous results were obtained for two α-ketals with equatorial OH groups. In hexane solution, where strong intra-molecular H-bonding is expected, the spectra of 3β-hydroxy-5α-cholestan-4-one and the 5β-hydroxy-6-one revealed an unmistakable contribution due to the equatorial substituent. This effect in methanol, where the polar nature of the solvent would be expected to weaken intra-molecular hydrogen bonds was no longer significant in the 3β-hydroxy-4-one but was still apparent in the 5β-hydroxy-6-one. The influence of strong intra-molecular H-bonding was evident as strong end absorption at 210-15 nm in the C.D. spectra of these compounds, particularly in hexane solution. Significant changes were observed in the corresponding OAc-derivatives. The axial OAc-group of the 5α and 5β-acetoxy-4-ones and the 3α-acetoxy-2-ones make a strong contribution to the ketone Cotton effect, but of a sign opposite to that predicted by the Octant rule -i.e. (anti-Octant contribution). The sign of the Cotton effect in the 5α-acetoxy-6-one accords with prediction, but the magnitude of the effect is strongly reduced by comparison with that of the corresponding OH-compound. The effect of this anti-Octant behavior of axial OAc-group is demonstrated clearly in the case of 5-hydroxy-5β-cholestan-4-one where acetylation of the tertiary OH-group leads to reversal of the sign of the ketone n-π effect Fig 12. The C.D. spectra of 3β- acetoxy-5α-cholestan-2-one and 3β-acetoxy 5α-cholestan-4-one and the data already reported in the literature (Table V, Table VI) and Table VIII)for

Table VIII

c.d and O.R.D data for related derivatives of 5α-cholestane; c.d. curves measured for solutions in dioxan (D) or ethanol(E); O.R.D curves measured for solutions in methanol-dioxan (2:1)

	C.D			O.R.D	
	Solvent	λ(mμ)	Δε	λ(mμ)	a
3β-hydroxy-4-one	D E	286 287	-1.91 -2.32	303/263	-101
3β-acetoxy-4-one	D E	290-295 289	-1.82 -2.08	305/265 222	-105 +59a
4α-hydroxy-3-one	D	290	+1.32	298/258	+62
	E	283	+1.12		
4α-acetoxy-3-one	D	287 227	+0.95 +0.44	298/259 226	+39 -5^{a}
	E	284	+0.83		
		227	+0.64		

various A-ring equatorial α-ketal acetates are in agreement with the Octant rule since these OAc groups contribute insignificantly to Cotton effects of the corresponding parent ketones. The result

