Tetrahedron Vol 23, pp 3449 to 3503 Pergamon Press Ltd 1967 Printed in Great Britain

OPTICAL ROTATORY DISPERSION AND CIRCULAR DICHROISM OF AROMATIC COMPOUNDS: A GENERAL SURVEY†

P. CRABBÉ
Syntex, S.A., Mexico, and Universidad Nacional Autonoma de Mexico
and
W. KLYNE
Westfield College, London, N.W.3

(*Received* 5 *October* 1966; *accepted for publication* 17 *December* 1966)

Abstract—A general survey of optical rotatory dispersion (ORD) and circular dichroism (CD) studies on aromatic compounds is given. Recent developments in equipment permit observation of Cotton effects associated with the α-band (ca. 260–280 mμ), and often of those associated with the *p*-band (ca. 220–240 mμ).

The chromophores may be classified as (i) inherently dissymmetric or twisted chromophores (e.g. overcrowded polycyclic compounds, biaryls); (ii) coupled oscillators consisting of two *non-conjugated* aryl or related groups (e.g. calycanthine, lignans, benzyltetrahydroisoquinolines); (iii) single aryl chromophores perturbed by dissymmetric surroundings (e.g. oestrogenic steroids, indoles, mandelic acid derivatives, nucleosides).

In classes (ii) and (iii) the rigid structures are dealt with before the flexible structures; since the geometry of the rigid structures is more precisely known, they can be better considered in theoretical terms.

Many of the studies are of very piecemeal character, and it is hoped that this review will suggest areas where further work is likely to be most profitable. Applications of theory have been possible so far only within very limited fields.

1. INTRODUCTION

THE Cotton effects exhibited by optically active aromatic substances have not as yet been adequately studied.[1–5] It is only in restricted fields that attempts have been made to relate the sign of the Cotton effects to the configuration of an asymmetric centre (or centres) near an aromatic chromophore, or to the chirality of the molecule as a whole.

---

† This paper is Part 43 in the Westfield College series on Optical Rotatory Dispersion; for Part 42, see W. Klyne, R. J. Swan, N. J. Dastoor, A. A. Gorman and H. Schmid, *Helv. Chim. Acta* **50**, 115 (1967).

[1] P. Crabbé, *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*. Holden-Day, San Francisco (1965).

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

[3] W. Klyne in *Advances in Organic Chemistry* (Edited by R. A. Rapheal, E. C. Taylor and H. Wynberg) Vol. 1; p. 239. Interscience, New York (1960).

[4] G. G. Lyle and R. E. Lyle in *Determination of Organic Structures by Physical Methods* (Edited by F. C. Nachod and W. D. Phillips) Vol. 2; p. 1. Academic Press, New York (1962).

[5] L. Velluz, M. Legrand and M. Grosjean, *Optical Circular Dichroism. Principles, Measurements and Applications*. Verlag Chemie, Weinheim (1965).

The development of ORD and more recently CD equipment which permits the penetration of the absorption bands of aromatic compounds in the region of the α-band (260–280 mμ) (for nomenclature see Table 1)[6] and sometimes below 240 mμ, has led to a good deal of exploration of the aromatic field over the last three years. At present this work is of a piecemeal character, but a pattern begins to appear, and it seems to be the appropriate time to make a general survey of the field. This will at least systematize the fragmentary data now available, and enable organic chemists to see where there are gaps in our knowledge. We are well aware of the highly tentative nature of some of the generalizations suggested here, but we hope they may serve to suggest lines for future progress.

Although theoretical studies are as yet limited to a few groups of compounds, which have been intensively studied, empirical approaches show that from the sign and magnitude of the Cotton effect(s), the stereochemistry, including the absolute configuration of asymmetric centres, and the conformation of rings or conjugated systems, may often be deduced.

The criteria of aromaticity are of three types:[7] (a) the presence of $(4n + 2)$ out-of-plane π-electrons, as stated by Hückel;[8] (b) a reasonably planar configuration; (c) a ring-size below certain limits. Hence, "a compound is considered to be aromatic if there is a measureable degree of cyclic delocalization of a π-electron system in the ground state of the molecule".[7]

Aromatic compounds usually show three major transitions between 180 and 300 mμ; two strong absorption bands appear near 180 mμ and 200 mμ, and a weak band, usually showing considerably fine structure, appears at about 260 mμ.[6] Several different nomenclature systems are used for the first three UV absorption bands of aromatic structures;[6] going (usually) from longer to shorter wavelengths, i.e. from lower to higher frequencies, they are as in Table 1. In the present paper we shall refer mainly to the weak α or ^1L_b band around 260 mμ.

If an aromatic compound is symmetrical (e.g. benzene) the weak transition at 260 mμ is a formally "forbidden" band.[6] However, in any *dissymmetric* aromatic system, this π–π*-transition at ca. 260 mμ will become optically active.

Dissymmetric aromatic compounds are of widely differing types. These compounds

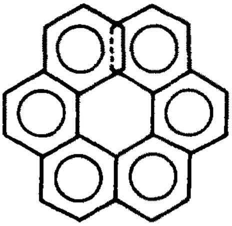
---

[6] [a] H. H. Jaffé and M. Orchin, *Theory and Applications of Ultraviolet Spectroscopy*. Wiley, New York (1962);
[b] A. I. Scott, *Interpretation of the Ultraviolet Spectra of Natural Products*. Pergamon Press, London (1963);
[c] A. E. Gillam and E. S. Stern, *An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry*. Arnold, London (1958);
[d] J. R. Platt, *J. Chem. Phys.* **17**, 484 (1949);
[e] L. Salem, *The Molecular Orbital Theory of Conjugated Systems*. Benjamin, New York (1960);
[f] J. W. Sidman, *Chem. Rev.* **58**, 689 (1958);
[g] S. F. Mason, *Quart. Rev.* **15**, 287 (1961).

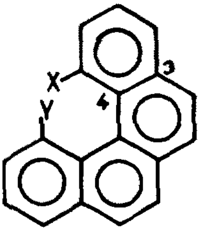
[7] [a] F. Sondheimer, *Pure and Applied Chem.* **7**, 363 (1963);
[b] J. A. Elvidge and L. M. Jackman, *J. Chem. Soc.* 859 (1961);
[c] L. M. Jackman, F. Sondheimer, Y. Amiel, D. A. Ben-Efraim, Y. Gaoni, R. Wolovsky and A. A. Bothner-By, *J. Am. Chem. Soc.* **84**, 4307 (1962).

[8] [a] E. Hückel, *Z. Physik* **70**, 204 (1931);
[b] E. Hückel, *Grundzüge der Theorie ungesättigter und aromatischer Verbindungen*. Verlag Chemie, Berlin, (1938).

range from polycyclic structures of dissymmetric character such as hexahelicene[9] (**1**) and the various benzphenanthrene derivatives (**2**) on the one hand, to compounds containing a simple benzene ring attached to a classical "asymmetric carbon atom" as, e.g., in mandelic acid, on the other hand.



Hexahelicene
1



3,4-Benzphenanthrenes
2

TABLE 1. NOMENCLATURE FOR THE THREE UV ABSORPTION BANDS OF AROMATIC COMPOUNDS IN THE 180–280 mμ REGION[6]

Wavelength region (approximate)	Designation of the band
260–280 mμ	α ^1L_b $^1A_{1g} \rightarrow {}^1B_{2u}$ $^1A \rightarrow {}^1L_b$ B
200–220 mμ	*p* ^1L_a $^1A_{1g} \rightarrow {}^1B_{1u}$ $^1A \rightarrow {}^1L_a$ E_2
180–190 mμ	β ^1B_a $^1A_{1g} \rightarrow {}^1E_{1u}$ $^1A \rightarrow {}^1B$ E_1

---

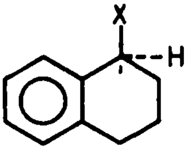
[6] [a] A. Moscowitz, *Tetrahedron* **13**, 48 (1961);
[b] A. Moscowitz, in *Advances in Chemical Physics*, (Edited by I. Prigogine) Vol. IV. Interscience, New York (1962);
[c] O. E. Weigang, jr., J. A. Turner and P. A. Trouard, *J. Chem. Phys.* **45**, 1126 (1966).

The two extremes of this range correspond to the two classes of dissymmetric structures suggested in one of their important papers by Moscowitz, Djerassi, Mislow *et al.*[10] *viz*:— those with *inherently dissymmetric chromophores*, and those with symmetrical but *asymmetrically perturbed chromophores*. In the sequel it will be seen that within the aromatic field there are many intermediate stages between these two extremes.

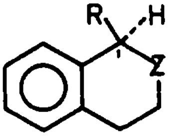
On all grounds it is easier to treat compounds of a fixed conformation or shape than those in which the conformation is flexible. Whilst proceeding from the inherently dissymmetric chromophores to the essentially symmetric but perturbed types, we shall at each stage deal logically with the more rigid before the more flexible structures.

Definitions of structures (cf. formulae **3**–**8**)

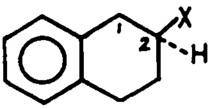
(1) As defined above, "aromatic" generally means a benzene ring with or without substituents; it can also mean naphthalene or a hetero-structure like furan, pyrazole, indole, pyrimidine or purine in nucleosides, etc.



3

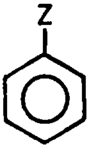


4

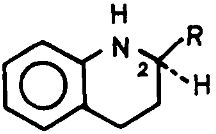


5

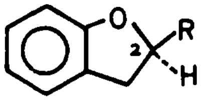
In **3** C1 is benzylic
In **4** Z is a benzylic hetero atom
In **5** C2 is phenethylic



6



7



8

In **6** (Z = $-OR$, $-NR_2$, $-Br$), Z is arylic
In **7** and **8**, N and O are arylic heteroatoms.

(2) Heteroatoms (O, N, S, halogen) directly attached to an aromatic ring are called *arylic*; this term is used *both* for hetero-substituents not associated with the alicyclic part of structure (e.g. $-OH$, $-OMe$, $-NH_2$, $-NHAc$, $-Br$, etc.), *and* also for heteroatoms in a reduced ring and adjacent to an aromatic nucleus—e.g. N in 1,2,3,4-tetrahydroquinoline (**7**) or O in 2,3-dihydrobenzfuran (**8**).

---

[10] [a] K. Mislow, M. A. Glass, R. E. O'Brien, P. Rutkin, D. H. Steinberg and C. Djerassi, *J. Am. Chem. Soc.* **82**, 4740 (1960);
[b] K. Mislow, M. A. Glass, R. E. O'Brien, P. Rutkin, D. H. Steinberg, J. Weiss and C. Djerassi, *Ibid.* **84**, 1455 (1962);
[c] E. Bunnenberg, C. Djerassi, K. Mislow and A. Moscowitz, *Ibid.* **84**, 2823 (1962);
[d] K. Mislow, *Ann. N.Y. Acad. Sci* **93**, 459 (1962);
[e] A. Moscowitz, K. Mislow, M. A. W. Glass and C. Djerassi, *J. Am. Chem. Soc.* **84**, 1945 (1962).
[f] K. Mislow, E. Bunnenberg, R. Records, K. Wellman and C. Djerassi, *Ibid.* **85**, 1342 (1963).

(3) Centres of asymmetry which are adjacent to an aromatic ring are called *benzylic*, e.g. C-1 in **3**; centres of asymmetry which are separated from an aromatic ring by CH_2, or another saturated group, are called *phenethylic*., e.g. C-2 in **5**.

Definitions and units for curves

Wave-lengths (λ) are in mμ.

ORD curves. Rotations are *molecular* rotations, $[\phi]$. The *Amplitude* (a) of a Cotton effect is defined as 10^{-2} ($[\phi]$ at 1st extremum *minus* $[\phi]$ at 2nd extremum). If the second extremum was not reached, the value is shown as a!

CD curves. Values for maxima are given as $\Delta\varepsilon = (\varepsilon_l - \varepsilon_r)$, or (in a few cases) as (θ), molecular ellipticity.

$\theta = 3300. \Delta\varepsilon$

For an ideal case (Ref. 1, p. 19) ORD amplitude and CD maximum are interrelated as follows: $a = 40{\cdot}28\ \Delta\varepsilon$ or $a = 0{\cdot}0122\ \theta$.

Absolute configuration. In most cases this is designated according to the Sequence Rule (R, S system) of Cahn, Ingold and Prelog (Ref. 14). In other cases the older D,L convention is used when convenient.

II. THE INHERENTLY DISSYMMETRIC CHROMOPHORES

Overcrowded structures. The most rigid structures of this type are those compounds in which the aromatic system is of an angular polycyclic type (the overcrowded structures). Among these hexahelicene (**1**)[9] is the classic example, followed by several recent studies on compounds of the 3,4-benzphenanthrene type **2**. These have been fully dealt with elsewhere by Moscowitz, Mislow *et al.*[9, 11] and by Mason.[12] Recent

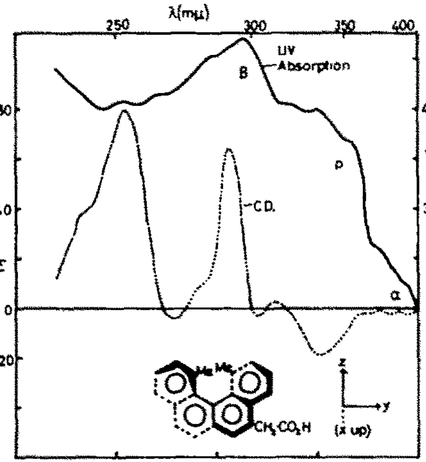


FIG. 1. UV Absorption (———) and CD curves (-----) of (−)-1,12-dimethylbenzo[c]-phenanthrene-5-acetic acid (from Kemp and Mason, Ref. 12*a*).

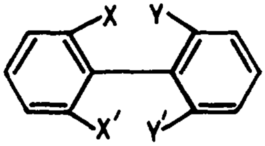
---

[11] A. Moscowitz, *Optical Rotatory Dispersion Applications to Organic Chemistry* (Edited by C. Djerassi) Chap. 12. McGraw-Hill, New York (1960).

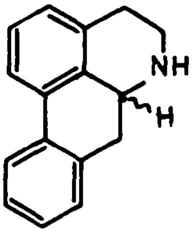
[12] [a] C. M. Kemp and S. F. Mason, *Chem. Comm.* 559 (1965);
[b] C. M. Kemp and S. F. Mason, *Tetrahedron* **22**, 629 (1966).

work by Kemp and Mason[12] shows how the chirality (helicity or sense of skew)[13] (*M* or *P* in the newest terminology of Cahn, Ingold and Prelog)[14] of certain 3,4-benzophenanthrene derivatives **2** may be determined from the signs of the CD maxima associated with their *p*- and β-bands (Fig. 1).

Biaryls. The next class consists of the skewed biaryls **9**; these have already been considered fully on the general treatment of Djerassi, Mislow, and Moscowitz[10] (Fig. 2). Compounds of this type include natural products such as the aporphines[15] **10**, which provide excellent rigidified analogues, some colchicine derivatives,[16] as well as some dihydrophenanthrenes.[17–19] Binaphthyl and bianthryl compounds of this type have been discussed recently.[20,21] A recent paper[21a] deals with the *infra-red* ORD of two complex dibenz-cycloalkene derivatives.



Biaryls
9



Aporphines
10

Figure 2 shows the relationship between UV, ORD and CD curves for a typical biaryl:(*S*)-2,2′-dimethyl-6,6′-dinitrobiphenyl (**9**; X = Y = Me, X′ = Y′ = NO_2).[10]

As shown in Fig. 2, one can distinguish three main regions of absorption. The 350–340 mμ UV absorption band is hardly detected; a weak CD and ORD Cotton effect is however observed ca. 350 mμ. In the 310–300 mμ region, the UV curve shows an inflexion, with which a strong *negative* Cotton effect is associated (at 298 mμ). The third band appears at 260 mμ, and corresponds to a strong π–π^* transition in the UV. A very strong *positive* Cotton effect is observed by CD around 251 mμ. Moreover, the ORD curve also shows a strong positive Cotton effect, although the first extremum is probably joined up with the second extremum of the 300 mμ negative Cotton effect mentioned above.

This figure illustrates well the facts that (i) UV inflexions, which are hidden under the shoulder of a stronger absorption band, are often shown up well by CD; (ii) the

---

[13] [a] K. Mislow, *Introduction to Stereochemistry*. Benjamin, N.Y. (1965);
[b] E. L. Eliel, *Stereochemistry of Carbon Compounds*. McGraw-Hill, New York (1962).

[14] [a] R. S. Cahn and C. K. Ingold, *J. Chem. Soc.* 612 (1951);
[b] R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia* **12**, 81 (1956);
[c] R. S. Cahn, C. K. Ingold and V. Prelog, *Angew. Chem.* (Internat. Ed.) **5**, 385 (1966).

[15] C. Djerassi, K. Mislow and M. Shamma, *Experientia* **18**, 53 (1962); J. C. Craig and S. K. Roy, *Tetrahedron* **21**, 395 (1965).

[16] J. Hrbek, J. P. Jennings, W. Klyne and F. Šantavý, *Coll. Czech. Chem. Comm.* **29** 2822 (1964).

[17] K. Mislow and H. B. Hopps, *J. Am. Chem. Soc.* **84**, 3018 (1962).

[18] [a] T. R. Hollands, P. de Mayo, M. Nisbet and P. Crabbé, *Canad. J. Chem.* **43**, 3008 (1965); see also:
[b] P. Crabbé, *Vietnamica Chimica Acta*, **1** (1967).

[19] P. Crabbé, *Ind. Chim. Belge* **31**, 131 (1966).

[20] R. Grinter and S. F. Mason, *Trans. Faraday Soc.* **60**, 274 (1964).

[21] G. M. Badger, R. J. Drewer and G. E. Lewis, *J. Chem. Soc.* 4268 (1962).

[21] [a] H. R. Wyss and Hs. H. Günthard, *Helv. Chim. Acta* **49**, 660 (1966).

