1066. *Optical Rotatory Dispersion. Part II.*[1] *3-Monohydroxy-steroids, 3,17-Dihydroxy-steroids, and their Derivatives.*

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Rotatory-dispersion curves of complete series of isomeric androstan-3-ols and of androstane-3,17-diols and their derivatives have been determined.

The results for the 3,17-diols and their derivatives are compared with those calculated from the data for the corresponding 3- and 17-mono-substituted compounds; interaction of groups at positions 3 and 17 is assessed.

THE first paper of this series[1] described the determination of the rotatory-dispersion curves of complete series of 17- and 20-monosubstituted steroids. It was shown that non-ketonic substituents in a steroid molecule make a marked contribution to the rotatory-dispersion curve of the compound. These contributions vary, not only with the nature of the substituent, but also with the position and configuration of substitution in the nucleus.

This paper describes, first, the results obtained with two complete series of 5α- and 5β-androstan-3-ols, their acetates, and their benzoates. All the curves considered are plain (for nomenclature, see ref. 2) since the spectral range studied (600—300 mμ) does not include an absorption band.

We then describe the results obtained from rotatory-dispersion studies of all the isomeric 3,17-diols of both the 5α- and 5β-androstane series, together with their diacetates and dibenzoates. For a di- or poly-substituted steroid the total rotation at any given wavelength may be considered as the arithmetical sum of the rotation contributions of the steroid nucleus and of each substituent. For some compounds the " calculated " results obtained by simple addition of these contributions do not agree with the experimental results. These discrepancies must be due to long-range interaction of the substitutents.

Such interaction of substituents has been studied extensively for " monochromatic " molecular-rotation differences ($[M]_D$ values; for reviews see refs. 3 and 4). One of the objects of this work was to test how far the complete rotatory-dispersion curves for

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[1] Part I, Jones (now Marshall-Jones) and Klyne, *J.*, 1960, 871.

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

[3] Barton and Klyne, *Chem. and Ind.*, 1948, 755.

[4] Klyne, in " Determination of Organic Structures by Physical Methods," ed. Braude and Nachod, Academic Press, New York, 1955.

substituents are additive. In the case of 3,17-disubstituted steroids it was thought that, as the two substituents were at opposite ends of the molecule there would be little chance of reaction between them, and the dispersion curves should be simply additive.

" Calculated " dispersion curves were obtained for each compound in the series by adding together the curves of the corresponding monosubstituted compounds, and subtracting the " background " curve for the corresponding hydrocarbon. The subtraction was necessary, since otherwise the " background " would be included twice. Each " calculated " curve was then compared with the experimental curve for the same compound.

In Part I [1] we discussed the graphical analysis of the results for 17- and 20-monosubstituted steroids to obtain equations of the Drude type. A similar analysis of the results in the present paper was carried out, but since the general conclusion (as in Part I) was that for many structural studies the calculation of Drude equation constants is not worth the labour involved, we omit the details here (see ref. 5).

Units and Symbols.—Wavelength (λ) is in mμ. For molecular rotation we have

$$[\phi] = [\alpha] \times \text{mol. wt.}/100.$$

RESULTS

All compounds were studied in methanol solution from 600 to 300 mμ; all the curves were plain curves, and with one exception did not change sign within the range measured.

3- *and* 17-*Monosubstituted Compounds.*—Table 1 gives the molecular rotations at 600, 500, and 300 mμ for the isomeric androstan-3-ols and their acetates and benzoates. It is apparent that most of the differences between the curves for corresponding alcohols, acetates, and benzoates of the 3-mono-substituted series are relatively small, even at low wavelengths. This is in marked contrast to the curves for the 17- and 20-monosubstituted compounds,[1] for which the benzoate curves, in particular, diverge widely from those of the corresponding alcohols. The molecular rotations at 300 mμ for 17- and 20-monobenzoates are of the order of ±1000°; this difference is probably a reflection of the fact that in the 3-substituted compounds the CH·OBz group is separated from asymmetric centres on either side by methylene groups, whereas in the 17- and 20-substituted series it is immediately adjacent to an asymmetric centre (cf. Stokes and Bergmann [6]).

TABLE 1.

Rotatory dispersion data for 3- and 17-monosubstituted androstane derivatives.

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

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

Androstane deriv.	5α-Series	5β-Series	Androstane deriv.	5α-Series †	5β-Series
3α-OH	+50°, 60°, 190°	+50°, 90°, 310°	17α-OH	−25°, 45°, 150°	−80°, 90°, 270°
3β-OH	+25, 30, 70	+35, 40, 150	17β-OH	+30, 50, 140	+70, 70, 200
3α-OAc	+80, 95, 160	+140, 180, 150	17α-OAc	+10, 10, 80	Not available
3β-OAc	−35, 40, 220	−5, 5, 70	17β-OAc	+150, 60, −380	,, ,,
3α-OBz	−40, 40, 310	+60, 100, 350	17α-OBz	−240, 310, 1270	−190, 220, 1130
3β-OBz	−25, 5, +220 *	+110, 150, 420	17β-OBz	+210, 310, 1710	+180, 320, 1800

* [φ] is at 0° at 460 mμ. † Repeated from ref. 1 for comparison.