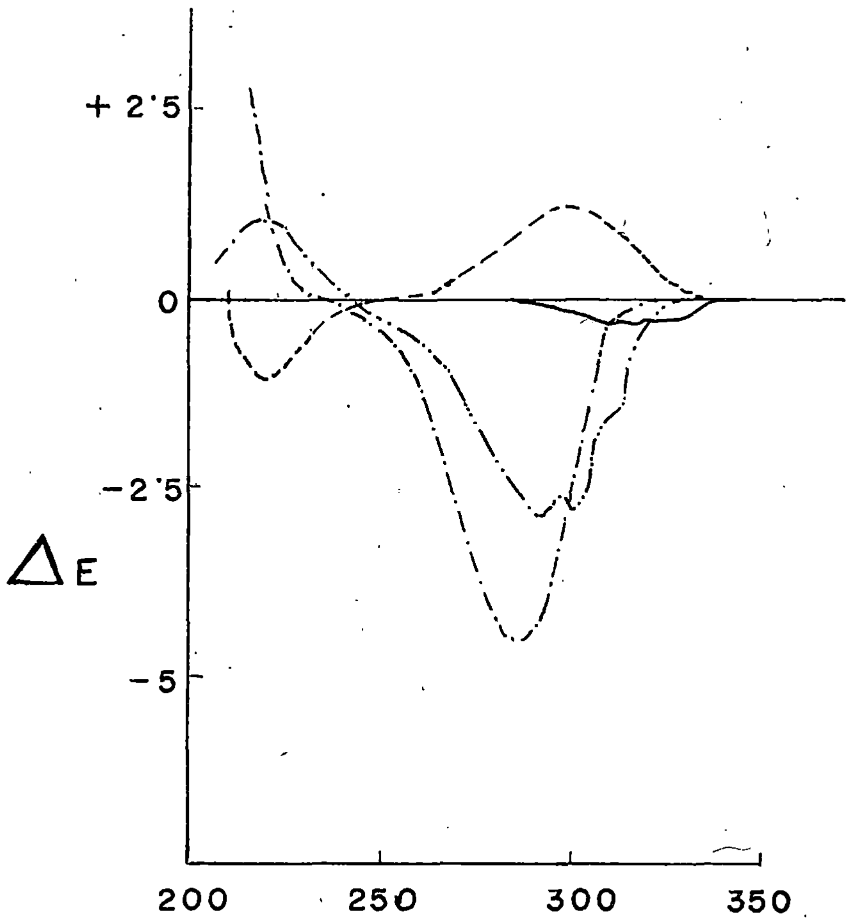


Fig-12 CDspectra in haxene solution

5-hydroxy-5β-cholestan-4-one - ·· ·· ————

5-acetoxy-5β-cholestan-4-one ·· ·· ·· - - - - - - -

5-hydroxy-5β-cholestan-6-one ·· ·· ··—·—·—·—

5-acetoxy-5β-cholestan- -one ·· ·· ··—··—··—··-

reported by Enslin and his coworkers[50] on the 5β-acetoxy-6-one is however, an important exception since this equatorial OAc-group makes a demonstrable positive contribution in both hexane and methanol (Table VII).

Enslin and his colleague studied the space-filling models (Courtauld Atomic Models) of the above α-ketals and their acetates and made the following observations (1) free rotation of the OH-groups of all the α-ketals is possible, but in axial cases, 1,3-diaxial interactions suggest some conformational preference- which is strengthened by the known (albeit weak) OH — πCH bond[51]. (2) In compounds with an equatorial OH-group, the strong OH···· n-OH bond[51] should result in a conformational preference. (3) In axial OAc compounds there is complete restriction of rotation about the -C-O- bond of the OAc group. In the equatorial OAc- compounds such rotation is also severely contained, but not to the same extent as axial cases. However, one notable exception is 5-acetoxy-5β-cholestan-6-one, where rotation about the C-O bond of the equatorial (relative to the 6-ketone) α-substituent is completely frozen since this function is at a cis-ring junction and is therefore axial relative to the A-ring. Significantly, this is also the one-α-ketal acetate in which an equatorial OAc-group makes a remarkable contribution to the ketone $n-\pi^*$ Cotton effect.

(4) Due to the severe rotational barrier imposed upon OAc-groups in these compounds, two discrete conformers appear to be possible, in one in which the OAc-carbonyl group is oriented toward the ketone

and in the other, away. It is therefore feasible that in the former the proximity of the two optically active functions may lead to coupling of their respective n-π^* transitions. It is also possible that a more important factor - that is perturbation of the ketone n-π^* transition by the lone pairs on the "ether oxygen" of the adjacent OAc group and the spatial orientation of these lone pairs relative to the ketone may be decisive in determining anomalous behaviour.

(5) Since the models demonstrate that conformational preferences of the α-substituents exist, and further that the constrained orientation of the C-O-oxygen lone pairs in each α-ketol acetate differs from that preferred in each α-ketol, this difference may well influence the amplitude and sign of the ketone n-π^* transition. Consequently, any factor which alters the lone pair orientation in a sterically restricted environment will result in an observable effect upon this transition whether the α-substituent is equatorial or axial.

Snatzke and Veithen recently[52] studied the C.D. curves of 5-amino-5α-cholestan-6-one and its N-acetyl derivative and they observed a large difference in amplitude between the C.D. maxima of 5-amino-5α-cholestan-6-one and its N-acetyl derivative. Enslin and his colleagues suggest that here also, a difference in orientation of the nitrogen lone pairs of the two compounds relative to the CO-group could play a role.

Recently, Bartlett and his co-workers[53] measured the o.r.d and c.d. of a series of hydroxy and acetoxy derivatives of (+) bornan-2-one [(+) Camphor 37 $R^1 = R^2 = H$] and (-) bornan-3-one [(-)-epi-camphor 38; $R^1 = R^2 = H$] which are summarised in Table IX. These data also present a clear picture of apparent anti-Octant effect by oxygen containing substituents.