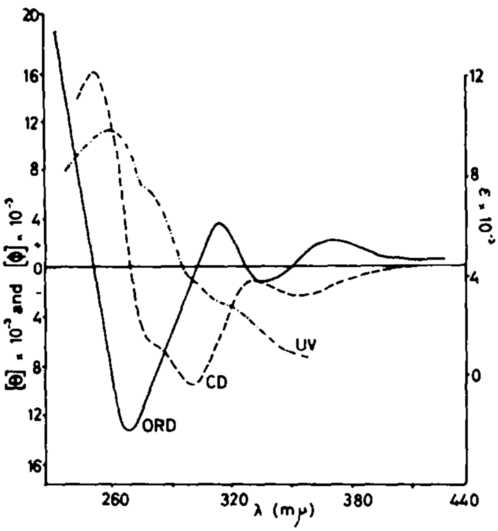


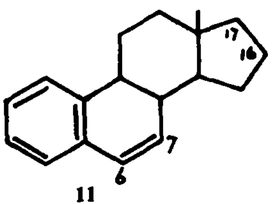
Fig. 2. UV absorption (-·-·-·), CE (- - - - -), and ORD (———) curves of (*S*)-2,2'-dimethyl-6,6'-dinitrobiphenyl (based on Ref. 1. p. 182, and Ref. 10f).

CD curve "pulls apart" the Cotton effects of neighbouring absorption bands more efficiently than does the ORD curve, in which these may overlap; (iii) very large Cotton effects in inaccessible regions of the spectrum ("invisible giants") are indicated by their "tails", which stretch into regions accessible by ORD—although for CD measurements the wavelength of the absorption band must be reached in order to draw stereochemical conclusions.

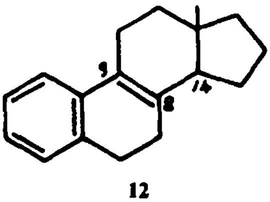
A recent application of ORD and CD to bithienyls by Gronowitz[21b] may be also noted.

Other Conjugated Structures

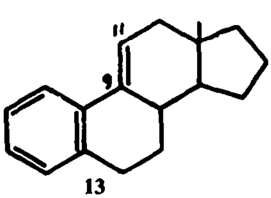
Styrenes. The next class, which has not hitherto been fully considered elsewhere, is that of the skewed styrenes. These may be considered as formally analogous to a



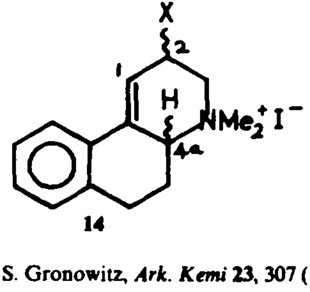
11



12



13



14

[21b] S. Gronowitz, *Ark. Kemi* **23**, 307 (1965).

biaryl, except that one aromatic nucleus is replaced by an olefinic double bond. Examples of hexahydronaphthalenes, which are "rigidified styrenes", are shown in Fig. 3. Table 2 gives the ORD data for skewed styrenes belonging to the steroid series (**11**, **12**, **13**)[22, 23] and the hexahydrobenzo[*f*]quinolines (**14**).[25] The chirality of the conjugated system in the Δ^6-oestrogens (**11**) (left-handed helix; negative Cotton effect) is opposite to that in the Δ^8 and $\Delta^{9(11)}$ compounds **12**, **13** (right-handed helix; positive Cotton effect). The nature of the substituent at C-3 (H, OH, OAc, OMe, OBz) sometimes has an important influence on the amplitude of the Cotton effect of such styrenes, although not on its sign; substituents at C_{16} and C_{17} have lesser effects. Since the Δ^8-14β-steroid (**12b**)[26] exhibits a positive Cotton effect in the 260 mμ region, one can deduce its conformation; the 7-methylene group is very probably below the plane of ring A and the 8(9) double bond, and the 12-methylene group is in this plane. In this conformation the non-bonded interactions between hydrogen atoms are minimal.

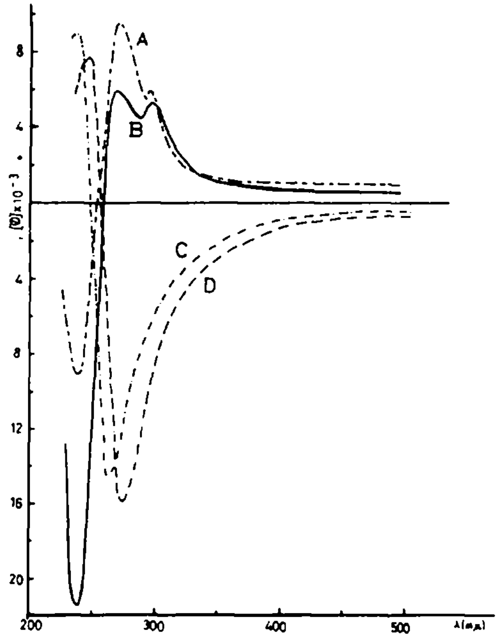


FIG. 3. ORD Curves of "rigidified styrenes"

A	(– – – – –)	$\Delta^{9(11)}$-Oestrogen	(13*b*)
B	(————)	Hexahydrobenzo(f)quinoline, with 4aβH	(14*b*)
C	(–·–·–·)	Hexahydrobenzo(f)quinoline, with 4aαH	(14*a*)
D	(– – – – –)	Δ^6-Oestrogen	(11c)

(based on Ref. 1, p. 254, and Ref. 25).

---

[22] [a] See Ref. 1, p. 253;
[b] P. Crabbé, in *An Introduction to Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*. Advanced Institute for Study of Optical Rotatory Dispersion and Circular Dichroism, Bonn, September 1965, Heyden (1967).

[23] Some physical properties of *cis*- and *trans*-styrenes have been mentioned by Havinga and *et al.*, see: M. E. Kronenberg and E. Havinga, *Rec. Trav. Chim.* **84**, 17 (1965), and Refs cited therein.

[24] These compounds came from the Syntex Steroid Collection.

[25] These N-methylhexahydrobenzo-[*f*]-quinolines are due to the courtesy of Dr. H. G. Leeman, Sandoz A.G., Basel, cf. H. G. Leeman and S. Fabbri, *Helv. Chim. Acta* **42**, 2696 (1959).

TABLE 2. RIGID STYRENE-TYPE STRUCTURES

ORD data; solvent, dioxan.

Compound	Substituents in aromatic ring A (*or on double bond**)	Other substituents	Amplitude '*a*' of styrene chromophore	Wavelengths at extrema λ (mμ)	Ref.
	Δ^6-oestrogens (11)				
11a	3-OH	17β-OAc	−94	273/255	24
b	3-OH	17-OCH$_2$·CH$_2$·O-	−283	274/256	24
c	3-OAc	17β-OAc	−236	276/247	24
d	3-OAc	17-OCH$_2$·CH$_2$·O-	−337	273/238	24
e	3-OAc	Spirostan	−129	276/244	24
f	3-OBz	17β-OH	−316	270/244	24
g	3-OAc, 7-OAc*	17:0	−40	276/256	24
h	3-OH, 1,2-Dimethyl	17β-OAc	−113	285/256	24
i	3-OAc, 1-Me	17β-OAc	−309	278/237	24
j	3-OAc, 1-Me	Spirostan	−150	279/260	24
k	1-Me, 3-OMe	17β-OH	−118	279/255	24
	Δ^8-*oestrogens* (12)				
12a	3-OMe	17:0 (14βH)	+601	276/248	26
b	3-OMe	17α-OH, 17βC≡CH (14βH)	+288	278/224	26
	$\Delta^{9,(11)}$-*oestrogens* (13)				
13a	3-OH	17β-OH	+203	264/240	24
b	3-OAc	17β-OAc	+194	288/238	24
c	3-OMe	17β-OH	+210	260/235	24
d	3-OAc	17β-C(O$_2$C$_2$H$_4$)Me†	+169	268/243	24
Hexahydrobenzo-(f)quinolines (14)					
14a	4aα-H, 2ξ-OH		−236	263/238	25
b	4aβ-H, 2ξ-OH		+268	267/239	25
c	4aβ-H, 2ξ-OH, 2ξ-Me		+422	276/236	25

* Enol-acetate. † 20-ethylene ketal.

The absolute configurations at C-4a of the N-methyl-hexahydrobenzo-[*f*]-quinolines (**14**)[25] are allotted in accordance with the same principles (cf. Fig. 3).

Substitution. It may be that the patterns of substitution in the aromatic nuclei themselves are *not* of *primary* importance in determining the ORD behaviour of such twisted chromophores. The empirical studies of many alkaloids and lignans (cf. pp. 16–17—below) lead us to think that the general structure and stereochemistry are the major factors responsible for the optical properties (with arylic substitution in many cases, a secondary one). However, this is at present a statement of opinion.*

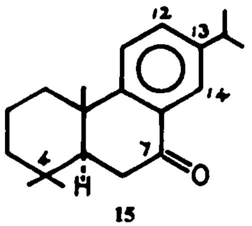
Several of the styrene-type oestrogens in Table 2 also illustrate this point; substitution on an olefinic double bond by a polar group such as, e.g. acetoxyl (in an enol-acetate) makes a major difference in the amplitude (cf. compound **11g**), no doubt as a result of the inductive effect of the substituent. Methyl would presumably affect the amplitude in a much less pronounced fashion.

The substituent at C-17 seems to influence considerably the amplitude of the Cotton effect associated with the styrene chromophore (cf. compounds **12a** and **12b** in Table 2). This influence may be due to a change in the degree of chirality of the styrene chromophore, or to conformational mobility, or perhaps to non-conjugative interaction (in **12a**) between the groups C=O at 17 and C=C at 8(9), which are separated by only two saturated carbon atoms (cf. p. 18 below). †

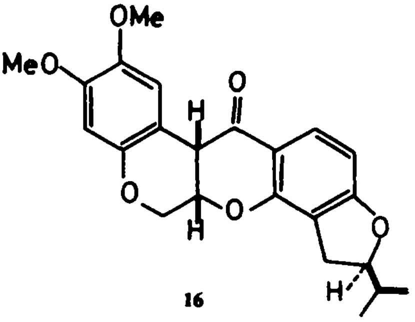
Aryl ketones. The conjugated aryl ketones, e.g. **15** and **16**, which may be considered as substituted acetophenones, or better 1-tetralones, have been studied by Bose, Cambie *et al.*[27] and by Snatzke.[28a]

These studies have so far been largely restricted, for instrumental reasons, to the $n \rightarrow \pi^*$ transition at ca. 320 mμ, which is not aromatic. When exploration of the lower wavelength regions is more thorough,[28b] the true aromatic Cotton effects can be profitably discussed.

The rotenoids (**16**) constitute a rather complex group of conjugated aryl ketones,



15



16

---

* But see the important note added in Press on p. 12.

† A non-rigid skewed styrene type is represented by a degradation product of tazettine (Highet *et al*[26a]).

[26] P. Crabbé, A. Cruz and J. Iriarte, *Tetrahedron* submitted for publication.

[26a] R. J. Highet, P. F. Highet and J. C. N. Ma, *Tetrahedron Letters* 1049 (1966); R. J. Highet and P. F. Highet, *Ibid.* 4099 (1966).

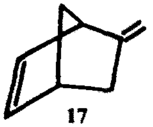
[27] [a] A. K. Bose, M. S. Manhas, R. C. Cambie and L. N. Mander, *J. Chem. Soc.* **84**, 3201 (1962);
[b] R. C. Cambie, L. N. Mander, A. K. Bose and M. S. Manhas, *Tetrahedron* **20**, 409 (1964);
[c] A. K. Bose, M. S. Manhas and R. C. Cambie, *J. Org. Chem.* **30**, 501 (1965).

[28] [a] G. Snatzke, *Tetrahedron* **21**, 439 (1965);
[b] J.-C. Bloch and S. R. Wallis, work in progress.

containing another non-conjugated aryl group in addition. Extensive studies have been carried out by Djerassi and Ollis *et al.*[29]

III HOMOCONJUGATED SYSTEMS

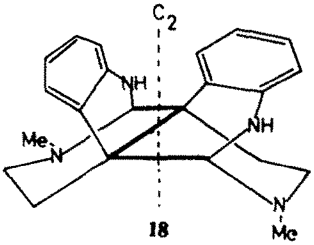
By the term "homoconjugated", we mean compounds in which two aromatic nuclei *or* one aromatic and one other chromophore are separated by one (or possibly two) saturated carbon atoms. These compounds can perhaps best be treated on the coupled oscillator model of Moffitt,[30] which is related to the classical work of Kuhn;[31] see also the discussions by Moscowitz, Mislow *et al.*[10d, 10e] which include β,γ-unsaturated ketones and the non-conjugated diene **17**.



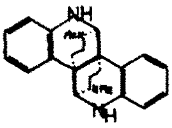
17

Rigid system

(1) *Calycanthine.* A perfect example of a rigid system, which represents an elegant choice for the application of theory, is the alkaloid calycanthine (**18**) studied by Mason.[32] From the purely steric viewpoint this molecule may be considered as a dibenzo-*cis*-hexalin (**18A**) modified by substitution (two NH groups for two CH_2) and rigidified by cross-links (dashed lines in **18A**).

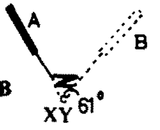


18

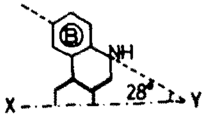


18A

(*cis*-decalin backbone emphasized by heavy lines)



18B



18C

imaginary line XY where two aromatic planes meet

Mason[32] considers the compound on the coupled oscillator theory as consisting optically of two aniline chromophores; the planes of the two aromatic rings make an angle of 61° with one another (**18B**), and the two-fold axis of each aniline residue

---

[29] C. Djerassi, W. D. Ollis and R. C. Russell, *J. Chem. Soc.* 1448 (1961).

[30] W. Moffitt, *Proc. U.S. Nat. Acad. Sci.* **42**, 736 (1956).

[31] W. Kuhn, *Z. Physikal. Chem.* (B)**4**, 14 (1929).

[32] [a] S. F. Mason, *Proc. Chem. Soc.* 362 (1962);
[b] S. F. Mason and G. W. Vane, *J. Chem. Soc.* **B**, 370 (1966);
[c] S. F. Mason, *Newer Physical Methods in Organic Chemistry* (Edited by R. Bonnett and J. G. Davis). United Trade Press, London (1966); also *Proc. Roy. Soc.*, *A*, **297**, 3 (1967).

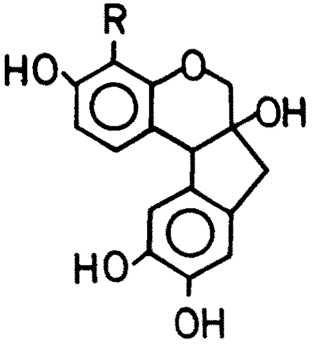
makes an angle of 28° with this intersection (**18C**). The author then calculates the dipole strengths of the transitions in calycanthine, and relates them to the two CD bands associated with the 310 mμ absorption band. This analysis permits the allotment of the absolute configuration shown in **18**. Other, less rigid, structures are also considered.[32b]

Added in Proof—March 1967.

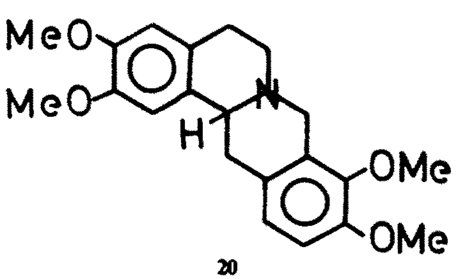
Mason *et al.*[32d] have extended this method to argemonine and to Tröger's base. These compounds had previously been studied empirically by Červinka *et al.*[32e] and Mason points out that "this particular comparison illustrates the shortcomings inherent in the empirical comparison of Cotton-effect curves". The non-empirical comparison, in which the orientation of the transition dipoles for the different chromophores is considered, gives the *opposite* answer for the absolute configuration of Tröger's base from that obtained empirically,[32e] using a simple but faulty analogy.

(ii) *Brazilin and haematoxylin.* Another rigid type is represented by the heterocyclic compounds brazilin and haematoxylin (**19A, B**) studied as their tetra-acetate and penta-acetate by Craig.[33a] These compounds give strong fairly simple negative Cotton effects between ca 285 and 273 mμ; (**19A**) $a = -234$; and (**19B**) $a = -130$. Other derivatives have been examined in one of our laboratories (Swan[34]), and the results confirm and supplement those of Craig. The absolute configuration of this group of compounds is as yet unknown.

Several studies on the pterocarpin and mopanol groups may also be mentioned here.[33b, 34]



19A R=H, Brazilin
19B R=OH, Haematoxylin



20
Tetrahydro-palmatine

(iii) *Tetrahydropalmatine.* This is a simple example of a dibenzoquinolizidine (berbine) structure (**20**); ORD curves have been studied by Lyle,[35] and by Craig and Roy.[36] The evidence for absolute configuration depends on monochromatic rotations (Corrodi and Hardegger).[37] The ORD curves reproduced by Craig[36] do not appear to show any close relation to the UV absorption.

[32] [d] S. F. Mason, K. Schofield, R. J. Wells, J. S. Whitehurst and G. W. Vane, *Tetrahedron Letters* 137 (1967); cf. also A. C. Barker and A. R. Battersby, *Ibid.* p 135 (chemical evidence).

[32] [e] O. Červinka, A. Fábryová and V. Novák, *Tetrahedron Letters* 5375 (1966).

[33] [a] J. C. Craig, A. R. Naik, R. Pratt and E. Johnson, *J. Org. Chem.* **30**, 1573 (1965);
[b] S. E. Drewes and D. G. Roux, *J. Chem. Soc.* **C**, 1644 (1966).

[34] R. J. Swan, Ph.D. Thesis, London, 1966, and unpublished data.

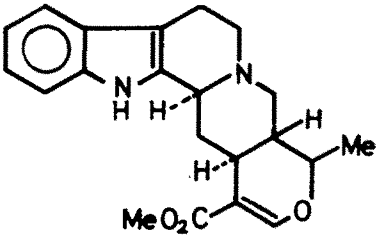
[35] G. G. Lyle, *J. Org. Chem.* **25**, 1779 (1960).

[36] J. C. Craig and S. K. Roy, *Tetrahedron* **21**, 401 (1965).

[37] H. Corrodi and E. Hardegger, *Helv. Chim. Acta* **39**, 889 (1956).

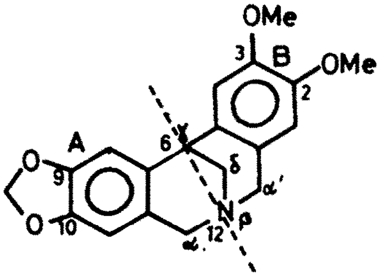
(Since this paper was first submitted, data for CD curves on further alkaloids of this group have appeared; see Ref. 80).

