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

Δ^4-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 $[M]_{obsd} - [M]_{calcd}$: ±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 $[M]_{obsd} - [M]_{calcd}$: ±2.2%, 700–425 mμ.

Δ^1-Androstene-3,17-dione (VIII), m.p. 141–142°; λ_{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 $[M]_{obsd} - [M]_{calcd}$: ±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

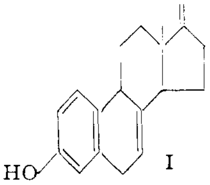
RECEIVED MARCH 16, 1955

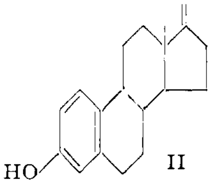
The rotatory dispersion curves of testosterone, progesterone and of all the important estrogenic and cortical hormones are given, emphasis being placed on the correlation of certain structural features with the shapes of the dispersion curves.

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


I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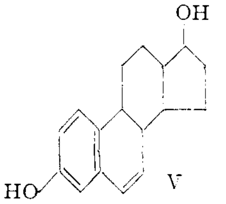
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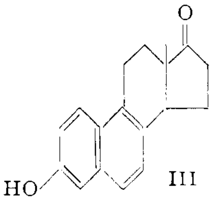
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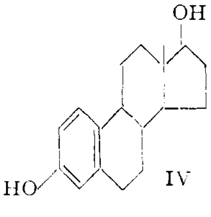
IV

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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).

(Fig. 1) shows a slow rise in a positive direction with decreasing wave length. Estrone (II), on the other hand, which possesses a 17-keto group shows the typical sharp rotation peak at 320 mμ assigned to this group.[1] Equilin (I), with an additional non-conjugated double bond, exhibits essentially the same type of curve, the highly positive 17-keto peak being located at *ca.* 317.5 mμ. Measurements on equilenin (III) could not be carried further than 360 mμ because of the intense light absorption up to 340 mμ associated with the naphthol system.[4] The shape of the curve (Fig. 1), however, does suggest that a rotation peak similar to that in the other two carbonyl containing estrogens (I, II) exists here also.

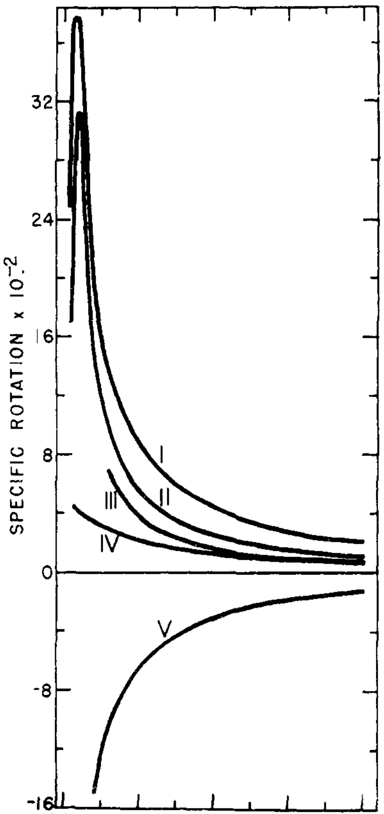
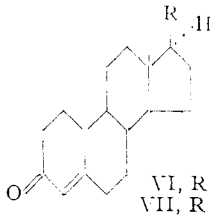
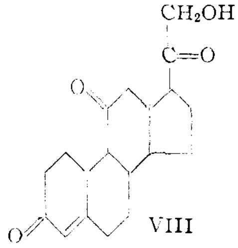


Fig. 1.—Rotatory dispersion curves of: equilin (I), estrone (II), equilenin (III), estradiol (IV), 6-dehydroestradiol (V).

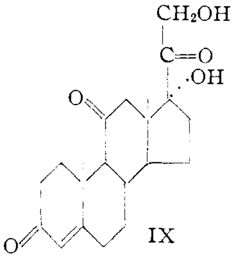
The rotatory dispersion curve (Fig. 1) of 6-dehydroestradiol (V) is interesting when contrasted to that of estradiol (IV). While the latter rises slowly in a positive direction, the introduction of the 6,7-double bond in V causes the rotation to be negative throughout the range measured, increasing in steepness to the large negative value of [α] −1602° at 335 mμ beyond which measurements could not be taken because of the strong light absorption at 302 mμ associated with this chromophore.[5] Whether this striking effect is due to the particular location of the double bond within the molecule or to the fact that it is in conjugation with the aromatic ring A cannot be decided definitely at this point, although the first alternative may well be true as the introduction of an isolated 6,7-double bond generally causes a large negative rotation at the sodium D line[6] and, in fact, over the entire spectral range studied.[7]



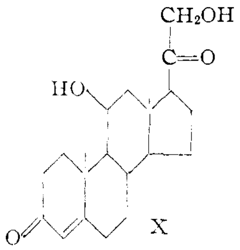
VI, R = $-\overset{O}{\overset{\|}{C}}-CH_3$
VII, R = —OH