Table IX

C.D. of bornanone derivatives: Summary of $\Delta\epsilon$ values and differences ($\Delta\Delta\epsilon$).Solvent, Hexane. Principal c.d. maxima only are shown. Signs of $\Delta\Delta\epsilon$ are "Anti-Octant" in every case.

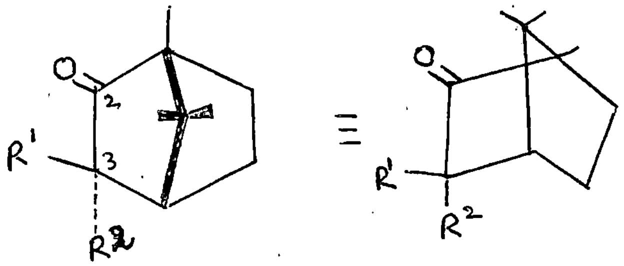
Hydroxy groups	λ/nm	$\Delta\lambda$/nm	$\Delta\epsilon$	$\Delta\Delta\epsilon$
Bornan-2-one	303	17	+1.50	
endo-3-OH	320[a]	+17	+0.31[a]	-1.19
exo-3-OH	304	+1	+1.85	+0.35
Bornan-3-one	306		-1.46	
endo-2-OH	317[b]	+11	-0.76	+0.70
exo-2-OH	304	-2	-2.07	-0.61
Acetoxy groups				
Bornan-2-one	303		+1.50	
endo-3-OAc	325[c]	+22	+0.36[e]	-1.14

Table IX (Contd.)

Hydroxy groups	λ/nm	$\Delta\lambda$/nm	$\Delta\epsilon$	$\Delta\Delta\epsilon$
Acetoxy groups				
exo-3-OAc	304	+1	+2.18	+0.68
Bornan-3-one	306		-1.46	
endo-2-OAc	327^d	+21	-0.23^d	+1.23
exo-2-OAc	308	+2	-2.34	-0.88

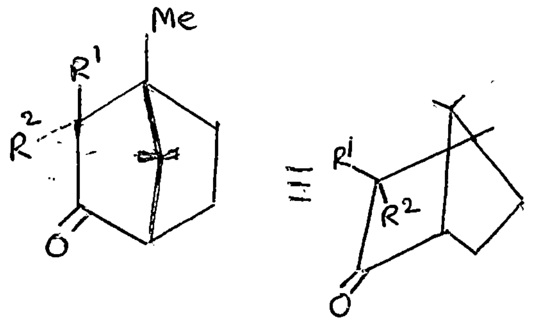
Additional maxima of opposite sign at shorter wavelength.

	$\Delta\epsilon$	λ/nm		$\Delta\epsilon$	λ/nm
a	-0.20	288	c	-0.09	283
b	+0.16	283	d	+0.35	292



37

(+)-Bornan-2-one
[(+)-Camphor]



38

(-) Bornan-3-one
[(-) epi-Camphor]

All the C.D. substituent differences ($\Delta\Delta\epsilon$) values for solutions in hexane in Table IX above are of "Anti-Octant" sign. The endo-isomer in each pair produces the larger effect, although the magnitudes of the differences vary. The C.d data for solutions in dioxan and methanol (Table X) show a similar trend, except that endo-2-hydroxy bornan-3-one shows a small "Octant" substituent effect in methanol.

According to the authors, all the hydroxy ketones exhibited very little or no fine structure in their c.d. curves even in hexane, which may be the result of intramolecular hydrogen-bonding between the hydroxy and ketone groups in non-polar solvent. Joris and Schleyer[51] have found evidence for moderately strong hydrogen bonding in the I.R. spectra of some related hydroxy ketones in carbon tetrachloride. In the case of exo-hydroxy ketones 37 (R^1 = OH, R^2 = H) and 38 (R^1 = OH, R^2 = H) there is no appreciable bathochromic solvent shift between methanol and hexane, in contrast the parent ketones, however, show a pronounced shift on changing the solvent.

