Tetrahedron, 1961, Vol. 13, pp. 29 to 47. Pergamon Press Inc., Printed in Northern Ireland

OPTICAL ROTATORY DISPERSION

SOME APPLICATIONS TO STRUCTURAL AND STEREOCHEMICAL PROBLEMS IN ORGANIC CHEMISTRY

W. KLYNE*
Westfield College, University of London

THIS paper deals with work that has been carried out in parallel with the studies of Djerassi (discussed in the previous paper[1]) although starting at a much later date. The first half of the paper is concerned with ketones; in this field our thinking has been guided by the Octant Rule, ever since the Harvard discussions of July and August, 1958.[2] The theoretical and practical aspects of the Octant Rule have already been discussed here by Moscowitz[3] and Djerassi[1], and the present paper deals with some applications which have specially interested me. In this treatment many experimental data are taken from Djerassi's papers—and some are from published and unpublished work by Prof. G. Ourisson of Strasbourg.

The second half of the paper deals with some, as yet rather unrewarding, studies on plain curves (for nomenclature[4])—i.e. on compounds which have no absorption band within the range of wavelengths studied.

Ketones

1. *General*

In this paper the sign and amplitude of the Cotton effect will be considered as the principal characteristics of the dispersion curves of saturated ketones. All rotations are given as molecular rotations $[\phi]$; amplitudes (a) are given as the algebraic difference between $[\phi]$ for peak and trough—divided by 100 for convenience.

In some cases the extremum (peak or trough) of lower wavelength could not be reached; in such cases the 'amplitude' given is the algebraic difference between the peak (or trough) of higher wavelength and the rotation for the lowest wavelength that could be measured. The true amplitude may therefore be greater than the value given, which is distinguished by an exclamation mark (!).

2. *Cotton effect. Lack of influence of remote substituents*

Many examples have been given in Djerassi's work (reviews [5-8]) of the fact that substituents remote from a carbonyl group have little influence on the amplitude of

---

* Formerly at Postgraduate Medical School, London.

[1] C. Djerassi, *Tetrahedron.* **13**, 13 (1961).

[2] W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, in preparation.

[3] A. Moscowitz, *Tetrahedron* **13**, 48 (1961).

[4] C. Djerassi and W. Klyne, *Proc. Chem. Soc.* 55 (1957).

[5] C. Djerassi, *Optical Rotatory Dispersion: Applications in Organic Chemistry.* McGraw Hill, New York (1960).

[6] C. Djerassi, *Rec. Chem. Progr.* **20**, 101 (1959).

[7] W. Klyne, *Advances in Organic Chemistry* (Edited by R. A. Raphael) Vol. I. Interscience, New York (1960).

[8] W. Klyne and A. C. Parker, *Physical Methods of Organic Chemistry* (Edited by A. Weissberger) 3rd Ed. Interscience, New York (1960).

its Cotton effect. We have, in the course of other work, assembled data for three series of steroid ketones (Formulae I, II, III), which enable us to confirm these findings, and make a roughly quantitative statement (see Table 1).

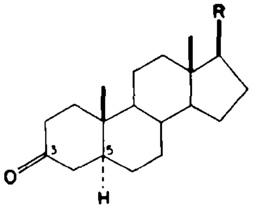
For substituents on a rigid skeleton such as that of the steroids, the introduction of alkyl, hydroxyl or even benzoyloxy groups at distances of 7 or 8 Å from a carbonyl group makes a barely significant difference to the amplitude of the Cotton effect.

TABLE 1. STEROID KETONES. ABSENCE OF EFFECT BY REMOTE SUBSTITUENTS ON AMPLITUDE OF DISPERSION CURVES*†

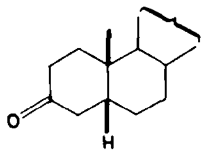
Compound	Formula	Amplitude
3-Oxo-5α-steroids (Formula I)		
5α-Androstan-3-one	R = H	+52
5α-Pregnan-3-one	R = Et	+53
5α-Pregnan-3-one,20β-hydroxy	R = CHOH.Me	+57
5α-Cholestan-3-one	R = C_8H_{17}	+56[a]
5α-Stigmastan-3-one	R = $C_{10}H_{21}$	+54
5α-Spirostan-3-one	R = $C_8H_{14}O_2$	+61[b]
3-Oxo-5α-etianate, methyl	R = CO_2Me	+50
3-Oxo-5β-steroids (Formula II)		
5β-Androstan-3-one	R = H	−11
5β-Androstan,17α-hydroxy	R = OH(α)	−17
5β-Androstan,17β-hydroxy	R = OH(β)	−22
5β-Androstan,17β-acetoxy	R = OAc(β)	−20
5β-Cholestan-3-one	R = C_8H_{17}	−25
3-Oxo-5β-cholanate, methyl	R = $CHMe.[CH_2]_2.CO_2Me$	−19!
17-Oxosteroids (Formula III)		
5α-Androstan-17-one		+145
5α-Androstan,3α-hydroxy		+144
5α-Androstan,3β-hydroxy		+148
5α-Androstan,3α-thiol		+139
5α-Androstan,3β-thiol		+136
5β-Androstan-17-one		+149
5β-Androstan-3α-hydroxy		+145
5β-Androstan-3β-hydroxy		+142
Androst-5-en-17-one,3β-hydroxy		+143

* Solvent, methanol, unless otherwise indicated.
† See Djerassi *et al.*, *J. Amer. Chem. Soc.* **78**, 3163, 3761, 6362 (1956).
[a] Duplicate determination, +60
[b] +65 in $CHCl_3$

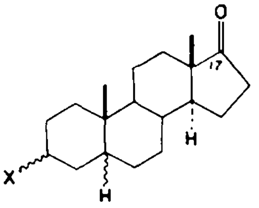
Substituents closer to the carbonyl group, e.g. 17- or 20-substituents in an 11-oxosteroid (IV), do make a significant difference to the Cotton effect of the carbonyl group, as might be expected; studies are in progress jointly with Professor E. R. H. Jones (Oxford), but are as yet incomplete; two compounds have been found (3α,20β-diacetoxy-5β-pregnan-11-one and methyl 3α-acetoxy-11-oxo-5β-etianate) in which the Cotton effect is almost suppressed. Until we have studied a more extended series of



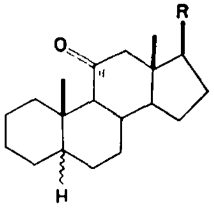
I



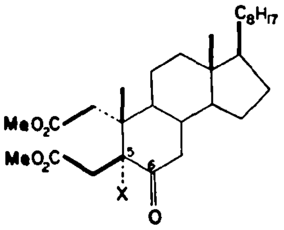
II



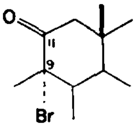
III



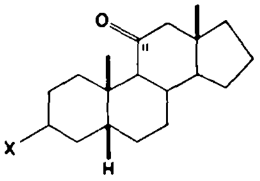
IV



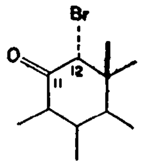
V



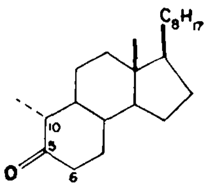
VI



VII



VIII



IX

compounds, speculations regarding the reasons for these abnormal curves are premature.

