174. *Optical Rotatory Dispersion. Part I. 17- and 20-Monohydroxy-steroids and their Derivatives.*

By P. M. Jones and W. Klyne.

The rotatory dispersion curves of some steroid hydrocarbons and complete series of 17- and 20-monosubstituted steroids have been determined. The data have been examined in different ways in order to find the most appropriate way of dealing with plain dispersion curves for structural purposes.

It is suggested that the value of the molecular rotation at 300 mμ is of more use than the value at the D line, and that elaborate mathematical treatment of the curves is unprofitable.

The recent introduction of a commercial spectropolarimeter by O. C. Rudolph & Sons, Caldwell, N.J.,[1,2] has made it possible for organic chemists to measure optical rotatory dispersion curves (from 700 to 270 mμ) as a routine operation, and to use them as an aid in structural work. The only extensive studies made hitherto with this new tool are those of Djerassi and his colleagues (for reviews see refs. 3 and 4); they concentrated attention on ketones which give very characteristic Cotton-effect curves on account of the weak carbonyl absorption band at about 300 mμ (for nomenclature see ref. 5).

Compounds which do not absorb light specifically within the spectral range studied do not show Cotton effects, but have plain curves rising or falling more or less steeply towards shorter wavelengths. Extensive and careful studies were carried out by earlier workers using tedious photographic methods (for summaries see Lowry,[6] Levene and Rothen,[7] and Klyne [4]), with the aim of fitting equations of the Drude type to the curves. Similar attempts were made by Djerassi *et al.* in their first studies on rotatory dispersion,[8] but these were soon abandoned because the amount of structural information gained did not warrant the labour.

We felt it worth while examining a series of simple non-ketonic steroids in order to find the best ways of using rotatory dispersion curves as an empirical tool in structural and stereochemical studies with non-absorbing compounds. The successful application of " monochromatic " molecular rotation measurements (usually for the sodium D line at 589 mμ; for reviews see ref. 9) led us to believe that " polychromatic " rotation measurements could hardly fail to give more information.

This paper describes the results obtained with complete isomeric series of 17- and

[1] Rudolph, *J. Opt. Soc. Amer.*, 1955, **45**, 50.

[2] Rudolph, *Proc. Instr. Soc. Amer.*, 1956, Paper 56–3–1.

[3] Djerassi, *Bull. Soc. chim. France*, 1957, 741; *Record Chem. Progr.*, 1959, **20**, 101.

[4] Klyne, in " Newer Methods of Organic Chemistry," ed. Raphael, *Interscience Publ. Inc.*, New York, 1959.

[5] Djerassi and Klyne, *Proc. Chem. Soc.*, 1957, 55.

[6] Lowry, " Optical Rotatory Power," Longmans Green, London, 1935.

[7] Leven and Rothen in " Organic Chemistry," ed. Gilman, 1st edn., chap. 21, Wiley, New York, 1938.

[8] Djerassi *et al.*, *J. Amer. Chem. Soc.*, 1955, **77**, 4354, 4359, 4364.

[9] Mills and Klyne, *Progr. Stereochem.*, 1954, **1**, 177; Klyne in " Determination of Organic Structures by Physical Methods," ed. Braude and Nachod, Academic Press, New York, 1955.

20-monohydroxy-steroids and their acetates and benzoates, and also with some steroid hydrocarbons. A study of steroids carrying single substituents at positions in the A and the B ring, especially at $C_{(3)}$, is being carried out jointly with Professor C. W. Shoppee, F.R.S. (Sydney), and Dr. G. H. R. Summers (Swansea).

After this paper was submitted for publication, two other contributions on dispersion curves of non-absorbing compounds appeared (Mateos and Cram,[10] Lyle [11]).

Units and Symbols.—Wavelength (λ) is in mμ. Molecular rotation, $[\phi] = \alpha \times$ mol. wt./100.

The symbol $[\phi]$ is used in preference to $[M]$ because (*a*) angles are generally indicated by small Greek letters, (*b*) $[M]$ is used for other quantities. The use of $[\phi]$ was suggested to one of us by the late Dr. W. Moffitt (Harvard), and is included in proposals at present under consideration by the Commission of Molecular Spectroscopy of I.U.P.A.C.

