1329. *Optical Rotatory Dispersion. Part XXVI.*[1] *Some Bridged Ring Lactones*

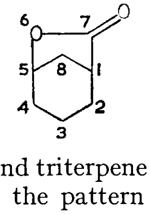
By J. P. Jennings, W. Klyne, and Patricia M. Scopes

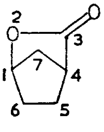
The optical rotatory dispersion curves have been measured for a number of bridged ring lactones, most of which give Cotton effects with a first extremum at about 233 mμ. These compounds are discussed in terms of the lactone sector rule, which affords a satisfactory explanation of the experimental data reported.

An earlier Paper in this Series [2] described the optical rotatory dispersion (o.r.d.) of several groups of bicyclic and polycyclic compounds in which a five- or six-membered lactone ring is fused to other carbocyclic rings. Most of these compounds showed Cotton effects with a first extremum at about 225 mμ (related to their weak absorption band at 215 mμ [3]). The signs and magnitudes of these Cotton effects were discussed in terms of the lactone sector rule, and it was shown that this semi-quantitative approach enabled a satisfactory explanation to be offered for the experimental data. Other studies of the o.r.d. of lactones have been made by Wolf,[4] and by Okuda *et al.*[5]

In this Paper we present the data for some further stereochemical types, in which the lactone group –OCO– bridges a carbocyclic ring: the 6-oxa-7-oxobicyclo[3,2,1]octane type (I) and the 2-oxa-3-oxobicyclo[2,2,1]heptane type (II). Our examples are taken

(I)





(II)

from the fields of steroid and triterpene chemistry in which bridged lactones are of common occurrence. This follows the pattern developed for the study of ketones in which the

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[1] Part XXV, W. Klyne and R. J. Swan, *Chem. and Ind.*, 1965, 2018.

[2] J. P. Jennings, W. Klyne, and P. M. Scopes, preceding Paper.

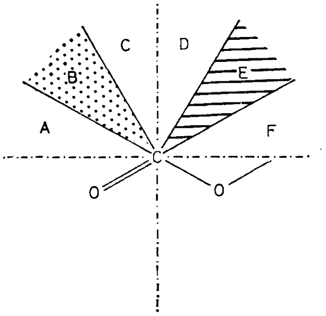
[3] S. F. Mason, *Quart. Rev.*, 1961, **15**, 287.

[4] H. Wolf, *Tetrahedron Letters*, 1965, 1075.

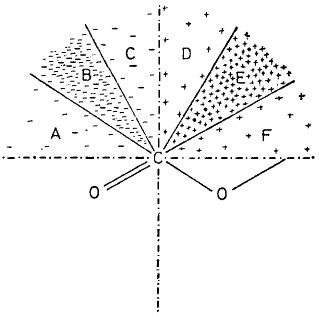
[5] T. Okuda, S. Marigaya, and A. Kiyomoto, *Chem. and Pharm. Bull* (*Japan*), 1964, **12**, 504.

octant rule was first applied to six- and five-membered ketones,[6] and subsequently to bridged ring ketones.[7]

As for the simpler compounds, the bridged lactones may be discussed semi-quantitatively in terms of the lactone sector rule,[2] which correlates the geometry of the asymmetric surroundings of the chromophore with the sign, and (in some cases) the magnitude of the lactone Cotton effect. In order to make this correlation, it is necessary to consider two views of any particular molecule, first, an " octant " projection, in which the molecule is viewed along the bisectrix of the $\widehat{OCO}$ angle and secondly a " sector " projection in which the molecule is viewed from above, perpendicular to the plane of the lactone group. Atoms which lie in the back upper right or lower left octants, particularly within the sector of high contribution (E) (III), make positive contributions to the rotation of the molecule as a whole. Conversely, atoms which lie in the back upper left or lower right octants, and particularly within the sector of high contribution (B) make negative contributions to the total rotation. Atoms which fall in other sectors make much smaller contributions to the total rotation than those in B or E, but atoms near the sector boundaries A/B, B/C and D/E, E/F, may make significant rotation contributions (cf. IV).



