[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

Optical Rotatory Dispersion Studies. I. The Androstane Series[1]

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A general experimental and theoretical introduction to rotatory dispersion in the steroid field is given. Detailed data are given for a series of ketones of the androstane series and certain rotatory dispersion features have been correlated with specific structural moieties, *viz.*, saturated 3-ketone and/or 17-ketone, Δ^1- and Δ^4-3,17-diketone.

Introduction

Measurements of optical rotatory dispersion have been carried out by various workers since the time of Biot,[2] who five years after his discovery of optical activity published some rough measurements of the optical rotation of quartz at the wave lengths corresponding to the limits between the seven simple colors. Dispersion measurements in the ultraviolet region of the spectrum were first carried out by Soret and Sarasin[3] using various spectral lines of a cadmium arc and a fluorescent screen. Subsequent improvements in instrumentation and experimental procedures have been reviewed completely by Heller.[4] Detailed rotatory dispersion measurements have been carried out with many simple organic compounds,[5] but cursory studies in the steroid series appear to have been limited to cholesterol[5a,6,7] and some of its derivatives and cortisone acetate.[7]

The development in recent years of photomultiplier tubes has made possible for the first time the construction of a spectropolarimeter capable of operating at any desired wave length within a certain range, which includes the visible and near ultraviolet regions of the spectrum, the rotation being determined directly without having to resort to photographic plates. This instrument (Rudolph Model 200 S-80) is commercially available[8] and its construction will be described in detail in another journal.[9]

These advances in instrumentation have encouraged us to undertake a systematic study of the rotatory dispersion of more complex organic structures and we have focused our attention initially on steroids. It was felt that in the steroid series—where so many closely related compounds are available and where a fused, polycyclic system with a contiguous chain of five to eight asymmetric carbon atoms can be found—relatively minor structural alterations might manifest themselves in observable rotatory dispersion changes. An attempt was made, therefore, to determine whether a correlation between certain features of rotatory dispersion curves and structural characteristics could be accomplished which would make available an additional tool for the characterization of these substances. A further reason for choosing steroids was that probably in no other field of organic chemistry has so extensive a correlation been made between structure and ultraviolet absorption[10] and such information is often required for the proper interpretation of rotatory dispersion curves. The results in the steroid series also might indicate the feasibility of extending such a systematic study to other classes of complex organic compounds (*e.g.*, triterpenes).

This first paper is limited to a general introduction of the subject, to a discussion of the experimental procedures employed in this and all subsequent studies from our laboratory, and to our results in the androstane series where the effect of conjugated and non-conjugated carbonyl groups upon rotatory dispersion was examined.

General Experimental Procedure

Instrument.—The Rudolph[8] photoelectric spectropolarimeter model 200S-80 consists of four components: Rudolph circular scale high precision polarimeter (model 80), a Beckman quartz monochromator, light sources (to be discussed below) and a Photovolt Multiplier Photometer (model 520-M) with interchangeable photomultiplier tubes for use in the visible (RCA IP21) and ultraviolet (RCA IP28) regions.

Operation.—A solution of the compound under investigation was made up in purified dioxane[11] and then introduced into a 1-dm. (3.5 mm. bore, total capacity less than 2 cc.) center-filled polarimeter tube with cemented-on fused quartz cover glasses (obtained from O. C. Rudolph[8]). This arrangement was necessary when working in the ultraviolet in order to avoid changes in stress birefringence caused by variations in the degree of tightening of the cover glasses of standard polarimeter tubes; furthermore, it eliminated any leakage over the course of the whole series of readings. The quartz cover glasses were carefully selected and tested for freedom from birefringence both before and after cementing. The tubes were fitted with a ground glass stopper and measurements always were taken with the tube

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[1] We should like to acknowledge the generous support of the National Science Foundation which made possible the participation of one of us (E.W.F.) as a predoctorate research fellow and which provided funds for the purchase of the spectropolarimeter.

[2] J. B. Biot, *Mem. Acad. Sci.*, **2**, 41 (1817).

[3] J. L. Soret and E. Sarasin, *Compt. rend.*, **95**, 636 (1882). The use of a photographic plate at the eye-piece of the polarimeter was introduced by P. Joubin, *Ann. chim. phys.*, **16**, 78 (1889).

[4] W. Heller in A. Weissberger's "Physical Methods of Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1949, 2nd edit., Vol. I, Part II, Chapter XXIII ("Polarimetry").

[5] (a) T. M. Lowry, "Optical Rotatory Power," Longmans, Green & Co., New York, N. Y., 1935; (b) P. A. Levene and A. Rothen in H. Gilman's "Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1938, first edit., Vol. II, chapter 21 ("Rotatory Dispersion").

[6] O. Lindenmayer, *J. prakt. Chem.*, [1], **90**, 323 (1863); L. Tschugaeff, *Z. physik. Chem.*, **76**, 469 (1911); M. G. Vavon and B. Jakubowicz, *Bull. soc. chim. France*, [4] **53**, 581 (1933).

[7] E. Brand, E. Washburn, B. F. Erlanger, E. Ellenbogen, J. Daniel, F. Lippmann and M. Scheu, THIS JOURNAL, **76**, 5037 (1954).

[8] O. C. Rudolph and Sons, Caldwell, N. J.

[9] H. Rudolph, *J. Opt. Soc. Am.*, to be published.