(iv) *Heteroyohimbine alkaloids.* The ORD curves of the heteroyohimbine alkaloids (**21**) discussed by Finch, Taylor, Klyne *et al.*[38] have as their most striking feature a large Cotton effect in the region of 250–230 mμ; this appears to be due to interaction between the methoxylcarbonyl-enol ether grouping ($MeO_2C \cdot C{:}C{-}OR$) in ring *E* and the indole nucleus. The sign of the Cotton effect is related to the chirality of this coupled oscillator.



21

(v) *A nearly-rigid system: Quasi-enantiomeric conformers.* Another example, where ORD "highlights" the skewing of an apparently almost symmetrical molecule, is the following. The azocine derivative **22** (2,3-dimethoxy-6,12-methano-9,10-methylenedioxy-5,6,12,13-tetrahydro(7H) dibenz[c,f]azocine) prepared by Wildman *et al.*[39] appears to be almost symmetrical, because the difference between the two "halves" of the molecule is only that of two methoxyl groups *versus* a methylenedioxy group. Nevertheless this compound has a strong aromatic Cotton effect (*a*, −88; 310/283 mμ and *a*, +565; 254/238 mμ); this must be due to the essentially twisted character of the molecule, leading to interaction between the two π-electron systems.



22

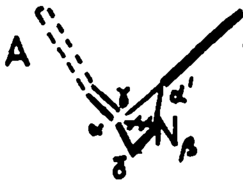
Disregarding for the moment the arylic substituents, the constitutional formula **22** has an *apparent* plane of symmetry (dashed line). Study of Dreiding models shows however that **22** would probably exist as a mixture of two conformations of enantiomeric type, as **22A** and its mirror image. The actual existence of a pronounced Cotton

---

[38] N. Finch, W. I. Taylor, T. R. Emerson, W. Klyne and R. J. Swan, *Tetrahedron* **22**, 1327 (1966).

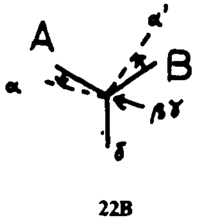
[39] Y. Inibushi, H. M. Fales, E. W. Warnhoff and W. C. Wildman, *J. Org. Chem.* **25**, 2153 (1960).

effect in the ORD curve of 22 must be due to a preponderance of one conformer, arising from subtle electronic effects of the arylic substituents in the two terminal rings.



22A

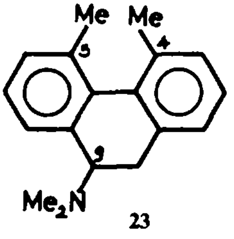
Intersection of aromatic planes is (nearly) along αγ



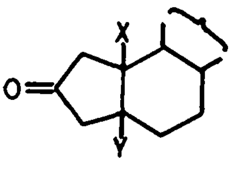
22B

Chirality along (imaginary) bond γβ is negative

This provides a third example of a stereochemical phenomenon which has come to the surface only in the last two years—*viz.* that of structures which appear *constitutionally* to be of point-group C_{2v}[40] and therefore *non-chiral*; but which *conformationally* belong to the *chiral* point-group C_2, and therefore exist as one or the other (or a mixture) of a pair of nearly enantiomeric interconvertible conformers. The previous examples of related problems are the 9-dimethylamino-9,10-dihydro-4,5-dimethylphenanthrene **23** of Mislow and Joshua,[41] and the *cis*-hexahydroindan-2-ones **24** (Klyne[42]).



23



24

Partially Rigid Systems

(v) *Lignans*: *4-Aryltetralins.* Many good examples of a partially rigidified system are found in the 4-aryl-tetralins of the lignan series (general formula, **25**).

Swan and Klyne[43] have studied the ORD curves of more than 100 members of this group, which includes many important natural products, e.g. podophyllotoxin, the peltatins, the conidendrins, and their derivatives (general formula, **25**).

The compounds all give two Cotton effects, the first between 290 and 280 mμ and the second between 245 and 230 mμ. The second Cotton effect is not easy to study, because it lies near the lower wavelength limit which can be reached by the presently available instruments; it appears to be opposite in sign to the first Cotton effect in nearly all cases. We deal here with the regularities found in the first Cotton effect.

---

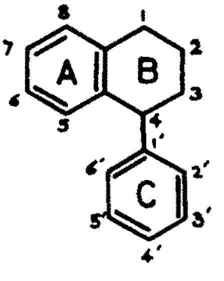
[40] For a convenient survey of point-groups, see H. H. Jaffé and M. Orchin, *Symmetry in Chemistry*. Wiley, New York (1965).

[41] K. Mislow and H. Joshua, *J. Am. Chem. Soc.* **87**, 666 (1965).

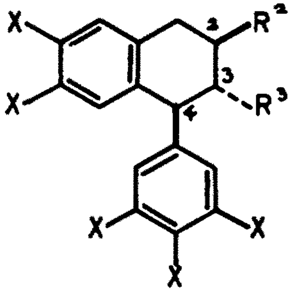
[42] W. Klyne, *Anal. Real. Soc. Esp. Fis. Quim.* **B62**, 371 (1966).

[43] [a] R. J. Swan and W. Klyne, *Chem. & Ind.* 1218 (1965).
[b] W. Klyne, R. Stevenson and R. J. Swan, *J. Chem. Soc.* C, 893 (1966);
[c] R. J. Swan, W. Klyne and H. MacLean, *Canad. J. Chem.* **45**, 319 (1967).

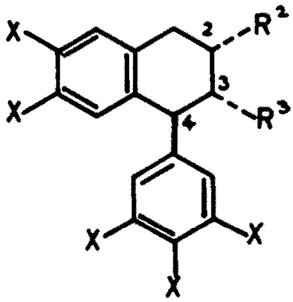
The compounds may be considered as falling into three general diastereoisomeric classes (each, of course, in two enantiomeric forms); these may be represented by the formulae **26**, **27** and **28** with their enantiomers. The substituents R^2, R^3 (and R^1 in type **28**) are Me, CH_2OH, CH_2OTs, CO_2H, CO_2Me, etc.—or $-CH_2{\cdot}O{\cdot}CO-$, $-CH_2{\cdot}O{\cdot}CH_2-$ linking C(2) and C(3); the substituents X at positions 6,7,3′,4′ and 5′ are usually OH, OMe (or $-O{\cdot}CH_2{\cdot}O-$ linking C(6) and C(7)). (The enantiomer of a given formula is designated by the prefix *E*).



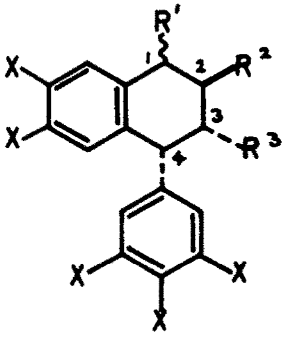
25



26



27



28

The overriding generalization is that all 4β-aryl compounds give *negative* Cotton effects and all 4α-aryl compounds give *positive* Cotton effects. Table 3 summarizes the ranges of amplitudes which were found, and some typical ORD curves are given in Fig. 4.

Our studies of CD curves in this field[44, 34] are as yet preliminary, but as might be expected on theoretical grounds, the CD curves promise to give a clearer picture, since they separate the Cotton effects of neighbouring absorption bands in a more satisfactory way than the ORD curves.

Some tentative comments on the effect of substituents at C-1, 2 and 3 in the alicyclic ring have already been made.[43a] Here one may draw attention to a point concerning substitution in the mobile aromatic ring C, which can pivot about the bond joining it to C-4. All compounds of Classes (*E*26) and (*E*27) have three MeO groups at positions

---

[44] [a] R. J. Swan and W. Klyne, *Newer Physical Methods in Organic Chemistry* (Edited by R. Bonnett and J. G. Davis). United Trade Press, London (1966);

[b] W. Klyne, *Proc. Roy. Soc. A.*, **297**, 66 (1967).

Table 3. 4-Aryl-tetralins

Signs and amplitudes of first ORD Cotton effects
at 290–280 mμ.[43a]
Solvent: methanol

Type	Configuration	No. of compounds	Sign and amplitude of ORD cotton effect a
26	2β, 3α, 4β	20	−290 to 410
E26*	2α, 3β, 4α	3	+180 to 260
27	2α, 3α, 4β	8	−100 to 200
E27	2β, 3β, 4α†	15	+80 to 130
28	2β, 3α, 4α†	30	+25 to 90

* E indicates "enartiomer of".

† Many of the compounds in these two classes have substituents at C(1) (either 1α or 1β).

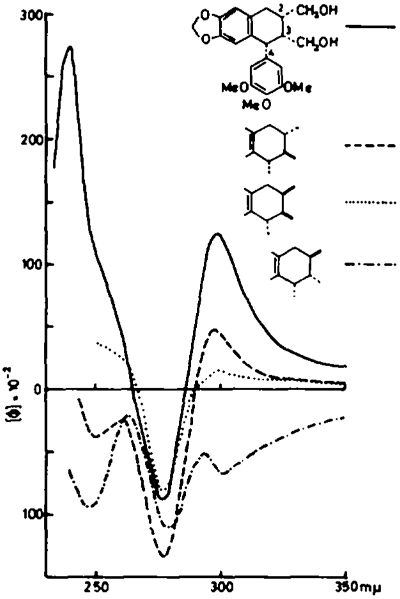


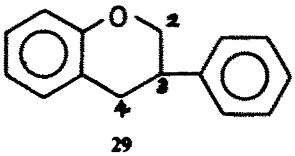
Fig. 4. ORD Curves in methanol of stereoisomeric lignans; 2,3-bis(hydroxymethyl)6,7-methylenedioxy-4-(3′,4′,5′-trimethoxyphenyl)tetralins (———) 2α,3α; (- - - - -) 2α,3β; (. . . . . .) 2β,3β; (-·-·-·-·) 2β,3α. (From Swan, Ref. 34).

3′, 4′ and 5′ in ring C, while the comparable compounds in Classes **26** and **27** have *two* such MeO groups (at 3′ and 4′). The amplitudes for Classes (*E***26**) and (*E***27**) are about two-thirds of those for Classes **26** and **27**.

ORD measurements have been used to determine the absolute configuration of the lignans otobain[43b] and plicatic acid.[43c]

A few 2-aza-analogues of lignans—dehydrococcinine derivatives (as **25**, with NH instead of CH_2 at position 2) from Wildman[39]—have been examined by Swan.[34] The ORD curves are generally similar in shape to those of the carbocyclic structures **25**.*

Flavans. Extensive studies have been carried out by Clark-Lewis, Ollis and others[45] on flavans of various kinds, especially iso-flavans (**29**). Many of these curves need to be repeated with instruments covering the 260–280 mμ absorption region. Some preliminary measurements on catechin derivatives have been made in this region.[34]



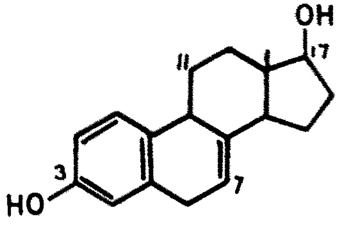
29

Benzyl-olefin and Benzyl-ketone types

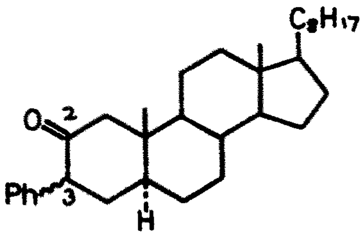
We next turn to structures in which an aromatic nucleus is homoconjugated with a double bond (C=C or C=O).

(vi) *Benzylolefin types.* Examples of these are Δ^7-aromatic steroids such as dihydroequilin (**30**): this compound (from Ayerst, McKenna & Co., Montreal) has a small positive Cotton effect (*a*, +22) between 290 and 265 mμ).

(vii) *Homoconjugated aryl ketones.* The very intense Cotton effect exhibited by some of these chromophores can be interpreted in terms of homoconjugation of



30



31 3α—Ph
32 3β—Ph

---

* Some interesting 1,4-diphenyltetralins, with an additional heterocyclic ring at positions 2 and 3, have recently been studied by Quinkert *et al.*[44c]

[44] [c] G. Quinkert, K. Opitz, W. W. Wiersdorff and M. Finke, *Ann. Chem.* **693**, 44 (1966).

[45] J. W. Clark-Lewis, I. Dainis and C. Ramsay, *Aust. J. Chem.* **18**, 1035 (1965). J. W. Clark-Lewis and R. W. Jemison, *Ibid.* **18**, 1791 (1965); W. D. Ollis, M. J. Ramsay and I. O. Sutherland, *Ibid.* **18**, 1787 (1965).

carbonyl and benzene π-electrons.[10c,d] Cookson *et al.*[46,47] have indicated that in the 3-phenyl-5α-cholestan-2-ones, the very strong positive Cotton effect ($a = +374$) of the axial 3α-isomer **31**, which is accompanied by the typically intense absorption in the carbonyl region, (ε_{max} 220, at 299 mμ) suggests the prevalance of conformations in which the orientation of the benzene π-electrons relative to electrons of the carbonyl group is geometrically favorable to enhancement of absorption. Furthermore, the sign of the Cotton effect of **31** is in harmony with the geometry B of Fig. 5,[10e] for the absolute configuration indicated. On the other hand, the equatorial 3β-phenyl-isomer **32**, in which such orientations are not possible, has a normal absorption spectrum and molecular amplitude ($a = +45$). The recent paper by McKenzie *et al.*[48] suggests that the conformational situation may be more complicated.

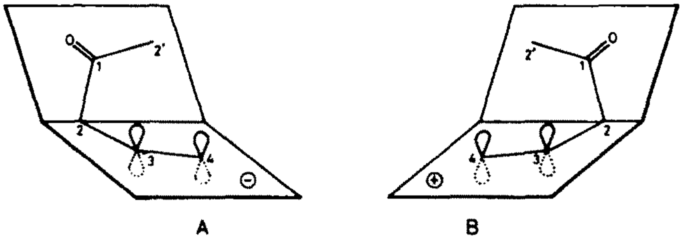
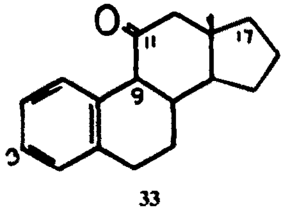


FIG. 5. Representation of the enantiomeric chromophores associated with dissymmetric β,γ-unsaturated ketones (from Moscowitz, *et al.*, Ref. 10*e*, and Ref. 1, p. 232).

Moscowitz *et al.*[10e] treated a wider range of compounds in terms of the coupling between the π-orbitals of two unconjugated π-systems.

11-*Oxo-aromatic steroids*. The CD technique has permitted a detailed study of the conformation of the 11-oxo-*A*-ring aromatic steroids (**33a**–**33h** listed in Table 4. The isomeric compounds (**33a**, **33b**),[49] for example, differ in the configuration of the hydrogen atom at C-9. The very strong positive Cotton effect of (**33b**) can be interpreted in terms of homoconjugation of the carbonyl and benzene π-electrons, since the geometry is favorable to such interactions. (Ref. 1, p. 238).



33

Table 4 shows that the compounds with the 9βH-stereochemistry always exhibit a much more positive Cotton effect than the 9αH-isomers. Moreover, since a 20-keto-steroid (in a 17β-side chain) presents a strong positive carbonyl Cotton effect ($a = +190$; $\theta . 10^{-2} = +112$),[1,2] and provided there is no vicinal effect between the 11 and 20-carbonyl groups, a negative Cotton effect generally seems to be associated

---

[46] a R. C. Cookson and S. McKenzie, *Proc. Chem. Soc.* 423 (1961);
b R. C. Cookson and J. Hudec, *J. Chem. Soc.* 429 (1962).

[47] R. C. Cookson and N. S. Wariyar, *J. Chem. Soc.* 2302 (1956).

[48] S. McKenzie, S. F. Marsocci and H. C. Lampe, *J. Org. Chem.* **30**, 3328 (1965).

[49] J. A. Edwards, P. Crabbé and A. Bowers, *J. Am. Chem. Soc.* **85**, 3313 (1963).

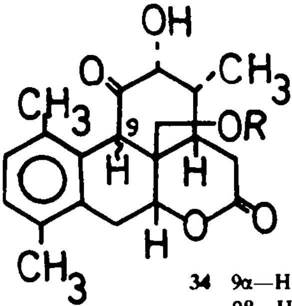
with the homoconjugated 11-ketochromophore with 9α-H stereochemistry as in **33a**, **33c** and **33e**.

However a small positive Cotton effect is associated with the same chromophore in **33g** although this has 9α-H; thus indicating that ring *C* in 1-methyl-11-oxo-*A*-aromatic-steroids probably has a different conformation. Table 4 shows finally that the nature of the substituent at C-3 does not modify the sign, but has only a slight influence on the intensity of the Cotton effect associated with these homoconjugated chromophores.

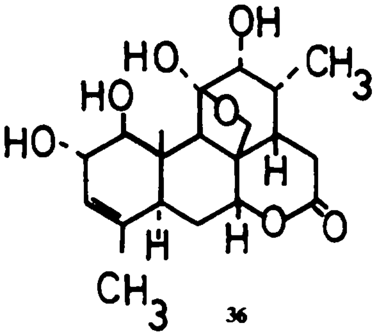
TABLE 4. "HOMOCONJUGATED" BENZYLKETONES—*A*-RING AROMATIC 11-OXOSTEROIDS

CD data; Solvent, dioxan.

Compound	Substituents in aromatic ring *A*	Substituents in ring *D*	Molecular ellipticity: θ . 10^{-2}		Ref.
			9αH	9βH	
33a, b	3-OMe	17β-CO · CH_3	+89	+502	1, 49
c, d	3-OH	17β-CO · CH_3	+87	+502	49, 50
e, f	3-OBz	17β-CO · CH_3	+98	+342	49, 50
g, h	1-Me, 3-OAc	17α-OH, 17β-CO · CH_2OAc	+162	+267	1, 49



34 9α—H, R = Ac
9β—H, R = H



36

Chaparrol. Similar reasoning has been used to assign the stereochemistry at C-9 in chaparrol mono-acetate (**34**) and neochaparrol (**35**), obtained from the terpene chaparrin (**36**).[18] Chaparrol mono-acetate (**34**) exhibits a negative Cotton effect (*a*, −56), in agreement with the Octant rule for ketones,[51] whereas neochaparrol (**35**) has a very strong positive Cotton effect (*a*, +250), in agreement with the stereochemistry proposed for this homoconjugated π-system.[18, 19]

(viii) β-*Anilinoacrylic esters.* The homoconjugated systems in which a heteroatom (N) lies between the two unsaturated units include certain alkaloids of the aspidospermine and strychnine groups, most of which may be considered as β-anilinoacrylic esters (**37**). These compounds (Schmid and Klyne *et al.*[52]) which belong to the

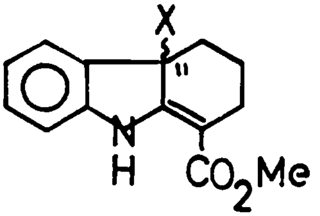
---

[50] J. A. Edwards and J. B. Siddall, in preparation.