RESULTS

All compounds were measured in methanol solution from 600 to 300 mμ (some down to 270 mμ); all the curves were plain curves,[5] and with few exceptions the sign of the rotation did not change within the range measured. Plain curves are to be expected since the hydroxy- and acetoxy-compounds have no absorption bands above 200 mμ. Our results (see p. 874) show that, although the benzoates have an absorption band at about 270 mμ, this is not optically active.

TABLE 1. *Rotatory dispersion data for steroid hydrocarbons.*

Curves measured in methanol–chloroform (80 : 20 v/v) from 600 to 280 mμ; concn. 4 mg./c.c. for androstanes, 2 mg./c.c. for pregnanes and cholestanes. All curves are plain.

Values given are molecular rotation $[\phi]$ * at 600, 500, and 300 mμ (in that order).

	5α-Series	5β-Series
Androstane	+5, 10, 40	+5, 5, −10 †
Pregnane	+55, 75, 280	+45, 65, 210
Cholestane	+100, 150, 550	+110, 160, 530

* Degree signs are omitted. † None of the values for 5β-androstane is significantly different from zero.

TABLE 2. *Rotatory dispersion data for* 17- *and* 20-*monosubstituted steroids.*

Curves were measured in methanol from 600 to 300 mμ. All are plain curves and do not change sign, except that marked *.

Values given are molecular rotations $[\phi]$ † at 600, 500, and 300 mμ (in that order).

	17- or 20-Substituent		
	OH	OAc	OBz
5α-Androstan-17α-ol	−25, 45, 150	+10, 10, 80	−240, 310, 1270
,, -17β-ol	+30, 50, 140	+150, 60, −380 *	+210, 310, 1710
5α-Pregnan-20α-ol	+25, 50, 280	+25, 65, 160	+100, 240, 1120
,, -20β-ol	+20, 40, 150	+180, 210, 890	−110, 180, 870

* $[\phi]$ is 0 at 410 mμ. † Degree signs are omitted.

Table 1 gives the molecular rotations at 600 mμ (for practical purposes this is the same as the classical D line rotation at 589 mμ), 500 mμ, and 300 mμ, for six steroid hydrocarbons, and the 5α- and 5β-isomers of androstane, pregnane, and cholestane, which represent base lines for many calculations in these series.

Table 2 gives similar data for the 17- and 20-monosubstituted steroids. Representative dispersion curves are shown in Fig. 1.

Graphical Analysis.—Table 3 and Fig. 2 show the results of a simple analysis of the data in which $1/[\phi]$ is plotted against λ^2. Compounds which give a straight-line plot when so treated are those which follow a single-term Drude equation (1) (cf. refs. 6 and 12) within the wavelength range studied.

$$[\phi] = A/(\lambda^2 - \lambda_0^2) \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (1)$$

where A is a constant and λ_0 is the characteristic wavelength.

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[10] Mateos and Cram, *J. Amer. Chem. Soc.*, 1959, **81**, 2756.

[11] Lyle, Abs. 136th Meeting Amer. Chem. Soc., 1959, p. 71P.

[12] Drude, " Lehrbuch der Optik," 2nd edn., Hirzel, Leipzig, 1906.

TABLE 3. *Plots of* $1/[\phi]$ *against* λ^2; *intercepts and slopes.*

These are the *apparent* λ_0 and A values for one-term Drude equations.

	Apparent λ_0 (mμ)	10^7A		Apparent λ_0 (mμ)	10^7A
5α-Androstane	204	+0·17	5α-Androstan-17α-OAc	158	+0·54
5β- ,, *	—	—	,, 17β-OAc * ...	—	—
5α-Pregnane	167	+1·6	5α-Pregnan-20α-OAc	134	+1·2
5β- ,, ...	135	+1·5	,, 20β-OAc	205	+4·4
5α-Cholestane	179	+3·1	5α-Androstan-17α-OBz	212	−6·2
5β- ,, ...	148	+3·5	,, 17β-OBz	220	+6·0
5α-Androstan-17α-OH	158	−1·0	5α-Pregnan-20α-OBz	214	+5·2
,, 17β-OH	118	+1·1	- ,, 20β-OBz	219	−3·4
5α-Pregnan-20α-OH	205	+1·3			
,, 20β-OH	190	+0·8			

* Values cannot be calculated as $[\phi]$ changes sign. † λ_0, 234 mμ in dioxan (Djerassi *et al.*[8]).