The acetoxy-ketones are in many ways analogous to the hydroxy compounds, but with the unusual features exaggerated.

The authors stated that "there is no certainty that the conformation of the acetoxy-group itself is fixed, although the perferred conformation of many other acetoxy-compounds[54] appears to be

Table X

Cotton effects of camphor and epi-camphor derivatives

Temperature, 22-24^{o}
Solvents: M, methanol; D, dioxan; H, hexane; polarities as measured by E_T values are respectively 55.5, 36.0 and 30.9. $a/\Delta\epsilon$ should be 40.28 in the theoretical case of a perfect Gaussian c.d. curve. The experimental values are given to the nearest whole number.
Fine structure: O, none; W, weak; M, medium; S, strong. The partial band of largest $\Delta\epsilon_{max}$ is shown in italics.
* $[\Phi] x 10^{-2}$ for single extremum.

Compound	Solvent	U.v. absorption λ_{max}/nm; (ϵ_{max} in parentheses)	C.d. λ/nm	$\Delta\epsilon$	O.r.d. λ/nm of extrema	a	$a/\Delta\epsilon$	Fine structure (c.d.)
Bornan-2-one (+)-Camphor	M	290(30)	295	+1.39	314/276	+58	42	O
	D		309sh	+1.04				
			299	+1.45	315/275	+63	43	W
			290sh	+1.20				
	H	292(24)	314sh	+1.01				
			303	+1.50	320/277	+63	42	MW
			294sh	+1.34				
endo-3-Hydroxybornan-2-one	M		314	+0.71	330/294	+36	43	O
	D		324	+0.61				
			314	+0.53	323/300	+31	49	W
			320	+0.31	331/303	+19	52	O
	H		288	-0.20	303/273	-9	42	
exo-3-Hydroxybornan-2-one	M	303(34)	307	+1.64	328/287	+67	41	O
	D		311	+1.70	333/287	+69	41	O
	H	301(31)	304	+1.85	329/283	+86	46	O

Table X (Contd.)

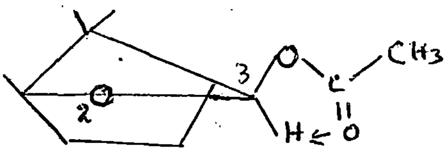
Compound	Solvent	U.v.absorption λ_{max}/nm; (ϵ_{max} in parentheses)	C.d. λ/nm	$\Delta\epsilon$	O.r.d. λ/nm of extrema	a	$a/\Delta\epsilon$	Fine structure (c.d.)
endo-3-Acetoxybornan-2-one	M		333	-0.03	330*	-2*pk		
			323	+0.06				W
			292	-0.425	306/270	-19	45	
	D		323	+0.365	330/306	+16	44	M
			312	+0.300				
			288	-0.155	306/270	-11	37	
	H	302(45)	325	+0.36	331/308	+17	47	MS
			313	+0.34				
			304sh	+0.10	303/263	-8		
			283	-0.09				
exo-3-Acetoxybornan-2-one	M		305	2.15	325/285	+95	44	0
	D		307	2.23	327/285	+103	46	0
	H	290(71)	304	2.18	328/285	+93	43	0
Bornan-3-one (-)-epi-Camphor	M		299sh	-1.58		-62	38	W
			295	-1.65	310/271			
	D		312sh	-1.04				
			303	-1.52	316/276	-64	42	W
			294sh	-1.36				
	H	295(27)	317sh	-0.93	[illegible]			
			306	-1.46	320/276	-62	42	M
			296sh	-1.34				

Contd.

Table X (Contd)