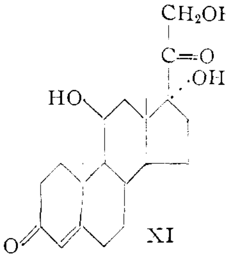
VIII



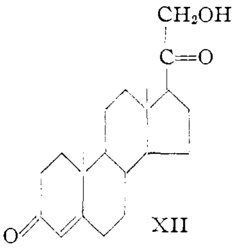
IX



X



XI



XII

The remaining hormones to be discussed all possess the Δ^4-3-keto grouping and their rotatory dispersion curves all show the "maximum"[8] at 357.5–360 mμ and "minima" at 367.5–370 mμ and 352.5–355 mμ which have been shown earlier[1] to be characteristic of Δ^4-3-ketones. Neither the wave length at which this feature appears nor the distance in terms of rotation between the positive (357.5–360 mμ) and negative (367.5–370 mμ) peaks (*i.e.*, the degree of optical activity of the chromophore concerned) are altered with varying substitution at C-11 or C-17. Inspection of Figs. 2 and 3 demonstrates, however, that when the position of these peaks on the rotation scale is considered, the compounds fall into three groups: (a) the positive (360 mμ) peak of testosterone (VII) occurs at [α] −88°, (b) that of progesterone (VI), corticosterone (X), hydrocortisone (XI) and 11-desoxycorticosterone (XII) ranges between [α] +428° and +578°, while (c) that of the 11-ketosteroids, 11-dehydrocorticosterone (VIII) and cortisone (IX) is found in the region [α] +1016° to +1058°.

Before proceeding to interpret this division into three groups on the basis of the *intensity* of the Δ^4-3-keto 350–400 mμ region, it is necessary to con-

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(5) C. Djerassi, G. Rosenkranz, J. Romo, S. Kaufmann and J. Pataki, THIS JOURNAL, **72**, 4534 (1952).

(6) D. H. R. Barton and W. J. Rosenfelder, *Nature*, **164**, 316 (1949); O. Wintersteiner and M. Moore, *ibid.*, **164**, 317 (1949), and later papers by both groups.

(7) A. E. Lippman, E. W. Foltz and C. Djerassi, THIS JOURNAL, **77**, 4364 (1955).

(8) See reference 1 for definition of terms and experimental procedure.

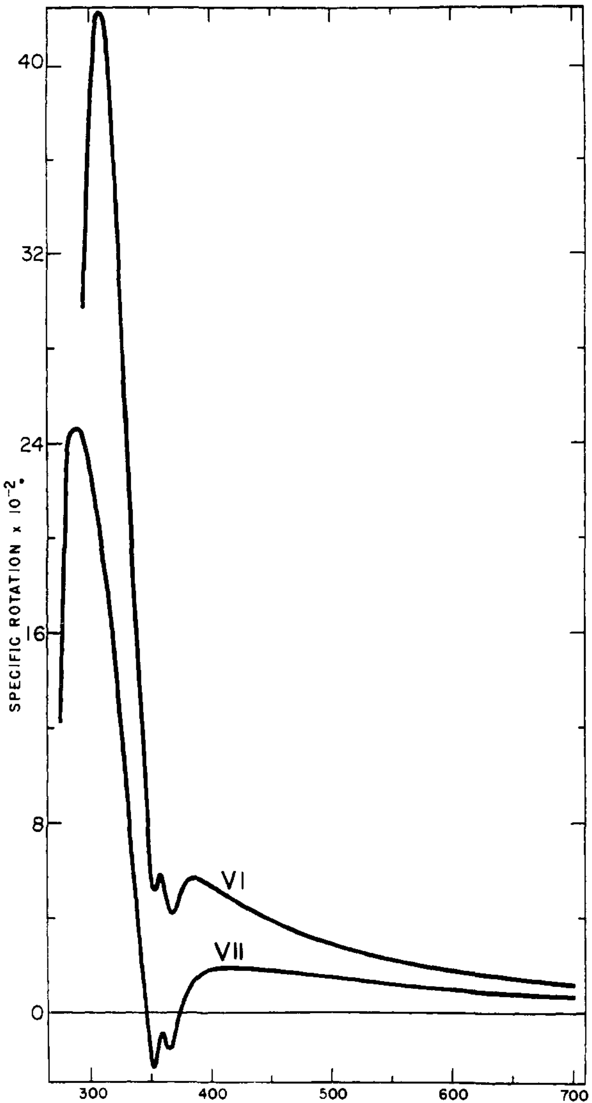


Fig. 2.—Rotatory dispersion curves of: progesterone (VI), testosterone (VII).