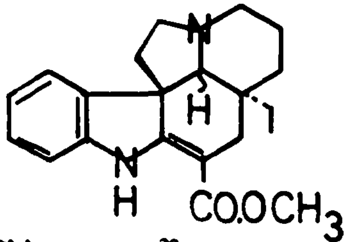
[51] W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, *J. Am. Chem. Soc.* **83**, 4013 (1961).

[52] W. Klyne, R. J. Swan, B. W. Bycroft, D. Schumann and H. Schmid, *Helv. Chim. Acta* **48**, 3 (1965).

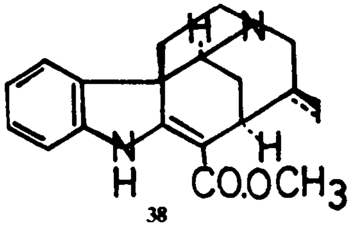
aspidospermine and strychnine-like groups (**38**, **39**) show two Cotton effects, generally, one (*a*) between 340 and 270 mμ, and the other (*b*) below 250 mμ. The signs of these Cotton effects are related to the neighbouring centre of asymmetry (C-11) as follows: 11α-X: *a* positive, *b* negative; 11β-X: *a* negative, *b* positive. The relevant data are summarized in Table 5; for further details see Ref. 52.



37



39



38

Table 5. β-Anilinoacrylic esters

ORD data in methanol[52]

Compound	Cotton effects: First (340–270 mμ) Amplitude (*a*)	Cotton effects: Second (250 mμ) First extremum $[\phi] \times 10^{-2}$
Strychnine-like system (**38**)		
(−)-Akuammicine	−1514	+763
(−)-19,20-Dihydroakuammicine	−1315	+815
(+)-Condylocarpine	+1339	−476
(+)-Tubotaiwine	+1382	−748
Aspidospermine-like system (**39**)		
(−)-Vincadifformine	−1008	+373
(−)-Tabersonine	−1427	+629

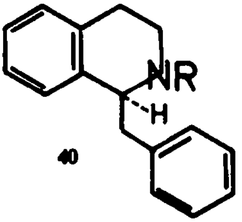
A more flexible, and more extended, type is represented by the following group.

(ix) *Benzyltetrahydroisoquinolines.* Battersby *et al.*[53] and Cymerman Craig and Roy[54] have studied the ORD curves of a number of 1-benzyltetrahydroisoquinolines of the general formula **40**, and its enantiomer.

---

[53] A. R. Battersby, I. R. C. Bick, W. Klyne, J. P. Jennings, P.M. Scopes and M. J. Vernengo, *J. Chem. Soc.* 2239 (1965).

[54] J. C. Craig, M. Martin-Smith, S. K. Roy and J. B. Stenlake, *Tetrahedron* **22**, 1335 (1966); see also Ref. 36.



40

The compounds, which might be considered as dihomoconjugated, show an aromatic Cotton effect at about 290–270 mμ, and also the first extremum of a second Cotton effect at about 240 mμ. All members of the *S*-series have two positive Cotton effects, while the enantiomeric *R*-compounds have double negative curves. A summary of the results is given in Table 6, and examples are shown in Fig. 6.

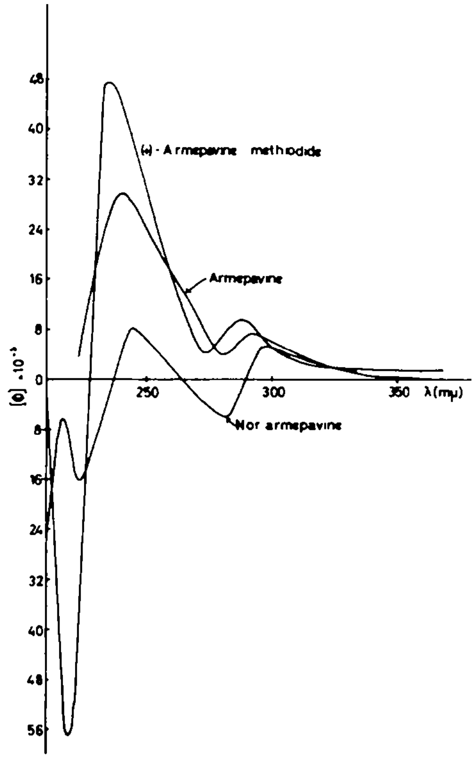


FIG. 6. Typical ORD curves of benzyltetrahydroisoquinolines; norarmepavine, armepavine and armepavine methiodide. All compounds have 1(*S*)-configuration; curves in methanol (from Refs. 53 and 54).

Recent evidence[54, 55] suggests that quaternization of nitrogen in a benzyltetrahydroisoquinoline makes no change in the sign of the ORD curve, although there may be changes in wavelength and amplitude of the Cotton effect.

---

[55] S. M. Albonico, J. Comin, A. M. Kuck, E. Sanchez, P. M. Scopes, R. J. Swan and M. J. Vernengo, *J. Chem. Soc.* C, 1340 (1966).

TABLE 6. ORD OF 1-BENZYLTETRAHYDROISOQUINOLINES (40) AND QUATERNARY DERIVATIVES

First Cotton effect: *a* is amplitude at ca. 290–270 mμ.
Second Cotton effect: *a* is amplitude at ca 240–220 mμ; where figure is shown in italics it is $[\phi] \times 10^{-2}$ value for first extremum at ca. 240 mμ; i.e. approximately a "half-amplitude".

Refs 53, 55— or, where shown by *, Refs 54, 36 (Craig); † Ref. 57b (Preininger *et al.*)

Compound	Substituents at				1st Cotton effect		2nd Cotton effect	
	N	C-7	C-11	C-12	*a*		*a*	
	R^1	R^2	R^3	R^4	*S*(+)	*R*(−)	*S*(+)	*R*(−)
Armepavine	Me	MeO	H	HO	+113	−173* −158†	+297	−151* *−409*†
Armepavine methiodide	$Me_2^+I^-$	MeO	H	HO	+52		+1064	
O-Methyl armepavine	Me	MeO	H	MeO		−313†		*−814*†
O-Methyl-armepavine methiodide	$Me_2^+I^-$	MeO	H	MeO		−66		−776
Norarmepavine	H	MeO	H	HO	+110*		+242*	
(−)-Petaline iodide ‡	$Me_2^+I^-$	MeO	H	MeO		−50*		−121*
Laudinidine	Me	MeO	HO	MeO		−602		−478
Laudanosine	Me	MeO	MeO	MeO	+185*		+322*	
Laudanosine hydrochloride	MeH^+Cl^-	MeO	MeO	MeO	+211*		+436*	
Laudanosine methiodide	$Me_2^+I^-$	MeO	MeO	MeO	+70 +105*		+516 +296*	
N-Acetyltetra-hydropapaverine	MeCO	MeO	MeO	MeO	+78	−104	*+92*!	*−110*
N-Benzoyl-tetrahydro-papaverine	PhCO	MeO	MeO	MeO	+142	−135		
Reticuline hydrochloride	MeH^+Cl^-	HO	HO	MeO	+83	−94	*+168*	*−148*
Orientaline hydrochloride	MeH^+Cl^-	HO	MeO	HO	+48	−85	*+156*	*−136*
O,O′-dibenzyl-reticuline	Me	$PhCH_2O$	$PhCH_2O$	MeO	+84	−141	*+195*	*−260*
O,O′-Dibenzyl-orientaline	Me	$PhCH_2O$	MeO	$PhCH_2O$	+93	−129	*+203*!	*−266*

‡ Configuration allotted in Ref. 54 on the basis of ORD curve.

Related work is that of Rheiner and Brossi[56] on tetrahydro-N-methyl-1-(2-phenylethyl)isoquinolines, i.e. compounds in which there is an *additional* saturated carbon atom between the two aromatic nuclei. ORD evidence has been used to allot the absolute configuration to the fragments obtained from the bis(phenylethylisoquinoline) alkaloid melanthoidine (Battersby *et al.*,[57a]) and to the aglycone from latericin.[57b]

ORD curves have also been reported for some phthalide-isoquinoline alkaloids of the narcotine-hydrastine group. (Ohta,[58] also work in progress, Snatzke, Šantavý, Bláha, Klyne *et al.*).

The stereochemistry (configuration and conformation) of the very flexible bis-(benzyltetrahydroisoquinolines) is too complex to permit interpretation of their ORD curves at present, though useful empirical correlations have been found.[53]

(x) *Flexible homoconjugated compounds.* Some diphenylpropylamines have recently been submitted to an ORD examination.[59] Fig. 7 reproduces the ORD and UV

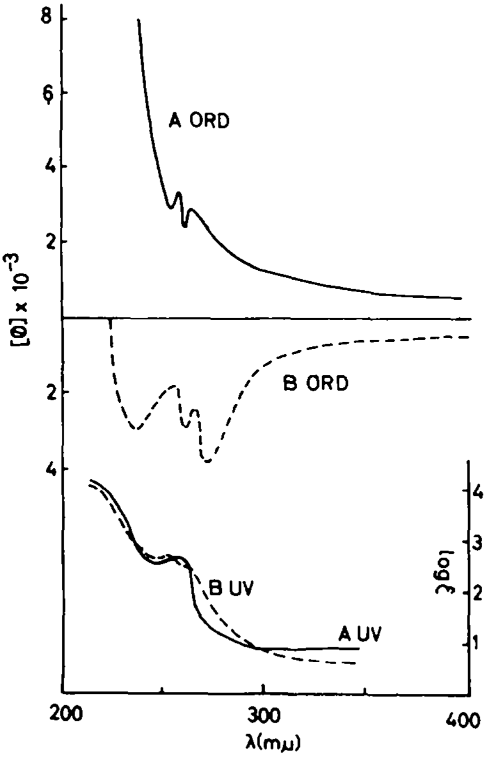


FIG. 7. UV absorption and ORD curves of:

A (———) D-1-cyano-2-methyl-1,1-diphenylpropane-3-N,N-dimethylamine (41)
B (-----) D-1-cyano-1,1-diphenylbutane-3-N,N-dimethylamine (42)
(from Ref. 59).

---

[56] A. Rheiner, Jr. and A. Brossi, *Experientia* 22, 488 (1964).

[57] [a] A. R. Battersby, R. B. Herbert and F. Šantavý, *Chem. Comm.* 415 (1965);
[b] V. Preininger, A. D. Cross and F. Šantavý. *Coll. Czech Chem. Comm.* 31, 3345 (1966).

[58] M. Ohta, H. Tani, S. Morozumi, S. Kodaira and K. Kuriyama, *Tetrahedron Letters* 1857 (1963).

[59] P. Crabbé, P. Demoen and P. Janssen, *Bull. Soc. Chim. Fr.* 2855 (1965).

absorption curves of D-1-cyano-2-methyl-1,1-diphenylpropane-3-N'N-dimethylamine (**41**). This D-isomer exhibits a positive multiple Cotton effect associated with the aromatic α-band at ca. 265 mμ. The strong optical activity around 300 mμ may be due to homo-conjugation between the triple bond of the nitrile grouping and the Ph groups.

$$NC.CPh_2.CHMe.CH_2.NMe_2$$

41

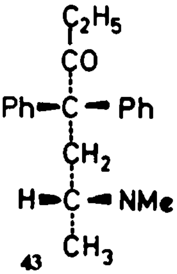
$$NC.CPh_2.CH_2.CHMe.NMe_2$$

42

Fig. 7 also shows the ORD and UV curves of an isomeric diphenylpropylamine **42** (1-cyano-1, 1-diphenyl-butane-3-N,N-dimethylamine), in which the asymmetric centre is separated from the CPh_2 group by one methylene. The D-isomer exhibits[59] a negative multiple Cotton effect at ca. 270 mμ. This phenomenon of inversion of the Cotton effect, by introduction of a methylene grouping between an asymmetric centre and a chromophore,[19] has been noted previously for saturated ketones.[60] The Cotton effect occurring at low wavelength in **42** is much weaker than that in **41**.[59]

It is significant that the UV absorption curves of the position-isomers (**41**, **42**) are almost identical; whilst the ORD curves, which reflect the *chirality* of the structure, and in particular of the chromophore *vis-à-vis* the asymmetric centre, are very different.

The ORD curves for D-(−) and L-(+)-methadone hydrochlorides (**43**)[61] exhibit multiple positive and negative Cotton effects in the 260 mμ region respectively.



43

To this class of flexible, homoconjugated compounds belong diarylmethanes and the corresponding quinones such as latifolin (**44**) and related substances,[62-64] and

---

[60] [a] P. A. Levene and A. Rothen, *J. Chem. Phys.* **4**, 48 (1936);
[b] C. Djerassi and L. E. Geller, *J. Am. Chem. Soc.* **81**, 2789 (1959): see also Ref. 2.

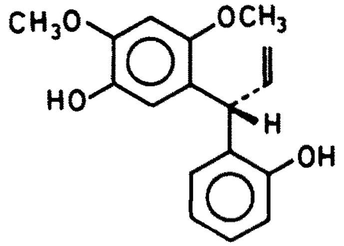
[61] Private communication from Professor J. Cymerman Craig, University of California, San Francisco Medical Center, Calif.

[62] W. Klyne and D. Donnelly; unpublished results.

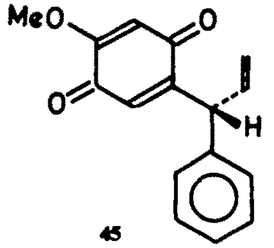
[63] D. Kumari, S. K. Mukerjee and T. R. Seshadri, *Tetrahedron Letters* 3767 (1966).

[64] [a] W. B. Eyton, W. D. Ollis, I. O. Sutherland, O. R. Gottlieb, M. Taveira Magalhaes and L. M. Jackman, *Tetrahedron* **21**, 2683 (1966);
[b] W. B. Eyton, W. D. Ollis, I. O. Sutherland, O. R. Gottlieb, M. Taveira Magalhaes and L. M. Jackman, *Ibid.* **21**, 2697 (1966).

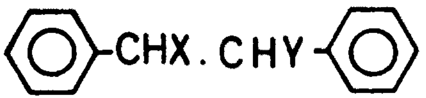
the dalbergiones (**45**), in which one "aromatic" group is quinonoid in character;[62–63] these have been studied extensively by Ollis *et al.*[64] Dihomoconjugated representatives, such as diaryl-ethanes (**46**) may also be mentioned.[65] Methyl-α-naphthylphenylmethane [and its silane and germane analogues; general formula Me(Ph)($C_{10}H_7$)XH] have been studied by Brook.[66]



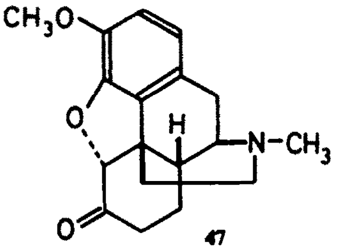
44
Latifolin



45
Dalbergione



46



47
Dihydrocodeinone

The rather complex CD curves of dihomoconjugated aryl ketones of the morphine series (e.g. **47**) which show carbonyl, aromatic and charge-transfer bands are discussed by Rüll.[67]

It is to be hoped that in due course the general coupled-oscillator treatment applied by Mason[32] to calycanthine can be applied in turn to all other structures discussed on pp. 12–25. The strategy must be to deal with other less symmetrical, but none the less *rigid*, structures first—and then the more flexible ones, where the aim must be to use ORD and CD (probably in combination with other physical techniques) to determine preferred conformations.

IV SYMMETRICAL CHROMOPHORES WHICH ARE DISSYMMETRICALLY PERTURBED

The second major class of aromatic compounds is that in which there is only one chromophore (a single aromatic system) which has many elements of symmetry but is dissymmetrically perturbed by "a centre or centres of asymmetry". Some evidence

---

[65] [a] J. L. Mateos and D. J. Cram, *J. Am. Chem. Soc.* **81**, 2756 (1959);
[b] G. G. Lyle and W. Lacroix, *J. Org. Chem.* **28**, 900 (1963);
[c] A. Weissberger and W. Klyne; unpublished results.

[66] A. G. Brook, *J. Am. Chem. Soc.* **85**, 3051 (1963).

[67] T. Rüll, *Bull. Soc. Chim. Fr.* 3715 (1965).

suggests that a heterosubstituent on the aromatic ring itself (arylic substituent) is necessary to provide an *optically active transition of high intensity*;[68-72] there are however several exceptions (cf. pp. 31–32).

It may be hoped that at some later date one or more Segment Rules (similar to the well-known Octant Rule for ketones) may be proposed to correlate the geometry of perturbed aromatic chromophores in an asymmetric surrounding with the signs and amplitudes of the Cotton effects produced. The important fundamental paper of Schellman[73] on symmetry rules points the way to a general consideration of the geometrical problems. It is worth emphasizing however that the *nature* of the perturbing groups, as well as the geometry, must be considered in every case.

Some tentative progress for particular classes of compounds has recently been made by Brewster and Buta[74] (see pp. 30–1, below) for simple indane derivatives; Takeda and Kotera *et al.*[75] and Wildman[76a] (Amaryllidaceae alkaloids); other treatments have been suggested in discussion by Snatzke.[76b]

So far the bulk of work on ORD and CD of aromatic compounds has been concerned with series of compounds (natural products and their derivatives) already available for other purposes. The time has come when it will be necessary to design and synthesize structures deliberately planned[74] to test rival hypotheses, and/or to give reference values for the amplitudes or molecular ellipticities associated with particular groups. (cf. much pioneering work by Djerassi's school on ketones—Ref. 1. pp. 85–89).