(III)



(IV)

TABLE 1

Summary of Cotton effects at approx. 235 mμ

Class of compound	Formula	No. of samples	Sign of lactone Cotton effect Predicted from sector rule	Found
6-Oxa-7-oxobicyclo[3,2,1]*octanes*				
19 $\longrightarrow$ 2β-Lactones of 5α-steroid	(V)	3	+	+
19 $\longrightarrow$ 6β-Lactones of 5α-steroid	(VI)	2	+	+
18 $\longrightarrow$ 11β-Lactones of 5β-steroid	(VII)	1	+	+
28 $\longrightarrow$ 13β-Lactones of 18α-oleanane	(VIII)	2	+	+
28 $\longrightarrow$ 13β-Lactones of 18β-oleanane	(IX)	1	+	?+
28 $\longrightarrow$ 21β-Lactones of 18β-oleanane	(X)	1	+	+
28 $\longrightarrow$ 19β-Lactones of 18α-oleanane	(XI)	2	—	—
28 $\longrightarrow$ 15β-Lactones of 18β-oleanane	(XII)	1	—	—
19 $\longrightarrow$ 4β-Lactones of 5α-steroid	(XIII)	1	—	—
2-Oxa-3-oxobicyclo[2,2,1]*octanes*				
17β $\longrightarrow$ 14β-Lactones of 5β,14β-steroid	(XIV)	2	?	+
28 $\longrightarrow$ 19β-Lactones of lupane	(XV)	2	+	+

A comparison of the experimental results and the sector rule predictions for various stereochemical types of bridged lactones is shown in Table 1. It may be noted that the first extremum of the Cotton effect occurs at slightly higher wavelengths (233—235 mμ)

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[6] W. Moffitt, A. Moscowitz, R. B. Woodward, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, 1961, **83**, 4013; C. Djerassi and W. Klyne, *J.*, 1962, 4929; 1963, 2390.

[7] W. Klyne, *Tetrahedron*, 1961, **13**, 29.

in bridged lactones than in the simpler molecules described in our earlier Paper[2] (225—227 mμ). This corresponds to the absorption band of the –COO– group, which in a typical bridged compound, the 19 $\longrightarrow$ 2β-lactone of 2β,3α-dihydroxy-5α-cholestan-19-oic acid, has a shoulder, $\varepsilon = 150$, at 218 mμ.

Symbols on Octant and Sector Projections.—The following symbols are used where necessary to indicate the contributions of particular significant atoms (cf. ref. 6). The

TABLE 2

Optical rotatory dispersion of some bridged ring lactones

Solvent, methanol; pk = peak; tr = trough; ! = lowest wavelength measured.

Compound	General formula	[φ] at first extremum		[φ] at lowest wave-length measured		Source and reference
		$[\phi] \times 10^{-2}$	λ (mμ)	$[\phi] \times 10^{-2}$	λ (mμ)	
6-Oxa-7-oxobicyclo[3,2,1]*octanes*						
2β-Hydroxy-17β-propionoxy-5α-androstan-19-oic acid lactone	(V)	+41 pk	235	−93!	208	A/1
2β,3α-Dihydroxy-5α-cholestan-19-oic acid 19 $\longrightarrow$ 2β-lactone	(V)	+64 pk	237	−60!	212	B/2
2β-Hydroxy-3-oxo-5α-cholestan-19-oic acid lactone *	(V)	+54 pk	235	−55!	208	B/2
3β,6β,17β-Trihydroxy-5α-androstan-19-oic acid 19 $\longrightarrow$ 6β-lactone	(VI)	+37 pk	233	−33!	217	A/1
6β-Hydroxy-3,17-dioxo-5α-androstan-19-oic acid lactone diethylene ketal	(VI)	+25 pk	234	−103!	212	A/1
3β-Acetoxy-11β,20-dihydroxy-5β-pregnan-18-oic acid 18 $\longrightarrow$ 11β-lactone	(VII)	+58 pk	234	−18!	214	A/3
3β,13β-Dihydroxy-18α-oleanan-28-oic acid 28 $\longrightarrow$ 13β-lactone	(VIII)	+41 pk	232	−53!	213	C/4
3β-Acetoxy-13β-hydroxy-18α-oleanan-28-oic acid lactone	(VIII)	+10!	270 †			C/4
3β,13β-Dihydroxy-18β-oleanan-28-oic acid 28 $\longrightarrow$ 13β-lactone	(IX)	+3!	270 †			C/4
3β,21β-Dihydroxy-18β-olean-12-en-28-oic acid 28 $\longrightarrow$ 21β-lactone	(X)	+42 pk	234	−13!	224	D/5
3β,19β-Dihydroxy-18α-oleanan-28-oic acid 28 $\longrightarrow$ 19β-lactone	(XI)	−1 tr	230	+12!	214	C/6
19β-Hydroxy-3-oxo-18α-oleanan-28-oic acid lactone	(XI)	−4 tr	233	+26!	227	F/7
3β,15β,22α-Trihydroxy-18β-olean-12-en-28-oic acid 28 $\longrightarrow$ 15β-lactone	(XII)			−128!	225	D/8
4β-Hydroxy-17β-propionoxy-5α-androstan-19-oic acid lactone	(XIII)	−34 tr	235	+33!	213	A/1
2-Oxa-3-oxobicyclo[2,2,1]*heptanes*						
14β-Hydroxy-(5β,14β)-androstane-17β,carboxylic acid lactone	(XIV)	−3 pk	227	−68!	208	E/9
3β,11α-Diacetoxy-14β-hydroxy-(5β,14β)-androstane-17β-carboxylic acid lactone	(XIV)	−4 pk	225	−45!	213	E/9
3β-Acetoxy-19β,20-dihydroxylupan-28-oic acid 28 $\longrightarrow$ 19β-lactone	(XV)	+43 pk	221	+39!	214	D/10
3β-Acetoxy-19β-hydroxylupa-20(30)en-28-oic acid lactone	(XV)	−5 pk	238	−89!	216	D/10

