16α-Piperidino-5-pregnene-3β,20-diol.—16α-Piperidino-5-pregnen-3β-ol-20-one (4 g.) was suspended in 50 ml. of methanol containing 2 ml. of water, and to this was added a solution of 4 g. of sodium borohydride in 30 ml. of methanol. The mixture was heated to boiling, and the solution obtained was allowed to stand overnight at room temperature. The mixture was poured into 400 ml. of water and the precipitate collected. The air-dried material was crystallized from isopropyl alcohol, collected and dried, wt. 3.3 g., m.p. 145–175°. The infrared spectrum showed no carbonyl peak.

Five crystallizations from ethanol and methanol gave one epimer, probably 20β-,[20] m.p. 184–186°, $[\alpha]^{25}D$ −97.6°.[19] The hydrochloride had m.p. 292.5–293° dec., $[\alpha]^{25}D$ −43.7°.[19]

The mother liquor gave fractions with lower rotations, but another pure epimer was not isolated.

The methiodide prepared by refluxing in methyl iodide and crystallization from acetone–methanol and methanol, melted at 299–300° dec.

Anal. Calcd. for $C_{27}H_{46}NO_2I$: I, 23.34. Found: I, 23.68.

16α-Piperidino-allopregnane-3β,20-diol.—16α-Piperidino-5-pregnene-3β,20-diol (24 g.) was dissolved in 100 ml. of acetic acid and shaken with 2 g. of platinum oxide under hydrogen in the Parr apparatus for about one hour until absorption ceased (*ca.* 6 lb. pressure decrease). The mixture was filtered and the filtrate was poured into 2 l. of water containing 250 g. of potassium hydroxide. The precipitate which formed was collected and refluxed in 700 ml. of methanol with 12 g. of potassium hydroxide in 50 ml. of water for 1.5 hr. The solution was concentrated and the residue treated with 2 l. of water. This product was collected, dried at 60° *in vacuo* for 3 hours and overnight *in vacuo* but still contained water (wt. 49 g.). In order to dry it the material was dissolved in benzene, separated from a water layer, and the benzene layer concentrated to 150 ml. The product crystallized on standing, and was filtered off and dried at 60° for 30 min., wt. 18.5 g., m.p. 178–179°. The mother liquor gave further crops. Several crystallizations from benzene or acetone gave the desired product, probably 20β,[20] which had m.p. 178–180°, $[\alpha]^{25}D$ −55.2°, and an infrared spectrum (Nujol mull) with peaks at 2.80 and 3.12 μ.[19]

Concentration of an acetone mother liquor gave a second form (possibly 20α),[20] m.p. 185–190°, $[\alpha]^{25}D$ −57.0, differing slightly as expected in the infrared spectrum (Nujol mull) with a peak at 3.12 and a shoulder at 2.96 μ.[19]

The methiodide was prepared in the usual way and crystallized from methanol, m.p. 286–288° dec.

Anal. Calcd. for $C_{27}H_{48}NO_2I$: I, 23.26. Found: I, 23.22.

BLOOMFIELD, N. J.

(20) *Inter alia, cf.* E. L. Shapiro, D. Gould and E. B. Hershberg, THIS JOURNAL, **77**, 2912 (1955); L. H. Sarett, M. Feurer and K. Folkers, *ibid.*, **73**, 1777 (1951); N. L. Wendler, Huang-Minlon and M. Tishler, *ibid.*, **73**, 3818 (1951).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

Optical Rotatory Dispersion Studies. V.[1] The Effect of Isolated Carbonyl Groups and Double Bonds in the Cholestane Series[2]

BY CARL DJERASSI, W. CLOSSON AND A. E. LIPPMAN

RECEIVED SEPTEMBER 12, 1955

Rotatory dispersion curves of various saturated ketocholestanes are presented and it is demonstrated that this method represents a useful new tool for the location of single carbonyl groups in the steroid molecule. The effect of isolated double bonds on the rotatory dispersion has been examined in the cholestane series.