The logical sub-division of this general class of compounds is difficult and the following suggestions are put forward tentatively. We consider first structures which are bicyclic or polycyclic, with *one* aromatic ring and at least *one* alicyclic ring (for a summary, see Table 7). Compounds in which the only asymmetric centre(s) are in a flexible side chain are considered in Section V (pp. 48–55).

Our subclassification must take account of (i) the relation between centre or centres of asymmetry and the aryl nucleus, (ii) the presence or absence of heteroatoms with lone-pairs adjacent to these centres of asymmetry, and (iii) the pattern of substitution on the aryl nucleus itself (character and local symmetry).

Centres of asymmetry

Factors (i) *and* (ii). The centre(s) of asymmetry in the side-chain (or second-ring) may be associated with (*a*) alkyl groups; (*b*) heteroatoms with lone-pairs of electrons

---

[68] A. Moscowitz, A. Rosenberg and A. E. Hausen, *J. Am. Chem. Soc.* **87**, 1813 (1965).

[69] L. Verbit, *J. Am. Chem. Soc.* **87**, 1617 (1965).

[70] T. M. Hooker, Jr. and C. Tanford, *J. Am. Chem. Soc.* **86**, 4989 (1964).

[71] A. Yogev and Y. Mazur, *Chem. Comm.* 388, (1965).

[72] L. Velluz and M. Legrand, *Angew. Chem.* (Int. Ed.), **4**, 838 (1965).

[73] J. A. Schellman, *J. Chem. Phys.* **44**, 55 (1966).

[74] [a] J. H. Brewster and J. G. Buta, *J. Am. Chem. Soc.* **88**, 2233 (1966);
[b] J. G. Buta, Ph.D. Thesis, Purdue University, 1965.

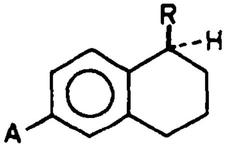
[75] K. Kotera, Y. Hamada, K. Tori, K. Aono and K. Kuriyama, *Tetrahedron Letters* 2009 (1966); K. Kuriyama, T. Iwata, M. Moriyama, K. Kotera, Y. Hamada, R. Mitsui and K. Takeda, *J. Chem. Soc.* **B**, 46 (1967).

[76] [a] W. C. Wildman, Paper at *4th IUPAC International Symposium on the Chemistry of Natural Products*. Stockholm, June (1966);
[b] G. Snatzke, Discussion on paper by Kotera, Oxford, July 1966.

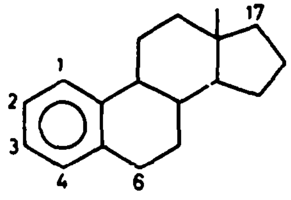
TABLE 7. RIGID COMPOUNDS WITH PERTURBED AROMATIC CHROMOPHORES CLASSIFICATION

No arylic substituents	With arylic substituents
1. *No benzylic heteroatoms*	
1-Alkyl-tetralin (**48**, R=Alk; A=H)	Steroid oestrogens: *A* ring aromatic, with OH (without alcoholic OH near *A* ring; (**49**, **58**, **59**, **60**);
1-Alkyl-indane (**53j**)	also D-homo-ring aromatic (enantiomeric type) (**50**).
2. *With benzylic heteroatoms*	
2a. *Not in ring B*	
1-Tetralol	6-Hydroxy-oestrogen (**49**; with OH at 6α or 6β)
(**48**, R—OH; A=H)	Tetralin-1,5-diol (**48**; R=A=OH)
1-Indanol (**53g**)	Morphine-thebaine derivatives (**57**, **64**, **65**, **66**)
Morphinans (**55**, **56**)	Chaparrol derivatives (**61**, **62**)
2b. *In ring B*	
Benzquinolizidine (**51**)	Tetrahydroisoquinolines (**68**)
3. *Arylic heteroatoms in ring B*	
	Tetrahydroquinoline (**7**)
	Dihydrobenzfuran (**8**; **67**)
	Dihydro-indoles;
	Aspidospermine type (**69**, **70**)
	Neblinine type (**72**)
4. *Heteroaromatic structures*	
	Tetrahydroharman (**73**, **74**)
	Steroid-indole (**75**)
	Yohimbine type; (**77**, **78**) (N_b is benzylic on indole; Na is heteroaromatic)
	Quebrachamine; (**76**) (N_b is phenethylic on indole; Na is heteroaromatic).
	Indolenines (**79**, **80**, **81**)
Other Chromophores	
	Tropones (**82**, **83**)
	Pyrazoles (**84**)
	Furans (**85**, **86**, **87**)

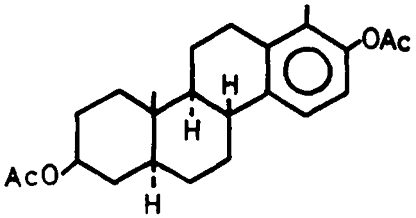
In classes 3 and 4 the heteroatom serves to make the aromatic unit unsymmetrical; therefore all compounds may be considered as carrying arylic substituents.



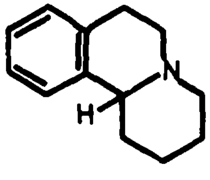
48



49



50



51

(either in or out of the second ring); (*c*) heteroatoms without lone-pairs (e.g. quaternary ammonium groups).

Geometrical basis for optical activity of aromatic transitions

The rotational strength (R_k) of a transition *k* of a chromophore is related to its electric (μ_e^k) and magnetic (μ_m^k) dipole transition moments by the following equation:[68, 77]

$$R_k = \mu_e^k \cdot \mu_m^k \cos\theta$$

θ being the angle between the two transition moments.

According to Moscowitz,[68] the weakness of the 260 mμ Cotton effect of many aromatic compounds is due to the C_{2v} effective local symmetry of the aromatic ring. If the π-molecular orbitals of the system are constructed solely from linear combinations of $2p_z$ orbitals of carbon, then all π–π^* transitions from the ground state have their nonvanishing electric dipole transition moments μ_e^k directed *in the plane* of the ring, and their non-vanishing magnetic dipole transition moments μ_m^k directed *perpendicular* to that plane; cos θ is zero. No amount of mixing of the transitions among themselves, therefore, can lead to a nonvanishing scalar product ($R_k = \mu_e^k . \mu_m^k$), and thus to optically active $\pi \rightarrow \pi^*$ transitions.

To produce an optically active $\pi \rightarrow \pi^*$ transition by mixing in of other transitions, the essential factor is the generation of an in-plane magnetic moment (μ_m in the right direction). This is most readily brought about by lone-pairs of electrons in the vicinity of the aromatic nucleus (see pp. 29–30), but it could come from other sources.

In quaternary ammonium compounds[55] the transition giving a significant in-plane magnetic moment might be of s-π^* character, or might involve *d*-orbitals.

Substitution in the aryl nucleus itself

Factor (iii). This is usually of prime importance in determining the magnitude of

---

[77] [a] E. U. Condon, W. Altar and H. Eyring, *J. Chem. Phys.* 5, 753 (1937);
[b] See also Refs. 11 and 23;
[c] D. J. Caldwell and H. Eyring, *Ann. Rev. Phys. Chem.* 15, 281 (1964).

the Cotton effect. (cf. Moscowitz[68] and Mazur[71]). It appears that in most cases an arylic hetero-substituent is necessary to make a π–π^* transition optically active and hence to give a significant Cotton effect at 260 mμ.

A pair of compounds illustrating the importance of arylic hetero-atoms is provided by the aromatic aminoacids L-phenylalanine and L-tyrosine (its *p*-hydroxy-analogue) (**52A**, **52B**).[68–70]

As pointed out by Moscowitz[68] the unsubstituted compound **52A** gives an almost negligible Cotton effect at 260 mμ; whilst in **52B** the OH group gives rise to a much larger Cotton effect ($a = +12$) (cf. Fig. 8).[68–70, 78]

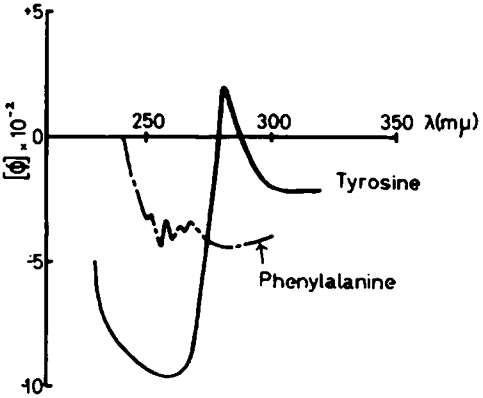
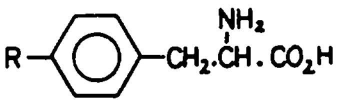


FIG. 8. Comparison of ORD curves of aromatic compounds without and with arylic hetero-substituents; (– · – · –) L-phenylalanine (52A) and (———) L-tyrosine (L-*p*-hydroxyphenylalanine) (52B) (based on Moscowitz *et al.*, Ref. 68, and Hooker and Tanford, Ref. 70).



$$R-C_6H_4-CH_2.\overset{NH_2}{CH}.CO_2H$$

52A R = H
52B R = OH

The extreme weakness of the Cotton effect associated with phenylalanine (**52A**) is due to the unfavourable geometry of the electric and magnetic dipole transition moments in this structure as discussed above. If the possibilities of charge-transfer, or of the mixing of transitions between the aromatic and amino-acid groups can be ignored, then the requisite in-plane μ_m^t can be achieved only by mixing the π–π^* transitions with some perpendicular transitions of the aromatic chromophore (e.g. a σ–π^* or n–π^* transition), or expanding the basis set and invoking, e.g. 3*d* orbitals.

---

[78] [a] M. Billardon, *C.R. Acad. Sci.*, *Paris* **251**, 535, 1759 (1960);
[b] E. Iizuka and J. T. Yang, *Biochemistry* **3**, 1519 (1964);
[c] G. D. Fasman, E. Bodenheimer and C. Lindblow, *Ibid.* **3**, 1665 (1964);
[d] S. Beychok and G. D. Fasman, *Ibid.* **3**, 1675 (1964);
[e] J. A. Schellman and C. G. Schellman, *Arch. Biochem. Biophys.* **65**, 58 (1956).

In tyrosine (**52B**), the oxygen atom of the phenolic OH group attached to the aromatic chromophore is a ready source of nonbonding orbitals for n–π* transitions. Hence, the long wavelength aromatic Cotton effect can easily be detected.[70, 78] Conversely, in phenylalanine (**52A**), where the 260 mμ μ_e^k is itself only very weakly allowed to begin with, this important mechanism for producing a properly directed μ_m^k is absent; this explains the faintness of the 260 mμ Cotton effect in phenylalanine (**52A**),[68] (pp. 33–5).

The same concepts may be applied to the substantial differences observed in the Cotton effects associated with the aromatic steroids carrying different substituents, listed in Table 8 (pp. 33–5).

Comparison of rigid and flexible systems

We next consider an example in which rigid and non-rigid structures of the same chemical type are compared. These are represented by the indane-1-amine (**53i**)[74] and α-phenyl-ethylamine[74, 79] (**54**, R′ = NH_2) as hydrochlorides. Comparison of the curves in Fig. 9 shows that the Cotton effect at about 280 mμ is negligible (*a*, −4) for the flexible compound **54**, but of significant size (*a*, +32) for the rigid indane derivative **53i**. See further discussion on p. 36.

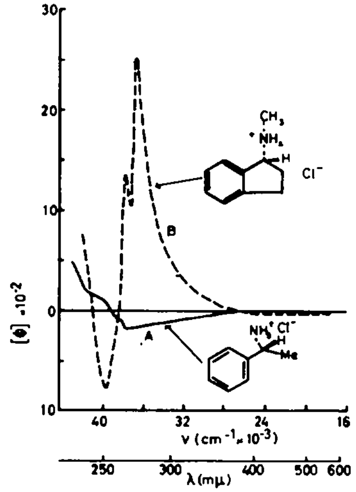


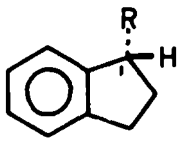
Fig. 9. Comparison of ORD curves of aromatic compounds with non-rigid and rigid side-chains of the same chemical type. *A*, (*R*)-α-phenylethylamine; B, (*R*) indane-1-N-methyl amine (both as hydrochlorides) (based on Brewster and Buta, Ref. 74, and La Manna *et al.*, Ref. 79).

Anomalies

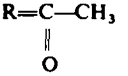
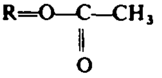
There are, however, some anomalies. The morphinans (**55**, **56** = *E***55**) (Ref. 1, p. 290) have no arylic substituent, but nevertheless show a good Cotton effect (*a*, ±25) (cf. Fig. 11). **57** which has an arylic OMe substituent (at C-3), has a slightly higher molecular amplitude (*a*, about +35); the dihydro-derivative of **57** would be desirable to study, in order to avoid any possible complications by the olefinic double

---

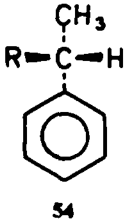
[79] A. La Manna, V. Ghislandi, P. M. Scopes and R. J. Swan, *Il Farmaco* (Ediz. Sci.) **20**, 842 (1965).



53

a, $R{=}H$
b, $R{=}CO_2H$
c, $R{=}CO_2^-Na^+$
d, $R{=}CH_2OH$
e, 
$R{=}\underset{\overset{\|}{O}}{C}{-}CH_3$
f, 
$R{=}O{-}\underset{\overset{\|}{O}}{C}{-}CH_3$

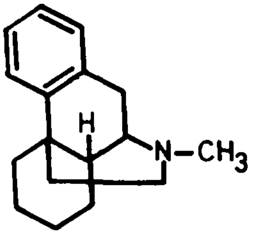
g, $R{=}OH$
h, $R{=}NH_2$
i, $R{=}NH_3^+Cl^-$
j, $R{=}CH_3$
k, $R{=}\overset{+}{N}H_2 \cdot CH_3Cl^-$



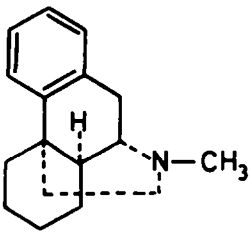
54

bond at C-6,7 present in **57**. Other compounds of the morphine series are discussed below (pp. 39–40).

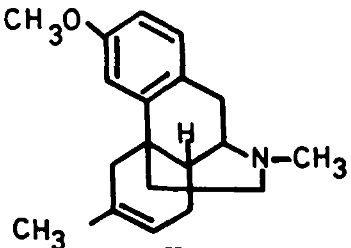
On the other hand, possession of an arylic OH group is not sufficient in itself to guarantee a strong Cotton effect; cf. the work of Yogev and Mazur[71] on certain A-ring aromatic steroids (oestrogens) **49** with varying arylic substituents. We may consider, for example, compounds **58** and **59**, where the local surroundings of the OH



55



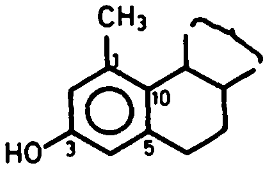
56 = E55



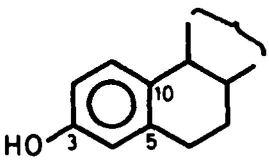
57

group are symmetrical, (cf. **58A**, **59A**); here the aromatic Cotton effect at about 260 mμ is weak.

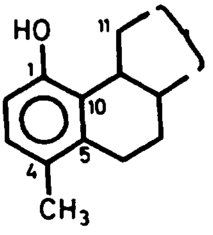
In contrast, compound **60**, which is *not* symmetrical about the OH group **60A**, shows a strong Cotton effect at 280–260 mμ. The greatly increased rotational strength of the structure of type **60** may be due to the relative geometry of the electric and magnetic moments (i.e. a more favourable cos θ factor, cf. p. 28, or it may also be due to hindered rotation of the OH group at C-1 by an adjacent methylene group (C-11).



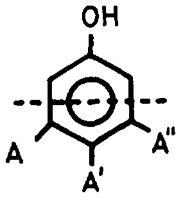
58



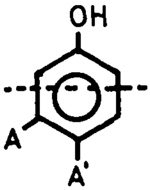
59



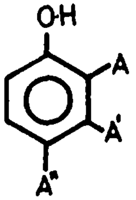
60



58A



59A



60A

In these formulae AA'A'' stand for an alkyl group or part of an alicyclic ring.

Oestrogens

The oestrogenic steroids (**49**) and related compounds (**50**, **61**, **62**) provide a wide range of other substances with differing stereochemistry, arylic and benzylic substituents.[71,72,80-86] The aromatic Cotton effects of some such compounds are summarized in Table 8.

---

[80] M. Legrand and R. Viennet, *Bull. Soc. Chim. Fr.* 2798 (1966).

[81] This compound was prepared by Professor G. Ourisson and Mlle F. Lederer, University of Strasbourg.

[82] J. Levisalles, W. Klyne and W. Mose; unpublished results; compounds from University of Nancy.

[83] We are much indebted to Dr. O. Wintersteiner. The Squibb Institute for Medical Research, New Brunswick, N.J., for these samples; see: O. Wintersteiner and M. Moore, *J. Am. Chem. Soc.* **81**. 442 (1959).

[84] C. J. Sih, S. S. Lee, Y. Y. Tsong and K. C. Wang, *J. Am. Chem. Soc.* **87**, 1385 (1965) and related papers.

[85] H. Audier, M. Fétizon and J. C. Gramain, *Bull. Soc. Chim. Fr.* 3088 (1965).

[86] We are most grateful to Dr. W. F. Johns, G. D. Searle, Chicago, for these samples; see W. F. Johns, *J. Org. Chem.* **30**, 3993 (1965).

[87] U. Weiss and T. Rüll, *Bull. Soc. Chim. Fr.* 3707 (1965).

[88] K. Kuriyama (Shionogi Research Laboratory) unpublished results; cf. Ref. 1, p. 289.

[89] Samples kindly provided by Professor V. Prelog, E.T.H.: Zürich; unpublished results; curves measured at Westfield College.

[90] D. Battail-Robert and D. Gagnaire, *Bull. Soc. Chim. Fr.* 208, (1966).

TABLE 8. COTTON EFFECTS OF SOME AROMATIC STEROIDS

Solvents: D = dioxan; E = ethanol; H = hexane; M = methanol;
Other abbreviations: BMD = bismethylenedioxy derivative of corticoid side-chain; Spiro = spirostan side-chain.
Values under Cotton effects are as follows:
Wavelengths $\lambda\lambda$ (mμ) are for extrema in ORD and maxima in CD.
ORD magnitudes shown as *a* are amplitudes ($a \times 10^{-2}$):
values shown as $[\phi]$ are (molecular rotation at first extremum) $\times 10^{-2}$ (i.e. approximately a "half-amplitude").
CD magnitudes are $\Delta\varepsilon$ values.