The phrase " within the wavelength range studied " is emphasized, because in many classical studies much labour was given to calculation over one range of wavelengths. These results then had to be discarded after a few years when measurements over a wider spectral range showed that the first calculations were inadequate.

FIG. 1. *Rotatory dispersion curves of* 17-*substituted* 5α-*androstanes.* *A*, 17α-OH; *B*, 17β-OH; *C*, 17α-OAc; *D*, 17β-OAc; *E*, 17α-OBz; *F*, 17β-OBz.

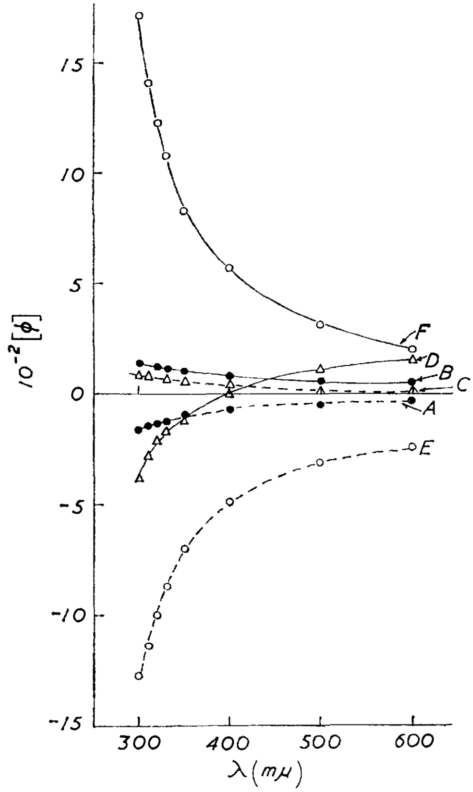
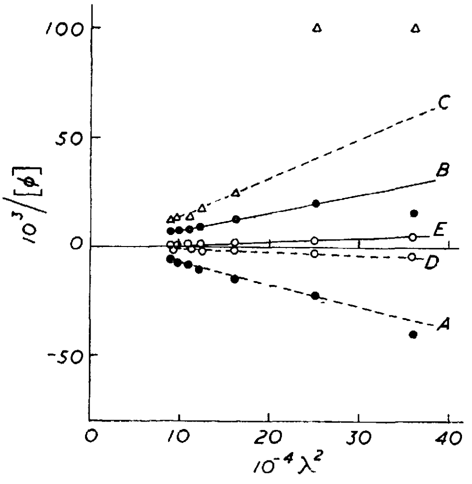


FIG. 2. *Drude plots for rotations of* 17α-*substituted* 5α-*androstanes*; $1/[\phi]$ *plotted against* λ^2. *A*, 17α-OH; *B*, 17β-OH; *C*, 17α-OAc; *D*, 17α-OBz; *E*, 17β-OBz.



The values of λ_0 obtained by the simple method of plotting described above are of two kinds: (i) those which lie at or near the maximum of an absorption band [$\lambda_{\text{max.}}$ (abs.)] and (ii) those which are not thus related to an absorption band (cf. the discussion by Balfe [13]). For compounds of the first type the single-term Drude equation has a real physical meaning;

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[13] Balfe, *J.*, 1950, 1871.

it expresses the fact that the dispersion curve over the given spectral range is essentially determined by the nearest optically active absorption band. In these cases the Drude constant A is a true characteristic of the compound, or of a specific function (say the benzoyloxy-group) in a particular stereochemical environment. For compounds of the second type, the single-term equation has no physical meaning; it is presumably a fortuitous simplification of a two-term or three-term equation. The above treatment represents only the first stage of the analysis proposed by Heller.[14]

For many compounds it was possible to fit a straight line to the Drude plot by eye. The slopes and intercepts of these lines gave *apparent* values of A and λ. In other cases where the points were widely scattered a mathematical analysis [14] was used to give the best-fitting line. The slope and intercept of this calculated line gave no more information than one fitted by eye.