3. *Use of the Octant Rule for configurational allotments*

The following examples illustrate the use of the Octant Rule (or its forerunner, of more restricted scope, the axial α-haloketone rule[9]).

[9] C. Djerassi and W. Klyne, *J. Amer. Chem. Soc.* 79, 1506 (1957); C. Djerassi, J. Osiecki, R. Riniker and B. Riniker *Ibid.* 80, 1216 (1958).

Summers[10] in Swansea obtained by bromination of the 6-oxo-2:3-seco-steroid (V, X = H) a bromocompound which showed a very large negative Cotton effect; this indicates conclusively that the bromine is *axial* and in the 5α-position (V; X = Br). Amplitudes (V, X = H) −63; (V, X = Br) −368.

Jones and his colleagues[11] in Oxford in their studies of 11-oxosteroids (VII) obtained three pairs of α-bromo derivatives; the large amplitude-contributions of the bromine substituents (one positive and one negative in each pair) show that these are 9α-bromo and 12α-bromo compounds (VI and VIII) respectively. See Table 2, and compare previous results by Djerassi *et al.*[9]

TABLE 2. 9α- AND 12α-BROMO-11-OXOSTEROIDS*†

Compound	Amplitudes (*a*)		
	11-CO without α-substituent	9α-Br-11-CO	12α-Br-11-CO
5β-Androstan-11-one,3α-hydroxy or 3α-acetoxy	−13	−204	−206, −214
5β-Androstan-11-one, 3-ethylenedioxy	−11	−247	−242
5β-Androstan-3,11-dione	−15	−222	−199

* Solvent, methanol

† See Djerassi *et al.*[9]

Similar use of rotatory dispersion curves for configurational allotments has been made by Jones *et al.*[12] in their studies on steroids lacking ring A (de-A-cholestan-5-ones; IX). The reference compound without a bromine substituent (IX) was measured by Djerassi (*a*, −76); three different monobromo compounds gave the following results in our hands.

6α-bromo (equatorial) *a*, −88
6β-bromo (axial) *a*, −332
10β-bromo (axial) *a*, +205!

Barton and Gilham[13] obtained from lumisantonin a *trans*-2-decalone, the negative Cotton effect of which (*a*, −79) showed that it was of type (X)—enantiomeric in type to a 2-oxosteroid.

Prelog and Smith[14] deduced the (9*R*) absolute configuration of a 10-hydroxy-*trans*-2-decalone (XI) from its negative Cotton effect (*a*, −67).

4. *2-Hydroxycyclohexanones and the Octant Rule*

Hitherto the various authors interested in the Octant Rule have refrained from bringing α-ketols of the 2-hydroxycyclohexanone type into consideration—perhaps because of a suspicion that hydrogen-bonding, solvation or other factors might

---

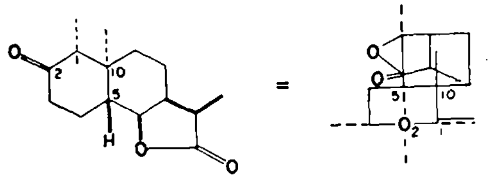
[10] G. H. R. Summers, *J. Chem. Soc.* In preparation.

[11] E. R. H. Jones *et al.* Unpublished work.

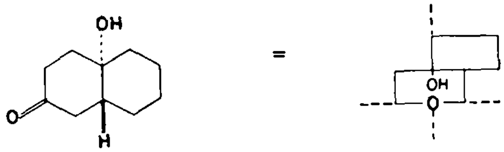
[12] E. R. H. Jones *et al.* Unpublished work.

[13] D. H. R. Barton and P. T. Gilham, *Proc. Chem. Soc.* 391 (1959).

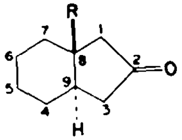
[14] V. Prelog and H. E. Smith, *Helv. Chim. Acta* **42**, 2624 (1959).



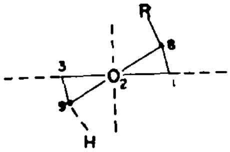
X



XI



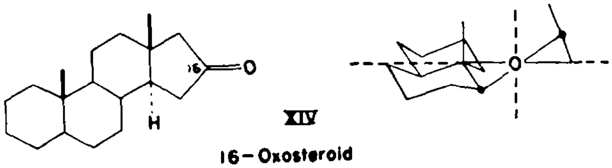
XII



XII A

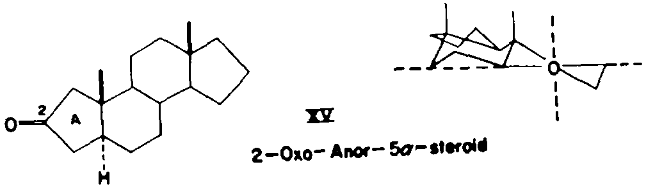
C-4,5,6,7 lie approximately behind
C-3,9,8,1 respectively

XIII



XIV

16-Oxosteroid



XV

2-Oxo-Anor-5α-steroid

complicate the situation. It now seems, however, appropriate to survey the available data—chiefly from Djerassi's work,[15] with some additions of our own.

A very condensed survey is given in Table 3; from this the following groups have been omitted for the reasons given.

(*a*) cyclopentanone ketols—e.g. 16,17-ketols—because the shape of the five membered ring is inadequately known (cf. Fishman and Djerassi,[16] also later pp. 5-10).

(*b*) some D-homosteroid ketols—17,17*a*-ketols—since certain simple ketones of this series behave abnormally.

(*c*) 14β-steroids (i.e. C,D-*cis* fused steroids)—because the conformation of the C ring is not definitely known.

Table 3 shows that for the remaining steroid α-ketols it is generally true that (*a*) *equatorial* hydroxyl or acyloxy substituents have little influence on the Cotton effect; (*b*) *axial* hydroxyl or acyloxy substituents in rings A and B make large contributions to the Cotton effects of the *same* sign as chlorine or bromine in the same positions; (*c*) *axial* hydroxy or acyloxy substituents in ring C make large contributions to the Cotton effect of the *opposite* sign to those given by chlorine and bromine in the same position.