In earlier papers,[3] it has been demonstrated that certain structural changes in the steroid molecule, particularly those involving carbonyl groups, are amenable to correlation with rotatory dispersion curves. For instance, the Δ^4-3-keto moiety could be recognized in a variety of steroids with or without additional substituents by virtue of certain characteristic features ("maxima" and "minima"[4]) in the dispersion curves. While this represents an observation of considerable theoretical interest, from a practical standpoint it is simpler to recognize a Δ^4-3-ketone through certain ultraviolet and infrared absorption bands. This does not, however, apply to locating *saturated* carbonyl groups in the steroid molecule. Ultraviolet absorption spectra are only of very limited value[5] in this respect while infrared spectra are mainly helpful in differentiating between 5- and 6-membered ring ketones although more subtle correlations have also been attempted.[6]

We should now like to report some observations which suggest that the rotatory dispersion curve can become a very promising adjunct to steroid (and possibly triterpenoid) methodology insofar as the *location of isolated, saturated carbonyl groups* in the molecule is concerned and that structural conclusions appear possible which cannot be made with either the use of ultraviolet or infrared spectroscopy alone.

The present study is limited to the cholestane series and thanks to the generosity of various colleagues[7] it has been possible to determine the effect upon the rotatory dispersion curve of carbonyl groups in all but two of the possible locations in the nucleus. As can be seen from Figs. 1 and 2, the individual curves differ sufficiently so that they can be used for characterization purposes. In some

(1) Paper IV, C. Djerassi and R. Ehrlich, THIS JOURNAL, **78**, 440 (1956).

(2) Supported by a research grant from the Damon Runyon Memorial Fund for Cancer Research. We are indebted to the National Science Foundation for funds covering the purchase of the spectropolarimeter.

(3) (a) C. Djerassi, E. W. Foltz and A. E. Lippman, THIS JOURNAL, **77**, 4350 (1955); (b) E. W. Foltz, A. E. Lippman and C. Djerassi, *ibid.*, **77**, 4359 (1955); (c) A. E. Lippman, E. W. Foltz and C. Djerassi, *ibid.*, **77**, 4364 (1955).

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

(5) O. Schindler and T. Reichstein (*Helv. Chim. Acta*, **37**, 667 (1954)) have pointed out that the low intensity band in the 300 mμ region can sometimes be used to differentiate between 11- and 12-keto steroids, but that even slight structural alterations can affect the spectra to a marked extent.

(6) *Cf.* R. N. Jones and F. Herling, *J. Org. Chem.*, **19**, 1252 (1954).

(7) We are greatly indebted to the following investigators for specimens: D. H. R. Barton, R. C. Cookson, E. J. Corey, L. F. Fieser, W. Klyne, E. Mosettig, T. Reichstein, C. Tamm and R. B. Turner.

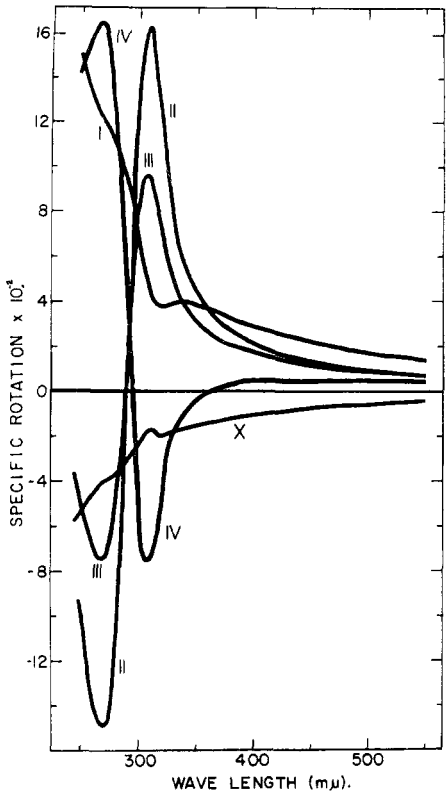


Fig. 1.—Rotatory dispersion curves (methanol solution) of: cholestan-1-one (I), cholestan-2-one (II), cholestan-3-one (III), cholestan-4-one (IV) and D-homoandrostan-3β-ol-17a-one (X).

