

## Application of the Exciton Chirality Method for the Stereochemical Assignment of Remote Groups. Determination of the $\alpha$ - or $\beta$ -Configuration of a 2-Hydroxy-substituent in 2,17- and 2,16-Dihydroxy-A-nor-5 $\alpha$ -androstane and -estrane Derivatives

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The c.d. of dibenzoate and bis-*p*-methoxybenzoate derivatives of 2,17- and 2,16-dihydroxy-A-nor-5 $\alpha$ -androstanes and -estrans has been shown to arise principally from the coulombic coupling of the long-axis polarized excitation moments of the two benzoate groups. Analysis of the c.d. spectra in the light of the exciton chirality method allows an immediate determination of the  $\alpha$ - or  $\beta$ -configuration of the 2-OH group, providing that the configuration of the 17- or 16-OH group is known. The c.d. spectra are qualitatively unaffected by the presence of additional ethynyl or methyl substituents in the molecule. The sign of the lower-energy component of the exciton c.d. couplet is given by the sign of the torsion angle  $\theta = \text{O}(2)\text{-C}(2)\text{-C}(17)\text{-O}(17)$ , or  $\text{O}(2)\text{-C}(2)\text{-C}(16)\text{-O}(16)$ , the values of which can be deduced from X-ray data or Dreiding models. In spite of the weak coupling, due to the remoteness of the two interacting chromophores, observed and calculated rotational strengths are in fairly satisfactory agreement.

THE establishment of the stereochemistry of a 2-hydroxy-substituent in A-nor-5 $\alpha$ -steroids is not a trivial problem. Even the relatively simple case of the 2-A-norcholestanol epimers has led to controversial assignments, until the correct configurations of the secondary hydroxy-groups were finally settled on the basis of chemical correlations.<sup>1</sup>

Further difficulties arise in the case of tertiary alcohols such as 2-ethynyl-2-hydroxy- or 2-hydroxy-2-methyl-A-nor-5 $\alpha$ -androstane and -estrane derivatives, which have been the subject of considerable interest in view of their hormonal and antihormonal properties; the ability of these compounds to bind to the estrogenic or androgenic receptors seems to be governed to a large extent by the  $\alpha$ - or  $\beta$ -position of the 2-hydroxy-group.<sup>2</sup>

In a series of such A-nor-5 $\alpha$ -androstanes the configuration of the 2-hydroxy-groups has been inferred from <sup>1</sup>H n.m.r. and o.r.d. data;<sup>3</sup> the structure of one of the compounds was later established by X-ray crystallography<sup>4</sup> in order to assess the reliability of the above method, and to gain information on the conformation of ring A. On the other hand, the n.m.r. method cannot be used very safely in the A-nor-5 $\alpha$ -estrane series, owing to the lack of the 10-methyl group. The proposed C-2 configurations,<sup>5,6</sup> deriving only from more or less evident analogies with the o.r.d. curves, were nevertheless supported, in general, by the biological activities of the supposed  $\alpha$ - or  $\beta$ -OH epimers, and, in one case, by X-ray crystallography.<sup>5</sup>

The aim of the present work is to provide a rather simple physical method allowing the immediate stereochemical assignment of a 2-OH group. Since most A-nor-5 $\alpha$ -steroids have (or may readily have) a 17-OH group of known configuration (usually  $\beta$ ), we expected that the c.d. properties of their 2,17-dibenzoate derivatives would allow such a determination, in the light of the exciton chirality method,<sup>7-9</sup> in spite of the unusual remoteness between the two interacting groups.

### RESULTS

The mono- and di-hydroxy-A-nor-5 $\alpha$ -steroids involved in the present study have been described in previous papers.<sup>2-6</sup>

The corresponding benzoate and *p*-methoxybenzoate derivatives were obtained by the usual methods as described briefly in the Experimental section; their m.p.s, optical rotations, u.v. spectra, and c.d. spectra are summarized in Tables 1—3.

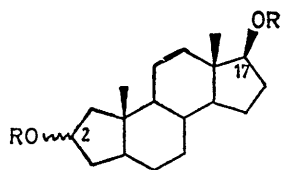
Table 1 contains a series of epimeric 2,17 $\beta$ -dibenzoates (1a)—(6a) and (1b)—(6b); indexes (a) and (b) refer to the *trans*- and *cis*-isomers, respectively. Three related 2 $\alpha$ -, 2 $\beta$ -, and 17 $\beta$ -monobenzoates (8)—(10) are described in Table 2 for comparison.

Table 3 deals with various bis-*p*-methoxybenzoate derivatives. The first two entries (7a) and (7b) correspond to the dibenzoates (1a) and (1b) described in Table 1. Five compounds (11a, b), (12), and (13a, b), provide examples of 2,17 $\alpha$ -, 2,16 $\alpha$ -, and 2,16 $\beta$ -structures, whose c.d. properties will be discussed later.

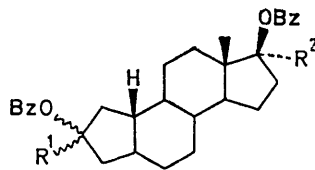
In the 300—200 nm range the u.v. absorption spectra of compounds (1)—(6) and (8)—(10) arise principally from the benzoate chromophore, which exhibits two electronic transitions in this region: at 280 ( $\epsilon$  ca. 1 000), and 230 nm ( $\epsilon$  ca. 14 000). As shown from the data in Tables 1 and 2, these characteristics do not change appreciably when the benzoate groups are linked to the steroid frame. The ethynyl group usually does not significantly interfere with the benzoate chromophore, with the possible exception of compounds (6a,b), the u.v. bands of which are moderately enhanced and slightly shifted to higher energy.