This anomaly is stated without any suggestion of a possible solution; it may be that a modified chair conformation of ring C is partly responsible.

5. *Hexahydroindanones and related ketones*

It has been clear for some months that difficulties would arise in applying to alicyclic ketones in which the carbonyl group is in a five-membered ring, the Octant Rule which has been so successful in summarizing the results for the cyclohexanones and related ketones.

Recent findings in the hexahydroindanone series have led me to suggest that the skewed nature of the five-membered ring itself exerts a strong influence on the symmetry of the carbonyl group here—in contrast to the six-membered ring, where the ring itself is perfectly symmetrical about the carbonyl group, and asymmetry is due to the second-order effects of substituents.

Lack of precise knowledge about the shapes of five-membered rings[16–20] precludes any detailed quantitative treatment, but the following notes sketch a rough picture which seems to cover the major features. (Most data are taken from Djerassi's papers; refs. see Table 4.)

trans-*Hexahydroindan*-2-*ones*. These compounds of general formula (XII) are distinguished by the very large amplitudes of their Cotton effects (greater than 200). Until recently they have been represented by the compound carrying a methyl group at one ring junction (XII, R = Me), and extended analogues of this (16-oxo- and A-nor-2-oxo-steroids).

Recently Miss P. Bourn (I.C.I. Ltd., Welwyn) has prepared the non-methylated

---

[15] C. Djerassi, O. Halpern, V. Halpern, O. Schindler and C. Tamm, *Helv. Chim. Acta* **41**, 250 (1958).

[16] J. Fishman and C. Djerassi, *Experientia* **16**, 138 (1960). (I am indebted to Prof. C. Djerassi for a copy of this paper before publication.)

[17] C. G. Le Fevre and R. J. W. Le Fevre, *J. Chem. Soc.* 3549 (1956).

[18] K. S. Pitzer and W. E. Donath, *J. Amer. Chem. Soc.* **81**, 3213 (1959).

[19] F. V. Brutcher, T. Roberts, S. J. Barr and N. Pearson, *J. Amer. Chem. Soc.* **81**, 4915 (1959).

[20] C. W. Shoppee, R. H. Jenkins and G. H. R. Summers, *J. Chem. Soc.* 3048 (1959).

TABLE 3. α-KETOLS AND THEIR ACETATES*†

No reference is made to different substituents at C-3 for 11- and 12-oxo-compounds.

Position of keto group	Series	α-Substituents OR	Amplitude (*a*)	Contribution of OR (Δ*a*)	Reference and source
3	5α-Cholestane	none	+58		*a*
		2α-OAc (eq.)	+66	+8	*a*, *p*
		2β-OAc (ax.)	+116	+58	*a*, *p*
3	4,4,Dimethyl-5α-cholestane	none	−12		*b*
		2α-OAc (eq.)	+38	−50	*a*, *q*
		2β-OAc (ax.)§	+124	+136	*a*, *q*
4	5α-Cholestane	none	−95		*c*
		5α-OH (ax.)	−45	+50	*d*
6	5α-Cholestane	none	−78		*c*
		5α-OH (ax.)	−110	−32	*d*
		5α-OAc (ax.)	−89	−11	*d*
11	5α-Spirostan	none	+43D		
		12β-OH (eq.)	+44!D	+1!	*d*
		12β-OAc (eq.)	+42!D	−1!	*d*
		12α-OH (ax.)	+42D	−1	*d*
		12α-OAc (ax.)	+88D	+45	*d*
11	5β-Cholanate	none			
		12β-OH (eq.)	+14!		*d*
		12β-OAc (eq.)	+28		*d*
		12α-OAc (ax.)	+73		*d*
11	5α-Ergostane	none	+19		*a*, *r*
		9α-OH (ax.)	+68	+49	*a*, *r*
11	5α-Ergostane	none	+12		*c*
		12α-OAc (ax.)	+85	+73	*a*, *r*
11	5β-Etianate	none	+10		*a*, *s*
		12α-OH (ax.)	+40	+30	*a*, *s*
		12α-OAc (ax.)	+44	+34	*a*, *s*
		12β-OAc (eq.)	+17!D	+7!	*d*
12	5α-Spirostan	none			
		11α-OAc (eq.)	+41!D		*d*
		11β-OH (ax.)	+77D		*d*
		11β-OAc (ax.)	+162D		*d*
12	5β-Cholanate	none	+10		*d*
		11α-OH (eq.)	+17!	+7!	*d*
		11β-OH (ax.)	+39	+29	*d*
12	5β-Etianate	none			
		11α-OAc (eq.)	+30!D		*d*
		11β-OAc (ax.)	+117!D		*d*

[a] Own work.

[b] C. Djerassi, O. Halpern, V. Halpern and R. Riniker, *J. Amer. Chem. Soc.* **80**, 4001 (1958).

[c] C. Djerassi, W. Closson and A. E. Lippman, *J. Amer. Chem. Soc.* **78**, 3163 (1956).

[d] C. Djerassi, *et al.*[14]

[p] Prof. H. B. Henbest, Belfast.

[q] Dr. T. G. Halsall, Oxford.

[r] Prof. E. R. H. Jones, Oxford.

[s] Dr. O. Schindler, Basel.

* Solvent, methanol, except for values marked D which are in dioxan.

† For previous work see chiefly Djerassi *et al.*[14]

§ Compound may have boat conformation of ring A.