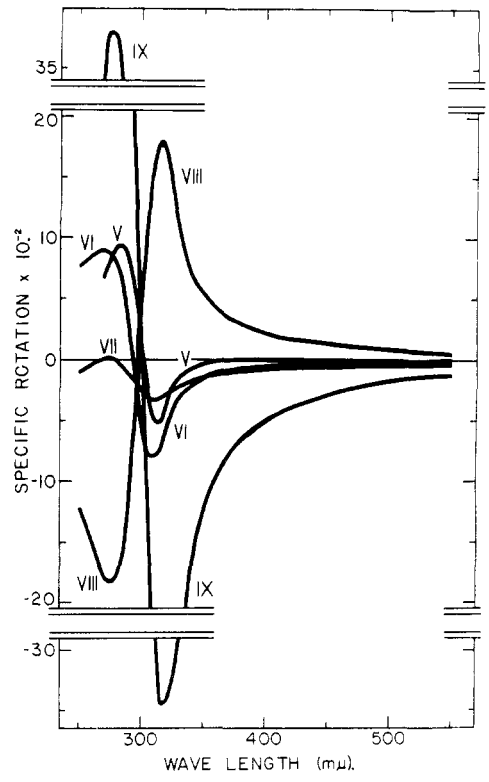


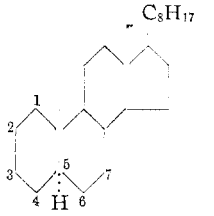
Fig. 2.—Rotatory dispersion curves (methanol solution) of: cholestan-3,6-dione (V), 3β-acetoxycholestan-6-one (VI), 3β-acetoxycholestan-7-one (VII), cholestan-3β-ol-15-one (VIII) and coprostan-16-one (IX).

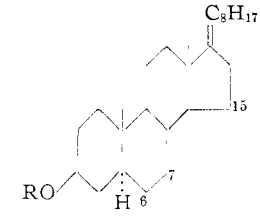
instances, where the shapes of the curves are similar (*e.g.* cholestan-2-one (II) and cholestan-3β-ol-15-one (VIII)), the infrared spectrum will often eliminate one of the possibilities.

All of the earlier measurements[1,3a-c] have been carried out with a zirconium lamp which limited the spectral range from 700 to 290–300 mμ. By means of a special xenon lamp and power assembly,[8] and utilizing methanol as solvent, it has been possible to extend the range downward to *ca.* 250 mμ with the important consequence that the optically active absorption band near 300 mμ usually associated with the carbonyl group could now be defined by both its peaks rather than by extrapolation through the zero line.

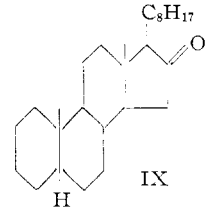
Cholestan-1-one (I) exhibits a unique dispersion curve (Fig. 1), which serves to differentiate it from all other ketones since it does not possess a pronounced positive or negative peak. The only other compound showing such a behavior (as a rough mirror image) is D-homoandrostan-3β-ol-17a-one (X) and it is immediately apparent that the environment around the carbonyl group in both compounds is similar. This does not necessarily mean that the ketonic function in I and X is optically inactive but rather that it is weakly active and falls under the influence of a general, strongly positive (or negative) rotation which as yet cannot be attributed to any particular structural grouping. Nevertheless, the shape of the curve is highly characteristic and as such quite unambiguous in locating the 1-keto group.

(8) Commercially available from O. C. Rudolph & Sons, Caldwell, N. J.