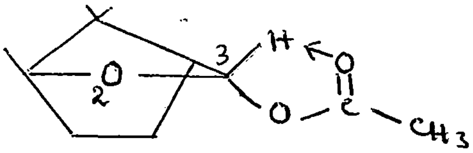
Compound	Solvent	U.v. absorption λ_{max}/nm; (ϵ_{max} in parentheses)	C.d. λ/nm	$\Delta\epsilon$	O.r.d. λ/nm of extrema	a	$a/\Delta\epsilon$	Fine structure (c.d.)
endo-2-Hydroxy-bornan-3-one	M		313	-1.78	329/289	-79	44	0
	D		329sh	-1.16				
			316	-1.34	331/297	-60	45	0
	H	300(19)	317	-0.76	330/297	-37	49	0
			283	+0.16				
exo-2-Hydroxy-bornan-3-one	M	303(37)	307	-1.64	325/281	-64	39	0
	D		311	-1.80	330/285	-72	40	0
	H	302(26)	304	-2.07	323/278	-82	40	0
2ndo-2-Acetoxy-bornan-3-one	M		333	+0.02	333	+7*		-
			325	-0.05				
			293	+0.55	310/272	+19	35	0
	D		325	-0.25	331/308	-16	64	
			315sh	-0.09				W
			291	+0.38	308/273	+17	45	
	H	304(54)	327	-0.23	332/311	-14	61	W
			316sh	-0.08				
			292	+0.35	311/269	+15	43	
exo-2-Acetoxy-bornan-3-one	M		303	-2.40	326/280	-122	51	0
	D		308	-2.57	330/285	-115	45	0
	H	304(48)	308	-2.34	332/284	-105	45	0

of the type found by Mathieson[55] for secondary acetoxy groups, in which the carbonyl is eclipsed with secondary hydrogen (as in projection 39a and 39b).



39a

3β-exo



39b

3α-endo

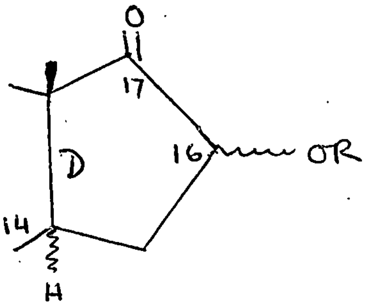
This should not be taken for granted in the present series of compounds because d~~e~~ipole- d~~e~~ipole interaction between the ketone and the ester carbonyl group may significantly alter the situation.

The endo-acetoxy ketones (137, R^1 = H, R^2 = OAc) and (38, R^1 = H, R^2 = OAc) exhibit complex c.d. curves, possibly owing to s~~a~~olvation. The exo-compounds (acetoxy) show simpler curves than the endo-epimers. They do not show c.d. maxima of opposite si~~ng~~gn (Table X).

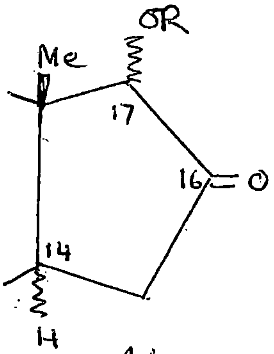
It will be observed that the four compounds (indicated by foot notes in Table IX) which show double c.d. maxima of opposite signs are the *endo*-3-hydroxy-2-one and the *endo*-2-hydroxy-3-one (in hexane only) and the corresponding *endo*-acetoxy ketones in all these solvents; in all cases this additional maximum (Ca 290 nm) shows an "Anti-Octant" effect with respect to the parent compound's maximum at 303 nm.

The authors have discussed in the paper the possible explanations for this effect. According to them, since the bornanones have relatively rigid structures conformational equilibria in the carbon framework can probably be excluded. Although a moderate degree of flexibility in substituted bornanes and related compounds has recently been demonstrated from X-ray studies[56], the authors suggest that the possible distortions are unlikely to alter significantly the Octant dispositions of structural features in these compounds and should not afford two conformationally distinct species. Further, they stated that although there is the possibility of two or more conformers about the C-OH and C-OAc bonds- such conformer are not likely to afford C.d. maxima of opposite sign. They, however suggest that there is the possibility that the "double humped" curves represent permitted and forbidden branches of the same transition.

Fishman and coworker[57] studied the O.r.d. of steroid ring-D Ketol-acetates (<u>40</u>, <u>41</u>) which also present another example of "Anti-Octant" effect by oxygen-containing substituents (Table XI).The



<u>40</u>



<u>41</u>

anti-Octant A a values for OAc found in the bornanone series in Methanol (Ca ± 60) agree well with values (Table X) recorded for the steroidal acetate <u>40</u> and <u>41</u>.