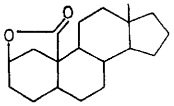
* Also shows ketonic Cotton effect $[\phi] \times 10^{-2}$ + 29, pk (318 mμ), + 5, tr (280 mμ), *a* + 24.
† Solvent, chloroform–methanol; no further penetration possible.

1. K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, 1962, **45**, 2575, and unpublished work. 2. R. Kwok and M. E. Wolff, *J. Org. Chem.*, 1963, **28**, 423. 3. J. Kalvoda, K. Heusler, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, 1963, **46**, 618, and unpublished work. 4. D. H. R. Barton and N. J. Holness, *J.*, 1952, 78. 5. C. Djerassi and J. S. Mills, *J. Amer. Chem. Soc.*, 1958, **80**, 1236. 6. D. H. R. Barton, W. Carruthers, and K. H. Overton, *J.*, 1956, 788. 7. G. S. Davy, T. G. Halsall, E. R. H. Jones, and G. D. Meakins, *J.*, 1951, 2702. 8. C. Djerassi, E. Farkas, A. J. Lemin, J. C. Collins, and F. Walles, *J. Amer. Chem. Soc.*, 1954, **76**, 2969. 9. A. Lardon and T. Reichstein, *Helv. Chim. Acta*, 1962, **45**, 943. 10. C. Djerassi, L. M. Liu, E. Farkas, A. E. Lippmann, A. J. Lemin, L. E. Geller, R. N. McDonald, and B. J. Taylor, *J. Amer. Chem. Soc.*, 1955, **77**, 1200.

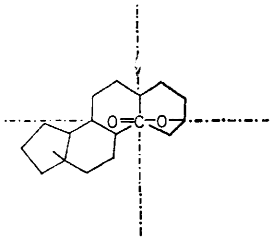
use of these symbols is most clearly illustrated by the general formulæ (XVI) and (XVII) on p. 7236.

Atoms in sectors	Contribution Positive	 Negative
Back upper	●	○
Back lower	■	□
Front upper	▲	△
Front lower	⧫	◊

× × Atoms symmetrically disposed; contributions cancel.