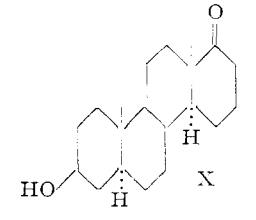




I, carbonyl at C-1
II, carbonyl at C-2
III, carbonyl at C-3
IV, carbonyl at C-4
V, carbonyl at C-3 and C-6
VI, carbonyl at C-6; R = Ac
VII, carbonyl at C-7; R = Ac
VIII, carbonyl at C-15; R = H
XI, 1–2 double bond
XII, 2–3 double bond
XIII, 3–4 double bond
XIV, 4–5 double bond
XV, 5–6 double bond
XVI, 6–7 double bond



IX



X

In their general shapes, the dispersion curves (Fig. 1) of cholestan-2-one (II) ("maximum" $[\alpha]_{310}$ +1632°, "minimum" $[\alpha]_{267}$ −1514°, optically active absorption band at 289 mμ) and choles-

tan-3-one (III)[9] ("maximum" $[\alpha]_{307}$ +959°, "minimum" $[\alpha]_{267}$ −740°, optically active absorption band at 287 mμ) are quite similar and the chief basis of differentiation in this instance must rest upon the intensity of rotation which is very much higher in the 2-ketone II. The utility of considering the intensity in conjunction with the wave length has already been pointed out with certain hormones,[3b] but admittedly a greater number of hitherto unknown 2-keto steroids would have to be measured before this conclusion could be considered unambiguous.

Cholestan-4-one (IV) can be separated readily from the other ring A ketone since its optically active absorption band is entered from the negative rather than the positive side (Fig. 1).

Two other 6-membered ketones (Fig. 2) which exhibit first a "minimum" are cholestan-3β-ol-6-one acetate (VI) and its 7-keto (VII) isomer. A differentiation, however, appears possible on the basis of the intensity of the rotations, it being greatest in the 6-ketone,[10] and in the case of the 7-ketone VII even by its shape, the flatness of the peaks showing a relatively weak optical activity associated with that group. Since the dispersion curves of cholestan-3-one (III) (Fig. 1) and the 6-ketone (VI) (Fig. 2) are roughly mirror images around the zero axis, it seemed of interest to determine the rotatory dispersion spectrum of cholestan-3,6-dione (V) in which both carbonyl groups are in the same molecule. The resulting curve (Fig. 2) is clearly not the summation of the two individual ones (III and VI)[11] but comment on this topic is reserved for a report on carbonyl-containing bile acids, where a considerable number of poly-ketonic examples are available.

The curves for the two possible ring D ketones, cholestan-3β-ol-15-one (VIII) and coprostan-16-one (IX)[12] are reproduced in Fig. 2 and the differences between the two spectra are immediately obvious. The 15-ketone, qualitatively and to a certain extent even quantitatively, resembles 17-keto steroids,[3a] while the only other available 16-ketone dispersion spectrum (kryptogenin[1,13]) shows the same tremendous "minimum" which defines the long wave length side of the optically active absorption band of coprostan-16-one (IX). These two cyclopentanones (VIII, IX) offer a good illustration of an instance where the rotatory dispersion curve is much more useful for localization purposes than the infrared spectrum.

With two exceptions, all of the above carbonyl-containing sterols exhibit optically active absorption bands within the limits 287 (III) to 296 mμ (VIII, IX) which is in approximate agreement[14] with the observed ultraviolet absorption maxima and confirms that all of these carbonyl groups are optically active and that those particular bands should be assigned to them. The exceptions, which have already been commented upon above, are the 1- (I) and D-homo-17a-ketone (X) and no conclusive explanation can be offered at this time.

In connection with a study of the heats of hydrogenation of steroidal olefins, Turner[15] synthesized a series of cholestenes in a high state of purity and rotatory dispersion curves (dioxane solution) of six of them are given in Fig. 3. In two instances, cholest-5-ene (XV) and cholest-6-ene (XVI), the corresponding 3-hydroxy or acetoxy derivatives have already been measured[3c] and the respective spectra are extremely similar. Cholest-6-ene (XVI) exhibits by far the most negative rotation throughout the entire spectral range[16] which also applies to the corresponding estradiol derivative.[3b] No satisfactory explanation seems to be available to