The c.d. spectra of the monobenzoates (8)—(10) display two Cotton effects centred in the vicinity of the u.v. maxima, at ca. 280 ( $\Delta\epsilon$  ca.  $\pm 0.2$ ) and 230 nm ( $\Delta\epsilon \pm 2\text{--}5$ ). Interpretation of the c.d. signs at 230 nm by using the proposed sector rule<sup>10</sup> does not seem to us unambiguous. Nevertheless, a knowledge of each individual c.d. contribution of the 2 $\alpha$ -, 2 $\beta$ -, and 17 $\beta$ -benzoate groups is not without interest, as shown below.

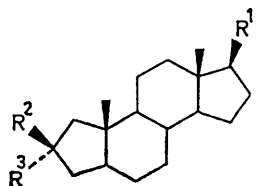
The c.d. spectra of the dibenzoates (1)—(6) contrast markedly with those of the above-mentioned monobenzoates, and, in particular, cannot be explained on the basis of the simple additivity of the 2- and 17-benzoate group contributions. Each of the 2 $\alpha$ ,17 $\beta$ - and 2 $\beta$ ,17 $\beta$ -series displays a characteristic c.d. pattern, irrespective of the presence of additional 2- and 17-methyl or -ethynyl substituents, or of a 10-methyl group. Both series exhibit a weak positive band at 270—280 nm, connected with the first u.v. transition; they differ strikingly in the 220—250 nm region corresponding to the second u.v. transition.



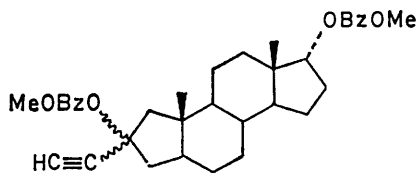
- (1)  $R = OBz$  (7)  $R = OBzOMe$   
 a, 2 $\alpha$ , 17 $\beta$   
 b, 2 $\beta$ , 17 $\beta$



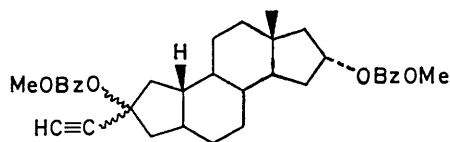
- (2a) 2 $\alpha$ -OBz  $R^1 = \beta-H$ ,  $R^2 = H$   
 (2b) 2 $\beta$ -OBz  $R^1 = \alpha-H$ ,  $R^2 = H$   
 (3a) 2 $\alpha$ -OBz  $R^1 = \beta-Me$ ,  $R^2 = H$   
 (3b) 2 $\beta$ -OBz  $R^1 = \alpha-Me$ ,  $R^2 = H$   
 (4a) 2 $\alpha$ -OBz  $R^1 = \beta-H$ ,  $R^2 = -C\equiv CH$   
 (4b) 2 $\beta$ -OBz  $R^1 = \alpha-H$ ,  $R^2 = -C\equiv CH$   
 (5a) 2 $\alpha$ -OBz  $R^1 = \beta-H$ ,  $R^2 = Me$   
 (5b) 2 $\beta$ -OBz  $R^1 = \alpha-H$ ,  $R^2 = Me$   
 (6a) 2 $\alpha$ -OBz  $R^1 = \beta-C\equiv CH$ ,  $R^2 = H$   
 (6b) 2 $\beta$ -OBz  $R^1 = \alpha-C\equiv CH$ ,  $R^2 = H$



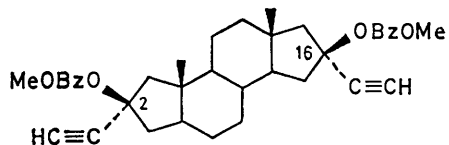
- (8)  $R^1 = OH$ ,  $R^2 = OBz$ ,  $R^3 = H$   
 (9)  $R^1 = OH$ ,  $R^2 = -C\equiv CH$ ,  $R^3 = OBz$   
 (10)  $R^1 = OBz$ ,  $R^2 = R^3 = H$



- (11a) 2 $\beta$ -OBzOMe  
 (11b) 2 $\alpha$ -OBzOMe



- (13a) 2 $\beta$ -OBzOMe  
 (13b) 2 $\alpha$ -OBzOMe



(12)

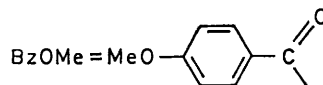
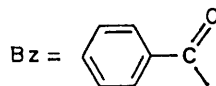


TABLE 1

M.p.s, specific rotations, u.v. and c.d. spectra of epimeric 2 $\alpha$ ,17 $\beta$ - and 2 $\beta$ ,17 $\beta$ -dibenzoates in the A-nor-5 $\alpha$ -androstande and -estrane series