[10] L. Dorfman, *Chem. Revs.*, **53**, 47 (1953).

[11] Since it is essential that the same solvent be used for all of the compounds, dioxane and chloroform were the obvious choices since most steroids are soluble in them and these solvents do not show appreciable absorption in the spectral range studied. Chloroform would have been preferable, since most molecular rotation difference values in the steroid series are reported for this solvent, but considerable experimentation led us to reject it in favor of dioxane (purified according to L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, 2nd edit., p. 368) because of its higher boiling point. This proved to be a decided advantage since measurements on the same solution had to be carried out for a period of several hours and the rate of evaporation had to be kept at a minimum.

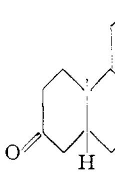
in the same location in the polarimeter trough (very close to the polarizer prism). Readings were taken in duplicate by the method of symmetrical angles[4,12] and blank readings (with pure dioxane) were performed daily at 650, 550, 450, and 350 $m\mu$. These did not differ significantly from each other and their mean value was subtracted from each sample reading to obtain the reported measurement. The zero point of the empty instrument also was checked daily.

The light source used for all experiments reported in this and the following papers was a glass-jacketed Sylvania K-100 concentrated arc Zirconium lamp. A quartz-jacketed Hanovia 10-C-1 Xenon compact arc lamp was employed occasionally, but its general use was prevented because of difficulties in our hands with the unsatisfactory light stability of this lamp. Of the two photomultiplier tubes attached to the instrument, the ultraviolet-sensitive tube (RCA IP28) was found to be satisfactory up to 700 $m\mu$ and hence was used exclusively throughout the spectral range covered. The diaphragm aperture was set at 3.0 mm. (*i.e.*, slightly smaller than the bore of the polarimeter tube) and the slit width of the Beckman monochromator was 0.1 mm. if this afforded sufficiently intense transmitted light. Otherwise, it was increased stepwise to 0.2, 0.5, 1.0 and 2.0 mm. as the transmitted light decreased in intensity.

Temperatures were recorded (see experimental results) for each run but no control was instituted, the fluctuations having been those encountered in ordinary room temperature in an isolated room employed only for this polarimetric study.

Frequency of Readings.—Typical wave lengths at which measurements were taken: 700, 650, 620, 589 (sodium D line), 550, 520–400 (in 20 $m\mu$ intervals) and 400–300 $m\mu$ (in 10 $m\mu$ intervals). In the region of "maxima" and "minima," readings were carried out at 2.5 $m\mu$ intervals, except for the 320–300 $m\mu$ region where this was done at 5 $m\mu$ intervals.

Discussion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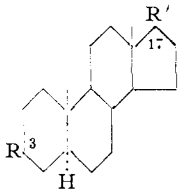
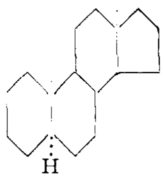


II, R = R' = O
III, R = H_2; R' = O
IV, R = O; R' = H_2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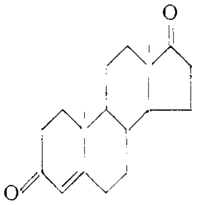
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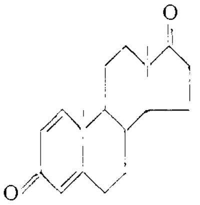
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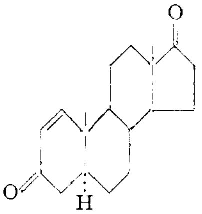
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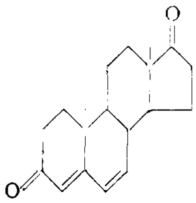
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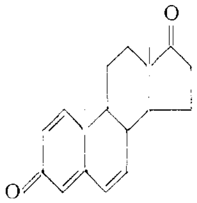
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A brief discussion of optical activity and optically active absorption bands seems necessary at this time in order to clarify the frame within which the results of this and succeeding papers will be considered.

The optical activity of a compound is due to the fact that it contains a chromophore which is so situated in the asymmetric environment of the rest of the molecule that it affects to a different extent the velocity of right and left circularly polarized light. A beam of plane-polarized light may be regarded as being made up of two such coherent components, which after passage through the optically active medium recombine to give again a plane-polarized beam. The resulting phase difference between these right and left circularly polarized components causes the plane of polarization to be rotated to an extent depending on the degree of asymmetry of the chromophore and on the proximity, in terms of wave length, of the absorption peak of this chromophore to the wave length of the incident polarized light. The extent of positive or negative rotation, therefore, will increase as measurements are taken from the infrared side of the spectrum to within the neighborhood of an optically active absorption band (which is usually situated in the ultraviolet in the type of steroids now under investigation). When measurements can be continued *through* the absorption band (*e.g.*, Fig. 3), the rotation will be found to rise rapidly to a sharp peak, then fall rapidly and rise to a similarly sharp peak of opposite sign. Beyond this point the rotation will decrease gradually as the wave length of the incident light recedes from that at the absorption peak of the chromophore. *This absorption peak of the chromophore is situated at the mean of the wave lengths at which the positive and negative peaks*[13] *of rotation occur.* The distance between the positive and negative peaks in terms of rotation can be taken as a measure of the degree of asymmetry of the chromophore in that it indicates the extent to which the latter contributes to the optical activity of the compound. In a molecule as complex as the steroids, the optical activity of the substance is due to more than one optically active chromophore and this is reflected in the shape of many of the rotatory dispersion curves described in this and the following two papers.[14,15]

The rotatory dispersion curve (Fig. 1)[16] of the completely unsubstituted reference compound, androstane (V), is unspectacular within the spectral range studied, as is to be expected of a saturated hydrocarbon which can have no chromophores except in the inaccessible, far ultraviolet below 200 $m\mu$. This curve represents the behavior of the unsubstituted steroid skeleton against the background of which our other results can be interpreted.