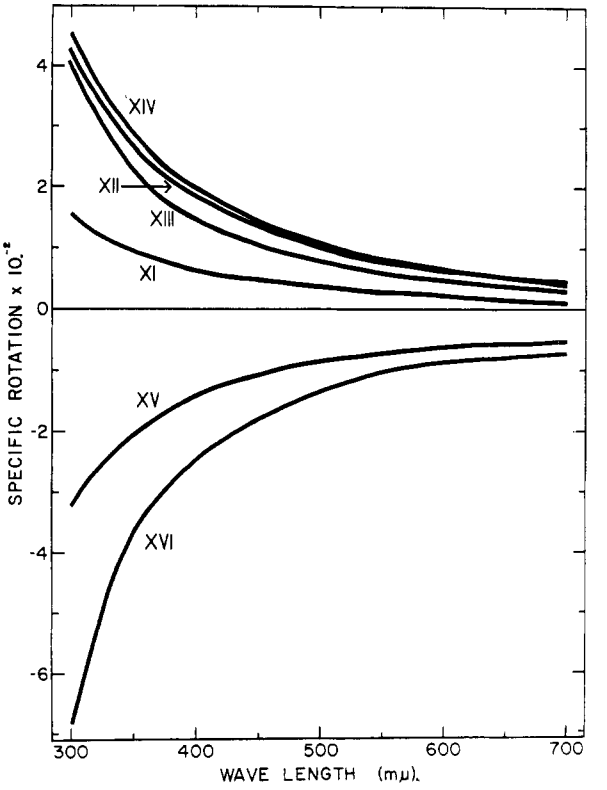


Fig. 3.—Rotatory dispersion curves (dioxane solution) of: cholest-1-ene (XI), cholest-2-ene (XII), cholest-3-ene (XIII), cholest-4-ene (XIV), cholest-5-ene (XV) and cholest-6-ene (XVI).

(9) This substance has already been measured earlier[3c] in dioxane solution with a zirconium lamp to 285 mμ, but the new curve covering the entire range to 245 mμ in methanol solution is reproduced for comparison purposes with the other ketones.

(10) The rotatory dispersion curve of 3,5-cyclocholestan-6-one reported earlier (ref. 3c) is qualitatively and quantitatively quite similar to the presently described cholestan-3β-ol-6-one acetate (VI), thus showing that the effect of the cyclopropane ring in this case is negligible.

(11) Admittedly, this ignores the possible effect of the 3-acetoxy group in VI which, however, appears to be negligible.

(12) The corresponding cholestane compound was not available, but isomerization at C-5 should play only a negligible role (*cf.* ref. 3a for pertinent examples).

(13) For solubility reasons, this had to be measured in dioxane solution and it was not possible to define the "maximum" in that instance.

(14) The small discrepancy between the observed ultraviolet absorption maximum and the position of the optically active absorption band, as derived from the rotatory dispersion spectrum, has already been noticed and discussed earlier (for leading references see H. S. French and M. Naps, THIS JOURNAL, **58**, 2303 (1936), and E. Hückel, *Z. Elektrochem.*, **50**, 13 (1944)).

(15) R. B. Turner, Abstracts, XIV Internat. Cong. of Pure and Appl. Chem., Zurich, 1955, p. 387.

(16) This substance (XVI) was also studied in methanol solution with a xenon lamp down to 250 mμ without, however, reaching a "minimum."

explain the differences in the dispersion curves and no correlation between the steepness of the slope (implying the more rapid approach of a "maximum" or "minimum") and the degree of substitution of the double bond can be discerned. The latter would have been the most obvious explanation, the most highly substituted double bond absorbing toward higher wave length in which case its optically active absorption band (if one is indeed present) would appear sooner. An alternative explanation, which would take into consideration the relative distortion of the shape of the steroid molecule and consequent rotatory reflection by the introduction of double bonds at various positions, cannot as yet be put on a precise basis.