Compound	M.p. (°C) †	[ $\alpha$ ] <sup>25</sup> (°) <sup>a</sup>	U.v. $\lambda$ /nm ( $\epsilon$ ) <sup>b, c</sup>	C.d. $\lambda$ /nm ( $\Delta\epsilon$ ) <sup>b</sup>			
				(a) 2 $\alpha$ ,17 $\beta$ -Dibenzoates			
(1a)	140	+85*	228 (29 700)	236.5 (+17.8)			
(2a)	144	+100	228 (29 900)	235 (+16.4)			
(3a)	108	+105	228 (29 200)	235 (+16.6)			
(4a)	182	+40	228 (35 800)	236 (+13.8)			
(5a)	127	+63.5	228 (31 300)	236 (+13.2)	215 <sup>d</sup> (+1.4)		
(6a)	Oil	+70	226 (44 700)	235 (+14.3)		272 (+0.16)	
(b) 2 $\beta$ ,17 $\beta$ -Dibenzoates							
(1b)	167	+3*	228 (30 700)	222 (+2.5)	239 (-4.5)	274 (+0.14)	282 (+0.16)
(2b)	97	+13	228 (28 400)	221 (+2.8)	237 (-5.1)	274 (+0.17)	282 (+0.19)
(3b)	162	+6	228 (30 400)	221 (+2.7)	236 (-3.5)	273 (+0.23)	281 (+0.27)
(4b)	224	-38	229 (29 500)	221 (+2.5)	236 (-6.3)	255 <sup>e</sup> (+0.84)	
(5b)	164	-6.5	228 (29 900)	223 (+2.1)	238 (-6.0)		
(6b)	170	+40	226 (52 100)	223 (+4.7)	239 (-3.1)		282 (+0.19)

<sup>a</sup> Specific rotations in dioxan (*c* 1) at 578 nm or (\*) 589 nm. <sup>b</sup>  $\lambda$ , wavelength of the maxima (u.v.) or extrema (c.d.);  $\epsilon$  and  $\Delta\epsilon$  are given in mol<sup>-1</sup>; all spectra recorded in methanol. <sup>c</sup> The u.v. spectra of (1)–(6) all display a weak <sup>1</sup>L<sub>b</sub> transition at 272–273 nm with log  $\epsilon$  3.2–3.7. <sup>d</sup> Minimum. <sup>e</sup> Shoulder.

$$\dagger \text{ } ^\circ\text{C} = \text{K} - 273.15.$$

TABLE 2

M.p.s, specific rotations, and u.v. and c.d. spectra of selected 2 $\beta$ -, 2 $\alpha$ -, and 17 $\beta$ -monobenzoates in the A-nor-5 $\alpha$ -androstande series

Compound	M.p. (°C)	[ $\alpha$ ] <sup>25</sup> (°)	U.v. $\lambda$ /nm ( $\epsilon$ )		C.d. $\lambda$ /nm ( $\Delta\epsilon$ )			
(8)	2 $\beta$	~120	-20*	229 (12 000)	272 (950)	230 (-2.5)	275 (-0.09)	283 (-0.07)
(9)	2 $\alpha$	Oil	+11	229 (12 200)	273 (850)	231 (+2.2)		
(10)	17 $\beta$	130	+47	229 (14 700)	273 (950)	230 (+4.1)	274 (+0.16)	281 (+0.17)

\* At 589 n.m., conditions as in Table 1.

TABLE 3

M.p.s, specific rotations, and u.v. and c.d. spectra of several 2,16- and 2,17-bis-*p*-methoxybenzoates in the A-nor-5 $\alpha$ -androstande and -estrane series

Compound	M.p. (°C)	[ $\alpha$ ] <sup>25</sup> (°) <sup>a</sup>	U.v. $\lambda$ /nm ( $\epsilon$ ) <sup>b</sup>	C.d. $\lambda$ /nm ( $\Delta\epsilon$ ) <sup>c</sup>	
(7a)	2 $\alpha$ ,17 $\beta$	144	+117.5	255 (50 000)	243 (-1) 263 (+18.8)
(7b)	2 $\beta$ ,17 $\beta$	173	-9.5	256 (44 800)	248 (+5.1) 266 (-6.1)
(11a)	2 $\beta$ ,17 $\alpha$	Oil	-68 †	256 (30 900)	242 (+0.5) 268 (-8.9)
(11b)	2 $\alpha$ ,17 $\alpha$	174	-20 †	255 (32 300)	247 (-3.5) 267 (+4.5)
(12)	2 $\beta$ ,16 $\beta$	188	-12	257 (39 700)	248 (-3.1) 269 (+2.9)
(13a)	2 $\beta$ ,16 $\alpha$	166	+12.5 †	256 (36 600)	ca. 240–250 (+1.6)
(13b)	2 $\alpha$ ,16 $\alpha$	153	+3 †	256 (35 500)	248 (+3.5) 269 (-0.8)

<sup>a</sup> Specific rotation at 578 nm in dioxan (*c* 1 or † 0.4). <sup>b</sup> In methanol. <sup>c</sup> In methanol-dioxan 9 : 1.

The c.d. pattern of the *cis*-dibenzoates (1b)–(6b) mainly consists of two Cotton effects of opposite signs and comparable magnitudes located at 222 ( $\Delta\epsilon$  +2—+5) and 236 nm ( $\Delta\epsilon$  -3 to -6). This c.d. couplet, having the characteristic exciton shape, is centred at the corresponding u.v. maximum (228–229 nm).