Benzoates. These have absorption bands at 273 and 230 mμ (log $\varepsilon_{\text{max.}}$ approx. 3 and 4 respectively). The plots of $1/[\phi]$ against λ^2 give satisfactory lines * with values of λ_0 at 210—220 mμ, corresponding to the stronger absorption band. The A values in the Drude equation (slope of the λ^2–$1/[\phi]$ curves) are then seen to be structural characteristics of the benzoate group in various positions. The weak absorption band at 273 mμ appears to be optically inactive.

None of the other compounds studied has absorption bands except in the far-ultraviolet region (about 180 mμ).

Hydrocarbons. All of these (except 5β-androstane) give satisfactory straight line plots of $1/[\phi]$ against λ^2. The λ_0 values for four compounds (5α- and 5β-pregnane; 5α- and 5β-cholestane) fall between 140 and 180 mμ, similar to values obtained for simple hydrocarbons (cf. refs. 7 and 15).

Alcohols and acetates. Most of these also give satisfactory straight-line plots, but the apparent λ_0 values range from 115 to 205 mμ. The far-ultraviolet absorption bands are at 180 mμ; the apparent λ_0 values therefore have no physical meaning.

These results (except for the benzoates) confirm the opinion expressed by Djerassi *et al.*[8] that for many structural studies the calculation of Drude equations is not worth the labour involved.

Other simple methods of presenting data. We have tested several different ways of presenting rotatory-dispersion data for the plain curves discussed in this paper, including (*a*) the ratio $[\phi]_{300} : [\phi]_{500}$ (a modification of the dispersion ratio commonly used in classical work), (*b*) the difference $[\phi]_{300} - [\phi]_{350}$ (a measure of the slope of the curve over the stated range of wavelengths), and (*c*) the relative slope $2([\phi]_{300} - [\phi]_{350})/([\phi]_{300} + [\phi]_{350})$ (for details see Jones [16]).

For the small range of compounds considered here none of these measures seems to be of any greater utility than the value of $[\phi]$ at a convenient short wavelength, *e.g.*, $[\phi]_{300}$; compounds containing other functional groups should be considered before any general conclusions can be drawn (cf. Lyle [11]).

Contributions of Substituents: $\Delta[\phi]$ *Values.*—For many structural purposes it is necessary to calculate the contributions of substituents to the molecular rotation; the contribution of a substituent ($\Delta[\phi]$ — X) is ($[\phi]$ for a compound *with* the substituent) *minus* ($[\phi]$ for the corresponding compound *without* the substituent). This definition is similar to that given for "monochromatic" rotation differences [ΔM_{D} values in earlier studies (cf. Barton and Klyne [17])].

For 17-substituents in the androstane series the $\Delta[\phi]$ values can be taken as equal to the molecular rotations of the 17-monosubstituted compounds, since the $[\phi]$ values for 5α-androstane itself are practically zero. In the 20-substituted pregnanes, however, subtraction of the $[\phi]$ values for 5α-pregnane (the "background") is necessary (Table 4)—although this process makes no significant difference to the large $[\phi]$ values for the 20α- and 20β-benzoates. The Δ values for the 20α- and 20β-hydroxyl substituents are of interest; the dispersion curves of the two hydroxy-compounds are both plain positive, as is that for the hydrocarbon 5α-pregnane. The curve for the 20α-hydroxy-compound is almost identical with that for the hydrocarbon within the limits of experimental error; that for the 20β-hydroxy-compound lies *below* that for the hydrocarbon. The $\Delta\phi$ curve for 20β-OH is therefore a negative curve.

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* Some values at 600 mμ are anomalous, but this is presumably due to experimental error (see p. 876).

[14] Heller, *J. Phys. Chem.*, 1958, **62**, 1569.
[15] Levene and Rothen, *J. Org. Chem.*, 1936, **1**, 76; Kenyon and Pratt, *J.*, 1939, 633.
[16] Jones, M.Sc. Thesis, London, 1959.
[17] Barton and Klyne, *Chem. and Ind.*, 1948, 755.