(V)



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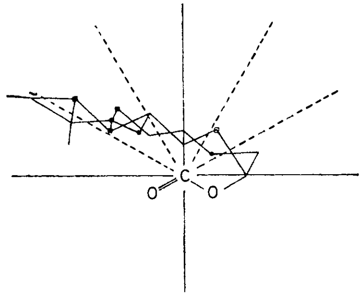
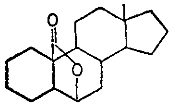


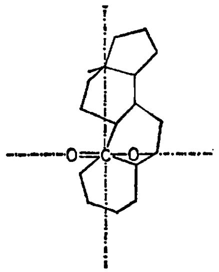
(Vb)

Lactones of the 6-*Oxa*-7-*oxobicyclo*[3,2,1]*octane Type*.—19 → 2β-*Lactones of* 5α-*steroids*. Three compounds of this type (V) have been examined (see Table 2) and all have strong positive Cotton effects with a first extremum at about 235 mμ. This is as would be expected from a consideration of the relevant octant and sector projections (Va and Vb) which show that the contributions of several pairs of atoms will cancel and that on balance, the significant atoms lie in the upper right and lower left sectors. The first example of type (V) has a propionoxy-group at the 17β-position and gives a strong positive Cotton effect [ϕ] +4100 at 235 mμ. Parallel measurements on a 17β-propionoxy-compound without the 19 → 2β-bridge show no Cotton effect down to 220 mμ and therefore the observed peak may clearly be ascribed to the lactone chromophore. Another example of type (V), 2β-hydroxy-3-oxo-5-α-cholestan-19-oic acid lactone, contains two chromophores, the carbonyl and the lactone groups. Each of these shows its own characteristic Cotton effect, although the amplitude, *a* + 24, for the ketone is smaller than is usually observed for 3-oxo-5α-steroids.

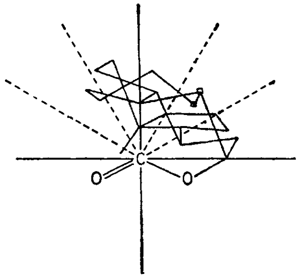
19 → 6β-*Lactones of* 5α-*steroids*. Lactones of this general type (VI) also have positive Cotton effects, in accordance with predictions from (VIa) and (VIb). The sector diagram for this molecule is complicated but it may be noted that only two atoms (4 and 5 of the A ring) fall in a region of high negative contribution. Other atoms either make a positive contribution or fall in a sector of low negative contribution (3, 11, 12). On balance, a positive Cotton effect would be predicted.



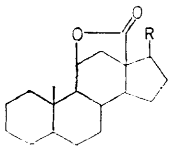
(VI)



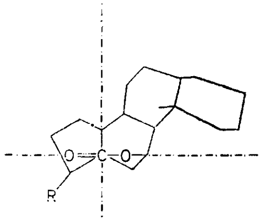
(VIa)



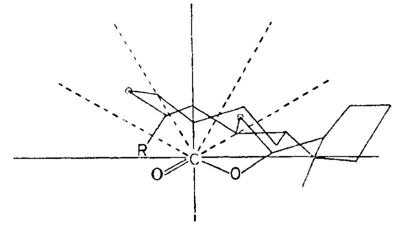
(VIb)



(VII)



(VIIa)

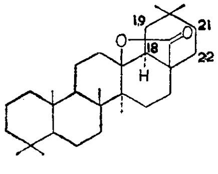


(VIIb)

18 ⟶ 11β-*Lactones of steroids.* Only one example is available of this general type (VII) but its strong positive Cotton effect is in agreement with the prediction of the sector rule (VIIa and VIIb). Two atoms only (16 and 12) make substantial negative contributions; other atoms make positive or low contributions to the total rotation, and the contributions of several atoms cancel in pairs. The net prediction is for a positive Cotton effect, borne out by a value of $[\phi]$ +5800 at the peak for the compound examined.

28 ⟶ 13β-*Lactones of* 18α-*oleanane.* In the stereochemical type (VIII), ring E lies almost symmetrically about the plane bisecting the $\widehat{OCO}$ angle and the contributions of the atoms 22 and 18, and 21 and 19 cancel (approximately) in pairs. Rings A and B (remote from the chromophore) lie in a front sector of low negative contribution, and it is the contributions of the atoms or rings D and C (near the chromophore and in *positive* sectors) which appear to determine the sign of the Cotton effect. This is consistent with the general finding that atoms close to a chromophore have a much greater effect on the rotation than those further away. Only one example of this type, 3β,13β-dihydroxy-18α-oleanan-28-oic acid 28 ⟶ 13β-lactone, could be examined to low wavelength and gave a peak $[\phi]$ +4100 at 232 mμ. The analogous compound witha 3β-acetoxy-substituent was insufficiently soluble in methanol for useful measurements to be made at low wavelengths. However, this compound was examined on a Rudolph polarimeter in chloroform–methanol solution and gave a curve which showed a strong positive trend down to 270 mμ.