SUMMARY FOR AXIAL α-KETOLS

C:O	COH	Octant behaviour*
3 (5α)	2	✓
4	5α	✓
6	5α	✓
11	9	✓
11	12	×
12	11	×

* ✓ Normal × Abnormal

TABLE 4. SUMMARY OF HEXAHYDROINDANONES

Compound	Significant atoms			Cotton effect		
	Cyclopentanone ring	Adjacent cyclohexanone ring	Remote rings	Estimated	Found (*a*)	References
		trans-2-*Ketones*				
trans-Hexahydroindan-2-one	2 − −	−	none	− −	−222	*a*
Ditto, with 8-methyl	2 − −	−	none	− −	−219	*b*
16-Oxosteroid	2 − −	−	±	− −	−264	*b*
2-Oxo-5α-Anorsteroid	2 + +	+	+	+ +	+234	*b*
2-Oxo-4,4-dimethyl-5α-A-norsteroid	2 + +	+	+	+ +	+221	*j*§
		trans-1-*Ketones*				
trans-Hexahydroindan-1-one (8-methyl)	1 +	+	none	+	+88	*b*
17-Oxo-14α-steroid	1 +	+	+	+ +	+140	*b*
17-Oxo-18-nor, 14-methylsteroid (from dammarane)	1 +	+	+	+ +	+180†	*d*
15-Oxo-14α-steroid	1 +	+	+ ? N.O.*	+	+120	*c*
Trisnor-17β-hopan-21-one	1 − **	−	±	−	−208	*e*
3-Oxo-5α-A-nor-steroid	1 − **	−	−	− −	−199	*f*
3-Oxo-5α-A-nor-19-nor-steroid	1 −	−	−	− −	−215	*f*
		cis-2-*Ketones*				
2-Oxo-5β-A-norsteroid	2 − −	+	−	−	−150	*b*
cis-Hexahydroindan-1-one (8-methyl) A††	1 −	+	none	−	+20 (approx)	*g*
cis-Hexahydroindan-1-one (8-methyl) B	1 +	+	none	+ +		
17-Oxo-14β-steroid	1 −	+	±	?	+34	*b*
3-Oxo-5β-A-norsteroid	1 +	+	+	+ +	+133	*b*
Trisnor-17α-hopan-21-one	1 +	+	+	+ +	+118	*e,h*
15-Oxo-14β-steroid	1 −	−	± N.O.*	−	−125	*k*
Trisnorlupan-19-one	1 +	+	± N.O.*	+	+80	*h*
17-Oxo-13α-steroid (18-nor, 14-methyl; from dammarane)	1 −	−	−	−	−110 (approx)	*d*

[a] Bourn and Klyne[21].
[b] Djerassi, Riniker and Riniker[28].
[c] C. Djerassi, W. Closson and A. E. Lippman, *J. Amer. Chem. Soc.* **78**, 3163 (1956).
[d] J. Bielmann, P. Crabbé and G. Ourisson, *Tetrahedron* **3**, 303 (1958).
[e] Own work (unpublished); samples from Dr. T. G. Halsall (Oxford).
[f] G. Ourisson, *et al.*, unpublished.
[g] Acklin and Prelog[22].
[h] C. Djerassi, J. Osiecki and W. Closson, *J. Amer. Chem. Soc.* **81**, 4587 (1959).
[j] R. Hanna, C. Sandris and G. Ourisson, *Bull. Soc. Chim. Fr.* 1454 (1959).
[k] Lardon, Sigg and Reichstein[23].
* Includes atoms in near octants; effects doubtful.
** Also angular methyl group.
† Approximate estimate from incomplete curve.
†† Two conformations, A, steroid-like; B, steroid-unlike.
§ The contributions of the *gem*-dimethyl group at C-4 apparently cancel almost exactly: this illustrates the character of "bisectional" bonds.[19]

analogue (XII, R = H) (cf. Hückel, Linstead), and the R.D. curve of this, measured in our laboratory, shows a large negative Cotton effect almost identical with that of (XII, R = Me).[21] The angle methyl group is not, therefore responsible for the large Cotton effect; inspection of models in the light of the Octant Rule led to the conclusion that it would not be responsible.

The asymmetry of the structure (XII, R = H) lies, then, in the ring system itself and consideration of models leads us to suggest that the asymmetry of the two atoms

---

[21] P. M. Bourn and W. Klyne, *J. Chem. Soc.* 2044 (1960).

C-8 and C-9 (or of the bonds marked * * in formula XIIA) with reference to the carbonyl group is responsible for the very large Cotton effect.

These tentative ideas were discussed with colleagues in Zürich and Basel, several of whom (notably Professor Prelog) emphasized that this skewed ring system in XIIA contrasts sharply with the symmetrical ring system in a cyclohexanone (XIII), where any asymmetry is of "second-order" due to substituents, not to the ring itself. It is therefore not unreasonable to ascribe the large measure of asymmetry in the carbonyl group of XII to these skewed ring-atoms.

We do not know the *exact* shape of the cyclopentanone ring[16–20] although the latest evidence seems to suggest a 'half-chair' conformation. It is convenient to assume that the shapes of the structures built up from atomic models with the regular valency angles represent approximately the true shape of the molecules. (The author uses the models made by Crystal Structures Ltd., Cambridge.)

We then obtain for the *trans*-2-ketones of type XII the picture XIIA, in which the *two* atoms C-8 and C-9 and the *two* ring-bonds which are hyperconjugated with the carbonyl group (Cl-8 and C3-9) are skewed in relation to the symmetry planes of this group.

The experimental values for the amplitudes of (XII, R = H) (−222) and (XII, R = Me) (−219) shows that the contribution of these skewed bonds (or the atoms C-8, C-9) to the Cotton effect is of the order of −200; that the effect of the angle methyl group is negligible is explained on the grounds that it is rather near the vertical symmetry plane of the octant system and its 'second-order' effects are overwhelmed by the 'first-order' effects of the ring system.

Extended trans-2-*ketones*. Two important examples of this class are the well-known 16-oxo and 5α-Anor-2-oxosteroids (XIV and XV). In both cases the additional rings are roughly symmetrical about the horizontal plane; in accordance with this the amplitudes (−264, +234) are not greatly increased. Ourisson (ref. *j*, Table 4) has measured the corresponding 2-oxo compound with *gem*-dimethyl at C3 (XVI, R = R′ = H). Any monomethyl analogues (XVI, R = H, R′ = Me or *vice versa*) would be interesting to study.

These results and those for groups subsequently discussed are summarized in Table 4.

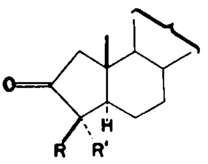
trans-*Hexahydroindan*-1-*ones*. The 8-methyl-*trans*-hexahydroindanone-1 (XVII), which is the bicyclic analogue of a 17-oxosteroid, shows a moderate positive amplitude (+88). The picture shown in XVIIA is compatible with this; a *single* atom in the cyclopentanone ring (C-9) is severely skewed in a positive octant (and C-3 is less skewed in a negative octant). There are also some "ordinary" positive contributions from C-5 and C-6 (C-7 and C-8Me cancel *very* roughly).

The increased amplitude of 17-oxosteroids (XVIII) is due to added atoms (of the A and B rings) in a positive octant (*a*, +140). The ring B-aromatic steroid (3-hydroxy-oestra-5,7,9(10)-trien-17-one) in which the A and B rings are nearer to a symmetry plane (XIX; *a*, +75!) shows an amplitude nearer to that of XVII.

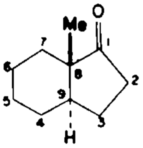
The 14α-15-oxosteroid (XX) shows an amplitude similar to that of the 17-oxo compound (+120 to +140); this case might be complicated by atoms of rings A and B coming in a near octant.