TABLE 4. $\Delta[\phi]$ *Values for 20-substituents.*

$\Delta[\phi] - \mathrm{X} = [\phi]$ (compound R–X) *minus* $[\phi]$ (compound R–H).

Values are molecular-rotation contributions at 600, 500, and 300 mμ (in that order).

Series	$\Delta[\phi]$ — OH	$\Delta[\phi]$ — OAc	$\Delta[\phi]$ — OBz
20α-	−30, 25, 0	−30, 10, 120	+45, 165, 800
20β-	−35, 35, 130	+125, 135, 610	−165, 260, 1150

Drude Plots for Contributions of Substituents.—The simple Drude treatment was applied to the contributions of substituents in two ways:

(1) The observed molecular rotation of the hydrocarbon at each individual wavelength was subtracted from that of the substituted compound, giving a series of $\Delta[\phi]$ values (Table 4). A new Drude plot was made of λ^2 against $1/\Delta[\phi]$, the best straight line was drawn through the points, and its slope A' and intercept λ_0' were measured. (A' may be called the "differential slope" for the substituent.)

(2) The slope (given by the Drude constant A) of the hydrocarbon was subtracted from that of the substituted compound in each case. This gave the "slope difference," called ΔA, for the contribution of X in the compound (R–X):

$$\Delta A(\mathrm{X}) = A(\mathrm{R{-}X}) - A(\mathrm{R{-}H})$$

The results of these two treatments are summarized in Table 5.

TABLE 5. *Apparent* λ_0 *and A values for the contributions of functional groups in 20-substituted 5α-pregnanes.*

Values in columns (1) and (2) are calculated from the $\Delta[\phi]$ values for the substituents (cf. Table 4). The ΔA values in column (3) are obtained by subtracting the A value for 5α-pregnane itself (+1·6) from the A values of the substituted compounds.

Subst.	(1) λ_0' (mμ)	(2) $10^7A'$	(3) $10^7\Delta A$	Subst.	(1) λ_0' (mμ)	(2) $10^7A'$	(3) $10^7\Delta A$
20α-OH	—*	—*	−0·3	20β-OAc	210	+2·9	+2·8
20β-OH	200	−0·62	−0·8	20α-OBz	205	+3·9	+3·6
20α-OAc	—*	—*	−0·4	20β-OBz	205	−5·4	−5·0

* Values of $\Delta[\phi]$ are so irregular that λ_0' and A' cannot be calculated.

EXPERIMENTAL

Rotations.—Optical rotations were determined with a Rudolph photoelectric spectropolarimeter [1] (model 200) fitted with an oscillating polariser (model 200A).[2] A Unicam SP.500 spectrophotometer (with the cell unit removed) was used as monochromator, and a Siemens xenon arc (375 w, A.C., type XC) as source of illumination. The wavelength calibration of the monochromator was checked with a mercury-arc lamp. Symmetrical angle setting, 2°; slit-width, 2 mm. throughout.

The tube for the solution was a centre-filling tube, 1 dm. long, of capacity approx. 3 c.c. The solvent was methanol and the concentration approx. 1 mg./c.c., unless otherwise stated. Temperatures were 18—21°.

A series of control readings with methanol were taken before and after each set of observations with solutions. Readings were made in duplicate by the method of symmetrical angles at 600, 500, 400, 350, 330, 320, 310, and 300 mμ (for some compounds also at 290, 280, and 270 mμ). Duplicate readings generally agreed within 0·002°.

The time required for a set of readings in duplicate was approx. 30 min.; to this must be added 15 min., during which the tube was allowed to lie in the polarimeter to come to the ambient temperature.

Precision of Measurements.—Replicate measurements at four wavelengths were made with five separate portions of each of two steroid solutions for the purpose of estimating the precision of the method. A representative set of observations is given in Table 6.