The *trans*-dibenzoates (1a)–(6a) only exhibit in the same region a single positive band at 236 nm ( $\Delta\epsilon$  ca. +15), which is distinctly red-shifted with respect to the u.v. maximum. In all likelihood this positive Cotton effect represents the lower energy component of an exciton couplet

whose higher energy counterpart is hidden, probably for the reason discussed below. That this idea is acceptable is suggested by the u.v. and c.d. behaviour of the related bis-*p*-methoxybenzoate derivatives (7a and b), reported in Table 3 and Figure 1. As the presence of the *p*-methoxy-substituents produces a red shift of the u.v. band from 230 to 255 nm, the c.d. of the *trans*-isomer (7a) now shows a couplet consisting of a weak negative band at 243 nm, followed by a stronger positive band at 263 nm. The *cis*-isomer (7b) exhibits the expected exciton couplet centred at 255 nm.

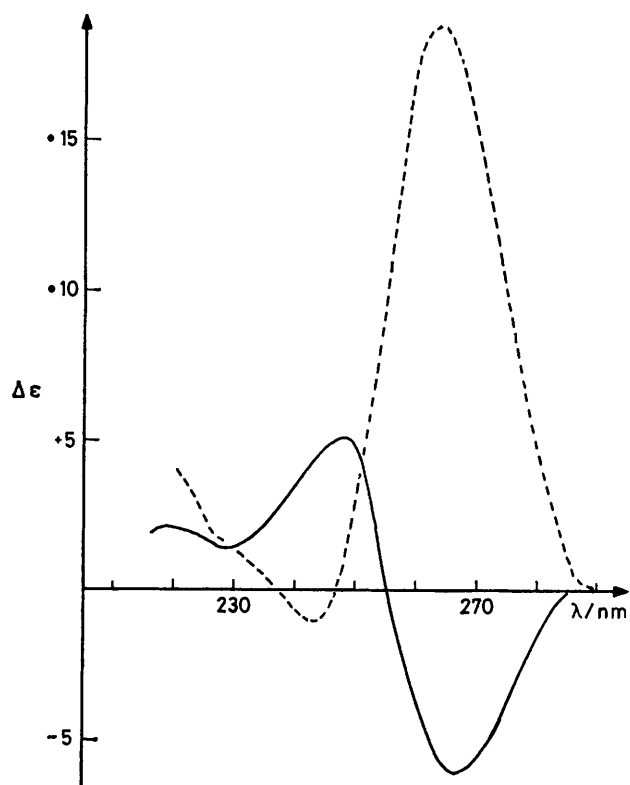
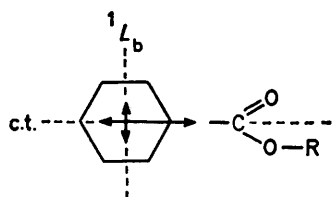


FIGURE 1 C.d. spectra of the bis-(*p*-methoxybenzoates) (7a) (---), and (7b) (—)

#### DISCUSSION

As already stated above the benzoate chromophore exhibits two  $\pi \rightarrow \pi^*$  transitions in the near u.v. The  ${}^1L$ -benzene-like transition at 280 nm, and the intramolecular Ar  $\leftrightarrow$  COO charge transfer (c.t.) transition at 230 nm are polarized along the short and long axes of the group, respectively, as sketched in Scheme 1.<sup>7,10</sup> The oscillatory nature of the electric transition moments is indicated by the double-headed arrows. The introduction of a *p*-methoxy-substituent causes a shift of the transitions towards lower energy (from 230 to 255 nm for the c.t. transition), without affecting the polarization directions.



SCHEME 1

Admittedly,<sup>7</sup> the preferred conformations of the benzoate group are those in which the Ar-C and R-O bonds adopt an antiparallel relationship (Scheme 1). Owing to the rotational freedom of the phenyl group around the Ar-C (or O-R) direction, the electric moment of the  ${}^1L_b$  transition tends to vanish; as a consequence the c.d. associated with the 280 nm band has a very

weak intensity. Contrariwise, the c.t. transition moment maintains with respect to the molecular frame an average orientation, approximately parallel to the O-R bond. In view of the rigidity of the A-nor-5 $\alpha$ -steroid structure, the spatial mutual orientation of the c.t. transition moments of the 2- and 17-benzoate groups should be fairly well defined. They are sketched in Figures 2 and 3

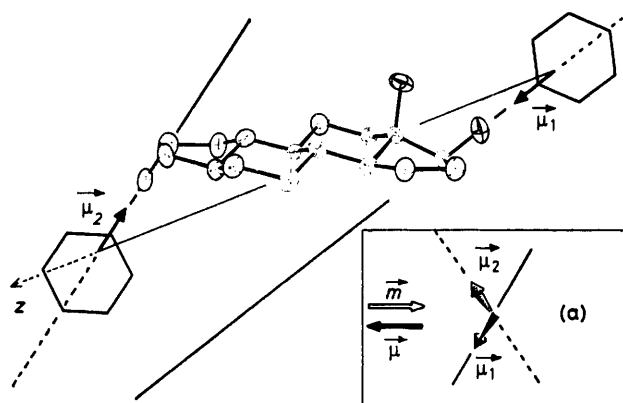


FIGURE 2 In-phase coupling of the transition moments in the 2 $\alpha$ ,17 $\beta$ -dibenzoates; (a) view along the *z* axis