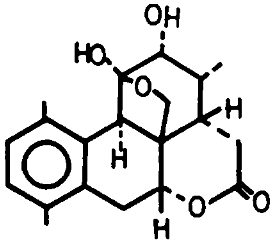
Compound	Substituents			Solvent	Cotton effects			Ref.
	A-ring (arylic)	B/C rings	D-ring and side-chain		$\lambda\lambda$ (mμ)	ORD *a* or $[\phi]$	CD ($\Delta\varepsilon$)	
A-ring aromatic; Normal 9α-configuration								
49, 1	none	none	17β-OH	ED		negl.		71
2	2-Me	none	17β-OH	ED		negl.		71
3	2,3,4-Me$_3$	none	C_8H_{17}	H	250	$[\phi]$ +9		81
4	1-OH, 4-Me	none	17β-OH	E	288 232		+2·5 +2·0	80
5	1-OH, 4-Me	none	C_8H_{17}	M	286/261	*a*, +79		82
6	1-OMe, 4-Me	none	C_8H_{17}	M	286/260	*a*, +139		82
7	2-OH, 3,4-Me$_2$	none	C_8H_{17}	M	286/263	*a*, +4		82
8	2-OMe, 3,4-Me$_2$	none	C_8H_{17}	M	287/243	*a*, −45		82
9	3-OH	none	17β-OH	ED	1st 2nd	small large		71
				E	280 230		−0·6 +3·2	72
10	3-OH, 1-Me	none	17β-OH	ED		negl.		71

TABLE 8 (*continued*)

Compound	Substituents			Cotton effects				Ref.
	A-ring (arylic)	B/C rings	D-ring and side-chain	Solvent	$\lambda\lambda$ (mμ)	ORD a or $[\phi]$	CD ($\Delta\varepsilon$)	
49, 11	3-OH, 2-Me	none	17β-OH	E	280 233		+0·2 +3·8	80
12	3-OH, 4-Me	none	17β-OH	E	282 230		−0·7 +2·5	80
13	3-OH, 1,4-Me_2	none	C_8H_{17}	M	296/283	a, +20		82
14	3-OMe	none	17α, 20β(OH)$_2$	M	286/263 236	a, −16 $[\phi]$ +53		24
15	3-OMe	none	17,20,21-BMD	MC	290/274 236	a, +10 $[\phi]$ +24		24
16	3-OMe	none	17,20,21-BMD	M	286/226 234/218	a, −11 a, +83		24
17	3-OMe, 2-Me	none	17β-OH	M	294/287	weak +ve C.E.		86
18	3-OMe, 4-Me	none	17β-OH	M	284	weak −ve C.E.		86
19	3-OMe, 2-CH_2OH	none	17β-OH	M	290 259	weak −ve C.E.		86
20	3-OMe, 4-CH_2OH	none	17β-OH	M	287 263	weak −ve C.E.		86
21	3-OAc, 1-Me	none	Spiro		278/249	a, −164?		24
22	3-OAc	6α-OAc	17β-OAc	M	224	$[\phi]$ −105		82
23	3-OH	6β-OH	17β-OH	M	283/261 229/213!	a, −18 a, +232!		83

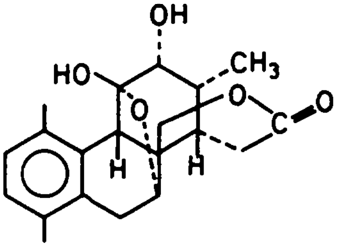
TABLE 8 (*continued*)

49, 24	3-OAc	6β-OAc	17β-OAc	M	faint −ve C.E. 224/208	 *a*,	 +394		83
25	3-OH	9α-OH	17β-OH	M	284/263	*a*,	−19		84
A-ring aromatic; Abnormal 9β-configuration									
26	3-OH	none	17β-OH	M	263 233/212	weak C.E. *a*,	 −110		24
27	3-OH	none	17,20,21-BMD	M/C	290/275	*a*,	+37		50
28	3-OMe	none	17β-OH	M	285/233	*a*,	+67		24
29	3-OMe	none	17α, 20β(OH)$_2$	M	286/260 234	*a*, [*ϕ*]	+16 −58		24
30	3-OAc	none	17,20,21-BMD	M	276/250 225	*a*, [*ϕ*]	+24 −49		50
31	3-OH	9β-OH	17β-OH	M	286/272	*a*,	+14		84
Other compounds									
50	Aromatic D-homo							complex (essentially −ve)	24
61A	Chaparrol	(9α-H)		D	283/270	*a*,	+24		18, 19
61B	Isochaparrol	(9β-H)		D	288/278	*a*,	−4		18, 19

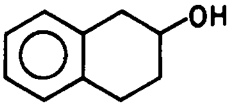


61

Chaparrol



62



63

Tetralols

(+) and (−)-β-Tetralols (**63**, *E***63**) give almost plain curves ([ϕ], ±3800 at 227 mμ), with only a slight inflection in the region of 270 mμ.[89, 90] Here the side-chain substituent is relatively remote from the aromatic nucleus in a phenethylic position ($Ar \cdot CH_2 \cdot CHR \cdot OH$).

1-*Substituted Indanes*

Brewster and Buta[74] prepared a series of optically active 1-substituted indanes (general formula, **53**) from the (+)-1-carboxylic acid (**53b**) by reactions which ensured retention of configuration (*R*) at the asymmetric centre. Fredga[91] had resolved the acid and had proved the absolute configuration. The ORD curves of these indanes showed weak aromatic Cotton effects in the 260–270 mμ region for the acid, carbinol, methyl-ketone, alcohol, acetate, amine and amine salt (**53b, d, e, f, g, h, i**). However, no Cotton effect was observed in the ORD curves of the Me derivative **53j** and of the carboxylate salt **53c**. Some related compounds have been prepared recently by Gagnaire *et al.*[90]

Three representative curves are shown in Fig. 10. The compounds had positive multiple Cotton effects of varying intensity, the amplitudes being greatest for compounds where the 1-substituent has a positive charge or can perhaps hydrogen-bond with the nucleus (an exception is the methyl-ketone **53e**, the βγ-aryl-carbonyl chromophore of which must probably be considered as a coupled oscillator; this shows a *negative* Cotton effect).

Brewster and Buta's work was undertaken in order to determine whether the rotatory properties of an optically active molecule having a "fixed" Ph group adjacent to the asymmetric centre would differ significantly from those of a similar molecule in which the Ph group could rotate freely. It had been anticipated that Ph compounds, having weak absorption bands in the near UV, might well exhibit rotatory properties different from those expected by an application of the Conformational Dissymmetry Rule,[92] that rule applying to effects related to strong absorption bands. According to Kuhn,[93] interference with free rotation of the Ph group would be significant for the

---

[91] A. Fredga, *Chem. Ber.* **89**, 322 (1956).

[92] J. H. Brewster, *J. Am. Chem. Soc.* **81**, 5475, 5483, 5493 (1959).

[93] W. Kuhn, *Ann. Rev. Phys. Chem.* **9**, 417 (1958).

consideration of optical activity; the vicinal effect of the "fixed" Ph group would be different from that effect due to the freely rotating Ph group, the latter being cylindrically symmetrical.

Several of the compounds of type **53** were compared with their analogues of the α-phenylethyl series (as **54**), in which the Ph group is essentially free to rotate.

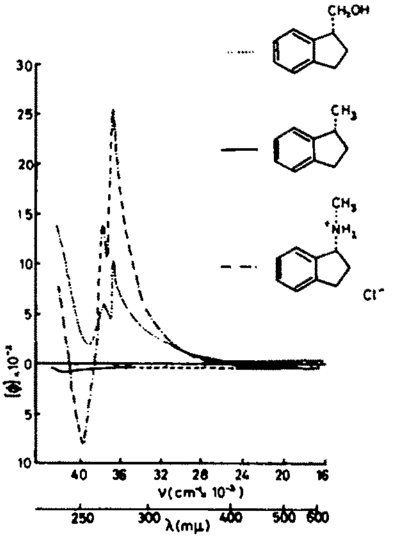


FIG. 10. ORD Curves of representative 1-substituted-indane derivatives in methanol; configuration (*R*) (———), 1-methyl (**53j**); (········) 1-hydroxymethyl (**53d**); (—·—·—) 1-N-methylamino, as hydrochloride (**53i**) (from Ref. 74*a*).

The α-phenylethyl compounds **54** had much *smaller* Cotton effects than their indane analogues, and the signs were opposite, i.e. the compounds **54** had negative Cotton effects at about 260 mμ. The results were considered[74b] in the light of the Eyring-Jones treatment[94] of optical activity.

These compounds will, as suggested by Brewster and Buta in the Discussion of their paper,[74a] be valuable reference compounds for Segment Rules (cf. Schellman[73]).

Benzodihydrofuran

The benzodihydrofuran type is represented by toxol (**64**),[97] which gives a strong negative Cotton effect between 290 and 250 mμ ($a = -200$). The situation is complicated here by the CO group conjugated with the aromatic chromophore; although

---

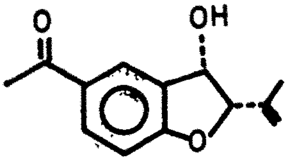
[94] [a] L. L. Jones and H. Eyring, *Tetrahedron* **13**, 235 (1961);
[b] L. L. Jones and H. Eyring, *J. Chem. Educ.* **38**, 601 (1961).

[95] [a] Z. Horii, M. Ikeda, Y. Yamawaki, T. Tamura, S. Saito and K. Kotera, *Tetrahedron* **19**, 2101 (1964);
[b] Correction; *Ibid.* **20**, 1106 (1965).

[96] J. Trojánek, Z. Koblicová and K. Bláha, *Chem. & Ind.* 1261 (1965).

[97] L. H. Zalkow, N. Burke, G. Cabat and E. A. Grula, *J. Med. Pharm. Chem.* **5**, 1342 (1962); L. H. Zalkow and N. Burke, *Chem. & Ind.* 292 (1963). We are most indebted to Professor L. H. Zalkow, Georgia Institute of Technology, for a sample of toxol.

[97] [a] V. N. Dobrynin, A. I. Gurevich, M. G. Karapetyan, M. N. Kolosov and M. M. Shemyakin, *Tetrahedron Letters* 901 (1962).



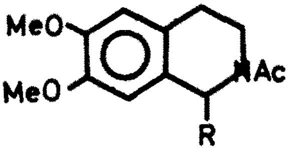
64

this CO group must be conformationally free, and is remote from the asymmetric centres, its effect cannot be neglected, since one is dealing here with an acetophenone chromophore and not a simple aromatic ring.

Some dihydroisobenzfurans (substituted phthalides) have been studied by Dobrynin *et al.*[97a] in connection with the stereochemistry of the tetracyclins.

Tetrahydroisoquinolines

Simple 1-substituted tetrahydroisoquinolines (65) show a small aromatic Cotton effect[53] in the region of 290–270 mμ. 1β-Substituted compounds (*S*-series)[14] give positive effects; 1α-(*R*) compounds give negative Cotton effects. (Table 9). Benzyltetrahydroisoquinolines, which contain two aromatic nuclei per molecule, have been considered in an earlier section (see Table 6, pp. 20–2).



65

1-Alkyltetrahydroisoquinoline

TABLE 9. SIMPLE TETRAHYDROISOQUINOLINES (65)
ORD curves in methanol (Ref. 53).

Series	Substituents at C – 1 R^1	Substituents at N R^2	Amplitude *a*
1β (*S*)	CH_2OH	Ac	+22
1α (*R*)	CH_2OH	Ac	−36
1β (*S*)	Me	$SO_2C_7H_7$*	+52
1α (*R*)	CH_2OSO_2Me	SO_2Me	−13

* Toluene-*p*-sulphonyl.

Benzquinolizidines

The benzquinolizidine (51) studied by Horii *et al.*[95] represents a very simple rigid type of heteroaromatic structure with no arylic substituent. Its ORD curve shows a small negative Cotton effect (*a*, ca. −10) on a strong positive background. (Note that the curves given on p. 2103 of Ref. 95*a* must be transposed; see correction, Ref. 95*b*). We have recently confirmed these curves in one of our laboratories, using samples kindly sent by Dr. K. Bláha, Prague.[96, 34]

Morphine derivatives

An extensive series of CD measurements on morphine derivatives have been made by Weiss and Rüll;[87] here we consider only the compounds with no strong chromophore other than the aromatic nucleus. ORD curves of similar compounds measured by Kuriyama[88] (reported in Ref. 1, pp. 287–289) include some pairs of enantiomers (cf. Fig. 11 and Table 10).

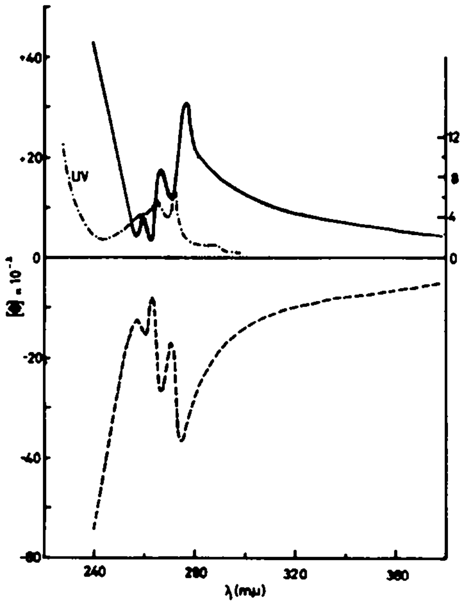
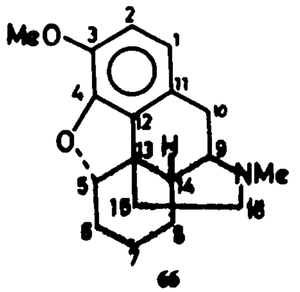
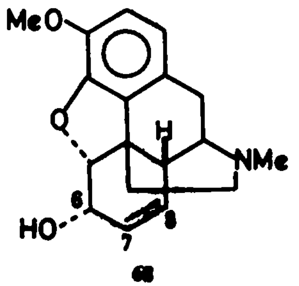


FIG. 11. UV Absorption (-·-·-) and ORD (———, -----) curves of N-methyl-morphinans in methanol (from Ref. 1, p. 291).
(-----) ORD curve for (55), with 9,13-bridge β;
(———) for (56 = *E*55), with 9,13-bridge α.



66

67 with Δ^6 (7)



68

TABLE 10. ORD and CD DATA ON REPRESENTATIVE MORPHINE DERIVATIVES

Solvents: C = chloroform; E = ethanol; M = methanol.

Formula no.	Name	Cotton effect			Solvent	Ref.
		Wavelength(s) λλ (mμ)	Amplitude *a* or Δε			
(A)	*Morphinan derivatives* without *4,5-oxide bridge*					
55	N-methylmorphinan	275/263	*a*	−28	M	88
	(−)-3-Methoxy-N-methylmorphinan	~285 240	Δε	−1·96 −0·3	M	87
	(−)-3-Methoxy-4-hydroxy- (−)-3-Methoxy-4-hydroxy-(tetrahydrodesoxycodeine)	285 241	Δε	−1·06 −1·0!	C	87
57	3-Methoxy-6-methyl-Δ⁶-N-methylmorphinan	288/270	*a*	−44	M	88
(B)	*Derivatives* with *4,5-oxide bridge*					
66	Dihydrodesoxycodeine D	281 242	Δε	−3·0 +7·1	M	87
	Dihydrodesoxycodeine D	288/265	*a*	−110	M	88
67	Desoxycodeine C	282 243	Δε	−6·0 +7·25	M	87
	Dihydrocodeine	290/265	*a*	−143	M	88
68	Codeine	289 245	Δε	−2·35 +13·4	E	87

The CD curves of the morphine alkaloids proper (66, 67, 68), with an oxygen bridge from C-4 to C-5, show a negative maximum at about 280 mμ and a positive maximum at about 240 mμ. Derivatives in which the oxygen bridge is absent (as 55) show two *weak* negative maxima in the same regions. The ORD curves for both series cover only the first Cotton effect, which is negative in agreement with the CD results.

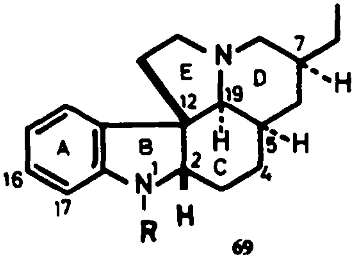
Dihydroindoles

The dihydroindole series is represented[52] by alkaloids of the aspidospermine and strychnine-like types (69, 70; R = H). Some typical ORD results are summarized in Table 11.

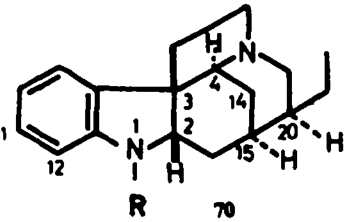
TABLE 11. ORD OF DIHYDROINDOLES

All curves in methanol: molecular amplitudes are for the Cotton effect of longest wavelength.

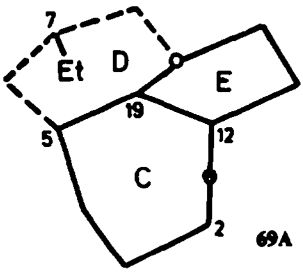
Compound	Molecular amplitude *a* (310–250 mμ)	Ref.
(+)-Aspidospermidine	−51	52
(+)-N-Deacetylaspidospermine	−66	52
Obscurinervine (72A)	−50	99
Obscurinervidine (72B)	−50	99
Neblinine (72C)	−25	99



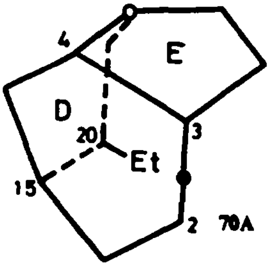
69



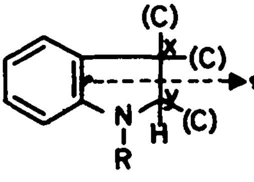
70



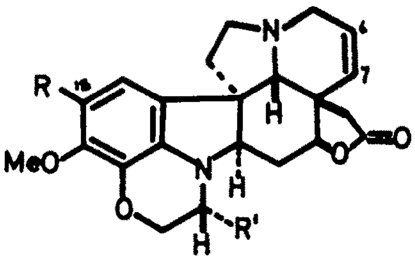
69A



70A



71



72

A: R = OMe; R' = Et
B: R = OMe; R' = Me
C: R = H; R' = Me

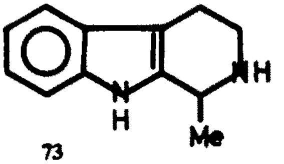
Still more complex polycyclic structures, which are also essentially dihydroindoles for our present purpose, are the neblinine-obscurinervine group (72), studied by Brown and Djerassi.[99] Their first Cotton effect is around or above 300 mμ and is *negative*; their second Cotton effect (first extremum at 270 mμ) is also *negative*. The mid-point of the first Cotton effect agrees well with the first UV absorption max; 315 mμ for R = MeO at C-15, but 300 mμ for R = H at C-15. The amplitudes of the first Cotton effects for all these non-acylated compounds are moderate ($a = -20$ to -60).