The introduction of a ketonic function at position 3, as in androstan-3-one (IV), produces a marked change. The dispersion curve (Fig. 1) rises to a sharp peak at 315 $m\mu$ ($[\alpha]$ +916°) and on extrapolation would cut the wave length axis (zero rotation) at about 295–300 $m\mu$, which is close to the ob-

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[12] J. Kenyon, *Nature*, **117**, 304 (1926).

[13] This explains why the terms *maxima* and *minima* used in ultraviolet absorption curves are unsatisfactory when applied to rotatory dispersion curves (see ref. 19).

[14] E. W. Foltz, A. E. Lippman and C. Djerassi, This Journal, **77**, 4359 (1955).

[15] A. E. Lippman, E. W. Foltz and C. Djerassi, *ibid.*, **77**, 4364 (1955).

[16] The Roman numerals of the curves correspond to those of the structural formulas given in the text of this paper.

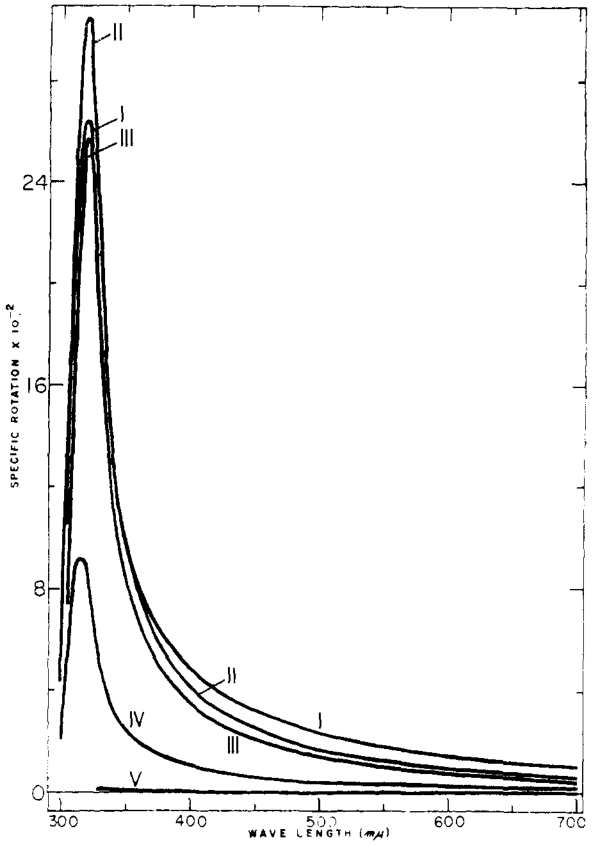

Fig. 1.—Rotatory dispersion curves of: etiocholane-3,17-dione (I), androstane-3,17-dione (II), androstan-17-one (III), androstan-3-one (IV) and androstane (V).

served[17] ultraviolet absorption maximum at 284–287 mμ. The shape of the curve indicates that it represents the passage through an optically active absorption band which must be ascribed to the 3-keto function. If measurements could have been carried out below 300 mμ, it would have been expected that a similar negative peak would have been reached at *ca.* 280 mμ.

The introduction of a single keto group in the five-membered ring as in androstan-17-one (III) causes a similar peak to occur in the dispersion curve (Fig. 1), which, however, is shifted toward longer wave length (320 mμ) and which is much more intense ([α] +2572°) than the corresponding one in androstan-3-one (IV). The curve intersects the zero line at 303 mμ which again is in reasonable agreement with the observed[17] ultraviolet absorption maximum at 294–297 mμ. We consider this small shift (315 mμ *vs.* 320 mμ) toward longer wave length more significant than any exact correspondence between the value obtained by extrapolation and that measured experimentally with the ultraviolet spectrophotometer, since the low intensity absorption spectra in this region are ill defined, with absorption maxima being only vaguely outlined against a background of general absorption. Qualitatively, the bathochromic shift is general for going from six-membered to five-membered ring ketones.[10,18] The curve (Fig. 1) of androstane-3,17-dione (II) appears largely governed by the presence of the 17-keto group since it shows the characteristic peak at 320 mμ intensified somewhat ([α] +3054° as compared to +2572° for III) by the added effect due to the 3-keto function. The curve of its 5β-isomer, etiocholane-3,17-dione (I), differs little from it, but exhibits generally higher rotation except near its peak. As can be seen from the above four ketones (I–IV), the C-17 keto group shows much greater activity and this might possibly be attributed to its greater proximity to an asymmetric center (at C-13); the asymmetric center (C-5) closest to the C-3 keto group is two carbon atoms away.