sider the sharp rotation peak exhibited by all these compounds (except for testosterone (VII)) in the region below 320 mμ (Figs. 3 and 4). This sharp peak is similar in position and intensity to that previously[1] attributed to the isolated 17-keto function but slightly less constant in wave length (range 310–320 mμ). The hormones concerned (VI, VIII–XII) all possess a carbonyl group at C-20 and this is situated next to an asymmetric center (C-17) just as is the case with the 17-keto group[1] which is adjacent to the asymmetric carbon C-13. Therefore, we ascribe this rotation peak to the passage of the dispersion curve through the absorption band of an optically active chromophore associated with the 20-keto function. This could be confirmed with pregnan-3β-ol-20-one (XVII) which contains no additional chromophore other than the 20-keto grouping and which exhibited (Fig. 5) a high peak at 312.5 mμ. The peak of androstan-17-one (XVI) also is shown in Fig. 5 in order to permit a comparison between an isolated 20- and 17-keto steroid.

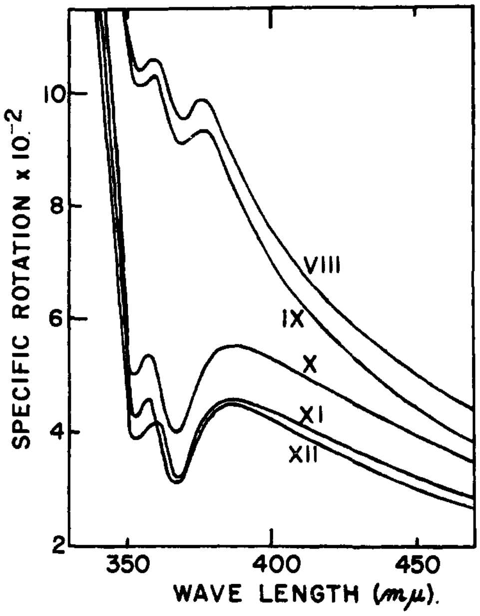


Fig. 3.—Rotatory dispersion curves (330–470 mμ) of: 11-dehydrocorticosterone (VIII), cortisone (IX), corticosterone (X), hydrocortisone (XI), 11-desoxycorticosterone (XII).

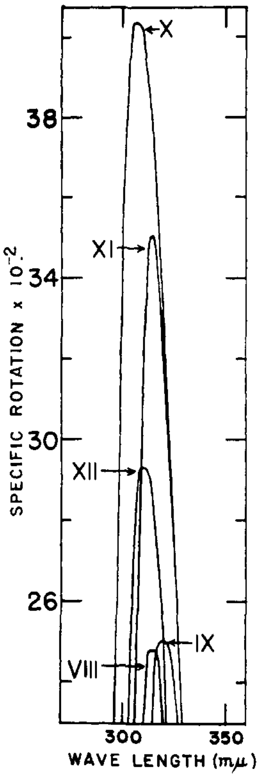


Fig. 4.—Rotatory dispersion curves (295–350 mμ) of: 11-dehydrocorticosterone (VIII), cortisone (IX), corticosterone (X), hydrocortisone (XI), 11-desoxycorticosterone (XII).

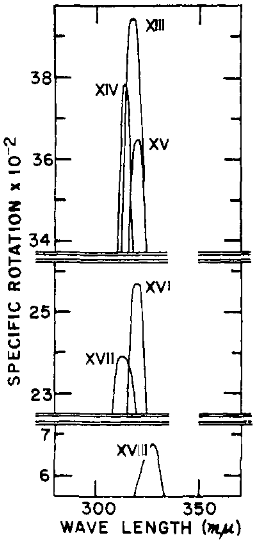
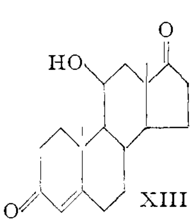
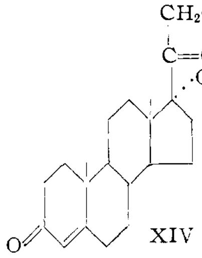


Fig. 5.—Rotatory dispersion curves (300–350 mμ) of: 11β-hydroxy-Δ^4-androstene - 3,17 - dione (XIII), Reichstein's Substance S (XIV), Δ^4-androstene-3,17-dione (XV), androstan-17-one (XVI), pregnan - 3β - ol - 20 - one (XVII), etiocholane-3α, 17β-diol-11-one (XVIII).

As mentioned above, the exact position of this peak in these hormones varies slightly with different substituents in the molecule, but the range of variation (*ca.* 10 mμ) is sufficiently slight so that no correlations could be based on it. On the other hand, the intensity (*i.e.*, degree of asymmetry) of this peak varies more so—the observed rotation peaks ranging from [α] *ca.* +2500°, for the two 11-ketosteroids VIII and IX, all the way to +4215° (the highest specific rotation observed so far in the steroid series) for progesterone (VI). In Fig. 5 a few supplementary compounds (XIII–XVI) have been collected for this region in order to make possible some intensity comparisons. The introduction of an 11β-hydroxy group in the 17-keto series (XIII *vs.* XV and XVI) and 20-keto-21-hydroxy series (X *vs.* XII in Fig. 4) results in increased positive rotation, but the opposite effect is noted when an additional 17α-hydroxy substituent is present (hydrocortisone (XI) *vs.* Compound S (XIV)).