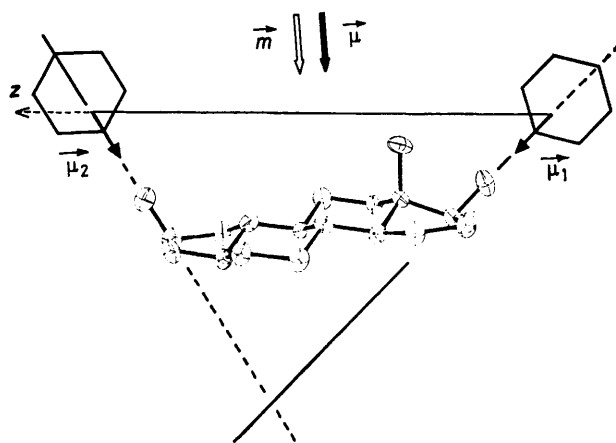


FIGURE 3 In-phase coupling of the transition moments in the 2 $\beta$ ,17 $\beta$ -dibenzoates

for the 2 $\alpha$ ,17 $\beta$ - and 2 $\beta$ ,17 $\beta$ -configurations; the conformation of the steroid backbone (in particular, that of the A and D rings) is that observed in the crystal state for a related A-nor-5 $\alpha$ -estrane derivative.<sup>5</sup>

According to the degenerate  $\mu_1$ - $\mu_2$  mechanism,<sup>8</sup> the coulombic in-phase and out-of-phase coupling modes of the two isoenergetic c.t. transition moments generate the two components of the exciton couplet visible in the c.d. spectra. Only the in-phase (or symmetric) coupling mode is represented in Figures 2 and 3, by using single-headed arrows directed along Ar  $\rightarrow$  COO in both 2- and 17-groups. The out-of-phase (antisymmetric) mode is obtained by inverting one of the arrows.

It is clear from Figures 2 and 3 that in both the 2 $\alpha$ ,17 $\beta$ - and 2 $\beta$ ,17 $\beta$ -series the in-phase coupling mode should be associated to the higher-energy component of the c.d.

couplet, owing to the coulombic repulsion of the electric transition dipoles in the head-to-head arrangement.

In the *trans*-compounds (1a)—(7a), the in-phase coupling of the  $\vec{\mu}_1$  and  $\vec{\mu}_2$  dipoles leads to a resulting electric transition dipole  $\vec{\mu}$  approximately located in the mean plane of the steroid frame and directed, in Figure 2, towards the reader. The magnetic transition moment  $\vec{m}$  generated by the corresponding charge displacement is antiparallel to  $\vec{\mu}$ , as shown more clearly in Figure 2a, where the spatial mutual orientation of dipoles  $\vec{\mu}_1$  and  $\vec{\mu}_2$  is projected onto a plane perpendicular to the  $z$  axis. The scalar product  $\vec{\mu} \cdot \vec{m}$  being negative, a negative c.d. is expected for the higher energy exciton component, and, conversely, a positive c.d. for the lower energy counterpart.

The c.d. spectrum of the bis-*p*-methoxybenzoate (7a) actually shows this sequence of signs (Figure 1). However, the negative band is very weak, and even does not exist at all in the dibenzoates (1a)—(6a). The dissymmetry of exciton couplets may have different origins, including additional non-degenerate coupling of the considered transition with other transitions having relatively similar energies.<sup>11</sup> However, the most likely explanation in this case is the contribution of the individual benzoate c.d. which arises from the interaction of the c.t. transition moment of each group with induced moments in the A or D rings. As it is clear from Table 2 the individual contributions to the c.d. at 230 nm of the 2 $\alpha$ - and 17 $\beta$ -benzoate groups are both positive; this monobenzoate c.d. cannot be entirely ignored here, because the exciton c.d. of the 2,17-dibenzoates is relatively weak (see below). As a matter of fact the addition of the two mechanisms accounts fairly well for the cancellation of the negative band, and, on the other hand, for the enhancement of the positive band in the 2 $\alpha$ ,17 $\beta$ -epimers.

In the *cis* derivatives (1b)—(7b), the in-phase coupling generates a resulting electric transition moment  $\vec{\mu}$  which is perpendicular to the molecular plane, and parallel to the magnetic transition moment  $\vec{m}$  generated by the charge displacement (Figure 3). Thus we expect a positive-negative sequence of the c.d. signs, from high to low energy, in agreement with experimental results. In these *cis*-compounds the individual contributions of the 2 $\beta$ - and 17 $\beta$ -benzoate groups, having similar magnitudes and opposite signs, mutually cancel; as a consequence the c.d. spectra of (1b)—(7b) display nearly perfect exciton couplets.