Introduction of one or more double bonds in conjugation with the 3-keto function results in more complicated rotatory dispersion curves (Figs. 2, 3) in which certain features can be related empirically with structural moieties. Thus Δ^4-androstene-3,17-dione (VI) shows a "maximum"[19] at 357.5 mμ and "minima"[19] at 367.5 and 355 mμ, the position of which can be related conclusively to the Δ^4-3-keto system as is supported amply in subsequent papers on similar compounds in the hormone[14] and cholestane[15] series. These "maxima" and "minima" define numerically the optically active absorption band (assigned to the Δ^4-3-keto function) at 362.5 mμ associated with a negative peak at 367.5 mμ and a positive one at 357.5 mμ.

The isomeric Δ^1-androstene-3,17-dione (VIII) exhibits a similar (though shifted) feature (Fig. 2) with a negative peak at 382.5 mμ and a positive peak at 370 mμ, corresponding to an optically active band (due to the Δ^1-3-keto system) at 376 mμ. The characteristic shape for this structural feature (compare cholestane series[15]) is defined by the "maximum" at 370 mμ and the "minima" at 382.5 and 367.5 mμ. The peak of rotation at 320 mμ, found in both compounds VI and VIII, and which is ascribed to the 17-keto chromophore (see above) is somewhat stronger in the present cases ([α] +3650° and +3816°) than in the saturated androstane-3,17-dione (II) ([α] +3054°). Three possibilities offer themselves as likely answers: (a) there remains a rotatory contribution at that wave length associated with the saturated 3-keto group; (b) the introduction of the conjugated double bond increases the asymmetry of the 17-keto group; (c) another and as yet unidentified factor enters into play. Our results with steroids which possess no additional keto group (testosterone,[14] Δ^4-cholesten-3-one[15]) seem to support the third hypothesis.

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[17] We have measured the low-intensity ultraviolet absorption of all of the ketones in dioxane solution in the region 280–370 mμ and the data are recorded in the Experimental section.

[18] G. Forster, R. Skrabal and J. Wagner, *Z. Elektrochem.*, **43**, 290 (1937).

[19] As pointed out earlier (ref. 13), the use of the terms *maxima* and *minima* appears undesirable in rotatory dispersion curves. When used in quotation marks in this and subsequent papers, this is simply done for the sake of convenience in order to define numerically the shape of the curve, since the latter is of striking importance and reproducibility in the empirical correlation of structure and *shape* of dispersion curve. "Maxima" and "minima" should not necessarily be considered synonymous with *negative* and *positive* peaks corresponding to an optically active absorption band. For instance, the broad "maximum" at 385 mμ (Fig. 2) of Δ^4-androstene-3,17-dione (VI) is not related to the positive peak of an optically active absorption band. Rather, it represents the positive partial rotation over the 400–700 mμ region now falling under the influence of a stronger negative partial rotation due to entry into the optically active absorption band at 362.5 mμ, the first peak of which is negative.

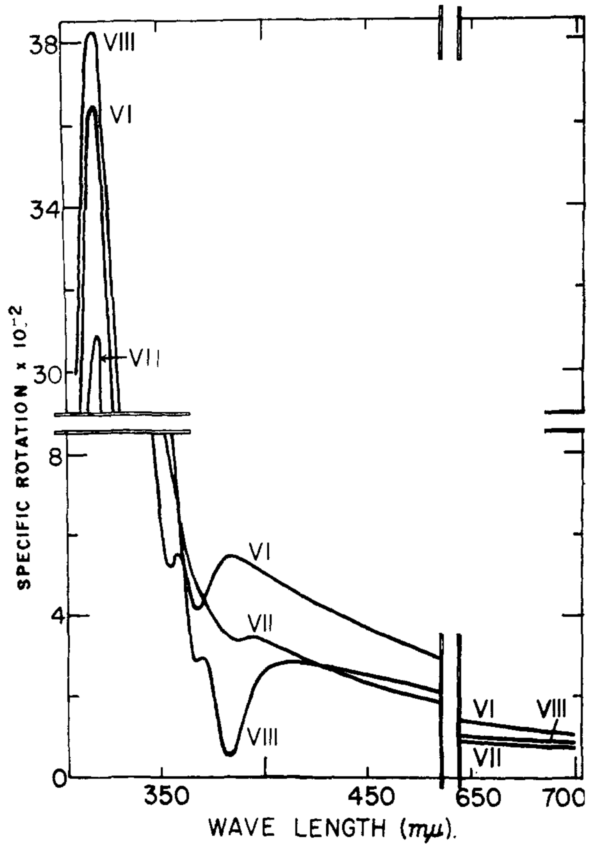

Fig. 2.—Rotatory dispersion curves of: Δ^4-androstene-3,17-dione (VI), $\Delta^{1,4}$-androstadiene-3,17-dione (VII) and Δ^1-androstene-3,17-dione (VIII).

The dispersion curve (Fig. 2) of $\Delta^{1,4}$-androstadiene-3,17-dione (VII) is not the arithmetic mean of that of Δ^1- and Δ^4-androstene-3,17-dione; the irregular nature in the 420–360 mμ region suggests that it represents the superimposition of several effects. The peak rotation ($[\alpha]$ +3087°) at 320 mμ is nearly identical with that of the saturated androstane-3,17-dione (II), *i.e.*, appreciably lower than the unsaturated diketones VI and VIII.