XIII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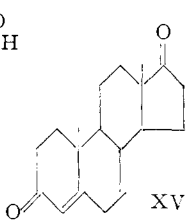
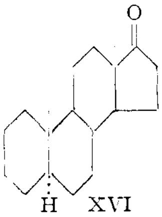
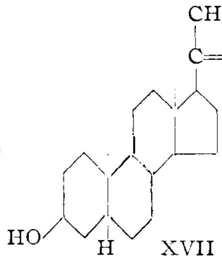
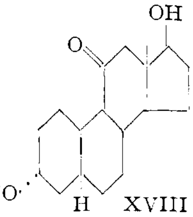

XV


XVI


XVII


XVIII

An interpretation of the existence of three groups (on the basis of intensity) in the important 350–400 mμ region now can be presented. Testosterone (VII) (Fig. 2), the single member of group (a), is also the only hormone which does not have any ketonic function in its molecule other than that in conjugation with the 4,5-double bond. Its flat rotation peak at 290 mμ, similar to that found in Δ⁴-cholesten-3-one,[7] is ascribed to a separate effect of the conjugated system, not necessarily[7] the passage of the curve through another optically active absorption band. Since this flat rotation peak is situated at a shorter wave length (290 mμ), it makes its presence less felt in the 350–400 mμ region than the sharp peak (312.5 mμ) of a 20-ketone (XVII). The first of the peaks (at 365 mμ) of testosterone (VII) from the long wave length side is negative (first "minimum") and it is more effective in pulling the dispersion curve to the negative side than when it is in competition with the large positive rotation contribution in the vicinity of the peak (*ca.* 312.5 mμ) due to the 20-keto group. This is illustrated in a striking manner in Fig. 2 by comparison with progesterone (VI).

The curious behavior of the third group (c), made up of the two 11-ketosteroids VIII and IX in which the double peaks in the 350–400 mμ region occur at a much more positive rotation in spite of the fact that their peak (at 310–320 mμ) due to the 20-keto group is significantly lower than that in other 20-ketones (group (b)), can only find an explanation in the assumption that the additional 11-keto substituent is also optically active. If the absorption band responsible for this activity (even though less intense) is situated at a somewhat longer wave length than that due to the 20-keto group, its effect will be felt more in the 350–400 mμ region, causing the double peaks there to occur higher up on the rotation scale. This was found to be the case. If the positive rotation peak of the 11-keto group is not too strong, it may become obscured by the superimposition of contributions made by the 20-keto group and the Δ^4-3-keto chromophore. The negative peak at the shorter wave length side of the weaker 11-keto band may coincide with the very strong positive peak of the band corresponding to the 20-keto function, which this would result in decrease of intensity of the latter band as observed (see Fig. 4 where the two 11-keto steroids VIII and IX show the lowest rotation). This explanation could be proved rather conclusively when, subsequent to the first preparation of this manuscript, there became available for measurement a steroid, etiocholane-3α,17β-diol-11-one (XVIII), the rotatory dispersion curve (Fig. 5) of which exhibited all of the features (bathochromic shift coupled with low activity) predicted above for the isolated 11-keto group. These results also are completely compatible with the observation[9] that the low intensity absorption peak of the 11-keto group occurs at about 10–15 mμ longer wave length than the average steroid ketone.

Finally, it should be mentioned that Brand and co-workers[10] recently have carried out rotatory dispersion measurements of cortisone acetate in chloroform and methanol solution over the range 750–340 mμ without observing any peaks in the dispersion curves. Their failure to detect the striking features outlined above resides in the fact that they usually took measurements only in 50-mμ intervals; in the critical range of 350–400 mμ, only two readings are reported, one at each of these two wave lengths, thus precluding the possibility of detecting the effect of the Δ^4-3-keto moiety. On the basis of their results with two steroids, cholesterol and cortisone acetate, these authors[10] state that "the results with steroids indicate that the presence of many asymmetric centers is not incompatible with normal dispersion." This assumption must be considered incorrect in the light of our data and emphasizes the danger inherent in running measurements in large intervals.

Mathematical Results

Just as in the androstane series,[1] an attempt was made by a procedure outlined elsewhere,[7] to fit one-term and two-term Drude equations to the present series and this proved to be successful in all but four cases (V, VI, VII, X). Of these, all except one

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(9) O. Schindler and T. Reichstein, *Helv. Chim. Acta*, **37**, 667 (1954), and references cited therein.

(10) E. Brand, E. Washburn, B. F. Erlanger, E. Ellenbogen, J. Daniel, F. Lippmann and M. Scheu, This Journal, **76**, 5037 (1954).