The foregoing qualitative analysis is entirely confirmed by the semi-quantitative treatment of the degenerate coupled-oscillator mechanism. In the exciton approximation,<sup>7-9</sup> two isoenergetic transition point-dipoles  $\vec{\mu}_1$  and  $\vec{\mu}_2$  coulombically couple to give two rotational strengths  $R_+$  and  $R_-$  with equal magnitude and opposite signs [equation (I)] where  $R_+$  refers to the

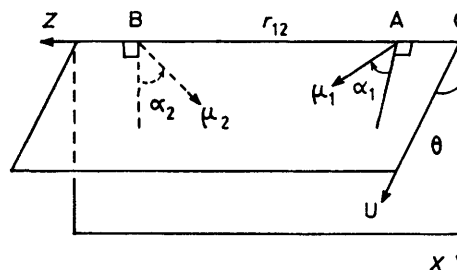
in-phase coupling mode of the two oscillators. In

$$R_+ = -\frac{\pi}{2} \tilde{\nu} [\vec{r}_{12} \cdot \vec{\mu}_1 \times \vec{\mu}_2] = -R_- \quad (\text{I})$$

equation (I),  $\vec{r}_{12}$  is the vector directed from the point-dipole  $\vec{\mu}_1$  to the point-dipole  $\vec{\mu}_2$ , and  $\tilde{\nu}$  is the wavenumber of the transition of the isolated chromophore. In principle, the wavenumber separation  $\Delta\tilde{\nu} = (\tilde{\nu}_+ - \tilde{\nu}_-)$  between the in-phase and out-of-phase modes depends on the interaction energy  $V$  of the two transition dipoles according to the relation  $\Delta\tilde{\nu} = 2V/hc$ . In practice  $V$  can be approximated by the dipole-dipole potential [equation (II)].

$$V = \frac{\vec{\mu}_1 \cdot \vec{\mu}_2}{r_{12}^3} - 3 \frac{(\vec{\mu}_2 \cdot \vec{r}_{12})(\vec{\mu}_1 \cdot \vec{r}_{12})}{r_{12}^5} \quad (\text{II})$$

The geometry of any dibenzoate can be defined as depicted in Scheme 2. Although the latter specifically



SCHEME 2

concerns the 2 $\beta$ ,17 $\beta$ -system, it can easily be adapted to any other case (including non-steroidal compounds). The point-dipoles  $\vec{\mu}_1$  and  $\vec{\mu}_2$  belong to the 17- and 2-benzoate groups, with their origins A and B being arbitrarily located in the vicinity of the carbon atoms bearing the carboxy-functions. Moreover, the exact position of the transition dipoles does not represent a critical problem here, in view of the large separation between the two chromophores. The  $z$  axis is defined as along  $\vec{AB}$  ( $= \vec{r}_{12}$ ), whereas vectors  $\vec{\mu}_1$  and  $\vec{\mu}_2$  are located in the  $uOz$  and  $xOz$  planes, respectively. The dihedral angle  $\widehat{xOu} = \theta$  (with  $0 \leq |\theta| \leq 180^\circ$ ) is also defined as being the torsion angle  $\mu_1 - A - B - \mu_2$ ; the latter is practically equivalent to the torsion angle  $O(17)-C(17)-C(2)-O(2)$ , the value and sign of which can be obtained from crystallographic data or Dreiding models. Finally, angles  $\alpha_1$  and  $\alpha_2$  define the tilt of the transition moment vectors with respect to the  $z$ -axis. Using these conventions, the rotational strengths deduced from equation (I) are given by equation (III) where  $D = \mu_1 \mu_2$ , the dipole strength of

$$R_+ = -\frac{\pi}{2} \tilde{\nu} r_{12} D \cos\alpha_1 \cos\alpha_2 \sin\theta = -R_- \quad (\text{III})$$

the c.t. transition in the isolated chromophore, experimentally accessible from the area of the corresponding u.v. band of a monobenzoate.<sup>8,12</sup> In the 2,17-dibenzoates studied here we have approximately  $\alpha_1 \sim -\alpha_2 = \alpha$  (the

same holds true for the 2,16-derivatives discussed below); equation (III) thus simplifies to (IV).

$$R_+ = -\frac{\pi}{2} \bar{\nu} r_{12} D \cos^2 \alpha \sin \theta = -R_- \quad (\text{IV})$$

The theoretical separation between the in-phase and out-of-phase modes, deduced from equation (II), is given by (V) which, when  $\alpha_1 \sim -\alpha_2 = \alpha$  reduces to (VI).

$$\Delta\bar{\nu} = \frac{2D}{hcr^3_{12}} (\cos\alpha_1 \cos\alpha_2 \cos\theta - 2 \sin\alpha_1 \sin\alpha_2) \quad (\text{V})$$

$$\Delta\bar{\nu} = \frac{2D}{hcr^3_{12}} (\cos^2\alpha \cos\theta + 2 \sin^2\alpha) \quad (\text{VI})$$

Numerical calculations were carried out specifically for the bis-*p*-methoxybenzoates (7a, and b), but the import of the result is valid for all other 2 $\alpha$ ,17 $\beta$ - and 2 $\beta$ ,17 $\beta$ -dibenzoates. The distance  $r_{12}$  is estimated from Dreiding models to *ca.*  $15 \times 10^{-8}$  cm for both *trans*- and *cis*-epimers. The angle  $\alpha$  is not critical; a value of  $45^\circ$ \* seems realistic.

separated by a small frequency interval, partially overlap.<sup>13</sup>

As a consequence the observed splitting between the exciton components becomes larger than the  $\Delta\bar{\nu}$  value expected from equation (VI). In effect, the experimental frequency interval in (7a and b), *ca.*  $2\,900\text{ cm}^{-1}$ , approaches the value of the u.v. band width at half maximum,  $\sigma\,3\,300\text{ cm}^{-1}$ . As a result of the partial band cancellation, the observed rotational strengths are reduced with respect to the values suggested from equation (IV) by the approximate ratio<sup>13</sup>  $\Delta\bar{\nu}/\sigma$ . This is effectively verified in the case of compounds (7a and b), for which the calculated rotational strengths [equation (IV)] corrected by the  $\Delta\bar{\nu}/\sigma$  ratio, are in fairly satisfactory agreement with the observed values obtained from the c.d. band areas (Table 4).