Three other examples from the work of Ourisson are included in Table 4.

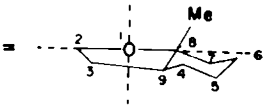
cis-*Hexahydroindan*-2-*ones*. Only one example is available here, the 5β-A-nor-2-oxo



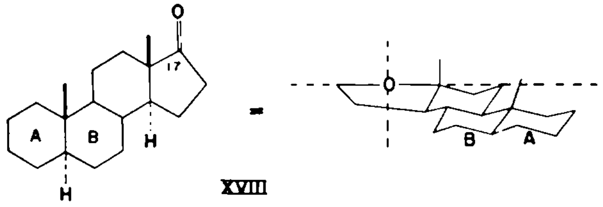
XVI



XVII

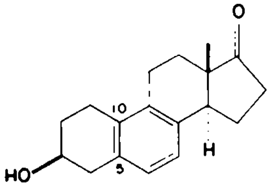


XVII A

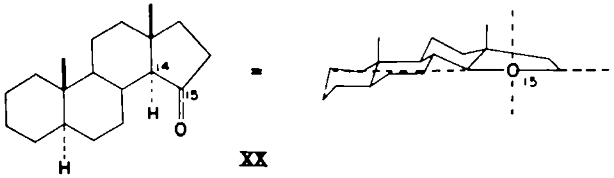


XVIII

17-Oxo-14α-steroid

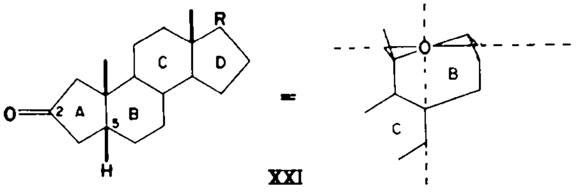


XIX



XX

15-Oxo-14α-steroid



XXI

2-Oxo-Anor-5β-steroid

steroid XXI (*a*, −150). Here we have *two* skewed negative ring atoms (C-5 and C-10, two appreciable positive combinations from next nearest atoms C-7 and C-19, and number of very small negative contributions in rings C and D.

cis-*Hexahydroindan*-1-*ones*. The simple compound XXII has been recently measured (Acklin and Prelog[22]) and found to have a small positive Cotton effect (+20, approx.). The picture shown by XXIIA—the conformation favoured by

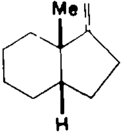
---

[22] W. Acklin and V. Prelog, *Helv. Chim. Acta* **42**, 1239 (1959).

Prelog—does not seem to fit this value well. XXIIA would have a single skewed ring atom (C-9; negative) and two small positive contributions from C-5 and C-6 (C-7 and C-8Me cancel). The alternative conformation XXIIB would have a single *positive* skewed ring atom and some positive contributions from the six-membered ring—i.e. its total Cotton effect would be rather strongly positive.

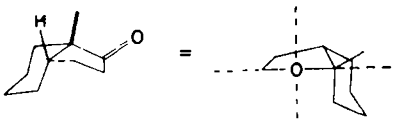
The disagreement of the experimental result with these predictions suggests that the true conformation must be a distorted form (perhaps of XXIIA)—or conceivably there is a conformational equilibrium (XXIIA + B).

This matter can be tested further by considering some extended compounds of the steroid series. The 14β-17-oxosteroid (XXIII; *a*, +34) has a number of additional atoms (in the B and A rings) in both positive and negative octants; XXIII *must* have



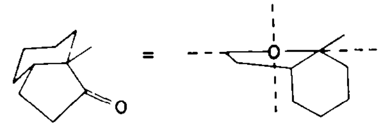
XXII

=

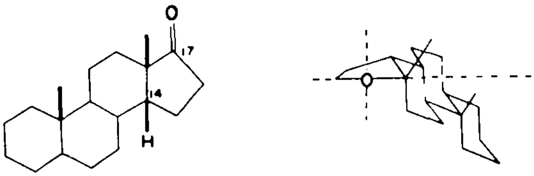


XXII A

or



XXII B



XXIII

17-Oxo-14β-steroid

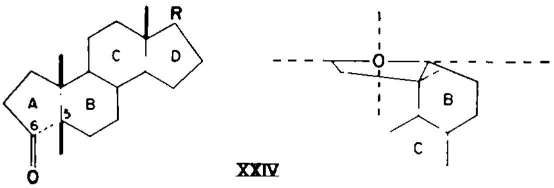
the conformation shown (similar to XXIIA), and the conformation as XXIIB is impossible.

Some other examples are available, in which the keto group is adjacent to a ring junction carrying hydrogen instead of methyl. 3-Oxo-5β-Anor steroids (XXIV) have one skewed positive ring atom, and many ordinary positive contributions; the observed amplitude (+133) supports this analysis. The triterpene derivative, trisnorhopan-21-one (XXV) is a very close analogue of a 3-oxo-5β-Anor steroid; it shows a similar strong positive Cotton effect (*a*, +118).

The 15-oxo-14β-steroid (XXVI) (Lardon, Sigg and Reichstein[23]) is roughly enantiomeric to (XXIV) and has (*a*, −125). The picture might be complicated here by 'near octant' effects from rings A and B. 3β-Acetoxy-trisnorlupan-19-one (XXVII) is very similar to the enantiomer of a 15-oxo-14β-steroid; its Cotton effect is positive (+80).

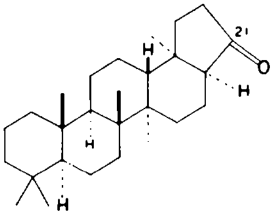
In all the above no account has been taken of the possibility that the six-membered

[23] A. Lardon, H. P. Sigg and T. Reichstein, *Helv. Chim. Acta* **42**, 1457 (1959).



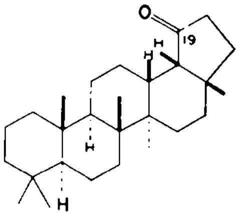
XXIV

3-Oxo-Anor-5β-steroid



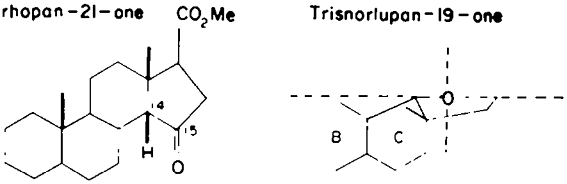
XXV

Trisnorhopan-21-one



XXVII

Trisnorlupan-19-one



XXVI

15-Oxo-14β-steroid

ring adjacent to the cyclopentanone ring may well be a distorted chair, or a form intermediate between a chair and a boat.*

It may be remarked here that the very general and close agreement between the *predictions* of the Octant Rule (based on perfect chair forms of cyclohexane rings) and the *experimental findings* in the extended cyclohexanone series is indirect evidence for the conclusion that the cyclohexane rings are of nearly perfect form in most of the compounds concerned.