(testosterone (VII)) had only been measured at c = 0.1 concentration which, according to our earlier experience,[1] may cause difficulties in the mathematical treatment. It is noteworthy that in three instances (II, III, VIII), where satisfactory equations were derived, it was possible to fit both a one-term and a two-term Drude equation to the same data over much the same range (outside the optically active absorption band). The λ_0 values calculated from each such pair of equations are in reasonable agreement with each other and with the physical significance attributed to these constants.

The calculated λ_0 values for hydrocortisone (XI) (235 mμ) and desoxycorticosterone (XII) (258 mμ) confirm the tentative conclusion reached earlier[1] that the chromophore at 240 mμ due to the Δ^4-3-keto grouping is optically active. The values of λ_0 for the two 11-keto hormones, 11-dehydrocorticosterone (VIII) (273 or 294 mμ depending upon the equation) and cortisone (IX) (286 mμ), are somewhat high and presumably reflect added rotatory contributions due to other chromophores. The rotatory dispersion results of Brand, *et al.*,[10] on cortisone acetate already commented on above were expressed by them in the form of two-term Drude equations, one covering the results in chloroform and the other in methanol. It appears impossible to determine whether such equations represent the best fit, or, indeed any fit at all, since only four values were available on which these equations could be tested. Little significance can be attached to these results since two of these values (340 and 350 mμ) have been shown by us to lie near a region of anomalous dispersion due to passage of the dispersion curve through an optically active band associated with the Δ^4-3-keto group.

The close agreement between the calculated λ_0 values for equilin (I) (282 mμ), estrone (II) (291 or 303 mμ depending upon equation) and estradiol (IV) (282 mμ) with the absorption peak of their phenolic chromophore (*ca.* 280 mμ) leads to the tentative assumption that this particular chromophore is optically active, although in the first two cases the 17-keto chromophore, shown earlier[1] to be optically active, undoubtedly plays a part.

Experimental Results[8]

Equilin (I), m.p. 238–240°, furnished by Dr. J. A. Moore, Parke, Davis and Co. R.D. (Fig. 1): $[\alpha]_{700}$ + 208°, $[\alpha]_{589}$ + 256°, $[\alpha]_{305}$ +2500°, "max." $[\alpha]_{317.5}$ +3778°; c = 0.10; temp. 24–26°. Drude equation: $[M] = 160/(\lambda^2 - 0.0789) + 69.3/\lambda^2$; λ_0 282 mμ; % deviation $[M]_{obsd} - [M]_{calcd}$: ±1.4%, 620–350 mμ; ±3.4%, 650–350 mμ.

Estrone (II), m.p. 260–261°; λ_{max} 289, 281–282 mμ, log ϵ 3.38, 3.42, shoulder 315 mμ, log 1.68; from Syntex, S.A. R.D. (Fig. 1): $[\alpha]_{700}$ +109°, $[\alpha]_{589}$ +160°, $[\alpha]_{310}$ +1715°, "max." $[\alpha]_{320}$ +3064°; c = 0.10; temp. 23–25°; Drude equation: one-term, $[M] = 113/(\lambda^2 - 0.0846)$; λ_0 291 mμ; % deviation $[M]_{obsd} - [M]_{calcd}$: ±0.8%, 650–370 mμ; ±2.1%, 700–360 mμ. Two-term, $[M] = 89.5/(\lambda^2 - 0.0920) + 28.8/\lambda^2$; λ_0 303 mμ; % deviation $[M]_{obsd} - [M]_{calcd}$: ±1.2%, 650–350 mμ; ±3.2%, 700–325 mμ.

Equilenin (III), m.p. 252–254°. R.D. (Fig. 1): $[\alpha]_{700}$ +68°, $[\alpha]_{589}$ + 100°, $[\alpha]_{360}$ +672°; c = 0.10; temp. 23–24°. Drude equation: $[M] = 65.7/(\lambda^2 - 0.0956)$; λ_0 309 mμ; % deviation $[M]_{obsd} - [M]_{calcd}$: ±1.4%, 700–365 mμ. Two-term, $[M] = 62.8/(\lambda^2 - 0.0970) + 3.73/\lambda^2$; λ_0 311 mμ; % deviation $[M]_{obsd} - [M]_{calcd}$: ±1.0%, 700–370 mμ; ±1.4%, 700–370 mμ; ±2.2%, 700–365 mμ.

Estradiol (IV), m.p. 178–179°, from Syntex, S.A. R.D. (Fig. 1): $[\alpha]_{700}$ +72°, $[\alpha]_{589}$ +98°, $[\alpha]_{315}$ +441°; c = 0.10; temp. 24–25°. Drude equation: $[M] = 9.52/(\lambda^2 - 0.0798) + 7.96/\lambda^2$; λ_0 282 mμ; % deviation $[M]_{obsd} - [M]_{calcd}$: ±2.9%, 650–330 mμ.