N-Acyldihydroindoles[98] of the aspidospermine and strychnine-like series (69, 70; R = Ac) are characterized by ORD curves with amplitudes (up to ±1000) much larger than those for unacetylated compounds (69, 70; R = H).

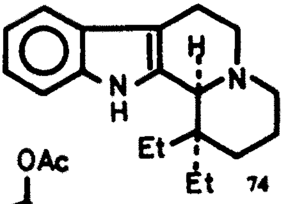
The asymmetry of these structures (69, 70) may be considered in terms of a projection 71 along the axis $p \rightarrow q$ of the dihydroindole system. Examples are shown at 69A and 70A, and typical curves are given in Fig. 12.

Indoles

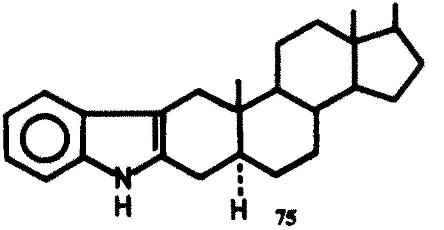
Several widely differing classes of compounds so far studied include the indole nucleus as their principal chromophores.



73



74



OAc

75

---

[98] W. Klyne, R. J. Swan, B. W. Bycroft and H. Schmid, *Helv. Chim. Acta* **49**, 833 (1966).

[99] K. S. Brown and C. Djerassi, *J. Am. Chem. Soc.* **86**, 2451 (1964).

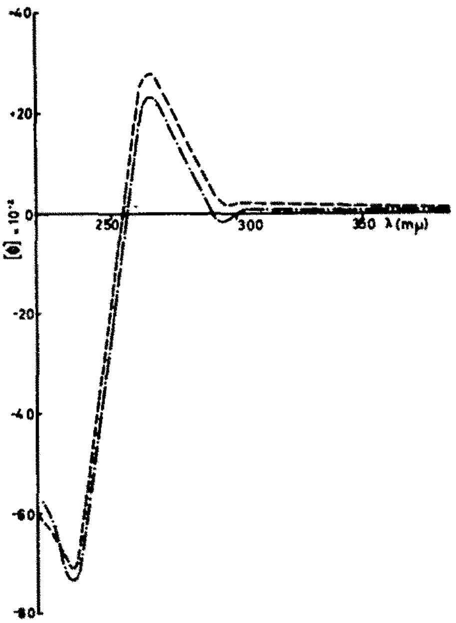
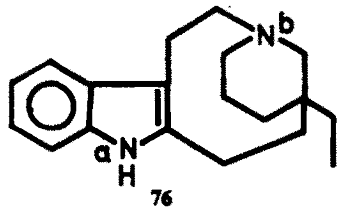


FIG. 12. ORD Curves of typical N-acyl-dihydroindoles in methanol.
(–·–·–) Na-Acetyl-7-ethyl-5-desethylaspidospermidine
(– – – –) Na-Acetyltubifolidine
(From Schmid *et al.*, Ref. 98).

Tetrahydroharman (73)[96] gave a negligible Cotton effect in the 260–280 mμ region; however, the tetracyclic compound 74 (Trojánek *et al.*[96]) gave a considerable positive Cotton effect (*a*, +82) between 300 and 250 mμ. The steroid 2,3-indole 75 has a positive Cotton effect in the 260 mμ region (*a*, +75).[100, 101]



76

(–)-Quebrachamine (76) has a 9-membered ring fused to the indole nucleus; it has only one centre of asymmetry and one hetero atom (N_b), each separated from the chromophore by two methylene groups. It gives a weak negative Cotton effect[102] in the 300–250 mμ region, followed by an intense positive Cotton effect between 240 and 220 mμ.

Finally, a wide variety of yohimbine derivatives and related compounds 77, 78

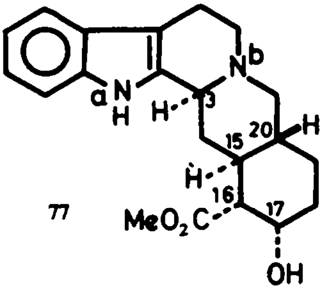
---

[100] This substance was prepared by Dr. J. C. Orr in Syntex S.A.

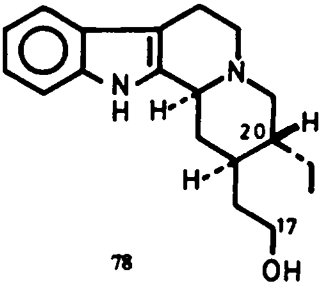
[101] For the synthesis of such compounds, see for example: Y. Ban and Y. Sato, *Chem. Pharm. Bull. Japan* 13, 1073 (1965); M. G. Lester, V. Petrow and O. Stephenson, *Tetrahedron* 21, 1761 (1965).

[102] W. Klyne, R. J. Swan, N. J. Dastoor, A. A. Gorman and H. Schmid, *Helv. Chim. Acta* 50, 115 (1967).

have been investigated.[36, 102, 103] In the simpler compounds the sign of the Cotton effect in the region 290–250 mμ depends on the stereochemistry at C-3 (Table 12). The heteroyohimbines[38] with another chromophore in ring *E*, which should probably be considered on the coupled-oscillator model; are considered on p. 11–12.*



77



78

Table 12. ORD of Yohimbine derivatives

All curves in methanol (Ref. 102).

Compound	Configuration	*a*	Wavelengths of peaks and troughs (mμ)
Yohimbine (**77**)	3α-H	+92	294/252
ψ-Yohimbine	3β-H	−170	294/258
Dihydrocorynantheol (**78**)	3α-H	+125	282/251
Isodihydrocorynantheol	3β-H	−51	298/253

Indolenines

Schmid, Klyne *et al.*[52] have studied the ORD curves of a range of alkaloids of the aspidospermine and strychnine types. For the indolenines of general type **79** the sign of the first Cotton effect at 290–240 mμ depends on the configuration at the centre C-11 (numbering as in **79**) adjacent to the chromophore (11α-X, positive; 11β-X, negative). The skeletons in which the chromophore is bound are represented by **80** and **81**. Amplitudes are given in Table 13 (cf. also Fig. 13).[52] The very intense Cotton effect observed for these compounds is reminiscent of inherently dissymmetric chromophores. This could be due to the styrene-like chromophore which is present, and/or to orbital overlap between the benzene ring, the N_a=C double bond and the lone-pair of electrons of the second nitrogen atom (N_b). As in optically active styrenes (see pp. 7–9), the chirality of the chromophore probably depends upon the configuration at the centre C-11.

Other chromophores

Tropones. The ORD and UV absorption curves for a pair of isomeric tropone-steroids[104] (**82**, **83**) are given in Fig. 14. The UV spectra of these isomers are very

---

* Beckett *et al.*[103a] have recently published extensive ORD and CD studies on *Mitragyna* alkaloids of the corynantheine group.

[103] N. Finch, C. W. Gemenden, I. Hsiu-Chu Hsu, A. Kerr, G. A. Sim and W. I. Taylor, *J. Am. Chem. Soc.* **87**, 2229 (1965).

[103] [a] C. M. Lee, W. F. Trager and A. H. Beckett, *Tetrahedron* **23**, 375 (1967). W. F. Trager, C. M. Lee, J. D. Phillipson and A. H. Beckett, *Tetrahedron* **23**, 1043 (1967).

[104] E. Denot and P. Crabbé, unpublished results, see also Ref. 19.

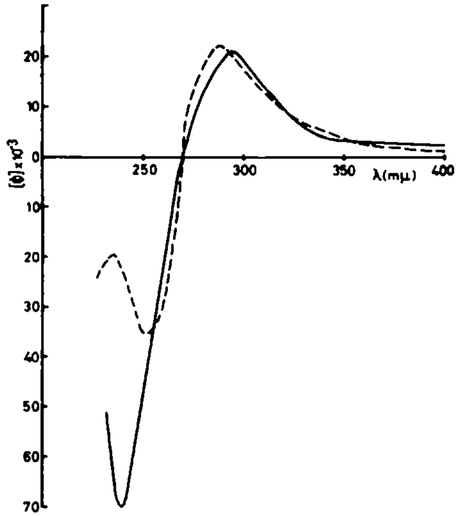
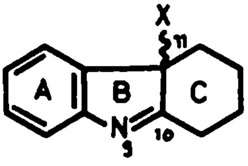
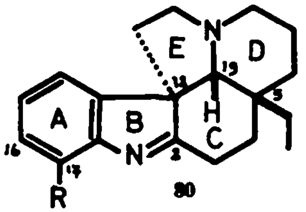


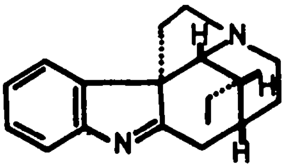
FIG. 13. ORD curves of typical indolenines in methanol.
(———), (+)-condyfoline (80)
(-----), (+)-1,2-dehydroaspidospermidine (81)
(From Schmid *et al.*, Ref. 52).



79



80
Aspidospermine-type



81
Strychnine-type

TABLE 13. INDOLENINES
ORD CURVES IN METHANOL (Ref. 52).

Compound	First Cotton Effect Amplitude 10^{-2} (*a*) (290–240 mμ)
Strychnine-like system (81)	
(+)-Condyfoline	+911
(−)-Tubifoline	−1414
Aspidospermine-like system (80)	
(+)-1,2-Dehydroaspidospermidine	+579
(+)-1,2-Dehydro-N-deacetyl-aspidospermine	+550

similar, but their ORD curves exhibit Cotton effects of opposite sign below 250 mμ; the 3-tropone **82** has a positive Cotton effect, whereas its 4-tropone analogue **83** gives a negative Cotton effect.

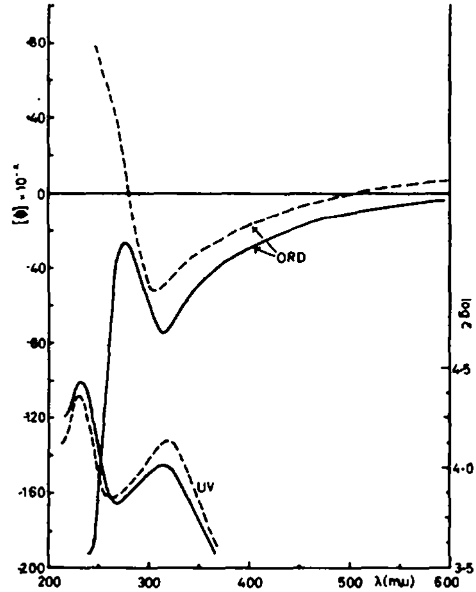
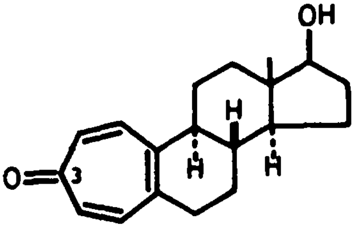
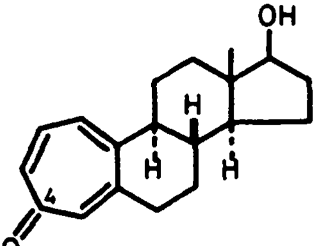


Fig. 14. UV and ORD curves of 17β-hydroxy-*A*-homo-oestra-1,4(4a),5(10)-trien-3-one (———) and 17β-hydroxy-*A*-homo-oestra-1(10),2,4a(5)-trien-4-one (- - - - -) (Ref. 104).



82



83

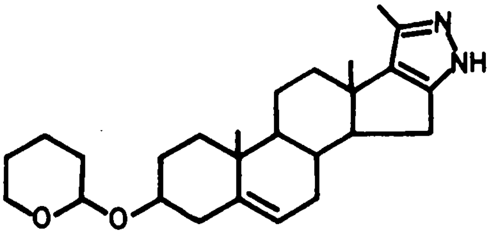
Pyrazoles. The steroid 16,20-pyrazole **84A**[105] (as the 3-tetrahydropyranyl ether) contains no other chromophore; its ORD curve shows that when in an asymmetric surrounding, the pyrazole chromophore is optically active. Both the pyrazole **84A** and its N-acetyl derivative **84B** give negative Cotton effects in the 230 mμ region.

Furans. The ORD curves of optically active molecules containing a furan ring are reproduced in Fig. 15. While the monoterpene menthofuran **85**[106] exhibits a strong

---

[105] These compounds were prepared by Mr. J. Iriarte in the Syntex Research Laboratories, Mexico.

[106] We are most grateful to Professor L. H. Zalkow, Georgia Institute of Technology, for a sample of menthofuran.



84

positive Cotton effect, the diterpene cafestol 86[107] shows a strong negative Cotton effect in the 220 mμ region.

ORD has been applied for the assignment of absolute configuration to α-methyl-α′-(β-furyl)-tetrahydrofuran (87) from sweet potato fusel oil.[108]

Quinoxaline and related compounds. The steroid quinoxaline (88)[109] shows two positive Cotton effects, $[\phi]_{333}$ +1200°; $[\phi]_{319}$ −600°; $[\phi]_{255}$ +7500°), corresponding to the two UV maxima; the unusual shape of the curve at about 255 mμ may be the

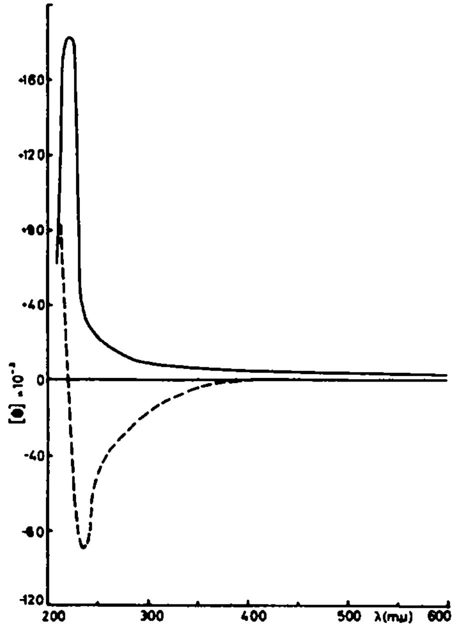


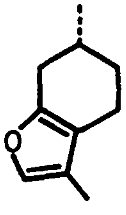
FIG. 15. ORD Curves of menthofuran (———) and of cafestol (-----) (Refs 106, 107).

---

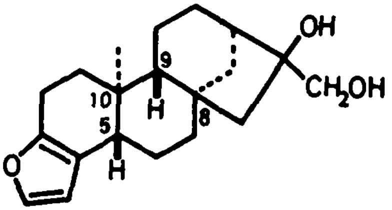
[107] We thank Professor C. Djerassi, Stanford University, for a sample of cafestol; see: C. Djerassi, M. Cais and L. A. Mitscher, *J. Am. Chem. Soc.* **80**, 247 (1958); *Ibid.* **81**, 2386 (1959); R. A. Finnegan and C. Djerassi, *Ibid.* **82**, 4342 (1960); A. I. Scott, F. McCapra, F. Comer, S. A. Sutherland, D. W. Young, G. A. Sim and G. Ferguson, *Tetrahedron* **20**, 1339 (1964).

[108] M. Ogama and Y. Hirose, *J. Chem. Soc. Japan* **86**, 1335 (1965).

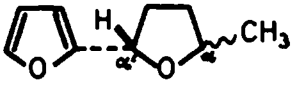
[109] This compound was prepared by Dr. St. Kaufmann, Syntex S.A. to whom we are indebted for a sample; cf. St. Kaufmann, *J. Org. Chem.* 31, 2395 (1966).



85

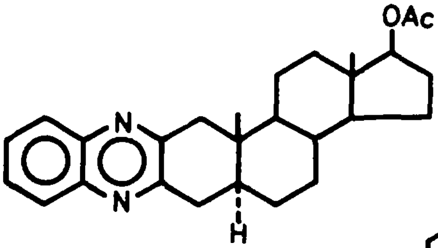


86

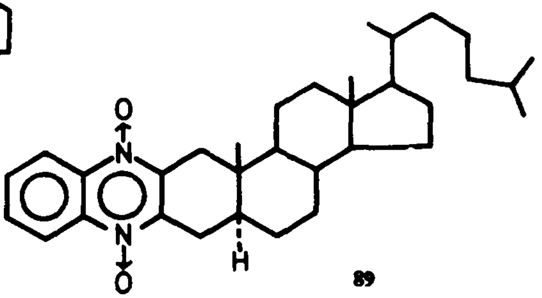


87

resultant of two Cotton effects of opposite sign. The N-oxide derivative 89[110] exhibits a positive Cotton effect at ca. 395 mμ (*a* +86).



88



89

V. FLEXIBLE COMPOUNDS

Many scattered ORD measurements have been made on simple compounds, the aryl groups of which should be conformationally free to rotate. The results are outlined in Table 14.

As in other fields, adequate treatment of these flexible aromatic compounds must await the successful outcome of attempts to rationalize the ORD and CD behaviour of the corresponding rigid structures. In particular symmetry rules for aromatic chromophores, as discussed in principle by Schellman,[73] must be established. The application of such rules to flexible compounds may then help in the study of preferred conformations, as it has already with flexible ketones (Ref. 1, pp. 132–134).

For many compounds the curves could profitably be measured again with modern equipment that will penetrate farther into the UV, and also permit more sensitive measurements in the 260–280 mμ region (cf. recent careful measurements on phenylalanine;[68] and discussion on pp. 29–30).