It may be noted that the corresponding lactone in the oleanane series with 18β-hydrogen (IX) would also be expected to have a positive Cotton effect. Most of the molecule is identical to the 18α-isomer and although ring E is in a different position relative to rings A—D, it is still symmetrical about the plane bisecting the $\widehat{OCO}$ angle. We have examined one lactone of this type in chloroform solution down to 270 mμ and the curve showed a positive trend although no extremum was reached. These values are included in Table 2 for comparison.



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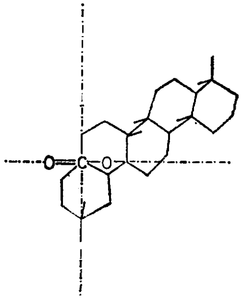
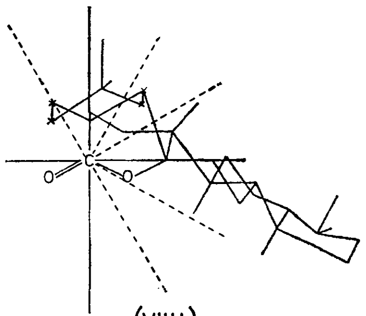
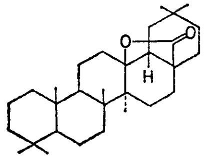


(VIIIa)



(VIIIb)

28 ⟶ 21β-*Lactones of* 18β-*oleanane.* For this general type (X), the octant diagram (Xa) is difficult to interpret as the rings lie behind one another, but the sector diagram



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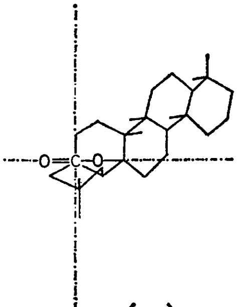
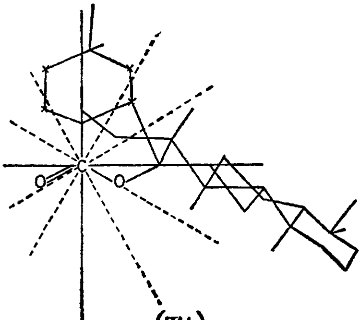


(IXa)



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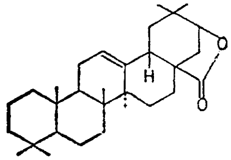
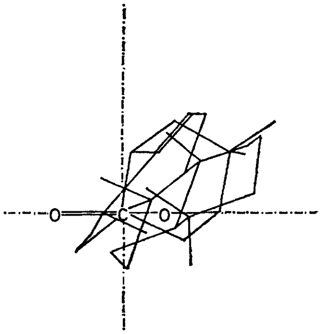


(X)



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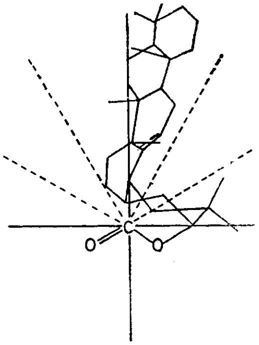
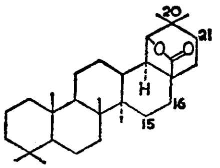


(Xb)

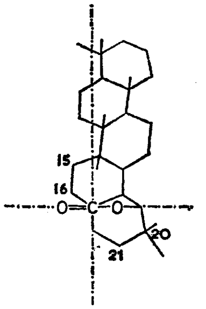
(Xb) predicts a positive rotation. The single example which we have examined has [ϕ] +4200 at the peak in accordance with the prediction.