Experimental

With one exception,[16] all cholestenes (XI–XVI) were measured in dioxane solution, while the ketones (I–X) were investigated in methanol solution. The experimental procedure has already been outlined in detail[3a] and was also followed in this investigation except that all readings below 300 mμ were taken with a 150-watt xenon arc lamp (Hanovia 10-C-1). The lamp was operated on direct current with a special commercially available power supply unit.[8]

Cholestan-1-one (I) (C. Tamm and T. Reichstein): R.D. (Fig. 1): $[\alpha]_{700}$ +76°, $[\alpha]_{589}$ +115°, $[\alpha]_{245}$ +1774°, "max." $[\alpha]_{338}$ +403°, "min." $[\alpha]_{318}$ +374°, *c* 0.15, temp. 26–28°, λ_{max}^{MeOH} 285 mμ.[17]

Cholestan-2-one (II) (D. H. R. Barton), R.D. (Fig. 1): $[\alpha]_{700}$ +39°, $[\alpha]_{589}$ +59°, $[\alpha]_{250}$ −972°, "max." $[\alpha]_{310}$ +1632°, "min." $[\alpha]_{287}$ −1514°, *c* 0.1, temp. 23–26°, ultraviolet inflection, 286–290 mμ, log ε 2.24.

Cholestan-3-one (III)[3c], R.D. (Fig. 1): $[\alpha]_{700}$ +37°, $[\alpha]_{589}$ +55°, $[\alpha]_{245}$ −362°, "max." $[\alpha]_{307}$ +959°, "min." $[\alpha]_{267}$ −740°, *c* 0.1, temp. 29–31°.

(17) P. Striebel and C. Tamm (*Helv. Chim. Acta*, **37**, 1094 (1954)) report λ_{max} 297 mμ in ether.

Cholestan-4-one (IV) (L. F. Fieser and D. H. R. Barton), R.D. (Fig. 1): $[\alpha]_{700}$ +26°, $[\alpha]_{589}$ +29° $[\alpha]_{260}$ +1580°, "max." $[\alpha]_{267.5}$ +1650°, "min." $[\alpha]_{307.5}$ −780°, *c* 0.5, temp. 26–27°, λ_{max}^{MeOH} 290–295 mμ, log ε 1.56.

Cholestane-3,6-dione (V), (L. F. Fieser), R.D. (Fig. 2): $[\alpha]_{700}$ −15°, $[\alpha]_{589}$ +10°, $[\alpha]_{270}$ +667°, "max." $[\alpha]_{282}$ +944°, "min." $[\alpha]_{315}$ −521°, *c* 0.04, temp. 27–29°, λ_{max}^{MeOH} 294–296 mμ, log ε 1.75.

3β-Acetoxycholestan-6-one (VI), (R. C. Cookson), R.D. (Fig. 2): $[\alpha]_{700}$ −2°, $[\alpha]_{589}$ −17°, $[\alpha]_{240}$ +591°, "max." $[\alpha]_{270}$ +906°, "min." $[\alpha]_{306}$ −799°, *c* 0.1, temp. 24–26°, λ_{max}^{MeOH} 290–292 mμ, log ε 1.51.

3β-Acetoxycholestan-7-one (VII), (E. J. Corey), R.D. (Fig. 2): $[\alpha]_{700}$ −28°, $[\alpha]_{589}$ −36°, $[\alpha]_{250}$ −111°, "max." $[\alpha]_{274}$ +15°, "min." $[\alpha]_{310}$ −342°, *c* 0.1, temp. 25–27°, λ_{max}^{MeOH} 285–287 mμ, log ε 1.41.

Cholestan-3β-ol-15-one (VIII), (D. H. R. Barton), R.D. (Fig. 2): $[\alpha]_{700}$ +27°, $[\alpha]_{589}$ +49°, $[\alpha]_{250}$ −1230°, "max." $[\alpha]_{316}$ +1780°, "min." $[\alpha]_{275}$ −1835°, *c* 0.1, temp. 25–26°, ultraviolet inflection, 290–296 mμ, log ε 1.53.

Coprostan-16-one (IX), (E. Mosettig), R.D. (Fig. 2): $[\alpha]_{700}$ −77°, $[\alpha]_{589}$ −114°, $[\alpha]_{250}$ +2360°, "max." $[\alpha]_{276}$ +3800°, "min." $[\alpha]_{317}$ −3452°, *c* 0.1, temp. 25–26°, λ_{max}^{MeOH} 299–303 mμ, log ε 1.47.