Some Bridged-ring Ketones

6. *Bicyclo* [3,2,1] *octan-2-ones*

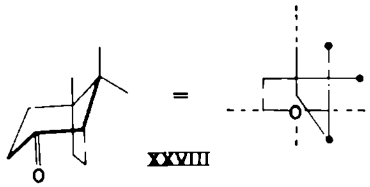
These compounds (XXVIII–XXX) are only slightly distorted cyclohexanones and a few data collected by Prof. Ourisson suggest that the Octant Rule may be applied to them without difficulty.

(+)-Homoepicamphor (XXVIII) and (−)-homocamphor (XXIX) show positive and negative curves respectively. Measurements were incomplete but the rotations at peak and trough (~310 mμ) respectively indicated that the amplitudes would be approximately ±60. These values tally with the octant diagram which, if one considers the structures as a substituted cyclohexanone, show in each case a (somewhat displaced) 2-axial methyl group having a greater effect than the *gem*-dimethyl at C-3 (cyclohexanone numbering).

"R"-Homocamphenilone (obtained from (+)-camphor) was found by Ourisson to have a strong positive Cotton effect (*a*, +110); this supports the formula (XXX),

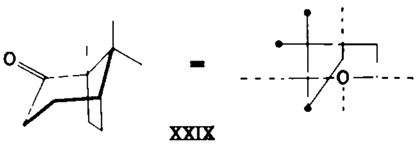
---

* The results of Djerassi, Marshall and Nakano, *J. Amer. Chem. Soc.* **80**, 4853 (1958) on decalones and related hexahydroindan-5-ones tend to discount this argument.



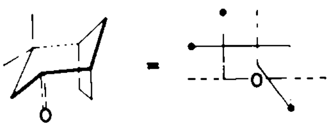
XXVIII

(+)-Homoepicamphor



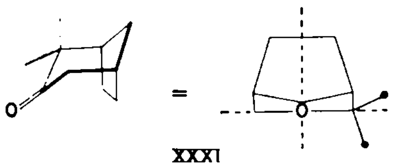
XXIX

(−)-Homocamphor



XXX

"R"-Homocamphenilone



XXXI

and not that of the positional isomer (XXXI), which would have a small positive Cotton effect.

7. *Bicyclo* [3,2,1] *octan-6-ones*

These are important reference compounds for a number of different groups of natural products. Within the last few months the absolute configurations of two members of the group have been determined by reference to cyclohexanone types obtained by further degradation. They are the nor-ketones (XXXIII) from phyllocladene (XXXII), and (XXXVIII) from gibberellic acid (XXXV). My own attempts to solve the problem of the absolute configurations by direct application of the Octant Rule to these bridged-ring ketones were quite unsuccessful. Perhaps a quantitative treatment may have better fortune.

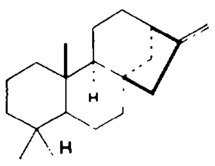
The decalone-type structure (XXXIV) obtained from phyllocladene shows a strong positive Cotton effect (*a*, +81, in dioxan) (Djerassi *et al.*[24]); a similar compound with CN in place of CO_2Me kindly supplied by Dr. R. Hodges of Glasgow gave (*a*, +65!) in our hands. The correlation between phyllocladene and manool achieved by Grant and Hodges[25] fixed the configuration of the A/B ring junction in phyllocladene—and this together with the rotational arguments of Djerassi *et al.*[24] determines the whole

[24] C. Djerassi, M. Cais and L. A. Mitscher, *J. Amer. Chem. Soc.* **81**, 2386 (1959).

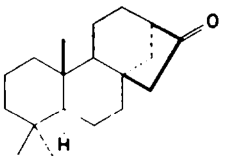
[25] P. K. Grant and R. Hodges, *Tetrahedron Letters* No. 10, 21 (1959) *Tetrahedron* **8**, 261 (1960). R. Henderson and R. Hodges, *Ibid.* **11**, 226 (1960); cf. also L. H. Briggs *et al.*, *Tetrahedron Letters* No. 8, 13 (1959).

stereochemistry of the nor-ketone as XXXIII, and therefore of phyllocladene as XXXII.

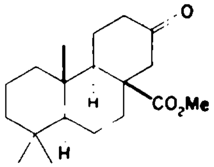
Similar arguments apply to the C/D ring area of the gibberellic acid series, discussed in preliminary notes by Cross, Grove, *et al.*[26] and by Stork and Newman[27].



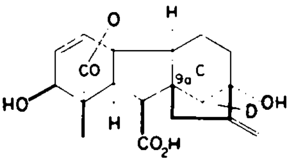
Phyllocladene
XXXII



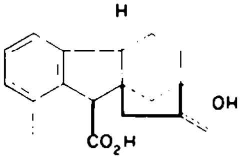
XXXIII



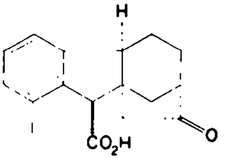
XXXIV



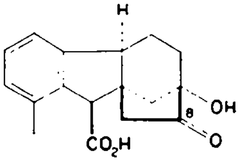
Gibberellic acid
XXXV



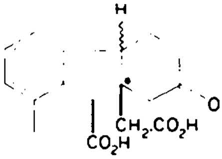
Allogibberic acid
XXXVI



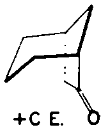
Gibberic acid
XXXVII



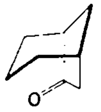
Nor-ketone from allogibberic acid
XXXVIII



Hexahydrofluorenone type by fission of ring D
XXXIX



+C E.
XL



-C E
XLI

The hexahydrofluorenones of general type (XXXIX) in which the original configuration at C-9a* is unchanged all have positive Cotton effect curves, indicating the stereochemistry shown. The bridged-ring nor-ketones (XXXVIII) obtained by merely removing the methylene group at C-8 show positive curves; whilst those of type (XXXVII) (gibberic acids) produced by Wagner-Meerwein rearrangement show negative curves.

These results indicate that the bridged-ring bicyclo [3,2,1] structures of general type (XL) have positive Cotton effects, and those of the enantiomeric type (XLI) have negative effects. The application of these reference values (cf. Table 5) to the extensive observations of Djerassi's school on cafestol[24] steviol,[28] and the *Garrya* alkaloids[28] follows logically.