The signs of the rotational strengths predicted by equations (IV) and (VI) are consistent with those deduced from the above qualitative analysis, and with the

TABLE 4

Experimental and calculated rotational strengths for selected 2,16- and 2,17-bis-*p*-methoxybenzoates in the A-nor-5 $\alpha$ -androstane and -estrane series

Compound		$\theta$ ( $^\circ$ ) <sup>a</sup>	Rotational strengths ( $10^{-40}$ c.g.s. units)			
			Measured		Calc. <sup>b, c</sup> $R_-$	$\Delta\bar{\nu}$ <sup>c, e</sup>
			$R_+$	$R_-$		
(7a)	2 $\alpha$ ,17 $\beta$	+122	-0.6	+34	+16	+55
(7b)	2 $\beta$ ,17 $\beta$	-23	+8	-9	-15	+109
(11a)	2 $\beta$ ,17 $\alpha$	-132	+0.3	-15.7	-13	+50
(11b)	2 $\alpha$ ,17 $\alpha$	+13	-5.4	+7.4	+8.7	+110
(12)	2 $\beta$ ,16 $\beta$	+37	-4.4	+5	+19	+86
(13a)	2 $\beta$ ,16 $\alpha$	$\sim 180$	$(\sim +5)$ <sup>d</sup>		$\sim 0$	+31
(13b)	2 $\alpha$ ,16 $\alpha$	-10	+6.5	-0.9	-5.9	+92

<sup>a</sup> Mean values of the torsion angles estimated from X-ray atomic co-ordinates in 2 $\alpha$ ,17 $\alpha$ -bischloroethynyl-2 $\beta$ ,17 $\beta$ -dihydroxy-A-nor-5 $\alpha$ -estrane,<sup>5</sup> and in 2 $\alpha$ ,16 $\alpha$ -diethynyl-2 $\beta$ ,16 $\beta$ -dihydroxy-A-nor-5 $\alpha$ -androstane.<sup>4</sup> <sup>b</sup> Calculated values refer to  $R_-$  [equation (IV)]  $\times \Delta\bar{\nu}/\sigma$ , with  $\sigma\,3\,300\text{ cm}^{-1}$ . <sup>c</sup>  $\Delta\bar{\nu} = (\bar{\nu}_+ - \bar{\nu}_-)$  in  $\text{cm}^{-1}$  is calculated from equation (VI). <sup>d</sup> No exciton couplet observed. <sup>e</sup> The distance  $r_{12}$  was estimated to 15 and 16 Å in the 2,17- and 2,16-derivatives, respectively.

The dipole strength  $D = 2.5 \times 10^{-35}$  c.g.s. units is estimated from the u.v. spectrum of methyl *p*-methoxybenzoate.<sup>12</sup> The most important parameter is angle  $\theta$ , which defines the chirality of the dibenzoate interaction. Although the crystal-state conformation of an A-nor-5 $\alpha$ -androstane derivative<sup>4</sup> has been found to be slightly different from that of a related A-nor-5 $\alpha$ -estrane (which lacks the 10-methyl group),<sup>5</sup> the corresponding torsion angles calculated from the X-ray atomic co-ordinates do not appreciably differ ( $\pm 5^\circ$ ) in both series; angles  $\theta$  are estimated to *ca.*  $+122$  and  $-23^\circ$ , in (7a and b), respectively. Alternatively, Dreiding models afford the correct signs and relatively accurate values of  $\theta$ .

Using these numerical data, the frequency intervals,  $\Delta\bar{\nu}$ , expected from equation (VI), are calculated as  $+55$  and  $+109\text{ cm}^{-1}$  for (7a and b), respectively. The positive signs indicate that the in-phase component is found at high energy, as suggested above on a qualitative basis. Owing to the large distance  $r_{12}$  between the two interacting groups, the values of  $\Delta\bar{\nu}$  are small (weak coupling); in such cases the two oppositely signed c.d. bands, being

\*  $1^\circ = (\pi/180)$  rad.

observed c.d. spectra. Namely, a negative torsion angle  $\theta$  generates a negative c.d. for the lower energy component of the exciton couplet, in accordance with the 'dibenzoate chirality rule'.<sup>7</sup>

The same treatment holds for the 2,17 $\alpha$ -, 2,16 $\alpha$ -, and 2,16 $\beta$ -bis-*p*-methoxybenzoate derivatives (11)–(13) whose c.d. spectra are reported in Table 3 and Figure 4. The observed and predicted c.d. signs agree, and the calculated rotational strengths have a relatively correct magnitude (Table 4). Interestingly, the 2 $\beta$ - and 16 $\alpha$ -groups in (13a) are antiparallel, hence  $\theta = 180^\circ$ , and the exciton c.d. is expected to vanish; the observed c.d. spectrum actually exhibits a relatively weak and flat band in the 230–260 nm region, which probably represents the sum of the individual c.d. contributions of the 2- and 16-groups.