D-Homoandrostan-3β-ol-17a-one (X), (W. Klyne), R.D. (Fig. 1): $[\alpha]_{700}$ −22°, $[\alpha]_{589}$ −38° $[\alpha]_{245}$ −577°, "max." $[\alpha]_{312}$ −166°, "min." $[\alpha]_{320}$ −193°, *c* 0.1, temp. 29–31°, λ_{max}^{MeOH} 275–277 mμ, log ε 1.70.

Cholest-1-ene (XI),[15] R.D. (Fig. 3): $[\alpha]_{700}$ +8.8°, $[\alpha]_{589}$ +20°, $[\alpha]_{300}$ +142°, *c* 0.1, temp. 23–25°.

Cholest-2-ene (XII),[15] R.D. (Fig. 3): $[\alpha]_{700}$ +47°, $[\alpha]_{589}$ +68°, $[\alpha]_{290}$ +445°, *c* 0.1, temp. 24–25°.

Cholest-3-ene (XIII),[15] R.D. (Fig. 3): $[\alpha]_{700}$ +30°, $[\alpha]_{589}$ +49°, $[\alpha]_{300}$ +410°, *c* 0.1, temp. 24–26°.

Cholest-4-ene (XIV),[15] R. D. (Fig. 3): $[\alpha]_{700}$ +39°, $[\alpha]_{589}$ +72.5°, $[\alpha]_{300}$ +448°, *c* 0.1, temp. 24–25°.

Cholest-5-ene (XV),[15] R.D. (Fig. 3): $[\alpha]_{700}$ −50°, $[\alpha]_{589}$ −64°, $[\alpha]_{300}$ −321°, *c* 0.1, temp. 24–27°.

Cholest-6-ene (XVI),[15,16] R.D. (Fig. 3): $[\alpha]_{700}$ −68°, $[\alpha]_{589}$ −93°, $[\alpha]_{290}$ −773°, *c* 0.1, temp. 26–28°.

DETROIT, MICHIGAN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

The Constitution and Stereochemistry of Digitogenin[1]

BY CARL DJERASSI, THURMAN T. GROSSNICKLE[2] AND LEROY B. HIGH

RECEIVED DECEMBER 2, 1955

Degradative evidence is presented that digitogenin is 22a,25a,5α-spirostane-2α,3β,15β-triol (Ia), thus representing the first naturally occurring C-15 hydroxylated steroid. Attention is called to certain stereochemical features in fused hydrindanone systems.

The chemistry of digitogenin, the aglycone of the saponin digitonin, has been summarized adequately by Fieser and Fieser[3] who in 1949 pointed out that "the structure of digitogenin, the earliest known and most extensively investigated of all the sapogenins, is still uncertain." This was the existing state of affairs when we took up this structural problem in 1953, since no further publications on this subject had appeared in the intervening period. Our results, which have led to the elucidation of the structure and stereochemistry of this sapogenin, have been recorded in a series of preliminary communications[4–7] and we should now like to present the experimental details on which these brief reports were based.

Location of the Third Hydroxyl Group

The gross structural features of digitogenin had already been established by Tschesche,[8] who had subjected the oxidation product of digitogenin (I), digitogenic acid (now known to be II), to Wolff–Kishner reduction *via* its semicarbazone and had isolated a small amount of gitogenic acid (III), derivable by scission of ring A of gitogenin (IV).

(1) Supported by a research grant from the American Cancer Society through the Committee on Growth of the National Research Council.

(2) Monsanto Predoctorate Research Fellow, 1952–1954.

(3) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, N. Y., 1949, chapter VIII.

(4) C. Djerassi and T. T. Grossnickle, *Chemistry & Industry*, 728 (1954).

(5) C. Djerassi, T. T. Grossnickle and L. B. High, *ibid.*, 473 (1955).

(6) C. Djerassi, L. B. High, T. T. Grossnickle, R. Ehrlich, J. A. Moore and R. B. Scott, *ibid.*, 474 (1955).

(7) C. Djerassi, L. B. High, J. Fried and E. F. Sabo, THIS JOURNAL, **77**, 3673 (1955).

(8) R. Tschesche, *Ber.*, **68**, 1090 (1935).