Since, halogeno-substituents α-to the carbonyl in ring D of steroids show normal Octant effects on the o.r.d. and c.d. curves, it may be presumed that they cause no major distortion of Ring D. In the present case, also it is reasonable to assume that "Anti-Octant" behaviour of acetoxy group in ring D arises due to some cause other than conformational change.

Table XI

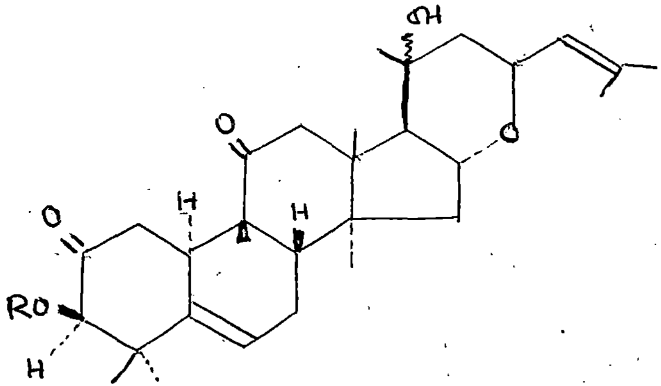
O.R.D. data for Steroid ring D Ketol acetates[56]

Solvent-dioxan.

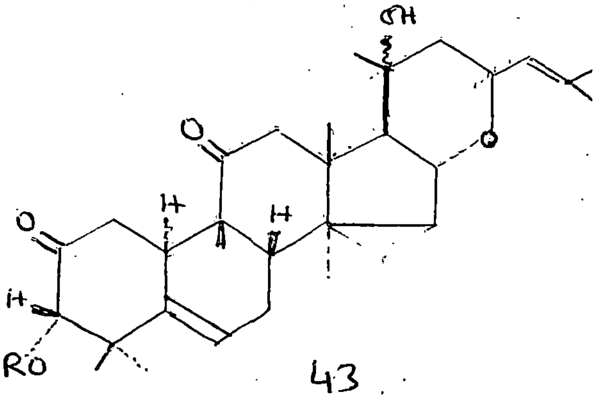
Ketone or acetoxy-ketone	a	Δa for OAc
14α-Configuration		
17-CO	+132	
17-CO; 16α -OAc	+176	+44
17 CO; 16 β-OAc	+85	-47
16 CO;	-264	
16 CO; 17α -OAc	-313	-49
16-CO; 17 β-OAc	-202	+62
14 β -Configuration		
17 CO;	+35	
17 CO; 16α -OAc	+51	+16
17 CO; 16β -OAc	-57	-92
16 CO	+110	
16 CO; 17α -OAc	+ 96	-14
16 CO; 17β -OAc	+194	+84

C.D. measurements and Stereochemistry of the epimeric 3-hydroxy-2-Ketones viz. anhydro-22-deoxo isocu~~f~~curbitacins D and anhydro-22-deoxo-3-epi-isocurcurbitacin D:

In 1967, G.Snatzke and his co-workers[58] deduced the stereochemistry of the epimer~~s~~ic-3-hydroxy-2-ketones- the isomers (42; 43, R = H) on the basis of c.d. and other physical data.



42



43

The isomers 42 (R = H) and 43 (R = H) exhibited U.V maxima of 288-289 nm. The corresponding acetates (42; R = Ac) and (43 R = Ac) had U.V. maxima at 291 nm, while the I.R. peak due to the 2-ketone group appeared at 1736-37 cm^{-1}. These results indicated an equatorial conformation of the 3-hydroxyl or 3-acetoxy group in these compounds. The bathochromic shift (2 to 6 nm) of the c.d.

maxima on acetylation of the isomers (42, R = H) and (43, R = H), $\Delta\epsilon$ max remaining unaltered (Table XII and Fig. 13)also supported this conclusion. On the basis of the U.V. shift rules the fact that the C.d. maxima of the isomer (43; R = H) and its acetate (43; R = Ac) appear at a higher wavelength than those of the isomer (42; R = H) and its acetate (42; R = Ac)could have been considered as evidence for an axial orientation of the OR group in (43, R = H or Ac). Similarly from the N.M.R spectral data, the fact that proton at position 3 resonates at a higher field (43, R = Ac) at τ 5.05 than in 42 (R = Ac) at τ 4.92, could have been considered as evidence for an equatorial hydrogen (axial OAc group) in isomer 43 (R = OAc).