Of considerable interest are the dispersion curves (Fig. 3) of $\Delta^{4,6}$-androstadiene-3,17-dione (IX) and of $\Delta^{1,4,6}$-androstatriene-3,17-dione (X), since they illustrate well the shape of a rotatory dispersion curve on passage through an optically active absorption band; the very characteristic "maxima" and "minima" are listed in the experimental portion and both compounds exhibit two optically active absorption bands. The low intensity absorption spectra[17] of these two compounds are quite complicated; the $\Delta^{4,6}$-diene-dione IX has a broad maximum at 336–346 mμ and the $\Delta^{1,4,6}$-triene-dione X a maximum at 346–348 mμ, but in addition there are numerous shoulders and inflections in the region 370–390 mμ in the spectra of both substances. No obvious correlation between the absorption spectra and the rotatory dispersion curves of these two compounds can be made at this time other than to point out that the main optically active absorption band of the $\Delta^{4,6}$-derivative IX is at a lower wave length, 365 mμ (positive peak at 390 mμ, negative peak at 340 mμ) than that of the $\Delta^{1,4,6}$-triene X which occurs at 375 mμ (positive peak at 405 mμ, negative peak at 345 mμ).

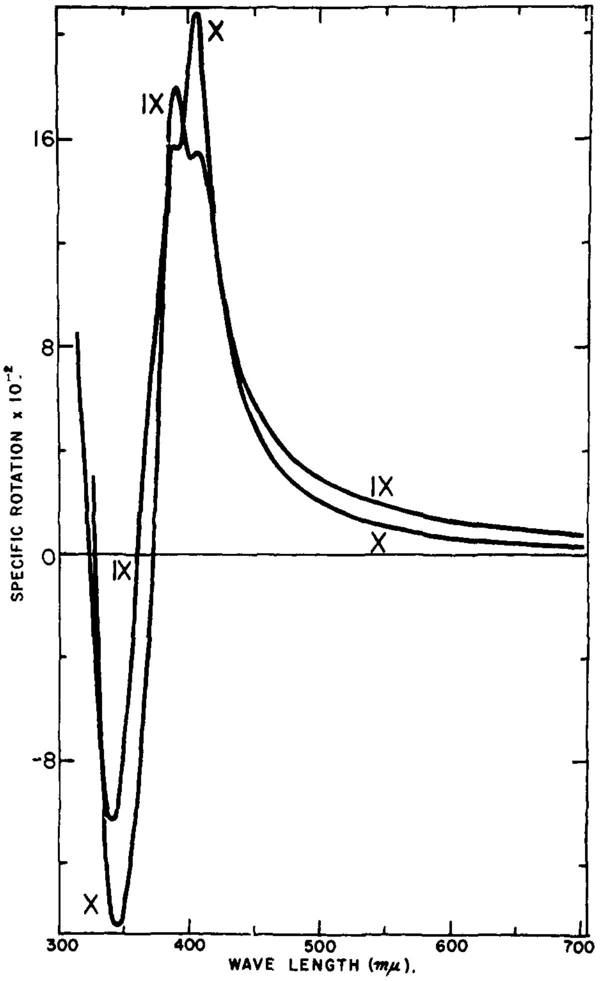

Fig. 3.—Rotatory dispersion curves of: $\Delta^{4,6}$-androstadiene-3,17-dione (IX) and $\Delta^{1,4,6}$-androstatriene-3,17-dione (X).

In summary, it can be stated that characteristic features in the dispersion curves can be assigned to isolated ketone functions (300–320 mμ region) and especially to unsaturated ketones where the 350–420 mμ region is particularly important since it includes typical features for each moiety.

Mathematical Results

The relationship between optical rotation and wave length *outside* the region of an optically active absorption band[20] can be expressed by a Drude equation.[5] The first term, $[M] = k/(\lambda^2 - \lambda_0^2)$ expresses the contribution to the total molecular ($[M]$) rotation (at any particular wave length λ) of a given optically active chromophore which has an absorption peak at wave length λ_0. Where a second term appears, this must be taken to encompass all the remaining rotatory contributions due to optically active bands situated further in the ultraviolet. The constant λ_0 usually does not coincide exactly with the measured peak of light absorption

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(20) From our standpoint—correlation of structure with shape of rotatory dispersion curve—this is the least significant region (usually *ca.* 700–400 mμ).

and even in simple compounds it is generally displaced by about 5 mμ toward longer wave length.[5a] In the case of the more complicated steroid molecule, such discrepancies will be expected to be more serious, especially if several strong optically active chomophores are present and this was found indeed to be the case.

It was attempted to fit both one-term and two-term Drude equations to our experimental data by computation methods which are discussed in detail in the third paper[15] of this series. Such equations could be fitted satisfactorily to eight out of the ten compounds over a spectral range which in each case is indicated in the experimental section, a deviation of less than 3% between the calculated and experimental value usually being considered acceptable.