6-Dehydroestradiol (V), m.p. 229.5–230.5°. R.D. (Fig. 1): $[\alpha]_{700}$ −132°, $[\alpha]_{589}$ −186°, $[\alpha]_{335}$ −1602°; c = 0.10; temp. 24–26°. Drude equation: $[M] = -141/(\lambda^2 - 0.0800)$; λ_0 283 mμ; % deviation $[M]_{obsd} - [M]_{calcd}$: ±1.7%; 520–335 mμ.

Progesterone (VI), m.p. 128–129°; λ_{max} 292–294, 330–332 mμ, log ϵ 1.75, 1.68, shoulders 301–305, 313–317 mμ, log ϵ 1.74, 1.71, inflection 343 mμ, log ϵ 1.57; furnished by Syntex, S.A. R.D. (Fig. 2): $[\alpha]_{700}$ +120°, $[\alpha]_{589}$ +183°, $[\alpha]_{300}$ +2977°, "max." $[\alpha]_{385}$ +568°, "min." $[\alpha]_{367.5}$ +418°, "max." $[\alpha]_{357.5}$ + 578°, "min." $[\alpha]_{352.5}$ + 513°, "max." $[\alpha]_{315}$ +4215°; c = 0.10; temp. 24–25°.

Testosterone (VII), m.p. 153.5–154.5°; λ_{max} 330–331 mμ, log ϵ 1.66, shoulder 322–325 mμ, log ϵ 1.64; inflections 362, 355, 346, 340 mμ, log ϵ 1.10, 1.23, 1.51, 1.56; from Syntex, S.A. R.D. (Fig. 2): $[\alpha]_{700}$ +68°, $[\alpha]_{589}$ +101°, $[\alpha]_{275}$ +1231°, "max." $[\alpha]_{420}$ +190°, "min." $[\alpha]_{365}$ −155°, "max." $[\alpha]_{360}$ −88°, "min." $[\alpha]_{352}$ −239°, "max." $[\alpha]_{290}$ +2462°; c = 0.10; temp. 24–25°. R.D.: $[\alpha]_{700}$ +69.0°, $[\alpha]_{589}$ +100.8°, $[\alpha]_{375}$ +35.0°, "max." $[\alpha]_{420}$ +192.3°; c = 1.00.

11-Dehydrocorticosterone (VIII), m.p. 175–180°; shoulder 311–313 mμ, log ϵ 2.08; inflections 290, 302, 335, 344, 352 mμ, log ϵ 2.20, 2.15, 1.87, 1.73, 1.65; furnished by Dr. K. Pfister, Merck and Co., Inc. R.D. (Figs. 3 and 4): $[\alpha]_{700}$ +159°, $[\alpha]_{589}$ +235°, $[\alpha]_{300}$ +1385°, "max." $[\alpha]_{377.5}$ +987°, "min." $[\alpha]_{370}$ + 954°, "max." $[\alpha]_{357.5-360}$ +1058°, 'min." $[\alpha]_{355}$ + 1042°, "max." $[\alpha]_{315}$ +2488°; c = 0.10; temp. 23–25°. Drude equation: one-term, $[M] = 222/(\lambda^2 - 0.0747)$; λ_0 273 mμ; % deviation $[M]_{obsd} - [M]_{calcd}$: ±0.8%, 650–400 mμ; ±1.7%, 650–390 mμ. Two-term, $[M] = 169/(\lambda^2 - 0.0864) + 58.8/\lambda^2$; λ_0 294 mμ; % deviation ±1.2%, 650–380 mμ; ±1.9%, 700–380 mμ.

Cortisone (**IX**), m.p. 215–217°; λ_{max} 284–285 mμ, log ϵ 2.15, shoulder 332 mμ, log ϵ 1.65; inflections 318, 340, 348, 360 mμ, log ϵ 1.82, 1.56, 1.47, 1.15; Syntex, S.A. R.D. (Figs. 3 and 4): $[\alpha]_{700}$ +122°, $[\alpha]_{589}$ +196°, $[\alpha]_{305}$ +891°, "max." $[\alpha]_{378}$ +933°, "min." $[\alpha]_{368}$ +909°, "max." $[\alpha]_{360}$ +1016°, "min." $[\alpha]_{355}$ +1002°, "max." $[\alpha]_{320}$ + 2575°; c = 0.10; temp. 24–26°. R.D.: $[\alpha]_{700}$ +127.7°, $[\alpha]_{589}$ +195.1°, $[\alpha]_{370}$ +880.5°, "max." $[\alpha]_{375}$ +887.1°; c = 1.00; temp. 24–25°. Drude equation: $[M] = 188/(\lambda^2 - 0.0816)$, from c = 1.00 data; λ_0 286 mμ; % deviation $[M]_{obsd} - [M]_{calcd}$: ±0.7%, 700–425 mμ.