---

[26] B. E. Cross, J. F. Grove, P. McCloskey, T. P. C. Mulholland and W. Klyne, *Chem. & Ind.* 1345 (1959) and previous references there.

[27] G. Stork and H. Newman, *J. Amer. Chem. Soc.* **81**, 3168, 5519 (1959).

[28] C. Djerassi, B. Riniker and R. Riniker, *J. Amer. Chem. Soc.* **78**, 6362 (1956).

TABLE 5. BICYCLO [3,2,1] OCTAN-6-ONES*

	a	Ref.
Type XL		
From phyllocladene	+108 D	28
From gibberellic acid	+52, +88	a
From cafestol	+113 D	28
Enantiomeric type XLI		
From steviol	−93	28
Gibberic acid	−90	a
Cuachichicine	−19	28

* Solvent, methanol, except for values marked D, which are in dioxan.

[a] Own work; cf. also ref.[27]

8. *Bicyclo* [2,2,1] *heptan-2-ones*

Ourisson and his colleagues[29] have studied a number of these compounds (type XLII) and the following notes represent my own attempt to consider their results in the light of the Octant Rule. This is an alternative treatment to that given by Jacob, Ourisson and Rassat[29] in which they consider the relative *bulk* of two bridges. It is not yet possible to apply the Octant Rule in such a way as to predict the Cotton effect of the fundamental skeleton (XLII), but the contributions of substituents (e.g. methyl groups) generally follow the pattern expected from the Rule. In other words when the substituted compounds are considered in pairs, the differences in amplitude are nearly all of the sign expected. However, the results are not such that one could use them to predict the Cotton effects of any but *very* closely analogous compounds.

All observations and calculations based on models at this stage necessarily assume perfect tetrahedral angles throughout. This assumption is almost certainly incorrect—but at present we have no better data for valency angles etc. available.

In (+)-camphenilone XLIII only two atoms (6 and 7) are significant, since 3a and 3b are in approximately symmetrical positions. The observed amplitude (+18) is therefore the best estimate we have at present for the fundamental skeleton XLII.

The comparison of αα-dimethylcamphor (L) (a —50!) and camphor itself (a −47) (XLVI) shows that C-3a and C-3b together have a *small* contribution, probably negative. However, since it is small, their contributions do roughly cancel.

The bridge-head methyl group (1a) in fenchone deserves comment. Comparison of (XLV)-(XLIII) indicates that this group has a negligible positive effect (Δa, +3). On the perfect tetrahedral model 1a is just in the upper right octant (*negative*)—but it is so near the vertical C plane (position of which is arbitrary) that any prediction would be unsafe. The *experimental* value alone is significant.

Let us now compare αα-dimethylcamphor (L) and fenchone (XLV). The addition of the *gem*-dimethyl group (7a and 7b) makes a contribution (Δa) of −70 or more. The position of C-7b (very near a vertical symmetry plane) suggests that its contribution would be *small*. C-7a would be expected to have a large negative contribution, but not as big as −70 a units. This may be due to repulsion between C-7b and C-3b with consequent distortion of the ring system.

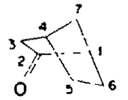
The effect of the *gem*-dimethyl group (C-5a, C-5b) may be estimated by the comparison (XLVII—XLIII) as $\Delta a = -28$. The Octant Rule suggests for C-5a and C-5b moderate negative and small positive contributions respectively; together the contribution should be a small negative one, which agrees with experiment.

Gervais and Rassat, working in Paris,[29a] have noted striking solvent differences for the dispersion curves of isofenchone (XLIX) and epiisofenchone. No explanation of these differences can be given at present, but it is pertinent to draw attention to the findings of Kuhn[30] in classical work on camphor 30 years ago. Kuhn's calculations, taking into account circular dichroism, suggested that the absorption and dispersion curves in the region of 290 mμ might be more complex than at first sight appeared.

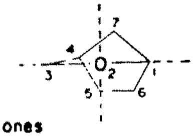
To summarize this discussion on bridged-ring ketones; the application of the Octant Rule in this field, as with cyclopentanones, is by no means simple, and many interesting problems remain unsolved. All that has been done here is to set some of the data together.

Plain Curves

It was soon clear from Djerassi's work that plain curves could never give as much structural information as Cotton effect curves; none the less we felt that it was desirable to explore further the field of nonabsorbing compounds (i.e. compounds

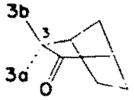


= XLII



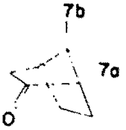
Bicyclo (2,2,1) heptan-2-ones
Reference (29). Values in parentheses are amplitudes; solvent, methanol unless otherwise stated

(+)-Camphenilone XLIII



(+18)

(−)-α-Fenchocamphorone XLIV



(−65)

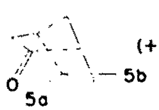
(+)-Fenchone XLV

(+21)

(−)-Camphor XLVI

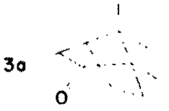
(−47)

(+)-β-Fenchocamphorone XLVII



(+10)

(−)-α-Methylcamphor(endo) XLVIII

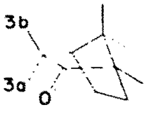


(−41!)

(+)-Isofenchone XLIX

(+19?)
(−30 in cyclohexane)

(−)-αα-Dimethylcamphor L



(−50!)

---

[29] G. Jacob, G. Ourisson and A. Rassat, *Bull. Soc. Chim. Fr.* 1374 (1959).

[29a] H. P. Gervais and A. Rassat, *Bull. Soc. Chim. Fr.* In press (1961).

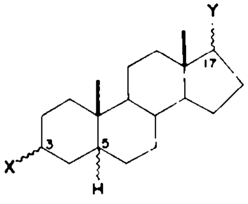
[30] W. Kuhn and H. K. Gore, *Z. Phys. Chem.* B12, 389 (1931); W. Kuhn and H. L. Lehmann, *Z. Elektrochem.*

with no absorption above about 280 mμ) since the dispersion curves must necessarily give more information than "monochromatic" rotation measurements at 589 mμ.

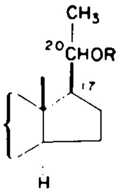
Our work has been largely carried out on steroids from our own and colleagues' stocks, and from the Medical Research Council's Steroid Reference Collection, and also on a variety of other natural products.

The questions which we have tried to answer are (i) what are the most suitable data for structural purposes to be obtained from plain curves (Drude constants, dispersion ratios, or simply [ϕ] values at a given wavelength?); (ii) how does vicinal action (between nonabsorbing functions in the same compound) vary with wavelength?; (iii) how closely do the dispersion curves of a homologous series of configurationally related compounds resemble one another?