It is pertinent to note that in three cases (VI, VII, IX) where experimental results were obtained at two concentrations (c = 1 or 0.1), the results obtained from the higher concentration could be made to fit a Drude equation while the others could not.[21] Of the two compounds (VIII, X) for which no satisfactory equation could be derived, Δ^1-androstene-3,17-dione (VIII) has been measured only at the lower concentration. The reason in this and similar instances was that light absorption of the sample in c = 1 concentration prevented measurements to be carried out to sufficiently short wave lengths in order to define the rotation peak near 320 mμ. In the case of the other compound, $\Delta^{1,4,6}$-androstatriene-3,17-dione (X), only a very small portion of the measured spectrum (Fig. 3) lies outside the region of optically active absorption, within which the Drude equation is not applicable. On both these grounds, androstane (V), measured at the higher concentration and transparent throughout the spectral range studied (Fig. 1), would be expected to be fitted easily to a suitable equation. On the basis of the criteria set up in our computations[15] the agreement is the poorest in this series, with some of the smaller values deviating as much as 50%. This must be due to the extreme smallness of the readings, with resulting lesser accuracy; a deviation of the calculated molecular rotation from the observed value of the order of only 1–2° can amount here to a 50% deviation.

In the Experimental section, in addition to the Drude equation, the calculated value of λ_0 also is given in each instance. As pointed out above, in as complicated a molecule as a substituted steroid, this value of λ_0 will not necessarily agree with the observed ultraviolet absorption maximum. Thus, the fact that the calculated value (250 mμ) of λ_0 for Δ^4-androstene-3,17-dione (VI) is reasonably close to the observed[10] *ultraviolet* absorption maximum (*ca.* 240 mμ) of the Δ^4-3-keto grouping does not necessarily demonstrate conclusively that this particular chromophore is responsible for the observed rotation of the substance in the *visible* spectrum. However, it is quite likely that this is the case and that the strong chromophore (corresponding to the 240 mμ maximum) associated with the Δ^4-3-keto system is optically active as was shown to be the case for the low intensity, long wave length, carbonyl chromophore (max. at 304 mμ) by the more direct procedure of extrapolation through the zero rotation line (*vide supra*). It should be noted that the unambiguous and direct method of actually following the dispersion curve through the active absorption band (in the 240–250 mμ region) is unlikely to be feasible experimentally with such strongly absorbing chromophores as the Δ^4-3-keto grouping, even in the absence of limitations imposed by the nature of the light source and the light transmitting properties of the solvent.

The calculated λ_0 values (280 and 408 mμ, respectively) of the conjugated $\Delta^{1,4}$-(VII) and $\Delta^{4,6}$-(IX) diene-diones are removed much further from their respective absorption maxima[10] (244 and 282 mμ). The changes in λ_0 are in the right direction, increasing with increased absorption, but the value for the $\Delta^{4,6}$-diene IX appears to be unreasonably high.

The results with the four unconjugated ketones of this series (I–IV) confirm what had already been established by the graphic extrapolation method through the zero rotation axis, namely, that the ketonic absorption band is optically active in all four compounds. The range (306–314 mμ) of the calculated λ_0 value falls close to the observed position (285–297 mμ) of the low intensity absorption band of the isolated carbonyl group.

Experimental Results

General Comments.—Where the source of the substance is not given, it represents material of analytical purity from the collection of one of the authors (C.D.). Samples obtained from Syntex, S.A., Mexico City, were checked for purity by paper chromatographic assays through the courtesy of Dr. A. Zaffaroni. Ultraviolet absorption spectra were measured in dioxane solution with an automatically recording Warren Spectracord attached to a Beckman DU ultraviolet spectrophotometer.

Rotatory dispersion (R.D.) values are given for the upper and lower limit of the spectral range covered, for 589 mμ (sodium D line) and for all "maxima" and "minima" (see ref. 19). Observed rotations at any wave length represent the average of duplicate readings agreeing generally within ±0.002° except at the lower wave lengths where larger deviations were encountered and whereupon more than two readings were taken. Furthermore, each compound was run in duplicate (new solutions made up) and the recorded specific rotations represent the average of two values agreeing within 3%. Concentrations are given as either c = 1.00 (50 mg. in 5 cc.) or c = 0.10 (10 mg. in 10 cc.). The temperature given refers to the range over the entire series of readings.

Whenever a Drude equation could be obtained for a given compound, this is listed together with the calculated value of λ_0. The wave length range over which the equation fits together with the average % deviation also is given and it should be noticed that all rotations in the Drude equations are expressed as *molecular rotations* ([M]) rather than specific rotations ([α]), which are used throughout the rest of this work.

Actual readings at each wave length and the correspondence at each point between the observed and calculated values are listed in detail in the Ph.D. thesis (1955) of Eleanor W. Foltz and may be obtained on interlibrary loan from the Wayne University Library.

Etiocholane-3,17-dione (I), m.p. 120–123°; $\lambda_{max.}$ 292–297 mμ, log ϵ 1.64. R.D. (Fig. 1): $[\alpha]_{700}$ + 106°, $[\alpha]_{589}$ + 150°, $[\alpha]_{305}$ + 1204°, "max."$[\alpha]_{320}$ + 2640°; c = 0.10; temp. 23–24°. Drude equation: $[M] = 73.6/(\lambda^2 - 0.0934) + 49.4/\lambda^2$; λ_0 306 mμ; % deviation $[M]_{obsd} - [M]_{calcd}$: ±1.7%, 650-370 mμ; ±2.6%, 650-350 mμ.