Table XII

Circular dichroism of ring A-Keto Chromophores

Compound	Position of maxima in $m\mu$, $\Delta\epsilon$ in parentheses[58]
(42, R =H)	275sh (-3.02), 285(-3.46), 304sh(-1.15) 315 sh (-o.12), 318 (0), 325 (+0.37)
(42 R = Ac)	279sh (-2.31), 291(-3.00), 298sh (-2.75)
(43, R = H)	250 (+0.13), 270(0), 295(-0.52), 304(-0.40)
(43, R = Ac)	267 (+0.08, 273(0), 297 (-0.48), 305(-0.40)

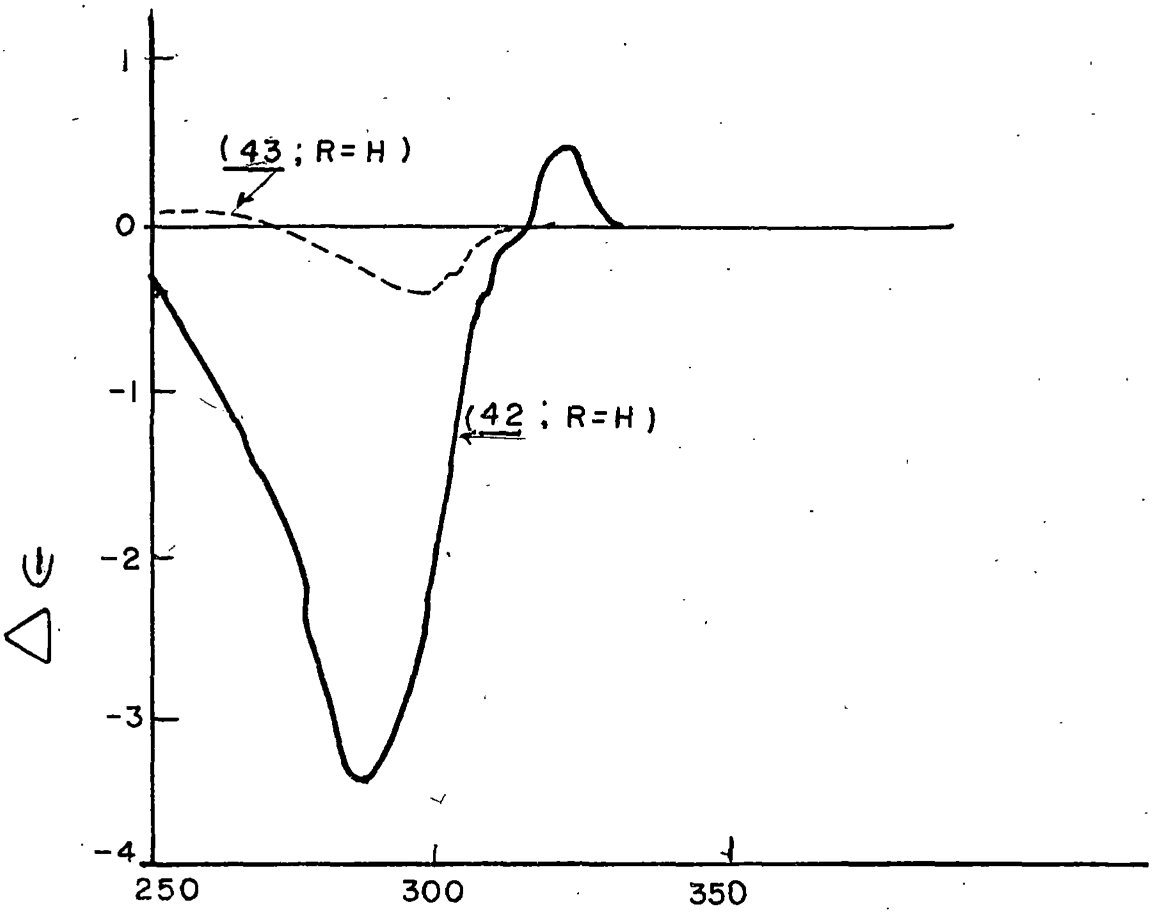


Fig. 13. Cotton effects of ring A → chromophore in 3-hydroxy-2-ketones (42 R=H) and (43 R=H)