Corticosterone (**X**), m.p. 181–185°; slight λ_{max} 319, 329 mμ, log ϵ 1.93, 1.92, shoulders 290, 340–342 mμ, log ϵ 2.14, 179, inflection 358 mμ, log ϵ 1.43; supplied by Dr. K. Pfister, Merck and Co., Inc. R.D. (Figs. 3 and 4): $[\alpha]_{700}$ +134°, $[\alpha]_{589}$ +194°, $[\alpha]_{295}$ +1989°, "max." $[\alpha]_{385}$ +551°, "min." $[\alpha]_{367.5}$ + 398°, "max." $[\alpha]_{357.5}$ + 534°, "min." $[\alpha]_{352.5}$ +512°, "max." $[\alpha]_{305-310}$ +4022°; c = 0.10; temp. 23–25°.

Hydrocortisone (**XI**), m.p. 215–218°; λ_{max} 290 mμ, log ϵ 2.01; inflections 315, 324, 332, 338, 346, 357 mμ, log ϵ 1.82, 1.75, 1.73, 1.65, 1.56, 1.23; furnished by Dr. K. Pfister, Merck and Co., Inc. R.D. (Figs. 3 and 4): $[\alpha]_{700}$ +113°, $[\alpha]_{589}$ + 162°, $[\alpha]_{300}$ +1202°, "max." $[\alpha]_{385}$ +456°, "min." $[\alpha]_{367.5}$ +312°, "max." $[\alpha]_{357.5}$ +460°, "min." $[\alpha]_{352.5}$ +428°, "max." $[\alpha]_{315}$ +3506°; c = 0.10; temp. 23–25°. Drude equation: $[M] = 172/(\lambda^2 - 0.0551)$; λ_0 235 mμ; % deviation $[M]_{obsd} - [M]_{calcd}$: ±1.0%, 620–410 mμ; ±3.7%, 700–400 mμ.

Desoxycorticosterone (**XII**), m.p. 139–140°; shoulders 285–289, 333, 347 mμ, log ϵ 2.04, 1.71, 1.56; inflections 321, 357, 365 mμ, log ϵ 1.74, 1.28, 1.07; from Syntex, S.A. R.D. (Figs. 3 and 4): $[\alpha]_{700}$ +94°, $[\alpha]_{589}$ +149°, $[\alpha]_{300}$ +1731°, "max." $[\alpha]_{385}$ +448°, "min." $[\alpha]_{367.5}$ +325°, "max." $[\alpha]_{360}$ + 428°, "min." $[\alpha]_{352.5}$ +394°, "max." $[\alpha]_{310}$ +2952°; c = 0.10; temp. 24.5–26.5°. R.D.: $[\alpha]_{700}$ +110.6°, $[\alpha]_{375}$ +437.3°, "max." $[\alpha]_{385}$ +476.1°; c = 1.00; temp. 24–25°. Drude equation: $[M] = 154/(\lambda^2 + 0.0667)$, from c = 1.00 data; λ_0 258 mμ; % deviation $[M]_{obsd} - [M]_{calcd}$: ±0.5%, 700–475 mμ; ±1.2%, 700–450 mμ.

Δ^4-Androstene-11β-ol-3,17-dione (**XIII**), m.p. 194–199°. R.D. (Fig. 5): "max." $[\alpha]_{317.5}$ +3945°; c = 0.10; temp. 24–25°.[11]

17α-Hydroxydesoxycorticosterone (**XIV**), m.p. 205–210°; λ_{max} 286–289 mμ, log ϵ 2.03, shoulders 349, 330 mμ, log ϵ

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[11] Data based on one determination.

1.47, 1.70; inflections 364, 358, 340, 315 mμ, log ε 0.97, 1.17, 1.60, 1.78; from Syntex, S.A. R.D. (Fig. 5): "max." $[\alpha]_{312.5}$ + 3786°; c = 0.10; temp. 23–24°.[11]

Pregnane-3β-ol-20-one (**XVII**), m.p. 144–146°; λ_{max} 238–291 mμ, log ε 1.53; supplied by Syntex, S.A. R.D. (Fig. 5): $[\alpha]_{700}$ + 55°, $[\alpha]_{589}$ +85°, $[\alpha]_{295}$ +601°, "max." $[\alpha]_{312.5}$ + 2393°; c = 0.10; temp. 25°.[11]

Etiocholane-3α,17β-diol-11-one (**XVIII**), m.p. 261–262°; λ_{max} 302–303 mμ, log ε 1.51, shoulders 311–313, 292–294 mμ, log ε 1.46, 1.46; inflections 320, 325 mμ, log ε 1.28, 1.16; supplied by Dr. E. B. Hershberg and Dr. H. L. Herzog, Schering Corp. R.D. (Fig. 5): $[\alpha]_{700}$ +39°, $[\alpha]_{589}$ +59°, $[\alpha]_{300}$ +53°, "max." $[\alpha]_{327.5}$ +679°; c = 0.10; temp. 24°.[11]

DETROIT, MICHIGAN

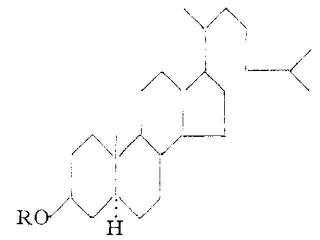
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

Optical Rotatory Dispersion Studies. III.[1] The Cholestane Series[2]

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

RECEIVED MARCH 16, 1955

The rotatory dispersion curves of various isomeric cholestenols and ketones of the cholestane series are reported and discussed. Some of the mathematical implications are also presented.