Table 1 also gives some data for 17-substituted androstanes (cf. ref. 1).

3,17-*Disubstituted Compounds.*—Table 2 gives the observed molecular rotations at 600, 500, and 300 mμ for the isomeric androstane-3,17-diols, their diacetates, and dibenzoates, and the corresponding calculated rotations. The rotation contributions of substituents at $C_{(3)}$ are relatively small (see above), whereas those of substituents at $C_{(17)}$ are large.[1] The sign and shape of the dispersion curves of the 3,17-disubstituted compounds are thus dominated by the

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[5] Jones, M.Sc. Thesis, London, 1959.

[6] Stokes and Bergmann, *J. Org. Chem.*, 1952, **17**, 1194.

TABLE 2.

Rotatory dispersion data for 3,17-disubstituted androstane derivatives.

For notes see Table 1.

	Observed			Calculated		
5α-Androstane-3α,17α-diol	−25°,	25°,	210°	+20°,	5°,	0°
,, -3α-17β- ,, ...	+85,	95,	250	+75,	100,	290
,, -3β,17α- ,, ...	−75,	100,	220	−5,	25,	120
,, -3β,17β- ,, ...	0,	+20,	125	+50,	70,	170
5β-Androstane-3α,17α- ,, ...	0,	−15,	65	−30,	0,	+40
,, -3α,17β- ,, ...	+95,	115,	295	+120,	160,	510
,, -3β,17α- ,, ...	−40,	70,	260	−45,	50,	120
,, -3β,17β- ,, ...	+50,	60,	170	+105,	110,	350
5α-Androstane-3α,17α-diol diacetate	+30,	40,	120	+85,	95,	200
,, -3α,17β- ,, ...	+95,	110,	320	+225,	145,	−260
,, -3β,17α- ,, ...	+20,	20,	20	−30,	40,	180
,, -3β,17β- ,, ...	−45,	60,	180	+110,	10,	−640
5β-Androstane-3α,17α- ,, ...	+120,	190,	680	+150,	190,	230
,, -3α,17β- ,, ...	+160,	260,	680	+290,	240,	−230
,, -3β,17α- ,, ...	+80,	110,	220	+5,	5,	10
,, -3β,17β- ,, ...	+100,	120,	260	+145,	55,	−450
5α-Androstane-3α,17α-diol dibenzoates	+110,	150,	680 *	−285,	360,	1620 *
,, -3α,17β- ,, ...	+390,	510,	2780	+165,	260,	1360
,, -3β,17α- ,, ...	−120,	170,	720	−270,	325,	1090
,, -3β,17β- ,, ...	+200,	320,	1660	+180,	295,	1890
5β-Androstane-3α,17α- ,, ...	+90,	170,	1460 *	−130,	120,	780 *
,, -3α,17β- ,, ...	+380,	710,	3980	+240,	420,	2150
,, -3β,17α- ,, ...	−160,	170,	780	−80,	70,	710
,, -3β,17β- ,, ...	+190,	300,	1460	+290,	470,	2220

* See text.

effects of the 17-substituents. As might have been expected, discrepancies between observed and calculated curves are often greater for compounds containing the bulkier and more polarisable acetate and benzoate groups than for the hydroxy-compounds.

Two compounds show such large differences between observed and calculated curves as to merit special attention; these are 5α- and 5β-androstane-3α,17α-diol dibenzoates. For both the observed curves are strongly positive but the calculated curves are strongly negative. The observed results were checked twice, and the identity of the 5β-dibenzoate (a new compound) was checked by hydrolysis to the known diol and by an alternative synthesis. 17α-Hydroxy-5β-androstan-3-one was converted into its benzoate, which was then reduced with sodium borohydride to 17α-benzoyloxy-5β-androstan-3α-ol. The dispersion curve of this monobenzoate was in good agreement with the calculated curve. This confirms the fact that no alteration in configuration at $C_{(17)}$ has taken place. The monobenzoate was finally benzoylated, giving material identical with the previous sample of dibenzoate (m. p., mixed m. p., and dispersion curve). It can only be suggested that these grossly anomalous results may be due to the dibenzoates taking up an abnormal conformation, *e.g.*, a boat form of ring A or some other flexible form intermediate between chair and boat such as the " twist " conformation proposed by Johnson *et al.*[7]

EXPERIMENTAL

Optical rotations were determined with a Rudolph photoelectric spectropolarimeter as described in Part I [1] (tube, 1 dm.; 18—22°; 1 mg./c.c.).