These conclusions are, however, valid only if it is assumed that ring A is in the chair conformation in both isomers. In compounds with ring A in twist conformation e.g. in 2β-acetoxy cholestan-3-one[48] and 2β - bromo lanost-8-en-3-one[59] the Cotton effects show a hypsochromic shift compared to the 2α-isomers in the chair conformation. Furthermore, in the n.m.r. spectra of 2α-and 2β-acetoxy cholestan-3-one it has been found that the proton at position 2 resonates at lower field when it is axial on a twist ring (τ4.88 in 2β-isomer) than when it is axial on a chair ring (τ4.93 in 2α-isomer)[48]. Thus an equatorial conformation of the acetoxy group in both isomers (<u>42</u>, R = Ac) and (<u>43</u>, R = Ac) would require that ring A is in the twist conformation in the first case and in the chair conformation in the second.

The c.d. maxima of the isomers (<u>42</u>, R = H) and (<u>43</u>, R = H) differ in their amplitudes considerably (Table XII) indicating that the ring A in these two compounds has different conformations. From an Octant projection of the 2-ketone in the all chair form; one can predict a moderate negative Cotton effect <u>Fig. 14</u>; the C and D rings are somewhat mobile relative to ring A as a result of the Δ^5- double bond.

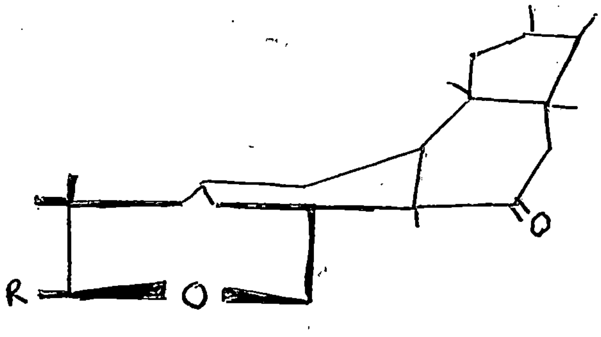


Fig. 14 Octant projection of a 2-oxo-cu~~r~~curbitacin (R = OH or OAc) Ring A in chair conformation.

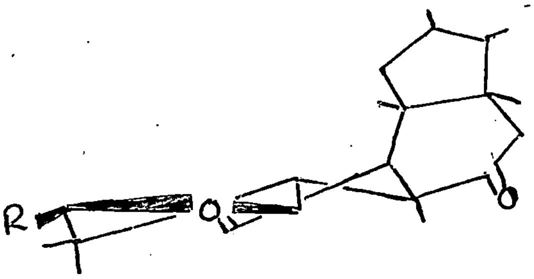


Fig. 15 Octant projection of a 2-oxo cu~~r~~curbitacin (R = OH or OAc). Ring A in twist conformation.

In the twist form (Figure 15), according to known rules^{25,47} a strongly negative Cotton effect can be predicted since the 2-ketone is one of the points of the twist. On the basis of above, the authors assigned isomer (<u>43</u>, R = H) a structure with ring A in the chair form and isomer (<u>42</u>, R = H), a structure with ring A in the twist form.

From considerations of (a) different interactions (b) energy differences between the chair form and twist from (c) geometry for hydrogen bonding, the authors deduced that ring A will prefer a conformation in which the hydroxyl group is in the equatorial position. For R = Ac in the 3β -isomer (<u>42</u>) in the all chair conformation there is a destablis~~h~~ing repulsion between this axial group and the 1β-hydrogen. In the twist form, a 3α-axial acetoxy group suffers a flag-pole-flag-pole interaction with the 10α-hydrogen. From the above considerations they assigned OR group in compound (<u>43</u>, R = H or OAc) as 3α-configuration (ring A chair) and compound (<u>42</u>, R = H or Ac) as 3β-configurat~~e~~ion. It may be noted that in the two isomers, the double bond is in the nodal plane (x, z) of the CO-group and is therefore not expected to exert any direct influence upon the chromophore.