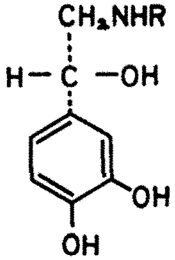
Most of these flexible compounds have very weak aromatic Cotton effects for reasons already considered. This may in itself be of structural significance; however,

---

[110] M. J. Haddadin and C. H. Issidorides, *Tetrahedron Letters* 3253 (1965).

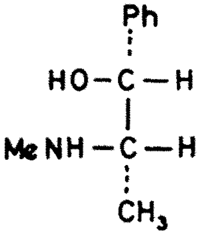
the *signs* of these weak Cotton effects should be used with caution for the allotment of absolute configuration.

Many references to different types of aryl-substituted hydrocarbons, alcohols and amines[62-65, 69, 111-117] show that these compounds give ORD curves which are essentially plain or with very small Cotton effects in the region 260–280 mμ, generally better detected by CD. However, some other similar compounds which carry arylic substituents [adrenaline and noradrenaline, **90**] give significant Cotton effects in this region.[118, 119] Mateos and Cram[65] found that some of the aryl-substituted alcohols showed notable changes in their ORD curves, when these were measured in solvents of different polarity, indicating probable variations in the degree of H-bonding with the solvents.



90

R = Me, Adrenaline
R = H, Noradrenaline



91

Ephedrine

Considering compounds with two centres of asymmetry, the first extrema of the Cotton effects of ephedrine (**91**), halostachine and phenylephrine have been reported by Lyle.[120, 121] C-Aryl and O-aryl derivatives of carbohydrates (**92**, **93**) also give Cotton effects.[122, 123]

---

[111] L. Verbit, S. Mitsui and Y. Senda, *Tetrahedron* **22**, 753 (1966).

[112] V. K. Honwad and A. S. Rao, *Tetrahedron* **20**, 2921 (1964).

[113] D. G. Neilson, R. J. Swan and W. Klyne; unpublished observations.

[114] A. Fredga, J. P. Jennings, W. Klyne, P. M. Scopes, B. Sjöberg and S. Sjöberg, *J. Chem. Soc.* 3928 (1965).

[115] A. Rothen and P. A. Levene, *J. Chem. Phys.* 7, 975 (1938); P. A. Levene and A. Rothen, *J. Biol. Chem.* **127**, 237 (1939).

[116] C. H. Hassall and J. Weatherston, *J. Chem. Soc.* 2844 (1965); cf. C. Djerassi *Record Chem. Progress* **20**, 138 (1959).

[117] [a] V. M. Potapov and A. P. Terentiev, *J. Gen. Chem. U.S.S.R.* **31**, 927 (1961);
[b] V. M. Potapov, V. M. Demyanovich and A. P. Terentiev, *J. Gen. Chem. USSR* **35**, 1538 (1965).

[118] J. Cymerman Craig and S. J. Roy, *Tetrahedron* **21**, 1847 (1965).

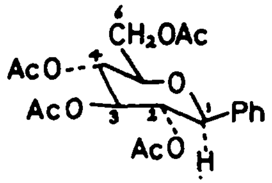
[119] A. La Manna and V. Ghislandi, *Il Farmaco* **19**, 377 (1964).

[120] G. G. Lyle, *J. Org. Chem.* **25**, 1779 (1960).

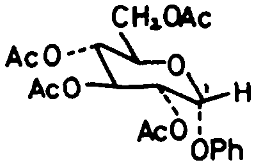
[121] I. P. Dirkx and T. J. de Boer, *Rec. Trav. Chim. Pays. Bas*, **83**, 535 (1964).

[122] [a] R. J. Ferrier and R. J. Swan; unpublished observations;
[b] J. Staněk, W. Klyne and R. J. Swan, unpublished observations.

[123] Y. A. Zhdanov, G. A. Korolyshenko, G. N. Dorofenko and G. V. Bogdanova, *Dokl Akad. Nauk SSSR* **152**, 102 (1963) and earlier Refs. there.



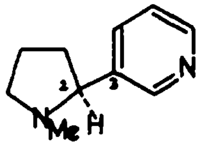
92



93

We next turn to compounds which contain both an aromatic nucleus and one or more carboxyl (or related) groups.[68, 69, 113, 114, 124–6] Here again compounds where *no* arylic substituents are present generally give negligible or weak Cotton effects, although Kuhn and Biller[125] reported Cotton effects for some derivatives of mandelic and atrolactic acids. Related compounds with arylic substituents give moderate Cotton effects.[68–70]

Few simple dissymmetric derivatives of pyridine have as yet been studied, but three alkaloids measured by Craig[128] all give strong Cotton effects (cf. 94).*



94

S-Nicotine

Space does not permit extended references to compounds containing aryl groups with other double bonds lying in conjugation between the aryl nucleus and the asymmetric centre; however many of these give strong Cotton effects, and Refs.[130–135] are given in Table 14.

Angolensin (which is a ring-opened neoflavonoid; Ollis *et al.*)[45] may be considered as a 1-aryl-1-benzoylethane (Ar · CO · CHMe · Ar′) in this series.

Recently considerable attention has been paid to asymmetric sulphoxides, many

---

* Some cinchona alkaloids, which contain the quinoline chromophore with a complex side-chain, have been studied by Lyle and Gaffield.[128a]

[124] T. R. Emerson, D. F. Ewing, W. Klyne, D. G. Neilson, D. A. V. Peters, L. H. Roach and R. J. Swan, *J. Chem. Soc.* 4007 (1965).

[125] W. Kuhn and H. Biller, *Z. Physikal. Chem.* **B.29**, 1 (1935); S. Osman, Ph.D. Thesis, Purdue University (1960).

[126] B. Sjöberg, *Acta. Chem. Scand.* **14**, 273 (1960).

[127] L. Verbit, S. Mitsui and Y. Senda, *Tetrahedron* **22**, 753 (1966).

[128] See Ref. 36 and Refs cited therein.

[128a] G. G. Lyle and W. Gaffield, *Tetrahedron* **23**, 51 (1967).

[129] D. G. Neilson and R. J. Swan; unpublished observations.

[130] J. H. Brewster and S. F. Osman, *J. Am. Chem. Soc.* **82**, 5754 (1960).

[131] A. La Manna and V. Ghislandi, *Il Farmaco* **19**, 480 (1964).

[132] F. Nerdel, K. Becker and G. Kresze, *Chem. Ber.* **89**, 2862 (1956).

[132a] G. C. Barrett, *J. Chem. Soc.* (C), 1 (1967).

[133] M. E. Warren, Jr. and H. E. Smith, *J. Am. Chem. Soc.* **87**, 1757 (1965).

[134] E. O. Bishop, G. J. F. Chittenden, R. D. Guthrie, A. F. Johnson and J. F. McCarthy, *Chem. Comm.* 93 (1965).

[135] H. E. Smith, M. E. Warren, Jr. and A. W. Ingersoll, *J. Am. Chem. Soc.* **84**, 1513 (1962); H. E. Smith, S. L. Cook, and M. E. Warren, Jr., *J. Org. Chem.* **29**, 2265 (1964).

TABLE 14. FLEXIBLE COMPOUNDS CONTAINING AN AROMATIC NUCLEUS AND ONE OR MORE ASYMMETRIC CENTRES IN A SIDE-CHAIN

Compounds	Aromatic Cotton effect $\lambda\lambda$ (mμ)	Aromatic Cotton effect a^*	Solvent	Authors	Ref.
	Hydrocarbons, alcohols and amines				
(*S*)-2-Phenylbutane Me—CHPh—Et	260	very small	Iso-octane	Verbit	69
(*S*)-2-Phenylbutane (derivatives from *ar*-Turmerone)	(only plain section of curve above 300 mμ measured)			Rao	112
(*S*)-2-Phenylbutan-1-ol HO—$CH_2 \cdot CHPh \cdot Et$	—	nil	MeOH	Neilson *et. al.*	113
2-Phenylbutane-1,4-diol $HO \cdot CH_2CHPh \cdot CH_2CH_2OH$	—	nil	MeOH	Fredga *et al.*	114
4-Phenylpentane-1,4-diol	267/263	+4	MeOH	Verbit	111
(*S*)-(−)-Methylphenyl carbinol (1-Phenylethanol) Ph—CHOH—CH_3	270/260 (also C.D.)	+2 +7	MeOH Iso-octane	Verbit	69
$Ph \cdot CHR^1 \cdot CH(OH)R^2$ (several examples)	Some diastereoisomers show apparent C.E. with first extremum at 310 mμ.				65*a*
Other aryl carbinols				Levene, Rothen	115
Dibenzylcarbinol or 1,3-diaryl propan-2-ol types	Essentially plain			Hassall	116
(*R*)-Phenylethane-1,2-diol	268/250	+7	MeOH	Neilson	113
(*R*)-1-Phenylethylamine $Ph \cdot CHNH_2 \cdot Me$				Potapov, Terentiev	117
(*R*)-1-Phenylethylamine $Ph \cdot CHNH_2 \cdot Me$ (as HCl)		−4	MeOH		74, 79
(*S*)-(+)-2-Amino-1-phenylpropane		negligible	MeOH	LaManna	79
(*R*)-Adrenaline (90, R = Me)	277/260 238	*a* − 33 [ϕ] − 24	EtOH	Craig	118
(*R*)-Nor-adrenaline (90, R = H)	277/260 238	*a* − 19 [ϕ] − 50	EtOH	Craig, LaManna	118, 119
(−) (1*R*,2*S*)-Ephedrine (91)	270/255	+13	EtOH	Lyle, Dirkx	120, 121

TABLE 14 (*continued*)

Compounds	Aromatic Cotton effect		Solvent	Authors	Ref.
	$\lambda\lambda$ (mμ)	a^*			
	Carboxylic acids and derivatives				
(*S*)-(+)-Phenylbutyric acid Ph · CHEt · CO_2H	231 (carboxyl, *not* aromatic peak)	[ϕ] + 87	Hexane	Swan	34, 64
(*R*)-(−)-Mandelic acid Ph · CHOH · CO_2H		nil†	MeOH	Emerson *et al.*	124, 129
(*R*)-(−)-2-MeO-Mandelic acid		small	MeOH	Kuhn	124, 125
(*R*)-3,4-OCH_2O-Mandelic acid		nil	MeOH	Neilson	113
(*R*)-Mandelamidinium chloride Ph · CHOH · C-C(NH_2) · $NH_2^+Cl^-$		nil	MeOH	Emerson *et al.*	124
(*R*)-2-MeO-Mandelamidinium chloride	280/261	−26	MeOH	Emerson *et al.*	124
(*R*)-Hydratropic acid Ph · CHMe · CO_2H	270	small		Sjöberg	126 124
(*S*)-Phenylsuccinic acid HO_2C · CHPh · CH_2 · CO_2H	Essentially plain		MeOH	Fredga *et al.*	114
(*S*)-Phenylalanine Ph · CH_2CHNH_2 · CO_2H	260	very faint	H_2O	Moscowitz	68
(*S*)-*p*HO-Phenylalanine (Tyrosine)	280/260	+12	H_2O	Hooker and Tanford, Fassman *et al.*	70, 78
Other hydroxyacids and derivatives				Verbit	111
	Glycosides				
1β-*C*-Phenyl-1-deoxy D-glucopyranose (2,3,4,6-tetra-O-acetate (92))	273/260	+14	MeOH	Ferrier and Swan	122*a*
Phenyl-α-D-glucopyranoside (2,3,4,6-tetra-O-acetate (93))	275/261	+4?	MeOH	Staněk, Swan	122*b*

Phenyl-α-D-glucopyranoside (not acetylated)	273/261	−15	MeOH	Staněk, Swan	122*b*
		Pyridine derivatives			
2(3-Pyridyl) derivatives of *N*-Methylpyrrolidine (*S*-nicotine) (94)		−80	EtOH	Craig	128
2(3-Pyridyl) derivatives of Piperidine (*S*-anabasine)		−48	EtOH	Craig	128
2(3-Pyridyl) derivatives of N-methyl-5-pyrrolidone (*S*-cotinine)		−59	EtOH	Craig	128
		Other more complex chromophores			
(Listed for reference only)					
Phthalyl and similar derivatives of amines					130 131
Benzal and salicylidene derivatives of amines					132, 133, 135–37
N-Thiobenzoylamino acids					132a
Phenylazo-sugars					134
Aryl sulphoxides					138, 139

---

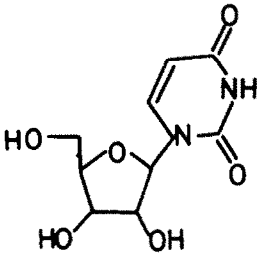
* [ϕ] values given in this column are for peaks or troughs, and are molecular rotations × 10^{-2}.

† Weak aromatic Cotton effect reported in Ref. 111.

of which contain one (or two) aryl groups, especially in the work of Mislow,[138] and Gaffield.[139]

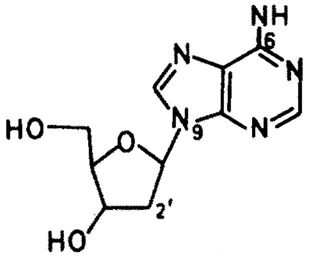
Nucleosides and nucleotides

A special group of compounds, in which the ring-system *itself* (pyrimidine or purine) has little or no symmetry apart from the plane of the ring, consists of the nucleosides and nucleotides. Representative formulae of a pyrimidine-riboside and of a purine-2′-deoxyriboside are **95** and **96**. For a discussion of UV absorption, see Ref.[140]



95

Uridine
(Uracil 3-β-D-riboside)



96

Deoxyadenosine
(6-Aminopurine
9-(2′-deoxy-β-D-riboside))

Much work has already been done on ORD and CD of polynucleotides, partly to study their helical character in connection with biochemical problems (for reviews see for example Ref. 141 and a recent "Annual Report", Ref. 142). Studies on the monomers and oligomers (Refs. 143–154) indicate that there are many interesting problems in this field quite apart from its great biochemical importance. The ring systems involved (pyrimidine and purine), which contain several hetero-ring-atoms,

[136] H. E. Smith and T. C. Willis, *J. Org. Chem.* **30**, 2654 (1965).

[137] H. E. Smith and R. Records, *Tetrahedron* **22**, 813 (1966).

[138] K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons and A. L. Ternay, Jr., *J. Am. Chem. Soc.* **87**, 1958 (1965).

[139] K. K. Anderson, W. Gaffield, N. E. Papanikolaou, J. W. Foley and R. I. Perkins, *J. Am. Chem. Soc.* **86**, 5637 (1964).

[140] L. B. Clark and I. Tinoco, Jr., *J. Amer. Chem. Soc.* **87**, 16 (1965).

[141] J. Brahams, *Proc. Roy Soc.*, A **297**, 150 (1967).

[142] T. L. V. Ulbricht, *Ann. Rep. Chem. Soc.* **62**, 402 (1965).

[143] T. L. V. Ulbricht, T. R. Emerson, R. J. Swan and W. Klyne, *Tetrahedron Letters* No. 13, 965 (1964).

[144] J. T. Yang and T. Samejima, *J. Am. Chem. Soc.* **85**, 4039 (1963).

[145] I. Frič, J. Smekal and J. Farkas, *Tetrahedron Letters* 75 (1966).

[146] E. Walton, F. W. Holly, G. E. Boxer and R. F. Nutt, *J. Org. Chem.* **31**, 1163 (1966).

[147] T. Hashizume and H. Iwamura, *Tetrahedron Letters* 3095 (1965).

[148] T. R. Emerson, R. J. Swan and T. L. V. Ulbricht, *Biochem. Biophys. Res. Comm.* **22**, 505 (1966).

[149] R. T. Simpson and B. L. Vallee, *Biochem. Biophys. Res. Comm.* **22**, 712 (1966).

[150] T. L. V. Ulbricht, T. R. Emerson and R. J. Swan, *Tetrahedron Letters* 1561 (1966).

[151] R. B. Homer and S. F. Mason, *Chem. Comm.* 332 (1966).

[152] T. L. V. Ulbricht, T. R. Emerson and R. J. Swan, *Biochem. Biophys. Res. Comm.* **19**, 643 (1965).

[153] M. L. Wolfrom, H. G. Garg and D. Horton, *J. Org. Chem.* **30**, 1556 (1965).

[154] H. Yonehara and N. Otake, *Tetrahedron Letters* 3785 (1966).

are very easily perturbed, and give strong Cotton effects, generally between 250 and 300 mμ. Some ORD data are summarized in Table 15.

Some speculations regarding preferred conformations of the asymmetric (carbohydrate) unit relative to the heteroaromatic chromophore have been presented by Ulbricht *et al.*[150] Whilst it would have been expected that α- and β-anomers would give curves of roughly enantiomeric types, it is of interest to note that a pyrimidine and a purine derivative of the same anomeric type give Cotton effects of *opposite* sign.

TABLE 15. ORD AMPLITUDES OF REPRESENTATIVE NUCLEOSIDES AND NUCLEOTIDES

All from Ref. 143 unless stated otherwise.

	ORD Amplitudes	
	α-Anomer	β-Anomer
Pyrimidine nucleosides and nucleotides		
(extrema 280–290/245–265 mμ)		
Thymidine	−104	+95
Thymidine 5'PO$_3$H		+71
D-Arabinofuranosylthymine	−103(a)	+293(a)
D-Ribofuranosylthymine,2'-deoxy	−138(a)	+85(a)
Uridine		+117
Uridine 5'-fluoro-5'-deoxy	−159	+120
Cytidine		+152
Cytidine 2'-deoxy (HCl)	−175	+111
Cytidine 2'-deoxy 5'-PO$_3$H		+124
Purine nucleosides and nucleotides		
(extrema 290–270/250–230 mμ)		
Adenosine	+123	−58
Adenosine 2'-deoxy	+80	−*
Adenosine 2'-deoxy 5'-PO$_3$H		−27
Guanosine		−*
Guanosine 2'-deoxy		−*
Guanosine 2'-deoxy 5'-PO$_3$H		−29
Inosine		−59

* Curve incomplete: only sign can be given.

(a) Ref. 145.

Acknowledgements.—We are greatly indebted to the many colleagues who have kindly provided samples for measurement or who have permitted us to quote unpublished data. W. K. is grateful to the Science Research Council for a grant, and to Wendy Mose and Felicity Titheridge for much assistance in the preparation of the manuscript.