Androstane-3,17-dione (II), m.p. 129–130°; $\lambda_{max.}$ 289–294 mμ, log ϵ 2.02; from Syntex, S. A. R.D. (Fig. 1): $[\alpha]_{700}$ + 55°, $[\alpha]_{589}$ + 94°, $[\alpha]_{305}$ + 1069°, "max." $[\alpha]_{320}$

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[21] This must be due to the fact that the lesser percentage accuracy inherent in measurements obtained at the lower concentration (when the rotation is small) makes it much more difficult to obtain a Drude equation which would fit closely enough to meet the requirement which we consider desirable (see ref. 15).

+3054°; c = 0.10; temp. 30.5–31°. Drude equation: $[M] = 115/(\lambda^2 - 0.0868) - 55.7/\lambda^2$; λ_0 294 mμ; % deviation $[M]_{\text{obsd}} - [M]_{\text{calcd}}$: ±2.2%, 550–355 mμ.

Androstan-17-one (III), m.p. 119–120°; $\lambda_{\max.}$ 294–297 mμ, log ε 1.83; supplied by Syntex, S. A. R. D. (Fig. 1): $[\alpha]_{700}$ + 44°, $[\alpha]_{589}$ + 82°, $[\alpha]_{300}$ − 250°, "max." $[\alpha]_{320}$ + 2572; c = 0.10; temp. 29–31°. Drude equation: $[M] = 69.7/(\lambda^2 - 0.0942) - 17.3/\lambda^2$; λ_0 307 mμ; % deviation $[M]_{\text{obsd}} - [M]_{\text{calcd}}$: ±1.7%, 589–340 mμ ±2.7%, 589–325 mμ.

Androstan-3-one (IV), m.p. 99.2–99.8°; $\lambda_{\max.}$ 284–287 mμ, log ε 1.67; supplied by Dr. H. B. MacPhillamy, Ciba Pharmaceutical Products, Inc. R.D. (Fig. 1): $[\alpha]_{700}$ + 17.0°, $[\alpha]_{589}$ + 25.0°, $[\alpha]_{300}$ + 212°, "max." $[\alpha]_{315}$ + 916°; c = 1.00 from 700–320 mμ, c = 0.10 from 360–300 mμ; temp. 24°. Drude equation: $[M] = 17.1/(\lambda^2 - 0.0987)$; λ_0 314 mμ; % deviation $[M]_{\text{obsd}} - [M]_{\text{calcd}}$: ±2.2%, 650–360 mμ.

Androstane (V), m.p. 40–43°. R.D. (Fig. 1): $[\alpha]_{700}$ + 0.4°, $[\alpha]_{589}$ + 0.7°, $[\alpha]_{330}$ + 11.8°; c = 1.00; temp. 28–29°. Drude equation: $[M] = 2.53/(\lambda^2 - 0.0550) - 1.75/\lambda^2$; λ_0 234 mμ; % deviation $[M]_{\text{obsd}} - [M]_{\text{calcd}}$ ±1.0° (18.9 − 0.3%), 520–330 mμ, ±1.8° (63.0–0.3%), 700–330 mμ; see comments in Discussion section concerning this deviation.

Δ⁴-Androstene-3,17-dione (VI), m.p. 178–179°, $\lambda_{\max.}$ 304 mμ, log ε 1.79, shoulders 297, 313, 327–332 mμ, log ε 1.76, 1.76, 1.65; inflections 340, 346, 356, 360 mμ, log ε 1.56, 1.51, 1.23, 1.13; from Syntex, S.A. R.D. (Fig. 2): $[\alpha]_{700}$ + 111°, $[\alpha]_{589}$ + 176°, $[\alpha]_{310}$ +2617°, "max."$[\alpha]_{385}$ + 546°, "min."$[\alpha]_{367\cdot5}$ + 408°, "max."$[\alpha]_{357\cdot5}$ + 552°, "min."$[\alpha]_{355}$ + 520°, "max."$[\alpha]_{320}$ + 3650°; c = 0.10; temp. 24–25°. R.D.: $[\alpha]_{700}$ + 122.7°, $[\alpha]_{589}$ +184.6°, $[\alpha]_{400}$ +516.2°; c = 1.00; temp. 24–25°. Drude equation: $[M] = 151/(\lambda^2 - 0.0627)$, from c = 1.00 data; λ_0 250 mμ; % deviation $[M]_{\text{obsd}} - [M]_{\text{calcd}}$: ±0.7%, 700–425 mμ.

$\Delta^{1,4}$-Androstadiene-3,17-dione (VII), m.p. 140–143°; $\lambda_{\max.}$ 347–348, 336–337 mμ, log ε 1.36, 1.41; inflections 364, 357, 303, 293 mμ, log ε 1.16, 1.24, 1.75, 1.81; from Syntex, S.A. R.D. (Fig. 2): $[\alpha]_{700}$ +78°, $[\alpha]_{589}$ +111°, $[\alpha]_{305}$ +1294°, slight "max."$[\alpha]_{392.5}$ + 345°, slight "min." $[\alpha]_{385}$ + 337°, "max."$[\alpha]_{320}$ + 3087°; c = 0.10; temp. 23.5–24.5°. R.D.: $[\alpha]_{700}$ + 68.2°, $[\alpha]_{589}$ + 103.8°, $[\alpha]_{400}$ +328.6°; c = 1.00; temp. 24–25°. Drude equation: $[M] = 80.9/(\lambda^2 - 0.0784)$, from c = 1.00 data; λ_0 280 mμ; % deviation $[M]_{\text{obsd}} - [M]_{\text{calcd}}$: ±2.2%, 700–425 mμ.