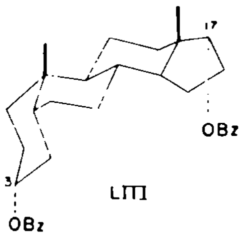
Since the Conference was held, four important papers[30a] on optically active acids have been published by Dr. B. Sjöberg, describing work done in Prof. Djerassi's laboratory.



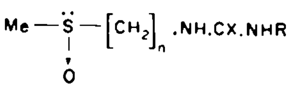
LI



LII



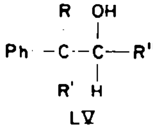
LIII



$$\mathrm{Me{-}\underset{\downarrow\atop O}{\overset{\cdot\cdot}{S}}{-}[CH_2]_n.NH.CX.NHR}$$

LIV

Sulphoxides



$$\mathrm{Ph{-}\underset{R'}{\overset{R}{C}}{-}\underset{H}{\overset{OH}{C}}{-}R''}$$

LV

R = H or alkyl

R',R'' = alkyl

9. *Monosubstituted steroids*

In this work (with Mr. P. M. Jones) we have studied complete series of isomeric 3-, 17- and 20-monosubstituted steroids (LI, LII). The results[31] may be summed up as follows; (i) the rotations—or better the rotation contributions of the substituents (cf. below)—are in all cases much greater at 300 mμ than at 589 mμ; (ii) none of the functions readily calculated from the dispersion curves appears at present to give any

---

[30a] B. Sjöberg, *Acta Chem. Scand.* (1960); *Ark. Kemi* (1960).

[31] P. M. Jones and W. Klyne, *J. Chem. Soc.* 871 (1960).

more useful *structural* information than the simple value of [ϕ] at 300 mμ. These results are very much what might have been expected from the earlier results of Djerassi *et al.*[32]*, although a much wider range of functional groups should be studied before any generally valid conclusions can be drawn.

It may be pointed out that while the fundamental steroid hydrocarbon skeleton (5α- or 5β-androstane) has an almost negligible rotation, even at 300 mμ, other steroid hydrocarbons carrying substituents at C-17 (5α- and 5β-pregnanes and cholestanes) have appreciable rotations at 300 mμ (Table 6). These rotations should be subtracted from the rotations of monosubstituted pregnanes and cholestanes to obtained rotation contributions ($\Delta\phi$ values) for the substituents themselves.

TABLE 6. STEROID HYDROCARBONS

	[ϕ] at 300 mμ	
	5α	5β
Androstane	+40	−10
Pregnane	−280	+210
Cholestane	−550	+530

10. *Disubstituted steroids*

The complete isomeric series of 5α- and 5β-androstan-3:17-diols and their diacetates and dibenzoates has been studied.[33] In general the vicinal action at 300 mμ follows the same pattern as it does at 589 mμ. In other words for disubstituted compounds where the 'old-fashioned' monochromatic ΔM_D values for the individual substituents are additive, the dispersion curves are additive; for compounds where there is moderate divergence between observed and calculated M_D values, the observed and calculated dispersion curves show a similar moderate divergence.

There is however one apparently glaring exception to the rule of (at least approximate) additivity—viz. 5β-androstane-3α,17α-diol dibenzoate (LIII). The *observed* values for [ϕ] were +90 (600 mμ) +170 (500 mμ) and +1460 (300 mμ); the corresponding values *calculated* from those for 3α- and 17α-monosubstituted compounds were −180, −210, −920. No explanation for this behavior can be advanced as yet, but the possibility of "interference" between two benzoate groups on the α-side of the molecule must be envisaged; this might be accentuated if ring A is a deformed chair or boat.

11. *A homologous series—some asymmetric sulphoxides*

No extensive set of rotatory dispersion curves of a homologous series has appeared as such in the recent literature. There are several sets (over restricted wavelength ranges) in the classical literature, and data must be available for a considerable series of aminoacids in the work of the Bethesda group (Greenstein *et al.*[34]), but only Drude constants are given in their papers.

The valuable work of Schellman (see this vol. p. 176 and Chap. 15 of ref. 5) on aminoacids was not available before the Conference.

---

* Cf. ref. 5, Chap. 1 and 16.

[32] C. Djerassi, E. W. Foltz and A. E. Lippman, *J. Amer. Chem. Soc.* 77, 4354, 4359, 4364 (1955).

[33] P. M. Jones and W. Klyne, *J. Chem. Soc.* 871 (1960); see also P. M. Jones, M.Sc. Thesis, London (1959).

[34] M. C. Otey, J. P. Greenstein, M. Winitz and S. M. Birnbaum, *J. Amer. Chem. Soc.* 77, 3112 (1955).

In collaboration with Professor A. Kjaer of Copenhagen[35] we have measured a series of asymmetric sulphoxides of the general type (LIV) where n = 5–10, X is S or O, and R is H, Ph or CH_2Ph. As might be expected, the dispersion curves of the various members of this homologous series are almost superimposable. For 12 examples [ϕ] (300 mμ) lies between −950 and −1080.

12. *Other work*

Other recent work on plain curves includes studies by Mateos and Cram[36] on aralkyl derivatives of the general type (LV), by Lyle[37] on α-aralkylamines (some of these show partial Cotton effects), by Bose and Struck on diterpenes.[38] We have work in progress on isoquinoline and emetine alkaloids with Dr. A. R. Battersby (Bristol) and on lignans with Professor H. Erdtman (Stockholm).

Acknowledgements—I am greatly indebted to the Wellcome Trust for the generous provision of a spectropolarimeter, to Messrs. Imperial Chemical Industries Ltd. for other equipment, to the Department of Scientific and Industrial Research for a grant and to the U.S. Army Research and Development Group in Frankfurt-am-Main for a contract.

I am grateful to Prof. Carl Djerassi and Prof. Guy Ourisson for the free and continuing exchange of data and ideas; to the many colleagues who have supplied samples for our work, including the pharmaceutical firms who have so generously assisted the Medical Research Council's Steroid Reference Collection; and Mr. P. M. Jones, Mrs. Janet Day and Miss Jane Jackson, who have operated the polarimeter.

[35] W. Klyne, J. Day and A. Kjaer, *Acta Chem. Scand.* **14**, 215 (1960).
[36] J. L. Mateos and D. J. Cram, *J. Amer. Chem. Soc.* **81**, 2756 (1959).
[37] G. Lyle, *J. Org. Chem.* **25**, 1779 (1960).
[38] A. K. Bose and W. A. Struck, *Chem. & Ind.* 1628 (1959).