28 ⟶ 19β-*Lactones of* 18α-*oleanane.* For these compounds (XI), as for the 28 ⟶ 13β-lactones (VIII), the rings remote from the chromophore appear to have little or no effect on the optical rotation and the o.r.d. curves show negative Cotton effects. If we consider rings D and E, atoms 15, 16, 20, and 21 fall in sectors of significant negative contribution, while only atoms 13 and 18 fall in a region of positive contribution. The remote rings (A, B, and C) fall mainly in regions of low positive contribution, but their effect at some distance from the chromophore is insufficient to outweigh the near atoms in negative sectors.

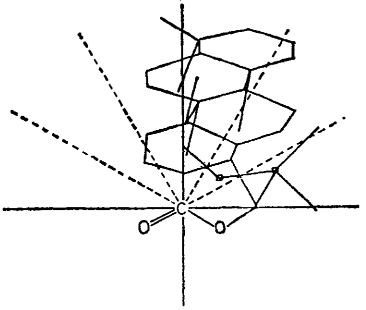
28 ⟶ 15β-*Lactones of* 18β-*oleanane.* The octant and sector diagrams (XIIa and XIIb) would predict strong negative rotations for these compounds, since only one near atom (16) falls in a region of significant positive effect and all other atoms are in sectors



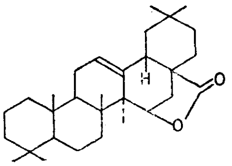
(XI)



(XIa)



(XIb)



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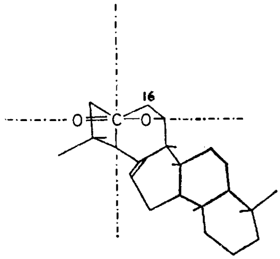
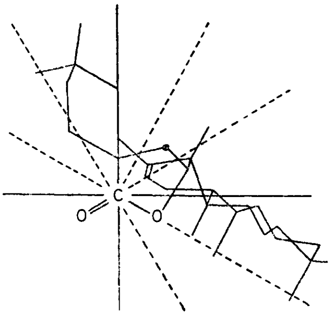


(XIIa)

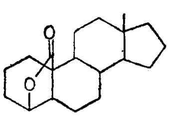


(XIIb)

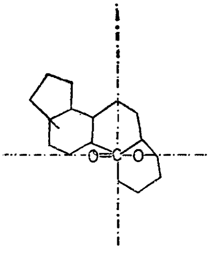
of negative contribution. Remote rings (A and B) project into a front sector of low positive contribution. We have examined only one compound of this group, and although the first extremum of the Cotton effect was not reached, it showed a strong negative rotation at 225 mμ in accord with expectation.

19 → 4β-*Lactones of* 5α-*steroids.* For this stereochemical type (XIII) a negative rotation would be clearly predicted by the octant and sector diagrams (XIIIa and XIIIb). Only atom 6 falls in a sector of significant positive contribution and other atoms either cancel or make negative contributions. This is borne out in practice by the example we have measured which has [φ] −3400 at 235 mμ.

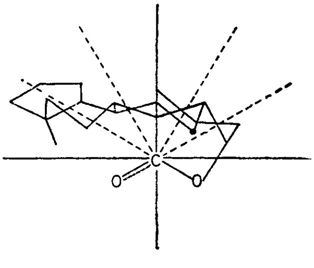
General conclusions. The lactones discussed above (V)—(XIII) which are all of the general bicyclo[3,2,1]octane type represent many different stereochemical sub-groups, but some connection may be made between them. If one considers *only* the lactone group and the six-membered carbocyclic ring which it bridges, then these compounds can be divided into two main classes each of which has this part of the structure in common (see XVI and XVII). From the immediate environment of the chromophore (as in XVI), positive Cotton effects would be predicted for compounds of all types (V)—(X), and this is in accordance with experimental results. Conversely, types (XI)—(XIII), general class (XVII), which have the immediate environment of the lactone group enantiomeric to that in types (V)—(X) have negative Cotton effects in agreement with the prediction.



(XIII)



(XIIIa)



(XIIIb)

These findings confirm that it is the immediate environment of a chromophore which has the greatest effect on and in many cases determines the sign of the Cotton effect. This has repeatedly been shown to be true in the case of ketonic Cotton effects by the studies of Djerassi, Ourisson, and ourselves. (For a thorough modern survey, see Crabbé.[8])

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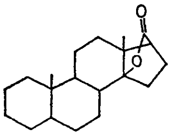
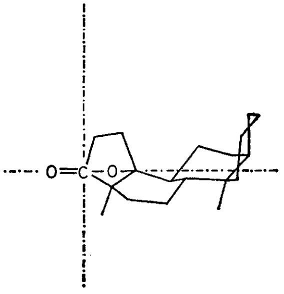
[8] P. Crabbé, " Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, 1965.