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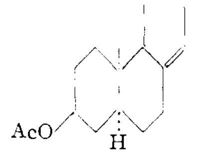
II, R = CH$_3$CO



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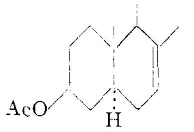

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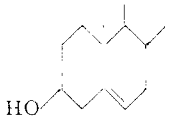

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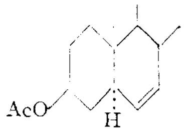

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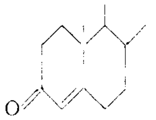

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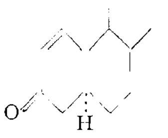

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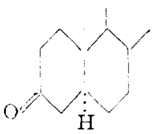

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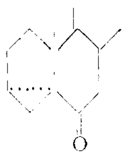
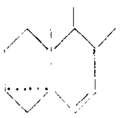


X


XI

Cholesterol (V) is one of the very few steroids, the rotatory dispersion of which has been examined prior to our own investigations[1,3] in this field and initial measurements with this substance in the visible region have been carried out as early as 1863.[4a] We now have measured the rotatory dispersion of various members of the cholestane series and in particular of various double bond isomers of cholesterol. These substances, lacking strong chromophores such as carbonyl groups, should show "normal" dispersion curves and hence should be more amenable to mathematical treatment. We also have included several ketones of the cholestane series in order to complement the earlier studies[1,3] of the rotatory dispersion of carbonyl-containing steroids.

The dispersion curves of the ketones studied in this series are shown in Fig. 2 and the results fully confirm the earlier conclusions.[1,3] Cholestan-3-one (IX) is very similar to androstan-3-one, discussed previously,[3] in that it shows the positive rotation peak at 315 mμ ascribed to a weakly asymmetric chromophore associated with the carbonyl function at C-3; furthermore, this substance shows the negligible effect that the cholestane side chain appears to have on the rotation of the molecule.

Considering the region 350–400 mμ, so important for unsaturated ketones,[1,3] Δ^4-cholesten-3-one (VII) exhibits a "maximum"[5] at 360 mμ and "minima" at 365 and 350 mμ, corresponding to an optically active absorption band at 355 mμ (mean of positive peak at 360 mμ and negative peak at 350 mμ). While the position of this band (and the peaks defining it) is in accord with that of other Δ^4-3-keto steroids,[1,3] it is noteworthy that these two peaks occur at a negative rotation. The only other Δ^4-3-ketone exhibiting such a behavior is testosterone[1] and these two compounds are the only Δ^4-3-keto steroids in our series[1,3] which do not have an additional saturated carbonyl group elsewhere in the molecule. Another typical property of these two unsaturated ketones is that the "minimum" at 365 mμ occurs at a more positive rotation than the "minimum" at 350 mμ and both these features can be considered as the true characteristics of the Δ^4-3-keto dispersion curve. In all the other Δ^4-3-ketosteroids,[1,3] this order is reversed and this clearly is due to the fact that in those instances the Δ^4-3-keto band is coming under the influence of the very much stronger and highly positive band (in the 320 mμ region) corresponding to the additional saturated carbonyl group (at C-11, 17 or 20) which tends to "pull up" this part of the curve to more positive rotation values. It should be emphasized, however, that this does not interfere with the recognition of the Δ^4-3-keto moiety through its rotatory dispersion band, but rather offers a further refinement of this method through a consideration of both *position* and *relative intensity* of "maxima" and "minima."

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(1) Paper II, E. W. Foltz, A. E. Lippman and C. Djerassi, THIS JOURNAL, **77**, 4359 (1955).

(2) Supported by a grant from the National Science Foundation.

(3) C. Djerassi, E. W. Foltz and A. E. Lippman, THIS JOURNAL, **77**, 4354 (1955).

(4) (a) O. Lindenmayer, *J. prakt. Chem.*, [1] **90**, 323 (1863); (b) L. Tschugaeff, *Z. physik. Chem.*, **76**, 469 (1911). (c) Cholesterol has been measured over the range 260–750 mμ by E. Brand, E. Washburn, B. F. Erlanger, E. Ellenbogen, J. Daniel, F. Lippmann and M. Scheu, THIS JOURNAL, **76**, 5037 (1954).

(5) See ref. 3 for a definition of terms and general experimental procedure.