Compounds.—These were 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 [ϕ] of chloroform solutions (measured with a visual polarimeter) are listed below in that order. Previous references to most compounds are given in Elsevier's " Encyclopædia " [8] and by Mathieu and Petit.[9]

3-*Monosubstituted Compounds.*—5α-Androstane derivatives: 3α-OH, 146—148°, +6°; 3β-OH, 148—150°, +3°; 3α-OAc, 130—131°, +10°; 3β-OAc, 70—72°, −40° (Butenandt *et al.*[10]

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[7] Johnson, Baver, Margrave, Frisch, Dreger, and Hubbard, *J. Amer. Chem. Soc.*, 1961, **83**, 606.

[8] Elsevier's " Encyclopaedia of Organic Chemistry," Vol. XIV, 1940, and Supplement, Amsterdam, 1954.

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

[10] Butenandt, Poschmann, Failer, Schiedt, and Biekert, *Annalen*, 1951, **575**, 123.

give m. p. 87—88° for the unsolvated compound); 3α-OBz, 149—150°, −14°; 3β-OBz, 146—148°, −8°; 5β-Androstane derivatives: 3α-OH, 145—146°, +29° (Prelog *et al.*[11] give +19°); 3β-OH, 143—144°, +6°; 3α-OAc, 110—111°, +91°; 3β-OAc, gum, +7°; 3α-OBz, 105—106°, +73°; 3β-OBz, 170—172°, +36°.

New compounds are: 5α- * (Found: C, 77·6; H, 10·7. $C_{21}H_{34}O_2,\frac{1}{2}CH_3{\cdot}OH$ requires C, 77·2; H, 10·8%) and 5β-*androstan-3α-yl acetate* * (Found: C, 77·8; H, 10·9%); 5α-*androstan*-3α- (Found: C, 82·0; H, 9·8. $C_{26}H_{36}O_2$ requires C, 82·1; H, 9·55%) and -3β-*yl benzoate* (Found: C, 81·9; H, 9·7%); 5β-*androstan*-3α- (Found: C, 82·4; H, 9·2%) and -3β-*yl benzoate* (Found: C, 81·8; H, 9·25%).

3,17-*Disubstituted Compounds.*—5α-*Androstane derivatives.* Diols: 3α,17α-, 229—230°, −40°; 3α,17β-, 224—225°, +55°; 3β,17α-, 221—222°, −21°; 3β,17β-, 167—168°, +16°. Diacetates: 3α,17α-, gum, (sample lost); 3α,17β-, 161—162°, +64°; 3β,17α-, 145—146°, −42°; 3β,17β-, 127—128°, +4°. Dibenzoates: 3α,17α-, gum, +110°; 3α,17β-, 209—210°, +346°; 3β,17α-, 185—186°, −101°; 3β,17β-, 198—200°, +188°.

5β-*Androstane derivatives.* Diols: 3α,17α-, 227—228°, −7°; 3α,17β-, 233—235°, +73°; 3β,17α-, 216—217°, −35°; 3β,17β-, 150—153° and 165—166° (these appear to be different crystalline forms; cf. ref. 12), +49°. Diacetates: 3α,17α-, 75—76°, 0°; 3α,17β-, 123—124°, +137°; 3β,17α-, 159—160°, +1°; 3β,17β-, 112—113°, +21°. Dibenzoates: 3α,17α-, 213—214°, +105°; 3α,17β-, 163—164°, +462°; 3β,17α-, 186—188°, −107°; 3β,17β-, 147—148°, +196°.

New compounds are: 5β-*androstane*-3β,17α- (Found: C, 73·5; H, 9·6. $C_{23}H_{36}O_4$ requires C, 73·4; H, 9·60%), and 3β,17β-*diol diacetate* (Found: C, 73·2; H, 9·8%); 5α-*androstane*-3α,17β- (Found: C, 79·5; H, 7·6. $C_{33}H_{40}O_4$ requires C, 79·2; H, 8·05%), 3β,17α- (Found: C, 79·3; H, 8·0%), and -3β,17β-*diol dibenzoate* (Found: C, 79·1; H, 7·9%); 5β-*androstane*-3α,17α- (Found: C, 78·9; H, 7·9%), -3α,17β- (Found: C, 79·4; H, 8·0%), -3β,17α- (Found: C, 79·6; H, 8·35%), and -3β,17β-*diol dibenzoate* (Found: C, 79·1; H, 8·1%).

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* These compounds have not been obtained unsolvated; see Jones [5] for full discussion.

[11] Prelog, Ruzicka, Meister, and Wieland, *Helv. Chim. Acta*, 1945, **28**, 618.

[12] Fieser and Wei-Yuan Huang, *J. Amer. Chem. Soc.*, 1953, **75**, 4837.