The standard deviation of a single observation (α) (in 0·001°) was 2·2 (39 measurements). The standard deviation of a single measurement of the molecular rotation (ϕ) of a compound of molecular weight 400 was therefore 9. Expressed in non-statistical language, the scatter of individual observations was generally within ±0·005° of the mean, and therefore the scatter of calculated molecular rotations was within ±20 of the mean (usually less). For the sake of convenience, all results for ϕ in the Tables are rounded off to the nearest 10°.

The values for $[\phi]$ at 600 mμ are probably less *accurate* than those at lower wavelengths. The observed rotations (α) are small and the percentage errors are therefore great. The values at 500 mμ are more reliable because, although the observed rotations are still small, the xenon arc emits more light, and the photo-tube is more sensitive, at 500 mμ than at 600 mμ. The unreliability of the values at 600 mμ was first suspected from the fact that on many Drude curves (Table 3 and Fig. 2) the points for 600 mμ diverge widely from the straight-line plot covering the lower wavelengths.

Compounds.—These were all made by standard methods from materials generously supplied for the M.R.C. Steroid Reference Collection by the pharmaceutical industry.

The m. p. (corrected) and molecular rotations $[\phi]$ in $CHCl_3$ (measured with a visual polarimeter) are listed below, in that order. Previous references to most compounds are given in Elsevier's Encyclopædia[18] and in the Table of steroid rotations compiled by Mathieu and Petit.[19]

TABLE 6. *Precision of measurements with polarimeter.*

5α-Androstan-17β-ol (1 mg./c.c.) in methanol–chloroform (4 : 1, v/v); 1 dm. tube (all readings positive).

λ (mμ)	Observed readings (α) (− blank) in 0·001°	Mean
600	5, 4, 6, 12, 10	7
500	17, 16, 19, 20, 20	18
400	29, 29, 28, 28, 28	28
300	63, 63, 63, 63, 55	61

Androstane: 5α, 48—49°, +2°; 5β-, 80—81°, +4°.

Pregnane: 5α-, 84—85°, +52°; 5β-, 82—83°, +57°.

Cholestane: 5α-, 79—80°, +91°; 5β-, 71—72°, +95°.

5α-Androstane derivatives: 17α-OH, 152—153°, −25° {Shoppee *et al.*[20] give $[\phi]_D$ −20°, −16° (two samples); the value +37° given by Ruzicka *et al.*[21] involves presumably an error of sign}; 17β-OH, 170—171°, +33°; 17α-OAc, 97—98°, −9°; 17β-OAc, 81—82°, +6°; 17α-OBz, 116—117°, −122°; 17β-OBz, 163—165°, +195°.

5α-Pregnane derivatives: 20α-OH, 146—147°, +42°; 20β-OH, double m. p. 142—144°, 148—150°, $[\phi]$ +12°; 20α-OAc, 127°, +35°; 20β-OAc, 161—164°, +105°; 20α-OBz, 162—164°, +151°; 20β-OBz, 149—150°, −102°.

New compounds are: *5α-androstan-17α-yl benzoate* (Found: C, 82·1; H, 9·5. $C_{26}H_{36}O_2$ requires C, 82·1; H, 9·6%), and *5α-pregnan-20α-* (Found: C, 82·0; H, 9·8. $C_{28}H_{40}O_2$ requires C, 82·3; H, 9·9%) and *-20β-yl benzoate* (Found: C, 82·7; H, 9·6%) (the last two compounds were prepared by Dr. G. Baumgartner).

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POSTGRADUATE MEDICAL SCHOOL, DUCANE ROAD, LONDON, W.12.
MEDICAL RESEARCH COUNCIL,
STEROID REFERENCE COLLECTION.

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[18] Elsevier's "Encyclopædia of Organic Chemistry," Vol. XIV, 1940, and Supplement, 1954.

[19] Mathieu and Petit, "Pouvoir Rotatoire Naturel, Tome I, Stéroïdes," Masson, Paris, 1956.

[20] Shoppee, Lewis, and Elks, *Chem. and Ind.*, 1950, 454; Shoppee, Jenkins, and Summers, *J.*, 1958, 3048.

[21] Ruzicka and Muhr, *Helv. Chim. Acta*, 1944, **27**, 503.