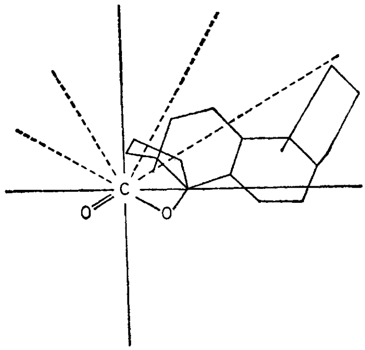
The members of these two groups of lactones (XVI) and (XVII) differ significantly in many major features, but the enantiomeric nature of the immediate environment of the chromophore in the two main classes does appear to dominate the o.r.d. behaviour in the region of the lactone absorption.



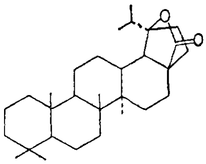
(XIV)



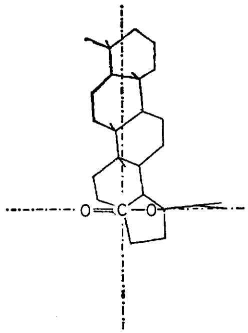
(XIVa)



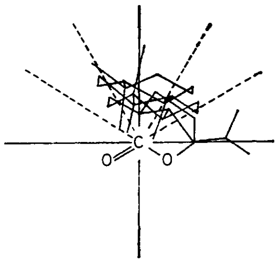
(XIVb)



(XV)



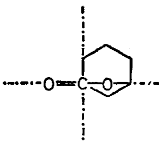
(XVa)



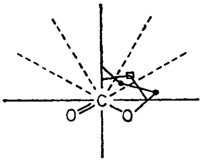
(XVb)

Lactones of the 2-*Oxa*-3-*oxobicyclo*[2,2,1]*heptane Type*.—17β ⟶ 14β-*Lactones of* 5β,14β-*steroids*. The experimental results for this type of lactone (XIV) show positive Cotton effects superimposed on a strongly negative background, so that the rotations are only —300 and —400, respectively, at the peaks. This might be expected from the octant and sector diagrams (XIVa and XIVb) which show a large number of closely balanced atoms, from which it is difficult to make a clear prediction.

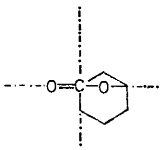
28 ⟶ 19β-*Lactones of lupane*. For this general class (XV) a positive Cotton effect is clearly predicted by the combined octant and sector diagrams (XVa and XVb). Both compounds we have examined give positive Cotton effects, but in one case this is superimposed on a strong negative background and the actual molecular rotation is negative at the peak (—500 at 238 mμ). This may be due to the effect of the 20(30)-double bond in the lupane skeleton.



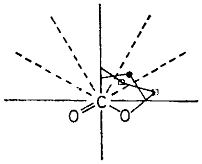
(XVIa)



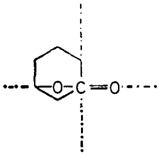
(XVIb)



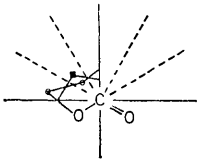
(XVIIa)



(XVIIb)



(XVIIc)



(XVIId)

(XVII a, b) and (XVII c, d) are alternative representations of the enantiomer of (XVI a, b).

Conclusion. Eleven stereochemical types of bridged ring lactone have been discussed in this Paper in terms of the lactone sector rule, to which no exceptions have been found. It appears that this rule will continue to offer a useful framework for the discussion of lactone stereochemistry.

EXPERIMENTAL

Optical rotatory dispersion curves were measured on the Bellingham & Stanley/Bendix Ericsson automatic recording spectropolarimeter, " Polarmatic 62 " modified as described in *J.*, 1965, **294**. Solvent, methanol; l = 0·1 dm.; t = 20—25°; c = 1 mg./ml. or less.

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