Δ¹-Androstene-3,17-dione (VIII), m.p. 141–142°; $\lambda_{\max}$ 294–304 mμ, log ε 1.98, shoulder 332–340 mμ, log ε 1.70. R.D. (Fig. 2): $[\alpha]_{700}$ +83°, $[\alpha]_{589}$ + 128°, $[\alpha]_{305}$ +1907°, "max."$[\alpha]_{415}$ +286°, "min."$[\alpha]_{382\cdot5}$ +53°, "max."$[\alpha]_{370}$ + 296°, "min."$[\alpha]_{367\cdot5}$ + 288°, "max."$[\alpha]_{320}$ + 3816°; c = 0.10; temp. 25–26.5°.

$\Delta^{4,6}$-Androstadiene-3,17-dione (IX), m.p. 168–169.5°; $\lambda_{\max.}$ 336–346 mμ, log ε 1.87; inflection 362, 371, 377, 390 mμ, log ε 1.76, 1.63, 1.53, 1.13. R.D. (Fig. 3): $[\alpha]_{700}$ +73°, $[\alpha]_{589}$ +138°, $[\alpha]_{315}$ +851°, "max."$[\alpha]_{407\cdot5}$ +1544°, "min."$[\alpha]_{402\cdot5}$ +1533°, "max." $[\alpha]_{390}$ +1795°, "min." $[\alpha]_{340}$ −1030°; c = 0.10; temp. 24–25°. R.D.: $[\alpha]_{700}$ +73.8°, $[\alpha]_{589}$ + 138.6°, $[\alpha]_{425}$ + 971.4°; c = 1.00; temp. 24–25°. Drude equation: $[M] = 70.1/(\lambda^2 - 0.167)$; λ_0 408 mμ; % deviation $[M]_{\text{obsd}} - [M]_{\text{calcd}}$: ±1.3%, 675–525 mμ; ±3.3% 700–500 mμ.

$\Delta^{1,4,6}$-Androstatriene-3,17-dione (X), m.p. 165–168°; $\lambda_{\max.}$ 346–348 mμ, log ε 1.98, shoulder 360 mμ, log ε 1.93; inflections 370, 377, 382, 388 mμ, log ε 1.83, 1.77, 1.70, 1.54. R.D. (Fig. 3): $[\alpha]_{700}$ +32°, $[\alpha]_{589}$ +71°, $[\alpha]_{330}$ − 137°, "max."$[\alpha]_{405}$ + 2072°, "min."$[\alpha]_{390}$ + 1565°, $[\alpha]_{387\cdot5}$ +1572°, "min."$[\alpha]_{345}$ − 1446°; c = 0.10; temp. 26–28°. R.D.: $[\alpha]_{700}$ + 27.5°, $[\alpha]_{589}$ + 67.8°, $[\alpha]_{425}$ + 959.2°; c = 1.00; temp. 24–25°.

DETROIT, MICHIGAN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

Optical Rotatory Dispersion Studies. II.[1] Steroid Hormones[2,3]

BY ELEANOR W. FOLTZ, A. E. LIPPMAN AND CARL DJERASSI

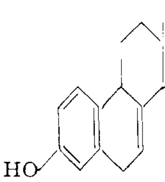
RECEIVED MARCH 16, 1955

The rotatory dispersion curves of testosterone, progesterone and of all the important estrogenic and cortical hormones are given, emphasis being placed on the correlation of certain structural features with the shapes of the dispersion curves.

The ultimate aim of this series of investigations is to provide an additional tool for the identification of certain structural features in the steroid series and the present paper is concerned with an examination of the rotatory dispersion curves of the most important, physiologically active, steroid hormones.

The estrogenic hormones differ from all other naturally occurring steroids in possessing an aromatic ring A with consequent absence of the C-19 angular methyl group. The aromatic nature of ring A causes intense absorption near 280 mμ[4] but it was nevertheless possible in several instances to carry dispersion measurements to the neighborhood of 305 mμ.

Estradiol (IV) represents the basic compound in this series since the phenolic ring is the only important chromophore and its rotatory dispersion curve



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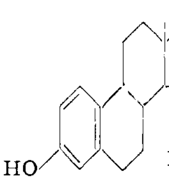

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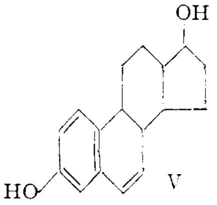

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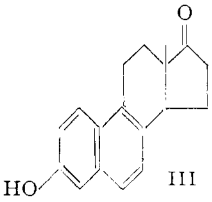

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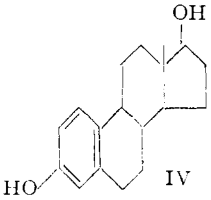

IV

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[1] Paper I, C. Djerassi, E. W. Foltz and A. E. Lippman, THIS JOURNAL, **77**, 4354 (1955).

[2] Presented in part at the December 1954 Meeting of the American Association for the Advancement of Science in Berkeley, California.

[3] Supported by a research grant from the Damon Runyon Memorial Fund for Cancer Research.

[4] *Cf.* L. Dorfman, *Chem. Revs.*, **53**, 47 (1953).