It may seem surprising that, in spite of the large separation between the 2- and 17- (or 16-) groups, the c.d. of these compounds is due principally to the coulombic coupling of the benzoate c.t. transition moments. To our knowledge the so-called 'dibenzoate chirality method' which is based upon the exciton mechanism

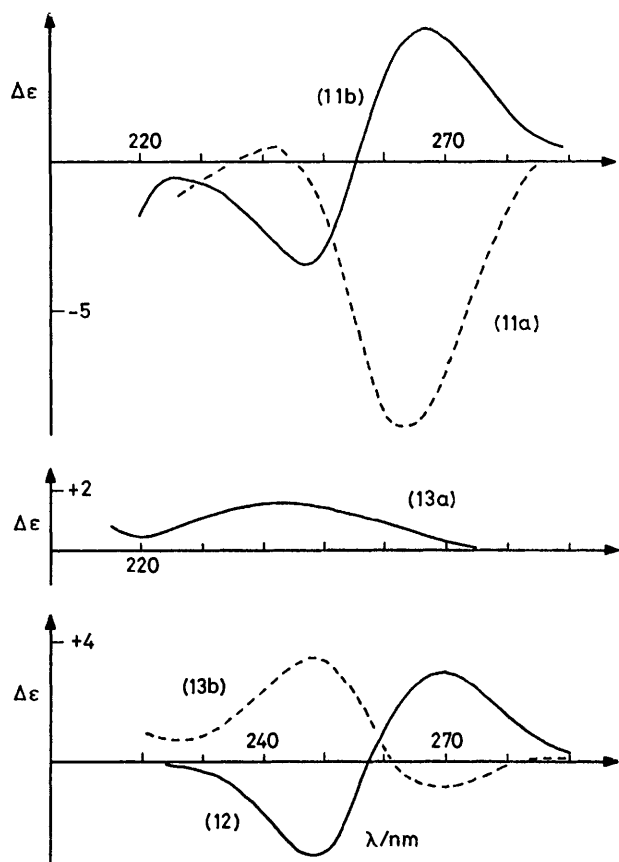


FIGURE 4 C.d. spectra of various 2,17- and 2,16-bis-*p*-methoxybenzoates

has only been employed for stereochemical assignments in 1,2-, 1,3-, and 1,4-diols (*e.g.*, 5 $\alpha$ -cholestane 3 $\beta$ ,6 $\beta$ -dibenzoate).<sup>7</sup> The present experimental findings and calculations confirm that the same mechanism holds for more remote dibenzoate systems, thus allowing easy and safe configurational determinations of remote hydroxy-groups.

#### EXPERIMENTAL

The c.d. and u.v. spectra were recorded on a Jouan Dichrograph II instrument and on a Perkin-Elmer 554 spectrophotometer, respectively. M.p.s were taken on a Kofler Hotbench apparatus and rotations were measured on a Perkin-Elmer 241 automatic spectropolarimeter. <sup>1</sup>H N.m.r. and i.r. spectra were recorded on Perkin-Elmer R32 and Perkin-Elmer 297 spectrometers.

The dipole strength of the *p*-methoxybenzoate transition at 255 nm was experimentally obtained from the u.v. spectrum of methyl *p*-methoxybenzoate (in ethanol) by using the integral  $D \sim 91.8 \times 10^{-40} 1/\lambda_{\max} \int \epsilon d\lambda$  (c.g.s. units).

Experimental rotatory strengths were obtained similarly from the c.d. band areas, according to the relationship  $R \sim 22.9 \cdot 10^{-40} 1/\lambda_{\max} \int \Delta \epsilon d\lambda$  (c.g.s. units).

**Preparation of the Benzoate and *p*-Methoxybenzoate Derivatives.**—The previously described<sup>2-6</sup> steroidal alcohols and excess of benzoyl or *p*-methoxybenzoyl chloride were allowed to react in dry pyridine at room temperature overnight. After the usual work-up, the isolated crude esters were purified by t.l.c. on silica gel, using either pure dichloromethane or a mixture of cyclohexane–ethyl acetate (7 : 3 v/v) as eluant. With the exception of (9) and (11a), the compounds were finally recrystallized from ethanol; their m.p.s and specific rotations are assembled in Tables 1–3. All compounds gave <sup>1</sup>H n.m.r. and i.r. spectra consistent with their structures.

**Elemental Analyses.**—Compounds (1), (5), and (8)–(10) have been described; <sup>2-6</sup> compounds (4), (11), and (13) were not submitted to combustion analysis in view of their scarcity. (2a), Found: C, 78.7; H, 7.5. (2b), Found: C, 79.0; H, 7.6. C<sub>31</sub>H<sub>36</sub>O<sub>4</sub> requires C, 78.8; H, 7.7%. (3b), Found: C, 78.7; H, 7.9. C<sub>32</sub>H<sub>38</sub>O<sub>4</sub> requires C, 79.0; H, 7.9%. (7a), Found: C, 74.5; H, 7.4. (7b), Found: C, 74.6; H, 7.7. C<sub>34</sub>H<sub>42</sub>O<sub>6</sub> requires C, 74.7; H, 7.7%. (12), Found: C, 77.0; H, 7.7. C<sub>38</sub>H<sub>42</sub>O<sub>6</sub> requires C, 76.7; H, 7.1%.

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